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REVIEW PAPER

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Management of morning hypertension: a consensus statement of an Asian expert panel

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Morning blood pressure (BP) surge is an important aspect of hypertension research. Morning BP monitoring could be a clinically relevant concept in the therapeutic management of hypertension and in the prevention of cardiovascular complications by defining and treating morning hypertension. Because antihypertensive medication is often taken in the morning, uncontrolled morning BP during the trough effect hours could be a hallmark of inadequate choice of antihypertensive regimen, such as the use of short- or intermediate-acting drugs, underdosing of drugs, or no use or underuse of combination therapy. To improve the management of hypertension in general and morning hypertension in particular, long-acting antihypertensive drugs should be used in appropriate, often full dosages and in proper combinations. The clinical usefulness of antihypertensive drugs with specific mechanisms for morning BP or split or timed dosing of long-acting drugs in controlling morning BP remains under investigation.

1 | INTRODUCTION

Ischemic stroke[1] and coronary events[2] often occur in the early morning hours. Blood pressure (BP) also usually peaks in the morning.[3] This parallel phenomenon suggests that high BP in the morning may be particularly important for the occurrence of cardiovascular events. A prospective observational study in Japan first demonstrated that morning BP surge, defined as a systolic BP increase from nighttime sleeping to early morning awaking hours, was associated with the incidence of stroke.[4] This association was independent of mean 24-hour

ambulatory systolic BP and other cardiovascular risk factors.[4] The finding was confirmed by most, although not all, subsequent studies.[5]

Morning BP surge measurement requires ambulatory BP monitoring (ABPM), and has low reproducibility. The focus therefore shifted from BP surge to the level of morning BP. Almost immediately after morning BP surge was shown to be clinically relevant, the investigators found that the risk of morning surge was mainly attributable to the elevated morning BP.[6] Morning BP can be assessed by ABPM as well as home BP monitoring. Morning hypertension can be defined according to the level of morning BP. Uncontrolled morning hypertension is common even in patients with controlled clinic BP, and is associated with the risk of cardiovascular events.[7]

Morning BP may be particularly relevant for the management of hypertension in Asia. A recent study demonstrated that Japanese persons had a much larger morning BP surge and higher morning BP than Europeans.[8] This ethnic difference is incompletely understood. There may be pathophysiological mechanisms, such as the activation of sympathetic nervous system[9] or increased dietary sodium intake.[10] However, the inadequate use of antihypertensive drugs, such as the use of short- or intermediate-acting drugs, underdose of drugs, or underuse of combination antihypertensive therapy, might be the main cause of uncontrolled morning hypertension in Asia.[11] In 2014, the Council on Hypertension of the Chinese Society of Cardiology published expert recommendations on the management of morning hypertension.[12] The discussion was recently expanded to Asia for the publication of a scientific review[13] and a consensus statement. In the published review article, we performed a systematic literature search and summarized the evidence on morning BP.[13] The panel of the present consensus statement is composed of experts representing each of the national or regional hypertension guidelines in Asia.

2 | DEFINITION OF MORNING HYPERTENSION

Morning is defined as the period between 6 AM and 10 AM. China is a large country with more than one time zone, but Beijing time is currently used. The morning period in China can and should have different definitions, ie, 5 AM to 9 AM in eastern China (1 hour ahead) and 7 AM to 11 AM or 8 AM to 12 PM in western China (1 to 2 hours behind).

BP measured in the morning can be used for the diagnosis and therapeutic monitoring of morning hypertension. Morning BP can be assessed by home or ambulatory monitoring or both techniques. For home BP monitoring, morning BP is the average of two or three readings taken within an hour of waking up. If ABPM is performed, morning BP is the average of BP readings within 2 hours of waking up. If the patient's diary on the time of waking up is not available, morning BP would be the average of BP readings in the morning (usually between 6 AM and 10 AM).

