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GUIDELINES

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# Management of nocturnal hypertension: An expert consensus document from Chinese Hypertension League

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## Abstract

Nocturnal hypertension is highly prevalent among Chinese and Asian populations, which is mainly attributed to high salt intake and high salt sensitivity. Nocturnal hypertension increases the risk of cardiovascular and all-cause mortality, independent of daytime blood pressure (BP). However, it can usually be detected by 24-h ambulatory BP monitoring, rather than routine office or home BP measurement, thus is often underdiagnosed in clinical practice. Currently, no specific guidance is available for the management of nocturnal hypertension in China or worldwide. Experts from the Chinese Hypertension League summarized the epidemiologic and pathophysiologic characteristics and clinical phenotype of nocturnal hypertension and provided consensus recommendations on optimal management of nocturnal hypertension, with the goal of maximally reducing the cardiovascular disease risks. In this consensus document, 24-h ABPM is recommended for screening and diagnosis of nocturnal hypertension, especially in the elderly, patients with diabetes, chronic kidney diseases, obstructive sleep apnea and other conditions prone to high nocturnal BP. Lifestyle modifications including salt intake restriction, exercise, weight loss, sleep improvement, and mental stress relief are recommended. Long-acting antihypertensive medications are preferred for nocturnal and 24-h BP control. Some newly developed agents, renal denervation, and other device-based therapy on nocturnal BP reduction are evaluated.

**KEYWORDS**
clinical management, expert consensus, nocturnal hypertension

## 1 | INTRODUCTION

Nocturnal hypertension usually refers to the clinical condition of elevated nighttime blood pressure (BP) detected by 24-h ambulatory BP monitoring (ABPM).[1–3] High prevalence of nocturnal hypertension was found in Chinese, Japanese, and other Asian populations rather than in Caucasians, which was probably associated with high salt intake and salt sensitivity.[4–6] Nocturnal hypertension is considered to be a risk factor of target organ damage, cardiovascular, and all-cause mortality, independent of daytime BP.[7–13] However, due to the disadvantages of routine office BP measurement and home BP monitoring (HBPM) in daily practice, nocturnal hypertension has not been fully recognized and usually underdiagnosed.

Currently, there are no specific guidelines for the management of nocturnal hypertension. Experts from the Chinese Hypertension League systemically reviewed the literature, summarized the key points, and reached this consensus to provide recommendations and suggestions for the management of nocturnal hypertension in clinical practice.

## 2 | DEFINITION AND EPIDEMIOLOGY

According to 2018 Chinese and European guidelines for the management of arterial hypertension, nocturnal hypertension is defined as mean nighttime systolic BP ≥120 mm Hg and/or mean diastolic BP ≥ 70 mm Hg, regardless of nighttime BP dipping patterns or daytime BP.[2,3] Meanwhile, isolated nocturnal hypertension is a specific condition with mean nighttime BP ≥ 120/70 mm Hg while daytime BP < 135/85 mm Hg, which is more insidious and difficult to identify.[4,5] Patients with mean nighttime BP ≥ 120/70 mm Hg while daytime BP < 135/85 mm Hg on antihypertensive medications can be diagnosed as uncontrolled nocturnal hypertension.

There is a lack of large-scale epidemiological data on the prevalence of nocturnal hypertension. A cohort study in China revealed the prevalence of isolated nocturnal hypertension was 10.9%.[4] The analysis of international ABPM databases showed the prevalence of isolated nocturnal hypertension in Asian and South African populations was about 10%, while 6%—7.9% in Europeans, indicating obvious regional and racial differences.[5] The elderly, people with high-salt diet, sleep disorders, frequent nocturia, obstructive sleep apnea syndrome (OSAS), chronic kidney diseases (CKD), diabetes, chronic heart failure (CHF), cerebrovascular disease or peripheral arterial disease, as well as those with anxiety and depression, are susceptible to nocturnal hypertension.[12–20]

## 3 | PATHOPHYSIOLOGY

Nocturnal hypertension is associated with the changes of various neurohumoral regulatory factors. The key factors are the

