

## REVIEW

# Systolic hypertension: an increasing clinical challenge in Asia

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Systolic hypertension, the predominant form of hypertension in patients aged over 50–60 years, is a growing health issue as the Asian population ages. Elevated systolic blood pressure is mainly caused by arterial stiffening, resulting from age-related vascular changes. Elevated systolic pressure increases the risk of cardiovascular disease, mortality and renal function decline, and this risk may increase at lower systolic pressure levels in Asian than Western subjects. Hence, effective systolic pressure lowering is particularly important in Asians yet blood pressure control remains inadequate despite the availability of numerous antihypertensive medications. Reasons for poor blood pressure control include low awareness of hypertension among health-care professionals and patients, under-treatment, and tolerability problems with antihypertensive drugs. Current antihypertensive treatments also lack effects on the underlying vascular pathology of systolic hypertension, so novel drugs that address the pathophysiology of arterial stiffening are needed for optimal management of systolic hypertension and its cardiovascular complications.

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## INTRODUCTION

Hypertension is a global public health issue and a major cause of morbidity and mortality, reported to be responsible for almost 13% of all deaths and 3.7% of total disability-adjusted life-years.<sup>1</sup> The worldwide prevalence of hypertension in individuals aged  $\geq 25$  years was estimated to be approximately 40% in 2008.<sup>1</sup> This is equivalent to almost one billion people, and is predicted to increase to over 1.5 billion people by 2025.<sup>1,2</sup> The prevalence of hypertension is similarly high across different Asian countries, ranging from 30% in the Republic of Korea to 47% in Mongolia.<sup>3</sup> Prevalence also increases with advancing age.<sup>4–8</sup> For example, the prevalence in Chinese patients is 39% overall,<sup>3</sup> 59.4% in patients aged  $\geq 60$  years<sup>4</sup> and 72.8% in those aged  $\geq 75$  years.<sup>6</sup> With a rapidly aging population, the prevalence of hypertension and related cardiovascular morbidity in Asian patients continues to rise, placing a substantial and escalating social and economic burden on this region.<sup>8–10</sup>

The risk of cardiovascular disease (for example, stroke and peripheral arterial disease) in the Asian population is significantly increased with uncontrolled blood pressure (BP) and differs from that seen in patients from Western regions.<sup>11–14</sup> In an analysis of data from the Asia Pacific Cohort Studies Collaboration, Asian patients with hypertension had a 4.5-fold higher risk of cardiovascular disease *vs.* those with normal BP.<sup>15</sup> Furthermore, the relationship between overall

cardiovascular risk and hypertension was shown to be significantly stronger for Asian patients compared with participants from Australia and New Zealand (hazard ratios: 4.5 *vs.* 2.1;  $P < 0.001$ ).<sup>15</sup> Elevated systolic BP (SBP) in particular is a key risk factor for cardiovascular disease in both Asian and Western populations.<sup>16,17</sup> Data from the Asia Pacific Cohort Studies Collaboration have shown that the risk of coronary heart disease (CHD) and stroke increases linearly as levels of SBP increase.<sup>18</sup> In particular, the linear relationship between SBP and stroke risk is markedly more pronounced in Asian patients than in Caucasian populations (Figure 1).<sup>18</sup> This may be attributable to the higher proportion of hemorrhagic *vs.* ischemic strokes reported in the Asian population, as hemorrhagic strokes correlate more closely with BP than do ischemic strokes. Overall, stroke is generally more common than CHD in Asians, whereas the converse is seen in Western subjects.<sup>19,20</sup> Evidence suggests that in addition to the risks posed by elevated SBP, visit-to-visit variability in SBP may also represent a predictor of cardiovascular disease, including stroke.<sup>21,22</sup>

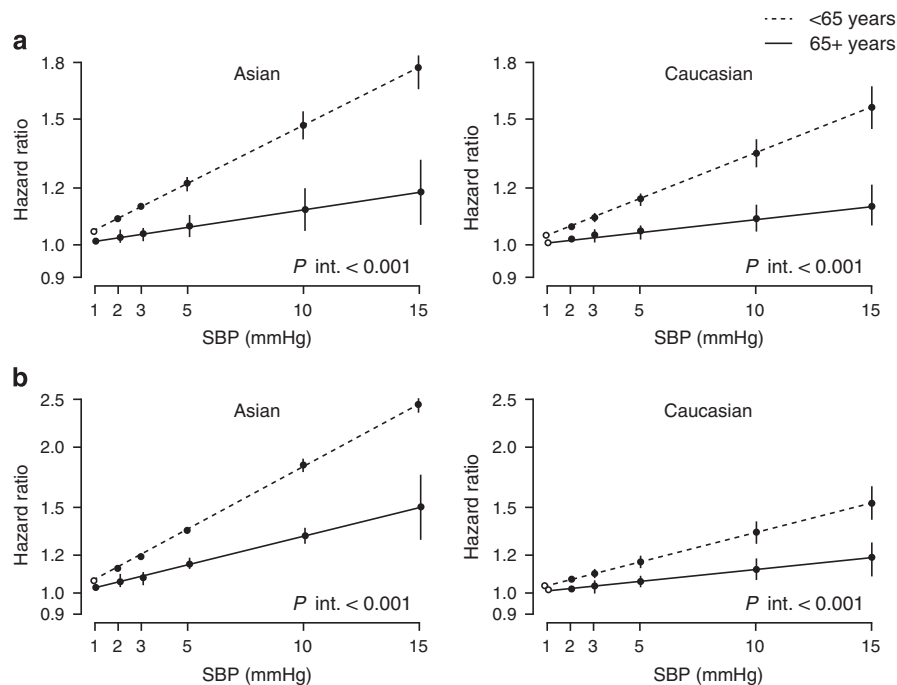
Here we review the increasing burden of hypertension, focusing on systolic hypertension, the key risk factors for its development and the impact that raised SBP has on cardiovascular disease in Asian patients. We also discuss the challenges of managing hypertension and the current status of BP control, highlighting the unmet clinical needs that are apparent in Asian regions.

