

Diversity of and initiatives for hypertension management in Asia—Why we need the HOPE Asia Network

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Abstract

The Hypertension Cardiovascular Outcome Prevention and Evidence in Asia (HOPE Asia) Network was set up to improve the management of hypertension in Asia with the ultimate goal of achieving “zero” cardiovascular events. Asia is a diverse continent, and the prevalence of hypertension has increased over the last 30 years. There are a number of Asia-specific features of hypertension and hypertension-related cardiovascular complications, which means that a region-specific approach is needed. White-coat hypertension will become more of an issue over time as Asian populations age, and masked hypertension is more prevalent in Asian than in Western countries. Identifying and treating masked hypertension is important to reduce cardiovascular risk. Abnormal patterns of blood pressure (BP) variability common in Asia include exaggerated early morning BP surge and nocturnal hypertension. These are also important cardiovascular risk factors that need to be managed. Home blood pressure monitoring (HBPM) is an important tool for detecting white-coat and masked hypertension, and monitoring BP variability, and practices in Asia are variable. Use of HBPM is important given the Asia-specific features of hypertension, and strategies are needed to improve and standardize HBPM usage. Development of HBPM devices capable of measuring nocturnal BP along with other information and communication technology-based strategies are key developments in the widespread implementation of anticipation medicine strategies to detect and prevent cardiovascular events in patients with hypertension. Region-wide differences in hypertension prevalence, control, and management practices in Asia highlight the importance of information sharing to facilitate best practices.

1 | INTRODUCTION

Hypertension is an important global health issue. Using population data from 154 countries, the estimated number of adults with systolic blood pressure (SBP) of ≥ 140 mm Hg in 2015 was 874 million, and the number of those with SBP of at least 110–115 mm Hg was 3.5 billion.¹ It is well known that elevated blood pressure (BP) is associated with cardiovascular morbidity and mortality, and that good blood pressure (BP) control is an effective approach to reducing the risk of hypertension-related target organ damage and cardiovascular events.^{2,3} Nevertheless, the cardiovascular complications of hypertension continue to cause significant morbidity and mortality worldwide, largely due to inadequate strategies for the prevention, diagnosis, and control of hypertension in an aging worldwide population, many of whom are experiencing changing social and economic conditions.³

The mission of the Hypertension Cardiovascular Outcome Prevention and Evidence in Asia (HOPE Asia) Network is to improve the management of hypertension and organ protection with the ultimate goal of achieving “zero” cardiovascular events in Asia. There are three main strategies to allow this goal to be achieved: (a) examination and analysis of existing hypertension-related evidence; (b) development of consensus on clinically relevant themes in hypertension;

and (c) performing Asia-wide clinical studies in the field.⁴ The HOPE Asia Network is a member of the World Hypertension League (WHL) and will contribute to the WHL's mission of confronting the global hypertension epidemic and the associated high burden of disability and premature death.

Asia is a diverse continent. The majority of countries are lower to upper middle income, but the region includes some high (eg, Japan, Korea) and some lower (eg, Cambodia) income countries. Hypertension prevalence rates vary between countries.^{5,6} Perhaps, a more significant issue than high prevalence rates is the low level of awareness and treatment in some countries.⁷

Diversity in the region in terms of the number of individuals with raised BP was highlighted in a 2015 global analysis of BP trend prevalence.⁸ South Korea has one of the lowest prevalence rates for raised BP, whereas rates in South Asia and China were much higher.⁸ The high population density in parts of Asia means that the absolute number of individuals affected by hypertension is substantial. Based on 2015 figures, 258 million (23%) of the 1.13 billion adults with raised BP lived in South Asia (of whom 199 million resided in India) and another 235 million (21%) lived in East Asia (226 million in China).⁸ Thus, the negative consequences of high BP and poor BP control are significant, highlighting hypertension as an important public health concern for the region. Obesity is another growing

