Hypertension Research (2009) 32, 6–10

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GUIDELINES (JSH 2009)

Chapter 1. Epidemiology of hypertension

Hypertension Research (2009) **32,** 6–10; doi:10.1038/hr.2008.9

POINT 1

1. **The number of hypertensive people in Japan has reached approx 40 million.**
2. **The average blood pressure levels of the Japanese decreased markedly following a peak in 1965–1990. This decrease closely coincided with the decrease in mortality rate due to stroke in Japan.**
3. **Morbidity and mortality rates due to diseases such as stroke, myocardial infarction, heart disease and chronic renal disease increase with elevating blood pressure. The effects of hypertension are more specific to stroke than to myocardial infarction, and, in Japan, the morbidity rate due to stroke is still higher than that due to myocardial infarction.**
4. **From young through to elderly people, morbidity and mortality rates from cardiovascular disease increase with a increase in blood pressure level.**
5. **The risk of developing and dying from cardiovascular disease is 1.5–2.4 times higher in those with metabolic syndrome or multiple risk factors.**
6. **The mean salt intake of the Japanese still remains at about 11 g day^{-1}, and hence the state of a high salt intake persists. Reducing salt intake is extremely important for lowering blood pressure.**
7. **Hypertension is untreated in 80–90% of young hypertensive patients but should be attempted to be controlled through lifestyle modifications at least.**
8. **Hypertension is estimated to be insufficiently managed in about half of patients, and therefore stricter management is necessary.**
9. **In the Japanese population, a 2-mm Hg decrease in average systolic blood pressure has been estimated to lead to decreases of approx 6 and 5% in the morbidity rates due to stroke and ischemic heart disease, respectively. Environmental improvements to encourage the Japanese to adopt blood pressure control measures, including a reduction in salt intake, are awaited.**

1) MORBIDITY RATE DUE TO HYPERTENSION AND THE NUMBER OF HYPERTENSIVE PATIENTS IN JAPAN

According to the 5th Basic Survey of Cardiovascular Diseases in 2000, 47.5% of Japanese men and 43.8% of Japanese women aged $\geqslant$30 years had a systolic blood pressure of $\geqslant$140 mm Hg or a diastolic blood pressure of $\geqslant$90 mm Hg, or were taking antihypertensive drugs, and the total number of hypertensive patients was approx 40 million. Similar values were also reported in the quick report of the National Health and Nutrition Survey in 2006. The number of hypertensive Japanese is expected to increase further with the growth in the elderly population.

2) CHANGES IN AVERAGE BLOOD PRESSURE LEVELS OF THE JAPANESE

In Japan, with the successful management of infections following World War II, the age-adjusted mortality rate due to stroke increased rapidly and reached a peak in 1965. It then decreased rapidly until 1990, and the life expectancy of the Japanese became the longest in the world.[1] During this period, the morbidity rate from stroke decreased, contributing greatly to the reduction in mortality rate due to stroke, and the decrease in average blood pressure levels of the Japanese played an important role in these changes. According to the National Health and Nutrition Surveys, average systolic blood pressure levels of the Japanese increased from 1956, for which the earliest data are available, peaked at around 1965 and decreased in 1990 (Figure 1-1).[1] This decreasing tendency of blood pressure in the Japanese has also been shown by epidemiological surveys performed in Hisayama Town, Akita and Osaka.[2,3]

3) HYPERTENSION AND THE OCCURRENCE AND PROGNOSIS OF CARDIOVASCULAR DISEASE

a. High incidence of stroke due to hypertension

The morbidity and mortality rates due to stroke increase with average blood pressure levels. Hypertension has a highly specific and close relationship with stroke, and, in Japan, the morbidity and mortality rates due to stroke are still higher than those of ischemic heart disease or myocardial infarction.[1] However, with the decrease in mortality rate due to stroke, the mortality rate from all heart diseases has become slightly higher than that due to stroke.

According to the Vital Statistics of Japan (2005), the age-adjusted mortality rate due to stroke was about three times higher than that due to acute myocardial infarction.[1] The morbidity rate from stroke was also four times higher than that from myocardial infarction in a morbidity survey of Okinawa Prefecture based on disease registration encompassing the entire prefecture.[4] When the incidence rates of stroke and myocardial infarction in six Japanese cohorts aged 35–64 years were surveyed in 1989–1993, the incidence rate due to stroke was found to be 3–6 times higher in men and 4–12 times higher in women than that of myocardial infarction.[1]

Stepwise positive correlations have been reported between hypertension and the morbidity and mortality rates from stroke.[5–7] According to the subtype of stroke, cerebral hemorrhage was more closely related to blood pressure than cerebral infarction, but both showed

stepwise positive correlations with blood pressure. In the follow-up investigation of the Hisayama Study, a stepwise, strong positive correlation was observed between blood pressure and stroke (Figure 1-2).[8] Furthermore, the incidence of lacuna infarction revealed a close correlation with the grades of hypertension shown in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI), USA.[7]

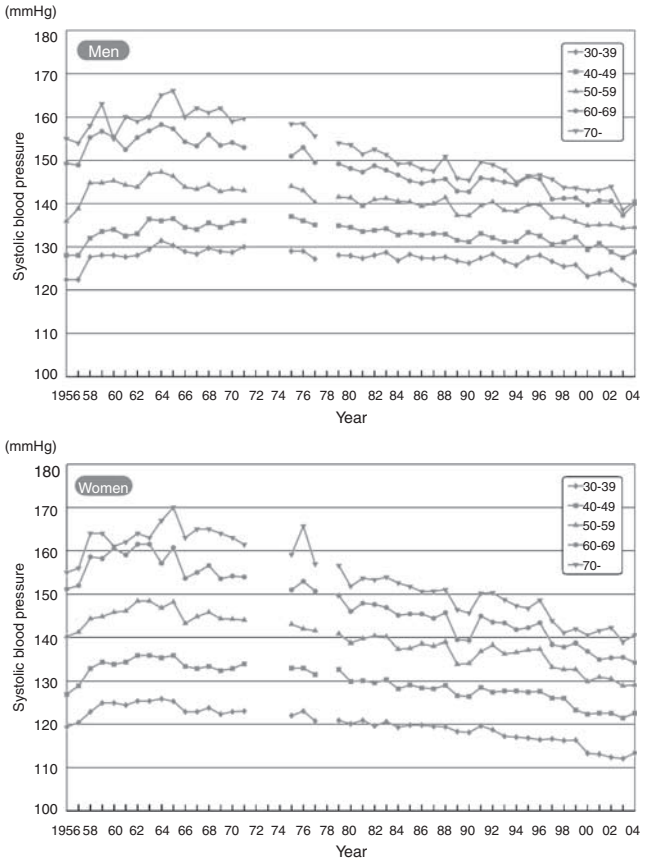

Figure 1-1 Changes in the average systolic blood pressure of the Japanese by sex and age. Reproduced from Ueshima *et al.*[1]

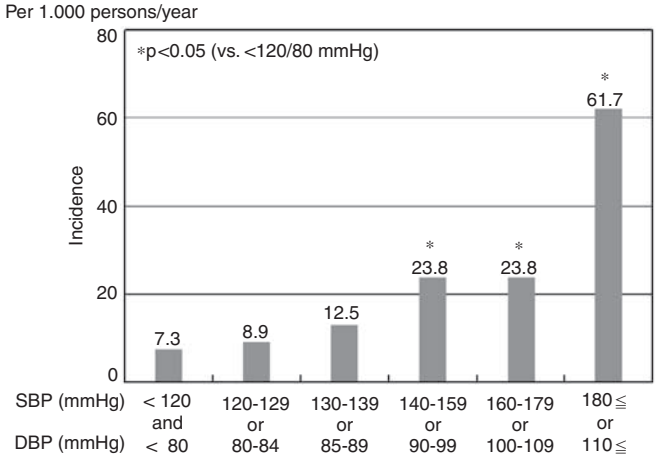

Figure 1-2 Incidence of stroke by blood pressure. Group 1 of Hisayama Study, men and women aged ⩾60 years. Sex- and age-adjusted data of 580 people followed up over 32 years. Reproduced from Arima *et al.*[8]

The strong relationship between the JNC-VI blood pressure grades and mortality rate due to stroke was also shown clearly by NIPPON DATA80, in which a representative group of about 10 000 Japanese was followed up for 14 years.[6]

The relative risks of morbidity and mortality from stroke according to blood pressure, as indicated by follow-up studies in Japan and abroad, are also presented as data of Health Japan 21. According to these data, an elevation of 10 mm Hg in the systolic pressure increases the morbidity and mortality rates due to stroke by about 20% in men and about 15% in women.

Blood pressure is also related to stroke in the elderly, although the relationship is weaker than in young or middle-aged people. The relationship was clear, though weak, in a meta-analysis integrating many cohort studies in Western countries and Japan.[9] Similar results were also obtained in the Asia-Pacific Cohort Studies Collaboration in a study summarizing the results for the Asia-Pacific regions.[5] In the Asia-Pacific Cohort Studies Collaboration, the risk of stroke shows a log-linear association with the normal systolic blood pressure from the age groups <65 years to $\geqslant 70$ years, although the association becomes weaker in the elderly than in the younger group (Figure 1-3).

b. Development of heart disease due to hypertension

The relationship between hypertension and heart disease was similar to that between hypertension and stroke, although weaker. The results are similar when heart disease is specified as coronary heart disease. In men, morbidity and mortality rates due to coronary artery disease increase by about 15% with a 10 mm Hg increase in systolic blood pressure.

c. Hypertension and prognosis of chronic kidney disease

Patients with chronic kidney disease have a poorer prognosis and higher risk of stroke, myocardial infarction and total death with an increase in mean blood pressure. Blood pressure control alleviates kidney disorders and reduces cardiovascular risk in later life.[10] In Japan also, cohort studies such as the Hisayama Study and NIPPON DATA90 have shown that cardiovascular morbidity and mortality risks are higher in those with a lower estimated glomerular filtration rate.[11,12] In addition, NIPPON DATA80 indicated that those with positive proteinuria have an increased risk of death due to cardiovascular disease.

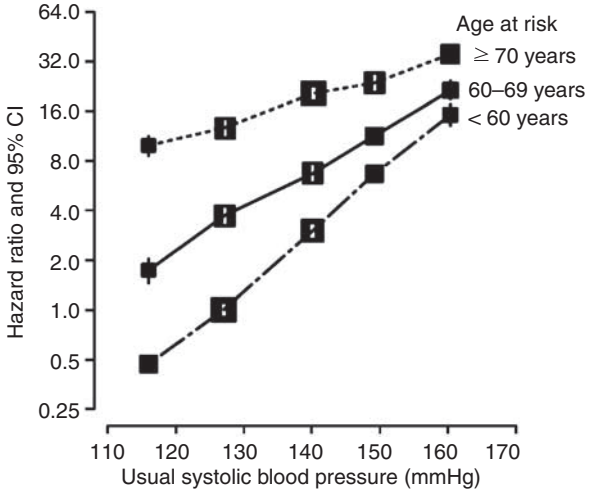

Figure 1-3 Risk of stroke against usual systolic blood pressure by age group. Reproduced from Lawes *et al.*[5]

d. Clustering of risks, metabolic syndrome and cardiovascular disease

The presence of a high morbidity rate due to cardiovascular disease in people with metabolic syndrome has been sufficiently established by epidemiological studies in Western countries. In epidemiological studies in Japan, morbidity and mortality rates from cardiovascular disease were 1.5–2.4 times higher in those with metabolic syndrome.[13–16] These risks were also higher in those with more risk factors for metabolic syndrome.[17] Moreover, NIPPON DATA[18] and an epidemiological study in Ehime presented results suggesting the importance of an accumulation of risks regardless of the presence or absence of obesity,[19] and NIPPON DATA[18] reported results suggesting the importance of the presence or absence of abnormal glucose tolerance.

e. Relationship of average blood pressure with cardiovascular and total mortality risk at various age levels

Meta-analyses that integrated the results of many cohort studies at an individual level have revealed that cardiovascular morbidity and mortality risks increase with blood pressure levels in all age groups.[5,9] NIPPON DATA80 also evaluated cardiovascular mortality risk by dividing the subjects into age groups of 30–64, 65–74 and ⩾75 years, and reported that the relative risk was lower in the two latter groups than in the former group, but that the cardiovascular mortality risk increased with blood pressure category (Figure 1-4).[20] Moreover, a large meta-analysis incorporating cohort studies in Japan clarified increases in the total mortality rate with blood pressure level for both young and elderly people (Figure 1-5).[21]

f. Relationship of various blood pressure parameters with cardiovascular morbidity risk

As for the relationship between various blood pressure parameters and the risk of cardiovascular morbidity, systolic blood pressure has been shown to facilitate the most accurate prognosis and to be more closely related to cardiovascular disease than diastolic blood pressure or pulse pressure by a large meta-analysis encompassing cohort studies in the Asia-Oceania region.[22] Cohort studies by Oyabe and Ohasama also reported similar results.[23,24]

g. Prognosis of stroke

According to a World Health Organization joint study on the morbidity rates from stroke and myocardial infarction (MONICA), the case fatality rate in patients with stroke aged 35–64 years within 28 days of onset was about 30%, despite variation among groups.[25] On the basis of the registration of stroke patients in Japan around 1990, the age-adjusted case fatality rate in all patients within 28 days of onset was about 15%.[4,26–28] Among stroke subtypes, the case fatality rate was highest for subarachnoid hemorrhage, being about 30%, followed by cerebral hemorrhage, about 20%, and cerebral infarction, about 10%. In the Hisayama study between the early 1970s and early 1980s, the case fatality rate within 1 year of the first episode of stroke reached 40% in patients aged ⩾40 years.[29] The case fatality rate within 28 days was 25% in men and 22% in women.[29] According to the registration of stroke patients in Oyabe City (Toyama Prefecture), the case fatality rate within 28 days decreased by 21% in men and by 25% in women from 1980 to 1990.[28] The percentage of people who needed assistance due to impaired activities of daily living (ADL) 1 year after the onset of stroke was about 29–45%, indicating the extreme importance of the management of hypertension as a preventive measure against stroke from the point of view of the prevention of bed-ridden disability.

4) CHARACTERISTICS OF HYPERTENSION IN THE JAPANESE

a. High salt intake

An excessive intake of salt was one of the causes of the high prevalence of hypertension and stroke in the past in Japan. A high salt intake increases the blood pressure. INTERSALT showed by analysis of 24-h urine collection that blood pressure was high in groups with a high salt intake and that a positive correlation was present between salt intake and blood pressure in individuals.[30]

Currently, the salt intake of the Japanese estimated by analysis of 24-h urine collection is approx 12 g day^{-1}.[30–32] It is lower in women than in men in proportion to energy intake. According to INTERSALT, the estimated salt intake in Japanese women in their 20s was about 10 g in 1985,[30] and according to INTERMAP, the estimated salt intake in men aged 40–59 years by analysis of 24-h urine collection was about 12 g in 1997.[32] In 240 working men aged 35–60 years surveyed

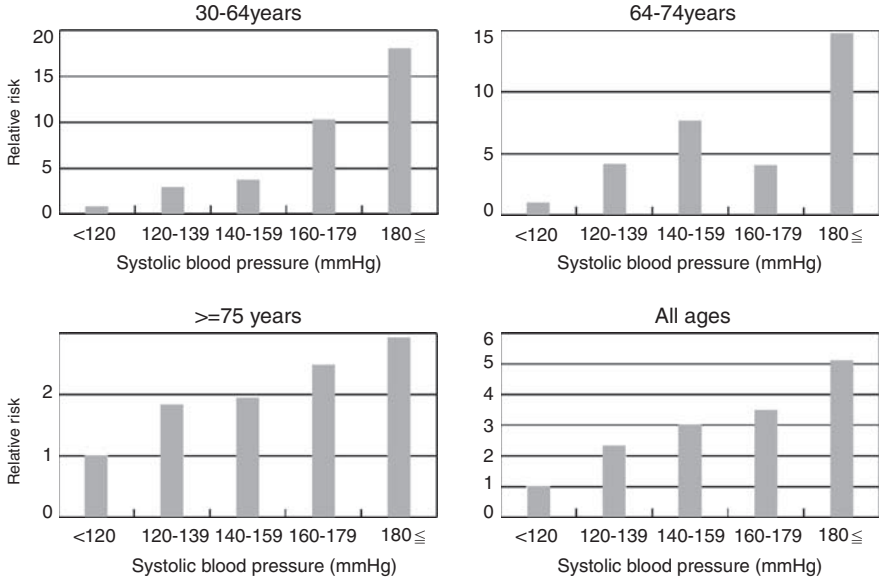

Figure 1-4 Relative risk of death due to cardiovascular diseases by age and systolic blood pressure level as indicated by NIPPON DATA80 (3779 men, 19-year follow-up).[20]

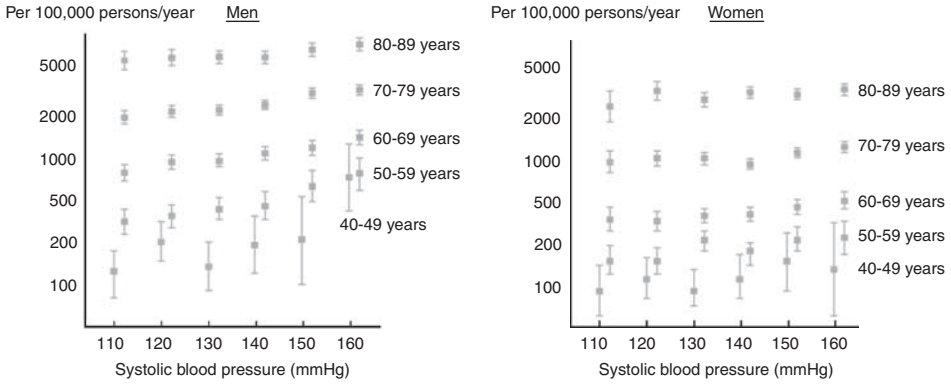

Figure 1-5 Relationships between systolic blood pressure and total mortality by age and sex. Adjusted for smoking, alcohol intake and BMI. Meta-analysis of data from 70 558 men and 117 583 women followed up over 9.8 years.[21]

in 2000, salt intake estimated by analysis of 24-h urine collection was about 11 g.

According to the results of the National Health and Nutrition Survey in 2006, the daily salt intake of the Japanese was approx 11 g (12.2 g in men and 10.5 g in women), and hence the current average salt intake of the Japanese is considered to be 11–12 g day^{-1}.

With regard to the results of past analyses of 24-h urine collection, the estimated salt intake in the Tohoku District was as high as 25 g in the 1950s.

The target salt intake proposed by Health Japan 21 is <10 g day^{-1} but no marked decrease has been noted during the past 10 years according to the results of the analysis of 24-h urine collection, and hence this target remains to be attained.[30–32] Salt intake is high in East Asia, including Japan. Particularly, Na excretion per unit body weight determined by 24-h urine collection was high in China, Korea and Japan among the 52 groups in 32 countries of the world surveyed in INTERSALT.[33]

A decrease in average salt intake affects the average blood pressure level of a given population. INTERSALT estimated that a decrease of 6 g day^{-1} in salt intake would reduce the elevation in systolic pressure level after 30 years by 9 mm Hg.[30] DASH, in which the effect of the control of salt intake on blood pressure was evaluated, reported values similar to those estimated by INTERSALT.[34] Further efforts to reduce salt intake are necessary for controlling hypertension in Japan.

b. Changes in the degree of obesity and frequency of metabolic syndrome

Obesity is less common in Japan than in other advanced industrialized countries. However, body mass index (BMI, kg m^{-2}), which is an index of obesity, is found to increase annually in men, whereas it is seen to decrease slightly in women until their 50s.

Regarding the characteristics of hypertensive Japanese, lean people with a very high salt intake account for a high percentage, but the number of obese hypertensives has increased recently, particularly in the male population.

In the United States, BMI has shown marked increases since 1990, and hypertension associated with metabolic syndrome is growing in significance. In Japan, mean BMI is about 23.5 kg m^{-2}, which differs markedly from that in the United States, where it is $\geqslant$28 kg m^{-2}.[32] However, hypertension associated with obesity appears to be increasing in Japanese men.[35] According to the National Health and Nutrition Survey in 2006, the percentage of people strongly suspected to have metabolic syndrome was 24.4% of men and 12.1% of women, and the percentages of those at high risk were 27.1 and 8.2%, respectively.

c. Untreated hypertensive patients and poor management of hypertension

If a blood pressure of $\geqslant$140/90 mm Hg is defined as hypertension, 80–90% of hypertensive patients in their 30s and 40s are untreated in Japan. These people must at least try to normalize their blood pressure through lifestyle modifications. In a survey of 6186 male and female workers aged $\geqslant$20 years performed at 12 companies in 2000–2001, about 70% with hypertension in their 30s were untreated.[36] Of the hypertensive men in their 40s and 50s, 44 and 39%, respectively, were untreated. At these companies, a high percentage of workers underwent annual health screening, but the percentage of those in their 40s and 50s who recognized that they were hypertensive was only 71–77%.

The Ohasama Study investigated the state of blood pressure control in patients undergoing depressor therapy. The results indicated that control of blood pressure was inadequate in about half of patients on the basis of either the routine outpatient blood pressure or home blood pressure measurement.[37] In addition, in a study of the state of treatment of those undergoing antihypertensive therapy by family doctors all over Japan on the basis of blood pressure measured at home (J-HOME), home blood pressure was in the hypertensive range in approx half of the 1533 hypertensive patients. In this study also, hypertension was poorly controlled in approx half of patients.

5) PREVENTIVE MEASURES AGAINST HYPERTENSION FROM THE POINT OF VIEW OF PUBLIC HEALTH

According to NIPPON DATA80, more than half of the deaths due to stroke occurred in patients with a blood pressure in a mildly hypertensive range or lower (systolic blood pressure $<$160 mm Hg and diastolic blood pressure $<$100 mm Hg).[6] Therefore, it is more important to promote a reduction in the average blood pressure of the general population than specifically target only hypertensive patients.

Factors that affect blood pressure levels of the general population include age, intakes of salt and potassium, protein, calcium, magnesium and fatty acids, degree of obesity, alcohol intake and physical activity level. With the exception of residents of unacculturated areas, blood pressure increases with age, and an excessive salt intake is suspected to be a cause of this increase.[30] Salt intake is still high in Japan. Systolic blood pressure is expected to be reduced by 1–4 mm Hg through a 3-g decrease in daily salt intake.[38] In men, also, increases in the degree of obesity are considered to prevent decreases in average blood pressure.[35] A high alcohol intake in middle-aged men is also considered to be a factor preventing average blood pressure reduction.

Table 1-1 Estimated decreases in the numbers of patients having, dying from and suffering impaired ADL due to stroke, having, dying from ischemic heart disease and dying from cardiovascular diseases associated with a decrease in the systolic blood pressure (−2 mm Hg)

Decrease in blood pressure (−2 mm Hg)	*Stroke*	*Ischemic heart disease*	*Cardiovascular diseases*
Decrease in the number of deaths	9127	3944	21055
Decrease in the number of patients	19757	5367	—
Decrease in the number of patients suffering impaired ADL	3488	—	—

Abbreviation: ADL, activity of daily living.

Although genetic predisposition affects individual blood pressures, no genetic factor affecting the average blood pressure of the general population has been identified. (See inherited hypertension in Chapter 12.)

A decrease of only 1-2 mm Hg in the average blood pressure is known to markedly affect morbidity and mortality rates due to stroke and myocardial infarction.[39] Health Japan 21 collated the results of epidemiological studies in Japan and calculated expected decreases in morbidity rates from stroke and ischemic heart disease associated with decreases in the average blood pressure of the Japanese. According to this calculation, a decrease of 2 mm Hg in the average systolic blood pressure is expected to reduce morbidity rates from stroke and ischemic heart disease by 6.4 and 5.4%, respectively. It is also expected to reduce the number of deaths due to stroke by about 9000 and the number of patients with an impaired ADL level by about 3500 (Table 1-1). The decrease in the number of deaths due to ischemic heart disease will be about 4000.

To reduce the average salt intake of the population, intensive guidance to follow a low-salt diet is required. However, INTERMAP showed that the actual reduction in salt intake in those who were following a low-salt diet was about 1–2 g day^{-1}. Therefore, hypertensive patients and others who need to reduce their salt intake should create an environment in which they can readily comply with a low-salt regimen. In addition, to reduce average blood pressure, it is necessary to create an environment in which many people spontaneously reduce their salt intake.

In Japan, nutritional labels on foods mention only some nutrients and additives, and labeling related to the content of salt and other necessary nutrients is not obligatory. In addition, if the Na content is indicated, the equivalent salt intake is not, and there is no mention as to what percentage of the daily allowance the salt content of the food accounts for, whereas this is indicated in labeling in the United States. These measures are extremely important for managing hypertension.

Citation Information

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

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.

Please refer to the title page for the full list of authors.

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GUIDELINES (JSH 2009)

Chapter 2. Measurement and clinical evaluation of blood pressure

Hypertension Research (2009) **32,** 11–23; doi:10.1038/hr.2008.2

POINT 2A
Blood pressure measurement

1. **Clinic blood pressure should be measured by maintaining the arm-cuff position at the heart level during rest in a seated position. The measurement must be performed two or more times at intervals of 1–2 min, and the mean value of two measurements that provide stable values (difference in the values <5 mm Hg) should be used. Diagnosis of hypertension should be based on clinic blood pressures measured on at least two different occasions.**
2. **Clinic blood pressure is measured by the auscultation method using a mercury sphygmomanometer, which is the standard procedure, but the use of an automatic sphygmomanometer is also permitted.**
3. **Home blood pressure measurement and 24-h ambulatory blood pressure (ABP) monitoring (ABPM) are useful for the diagnosis of hypertension, white coat hypertension and masked hypertension, as well as for evaluating the drug effect and its duration. They should be used as references in daily clinical practice.**
4. **Home blood pressure should be measured with upper-arm devices.**
5. **Criteria for hypertension differ between clinic blood pressure, 24-h ABP and home blood pressure. A clinic blood pressure of $\geqslant$140/90 mm Hg, a home blood pressure of $\geqslant$135/85 mm Hg and a mean 24-h ABP of $\geqslant$130/80 mm Hg are regarded as indicators of hypertension.**
6. **A normal home blood pressure is $<$125/80 mm Hg.**
7. **Masked hypertension and white coat hypertension must always be considered in the management of hypertension. In addition, for the diagnosis and treatment of resistant hypertension, home blood pressure measurement and 24-h ABPM are indispensable.**
8. **In treating hypertension, attention must also be given to the pattern of diurnal blood pressure changes (non-dipper, riser, dipper, extreme dipper), nighttime blood pressure, early-morning blood pressure and blood pressure at the workplace.**

1) BLOOD PRESSURE MEASUREMENT

a. Blood pressure measurement in the outpatient clinic (blood pressure measurement in a clinical setting)

Correct measurement of blood pressure is necessary for the diagnosis of hypertension. In a clinical setting (for example, an outpatient clinic), blood pressure is measured by the auscultation method using a mercury or aneroid sphygmomanometer, or using an automatic sphygmomanometer that has been calibrated by the auscultation method, and maintaining the arm-cuff position at the heart level. Nowadays, the use of a mercury sphygmomanometer is often avoided, especially in Europe, because of the possibility of environmental pollution by mercury. Table 2-1 shows the standard procedure for sphygmomanometry. Although clinic blood pressure measurement is still regarded as a standard for the diagnosis of hypertension, its clinical value has been questioned in various aspects. Clinic blood pressure measurement, in strict accordance with the procedure shown in Table 2-1, is known to more accurately reflect the true blood pressure than data obtained by disregarding this procedure, and is found to have a clinical value at least comparable to that of ambulatory blood pressure (ABP) monitoring (ABPM) or home blood pressure measurement.[40] However, blood pressure is rarely measured in accordance with such a guideline in a screening or clinical setting. In addition, the accuracy of measurement is often disregarded or ignored.

The Guidelines strongly recommend compliance with the procedure shown in Table 2-1 for the measurement of clinic blood pressure. In sphygmomanometry by the auscultation method, however, problems of terminal digit preference, that is, the tendency to round off the reading of the height of the mercury column to 0 or 5, and auscultation gap exist.

The following are other points of caution for the measurement of clinic blood pressure. For blood pressure measurement in adults, cuffs with rubber bags 13 cm wide and 22–24 cm long are usually used. Internationally, however, cuffs with a width of $\geqslant$40% of the brachial girth and a length sufficient to cover at least 80% of the brachial girth are recommended.

If pulses of the lower limb arteries (femoral, popliteal and dorsalis pedis arteries) are weak or not palpable, blood pressure is measured in the leg to exclude arteriosclerosis obliterans and aortic coarctation (particularly in young patients). For the measurement of blood pressure in the leg, an arm cuff is applied to the ankle, and auscultation is performed using the dorsalis pedis or posterior tibial artery, or the cuff is applied to the thigh (using a cuff with a rubber bag that is 20% wider than the femoral diameter, that is, 15–18 cm), and auscultation is performed using the popliteal artery.

In patients with arrhythmia (premature beats), systolic blood pressure is overestimated and diastolic blood pressure is underestimated by the auscultation method.[42] The effects of arrhythmia must be excluded by repeating the measurement three or more times. In

Table 2-1 Measurement of the clinic blood pressure

1. *Device*
a. The auscultation method using a mercury or aneroid sphygmomanometer, of which the accuracy has been validated, is employed. The use of an electronic sphygmomanometer of which the accuracy has been validated is also recommended.[a]
b. A cuff with a bladder 13 cm wide and 22–24 cm long meeting the Japanese Industrial Standard is used.
(A cuff for children is used in children with a brachial girth of <27 cm. When the arms are thick (arm girth: $\geqslant 34$ cm), a large cuff for adults is used.)

2. *Measurement conditions*
a. A quiet, appropriate environment at room temperature.
b. After resting for a few minutes in a seated position with the legs not crossed.
c. No conversation.
d. Smoking and alcohol/caffeine consumption should be avoided before measurement.

3. *Measurement methods*
a. The arm cuff is maintained at the heart level.
b. The cuff is rapidly inflated.
c. The rate of cuff deflation is 2–3 mm Hg per beat or second.
d. In the auscultation method, the blood pressure at the first Korotkoff sound is regarded as the systolic blood pressure, and that at the fifth Korotkoff sound as the diastolic blood pressure.

4. *Frequency of measurement*
a. Measurement is performed two or more times at 1- to 2-min intervals in one clinic visit.
b. When two measurements differ markedly, additional measurement is performed.

5. *Evaluation*
a. The mean value of two measurements that provide stable values[b] is adopted as the clinic blood pressure value.
b. Hypertension should be diagnosed on the basis of blood pressures measured on at least two different occasions.

6. *Other points requiring caution*
a. On the initial clinic visit, bilateral brachial blood pressure should be confirmed.
b. The cuff should not be attached over thick shirts or jackets. Furthermore, the upper arm should not be compressed by tucking up sleeves.
c. In persons with diabetes or elderly persons, the blood pressure should be measured after 1- and 3-min standing to confirm the presence of orthostatic hypotension.
d. Examiners with sufficient audibility who have completed training for measurement should perform auscultation.
e. The pulse rate must also be measured and recorded.

[a]Recently, it has been recommended that an electronic sphygmomanometer should be used for reasons such as the environmental pollution of mercury, difficulty in managing mercury column accuracy and inaccuracy of the aneroid sphygmomanometer. Furthermore, a hybrid sphygmomanometer with an electronic analogue column is available instead of a mercury sphygmomanometer. When an automatic rolling-type sphygmomanometer is used in the waiting room, measurement should be performed under sufficient guidance and management to avoid errors.
[b]Stable values mean that the difference between measurements is less than 5 mm Hg.

patients with atrial fibrillation, accurate sphygmomanometry is often difficult, but average values of systolic and diastolic blood pressures can be obtained by the cuff-oscillometric method unless the patients have bradycardia and the smoothness of consecutive pressure waves is lost.[42]

In pregnant women, Korotkoff sounds are occasionally heard at 0 mm Hg. In this case, the blood pressure at the fourth Korotkoff sound (muffling of the sound) is regarded as the diastolic pressure.

There is as yet no highly accurate or consistent method for indirect sphygmomanometry during exercise. Added to this, there are no sufficient grounds for the evaluation of blood pressure during exercise for the general diagnosis of hypertension.[42]

As blood pressure can be extremely variable and can elevate substantially on certain occasions, usually in a clinical setting, a diagnosis of hypertension should be made on the basis of blood pressure measurements taken on two or more different occasions.

b. Blood pressure measurement in a non-clinical setting

ABPM and self-measurement of blood pressure at home (home blood pressure measurement) are methods for blood pressure measurement in a non-clinical setting. Ambulatory and home blood pressures are often considered to have clinical values comparable to, or greater than, that of clinic blood pressure. These blood pressure measurements also have value as blood pressure information differing in nature (Table 2-2).

Home blood pressure measurement. Home blood pressure measurement is useful for improving the treatment adherence of patients and for preventing an excessive or insufficient antihypertensive effect of drugs. Measurement before taking a drug is particularly useful to assess the duration of the drug effect (for example, morning effect/evening effect ratio (M/E ratio)).[43] Home blood pressure measurement is also useful for the diagnosis of white coat, morning and masked hypertension. Home blood pressure measurement is extremely useful for the diagnosis of resistant hypertension and for deciding the therapeutic strategy.[44] On account of these merits, home blood pressure measurement has been reported to have a very high efficiency in medical economics.[45] Home blood pressure measurement is widely prevalent in Japan. According to a nation-wide survey in 2004–2005 in Japan, 90% of clinicians recommended home blood pressure measurement and 77% of hypertensive patients have a sphygmomanometer at home. Guidelines for home blood pressure measurement have been proposed by The Japanese Society of Hypertension.[49] An upper-arm-cuff device based on the cuff-oscillometric principle that has been confirmed in an individual to yield differences within 5 mm Hg compared with those of the auscultation method is used for home blood pressure measurement. It is recommended to measure blood pressure within 1 h of waking, after urination, after 1–2-min rest in a seated position, before taking antihypertensive drugs and before breakfast in the morning, and before retiring and after 1–2-min rest in a seated position in the evening (Table 2-3). Blood pressure measured before retiring is sometimes affected by alcohol consumption as well as bathing. However, these conditions are not prohibitive for blood pressure measurement before retiring, as prohibition of alcohol consumption and/or bathing before measurements can lower compliance for measurement. When measurements are taken under these conditions, subjects should record this information in addition to the actual blood pressure values. Measurements before dinner and before taking drugs in the evening may also be indicated for the evaluation of drug effects. The clinical value of home blood pressure measurement is sufficient even when conducted only once each morning and each evening if this is continued over a long period. Patients often perform multiple measurements on each occasion,[47] but adherence to measurement decreases if too many measurements are requested on each occasion.[47] In daily practice, the values of multiple measurements on one occasion, their mean and variability must also be evaluated if necessary; therefore, all values measured are recommended to be recorded and reported.[46,47] There is no consensus as to which of the measured values should be used for the clinical

Table 2-2 Characteristics of each type of blood pressure measurement

	Clinic blood pressure	*Ambulatory blood pressure*	*Home blood pressure*
Frequency of measurement	Low	High	High
Measurement standardization	Difficult	Unnecessary	Possible
Evaluation of short-term variability	Impossible	Possible	Impossible
Evaluation of diurnal changes (evaluation of nocturnal blood pressure)[a]	Impossible	Possible	Possible[a]
Drug efficacy assessment	Possible	Appropriate	Optimal
Evaluation of the duration of drug efficacy	Impossible	Possible	Most favorable
Evaluation of long-term changes	Impossible	Impossible	Possible
Reproducibility	Unfavorable	Favorable	Most favorable
White coat phenomenon	Present	Absent	Absent

[a]Home blood-pressure-measuring devices that can monitor blood pressure during sleep at night are available.

Table 2-3 Measurement of home blood pressure

1. Devices based on cuff-oscillometric method using upper arm cuff.
2. Measurement conditions
   Essential conditions
   a. Morning: within 1 h after waking up, after urination, before dosing in the morning, before breakfast, after 1- to 2-min resting in a sitting position.
   b. Night: before retiring, after 1- to 2-min resting in a sitting position.
   Selection conditions
   a. According to instructions: before dinner, before dosing in the evening, before bathing, before alcohol consumption.
   b. Others (if necessary): in the presence of symptoms, during the daytime on holidays; in some devices, measurement during sleep at night is possible.
3. Frequency of measurement: one to three times per occasion.[a]
4. Measurement period: as long as possible.
5. Recording: all values should be recorded.

[a]Many measurements should not be requested.
Note 1: In patients who are anxious about home blood pressure measurement, it should be avoided.
Note 2: Physicians must explain to the patients that they should not emotionally overcome by individual values.
Note 3: Patients should be instructed not to self-modify the treatment regimen based on self-measurements.

evaluation of home blood pressure. However, in the guidelines for the treatment of hypertension in various countries, which are described later, reference values of home blood pressure were derived from epidemiological studies where home blood pressure was measured once on each occasion and were averaged over a certain period. Also, a study in Japan showed that the mean of the values obtained on one occasion is highly reproducible, and that there was only a slight difference between the average of a single value and the average of the mean value of multiple measurements on each occasion over a certain period.[48] Moreover, even single home blood pressure measurement has been shown to have a better predictive power than a clinic blood pressure measurement.[49]

The Guidelines of The Japanese Society of Hypertension recommend that 'the mean value of the first measurement on each occasion of the morning and evening measurements over a long period should be used' for common clinical evaluation.[46] The JSH Guidelines assert that using the mean value of the first measurement taken each morning and evening over a certain period (5-7 times per week) is the basic principle for defining hypertension and normotension, while each value, as well as the mean of all values obtained by multiple measurements on a single occasion (1-3 times per occasion), provide valuable clinical information. Therefore, the Guidelines emphasize the importance of recording all values measured. As the interval between hospital visits is usually 2–4 weeks, it is practical to calculate the mean home blood pressure every 2–4 weeks, but clinical evaluation is also possible using the mean value of the measurements taken over the 5–7 days immediately preceding the visit.[46] For the short-term evaluation of drug effects and evaluation of the blood pressure at a certain point of time, calculation of the mean of all values obtained by multiple measurements on each occasion increases the number of available data and enhances the clinical value of home blood pressure. As the home blood pressure can be measured many times over a long period, it is also useful for the evaluation of blood pressure variability over an extended period, such as seasonal variations of blood pressure.[50]

The finger-cuff device for blood pressure measurement is inaccurate. The wrist-cuff device for blood pressure measurement is easy to use, but often provides inaccurate measurements because of the difficulty in correcting the difference of hydrostatic pressure between heart level and wrist level, and because of the difficulty in completely compressing arteries due to anatomical issues with the wrist.[51] At present, therefore, a blood-pressure-measuring device with an upper-arm cuff is used for home blood pressure measurement. The accuracy of upper-arm-cuff devices for home blood pressure measurement using the cuff-oscillometric method is generally acceptable as long as they are the products of Japanese companies. The results of tests of the accuracy of various home blood-pressure-measuring devices are provided at www.dableducational.org or http://www.bhsoc.org/blood_pressure_list.stm.

Home blood pressure has been reported to be a more reliable predictor of prognosis than clinic blood pressure.[52,53] As clinical data regarding the relationship between home blood pressure and the incidence of cardiovascular disease or prognosis have been accumulated,[54–59] its clinical application is expected to widen further. Home blood pressure tends to be lower than clinic blood pressure. Recently, diagnosis of hypertension has increasingly been made on the basis of home blood pressure measurements. According to the JNC VI,[60] JNC7[38] and 2003 ESH-ESC Guidelines,[61] 135/80 mm Hg is adopted as a criterion for the diagnosis of hypertension on the basis of worldwide cross-sectional studies and the prospective study in Ohasama, Japan. The WHO/ISH Guidelines published in 1999 reported that a home blood pressure of 125/80 mm Hg is equivalent to a clinic blood pressure of 140/90 mm Hg.[62] Therefore, a blood pressure $<$125/80 mm Hg is considered to be normal. In the Ohasama Study, the criterion for hypertension, tentatively defined as the home blood pressure at which the relative risk of death increases by 10% compared with the home blood pressure at which total mortality is lowest, was 137/84 mm Hg.[63] Added to this, in the Ohasama Study, as the home

Table 2-4 Criteria for hypertension in different measurement methods

	Systolic blood pressure (mm Hg)	*Diastolic blood pressure (mm Hg)*
Clinic blood pressure	140	90
Home blood pressure	135	85
Ambulatory blood pressure		
24-h	130	80
Day	135	85
Night	120	70

Table 2-5 Expected target blood pressure levels of antihypertensive treatment

	Clinic blood pressure	*Home blood pressure*
Young/middle-aged persons	<130/85 mm Hg	<125/80 mm Hg
Elderly persons	<140/90 mm Hg	<135/85 mm Hg
Diabetics		
Patients with kidney disease	<130/80 mm Hg	<125/75 mm Hg
Patients after myocardial infarction		
Patients with cerebrovascular disorders	<140/90 mm Hg	<135/85 mm Hg

Note: As the criteria for hypertension include a clinic blood pressure of 140/90 mm Hg and a home blood pressure of 135/85 mm Hg, the differences between clinic blood pressure and home blood pressure (5 mm Hg) were simply applied to the clinic blood pressure in each condition and derived provisional target home blood pressure levels.

blood pressure at which the relative risk of cardiovascular mortality is lowest is 120–127/72–76 mm Hg, and as the relative risk increases significantly at ⩾138/83 mm Hg,[64] the JSH2004 Guidelines adopted 135/85 mm Hg as the criterion for hypertension based on home blood pressure[65] to make it consistent with the guidelines in other countries. On the other hand, the 2007 ESH-ESC Guidelines proposed 130–135/85 mm Hg as the criterion for hypertension based on home blood pressure, with flexibility in the systolic blood pressure.[66] However, as the criterion used in the JSH2004 Guidelines is being increasingly recognized, the Guidelines have adopted 135/85 mm Hg as the criterion for hypertension (Table 2-4) and have regarded values <125/80 mm Hg as normal blood pressure. Therefore, a blood pressure of ⩾125/80 mm Hg and <135/85 mm Hg should not be considered normal, and should be recognized as being high-normal.

The criterion for normal home blood pressure differs from the target blood pressure level for antihypertensive treatment. The establishment of such target levels will not be possible until the results of an intervention study based on home blood pressure become available,[67] but provisional target control levels based on home blood pressure obtained from the relationship between clinic and home blood pressures are shown in Table 2-5. (See Figure 3-1 in Chapter 3 for details of target blood pressure control levels based on clinic blood pressure.)

Ambulatory blood pressure monitoring. As accurate automatic devices based on the cuff-oscillometric method have been developed,[68–70] blood pressure measurement outside the clinic during activity (ambulatory subjects) has become possible through the use of non-invasive ABPM devices at intervals of 15–30 min over 24 h. The ABPM can provide a 24-h blood pressure profile and blood pressure information over 24 h as well as during specific periods, for example, in the daytime, nighttime and early morning. In Japan, ABPM is widely used and the practice guidelines for ABPM have been published.[71] Usually, blood pressure is high during waking hours and low during sleep. It has also been shown that the 24-h average of ABP is correlated more closely with hypertensive target organ damage than with clinic blood pressure, and that it is closely associated with the regression of target organ damage mediated by antihypertensive medication.[72,73] Moreover, ABPM allows more accurate prediction of the incidence of cardiovascular disease than clinic blood pressure in the general population, elderly population and in hypertensive patients.[40,74–79]

ABPM is particularly useful for the diagnosis of white coat hypertension and masked hypertension (see below). The indications for the use of ABPM are diagnosis of white coat hypertension, poorly controlled hypertension and resistant hypertension. The normal ABP has not been defined, but the mean ± s.d. of the 24-h ABP measured in 634 normotensive Japanese aged 18–93 years was 119 ± 9/70 ± 6 mm Hg in men and 110 ± 10/64 ± 7 mm Hg in women.[80] The JNC VI and JNC7 propose a blood pressure during waking hours of ⩾135/85 mm Hg and during sleep of ⩾120/75 mm Hg to be indicative of hypertension.[38,60] According to the 1999 WHO/ISH Guidelines[62] and 2003 ESH-ESC Guidelines,[61] a 24-h ABP of 125/80 mm Hg is equivalent to an outpatient blood pressure of 140/90 mm Hg. Also, the International Database including the Ohasama Study proposed an ABP of 130/80 mm Hg over 24 h, 140/85 mm Hg during the daytime and 120/70 mm Hg during the nighttime as criteria for hypertension.[81] Following these reports, a mean 24-h ABP of ⩾130/80 mm Hg should be regarded as hypertension (Table 2-4). The 2007 ESH-ESC Guidelines also adopted a mean daytime ABP of ⩾135/85 mm Hg and a mean nighttime ABP of ⩾120/70 mm Hg as criteria for hypertension.[66]

Recently, an increase in short-term variation in ABP has been shown to be a risk factor for cardiovascular disease, adding a new clinical significance to ABPM.[82] As ABPM has been covered by medical insurance since April 2008 in Japan, it is expected to be used more widely and to contribute to the diagnosis and treatment of hypertension.

Information obtained by clinic blood pressure measurements, home blood pressure measurements, 24-h ambulatory blood pressure monitoring and other methods.

White coat hypertension/white coat phenomenon (effect). White coat hypertension is a condition in which blood pressure measured in a clinical setting (for example, at an outpatient clinic) is always at a hypertensive level but that measured in a non-medical setting (for example, home blood pressure, ABP) is always normal. Therefore, home blood pressure measurement or ABPM is indispensable for the diagnosis of white coat hypertension or the white coat phenomenon (effect). This definition of white coat hypertension applies to untreated patients. The differences between blood pressure measured in the clinical setting and that measured in the non-clinical setting are also observed in patients being treated, a finding called the white coat phenomenon (effect). If blood pressure measured in a clinical setting is hypertensive, and that measured in a non-clinical setting is normal in patients who are undergoing treatment, such a condition must be specified as 'white coat hypertension under treatment'. Whether white coat hypertension is harmful remains to be clarified, but white coat hypertension is known to develop into true sustained hypertension in a high percentage of patients,[83] and the risk of stroke in patients with

white coat hypertension was shown to be comparable to that in patients with true sustained hypertension in a 9-year follow-up.[84]

Masked hypertension. Masked hypertension is a condition opposite to white coat hypertension—that is, the blood pressure measured in a clinical setting is normal, but that measured in a non-clinical setting is always at a hypertensive level. It is observed in both treated and untreated patients. This phenomenon is called masked hypertension, because hypertension is undetectable in the clinic. It is related to a rise in blood pressure in the morning as part of physiologic and pathophysiologic changes in diurnal variation of the blood pressure[85,86] (for example, non-dipper, riser and morning surge) and morning hypertension as a result of the insufficient duration of drug effect, allowing the blood pressure to return to a hypertensive level before the next administration.[87] This condition can be detected by home blood pressure measurement as well as ABPM. The prognosis of masked hypertension is clearly poor.[88,89] Workplace hypertension is a cause of masked hypertension.[90]

Morning hypertension. Although there is no strict definition of morning hypertension, a hypertension specifically observed shortly after waking may be defined as morning hypertension. In terms of the absolute values observed by home blood pressure measurement or ABPM, those measured in the morning of $\geqslant$135/85 mm Hg may be regarded as morning hypertension, but, to be faithful to the definition of high blood pressure observed specifically in the morning, measurements taken in the morning must be shown to be higher than those taken before going to bed. Morning hypertension is associated with two types of circadian blood pressure variation. One is the morning surge; that is, a rapid increase in blood pressure after waking from a low level overnight. The other is morning hypertension observed in non-dippers; that is, those who show no nocturnal dip in blood pressure, or risers, that is, those who show a nocturnal increase in blood pressure. Both of these types are considered to be possible risk factors for cardiovascular disease.[85,87,91–94]

Nighttime blood pressure. Blood pressure measured during sleep by ABPM is referred to as nighttime blood pressure. Recently, it has become possible to automatically measure blood pressure during sleep using a home blood-pressure-measuring device.[95] A decrease of 10–20% in the blood pressure during the night compared with the daytime level is classified as a dipper (normal), a decrease of 0–10% as a non-dipper, an increase in the blood pressure during the night compared with the daytime level as a riser, and a decrease of $\geqslant$20% as an extreme dipper. The prognosis is poor in non-dippers and risers.[79,85,96–99] Hypertensive target organ damage such as asymptomatic lacuna infarction, left ventricular hypertrophy (LVH) and microalbuminuria are observed more frequently in non-dippers and risers than in dippers.[96–98] Also, prospective studies have shown that the risk of cardiovascular events is higher in non-dippers than in dippers.[79,85,99] However, in the J-MUBA, evaluating more than 600 Japanese hypertensive patients, many non-dippers were found even among patients showing no target organ damage.[100] According to the results of the Ohasama Study, the risk of cardiovascular events was also high in non-dippers among normotensive individuals.[99] As a result of these findings, the clinical significance of nighttime blood pressure is attracting attention. Although it has been reported that asymptomatic cerebral infarction is observed more frequently in elderly extreme dippers,[101] the risk to extreme dippers is comparable to that of dippers in the general population.[85] Both large-scale intervention study[76] and an international joint study[102] have also suggested that an increase in nighttime blood pressure is linearly related to an increase in the risk of cardiovascular disease; therefore, a low nighttime blood pressure is considered to be associated with a more favorable prognosis.

Central blood pressure. The blood pressure at the root of the aorta is generally called the central blood pressure. Central blood pressure is determined indirectly and noninvasively by converting the radial artery pressure waveform recorded by applanation tonometry into an aortic pressure waveform using a transfer function,[103] or by recording the carotid artery pressure waveform as a substitute for the aortic pressure waveform and correcting it for brachial blood pressure.[104] A method to estimate central blood pressure from the late (second) peak pressure in the radial artery pressure waveform using a linear function is also being evaluated.[105] Central blood pressure is known to show different values from conventional brachial blood pressure due to the variable superimposition of incoming and reflected pressure waves along the arterial tree. Central blood pressure and augmentation index (AI), an index of wave reflection, both of which increase in the presence of cardiovascular risk factors and reflect pressure loads on major organs including the heart, are estimated to be related more closely to hypertensive target organ damage than brachial blood pressure.[65] Antihypertensive drugs exhibit different blood-pressure-lowering effects on the central and brachial blood pressures, and the measurement of central blood pressure may help identify the differential effects of drugs, which are not observed in the measurement of brachial blood pressure.[106] Recent studies have suggested that central blood pressure and AI are related to cardiovascular events independently of brachial blood pressure and may serve as markers of the regression of target organ damage associated with antihypertensive treatment.[107,108] However, the prognostic value of central blood pressure must still be validated by future large-scale observational and interventional studies. In Japan, a device for measuring central blood pressure and AI from radial artery pulse waves (Omron Healthcare, HEM7000AI) is used.

Pulse rate. Extensive evidence that pulse rate is related to cardiovascular morbidity and mortality and total mortality has been accumulated.[109–112] In particular, pulse rates derived from ABPM[113] and home blood pressure measurement have a high predictive value for prognosis.[114] However, there is as yet no convincing evidence that the control of pulse rate at an optimal level improves outcome; therefore, no optimal pulse rate has been determined.

Isolated systolic hypertension and pulse pressures. Isolated systolic hypertension is a strong risk factor for cardiovascular disease in middle-aged and elderly individuals.[54,115,116] Therefore, pulse pressure is known to be a strong predictive factor for the occurrence of cardiovascular disease.[117,118] However, in Japan, systolic and mean blood pressures have a greater predictive power for the occurrence of stroke than pulse pressure.[23,24]

These facts are revealed more clearly by home blood pressure measurement and ABPM.[24,54]

POINT 2B
Definition and classification of blood pressure levels and evaluation of risk factors

1. **Blood pressure is classified into optimal, normal and high-normal, and the corresponding levels are classified into grade I, grade II and grade III hypertension, respectively.**
2. **Hypertensive patients are stratified into low-, moderate- and high-risk groups according to the presence or absence of risk**

factors other than blood pressure, hypertensive target organ damage and cardiovascular disease. In particular, the presence of diabetes mellitus and chronic kidney disease increases the risk. Attention to metabolic syndrome including a high-normal blood pressure as a component is also necessary.

3. **Hypertension is classified into primary (essential) and secondary hypertension. Secondary hypertension is suggested by medical history, physical findings and results of general laboratory tests, and specific tests are performed to confirm the diagnosis if necessary.**
4. **The treatment program should be prepared according to stratification of the risk; all patients must be guided to modify their lifestyle, and antihypertensive medication should be started if necessary to achieve the target blood pressure level.**

2) DEFINITION AND CLASSIFICATION OF BLOOD PRESSURE LEVELS AND EVALUATION OF RISK FACTORS

a. Classification of blood pressure levels

Although a positive correlation is observed between blood pressure and risk of cardiovascular disease, blood pressure values are distributed continuously and hypertension is defined artificially. In the 1999 WHO/ISH Guidelines,[62] the diagnostic criteria for hypertension were combined, in principle, with the JNC VI diagnostic criteria to avoid confusion.[60] Thereafter, the guidelines were revised in the JNC7 in 2003,[38] 2003 ESH-ESC Guidelines,[61] 2003 WHO/ISH Statement[119] and 2007 ESH-ESC Guidelines,[66] all of which defined a blood pressure of $\geqslant$140/90 mm Hg as indicative of hypertension.

