



Isolated Systolic Hypertension: An Update After SPRINT

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ABSTRACT

Isolated systolic hypertension is the most common hemodynamic form of hypertension in the elderly. With a rapidly aging population, the prevalence of hypertension, particularly isolated systolic hypertension, is expected to increase substantially. This phenomenon of increasing systolic pressure in the elderly is believed to be secondary to pathophysiological changes of aging as well as modifiable risk factors. Isolated systolic hypertension is associated with substantial mortality and morbidity, particularly of cerebrovascular disease. It is a rapidly growing public health concern and its management continues to remain a challenge to practicing physicians. Recent studies like the Systolic Blood Pressure Intervention Trial (SPRINT) and Heart Outcomes Prevention Evaluation (HOPE)-3 have implications for antihypertensive therapy in general and for the management of isolated systolic hypertension in particular. In this article we will review: 1) epidemiology and pathophysiologic mechanisms, 2) impact of isolated systolic hypertension on cardiovascular outcomes, 3) optimal management strategies, and 4) systolic blood pressure goals in the light of SPRINT and HOPE 3 trials. © 2016 Elsevier Inc. All rights reserved. • *The American Journal of Medicine* (2016) 129, 1251-1258

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Isolated systolic hypertension is defined as systolic blood pressure (BP) ≥ 140 mm Hg and diastolic BP < 90 mm Hg.¹ It is predominantly present in elderly patients, however, it is not uncommon in young and middle-aged adults. There is a linear increase in both the systolic and diastolic BP up to the fifth or sixth decade of life, after which there is a gradual decrease in the diastolic pressure while systolic pressure continues to increase.² This phenomenon of increasing systolic BP in the elderly is believed to be secondary to modifiable and hereditary risk factors as well as pathophysiological changes of aging. As per data from the Framingham Heart Study, normotensive persons reaching age 65 years had a 90% lifetime risk of developing hypertension

(predominantly of the systolic subtype) if they lived a further 20 to 25 years.³ With a rapidly aging population in the US, the prevalence of hypertension, particularly isolated systolic hypertension, is expected to increase substantially. In this article we will review: 1) epidemiology and pathophysiologic mechanisms, 2) impact of isolated systolic hypertension on cardiovascular mortality and morbidity, 3) optimal management strategies, and 4) critical appraisal of systolic BP goals in light of the Systolic Blood Pressure Intervention Trial (SPRINT) and Heart Outcomes Prevention Evaluation (HOPE)-3 trials.

EPIDEMIOLOGY

The prevalence of untreated hypertensive adults with isolated systolic hypertension according to 1999-2010 National Health and Nutrition Examination Survey data amounts to 9.4%, of which 29.4% occurred in the elderly, ≥ 60 years, as compared with 6.0% in ages 40-59 years and 1.8% in ages 18-39 years.^{4,5} In the elderly population, women, non-Hispanic blacks, and those with only secondary school education were more likely to be affected.⁵ With more aggressive management of hypertension, the percentage of elderly

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patients on ≥ 3 antihypertensives has almost tripled (from 9% in 1988-1994 to 26% in 2005-2010); whereas those on 1-2 antihypertensive medications has only increased to 54% from 50%. Over the cross-sectional periods of 1999-2004 and 2005-2010, the prevalence of untreated isolated systolic hypertension in elderly patients decreased from 33.6% to 25.1%.⁴ Despite this improvement, its effective management in the elderly continues to remain an important public health concern and a continuous challenge to clinicians.

PATHOPHYSIOLOGIC MECHANISMS

Isolated systolic hypertension can develop either from “burned out” diastolic hypertension in patients with long-term essential hypertension, or from a *de novo* increase in systolic BP secondary to increased arterial stiffness in previously normotensive individuals.⁶ Secondary causes of *de novo* systolic hypertension include type 1 diabetes, osteoporosis with vascular calcifications, accelerated atherosclerosis from chronic kidney disease, peripheral vascular disease, altered elastin formation during intrauterine fetal growth retardation, thyrotoxicosis, repaired coarctation of the aorta, and ageing of the proximal aorta.⁶ The pathophysiological changes of arterial wall ageing that predispose the elderly to isolated systolic hypertension include endothelial dysfunction, arterial vascular smooth stiffening, proinflammatory release, insensitivity to vasodilators, and elastin calcifications⁷ (Figure 1).