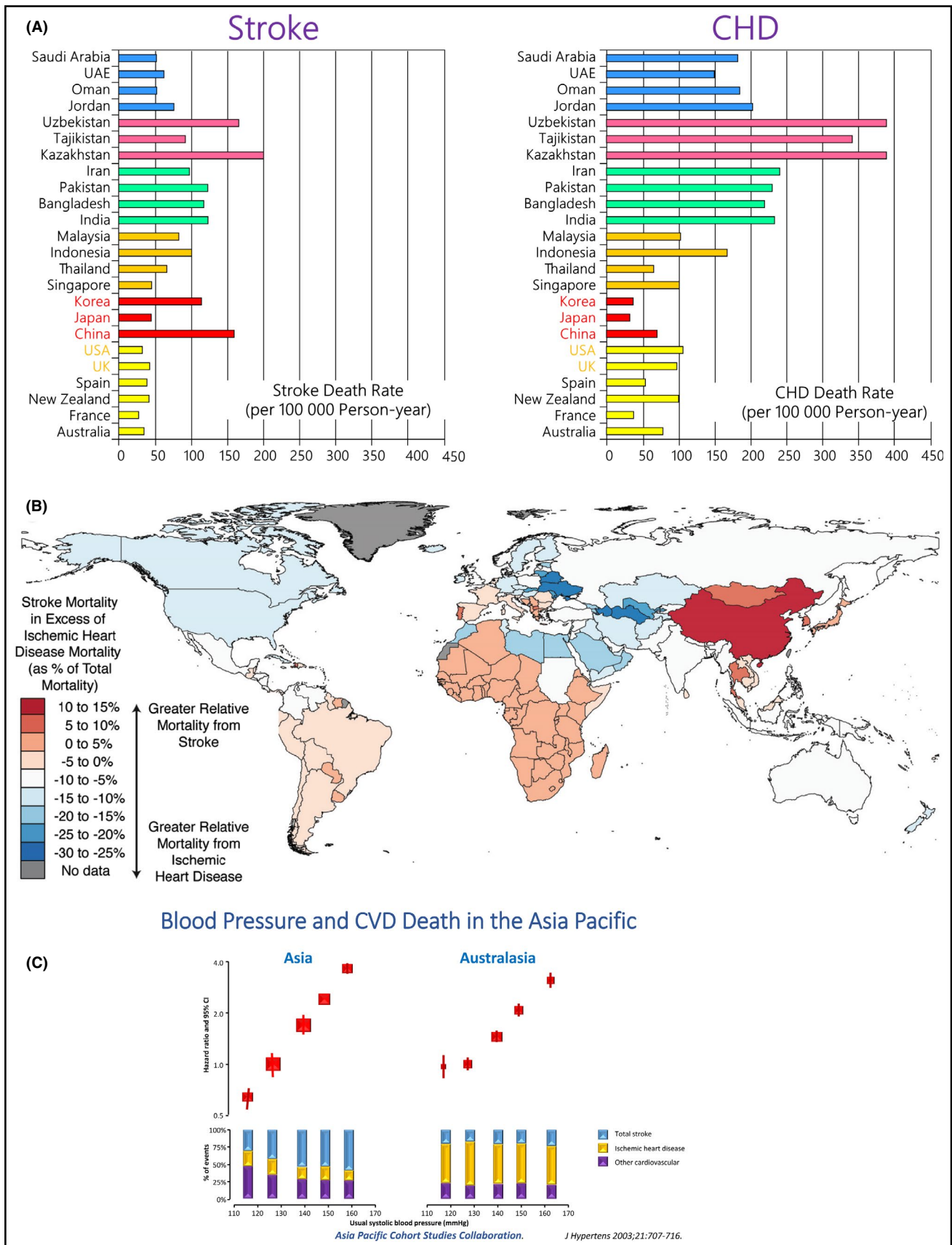


FIGURE 1 Age-standardized cardiovascular death rates for stroke and coronary heart disease (CHD; reproduced from Ueshima et al,¹⁰ with permission) (A); and excess of stroke mortality compared with CHD mortality (reproduced from Kim,¹¹ with permission) (B); and association between blood pressure and cardiovascular death in Asia vs Australasia in the Asia Pacific Cohort Studies Collaboration (C)¹²

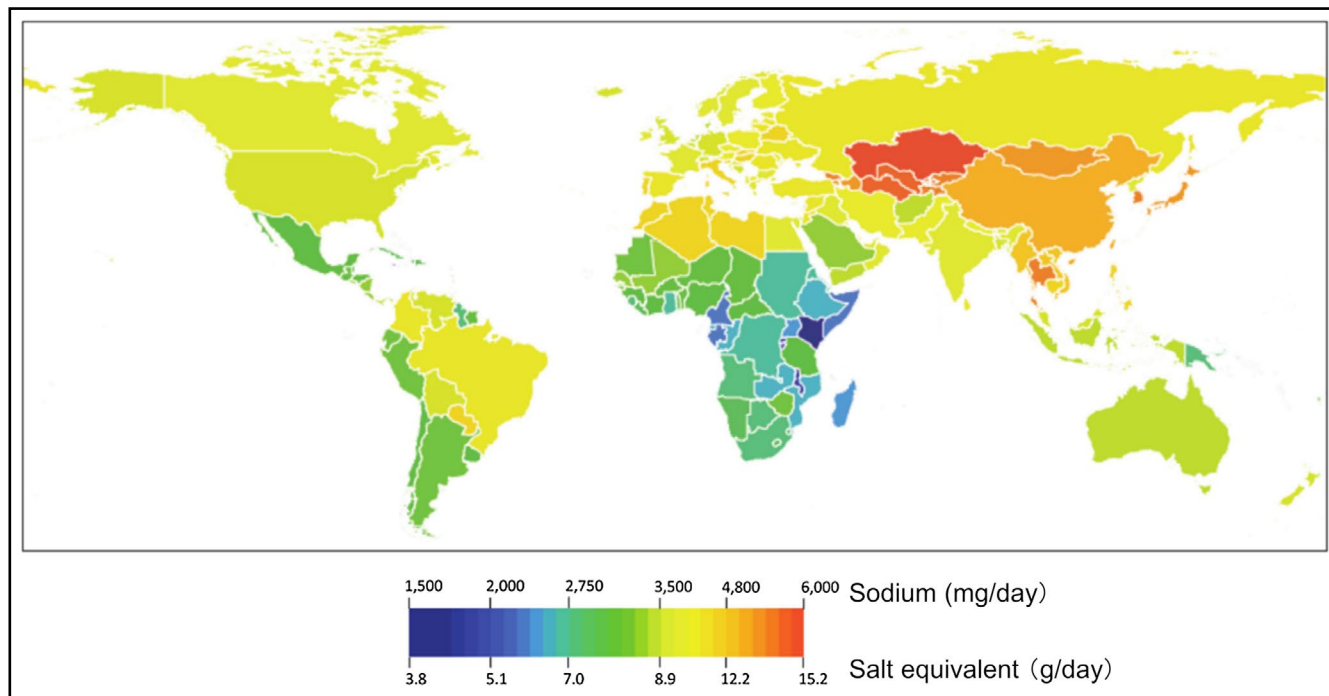


FIGURE 2 Salt intake in 2010 for adults aged >20 y (reproduced from Powles et al,¹⁰⁵ with permission)

issue in Asia. A worldwide population survey showed consistent increases in body mass index over time in Asia and Oceania, although to a lesser extent in the high-income Asia-Pacific region.⁹