Morning hypertension refers to high BP in the morning period, regardless of BP during the rest of the hours of the day. Morning hypertension is defined as morning BP ≥135/85 mm Hg for both ABPM and home BP monitoring. Clinic BP measurement can be used for screening morning hypertension. The diagnostic threshold is a BP ≥140/90 mm Hg. Morning hypertension in this consensus document includes but is not limited to masked morning hypertension, which was defined in the 2014 Japanese Society of Hypertension Guidelines for the Management of Hypertension as an elevated ABPM or home BP in the morning (≥135/85 mm Hg) and a normal clinic BP (<140/90 mm Hg).[14]

3 | MECHANISMS OF MORNING HYPERTENSION

The pathophysiology of morning hypertension is not completely understood. Several regulatory mechanisms are thought to or have been found to play a part. The primary cause of the BP increase in the morning may be the activation of the sympathetic nervous system.[9] Indeed, morning BP was higher during working weekdays, especially Monday, than during weekends,[15] and during spring and winter than during summer and autumn,[16] probably because of high stress caused by work or cold weather. Dietary salt may also be an important contributing factor to aggravate morning BP surge.[10] In a clinical experimental study, high salt dietary intake increased early morning BP in patients with salt-insensitive hypertension.[10]

In treated hypertension, inadequate use of antihypertensive drugs may be a cause of uncontrolled morning hypertension. Short- or intermediate-acting antihypertensive drugs are often used in China and other Asian countries. Low-dose medication is not only used initially but also continuously, and combination therapy is underused, even though BP is not controlled to the target level. In a study involving outpatients in a tertiary hospital in Beijing, the prevalence of uncontrolled morning hypertension varied substantially across the use of several calcium channel blockers: 46.3% (n = 136) with amlodipine, 70.5% (n = 78) with a nifedipine gastrointestinal therapeutic system, and 73.8% (n = 34) with slow-release felodipine.[17]

4 | CARDIOVASCULAR RISK OF MORNING HYPERTENSION

There is limited evidence on the prevalence and risks of masked morning hypertension in untreated persons. As BP usually peaks in the early morning hours, masked morning hypertension may not be rare. In the Ohasama study (n = 812), the prevalence of masked morning hypertension was 7% (clinic BP <140/90 mm Hg and home BP in the morning ≥135/85 mm Hg).[18] In the Hisayama study, with a similar home BP assessment (n = 2915), the prevalence of total masked hypertension was 21.9%.[19]

There is evidence that uncontrolled morning hypertension is common and confers high cardiovascular risk in patients with treated hypertension. In patients with treated hypertension who had either controlled or uncontrolled clinic BP, the prevalence of morning hypertension defined according to ABPM[20] or home BP[21–23] ranged from 15.9% (n = 173)[21] and 17.5% (n = 1312)[20] in two Korean studies to

43.6% (n = 181)[22] and 60.7% (n = 1087)[23] in two Japanese studies. In patients with treated hypertension who had controlled clinic BP (<140/90 mm Hg), the prevalence of masked uncontrolled morning hypertension defined according to home BP in the morning (≥135/85 mm Hg) was 23.1% (n = 3303) in a Japanese study[24] and 55.9% (n = 2043) in a European study.[25]

Regardless of the level of clinic BP, patients with morning hypertension had a significantly increased risk of cardiovascular events.[9,26,27] In the J-HOP (Japan Morning Surge Home Blood Pressure) study, patients with uncontrolled morning BP had a higher risk of stroke (≥135 mm Hg, n = 2320; hazard ratio [HR], 2.45, 2.80, 3.58, and 6.52 in the systolic BP ranges of 135–144, 145–154, 155–164, and ≥165 mm Hg, respectively) than those with controlled morning BP at home (<135 mm Hg, n = 1958).[26] In the HONEST (Home Blood Pressure Measurement With Olmesartan Naive Patients to Establish Standard Target Blood Pressure) study,[27] 21 341 patients were treated with an olmesartan-based antihypertensive regimen. Compared with patients with a morning home BP <125 mm Hg, patients with uncontrolled morning BP (≥155 mm Hg) had a higher risk of stroke (hazard ratio, 6.01) and coronary events (hazard ratio, 6.24).[7] Even in the presence of well-controlled clinic systolic BP (<130 mm Hg), patients with a morning home systolic BP ≥145 mm Hg had a higher cardiovascular risk (hazard ratio, 2.47) than those with a morning home systolic BP <125 mm Hg.[27]

5 | ASSESSMENT OF MORNING BP

Morning BP can and should be measured by home BP monitoring and ABPM (Table 1). Clinic BP can be used for screening. If clinic BP in the morning is ≥140/90 mm Hg, ambulatory or home BP measurement should be performed for the identification and diagnosis of morning hypertension. All patients with hypertension should assess their morning BP. For shift workers, 24-hour ambulatory or home BP measurement should preferably be performed on nonshift working days.

