

Consensus Document on Improving Hypertension Management in Asian Patients, Taking Into Account Asian Characteristics

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Hypertension is the major cause of mortality and the leading cause of cardiovascular disease worldwide. Blood pressure (BP) lowering either by lifestyle modification or medication leads to a reduction in cardiovascular events. However, there are significant ethnic differences in the determinants of hypertension and in the risk of hypertension-related demographics of cardiovascular disease.¹⁻⁴ In Asian countries, stroke, especially hemorrhagic stroke, and nonischemic heart failure (HF) are more common than in Western countries. Stroke and HF are more closely related to hypertension than coronary artery disease or renal disease. In addition, data from the Asia Pacific Cohort Studies Collaboration show that the association between BP and cardiovascular disease is stronger in Asian patients than in white patients from Australia and New Zealand.^{5,6} In terms of the characteristics of determinants of hypertension, Asians are more likely to have higher salt sensitivity and salt intake than Western populations. Genetically, Asians are likely to have factors relating to salt-sensitive gene polymorphism of the renin-angiotensin system (RAS).⁷ In fact, Japanese people are more likely to develop pre-hypertension and hypertension even with a small increase in body mass index, and the body mass index associated with pre-hypertension was lower than that in Western countries.⁸

A previous survey of senior doctors in Asia demonstrated a need for Asian guidelines that take into account Asian characteristics of cardiovascular disease.⁹ Here, we have developed a consensus document for more optimal management of hypertension in East Asian people, which takes into consideration ethnic-specific characteristics.

Asian Characteristics of Hypertension and Cardiovascular Disease

Consensus Statements

1. Stroke, especially hemorrhagic stroke, and nonischemic HF are common outcomes of hypertension-related cardiovascular disease in Asia.
2. The association between BP and cardiovascular disease is stronger in Asia than in the West.

3. Higher salt sensitivity, even with mild obesity and higher salt intake, is an Asian characteristic of hypertension.

Out-of-Office BP

Consensus Statements

1. Out-of-office BP measurement is recommended for the detection of white-coat hypertension.
2. It is important to accurately detect and manage masked (or masked uncontrolled) hypertension.
3. The initial focus should be on morning BP, then nocturnal BP, in Asian populations.

One of the most important roles of measuring out-of-office BP is to exclude white-coat hypertension. Many publications have reported findings of no increased cardiovascular risk with white-coat hypertension compared with true normotension.^{10,11} In addition, the NICE guidelines (National Institute for Clinical Excellence) have recommended the use of ambulatory BP monitoring (ABPM) for detecting white-coat hypertension.¹²

There is accumulating evidence that masked (or masked uncontrolled) hypertension, defined by normal office BP and elevated out-of-office BP, provides an equivalent risk of cardiovascular events as sustained hypertension, defined by both elevated office BP and out-of-office BP. Evidence from the ARTEMIS database (Ambulatory Blood Pressure Registry Telemonitoring of Hypertension and Cardiovascular Risk) showed that masked hypertension and masked uncontrolled hypertension were more likely to be diagnosed in Asia than in any other region.¹³ This emphasizes the importance of detecting and managing masked hypertension and masked uncontrolled hypertension in Asians, as part of hypertension treatment. Furthermore, morning BP should be the initial focus for the management of out-of-office BP in Asians,¹⁴ for the following reasons: (1) both morning BP surge detected by ABPM and morning BP measured at home were predictors of cardiovascular outcome independent of office BP level in Japanese hypertensive patients.^{15,16} (2) Morning BP surge in Asian populations may be higher than in Western populations even after adjustment for age, office BP, and 24-hour BP.¹⁷ (3) Morning BP

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measured at home provided superior model discrimination for stroke incidence compared with evening BP after adjustment for covariates, including office BP, in the Japanese general practice population.¹⁸ (4) The multicenter HOMED-BP study (Hypertension Objective Treatment Based on Measurement by Electrical Devices of BP) showed the feasibility of adjusting antihypertensive drug treatment based on morning BP measured at home in Japanese hypertensive patients.¹⁹

Moreover, even in the situation of controlled morning BP (<135/85 mmHg) at home, approximately one quarter of patients exhibited masked nocturnal hypertension ($\geq 120/70$ mmHg) detected by home BP monitoring (HBPM).²⁰ Some studies have suggested that nocturnal hypertension is associated with high sodium intake and salt sensitivity, which may seem to be specific characteristics of hypertension in Asian populations.²¹ International epidemiological data have demonstrated that increased nocturnal BP is a powerful predictor of cardiovascular outcomes, especially in treated hypertensive patients.^{22,23} In addition, isolated nocturnal hypertension may be more prevalent in Asians than Europeans.²³ Thus, the management of both morning and nocturnal BP is important in Asian populations.