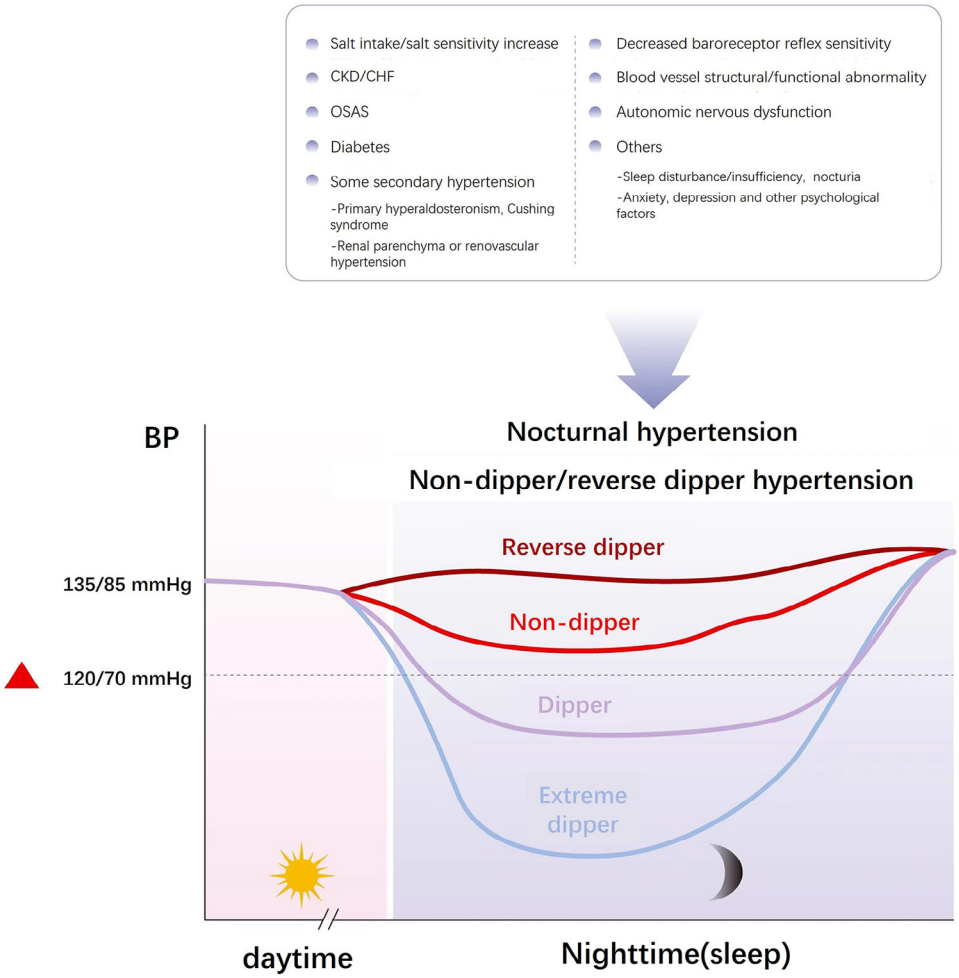


**FIGURE 1** Pathophysiology of nocturnal hypertension and blood pressure dipping patterns. The following four blood pressure dipping patterns are defined according to the average drop of nighttime blood pressure compared with daytime: extreme dipper, >20%; dipper, 10%–20%; nondipper <10%; reverse dipper, nighttime blood pressure is higher than daytime. CHF, chronic heart failure; CKD, chronic kidney disease; OSAS, obstructive sleep apnea syndrome.

increase of circulating volume and abnormal sympathetic activity at night.

Physiological or pathological factors closely related to nocturnal hypertension are summarized as follows (Figure 1): (1) One of the important mechanisms of nocturnal hypertension in Asian population is the excessive salt intake or high salt sensitivity, which leads to the increasing need of renal sodium excretion (pressure natriuretic effect) at night and resulting in an increased renal perfusion pressure and the occurrence of nocturnal hypertension or nondipper hypertension.[15,16] (2) Patients with chronic renal or cardiac dysfunction have an increased circulatory volume, leading to more venous return in the supine position which might increase BP at night.[20] (3) Patients with diabetes, Parkinson's disease, sleep disorders or autonomic nerve dysfunction may have increased sympathetic activity at night, leading to the disturbance of normal BP circadian as well as the occurrence of nocturnal hypertension.[20] (4) In patients with OSAS, nocturnal hypoxemia can also cause abnormal sympathetic activation, resulting in elevated BP and even adverse cardiovascular events.[21] (5) In elderly patients with decreased elasticity of large arteries, arterial stiffness or atherosclerosis, vascular endothelial dysfunction or decreased BP autoregulation capacity resulted from decreased baroreceptor reflex sensitivity, etc. BP circadian rhythm disorders and nocturnal hypertension often occur. Some elderly patients with orthostatic hypotension can be accompanied by supine nocturnal hypertension.[20,22] (6) Some secondary hypertension, such as primary hyperaldosteronism, Cushing's syndrome, renal parenchyma or renovascular hypertension, usually have excessive volume load and show as nocturnal hypertension.[20] (7) High environmental temperature during sleeping (such as in summer), insufficient sleep or frequent waking up at night, anxiety, depression, cognitive dysfunction and other psychological factors can also cause elevated BP at night.[20]

## 4 | CLINICAL PHENOTYPES

According to the results of 24-h ABPM, most of the patients with nocturnal hypertension demonstrated as sustained hypertension during day and night, and some patients had isolated nocturnal hypertension.

### 4.1 | Day–night sustained hypertension

Day–night sustained hypertension is referred to the situation when ABPM showed the mean daytime BP ≥ 135/85 mm Hg and nighttime BP ≥ 120/70 mm Hg. According to the difference between mean daytime and nighttime BP, it can be divided into the following patterns: dipper (nighttime BP drops by 10%—20% on average compared with daytime BP), nondipper (nighttime BP drops by <10%) and reverse dipper (nighttime BP is higher than daytime BP), etc.[1,23] The incidence of nondipper or reverse dipper hypertension is higher in patients with old age, obesity, OSAS, CKD, and diabetes.[14] Since patients with day-night sustained hypertension are at high risk of target organ damage and adverse cardiovascular events, it is necessary to evaluate circadian rhythm via ABPM and try to reach a goal of 24-h BP control.[14]