With increasing age and progression of atherosclerosis, there is increased deposition of arterial calcium and collagen associated with fraying of arterial elastin. The resultant reduction in arterial elasticity and compliance leads to a decrease of the lumen-to-wall ratio and increased arterial stiffness.⁸ These changes specially involve predominantly large arteries and the aorta. Translational research has shown that increased systolic BP leads to increased levels of enzymes or proinflammatory action, which gives rise to endothelial dysfunction. For example, matrix metalloproteinase enzymes inhibit vasodilation via degradation of endothelial nitric oxide synthase and promote vasoconstriction via cleavage of vasoconstricting peptides.⁹ Furthermore, matrix metalloproteinase enzymes play a role in the development of atherosclerosis, which leads to intima and media thickening.¹⁰ This increased rigidity leads to elevation in systolic pressures and further decline in diastolic pressures, creating increased pulse pressures and thus, a diminished Windkessel effect.^{8,11} Pulse wave velocity, used to measure arterial stiffness,

increases with decreased arterial compliance. A faster velocity triggers a speedier reflected pressure wave, which, in turn, causes a ventricular-vascular mismatch resulting in increased left ventricular afterload and systolic pressure.^{11,12}

Chronic diseases often concomitant in elderly patients with hypertension, such as diabetes mellitus, chronic kidney disease, hyperlipidemia, and smoking further contribute to this pathological process by accelerating atherosclerosis and arterial stiffening.⁶ The left ventricle stiffens and hypertrophies in order to maintain appropriate cardiac output against increased afterload and decreased compliance from a stiffened arterial tree. This ventricular remodeling results in decreased diastolic filling and impaired diastolic relaxation. This, together with stiffening of the arterial tree and the diminished Windkessel function of the aorta, causes increased reactivity of the systolic BP secondary to fluctuations in volume status. Eventually, elevated pulse pressures and labile systolic pressures across the microvasculature may result in vessel damage and “flow ischemia” of the end organs.^{6,12} The renin-angiotensin-aldosterone system

(RAAS) is implicated to some extent in the pathogenesis of isolated systolic hypertension through mechanisms that increase vascular thickness, stiffening, and loss of contractility such as altering the elastin-collagen content of the arterial wall, thickening and fibrotic remodeling of the vascular intima, and inducing proliferation of arterial smooth-muscle cells.¹³ However, there is a gradual progressive decline in plasma renin activity with age, and the role of renin-angiotensin-aldosterone system is modulated by several other factors such as sodium intake and comorbidities.^{14,15}

SYSTOLIC BLOOD PRESSURE, ISOLATED SYSTOLIC HYPERTENSION AND CARDIOVASCULAR RISK

Systolic BP is a major determinant of cardiovascular risk. In a meta-analysis of individual data of one million adults from 61 observational studies, increase in systolic BP was directly and significantly related to cardiovascular and all-cause mortality, without any evidence of a threshold effect down to at least 115/75 mm Hg.¹⁶ Studies evaluating 24-hour ambulatory BP showed similar detrimental effect of elevated systolic BP. A meta-analysis of 20 studies involving 9299 individuals and 11.1 years of follow-up showed a strong association between 24-hour systolic BP and cardiovascular mortality, all-cause mortality, stroke, and cardiac events.¹⁷ While diastolic BP is important,

CLINICAL SIGNIFICANCE

- Isolated systolic hypertension (ISH) is the most common form of hypertension in the elderly.
- Dihydropyridine-type calcium channel blockers and thiazide-like diuretics are preferred first-line agents.
- Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers can be used when compelling indications are present. Beta-blockers should be avoided.
- Optimal blood pressure in patients with ISH is not well studied, and a systolic blood pressure goal of <140 mm Hg seems reasonable; however, management should be individualized for each patient.

