

Report

Guidelines for Hypertension in the Elderly — 1999 Revised Version —

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Hypertension is a major risk factor contributing to the second and third most frequent causes of death in Japan: cerebrovascular diseases and heart diseases. Hypertension incidence increases with age, occurring in approximately 60% of Japanese aged 65 yr and older (1), and being the most prevalent disease in Japan (2). In our country, where the elderly population has been increasing, hypertension is one of the most important diseases to be controlled and treated, and counter measures against the disease have drawn much public attention. Hypertension in the elderly consists mostly of essential hypertension, and its pathophysiology differs in many ways from that of essential hypertension in the young or middle-aged. However, isolated systolic hypertension (systolic pressure 140 mmHg or greater, diastolic pressure below 90 mmHg) has been increasing in the elderly. Isolated systolic hypertension is divided into two groups, namely so-called "burned out" and "*de novo*" type systolic hypertension. The former type of hypertension generally starts in middle age as essential hypertension until, eventually, the diastolic pressure becomes reduced in old age; while the latter type of hypertension appears in old age due to reduced vascular compliance in large arteries. In addition, there are also cases of secondary hypertension due to specific causes such as renovascular hypertension.

In the elderly, it has been reported that systolic blood pressure, more than diastolic blood pressure is strongly associated with cardiovascular diseases, especially stroke, coronary artery disease, cardiac failure, end-stage renal disease, and all-cause mortality (3). Furthermore, it has become apparent that raised pulse pressure (systolic blood pressure-diastolic blood pressure) may increase the risk of such diseases (4).

The pathophysiology of hypertension in the elder-

ly is characterized by increased total peripheral vascular resistance, decreased compliance of large and medium-sized arteries, a tendency toward decrease in cardiac output, decreased circulating blood volume, increased instability of blood pressure due to decreased baroreceptor function, decreased blood flow and dysfunction of autoregulation in the brain, heart and kidney. Therefore, given the above-mentioned pathophysiological characteristics, hypertension in the elderly should be treated. In addition, as with other diseases in the elderly, it is necessary to pay attention to the ADL, QOL and drug compliance of patients.

Based on large-scale intervention trials in Western countries and China, treatment of hypertension including systolic hypertension in the elderly has been widely confirmed to be effective (5-10). However, the efficacy of such treatment of hypertensive patients aged 85 yr or older is less certain. It has been proved that occurrence of cerebrovascular disease, coronary artery disease and cardiac failure, in addition to all-cause mortality are decreased by diuretics or long-acting dihydropyridine Ca antagonists. Although treatment of hypertension in the elderly with β -blockers significantly decreases morbidity and mortality of cerebrovascular disease, it has not been shown to demonstrate a significant decrease in morbidity and mortality of coronary artery disease (11). In the United States in 1994, the therapeutic guidelines of hypertension in the elderly were published by the National High Blood Pressure Education Program Working Group (3). However, general information on treatment of hypertension in the elderly is described in hypertension control guidelines. For example, in the JNC VI (12), hypertension in the elderly is discussed in Section 4, "Special Populations and Situations".

The hypertension control guidelines published in

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Table 1. Blood Pressure of Healthy Elderly Individuals by Age and Sex

	Age	<i>n</i>	Systolic Pressure	Diastolic Pressure
Male	65-69	104	127.8±16.3	78.4±7.9
	70-74	75	130.9±20.8	76.4±9.3
	75-79	74	136.9±19.2	75.9±11.8
	80-84	49	140.3±17.4	77.7±12.0
	85-89	16	137.1±17.8	74.1±18.3
Female	65-69	101	134.9±17.5	78.3±10.3
	70-74	92	130.8±18.2	74.4±9.1
	75-79	78	133.6±18.8	74.5±9.8
	80-84	52	139.8±20.8	75.8±10.1
	85-89	19	135.6±19.8	73.4±9.6

Blood pressure (Mean±SD) of healthy elderly individuals by age (no antihypertensive drug, obesity, emaciation nor ECG abnormality) reported by the Ministry of Health and Welfare "Study Group on Normal Values of Laboratory Tests in the Elderly", Subgroup on Blood Pressure (Chairholder: Jyun Fujii) (Ref. 17)

the USA and Europe are fundamentally for Caucasians. Although these guidelines provide a detailed summary of extensive results on hypertension studies throughout the world, and thus should also be useful for the control and treatment of hypertension in Japan, their applicability to Japanese hypertensive patients might be somewhat limited by differences in genetic and social background. To address this problem, the present work constitutes a revised version of "Guidelines on Treatment of Hypertension in the Elderly, 1995" (13) prepared by the Comprehensive Research Projects on Aging and Health, the Ministry of Health and Welfare, the Research Group for "Guidelines on Treatment of Hypertension in the Elderly" (Chair: Prof. Toshio Ogihara, Osaka University). The revised version was prepared by the Research Group on "Long-term Prognosis of Hypertension in the Elderly" (Chair: Prof. Kunio Hiwada, Ehime University) of the above project which consisted of almost the same members as the Ogihara Group. As the first step in developing the revised version, a questionnaire was sent to many hypertension specialists in Japan, asking their opinions on the 1995 version of the guidelines (14). The fundamental concept of this report is the same as that of the original version. Namely, based on evidence-based medicine, it is presented as hypertension treatment guidelines specific to the Japanese, considering our lifestyle, but incorporating the results obtained in the Western countries. As much as possible, the opinions and criticisms of the specialists are reflected in the revision. However, because no criteria for the selection of antihypertensive drugs in the Japanese based on large-scale studies or intervention trials were available, the section 6 "Antihypertensive Drug Therapy" in this report was prepared as consensus-based guidelines.

This report on hypertension in the elderly includes discussion of the following: its characteristics, diagnostic precautions, treatment necessity, indications, target blood pressure, lifestyle modifications, antihypertensive drug therapy, treatment and precautions in patients with complication, notable drug

interaction and consideration of QOL. However, the guidelines are not intended to present the uniform therapeutic methods for hypertension in the elderly, but rather to show the basic concepts. Upon selection of antihypertensive drugs, the best choice currently available is presented. However, the effectiveness of individual drugs for hypertension in the elderly needs to be verified by the results of intervention trials of Ca antagonists and ACE inhibitors in Japan and other countries.

1. Blood Pressure Levels and Their Diurnal Variation in the Elderly

1. Aging and Blood Pressure Levels

Blood pressure changes with age. Systolic pressure increases and diastolic pressure decreases with advancing age, resulting in an increased pulse pressure in the elderly (15). Thus, the prevalence of systolic hypertension also increases with advancing age. These changes in hypertension with age are due mainly to reduced elasticity of the aorta (compliance) (16).

Hypertension in adults is defined as systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg (12). However, since blood pressure changes with age, the blood pressure to be treated by antihypertensive drugs and the therapeutic goal pressure should be determined independently for the elderly. Table 1 indicates blood pressure values by age obtained in 1992 by the Ministry of Health and Welfare Research Group from healthy elderly Japanese who were not taking any antihypertensive drugs (17). Even in the elderly aged 65 yr or older, systolic pressure increased and diastolic pressure decreased slightly with age. The blood pressures for the total number of patients aged 65 to 94 yr were $133 \pm 19/77 \pm 11$ mmHg (mean $\pm$ SD) for males and $134 \pm 19/76 \pm 10$ mmHg for females. According to the Hisayama-cho report (18), among those aged 60 yr or older, the cumulative morbidity of cardiovascular diseases is significantly higher among those with systolic pressure of at least 140 mmHg or diastolic pressure of at least 80 mmHg.

Table 2. Reference Values of 24 h Blood Pressure in the Elderly

Reporter	Individuals	Age (yr)	Sex	n	24 h BP	Daytime BP	Nighttime BP
Imai Y, <i>et al</i> (22)	Area, Random BP Normals	60-69	M	54	146/86	153/91	141/82
			F	72	150/85	159/91	141/87
		70-79	M	25	151/84	157/90	148/80
			F	26	152/86	162/93	152/80
O'Brien E, <i>et al</i> (23)	Employees	50-59	M	54	151/98	155/103	140/90
		95 percentile	F	72	160/87	177/97	133/75

2. Diurnal Variation of Blood Pressure in the Elderly

1) Diurnal variation of blood pressure in the elderly

Various circadian rhythms have been recognized with respect to blood pressure including variation due to each cardiac output, respiratory-related variation, baroreceptor reflex-dependent short-term variation, 24-h variation, and seasonal long-term variation. Twenty-four variation, *i.e.*, diurnal blood pressure variation, is currently receiving the most attention. Drayer *et al.* (19) monitored blood pressure continuously over a 24-h period in hypertensive patients and found that it decreased during sleep, reached the lowest level at hours 0-4:00, increased just before wakeup, remained elevated throughout the day, and gradually decreased in the afternoon to evening.

Physical activity is the most important among the factors influencing diurnal blood pressure variation, though mental activity also plays an important role. Some reports have indicated that diurnal variation of blood pressure may be dependent on diurnal variations recognized in the endocrinological and autonomic nervous systems (20, 21). For example, nocturnal depression of blood pressure cannot be recognized in the patients with Cushing syndrome or other autoimmune diseases treated with adrenocorticosteroids (20). Lack of nocturnal blood pressure depression may be seen in patients with various autonomic nervous system disorders, such as multiple system atrophy, Parkinsonism, spinocerebellar degeneration, diabetic autonomic nervous disorders, and nocturnal blood pressure may even be elevated, demonstrating a reversed diurnal variation pattern (21).

The diurnal variation of blood pressure in healthy elderly individuals is similar to that in the elderly with hypertension mentioned previously: *i.e.*, blood pressure decreases after asleep, increases in the early morning, decreases in the afternoon, increases temporarily in the evening, and decreases after asleep. Reference values of diurnal variation of blood pressure in the elderly have not yet been established yet, but the results shown in Table 2 have been reported (22, 23).

2) Twenty-four hour blood pressure mean value

Measurement of diurnal variation of blood pressure has been reported to have clinical significance (24, 25), suggesting that the 24 h mean is better correlated than random pressure values to prevalence of hypertensive target-organ disorders (left ventricular hypertrophy, fundoscopic changes, renal disorders,

arteriosclerotic diseases) and cardiovascular diseases. In an MRI study of elderly hypertensive patients in Japan, cerebral micro-infarct (lacuna infarct) was demonstrated frequently in the cases with an elevated mean value of 24-h blood pressure (26). These studies suggested that the mean value of 24-h blood pressure is more useful than random blood pressure values for the evaluation of prognosis of hypertension.

3) Nocturnal blood pressure

Many recent clinical studies have emphasized the significance of nocturnal blood pressure. Individuals showing nocturnal depression of blood pressure are known as dippers, while those without nocturnal depression are referred as non-dippers. The frequency of non-dipper status have been reported to increase with advancing age, and to be associated with high prevalence of ischemic heart diseases and cerebrovascular disorders (27). According to the results of an MRI study on asymptomatic hypertensive elderly in Japan, the occurrence of cerebral micro-infarct (lacuna infarct) was reported to increase significantly among non-dippers relative to dippers (28). A recent prospective study on prevalence of cardiovascular events reported that such events were also higher among non-dippers than dippers (29). Extreme dipper who demonstrates nocturnal blood pressure depression of more than 20% of the daytime blood pressure was reported, as similar to dipper, to have more advanced asymptomatic cerebrovascular disorders than dipper (30).

4) Blood pressure elevation in early morning

Among diurnal variations of blood pressure, rapid increase in early morning blood pressure (4-6 a.m.), a so-called "morning surge", is thought to be related to prevalence of cardiovascular diseases. In fact, it is well known that acute myocardial infarction, sudden death and cerebral bleeding occur frequently in early morning. Morning surge appears to be due to physical activity after wake-up, but it has also been demonstrated in some cases even before wake-up. Morning surge has not been well defined, but an early morning pressure elevation at least 50 mmHg (corresponding to the 90 percentiles of early morning elevation among normotensive individuals) has generally been accepted as a reference, and using this reference, morning surge has been recognized in 52.6% of the elderly with essential hypertension (31).

5) *White coat hypertension*

Determination of diurnal variation of blood pressure is useful for diagnosis of so-called "white coat hypertension". White coat hypertension is defined as hypertension demonstrated only at the outpatient clinic and not demonstrated at home (32), and its prevalence increases with advancing age. White coat hypertension (defined as diastolic pressure at the outpatient clinic of 90-104 mmHg, and a daytime blood pressure mean of 134/90 mmHg or less) is reported to occur in 42% of elderly patients with systolic hypertension aged 65 yr or older (33). Patients with white coat hypertension may suffer from marked depression of home blood pressure, and particularly of nocturnal blood pressure, by antihypertensive drug treatment. Some investigators claim that the presence of white coat hypertension is not a risk factor for cardiovascular diseases, while some take a different view, since the weight of left ventricular muscle in white coat hypertension is intermediate between those of true hypertension and normotension (34).

6) *Indication of measuring diurnal variation of blood pressure in the elderly*

Diurnal variation of blood pressure monitored at every 15 min to 1 h can be measured even at an ambulatory state, because a portable non-invasive sphygmomanometer is widely available at present. However, it is difficult to perform such monitoring for all patients with hypertension. Practically speaking, therefore, the monitoring should be applied selectively to only those cases which show: (1) extremely variable random ambulatory blood pressure; (2) no target-organ disorders even with hypertension; (3) a significant difference between home and random blood pressures, suggestive of white coat hypertension; (4) no significant improvement after antihypertensive treatment; (5) autonomic nerve disorders such as diabetic neuropathy; (6) signs suggestive of postural orthostatic or postprandial hypotension; (7) signs necessitating measurement of nocturnal blood pressure; or (8) paroxysmal hypertension.

