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Kazuomi Kario MD, PhD¹  | Ji-Guang Wang MD, PhD²  |
 Yook-Chin Chia MBBS, FRCP^{3,4}  | Tzung-Dau Wang MD, PhD^{5,6}  | Yan Li MD, PhD⁷  |
 Saulat Siddique MBBSMRCP (UK), FRCP (Lon)⁸  | Jinho Shin MD⁹  |
 Yuda Turana MD, PhD¹⁰  | Peera Buranakitjaroen MD, MScD, Phil¹¹  |
 Chen-Huan Chen MD¹²  | Hao-Min Cheng MD, PhD^{13,14,15,16}  |
 Minh Van Huynh MD, PhD¹⁷ | Jennifer Nailes MD, MSPH¹⁸  |
 Apichard Sukonthasarn MD¹⁹  | Yuqing Zhang MD²⁰  | Jorge Sison MD²¹ |
 Arieska Ann Soenarta MD²² | Sungha Park MD, PhD²³  |
 Guru Prasad Sogunuru MD, DM^{24,25}  | Jam Chin Tay MBBS, FAMS²⁶  |
 Boon Wee Teo MB, BCh²⁷  | Kelvin Tsoi BSc, PhD²⁸  | Narsingh Verma MD²⁹  |
 Satoshi Hoshida MD, PhD¹ 

¹Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

²Department of Cardiovascular Medicine, the Shanghai Institute of Hypertension, Shanghai Key Laboratory of Hypertension, State Key Laboratory of Medical Genomics, National Research Centre for Translational Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

³Department of Medical Sciences, School of Medical and Life Sciences, Sunway University, Bandar Sunway, Malaysia

⁴Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

⁵Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan

⁶Division of Hospital Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan

⁷Department of Cardiovascular Medicine, Shanghai Key Lab of Hypertension, Shanghai Institute of Hypertension, National Research Centre for Translational Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

⁸Punjab Medical Center, Lahore, Pakistan

⁹Faculty of Cardiology Service, Hanyang University Medical Center, Seoul, Korea

¹⁰Departement of Neurology, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia

¹¹Division of Hypertension, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

¹²Department of Internal Medicine, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan

¹³Center for Evidence-based Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

¹⁴Ph.D. Program of Interdisciplinary Medicine (PIM), National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan

¹⁵Institute of Public Health, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan

¹⁶Institute of Health and Welfare Policy, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan

¹⁷Department of Internal Medicine, University of Medicine and Pharmacy, Hue University, Hue, Vietnam

¹⁸Department of Preventive and Community Medicine and Research Institute for Health Sciences, University of the East Ramon Magsaysay Memorial Medical Center Inc., Quezon City, Philippines

¹⁹Cardiology Division, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

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²⁰Divisions of Hypertension and Heart Failure, Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

²¹Section of Cardiology, Department of Medicine, Medical Center Manila, Manila, Philippines

²²Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia-National Cardiovascular Center, Harapan Kita, Jakarta, Indonesia

²³Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University Health System, Seoul, Korea

²⁴Fortis Hospitals, Chennai, Tamil Nadu, India

²⁵College of Medical Sciences, Kathmandu University, Bharatpur, Nepal

²⁶Department of General Medicine, Tan Tock Seng Hospital, Singapore

²⁷Division of Nephrology Department of Medicine, Yong Loo Lin School of Medicine, Singapore

²⁸JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Shatin, Hong Kong

²⁹Department of Physiology, King George's Medical University, Lucknow, India

Correspondence

Kazuomi Kario, MD, PhD, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan.
Email: kkario@jichi.ac.jp

Abstract

Morning hypertension is an important clinical target in the management of hypertension for perfect 24-h blood pressure (BP) control. Morning hypertension is generally categorized into two types: “morning surge” type and “sustained nocturnal and morning hypertension” type. The “morning surge” type is characterized by an exaggerated morning blood pressure surge (MBPS), and the “sustained nocturnal and morning hypertension” type with continuous hypertension from nighttime to morning (non-dipper/riser type). They can be detected by home and ambulatory blood pressure measurements (HBPM and ABPM). These two forms of morning hypertension both increase the risk of cardiovascular and renal diseases, but may occur via different pathogenic mechanisms and are associated with different conditions. Morning hypertension should be treated to achieve a morning BP level of < 135/85 mmHg, regardless of the office BP. The second target morning BP levels is < 125/75 mmHg for high-risk patients with morning hypertension and concomitant diseases. Morning hypertension is more frequently found in Asians, than in Westerners. Thus, the management of morning hypertension is especially important in Asia. The detection of morning hypertension and the individual home BP-guided treatment approach targeting morning BP in combination with ABPM, and the optimal treatment of morning hypertension would reduce cardiovascular events in Asia.

