Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004)

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(in alphabetical order)

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1. Epidemiology of Hypertension

1) Changes in the Average Blood Pressure of the Japanese

It is well known that the prevalence of, and the mortality rate due to, stroke have decreased recently with decline in the average blood pressure of the Japanese. In Japan, the age-adjusted mortality rate due to stroke had been the highest in the world, but it decreased rapidly after 1965, and the average lifespan of the Japanese became the longest in the world (*1*). The decrease in the average blood pressure of the Japanese has contributed greatly to this prolongation of the lifespan. According to the National Nutrition Survey in Japan, the average blood pressure increased from 1956, when the survey was started, to a peak in 1965 but decreased until 1990 (Fig. 1-1). The decreases after 1990 have been nominal. The time when the mortality rate due to stroke was highest is in close agreement with the time when the average blood pressure of the Japanese was highest (1965) (*2*). Such decreases in the average blood pressure of the Japanese have been reported also by epidemiological studies in Hisayama, Akita, and Osaka (*3*, *4*).

2) Hypertension and Occurrence of Cardiovascular Diseases and Its Prognosis

a. High Incidence of Stroke Due to Hypertension

The incidence of, and mortality rate due to, stroke are high when the average blood pressure is high. Hypertension is specifically related to stroke, and the incidence of, and mortality rate due to, stroke are still higher than the incidence of, and mortality rate due to, myocardial infarction in Japan (*5*–*7*). Table 1-1 shows the mortality rates due to stroke, coronary heart disease, and acute myocardial infarction by age according to the Population Survey Report of Japan. The mortality rate due to cerebrovascular disease is 1.8 times higher than that due to coronary heart disease (ischemic heart disease) in the entire population (*5*). According also to an incidence survey in Okinawa based on prefectural patient registration, the incidence of myocardial infarction was one-fourth that of stroke (*7*). Hypertension is positively related to the incidence of, and mortality rate due to, stroke in a stepwise manner (*8*–*11*). Among the stroke types, the blood pressure was more closely related to cerebral hemorrhage than to cerebral infarction, but similar stepwise relationships were observed. In a follow-up survey of the study in Hisayama, a stepwise close relationship was observed between the blood pressure and cerebral infarction (Fig. 1-2) (*9*). In the Hisayama study, the incidence of lacunar infarct was closely correlated with the severity of hypertension graded in the Sixth Report of the Joint National Committee on Hypertension, USA (JNC VI) (*11*). The close relationship between the grade of hypertension and the mortality rate due to stroke indicated by the JNC VI was clearly observed also in National Integrated Projects for Prospective Observation of Non-communicable Disease and Its Trend in the Aged (NIPPON DATA 80) based on a 14-year follow-up of a representative Japanese population of about 10,000 persons (*10*).

Findings attached to the Health Promotion Strategy of Japan for the 21st Century (Health Japan 21st), which summarize results of epidemiological studies in Japan and abroad, show relative risks of the development of, and death due to, stroke according to the blood pressure (*12*). These findings indicate that an increase in the systolic blood pressure of 10 mmHg corresponds to about 20% increase in men and about 15% increase in women in the risks for the development of, and death due to, stroke (Table 1-2).

In elderly people, the relationship between the blood pressure and stroke is weaker than in younger people. In Hisayama Study, the relationship between stroke and hypertension according to the classification of the JNC VI was weaker in those aged 80 years and above than in those aged 60–79 years (*13*), but this relationship was clear even when it was weak in a metaanalysis integrating many cohort studies in Western countries and Japan (*14*). Similar results were obtained also in an investigation summarizing cohort studies of Asia Pacific regions (*8*).

b. Development of Heart Diseases Due to Hypertension

The relationship between hypertension and heart disease was similar to that between hypertension and stroke though it is weaker. The results were also similar when heart disease is specified as coronary heart disease. In men, the risks for the development of, and death due to, coronary heart disease increase by about 15% with an increase in the systolic blood pressure of 10 mmHg (*12*).

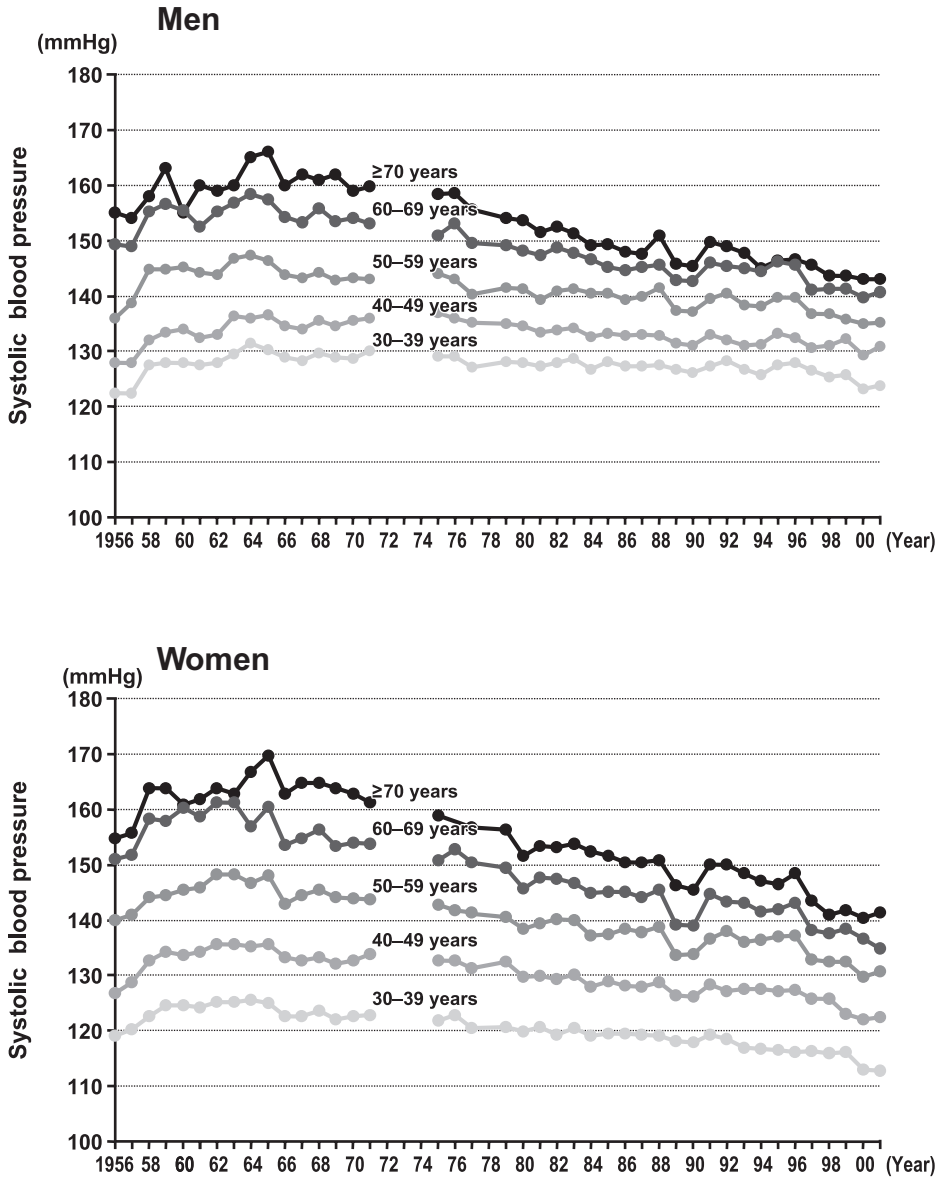

Fig. 1-1. *Annual changes in the mean systolic blood pressure by age (based on the National Nutrition Surveys 1956–2001, Ministry of Health, Labor and Welfare).*

c. Prognosis of Stroke and Heart Disease

In a joint study of the World Health Organization (WHO) on the incidences of stroke and myocardial infarction (Multinational Monitoring of Determinants and Trends in Cardiovascular Disease: MONICA), the mortality rate in patients with stroke aged 35–64 years within 28 days after the onset was about 30% with some variations among groups (*15*). This mortality rate is about 15% according to the Japanese registration of stroke patients (*6*, *7*, *16*). The mortality rate is highest for subarachnoid hemorrhage among stroke types, followed by cerebral hemorrhage (16–24%). One year after the onset of stroke, 29–45% needed assistance in activities of daily living (ADL), and the control of hypertension as a measure to prevent stroke is extremely important for the prevention of elderly disabilities (*6*).

3) Characteristics of Hypertension in the Japanese

a. High Salt Intake

One reason for the high prevalence of hypertension and high incidence of stroke in the past Japan was a high salt intake, which is known to increase the blood pressure. In the International Study of Salt and Blood Pressure (INTERSALT), the

Table 1-1. Comparison of Age-Specific Mortality Rates Due to Cerebrovascular Disease and Coronary Heart Disease by Age (2002, per 100,000 Persons)

	Population means	Age-specific mortality rate (years)										
		40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90<
Cerebrovascular disease												
Men	101.0	15.9	26.3	44.3	63.4	91.0	164.6	297.3	539.3	1,071.4	1,937.1	3,067.6
Women	105.6	6.9	13.6	20.7	30.0	43.0	77.3	142.5	311.0	583.8	1,411.3	2,730.2
Total	103.4	11.5	19.7	32.5	46.4	66.3	118.6	213.0	405.2	817.0	1,574.1	2,810.0
Coronary heart disease (Ischemic heart disease)												
Men	63.6	12.4	20.8	37.7	52.9	83.0	127.7	205.1	329.7	559.0	937.3	1,349.0
Women	50.3	2.3	4.0	7.8	12.6	24.1	34.8	78.1	171.7	357.0	642.3	1,056.0
Total	56.7	7.3	12.6	22.7	33.4	52.7	84.1	139.6	236.7	426.5	742.7	1,129.3
Acute myocardial infarction												
Men	40.7	8.3	13.8	24.5	36.2	53.0	83.6	133.3	216.7	355.4	583.4	795.7
Women	32.0	1.4	2.5	5.1	8.0	16.1	29.6	55.7	112.3	231.5	415.9	613.4
Total	36.2	4.8	6.2	14.8	21.0	34.0	55.2	91.0	155.4	274.1	467.8	657.5
Cerebrovascular disease/Coronary heart disease ratio												
Men	1.6	1.3	1.3	1.2	1.2	1.1	1.3	1.5	1.6	1.9	2.1	2.3
Women	2.1	3.0	3.3	2.7	2.4	1.8	2.2	1.8	1.8	1.6	2.2	2.6
Total	1.8	1.6	1.6	1.4	1.4	1.3	1.4	1.5	1.7	1.9	2.1	2.5
Cerebrovascular disease/Acute myocardial infarction ratio												
Men	2.5	1.9	1.9	1.8	1.8	1.7	2.0	2.2	2.5	3.0	3.3	3.9
Women	3.3	4.9	5.4	4.1	3.8	2.7	2.6	2.6	2.8	2.5	3.4	4.5
Total	2.9	2.4	3.2	2.2	2.2	2.0	2.2	2.3	2.6	3.0	3.4	4.3

Reproduced from reference *5*.

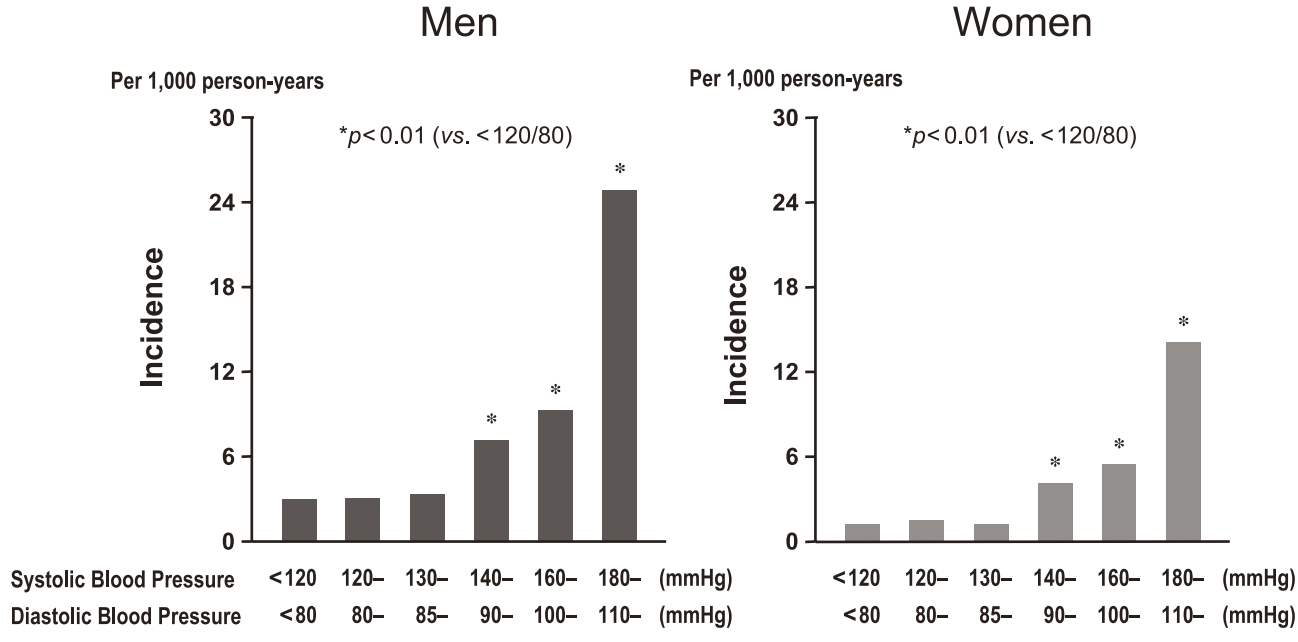

Fig. 1-2. *Incidence of cerebral infarction by the blood pressure. Residents of Hisayama not medicated for hypertension, age-adjusted data in 1961–1993 (cited from reference 9)*

Table 1-2. Japanese and International Epidemiologic Data Concerning Relationship between Increase in Systolic Blood Pressure of 10 mmHg and Relative Risk for Stroke

Cohort	Analyzed age range	Endpoint	Sample size (persons)	Years of follow-up	Relative risk (10 mmHg)	CI (statistical significance)
Men						
International						
MRFIT	35–	Death	347,978	11.6	1.48	$p<0.001$
Framingham	55–84	Event	2,372	10	1.91	$p<0.05$
Honolulu Heart Program	45–	Event	7,895	6	1.52	$p<0.05$
Japan						
Hisayama	40–	Event	707	23	2.35*	$p<0.01$
Hiroshima	45–	Event	4,126	26	1.29	1.20–1.39
Akita	45–	Event	1,278	25	1.34	$p<0.05$
Osaka	40–59	Event	1,717	25	1.31	$p<0.001$
Shibata	40–	Event	954	15.5	1.17	1.09–1.26
NIPPON DATA 80	30–	Death	4,727	14	1.19	1.10–1.29
NIPPON DATA 80	30–69 (at start)	Death	3,813	14	1.27	1.14–1.42
Age-adjusted relative risk	≥30				1.20	
Women						
International						
Framingham	55–84	Event	3,362	10	1.68	$p<0.05$
Japan						
Hisayama	40–	Event	914	23	2.62*	$p<0.01$
Hiroshima	45–	Event	7,033	26	1.29	1.20–1.39
Shibata	40–	Event	1,341	15.5	1.29	$p<0.05$
NIPPON DATA 80	30–	Death	5,399	14	1.14	1.05–1.25
NIPPON DATA 80	30–69 (at start)	Death	4,874	14	1.44	1.28–1.61
Age-adjusted relative risk	≥30				1.15	

Multiple regression analysis (other risk factors taken into consideration). CI, confidence interval; MRFIT, Multiple Risk Factors Intervention Trial. *Relative risk in Hisayama concerns whether the person was hypertensive or not. Reproduced with modification from reference *12*.

blood pressure was high in a group considered from analysis of 24-h urine collection to have a high salt intake, and there was also a positive correlation between the blood pressure and the salt intake in the individual level (*17*).

Presently, the salt intake of the Japanese is about 12 g/day according to the results of analysis of 24-h urine collection (*17–19*). The salt intake is lower in women than in men in proportion to the smaller energy intake, and the estimated salt intake in Japanese women in their 20s was about 10 g according to the INTERSALT in 1985 (*17*). The estimated salt intake in men aged 40–59 years by analysis of 24-h urine collection in the International Collaborative Study of Macro- and Micronutrients and Blood Pressure (INTERMAP) was about 12 g/day in 1997 (*19*). In 240 male workers aged 35–60 years surveyed in 2000, the salt intake was estimated by analysis of 24-h pooled urine to be about 11 g/day (*20*).

Since the average salt intake of the Japanese is about 11.5 g/day according to the National Nutrition Survey of the Japan, the present average salt intake of the Japanese is considered to be about 11–12 g/day.

The salt intake estimated by analysis of 24-h urine collection was as high as 25 g/day in the Tohoku District in the 1950s (*21*). Compared with this value, the salt intake of the Japanese has decreased markedly to the present level.

However, the target salt intake cited by "Health Japan 21st" is less than 10 g/day (*12*), and this target has not been attained, with the results of analysis of pooled urine suggesting that the salt intake has not decreased markedly for more than 10 years (*17–19*). The salt intake is high in East Asian regions including Japan, and the sodium excretion in 24-h urine collection is high in China, Korea, and Japan among the 52 groups of 32 countries surveyed in the INTERSALT (*22*).

Decreases in the salt intake are related to decreases in the blood pressure in a given population. The INTERSALT estimated that a decrease in the salt intake of 6 g/day in a population leads to suppression of the increase in the systolic blood pressure by a mean of 9 mmHg after 30 years (*17*). The Dietary Approaches to Stop Hypertension (DASH)–Sodium

Table 1-3. Decrease in Mortality Rate, Incidence, and Impairment of Activities of Daily Living (ADL) Due to Stroke Associated with Decrease in Systolic Blood Pressure (Estimated Values)

	Decrease in systolic blood pressure (mmHg)				
	1	2	3	4	5
Decrease in mortality rate (%)	3.2	6.4	9.6	12.8	16.0
Decrease in deaths (*n*)	4,563.7	9,127.5	13,691.2	18,255.0	22,818.7
Decrease in patients (*n*)	9,878.5	19,757.1	29,635.6	39,514.2	49,392.7
Decrease in patients with impaired ADL (*n*)	1,744.2	3,488.4	5,232.5	6,976.7	8,720.9

Based on data of reference *12* with modification.

evaluated effects of decreases in the dietary salt intake on the blood pressure and reported effects similar to those estimated by the INTERSALT (*23*). Further decreases in the salt intake are considered to be needed in Japan for the prevention of hypertension.

b. Obesity

The percentage of obese individuals is lower in Japan than in industrialized Western countries. However, the body mass index (BMI, kg/m^2), which is an index of obesity, is increasing annually in Japanese men (*24*). In contrast, it is decreasing in women in their teens to their 50s. As for characteristics of hypertensive Japanese, many hypertensive patients used to be lean with a very high salt intake, but obese hypertensive patients have increased recently, particularly among men.

In the United States, the BMI has increased markedly since 1990, and hypertension associated with metabolic syndrome has begun to account for an increasing proportion. In Japan, the mean BMI is fortunately about 23.5, and the situation is different from that in the United States, where the mean BMI is 28 or higher (*19*, *24*). However, hypertension associated with obesity is considered to be increasing in Japanese men.

c. Untreated Hypertensive Patients and Poor Management of Hypertension

When a blood pressure of 140/90 mmHg or higher is defined as hypertension, 80–90% of hypertensive patients in their 30s and 40s are untreated in Japan (*24–26*). These people must at least try to normalize the blood pressure by lifestyle modifications. The fact that 65% or more of hypertensive people in their 50s are untreated in both men and women is a major problem that must be addressed for the prevention of cardiovascular disorders including their non-pharmacological therapies.

In Ohasama Study, the state of blood pressure control in patients undergoing antihypertensive treatment was investigated. According to the results of this study, the blood pressure control was inadequate in more than half the patients on the basis of both the outpatient measurement and home measurement of the blood pressure (*27*). Moreover, according to a study of the state of treatment based on home blood pressure in 1,533 patients treated for hypertension by their home doctors (Japan Home *versus* Office Blood Pressure Measurement Evaluation: J-HOME), home blood pressure was classified as hypertension in about half of these patients (*28*). Therefore, the state of blood pressure control was inadequate in about half the patients also in this study.

4) Preventive Measures against Hypertension from the Viewpoint of Public Health

According to the NIPPON DATA 80, more than half of the deaths due to stroke occurred in the group with mild hypertension (systolic blood pressure <160 mmHg, diastolic blood pressure <100 mmHg) (*10*). Therefore, it is important to reduce the blood pressure not specifically in hypertensive patients but also in the general population.

Factors that affect the average blood pressure of the general population include the salt, potassium (K), calcium (Ca), and magnesium (Mg) intake, obesity, alcohol intake, and physical activities. Particularly, in Japan, the salt intake remains high, and a decrease in the salt intake of 3 g/day is expected to result in a decrease in the systolic blood pressure of 1–4 mmHg (*12*, *29*).

A decrease in the average blood pressure of the population even by 1–2 mmHg is known to exert major effects on the incidences of, and mortality rates due to, stroke and myocardial infarction (*12*, *30*). In "Health Japan 21st," epidemiological studies in Japan were reviewed, and decreases in the mortality rates due to stroke and myocardial infarction expected from decreases in the average blood pressure of the population were calculated. According to the calculations, a decrease in the mean systolic blood pressure of 2 mmHg in the Japanese population is expected to lead to a 6.4% decrease in the mortality rate due to stroke, a decrease of about 9,000 deaths due to stroke, and prevention of deterioration of ADL in about 3,500 patients (Table 1-3) (*12*).

To reduce the average salt intake of the population, painstaking guidance of hypertensive patients in the low-salt diet is needed first. However, the INTERMAP showed that the actual reduction in the salt intake in those who were observing a low-salt diet was about 1–2 g/day (*31*). Therefore, for hypertensive patients and those who must reduce the salt intake, it is necessary to create an environment in which they

can readily comply with a low-salt regimen. Also, to reduce the average blood pressure of the Japanese, it is necessary to create an environment in which many people spontaneously reduce the salt intake.

In Japan, nutritional information of food is limited to particular nutrients and additives, and presentation of information concerning the contents of salt and other necessary nutrients is not mandatory. In addition, if the sodium (Na) content is shown, it is not converted to the salt content, and there is no mention as to what percentage of the daily allowance the salt content accounts for, which is done in the United States. These measures are extremely important for the prevention of hypertension and must be evaluated for the future.

Summary

1) The average blood pressure of the Japanese decreased markedly after a peak in 1965 to 1990. This decrease was in close agreement with the decrease in the mortality rate due to stroke in Japan.
2) The incidences of, and mortality rates due to, stroke, myocardial infarction, and heart disease are higher as the average blood pressure is higher. The effects of hypertension are more specific to stroke than to myocardial infarction, and the incidence of stroke is still higher than that of myocardial infarction in Japan.
3) The average salt intake of the Japanese is still about 12 g/day, and a high salt intake is persisting. According to the results of analysis of pooled urine, no large decrease in the salt intake has been observed since the 1980s. Reducing the salt intake is an extremely important point in reducing the average blood pressure of the Japanese.
4) In young people, 80–90% of the hypertensive patients are untreated. Their blood pressure must be reduced at least by lifestyle modifications.
5) The control of the blood pressure is estimated to be unsatisfactory in about half the hypertensive patients, and stricter control of the blood pressure is necessary.
6) A decrease in the average systolic blood pressure of 2 mmHg is estimated to result in about 6% decrease in the mortality rate due to stroke. Improvements in the environment that encourage decreases in the blood pressure including reductions in the salt intake are necessary for the Japanese.

2. Measurement and Clinical Evaluation of the Blood Pressure

1) Measurement of Blood Pressure

a. Measurement of Blood Pressure at the Clinical Setting

Correct measurement of the blood pressure is necessary for the diagnosis of hypertension. In the clinical setting (*e.g.*, outpatient clinic), the blood pressure is measured by the auscultation method using a mercury sphygmomanometer or an aneroid sphygmomanometer, or using an automatic sphygmomanometer which has been calibrated by the auscultation method, by maintaining the arm-cuff position at the heart level. Recently, the use of the mercury sphygmomanometer is often avoided especially in Europe because of the possibility of environmental pollution by mercury. Since intake of caffeine-containing beverages and smoking have been shown to cause a temporary increase in the blood pressure (*32*, *33*), the blood pressure is measured in the clinical setting avoiding intake of caffeine-containing beverages and smoking for 30 min before measurements. The blood pressure is measured after rest in the seated position for at least 5 min.

A rubber cuff 13 cm wide and 22–24 cm long adapted to the Japanese Industrial Standards (JIS) is usually used for the measurement of blood pressure in adults. Internationally, a rubber cuff with a width extending over 40% of the upper arm (brachial) girth and a length covering at least 80% of the upper arm girth is recommended. Special cuffs are used for children and individuals with thick arm larger than the standard.

The value recorded at the first Korotkoff sound is regarded as the systolic blood pressure, and that at the fifth Korotkoff sound as the diastolic blood pressure. Auscultation gaps may result in false results. A rapid increase in cuff pressure is necessary to avoid forearm congestion and, thus, to avoid auscultation gap. The palpation method should be used concomitantly if necessary. Measurements should be performed several times at intervals of 1–2 min, and the mean of two stable measurements (difference <5 mmHg) is regarded as one's blood pressure. By the auscultation method, the cuff should be deflated at a rate of 2–3 mmHg/beat or second (*34*). At the initial examination, the blood pressure should be measured in the bilateral arms, and when there is a difference between the right and left, the higher value is adopted. The blood pressure should be measured in the recumbent or standing position in elderly patients or diabetic patients. The blood pressure is measured in the leg if the pulse of the lower limb arteries (femoral artery, popliteal artery, dorsal artery of foot) is weak or not palpable, or to exclude coarctation of aorta in young hypertensive patients. For the measurement of the blood pressure in the leg, an arm-cuff for blood pressure measurement is applicable to the ankle, and auscultation is performed at the posterior tibial artery, or the cuff is applied to the thigh (using a rubber cuff 15–18 cm wide, and/or a rubber cuff width is 20% greater than the diameter of thigh), and auscultation is performed at the popliteal artery.

Since blood pressure varies, the diagnosis of hypertension should be made on the basis of the values obtained at least on 2 different occasions.

b. Home Blood Pressure Measurement

Self-measurements of the blood pressure at home (home blood pressure) are useful for improving the compliance of patients to the treatment, and evaluating an excess lowering of blood pressure by antihypertensive treatment or insufficient antihypertensive medication. Home measurement before taking daily dose of antihypertensive medication, usually in the morning, is particularly useful for the evaluation of the duration of drug effects (*35*). It is also useful for the diagnosis of white coat hypertension. In this connection, it is useful also for the diagnosis of morning hypertension and reverse white coat hypertension (white coat normotension, masked hypertension). The Japanese Society of Hypertension Guidelines for Self-Monitoring of Blood Pressure at Home have been published in 2003 (*36*). An upper arm-cuff device based on cuff oscillometric principle that has been confirmed in an individual to yield differences within 5 mmHg compared with those of the auscultation method is used for the home blood pressure measurement. Measurement within 1 h after getting up, after urination, after rest in the seated position for 1–2 min, before taking antihypertensive drugs, and before breakfast is recommended in the morning, and measurement before going to bed and after rest in the seated position for 1–2 min is recommended in the evening. Home blood pressure measurement even once each in the morning and in the evening, is of sufficient clinical value if continued over a long period, but

patients usually measure the blood pressure two or more times at each single occasion. In clinical practice, the value on each measurement, mean value, and variation of multiple measurements on a single occasion must be evaluated when necessary. Therefore, it is recommended that the results of all measurements be recorded and reported. There is no consensus as to which of the values obtained by measurements at home should be clinically evaluated. However, the results of many epidemiological studies that provided the standards of the home blood pressure in the international guidelines for the treatment of hypertension mentioned below have been derived as the mean value of measurements performed once on each occasion.

Therefore, the Japanese Society of Hypertension Guidelines for Self- Monitoring of Blood Pressure at Home stated, "The mean values of the first measurement of each occasion in the morning and in the evening calculated from data collected over a long period should be used" for common clinical evaluation (*36*), but more generous application is necessary for clinical practice. At home, measurements can be repeated many times over a long period, and the data are useful for the evaluation of long-term changes in the blood pressure, such as seasonal variations (*37*). Finger-type devices for self-measurements are inaccurate. Wrist-type devices are practical, but often provide inaccurate measurements because of the difficulty to correct the difference of hydrostatic pressure between heart level and wrist level and of difficulty to compress arteries completely due to anatomical issue of the wrist (*38*). Presently, therefore, upper arm-cuff devices should be used for home blood pressure measurement (*39*, *40*). The home blood pressure has been reported to have a better predictive power for prognosis of hypertension than that measured at medical environment (casual-clinic blood pressure) (*41*). Further clinical implication is expected following the accumulation of evidence on the relationship of the home blood pressure with the prognosis of hypertension. The home blood pressure is generally lower than the casual-clinic blood pressure. Recently, reference values of the home blood pressure have become widely accepted. The guidelines of the JNC VI (*42*), the Seventh Report of the Joint National Committee (JNC 7) (*29*), and 2003 European Society of Hypertension–European Society of Cardiology (ESH-ESC) (*43*) adopted 135/85 mmHg as the cut-off point of hypertension on the basis of the results of cross-sectional surveys in Western countries and the long-term cohort study from Ohasama, Japan. However, according to the 1999 World Health Organization/International Society of Hypertension (WHO/ISH) guidelines, it has been reported that 125/80 mmHg of the home blood pressure is equivalent to 140/90 mmHg of the casual-clinic blood pressure (*44*). Therefore, blood pressures less than 125/80 mmHg are considered to be normal. In the Ohasama Study, which is the only one prospective study based on the home blood pressure in the world, 137/84 mmHg was regarded as a level at which the relative risk for death increases by 10% compared with the blood pressure at which the total mortality is lowest (*45*). Also, the home blood pressure at which the relative risk for death due to cardiovascular diseases is the lowest is 120–127/72–76 mmHg, with significant increases in the relative risk at 138/83 mmHg or above (*46*). Therefore, the JSH 2000 guidelines determined 135/80 mmHg as the cut-off point of hypertension by the home blood pressure (*47*). Because of the difference of the criteria for hypertension of the home blood pressure between Western countries and Japan, the Japanese Society of Hypertension Guidelines for Self-Monitoring of Blood Pressure at Home stated, "Home blood pressures 135/80 mmHg or higher should be diagnosed as hypertension, and those 135/85 mmHg or higher to be definite hypertension that need treatment. Also, home-measured blood pressures less than 125/80 mmHg should be regarded as normal, and those less than 125/75 mmHg as definitely normal" (*36*).

However, in the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2004 (JSH 2004), reference values were simplified, *i.e.*, values 135/85 mmHg or higher were considered to be hypertension, and those less than 125/80 mmHg to be normal. These are consistent with those of international guidelines. The normotensive value of the home blood pressure differs from the target level of the home blood pressure brought by antihypertensive treatment. The results of intervention studies based on home blood pressures are awaited for the determination of the latter value (*48*).

c. Ambulatory Blood Pressure Monitoring

Since accurate automatic devices based on cuff-oscillometric method have been developed (*49–51*), blood pressure measurement outside the clinic during free activities of subjects (ambulatory subjects) has become possible by non-invasive ambulatory blood pressure monitoring (ABPM) devices at intervals of 15–30 min for 24 h. The ABPM can provide the 24-h blood pressure profile and blood pressure information concerning specific periods of the day including the daytime, the nighttime, and the early morning. In Japan ABPM is widely used and the practice guideline for ABPM has been published (*52*). It has been found that the blood pressure is usually high during waking hours and low during sleep. It has also been shown that the 24-h average of ambulatory blood pressure (ABP) is correlated more closely with hypertensive target organ damage than the casual-clinic blood pressure, and that it is closely associated with regression of target organ damage mediated by antihypertensive medication (*53*, *54*). Moreover, ABPM allows more accurate prediction of the occurrence of cardiovascular diseases than the casual clinic blood pressure in the general population, elderly populations, and hypertensive populations (*55–59*).

The blood pressure generally decreases during night sleep also in hypertensive patients (dippers), but some patients show no or restricted nocturnal decrease in the blood pressure (non-dippers) or show nocturnal increase in the blood pres-

sure (inverted-dippers, riser). Hypertensive organ damage such as asymptomatic lacunar infarction, left ventricular hypertrophy, and microalbuminuria are observed more frequently in non-dippers and inverted-dippers than in dippers (*60–62*). Dipper is defined that the nocturnal decrease in the blood pressure is 10% of the daytime blood pressure or greater. In addition, a prospective study showed that the risk for cardiovascular events was higher in non-dippers than in dippers (*63*). However, according to the Japanese Multicenter Study on Barnidipine with ABPM (J-MUBA) involving more than 600 Japanese hypertensive subjects, many non-dippers were free of target organ damage (*64*). On the other hand, the results of the Ohasama Study indicated that the risk for cardiovascular events was high in non-dippers among normotensive individuals (*65*). According to these observations the clinical significance of the nighttime blood pressure has been noticed. When individuals who show a 20% or greater decrease in the blood pressure during the nighttime compared with the daytime level are defined as extreme dippers, the prevalence of asymptomatic cerebral infarction has been reported to be high in elderly extreme dippers (*66*), but to be similar between extreme dippers and normal dippers in the general population (*67*). Further evaluation is necessary concerning the clinical significance of extreme dippers. Recently, morning hypertension and morning surge, the latter is a rapid increase in the blood pressure after awakening early in the morning from a low level during the nighttime, have been noted in relation to cardiovascular events that occurred in the morning (*68*, *69*).

ABPM is particularly useful for the diagnosis of white coat hypertension and masked hypertension. The indications for the use of ABPM are diagnosis of white coat hypertension and for the diagnosis of refractory hypertension. Although the normal blood pressure on ABPM has not been defined, the mean±SD of the values obtained by 24-h ABPM from 634 normotensive Japanese aged 18–93 years was 119±9/70±6 mmHg in men and 110±10/64±7 mmHg in women (*70*). The JNC VI and JNC 7 propose that a subject should be considered hypertensive when the daytime blood pressure is 135/85 mmHg or higher and the nighttime blood pressure during sleep is 120/75 mmHg or higher (*29*, *42*). According to the 1999 WHO/ISH guidelines (*44*) and the 2003 ESH-ESC guidelines (*43*), 125/80 mmHg of ABPM is equivalent to 140/90 mmHg of casual-clinic measurement. Also, the Ohasama Study suggested that 135/80 mmHg of 24-h ABPM should be a criterion for hypertension (*71*). On the basis of these reports, individuals with 135/80 mmHg or higher on 24-h ABPM should be regarded as hypertensive.

Recently, an increase in short-term variability of the blood pressure based on ABPM has been shown to be a risk factor for cardiovascular diseases, adding a new aspect to the clinical significance of ABPM (*72*).

d. Information Obtained by the Home Blood Pressure Measurement and Ambulatory Blood Pressure Monitoring

i. White Coat Hypertension

White coat hypertension is a condition in which the blood pressure measured in a medical environment (*e.g.*, at the outpatient clinic) is always at a hypertensive level but that measured in a non-medical environment (*e.g.*, home blood pressure, ABPM) is always normal. This is a definition applied to untreated patients. Differences between the blood pressure measured in the clinical setting and that measured in the non-clinical setting (home blood pressure, ABPM) are also observed in patients being treated, a finding called the white coat phenomenon. Whether white coat hypertension is harmful or not has not been established.

ii. Reverse White Coat Hypertension (Masked Hypertension)

A condition opposite to white coat hypertension, *i.e.*, while the blood pressure measured in the medical setting is normal, that measured in the non-medical setting is always at a hypertensive level. This phenomenon is observed in both treated and untreated patients. Such condition is also called masked hypertension, because hypertension is covered at the clinic. It is related to the morning increase in the blood pressure which is mediated by physiological circadian blood pressure variation and by attenuation of the drug effect before the next dosing of antihypertensive drugs. Such phenomenon is practically determined by the home blood pressure measurement.

iii. Morning Hypertension

Although there is no strict definition of morning hypertension, hypertension specifically observed shortly after awakening may be defined as morning hypertension. In terms of the absolute values observed by the home blood pressure measurement, a condition in which the home blood pressure in the morning is 135/85 mmHg or higher may be regarded as morning hypertension, but the blood pressure measured in the morning must be higher than that measured in the evening to fulfill the criterion, *i.e.*, the blood pressure is high specifically in the morning. This morning hypertension is associated with 2 types of circadian blood pressure variation. One is the morning surge, *i.e.*, a rapid increase in the blood pressure after waking up from a low level during the nighttime. The other is the hypertension in the morning observed in non-dippers, who show no or restricted nocturnal decrease in the blood pressure, or inverted-dippers, who show nocturnal increase in the blood pressure. Both types of morning hypertension are considered to be possible risk factors for cardiovascular diseases.

iv. Nighttime Blood Pressure

The blood pressure measured during sleep by ABPM is called

Table 2-1. Classification of Blood Pressure in Adults

Category	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
Optimal	<120	and	<80
Normal	<130	and	<85
High-normal	130–139	and/or	85–89
Mild hypertension	140–159	and/or	90–99
Moderate hypertension	160–179	and/or	100–109
Severe hypertension	≥180	and/or	≥110
Systolic hypertension	≥140	and	<90

Table 2-2. Risk Factors for Cardiovascular Disease

Hypertension
Cigarette smoking
Diabetes mellitus
Dyslipidemia (hypercholesterolemia, low HDL-cholesterolemia)
Obesity (particularly visceral obesity)
Microalbuminuria
Age (≥60 years for men, ≥65 years for women)
Family history of premature cardiovascular disease

HDL, high-density lipoprotein.

Table 2-3. Organ Damage/Cardiovascular Disease

Brain
Cerebral hemorrhage, cerebral infarction
Asymptomatic cerebrovascular disease
Transient ischemic attack
Cognitive dysfunction
Heart
Left ventricular hypertrophy
Angina pectoris, myocardial infarction
Heart failure
Kidney
Proteinuria
Renal disease/renal failure
(serum creatinine: men≥1.3 mg/dl, women≥1.2 mg/dl)*
Blood vessel
Atheromatous plaques
Intima-media thickness of carotid artery >0.9 mm*
Aortic dissection
Arteriosclerosis obliterans
Ocular fundus
Hypertensive retinopathy

*Cited from reference *43*.

the nighttime blood pressure. Recently, it has become possible to automatically measure the blood pressure during sleep in the middle of the night using a home blood pressure measuring device. A decrease in the blood pressure of 10–20% during the night compared with the daytime level is classified as normal (dipper), a decrease of 0–10% as the non-dipper, an increase in the blood pressure during the night compared with the daytime level as the inverted-dipper, and a decrease of 20% or more as the extreme dipper. The prognosis is definitely poor in non-dippers and inverted-dippers, but there is no consensus as to the prognosis of extreme dippers.

2) Classification of Blood Pressure Values and Evaluation of Risk Factors

a. Classification of Blood Pressure Values

Although a positive correlation is observed between the blood pressure level and the risk for cardiovascular diseases, the values of the blood pressure are distributed continuously while the criteria of hypertension are determined artificially. In the 1999 WHO/ISH guidelines (*44*), the diagnostic criteria of hypertension were made basically the same as those of the JNC VI (*42*). The guidelines were then revised in 2003 as the JNC 7 (*29*), 2003 ESH-ESC guidelines (*43*), and 2003 WHO/ISH statement (*73*). In all these guidelines, hypertension is defined as 140/90 mmHg or higher. According to the Hisayama Study of Japan, the cumulative mortality rate due to cardiovascular diseases was the lowest when the systolic and diastolic blood pressures were less than 120 mmHg and less than 80 mmHg, respectively. Also, in the population including elderly people, the risk for cardiovascular diseases was significantly higher when the systolic blood pressure was 140 mmHg or higher than when it was less than 120 mmHg, and when the diastolic blood pressure was 90 mmHg or higher than when it was less than 80 mmHg (*13*, *74*). Moreover, according to the Tanno/Sobetu Study, an 18-year prospective epidemiological study in Hokkaido, a systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure of 90 mmHg or higher were significant risk factors for cardiovascular mortality and total mortality (*75*). Similarly, an increase in the mortality rate due to all cardiovascular diseases was observed at a blood pressure of 140/90 mmHg or higher in NIPPON DATA 80 (*10*). On the basis of these reports, the JSH 2004 guidelines also adopted 140/90 mmHg or higher as a criterion for hypertension. The JSH 2000 guidelines (*47*) adopted the same categorization of the blood pres-

Table 2-4. Stratification of Risk of Hypertensive Patients

Risk factors other than blood pressure	Category of hypertension		
	Mild (140–159/90–99 mmHg)	Moderate (160–179/100–109 mmHg)	Severe (≥180/≥110 mmHg)
None	Low risk	Moderate risk	High risk
Having 1–2 risk factors not including diabetes mellitus	Moderate risk	Moderate risk	High risk
Having diabetes mellitus, organ damage, cardiovascular disease, or 3 or more risk factors	High risk	High risk	High risk

sure as that of the 1999 WHO/ISH guidelines (*44*) and the 2003 ESH-ESC guidelines (*43*). The introduction of the new concept of "prehypertension" was unnecessary as the concept of high-normal pressure sufficiently indicates the need for primary prevention of hypertension. Also, by regarding a blood pressure less than 120/80 mmHg as the optimal blood pressure, the guidelines suggest that a normal blood pressure in a range of 120–129/80–84 mmHg is already above the optimal blood pressure level. Moreover, regarding a blood pressure of 180/110 mmHg or higher as severe hypertension is clinically significant, and as this concept was retained in both the 2003 ESH-ESC guidelines (*43*) and 2003 WHO/ISH statement (*73*), it was also adopted in the JSH 2004 guidelines. Since changes in the definitions and classifications at each revision of the guidelines bring unnecessary confusion in clinical practice, the definitions and classifications of the JSH 2000 guidelines were adopted without changes in the JSH 2004 guidelines (Table 2-1).

