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.¹ The worldwide prevalence of hypertension in individuals aged ≥ 25 years was estimated to be approximately 40% in 2008.¹ This is equivalent to almost one billion people, and is predicted to increase to over 1.5 billion people by 2025.¹² The prevalence of hypertension is similarly high across different Asian countries, ranging from 30% in the Republic of Korea to 47% in Mongolia.³ Prevalence also increases with advancing age.⁴⁻⁸ For example, the prevalence in Chinese patients is 39% overall,³ 59.4% in patients aged ≥ 60 years³ and 72.8% in those aged ≥ 75 years.⁶ 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.⁵⁻¹⁰

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.¹¹⁻¹⁴ 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.¹⁵ 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).¹⁵ Elevated systolic BP (SBP) in particular is a key risk factor for cardiovascular disease in both Asian and Western populations.¹⁶,¹⁷ 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.¹⁸ In particular, the linear relationship between SBP and stroke risk is markedly more pronounced in Asian patients than in Caucasian populations (Figure 1).¹⁸ 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.¹⁹,²⁰ 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.²¹,²²

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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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.\textsuperscript{17} 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.\textsuperscript{17,23,24} 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).\textsuperscript{25} This has been corroborated by numerous other studies conducted across the region.\textsuperscript{26–28} 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).\textsuperscript{28,29}

As would be expected, the prevalence of isolated systolic hypertension in Asians, which is reported to be 3.9–12.5%, is age dependent.\textsuperscript{27–31} 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.\textsuperscript{28–30}

The increasing proportion of older patients across Asia means that the burden of systolic hypertension is growing.\textsuperscript{9,10,26,32} 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.\textsuperscript{9,10} 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.\textsuperscript{33} 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.\textsuperscript{23,34} Deficiency of the natriuretic peptide system is also a key component in the development of hypertension,\textsuperscript{34} as natriuretic peptides inhibit the activity of both the renin–angiotensin–aldosterone system and the sympathetic nervous system, and endothelial dysfunction.\textsuperscript{23,34} Arterial stiffening is recognized to be a precursor of the development of systolic hypertension, whereas
hypertension itself can contribute to endothelial dysfunction. 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. 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.

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

**KEY RISK FACTORS OF SYSTOLIC HYPERTENSION IN ASIAN PATIENTS**

**High dietary salt**

Asians generally have a higher salt intake than Westerners. Excessive salt intake is associated with significantly increased SBP and BP-dependent progression of cardiovascular disease and stroke. In an early Taiwanese study, salt intake and hypertension were found to be independent risk factors for stroke. Similarly, a large prospective Japanese study showed that a 100-mmol increase in daily sodium intake increased death from stroke by 83%. Even modest reductions in dietary sodium result in clinically significant reductions in SBP, as well as improving renal function and arterial stiffness. Reducing dietary sodium may be particularly effective in reducing SBP in older patients. 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. In a large Indian study, the prevalence of isolated systolic hypertension increased from 2.8% among patients with a BMI < 18.5 kg m⁻² to 21.1% in those with a BMI ≥ 30 kg m⁻². Abdominal obesity assessed by waist circumference was shown to be particularly important for predicting systolic hypertension in large studies of Chinese and Korean women, whereas BMI (denoting general obesity) appears to have a more important influence on uncontrolled hypertension in men. Being overweight or obese also predicts increased SBP and incident hypertension in patients with prehypertension. Indeed, a linear relationship between BMI and risk of prehypertension was demonstrated in a cross-sectional Japanese study.

The impact of obesity on hypertension appears to be elevated in Asian subjects compared with Western subjects, a BMI of 25 kg m⁻² in Asians has a similar impact on prehypertension and hypertension as a BMI of 30 kg m⁻² in Western individuals. Obesity and associated metabolic syndrome are becoming more common in Asian regions. Both of these conditions increase salt sensitivity. 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. 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. 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%. Figure 4 shows the linear association between usual SBP and hemorrhagic stroke, ischemic stroke and other strokes in the Asia-Pacific region. A similar linear relationship between increasing levels of SBP and stroke risk was demonstrated in a Japanese study. 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. Two large population-based cohort studies reported that SBP is a stronger independent predictor of cardiovascular disease and stroke compared with DBP. SBP is also the strongest risk factor for renal death, with each 19 mm Hg increase correlating to a > 80% higher risk.