Morning Hypertension

Consensus Statements

1. Morning BP surge, defined as the change from night-time sleeping to morning waking hours, or the mean level of BP readings within 1 to 2 hours of waking, confers cardiovascular risk independent of the 24-hour ambulatory BP.
2. Morning BP control can and should be improved with the use of long-acting antihypertensive drugs in appropriate, often full, dosages and in proper combinations.

Both ischemic stroke and coronary events often occur in the early morning hours.^{24,25} BP usually also peaks in the morning.²⁶ These parallel phenomena suggest 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 night-time sleeping to early morning waking hours, was associated with stroke, which was independent of the mean 24-hour ambulatory systolic BP and other cardiovascular risk factors.¹⁵ The finding was corroborated by a much larger study of patients in IDACO (International Database of ABP in Relation to Cardiovascular Outcome).²⁷

The risk of morning surge is mainly attributable to elevated morning BP.²⁸ The level of morning BP, which can be assessed by either ABPM or HBPM, is used to define morning hypertension. Uncontrolled morning hypertension is common even in patients with controlled clinic BP and is associated with an increased risk of cardiovascular events.²⁹

Morning BP may be particularly relevant for the management of hypertension in Asia. A recent study demonstrated that Japanese patients had a much larger morning BP surge and higher morning BP than European patients.¹⁷ This ethnic difference is not completely understood. Pathophysiological mechanisms, such as activation of the sympathetic nervous system³⁰ or increased dietary sodium intake, may be involved.³¹ However, inadequate use of antihypertensive drugs, such as

the use of short- or intermediate-acting drugs, underdosing of drugs, or underuse of combination antihypertensive therapy, might be the main cause of uncontrolled morning hypertension in Asia.³² In an expert recommendation published in 2014, the Council on Hypertension of the Chinese Society of Cardiology recommended the use of long-acting drugs in appropriate (often full) dosages, and in proper combinations, for morning BP control.³³ If not controlled by these therapeutic approaches, bedtime dosing of the antihypertensive drug can be considered. The discussion was recently expanded to Asia,¹⁴ and a consensus statement by an expert panel in Asia was published.³⁴

Vascular Aging

Consensus Statements

1. Vascular aging is expected to become the dominant phenotype of hypertension in many countries, especially in Asia.
2. Future randomized controlled trials are required to support that the diagnosis and monitoring of vascular aging in hypertension are best managed with the central BP strategy.

Vascular aging, characterized by increased arterial stiffness and wave reflection, is a major risk factor for the development of hypertension, especially in older subjects.³⁵ Vascular aging-related hypertension is characterized by a high pulse pressure at the central aorta.³⁵ Central pulse pressure is determined by both aortic stiffness and aortic root geometry.³⁵ A smaller aortic root diameter results in higher aortic characteristic impedance which may, in turn, increase the pulse pressure at the aortic root.³⁵⁻³⁷

Asian patients usually have a smaller aortic root diameter than white patients, partly because of a smaller body size.³⁸ However, Asian patients may have a larger aortic root diameter than white patients after adjustment for age, height, and weight.³⁹ Therefore, Asian populations, compared with Western populations, may have a particular predisposition to increased central aortic pulse pressure because of the relatively larger diameter and thinner media at the proximal aorta that modulates the interaction between ventricular ejection and arterial load.⁴⁰ Asians tend to be shorter than their Western counterparts, which contributes to increased augmentation of central pulse pressure from peripheral arterial wave reflections,⁴¹ an independent determinant of incident hypertension.⁴²

The Asian population is aging rapidly. Asians also generally have smaller stature and may have a greater wall stress and stiffness at the proximal aorta than white populations. Putting these 3 factors into the context of vascular aging suggests that vascular aging may have a greater significance on hypertension outcomes of Asian patients than Western patients.

Ideally, central BP should be monitored in aging Asian populations to accurately diagnose isolated central hypertension. However, there is ongoing controversy on whether the lack of consistently higher predictive value of central BP compared with brachial BP reflects a true pathophysiological issue or is potentially biased by an inadequate method used for central aortic BP measurement. There is a need for studies to compare central BP-guided therapeutic strategies with classic guideline-guided strategies for the prevention of cardiovascular events.

