GUIDELINES (JSH 2014)

Chapter 8. Hypertension in the elderly

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POINT 8

1. Nondrug therapy should be positively performed, but strategies should be individually selected, considering the patient's quality of life (QOL) (Recommendation grade: B, Evidence level: II).
2. Drug therapy should be indicated for patients with a blood pressure of $\geq 140/90$ mm Hg on principle. However, treatment indication must be individually assessed in persons, aged over 75 years, with a systolic blood pressure of 140–149 mm Hg or frail elderly, such as subjects who are unable to accomplish 6 m walking (Recommendation grade: B, Evidence level: II).
3. Ca channel blockers, ARBs, angiotensin-converting enzyme (ACE) inhibitors and low-dose diuretics are recommended as first-line antihypertensive drugs in elderly and nonelderly patients. Usually, the initial dose should be half of the standard dose. If antihypertensive effects are insufficient, combination therapy of these drugs should be initiated (Recommendation grade: A, Evidence level: I).
4. In patients with complications, choice of antihypertensive drugs should be individualized (Recommendation grade: B, Evidence level: II).
5. Blood pressure should be gradually reduced with due attention to adverse effects, organ damages and QOL. In patients with orthostatic hypotension, it must be more slowly controlled (Recommendation grade: C1, Evidence level: VI).
6. Target blood pressure in persons aged 65–74 years should be $<140/90$ mm Hg and that in those aged over 75 years should be $<150/90$ mm Hg. If treatment is well tolerated, more aggressive blood pressure control $<140/90$ mm Hg may further improve the outcome (Recommendation grade: B, Evidence level: II).
7. In patients with coronary artery disease, the risk of cardiac events may increase if diastolic blood pressure is <70 mm Hg. Therefore, blood pressure control should be performed while monitoring the absence of significant coronary stenosis, symptoms of myocardial ischemia and electrocardiographic findings (Recommendation grade: C1, Evidence level: IVa).

1. CHARACTERISTICS OF HYPERTENSION IN THE ELDERLY

Japan is a super-aged society in which the elderly aged over 65 years account for 23.3% of the population (in 2011) and those aged over 75 years account for 11.5%. Hypertension increases with age, and, according to the National Health and Nutrition Survey of Japan

(2011),⁸²⁶ hypertension is prevalent in 66% of those aged 65–74 years and 80% of those aged over 75 years. Generally, elderly individuals have multiple diseases and often show atypical presentations. There are marked individual differences in the physiological function even at the same age. When dividing the elderly based on age, caution is needed. In particular, old-old elderly persons aged over 75 years often show pathophysiological changes differing from those in nonelderly persons. The contents described in this chapter are more significant for treating old-old elderly persons.

Age-related physiological/pathological changes associated with blood pressure control in hypertensive patients are presented:

- Cardiovascular system: Atherosclerosis/reduction of vascular elasticity, left ventricular hypertrophy/diastolic dysfunction.
- Nervous system: Impairment of the baroreceptor reflex, reduction of β -receptor function.
- Water/electrolyte metabolism: Impairment of body fluid regulation related to deterioration in renal function, vulnerability of electrolyte homeostasis (particularly, hyponatremia and hypokalemia).
- Glucose metabolism: Increased insulin resistance, impaired glucose tolerance.
- Endocrine system: Declines in the renin–angiotensin, kallikrein–kinin, prostaglandin and renal dopamine systems, impairment of the pressor and depressor systems.
- The characteristics of hypertension in the elderly associated with these age-related changes or the progression of atherosclerosis are shown in Table 8-1.

2. CRITERIA FOR HYPERTENSION IN THE ELDERLY AND EPIDEMIOLOGICAL FINDINGS

A positive correlation was observed between an increase in blood pressure and the logarithmically transformed cardiovascular mortality rate in the Hisayama Study¹⁰⁵ and in the meta-analysis of approximately one million people with no history of cardiovascular disease in 61 prospective studies.²⁸⁷ This correlation was still observed in those in their 80s, and absolute cardiovascular risk increased with age, whereas the slope of correlation became gentler in old age. In NIPPON DATA80, which is a 19-year follow-up study in Japan, an increase in blood pressure was also positively correlated with an increase in the risk of cardiovascular death.²³⁴ On the other hand, there are epidemiological studies that report the presence of a blood pressure threshold related to increases in cardiovascular risk and mortality rate. However, the threshold may be influenced by the analytical method, number of subjects, observation period and outcome (disease onset or disease-related death). On the basis of these

Table 8-1 Precautions in the diagnosis of hypertension in the elderly*Characteristics of hypertension in the elderly*

- Increased fluctuation of blood pressure
- Increase in systolic hypertension
- Increase in white coat hypertension
- Increase in orthostatic hypotension or postprandial blood pressure reduction
- Increase in the non-dipper-type nighttime blood pressure
- Increase in the incidence of patients with a morning surge
- Decreases in the vital organ perfusion and reserve
- Impairment of autoregulation of vital organ perfusion

Comprehensive evaluation of the blood pressure level

- Blood pressure is repeatedly measured.
- Home or 24-h blood pressure measurement is concomitantly performed.
- Blood pressure in a standing position is measured before and after the start of drug therapy, after switching the regimen, or at the appearance of dizziness (if systolic blood pressure decreases by 20 mm Hg or more 3 min after standing up, a diagnosis of orthostatic hypotension is made).⁸³⁹
- Conditions for measurement should be considered (after meals, after taking drugs and so on).
- If symptoms of diet-associated blood pressure reduction (such as dizziness) are present, 24-h or postprandial blood pressure measurement should be performed (if systolic blood pressure in a sitting position decreases by 20 mm Hg or more 1 h after meals, a diagnosis of postprandial blood pressure reduction is made).⁸³⁹

Diagnosis of latent complications

- The diagnosis of atrial fibrillation, aortic valve stenosis, aortic aneurysm, renovascular hypertension or carotid artery stenosis is important because therapeutic strategy differs.
- Thoracic/abdominal/cervical auscultation and abdominal palpation should be conducted for screening.

results, basically, cardiovascular risk is lower at a lower blood pressure even in elderly people. The same criterion of hypertension as that for nonelderly persons was set for elderly people.