In the Hisayama Study in Japan, the cumulative mortality rate due to cardiovascular disease was lowest when the systolic and diastolic blood pressures were $<$120 mm Hg and $<$80 mm Hg, respectively, and the risk of cardiovascular disease increased significantly when the systolic blood pressure was $\geqslant$140 mm Hg compared with $<$120 mm Hg, and when the diastolic blood pressure was $\geqslant$90 mm Hg compared with $<$80 mm Hg, including in elderly individuals.[109] Moreover, according to the Tanno/Sobetsu Study, an 18-year prospective epidemiological study in Hokkaido, Japan, a systolic blood pressure of $\geqslant$140 mm Hg and a diastolic blood pressure of $\geqslant$90 mm Hg were considered significant risk factors for cardiovascular and total mortality.[120] Similarly, in NIPPON DATA 80, a significant increase in mortality rate due to cardiovascular disease was observed at a blood pressure of $\geqslant$140/90 mm Hg.[6]

The JSH 2004 Guidelines classified hypertensive blood pressure levels into mild, moderate and severe hypertension, but they have been expressed as grade I, grade II and grade III hypertension, respectively, in the Guidelines to avoid confusion, because even a mild hypertension may be high-risk hypertension. In the Guidelines, hypertension of grade I or above was also defined as a blood pressure of $\geqslant$140/90 mm Hg, as in the earlier guidelines, and the same criteria for the classification of blood pressure levels have been adopted as those of the 1999 WHO/ISH Guidelines,[62] 2003 ESH-ESC Guidelines[61] and 2007 ESH-ESC Guidelines.[66]

However, according to the results of the meta-analysis of data from approx 1 million people obtained from observational studies in various countries, including the epidemiological data from Japan, the risk of cardiovascular disease increased linearly with blood pressure higher than 110–115/70–75 mm Hg.[9] Similar to observational studies conducted in Western countries[121,122] the results of Japanese studies[17,21,123] have shown the mortality rate from cardiovascular disease to be higher in people with a high-normal blood pressure (130–139/85–89 mm Hg) than in those with a normal or optimal blood pressure. The fact that an optimal blood pressure was defined as $<$120/80 mm Hg indicates that a normal pressure of 120–129/80–84 mm Hg is already above the optimal range. Furthermore, the evidence from the Framingham Study indicated that in individuals with a normal or a high-normal blood pressure, the chances of developing hypertension are higher than in those with an optimal blood pressure at all ages (Table 2-6).[124]

Table 2-6 Definition and classification of blood pressure levels (mm Hg) in adults

Classification	*Systolic blood pressure and diastolic blood pressure*
Optimal blood pressure	$<$120 and $<$80
Normal blood pressure	$<$130 and $<$85
High-normal blood pressure	130–139 and/or 85–89
Grade I hypertension	140–159 and/or 90–99
Grade II hypertension	160–179 and/or 100–109
Grade III hypertension	$\geqslant$180 and/or $\geqslant$110
Isolated systolic hypertension	$\geqslant$140 and $<$90

These classifications of blood pressure levels are criteria for diagnosis based on observational studies, and do not necessarily indicate a level at which antihypertensive medication should be started or a target level of blood pressure control. The diagnosis of hypertension should be based on multiple blood pressure measurements, taken on separate occasions over a period of time. Systolic and diastolic blood pressures are mutually independent risk factors, and if they belong to different blood pressure categories, the individual is classified by the higher category.

b. Risk factors for cardiovascular disease

Although hypertension is the most important risk factor for stroke, it is only one of the risk factors for cardiovascular disease. The prognosis of hypertensive patients is markedly affected not only by blood pressure but also by risk factors other than hypertension, the severity of target organ damage secondary to hypertension and the presence or absence of cardiovascular complications (Table 2-7). For the diagnosis and treatment of hypertension, blood pressure, risk factors for cardiovascular disease (Table 2-7A) and the presence or absence of target organ damage/cardiovascular disease (Table 2-7B) are evaluated in addition to the differential diagnosis between primary and secondary hypertension.

c. Risk stratification for evaluation of the prognosis

In addition to blood pressure, the presence or absence of other risk factors—smoking, diabetes mellitus, dyslipidemia such as high low-density lipoprotein (LDL) cholesterol and low high-density lipoprotein (HDL) cholesterol, obesity (particularly abdominal obesity), chronic kidney disease (CKD), old age, family history of premature cardiovascular disease—hypertensive target organ damage and cardiovascular disease should be evaluated. As the risk for cerebrovascular and cardiovascular disease increases with prolongation of the follow-up period even in low- and moderate-risk patients, attention must also be paid to the duration of hypertension.[125]

Metabolic syndrome based on the diagnostic criteria for the Japanese[126] was added as a risk factor for cardiovascular disease in the Guidelines. However, in Tables 2-7A and 2-8, metabolic syndrome is mentioned from a preventive point of view. As established diabetes

Table 2-7 Prognostic factors for risk stratification to use in planning hypertension management

A. *Risk factors for cardiovascular disease*
Advanced age
Smoking
Systolic/diastolic blood pressure levels
Dyslipidemia
Low-HDL-cholesterol (<40 mg per 100 ml)
High-LDL-cholesterol (⩾140 mg per 100 ml)
High triglyceride (⩾150 mg per 100 ml)
Microalbuminuria
CKD
Obesity (BMI⩾25) (especially, abdominal obesity)
Metabolic syndrome[a]
Family history of premature cardiovascular disease
Diabetes
Fasting plasma glucose: ⩾126 mg per 100 ml or glucose tolerance test: 2-h value ⩾200 mg per 100 ml
B. *Target organ damages/cardiovascular disease*
Brain
Cerebral hemorrhage/cerebral infarction
Asymptomatic cerebrovascular diseases
Transient ischemic attack
Heart
Left ventricular hypertrophy (electrocardiogram, echocardiogram)
Angina pectoris/myocardial infarction/coronary revascularization
Heart failure
Kidney
Proteinuria (including microalbuminuria)
Decreased eGFR[b] (<60 ml per min per 1.73 m^2)
CKD, established kidney disease (diabetic nephropathy/renal failure)
Blood vessels
Atheromatous plaque
Carotid intima–media thickness >1.0 mm
Aortic disease
Arteriosclerosis obliterans (decreased ABI<0.9)
Ocular fundus
Advanced hypertensive retinopathy

Abbreviations: ABI, ankle-brachial index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Metabolic syndrome: Patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level, and/or impaired glucose tolerance that does not lead to diabetes) and/or abnormalities in lipid metabolism in addition to a high-normal or higher blood pressure level and abdominal obesity (males: ⩾85 cm, females: ⩾90 cm).
[b]The eGFR is calculated using the following formula for Japanese:
$eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$ ($\times 0.739$; females).

mellitus is a strong independent risk factor, it is mentioned separately in Tables 2-7A and 2-8. In these Tables, metabolic syndrome is defined as a condition with a high-normal or higher blood pressure, and obesity (particularly abdominal obesity) as an essential factor concurrent with abnormal glucose level (an impaired fasting glucose level or an abnormal glucose tolerance below the diabetic level) or dyslipidemia.

In addition, CKD was added to these Guidelines as a new risk factor. CKD is known to represent hypertensive target organ damage, as well as to be a risk factor for cardiovascular disease.[11,127–132] The risk is particularly high when diabetes mellitus and/or CKD are present, and the JNC7[38] and 2007 ESH-ESC Guidelines[66] recommend aggressive antihypertensive treatment on the basis of the results of many interventional studies.[130,133-136] The Hisayama Study also showed that diabetes mellitus is a major risk factor for cerebral infarction and ischemic heart disease.[137] Recently, the number of patients developing chronic renal failure from diabetic nephropathy has increased markedly in Japan.[138]

In patients with both hypertension and diabetes mellitus, the outcome has been shown to be improved by strict antihypertensive medication.[134–136,139,140] As treatment for hypertension has also been shown to be important in controlling the progression of renal diseases, including diabetic nephropathy,[134,136,140–142] the aggressive management of hypertension is important, particularly when diabetes mellitus or renal diseases are complicating factors.

The 1999 WHO/ISH Guidelines[62] classified hypertension into four risk levels (low, medium, high and very high) according to the 10-year absolute risk of cardiovascular disease in individuals aged 45–80 years (mean: 60 years) from the Framingham Study. The JNC7[38] emphasized the population strategy and attached the blood pressure level *per se*, but the earlier JNC VI[60] worked out the high-risk strategy by stratifying hypertensive patients into three levels depending on risk factors.

Although the 1999 WHO/ISH Guidelines,[62] 2003 ESH-ESC Guidelines[61] and 2007 ESH-ESC Guidelines[66] stratified hypertensive patients into low-, middle-, high- and very high-risk groups according to risk factors, they proposed the same therapeutic strategy for high- and very high-risk groups.

As the high-risk strategy as well as population strategy is considered to be extremely effective in Japan, the Guidelines classify hypertensive patients into low-, medium- and high-risk groups according to blood pressure category and presence or absence of risk factors, hypertensive target organ damage and cardiovascular disease (risk strata), as shown in Table 2-8. In the Guidelines, the risk is considered to be high even in patients with a high-normal blood pressure if they have diabetes mellitus, CKD, three or more risk factors, target organ damage or cardiovascular disease, and appropriate antihypertensive therapy must be initiated. On the basis of the current state of antihypertensive therapy in Japan, patients with grade II hypertension as well as 1–2 risk factors or metabolic syndrome (risk stratum-2) were classified as a high-risk group.[143] Cardiovascular risk stratification is essentially based on the evidence of the Framingham Study, in which cardiovascular events in the untreated population have been recorded since the 1940s. At present, there is no study in which absolute cardiovascular risk has been evaluated in untreated patients with grade II hypertension as well as risk stratum-2. In the Ohasama Study, although many patients with grade II hypertension were treated with antihypertensive drugs, those with grade II hypertension as well as risk stratum-2 had a very high absolute risk for stroke.[143] As this absolute risk is similar to that in patients with risk stratum-3 or grade III hypertension, it is reasonable to assume that those with grade II hypertension as well as risk stratum-2 have a high risk.

d. Typing of hypertension

About 90% of hypertension is essential hypertension. The diagnosis of essential hypertension is made by the exclusion of secondary hypertension. Essential hypertension includes white coat hypertension (clinic hypertension), in which hypertension is observed only in a

Table 2-8 Stratification of cerebrovascular/cardiovascular risk in four categories on the basis of (clinic) blood pressure classification and risk strata

Blood pressure classification / *Risk strata (risk factors other than blood pressure)*	*High-normal blood pressure 130–139/85–89 mm Hg*	*Grade I hypertension 140–159/90–99 mm Hg*	*Grade II hypertension 160–179/100–109 mm Hg*	*Grade III hypertension ⩾180⩾110 mm Hg*
Risk stratum-1 (no other risk factors)	No additive risk	Low risk	Moderate risk	High risk
Risk stratum-2[a] (one to two risk factors (other than diabetes) or metabolic syndrome)[b]	Moderate risk[c]	Moderate risk	High risk	High risk
Risk stratum-3[a] (three or more risk factors, diabetes, CKD, target organ damage/cardiovascular disease)	High risk[c]	High risk	High risk	High risk

Abbreviation: CKD, chronic kidney disease.
[a]When obesity and dyslipidemia are present in the absence of other risk factors, risk factors other than the blood pressure level are counted as two, and the risk is classified as the risk stratum-2. However, when other risk factors are present, the total of risk factors is calculated as three or more, and the risk is classified as the risk stratum-3.
[b]Metabolic syndrome in risk stratum-2 indicates patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level of 110–125 mg dl^{-1} and/or impaired glucose tolerance that does not lead to diabetes), or abnormalities in lipid metabolism in addition to a high-normal or higher blood pressure level and abdominal obesity (males: ⩾85 cm, females: ⩾90 cm).
[c]Treatment in moderate- and high-risk groups with high-normal blood pressure values is based on the algorithm for treatment of hypertension at initial visit. The management of common cardiovascular risks is important here.

medical setting (for example, in outpatient clinics). The diagnosis of white coat hypertension is made by home blood pressure measurement and ABPM, as well as by measurement of blood pressure at the clinic. The frequency of isolated systolic hypertension increases in elderly people, because systolic blood pressure increases whereas diastolic blood pressure often decreases due to a reduced compliance of the aorta caused by atherosclerosis. Several studies, including the Framingham Study, Ohasama Study and Hisayama Study,[54,109,110,115,116] showed that isolated systolic hypertension is a strong risk factor for cerebral and myocardial infarction in elderly people. Isolated systolic hypertension in the elderly is classified into the burned-out type, caused by a decrease in diastolic blood pressure in essential hypertension, and the *de novo* type, caused by a novel elevation of systolic blood pressure in old age.

POINT 2C
Examination and diagnosis

1. **For the examination of hypertension, the overall evaluation of cardiovascular risk in individual patients and examinations for the diagnosis of secondary hypertension should be performed by considering the cost-effectiveness.**
2. **For the overall evaluation of cardiovascular risk, factors related to metabolic syndrome and CKD and hypertensive target organ damage are evaluated in addition to blood pressure, including home blood pressure.**
3. **The evaluation of target organ damage should be started from the high-normal blood pressure range in high-risk patients with diabetes mellitus or a history of cardiovascular disease.**
4. **Echocardiography, carotid ultrasonography and brain MRI are representative, special methods of examination for evaluating target organ damage, and the recommended method should be performed appropriately.**
5. **If secondary hypertension is suspected from history taking, physical examination and general laboratory investigation, special screening tests should be performed.**

3) EXAMINATION AND DIAGNOSIS

For the diagnosis and treatment of hypertensive patients, (1) essential and secondary hypertension should be differentiated, (2) the presence or absence of cardiovascular risk factors (particularly those related to metabolic syndrome and CKD) and (3) the underlying lifestyle should be clarified, and the severity of hypertension should be evaluated considering (4) concurrent cardiovascular disease and hypertensive target organ damage, as well as (5) home blood pressure.

a. History (Table 2-9)

The time of detecting hypertension and its circumstances (health screening, examination, self-measurement, and so on), duration, severity and course of treatment should be established. Particularly, if hypertension has been treated, the types of antihypertensive medications used and their effectiveness and adverse effects should be verified.

With regard to family history, the presence or absence of hypertension, diabetes mellitus and cardiovascular disease, age of onsets, low birth weight or overweight in childhood, and, in women, whether they have had hypertension, diabetes mellitus and proteinuria during pregnancy should be ascertained.

Lifestyle should be clarified in detail by asking patients about their exercise habits (frequency and intensity), sleep habits (duration and quality of sleep), dietary habits (content of meals, salt content, preference for sweets, and so on), intake of alcohol or soft drinks and smoking (amount and period), personality and psychological state (anxiety and depressive tendency) and severity of stress (workplace, home).

Hypertensive patients are usually asymptomatic, but whether they have specific symptoms suggesting secondary hypertension or hypertensive complications and target organ damage should be clarified. As for signs suggestive of secondary hypertension, whether the patient has symptoms such as nocturnal pollakiuria or nocturnal dyspnea, early-morning headache, daytime sleepiness, depression and reduced concentration, or whether there are signs suggestive of sleep apnea syndrome, such as reports of snoring and apnea by the family, should be checked, in addition to the course of body weight increases and other risk factors related to metabolic syndrome (diabetes and dyslipidemia). Moreover, history of hematuria, proteinuria and nocturnal pollakiuria, and the use of non-steroidal anti-inflammatory drugs, *kampo* drugs, oral contraceptives, and so on, should be verified.

Inquiries should be made into history of target organ damage and cardiovascular disease. The presence or absence of symptoms such as transient ischemic attacks, muscle weakness, dizziness, headache and visual impairment related to cerebrovascular disorders; dyspnea (exertional, nighttime), weight gain, lower limb edema, palpitation and

Table 2-9 Points regarding medical history

1. History of hypertension and treatment	Previous blood pressure level, duration of hypertension and treatment course Efficacy and side effects of antihypertensive drugs
2. Predisposition to hypertension and pregnancy	
Family history	Parents' histories of hypertension, diabetes and cardiovascular disease (onset and age at onset)
Birth weight/weight gain during childhood	
Pregnancy	Pregnancy hypertension, diabetes, proteinuria
3. Lifestyle	
Exercise	
Sleep	Sleep time, quality of sleep
Diet	Dietary contents/preferences, alcohol consumption, beverages
Smoking	
Personality/psychological state	Depressive tendency, degree of stress (workplace, home)
4. Information suggesting secondary hypertension	
Obesity	Course of weight gain
Sleep apnea syndrome	Nocturnal pollakiuria, nocturnal dyspnea, headache, daytime sleepiness, depression, reduced concentration, snoring/apnea (information from patients' families)
Kidney disease	Nocturnal pollakiuria, hematuria, family history (polycystic kidney)
Drugs	Non-steroidal anti-inflammatory drugs, *kampo* drugs, oral contraceptives
Pheochromocytoma	Paroxysmal blood-pressure increase, palpitation, sweating, headache
Primary aldosteronism/renovascular hypertension	Weakness, periodic paralysis of the limbs, polyuria, hypokalemia
5. Organ disorders	
Cerebrovascular disorders	Transient ischemic attacks, muscular weakness, vertigo, headache, vision disorder
Heart disease	Dyspnea (exertional/nocturnal attacks), weight gain, edema of the lower limbs, palpitation, chest pain
Kidney disease	Polyuria, nocturnal pollakiuria, hematuria, proteinuria
Peripheral arterial disease	Intermittent claudication, coldness of the lower limbs

Table 2-10 Physical findings

1. Blood pressure/pulse rate	
Resting in the sitting position (blood pressure laterality and orthostatic changes in blood pressure and pulse rate on initial examination)	
2. General condition and obesity	
Height/body weight	
BMI [body mass index: body weight (kg)/{height (m)}^{2}]	Obesity, BMI $\geqslant 25\,kg\,m^{-2}$
Waist circumference (standing-position measurement at the umbilical level)	Abdominal obesity, male>=85 cm, female>=90 cm
Dermal findings	Striated abdominal wall skin, hypertrichosis (Cushing's syndrome)
3. Facial/cervical regions	
Anemia, jaundice	
Fundic findings	
Goiter	
Carotid artery murmurs	
Dilatation of the jugular vein	
4. Thoracic region	
Heart	Apical beat and thrill on palpation (strongest point and extent of palpation), cardiac murmurs, gallop rhythms, arrhythmia on auscultation
Lung field	Rales
5. Abdomen	Vascular murmurs and the direction of their projection, liver enlargement and tenderness, kidney enlargement (polycystic kidney)
6. Limbs	Arterial pulse (radial artery, dorsal artery of the foot, posterior tibial artery, femoral artery) on palpation (disappearance, attenuation, laterality), coldness, ischemic ulcers, edema
7. Nerves	Dyskinesia of the limbs, sensory disturbance, increased tendon reflex

chest pain related to heart disease; pollakiuria, nocturia, hematuria and proteinuria related to kidney disease; and intermittent claudication and coldness of the lower limbs related to peripheral artery disease should be investigated.

b. Examination (physical findings) (Table 2-10)

In addition to resting blood pressure and heart rate in a sitting position, the left–right difference in blood pressure and orthostatic changes in blood pressure and heart rate should be checked during initial examination.

Height and body weight are measured, and the degree of systemic obesity is evaluated by calculating the body mass index (BMI) [body weight (kg)/{height (m)}^{2}]. Furthermore, waist circumference is measured (in the standing position at the umbilical level) and the degree of abdominal obesity is evaluated.

Also, the presence or absence of findings suggesting secondary hypertension, heart failure, atherosclerosis and cerebrovascular or cardiovascular disease is examined. The skin is examined for abdominal striae and hirsutism (Cushing's syndrome); the face and neck region is examined for anemia/jaundice, thyroid goiter, carotid artery murmurs, jugular vein dilation and ophthalmoscopic findings; as for the chest, palpation of the apical beat and thrill (strongest point and palpation area) and auscultation for heart murmurs, gallop rhythms, arrhythmias and rales in the lung fields are performed.

The abdominal region is examined for vascular murmurs and directions of their projection, liver enlargement and tenderness and kidney enlargement (polycystic kidney); the limbs are examined by palpation (disappearance, weakening and lateral difference) of arterial pulse (radial, dorsalis pedis, posterior tibial and femoral arteries), cold sensation, ischemic ulcer, edema, motor disturbances, sensory disturbances, increased tendon reflex, and so on.

c. Laboratory examinations (Table 2-11)

Laboratory examinations for the overall assessment of cardiovascular risk in individual patients and for diagnosis of secondary hypertension are performed by considering cost-effectiveness.

Table 2-11 Clinical examination

1.	General examinations (essential on initial consultation, at least once a year during antihypertensive treatment):	
	Hematology	Blood cell counts, hemoglobin, hematocrit, urea nitrogen (BUN), creatinine, uric acid, Na, K, Cl, fasting plasma glucose, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, GOT, GPT, γGTP, eGFR (ml per min per 1.73 m^2)=$194\times Cr^{-1.094}\times age^{-0.287}$ (female: $\times 0.739$)
	Urinalysis	Proteinuria (−, +, ++, +++), hematuria, cast
	Chest X-ray	Cardiothoracic ratio
	Electrocardiography	Left ventricular hypertrophy, ST-T change, arrhythmia such as atrial fibrillation
	Home blood pressure measurement (every day if possible)	
2.	Recommended specific examinations (if necessary on initial consultation/during antihypertensive treatment):	
	Evaluation of hypertensive target organ damage	
	Funduscopy (essential in the presence of diabetes)	
	Brain	Cognitive function test, depression assessment, brain MRI (T1, T2, T2*, FLAIR), MR angiography
	Kidney	Urinary albumin excretion [urinary albumin level (mg g^{-1} creatinine correction)]
	Heart	Echocardiography
	Blood vessels	Carotid ultrasonography, ankle-brachial pressure index (ABI), pulse wave velocity (PWV), augmentation index (AI)
	Glucose metabolism	Hemoglobin A_{1c}, 75 g oral glucose tolerance test (if the fasting plasma glucose >100 mg per 100 ml)
	Inflammation	High-sensitive CRP
	Measurement of 24-h ambulatory and nocturnal home blood pressures	
	Secondary hypertension screening, plasma renin activity, blood aldosterone, cortisol, 3 fractions of catecholamine (blood collection at rest early in the morning), casual urinary metanephrine fraction (Cr), catecholamines in 24-h urine, nighttime percutaneous oxygen partial pressure monitoring, abdominal ultrasonography (kidney, adrenal gland)	
3.	Specific examinations by specialists:	
	Diagnosis of secondary hypertension	Adrenal gland CT (including contrast-enhanced CT), renal ultrasonography (including the evaluation of the renal blood flow by the Doppler technique), renal scintigraphy, adrenocortical scintigraphy, iodine 131-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, adrenal venous sampling and polysomnography

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Examinations that are not covered by health insurance under a diagnosis of hypertension alone are included.

General laboratory examinations. General examinations that should be performed during the initial examination of hypertensive patients and at least once a year during antihypertensive treatment are general urinalysis, blood cell tests, blood chemistry tests concerning blood urea nitrogen (BUN), creatinine (Cr), uric acid, sodium (Na), potassium (K), chlorine (Cl), fasting triglyceride level, HDL-cholesterol, total cholesterol, LDL-cholesterol, glucose, total bilirubin, glutamic oxalacetate transaminase (GOT), glutamic pyruvic transaminase (GPT), and gamma-glutamyl transpeptidase (γGTP), chest X-rays (cardiothoracic ratio), and ECG (LVH, ST-T change and arrhythmias such as atrial fibrillation). In addition, the estimated glomerular filtration rate (eGFR) is calculated from the serum Cr level. Home blood pressure should also be monitored.

Evaluation of glucose tolerance and inflammatory risk factor. The Hb A_{1c} level should be examined when appropriate (not covered by insurance for hypertension alone in Japan), and, if the fasting plasma glucose level is >100 mg per 100 ml, a 75-g oral glucose tolerance test should be performed for the diagnosis of diabetes mellitus or impaired glucose tolerance.[144] Although the blood level of high-sensitive C-reactive protein (CRP) is lower in Japanese than in Western populations, it is related to the progression of carotid artery atherosclerosis and silent cerebral infarct[145–147] and is a risk factor for future stroke.[147]

Examinations for secondary hypertension screening. For the screening of patients suggested to have secondary hypertension on the basis of the results of history taking, physical examinations and general laboratory investigations, examination of the plasma renin activity and hormone levels, including aldosterone, cortisol, ACTH and three fractions of catecholamines in blood sampled after 30-min bed rest in the morning, examination of three fractions of metanephrine or three fractions of catecholamine in 24-h collected urine samples and abdominal ultrasonography are recommended. (See the section on endocrine hypertension in Chapter 12). Examinations such as nighttime pulse oxymetry may be performed for the diagnosis of sleep apnea syndrome.

Special examinations performed by experts for the definitive diagnosis of secondary hypertension include adrenal gland CT (including contrast-enhanced CT), renal ultrasonography (including the evaluation of the renal blood flow by the Doppler technique), renal scintigraphy, adrenocortical scintigraphy, iodine 131-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, adrenal venous sampling and polysomnography.

Evaluation of hypertensive target organ damage. It is now possible to diagnose target organ damage in hypertensive patients, estimate the future risk of cardiovascular disease even in asymptomatic patients by various examinations and use the findings for antihypertensive treatment (Table 2-12). Such an evaluation of target organ damage should be started at a stage of high-normal blood pressure in high-risk patients with diabetes mellitus, chronic kidney disease, and a history of cardiovascular events.

Brain and eyegrounds. Asymptomatic cerebrovascular disorders (silent cerebral infarcts, deep white matter lesions and cerebral microbleeds) are strong risk factors for stroke and dementia and are related to depression and falls in elderly people. MRI is much more effective than CT for the evaluation of these asymptomatic cerebrovascular disorders. The judgment of whether a lesion is subacute or is an old infarction is possible only using fluid-attenuated inversion recovery (FLAIR) images of MRI. The silent cerebral infarcts detected by MRI are the strongest specific predictors for stroke, and, according

to the results of follow-up studies in Japan, the relative risk of stroke in patients positive for this finding is 5–10 times higher than those without.[148,149] Deep white matter lesions that are negative on T_1-weighted imaging and positive on T_2^*-weighted imaging also increase the risk of stroke about 3–5 times.[150] In addition, cerebral microbleeds, which can be detected by T_2-weighted imaging of MRI alone, are a risk factor for future cerebral hemorrhage.[151] Magnetic resonance angiography is useful for the detection of stenotic lesions of the intracranial main cerebral and carotid arteries and cerebral aneurysms.

In elderly hypertensive patients, the evaluation of mild cognitive impairment[152] through cognitive function tests (the mini-mental state examination or Hasegawa dementia scale) and evaluation of depression on the basis of the Geriatric Depression Scale (GDS) and Beck Depression Inventory (BDI) are also useful for estimation of the risk of future occurrence of dementia and cardiovascular disease.

Papilledema, observed in hypertensive encephalopathy as one of the hypertensive emergencies, and eyeground bleeding, a finding of severe hypertension, can be confirmed by ophthalmoscopy. These severe eyeground findings are related to cardiovascular risk. In particular, ophthalmoscopy is essential when hypertension is complicated by diabetes mellitus. Also, sclerosis and narrowing of the eyeground arteries progress with the remodeling of resistance vessels (a possible cause of hypertension), precede the occurrence of hypertension and diabetes mellitus, are related to asymptomatic cerebral infarction and increase the risk of future cardiovascular disease.[153]

Heart. LVH detected by ECG is related to the prognosis of stroke as well as heart disease, including heart failure. The Sokolow–Lyon voltage (Sokolow–Lyon-ECG-LVH: SV_1+RV_5 [RV_6] >35 mm; RV_5 [RV_6] >26 mm), the Cornel voltage (Cornel voltage-ECG-LVH: $RaV_L+SV_3>28$ mm in men; $RaV_L+SV_3>20$ mm in women) and the Cornel Product (Cornel voltage$\times$QRS width >2440 mm ms) are often used for the diagnosis of LVH. LVH accompanied by 'strain type' (ST) depression is observed in about 20% of patients with resistant hypertension, is often concurrent with ischemic heart disease and CKD as well as the 24-h systolic blood pressure or maximum corrected QT interval (QTc) duration, and increases the risk of cardiovascular disorders.[154] The QT duration is prolonged, and variation in the QT duration among leads (QT dispersion) increases with the progression of LVH; both are determinants of a poor cardiovascular prognosis. The Sokolow–Lyon voltage and the Cornel Product significantly decrease on antihypertensive treatment, and the degree of this decrease is related to the decrease in the risk of major cardiovascular diseases, including atrial fibrillation, heart failure and sudden cardiac death.[155] Therefore, intensive antihypertensive treatment aimed at the regression of ECG-LVH in addition to blood pressure control is effective for hypertensive patients showing ECG-LVH.

Atrial fibrillation may occur over the course of the progression of hypertensive heart disease, and non-valvular atrial fibrillation is a very strong risk factor for cerebral infarction, with a relative risk greater than five times. According to the results of a follow-up study of local residents, metabolic syndrome increases the risk of the new occurrence of atrial fibrillation three times.[156] Therefore, in hypertensive patients with metabolic syndrome, antihypertensive therapy must be conducted while paying attention to the appearance of new atrial fibrillation during examinations, in addition to the history of paroxysmal atrial fibrillation.

Echocardiography is superior to ECG for the quantitative evaluation of the cardiac load due to hypertension. It also facilitates evaluation of the cardiac function as well as calculation of left ventricular mass, and is useful for the diagnosis of hypertensive heart failure. The left ventricular mass index is the strongest determinant of stroke and cardiovascular disease, including heart failure. Furthermore, concentric hypertrophy accompanied by relative wall thickening (left ventricular wall thickness/lumen >0.42) in addition

Table 2-12 Examination parameters for hypertensive target organ damage

1. Brain	Cephalic MRI (T1, T2, T_2^*, FLAIR)	Silent cerebral infarcts, deep white matter lesions, cerebral microbleeds
	MR angiography[a]	Stenosis of the main cerebral/carotid arteries, cerebral aneurysms
	Cognitive function test	Mild dementia MMSE score $\leqslant$26 points, Hasegawa dementia scale score $\leqslant$25 points)
	Depression assessment test	(Mild) depression (GDS score $\geqslant$10 points; BDI $\geqslant$10 points)
2. Heart	Electrocardiography	Left ventricular hypertrophy (Sokolow–Lyon voltage, Cornel voltage criteria, Cornel product, strain type), prolongation of the QT duration, increases in QT dispersion, abnormal Q waves, atrial fibrillation
	Echocardiography	Left ventricular mass index, left ventricular relative wall thickness, left ventricular ejection fraction, left ventricular diastolic function, atrial dimension
	Coronary MDCT[a]	Evaluation of calcified lesions, coronary stenosis, and plaque
	Cardiac MRI[a]	Left ventricular hypertrophy, left atrial hypertrophy
3. Kidney	eGFR (ml per min per 1.73 m^2) Proteinuria	
	Urinary excretion of albumin [urinary albumin level ($mg\,g^{-1}$ creatinine correction)][b]	Microalbuminuria (spot urine) $>30\,mg\,g^{-1}$ creatinine
4. Blood vessels	Carotid ultrasonography	IMT, max IMT (abnormal: >1.0 mm), plaque, stenoses
	ABI	Peripheral arterial disease (ABI <0.9)
	PWV	Carotid/femoral artery (cf)-PWV, brachial/ankle (ba)-PWV
	AI[a]	Carotid artery AI, tibial artery AI
	Endothelial function test[a]	Blood flow-dependent vasodilation
5. Autonomic nerves	Standing test	Orthostatic hypotension, orthostatic hypertension
	24-h ABPM	Nocturnal blood-pressure-fall attenuation (non-dipper type), nocturnal blood-pressure increase (riser type)

Abbreviations: ABI, ankle-brachial pressure index; ABPM, ambulatory blood pressure monitoring; AI, augmentation index; BDI, Beck Depression Inventory; eGFR, estimated glomerular filtration rate; GDS, Geriatric Depression Scale; IMT, intima–media thickness; MMSE, mini-mental score examination; PWV, pulse wave velocity.
[a]Special test.
[b]The urinary excretion of albumin is not covered by health insurance under a diagnosis of hypertension alone in Japan.

to an increase in the left ventricular mass index is a pattern of hypertensive left ventricular geometric remodeling with the poorest cardiovascular prognosis, and improvement in the left ventricular remodeling due to antihypertensive treatment improves the cardiovascular prognosis.[157] Diabetes mellitus as well as hypertension affects the left ventricular remodeling. An increase in the 24-h systolic blood pressure increases the left ventricular mass index, the presence of diabetes mellitus increases the relative wall thickness, and the frequency of concentric hypertrophy increases in diabetic hypertensive patients.[158] Regarding cardiac function, diastolic function decreases before reductions in the values of parameters of the left ventricular systolic function, such as the ejection fraction. This decrease in the left ventricular diastolic function may precede the progression of LVH and cause heart failure with an intact left ventricular systolic function, which is observed in more than 50% of elderly patients with heart failure. In addition, the left atrium dilates with a decrease in the left ventricular diastolic function, and left atrial dilation is a risk factor for future atrial fibrillation.

The blood level of brain natriuretic peptide (BNP),[159] which was isolated and identified in Japan, increases markedly in patients with symptomatic heart failure due to left ventricular systolic and diastolic dysfunction, and it has been widely used clinically for the diagnosis of this condition and evaluation of therapeutic effects. Clinically, it is useful for the screening of hypertensive patients with dyspnea for heart failure.

Multidetector-row CT (MDCT) is useful for the noninvasive screening of hypertensive patients with chest pain for coronary artery diseases.

Kidney. In Japan, CKD has also been shown to be a risk factor for cardiovascular disease.[11,160] CKD is defined as kidney damage or estimated glomerular filtration rate (eGFR) <60 ml per min per 1.73 m^2 for $\geqslant 3$ months.[161] A formula prepared for the calculation of the eGFR in Japanese is as follows:[162] eGFR (ml per min per 1.73 m^2)$=194\times Cr^{-1.094}\times age^{-0.287}(\times 0.739$, if female).

A diagnosis of microalbuminuria is made when the urinary albumin excretion in spot urine is 30–300 mg g^{-1} Cr or that in 24-h urine is 30–300 mg day^{-1}. However, there is no threshold of cardiovascular risk even in the normal range (<30 mg g^{-1} Cr), and the risks for cardiovascular death and total death decrease with decreased levels of urinary albumin excretion. Microalbuminuria appears under the influence of many risk factors, including those related to metabolic syndrome and inflammation as well as hypertension, and it is related to the future occurrence of hypertension and, in particular, increases in nighttime blood pressure even in normotensive individuals.[163]

The disappearance of microalbuminuria during the course of antihypertensive treatment is related to a decrease in the risk of cardiovascular disease independently of a reduction in blood pressure.[164] Therefore, decreased levels of urinary albumin excretion and the disappearance of microalbuminuria are factors for the evaluation of the effectiveness of antihypertensive treatment in high-risk hypertensive patients showing microalbuminuria.

Blood vessels. For more appropriate prevention and treatment of cardiovascular disease, it is important to evaluate the functional and structural changes in the arterial system noninvasively in the asymptomatic stage.

Carotid ultrasonography facilitates evaluation of the degree of atherosclerosis on the basis of the intima–media thickness (IMT), plaques and stenoses. These vascular echo indices are affected by hypertension and risk factors related to metabolic syndrome and are predictive of the future risk of cerebral and myocardial infarction. In addition, as their values improve through the treatment of hypertension, diabetes, hyperlipidemia, and so on, they are useful as indices for the evaluation of therapeutic effects.

Regarding the IMT, the measurement site and method for the calculation of the mean vary, but the max IMT, which includes the plaque thickness, can be determined with high reproducibility, and the Japanese Academy of Neurosonography recommends the max IMT (IMT-C_{max}) in the distal wall of the common carotid artery as an index of atherosclerosis.[165] The IMT increases when hypertension, diabetes and dyslipidemia are present. The risks of cerebrovascular disorders and coronary artery disease increase linearly with increases in the IMT,[165] which is considered to be abnormal when it exceeds 1.0 mm. Elevated lesions with a height of $\geqslant 1.1$ mm are called plaques, and increases in the height and number of plaques are related to elevations in cardiovascular risk.[166] The risk of symptomatic cerebral infarction is particularly high if plaques show ulceration on the surface and low irregular internal echo levels. The quantitative evaluation of plaque properties has also been attempted.[167] Plaques and stenoses occur frequently at the origin of the internal carotid artery, and carotid artery stenosis $\geqslant 70\%$ may be regarded as as an indicator of carotid endarterectomy and carotid artery stent dilation.

The ankle-brachial pressure index (ABI) is the ratio of the systolic blood pressure between the lower and upper limbs. Its decrease suggests not only the presence of peripheral artery disease but also risk of the future occurrence of stroke and dementia.[168] An ABI of <0.9 is considered to be abnormal and to suggest the presence of peripheral artery disease.

The pulse wave velocity (PWV) is an index based on increases in the velocity of pulse wave transmission through blood vessels with increasing arterial stiffness. The PWV is affected most notably by age and hypertension, but it also increases in the presence of risk factors such as smoking, diabetes mellitus and dyslipidemia. The PWV is related to the risk of occurrence of cardiovascular diseases even after correction for the other risk factors. The PWV between the carotid and femoral arteries (cf-PWV) has been used world-wide and has been shown to be correlated with cardiovascular outcome. Recently, a device to automatically measure the PWV between the brachial and ankle arteries (ba-PWV) simultaneously with the ABI has been developed, and simpler and more reproducible measurement of the PWV has become possible.[169] The results of follow-up studies on the relationship between the ba-PWV and the occurrence of cardiovascular events have not been reported, but it is closely correlated with cardiovascular risk factors and the stage of hypertensive target organ damage, similar to the cf-PWV.[170,171] In addition, as it is a good predictor of the future occurrence of hypertension among patients with a high-normal blood pressure,[172] it may be an alternative to the cf-PWV as an index of arterial stiffness. Although the PWV is reduced by antihypertensive treatment, the decrease is partly due to functional changes caused by a decrease in blood pressure and does not necessarily reflect structural improvements in arterial stiffness.

The arterial pressure pulse wave is derived from ejection waves from the left ventricle and reflection waves from peripheral vessels, and the AI is considered to represent reflection waves. As the AI is affected not only by arterial stiffness of elastic vessels, which determines the time of arrival of reflection waves via the PWV, but also by arterioles, which reflect ejection waves, it is expected to be useful as an index of the function and structure of the entire arterial system. The AI is correlated with cardiovascular risk but is also affected by heart rate, height and cardiac function. Following the recent development of a device that allows not only easy measurement of the AI in the radial or

common carotid artery but also estimation of the central arterial pressure, the clinical significance of the AI is being investigated.[173]

The endothelial flow-dependent vascular dilation, an index of the vascular endothelial function, decreases under the influence of various cardiovascular risk factors and improves through exercise and drug therapies. In patients with coronary artery disease, impairment of the endothelial function has been reported to worsen prognosis. As many clinical studies have shown the usefulness of endothelial function tests, the establishment of a simple standard procedure for its measurement and reference values is awaited.

Autonomic nervous system. Autonomic nervous system disorders are causes of hypertension, promote the progression of hypertensive target organ damage and are involved in the induction of cardiovascular disease. Therefore, impairment of the autonomic nervous system itself may be regarded as a form of target organ damage.

Orthostatic blood pressure dysregulation, a disorder of the autonomic nervous system, is observed more frequently in elderly people and diabetic patients and is related to the progression of target organ damage and adverse long-term survival.[174,175] The head-up tilting test using a tilted table is necessary for the detailed evaluation of orthostatic hypotension, but the active standing test is a simple method that can be used in daily practice. In this test, the blood pressure measured 1–3 min after standing up is compared with that measured 1–2 times after a 5-min rest in a seated (or recumbent) position, and the change in blood pressure is evaluated. Many patients with orthostatic hypotension show abnormal diurnal changes in blood pressure,[176] classified as non-dippers with reduced nocturnal depression of blood pressure, or as risers with nocturnal elevation of blood pressure. Clinically, examination of blood pressure during the nighttime by ABPM is recommended for patients with orthostatic hypotension, particularly if they have target organ damage. Conversely, orthostatic hypertension or an increase in blood pressure on standing has also been reported to be related to large vessel disorders, target organ damage such as asymptomatic cerebral infarction, LVH and microalbuminuria, as well as morning hypertension.[175–177]

Non-dipper- and riser-type abnormalities of diurnal blood pressure changes are related to autonomic nervous system disorders.[176]

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Chapter 3. Principles of treatment

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POINT 3

1. **The objectives of treatment are to control hypertension and prevent the occurrence of cardiovascular diseases due to sustained high blood pressure, thereby reducing mortality. In patients who have already developed cardiovascular disease, treatment is aimed at preventing their progression or recurrence, reducing mortality and improving the quality of life (QOL).**
2. **Treatment is necessary for all patients with hypertension (blood pressure $\geqslant$140/90 mm Hg) and for those with a blood pressure of $\geqslant$130/80 mm Hg if they have diabetes, chronic kidney disease (CKD) or myocardial infarction. The recommended target for blood pressure control is $<$130/85 mm Hg in young and middle-aged people. It should be $<$130/80 mm Hg in those with diabetes mellitus, CKD or myocardial infarction and $<$140/90 mm Hg in elderly people and patients with cerebrovascular diseases.**
3. **Antihypertensive treatment consists of lifestyle modifications (step 1) and antihypertensive drug therapy (step 2). Lifestyle modifications include restriction of salt intake and, if the patient is obese, weight control and exercise, restriction of alcohol intake, promotion of fruit and vegetable consumption, restriction of intake of saturated fatty acids and total lipids, and cessation of smoking (see Chapter 4). To prevent hypertension, one has to modify his or her lifestyle. The time of initiating antihypertensive drug therapy should be determined according to the level of blood pressure and the presence or absence of risk factors for cardiovascular disease and organ damage.**
4. **In principle, antihypertensive drug therapy should be started with a low dose of a long-acting drug once a day. If the dose must be increased, twice-daily administration may be considered. Appropriate combinations of drugs (combination therapy) are recommended to prevent adverse effects and enhance antihypertensive effects. Combination therapy should be considered from the outset for grade II or more severe hypertension.**
5. **Home blood pressure measurement is useful not only for the diagnosis of white coat hypertension and masked hypertension, but also for evaluating the effectiveness of antihypertensive treatment. It is also important to maintain good patient concordance (adherence) (see Chapter 2). Patients with white coat hypertension should be followed up periodically (every 3–6 months) even without treatment.**
6. **The QOL of patients with hypertension is affected by physical and psychological problems due to hypertension itself, the effects of antihypertensive drug therapy (including adverse effects) and the doctor–patient relationship.**
7. **In addition to sufficient communication, information, and consideration of the QOL and adverse effects, reducing the amount and frequency of medication is effective in improving adherence and controlling blood pressure.**
8. **The attending physician must eventually determine treatment by comprehensively evaluating the results of epidemiological and clinical studies, the clinical background of the patient, the pharmacological actions and cost of antihypertensive drugs, and also the long-term cost-effectiveness of antihypertensive treatment.**

1) OBJECTIVES OF TREATMENT

The objectives of antihypertensive treatment are to prevent the occurrence of cardiovascular disease due to damage to the heart and blood vessels caused by sustained high blood pressure, and consequent functional impairment and death. In patients who have already developed cardiovascular disease, treatment is aimed at preventing progression or recurrence, reducing mortality and, thus, helping patients with hypertension to lead their lives as do healthy people.

The higher the risk of cardiovascular disease, the greater the effect of hypertension treatment.[178] The results of randomized case–control comparative studies provide the best scientific basis for evaluating the effects of antihypertensive treatment (lifestyle modifications and drug therapy). However, the effects of antihypertensive drug therapy are often underestimated in randomized case–control comparative studies, and the duration of such studies is only a few years, whereas hypertension is treated over a lifetime. Therefore, the significance of the results of randomized case–control comparative studies is limited.[60]

Evaluating the therapeutic effects on hypertension through clinical trials of a few years' duration is easy as the patients are likely to experience more bouts during the study. Therefore, many recent studies have been conducted using elderly and high-risk patients.

The results of large placebo-controlled randomized comparative studies conducted in foreign countries have established that antihypertensive drug therapy has many beneficial effects on patients with hypertension. Antihypertensive drug therapy clearly reduces the incidence and mortality rate of cardiovascular diseases.[179]

According to the analysis of the results of clinical studies conducted abroad, the relative risk of stroke decreases by 30–40% and that

of ischemic heart disease decreases by 15–20%, with a reduction of 10–20 mm Hg in the systolic blood pressure and 5–10 mm Hg in the diastolic blood pressure. In these studies, the decrease in absolute risk due to antihypertensive drug therapy was greater with increasing blood pressure level and age pre-treatment. Analysis of the results of studies of patients with systolic hypertension also showed that stroke and ischemic heart disease are reduced by 30% and over 20%, respectively, by a decrease of 10 mm Hg in the systolic blood pressure.[116]

As the incidence of stroke and ischemic heart disease in Japan differs from that in Western countries, the above results cannot be applied directly to the Japanese population. However, antihypertensive drug therapy is considered to be more effective in patients with high blood pressure and older patients regardless of ethnicity.

The relative risk is higher in young and middle-aged patients with hypertension than in normotensive individuals of the same age, but absolute risk is low compared with elderly patients. In addition, a decrease in the absolute risk due to treatment is lesser in younger than in elderly patients. Therefore, the necessity of long-term antihypertensive treatment in young and middle-aged hypertensive patients should be recognized.

As the incidence of stroke is several times higher than that of ischemic heart disease in Japan, unlike in Western countries, antihypertensive drug therapy is expected to be more effective in Japan. According to a meta-analysis of the preventive effect of antihypertensive drug therapy on the occurrence of cardiovascular disease, the decrease in risk due to treatment did not differ between men and women.[180]

2) PLANNING OF HYPERTENSION MANAGEMENT AT INITIAL EXAMINATION

If blood pressure is high at initial examination, it is usually measured several times on another day. In addition, the patient is instructed to measure home blood pressure to eliminate white coat hypertension, white coat phenomenon and masked hypertension, and the overall risk of the patient developing cardiovascular disease, including the presence or absence and severity of organ damage, is assessed.

Lifestyle modifications must be made by all patients particularly those in high-risk groups. Patients with metabolic syndrome (MetS) that has markedly increased recently and is considered an important risk factor for hypertension, diabetes mellitus, chronic kidney disease (CKD) and cardiovascular disease, strict and sustained lifestyle modifications should be practiced rigorously. The prevention and management of MetS and support for patients with MetS are core issues in the Specific Health Screening and Health Guidance initiated in April 2008, in Japan. In addition, if home blood pressure or ambulatory blood pressure monitoring (ABPM) (covered by health insurance since April 2008, in Japan) differs widely from clinic blood pressure, it is appropriate to determine a therapeutic strategy by attaching greater importance to home blood pressure or ABP than to clinic blood pressure. After evaluating the overall risk of cardiovascular disease, the evaluation, therapeutic strategy and target control levels of clinic and home blood pressures should be explained to the patient until the patient sufficiently understands them.

In low-risk patients with a blood pressure of 140–149/90–99 mm Hg (grade I hypertension) but no other risk factors, organ damage or cardiovascular disease, lifestyle is modified, and blood pressure is measured again after a certain period (within 3 months). Risk is stratified by blood pressure on repeat measurement, and therapeutic strategy is determined according to Figure 3-1. As many recent observational studies have shown, the risk of cardiovascular disease

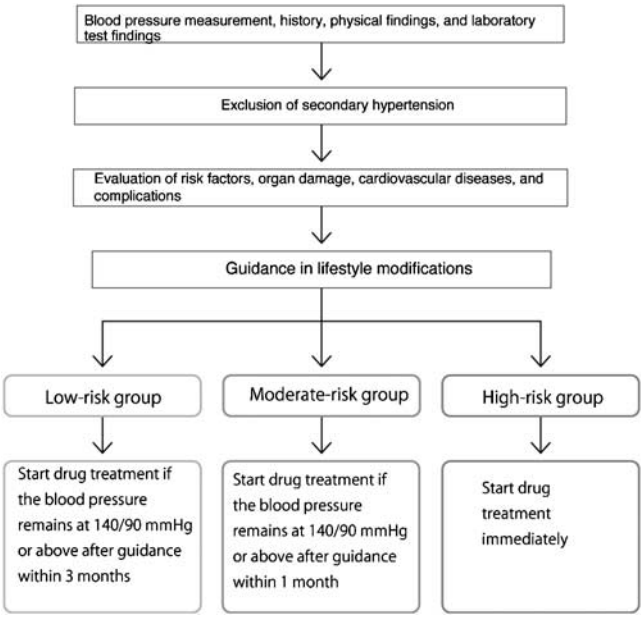

Figure 3-1 Planning of hypertension management at the initial examination. High-risk patients with high-normal blood pressure should be treated first by lifestyle modification. If their blood pressure does not reach the target level, then drug therapy should be considered.

increases in normal blood pressure ($<$130/85 mm Hg)[8,9,109] as well as in high-normal blood pressure (130–139/85–90 mm Hg)[17,121–123] compared with optimal blood pressure ($<$120/80 mm Hg); therefore, the threshold systolic blood pressure for the initiation of antihypertensive drug therapy has been lowered. As a result, even in low-risk patients, if blood pressure is not reduced to $<$140/90 mm Hg through lifestyle modifications alone, antihypertensive drug therapy is started after a certain period (within 3 months). In contrast, even when blood pressure at initial examination is classed as grade I hypertension, a therapeutic strategy matched to the risk should be established and executed according to Figure 3-1 if the risk is judged to be moderate or high, depending on the number of risk factors and organ damage, including diabetes mellitus and CKD or established cardiovascular disease.

If blood pressure at initial examination is 160–179/100–109 mm Hg (grade II), having excluded white coat hypertension or white coat phenomenon by measuring home blood pressure, and if the overall risk is judged to be moderate by risk assessment, antihypertensive drug therapy should be initiated after a period of lifestyle modification (within 1 month). Antihypertensive drug therapy should be initiated immediately if the risk is judged to be high even in patients showing grade II hypertension at initial examination (Figure 3-1). If blood pressure is $\geqslant$180/110 mm Hg (grade III) at initial examination, the risk is judged to be high and antihypertensive drug therapy must be initiated immediately (within a few days).

Patients with organ damage or other diseases such as diabetes mellitus, CKD, cerebrovascular disorders and heart disease are judged to be high-risk even if their blood pressure is $<$140/90 mm Hg (Table 2-8). Strict, immediate and adequate antihypertensive drug therapy should be considered if blood pressure does not reach target level despite lifestyle modifications (see Chapters 4, 5, 6 and 7).

Based on the results of large-scale clinical studies, there is no evidence supporting the effectiveness of antihypertensive drug therapy in patients with MetS with a high-normal blood pressure (130–139/

85–89 mm Hg), a fasting blood glucose level of 110–125 mg per 100 ml (not diabetic) and no organ damage. Therefore, the 2007 ESH/ESC Guidelines judged the risk of such patients with MetS to be high, the second rank after ultra-high, but suggested no more than strict lifestyle modifications for their treatment, commenting that aggressive drug therapy cannot be recommended at that stage.[66] The present Guidelines also recommend strict lifestyle modifications as an initial treatment for such patients with MetS (see Chapter 7).

3) PATIENTS TO BE TREATED AND TARGET BLOOD PRESSURE

a. Patients to be treated

Age. Hypertension should be treated in patients of all ages. However, the results of observational studies in elderly people performed in Western countries suggest that hypertension may not be a risk factor for cardiovascular disease in people aged ⩾80 years.[178,181] However, the HYVET,[182] performed recently in people aged ⩾80 years, showed that antihypertensive drug therapy reduces mortality due to stroke and total mortality (see Chapter 8).

Blood pressure levels. The results of a meta-analysis of 61 studies prospectively evaluating the relationship between blood pressure and death from cardiovascular disease[9] indicated that cardiovascular mortality increases when blood pressure is ⩾115/75 mm Hg. Long-term observation in the Framingham Study[122] showed that the risk of cardiovascular disease doubles in people with a high-normal blood pressure compared with those with an optimal blood pressure. Therefore, the JNC7[38] recommended lifestyle modifications for patients with prehypertension (120–139/80–89 mm Hg) and antihypertensive drug therapy in combination with lifestyle modifications for those with hypertension (⩾140/⩾90 mm Hg).

As for the epidemiological studies in Japan, death from cardiovascular disease increased significantly in the Tanno/Sobetsu Study[183] in Hokkaido, and the incidence of stroke increased significantly in the Hisayama Study[8] in Fukuoka, when blood pressure was ⩾140/90 mm Hg. In these Guidelines, a blood pressure of ⩾140/90 mm Hg is defined as hypertension, similar to the JSH2004 Guidelines.[65] Therefore, patients, including the elderly, with a blood pressure ⩾140/90 mm Hg, should be treated.

If hypertension is complicated by diabetes mellitus, CKD or myocardial infarction, a blood pressure of ⩾130/80 mm Hg is considered to require treatment. Lifestyle should be modified in patients with a high-normal blood pressure and those with a normal blood pressure and diabetes mellitus, CKD, MetS, multiple risk factors, organ damage or cardiovascular disease. In addition, antihypertensive drug therapy is indicated for all types of hypertension and high-normal blood pressure if it is concurrent with diabetes mellitus, CKD or myocardial infarction.

b. Target levels of blood pressure control

In the JSH2004 Guidelines, the target level of blood pressure control was <130/85 mm Hg in young and middle-aged individuals, <130/80 mm Hg in those with diabetes or kidney disease and <140/90 mm Hg in elderly people. The results of the HOT[139] and recent FEVER[184] studies suggest that <140/90 mm Hg should be a general target. The 2007 ESH/ESC Guidelines[66] set <130/80 mm Hg as a target, because studies including the *post hoc* study[185] of the PROGRESS,[135] EUROPA,[186] ACTION[187] and CAMELOT[188] suggested that a strict control of the blood pressure leads to a decrease in cardiovascular events, not only in patients with diabetes or kidney disease but also in those with cerebrovascular or coronary artery disease. These Guidelines set a target of blood pressure control of <130/85 mm Hg for young and middle-aged people and <130/80 mm Hg for those with diabetes mellitus, CKD or myocardial infarction. In elderly people, the eventual target of control is <140/90 mm Hg. However, as many elderly people aged ⩾75 years have organ damage, antihypertensive drug therapy may cause ischemia of important organs. Therefore, it is important to conduct antihypertensive therapy by paying careful attention to changes in symptoms and laboratory test results (Table 3-1).

Table 3-1 Target levels of blood pressure control

Young and middle-aged patients	<130/85 mm Hg
Elderly patients	<140/90 mm Hg
Diabetic patients	<130/80 mm Hg
Patients with kidney diseases	
Patients after myocardial infarction	
Patients with cerebrovascular diseases	<140/90 mm Hg

4) SELECTION OF TREATMENTS

Genetic and environmental factors are intricately involved in the occurrence and progression of essential hypertension. Therefore, treatment for hypertension cannot be considered without the correction of lifestyle-related problems (non-drug therapy), many of which are environmental factors. However, as mentioned in treatment I of Chapter 4, few patients achieve the target of blood pressure control through lifestyle modifications alone, and drug therapy is necessary in most cases. For each patient with hypertension, 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 disease and cardiovascular complications (Figure 3-1).

Patients with hypertension can be classified using the risk profile into low-, moderate- and high-risk groups, but antihypertensive drug therapy is indicated even in patients with high-normal blood pressure if they have diabetes mellitus, cardiovascular disease or CKD.

a. Lifestyle modifications

Hypertension is a lifestyle-related disease, and it has been shown to be not only prevented but also managed by lifestyle modifications.[189–191] A high-normal or high blood pressure is an indication for lifestyle modifications in all patients. If hypertension is concurrent with risk factors for cardiovascular disease, such as dyslipidemia and diabetes mellitus, lifestyle modifications are of particular importance as they can reduce these risk factors at minimal cost and effort.

Although many patients fail to achieve the target of blood pressure control through lifestyle modifications alone, they can at least reduce the types and doses of the necessary antihypertensive drugs.[192,193] Lifestyle modifications must be maintained even after the initiation of antihypertensive drug therapy. They include restriction of salt intake, increased fruit and vegetable consumption, restriction of cholesterol and intake of saturated fatty acids, maintenance of an appropriate body weight, restriction of alcohol intake, exercise and cessation of smoking. Lifestyle modifications should be kept in mind for the prevention of hypertension in the future.

b. Time to start antihypertensive drug therapy

In low- or moderate-risk patients with hypertension, antihypertensive drug therapy is started if the blood pressure cannot be reduced to <140/90 mm Hg within a given period of time through lifestyle modifications alone. In high-risk patients, that is patients with hypertension complicated by diabetes mellitus, cardiovascular disease or CKD, antihypertensive drug therapy should be initiated simulta-

neously with lifestyle modifications. Emergencies related to hypertension require the immediate initiation of drug therapy, but such patients should be referred to hypertension specialists. Elderly patients should also be treated with drugs if their blood pressure is ⩾140/90 mm Hg, but the blood pressure level at which drug therapy should be commenced is unclear in those aged ⩾80 years (see Chapter 8).

c. Antihypertensive drug therapy

Many Japanese patients with hypertension require drug therapy. The major antihypertensive drugs used in Japan include calcium (Ca) antagonists (dihydropyridines and diltiazem), renin–angiotensin (RA) system inhibitors such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), diuretics (thiazide and thiazide-like diuretics, K-sparing diuretics and loop diuretics), β-blockers (including αβ-blockers), α-blockers and drugs with central nervous system actions (methyldopa, clonidine and so on). Antihypertensive drugs with different mechanisms of action also have characteristic adverse effects. From the point of view of the evidence-based selection of drugs, the usefulness of diuretics, Ca antagonists, ACE inhibitors and ARBs has been established by many reports. Recently, the results of large-scale clinical trials indicating the usefulness of ARBs and Ca antagonists have been reported in Japanese patients with hypertension.[194,195] β-blockers have also been shown to be useful, but their inhibitory effects on stroke are reported to be weaker than those of other antihypertensive drugs.[196,197]

According to the results of randomized intervention studies comparing antihypertensive drugs and the meta-analyses of these reports, some drugs are suggested to be more effective for the prevention of certain cardiovascular diseases. Generally, however, the prevention of cardiovascular disease by antihypertensive drugs is ascribed primarily to a decrease in blood pressure rather than to the effects of particular drugs. Although recent large-scale clinical intervention studies in high-risk patients with hypertension[198,199] suggested the importance of an early reduction (1–3 months) in blood pressure, they also suggested the danger of sudden changes in the treatment regimen.

Whatever the antihypertensive drugs chosen, there are principles for their use. (1) Select a drug that is effective by once-a-day administration, in principle. (2) Start drug therapy at a low dose. In particular, commence administration of a thiazide diuretic using half or quarter of the tablet, as the initial dose mentioned for the Japanese drugs is too high. (3) Combination therapy should be considered from the outset for grade II or more severe hypertension (⩾160/100 mm Hg), and drugs should be combined appropriately to prevent adverse effects and enhance the depressor effect (see Chapter 5). (4) If the first drug shows only a weak depressor effect or is poorly tolerated, replace with a drug showing a different action mechanism. (5) If hypertension is complicated by other diseases, select antihypertensive drugs by paying due attention to indications and contraindications. Also, make sure to verify the interactions of antihypertensive drugs with drugs administered for the treatment of other diseases.