Elderly

Consensus Statements

1. The recommended BP target for the older hypertensive population is <140/90 mmHg.
2. However, when patients have an increased risk of hypotensive or renal side effects, or electrolyte abnormalities, a goal of <150/90 mmHg may be considered.
3. To achieve BP goal and to prevent stroke and HF in the older population, calcium channel blockers (CCBs), RAS blockers, and diuretics are recommended.

The definition of the older adult varies from >60 to >75 years in clinical trials and between the various hypertension management guidelines.^{43–47} Most guidelines agree that the very old should be defined as >80 years, and in these patients, drug treatment should be titrated cautiously to avert adverse responses and excessive BP lowering.

People of older age commonly have increased sympathetic nervous system activity, increased BP variability, impaired BP homeostasis such as orthostatic hypotension or postprandial hypotension, and increased salt sensitivity.^{48–50} Hypertension in older individuals is characterized by a predominance of isolated systolic hypertension, and systolic BP is the main determinant of risk and the target of drug therapy in this population. Multiple mechanisms, including stiffening of the large arteries, endothelial dysfunction, cardiac remodeling, autonomic dysregulation, and renal aspects, contribute to the high prevalence of hypertension in older patients and increases cardiovascular morbidity and mortality. Older hypertensive adults experience cardiovascular events at a rate of 2× to 3× higher than younger patients with the same levels of BP.⁵¹

Therefore, controlling BP to target in the older hypertensive population is important. This is recommended based on the strength of data which have shown that target BP in older patients should be at least <140/90 mmHg.^{52,53} The intensive treatment of SPRINT (Systolic Blood Pressure Intervention Trial) patients aged ≥75 years, targeting a systolic BP of <120 mmHg as compared with <140 mmHg, achieved a significant 34% reduction in fatal and nonfatal cardiovascular events and a 33% reduction in all-cause mortality.^{54,55} Meanwhile, the HYVET study (Hypertension in the Very Elderly Trial) suggested that a goal of <150/90 mmHg was reasonable in patients aged ≥80 years.⁵⁶

If the systolic BP target for older patients remains at <150 mmHg, the available evidence indicates that, compared with a systolic BP of <140 mmHg, the relative risk of stroke would be increased by 30% to 40%. Nevertheless, a systolic BP target of <150 mmHg may be appropriate for older patients who have an increased risk of hypotensive or renal side effects or electrolyte abnormalities. In the 2017 American (American College of Cardiology/American Heart Association) guidelines for the prevention, detection, evaluation, and management of high BP in adults, it was generally recommended that initiation of antihypertensive therapy should be undertaken cautiously in older people, orthostatic hypotension, and falls should be monitored.⁵⁷

In clinical practice, a staged approach for BP goal attainment may be recommended in older hypertensive patients. The first systolic BP target would be <150 mmHg; then, if tolerated and achievable, <140 mmHg; then, ideally, if tolerated and achievable, <130 mmHg.⁵⁸ This final goal is in line

with the 2017 American College of Cardiology/American Heart Association guideline, which recommended a systolic BP treatment goal of <130 mmHg for noninstitutionalized ambulatory community-dwelling adults (≥65 years) with an average systolic BP of ≥130 mmHg.⁵⁷

Because stroke is the most important cause of cardiovascular mortality in older Asian populations,⁵⁹ more thorough BP regulation is needed in this group. These populations are also more prone to a higher incidence of side effects and an increased risk of BP variability than the general population, and, thus, measuring home BP in older subjects, in addition to usual clinic BP, is recommended where available. The pathophysiologic concept is important in the treatment of hypertension in older adults: in people with vascular aging and arterial stiffness, such as the elderly, BP is highly volume dependent; thus, these patients typically respond well to a low-dose diuretic or calcium antagonist.⁶⁰ Most older patients require multiple antihypertensive agents to control BP. The angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be considered for patients with diabetes mellitus and if there are compelling indications, such as chronic systolic HF, post-myocardial infarction, or chronic kidney disease (CKD).⁶¹

Type 2 Diabetes Mellitus

Consensus Statement

1. In Asians, a treatment goal of BP <130/80 mmHg can be considered in hypertensive subjects with type 2 diabetes mellitus.