2 | ASIA-SPECIFIC FACTORS

There are several differences in the profile of hypertension and hypertension risk in Asians compared with Western populations. In contrast to Western countries, stroke is a more common complication of hypertension than is coronary heart disease (CHD) in some parts of Asia,¹⁰ and there is a higher burden of stroke-related vs CHD-related mortality in some parts of Asia (Figure 1).^{10,11} In addition, the slope of the association between increasing SBP and the rate of cardiovascular events has been shown to be steeper in Asians than in Western/Caucasian populations (Figure 1).¹² Another important factor is obesity, the prevalence of which is increasing rapidly in Asia,¹³ and the impact of obesity on BP may differ between Asians and Caucasians. For example, Asians are likely to develop pre-hypertension and high BP at a lower BMI and with smaller BMI increments than Europeans.^{14,15} Furthermore, obesity and the metabolic syndrome are known to increase salt sensitivity, and Asians are more likely to have a genetic predisposition to salt sensitivity.¹⁵ Asians also have a high salt intake (Figure 2), which combines with greater salt sensitivity to increase mean BP to a greater extent in Asians than in Caucasians. Available data also suggest that BP variability (BPV), especially an exaggerated morning BP surge and nocturnal hypertension, is greater in Asians than in Westerners.¹⁶⁻²⁰ This is relevant because abnormal BPV is known to increase the risk of cardiovascular events.^{21,22}

In terms of manifestations of cardiovascular disease (CVD), Asians have a lower prevalence of atrial fibrillation (AF) than Caucasians ($\approx 1\%$ vs $\approx 1\%$ - 2%) but the overall disease burden of AF in Asia is high because of the larger proportion of older individuals in the population.²³ Based on data from a large study conducted in Taiwan, approximately one in seven individuals aged >20 years in Asia will develop AF in their lifetime²⁴; these rates are lower than those reported for Caucasians in the Framingham Heart Study²⁵ and the Rotterdam study.²⁶ Rates of heart failure also appear to be slightly lower in Asian vs Western populations but, as for AF, the number of patients in Asia who develop heart failure each year is high, indicating that the worldwide heart failure pandemic includes Asia.²⁷ Given that an increase in CHD prevalence often occurs in parallel with better socioeconomic prosperity, the improving socioeconomic status across much of Asia means that the region has high rates of CHD and CHD mortality.²⁸ It has been estimated that over 60% of the global CHD burden occurs in developing countries, especially in Asia.²⁹

The risk of cardiovascular events shows seasonal variation, usually peaking in winter. However, available data suggest that this interaction is more complex than a direct influence of seasonal factors (eg, daylight exposure, ambient temperature) and actually results from a more complex interaction between an individual and his/her environment.³⁰ Data from Asia show higher absolute BP values in winter,³¹ winter increases in the incidence of both cardiac and cerebrovascular disease in Japan,³² winter peaks of acute coronary syndrome in China and ischemic heart disease- and heart failure-related events in Hong Kong,³³⁻³⁵ and associations between mean temperature and the occurrence of intracerebral hemorrhage in South Korea.³⁶