KEYWORDS

antihypertensive medication, Asia, bedtime dosing, hypertension, morning, personalized approach

1 | BACKGROUND AND RATIONALE OF CONSENSUS

Morning hypertension is an important and effective clinical target in the management of hypertension for perfect 24-h blood pressure (BP) control.¹ There is accumulating evidence that morning hypertension confers high risk for cardiovascular events especially in Asia.²⁻⁶ In particular, for medicated patients with hypertension, once daily dosing of antihypertensive drugs means that the trough BP-lowering effects are often in the morning, immediately prior to the next dose. Thus, morning BP control is the “blind spot” for current hypertensive medication.¹

Two types of morning hypertension can be detected by home and ambulatory blood pressure measurements (HBPM and ABPM). One is the “morning surge” type, characterized by an exaggerated morning blood pressure surge (MBPS), and the other is the “sustained nocturnal and morning hypertension” type with continuous hypertension from nighttime to morning (non-dipper/riser type) (Figure 1).^{1,7} These two forms of morning hypertension both increase the risk of cardiovascular and renal diseases,⁸ but may occur via different pathogenic mechanisms and are associated with different conditions.¹ These two types, exaggerated MBPS,⁹ and nocturnal hypertension,¹⁰ are more frequently found in Asians, than in Westerners. Thus, the management

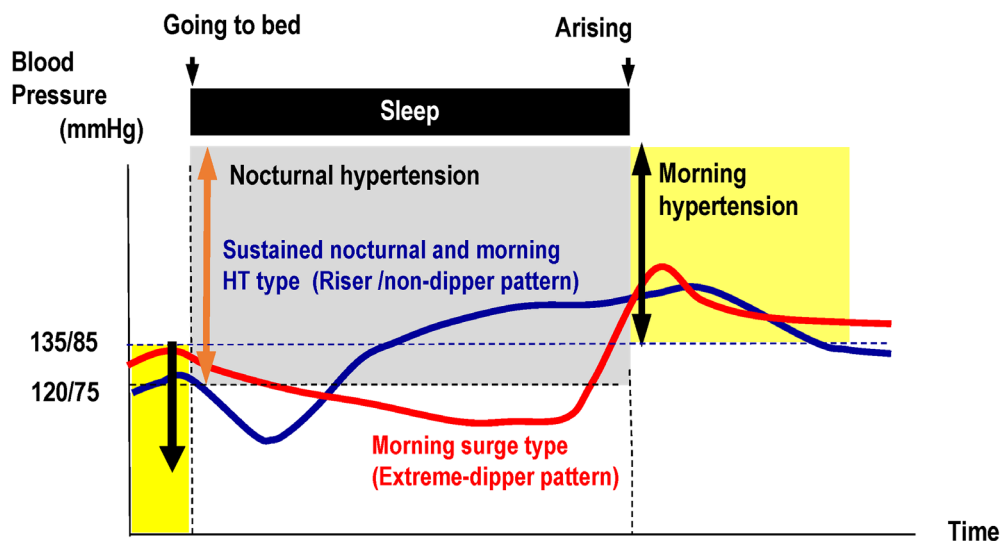


FIGURE 1 Two types of morning hypertension. Reprinted from Kario K. *Am J Hypertens* 2005;18:149-151

of morning hypertension is especially important in Asia and we have focused on its management.¹¹⁻¹³

Home BP-guided approach is the emerging management of hypertension and recommended for clinical practice¹⁴⁻¹⁹ and it is facilitated for telemedicine in the era of COVID-19.^{20,21} Morning BP can easily be self-measured using a HBPM device. In 2022, the HOPE Asia Network has introduced seven action approaches for the management of hypertension in Asia.²² Among the seven approaches, reducing morning home BP is considered as the first therapeutic target. Here, we release an updated consensus statement on the practical management of morning hypertension in Asia (Tables 1 and 2).