The mean of the blood pressures measured without taking antihypertensive drugs at the outpatient clinic on several visits is used for categorization of the blood pressure. Either systolic blood pressure or diastolic blood pressure is independent risk factor. If the systolic and diastolic blood pressures fall in different categories, either systolic blood pressure or diastolic blood pressure adopted the higher category is taken for the diagnosis.

b. Risk Factors for Cardiovascular Diseases

Although hypertension is the most important risk factor for stroke, it is only one of the many risk factors for all cardiovascular diseases. The prognosis of hypertensive patients is markedly affected not only by the blood pressure but also by risk factors other than hypertension, the degree of target organ damage secondary to hypertension, and the presence or absence of cardiovascular complications (Tables 2-2 and 2-3). For the treatment of hypertension, the blood pressure and risk factors for cardiovascular diseases are evaluated in addition to the differential diagnosis between essential hypertension and secondary hypertension.

c. Stratification of Risk for Evaluation of the Prognosis

Risk factors other than the blood pressure (smoking, diabetes mellitus, dyslipidemia such as hypercholesterolemia, obesity, microalbuminuria, age, and family history of premature cardiovascular diseases), hypertensive target organ damage, and presence or absence of cardiovascular diseases should be evaluated for the stratification of risk. Since the risk for cerebrovascular and cardiovascular diseases increases with prolongation of the follow-up period even in low-risk or moderate-risk patients, attention must be paid also to the duration of hypertension (*76*). The risk is particularly high when hypertension is complicated by diabetes mellitus, and aggressive antihypertensive therapy is recommended for such patients by the JNC 7 (*29*) and 2003 ESH-ESC guidelines (*43*). The Hisayama Study also indicated that diabetes mellitus is a major risk factor for cerebral infarction and ischemic heart disease (*77*). In Japan a progression of diabetic nephropathy to chronic renal failure have markedly increased (*78*). In patients with hypertension complicated by diabetes mellitus, the outcome has been shown to improve by strict control of blood pressure (*79–81*). Moreover, as treatment for hypertension has been shown to be important for the control of progression of renal diseases including diabetic nephropathy (*82–84*), aggressive management of hypertension is important particularly when hypertensive patients also have diabetes mellitus or renal diseases. The 1999 WHO/ISH guidelines (*44*) classify hypertension into 4 risk levels (low, moderate, high, very high) according to the absolute risk for the occurrence of cardiovascular diseases during a 10-year follow-up of individuals aged 45–80 years (mean 60 years) on the basis of the Framingham study. While the greatest emphasis is placed on the blood pressure levels in the JNC 7 from the viewpoint of population strategy, the therapeutic approach was determined by stratifying hypertensive patients into 3 groups depending on risk factors in the earlier JNC VI. In contrast, the 1999 WHO/ISH guidelines and 2003 ESH-ESC guidelines stratified patients into 4 groups according to risk factors. However, the therapeutic approach was the same for the high risk group and very high risk group mentioned in the 1999 WHO/ISH and 2003 ESH-ESC guidelines. The high risk strategy as well as the population strategy is considered

Table 2-5. Laboratory Examinations for Hypertension

Routine examinations
• Urinalysis, blood cell counts
• Blood biochemistry: Urea nitrogen (BUN), creatinine, uric acid, Na, K, Cl, Ca, Pi, fasting blood glucose, hemoglobin A_{1c}, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, total protein, GOT, GPT, γGTP, LDH, bilirubin
• Chest X-ray, ECG, funduscopy
Examinations for target organ damage
• Brain: Head CT or MRI
• Heart: Echocardiography
• Kidney: Urinary albumin quantification*
• Blood vessels: Carotid ultrasonography, ankle-brachial pressure index (ABI), pulse-wave velocity (PWV), augmentation index, high-sensitivity CRP
Examinations for screening for secondary hypertension
• Measurement of plasma renin, aldosterone, cortisol, catecholamines; measurement of urinary catecholamines; ultrasonography and CT of the kidneys and adrenal glands

*Examined also as a routine test.

to be extremely effective in Japan. The JSH 2004 guidelines stratify hypertensive patients into low risk, moderate risk, and high risk groups according to blood pressure ranges, major risk factors (diabetes and other risk factors), hypertensive organ damage, and cardiovascular diseases as shown in Table 2-4. These guidelines also recommend those in the blood pressure range of 130–139/80–89 mmHg to consider the beginning of antihypertensive treatment and to maintain a normal blood pressure (<130/80 mmHg) if they have diabetes mellitus or chronic kidney diseases.

d. Types of Hypertension

More than 90% of hypertensive population is essential hypertension, but the diagnosis of essential hypertension is made after exclusion of secondary hypertension. A certain proportion of hypertension are white coat hypertension (isolated clinic hypertension), *i.e.*, hypertension observed only in the clinical setting (*e.g.*, outpatient clinics). White coat hypertension is diagnosed by the home blood pressure measurement or ABPM as well as measurement at the clinic.

The frequency of isolated systolic hypertension increases with increase in age, because the systolic blood pressure often increases with decrease in the diastolic blood pressure due to the decreased compliance of the large elastic arteries like the aorta which is mediated by atherosclerosis. The Framingham Study (*85*) and the Hisayama Study (*74*) showed that the systolic blood pressure is a strong risk factor for cerebral infarction and myocardial infarction in the elderly. Systolic hypertension in elderly patients is classified into the burned out type caused by a decrease in the diastolic blood pressure in essential hypertension, and the *de novo* type caused by a new elevation of the systolic blood pressure in old age.

3) Examination and Diagnosis

In the diagnosis and treatment of hypertensive patients, (1) to exclude the secondary causes for hypertension, (2) to evaluate other related risk factors for cardiovascular diseases and coexisting illness, and (3) to define the severity of hypertension including the presence or absence of hypertensive target organ damages must be taken into consideration.

a. History

The physician must inquire the time of detection, circumstances of detection (health screening, physical examination, self-measurement, *etc*.), duration, severity, and therapeutic course of hypertension. Particularly, responses to antihypertensive medications and their classes must be clarified. The use of any drugs for complications and drugs that affect the blood pressure (glycyrrhizin, non-steroidal anti-inflammatory drugs, oral contraceptives, cyclosporine, *etc*.) must also be clarified.

Hypertension is usually asymptomatic, but whether there are specific symptoms suggestive of secondary hypertension, hypertensive complications, and target organ damages must be checked.

Inquiry about whether the patient has a history of stroke, heart diseases, kidney diseases, peripheral arterial diseases, gestosis, diabetes mellitus, gout, hyperlipidemia, lung diseases (particularly bronchial asthma), and endocrine diseases is essential.

In addition to hypertension, attention must also be paid to the family histories of diabetes mellitus, abnormalities of lipid metabolism, cerebrovascular or cardiovascular disorders with an early onset, and kidney diseases.

Information concerning the quantity and duration of alcohol drinking and smoking, exercise habit, dietary and nutri-

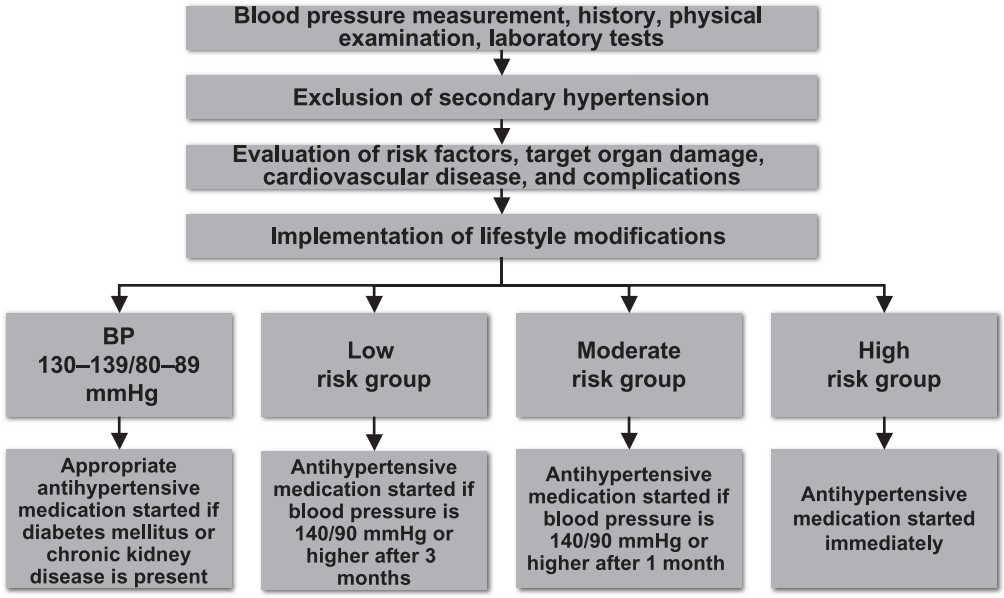

Fig. 2-1. *Algorithm for treatment of hypertension at initial visit.*

tional tendencies, and (permanent or temporary) stressful situations related to work and family affairs must also be obtained.

b. Examination (Physical Findings)

In addition to the blood pressure and heart rate, the height, body weight, BMI (kg/m^2), and abdominal circumference are measured. The presence or absence of funduscopic findings, goiter, and distension of the jugular vein is examined, and auscultation is performed for cardiac murmur, third and fourth heart sounds, and pulmonary rales. The presence or absence of liver enlargement, abdominal masses, and abdominal vascular murmur is checked, and subcutaneous fat is examined. The pulse and murmur of the limb and carotid arteries and the presence or absence of edema are checked.

c. Laboratory Examinations (Table 2-5)

Routine tests for hypertensive patients include urinalysis, blood cell counts, blood biochemical examinations (blood urea nitrogen [BUN], creatinine, uric acid, sodium [Na], potassium [K], chloride [Cl], calcium [Ca], phosphorus [Pi], fasting total-cholesterol, triglycerides, high-density lipoprotein [HDL]–cholesterol, low-density lipoprotein [LDL]–cholesterol, blood glucose, hemoglobin A_{1c}), chest radiography (cardiothoracic ratio), and ECG (left ventricular hypertrophy, ST-T changes, arrhythmias such as atrial fibrillation) as essential items. Fundscopy and measurement of the total protein, GOT, GPT, γ-GTP, LDH, and bilirubin are performed if possible.

d. Diagnosis of Hypertensive Target Organ Damage

Target organ damage and peripheral arterial diseases may be diagnosed in hypertensive patients by various examinations, and the risk for the future occurrence of diseases may be estimated even when the patients are asymptomatic.

i. Brain

Asymptomatic cerebrovascular disorders detected by brain MRI or CT have been confirmed to be a strong risk factor for stroke. Non-invasive imaging of cerebral vessels by MRI (MRA) is also possible. It is useful for stratification of the risk for hypertension in the elderly (*86*).

ii. Heart

Echocardiography is superior to ECG for quantitative evaluation of the cardiac load of hypertension. Echocardiography allows evaluation of the cardiac function as well as the heart weight and is useful for the diagnosis of hypertensive heart failure. Even when the values of systolic parameters are not reduced, heart failure due to impairment of diastolic function is often observed particularly in elderly patients with hypertensive heart diseases (*87*).

iii. Kidney

The creatinine clearance (Ccr, calculated from the serum creatinine level; see Table 6-2) and urinary albumin concentration (24-h albumin excretion, albumin/creatinine ratio) are powerful predictive factors of the occurrence of cardiovascular disorders, and their evaluation is indispensable in patients with diabetes mellitus or kidney disease (*88*).

iv. Blood Vessels

Detection of intima-media thickness (IMT) and plaques by carotid ultrasonography are useful for the prognosis of high-risk patients such as those with diabetes mellitus as well as patients with cerebrovascular disorders (*89*). Parameters obtained by analysis of arterial pulse waves such as the ankle–brachial pressure index (ABI), pulse wave velocity (PWV), and augmentation index are excellent indices of the arterial compliance, and its usefulness is being recognized along with the systolic blood pressure and pulse pressure (*90*). Although attention is directed to various tests of vascular endothelial function, the usefulness of high-sensitivity C-reactive protein (CRP) for the evaluation of the risk of patients with cardiovascular disorders with no other risk factors as well as patients with metabolic syndrome has been studied in greatest detail to date (*91*).

4) Planning for the Control of Hypertension at the Initial Examination

If the blood pressure is high at the initial examination, it is usually measured a few additional times on different days. During this period, the patient is examined for the severity of hypertension, target organ damage, and risk factors other than hypertension, and the overall cardiovascular risk of the patient is evaluated (Fig. 2-1).

Lifestyle modifications must be strictly observed by all patients. If there is a wide difference between the blood pressure measured at home or by ABPM and that measured at the clinic, the determination of the therapeutic approach on the basis of the values obtained by home measurement or ABPM is considered to be more reasonable although evidence that supports this policy is still inadequate.

In patients with mild hypertension showing blood pressures of 140–159/90–99 mmHg at the initial examination and having no organ damage or complication, the blood pressure is measured again within 3 months. The blood pressure often returns to a normal level during this period. Concerning low-risk or moderate-risk hypertensive patients, those in whom the blood pressure is 160/90 mmHg or higher, including elderly patients, are selected for most clinical trials, so that there is no ground for the judgment of whether antihyperetensive therapy is effective for hypertension at less than 160/90 mmHg. However, many recent studies indicating that even a high normal blood pressure (130–139/85–89 mmHg) increases the cardiovascular risk are considered to warrant lowering the threshold of the systolic blood pressure for starting antihypertensive medication (*73*). Therefore, antihypertensive medication should be started also in low-risk patients if the blood pressure does not decrease below 140/90 mmHg within 3 months by lifestyle modifications alone.

If the blood pressure at the initial examination is 160/100 mmHg or higher, the patient should be advised to monitor the blood pressure at home if possible to clarify whether the patient has white coat hypertension or shows excessive white coat phenomenon. If these conditions have been excluded, antihypertensive medication should be started after 1 month in moderate-risk patients (160–179/100–109 mmHg). In severely hypertensive patients (180/110 mmHg or higher; high-risk patients), antihypertensive therapy should be started immediately (within a few days).

On the basis of the results of randomized controlled trials, treatment with appropriate antihypertensive agents depending on the condition should be indicated for patients with diabetes mellitus or chronic kidney disease even when the blood pressure is less than 140/90 mmHg (*73*).

Summary

1) The blood pressure should be measured by keeping the arm-cuff at the heart level while the patient is resting in the seated position. Measurement should be repeated several times at intervals of 1–2 min, and the mean of 2 stabilized values (difference less than 5 mmHg) is adopted as the value of the blood pressure. The diagnosis of hypertension should be made on the basis of values on at least 2 different occasions.
2) Home blood pressure measurement and ABPM using automatic devices are useful for the diagnosis of hypertension and white coat hypertension, masked hypertension, and evaluation of drug effects and their duration. The results of home blood pressure measurement or ABPM should be referred as information for clinical practice. An average home blood pressure of 135/85 mmHg or higher and an average 24 h blood pressure of 135/80 mmHg or higher recorded by ABPM should be regarded as hypertension.
3) The criteria for categorization of the blood pressure are the same as those of the JSH 2000 guidelines.
4) Hypertensive patients are classified into the low risk, moderate-risk, and high risk groups according to the presence or absence of risk factors other than the blood pressure, hypertensive target organ damage, and cardiovascular diseases.
5) Hypertension is classified into essential hypertension (including white coat hypertension) and secondary hypertension. Secondary hypertension is diagnosed on the basis of findings on inquiry, physical examinations, and general laboratory tests, but by performing special examinations if necessary.
6) A therapeutic plan is formulated according to stratification of risks, and while having all patients strictly observe lifestyle modifications, antihypertensive medication necessary to attain the target blood pressure is started.

3. Basic Principles of Treatment

1) Objectives of Treatment

The objective of treatment for hypertension is to prevent the occurrence of, and consequent death due to, cardiovascular diseases caused by a sustained high blood pressure and to help hypertensive patients lead full lives.

The 2003 ESH-ESC guidelines and WHO/ISH statement emphasized absolute effects of treatment as scientific evidence of the effectiveness of treatment (*43*, *73*). The effects of treatment for hypertension are larger as the risk for the occurrence of cardiovascular diseases is higher in each hypertensive patient (*92*). While the results obtained by a randomized controlled trial are the best scientific evidence for the effectiveness of antihypertensive treatment (lifestyle modifications and drug therapy), the effects of antihypertensive drug treatment may be underestimated by randomized controlled trials, and the results of randomized controlled trials, which encompasses only several years, have limitations, because treatment for hypertension is lifelong (*42*).

From the results of large-scale randomized controlled trials using a placebo performed in various foreign countries in the past, antihypertensive drug treatment was shown to exert many beneficial effects on hypertensive patients. First, drug treatment clearly reduces the incidence of, and mortality rate due to, cardiovascular diseases (*93–96*). For example, according to a review of 17 clinical trials of antihypertensive medications performed abroad (*97*), which were all targeted to systolic and diastolic hypertension except for the Systolic Hypertension in the Elderly Program (SHEP), the total number of patients analyzed was 47,653, and their mean age, weighed for the sample size, was 56 years. Of these patients, 12,483 were aged 60 years or above at registration. The male-female ratio of the patients was nearly even, and the mean follow-up period was 4.7 years. The study design was the randomized double-blind scheme in 9 trials, randomized single-blind scheme in 4, and open study in the remaining 4. As is clear from the periods in which these trials were carried out, the drugs used were primarily diuretics and β-blockers with some exceptions. With the exception of the SHEP, controlling the diastolic blood pressure to 90 mmHg or lower was the target of intervention. However, the trial drugs reduced the diastolic blood pressure by a mean of 6.5 mmHg and the systolic blood pressure by a mean of 16.0 mmHg after weighting for the sample size.

As a result, stroke occurred in a total of 1,360 patients, and ischemic heart disease occurred in a total of 2,038 patients (Table 3-1). The incidence of ischemic heart disease was about 1.5 times higher than that of stroke, clearly indicating a characteristic of Western populations (*96*). However, the antihypertensive medications reduced the risk for the incidence of stroke by 38% and the risk for the incidence of ischemic heart disease by 16%. Concerning the usefulness of antihypertensive medications according to the diastolic blood pressure levels at the registration, absolute effects on risk reduction differed clearly among the groups with a diastolic blood pressure less than 110 mmHg, 110–114 mmHg, and 115 mmHg or higher. Stroke was prevented in 9, 19, and 35 patients, and ischemic heart disease was prevented in 5, 12, and 15 patients, respectively, per 1,000 patients. Therefore, the usefulness of antihypertensive medications increased with the diastolic blood pressure levels. As for the age, an absolute preventive effect on the occurrence of stroke was observed in 9 of those aged less than 60 years and 23 of those aged 60 years or above; an absolute preventive effect on the incidence of ischemic heart disease was observed in 5 and 13, respectively, per 1,000 patients. The usefulness of antihypertensive medication increased with the patients' age.

However, as the incidences of stroke and ischemic heart disease are different between Japan and Western countries (*98*), the above results cannot be applied directly to Japan. Yet, the usefulness of antihypertensive medications is considered to increase with the blood pressure levels and patients' age regardless of the race.

Recently, the importance of the systolic blood pressure as a risk factor has been recognized (*99*). According to the results of analysis of the data of the patients with systolic hypertension selected from 3 clinical trials using elderly patients with systolic hypertension and 5 clinical trials using patients with hypertension, the total number of patients was 15,693, and the mean age was 70 years. The median follow-up period was 3.8 years. The mean decrease in the systolic blood pressure was 10.4 mmHg, and that in the diastolic blood pressure was 4.1 mmHg, in the trial drug group. The risks for the occurrence of stroke and ischemic heart disease were shown to be reduced by 30% and 23%, respectively (Table 3-2) (*99*). In Japan, where the incidence of stroke is several times higher than that of ischemic heart disease unlike Western countries, the usefulness of antihypertensive drug treatment is expected to be higher. According to a metaanalysis of the preventive effect of antihypertensive medications on cardiovascular diseases,

Table 3-1. Decrease in Risk of Cardiovascular Disease and Death by Treatment with Antihypertensive Drugs in Patients with Systolic/Diastolic Hypertension

	Number of patients who developed the condition		% Decrease of risk (95% CI)	*p* value
	Medication (*n*=23,487)	Placebo (*n*=23,806)		
All strokes	525	835	38 (31–45)	<0.001
Fatal strokes	140	234	40 (26–51)	<0.001
All ischemic heart diseases	934	1,104	16 (8–23)	<0.001
Fatal ischemic heart disease	470	560	16 (5–26)	0.006
Cardiovascular disease death	768	964	21 (13–28)	<0.001
All deaths	1,435	1,634	13 (6–19)	<0.001

Cited from reference *97*.

Table 3-2. Decrease in Risk of Cardiovascular Disease and Death by Treatment with Antihypertensive Drugs in Patients with Systolic Hypertension

	Number of patients who developed the condition		% Decrease of risk (95% CI)	*p* value
	Medication (*n*=7,936)	Placebo (*n*=7,757)		
All strokes	279	387	30 (18–41)	<0.0001
All ischemic heart diseases	293	373	23 (10–34)	<0.0001
All cardiovascular events	647	835	26 (17–34)	<0.0001
Cardiovascular disease death	329	392	18 (14–29)	0.01
All deaths	656	734	13 (2–22)	0.02

Cited from reference *99*.

there was no gender difference in the decrease in the risk reduction by the treatment (*100*).

2) Patients to Be Treated and Target Levels of Blood Pressure

a. Patients to Be Treated

i. Age

Hypertension should be treated in patients of all ages. However, the results of intervention studies in elderly patients conducted in Western countries (*92*, *101*) suggest that hypertension may not be a risk for cardiovascular diseases in individuals aged 80 years or above, and that treatment for hypertension may not be effective in very old individuals (see 8. Hypertension in the Elderly).

ii. Blood Pressure

The 2003 ESH-ESC guidelines and WHO/ISH statement defined a blood pressure of 140/90 mmHg or higher as hypertension similarly to the JSH 2000 guidelines and stratified hypertensive patients according to the risk for cardiovascular diseases. According to the results of a metaanalysis of 61 prospective studies on the relationship between the blood pressure and cardiovascular death (*102*), cardiovascular deaths were shown to increase with the blood pressure in a range of 115–185/75–115 mmHg. Long-term observation by the Framingham Heart Study (*103*) showed that the risk for cardiovascular diseases doubled in individuals with a high normal blood pressure compared with those with an optimal blood pressure. Therefore, the JNC 7 (*104*) considered prehypertension (120–139/80–89 mmHg) to be an indication of lifestyle modifications and hypertension (≥140/≥90 mmHg) to be an indication of antihypertensive drug treatment combined with lifestyle modifications.

As for epidemiological studies performed in Japan, the Tanno-Sobetsu Study (Hokkaido) (*105*) showed a significant increase in cardiovascular deaths, and the Hisayama Study (Fukuoka) (*13*) showed a significant increase in the incidence of stroke, at a blood pressure of 140/90 mmHg or higher. The categorization of the blood pressure in the current guidelines is based on these results.

In elderly people, also, hypertension at 140/90 mmHg or higher is considered to be an indication for treatment (see 8. Hypertension in the Elderly).

b. Target Levels of Blood Pressure (Fig. 3-1)

The JNC 7, 2003 ESH-ESC guidelines, and WHO/ISH statement set the target level of blood pressure control at less than 140/90 mmHg and less than 130/80 mmHg for patients having diabetes mellitus or renal disorders (chronic kidney diseases). The 1999 WHO/ISH guidelines (*44*) and JSH 2000 guidelines (*47*) set the target level of blood pressure control at less than 130/85 mmHg for young and middle-aged individuals. In the JSH 2004 guidelines, the target level of blood pres-

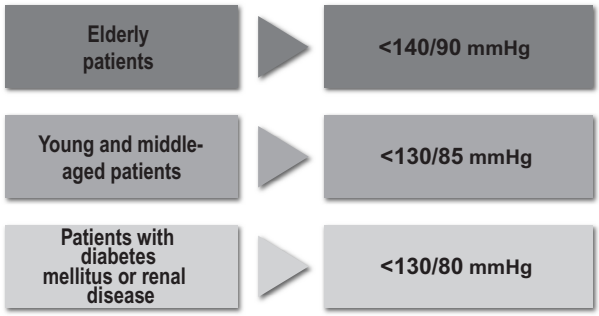

Fig. 3-1. *Target blood pressure levels.*

sure control is set at less than 130/85 mmHg for young and middle-aged individuals and less than 130/80 mmHg for individuals with diabetes mellitus or renal disease. J-curve phenomena have been reported in patients with cerebrovascular disease and coronary artery diseases, but large-scale prospective clinical trials have indicated that cardiovascular diseases can be prevented by strict control of the blood pressure (*79*, *106–109*). For elderly people, also, the eventual target of blood pressure control is set at less than 140/90 mmHg, but people aged 75 years or above often have organ damage, and antihypertensive drug treatment may cause circulatory disturbances in important organs. Therefore, careful administration of antihypertensive drugs by monitoring changes in symptoms and laboratory findings is necessary.

3) Selection of Treatments

Genetic factors and environmental factors are closely involved in the occurrence and progression of essential hypertension. Therefore, treatment for hypertension cannot be considered without correction of lifestyle problems (non-drug therapy), which account for many of the environmental factors. However, few patients attain the target level of blood pressure control by lifestyle modifications alone, and drug therapy is necessary in most patients. For each hypertensive patient, an outline of the treatment plan is formulated according to stratification of the risk by comprehensive evaluation of the severity of hypertension, risk factors for cardiovascular diseases, and cardiovascular complications (see Fig. 2-1 in 2. Measurement and Clinical Evaluation of the Blood Pressure).

Hypertensive patients can be classified according to risk stratification into low-risk, moderate-risk, and high-risk groups, but antihypertensive drug treatment is indicated in patients with a blood pressure of 130–139/80–89 mmHg if they have diabetes mellitus or renal disease.

a. Lifestyle Modifications

In 1996, the Public Hygiene Council advised introduction of the concept of "lifestyle-related diseases" to attract attention to the importance of the lifestyle, promote voluntary effort to protect health, and establish a lifelong system for supporting individual efforts to correct the lifestyle by the entire society. This advice emphasized the principle of preventing the occurrence of diseases by establishing a healthy lifestyle. Hypertension is a lifestyle-related disease, and lifestyle modifications have not only been suggested to be effective for its prevention but have also been proved to have an antihypertensive effect (*110–113*). Lifestyle modifications are an important therapeutic measure particularly when hypertension is accompanied by other risk factors for cardiovascular diseases such as abnormalities of lipid metabolism and diabetes mellitus. These risk factors can be reduced simultaneously at the minimum cost by lifestyle modifications.

In many hypertensive patients, the target level of blood pressure control cannot be attained by lifestyle modifications alone, but the number and doses of antihypertensive drugs can be reduced by lifestyle modifications (*114*, *115*). Lifestyle modifications include restricting the salt intake, increasing the vegetable and fruit intake, restricting the intake of cholesterols and saturated fatty acids, maintaining an appropriate body weight, restricting the alcohol intake, exercising, and to quit smoking.

b. Time to Start Antihypertensive Drug Treatment

In patients with low-risk or moderate-risk hypertension, antihypertensive drug treatment is started if the blood pressure cannot be reduced below 140/90 mmHg within a target period even with lifestyle modifications. In patients with diabetes mellitus or renal disease, antihypertensive drug treatment is started if the blood pressure cannot be reduced below 130/80 mmHg within a period even after lifestyle modifications. In patients with high-risk hypertension, antihypertensive medication is started simultaneously with lifestyle modifications. Patients with hypertensive emergency immediately require antihypertensive medication, and they should be referred to a specialist in the treatment for hypertension (a Fellow of the Japanese Society of Hypertension; FJSH). Antihypertensive medication is indicated also to elderly patients if the blood pressure is 140/90 mmHg or higher.

c. Antihypertensive Drug Treatment

Antihypertensive drug treatment is necessary for many hypertensive patients.

In Japan, the antihypertensive drugs used today include Ca antagonists (dihydropyrdines and diltiazem), renin-angiotensin (RA) system inhibitors such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), diuretics (thiazide and thiazide-like diuretics, K-sparing diuretics, loop diuretics), β-blockers (including αβ-blockers), α-blockers, and central sympathetic suppressors (methyldopa, clonidine, *etc*.). Antihypertensive drugs with

different action mechanisms have characteristic adverse effects. From the viewpoint of evidence-based selection of drugs, the usefulness of diuretics, β-blockers, Ca antagonists, and ACE inhibitors has been established by many reports. Recently, results of large-scale clinical trials indicating the usefulness of ARB in hypertensive patients have been accumulated (*116–118*).

According to the results of large-scale clinical trials comparing antihypertensive drugs each other and of their metaanalyses, some drugs are suggested to be more effective for the prevention of cardiovascular morbidity and mortality. Generally, however, the prevention of cardiovascular diseases by antihypertensive drugs is ascribed primarily to a decrease in the blood pressure rather than the effect of a particular drug. While recent large-scale clinical trials in high-risk hypertensive patients (*118*, *119*) suggested the importance of the early reduction (within 1–3 months) of the blood pressure, they also suggested the danger of sudden changes in the contents of the treatment.

There are fundamental principles how to use antihypertensive drugs. (1) Select a drug that is effective by once-a-day administration, in principle (*120*). (2) Start drug treatment at a low dose. Particularly, start the administration of a thiazide diuretic at half or a quarter of a tablet. (3) To avoid adverse effects and enhance the antihypertensive effect an appropriate combination therapy should be used (see 5. Treatment with Antihypretensive Drugs). (4) If the first drug has little antihypertensive effect or is poorly tolerated, replace it for a drug with a different action mechanism. (5) If the patient is suffered from other diseases, select a drug according to their indications and contraindications. Also, make sure to check interactions of the antihypertensive drugs with the drugs administered for the treatment of other diseases.

A better therapeutic plan should be formulated for each patient by modifying the initial plan according to his/her condition. If a patient is diagnosed to have white coat hypertension (isolated office hypertension (*44*)), the decision of whether the patient should be treated is made by evaluating the presence or absence of risk factors and target organ damage. The patients should be followed up carefully every 6 months even if it has been decided to not to treat the patient. In reverse white coat hypertension (*121*), in which the clinic blood pressure is normal but the ambulatory blood pressure is high, whether the patient has organ damage must be evaluated.

4) Other Points of Attention

a. Initial Treatment

The objectives of the initial treatment are to select drugs effective for reducing the blood pressure to the target level and to adjust their doses. Therefore, if the blood pressure cannot be reduced to the target level by low-dose monotherapy, the next step is to increase the dose of the first drug, to switch to a different drug, or to move to combination therapy. Generally, the treatment for low-risk or moderate-risk hypertension is started by low-dose monotherapy, and if the decrease in the blood pressure is insufficient, the dose may be increased, or the drug may be replaced for, or combined with, another drug with a different action mechanism. For severe hypertension or high-risk hypertension, combination therapy should be considered at the initial treatment. Combinations of a RA system inhibitor with a diuretic or a Ca antagonist and those of a Ca antagonist (dihydropyridine) with a β-blocker or a RA system inhibitor are recommended.

b. Long-Term Treatment (Continuous Treatment)

The objective of long-term treatment is to prevent cardiovascular morbidity and mortality by maintaining a target level of blood pressure over a long period.

Since hypertensive patients have no marked discomfort or symptoms, and since the treatment for hypertension continues over a long period, some patients stop visiting medical facilities. It is an important task of the attending physician to devise measures to have patients continue coming to the hospital, observing lifestyle modifications, and taking drugs as instructed. The patient's conformity to the physician's instructions and advice or the degree of this conformity is called the compliance. For satisfactory continuation of treatment, the physician must maintain close communication with the patient and sufficiently explain hypertension as a disease, methods for its treatment, effects expected from its treatment, and expected adverse effects of drugs. Since patients may mistake decreases in the blood pressure due to drug treatment for cure of hypertension and discontinue treatment (*122*), sufficient explanation of this point is also necessary. It is important to maintain a good patient-physician (hospital) relationship by gaining confidence through providing sufficient information, because the sufficiency of communication with the physician and the degree of patient satisfaction with the medical staff markedly affect the patient's quality of life (QOL) (*123*). In long-term treatment, the management of not only the blood pressure but also other risk factors must be considered. Also, patient-participated treatment is desirable to protect the patient's QOL by respecting convenience of the patient's daily living and social activities.

c. Attention to the Quality of Life

Since the treatment for hypertension continues over a long period, attention to the protection of the patient's QOL is necessary to ensure continuation of the treatment. The QOL of hypertensive patients is not markedly impaired compared with that of patients with other serious diseases. However, patients more often have problems with the emotional state or reactions, sleep, cardiac or gastrointestinal conditions, and sense of satisfaction with life as the blood pressure is higher (*124*). Moreover, the QOL is markedly affected by aging. The

degree of impairment of QOL increases, and its individual variation widens, as the patients are older (*125*). As the QOL reflects a wide range of the patients' living including perceived physical symptoms, psychological state, degree of mental and physical satisfaction, sense of well-being, work, hobbies, social activities, home, and sexual life, these items should be evaluated as objectively and comprehensively as possible.

Sufficient attention is also necessary about impairment of the QOL due to adverse effects of antihypertensive drugs. The large-scale randomized controlled trial performed by Croog *et al*. is considered to be noteworthy (*126*). Subsequently, many comparative studies of multiple antihypertensive drugs have been carried out, and statistical analyses of the results of these studies combined have been reported (*127*, *128*). As suggested by the Hypertension Optimal Treatment (HOT) Study, a decrease in the blood pressure itself appears to exert favorable effects on the QOL. Erectile dysfunction (ED) increases with aging aged 50 years or above, and hypertension itself has been reported to increase the frequency of ED (*129*). Antihypertensive treatment has also been suggested to cause ED by reducing the blood flow of genital organs, but this view has been refuted by some reports (*130*, *131*). Phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil have been reported not to cause adverse effects when they are used concomitantly with antihypertensive drugs other than nitrates (*132*).

Summary

1) The objectives of treatment for hypertension are to prevent the occurrence of, and consequent death due to, cardiovascular diseases as a result of a sustained high blood pressure and to help hypertensive patients lead full lives.
2) Treatment is necessary for all hypertensive patients (blood pressure 140/90 mmHg or higher) but for hypertensive patients with diabetes mellitus or renal disease at 130/80 mmHg or higher.
3) Antihypertensive treatment consists of lifestyle modifications (Stage 1) and drug therapy (Stage 2). The time of the beginning of drug therapy is determined in each patient according to the blood pressure, the presence or absence of risk factors for cardiovascular diseases, presence or absence of organ damage due to hypertension, and presence or absence of cardiovascular diseases.
4) Lifestyle modifications include restriction of the salt intake, promotion of the intake of vegetables and fruits, restriction of the intake of saturated fatty acids and total lipid, control of the body weight if the patient is obese, exercise, restriction of the alcohol intake, and quitting smoking.
5) In principle, an antihypertensive drug should be started by administration once a day at a low dose. If the dose is increased, the administration twice a day should also be considered. Appropriate combinations of drugs (combination therapy) are recommended to prevent the adverse effects and to enhance the antihypertensive effect.
6) Patients with white coat hypertension (isolated office hypertension) must be followed up every 6 months even when they are not treated.
7) For satisfactory continuation of treatment, physicians must endeavor to create a good patient-physician (hospital) relationship by maintaining sufficient communication and gaining trust through providing necessary information.
8) The QOL of hypertensive patients is affected by physical and mental problems due to hypertension itself, effects of antihypertensive drugs (including adverse effects), and patient-physician (hospital) relationship. The QOL is impaired to a greater degree in older patients.
9) The attending physician must eventually determine the treatment by evaluating information including the results of laboratory tests, clinical background of the patient, and pharmacological actions of the drugs.

4. Lifestyle Modifications

Genetic predispositions and environmental factors are involved in the development of hypertension, and the environmental triggers are primarily those related to changes in the lifestyle associated with civilization. Lifestyle modifications (non-therapy) such as reducing the salt intake, weight control, moderation of drinking, and exercise not only have antihypertensive effects by themselves but also enhance the effects of antihypertensive medications and help reducing the dose of drugs. All hypertensive patients, in principle, should be given education and guidance in lifestyle modifications also for the prevention of cardiovascular diseases and alleviation of risk factors other than hypertension (diabetes mellitus, hyperlipidemia, *etc*.).

Table 4-1 shows the items of lifestyle modifications, and Fig. 4-1 shows expected decreases in the blood pressure by various lifestyle modifications (*29*).

1) Restriction of the Salt Intake (Reduced-Salt Diet)

Excess intake of salt has long been suggested to increase the blood pressure by epidemiological studies. For example, INTERSALT (*17*) demonstrated a positive correlation between the salt intake and the frequency of hypertension on the basis of data from more than 10,000 persons of 52 groups in 32 countries of the world. According to this study, a decrease in the blood pressure associated with restriction of the salt intake was small when the salt intake was 3 g/day or higher but was notable when it was less than 3 g/day. Originally, the salt intake of human beings was only 0.5–3 g/day (*133*), and the period in which human beings ingested a high level of salt is very short in the history of mankind. Therefore, strict restriction of the salt intake to less than 3 g/day appears to be justified. However, in Japan, where the average salt intake remains 11–12 g/day despite a tendency of decrease (Fig. 4-2) (*134*), salt is added to most processed foods, and seasonings containing high levels of salt are widely used, so that strict restriction of the salt intake is difficult to practice without altering the nutritional balance. For this reason, moderate restriction of the salt intake is generally recommended. Among large-scale clinical studies performed in Western countries, the Trial of Nonpharmacologic Intervention in the Elderly (TONE) reported a significant decrease in the blood pressure without a problematic adverse effect as a result of a decrease in the mean salt intake from 8.5 g/day to 6.1 g/day in elderly hypertensive patients (*111*). In DASH-Sodium trial, the blood pressure showed linear significant decreases with the salt intake from 8.7 g/day to 3.0 g/day whether or not the subjects practiced the DASH diet (low cholesterol and saturated fatty acid levels, high K, Ca, Mg, and an increased dietary fiber content) (*23*). On the basis of the results of these large-scale clinical studies, guidelines of Western countries recommend restriction of the salt intake to less than 6 g/day as a provisional target. In Japan, also, in consideration of the gradual decrease in the salt intake, restriction of the salt intake to less than 6 g/day is recommended, following Western guidelines.

Since an ideal salt intake is extremely difficult to be achieved in a healthy manner in the modern society, it is important to conduct salt-reducing campaigns for the entire society, and administrative guidance of food processing businesses to reduce the salt content should be introduced. There is also a report that the blood pressure was successfully reduced in young individuals (high school students) by reducing the salt intake through dietary guidance (*135*). Education and guidance of children and adolescents, who have not established a dietary habit, should be improved for the future.

Presently, the Na content (mg/100 g or mg/100 ml) instead of the salt content is shown in nutritional labels of foods in Japan. Since dietary guidance in terms of the salt intake (g/day) is a common practice, nutritional labeling should be changed to the salt content for convenience (g/100 g or g/100 ml). The relationship between the Na content and salt content is represented by

$$\text{Salt (g)} = \text{Na (mg)} \times 2.54/1{,}000.$$

At present, it is necessary to teach this equation to patients so that they can calculate the salt content by themselves.

The effect of the salt intake on the blood pressure (salt sensitivity) varies individually (*136*), and pressor effect of excessive salt intake is notable in people with a family history of hypertension and the elderly. According to studies in Japan, the frequency of cardiovascular complications is high in salt-sensitive hypertensive patients (*137*). It is related to an increase in the intraglomerular pressure and abnormalities of diurnal changes in the blood pressure, and these abnormalities can be corrected by reducing the salt intake. However, there is no simple method for the examination of salt sensitivity suitable for routine clinical use. Moreover, salt has been shown to damage the cardiac vessels independently from the blood

Table 4-1. Lifestyle Modifications

1) Restriction of salt intake to less than 6 g/day
2) Increased intake of vegetables and fruits*
Restriction of intake of cholesterol and saturated fatty acid
3) Maintenance of appropriate body weight: Not exceeding BMI ([body weight (kg)]/[height (m)]^2) of 25
4) Exercise: Indicated for hypertensive patients without cardiovascular disease. Regular aerobic exercise for 30 min or longer every day
5) Restriction of alcohol intake: 20–30 g/day or less in terms of ethanol for men and 10–20 g/day or less for women
6) No smoking
Comprehensive modification of lifestyle is more effective

*Increased intake of vegetables and fruits is not recommended in patients with severe renal dysfunction, because it may induce hyperkalemia. Increased intake of fruits is not recommended in diabetic patients, because it may lead to an increase in calorie.

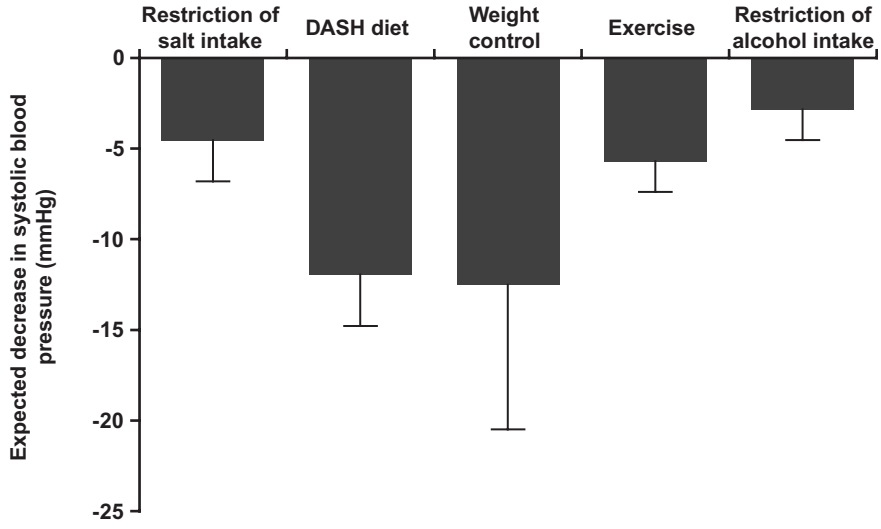

Fig. 4-1. *Decrease in blood pressure by lifestyle modifications (reproduced from the JNC 7 with changes) (29). Restriction of salt intake: decrease in salt intake to less than 6 g/day. DASH diet: see Table 4-2. Weight control: decrease in body weight by 10 kg. Exercise: fast walking for at least 30 min almost every day. Restriction of alcohol intake: limit of the alcohol intake to 30 g/day or less in men and 15 g/day or less in women.*

pressure. Therefore, restriction of the salt intake should be a target not only for hypertensive patients but also for the entire society.