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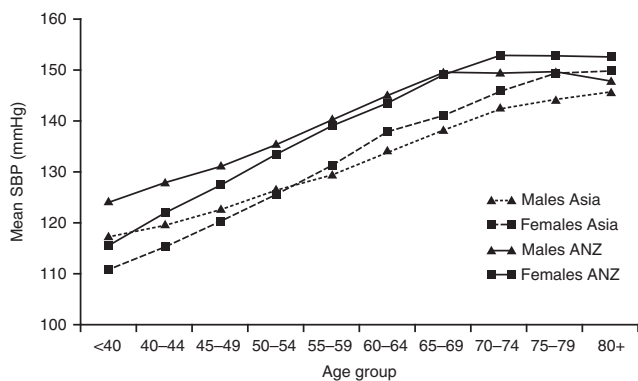
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**Figure 1** The higher risk of (a) fatal and nonfatal coronary heart disease and (b) stroke, associated with higher systolic blood pressure levels by age and region in the Asia Pacific Cohort Studies Collaboration. SBP, systolic blood pressure. Reprinted with permission from Perkovic *et al.*<sup>18</sup>



**Figure 2** Systolic blood pressure increases with age in Asian patients. ANZ, Australia and New Zealand; SBP, systolic blood pressure. Reprinted with permission from Asia Pacific Cohort Studies Collaboration.<sup>25</sup>

## EPIDEMIOLOGY OF SYSTOLIC HYPERTENSION IN ASIAN POPULATIONS

Hypertension is generally defined as SBP of  $\geq 140$  mm Hg and/or diastolic BP (DBP) of  $\geq 90$  mm Hg. Systolic hypertension can occur with DBP  $\geq 90$  mm Hg (systolic/diastolic hypertension) or with normal DBP (isolated systolic hypertension), and is the predominant form of hypertension in patients  $\geq 60$  years old.<sup>17</sup> SBP increases after the age of 50–60 years, whereas DBP tends to decrease because of age-related changes in arterial vasculature, leading to a widening of pulse pressure (the difference between SBP and DBP). This suggests that SBP is the more important of the two BP components in the aging population.<sup>17,23,24</sup> A meta-analysis of 41 cohort studies conducted by the Asia Pacific Cohort Studies Collaboration clearly illustrated the progressive increase in SBP with advancing age in Asian patients (Figure 2).<sup>25</sup> This has been corroborated by numerous other studies conducted across the region.<sup>26–28</sup> Furthermore, a decrease in the

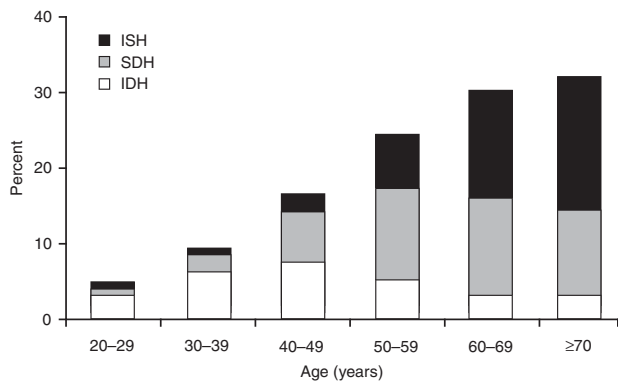
prevalence of diastolic hypertension with age (presumably reflecting age-related changes in DBP) has also been reported in clinical studies in Asians (Figure 3).<sup>28,29</sup>

As would be expected, the prevalence of isolated systolic hypertension in Asians, which is reported to be 3.9–12.5%, is age dependent.<sup>27–31</sup> Several studies in Asian populations have reported that the increase in prevalence is particularly noticeable in subjects aged at least 60–65 years compared with younger individuals.<sup>28–30</sup>

The increasing proportion of older patients across Asia means that the burden of systolic hypertension is growing.<sup>9,10,26,32</sup> It is also anticipated that this increase will be more pronounced than in the rest of the world, primarily as a result of lifestyle changes such as consuming Western-style diets and undertaking less physical activity.<sup>9,10</sup> Hence, reducing SBP should be a primary goal for preventing cardiovascular disease in Asia, particularly in older patients with hypertension.