### 4.2 | Isolated nocturnal hypertension

Isolated nocturnal hypertension is defined as average nighttime BP≥120/70 mm Hg in ABPM without the use of antihypertensive agents, while daytime BP does not reach the diagnostic threshold of hypertension. As a type of masked hypertension, isolated nocturnal hypertension is usually screened and diagnosed by ABPM[5] and easy to be neglected in the clinical practice.[4] Current studies indicate that patients with isolated nocturnal hypertension tend to be older, male sex, higher body mass index (BMI), more alcohol intake, faster nighttime pulse rate and elevated level of blood cholesterol or glucose.[4,24] For men, smokers, overweight people, and patients with metabolic syndrome or CKD, or those with high-normal office BP and obvious target organ damage without other cardiovascular risk factors, 24-h ABPM should be performed to identify isolated nocturnal hypertension.[25]

### 4.3 | Other types of nocturnal hypertension

Some elderly may present with orthostatic hypotension combined with supine nocturnal hypertension, which is mostly related to increased stiffness of large arteries, decreased baroreflex sensitivity and autonomic nerve dysfunction.[26,27] In patients treated with antihypertensive medications, uncontrolled nocturnal hypertension may occur if the efficacy of the drugs cannot be maintained for 24 h. Although the daytime office BP or ambulatory BP is well controlled, the nighttime BP may still be at a high level.[20,24] Some nocturnal hypertension can extend to the early morning period and develop to morning hypertension.[23] Nondipper/reverse dipper BP pattern usually occur in patients with nocturnal hypertension, yet can be seen in normotensive patients. In hypertensive patients with diabetes, the incidence of nondipper can be 30%.[28] A meta-analysis has shown that nondipper pattern is associated with higher risk of all-cause death and cardiovascular events,[29] but the conclusion is still under debate and needs to be confirmed with further investigations.

## 5 | TARGET ORGAN DAMAGE AND CARDIOVASCULAR EVENTS

Current studies have shown that in normotensive patients and hypertensive, diabetic, or CKD patients, elevated nocturnal BP is closely related to asymptomatic target organ damage (increased pulse wave velocity, carotid intima-media thickness or myocardial hypertrophy, etc.) as well as increased risk of cardiac and renal events (Tables 1 and 2).[30–41]

## 6 | DIAGNOSIS AND BP MONITORING

The 24-h ABPM is the routine method for monitoring BP circadian rhythm and the standardized method for clinical diagnose of nocturnal hypertension. According to the 2020 Chinese Hypertension League guidelines on ABPM, the diagnostic threshold of nighttime BP corresponding to office BP 140/90 mm Hg (grade 1 hypertension) and 160/100 mm Hg (grade 2) were 120/70 mm Hg and 130/80 mm Hg, respectively.[25,42] It is recommended to define the sleep period recorded by the patient on the day of ABPM as the nighttime period. If the patient does not have a diary of activities and sleep time record, fixed-narrow time intervals can be used, such as taking 23:00–5:00 as the night period. Qualified ABPM for nighttime BP should be measured every 30 min with at least seven valid readings during the night period.[25] A 24-h ABPM record is well-reproducible in short-term for the diagnosis of nocturnal hypertension, but is less-reproducible for the diagnosis of dipper and nondipper BP pattern. Studies showed that 18% of the untreated hypertensive patients changed their diagnosis of nocturnal hypertension, 24% changed the BP patterns (dipper or nondipper) after a repeated ABPM within 1 month.[43] Therefore, if available, it is recommended to repeat the 24-h ABPM in 3—6 months to confirm the diagnosis of nocturnal hypertension,[1] especially in patients with poor sleep on the day of ABPM. In special cases, such as patients on hemodialysis, a 44—48 h ABPM is recommended.[44]

In recent years, some newly developed electronic upper arm or wearable wrist-type BP monitors can also be used for HBPM at night, for screening nocturnal hypertension and long-term follow-up.[20] The reproducibility of nighttime HBPM is good. A validated HBPM should include at least two consecutive nights with three readings per night.[45] In a Japanese cohort study, the nighttime BP level measured by HBPM (using an upper arm electronic sphygmomanometer, automatically measure BP at 2:00, 3:00, and 4:00 AM) for 14 consecutive days were slightly higher (2.6 mm Hg in difference) in systolic BP and lower (0.7 mm Hg) in diastolic BP, but comparable to nighttime BP levels measured by ABPM.[8] Meta-analysis also showed the nighttime BP levels by HBPM and by ABPM were essentially equivalent, with a slight difference of 1.4/0.2 mm Hg,[46] indicating in general the agreement between nighttime home and ambulatory BP measurement. Thus, the diagnostic BP threshold of ABPM can be used to define nocturnal hypertension by HBPM, that is, the mean nighttime BP ≥ 120/70 mm Hg. The consistency of HBPM and ABPM for the diagnose of nocturnal hypertension was good (79% at first night, 81% at second night and 80% for two night testing).[47] The correlation between HBPM and target organ damage