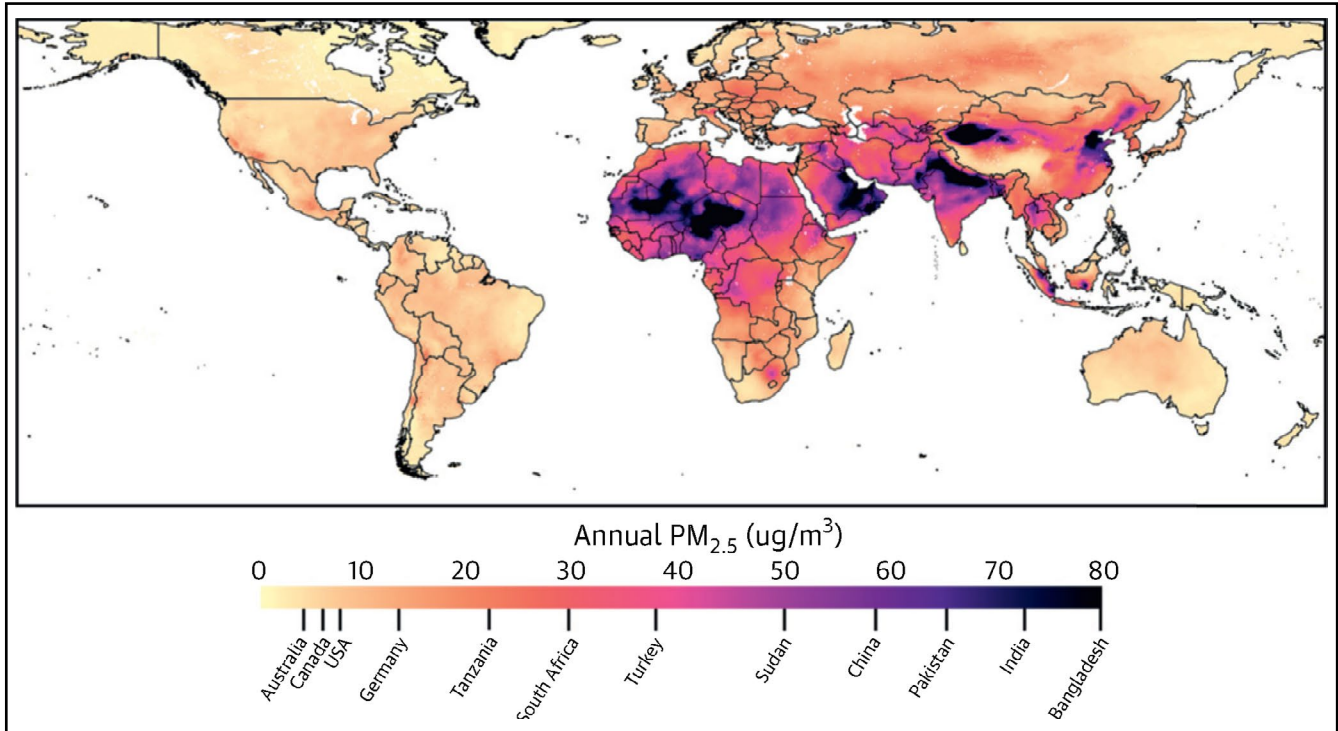
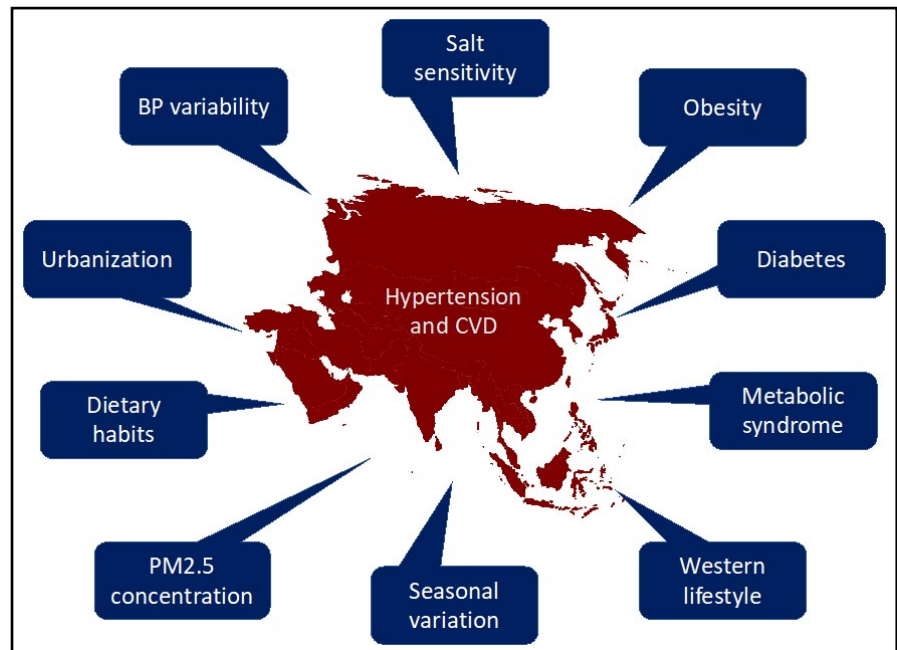


FIGURE 3 “Heat map” showing annual global levels of fine particulate matter $<2.5 \mu\text{g}$ ($\text{PM}_{2.5}$; reproduced from Rajagopalan S,⁴¹ with permission)

FIGURE 4 Factors contributing to hypertension and cardiovascular disease (CVD) in Asia. BP, blood pressure; $\text{PM}_{2.5}$, fine particulate matter $<2.5 \mu\text{g}$



Fine particulate matter $<2.5 \mu\text{g}$ ($\text{PM}_{2.5}$) has been identified as a significant and important contributor to the occurrence of hypertension.³⁷⁻⁴⁰ This is particularly relevant in Asia because $\text{PM}_{2.5}$ levels in China, Pakistan, India, and Bangladesh are among the highest in the world (Figure 3). Evidence for the association between air pollution and cardiovascular disease has recently been comprehensively reviewed.⁴¹ Looking at Asian studies, data from Japan showed that

the combination of low temperature and high $\text{PM}_{2.5}$ concentration substantially and significantly increased the likelihood of morning hypertension compared with times when temperature was high and $\text{PM}_{2.5}$ concentration was low.⁴² In Thailand, National Health Examination Survey data show that the prevalence of hypertension is the highest in northern region, which also has a high proportion of days with extremely high $\text{PM}_{2.5}$ levels.

The varied factors contributing to hypertension and CVD in Asia are summarized in Figure 4.

3 | WHITE-COAT HYPERTENSION IN ASIA

The worldwide prevalence of white-coat hypertension based on data from the Ambulatory blood pressure Registry TEleMonitoring of hypertension and cardiovascular rISk (ARTEMIS) project in patients referred for hypertension was 23%.²⁰ There are limited Asia-specific data, but the prevalence of white-coat hypertension in volunteers with no prior cardiovascular disease or antihypertensive treatment in a community-based survey from Taiwan was somewhat lower at 12%.⁴³ Importantly for the rapidly aging population demographic seen in Asia, the prevalence of white-coat hypertension is higher in the elderly.²⁰

Currently available evidence suggests that the cardiovascular risk associated with white-coat hypertension in the absence of other coexisting risk factors is negligible.⁴⁴⁻⁴⁷ In the Japan Morning Surge-Home Blood Pressure (J-HOP) study, white-coat hypertension detected using home blood pressure monitoring (HBPM) was not significantly associated with stroke risk over a median follow-up duration of 3.9 years.⁴⁸ Conversely, data from a population-based study (also conducted in Japan) documented a significant independent association between white-coat hypertension diagnosed based on elevated office BP and normal home or ambulatory BP and increased stroke risk.⁴⁹ Nevertheless, the majority of data suggest no increased risk of CVD events in low-risk patients who have white-coat hypertension, as shown by data from a general Japanese population ($n = 1332$) who were followed for 10 years; there were no significant differences in the risk of cardiovascular mortality and stroke morbidity in individuals with white-coat hypertension compared with normotensives (RR 1.28, 95% CI 0.76-2.14).⁵⁰