2) Increases in the Intake of Vegetables and Fruits and Restriction of the Intake of Cholesterol and Saturated Fatty Acids

Recently, a clinical trial of a diet with low-fat dairy products (low in saturated fatty acids and cholesterol and high in Ca) and high vegetable and fruit intake (high in K, Mg, and dietary fiber) called DASH (*23*, *110*), was performed in the Western countries, and a significant decrease in the blood pressure, *i.e.* 11.4/5.5 mmHg in moderately hypertensive patients, was reported. These results suggest that a combination of increases in K (*138*), Mg (*139*), and Ca (*140*) with mild antihypertensive effects and restriction of the fat intake is expected to reduce the blood pressure, indicating the importance of a comprehensive dietary therapy. However, increases in the intake of vegetables and fruits are not recommended in patients with severe renal dysfunction because of the possibility of hyperkalemia due to reduced renal excretion of K. Also, increases in the intake of fruits are not recommended in diabetic patients, because intake of fruits with high fructose contents may lead to an increase in the energy intake. When the nutritional composition of the DASH diet is compared with that of a typical diet of Japanese men and women aged 40–59 years calculated from the results of INTERMAP (*141*) (Table 4-2), the Japanese diet is relatively close to the DASH diet in that the fat content is lower, and the carbohydrate content is higher, than in the Western diet. In the Japanese diet, however, the contents of dietary fiber, K, Mg, and Ca were higher

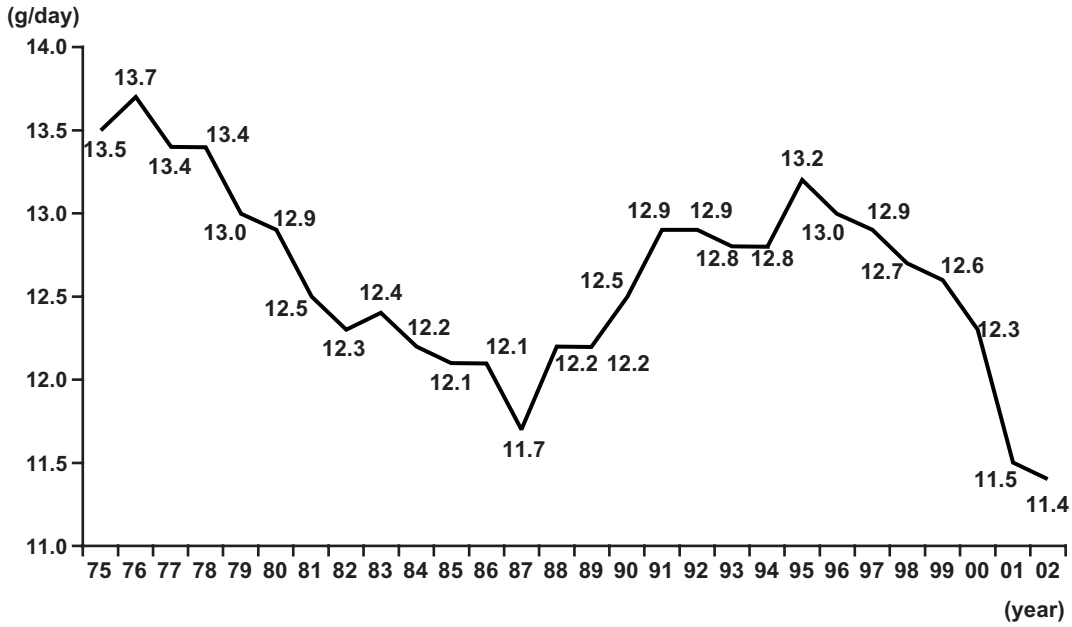

Fig. 4-2. *Annual changes in the salt intake (g/day) of Japanese (cited from reference* 134*).*

Table 4-2. Comparison between DASH Diet and Japanese Diet

Nutritional component	Control diet (Typical American diet)*	Vegetable/fruit diet*	DASH diet*	Typical Japanese diet†	
				Men	Women
Fat (%)	37	37	27	23.7	26.1
Saturated fatty acids	16	16	6	6.1	7.1
Mono-unsaturated fatty acids	13	13	13	8.6	9.4
Poly-unsaturated fatty acids	8	8	8	6.2	6.6
Carbohydrates (%)	48	48	55	52.3	56.2
Proteins (%)	15	15	18	15.8	16.1
Cholesterol (mg/day)	300	300	150	446	359
Dietary fiber (g/day)	9	31	31	15.5	15.8
K (mg/day)	1,700	4,700	4,700	1,920	1,891
Mg (mg/day)	165	500	500	288	250
Ca (mg/day)	450	450	1,240	605	607
Na (mg/day)	3,000	3,000	3,000	4,843	4,278
(Energy level [kcal])‡	(2,100)	(2,100)	(2,100)	(2,278)	(1,798)

Cited from references **23* and †*141*. ‡While the energy level was uniform at 2,100 kcal in the control, vegetable/fruit, and DASH diet, it varied widely, particularly in women, in the INTERMAP. The calculations of INTERMAP were made on the basis of these results.

than in the Western diet, but they were considerably lower than in the DASH diet, and the Na content was 1.5 times higher than in the Western diet. The cholesterol content, which was higher than in the Western diet (particularly in men), was the greatest problem of the Japanese diet. In Japan, the intake of fat, particularly animal fat increased markedly, and the intake of carbohydrates decreased, after the World War II. The increase in the fat intake in children is a problem that needs particular attention. Therefore, a diet close to the DASH diet can be attained in Japan by returning to the traditional Japanese diet, avoiding high-cholesterol foods such as eggs, and supplementing it with low-fat dairy products.

Since hyperlipidemia is one of the major risk factors for ischemic heart disease, hypertensive patients should reduce the intake of cholesterol and saturated fatty acids also for the prevention of hyperlipidemia.

3) Maintaining a Proper Body Weight (Weight Control)

Obesity is defined as a BMI ([body weight (kg)]/[height (m)]^2) of 25 or higher (*142*). While obesity has been shown by many epidemiological studies to be an important risk factor for hypertension (*143*), it is considered to induce hyperglycemia, hypertriglyceridemia, hyper-LDL-cholesterolemia, and hypo-HDL-cholesterolemia and to be closely related to metabolic syndrome, which is an important risk factor for cardiovascular diseases. An increase in visceral fat deposition (visceral obesity) is particularly important.

The antihypertensive effect of the weight control has been established. A large-scale clinical trial TONE reported that the blood pressure was reduced significantly by reducing the body weight by 4.5 kg (*111*). In Japan, also, the blood pressure was reportedly reduced by a mean decrease in the body weight of 4.1 kg (*144*). Weight control has also been reported to lead to a decrease in the dose of antihypertensive medication and improvements in metabolic indices (*145*). There has also been a report that enhanced inflammatory reactions and abnormalities of vascular endothelial functions observed in metabolic syndrome were corrected by weight control (*146*). For obese hypertensive patients, weight control should be recommended first, and they should be guided to perform stress-free long-term weight control in consideration that an appreciable decrease in the blood pressure can be expected even from a loss of 4–5 kg. For non-obese hypertensive patients, it is important to maintain an appropriate body weight.

4) Exercise Therapy

Exercisers generally have a low blood pressure, and exercise therapy is effective for reducing the blood pressure. In addition, physically active individuals are reported to be less frequently obese, more often have normal serum lipid levels, and have fewer risks for cardiovascular diseases (*147*). Since, in fact, exercise enhances the insulin sensitivity, it is expected to alleviate a condition of metabolic syndrome.

Mild dynamic isotonic exercises, which are aerobic (*e.g.*, fast walking, running, and walking in a pool), are suited for exercise therapy. Mild exercise means a level corresponding to about 50% of the maximum oxygen uptake (*148*). The increase in the blood pressure is more notable during vigorous exercise, and the same exercise may become anaerobic when its intensity increases. Recommendable duration and frequency of exercise are 30 min or longer per day and daily as much as possible. (Since it has recently been reported that even light exercise reduced the blood pressure in inactive patients with mild hypertension (*149*), exercise of a shorter duration and a lower frequency may also be effective.) Such exercise continued for 10 weeks has been reported to have reduced the systolic blood pressure by 20 mmHg or more and the diastolic blood pressure by 10 mmHg or more with a mean decrease of 11/6 mmHg in 50% of the patients (*150*). However, appropriate candidates for exercise therapy are patients with mild or moderate hypertension with no cardiovascular complication. Since patients with cardiovascular diseases such as heart failure, ischemic heart disease, and stroke are likely to suffer cardiovascular events during exercise due to an increase in the blood pressure, medical check must be performed before the start of exercise therapy, and appropriate guidance including contraindications and restrictions must be provided. Also, in patients with renal failure, contraindications and restrictions of exercise are needed according to "the Guidelines for Lifestyle and Dietary Therapy for Patients with Kidney Diseases" (*151*). Mild aerobic exercise has also been reported to have reduced the blood pressure in elderly patients without adverse effects (*152*, *153*). Therefore, exercise should not be restricted simply because of old age, but the candidates should be evaluated for the presence or absence of cardiovascular diseases before prescribing exercise therapy.

5) Restriction of Alcohol Intake (Moderation in Drinking)

Drinking is known to increase the blood pressure (*143*). According to the basic research on cardiovascular diseases in 1980 (*154*), the blood pressure was higher as the alcohol intake was higher in male drinkers, and the difference in the blood pressure between those who drank every day and non-regular drinkers corresponded to an age difference of about 10 years. Moreover, in the INTERSALT (*155*), drinking showed a positive correlation with the blood pressure independently of other factors. Particularly in men, drinking is a risk factor for stroke, and it is considered to be more closely related to cerebral hemorrhage than cerebral infarction. A single drink of alcohol causes a dip in the blood pressure due to vasodilation, which continues for a few hours, but moderation in drinking decreases the blood pressure (*156*). The antihypertensive effect of moderation in drinking appears within 1–2 weeks. Although sudden withdrawal of alcohol may cause a significant increase in the blood pressure in heavy drinkers, the blood pressure decreases within a few days as abstinence continues. Alcohol intake should be restricted to 20–30 g/day or less in terms of ethanol (about 1 "go" of sake) in men and 10–20 g/day or less in women.

6) No Smoking

Smoking is known to cause a temporary increase in the blood pressure, but it does not cause hypertension as its chronic effect (*157*). However, smoking is known to reduce the antihypertensive effect of β-blockers. Smoking is a powerful risk factor for ischemic heart disease and stroke as well as non-cardiovascular diseases such as cancer (*157*). In smokers with a history of myocardial infarction, no smoking has been reported to be effective for secondary prevention (*158*).

Therefore, hypertensive patients should give up smoking for the prevention of cardiovascular complications.

7) Other Cautions about Daily Living

As results primarily of animal experiments have indicated that oxidative stress plays an important role in increases in the blood pressure and the occurrence and development of cardiovascular diseases, antioxidants are speculated to have antihypertensive effects and organ protecting effects also in humans. However, many studies failed to prove antioxidants (vitamin C, vitamin E, *etc*.) to be effective in humans (*159*, *160*), and, presently, recommendation for their administration is not warranted.

The relationship between emotional stress and the blood pressure is not consistent, and further evaluation of problems including the method for stress assessment is necessary. Attempts to reduce the blood pressure by stress management have been made, and biofeedback and relaxation have been evaluated. However, while the effectiveness of these techniques has been supported by some reports, it has been challenged by many others, and they have not been established as antihypertensive treatments.

Epidemiological studies showed that the blood pressure is higher during winter, indicating that the cold increases the blood pressure. Also, the increase in the mortality rate due to cardiovascular diseases in winter is greater when heating of the house or clothing is inadequate (*161*). Therefore, hypertensive patients should protect themselves from the cold in winter by deliberate heating and clothing, and the toilet and bathroom, which are likely to be overlooked, should also be heated sufficiently.

In taking a bath, the water temperature should not be too high. Since the increase in the blood pressure has been reported to be nominal when the room temperature is 20°C or higher and the water temperature is 40°C or lower, bathing in water at 38–42°C for 5–10 min is a reasonable guideline. A public bath, where the water is generally too hot, is not recommended. Cold water bathing and sauna should be avoided.

Straining for bowel movements due to constipation increases the blood pressure, so that instructions for the prevention of constipation should be given, and the administration of laxatives should be considered, if necessary.

Although sexual activity increases the blood pressure, hypertension rarely interferes with sexual life. However, patients with cardiovascular diseases should avoid strenuous sexual activity.

8) Comprehensive Lifestyle Modifications

The DASH (*110*) and DASH-Sodium (*23*) indicated that more comprehensive improvements in the diet markedly decrease the blood pressure. The TONE (*111*) also suggested that a combination of a decrease in the salt intake and weight control is more effective for the management of the blood pressure and prevention of cardiovascular diseases. Furthermore, according to a recent report (*162*), the blood pressure was reduced more notably when lifestyle modifications consisting of restriction of the salt intake, weight control, exercise, and moderation in drinking were combined with the DASH diet. Thus, comprehensive lifestyle modifications are advisable.

Summary

1) Lifestyle modifications are important for hypertensive patients.
2) Concerning the diet, the salt intake should be reduced to less than 6 g/day, the intake of vegetables and fruits should be increased, and the intake of cholesterol and saturated fatty acid should be restricted. Obese patients should reduce the body weight, and others should maintain an appropriate body weight. However, increased intake of vegetables and fruits is not recommended to patients with severe renal dysfunction, because it may cause hyperkalemia. Also, increased intake of fruits is not recommended to diabetic patients, because it may result in an increase in the energy intake.
3) For exercise therapy, regular practice of mild aerobic exercise at about 50% of the maximum oxygen uptake is recommended. Since exercise therapy may be a contraindication to patients with cardiovascular complications, a check for cardiovascular diseases is necessary before prescribing exercise therapy.
4) The alcohol intake should also be restricted to 20–30 g/day or less in terms of ethanol for men and 10–20 g/day or less for women.
5) Smoking should be given up.
6) Comprehensive lifestyle modifications are more effective.

5. Treatment with Antihypertensive Drugs

1) Basic Principles for Choice of Antihypertensive Drugs

Randomized controlled trials of antihypertensive medications have been performed for more than 30 years. In general, diuretics or β-blockers were used in an early period. Recently, however, the results of trials using Ca antagonists, ACE inhibitors, or ARBs as basic drugs have been reported, and evidences concerning the efficacy of various classes of antihypertensive drugs are being obtained.

According to the metaanalyses by the Blood Pressure Lowering Treatment Trialists' Collaboration (*163*) and Staessen *et al*. (*164*), Ca antagonists reduced stroke by 38% and coronary artery diseases by 20% in comparison with placebo, but increased heart failure by 21%, though not significantly. Compared with diuretics and β-blockers, Ca antagonists reduced stroke by 7–8%, though not significantly, caused little change in the frequency of coronary artery diseases, and increased heart failure by 33%.

ACE inhibitors reduced stroke by 28%, coronary artery diseases by 22%, and heart failure by 18% compared with placebo. They reduced stroke by 9–10%, though not significantly, caused little change in the frequency of coronary artery diseases, and increased heart failure by 4–7%, though not significantly, compared with diuretics or β-blockers.

ARBs reduced stroke by 21–24%, caused little change in the frequency of coronary artery diseases, and reduced heart failure by 16% compared with diuretics or β-blockers.

In Japanese studies, also, no significant difference was observed in the frequency of cerebrovascular disorders or ischemic heart disease among patients treated with various antihypertensives (*165–169*). Therefore, the effectiveness of antihypertensive medications is considered to be derived primarily from the blood pressure lowering effect itself rather than the characteristic actions of various classes of antihypertensive drugs (*43*).

a. Choice of Antihypertensive Drugs

Ca antagonists, ARBs, ACE inhibitors, diuretics, β-blockers (including αβ-blockers), and α-blockers are the major antihypertensive drugs used today (*43*). Evidence concerning α-blockers is sparse compared with that concerning other antihypertensive drugs.

Antihypertensive drugs are selected for individual patients by considering the following factors in addition to their age and sex. If there is no positive indication, an antihypertensive drug considered to be the most appropriate is selected as the first choice from major antihypertensive drugs.

- Cardiovascular risk factors—hyperlipidemia, obesity, glucose intolerance, *etc*.
- Target organ damage, cardiovascular diseases
- Adverse effects of antihypertensive drugs, drug prices, QOL, effects on sexual functions

Indications and contraindications of various antihypertensive drugs are shown in Table 5-1.

b. Use of Antihypertensive Drugs

- Start antihypertensive medication with a single drug (including a fixed combination drug after it is approved) at a low dose.
- Use a long-acting antihypertensive drug that is effective by administration once a day.
- Attainment of the target of blood pressure control within 2–3 months should be intended. Measurement of the blood pressure every 2 (to 4) weeks is desirable until the blood pressure reaches the target of blood pressure control.
- If a target of blood pressure control of less than 140/90 mmHg on the measurement at the outpatient clinic (less than 130/85 mmHg, if possible, in non-elderly patients) cannot be attained, the dose should be increased or the initial drug should be combined with another antihypertensive drug of a different class that is expected to produce an additive or synergistic effect. If little decrease in the blood pressure is observed, the initial drug should be substituted for an antihypertensive drug of another class. The dose may be increased if tolerated, but not to twice the ordinary dose or higher. The following combinations of two drugs are being used clinically.
  (1) A Ca antagonist and an ARB
  (2) A Ca antagonist and an ACE inhibitor
  (3) A dihydropyridine Ca antagonist and a β-blocker
  (4) An ARB and a diuretic
  (5) An ACE inhibitor and a diuretic
  (6) A diuretic and a β-blocker
  (7) A β-blocker and an α-blocker
  (8) A Ca antagonist and a diuretic

Table 5-1. Indications and Contraindications of Major Antihypertensive Drugs

Antihypertensive drug	Indications	Contraindications
Ca antagonist	Post-cerebrovascular disease, angina pectoris, left ventricular hypertrophy, diabetes mellitus, elderly	A-V block (diltiazem)
ARB	Post-cerebrovascular disease, heart failure, post-myocardial infarction, left ventricular hypertrophy, chronic kidney disease, diabetes mellitus, elderly	Pregnancy, hyperkalemia, bilateral renal artery stenosis
ACE inhibitor	Post-cerebrovascular disease, heart failure, post-myocardial infarction, left ventricular hypertrophy, chronic kidney disease, diabetes mellitus, elderly	Pregnancy, hyperkalemia, bilateral renal artery stenosis
Diuretic	Post-cerebrovascular disease, heart failure, renal failure (loop diuretic), elderly	Gout
β-Blocker	Angina pectoris, post-myocardial infarction, tachycardia, heart failure	Asthma, A-V block, peripheral vascular disease
α-Blocker	Hyperlipidemia, prostate hypertrophy	Orthostatic hypotension

A-V, atrioventricular.

- The administration of a low-dose diuretic enhances the effect of other antihypertensive drugs. If the decrease in the blood pressure is insufficient by the treatment using two drugs not including a diuretic, select a diuretic as the third drug, in principle.
- The control of the blood pressure for 24 h is desirable. If the patient has morning hypertension or reverse white coat hypertension, try administration of an antihypertensive drug with a longer duration of action, an α-blocker, or a centrally acting sympatholytic drug before going to bed.
- If the target level of blood pressure control cannot be attained even 6 months after the beginning of the treatment, refer the patient to a hypertension specialist (FJSH).

c. Drug Interactions

Among antihypertensive drugs, the concomitant use of a Ca antagonist that causes bradycardia such as diltiazem with a β-blocker should be avoided.

In addition, as Ca antagonists (such as nifedipine) may increase the blood concentration of digitalis, they must be used carefully. Also, H_2-blockers such as cimetidine and ranitidine and grapefruit juice enhance the effects of Ca antagonists (such as nifedipine). Furthermore, the effects of antihypertensive drugs including diuretics, β-blockers, and ACE inhibitors are attenuated by the concomitant use of a non-steroidal anti-inflammatory drug.

d. Dose Reduction and Withdrawal of Antihypertensive Drugs

Antihypertensive medication must often be continued lifetime. However, antihypertensive drugs may be reduced in dosage or withdrawn by modifications of the lifestyle. If the blood pressure has been reduced to a level considerably below the target of blood pressure control for a long period, the medication may be tapered or even be withdrawn on condition that an appropriate lifestyle is maintained and the blood pressure be periodically checked.

2) Characteristics and Major Adverse Effects of Various Antihypertensive Drugs

The antihypertensive drugs used in Japan today can be classified into Ca antagonists, which cause vasodilation by inhibiting the influx of Ca^{2+} into vascular smooth muscle cells, ACE inhibitors, which inhibit the production of angiotensin II, ARBs, which block the action of angiotensin II at the receptor level, diuretics, which promote the excretion of Na and water through the kidney, sympatholytic agents, which cause central or peripheral inhibition of the sympathetic nervous system, and vasodilators, which dilate peripheral blood vessels by direct actions.

Characteristics and major adverse effects of these antihypertensive drugs are described below.

a. Ca Antagonists

Ca antagonists were developed as a treatment for angina pectoris, but they were later found to dilate peripheral arterioles as well as the coronary artery to produce an antihypertensive effect. The danger of the occurrence of ischemic heart disease during the use of Ca antagonists used to be suggested, but this danger was shown by subsequent research to be limited to short-acing Ca antagonists (*109*).

Ca antagonists are the antihypertensive drugs most widely used in Japan today, and they are recommended as the initial drugs for relatively aged hypertensive patients without complication, because they have no serious adverse effects, and are the most inexpensive next to diuretics.

Dihyropyridine Ca antagonists and benzodiazepine Ca antagonists are used as antihypertensive drugs, in Japan and only diltiazem belongs to the latter group. Compared with nifedipine, which was developed earliest, the action time and effects of amlodipine, efonidipine, cilnidipine, and azelnidipine differ considerably. While nifedipine produces a rapid and powerful antihypertensive effect, short-acting type nifedipine capsules, in particular, cause a rapid decrease in the blood pressure and a resultant enhancement of the activities of the sympathetic nervous system and RA system, and increases in heart rate and cardiac work. As their effects decrease in 2–3 h, the blood pressure becomes unstable, possibly exacerbating ischemic heart disease (*170*). Amlodipine has the longest action and often causes lower limb edema as an adverse effect in Western populations, but few adverse effects have been reported in the Japanese. Efonidipine has a kidney protecting effect as well as a heart protecting effect due to its inhibitory effect on the T-type Ca channel as well as the L-type Ca channel (*171*). Cilnidipine causes suppression of sympathetic activities associated with a decrease in the blood pressure due to its inhibitory effect on the N-type as well as L-type Ca channel (*172*). Azelnidipine (*173*), which was introduced recently, has a slow onset and long duration of antihypertensive action and causes no marked changes in the heart rate. Diltiazem has mild antihypertensive effect and it inhibits the cardiac conduction system and characteristically causes a mild decrease in the cardiac contractility and a decrease in the heart rate.

Ca antagonists are advantageous as antihypertensive drugs in that they maintain the cerebral, coronary, renal, and peripheral circulations in an adequate state without adverse effects on carbohydrate or lipid metabolism while they consistently decrease the blood pressure. They have also been proved to prevent the progression of arteriosclerosis (*174*). The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) demonstrated the effectiveness of amlodipine for the prevention of cardiovascular diseases. The safety of its use in hypertensive patients who are expecting pregnancy or those in an early stage of pregnancy has not been established.

Ca antagonists occasionally cause hot flushes, headache, palpitation, edema of the upper and lower limbs, constipation, and gingival hypertrophy as adverse effects. Diltiazem may cause bradycardia or atrioventricular (A-V) block by suppressing the cardiac conduction system, and its concurrent use with a β-blocker should be avoided for precaution. While increases in cancer and gastrointestinal bleeding were reported, this view was refuted by a subsequent report (*109*).

b. Angiotensin II Receptor Blockers

Many known actions of angiotensin II are mediated by the type 1 receptor. ARBs produce an antihypertensive effect by selectively inhibiting the action of angiotensin II on type 1 receptors. ARBs are used widely as antihypertensive drugs, following Ca antagonists in Japan, because they produce satisfactory antihypertensive effects with few adverse effects. However, they are the most expensive.

Dilation of peripheral blood vessels, inhibition of aldosterone secretion, and inhibition of the release of noradrenaline from sympathetic nerve terminals have been suggested as mechanisms of their antihypertensive effect. Since enzymes that convert angiotensin I to angiotensin II such as chymase and cathepsin G as well as ACE are present in the cardiovascular system, angiotensin II is produced even when ACE is inhibited. Therefore, ARBs are considered to inhibit the RA system more specifically than ACE inhibitors. In addition, when an ARB is used, renin production is increased, causing an increase in the production of angiotensin II, which, by acting on type 2 receptors, is considered to prevent an increase in the blood pressure and progression of organ damages.

ARBs show slow but consistent antihypertensive effects and produce excellent additive or synergistic effects when used in combination with a diuretic or Ca antagonist. Similarly to ACE inhibitors, they have been shown to have heart and kidney protecting effects. Fixed-combination preparations of an ARB and a diuretic have excellent antihypertensive effects and are expected to be marketed in the near future. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE), Study on Cognition and Prognosis in the Elderly (SCOPE), and VALUE also showed ARBs to be effective for the prevention of stroke and to reduce the incidence of diabetes mellitus in its users (*116–118*).

ARBs have few adverse effects (*175–177*). The frequency of adverse effects, which are only mild symptoms such as dizziness and palpitation, is comparable to that in patients administered placebo, and ARBs are advantageous for continuation of treatment.

Concerning precautions for use, ARBs are contraindicated for hypertension in pregnant patients, patients with bilateral renal artery stenosis, or patients with a single kidney with renal artery stenosis, because they may cause rapid decrease in renal function. The use of ARBs in hypertensive patients with hyperkalemia should also be avoided.

c. Angiotensin-Converting Enzyme Inhibitors

The antihypertensive effect of ACE inhibitors is derived primarily from inhibition of ACE in circulating blood and organs such as the cardiovascular system and a consequent decrease in angiotensin II production. Therefore, the antihypertensive effect is more notable in patients with increased RA system. However, since they cause increases in bradykinin, prostaglandin E_2, prostaglandin I_2, and nitric oxide by inhibiting kinase II, they produce an antihypertensive effect also in patients with the suppressed RA system. Their antihypertensive effect is relatively satisfactory similarly to that of ARBs, but their use has been decreasing because of cough as its adverse effect.

The antihypertensive effect of ACE inhibitors is based on peripheral vasodilation, but their antihypertensive effect is not accompanied by enhancement of the sympathetic activity or an increase in the heart rate or Na-water retention.

In addition to the antihypertensive effect, they alleviate cardiac hypertrophy and thickening of the vascular wall and prevent the progression of arteriosclerosis. They exert no adverse effect on carbohydrate metabolism or lipid metabolism and alleviate insulin resistance. In addition, by reducing the angiotensin II production, ACE inhibitors also produce an excellent kidney protecting effect such as a decrease in urinary protein as they reduce the intraglomerular pressure by dilating efferent arterioles of the kidney and inhibit the action of angiotensin II on glomerular mesangium. The kidney protecting effect of ACE inhibitors is observed independently of changes in the systemic blood pressure (*178*). ACE inhibitors are also effective for the treatment of patients with heart failure and for improving the outcomes of patients with myocardial infarction. The Perindopril Protection against Recurrent Stroke Study (PROGRESS) (*106*) demonstrated that a combination of perindopril and a diuretic was effective for the secondary prevention of stroke. However, perindopril was often used alone in a substudy of Japanese patients, and no significant difference compared with placebo was observed (*179*).

As for adverse effects, cough is observed in 20–30% of the users of ACE inhibitors due to an increase in bradykinin (*180*), and dyspnea due to angioedema is infrequently noted. Among precautions for use, ACE inhibitors must not be used in pregnant hypertensive patients, patients with bilateral renal artery stenosis or those with a single kidney with renal artery stenosis, because they may rapidly reduce renal function. Their use in hypertensive patients with hyperkalemia should also be avoided.

d. Diuretics

Diuretics produce an antihypertensive effect by inhibiting Na and water reabsorption in the renal tubules and reducing the circulating blood volume. Although the cardiac output decreases with a decrease in the circulating blood volume shortly after the beginning of the administration of diuretics, the cardiac output is gradually restored as the administration is continued, and the antihypertensive effect is maintained by a decrease in the peripheral vascular resistance (*181*).

Among diuretics, thiazide and thiazide-like diuretics, loop diuretics, and K-sparing diuretics are used as antihypertensive drugs. These drugs have different antihypertensive effects and adverse effects, and must be used selectively according to the patient's condition. Diuretics are considered the first choice in many countries because of their relatively satisfactory antihypertensive effects and reasonable prices. However, they are often used in combination with other drugs because of their metabolic adverse effects.

i. Thiazide and Thiazide-Like Diuretics

These drugs produce an antihypertensive effect by inhibiting Na reabsorption in distal tubules and reducing the circulating blood volume. Thiazide-like diuretics differ in structure from thiazide diuretics but have similar actions. Chlortalidone was used in the SHEP and ALLHAT, and was proved to be useful for the prevention of cardiovascular diseases.

Both thiazide and thiazide-like diuretics promote K as well as Na excretion and are likely to cause hypokalemia. Severe hypokalemia has been reported to increase the risk for arrhythmia and sudden death, and to abolish the cardiovascular organ protecting effect. Although these adverse effects can be prevented considerably by the administration at a low dose (1/4–1/2 of the common dose) or in combination with an ARB or ACE inhibitor, changes in the serum K level must be monitored carefully, and supplementation of KCl or the concurrent use of a K-sparing diuretic such as spironolactone or triamterene is necessary if hypokalemia appears. Other adverse effects that require attention include gout, hyperlipidemia, glucose intolerance (diabetes mellitus), ED, and hemoconcentration due to dehydration. In addition, photosensitivity dermatitis and bone marrow depression may be observed as rare adverse effects specific to thiazide diuretics.

Since metabolic changes may adversely affect the long-term outcome, thiazide and thiazide-like diuretics must be administered in low doses to minimize their adverse effects.

ii. K-Sparing Diuretics and Aldosterone Antagonists

Spironolactone, an aldosterone antagonist, acts on distal tubules and collecting tubules, antagonizes mineralocorticoids such as aldosterone, inhibits reabsorption of Na and excretion of K^+ and hydrogen (H^+), and produces an antihypertensive effect without loss of K^+.

Recently, cardiovascular damage due to the direct action of aldosterone has been suggested, and the addition of spironolactone to the conventional regimen has been reported to reduce the mortality rate of patients with severe heart failure (*182*).

As for adverse effects, ED and gynecomastia are observed frequently in men and breast pain and menstrual abnormalities in women. Hyperkalemia may also occur in patients with renal disorders. Eplerenone with fewer adverse effects is used in the United States, and application for its manufacturing has been submitted also in Japan (*183*).

Triamterene acts primarily on the distal tubules, inhibits the exchange of Na^+ and K^+ independently of mineralocorticoids, promotes Na excretion without losing K, and produces a mild antihypertensive effect. Since its antihypertensive effect is weak when administered alone, it is used in combination with a thiazide diuretic, a thiazide-like diuretic, or a loop diuretic.

As for adverse effects, K-sparing diuretics and aldosterone antagonists may cause nephrolithasis and rapid suppression of renal function when used in combination with prostaglandin production inhibitors such as indomethacin.

iii. Loop Diuretics

Loop diuretics produce a potent diuretic effect by inhibiting the cotransport of $Na^+/K^+/Cl^-$ on the luminal side of the ascending limb of Henle's loop and, thus, inhibiting the reabsorption of Cl^-. Therefore, loop diuretics are recommended for diuresis of hypertensive patients with renal failure showing a serum creatinine level of 2 mg/dl or higher.

Loop diuretics cause adverse effects similar to those of thiazide diuretics such as hypokalemia, hyperuricemia, hyperlipidemia, and glucose intolerance, but they more often cause hemoconcentration due to dehydration than thiazide diuretics. They may also cause pancreatitis and rash.

To reduce adverse effects, loop diuretics must be used at the minimum necessary dose.

e. β-Blockers (Including αβ-Blockers)

β-Blockers have been used widely for the treatment of hypertension along with diuretics. Details of the mechanism of their antihypertensive effect have not been clarified to date, and a decrease in the cardiac output, decreases in renin production and secretion, and inhibition of the sympathetic activities from the central nervous system have been suggested as possibilities. The peripheral vascular resistance increases with a decrease in cardiac output shortly after the beginning of their use, but it gradually returns to the original level on their prolonged use, while these responses vary among β-blockers.

Properties of the β-blocker vary considerably among its types. A β-blocker is classified according to whether it selectively blocks β_1-receptors present in the heart or it also blocks β_2-receptors present in organs other than the heart, whether it is lipid soluble or water soluble, and whether it has an intrinsic sympathomimetic activity (ISA) or not. Many newer β-blockers have a Ca channel blocking action or K channel opening action, and a peripheral vasodilating action.

The use of β-blockers that have no ISA is recommended for preventing the recurrence of myocardial infarction, preventing ischemic heart disease, and improving the outcome of heart failure.

Adverse effects common to all β-blockers include induction of bronchial asthma, exacerbation of chronic obstructive pulmonary disease, bradycardia or A-V block, decline of energy, and reduced athletic abilities in athletes. In diabetic patients on insulin therapy, delay of the detection of hypoglycemic attacks may be a problem of the use of β-blockers. In addition, induction of angina pectoris and a temporary increase in the blood pressure may be observed as withdrawal syndrome when a β-blocker is suddenly withdrawn after its prolonged use.

Furthermore, as lipid soluble β-blockers are transported to the brain, they are likely to cause adverse effects due to their actions on the central nervous system such as nightmare. Also, β-blockers that have no vasodilating action are likely to cause peripheral circulation disorders and exacerbate obstructive arterial diseases. β-Blockers without ISA exert adverse effects on lipid metabolism such as an increase in the serum triglyceride level and a decrease in the HDL-cholesterol level. A sudden increase in creatine phosphokinase (CPK) may be observed during the use of β-blockers with ISA (*184*).

Among β-blockers, those that have a strong α-blocker action are called αβ-blockers. The advantage of these drugs is that they also produce a peripheral vasodilating effect due to the α-blocking action in addition to the β-blocking action, and they are useful for the treatment of diseases such as pheochromocytoma, in which both α- and β-receptors must be suppressed. Additionally, labetalol has been confirmed through accumulation of many clinical experiences to be relatively safe for the treatment of hypertension of pregnancy.

Adverse effects of αβ-blockers are similar to those of non-selective β-blockers. As for other adverse effects, dizziness on standing up is more likely to occur as the α-blocking action is stronger.

f. α-Blockers

α-Blockers are drugs that selectively block α-receptors among sympathetic receptors. Today, α-blockers that selectively block α_1-receptors are used as antihypertensive drugs. α_1-Receptors are present on the smooth muscle side of myoneural junctions of sympathetic nerve terminals, and α-blockers produce a vasodilating effect by blocking the action of noradrenaline on these receptors. α_2-Receptors are present on the nerve side as well as the smooth muscle side of sympathetic nerve terminals and, receiving the action of noradrenaline released from the sympathetic nerve terminals, inhibit further release of noradrenaline by suppressing the sympathetic activity. Because of this action, α-blockers that selectively block α_1-receptors infrequently cause tachycardia unlike non-selective α-blockers.

Since the antihypertensive effect of α-blockers is based on vasodilation of peripheral arterioles, they are more effective in patients with strong sympathetic activities. Also, the administration of an α-blocker with a long term action time such as doxazosin before going to bed is effective for preventing an early morning increase in the blood pressure.

α-Blockers improve carbohydrate and lipid metabolism and alleviate dysuria in patients with prostate hypertrophy. Their adverse effects are dizziness on standing up and vertigo. The incidence of heart failure during 1 year was 2.03% in the ALLHAT (*109*), but it was 0.17% according to a large-scale investigation by the Japan Physicians' Association (*185*).

g. Other Sympatholytic Agents—Centrally and Peripherally Acting Drugs

i. Central Sympatholytic Agents

Central sympatholytic agents suppress sympathetic activities by acting on α_2-receptors in the brain and produce an antihypertensive effect by suppressing peripheral vasoconstriction. While central sympatholytic agents such as clonidine, meth-

yldopa, and guanabenz are used, the frequency of their use is decreasing. Methyldopa is used for the treatment of hypertension of pregnancy.

Their adverse effects include drawsiness, thirst, ED, and dizziness on standing up, and methyldopa may cause liver disorders. Clonidine must be used carefully, because its sudden withdrawal may cause a rapid increase in blood pressure.

ii. Peripheral Sympatholytic Agents

Although peripheral sympatholytic agents such as rawolfia alkaloids (reserpines) show excellent antihypertensive effects, the frequency of their use is decreasing because of adverse effects such as nasal obstruction, depression, and gastric ulcer due to gastric hypersecretion.

h. Classic Vasodilators

Classic vasodilators act directly on vascular smooth muscle and produce an antihypertensive effect by inducing vasodilation. The frequency of their use has decreased, but hydralazine is used today with methyldopa or β-blockers for the treatment of hypertension during pregnancy possibly as the only exception.

Their adverse effects are hot flushes, palpitation, and headache associated with vasodilation, and systemic lupus erythematosus (SLE)–like symptoms may be observed when they are used at a large dose.

3) Designated Health-Promoting Foods

Designated health-promoting foods are prepared by adding components that improve the physical condition, the health-promoting effects of which have been medically and nutritionally demonstrated, and the uses and effects of which have been approved by the Minister of Health, Labor and Welfare. Components useful for the control of the blood pressure include peptides such as caseine dodecapeptides, sardine peptide, dried bonito oligopeptide, and lactotripeptide and *tochu* leaf derivatives (geniposid acid), and they are contained in products such as Amyl S, Peptide Soup, and *Tochu* 120. The antihypertensive effects of these foods are often based on ACE inhibition, and their ingestion in quantities larger than is indicated should be avoided.

Summary

1) In the use of antihypertensive drugs, characteristics and adverse effects of each drug should be well realized, and select the drug most appropriate for the condition of each patient.
2) Major antihypertensive drugs in clinical use are Ca antagonists, ARBs, ACE inhibitors, low-doses of diuretics, β-blockers, and α-blockers. There are situations that warrant the use of particular classes of antihypertensive drugs.
3) Use long-acting antihypertensive drugs to obtain a consistent antihypertensive effect for 24 h.
4) A combination of 2 or more drugs is often necessary to attain the target of blood pressure control. A diuretic should be added as the third drug, in principle, when the blood pressure cannot be reduced sufficiently by a combination of 2 drugs not including a diuretic.
5) If the target of blood pressure control cannot be attained, consult a hypertension specialist (FJSH).

6. Hypertension Associated with Organ Damage

1) Cerebrovascular Disease

In Japan, cerebrovascular disease accounts for a high percentage of hypertensive target organ damage, and hypertensive patients with cerebrovascular complications are expected to increase further due to progressive aging of the population. In this sense, the PROGRESS (*106*), which was the first full-scale study to evaluate the preventive effect of antihypertensive treatment on recurrence in patients with a history of cerebrovascular disease, was very significant. Also, since a high percentage of elderly hypertensive patients are known to have asymptomatic cerebrovascular disease, the correct therapy for hypertensive patients with asymptomatic cerebrovascular complications is another very important problem. Furthermore, thrombolytic therapy has been established as a routine approach to cerebral infarction during the hyperacute period, particularly in Western countries, so antihypertensive treatment in the acute period has also become an important clinical issue and this problem is discussed in the Guidelines for the Management of Stroke 2004 (*186*).

a. Acute Phase

The blood pressure is increased within 1–2 weeks after stroke regardless of whether the patient has cerebral hemorrhage or cerebral infarction. The increase of blood pressure associated with the onset is considered to be due to protective responses of the body to factors such as stress, urinary retension, headache, brain ischemia, and increased intracranial pressure due to edema and hematoma. In many patients, high blood pressure resolves within a few days without antihypertensive medication as a result of bed rest, bladder catheterization, pain control, and treatment of cerebral edema (*187*, *188*).

Autoregulation of the cerebral blood flow is shifted to the right by hypertension (*189*), but autoregulation fails in the acute phase of stroke and cerebral blood flow decreases along with even a slight decrease of the systemic blood pressure. Thus, the regional cerebral blood flow at the ischemic focus and the penumbra around it (a region of reversible damage where functional recovery may occur with recovery of blood flow) decreases further with a decrease of the systemic blood pressure, possibly resulting in enlargement of the zone of tissue loss (infarction) (*190*). Since the ischemic zone is affected by vasospasm, drugs with a vasodilatory action may cause so-called intracerebral steal, *i.e.*, dilation of vessels in normal areas alone that causes a decrease of blood flow at the ischemic focus. For these reasons, aggressive antihypertensive treatment is not performed during the acute phase of stroke, in principle (Fig. 6-1) (*191*).

However, severe hypertension should be treated even in the acute phase, although data concerning the appropriate blood pressure at which treatment should be started are insufficient (*192*). Moreover, performance of antihypertensive treatment immediately after the onset should be done carefully with frequent assessment of neurological signs and symptoms after making a reasonable differential diagnosis of stroke, except when hypertensive encephalopathy or subarachnoid hemorrhage is strongly suspected. The blood pressure should be measured twice at an interval of 5 min or longer, and if the diastolic blood pressure remains at 140 mmHg or higher, emergency antihypertensive treatment should be started with intravenous agents (*193*). If the diastolic blood pressure is less than 140 mmHg, the blood pressure should be measured at least twice at an interval of 20 min or more after the patient has rested. In patients with cerebral infarction, antihypertensive treatment should be commenced if the blood pressure is 220/120 mmHg or higher or the mean blood pressure is 130 mmHg or higher (*188*). Unfortunately, these criteria are not based on sufficient evidence. In the Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) (*194*), patients received the ARB candesartan for 1 week if they had cerebral infarction within 36–72 h after the onset, motor paralysis, and a systolic blood pressure of 200 mmHg or more, a diastolic blood pressure of 110 mmHg or more, a mean systolic blood pressure (2 measurements) of 180 mmHg or more, or a mean diastolic blood pressure (2 measurements) of 105 mmHg or more. As a result, there was no significant difference in the outcome of stroke (the primary endpoint), but the mortality rate and the occurrence of cardiovascular events up to 1 year after the onset (the secondary endpoints) were significantly reduced in the candesartan group compared with the placebo control group (the relative risk was reduced by 48%). Although ACCESS investigated a relatively small number of patients with limited varieties of cerebral infarction (mainly lacunar infarction), these results indicate the importance of planning and performing clinical trials on antihypertensive

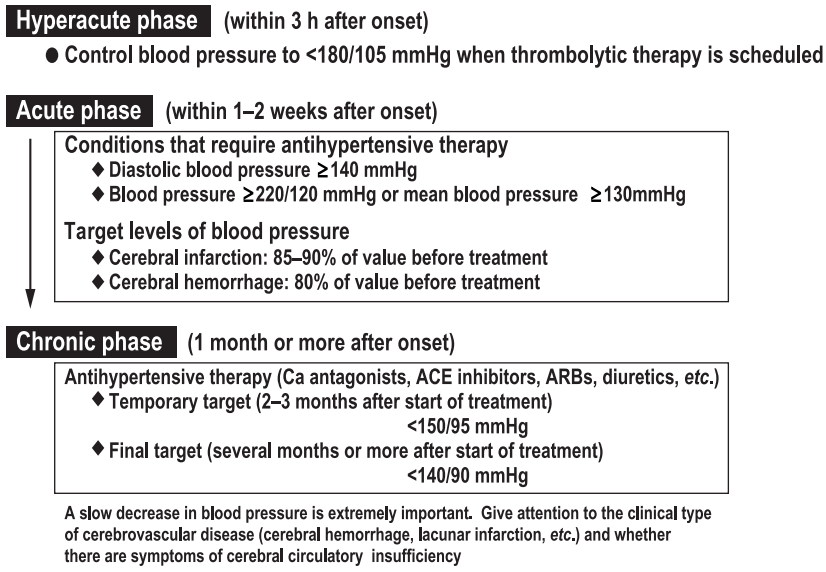

Fig. 6-1. *Treatment for hypertension complicated by cerebrovascular disease.*

therapy during the acute phase of infarction.