7) *Home blood pressure*

Blood pressure information other than random pressure measured at outpatient clinic is useful for diagnosis and evaluation of therapeutic outcomes, particularly in management of the elderly hypertensive patients showing unstable variation. In addition, self-testing will activate patients' willingness for treatment of hypertension. Recently many types of sphygmomanometers of home use are sold as over-the-counter instrument, but the types with which blood pressure is measured at wrists or fingers may show significant variability of their readings and cannot be recommended (35). Even the home types with which blood pressure is measured at upper arms may be recommended to be periodically checked in comparison with mercury sphygmomanometer. Patients should be instructed to measure blood pressure in similar time and conditions at each measurement. It is preferably measured

twice daily before antihypertensive medication after getting-up in the morning and in the evening/night when antihypertensive drugs are still in effect.

Reference values of home blood pressure in the elderly have not been established, but in the study on community population without taking any antihypertensive drugs the 95 percentile home blood pressure value measured in the morning was reported 154/90 mmHg among the elderly aged 60 yr and older (36).

2. *Matters of Special Attention*

1. *Diagnostic Criteria and Classifications of Hypertension in the Elderly*

One of the characteristics for hypertension in the elderly is high prevalence of systolic hypertension caused by suppressed Windkessel effect based on arteriosclerosis. No special diagnostic criteria for hypertension in the elderly were stated in WHO-ISH guidelines (37) and the Report of US Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) (12); systolic pressure of 140 mmHg and greater or diastolic pressure of 90 mmHg and greater as in general adults. In the intervention trials by Systolic Hypertension in the Elderly Program (SHEP) (5), systolic hypertension was treated at systolic pressure of 160 mmHg and greater and diastolic pressure of below 90 mmHg which differ from diagnostic criteria of both guidelines (12, 37). Such difference has been pointed out also by some Japanese investigators (38). Conventionally in the Western countries systolic blood pressure tended not to be paid much attention as a risk factor for cardiovascular diseases, but in many epidemiological studies reported were that the patients with elevated systolic pressure demonstrated significantly high prevalence of cardiovascular diseases, as in those with elevated diastolic pressure. In the therapeutic guidelines by JNC VI (12) and WHO-ISH (37) also emphasized was the importance of managing systolic hypertension.

2. *Diagnostic Considerations for Hypertension in the Elderly*

1) *Medical history taking*

Anamnesis is important in diagnosis of any diseases including hypertension. Thus patients are asked about the length, severity, subjective symptoms, and eventfulness of hypertensive symptoms and subjective symptoms. In relation to secondary hypertension, they are questioned about the presence of weight change, nocturia, and weakness or proteinuria, all of which are highly important in the differential diagnosis of secondary hypertension, as will be discussed later. Since essential hypertension might be related to some genetic and environmental factors, symptoms and past history of cardiovascular and renal diseases should be included in addition to family history of hypertension.

2) *Measurement of blood pressure*

Hypertension should not be diagnosed by single

Table 3. The Elderly Suggestive of Secondary Hypertension

1. Diastolic pressure ≥ 105 mmHg found after 55 yr of age (suggestive of renovascular hypertension)
2. Drug-resistant hypertension controlled by antihypertensive drugs in the past (suggestive of renovascular hypertension)
3. Hypokalemia (suggestive of primary aldosteronism, renovascular hypertension)
4. Moderate or severe renal disorders (suggestive of renal parenchymal hypertension)
5. Abdominal vascular bruits (suggestive of renovascular hypertension, aortic sclerosis)

measurement of blood pressure. If the first blood pressure value is elevated, excluding systolic pressure of 180 mmHg or greater or diastolic pressure of 110 mmHg or greater, or both blood pressure is measured at two or more consecutive visits within the following 4 wk. A stable systolic pressure mean of 140 mmHg or greater, a stable diastolic pressure mean of 90 mmHg or greater, or both may be diagnosed as hypertension (12, 37).

3) *Discrepancy on auscultation*

After the first Korotkoff sound is heard on auscultation, it may be discontinued for a while and appear again thereafter. In this case, the first sound is considered for systolic pressure, but it may be underestimated without careful auscultation. In order to avoid this under-estimation in the elderly, a palpation technique should be combined with sufficiently high pressure in the sphygmomanometer cuff.

4) *Pseudohypertension*

Pseudohypertension is recognized in those cases of advanced arteriosclerosis in which the arteries are not compressed completely by the arm cuff, thus resulting in a blood pressure reading higher than that measured by a direct method. Osler's procedure (39) is reported to be useful for differentiation of pseudohypertension. Upon sufficiently strong compression with the arm cuff, Osler's positive sign is characterized by a palpable radial artery without beats, and it tends to be associated with pseudohypertension. The possibility of pseudohypertension should be considered for the patient with marked elevation of blood pressure not accompanying target-organ damage, although pseudohypertension is reported to be infrequently recognized in such cases (40).

5) *Fluctuation of blood pressure*

Blood pressure values fluctuate significantly in all individuals, healthy or otherwise. They vary much more in the elderly than in young individuals, since in the elderly the buffer capacity for controlling blood pressure fluctuation is decreased due to suppression of baroreceptor sensitivity. Blood pressure in the elderly tends to be significantly elevated due to mental stress during conversation with physicians, although in some cases it may become almost normal after several patient/physician encounters. In cases in which elevated blood pressure is seen without target-organ disorders, the possibility of elevated blood pressure due to mental stress or white coat hypertension is suggested, and thus the

pressure may decrease when measured by an automatic sphygmomanometer in an isolated room. Therefore, single blood pressure measurement is not sufficient for making any decision during the management of hypertension in the elderly, and several visits at 2-4 wk intervals for the measurement of blood pressure may be necessary. It is also important to utilize home testing (41). Orthostatic and postprandial hypotension are frequently encountered in the elderly. Therefore, blood pressure should be measured in sitting and standing positions as well as in a supine position. In addition, a patient's dietary schedule may be questioned, to rule out the possibility of postprandial hypotension.

6) *Diagnosis of secondary hypertension in the elderly*

The frequency of secondary hypertension in the elderly has been reported as approximately 5%, a rate similar to that in young and middle-aged individuals (42). However, the content of secondary hypertension is different for the foremost group; *i.e.*, endocrinological hypertension due to aldosteronism, pheochromocytoma, Cushing syndrome, etc., are infrequent in the elderly, while renal hypertension is most frequently encountered.

Renovascular hypertension is the most frequently occurring type of secondary hypertension in the elderly (43). Symptoms and findings suggestive of renovascular hypertension are listed in Table 3, and the diagnostic criteria for this disease and other types of secondary hypertension in the elderly are discussed below.

Renovascular hypertension: Mostly due to arteriosclerosis in the elderly, and abnormal findings are recognized usually in bilateral renal arteries. Renovascular hypertension combined with or without essential hypertension should be ruled out when abdominal vascular bruits, rapid elevation of blood pressure during treatment of hypertension, decreased effect of antihypertensive drugs, or deterioration of renal function caused by ACE inhibitors are recognized. Possibility of the disease should always be considered in new cases of hypertension in the elderly with reference to elevated plasma renin activity and hypokalemia. Special laboratory examinations such as renography, renal scintigraphy and Doppler ultrasonography may also be useful. Angiography of renal arteries and plasma renin activity measurement on samples drawn from bilateral renal veins can be used for a definitive diagnosis.

Renal hypertension: In the elderly, caused more frequently by chronic glomerulonephritis, diabetic

Table 4. Classification of the Stages of Hypertension by the Extent of Target-Organ Disorders (WHO/ISH, 1993)

Stage I	No objective signs of organ changes
Stage II	At least one of the following signs of organ - Left ventricular hypertrophy (radiogram, electrocardiogram, echocardiogram) - Generalized and focal narrowing of the retinal arteries - Proteinuria and/or slight elevation of plasma creatinine concentration (1.2-2.0 mg/dl) - Ultrasound or radiological evidence of atherosclerotic plaque (carotid artery, aorta, iliac and femoral artery)
Stage III	Both symptoms and signs have appeared as a result of organ damage. These include - Heart - Angina pectoris - Myocardial infarction - Heart failure - Brain - Stroke - Transient ischemic attack - Hypertensive encephalopathy - Optic fundi - Retinal hemorrhages and exudates with or without papilledema - Kidneys - Plasma creatinine concentration >2.0 mg/dl - Renal failure - Vessels - Dissecting aneurysm - Symptomatic arterial occlusive diseases

nephropathy, chronic pyelonephritis, and amyloidosis than it is by those conditions in young and middle-aged hypertensives. Measurement of serum creatinine, endogenous creatinine clearance and urinalysis (hematuria, proteinuria, urinary sediments) are useful for diagnosis, and onset of hypertension and proteinuria should be confirmed especially in the cases with renal dysfunction.

Primary aldosteronism: Elderly individuals frequently take herbal medications, and this can occasionally result in pseudo-aldosteronism. In order to rule out this condition, patients should be asked to describe any regularly taken herbal medications, as well as about the presence of such symptoms as weakness of the extremities, polydipsia and polyuria. Diuretics tend to be attributed to hypokalemia, but differentiation between this disease and primary aldosteronism can often be aided by confirmation of suppressed renin activity and elevated aldosterone in plasma.

Pheochromocytoma: Because of the significantly large fluctuation of blood pressure in the elderly, paroxysmal fluctuating hypertension characteristic of pheochromocytoma tends to be overlooked. It should be ruled out when hypertension is complicated with headache, palpitation, tachycardia, perspiration, weight loss, or hyperglycemia. Pheochromocytoma can be definitively diagnosed by assay for increased blood and urinary catecholamine and catecholamine metabolites, along with abdominal CT and ¹³¹I-MIBG scintigraphy to confirm the presence of a tumor mass.

Cushing syndrome: Rarely encountered in the elderly, and suggested by its characteristic physical signs. An ectopic ACTH-producing tumor associated with lung cancer (small cell carcinoma), pancreatic cancer, etc., may be encountered.

7) Classification of severity of hypertension

Prognosis of hypertension cannot be determined by blood pressure values alone, but rather is strongly correlated with the extent of target-organ disorders. Severity of blood pressure elevation may not necessarily be matched with that of target-organ disorders. In Japan, the 1993 WHO-ISH classification (44) is used widely (Table 4). Latent cardiovascular diseases are frequently present in the elderly, particularly left ventricular hypertrophy as detected by electrocardiography and echo-cardiography. Although hypertension in the elderly is also often associated with coronary arterial diseases, in elderly patients these may be difficult to screen for by means of exercise tests. With the increasingly wide use of MRI, it has become apparent that asymptomatic cerebral infarction is very commonly found in case of hypertension in the elderly (26). Therefore, hypertension in the elderly must be carefully diagnosed not only etiologically but also in relation to the severity of target-organ disorders.

3. Necessity of Treatment for Hypertension in the Elderly

In Japan, where the elderly population has been in-

creasing rapidly, it is expected that the incidence of hypertension will continue to increase and thus management of hypertension in the elderly is an important problem both medically and socially. According to the Fourth National Survey of Circulatory Disorders, published in 1990 by the Ministry of Health and Welfare of Japan, and including of a total of 10,956 individuals aged 30 yr or older, the incidence of hypertension (140/90 mmHg and greater) among those aged 70 yr or older, irrespective of treatment by antihypertensive medication was 75.5% in males and 78.9% in females (45). The usefulness of antihypertensive drugs for treatment of hypertension in the elderly has been proved through various intervention trials, although no large-scale intervention trial has been reported in Japan. In a small-scale study on hypertension in the elderly, the usefulness of antihypertensive treatment was reported in cases of hypertension of 170/90 mmHg and greater (46).

1. Necessity of Treatment for Systolic Hypertension

It has been demonstrated through Framingham and Hisayama-cho studies that elevation of both systolic and diastolic blood pressures are important risk factors of cardiovascular diseases. The effectiveness of treatment for systolic hypertension in the elderly was proved by a SHEP trial in the USA (5), in which patients aged 60 yr and over with systolic hypertension were divided into an active treatment group (chlorthalidone as step 1 medication) and a placebo group. During the 4.5-yr follow-up, active treatment significantly decreased the incidence of cerebrovascular disorders, coronary arterial diseases and cardiac failure. In addition, frequency of cerebrovascular disorders was shown to decrease significantly in a Syst-Eur (Systolic Hypertension in Europe) trial (9) and Syst-China (Systolic Hypertension in China) trial (10), in which patients aged 60 yr or older were treated for systolic hypertension by administration of the long-acting Ca antagonist, nifedipine (Table 5).

2. Usefulness of Treatment for Diastolic Hypertension

The EWPHE trial (46) was the first large-scale intervention trial consisting solely of elderly hypertensive patients. Intervention trials for hypertension in the elderly, excluding the SHEP trial (5), Syst-Eur trial (9) and Syst-China trial (10), have generally focused on both systolic and diastolic hypertension, while only the STOP-Hypertension trial used entry criteria of diastolic blood pressure ranging 105-120 mmHg irrespective of systolic blood pressure levels (6). Table 5 lists the principal intervention trials, in which the averaged diastolic pressure at entry ranged 91-102 mmHg and the averaged systolic pressure mean at entry ranged 168-197 mmHg (5-10, 47, 48). These trials confirm the preventive effect of antihypertensive drugs against cardiovascular diseases. Although the partial influence of systolic blood pressure cannot be excluded, elderly individuals with a diastolic pressure of 90-95 mmHg or greater would appear to be reasonable candidates for antihypertensive drug treatment.