Figure 3-1 shows a flow chart of antihypertensive treatment in adults. This is no more than a principle for daily clinical practice; more appropriate treatments should be designed for individual patients depending on condition. Home blood pressure measurement is useful for the diagnosis of white coat hypertention[62] and masked (reverse white coat)[200] hypertension and for the evaluation of the effectiveness of antihypertensive treatments. In patients with white coat hypertension, a decision on whether it should be treated must be made by considering the risk factors and the presence or absence of target organ damage. Even if drug therapy is not performed, patients must be followed up carefully every 3–6 months. In patients with masked hypertension, its cause must be examined, and the presence or absence of organ damage must be evaluated.

5) OTHER POINTS REQUIRING ATTENTION

a. Initial treatment

The objective of initial treatment is to select antihypertensive drugs effective for reducing blood pressure to the target level and adjust their doses. Therefore, antihypertensive drugs may have to be changed or used in combination, or their doses may have to be increased, until blood pressure decreases to the target level. Generally, antihypertensive drug therapy for grade I hypertension should be started using a single drug at the minimum dose, and if the reduction in blood pressure is insufficient, the dose should be increased or the drug replaced for, or combined with, another drug with a different mechanism of action. For the treatment of grade II–III or high-risk hypertension, combination therapy should be considered from the outset. For combination therapy, the combination of a RA system inhibitor with a diuretic or Ca antagonist or that of a Ca antagonist (dihydropyridines) and a β-blocker are recommended. The combination of a diuretic and a β-blocker should be avoided in patients with obesity or MetS, because new onset of diabetes mellitus is observed more frequently than with other combinations of antihypertensive drugs.[201]

b. Long-term treatment (continuous treatment)

The objective of long-term treatment is to prevent cardiovascular disease by maintaining a target blood pressure level over a long period and comprehensively managing risk factors other than blood pressure.

As patients with hypertension generally have no marked symptoms or signs, and as 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 ensure patients continue coming to the hospital, observe lifestyle modifications and take drugs as instructed. For the satisfactory continuation of treatment, it is important for physicians to maintain a good doctor–patient relationship by continuing close communication with patients and sufficiently explaining hypertension as a disease, the treatment methods, the results expected from treatments and the expected adverse effects of antihypertensive drugs. As patients may misunderstand a reduction of their blood pressure due to antihypertensive drugs to mean their hypertension has been cured and so quit treatment,[202] sufficient explanation is necessary. The sufficiency of communication with the physician and the degree of patient satisfaction with the medical staff markedly affect the patient's QOL.[203] Patient-involved treatment that is formulated by considering the patient's QOL and does not interfere with the patient's daily living or social activities is desirable.

c. Attention to the QOL

Although impairment of the QOL is milder in patients with hypertension than in those with other serious diseases, QOL has been shown to be impaired by being conscious of hypertension.[204,205] Problems with emotional state and responses, sleep, heart and digestive functions, and sense of satisfaction appear with increases in blood pressure.[206] Age also markedly affects the QOL. The degree of impairment of the QOL increases and individual differences widen as age advances.[207] As QOL is evaluated on the basis of a wide range of aspects, including physical symptoms, psychological state, degrees of mental and physical satisfaction, sense of well-being, work, hobbies, social activities, home

and sex life, these items should be assessed as objectively and comprehensively as possible.[208]

Although sufficient attention must be given to impairment of the QOL due to the adverse effects of antihypertensive drugs, QOL has been reported to improve with treatment of hypertension.[209,210] As treatment for hypertension continues over a long period, consideration not to reduce the QOL of patients with hypertension is important to ensure the continuation of treatment.

d. Concordance/adherence

Concordance means the participation of a patient with sufficient knowledge in the management of his or her disease and the implementation of treatment agreed between the physician and patient.[211] As hypertension is often asymptomatic, adherence (continuation of treatment) is poor, it tends to be left untreated and drug therapy is often discontinued. However, treatment with emphasis on concordance is considered to improve adherence and to lead to the prevention of cardiovascular disease.

According to a questionnaire survey of Japanese patients with hypertension, less than 50% of patients answered that the objective of the antihypertensive treatment was the prevention of cardiovascular disease, which suggests that the objective is not sufficiently understood.[212] In addition, in a questionnaire survey of patients who dropped out from antihypertensive drug therapy, many patients thought that hypertension had been cured when their blood pressure decreased,[202] suggesting a poor understanding of the importance of adherence to antihypertensive treatment. Another questionnaire survey showed that both physicians and patients considered the willingness to listen to patients to be the most important aspect of an ideal physician, but both physicians and patients were aware that the amount of consultation time is insufficient to facilitate this.[212] Providing sufficient information to patients has been shown to improve adherence and the state of blood pressure control.[213,214] Also, as the adverse effects of antihypertensive medication reduce adherence, sufficient attention should be paid to such effects.

According to another questionnaire survey in Japan, few patients were eager to be actively involved in the determination of therapeutic strategy or selection of drugs, but many were interested in the adverse effects and were reluctant to consent to changes in drugs or increases in the dose because of anxiety over these effects.[215] Furthermore, adherence tended to deteriorate with increases in the number of tablets to be taken.[215] A reduction in the number of tablets to be taken, the daily frequency of taking drugs[216] and the use of fixed combinations of two drugs[217] have been reported to be useful in improving adherence. Table 3-2 summarizes the methods for treatment, in which the physician and the patient share an understanding as partners.

e. Cost-effectiveness of antihypertensive treatment

Treatment for hypertension is a major problem when considering its proportion of the total medical expenditure, and pharmacoeconomic analyses have been carried out to evaluate its effects and cost on the basis of the results of various clinical studies.[218,219]

The effectiveness of antihypertensive treatment is evaluated according to indices including the degree of decrease in blood pressure and preventive effect on the occurrence of cardiovascular disease. In addition to the new onset of diabetes mellitus and metabolic changes such as hyperuricemia, negative effects such as reduction in the QOL are also included.

Cheaper generic formulations are available in some branded hypertensive products. The cost of treatment for hypertension includes the cost of antihypertensive drugs, the cost of treatment for cardiovascular disease due to hypertension and new-onset metabolic disorders. The effects of new-onset metabolic disorders on cardiovascular disease may not be clarified by the results of large-scale clinical trials alone, which are performed over a period of about 5 years;[220] therefore, evaluations using simulation models are being performed for the comprehensive assessment of the cost-effectiveness of long-term treatment for hypertension. Results of these evaluations suggest that antihypertensive drug treatment is more cost-effective than no treatment,[221] and that treatment primarily using diuretics at a standard dose is not necessarily cost-effective in long-term treatment.[222,223]

Table 3-2 How to conduct treatment for the physician and patient as partners by reaching a shared understanding

- Talking with the patient about the risk of hypertension and the effects of treatment
- Clearly explaining the treatment plans orally and in writing
- Tailoring the treatment plans to the patient's lifestyle
- Providing information about hypertension and the treatment plans to the patient's partner and family
- Using methods based on behavioral theories such as measuring the blood pressure at home and devising measures to remember to take drugs
- Paying attention to adverse effects and changing the dose or the drug if necessary
- Simplifying the regimen by reducing the number of tablets to be taken and the number of times of taking drugs daily, using fixed combinations and so on
- Talking with the patient about adherence and his/her problems
- Providing a system to support the patient to continue to take drugs, visit the hospital and modify the lifestyle
- Explaining the lifetime costs and effects of treatments

(Cited with partial modification from the ESH-ESC 2007[85])

Citation Information

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GUIDELINES (JSH 2009)

Chapter 4. Lifestyle modifications

Hypertension Research (2009) **32,** 29–32; doi:10.1038/hr.2008.4

POINT 4

1. ***Salt restriction*: The target of salt restriction is $<6\,g\,day^{-1}$, but an even lower salt intake is better. Salt intake can be safely restricted to $3.8\,g\,day^{-1}$. At general medical facilities, it is practical to evaluate salt intake using spot urine samples (with correction for creatinine). As salt content in many processed foods is indicated in terms of the sodium (Na) content, Na content should be converted to salt content by the equation (Na content [g]$\times$2.5=salt content [g]) for salt restriction guidance.**
2. ***Nutrients other than salt*: The intake of fruit and vegetables should be increased, and that of cholesterol and saturated fatty acids should be reduced. Fish (fish oil) intake should also be increased.**
3. ***Maintaining an appropriate body weight*: The target body mass index (BMI: body weight [kg]$\div${height [m]}^{2}) is $<25\,kg\,m^{-2}$, but a significant decrease in blood pressure can be achieved by reducing body weight by 4–5 kg. Waist circumference should also be maintained at an appropriate level.**
4. ***Exercise*: Exercise, primarily periodic (30 min or longer daily if possible) aerobic exercise, at a moderate intensity, should be practiced. This applies to hypertensive patients with no cardiovascular disorders. In high-risk patients, medical checks must be performed in advance and the necessary measures taken.**
5. ***Restriction of alcohol intake*: Alcohol intake should be restricted to $\leqslant$20–30 ml ethanol day^{-1} in men and $\leqslant$10–20 ml ethanol day^{-1} in women.**
6. ***Quitting smoking*: Smoking (including passive smoking) should be avoided as it is a strong risk factor for cardiovascular disease and has been suggested to affect blood pressure levels.**
7. ***Others*: Exposure to cold should be avoided. Emotional stress should be managed.**
8. **In combination lifestyle modifications are more effective in reducing blood pressure levels and preventing hypertension.**

Genetic and environmental factors are involved in the development of hypertension, and environmental factors are affected by lifestyle. Lifestyle modifications can lead to a mild decrease in blood pressure and so allow a reduction in the dose of antihypertensive drugs. All hypertensive patients should get education and guidance regarding lifestyle modifications to prevent the concurrence of cardiovascular disease and risk factors other than hypertension. Table 4-1 lists lifestyle modifications, and Figure 4-1 shows the reduction in blood pressure expected from the modification of each item.

1) SALT RESTRICTION

An excessive salt intake has been suggested to be related to high blood pressure by observational studies including the INTERSALT.[30] The hypotensive effect of salt restriction has also been shown by many large-scale intervention studies in Western countries,[224,225] such as the DASH-Sodium.[34] According to the results of these clinical studies, blood pressure was not significantly decreased without reducing salt intake to $6\,g\,day^{-1}$. On the basis of these results, Western guidelines recommend a salt intake of $<6\,g\,day^{-1}$. Similarly, these Guidelines also set a target restricting salt intake to $<6\,g\,day$.[224] The Working Group for Dietary Salt Reduction of The Japanese Society of Hypertension provides useful recipes as a reference to achieve a daily diet containing $6\,g\,day^{-1}$.[226]

According to the relationship between mean salt intake and blood pressure shown in the INTERSALT,[30] blood pressure decreased slightly with a salt intake of approximately $\geqslant 3\,g\,day^{-1}$, but sharply when the intake was $<3\,g\,day^{-1}$. It is reported that salt intake was originally $0.5–3\,g\,day^{-1}$ in precivilized humans, so a very low salt intake is likely to be appropriate. However, as intervention studies have confirmed that salt intake can be safely reduced to as little as $3.8\,g\,day^{-1}$,[34] the recommendations of the American Heart Association (AHA) in 2006[227,228] and the European Society of Hypertension-European Society of Cardiology (ESH-ESC) in 2007[66] are that optimal salt intake should be $3.8\,g\,day^{-1}$.

The target of restricting salt intake to $<6\,g\,day^{-1}$ is very strict in Japan, because mean salt intake still exceeds $10\,g\,day^{-1}$. Consequently, a greater effort is necessary in Japan to achieve this target than it is in Western countries, where salt intake is lower. Whereas salt intake varies widely among individual patients, it is $<6\,g\,day^{-1}$ in about 20% of patients who are making conscious efforts to reduce their salt intake,[229] and so it is important to propose a strict target of salt reduction. However, it is difficult for many patients to achieve this target. As the effectiveness of salt restriction is considered to depend on its strictness (meta-analysis indicated a decrease in systolic blood pressure of about 1 mmHg with a decrease in salt intake of $1\,g\,day^{-1}$ [225]), guidance should be given to gradually reduce salt intake over a long period. Recently, a follow-up study of the TOHP reported that salt restriction reduces the long-term risk of cardiovascular disease.[230]

Presently, the Na rather than salt content is required to be included in the nutritional information of processed foods, but dietary guidance is made in terms of salt content (g). Therefore, patients must be taught to convert the Na content (indicated in grams) into the salt content by multiplying it by 2.5. Salt sold as 'natural salt' is made up mostly of NaCl, with very low amounts of other minerals, and its alternative use has little benefit compared with the use of common salt. The components of some natural salts are indicated in terms of

Na content, which, therefore, must be multiplied by 2.5 to calculate salt (NaCl) content. The evaluation of salt intake is indispensable in salt restriction guidance, and using spot urine samples (Na/creatinine [Cr] ratio) is practical at general medical facilities (Table 4-2).[231] The reliability of findings should be improved using a calculation formula incorporating the estimated 24-h urinary Cr excretion based on age, height, and body weight.[231]

It is extremely difficult to practice a very strict and optimal salt restriction regimen in the present social environment, and public health activities are necessary to achieve low salt intake in patients. Also, as it is possible that salt restriction in childhood suppresses blood pressure elevations over a long term period,[232] education and guidance for children are also needed in order to establish healthy dietary habits.

Table 4-1 Items of lifestyle modifications

1. Salt restriction to $<6\,g\,day^{-1}$
2. Increased intake of fruits and vegetables*
   Reduced intake of cholesterol and saturated fatty acids
   Increased intake of fish (fish oil)
3. Maintaining an appropriate body weight: BMI (body weight [kg] ÷ {height [m]}^{2}) $<25\,kg\,m^{-2}$
4. Exercise: In hypertensive patients with no cardiovascular disease, exercise, which is primarily a moderate aerobic exercise, should be performed periodically (for $\geqslant$30 min daily if possible)
5. Restriction of alcohol intake: $\leqslant$20–30 ml per day in men and $\leqslant$10–20 ml per day in women as ethanol
6. Quitting smoking

Abbreviation: BMI, body mass index.
Comprehensive lifestyle modifications are more effective.
*An increased intake of fruit and vegetables is not recommended for patients with severe renal dysfunction because of the risk of hyperkalemia. An excessive intake of fruit with a high fructose content is not recommended in patients who need to undergo a restricted energy intake, such as obese and diabetic patients.

2) FRUITS, VEGETABLES, FISH, CHOLESTEROL, SATURATED FATTY ACIDS, AND SO ON

The DASH clinical trial [34,189] employed a diet rich in fruit, vegetables, and low-fat dairy products (low in saturated fatty acids and

Table 4-2 Guidelines for evaluation of salt intake

Evaluation method	*Recommendability*	*Primary users*
Measurement of the Na content in 24-h pooled urine, or weighting or a questionnaire survey by a nutritionist	These methods are highly reliable and recommendable, but are complicated. Recommended if the cooperation of patients and ability of facilities are secured	Special facilities for hypertension treatment
Estimation as Na/Cr ratio based on measurement of the Na and Cr in spot urine samples[a]	Although the reliability is relatively low, the method is simple and is recommended as a practical evaluation procedure	Medical facilities in general
Estimation in early morning urine (nighttime urine) using an electronic salt sensor installed with calculation formula[b]	Although the reliability is low, the method is recommendable. It is convenient and can be performed by the patients themselves	Patients themselves

Abbreviation: Cr, creatinine.
[a]Early-morning urine (nighttime urine) may also be used; the reliability is increased by the use of the calculation formula incorporating the estimated 24-h Cr excretion:
24-h Na excretion (mEq day^{-1})={21.98×(Na$_s$/Cr$_s$)×Pr.UCr$_{24}$}$^{0.392}$.
Na$_s$: Na concentration in a spot urine sample (mEq l^{-1}).
Cr$_s$: Cr concentration in a spot urine sample (mg l^{-1}).
Pr.UCr$_{24}$: Estimated 24-h urinary Cr excretion (mg day^{-1}). Pr.UCr$_{24}$=
–2.04×age+14.89×body weight (kg)+16.14×height (cm)–2244.45.
In addition, Na content indicated in mEq day^{-1} is converted to the salt or Na content indicated in g day^{-1}.
Estimated salt intake (g day^{-1}) : estimated urinary Na (mEq day^{-1})×0.0585.
Estimated Na intake (g day^{-1}) : estimated urinary Na (mEq day^{-1})×0.023.
[b]Methods using a test paper or a simple salt sensor are convenient but unreliable, so that quantitative evaluation is difficult.
Source: Turnbull *et al.*[256]

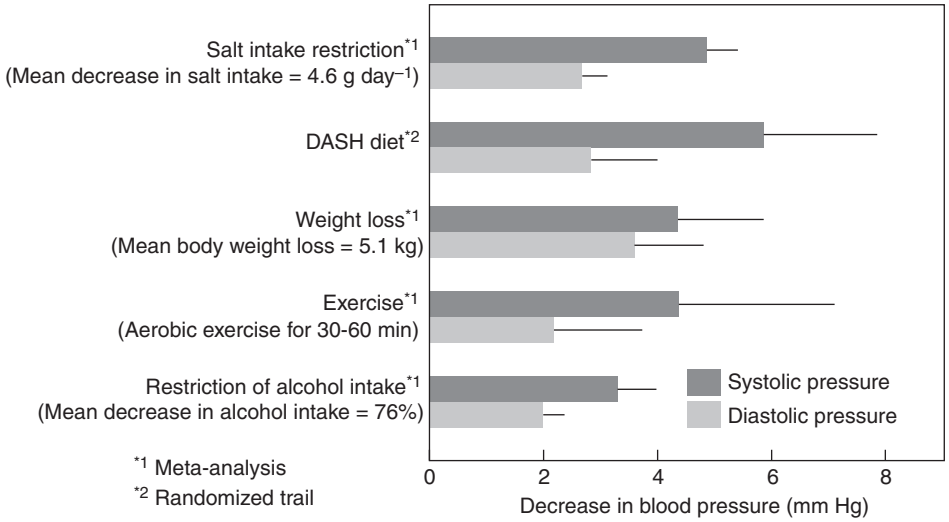

Figure 4-1 Decreases in blood pressure levels through lifestyle modifications. References: The results of He *et al.*[225] (salt intake restriction), Sacks *et al.*[34] (DASH diet), Neter *et al.*[239] (weight loss), Dickinson *et al.*[240] (exercise) and Xin *et al.*[247] (restriction of alcohol intake) were used. The results above were cited from papers in Western countries. Concerning the data from meta-analyses, the lifestyle modification is shown in parentheses. However, as the effects of lifestyle modifications are also affected by the lifestyle of patients before modification, their genetic background, and so on, this figure cannot be applied directly to the Japanese. Data concerning the DASH diet were cited from a original paper, because there was no meta-analysis. It is not guaranteed that a similar reduction in blood pressure is observed in Japanese hypertensive patients in the long-term, because the study was performed on a small number of subjects (n=412) and over a short period (30 days).

cholesterol and high in calcium [Ca], potassium [K], magnesium [Mg], and dietary fiber) in Western countries, and this diet was shown to have a significant hypotensive effect. Ca and Mg were expected to exhibit hypotensive effects because of the findings of epidemiological studies that blood pressure is low in people who drink hard water, but, in a small-scale intervention study blood pressure was only slightly decreased with Ca or Mg loading. Na is known to be added, and K to be lost, in food processing, and K deficiency as well as an excessive salt intake has been suggested to be a cause of hypertension in industrialized countries. In its reports on dietary therapy, the AHA has discussed K supplementation as a useful antihypertensive treatment,[228] but its effect is limited. However, as treatments with mild hypotensive effects may produce a sufficient effect if they are combined, an increased intake of fruit and vegetables in combination with a restriction of cholesterol and saturated fatty acids should be included in antihypertensive dietary therapy. Although there are few recommendable references of the DASH diet in Japan, the 'Japanese Food Guide Spinning Top' may be useful (although it was prepared for healthy people).[233] This guide counts foods according to the DASH diet plan, and recommends 5–6 servings (SVs) of vegetables and 2 SVs of fruit daily. This does not require complicated calculation and is useful for the approximate evaluation of food intake. However, an increased intake of fruit and vegetables is not recommended for patients with severe renal dysfunction because of the risk of hyperkalemia. Also, an excessive intake of fruit with a high fructose content is inadvisable for people who need to restrict their energy intake, such as obese and diabetic patients. A restriction of the intake of cholesterol and saturated fatty acids is also useful for the prevention of abnormalities of lipid metabolism. The DASH diet has been suggested to have a natriuretic and a metabolic risk factor-reducing effect.[234] As a recent epidemiological study reported that metabolic syndrome was less common in people with a high Mg intake, Mg may play an important role in the latter effect of the DASH diet.

According to the results of the INTERMAP study, blood pressure tends to be lower in people with a high intake of ω3 polyunsaturated fatty acids (rich in fish oil).[235] A meta-analysis of intervention studies showed that an increase in the intake of fish oil causes a decrease in blood pressure in hypertensive patients,[236] although a relatively high dose ($\geqslant 3\,g\,day^{-1}$) is necessary to achieve a significant hypotensive effect. The AHA[227] and ESH-ESC Guidelines[66] also recommend a high fish intake in hypertensive patients. Incidentally, the 'Japanese Food Guide Spinning Top'[233] recommends 2 SVs of fish daily. Moreover, a cohort study in Japan (JPHC Study)[237] reported a lower incidence of myocardial infarction in people with a higher fish intake. However, fish consumption involves the risk of mercury contamination,[227] although the degree varies among species. Tuna, yellowtail, and bonito, which have been reported to show high mercury levels, are not recommended for children, pregnant women, and women who may become pregnant.

Regarding the effects of an increased intake of antioxidant foods and dietary fiber or a decreased intake of carbohydrates on blood pressure, there is no evidence worth mentioning in these Guidelines.

3) MAINTAINING A PROPER BODY WEIGHT

As obesity is an important risk factor for hypertension, obese individuals should aim to reduce their BMI to $<25\,kg/m^2$, and non-obese individuals should maintain this level. Visceral obesity, in particular, induces not only hypertension but also abnormalities of glucose and lipid metabolism and is closely related to metabolic syndrome.[126] According to the Framingham Study,[238] blood pressure increases with the amount of visceral fat even in people with a similar BMI. Therefore, waist circumference should also be considered when practising weight control (<85 cm in men, <90 cm in women).[126]

The hypotensive effect of weight loss has been established, and blood pressure is significantly decreased by a weight loss of 4–5 kg.[239] Abnormalities of metabolic indices are also corrected by weight loss. In addition, weight loss has been reported to alleviate the enhancement of inflammatory reactions and abnormalities of vascular endothelial function, which are observed under conditions including metabolic syndrome. Obese hypertensive patients should first practice weight control, but should follow this with a stress-free, long-term weight-loss plan.

4) EXERCISE

The hypotensive effect of exercise has been established.[240] Aerobic exercise of a moderate intensity has been shown to reduce blood pressure, decrease body weight, body fat, and waist circumference, and improve insulin sensitivity and HDL-cholesterol level. Furthermore, a low physical activity level is an independent risk factor for cardiovascular death. Therefore, exercise is an important part of lifestyle modification for hypertensive patients.

Aerobic exercise such as walking (fast walking that mildly increases the heart rate) is suitable for the prevention and treatment of lifestyle-related diseases, including hypertension. This should be supplemented by mild resistance exercise, which is effective for increasing lean body mass and preventing osteoporosis and lower back pain, and stretching exercise, which improves the motion range and function of joints. There are also reports that the cardiovascular protective effect increases with the intensity of exercise, and the American College of Sports Medicine (ACSM)/AHA recommends mixing high- with moderate-intensity exercise for the general public.[241] In hypertensive patients, however, blood pressure increases during exercise if intensity is too high,[242] and high-intensity exercise has been reported to exacerbate the prognosis, unlike that in normotensive individuals.[243] Therefore, strenuous exercise is not recommended for hypertensive patients. Exercise should be performed periodically, that is, for $\geqslant 30$ min daily if possible, but this goal is considered to have been achieved if exercise of at least 10-min duration has been repeated to achieve a daily total of $\geqslant 30$ min.[241] 'The Exercise Guide 2006' (http://www.mhlw.go.jp/bunya/kenkou/undou01/pdf/data.pdf) classified physical activities into exercise and activities of daily living, and proposed an approach to increase the physical activity level primarily by increasing the latter. In patient education, also, it is considered more practical to advise patients to increase the physical activity level of their daily lives.

Candidates for exercise therapy are moderately or mildly hypertensive patients with no cardiovascular disease. In high-risk patients, a medical check must be performed in advance, and exercise should be restricted or advised against if necessary. As aerobic exercise has been reported to induce a decrease in blood pressure without complications even in elderly patients,[244] exercise should not be restricted owing to old age alone, but a prior medical check is necessary.

5) RESTRICTION OF ALCOHOL INTAKE

Alcohol consumption over a long period can lead to an increase in blood pressure.[245] Heavy drinking induces hypertension, and can also cause stroke and alcoholic cardiomyopathy as well as cancer, resulting in an increased mortality rate. On the other hand, moderate drinking has been reported to decrease mortality rate.[246] However, objections have been raised to the view that there is a U-shaped (or J-shaped) relationship between drinking and mortality rate;[66] further evaluation is therefore needed before a conclusion can

be reached regarding the protective cardiovascular effect of moderate drinking.

A bolus administration of alcohol causes a decrease in blood pressure that is sustained for several hours, but blood pressure increases thereafter. Therefore, a restriction of alcohol consumption reduces blood pressure.[247] It has been reported that about an 80% reduction in alcohol intake is followed by a decrease in blood pressure in 1–2 weeks. In heavy drinkers, blood pressure is increased after an abrupt restriction of drinking, but it can be reduced if the restriction is continued. Drinking, in terms of ethanol intake, should be restricted to 20–30 ml (equivalent to 180 ml of *sake*, 500 ml of beer, <90 ml of *shochu*, a double whisky or brandy, and 2 glasses of wine) day^{-1} in men and 10–20 ml day^{-1} in women.

6) SMOKING CESSATION

Smoking transiently increases the blood pressure. As the duration of high blood pressure after smoking a cigarette is reported to be $\geqslant 15$ min,[248] it may persist during the daytime in heavy smokers. In fact, there are reports that daytime ambulatory blood pressure is increased in smokers[249] and that smoking often causes masked hypertension.[250] However, mean BMI and blood pressure are generally lower in smokers than in non-smokers. Therefore, despite recent reports on the effect of smoking on the development of hypertension, the overall effect of smoking on blood pressure has not been established.[228] However, smoking is known to be a risk factor for renovascular hypertension.

Smoking is a strong risk factor for not only non-cardiovascular diseases including cancer but also ischemic heart disease and stroke. Moreover, smoking is reportedly related to metabolic syndrome.[251] Non-smokers are harmed through passive smoking as well as the smokers themselves. Not only hypertensive patients with cardiovascular risks but also healthy people should quit smoking. The World Health Organization (WHO) adopted a framework anti-smoking treaty, which Japan ratified in 2004. This prompted countries and various organizations to go forward in anti-smoking activities. The Japanese Society of Hypertension also announced its anti-smoking declaration in 2007 and is making efforts toward its implementation (http://www.jpnsh.org/news/tobaccocontrol.pdf). Smokers should be repeatedly advised and encouraged to quit smoking, and the use of drugs to assist quitting should also be considered if necessary.

7) OTHER LIFESTYLE MODIFICATIONS

It is well known that exposure to cold elevates the blood pressure, which, consequently, is increased during winter. The cardiovascular mortality rate during winter is greater as protective measures against the cold are inadequate.[252] Therefore, the homes of hypertensive patients should be adequately heated in winter, with particular attention to heating of the toilet, bathroom, and dressing room, which is often disregarded.

Reports on the relationship between emotional stress and blood pressure are contradictory, but a recent meta-analysis indicated the effectiveness of stress management.[246] Therefore, techniques such as biofeedback and relaxation may be worth attempting in some hypertensive patients.

When bathing, the water should not be too hot. Blood pressure has been reported to show little increase when bathroom temperature is $\geqslant 20\,^{\circ}$C and water temperature is $\leqslant 40\,^{\circ}$C. A water temperature of 38–42 $^{\circ}$C and a duration of 5–10 min are advisable when taking a bath. The water temperature of *sento* (Japanese bathhouses) is often too high. Hypertensive patients should avoid bathing in cold water and saunas.

As straining to defecate increases the blood pressure, guidance for the prevention of constipation should be given, and, if necessary, laxatives should be administered.

Sexual intercourse also raises the blood pressure, but hypertension poses few problems to the sex life. However, hypertensive patients with cardiovascular diseases should refrain from vigorous sexual activity.

8) COMPREHENSIVE LIFESTYLE MODIFICATIONS

The DASH[189] and DASH-Sodium[34] studies suggested that comprehensive improvements in diet facilitate a marked decrease in blood pressure. Also, the TONE[253] study showed that a combination of restricting salt intake and weight loss is more likely to reduce blood pressure and prevent cardiovascular diseases even when they are practiced less rigorously. A more marked decrease in blood pressure has been reported to be achieved by a combination of salt intake restriction, weight loss, exercise, restriction of alcohol intake, and a DASH diet.[254] Therefore, comprehensive lifestyle modifications are recommended.

Lifestyle modifications should be started in childhood to prevent lifestyle-related diseases, including hypertension.

9) FOOD FOR SPECIFIED HEALTH USES (FOSHU)

FOSHU are foods that are supplemented with components exhibiting physical-conditioning effects, have been demonstrated medically and nutritionally to have a health-protecting effect, and have been approved by the Ministry of Health, Labour, and Welfare. They are labeled with information including 'health-protecting effects' and 'functions of nutritional components'. The hypotensive effects of foods considered effective for blood pressure control are often based on an ACE-inhibiting activity, but the indicated 'recommended daily intake' should be strictly observed. Patients must also be informed that the intake of FOSHU cannot be a substitute for antihypertensive medication. A warning to consult a physician should be given to patients already on antihypertensive medication if they wish to use such foods. Information on FOSHU is available at the homepages of the National Institute of Health and Nutrition (http://hfnet.nih.go.jp/contents/sp_health_listA008.html) and the Ministry of Health, Labour and Welfare (http://www-bm.mhlw.go.jp/topics/bukyoku/iyaku/syoku-anzen/hokenkinou/hyouziseido.html).

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GUIDELINES (JSH 2009)

Chapter 5. Treatment with antihypertensive drugs

Hypertension Research (2009) **32,** 33–39; doi:10.1038/hr.2008.5

POINT 5A

1. **The preventive effects of antihypertensive drugs on cardiovascular disease are determined by the degree to which blood pressure decreases rather than its class.**
2. **The antihypertensive drug to be first administered alone or concomitantly with other drugs should be selected from Ca channel blockers, angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, diuretics and β-blockers.**
3. **Appropriate antihypertensive drugs should be selected considering positive indications, contraindications, conditions that require the careful use of drugs and the presence or absence of complications.**
4. **Antihypertensive drugs are administered once a day, in principle, but as it is more important to control the blood pressure over 24 h, splitting the dose into twice a day is desirable in some situations.**
5. **The use of two or three drugs in combination is often necessary to achieve the target of blood pressure control. A low dose of a diuretic should be included in this combination.**
6. **Among the combinations of two drugs, those of a renin–angiotensin (RA) system inhibitor (ARB or ACE inhibitor)+Ca channel blocker, RA system inhibitor+diuretic, Ca channel blocker+diuretic and Ca channel blocker+β-blocker are recommended.**
7. **Simplification of the prescription using fixed-combination drugs is useful for improving adherence and controlling blood pressure.**
8. **A gradual reduction in blood pressure is desirable in hypertensive patients in general, particularly in elderly patients, but the target control level should be achieved within a few weeks in high-risk patients, such as those with grade III hypertension and multiple risk factors.**

1) BASIC PRINCIPLES FOR THE SELECTION OF ANTIHYPERTENSIVE DRUGS

As blood pressure increases, it is more difficult to control it at the target level through lifestyle modifications alone, and treatment with antihypertensive drugs becomes necessary. The occurrence of cerebrovascular and cardiovascular disorders can be prevented by reducing the blood pressure with antihypertensive drugs. Meta-analyses of large clinical studies have shown that this effect is proportionate to the degree of decrease in blood pressure rather than the class of antihypertensive drug.[255,256] The antihypertensive drug with the greatest hypotensive effect and suited for various accompanying conditions should be selected for each hypertensive patient.

a. First choices

Several classes of antihypertensive drugs are available today. Among these, the drug to be used as a first line of treatment should be selected from Ca channel blockers, ARBs, ACE inhibitors, diuretics and β-blockers (including αβ-blockers). All these drugs, alone or in combination, show a sufficient hypotensive effect and tolerability in hypertensive patients in general, and extensive evidence that they suppress the occurrence of cerebrovascular and cardiovascular disease has been accumulated. The results of large clinical studies suggest that these five drug classes have positive indications and contraindications. Appropriate drugs should be selected for patients having certain conditions. According to recent results,[196,197] a β-blocker is not necessarily the first choice for elderly patients without complications or for hypertensive patients with abnormal glucose or lipid metabolism. If there is no complicating condition, some reports have recommended a renin–angiotensin (RA) system inhibitor (ARB, ACE inhibitor) or a β-blocker for young patients and a diuretic or a Ca channel blocker for elderly patients because of age-related differences in the mechanism of hypertension,[257,258] but another report has refuted the difference in antihypertensive effect according to age.[259] At any rate, the frequency with which the target control level can be achieved using a single drug is low.[258]

b. Use of antihypertensive drugs

The ultimate objective of antihypertensive treatment is to prevent cerebrovascular or cardiovascular disease. Once antihypertensive drug therapy has been started, the realization of the target control level should always be borne in mind. However, the reality is unsatisfactory, as various investigations have indicated that the target is achieved in only approx 50% of those taking antihypertensive medication.[260]

The administration of antihypertensive drugs should be started by selecting one from the class of major antihypertensive drugs at a low dose for uncomplicated grade I hypertension ($<160/100$ mm Hg). If adverse effects appear or little hypotensive effect is noted, the drug should be replaced by one from another class. If the hypotensive effect is still insufficient, the dose should be increased or a small dose of an antihypertensive drug from a different class should be used concomitantly.[261] However, an increase in the dose of antihypertensive drugs other than ACE inhibitors and ARBs increases the frequency of adverse effects.[262] Even in grade I hypertension, antihypertensive medication may be started with a single drug at a routine dose or combination therapy at low doses if the target control level is set low due to high risk, or if there is an antihypertensive drug with a positive

indication. In grade II or more severe hypertension (⩾160/100 mm Hg), antihypertensive medication may be started with a single drug at a routine dose or with a combination of two drugs at low doses.[38,66] If the hypotensive effect is insufficient, single-drug therapy may be stepped up to combination therapy, or, if the medication has been started with a combination of drugs at low doses, the doses may be increased to routine levels or the combination changed. If the target control level still cannot be achieved, a combination of three drugs should be introduced. As the use of a small dose of a diuretic rarely causes adverse effects and synergistically increases the hypotensive effect when used with other antihypertensive drugs, it should be used positively in combination therapy.[38] If necessary, four drugs may be used in combination.

To facilitate long-term adherence, antihypertensive drugs effective with once-a-day administration are desirable. Many clinical studies have suggested the importance of 24-h blood pressure control by also paying attention to the non-clinic blood pressure. The effects of many antihypertensive drugs commercially available today do not persist for 24 h if used clinically. If the trough blood pressure measured at home is high, the time of administration may be tentatively changed from morning to evening, the dose split into morning and evening, or an additional dose taken in the evening or before going to bed.[263]

A gradual rate of blood pressure reduction that achieves the target level in a few months is desirable, because it causes fewer adverse effects. In particular, in elderly patients in whom the ability to regulate blood pressure is reduced, a rapid decrease should be avoided. However, with patients at high risk of cerebrovascular or cardiovascular disease, there are results indicating that the difference in the rate of blood pressure reduction during the first 1–3 months after commencing treatment affected the subsequent occurrence of disease; therefore in these cases, the attainment of the target level within several weeks is recommended.[198]

c. Drug interactions

Interactions between antihypertensive drugs may enhance the hypotensive effect or offset adverse effects in some combinations, but may aggravate adverse effects in others.[264] Particular attention is necessary with regard to the enhancement of the cardioinhibitory effect by a combination of a β-blocker and a non-dihydropyridine (non-DHP) Ca channel blocker, aggravation of hyperkalemia by a combination of an RA system inhibitor and an aldosterone antagonist, and increase in the frequency of withdrawal syndrome by a combination of a central sympatholytic drug and a β-blocker. Interactions between antihypertensive drugs and drugs for the treatment of other diseases include the attenuation of the hypotensive effects of diuretics, β-blockers and ACE inhibitors by non-steroidal anti-inflammatory drugs, enhancement of the hypotensive effects of Ca channel blockers and β-blockers by histamine H_2-receptor blockers and an increase in the blood digoxin concentration by a combination of digoxin and a non-DHP Ca channel blocker. The concomitant use of an ARB or an ACE inhibitor with a non-steroidal anti-inflammatory drug or a diuretic may cause acute renal insufficiency or an excessive decrease in blood pressure, particularly in elderly patients, with dehydration or under restriction of salt intake. A well-known example of food–drug interaction is an increase in the blood concentration of DHP Ca channel blockers (particularly felodipine and nisoldipine) after their administration following the consumption of grapefruit or grapefruit juice.

d. Dose reduction and withdrawal of antihypertensive drugs

Blood pressure shows seasonal fluctuations, and a temporary decrease in the dose or withdrawal may be considered in patients who show a decrease in blood pressure in summer. Conversely, due to the increase in blood pressure in winter, the increase in dose or the readministration of the antihypertensive drug becomes necessary. Even if a normal blood pressure has been maintained for ⩾1 year by antihypertensive medication, blood pressure often increases to a hypertensive level usually within 6 months of a reduction in dose or withdrawal of the drug. The percentage of patients in whom blood pressure could be maintained after the withdrawal of antihypertensive medication varies widely among studies from 3 to 74%. The characteristics of patients in whom a normal blood pressure could be maintained even after withdrawal include having grade I hypertension before treatment, a young age, normal body weight, low salt intake, being a non-drinker, using only one antihypertensive drug and having no organ damage.[265] Therefore, withdrawal of antihypertensive medication may be attempted exclusively in patients with grade I hypertension without organ damage or complications on the condition that an appropriate lifestyle is maintained and blood pressure is monitored periodically.

2) CHARACTERISTICS AND MAJOR ADVERSE EFFECTS OF VARIOUS ANTIHYPERTENSIVE DRUGS

Table 5-1 shows the positive indications of major antihypertensive drugs, and Table 5-2 shows their contraindications and conditions in which they must be used with caution.

a. Ca channel blockers

Ca channel blockers produce hypotensive effects by inhibiting the L-type voltage-dependent Ca channel involved in the influx of extracellular Ca ions, thus relaxing the vascular smooth muscle and reducing peripheral vascular resistance. They are classified into DHPs, benzothiazepines and phenylalkylamines, of which the first two are used as antihypertensive drugs in Japan. Their primary pharmacological actions are: (1) coronary and peripheral vasodilation, (2) suppression of the cardiac contractile force and (3) suppression of the conduction system. DHPs rapidly and potently reduce blood pressure and show little cardioinhibitory effect at clinical doses. They rather induce tachycardia due to a reflex increase in the sympathetic tone. Non-DHP Ca channel blockers have slower and

Table 5-1 Positive indications of major antihypertensive drugs

	Ca channel blockers	*ARB/ACE inhibitors*	*Diuretics*	*β-Blockers*
Left ventricular hypertrophy	O	O		
Heart failure		O[a]	O	O[a]
Prevention of atrial fibrillation		O		
Tachycardia	O[b]			O
Angina pectoris	O			O[c]
Postmyocardial infarction		O		O
Proteinuria		O		
Renal insufficiency		O	O[d]	
Chronic phase of cerebrovascular disorders	O	O	O	
Diabetes mellitus/MetS[e]		O		
Elderly patients	O[f]	O	O	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; MetS, metabolic syndrome.
[a]Should be started from a low dose and titrated carefully.
[b]Non-dihydropyridine Ca channel blockers.
[c]Caution is needed in coronary spastic angina pectoris.
[d]Loop diuretic.
[e]Metabolic syndrome.
[f]Dihydropyridine Ca channel blockers.

Table 5-2 Contraindications of major antihypertensive drugs or conditions that require careful use of drugs

	Contraindications	*Conditions that require careful use*
Ca channel blockers	Bradycardia (non-DHPs)	Heart failure
ARB	Pregnancy	Renal artery stenosis[a]
	Hyperkalemia	
ACE inhibitors	Pregnancy	Renal artery stenosis[a]
	Angioneurotic edema	
	Hyperkalemia	
Diuretics	Gout	Pregnancy
	Hypokalemia	Impaired glucose tolerance
β-Blockers	Asthma	Abnormal glucose tolerance
	Marked bradycardia	Obstructive pulmonary disease
		Peripheral artery disease

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; DHP, dihydropyridine.
[a]Contraindication if bilateral.

milder hypotensive effects accompanied by a cardioinhibitory effect. Of the antihypertensive drugs currently available, DHP Ca channel blockers have the greatest hypotensive efficacy without affecting organ blood flow; therefore, they are positively indicated in hypertension complicated by organ damage and hypertension in elderly patients and are used as the first choice drug in many patients. Many DHPs are administered once a day. Amlodipine, in particular, has the longest half-life in the circulation, with a consequent long duration of action and milder adverse effects, such as a reflex sympathomimetic action. It exerts no adverse effect on glucose, lipid or electrolyte metabolism. It has also been reported to induce the regression of left ventricular hypertrophy and delay the progression of atherosclerotic plaques.[266,267] Some Ca channel blockers, which inhibit N-type or T-type Ca channels and have sympatholytic actions, are unlikely to cause tachycardia and have been reported to show antiproteinuric effects in hypertension complicated by kidney disorders.[268–271] Palpitations, headache, hot flushes, edema, gingival growth and constipation are among the known adverse effects of Ca channel blockers. Non-DHP Ca channel blockers must not be used in patients with heart failure or marked bradycardia because of their cardioinhibitory actions, and sufficient caution is necessary regarding their use in elderly patients with latent cardiac disorders or their concomitant use with digitalis or β-blockers.

b. ARBs

ARBs are the most widely used antihypertensive drugs in Japan after Ca channel blockers. They produce a hypotensive effect by specifically binding to angiotensin II (AII) type 1 receptors and inhibiting the strong vasoconstriction, body fluid retention and sympathomimetic action mediated by AII. Therefore, the decrease in blood pressure induced by ARBs is correlated to an extent with the renin activity in individual patients. Within tissues, ARBs completely inhibit AII action at the receptor level in AII production not mediated by ACE (mediated by chymase). The administration of ARBs causes an increase in blood AII level and stimulates type 2 receptors, which antagonize the cardiovascular action of AII. It also inhibits the stimulation of mechanoreceptors, such as by stretching.[272] With these mechanisms combined, ARBs may not only reduce blood pressure but also directly inhibit organ damage and consequently prevent the occurrence of diseases.[194] ARBs are used alone or in combination with diuretics and Ca channel blockers for the treatment of grade I–III hypertension. The cardioprotective effects of ARBs are that they inhibit cardiac hypertrophy and improve the outcome of heart failure. In preventing ischemic heart disease, although ARBs had been thought to be inferior to ACE inhibitors, recent large-scale clinical trials have shown a comparable effect between ARBs and ACE inhibitors.[256,273] In the kidneys, ARBs dilate efferent arterioles, reduce the intraglomerular pressure, alleviate proteinuria and prevent exacerbation of the renal function in the long term. They have also been reported to improve the regulation of cerebral blood flow, prevent atherosclerosis and inhibit the occurrence of atrial fibrillation.[198,274] In addition, they improve insulin sensitivity and prevent the new occurrence of diabetes mellitus.[195] For these reasons, ARBs are used as the first choice for patients with complications of the heart, kidney or brain and those with diabetes mellitus. The combination with a diuretic is advantageous not only because of the synergism of hypotensive effects but also because it offsets adverse effects on electrolyte and glucose metabolism.

The adverse effects are infrequent regardless of the dose.[262] However, administration to pregnant or breast-feeding women or to patients with severe liver damage is contraindicated, and measures such as reducing the dose are necessary if the creatinine level is $\geqslant 2$ mg per 100 ml. ARBs must not be used in patients with bilateral renal artery stenosis or patients with one kidney and unilateral renal artery stenosis, in principle, because of the risk of a rapid decrease in renal function. A decrease in body fluid volume and Na deficiency are also quasi-contraindications. Attention to hyperkalemia is necessary while using ARBs with a potassium-sparing diuretic.

c. ACE inhibitors

ACE inhibitors simultaneously inhibit the RA system, which is a strong pressor system, in blood and tissue and stimulate the kallikrein–kinin–prostaglandin system, which is a depressor system. Similar to ARBs, ACE inhibitors are expected to alleviate organ damage or prevent its progression independently of a decrease in blood pressure by suppressing tissue angiotensin, and are recommended in patients with various organ complications and diabetes mellitus. A meta-analysis comparing ACE inhibitors with ARBs indicated that the former have a stronger suppressive effect on the occurrence of myocardial infarction.[256] However, the ONTARGET,[273] which directly compared them, showed no difference. The hypotensive effect of an ACE inhibitor is nearly the same as, or slightly weaker than, that of an ARB. The most frequent adverse effect is dry cough due to enhancement of bradykinin activity, which is observed in 20–30% of patients within 1 week to several months after commencing administration, but it is quickly resolved by the discontinuation of treatment. The induction of a cough has also been suggested to prevent aspiration pneumonia in elderly patients taking ACE inhibitors.[275] Dyspnea due to angioneurotic edema occurs infrequently. As the drugs are excreted through the kidney, their administration should be started at a low dose in patients with kidney damage. Those that are metabolized by both the liver and kidney are convenient to use. Other adverse effects and cautions are the same as those of ARBs.

d. Diuretics

According to various surveys, the frequency of hypertensive patients treated with diuretics is markedly low in Japan, being less than 10%. Considering the high salt intake of the Japanese, the importance of restricting salt intake and the comparable effectiveness of diuretics for the treatment of hypertension, which has been shown by large-scale clinical studies including those in Japan,[276] diuretics should be used more frequently. In addition, diuretics are inexpensive, to the advantage of pharmaco-economics.

Thiazide diuretics as well as their analogs are primarily used as antihypertensive drugs. They produce hypotensive effects by decreasing peripheral vascular resistance in the long term, while they reduce circulating blood volume in the short term by inhibiting Na reabsorption by the distal convoluted tubules. Diuretics have effects on metabolism and may cause hypokalemia, impaired glucose tolerance and hyperuricemia, which is a major reason for the hesitation in their use. However, these defects can be minimized without marked attenuation of the hypotensive effect by using diuretics at a low dose (1/4 to 1/2 of the tablet).[262] Diuretics are expected to be particularly effective in patients with increased salt sensitivity, such as the elderly, and in patients with low renin hypertension, kidney disorders, diabetes mellitus and insulin resistance. Although the hypotensive effect can be augmented by their concomitant use with other antihypertensive drugs, their combination with β-blockers cannot be recommended because of the latter's adverse effect on glucose and lipid metabolism. Diuretics are ineffective and should be avoided when the serum creatinine level is $\geqslant$2.0 mg per 100 ml. Potassium preparations and potassium-sparing diuretics should be used concomitantly for the treatment of hypokalemia, and guidance to increase the intake of foods with a high potassium content, such as citrus fruits should be given.

Loop diuretics cause diuresis by inhibiting NaCl reabsorption in the ascending limbs of the loop of Henle. They have stronger diuretic effects but weaker hypotensive effects with a shorter duration than thiazide diuretics. As they are also effective in patients with a reduced renal function, they are used for the treatment of patients with hypertension and congestive heart failure, as well as patients with a creatinine level of $\geqslant$2 mg per 100 ml.

e. β-Blockers (including αβ-blockers)

β-Blockers lower blood pressure by reducing cardiac output, suppressing renin production and inhibiting central sympathetic activities. Although peripheral vascular resistance increases shortly after the initiation of treatment, it returns to its original level after long-term treatment. Indications for the use of beta-blockers are hypertension in young patients showing sympathetic hyperactivity, angina on effort, after myocardial infarction, hypertension complicated by tachycardia, hypertension with a high cardiac output, including that caused by hyperthyroidism, high renin hypertension and aortic dissection. Supervision by a cardiologist is recommended while using β-blockers for improving the outcome of heart failure with systolic dysfunction. However, a recent meta-analysis suggested that β-blockers have an efficacy comparable to that of other antihypertensive drugs in suppressing the occurrence of cardiovascular disease, but that they have a lower preventive effect on the occurrence of stroke in elderly patients.[277] In a large clinical study of high-risk hypertensive patients with multiple risk factors (ASCOT-BPLA), the combination of a β-blocker and a diuretic was found to be inferior to that of a Ca channel blocker and an ACE inhibitor in preventing the occurrence of cardiovascular disease.[197] β-blockers exert adverse effects on glucose and lipid metabolism when used alone or in combination with diuretics.[278] Therefore, they are not the first choice of treatment in elderly patients or when hypertension is complicated by other diseases such as diabetes mellitus and abnormal glucose tolerance. However, as it has been reported that αβ-blockers, which also have a vasodilating α-blocking action, particularly carvedilol, specifically showed no metabolic adverse effect on their concomitant use with RA system inhibitors, a clinical study to evaluate the long-term outcome is necessary.[279]

Obstructive pulmonary diseases such as bronchial asthma, bradycardia, second-degree or severer AV block, Raynaud's phenomenon and pheochromocytoma are contraindications for β-blockers. If they are used for the treatment of vasospastic angina pectoris, they should be used concomitantly with Ca channel blockers. As their sudden discontinuation may induce withdrawal symptoms such as angina pectoris and hypertensive attacks, their dose should be gradually reduced before withdrawal.[280] Caution is needed in their concomitant use with verapamil or diltiazem, because it is most likely to induce bradycardia and heart failure.

The antihypertensive drugs mentioned below not only have a limited hypotensive effect but also lack evidence of improving cardiovascular prognosis based on clinical studies. Therefore, they should be used concomitantly with major antihypertensive drugs only when indications are present.

f. α-Blockers

α-Blockers selectively block α_1-receptors on the smooth muscle side of the sympathetic nerve terminal. They do not inhibit suppressive α_2-receptors on the sympathetic nerve terminal side and rarely cause tachycardia, especially when they are the long-acting type. Urination disorders associated with prostatic hypertrophy. They are used for blood pressure control before surgery on pheochromocytoma and are administered before sleep for treatment of morning hypertension. They exert favorable effects on lipid metabolism, such as decreases in the total cholesterol and triglyceride levels and increase in the high-density lipoprotein-cholesterol level. As first-dose phenomena, they may cause dizziness, palpitation and syncope due to orthostatic hypotension. Therefore, their administration should be started at a low dose with gradual increases.

g. Other sympatholytic drugs—centrally and peripherally acting drugs

Centrally acting sympatholytic drugs. They reduce blood pressure by stimulating α_2-receptors in the vasomotor center and inhibiting sympathetic activities. They cause many adverse effects, such as sleepiness, thirst, malaise, symptoms resembling Raynaud's phenomenon and impotence, and are usually used when other drugs are not tolerated. They may also be administered to patients with renal dysfunction. They are administered before sleep for treatment of morning hypertension, which alleviates their adverse effects. Methyldopa is used for treatment of gestational hypertension. The sudden discontinuation of clonidine administration may induce withdrawal symptoms. As the administration of centrally acting sympatholytic drugs causes sodium and water retention, the concomitant use of diuretics is recommended.

Peripherally acting sympatholytic drugs. They deplete norepinephrine stored in sympathetic nerve terminals. Despite their strong hypotensive effects, they are used infrequently due to many adverse effects. The important adverse effects of reserpine are depression, Parkinsonian syndrome and gastric ulcer due to hyperchylia.

h. Classic vasodilators

Classic vasodilators dilate blood vessels by acting directly on the vascular smooth muscle. As hydralazine acts quickly, it can also be used for the treatment of hypertensive emergencies. With regard to adverse effects, angina pectoris may be induced. Other adverse effects are headache, palpitation, tachycardia and edema; fulminant hepatitis has been reported, and hence liver disorder is a contraindication. Symptoms resembling those of systemic lupus erythematosus may appear when classic vasodilators are used continuously.

i. Aldosterone antagonists and potassium-sparing diuretics

These drugs promote Na excretion without the loss of K by acting on the distal convoluted tubules and common collecting ducts. Triamterene produces a similar effect independently of aldosterone by suppressing the amiloride-sensitive epithelial Na channel. It is often used with thiazide diuretics. Aldosterone antagonists are expected to be particularly effective for the treatment of low renin hypertension.[281] Also, as aldosterone has a toxic effect on the cardiovascular system, aldosterone antagonists have an organ-protecting effect. Clinical studies have shown that the outcome of heart failure or myocardial infarction is improved by aldosterone antagonists.[282,283] Whereas spironolactone has adverse effects, such as erectile dysfunction, gynecomastia and menorrhalgia, a selective aldosterone antagonist (eprelenone) has fewer adverse effects. Aldosterone antagonists may cause hyperkalemia when used with an RA system inhibitor or in patients with kidney dysfunction. They have also been reported to be useful as an additional drug for the treatment of resistant hypertension.[284]

3) COMBINATION THERAPY

As evidence based on large clinical studies of combinations of different classes of antihypertensive drugs is insufficient, combination therapies were performed in LIFE, VALUE, ASCOT-BPLA, ACTION and INVEST, providing the results as references. Also, the usefulness of combinations of drugs that cancel out each other's adverse effects, such as that of a diuretic and an ACE inhibitor (or ARB), is also supported from the point of view of pharmacological actions.

The eight combinations of two drugs recommended by the JSH2004 Guidelines[65] can be classified into those that were supported by large clinical studies in relative terms (Figure 1) and those that have scarcely been evaluated in large clinical studies. RA system inhibitor+Ca channel blocker was suggested by ASCOT-BPLA,[197] and RA system inhibitor+diuretic was suggested by LIFE,[196] to be better than β-blocker+diuretic. In Japan, the hypotensive effect of an ARB or ACE inhibitor+Ca channel blocker has been established.[268,285,286] In Japan, COPE, which compares Ca channel blocker+diuretic and Ca channel blocker+β-blocker with Ca channel blocker+ARB, and COLM, which compares ARB+diuretic with ARB+Ca channel blocker, regarding the morbidity and mortality of cardiovascular disease are in progress. In INVEST, ACE inhibitor+non-DHP Ca channel blocker was equivalent to β-blocker+diuretic.[287] In VALUE, Ca channel blocker+diuretic and ARB+diuretic were almost comparable.[198] β-blocker+Ca channel blocker was used in many patients in ACTION[288] and was particularly effective in hypertensive patients.[187] β-blocker+α-blocker can be used clinically, but lacks evidence based on large clinical studies.

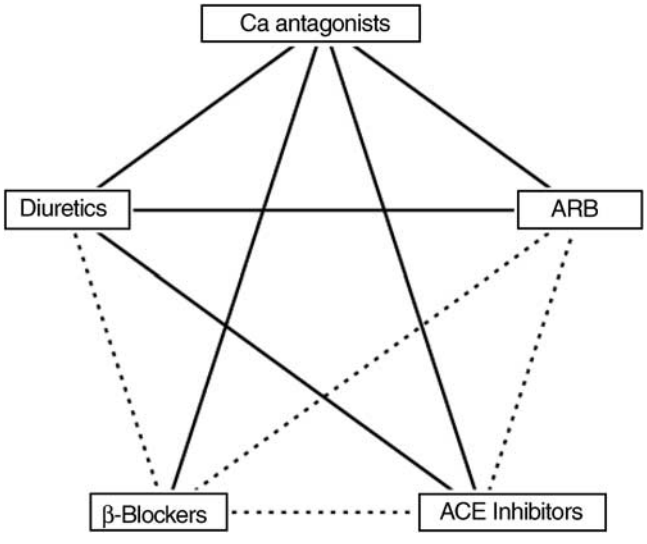

Figure 1 Combination of two drugs.