Although CVD risk is not usually an issue in patients with white-coat hypertension in the absence of other risk factors, effective detection of white-coat hypertension remains important so that over-treatment can be avoided. Not only does over-use of antihypertensives have a negative impact on healthcare expenditure, it also unnecessarily exposes individuals to the potential risks associated with antihypertensive drug therapy (eg, hypotension, especially in the elderly).⁵¹ Nevertheless, regular (eg, annual) monitoring of patients with white-coat hypertension might be reasonable to allow detection of progression to sustained hypertension,⁵²⁻⁵⁴ which would be an indication for therapeutic intervention.

4 | MASKED HYPERTENSION IN ASIA

Masked hypertension is a significant clinical entity given that it has been linked with increased risk of target organ damage and CVD.⁵⁵ Global prevalence rates for masked hypertension range from 7% to 20%,⁵⁶⁻⁶¹ and Asia-specific rates are at the top end of that range (20% in untreated Chinese outpatients).⁶¹ In the ARTEMIS registry,

the prevalence of masked hypertension detected using ambulatory BP monitoring (ABPM) showed significant variation between geographic region, being much higher in Asia (16%) than in Europe (9%).²⁰

In contrast to white-coat hypertension, there is a good body of evidence for the detrimental cardiovascular effects of masked hypertension. Data from Asia are consistent with the overall literature in this area. In terms of target organ damage, impaired flow-mediated vasodilatation in the brachial artery was documented in a Japanese study of patients with masked hypertension and at least one CVD risk factor.⁶² In addition, data from a general population (aged ≥ 40 years) in Japan showed that masked hypertension was significantly associated with the presence of albuminuria (a marker of renal function impairment) after adjustment for other risk factors.⁶³ In another study from Japan conducted in patients with type 2 diabetes, the risk of progression to microalbuminuria was higher in the presence of masked hypertension vs sustained hypertension.⁶⁴ Retrospective analysis of data from two large Japanese studies suggests that treatment of masked hypertension with intensive antihypertensive therapy targeting morning home BP can improve parameters indicative of target organ damage.⁶⁵

In the Ohasama study, increases in stroke morbidity and cardiovascular mortality were similar in the presence of masked hypertension and sustained hypertension.⁵⁰ The increased stroke risk associated with masked hypertension was seen when the phenomenon was detected using ABPM and HBPM, ABPM only or HBPM only.⁴⁹ Increased stroke risk in patients with masked hypertension was also documented in the J-HOP study.⁴⁸

5 | MORNING AND NOCTURNAL HYPERTENSION IN ASIA

Due to the influence of a number of factors (eg, neuro-hormonal effects, environment, behavior), there are diurnal and circadian variations in BP. BP tends to be higher in the morning and lower at night. Variations to this physiological pattern (eg, excessive morning BP surge and/or lack of nocturnal fall [non-dipper pattern] or an overnight increase [riser pattern] in BP) are pathological forms of BPV that are particularly common in Asian patients. Data from the ARTEMIS study showed that patients with resistant hypertension from Japan have significantly higher morning and moving peak morning systolic BP, and morning and nighttime dynamic BP surge, compared with black and white Americans.¹⁶

5.1 | Excessive morning BP surge

The association between excessive early morning BP surge and increased stroke risk was first demonstrated by Kario et al⁶⁶ in elderly hypertensive patients from Japan. In addition, morning BP surge was associated with cerebral hemorrhage in another Japanese population study.⁶⁷ In studies conducted in Asia (predominantly Japan),

exaggerated early morning BP surge has also been associated with target organ damage, including increased left ventricular mass index and left ventricular hypertrophy, impaired diastolic function, increased carotid intima-media thickness, inflammation, and asymptomatic intracranial stenosis.⁶⁸⁻⁷²

5.2 | Nocturnal hypertension

Evaluated using ABPM, nocturnal hypertension and a non-dipper/riser pattern have been reported to increase the risk of target organ damage and cardiovascular events.⁷³⁻⁷⁶ For example, the proportion of patients with silent cerebral infarcts detected on brain magnetic resonance imaging was significantly higher in elderly Japanese hypertensive patients with a riser vs dipping pattern of nighttime BP ($P = .03$); riser patients also had a worse prognosis in terms of stroke and cardiac events.^{74,77} Furthermore, riser pattern has been shown to closely associate with the development of heart failure with preserved ejection fraction and increase the risk of cardiovascular events in these patients.^{78,79} In another Japanese study of elderly patients with hypertension, those with a non-dipper pattern of both nighttime BP and nighttime pulse rate had the worst cardiovascular prognosis compared with other dipping patterns.⁸⁰

6 | HBPM IN ASIA

HBPM is an effective method to improve awareness and control of hypertension. Management of BP based on HBPM has been shown to result in better BP control (assessed using ABPM) and is therefore

recommended for titration of antihypertensive medication.⁸¹ HBPM can also help identify white-coat (uncontrolled) hypertension and masked (uncontrolled) hypertension, and evaluate long-term BPV.^{82,83} Because of the tighter relationship of BP with cardiovascular events, higher prevalence of masked uncontrolled hypertension, higher morning BP and greater BPV in Asian patients, HBPM is likely to be of greater importance in Asian than in Western populations.⁸⁴ The current status of HBPM in Asia has been reviewed previously,⁷ and details of current usage of HBPM and local guideline recommendations for each country in the HOPE Asia Network are summarized in specific country reports in this issue.

