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REVIEW PAPER

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Isolated systolic hypertension in Asia

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Abstract

Isolated systolic hypertension (ISH) is the most common type of essential hypertension in the elderly and young adults. With rapid industrialization and population aging, the prevalence of ISH in Asia will rise substantially. Asian populations have distinct epidemiological features, risk factors and are especially vulnerable to ISH. There is a pressing need for Asian countries to formulate their unique strategies for control of ISH. In this review, we focus on the (1) epidemiology and pathophysiology, (2) risk factors and impact on outcomes, and (3) treatment goal and strategy for ISH in Asia.

1 | INTRODUCTION

Hypertension is the most common modifiable risk factor for cardiovascular disease and the leading cause of morbidity and mortality across the globe.[1] Isolated systolic hypertension (ISH) is defined as systolic blood pressure (SBP) ≥ 130 mmHg and diastolic blood pressure (DBP) < 80 mmHg in the American guidelines and SBP ≥ 140 mmHg and DBP < 90 mmHg in the European and most hypertension guidelines.[2,3] ISH is the predominant form of hypertension in the elderly but is also common in younger individuals as well. For young adults and adolescents, ISH is the most common form of hypertension.[4–6] As humans age, SBP continues a linear rise but DBP starts to fall after mid-50 years of age.[4,7] This phenomenon contributes to the high prevalence of ISH in the elderly

and the increasing pulse pressure with increasing age. The risk of cardiovascular disease increases substantially with uncontrolled ISH regardless of age.[5,8,9] Many studies have demonstrated the benefit of controlling ISH even in the most elderly population.[10–14] With the rapid trend of westernized lifestyle and population aging occurring almost all countries across Asia, the burden of ISH will no doubt rise. Thus, it is an inescapable duty for Asian physicians to recognize and manage ISH properly. In this article, we will review the (1) epidemiology and pathophysiology, (2) risk factors and impact on outcomes, and (3) treatment goal and strategy for ISH in Asia.

2 | EPIDEMIOLOGY

Asia is a vast and diverse continent both in geographical terms and in socioeconomic terms. The prevalence of ISH varies dramatically across Asia.[15–21] Generally, ISH is less prevalent in the rural area but is much more common in the developed regions where the prevalence seems to rival that of western countries.[22–25] However, with the rapid spreading of industrialization and westernized lifestyle to rural Asia, the difference between urban and rural areas is becoming insignificant.[26] Over the past decades, there has been a sharp rise in the prevalence of hypertension in the middle-income Asian countries as their population was aging and rapid industrialization took place, while the blood pressure levels seemed to have decreased in high-income regions under improved healthcare systems.[27–29] Similar to western cohorts, the proportion of ISH among those diagnosed with hypertension rises consistently with increasing age in Asian cohorts. However, the proportion of ISH in Asian populations is significantly lower than that of western cohorts in all age groups. This difference is consistent in various Asian countries.[18,25,30,31] This discrepancy may partly be attributed by the low recognition and treatment rate of systolic-diastolic hypertension (SDH) in Asia.[27,32–34] The awareness and treatment rates of hypertension varied greatly among Asian countries, with high-income regions such as Japan and Korean having the best performance while countries with vast developing regions such as China and India having the worst control rates.[35–38] However, even in the most affluent regions of Asia, hypertension awareness and control rates are still lower than that of north American and west European countries.[39] Nevertheless, Asian countries should expect to have a surge of ISH patients in the near future due to improved control of SDH and population aging. Understanding the epidemiological and hemodynamic features of Asian ISH may help formulate effective control strategies.