**TABLE 1** Nighttime BP and asymptomatic target organ damage.

| Study author, year | Patient population | Sample size | Main results |
|---|---|---|---|
| Li Y, 2007[4] | General population | 677 | The baPWV increased significantly in patients with isolated nocturnal hypertension or day-night sustained hypertension. |
| Liu J, 2022[7] | Young and middle-aged adults with non-dipper hypertension | 77 | In untreated young and middle-aged adults with non-dipper hypertension, nighttime BP, but not night/day BP ratio, was strongly associated with arterial stiffness (baPWV). |
| Hoshide S, 2007[30] | Community residents | 165 | In hypertensive patients with well controlled self-measured home BP, masked nocturnal hypertension was associated with the increase of CIMT and RWT. |
| Lee SH, 2011[31] | Diabetics | 82 | In patients with type 1 diabetes, nocturnal hypertension was associated with the increase of CIMT. |
| Hoshide S, 2003[32] | Community residents | 74 | Compared with dipper hypertension, non-dipper hypertension was associated with myocardial hypertrophy and remodeling (LVMI) in normotensive community residents. |
| Perez-Lloret S, 2008[33] | Outpatients | 223 | Nocturnal hypertension was closely associated with left ventricular hypertrophy measured by echocardiography regardless of antihypertensive treatment. |
| Cicconetti P, 2003[34] | Elderly patients with ISH | 64 | Nighttime BP level was closely related to LVMI in elderly patients with ISH, of whom with non-dipper hypertension have increased left ventricular mass than those with dipper hypertension. |
| Mousa T, 2004[35] | Man with or without CAD | 136 | Non-dipper BP pattern was significantly associated with moderated to severe coronary artery stenosis independent of clinical symptoms, total cholesterol and daytime BP. |
| Henskens LH, 2008[36] | Hypertensive patients | 218 | The prevalence of brain microbleeds identified by MRI was significantly increased in patients with nocturnal hypertension. |
| Yano Y, 2012[37] | Hypertensive patients | 252 | The control of nighttime BP was associated with the decrease of urine microalbumin excretion and the level of BNP. |
| Shimizu M, 2012[38] | Hypertensive patients | 254 | The reduction of nighttime BP was significantly associated with the decrease of BNP level independent of daytime BP and the administration time of antihypertensives. |

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BNP, brain natriuretic peptide; BP, blood pressure; CAD, cardiovascular disease; CIMT, carotid intima-media thickness; ISH, isolated systolic hypertension; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; RWT, relative wall thickness.

was also basically consistent with that of ABPM.[46] Moreover, home nighttime BP can predict adverse cardiovascular events independent of office BP or home morning BP.[48,49]

In the context of nighttime BP monitoring, the wrist-type BP monitor can be more comfortable and have less interference to sleep than upper arm device, but the recorded BP value is lower.[50] A newly developed wrist BP monitor overcomes the influence of different body positions on the accuracy of nighttime BP measurement,[51] a more comfortable wrist watch BP monitor has been validated in adult Chinese,[52] other convenient cuffless wearable devices with accuracy on nighttime BP measurement are still under development.[20]

## 7 | TREATMENT

There is still a lack of large scale randomized controlled trial (RCT) evidence on the optimal BP target and the improvement of prognosis for nocturnal hypertension. However, elevated BP, especially at night, significantly increased cardiovascular risk and there was a high consistency of cardiovascular benefits of antihypertensive treatment in different populations. Thus, the treatment principles of general hypertension population are also applicable to nocturnal hypertension.

Treatment principles include: (1) Identify and try to remove the causative factors if possible. (2) Lifestyle changes combined with medications and other treatment measures. (3) Using long-acting antihypertensive agents at full dose or combination therapy to control nocturnal hypertension. (4) Choose the effective nighttime BP-lowering treatment strategy individually.

BP targets: In principle, means nighttime BP should be controlled below 120/70 mm Hg. The BP target can be adjusted according to the patient's tolerance, especially in the elderly and patients with coronary artery disease (CAD).

### 7.1 | Identify and remove the causative factors

For nocturnal hypertension patients with high-sodium diet, the sodium (salt) intake should be strictly restricted. Patients with uncontrolled

**TABLE 2** Nighttime BP and cardiovascular events.

| Study author, year | Patient population | Sample size | Main results |
|---|---|---|---|
| IDACO investigators, 2007[13] | Participants with ABPM in Denmark, Belgium, Japan, Sweden, Uruguay, and China | 7458 | Adjusted for daytime BP, nighttime BP predicted total ($n = 983$; $p < .0001$), cardiovascular ($n = 387$; $p < .01$), and non-cardiovascular ($n = 560$; $p < .001$) mortality. Conversely, adjusted for nighttime BP, daytime BP predicted only non-cardiovascular mortality ($p < .05$), with lower BP levels being associated with increased risk. |
| IDACO investigators, 2010[24] | Participants of Europeans, Asians, and South Americans with ABPM | 8711 | Compared with daytime BP, nighttime BP was more closely related to fatal and non-fatal cardiovascular event, especially in patients with antihypertensive treatment. Compared with isolated nocturnal hypertensive patients and isolated daytime hypertensive patients, those with day-night sustained hypertension had the highest risk of all-cause mortality(HR 1.51, $p < .001$), all cardiovascular events (HR 2.48, $p < .001$) and cardiovascular mortality (HR 2.19, $p < .001$); isolated nocturnal hypertension was associated with increased risk of all-cause mortality (HR 1.29, $p = .045$) and all cardiovascular events (HR 1.38, $p = .037$); compared with isolated daytime hypertension (HR 1.07, $p = .56$), isolated nocturnal hypertension was more closely associated with the increase of all-cause mortality risk. |
| Roush GC, 2014[11] | Nine hypertensive cohorts from Europe, Brazil, and Japan | 13 844 | Compared with daytime systolic BP and clinic systolic BP, increased nighttime systolic BP independently predicted higher cardiovascular events in most cohorts, and, overall, nighttime systolic BP independently predicted cardiovascular events, whereas clinic systolic BP and daytime systolic BP lost their predictive ability entirely. |
| Salles GF, 2016[39] | Hypertensive patients | 17 312 | Compared with dipper hypertension, non-dipper/reverse dipper was associated with higher risk of cardiovascular events. |
| Fujiwara T, 2020[40] | Outpatients with a history of CVD or risk factors who performed nocturnal HBPM | 2745 | The cumulative incidence of CVD events was higher in those with masked nocturnal hypertension and sustained hypertension than in the controlled BP group. Results from Cox models suggested that masked nocturnal hypertension (adjusted hazard ratio, 1.57 [95% CI, 1.00−2.46]) and sustained hypertension (adjusted hazard ratio, 1.97 [95% CI, 1.26−3.06]) were associated with increased risk of CVD events. |
| Kario K, 2020[41] | Patients with at least one cardiovascular risk factor | 6359 | Nighttime BP level and reverse dipper pattern were independently associated with the risk of total cardiovascular events, especially heart failure. |
| Wang Q, 2021[12] | Patients with CKD stages 1−4 | 2024 | Isolated nocturnal systolic hypertension increased the risk of cardiovascular events (HR 3.17; 95% CI 1.61-6.23), nocturnal systolic-diastolic hypertension increased the risk of renal failure (HR 1.71; 95% CI 1.17–2.49) and cardiovascular events (HR 2.19; 95%CI 1.24–3.86). |
| Fu X, 2022[19] | CKD patients | 675 | Isolated nighttime masked uncontrolled hypertension was significantly associated with increased risk of the composite kidney outcome (HR 4.27, 95%CI 1.69–10.77); day-night masked uncontrolled hypertension was significantly associated with the increased risk of left ventricular hypertrophy (OR 3.26, 95%CI 1.15–9.25). |