In patients undergoing thrombolytic therapy with intravenous injection of tissue plasminogen activator (t-PA) during the hyperacute phase within 3 h after the onset, intravenous antihypertensive treatment is necessary when the systolic blood pressure is 180 mmHg or more or the diastolic blood pressure is 105 mmHg or more, and maintenance of the systolic blood pressure below 180 mmHg and the diastolic blood pressure below 105 mmHg by careful management for 24 h during and after t-PA therapy is required (*186*, *195*).

The treatment of cerebral hemorrhage is more controversial, and sufficient evidence is not available. However, in the Guidelines for the Management of Stroke 2004 (*186*), antihypertensive therapy is not considered necessary when the systolic blood pressure is less than 180 mmHg and the diastolic blood pressure is less than 105 mmHg, but is recommended when the systolic blood pressure remains at 180 mmHg or more, the diastolic blood pressure remains at 105 mmHg or more, or the mean blood pressure remains at 130 mmHg or more for at least 20 min, following the European and American guidelines (*187*, *188*).

Short-acting drugs with a readily adjustable dosage are the appropriate antihypertensive medications. In Western countries, intravenous injection of the αβ-blocker labetalol or the ACE inhibitor enalapril is recommended. In Japan, however, intravenous preparations of these drugs are not available, so low-dose intravenous infusion of the Ca antagonists nicardipine or diltiazem is a choice of therapy, or conventional drugs such as nitroglycerin and nitroprusside are used. Paying attention to the possibility that these drugs may increase the intracranial pressure is necessary. In Japan, "incomplete hemostasis after intracranial hemorrhage and increased intracranial pressure in the acute phase of stoke" are mentioned as contraindications for Ca antagonists such as nicardipine and nilvadipine. Also, sublingual administration of nifedipine capsules must be avoided, because this may cause a rapid decrease of the blood pressure. The target blood pressure varies according to the type of stroke; it should be 85–90% of the pretreatment level in patients with cerebral infarction and 80% of the pretreatment level in those with cerebral hemorrhage. If hemorrhagic infarction, acute myocardial infarction, heart failure, or aortic dissection is present, more aggressive antihypertensive treatment will be necessary. Also, parenteral treatment should be switched to oral therapy as soon as possible.

Rehabilitation from an early phase is necessary to improve the ADL of stroke patients, and the blood pressure should be monitored carefully during bedside rehabilitation to detect any associated changes.

b. Chronic Phase

Stroke is known to occur far more frequently in patients with a previous history of this condition than in those with no history. Therefore, appropriate control of hypertension, which is the main risk factor for stroke, is extremely important for the management of these patients in the chronic phase. The results of retrospective studies performed in Japan have suggested that marked differences exist among stroke types with respect to the relationship between the blood pressure after stroke and the recurrence rate, and it has been reported that a J-curve was observed for the relation between recurrence and the diastolic blood pressure in patients with cerebral infarction but not in patients with cerebral hemorrhage (*196*). However, metaanalysis of 6,752 patients by collaborators of the Individual Data Analysis of Antihypertensive Intervention

Trials (INDANA) (*197*), summarizing 9 clinical trials on antihypertensive treatment in patients with a history of stroke, indicated a significant decrease (28%) in the relative risk of recurrence for the group receiving antihypertensive treatment compared with the untreated group. In this context, the PROGRESS trial (*106*) involved many Japanese researchers and was extremely important.

In the PROGRESS trial, the relative risk of recurrent stroke, which was the primary endpoint, was reduced by 28% in the perindopril group (more than half of the patients in this group were also on diuretic therapy) compared with the placebo group. Concerning the secondary endpoints, a 26% reduction of cardiovascular events was also demonstrated, although this effect was greater in patients with cerebral hemorrhage (the odds ratio was 0.50 for cerebral hemorrhage *vs*. 0.76 for ischemic stroke). In addition, the occurrence of dementia, severe cognitive disorder (*198*), and impairment of ADL or disability requiring care was significantly reduced in patients with recurrent stroke by perindopril treatment (*199*). Moreover, this drug reduced the occurrence of lacunar infarction, cardiogenic cerebral embolism, and atherothrombotic cerebral infarction, which are the 3 major clinical varieties of ischemic stroke, by 23%, 23%, and 39%, respectively, and its preventive effect on atherothrombotic cerebral infarction was statistically significant (*200*). In the PROGRESS CT substudy performed in Japan, there was no significant difference in the frequency of asymptomatic cerebral infarction or brain atrophy between the two groups, and the diastolic blood pressure at enrollment was shown to be an independent risk factor for these conditions (*179*).

The above results established that recurrence of stroke could be reduced by 28% over 4–5 years through a sustained reduction of the blood pressure from the initial level of 147/86 mmHg to about 138/82 mmHg due to administration of perindopril (4 mg/day) and/or the diuretic indapamide (2 mg/day) in addition to conventional therapy in patients with a mean age of 64 years, thus emphasizing the importance of blood pressure control during the chronic phase.

Antihypertensive treatment is usually started in the chronic phase at 1 month or more after the onset of stroke. The temporary blood pressure target is to achieve a level of less than 150/95 mmHg by 2–3 months after the start of treatment, taking factors such as the patient's age into consideration. A level below 140/90 mmHg would be a reasonable final target for all stroke types. Maintaining the blood pressure at a slightly lower level is desirable in patients with cerebral hemorrhage or lacunar infarction (*201*).

The blood pressure should be reduced gradually to the temporary target over 2–3 months at a minimum. If the patient complains of dizziness, unsteadiness, tiredness, heavy headedness, numbness, weakness, reduced volition, or exacerbation of neurological signs and symptoms during treatment, cerebral circulatory insufficiency due to the medication is possible, and decreasing the dose or changing the drug will be necessary. If the temporary target can be attained safely, whether or not the blood pressure should be reduced further must be determined, and the blood pressure should then be lowered to the final target over several months, if this is necessary.

Table 6-1. Acute Effects of Various Antihypertensive Agents on Cerebral Circulation and Metabolism

Antihypertensive	Cerebral blood flow	Lower limit of autoregulation of cerebral circulation	Cerebral metabolism
Ca antagonists	↑	↓	→
ACE inhibitors	→↑	↓	→
α-Blockers	→↑	↓	
β-Blockers	↓ (↑)*	→↑ (↓)*	↓
Diuretics	↓		
ARBs	→↑	↓	

↑, increase; ↓, decrease; →, no change. *Vasodilator type β-blockers.

Drugs should be selected in consideration of their effects on cerebral hemodynamics. Table 6-1 shows the major acute effects of various antihypertensive agents on cerebral blood flow and cerebral metabolism. In addition to the combination of an ACE inhibitor and a low-dose diuretic, which was shown to be useful by PROGRESS, ARBs and long-acting Ca antagonists are suggested to be markedly effective for the prevention of stroke and dementia.

c. Asymptomatic Phase

Diagnosis of asymptomatic cerebrovascular disease has increased markedly due to improvement of imaging techniques such as CT and MRI. The diagnostic criteria for asymptomatic cerebrovascular disease issued in 1997 (*202*) are still used. Asymptomatic cerebrovascular disease is classified into cerebral parenchymal lesions or cerebral vascular lesions on imaging studies. In relation to hypertension, however, most attention is focused on asymptomatic cerebral infarction, which accounts for the majority of the cerebral parenchymal lesions. Asymptomatic cerebral infarcts are mainly small lesions similar to lacunar infarcts and are considered to be a manifestation of small vessel disease, for which hypertension and aging are the most important risk factors. The presence or progression of such infarcts are independent risk factors for the occurrence of stroke, decreased cognitive function, and dementia according to studies performed in Japan and abroad (*186*, *203–206*), and the correct approach to this condition will be extremely important for the future treatment of hypertension. Asymptomatic cerebral infarction has been reported to resemble cardiogenic cerebral embolism or atherothrombotic cerebral infarction in not a few patients, and its treatment with clarification of the etiological mechanism is recommended as in the case of symptomatic

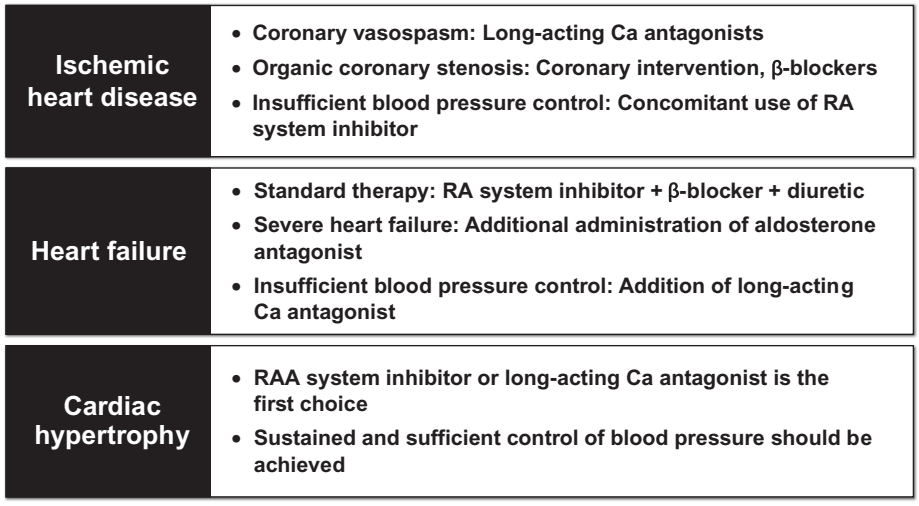

Fig. 6-2. *Treatment for hypertension complicated by heart disease. RAA system, renin-angiotensin-aldosterone system.*

cerebral infarction. Frequent detection of asymptomatic cerebral hemorrhage (microhemorrhage) by T_2-weighted MRI has also attracted attention (*203*, *207–209*). In principle, the target blood pressure for treatment of hypertensive patients with asymptomatic cerebral infarction or cerebral hemorrhage and the suitable drugs for this purpose are the same as those for chronic cerebrovascular disease, but the results of the PROGRESS CT substudy suggest that more effective treatment is needed (*179*).

In addition, the detection of asymptomatic carotid artery stenosis and unruptured cerebral aneurysms has also increased, and patients with these conditions have been identified as a high-risk group for stroke (*186*, *203*). Because the significance of antihypertensive therapy for these conditions has not been established, it is important to evaluate the need for surgical treatment before starting drug therapy.

Since patients with asymptomatic cerebrovascular disease show marked anxiety about this condition and its treatment, obtaining their informed consent is important (*203*).

2) Heart Diseases

The heart is one of the important target organs of hypertension. The pressure loads during systole and diastole induce cardiac hypertrophy and increase the risk for coronary atherosclerosis. Cardiac hypertrophy and coronary atherosclerosis lead to ischemic heart disease, heart failure, arrhythmia, and sudden death. Heart diseases are the most frequent among complications of hypertension and account for 25% of all complications according to a follow-up study of Japanese hypertensive patients receiving drug therapy (*210*). The concurrence of risk factors such as hyperlipidemia, diabetes mellitus, and smoking with hypertension has been suggested to increase ischemic heart disease, heart failure, and sudden death by a study in Japan (*211*). Sufficient control of hypertension (to less than 140/90 mmHg) is important to reduce the mortality rate due to cardiovascular diseases and the incidence of cardiovascular events (*109*, *212*) (Fig. 6-2).

a. Ischemic Heart Disease

The incidence of ischemic heart disease is increased by hypertension, but it is reduced only slightly by conventional antihypertensive medications consisting primarily of diuretics and β-blockers (*213*). Since the incidence of stroke has been reduced markedly by antihypertensive medication, risk factors other than hypertension may play relatively important roles in ischemic heart disease. Recent studies suggested that Ca antagonists and inhibitors of the RA system (ACE inhibitors and ARBs) also reduce the incidence of ischemic heart disease (*107*, *174*, *214*, *215*). Studies performed in Japan have also shown, though in small numbers of patients, that ARBs and Ca antagonists prevent cardiovascular diseases in patients with coronary artery diseases similarly to ACE inhibitors (*169*, *216*, *217*). For the control of the occurrence and progression of ischemic heart disease, treatment for not only hypertension but also other risk factors is important. Particularly, the treatment for hyper-LDL-cholesterolemia with an 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor has been reported to be effective for the primary and secondary prevention of cardiac events due to ischemic heart disease (*218*). A small dose of aspirin (*79*) and stopping smoking are also effective.

i. Angina Pectoris

For the treatment of hypertension complicated by angina pectoris, Ca antagonists and β-blockers, which have anti-anginal effects, are the first choices. Angina pectoris may be caused by significant organic coronary stenosis or coronary vasospasm, or, not infrequently, by both. Since angina pectoris

due to coronary vasospasm responds markedly to Ca antagonists, Ca antagonists are the first choice for the treatment of hypertension complicated by angina pectoris at rest or rest and effort angina, in which coronary vasospasm is considered to be involved. Both β-blockers and Ca antagonists are effective for the treatment of effort angina due to organic coronary stenosis. In Japan, the frequency of angina pectoris related to coronary vasospasm is high. β-Blockers have been suggested to exacerbate coronary vasospasm. Thus, a Ca antagonist alone or in combination with a β-blocker is recommended when the mechanism of angina pectoris is unclear.

All Ca antagonists are effective as anti-anginal drugs, but long-acting Ca antagonists are more appropriate, because (1) they less frequently cause reflex tachycardia associated with a decrease in the blood pressure, and (2) the administration need not be timed for the occurrence of angina pectoris. Short-acting Ca antagonists may induce myocardial ischemia due to a rapid decrease in blood pressure or reflex tachycardia in patients with significant coronary stenosis. However, 1–2 weeks are needed before some long-acting Ca antagonists begin to produce a sufficient anti-anginal effect. In such a case, a short-acting drug is necessary only in an early stage of treatment. This is different from the treatment for hypertension, in which the rapid antihypertensive effect may not be needed.

Since the anti-anginal effect of β-blockers is derived primarily from their bradycardiac effect, those that have no ISA must be selected for the treatment of angina pectoris. There is no marked difference in the anti-anginal effect between selective β_1-blockers and non-selective β-blockers.

In patients with angina pectoris due to significant coronary stenosis, caution is necessary in the introduction of antihypertensive therapy, because an excessive decrease in the blood pressure may induce anginal attacks. If the patient has an indication for coronary intervention, sufficient antihypertensive therapy should be introduced after resolving anginal symptoms and signs of ischemia by bypass surgery or percutaneous transluminal coronary angioplasty.

ii. Old Myocardial Infarction

Large-scale clinical trials in Western countries have clarified that β-blockers with no ISA significantly reduce the recurrence of myocardial infarction and sudden death in patients with old myocardial infarction (*219*, *220*). In Japan, the frequency of the use of β-blockers is low, partly because of the high incidence coronary vasospasm. β-Blockers are a possible choice for patients with old myocardial infarction having significant organic coronary lesions. However, long-acting Ca antagonists do not exacerbate the outcome (*109*). Also, there is a report that diltiazem, a Ca antagonist, reduced the recurrence of myocardial infarction in patients with non-Q wave infarction with no heart failure (*221*). According to most follow-up studies performed in Japan, β-blockers and long-acting Ca antagonists reduced the incidence of cardiac events, but short-acting Ca antagonists tended to exacerbate it (*169*, *222*, *223*).

In patients with reduced left ventricular contractility due to extensive myocardial infarction (ejection fraction ≤40%), RA system inhibitors have been shown to suppress left ventricular remodeling (ventricular dilation, myocardial hypertrophy, interstitial fibrosis) and to subsequently reduce the incidences of heart failure and sudden death (*224*, *225*). Ventricular remodeling has been suggested to play a very important role in the progression of myocardial damage and the occurrence and exacerbation of heart failure. Left ventricular dilation and left ventricular systolic dysfunction due to myocardial infarction are good indications for RA system inhibitors. Moreover, the addition of a selective aldosterone antagonist to a RA system inhibitor, a β-blocker, and a diuretic has been reported to further improve the outcome of patients with low cardiac function after myocardial infarction (*226*).

b. Treatment for Heart Failure Using Antihypertensive Drugs

Although hypertension has been shown to be the most frequent underlying disease of heart failure by epidemiological studies in Western countries, there has not been a comparable study in Japan. Also, large-scale clinical trials have shown that antihypertensive treatment reduces the incidence of heart failure in hypertensive patients (*227*). However, patients with heart failure often have a normal or low blood pressure. Therefore, in patients with heart failure, antihypertensive drugs are not necessarily used for reducing the blood pressure but are used primarily for improving their QOL or the outcome.

i. Heart Failure Due to Left Ventricular Systolic Dysfunction

RA system inhibitors improve the long-term outcomes of chronic heart failure and myocardial infarction and reduce the frequency of hospitalization due to heart failure regardless of symptoms of heart failure or the magnitude of the left ventricular dysfunction (*225*, *226*, *228–233*). β-Blockers improve the outcome of patients with heart failure and reduce the frequency of hospitalization regardless of symptoms (*220*, *234–237*). Diuretics are used for the treatment or prevention of organ congestion. Therefore, a combination of a RA system inhibitor + a β-blocker + a diuretic is a standard regimen for the treatment of heart failure (*238*). Aldosterone antagonists further improve the outcome of patients with severe heart failure receiving the standard treatment (*182*, *226*).

In large-scale clinical trials, RA system inhibitors and β-blockers, which have been shown to improve the outcome of heart failure, have been used in larger doses than they are used for the treatment of hypertension. However, as the RA system is activated in heart failure, RA system inhibitors produce marked antihypertensive effects. Therefore, their administration should be started at a low dose (*e.g.*, 1/4–1/2 of a conventional dose for hypertension treatment), and the dose should be increased gradually by confirming the absence of

adverse effects such as hypotension and deterioration of renal function. Also, β-blockers should be introduced after using RA system inhibitors regardless of the severity of heart failure, but they must be introduced with utmost caution, because they may exacerbate heart failure. In patients with reduced cardiac function, their administration should be started at a very low dose (1/8–1/4 of the dose for the treatment of hypertension), and the dose should be increased slowly by confirming the absence of heart failure, bradycardia, and hypotension.

In patients with hypertension complicated by heart failure due to left ventricular systolic dysfunction, the control of hypertension is important for the treatment of heart failure, because hypertension suppresses left ventricular systolic function, which is markedly affected by afterload in heart failure. Also, as hypertension promotes left ventricular remodeling and exacerbates myocardial damage, treatment for hypertension is important for improving the long-term outcome. Amlodipine has been shown not to exacerbate the outcome of patients with heart failure (*109*, *239*). Therefore, a long-acting dihydropyridine Ca antagonist should be added if blood pressure control is insufficient despite the standard regimen for heart failure.

ii. Heart Failure Due to Diastolic Dysfunction

It has been revealed that systolic function is normal, and diastolic dysfunction is the primary cause of heart failure, in about a half of the patients hospitalized due to heart failure. The most frequent underlying disease is hypertensive heart disease, and its frequency is high in elderly patients and women, in particular. In patients with hypertensive heart diseases, impairment of left ventricular diastolic function is observed from an early stage due to cardiac hypertrophy and myocardial fibrosis. Therefore, treatment for hypertension is expected to alleviate cardiac hypertrophy and myocardial fibrosis and to reverse diastolic dysfunction. As tachycardia, particularly atrial fibrillation, induces heart failure, its prevention and appropriate control of the heart rate are important. Moreover, the possibility of diastolic dysfunction due to latent ischemic heart disease must be considered. Although there are not many references concerning the treatment for heart failure due to diastolic dysfunction, ARBs reduce the frequency of hospitalization of heart failure patients with preserved systolic function (*233*).

c. Cardiac Hypertrophy

Cardiac hypertrophy is caused by a pressure load and is often reversed by sustained antihypertensive treatment. Epidemiological research has established that cardiac hypertrophy is an independent risk factor that determines the outcome of hypertensive patients. The mortality rate and incidences of cardiac events due to ischemic heart disease and heart failure are high in patients with cardiac hypertrophy (*87*). It has been reported that the incidence of cardiac events decreases in patients who show regression of cardiac hypertrophy due to treatment for hypertension compared with those who show no regression (*240*). Since both systolic hypertension and diastolic hypertension are involved as stimuli to induce myocardial hypertrophy, both hypertensions must be controlled for the treatment of cardiac hypertrophy.

There are few reports regarding the direct comparison of the abilities of various drugs to regress cardiac hypertrophy, but RA system inhibitors have been reported to have the strongest effect according to a metaanalysis (*241*). There is also a Japanese report that the addition of an aldosterone antagonist enhanced the ability of an ACE inhibitor to regress cardiac hypertropy (*242*). However, the most important factor for inducing regression of cardiac hypertrophy is a sufficient control of the blood pressure. Thus, regression of cardiac hypertrophy can be expected by sustained control of the blood pressure with long-acting Ca antagonists, which are widely used as the first choice antihypertensive drugs today in Japan (*243*).

3) Kidney Diseases

a. Renal Function and Blood Pressure

Hypertension exerts various functional or structural alterations on the kidney from an early stage. Kidney disorders, on the other hand, may cause hypertension. Hypertension and the kidney are closely related to each other. Hypertension impairs the renal function, impairment of the renal function exacerbates hypertension, and they form a vicious cycle. Therefore, strict management of the blood pressure as well as the treatment for the primary kidney disease are important.

The renal function decreases with aging after the third decade of life. The glomerular filtration rate (GFR) usually decreases at a rate of about 1 ml/min annually. The age-associated decrease in the renal function is linearly associated with the blood pressure, and the decrease in the GFR may reach 4–8 ml/min annually in hypertensive patients (*244*). In the Multiple Risk Factor Intervention Trial (MRFIT), no J-curve is observed in the relationship between the incidence of renal failure and the blood pressure, and the incidence of end-stage renal failure was lowest at the optimal blood pressure and increased with the blood pressure (*245*). In Japan, similar results were obtained by a study in which about 100,000 general population in Okinawa were followed up for 17 years (*246*). In both men and women, the relative risk increased by about 20–30% with an increase in the systolic or diastolic blood pressure of 10 mmHg equally in diabetic and non-diabetic individuals. Moreover, hypertension has been suggested to be a risk factor for the development of new-onset renal dysfunction by a sub-analysis of the Systolic Hypertension in Europe (Syst-Eur) Study (*247*) and by the report that in hypertensive patients whose kidney function was initially normal, new renal dysfunction occurred more frequently as the blood pressure during treatment was higher (*248*).

Table 6-2. Definition of Chronic Kidney Disease*

1. Structural or functional abnormalities: Abnormal findings on histological examinations, urinalysis, biochemical examinations, or imaging studies for a duration 3 months or longer regardless of GFR
2. GFR <60 ml/min/1.73 m^2 regardless of the primary disease

Cockcroft-Gault equation

$$Ccr^{\dagger}\ (ml/min) = \frac{(140 - age) \times body\ weight}{72 \times serum\ creatinine\ level}$$

($^{\dagger}\times 0.85$ in women)

*Adopted from 2002 NKF guidelines.

Chronic kidney diseases often cause no or few symptoms. Also, it is difficult to prevent the progression of advanced renal dysfunction to end-stage renal failure. Therefore, early detection and treatment of kidney diseases are important. The serum creatinine level is widely used for the evaluation of the renal function, but it is markedly affected by the body weight. The guidelines of the National Kidney Foundation (NKF) recommend the assessment of the renal function by estimating the GFR from the serum creatinine level, body weight, age, and gender (*249*). Table 6-2 shows a typical equation for the calculation. Chronic kidney disease is defined as an estimated GFR of less than 60 ml/min/1.73 m^2 or an abnormality of the kidney structure or function persisting for 3 months or longer independently of the GFR. Concerning the latter criterion, the importance of albuminuria is emphasized. The renal function can be assessed also in the outpatient clinic by calculating the ratio (mg/g creatinine [g Cr]) between the urinary protein (or albumin) level (mg/dl) and the urinary creatinine level (mg/dl) from the results of spot urinalysis.

b. Chronic Kidney Diseases and Cardiovascular Diseases

The mortality rate due to cardiovascular events is high in patients with chronic kidney diseases (*250*). While the incidence of cardiovascular events is known to be high in patients undergoing dialysis, renal dysfunction with a serum creatinine level of about 1.5 mg/dl (corresponding to an estimated GFR of less than 60 ml/min) has been shown to be a powerful risk factor for the occurrence of, and death due to, cardiovascular events in many cohorts including elderly, hypertensive, heart failure, and diabetic patients (*251–255*). Proteinuria is a strong risk factor for death due to cardiovascular events as well as a risk factor for end-stage renal failure (*256*, *257*). The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) showed that proteinuria is a risk factor comparable to a history of myocardial infarction (*257*). Also, while albuminuria has been established as an index suggestive of the progression of type 1 and type 2 diabetes mellitus to diabetic nephropathy, it has been reported to be a more powerful predictor for death due to cardiovascular events (*258*). Furthermore, albuminuria has been reported recently to be a risk factor for cardiovascular and non-cardiovascular death also in non-diabetic hypertensive patients and the general population (*259*, *260*). Patients with chronic kidney diseases are increasing due to the aging of the population and the increase in the prevalence of diabetes mellitus. Patients with chronic kidney diseases often have other cardiovascular complications. Therefore, patients in whom hypertension is complicated by proteinuria and moderate renal dysfunction should be treated as a high-risk group.

c. Lifestyle Modifications

It has been reported that obesity is related to end-stage renal failure and proteinuria and that proteinuria is reduced by weight control (*261*, *262*). Also, smoking has been shown to exacerbate proteinuria and renal dysfunction in patients with diabetic and non-diabetic nephropathy (*263*). Considering the fact that the risk for cardiovascular death is high in patients with chronic kidney diseases, the importance of maintaining an appropriate body weight and smoke cessation cannot be overemphasized.

Restriction of salt and protein intake is important for the management of blood pressure and prevention of the progression of renal dysfunction (*151*). Since salt sensitivity is often enhanced in hypertensive patients with kidney diseases, restriction of salt intake is expected to be particularly effective for reducing the blood pressure. Restriction of salt intake enhances the anti-proteinuric effects of ACE inhibitors and ARBs. The target salt intake should be 6 g/day or less in patients with chronic renal failure and 4–5 g/day or less in patients with complications such as refractory hypertension and edema. Restriction of protein intake has been shown to reduce the relative risk for the progression of renal failure and renal death (*264*). The protein intake should be restricted to 0.6–0.7 g/kg ideal body weight/day if the Ccr is 70 ml/min or less. Protein intake of 0.4–0.5 g/kg ideal body weight/day is reported to be recommendable if the Ccr is 30 ml/min or less.

Vigorous exercise or overworking that would reduce the renal blood flow should be avoided in patients with renal failure, and careful evaluation of indications of exercise therapy is necessary (*151*).

d. Antihypertensive Drug Treament (Fig. 6-3)

Renal function declines more rapidly as the blood pressure is higher (*244*), and therefore, the control of the blood pressure is the most important in renal failure. In the Modification of Diet in Renal Disease (MDRD) Study, the progression of renal dysfunction was shown to be slower in the group under strict blood pressure control than in the group with ordinary blood pressure control (*265*). According to a metaanalysis of 11 randomized controlled trials, the occurrence of end-stage renal failure and the doubling of serum creatinine level were

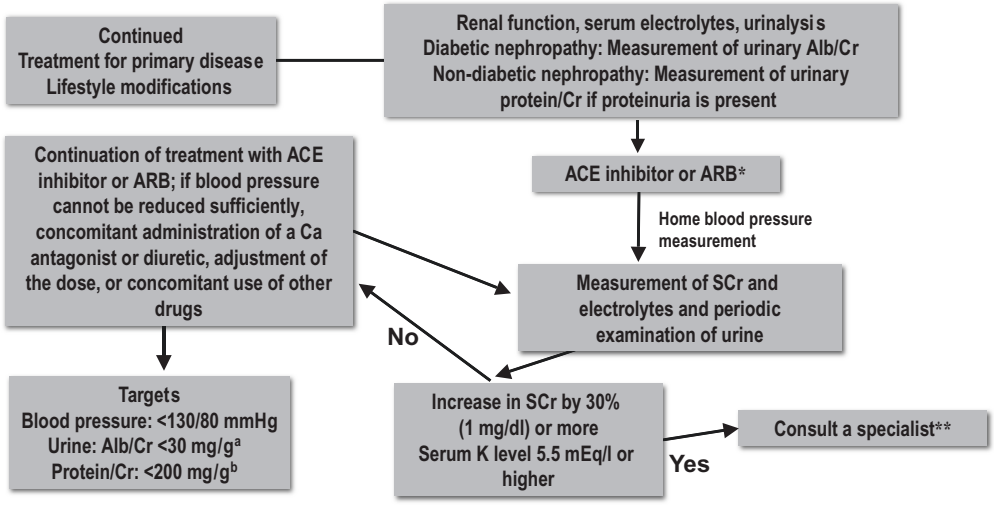

Fig. 6-3. *Therapeutic algorithm for hypertension complicated by chronic kidney disease. *Administration should be started at the minimum dose when serum creatinine level is 2.0 mg/dl or higher. **Causes: renal artery stenosis, NSAIDs, heart failure, dehydration, abnormality in urinary tract,* etc. *[a]Diabetic nephropathy. [b]Non-diabetic nephropathy. Alb/Cr, urinary albumin/creatinine ratio; SCr, serum creatinine.*

lowest when the systolic blood pressure was less than 130 mmHg (*266*). Therefore, the target of blood pressure should be set at less than 130/80 mmHg in patients with chronic kidney diseases. Moreover, according to the MDRD Study (*265*), the target should be less than 125/75 mmHg in patients with a urinary protein excretion of 1 g/day or higher. In the African American Study of Kidney Disease and Hypertension (AASK) Study, African Americans with nephrosclerosis were treated with β-blockers, Ca antagonists, or ACE inhibitors as basic drugs and with either an ordinary or strict target of blood pressure control (*267*). Although the percent decrease in the renal function showed no difference according to the strictness of blood pressure control, it was significantly lower in the group treated with ACE inhibitors than in the group treated with Ca antagonists. The renal protective effect of ACE inhibitors was particularly notable in patients with a high urinary protein level and those with reduced renal function (GFR <40 ml/min).

Proteinuria has long been considered as an index of glomerular and vascular damages, it is now considered to exacerbate the renal dysfunction by itself (*268–270*). In fact, it has been reported that reduction of proteinuria is closely related to inhibition of the progression of renal dysfunction (*271*). This effect is independent of the blood pressure. Therefore, it is important to reduce urinary protein or albumin excretion as close to the normal level as possible. For this purpose, the administration of ACE inhibitors or ARBs is necessary along with strict control of the blood pressure. The guidelines of the NKF set the target urinary albumin level at less than 30 mg/g Cr for patients with diabetic nephropathy and the target urinary protein excretion at less than 200 mg/g Cr for patients with non-diabetic nephropathy (*272*).

Inhibition of the RA system is effective for preventing or retarding the progression of renal dysfunction whether its cause is diabetic or non-diabetic renal disease (*273–276*). It is particularly effective in patients with marked proteinuria, but, according to metaanalyses (*273*, *275*, *276*), the renoprotective effect of ACE inhibitors cannot be explained by the decrease in blood pressure or urinary protein level alone. RA system inhibitors exhibit the antihypertensive and anti-proteinuric effects at different doses (*277*). Therefore, their doses should be determined on the basis of the urinary protein (albumin) as well as the blood pressure levels. In fact, in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA2) Study (*274*), progression from microalbuminuria to overt nephropathy occurred less frequently in the group treated with a high dose (300 mg/day) than a low dose (150 mg/day) of irbesartan. Also, a combination of an ACE inhibitor and an ARB is reported to be more effective than either drug alone for the treatment of non-diabetic nephropathy (*278*).

Since RA system inhibitors not only reduce the systemic blood pressure but also mitigate glomerular hypertension by dilating the efferent arterioles, they may reduce the GFR. However, this decrease in the GFR does not indicate the progression of renal tissue damage but is a functional change, because the GFR recovers with discontinuation of the administration (*279*). As there are reports that the renal function was well maintained over a longer period in patients who showed decreases in the renal function in an early phase of treatment, careful observation suffices in patients showing a mild increase in the serum creatinine level (up to 30% or 1 mg/dl).

Since decreases in the renal function appear within a few days after the beginning of the administration, the serum creatinine level should be checked before and within 2 weeks (1 week if possible) of administration. If exacerbation of the renal function is observed, its cause such as renal artery stenosis must be investigated (*280*). Increases in the serum K level are occasionally observed, and they should be managed by the addition of a diuretic or the administration of Na bicarbonate (*280*, *281*). The administration of non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, because they exacerbate renal dysfunction and increase serum K level. Adverse effects of RA system inhibitors are likely to appear in patients with advanced kidney disorders. However, RA system inhibitors are reported to exert greater effects as renal dysfunction is more advanced (*267*, *273*, *275*, *276*). Therefore, the administration of RA system inhibitors should be started at a low dose by monitoring the serum creatinine and K levels even when the serum creatinine level is 2 mg/dl or higher. Also, as ACE inhibitors, with some exceptions, are excreted through the kidney, their doses must be adjusted in patients with reduced renal function. On the other hand, the necessity of dose adjustment is less in ARBs, which are excreted in bile.

RA system inhibitors have been shown to be effective in patients with kidney diseases by many clinical trials, and ACE inhibitors or ARBs are the first choice for the treatment. Some studies reported that the effects of long-acting Ca antagonists were comparable to those of ACE inhibitors (*168*, *282*), but their renoprotective effects are based on their powerful blood pressure–lowering action regardless of the pathophysiology of the deseases (*82*). A multi-drug combination therapy is reported to be necessary for attaining the target blood pressure level in patients with renal dysfunction (*244*). Therefore, the blood pressure should be reduced sufficiently in an early stage by using multiple drugs. As the antihypertensive and anti-proteinuric effects of RA system inhibitors are enhanced by restriction of the salt intake, the concomitant use of a diuretic is often necessary. A low dose of a thiazide diuretic is effective, but a loop diuretic should be used when the serum creatinine level is 2.0 mg/dl or higher. Caution against electrolyte imbalance such as hypokalemia and dehydration is necessary during intensive diuretic treatment. Recently, aldosterone antagonists were reported to reduce proteinuria (*283*, *284*), but, because of the risk of hyperkalemia, they should be administered very cautiously in patients with renal dysfunction with careful evaluation of indications.

e. Patients Undergoing Dialysis

In patients undergoing dialysis, cardiovascular complications exert serious effects on the prognosis. The most frequent cause of death is heart failure, followed by infections and stroke (*285*). The blood pressure is an important prognostic factor in patients undergoing dialysis (*286–288*). Moreover, left ventricular hypertrophy is often observed in dialysis patients (*289*) and is considered to be an important prognostic factor (*290*). The frequency of hypertension in dialysis patients decreases as the duration of dialysis therapy becomes longer, and some patients develop hypotension. Therefore, it is important to adjust antihypertensive medication according to the patient's condition.

As for therapeutic principles, the volume-dependent increase in blood pressure must be controlled first. An appropriate dry weight (target weight necessary for the control of the body fluid volume) must be determined for each patient, and the patient should be instructed to control the inter-dialysis body weight gain within 5% of the dry weight.

Many patients undergoing dialysis have little urine output, and diuretics are ineffective. However, some patients excrete several hundred milliliters of urine per day even after the introduction of dialysis, in which case loop diuretics such as furosemide are used. Since a relatively large dose is often necessary, careful observation for adverse effects such as hearing disorders is needed.

If hypertension persists even after achieving an appropriate dry weight, antihypertensive medication becomes necessary. For the choice of medication, not only the mechanism of actions but also drug metabolism, excretion route, dialyzability and duration of action should also be considered. Also, if marked hypotension is observed during dialysis, modifications of the regimen such as skipping the administration in the morning on the days of dialysis are necessary.

In patients undergoing dialysis, a U-shaped relationship is observed between the blood pressure level and the survival rate, and the mortality rate is lowest when the systolic blood pressure is 120–160 mmHg (*286*, *287*). The reason for a high mortality rate in the group with a low blood pressure is considered to be due to increased deaths unrelated to cardiovascular events. Also, the prognosis is poorer as the pulse pressure is greater (*287*). There is no consensus concerning drugs that prevent cardiovascular events, but Ca antagonists (*291*), β-blockers (*292*), and ACE inhibitors (*293*, *294*) have been reported to be effective. Recently, ARBs were reported to be effective for inducing regression of cardiac hypertrophy (*295*, *296*).

To minimize changes in the blood pressure due to dialysis, non-dialyzable drugs should be selected. Changes in the blood pressure during dialysis have been reported to be small with Ca antagonists, which are non-dialyzable. Many ACE inhibitors are dialyzable, but some are not. ACE inhibitors may induce anaphylactic shock if a negatively charged dialyzer is used. This applies to polyacrilonitrile membrane dialyzers and dextran sulfate cellulose dialyzers, and ACE inhibitors are contraindicated under the use of such dialyzers. ACE inhibitors have been reported to exacerbate renal anemia and to increase the necessary dose of erythropoietin. ARBs are also non-dialyzable and are reported to be useful as antihypertensives for dialysis patients (*297*). Unlike ACE inhibitors, ARBs do not induce anaphylactic shock even the use of negatively charged dialyzers. α-Blockers, which are not dialyzable, are also effective, but orthostatic hypotension as their

adverse effect may interfere with dialysis. Many β-blockers are lipid-soluble and non-dialyzable. As β-blockers suppress the cardiac function, an attention to the possible occurrence of heart failure is necessary in patients undergoing dialysis. The caution for increases in the serum K level is also necessary.

4) Vascular Diseases

a. Aortic Aneurysm

i. Aortic Dissection

Acute aortic dissection is an emergency hypertensive disease that requires a prompt reduction of blood pressure. Antihypertensive treatment reduces the risk of progression of aortic dissection or rupture of the aorta (*298*). If aortic dissection is suspected, analgesic treatment using drugs such as morphine and immediate control of blood pressure should be performed before examinations such as CT and angiography. If the ascending thoracic aorta is involved (Stanford type A), the risk of rupture is high; surgical treatment in the acute period should be performed. If dissection is limited within the descending thoracic aorta (type B), antihypertensive treatment should be continued.

Intravenous administration of nitroglycerin, nitroprusside, nicardipine, or diltiazem is indispensable for achieving a prompt decrease in the blood pressure. Since drugs other than diltiazem increase the heart rate, β-blockers must be administered simultaneously either orally or intravenously. Heart rate is recommended to be controlled at 60–80 beats/min (*299*). The systolic blood pressure should be maintained at 110–120 mmHg or less unless hemodynamic disorders occur in the major organs such as the brain and kidney (*300*).

The treatment may be shifted to oral antihypertensive treatment after a few days if the condition is stable. Combination administration of multiple antihypertensive drugs is often necessary to maintain a sufficient decrease in blood pressure. The antihypertensive treatment should include a β-blocker if there is no contraindication.

Continuation of antihypertensive treatment is necessary in the chronic period of aortic dissection or after surgical treatment with a target systolic blood pressure of 120 mmHg or less.

ii. Aortic Aneurysm

Aortic aneurysms should be treated surgically when their diameters are large or rapidly increasing, and the risk of rupture is judged to be high. If hypertension complicates aortic aneurysm, blood pressure should be controlled as low as possible unless hemodynamic disorders occur in the major organs.

b. Atherosclerotic Peripheral Arterial Obstruction

Anti-platelet agents, anti-coagulants, and peripheral vasodilators are used for conservative treatment. If the condition is complicated by hypertension, Ca antagonists, ARBs, ACE inhibitors, and α-blockers with peripheral vasodilating actions are recommended.

Summary

Cerebrovascular Disease

1) In the acute phase of 1–2 weeks after the onset of stroke, the blood pressure is often increased regardless of whether the patient has cerebral hemorrhage or infarction. However, aggressive antihypertensive treatment is not performed, unless the systolic blood pressure is 220 mmHg or more, and the diastolic blood pressure is 120 mmHg or more, because such treatment may reduce blood flow in the lesion. In patients who receive thrombolytic therapy during the hyperacute phase within 3 h after the onset, it should be noted that the blood pressure must be maintained below 180/105 mmHg.
2) If hypertension persists for more than 1 month after a stroke, reduce the blood pressure to a temporary target level of less than 150/95 mmHg slowly over 2–3 months or longer. Then continue treatment with a final target of less than 140/90 mmHg. Treatment should be done by using an ACE inhibitor coupled with a low-dose diuretic, or a Ca antagonist or an ARB.
3) Concerning asymptomatic cerebrovascular disease, the treatment of hypertension associated with asymptomatic cerebral infarction and asymptomatic cerebral hemorrhage is the same as that associated with chronic stroke. In patients with asymptomatic carotid artery stenosis or unruptured cerebral aneurysm, the indications for surgical treatment should be evaluated before starting medical therapy. Obtaining informed consent is essential before treatment of such conditions.

Heart Diseases

1) Hypertension complicated by angina pectoris is a good indication for Ca antagonists and β-blockers with no ISA. The target of blood pressure control is less than 140/90 mmHg.
2) In patients after myocardial infarction, β-blockers, RA system inhibitors (ACE inhibitors, ARBs), and aldosterone antagonists reduce the mortality rate and improve the outcome.
3) In patients with heart failure, antihypertensives are used not for reducing blood pressure but for improvement of their QOL or outcome. Combination therapy using a RA system inhibitor + a β-blocker + a diuretic is a standard treatment for heart failure, which reduces the mortality rate and improves the outcome. However, in introducing a RA system inhibitor or a β-blocker, the dose should be adjusted carefully and slowly from a low dose by observ-

ing the patient for exacerbation of heart failure, hypotension, bradycardia (β-blockers), and renal dysfunction. Aldosterone antagonists further improve the outcome of patients with severe heart failure already given the standard treatment. Sufficient antihypertensive medication is important for the treatment of hypertension complicated by heart failure, and a Ca antagonist should be added if the control of the blood pressure is insufficient.

4) Regression of cardiac hypertrophy has been suggested to be associated with an improvement in the outcome. Although any antihypertensive drug is expected to induce regression of cardiac hypertrophy when sufficient and stable control of the blood pressure is achieved, the effects of RA system inhibitors and long-acting Ca antagonists are the best for this purpose.