ABPM is preferable for the diagnosis of morning hypertension. ABPM should be programmed to allow a sufficient number of readings for evaluation. According to current guideline recommendations, daytime and nighttime BP should be measured every 20 and 30 minutes, respectively.[28] A valid ambulatory recording should include at least 70% of readings, and 20 daytime and seven nighttime readings. ABPM should preferably be performed on a day of regular daily activities. The patient should keep a diary to record daily activities, especially sleep and wake time.[28]

Home BP monitoring is a practical method to assess morning BP, especially for long-term therapeutic monitoring. Home BP can be measured by the patient or by guardians/family members. Home BP should be taken within 1 hour of awaking, usually in the period from 6 AM to 10 AM, after urination but before drug intake and breakfast, while the patient is seated with both feet on the ground. According to current guideline recommendations, two or three readings are taken every morning for five to seven successive days. The average of these BP readings is used for evaluation.[29]

Clinic BP can be measured by health professionals or using unobserved BP-measuring devices. The latter technique might be devoid of some white-coat effect. Measurements should be taken between 6 AM and 10 AM and before drug intake. Usually two readings are taken and averaged for evaluation. If there is a difference of more than 10 mm Hg between the two successive readings, a third measurement should be taken. The average of two nearby readings was used for evaluation.

6 | TREATMENT OF MORNING HYPERTENSION

Current ABPM guidelines[28] and several hypertension guidelines highlight the importance of morning BP or morning hypertension.[14] However, none of these guidelines, including those from Asia,[14] specifically address the treatment of morning hypertension. A possible reason is the absence of outcome trial evidence on the benefit of treating morning hypertension for cardiovascular prevention. Nonetheless, in the Heart Outcomes Prevention Evaluation (HOPE) trial, bedtime dosing of ramipril, compared with placebo, reduced the risk of stroke and other cardiovascular events.[30] The difference in clinic BP measured in the daytime working hours was only 3.3/1.0 mm Hg. In an ABPM substudy of the HOPE trial, however, the difference in systolic/diastolic BP was much larger at night (17/8 mm Hg) than during the day (6/2 mm Hg).[31] The outcome benefit therefore might be attributable to BP control at night and likely in the succeeding morning hours. However, the CONVINCE (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints) trial[32] did not confirm superiority of bedtime dosing of verapamil to morning dosing of atenolol or hydrochlorothiazide in the prevention of cardiovascular events, with similar

TABLE 1 Assessment of morning BP and hypertension

	Ambulatory BP	Home BP	Clinic BP
Time of day	Within 2 h of waking up, or 6 AM to 10 AM	Within 1 h of waking up, or 6 AM to 10 AM	6 AM to 10 AM
BP readings	All readings during 2 h after waking up	2 or 3 readings during 1 h after waking up	2 or 3 readings from 6 AM to 10 AM
Criteria for morning hypertension	≥135/85 mm Hg	≥135/85 mm Hg	≥140/90 mm Hg
Clinical usefulness	Diagnosis	Diagnosis	Screening

Abbreviation: BP, blood pressure.

clinic BP control in the two treatment groups. Ambulatory or home BP was not measured in the CONVINCE trial.

There is some evidence on the difference between various treatment strategies in morning BP control. Current hypertension guidelines recommend several treatment strategies for better BP control, such as the use of long-acting drugs, full dose or maximum dose of medications, and combination therapy.[14] These strategies may improve morning BP control.