The impact of raised SBP on cardiovascular risk has been shown to vary with different patient characteristics. First, the effect of elevated
SBP on cardiovascular disease increases substantially with age (Figure 1). In Japanese patients aged \(\geq 75\) years with high-risk hypertension, cardiovascular risk significantly increased when SBP was \(\geq 150\) mm Hg. 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. 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. The opposite was true for the association between SBP and renal death. 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. 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.

**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. 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. 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. 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.

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), β-blocker or thiazide diuretic) on cardiovascular events and BP control was assessed in 3501 patients with hypertension aged 40–85 years. 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. 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 and elderly patients with hypertension.

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. 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 versus 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. 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. 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. Therefore, local country guidelines or standard clinical practice guide the management of hypertension throughout Asia. The major features and themes of Chinese, Japanese, Korean and Taiwanese hypertension guidelines are similar to European and US guidelines, 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. The current Japanese hypertension guidelines recommend a BP target of <150/90 mm Hg for elderly patients aged ≥75 years, whereas in the Chinese guidelines, the same BP target is recommended for elderly patients aged ≥65 years.

Local guidelines give limited guidance specifically on the management of systolic hypertension, although some experts acknowledge its higher prevalence in the elderly population. Antihypertensive treatment is recommended in elderly patients but it is advised that BP reduction should be more gradual in this patient population. The Japanese and Taiwanese guidelines recognize that lowering elevated SBP is important even in patients who have low DBP. 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.

Awareness and implementation of local guidelines is generally inadequate in many Asian regions. 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. 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. 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, β-blockers, ACEIs, ARBs, CCBs and direct vasodilators. The most commonly used antihypertensive drugs in Asian countries are the CCBs, generally followed by ACEIs and ARBs, although β-blockers are also frequently prescribed in Taiwan. Patients receiving a CCB have been reported to achieve the highest rates of BP control, whereas ARBs and ACEIs may have tolerability and/or adherence advantages. Use of ARBs has increased in recent years, possibly in response to the greater number of ARBs becoming available. 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 and to the perception that diuretics affect kidney function in traditional Chinese medicine, so these agents are not as suitable for hypertension. As in Western hypertensive patients, many Asian patients will require at least two antihypertensive medications to achieve their BP targets and use of single-pill combinations can improve the convenience and simplicity of the drug regimen.

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. However, Taiwanese guidelines specifically recommend treatment with a thiazide diuretic, CCB or ARB for isolated systolic hypertension. 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. Korean guidelines highlight that CCBs and diuretics are effective first-line therapies for older patients. Specific drugs may also be required for patients with...
associated conditions such as heart failure, diabetes, chronic kidney disease or recurrent stroke.\textsuperscript{9,97,98}

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,\textsuperscript{108} hypertension remains an area of significant unmet medical needs. BP control is often suboptimal in clinical practice,\textsuperscript{109,98} with rates among Asian patients with hypertension rarely exceeding 50\% and reported to be < 1\% in certain communities.\textsuperscript{9,109-114} 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 treatment reason for the low control rate in all hypertensive patients (6\%).\textsuperscript{115} Lack of SBP control is a particular problem, especially in older Asian patients.\textsuperscript{64,116}

Currently available antihypertensive agents are associated with numerous side effects, some of which are class dependent and/or potentially serious, including new-onset diabetes.\textsuperscript{117} Some side effects, such as ACEI-induced cough, may also be more pronounced in Asian patients.\textsuperscript{119} 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.\textsuperscript{10,119}

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.\textsuperscript{120} 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.\textsuperscript{121} 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 unnecessarily low among Asian health-care professionals, patients and the public, and is one of the major contributors to the poor rates of BP control.\textsuperscript{10} Many studies in Asian communities have shown that 50–80\% of people are unaware of the condition and/or that it is potentially fatal.\textsuperscript{109-113,115,116,122} 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.\textsuperscript{123,124}