3 | PATHOPHYSIOLOGY

The major pathophysiology of ISH is a reduced compliance of the large elastic arteries, in contrast to the long-term vasoconstriction of arterioles causing SDH.[40] The hemodynamics of ISH patients are characterized by a marked increase in arterial stiffness and aortic characteristic impedance, a moderate increase in wave reflections, a marked increase in central SBP and central pulse pressure and a mild increase in total peripheral resistance.[41–44] However, the role of wave reflections in the pathogenesis of ISH may be considered unimportant because central blood pressure is predominantly driven by forward traveling waves,[45] and peripherally reflected waves do not materially change arrival timing with age,[46] may be attenuated by wave entrapment in the aorta due to re-reflection of the reflected waves,[47] and thus may have an extremely minor influence on central blood pressure. ISH is often classified into the burned-out type, which is a result of aging-related decrease in DBP in the established SDH, and the de novo type caused by a novel increase of SBP.[40] In the Framingham study population with ISH, as many as 40% did not go through a period of SDH.[48] The predominant cause of ISH is vascular aging-associated large artery stiffening while for young adults, ISH is often associated with several secondary causes that include insulin resistance, osteoporosis with vascular calcifications, accelerated atherosclerosis from chronic kidney disease, peripheral vascular disease, altered elastin formation during intrauterine fetal growth retardation, thyrotoxicosis, and the repaired coarctation of the aorta.[49,50] The hemodynamic features of ISH give rise to a myriad of downstream effects including endothelial dysfunction, increased inflammatory cytokines levels, end-organ hypoperfusion, and activation of the renin angiotensin-aldosterone system and sympathetic tone.[51] These downstream effects in turn further enhance arterial stiffness through reduced vasodilatation, accelerated atherosclerosis, and left ventricle remodeling,[51–53] forming a downward spiral toward worse ISH and higher cardiovascular risk if ISH remains uncontrolled. Asian are generally shorter and thinner than their western counterparts. The aortic roots of Asian people are relatively larger after adjustment for age, height, and weight.[54] This difference may contribute 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.[55] The shorter stature of Asian people may further amplify the augmentation of central pulse pressure from peripheral arterial wave reflections.[56] These factors in combination may increase the susceptibility of Asian to develop hypertension, especially in late life when aortic root cannot be further dilated to buffer the rise of central aortic SBP.[57]

4 | RISK FACTORS FOR ISH

Isolated systolic hypertension is attributed by a complex mix of modifiable and hereditary risk factors on top of the underlying pathophysiologic change of aging.[51] Previous western studies have demonstrated that advancing age, female sex, all components of the blood pressure, and overweight are the main determinants of ISH.[58,59] For young individuals, male sex, obesity, lower education level, and smoking are associated with ISH.[60] However, the determinants of ISH are quite varied in Asian studies. In a previous national survey in Korea, ISH was independently associated with advanced age, body mass index (BMI), triglycerides levels, monthly

income, and alcohol intake.[18] In this study enrolling middle age and older adults, ISH was more frequently found in male patients.[18] In a cross-sectional study conducted in rural China, ISH was positively correlated with age, female sex, smoking, alcohol intake, BMI, and salt intake.[51] Blood pressure in Asian people is more susceptible to the effect of body weight gain. As demonstrated in several Japanese studies, a BMI of 25 kg/m^2 in Asians has a similar impact on the development of pre-hypertension and hypertension as a BMI of 30 kg/m^2 in Western individuals.[61,62] In addition, Asians are genetically more susceptible to salt ingestion-induced blood pressure elevation, while at the same time, Asian diets contain more sodium than western diets.[63] The combined effect of greater salt sensitivity and salt intake exerts a greater increase in blood pressure attributable to diets in Asians.

Other cross-sectional studies in Taiwan and rural India showed largely similar results but sex was not found to be a significant determinant for ISH.[15,26] The relationship between sex and risk of ISH may be age dependent. As seen in a large cohort of younger population, ISH patients were predominately men.[5] However, the prevalence of ISH in women quickly catches up after they pass 50 years old.[15,64] This difference can be explained by the synergistic antihypertensive effect of progesterone and estrogen and the lack of the pro-hypertensive effect of androgen.[65] The observed blood pressure-lowering effect during pregnancy or during hormone supplement may further support this association.[66]

5 | IMPACT OF ISH ON ASIAN POPULATIONS

The impact of individual components of blood pressure has been investigated in the past decade. In a large retrospective cohort study of over 1 million patients, both systolic hypertension and diastolic hypertension have been demonstrated to be independent predictors for the compositive outcome of myocardial infarction, ischemic stroke, and hemorrhagic stroke (hazard ratio:1.18, 95% confidence interval [CI], 1.17–1.18; and 1.06, 95% CI, 1.06–1.07, respectively).[67] This study, like many other studies done before, showed that SBP had a greater effect on outcomes than DBP.[64] On the other hand, pulse pressure has been established as a strong predictor for cardiovascular disease as compared with SBP and DBP.[68] These newer studies have validated the lower threshold of 130/80 mmHg for defining hypertension in the American hypertension guidelines.[69] These evidence, alone with other studies, suggest that ISH is a singular risk factor for cardiovascular disease in the elderly and probably the young population alike.[18,70] However, the effect of hypertension on cardiovascular health is by no means equal among different populations. The Asian people, as compared with their western counterpart, are particularly vulnerable to the effect of systolic hypertension. In contrast to western countries, strokes, especially hemorrhagic stroke, are more common complications of hypertension.[71,72] The Asia Pacific Cohort Studies Collaboration (APCSC) study has demonstrated a significantly stronger association between overall cardiovascular risk and hypertension for Asian patients compared with participants from Australia and New Zealand (hazard ratios: 4.5 vs. 2.1; $p < .001$).[73] 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 Australian/New Zealander who are predominantly Caucasians.[74] In western populations, there was a linear association between SBP and cardiovascular outcomes while a J-curved association was observed for DBP.[67,75] The harm associated with an increase in SBP was directly and significantly related to adverse cardiovascular outcomes without any evidence of a threshold effect down to at least 115/75 mmHg.[76] On the other hand, the Asia Pacific Cohort Studies Collaboration cohort study of over 30 000 patients have shown a clear association between adverse CV outcomes and all subtypes of hypertension, including ISH and pre-hypertension (SBP/DBP ≥ 120/80 mmHg).[73] Other Asian cohorts have also confirmed the adverse impact of SBP on CV outcomes.[77] Thus, the available evidence supports that Asians are particularly vulnerable to the adverse effect of ISH.

