

Report

Guidelines for the Management of Hypertension for General Practitioners

Japanese Society of Hypertension Guidelines Subcommittee for
the Management of Hypertension

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Introduction

Many epidemiological studies have shown that hypertension is, irrespective of ethnicity, a major risk factor for cardiovascular diseases and closely related to mortality. An epidemiological study conducted on the general population of Hisaya-

ma, Japan, demonstrated that mildly hypertensive individuals with blood pressure of 140–159/90–99 mmHg had a significantly higher incidence of cerebral infarction than did subjects with lower blood pressure, and that increasing blood pressure was positively related to the incidence of stroke (1) (Fig. 1). This correlation is more obvious for cerebral hemorrhage than cerebral infarction. Hypertension is a risk factor

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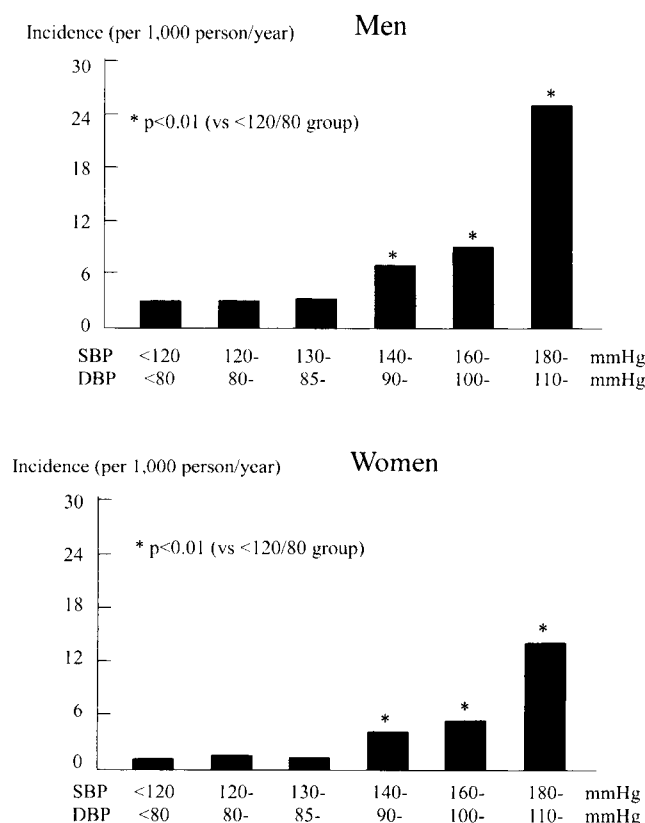


Fig. 1. Age-adjusted incidence of cerebral infarction by blood pressure groups in general population not taking anti-hypertensive drugs, the Hisayama Study, 1961-1993.

for ischemic heart disease and renal disease as well.

Health Japan 21, proposed by the Health Service Bureau of the Japanese Ministry of Health and Welfare, estimated that an average 2-mmHg reduction of systolic blood pressure in the whole population would reduce stroke occurrence by 20,000 and stroke death by 10,000, and decrease the number of subjects disabled or experiencing decreased activities of daily living by 3,500. Moreover, if a decrease in deaths from ischemic heart disease is taken into account, the deaths from all cardiovascular diseases would be decreased by 20,000. Thus, nationwide antihypertensive measures are extremely important for the prevention of cardiovascular diseases.

Necessity for the Treatment of Hypertension

Blood pressure levels of the Japanese population have appeared to be decreasing since the first half of the 1960s, when levels had reached their highest. This is partially attributed to the increasing number of patients who take antihypertensive drugs. However, multicenter trials (2) conducted in Japan showed that the average blood pressure level of patients aged 50 years and over who are receiving antihypertensive treatment was 143/81 mmHg, indicating that about half of the patients did not achieve the target blood pressure

level, that is, lower than 140/90 mmHg. Therefore, the present state of hypertensive treatments in our country is hardly satisfactory.

Hypertension is one of the lifestyle-related diseases, and the importance of reducing dietary salt intake and weight control is obvious. Traditionally salt intake among the Japanese population has been high, although it had been decreasing in recent years. The National Nutrition Surveys found, however, that dietary salt intake in Japanese is rising again after hitting the lowest value of 11.7g/day in 1987. In 1995 it reached 13.2 g/day, which is as high as the average intake in the 1970s. The reasons for these phenomena should be investigated, and the importance of reducing dietary salt intake should be reemphasized. Campaigns aimed at teaching people about the importance of cardiovascular risk factors and giving them appropriate instructions about the management of hypertension are crucial. Early detection of hypertension is important, and the management of hypertension should be stringently implemented. It is especially important to instruct younger people, who should have access to information in their communities and workplaces and from their local governments.