7 | ANTIHYPERTENSIVE MANAGEMENT IN ASIA

Effectively lowering BP, rather than the choice of agent, is the most important goal when trying to reduce cardiovascular risk.⁸⁵ Lower targets for goal BP are increasingly being recognized and recommended in major hypertension guidelines.^{54,81} Preferred antihypertensive agents in Asia are chosen based on their ability to deliver good 24-hour control of BP in the setting of Asia-specific hypertension characteristics (eg, salt sensitivity and relative risk of stroke vs CHD). Evaluation of data from the Eastern Asian region comparing a calcium channel blocker (CCB) with an agent from another antihypertensive class showed that reductions in 24-hour BP were greater with CCBs (by 5 mm Hg for SBP and 3 mm Hg for DBP).⁸⁶ In addition, data from Thailand showed that response rates to antihypertensive monotherapy were greatest for CCBs followed by diuretics.⁸⁷ It is perhaps therefore not surprising that CCBs are widely used in Asia,

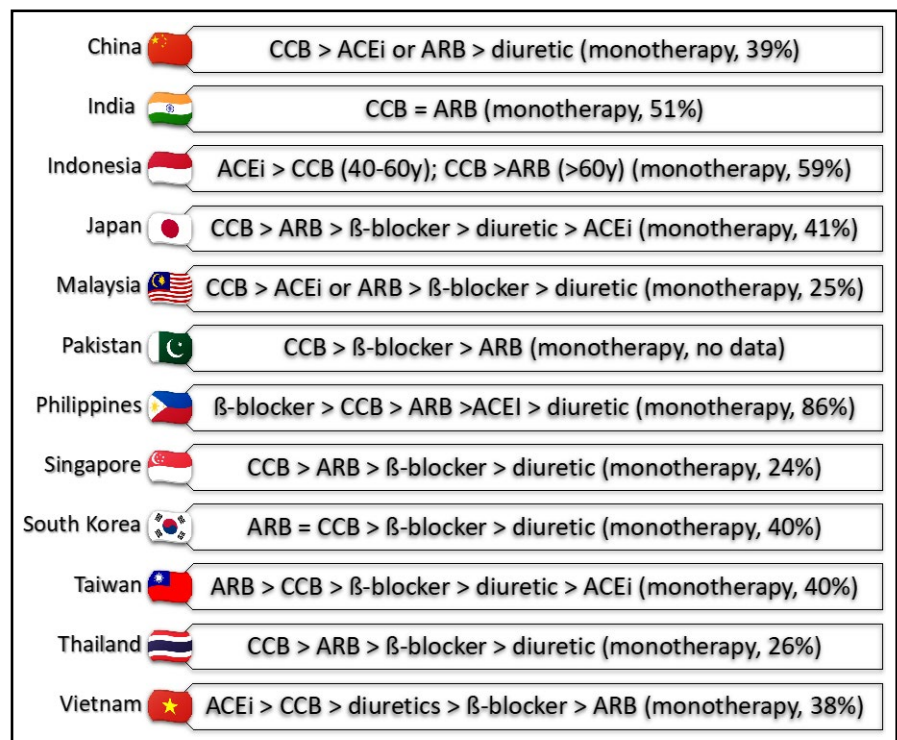


FIGURE 5 Usage of antihypertensives and proportion of patients receiving antihypertensive monotherapy by country. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