To summarize the meta-analytic results of 9 principal trials on the treatment of hypertension in individuals aged 60 yr or older: overall deaths decreased 12%, deaths due to stroke 36%, and deaths due to coronary artery diseases 25%; overall morbidity of cerebrovascular disorders decreased 35% and coronary arterial diseases 15%; thus, the effectiveness of the treatment was apparent (49).

3. Management/Treatment Guidelines of Hypertension in the Elderly Developed in Foreign Countries and Their Problems

Based on various intervention trials and epidemiological studies, several management/treatment guidelines have been proposed: the JNC V, WHO/ISH, UK, Canada, and New Zealand guidelines in 1993; the JNC VI in 1997, and the WHO-ISH in 1999 (12, 37, 44, 50-53). The 1999 WHO-ISH proposes that the therapeutic goal of blood pressure for hypertension in the elderly should be 140/90 mmHg, being slightly higher than that (120-130/80 mmHg) for young patients. According to the results of questionnaires given to Japanese hypertension experts, the goal of blood pressure for the elderly aged 60 yr and greater was most frequently reported to be below 150 mmHg, and below 160 mmHg for the elderly aged 80 yr and greater (38). Hypertension in the elderly is higher risk for cardiovascular diseases than in the young and middle-aged, and it has been reported that antihypertensive drug treatment should have more preventive effects for cardiovascular diseases (54). The New Zealand therapeutic guidelines recommend that antihypertensive drug treatment be given to those who have a 20% or higher prevalence rate of cardiovascular diseases over the next 10 yr, and risk factors other than hypertension is emphasized in the guidelines. On the other hand, blood pressure may not influence the prognosis for longevity in the very elderly. The STOP-Hypertension trial recognized the usefulness of treating hypertension in the elderly aged up to 84 yr (6), and no therapeutic effect was proved for the elderly aged over 80 yr in the EWPHE trial (47). However, between-individual variation is relatively large in the elderly, the age of each patient should not be overly emphasized. However, even the very elderly aged over 85 yr with marked hypertension (e.g., 180/110 mmHg) may be treated clinically. In the above-mentioned survey of Japanese hypertension specialists, roughly half of the respondents reported that they give no special consideration to an upper age-limit for treatment of hypertension (38). Active antihypertensive treatment is necessary for cases with critical complications. It has been reported that excessive blood pressure reduction may cause cardiovascular disease (the so-called "J-curve phenomenon") (55). Therefore, treatment of hypertension in the elderly should be given cautiously and gradually.

4. Selection of the Patients and Target Blood Pressure

Elderly hypertensive patients frequently have multiple organ damage and impaired physiological func-

Table 5. Principal Intervention Trials for Hypertension in the Elderly

	EWPHE	HEP	SHEP	STOP
Age (yr)	≥60	60-79	≥60	70-84
No. of cases	840	884	4,736	1,627
Blood pressure at entry (mmHg)				
Systolic pressure	160-239	170-280	160-219	180-230
&	&	&	&	&
Diastolic pressure	90-119	105-120	<90	≥90 or 105-120
Blood pressure before treatment (mmHg)	180/101	197/100	177/77	195/102
Antihypertensives	diuretics	β-blockers	diuretics	(1) β-blockers
(†: secondary combined drug)	methyldopa	diuretics methyldopa	β-blockers	(2) diuretics
Test method	double blind	open	double blind	double blind
Follow-up period (yr)	4.7	4.4	4.5	2.1
Blood pressure after treatment (mmHg)				
Active treatment group	150/85	162/77	144/68	167/87
Placebo group	171/95	180/88	155/71	186/99
Treatment effects (relative risk)				
Cerebrovascular disease	0.64	0.58*	0.67*	0.53*
Coronary arterial diseases	0.82	1.03	0.73*	0.87#
Cardiac failure	0.78	0.68	0.45*	0.49*
Cardiovascular diseases, Total	0.71*	0.76*	0.68*	0.60*

	MRC II	STONE	Syst-Eur	Syst-China
Age (yr)	65-74	60-79	≥60	≥60
No. of cases	4,396	1,632	4,695	2,394
Blood pressure at entry (mmHg)				
Systolic pressure	160-209	≥160	160-219	160-219
&	&	&/or	&	&
Diastolic pressure	<115	≥96	<95	<95
Blood pressure before treatment (mmHg)	185/91	168/98	174/86	170/86
Antihypertensives	(1) β-blockers	Ca antagonists	Ca antagonists	Ca antagonists
(†: secondary combined drug)	(2) diuretics	ACE inhibitors diuretics	ACE inhibitors diuretics	ACE inhibitors diuretics
Test method	single blind	single blind	double blind	single blind
Follow-up period (yr)	5.8	3.0	2.0	4.0
Blood pressure after treatment (mmHg)				
Active treatment group	152/77	146/85	151/79	150/81
Placebo group	166/83	155/90	161/84	159/84
Treatment effects (relative risk)				
Cerebrovascular disease	0.75*	0.43*	0.58*	0.62*
Coronary arterial diseases	0.81		0.70#	1.06#
Cardiac failure		0.32	0.71	0.42
Cardiovascular diseases, Total	0.83*	0.40*	0.69*	0.63*

*Statistically significant, #myocardial infarction only, HEP, MRC pressure is estimated value.

tions compared to the young and middle-aged hypertensives, and thus are more likely to develop various adverse effects and complications with antihypertensive treatment. For this reason, it is of primary importance to evaluate the necessity of antihypertensive treatment, and then, if judged necessary, antihypertensive treatment should cautiously be initiated, in full consideration of the target

blood pressure and speed of blood pressure reduction as well as the physical, mental and social conditions of each individual.

1. Selection of the Patients to Be Treated

1) Age

In a Finnish study on the 5-yr survival rate among a very-elderly population, 83% of whom were aged

Table 6. Blood Pressure to Be Treated by Antihypertensive Drugs and Goal Blood Pressure on Hypertension in the Elderly

	60-69 yr	70-79 yr	80 yr and older
Blood pressures to be treated (mmHg)			
Systolic pressure	≥140-160	≥160-170	≥160-180
Diastolic pressure	≥90	≥90	≥90
Goal of blood pressures by treatment (mmHg)			
Systolic pressure	≤140	≤150-160	≤160-170
Diastolic pressure	<90	<90	<90

85 yr or older (56), the survival rate was highest in the group with systolic pressure of 160 mmHg or greater and diastolic pressure of 90 mmHg or greater, whereas it was lowest in the group with low blood pressure. Thus, hypertension appears to be unrelated to longevity among the very-elderly aged over 85 yr; however, half of the individuals studied were hospitalized due to illness. The same investigators later performed a similar study among healthy very-elderly people, and reported that the lowest mortality rate was observed in the group with systolic pressure of 140-169 mmHg and diastolic pressure of 70-90 mmHg and the mortality increased in all other groups, *i.e.*, those who had either higher or lower blood pressure than that in the low-mortality group (57). There have been no clear evidences of the benefit of antihypertensive treatment among the elderly aged over 85 yr in other studies, such as the EWPHE (46), STOP-Hypertension (6) and Syst-Eur (58) studies. Thus, hypertension may not necessarily be a risk factor in the very-elderly aged 85 yr or older, and antihypertensive treatment may not be expected to have a favorable effect in this group. Therefore, treatment of hypertension in the elderly aged 85 yr or older should generally be limited to lifestyle modification. Exceptionally, those of which hypertension seems to adversely affect the circulatory system should be treated with antihypertensive drug.

2) Blood pressure levels indicating antihypertensive drugs treatment

Both systolic and diastolic blood pressure levels are important for initiating drug treatment even in the elderly. However, many investigators believe that the initial blood pressure levels for starting antihypertensive drug treatment in the elderly may be set at the different level from those in the young and middle-aged, who tend to have less target-organ damage (38). In the above-mentioned survey of Japanese hypertension specialists, the majority of respondents reported that the blood pressure for initiating drug treatment in the elderly should be a systolic pressure of 140-160 mmHg or greater and a diastolic pressure of 90 mmHg or greater. Indeed, the large-scale intervention trials performed in Europe and the USA in the elderly also reported that the blood pressure to be treated is a systolic pressure of 160 mmHg or greater and a diastolic pressure of 90-100 mmHg. Because these studies have clearly demonstrated the benefit of antihypertensive treatment for the elderly, it is recommended that anti-

hypertensive treatment should be initiated when the blood pressure reaches or exceeds these levels. It has been reported that the blood pressure in the elderly aged 70 yr or older may be inversely correlated with life expectancy (59). Therefore, the systolic pressure for initiating antihypertensive treatment should be set at the level, approximately age plus 100 mmHg (Table 6). This cut-off point is in general agreement with the results of the survey of hypertension specialists in Japan (14).

Upon initiating antihypertensive drug treatment, the following factors should be considered: cardiovascular diseases (left ventricular hypertrophy, ischemic heart diseases, cerebrovascular disorders, renal dysfunction), diabetes mellitus, hyperlipidemia, and family history of cardiovascular diseases. Since these factors are likely to promote the development of cardiovascular events, patients who have these complications should be followed up more frequently and the blood pressure level for treatment should be set at a lower level.

If more than one complications are present, antihypertensive treatment may be necessary even in cases with the blood pressure of 140-159/90-99 mmHg, or Stage 1 of JNC VI classification (12) or Grade 1 of WHO/ISH 1999 classification (37). In severe hypertension with systolic pressure of 180 mmHg or greater and/or diastolic pressure of 110 mmHg or greater, or Stage 3 of JNC-VI or Grade 3 of WHO-ISH 1999 (37), antihypertensive treatment should be started immediately.

2. Therapeutic Goal of Blood Pressure

In general, the therapeutic goal of blood pressure in the elderly should be set at a higher level than that in the young and middle-aged. This recommendation is based on the facts that the elderly tend to already have target-organ damage, exhibit altered cerebral autoregulation, and/or develop drug side effects.

Drug therapy for mild hypertension has been proved to decrease morbidity and mortality of cardiovascular diseases in various randomized controlled trials. Reduction of average 10 mmHg in systolic and 5-6 mmHg in diastolic decreased the prevalence of stroke by 42% and of coronary artery diseases by 14% in comparison with a placebo group (60). Similar results were reported by decreasing systolic pressure by 12-19 mmHg and diastolic pressure by 4-10 mmHg in intervention trials for the elderly. On the other hand, the reduction of blood pressure from the baseline value was 22-35

mmHg of systolic blood pressure and 13–23 mmHg of diastolic blood pressure in those trials. Since the possible existence of J-curve phenomenon has been reported (61–63), one must be cautious when reducing systolic pressure to below 150 mmHg or diastolic pressure to below 90 mmHg. However, a HOT trial (mean age, 61.5 yr), designed to study the J-curve phenomenon (64), found that the maximum favorable effect was achieved at systolic pressure of 130–140 mmHg and diastolic pressure of 80–85 mmHg, and furthermore, that no significant increase in morbidity or mortality of cardiovascular diseases was observed even at levels below these ideal values. Considering these facts, the therapeutic goal of blood pressure for individuals in their age of 60s may be systolic pressure below 140 mmHg and diastolic pressure below 90 mmHg, if tolerable, although it may depend on the pre-treatment blood pressure levels. For individuals in their age of 70s, however, a higher target blood pressure may be set, since these cases are more likely to be complicated by target-organ damages. Table 6 shows the therapeutic goal of blood pressures approved by many hypertension specialists in Japan.

During antihypertensive drug treatment in elderly hypertensives, postprandial and orthostatic hypotension and excessive reduction of nocturnal blood pressure may sometimes occur and aggravate ischemia of important organs. Indeed, these reductions of blood pressure might be associated with an increased risk for cardiovascular diseases (61–63). Twenty-four-hour blood pressure monitoring by a portable automatic sphygmomanometer is useful to confirm adequacy of the treatment for an individual patient. Home blood pressure monitoring is also recommended (65).

In patients with stenosis of the major arteries supplying important organs, organ blood flow is highly dependent on blood pressure, and thus excessive reduction of blood pressure may induce ischemia. Before treatment, therefore, it is recommended that all important organs, particularly the brain, heart, and kidneys, should be evaluated for the presence of vascular lesion. Surgical intervention (endoarterectomy, percutaneous angioplasty) may be considered for risky vascular stenosis. If surgical intervention is not feasible, then the target blood pressure should be carefully determined not so as to worsen the clinical symptoms and laboratory findings.

3. Speed of Blood Pressure Reduction

Doses of antihypertensive drugs must be titrated gradually and cautiously in the elderly, because metabolism and excretion of drugs are delayed due to decreased functions of the liver and kidneys by aging (66), and the organs with stenosis or occlusion of the major arteries may develop ischemia easily upon rapid reduction of blood pressure. At the initial stage, antihypertensive treatment should be started at half the usual dose given to non-elderly patients, and may be increased at intervals of more than 4 wk with a goal of the target blood pressure being achieved in 2 mo or longer.

5. Modification of Lifestyle

Recently, the Ministry of Health and Welfare of Japan changed the term “adult diseases” to “lifestyle diseases”, emphasizing the importance of lifestyle in their development. Hypertension is also cured by modification of lifestyle, although the efficacy of lifestyle change varies among individuals. In the JNC VI (12) and WHO/ISH (37) guidelines, it is recommended that non-medication therapy be used as the first step for treatment of hypertension, and that it be continued even after antihypertensive drug therapy is started. Moderate hypertension can be corrected only by lifestyle modification, but mild hypertension can be normalized by administration of small doses of antihypertensive drugs. Non-medication therapy is useful for the prevention of side effects of antihypertensive drugs and for the improvement of quality of life (QOL). However, elderly individuals tend to have firmly established lifestyles and to be resistant to lifestyle modification. For example, family members may not cooperate sufficiently with recommended dietary changes, and other lifestyle modifications may be difficult for practical reasons.