In the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), strict BP control, defined as a target systolic BP of <120 mmHg, failed to show benefit over usual BP control, defined as a target systolic BP of <140 mmHg.⁶² However, there was a significant 37% reduction in nonfatal stroke and 41% reduction in total stroke in the strict BP-lowering group.⁶² In a recent meta-analysis of 49 clinical trials of antihypertensive treatment involving 73 738 type 2 diabetic subjects, there was no evidence for benefit in reducing systolic BP to <130 mmHg except for stroke reduction.⁶³ In Asians, the predominant cardiovascular events associated with hypertension are strokes, whereas in whites, ischemic heart disease is the most frequent cardiovascular outcome.⁶⁴ Thus, the target systolic BP of 130 mmHg can be considered in Asian hypertensive subjects with type 2 diabetes mellitus.⁶⁵

Chronic Kidney Disease

Consensus Statements

1. The prevalence of CKD is higher in hypertensive patients than in the general population, and the prevalence of CKD associated with hypertension in Asian populations is increasing.
2. Hypertensive patients require more intensive out-of-office BP evaluation and comprehensive cardiovascular evaluation in the presence of CKD.
3. Intensive BP control is required for patients with CKD to preserve renal function and to prevent cardiovascular events.

In Asia, the prevalence of CKD is much higher in hypertensive patients than in the overall population.^{66–69} According to a Chinese national survey, the prevalence of CKD was 18.9%

in hypertensive patients (n=16691) and 10.8% in the overall population (n=47204).⁶⁶ Moreover, the prevalence of concomitant CKD and hypertension is increasing in Asia. Surveys performed in Japan in 1974, 1988, and 2002 showed that the prevalence of CKD increased in both treated (18.8%, 23.8%, and 36.1%, respectively) and untreated (16.6%, 17.5%, and 28.8%, respectively) hypertensive patients.⁷⁰

In the presence of CKD, hypertensive patients often require more intensive BP measurement by ABPM and HBPM because they may have greater BP variability and higher nighttime BP.^{71–74} To accurately evaluate BP and detect treatment-naïve or uncontrolled nocturnal hypertension in patients with CKD, ABPM must be performed.^{75,76} HBPM might be helpful in the screening of nocturnal hypertension.² It is, therefore, imperative to perform more out-of-office BP measurements in Asian patients with CKD.

Most current hypertension and CKD guidelines recommend more intensive BP lowering in hypertensive patients with CKD.^{43,77–85} In Asians, the major complication of hypertension is stroke; thus, the BP target might be different to that for Western populations although this needs to be further investigated. Intensive BP control to 130/80 mmHg is often required to prevent CKD progression and stroke.

Atrial Fibrillation

Consensus Statement

1. In hypertensive subjects with atrial fibrillation (AF) undergoing anticoagulation, a target systolic BP of <130 mmHg can be considered to minimize the risk of hemorrhagic stroke.

The presence of hypertension significantly increases the risk of stroke and excess bleeding in patients with AF; as such, strict BP control and anticoagulation are needed to minimize cardiovascular risk.^{86–88} Hypertensive patients with AF are unique to other hypertensive subjects in that most patients receive anticoagulation to minimize the risk of embolic complications. Therefore, the target BP in this subset of patients may be different to that of other hypertensive patients. Post hoc analyses or analyses from registry studies have suggested that, in patients receiving antiplatelet or anticoagulation therapy, a lower BP target may be needed to minimize the bleeding risk. In the post hoc analysis of PROGRESS (Perindopril Protection Against Recurrent Stroke Study), in patients with a history of cerebrovascular disease (with or without AF), active treatment with perindopril, with or without indapamide, in patients already receiving antithrombotic therapy resulted in a reduction of intracranial bleeding by 46%, with the lowest risk of bleeding being associated with a median systolic BP of 113 mmHg.⁸⁹ Also, in the J-Rhythm registry of 7406 patients with nonvalvular AF followed for 2 years, a systolic BP \geq 136 mmHg was an independent risk factor for thromboembolism and major hemorrhage.⁹⁰ Therefore, a target BP of 130 mmHg can be considered for minimizing the risk of intracranial hemorrhage in hypertensive subjects with AF who are also receiving anticoagulation therapy. This has added importance for Asian patients, who are more prone to stroke and bleeding complications arising from anticoagulation treatment.

Secondary Prevention of Stroke

Consensus Statements

1. Stroke is among the leading causes of death and represents a large disease burden in East Asian countries, and it may be related to high sodium intake.
2. The relationship between BP reduction and the risk of recurrent stroke is less pronounced than in primary prevention, but BP reduction still substantially benefits patients who survive stroke events.
3. Evidence from randomized, controlled trials supports the use of diuretic-based treatment, especially when combined with an angiotensin-converting enzyme inhibitor, for the secondary prevention of stroke and vascular events in poststroke patients.
4. High BP and increased BP variability are associated with worse outcomes in patients after stroke. CCBs, with their superior effectiveness for the control of BP variability, can be considered in the management of poststroke hypertension.