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\%.\textsuperscript{4,109-113} 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.\textsuperscript{10} 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.\textsuperscript{125}

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.\textsuperscript{120,126} 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.\textsuperscript{120} 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.\textsuperscript{127} 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.\textsuperscript{127} Across Asia, the demand for better quality health care is increasing. Yet as national health systems across Asia are evolving at contrasting rates,\textsuperscript{127} 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.\textsuperscript{128,129} However, uncontrolled hypertension remains a significant problem even when such interventions are implemented.\textsuperscript{129} Improving the awareness of hypertension and ensuring patients are treated appropriately would undoubtedly improve BP control rates.\textsuperscript{10} Nonetheless, many patients remain uncontrolled even when currently available therapies are prescribed.\textsuperscript{120} Lack of BP control is primarily because of insufficient reduction in SBP, particularly in aging populations,\textsuperscript{130} which is a consequence of age-related vascular stiffening.\textsuperscript{131} 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.\textsuperscript{132} 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.\textsuperscript{133} A number of new therapies targeting vascular pathophysiology, which may lower SBP, are currently in clinical development.\textsuperscript{133-136} These include a first-in-class angiotensin receptor neprilysin inhibitor (LCZ696), a dual-specificity AT1R and endothelin A receptor antagonist (PS433540), an aldosterone synthase inhibitor (LCI699), a natriuretic peptide receptor antagonist (PL3994) and a soluble epoxide hydrolase inhibitor (AR9281).\textsuperscript{135,136}
CONFLICT OF INTEREST
the management of Asian patients with systolic hypertension.
therapeutic options that target the underlying vascular pathophysiol-
professionals and patients may help reduce the escalating social and
BP control rates are unacceptably low in Asian regions. Increasing
elevated SBP is a key risk factor for cardiovascular disease and
lifestyle changes in Asian individuals and other factors, such as
excessive salt intake and increased sensitivity to weight gain. As
Despite the availability of numerous antihypertensive medications,
control rates are unnecessarily 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.