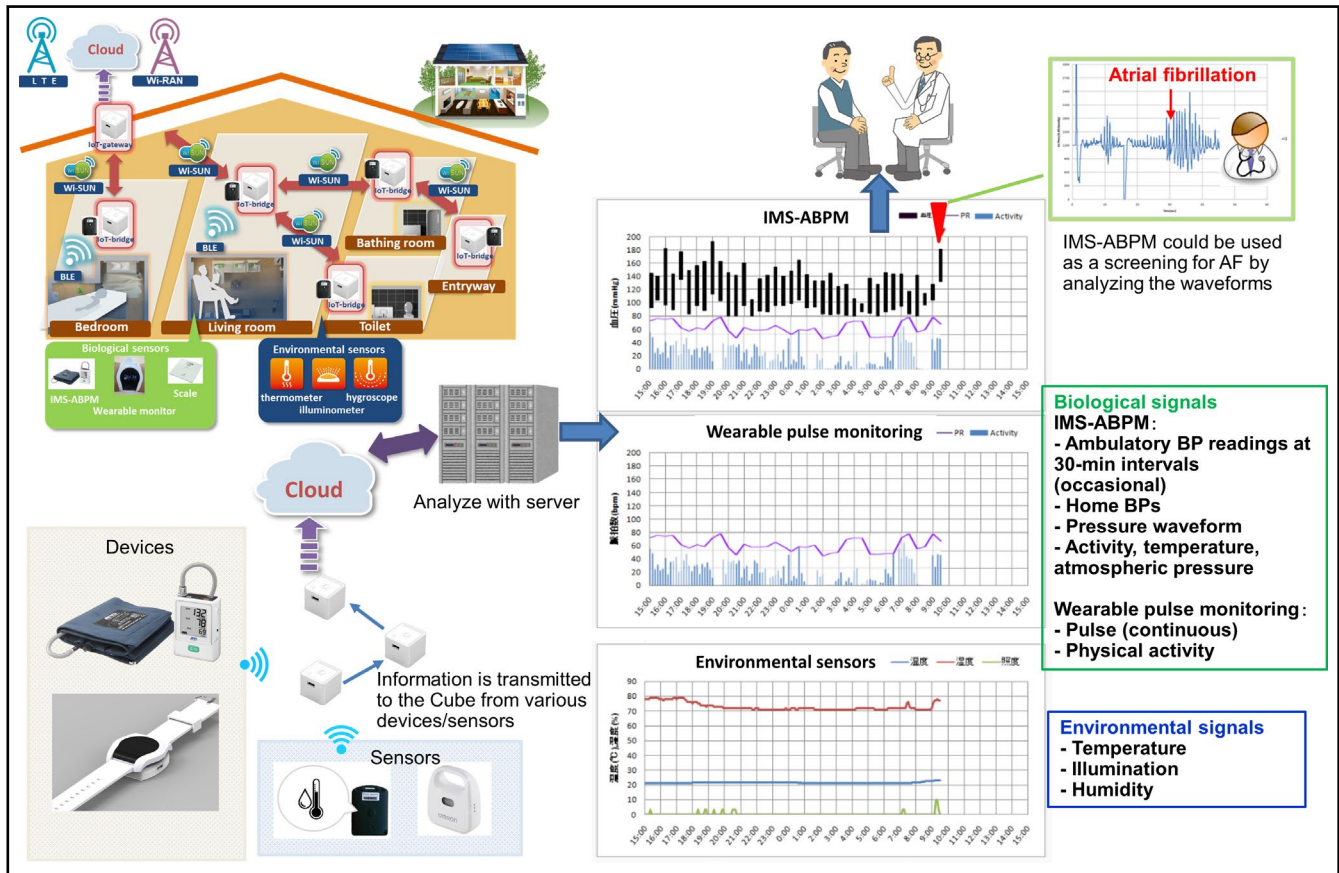


FIGURE 6 Schematic of a potential information communication technology (ICT)-based, integrated approach to the individualized management of hypertension (reproduced from Kario et al.,¹⁰² with permission). ABPM, ambulatory blood pressure monitoring; BP, blood pressure; IMS, ICT-based multisensor

as are angiotensin receptor blockers in most countries (Figure 5). Use of monotherapy varies by region, but is quite high in some countries (Figure 5), despite the fact that combination therapy is often required to achieve BP control. Additional details of antihypertensive therapy by country/region are provided in specific reports in this issue.

8 | DEVELOPMENT OF NOCTURNAL HBPM DEVICES AND EVIDENCE

To date, ABPM has been the gold standard for monitoring nighttime BP. HBPM is also recommended for out-of-office BP measurement, but has traditionally been used primarily during waking hours. A collaboration between Jichi Medical University and Omron Healthcare Co., Ltd. has seen the development of a semiautomatic nocturnal HBPM device (Medinote; Omron Healthcare Inc). This device automatically measures BP at fixed intervals during sleep using a cuff placed on the patient's arm just before going to bed; BP data are stored in the device memory. It was used to monitor nighttime BP in the J-HOP study, which showed that self-measurement of nighttime home BP was feasible and recorded BP values similar to those obtained with ABPM.⁸⁸⁻⁹¹ Data from J-HOP also showed that nighttime

home BP was a reliable indicator of target organ damage,^{89,90} even more so than nighttime ABPM determined using ABPM.⁹⁰ The Medinote device was also used in the Japan Target Organ Protection (J-TOP) trial, and the first time nighttime home BP was assessed in a clinical intervention trial.^{92,93} The results showed that nighttime home BP was more closely associated with regression of left ventricular hypertrophy during therapy than clinic BP.⁹³

An updated version of the nocturnal HBPM device (HEM-7252G-HP; Omron), which includes a temperature sensor, is now available and was successfully used in studies evaluating the effects of different antihypertensive therapy combinations on uncontrolled nocturnal hypertension or the morning BP surge.^{94,95}

9 | ICT AND FUTURE DIRECTIONS FOR THE HOPE ASIA NETWORK

Recent technology developments suggest that use of information and communication technology (ICT)-based HBPM devices, which perform automatic, fixed-interval BP measurement during sleep and store or transmit the data (such as those described above), could facilitate a novel approach to patient management.⁹⁶ In addition, there are a number of other ICT-based devices that provide important