2 | DEFINITION OF MORNING HYPERTENSION

Morning hypertension was first broadly defined as the average of the measured morning BPs $\geq 135/85$ mmHg, regardless of office BP and BP levels measured at the other time periods.²³ This could be evaluated by HBPM, ABPM, or wearable (oscillometric) BP measurements (WBPM).

Masked morning hypertension is defined as morning hypertension with office BPs $< 140/90$ mmHg but average morning HBPM $\geq 135/85$ mmHg. Masked uncontrolled morning hypertension is masked morning hypertension on medication. The incidence of masked morning uncontrolled hypertension increases after initiation of antihypertensive treatment. Even with an increase in number of antihypertensive medications of two or more, masked uncontrolled morning hypertension remains at 50% or higher (data not shown) in HI-JAMP study.²⁴ But the reproducibility of the diagnosis of masked uncontrolled hypertension by HBPM itself is poor because of poor reproducibility of office BP measurement.²⁵ So HBPM directed treatment may be more consistent in the monitoring of the therapeutic response.

There are two types of morning hypertension. One is the morning surge type, and another is sustained nocturnal and morning

hypertension type with transition from nocturnal hypertension.¹⁸ Although morning BP surge has been well recognized as a risk of cardiovascular events,^{26,27} a recent ABPM prospective study demonstrated that morning BP surge increased stroke risk in the group with a dipper pattern, but not in the non-dipper group.²⁸

3 | DEVICE AND ASSESSMENT OF MORNING BP

Validated upper-arm HBPM and ABPM devices are essentially recommended to measure morning BP. Their characteristics are summarized in the Table 3.

3.1 | HBPM

Morning home BP is the average of the BPs self-measured after 2-min rest in seated position, twice with 1-min interval after urination, before taking morning pills, and within 1 h after rising in the morning, for > 5 days (> 10 measures).¹

The maximum morning home systolic BP is the maximum of two measures on one occasion during 1-week of measurements. Lower temperature increases morning BP variability and triggers maximum morning home BP.²⁹

3.2 | ABPM

Morning ambulatory BP is the average of BPs automatically measured for 2 h (four measures with 30 min-interval each by ABPM) after rising.¹ If the arising time is not available, morning ambulatory BP (fixed-time) is defined as the average of BPs during 7:00-8:59 a.m.¹ Arising time is more accurately determined by Actigraph® in combination with an upright position sensor. Physical activity and upright

TABLE 1 The HOPE Asia Network 2022 update to the consensus on morning hypertension management**1. Definition**

- Morning hypertension is diagnosed by HBPM, ABPM, or WBPM as the average of the measured morning BPs $\geq 135/85$ mmHg, regardless of office BP and BP levels measured at the other time periods.
- Masked morning hypertension is defined as morning hypertension with office BP $< 140/90$ mmHg.
- Masked uncontrolled morning hypertension is masked morning hypertension on medication.
- There are two types of morning hypertension. One is the morning surge type, and the other is sustained nocturnal and morning hypertension type.

2. Device and assessment

- Validated upper-arm HBPM and ABPM devices are essentially recommended to measure morning BP.
- Morning home BP is the average of the BPs self-measured after 2 min-rest in seated position, twice with 1 min-interval after urination, before taking morning pills, and within 1 h after arising in the morning, with > 5 days of measurements (> 10 measures).
- Morning ambulatory BP is the average of BPs automatically measured for 2-h (four measures with 30 min-interval by ABPM) after arising. If the arising time is not available, morning ambulatory BP (fixed-time) is defined as the average of BPs during 7:00–8:59 a.m.
- ABPM is recommended to evaluate nocturnal hypertension and simultaneously to differentiate between “morning surge” and “sustained nocturnal and morning hypertension” types. Wrist and upper-arm nighttime HBPM devices (oscillometric) may be available to measure nighttime BP.
- WBPM (oscillometric device) could be used to measure morning BPs, when it is used under similar conditions as HBPM (measured in the sitting condition, within 1-h after arising). Wearable morning home BP, could also be used when it is used under similar conditions as ABPM (measured during 2-h after arising in the ambulatory situation). Upper-arm WBPM is recommended, but wrist WBPM may alternatively be used, when individual wrist-brachial systolic BP difference is confirmed < 5 mmHg.
- Cuff-less device is not recommended to obtain morning BP values for the diagnosis and treatment of hypertension in clinical practice.