3. DIAGNOSIS**1) Diagnosis considering fluctuation of blood pressure**

The comprehensive diagnosis of the blood pressure level is shown in Table 8-1. In elderly patients with hypertension, blood pressure fluctuates widely, and measurement condition is easy to affect blood pressure.⁸²⁷ A study involving elderly patients (mean age: 70 years) indicated that cardiovascular risk was high in patients with masked hypertension (reverse white coat hypertension).¹³⁵ On the initial visit, blood pressure should be measured simultaneously by the palpation method to avoid overlooking auscultatory gaps (disappearance of Korotkoff sounds) and pseudohypertension (the artery cannot be compressed using a cuff owing to marked arteriosclerosis with vascular calcification).⁸²⁸ However, the incidence of pseudohypertension is low in Japan.

2) Diagnostic consideration of secondary hypertension

In addition to differential diagnosis in a treatment plan on the initial visit, attention to secondary hypertension should be paid in patients who show a marked increase in blood pressure in a short period, poor control and treatment resistance. In particular, renovascular hypertension due to atherosclerosis or primary aldosteronism, an endocrine hypertension, must be considered in elderly patients.

Many elderly patients take multiple drugs, and drug-induced hypertension may occur. An inquiry regarding prescriptions in other

hospitals/clinics or department and health foods/supplements is important. An inquiry regarding Licorice-containing substances (such as traditional Chinese herbal medicines) and nonsteroidal anti-inflammatory drugs is essential. It was reported that there was an increase in blood pressure in elderly patients undergoing molecular target therapy for diseases such as cancer and age-related macular degeneration (see Section 7 of Chapter 13, DRUG-INDUCED HYPERTENSION).

3) Diagnosis of target organ damage and complications

Although diagnostic methods are basically similar to those for nonelderly patients, elderly patients often show asymptomatic multiple organ damage. Points to diagnose latent complications are presented in Table 8-1. The diagnosis of carotid artery stenosis is important, because in patients with bilateral >75% carotid artery stenosis a decrease in blood pressure leads to an increase in stroke risk.²⁸²

4. TREATMENT**1) Effects of antihypertensive therapy in the elderly**

In elderly patients, medical intervention should aim either to maintain their activities of daily living or to prevent decline in activities of daily living. The prevention of cardiovascular disease, a major complication of hypertension, is consistent with this purpose. In addition, effects of antihypertensive therapy of cognitive function and fall/fracture are also important as factors for being bedridden.

Randomized, placebo-controlled studies have shown the preventive effects of antihypertensive drugs on cardiovascular diseases (Table 8-2). In these studies, diuretics, β -blockers and Ca channel blockers were chosen as first-line drugs. According to a meta-analysis of nine major clinical studies on the treatment of hypertension in elderly patients (aged over 60 years), antihypertensive drug treatment significantly reduced all-cause mortality by 12%, death from stroke by 36%, death from coronary artery disease by 25%, the incidence of stroke by 35% and that of coronary artery disease by 15%.⁸²⁹

In the Hypertension in the Very Elderly Trial (HYVET), involving patients with hypertension (mean blood pressure: 173/91 mm Hg) aged over 80 years, treatment was performed using diuretics (ACE inhibitors were added when the antihypertensive effect was insufficient) with a target of <150/80 mmHg, and a significant 30% decrease in the incidence of stroke, 21% decrease in all-cause mortality, 64% decrease in the incidence of heart failure and 34% decrease in the incidence of cardiovascular events were observed.²⁴⁴ In addition, there was no increase in the incidence of dementia,⁸³⁰ and the incidence of fracture decreased.⁸³¹

Although no randomized controlled study has compared the incidence of cardiovascular events between placebo and antihypertensive drug groups in Japanese patients, Chinese patients accounted for 40% of the subjects of the Syst-China,⁸³² STONE⁸³³ and HYVET. The above results can be extrapolated to Japanese patients. Thus, antihypertensive treatment should be aggressively performed even in elderly patients, including those aged over 80 years.

2) Subjects to be treated with antihypertensive drugs and target levels of blood pressure

(1) *Subjects to be treated.* In randomized controlled studies involving elderly hypertensives, in which the effectiveness of antihypertensive therapy was demonstrated, registration criteria included a systolic blood pressure of ≥ 160 mm Hg and a diastolic blood pressure of ≥ 90 –100 mm Hg. Therefore, in principle, antihypertensive drugs should be started in patients with a blood pressure of $\geq 160/90$ mm Hg. With regard to patients with grade I hypertension at

Table 8-2 Placebo-controlled comparative studies investigating the preventive effects of antihypertensive drugs on cardiovascular events involving elderly patients (presented in the order of a lower systolic blood pressure achieved in the drug group)