## PATHOPHYSIOLOGY OF SYSTOLIC HYPERTENSION

The primary underlying cause of age-related increases in SBP is arterial stiffening.<sup>33</sup> Arterial stiffening results from a range of structural and functional changes to the aging vasculature, including arterial wall thickening, smooth muscle cell hypertrophy, inflammation, nitric oxide deficiency, fragmentation of elastin and increased dilatation. These changes occur mainly as a consequence of volume expansion, activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, and endothelial dysfunction.<sup>23,34</sup> Deficiency of the natriuretic peptide system is also a key component in the development of hypertension,<sup>34</sup> as natriuretic peptides inhibit the activity of both the renin–angiotensin–aldosterone system and the sympathetic nervous system and have a range of physiological effects including natriuresis and diuresis, vasodilatation, antiproliferation, antihypertrophy, antifibrosis, vascular regeneration and attenuation of cardiovascular remodeling.<sup>35–37</sup> Arterial stiffening is recognized to be a precursor of the development of systolic hypertension, whereas



**Figure 3** Diastolic hypertension becomes less prevalent with increasing patient age. IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic-diastolic hypertension. Reprinted with permission from Macmillan Publishers: *Journal of Human Hypertension*.<sup>28</sup>

hypertension itself can contribute to endothelial dysfunction.<sup>38</sup> Reduced arterial compliance can also result from factors that damage the endothelium such as high dietary salt intake, cigarette smoking, diabetes mellitus and estrogen deficiency.

The loss of arterial elasticity increases pulse wave velocity so that the forward pressure wave that travels from the heart to the periphery is reflected back early toward the heart, returning in late systole rather than early diastole.<sup>39</sup> This leads to increased SBP, reduced DBP and widened pulse pressure. The increased aortic stiffness and decreased aortic compliance in patients with hypertension have been shown to increase with duration of hypertension.<sup>40</sup>

Arterial stiffness is well established as a predictor of stroke, cardiovascular disease and decline in renal function in patients with hypertension.<sup>33</sup> This relationship has been confirmed in Asian populations.<sup>41-43</sup> In Asian patients with hypertension, increasing arterial stiffness was significantly associated with stroke<sup>41,43</sup> and cardiovascular disease,<sup>43</sup> and predicted 15-year cardiovascular mortality.<sup>42</sup> Other studies conducted in Asian regions have shown that arterial stiffening predicts cardiovascular morbidity and mortality in elderly subjects,<sup>44</sup> patients with end-stage renal disease<sup>45</sup> and patients with acute coronary syndrome.<sup>46</sup> In a Japanese study, arterial stiffness was significantly and independently associated with renal function decline.<sup>47</sup>

## KEY RISK FACTORS OF SYSTOLIC HYPERTENSION IN ASIAN PATIENTS

### High dietary salt

Asians generally have a higher salt intake than Westerners.<sup>48,49</sup> Excessive salt intake is associated with significantly increased SBP<sup>50-52</sup> and BP-dependent progression of cardiovascular disease and stroke.<sup>49,53-56</sup> In an early Taiwanese study, salt intake and hypertension were found to be independent risk factors for stroke.<sup>54</sup> Similarly, a large prospective Japanese study showed that a 100-mmol increase in daily sodium intake increased death from stroke by 83%.<sup>56</sup>

Salt intake is more closely correlated with central hemodynamics than peripheral hemodynamics of the brachial artery in patients with hypertension.<sup>57,58</sup> Salt intake predominantly influences central BP, which is implicated in the development of arterial stiffening and directly affects stroke and renal disease. It is noteworthy, therefore, that measuring brachial BP is likely to underestimate the detrimental effects of salt intake on central BP.<sup>58</sup> High salt intake may also increase the risk of stroke and cardiovascular disease independently of the effects of elevated BP,<sup>55</sup> a hypothesis that has been supported by

research demonstrating that dietary sodium alters vascular endothelial function independently of SBP changes.<sup>59</sup>

Reducing dietary sodium effectively reduces SBP in Asian patients.<sup>60,61</sup> Substitution of normal salt with reduced sodium, high-potassium salt has been shown to significantly reduce SBP in Chinese patients with hypertension.<sup>60</sup> Even modest reductions in dietary sodium result in clinically significant reductions in SBP, as well as improving renal function and arterial stiffness.<sup>61</sup> Reducing dietary sodium may be particularly effective in reducing SBP in older patients.<sup>62</sup> Hence, salt reduction strategies may help to alleviate the burden of hypertension, and reduce the associated cardiovascular complications.