Aldosterone antagonists are often used with Ca channel blockers, diuretics or β-blockers. Renin inhibitors, which are not yet marketed in Japan, are often used with Ca channel blockers or diuretics as a kind of RA system inhibitor. According to ONTARGET, which evaluated the effect of combination therapy using ARBs and ACE inhibitors in high-risk patients, this combination was not considered useful.[273]

Regarding combinations of three drugs, the JSH2004 Guidelines recommend the addition of a diuretic if two-drug combinations do not include one. α-blockers[289] and spironolactone have also been used as a third drug, and their usefulness has been reported.[284]

4) FIXED-COMBINATION DRUGS

A reduction in the number of tablets to be taken and simplification of the prescription through the use of fixed-combination drugs is advantageous for improving adherence.[217] ADVANCE,[290] which compared the effects of a fixed-combination drug of an ACE inhibitor and diuretic with a placebo in diabetic patients, indicated the usefulness of the fixed-combination drug. The percentage of patients who continued taking the drug was similar between the fixed-combination drug and placebo. In ACCOMPLISH,[291] which compared treatments using a fixed-combination drug of an ACE inhibitor and a Ca channel blocker and that of an ACE inhibitor and a diuretic in hypertensive patients, approx 50% of the patients were treated with the fixed-combination drug alone in both groups, and the target level of blood pressure control could be attained with a relatively small number of drugs. The fixed-combination drug of an ACE inhibitor and a Ca channel blocker showed a greater preventive effect on cardiovascular disease. In many countries, many fixed-combination drugs, primarily those combining a diuretic with another drug, are marketed. Fixed-combination drugs of a diuretic and an ARB are currently available in Japan, and, with the addition of a fixed-combination drug of an ARB and a Ca channel blocker, fixed-combination drugs are expected to be used more frequently.

POINT 5B

Poorly controlled and resistant hypertension

1. **In resistant hypertension, obesity, sleep apnea syndrome, white coat hypertension/white coat phenomenon, poor adherence and volume overload due to various causes, inappropriate selection of antihypertensive drugs and attenuation of the hypotensive effect by the use of other drugs should be considered.**
2. **After sufficient inquiry and communication with the patient, necessary lifestyle modifications and measures for improving adherence should be implemented. Combination therapy with multiple drugs including a diuretic should also be used.**
3. **Patients with poorly controlled and resistant hypertension are more likely to have organ damage and high cardiovascular risk, and may have secondary causes of hypertension. Therefore, consultation with a hypertension specialist should be sought at an appropriate time.**

5) MANAGEMENT OF POORLY CONTROLLED AND RESISTANT HYPERTENSION

a. Definition and prevalence

In many hypertensive patients, blood pressure does not decrease to the target level even with the administration of antihypertensive

drugs. If, in such patients, blood pressure does not decrease to the target level even with lifestyle modifications and the sustained administration of three or more antihypertensive drugs including a diuretic at appropriate doses, the condition is called resistant or refractory hypertension. However, it is considered more practical to regard hypertension that continues to be poorly controlled despite the administration of 2–3 antihypertensive drugs as difficult-to-control[292] or poorly controlled hypertension and to treat it by using special measures, although it does not meet the definition of resistant hypertension. Even in poorly controlled or resistant hypertension, blood pressure may be sufficiently reduced by correcting factors such as those mentioned in Table 5-3. However, as such hypertension is often complicated by asymptomatic organ damage,[293] and as many patients with such hypertension belong to the high-risk group, consultation with a hypertension specialist should be sought at an appropriate time.

The prevalence of resistant hypertension varies among study populations. It is reported to be $<10\%$ at general clinics, but may exceed 50% at outpatient nephrology or hypertension clinics.[294] Regarding studies in Japan, the prevalence of patients in whom the control of home or clinic blood pressure was inadequate even with the administration of three or more drugs was calculated to be 13% (434/3400), according to J-HOME.[44] In cohorts including a high percentage of high-risk hypertensive patients (for example, those of large clinical trials such as ALLHAT, CONVINCE, LIFE, INSIGHT and VALUE), blood pressure was reportedly not reduced to the target level ($<140/90$ mm Hg) in about 30–50%.[196,198,295–297] In the first three studies, approx 40% of patients were taking three or more antihypertensive drugs. In CASE-J, performed in Japan, the number of drugs used was 1.4–1.5, but blood pressure could be controlled to the target level in approx 60% of patients,[298] so the percentage of patients with resistant hypertension is considered to have been low.

As for the state of blood pressure control revealed by Japanese cross-sectional studies such as J-HOME (involving the use of a mean of 1.7 antihypertensive drugs), in which general physicians participated, the percentage of patients with poorly controlled hypertension based on clinic blood pressure was 58%, but that based on home blood pressure ($\geqslant 135/85$ mm Hg) was 66%. Both clinic and home blood pressures were controlled adequately in 19%.[299] The target control level of clinic blood pressure is $<130/85$ mm Hg in young or middle-aged patients and $<130/80$ mm Hg in patients with diabetes mellitus, but these control levels were achieved in only 16–19 and 11% of the respective groups according to another cross-sectional study (mean number of drugs, 1.4).[300]

The results of cross-sectional studies are considered to represent the state of blood pressure control in general clinical practice. They suggest that this is poor in many patients. Assessment based on home blood pressure or 24-h ambulatory blood pressure must still be evaluated.

Table 5-3 Factors of poor control and resistance of hypertension and measures against them

Factors	*Measures*
Problems with blood pressure measurement	
Use of too small a cuff (air bladder)	Use of a cuff with a width of 40% of the brachial girth and a length sufficient to cover at least 80% of the brachial girth
Pseudohypertension	Attention to marked atherosclerosis
White coat hypertension/white coat phenomenon	Measurement of the home blood pressure or ambulatory blood pressure
Poor adherence	Overcoming the anxiety on long-term pill-taking by sufficient explanation. Changing the drug if adverse effects are observed. Considering psychological factors if drug maladjustment is repeated. Considering economic problems. Considering the dosing schedule matched with the patient's lifestyle. Showing the physician's positive and empathetic attitude
Lifestyle problems	
Progression of obesity	Repeated guidance in restriction of energy intake and exercise
Excessive drinking	Guidance to restrict the alcohol intake at $\leqslant$20–30 ml ethanol per day
Sleep apnea syndrome	CPAP and so on (see another chapter)
Volume overload	
Excessive salt intake	Explanation of the significance and necessity of salt intake restriction. Repeated guidance in cooperation with a nutritionist
Inappropriate use of diuretics	In combinations of three or more drugs, one should be a diuretic. Selection of a loop diuretic in patients with reduced renal function (serum creatinine level $\geqslant$2 mg per 100 ml). Measures to maintain the diuretic effect
Progression of renal dysfunction	Guidance in salt intake restriction and use of diuretics according to the above principles
Concomitant use of drugs or nutritional supplements that antagonize antihypertensive drugs or those that may increase the blood pressure by themselves	If oral contraceptives, corticosteroids, non-steroidal anti-inflammatory drugs (including selective COX-2 inhibitors), *Kampo* formulas containing licorice, cyclosporine, erythropoietin or antidepressants are used concomitantly, consult the physicians who prescribed them, and discontinue the administration or reduce the dose as much as possible. Select antihypertensive drugs considering the pressor mechanisms of the other drugs and drug interactions
Concomitant use of antihypertensive drugs with similar action mechanisms	Combinations of antihypertensive drugs that have different action mechanisms and cancel out compensatory responses
Secondary hypertension	See Chapter 12

Abbreviations: CPAP, continuous positive airway pressure; COX, cyclooxygenase.

b. Factors of resistance to treatment and approaches to them

Factors of resistant hypertension include failure to measure correct blood pressure (white coat hypertension/white coat phenomenon, inappropriate cuff size, pseudohypertension, etc.), insufficient antihypertensive treatment (poor concordance, inadequate lifestyle modifications, insufficient use of antihypertensive drugs, etc.) and the presence of a condition that prevents a decrease in blood pressure (volume overload, obesity, sleep apnea syndrome, excessive drinking, intake of drugs or foods that attenuate the effects of hypotensive drugs, etc.). Secondary hypertension may also be overlooked.

The resistance of hypertension is often ascribed to the volume overload that results from excessive salt intake, no use or inadequate use of diuretics and the presence of renal insufficiency. If poor control of blood pressure is caused by such factors, blood pressure is often reduced by the appropriate use of diuretics. Patient concordance is also a major problem. If the explanation given to the patient regarding medication is insufficient, and the patient is not sufficiently willing to comply with antihypertensive treatment, or if the physician fails to notice any adverse effects of the medication, adherence tends to be unsatisfactory. According to a survey of patients who were continuously treated at outpatient hypertension clinics for 10 years, many patients who showed adequate blood pressure control had a better understanding of antihypertensive treatment, showed less weight gain and were prescribed Ca channel blockers or ARBs.[301] Also, a survey of the state of blood pressure control and its factors indicated that the attitude of physicians to the treatment was the most important factor.[302] From these reports, a positive attitude of the physician to the treatment, that is, efforts to have the patient better understand the antihypertensive treatment, encouragement to modify lifestyle and the selection of appropriate antihypertensive drugs, is important in improving the state of blood pressure control. Considering the patient's economic and psychological problems is also necessary. Short-term hospitalization to promote the patient's understanding of antihypertensive treatment and adjustment of drugs should also be considered.

If sufficient blood pressure control cannot be achieved, the presence of the factors mentioned in Table 5-3 must be evaluated. If there is no sign of secondary hypertension or no problem with the measurement of blood pressure or drug compliance, but the hypotensive effect is insufficient even on treatment using three or more drugs, lifestyle guidance including salt intake restriction and the achievement of an appropriate body weight should be given again. Regarding the adjustment of drugs, if no diuretic has been used, its use should be started, and its dose and type should be optimized (Table 5-4).[292] The administration of a thiazide diuretic should be started at half a tablet and increased to a maximum of two tablets. In patients with renal insufficiency, a loop diuretic should be used. Among loop diuretics, furosemide has a short duration of action, so it must be administered 2 (or 3) times a day to obtain sufficient water and sodium diuresis and decrease in blood pressure. The use of a diuretic with a longer duration of action (for example, torasemide) should also be considered.

Other than diuretics, 2–3 drugs should be selected from three classes, that is, Ca channel blockers, ACE inhibitors or ARBs, and β-blockers or α-blockers (including αβ-blockers). However, little data exist indicating which combinations of three or more drugs are useful. Therefore, specific combinations are mostly recommended on the basis of physiological principles, clinical experiences or studies of a small number of patients. The additional administration of a small dose of an aldosterone antagonist (12.5–25 mg if spironolactone) has been reported to be effective.[284,303] The use of two or more drugs of the same class should be avoided, in principle, but the concomitant use of an ACE inhibitor and an ARB, a β-blocker and an α-blocker or a central sympatholytic drug, and a thiazide diuretic and an aldosterone antagonist is possible. In resistant hypertension, if the duration of action of an antihypertensive drug is insufficient, a period of poor blood pressure control is most likely to occur (including morning hypertension). To control blood pressure at the target level over 24 h, diurnal changes in blood pressure should be evaluated by morning and evening measurements of home blood pressure or 24-h ambulatory blood pressure monitoring, and adjustment of the time of administration (chronotherapy) as well as the type of antihypertensive drugs is necessary (administration of a long-acting drug in the morning and evening or in the morning and before going to bed). As adverse effects and an excessive decrease in blood pressure are most likely to occur during the use of multiple drugs or at high doses, sufficient caution is necessary, and consultation with a hypertension specialist at an appropriate time is recommended.

A statement has recently been issued that defines resistant hypertension as hypertension that can be controlled at a target level using four or more drugs and suggests that evaluating factors of resistance and the possibility of secondary hypertension may benefit patients.[304]

Table 5-4 Optimization of drug therapy for resistant hypertension in which the target level of blood pressure control cannot be achieved using three drugs including a diuretic

Adjustment of the balance among the three drug categories
Vasodilators: ACE inhibitors, ARB, dihydropyridine Ca channel blockers
Heart-rate-lowering agents: β-blockers, non-dihydropyridine Ca channel blockers
Diuretics (Selected according to the renal function. Measures to maintain the diuretic effect should be taken.)
An increase in the dose or frequency of administration (1→2 times a day)
Addition of an aldosterone antagonist (caution against hyperkalemia)
Consultation with a hypertension specialist at an appropriate time
Additional combination therapies
Use of αβ-blockers (labetalol, carvedilol)
Concomitant use of dihydropyridine and non-dihydropyridine Ca channel blockers
Concomitant use of an ACE inhibitor and ARB (follow the serum K and Cr levels)
Concomitant use of two drugs from aldosterone antagonists, thiazide diuretics and loop diuretics
Addition of an α-blocker or a central sympatholytic drug
Addition of the direct vasodilator hydralazine (Management of tachycardia and an increase in the body fluid is necessary.)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.
Cited with modification from Cuspidi *et al.*[293]

Citation Information

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GUIDELINES (JSH 2009)

Chapter 6. Hypertension associated with organ damage

Hypertension Research (2009) **32,** 40–50; doi:10.1038/hr.2008.10

POINT 6A
Cerebrovascular disease

1. **From the hyperacute phase (within 3 hours of onset) to the acute phase (within 1–2 weeks of onset) of cerebrovascular disease, the indications and target of antihypertensive therapy differ according to the clinical type of the disease. In patients in the hyperacute phase of cerebral infarction awaiting thrombolytic therapy by the i.v. injection of a tissue plasminogen activator (t-PA), antihypertensive treatment by i.v. administration is considered necessary when systolic blood pressure is >185 mm Hg or diastolic pressure is >110 mm Hg, and blood pressure should be controlled at <180 mm Hg systolic and <105 mm Hg diastolic by strict management over 24 h both during and after treatment. In cerebral infarction that is not an indication for thrombolytic therapy, antihypertensive therapy is indicated when systolic blood pressure is >220 mm Hg or diastolic pressure is >120 mm Hg. In cerebral hemorrhage, a systolic blood pressure >180 mm Hg or a mean blood pressure >130 mm Hg is an indication for antihypertensive therapy. The target of blood pressure control should be 85–90% of the value before treatment for cerebral infarction and 80% of that for cerebral hemorrhage.**
2. **Treatments recommended in the acute phase of cerebrovascular disease include the intravenous instillation of a very low dose of nicardipine, diltiazem, nitroglycerin and nitroprusside. However, caution against the possibility of an increase in intracranial pressure is necessary. The sublingual administration of nifedipine should be avoided, because it may induce a rapid decrease in blood pressure.**
3. **In the chronic phase of cerebrovascular disease (1 month or more after onset), the eventual target of blood pressure control should be $<140/90$ mm Hg. Just as decreasing the blood pressure slowly and paying attention to the clinical disease type (cerebral hemorrhage, lacunar infarction, etc.) are extremely important, the presence or absence of stenosis/obstruction of a main trunk of the cerebral arteries and the presence or absence of symptoms of cerebral circulatory insufficiency are also important. If the bilateral carotid arteries are markedly narrowed, or a main trunk of the cerebral arteries is obstructed, caution against an excessive decrease in blood pressure is necessary. A target of blood pressure control even lower than 140/90 mm Hg is recommended for patients with lacunar infarction or cerebral hemorrhage.**
4. **Antihypertensive drugs recommended in the chronic phase of cerebrovascular disease are Ca channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, etc. In hypertensive patients with diabetes mellitus or atrial fibrillation, ACE inhibitors and ARBs are recommended.**
5. **In antihypertensive therapy for hypertensive patients with silent cerebral infarction or silent cerebral hemorrhage, the target of blood pressure control and the choice of antihypertensive drugs are the same as those for the chronic phase of cerebrovascular disease.**

1) CEREBROVASCULAR DISEASE

In Japan, cerebrovascular disease accounts for a high percentage of hypertensive organ damage, and the number of patients with cerebrovascular disease, particularly those with cerebral infarction, is increasing with the aging of the population (Table 6-1). Many patients with cerebrovascular disease develop hypertension in the acute phase, and blood pressure control in the acute phase is an initial problem. In particular, as thrombolytic therapy has also begun to be performed for cerebral infarction in the hyperacute phase in Japan, how antihypertensive therapy should be conducted in this phase has also become an important clinical issue. Furthermore, hypertension is the most important risk factor related to the recurrence of cerebrovascular disease, and blood pressure management for the prevention of recurrence is important. In addition, as a high percentage of elderly hypertensive patients are known to have asymptomatic cerebrovascular disease, antihypertensive treatment for hypertensive patients with silent cerebrovascular disease is also extremely important.

a. Acute phase

In the acute phase, within 1–2 weeks of the onset of cerebrovascular disease, a high blood pressure is observed regardless of whether the disease is cerebral hemorrhage or cerebral infarction. This increase in blood pressure associated with the onset is considered to be a biological protective reaction to stress, urinary retention, headache, brain tissue ischemia, and an increase in intracranial pressure due to edema and hematoma. In many patients, blood pressure decreases within a few days by rest, urination by bladder catheterization, pain control and the treatment of brain edema without the administration of antihypertensive drugs.[305,306]

The range of autoregulation of cerebral blood flow is shifted to the right due to hypertension,[28] autoregulation itself disappears in the acute phase of cerebrovascular disease, and cerebral blood flow decreases even with a slight reduction in blood pressure. Thus,

Table 6-1 Treatment for hypertension complicated by cerebrovascular diseases

	Conditions to treat	*Target BP level*	*Drugs*
Hyperacute phase (within 3 h after onset)	Patients awaiting thrombolytic therapy SBP > 185 mm Hg or DBP > 110 mm Hg	Patients awaiting thrombolytic therapy < 180/105 mm Hg During and after thrombolytic therapy (over 24 h)	Low-dose intravenous instillation of nicardipine, diltiazem, nitroglycerin or nitroprusside
Acute phase (within 1–2 weeks after onset)			
Cerebral infarction	SBP > 220 mm Hg or DBP > 120 mm Hg	85–90% of the value before treatment	Low-dose intravenous instillation of nicardipine, diltiazem, nitroglycerin or nitroprusside[a,b]
Cerebral hemorrhage	SBP > 180 mm Hg or MBP > 130 mm Hg	80% of the value before treatment	
Chronic phase (1 month or longer after onset)[c]		< 140/90 mm Hg (1–3 months after the beginning of treatment)[d]	Ca channel blockers, ACE inhibitors, ARB, diuretics, etc.[e]

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.
[a]Caution against the risk of an increase in the intracranial pressure is necessary.
[b]Sublingual administration of nifedipine should be avoided because of the possibility of a rapid decrease in the blood pressure.
[c]May be started after 1–2 weeks, when acute-phase treatment is completed.
[d]Caution against an excessive decrease is needed, particularly in marked bilateral carotid artery stenosis or obstruction of a main trunk of the cerebral arteries. In lacunar infarction and cerebral hemorrhage, a target even lower than 140/90 mm Hg is recommended.
[e]ACE inhibitors and ARBs are recommended in patients with diabetes mellitus or atrial fibrillation.

lowering blood pressure further reduces local cerebral blood flow in the lesion and the surrounding penumbra region (area of reversible damage in which functional recovery with restoration of blood pressure is expected), possibly causing enlargement of the lesion (infarction).[307] As the ischemic area is in a state of vasoparalysis, vasodilator drugs only dilate blood vessels of the intact areas, with a decrease in blood flow in the lesion, which is called intracranial steal. For these reasons, aggressive antihypertensive treatment is not performed, in principle, in the acute phase of cerebrovascular disease.[308]

However, if blood pressure increases markedly, antihypertensive treatment is carried out even in the acute phase of cerebral vascular disease, but data suggesting at what blood pressure level antihypertensive treatment should be initiated are insufficient.[309] Antihypertensive treatment immediately after the onset of the disease must be performed cautiously, with an accurate diagnosis of the disease type and frequent examination for neurological signs and symptoms except when hypertensive encephalopathy is strongly suspected. Blood pressure should be measured twice at an interval of $\geqslant$5 min, and if a diastolic pressure of $\geqslant$140 mm Hg persists, emergency antihypertensive treatment should be started using i.v. preparations.[310] If diastolic blood pressure is $<$140 mm Hg, blood pressure should be measured at least twice at an interval of $\geqslant$20 min after a period of rest, and antihypertensive treatment should be performed when systolic pressure is $>$220 mm Hg or diastolic pressure is $>$120 mm Hg.[311]

In patients expected to undergo thrombolytic therapy by intravenous injection of a tissue plasminogen activator (t-PA) in the hyperacute phase within 3 h of onset of the disease, antihypertensive treatment by i.v. administration is considered necessary when the systolic blood pressure is $>$185 mm Hg or the diastolic pressure is $>$110 mm Hg, and blood pressure should be controlled at $<$180 mm Hg systolic and at $<$105 mm Hg diastolic by strict management over 24 h, including during and after treatment.[311]

In ACCESS,[312] patients with cerebral infarction showing motor paralysis in whom systolic blood pressure was $\geqslant$200 mm Hg or diastolic pressure was $\geqslant$110 mm Hg 6–24 h after admission, or in whom systolic blood pressure was $\geqslant$180 mm Hg or diastolic pressure was $\geqslant$105 mm Hg 24–36 h after admission were treated with the ARB candesartan for 1 week. Although no significant difference was noted in the outcome of stroke, which was the primary end point, the mortality rate after 1 year and the occurrence of cardiovascular events, which was the secondary end point, were significantly reduced. ARBs are expected to have an organ-protective effect, but further verification on a larger number of patients is necessary.

Although evidence related to cerebral hemorrhage is insufficient, antihypertensive treatment should be started according to the Guidelines of the American Stroke Association if a systolic blood pressure $>$180 mm Hg or a mean blood pressure $>$130 mm Hg persists.[313]

Recently, the results of the INTERACT pilot trial have been reported, in which patients with hyperacute intracerebral hemorrhage (within 6 h of onset) were enrolled.[314] The trial compared the intensive lowering of blood pressure (target systolic blood pressure 140 mm Hg) with the standard guideline-based management of blood pressure (target systolic blood pressure 180 mm Hg), and the hematoma growth at 24 h tended to decrease in the intensive group (P=0.05). Although the intensive lowering of blood pressure did not alter the risks of adverse events or clinical outcomes at 90 days, a large randomized trial is needed to define the effects of such treatment on the clinical outcomes in patients with hyperacute intracerebral hemorrhage.

In the acute phase of subarachnoid hemorrhage, prevention of rebleeding is important, and sufficient control of blood pressure, sedation and pain control is desirable. There is no evidence regarding the blood pressure level at which antihypertensive treatment should be started or regarding the target of blood pressure control.

Drugs that act quickly and allow dose adjustment are desirable. The Ca channel blockers nicardipine and diltiazem or nitroglycerine and nitroprusside, which have long been used, are administered by low-dose i.v. instillation. However, caution against the possibility that the treatment may increase the intracranial pressure is necessary. In Japan, intracranial hemorrhage before complete hemostasis and an increase in the intracranial pressure in the acute phase of stroke are considered to be contraindications for Ca channel blockers such as nicardipine and nilvadipine. Added to this, the sublingual administration of nifedipine capsules should be avoided, because it may induce a rapid decrease in blood pressure. The target of blood pressure control varies with disease type, but blood pressure should be reduced to 85–90% of

the value before treatment in cerebral infarction and to 80% of that before treatment in cerebral hemorrhage. More aggressive measures to reduce blood pressure are necessary if intracranial hemorrhage is accompanied by hemorrhagic infarct, acute myocardial infarction, heart failure or aortic dissection. Antihypertensive treatment by injection should be substituted for oral treatment as early as possible.

Rehabilitation from an early stage is necessary for improving the activities of daily living (ADL) of stroke patients, but attention must be paid to changes in blood pressure while conducting rehabilitation at the bedside.

b. Chronic phase

Patients with a history of cerebrovascular disease are known to frequently develop new cerebrovascular disease, and the control of hypertension, which is its greatest risk factor, is extremely important for the treatment of patients in the chronic phase of cerebrovascular disease. According to the results of a retrospective study in Japan, the relationship between blood pressure after cerebrovascular disease and the recurrence rate varies markedly among disease types, and the report of a J-shaped relationship between the recurrence of cerebral infarction and diastolic pressure, which is not observed in cerebral hemorrhage, has attracted attention.[315]

Since 1990, relatively large studies on the relationship between the prevention of recurrence of cerebrovascular disease and blood pressure have been carried out,[135,316–320] with a systematic review.[321] Antihypertensive drug therapy significantly reduces the recurrence of all types of cerebrovascular disease, recurrence of non-fatal cerebral infarction, and occurrence of myocardial infarction and all vascular events.

In PROGRESS,[135] the recurrence rate of cerebrovascular disease was reduced by 28% in patients with a mean age of 64 years by reducing blood pressure from 147/86 mm Hg to about 138/82 mm Hg through the additional administration of perindopril ($4\,mg\,day^{-1}$) or the diuretic indapamide ($2\,mg\,day^{-1}$). Its subanalysis[185] also indicated that the frequencies of cerebral hemorrhage and cerebral infarction were lower in patients in whom blood pressure was controlled at a lower level (a systolic blood pressure of about 120 mm Hg). In PRoFESS,[322] 20,332 patients 55 years of age or older who had recently had an ischemic stroke (median interval from stroke to randomization was 15 days) were assigned to receive telmisartan (80 mg daily) or a placebo. During a mean follow-up after 2.5 years, mean blood pressure was 3.8/2.0 mm Hg lower in the telmisartan group than in the placebo group. Therapy with telmisartan did not significantly lower the rate of recurrence of stroke or major cardiovascular events.

Target of blood pressure control. The AHA/ASA Guidelines[323] propose no clear target of blood pressure control or degree of blood pressure reduction and consider that they vary among individual patients. A mean decrease in blood pressure of about 10/5 mm Hg is effective. The JNC7 emphasizes that a normal blood pressure is defined as $<120/80$ mm Hg.

On the other hand, the ESH/ESC Guidelines for the Management of Arterial Hypertension revised in 2007[66] recommend $<130/80$ mm Hg as a target of blood pressure control for patients in the chronic phase of cerebrovascular disease, reflecting the results of PROGRESS. However, these results cannot be applied entirely if there is obstruction or marked stenosis in a main trunk of the cerebral arteries, and measures tailored to individual patients are required. Rothwell *et al.*[324] reported that the risk of cerebrovascular disease increased significantly in symptomatic patients who showed $\geqslant 70\%$ stenosis of the bilateral carotid arteries when the systolic pressure decreased to 140 mm Hg, but that no increase in the risk was observed in patients with $\geqslant 70\%$ unilateral carotid artery stenosis even when the systolic blood pressure decreased to the same level. According to WASID,[325] in patients with symptomatic intracranial artery (internal carotid, middle cerebral, vertebral or basilar artery) stenosis, blood pressure was not related to the risk of ischemic cerebrovascular disease in those who showed a marked stenosis of $\geqslant 70\%$, but the risk was higher in those who showed a moderate stenosis of $<70\%$ when the systolic blood pressure was $\geqslant 160$ mm Hg. In addition, the hemodynamics is considered to differ between vascular stenosis and obstruction, and there is no useful evidence as a reference for the relationship between blood pressure and risk of ischemic cerebrovascular disease in patients with unilateral obstruction of the internal carotid or basilar artery. In the chronic phase of cerebrovascular disease, the optimal blood pressure may vary among individual patients because it is affected by various factors, including age, presence or absence of complications such as diabetes mellitus, degree of vascular obstruction/stenosis, site of the vascular lesion, degree of collateral circulation and degree of impairment of autoregulation of the cerebral circulation.

Antihypertensive drug therapy is usually started in the chronic phase 1 month or more after onset. However, it may be started 1–2 weeks after onset, when treatment in the acute phase has been completed. It is important to reduce the blood pressure slowly over 1–3 months after the beginning of treatment, and $<140/90$ mm Hg is considered to be appropriate as a final target control level, except in patients with marked stenosis of the bilateral internal carotid arteries or obstruction of a main trunk of the cerebral arteries, although a single standard cannot be applied universally because of individual differences. A target level even lower than 140/90 mm Hg is recommended for cerebral hemorrhage or lacunar infarction.[326] If the patient complains of dizziness, lightheadedness, tiredness, a heavy feeling of the head, numbness, weakness, loss of energy or exacerbation of neurological signs or symptoms during treatment, these may be symptoms of cerebral circulatory insufficiency due to a decrease in blood pressure, and a decrease in the dose or change in the type of antihypertensive drug is necessary. Particular caution is needed in patients with obstruction of a main trunk of the cerebral arteries (especially in the vertebral-basilar artery system), because dysautoregulation of the cerebral circulation may persist for 3 months or more.

Recommended classes of antihypertensive drugs. Ca channel blockers, ACE inhibitors, ARBs and diuretics are recommended. In patients with diabetes mellitus and those with atrial fibrillation, in particular, ACE inhibitors and ARBs, which also prevent the new onset of diabetes mellitus, correct insulin resistance and suppress the occurrence of atrial fibrillation, are recommended.

In PROGRESS,[135] a combination of an ACE inhibitor and a diuretic was suggested to reduce the recurrence rate of cerebrovascular disease and prevent the occurrence of dementia. In MOSES,[320] a significantly lower percentage of patients in the ARB (eprosartan) group than those in the Ca channel blocker (nitrendipine) group showed the primary end points (all deaths, all cardiovascular and cerebrovascular events) and, among the secondary end points, cerebrovascular events.

The AHA/ASA Guidelines[323] recommend a diuretic alone and a diuretic+ACE inhibitor. Proposing that drugs should be selected for each patient depending on background factors (extracranial obstructive vascular diseases, renal disorders, heart disease, diabetes, etc.), they also recommended ACE inhibitors and ARBs for patients with diabetes mellitus or atrial fibrillation. In the 2007 ESH-ESC Guidelines for the Management of Arterial Hypertension,[66] all classes of antihypertensive drugs are recommended, because they consider that most of the benefit obtained from drugs can be ascribed to a decrease

in blood pressure. Although differences among drugs are considered to be masked if a rigorous target of blood pressure control is attained, there are also results indicating differences among drugs despite a similar decrease in blood pressure, such as those shown by MOSES.[320]

c. Asymptomatic phase

The diagnostic criteria issued in 1997[327] are used for the diagnosis of asymptomatic cerebrovascular disease. A major portion of silent cerebral infarction important in connection with hypertension is considered to involve a small lesion similar to lacunar infarction, a minor vascular disease for which hypertension and age are the greatest risk factors. Its presence and progression are independent risk factors for cerebrovascular disease and impairment of cognitive function.[148,150,327–329] Asymptomatic cerebral hemorrhage (microhemorrhage), which is detected mostly by T_2-weighted MRI, is attracting attention.[328,330–332]

In principle, the target of blood pressure control in hypotensive treatment and useful antihypertensive drugs for hypertensive patients with silent cerebral infarction or cerebral hemorrhage are the same as those for the chronic phase of cerebrovascular disease, but the results of a CT substudy[333] of PROGRESS suggested that more sufficient antihypertensive treatment is desirable. Silent cerebral infarction is an index of target organ damage along with white matter lesions, and non-dipper, riser and morning surge observed by 24-h blood pressure monitoring are its risk factors.[86,101,334,335] Blood pressure control over 24 h and early in the morning is important.

In addition, asymptomatic carotid artery stenosis and unruptured cerebral aneurysms are also frequently detected, and they have been shown to be risk factors for the occurrence of cerebrovascular disease.[327,328] With regard to asymptomatic carotid artery stenosis, the evaluation of indications for surgical treatment before the initiation of antihypertensive treatment is important. If the patient has a familial history of subarachnoid hemorrhage or unruptured cerebral aneurysm, aggressive antihypertensive treatment is recommended.

In the asymptomatic phase, patients feel high-level anxiety over the condition of cerebrovascular disease and treatment, and so sufficient informed consent is extremely important.[327]

POINT 6B

Coronary heart diseases

1. **Careful and sufficient reduction of blood pressure is important in coronary artery disease. The target of blood pressure control should be $<$140/90 mm Hg, in principle.**
2. **In patients with old myocardial infarction, β-blockers, renin-angiotensin (RA) system inhibitors (ACE inhibitors, ARBs) and aldosterone antagonists reduce the mortality rate and improve prognosis. Careful reduction of blood pressure to $<$130/80 mm Hg is desirable.**
3. **Hypertension complicated by angina pectoris due to organic coronary artery stenosis is a good indication for long-acting Ca channel blockers and β-blockers with no endogenous sympathomimetic action.**
4. **Vasospastic angina pectoris is a good indication for Ca channel blockers.**

Heart failure

1. **In patients with heart failure, antihypertensive drugs are not necessarily used for reducing blood pressure but for improving QOL and/or prognosis.**
2. **The combination of an RA system inhibitor+β-blocker+diuretic is a standard treatment for heart failure, and it reduces the mortality rate and improves prognosis. However, RA system inhibitors and β-blockers should be introduced at low doses, and their doses should be increased carefully, with due attention to the exacerbation of heart failure, hypotension, bradycardia (β-blockers), renal dysfunction, etc.**
3. **Aldosterone antagonists further improve the prognosis of patients with severe heart failure undergoing standard treatment.**
4. **In hypertension complicated by heart failure, sufficient lowering of the blood pressure is important, and, if the decrease in blood pressure is insufficient, a long-acting Ca channel blocker should be added.**

Cardiac hypertrophy

1. **Regression of cardiac hypertrophy leads to an improvement in prognosis.**
2. **Any antihypertensive drug can induce the regression of cardiac hypertrophy by maintaining a sufficient decrease in blood pressure. The target of blood pressure control should be $<$140/90 mm Hg.**
3. **RA system inhibitors and long-acting Ca channel blockers, in particular, are effective for the regression of cardiac hypertrophy.**

Atrial fibrillation

4. **Hypertension is a risk factor for atrial fibrillation. The occurrence of atrial fibrillation is suggested to be prevented by sufficient antihypertensive treatment primarily with RA system inhibitors.**

2) HEART DISEASES

The heart is one of the important target organs of hypertension (Table 6-2). Increases in systolic and diastolic pressure loads induce myocardial remodeling, such as cardiac hypertrophy and myocardial fibrosis and coronary endothelial damage (Table 6-2). Risk factors such as dyslipidemia, diabetes mellitus and smoking increase the risk of myocardial ischemia and coronary atherosclerosis. The progression of myocardial remodeling and coronary atherosclerosis leads to coronary artery disease, heart failure, arrhythmia and sudden death. Therefore, a sufficient reduction in systolic blood pressure is important to reduce the cardiovascular mortality rate and cardiovascular events.[66,194,195,295,336]

a. Coronary artery disease

Hypertension increases the incidence of coronary artery disease. However, conventional antihypertensive drug therapy primarily using diuretics and β-blockers does not markedly reduce the incidence of coronary artery disease, whereas it markedly decreases the incidence of stroke.[337] Effects of risk factors other than hypertension on the occurrence of coronary artery disease may make a marked difference. Recent studies have suggested that long-acting Ca channel blockers and RA system inhibitors (ACE inhibitors and ARBs) reduce the incidence of coronary artery disease.[186,187,319,338] Furthermore, clinical trials in Japan have suggested that cardiac events can be prevented in patients with coronary artery disease by sufficiently reducing the

Table 6-2 Treatment for hypertension complicated by heart disease

Angina pectoris	Organic coronary stenosis[a]	β-Blockers, long-acting Ca channel blockers
	Coronary vasospasm	Long-acting Ca channel blockers
	Insufficient decrease in the blood pressure	Addition of an RA system inhibitor
Old myocardial infarction	Blood pressure should be reduced carefully to $<130/80$ mm Hg	
	RA system inhibitors or β-blockers are the first choice	
	Insufficient decrease in blood pressure	Addition of a long-acting Ca channel blocker or diuretic
	Systolic dysfunction	Addition of an aldosterone antagonist
Heart failure	Standard treatment	RA system inhibitor[b]+β-blocker[b]+diuretic
	Severe heart failure	Addition of an aldosterone antagonist
	Insufficient decrease in blood pressure	Addition of a long-acting Ca channel blocker
Cardiac hypertrophy	A sustained and sufficient decrease in blood pressure should be attempted	
	An RA system inhibitor/long-acting Ca channel blocker is the first choice	
Atrial fibrillation	Sufficient antihypertensive therapy mainly by RA system inhibitors is recommended (especially in patients with paroxysmal atrial fibrillation, heart failure, left ventricular hypertrophy, or left atrial enlargement).	
	For patients with chronic atrial fibrillation, a beta antagonist or non-DHP Ca channel blocker should be considered for rate control therapy.	

[a]Coronary intervention may be performed if there are indications.
[b]In patients with reduced systolic function, medication should be started at a low dose, and the dose should be increased carefully and slowly.

blood pressure using RA system inhibitors or long-acting Ca channel blockers.[194,195,339,340]

To prevent coronary artery disease, the management of other risk factors in addition to antihypertensive treatment is important. Particularly, treatment of hyper-low-density lipoprotein-cholesterolemia using 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors has been shown to be effective for the primary and, in particular, secondary prevention of cardiac events due to coronary artery disease.[341] A small dose of aspirin and cessation of smoking are also effective.[139]

Although evidence regarding the target of blood pressure control in hypertensive patients with coronary artery disease is insufficient, ACTION and JMIC-B suggest that the current consensus for the target of blood pressure is $<140/90$ mm Hg.[187,340] However, as the risk of cardiovascular events is particularly high in hypertensive patients with a history of myocardial infarction, it is recommended to reduce blood pressure carefully to $<130/80$ mm Hg.[66] It has also been suggested that, in hypertension accompanied by coronary artery disease, a decrease in blood pressure below a certain level causes a reduction in the diastolic coronary perfusion pressure and induces myocardial ischemia to worsen the prognosis (J-shaped phenomenon). However, these reports were based on retrospective analyses[342,343] and have not been validated.

Angina pectoris. In hypertension complicated by angina pectoris, Ca channel blockers and β-blockers having antianginal actions are the first choices. Angina pectoris is caused by significant stenosis and/or vasospasm of the coronary artery, and both are often involved simultaneously. As angina pectoris due to coronary vasospasm responds well to Ca channel blockers, they are the first choice in hypertension complicated by angina at rest and angina on effort. Both β-blockers and Ca channel blockers are effective for the treatment of angina on effort due to organic coronary artery stenosis. In Japan, angina pectoris attributed to coronary vasospasm is frequently observed, and as β-blockers have been suggested to exacerbate coronary vasospasm, a Ca channel blocker or a combination of a Ca channel blocker and a β-blocker is recommended when the mechanism of angina pectoris is unclear.

Although all Ca channel blockers are effective as antianginal drugs, long-acting Ca channel blockers are recommended, (1) because reflex tachycardia associated with a decrease in blood pressure is observed less frequently, and (2) because the time of administration need not be adjusted to the time of the frequent occurrence of anginal attacks. Regarding short-acting Ca channel blockers, a rapid decrease in blood pressure or reflex tachycardia may induce myocardial ischemia in patients with severe coronary artery stenosis.

As the antianginal actions of β-blockers are primarily ascribed to their negative chronotropic actions, drugs with no endogenous sympathomimetic action should be selected for the treatment of angina pectoris. There is no difference in the antianginal effect of selective and non-selective β_1-blockers. Added to this, as the blood-pressure-lowering effect is weak with a β-blocker alone,[344,345] its combination with a long-acting Ca channel blocker or an RA system inhibitor is necessary if the decrease in blood pressure is insufficient.

In angina pectoris due to significant coronary artery stenosis, coronary bypass surgery and percutaneous transluminal coronary angioplasty are effective for the control of anginal pain, so unnecessary adherence to drug therapy alone should be avoided.

Old myocardial infarction. In large clinical studies in Western countries, β-blockers with no endogenous sympathomimetic action were found to significantly reduce the recurrence of myocardial infarction and sudden death in patients who had had myocardial infarction.[346,347] In Japan, β-blockers are used less frequently, partly because of anxiety over coronary vasospasm. However, in patients who have had old myocardial infarction showing marked organic coronary artery lesions, β-blockers are an option. Short-acting Ca channel blockers may increase cardiac accidents, but long-acting Ca channel blockers do not worsen the prognosis.[295] In addition, diltiazem reduced the recurrence of myocardial infarction in patients with non-Q wave infarction without heart failure.[348] In follow-up studies of a large number of patients conducted in Japan, both β-blockers and long-acting Ca channel blockers were found to reduce the incidence of cardiac events,[340,349,350] but short-acting Ca channel blockers tended to exacerbate them.[351]

In patients with systolic dysfunction after extensive myocardial infarction (ejection fraction $\leqslant 40\%$), RA system inhibitors have been shown to prevent left ventricular remodeling (ventricular dilation, myocardial hypertrophy, interstitial fibrosis) and reduce the morbidity of heart failure and sudden death.[352,353] Ventricular remodeling plays an important role in the progression of myocardial damage and the occurrence and exacerbation of heart failure. Therefore, left ventricular dilation and systolic dysfunction due to myocardial infarction are good indications for RA system inhibitors. In addition, in patients with a reduced cardiac function after myocardial infarction, the prognosis is further improved by the administration of

an aldosterone antagonist in addition to an RA system inhibitor, a β-blocker and a diuretic.[283]

b. Treatment of heart failure using antihypertensive drugs

Epidemiological studies in Western countries have shown that hypertension is the most frequent underlying cause of heart failure, and similar results have been obtained in a patient registration study in Japan.[354] Large clinical studies in Western countries have also shown that antihypertensive treatment reduces the incidence of heart failure in hypertensive patients.[355]

Many patients with heart failure have a normal or low blood pressure. Therefore, in patients with heart failure, antihypertensive drugs are not necessarily used for reducing blood pressure but, more importantly, for improving the QOL and prognosis.

Heart failure due to systolic dysfunction. RA system inhibitors improve the long-term prognosis of chronic heart failure and myocardial infarction and reduce the frequency of hospitalization regardless of the presence or absence of symptoms of heart failure or the degree of left ventricular dysfunction.[283,353,356–361] Treatment with β-blockers should be started at a low dose and increased gradually with caution. β-blockers improve the prognosis of patients with heart failure accompanied by systolic dysfunction and reduce the frequency of hospitalization.[347,362–365] Added to them, diuretics are used for the treatment and prevention of organ congestion. Therefore, the combination of an RA inhibitor+β-blocker+diuretic is a standard treatment for heart failure.[366] Moreover, the addition of an aldosterone antagonist further improves the prognosis of patients with severe heart failure undergoing the standard treatment.[282,320]

The doses of RA system inhibitors and β-blockers that improved the prognosis of heart failure in large clinical studies were higher than those used for the treatment of hypertension in Japan. However, as the RA system is activated in heart failure, RA system inhibitors may induce hypotension. Therefore, their administration should be started at a low dose (for example, 1/4–1/2 of a tablet regardless of the dosage form), and the dose should be gradually increased by confirming the absence of adverse effects such as hypotension and renal dysfunction. In addition, the use of β-blockers should be attempted as much as possible after RA system inhibitors regardless of the severity of heart failure, but utmost caution is necessary at the beginning of their use because of the risk of exacerbating heart failure. In patients with systolic dysfunction, the administration of β-blockers should be started at a very low dose (1/8–1/4 of the dose for hypertension), and the dose should be increased slowly by confirming the absence of heart failure, bradycardia and hypotension.

In hypertensive patients with heart failure due to systolic dysfunction, the treatment of hypertension is important, because the left ventricular function is markedly affected by afterload in patients with heart failure, and hypertension suppresses the left ventricular function and aggravates heart failure. In addition, as hypertension promotes left ventricular remodeling and the progression of myocardial damage, treatment of hypertension is important to improve the long-term prognosis. Long-acting dihydropyridine Ca channel blockers have been shown not to worsen the prognosis of heart failure patients.[295,367] Therefore, if a sufficient blood-pressure-lowering effect cannot be obtained with antihypertensive drugs used for the standard treatment of heart failure, a long-acting dihydropyridine Ca channel blocker may be added.

Heart failure due to diastolic dysfunction. Impairment of diastolic, but not systolic, function is the primary cause of heart failure, in nearly half of the patients hospitalized due to heart failure. Hypertensive heart disease is the most frequent underlying disease, particularly in elderly and female patients. In patients with hypertensive heart disease, the left ventricular diastolic dysfunction 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 improve diastolic function. In addition, as tachycardia, particularly atrial fibrillation, often induces heart failure, its prevention and appropriate control of the heart rate are important. The possibility of diastolic dysfunction due to latent coronary artery diseases should also be considered. Although there have been few reports on the treatment of heart failure due to diastolic dysfunction, ARBs reduce the frequency of hospitalization as well as preserving systolic function.[361]

c. Cardiac hypertrophy

Cardiac hypertrophy is caused by pressure load and often regresses through sustained antihypertensive treatment. Epidemiological studies have revealed that cardiac hypertrophy is one of the independent factors that determine the prognosis of hypertensive patients. The mortality rate and incidence of cardiac events or heart failure due to coronary artery disease are high in patients with cardiac hypertrophy.[368] The incidence of cardiac events and sudden death decreases in patients who show regression of cardiac hypertrophy by antihypertensive treatment compared with those who do not.[369,370] As both systolic and diastolic hypertensions serve as stimuli of cardiac hypertrophy, both must be controlled for its treatment.

There are few clinical trials specifically designed to directly compare the cardiac hypertrophy-regressing effects among various antihypertensive drugs. A meta-analysis of large clinical trials has reported that RA system inhibitors and long-acting Ca channel blockers are the most effective drugs.[371] There are also reports in Japan that a more marked cardiac hypertrophy-regressing effect was observed by the concomitant use of aldosterone antagonists with ACE inhibitors or ARBs.[372,373] However, the most important factor in the regression of cardiac hypertrophy is a sufficient decrease in blood pressure, so that all drugs widely used as the first choice today are expected to regress cardiac hypertrophy through sustained control of blood pressure.[374]

d. Atrial fibrillation (prevention)

Atrial fibrillation increases the incidence of, and mortality due to, cardiovascular events 2–5 times, because it markedly increases the risk of cardiogenic brain embolism.[375,376] Hypertension is the most important risk factor for atrial fibrillation.[377] Particularly, left ventricular hypertrophy and left atrial dilation are independent risk factors for the new onset of atrial fibrillation. Atrial fibrillation decreases with the regression of left ventricular hypertrophy by antihypertensive treatment.[378] As hypertension increases the risk of stroke and arterial embolism in patients with chronic atrial fibrillation, blood pressure control is important in such patients.[379,380]

Recently, many large clinical studies have reported that the new onset of atrial fibrillation can be prevented by RA system inhibitors.[381,382] RA system inhibitors have been shown to reduce the incidence of the onset of atrial fibrillation in patients with heart failure complicated by paroxysmal atrial fibrillation.[383] In Japan, ACE inhibitors are reported to reduce the transition rate from paroxysmal to chronic atrial fibrillation.[384] Therefore, sufficient blood pressure control primarily using RA system inhibitors is recommended from the point of view of preventing atrial fibrillation in patients with hypertension, particularly if it is accompanied by left ventricular hypertrophy or left atrial dilation.[385]

POINT 6C
Kidney diseases

1. **As the risk of cardiovascular accidents is high in patients with chronic kidney disease (CKD), its early detection is extremely important. For this purpose, urinalysis and calculation of the estimated glomerular filtration rate (eGFR) should be performed in all hypertensive patients.**
2. **Albuminuria is closely related to the progression of kidney damage and the occurrence of cardiovascular disease (CVD), and its control is important for the simultaneous protection of the heart and kidneys.**
3. **The three principles of blood-pressure-lowering therapy are: (1) achieving the target of blood pressure control, (2) inhibition of the renin–angiotensin system and (3) control/normalization of the urinary albumin or protein levels.**
4. **Regarding lifestyle, smoking cessation, reduction of salt intake, maintenance of an appropriate body weight and restriction of protein intake according to renal function should be practiced. Exercise guidance should be given depending on renal function.**
5. **Target blood pressure should be $<130/80$ mm Hg; if the urinary protein level is $\geqslant 1$ g per day, it should be $<125/75$ mm Hg.**
6. **An ACE inhibitor or ARB is the first choice, and the dose should be increased according to the level of urinary albumin excretion. If the serum creatinine level is $\geqslant 2$ mg dl^{-1}, its administration should be started at a low dose, with due attention to possible increases in the serum creatinine and potassium levels.**
7. **Combination therapy with several antihypertensive drugs is often required. In using diuretics, thiazides should be selected if the GFR is 30 ml min^{-1} per 1.73 m^2 or higher, and loop diuretics should be selected if it is less than 30 ml min^{-1} per 1.73 m^2.**
8. **For patients undergoing hemodialysis, antihypertensive drugs should be selected considering the drug metabolism, excretion route and dialyzability.**

3) KIDNEY DISEASES

a. Renal function and blood pressure

Hypertension causes functional or structural changes to varying degrees in the kidney from an early stage. Renal dysfunction may also cause hypertension. Hypertension and the kidney are closely related to each other, and a vicious circle is established as hypertension exacerbates renal dysfunction, and vice versa. Therefore, strict management of blood pressure as well as treatment of the primary disease is important.

Renal function declines with age after the 30s, and the GFR is usually considered to decrease at a rate of about 1 ml min^{-1} year^{-1}, but age-associated decreases in the GFR estimated from the Japanese health screening data have been reported to be very small (about 0.3 ml min^{-1} year^{-1}).[386] However, it may decrease at a rate of 4–8 ml min^{-1} year^{-1} in hypertensive patients.[387] There is no J-shaped curve between the occurrence of renal insufficiency and blood pressure level, and the incidence of end-stage renal failure is lowest at the optimal blood pressure and increases with blood pressure.[388,389]

In Japan, major causes of chronic dialysis are diabetic nephropathy, glomerulonephritis and nephrosclerosis. The number of patients undergoing chronic dialysis has steadily increased, and diabetic nephropathy and nephrosclerosis are primary causes of this increase. In contrast, the number of new patients who become dependent on dialysis due to chronic glomerular nephritis has begun to decrease.[138] Patients with CKD have few symptoms, and the progression from advanced renal dysfunction to end-stage renal failure is difficult to prevent. Therefore, the early detection and treatment of renal damage are important.

Table 6-3 Formula for GFR estimation, definition and staging of CKD

GFR estimation formula for Japanese:

eGFR$=194\times Cr^{-1.094}\times age^{-0.287}\times 0.739$ (if female).

Definition of CKD:

(1) kidney damage clearly indicated by urinalysis, imaging studies, hematological tests, and pathological examinations. Proteinuria is of particular importance.
(2) GFR <60 ml min^{-1} per 1.73 m^2.
Continuation of (1) or (2) or both for 3 months or longer.

Staging of CKD

Stage	*Explanation of severity*	*Staging by GFR (ml min^{-1} per 1.73 m^2)*
	High-risk group	$\geqslant 90$ (with risk factors for CKD)
1	Kidney disorder is present, but the GFR is normal or enhanced	$\geqslant 90$
2	Kidney disorder is present, and the GFR is slightly reduced	60–89
3	The GFR is moderately reduced	30–59
4	The GFR is markedly reduced	15–29
5	Renal insufficiency	<15

'D' is attached to indicate a dialysis patient (hemodialysis, peritoneal dialysis), and 'T' to indicate a recipient of kidney transplantation.

b. Chronic kidney disease and cardiovascular disease

Renal dysfunction and proteinuria are known to be risk factors for end-stage renal failure,[161,390–394] but they have also recently been found to be strong risk factors for CVD.[11,12,131,132] The concept of CKD was introduced for preventing the occurrence of CVD as well as renal insufficiency by the early detection and treatment of renal diseases.[395] Table 6-3 shows a definition of CKD, criteria for its staging and a formula for the calculation of the eGFR prepared by the Japanese Society of Nephrology on the basis of inulin clearance.[162] It should be noted that, in CKD patients, the CVD morbidity and mortality are several times or even more than 10 times higher than the incidence of end-stage renal failure.[393] The eGFR should be calculated, and urinalysis should be performed, in all hypertensive patients for the early detection of CKD. If dip-stick proteinuria is 1+ or higher, quantitative evaluation should be made according to the urinary protein/creatinine ratio, and in patients with diabetic nephropathy, the urinary albumin/creatinine ratio should be measured.

CKD has been shown to be a risk factor for CVD not only in the general population[11,12,131,132,393,394,396] but also in patients with heart failure,[397] myocardial infarction,[398] diabetes mellitus[399] and hypertension,[400] and in elderly people.[401] As the risk of CKD is significant even after correction for classical risk factors, including hypertension, dyslipidemia and diabetes mellitus, CKD itself is considered to be involved in the development of CVD. The proposed mechanism may involve oxidative stress, inflammation and abnormal Ca-P metabolism, which are called non-classical risk factors.[395] CVD and CKD are considered to have a common basis, and latent CVD is likely to be

present in CKD.[402] In fact, 50% or more stenosis has been found in the coronary artery of approx 50% of patients with no history of heart disease at the initiation of dialysis.[403]

Microalbuminuria has been established as a risk factor for the development of overt nephropathy and death in diabetic patients,[404,405] but it has also recently been shown to be a strong predictive factor for the occurrence of CVD in hypertensive patients and the general population.[406,407] Moreover, a high prevalence of cardiovascular complications such as lacunar infarction[408] and a low survival rate[128,164,406,409] have been reported even in patients with albuminuria of about 10 mg g^{-1} creatinine (Cr). In diseases in which urinary albumin is not observed at an early stage (hypertension, diabetes mellitus, etc.), the appearance of albumin in urine even at a very low level has important pathological significance. The 2007 ESH/ESC Guidelines state that the term 'microalbuminuria' may be misleading because it falsely suggests a minor damage.[66] Albuminuria is correlated with impairment of the vascular endothelial function and is closely related to abdominal obesity and the salt sensitivity of blood pressure, but details of the mechanism that relates albuminuria to CVD are unknown.

Epidemiological studies have shown that CKD patients are more prevalent than expected. The population with CKD at stage III or above is estimated to be 8.1% of the adult population in the United States[410] and about 10% in Japan (excluding patients undergoing hemodialysis in both countries). In Japan, with aging of the population, patients with lifestyle-related diseases such as obesity, hypertension and diabetes mellitus are increasing. Thus, early detection, treatment and prevention of CKD are important.

c. Diabetic nephropathy

Diabetic nephropathy is the leading cause for initiation of dialysis in Japan, accounting for about 40% of diabetic patients. The increase in diabetic nephropathy has been related to an increase in the number of diabetic patients and their low consultation rate and adherence, and nephropathy is considered to be present in about 40% of diabetic patients in Japan.[411] Diabetic nephropathy is staged according to the urinary albumin excretion rate, and its staging is not consistent with that of CKD. Some diabetic patients show a normal urinary albumin level but have GFR <60 ml min^{-1} per 1.73 m^2. As type II diabetes occurs more frequently in hypertensive patients, kidney damage due to obesity or hypertension underlies the disease in some patients. In patients with diabetic nephropathy, the survival rate is poor, and the mortality rate increases with the urinary albumin level and severity of renal dysfunction. Periodic monitoring of the urinary albumin level and GFR is necessary.

Treatment for diabetic nephropathy involves the intensive management of multiple risk factors, and antihypertensive treatment is the same as that for CKD. However, a more aggressive blood-pressure-lowering treatment may be effective, and a decrease in urinary albumin excretion by controlling systolic blood pressure to $\leqslant$120 mm Hg has been reported.[412,413] Recently, it has also been shown in Japan that the progression of nephropathy can be prevented, and its remission or regression achieved by intensive treatment, and that the remission or regression of diabetic nephropathy is closely related to the prevention of CVD as well as renal failure.[414] SMART[415] and INNOVATION[416] indicated that the administration of RA system inhibitors as well as a sufficient reduction in blood pressure is needed for inducing remission and regression. ARBs at a high dose are particularly effective in advanced microalbuminuria with a urinary albumin level of 100–300 mg g^{-1} creatinine.[416,417]

d. Lifestyle modifications

An inappropriate lifestyle is the major background factor for the present increase in CKD patients. Obesity and an excessive salt intake accelerate kidney damage by mechanisms dependent on and independent of blood pressure. Lifestyle modifications are the most basic and important factor in the treatment of CKD, in which maintaining an appropriate body weight, restricting salt intake and cessation of smoking are essential.

There are reports that obesity is involved in the development of end-stage renal failure and proteinuria and that proteinuria is alleviated by weight reduction.[418–420] In addition, smoking has been reported to exert adverse effects on proteinuria and renal dysfunction in both diabetic and non-diabetic nephropathy.[421,422] Considering the high risk of cardiovascular death in CKD patients, maintaining an appropriate body weight and smoking cessation are crucial.