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HBPM, home blood pressure monitoring; HR, hazard ratio; IDACO, international database on ambulatory blood pressure monitoring in relation to cardiovascular outcomes; OR, odds ratio.

nocturnal hypertension caused by inappropriate use of intermediate- or short-acting antihypertensive agents should switch to long-acting antihypertensive medications.

Some patients with Parkinson's disease often have orthostatic hypotension and supine hypertension simultaneously.[22] On the one hand, supine hypertension may be aggravated by the treatment of orthostatic hypotension, on the other hand the use of dopamine receptor agonists as well as antihypertensives may induce orthostatic hypotension.[53] Therefore, it is necessary to carefully evaluate the BP pattern of patients during the day and night, and select appropriate management strategy for patients with nocturnal (supine) hypertension in order to avoid adverse events, such as falls.

Patients with CKD, CHF, diabetes, OSAS, autonomic nervous dysfunction and some secondary hypertension are susceptible to nocturnal hypertension. For these patients, evaluation and intervention of fluid overload and nocturnal sympathetic activation should be carried out, and effective treatment should be given for the primary diseases. For example, continuous positive airway pressure (CPAP) can improve hypoxia in patients with OSAS and also decrease night BP significantly.[54]

## 7.2 | Lifestyle modifications

Lifestyle modifications for general hypertension population are also suitable for patients with nocturnal hypertension, including sodium intake restriction, healthy diet, smoking cessation, moderate alcohol consumption, appropriate physical exercise, weight control, sleep improvement, and mental stress relief.[55]

Excessive dietary sodium intake and insufficient dietary potassium intake are common in Chinese residents, which is one of the important risk factors for hypertension. Excessive sodium intake and salt sensitivity are closely related to the occurrence of nocturnal hypertension.[15,16] Rational sodium restriction is helpful to reduce BP level. A recent meta-analysis involving 133 RCTs of sodium restriction with 12 197 patients showed that when the average 24-h urinary sodium excretion was reduced by 130 mmol (about 7.6 g salt), the average systolic and diastolic BP can be reduced by 4.3 and 2.1 mm Hg, respectively. The reduction in urinary sodium excretion rate was positively correlated with the degree of BP reduction, especially in hypertensive patients, elderly people, and nonwhite population.[56] A study from China revealed potassium supplementation (4.5 g potassium chloride/d) can significantly improve the insufficient decrease of nighttime BP caused by excessive sodium intake (18 g salt/d) in salt-sensitive people.[57] Currently, the World Health Organization (WHO) and relevant hypertension guidelines recommend daily salt intake less than 5 g in adults,[58] with appropriate consumption of potassium-rich foods (such as fresh fruits, vegetables and beans), and those with normal renal function can choose potassium-enriched substitutes.[53,59]

The occurrence of nocturnal hypertension is also associated with mental and psychological factors such as poor sleeping environment, sleep disorders, anxiety and stress, which can be dealt with. For patients with sleeping issues, improving the sleeping environment and ensuring the effective sleep of 6–8 h at night are important. Patients with frequent nocturia due to lower urinary tract symptoms caused by prostatic hyperplasia and overactive bladder should reduce water intake in the evening and receive relevant treatment. Medications that increase nocturia, such as diuretics, should also be avoided before sleep. Patients with mental stress and anxiety can take stress management and individualized cognitive behavioral intervention under the guidance of doctors, and seek help from mental health specialists if necessary.[55]