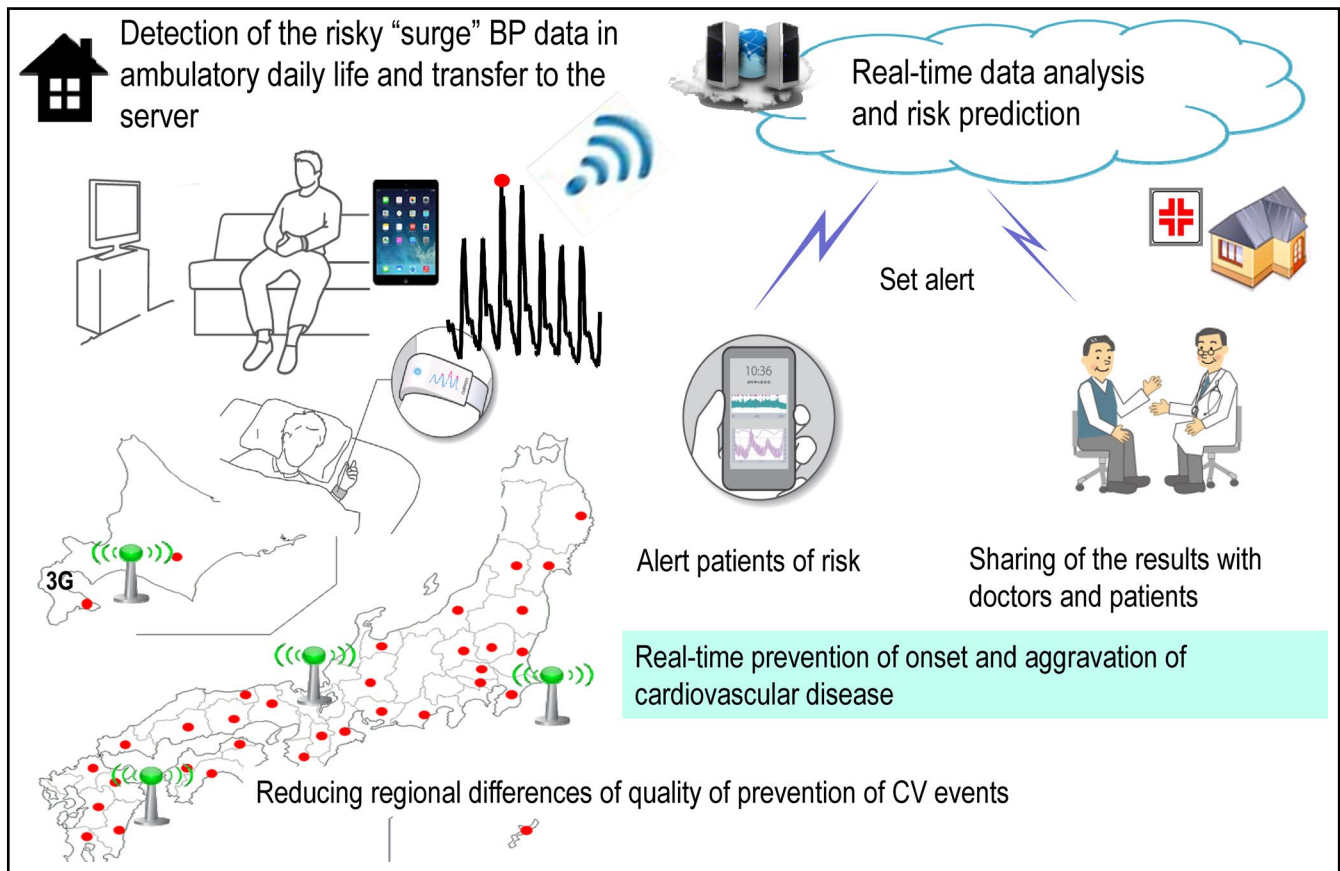


FIGURE 7 Example of how information communication technology (ICT)-based technology could be used to facilitate the management of hypertension to reduce the risk of cardiovascular events. BP, blood pressure; CV, cardiovascular

data for optimization of patient management. These include the addition of a nighttime trigger function (where hypoxia and heart rate are determined using pulse oximetry and BP measurements are taken repeatedly in higher risk situations, as used in a clinical trial of hypertensive patients with sleep apnea⁹⁷), beat-by-beat continuous surge BP monitoring via a wearable device, and determination of environmental factors (eg, temperature, stress, and exercise, Figure 6). Health information technology (HIT) solutions like this are increasingly being recognized as important advances in health care and the important and emerging role of HIT was highlighted in the latest version of the American College of Cardiology/American Heart Association hypertension guidelines.⁵⁴ BP management using a home BP device with a graphic display of weekly averaged BP values has been shown to facilitate faster BP control than a standard device,⁹⁸ suggesting the integrated ICT-based HBPM technologies are an important approach to anticipation medicine. Anticipation medicine is defined as medicine that predicts the time and place of the onset of cardiovascular events based on a time-series of data to provide a patient and/or physician with advanced warning of potential risk factors, resulting in proactive, real-time risk reduction (Figure 7).

Wearable technologies for evaluation of home BP have recently been validated,^{99,100} opening the way for their use in clinical practice. Using these devices and an ICT platform, physicians will be able

to obtain data for the evaluation and anticipation of 24-hour BP control at the individual level, allowing them to work toward the goal of achieving "perfect 24-hour BP control," resulting in a "zero" rate of cardiovascular events.¹⁰¹⁻¹⁰³

10 | PERSPECTIVES AND CONCLUSIONS

All countries and regions in Asia face the growing problem of non-communicable diseases (NCDs), of which hypertension and CVD are a significant part. The World Health Organization has proposed nine voluntary global targets to control NCDs by 2025, one of which is to reduce the prevalence of hypertension by 25%.¹⁰⁴ Given the unique features of hypertension in Asia, specific evidence is essential to ensure that local guidelines and practice recommend strategies that will be effective in the target populations. Increasing using of HBPM and related ICT-based advances will provide HIT solutions that maximize the potential to improve outcomes. Using such an approach will contribute to anticipation medicine strategies designed to detect and prevent cardiovascular events in patients with hypertension. Variations in practices and BP control rates across Asia highlight the importance of information sharing in the region to facilitate best practice for the effective management of hypertension and prevention of cardiovascular disease.

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AUTHOR CONTRIBUTIONS

K.K. and J-G.W. were responsible for the conception and design of the consensus, drafting the manuscript, providing critical review and revision of the manuscript, and the decision to submit the manuscript. Y-C.C., A.S., Y.T., J.S., C-H.C., P.B., J.N., S.H., S.S., J.S., A.A.S., G.P.S., J.C.T., B.W.T., Y-Q.Z., S.P., H.V.M., N.T., T.K., N.V., and T-D.W. were responsible for drafting the manuscript, providing critical review and revision of the manuscript, and the decision to submit the manuscript.

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