Restriction of salt and protein intake is important to control blood pressure and prevent the progression of renal dysfunction.[423,424] As salt sensitivity is often enhanced in hypertensive patients with CKD, restriction of salt intake would be effective for reducing blood pressure. Salt restriction enhances the hypotensive and antiproteinuric effects of ACE inhibitors and ARBs. Salt intake should be restricted to $\leqslant$6 g day^{-1} in chronic renal insufficiency and to $\leqslant$4–5 g day^{-1} in patients with resistant hypertension or edema. Restriction of protein intake has been shown to prevent the progression of renal insufficiency

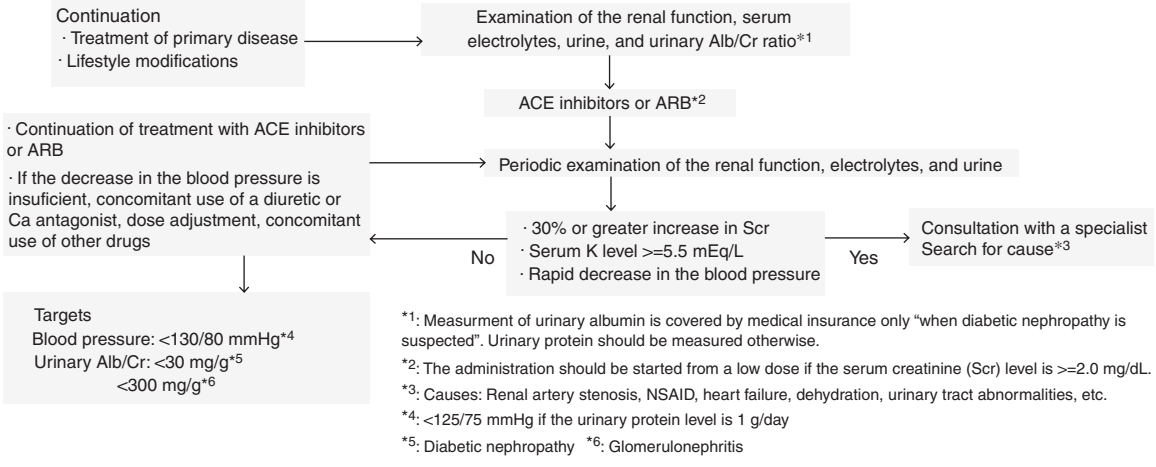

Figure 6-1 Therapeutic plans for hypertension complicated by chronic kidney diseases (CKD).

and reduce the relative risk of death.[425] Protein intake should be restricted to 0.6–0.8 g kg^{-1} standard weight per day in patients with CKD with stage 3 (GFR < 60 ml min^{-1} per 1.73 m^2) or above.[424]

Exercise should be guided according to the renal function. Vigorous exercise that would reduce the renal blood flow should be avoided in patients with renal insufficiency.[423]

e. Treatment using antihypertensive drugs

The objective of antihypertensive treatment in CKD patients is to inhibit or prevent the progression of renal dysfunction and to prevent the occurrence or recurrence of CVD by reducing blood pressure (Figure 6-1). The three principles of blood-pressure-lowering treatment for CKD patients are: (1) achieving the target of blood pressure control, (2) suppressing the RA system and (3) reducing or, if possible, normalizing urinary albumin and protein excretion.

The higher the blood pressure, the higher the rate of decline in renal function;[387] therefore, management of blood pressure is extremely important for inhibiting the decline in renal function. According to a meta-analysis of randomized controlled trials, the development of end-stage renal failure and doubling of the serum creatinine level were inhibited by reducing systolic blood pressure to < 130 mm Hg.[426] Therefore, the target of blood pressure control should be < 130/80 mm Hg. According to the MDRD Study,[427] the target of blood pressure control should be < 125/75 mm Hg if urinary protein excretion is ⩾ 1 g day^{-1}. Although RA system inhibitors reduce urinary albumin and protein excretion and have pressure-independent renoprotective actions, further renoprotection can be obtained by achieving a sufficient reduction in blood pressure.[417,428] If blood pressure is ⩾ 130/80 mm Hg, drug therapy should be started in principle with simultaneous lifestyle modifications, and blood pressure and urinary albumin or protein excretion should be followed up.

Many clinical studies have shown the renoprotective effect of RA system inhibitors, and an ACE inhibitor or ARB is the first choice for the treatment of CKD. As they are particularly effective in patients with a high urinary protein level,[426,429,430] an ACE inhibitor or ARB should be administered, except in special cases such as those with contraindications. Dissociation is observed between the blood-pressure-lowering doses and anti-proteinuric doses of RA system inhibitors.[431,432] Therefore, their doses should be titrated according to the urinary protein or albumin excretion as well as the blood pressure level. Added to this, a combination of an ACE inhibitor and an ARB has been suggested by meta-analysis to be more effective than either drug alone in reducing urinary albumin or protein excretion.[433,434]

Usually, RA system inhibitors produce gradual reductions in blood pressure, and they rarely cause a rapid decrease in blood pressure after administration. If a rapid decline in blood pressure is observed, it may be caused by dehydration, extreme restriction of salt intake, excessive administration of a diuretic or renal artery stenosis. Measurement of home blood pressure is effective in detecting a rapid decline in blood pressure. If an excessive decrease in blood pressure (⩾ 30 mm Hg systolic) is observed immediately after administration, its cause should be evaluated, and referral to a hypertension specialist should be considered.

Advanced renal dysfunction was used to be considered a contraindication for ACE inhibitors, but their renoprotective effect is now known to be particularly notable in patients with reduced renal function.[429,435] In addition, it has been reported that RA system inhibitors suppress the occurrence of CVD and that this effect is particularly marked in CKD patients.[400,436] Therefore, from the point of view of the simultaneous protection of the heart and kidneys, it is recommended, even when the serum creatinine level is ⩾ 2 mg per 100 ml, to start administering RA system inhibitors from a low dose and increase the dose gradually, with careful monitoring of the serum creatinine and potassium levels.

Urinary protein not only indicates glomerular or vascular damage but is also considered to exacerbate the renal function. Indeed, decreases in urinary protein level have been reported to have a preventive effect against the progression of renal dysfunction regardless of blood pressure.[390,430,437] Furthermore, a decrease in urinary albumin has been shown to be closely related to a decrease in CVD.[164,438] Therefore, reducing the urinary protein or albumin excretion to a normal level as much as possible is important for preventing the progression of renal dysfunction and the occurrence of CVD. For reducing urinary protein or albumin excretion, the administration of an ACE inhibitor or ARB along with strict blood pressure control is necessary, and the use of either drug at a high dose or the combination of both is also useful.

RA system inhibitors ameliorate glomerular hypertension/hyperfiltration by reducing the systemic blood pressure and dilating the efferent arterioles, and therefore the GFR may decrease occasionally. However, this decrease is a reflection of functional change rather than the progression of renal tissue damage, because the GFR returns to its previous level on discontinuing the drug.[439] As there is also a report that in those whose renal function declined temporarily shortly after the beginning of the administration, renal function was well maintained over a long period thereafter, careful observation as to whether the increase in serum creatinine level is mild (⩽ 30%) is recommended. As a decrease in renal function usually becomes apparent within a few days after commencing administration, serum creatinine level should be measured before and 2 weeks (1 week if possible) after the first administration. If exacerbation of renal function is noted, its cause, such as bilateral renal artery stenosis, should be sought. An increase in the serum K level may also be observed, and its treatment comprises the concomitant use of a diuretic or administration of sodium bicarbonate. The administration of NSAIDs should be avoided, because they exacerbate renal function and increase the serum K level. Added to this, as ACE inhibitors are excreted via the kidney, with some exceptions, their dose adjustment is necessary in patients with reduced renal function. However, dose adjustment is mostly unnecessary for ARBs, which are excreted via the bile.

In CKD patients, multiple drug combination therapy is necessary to achieve the target blood pressure.[387] In CKD, the salt sensitivity of blood pressure is enhanced, and an excess body fluid volume is involved in the aggravation of hypertension. In addition, the hypotensive and antiproteinuric effects of RA system inhibitors are dependent on the body fluid volume. Therefore, management of the body fluid volume is extremely important. If the body fluid volume cannot be controlled sufficiently by salt restriction guidance, the hypotensive and antiproteinuric effects of RA system inhibitors are expected to be enhanced by the concomitant use of a diuretic. A diuretic was used concomitantly in most patients in a clinical study that showed the renoprotective effect of RA system inhibitors. The Guidelines of the National Kidney Foundation (NKF) suggest diuretics as the second choice.[440] A low dose of a thiazide diuretic should be used if the GFR is 30 ml min^{-1} per 1.73 m^2 or higher, and a loop diuretic should be used if the GFR is below this level. Attention to electrolyte abnormalities such as hypokalemia and dehydration is necessary in aggressive diuretic treatment. Recently, aldosterone blockers have been reported to reduce urinary protein excretion,[441,442] but they should be administered with utmost caution to patients with renal dysfunction because of the risk of hyperkalemia.

Evidence related to the renoprotective effect of long-acting Ca channel blockers is insufficient. The usefulness of Ca channel blockers lies in their strong hypotensive effect, which is unaffected by disease type. Patients with renal dysfunction often exhibit grade II or III hypertension, and multiple drug combination therapy including a Ca channel blocker is often required to achieve the target of blood pressure control. Indeed, a combination of an ARB and a Ca channel blocker has been reported to have more favorable hypotensive and antialbuminuric effects than an increase in the dose of an ARB.[285] In the REIN-2,[443] however, the occurrence of end-stage renal failure could not be prevented even by further reducing blood pressure with a combination of an ACE inhibitor and a Ca channel blocker. Ca channel blockers have diverse characteristics, and clinical studies reported that some Ca channel blockers showed antiproteinuric effects similar to those of ACE inhibitors.[444–446] Added to this, differences in the antiproteinuric effect were reported among Ca channel blockers when they were combined with RA system inhibitors.[268,447] If blood pressure cannot be reduced sufficiently even by multiple drug combination therapy, conditions such as secondary hypertension should be considered even in CKD patients, and consultation with a specialist is recommended.

f. Patients undergoing dialysis

In patients undergoing hemodialysis, the U-shaped phenomenon is observed in the relationship between blood pressure and survival, and mortality rate is lowest when systolic blood pressure is 120–160 mm Hg.[488–490] The relationship between blood pressure and survival is affected by the history of dialysis or the duration of follow-up, and a poor outcome is correlated with a low blood pressure in an early observation period but with a high blood pressure over a long follow-up period.[449] As prognosis of dialysis patients is poor, and risk factors other than blood pressure markedly affect it, the relationship between blood pressure and outcome is difficult to clarify. In addition, because of problems such as the timing of measurements, as blood pressure differs before and after dialysis, insufficient evidence has been obtained regarding blood pressure control in dialysis patients.

Recently, the usefulness of ABPM and home blood pressure has been suggested.[451, 452] Particularly, it has been reported that the mean of home blood pressures measured 3 times a day over a week better reflects survival than blood pressure measured before or after dialysis, and that a provisional target of systolic blood pressure would be 125–145 mm Hg.[451]

An increase in pulse pressure is correlated with a poor outcome in dialysis patients, and the outcome is poorer as the diastolic pressure becomes lower at the same systolic pressure, and as systolic blood pressure becomes higher at the same diastolic pressure.[453] In addition, the overall mortality rate has been reported to rise significantly when the weekly mean of the pulse pressure based on home blood pressure measured twice a day exceeds 70 mm Hg.[452] Moreover, a decrease in blood pressure during dialysis and orthostatic hypotension immediately after dialysis have also been reported to be independent risk factors of all-cause mortality.[454]

Recently, the PWV, AI and ABI are used as indices of vascular damage, and have also been shown to be related to the survival of dialysis patients.[455,456] In addition, cardiac hypertrophy is observed in a high percentage of dialysis patients, and changes in left ventricular mass are also related to survival.[457] As risk factors other than blood pressure are closely related to the survival of dialysis patients, antihypertensive treatment should be designed by considering various indices rather than blood pressure alone, but this is a subject for future studies.

As for the therapeutic approach, volume-dependent components of blood pressure should be controlled first. The dry weight (target body weight necessary for body fluid volume management) must be set appropriately, and guidance should be given to limit the body weight gained from one dialysis session to the next within 5% of the dry weight.

Urinary volume is minimal in many dialysis patients, and diuretics are ineffective. However, a urinary volume of several hundred milliliters per day may be observed even after the initiation of dialysis, and loop diuretics such as furosemide may be used in such patients. The use of diuretics has been suggested to contribute to the maintenance of residual renal function and facilitate body weight management.[458] As a relatively high dose is often required, attention to adverse effects such as hearing disturbance is needed.

Treatment using antihypertensive drugs is necessary if hypertension persists even after achieving an appropriate dry weight. Drugs should be selected considering the metabolism, the excretion route, dialyzability and duration of action, as well as the mechanism of action. If a marked decrease in blood pressure is observed during dialysis, adjustments such as omitting the administration of the drug in the morning of the day of dialysis are necessary. There is as yet no consensus on drugs inhibiting cardiovascular accidents, but Ca channel blockers,[459] β-blockers[460] and ACE inhibitors[455,461,462] have been reported to be effective. ARBs have recently been reported to be effective in inducing the regression of cardiac hypertrophy and improving the PWV.[462–464] There is also a report that ARB are useful for protecting the residual renal function in patients undergoing peritoneal dialysis.[465]

Non-dialyzable drugs should be selected to minimize changes in blood pressure due to dialysis. Ca channel blockers and ARBs have low dialyzabilities and cause less changes in blood pressure during dialysis. Many ACE inhibitors are dialyzable, but some are not. ACE inhibitors may induce anaphylactic shock-like symptoms if a negatively charged dialytic membrane is used. This applies to dialyzers using a polyacrylonitrile membrane and adsorbers using dextran sulfate cellulose, and they are contraindications for ACE inhibitors. ACE inhibitors and ARBs have been reported to exacerbate renal anemia and increase the required amount of erythropoietin. Whereas α-blockers have no dialyzability and are easy to use, orthostatic hypotension, which is one of the adverse effects, may interfere with the implementation of dialysis. Many β-blockers are lipid-soluble and are not dialyzable. As they suppress cardiac function, attention to the occurrence of heart failure and an increase in serum K level is necessary in dialysis patients with an unstable body fluid volume.

POINT 6D
Vascular diseases

1. **Acute aortic dissection requires immediate blood pressure reduction and pain control. It is recommended to control the systolic blood pressure to <120 mm Hg.**
2. **In chronic aortic dissection or aortic aneurysm, strict antihypertensive treatment and guidance regarding smoking cessation must be given, and careful observation for aortic expansion/dissection is necessary.**
3. **In patients with atherosclerotic peripheral arterial disease, a supervised exercise training program is recommended. Added to this, an intensive risk factor management including strict control of blood pressure is expected to reduce the concurrence of cardiovascular events.**

4) VASCULAR DISEASES

a. Aortic aneurysm

Aortic dissection. Acute aortic dissection is a hypertensive emergency that requires immediate blood pressure reduction, pain control and complete rest. It is recommended to maintain systolic blood pressure at 100–120 mm Hg by continuous infusion of a Ca channel blocker (nicardipine, diltiazem), nitroglycerin, nitroprusside or a β-blocker, but there is no established evidence regarding target systolic pressure or the effect of a β-blocker in the combination.[466] When a diltiazem and a β-blocker are used concomitantly, caution against bradycardia is necessary. The site and morphology of dissection and the presence or absence of peripheral circulatory disorders due to the stenosis/obstruction of arteries branching from the aorta should be evaluated continuously and carefully, and surgical treatment should be considered if necessary.

In chronic aortic dissection, strict control of blood pressure for prevention of re-dissection or rupture is also recommended, although there is no established evidence regarding the target systolic blood pressure or the selection of antihypertensive drugs.

Aortic aneurysm. As aortic aneurysm is asymptomatic in most patients, it is often detected incidentally on health screening or examination for other diseases. However, once it ruptures, the mortality rate is very high, and, even if patients come to the hospital in a stage of threatened rupture, the survival rate is low because of unstable hemodynamics.[467] Therefore, if aortic aneurysm has been diagnosed, surgical treatment should be considered at an appropriate time without overlooking the tendency of enlargement.[468]

Strict antihypertensive treatment for thoracic aortic aneurysm is important, and systolic blood pressure is recommended to be maintained at 105–120 mm Hg, although no evidence regarding the target of blood pressure control has been established. As for the selection of antihypertensive drugs, there is a report of a randomized controlled trial in which the administration of β-blockers was effective for the prevention of aneurysm enlargement in patients with Marfan's syndrome.[469] It has been reported that treatment with ARBs in pediatric patients with Marfan's syndrome significantly slowed the rate of progressive aortic root dilation in a recent small-cohort study.[470] A randomized clinical trial comparing aortic root growth in patients with Marfan's syndrome receiving atenolol or losartan is ongoing.[471]

However, there is no established evidence regarding the effects of strict antihypertensive therapy or β-blockers on abdominal aortic aneurysm. In patients admitted with a diagnosis of abdominal aortic aneurysm, the frequency of ruptured aneurysm was reported to be significantly lower in those who received ACE inhibitors before admission in a recent large case–control study.[472] Undoubtedly, atherosclerosis is closely associated with the etiology of abdominal aortic aneurysm. Whereas the effectiveness of internal treatment for the prevention of enlargement or rupture of aneurysm has not been confirmed by large randomized controlled studies, the importance of smoking cessation has been reported.[473]

b. Atherosclerotic peripheral arterial disease

Peripheral circulatory disorders due to atherosclerotic vascular lesions are classified according to their severity into Fontaine grade I (no symptom, numbness, coldness), grade II (intermittent claudication), III (pain at rest) and IV (gangrene/ischemic ulcer). The objectives of treatment are the alleviation of symptoms of ischemia and prevention of cerebrocardiovascular events, which often complicate peripheral circulatory disorders. Systematic execution of an exercise program under supervision has been reported to be effective for alleviating ischemic symptoms in the lower limbs.[474] Strict blood pressure control is more important for preventing cerebrocardiovascular events rather than for improving ischemic symptoms in the lower limbs.[475] Therefore, appropriate antihypertensive drugs should be selected according to the complications or patient's conditions that require careful use of drugs (see Chapter 5). The administration of ACE inhibitors to patients with symptomatic atherosclerotic peripheral arterial disease has been reported to have suppressed cerebrocardiovascular events by about 25% in a large randomized controlled study.[319] β-blockers have been considered to exacerbate ischemic symptoms in the lower limb; however, their safe use has been reported in a randomized study involving patients with intermittent claudication.[476] They can be used in patients with heart failure and ischemic heart disease, which often complicate atherosclerotic peripheral arterial disease. It is recommended to refer patients with severe atherosclerotic peripheral arterial disease to a specialist, because they may have indications suggesting percutaneous transluminal angioplasty, surgical vascular reconstruction and vascular regenerative therapy.

Citation Information

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GUIDELINES (JSH 2009)

Chapter 7. Hypertension complicated by other diseases

Hypertension Research (2009) **32,** 51–56; doi:10.1038/hr.2008.11

POINT 7A
Diabetes mellitus

1. **The target of blood pressure control in hypertension complicated with diabetes mellitus should be <130/80 mm Hg.**
2. **When selecting antihypertensive drugs for diabetic hypertensive patients, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) is recommended as the first choice because of the positive effects on glucose and lipid metabolism and for the prevention of complications, and a Ca blocker and low-dose of thiazide diuretic should be used concomitantly for blood pressure control. When hypertension is complicated with angina on effort or old myocardial infarction, β-blockers, which have a cardioprotective effect, can also be used for blood pressure control.**

Dyslipidemia

1. **When selecting antihypertensive drugs for hypertension with dyslipidemia, α-blockers, ACE inhibitors, Ca channel blockers, and ARBs that improve or do not exacerbate lipid metabolism are considered appropriate.**

1) DIABETES MELLITUS

In diabetic patients, blood pressure should be measured in both a recumbent and standing as well as a sitting position, because orthostatic hypotension is observed in some patients. The frequency of hypertension is about two times higher in diabetic than in nondiabetic individuals according to results in Japan.[477] In addition, the frequency of diabetes mellitus is two to three times higher in hypertensive patients,[477] and an etiological relationship between the two diseases has been suggested, that is, type II diabetes and hypertension are major factors of metabolic syndrome (discussed later), having insulin resistance as a common background factor.

Microvascular complications of diabetes mellitus include nephropathy, neuropathy and retinopathy. These conditions may not only cause severe impairment of physical functions and quality of life (QOL) but also affect survival. Both diabetes mellitus and hypertension are important risk factors for macrovascular disease due to atherosclerosis, and the frequencies of cerebrovascular disease and ischemic heart disease are known to be markedly elevated by their concurrence.[478] Therefore, strict control of blood pressure as well as blood glucose level is important for the prevention and treatment of micro- and macrovascular diseases.

With regard to the blood pressure control level in hypertensive patients with diabetes mellitus, the risk of cardiovascular events was significantly reduced in a group managed with a target diastolic pressure of ⩽80 mm Hg compared with a group managed with a target of ⩽85 or ⩽90 mm Hg in HOT,[139] in which antihypertensive treatment was performed primarily using Ca channel blockers. Moreover, the results of UKPDS39 showing that the risk of macro- and microvascular diseases was markedly reduced by lowering mean blood pressure from 157/87 to 147/82 mm Hg[479] and the results of a clinical trial, which also indicated the usefulness of antihypertensive treatment in normotensive diabetic patients,[480] suggest that the therapeutic effect can be increased by setting a lower target of blood pressure control for hypertension complicated with diabetes mellitus. On the basis of these results, the JNC-VI, 1999 WHO/ISH Guidelines, and JSH2000 Guidelines recommended the initiation of antihypertensive treatment for diabetic patients with a high-normal blood pressure of ⩾130/85 mm Hg. However, the recommendations of the American Diabetic Association (ADA) in 2007,[481] JNC7 (2003),[38] and ESH/ESC Guidelines (2007)[66] set <130/80 mm Hg as a target level of blood pressure control by setting aside the category of high-normal blood pressure on the basis of the results of the HOT[139] and UKPDS39.[478] In the Tanno–Sobetsu cho Study of Japan,[482] the mortality rate due to cardiovascular disease was significantly higher in the group with a systolic pressure of ⩾130 mm Hg and a diastolic pressure of ⩾80 mm Hg than in the group with an optimal blood pressure of <120/80 mm Hg in borderline diabetic/diabetic patients. Therefore, the results in Japan also support a target blood pressure of <130/80 mm Hg for hypertensive patients with diabetes mellitus. Blood pressure control should be particularly strict in patients with diabetic nephropathy, and <125/75 mm Hg should be the target when the urinary protein level is ⩾1 g per day.

Treatment should be started when blood pressure is ⩾130/80 mm Hg. In diabetic patients with hypertension, nondrug therapies such as weight control and exercise therapy are expected to promote a decrease in blood pressure associated with an improvement in glucose tolerance through increased insulin resistance. Therefore, for hypertensives with diabetes mellitus, strict lifestyle modifications including weight control, exercise, and restriction of salt intake and the simultaneous initiation of antihypertensive medication are the principal treatments. If the target of blood pressure control is expected to be achieved solely through lifestyle modifications in patients with a blood pressure of 130–139/80–89 mm Hg, control through such modifications may be attempted over a period not exceeding 3 months.

In drug therapy treatment for hypertensives with diabetes mellitus, sufficient consideration of the effects of each antihypertensive drug on insulin sensitivity and glucose and lipid metabolism is necessary.

Diuretics and β-blockers have been reported to reduce insulin sensitivity and increase the triglyceride level. Furthermore, β-blockers make symptoms of hypoglycemia in diabetic patients less perceivable, and disadvantages of both drugs with regard to glucose metabolism have been suggested. In contrast, some β-blockers that reduce the peripheral vascular resistance have been reported to improve insulin resistance with no adverse effect on lipid metabolism. ACE inhibitors, ARBs,[483] and dihydropyridine Ca channel blockers, which improve insulin sensitivity and exert no adverse effect on lipid metabolism, are recommended from a metabolic point of view. A comparison of the three classes of drugs showed that ARBs and ACE inhibitors were more effective than Ca channel blockers in suppressing the new occurrence of diabetes mellitus,[195,198,295] suggesting that ARBs and ACE inhibitors have more favorable effects on insulin resistance than Ca channel blockers. Although α-blockers improve glucose and lipid metabolism, whether they prevent target organ damage is unclear.

With regard to the preventive effects of various antihypertensive drugs in diabetic hypertensive patients, ACE inhibitors have been shown to prevent declines in renal function and reduce the frequency of transition to dialysis therapy, even in nonhypertensive patients with type I diabetes accompanied by proteinuria.[484] In type II diabetic nephropathy, the J-MIND[485] performed in Japan showed that Ca channel blockers and ACE inhibitors have comparable effects on proteinuria and renal function in patients with diabetic nephropathy, and the UKPDS39[479] indicated that ACE inhibitors and β-blockers are equally effective in preventing microvascular disease in diabetic hypertensive patients. RENAAL,[140] IDNT,[467] IRMA-2,[486] and MARVAL[487] also suggested the effectiveness of ARBs for the treatment of type II diabetic nephropathy. In addition, in Japan, the SMART[415] and INNOVATION[416] studies also showed the usefulness of ARBs. Thus, ACE inhibitors and ARBs are clearly useful for the management of diabetic nephropathy, and their administration is recommended if microalbuminuria is observed regardless of the presence or absence of hypertension, but caution is needed because many of these treatments are not covered by medical insurance when blood pressure is $<130/80$ mm Hg.

In hypertensive patients with diabetes mellitus, CAPPP[488] showed the usefulness of ACE inhibitors, and the HOT[139] and Syst-Eur[489] studies reported the usefulness of Ca channel blockers for the prevention of cardiovascular accidents. UKPDS39[479] also indicated that treatment using an ACE inhibitor or a β-blocker was similarly useful. In IDNT,[435] ARBs induced a 4/3 mm Hg greater decrease in systolic pressure/diastolic pressure than did the placebos, and although no difference was noted in the preventive effect against myocardial infarction or stroke, it was significantly more effective in the prevention of congestive heart failure. In addition, Ca channel blockers showed an antihypertensive effect 3/3 mm Hg greater than the placebos, and although no difference in the preventive effect against heart failure was noted, they showed a significantly stronger preventive effect against myocardial infarction and a more marked preventive effect against stroke. These results suggest a difference between ARBs and Ca channel blockers in the preventive effect on cardiovascular disease. With regard to the outcome of macrovascular diseases in type II diabetic patients, LIFE[196] reported that ARBs were significantly more effective than β-blockers in preventing cardiovascular disease. Thus, ACE inhibitors, ARBs and Ca channel blockers have been confirmed to be useful for the prevention of cardiovascular accidents in diabetic hypertensive patients. As for a comparison between ACE inhibitors and Ca channel blockers, their preventive effects were evaluated in the smaller studies ABCD[490] and FACET,[491] and the results suggest that ACE inhibitors are more useful than Ca channel blockers. However, no difference was observed by subanalysis of ALLHAT,[492] and further evaluation is necessary to clarify the differences between the effects of ACE inhibitors and Ca channel blockers on macrovascular disease.

With regard to the selection of antihypertensive drugs for diabetic hypertensive patients, ACE inhibitors, ARBs, and long-acting dihydropyridine Ca channel blockers are recommended because of their effects on glucose and lipid metabolism and preventive effects on complications. However, considering evidence with regard to improvements in glucose metabolism and organ protection, a renin-angiotensin (RA) system inhibitor (ARB, ACE inhibitor) should be used first, and, if the decrease in blood pressure is insufficient, a Ca channel blocker or a low dose of a thiazide diuretic should be used in addition as a second choice; if a further decrease in blood pressure is necessary, three drugs should be employed simultaneously. In GUARD,[493] in which Ca channel blockers and diuretics were compared as a drug to be combined with an RA system inhibitor for the treatment of diabetic nephropathy, combination with a diuretic was more effective for controlling proteinuria, but combination with a Ca channel blocker was more effective for maintaining the eGFR. In patients with angina on effort or old myocardial infarction, β-blockers can also be used for blood pressure control because of their cardioprotective effects. Figure 7-1 shows a therapeutic guideline for hypertension with diabetes mellitus.

2) DYSLIPIDEMIA

As the J-LIT of Japan[494] has shown, the risk of atherosclerosis clearly increases when hypertension is complicated by hypercholesterolemia, and the aggressive management of both diseases is necessary in such patients. The results of recent clinical studies, including ASCOT-LLA,[496] suggest that the occurrence and recurrence of ischemic heart disease and stroke can be prevented by serum low-density lipoprotein (LDL)-cholesterol-reducing treatment in patients with hypertension with hyper-LDL-cholesterolemia, and the Japanese Guidelines for the Prevention of Atherosclerotic Diseases also propose

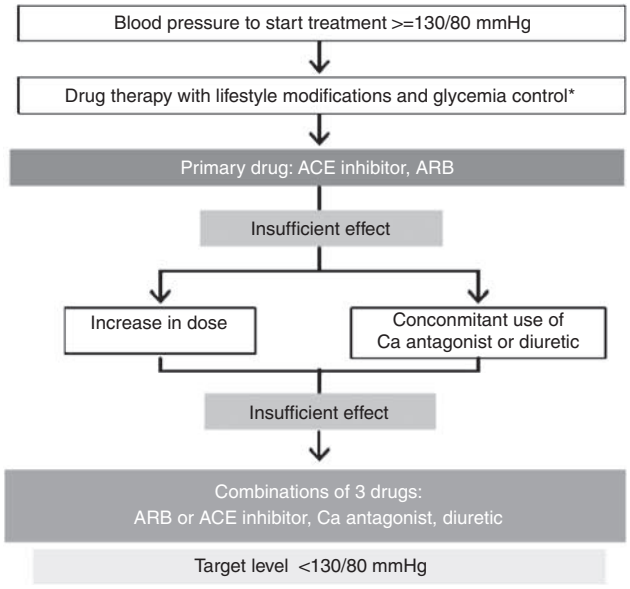

Figure 7-1 Treatment plan for hypertension complicated by diabetes mellitus. *If the blood pressure is 130–139/80–89 mm Hg, and the target of blood pressure control is expected to be achieved through lifestyle modifications, blood pressure control by such modifications may be attempted over a period not exceeding 3 months.

a stricter control of LDL-cholesterol level if it is complicated by risk factors including hypertension. For patients showing both hyper-LDL-cholesterolemia and hypertension, lifestyle modifications, that is, correction of obesity, restriction of saturated fatty acid, cholesterol, and alcohol intake, and an increase in the amount of exercise should be strongly advised. If hypercholesterolemia cannot be resolved by general treatment, drug therapy primarily using an HMG-CoA reductase inhibitor should be performed simultaneously. In patients with hypertension and hypercholesterolemia, the cholesterol level should be controlled to an appropriate therapeutic target level by lifestyle modifications and the use of antihypercholesterolemic drugs. If hypertriglyceridemia or hypo-high-density lipoprotein (HDL)-cholesterolemia is concurrent with hypertension, the presence of insulin resistance or metabolic syndrome should be considered, and this type of dyslipidemia should be corrected by lifestyle modifications and the use of drugs such as fibrates, in principle. If no improvement is noted in dyslipidemia even after practicing lifestyle modifications for 6 months or longer, drugs such as fibrates should be used to correct it.

Concerning the target of blood pressure control in hypercholesterolemic patients, subanalysis of the J-LIT[123] showed that the frequency of cardiovascular diseases increased significantly when blood pressure was $\geqslant$130/80 mm Hg in a hypercholesterolemic group with a total cholesterol level of $\geqslant$220 mg dl^{-1} under statin administration, whereas it increased significantly when blood pressure was $\geqslant$140/90 mm Hg in the group with a cholesterol level controlled to within a normal range. If future epidemiological studies yield similar results, the target of blood pressure control for dyslipidemic patients may be lowered. In selecting antihypertensive drugs for dyslipidemic patients, the effects of various antihypertensive drugs on lipid metabolism must be considered. Thiazide and loop diuretics at high doses are known to elevate the serum total cholesterol, triglyceride, and LDL-cholesterol levels, but whether thiazides at a low dose also increase lipids is unclear. β-blockers have been reported to increase the serum triglyceride level or reduce the HDL-cholesterol level. α-blockers reduce the serum cholesterol level and increase the HDL-cholesterol level. ACE inhibitors, ARBs, Ca channel blockers, and central sympathomimetic drugs have no effect on serum lipid levels.

For hypertensive patients with dyslipidemia, antihypertensive drugs that improve or have no adverse effect on, lipid metabolism, such as α-blockers, ACE inhibitors, Ca channel blockers, and ARBs, are desirable from a metabolic point of view.

POINT 7B
Obesity

1. **Hypertension accompanied with obesity is treated by drug therapy as well as by dietary and exercise therapies to control body weight. Antihypertensive drugs should be selected according to the characteristics of their effects on metabolism, and ARBs and ACE inhibitors are recommended.**

Metabolic syndrome

1. **Metabolic syndrome is also an important factor responsible for cardiovascular disease in Japan. Hypertension in patients with metabolic syndrome should be treated with attention to the correction of abdominal obesity and insulin resistance, and ARBs and ACE inhibitors are recommended.**

3) OBESITY

The frequency of hypertension is reported to be two to three times higher in obese than nonobese individuals.[496] In particular, excessive weight gain from a young age is an important risk factor for hypertension. The sympathetic nervous system, sodium retention/salt sensitivity and insulin resistance have been suggested to be involved in the etiology of hypertension accompanied by obesity. Sleep apnea syndrome is occasionally observed in obese patients, and it may be a factor involved in the progression of hypertension.

In treating hypertension, risk factors for cardiovascular disease, which often complicate obesity, must be reduced. Weight control through dietary and exercise therapies should be attempted first, but, if the decrease in blood pressure is insufficient even after guidance in weight control, drug therapy should be introduced. It is practical to select antihypertensive drugs on the basis of characteristics other than antihypertensive effect, and ACE inhibitors and ARBs are recommended because of their favorable effects on abnormal glucose metabolism and insulin resistance. In CASE-J,[195] a large clinical study performed in Japan, the new occurrence of diabetes mellitus was significantly lower in the group treated with the ARB candesartan even in the case of obesity. Thiazide diuretics exert no marked effect on metabolism if administered at half the routine dose. Hypertension with obesity is often resistant to treatment, and the concomitant use of a thiazide diuretic is useful in such patients.

4) METABOLIC SYNDROME

The concurrence of hypertension, dyslipidemia (hypertriglyceridemia, hypo-HDL-cholesterolemia), obesity and abnormal glucose metabolism has been shown by many epidemiological studies to synergistically increase the risk of atherosclerotic diseases, including ischemic heart disease. As insulin resistance is involved as a common background factor in these risk factors of atherosclerotic diseases, the condition has been referred to by various names including multiple risk factor syndrome, insulin resistance syndrome and visceral fat syndrome, but the term 'metabolic syndrome' proposed by the National Cholesterol Education Program (NCEP) ATP-III (2001) has recently become universal.[497] The diagnostic criteria of the NCEP-ATP-III for metabolic syndrome are a high blood pressure ($\geqslant$130/85 mm Hg), abnormal glucose tolerance (fasting blood glucose level $\geqslant$110 mg dl^{-1}), visceral fat type obesity (waist circumference $\geqslant$102 cm for men, $\geqslant$88 cm for women), hypertriglyceridemia ($\geqslant$150 mg dl^{-1}), and hypo-HDL-cholesterolemia ($<$40 mg dl^{-1} for men, $<$50 mg dl^{-1} for women) and a condition involving three or more of these five risk factors is regarded as metabolic syndrome.

Diagnostic criteria in Japan were proposed in April 2005 by a joint committee of eight related scientific societies, including The Japanese Society of Hypertension.[126] According to the criteria shown in Table 7-1, hypertension in metabolic syndrome is accompanied by abdominal obesity concurrent with either abnormal glucose or abnormal lipid metabolism. The main target organ damages related to metabolic syndrome are cardiovascular disease and diabetes mellitus. In the Tanno–Sobetsu cho Study, the incidence was 1.87[482] and 2.17 times[498] higher for cardiovascular disease and diabetes mellitus, respectively, in patients with metabolic syndrome. Table 7-2 shows the therapeutic approaches. Treatment for metabolic syndrome differs according to the presence or absence of diabetes mellitus. Without diabetes, antihypertensive drugs are prescribed when the blood pressure is $\geqslant$140/90 mm Hg, and only lifestyle modifications are indicated when it is 130–139/85–89 mm Hg. The target of blood pressure control is $<$130/85 mm Hg. If diabetes is present, antihypertensive drug therapy should also be started when the blood pressure is

Table 7-1 Diagnostic criteria for metabolic syndrome (new criteria prepared jointly by eight societies (April 2005))

• Abdominal fat accumulation	
Waist circumference	⩾85 cm for men, ⩾90 cm for women
(Corresponds to a visceral fat area of ⩾100 cm^2 in both men and women)	
Two or more of the following in addition to the above.	
• Lipid levels	
Hypertriglyceridemia	⩾150 mg dl^{-1}
and/or	
Hypo-HDL-cholesterolemia	<40 mg dl^{-1} for both men and women
• Blood pressure	
Systolic pressure	⩾130 mm Hg
and/or	
Diastolic pressure	⩾85 mm Hg
• Blood glucose level	
Fasting hyperglycemia	⩾110 mg dl^{-1}

Abbreviation: HDL, high-density lipoprotein.

Table 7-2 Treatment for hypertension complicated by metabolic syndrome

• Diabetes (−)	BP ⩾140/90 mm Hg
	Treatment for hypertension
	BP 130–139/85–89 mm Hg
	Lifestyle modifications
• Diabetes (+)	BP ⩾130/80 mm Hg
	Treatment for hypertension

Abbreviation: BP, blood pressure.
Selection of antihypertensive drugs: selected primarily from ARB and ACE inhibitors with a strong insulin resistance-reducing effect.

⩾130/80 mm Hg in patients with metabolic syndrome with a target of <130/80 mm Hg. The aim of treatment is the correction of abdominal obesity through dietary and exercise therapies. If antihypertensive drugs are used, ARBs, ACE inhibitors, Ca channel blockers and α-blockers that improve insulin resistance are desirable. Control of the new occurrence of diabetes mellitus is related to the alleviation of insulin resistance, and this relationship has been established in clinical studies using ARBs and ACE inhibitors. Although Ca channel blockers have also been shown to reduce the occurrence of diabetes, this effect is significantly lower than that of ARBs or ACE inhibitors, as suggested by VALUE,[198] CASE-J,[195] and ALLHAT,[295] so that RA system inhibitors such as ARBs and ACE inhibitors are recommended first. The greater effectiveness of ARBs than Ca channel blockers in obese people shown by CASE-J[195] also supports this recommendation. However, there is no sound evidence that RA system inhibitors are effective in the prevention of cardiovascular disease in patients with hypertension in metabolic syndrome.[295]

POINT 7C
Sleep apnea syndrome

1. **Sleep apnea syndrome increases with obesity and, being a risk factor for metabolic syndrome, is considered to be a pathological cause of secondary hypertension, which is also expected to increase in Japan.**
2. **In Japan, sleep apnea syndrome is often observed in non-obese individuals having particular skeletal characteristics of the face, such as micrognathia.**
3. **In addition to typical patients, who are obese and complain of sleepiness during the daytime, patients who exhibit nocturia, nocturnal dyspnea, cardiovascular events with a night-time onset, resistant hypertension, particularly resistant morning hypertension, and left ventricular hypertrophy despite a normal blood pressure should be suspected of having sleep apnea syndrome.**
4. **In many patients with sleep apnea syndrome, 'non-dipper/riser' type nocturnal hypertension with changes in blood pressure during nocturnal hypoxic attacks is observed, and high blood pressure is sustained until the morning and detected as morning hypertension.**
5. **Patients with mild-to-moderate hypertension complicated by severe sleep apnea syndrome should be treated by continuous positive airway pressure (CPAP) first.**
6. **Strict antihypertensive treatment with a low target level of blood pressure control should be administered with particular attention to the nocturnal blood pressure to minimize an increase in the negative intrathoracic pressure load on the thoracic aorta and heart during sleep.**

5) SLEEP APNEA SYNDROME

Obstructive sleep apnea syndrome (OSAS) is a disease in which hypoxemia occurs periodically during sleep owing to respiratory arrest caused by collapse of the upper airway. It has recently attracted attention as a risk factor for cardiovascular diseases such as ischemic heart disease, heart failure, and cerebrovascular diseases, including silent cerebral infarction, in addition to night time sudden cardiac death.[499,500] Moreover, OSAS is a causative factor for hypertension and is one of the most frequent causes of secondary hypertension.[499] As OSAS, which enhances the risk of metabolic syndrome,[501–503] is also expected to increase in Japan, its appropriate diagnosis and treatment have great significance for the efficient diagnosis and treatment of hypertension.

OSAS increases with obesity, but, in Japan, it is also frequently observed in nonobese individuals with particular skeletal characteristics of the face such as micrognathia.[504] It is important to suspect OSAS not only in typical obese and hypertensive patients having symptoms such as daytime sleepiness, reduced concentration, depression and snoring but also in patients exhibiting nocturia, nocturnal dyspnea (feelings of suffocation), a history of cardiovascular events with a nocturnal onset (myocardial infarction, stroke, acute aortic dissection, supraventricular or ventricular arrhythmia, etc.), resistant hypertension (particularly resistant morning hypertension) and left ventricular hypertrophy despite normal blood pressure, because hypertensive patients are often asymptomatic (Table 7-3).[499,505-508] OSAS is diagnosed and staged by sleep polygraphy, and is considered to be mild when the apnea–hypopnea index (number of apneic or hypopneic periods per hour) is 5–15, moderate when it is 15–30 and severe when it is ⩾30.

In OSAS, non-dipper hypertension as well as daytime hypertension is frequently observed, and nocturnal high blood pressure is sustained to the morning and often detected as morning hypertension by home blood pressure measurement.[509–511] OSAS causes hypertension or an increase in fluctuation of the blood pressure by a wide variety of mechanisms. Activation of the sympathetic nervous system[509–512] and renin–angiotensin–aldosterone (RAA) system[513] increases in oxidative stress[514,515] and inflammatory reactions,[516] leptin resistance[517] and insulin resistance[518] are considered to be involved in a complex manner. Furthermore, in nondipper hypertension with OSAS, marked surges of blood pressure are observed during apneic periods, possibly inducing cardiovascular events with a night time onset.[519] Recently, an enhancement of the morning surge has been reported in children with

Table 7-3 Keywords for the detection of obstructive sleep apnea syndrome

Symptoms	Daytime sleepiness, reduced concentration, depression, indefinite complaints (headache, malaise) at awakening or in the morning, marked snoring, frequent awakening during the night, nocturia, and nocturnal dyspnea (feelings of suffocation)
Physical findings	Obesity, micrognathia
Findings on examinations	Resistant morning hypertension (including nocturnal hypertension) Left ventricular hypertrophy (particularly when the clinic and home blood pressures are normal) Cardiovascular events (including atrial fibrillation and ventricular arrhythmias) with a night-time onset Metabolic syndrome

OSAS who have not developed atherosclerosis.[520] In OSAS, increases in the vascular responsiveness and chemoreceptor sensitivity due to nocturnal hypoxemia may enhance pressor responses to stimulation such as sympathetic activities, increase changes in the blood pressure and aggravate the cardiovascular risk.

As for treatment, CPAP maintenance should be performed first in patients with mild-to-moderate hypertension complicated by moderate-to-severe OSAS. According to reports to date, blood pressure was lowered, [521,522] nocturnal blood surges were reduced[519] and cardiovascular prognosis was improved[523,524] in most patients by CPAP. However, in hypertensive OSAS patients without daytime sleepiness a decrease in daytime blood pressure by CPAP has often been insufficient, and adherence to treatment has been low.[525,526] As the risk of cardiovascular disease is considered to remain high in hypertensive patients with OSAS with no indication of CPAP or who cannot tolerate more aggressive antihypertensive treatment, particularly with the control of nighttime blood pressure, is recommended to avoid the increase in negative intrathoracic pressure load on the thoracic aorta and the heart during apneic periods (which may reach 80 mm Hg). There is no clear evidence with regard to the selection of antihypertensive drugs for hypertensive patients with OSAS without CPAP. In the evaluation of a small number of patients, a significant decrease in clinical diastolic blood pressure was observed with β-blockers compared with Ca channel blockers, ACE inhibitors, diuretics, or ARBs. In addition, although there was no difference in the decrease in daytime blood pressure between patients treated with β-blockers and those treated with other drugs, the decreases in nighttime systolic and diastolic pressures were significantly greater in those treated with β-blockers than in those treated with Ca channel blockers, ACE inhibitors or ARBs (no difference compared with diuretics).[527] However, it is reported that daytime blood pressure could be reduced by treatment with a single antihypertensive drug including β-blockers, but it was difficult to control nocturnal blood pressure,[528] and no consensus has been reached with regard to the effectiveness of β-blockers. For the prevention of target organ damage, RAA system inhibitors are considered to be effective because many patients with OSAS, particularly when it is complicated by obesity, show hyperactivity of the RAA system and left ventricular hypertrophy. In hypertensive OSAS patients, the administration of a diuretic is expected to resolve laryngeal edema and alleviate OSAS.[529] However, in OSAS patients in whom dry cough is induced by ACE inhibitors, cough may cause inflammation in the upper airway, leading to the exacerbation of OSAS itself.[530]

POINT 7D
Bronchial asthma and chronic obstructive pulmonary disease

1. **β-blockers and αβ-blockers must not be used as antihypertensive drugs in patients with bronchial asthma or chronic obstructive pulmonary disease. ACE inhibitors are not recommended because they may cause dry cough as an adverse effect and increase airway sensitivity. Ca channel blockers, ARBs, and a low dose of diuretics may be used.**

Liver diseases

1. **As severe liver dysfunction increases the plasma concentrations of antihypertensive drugs metabolized by the liver, adjustment including a reduction in dose is necessary.**
2. **β-blockers may reduce the risk of gastrointestinal bleeding and death in patients with liver cirrhosis. RA system inhibitors may prevent fibrosis of the liver.**

6) BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In bronchial asthma and chronic obstructive pulmonary disease, not only lung (bronchial) lesions but also fatigue of the respiratory muscles, reduced oxygen transport ability of blood, decline in cardiovascular function, enhancement of sympathetic activity, and activation of the RA system are involved in a complex manner. Although a conclusion has not been reached concerning the problem of whether excessive salt intake increases bronchial sensitivity,[531] salt restriction at least does not exert an adverse effect on bronchial asthma complicating hypertension. In addition, appropriate exercise guidance depending on the disease type and severity is necessary because exercise may induce asthmatic attacks.

In patients with bronchial asthma or chronic obstructive pulmonary disease or its history, β-blockers as antihypertensive drugs are contraindicated regardless of whether they are β_1-selective or non-selective, because they may induce airway spasms. In addition, α,β-blockers are not used because they may induce airway spasms owing to β-blocking action. ACE inhibitors are known to suppress the occurrence of pneumonia in elderly patients by reducing the threshold of the cough reflex,[532,533] but they are not recommended for patients with bronchial asthma because they enhance airway sensitivity. ARBs, which belong to RA system inhibitors with ACE inhibitors, may be used because they do not affect airway sensitivity or bronchial smooth muscle. In a study in which ARBs were administered to patients with chronic obstructive pulmonary disease, alleviation of hyperinflation of the lungs and hypoxia-induced hypervolemia was reported.[534] Both α_1-blockers and Ca channel blockers reduce the bronchial smooth muscle tone, and bronchial asthma and chronic obstructive pulmonary disease are good indicators. Antihypertensive diuretics should be used at a low dose with appropriate guidance regarding water intake, because they make sputum discharge difficult if they cause dehydration.

Attacks of bronchial asthma are a major cause of stress in patients and increase blood pressure. In addition, β_2-stimulators and steroids, which are used for the treatment of bronchial asthma, may elevate the blood pressure, so that attention to drug interactions is also necessary. In addition, although antihypertensive drugs are considered to cause drug-induced pulmonary disorders less frequently than other drugs, attention must always be paid to their occurrence.

7) LIVER DISEASES

Generally, in advanced liver cirrhosis, blood pressure tends to decrease through changes in the hemodynamics and concentrations of physiologically active agents in blood, but usual antihypertensive treatment should be performed if hypertension is present. If edema is noted, there is a possibility of secondary aldosteronism, and attention to changes in the plasma electrolyte concentrations is necessary for using RA system inhibitors or diuretics. The liver is an important organ for drug metabolism, and a marked decrease in the hepatic function due to diseases such as liver cirrhosis may induce a delay in the activation of prodrugs and a rise in the plasma concentrations of drugs metabolized by the liver. As the plasma concentrations of antihypertensive drugs metabolized in the liver may increase in patients with advanced liver cirrhosis, caution such as a reduction of the dose and prolongation of administration intervals is necessary at initial use. Drug-induced hepatopathy owing to labetalol and methyldopa is well known, and these drugs must not be administered to patients with liver dysfunction.

There have been reports of some meta-analyses that noncardioselective β-blockers such as propranolol lower the risk of gastrointestinal bleeding and death in liver cirrhosis patients by reducing portal pressure.[535] However, antihypertensive diuretics such as hydrochlorothiazide, chlorthalidone, and furosemide should be used carefully in liver cirrhosis patients, because they may induce hepatic coma through their rapid diuretic action. RA system inhibitors such as ARBs and ACE inhibitors have been suggested by basic studies to prevent fibrosis in the transitional period from chronic hepatitis to liver cirrhosis, but there is no report of results involving a large number of subjects. In nonalcoholic steato-hepatitis (NASH), ARBs are reported to be effective for reversing pathological changes such as fibrosis.[536]

POINT 7E
Gout/hyperuricemia

1. **In hypertension complicated by hyperuricemia, lifestyle guidance such as restriction of energy intake, routine practice of aerobic exercise and restriction of intake of foods and beverages with a very high purine content (for example, beer) should be started at a serum urate level of $\geqslant 7\,mg\,dl^{-1}$, and the initiation of urate-lowering drugs with lifestyle modifications should be considered when it is $\geqslant 8\,mg\,dl^{-1}$. As for the target of control of the serum urate level during antihypertensive treatment, $\leqslant 6\,mg\,dl^{-1}$ should be maintained.**
2. **Thiazide and loop diuretics, which cause hyperuricemia, should not be used in patients who are likely to develop gout.**
3. **ACE inhibitors, Ca channel blockers, and α-blockers have no adverse effect on urate metabolism. Although ARBs do not affect the urate level, losartan reduces it.**

8) GOUT/HYPERURICEMIA

Urate is the final metabolic product of purine metabolites, and its serum concentration is determined by its production in the body and excretion through the kidney. Urate has a simultaneous antioxidant action and marked vasotoxicity, and hyperuricemia has often been reported to be an independent risk factor for atherosclerosis. However, no large clinical study has shown a reduction of the occurrence of cardiovascular disease through urate-lowering treatment, and so whether urate is a risk factor or disease marker is not clear. As hypertensive patients show reduced urate excretion and increased urate synthesis, reflecting anaerobic metabolism of cells, hypertension is often complicated by hyperuricemia.

The serum urate level in hypertensive patients is correlated with not only the risk of gout but also kidney damage and cardiovascular accidents, though evidence based on an interventional study is lacking. We therefore recommend control of the urate level on the basis of the 6–7–8 rules for comprehensive risk avoidance according to the Guidelines for the Management of Hyperuricemia and Gout[537] by the Japanese Society of Gout and Nucleic Acid Metabolism. That is, a serum urate level of $\geqslant 7\,mg\,dl^{-1}$ is defined as hyperuricemia, and a correction of the serum urate level is started by lifestyle guidance if hypertension is concurrent with hyperuricemia. If the serum urate level still increases or is $\geqslant 8\,mg\,dl^{-1}$, urate-lowering therapy should be considered. The serum urate level during antihypertensive treatment should be maintained at $\leqslant 6\,mg\,dl^{-1}$. As many patients with hypertension complicated by hyperuricemia have obesity or metabolic syndrome, lifestyle modifications such as restriction of energy intake, routine aerobic exercise, and restriction of intake of foods and beverages with a markedly high purine content (beer, in particular) are necessary. Lifestyle modifications for hypertensive patients, such as restriction of salt intake, should be included in dietary therapy. If the urate level cannot be reduced sufficiently through lifestyle modifications alone, the addition of a urate-lowering drug suited for the type of hyperuricemia should be considered. Urate-lowering drugs include inhibitors of urate synthesis (xanthine oxidase inhibitors) and urate transporter (URAT1) inhibitors, which promote urate excretion. In hyperuricemic patients, the urinary pH is often low, and it should be adjusted to $\geqslant 6.0$ and <7.0 to increase the solubility of urate in urine. If alkalinization of the urine is necessary, fixed combination drugs of sodium bicarbonate or those of Na citrate/K citrate may be administered. The latter are adjusted to reduce the Na intake compared with sodium bicarbonate, but attention showed be paid to an increase in the serum K level.

Antihypertensive drugs exert various effects on the urate level. As a rapid decrease in extracellular fluid owing to thiazide or loop diuretics may cause hyperuricemia and induce gout, these drugs should not be used in patients who are prone to developing gout. Potassium-sparing diuretics, such as spironolactone, triamterene and eprelenone, have no adverse effects on urate metabolism. The administration of a β-blocker at a very high dose increases the serum urate level. A very high dose of an α,β-blocker also increases serum urate. ACE inhibitors, Ca channel blockers and α-blockers have been reported to reduce the serum urate level in some reports but have no effect in others. α-Methyldopa has no effect on the serum urate level. With regard to ARBs, some ARBs have been suggested to promote urate reabsorption in the renal tubules, but they exert no clear effect on the serum urate level. Losartan, an ARB, reduces the serum urate level by a mean of $0.7\,mg\,dl^{-1}$ by inhibiting the action of URAT1 in the renal tubules.[538,539] In LIFE, which showed the superiority of the target organ-protective effect of losartan over β-blockers in severely hypertensive patients, 28% of the organ-protective effect of losartan, which cannot be explained by its antihypertensive effect alone, was suggested to be derived from an improvement in the urate level.[540] In fixed combination drugs of ARB and thiazide diuretics, the type of ARB and dose of the diuretic to be combined are adjusted to avoid an excessive increase in the serum urate level.

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GUIDELINES (JSH 2009)

Chapter 8. Hypertension in the elderly

Hypertension Research (2009) **32,** 57–62; doi:10.1038/hr.2008.6

POINT 8

1. **Treatment sufficient to achieve the final target of blood pressure control should be performed in elderly patients. Prognosis is expected to improve by reducing blood pressure to $<$140/90 mm Hg at all ages. In patients that have been well treated before the age of 65 years, the same antihypertensive treatment should be continued after the age of 65 years.**
2. **Blood pressure should be reduced gradually, with due attention to the appearance of adverse effects.**
3. **Nondrug therapies should be conducted by determining approaches individually, with regard to the quality of life (QOL).**
4. **In antihypertensive drug treatment, a calcium (Ca) antagonist, angiotensin receptor blocker (ARB), agiotensin-converting enzyme (ACE) inhibitor or a low-dose diuretic should be the first choice. Generally, treatment should be started at half the routine dose. If the antihypertensive effect is insufficient, these drugs should be used in combination.**
5. **If there are complications, the optimal antihypertensive drug should be selected for each patient by referring to Chapter 6 and Chapter 7. Blood pressure should be reduced carefully by paying attention to organ damage and QOL.**

1) CHARACTERISTICS OF HYPERTENSION IN THE ELDERLY

Japan is a super-aged society, in which the elderly account for approximately 21% of the population and those aged $\geqslant$75 years account for approximately 10%. Hypertension increases with age, and, according to the National Health and Nutrition Survey of Japan (2006), 61% of those in their 60 s and 72% of those aged above 70 years have hypertension.

Systolic pressure increases, but diastolic pressure tends to decrease, with age, causing an increase in pulse pressure. These increases in systolic and pulse pressure are important risk factors for cardiovascular disease in elderly people. The rise in pulse pressure is the result of a decline in the Windkessel function owing to a decrease in the extensibility of the aortic wall associated with the progression of atherosclerosis. According to the Hisayama Study, in which participants were aged $\geqslant$60 years; the cumulative incidence of cardiovascular disease increased significantly when systolic pressure was $\geqslant$140 mm Hg and diastolic pressure was $\geqslant$80 mm Hg.[8]

The hemodynamics of hypertension in the elderly is characterized by arteriosclerosis and a decrease in vascular elasticity, a decrease in the baroreceptor reflex, cardiac hypertrophy and a decrease in the diastolic function of the left ventricle, and impairment of body fluid volume regulation, with a consequent decrease in blood flow and dysfunction of autoregulation in major organs. In addition, autoregulation of the blood flow of target organs is impaired, and the lower limit of blood pressure shifts toward the hypertensive side. For this reason, a rapid and marked decrease in blood pressure may cause circulatory disorders of such organs and hence blood pressure must be reduced with care. Similar attention must be paid to renal dysfunction and adverse effects due to an excessive decrease in blood pressure. However, long-term control of blood pressure is clearly effective in preventing cardiovascular events and progression of organ damage. Therefore, aggressive control of the blood pressure is also desirable in elderly patients.