1. Diet

1) Salt intake restriction

In the Intersalt study (67) a significant correlation between urinary sodium excretion and elevation of blood pressure was recognized with age. In addition, it has been established that blood pressure tends to remain low even in advancing age in communities where urinary sodium excretion is low, and that the relationship between salt intake and blood pressure elevation is important. Based on the responses to abundant salt intake, patients with essential hypertension can be divided into two groups, a salt-sensitive group showing elevation of blood pressure and a non-salt sensitive group showing no elevation of blood pressure (68). In general, elderly individuals show high sensitivity to salt, and thus hypertension can be well corrected by restriction of salt intake.

Accordingly, mild and moderate hypertension in the elderly should be treated first by restriction of salt intake, and by other methods only if salt restriction fails to achieve a favorable response. The TONE trial (69) reported the effectiveness of salt intake restriction and weight-reduction for treatment of hypertension in the elderly. The JNC VI recommends restricting dietary salt intake to less than 6 g sodium chloride per d. However, a strict restriction of salt intake from about 13 g/d (the mean salt intake in Japan) down to 6 g/d may cause loss of appetite and deteriorate QOL in the elderly. Therefore, it is recommended that salt intake be initially restricted to below 10 g/d, and then slowly decreased thereafter.

2) Potassium intake

Potassium itself is not significantly effective for hypertension. However, it is thought that increased

potassium intake directly reduces the risk of cerebral stroke (70), and that potassium depletion may induce hypertension and ventricular premature beats. Therefore, increased potassium intake seems effective for the prevention of cardiovascular diseases. However, increased potassium intake is more effective for lowering blood pressure in patients with high dietary salt intake than in those with low salt intake. Since it is recognized that dietary sodium/potassium ratio is well correlated with blood pressure levels, intake of a diet with a low sodium/potassium ratio is recommended. In the elderly, however, careful attention must be paid to cases with renal dysfunction, cases with hyporeninemic hypoaldosteronism complicated with diabetes mellitus, or cases requiring administration of aldosterone antagonists.

3) Calcium and magnesium intake

A negative correlation has been recognized epidemiologically between blood pressure and dietary intake of calcium and magnesium (71, 72). In Japan, the mean dietary intake of calcium is less than the required 600 mg/d, and in fact is half of the amount (800-1300 mg per d) taken in the western countries. Therefore, dietary calcium intake is recommended to be more than 600 mg per d. It has been reported in Japan that the supplementation of magnesium intake is effective for lowering blood pressure in hypertensive patients (73).

4) Fat

Since fish oil (eicosapentaenoic acid) is said to have anti-atherogenic and anti-hypertensive effects, dietary intake of blue fishes may contribute to the prevention of atherosclerotic diseases. Hyperlipidemia is one of the important risk factors for atherosclerosis, and restriction of dietary fat intake should be recommended for hyperlipidemic patients.

2. Exercise

Studies related to exercise and mortality have generally agreed that physical activity is inversely correlated with mortality due to circulatory diseases, and thus adequate exercise is suggested to prevent atherosclerosis (74). Exercise treatment is reported to decrease systolic blood pressure by 8-18 mmHg and diastolic blood pressure by 5-16 mmHg (75). Exercise treatment is one of the best choices for mild hypertension. However, isometric exercise significantly increases both systolic and diastolic blood pressure, and thus cannot be recommended for treating hypertension. Isotonic and aerobic exercises lower diastolic blood pressure and negligibly increase systolic blood pressure during physical activity, and thus can be recommended for treating hypertension. The strength of exercise is recommended to be 40-60% of the maximum oxygen intake; an approximately 10 mmHg depression in systolic blood pressure may be expected by 30-40 min of exercise 3-5 times per wk (76). Exercise helps not only to lower blood pressure, but also to improve insulin resistance and lower serum triglyceride. While it is not practical to measure the

maximum oxygen intake in all patients, a target of 110 beats per min is used for patients aged 60 yr or older, as estimated from the relation between heart rate and physical activity at 50% maximum oxygen intake at various ages. Therefore, it is recommended that exercise treatment consist of isotonic exercise for 30-40 min, 3-5 times a week, and that this regime be continued indefinitely. However, exercise treatment for hypertension is not suitable for patients with ischemic heart diseases, heart failure, renal failure or orthopedic complications.

3. Weight Reduction

Obesity is closely associated with blood pressure elevation, most likely due to insulin resistance and sympathetic nervous system involvement. It is well known that weight reduction in obese patients effectively lowers blood pressure. In fact, weight reduction has been shown to lower blood pressure in 80% of cases, regardless of the extent of obesity, and thus should be widely applied as a useful anti-hypertensive treatment (77). Hypertension is also related to distribution of body fat. Fat distribution mainly in the upper body, namely a waist/hip ratio of 1.0 or more for males or 0.8 or more for females, is said to increase mortality due to hypertension, hyperlipidemia, diabetes mellitus or coronary artery diseases.

4. Daily Favorites

1) Alcohol

Alcohol intake is positively correlated to blood pressure (12). Moderate and heavy drinkers (30 ml ethanol or more per d) tend to be significantly more hypertensive than non-drinkers.

2) Smoking

Smoking itself may not be directly implicated in raising blood pressure, but it is one of the major risk factors of cardiovascular diseases. It is, therefore, advised that hypertensive patients avoid cigarette smoking, given that treatment of hypertension is aimed mainly at preventing cardiovascular diseases.

6. Antihypertensive Drug Therapy

Hypertension in the elderly is a major risk factor for cerebrovascular diseases, coronary artery diseases, cardiac failure, end-stage renal diseases, arteriosclerosis obliterans and all-cause mortality (3), and systolic blood pressure is a better predictor of the events than is diastolic blood pressure. It has become clear that increased pulse pressure (systolic blood pressure-diastolic blood pressure) is a good indicator for risk of cardiovascular diseases (4). Since the late 1980s, several large intervention trials have been performed on hypertension in persons aged 60 yr or older, and all have demonstrated the effectiveness of antihypertensive drug therapy. However, antihypertensive drug therapy has not been definitely confirmed to be effective in very old hypertensive patients (85 yr or older), and thus its effectiveness may be limited after a certain age (49).

Considering these limitations, guidelines for anti-hypertensive drug therapy are presented as follows.

1. Antihypertensive Drugs Used in Large-Scale Intervention Trials for Hypertension in the Elderly

The major antihypertensive drugs conventionally used in large-scale intervention trials for hypertension in the elderly are diuretics and β -blockers. In addition, long-acting Ca antagonists have been used as a first step in several recent large-scale intervention trials for hypertension in the elderly (8-10). Messerli *et al.* (11) analyzed the results of the randomized controlled trials using diuretics and β -blockers for hypertension in the elderly, and reported that diuretics were efficacious for reduction of cerebrovascular events, stroke mortality, coronary artery disease, cardiovascular mortality, all-cause mortality in comparison to a placebo group, but β -blockers were not significantly efficacious for reduction of coronary artery disease, cardiovascular mortality or all-cause mortality. In the Syst-Eur trial (9) and Syst-China trial (10), a long-acting Ca antagonist significantly reduced morbidity of stroke, non-fatal cardiac diseases, total cardiac diseases, and fatal and non-fatal cardiovascular diseases. A long-term treatment trial (NICS-EH) of hypertension in the Japanese patients (78), although utilizing a relatively small number of participants, reported that a dihydropyridine Ca antagonist was as effective as diuretics for the prevention of cardiovascular diseases.

2. Antihypertensive Drugs for Treating Hypertension in the Elderly, Selected by Hypertension Specialists in Japan

According to the results of a 1993 questionnaire-survey of hypertension specialists in Japan (123 physicians responded, 84% response rate), long-acting Ca antagonists were the first choice of 75% of respondents for treatment of elderly hypertensive patients without complications, while ACE inhibitors were the first choice of 15%. Each 2% of respondents selected diuretics and β -blockers which were strongly recommended as the first choice by the JNC V in 1992. None of the respondents reported using β -blockers. Sixty one percent of respondents recommended that β -blockers not be used to treat hypertension in the elderly, and 40% and 17% of respondents recommended that α -blockers and diuretics not be so used, respectively. Based on these results, it would appear that the choice of antihypertensive drugs by Japanese specialists is not always evidence-based, with some specialists instinctively preferring newer drugs, such as Ca antagonists and ACE inhibitors. Based on the consensus of this survey, "Guidelines on Treatment of Hypertension in the Elderly 1995" were published in 1995 (13). In 1996, a questionnaire on the "Guidelines on Treatment of Hypertension in the Elderly 1995" (14) were sent to the previous respondents, and this time elicited the participation of 102 specialists (77%). Sixty five percent of the responding physicians selected long-acting Ca antagonists and ACE inhibitors as the first choice for hyperten-

sion without complications in the elderly, while diuretics and β -blockers were selected by 17%. However, only 3% of the respondents denied Ca antagonists as the first choice in the treatment of hypertension in the elderly. The 1995 Guidelines recommended β -blockers and α -blockers as relatively contraindicated for the treatment of hypertension in the elderly, but in the second questionnaire about a half of the respondents recognized both blockers to be safe for use in the elderly. In the JNC VI (12), based on the results in the Syst-Eur trial (9), long-acting dihydropyridine Ca antagonists were also recommended for the treatment of hypertension in the elderly. In the Syst-China trial and HOT study, which included elderly hypertensive patients with complications (64), dihydropyridine Ca antagonists were also used as a first step, and their effectiveness was verified.

3. Selection of Antihypertensive Drugs

The following drugs are recommended as the first choice drug. (1) The possibility of administration once or twice a day in order to maintain good compliance. (2) Long-acting (T/P ratio, at least 50% or more), 24 h or longer, in order to be effective for rapid elevation of blood pressure in early morning. (3) Low price as compared with comparable drugs of the same efficacy.

1) Patients without complications

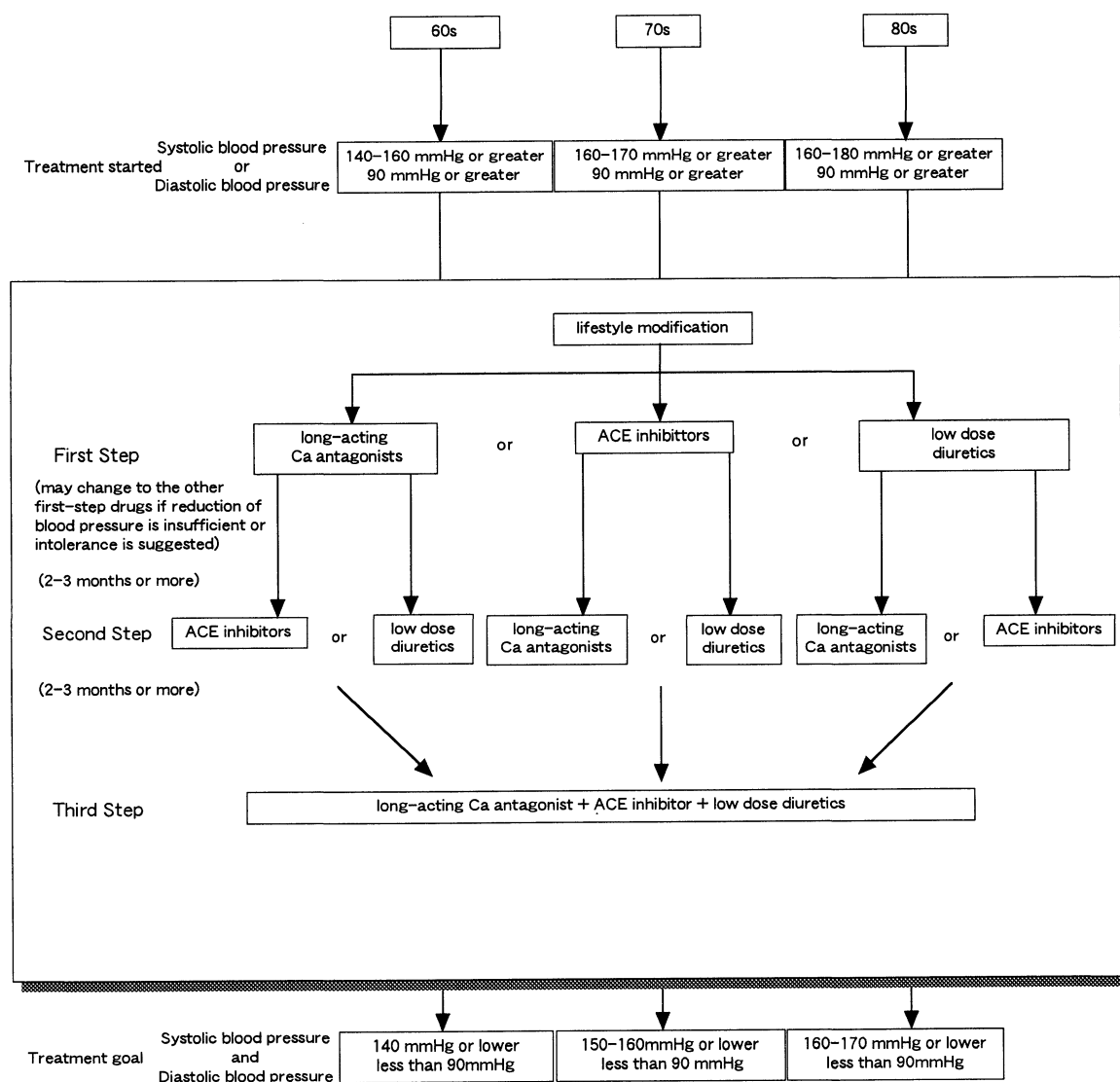
First choice drug: long-acting (once or twice a day) Ca antagonists, ACE inhibitors (angiotensin II receptor antagonists if coughing is a complaint) or small dose of thiazide diuretics (+ potassium-sparing diuretics). A therapeutic flow chart is shown in the Fig. 1.