## 7.3 | Use long-acting antihypertensive medications

The application of long-acting antihypertensive medications is an important measure for nocturnal BP control. WHO requires that long-acting antihypertensive agents be administered once daily with a trough to peak ratio of at least 50%. Current guidelines recommend five major classes of antihypertensive agents, including diuretics, $\beta$-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) and long-acting drugs are preferred. However, large scale, head-to-head RCTs of different antihypertensive medications on nighttime BP control and prognostic outcome in patients with nocturnal hypertension are still lacking. In a small size RCT in the United States, 54 patients with stage 1 hypertension (BP 140–159/90–99 mm Hg) were randomized to receive chlorthalidone 6.25 mg ($n = 16$), hydrochlorothiazide 12.5 mg ($n = 18$), or controlled-release hydrochlorothiazide 12.5 mg ($n = 20$). At weeks 4 and 12, significant reductions in systolic and diastolic 24-h ambulatory and nighttime BP were observed with chlorthalidone and controlled-release hydrochlorothiazide but not with hydrochlorothiazide ($p < .01$, respectively). At weeks 4 ($p = .015$) and 12 ($p = .020$), nighttime systolic BP was significantly lower in the former two groups than in the hydrochlorothiazide group, indicating the advantage of nighttime BP control with long-acting BP-lowering agents.[60] Another small RCT in Japan showed single-pill combination (SPC) of irbesartan+amlodipine could better reduce nighttime home systolic BP in patients with uncontrolled nocturnal hypertension than irbesartan+trichlormethiazide. However, further analysis found no significant difference of nighttime BP reduction between the two combination therapies in patients with salt-sensitive hypertension complicated with diabetes, CKD, and old age.[61] In clinical practice, the long-acting antihypertensive agents of the above five classes can be selected for the treatment of nocturnal hypertension according to the condition of patients. Long half-life antihypertensives such as amlodipine, perindopril and telmisartan or controlled-release formulations such as nifedipine gastrointestinal therapeutic system (GITS), metoprolol controlled-release/extended release (CR/XL) and doxazosin XL are recommended to be used at maximally tolerated dose or in combination of two or more to achieve 24-h BP control.[62–64]

It is generally assumed that BP-lowering effects of drugs with half-lives less than 6–8 h are time-dependent, that is so-called "therapeutic window" (the treatment effects attenuate or disappear with time). In contrast, "true" long-acting antihypertensive drugs with half-lives of 15 h or more can maintain efficacy for up to 24 h when administered once daily, irrespective of morning or evening administration.[64] As for some antihypertensive agents with short half-lives (less than 8 h), such as metoprolol, losartan and valsartan, the BP is usually not well-controlled at night after routine morning administration, so it is often required twice a day to maintain 24-h BP control in the clinical practice.[65,66]

## 7.4 | Chronotherapy

Chronotherapy refers to the therapeutic strategy in which drug administration is based on the BP circadian of patients to achieve optimal BP control, decrease adverse effects and improve clinical outcomes.[67] In the past, some small size trials of chronotherapy and combined controlled release drug delivery technology have been investigated for nighttime BP control and nondipper hypertension, but the results are debatable.

In an RCT in the United States, routine morning administration of controlled-onset extended-release (COER) verapamil hydrochloride tablets could significantly reduce nighttime BP compared with placebo, and the reduction was greater in patients with nondipper than those with dipper hypertension.[68] However, another RCT compared COER verapamil administered at bedtime with conventional nifedipine GITS administered in the morning, the results showed that the two therapies reduced daytime BP and morning BP similarly, but the latter reduced nighttime BP more significantly than the former.[69] A Spanish study showed that valsartan administered at bedtime rather than in the morning could significantly reduce nighttime BP in elderly patients with hypertension.[70] However, some recent RCTs failed to show the BP control advantage of taking antihypertensives at bedtime.[71–73] The HARMONY trial conducted by the United Kingdom and Greece showed the BP control efficacy did not differ between morning and evening dosing regarding to daytime BP, nighttime BP and 24-h BP.[71] The NARRAS trial included young and middle-aged adults with nondipper hypertension in China demonstrated that there was no significant difference in the nighttime BP control and dipping rhythm restoration between long-acting nifedipine GITS and amlodipine, irrespective of dosing time (morning or evening).[72] In addition, the CHOSA trial conducted in Australia showed that taking perindopril in the morning or at night did not differ on nighttime BP control in patients with OSAS and hypertension, regardless of CPAP treatment; taking medication in the morning can decrease daytime BP even better.[73] A community-based intervention trial of hypertension in Spain, the Hygia Chronotherapy trial, showed that taking antihypertensives at bedtime significantly improved BP control and reduced cardiovascular composite endpoints as well as cardiovascular death.[74] However, there were some limitations such as ambiguous randomization process and ethical issues, which caused great controversy. Moreover, the TIME study, a RCT of chronotherapy for hypertension recently conducted in the United Kingdom, has further confirmed that there was no difference in cardiovascular outcomes and mortality between morning and evening administration of antihypertensives in patients with hypertension.[75]

An important reason for the inconsistent results of the above clinical studies is that the pharmacokinetic characteristics, formulation, half-lives and active durations of drugs are different. For drugs with true long half-lives or controlled-release formulation, relevant studies have shown that the antihypertensive efficacy is not significantly influenced by drug administration time.[72,73]

Therefore, the use of long-acting antihypertensives is the basis for achieving 24-h BP control, and current clinical evidence did not support or warrant changing the routine medication administration time from morning to evening.[72] In addition, the TIME study showed that patients taking antihypertensives at night had a higher nonadherence rate compared with routine daytime administration.[75] The recent consensus statement of the International Society of Hypertension (ISH) also recommended long-acting antihypertensives be taken once in the morning to achieve 24-h BP control, and bedtime medication was not routinely recommended.[76]

