Optimal treatment of hypertension in the elderly: A Korean perspective

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With the progression of the aging population, common diseases of the elderly have become the center of attention in most developed countries. Hypertension is one of the most common morbid conditions in the elderly and has a great impact on their health status because it is the main risk factor of cardiovascular and cerebrovascular diseases. However, a considerable amount of uncertainty remains regarding hypertension in the elderly, such as the benefits of hypertension control in oldest-old populations, the optimal level of blood pressure control, and the efficacy of antihypertensive drugs for the prevention of cognitive dysfunction. While there are many controversial issues concerning the optimal management of hypertension in the elderly, the number of elderly hypertensive patients that require treatment is expected to increase due to the aging population. As a result, knowledge regarding the mechanisms of hypertension in the elderly and specific consideration in managing hypertensive elderly patients are needed to improve the clinical outcome. Furthermore, new therapeutic interventions that are aimed at attenuating age-related vascular changes should be investigated, because hypertension in the elderly, especially isolated systolic hypertension has specific characteristics of increased arterial stiffness in most cases.

Keywords: cardiovascular disease, elderly, hypertension.

Introduction

With the increasing elderly population, it is important to understand the individual diseases that are prevalent and have great impacts on the health states of elderly subjects. Hypertension is one of the most common diseases in the elderly, and it is an important but modifiable risk factor for cardiovascular and cerebrovascular diseases, the leading causes of death and disability in the elderly.

Age is the dominant risk factor for the development of hypertension. Aging-related vascular structural and functional changes make older people vulnerable to hypertension. In other words, the prevalence of hypertension increases with age. All adults who are normotensive at 50 years of age have a more than 90% probability of becoming hypertensive during the remainder of their lifetime. In addition, it is believed that increasing age contributes to an increased time of exposure to cardiovascular risk factors. According to this view, time indirectly confers an increased risk for the occurrence, severity and extent of the cardiovascular diseases in older persons.

Recently, the improvement of public awareness has made more hypertensive people be diagnosed and treated during their mid-life. As a result, the morbidity and mortality related to strokes, myocardial infarctions and heart failure have significantly decreased in the middle-aged population. However, the postponement of these hypertension-related adverse events could have major adverse negative consequences in terms of increased health-care expenditures and disability payments of the older population.
Although hypertension is the predominant and most frequent cardiovascular risk factor in older adults, hypertension in the elderly was considered as a normal physiological change and was not indicated for active treatment. Furthermore, isolated systolic hypertension (ISH), a typical characteristic of elderly hypertension, has not been considered a target of treatment but is rather considered an age-related change.

In addition, there is some concern regarding the benefit of hypertension treatment in oldest-old patients. Therefore, despite numerous trials demonstrating the benefit of lowering blood pressure (BP) in hypertensive patients, some physicians are still reluctant to treat hypertension in the elderly population. As a result, hypertension control rates are unacceptably low in the elderly population, and the prevalence of hypertension-related cardiovascular diseases remains high.

Although the clinical significance of elderly hypertension has been well known, it is true that a lot of uncertainty remains regarding hypertension in the elderly. Moreover, until recently, convincing mechanistic or molecular explanations for the increased cardiovascular risks conferred by aging have been elusive. While there are many controversial issues regarding the management of hypertension in the elderly, the number of elderly hypertensive patients that require treatment is expected to increase because of the aging of the population. Thus, knowledge regarding the characteristics of elderly hypertension and specific consideration in managing hypertensive elderly patients are needed to improve the clinical outcome.

In this review, the evidence for the benefits of treating elderly hypertension is briefly reviewed, and unsolved issues regarding elderly hypertension are summarized for a better understanding of this important clinical issue of the aging society.

Characteristics of elderly hypertension: aging-related vascular change and its consequences in elderly hypertension

Vascular aging is associated with alterations in a number of structural and functional properties of the large arteries, including diameter, wall thickness, wall stiffness and endothelial function. It is well known that vascular aging per se is an independent risk factor for the development of hypertension and increases the risk of cardiovascular events. In addition, these age-associated changes are also accelerated in the presence of cardiovascular diseases, and these changes themselves are risk factors for the occurrence or progression of cardiovascular diseases.

Among the age-related vascular changes, increased arterial stiffness is the most typical structural property of vascular aging, which is the principal pathophysiological characteristic explaining systolic hypertension. An age-related increase in central aortic stiffness is associated with an increase in the amplitudes of the forward and reflected pressure waves. Furthermore, early return of reflected waves also contributes to systolic hypertension and widening pulse pressure.