A. Long-acting dihydropyridine Ca antagonists

Ca antagonists are usually classified into two groups: dihydropyridines and benzothiazepine (diltiazem). The anti-hypertensive effects of dihydropyridine Ca antagonists depend on decrease in peripheral vascular resistance, accompanying reflex increase in heart rates and cardiac outputs. These drugs which have been improved to act slowly and for a longer period of time, with little stimulatory effect for sympathetic nerve system and renin-angiotensin system, are now available in the market. In some patients, diltiazem shows inhibitory effects on the sinus node and atrio-ventricular conduction system, resulting in conduction disturbance and bradycardia.

Benefits of Ca antagonists

Summarizing the benefits of Ca antagonists for the treatment of hypertension in the elderly, we can say that these drugs demonstrate excellent effect in blood pressure reduction, and that, according to the STONE, Syst-Eur, and Syst-China trials, they clearly reduce the morbidity and mortality of cardiovascular diseases. Ca antagonists are expected to be effective for hypertensive patients complicated by such conditions as angina pectoris (dihydropyridines and diltiazem), atrial fibrillation (diltiazem),



※ Change to angiotensin II receptor antagonists, in the case of cough with ACE inhibitors.

Fig 1. Flow chart for hypertension in the elderly without complications.

and diabetes mellitus with proteinuria (both Ca antagonists) (12). Neither type of Ca antagonist has any adverse effects on carbohydrate, lipid or uric acid metabolism. They have few contraindications, and can be used in combination with other classes of antihypertensive drugs. Finally, the Syst-Eur trial recently reported on an anti-dementia effect of nitrendipine (79), which should be confirmed further.

Disadvantages of Ca antagonists

In the elderly, diltiazem is prone to cause adverse effects on the heart, such as conduction disturbance, bradycardia, inhibition of systolic function, etc. Care must be given to avoid constipation. Dihydropyridine Ca antagonists may cause ankle edema, which may be differentiated from congestive heart failure. Care must be given also to avoid gingival

hypertrophy.

B. ACE inhibitors

No large-scale intervention trial has been reported on the use of ACE inhibitors to treat hypertension in the elderly. However, ACE inhibitors are selected to be the first choice, based on the results of many clinical studies demonstrating their protective effects on target organs.

Benefits of ACE inhibitors

Elderly individuals generally show low plasma renin activity, but the antihypertensive effect of ACE inhibitors is almost the same in elderly as in young and middle-aged hypertensives. Their antihypertensive effects are the same as or higher than diuretics. ACE inhibitors effectively lower the blood pressure

by about 70% of mild and moderate essential hypertensive patients in the elderly. ACE inhibitors have the compelling indication for hypertensive patients complicated by congestive heart failure from systolic dysfunction. ACE inhibitors have been shown to provide beneficial effects in preventing left ventricular remodeling after myocardial infarction, and in regressing left ventricular hypertrophy. ACE inhibitors are compellingly indicated for patients with diabetes mellitus with proteinuria. In addition, they are effective for protecting renal function in patients with renal failure (serum creatinine level, below 3 mg/dl) (80). They have few contraindications and can be combined with other classes of antihypertensive drugs.

Disadvantages of ACE inhibitors

The major adverse effect of ACE inhibitors is dry cough, which is especially in women, and, less frequently, angioedema. ACE inhibitors are relatively contraindicated when the serum creatinine level is 2 mg/dl or greater, and contraindicated for bilateral renovascular hypertension.

B'. Angiotensin II receptor antagonists

Angiotensin II receptor antagonists are now available in Japan, and their antihypertensive effect is equivalent to that of ACE inhibitors, but they do not cause dry cough, angioedema associated with ACE inhibitors. Although there is no evidence documenting long-term cardiac and renal protection in patients with these conditions, they may be expected to show the protection of organ damage demonstrated by ACE inhibitors.

C. Diuretics

Large-scale intervention trials for hypertension in the elderly in Western countries have established that low doses of diuretics are useful for the prevention of cardiovascular morbidity and mortality (81). In the NICS-EH, diuretics were shown to be as effective as a Ca antagonist at treating hypertension in the elderly, but more patients dropped out from the trial than in those with a Ca antagonist (78). Considering the current status of drug prescriptions in Japan and also the results obtained in the NICS-EH trial, diuretics should be used in combination with long-acting Ca antagonists and/or ACE inhibitors.

Benefits of diuretics

Diuretics are recommended for treatment of hypertensive patients who have a tendency to water retention. Thiazide diuretics tend to inhibit urinary calcium excretion, and maybe useful for the prevention of osteoporosis. Diuretics can be used in combination with other classes of antihypertensive drugs, and may even increase their inherent effects. They are inexpensive.

Disadvantages of diuretics

Diuretics may cause a variety of unwanted effects such as hypokalemia, elevation of serum LDL-cholesterol levels, decrease of HDL-cholesterol

levels, elevation of blood uric acid levels, reduced glucose tolerance, ventricular ectopic beats and impotence. However, these adverse effects are infrequently recognized with low doses. Because glucose tolerance and renal function decline with aging, blood chemistry examinations are to be monitored periodically.

4. Combination Therapy

Combination therapy should be considered when monotherapy of more than 2-3 mo is not successful to reduce blood pressure below 150/90 mmHg (Fig. 1).

1) Hypertension without complications

The following combinations of antihypertensive drugs are recommended: Ca antagonist + ACE inhibitor, Ca antagonist + low dose diuretic, ACE inhibitor + low dose diuretic, or a combination of the drugs of first choice. Other antihypertensive drugs, such as β -blockers, α -blockers, or $\alpha\beta$ -blockers may be used if necessary (Fig. 1).

2) Hypertension with complications

In hypertensive patients with complications, the first choice drug is selected according to the complications recognized. Table 7 lists the first choice and combination drugs for the complications frequently recognized in the elderly.

5. Antihypertensive Drugs to Be Prescribed with Caution

Drugs acting on the central nervous system such as reserpine, methyldopa, clonidine, etc., are relatively contraindicated for hypertension in the elderly. In Japan, β -blockers and α -blockers have not been used commonly for hypertension in the elderly, because the elderly hypertensive patients frequently have complications that are contraindicated or for which β -blockers are to be used only with special conditions.

Cautions on β -blockers

As indicated above (11), and since hypertensive patients in the elderly are often complicated by congestive heart failure, bradycardia, arteriosclerosis obliterans, chronic obstructive pulmonary diseases, and diabetes mellitus or impaired glucose tolerance, β -blockers are contraindicated or should be prescribed with extreme caution. These complications may be present in an occult form in the elderly.

Cautions on α -blockers

In elderly hypertensive patients, α -blockers should be prescribed cautiously because they frequently induce postural hypotension due to decreased reflex sensitivity of the baroreceptor. Postural hypotension may cause dizziness and syncope, occasionally resulting in falls and bone fracture.

Table 7. Antihypertensive Drugs of the First Choice and the Combined for the Hypertensive Elderly Patients with Complications

Complications	Long-acting Ca antagonists (dihydropyridine)	ACE inhibitors	Diuretics	β -Blockers	α -Blockers
Cerebral infarction, chronic stage	○	○			
Cerebral bleeding, chronic stage	○	○			
Ischemic heart disease	○	○		○* ³	
Heart failure		○	○	△	
Renal insufficiency	○	○* ¹	○* ²		
Diabetes mellitus	○	○	△	△	
Hyperlipidemia	○	○	△	△	○
Gout (Hyperuricemia)	○	○	×		
Chronic obstructive pulmonary diseases	○			×	
Arteriosclerosis obliterans	○	○	△	×	
Osteoporosis			○		
Benign prostatic hypertrophy					○

○: First choice, △: Careful in use, ×: Contraindication

*¹: Contraindication for 2 mg/dl or greater of serum creatinine, *²: furosemide, *³: Contraindication for coronary angiospastic angina.

7. Precautions on Antihypertensive Treatment in Patients with Complications

1. Cerebrovascular Diseases

Treatment of hypertension complicated with cerebrovascular diseases is aimed at preventing the progression of brain ischemia and edema and re-bleeding or expansion of hematoma in the acute hemorrhagic stroke, and at reducing the recurrence of stroke in the chronic stage. In this regard, however, antihypertensive treatment is important, careful consideration of the cerebral hemodynamics is necessary.

1) Hypertension and cerebral circulation

Autoregulation of the brain keeps cerebral blood flow constant within a certain range against blood pressure alterations. In hypertensive patients, however, the upper and lower limits of autoregulation are shifted to a higher blood pressure level (82). When complicated with cerebrovascular diseases, cerebral blood flow at rest is reduced not only in the related lesions but also in other areas of the brain (83). Because of advanced arteriosclerotic changes and of reduced vasodilator capacity of the brain, cerebral blood flow remains low and its autoregulation shifts to a higher blood pressure level.

2) Treatment

Treatment of hypertension complicated with cerebrovascular diseases differs according to the stage (acute or chronic) and type of stroke (cerebral hemorrhage, cerebral thrombosis, cerebral embolism, etc.). Before treatment, therefore, it is necessary to determine the type of stroke by means of medical history, clinical findings, brain imagings including CT and MRI, and other examinations. It is

also important to detect stenosis or occlusion of the major arteries by means of non-invasive examinations such as carotid ultrasonography, trans-cranial ultrasonography, or magnetic resonance angiography (MRA), followed by conventional angiography, if necessary. In the case of cerebral embolism, echocardiography may be necessary for detecting the embolic source in the heart.

A. Acute stage

Blood pressure is elevated at the acute stage of stroke, regardless of bleeding or infarction, which may be induced by acute stress or reaction to compensate for reduced cerebral perfusion pressure due to increased intracranial pressure. Acute rise in the blood pressure may gradually fall with time even without treatment. Cerebral autoregulation is impaired in the acute stage, and then cerebral blood flow becomes dependent on blood pressure, easily resulting in cerebral ischemia due to reduction of blood pressure (84). However, in cases with excessively marked elevation of blood pressure which may cause aggravation of cerebral edema, antihypertensive treatment should be initiated with careful monitoring of neurological signs and symptoms. When systolic blood pressure exceeds more greatly 200 mmHg or higher and persists for a certain period of time (1 h or longer), and in those with cardiac failure, ischemic heart diseases, aortic aneurysm, etc., blood pressure should be controlled gradually by intravenous administration of trimetaphane, nicardipine or diltiazem. Special care should be given for treating with Ca antagonists, which may increase intracranial pressure. Short acting Ca antagonist such as sublingual administration of nifedipine is contraindicated. Blood pressure should be lowered gradually to around 180/100 mmHg, but not to normotensive levels. Excessive

reduction of blood pressure may be especially hazardous. On the other hand, antihypertensive treatment is generally not recommended in the case of cerebral infarction, but antihypertensive drug treatment may be required when systolic pressure is 220 mmHg or greater or the mean pressure exceeds 130 mmHg (85). In patients who receive thrombolytic therapy and have blood pressure of over 180 mmHg systolic and 105 mmHg or over diastolic, especially when the blood pressures rise within the first 24 h of the treatment, antihypertensive drugs should be administered intravenously for preventing hemorrhagic event while carefully monitoring neurological symptoms (12).

B. Chronic stage

When hypertension persists for more than 1 mo after acute strokes, antihypertensive treatment should be initiated taking account of blood pressure level, age and the extent of brain damage and other organ damages regardless of hemorrhage or infarction.

Controversy remains with regard to the secondary prevention of stroke by antihypertensive drugs. In general, however, although the target blood pressure may differ according to age or type and severity of strokes, the blood pressure levels indicating drug treatment is a systolic pressure of 160-190 mmHg or greater and a diastolic pressure of 90-100 mmHg, which levels are slightly higher than those for non-complicated elderly hypertensives. At the initial stage of treatment, the target blood pressure level should be set at below 150-170 mmHg systolic and below 90-100 mmHg diastolic. Since cerebral hemorrhage is more closely related with hypertension than cerebral infarction, the target blood pressure in cerebral hemorrhage should be set slightly lower by 5-10 mmHg systolic or diastolic than in cerebral infarction. The J-curve phenomenon between diastolic pressure and recurrence rate of cerebral infarction has been reported (63), and thus the blood pressure should not be lowered excessively. Furthermore, blood pressure should be reduced gradually, and treatment should be initiated at half the usual doses and increased at more than 4 wk intervals, with a goal of reaching the target blood pressure by taking 2 mo or more. During long-term antihypertensive treatment, blood pressure may fall to well below the initially expected level (sometimes to within the normotensive range), but the lowered level may be retained unless the symptoms become manifest suggesting compromised cerebral circulation.