CONFICT OF INTEREST
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1 WHO Global Health Observatory. Prevalence of raised blood pressure: situations and trends. http://www.who.int/gho/ncri/factors/blood_pressure_prevalence_text/en/ (accessed 10 June 2014).
2 Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: a systematic review. J Hypertens 2004; 22: 11-19.
3 World Health Organization Prevalence of raised blood pressure, ages 25+, 2008. http://gamapserver.who.int/hlthinteractive_char/bnr/crin/cri/factors/blood_pressure_prevalence/asia.html (accessed 10 June 2014).
4 Sheng CS, Liu M, Kang YY, Wei FF, Zhang L, Li GL, Dong Q, Huang QF, Li Y, Wang JS. Prevalence, awareness, treatment and control of hypertension in elderly Chinese. Hypertens Res 2013; 36: 824-828.
5 Davaran S, Grimmins E, Takahashi A, Saito Y. Socioeconomic correlates of four indices of blood pressure and hypertension among older persons in Japan. Gerontology 2013; 59: 392-400.
6 Li YC, Wang LM, Jiay G, Li XY, Zhang M, Hu N. Prevalence of hypertension among Chinese adults in 2010. Zhonghua Yu Fang Yi Xue Za Zhi 2012; 46: 409-413 (in Chinese).
7 Gupta R, Sharma KK, Gupta A, Agrawal A, Mohan J, Gupta VP, Khedr RS, Guptha S. Persistent high prevalence of cardiovascular risk factors in the urban middle class in India: Jaipur Heart Watch-5. J Assoc Physicians India 2012; 60: 11-16.
8 Lee JH, Yang DH, Park HS, Cho Y, Jun JE, Park WH, Chun BY, Shin JT, Shin DH, Lee KS, Kim KS, Kim KB, Kim YJ, Chae SC. Incidence of hypertension in Korea: 5-year follow-up study. J Korean Med Sci 2011; 26: 1286-1292.
9 Chiang CE, Wang TD, Li YH, Lin TH, Chien KL, Yeh HI, Shyu KG, Tsai WC, Chao TH, Hwang JJ, Chiang FT, Chen JH. 2010 guidelines of the Taiwan Society of Cardiology for the management of hypertension. J Formos Med Assoc 2010; 109: 740-773.
10 Chung N, Baek S, Chen MF, Liu CS, Park CG, Park J, Saruta T, Shimamoto K, Wu Z, Zhu J, Fujita T. Expert recommendations on the challenges of hypertension in Asia. Int J Clin Pract 2008; 62: 1306-1312.
11 Kario K. Proposal of a new strategy for ambulatory blood pressure profile-based management of resistant hypertension in the era of renal denervation. Hypertension Res 2013; 36: 564.
12 Kang DG, Jeong MH, Ahn Y, Chae SC, Hur SH, Hong TJ, Kim YJ, Seong IW, Chae JK, Rhee Y, Chae IH, Cho MC, Kim JS, Kim CH, Jang YS, Yoon J, Seung KB. Park SJ. Clinical effects of hypertension on the mortality of patients with acute myocardial infarction. J Korean Med Sci 2009; 24: 800-806.
13 Shimamoto K, Fujita T, Ito S, Naitomi H, Oghara T, Shimada K, Tanaka H, Yokoi K. Impact of blood pressure control on cardiovascular events in 26,512 Japanese hypertensive patients: the Japan Hypertension Evaluation with Angiotensin I Antagonist Losartan Therapy (J-HEALTH) study, a prospective nationwide observational study. Hypertension Res 2008; 31: 469-478.
14 Yang X, Sun K, Zhang W, Wu H, Zhang H, Hui R. Prevalence of and risk factors for peripheral arterial disease in the patients with hypertension among Han Chinese. J Vasc Surg 2007; 46: 296-302.
15 Arima H, Munakami Y, Lam TH, Kim HC, Ueshima H, Woo J, Suh I, Fang X, Woodward M. Effects of prehypertension and hypertension subtype on cardiovascular disease in the Asia-Pacific region. Hypertension Res 2012; 59: 1118-1123.
16 Kengne AP, Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Gu DF, Suh I, Woodward M. Systolic hypertension, diabetes and the risk of cardiovascular diseases in the Asia-Pacific region. J Hypertension 2007; 25: 1205-1213.
17 Franklin SS, Jacobs MJ, Wong ND, L’Italien GJ, Lapuerta P. Prevalence of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES III). Hypertension 2001; 37: 869-874.
18 Perkovic V, Huxley R, Wu Y, Prabhakaran D, MacMahon S. The burden of blood pressure-related disease: a neglected priority for global health. Hypertension 2007; 50: 991-997.