Among metabolic characteristics, increases in susceptibility to disturbances of electrolyte homeostasis (particularly, hyponatremia and hypokalemia), insulin resistance and glucose intolerance are important in elderly patients.

Characteristics of blood pressure in elderly patients with hypertension include (1) increasing systolic and pulse pressure, (2) instability of blood pressure, (3) increase in orthostatic and postprandial hypotension, (4) increase in the nondipper-type nighttime blood pressure, (5) increase in morning surge, (6) increase in white coat hypertension, (7) presence of patients with auscultatory gaps (disappearance of Korotkoff sounds) and (8) presence of pseudohypertension (a higher blood pressure indicated by the manchette method compared with the direct method; however, the frequency of pseudohypertension is low in evaluations in Japan). Impairment of both the pressor and depressor systems, including the nervous system (impairment of baroreceptor reflex, impairment of β-receptor function and so on) and humoral blood pressure-regulating mechanisms (decline in the renin–angiotensin system, kallikrein–kinin system, prostaglandin system, renal dopamine system and so on), are involved in these phenomena.

2) CRITERION FOR HYPERTENSION IN THE ELDERLY AND RESULTS OF EPIDEMIOLOGICAL STUDIES

The criterion for hypertension should be blood pressure $\geqslant$140/90 mm Hg for elderly people as well as for adults in general. A positive correlation was observed between increase in blood pressure and elevation in cardiovascular risk in the Hisayama Study[8] and in the meta-analysis[9] of approximately one million people with no history of cardiovascular disease in 61 prospective studies of people in old age. This correlation was still observed in those in their 80s, and absolute cardiovascular risk increased with age whereas the slope of correlation became gentler in old age. In NIPPON DATA80, which is a 19-year follow-up study in Japan, an increase in blood pressure was also positively correlated with an increase in the risk of cardiovascular death.[20] On the basis of these results, the same

criterion of hypertension as that for adults in general was set for elderly people.

However, there are epidemiological studies that report the presence of a blood pressure threshold related to increases in cardiovascular risk and mortality rate. On re-analysis of the results of the Framingham Study,[541] in which the threshold of blood pressure for an increase in mortality was calculated, blood pressure was found to increase with age and was approximately 160 mm Hg for men and approximately 170 mm Hg for women in early old age (65–74 years). In the Hisayama Study, the risk increased significantly to $\geqslant$140 mm Hg in those aged between 60 and 79 years and $\geqslant$180 mm Hg in those aged $\geqslant$80 years.[8]

Furthermore, in prospective studies in local residents aged $\geqslant$85 years, a negative correlation was noted between blood pressure and life span. In Vantaa 85+[542] and Leiden 85+,[543] performed in separate populations, the outcome was better in the group with systolic pressure of $\geqslant$160 mm Hg than in the group with systolic pressure $<$140 mm Hg.

Taken together, it is generally considered that cardiovascular risk is lower at a lower blood pressure even in elderly people. The discrepancies in the results depending on the study participants and analysis outcomes suggest that the clinical importance of hypertension differs among subpopulations of elderly people classified by age and pathological condition. However, these are the results of epidemiological studies and do not indicate criteria useful for intervention with antihypertensive drug therapy.

3) DIAGNOSIS

a. Diagnosis considering fluctuation of blood pressure

As blood pressure fluctuates markedly in elderly patients with hypertension, it must be measured repeatedly on different days to confirm that it is consistently high. As the frequency of orthostatic hypotension increases, the measurement of blood pressure in the standing position (within 3 min after standing up) is important and must be performed before and after the beginning of treatment. Blood pressure should be measured simultaneously by the palpation method to avoid overlooking pseudohypertension and auscultatory gaps. Home blood pressure measurement and 24-h ambulatory blood pressure monitoring are both useful for evaluating the fluctuation of blood pressure, white coat hypertension, morning hypertension and masked hypertension (reverse white coat hypertension) in daily practice. Masked hypertension has been reported to increase cardiovascular risk in elderly participants (mean age, 70 years).[88]

b. Differential diagnosis of secondary hypertension

Attention to secondary hypertension should be paid, particularly to renovascular hypertension due to atherosclerosis and primary aldosteronism, an endocrine hypertension. Secondary hypertension is indicated in patients who show a significant increase in blood pressure within a short term, an exacerbation of blood pressure control and refractory hypertension. Auscultation of abdominal vascular murmur is useful for the diagnosis of renovascular hypertension. If a rapid decline in renal function is observed during treatment with an ACE inhibitor or ARB, bilateral renovascular hypertension should be suspected. If a tendency toward hypokalemia is noted, primary aldosteronism should be suspected. Attention to drug-induced hypertension is also necessary.

c. Diagnosis of target organ damage and complications

The presence or absence of damage to target organs such as the brain, heart and kidneys owing to hypertension is important for the determination of therapeutic approach and selection of drugs in elderly patients as well as in adults in general. As elderly patients often show asymptomatic multiple organ damage, efforts to detect latent complications are necessary. Reports suggest that attention to a decrease in diastolic pressure is also necessary in patients with systolic hypertension complicated by ischemic heart disease,[544] and that reducing blood pressure increases the risk of stroke in patients with 75% or more stenosis of the bilateral carotid arteries,[324] so that particular attention is required in such patients. Regarding the relationship between the diagnosis of complications and treatment, the presence or absence of complications such as respiratory diseases (particularly obstructive pulmonary disease) and metabolic complications (diabetes mellitus, dyslipidemia and hypokalemia) is also important for the choice of antihypertensive drugs.

4) TREATMENT

a. Effects of antihypertensive therapy in the elderly

Randomized controlled studies using a placebo as a control have shown the preventive effects of antihypertensive drugs against cardiovascular diseases in elderly hypertensive participants aged $\geqslant$60 or 70 years[545]—in EWPHE, STOP-Hypertension and MRC II using diuretics and β-blockers, and in the SCOPE using ARBs. As for isolated systolic hypertension, which is commonly observed in elderly people, it is shown by SHEP using diuretics and by Syst-Eur, Syst-China and STONE using calcium (Ca) antagonists. Hypertension with a systolic pressure of $\geqslant$160 mm Hg was treated in many of these studies, and mean systolic pressure was reduced from 166–197 mm Hg before treatment to almost 140–150 mm Hg.

According to a meta-analysis of nine major clinical studies on the treatment of hypertension in elderly patients, antihypertensive drug treatment significantly reduced all-cause death by 12%, death from stroke by 36% and death from ischemic heart disease by 25%; it also significantly reduced the incidence of cerebrovascular disease by 35% and the incidence of ischemic heart disease by 15%.[546] In HYVET, involving patients with hypertension (mean blood pressure: 173/91 mm Hg) aged $\geqslant$80 years, treatment was performed using diuretics (ACE inhibitors were added when the antihypertensive effect was insufficient) with a target of $<$150/80 mm Hg, and a significant 30% decrease in death from stroke, 21% decrease in death from any cause, 64% decrease in heart failure and 34% decrease in cardiovascular events were observed.[182] In the second year, blood pressure was reduced to 144/78 mm Hg in the active treatment group.

Thus, adequate antihypertensive treatment is also recommended in elderly patients. However, HYVET or other studies do not provide clear evidence supporting the usefulness of reducing blood pressure to $<$140 mm Hg in those patients aged $\geqslant$80 years or antihypertensive treatment for grade I hypertension in elderly people; therefore, blood pressure must be reduced cautiously.

b. Indications for antihypertensive therapy and target levels of blood pressure

Indications for treatment. Indications for antihypertensive treatment are evaluated from patients' characteristics obtained from randomized placebo-controlled studies in which the usefulness of antihypertensive treatment was confirmed. In studies involving only elderly patients with hypertension, those with a systolic pressure of $\geqslant$160 mm Hg and a diastolic pressure of $\geqslant$90–100 mm Hg were selected as participants. In contrast, there is no clear evidence supporting the usefulness of antihypertensive treatment in elderly patients with grade I hypertension at a moderate risk level, but it has been reported that a Ca antagonist regressed cardiac hypertrophy and improved the

quality of life (QOL).[547] From these observations, elderly patients with a blood pressure of ⩾140/90 mm Hg are regarded as indicators for treatment.

Target control levels. In elderly patients, sufficient antihypertensive treatment should be performed with a target of <140/90 mm Hg, which is a criterion for hypertension. In patients who have been treated before the age of 65 years and have controlled blood pressure at <130/85 mm Hg, there is no need to attenuate treatment after the age of 65 years.

Blood pressure levels obtained in large clinical studies and the results of comparisons among the groups that were set at different target levels provide useful information for setting the target blood pressure. In recent large clinical studies in elderly patients with hypertension, the mean systolic and diastolic pressures after treatment were 141–152 and 77–85 mm Hg, respectively (Table 8-1). In many studies using antihypertensive drugs in which about half of the participants were elderly,[198,295,319] blood pressure could also be reduced to <140/90 mm Hg, and the usefulness of antihypertensive treatment was confirmed, although some of these studies included participants without hypertension.

The strategy that reducing blood pressure to <140 mm Hg in elderly patients with a systolic pressure of ⩾160 mm Hg was not borne out by the results of SHEP, a subanalysis of HOT and JATOS.[548] In SHEP, treatment most notably reduced the risk of stroke in the group in which blood pressure was reduced to <150 mm Hg, but the significance of this effect disappeared in the group in which blood pressure was reduced to <140 mm Hg.[549] In HOT, which was a group comparative study regarding the target of blood pressure control, the-lower-the-better relationship disappeared in participants aged ⩾65 years.[550] According to the results of JATOS, which performed a group comparison related to target control level in elderly patients with hypertension, no difference was noted in the outcome, including those with cardiovascular disease, between the group treated with a target of <140 mm Hg and that treated with a target of 140–160 mm Hg. Whether the outcome is improved by strict control of blood pressure in elderly people is presently unclear from the results of group comparative studies on target control level.

As for the risk of an excessive decrease in blood pressure, analysis of diastolic blood pressure achieved has provided retrospective evidence supporting the J-shaped phenomenon, but the threshold has not been consistent, and no clear conclusion has been reached with regard to the presence of the J-shaped phenomenon for systolic pressure. In SHEP, cardiovascular events increased when diastolic pressure was <60 mm Hg.[551] Subanalysis of Syst-Eur warned against reducing diastolic blood pressure to <70 mm Hg in patients with systolic hypertension complicated by ischemic heart disease.[544] In PATE-Hypertension,[552] performed in Japan, cardiovascular events increased when systolic pressure was reduced to <120 mm Hg, but the total number of events was small, and further evaluation is necessary. In recent large clinical studies that enrolled a large number of elderly patients with hypertension, such as INSIGHT, ALLHAT and VALUE, the J-shaped phenomenon was not observed even when blood pressure was reduced to approximately 135–138/75–82 mm Hg. In JATOS[548] and a subanalysis of CASE-J,[298] in addition, a target of <140 mm Hg was achieved in elderly patients without an increase in adverse events. Therefore, although the risk of an excessive decrease in blood pressure is generally low, the target level of systolic pressure should be attained with sufficient attention to changes in the diastolic pressure and ischemic heart disease in patients with low diastolic pressure.

Gradual reduction in blood pressure. In elderly patients with hypertension, particular attention must be paid to the speed of blood pressure reduction because of organ circulation disorders and impairment of autoregulation. Blood pressure should be reduced gradually, antihypertensive drug treatment should be started generally at half the regular dose, and the dose should be increased at an interval of 4 weeks to 3 months by evaluating the presence or absence of signs of brain ischemia, such as dizziness and orthostatic dizziness, symptoms of angina pectoris, ECG changes indicating myocardial ischemia and decline in the QOL. Although <140/90 mm Hg should be the final target of blood pressure control in patients aged ⩾75 years with grade II or III hypertension (⩾160 mm Hg), blood pressure should be reduced carefully by setting an intermediate target of <150/90 mm Hg. This recommendation is supported by the results of JATOS[548] and the subanalysis of CASE-J[298] performed in Japan. In HYVET, in which the participants were patients aged ⩾80 years with grade II or more severe hypertension, target control level was <150/80 mm Hg, and whether the dose should be increased was evaluated every 3 months and the mean blood pressure in the treated group after 2 years was 144/78 mm Hg.[182] Blood pressure should also be reduced slowly and carefully in patients with a large pulse pressure, because advanced atherosclerosis is suspected.

c. Lifestyle modifications

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

Dietary therapy. As elderly people generally have high salt sensitivity, salt intake restriction is effective. The target of salt intake restriction should be 6 g day^{-1}, but caution is needed, because excessive salt intake restriction may cause dehydration. Weight control is also effective in obese individuals.[190] Potassium intake has a mild antihypertensive effect and contributes to the prevention of cardiovascular disease such as stroke. Generally, a potassium-rich diet is recommended, but attention to hyperkalemia associated with renal dysfunction or diabetes is necessary, and potassium intake should be restricted in such patients.

Calcium and magnesium (Mg) intakes have been reported to be negatively correlated with blood pressure, and increasing Ca intake (⩾800 mg day^{-1}) should also be encouraged for the prevention of osteoporosis. Mg supplementation has been shown to have a mild antihypertensive effect.

Exercise therapy. Grade I hypertension was also a good indication for exercise therapy in elderly patients with a mean age of 75 years.[553] For those aged ⩾60 years, mild exercise at a heart rate of approximately 110 b.p.m. (beats per minute; fast walking and so on) should be performed regularly for 30–40 min per session, and three or more times a week. However, exercise is impossible if there are complications such as ischemic heart disease, heart failure, renal insufficiency and joint disease.

Drinking and smoking. The level of alcohol intake is positively correlated with blood pressure and alcohol intake should be restricted to ⩽20–30 ml ethanol per day in elderly people. Although the effect of smoking on blood pressure is mild, it is a strong risk factor for cardiovascular disease and therefore the patient should quit smoking, in principle.

Table 8-1 Major clinical studies in elderly patients with hypertension and those performed in Japan

	STOP-2	*ANBP-2*	*SCOPE*	*HYVET*	*NICS-EH*	*PATE-HT*	*JATOS*	*CASE-J (subanalysis)*
Participants' age (years)	70–84	65–84	70–89	⩾80	⩾60	⩾60	65–85	75–84
Mean age (years)	76	71.9	76.4	83.6	69.8	70	73.6	78.3
Number of participants	6614	6083	4964	3845	414	1748	4418	751
Antihypertensive drugs	(1) β-Blockers/ diuretics, (2) Ca antagonists (3) ACE inhibitors	(1) ACE inhibitors (2) diuretics	(1) ARB (2) placebo ± additional drug	(1) Diuretic ± ACE inhibitor (2) placebo	(1) Ca antagonists (2) diuretics	(1) ACE inhibitors (2) Ca antagonists	Ca antagonists: (1) strict (2) mild	(1) ARB (2) Ca antagonist
Study design	PROBE	PROBE	Double-blind	Double-blind	Double-blind	Open	PROBE	PROBE
Follow-up period (years)	4	4.1	3.7	2.1	5	2.4	2	3.2
Blood pressure before treatment (mm Hg)	194/98	168/91	166/90	173/91	172/94	(1)151/84 (2)148/82	172/89	168/89
Blood pressure after treatment (mm Hg)	(1)158/81 (2)159/80	(1)141/79 (2)142/79	(1)145/80 (2)149/82	(1)144/78 (2)159/84	(1)147/81 (2)147/79	(1)142/80 (2)141/78	(1)136/75 (2)146/78	141/76
Primary end point	CV death	CV event	CV event	Stroke	CV event	CV event	CV event	CV event
Results of primary end point	NS	(1) was useful (P=0.05)	NS	(1) was useful (P=0.055)	NS	NS	NS	NS
Other results		(1) was useful in men	(1) reduced lethal stroke (P=0.04)	(1) reduced total mortality by 21% (P=0.019)		Cardiac events increased when the blood pressure was reduced to <120 mm Hg		CV events increased when the blood pressure remained at ⩾150 mm Hg

Abbreviations: CV, cardiovascular; NS, not significant.
Blood pressure values after treatment in the HYVET comprised data in the second year. The results for the primary evaluation item in the HYVET were not significant because the study was discontinued because of a significant decrease in total mortality. Therefore, the table shows that (1) was useful.

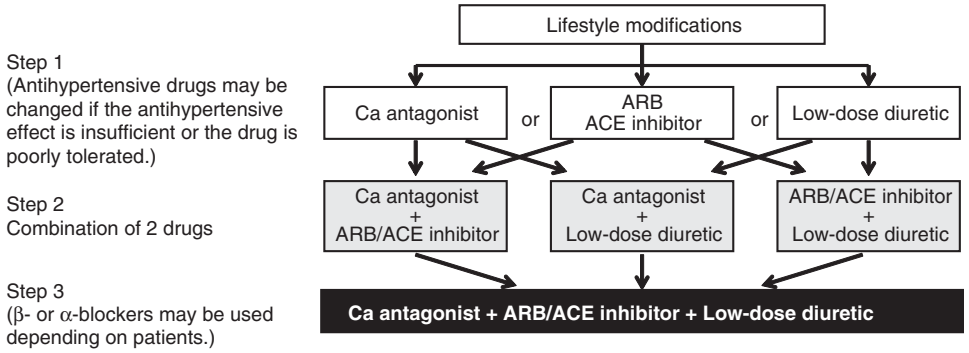

Figure 8-1 Treatment algorithm for elderly patients with hypertension. Antihypertensive drug treatment should be started generally at half the regular dose, and the dose should be increased at an interval of 4 weeks to 3 months. The final target of blood pressure is <140/90 mmHg. In patients aged ⩾75 years with grade II or III hypertension (⩾160 mmHg), blood pressure should be reduced carefully by setting an intermediate target of <150/90 mmHg.

d. Choice of antihypertensive drugs

Antihypertensive drugs must be selected considering the characteristics of hypertension in elderly patients, such as reduced organ blood flow, impairment of autoregulation and orthostatic hypotension, and according to complications if they are present. In the following sections, the evidence-based selection of drugs is discussed by assuming that positive indications are present when the patients have specific complications and absent otherwise.

Patients without complications. A Ca antagonist, ARB, ACE inhibitor or a low-dose thiazide diuretic is appropriate as the first choice. Figure 8-1 shows the serial steps of treatment. If the antihypertensive effect is insufficient, or if the treatment is poorly tolerated, the first choice may be replaced by another drug. If the antihypertensive effect is insufficient with a single drug, combination therapy should be conducted according to Figure 8-1.

The effectiveness of Ca antagonists for the treatment of hypertension in the elderly, including isolated systolic hypertension, has been

established by studies[545] such as STONE, Syst-Eur, Syst-China, NICS-EH,[276] STOP-Hypertension-2,[259] PATE-Hypertension,[552] and CASE-J subanalysis.[298] Subanalysis of the Syst-Eur also suggested that a Ca antagonist (nitrendipine) has a preventive effect on dementia (particularly Alzheimer's disease).[555] It has few contraindications and can be used with a wide range of other antihypertensive drugs. Attention to conduction disorder, bradycardia and heart failure is necessary on using diltiazem. Ca antagonists are the antihypertensive drugs used most widely in Japan today as many meta-analyses have indicated that they have an excellent stroke-preventing effect,[255] and hence they are highly useful in Japan, where stroke is a major complication of hypertension.

ARBs can also be the first choice as they have few adverse effects, excellent tolerability and produces a sufficient antihypertensive effect in elderly hypertensive patients. The LIFE[556] and SCOPE,[557] in which subanalyses regarding isolated systolic hypertension, a condition frequently observed in elderly people, were performed, are considered to have established the usefulness of ARBs in elderly patients with hypertension. Furthermore, in the subanalysis of the CASE-J involving elderly people,[298] the group treated with an ARB (candesartan) showed no difference in the incidence of events from the group treated with a Ca antagonist (amlodipine), the usefulness of which has been established in elderly patients with hypertension. The percentage of candesartan-treated patients who received other antihypertensive drugs was larger than that of the amlodipine-treated patients (54.5 and 42.7%) in CASE-J.[195] Therefore, combination therapy should be positively considered to achieve the target blood pressure strictly in elderly patients.

In the STOP-Hypertension-2, the effectiveness of ACE inhibitors for the prevention of cardiovascular events in elderly patients with hypertension was comparable to that of conventional antihypertensive drugs such as diuretics and that of Ca antagonists.[259] In the ANBP2, an ACE inhibitor (enalapril) was more effective than diuretics, particularly in men.[558] According to the PATE-Hypertension performed in Japan, in which elderly patients with hypertension (aged $\geqslant$60 years) under treatment were followed up for 3 years, no significant difference was observed in the incidence of cardiovascular complications between the Ca antagonist (manidipine) and ACE inhibitor (delapril) groups, although it was not a randomized controlled study. However, the dropout rate was significantly higher in the ACE inhibitor group than in the Ca antagonist group, and many dropouts were because due to cough.[552] In elderly patients, aspiration pneumonia accounts for a high percentage of pneumonia and is often related to survival. ACE inhibitors have been reported to reduce the frequency of aspiration pneumonia by enhancing the cough reflex.[532,533]

The usefulness of diuretics has been established by many large-scale clinical studies, including the EWPHE, SHEP and STOP-Hypertension. In the HYVET, in which the participants were patients with grade II or severer hypertension aged $\geqslant$80 years, a diuretic (indapamide) was used as the basic drug in the antihypertensive treatment group.[182] An ACE inhibitor (perindopril) was used as an additional antihypertensive drug to achieve the target blood pressure ($<$150/80 mm Hg), and these drugs were used in combination in 73% of the patients in the second year of the study. The NICS-EH, a double-blind randomized controlled study in elderly patients with hypertension (aged $\geqslant$60 years, with a mean age of 69.8 $\pm$ 6.5 years) performed in Japan, showed no difference in the incidence of cardiovascular complications between the Ca antagonist (sustained-release nicardipine) group and the diuretic (trichlormethiazide) group. The tolerability based on the medical dropout rate tended to be higher in the Ca antagonist group.[276] In the ANBP2, the risk of lethal stroke was significantly lower in the diuretic group than in the ACE inhibitor group.[558] Diuretics should be used at a low dose with due attention to the effects on complications such as impairment of glucose tolerance, hyperuricemia and dyslipidemia. Diuretics are extremely useful as drugs in combination with Ca antagonists, ARB and ACE inhibitors.

As for β-blockers, which are a first choice for adults in general, some meta-analyses failed to establish their preventive effect on ischemic heart disease, cardiovascular death or total death in elderly patients with hypertension,[277] but others indicated that they are equally effective for reducing the cardiovascular risk compared with the drugs shown in Figure 8-1.[559] However, elderly patients often have contraindications to β-blockers or conditions that require caution in their use, so that a β-blocker is not recommended as the first choice for hypertension in elderly patients.

α-Blockers are effective in treating patients with prostatic hypertrophy, but they are not recommended as the first choice because of the high prevalence of orthostatic hypotension in elderly people.

Patients with complications. As elderly patients with hypertension often have complications, the target blood pressure and choice of antihypertensive drugs should be considered individually depending on the complications. Complication of hypertension by cerebrovascular diseases, nephropathy, ischemic heart disease, diabetes mellitus and dyslipidemia creates a high-risk state that generally requires more aggressive antihypertensive treatment. Table 8-2 shows whether various antihypertensive drugs are indicated or contraindicated for various complications. The Table includes conditions frequently observed in, or characteristic of, elderly people, such as chronic obstructive pulmonary disease, aspiration pneumonia, peripheral artery disease and osteoporosis.

In elderly hypertensive patients with cerebrovascular disease (chronic phase), it is important to maintain the cerebral blood flow, and blood pressure should be reduced slowly, particularly after cerebral infarction. Ca antagonists, ARB/ACE inhibitors and diuretics (combined with the first two) are used. In the PROGRESS (mean age, 64 $\pm$ 10 years), a combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) was useful for the prevention of recurrence (secondary prevention).[135] In the MOSES (mean age, 68 $\pm$ 10 years), an ARB (eprosartan) was more useful than a Ca antagonist (nitrendipine) for the prevention of recurrence (secondary prevention).[320]

Although there is no specific point regarding the selection of drugs for elderly hypertensive patients with ischemic heart disease or heart failure, β-blockers should be administered with particular caution toward adverse effects.

In elderly hypertensive patients with nephropathy, blood pressure control as well as dietary therapy is important. Their treatment is basically the same as that for hypertensive patients with chronic kidney disease in general using an ARB/ACE inhibitor as a primary drug. However, the participants of most large-scale clinical studies were aged $\leqslant$70 years, and there is little evidence for the drug selection or target of blood pressure control, particularly, for patients aged $\geqslant$75 years. Careful blood pressure control with sufficient attention to changes in renal function, proteinuria and albuminuria is required.

In elderly hypertensive patients with diabetes mellitus, aggressive antihypertensive treatment as well as the management of diabetes is necessary. The choice of antihypertensive drugs and setting of the target blood pressure are the same as those for general treatment for hypertensive patients with diabetes mellitus using an ARB/ACE inhibitor as a primary drug. However, few studies have been conducted in participants including those in late old age, similarly to studies in hypertensive patients with nephropathy, and the partici-

Table 8-2 Indication of antihypertensive drugs for elderly hypertensive patients with complications

Complication	*Ca antagonists (dihydropyridine)*	*ARB/ACE inhibitors*	*Diuretics*	*β-Blockers*
Previous stroke	○	○	○[a]	
Ischemic heart disease	○	○		○[b]
Heart failure		○	○	Δ[c]
Chronic kidney disease	○[d]	○[e]	○[d,f]	
Diabetes mellitus	○[d]	○	Δ	Δ
Dyslipidemia	○	○	Δ	Δ
Hyperuricemia	○	○[g]	Δ	
Asthma/chronic obstructive pulmonary disease				X
Aspiration pneumonia[h]		ACE inhibitors		X
Peripheral artery disease	○	○	Δ	
Osteoporosis			○[i]	

○: preferred; blank: usable; Δ: use with caution; X: contraindicated.
[a]Caution against dehydration is needed.
[b]As exacerbation is possible in coronary vasospastic angina, precautions, including the concomitant use of a Ca antagonist, are necessary.
[c]Should be started at a low dose and used carefully by observing the clinical course.
[d]Should be used aggressively if the blood pressure cannot be reduced sufficiently with ARB/ACE inhibitors.
[e]Must be administered carefully if the creatinine level is ⩾2 mg per 100 ml.
[f]Loop diuretics if the creatinine level is ⩾2 mg per 100 ml.
[g]Losartan reduces the uric acid level.
[h]Patients showing repeated episodes of aspiration pneumonia including latent ones.
[i]Thiazide diuretics.

pants in many studies were aged ⩽75 years. Large-scale clinical studies in which subanalysis involving patients with diabetes was performed include the PROGRESS (761 patients, mean age: 64 years),[560] Syst-Eur (492 patients, mean age: 70 years),[489] HOT (1501 patients, mean age: 62 years),[139] STOP-2 (719 patients, mean age: 76 years),[561] LIFE (1195 patients, mean age: 67 years),[274] INSIGHT (1302 patients, mean age: 65 years)[562] and ALLHAT (13 101 patients, mean age: 67 years).[563] The treatment was compared with a placebo in the PROGRESS and Syst-Eur, and although reducing the blood pressure has been confirmed to be effective for the prevention of stroke and cardiovascular events, blood pressure could not be reduced to <130/80 mm Hg.

The information concerning other complications and drug selection provided in Table 8-2 is not based on evidence such as a decrease in cardiovascular risk, but includes recommendations and cautions based on pharmacological actions and so on. Thiazide diuretics may contribute to the prevention of osteoporosis because of their Ca excretion-inhibiting action. As their effects on fracture are being evaluated in the HYVET, their usefulness for the management of osteoporosis is expected to be clarified.

e. Other points requiring attention

In elderly patients with refractory hypertension, attention not only to secondary hypertension such as endocrine and renal parenchymal hypertension but also to drug-induced hypertension is necessary. Inquiry about the use of health foods and supplements as well as prescriptions at other hospitals and departments, and about the use of glycyrrhiza and non-steroidal anti-inflammatory drugs is essential.

Another point regarding refractory hypertension relates to medication adherence. Long-acting drugs with a trough/peak ratio of ⩾50% effectiveness for the control of morning hypertension by 1 or 2 administrations per day are recommended. Declines in medication adherence associated with dementia must also be considered in elderly patients. The possibility of forgetting to take drugs because of impairment of cognitive function should be evaluated even in patients who are capable of communication during the medical examination. Compliance management by the family or caregiver may be necessary. The packing of drugs into one bag is effective not only for maintaining adherence but also for enhancing the effect of medication in elderly patients.[214]

Citation Information

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

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Please refer to the title page for the full list of authors.

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GUIDELINES (JSH 2009)

Chapter 9. Hypertension in women

Hypertension Research (2009) **32,** 63–65; doi:10.1038/hr.2008.7

POINT 9
Pregnancy-induced hypertension

1. **Hypertension observed in pregnancy should be understood as hypertension under special conditions.**
2. **Hypertension is divided into two types: one which occurs after the 20th week of gestation and the other which exists before pregnancy.**
3. **In pregnancy-induced hypertension:**
   - i. **Hypertension (⩾140/90 mm Hg) with or without proteinuria occurring after the 20th week of gestation but resolving by the 12th week of postpartum is defined as pregnancy-induced hypertension.**
   - ii. **Mild hypertension in pregnancy should not be treated aggressively.**
   - iii. **Severe hypertension in pregnancy should be treated.**
   - iv. **See Table 9-2 for definitions of mild and severe hypertension.**
4. **In pregnant women with pre-existing hypertension, any changes to antihypertensive drug treatment should be made with caution.**
5. **Methyldopa, hydralazine hydrochloride and labetalol are primary antihypertensive drugs, but Ca channel blockers may also be used cautiously with sufficient informed consent of the patient.**
6. **Pregnancy-induced hypertension is a contraindication to the use of ACE inhibitors and angiotensin II receptor blockers (ARB).**

Postmenopausal hypertension

7. **As blood pressure may be increased by oral contraceptives or hormone replacement therapy, close observation is needed.**
8. **The pathophysiology and treatment of hypertension in women, including postmenopausal women, may differ from those in men.**

The tendency to emphasize gender differences is growing in medical fields.[564] With regard to cardiovascular disease, in particular, vast differences in the pathogenic processes and their outcomes have been clarified.[565] Recent epidemiological studies have shown that pregnancy and childbirth are important as basic differences and that they exert marked effects on cardiovascular disease in women.[566] However, the prevalence of hypertension increases rapidly in women after menopause and becomes comparable to that in men after about 65 years of age (Figure 9-1).

In this chapter, two major categories of hypertension in women, that is, hypertension related to pregnancy and hypertension in the postmenopausal period, are discussed.

1) HYPERTENSION RELATED TO PREGNANCY

Hypertension observed during pregnancy is defined as pregnancy-induced hypertension. Table 9-1 shows the typing of the disease and Table 9-2 shows the classification of hypertension. Hypertension in pregnant women is also classified according to symptoms and the time of onset, but, for this, readers should refer to the definition and classification of pregnancy-induced hypertension by the Japan Society for the Study of Hypertension in Pregnancy.[567] Hypertension in pregnant women may be pregnancy-induced, essential or secondary, and careful examination is necessary. As with other types of hypertension, 24-h ambulatory blood pressure monitoring has been reported to be useful for predicting proteinuria, neonate weight and the possibility of premature birth.[568]

a. Antihypertensive drug treatment for hypertension in pregnant women

Mild pregnancy-induced hypertension. There are various difficulties in designing and securing subjects for randomized controlled studies for evaluating the appropriateness of antihypertensive drug treatment in patients with mild pregnancy-induced hypertension. Therefore, related evidence is scarce both in Japan and overseas. However, meta-analysis to date has shown that the transition rate of mild hypertension (systolic blood pressure 140–159 mm Hg, diastolic pressure 90–109 mm Hg) with no target organ damage to severe hypertension (systolic blood pressure ⩾170 mm Hg, diastolic pressure ⩾110 mm Hg) was 50% or less in the group that received antihypertensive drug treatment compared with the control group, but there was no difference in the frequency of its progression to pre-eclampsia, and there was no significant difference in the frequency of perinatal death or premature delivery.[569] On the basis of these results, antihypertensive treatment for mild hypertension during pregnancy is often viewed negatively.[570] In mild hypertension, blood pressure often decreases after the discontinuation of antihypertensive medication that had been taken before pregnancy, but the re-introduction of antihypertensive treatment is recommended at a systolic blood pressure of about 160 mm Hg and a diastolic blood pressure of about 110 mm Hg.[571]

Moreover, according to meta-analyses regarding the effects on fetuses, the results of studies using any antihypertensive drug indicated a direct relationship between a decrease in mean blood pressure in the range of 107–129 mm Hg and low birth weight.[572]

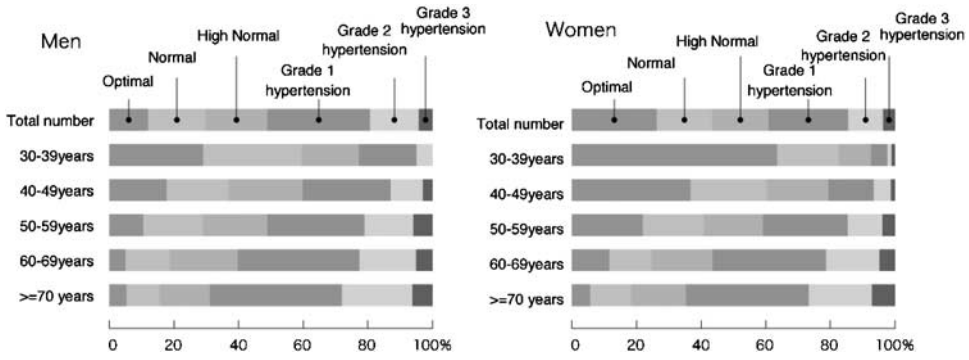

Figure 9-1 Percentage of various blood pressure categories by gender and age.

Table 9-1 Definition and classification of pregnancy-induced hypertension

Definition

(i) Gestational hypertension
Hypertension (systolic blood pressure ⩾140 mm Hg or diastolic pressure ⩾90 mm Hg) with or without proteinuria occurring after the 20th week of gestation but resolving by the 12th week of postpartum is defined as pregnancy-induced hypertension. It is essential for diagnosis to exclude any background disease that could cause hypertension or proteinuria.

(ii) Pre-eclampsia
Hypertension (systolic blood pressure ⩾140 mm Hg or diastolic blood pressure ⩾90 mm Hg) with proteinuria (basically ⩾300 mg per day) occurring after the 20th week of gestation but resolving by the 12th week of postpartum.

(iii) Eclampsia
Seizure occurring after the 20th week of gestation. Exclusion of epilepsy as well as other neurogenic disorders is essential.

(iv) Superimposed pre-eclampsia
(a) Chronic hypertension diagnosed before pregnancy or before the 20th week of gestation, along with proteinuria emerging after the 20th week of gestation.
(b) Aggravation of pre-existing (before pregnancy or before the 20th week of gestation) hypertension and proteinuria after the 20th week of gestation. Either one or both aggravations are acceptable.
(c) Hypertension emerging after the 20th week of gestation in patients with pre-existing renal diseases that manifest solely proteinuria.

Table 9-2 Subclass by symptoms

Severity

Mild pregnancy-induced hypertension
Systolic blood pressure >140 mm Hg but not exceeding 160 mm Hg and/or diastolic blood pressure >90 mm Hg but not exceeding 110 mm Hg.
Proteinuria >300 mg per day but not exceeding 2 g per day.

Severe pregnancy-induced hypertension
Systolic blood pressure >160 mm Hg and/or diastolic blood pressure >110 mm Hg.
Proteinuria >2 g per day.
Correlation of 24-h urine quantitation and randomly sampled urine assay is substantially poor. Thus, a 24-h urine sample should be used. Under the circumstances that only randomly sampled urine is available, repeated test results of 3+ are considered to be severe.

Severe pregnancy-induced hypertension. Severe pregnancy-induced hypertension is often treated on the basis of experience without sufficient evidence. The presence of target organ damage is a positive indication for antihypertensive treatment,[573] and as high blood pressure can cause damage to the mother's brain, cardiovascular system, kidneys, and so on, antihypertensive treatment must be initiated promptly. However, the primary objective of treatment for severe hypertension is the prevention of damage to the mother's organs, and there is insufficient data on whether the treatment is also beneficial to fetuses.[574]

On the basis of these opinions, the ESH/ESC Guidelines recommend that antihypertensive drug treatment should be started when systolic blood pressure is ⩾150 mm Hg and diastolic blood pressure is ⩾95 mm Hg, and that it should be administered more aggressively (systolic blood pressure ⩽140 mm Hg, diastolic blood pressure ⩽90 mm Hg) if there is a history of pregnancy-induced hypertension or hypertension before pregnancy.[66]

Pregnancy with pre-existing hypertension. Controlling blood pressure at ⩽140/90 mm Hg allows a normal pregnancy and delivery. If the patient is undergoing multiple-drug antihypertensive treatment, has target organ damage, has had delivery at a mature age (⩾35 years), or is obese or diabetic, prompt consultation with a hypertension specialist and an obstetrician is necessary.

Pre-eclampsia. Pre-eclampsia should be understood as a multiple organ disease. It causes HELLP syndrome (hemolysis, elevated liver enzymes and low platelets syndrome), pulmonary edema, renal failure, disseminated intravascular coagulation, cerebrovascular disease, abruptio placentae, and so on, as well as eclampsia in the mother. It also increases the mortality and morbidity rates of infants through placental dysfunction.

b. Antihypertensive drugs

The drugs that were used most frequently were methyldopa and hydralazine hydrochloride. Since the safety of these drugs has been sufficiently established, they have been used as primary antihypertensive drugs for the treatment of hypertension in pregnancy to date.[575]

However, as these drugs will not be in routine use until their use is supported by Western guidelines, the usefulness of Ca channel blockers is only gradually being recognized.[66] In Japan, pregnancy is a contraindication to the use of many Ca channel blockers, but as there have been few reports of serious adverse effects[576] and as they are recommended by overseas guidelines, their use with sufficient informed consent may be permitted in the future.[564]

Among β-blockers, labetalol hydrochloride, an αβ-blocker, is primarily used.

Pregnancy is considered to be a contraindication to the use of ACE inhibitors and angiotensin II receptor blockers (ARBs),[577] as both

have been reported to cause various disorders in fetuses, such as oligoamnios, renal insufficiency and growth disorders.[578] However, according to the results from women who unexpectedly became pregnant during their use, these disorders did not always occur, and their frequency was relatively low.[579] Nevertheless, ACE inhibitors and ARBs are still contraindicated for use in pregnant women.

Concerning diuretics, pre-eclampsia is theoretically accompanied by hemoconcentration and a decrease in the circulating blood volume, and diuretics are likely to exacerbate these conditions, causing a decrease in the placental blood flow. Therefore, diuretics must not be used, in principle, in patients with pre-eclampsia unless there is pulmonary edema or signs of heart failure. On the other hand, if diuretics have been used before pregnancy, their continued use has not been reported to cause a marked decrease in the placental blood flow.[580]

c. Non-drug antihypertensive treatments

None of the non-drug treatments, such as salt restriction, weight control and calcium supplementation, has been shown to be effective in the control of hypertension in pregnancy. A low dose of aspirin, however, has been suggested to prevent the progression of pre-eclampsia occurring within the 20–28th week of gestation.[581]

Magnesium sulfate ($MgSO_4$), which is not an antihypertensive drug, is widely used for the prevention of eclampsia during the induction of delivery in patients with impending eclampsia.[582] An intravenous injection of $MgSO_4$ (4 g of $MgSO_4$ in 100 ml of 5% glucose solution over 10–15 min) followed by its administration at 1–2 g h^{-1} is considered to be the most effective treatment.

d. Breast feeding

Caution is needed when breast feeding because a small percentage of most antihypertensive drugs is secreted in breast milk. The discontinuation of antihypertensive medication should be considered if the diastolic blood pressure is <100 mm Hg. However, if hypertension is severer, priority should be given to antihypertensive drug treatment, and breast feeding should be discontinued. Among antihypertensive drugs, captopril, an angiotensin converting enzyme inhibitor, and hydrochlorothiazide, a diuretic, are compatible antihypertensive drugs with breastfeeding.[583]

2. HYPERTENSION RELATED TO POSTMENOPAUSAL WOMEN

Various changes, including changes in the cardiovascular system, occur in postmenopausal women.[584] Dyslipidemia, for example, markedly affects the cardiovascular system.[585] Blood pressure is considered to increase after menopause by some, but is not considered to change markedly by others, and therefore no consensus has been reached.[586] It seems certain, however, that a notable percentage of women who showed a normal or low blood pressure until about 35 years of age exhibit a rapid increase in blood pressure or are diagnosed as hypertensive after menopause.[587] In addition, the possibility of white coat hypertension must not be forgotten in postmenopausal women. Furthermore, various changes (for example, weight gain and changes in hormone levels such as estrogen) occur in this period, possibly facilitating increases in blood pressure.[587] Psychological factors may also increase the changeability of the blood pressure and make sufficient antihypertensive drug treatment difficult. Hormones, psychotropic drugs or *Kampo* drugs are used for the treatment of such cases of hypertension in the postmenopausal period, but the results are unsatisfactory.[588] Estrogen is used for the treatment of postmenopausal syndrome but has been considered to cause adverse effects at a high dose, such as an increase in blood pressure and thromboembolism.[589] Although increased angiotensinogen synthesis and the subsequent enhanced production of angiotensin II are speculated to contribute to the estrogen-induced elevation of blood pressure, the precise mechanism remains unclear. In postmenopausal women, hormone replacement therapy is not considered to affect the blood pressure, but it may cause an increase in blood pressure in patients with a predisposition to hypertension, so that a follow-up with blood pressure measurement every few months is necessary.[590] According to the Women's Health Initiative (WHI) report, estrogen increased cardiovascular events in postmenopausal women;[589] therefore its careful use at a low dose is now recommended and so estrogen-induced hypertension has become rare.[591] In Japan, medroxyprogesterone acetate (progestogen), which is considered to have no marked effect on the blood pressure, is employed as a progesterone to be used concomitantly with estrogen for hormone replacement therapy.

A point to be noted here is that responses to renin–angiotensin system inhibitors differ between men and women. Blood pressure may be easier to control with renin–angiotensin system inhibitors in men than in women.[592] Although the cause of this difference is unclear, there is a possibility that the balance between estrogen and progesterone is disturbed in postmenopausal women and that the resultant tendency of water retention causes a condition resembling salt-dependent hypertension.[593] This makes diuretics a promising candidate as the first choice, but deciding upon which drug is appropriate for the treatment of postmenopausal women or what target should be set for the control of their blood pressure is a subject for future evaluation.[594] Moreover, obesity has recently been suggested to be an important risk factor for estrogen-dependent tumors, such as cancers of the uterine body and breast as well as cardiovascular and metabolic abnormalities, not only in men but also in postmenopausal women.[595] In addition, a close relationship between a history of pregnancy-induced hypertension and hypertension or nephropathy in postmenopausal women is being clarified.[596,597]

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GUIDELINES (JSH 2009)

Chapter 10. Hypertension in children

Hypertension Research (2009) **32,** 66–69; doi:10.1038/hr.2008.8

POINT 10

1. **Hypertension in children and adolescents is usually essential hypertension and is often complicated by obesity.**
2. **A marked increase in blood pressure is suggestive of secondary hypertension. Renal hypertension, particularly that due to congenital renal anomalies, is common in children.**
3. **Essential hypertension in children and adolescents is frequently complicated by left ventricular hypertrophy and can progress into adult essential hypertension.**
4. **For the treatment of essential hypertension, non-pharmacologic interventions should be attempted for 3–6 months. If these prove ineffective, pharmacologic therapy should be considered.**
5. **Indications for pharmacologic therapy in children include insufficient response to lifestyle modifications and complication by left ventricular hypertrophy. Ca channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are recommended.**

1) CHARACTERISTICS OF HYPERTENSION IN CHILDREN AND ADOLESCENTS

On blood pressure screening, essential hypertension is detected in 0.1–1% of fourth to ninth graders and approximately 3% of high school students.

Secondary hypertension is also detected, but it is infrequent. Generally, essential hypertension is mild with no clinical symptoms, but its complication by left ventricular hypertrophy and progression into adult hypertension are problems.

Essential hypertension is often found in obese children. The number of obese children has increased gradually since 1977, although the rate of increase has slowed during the last 10 years.

2) CRITERIA FOR HYPERTENSION

a. Blood pressure measurement

Accurate blood pressure measurement is indispensable for the diagnosis of hypertension. Blood pressure should be taken in a seated or supine position and, in small children, on the laps of a parent. The selection of an appropriate size cuff is also important. With mercury sphygmomanometers, cuffs of 7-cm wide for 3- to 6-year-olds, 9-cm wide for 6- to 9-year-olds and 12-cm wide (adult size) for those aged 9 years and above are recommended. However, the cuff should be selected according to the size of the child's upper arm rather than their age, and one with an inflatable bladder width exceeding 40% of the arm circumference at a point midway between the olecranon and the acromion and a length sufficient to cover 80% of more of the arm circumferences should be used.

b. Screening criteria

In the United States, detailed criteria for hypertension in children are determined according to sex, age and height.[598] In Japan, however, reports concerning blood pressure in children are few, and the criteria shown in Table 10-1 were established (in the 2000 and 2004 editions of these Guidelines) on the basis of limited data.[65] The criteria relating to systolic blood pressure were approximately 10 mm Hg higher than those in the US, but when the blood pressure levels of approximately 40 000 elementary school and junior high school students in Japan measured by the Association of Preventive Medicine were evaluated according to these criteria, the prevalence of hypertension was 1.4% in male fourth graders, 1.8% in female fourth graders, 0.7% in male seventh graders and 1.3% in female seventh graders, which was generally in agreement with an earlier report. Therefore, the criteria calculated from data of general blood pressure examinations are considered to be appropriate for hypertension screening.

c. Criteria for blood pressure control

Criteria must be established from reliable blood pressure data and show values for different age levels. Table 10-2 shows the criteria for hypertension (95 percentiles) derived from the data of blood pressure measurement fulfilling these requirements.[599] Blood pressure should be measured after sufficient rest in a quiet environment using an appropriate cuff. The value of the third of three consecutive measurements using automatic devices should be adopted. The systolic blood pressure of these criteria is close to the US criteria for hypertension for individuals at the 50th percentile in height.[598] As the diastolic pressure is lower than the US criteria using a mercury sphygmomanometer, the method of measurement should be indicated as a note. In children with underlying diseases such as diabetes and kidney disease, in whom

Table 10-1 Criteria for hypertension screening

	Systolic blood pressure (mm Hg)	*Diastolic blood pressure (mm Hg)*
Pre-school children	⩾120	⩾70
Elementary school		
First to third graders	⩾130	⩾80
Fourth to sixth graders	⩾135	⩾80
Junior high school		
Boys	⩾140	⩾85
Girls	⩾135	⩾80
High school	⩾140	⩾85

Same as the JSH2004 criteria for hypertension.[65]

Table 10-2 Criteria of hypertension for blood pressure management

Grade	Boys		Girls	
	Systolic	Diastolic	Systolic	Diastolic
Elementary school				
First	107	60	108	60
Second	112	63	108	60
Third	114	62	111	61
Fourth	116	63	121	66
Fifth	117	63	119	66
Sixth	119	63	119	65
Junior high school				
Seventh	125	66	126	68
Eighth	130	66	126	68
Ninth	136	68	128	70

As the criteria are set according to the mean height, they increase or decrease with the height.[599]

strict blood pressure management is necessary, the criteria shown in Table 10-2 are recommended.

In high school students, when the mean of the values on the second and third of three consecutive measurements using an automatic devices was used, and the 94th percentile value of systolic blood pressure and the 91st percentile and 95th percentile values of diastolic pressure in males and females, respectively, were set as criteria, they were 135/75 mm Hg for males and 120/75 mm Hg for females. Although these values are considerably lower than those reported earlier, it should be noted that the individuals were volunteers interested in lifestyle-related diseases and that those with a BMI of 30 or higher were excluded.

3) PATHOLOGICAL FEATURES OF HYPERTENSION IN CHILDREN

Hypertension detected by blood pressure screening is mostly essential hypertension. The diagnosis of essential hypertension in children is made in consideration of age (adolescence), degree of hypertension (mild), obesity, familial history or lack of symptoms suggestive of secondary hypertension. Children up to the third grade may be excluded from the diagnosis of essential hypertension.

The possibility of secondary hypertension increases with younger age or higher blood pressure. Hypertension related to kidney disease accounts for 60–80% of secondary hypertension in children, and scarred kidney (reflux nephropathy) associated with vesicoureteral reflux and chronic renal failure due to congenital renal abnormalities requires particular attention.

4) OBESITY AND HYPERTENSION

Hypertension is observed more frequently in obese children from the fourth to ninth grade (3–5%) than in those with a standard body size (0.5%).[600] The prevalence of hypertension increases with the degree of obesity. Isolated systolic hypertension, which is a characteristic of obese children, is observed in 1.6% of males and 3.1% of females with mild obesity but in 8.3% of males and 12.5% of females with marked obesity.[600] As hypertension and obesity in children frequently develop into essential hypertension and obesity in adulthood, they should be corrected during childhood.

5) NUTRITION OF THE FETAL PERIOD AND HYPERTENSION

Recently, there have been many reports that nutrition during embryonic and fetal development is related to the occurrence of lifestyle-related diseases. According to results in Japan, blood pressure at the age of 3 years was higher with decreasing birth weight and increasing body weight.[601] Moreover, in a 20-year follow-up of 4626 individuals from birth, blood pressure was higher as birth weight decreased, and the serum cholesterol level was higher with lower increases in height from 3 to 20 years.[602]

A study of markedly obese children reported that those with a lower birth weight are more vulnerable to metabolic syndrome including hypertension.[603] According to the Vital Statistics of Japan by the Ministry of Health, Labour and Welfare, the mean birth weight decreased from 3.19 kg in 1980 to 3.01 kg in 2005, and the percentage of low-birth-weight infants (<2500 g) increased from 5.18% in 1980 to 9.53% in 2005. These changes may be partly explained by the inadequate dietary intake of pregnant women, and a well-balanced diet is recommended both before and during pregnancy. Therefore, it is important to acquire an appropriate dietary habit during childhood for the prevention of lifestyle-related diseases not only in the future but also in the next generation.

6) PROBLEMS WITH ESSENTIAL HYPERTENSION IN CHILDREN AND ADOLESCENTS

Problems with essential hypertension in children and adolescents include complications (target organ damage) and the progression into adult essential hypertension. As a complication, left ventricular hypertrophy is observed in 10–46% of patients.[604]

According to the results of comparisons of blood pressure at junior high school age and after 20 years in Japan, 20.9% of hypertensive junior high school students were still hypertensive after 20 years, whereas 5.5% of normotensive individuals became hypertensive.[605] In a study in which college students were re-examined after 8–26 years, hypertension was observed in 44.6% of the hypertensive but only 9.2% of the normotensive group.[606] In an overseas large-scale study that followed up 1505 children aged 5–14 years for 15 years or longer (Bogalusa Heart Study),[607] twice the expected number of individuals (40% for systolic blood pressure and 37% for diastolic blood pressure) whose levels were in the highest quintile in childhood remained there 15 years later. The prevalence of hypertension at the age of 20–31 years was much higher in individuals whose childhood blood pressure was in the top quintile: 3.6 times higher (18 vs 5%) in systolic blood pressure and 2.6 times higher (15 vs 5.8%) in diastolic blood compared with individuals in every other quintile.

7) LIFESTYLE MODIFICATIONS IN CHILDHOOD (PRIMARY PREVENTION OF HYPERTENSION)

It is extremely important to establish an appropriate lifestyle (dietary and exercise habits) from early childhood for the longterm prevention of lifestyle-related diseases.

a. Diet

Treatment for obesity involves restricting energy intake, balancing nutritional intake, and correcting unfavorable eating habits. Concurrent dietary and exercise therapies are more effective for the treatment of hypertension associated with obesity.

Epidemiologically, an excessive salt intake is involved in an increase in blood pressure. Salt restriction practiced from the neonatal period suppresses increases in blood pressure in childhood.[232] In addition, atherosclerosis begins in childhood, and the serum lipid levels in Japanese teenagers are elevating progressively. Therefore, appropriate dietary habits must be established through guidance

(education) on restricting salt and following a low-fat diet from early childhood. Salt restriction and the encouragement of potassium intake recommended as well as in adults (see Chapter 4).

b. Exercise

For the correction of obesity, exercise for pleasure is recommended. The total amount of daily exercise is more important than the exercise intensity for the prevention of increases in blood pressure whether obesity is present or not.

8) MANAGEMENT OF HYPERTENSION

Figure 10-1 shows the procedure for managing hypertension in children. In children and adolescents who are found to be mildly hypertensive through health screening, blood pressure should be measured repeatedly on different occasions. Blood pressure that always exceeds the screening criteria strongly suggests secondary hypertension in the absence of moderate or severe obesity. If there are no abnormal findings on physical examination, close examination, primarily of the kidneys, should be performed. Congenital renal abnormalities must always be considered, particularly in infants. Home blood pressure measurement is also useful for the exclusion of white coat hypertension in children. Twenty-four-hour ambulatory blood pressure monitoring is useful not only for the diagnosis of white coat hypertension but also for the detection of target organ damage.[604] The target of blood pressure control should be the diagnostic criteria of clinical blood pressure or below, but a lower target should be set for children with underlying diseases such as diabetes mellitus and chronic kidney disease.