Atherothrombotic cerebral infarction showing the watershed infarct commonly occurs in cases with stenosis or occlusion of the internal carotid or other intracranial major arteries, and thus such patients should be treated more cautiously, by maintaining a slightly higher blood pressure level than in those with lacunar infarction or cardiogenic embolism. Antihypertensive drug therapy may have to be reduced in dosage or discontinued, if over-dose is suggested by clinical symptoms such as dizziness, fainting, a sensation of heaviness in the head, or a decrease in memory and willingness suggesting insuf-

ficient cerebral perfusion, and then surgical treatment (endoarterectomy, extra- and intracranial bypass, or angioplasty) may be considered. The therapeutic target blood pressure must be determined for each individual patient through careful monitoring of symptoms, signs and laboratory test results. In addition to hypertension, other risk factors for cerebral infarction, such as diabetes mellitus, hyperlipidemia, smoking, alcohol intake, etc., must be controlled.

C. Selection of antihypertensive drugs at the chronic stage

Antihypertensive drugs must be selected in consideration of their direct and indirect pharmacological effects against cerebral vessels and metabolisms. Antihypertensive drugs with adverse effects against cerebral blood flow and metabolism (*i.e.*, reduction of cerebral blood flow) or the brain function should be avoided.

Dihydropyridine Ca antagonists have been demonstrated to dilate cerebral arteries and increase cerebral blood flow in addition to contributing an antihypertensive effect (86), and certain long-acting Ca antagonists may improve or shift the lower limit of the autoregulation to the left (87). Benzothiazepine Ca antagonists may cause bradycardia, atrio-ventricular block and reduction of cardiac output due to suppression of cardiac function, which may not be beneficial for the brain. ACE inhibitors shift the lower limit of cerebral autoregulation to the left with a little or slight increase in cerebral blood flow (88). Furthermore, ACE inhibitors improve thickening of vascular walls and have no adverse effects on lipid profile, glucose tolerance, or central nervous system (89). Acute administration of classical β -blockers reduces cerebral blood flow; however, chronic administration does not change much cerebral blood flow. β -blockers should be avoided in patients with congestive heart failure, atrio-ventricular block or bradycardia. They are, however, suitable for patients with old myocardial infarction or exertional angina pectoris. β -blockers with vasodilatory action may increase cerebral blood flow (90) and improve the lower limit of autoregulation. α -blockers and $\alpha\beta$ -blockers may increase cerebral blood flow by direct effects on cerebral blood vessels richly innervated with sympathetic nerves, and long-acting α -blockers may be used even in the elderly. However, α -blockers often induce orthostatic hypotension by blocking the peripheral sympathetic nerves, and thus they should be started at small doses and titrated with frequent monitoring of standing blood pressure. Since diuretics may cause electrolyte imbalance or metabolic disorders in addition to reduce cerebral blood flow by increased hematocrit, they should be prescribed in a small dose to minimize their adverse effects. Sometimes potassium supplementation may be required.

Anti-platelet drugs (aspirin or ticlopidine) or anticoagulants (warfarin) are also recommended in order to prevent the recurrence of artery-to-artery embolism in atherothrombotic infarction, or cardiogenic embolism with arterial fibrillation.

2. Ischemic Heart Diseases

Hypertension is well known as one of the important risk factors of ischemic heart diseases, as demonstrated by the Framingham and many other studies (91). Hypertension causes not only acceleration of coronary atherosclerosis, but also frequently cardiac hypertrophy due to continuous mechanical overload. In the hypertrophied heart, myocardial oxygen consumption is increased due to an afterload increase, and coronary flow reserve is decreased due to insufficient proliferation of the coronary capillaries and a decrease in reflex vasodilatation of the coronary arteries (92-94). Thus, both coronary atherosclerosis and cardiac hypertrophy strongly influence the pathogenesis of ischemic heart disease.

1) Diagnosis

The clinical symptoms of ischemic heart disease in the elderly are often atypical. Nearly one-half of patients with myocardial infarction do not experience chest pain, and many cases begin with cognitive disorders, disturbance of consciousness or other symptoms suggestive of heart failure. Non-invasive diagnostic procedures for acute myocardial infarction include echocardiography, electrocardiography, blood CPK-MB and troponin-T. Ischemic evidence in effort angina pectoris, unstable angina pectoris and old myocardial infarction can be confirmed by evaluating ventricular wall motion by means of stress electrocardiography, Holter electrocardiography, or myocardial scintigraphy or by simple echocardiographic evaluation of ventricular wall motion, and these laboratory tests are also useful in follow-up studies.

2) Treatment

Treatment of hypertension complicated with ischemic heart diseases is aimed at prevention of angina attacks, development of myocardial infarction, and recurrence of myocardial infarction, and at maintenance of cardiac functions by the prevention of left ventricular remodeling. Therefore, selection of antihypertensive drugs must be based not only on their ability to lower blood pressure, but also on other effects against coronary atherosclerosis, coronary blood flow, cardiac load and myocardial protection.

A. Therapeutic target blood pressure

Antihypertensive drug therapy is given to patients with systolic pressure of 160 mmHg or greater and diastolic pressure of 90 mmHg or greater. The target blood pressures are a systolic pressure of below 140 mmHg and a diastolic pressure of below 90 mmHg. However, excessive reduction of blood pressure may result in development of ischemic heart diseases, and thus blood pressure must be carefully controlled.

B. Selection of antihypertensive drugs

β -Blockers and long-acting Ca antagonists are recommended for hypertension complicated with effort angina because these drugs decrease cardiac afterload of the left ventricle and reduce myocardial oxygen consumption. ACE inhibitors are the first

choice in cases with myocardial infarction because of their inhibitory action against left ventricular remodeling (95).

a) Ca antagonists

Dihydropyridine Ca antagonists lower blood pressure remarkably and increase coronary blood flow with little effects on glucose or lipid metabolisms, and thus they are suitable for cases of hypertension complicated by angina pectoris. Long-acting Ca antagonists are suitable for patients with rest angina and unstable angina, because they inhibit coronary spasms. Benzothiazepine Ca antagonists tend to inhibit cardiac functions and induce bradycardia, and thus should be used cautiously in elderly patients. Ca antagonists usually do not improve the prognosis of hypertension after myocardial infarction (96), but may be effective in combination with ACE inhibitors.

b) β -Blockers

β -Blockers have both negative chronotropic and negative inotropic effects, decrease myocardial oxygen consumption caused by decreased heart rate and myocardial contractility, and are effective for angina with improved myocardial ischemia. β -Blockers are especially effective for hypertension complicated with effort angina, because they effectively decrease increased heart rate and elevated blood pressure on physical exercise and increase exertional tolerance. However, they are contraindicated for unstable angina and effort angina associated with severe coronary stenosis and coronary spasm, because they worsen the clinical symptoms of these diseases. β -Blockers without intrinsic sympathomimetic activity (ISA) have superior cardiac protective effects, and are known to effectively prevent the recurrence of myocardial infarction (97). They are contraindicated, however, for patients with bronchial asthma or chronic obstructive pulmonary diseases, and should be used cautiously for those elderly patients whose cases are frequently complicated by conduction disorders, bradycardia and cardiac failure.

c) ACE inhibitors

ACE inhibitors not only decrease cardiac afterload to decreased total peripheral vascular resistance, but also protect the myocardium, inhibit left ventricular remodeling (95), and improve the prognosis of cardiac failure (98). Therefore, ACE inhibitors are the first choice for patients with cardiac failure complicated by hypertension after myocardial infarction. However, they are contraindicated for cases with moderate or severe renal failure, and a small initial dose should be prescribed in elderly patients who commonly exhibit latent renal insufficiency.

d) Diuretics

Diuretics display excellent antihypertensive effects in the elderly, and are expected to inhibit cardiac hypertrophy and dilatation. Interventional mega-trials performed in Western countries have also con-

firmed the efficacy of diuretics for treatment of hypertension in the elderly (6, 99). However, care must be taken with regard to their various side effects, such as hyperlipidemia, glucose metabolic disorders, dehydration and, in case with cardiac hypertrophy, arrhythmia due to hypokalemia.

e) α -Blockers

α -Blockers exert vasodilative effects on both arteries and veins, and thus reduce cardiac load; they have no adverse effects on glucose or lipid metabolisms. However, elderly patients administered α -blockers are likely to develop orthostatic hypotension, and thus these drugs should be prescribed cautiously with a initial small dose.

f) Nitrites

Oral nitrites are effective for preventing anginal attacks. Continuous intravenous infusion of nitrites is most suitable in the acute stage of myocardial infarction associated with hypertension.

3. Heart Failure

Hypertension causes cardiac hypertrophy and ischemic heart diseases due to acceleration of coronary atherosclerosis and decreased coronary reserve, and both cardiac hypertrophy and ischemic heart diseases play an important role in the development of heart failure. In elderly patients, distensibility of the left ventricle is decreased in spite of its normal contractility (100, 101), and heart failure will develop as a result of either atrial fibrillation or flutter in the absence of any basic disease, arrhythmia due to conduction defects or left ventricular diastolic disorder due to cardiac amyloidosis.

1) Diagnosis

Occasionally, heart failure in the elderly may be accompanied by cerebral symptoms such as disturbance of consciousness, disorientation of delirium. Chest X-ray films can be used to detect cardiac enlargement, increased pulmonary vascularity, changes in pulmonary interstitial tissue or pleural effusion. Cardiac function can be easily evaluated and monitored by means of echocardiography and the determination of peripheral venous pressure (normally 5-10 cm H₂O). Electrocardiography is useful for diagnosing ischemic heart diseases, cardiac hypertrophy, arrhythmia and conduction defects.

2) Treatment

Treatment of heart failure is aimed at reducing cardiac work, correcting over-hydration, and increasing myocardial contractility. Any diseases underlining heart failure should be carefully evaluated.

A. Hypertension associated with acute left-side heart failure

Acute left-sided heart failure is a hypertensive emergency, and should be corrected with anti-hypertensive treatment by reducing cardiac afterload and myocardial oxygen consumption and thereby increasing cardiac output. It can be treated effec-

tively by oral administration of ACE inhibitors or continuous intravenous infusion of nitrites or Ca antagonists (nicardipine) in combination with intravenous injection of furosemide. In elderly patients, however, special precautions must be taken to avoid development of reduced blood flow of the coronary arteries, brain and kidneys due to acute reduction of blood pressure.

B. Hypertension associated with chronic heart failure

Left ventricular distensibility is decreased even in the healthy elderly, and the elderly with cardiac diseases frequently develop heart failure even though left ventricular contractility remains normal. Cardiac hypertrophy even without coronary stenosis is prone to develop into myocardial ischemia due to decreased coronary flow reserve due in turn, to insufficient coronary vasodilatation and relatively reduced coronary capillary proliferation (92-94). Therefore, treatment of hypertension is aimed at first regressing cardiac hypertrophy and then protecting the myocardium, in order to maintain and improve cardiac functions and coronary blood flow. In principle, the therapeutic target blood pressures will be the normal levels (below 140/90 mmHg).

C. Selection of antihypertensive drugs

a) Diuretics

Hypertension complicated with pulmonary edema, pleural effusion or peripheral edema is treated mainly with loop diuretics, because they decrease venous blood flow and venous blood pressure, resulting in improvement of edema. In addition, they improve pulmonary congestion by decreasing pulmonary capillary wedge pressure. Decrease in end-diastolic volume due to diuresis causes a decrease in preload and hence, decrease in cardiac work and myocardial oxygen consumption, enabling the improvement of heart failure. Special care should be given in cases of elderly patients with dehydration, decreased cerebral or renal blood flows due to diuresis, or arrhythmia due to hypokalemia, the latter of which may necessitate administration of aldosterone antagonist.

b) ACE Inhibitors

ACE Inhibitors are effective for vasodilatation in both arteries and veins, resulting in reduced cardiac loading, myocardial protection, and then improvement of the prognosis of heart failure (98). Thus, ACE inhibitors are extremely useful antihypertensive drugs, which should be the first choice drug in cases with heart failure. In those elderly patients who frequently experience renal dysfunction, an initial small dose is recommended.

c) β -Blockers

Carvedilol has been shown to improve the prognosis of chronic heart failure due to left ventricular systolic dysfunction (102). Usually, a small initial dose of β -blockers is recommended, followed by gradually increased doses, although the efficacy of this regime remains to be confirmed. However, the indica-

tion of β -blockers in the elderly should be limited, especially for the patients whose cases are complicated by obstructive pulmonary diseases, arteriosclerosis obliterans, diabetes mellitus or bradycardia.

d) Ca antagonists

Ca antagonists are arterial vasodilator. Their marked peripheral vasodilatation decreases the myocardial oxygen consumption due to decrease in cardiac afterload, and increases coronary blood flow due to coronary vasodilatation. Long-acting Ca antagonists (amlodipine or felodipine) are useful for improvement of the prognosis of non-ischemic heart failure (8).

4. Diabetes Mellitus

Hypertension is commonly complicated by diabetes mellitus or *vice versa* (103). In addition, morbidity of hypertension and carbohydrate metabolic abnormality increases with aging (104, 105), and thus hypertension in the elderly is frequently associated with carbohydrate metabolic abnormality. It has been suggested that essential hypertension and carbohydrate/lipids metabolic disorders belong to so-called insulin-resistant syndrome in cases where there is a background of insulin resistance (106), and elderly patients are known to have decreased insulin sensitivity (103). Cases of diabetes mellitus associated with essential hypertension are mostly cases of non-insulin dependent diabetes mellitus (NIDDM), both in elderly and non-elderly patients. Pathogenesis of NIDDM is known to be related to both decreased insulin secretion and increased insulin resistance based on aging and heredity. The etiology and pathogenesis of essential hypertension are likely to be related also to decreased insulin sensitivity and hyperinsulinemia, and the complications of NIDDM and/or obesity decrease insulin sensitivity. The complication of diabetes mellitus in case of hypertension increases the prevalence of arteriosclerotic diseases, and thus hypertension must be more strictly controlled in such cases (JNC VI). Essential hypertension complicated by diabetes mellitus is pathophysiologically characterized by increased body fluid and decreased renin-angiotensin system and sympathetic nervous activity (107, 108). When complicated by diabetic nephropathy, hypertension may be more influenced by renal involvement, causing marked increases in body fluid and sodium (107). Furthermore, hypertension itself may cause aggravation of diabetic nephropathy, prevention of which involves adequate management of hypertension and glomerular hyperfiltration.