Renal Diseases

1) The risk for cardiovascular events is high in hypertensive patients with chronic kidney diseases, and early detection of renal damages is extremely important. Urinalysis and estimation of the GFR are useful for early detection.
2) Hypertension and proteinuria are both important risk factors that promote the progression of kidney deseases, and their control is extremely important for improving the outcome of renal failure.
3) For lifestyle modifications, restriction of salt and protein intake is important, and vigorous exercise and overworking should be avoided in patients with renal failure.
4) The target of blood pressure control is less than 130/80 mmHg.
5) ACE inhibitors and ARBs reduce proteinuria and exert renoprotective actions. When the serum creatinine level is 2.0 mg/dl or above, they should be used from a low dose with careful monitoring of the serum creatinine and K levels. Diuretics are indispensable when there is a tendency of body fluid retention, and loop diuretics should be used when the serum creatinine level is 2.0 mg/dl or above.
6) In selecting antihypertensives for patients undergoing dialysis, attention should be paid to metabolism, excretion routes, and dialyzability of the drugs.

7. Hypertension Complicated by Other Diseases

1) Diabetes Mellitus

In diabetic patients, the blood pressure should be measured in the supine and upright positions in addition to the sitting position, because some patients exhibit orthostatic hypotension. The prevalence of hypertension in diabetic patients is about 2 times higher than that in non-diabetic individuals in Japan (*301*). Also, the prevalence of diabetes in hypertensive patients is 2–3 times higher than that in normotensive individuals (*302*), and an etiologic relationship between the two conditions has been suggested. That is, type 2 diabetes mellitus and hypertension are considered to have insulin resistance as a common background and to be major factors of metabolic syndrome.

Microvascular complications of diabetes mellitus include nephropathy, neuropathy, and retinopathy, which are disorders that may not only cause serious functional impairment but also affect the survival as well as the QOL. Both diabetes mellitus and hypertension are important risk factors for macrovascular complications due to atherosclerosis, and their combination is known to markedly increase the incidences of cerebrovascular diseases and ischemic heart disease (*302*). Therefore, in patients with hypertension complicated by diabetes mellitus, strict management of the blood pressure as well as the blood glucose level is necessary to prevent and improve microvascular and macrovascular complications.

Concerning the level of blood pressure control in diabetic hypertensive patients, the HOT (*79*), a trial of antihypertensive medication using a Ca antagonist as the basic drug, reported that the risk for cardiovascular events was significantly reduced in the group managed with the lowest target diastolic blood pressure of 80 mmHg or less than in the groups managed with higher target diastolic blood pressures of 85 mmHg or less and 90 mmHg or less. Also, from the results of the United Kingdom Prospective Diabetes Study (UKPDS) (*303*) that the risk for macrovascular and microvascular complications could be more markedly decreased by reducing the mean blood pressure to 147/82 mmHg than to 157/87 mmHg and from the results of a clinical trial that demonstrated that antihypertensive medication was beneficial also in normotensive diabetic patients (*304*), setting the target of blood pressure control at a lower level is considered to lead to greater therapeutic effects in diabetic hypertensive patients. On the basis of these results, the therapeutic target of blood pressure level for diabetic hypertensive patients is set at a relatively low level, and the JNC VI, 1999 WHO/ISH guidelines, and JSH 2000 guidelines included a high-normal blood pressure, *i.e.*, 130/85 mmHg or higher, as an indication for antihypertensive treatment. However, the recommendation of the American Diabetic Association 2002 (*302*), JNC 7 (*29*), and 2003 ESH-ESC (*43*) guidelines set less than 130/80 mmHg as the target of blood pressure control on the basis of the results of the HOT (*79*) and UKPDS (*303*), unrelated to the categorization of high-normal blood pressure. In the Tanno-Sobetsu Study in Japan (*305*), the mortality rate due to cardiovascular events was significantly higher in patients with borderline diabetes mellitus or diabetes mellitus with a systolic blood pressure of 130 mmHg or higher and a diastolic blood pressure of 80 mmHg or higher than in those with an optimal blood pressure of less than 120/80 mmHg, supporting the target level of blood pressure control of less than 130/80 mmHg also for Japanese diabetic hypertensive patients. In patients with diabetic nephropathy, the blood pressure should be controlled strictly, and the target level of blood pressure should be 125/75 mmHg for patients in whom the urinary protein excretion is 1 g/day or higher.

When the blood pressure is 130/80 mmHg or higher, lifestyle modifications such as weight reduction and exercise therapy should be started, but antihypertensive medication should be introduced when the effects of lifestyle modifications are insufficient after 3–6 months. In patients with a blood pressure of 140/90 mmHg or higher, antihypertensive medication should be started simultaneously with lifestyle modifications. In non-drug therapies such as weight reduction and exercise therapy for hypertensive diabetic patients, the blood pressure is expected to decrease with improvements in glucose tolerance *via* improvements in insulin resistance.

In drug therapy for hypertension complicated by diabetes mellitus, sufficient consideration to the effects of each antihypertensive on insulin sensitivity, glucose metabolism, and lipid metabolism is necessary. Diuretics and β-blockers have been reported to reduce the insulin sensitivity and to increase the triglyceride level. β-Blockers also mask the symptoms of hypoglycemia in diabetic patients, and disadvantages of both drugs with regard to glucose metabolism have been reported. Since ACE inhibitors (*304*), ARBs (*306*), and long-acting

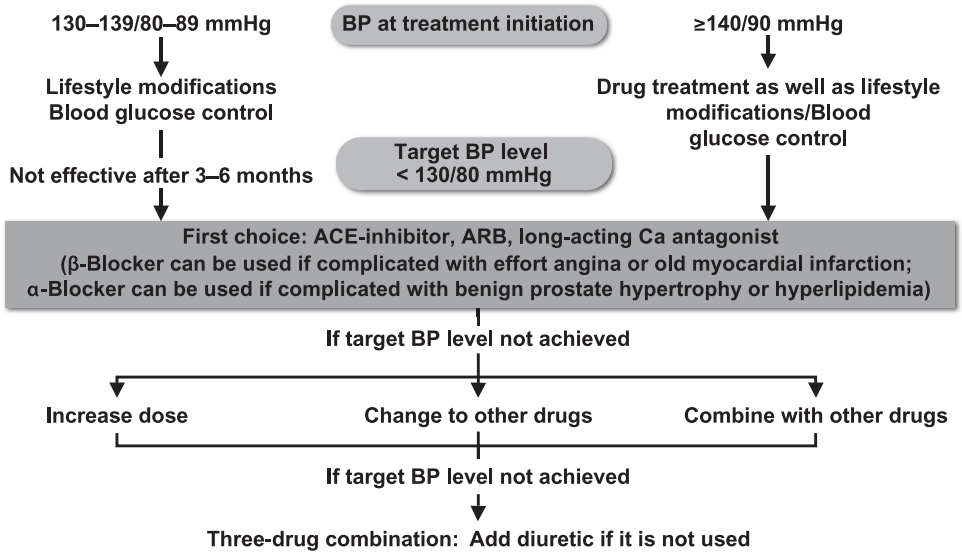

Fig. 7-1. *Treatment plan for hypertension complicated by diabetes.*

dihydropyridine Ca antagonists improve the insulin sensitivity and exert no effect on lipid metabolism, the use of drugs of these 3 classes is recommended. While α-blockers improve carbohydrate and lipid metabolism, there is no clear evidence of organ protection.

Concerning the preventive effects of various antihypertensives against complications in diabetic hypertensive patients, ACE inhibitors have been shown to prevent the progression of the renal dysfunction and reduce the frequency of the induction of dialysis therapy in patients with type 1 diabetes mellitus accompanied by proteinuria also in non-hypertensive patients (*307*). The Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetes (J-MIND) Study (*168*) performed in Japan showed that Ca antagonists and ACE inhibitors have comparable effects on proteinuria and renal function in patients with type 2 diabetic nephropathy, and UKPDS (*303*) showed that ACE inhibitors and β-blockers equally prevent microvascular complications in diabetic hypertensive patients. Concerning the effects of ARBs on type 2 diabetic nephropathy, their effectiveness has been demonstrated recently by the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) (*83*), Irbesartan Diabetic Nephropathy Trial (IDNT) (*273*), IRMA2 (*274*), and Microalbuminuria Reduction with Valsartan (MARVAL) (*308)*. Thus, as the usefulness of ACE inhibitors and ARBs for the treatment of diabetic nephropathy is evident, it is recommended to treat with ACE inhibitors or ARBs when they have microalbuminuria regardless of the presence or absence of hypertension.

Concerning the prevention of cardiovascular events in diabetic hypertensive patients, the Captopril Prevention Project (CAPPP) (*309*) demonstrated the usefulness of ACE inhibitors, and the HOT (*79*) and Syst-Eur (*310*) clarified the usefulness of Ca antagonists. However, treatments using an ACE inhibitor or a β-blocker as the basic drug were comparable in the UKPDS (*303*), and ARBs and Ca antagonists were nearly equally effective in the IDNT (*273*), for improving the outcome of macrovascular complications in patients with type 2 diabetes. In the LIFE (*116*), ARBs significantly prevented cardiovascular events compared with β-blockers. Thus, ACE inhibitors, ARBs, and Ca antagonists have been confirmed to be useful for the prevention of cardiovascular events in diabetic hypertensive patients. Concerning comparisons between ACE inhibitors and Ca antagonists, their preventive effects have been evaluated in the Appropriate Blood Pressure Control in Diabetes Trial (ABCD) (*311*) and the Fosinopril *versus* Amlodipine Cardiovascular Events Randomized Trial (FACET) (*312*), though both of them were small-scale studies. While ACE inhibitors were suggested to be more useful than Ca antagonists in these studies, no difference was observed between them by sub-analysis of the ALLHAT (*109*), and further evaluation is necessary before differences in the effects of ACE inhibitors and Ca antagonists on macrovascular complications can be clarified.

Concerning the selection of antihypertensive drugs for diabetic hypertensive patients, an ACE inhibitor, ARB, or long-acting dihydropyridine Ca antagonist is recommended as the first choice on the basis of their effects on glucose and lipid metabolism and preventive effects on complications. Also, in patients with angina on effort and old myocardial infarction, β-blockers are also usable for the protection of the heart. Since α-blockers improve the insulin resistance and the lipid metabolism and are used as a treatment for benign prostate hypertrophy, they can be used as the first choice for the treatment of hypertension complicated by hyperlipidemia or prostate hypertrophy. However, attention to orthostatic

hypotension is necessary if there is diabetic neuropathy. Figure 7-1 shows the therapeutic guidelines of hypertension complicated by diabetes mellitus.
(This manuscript has been approved by the Joint Guidelines Evaluation Committee of the Japanese Society of Hypertension and Japan Diabetes Society.)

2) Hyperlipidemia

Since a combination of hypercholesterolemia and hypertension is known to increase the risk for atherosclerosis also from the results of the Japan Lipid Intervention Trial (J-LIT) in Japan (*313*), aggressive management of both diseases is necessary in such patients. The results of recent clinical trials such as the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) (*314*) suggest that the primary and secondary prevention of ischemic heart disease and stroke can be expected in patients with hypercholesterolemia complicated by hypertension by aggressive serum cholesterol reducing therapy, and more strict management of the cholesterol level has been proposed for patients when hyperlipidemia is complicated by other risk factors including hypertension by Japanese Guidelines for the Management of Hyperlipidemia. In patients with a high serum cholesterol level and a high blood pressure, lifestyle modifications, *i.e.*, weight reduction, restriction of the intake of saturated fatty acids, cholesterol, and alcohol, and increase in the physical activity, should be strongly instructed first. If hypercholesterolemia is not alleviated by non-pharmacological therapy, drug therapy primarily with an HMG-CoA reductase inhibitor should be performed concomitantly. In hypertensive and hypercholesterolemic patients, the serum cholesterol level should be reduced to an appropriate therapeutic target by lifestyle modifications and antihyperlipidemic medications. If hypertension is accompanied by hypertriglyceridemia or hypo-HDL-cholesterolemia, insulin-resistant metabolic syndrome should be considered, and hyperlipidemia in such patients should be treated by lifestyle modifications and drug therapy using fibrates.

In selecting antihypertensive drugs for hyperlipidemic patients, effects of various antihypertensive drugs on lipid metabolism must be considered. While high doses of thiazide diuretics and loop diuretics are known to increase the serum total cholesterol, triglyceride, and LDL-cholesterol levels, whether low doses of thiazide diuretics increase these serum lipid levels is unclear. β-Blockers have been suggested to increase the serum triglyceride and reduce the HDL-cholesterol. α-Blockers reduce the serum cholesterol and increase the HDL-cholesterol. ACE inhibitors, ARBs, Ca antagonists, and central sympatholytic drugs do not affect serum lipid levels.

In selecting antihypertensive drugs for hypertensive and hyperlipidemic patients, drugs that improve, or do not exacerbate lipid metabolism such as α-blockers, ACE inhibitors, Ca antagonists, and ARBs are recommended.

3) Obesity

The frequency of hypertension in obese individuals is reported to be 2–3 times higher than in non-obese individuals (*315*). Overweight from youth is a particularly important risk factor for hypertension. The sympathetic nervous system, Na retention/salt sensitivity, and insulin resistance have been suggested to be involved in the etiology of hypertension accompanied by obesity. Obesity may be accompanied by sleep apnea syndrome, and sleep apnea syndrome may cause or exacerbate hypertension.

In antihypertensive therapy, risk factors for cardiovascular diseases, which often concur with obesity, must be reduced. First, weight reduction by dietary therapy and exercise therapy should be prescribed, but drug therapy should be started if the blood pressure reduction is insufficient even 6 months after the beginning of the guidance. The selection of antihypertensive drugs on the basis of characteristics other than their antihypertensive effects is practical, and α-blockers are recommended when there are abnormalities of lipid metabolism, and ACE inhibitors or ARBs are recommended when abnormalities of glucose metabolism/insulin resistance are noted. The side effects of thiazide diuretics on glucose and lipid metabolism are small when administered at half the tablet. Hypertension accompanied by obesity is often refractory, and, in such patients, thiazide diuretics are useful as a concomitant medication.

4) Metabolic Syndrome

Many epidemiological studies have established that the concurrence of hypertension, hyperlipidemia (hypertriglyceridemia, hypo-HDL-cholesterolemia), obesity, and abnormal glucose metabolism synergistically increase atherosclerotic diseases including ischemic heart disease. Insulin resistance is involved as a common background in these risk factors for atherosclerotic diseases, and the condition has been called by various names including multiple risk factor syndrome, insulin resistance syndrome, and abdominal obesity syndrome. Recently, metabolic syndrome (*316*), proposed in the National Cholesterol Education Program–Adult Treatment Panel (NCEP-ATP)-III (2001) of the United States, has become a universal term. The diagnostic criteria for metabolic syndrome presented by the Joint Committee of 7 scientific societies including the Japanese Society of Hypertension are the concurrence of visceral obesity (abdominal circumference ≥85 cm in men, ≥90 cm in women) and 2 or more of the following 3 risk factors: High-normal blood pressure (≥130/85 mmHg), impaired glucose tolerance (fasting blood glucose level ≥110 mg/dl), and hypertriglyceridemia (≥150 mg/dl), or hypo-HDL-cholesterolemia (<40 mg/dl in men and women).

5) Bronchial Asthma and Chronic Obstructive Pulmonary Disease

In hypertensive patients with bronchial asthma or chronic obstructive pulmonary disease, lifestyle modifications are necessary as in hypertensive patients. Smoking is involved in the occurrence and exacerbation of chronic bronchitis, induces attacks of bronchial asthma, and exacerbates chronic obstructive pulmonary disease. Symptoms are often alleviated by quitting smoking. Marked body weight gains increase the oxygen requirement. Weight control is necessary in obese hypertensive patients, because it improves the respiratory function as well as reduces the blood pressure. Since excessive salt intake may enhance bronchial hypersensitivity leading to an exacerbation of asthma, the salt intake should be restricted for the management of hypertension and asthma. In asthmatic patients, exercise may induce attacks of asthma (exercise-induced asthma). Therefore, it is important to warm up gradually to start exercising in attack-free periods, and to avoid it in cold, and to avoid sudden vigorous exercise.

Antihypertensive drugs should be chosen based on (1) effects of the drugs on both hypertension and respiratory disease, (2) pharmacological interactions between the drugs for the two diseases, and (3) conditions of respiratory disease as well as blood pressure control. Both dihydropyridine Ca antagonists and non-dihydropyridine Ca antagonists have few adverse effects on the respiratory function in asthmatic patients. Since the clinical significance of an increase in the pulmonary shunt blood flow in the hypoventilated area (decrease in arterial oxygen tension) and suppression of diaphragmatic movements (respiratory muscles) by Ca antagonists is small, Ca antagonists are used for the treatment of patients with respiratory disorders. ARBs have been reported to suppress enhanced bronchial responses without exacerbating cough or suppressing the respiratory function in hypertensive patients with bronchial asthma (*317*), and they are considered to be safe antihypertensive drugs. ACE inhibitors have been suggested to cause no changes in asthmatic symptoms and to have no effect on the respiratory function. However, asthma may be accompanied by respiratory inflammation, and as ACE inhibitors enhance the bronchial hypersensitivity and increase the frequency of cough, their use is not necessarily recommendable. Latent microaspiration is involved in most cases of senile pneumonia, and ACE inhibitors have been reported to reduce the frequency of aspiration pulmonary disease, but their effectiveness for the prevention of aspiration pneumonia has not been established. Diuretics have been considered usable in patients with chronic respiratory disorders including asthma. However, fluid supplementation is effective for removing bronchial secretion in chronic respiratory diseases, and diuretics may increase the viscosity of bronchial secretion and exacerbate the condition. Moreover, the activation of the RA system by diuretics contracts the pulmonary vascular bed, possibly exacerbating hypoxemia (*318*). Therefore, diuretics should be administered to patients with chronic respiratory disorders at low doses (particularly, avoiding overdosing), and fluid supplementation should be managed carefully. If hypokalemia is caused by a diuretic used concomitantly with a β_2-stimulator, a thiazide diuretic and a K-sparing diuretic should be used simultaneously. α-Blockers are recommended as safe antihypertensive drugs for hypertensive patients with chronic obstructive pulmonary disease and bronchial asthma, because they do not suppress the respiratory function.

On the other hand, asthma and chronic obstructive pulmonary disease are absolute or relative contraindications for all β-blockers. β-Blockers are considered to exacerbate these diseases by blocking bronchial smooth muscle β_2-receptors, thus, increasing the airway resistance. Even β_1-selective β-blockers should not be used, because of their mild β_2-blocking action. It has been reported that respiratory events were induced even by ophthalmic solution of β-blockers in patients with asthma. Also, β-blockers occasionally reduce the bronchodilator effects of sympathetic stimulators, and sympathetic stimulators increase blood pressure due to enhancement of stimulating effects of vascular α-receptors under vascular β_2-receptor blockade.

6) Gout and Hyperuricemia

Although the role of hyperuricemia as an independent cardiovascular risk factor is controversial, a correlation between an increase in serum uric acid and cardiovascular death (*319*), and a correlation between an increase in serum uric acid and the occurrence of cardiovascular events in patients with mild to moderate hypertension even under satisfactory blood pressure control (with and without the use of diuretics) (*320*) have been reported in large-scale follow-up studies. Therefore, it is reasonable to manage hyperuricemia in gout patients not only for the prevention of gouty arthritis but also as a risk factor for cardiovascular disease.

Uric acid is generated in the degradation process of purine bodies and is excreted and reabsorbed in renal tubules. Hyperuricemia is classified according to the causative mechanism into the high uric acid production type, low uric acid excretion type, and mixed type. Hyperuricemia appears to be significant as (1) a risk factor for hypertensive renal disorders and (2) an index of metabolic abnormalities such as insulin resistance (because hyperinsulinemia promotes renal Na reabsorption and reduces uric acid excretion).

Lifestyle modifications in patients with hypertension complicated by gout/hyperuricemia include (1) weight control (because serum uric acid increases with weight gain and decreases with weight loss), (2) restriction of alcohol intake (because the risk of gout has been reported to increase with alcohol intake (*321*); beer, in particular, should be avoided because of its high content of purine bodies), (3) strict observance of high fluid intake (because oliguria promotes reabsorption of uric acid, but urinary excretion of uric acid goes

up with increased urine volume), (4) control of blood pressure and improvement of insulin sensitivity by moderate exercise (vigorous exercise should be avoided, because it increases serum uric acid), (5) restriction of salt intake (to reduce dose of diuretics as well as blood pressure), and (6) stress management.

Since antihypertensive drugs exert different effects on uric acid metabolism in hypertensive patients with hyperuricemia, drugs and their doses should be determined carefully. Many reports suggest that Ca antagonists, ACE inhibitors, and α-blockers cause no change in serum uric acid. Most of the ARBs have no effect on serum uric acid. Losartan increases urinary excretion of uric acid, though slightly, causing a decrease in serum uric acid. Combined therapy of losartan and a diuretic has been suggested to prevent an increase in serum uric acid induced by diuretics. β-Blockers have been reported to slightly increase serum uric acid.

Thiazide diuretics must not be used in patients with gout or its predispositions, because it may induce acute attacks of gouty arthritis. Thiazide diuretics have been reported not to markedly increase the serum uric acid when used at low doses. In the SHEP, chlortalidone was used at 12.5–25 mg/day as the initial drug, resulting in reduced occurrence of stroke and major cardiovascular events. However, in this study, an increase of serum uric acid less than 1 mg/dl in the diuretic group was associated with a hazard ratio of 0.58 for coronary events compared with those with a serum uric acid increase 1 mg/dl or more (*322*). These results suggest that diuretics should be avoided or be used at low doses in hyperuricemic patients even when they have no gout.

In diuretic therapy (though usually not used) in patients with hyperuricemia or predispositions to gout, the urine volume should be maintained, and a urine alkalizer should be administered, to induce dissolution of uric acid, and antihyperuricemic drugs (an inhibitor of uric acid synthesis and/or a promoter of its excretion) should be used concomitantly, in addition to the above measures. The optimal range of the serum uric acid in gouty patients is reported to be 4.6–6.6 mg/dl from its relationship with the occurrence of arthritis (*323*). According to the guidelines for the treatment of hyperuricemia and gout of the Japanese Society of Gout and Nucleic Acid Metabolism, hyperuricemia is defined as a serum uric acid of 7.0 mg/dl or higher, and control of the serum uric acid at 6.0 mg/dl or less is recommended. For hypertensive patients, the guidelines recommend that treatment using an antihyperuricemic drug should be started if serum uric acid is 8.0 mg/dl or higher even if they remain asymptomatic (*324*).

7) Liver Diseases

Mechanism of hepatotoxicity induced by most antihypertensive drugs is considered to be ideosyncratic. Ca antagonists and ACE inhibitors rarely cause liver dysfunction. Reports of hepatotoxicity due to ARBs are also very few, and it was resolved by withdrawal of the drugs in most cases. β-Blockers have low hepatotoxicity except labetalol. Labetalol has been reported to have caused severe hepatitis accompanied by hepatocyte necrosis. A metaanalysis suggested that propranolol reduces the risk for gastrointestinal bleeding and death in patients with liver cirrhosis (*325*). Methyldopa has been known to frequently cause liver dysfunction, but there have not been many reports, because the frequency of its prescription has decreased recently. An active liver disease and a history of liver diseases due to methyldopa are contraindications of methyldopa. The diuretics (hydrochlorothiazide, chlortalidone, and furosemide) may cause hepatic coma in patients with severe liver cirrhosis and must be used carefully. In hypertensive patients with acute and chronic liver dysfunction, adverse effects of antihypertensive agents must always be kept in mind and liver function checked at regular intervals during the period of medication (particularly in an early period), and, if a liver disease due to medication is suspected, the medication must be discontinued, and the liver function must be checked.

Drugs are classified into (1) those metabolized primarily by the liver and scarcely excreted in an unmetabolized form *via* the kidney (hepatic metabolism type), (2) those primarily excreted in an unmetabolized form *via* the kidney (renal excretion type), and (3) those that are both metabolized by the liver and excreted *via* the kidney (intermediate type). When hepatic metabolism type antihypertensive drugs are used in patients with liver dysfunction, in whom the first-pass effect of the liver is reduced, the blood concentration of the drug is elevated, its elimination half-life is prolonged, and its bioavailability is increased, resulting in an enhancement of its effect. Therefore, these antihypertensive drugs should be started from a low dose and the dosing intervals should be extended. Hepatic metabolism type antihypertensive drugs include ARBs, dihydropyridine Ca antagonists (nifedipine and nilvadipine), some β-blockers (propranolol, metoprolol, and labetalol), and α-blockers (prazosin and doxazosin).

Dose adjustment for liver diseases is unnecessary in the use of renal excretion type antihypertensive drugs. Most of the ACE inhibitors (captopril, lisinopril) are the renal excretion type. Although the conversion of ACE inhibitors, which are prodrugs, into active forms in the liver is delayed, it exerts little effect on their actual ACE-inhibiting activities. Some β-blockers (atenolol and nadolol) are also the renal excretion type and can be used in ordinary doses. Diuretics (hydrochlorothiazide, chlortalidone, and furosemide) are also mostly excreted *via* the kidney in unmetabolized forms.

Summary

1) Set the target of blood pressure control at less than 130/80 mmHg for patients with hypertension complicated by diabetes mellitus.
2) In selecting antihypertensives for the treatment of hypertension complicated by diabetes mellitus, an ACE inhibitor, an ARB, or a long-acting dihydropyridine Ca

antagonist is recommended as the first choice on the basis of their effects on carbohydrate and lipid metabolism and preventive effects on complications. In hypertensive patients with effort angina or old myocardial infarction, β-blockers may be used for their cardiac protecting effects. α-Blockers are also usable when hypertension is complicated by hyperlipidemia or prostate hypertrophy.

3) For the treatment of hypertension complicated by hyperlipidemia, α-blockers, ACE inhibitors, Ca antagonists, and ARBs, which improve, or do not exacerbate, lipid metabolism, should be selected.
4) In treating hypertension accompanied by obesity, antihypertensive medication should be coupled with weight control by dietary therapy and exercise therapy. ARBs, ACE inhibitors, and α-blockers are recommended because of their metabolic characteristics.
5) Metabolic syndrome is an important factor for cardiovascular diseases also in Japan, and attention to the management of insulin resistance is necessary in treating hypertensive patients with metabolic syndrome.
6) ARBs and dihydropyridine Ca antagonists are usually used for the treatment of hypertension in patients with bronchial asthma or chronic obstructive pulmonary disease. ACE inhibitors, which enhance the airway sensitivity, are not necessarily recommendable. Bronchial asthma is a contraindication for β-blockers and αβ-blockers, and their use is also avoided usually in patients with chronic obstructive pulmonary disease.
7) Ca antagonists, ACE inhibitors, and α-blockers can be used in patients with gout or hyperuricemia without considering their effects on serum uric acid. Most of ARBs also have no effect on serum uric acid. Losartan, an ARB, is regarded as a promising drug because of its uric acid excreting action. Gout and hyperuricemia are contraindications for diuretics, because they may increase serum uric acid and induce attacks of arthritis in gouty patients.
8) In hypertensive patients with liver diseases, the liver function should be checked at regular intervals, and, if drug-induced liver diseases are considered possible, the medication should be discontinued, and the liver functions be checked. Active liver disease and a history of liver disease due to methyldopa are contraindications for methyldopa. In patients with markedly reduced hepatic function due to diseases such as liver cirrhosis, renal excretion type antihypertensive drugs are a better choice than hepatic metabolism type ones.

8. Hypertension in the Elderly

1) Characteristics of Hypertension in the Elderly

The prevalence of hypertension increases with age. In Japan, about 60% of people aged 65 years or above have hypertension, and the largest number of patients seek for medical consultation for hypertension among all diseases (*326*).

Systolic blood pressure increases, but diastolic blood pressure tends to decrease with age, causing widening of pulse pressure, difference between systolic and diastolic blood pressure. The increase in systolic blood pressure and the widening of pulse pressure are important risk factors for cardiovascular diseases in the elderly (*327–329*). The widening of pulse pressure is ascribed to decrease in the Windkessel function due to a decrease in the elasticity of aortic wall associated with the progression of arteriosclerosis. According to the Hisayama Study, in which the subjects were aged 60 years or above, the cumulative prevalence of cardiovascular diseases was significantly higher when the systolic blood pressure was 140 mmHg or higher and diastolic blood pressure was 80 mmHg or higher (*13*).

Hemodynamic characteristics of hypertension in the elderly are marked increase in total peripheral vascular resistance, decrease in circulating blood volume, tendency toward decrease in cardiac output, and diastolic dysfunction. These changes result in decreases in blood flow of major organs such as brain, heart, and kidney, disturbances of autoregulation of blood flow of target organs, and a shift of the lower limit of blood pressure to hypertensive side. Therefore, a sudden and excessive decrease in blood pressure may cause circulatory disturbance of these organs, and more gradual control of blood pressure is necessary in patients with a history of cerebral infarction or myocardial infarction (Fig. 8-1).

The reserves of all organs of the body decrease with age. Decrease in renal function is particularly important for treatment of hypertension. The renal blood flow, GFR, and renal tubular function decrease with aging. Impairment of renal function affects pharmacokinetics of renal excretion type drugs, and their blood concentrations become more likely to increase, so that attention to excessive decreases in blood pressure and adverse effects is necessary. Increased susceptibility to disturbances of electrolyte homeostasis (particularly, hyponatremia and hypokalemia), age-associated increases in insulin resistance, and increases in frequency of impairment of glucose tolerance are important metabolic characteristics.

Characteristics of hypertension in the elderly are (1) an increase in systolic blood pressure and widening of pulse pressure, (2) pseudohypertension (higher values determined by manchette method than by direct method; however not frequently observed in Japanese studies), (3) auscultatory gap (disappearance of Korotkoff sound), (4) variability of blood pressure, (5) increases in orthostatic hypotension and postprandial hypotension, (6) changes in diurnal variations in blood pressure (increases in non-dippers and extreme dippers), (7) increases in morning hypertension, and (8) increases in white coat hypertension. These phenomena are related to age-associated disorders of either pressor or depressor system including nervous system (impairment of baroreflex, and decrease of β-receptor function) and humoral blood pressure control system (decrease of the RA system, kallikrein-kinin system, prostaglandins, and renal dopamine system) (*330*).

2) Criteria and Diagnosis of Hypertension in the Elderly

According to metaanalysis of epidemiological studies, cardiovascular risk increases with increases in systolic blood pressure above 115 mmHg and diastolic blood pressure above 75 mmHg. This relationship between the cardiovascular risk and the blood pressure is observed regardless of age although the increase in the risk becomes more gradual in the elderly (*14*). Therefore, the criterion of hypertension in the elderly should be 140/90 mmHg or higher similarly to adults in general. However, many epidemiological studies have suggested that there is a threshold in the increase in the cardiovascular risk due to hypertension. In the Framingham Study, a clear J-curve was observed as a result of 18-year follow-up of people aged 65 years or above with cardiovascular complications, and the risk was lowest in the group with blood pressure of 140–150 mmHg (*331*). An age-associated shift of the threshold of the cardiovascular risk to the right was also observed in the re-analysis of the Framingham Study by Port *et al*. (*332*).

The Hisayama Study, NIPPON DATA 80, and Tanno-Sobetsu Study are typical epidemiological studies on the relationship between blood pressure and the risk for cardiovascular complications in the elderly. In the Hisayama Study, while the risk of cardiovascular complications increased at blood pressures of 140 mmHg or higher up to the age of the 70s, this relationship disappeared in the 80s (*13*). In the NIPPON

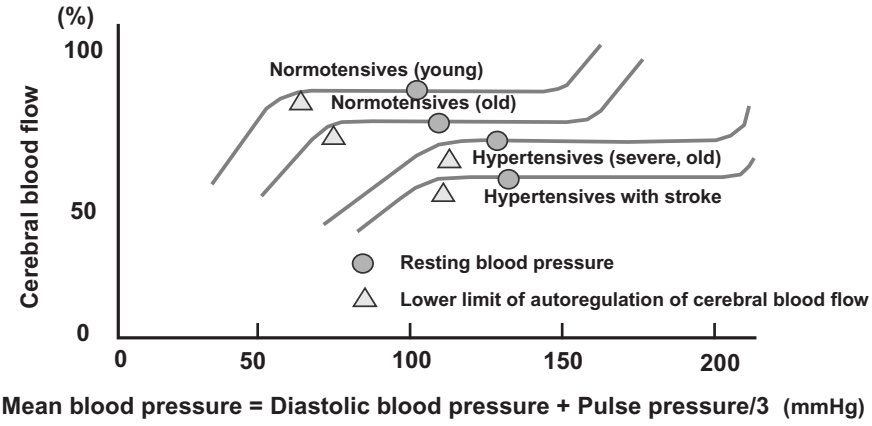

Fig. 8-1. *Cerebral blood flow and range of its autoregulation in normotensives, hypertensives, and hypertensives with stroke. In hypertensive patients, the resting cerebral blood flow decreases, and the lower limit of its autoregulation increases (shifts to the right) (original figure by Masatoshi Fujishima).*

DATA 80, blood pressure was correlated with the risk up to the age of 60 years, but the cardiovascular mortality rate was lowest when systolic blood pressure was 140–160 mmHg in those aged 61 years or above, showing a J-curve (*333*). In the Tanno-Sobetsu Study, the outcome was shown to be poor when systolic blood pressure was 160 mmHg or higher in those aged 60 years or above (*334*).

These results were obtained by epidemiological studies and do not indicate criteria for the introduction of antihypertensive medication. Indeed, antihypertensive treatment has been applied at a blood pressure of 160 mmHg or higher or 95 mmHg or higher in many of the intervention studies in elderly hypertensive patients performed in Japan and abroad, so that 140/90 mmHg or higher cannot be immediately accepted as a criterion for the initiation of antihypertensive medication.

Since blood pressure markedly fluctuates in elderly hypertensive patients, blood pressure must be measured repeatedly on different days, and must be confirmed to be always hypertensive, for their diagnosis and treatment. As they often have orthostatic hypotension, measurement of standing blood pressure (measured within 3 min after standing up) is important, and must be performed before and after the beginning of treatment. Sphygmomanometry by the palpation method must be performed simultaneously not to overlook pseudohypertension or auscultatory gap. ABPM is useful for the evaluation of variability of blood pressure, white coat hypertension, morning surge, masked hypertension, and non-dipper. Non-dipper type and extreme dipper type diurnal changes in the blood pressure and morning hypertension are known to be frequently accompanied by asymptomatic cerebral infarction (lacuna) (*69*, *335*). Home measurement of blood pressure is beneficial for routine clinical evaluation of elderly hypertensive patients (*336*).

While secondary hypertension, particularly endocrine hypertension, is rare in the elderly, renovascular hypertension due to atherosclerosis may be observed. If a sudden increase in blood pressure occurs, or if the renal function is rapidly decreased during treatment with ACE inhibitors or ARBs, bilateral renovascular hypertension must be considered. Auscultation of abdominal vascular bruit is helpful.

The presence or absence of damage of target organ such as brain, heart, and kidney is important for the selection of the drugs. Atypicality and multiple morbidities are characteristics of particular importance in elderly patients, and efforts to find latent complications are necessary. Whether patients have respiratory disease (particularly, obstructive pulmonary disease) or metabolic complication (diabetes mellitus, hyperlipidemia, hypokalemia) is important for selection of antihypertensive drugs.

3) Treatment

a. Effects of Antihypertensive Therapy in the Elderly

Large-scale clinical trials performed in Western countries such as the European Working Party on High Blood Pressure in the Elderly Trial (EWPHE) (*337*), the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) (*338*), and Medical Research Council Trial of Treatment of Hypertension in Older Adults (MRC II) (*339*) have demonstrated that cardiovascular mortality and morbidity (particularly, cerebrovascular disease) were decreased significantly by treatment with diuretics or β-blockers compared with placebo in patients aged 60 or 70 years or above (in many of whom systolic blood pressure was 160 mmHg or higher and diastolic blood pressure was 90 mmHg or higher). Also, the efficacy of antihypertensive therapy has been established by large-scale clinical trials in patients with systolic hypertension (systolic blood pressure ≥160 mmHg, diastolic blood pressure <90 or

Table 8-1. Major Clinical Trials in Elderly Hypertensive Patients (1): Comparisons with Placebo

	EWPHE	HEP	SHEP	STOP-Hypertension	MRC II	STONE	Syst-Eur	Syst-China
Age of subjects (years)	≥60	60–79	≥60	70–84	65–74	60–79	≥60	≥60
Number of subjects	840	884	4,736	1,627	4,396	1,632	4,695	2,394
Blood pressure at entry								
Systolic (mmHg)	160–239 and	170–280 and	160–219 and	180–230 and/or	160–209 and	≥160 and/or	160–219 and	160–219 and
Diastolic (mmHg)	90–119	105–120	<90	105–120	<115	≥96	<95	<95
Blood pressure before treatment (mmHg)	180/101	197/100	177/77	195/102	185/91	168/98	174/86	170/86
Antihypertensive drugs	Diuretics Methyldopa†	β-Blockers Diuretics† Methyldopa†	Diuretics β-Blockers†	(1) β-Blockers (2) Diuretics	(1) β-Blockers (2) Diuretics	Ca antagonists ACE inhibitors† Diuretics†	Ca antagonists ACE inhibitors† Diuretics†	Ca antagonists ACE inhibitors† Diuretics†
Trial method	Double-blind	Open	Double-blind	Double-blind	Single-blind	Single-blind	Double-blind	Single-blind
Follow-up period (years)	4.7	4.4	4.5	2.1	5.8	3.0	2.0	4.0
Blood pressure after treatment (mmHg)								
Treatment group	150/85	162/77	144/68	167/87	152/77	146/85	151/79	150/81
Control group	171/95	180/88	155/71	186/99	166/83	155/90	161/84	159/84
Therapeutic effect (relative risk)								
Cerebrovascular disease	0.64	0.58*	0.67*	0.53*	0.75*	0.43*	0.58*	0.62*
Coronary artery disease	0.82	1.03	0.73*	0.87*	0.81		0.70*	1.06#
Heart failure	0.78	0.68	0.45*	0.49*		0.32	0.71	0.42
All cardiovascular disease	0.71*	0.76*	0.68*	0.60*	0.83*	0.40*	0.69*	0.63*

Blood pressures in HEP and MRC II are estimated values. *Significant difference. #Myocardial infarction alone. †Secondary combination.

95 mmHg) such as SHEP (using a diuretic as the first choice) (*340*), Syst-Eur (*341*), and the Systolic Hypertension in China (Syst-China) (using the Ca antagonist nitrendipine as the first choice) (*342*). In the Shanghai Trial of Nifedipine in the Elderly (STONE) (in which long-acting nifedipine was the first choice) (*343*) and Syst-China, in particular, the efficacy of a Ca antagonist was demonstrated in the Chinese, who are racially close to the Japanese, and the significant suppression of cerebrovascular diseases observed in these studies is highly suggestive also to the Japanese.

Table 8-1 shows outlines of representative intervention studies performed in elderly hypertensive patients. In patients with systolic blood pressure of 160 mmHg or higher, average systolic blood pressures of 168–197 mmHg before treatment were reduced mostly to 140–150 mmHg after treatment.

According to a metaanalysis of 9 major large-scale clinical trials of treatment for hypertension in the elderly aged 60 years or above, antihypertensive treatment significantly reduced all cause deaths by 12%, deaths due to stroke by 36%, and deaths due to ischemic heart disease by 25%. It also significantly reduced the incidence of cerebrovascular diseases by 35% and the incidence of ischemic heart disease by 15% (*344*). Similar results have been confirmed also by a recent metaanalysis (*345*).

The effectiveness of antihypertensive treatment was not clear in patients aged 80 years or above in the EWPHE and Syst-Eur (*337*, *341*). However, according to a metaanalysis of large-scale clinical trials concerning the data of very old patients aged 80 years or above, while the incidences of stroke, cardiovascular events, and heart failure were significantly reduced by antihypertensive treatment by 34%, 22%, and 39%, respectively, no significant decrease was observed in deaths due to cardiovascular diseases (*345*). The Hypertension in the Very Elderly Trial (HYVET) is being performed presently in very old patients, and benefits of treatment are expected to be clarified further.

As for large-scale clinical trials in elderly hypertensive patients, the National Intervention Cooperative Study in Elderly Hypertensives (NICS-EH) was a double-blind trial with a 5-year follow-up of hypertensive patients aged 60 years or above using a Ca antagonist (nicardipine slow-release tablets) and a diuretic (trichlormethiazide). The incidence of cardio-

vascular complications was 27.8/1,000 person-years in the Ca antagonist group and 26.8/1,000 person-years in the diuretic group, with no significant difference (*165*). The incidence of cardiovascular complications in the NICS-EH was close to those in the SHEP (*340*) and Syst-Eur (*341*) carried out in Western countries and indicated the efficacy of these drugs. However, the ratio between stroke and myocardial infarction was about 4:1 in the NICS-EH, indicating that stroke is prevalent in Japan (*165*). The tolerability based on the dropout rate by medical reasons tended to be higher for the Ca antagonist (*346*).