### Obesity and overweight

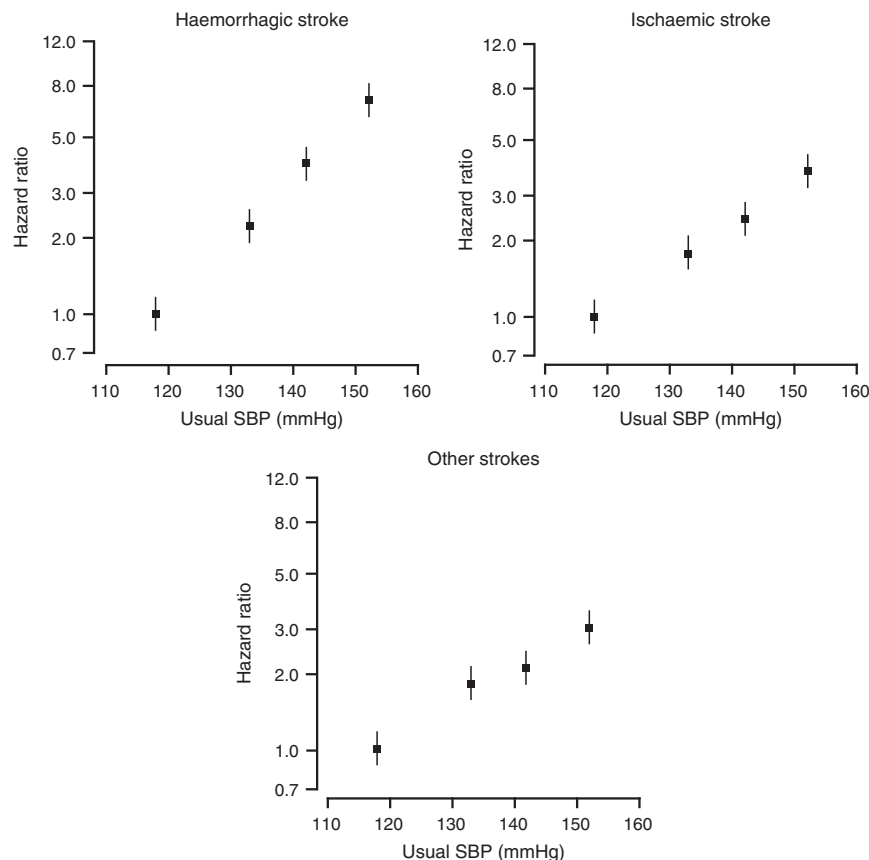
The prevalence of systolic hypertension or raised SBP increases with increasing body mass index (BMI) and waist circumference in Asian subjects.<sup>28,30,63-65</sup> In a large Indian study, the prevalence of isolated systolic hypertension increased from 2.8% among patients with a BMI < 18.5 kg m<sup>-2</sup> to 21.1% in those with a BMI ≥ 30 kg m<sup>-2</sup>.<sup>30</sup> Abdominal obesity assessed by waist circumference was shown to be particularly important for predicting systolic hypertension in large studies of Chinese and Korean women,<sup>63,64</sup> whereas BMI (denoting general obesity) appears to have a more important influence on uncontrolled hypertension in men.<sup>64</sup> Being overweight or obese also predicts increased SBP and incident hypertension in patients with prehypertension.<sup>52</sup> Indeed, a linear relationship between BMI and risk of prehypertension was demonstrated in a cross-sectional Japanese study.<sup>65</sup>

The impact of obesity on hypertension appears to be elevated in Asian subjects compared with Western subjects;<sup>11</sup> a BMI of 25 kg m<sup>-2</sup> in Asians has a similar impact on prehypertension and hypertension as a BMI of 30 kg m<sup>-2</sup> in Western individuals.<sup>66,67</sup> Obesity and associated metabolic syndrome are becoming more common in Asian regions.<sup>68</sup> Both of these conditions increase salt sensitivity.<sup>69,70</sup> Hence, Asians with high salt intake or salt sensitivity may experience increases in BP if they are overweight or only mildly obese.