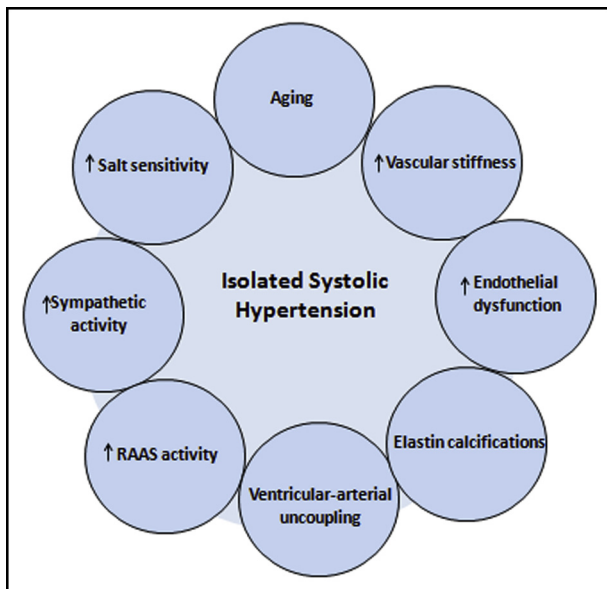


Figure 1 Pathophysiologic mechanisms associated with isolated systolic hypertension. RAAS = renin-angiotensin-aldosterone system.

controversy exists on the impact of diastolic BP per se on cardiovascular outcomes.^{18,19}

Numerous epidemiologic studies have shown that isolated systolic hypertension is independently associated with future cardiovascular events.²⁰⁻²² The initial studies used the criteria of systolic BP ≥ 160 mm Hg and diastolic BP < 95 mm Hg to define isolated systolic hypertension. In 1997, the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure introduced a revised definition: systolic BP ≥ 140 mm Hg and diastolic BP < 90 mm Hg,²³ which was subsequently adopted by the 1999 World Health Organization–International Society of Hypertension guidelines.²⁴ The 2013 European Society of Cardiology/European Society of Hypertension guidelines for management of arterial hypertension¹ further categorize isolated systolic hypertension into grade 1, 2, or 3 according to systolic BP values (Table 1). In a propensity-match analysis from Cardiovascular Health Study cohort involving 2520 participants and 8.7 years of follow-up, isolated systolic hypertension was associated with 34% increase in coronary artery disease, 33% increase in cerebrovascular disease, and 26% increase in incident heart failure.²⁵ Recently, in a multicenter international study of 8341 untreated individuals, isolated systolic hypertension (defined as 24-hour ambulatory systolic BP ≥ 130 mm Hg) was independently associated with all-cause mortality and fatal and nonfatal cardiovascular outcomes over a period of 11 years.²⁶ *Mutatis mutandis*, systolic BP reduction has been associated with improved outcomes. In a large meta-analysis of 123 studies involving 631,815 individuals, systolic BP reduction of 10 mm Hg was associated with significant reduction of major cardiovascular disease events (20%), coronary heart disease (17%), stroke (17%), heart failure (18%), and all-cause mortality (13%).²⁷

RANDOMIZED CONTROL TRIALS FOR ISOLATED SYSTOLIC HYPERTENSION

Four landmark randomized trials²⁸⁻³¹ provided ironclad evidence for treatment of isolated systolic hypertension in the elderly (Table 2). The primary end point in all the 4 placebo-controlled trials was incidence of fatal and nonfatal stroke, which was significantly lower in the active treatment arm (Figure 2). All 4 trials defined isolated systolic hypertension as systolic BP ≥ 160 mm Hg. An individual-patient meta-analysis of 15,693 patients with isolated systolic hypertension from 8 randomized trials showed that active treatment reduced all-cause mortality by 13%, cardiovascular mortality by 18%, all cardiovascular events by 26%, stroke by 30%, and coronary events by 23%.³² Absolute benefit was found to be larger in men, in patients ≥ 70 years, and in those with previous cardiovascular complications or wider pulse pressure.

ANTIHYPERTENSIVE AGENTS IN ISOLATED SYSTOLIC HYPERTENSION

Primary Drugs: Thiazide-like diuretics and Dihydropyridine calcium channel blockers (CCB)

Secondary Drugs: Angiotensin-Converting Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB)

From the above randomized trials it becomes clear that thiazide-like diuretics (chlorthalidone and indapamide) as well as CCBs of the dihydropyridine type (eg, amlodipine, nitrendipine, nifedipine) substantially reduce the risk of stroke and of other morbid events. Based on the data in aggregate, CCBs and thiazide-like diuretics should therefore be preferred first-line agents for management of isolated systolic hypertension (Figure 3). Of note, there are no data showing that hydrochlorothiazide reduces morbidity and mortality similar to chlorthalidone and indapamide.