Accordingly, it is a major determinant of increased systolic and pulse pressure despite the decrease of diastolic pressure with increasing age. This phenomenon may facilitate forward transmission of potentially deleterious pressure pulsations into the periphery.

Several epidemiological data suggest that increased pulse pressure in the elderly population has more clinical significance than other BP indices in predicting the future risk of cardiovascular events. The mechanisms for such alterations remain largely unknown. However, aging-related structural modifications of the arterial wall, which include increases in medial thickness, collagen content, and collagen/elastin ratio, but decreases in elastin density and the number of nuclei of vascular smooth muscle cells, might be the determinant mechanism explaining arterial stiffness. In other words, increased pulse pressure is a sensitive indicator of vascular aging, so it might have more clinical meaning in the aged population.

Likewise, structural alterations of small artery walls and cardiac maladaptation in association with increased pulse pressure are significant cardiovascular risk factors in elderly hypertensive subjects. Increased sodium sensitivity and nitric oxide (NO) deficiency are another feature which might be helpful to understand the mechanisms of ISH in the elderly. A host of biochemical, enzymatic and cellular alterations that are factors for accelerated arterial aging have also been implicated in the pathogenesis and progression of arterial diseases with aging.

In the near future, new therapeutic interventions targeting these vascular alterations are thus putative candidates aimed at attenuating arterial aging, similar to the lifestyle and pharmacological interventions that have already been proven effective.

Clinical benefit of antihypertensive treatment in the elderly: all elderly patients get benefits with active treatment of hypertension?

There has been concern regarding the hazardous effects of BP control in the elderly population. In fact, there has been a few reports that drug treatment may be less effective or even dangerous in patients with hypertension aged 80 years and older. Although experience from major randomized, double-blinded placebo-controlled trials have clearly shown that active treatment is associated with a significant reduction of stroke rates, major cardiovascular disease and mortality in elderly patients, there remains much
uncertainty regarding optimal management of hypertension in the elderly.

Most of the previous studies have included systolic hypertension (systolic BP [SBP], \(\geq 160\) mmHg), so it is uncertain whether active treatment of elderly patients whose BP is maintained between 140–160 mmHg might also be beneficial.\(^{24}\) Furthermore, the oldest-old subjects have not been included in most of the clinical trials to evaluate the efficacy and safety of antihypertensive medications. Most early clinical trials on hypertension enrolled very few individuals more than 80 years of age because of concerns regarding their relatively short life expectancy and high risk of non-cardiac death. Therefore, very little evidence has been reported that supports the benefits of treating hypertension in this subgroup of the elderly population.

With the increase of human lifespan and growing of the elderly population, the issue concerning antihypertensive treatment in this population has been worth noticing. Older individuals are, by definition, at a higher absolute risk of all cardiovascular events and death; therefore, treatment is more cost-effective for them. Moreover, the non-cardiac clinical endpoint might have a clinical significance in these aged populations. In fact, cognitive function, independent functional status and quality of life are more meaningful parameters for the elderly. As a result, evidence from clinical trials that focus exclusively on elderly people might be helpful for the optimal management of elderly hypertension.

The Hypertension in the Very Elderly Trial (HYVET) study is a currently ongoing study assessing the efficacy and safety of antihypertensive drug treatment to reduce the risk of stroke and other cardiovascular endpoints in patients aged more than 80 years.\(^{26}\) Subsidiary projects in the trial, which examine quality of life, falls and cognitive function, will enlighten the overall benefits and risks in this age group.\(^{27,28}\) Until we have the results of the HYVET and other studies of large groups of subjects aged more than 80 years, each patient must be carefully assessed, and the possible benefits of antihypertensive treatment must be weighed against the risks, which tend to increase with age.

### Optimal level of BP control in the elderly: the lower the better for elderly patients?

Another unsolved issue in elderly hypertension is the optimal level of BP control in elderly patients. It is now clear that systolic hypertension in elderly patients enhances the risk of cardiovascular events, and that active treatment reduces the risk of cardiac events, such as stroke, myocardial infarction and cardiac death. The optimal level of BP control in elderly patients has not yet been completely established.

Considering the multiple comorbidity and aging-related functional decline in the elderly population, the risk profiles in elderly hypertensive subjects seem to be higher than those in younger subjects. Recent guidelines have emphasized stricter BP control in the high-risk groups, such as those with diabetes and chronic kidney diseases. It is well known that the prevalence of diabetes and chronic kidney diseases increases with age due to insulin resistance and aging-related renal impairment. Moreover, a long duration of hypertension in elderly hypertensive patients increases the risk of renal impairment and also enhances the chance of chronic kidney diseases.