3. Treatment flow

- 1) Target morning BP is $< 135/85$ mmHg in general, and $< 125/75$ mmHg for high-risk group.
- 2) Strict salt reduction < 6 g per day, body weight reduction, and exercise are recommended first, and together with antihypertensives drugs when required.
- 3) Medication
 - a. Long acting CCB or RASi
 - b. If morning BP is not controlled, change timing of morning dosing to twice per day (or bedtime dosing could be considered case-by-case)
 - c. Single pill combination (SPC) is recommended when needed (combine CCB, RASi, Diuretics, or MR antagonist).
 - d. ARNI and SGLT2 inhibitors are also available to reduce morning BP.
 - e. If BP is still not controlled, beta-blocker or alpha-blocker could be added
- 4) Renal denervation is useful for morning BP reduction.

Abbreviations: ABPM, ambulatory BP monitoring; HBPM, home BP monitoring; WBPM, wearable BP monitoring.

positional change affect more morning ambulatory BP than simple eye-opening at supine position.²⁹ Morning BP, irrespective of the assessment methods and definitions, was generally reproducible and significantly associated with vascular indices.³⁰ Nevertheless, morning home BP might be preferred than ambulatory measurements because of better reproducibility and stronger correlation with vascular indices.

ABPM is recommended to evaluate nocturnal hypertension and simultaneously to differentiate between “morning surge” and “sustained nocturnal and morning hypertension” types. The simultaneous assessment of nocturnal hypertension would be useful for the high-risk patients with diabetes CKD, sleep apnea, and history of atherosclerotic CVD, heart failure, and/or in drug-resistant hypertension.³² These high-risk patients are likely to have nocturnal hypertension and nocturnal hypertension per se increases their cardiovascular risk. Wrist and upper-arm nighttime HBPM devices (oscillometric) are available

to measure nighttime BP,^{33,34} but currently are mainly for research purposes.

3.3 | WBPM

WBPM (oscillometric device) could be used to measure morning BPs, when it is used under similar conditions as HBPM (measured in the sitting position, within 1-h after arising). Wearable morning home BP,³⁵ could also be used when it is used under similar conditions as ABPM (measured during 2-h after arising in the ambulatory situation). Upper-arm WBPM is recommended, but wrist WBPM may alternatively be used, when individual wrist-brachial systolic BP difference is confirmed as < 5 mmHg.³⁶ Cuff-less device is not recommended to obtain the morning BP values for the diagnosis and treatment of hypertension in clinical practice.

TABLE 2 2022 updated evidence for morning hypertension management**Cardiovascular risk**

Cardiovascular event risk is the lowest under the condition of the average of morning home systolic BP (SBP) < 125 mmHg in the high-risk hypertensive patients.

Maximum home systolic BP > 170 mmHg (one third found in the morning), or morning-evening differences of home systolic BP > 20 mmHg are at risk for cardiovascular events on the top of risk of morning hypertension.

Sustained maximum home systolic BP < 140 mmHg (stable controlled status) is associated with markedly less risk within a few years.

Morning wearable BPs (the peak and average) detected by watch-type wearable BP monitoring are significantly correlated with left ventricular mass index measured by cardiac MRI.

In STEP, a RCT in elderly hypertensive patients, approximate 7.5 mmHg difference in morning home systolic BP between the strict BP control and the standard control groups accounted for 26% difference in cardiovascular events.

Antihypertensive medication

SGLT2i significantly decreased morning home BP in diabetic hypertensive patients.

ARNI more effectively reduced morning ambulatory BP in Asia than in Western countries.

A new highly selective MR blocker, esaxerenone, is effective to reduce morning ambulatory BP especially in the elderly hypertensive patients.

Digital therapeutics and renal denervation

Hypertension digital therapeutics (therapeutic App) significantly lowers morning home BP.

3-year long-term BP lowering effect of renal denervation was confirmed without adverse effect.

4 | RECENT AND NEW EVIDENCE FOR MORNING HYPERTENSION

International guidelines for the management of hypertension recommends home and ambulatory daytime BP levels < 135/85 mmHg. Thus, we set the target morning BP level to < 135/85 mmHg. Recently, several RCTs of antihypertensive treatment evaluated the morning home and/or ambulatory BPs. The STEP study,³⁷ a RCT of strict versus standard BP control in the elderly, and HERB DH1,³⁸ a RCT of digital therapeutics, a study that evaluated morning home BP, and SPYRAL HTN-ON-Med feasibility study,³⁹ a sham-controlled RCT of renal denervation, all evaluated the morning ambulatory BP.