Indications of drug treatment include: (1) symptomatic hypertension, (2) secondary hypertension, (3) complication by target organ damage, (4) complication by diabetes, (5) complication by chronic kidney disease and (6) hypertension persisting even after non-pharmacologic interventions (diet and exercise) over 3–6 months.[598]

a. Non-pharmacologic interventions

Since essential hypertension in children and adolescents is often mild, drug treatment should be considered only after attempting non-pharmacologic interventions for 3–6 months. As there is a report of success in reducing blood pressure by restricting the salt intake of high school students, this regime should be started. Dynamic

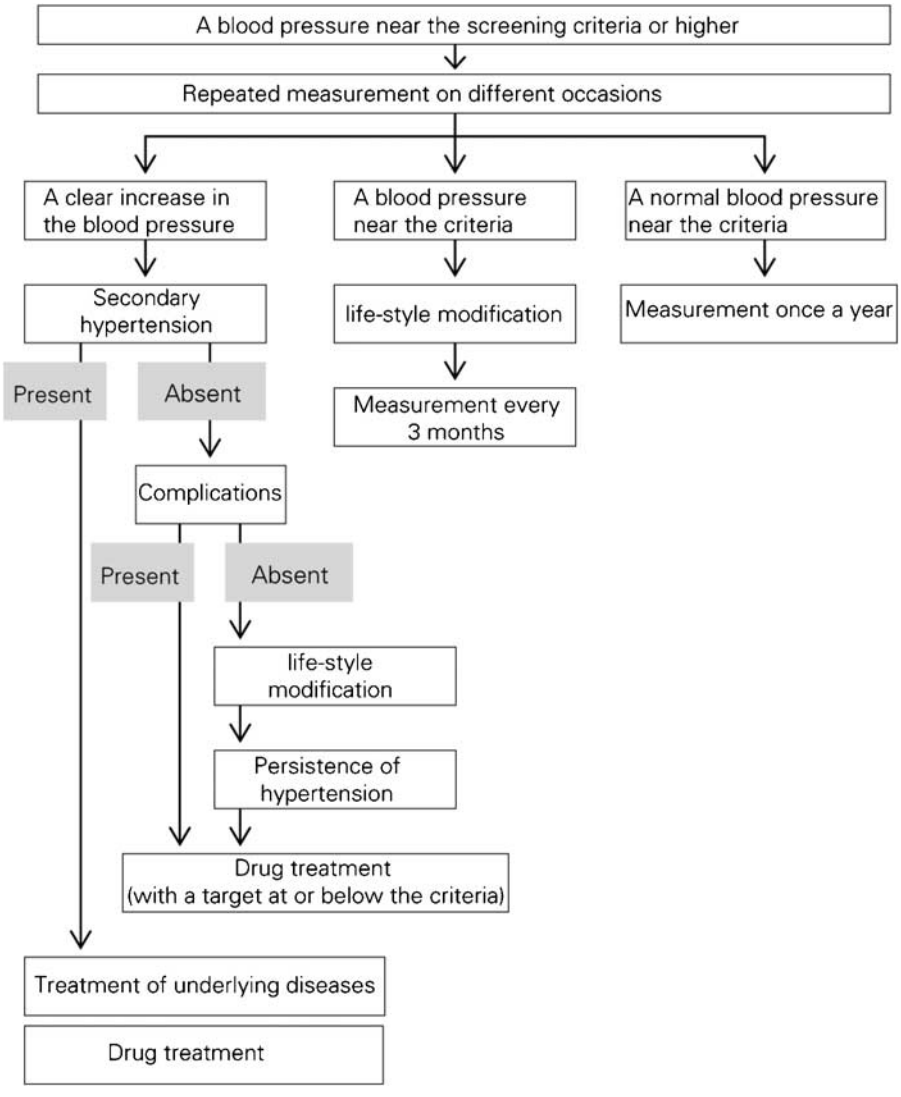

Figure 10-1 Procedure for hypertension management in children.

exercise (isotonic exercise) should be encouraged unless there are complications, because it not only reduces obesity but also produces a direct antihypertensive effect (see Chapter 4).

b. Drug treatment

The first choice of antihypertensive drug is an ACE inhibitor or a Ca channel blocker. ACE inhibitors such as captopril, enalapril and lisinopril have been confirmed to be effective and safe in children. ARBs are also used in children. Among Ca channel blockers, nifedipine and amlodipine are used frequently.

c. Antihypertensive drugs for special situations

β-blockers or Ca channel blockers should be used if there is migraine, and ACE inhibitors or ARBs, from which a kidney protective effect is expected, should be used if there is diabetes mellitus or chronic kidney disease. In patients showing left ventricular hypertrophy, ACE inhibitors and ARBs should be used to attenuate the actions of growth factors (TGF-β, angiotensin II and so on).[598]

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Chapter 11. Treatment of hypertension under special conditions

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POINT 11A
White coat hypertension

1. **White coat hypertension is observed in 15–30% of hypertensive patients, and its frequency increases in elderly people.**
2. **The risk of white coat hypertension developing into sustained hypertension and leading to cardiovascular events appears to be high.**
3. **White coat hypertension is defined as an average clinic blood pressure $>$140/90 mm Hg and an average home blood pressure $\leqslant$135/85 mm Hg or an average 24-h blood pressure on ambulatory blood pressure monitoring (ABPM) $\leqslant$130/80 mm Hg.**
4. **White coat hypertension basically requires lifestyle modifications and close follow-up, but the administration of antihypertensive drugs should also be considered if the risk of organ damage or cardiovascular events is high.**

Masked hypertension

1. **Masked hypertension is observed in 10–15% of the normotensive general population and about 30% of treated hypertensive patients with apparently well-controlled clinic blood pressure of $\leqslant$140/90 mm Hg.**
2. **Cardiovascular risk is two to three times higher compared with that at a normal blood pressure and is comparable with that in sustained hypertension.**
3. **A diagnosis of masked hypertension is made when the average clinic blood pressure is $\leqslant$140/90 mm Hg and home blood pressure is $\geqslant$135/80 mm Hg or the average 24-h blood pressure on ABPM is $\geqslant$130/80 mm Hg.**
4. **Masked hypertension includes morning hypertension, stress-induced hypertension, such as workplace hypertension, and nocturnal hypertension.**
5. **In antihypertensive treatment based on the morning blood pressure, it should be controlled at $\leqslant$135/85 mm Hg.**

1) HYPERTENSION BASED ON DIURNAL CHANGES IN BLOOD PRESSURE

Clinic blood pressure is not necessarily in agreement with the out-of-clinic blood pressures measured during daily activities such as those measured at home or on ABPM. Blood pressure can be classified into normotension, white coat hypertension, masked hypertension and sustained hypertension according to clinic and out-of-clinic blood pressures (Figure 11-1).[608]

a. White coat hypertension

White coat hypertension is a condition in which blood pressure measured in clinic is hypertensive but that measured out of the clinic is normal in untreated patients (Figure 11-1).[608] White coat hypertension is defined as an average clinic blood pressure of $\geqslant$140/90 mm Hg and an average home blood pressure or daytime blood pressure on ABPM of $<$135/85 mm Hg or an average 24-h blood pressure of $<$130/80 mm Hg on multiple measurements.

White coat hypertension is observed in 15–30% of patients diagnosed with hypertension by a clinic blood pressure of $\geqslant$140/90 mm Hg, and its frequency increases in elderly people.[608] Organ damage is mild, and cardiovascular prognosis is good in white coat hypertension compared with sustained hypertension.[79,149,608] However, it is controversial whether the outcome of white coat hypertension is comparable with that of normotension. The white coat phenomenon is not necessarily a benign condition and may be related to an increase in blood pressure under intense stress. White coat hypertension may develop into sustained hypertension in the future and may be a risk factor for cardiovascular events in the long term.[83,84,89,609] These risks are higher in individuals in whom the out-of-clinic systolic and diastolic pressures are in the high-normal range, being 125–135 and 80–85 mm Hg, respectively, and in those with other cardiovascular risk factors, such as obesity and metabolic syndrome, or organ damage, such as microalbuminuria.[609] Therefore, the evaluation of other risk factors and organ damage is necessary in treating white coat hypertension.

Basically, white coat hypertension should be treated by lifestyle modifications without drug treatment. Patients should be examined periodically, attention should be paid to stressful situations in daily lives, and changes in lifestyle and self-measurement of home blood pressure should be encouraged. Antihypertensive medication may be required in patients with high-risk white coat hypertension in whom out-of-clinic blood pressure is relatively high or is complicated by cardiovascular disease, organ damage, diabetes mellitus or metabolic syndrome.

b. Masked hypertension

Masked hypertension is a condition in which clinic blood pressure is normal but out-of-clinic blood pressure is hypertensive (Figure 11-1).[250,608] Masked hypertension is defined as an average

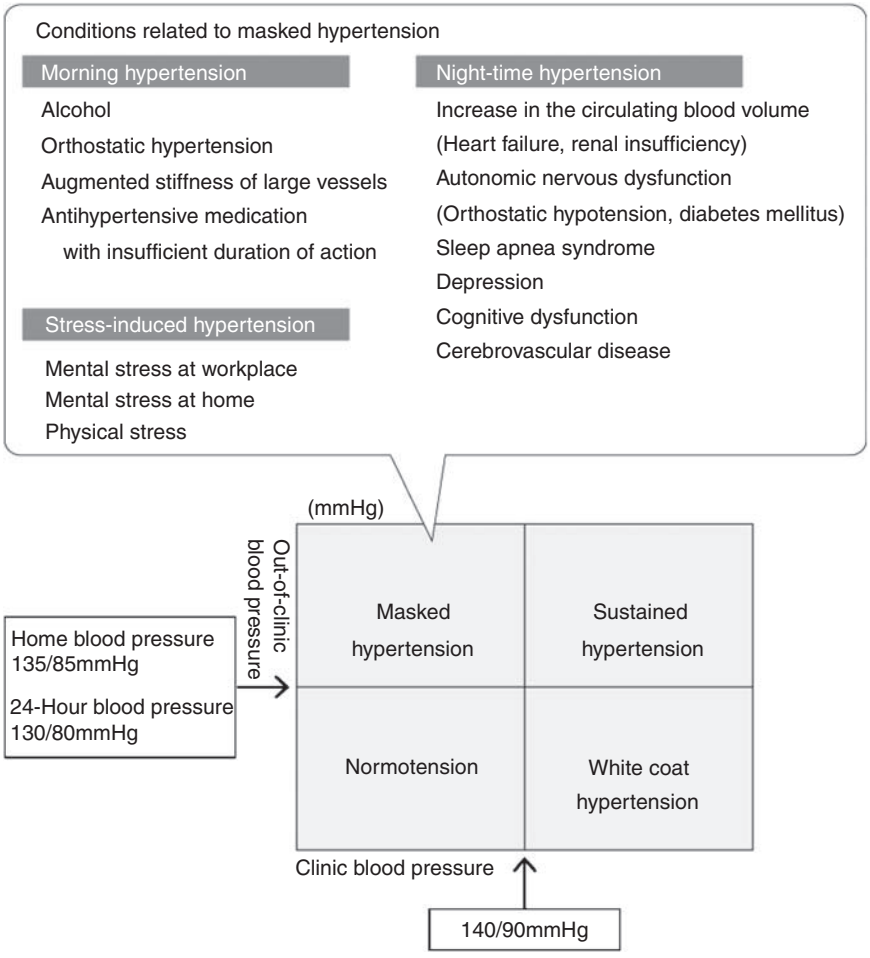

Figure 11-1 Diagnosis of white coat and masked hypertension.

clinic blood pressure on multiple measurements of $<140/90$ mm Hg and an average daytime blood pressure on multiple measurements at home or on ABPM of $\geqslant 135/85$ mm Hg or an average 24-h blood pressure of $\geqslant 130/80$ mm Hg.

Masked hypertension, which is defined by the clinic and out-of-clinic blood pressures, exhibits diverse pathological features. Morning, workplace and nocturnal hypertension constitutes masked hypertension.[610] These hypertensive states are distinguished by the period of increase in the out-of-clinic blood pressure.

Masked hypertension is observed in 10–15% of the general population with normotension and about 30% of hypertensive patients in whom blood pressure is adequately controlled by antihypertensive treatment to $<140/90$ mm Hg.[250,611] In masked hypertension, the risks of organ damage and cardiovascular events are significantly higher than in normotension or white coat hypertension and are comparable with those in sustained hypertension. Previous clinical studies have shown that masked hypertension is more often accompanied by metabolic abnormalities than normotension and is associated with advanced hypertensive organ damage, such as left ventricular hypertrophy and carotid artery thickening, whether the patient is treated or untreated.[612,613] The relative risk of cardiovascular disease in masked hypertension was two to three times higher than that in normotension and was comparable with that in sustained hypertension in follow-up studies of the general population and hypertensive patients undergoing treatment.[88,89,250,614]

The diagnosis and treatment of masked hypertension should be started with the measurement of home blood pressure. All hypertensive patients under antihypertensive treatment, patients with a high-normal blood pressure (130–139/85–89 mm Hg), smokers, heavy drinkers, people under intense mental stress (workplace, home), those with a high physical activity level, those with a high heart rate, those with abnormal orthostatic blood pressure changes (orthostatic hypertension, orthostatic hypotension), those with obesity, metabolic syndrome or diabetes mellitus and those with organ damage (particularly left ventricular hypertrophy) or cardiovascular disease constitute a high-risk group for masked hypertension (Table 11-1).[299,615,616] It is important to measure home blood pressure or ABPM in these high-risk individuals regardless of clinic blood pressure.

Points regarding antihypertensive treatment for masked hypertension are to control blood pressure in the normal range over 24 h, to perform antihypertensive treatment on the basis of early morning blood pressure and to maintain it at $<135/85$ mm Hg.

c. Morning hypertension

Although there is no consensus on the definition of morning hypertension, a condition in which blood pressure is specifically higher in the morning than at other times of day may be regarded as morning hypertension in a narrow sense. As the criterion of hypertension based on home blood pressure is 135/85 mm Hg, an

Table 11-1 High-risk groups suspected to have masked hypertension

- Hypertensive patients with antihypertensive treatment
- People with a high-normal blood pressure (130–139/85–89 mm Hg)
- Smokers, heavy drinkers
- People with a high mental stress level (workplace, home)
- People with a high physical activity level
- People with a high heart rate
- People with abnormal orthostatic changes in the blood pressure (orthostatic hypertension, orthostatic hypotension)
- Patients with obesity, metabolic syndrome or diabetes mellitus
- Patients with advanced target organ damage (particularly left ventricular hypertrophy, increased intima-media thickness of carotid artery)
- Patients with cardiovascular disease

average blood pressure early in the morning of $\geqslant$135/85 mm Hg is defined as morning hypertension in a broad sense.

Cardiovascular events frequently occur early in the morning, and blood pressure increases from the nighttime to early in the morning due to diurnal changes. As early morning blood pressure is significantly associated with the risk of brain, heart and kidney damage and all cardiovascular risks, morning hypertension, in which the blood pressure is increased in the time of the highest cardiovascular risk, is important.[93,610] Furthermore, the problem is that the greatest decrease in antihypertensive effect is attenuated early in the morning despite adequate control of clinic blood pressure in hypertensive patients on antihypertensive treatment.

Morning hypertension is associated with two types of circadian blood pressure variation. One is an extension of nocturnal hypertension. The other is the surge type, a rapid increase in blood pressure before and after waking up. Both types of morning hypertension are considered to be possible risk factors for cardiovascular disease. The greatest augmentation of variability in autonomic nervous activities and blood pressure in relation to reduced baroreceptor reflex is observed in the period from midnight to early morning.[617] Regardless of the 24-h blood pressure level, a high blood pressure level early in the morning, increased variability of the blood pressure and morning surge, that is, a rapid increase in blood pressure from midnight to early morning, are risk factors for cardiovascular events[86,91,618] and organ damage, such as left ventricular hypertrophy, carotid arteriosclerosis and silent cerebral infarction.[86,618-621] Moreover, the risk of cardiovascular events is considered to be enhanced early in the morning, as various risk factors—including increased platelet aggregation and thrombophilic tendencies, as well as increased activities of the sympathetic nervous system and neuroendocrine systems, such as the renin–angiotensin–aldosterone system (RAAS)—act additively or synergistically to exacerbate organ damage.

Target organ damage is more advanced in morning hypertension than in hypertension defined on the basis of clinic blood pressure,[622] and follow-up studies have reported that the risk of stroke[93,94] and a loss of functional independence in those aged 75 years or above is high.[57]

Factors involved in the morning surge include mental stress, habitual drinking and the severity of obstructive apnea syndrome in addition to cold exposure and age.[623] Therefore, appropriate heating of the house in the morning in winter, moderate drinking and good quality of sleep are suggested to be important as nondrug treatments of morning hypertension.

The addition of antihypertensive treatment targeted at controlling morning hypertension to conventional treatment is expected to facilitate complete control of blood pressure over 24 h, including at night, and allows more effective prevention of cardiovascular events. The target of blood pressure control should be $<$135/85 mm Hg early in the morning, but control at an even lower level ($<$130/80 mm Hg over 24 h) is desirable in high-risk hypertensive patients with diabetes or chronic kidney disease.

In morning hypertension, long-acting antihypertensive drugs, the actions of which continue over 24 h, should be used. Even when prescribing a once-daily long-acting antihypertensive drug, modifications such as splitting the dose into morning and evening are necessary if a high morning blood pressure is observed. In addition to the bedtime dosage of a Ca channel blocker, the administration of sympatholytic drugs (α-blockers, a centrally acting sympatholytic drug) and renin–angiotensin (RA) system inhibitors (angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)) before going to bed suppresses neurohumoral factors (the activities of which are enhanced early in the morning), significantly reduces morning blood pressure and protects target organs. Strict control of morning hypertension is usually difficult with a single antihypertensive drug, and combination therapy is often required. However, if the dose of an antihypertensive drug is increased to lower peak blood pressure at a particular time of day, symptoms such as malaise and dizziness may be exacerbated at other times due to an excessive fall in blood pressure. Timed antihypertensive therapy, in which different classes of antihypertensive drugs are administered at different times of day, may be necessary.

d. Nocturnal hypertension

Nocturnal hypertension is defined as an average nighttime blood pressure on ABPM of $\geqslant$120/70 mm Hg. In addition, the riser type, in which blood pressure is higher during the night than during the day, increases cardiovascular risk and is regarded as nocturnal hypertension in a narrow sense. Measurement of nighttime blood pressure and evaluation of abnormal diurnal changes in blood pressure such as in the riser type are performed by ABPM, which has been covered by medical insurance since April 2008. Recently, it has become possible to automatically measure blood pressure during sleep using a home blood pressure-measurement device.[95]

Nighttime blood pressure is less variable than daytime blood pressure and is more closely related to cardiovascular risk or cognitive function.[102,624] Blood pressure decreases by 10–20% during the nighttime compared with daytime blood pressure (normal diurnal changes, dipper) in normal diurnal blood pressure change. The risks of organ damage to the brain, heart and kidney, cardiovascular events and cardiovascular mortality are high in the nondipper type in which blunted nocturnal fall in blood pressure and in the riser type in which blood pressure increases during the nighttime.[85,335,610] It is detected as 'morning hypertension' on home blood pressure measurement when a high nighttime blood pressure persists even after awakening. Elevated nocturnal blood pressure promotes vascular damage and exaggerates cardiovascular risk, even though home blood pressure level is normal in the early morning and before going to bed.[625,626]

Nocturnal hypertension is a consequence of sleep disorders such as sleep apnea syndrome, an increase in circulating blood volume due to heart failure and renal insufficiency and disorders of the autonomic nervous system, such as those in diabetes mellitus, particularly orthostatic hypotension. Depression, impairment of cognitive function, brain atrophy and cerebrovascular disorders are also related to the nondipper type and riser type of nocturnal hypertension.

Restriction of salt intake and diuretics are useful for the control of nocturnal hypertension.[627] Furthermore, the administration of antihypertensive drugs before sleep that are targeted at controlling morning hypertension is recommended. There has been a report that a nondipper could be converted to a dipper type, and better 24-h blood pressure control could be achieved by changing the timing of administration of one of the drugs to before going to bed without increasing the number of drugs used.[628]

e. Stress-induced hypertension

A condition in which clinic blood pressure is normal but the average blood pressure in the daytime, during which the patient is exposed to stress at the workplace or home, consistently exceeds a criterion of 135/85 mm Hg for example, is regarded as stress-induced hypertension.

Mental and physical stress is known to affect the blood pressure measured by ABPM.[629] Workplace hypertension is a variation of stress-induced hypertension. Workplace hypertension, defined as blood pressure being normal on health screening or in the clinic but increased at the workplace under stress, is associated with obesity or a family history of hypertension.[90] ABPM or blood pressure measurement at the workplace is necessary to detect stress-induced hypertension, which could be missed by blood pressure measurement in the clinic or home blood pressure measurement in the morning and before sleep. Although evidence with regard to its clinical significance and its diagnosis and treatment is still insufficient, careful follow-up is necessary.

In shift workers, diurnal changes in blood pressure are dependent on the individual's sleeping pattern rather than daytime or nighttime hours. Therefore, antihypertensive drugs that are effective when administered once a day should be taken just after waking in the evening if the patient sleeps during the daytime. However, as sympathetic activities do not decrease sufficiently during daytime compared with nighttime sleep, a dip in blood pressure during sleep is less likely to occur, leading to a high frequency of nondipper-type abnormality in diurnal blood pressure changes in shift workers.[630]

POINT 11B
Hypertensive emergencies and urgencies

1. **In patients suspected of having a hypertensive emergency, the diagnosis and evaluation of the pathological condition must be performed by prompt examination, and treatment must be initiated without delay.**
2. **As acute target organ damage progresses in hypertension, complicating hypertensive encephalopathy or acute aortic dissection, hypertensive left ventricular failure accompanied by pulmonary edema, acute coronary syndrome accompanied by severe hypertension, pheochromocytoma crisis, eclampsia and so on, the patients must be admitted, and i.v. antihypertensive treatment must be started immediately. In principle, treatment should be conducted in facilities with a hypertension specialist. The same approach should be taken for accelerated-malignant hypertension.**
3. **Sustained marked hypertension (usually $\geqslant$180/120 mm Hg) not accompanied by the progression of acute organ damage is regarded as a hypertensive urgency, and control of blood pressure is attempted by oral medication. However, as many such patients have organ damage or show resistance to treatment, they should be referred to a hypertension specialist.**

2) DIAGNOSIS AND TREATMENT OF HYPERTENSIVE EMERGENCIES AND URGENCIES

a. Definition and classification

A hypertensive emergency is not simply an abnormally high blood pressure but is a condition in which acute damage has occurred and is progressing in target organs such as the brain, heart, kidney and large vessels due to marked hypertension (usually $\geqslant$180/120 mm Hg). It must be diagnosed promptly, and antihypertensive treatment must be started immediately. Hypertensive emergencies include hypertensive encephalopathy, hypertension complicated by acute aortic dissection, hypertensive left ventricular failure accompanied by pulmonary edema, acute coronary syndrome accompanied by marked hypertension, pheochromocytoma crisis, eclampsia and so on (Table 11-2).[631,632] Marked hypertension with no rapid progression of organ damage is regarded as a hypertensive urgency. In these cases, there is no evidence of improvement in the outcome by emergency antihypertensive treatment. Whether or not the condition is an emergency should not be judged according to blood pressure alone. Emergency antihypertensive treatment is not indicated even with an abnormally high blood pressure if there is no acute or progressive organ damage, but it is necessary in hypertensive encephalopathy due to eclampsia or acute glomerulonephritis and aortic dissection even when blood pressure is not abnormally high. The pathological condition must be clarified promptly (Table 11-3), the judgment of whether or not it is an emergency case must be made, and which drugs should be used, how they should be administered, what the target blood pressure level should be and how soon it could be attained must be determined. However, the initiation of treatment for emergencies must not be delayed by spending time on thorough evaluation.

b. Principles for treatment

Hypertensive emergencies must, in principle, be treated by hospitalization. Intravenous antihypertensive treatment should be performed in an intensive care unit or a similar environment. Invasive monitoring of blood pressure is desirable. Due to the presence of organ damage and vascular lesions, an unnecessarily rapid and excessive decrease in blood pressure is most likely to induce ischemic events, such as brain infarction, cortical amaurosis, myocardial infarction and progression of renal dysfunction due to a decrease in organ perfusion pressure. Therefore, the use of drugs and administration methods that allow the degree and rate of decrease in blood pressure to be predicted and the effects to be promptly adjusted is desirable. General targets of blood pressure control are a decrease in mean blood pressure of no more than 25% during the first 1 h and to a level of 160/100–110 mm Hg within the next 2–6 h.[38] However, in patients with aortic dissection, acute myocardial infarction, acute coronary syndrome and hypertensive encephalopathy with no preceding hypertension (acute glomerulonephritis, eclampsia and so on), blood pressure level at which treatment should be initiated and target control level should be set lower.

Once the initial target of blood pressure control has been reached, and oral medication is started, i.v. treatment is gradually reduced until discontinuation. Although few parenteral drugs for antihypertensive treatment are available in Japan, they are shown in Table 11-4, with their dosage/regimens, time needed to act and duration of actions, adverse effects, points requiring caution and special indications. With nitroprusside, the rate and degree of decrease in blood pressure are easy to adjust because of the rapid onset and short duration of its action. Cyanate poisoning is unlikely to occur at doses $<2\,\mu g\,kg^{-1}\,min^{-1}$. In Japan, however, due to the

Table 11-2 Hypertensive emergencies

- Accelerated-malignant hypertension with papilledema
- Hypertensive encephalopathy
- Severe hypertension[a] associated with acute organ damage
  - Atherothrombotic brain infarction
  - Brain hemorrhage
  - Subarachnoid hemorrhage
  - Head trauma
  - Acute aortic dissection
  - Acute left ventricular failure
  - Acute coronary syndrome
  - Acute or rapidly progressive renal failure
- Severe hypertension[a] after thrombolytic therapy for brain infarction
- Excess circulating catecholamines
  - Pheochromocytoma crisis
  - Interactions of monoamine oxidase inhibitors with foods or drugs
  - Use of sympathomimetic drugs
  - Rebound hypertension after sudden cessation of antihypertensive drugs
  - Automatic hyperreflexia after spinal cord injury
- Eclampsia
- Hypertensive emergencies related to surgery
  - Severe hypertension[a] in patients requiring emergency surgery
  - Postoperative hypertension
  - Postoperative bleeding from vascular suture lines
- Hypertension after coronary bypass surgery
- Severe body burns
- Severe epistaxis

Accelerated-malignant hypertension, perioperative hypertension, rebound hypertension, burns and epistaxis are classified as urgencies if they are not severe.
Prepared on the basis of refs. 702 and 703.
[a]'Severe hypertension' here is not in agreement with hypertension categories of the JSH2004 Guidelines. The blood pressure requiring emergency antihypertensive treatment should be evaluated in each condition. Prepared on the basis of Kaplan[631] and Rosei *et al.*[632]

Table 11-3 Check items for evaluating conditions suspected to be hypertensive emergencies

History, symptoms	
	History of diagnosis and treatment of hypertension, state of use of sympathomimetic drugs and other drugs
	Headache, visual impairment, neurological symptoms, nausea/vomiting, chest/back pain, cardiac/respiratory symptoms, oliguira, body weight changes and so on
Physical findings	
	Blood pressure: repeat measurements (diastolic pressure is often $\geqslant$120 mm Hg), laterality and so on
	Pulse, respiration, body temperature
	Evaluation of the body fluid volume: tachycardia, dehydration, edema, measurement of the blood pressure in the standing position and so on
	Central nervous system: disturbance of consciousness, convulsion, hemiparesis and so on
	Ocular fundus: linear or flame-shaped hemorrhage, soft exudate, retinal edema, papilledema and so on
	Neck: jugular vein distension, bruit and so on
	Chest: cardiac enlargement, heart murmur, sings of heart failure and so on
	Abdomen: hepatomegaly, bruit, (pulsatile) mass and so on
	Limbs: edema, arterial pulsation and so on
Emergency examinations	
	Urinalysis, blood cell count (including smears)
	Blood chemistry (urea nitrogen, creatinine, electrolytes, glucose, LDH, CPK and so on)
	ECG, chest X-rays, arterial blood gas analysis as indicated
	Cardiac and abdominal ultrasonography, brain CT scan or MRI, chest/abdominal CT scan, as indicated
	Blood sampling for the measurement of the plasma renin activity, aldosterone, catecholamine and BNP concentrations, as indicated

Abbreviations: BNP, brain natriuretic peptide; CPK, creatine phosphokinase; ECG, electrocardiogram; LDH, lactate dehydrogenase.
Intravenous injection of a low dose of phentolamine if pheochromocytoma is suspected.

lack of experience with the use of nitroprusside and its adverse effects, Ca channel blockers have been more frequently used. Caution is necessary in dose adjustment with Ca channel blockers because of their relatively long duration of effect.

In patients with hypertensive urgency, a long history of hypertension and chronic organ damage is often observed. This suggests that the lower limit of autoregulation of organ blood flow is high. Although antihypertensive treatment should be started within a few hours after diagnosis, blood pressure should be reduced relatively slowly to about 160/100 mm Hg over 24–48 h thereafter. Many hypertensive urgencies can be controlled by oral medication. Oral administration of the capsule contents of nifedipine or bolus i.v. injection of the Ca channel blocker, nicardipine, should be avoided as it can cause an excessive decrease in blood pressure and reflex tachycardia. Ca channel blockers with a relatively rapid onset of action (short-acting or intermediate-type Ca channel blockers), ACE inhibitors, the αβ-blocker, labetalol, or β-blockers should be administered orally, or loop diuretics may be used concomitantly depending on the condition. Dose adjustment is easy with captopril because of the rapid onset and relatively short duration of its action, but it should be started at a low dose (6.25–12.5 mg) as it may cause an excessive decrease in blood pressure in malignant hypertension and in a dehydrated state, in which activities of the RA system are enhanced. Caution is necessary in patients with renal dysfunction because hyperkalemia is most likely to occur 1–2 days after commencing treatment with ACE inhibitors. ACE inhibitors should not be used in patients suggested to have bilateral renovascular hypertension or renovascular hypertension with a functionally solitary kidney, as they may cause renal failure. If they are used, monitoring of the serum creatinine and potassium levels is necessary. In patients with hypertensive urgencies, initial treatment is possible at the outpatient clinic, but careful observation in the facility for 5–6 h after the beginning of administration and on an outpatient basis for 2–3 days thereafter with adjustment of the regimen is necessary. Then, the blood pressure should be controlled to the final target primarily using long-acting antihypertensive drugs, and antihypertensive treatment should be continued. However, treatment by hospitalization is also desirable for a hypertensive urgency in high-risk patients, such as those with a history of cardiovascular disease.

c. Hypertensive encephalopathy

Hypertensive encephalopathy is a condition in which a rapid or marked increase in blood pressure disrupts the autoregulation of cerebral blood flow, causing brain edema due to an unnecessarily high blood flow and pressure. It is most likely to occur when blood pressure rises to $\geqslant$220/110 mm Hg in chronically hypertensive patients and to $\geqslant$160/100 mm Hg in normotensive individuals.[633] Some patients show no proteinuria or hypertensive retinopathy. Hypertensive encephalopathy is the most severe hypertensive emergency leading to brain hemorrhage, disturbance of consciousness, coma and death without appropriate treatment. It is accompanied by exacerbating headache, nausea/vomiting, disturbance of consciousness, convulsions and so on, but focal symptoms are relatively rare. As emergency reduction of blood pressure must, in principle, be avoided in stroke, its exclusion is important. On MRI, vascular edema is often observed in the white matter of the parietal to occipital lobes.

Table 11-4 Parenteral drugs for the treatment of hypertensive emergencies

Drug	*Dosage/regime*	*Onset of action*	*Duration of action*	*Adverse effects/points requiring caution*	*Special indications*
Vasodilators					
Nicardipine	i.v. infusion $0.5–6\,\mu g\,kg^{-1}\,min^{-1}$	5–10 min	15–30 min	Tachycardia, headache, flushing, local phlebitis and so on	Most emergencies. Caution with high intracranial pressure or acute coronary syndrome
Diltiazem	i.v. infusion $5–15\,\mu g\,kg^{-1}\,min^{-1}$	Within 5 min	30 min	Bradycardia, AV block, sinus arrest and so on. A low dose in unstable angina	Most emergencies except acute heart failure
Nitroglycerin	i.v. infusion $5–100\,\mu g\,min^{-1}$	2–5 min	5–10 min	Headache, vomiting, tachycardia, methemoglobinemia, tolerance with prolonged use and so on. Must be protected from light	Acute coronary syndrome
Sodium nitroprusside	i.v. infusion $0.25–2\,\mu g\,kg^{-1}\,min^{-1}$	Immediate	1–2 min	Nausea, vomiting, tachycardia, cyanate poisoning at a high dose or prolonged administration and so on. Must be protected from light	Most emergencies. Caution with high intracranial pressure or renal dysfunction
Hydralazine	i.v. injection 10–20 mg	10–20 min	3–6 h	Tachycardia, flushing, headache, exacerbation of angina pectoris, sustained hypotension and so on	Eclampsia (not the first choice)
Sympatholytic drugs					
Phentolamine	i.v. injection 1–10 mg, infusion at $0.5–2\,mg\,min^{-1}$ after an initial bolus injection is also possible	1–2 min	3–10 min	Tachycardia, headache and so on	Pheochromocytoma, excess circulating catecholamines
Propranolol	i.v. injection 2–10 mg ($1\,mg\,min^{-1}$)→ 2–4 mg every 4–6 h			Bradycardia, AV block, heart failure and so on	Tachycardia induced by other drugs

Abbreviation: AV, arteriovenous.
If pulmonary edema, heart failure or body fluid retention is noted, or tolerance has developed, furosemide or carperitide should be used concomitantly.

As the autoregulation of cerebral blood flow is disturbed, a rapid and marked decrease in blood pressure is most likely to cause brain ischemia. Treatment should be started with i.v. preparations (continuous i.v. infusion). The rate of decrease in blood pressure should be adjusted by monitoring blood pressure and neurological symptoms. Treatment should be conducted to achieve an approximately 25% decrease in blood pressure over the first 2–3 h. Nicardipine, diltiazem and nitroprusside can be used. If an increase in extracellular fluid is observed, or resistance has developed, furosemide should be used concomitantly. Hydralazine, which increases the intracranial pressure, must be avoided.

d. Cerebrovascular disease
See Section 1 of Chapter 6.

e. Hypertensive acute left ventricular failure
Treatment for hypertensive left ventricular failure accompanied by pulmonary edema must be started immediately. Nitroprusside, which has a rapid onset of action and alleviates not only afterload, but also preload by dilating the venous system, is desirable, but nicardipine is also useful. Although nitroglycerin has a relatively weak antihypertensive effect, it is useful when hypertensive acute left ventricular failure is concurrent with ischemic heart disease. Furosemide should be used with these drugs to control pulmonary edema. If there is marked pulmonary congestion, carperitide (α-type human atrial natriuretic peptide preparation) should be used simultaneously.[634] Although no clear target of blood pressure control has been set, blood pressure should be reduced (usually an approximately 10–15% decrease in systolic blood pressure) by examining the symptomatic improvements. After blood pressure has been reduced to a certain level, treatment should be shifted to oral medication primarily using RA system inhibitors, such as ACE inhibitors and an ARB combined with Ca channel blockers, and so on.

f. Severe hypertension complicating acute coronary syndrome (acute myocardial infarction and unstable angina)
To treat angina attacks accompanied by an increase in blood pressure, a nitrite preparation should be administered sublingually or sprayed intra-orally first. If hypertension complicates acute coronary syndrome, nitroglycerin should be administered by continuous i.v. infusion to reduce the myocardial oxygen demand and increase the coronary blood flow as well as lower blood pressure. A β-blocker can be used concomitantly if there is no contraindication such as marked bradycardia. If a β-blocker cannot be used, or blood pressure cannot be reduced sufficiently, diltiazem should be used. The administration of β-blockers and ACE inhibitors from an early stage of myocardial infarction is reported to be useful for improving the outcome.

g. Aortic dissection
See Section 4 of Chapter 6.

h. Pheochromocytoma crisis
Pheochromocytoma crisis means a rapid increase in blood pressure due to an excessive secretion of catecholamines. Phentolamine should be administered at 2–5 mg every 5 min until blood pressure is stabilized. After i.v. injection of the first dose, phentolamine may be

administered by continuous i.v. infusion. Oral medication using drugs such as the selective α-blocker doxazosin should be started simultaneously. Although β-blockers are effective for the management of tachycardia, they should be used after the 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 also be performed in such situations.

i. Accelerated-malignant hypertension

In accelerated-malignant hypertension, diastolic blood pressure is ⩾120–130 mm Hg, and renal dysfunction progresses rapidly. If left untreated, the general condition rapidly deteriorates and cardiovascular complications, including heart failure, hypertensive encephalopathy and brain hemorrhage, occur, leading to a poor outcome. Its pathological characteristics are fibrinoid necrosis and proliferative intimitis following arteriolar endothelial damage and the infiltration of plasma components into the vascular wall due to prolonged, marked hypertension; pathological findings in the kidney are called malignant nephrosclerosis. In this condition, a vicious cycle of progressive renal dysfunction and an increase in blood pressure is established. Ophthalmoscopic findings include retinal hemorrhages, soft exudates, retinal edema and/or papilledema. In the brain, the autoregulation of blood flow is disrupted by vascular damage, and if brain edema occurs, hypertensive encephalopathy may result. When there was no effective antihypertensive treatment, the outcome of this pathological condition was as poor as that of malignant neoplasm, so it was called malignant hypertension. Malignant hypertension accompanied by papilledema (grade IV according to the Keith–Wagener classification) and accelerated hypertension accompanied by retinal hemorrhages and exudative lesions (grade III) used to be distinguished. However, as there is no difference between them in the progression of organ damage or survival rate, they have recently been combined as accelerated-malignant hypertension. As it is not an independent disease, it is appropriate to call it malignant-phase hypertension.[66] 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.[635] Its incidence has decreased recently due to the spread of antihypertensive treatment, improvements in social and living environments, and so on. According to results from the same facility, organ damage such as ophthalmoscopic findings, left ventricular hypertrophy and renal dysfunction were less advanced recently (1984–1999) than they have been in the past (1971–1983).[636,637] Not only essential but also secondary hypertension, such as renal parenchymal or renovascular hypertension, may lead to accelerated malignant hypertension.

Although accelerated-malignant hypertension is regarded as an urgency, the condition in which arteriolar lesions progress should be classified as an emergency.[66] The objective of treatment can often be achieved through oral medication. As many patients have a long history of hypertension, a rapid decrease in blood pressure is associated with the risk of ischemia of important organs. Blood pressure should be reduced to no less than a diastolic pressure of 100–110 mm Hg during the first 24 h.[66] ACE inhibitors and ARBs are expected to be effective because body fluid is reduced owing to pressure diuresis, and hyperactivity of the RA system is closely related to the pathogenesis in the conditions that resulted from essential hypertension[637] or the renal crisis of collagen diseases. However, as these drugs may cause an excessive decrease in blood pressure, their administration should be started at a low dose. Loop diuretics should be used if there is sodium/water retention.

POINT 11C
Transient increases in blood pressure

1. **The history of hypertension including blood pressure levels should be inquired, and if a marked temporary increase in blood pressure is not accompanied by progressive organ damage, emergency antihypertensive treatment is unnecessary except in cases of pheochromocytoma.**
2. **If a marked increase in blood pressure persists, Ca channel blockers or ACE inhibitors with an intermediate duration of action may be administered orally.**
3. **If sufficient inquiry suggests psychological factors, the patient may be referred to a specialist in mental health care.**

Preoperative and postoperative blood pressure management

1. **For the prevention of perioperative complications in hypertensive patients, a differential diagnosis of secondary hypertension, such as pheochromocytoma, and evaluation of hypertensive organ damage and complications, are important.**
2. **Blood pressure should be controlled by continuous oral or i.v. antihypertensive treatment throughout the perioperative period, including the administration on the morning of surgery.**
3. **β-blockers are useful for patients with a high risk of ischemic heart disease.**
4. **Administration of nifedipine capsules must be avoided because the degree or rate of decrease in blood pressure cannot be controlled.**
5. **Elimination of pain, anxiety and excitation is also important for controlling the increase in blood pressure.**

3) TRANSIENT INCREASES IN BLOOD PRESSURE

Marked transient increases in blood pressure, except those caused by pheochromocytoma, do not require emergency antihypertensive treatment unless there is progressive or chronic organ damage (Table 11-5). In elderly patients with impairment of the baroreflex mechanism, blood pressure markedly changes and may reach ⩾180–200/110–120 mm Hg. Nifedipine capsules may be administered to such patients, but should be avoided as the resultant rapid and excessive decrease in blood pressure may induce brain or myocardial infarction. Causes of an increase in blood pressure, such as pain and urinary retention, should be removed, and if blood pressure remains high even on repeated measurements, Ca channel blockers or ACE inhibitors with an intermediate duration of action (administered twice a day) may be administered orally.

Although hyperventilation reduces blood pressure in normal individuals, hyperventilation associated with anxiety increases it.[638] The latter is most likely to occur in hypertensive patients showing nonspecific intolerance to multiple antihypertensive drugs and patients who have experienced panic attacks. Blood pressure can be reduced by treatment for hyperventilation, but some patients may need psychological approaches. Panic disorder is a disease in which patients have repeated episodes of attacks of violent anxiety accompanied by various physical symptoms, including palpitation, dyspnea, chest pain, dizziness, nausea, abdominal pain and so on with a sudden onset (panic attacks), and a paroxysmal increase in blood pressure is observed during attacks due to hyperventilation or an increase in sympathetic tone. Diagnosis and treatment by a specialist are necessary.

Table 11-5 Conditions that may exhibit marked transient increases in blood pressure

- Impairment of the baroreflex mechanism
- Hyperventilation associated with anxiety
- Panic attacks (panic disorder)
- Pseudopheochromocytoma
- Pheochromocytoma

In 21 patients (among 700 consecutive new hypertensive patients) who exhibited physical symptoms such as paroxysmal headache, chest pain, dizziness, nausea, palpitation, flushing and diaphoresis, with hypertension frequently exceeding 200/110 mm Hg, pheochromocytoma was excluded by laboratory examinations, which revealed only mild elevation of plasma or urinary catecholamines, and imaging studies, and these pathological conditions were diagnosed as 'pseudopheochromocytoma';[639] consequently, the psychological background is attracting attention. Although overt anxiety or psychological stress related to the attacks is unclear, the involvement of past psychological stress has been suggested. The duration of attacks is 30 min to several hours, their frequency is one to two times a day to once every two to three months in many patients and blood pressure is normal or mildly elevated during attack-free periods. The condition could be controlled by psychotropic medication and psychotherapy (which was effective in some patients) in addition to the administration of αβ-blockers in 13 patients. These patients are strongly suspected of having pheochromocytoma by internists to whom patients present, but it must be understood that the control of repeated hypertensive attacks is difficult through antihypertensive medication alone and psychotherapeutic approaches are necessary.

4) PREOPERATIVE AND POSTOPERATIVE BLOOD PRESSURE MANAGEMENT

a. Preoperative evaluation of hypertension

Elective surgery is a good opportunity to assess hypertension and evaluate the therapeutic approach. In patients with untreated hypertension, perioperative risk assessment through the evaluation of hypertensive organ damage and complications, such as those of the brain, heart, kidney, blood vessels and fundus of the eye, as well as a differential diagnosis of secondary hypertension, is important. In particular, it is necessary to examine the presence or absence of conditions in which ischemic complications due to perioperative blood pressure decreases are most likely to occur, such as cerebrovascular disease, carotid artery stenosis, left ventricular hypertrophy, reduced coronary blood flow reserve, ischemic heart disease and renal dysfunction. If there is a risk of ischemic complications, consistent blood pressure management from the preoperative period is necessary to avoid excessive perioperative changes in blood pressure.

In patients suspected of having pheochromocytoma, examinations should be performed by postponing surgery, and if the diagnosis has been established, the tumor must be removed before the intended surgery. Conditions such as renovascular hypertension, primary aldosteronism and Cushing's syndrome pose few problems if blood pressure is controlled to grade I or lower level before surgery, but manageable secondary hypertension should be treated before elective surgery.

Grade I or II hypertension is not an independent risk factor for perioperative cardiovascular complications, but if blood pressure is $\geqslant$180/110 mm Hg before elective surgery, blood pressure control should precede surgery.[640] In patients with grade III hypertension, or high-risk hypertension undergoing endoscopic surgery and invasive examinations, the applicability of those procedures must be judged individually by evaluating their risks and merits.

b. Use of antihypertensive drugs in the perioperative period

Antihypertensive drugs should be administered until the day of surgery, in principle, and be resumed as soon as possible after surgery. In particular, if β-blockers are used, caution is necessary not to interrupt treatment considering the risk of increases in heart rate and blood pressure. β-blockers protect against perioperative stress and sympathetic hyperactivity and reduce the risk of ischemic cardiac complications and atrial fibrillation.[640] Therefore, if a patient with ischemic heart disease has not been treated with a β-blocker, its administration should begin. During surgery, propranolol should be used intravenously if necessary. When using diuretics, the possibility of postoperative dehydration and hypokalemia should be recognized, and if these conditions are manageable, their administration need not be discontinued. If the patient is being treated with an ACE inhibitor or an ARB, it may induce a decrease in blood pressure or renal function associated with a perioperative decrease in blood volume; therefore some reports recommend withholding these drugs on the morning of surgery.[640] It is necessary to judge individually whether ACE inhibitors or ARBs should be discontinued, particularly in elderly or high-risk patients.

Increases in blood pressure during an emergency or elective surgery should be controlled by the continuous i.v. infusion of Ca channel blockers (nicardipine, diltiazem), nitroglycerin, nitroprusside and so on. As hemodynamics remain unstable after surgery, antihypertensive treatment should be started as early as possible, intravenously if oral administration is impossible. Appropriate treatment is also necessary for factors that increase blood pressure, such as postoperative pain, anxiety and excitation. Administration of nifedipine capsules must be avoided because the degree or rate of blood pressure reduction cannot be controlled.

c. Dental surgery and blood pressure management

As cardiovascular disease such as stroke may also occur during dental treatment, evaluation of the presence or absence of hypertension and the state of blood pressure control is also necessary before dental treatment. If blood pressure is $\geqslant$180/110 mm Hg, medical consultation and referral should precede dental treatment except for emergency procedures.[641] Patients receiving antihypertensive medication should be advised to take their medication on the day of dental treatment. Dental procedures that involve pain or anxiety or require a prolonged time induce an increase in blood pressure.[642] As local anesthetics containing adrenaline (epinephrine) slightly increase blood pressure, their doses should be carefully determined while ensuring that there is sufficient anesthesia for pain control.[641,642] Prescription of a tranquilizer can be considered in patients complaining of intense anxiety.

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GUIDELINES (JSH 2009)

Chapter 12. Secondary hypertension

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OVERVIEW AND SCREENING

Hypertension is classified into essential and secondary hypertension according to cause. Although secondary hypertension is less frequent compared with essential hypertension, it may be cured by appropriate treatment. Therefore, its diagnosis is important, and the cause of hypertension should be considered in evaluating hypertensive patients.

Secondary hypertension has many types, as shown in Table 12-1. Renal parenchymal hypertension is caused by various kidney diseases such as chronic glomerulonephritis and polycystic kidney disease (PKD), and usually occurs along with reduced renal function. Renovascular hypertension (RVHT) is caused by renal artery stenosis and is usually accompanied by hyperactivity of the renin–angiotensin (RA) system. Primary aldosteronism (PA), Cushing's syndrome and pheochromocytoma are due to an excessive production of aldosterone, cortisol and catecholamines, respectively. Both a deficiency and excess of thyroid hormone may cause hypertension, and hyperparathyroidism is characterized by hypercalcemia. In aortic coarctation, blood pressure is high in the upper but low in the lower limbs. Sleep apnea syndrome is often accompanied by obesity, and blood pressure increases markedly during apneic periods. In brainstem vascular compression, compression of the ventrolateral medulla oblongata by blood vessels is observed. Neurogenic hypertension is also caused by increases in intracranial pressure due to brain tumor or other causes, cerebrovascular disorders, hyperventilation and panic disorder. Hypertension may also be brought on by various drugs that cause Na retention or sympathetic activation.

Although the frequency of secondary hypertension varies among populations, it has been reported to be approximately 5% in the general population. However, it is 50% or higher in young patients with severe hypertension. Renal hypertension is considered to be the most frequent form of secondary hypertension, but PA has been reported to be more prevalent than previously considered, and accounts for 3–10% of all hypertensive patients.[643,644] Hypothyroidism, sleep apnea syndrome and brainstem vascular compression are also observed in many hypertensive patients. Therefore, secondary hypertension is considered to account for about 10% of all hypertension.

Screening for secondary hypertension involves a close evaluation of history, physical examinations, and blood and urine tests. The possibility of secondary hypertension is higher in hypertension with an early onset, severe hypertension and resistant hypertension. Table 12-1 presents findings suggestive of major types of secondary hypertension and tests necessary for their differential diagnosis. Cushing's syndrome and pheochromocytoma usually present characteristic clinical features, but symptoms may not be clear, and similar symptoms are often observed in other diseases. The possibility of secondary hypertension should be considered in the diagnosis and treatment of all hypertensive patients.

POINT 12A

Renal parenchymal hypertension

1. **Renal parenchymal hypertension is hypertension occurring with renal parenchymal disorders and is one of the most frequent forms of secondary hypertension.**
2. **Although hypertension occurs from an early stage in glomerular disorders, it occurs in the terminal stage in renal interstitial disorders. However, hypertension occurs frequently from an early stage in PKD, one of the tubulointerstitial disorders.**
3. **As hypertension accelerates the progression of nephropathy, antihypertensive treatment is important for both the prevention of cardiovascular events and the protection of the kidney.**
4. **In glomerular disorders (glomerulonephritis and diabetic nephropathy), the glomerular capillary pressure generally increases and the urinary protein level remains high. An aggressive antihypertensive treatment (target: $<$125/75 mm Hg) primarily using RA system inhibitors is necessary.**
5. **In renal interstitial disorders (pyelonephritis and PKD) and hypertensive nephrosclerosis, the glomerular capillary pressure is generally normal or low, and the urinary protein level is low. The control of blood pressure to $<$130/80 mm Hg using antihypertensive drugs (of any type) should be attempted. However, if proteinuria increases, a more aggressive blood pressure control using RA system inhibitors would be required, as with glomerular disorders.**

1) RENAL PARENCHYMAL HYPERTENSION

Renal parenchymal hypertension, caused by renal parenchymal disorders, is a common form of secondary hypertension, accounting for 2–5% of all hypertension.[645–647] In the Hisayama Study, which followed up a general population aged $\geqslant$40 years, autopsy was performed on 131 hypertensive patients during the 20 years after 1961, and the frequency of secondary hypertension was 3.8%, with that of renal hypertension being 3.1%.[645]

Although the incidence of and mortality rates due to stroke and heart diseases have decreased due to improvements in antihypertensive treatment, the incidence of end-stage renal failure continues to increase. In the 35 192 patients in whom hemodialysis was initiated in 2006, the most frequent underlying disease was diabetic nephropathy (42.9%), with chronic glomerulonephritis being the second most frequent (25.6%) and nephrosclerosis being the third (9.4%). Together with PKD, which was the fourth most frequent underlying disease (2.4%), these four diseases accounted for 80%.[138] Most of these

Table 12-1 Major types of secondary hypertension, their suggestive findings and examinations necessary for differential diagnosis

Underlying disease or condition	*Suggestive findings*	*Examinations necessary for differential diagnosis*
Renal parenchymal hypertension	Proteinuria, hematuria, kidney dysfunction, a history of kidney disease	Seroimmunological test, renal ultrasonography/CT, kidney biopsy
Renovascular hypertension	Young age, rapid blood-pressure increase, abdominal vascular bruit, hypokalemia	PRA, PAC, renal Doppler ultrasonography, renal scintigraphy, angiography
Primary aldosteronism	Weakness of the limbs, nocturnal pollakiuria, hypokalemia	PRA, PAC, adrenal CT, saline or furosemide load test, adrenal venous blood collection
Cushing's syndrome	Central obesity, moon face, striated skin, hyperglycemia	Cortisol, ACTH, abdominal CT, brain (pituitary) MRI
Pheochromocytoma	Paroxysmal/labile hypertension, palpitation, headache, sweating, neurofibroma	Blood/urinary catecholamines and their metabolites, abdominal ultrasonography/CT, MIBG scintigraphy
Hypothyroidism	Bradycardia, edema, hypoactivity, increases in the levels of lipids, CPK and LDH	Thyroid hormone/autoantibody, thyroid ultrasonography
Hyperthyroidism	Tachycardia, sweating, weight loss, a decrease in the cholesterol level	Thyroid hormone/autoantibody, thyroid ultrasonography
Hyperparathyroidism	Hypercalcemia	Parathyroid hormone
Aortic coarctation	Differences in blood pressure between the upper and lower limbs, vascular murmurs	Thoracic (abdominal) CT, MRI/MRA, angiography
Brainstem vascular compression	Resistant hypertension, facial spasm, trigeminal neuralgia	Brain (medullary) MRI/MRA
Sleep apnea syndrome	Snoring, daytime sleepiness, obesity	Overnight sleep monitoring
Drug-induced hypertension	Previous drug administration, resistant hypertension, hypokalemia	Confirmation of previously administered drugs

Abbreviations: LDH, lactate dehydrogenase; MRA, magnetic resonance angiography; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

chronic kidney diseases (CKDs) induce hypertension, but hypertension promotes the progression of kidney damage and establishes a vicious circle leading to end-stage renal failure.[648,649] As there is no radical treatment for CKD at present, blood pressure control by antihypertensive drug therapy primarily using RA system inhibitors, angiotensin receptor blockers (ARBs) or agiotensin-converting enzyme (ACE) inhibitors, is extremely important for the prevention of end-stage renal failure. In Japan, marked regional differences are observed in the incidence of end-stage renal failure[650,651] and, as a negative correlation exists between its incidence and the prescribed amount of RA system inhibitors,[652] RA system inhibitors are considered to actually prevent the progression of CKD.

On account of the close relationship between CKD and hypertension, it is often difficult to determine if they are concurrent. If abnormal findings have been obtained on urinalysis, or renal dysfunction has appeared before hypertension, or if the presence of hypertension or proteinuria/renal dysfunction (superimposed pre-eclampsia) from an early period of pregnancy can be confirmed, hypertension is likely to be caused by CKD. Also, if hypertension is mild relative to abnormal urinary findings or kidney damage, or if there are few hypertensive cardiovascular complications concurrent with the kidney disorders, CKD is considered to underlie the hypertension. Urinalysis and measurement of the serum creatinine concentration should be performed in all hypertensive patients and, if abnormality persists, kidney morphology must be examined by ultrasonography or CT.

As prognosis may be improved by early treatment in CKD, it is recommended to refer patients suspected of having renal parenchymal disorders to nephrologists. Hypertensive nephrosclerosis, which causes renal dysfunction on the basis of essential hypertension, and diabetic nephropathy are discussed in Chapter 6.

a. Chronic glomerulonephritis

Patients with chronic glomerulonephritis frequently develop hypertension from an early stage. Blood pressure increases further with the progression of renal dysfunction, and hypertension occurs in nearly all patients with end-stage renal failure.[653] Hypertension is observed more often with the exacerbation of kidney biopsy findings. It may be caused by body fluid expansion due to Na retention (increased salt sensitivity), inappropriate activation of the RA system and an involvement of the sympathetic nervous system.[648,649,654,655]

The therapeutic strategy for hypertension associated with chronic glomerulonephritis is basically the same as that for diabetic nephropathy (Table 12-2). Generally, the urinary protein excretion is often $1\,g\,day^{-1}$ or higher, reflecting an increase in the glomerular capillary pressure. The basic treatment consists of reductions in salt and protein intake combined with guidance on smoking cessation.[423] Concerning antihypertensive drug therapy, aggressive treatment to reduce blood pressure to $<125/75$ mm Hg primarily using RA system inhibitors is important. Combination drug therapy including diuretics is often necessary.[387,440,656]

As RA system inhibitors reduce proteinuria even in normotensive IgA[657] and diabetic[416,487] nephropathy, they are used as kidney-protecting drugs. On the other hand, the kidney-protecting effect of RA system inhibitors on CKD that is not accompanied by proteinuria has not been established.

b. Chronic pyelonephritis

In renal interstitial disorders, typically chronic pyelonephritis, hypertension is rarely observed at an early stage and occurs only after renal dysfunction has progressed, unlike glomerular diseases such as glomerulonephritis and diabetic nephropathy.[653,658] It is the sixth most frequent disease leading to end-stage renal failure (0.8%), following rapidly progressive glomerulonephritis.[138] The glomerular capillary pressure is generally normal or low, and the urinary protein level is low (see Table 12-2). The target level of blood pressure control is $<130/80$ mm Hg, and the type of antihypertensive drug is not specified.

Chronic pyelonephritis often shows few symptoms in contrast to acute pyelonephritis. It rarely presents symptoms directly caused by

Table 12-2 Level of proteinuria and the goal of antihypertensive therapy with respect to underlying disease of CKD

Underlying disease	*Glomerular capillary pressure*	*Proteinuria*[a] *(g day^{-1})*	*Target blood pressure (mm Hg)*	*Recommended antihypertensive drugs*
Diabetic nephropathy, glomerulonephritis	High	Usually $\geqslant 1\,g\,day^{-1}$	$<125/75$[b]	RA system inhibitors
Nephrosclerosis, polycystic kidney, renal interstitial disorders	Normal–low	Usually $<1\,g\,day^{-1}$	$<130/80$	Any types[c]

Abbreviations: CKD, chronic kidney disease; RA, renin–angiotensin.
Some patients with diabetic nephropathy or glomerulonephritis are treated with RA system inhibitors to protect the kidney even in the absence of hypertension.
In CKD patients without proteinuria, kidney-protecting actions of RA system inhibitors have not been established.
[a]A reference urinary protein level of $1\,g\,day^{-1}$ was roughly established.
[b]In diabetic nephropathy or glomerulonephritis patients showing a urinary protein level of $<1\,g\,day^{-1}$, the target blood pressure values are $<130/80$ mm Hg.
[c]As urinary protein level increases, strict blood pressure control with RA system inhibitors should be recommended to lower glomerular capillary pressure.

urinary tract infection, and asymptomatic bacteriuria, lower urinary tract symptoms such as pollakiuria, discomfort of the lateral or dorsal lumbar region, and intermittent mild fever may be the only findings. If tubulointerstitial damage progresses, hypertension, Na loss, impairment of urine-concentrating ability, hyperkalemia and acidosis develop. Clinically, as the ability to concentrate urine is reduced and Na is lost, patients are likely to develop dehydration. Hypertension occurs only after renal dysfunction has markedly progressed. If the urinary protein level is $1\,g\,day^{-1}$ or higher, focal glomerulosclerosis based on tubulointerstitial damage is possible.[659] This condition requires aggressive antihypertensive treatment primarily using RA system inhibitors with a target blood pressure level of $<125/75$ mm Hg.