According to the J-shaped curve hypothesis, a major reduction in diastolic BP (DBP, \(< 65\) mmHg) might be associated with an increase in mortality. In hypertensive elderly individuals, lowering DBP might jeopardize appropriate blood flow in the brain, heart and kidney during the diastole. Moreover, it is unclear whether strict BP control is beneficial to the elderly population, especially the oldest-old population.\(^{29}\) Accordingly, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) goal for BP control (\(< 140/90\) mmHg and \(< 130/80\) mmHg in high risk group) seems too strict to achieve in elderly individuals.\(^{30}\) More clinical data regarding the optimal target BP goal in elderly patients, especially those who accompany a high risk, such as diabetes or renal impairment, need to be obtained.

The Japanese trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) study was a clinical trial investigating the role of strict BP control in elderly patients.\(^{31}\) The JATOS results are now available online (URL: http://www.jatos.jp/result/index.html). There was no benefit of strict SBP control (SBP, \(< 140\) mmHg) in elderly patients. The results must be considered in the management of elderly hypertension patients.

### Antihypertensive medication in the elderly: which is the best drug for the elderly?

It has been well known that calcium channel blockers and thiazide diuretics are recommended as the initial choice for elderly hypertensive patients.\(^{32}\) A recently published clinical study has clearly demonstrated that using newly developed antihypertensive medications have clinical benefit over the older drugs such as beta-blockers and diuretics in terms of reduction in cardiovascular and cerebrovascular events.\(^{33}\) Furthermore, newly developed angiotensin-converting enzyme inhibitors or angiotensin receptor blockers also have clinical benefit in elderly hypertensive patients.\(^{34-36}\)
Because elderly subjects usually accompany more cardiovascular risk factors than younger subjects, newly developed drugs blocking the rennin-angiotensin system might have a beneficial role besides their BP lowering effect. The efficacy and cost-effectiveness of these new drugs in elderly hypertensive patients need to be evaluated. Furthermore, several aspects, including safety, drug interaction and cognitive function, need to be considered as the requirements of the ideal agent for the elderly population. In general, drugs that meet the following criteria are recommended as first-line drugs for the elderly: (i) possibility of administration once or twice a day in order to maintain good adherence; (ii) long-acting effects (≥24 h with trough: peak ratio ≥50%), so as to be effective against the rapid elevation of BP early in the morning; and (iii) low cost compared with comparable drugs of similar efficacy.37

Hypertension control for the prevention of cognitive dysfunction: treating hypertension for the brain

Evidence has emerged that hypertension plays a part in the development and progression of cognitive impairment and dementia. High BP in the middle age implies a long-term cumulative effect, which leads to increased severity of atherosclerosis and more vascular comorbidities in late life.

Because post-stroke dementia is the most common form of vascular dementia (VD), the association between hypertension and VD can be easily understood.38 Among the various forms of VD, subcortical VD has an insidious clinical course without sensory-motor manifestations but with progressive changes in personality, mood, behavior or cognition. It is closely related with the disease of the subcortical small vessels of the medulla, which perpendicularly penetrate the brain cortex into the subjacent white substance without intertwining branches other than very fine capillaries, thus constituting many independent small vascular territories. The exposure of these small vessels to highly pulsatile pressure and flow explains microvascular damage, which results in white matter damage, lacunas and loss of cortical connections.38,39 The presence and extent of subcortical white matter lesion might also be associated with common geriatric syndromes such as falls, depression and urinary incontinence.40

Alzheimer’s disease (AD) is a neurodegenerative disease with impairment of cholinergic neurotransmission and intraneuronal accumulation of amyloid-β-protein. It is unlikely that hypertension might be associated with the development of AD. Nevertheless, accumulating evidence now suggests a strong link between AD and cardiovascular risk factors. Several clinical trials suggest a protective effect of antihyperten-

sive treatment against cognitive decline and dementia of both VD and AD.41,42

Effective antihypertensive therapy may protect against or postpone the onset of clinical dementia, especially stroke-related cognitive dysfunction, because appropriate antihypertensive therapy may have beneficial effects on both atherosclerotic and hemodynamic mechanisms.