4.1 | Cardiovascular disease risk

In the subanalysis of the HONEST study, cardiovascular event risk in the high-risk hypertensive patients with diabetes or history of stroke, was lowest in those whose average morning home systolic BPs was < 125 mmHg.³⁹ In the recent analysis of JHOP study, maximum home systolic BP (the maximum value of the average of three consecutive measures on one occasion, morning or evening, during the 14 days) of > 170 mmHg (one third found in the morning) was associated with > 10 times increased risk of cardiovascular events, than maximum home systolic BP < 140 mmHg.⁴⁰ This sustained maximum home systolic BP < 140 mmHg (always stable, stabilized BP control condition) is markedly at less risk within the next few years. In addition, morning-evening differences (morning minus evening) of home systolic BP > 20 mmHg was at risk for cardiovascular events independent of the home BPs (i.e., the average of morning and evening BPs).⁴¹ Morning wearable BPs (the peak and average) detected by watch-type wearable BP monitoring are significantly correlated with

left ventricular mass index measured by cardiac MRI.⁴² The intervention of antihypertensive drug for targeting morning hypertension provided the regression of hypertensive organ damages.⁴³⁻⁴⁵ In the STEP study, approximately 7.5 mmHg difference in morning home systolic BP between the strict BP control versus the standard control groups, resulted in a 26% difference in cardiovascular events.³⁶

4.2 | Antihypertensive medication

SGLT2i significantly decrease morning home BP in diabetic hypertensive patients.^{47,48} The SACRA study, a RCT of diabetic patients with uncontrolled nocturnal hypertension demonstrated that empagliflozin significantly lowered morning home systolic BP by 8.1 mmHg compared with the placebo control group.⁴⁷

In addition, an ARNI is more effective in reducing BPs in salt-sensitive Asians than in the Westerners.^{48,49}

ARNI more effectively lowers nighttime BP and NT-proBNP than daytime BP in Asians and older patients, who have salt-sensitive hypertension.⁴⁹ Morning ambulatory BP would be more significantly reduced by ARNi. A new highly selective mineralocorticoid-receptor (MR) blocker, esaxerenone, has been shown to be effective in reducing morning and evening ambulatory BP, especially in the elderly hypertensive patients, resulting in reduction of NT-proBNP level.⁵¹

4.3 | Digital therapeutics and renal denervation

Hypertension digital therapeutics (therapeutic App), which facilitate the six non-pharmacological interventions including sodium reduction, lowering body weight, exercise, keeping good sleep, stress management and alcohol restriction, with daily HBPM significantly lowers

TABLE 3 Role of HBPM and ABPM in the management of morning hypertension

	HBPM	ABPM
Availability	Good	Poor
Repeated measurement	Feasible	Difficult
Evaluation of subtype	Possible	Accurate
Reproducibility	Fair	Poor ^a
Day to day variability	Available	Not available

^aHypertension. 2019;74:137–144.

morning home systolic BP by 4.3 mmHg, compared with control group using daily HBPM and standard lifestyle modification by doctors. In this study, the standard lifestyle modification by doctors in combination with daily HBPM significantly lowered morning home systolic BP by 6.2 mmHg at 12 week of intervention, while digital therapeutics (+HBPM) lowered by 10.6 mmHg from baseline.³⁸ Thus, individual approach of better lifestyle modification, reinforced by the intensity of the App, in combination with daily HBPM would be effective in reducing morning home BP. Another interventional approach is renal denervation. The longer 3-year follow-up results of the sham-controlled RCT, SPYRAL HTN-ON Med feasibility study, demonstrated an 11.0 mmHg-lowering effect of renal denervation compared with sham on ambulatory morning systolic BP, without adverse effects at 36 months after the procedure.³⁹ However, several clinical trials of renal denervation did not achieve the primary endpoint.^{52,53} Whether renal denervation is effective for morning hypertension remains a subject of ongoing debate.

5 | CLINICAL MANAGEMENT FLOW OF MORNING HYPERTENSION

HBPM would be the first measurement to be used in the management of hypertension, and home BP-guided approach is recommended for all hypertensive patients.

For the diagnosis of morning hypertension, HBPM should be used first and should be done for all patients while ABPM is recommended in high-risk patients or in which the two types of morning hypertension needs to be defined.