	<i>SHEP</i> ⁸³⁵	<i>HYVET</i> ²⁴⁴	<i>STONE</i> ⁸³³	<i>Syst-China</i> ⁸³²	<i>EWPH</i> ⁸⁶³	<i>Syst-Eur</i> ⁸⁶⁴	<i>MRC II</i> ⁸⁶⁵	<i>HEP</i> ⁸⁶⁶	<i>STOP</i> ⁸⁶⁷
Subjects' age (years)	≥60	≥80	60–79	≥60	≥60	≥60	65–74	60–79	70–84
Mean age (years)	72	83.6	66	67	72	70	70	69	76
Number of subjects	4736	3845	1632	2394	840	4695	4396	884	1627
Study method	Double-blind	Double-blind	Single-blind	Single-blind	Double-blind	Double-blind	Single-blind	Open	Double-blind
Primary drug in the drug group	Diuretic	Diuretic	CCB	CCB	Diuretic	CCB	Beta-blocker/ diuretic	Beta-blocker	Beta-blocker/ diuretic
Additional drug in the drug group	Beta-blocker	ACE inhibitor	ACE inhibitor, diuretic	ACE inhibitor, diuretic	Methyldopa	ACE inhibitor, diuretic	Combination	Diuretic, methyldopa	Combination
Follow-up period (years)	4.5	2.1	3.0	4.0	4.7	2.0	5.8	4.4	2.1
Blood pressure before treatment (mm Hg)	177/77	173/91	168/98	170/86	180/101	174/86	185/91	197/100	195/102
Blood pressure achieved in the placebo group (mm Hg)	155/71	159/84	155/90	159/84	171/95	161/84	166/83	180/88	186/99
Blood pressure achieved in the drug group (mm Hg)	143/68	144/78	146/85	150/81	150/85	151/79	152/77	162/77	167/87
Difference in the systolic blood pressure achieved mm Hg)	12	15	9	9	21	10	14	18	19
Relative risk of cardiovascular events	0.68	0.66	0.4	0.63	0.71	0.69	0.83	0.76	0.6

Abbreviation: ACE, angiotensin-converting enzyme; STOP, STOP-Hypertension.
In all studies, there was a significant decrease in the relative risk of cardiovascular events.

moderate-risk level, although a study reported that a Ca channel blocker regressed cardiac hypertrophy and improved QOL (mean age of the subjects: 66 ± 6.8 years, patients aged over 65 years: 49%, mean blood pressure on registration: 149/83 mm Hg),⁸³⁴ we cannot apply this evidence for old-old elderly patients. With respect to randomized, placebo-controlled studies showing differences in the prognosis (Table 8-2), the blood pressure achieved in the placebo group was the lowest in the Systolic Hypertension in the Elderly Program Study (patients aged over 80 years: 13.7%). In the placebo and drug groups, blood pressure was reduced to 155 and 143 mm Hg, respectively.⁸³⁵ In the HYVET involving patients aged over 80 years, blood pressure was reduced to 159 and 144 mm Hg in the placebo and drug groups, respectively.²⁴⁴ Thus, there is no scientific basis in treating old-old elderly patients with a systolic blood pressure of 140–149 mm Hg.

An observational study suggests that some patient groups need individually set indications for antihypertensive therapy.⁸³⁶ The declining walking speed is an indicator for 'frailty' in the elderly population. For an elderly person who can walk a 6-m distance within <7.5 s (0.8 ms^{-1} or more), the presence of hypertension (≥ 140 mm Hg) negatively affects prognosis. However, for an elderly person who needs 7.5 s or longer to walk a 6-m distance, there are no significant differences in prognosis between the normotensive group and the hypertensive group. Even after correcting for the presence or absence of antihypertensive drug therapy, the same results were obtained. In the extremely slow-walker group, it may be risky to start antihypertensive drugs according to a criterion of ≥ 140 mm Hg.

In the National Institute for Health and Clinical Excellence Guidelines in England,⁸³⁷ it is described that antihypertensive drugs should be indicated for patients with grade II or III hypertension ($\geq 160/100$ mm Hg) among those aged over 80 years. According to a consensus by specialists regarding hypertension in the elderly in the

United States,⁸³⁸ antihypertensive drug therapy is recommended for patients with a systolic blood pressure of ≥ 150 mm Hg among those aged over 80 years. In the European Society of Hypertension/European Society of Cardiology Guidelines in 2013,¹²⁰ it is recommended, for the elderly, that antihypertensive drug therapy should be started if systolic blood pressure is ≥ 160 mm Hg. It is also described, for persons aged 79 years or younger, that the start of antihypertensive drug therapy may be considered at a blood pressure of 140–159 mm Hg, as a consensus-based recommendation. In elderly hypertensives who are not in the category, individual evaluation is needed for the introduction of antihypertensive drugs.

The guidelines recommend a blood pressure of $\geq 140/90$ mm Hg as a general criterion to start antihypertensive drugs in the elderly population, considering high incidence of stroke as a complication of hypertension in Japanese, which is closely associated with blood pressure. As a consensus, the Guidelines recommend that the introduction of antihypertensive drugs should be individually evaluated in persons, aged over 75 years, with a systolic blood pressure of 140–149 mm Hg or frail elderly, such as subjects who are unable to accomplish 6 m walking. However, because age- or physical activity-based categorization criteria are not well defined, indication for antihypertensive drugs should be comprehensively assessed considering those categorizations, complications and target blood pressures.