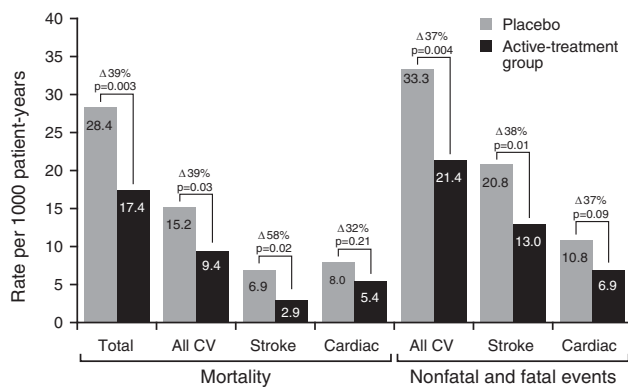
### CONSEQUENCES OF ELEVATED SBP

Data from the Asia Pacific Cohort Studies Collaboration found that raised SBP is a key risk factor for CHD, ischemic and hemorrhagic stroke, ischemic heart disease, and cardiovascular and renal deaths.<sup>15,16,25,71-73</sup> Total risk of cardiovascular disease was increased 4.5-fold in Asian patients with systolic-diastolic hypertension and 2.7-fold in those with isolated systolic hypertension compared with normotensive individuals.<sup>15</sup> Moreover, for every additional 10 mm Hg elevation in SBP the risk of CHD increases by 23%, ischemic stroke by 43% and hemorrhagic stroke by 74%.<sup>16</sup> Figure 4 shows the linear association between usual SBP and hemorrhagic stroke, ischemic stroke and other strokes in the Asia-Pacific region.<sup>74</sup> A similar linear relationship between increasing levels of SBP and stroke risk was demonstrated in a Japanese study.<sup>75</sup> In Asian patients from the Asia Pacific Cohort Studies Collaboration, SBP > 140 mm Hg was significantly and independently associated with subarachnoid hemorrhage, a subtype of stroke that is associated with high morbidity and mortality.<sup>76</sup> Two large population-based cohort studies reported that SBP is a stronger independent predictor of cardiovascular disease and stroke compared with DBP.<sup>75,77</sup> SBP is also the strongest risk factor for renal death, with each 19 mm Hg increase correlating to a > 80% higher risk.<sup>78</sup>

The impact of raised SBP on cardiovascular risk has been shown to vary with different patient characteristics. First, the effect of elevated



**Figure 4** There is a linear association between usual SBP and ischemic stroke, hemorrhagic stroke and other strokes in the Asia-Pacific region. SBP, systolic blood pressure. Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Stroke.<sup>74</sup>



**Figure 5** Antihypertensive treatment significantly reduces fatal and nonfatal outcomes in Asian patients with hypertension: the Syst-China trial. CV, cardiovascular; Syst-China, Systolic Hypertension in China.

SBP on cardiovascular disease increases substantially with age (Figure 1).<sup>18,25</sup> In Japanese patients aged  $\geq 75$  years with high-risk hypertension, cardiovascular risk significantly increased when SBP was  $\geq 150$  mm Hg.<sup>79</sup> In very elderly patients (aged  $\geq 80$  years) with cardiovascular disease (for example, angina or stroke) and taking antihypertensive medications, elevated SBP was significantly associated with total mortality.<sup>80</sup> Second, there appears to be a gender difference in the impact of elevated SBP on cardiovascular and renal risk. A 10 mm Hg increase in SBP was found to be associated with a 15% higher risk of CHD mortality in women than in men.<sup>81</sup> The opposite

was true for the association between SBP and renal death.<sup>78</sup> Third, cardiovascular risk may increase at lower thresholds for SBP and DBP in Asian compared with Western populations. For example, in a large cohort study in India, SBP  $\geq 120$  mm Hg and DBP  $\geq 90$  mm Hg were significantly associated with a greater risk of ischemic heart disease and stroke.<sup>77</sup> The associations between SBP and cardiovascular risk were also stronger in Asians compared with subjects from Australia and New Zealand in an Asia Pacific Cohort Studies Collaboration analysis.<sup>15</sup>

## MANAGEMENT OF SYSTOLIC HYPERTENSION

### Asian evidence on clinical outcome benefits of SBP control with antihypertensive drugs

A number of clinical trials conducted in Asian patients have demonstrated that lowering SBP is associated with reduced cardiovascular risk. The Systolic Hypertension in China trial investigated the effects of antihypertensive treatment on cardiovascular risk in 2394 Chinese patients aged at least 60 years.<sup>82</sup> After a median follow-up of 3 years, step-wise active treatment with a calcium channel blocker (CCB) with or without an angiotensin-converting enzyme inhibitor (ACEI) and/or a thiazide diuretic significantly reduced the rate of fatal and nonfatal strokes by 38%, stroke mortality by 58%, fatal and nonfatal cardiovascular events by 37%, cardiovascular mortality by 39% and total mortality by 39% (Figure 5). Additional analyses found that these beneficial effects were generally similar regardless of patients' characteristics such as gender, age, previous cardiovascular complications or geographical location.<sup>83</sup> Another study from China showed that a reduction in SBP/DBP (4.2/2.1 mm Hg) achieved by

adding a CCB to thiazide diuretic-based therapy was accompanied by significantly greater reductions in fatal and nonfatal stroke (27%), cardiovascular events (27%), cardiac events (35%) and cardiovascular deaths (33%) compared with diuretic-based therapy.<sup>84</sup> The Perindopril Protection Against Recurrent Stroke Study reported that BP-lowering effects of ACEI-based treatment resulted in fewer strokes and major cardiovascular events in Asian patients.<sup>85</sup>