Long-acting antihypertensive drugs have apparent advantages in controlling BP over 24 hours in comparison with short- or intermediate-acting drugs. In a comparative study between amlodipine and a nifedipine gastrointestinal therapeutic system, ambulatory BP was reduced by 22.6/12.6 mm Hg and 17.7/11.4 mm Hg, respectively, over 24 hours, 23.3/13.9 mm Hg and 18.8/13.0 mm Hg, respectively, in the daytime, and 18.5/8.0 mm Hg and 14.0/5.8 mm Hg, respectively, at night. BPs were different in all time periods. Maximum difference was observed in the early morning hours from 5 AM to 10 AM.[33] In the ambulatory BP substudy (n = 659) of the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial,[34] valsartan was significantly less effective than amlodipine in controlling BP at trough morning hours after drug ingestion, with an average systolic BP difference of approximately 3 mm Hg. These studies taken together demonstrated that even once-daily drugs had significant differences in controlling 24-hour BP, especially during the early morning hours, which are usually the trough hours when the drugs were taken in the morning. Among the five classes of guideline-recommended antihypertensive drugs, perindopril, telmisartan, bisoprolol, amlodipine, and chlorthalidone have the longest biological half-lives and potentially longest duration of BP-lowering action in the class (Table 2).

Recent hypertension guidelines recommended the use of a full or maximum dosage of antihypertensive drugs, regardless of monotherapy or combination therapy of two or more drugs.[14] Uptitration to a high dosage or even to the full or maximum dosage may not only increase efficacy of antihypertensive treatment but also improve the trough effect, especially for renin angiotensin system inhibitors with a shorter duration of action due to shorter plasma elimination half-life time (Table 2). In a study that compared telmisartan with valsartan, when valsartan was force-titrated to a higher dose, 160 mg/d from 80 mg/d, the difference from the longer half-life time drug telmisartan was only 2.4/1.8 mm Hg for the last 6 hours of 24-hour ABPM.[35] Even long-acting drugs, used as combination therapy, may increase morning BP control with full doses. In a dose comparison study of amlodipine/olmesartan combination, the 10/40 mg full-dose combination had the highest BP control over 24 hours and in the morning.[36]

Compared with monotherapy, even at high dosages, combination therapy of an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor plus a calcium channel blocker or diuretic may improve 24-hour BP control, especially during the trough effect morning hours. In a Japanese study, compared with losartan 100 mg/d (n = 55), losartan/hydrochlorothiazide 50/12.5 mg combination (n = 55) significantly improved BP control both in the morning and in the evening. The control rate of both morning and evening hypertension (<135/85 mm Hg) was 29.1% for losartan 100 mg/d and 54.5% for losartan/hydrochlorothiazide 50/12.5 mg combination.[37] Of particular note, in 25 patients with isolated morning hypertension, BP was controlled in nine of the 11 patients in the losartan/hydrochlorothiazide 50/12.5 mg combination group and in three of the 14 patients in the losartan 100 mg/d group (81.8% vs 21.4%; $P = .003$). Irrespective of treatment regimen, reduction in morning BP was associated with a significant reduction in urinary albumin excretion.[38] In another randomized, double-blind, parallel group study (n = 626), the combination of olmesartan/amlodipine was more effective in reducing BP over 24 hours, including the early morning and whole morning hours than those who were not adequately controlled with amlodipine

TABLE 2 Commonly used oral antihypertensive drugs

Class and drug	Biological half-life, h	Daily dose, mg	No. of doses per d
Angiotensin-converting enzyme inhibitor			
Benazepril	11	10–40	1 or 2
Captopril	1.9	50–150	2
Enalapril	11	2.5–40	1 or 2
Lisinopril	12	10–40	1
Perindopril	17	2–8	1
Ramipril	4	2.5–20	1 or 2
Angiotensin receptor blocker			
Candesartan	9	4–32	1
Irbesartan	15	75–300	1
Losartan	2	25–100	1 or 2
Olmesartan	13	10–40	1
Telmisartan	24	20–80	1
Valsartan	6	80–320	1
β-Blocker			
Atenolol	7	25–100	1
Bisoprolol	12	2.5–10	1
Metoprolol	3–7	50–200	1 or 2
Dihydropyridine calcium channel blocker			
Amlodipine	30–55	2.5–10	1
Felodipine ER	11–17	1.5–10	1
Lacidipine	13–19	2–4	1
Lercanidipine	8–10	10–20	1
Nifedipine GITS	2	20–80	1
Nitrendipine	8–24	10–40	1 or 2
Thiazide diuretic			
Chlorthalidone	40	25–50	1
Hydrochlorothiazide	5.6–14.8	12.5–50	1 or 2
Indapamide	14–18	1.25–5	1