(2) *Target blood pressure in the elderly.* Our recommendation on target blood pressure is based on the achieved blood pressure in large-scale clinical trials, which showed significant difference in cardiovascular events among groups, on target blood pressure levels set in group-comparing trials regarding target blood pressure and on results of epidemiological studies. Table 8-2 shows a list of comparative studies, involving elderly patients with hypertension, in which there

were significant differences in the incidence of cardiovascular events. On the basis of the results of the Systolic Hypertension in the Elderly Program Study, a target blood pressure of <150 mm Hg can be applied for the elderly. In addition, the FEVER Study, which enrolled patients who were on oral hydrochlorothiazide 12.5 mg but their blood pressure were higher than 140/90 mm Hg, carried out a sub-analysis on 3179 cases aged over 65 years. It revealed that the felodipine group achieved a blood pressure of 139.7/81.2 mm Hg, whereas the placebo group remained at a blood pressure of 145.5/83.6 mm Hg, and the cardiovascular events were 47% fewer in the felodipine group. This was a study involving Chinese patients, and the mean blood pressure achieved was below 140 mm Hg, being a reason for establishing the target of blood pressure control as <140 mm Hg for elderly patients with hypertension.⁸³⁹

Among comparative studies on target blood pressure, a subanalysis of the HOT Study compared elderly patients (mean age: 70.6 years) with three different targets of diastolic blood pressure.⁸⁴⁰ In patients aged over 65 years, blood pressure achieved 147/83 mm Hg in those with a target diastolic blood pressure of ≤ 90 mm Hg, 145/82 mm Hg in those with a target diastolic blood pressure of ≤ 85 mm Hg and 143/80 mm Hg in those with a target diastolic blood pressure of ≤ 80 mm Hg, respectively. No significant difference in the incidence of cardiovascular events was shown among the three groups. As presented in Table 8-3, two studies enrolling elderly hypertensives were conducted that compared the strict systolic blood pressure control group (<140 mm Hg) with the mild blood pressure control group: JATOS (mean age: 73.6 years, target blood pressure in the mild control group: 140–159 mm Hg)⁸⁴¹ and VALISH (mean age: 76.1

years, target blood pressure in the mild control group: 140–149 mm Hg).⁸⁴² Both studies were conducted in Japan, and neither of them showed a significant difference in event rate between the two groups. Owing to statistical power limitations, conclusion of these studies did not favor strict blood pressure control, nor mild blood pressure control. However, from the perspective of adverse events, it was suggested that a target systolic blood pressure of <140 mm Hg can be safely achieved even in elderly patients.

Concerning the relationship between blood pressure on registration and the occurrence of cardiovascular events in epidemiological studies, there was a positive correlation even at a blood pressure of <140/90 mm Hg in subjects including those aged over 80 years,²⁸⁷ as described above. This may also apply to hypertensive patients undergoing antihypertensive treatment to some degree.

In the National Institute for Health and Clinical Excellence Guidelines in England,⁸³⁷ it is recommended that the target blood pressure in persons aged over 80 years should be <150/90 mm Hg (antihypertensive drugs should be considered for patients with blood pressure ≥ 160 mm Hg). According to a consensus by specialists regarding hypertension in the elderly in the United States,⁸³⁸ the target blood pressure in persons aged over 80 years may be established as 140–145 mm Hg if tolerated (antihypertensive drugs should be considered for patients with blood pressure ≥ 150 mm Hg). In addition, it is described that, although blood pressure values below which vital organ perfusion is impaired are not known, blood pressure lower than 130/60 mm Hg should generally be avoided, if possible. In the European Society of Hypertension/European Society of Cardiology Guidelines in 2013,¹²⁰ it is recommended that blood pressure should be reduced to

Table 8-3 Large-scale clinical studies conducted in Japan regarding the treatment of hypertension in the elderly (multicenter collaborative randomized comparative studies)

Objective of comparison	Comparison of the target blood pressure		Comparison of two drugs		Comparison of combination therapy	
Study name	JATOS ⁸⁴¹	VALISH ⁸⁴²	NICS-EH ⁴¹³	CASE-J (subanalysis) ⁵¹²	COPE (subanalysis) ⁸⁵⁵	OSCAR ⁴³⁴
Subjects' age (years)	65–85	70–84	≥ 60	75–84	65–85	65–84
Mean age (years)	73.6	76.1	69.8	78.3	72.6	73.6
Number of patients	4418	3079	414	751 (≥ 75)	1533	1164
Antihypertensive drug	Ca channel blocker (felodipine), (1) Strict: <140 (2) Slow: 140–159	ARB (valsartan) (1) Strict: <140 (2) Slow: 140–159	(1) Ca channel blocker (nicardipine), (2) Diuretic (trichlormethiazide)	(1) Ca channel blocker (amlodipine) (2) ARB (candesartan)	Ca channel blocker (benidipine)+(1) Diuretic (2) ARB (3) β -blocker	ARB (olmesartan)+(1) Ca channel blocker (2) ARB at an increased dose
Study method	PROBE	PROBE	Double-blind	PROBE	PROBE	PROBE
Follow-up period (years)	2	3.1	5	3.2	3.6	3
Blood pressure before treatment (mm Hg)	172/89	(1) 170/82 (2) 170/81	172/94	168/89	(1) 155/85 (2) 155/85 (3) 155/85	(1) 157/85 (2) 158/85
Blood pressure after treatment (mm Hg)	(1) 136/75 (2) 146/78	(1) 137/75 (2) 142/77	(1) 147/81 (2) 147/79	141/76	(1) 134/73 (2) 135/74 (3) 134/74	(1) 133/73 (2) 131/74
Comparison of cardiovascular events	NS	NS	NS	NS	NS	NS
Other results				Increase in the incidence of cardiovascular events at a blood pressure achieved of ≥ 150 mm Hg	Incidence of stroke: (1) < (3)	Incidence of cardiovascular events in a group with a history of cardiovascular disease: (1) < (2)

Abbreviation: NS, not significant.
Blood pressure values are rounded off.