For nocturnal hypertension, including isolated nocturnal hypertension, there is still a lack of direct clinical trial evidence to guide antihypertensive treatment.[25] Therapies including morning dosing long-acting antihypertensives combined with additional afternoon/evening dosing intermediate-acting drugs for patients with day-night sustained hypertension, and bedtime dosing short- or intermediate-acting antihypertensives for patients with isolated nocturnal hypertension have been tried in clinical practice. Although the nighttime BP control with those therapies seemed to be positive, it still needs to be confirmed by well-designed clinical trials. In addition, the evidence of whether treating isolated nocturnal hypertension can improve clinical outcomes is still lacking. More researches on chronotherapy and the fundamental chronobiology are warranted.

## 7.5 | Application of innovative drugs

Recent studies indicated that some innovative drugs have good effects on nighttime BP control.

### 7.5.1 | Allisartan isoproxil

Allisartan isoproxil, an innovative drug developed independently by China, is a new nonpeptide angiotensin II receptor blocker. After oral administration, Allisartan isoproxil metabolized into EXP3174, a molecule with antihypertensive activity, by gastrointestinal esterase. According to a study of 24-h ABPM, after oral administration of 240 mg allisartan isoproxil once a day in the morning for 12 weeks, daytime and nighttime ambulatory BP decreased by 9.9/5.4 and 10.4/5.4 mm Hg, respectively.[77] In addition to blocking the renin-angiotensin-aldosterone system (RAAS), the dominant effect of allisartan isoproxil on reducing nighttime BP may be related to its effects on reduction of uric acid and sodium reabsorption.[78]

### 7.5.2 | Angiotensin receptor-neprilysin inhibitor

Angiotensin receptor-neprilysin inhibitor (ARNI) is a new class of antihypertensive agents that can increase sodium and water excretion and promote vasodilation by inhibit RAAS and block natriuretic peptide breakdown. One RCT in Asia, which mainly involved patients with mild to moderate hypertension, showed that ARNI (sacubitril/valsartan 200 mg/d) reduced daytime and nighttime BP levels by 11.4/5.9 and 13.4/7.4 mm Hg, respectively.[79] In PARAMETER study, ambulatory systolic BP reduction in the sacubitril/valsartan versus olmesartan

group during the trial were more pronounced at night compared with during the day, indicating preferential reduction of nighttime BP.[80] In a post hoc analysis of Japanese RCT, 24-h BP reduction with sacubitril/valsartan was compared to olmesartan, the between-group differences in nighttime systolic BP were more significant in the nondipper group.[81]

### 7.5.3 | Esaxerenone

Esaxerenone is a new generation of nonsteroidal highly selective mineralocorticoid receptor (MR) antagonist. In a post hoc analysis of the ESAX-HTN study, esaxerenone was demonstrated significant nighttime BP reduction from baseline compared with eplerenone, with the greatest effect in patients with a nondipper BP profile and in the elderly.[82] The nighttime BP-lowering effect of esaxerenone was again demonstrated in a recent published multicenter, open-label, prospective study in Japan. 101 patients with uncontrolled nocturnal hypertension being treated with an ARB or CCB were enrolled to take esaxerenone 2.5–5 mg once daily. During the 12-week study period, change in nighttime home systolic/diastolic BP from baseline to end of treatment measured by the brachial home BP device was −12.9/−5.4 mm Hg in the total population, similar BP reduction was also seen by the wrist device.[83]

### 7.5.4 | Sodium-glucose cotransporter 2 inhibitor

Sodium-glucose cotransporter 2 inhibitor (SGLT2i), a new antidiabetic drug, can also reduce daytime and nighttime BP. In SACRA study, Empagliflozin, but not placebo, significantly reduced nighttime systolic BP versus baseline (−6.3 mm Hg; $p = .004$); between-group difference in change from baseline was −4.3 mm Hg ($p = .159$).[84] Meta-analysis showed that, compared with placebo, SGLT2i reduced daytime BP by 5.25/2.62 mm Hg and nighttime BP by 3.62/1.60 mm Hg in patients with type 2 diabetes and hypertension, and different SGLT2i, such as canagliflozin, empagliflozin and dapagliflozin, had similar antihypertensive effect.[85]

### 7.5.5 | Aprocitentan

Aprocitentan is a dual endothelin receptor ETA/ETB antagonist. The recently published result of the PRECISON study showed both short-term and long-term BP control efficacy of aprocitentan in patients with resistant hypertension.[86] Treatment with aprocitentan 12.5 mg/d and 25 mg/d for 4 weeks can reduce daytime systolic BP by 3.8 and 5.3 mm Hg and nighttime systolic BP by 5.1 and 7.4 mm Hg more than placebo, respectively. After 32 weeks of continuous treatment with aprocitentan 25 mg/d and 4 weeks of withdrawal, daytime systolic BP increased by approximately 5 mm Hg and nighttime systolic BP increased by 8.5 mm Hg, suggesting that aprocitentan may have advantage in reducing BP at night than in daytime.

## 7.6 | Device-based treatment and interventional therapy

Device-based treatments and interventional therapies including CPAP, renal denervation (RDN), baroreflex activation therapy (BAT) and iliac arteriovenous anastomosis, etc. were reported to reduce daytime, nighttime and 24-h BP.[87–89] Among them, CPAP and RDN had more clinical evidences.