Compared with CCBs or thiazide-like diuretics (chlorthalidone or indapamide), ACEi/ARBs have distinctly less efficacy in patients with isolated systolic hypertension.

Table 1 Categories of ISH Based on Office Blood Pressure Measurements

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Isolated systolic hypertension - Grade I	140-159	< 90
Isolated systolic hypertension - Grade II	160-179	< 90
Isolated systolic hypertension - Grade III	≥ 180	< 90

BP = blood pressure; ISH = isolated systolic hypertension.

Based on 2013 European Society of Hypertension and of the European Society of Cardiology Guidelines for the management of arterial hypertension.¹

Table 2 Landmark Clinical Trials on Treatment of ISH

	SHEP	Sys-Eur	Sys-China	HYVET
Year	1991	1997	1998	2008
Participants	4736	4695	2394	3845
Age and sex	≥60 y, mean 72 y, 57% women	≥60 y, mean 70 y, 66% women	≥60 y, mean 66 y, 36% women	≥80 y, mean 84 y, 61% women
BP criteria	Systolic BP: 160-219 Diastolic BP: ≤90	Systolic BP: 160-219 Diastolic BP: ≤95	Systolic BP: 160-219 Diastolic BP: ≤95	Systolic BP: 160-199* Diastolic BP: ≤110
Active treatment arm	Chlorthalidone 12.5-25 mg	Nitrendipine 10-40 mg	Nitrendipine 10-40 mg	Indapamide sustained release 1.5 mg
Add-on therapy	Atenolol 25 mg, reserpine 0.05 mg	Enalapril 5-20 mg, HCTZ 12.5-25 mg	Captopril 12.5-50 mg, HCTZ 12.5-50 mg	Perindopril 2-4 mg
Primary outcome	Nonfatal and fatal stroke	Nonfatal and fatal stroke	Nonfatal and fatal stroke	Nonfatal and fatal stroke
Follow-up	4.5 y	2 y	3 y	2.1 y
Major findings	36% reduction in stroke, 25% reduction in coronary artery disease and 32% reduction in cardiovascular events	42% reduction in stroke, 26% reduction in cardiac end points, 31% reduction in cardiovascular events	38% reduction in stroke, 37% reduction in cardiovascular events, 39% all-cause mortality	30% reduction in stroke, 23% reduction in cardiovascular mortality, 21% reduction in all-cause mortality

BP = blood pressure; HCTZ = hydrochlorothiazide; HYVET = Hypertension in the Very Elderly Trial; ISH = isolated systolic hypertension; SHEP = Systolic Hypertension in the Elderly Program.

*32% of patients had ISH.

However, ACEi/ARBs can be considered if there are compelling indications such as chronic systolic heart failure, postmyocardial infarction, or chronic kidney disease. For patients with diabetes, recent analyses have shown similar efficacy of ACEi/ARBs compared with other antihypertensives.³³ In elderly patients, our recent meta-analysis showed no significant difference between ACEis and other antihypertensive agents for cardiovascular outcomes. Choice between different antihypertensive agents should be based on patient's comorbidities, tolerability, and clinical response. In general, management strategies should be decided on an individual basis, with the primary aim of optimum BP control, but using fewer medications or a regimen that minimizes adverse effects.

DRUG COMBINATIONS FOR ISOLATED SYSTOLIC HYPERTENSION

Primary: CCBs + Thiazide-like diuretics (Indapamide, Chlorthalidone)

Secondary: CCBs + ACEi or ARBs, Thiazide-like diuretics (Indapamide, Chlorthalidone) + ACEi or ARBs

The majority of patients eventually require combinations of 2 or more antihypertensive medications to reach goal BP. Evidence from the individual-therapy trials and available combination-therapy trials suggest that in patients who require more than one antihypertensive therapy, a combination of CCBs and thiazide-like diuretics should be the initial strategy.³⁴ The safety and tolerability of this regimen is equivalent to other combinations, including in high-risk patients and in patients over age 65 years.³⁵ In the presence of compelling

indications for ACEi/ARBs, combination therapy of either ACEi or ARBs with CCBs or thiazide-like diuretics can be considered. Thoughtful use of fixed-drug combinations will reduce pill burden and is prone to increase adherence.