Abbreviations: ER, extended-release; GITS, gastrointestinal therapeutic system.

The classes and drugs are listed alphabetically for the five classes of guideline-recommended antihypertensive drugs. Data were obtained from Wikipedia (accessed July 18, 2017).

monotherapy ($P < .0001$).[36] In a Japanese study of 263 patients with diabetes mellitus who were refractory to standard dose of angiotensin receptor blocker therapy, combination therapy of amlodipine/olmesartan reduced morning BP compared with high-dose angiotensin receptor blocker monotherapy.[39]

If short- or intermediate-acting antihypertensive medication is used, multiple split dosing (eg, two to three times a day) or dosing at a specific time (eg, bedtime) might increase the duration of action or effect at the specific time. However, when high or full doses and proper combinations of long-acting antihypertensive drugs are used, whether the split- or timed-dosing strategies are useful is inconclusive.[11] Morning BP surge or morning hypertension might be a consequence of the activation of the sympathetic nervous system after waking up, especially after getting up from bed.[13] Some researchers therefore propose the use of drugs with specific mechanisms, eg, sympathetic nervous system inhibitors. The α_1-blocker doxazosin, given once daily at bedtime, reduced BP in the morning and the rest of the hours of the day.[40] BP reduction in the morning was greater.

7 | CONSENSUS AND UNADDRESSED QUESTIONS

Morning BP may be a critical factor for the incidence of cardiovascular events and the management of hypertension. For morning BP surge, more evidence is needed to prove its clinical usefulness in the management of hypertension. Masked morning hypertension, as well as other forms of masked hypertension, requires more research. Morning BP monitoring could be a clinically relevant concept in the therapeutic management of hypertension and in the prevention of cardiovascular complications by defining and treating morning hypertension. Because antihypertensive medication is often taken in the morning, uncontrolled morning BP during trough effect hours could be a hallmark of inadequate choice of antihypertensive regimen, such as the use of short- or intermediate-acting drugs, underdosing of drugs, or no use or underuse of combination therapy. To improve the management of hypertension in general and morning hypertension in particular, long-acting antihypertensive drugs should be used in appropriate, often full dosages and in proper combinations. The clinical usefulness of antihypertensive drugs with specific mechanisms for morning BP or split or timed dosing of long-acting drugs in controlling morning BP remains under investigation.

CONFLICT OF INTEREST

Dr Ji-Guang Wang has received lecture and consultation fees from Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, MSD, Novartis, Omron, Pfizer, Sanofi, and Servier. Dr Kazuomi Kario has received honoraria from Mochida Pharmaceutical, Takeda, Daiichi Sankyo, Sumitomo Dainippon Pharma, Shionogi, AstraZeneca K.K., Mitsubishi Tanabe Pharma, Bayer Yakuhin, Pfizer Japan, Boehringer Ingelheim Japan, Astellas Pharma, and MSD K.K., and grants from Fukuda Denshi, Omron Healthcare, Bayer Yakuhin, MSD K.K., Mochida Pharmaceutical, Novartis Pharma K.K., Sumitomo Dainippon Pharma, Boehringer Ingelheim Japan, Daiichi Sankyo, Takeda Pharmaceutical, Astellas Pharma, Teijin Pharma, Bristol-Myers K.K, and Shionogi. Dr Chen-Huan Chen has received honoraria for lectures during scientific meetings sponsored or arranged by Boehringer-Ingelheim, Sanofi, Novartis, AstraZeneca, and Pfizer.

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