A number of studies have suggested that reduction in cardiovascular events may be achieved irrespective of the class of antihypertensive agent used. In the Japanese Combination Therapy of Hypertension to Prevent Cardiovascular Events trial, the impact of combination therapy with a CCB plus one additional antihypertensive agent (angiotensin receptor blockers (ARBs),  $\beta$ -blocker or thiazide diuretic) on cardiovascular events and BP control was assessed in 3501 patients with hypertension aged 40–85 years.<sup>86</sup> After a median follow-up of 3.6 years, all three CCB-based regimens reduced average BP to a similar extent and there were no differences in the composite primary end point (reduction in risk of cardiovascular events and achievement of target BP). ARB- or CCB-based treatment regimens were shown to confer comparable cardiovascular protective effects in the Candesartan Antihypertensive Survival Evaluation in Japan trial in 4728 high-risk patients with hypertension.<sup>79</sup> Similarly, there were no differences in the incidence of cardiovascular events or mortality between CCB- and ACEI-based treatment in Japanese studies of patients with hypertension and coronary artery disease<sup>87</sup> and elderly patients with hypertension.<sup>88</sup>

Other studies have investigated whether the target for SBP control influences the impact of treatment on cardiovascular events. The Valsartan in Elderly Isolated Systolic Hypertension trial was conducted in 3260 Japanese patients aged 70–84 years with isolated systolic hypertension to evaluate the impact of treatment with ARB-based therapy on cardiovascular events.<sup>89</sup> Patients were randomized according to the target level of SBP control: strict (<140 mm Hg) or moderate (140–150 mm Hg). After a median of 3 years' follow-up, SBP was reduced by 5.6 mm Hg in the strict *vs.* moderate control groups ( $P < 0.001$ ) but this was not accompanied by a significant decrease in the primary end point, a composite of fatal and nonfatal cardiovascular disease and renal failure.<sup>90</sup> The authors suggested that the lower than anticipated rates of the primary outcome were likely to have affected the power to detect between-group differences. Similar findings were reported in the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients in which patients aged 65–85 years received CCB-based therapy.<sup>91</sup> Strict SBP control (target of <140 mm Hg) achieved significantly lower BP compared with the mild control group (SBP target of 140–<160 mm Hg) but there was no difference in the combined incidence of cardiovascular disease and renal failure.

#### Guidelines on BP-lowering goals

There are no overall guidelines for the management of hypertension in Asia.<sup>92,93</sup> Therefore, local country guidelines or standard clinical practice guide the management of hypertension throughout Asia.<sup>92</sup> The major features and themes of Chinese, Japanese, Korean and Taiwanese hypertension guidelines are similar to European and US guidelines,<sup>92,94,95</sup> but there are a number of subtle differences between the Asian guidelines. For example, 120–139/80–89 mm Hg range is termed 'prehypertension' in Korea and Taiwan, 'normal high BP' in China, and defines both 'normal BP' and 'high-normal BP' in Japan.<sup>92,96–98</sup> The current Japanese hypertension guidelines recommend a BP target of <150/90 mm Hg for elderly patients aged

$\geq 75$  years, whereas in the Chinese guidelines, the same BP target is recommended for elderly patients aged  $\geq 65$  years.<sup>92,98</sup>

Local guidelines give limited guidance specifically on the management of systolic hypertension, although some experts acknowledge its higher prevalence in the elderly population.<sup>98</sup> Antihypertensive treatment is recommended in elderly patients but it is advised that BP reduction should be more gradual in this patient population.<sup>9,96–98</sup> The Japanese and Taiwanese guidelines recognize that lowering elevated SBP is important even in patients who have low DBP.<sup>9,98</sup> However, the Japanese guidelines recommend that in the presence of coronary artery disease, changes in DBP be monitored while lowering SBP to the target level.<sup>98</sup>

Awareness and implementation of local guidelines is generally inadequate in many Asian regions.<sup>10,99,100</sup> Development of Asian hypertension guidelines based on evidence from studies conducted in patients in the region would help to provide practical guidance on how best to achieve BP goals. The guidelines could also be adapted and translated according to the local needs, which would help to provide clear terminology and defined treatment goals.

#### Current treatment options

The primary goal of antihypertensive treatment is to lower BP, thereby reducing cardiovascular complications.<sup>9,97,98</sup> Non-pharmacological interventions for BP control recommended by Asian guidelines focus on lifestyle modifications, primarily reducing dietary sodium, weight loss, adopting a diet rich in fruit/vegetables and low-fat dairy products, physical activity, smoking cessation, and reducing alcohol intake.<sup>9,96–98</sup> However, few patients achieve BP goals through lifestyle modifications alone and antihypertensive drug therapy is generally required.