As chronic pyelonephritis occurs more frequently in women as a complication of vesicoureteral reflux, urological diagnosis and treatment are also important.

c. Polycystic kidney disease

Polycystic kidney disease is a disease in which a large number of cysts develop in the bilateral kidneys. Confirmation of the presence of many cysts in the bilateral kidneys by ultrasound tomography or CT is necessary for diagnosis.[660] The genes responsible for PKD are PKD1 (short arm of chromosome 16) and PKD2 (long arm of chromosome 4); the disease is transmitted by autosomal dominant inheritance in most patients and rarely by autosomal recessive inheritance. PKD1 accounts for 80–90% of the disease, with PKD2 accounting for the rest.[661] The number of patients treated for PKD at medical institutions accounts for 1 in 2000–4000 of the population.[662] The disease is progressive, and renal function decreases gradually, causing end-stage renal failure in about 40% of patients in their 50s.[662]

Hypertension is observed in about 60% of patients at an early stage, when renal function remains normal,[653,663] and it occurs in all patients with end-stage renal failure.[664] Cysts displace blood vessels, causing ischemia in local kidney tissues, and the resultant increase in renin secretion is involved in the occurrence of hypertension.[665] RA system inhibitors often show blood pressure-lowering effects, occasionally inducing rapid decreases in blood pressure and renal function. PKD is complicated by cerebral aneurysm in about 10% of patients, and as aneurysmal rupture causes intracranial hemorrhage, control of the blood pressure to $<130/80$ mm Hg is recommended, as with other CKDs.

It is not known whether RA system inhibitors also show kidney-protecting effects in PKD.[660,666-670] There are many reports that other treatments to reduce the glomerular capillary pressure; for example, strict blood pressure control[671] and dietary protein restriction,[672] are ineffective for the renal protection of PKD. Histopathologically, kidney ischemia rather than glomerular hypertension is considered to play a central role in the progression of kidney damage.

POINT 12B
Renovascular hypertension

1. **Renovascular hypertension is hypertension caused by stenosis or obstruction of the renal artery, and is observed in about 1% of all hypertensive patients. Its primary cause is atherosclerosis in middle-aged and elderly patients and fibromuscular dysplasia in younger patients. Atherosclerotic RVHT is often complicated by other vascular diseases such as ischemic heart disease, carotid and peripheral arterial diseases. Bilateral renal artery stenosis/obstruction causes progressive renal failure called ischemic nephropathy.**
2. **Renovascular hypertension often presents as severe or resistant hypertension. Abdominal vascular bruit, lateral difference in the kidney size, kidney dysfunction and hypokalemia are clues to the diagnosis, but they are not observed in all patients. If the renal function deteriorates after the administration of an RA system inhibitor, bilateral RVHT should be suspected.**
3. **Morphological (CT angiography, magnetic resonance angiography and renal arteriography) and functional (plasma renin activity and renography) examinations are important for the definitive diagnosis of RVHT. Renal Doppler ultrasonography is useful for both morphological and functional screening.**
4. **Percutaneous transluminal renal angioplasty (PTRA) is performed for the treatment of RVHT, but its indications require further evaluation. Although PTRA is effective in reducing blood pressure, evidence for its kidney-protecting effect is insufficient. Surgical vascular reconstruction may also be indicated. As for conservative treatment, blood pressure control should be attempted using antihypertensive drugs. RA system inhibitors are effective for unilateral RVHT, but must be avoided in bilateral RVHT.**

2) RENOVASCULAR HYPERTENSION

Renovascular hypertension is hypertension caused by stenosis or obstruction of the renal artery and is observed in about 1% of hypertensive patients. Its etiological mechanism is the activation of the RA system by a reduction in the renal perfusion pressure. The most frequent cause of renal artery stenosis is atherosclerosis, which is common in middle-aged and elderly people, followed by fibromuscular dysplasia, which occurs more frequently in young people. Aortitis syndrome (Takayasu's arteritis), which frequently affects

young women, is also occasionally noted. RVHT may also be caused by congenital malformations, aortic dissection, compression of the renal artery by extrarenal masses and thromboembolism. Stenosis is either unilateral or bilateral. Atherosclerosis usually occurs at the origin of the renal artery, whereas fibromuscular dysplasia occurs more often in the middle to distal parts.[673]

Atherosclerosis of the renal artery suggests advanced systemic arteriosclerosis, and is often complicated by other atherosclerotic vascular diseases. According to reports in Japan, renal artery stenosis was disclosed by autopsy in 12[674] and 10%[675] of patients with myocardial infarction and stroke, respectively, 7%[676] of those who underwent cardiac catheterization, and 27% of those with severe carotid artery stenosis.[677] Fibromuscular dysplasia has subtypes, such as intimal and medial thickening, and may be accompanied by other lesions of vascular stenosis. Aortitis syndrome is accompanied by findings of inflammation, stenosis or dilation of other large vessels, and lateral or vertical differences in the blood pressure are often noted.

Renovascular hypertension is often grade III and may cause malignant hypertension. Renal function may be normal, but it is impaired if stenosis exists bilaterally. Renal failure caused by bilateral renal artery stenosis is called ischemic nephropathy. Ischemic nephropathy accounts for about 10% of underlying diseases of end-stage renal failure[678] and causes the rapid progression of kidney damage in middle-aged and elderly people. If pulmonary edema that cannot be explained by cardiac function is noted, the possibility of ischemic nephropathy should be considered.

a. Diagnostic clues

Table 12-3 shows histories and clinical signs that suggest RVHT and ischemic nephropathy. However, these histories or signs are not observed in all patients.

b. Examinations for a definitive diagnosis

For the diagnosis of RVHT, it is important to confirm the presence of stenosis in the renal artery (morphological diagnosis) and hyperactivity of the RA system due to stenosis, causing hypertension (functional diagnosis) (Figure 12-1).

Table 12-3 Diagnostic clues to renovascular hypertension

Hypertension that develops at $\leqslant$30 years of age, or at $\geqslant$50 years of age
Recent onset or rapid exacerbation of hypertension
Grade III or resistant hypertension
Symptoms or findings of vascular disease in other sites
Deterioration of renal function after the start of treatment with ACE inhibitors or ARB
Abdominal vascular bruit
Laterality in the kidney size
Hypokalemia
Progressive renal failure, congestive heart failure and pulmonary edema

If RVHT is suspected, the plasma renin activity (PRA) should be measured first as a functional examination. PRA usually increases in patients with unilateral renal artery stenosis but is occasionally normal in patients with a long clinical course and those with bilateral stenosis. It should also be noted that PRA is affected by antihypertensive medication. Renal scintigraphy (renography) is useful for the evaluation of a split renal function and lateral difference in the renal blood flow. With captopril loading, the difference between the stenosed and intact sides becomes clearer. Measurement of PRA before and after captopril administration is also useful, because PRA shows an excessive increase after loading in RVHT. Split renal vein sampling, although invasive, may also be useful, and hypertension is considered to be due to renal artery stenosis if PRA on the stenosed side is $\geqslant$1.5 times higher than that on the intact side.

Non-invasive renal Doppler ultrasonography is highly useful for both morphological and functional screening.[679] Renal artery stenosis is evaluated by detecting the blood flow at the origin of the renal artery and in the segmental and interlobular arteries in the kidney. The resistance index based on the intrarenal blood flow pattern has been suggested to be an index for the prediction of the effectiveness of PTRA.[680] CT angiography and magnetic resonance angiography have been reported to be useful,[681] but indications for both examinations must be evaluated carefully in patients with a reduced renal function. Confirmative morphological examination is made by aortography or selective renal arteriography. For the evaluation of indications for treatment, particularly PTRA, morphological and functional examinations should be performed in combination, and angiography employing a contrast medium should be conducted only in patients expected to respond to revascularization.

c. Treatments

Vascular reconstruction. Percutaneous transluminal renal angioplasty is now performed frequently for the treatment of RVHT and renal artery stenosis. This procedure is relatively non-invasive and can be performed repeatedly compared with surgical revascularization. The initial success rate of PTRA is high for fibromuscular dysplasia,[682] and is considered to be the first choice unless it is technically difficult. The long-term prognosis of fibromuscular dysplasia after PTRA is also relatively good, but restenosis may occur.[683] In atherosclerotic renal artery stenosis, the initial response rate to PTRA using a balloon alone was relatively low, the restenosis rate was high and therapeutic results were not always satisfactory.[684] The therapeutic results are reported to have improved after the introduction of stent use.[685]

However, in a prospective study comparing PTRA with drug therapy against atherosclerotic renal artery stenosis, PTRA was shown to be effective for blood pressure control, but its effects on renal function

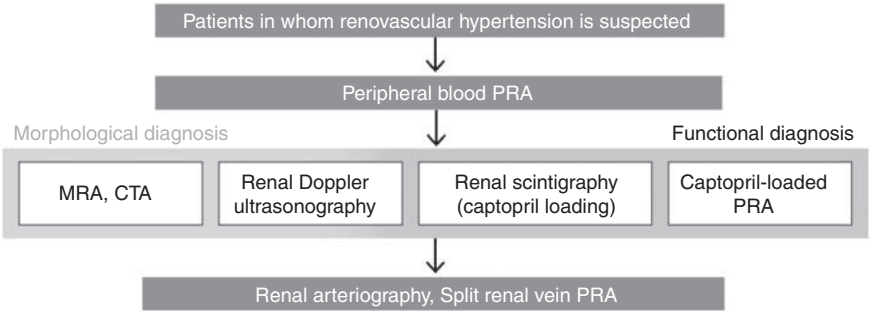


Figure 12-1 Examinations to make a definitive diagnosis of renovascular hypertension.

were unclear.[686] Recent systematic reviews reported that the blood pressure-reducing effect of PTRA was better than that of drug therapy in bilateral stenosis,[687] but was not statistically significant in overall analysis.[688] Also, in the PTRA group, the amount of antihypertensive drugs required was lower and cardiovascular or renovascular complications were fewer, but no difference was observed in renal function, compared with the drug therapy group.[688] Thus, no definite consensus has been reached regarding the usefulness of PTRA at present, and the results of large-scale clinical studies currently in progress are awaited. According to overseas guidelines for PTRA and stent placement, these treatments are recommended when a decrease in blood pressure, recovery of the kidneys and an alleviation of pulmonary edema due to ischemic nephropathy are expected.[689] Therefore, PTRA should be performed only after a sufficient evaluation of indications.

If vascular reconstruction by PTRA is difficult, or if hypertension is resistant to drug therapy, surgical reconstruction by bypass surgery or autologous kidney transplantation should be considered. Surgical vascular reconstruction has also been very effective in Japan. Further, in patients with severely impaired renal function but enhanced renin secretion on the stenosed side, blood pressure is expected to be reduced by nephrectomy.

Antihypertensive drug therapy. Treatment using antihypertensive drugs should be given until vascular reconstructive surgery and in patients in whom vascular reconstruction is impossible or should be avoided. Although β-blockers, which suppress the RA system, and ARB and ACE inhibitors are effective in lowering blood pressure, bilateral renal artery stenosis is a contraindication for ARBs and ACE inhibitors. Ca channel blockers have no marked effect on the RA system and are safe. The use of diuretics, which stimulate the RA system, should be limited to a complementary level, but the presence of renal failure may be an indication for use. When using ARBs and ACE inhibitors, they should be started at a low dose, and the dose should be adjusted by paying attention to excessive decreases in blood pressure, hyperkalemia and renal function. If the renal function deteriorates rapidly, administration should be discontinued, and the drugs should be substituted for other antihypertensive agents. As hypertension is often severe, multiple drug regimens may be required to control blood pressure in patients with RVHT.

POINT 12C
Endocrine hypertension

1. **As endocrine hypertension is often cured by appropriate treatment, patients should be referred without delay to the specialists of The Japanese Society of Hypertension and/or the Japan Endocrine Society.**
2. **It is noted that primary aldosteronism (PA) is a more common cause of hypertension than previously considered and that it often causes target organ damage. In hypertensive patients, especially in those at risk, it is recommended to measure both plasma aldosterone concentration (PAC) and PRA. If the PAC to PRA ratio (ARR) is >200 (PAC: pg ml^{-1}), confirmatory tests for aldosterone excess should be performed, followed by investigations to determine the localization of the lesion site. If the disease is unilateral, laparoscopic adrenalectomy is the treatment of choice. If it is bilateral, antihypertensive agents such as aldosterone antagonists are indicated.**
3. **For the diagnosis of Cushing's syndrome, attention should be paid to characteristic physical findings and the dexamethasone suppression test should be performed. In cases of adrenal incidentaloma, subclinical Cushing's syndrome should be diagnosed according to the diagnostic criteria of the Ministry of Health, Labour and Welfare, Japan.**
4. **Pheochromocytoma is diagnosed based on the measurement of catecholamines and their metabolites and imaging examinations. The tumor is occasionally found as adrenal incidentaloma even in elderly people. An α-blocker is the first choice of treatment. As about 10% of pheochromocytomas are malignant, a careful follow-up is necessary after initial surgery.**
5. **Characteristic physical findings are clues to the diagnoses of acromegaly, Basedow's disease and hypothyroidism. Hypercalcemia suggests primary hyperparathyroidism. In all these conditions, hypertension is often alleviated by the treatment of the causative disease.**

3) ENDOCRINE HYPERTENSION

Endocrine hypertension is a group of diseases in which hypertension is caused by excessive hormone secretion due to a tumor or hyperplasia of the endocrine organs. PA, Cushing's syndrome and pheochromocytoma are the major causes of endocrine hypertension. Although these causes of hypertension are often cured by treatments of the primary lesion, target organ damage may develop if not appropriately treated. In addition, some tumors causing hypertension could be histologically malignant. Appropriate diagnosis is therefore essential and patients should be referred to specialists of The Japanese Society of Hypertension and/or the Japan Endocrine Society without delay.

a. Primary aldosteronism

PA is typically associated with hypertension, suppressed renin secretion, hypokalemia, hypomagnesemia and metabolic alkalosis due to excess aldosterone secretion. Prevalence appears to be more frequent than previously considered and is reported to account for about 3–10% of all hypertensive patients, although lower prevalence has been suggested.[690–692] As the disease often damages target organs including the brain, cardiovascular system and kidneys,[693] early diagnosis and treatment are important. It occurs more often in women, with a male–female ratio of 1:1.5.

Diagnostic clues. PA should be suspected in all patients with hypertension, especially untreated patients. A screening test is strongly recommended in patients at higher risk,[694] including patients with hypokalemia (serum K level $\leqslant 3.5$ mEq l^{-1}, including hypokalemia induced by diuretics), grade II–III hypertension (about 10%), resistant hypertension (about 20%), adrenal incidentaloma (about 3%) and those aged $\leqslant 40$ years with target organ damages (Table 12-4). As the serum K level has recently been reported to be normal in about three out of four patients with PA,[695] PA cannot be excluded even in patients without hypokalemia.

Table 12-4 Hypertensive patients at higher risk of PA in whom a screening test is strongly recommended

Hypokalemia (including diuretic-induced hypokalemia)
Grade II/III hypertension
Resistant hypertension
Adrenal incidentaloma
Patients aged $\leqslant 40$ years with target organ damage

Abbreviation: PA, primary aldosteronism.

Screening tests.

Measurement of PRA and PAC. PRA and PAC should be measured simultaneously, particularly in the high-prevalence group mentioned above. As the values are affected by the time of blood sampling, posture, and antihypertensive medication, blood sampling under standard conditions (untreated, between early morning and 0900 hours, fasting, after at least 30 min of recumbancy) is desirable. As antihypertensive medication can cause a false-positive or false-negative result (Table 12-5), measurement is preferably performed in an untreated condition or after a 2-week medication-free period. If withdrawal of medication is difficult due to the necessity of blood pressure control, measurement is recommended to be performed after replacing the drugs with Ca channel blockers, α-blockers, and/or hydralazine, which have less marked effects on the PRA or PAC. As spironolactone has marked effects, it should be withdrawn for at least 2 months. Also, as values can show considerable variation even in the same patient, repeated measurements are recommended.[696] As PAC is expressed in ng per 100 ml or pg ml^{-1}, caution is required that absolute values expressed in the latter units are 10 times higher than those in the former.

Evaluation of the aldosterone to renin ratio (ARR). As the ARR increases in PA, it is useful for screening.[697] Although cutoff values ranging from 200 to 1000 (PAC: pg ml^{-1}) have been reported, 200 is recommended for screening. ARR is, however, markedly affected by a low renin level; PAC > 150 pg ml^{-1} has been proposed as a supplementary condition in addition to the ARR alone.[698]

Confirmatory tests. If the screening tests are positive, confirmatory tests should be performed to establish autonomous secretion of aldosterone independent of the RA system. The captopril challenge test[699] shows an excellent sensitivity despite a relatively low specificity and can be performed at the outpatient clinic because of its simplicity. The furosemide-upright test has been commonly performed in Japan, but it has a slightly lower sensitivity and specificity and may involve considerable physical stress. The saline infusion test,[700] commonly performed in the United States and other countries, has been reported to be excellent in sensitivity and specificity but is not indicated for patients with impaired cardiac and/or renal function (Table 12-6). If at least one of these tests is positive, investigations to determine the disease subtype and site of the lesion should be initiated.

Disease subtype and localization of the lesion site. Aldosterone-producing adenoma and idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia are major types of PA, but there are also rare types including glucocorticoid-remediable aldosteronism, adrenal cancer and unilateral adrenal hyperplasia. Comprehensive diagnosis is made by adrenal CT, adrenal scintigraphy and adrenal vein sampling.

Treatments. For unilateral aldosterone-producing adenoma, laparoscopic adrenalectomy is the treatment of choice. As the serum K level rapidly normalizes after surgery, blood pressure decreases slowly. Hypertension may not be completely normalized in patients with a 5-year or longer history of hypertension, essential hypertension, renal damage and resistance to spironolactone. The control of hypertension is usually improved. Strict control of hypertension and hypokalemia should be continued in patients with no surgical indications and those awaiting surgery. Although an aldosterone antagonist is the first-choice antihypertensive agent, blood pressure should be controlled through its concomitant use with Ca channel blockers, which have been reported to suppress aldosterone secretion after initiating administration. Eplerenone more selectively binds to mineralocorticoid receptors than spironolactone and less frequently causes adverse effects including gynecomastia. The efficacy of eplerenon in PA awaits investigation in a large number of patients. The preoperative administration of an aldosterone antagonist has been reported to reduce rapid postoperative changes in hemodynamics through the activation of the RA system or other mechanisms and to prevent electrolyte abnormalities and renal dysfunction.[701] On the other hand, as hypoaldosteronism after operation may cause hyperkalemia and hyponatremia, a careful postoperative management of body fluid volume and electrolyte concentration is mandatory.

Summary of the diagnostic procedure and timing of referral to the specialists. The Endocrine Society, USA, issued the Clinical Guidelines of Primary Aldosteronism,[694] and the Japan Endocrine Society also presents a diagnostic and therapeutic guide on its homepage.[702] Figure 12-2 shows the procedure for the diagnosis of PA on routine clinical practice of hypertension. In hypertensive patients, particularly those at a higher risk of PA, simultaneous measurement of PRA and PAC is strongly recommended. If the ARR exceeds 200 (PAC: pg ml^{-1}) and particularly if the PAC exceeds 150 pg ml^{-1}, patients should be referred to specialists in hypertension and/or endocrinology. It is noted, however, that ARR values can vary in each determination[696]

Table 12-5 Influence of various antihypertensive agents on PAC, PRA and ARR

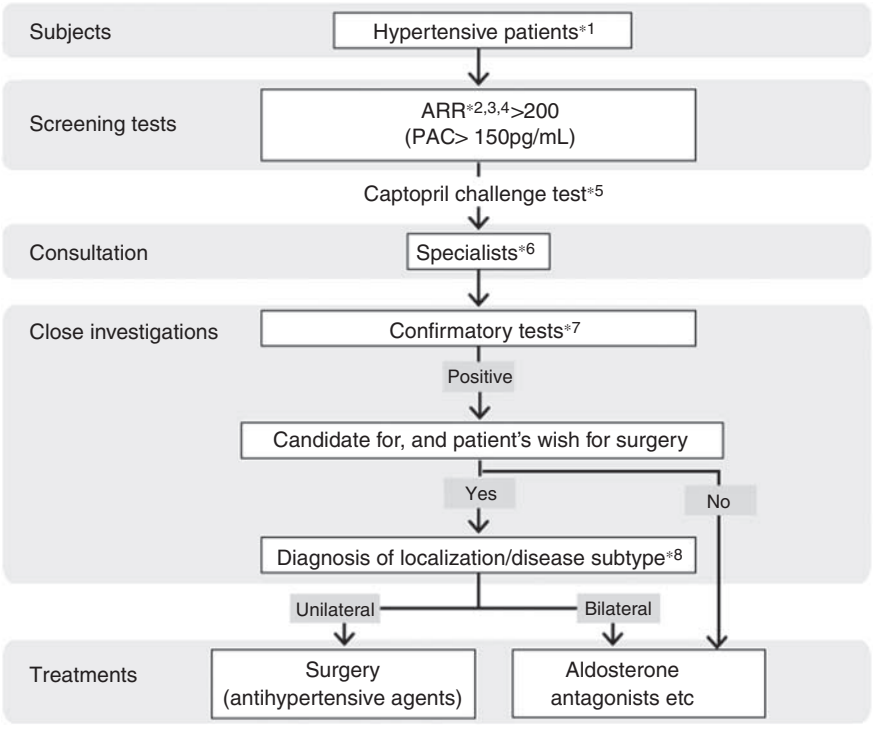
	PAC	*PRA*	*ARR*[a]
ACE inhibitors	↓	↑↑	↓[b]
ARB			
β-blockers	↓	↓↓	↑[c]
Ca channel blockers	→∼↓	↑	↓[b,d]
Aldosterone antagonists	↑	↑↑	↓[b]

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.
[a]ARR: PAC/PRA ratio.
[b]Possibility of false-negative results.
[c]Possibility of false-positive results.
[d]The influence is less marked than those of ACE inhibitors and ARBs.

Table 12-6 Confirmatory tests of aldosterone excess

	Methods	*Criteria for positive results*	*Adverse effects*
Captopril challenge test	Oral administration of captopril at 50 mg (crushed)	ARR (60 or 90 min) ⩾ 200 (or ⩾ 350)[a]	Hypotension
Furosemide-upright test	i.v. injection of furosemide at 40 mg and upright posture for 2 h	$PRA_{max} \leqslant 1.0$ ng ml^{-1} h^{-1} (or ⩽ 2.0)	Orthostatic hypotension, a decrease in the serum K level
Saline infusion test	i.v. drip infusion of saline at 2 l per 4 h	PAC (4 h) ⩾ 85 pg ml^{-1} (⩽ 50 ∼ 100)	Rise in blood pressure, not indicated in patients with impaired heart/kidney function, a decrease in the serum K level

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.
[a]ARR is calculated with PAC in the unit of pg ml^{-1}.



*1 Especially at higher risk (all patients if possible).
*2 ARR: PAC/PRA ratio
*3 Antihypertensive agents: Test after switching drugs to Ca channel antagonists and/or α-blockers.
*4 Repeated measurements are recommended.
*5 Cessation drugs in the morning of the test day, test should be done from early morning to 9 AM, fasting, after 30 minutes bed rest.
*6 Certified specialists of the Japan Society of Hypertension or Endocrinology.
*7 At least one of the following tests should be performed: captopril challenge, furosemide-upright, and saline infusion.
*8 Adrenal CT, adrenal scintigraphy, and/or adrenal vein sampling

Figure 12-2 Algorithm for the diagnosis of primary aldosteronism.

and so repeated measurements are recommended. Alternatively, patients may be referred after a captopril challenge test, which can be performed in the outpatient clinic. Specialists should perform at least one of the confirmatory tests and, if positive and surgery is indicated, decide on the execution of adrenal CT and adrenal vein sampling (Figure 12-2).

b. Other conditions associated with hypermineralocorticoid excess

Of the subtypes of congenital adrenocortical hyperplasia, deficiency of 17α-hydroxylase and 11β-hydroxylase causes hypertension with hypokalemia due to an increase in deoxycorticosterone. Glucocorticoid supplementation is the basic treatment of choice. Deoxycorticosterone (DOC)- and corticosterone-producing tumors are rare causes of mineralocorticoid excess.

c. Cushing's syndrome

Characteristic Cushing's signs, hypertension and diabetes mellitus are caused by the autonomous and excessive secretion of cortisol. The disease is observed more frequently in women, with a male–female ratio of 1:3–1:4. The disease conditions are classified into adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent forms. The former includes Cushing's syndrome due to adrenal adenoma and ACTH-independent macronodular adrenal hyperplasia, whereas the latter includes Cushing's disease due to ACTH-producing pituitary tumors and ectopic ACTH-producing tumors.

Diagnostic clues. Attention must be paid to characteristic physical findings including central obesity, moon face, buffalo humps, red striae, skin thinning and bruises and defeminizing symptoms such as hirsutism due to androgen excess. Additional findings, although not specific to the disease, include hypertension, diabetes mellitus, hyperlipidemia, osteoporosis, urolithiasis and nail trichophytosis. Cardiovascular complications such as heart failure are common and affect disease prognosis.[703] On general laboratory tests, eosinopenia and hypokalemia should be noted. As there is a report that 7.5% of patients with adrenal incidentaloma had Cushing's syndrome, a careful differential diagnosis is necessary.

Endocrinological examinations. Increases in plasma cortisol level and urinary free cortisol excretion, the absence of cortisol suppression on the dexamethasone suppression test (overnight method; 0.5 and 1 mg) and the disappearance of diurnal changes in the plasma cortisol level must be established. Then, whether the condition is ACTH dependent or independent must be determined by measuring the plasma ACTH and its response to a corticotropin-releasing hormone (CRH) challenge test. The adrenal and pituitary glands are subjected to imaging workup by adrenal CT and pituitary MRI, respectively.

Treatments. Treatments by laparoscopic adrenalectomy for adrenal adenoma, trans-sphenoidal hypophysectomy for Cushing's disease and surgical resection of the causative mass for ectopic ACTH-producing tumor are the treatments of choice. Although strict antihypertensive

therapy is necessary before surgery or in inoperable patients, Cushing's syndrome is generally refractory to medical treatment. Blockers of the RA system, Ca channel blockers, diuretics and α-blockers are used in combination.

Adrenal subclinical Cushing's syndrome. Although about 50% of adrenal incidentalomas are considered to be non-functioning, subclinical Cushing's syndrome is often observed in patients with 'apparently non-functioning' adrenal incidentaloma. The diagnostic criteria by the Ministry of Health, Labour and Welfare, Japan, include (1) the presence of an adrenal incidentaloma, (2) absence of Cushing's signs, (3) a normal basal blood cortisol level and (4) the absence of cortisol suppression on dexamethasone suppression test (overnight method) as essential findings. Diagnosis of adrenal subclinical Cushing's syndrome is made if there are additional subitems including the suppression of ACTH secretion. The syndrome is often complicated by hypertension, obesity and abnormal glucose tolerance, frequently exacerbated with time, but alleviated after surgery, so that surgery should be considered if possible. If the tumor is 4 cm or greater in diameter or increases in size, it should be resected, considering the possibility of malignancy.

Timing of referral to the specialists. If Cushing's syndrome is suspected due to characteristic Cushing's signs or the concurrence of resistant hypertension and diabetes mellitus, or if adrenal incidentaloma has been detected, patients should be referred to specialists.

d. Pheochromocytoma

Pheochromocytoma is associated with hypertension and abnormal glucose tolerance due to catecholamine excess. The disease is observed at any age, even in elderly people. As about 10% of the disease is either extra-adrenal, bilateral, multiple and malignant, it is called 'the 10% disease'. The disease may be observed as a lesion of multiple endocrine neoplasia, in which multiple lesions develop in endocrine glands, and attention to familial history is necessary. Pheochromocytoma can be diagnosed by the measurement of catecholamines and imaging examination, and blood pressure and catecholamine levels are normalized by resection of the tumor. The greatest problem is malignant pheochromocytoma. Its diagnosis is difficult at initial surgery if not associated with distant metastasis. Recently, the involvement of mutation of the pheochromocytoma-sensitive gene, particularly succinate dehydrogenase subunits B and D (SDHB and SDHD), has been suggested.[704] Pathophysiological significance and clinical implications, however, await further investigation.

Diagnostic clues. Symptoms including headache, palpitation, perspiration, pallor, weight loss and paroxysmal hypertension are suggestive of pheochromocytoma. Hypertensive crisis is induced by various stimuli including exercise, stress, excretion and alcohol consumption. It may also be induced by intravenous metoclopramide injection. The disease may be detected as adrenal incidentaloma.

Endocrinological examinations. Increases in the plasma catecholamine level, 24-h urinary catecholamine excretion and urinary excretions of the metabolites, metanephrine and normetanephrine, must be confirmed. Provocation tests (glucagon, metoclopramide) and the phentolamine (Regitin) test using a decrease in blood pressure as an index[1–12] are not recommended because of problems with specificity and safety. If the plasma noradrenaline level is increased, the clonidine, a central α_2-receptor agonist, test is useful.

Imaging workup. The localization of the tumor is determined by CT. However, as the use of a contrast medium is essentially contraindicated because of possible induction of hypertensive crisis, phentolamine and propranolol must be prepared if contrast enhancement is indicated. On MRI, a low signal intensity on T1-weighted and a high signal intensity on T2-weighted images are characteristic findings. If the localization of the tumor is unknown or extraadrenal, the whole body should be scanned by iodine-131 metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, MRI and/or CT. Although MIBG scintigraphy is useful for the detection of metastatic lesions of malignant pheochromocytoma, false-negative results are experienced if the lesion is small or functionally weak. Although 18-fluorine fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) is useful in patients with negative results on MIBG scintigraphy, it is not covered by medical insurance in Japan.

Treatments. Resection of the tumor is the treatment of choice. For preoperative blood pressure management, correction of the circulating plasma volume and prevention of intraoperative crises, α_1-blockers, such as doxazosin, should be administered. β-blockers are used for the treatment of tachycardia and arrhythmias with concomitant administration of α_1-blockers. As the differentiation between benign and malignant diseases is difficult by histopathological examination, a periodic postoperative follow-up is recommended. Pheochromocytoma crises should be treated by the intravenous injection or drip infusion of phentolamine, followed by the administration of selective α_1-blockers.

Timing of referral to the specialists. Palpitation and paroxysmal hypertension are suggestive of pheochromocytoma. Patients should be referred to specialists if a high blood catecholamine level, high metanephrine or normetanephrine level (corrected for creatinine) in a spot urine sample ($>300\,\mathrm{ng\,mg^{-1}\cdot Cr}$) or adrenal incidentaloma is noted.

e. Other endocrine hypertension

Acromegaly. Acromegaly is caused by growth hormone-producing pituitary adenoma. Hypertension is noted in about 40% of patients. The diagnosis is suggested by characteristic physical findings, including enlargement of the peripheral parts of limbs, and is established by high blood growth hormone and insulin-like growth factor-1 levels, the absence of growth hormone suppression on the 75 g oral glucose tolerance test (OGTT), paradoxical responses on the thyroid-releasing hormone (TRH) test and the presence of a pituitary tumor. Transsphenoidal hypophysectomy is the treatment of choice. Hypertension is treated with Ca channel blockers, blockers of the RA system, and others in combination.

Basedow's disease. Isolated systolic hypertension with an increased pulse pressure is characteristic. Signs and symptoms including palpitation, finger tremor, increased appetite, weight loss, goiter and exophthalmos suggest the disease. The diagnosis is based on the measurement of fT_3, fT_4, thyrotropin-releasing hormone (TSH) and thyroid autoantibody (TSAb or TRAb). The disease is treated by the administration of antithyroid drugs. 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. Patients should be referred to specialists for the differentiation of the disease from other thyrotoxic disorders such as painless thyroiditis.

Hypothyroidism. Hashimoto's disease is the major cause of hypothyroidism. It is, however, rarely diagnosed due to hypertension. Nonspecific symptoms such as malaise, goiter and hypercholesterolemia are clues to the diagnosis. Sodium levothyroxine replacement therapy

comprises the treatment. Hypertension can be treated with Ca channel blockers, blockers of the RA system, and others in combination.

Primary hyperparathyroidism. The disease is caused by parathyroid adenoma or hyperplasia. Hypertension is observed in about 20% of patients, but it rarely leads to diagnosis. Hypercalcemia and/or urolithiasis are clues to the diagnosis. Resection of the pathological parathyroid gland is the treatment of choice.

POINT 12D
Vascular hypertension

1. **Vascular hypertension includes aortitis syndrome (Takayasu's arteritis), other forms of angiitic hypertension (polyarteritis nodosa, generalized scleroderma), aortic coarctation and vascular hypertension accompanied by an increase in cardiac output (aortic insufficiency, patent ductus arteriosus, arteriovenous fistula and so on). Therapeutic principles matched for various diseases must be followed.**

Hypertension due to brain or central nervous system disorders

1. **Hypertension due to brain or central nervous system disorders includes that caused by an increase in intracranial pressure due to cerebrovascular disorders (cerebral hemorrhage, cerebral infarction and chronic subdural hemorrhage), brain tumor, encephalitis (myelitis), brain injury, and so on (Cushing's response) or compression by arteries around the rostral ventrolateral medulla, which is the center of sympathetic activities. Radical treatment for each cause should be performed first.**

Hereditary hypertension

1. **Essential hypertension is a multiple-factor disorder in which genetic and environmental factors are involved. Genetic factors are considered to be involved in 30–70% of patients.**
2. **The contribution of each individual gene polymorphism to hypertension is small, but salt sensitivity gene polymorphism is frequently observed in the Japanese population.**
3. **Congenital blood pressure abnormalities caused by single-gene abnormalities exist but are rare.**

4) VASCULAR HYPERTENSION

a. Arteritis syndrome (Takayasu's arteritis)

Arteritis syndrome (Takayasu's arteritis) is an as-yet-unexplained non-specific large-vessel arteritis that causes obstructive or dilating lesions in the aorta and its major branches, the pulmonary and coronary arteries.[705] This disease is observed more frequently in women, and its primary findings are lateral differences in the pulse and blood pressure, neck or abdominal bruit, and an enhanced carotid sinus reflex.[706] Hypertension is observed in about 40% of patients with aortitis syndrome and markedly affects the prognosis of this disease. Its diagnostic method using FDG-PET has recently been established.[707] Hypertension of this disease occurs by more than one pathogenic mechanism, and its variations are (1) RVHT, (2) hypertension due to aortic coarctation (variant aortic coarctation), (3) hypertension due to aortic insufficiency and (4) hypertension due to aortic wall sclerosis.[705,706]

Renovascular hypertension is observed in about 20% of patients with aortitis syndrome. In patients with bilateral subclavian artery stenosis, it must be remembered that the upper limb blood pressure is lower than the aortic blood pressure, leading to underestimation. Vascular reconstruction is indicated for aortic coarctation and RVHT when (1) antihypertensive drugs have become ineffective for the sufficient control of blood pressure, (2) antihypertensive treatment causes renal dysfunction, (3) congestive heart failure has occurred and (4) the renal artery has narrowed bilaterally.[705] PTRA for RVHT is mildly invasive and effective, but the restenosis rate is higher in this disease than in diseases such as fibromuscular dysplasia, and the long-term efficacy of this procedure is about 50%, which is lower than the 90% for successful bypass surgery. Moreover, aortic insufficiency is an important complication that determines the prognosis of this disease, so that, under an appropriate antihypertensive treatment, indications of aortic valve replacement (including Bentall's operation) should be evaluated following those for aortic insufficiency in general.

Surgical treatment for this disease should be performed after the complete resolution of active inflammation or control of inflammation with corticosteroids. Although the long-term outcome of surgery in patients with this disease is generally good, attention must be paid to the occurrence of anastomotic aneurysm and dilation of the rest of the ascending aorta.[708] Hypertension due to renal artery stenosis and aortic coarctation, congestive heart failure due to aortic insufficiency, ischemic heart disease, dissecting aneurysm and aneurysmal rupture are considered to be important lesions that determine the prognosis. Therefore, the long-term prognosis is expected to be improved by early and appropriate treatments with medicine (steroids and antihypertensive drugs) and appropriate surgical treatments for severely ill patients.[705]

Antihypertensive treatments for this disease are basically the same as those for renovascular or essential hypertension. However, as cerebral blood flow may be reduced in patients with stenotic lesions in the carotid artery, sufficient evaluation of, and attention to, the cerebral blood flow is necessary in conducting antihypertensive treatment.

b. Other forms of angiitis

Hypertension due to angiitic syndrome other than aortitis syndrome includes polyarteritis nodosa and progressive systemic scleroderma (PSS). Necrotic arteritis of small- and middle-sized muscular arteries of the whole body, including the renal artery in polyarteritis nodosa and spasms of the renal vessels in PSS,[709] is involved in the etiology of hypertension. Polyarteritis nodosa is complicated by hypertension ($>160/95$ mm Hg) in about 30% of patients, and some patients develop rapidly progressing nephritis. Patients with PSS often show renal crisis (malignant hypertension and renal failure). Other than PSS, causes of death in the acute period are cerebral hemorrhage, myocardial infarction, heart failure and renal failure, all of which are closely related to the hypertension they complicate; therefore, the importance of blood pressure control must be recognized. For conditions other than PSS, steroid pulse therapy and immunosuppressant therapies are performed in combination in the acute period. The method for blood pressure control is the same as that for renal parenchymal or essential hypertension. In PSS, a treatment basically the same as that for malignant hypertension is indicated, and ACE inhibitors and Ca channel blockers are markedly effective.

c. Coarctation of aorta

In this condition, blood pressure is increased in the upper limb proximal to the site of stenosis and reduced in the lower limb distal to the site of stenosis, with a systolic blood pressure difference between the upper and lower limbs of 20–30 mm Hg or greater. Proximal hypertension is an indication for the surgical relief of stenosis or

angioplasty using a balloon catheter in childhood, and a better outcome has been reported on earlier treatment.[710] In this disease, the RA system and sympathetic nervous system as well as mechanical factors such as an increase in the arterial reflection waves from the site of aortic coarctation,[711,712] an increase in the peripheral vascular resistance in the upper body and weakening of the Windkessel effect of the aorta are known to be involved in hypertension.[713] Hypertension may persist for a long period after repair depending on its preoperative duration, and antihypertensive treatments appropriate for the condition should be performed in such a situation.

d. Vascular hypertension accompanied by an increase in cardiac output

In patients with aortic insufficiency, patent ductus arteriosus, arteriovenous fistula, and so on, systemic hypertension may be caused primarily by an increase in the stroke volume.

Hypertension is cured by treatment of the primary disease in all these patients.

5) HYPERTENSION DUE TO DISEASES OF THE BRAIN OR CENTRAL NERVOUS SYSTEM

Hypertension due to cerebrovascular accidents (cerebral hemorrhage, cerebral infarction and chronic subdural hematoma) is described in detail in Chapter 6. In patients with intracranial diseases such as brain tumors (particularly those in the posterior cranial fossa), encephalitis (myelitis) and brain injury, peripheral sympathetic nervous system activities are increased through the mechanical stress increased intracranial pressure at the brainstem including the nuclei of the solitary tract of the medulla oblongata, possibly causing hypertension (Cushing's response),[648] but this rarely happens. Occasionally, patients with cerebrovascular accidents may present with paroxysmal hypertension and be misdiagnosed with pheochromocytoma. Also, the mechanism of hypertension caused by an increase in sympathetic activities due to the compression of the rostral ventrolateral medulla, which is the vasomotor center of sympathetic nervous system, by surrounding arteries, and patients in whom such hypertension was relieved by surgical decompression were reported in the 1980s.[714] Similar hypertensive cases have been reported on the involvement of an increased sympathetic activity due to the compression of the rostral ventrolateral medulla by surrounding arteries.[715–719]

Brain tumors should be detected promptly by head CT or MRI, and radical treatment such as removal or debulking of the tumor must be considered first. In patients with head trauma, early administration of an intravenous analgesic at a relatively high dose is considered useful in reducing intracranial pressure and controling hypertension. The therapeutic efficacy of decompressing rostral ventrolateral medulla has not been fully established, and the treatment is only considered for patients not responding to ordinary antihypertensive medication.[720] For medical treatment, β-blockers, α-blockers and centrally acting agents can be used first and may be combined with Ca channel blockers or other drugs if necessary.

6) HEREDITARY HYPERTENSION

Essential hypertension is a multifactorial disease in which many genetic and environmental factors are involved. The morbidity of hypertension is reported to be approximately 3.5 times higher in pairs of hypertensive siblings than in the general population,[721] and the contribution of genetic factors is estimated to be approximately 30–70%. Common individual variations in the nucleotide sequence of the genome observed in the general population are called 'genetic polymorphisms'. Many correlations between gene polymorphisms and the predisposition to hypertension or its complications have been reported primarily concerning the RA system, and multiple single-nucleotide polymorphisms[722] and candidate loci[723] were clarified by the genome-wide association study conducted in Japan as part of the Millennium Genome Project. However, the contribution of each gene polymorphism is relatively small, and the diagnosis of essential hypertension based on information concerning gene polymorphisms alone is considered difficult. On the other hand, the risk allele frequency of salt-sensitive hypertension was higher in the Japanese[724] population than in Caucasians. Therefore, the possible usefulness of information concerning gene polymorphisms for the design of lifestyle modifications, such as salt reduction, and selection of antihypertensive drugs has also been suggested.

In contrast, rare heritable blood pressure abnormalities caused by single gene mutation and diagnosed by gene analysis have been reported. Particularly, many such blood pressure abnormalities are due to gene mutations of channels or cotransporters regulating water and electrolyte balance at the renal tubular level,[725] and differential diagnosis should be considered when blood pressure abnormalities occur in children or are accompanied by electrolyte abnormalities. Table 12-7 shows the genes responsible for and clinical characteristics of hereditary blood pressure abnormalities.

In conducting gene analyses, adherence to the Ethics Guidelines for Human Genome/Gene Analysis Research[726] is essential.

POINT 12E
Drug-induced hypertension

1. **Non-steroidal anti-inflammatory drugs (NSAIDs) raise the blood pressure and antagonize the antihypertensive effects of diuretics, β-blockers, ACE inhibitors and ARBs. Their effects tend to be more notable in elderly people.**
2. **The administration of glycyrrhizin, a major active component of glycyrrhiza, at a high dose may induce hypertension accompanied by hypokalemia (pseudoaldosteronism). Attention is necessary particularly when using *kampo* drugs. If the discontinuation of administration is difficult, use an aldosterone antagonist.**
3. **Glucocorticoids also induce an increase in blood pressure if used at a large dose. If their administration is unavoidable, common antihypertensive drugs (Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics, and so on) should be used.**
4. **The use of cyclosporine, tacrolimus, erythropoietin, estrogen and drugs with sympathomimetic actions may cause an increase in blood pressure. If blood pressure increases during the use of these drugs, a reduction in the dose or discontinuation of administration should be considered. If they cannot be discontinued, use Ca channel blockers, ACE inhibitors, ARBs or α-blockers.**

7) DRUG-INDUCED HYPERTENSION

Drugs such as NSAIDs, glycyrrhizin preparations, glucocorticoids, cyclosporine, erythropoietin, oral contraceptives and sympathomimetic drugs are suggested to have hypertensive effects, induce hypertension and attenuate the blood pressure-lowering effects of antihypertensive drugs if used concomitantly (Table 12-8). Many hypertensive patients also have other diseases and consult multiple medical organizations. Therefore, if the blood pressure management

Table 12-7 Genes involved in congenital blood pressure abnormalities and their clinical features

Hereditary hypertension	*Causative genes*	*Clinical features*
Early-onset type hypertension with severe exacerbation during pregnancy	Mineralocorticoid receptor (MR) (*NR3C2*), autosomal dominant	Onset at <20 years of age, development of eclampsia, blood-pressure increase through the actions of progesterone on mutant MR
Glucocorticoid-remediable aldosteronism (GRA) (FH-I)	11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) chimera, autosomal dominant	Low PRA, high PAC, low K (rare), glucocorticoid/spirono-lactone responsiveness
11β-hydroxylase deficiency (11β-OHD)	11β-hydroxylase (*CYP11B1*), autosomal recessive	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, virilization
17α-hydroxylase deficiency (17α-OHD)	17α-hydroxylase (*CYP17*), autosomal recessive	Congenital adrenal hyperplasia, low PRA, high DOC, high ACTH, low cortisol, feminization
Liddle syndrome	Epithelial Na channel β/γ subunits (*SCNN1B, SCNN1G*), autosomal dominant	Low PRA, low PAC, metabolic alkalosis, Na retention, low K, triamterene responsiveness
Gordon syndrome (PHA IIC, IIB)	Serine–threonine kinase, (IIC: *WNK1*; IIB: *WNK4*), autosomal dominant	High K, low PRA, metabolic acidosis, normal PAC, thiazide responsiveness
Apparent mineralocorticoid excess (AME) (New syndrome)	11β-hydroxysteroid dehydrogenase (*HSD11B2*), autosomal recessive	Low PRA, low PAC, low K, delayed growth, metabolic alkalosis, spironolactone responsiveness
Metabolic defects cluster (hypertension, hypercholesterolemia, hypomagnesemia)	Mitochondrial tRNA, isoleucine (*MTTI*), maternal inheritance	Low Mg, low K, permeability: 50%, onset at <50 years of age
Hereditary hypotension		
Type 1/2 Bartter syndrome	Type 1: Na-K-2Cl cotransporter (*SLC12A1*), autosomal recessive Type 2: ATP-sensitive K channel (*KCNJ1*), autosomal recessive	Severe, low K, low Mg, metabolic alkalosis, hyperprosta-glandin E2 syndrome, high PRA, high PAC
Type 3/4 Bartter syndrome	Type 3: kidney Cl channel (*CLCNKB*), autosomal recessive Type 4: Barttin (*BSND*), autosomal recessive	Onset during childhood, polyuria, tetanus (rare), low K, high PRA, high PAC, hypocalciuria
Gitelman syndrome	Thiazide-sensitive Na-Cl cotransporter (*SLC12A3*), autosomal recessive	Onset during adolescence, milder than Bartter syndrome, hypocalciuria, high PRA, high PAC, low K, low Mg
PHA I	Mineralocorticoid receptor (*NR3C2*), autosomal dominant, epithelial Na channel α/β/γ subunit (*SCNN1A/B/G*), autosomal recessive	Onset during the neonatal period/infancy, high PRA, low Na, high K, age-related amelioration of symptoms

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity.

used to be adequate but has become difficult, or in poorly controlled hypertension, the possibility of drug-induced hypertension should be considered. Also, if these drugs are used, attention must be paid to blood pressure control, and their administration simply as routine must be avoided.

a. Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs cause water and Na retention and suppress vasodilation by inhibiting cyclooxygenase (COX) in the process of prostaglandin production from arachidonic acid in the kidney.[727] 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 inhibit prostaglandin production and increase blood pressure by suppressing the renal function. COX has two isoforms, COX-1 and COX-2, which is induced in inflammation. Although classic NSAIDs non-selectively inhibit both, there are also selective inhibitors of COX-2. The harmful effects of non-selective and selective COX-2 inhibitors on the cardiovascular system are related to the suppression ratio between COX-1 and COX-2, tissue-specific COX distribution and so on, rather than the selectivity. Therefore, similar caution is necessary when using NSAIDs that are non-selective as well as selective COX-2 inhibitors.[728–730]

In elderly people, NSAIDs often cause acute renal dysfunction, which further aggravates the rise in blood pressure, and they also increase the risk of heart failure if used concomitantly with diuretics compared with diuretics alone. Therefore, if NSAIDs are administered to elderly hypertensive patients, they should be used at a low dose for a limited period with careful observation and examination of the renal function.

Diuretics simultaneously inhibit the reabsorption of NaCl and stimulate prostacyclin production in the renal tubules. Therefore, the antihypertensive effects of diuretics are reduced when they are used with NSAIDs. The antihypertensive effects of ACE inhibitors and β-blockers are also reduced by their concomitant use with NSAIDs. The effects of their concomitant use with ARBs have not been evaluated sufficiently, but ARBs appear to be affected similarly to ACE inhibitors. The effects of NSAIDs on the antihypertensive effects of Ca channel blockers are considered to be minor.

b. Glycyrrhiza (licorice), glycyrrhizin

Glycyrrhiza is contained in drugs for liver and gastrointestinal diseases, many other *kampo* drugs, supplements, cosmetics and so on. Glycyrrhizin, a major active component of glycyrrhizia, inhibits 11β-hydroxylated steroid dehydrogenase, which metabolizes cortisol into inactive cortisone, enhances the actions of endogenous

Table 12-8 Drugs causing drug-induced hypertension and hypertension treatment

Causative drugs	*Etiologies of hypertension*	*Strategies to treat hypertension*
NSAIDs	Water/Na retention and vasodilator suppression through the inhibition of renal prostaglandin production, attenuation of the antihypertensive effects of ACE inhibitors/ARBs/β-blockers/diuretics	Dose reduction/discontinuation of NSAIDs, dose elevation of an antihypertensive drug that has been administered, Ca channel blockers
Glycyrrhiza (licorice), therapeutic drugs containing glycyrrhizin, drugs for digestive disorders, *kampo* drugs, supplements, cosmetics	Water/Na retention and K reduction through the enhancement of intrinsic steroid actions related to the prolongation of the half-life of cortisol associated with the inhibition of 11β-hydroxylated steroid dehydrogenase	Dose reduction/discontinuation of *kampo* drugs, aldosterone antagonist
Glucocorticoids	Increases in renin-substrate and erythropoietin productions and the inhibition of NO production may be involved in the mechanism, but it remains to be clarified.	Dose-reduction/discontinuation of glucocorticoids, Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics
Cyclosporine, tacrolimus	Nephrotoxicity, activation of the sympathetic nervous system, inhibition of calcineurin, vascular endothelial cell dysfunction	Ca channel blockers, combination therapy with Ca channel blockers and ACE inhibitors, diuretics
Erythropoietin	Enhancement of vascular viscosity, vascular endothelial dysfunction, an increase in the intracellular Na level	Dose reduction/discontinuation of erythropoietin, Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics
Estrogen, oral contraceptives, hormone replacement therapy	An increase in renin-substrate production	Discontinuation of estrogen preparations, ACE inhibitors, ARBs
Drugs with sympathomimetic actions, phenylpropanolamine, tricyclic/tetracyclic antidepressants, monoamine oxygenase inhibitors	α-Receptor stimulation, inhibition of catecholamine reuptake at the sympathetic nerve terminals	Dose reduction/discontinuation of drugs with sympathomimetic actions, α_1-blockers

Abbreviations: NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs.

steroids by prolonging the half-life of cortisol,[731] and enhances Na and water retention and reduces the potassium level, causing pseudoaldosteronism. The glycyrrhizin dose, administration period and age (>=60 years) are considered to be risk factors for glycyrrhizin-induced hypertension, but the occurrence of hypertension is rare unless glycyrrhizin is administered at a high dose over a prolonged period.

Glycyrrhizin-induced hypertension should be suspected if hypokalemia is concurrent with hypertension, and if the renin activity and plasma aldosterone level are reduced (pseudoaldosteronism). As the use of *kampo* drugs or supplements is rarely reported by patients themselves, the possibility of their use must be carefully evaluated. Clinically, glycyrrhizin-induced hypertension is resolved by the withdrawal of glycyrrhiza for a few weeks (maximum 4 months) or concomitant administration of an aldosterone antagonist.

c. Glucocorticoids

Glucocorticoids rarely cause hypertension at low doses even in the long-term treatment of asthma or rheumatoid arthritis. However, the long-term administration of glucocorticoids at intermediate doses frequently induces hypertension.[732] As with other drugs, blood pressure increased more notably in elderly patients with increases in the dose of prednisolone, and marked increases were observed when the dose was 20 mg day^{-1} or higher. Hypertension was observed in 37.1% of these elderly patients, and hypertensive patients more often had a familial history of hypertension than non-hypertensives.[733] The clarification of the mechanism of glucocorticoid-induced hypertension remains insufficient, although an increase in angiotensin II due to elevated renin substrate production, vasoconstriction due to an increase in erythropoietin production, inhibition of nitrogen monoxide production and impairment of vascular endothelial function due to the inhibition of nitrogen monoxide use by the excess production of superoxides have been suggested.[734]

Treatment is primarily a decrease in dose or withdrawal of the glucocorticoid. If this is difficult, blood pressure should be controlled with Ca channel blockers, ACE inhibitors, ARBs, β-blockers, diuretics, and so on.

d. Others

Cyclosporine and tacrolimus are used for immunosuppression after organ and bone marrow transplantation. Both of them frequently cause hypertension, although frequency varies with dose, treatment period and pathological conditions. Although the mechanism of the occurrence of hypertension has not been sufficiently clarified, the involvement of nephrotoxicity, stimulation of the sympathetic nervous system, inhibition of calcineurin and vascular endothelial cell dysfunction are suspected. Ca channel blockers are effective in the treatment of hypertension due to immunosuppressants, and their combination with ACE inhibitors has been reported to be even more effective.[735] Although diuretics are also effective, caution regarding uric acid metabolism is necessary in patients with kidney transplantation. As Ca channel blockers may increase the blood concentration of cyclosporine and tacrolimus, measurement of the blood concentrations of these immunosuppressants should be considered if necessary.

Although erythropoietin alleviates renal anemia, it increases the blood pressure. In Japan, an increase in blood pressure was reported in 29% of patients surveyed in postmarketing research.[736] Its possible mechanism involves increases in the hematocrit and blood viscosity

associated with recovery from anemia by erythropoietin treatment and a resultant increase in peripheral vascular resistance, but this possibility has been refuted by one report. An increase in the intracellular Na concentration, vascular endothelial dysfunction and genetic predisposition may also be involved. There is also a report that no increase in blood pressure due to erythropoietin was observed before hemodialysis.[737] However, although erythropoietin is reduced or discontinued if hypertension develops or if blood pressure increases, antihypertensive drugs have also been reported to be effective if the increase is mild.[738] On the other hand, blood pressure control has been reported to be insufficient despite the administration of antihypertensive drugs in chronic dialysis patients (patients registered at the Japanese Society for Dialysis Therapy), of whom 82% were taking erythropoietin.[739]

Estrogen is used in oral contraceptives and drugs for climacteric disturbance, but has been considered to cause an increase in blood pressure or thromboembolism at a high dose. Details of the mechanism of estrogen-induced hypertension have not been clarified, although an increased renin substrate production in the liver has been proposed. An investigation of the relationship between the use of oral contraceptives and health showed that oral contraceptives were safe, although blood pressure was slightly higher in users than in nonusers.[740] However, although the increase in blood pressure was dose dependent, caution is necessary even at a low dose. No sufficient analysis of the relationship between oral contraceptives and hypertension has been made in Japan. When using oral contraceptives, blood pressure should be measured periodically, their use should be discontinued if an increase in the blood pressure is observed and other contraceptive measures should be selected. If they cannot be discontinued, the administration of ACE inhibitors or ARBs should be considered. Concerning hormone replacement therapy, see hypertension related to menopause in Chapter 9.

Drugs with sympathomimetic actions may induce increases in the blood pressure. An overdose of phenylpropanolamine, which is contained in drugs for the common cold, may elevate the blood pressure. Caution is needed in its concomitant use during treatment with a β-blocker alone, because it may induce a state of dominant α-receptor stimulation and cause a marked increase in blood pressure. Tri- or tetracyclic antidepressants may also inhibit the antihypertensive effects of peripheral sympatholytic drugs by inhibiting catecholamine uptake by sympathetic nerve terminals and induce hypertensive crisis or hypertensive urgency.[741] Monoamine oxidase inhibitors, which are used for the treatment of Parkinson's disease, also cause an increase in blood pressure or orthostatic dysregulation. A monoamine oxidase inhibitor and a tricyclic antidepressant must not be used simultaneously. The concomitant use of a monoamine oxidase inhibitor with ephedrine or methylephedrine may also cause an elevation in blood pressure and tachycardia. If hypertension is induced by these drugs, a reduction of the dose or discontinuation of administration is necessary, but if discontinuation is impossible, α_1-blockers or central sympatholytic agents should be administered.

As metoclopramide, a dopamine (D2) receptor antagonist used for the treatment of gastrointestinal disorders, β-blockers and tricyclic antidepressants, may cause the clinical activation of pheochromocytoma and hypertensive crisis,[742] caution is needed in their use.

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KEY TO REFERENCES

CT: controlled trial; GL: guidelines/experts' opinion; MA: meta-analysis; OS: observational study; RT: randomized trial; RV: review.