1) Diagnosis

Glucose tolerance reduces with aging, but usually remains relatively mild. Therefore, the diagnostic criteria of diabetes mellitus in the elderly may be the same as in the young and middle-aged (fasting plasma glucose of 126 mg/dl or greater, according to the 1999 Japanese Diabetes Association guidelines). Plasma glucose levels after oral glucose intake will definitely increase with aging, and the diagnosis of diabetes mellitus should be made carefully if di-

agnosed only by oral glucose tolerance test results. In the cases with a 2-h plasma glucose level of 200-240 mg/dl, the principal treatments will be modification of diet and lifestyle; the prevalence of complications is reported to be higher in cases with a 2-h glucose level of over 240 mg/dl than at below this level (109). Diabetes mellitus in the elderly should be treated similarly as in the young and middle-aged.

2) Treatment

The therapeutic target blood pressure are a systolic pressure of below 140 mmHg and a diastolic pressure of below 90 mmHg. In the absence of any emergency, lifestyle modifications are considered first, followed by addition of antihypertensive drug therapy if improvement is insufficient. In the JNC VI, the therapeutic target blood pressure is recommended to be slightly lower than 130/85 mmHg in hypertension complicated by diabetes mellitus, and this target has recently gained wide acceptance.

A. Lifestyle modification

Obesity is prevalent among hypertensive cases complicated by NIDDM (110). Weight reduction by restriction of dietary calories is indispensable for obese patients, and it is useful not only for improvement of carbohydrate metabolism but also lowering of blood pressure. In practice, patients are advised to reduce weight by dietary and exercise treatments, avoiding foods with high cholesterol and saturated fatty acids. Salt restriction may be expected to lower blood pressure, but it should be made cautiously in patients with orthostatic hypotension due to diabetic neuropathy in elderly patients, who are generally prone to blood volume depletion.

B. Antihypertensive drug therapy

Antihypertensive drugs which may cause carbohydrate/lipid metabolic disorders should not be prescribed for a long period. Diuretics and β -blockers decrease insulin sensitivity and may cause deleterious effects on carbohydrate/lipids metabolism (111). In hypertensives whose cases are complicated by diabetes mellitus or obesity, reduced insulin sensitivity may be aggravated, and these drugs should not be used as the first choice. Recommended first-choice drugs are ACE inhibitors, Ca antagonists and α -blockers which do not have deleterious effects on carbohydrate/lipids metabolism. Improvement of carbohydrate/lipids metabolic disorders can be expected within 2-4 mo after administration of ACE inhibitors and α -blockers. In cases where these drugs are not sufficiently effective, triple combination therapy or combination with small doses of diuretics or β -blockers can be considered, since the combination of these drugs may reduce the adverse effects of each.

In elderly hypertensive patients, antihypertensive drugs should be prescribed cautiously. ACE inhibitors may act to protect the kidneys in diabetic nephropathy, but may aggravate renal function in the cases with serum creatinine of over 2.0 mg/dl. Special care should be taken when prescribing α -

blockers in cases of hypertension with diabetic neuropathy, since they may cause hypotension. In particular, excessive reduction of blood pressure due to Ca antagonists should be monitored in all cases.

5. Renal Diseases

Hypertension associated with renal diseases can be classified into those cases with chronic glomerulonephritis, with diabetic nephropathy and with nephrosclerosis (so-called hypertensive renal diseases). Renovascular hypertension may be encountered in association with renal arteriosclerosis in the elderly, especially in bilateral renal arterial stenosis resulting in decreased renal function (ischemic nephropathy). The terminal stage of renal diseases is known as uremia, and the most common reason for hemodialysis in Japan is still glomerulonephritis. For the past 10 or more years, however, the number of glomerulonephritis cases has been declining, whereas the numbers of diabetic nephropathy and nephrosclerosis cases have nearly doubled (112). Cases of mild or moderate hypertension are frequently associated with cerebrovascular diseases and cardiac diseases, but only rarely with renal diseases. However, renal insufficiency may proceed even in mild hypertension (113). In Japan, the number of patients treated with dialysis has been increasing consistently (112). Hypertension is definitely a risk factor for development of renal insufficiency, regardless of the type of renal insufficiency, and should be treated sufficiently to lower blood pressure.

1) Diagnosis

It is well known that renal function even in healthy individuals decreases with aging, and in the very elderly it is thought to decrease to roughly 50% of the level in young individuals (114). In hypertension in the elderly, associated renal diseases are closely related to both hypertension and renal arteriosclerosis. Renal function tests necessary at the initial visit include urinalysis and blood chemistry tests (serum creatinine, urea nitrogen, electrolytes and uric acid). In addition, routine examinations, such as chest X-ray and electrocardiography, should be performed in order to detect any cardiovascular diseases. If necessary, creatinine clearance may also be assessed to evaluate glomerular filtration rate (GFR), since serum creatinine levels, particularly in the elderly, may be within a normal range even though renal insufficiency exists. Renovascular hypertension should be ruled out in hypertensives showing rapid onset, resistance to treatment or progressive renal insufficiency.

2) Treatment

In hypertension with renal diseases, non-pharmacological treatment, particularly dietary treatment, is required. Restriction of protein intake (30-60 g/d) is required depending on the severity of renal insufficiency and salt intake (3-6 g/d) based on blood pressure levels and edema. Frequency of hypertensive renal diseases in hypertensives is not as high as

that of cerebrovascular and cardiac diseases. However, it has been reported that cases with blood pressure higher than 140/90 mmHg promote renal insufficiency faster than those with normal or adequately controlled blood pressure (115), and thus even mild hypertension may promote renal diseases. Elevation of intraglomerular pressure may be encountered from the early stage of diabetic nephropathy, and in such cases is probably related to the progression of renal diseases. Therefore, the therapeutic target blood pressure should be set a little lower, below 140-150/90 mmHg, in hypertension complicated with renal diseases. The JNC VI guidelines recommend a therapeutic goal of below 130/85 mmHg in the cases with proteinuria below 1 g/d, and of below 125/75 mmHg in those with proteinuria of 1 g/d or more (12). The so-called "J-curve phenomenon" has not been recognized between lowering of blood pressure and progression of renal insufficiency, but renal function should be monitored carefully in elderly hypertensives, since elevation of serum creatinine is commonly experienced in association with rapid lowering of blood pressure. A more than 50% decline of renal function may be expected in cases with serum creatinine of over 1.3 mg/dl, and such patients should be monitored by measuring the serum creatinine and electrolytes every 1-6 mo, and if necessary, by performing other laboratory tests every 6-12 mo.

A. Selection of antihypertensive drugs

Diuretics, ACE inhibitors and Ca antagonists are mainly prescribed in hypertension associated with renal insufficiency. A small dose of diuretics is recommended for the cases with body fluid retention, and at a serum creatinine level of over 1.5-2.0 mg/dl, loop diuretics are used instead of thiazide diuretics. ACE inhibitors are used for elderly hypertensives with mild renal dysfunction, and are expected to demonstrate long-term protection of the kidneys by decreasing systematic and intraglomerular blood pressure. Their effectiveness has also been proved clinically in diabetic nephropathy (116). However, ACE inhibitors are contraindicated for cases with moderate renal dysfunction (serum creatinine over 2.0 mg/dl), which they may further aggravate. Bilateral renovascular hypertension should be ruled out if rapid decline of renal functions is recognized in the elderly. Ca antagonists have mild diuretic action, and may be widely applicable, regardless of the severity of renal dysfunction. Most β -blockers do not significantly influence renal function, although some are reported to decrease renal blood flow (RBF) and GFR; those with trans-hepatic excretion are preferred. Vasodilators and sympatholytic drugs may demonstrate body fluid retention, and may be effective in combination with a small dose of diuretics. α -Blockers are well indicated for elderly patients with prostatic hypertrophy, but should be followed up for orthostatic hypotension in cases with renal insufficiency due to diabetic nephropathy.

6. Hyperlipidemia

Hyperlipidemia and hypertension, as well as di-

abetes mellitus, obesity and smoking, are important risk factors for development of arteriosclerosis, and because the combination of hypertension and hyperlipidemia may aggravate arteriosclerosis, these conditions should be adequately controlled.

In the elderly, aging itself is one of the important risk factors for arteriosclerosis, and in elderly subjects, hyperlipidemia was taken less important in arteriosclerosis than in young generation. However, many studies have demonstrated that hyperlipidemia in the elderly will also increase synergistically in morbidity of ischemic heart diseases (117).

Hypo-HDL-cholesterolemia is considered to be one of the important risk factors of arteriosclerosis (118). No conclusive report has yet been made as to whether hypertriglyceridemia is an independent risk factor of arteriosclerosis. At the present, it seems reasonable to suppose that hypertriglyceridemia in the elderly would be a risk factor in association with hypercholesterolemia, hypo-HDL-cholesterolemia, impaired glucose tolerance, obesity and so on.

1) Diagnosis

According to the Practice Guidelines for Hyperlipidemia reported in 1997 (119), the diagnostic criteria for hyperlipidemia include serum total cholesterol of 220 mg/dl or greater, triglyceride of 150 mg/dl or greater, and HDL-cholesterol of below 40 mg/dl. These diagnostic reference values may be applied also for the elderly. Hyperlipidemia should be differentiated into primary and secondary (diabetes mellitus, hypothyroidism, drug-induced, etc.) types.

2) Treatment

Hypertension complicated with hyperlipidemia is treated by antihypertensive drugs, such as Ca antagonists, ACE inhibitors and α -blockers, all of which have the advantages of not deteriorating lipid metabolism. If β -blockers are to be used, those with intrinsic sympathomimetic activity (ISA), should be selected, if possible. Orthostatic hypotension is monitored with α -blockers. The therapeutic target blood pressure would be below 140-150/90 mmHg, as in the other elderly patients. If hyperlipidemia cannot be corrected by general treatments such as dietary and exercise therapies, antihyperlipidemic drugs may be prescribed. Although there is no contraindication specific to the elderly, the following side effects must be considered: constipation with cholestyramine, low HDL-cholesterol with probucol, elevated creatine phosphokinase (CPK) and rhabdomyolysis with HMG-CoA reductase inhibitors, and facial hot flush with nicotinate derivatives. In consideration of the occult and manifest dysfunction of various organs in the elderly, drugs are initially prescribed in a small dose (1/2-1/3 of the adults). Responses to drugs in the elderly show significant inter-individual variations, and adequate dose of drugs to each patient must be determined carefully and slowly.

7. Arteriosclerosis Obliterans (ASO)

Patients with intermittent claudication, the most

characteristic symptom of ASO, complain of weakness and pain in the unilateral or bilateral extremities on walking, and eventually are unable to walk due to painful twitching of the lower extremities. Hypertensive patients whose cases are complicated by ASO should be treated with those antihypertensive drugs which improve blood circulation.

1) Diagnosis

Morbidity of ASO increases with aging, but many elderly patients may not complain of typical intermittent claudication or ischemic symptoms because of their low physical activity (120). Therefore, physical examination of elderly hypertensive patients at the first visit should include careful palpation of the upper and lower extremities, and especially the femoral, popliteal and dorsal arteries, to rule out ASO. If suggestive of ASO, blood flow in the corresponding areas is measured by doppler hemodromometer (120). During the follow-up encounters, patients are carefully monitored for any change in subjective complaints, and by palpation of extremities and non-invasive perfusion pressure measurement. ASO is usually classified by Fontaine's classification: stage I, no symptoms or mild cold flush and numbness; stage II, intermittent claudication; and stage III, cases in which the walking distance is decreased to below 30 meters with pains or in which there is pain at rest due to chronic ischemia, and which require surgical treatment.

2) Treatment

The principal treatment for ASO consists of surgical operation such as percutaneous transluminal angioplasty (PTA) for patients complaining of advanced intermittent claudication or for Fontaine stage III patients. Drug therapy is supplementary only. Antihypertensive drugs must be selected not to inhibit blood circulation including collateral circulation. In general, diuretics (120) and β -blockers (121) tend to cause aggravation of ischemic symptoms due to reduction of blood flow of the injured and collateral blood vessels. ACE inhibitors are also to be effective at maintaining or increasing blood flow of the lower extremities and thus improving exercise tolerance capacity (120-122). α -Blockers are also to be effective for patients with ASO (120), although no clinical evidence has yet been obtained. Dihydropyridine Ca antagonists have strong vasodilatation effects, and are recognized to be effective for patients with ASO (123). It has been reported that nicardipine administered to ASO patients with normal blood pressure resulted in worsening of clinical symptoms, probably due to stealing of blood from the injured blood vessels (122). Therefore, care must be taken in the administration of short acting drugs, that cause rapid vasodilatation. It has been reported that verapamil improves physical movement (124). β -Blockers without cardiac selectivity and vasodilatation are reported not to aggravate peripheral blood circulation (125), but should be administered cautiously to patients with ASO (12).