19 Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. J Atheroscler Thromb 2007; 14: 278-286.
20 Ishikawa Y, Ishikawa J, Ishihara K, Kaji E, Sato M, Pickering TG, Kario K. Prehypertension and the risk for cardiovascular disease in the Japanese general population: the Jichi Medical School Cohort Study. J Hypertens 2010; 28: 1630-1637.
21 Okada H, Fukui M, Tanaka M, Matsumoto S, Mineoka Y, Nakashimi N, Tomiyasu K, Nakano K, Hasegawa G, Nakamura N. Visit-to-visit variability in systolic blood pressure is a novel risk factor for the progression of coronary artery calcification. Hypertension Res 2013; 36: 996-999.
22 Rothwell PM, Howard SC, Dolan E, O’Brien D, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010; 375: 895-905.
23 Duprez DA. Systolic hypertension in the elderly: addressing an unmet need. Am J Med 2008; 121: 179-184.
24 Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. Lancet 2008; 371: 2219-2221.
25 Asia Pacific Cohort Studies Collaboration. The impact of cardiovascular risk factors on the age-related excess risk of coronary heart disease. Int J Epidemiology 2006; 35: 1029-1033.
26 He S, Chen XP, Chen XN, Li LX, Wan LY, Peng Y, Gong L, Cui CJ, Zhu Y, Huang DJ. Changes of prevalence of hypertension and blood pressure levels in 1061 adults in Chengdu from 1992 to 2007. Sichuan Da Xue Xue Bao Yi Xue Ban 2010; 49: 491-497, 535.
27 Li J, Xu C, Sun Z, Zheng L, Li J, Zhang D, Zhang X, Liu S, Zhao F, Hu D, Sun Y. Prevalence and risk factors for isolated untreated systolic hypertension in rural Mongolian and Han populations. Acta Cardiol 2008; 63: 389-393.
28 Kim JA, Kim SM, Choi YS, Yoon D, Lee JS, Park HS, Kim HA, Lee JO, Choi KJ. The prevalence and risk factors associated with isolated untreated systolic hypertension in Korea: the Korean National Health and Nutrition Survey 2001. J Hum Hypertens 2007; 21: 107-113.
29 Kim BG, Park JT, Ahn Y, Kimn K, Shin C. Geographical difference in the prevalence of isolated systolic hypertension in middle-aged men and women in Korea: the Korean Health and Genome Study. J Hum Hypertens 2005; 19: 877-883.
30 Mishra T, Idris MZ, Saran RK, Srivastava AK, Singh SK. Isolated systolic hypertension and its determinants – a cross-sectional study in the adult population of Lucknow District in North India. Indian J Community Med 2010; 35: 89-93.
31 Ruixing Y, Liu L, Jinzhen W, Weixiong L, Dezhai Y, Shangling P, Jiandong H. Prevalence and risk factors of isolated systolic hypertension among the urban and rural elderly in the Chinese elderly population: the Jichi Medical School Cohort Studies Collaboration. The impact of cardiovascular risk factors on the age-related excess risk of coronary heart disease. Int J Epidemiology 2006; 35: 1029-1033.
32 Ni X, Cui Z, Zhu Y, Shen H, Wang J, Song Z, Liu Y, Zhang X, Cao J, Liu W, Sun R. Trends of hypertension, awareness, treatment and control in rural areas of northern China during 1991-2011. J Hum Hypertens 2014; 28: 25-31.
33 Park S, Lakatta EG. Role of inflammation in the pathogenesis of arterial stiffness. Yonsei Med J 2012; 53: 258-261.
34 Opala MA, Anaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med 2003; 139: 761-776.
35 Gardener DG, Chen S, Glenn DJ, Grigsby CL. Molecular biology of the natriuretic peptide system: implications for physiology and hypertension. Hypertension 2007; 49: 415-426.
36 Pandey KN. Emerging roles of natriuretic peptides and their receptors in pathophysiology of hypertension and cardiovascular regulation. J Am Soc Hypertens 2008; 2: 210-226.
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37 Rubatto S, Sciannetta S, Valenti V, Starozone R, Volpe M. Natruretic peptides: an update on bioactivity, potential therapeutic use, and implication in cardiovascular diseases. Am J Hypertens 2008; 21: 733–741.