A large number of pharmacological treatments from different drug classes are recommended for the treatment of hypertension in Asia, for example, diuretics,  $\beta$ -blockers, ACEIs, ARBs, CCBs and direct vasodilators.<sup>9,96–98</sup> The most commonly used antihypertensive drugs in Asian countries are the CCBs,<sup>101</sup> generally followed by ACEIs and ARBs,<sup>100,102,103</sup> although  $\beta$ -blockers are also frequently prescribed in Taiwan.<sup>104</sup> Patients receiving a CCB have been reported to achieve the highest rates of BP control,<sup>102</sup> whereas ARBs and ACEIs may have tolerability and/or adherence advantages.<sup>103,105</sup> Use of ARBs has increased in recent years, possibly in response to the greater number of ARBs becoming available.<sup>103,104</sup> Low use of diuretics, despite cost advantages compared with other antihypertensive drug classes, may be related to the fact that diuretics in Asians are more likely to cause serious side effects, such as hypokalemia, because dietary potassium intake in Asians is low<sup>106</sup> and to the perception that diuresis affects kidney function in traditional Chinese medicine, so these agents are not as suitable for hypertension.<sup>104</sup> As in Western hypertensive patients, many Asian patients will require at least two antihypertensive medications to achieve their BP targets,<sup>9,97,98,107</sup> and use of single-pill combinations can improve the convenience and simplicity of the drug regimen.<sup>9,98</sup>

Selecting appropriate medications for individuals' needs is a particular challenge in Asian populations because of the lack of sufficient Asia-specific evidence for available therapies.<sup>10</sup> However, Taiwanese guidelines specifically recommend treatment with a thiazide diuretic, CCB or ARB for isolated systolic hypertension.<sup>9</sup> In elderly patients, who are most likely to have isolated systolic hypertension, Japanese guidelines recommend treatment with a CCB, ARB, ACEI or low-dose thiazide diuretic as first-line therapy.<sup>98</sup> Korean guidelines highlight that CCBs and diuretics are effective first-line therapies for older patients.<sup>97</sup> Specific drugs may also be required for patients with

associated conditions such as heart failure, diabetes, chronic kidney disease or recurrent stroke.<sup>9,97,98</sup>

### Limitations of contemporary drug therapy

Although existing antihypertensive drugs have demonstrated efficacy in lowering BP and reducing cardiovascular morbidity and mortality in numerous clinical trials,<sup>108</sup> hypertension remains an area of significant unmet medical needs. BP control is often suboptimal in clinical practice,<sup>10,98</sup> with rates among Asian patients with hypertension rarely exceeding 50% and reported to be <1% in certain communities.<sup>9,109–114</sup> In the 4th China National Nutrition and Health Survey in 2002, 82% of the Chinese hypertensive patients who were aware of the disease received antihypertensive treatment, yet the BP control rate was only 25% in this treated group, which in addition to the low awareness of hypertension (30%), was the major reason for the low control rate in all hypertensive patients (6%).<sup>115</sup> Lack of SBP control is a particular problem, especially in older Asian patients.<sup>64,116</sup>

Currently available antihypertensive agents are associated with numerous side effects, some of which are class dependent and/or potentially serious, including new-onset diabetes.<sup>117</sup> Some side effects, such as ACEI-induced cough, may also be more pronounced in Asian patients.<sup>118</sup> Concerns about side effects and a lack of confidence about the efficacy of 'Western' antihypertensive medications are common reasons for non-adherence among Asian patients, and are likely to affect BP control rates.<sup>10,119</sup>

The BP-lowering efficacy of current antihypertensive agents is well established but their ability to lower SBP levels to <140 mm Hg is compromised by their lack of effect on age-related arterial stiffening.<sup>120</sup> Moreover, the potential for improvement in vascular compliance with available ACEIs and ARBs may be hindered by the age-related decline in plasma renin activity.<sup>121</sup> At present, there are no treatments that specifically target the reduction of arterial stiffening. As such, the development of novel drugs with direct effects on the underlying causes of arterial stiffness, such as renin-angiotensin-aldosterone system and sympathetic nervous system activation alongside endothelial dysfunction and natriuretic peptide deficiency may be a key step toward optimizing the management of systolic hypertension and its complications.

## CLINICAL CHALLENGES OF HYPERTENSION IN ASIA

### Lack of awareness

Awareness of hypertension is unacceptably low among Asian health-care professionals, patients and the public, and is one of the major contributors to the poor rates of BP control.<sup>10</sup> Many studies in Asian communities have shown that 50–80% of people are unaware of the condition and/or that it is potentially fatal.<sup>109–113,115,116,122</sup> Poor patient knowledge about hypertension and the need for chronic therapy to achieve and maintain BP control often leads to lack of adherence, which therefore has a detrimental impact on BP-lowering strategies.<sup>123,124</sup>

### Under-treatment

Under-treatment of hypertension is a common problem in Asian countries, with rates of antihypertensive treatment for uncontrolled BP ranging widely from 2.6 to 65.8%.<sup>4,109–113</sup> In addition, physicians in Asian regions tend to prescribe lower doses of antihypertensive agents than recommended in Western countries because of concerns over tolerability, potentially leading to suboptimal dosing and insufficient titration for achieving BP goals;<sup>10</sup> however, evidence suggests that upward dose titration of antihypertensive agents in Asian patients with hypertension can provide incremental BP-lowering efficacy without, in

comparison with Western subjects, significantly affecting its tolerability profile.<sup>125</sup>