In 2014, the mortality attributed to cerebrovascular diseases ranked fourth in Japan, third in mainland China, and third in Taiwan, among all causes of death. In addition, Asian countries had the highest age- and sex-adjusted stroke mortality rate.⁹¹ High sodium intake increases BP,⁹² a risk factor for cardiovascular disease; thus, the high stroke mortality rate in Asia may be closely associated with dietary patterns of sodium intake in this region.^{92,93} Reduction in sodium intake can effectively reduce BP in a linear fashion, in which every 2.3 g/d sodium reduction can lead to a 3.82-mmHg decrease in systolic BP.⁹² For stroke survivors, the relationship between BP reduction and the risk of recurrent stroke⁹⁴ was less pronounced than that in primary prevention studies,⁹⁵ but adequate BP reduction can still substantially benefit these patients.^{94,96}

Evidence from randomized, controlled trials supports the use of diuretic-based treatment, especially when combined with an angiotensin-converting enzyme inhibitor, for the secondary prevention of recurrent stroke and vascular events.^{94,96,97} This finding implies that the adverse effect of high sodium intake may be reduced using a diuretic-based strategy. In addition, high BP and increased BP variability are associated with worse outcomes in patients after stroke.^{98–101} A systematic review and meta-analysis investigating the effects of antihypertensive drug class on BP variability showed that interindividual variation in systolic BP, of which 50% resulted from within-individual visit-to-visit systolic BP variability, was most reduced by CCBs.¹⁰² As such, CCBs can be considered useful for managing poststroke hypertension.¹⁰²

Antihypertensive Treatment

Consensus Statements

1. Strict BP control for the 24-hour period is important, especially in Asia.
2. A home BP-guided approach is the first practical step for strict BP control on the individual level.
3. Use of a long-acting and potent CCB and RAS inhibitor, with or without a diuretic, to control BP is preferable.

Strict BP control for the 24-hour period is important, especially in Asia.¹ SPRINT clearly demonstrated the benefit of strict BP control in high-risk or older hypertensive patients.¹⁰³ The

benefits of BP lowering may be even greater in Asian patients than in Western populations because the effect of BP lowering on stroke and HF is greater than on coronary artery disease.⁵³

A home BP-guided approach, especially targeting morning hypertension, is the first step for 24-hour BP control in the individual.^{14,81,104} For HBPM, a systolic BP target of 125 mmHg in the morning is probably ideal.¹⁰⁵ Based on the HONEST study (Home Blood Pressure Measurement With Olmesartan Naive Patients to Establish Standard Target Blood Pressure)^{16,29} and HOMED-BP study,¹⁹ the achieved home BP during anti-hypertensive treatment was a better predictor than office BP, suggesting that the lower the home BP, the better the cardiovascular prognosis until the systolic BP of <125 mmHg. However, an adequately powered randomized controlled clinical trial is needed to prove this. Use of a long-acting and potent CCB and RAS inhibitor, with or without a diuretic, is preferable when considering the characteristics of Asian hypertensive patients, such as higher salt intake and higher salt sensitivity.^{1,14,103} A long-acting CCB is effective for lowering office, home morning, and 24-hour ambulatory BP, reducing exaggerated BP variability independently of salt intake and salt sensitivity.^{106–108} Angiotensin receptor blockers are also effective for lowering office BP and home morning BP when used as monotherapy or in combination with a CCB or diuretic.^{109–111} Even within the same class, CCBs and RAS inhibitors vary in their potential to lower 24-hour BP. These differences may be enhanced in the salt-sensitive Asian population that typically also has a higher salt intake. A low-dose diuretic on top of a RAS inhibitor plus CCB^{110,112} is an effective strategy to reduce BP.

β -Blockers may be useful in special populations, such as in young hypertensive patients with increased heart rate or patients with coronary artery disease, AF, or HF.⁸¹ Renal denervation may be effective for treating uncontrolled nocturnal or morning hypertension,¹¹³ especially in Asian patients,¹¹⁴ because Asian patients with drug-resistant hypertension have higher morning and nocturnal BP variability than Western patients, even when office BP is comparable.¹¹⁵

Conclusion

Hypertension management that takes Asian characteristics into account can achieve more effective prevention of cardiovascular disease and target-organ damage in Asian countries. Because there is generally less evidence in Asian patients, however, more clinical studies to clarify Asian-specific characteristics for the management of hypertension are needed.

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