6 | TREATMENT TARGET OF ISH IN ASIAN POPULATIONS

The benefits of treating ISH have been established by many previous randomized control trials.[10–13] Fortunately, some of the pivotal trials have been conducted in Asia. The Systolic Hypertension in China trial (Sys-China) was a large prospective randomized controlled trial of 2394 participants with ISH.[78] After a median follow-up of 3 years, those in the active control arm had a significantly lower rate of stroke and cardiovascular events. The Hypertension in the Very Elderly Trial a trial aimed at evaluating the effect of treating SBP over 160 mmHg in the very elderly population, most of whom had ISH.[13] The trial was not done exclusively in Asia but 1526 of the 3845 patients were enrolled in China. The results showed a markedly reduced rate of death from any cause and cardiovascular death in the active treatment group. The VALISH study (Valsartan in Elderly Isolated Systolic Hypertension) recruited 3035 elderly patients in Japan.[79] In this trial, the authors showed that achieving a more intensive blood pressure goal (target SBP < 140 mmHg) was not associated with a significantly lower risk. However, targeting SBP < 140 mmHg was nonetheless deemed safe in the elderly patients over 70 years old. The Felodipine Event Reduction (FEVER) Study was a randomized trial of 9711 Chinese patients, aged 50–70 years, whose blood pressure was in the range of SBP 140–180 mmHg or DBP 90–100 mmHg.[80] The subjects were randomized to receive the addition of felodipine on top of the baseline hydrochlorothiazide therapy. After a total of 31 842 patient-years of follow-up, the risk for stroke and cardiovascular events were significant lower in the add-on group. These trials laid a solid foundation for the treatment of ISH. However, the target of ISH treatment and the timing to begin pharmacotherapy are more ambiguous. There has been some fierce debate regarding the target of blood pressure control. The SPIRINT trial

had undoubtedly shifted the balance toward more rigorous control.[81] The SPIRNT-SENIOR sub-analysis clearly demonstrated a similar benefit for aggressive hypertension control in the elderly patients.[82] However, whether these results can be applied to Asian populations is still unknown. In a subsequent analysis of the VALISH study, the on-treatment SBP between 130 and 144 mmHg was associated with the lowest risk while SBP above or below the range was associated with higher risks for cardiovascular disease and all-cause mortality (hazard ratios and 95% CI, 2.08 [1.12–3.83] and 2.29 [1.44–3.62], respectively).[83] The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) study which enrolled patients aged 65–85 years receiving calcium channel blocker-based therapy showed a similar result that strict SBP control (<140 mmHg) achieved a significantly lower SBP level compared with the mild control group (SBP target of 140–160 mm Hg) but was not associated with a lower incidence of combined cardiovascular disease and renal failure.[84] On the other hand, a large Chinese randomized trial by Wei and coworkers demonstrated that intensive antihypertensive treatment with achieved blood pressure ≤140/90 mmHg, as compared with standard treatment with achieved blood pressure ≤150/90 mmHg decreased total and cardiovascular mortality by 41.7% and 50.3%, respectively, and reduced fatal/nonfatal stroke by 42.0% and heart failure death by 62.7%.[85] These results were summarized in a recent meta-analysis, albeit many western studies were included in the analysis process. The author concluded that intensive blood pressure control (SBP < 140 mmHg) decreased major adverse cardiovascular events, including cardiovascular mortality and heart failure.[70] Thus, strict treatment of ISH in Asian populations is expected to provide more benefits than harms. Importantly, physicians need to be mindful of the pseudo-hypertension and spurious hypertension before starting treatment for ISH. The former is usually found in elders with non-compressible brachial artery while the latter is the results of exaggerated pressure amplification in healthy, athletically active young patients with slow heart rates and highly elastic central arteries.[86] These patients would have measurements compatible with ISH using regular brachial sphygmomanometer but would not benefit from antihypertensive treatment.