38 Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA 2012; 308: 875–881.

39 Izzo JL Jr, Shylock BF. Arterial stiffness: clinical relevance, measurement, and treatment. Rev Cardiovasc Med 2001; 2: 37–40.

40 Meekahisurudin R, Kamarj K, Murugan S, Thimaleasoukudoubramian P. Aortic stiffness and diastasibility among hypertensives. Ann NY Acad Sci 2009; 1173: E68–E71.

41 Xu TY, Li Y, Zhang Y, Zhu DL, Gao PJ. Association of stroke with ambulatory arterial stiffness index (AASI) in hypertensive patients. Clin Exp Hypertens 2011; 33: 304–308.

42 Wang KL, Cheng HM, Sung SH, Chuang SY, Li CH, Spurgeon HG, Ting CT, Najjar SS, Lakatta EG, Yin FC, Cheu P, Chen CH. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. Hypertension 2010; 55: 799–805.

43 Oshiki M, Tataria Y, Ito N, Takeya Y, Onishi M, Maekawa Y, Kato N, Kamide K, Rakugi H. The combination of chronic kidney disease and increased arterial stiffness is a predictor for stroke and cardiovascular events in hypertensive patients. Hypertens Res 2011; 34: 1209–1215.

44 Matsuoka O, Ohsuka K, Murakami S, Hotta N, Yamagata K, Kubo Y, Yamakana T, Shinagawa M, Nundota S, Nishihara Y, Shibata K, Salot H, Nishimura M, Jihene M, Wada T, Okumiyi K, Matubayashi Y, Yano S, Ichihara K, Cornilson G, Hallberg F, Ozawa T. Arterial stiffness independently predicts cardiovascular events in an elderly community – Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study. Biomarkers Pharmacomet 2005; 59 (Suppl 1): S40–S44.

45 Shoji T, Emoto M, Shirakawa K, Kikuyama Y, Kishimoto H, Ishimura E, Kakiya R, Tsujimoto Y, Kishimoto H, Ishimura E. Aortic stiffness and diastolic blood pressure among hypertensives: a community-based study. Hypertension 2010; 55: 799–805.

46 Jablonski KL, Racine ML, Geolfos CJ, Gates PE, Chonchol M, McQueen MB, Seals DR. Dietary sodium restriction reverses vascular endothelial dysfunction in middle-aged/older adults with moderately elevated systolic blood pressure. J Am Coll Cardiol 2013; 61: 335–343.

47 Zhou B, Wang HL, Wang WL, Wu XM, Fu LY, Shi JP. Long-term effects of salt substitution on blood pressure in a rural north Chinese population. J Hum Hypertens 2013; 27: 427–432.

48 He FJ, Marciniak M, Visagie E, Markandu ND, Arand V, Dalton RN, MacGregor GA. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. Hypertension 2009; 54: 482–488.

49 He J, Gu D, Chen J, Jaquishe CE, Rao DC, Hixon JE, Chen JC, Duan X, Huang JF, Chen CS, Kelly TN, Bazzano LA, Whelton PK. Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. J Hypertens 2009; 27: 48–54.

50 Zhang X, Yao S, Sun G, Yu S, Sun Z, Zheng L, Xu C, Li J, Sun Y. Total and abdominal obesity among rural Chinese women and the association with hypertension. Nutrition Research 2010; 30: 19–30.

51 Lee HS, Park YM, Kwon HS, Lee JH, Yoon KH, Son HY, Kim DS, Yam HM, Lee WC. Factors associated with control of blood pressure among elderly people diagnosed with hypertension in a rural area of South Korea: the Chungjgu Metabolic Disease Cohort Study (CmDC study). Blood Press 2010; 19: 31–39.

52 Kamawato R, Kohara K, Tabara Y, Miki T. High prevalence of hypertension is associated with the increased body mass index in community-dwelling Japanese. Tohoku J Exp Med 2008; 216: 353–361.

53 Ikikawa Y, Ishikawa J, Ishikawa S, Kayaba K, Nakamura Y, Shimada K, Kajii E, Pickering TG, Kario K. Prevalence and determinants of hypertension in a Japanese general population: the Jichi Medical School Cohort Study. Hypertens Res 2008; 31: 1323–1330.

54 Pfeuren K, Kroft JB, Mensah GA. Prevalence of heart disease and stroke risk factors in persons with hypertension in the United States, 1999–2000. Arch Intern Med 2004; 164: 2113–2118.

55 Kubo M, Hata J, Doi Y, Tanizaki Y, Lida M, Kyohara Y. Secular trends in the incidence of and risk factors for ischaemic stroke and its subtypes in Japanese population. Circulation 2011; 123: 1672–1673.

56 Uzu T, Kimura G, Yamashita A, Koketsu K, Arai S, Sugimoto T, Nishio Y, Maegawa H, Koya D, Haneda M, Kawashiga E. Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. J Hypertens 2009; 27: 2167–2173.

57 Chen J, Gu D, Huang J, Rao DC, Jaquishe CE, Hixon JE, Chen CS, Chen J, Lu D, Hui D, Rice T, Kelly TN, Hamm LL, Whelton PK, He J. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: a dietary intervention study. Lancet 2007; 370: 829–835.

58 Woodward M, Tsirou-Murikami R, Murakami Y, Suh I, Fang X, Ueshima H, Lam TH. The epidemiology of stroke amongst women in the Asia-Pacific region. Womens Health (East Lond Engl) 2011; 7: 305–317.