140–150 mm Hg in persons aged 79 years or younger with a systolic blood pressure of ≥ 160 mm Hg based on evidence. As a consensus, it is also recommended that a target blood pressure of < 140 mm Hg should be considered in healthy elderly persons and that the target blood pressure should be individually assessed in frail elderly. It is strongly recommended that, in those, aged over 80 years, with a systolic blood pressure of ≥ 160 mm Hg, blood pressure should be reduced to 140–150 mm Hg if the condition is physically and mentally favorable. In these guidelines, the contents are described focusing on patients whose blood pressure is reliably recommended to be reduced, regarding the HYVET protocol and achieved blood pressure as important among limited evidences at this age bracket.

The present guidelines recommend that target blood pressure should be $< 140/90$ mm Hg in persons aged 65–74 years and $< 150/90$ mm Hg in those aged 75 years or older, considering high incidence of stroke as a complication of hypertension in Japanese, which is closely associated with blood pressure. If those aged 75 years or older tolerate treatment, the prognosis may be further improved by aggressively targeting a blood pressure of $< 140/90$ mm Hg.

(3) *Circumstances under which the target blood pressure should be individually assessed.* If the age-based target blood pressure differs from that based on the presence of complications, age-based target blood pressure should be set as the first goal and a lower target based on the presence of complications should be aimed if tolerated. However, in old-old elderly patients, there is no evidence that recommends that a lower target level should be aimed in many cases, and, if a lower target level is aimed, adverse effects related to increases in the doses of antihypertensive drugs or an increase in economic burden must be considered. In particular, many elderly patients have chronic kidney disease, and the risk of acute kidney injury related to an excessive decrease in blood pressure must be considered.

In patients taking antithrombotic drugs because of cerebrovascular or cardiovascular diseases, the risk of cerebral hemorrhage or hemorrhagic infarction is high; therefore, strict blood pressure control should be performed.³²⁵ With respect to the concrete target blood pressure, see Section 7 of Chapter 3, OTHER POINTS REQUIRING ATTENTION and Section 1 of Chapter 6, CEREBROVASCULAR DISEASE).

In elderly persons, orthostatic hypotension and a postprandial decrease in blood pressure are frequently observed, and blood pressure often decreases owing to a decrease in food intake. Fluctuation of blood pressure is also large in most elderly persons. Therefore, home blood pressure should be proactively evaluated to manage blood pressure.

(4) *J-shaped phenomenon.* Some large-scale clinical trials, in which patients were divided into groups based on the achieved blood pressure in each patient, reported that the correlation between the blood pressure level and incidence of events was not a linear one, but the incidence of events increased when a blood pressure that was below a specific level was achieved. This is termed ‘J-shaped phenomenon’ from the shape of a curve showing the relationship between the two factors. Although analysis based on the achieved blood pressure cannot prove cause and effect, there is undeniable possibility of the reversion of cause and effect that the patients with high risks are likely to show low blood pressure. There is no J-shaped phenomenon in any comparative study in which several target blood pressures were established before the study. The study results with the J-shaped phenomenon have significance of suggesting precautions regarding the level of blood pressure reduction for achieving strict blood pressure control.

There are several reports on the J-shaped phenomenon: Systolic Hypertension in the Elderly Program (the incidence of cardiovascular events increased at a diastolic blood pressure of < 60 mm Hg),⁸⁴³ Syst-Eur (the incidence of events increased at a diastolic blood pressure of < 70 mm Hg in systolic hypertension patients with coronary artery disease),⁸⁴⁴ PATE-Hypertension (the incidence of cardiac events increased at a systolic blood pressure of < 120 mm Hg and there was no J-shaped phenomenon with respect to cerebral events),⁸⁴⁵ PATE-Hypertension 2 (the incidence of cardiac events increased at a systolic blood pressure of < 120 mm Hg and there was no J-shaped phenomenon in patients aged 74 years or younger)⁸⁴⁶ and INVEST involving hypertensive patients with coronary artery disease (the incidence of events was the lowest at a blood pressure of 135–140/70–75 mm Hg in patients aged over 70 years).⁸⁴⁷ Even an epidemiological study did not show a low incidence of events in patients with a blood pressure of $< 115/75$ mm Hg;²⁸⁷ it is not necessary to aggressively reduce blood pressure to a low level at which a J-shaped phenomenon is concerned.

However, the incidence of systolic hypertension is high in elderly patients, and diastolic blood pressure is often reduced to < 75 mm Hg to achieve the target of systolic blood pressure control. In particular, caution is needed in patients with coronary artery disease.^{844,847} Another subanalysis of the INVEST Study showed that the incidence of events reached a minimum at a blood pressure of 125/55 mm Hg in patients who underwent coronary bypass, with no J-shaped phenomenon, although the subjects were not limited to elderly patients.⁸⁴⁸ This suggests a mechanism by which a reduction in coronary blood flow related to a decrease in diastolic blood pressure causes ischemia-induced arrhythmia or heart failure, leading to the onset of events, and indicates the possibility that, if ischemia is relieved by coronary artery revascularization, the risk of the J-shaped phenomenon may be reduced.