CPAP is recommended for treatment of OSAS patients with daytime sleepiness or hypertension, especially for patients with moderate to severe OSAS. Patients with OSAS with symptoms of daytime sleepiness experience greater reductions in BP during CPAP therapy compared with those with asymptomatic OSAS.[90] In addition, reductions in BP have been shown to be greater as device usage increases, while a lack of daytime symptoms might also decrease adherence to CPAP therapy.[91,92] A meta-analysis of 10 RCTs showed that CPAP can effectively improve the 24-h BP control in patients with OSAS and resistant hypertension, the mean systolic/diastolic BP drop during daytime and nighttime can be 2.34/2.14 and 4.15/1.95 mm Hg, respectively.[93] The antihypertensive efficacy of CPAP is related to treatment adherence, patients who adhere to CPAP treatment for more than 5 days per week or more than 4 h per night can reduce home systolic/diastolic BP by 5.0/3.8 mm Hg more than nonadherent patients.[94]

With the development of RDN devices and improvement of operator skills, recent studies have shown that RDN has short-term and long-term antihypertensive effects, and the capacity to reduce daytime and nighttime BP is comparable.[95–97] Compared with sham procedure, RDN with the third-generation multielectrode radiofrequency catheter in the SPYRAL HTN-ON MED trial can reduce daytime and nighttime systolic/diastolic BP in patients with uncontrolled hypertension by 6.1/4.1 and 10.0/5.1 mm Hg at 6 months, respectively.[95] Similar results have been found in patients without any antihypertensive medication, with a BP reduction of 4.0/4.0 mm Hg at 3 months.[96] Moreover, by using intravascular ultrasound catheter, RDN can reduce daytime and nighttime BP by 4.5/1.8 and 3.9/2.8 mm Hg (respectively) more than sham procedure in patients with resistant hypertension at 2 months.[97] In addition, in a long-term follow-up study of SPYRAL HTN-ON MED trial, 36-month maximum nighttime systolic BP change was also significantly greater in the RDN group while morning maximum changes also trended lower for in the RDN group.[98] Although RDN has good BP-lowering efficacy and clinical application prospects, the proper indication, index of operation quality and long-term efficacy still need to be further clarified. Studies on the efficacy of RDN specifically in patients with nocturnal hypertension are lacking.

# 8 | UNSOLVED PROBLEMS AND FUTURE DIRECTIONS

At present, there are still many problems to be solved for the management of nocturnal hypertension, especially for isolated nocturnal hypertension. For example, in addition to ABPM, how can HBPM, especially smart wearable devices, play a role in the diagnosis of nocturnal

hypertension? What is the best treatment target and intervention strategy for isolated nocturnal hypertension? The development of intelligent HBPM devices with nighttime BP measurement function, that are accurate, ease-to-use, comfort and less sleep disturbance, is in urgent need.[99] Well-designed clinical trials should also be conducted in the future.

As for the treatment of isolated nocturnal hypertension, the following questions still need to be addressed: (1) Can BP-lowering therapy improve prognosis? (2) What are the effects of morning or evening administration of long-acting antihypertensive medications on daytime and nighttime BP? (3) Is evening administration of short- or intermediate-acting antihypertensive agents more effective in lowering nighttime BP without excessive daytime BP drop? (4) Among the commonly used five classes of antihypertensive agents, which is more effective on nighttime BP control? (5) Can the device-based therapies, such as RDN, be superior to pharmacological therapy for nocturnal hypertension? (6) Can medications designed for treatment of conditions other than hypertension, such as SGLT2i, effectively control nighttime BP?

All above need to be further investigated with large scale multicenter RCTs.

## 9 | RECOMMENDATIONS FOR THE MANAGEMENT OF NOCTURNAL HYPERTENSION

a. Patients with nighttime mean systolic BP≥120 mm Hg and/or diastolic BP≥70 mm Hg in 24-h ABPM can be diagnosed as nocturnal hypertension.
b. 24-h ABPM is recommended for newly diagnosed or poorly controlled hypertensive patients to screen nocturnal hypertension. Those with high salt diet, old age, obesity, diabetes, CKD, OSAS, sleep disorders and secondary hypertension should be screened specifically for nocturnal hypertension.
c. Validated home BP monitoring devices with nighttime BP measurement function can be used for routine follow-up in patients with nocturnal hypertension.
d. In principle, mean nighttime BP should be controlled below 120/70 mm Hg.
e. Primary and concomitant diseases, such as primary hyperaldosteronism, diabetes, CKD and OSAS, should be treated actively.
f. Effective lifestyle changes, including low-sodium diet, appropriate potassium supplement, sleep improvement and weight control, etc. are helpful to control nighttime BP.
g. Long-acting antihypertensive medications should be used at maximally tolerated dose or combined with two or more drugs of different mechanisms to achieve nighttime BP control.
h. Antihypertensive drugs with nighttime BP reduction property are preferred when available.

### AUTHOR CONTRIBUTIONS

Jing Liu conceived and wrote the outline of the consensus document. Jing Liu, Yan Li, and Xinjun Zhang wrote the first draft of the document. Jing Liu and Jiguang Wang initiated and supervised the process of consensus. All authors contributed to the revision of consensus and approved the final version and submission of the document.

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### CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated.

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