Physicians may also be concerned about the potentially harmful effects of excessive reduction in DBP when trying to attain SBP goals with antihypertensive drugs in older patients with hypertension.<sup>120,126</sup> Traditionally, guidelines emphasized the control of DBP as the most important factor when treating hypertension, and an increase in SBP was seen as a normal and inconsequential part of the aging process.<sup>120</sup> Therefore, poor understanding of the importance of SBP control among some physicians may limit the effectiveness of hypertension management.

### Diversity across Asia

Asia is a region of extensive social, economic, geographic and political diversity.<sup>127</sup> Consequently, the health status of populations across Asia varies markedly. For example, a strong inverse association between disease prevalence and national wealth typifies how economic diversity between countries can influence the impact of disease burden.<sup>127</sup> Across Asia, the demand for better quality health care is increasing. Yet as national health systems across Asia are evolving at contrasting rates,<sup>127</sup> it is likely that not all countries would be able to meet such demand in their current form. Indeed, the quality and provision of management strategies for systolic hypertension currently used across the region are likely to vary considerably, with developed countries more likely to facilitate optimal patient care than those less developed countries. Therefore, the enormous diversity evident in Asia today represents a significant hurdle to achieving uniform BP control across the region. Nevertheless, with most countries across Asia looking to fully embrace economic and social development in the coming years, existing gaps in health-care provision are expected to diminish, facilitating the improved management of hypertension throughout the majority of the region.

### Lack of therapeutic agents targeting arterial stiffening

Lifestyle and risk management advice from health-care professionals can help to lower BP in patients with hypertension and prevent the development of hypertension in patients identified to be at risk.<sup>128,129</sup> However, uncontrolled hypertension remains a significant problem even when such interventions are implemented.<sup>129</sup> Improving the awareness of hypertension and ensuring patients are treated appropriately would undoubtedly improve BP control rates.<sup>10</sup> Nonetheless, many patients remain uncontrolled even when currently available therapies are prescribed.<sup>120</sup> Lack of BP control is primarily because of insufficient reduction in SBP, particularly in aging populations,<sup>130</sup> which is a consequence of age-related vascular stiffening.<sup>131</sup> Clinical evidence has indicated that survival of patients with end-stage renal failure is improved by reductions in arterial stiffness (assessed by aortic pulse wave velocity) in response to BP lowering—patients without reductions in arterial stiffness in response to BP changes had an increased risk of all-cause and cardiovascular mortality.<sup>132</sup> However, age-related vascular changes are difficult to reverse with available antihypertensive medications.

Therefore, focusing on lowering SBP rather than DBP by reducing arterial stiffness may be an important therapeutic target for the future management of hypertension.<sup>38</sup> A number of new therapies targeting vascular pathophysiology, which may lower SBP, are currently in clinical development.<sup>133–136</sup> These include a first-in-class angiotensin receptor neprilysin inhibitor (LCZ696), a dual-specificity AT<sub>1</sub>R and endothelin A receptor antagonist (PS433540), an aldosterone synthase inhibitor (LCI699), a natriuretic peptide receptor antagonist (PL3994) and a soluble epoxide hydrolase inhibitor (AR9281).<sup>135,136</sup>

## SUMMARY

Hypertension remains a significant clinical problem in both Asia and the rest of the world. Systolic hypertension is the predominant form of hypertension in older patients and therefore represents a major and growing health burden in the aging population. The increase in the prevalence of elevated SBP is likely to be more pronounced in Asian than Western populations because of the adoption of detrimental lifestyle changes in Asian individuals and other factors, such as excessive salt intake and increased sensitivity to weight gain. As elevated SBP is a key risk factor for cardiovascular disease and mortality, reducing SBP should be a primary goal in the management of hypertension, particularly as patients are aging.

Despite the availability of numerous antihypertensive medications, BP control rates are unacceptably low in Asian regions. Increasing awareness and knowledge of hypertension among both health-care professionals and patients may help reduce the escalating social and economic burden of this disease. However, one of the key problems with currently available antihypertensive therapies is their lack of effect on the main determinant of SBP, namely arterial stiffness. Hence, new therapeutic options that target the underlying vascular pathophysiology of elevated SBP are needed to reduce the burden and consequences of systolic hypertension. In addition, research should be conducted to determine the roles of such new therapies specifically in the management of Asian patients with systolic hypertension.

## CONFLICT OF INTEREST

Professor Park reports no conflicts of interest. Professor Kario reports receiving research funding from Novartis. Professor Wang reports receiving honoraria from Pfizer for lectures and article contributions, and receiving research funding from Pfizer and Novartis.

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