Blood pressure should be lowered to a level that will not decrease the perfusion pressure of the dis-

eased extremity. It may be necessary to determine this level individually for each patient, depending on the extent of vascular stenosis and development of collateral circulation, but in general the target blood pressure should stay at around 150-160/90 mmHg, slightly higher than that for the elderly non-complicated hypertensives. After the initiation of treatment, patients are monitored by measuring blood pressure routinely at the upper arms and the diseased extremity by doppler hemodromometer, and also followed up by subjective complaints and periodically by thermography as to any clinical aggravation of ischemic symptoms.

For the management of ASO it is important not to overlook any complication, particularly the risk factors for atherosclerosis other than hypertension, such as hyperlipidemia and diabetes mellitus. Symptomatic ASO is classified by WHO/ISH grade III as a hypertensive organ disorder. Thus, the systematic arteries must be examined including the aorta and the carotid, renal, coronary and mesenteric arteries (120). Patients with ASO are frequently associated with renovascular hypertension (126), for which ACE inhibitors should be prescribed very cautiously. It is important to bear in mind that prognosis of ASO patients whose cases are complicated by ischemic heart diseases is very poor (127), and that antihypertensive drugs must be selected with extreme caution.

8. Drug Interactions with Antihypertensive Treatment

Elderly hypertensive patients frequently have other diseases, and they are likely to receive many drugs for concomitant diseases from other physicians. Thus, they tend to encounter various drug interactions with antihypertensive drugs. Decreased function of multiple organs, particularly renal function, due to aging may promote accumulation of drugs, resulting in development of adverse effects, exaggeration of drug interactions and further deterioration of organ functions. The drugs prescribed by other physicians must therefore be confirmed, and patients must be carefully monitored for possible drug interactions. The following are some of the possible drug interactions (Table 8). Central sympatholytic drugs and peripheral neuronal blockers are excluded, because they are rarely prescribed for elderly hypertensive patients.

1. Adverse Interactions between Antihypertensive Drugs

The combination of β -blockers and diltiazem may cause marked bradycardia, atrioventricular conduction disturbances or heart failure (128). The combination of potassium-sparing diuretics and either ACE inhibitors or angiotensin II antagonists may cause hyperkalemia, and such combinations are therefore contraindication for patients with renal insufficiency. In cases in which the renin-angiotensin system is activated by diuretics, additional administration of ACE inhibitors or angiotensin II antagonists may cause excessive reduction of blood pressure. The combination of α -blockers and either diuretics or β -

blockers may be likely to cause orthostatic hypotension.

2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) NSAIDs inhibit synthesis of prostaglandins, and may also inhibit the antihypertensive effects of ACE inhibitors, diuretics, β -blockers and α -blockers (129). When combined with triamterene indomethacin was reported to have induced acute renal failure (130). In cases with a decreased renal blood flow, combination of NSAIDs and ACE inhibitors is apt to induce decreased renal function and hyperkalemia. Among NSAIDs, indomethacin and piroxicam have strong adverse effects, and sulindac and aspirin have mild ones. Ca antagonists are little affected by NSAIDs.

3. Digitalis

Elevation of blood concentration of digoxin due to diltiazem seems to be mild (131), but its possibility should be kept in mind when the combination of the two drugs is made in the elderly. Elevation of digoxin concentration due to captopril has been reported in cases of severe heart failure (132). ACE inhibitors are apt to induce renal dysfunction in cases of heart failure, renal arterial stenosis and hypovolemia, and they should be used carefully in combination with digitalis. Combination of digitalis and potassium-losing diuretics may cause digitalis intoxication, and combination of digitalis with β -blockers or diltiazem may cause severe bradycardia.

4. Nitrates

Nitrates exert vasodilatory effects, and may have additive vasodilatory action in combination with various antihypertensive drugs. In cases complicated by coronary artery diseases and treated by nitrates, antihypertensive drugs should be carefully administered to avoid excessive fall in blood pressure, since J-curve phenomenon on coronary artery diseases is reported (133). Patients should be informed of possible excessive reduction of blood pressure and possible occurrence of orthostatic hypotension upon urgent use of nitrates.

5. Antiarrhythmic Drugs

Combination with β -blockers and diltiazem may cause severe bradycardia, arrhythmia and decreased cardiac function. Combination with potassium-losing diuretics may cause aggravation of proarrhythmic responses due to hypokalemia and hypomagnesemia.

6. H₂-blockers

Cimetidine inhibits cytochrome p-450 enzyme in the liver and may cause an increase in the serum concentrations of Ca antagonists and β -blockers (propranolol, metoprolol, labetalol, etc.) which are metabolized in the liver (134, 135). Ranitidine has mild affinity with the enzyme, but it is dose-dependent.

7. Antacids

Antacids inhibit gastrointestinal absorption of ACE

Table 8. Selected Interacting between Antihypertensive and Non-Antihypertensive Drugs

	Increasing antihypertensive effect	Decreasing antihypertensive effect	Effects on other drugs
Ca antagonists	Cimetidine, ranitidine, macrolide antibiotics, antifungal azoles: felodipine, nifedipine Grapefruit juice: some dihydropyridines	Rifampicin, phenobarbital: verapamil, felodipine	Digoxin, carbamazepine, midazolam: a rise in serum levels with verapamil, diltiazem Quinidine, theophylline: a rise in serum levels with verapamil Amiodalone: sinus arrest, atrioventricular block, cardiac arrest with diltiazem, nifedipine, reported Cyclosporine: a rise in serum levels with diltiazem, nifedipine, verapamil Lithium: neurotoxic effects with diltiazem, verapamil, reported
ACE inhibitors	Excessive fall in blood pressure with diuretics (volume depletion) Chlorpromazine	NSAIDs Antacids	Potassium: hyperkalemia NSAIDs: a decrease in renal function, hyperkalemia Digoxin: a rise in serum levels in severe heart failure Allopurinol: serum sickness-like syndrome and Stevens-Johnson syndrome with captopril, reported Antihyperglycemics: hypoglycemia, reported Lithium: a rise in serum levels
β -Blockers	Cimetidine, quinidine: β -blockers metabolized in the liver	NSAIDs Rifampicin, phenobarbital, smoking: β -blockers metabolized in the liver Antacids	Antihyperglycemics: masking and prolongation of hypoglycemia Digoxin: marked bradycardia with propranolol, reported Anti-arrhythmic drugs: possibilities of conduction defects, arrhythmia, decreased cardiac function Drugs for cold and nasal congestion containing sympathomimetics: an increase in blood pressure Digoxin: digitalis intoxication by hypokalemia Telfenadine, astemizole: QT prolongation, ventricular arrhythmia induced by hypokalemia Oral antihyperglycemics: an increase in requirement doses with potassium-losing diuretics, reported Aminoglycosides: an increased toxicity to kidneys and acoustic nerves with loop-diuretics NSAIDs: renal failure with triamterene, reported Amantadine: a rise in serum levels, reported Lithium: a rise in serum levels
Diuretics		NSAIDs Steroids Cholestyramine: thiazide diuretics	
α_1 -Blockers		NSAIDs	

Attention should be paid to potential interactions with antihypertensive drugs other than those listed in the Table. Angiotensin II antagonists are not listed because of paucity of information, but the interactions related to blockade of the renin-angiotensin-aldosterone system may develop as those with ACE inhibitors. Central sympatholytics and peripheral neuronal blockers are excluded. NSAIDs: non-steroidal antiinflammatory drugs, ACE: angiotensin-converting enzyme.

inhibitors and β -blockers (12, 136).

8. *Antihyperlipidemic Drugs*

Cholestyramine, an anion-exchange resin, inhibits intestinal absorption of thiazide diuretics (137). Therefore, diuretics should be administered 1 h before or 4 h after intake of cholestyramine.

9. *Antihyperuricemic Drugs*

It has been reported that a case of elderly patient complicated with heart failure and chronic renal failure resulted in death due to hypersensitivity (fever, arthralgia, erythema multiforme, etc.) following administration of allopurinol combined with captopril (138).

10. *Antihyperglycemic Drugs*

Combination with ACE inhibitors is reported to induce hypoglycemic attack (139). β -Blockers may mask the symptoms consistent with hypoglycemia, which could be prolonged. Potassium-losing diuretics may increase the requirement doses of oral antihyperglycemic drugs.

11. *Potassium*

Combination with potassium-sparing diuretics, ACE inhibitors or angiotensin II antagonists may cause hyperkalemia, and is contraindicated in cases of renal insufficiency.

12. *Drugs for the Common Cold*

During treatment with β -blockers, the administration of drugs for common cold/nasal congestion (many over-the-counter drugs, Dan Rich[®]) which contain phenylpropanolamine or other sympathomimetic drugs may increase blood pressure due to unopposed α adrenergic stimulation (12).

13. *Antiallergic Drugs*

Under the condition of hypokalemia and hypomagnesemia, terfenadine and astemizole may induce QT prolongation and ventricular arrhythmia (140), and are contraindicated during the administration of diuretics (141).

14. *Theophylline*

Its blood concentration rises in combination with diltiazem (134).

15. *Antibiotics and Antifungal Drugs*

Rifampicin may induce cytochrome p-450 enzyme, and inhibit the antihypertensive effects of Ca antagonists and β -blockers which are metabolized in the liver (12). Macrolide antibiotics such as erythromycin, clarithromycin, etc. and antifungal drugs such as itraconazole may increase the blood concentration of felodipine and nifedipine due to inhibition of the enzymes (134, 142). Combination of aminoglycosides and loop diuretics increase renal toxicity and acoustic nerve defects (143).

16. *Centrally Acting Drugs*

Diltiazem may raise blood concentration of triazolam (144) and midazolam (134) and increase their

sedative actions. Thiazide diuretics may increase the anti-Parkinsonism effects of amantadine (145). Diltiazem may raise the blood concentration of carbamazepine, resulting in developing neurotoxicity. ACE inhibitors and diuretics may raise the blood concentration of lithium, an anti-manic drug. Phenobarbital may decrease the blood concentration of felodipine.

17. *Cyclosporine*

Diltiazem and nicardipine increase the blood concentration of cyclosporine (134). However, felodipine and nifedipine do not demonstrate such an effect. It has been reported that the combination of cyclosporine and enalapril led to the development of renal failure (146).

18. *Grapefruit Juice*

A bitter constituent in grapefruit juice inhibits metabolism of Ca antagonists such as felodipine, nifedipine, nitrendipine, etc., and thus increases antihypertensive effects (147).

19. *Cyldenafil (Viagra[®])*

Cyldenafil is contraindicated for patients with ischemic heart diseases, and particularly for those taking nitrates; patients receiving multiple antihypertensive drugs may develop excessive reduction of blood pressure due to peripheral vasodilatation (148). The combination of cyldenafil and nipradilol (Hypadil[®]), an antihypertensive drug having NO radicals, is contraindicated.

9. *Considerations on QOL*

1. *Characteristics of QOL in the Elderly*

QOL has been drawing much attention in various fields of medical practice. Hypertension is associated with few subjective symptoms. For the management of hypertension (149), QOL has been understood in a broad sense to include not only physical, psychological and social factors, but also patients' moods, including those related to the will to live, and to the satisfaction and comfort derived from life (150). Elderly patients have much more complex QOL problems compared with young or middle-aged patients, because of their specific social and psychological conditions under which they live, as well as their multiple organ disorders aside from hypertension. Before any antihypertensive treatment is started, the following problems should be considered with respect to QOL of elderly hypertensive patients: 1) depressive tendencies, 2) complication by dementia; and 3) other diseases. Psychological state of the elderly is well characterized by loss of will to live. Physical and mental activities invariably decrease with aging, and a loss or weakening of the social and economic states of the elderly patients cannot be overlooked as important factors contributing to depression. Dementia is as important a problem as depression, and cognitive function in the elderly should be evaluated separately from QOL. Finally, elderly patients frequently suffer from chronic diseases, which definitely in-

fluence QOL, particularly in the case of diseases that significantly limit the activities of daily living (ADL).

2. Assessment of QOL in the Elderly

Assessment tools for QOL of elderly patients should be able to evaluate not only direct influences by physical diseases, but also various specific problems pertinent to this age group. A simpler and easily understandable questionnaire (151) is available, which adopt the concept of "Five dimensions for QOL assessment" developed by Levine and Croog (150). The questionnaire is also designed to evaluate general symptoms, willingness to work, physical symptoms, the quality of sleep, affection, sexual activity, satisfaction of living, self-regulation, daily activity, etc. A more detailed questionnaire for QOL assessment of elderly hypertensives (152) has been developed in Japan, which includes, as its main components, such items subjective and social indicators as 1) subjective inconvenience in daily life due to illness, 2) satisfaction for living, 3) emotional stability, 4) vitality for living, and 5) self-support for living, all of which are important parameters of QOL in the elderly.

3. Selection of Antihypertensive Drugs, Based on QOL

Important factors which may affect the QOL of elderly patients include the worsening of subjective symptoms or laboratory abnormalities due to adverse effects of drugs as well as numbers of adverse effects specific to individual antihypertensive drugs. ACE inhibitors, long-acting Ca antagonists, small doses of diuretics and some β -blockers are reported to have a little or no adverse effect on QOL of the elderly hypertensive patients (151, 153). In the HOT study in which elderly patients were treated with a long-acting Ca antagonist, felodipine, it was reported that the QOL was improved in direct proportion to the antihypertensive effects of the drug (154). Therefore, in order to maintain or improve QOL of elderly hypertensive patients, adequate drugs should be selected from these antihypertensive drugs individually for each patient, considering the presence of any complication. In general, ACE inhibitors, long-acting Ca antagonists are the drugs of choice for the treatment of hypertension in the elderly with regard to QOL.

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