In the Practitioner's Trial on the Efficancy of Antihypertensive Treatment in the Elderly Hypertension (PATE-Hypertension), in which elderly hypertensive patients aged 60 years or above who were being treated at the entry were followed-up for 3 years under treatment with either a Ca antagonist (manidipine) or an ACE inhibitor (delapril) alone, the incidence of cardiovascular complications was 19.7/1,000 person-years in the Ca antagonist group and 22.5/1,000 person-years in the ACE inhibitor group, with no significant difference. The results, which resembled those of the Syst-Eur, suggest the effectiveness of both drugs. However, the dropout rate was significantly higher in the ACE inhibitor group than in the Ca antagonist group, and the main cause of dropout was cough (*347*). The STOP-Hypertension 2 reported the effectiveness of Ca antagonists and ACE inhibitors, and the Second Australian National Blood Pressure Study (ANBP-2) reported the effectiveness of ACE inhibitors, particularly in men (*348*). Concerning ARBs, the SCOPE reported significant suppression of the occurrence of non-fatal stroke in the ARB (candesartan) group compared with the control group (*117*).

b. Indications for Antihypertensive Therapy and Target Levels of Blood Pressure

i. Indications for Antihypertensive Therapy

In the reported large-scale clinical trials in elderly hypertensive patients, antihypertensive effects were established when systolic blood pressure was 160 mmHg or higher and diastolic blood pressure was 90–100 mmHg or higher. There has been no large-scale clinical trial against mild hypertension with systolic blood pressures of 140–159 mmHg. However, in one short-term study in a small number of subjects, Ca antagonists were shown to be useful for the treatment of mild hypertension on the basis of improvements in cardiac hypertrophy and QOL (*349*). There is also a report that the blood pressure was inversely correlated with the survival in patients aged 70 years or above (*350*). In another study, hypertension was not a risk factor for death, and antihypertensive treatment did not reduce the mortality rate, in patients aged 85 years or above (*346*). Because of these observations, a Japanese investigation in experts set the blood pressure for the initiation of antihypertensive treatment at slightly higher levels for those in their 70s and 80s (*351*). Whether this is valid has not been clarified. Antihypertensive treatment should be started when the blood pressure is 160 mmHg or higher as in non-elderly patients. In patients with mild hypertension, however, the lifestyle must be modified first, and antihypertensive medication is started if blood pressure remains 140 mmHg or higher even after several months. Aggressive antihypertensive treatment should be performed when the patients have complications such as hypertensive heart failure and aortic aneurysm regardless of the age or blood pressure level.

ii. Target Levels of Blood Pressure

The JNC 7 and 2003 ESH-ESC guidelines, the target levels of blood pressure is less than 140/90 mmHg for all ages (*29*, *43*). However, there is no evidence that support less than 140/90 mmHg as an appropriate level of blood pressure control for elderly patients (*352*). Since many elderly patients already have organ damages due to atherosclerosis, particularly disturbances of autoregulation of cerebral blood flow, and since systolic blood pressure increases more or less with aging also in healthy people, the target levels of blood pressure is set at a slightly higher level for the elderly than for adults in general in Japan (*353*). In recent large-scale clinical trials, the average blood pressure after treatment has often been 141–152/77–85 mmHg (Tables 8-1 and 8-2). The sub-analyses of the SHEP and HOT have questioned the idea that systolic blood pressure at 160 mmHg or higher should be reduced to less than 140 mmHg in elderly hypertensive patients. In the SHEP, the preventive effect against stroke was strongest when blood pressure was reduced to less than 150 mmHg, and the statistical significance of the effect disappeared when blood pressure was reduced to less than 140 mmHg (*354*). In the HOT, the-lower-the-better relationship disappeared in those aged 65 years or above (*355*). In the SHEP, also, cardiovascular events increased when diastolic blood pressure was reduced to less than 60 mmHg (*356*), indicating that there is a limitation in the reduction of systolic blood pressure. In the PATE-Hypertension Study performed in Japan, also, a J-curve was observed, and cardiac events increased when systolic blood pressure was reduced to less than 130 mmHg (*347*).

To summarize the results of the above large-scale clinical trials and epidemiological studies, treating elderly hypertensive patients similarly to younger hypertensive patients is not justified. Elderly people are usually classified into those aged 65 years or above (young old), those aged 75 years or above (old old), and those aged 85 years or above (very old), in consideration of changes in physiologic function and frequencies of complications. The data of both epidemiological studies and large-scale clinical trials suggest that the outcome is expected to be improved by reducing the blood pressure to less than 140/90 mmHg at all ages, indicating that aggressive treatment of hypertension, if possible, is important also in elderly patients. Therefore, the target levels of blood pressure should be less than 140/90 mmHg in the young old age. In the old old age, also, it should be less than 140/90 mmHg, especially when hypertension is mild, but more careful management with a temporary target of less than 150/90 mmHg is

Table 8-2. Major Clinical Trials in Elderly Hypertensive Patients (2): Comparisons between Drugs

	STOP-Hypertension 2		ANBP-2	SCOPE	NICS-EH (Japan)	PATE-Hypertension (Japan)
Age of subjects (years)	70–84		65–84	70–89	≥60	≥60
Number of subjects	6,614		6,083	4,964	414	1,748
Blood pressure at entry						
Systolic (mmHg)	≥180 and/or		≥160 or	160–179 and/or	160–220 and	≥160 and/or
Diastolic (mmHg)	≥105		≥90 (if SBP ≥140)	90–99	<115	≥90
Blood pressure before treatment (mmHg)	194/98		168/91	166/90	172/94	(1) 151/84 (during treatment) (2) 148/82 (during treatment)
Antihypertensive drugs	(1) β-Blockers+Diuretics *vs.* (2) Ca antagonists (3) ACE inhibitors		(1) ACE inhibitors *vs.* (2) Diuretics	(1) ARB *vs.* (2) Placebo+Antihypertensives (84%)	(1) Ca antagonists *vs.* (2) Diuretics	(1) ACE inhibitors *vs.* (2) Ca antagonists
Trial method	PROBE		PROBE	Double-blind	Double-blind	Open
Follow-up period (years)	4.0		4.1	3.7	5.0	2.4
Blood pressure after treatment (mmHg)	(1) 158/81 (2) 159/80 (3) 159/82		(1) 141/79 (2) 142/79	(1) 145/80 (2) 149/82	(1) 147/81 (2) 147/79	(1) 142/80 (2) 141/78
Therapeutic effect	(2) *vs.* (1)	(3) *vs.* (1)	(1) *vs.* (2)	(1) *vs.* (2)	(1) *vs.* (2)	(1) *vs.* (2)
Cerebrovascular disease	0.88	0.90	0.90	0.76†	1.55	1.02
Coronary artery disease	1.18	0.90	0.86	1.10	1.03	1.15
Heart failure	1.09	0.83	0.85			
All cardiovascular disease	0.99	0.94	0.89*	0.89	1.19	1.14

*$p=0.05$, †$p=0.056$.

necessary for the treatment of moderate or severe hypertension at systolic blood pressure of 160 mmHg or higher, although the final target blood pressure should be less than 140/90 mmHg. In very old patients, antihypertensive medication is useful for the prevention of cardiovascular complications, but it has not been confirmed to reduce the mortality rate (*345*).

In elderly hypertensive patients, attention to the speed of decrease in the blood pressure is necessary because of the presence of disturbances of the tissue circulation or its autoregulation. Blood pressure should be reduced slowly, medication should be started at half the ordinary dose, the dose should be increased at least 4-week intervals by observing the patient for signs of ischemia such as dizziness, especially on standing up, and anginal symptoms, and the target blood pressure should be attained in 3–6 months.

c. Lifestyle Modifications

In elderly patients, also, non-pharmacological therapies (lifestyle modifications) such as restriction of salt intake, exercise, and weight control are beneficial and should be practiced by all means. However, lifestyle modifications may cause a decrease in the QOL if carried to extremes and should be limited to a stress-free level.

i. Diet

Since salt sensitivity is generally high in the elderly, restriction of salt intake is effective. The target level of salt restriction is 6 g/day, but excessive restriction of salt intake may cause dehydration. Weight control is also effective in obese individuals (*111*).

Increased K intake has a mild antihypertensive effect and a preventive effect against cardiovascular disease such as stroke. A K-rich diet is generally recommendable, but attention to hyperkalemia associated with renal dysfunction or diabetes mellitus is necessary, and K intake should be restricted in such cases.

There is a report that the Ca and Mg intake is negatively correlated with blood pressure, and Ca intake should be

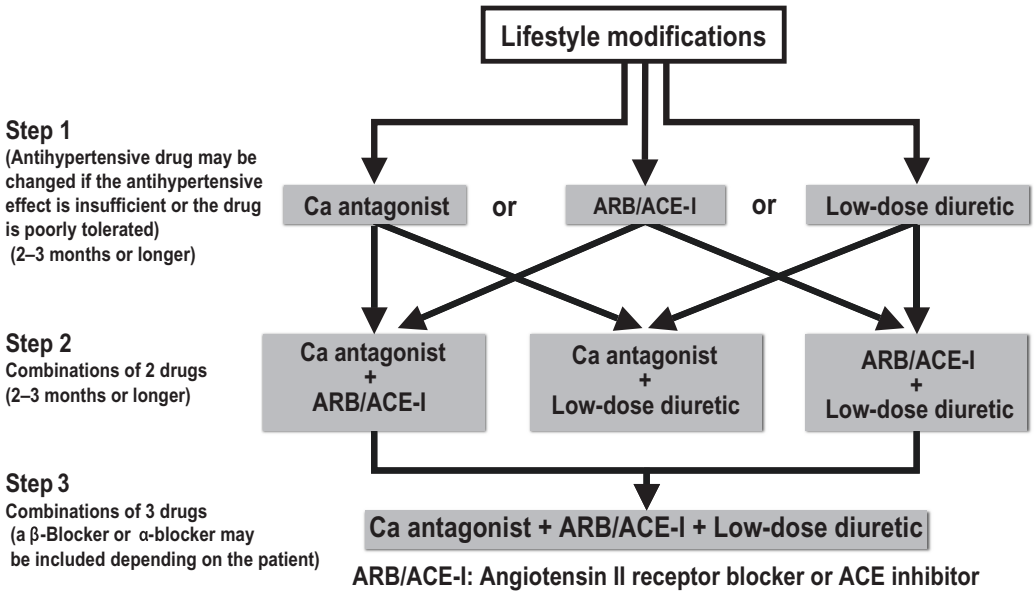

Fig. 8-2. *Treatment algorithm for elderly hypertensive patients.*

encouraged (≥800 mg/day) also for the prevention of osteoporosis. Supplementation of Mg has been shown to have a mild antihypertensive effect.

ii. Exercise

Mild hypertension in elderly people is a good indication for exercise therapy (*152*). For those aged 60 years or above, regular mild exercise (fast walking, *etc*.) at an intensity of about 110 beats/min, 30–40 min at a time, and 3 times or more per week is recommended. However, exercise is impossible if hypertension is complicated by ischemic heart disease, heart failure, renal failure, or bone or joint diseases.

iii. Alcohol Drinking and Smoking

Alcohol drinking and smoking have a positive correlation with blood pressure (*42*). Drinking should be restricted to 20–30 g/day in terms of ethanol in elderly people. While smoking affects the blood pressure only slightly, it is a strong risk factor for cardiovascular disease, so that no smoking is essential.

d. Choice of Antihypertensive Drugs

i. Patients without Complications

In elderly hypertensive patients, antihypertensive drugs should be selected in consideration of characteristics of elderly patients such as reduced organ blood flow, impairment of its autoregulation, and orthostatic hypotension as well as the state of hypertension itself and complications. Ca antagonists, ARBs, ACE inhibitors, or low dose of diuretics should be the first choice. Figure 8-2 shows serial steps of treatment. The first choice may be replaced by another drug if the antihypertensive effect is insufficient, or the drug is poorly tolerated. If no sufficient response is obtained with a single drug, combination therapy is introduced according to Fig. 8-2. Recommendable combinations are Ca antagonist with ARB or ACE inhibitor or ARB or ACE inhibitor with low dose of diuretic. If the antihypertensive effect is still insufficient, combinations of these 3 drugs may be used depending on the situation (*357*).

While β-blockers and α-blockers, which are used as first choices for adults in general, are usable also in elderly patients depending on the condition, drugs that are appropriate as the first choice are limited from the results of intervention studies and characteristics of elderly hypertensive patients. Moreover, the drug must be a long-acting type effective by administration once or twice a day to ensure good drug compliance and must be effective for alleviation of the morning surge (trough/peak ratio ≥50%).

The effectiveness of diuretics, Ca antagonists, ARBs, and ACE inhibitors has been established by large-scale clinical trials. However, the metaanalysis by Messerli *et al*. (*358*) failed to demonstrate the effectiveness of β-blockers for the prevention of ischemic heart disease, cardiovascular death, or total death. α-Blockers are poor candidates for the first choice because of the high frequency of orthostatic hypotension in elderly patients.

Diuretics have been shown to be useful by many large-scale clinical trials including the EWPHE, SHEP, and STOP-Hypertension. In Japan, also, the usefulness of diuretics has been established as indicated by the use a diuretic as a reference drug for a Ca antagonist in the NICS-EH. However, the range of patients to whom diuretics are applicable is limited in consideration of their effects on disturbances of glucose tolerance, hyperuricemia, and hyperlipidemia, and their toler-

Table 8-3. Indication of Antihypertensive Drugs for Elderly Hypertensive Patients with Complications

Complication	Ca antagonist (dihydropyridine)	ARB/ACE inhibitor	Diuretic	β-Blocker	α-Blocker
Chronic cerebrovascular disease	●	●	●[a]	○	○
Ischemic heart disease	●	●	○	●[b]	○
Heart failure	○	●	●	▲[c]	▲
Renal insufficiency	●	●[d]	●[e]	○	○
Diabetes mellitus	●	●	▲	▲	▲[f]
Hyperlipidemia	●	●	▲	▲	●
Gout	●	●	×	○	○
Chronic obstructive pulmonary disease	○	○	○	×	○
Arteriosclerosis obliterans	●	●	▲	×	○
Osteoporosis	○	○	●[g]	○	○
Prostate hypertrophy	○	○	○	○	●

●, strongly recommended; ○, usable; ▲, use with caution; ×, contraindicated. [a]Watch for dehydration; [b]coronary vasospastic angina is a contraindication; [c]should be started at a low dose and used carefully by observing the clinical course; [d]must be administered with caution when creatinine ≥2 mg/dl; [e]loop diuretic; [f]watch for orthostatic hypotension; [g]thiazide diuretic.

ability is slightly inferior to that of Ca antagonists (*346*). Therefore, a diuretic, if used, should be administered at a low dose. Diuretics are extremely useful when combined with Ca antagonists, ARBs, or ACE inhibitors.

The effectiveness of Ca antagonists for the treatment of elderly hypertensive patients including those with systolic hypertension has been established by the STONE (*343*), Syst-Eur (*341*), Syst-China (*342*), NICS-EH (*165*), STOP-Hypertension-2 (*359*), and PATE-Hypertension (*347*). Also, attention is directed to the preventive effect of a Ca antagonist (nitrendipine) against dementia (particularly, Alzheimer's dementia) suggested by a sub-study of the Syst-Eur (*360*). Ca antagonists have few contraindications and can be used in combination with many other antihypertensive drugs. Precautions against conduction disorders, bradycardia, and heart failure are necessary in using diltiazem. Ca antagonists are the most widely used antihypertensive drugs in Japan today (*351*). Since Ca antagonists have been suggested by many metaanalyses to have excellent preventive effects on stroke (*163*), they are highly useful in Japan, where stroke is a major complication of hypertension.

Antihypertensive effects of ACE inhibitors have been confirmed also in elderly hypertensive patients (*361*). Since they maintain the renal function as well as protect the heart by preventing left ventricular remodeling after congestive heart failure or myocardial infarction and inducing regression of cardiac hypertrophy, they are advantageous for the treatment of elderly hypertensive patients. They also have excellent QOL-improving effects. Therefore, ACE inhibitors can be the first choice for the treatment of hypertension in elderly patients (*362*). While the CAPPP confirmed a primary preventive effect of ACE inhibitors, the subjects were not limited to elderly people (*309*). In the STOP-Hypertension-2, the preventive effects of ACE inhibitor against cardiovascular events were comparable to diuretics or Ca antagonists (*359*). In PATE-Hypertension, performed in Japan using elderly hypertensive patients, the effectiveness of ACE inhibitor was comparable to that of Ca antagonist. However, the dropout rate was higher among the users of ACE inhibitor than in those of Ca antagonist due to cough (*347*). Cautious administration is required in using ACE inhibitors in elderly patients with a serum creatinine level of 2 mg/dl or higher. In the ANBP-2, an ACE inhibitor (enalapril) was more useful than a diuretic, particularly in men (*348*).

ARBs are comparable to ACE inhibitors in antihypertensive effect and their adverse effects do not include cough. Since they are expected to produce the organ protecting effects of ACE inhibitors and have been shown to produce sufficient antihypertensive effects also in elderly patients (*363*), they may be selected as the first choice. They have been demonstrated, and confirmed, to have beneficial effects in patients with type 2 diabetic nephropathy, those with heart failure, and those with heart failure after acute myocardial infarction by the RENAAL, Evaluation of Losartan in the Elderly (ELITE), Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM), and Valsartan in Acute Myocardial Infarction (VALLIANT). They were also reported to have an excellent preventive effect on stroke by a sub-analysis of the LIFE in patients with systolic hypertension (*364*), indicating the usefulness of ARBs for the treatment of elderly patients with systolic hypertension.

ii. Patients with Complications

Elderly hypertensive patients often have complications, and the target blood pressure should be determined, and antihypertensive drugs should be selected, in consideration of complications. The concurrence of cerebrovascular diseases, renal dysfunction, ischemic heart disease, diabetes mellitus, or hyperlipidemia with hypertension constitutes a high-risk state, which generally requires more aggressive antihyperten-

sive treatment. The target blood pressure should be less than 140/90 mmHg also in elderly patients, but the blood pressure should be reduced more carefully and gradually if the patient has cerebrovascular diseases or coronary artery disease. Table 8-3 shows various complications as indications or contraindications of antihypertensive drugs.

In elderly hypertensive patients with cerebrovascular diseases (chronic phase), maintenance of the cerebral blood flow is important, and blood pressure should be reduced slowly, particularly in patients after cerebral infarction. Ca antagonists, ARBs, and ACE inhibitors are used for their treatment. In the PROGESS, a combination of an ACE inhibitor and a diuretic was effective for prevention of recurrence of stroke (secondary prevention) (*106*).

β-Blockers are used when hypertension is complicated by effort angina, and Ca antagonists are used when it is complicated by vasospastic angina. If hypertension is complicated by chronic heart failure, ARBs (*365*), ACE inhibitors, and diuretics are recommended. Ca antagonists (amlodipine, felodipine) are also usable to control hypertension.

In elderly hypertensive patients with renal diseases, the management of hypertension as well as dietary therapy is important. If the serum creatinine level is above 2.0 mg/dl or the Ccr is less than 30 ml/min, the treatment should be started with an ARB or an ACE inhibitor, and a Ca antagonist should be added when the antihypertensive effect is insufficient. ARB or ACE inhibitor should be started carefully from a low dose. If a tendency of body fluid retention is observed, a low dose of loop diuretic should be used.

In elderly hypertensive patients with diabetes mellitus, more aggressive control of blood pressure is necessary along with management of diabetes. Drugs that exert no adverse effect on glucose tolerance should be selected, and ARBs, ACE inhibitors (*309*), and Ca antagonists are recommended unless there is an advanced renal dysfunction. In the Syst-Eur, a Ca antagonist (nitrendipine) was shown to be useful for the treatment for hypertension complicated diabetes mellitus (*310*). Many studies indicating the usefulness of ARBs for the treatment of type 2 diabetic nephropathy have been reported (*83*), and ARBs have been shown to prevent the new onset of diabetes mellitus as do ACE inhibitors (*116*, *231*). From these observations, ARBs are considered to be useful for the treatment of hypertension complicated by diabetes mellitus.

Summary

1) Elderly hypertensive patients have characteristics such as the increase in the frequency of systolic hypertension, widening of pulse pressure, and increase in the frequency of orthostatic hypotension due to the age-associated progression of arteriosclerosis. Therapeutic effects of diuretics, Ca antagonists, ARBs, and ACE inhibitors on hypertension in the elderly have been confirmed by large-scale clinical trials, and aggressive treatment is recommended up to the age of the early 80s. Since the outcome is expected to be improved by controlling the blood pressure to less than 140/90 mmHg at all age levels, a positive attitude to the treatment is important. The target levels of blood pressure should be less than 140/90 mmHg for those in young old (≥65 years). It should also be less than 140/90 mmHg for those in old old age (≥75 years), particularly when hypertension is mild. However, in patients with moderate or severe hypertension with systolic blood pressure of 160 mmHg or higher, the blood pressure should be reduced carefully to a temporary target levels of blood pressure of less than 150/90 mmHg and finally to less than 140/90 mmHg if possible.
2) While lifestyle modifications are useful, the therapeutic plan should be formulated individually in consideration of the QOL. For drug therapy, Ca antagonists, ARBs, ACE inhibitors, and a low dose of diuretics are desirable as the first choice. If the antihypertensive effect is insufficient, these drugs should be used in combinations. Generally, to reduce blood pressure slowly, the administration should be started at half the ordinary dose.
3) If there are complications, the antihypertensive drugs most appropriate for each patient should be selected. Since the organ blood flow is often impaired, blood pressure must be reduced carefully not to cause excessive drops.

9. Hypertension under Special Conditions

1) Refractory Hypertension

a. Definition and Frequency

Hypertension may be termed refractory hypertension when blood pressure cannot be reduced to the target level even when antihypertensive therapy using adequate doses of 3 or more drugs including diuretics has been continued after lifestyle modifications. Actually, however, a diagnosis of refractory hypertension is often made in Japan even when the drug therapy does not include a diuretic since diuretics are used infrequently. The updated statistics on incidence of refractory hypertension is not reported. In the large-scale clinical trials such as ALLHAT, Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE), LIFE, and INSIGHT, the target level blood pressure was set at less than 140/90 mmHg, and blood pressure could not be reduced to that level in about 30% to 50% of the patients (*109*, *116*, *258*, *366*). In the first 3 trials, about 40% of the patients were administered 3 or more drugs. In these trials, which included many high-risk patients, the frequency of refractory hypertension may have been overestimated. In Japan, results of large-scale clinical trials with the target blood pressure of less than 140/90 mmHg have not been obtained. According to an investigation performed on Japanese cardiologists in 2000, the target blood pressure mentioned in JSH 2000 guidelines was attained in only 41.5% of the hypertensive patients (*367*). In a study conducted in 2000 in physicians specializing in hypertension and those specializing in diabetes mellitus, blood pressure could be controlled at less than 140/90 mmHg in 40.5% of non-diabetic patients with hypertension and 38.3% of diabetic patients with hypertension (*368*). These studies were carried out at university hospitals or facilities specializing in the treatment of hypertension or diabetes mellitus, where patients with refractory hypertension are considered to be often referred. Blood pressure is not controlled under 140/90 mmHg in many patients encountered in daily clinical practice. However, the percentage of patients who have truly refractory hypertension is expected to be reduced by treating them in consideration of the following factors.

b. Causes and Preventive Measures (Table 9-1)

Factors that make hypertension refractory include failure to measure the correct blood pressure (white coat hypertension, mismatched cuff size, pseudo-hypertension, *etc*.), inadequate attitude of patients (poor drug compliance, inadequate lifestyle modifications, *etc*.), and actual poor responses of blood pressure (volume overload, obesity, sleep apnea syndrome, intake of drugs or foods that attenuate the effects of antihypertensive drugs, *etc*.). Also, secondary hypertension may be treated with a misdiagnosis of essential hypertension. In fact, excess salt intake, no use or inadequate use of diuretics, and the presence of renal insufficiency often make hypertension refractory due to volume overload. In such poorly-controlled hypertension, blood pressure is often reduced by the proper use of diuretics. Blood pressure control has reportedly been improved in patients with refractory hypertension by adjusting doses of diuretics according to the serial hemodynamic measurements using thoracic bioimpedance (*369*).

Poor compliance to antihypertensive drug therapy is another major problem. Insufficient explanation of medication to patients and consequent poor acceptance of the medication by patients and overlooking of adverse effects of drugs by attending physicians may lead to poor drug compliance. According to a study on patients who had been treated as outpatients for 10 years at a clinic specializing in the treatment of hypertension, a high percentage of patients with good control of blood pressure understood the significance of antihypertensive treatment well, showed less increase in body weight, and were administered Ca antagonists or ARBs (*370*). Also, a study on blood pressure control and its contributing factors indicated that the attitude of each attending physician was the most important factor for drug compliance (*371*). From these reports, a positive attitude of attending physicians to treatment, *i.e.*, their efforts to improve the patients' understanding about antihypertensive treatment, encouragement to modify the lifestyle, and proper selection of antihypertensive drugs, is important to improve the state of blood pressure control.

In patients with refractory hypertension, whether there are factors mentioned in Table 9-1 must be examined first. If there is no problem with blood pressure measurement or the state of drug compliance, and if antihypertensive effects are unsatisfactory even after treatment using 3 or more drugs for several months, guidance concerning restriction of salt intake and weight control must be given again. Next, if a diuretic has not been used, its administration should be started. If a diuretic has been used, its dose and type should be changed. The administration of a thiazide diuretic should be started at half a tablet and increased to 2 tablets at most. A loop diuretic

Table 9-1. Causes of Refractory Hypertension and Measures for Their Management

Causes	Measures
Problems in blood pressure measurement	
Use of cuff (bladders) with inadequate size	The width of the bladder within the cuff is 40% of the arm girth, and the length should encircle at least 80% of the arm
White coat hypertension	Home blood pressure measurement, ABPM
Poor compliance	Remove patient's anxiety over long-term pill-taking by sufficient explanation Change the drug if adverse effects are observed Formulate the administration schedule according to the patient's lifestyle
Volume overload	
Excess salt intake	Explain the significance and necessity of restriction of salt intake. Give repeated guidance in cooperation with a dietitian
Inadequate use of diuretics	When 3 or more drugs are used in combination, include a diuretic. Use a loop diuretic for patients with renal dysfunction (serum creatinine ≥2 mg/dl)
Worsening of renal dysfunction	Use diuretics according to the above principles
Problems with lifestyle	
Progress of obesity	Give repeated guidance on restriction of calorie intake Treat sleep apnea syndrome (with CPAP, *etc*.), if present
Excess alcohol intake	Give guidance to restrict alcohol intake to 20–30 g/day or less of ethanol
Problems with selection of drugs	
Simultaneous use of antihypertensive drugs with similar class of action	Combine antihypertensive drugs that have different action mechanisms and mutually cancel out compensatory responses
Simultaneous use of drugs or supplements that antagonize antihypertensive drugs or increase blood pressure *per se*	If the patient is using an oral contraceptive, corticosteroid, NSAID, Chinese preparation containing glycyrrhizin, cyclosporine, erythropoietin, or antidepressant, consult the physician who prescribed these drugs and withdraw or reduce them as much as possible. Select antihypertensive drugs according to the pressor mechanisms of the other drugs
Secondary hypertension	See 11. Secondary Hypertension

CPAP, continuous positive airway pressure.

should be used if a patient has renal dysfunction. Other than diuretics, 2–3 drugs should be selected from Ca antagonists, ACE inhibitors or ARBs, and β-blockers or αβ-blockers. There is a report that the addition of a low dose of an aldosterone antagonist (spironolactone 12.5–50 mg/day) was effective (*372*). The simultaneous use of drugs of the same class should be avoided, but a β-blocker may be coupled with an α-blocker or a central sympatholytics, and a thiazide diuretic may be coupled with an aldosterone antagonist. Since adverse effects and an excessive decrease in blood pressure are more likely to occur when multiple drugs are used in combination or in high doses, careful observation of the course is necessary. If the antihypertensive effect is still insufficient after these measures have been taken, advice of a hypertension specialist (FJSH) should be requested as the possibility of secondary hypertension is high.

2) Hypertensive Emergency and Urgency

a. Definitions and Classification

Hypertensive emergency is not simply a case with an abnormally high blood pressure. It is a pressing situation in which a marked increase in blood pressure (often exceeding 180/120 mmHg) is rapidly causing damages of target organs including the brain, heart, kidney, and large vessels, and an immediate decrease in blood pressure (not necessarily to normal ranges) is required. Hypertension that must be treated promptly is classified into emergency, in which blood pressure must be reduced immediately, and urgency, in which it should be reduced within a few hours, but their distinction is often difficult (*42*, *373*). Hypertensive emergency includes hypertensive encephalopathy, hypertension complicated by acute aortic dissection, hypertensive left ventricular failure accompanied by pulmonary edema, acute myocardial infarction and unstable angina accompanied by severe hypertension, pheochromocytoma crisis, and eclampsia (Table 9-2) (*373*). Accelerated/malignant hypertension is considered to be a condition that requires the beginning of treatment within a few hours and is classified as urgency. Emergency decrease in blood pressure is necessary in conditions such as hypertensive encephalopathy due to eclampsia or acute glomerulonephritis and aortic dissection even when blood pressure is not abnormally high.

The pathological profile must be clarified promptly (Table 9-3), whether the condition is emergency/urgency or not must

Table 9-2. Hypertensive Emergencies

Accelerated/malignant hypertension with papilledema
Cerebrovascular diseases
Hypertensive encephalopathy
Atherothrombotic brain infarction with severe hypertension
Intracerebral hemorrhage
Subarachnoid hemorrhage
Head trauma
Cardiac diseases
Acute aortic dissection
Acute left ventricular failure
Acute or impending myocardial infarction
After coronary bypass surgery
Renal diseases
Acute glomerulonephritis
Renovascular hypertension
Renal crisis from collagen disease
Severe hypertension after kidney transplantation
Excess circulating catecholamines
Pheochromocytoma crisis
Food or drug interaction with monoamine oxidase inhibitors
Sympathomimetic drug use (cocaine)
Rebound hypertension after sudden cessation of antihypertensive drugs
Automatic hyperreflexia after spinal cord injury
Eclampsia
Surgical conditions
Severe hypertension in patients requiring immediate surgery
Postoperative hypertension
Postoperative bleeding from vascular suture lines
Severe body burns
Severe epistaxis
Thrombotic thrombocytopenic purpura

Accelerated/malignant hypertension, perioperative hypertension, rebound hypertension, burns, and epistaxis may be included in urgencies if the condition is mild (cited from reference *373*).

be distinguished, and decisions concerning which drugs should be used, how they should be administered, to what level blood pressure should be reduced, and how quickly this goal should be attained must be made. However, in the emergency case, the start of treatment must not be delayed by wasting time on thorough evaluation.

b. Principles of Treatment

Hypertensive emergency should be treated by hospitalization, in principle. Unnecessarily rapid and excessive decrease in blood pressure is likely to induce ischemic events such as cerebral infarction, cortical amaurosis, myocardial infarction, and progression of renal dysfunction due to a decrease in organ perfusion pressure. Therefore, the use of antihypertensive drugs or measures that allow prediction of the degree and rate of decrease in blood pressure and immediate adjustment of their effects is desirable. A general target blood pressure is a decrease in mean blood pressure no more than 25% during the first 1 h and a decrease to 160/100–110 mmHg within 2–6 h (*104*). However, blood pressure at which the treatment should be started and the target blood pressure are lower in patients with aortic dissection, acute myocardial infarction or hypertensive encephalopathy (acute glomerulonephritis, eclampsia, *etc*.) in whom blood pressure was not high before the episode. After the initial target blood pressure has been reached, oral medication should be started, and parenteral drugs should be gradually withdrawn.

Hypertensive emergency should be managed initially with parenteral drugs, in principle. Invasive monitoring of blood pressure is recommended. Although parenteral drugs that can be used in such situations are limited in Japan, Table 9-4 shows their dosages and regimens, time of the onset and duration of their actions, their adverse effects and precautions for their use, and their major indications. Urgency can often be managed by oral medication. The administration of the contents of a nifedipine capsule and a bolus intravenous injection of nicardipine should be avoided, because they may cause an excessive decrease in blood pressure or reflex tachycardia. Oral administration of Ca antagonists with a relatively rapid onset of action (short-acting or intermediate-acting drugs), ACE inhibitors, an αβ-blocker labetalol, and β-blockers should be used, with a loop diuretic depending on the condition. Since captopril shows a quick onset of action and has a relatively short duration of action, its effect is highly adjustable, but its administration must be started at 6.25–12.5 mg, because it may cause an excessive decrease in blood pressure in malignant hypertension or dehydration, in which the RA system is activated. ACE inhibitors must be used carefully in patients with renal dysfunction, because they may cause hyperkalemia 1–2 days after the beginning of administration. They should not be used, or should be used by careful monitoring of serum creatinine and K levels, in patients suggested to have bilateral renovascular hypertension or renovascular hypertension with functionally solitary kidney because of the possibility of renal failure.

c. Hypertensive Encephalopathy

Hypertensive encephalopathy is a condition in which autoregulation of the cerebral blood flow is disrupted due to a rapid or marked increase in blood pressure, causing edema due to excessive blood flow and perfusion pressure. Hypertensive encephalopathy is likely to occur when blood pressure increases to 220/110 mmHg or higher in chronically hypertensive patients and to 160/100 mmHg or higher in previously normotensive individuals (*374*). It is the most serious emergency, and without appropriate treatment the outcomes are cerebral hemorrhage, coma, and death. The condition is accompanied by headache, nausea/vomiting, disturbance of

Table 9-3. Check Items for Evaluation of Patients Considered to Have Hypertensive Emergency

History and symptoms
Known duration and degree of hypertension and history of its treatment, medication including sympathomimetic agents, headache, visual disorders, neurological symptoms, nausea/vomiting, thoracic or back pain, cardiac or respiratory symptoms, oliguria, changes in body weight, *etc*.
Physical findings
Blood pressure: Diastolic blood pressure is often ≥120 mmHg; laterality, *etc*.
Pulse, respiration, body temperature
Body fluid volume: Dehydration, edema, blood pressure measurement in standing position, *etc*.
Central nervous system: Disturbance of consciousness, convulsions, hemiparesis, *etc*.
Ocular fundus: Linear or flame-shaped hemorrhage, soft exudates, retinal edema, papilledema, *etc*.
Neck: Jugular vein distension, bruit, *etc*.
Chest: Cardiac enlargement, heart murmur, signs of heart failure, *etc*.
Abdomen: Hepatomegaly, bruit, pulsatile mass, *etc*.
Limbs: Edema, arterial pulsation, *etc*.
Laboratory examinations
Urinalysis and blood cell count
Blood biochemistry (urea nitrogen, creatinine, electrolytes, glucose, LDH, CPK, *etc*.)
Arterial blood gas analysis, ECG, chest X-ray, abdominal X-ray
Cardiac and abdominal ultrasonography; head, chest, and abdominal CT, as indicated
Plasma renin activity, aldosterone concentration, and catecholamine concentrations as indicated
Intravenous injection of a low dose of phentolamine if pheochromocytoma is suggested

consciousness, and convulsion, and focal symptoms are rare. Proteinuria or hypertensive retinopathy is absent in some patients.

Since the autoregulation of cerebral blood flow is impaired, a rapid and large decrease in blood pressure is likely to cause cerebral ischemia. Treatment should be started with an intravenous preparation (continuous infusion), the dose of which is more adjustable. The rate of decrease in blood pressure must be adjusted by monitoring blood pressure and neurological symptoms. The treatment should be conducted by aiming to reduce blood pressure by about 25% within the first 2–3 h. Nitroprusside, nicardipine, and diltiazem are usable. Furosemide may be used simultaneously in patients who show an increase in extracellular fluid or develop resistance to antihypertensive treatment. Hydralazine, which increases the intracranial pressure, must be avoided.

d. Cerebrovascular Diseases

See the section of "Cerebrovascular Disease" in 6. Hypertension Associated with Organ Damage.

e. Acute Left Ventricular Failure and Pulmonary Edema

Hypertensive left ventricular failure causing pulmonary edema must be treated immediately. Nitroprusside, which reduces preload as well as afterload by dilating the venous system, is desirable. While the antihypertensive effect of nitroglycerin is relatively weak, it is useful when the condition is concurrent with ischemic heart disease. Pulmonary edema must be controlled by using furosemide with these drugs. Although no clear target blood pressure has been established, blood pressure should be reduced (usually by 10–15% in systolic blood pressure) by examining symptomatic changes. In consideration of more persistent benefit, the regimen should be shifted to a combination with ACE inhibitors or ARBs. If nitroprusside cannot be used, furosemide and RA system inhibitors may be used from the beginning.

f. Severe Hypertension Complicating Acute Coronary Syndrome, Acute Myocardial Infarction, or Unstable Angina

For anginal attacks accompanied by an increase in blood pressure, sublingual administration of nitrites should be the first treatment. For more sustained control of the disease, continuous intravenous infusion of nitroglycerin or diltiazem should be performed to reduce myocardial oxygen demand and to increase coronary blood flow as well as to reduce blood pressure. Propranolol should be added if tachycardia is observed. The administration of ACE inhibitors or β-blockers from the acute period of myocardial infarction is reported to be effective for improving the outcome.

g. Pheochromocytoma Crisis

Pheochromocytoma crisis means a rapid increase in blood pressure due to excessive secretion of catecholamines. Phentolamine should be administered at 2–5 mg every 5 min until

Table 9-4. Parenteral Drugs for Treatment of Hypertensive Emergency

Drug	Dosage/regimen	Onset of action	Duration of action	Adverse effects/precautions	Special indications
Sodium nitroprusside	i.v. infusion 0.25–2.0 (4.0) μg/kg/min	Immediate	1–2 min	Nausea, vomiting, tachycardia; cyanide poisoning on high-dose or prolonged administration, *etc*. Must be protected from light	Most emergencies Caution with high intracranial pressure or renal dysfunction
Nitroglycerin	i.v. infusion 5–100 μg/min	2–5 min	5–10 min	Headache, vomiting, tachycardia, methemoglobinemia, tolerance with prolonged use, *etc*. Must be protected from light	Acute coronary syndrome
Hydralazine	i.v. injection 10–20 mg	10–20 min	3–8 h	Tachycardia, flushing, headache, exacerbation of angina pectoris, persistent hypotension, *etc*.	Eclampsia
	i.m. injection 10–40 mg	20–30 min	4–6 h		
Nicardipine	i.v. infusion 0.5–6.0 μg/kg/min	5–10 min	60 min	Tachycardia, headache, flushing, local phlebitis, *etc*. Caution with heart failure	Most emergencies except acute heart failure Caution with increased intracranial pressure or acute coronary syndrome
Diltiazem	i.v. infusion 5–15 μg/kg/min	Within 5 min	30 min	Bradycardia, A-V block, sinus arrest, *etc*. Use at low doses for unstable angina	Most emergencies except acute heart failure
Phentolamine	i.v. injection 1–10 mg i.v. infusion at 0.5–2.0 mg/min after a bolus injection is also possible	1–2 min	3–10 min	Tachycardia, headache, *etc*.	Pheochromocytoma, catecholamine excess
Propranolol	i.v. injection 2–10 mg (1 mg/min) → 2–4 mg/every 4–6 h			Bradycardia, A-V block, heart failure, *etc*.	Prevention of tachycardia induced by vasodilators

If heart failure or retention of body fluid is observed, or if tolerance has developed, use furosemide simultaneously (prepared based primarily on references *42*, *104*, and *373*). i.v., intravenous; i.m., intramuscular.

blood pressure is stabilized. After the intravenous injection of the first dose, phentolamine may be administered by continuous intravenous infusion. Oral medication using drugs such as the selective α-blocker doxazosin should be started simultaneously. While β-blockers are effective for the management of tachycardia, they should be used after administration of α-blockers at a sufficient dose. Pheochromocytoma may cause hypertensive encephalopathy, acute left ventricular failure, or accelerated/malignant hypertension, and treatment mainly using an α-blocker should be performed in such situations.

h. Accelerated/Malignant Hypertension

In accelerated/malignant hypertension, diastolic blood pressure is 120–130 mmHg or higher and renal dysfunction rapidly progresses. If left untreated, the general condition rapidly deteriorates, and conditions including heart failure, hypertensive encephalopathy, and cerebral hemorrhage occur, leading to poor outcomes. Malignant hypertension accompanied by papilledema (grade IV according to the Keith-Wagener classification) and accelerated hypertension accompanied by exudative lesions (grade III) used to be distinguished. However, as there is no difference between them in the progression of organ damages or survival rate, they have recently been lumped together as accelerated/malignant hypertension. A high blood pressure at the onset of hypertension, interruption of antihypertensive treatment, and long-standing mental and physical stress are related to the development of malignant hypertension (*375*). According to the results at the same facility, organ damages such as ophthalmoscopic findings, left ventricular hypertrophy, and renal dysfunction were less advanced recently (1984–1999) than in the past (1971–1983)

(*376*, *377*). In the first period, the 5-year survival rate in patients with essential hypertension was 79%, and that in patients with chronic glomerulonephritis was 100%. Of the patients with chronic glomerulonephritis, 46% became maintained on dialysis within 12 months in the second period compared with 88% in the first period.

In patients with accelerated/malignant hypertension, blood pressure need not be reduced rapidly to the normal range, and control with oral medication is often possible. Many patients have a long history of hypertension, and a rapid reduction in blood pressure is likely to cause ischemia of important organs. If Na or water retention is observed, a loop diuretic should be used concomitantly. If accelerated/malignant hypertension has resulted from essential hypertension (*377*) or renal crisis of collagen disease, hyperactivity of the RA system is involved in the etiology, so that ACE inhibitors and ARBs are expected to be effective. However, their administration should be started at low doses to avoid an excessive decrease in blood pressure.

i. Cases with Increases in Blood Pressure Other than Hypertensive Emergency

A temporary marked increase in blood pressure without progressive organ dysfunction is considered to be false emergency. Elderly people and patients with anxiety show large changes in blood pressure, with blood pressure occasionally increasing to 180–200/110–120 mmHg or higher. However, emergency decrease in blood pressure is rarely required, unless there are symptoms or findings suggestive of acute target organ damages. The contents of a nifedipine capsule are occasionally administered to such patients, but this should be avoided, because it may cause cerebral infarction or myocardial infarction due to a rapid and excessive decrease in blood pressure, particularly in elderly patients. Causes of an increase in blood pressure such as pain and urinary retention, if present, must be removed. If blood pressure remains high on repeated measurements, Ca antagonists or ACE inhibitors of intermediate duration of action should be administered orally. For patients with anxiety, calming down of ventilation and anti-anxiety medication should be tried.

3) Blood Pressure Management at Pre- and Post-Surgery

Hypertension itself is generally not a contraindication for elective surgery. However, hypertensive organ damages and complications increase the risk for perioperative cardiovascular diseases. Therefore, hypertensive patients must be evaluated for left ventricular hypertrophy reduced coronary blood flow reserve, ischemic heart disease, carotid artery stenosis, cerebrovascular diseases, and renal dysfunction. These conditions increase the risk of ischemic complications due to an excessive perioperative decrease in blood pressure. Also, if left ventricular diastolic function is reduced, the function may be further reduced by an intraoperative or postoperative increase in blood pressure, causing pulmonary congestion. Elderly patients with systolic hypertension show wide changes in blood pressure before surgery, but they also show marked intraoperative changes in blood pressure and are likely to develop hypotension, which may cause ischemic complications. Therefore, to avoid excessive perioperative changes in blood pressure, control and stabilization of blood pressure is necessary before surgery. As preoperative blood pressure is higher, the risk of complications due to marked increase in blood pressure and tachycardia at intubation, intraoperative large changes in blood pressure, and hypertension immediately after surgery is greater. Day surgery should be avoided in hypertensive patients.

Blood pressure before elective surgery should be controlled if it is 180/110 mmHg or higher (*378*). A general target blood pressure is 140/90 mmHg. Blood pressure should be controlled preferably over a long period but over 2–3 weeks at least. If blood pressure is reduced in 2–3 days before the scheduled day of surgery, intraoperative changes in blood pressure tend to be large. If the time until surgery is limited, blood pressure should be controlled primarily using highly cardioselective β_1-blockers. And since patients who have been administered β-blockers over a long period are likely to develop intraoperative tachycardia, marked changes in blood pressure, and myocardial ischemia if they are withdrawn for surgery, their administration should be continued. Continuation of the administration of β-blockers not only prevents withdrawal syndrome but also reduces the risk of ischemic cardiac complications due to their protective effects against perioperative stress and sympathetic hyperactivity. If patients with ischemic heart disease have not been treated with β-blockers, their administration should be started before surgery. During surgery, propranolol may be administered intravenously if necessary. Antihypertensive drugs should be administered until the day of surgery, in principle. Concerning diuretics, the possibility of postoperative dehydration and hypokalemia should be considered, but their administration need not be discontinued if these conditions are manageable. If serum K level is less than 4.0 mEq/l before surgery, its correction is necessary. For emergency surgery and intraoperative increases in blood pressure, blood pressure should be reduced and maintained by continuous intraoperative infusion of Ca antagonists (nicardipine, diltiazem), nitroprusside, or nitroglycerine.