59 Woodward M, Huxley R, Lam TH, Barzi F, Laws CM, Ueshima H. Asia Pacific Cohort Studies Collaboration. A comparison of the associations between risk factors and cardiovascular disease in Asia and Australasia. Eur J Cardiovasc Prev Rehabil 2005; 12: 484–491.

60 Laws CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens 2003; 21: 707–716.

61 Nakamura K, Barzi F, Lam TH, Huxley R, Feiglin WV, Ueshima H, Woo J, Gu D, Ohkubo T, Laws CM, Suh I, Woodward M. Cigarette smoking, systolic blood pressure, and cardiovascular diseases in the Asia-Pacific region. Stroke 2008; 39: 1694–1702.

62 Ishikawa S, Kario K, Kayaba K, Gotob T, Nago N, Nakamura Y, Tsutsunmi A, Kajii E. Linear relationship between blood pressure and stroke: the Jichi Medical School Cohort Study. J Clin Hypertens (Greenwich) 2007; 9: 677–683.

63 Feiglin V, Parag V, Laws CM, Rodgers A, Suh I, Woodward M, Jamrozik K, Ueshima H. Smoking and elevated blood pressure are the most important risk factors for subclinical hemodynamic deterioration in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. Stroke 2005; 36: 1360–1365.

64 Sauvaget C, Ramadas K, Thomas G, Thara S, Sankaranarayana R. Prognosis criteria of usual systolic and diastolic blood pressure values in a prospective study in India. J Epidemiol Community Health 2010; 64: 366–372.

65 O’Seaghdha CM, Perkovic V, Lam TH, McGinn S, Barzi F, Gu DF, Cass A, Suh I, Munter P, Giles GG, Ueshima H, Woodward M, Huxley R. Blood pressure is a major risk factor for renal death: an analysis of 560 352 participants from the Asia-Pacific region. Hypertension 2009; 54: 509–515.

66 Ogihara T, Nakao K, Fukui T, Fukuyama K, Fujimoto A, Ueshima K, Oba K, Shimamoto K, Matsukura H, Saruta T. The optimal target blood pressure for antihypertensive treatment in Japanese elderly patients with high-risk hypertension: a subanalysis of the Canseverid Antihypertensive Survival Evaluation in Japan (CASE-J) trial. Hypertension Res 2008; 31: 1599–1601.

67 Kagiysoma S, Fukuhara M, Ansai T, Matsumura K, Soh I, Takata Y, Sonoki K, Awano S, Takehara T, Iida M. Association between blood pressure and mortality in 80-year-old subjects from a population-based prospective study in Japan. Hypertens Res 2008; 31: 265–270.

68 Huxley R, Woodward M, Barzi F, Wong JW, Pan WH, Patel A; Asia Pacific Cohort Studies Collaboration. Does sex matter in the associations between classic risk factors and fatal coronary heart disease in populations from the Asia-Pacific region? J Women’s Cardiovasc Med 2011; 5: 1829.

69 Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. J Hypertens 1998; 16: S33–S44.

70 Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. Arch Intern Med 2000; 160: 211–220.
with lack of blood pressure control in the community. Hypertension 2000; 36: 594–599.

131 Williams B. Evolution of hypertensive disease: a revolution in guidelines. Lancet 2006; 368: 6–8.

132 Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 2001; 103: 987–992.

133 Briet M, Schiffrin EL. Treatment of arterial remodeling in essential hypertension. Curr Hypertens Rep 2013; 15: 3–9.

134 Laurent S, Schlaich M, Esler M. New drugs, procedures, and devices for hypertension. Lancet 2012; 380: 591–600.

135 Segura J, Salazar J, Ruilope LM. Dual neurohormonal intervention in CV disease: angiotensin receptor and neprilysin inhibition. Expert Opin Investig Drugs 2013; 22: 915–925.

136 Paulis L, Steckelings UM, Unger T. Key advances in antihypertensive treatment. Nat Rev Cardiol 2012; 9: 276–285.