Thus, generally, the risk of excessively decreasing blood pressure is rare, but it is recommended that the target blood pressure should be achieved while monitoring changes in diastolic blood pressure and coronary artery disease in patients with systolic hypertension. In particular, the risk of cardiac events may increase in patients with coronary artery disease if diastolic blood pressure is reduced to < 70 mm Hg to achieve a target systolic blood pressure. Blood pressure control must be performed while confirming the absence of significant coronary stenosis, symptoms of myocardial ischemia and electrocardiographic findings.

(5) *Gradual reduction in blood pressure.* In elderly patients with hypertension, particular attention must be paid to the speed of blood pressure reduction for achieving the strict target blood pressure because of high incidence of impairment of vital organ perfusion or autoregulation. Antihypertensive drugs should be started generally at half the regular dose, and the dose should be increased at an interval of 4 weeks–3 months by evaluating the presence or absence of signs of brain ischemia, such as dizziness and orthostatic dizziness, symptoms of angina pectoris, electrocardiographic changes indicating myocardial ischemia and a decline in the QOL. In HYVET, in which the participants were hypertensive patients aged over 80 years, whether the dose should be increased was evaluated every 3 months.⁸⁴⁹ In patients with orthostatic hypotension or a postprandial decrease in blood pressure, the magnitude of decrease is greater at a higher blood pressure and symptoms more frequently occurred. In those with orthostatic hypotension, the magnitude of decrease in blood pressure on standing is often reduced by decreasing blood pressure.⁸⁵⁰ While paying attention to fall and a decline in the QOL, blood pressure

should be gradually reduced. In principle, α -blockers should not be used. Diuretics may also promote a decrease in blood pressure through a reduction in the circulating plasma volume.⁸³⁸

3) Lifestyle modifications

In elderly people, nondrug therapies (lifestyle modifications), such as restriction of salt intake, exercise and weight control, are useful,²⁸⁹ and should be positively practiced. However, marked changes in lifestyle may impair QOL, and hence lifestyle modifications should be limited to a stress-free level.

(1) *Dietary therapy.* Even in elderly people, basic strategies are restriction of salt intake and weight control for obesity.²⁸⁹ As elderly people generally have high salt sensitivity, salt intake restriction is effective. The target of salt intake restriction should be 6 g per day, but caution is needed because excessive salt intake restriction may cause dehydration on massive sweating. Furthermore, extreme changes in the taste reduce dietary intake, leading to malnutrition in some cases. Therefore, for guidance, the management of the general condition must also be emphasized. Generally, a potassium-rich diet is recommended, but attention to hyperkalemia associated with renal dysfunction or diabetes is necessary. Calcium intake should be 800 mg per day or more for the prevention of osteoporosis.

(2) *Exercise therapy.* Exercise therapy is also appropriate for elderly hypertensives (patients with grade I hypertension, with a mean age of 75 years).⁸⁵¹ In those aged over 60 years, mild exercise at a heart rate of ~ 110 beats per min, such as fast walking, should be performed regularly for 30–40 min per session three or more times a week. If there are complications such as coronary artery disease, heart failure, renal failure and bone and joint disease, whether exercise therapy should be performed must be individually evaluated based on specialists' opinions.

4) Selection of antihypertensive drugs

(1) *First-line antihypertensive drugs in the elderly.* Drugs that have been shown to be effective in placebo-controlled studies (including subanalyses) involving elderly patients with hypertension or drugs with systolic hypertension, and those that exhibited similar or more potent preventive effects on cardiovascular disease compared with those drugs in comparative controlled studies, have been selected as first-line drugs.

The effectiveness of thiazide diuretics (including thiazide-like diuretics), β -blockers and Ca channel blockers has been confirmed in placebo-controlled studies (Table 8-2). Of these, most β -blockers are contraindicated for elderly patients, or caution is needed for their use; they may not become a first-line drug for hypertension in the elderly. When administering diuretics, their influence on impaired glucose tolerance, hyperuricemia and dyslipidemia must be considered, and low-dose therapy should be performed to reduce these adverse effects. The STOP-Hypertension-2,⁸⁵² NICS-EH⁴¹³ and ALLHAT (age-stratified analysis)²³⁷ directly compared the effectiveness of a diuretic with that of a Ca channel blocker. There was no significant difference in the incidence of cardiovascular events between the two drugs in any study. In the NICS-EH Study, the tolerance to the Ca channel blocker, which was evaluated from the medical dropout rate, was better.

The effects of ARBs were examined by a subanalysis of LIFE, in which an ARB was compared with a β -blocker, involving patients with systolic hypertension,⁸⁵³ and a subanalysis of CASE-J, in which an ARB was compared with a Ca channel blocker, involving elderly

patients.⁵¹² The subanalysis of LIFE showed that there was no significant difference in the composite incidence of cardiovascular events, as a primary end point. However, the ARB (losartan) more potentially prevented the onset of stroke compared with the β -blocker (atenolol).⁸⁵³ This is the reason why a β -blocker is not selected as a first-line drug in elderly patients. The subanalysis of CASE-J involving elderly patients indicated that there was no difference in the incidence of events between the Ca channel blocker (amlodipine) and ARB (candesartan) groups.⁵¹² However, when analyzing all subjects including nonelderly patients, the proportion of patients undergoing combination therapy in the candesartan group was higher than in the amlodipine group (42.7 versus 54.7%).⁴⁶⁷