Since the hemodynamics are unstable for a few hours to a few days after surgery, antihypertensive therapy should be resumed as early as possible by the intravenous route if oral administration (including administration *via* the gastric tube) is impossible. The hemodynamic state should be stabilized by respiratory management and regulation of the body fluid volume with proper fluid supplementation. Factors of perioperative increases in blood pressure include preoperative anxiety, postoperative pain, excitation, hypercapnea, and hypervolemia, and the management of the causes of the increase in

blood pressure must be considered first. The administration of the contents of a nifedipine capsule, by which the degree or rate of decrease in blood pressure cannot be adjusted, must be avoided.

If a patient may have pheochromocytoma, surgery should be postponed, and examination should be continued. Once the diagnosis has been established, the tumor should be removed before the scheduled surgery. Renovascular hypertension, primary aldosteronism, and Cushing's syndrome do not interfere with general anesthesia if preoperative blood pressure is controlled to the range of mild hypertension. However, curable secondary hypertension should be treated first if the surgery is elective. In patients with atherosclerotic renovascular hypertension, there is the risk of cerebral ischemia, myocardial ischemia, and renal dysfunction, and evaluation of the possibility of, and preventive measures against, these conditions are important.

Since cardiovascular diseases such as stroke may occur during dental treatment, blood pressure must be controlled during as well as before dental treatment in hypertensive patients (*379*). Patients under antihypertensive medication should be instructed not to forget to take the drug on the day of dental treatment. The increase in blood pressure has been reported to be more notable during dental procedures that cause pain or anxiety (*379*, *380*). Although blood pressure is increased by local anesthetics containing epinephrine, the increase is slight. Therefore, if dental treatment is expected to be painful, a sufficient dose of anesthetics should be administered without hesitation (*379*, *380*). For patients complaining of intense anxiety, the administration of a tranquilizer should also be considered.

4) Hypertension in Women

Sex differences have been noted in various diseases, and the incidences and pathogenesis of cardiovascular diseases are known to differ in men and women. In women, the incidence of hypertension increases rapidly after menopause, and its prevalence becomes comparable to that in men after the age of 65. Women have also been reported to develop hypertension during pregnancy, as a result of hormone replacement therapy, and after the onset of menopause (*381*). Despite differences in their physio-pathological features, the organ protecting effects of antihypertensive agents were reported to be comparable in men and women (*100*).

What follows is a discussion of the clinical features and recommendations concerning hypertension related to pregnancy, hypertension related to hormone replacement therapy, and hypertension in postmenopausal women.

a. Hypertension in Pregnancy

Hypertension observed during pregnancy has been treated as toxemia of pregnancy particularly when proteinuria and edema are present; clinical data have confirmed an important role for hypertension in the development of this pathological process. A new definition and classification of toxemia of pregnancy were proposed by the Japanese Society of Toxemia of Pregnancy and the Japanese Society of Obstetrics and Gynecology (*382*); the treatment guidelines established by these organizations have been incorporated into our report. While the pathologic condition referred to as toxemia has been termed pregnancy hypertension syndrome by the Japanese Society of Toxemia of Pregnancy and the Japanese Society of Obstetrics and Gynecology, in the JSH 2004 guidelines, we refer to it as pregnancy-induced hypertension.

i. Classification of Hypertension in Pregnancy

1. Pregnancy-Induced Hypertension

A condition in which hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) occurs after Week 20 of pregnancy and resolves within 12 weeks after delivery.

2. Preeclampsia

A condition in which hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) occurs after Week 20 of pregnancy that is accompanied by proteinuria (≥300 mg/day) but which resolves within 12 weeks after delivery.

3. Eclampsia

A condition characterized by the development of a maternal convulsion after Week 20 of pregnancy, the presumption being that epilepsy and secondary convulsion have been excluded as diagnoses. This condition is referred to as gestational eclampsia, delivery eclampsia, or puerperal eclampsia depending on its time of occurrence.

4. Preeclampsia Superimposed on Chronic Hypertension and/or Renal Disease

(1) A condition in which hypertension is observed prior to pregnancy or prior to Week 20 of pregnancy and which is accompanied by proteinuria after Week 20 of pregnancy.

(2) A condition in which hypertension and proteinuria are observed prior to pregnancy or before Week 20 of pregnancy, either or both of which are exacerbated after Week 20 of pregnancy.

(3) A condition in which renal disease characterized only by proteinuria is present prior to pregnancy or before Week 20 of pregnancy, and in which hypertension occurs after Week 20 of pregnancy.

Although hypertension related to pregnancy has been classified according to its symptoms and time of onset, there is, as yet, no firm consensus regarding this classification system.

ii. Antihypertensive Drug Treatment

It has become increasingly more difficult to perform a randomized controlled trial involving pregnant subjects. However, a metaanalysis indicated that both mother and child

Table 9-5. Antihypertensive Drugs for Hypertension in Pregnancy

Drug	Dose	Transfer to fetus	Secretion into milk*	Adverse effects	
				Mother	Fetus
Methyldopa	500–2,000 mg 3–4 times/day	100%	Nominal	Depression, orthostatic hypotension	Hypotension
Clonidine	150–900 μg 2–3 times/day	Unknown	Unknown	Depression, thirst	Unknown
Propranolol	40–120 mg 2–3 times/day	25%	40–60%	Easy fatigability	Bradycardia
Metoprolol	40–120 mg 2–3 times/day	100%	100%	Easy fatigability	Bradycardia
Atenolol	50–100 mg once/day	100%	100%	Easy fatigability	Bradycardia
Pindolol	5–15 mg 2–3 times/day	Unknown	Unknown	Easy fatigability	Bradycardia
Labetalol	150–450 mg 3–4 times/day	50%	10–20%	Dizziness, myalgia	Unknown
Hydralazine	30–200 mg 3–4 times/day	100%	Nominal	Palpitation, tachycardia	Thrombocytopenia

Contraindication to ACE inhibitors and ARBs. Ca antagonists must be used carefully. *Concentration in maternal blood = 100%.

benefit from a lowering of maternal blood pressure (*383*). Furthermore, the outcome may depend on when hypertension occurred during pregnancy, which makes it difficult to formulate a uniform protocol. Since pregnant women are excluded from clinical trials, a large-scale clinical trial of treatment of hypertension in pregnancy is unlikely to be undertaken in Japan. Therefore, past results and foreign guidelines were used as references to formulate the treatment strategies below (*43*, *104*, *384*, *385*).

iii. Approaches to Treatment

There is no consensus concerning the blood pressure at which antihypertensive medication should be initiated in patients with hypertension in pregnancy.

In general, patients with hypertension receive non-drug therapy for several months before they are prescribed antihypertensive drugs, if necessary. Patients with hypertension in pregnancy, however, may have gone through delivery, and/or their blood pressure may have increased further over the course of a month. Data suggest that pregnant women with hypertension who are not treated with drugs are at increased risk. Therefore, antihypertensive medication should be initiated in pregnant women if their systolic blood pressure is 140 mmHg or higher, and/or if their diastolic blood pressure is 90 mmHg or higher, without waiting to see whether non-pharmacological therapies (restriction of salt intake, exercise therapy, *etc*.) are effective. Though the data are unclear regarding the best target blood pressure in these women, it would be prudent to set the target at less than 130/80 mmHg, considering the relationship between blood pressure and urinary protein excretion. Although antihypertensive medication may result in a reduction in placental blood flow, this is unlikely to occur in women whose blood pressure is maintained at 130/80 mmHg with antihypertensive drugs other than diuretics.

iv. Choice of Antihypertensive Drugs

The most commonly prescribed antihypertensive drugs are shown in Table 9-5. Ever since their safety has been established, methyldopa and hydralazine have been the primary agents used for the treatment of hypertension in pregnancy. Recently, the efficacy of Ca antagonists has been demonstrated, and their use has been approved in several Western countries (*43*, *104*, *384*). However, many Ca antagonists are contraindicated in pregnant women in Japan. Since Ca antagonists have few serious adverse effects (*386*), and since their use is recommended by the medical guidelines of Western countries, it is likely that they will soon gain acceptance as a treatment option in Japan as well. The αβ-blocker labetalol has also been prescribed for hypertension in pregnancy.

Hypertension in pregnancy is considered to be a contraindication for the use of ARBs and ACE inhibitors, both of which have been reported to cause various disorders including oligohydramnios, and fetal renal failure and growth disturbances (*387*). However, reports of the continued use of these drugs in patients who happened to become pregnant suggested that these side effects do not occur with high frequency (*388*). The foregoing notwithstanding, despite the low probability of adverse effects, pregnancy is still a contraindication for the use of ARBs and ACE inhibitors. Diuretics should also be avoided since they can theoretically reduce placental blood flow. Intravenous injection of magnesium sulfate ($MgSO_4$) is the most effective treatment for patients who have developed eclampsia.

Women with hypertension following pregnancy should dis-

cuss their breast feeding options with their physician, in light of the fact that most antihypertensive drugs are secreted into mother's milk at low concentrations. If a patient with hypertension has a diastolic blood pressure of less than 100 mmHg, withdrawal of antihypertensive medication for several months may be an option. However, if their hypertension is more severe, breast-feeding should be abandoned.

b. Hypertension Related to the Use of Oral Contraceptives and Estrogen Replacement Therapy

Estrogen, which is used as an oral contraceptive and as a treatment for climacteric disorders has been reported to increase blood pressure and induce thromboembolisms at high doses. Estrogen is thought to increase blood pressure by increasing angiotensin II production. Although sufficient Japanese data are lacking, hormone replacement therapy is thought to have no effect on blood pressure in postmenopausal women. However, as it may increase blood pressure in patients who have a predisposition to hypertension, follow-up blood pressure measurement every few months is recommended (*389*). On the other hand, since estrogen/progesterone preparations were shown to increase cardiovascular events as reported by the Women's Health Initiative (WHI), it has been recommended that only low doses of estrogen be used in these patients. As such, hypertension due to estrogen administration is considered to be rare (*390*). There have not been sufficient data obtained as yet regarding the hypertensive effects of oral contraceptives and hormone replacement therapy in Japanese women.

c. Hypertension in Postmenopausal Women

Whether or not blood pressure increases in postmenopausal women is unclear. It is clear that the other changes that women experience following menopause, such as body weight gain and fluctuations in hormone levels, may contribute to their increase in blood pressure (*391*). These, as well as psychological, factors often result in fluctuations in blood pressure that make treatment difficult. While hypertension in postmenopausal women has been reported to be successfully treated with hormonal therapy, psychotropic medications, and Chinese herbs, the efficacy of these approaches has not as yet been established (*392*, *393*).

Summary

Refractory Hypertension

1) In refractory hypertension, obesity, sleep apnea syndrome, white coat hypertension, poor drug compliance, volume overload, inappropriate combination of antihypertensive drugs, and pressor effects of other drugs must be considered first.
2) If blood pressure cannot be reduced even by appropriate treatments, consult a hypertension specialist, because there is the possibility of secondary hypertension.

Hypertensive Emergency and Urgency

1) Blood pressure reduction must be started immediately when hypertension complicated by hypertensive encephalopathy or acute aortic dissection, hypertensive left ventricular failure with pulmonary edema, acute myocardial infarction or unstable angina with severe hypertension, pheochromocytoma crisis, or eclampsia is observed, or within a few hours in accelerated/malignant hypertension. Also, referral of the patient to a facility with a hypertension specialist is desirable. Do not induce a rapid decrease in the blood pressure by treatments such as sublingual administration of a nifedipine capsule.
2) If hypertension is not accompanied by progressive organ damages, emergency decrease in blood pressure is rarely required.

Blood Pressure Management at Pre- and Post-Surgery

1) For the prevention of perioperative complications in hypertensive patients, hypertensive organ damages and complications should be evaluated and blood pressure control must be maintained by continuing antihypertensive medication through the perioperative period including the administration in the morning of the day of surgery.
2) β-Blockers are effective in patients with a high risk of ischemic heart disease.
3) Control of pain, anxiety, and excitation is also important for prevention of increases in blood pressure.

Hypertension in Women

1) Hypertension (blood pressure ≥140/90 mmHg) that appears after Week 20 of pregnancy is defined as pregnancy-induced hypertension.
2) Pregnancy-induced hypertension should be primarily treated with antihypertensive medication, specifically methyldopa and hydralazine, though Ca antagonists can also been used. Pregnancy is a contraindication for the use of ARBs and ACE inhibitors.
3) Women who use oral contraceptives or are on hormone replacement therapy should have their blood pressure monitored frequently.
4) The hypertension that develops in women, particularly postmenopausal women, may differ in its clinical features from that which develops in men; further evaluation of these differences needs to be carried out.

10. Hypertension in Children

1) Characteristics of Hypertension in Children and High School Students

On school health screening, hypertension is detected in 0.1–1% of the 4th to the 9th graders and in about 3% of high school students (*135*, *394*). Hypertension in subjects of this age range generally corresponds to essential hypertension although secondary hypertension is also observed infrequently. The increase in the blood pressure is generally mild in children and high school students with essential hypertension, and is often complicated by obesity. Since obese children are increasing annually as shown in Fig. 10-1, hypertensive children are also considered to be increasing. In the United States, the systolic blood pressure has increased by 1.3 mmHg, and the diastolic blood pressure by 3.3 mmHg, during the past 10 years in adolescents aged 8–17 years, and the increase in obesity has been suggested as a cause (*395*).

Elevated blood pressure in children that requires immediate antihypertensive medication is likely to be secondary hypertension. The possibility of secondary hypertension is greater as the age is lower and the blood pressure is higher. In fact, most of the hypertensive children admitted for close evaluation or treatment to 2 hospitals in London had secondary hypertension, and 80% had renal hypertension, in particular (*396*, *397*).

2) Measurement of Blood Pressure and Diagnostic Criteria of Hypertension for Children

The selection of a manchette of an appropriate size is important for blood pressure measurement in children. In Japan, commercial manchettes for mercurial sphygmomanometers 7 cm wide are used for children aged 3–5 years, those 9 cm wide for children aged 6–8 years, and those 12 cm wide (adult size) for children aged 9 years and above. However, as the true blood pressure can be measured more accurately by selecting a manchette according to the arm circumference (at point midway between the olecranon and the acromion) or physique than to age, a manchette that covers more than 40% of the upper arm circumference should be selected for children with a large physique.

The fifth Korotkoff sound should be adopted as the diastolic blood pressure. While criteria of hypertension corrected for the height have been reported in the United States (*398*), there are no such criteria in Japan. The JSH 2000 guidelines proposed diagnostic criteria of hypertension for preschool children, 1st–3rd graders, 4th–6th graders, junior high school students, and high school students on the basis of the average blood pressures by age and sex that had been described in major preceding reports (Table 10-1) (*394*, *399*, *400*).

There have been few subsequent studies in which data of the blood pressure in elementary school pupils and junior high school students were reported on the basis of manometry according to age (or grade). Table 10-2 shows criteria of hypertension (95 percentile values) derived from the results of group manometry performed by a relatively well-controlled method using Dinamapp type automatic sphygmomanometer (*401*).

3) Problems with Essential Hypertension in Children and High School Students

Essential hypertension in childhood or adolescence has been reported to be rarely complicated by serious organ damages because of its mildness but to be frequently accompanied by left ventricular or left atrial hypertrophy (*402*, *403*). Also, hypertension is a major risk factor for atherosclerosis and may develop into adult essential hypertension.

According to a re-investigation of normotensive and hypertensive junior high school students after 20 years (*404*), the frequency of hypertension was significantly higher in the previously hypertensive group (20.9%) than in the previously normotensive group (5.5%). While the family history, obesity, and excessive drinking, and smoking were related to the progression of hypertension (*404*), they were all known contributing factors for hypertension. Also, when college students were divided into a hypertensive group and a normotensive group and followed up after 8–26 years (mean 17 years), hypertension was observed in 44.6% of the hypertensive group and 9.2% of the normotensive group (*405*). The family history, obesity, drinking and smoking were also related to the progression of hypertension. Large-scale epidemiological studies in other countries have also revealed a tracking phenomenon from childhood to adulthood.

4) Lifestyle Modifications in Childhood (Primary Prevention of Hypertension)

It is an epidemiologic fact that excessive salt intake is

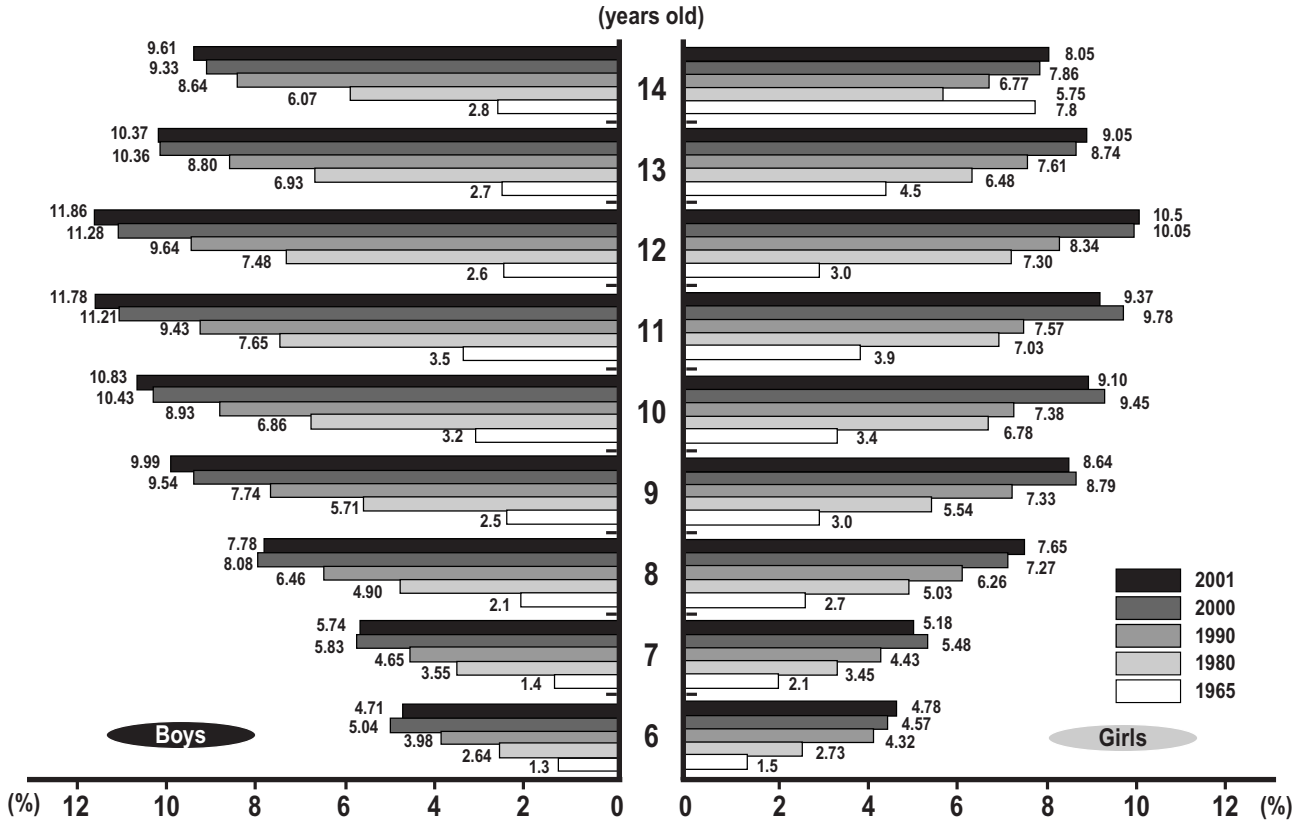

Fig. 10-1. *Changes in the frequency of obese children. Obese children: children with a body weight 120% or greater than mean body weight for height calculated by sex and age. Data from Report of School Health Statistics, Ministry of Education, Culture, Sports, Science and Technology of Japan.*

Table 10-1. Criteria of Hypertension and High-Normal Blood Pressure in Children and Adolescents

	Hypertension		High-normal blood pressure	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Pre-school children	≥120	≥70		
Elementary school				
1st–3rd graders	≥130	≥80	≥120	≥70
4th–6th gradres	≥135	≥80	≥125	≥70
Junior high school				
Boys	≥140	≥85	≥130	≥70
Girls	≥135	≥80	≥125	≥70
High school	≥140	≥85	≥130	≥75

SBP, systolic blood pressure; DBP, diastolic blood pressure.

involved in an increase in the blood pressure. Although there is no report in Japan that confirmed a preventive effect of restriction of the salt intake in children, there is a report abroad that restriction of the salt intake started in the neonatal period led to no increase in the blood pressure after 15 years (*406*). The blood pressure has also been reported to be lower in children nursed with mother's milk (*407*). It has also been shown that atherosclerosis begins in childhood and that the serum lipid levels are increasing annually in Japanese teenagers (*408*). Therefore, dietary guidance (education) concerning restriction of the salt intake and fat intake must be started from early childhood, when dietary habits are formed, to ensure the formation of proper dietary habits. Urgent lifestyle modifications (diet, exercise) should be introduced, particularly when the child has a marked family history of hypertension or is obese, even if the current blood pressure is normal.

Table 10-2. Criteria of Hypertension by Sex and Grade

	Boys		Girls	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Elementary school				
1st graders	107	60	108	60
2nd graders	112	63	108	60
3rd graders	114	62	111	61
4th graders	116	63	121	66
5th graders	117	63	119	66
6th graders	119	63	119	65
Junior high school				
1st graders	125	66	126	68
2nd graders	130	66	126	68
3rd graders	136	68	128	70

a. Dietary Therapy

Obesity is not only a major risk factor for cardiovascular diseases but is frequently complicated by hypertension, hyperlipidemia, and diabetes mellitus also in children (*409*). Moreover, as obesity in childhood frequently leads to obesity in adulthood (*410*), it must be resolved during childhood regardless of whether it is complicated by hypertension or not. In conducting dietary therapy, restriction of the energy intake, appropriate nutritional balance, and correction of inadequate eating patterns are principles.

Concerning the prevention of hypertension itself, restriction of salt intake and encouragement of K intake are the same as in adults (see 4. Lifestyle Modifications).

b. Exercise Therapy

Exercise therapy is indispensable for the control of obesity, and exercises that can be continued everyday are recommended, though their intensity may be low. In children who spend long hours in watching TV or playing video games, the time spent in these activities should be restricted with encouragement of exercise.

Dynamic exercises (isotonic exercises) are strongly recommended, because they have an antihypertensive effect. Static exercises (isometric exercises) are also recommended with the exception of weight lifting, but precaution against obesity is necessary in judo and sumo.

5) Management of Hypertension

In children and adolescents who were found to have mild hypertension by health screening or on other occasions, the blood pressure should be measured repeatedly on different opportunities, and white coat hypertension should be excluded by home measurement. ABPM is also useful for the diagnosis of white coat hypertension and reverse white coat hypertension (*411*).

Since childhood and adolescent essential hypertension is mild in many patients, non-pharmacological therapies including lifestyle modifications and management of obesity must be attempted for 3–6 months, before antihypertensive medication is considered. There is a report that the blood pressure could be successfully reduced in high school students by restriction of the salt intake (*135*), so that the salt intake must be reduced first as dietary therapy. Dynamic exercise (isotonic exercise) should be recommended unless the patient has complications, because it not only reduces obesity but also has a direct antihypertensive effect (see 4. Lifestyle Modifications).

6) Antihypertensive Drug Treatment

There has not been a report on antihypertensive medications in Japanese adolescents, but antihypertensive medication should be started if the patient has organ damages, or if the blood pressure remains above the target level even after non-pharmacological therapies. Since left ventricular hypertrophy is often observed as a complicating organ damage, ECG and echocardiography must be performed.

Antihypertensive drugs are selected primarily from ACE inhibitors and Ca antagonists by criteria similar to those for adults.

The only study in which the dose of an antihypertensive drug was evaluated in an adequate number of children in Japan was about nifedipine in children with kidney diseases (*412*). In this study, the administration of nifedipine was started at 0.2 mg/kg/day, and the mean dose at which responses were observed was 0.5 mg/kg/day. The dose for children is usually calculated from the body surface area, and the dose of most drugs for a 7-year-old child is about half the dose for adults. However, the administration of antihypertensive drugs should be started at a low dose, and the dose should be adjusted by careful monitoring of changes in the blood pressure. ARBs and ACE inhibitors are contraindicated in pregnant women and sexually active female teenagers

because of their effects on fetuses.

Once antihypertensive medication is started, the patients' families often worry whether it must be continued all life. However, there are patients in whom the blood pressure increases temporarily during adolescence and remains normal over a long period after withdrawal of medication (*413*). Therefore, gradual decreases in the dose half a year to 1 year after the beginning of the administration is an option. However, periodic blood pressure measurement should be continued over a long period, because the patients are likely to develop hypertension in the future.

Summary

1) Screening by blood pressure measurement reveals essential hypertension in 0.1–1% of elementary school pupils and junior high school students and about 3% of high school students. Hypertension in children is not only a risk factor for atherosclerosis but also frequently develops into adult essential hypertension.
2) For the primary prevention of hypertension, dietary guidance (education) primarily concerning restriction of the salt intake and encouragement of the K intake should be given from early childhood, when dietary habits are formed, to ensure the acquisition of proper dietary habits.
3) If essential hypertension is detected, non-pharmacological therapies such as lifestyle modifications and control of obesity should be attempted for 3–6 months. The salt intake should be reduced, the K intake increased, and exercise encouraged. Although static exercises (isometric exercises) are also recommended with the exception of weight lifting, precaution against obesity is necessary in judo or sumo.
4) If hypertension is symptomatic, if it is complicated by organ damages, or if the blood pressure remains above the target level even after non-pharmacological therapies, antihypertensive medication primarily with ACE inhibitors or Ca antagonists is started as in adult patients. ARBs and ACE inhibitors are contraindicated in pregnant women and sexually active female teenagers.

11. Secondary Hypertension

1) Prevalence of Secondary Hypertension

Hypertension due to particular identifiable causes is called secondary hypertension. At hypertension outpatient clinics in Western countries, secondary hypertension, more than 50% of which is renal parenchymal hypertension, is reported to be observed in less than 5% to 10% of the patients (Fig. 11-1) (*414–419*). Recently, however, there have been increasing reports that endocrine hypertension is more frequent. For example, one Japanese hospital reported that patients with endocrine hypertension and renovascular hypertension account for 9.1% of all hypertensive patients, and hypertension has been alleviated by treatment for the responsible diseases in 82% (*420*). Since secondary hypertension is often cured, or its symptoms alleviated, by treatment for responsible diseases, a positive approach to differential diagnosis is important (Table 11-1).

2) Renal Parenchymal Hypertension

Renal parenchymal hypertension is the most frequent secondary hypertension, accounting for 2–5% of all hypertension (*414–419*). According to the Hisayama Study, in which the subjects were the general population aged 40 years or older, and autopsy was performed in 131 hypertensive patients during the 20 years since 1961, the frequency of secondary hypertension was 3.8%, and that of renal hypertension was 3.1% (*421*).

The incidences of, and mortalities due to, stroke and heart diseases have been reduced by the treatment for hypertension, but the incidence of end-stage renal disease has continued to increase. In the 32,308 patients in whom dialysis was introduced in 2002, diabetic nephropathy increased markedly (12,630 patients, 39.1%) and became the top cause of dialysis, surpassing chronic glomerulonephritis (10,309 patients, 31.9%). Including nephorosclerosis and polycystic kidney disease, which are the third (2,536 patients, 7.8%) and fourth (779 patients, 2.4%) most frequent diseases in dialysis patients, the top 4 diseases account for 80% of the patients (*285*). Many of these chronic kidney diseases are complicated by hypertension, but hypertension is also a serious risk factor for renal dysfunction. Since there are limited methods for the control of the pathogenic mechanism of chronic kidney diseases today, the control of hypertension is extremely important for the prevention of end-stage renal disease. Nephrosclerosis related to essential hypertension was discussed in 6. Hypertension Associated with Organ Damage.

Chronic kidney diseases may cause hypertension, but the kidney is often damaged by hypertension. Therefore, if the two conditions are concurrent, it is often difficult to judge which the cause of the other is. Generally, hypertension is likely to be secondary to a kidney disease if the kidney disease, gestational nephropathy, or abnormal urinalysis is confirmed to have preceded hypertension. Also, a kidney disease is likely to be responsible for hypertension if hypertension is milder than abnormal urinalysis or renal disorder, or if there are few hypertensive cardiovascular complications other than the kidney disease. Urinalysis and the measurement of the serum creatinine level should be performed in all hypertensive patients, and, if abnormalities are persistently observed, evaluation of the renal morphology by ultrasonography or CT is necessary. Although specific treatments for kidney diseases, particularly renal parenchymal disorders, are limited, early treatment may improve the outcome. Therefore, if a kidney disease is considered possible, it is strongly recommended to promptly refer the patient to a specialist.

a. Diabetic Nephropathy

Most hypertensive patients newly diagnosed to have type 2 diabetes show a normal urinary albumin level and no sign of nephropathy (*422*). However, albuminuria is a predictor of the progression to overt nephropathy, a rapid increase in the complication rate of hypertension, and an increase in the risk for cardiovascular events (*423*). Moreover, with overt proteinuria, the damage of the renal parenchyma becomes nearly irreversible, and the probability of the progression to end-stage renal disease requiring dialysis increases. Therefore, early detection of microalbuminuria and aggressive treatment are important.

Basic principles of treatment for hypertension due to diabetic nephropathy are the same as those for hypertension complicated by diabetes mellitus. In normotensive patients with type 2 diabetes showing microalbuminuria (*424*) or normal urinary albumin (*425*), the occurrence or progression of nephropathy is prevented by the administration of ACE inhibitors. Moreover, ARBs have been demonstrated to be effective in patients with type 2 diabetes showing conditions from microalbuminuria (*274*) to overt proteinuria (*83*, *273*). According to metaanalyses in patients with diabetic nephrop-

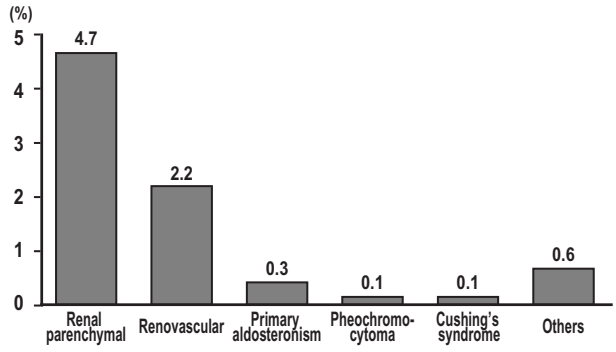

Fig. 11-1. *Prevalence of secondary hypertension (%). Calculated by weighted averaging of data in references* 414–419 *(percentages in 12,228 hypertensive patients).*

athy, long-acting Ca antagonists have effects comparable to those of ACE inhibitors (*282*, *426*). The J-MIND also showed that long-acting Ca antagonists inhibited the progression of diabetic nephropathy similarly to ACE inhibitors (*168*). Therefore, diabetic nephropathy should be treated from an early stage using ACE inhibitors or ARBs, and strict control of the blood pressure should be achieved by introducing multiple-drug combination therapy including long-acting Ca antagonists depending on the progression of the disease.

b. Chronic Glomerulonephritis

Among patients with chronic glomerulonephritis, the frequency of hypertension is relatively high, and those with marked impairment of renal function or marked abnormalities on renal biopsy are more likely to be hypertensive. Many factors including body fluid retention due to disturbance of salt excretion (increased salt sensitivity), inappropriate activation of the RA system, and activation of the sympathetic nervous system are considered to be involved in its etiology (*427*). Since hypertension, renal dysfunction, and proteinuria are independent risk factors for cardiovascular diseases, treatments in consideration of the protection of the kidney and alleviation of proteinuria as well as sufficient reduction of the blood pressure are necessary.

In patients with hypertension complicating chronic glomerulonephritis, restriction of the salt intake and protein intake is important as a non-phamacological treatment (*151*). It is important to achieve a sufficient decrease in the blood pressure primarily using ARBs or ACE inhibitors and Ca antagonists, and the use of multiple drugs is often necessary. In patients with IgA nephropathy, which is the most frequent form of chronic glomerulonephritis, accompanied by hypertension, ACE inhibitors are useful for reducing the urinary protein level and preventing the progression of the kidney disease (*428*). Moreover, ACE inhibitors alleviate proteinuria also in normotensive patients with IgA nephropathy (*429*). There is a report that the combination of an ACE inhibitor and an ARB is effective for the treatment of non-diabetic nephropathy including chronic glomerulonephritis (*278*).

c. Polycystic Kidney Disease

This is a disease in which multiple cysts develop in the bilateral kidneys. The confirmation of the presence of multiple cysts in the bilateral kidneys by ultrasonography or CT is important for its diagnosis (*430*). When polycystic kidney disease (PKD) is considered likely, referral to a nephrologist is desirable. The genes responsible for autosomal dominant PKD, which account for a majority of PKD, are PKD1 (short arm of chromosome 16) and PKD2 (long arm of chromosome 4), but there is also PKD caused by autosomal recessive inheritance. PKD1 is responsible in 80–90% of the PKD patients, and PKD2 in the remaining patients (*431*). The prevalence of PKD is one in every 2,000–4,000 persons (*432*).

The disease is progressive and ends in end-stage renal disease in about 40% of the patients in their 50s (*432*). While restriction of the salt intake is effective for the control of complicating hypertension, a low-protein diet has often been reported to be ineffective for the prevention of the progression of renal disease. Hypertension is observed in about 60% of the patients (*433*), and control of the blood pressure at 130/80 mmHg or less is recommended as in hypertension complicating other renal diseases, because hypertension promotes renal dysfunction and is a risk factor for intracranial hemorrhage. The RA system is often enhanced, and hypertension responds to ACE inhibitors (*434*). Since there has also been a report that ARBs and ACE inhibitors have kidney protecting effects, they are the first choices (*435*, *436*). However, as these antihypertensive drugs may cause rapid decreases in the blood pressure, they should be administered carefully from a low dose. Since hypokalemia has been suggested to be involved in the progression of renal cysts, caution is necessary in the use of loop diuretics. The incidence of intracranial hemorrhage, particular cerebral hemorrhage, is clearly high in patients with PKD, and intracranial aneurysms have been detected by MRI in about 10% of the patients. This percentage is clearly higher than in the general population (*437*). Familial concentration of the occurrence of intracranial hemorrhage has also been noted. Periodic check for intracranial aneurysms and sufficient control of the blood pressure are necessary for patients with PKD.

3) Renovascular Hypertension

Renovascular hypertension is caused by a reduction in the renal perfusion pressure due to hemodynamically significant stenosis of the renal artery and consequent activation of the RA system. It is observed in 0.5–1% of all hypertensive patients. Stenosis is caused primarily by fibromuscular dysplasia (about 24%), which occurs frequently in relatively young people, and by atherosclerosis (about 38%), which is observed frequently in middle-aged and aged individuals, but

Table 11-1. Findings Suggestive of Secondary Hypertension and Examinations Necessary for Its Differential Diagnosis

Causative disorder	Suggestive findings	Examinations
Renal parenchymal hypertension	Proteinuria, hematuria, abnormal urinary sediment, increase in serum creatinine level, hyperuricemia	Measurement of urinary protein (≥1 g/day), evaluation of renal function (estimation of GFR), immunological tests (serum complement levels, IgA), renal ultrasonography, CT, renal biopsy
Diabetic nephropathy	Long history of diabetes, glycosuria (proteinuria, edema)	Check for diabetic retinopathy, measurement of urinary albumin and protein, evaluation of renal function, renal ultrasonography (renal atrophy is rare)
Chronic pyelonephritis	Bacteriuria, hypotonic urine	Urine bacterial culture, IVP, renal ultrasonography
Renovascular hypertension	Sudden onset or exacerbation of hypertension in an elderly patient, hypertension in a young patient, abdominal bruit, hypokalemia	Measurement of PRA and PAC (captopril test), renal ultrasonography, CT, MRI, renal scintigraphy/renography, angiography, sampling from renal vein
Primary aldosteronism	History of limb weakness and paralysis, nocturia, hypokalemia	Simultaneous measurement of PRA and PAC (renin stimulation test), abdominal CT, MRI, sampling from adrenal vein, adrenocortical scintigraphy
Pheochromocytoma	Paroxysmal headache, palpitations, hyperhidrosis, labile hypertension, orthostatic hypotension	Measurement of plasma and urinary catecholamines, abdominal CT, MRI, ^{131}I-MIBG scintigraphy
Cushing's syndrome	Central obesity, moon face, skin striae, abnormal glucose tolerance, hypokalemia	Measurement of ACTH and cortisol (circadian rhythm, dexamethasone suppression test), head MRI, abdominal CT, MRI, adrenocortical scintigraphy
Hyperthyroidism	Body weight loss, hyperhidrosis, tachycardia, decrease in total cholesterol	Measurement of thyroid hormones, thyroid (neck) ultrasonography
Hypothyroidism	Bradycardia, edema, pericardial effusion, increase in total cholesterol, CPK, and LDH	Measurement of thyroid hormones, thyroid (neck) ultrasonography
Hyperparathyroidism	Hypercalcemia	Measurement of PTH
Vascular hypertension	Lateral differences in blood pressure, difference in blood pressure between upper and lower limbs, bruit	Chest and abdominal CT, MRI (MRA), angiography
Drug-induced hypertension	History of usage of drugs, refractory hypertension, hypokalemia	Re-evaluation of entire drug regimen

IVP, intravenous pyelography; PRA, plasma renin activity; PAC, plasma aldosterone concentration; MIBG, meta-iodobenzyl guanidine.

it is also caused by congenital malformation and renal aneurysm as well as aortitis syndrome (about 15%), which occurs frequently in young women. Stenosis is unilateral in 70–80% and bilateral in 20–30% of the patients, and atherosclerotic stenosis is often bilateral.

Patients with atherosclerosis of the renal arteries have advanced systemic atherosclerosis, and many of them show cardiovascular diseases, renal dysfunction, and proteinuria. The frequency of renal artery stenosis is high in high-risk patients and is even higher in those with hypertension, proteinuria, and renal dysfunction. According to reports in Japan, renal artery stenosis was demonstrated in 7% of the patients who had undergone cardiac catheterization for differential diagnosis of ischemic heart disease (*438*) and 12% of those in whom myocardial infarction was diagnosed by autopsy (*439*). However, renovascular hypertension does not occur in all of those with renal artery stenosis, and thus functional evaluation is necessary for its diagnosis. Renal failure due to an ischemia-induced decrease in the glomerular filtration rate or loss of the renal parenchyma is called ischemic nephropathy. Ischemic nephropathy accounts for 11–14% of end-stage renal disease (*440*). Ischemic nephropathy may be overlooked, and differential diagnosis is necessary if a middle-aged or aged patient exhibits rapid progression of renal dysfunction. Early detection and early treatment are important in renovascular hypertension, because systemic organ disorders and damage to the intact kidney progress rapidly. Also, it may cause serious hypertension or malignant hypertension.

a. Diagnostic Clues

In hypertension with no family history, hypertension in young people or elderly people with a rapid onset, refractory hypertension, and hypertension in patients with renal function reduced by the administration of ACE inhibitors or ARBs, renovascular hypertension should be considered. Abdominal bruit, difference in the size of the kidneys, hypokalemia, polycytemia, and progressive renal dysfunction are important diagnostic signs, which, however, are not observed in all patients. In addition, ischemic nephropathy must be considered in patients aged more than 60 years, those showing unexplained reduction in the renal function, those with marked atherosclerotic diseases, those with recurrent pulmonary edema that cannot be explained by the cardiac function alone, those with diabetes mellitus, those with hyperlipidemia, and those with a family history of heart disease (*441*).

b. Examinations for the Diagnosis

It is necessary to confirm that stenosis is present in the renal artery (morphological diagnosis) and that stenosis is causing hypertension by activating the RA system (functional diagnosis).

For screening, non-invasive ultrasonography, which permits comparison of the size of the bilateral kidneys and evaluation of the renal blood flow by the Doppler technique, is useful for the morphological diagnosis. An increase in the baseline renin activity and detection of excessive responses after captopril administration (captopril test) are useful for functional evaluation (*442*). In patients who show a reduction in the blood pressure after captopril administration, the blood pressure is expected to be reduced by vascular reconstruction. If the production of angiotensin II is blocked with an ACE inhibitor, the GFR and renal function decrease in the ischemic kidney with stenosis compared with the contralateral side. While the detection of functional decrease of the ischemic kidney by renal scintigraphy after the administration of an ACE inhibitor is useful for the prediction of the degree of decrease in the blood pressure after vascular reconstruction, the accuracy of this examination is reduced by the presence of renal failure (*443*, *444*). Double Doppler ultrasonography, which detects the renal artery by ultrasonography and determines the blood flow velocity at the site of stenosis by the Doppler technique, allows the calculation of the hemodynamic severity of stenosis, can be used also in renal failure, and permits the diagnosis of bilateral stenosis and complete obstruction (*445*). In addition, the calculation of the renal artery resistance coefficient may lead to the prediction of therapeutic effects (*446*).