However, there is little evidence that hypertension in later life also has the same negative effect on cognition. Indeed, based on some reports concerning the harmful cognitive effect of low BP, it seems that in older adults, and particularly in those who are very old, an appropriate level of BP may be required to retain cognitive function by maintaining adequate cerebral perfusion.43 However, the optimal BP remains unknown. The effect of antihypertensive treatment in the oldest-old population for the prevention of cognitive dysfunction may be answered with the results of the Hypertension in the Very Elderly Trial assessing cognitive decline and dementia incidence (HYVET-COG).48

Reducing BP is not enough to prevent cardiovascular cognitive diseases in elderly patients

BP variability

Previous studies have demonstrated that ambulatory BP variability is a significant and independent determinant of target organ damage and poor cardiovascular prognosis.44-48 Furthermore, BP variability is significantly associated with brain deep white matter lesions that are predisposing conditions of clinical stroke, dementia, depression and falls in the elderly.49,50

In the Systolic Hypertension in Europe (Syst-Eur) substudy, increased night-time SBP variability was found to be an independent risk factor for stroke, even after adjusting for BP levels and other confounding variables.51 As a result, the identification of increased BP variability by ambulatory monitoring may be a way to detect high risk patients of developing ischemic target organ damage, which could be aggravated by indiscriminate antihypertensive drug treatment. Specific measures to reduce the increased BP variability in elderly hypertensive patients need to be investigated, because individualized therapy based on ambulatory BP might spare the silent hypertensive-target-organ damage and clinical cardiovascular consequences governed by excessive BP variability.52

Global risk evaluation approach in elderly patients

Because elderly patients usually accompany multiple comorbidities, such as diabetes, renal impairment, lung disease, cognitive impairment and depression, consideration of the comorbidity is important for the proper
management of hypertension in the elderly. Another characteristic in elderly hypertension patients is orthostatic hypotension, which is sometimes associated with medication.

All of these findings suggest that more aggressive investigation to identify the global risk of the subject is much more important for the proper management of hypertension in elderly patients. A previous report has demonstrated that global risk assessment and management is superior to individual risk management. The results illustrate the limited potential of single risk factor management on the occurrence of cardiovascular diseases in the population. Instead, by taking multiple risk factors into account, global risk evaluation generally provides a more effective measure in the decision between treatment options than single risk factor measurement.

Korean perspective: current status of hypertension control in the community

The aging of society is clearly observed in Korea. The population aged over 65 years has already marked 7.2% in 2000. In other words, Korea has stepped into ‘the aging society’. The average life expectancy for Koreans was calculated as 74.4 years for men and 81.8 years for women in 2007, which has increased by 6 years and 5 years, respectively, as compared to a decade before. Although all developed countries face rapidly aging populations, the problem in Korea is expected to have the fastest pace due to the combination of a low fertility rate and increased longevity. The nation’s rapid aging will be a potential concern, which may threaten economic development and stability of the society itself.

A previous study reported that the age-adjusted prevalence of untreated ISH in the Korean population in a 2001 survey was 4.3%. The prevalence of untreated ISH in the Korean population appears to be much lower than that in other countries, such as China, the USA and Canada, where the prevalence of ISH was reported to be over 5%. However, considering the rapid increase of the aging population in Korea, the prevalence of ISH might increase in the near future.

We should know the exact current status of hypertension, its related comorbidity, the rate of BP control and the characteristics of antihypertensive drug treatment for the optimal management of hypertension in the elderly. We have designed and maintained the Korean Longitudinal Study on Health and Aging (KLoSHa), which is a population-based, prospective cohort study on health, aging and common geriatric diseases of elderly Koreans living in an urban community of Seongnam City. In our unpublished baseline study, we found that the prevalence of hypertension was 68.7%, which increased up to the age of 85 and slightly decreased thereafter.

Of the hypertensive patients, only 66.1% of the patients took some antihypertensive medications. BP was controlled in 38.5% of the hypertensive patients, with SBP being less controlled than DBP, especially in the oldest subgroup of the elderly population. Among the patients on antihypertensive medication, 46% were on a combination drug therapy. Our longitudinal study will provide the clinical significance of hypertension and its impact on functional status, cognitive function and quality of life in elderly Korean people.

Conclusions

Hypertension in the elderly is highly associated with vascular aging, and special attention is required to the characteristics of elderly patients for optimal treatment. Specific treatments targeting age-related vascular changes not only for retarding the progression of increased arterial stiffness and but also for improving age-related endothelial dysfunction need to be investigated.

When treating hypertension in elderly patients, the approach should be to identify global cardiovascular risk and consider the individual characteristics including functional status, cognitive function and quality of life. Furthermore, determining target BP and selecting antihypertensive drugs should be individualized for each elderly patient because elderly patients have multiple comorbidities. In addition, the benefit and optimal level of BP control in the oldest-old population must be investigated because many elderly hypertensive patients are currently being managed without definite evidence of related benefit.

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