The STOP-Hypertension-2,⁸⁵² in which an ACE inhibitor was compared with a diuretic or β -blocker, and ANBP-2⁸⁵⁴ and ALLHAT (age-stratified analysis),²³⁷ in which an ACE inhibitor was compared with a diuretic, have shown that the effectiveness of ACE inhibitors is similar to that of other drugs. In the PATE-Hypertension, which was conducted in Japan, involving 3-year follow-up of elderly patients with hypertension receiving treatment (aged over 60 years), there was no significant difference in the incidence of cardiovascular complications between the Ca channel blocker (manidipine) and ACE inhibitor (delapril) groups.³²⁵ However, in the latter, the discontinuation rate was significantly higher than that in the former. In most patients, treatment was discontinued because of cough.⁸⁴⁶

With respect to drugs to be predominantly used, the National Institute for Health and Clinical Excellence Guidelines in England⁸³⁷ recommend that Ca channel blockers should be selected as a first-line drug in patients aged 55 years or older. However, this cannot be concluded based on the results of comparison of preventive effects on cardiovascular events in large-scale clinical trials. In the European Society of Hypertension/European Society of Cardiology Guidelines in 2013,¹²⁰ all antihypertensive drugs, including β -blockers, are recommended for the treatment of hypertension in the elderly, and it is described that diuretics and Ca channel blockers may be appropriate for patients with systolic hypertension.

On the basis of these results, as first-line drugs, Ca channel blockers, ARBs, ACE inhibitors or low-dose thiazide diuretics are recommended at an equivalent level. Of these, a drug should be selected primarily to achieve the target blood pressure, considering individual background factors, adverse effects and health expenditure.

(2) *Combination therapy.* Few clinical studies have prospectively compared regimens for combination therapy involving elderly hypertensives, but the results of an age-stratified analysis of ACCOMPLISH (international study)⁴³⁷ and a subanalysis of the COPE trial, which was conducted in Japan, involving elderly patients,⁸⁵⁵ have been published (Table 8-3). The OSCAR Study, in which the efficacy of an ARB at an increased dose was compared with that of a combination of an ARB and a Ca channel blocker, is also significant for examining the effectiveness of combination therapy.⁴³³

In the ACCOMPLISH Study, a combination of an ACE inhibitor (benazepril) and a Ca channel blocker (amlodipine) was compared with that of benazepril and a diuretic (hydrochlorothiazide), and the incidence of complex cardiovascular events was lower in the ACE inhibitor+Ca channel blocker group. In the study, these two combination therapies were also compared in two subgroups consisting of 7640 patients aged over 65 years and 4703 aged over 70 years, respectively. The results in the two subgroups were similar to those in all subjects.⁴³⁷ In addition, in the OSCAR Study, the efficacy of an ARB (olmesartan) at a maximum dose was compared with that of a combination of the ARB at a standard dose and a Ca channel blocker,

and there was no difference in the incidence of cardiovascular events between the two groups.⁴³³

Internationally, evidence regarding Ca channel blocker-based combination therapy is limited to the COPE trial alone.⁸⁵⁵ In this trial, the results were compared among three combinations, a Ca channel blocker (benidipine)+a diuretic, benidipine+an ARB and benidipine+a β -blocker. A subanalysis involving elderly patients showed that there were no differences in the incidence of complex cardiovascular events, as a primary end point, among the three groups. However, in the diuretic-combined group, the incidence of stroke was lower than that in the β -blocker-combined group.

When selecting a combination regimen, blood pressure control to a target level should be primarily considered, but it is also necessary to consider adverse events such as side effects and health expenditure; the regimen must be individually selected.

On the basis of the above evidence regarding hypertension in the elderly, combination therapy with a Ca channel blocker, an ARB or ACE inhibitor and a low-dose diuretic, which are recommended as a first-line drug, should be performed. There is no sufficient evidence to determine which of two options, increasing the dose of each drug and combination therapy with other drugs, should be selected. If there is a drug to be more aggressively used for compelling indications, its dose may be increased. However, in other cases, a therapeutic strategy is selected based on the attending physician's consideration.

(3) *Compelling indication in the presence of complications.* As elderly patients often have complications, it is necessary to establish the target blood pressure and select antihypertensive drugs in accordance with the complications. However, evidence is not necessarily sufficient regarding frequent complications in the elderly, such as chronic kidney disease or diabetes mellitus. In particular, evidence in old-old elderly patients is extremely limited, and it is impossible to recommend the choice of antihypertensive drugs and target blood pressure based on evidence. Therefore, in principle, whether antihypertensive therapy should be applied must be individually evaluated based on general evidence.

Aspiration pneumonia and osteoporosis have been emphasized as conditions, characteristic of elderly persons, that influence the choice of antihypertensive drugs. No study has investigated the influence of antihypertensive drugs in hypertensive patients with these disorders, but the following drugs are recommended from the perspective of a decrease in the incidence of aspiration pneumonia or a decrease in the incidence of osteoporosis-associated fracture.

In elderly patients, aspiration pneumonia accounts for a high percentage of pneumonia and is often related to survival. ACE inhibitors have been reported to reduce the frequency of aspiration pneumonia in elderly patients by enhancing the cough reflex.^{856,857} If coughing is tolerable as a side effect, ACE inhibitors should be used in elderly patients with a history of aspiration pneumonia (including latent pneumonia).