According to a recent metaanalysis (*447*), angiography by contrast-enhanced CT and 3-dimentional MRA are highly effective for the diagnosis of renovascular stenosis. In patients who may have renovascular hypertension, one of these examinations should be selected depending on the renal function. For its treatment, detailed evaluation of renal blood vessels is necessary, and aortography or selective renal arteriography is eventually indispensable. In addition, the renin activity should be measured in the blood of the bilateral renal veins; if the value on one side is 1.5 times or higher than the value on the other side, stenosis is judged to be significant on the high-value side.

c. Treatments

i. Antihypertensive Drug Treatment

Treatment using antihypertensive drus should be performed until vascular reconstruction and in patients in whom vascular reconstruction is impossible. The effect of drug therapy is limited in patients with renal failure or bilateral renal artery stenosis. β-Blockers, ARBs, or ACE inhibitors, which suppress the RA system should be selected. Ca antagonists are also effective, but diuretics should be limited to a supplementary level, because they stimulate the RA system. The administration of ARBs and ACE inhibitors should be started at a low dose after confirming the absence of bilateral renal artery stenosis. The dose should be adjusted by paying attention to excessive decrease in the blood pressure in hypovolemic patients and hyperkalemia or progression of renal dysfunction in patients with reduced renal function. If renal dysfunction progresses rapidly, the administration must be discontinued immediately, and the drugs should be replaced by others.

ii. Vascular Reconstruction

Vascular reconstruction is the first principle treatment to remove the cause of renovascular hypertension. Percutaneous transluminal renal angioplasty (PTRA) should be considered first. This procedure is advantageous in that it is relatively less invasive and can be performed repeatedly. The success rate of PTRA against non-ostial stenosis of the renal artery is high, and the re-stenosis rate after 1 year has been reported to be 10–30% (*448*). Particularly, the therapeutic results of PTRA against fibromuscular dysplasia are satisfactory, with the initial success rate and the patency rate after 10 years having been reported to be 100% and 87%, respectively (*449*). On the other hand, atherosclerosis often causes ostial stenosis, and the therapeutic results of PTRA used to be often unsatisfactory; a relatively high initial success rate of 65–80% was accompanied by a high re-stenosis rate (*450*). Recently, however, the therapeutic results are improving with the use of the stent, and improvements in the renal function and blood pressure are also expected (*451*). For example, an initial success rate of 90% and a recurrence rate after 2 years of 20% have been reported (*452*). However, the results of a randomized prospective study of atherosclerotic renal artery stenosis failed to prove that a combination of PTRA and a stent is superior to drug therapy (*453*). PTRA is highly recommended for fibromuscular dysplasia, but its indication to atherosclerotic stenosis must be evaluated by carefully taking adverse effects and benefits into consideration.

If vascular reconstruction by PTRA is difficult, surgical vascular reconstruction such as bypass surgery and autologous kidney transplantation should be considered. Surgical vascular reconstruction has resulted in improvements or stabilization of the renal function in a high percentage of patients in Japan (*454*). If the unilateral kidney function is judged to be completely annihilated by unilateral renal artery stenosis, an improvement in the blood pressure is expected from nephrectomy (by laparoscopy or open surgery).

4) Endocrine Hypertension

The number of patients diagnosed to have endocrine hypertension is increasing with the improvements in the detection rate of incidental adrenal tumors due to the increased availability of, and ease to perform, ultrasonography and CT (*455*). However, as some adrenal tumors are malignant, and as the frequency of target organ disorders is not low, patients suspected to have endocrine hypertension must be promptly referred to hypertension specialists (FJSH, *etc*.).

a. Primary Aldosteronism and Similar Diseases

In primary aldosteronism, pathologic changes based on hyporeninemic volume-dependent hypertension, hypokalemia, hypomagnesemia, and metabolic alkalosis due to excess secretion of aldosternone and/or deoxycorticosterone (DOC), which has a mineralocorticoid action, are observed. Subjective and objective symptoms include thirst, polydipsia, polyuria, limb weakness, tetany, abnormal glucose tolerance, and a normal or slightly reduced serum uric acid level.

i. Primary Aldosteronism

Since this disease, which is not hypertension with a benign course, is often accompanied by target organ damage such as cerebrovascular disease, proteinuria, and renal failure (*456*, *457*), early diagnosis and treatment are important.

1. Surgical Treatment

Although removal of the adenoma or the affected adrenal gland is the radical treatment, laparoscopic surgery is recently recommended, because it is less invasive than conventional open surgery and allows relatively smooth postoperative recovery (*458*). Surgery completely resolves the feeling of weakness and muscle weakness due to hypokalemia. Hypertension is normalized in 60–88% of the patients (*456*, *459*). In patients with primary aldosteronism having a 5-year or longer history of hypertension and cardiovascular complications (*456*, *457*) or essential hypertension and those who show a poor response to preoperative spironolactone (aldosterone antagonist) (*460*), the blood pressure may not be normalized even after surgery, and antihypertensive medication may be necessary (*456*, *460*). However, hypertension is usually alleviated by surgery compared with the preoperative state, and the control of the blood pressure by antihypertensive medication becomes easier.

Spironolactone should be administered at 50–200 mg/day for 3–5 weeks before surgery (*461*), to correct hypokalemia and metabolic alkalosis and to reduce the risk for severe intraoperative or postoperative ventricular arrhythmia. After correction of these conditions, the blood pressure should be normalized by continuing the administration of spironolactone at a reduced dose in combination with a Ca antagonist. If the time until surgery is expected to be long, the blood pressure should be controlled with hypokalemia and hypomagnesemia by administering a Ca antagonist, which suppresses aldosterone secretion from the adrenal cortex (*462*), with a KCl preparation or triamterene from the beginning instead of spironolactone administration (*462*). This method is recommended as advantageous for the prevention of postoperative selective hypoaldosteronism (*462*), which is mentioned below. Caution is needed for a few weeks after surgery, particularly, in patients who have preoperatively received high-dose and prolonged administration of spironolactone, because hypokalemia and hyponatremia due to selective hypoaldosteronism (*461–463*) may appear. In such patients, the serum Na and K levels should be measured repeatedly, and if hyponatremia and hyperkalemia appear, Na should be supplemented by increasing the salt intake or intravenously administering saline, and hyperkalemia should be corrected by restricting the K intake or with ion-exchange resin. Also, some adenomas show autonomous excessive secretion of cortisol as well as aldosterone, and some patients exhibit hypotension for 1–2 years after surgery and require supplementary glucocorticoid administration (*464*).

2. Drug Treatment

Drug treatment should be selected for patients who reject surgery, those with aldosteronism that respond to glucocorticoids, and those judged to be inoperative for other reasons.

Based on periodic monitoring of the blood pressure and serum K level, (1) spironolactone alone, (2) a Ca antagonist with a KCl preparation or triamterene, (3) a Ca antagonist with a low dose of spironolactone (*465*), or (4) spironolactone at a low dose with a thiazide diuretic or loop diuretic after correction of hypokalemia may be selected. Since cardiovascular diseases such as cerebrovascular diseases develop in about 50% of patients even under blood pressure control by spironolactone administration, the preventive effect of spironolactone against these complications has been reported to be insufficient (*466*). The serum K level and blood pressure are normalized by the administration of spironolactone alone, but the aldosterone secretion is not normalized, and the plasma aldosterone level may even increase due to an increase in the serum K level. Also, on long-term administration of high-dose spironolactone alone, adverse effects such as gynecomastia in men and menstrual abnormalities in women may appear. In patients with marked renal failure, the administration of spironolactone or triamterene may induce hyperkalemia, and the administration of these drugs alone is

contraindicated. Eprelenone, which is expected to be approved shortly in Japan, is also considered to be effective, but the clinical effectiveness of its use in patients with aldosteronism has not been established. In patients with renal failure, a Ca antagonist and a loop diuretic (tracemide also has a weak anti-aldosterone activity) should be used, and a low dose (25 mg) of spironolactone can be used simultaneously when the serum K level is low. Also, discontinuation of the spironolactone administration invites reactivation of the disease.

Since a 3β-hydroxylated steroid dehydrogenase inhibitor (trilostane) also inhibits cortisol synthesis as well as aldosterone production, it should be administered by monitoring the serum K and cortisol levels.

Glucocorticoid-remediable aldosteronism is a disease caused by a gene abnormality and shows hyporeninemic hyperaldosteronism. For its treatment, dexamethasone, a glucocorticoid, is used in an early stage (for a short period), but combinations such as a relatively low dose of spironolactone and a Ca antagonist are effective with fewer adverse effects on long-term treatment.

ii. Idiopathic Aldosteronism

With the exception of aldosteronism due to unilateral hyperplasia, idiopathic aldosteronism is not an indication for adrenalectomy.

The principles of antihypertensive medication are the same as those for drug treatment for primary aldosteronism. However, as aldosterone secretion is under the control of the RA system in this disease, an ARB or ACE inhibitor should be used concomitantly when necessary (*461*). A 3β-hydroxylated steroid dehydrogenase inhibitor should be administered by monitoring the serum K and cortisol levels.

iii. Congenital Adrenocortical Hyperplasia

It is a disease caused by a gene abnormality, which may be 17α-hydroxylase deficiency (17α-OHD) or 11β-hydroxylase deficiency (11β-OHD). Both variations are adrenocorticotropic hormone (ACTH)–dependent and cause hypertension due to excess of DOC with a mineralocorticoid activity accompanied by hypoaldostrenonism or normoaldosteronism in the former and due to excess of DOC in the latter. Hypertension is accompanied by abnormalities of secondary sex characters (feminization of the external genitalia in men and primary amenorrhea in women) in 17α-OHD and by masculinization (premature sexual maturation in men and masculinization of external genitalia such as clitoromegaly in women) due to excess androgen in 11β-OHD. This condition has no indication for surgical treatment and is managed by drug treatment, the principles of which are the same as those for primary aldosteronism.

b. Cushing's Syndrome

Characteristic clinical features including so-called "Cushing's signs" such as moon face, centripetal obesity, and extensible skin striae due to excess glucocorticoid and abnormal glucose tolerance, are observed.

i. Adrenal Cushing's Syndrome

1. Adrenal Adenoma

Surgery is the first choice for the treatment of this disease, and drug therapy is only complementary. After surgical removal of adrenal adenoma (open surgery or laparoscopic surgery), hydrocortisone replacement therapy is performed until the cortical function of the atrophied intact adrenal gland recovers (*467*). Usually, replacement therapy must be continued for half a year to several years, during which caution against the occurrence of acute adrenal insufficiency due to stress is necessary.

In preoperative or emergency treatment, if there is no surgical indication, or if complete surgical resection of the tumor is impossible, drug therapy is performed using agents such as a central nervous system agonist (bromocriptine mesylate, *etc*.), a 3β-hydroxylated steroid dehydrogenase inhibitor, and a Ca antagonist.

2. Adrenal Cancer

The affected adrenal gland must be resected, but complete resection is rarely possible. In patients with inoperable adrenal cancer, recurrent cancer, or metastatic cancer, anticancer agents and a 3β-hydroxylated steroid dehydrogenase inhibitor are administered, but the treatment is not expected to be effective (*467*).

3. Adrenocorticotropic Hormone–Independent Large Nodal Hyperplasia and Primary Adrenocortical Nodular Dysplasia

For ACTH-independent large nodal hyperplasia (AIMAH) and primary adrenocortical nodular dysplasia (PPNAD), bilateral total adrenalectomy and lifetime glucocorticoid replacement therapy are usually indicated (*467*).

ii. Preclinical Adrenal Cushing's Syndrome

In Japan, slightly less than 10% of incidental adrenal tumors are reported to be cortisol-producing tumors (*455*). If a patient has been diagnosed to have preclinical adrenal Cushing's syndrome and shows hypertension, generalized obesity, or abnormal glucose tolerance, removal of the adrenal tumor should be considered. Surgery is expected to alleviate accessory symptoms such as hypertension and abnormal glucose tolerance, but not in all patients. Surgical resection is necessary if the tumor is 5 cm or greater or if the tumor is less than 5 cm but is growing (*468*). Though rarely, glucocorticoid replacement therapy may be necessary after resection of adrenal tumor.

iii. Adrenocorticotropic Hormone–Dependent Cushing's Syndrome

1. Pituitary Adenoma

This disease is also treated surgically, in principle. If complete resection of microadenomas is impossible, drug therapy same as that for adrenal Cushing's syndrome mentioned above is performed. However, the disease resists antihypertensive medications and is difficult to treat even for specialists in many patients (*469*).

2. Ectopic Adrenocorticotropic Hormone–Producing Tumors

Ectopic ACTH-producing tumors are often malignant tumors such as small-cell carcinoma of the lung and more frequently show hypertension, hypokalemia, edema, and pigmentation than the above "Cushing's signs" (*469*). Excess of DOC, which has a mineralocorticoid activity, is considered to be involved in hypokalemia. Surgical removal of the responsible tumor is the primary treatment, but patients with distant metastases are treated with anticancer agents, 3β-hydroxylated steroid dehydrogenase inhibitors, and antihypertensive drugs. Antihypertensive medication is a combination of a Ca antagonist and spironolactone.

c. Pheochromocytoma

This disease is a catecholamine-producing tumor and is called a 10% tumor (about 10% of this disease affects the bilateral adrenal glands, is malignant, and is of extra-adrenal origin). The disease is classified into the sustained type and paroxysmal type according to the type of hypertension. Other than hypertension, which is markedly variable, subjective symptoms include palpitation, excessive sweating, dizziness, nausea, vomiting, headache, hyperglycemia, body weight loss, and tremor, and diverse autonomic symptoms such as orthostatic hypotension are observed in the sustained type.

If pheochromocytoma appears likely, the patient should be referred to a specialist. Surgical resection is the radical treatment for this disease, but it should be performed after the determination of the exact location of the tumors (iodine 131-metaiodobenzylguanidine [^{131}I-MIBG] scintigraphy is effective for the determination of the sites and number of the lesions and whether there are metastatic lesions or not). It may be removed by open surgery or laparoscopic surgery, but open surgery is performed more often because marked attacks of hypertension may be induced by physical stimulation of the tumor. The indication of laparoscopic surgery should be evaluated carefully (*470*). The tumor should be removed after controlling the blood pressure and correcting hypovolemia.

Drug therapy is performed as preoperative treatment or as symptomatic treatment for inoperable patients. α-Blockers and β-blockers are administered to control the symptoms caused by catecholamine excess. The blood pressure must be stabilized primarily with α-blockers. According to a few prospective studies, the percent efficacy of doxazocin, which is a long-acting α-blocker, was 79.2% in all patients, 66.7% when it was used alone, and 91.7% when it was used with a β-blocker (*471*, *472*). The administration of a β-blocker alone is contraindicated, because it induces an increase in the blood pressure by making stimulation of α-receptors dominant. Although α-blockers must be administered at a higher dose than usual, its dose must be increased gradually by paying attention to orthostatic hypotension. A Ca antagonist or an ACE inhibitor should be added if the decrease in the blood pressure is insufficient (*473*).

During and after surgery, sufficient fluid supplementation is important, and the blood pressure, heart rate, and blood glucose level must be monitored frequently. Hypertensive crises due to surgical stress should be managed by intravenous injection of an α-blocker (phentolamine), a β-blocker, or a Ca antagonist. The administration of noradrenaline is necessary for a rapid postoperative decrease in the blood pressure.

Since benign or malignant recurrence of this disease has been reported in 16 (14%) of 114 patients diagnosed to be benign at surgery during a postoperative follow-up period of 17–194 months (*474*), careful follow-up is necessary after surgery. If malignant pheochromocytoma has metastatic lesions, chemotherapy (a combination of cyclophosphamide, vincrinstine, and dacarbazine) (*475*) and internal ^{131}I-MIBG irradiation are performed, and corticosteroid synthesis inhibitors are administered, but the effectiveness of these treatments is expected to be nominal.

d. Thyroid Diseases

i. Hyperthyroidism

The systolic blood pressure and heart rate decrease in many patients with normalization of the thyroid function due to treatment (*476*).

Hyperthyroidism is treated with antithyroid drugs, radioactive iodine or surgery (subtotal thyroidectomy). Drug treatment is the first choice, because it has no contraindication as the initial treatment, it can be replaced by another treatment at any time, and remission may be obtained by drug treatment alone. Radiological treatment and surgical treatment are indicated for patients with large goiter, those with recurrence on antithyroid medication, those with refractory hyperthyroidism, and those with serious adverse effects.

Drug treatment is performed primarily with antithyroid drugs (thiamazole, *etc.*). β-Blockers are effective for the control of palpitation, tachycardia, and systolic hypertension, and they are used from before the administration of antithyroid drugs until normalization of the thyroid function. Antihypertensives that suppress the RA system are not expected to be effective (*477*).

ii. Hypothyroidism

The blood pressure is normalized in many patients with normalization of the thyroid function due to treatment (*478*).

Thyroid hormone preparations include dried thyroid, synthetic T3 preparations, and synthetic T4 preparations, but syn-

thetic T4 preparations are usually used. The administration of thyroid hormone may induce angina pectoris and myocardial infarction and cause adrenal crises in patients with reduced adrenocortical function due to pituitary hypothyroidism or Schmidt's syndrome.

e. Hyperparathyroidism (Primary)

Hypertension is observed in about 20% of the patients with this disease. There is no treatment for this condition except resection of the morbid parathyroid gland, and hypertension is resolved in about half the patients by surgery (*479*). If adenoma is present, the affected parathyroid gland should be resected; hyperplasia should be treated by subtotal resection of the gland or total resection followed by partial autologous transplantation; extended resection including the surrounding tissues should be performed when parathyroid cancer is suspected.

f. Acromegaly

Hypertension is observed in about 30% of the patients with this disorder (*469*, *480*). Its radical treatment is removal of pituitary tumor (primarily by a transsphenoidal approach). While hypertension is alleviated by this treatment in most patients (*469*), normalization is infrequent. There is no consensus as to the necessity of postoperative adjuvant therapy, radiotherapy, or drug therapy (bromocriptine, octreotide) in patients who are not cured by surgical treatment (*469*).

5) Vascular Hypertension

a. Aortitis Syndrome

In Japan, this disease is observed frequently particularly in women, and its primary findings are lateral differences in the pulse and blood pressure, neck or abdominal bruit, and enhanced carotid sinus reflex (*481*). Hypertension is observed in about 40% of the patients with this disease (*482*), but its etiologic mechanism is not uniform; it may be (1) renovascular hypertension, (2) hypertension due to aortic stenosis (atypical aortic coarctation), (3) hypertension due to aortic insufficiency, or (4) hypertension due to sclerosis of the aortic wall (*481*). Renovascular hypertension is observed in about 20% of the patients with this disease (*483*). In patients with bilateral subclavian artery stenosis, the blood pressure of the upper limbs is lower than the aortic blood pressure, possibly leading to underestimation of hypertension. Although PTRA is mildly invasive and effective, the re-stenosis rate after this treatment is higher in this disease than in other diseases such as fibromuscular hyperplasia, and its long-term efficacy is about 50%, which is lower than about 90% for successful bypass surgery (*483*). Atypical aortic coarctation and aortic insufficiency are indications of surgical treatment. The latter, in particular, is an important complication that determines the outcome of this disease, and surgical indication must be evaluated under appropriate antihypertensive medication (*484*). It is recommended that surgical treatment for this disease be performed after disappearance of active inflammation or suppression of inflammation with steroids. In Japan, the long-term prognosis after surgery is generally favorable, but particular attention is necessary for anastomotic aneurysm (*485*).

Antihypertensive medication for this disease is the same as that for renovascular hypertension or essential hypertension. However, the cerebral blood flow may be reduced in patients with stenotic lesions in the carotid artery, and sufficient attention to the cerebral blood flow is necessary in antihypertensive treatment for such patients.

b. Other Angitis

Hypertension due to angitis syndrome other than aortitis syndrome include polyarteritis nodosa (PN) and progressive systemic scleroderma (PSS) (*486*). The etiology of hypertension is related to generalized necrotic arteritis of middle-sized and small muscle-shaped arteries and arterioles including the renal artery in PN, and to spasms of renal vessels in PSS. PN often shows the course of rapidly progressive nephritis, and PSS often takes the course of renal crisis (malignant hypertension, renal failure). Other than PSS, the causes of death in the acute period are conditions closely related to complicating hypertension such as cerebral hemorrhage, myocardial infarction, heart failure, and renal failure. Therefore, the importance of the blood pressure control must be recognized. With the exception of PSS, angitis hypertension in the acute period is treated by steroid pulse therapy and immunosuppressant therapy. The principles of the blood pressure control are the same as those for acute renal failure in PN and those for malignant hypertension in PSS, but ACE inhibitors and Ca antagonists are markedly effective in PSS.

c. Coarctation of Aorta

In this condition, hypertension of the upper limbs proximal to the site of stenosis and hypotension in the lower limbs distal to it are observed, and the difference in the systolic blood pressure between the upper and lower limbs reach 20–30 mmHg or more. Proximal hypertension is treated by surgical dilation of the narrowed vessel or angioplasty using a balloon catheter in childhood, and earlier treatment is considered to promise a better outcome (*487*). In addition to mechanical factors such as an increase in the peripheral vascular resistance in the upper part of the body and attenuation of the aortic Windkessel effect, the RA system and sympathetic nervous system are known to be involved in the etiology of hypertension associated with this disease (*488*). Hypertension persists for a long period even after repair depending on the preoperative duration of hypertension. In this event, antihypertensive medication suited for the condition should be performed.

d. Vascular Hypertension Accompanied by an Increase in the Cardiac Output

In conditions such as aortic insufficiency, persistent truncus arteriosus, and arteriovenous fistula, systolic hypertension occurs primarily due to an increase in the stroke volume.

In all these diseases, hypertension disappears after treatment for the primary disease.

6) Hypertension Due to Diseases of the Brain or the Central Nervous System

Hypertension in cerebrovascular disorders (cerebral hemorrhage, cerebral infarction, chronic subdural hematoma) has been discussed in detail in "Cerebrovascular Disease" in 6. Hypertension Associated with Organ Damage. In disorders of the central nervous system such as brain tumor, particularly tumor of the posterior cranial fossa, encephalomyelitis, and brain trauma, hypertension may occur as peripheral sympathetic activities are enhanced by mechanical stress to the brainstem including the nuclei of the solitary tract of the medulla oblongata due to increased intracranial pressure (Cushing's phenomenon) (*489*), but its frequency is low. Occasionally, paroxysmal hypertension is caused by increased intracranial pressure, and the condition may be misdiagnosed for pheochromocytoma. It has also been reported by a Japanese investigator that compression of the lateral areas of the cranial medulla oblongata, which is the center of sympathetic activities, enhances the sympathetic activities and causes an increase in the blood pressure but that the blood pressure is reduced by surgical decompression (*490*).

The responsible lesion should be detected promptly by head CT or MRI, and priority should be given to radical treatment such as removal, reduction of the size, or decompression. In head trauma, the administration of an intravenous anesthetic at a relatively high dose in an early period is considered to be useful for the control of the increase in the intracranial pressure and management of hypertension. Antihypertensive medication should consist primarily of β-blockers, α-blockers, and central sympatholytic agents combined with other drugs such as Ca antagonists.

7) Drug-Induced Hypertension

Drugs such as NSAIDs, glycyrrhizin preparations, glucocorticoids, cyclosporine, erythropoietin, estrogen (see "Hypertension in Women" in 9. Hypertension under Special Conditions), and sympathomimetic agents induce a rise in blood pressure and reduce the effects of antihypertensive drugs if used concomitantly. Many hypertensive patients have complications, are treated at different medical facilities, and are using drugs other than antihypertensives. Therefore, in treating hypertension (particularly in patients with refractory hypertension), whether the patient is using drugs with a pressor effect must be checked, and differential diagnosis for drug-induced hypertension must be made.

a. Non-Steroidal Anti-Inflammatory Drugs

NSAIDs suppress the production of prostaglandins from arachidonic acid in the kidney by inhibiting cyclooxygenase and cause water and Na retention and reduce vasodilation. In elderly patients and patients with renal dysfunction, renal prostaglandins maintain the renal function as a compensatory mechanism and contribute to the prevention of an increase in blood pressure. However, NSAIDs reduce the renal function by suppressing the prostaglandin production and are likely to cause an increase in the blood pressure. According to a metaanalysis of randomized trials studying the effects of NSAIDs on the blood pressure, they are reported to increase the blood pressure by a mean of about 5 mmHg (*491*). There is also a report that an elderly normotensive man without a history of hypertension exhibited marked increases in the blood pressure (to a hypertensive level) after the beginning of the administration of NSAIDs but that the blood pressure was normalized after discontinuation of the administration (*492*). In elderly patients, NSAIDs are likely to cause acute renal dysfunction, which promotes a further increase in the blood pressure, and the risk for heart failure is increased by the concomitant use of diuretics and NSAIDs compared with the use of diuretics alone (*493*). Therefore, when NSAIDs are used in elderly hypertensive patients, they should be used at a low dose with careful observation and examination of the renal function. Since the effects of selective cyclooxygenase-2 (COX-2) inhibitors are considered to be similar to those of non-selective NSAIDs (*494*), caution is necessary also in their use.

Concerning drug interactions, diuretics suppress reabsorption of NaCl at renal tubules and stimulate prostacyclin production. The actions of loop diuretics such as furosemide are partially prostaglandin-dependent. For this reason, the antihypertensive effects of diuretics are reduced when they are used concomitantly with NSAIDs. NSAIDs antagonize the antihypertensive effects of ACE inhibitors or β-blockers. There are reports that antihypertensive effects of ARBs are suppressed by their concomitant use of NSAIDs, but other reports refute it. The concomitant use of NSAIDS and Ca antagonists is considered to scarcely affect the antihypertensive effect.

b. Licorice (Glycyrrhizin)

Glycyrrhizin has been used in the treatment of liver disease, and gastrointestinal disorders, is contained in many Chinese herbal preparations. Most of its pharmacological effects are attributable to the enhancement of the actions of endogenous steroids and the steroidal action of glycyrrhizin itself. As for the enhancement of the actions of endogenous steroids, glycyrrhizin inhibits 11β-hydroxylated steroid dehydrogenase (11β-HSD), blocks conversion of cortisol into cortisone, and prolongs the half-life of cortisol. Cortisol has affinity to aldo-

sterone receptors similarly to aldosterone and binds to them, thus retaining Na and water and causing a decrease in K (pseudoaldosteronism). Licorice administration at 50–200 g/day (2–4 weeks) increase systolic blood pressure by 3.1–14.4 mmHg in healthy volunteers (*495*). Glycyrrhizin rarely causes hypertension unless it is administered at a high dose for a long period. In patients with essential hypertension, increases in the blood pressure induced by glycyrrhizin were reported to be greater than in normotensive individuals (*496*).

Hypertension induced by glycyrrhizin should be considered if hypertension is accompanied by hypokalemia, low renin activity, and a low plasma aldosterone level (pseudoaldosteronism). Clinically, this hypertension can be controlled by withdrawal of glycyrrhizin for a few weeks (4 months at the maximum). If withdrawal of glycyrrhizin is difficult, use an aldosterone antagonist.

c. Glucocorticoids

Glucocorticoids rarely cause hypertension if used at low doses even in long-tern treatment for asthma or rheumatoid arthritis. However, in elderly normotensive patients, more than 20 mg daily of glucocorticoid showed steroid-induced hypertension. Glucocorticoid-induced hypertension was seen in 37.1% of those patients, and was more common in those with positive family history of hypertension than in those with negative family history (*497*).

Glucocorticoid may cause an increase in the blood pressure due to Na and water retention *via* renal mineralocorticoid receptors (viewed negatively by many investigators) (*498*), an increase in angiotensin II due to an increase in the production of renin substrate (*499*), vasoconstriction due to increased erythropoietin production (*498*), suppression of nitric oxide (NO) production (*500*), and damage to the vascular endothelium due to excessive production of superoxides (*501*), but details are unclear. When healthy individuals were administered a mineralocorticoid or a glucocorticoid for a short period, both agents were reported to have increased the blood pressure and enhanced pressor responses. However, the two agents were reported to induce different hemodynamic responses (*502*).

The treatment is primarily a decrease in the dose or withdrawal of the glucocorticoid. If it is difficult, the blood pressure may be managed using diuretics, Ca antagonists, or ARBs.

d. Cyclosporine

Cyclosporine is a common immunosuppressive agent used in organ transplantation and bone marrow transplantation and for the treatment of some immunological disease. Hypertension was observed in 50–60% of patients followed up after kidney transplantation and 90% of those after heart transplantation. Cyclosporine-induced hypertension occurred in 10–80% of the patients several weeks after its initiation although the time until its occurrence varied with the dose of cyclosporine, duration of its administration, and level of renal function. The suggested mechanisms of the increase in the blood pressure include (1) changes in the renal circulation (hypertension associated with renovascular constriction and salt retention), (2) nephrotoxicity of cyclosporine which resembles chronic nephrosclerosis and is accompanied by chronic renal failure, and (3) enhancement of sympathetic stimulation (*503*). High-dose steroids used in combination with cyclosporine are also considered to be involved in hypertension *via* Na retention.

Ca antagonists and diuretics are used for the treatment of cyclosporine-induced hypertension, and some Ca antagonists (diltiazem, nicardipine, verapamil, *etc*.) must be used carefully, because they interfere with cyclosporine metabolism and increase its plasma concentration.

e. Erythropoietin

In patients with chronic renal failure, erythropoietin may alleviate anemia but simultaneously contribute a sudden onset or exacerbation of hypertension (hypertensive encephalopathy). Blood pressure elevation after initiation of erythropoietin may be attributable to an increase in the hematocrit with a resultant increases in blood viscosity and reduce hypoxic vasodilation. Therefore, in patients with renal anemia, who have been adjusted to a low hematocrit over a long period, a sudden increase in the hematocrit is considered to induce hypertension.

An onset or exacerbation of hypertension is observed in 20–30% of patients treated with erythropoietin, and increases in the blood pressure were noted in 29% of the patients in a post-marketing surveillance performed in Japan (*504*). It has been reported that the increase in the blood pressure induced by erythropoietin was greater in dialysis patients than in predialysis patients with chronic renal failure (*505*) and that it caused no remarkable changes in blood pressure in predialysis patients (*506*). The increases in the blood pressure in dialysis patients were reported to be greater in those with a family history of hypertension, suggesting an involvement of genetic predisposition (*507*).

Attention to changes in the hematocrit is necessary during (and after) the use of erythropoietin. Poor control of high blood pressure may result in hypertensive encephalopathy or cerebral hemorrhage. In the event of an increase in the blood pressure, adjustment of the volume of water removal during dialysis, addition or increases in the doses of antihypertensives, and a decrease in the dose of erythropoietin should be performed. Marked elevation in blood pressure may be ameliorated by reducing the red blood cell count by withdrawing erythropoietin and/or bloodletting.

f. Drugs with Sympathomimetic Actions

Catecholamine analogues, *e.g.*, phenylpropanolamine, are

contained in over the counter cold medicines and may cause an increase in the blood pressure by overdosing. In patients who have been administered β-blockers alone, the concomitant administration of these drugs needs caution, because it may cause a marked increase in the blood pressure. Tricyclic antidepressants suppress the catecholamine re-uptake by sympathetic nerve terminals and inhibit the antihypertensive effects of peripheral sympatholytic agents such as guanethidine and betanidine. There have been reports that the addition of imipramine caused hypertensive crises (230/124–130 mmHg) accompanied by tachycardia in elderly hypertensive patients being treated with clonidine (*508*) and that tetracyclic antidepressants caused hypertensive emergencies in patients being treated with clonidine (*509*). Monoamine oxidase (MAO) inhibitors are indicated for Parkinson's disease, but they occasionally cause an increase in the blood pressure and orthostatic hypotension. Combined therapy of an MAO inhibitor and a tricyclic antidepressant is a contraindication, because it may cause hypertension, syncope, or death. The simultaneous use of MAO inhibitors with ephedrine or methylephedrine may cause an increase in the blood pressure and tachycardia. Although the use of cocaine as a topical anesthetic is permitted, its illegal use is a problem. Cocaine causes an increase in the blood pressure by inhibiting the re-absorption of catecholamines by sympathetic nerve terminals. Metoclopramide, a dopaminergic antagonist with antiemetic effect, has a catecholamine release promoting activity and can unmask pheochromcytoma and causes hypertensive crises in patients with latent pheochromocytoma. Antidepressants, β-blockers, and opioids are also reported to cause manifestation of pheochromocytoma.

g. Others

Combination therapy of antihypertensives (β-blockers with methyldopa or clonidine) is known to cause paradoxical rise in blood pressure. While clonidine and a methyldopa metabolite are assumed to stimulate vascular α-receptors, details remain unknown. Withdrawal of clonidine has been reported to have caused an increase in the blood pressure. Catecholamine receptors are increased during the treatment with clonidine, and withdrawal of clonidine with a short half-life in the circulation, causes a marked increase in the blood pressure due to increases in catecholamines. Clonidine should be reduced gradually until complete withdrawal. In patients with combined therapy of clonidine and β-blockers such as propranolol, withdrawal of clonidine may cause a marked increase in blood pressure due to rebound catecholamine release and vascular β_2-receptor blocking effects.

Summary

Renal Parenchymal Hypertension

1) In renal parenchymal diseases, the prevention of end-stage renal disease is important, and strict control of the blood pressure from an early stage is necessary.
2) ARBs or ACE inhibitors should be used from an early stage of the treatment for diabetic and non-diabetic nephropathy, because they are expected to have kidney protecting effects.
3) The concomitant use of multiple drugs is usually necessary for strict control of the blood pressure, and antihypertensives such as Ca antagonists, diuretics, β-blockers, and α-blockers should be used in combinations as needed.
4) ARBs and ACE inhibitors are also effective for the treatment of polycystic kidney disease.

Renovascular Hypertension

1) Renovascular hypertension should be considered in patients with clinical features such as abdominal bruit, lateral difference in the kidney size, young age, resistance to treatment, and rapidly exacerbating hypertension.
2) The captopril test and kidney ultrasonography are useful for screening. Then, renal artery stenosis is evaluated by renal scintigraphy/renography, contrast CT, or contrast MRI, and the final diagnosis is made by arteriography.
3) Vascular reconstruction is the primary treatment, and PTRA should be tried first. PTRA is effective for fibromuscular dysplasia.
4) In atherosclerotic stenosis, the success rate is limited even by the combination of PTRA and stent, but the treatment may improve the renal function. Then, surgical vascular reconstruction such as bypass surgery and autologous kidney transplantation should be considered.
5) In drug therapy, β-blockers and antihypertensives that suppress the RA system such as ARBs and ACE inhibitors should be selected.

Endocrine Hypertension

1) If endocrine hypertension is considered possible, refer the patient to a specialist.
2) Hypertension is often alleviated or cured by resection of the tumor in patients with primary aldosteronism or Cushing's syndrome due to adrenocortical adenoma, ACTH-dependent Cushing's syndrome due to pituitary adenoma or ectopic ACTH-producing tumor, or phenochromocytoma originating from the adrenal medulla. Similarly, hypertension is often alleviated by resection of the tumor also in patients with morbid adrenal gland of primary hyperparathyroidism or pituitary tumor causing acromegaly.
3) Idiopathic aldosteronism due to bilateral adrenal gland hyperplasia is not an indication of surgery, and antihypertensive treatment is performed primarily using spironolactone and Ca antagonists.

4) Before resection of pheochromocytoma, the pathological condition caused by excess catecholamines should be corrected with α-blockers and β-blockers.
5) Hypertension may complicate either hyperthyroidism or hypothyroidism. Hypertension is controlled with normalization of the thyroid function by treatment.

Drug-Induced Hypertension

1) NSAIDs increase the blood pressure and antagonize the antihypertensive effects of diuretics, β-blockers, ACE inhibitors, and α-blockers. This effect tends to be more notable in elderly patients.
2) Hypertension accompanied by hypokalemia may be caused by high-dose administration of glycyrrhizin, which is a major pharmacologically active component of licorice. If withdrawal of glycyrrhizin is difficult, use an aldosterone antagonist.
3) A high dose of a glucocorticoid may also cause an increase in the blood pressure. If its withdrawal is impossible, the blood pressure should be controlled with Ca antagonists, diuretics, and ARBs.
4) Cyclosporine, erythropoietin, and drugs with sympathomimetic activities may cause an increase in the blood pressure. If blood pressure is increased during the use of these drugs, differential diagnosis for drug-induced hypertension is necessary.
5) Combined therapy of β-blockers with methyldopa or clonidine is known to cause paradoxical rise in blood pressure. Hypertension due to withdrawal of clonidine has also been reported. Clonidine should be gradually reduced to eventual withdrawal.

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Main Antihypertensive Drugs

Class and drug	Trade name	Dose and usual daily frequency	Maximum dose/day
Calcium antagonist			
amlodipine	Norvasc, Amlodin	2.5–5 mg OD	
aranidipine	Sapresta, Bec	5–10 mg OD	20 mg
azelnidipine	Calblock	8–16 mg OD	16 mg
barnidipine	Hypoca	5–15 mg OD morning	
benidipine	Coniel	2–4 mg OD morning	8 mg
cilnidipine	Atelec, Cinalong	5–10 mg OD morning	20 mg
diltiazem	Herbesser	30–60 mg/one time, 3 times/day	
diltiazem	Herbesser R	100–200 mg OD	
efonidipine	Landel	20–40 mg OD or 2 times/day	60 mg
felodipine	Munobal, Splendil	2.5–5 mg/one time, 2 times/day	20 mg
manidipine	Calslot	5–20 mg OD morning	
nicardipine	Perdipine	10–20 mg/one time, 3 times/day	
nicardipine	Perdipine LA	20–40 mg/one time, 2 times/day	
nifedipine	Adalat, Sepamit	10 mg/one time, 3 times/day	
nifedipine	Adalat L	10–20 mg/one time, 2 times/day	
nifedipine	Adalat CR	20–40 mg OD	
nilvadipine	Nivadil	2–4 mg/one time, 2 times/day	
nisoldipine	Baymycard	5–10 mg OD	
nitrendipine	Baylotensin	5–10 mg OD	
Angiotensin II receptor blocker (ARB)			
candesartan	Blopress	4–8 mg OD	12 mg
losartan	Nulotan	25–50 mg OD	100 mg
olmesartan	Olmetec	5–20 mg OD	40 mg
telmisartan	Micardis	20–40 mg OD	80 mg
valsartan	Diovan	40–80 mg OD	160 mg
Angiotensin converting enzyme (ACE) inhibitor			
alacepril	Cetapril	25–75 mg/day OD or 2 times/day	100 mg
benazepril	Cibacen	5–10 mg OD	
captopril	Captoril	37.5–75 mg/day, 3 times/day	150 mg
captopril	Captoril R	18.75–37.5 mg/day, 2 times/day	
cilazapril	Inhibace	0.5–2 mg OD	
delapril	Adecut	5–60 mg/day, 2 times/day	120 mg
enalapril	Renivace	5–10 mg OD	
imidapril	Tanatril, Novarok	5–10 mg OD	
lisinopril	Longes, Zestril	10–20 mg OD	
perindopril	Coversyl	2–4 mg OD	8 mg
quinapril	Conan	5–20 mg OD	
temocapril	Acecol	1–4 mg OD	
trandolapril	Odric, Preran	1–2 mg OD	
Diuretic			
Thiazide			
benzylhydrochlorothiazide	Behyd	4–8 mg/day, 2 times/day	
hydrochlorothiazide	Dichlotride	25–100 mg/one time, 1–2 times/day	
trichlormethiazide	Fluitran	2–8 mg/day, 1–2 times/day	
Thiazide-like			
chlortalidone	Hygroton	50–100 mg OD	
indapamide	Natrix	2 mg OD morning	

Class and drug	Trade name	Dose and usual daily frequency	Maximum dose/day
mefruside	Baycaron	25–50 mg/day OD morning or 2 times/day morning and lunch	
meticrane	Arresten	150 mg/day, 1–2 times/day	
tripamide	Normonal	15 mg/day OD morning or 1–2 times/day morning and lunch	
Loop			
furosemide	Lasix	40–80 mg OD	
furosemide	Eutensin	40 mg/one time, 1–2 times/day	
K-sparing			
spironolactone	Aldactone A	50–100 mg/day, 2–3 times/day	
triamteren	Triteren	90–200 mg/day, 2–3 times/day	
β-Blocker			
β1-selective, ISA(−)			
atenolol	Tenormin	50 mg OD	100 mg
betaxolol	Kerlong	5–10 mg OD	20 mg
bisoprolol	Maintate	5 mg OD	
metoprolol	Lopresor, Seloken	60–120 mg/day, 3 times/day	240 mg
metoprolol	Lopresor SR, Seloken L	120 mg OD morning	
β1-selective, ISA(+)			
acebutolol	Acetanol, Sectral	200–400 mg/day, 1–2 times/day	
celiprolol	Selectol	100–200 mg OD	
β1-non-selective, ISA(−)			
nadolol	Nadic	30–60 mg OD	
nipradilol	Hypadil	6–12 mg/one time, 2 times/day	18 mg
propranolol	Inderal	30–60 mg/day, 3 times/day	120 mg
propranolol	Inderal LA	60 mg OD	120 mg
tilisolol	Daim, Selecal	10–20 mg OD	30 mg
β1-non-selective, ISA(+)			
bopindolol	Sandonorm	1 mg OD	2 mg
bunitrolol	Betrilol	15–30 mg/day, 3 times/day	
bunitrolol	Betrilol L	20–40 mg OD morning	
carteolol	Mikelan	10–15 mg/day, 2–3 times/day	30 mg
carteolol	Mikelan LA	15 mg OD morning	30 mg
indenolol	Pulsan	60 mg/day, 3 times/day	180 mg
penbutolol	Betapressin	20 mg/day, 2 times/day morning and evening	40 mg
pindolol	Carvisken	15 mg/day, 3 times/day	
αβ-blocking			
amosulalol	Lowgan	20 mg/day, 2 times/day	60 mg
arotinolol	Almarl	20 mg/day, 2 times/day	30 mg
bevantolol	Calvan	100 mg/day, 2 times/day	200 mg
carvedilol	Artist	10–20 mg OD	
labetalol	Trandate	150 mg/day, 3 times/day	450 mg
α-Blocker			
bunazosin	Detantol	1.5 mg/day, 2–3 times/day, up-titelate	12 mg
bunazosin	Detantol R	3 mg OD, up-titelate	9 mg
doxazosin	Cardenalin	0.5 mg OD, up-titelate	8 mg
prazosin	Minipress	1–1.5 mg/day, 2–3 times/day, up-titelate	15 mg
terazosin	Hytracin, Vasomet	0.5 mg/day, 2 times/day, up-titelate	8 mg
urapidil	Ebrantil	30 mg/day, 2 times/day, up-titelate	120 mg
Direct vasodilator			
budralazine	Buterazine	90–120 mg/day, 2–3 times/day	180 mg
cadralazine	Cadral, Presmode	10 mg OD	20 mg
hydralazine	Apresoline	30–40 mg/day, 3–4 times/day	200 mg
todralazine	Apiracohl	30–120 mg/day, 3–4 times/day	

Class and drug	Trade name	Dose and usual daily frequency	Maximum dose/day
Centrally acting drug			
clonidine	Catapres	0.225–0.45 mg/day, 3 times/day	0.9 mg
guanabenz	Wytens	4 mg/day, 2 times/day	8 mg
guanfacine	Estulic	0.5 mg/day OD at bedtime or 2 times/day morning and at bedtime	1.5 mg
methyldopa	Aldomet	250–750 mg/day, 1–3 times/day	2,000 mg
Rauwolfia			
rescinnamine	Tsuruselpi S	0.25–1 mg/day, 1–2 times/day	
reserpine	Apoplon	0.2–0.5 mg/day, 1–3 times/day	

OD, one time/day. Dose: based on Japan Medical Drugs 2004 (Ver 27).