DRUGS TO AVOID: BETA-BLOCKERS

Evidence has shown that beta-blockers have little, if any, efficacy in management of hypertension.³⁶ As noted in the isolated systolic hypertension substudy of the Losartan Intervention For Endpoint reduction (LIFE-ISH) trial, atenolol was inferior to losartan for cardiovascular risk reduction.³⁷ In the second Swedish Trial in Old patients

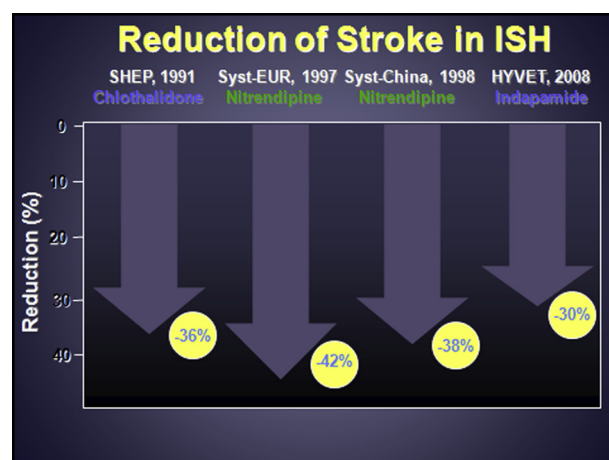


Figure 2 Reduction of stroke in landmark trials on treatment of isolated systolic hypertension. HYVET = Hypertension in the Very Elderly Trial; ISH = isolated systolic hypertension; SHEP = Systolic Hypertension in the Elderly Program.