7 | TREATMENT STRATEGY FOR ISH IN ASIA

Treatment of ISH can be achieved by the combination of lifestyle modification and pharmacological therapy. Lifestyle modification measures such as stress management, Dietary Approaches to Stop Hypertension (DASH) diet, exercise have been established in the western populations.[87–89] In a sub-study of the syst-China study, the potential benefits of antihypertensive treatment and smoking cessation were approximately similar.[90] A well performed trial by Yang and coworkers have demonstrated that SBP of ISH patients was significantly decreased after 6 months of low salt diet.[91] Thus, the lifestyle modification for ISH patients may include DASH diet, salt reduction, stress reduction, exercise, and weight loss.

Pharmacological therapy is essential for the treatment of ISH. Thiazide-like diuretics (chlorthalidone and indapamide) and dihydropyridine calcium channel blockers (CCB) are effective in reducing the risk of stroke and of other morbid events.[10,13,78] Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) are less efficacious in ISH.[51] However, ACEi/ARBs are preferred if the patient has compelling indications such as heart failure with reduced ejection fraction, previous infarction, diabetes, or chronic kidney disease.[92] Beta-blockers do not offer sufficient clinical benefit to justify their use for ISH populations.[93] Beta-blockers preferentially decrease the peripheral blood pressure while leave the central (aortic) blood pressure and aortic impedance elevated.[94] This effect is further compounded by the reduction in heart rate.[95]

In summary, CCBs and/or thiazide-like diuretics are the preferred first-line agents for management of ISH, and ACEi/ARBs and beta-blockers can be used if the patient has compelling indications. If blood pressure remains uncontrolled with a combination of two first-line agents, or there are adverse effects, other classes of drugs may be added.

8 | GUIDELINES FOR ISH IN ASIA

Despite the undeniable importance of ISH in the Asian populations, Asian society guidelines have provided limited recommendations for the management of ISH. The definition of ISH in the Chinese, Japanese, Korean, and Taiwanese hypertension guidelines used to follow that of the European and US guidelines.[40,96–99] However, the definition of ISH remains SBP ≥ 140 mmHg and DBP < 90 mmHg in the Asia pacific region, despite the US guidelines lowered the thresholds after the SPIRINT trial. Recommendations for the treatment of ISH are referred to the elderly hypertension section in the Asian hypertension guidelines. The treatment goal of elderly hypertension has undergone significant changes after the SPRINT trial. The 2017 guidelines of Taiwan recommend that the target blood pressure in patients over 75 years of age is SBP < 120 mmHg if automated office blood pressure (AOBP) is used and SBP < 140 mmHg if traditional blood pressure measurement is used. The target blood pressure in patients older than 65 years in the Korean guidelines is SBP < 140 mmHg/DBP < 90 mmHg unless the patients fit the SPRINT eligible criteria (over age 50 years with coronary artery disease, peripheral arterial disease, and aortic disease, heart failure, or left ventricular hypertrophy), for whom a target blood pressure of 130/80 mmHg can be considered.[96] The Japanese guidelines recommend a blood pressure target in patients older than 75 years of age to be <140/90 mmHg.[40] The Chinese guidelines recommend that blood pressure target in patients more than 65 years is <150/90 mmHg, and the final target level of blood pressure control is <140/90 mmHg.[98] Both the Taiwanese and Japanese guidelines emphasize the importance of controlling SBP even if DBP is low.

However, this recommendation is not mentioned in the Korea and Chinese guidelines.

In summary, ISH in the elderly should be treated to a target of <140/90 mmHg in office and may be treated to a target of SBP < 120 mmHg if AOBP is used, especially for the SPRINT eligible patients. As the burden of ISH is expected to increase in Asia, there is a pressing need for societies to make specific recommendations for ISH.

9 | CONCLUSIONS

Isolated systolic hypertension is the predominant form of hypertension in the elderly, and its prevalence is expected to increase in many parts of Asia. The prevalence and risk factors for ISH are quite varied among different regions in Asia. ISH carries a significant impact on cardiovascular outcomes and is especially dangerous to Asians. However, its awareness, treatment, and control rates are far from optimal. The current Asian guidelines have not provided a clear guidance for the management of ISH. Future research is required to fill the gap in the understanding of the risk factors, hemodynamic characteristics, and treatment response of ISH in Asia.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Tsung-Ying Tsai reviewed literature and wrote the first draft of the paper under the instruction from Chen-Huan Chen. Hao-Min Cheng, Shao-Yuan Chuang, Yook-Chin Chia, Arieska Ann Soenarta, Huynh Van Minh, Saulat Siddique, Yuda Turana, Jam Chin Tay, and Kazuomi Kario critically reviewed the draft and provided comments for revision.

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