In the HYVET involving hypertensive patients aged over 80 years, the results were compared between the drug and placebo groups, and there was a significant decrease in the incidence of fracture in the former.⁸³¹ In this group, a diuretic (indapamide) was used as the basal drug, and an ACE inhibitor (perindopril) was concomitantly used in approximately three-fourth of the patients. β -blockers have also been reported to promote bone metabolism and reduce the risk of fracture.^{858,859} However, β -blockers cannot be aggressively selected because of other pharmacological actions in the elderly. According to the results of a survey involving 370 000 elderly patients with hypertension in whom antihypertensive drugs were newly started using a

single drug, with no history of antihypertensive drug therapy within 1 year, the incidences of fracture in the thiazide diuretic (hazard ratio: 0.85) and ARB (hazard ratio: 0.76) groups were significantly lower than in the Ca channel blocker group.⁸⁶⁰ However, with regard to ARBs, no interventional study has investigated their preventive effects on fracture. In hypertensive patients with osteoporosis, osteoporosis should be adequately treated *per se*, and thiazide diuretics are recommended to treat hypertension if there is no compelling indication to the use of other drugs.

5) Other precautions based on the specificity of elderly patients

(1) *Precautions associated with the prevention of fall/fracture.* Fall and fracture are important factors for being bedridden in the elderly. General matters regarding prevention of fall/fracture and matters related to hypertension treatment are presented in Table 8-4). In elderly persons, an inquiry on a history of fall within

Table 8-4 Precautions based on the specificity of elderly persons

Precautions associated with the prevention of fall/fracture

- Fall/fracture in elderly persons accounts for more than 10% of the causes of being bedridden.
- An inquiry on a history of fall within 1 year should be conducted. If the history is present, intrinsic and extrinsic factors should be examined.
- Osteoporosis should be evaluated and treatment should be performed according to guidelines.
- Blood pressure should be gradually reduced regardless of the presence or absence of orthostatic hypotension.
- When antihypertensive drug therapy is newly started or changed, the risk of fracture may increase.
- If there is no antihypertensive drug to be aggressively indicated, thiazide diuretics should be used.

Dehydration- or environmental change-matched guidance for drug therapy

- Excessive salt restriction or dehydration (diarrhea, fever, excessive sweating in the summer, a decrease in dietary intake) sometimes enhances the responses to antihypertensive drugs. Patients must be instructed to consult the attending physician if the condition deteriorates with the above symptoms.
- Blood pressure sometimes changes with environmental changes such as admission to a nursing home (including salt restriction related to meals in the nursing home). Dose reduction or discontinuation must always be considered if necessary.

Evaluation of drug adherence and precautions for drug adherence management

- Various factors involved in a reduction in adherence (continuation of treatment)⁸⁶⁸
- Insufficient understanding of treatment by the patient (final target of antihypertensive treatment, dosage, drug efficacy and side effects)
- Cognitive impairment
- Impairment of the visual function or coordinated movement (ability to open the drug container)
- Complex prescription, a large number of drugs, recent switching of the prescription
- Precautions for the management of drug adherence with antihypertensive drugs
- Informed consent with supporting the understanding of treatment by the patient
- Simplification of prescriptions (use of long-acting antihypertensive drugs or fixed-combination drugs)
- One-dose packaging
- Utilization of pill calendars/cases
- Compliance management by the patient's family or nursing staff

at least 1 year should be conducted. If the history is present, management must be performed by dividing factors for fall into intrinsic and extrinsic factors.⁸⁶¹ Intrinsic factors are patient's physical factors, including the muscular/skeletal and central nervous systems, which are involved in motor/transfer ability, sensory/nervous system, which is involved in equilibrium function, and cardiovascular system such as orthostatic hypotension and arrhythmia. Extrinsic factors are primarily associated with the living environment. In addition, hyponic drug (especially benzodiazepine)-/psychotropic drug-/antihistamine drug-induced fall/fracture must also be considered.

With respect to the association of fall/fracture with antihypertensive drugs, a study indicated that the risk of fracture within 45 days after the start of prescription in elderly patients in whom antihypertensive drug therapy was newly started was 1.43 times higher than that before prescription or 90 days or more after prescription; caution is needed.⁸⁶² In patients receiving treatment, attention must also be paid when increasing the dose of antihypertensive drugs.

(2) *Dehydration- or environmental change-matched guidance for drug therapy.* As the functional capacity of various organs is reduced in elderly patients, fluctuation of blood pressure is large, and their responses to antihypertensive drugs are easy to be enhanced. In particular, guidance for drug therapy with respect to dehydration or environmental changes is sometimes required in elderly patients (Table 8-4).

(3) *Evaluation of drug adherence and precautions for drug adherence management.* Factors involved in a reduction in adherence (continuation of drug therapy) in elderly patients are presented in Table 8-4. The drug adherence-managing ability should be assessed by evaluating the family background, cognitive function, communicating

ability and activities of daily living.⁸⁶¹ In particular, a routine inquiry confirming that there is no change in physical condition cannot evaluate cognitive function. The inquiries to exclude cognitive function decline or the history taking from people around the patient might have to be conducted. There may be cases in which the patient intentionally excludes some drugs. The reasons vary, and treatment based on physician-patient concordance is important. Drug adherence should be evaluated based on the patient's and his/her family's/nursing staff's reports (residual drugs and drug nonadherence associated with the dosing method).

Points of compliance management in elderly patients are shown in Table 8-4. In particular, one-dose packaging has been reported to maintain elderly patients' drug adherence and improve pressure-lowering effects.³¹² However, there is a limitation: the doses of drugs cannot be regulated during the course. An increasing number of patients require comprehensive care involving the nursing staff. For drug adherence management by the nursing staff, prescriptions must be prepared, considering the number and time of visits. The target of treatment should be reviewed in accordance with the nursing state, and drug adherence management such as priority ranking of the prescription contents is necessary in some cases. It is also important to cooperate with the pharmacist.

Citation Information

We recommend that any citations to information in the Guidelines are presented in the following format:

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