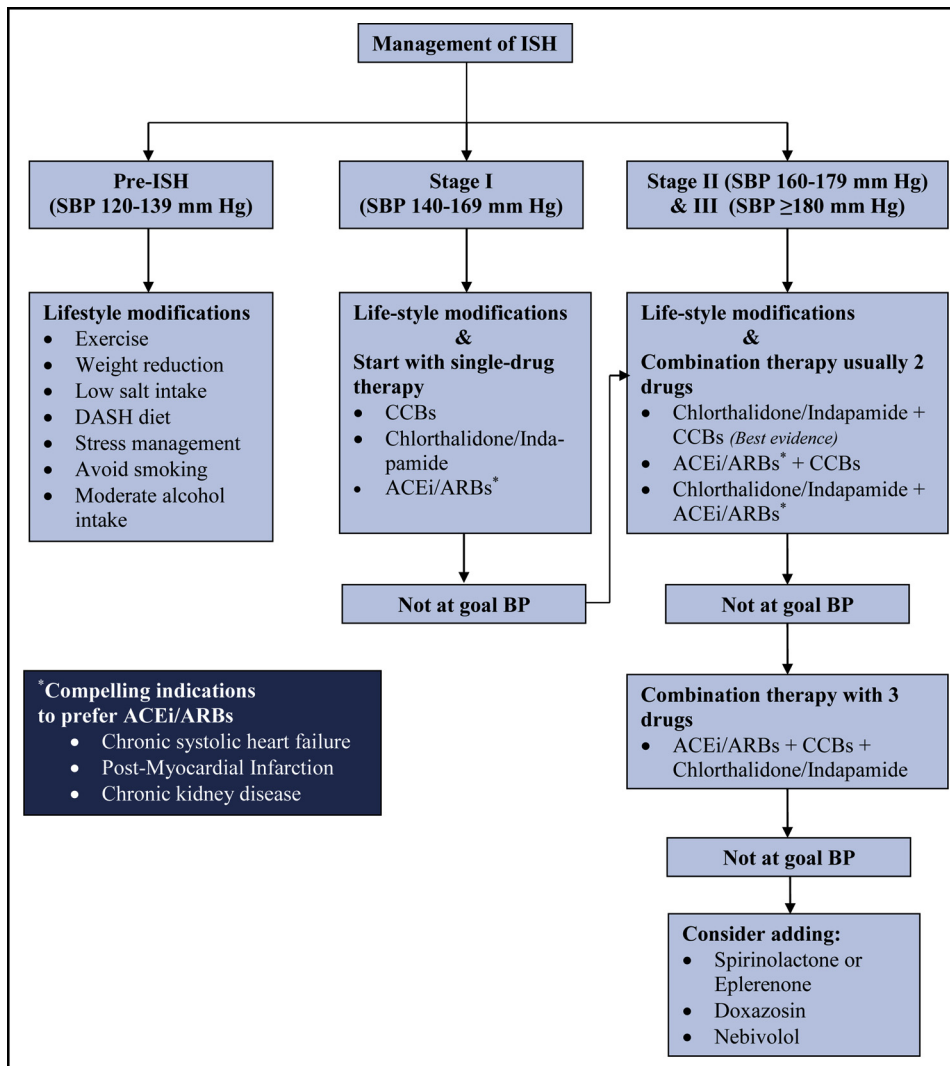


Figure 3 Management of isolated systolic hypertension. ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BP = blood pressure; CCB = calcium channel blocker; DASH = Dietary Approaches to Stop Hypertension; ISH = isolated systolic hypertension; SBP = systolic blood pressure.

with Hypertension (STOP-2) trial subgroup, the combination of diuretics and beta-blockers had the highest events for stroke, compared with ACEi and CCBs.³⁸ Part of the inefficacy of beta-blockers may be related to the observation that heart rate lowering increases central (aortic) BP. Beta-blockers exert a pseudo-antihypertensive effect wherein peripheral BP was lowered but central (aortic) BP remained distinctly elevated.³⁹ Moreover, reduction in heart rate exaggerates this effect.⁴⁰ Over the long-term, beta-blockers even can engender a pro-fibrotic effect on the arterial wall, which may contribute to an increase in arterial stiffness.⁴¹

SYSTOLIC BLOOD PRESSURE GOALS: DOES ONE SIZE FIT ALL?

Optimal or target systolic BP in patients with hypertension has been a topic of intense debate. The prior trials on

systolic BP goals not only showed inconsistent results, but were highly heterogeneous in terms of their patient cohorts, methodology, and BP goals. Furthermore, data pertaining to isolated systolic hypertension are limited. The earlier Systolic Hypertension in the Elderly Program (SHEP) trial²⁸ and the Hypertension in the Very Elderly Trial (HYVET)³¹ found significant benefits of antihypertensive treatment with the goal systolic BP in treatment arm of each trial <150 mm Hg. However, these trials were not designed to test specific target BP levels. The VALsartan in Elderly Isolated Systolic Hypertension (VALISH) trial⁴² attempted to identify the optimal BP goal in patients with isolated systolic hypertension. In the trial, 3079 elderly patients were randomized to either strict (<140 mm Hg) or moderate BP control (≥140 mm Hg to <150 mm Hg) and followed for 3 years. Among the 2 strategies, there was no significant difference in the incidence of the primary outcome:

composite of sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, heart failure death, other cardiovascular death, unplanned hospitalization for cardiovascular disease, and renal dysfunction (hazard ratio: 0.89, $P = .38$). No difference in the individual components of the primary outcome was found between the 2 groups. However, due to the low number of events, the trial was grossly underpowered.

The recently published SPRINT trial was specifically designed to investigate standard (systolic BP target of <120 mm Hg) vs intensive (systolic BP target of <140 mm Hg) treatment in patients with hypertension at risk for cardiovascular diseases.⁴³ This study randomized 9361 nondiabetic adults aged ≥ 50 years with no prior stroke who had an average systolic BP ≥ 130 mm Hg and were at additional risk for cardiovascular diseases. The mean age of the participants was 68 years and the mean baseline BP was 140/78 mm Hg. During follow-up, the mean systolic BP was 122 mm Hg in the intensive treatment group and 135 mm Hg in the standard treatment group. Intensive treatment reduced the primary composite outcome by 25% ($P < .001$) and all-cause mortality by 27% ($P = .003$), compared with the standard group. The benefit in primary outcome was largely driven by reduction in heart failure and cardiovascular death. Based on the SPRINT trial, it is estimated that about 16.8 million US adults may be eligible for antihypertensive treatment initiation or intensification.⁴⁴ We should consider, however, that BP measurements in SPRINT were done unlike in any other trial, as patients were left sitting in a quiet room without nurse or physician present.⁴⁵ As Kjeldsen et al⁴⁵ stated, implications thereof are 1) BPs taken in SPRINT cannot be directly compared with BPs in other trials, and 2) the treatment arm <120 mm Hg in SPRINT compares with a higher systolic BP value in the other trials. Overall, it means that the lower treatment arm in SPRINT translates into systolic BP <136 mm Hg, not very different from systolic BP <140 mm Hg, which is the currently recommended systolic BP target for most hypertensive people by all hypertension treatment guidelines.