Morning hypertension is the first target to focus on and should be treated to achieve a morning BP level of < 135/85 mmHg, regardless of the office BP. The second target morning BP levels is < 125/75 mmHg for high-risk patients with morning hypertension and concomitant diabetes, coronary artery disease, albuminuria, heart failure, taking antiplatelet or anticoagulant drugs, etc. ABPM is recommended for these high-risk patients to evaluate nighttime BP. Nighttime home BP monitoring may alternatively be used. The final goal is sufficient nighttime BP reduction and stabilized morning BP control without morning BP surge.¹

Several international guidelines recommend that exercise program included aerobic, resistance and isometric is the foundation of hypertensive treatment.^{53–55} Exercise training could be important for the

management of morning hypertension. Regarding antihypertensive treatment of morning hypertension, calcium channel blockers (CCB) are recommended for the elderly hypertensive patients with marked BP variability. RAS inhibitors are recommended for adult hypertensive patients, especially those with albuminuria. If morning BP is not controlled by one drug, ARB/CCB combination, or changing the ARB to sacubitril/valsartan, or adding thiazide-like diuretics or MR antagonist is effective. In addition, previous study reported that the administration of beta blocker reduced morning BP with parallel reduction morning heart rate.⁵⁶ If BP is still not controlled, beta-blocker or alpha-blocker could be added.⁴³

To achieve fast and strict BP control with improved drug adherence, single pill combinations (SPC) are recommended. A single-pill combination of cilnidipine, an L-/N-type CCB, and ARB effectively reduced morning home BP and morning BP variability.⁵⁷

Practically, when morning hypertension is not controlled by once daily morning dosing, switching to the drug with longer half-life or twice-daily dosing (morning and evening dosing). Bedtime dosing could be considered case-by-case.⁴⁵

Renal denervation may be considered for patients with uncontrolled morning and/or nocturnal hypertension treated with antihypertensive medications.⁵⁹

6 | PERSPECTIVES IN ASIA

Morning hypertension is the primary target of hypertension management in Asia. However, morning hypertension is still not sufficiently well controlled. The detection of morning hypertension and the individual home BP-guided treatment approach targeting morning BP in combination with ABPM, and the optimal treatment of morning hypertension would reduce cardiovascular events in Asia.

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





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CONFLICTS OF INTEREST

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ORCID

Kazuomi Kario MD, PhD  <https://orcid.org/0000-0002-8251-4480>
 Ji-Guang Wang MD, PhD  <https://orcid.org/0000-0001-8511-1524>
 Yook-Chin Chia MBBS, FRCP  <https://orcid.org/0000-0003-1995-0359>
 Tzung-Dau Wang MD, PhD  <https://orcid.org/0000-0002-7180-3607>
 Yan Li MD, PhD  <https://orcid.org/0000-0002-5825-5968>
 Saulat Siddique MBBSMRCP (UK), FRCP (Lon)  <https://orcid.org/0000-0003-1294-0430>
 Jinho Shin MD  <https://orcid.org/0000-0001-6706-6504>
 Yuda Turana MD, PhD  <https://orcid.org/0000-0003-4527-0285>
 Peera Buranakitjaroen MD, MScD, Phil  <https://orcid.org/0000-0002-4710-2413>
 Chen-Huan Chen MD  <https://orcid.org/0000-0002-9262-0287>
 Hao-Min Cheng MD, PhD  <https://orcid.org/0000-0002-3885-6600>
 Jennifer Nales MD, MSPH  <https://orcid.org/0000-0001-6334-0510>
 Apichard Sukonthasarn MD  <https://orcid.org/0000-0001-7569-9563>
 Yuqing Zhang MD  <https://orcid.org/0000-0001-8142-8305>
 Sungha Park MD, PhD  <https://orcid.org/0000-0002-7798-658X>
 Guru Prasad Sogunuru MD, DM  <https://orcid.org/0000-0002-1410-9328>
 Jam Chin Tay MBBS, FAMS  <https://orcid.org/0000-0001-7657-4383>
 Boon Wee Teo MB, BCh  <https://orcid.org/0000-0002-4911-8507>
 Kelvin Tsoi BSc, PhD  <https://orcid.org/0000-0001-5580-7686>
 Narsingh Verma MD  <https://orcid.org/0000-0003-0348-7419>
 Satoshi Hoshide MD, PhD  <https://orcid.org/0000-0001-7541-5751>

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