In general, based on the evidence from numerous epidemiological studies, systolic BP should be well controlled for reducing cardiovascular mortality. However, aggressive BP lowering may be harmful in elderly patients with ISH due to the risk for target organ hypoperfusion. Aggressive BP reduction in these patients is accompanied by a fall in diastolic BP as well. Conceivably, an excessive fall in BP could give rise to the J-curve phenomenon in that diastolic BP reduction could increase the risk of coronary heart disease and other morbid events.⁴⁶ In the recent HOPE 3 study, prespecified subgroup analysis only reduced stroke in patients with on-treatment systolic BP >143.5 mm Hg. In contrast, BP lowering with candesartan plus hydrochlorothiazide had no effect in patients with systolic BP 131.6–143.5 mm Hg or ≤ 131.5 mm Hg.⁴⁷ In isolated systolic hypertension, even more than in any other form of hypertension, we should remember a simple but inescapable truth in medicine: patients are genetically, physiologically,

metabolically, pathologically, psychologically, and culturally different. Accordingly, there never will be only one way to diagnose and treat. To lower BP of all hypertensive patients uniformly to ≤ 120 mm Hg is clearly absurd, regardless of the SPRINT results. We can only hope that despite (or even because of) SPRINT, physicians will continue to treat patients and not blood pressure numbers alone.⁴⁸

ISOLATED SYSTOLIC HYPERTENSION IN YOUNG AND MIDDLE-AGED INDIVIDUALS

The overall prevalence of isolated systolic hypertension in individuals aged 18–39 years and aged 40–59 years in the US is estimated 1.8% and 6%, respectively. In young individuals, it is thought that the systolic pressure is elevated predominantly in peripheral arteries, and not in central arteries, resulting in the higher amplification of the upper limb arterial pressure pulse wave.⁴⁹ It has also been shown that young patients with isolated systolic hypertension but low central BP have lower risk for development of hypertension needing treatment.⁵⁰ However, it is not a completely benign entity as previously thought. A recent study by Yano et al analyzed 27,081 individuals of 18 to 49 years of age free of coronary heart disease and antihypertensive therapy, from the Chicago Heart Association Detection Project in Industry data.⁵¹ During a 31-year follow-up period, isolated systolic hypertension was associated with increased risk for cardiovascular disease and coronary heart disease mortality compared with optimal-normal BP. With the increasing prevalence of obesity and metabolic syndrome in young individuals, the prevalence of isolated systolic hypertension is likely to further increase. However, based on the current pathophysiological understanding, it is not known whether BP measurement based solely on brachial cuff values is sufficient to diagnose and initiate treatment. Conceivably, the role of ambulatory 24-hour BP measurements and central hemodynamics should be elucidated. It is important to accurately diagnose isolated systolic hypertension in young individuals because it could have significant prognostic, therapeutic, and lifestyle implications on such patients.

CONCLUSIONS AND PERSPECTIVES

Isolated systolic hypertension is highly prevalent in the elderly and is a major cause of mortality and morbidity. Blood pressure control rates in these patients remain suboptimal at present. Appropriate evidence-based management strategies should be employed for management of BP. CCBs and thiazide-like diuretics (chlorthalidone, indapamide) reduce the risk of stroke, and should be considered as first-line agents. Nonetheless, most of the elderly patients require multiple antihypertensives to control BP. The optimal systolic BP target remains unclear, however, systolic BP goal of <140 mm Hg seems a reasonable strategy. Clearly, isolated systolic hypertension remains a common and challenging issue for practicing physicians.

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