For the prevention of cardiovascular diseases, priority should be placed on the management and treatment of hypertension. Due to the westernization of lifestyle among Japanese, obesity, diabetes and hyperlipidemia have been increasing in recent years, and these metabolic disorders are newly recognized risk factors for cardiovascular diseases in this population (3). Therefore, not only rigorous management of high blood pressure levels but also active management of risk factors other than hypertension is required to further prevent cardiovascular diseases.

Blood Pressure Measurement

Office (Clinic) Blood Pressure

Blood pressure should be measured with the subject in a sitting position at rest, using a mercury sphygmomanometer or an automatic sphygmomanometer with accuracy comparable to that of a mercury sphygmomanometer. Within 30 min prior to blood pressure measurement, smoking and the intake of any food that contains caffeine should be avoided. When measuring blood pressure, the sphygmomanometer cuff wound around the upper arm should be placed at heart level. Phase I Korotkoff sounds should be used to measure systolic blood pressure (SBP), and phase V Korotkoff sounds should be used to measure diastolic blood pressure (DBP). After at least two blood pressure measurements have been taken, the mean of the two stabilized blood pressure levels, that is, the two measurements whose difference in values is under 5 mmHg, should be adopted as the blood pressure.

The sphygmomanometer bladder generally used for adults is 13 cm wide by 22-24 cm long, as prescribed in the Japan Industrial Standards (JIS). A bladder with a width that is ap-

Table 1. Blood Pressure Classification in Adults

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

Table 2. Risk Factors for Cardiovascular Diseases

Hypertension
Smoking
Hypercholesterolemia
Diabetes
Advanced age (for men aged 60 years and older and for women aged 65 years and older)
Family history of juvenile onset cardiovascular diseases

proximately 40% of the upper arm circumference and a length that covers approximately 80% of the upper arm is internationally recommended. A special cuff should be used for children and obese people whose physical constitution exceeds the standard.

Home Blood Pressure

Home blood pressure measurement not only contributes to increased compliance with hypertension treatment but also helps people to evaluate the effects of antihypertensive drug treatment they are receiving. It is also helpful to identify isolated hypertension in patients who show hypertension only in office blood pressure measurements (so-called white-coat hypertension). In home blood pressure measurement, a hemodynamometer for the upper arm (4, 5) should be used and measurement should be performed in a sitting position at rest before meals and before taking antihypertensive medication. Home blood pressure levels are usually lower than office blood pressure levels. Blood pressure levels of 135/80 mmHg or greater should be treated as hypertension (6).

Twenty-Four-Hour Blood Pressure

Ambulatory blood pressure monitoring (ABPM) is useful for diagnosing and evaluating isolated office (white-coat) hypertension and refractory hypertension. Moreover, it has been shown that ABPM is more closely related to the degree of hypertensive organ damage than is casual blood pressure (7, 8). ABPM usually shows a lower blood pressure value than does clinic blood pressure. If the average blood pressure of a 24-h ABPM exceeds 135/80 mmHg, the subject should be

Table 3. Organ Damage and Cardiovascular Diseases

Heart
Left ventricular hypertrophy
History of angina pectoris and myocardial infarction
Heart failure
Brain
Cerebral hemorrhage, cerebral infarction
Transient ischemic attack
Kidneys
Proteinuria
Renal dysfunction, renal failure
Blood vessels
Atherosclerotic plaques
Aortic dissection
Occlusive arterial diseases

treated for hypertension.

Classification and Evaluation of Blood Pressure

Classification of Blood Pressure

Since the 1999 World Health Organization-International Society of Hypertension (WHO-ISH) guidelines' criteria (9) are substantially the same as the sixth report of the Joint National Committee (JNC VI) guidelines' criteria (10), the classification of blood pressure in the Japanese Society of Hypertension Guidelines (JSH 2000) corresponds to the 1999 WHO-ISH classification with the exception of borderline hypertension, which was excluded from JSH 2000 (Table 1). The suitability of these criteria has been proven in the investigation conducted in Japan (1, 11). The classification of clinic blood pressure levels should be based on the mean value of multiple blood pressure measurements made during several clinic visits. Several measurements should be performed during each visit, and the average of all the measurements should be used for classifying the person's blood pressure level. When a patient's SBP and DBP fall into different categories, the higher category should be applied.

Table 4. Stratification of Risk in Patients with Hypertension

Risk factors other than blood pressure	Blood pressure classification		
	Mild hypertension (140–159 / 90–99 mmHg)	Moderate hypertension (160–179 / 100–109 mmHg)	Severe hypertension (≥180 / ≥110 mmHg)
No risk factors	LOW RISK	MED RISK	HIGH RISK
Presence of risk factors beside diabetes	MED RISK	MED RISK	HIGH RISK
Presence of either diabetes, organ damage or cardiovascular disease	HIGH RISK	HIGH RISK	HIGH RISK

Table 5. Secondary Hypertension

Findings suggesting secondary hypertension	Classification of secondary hypertension
1. Clinical history young people, severe hypertension, resistant hypertension, acute onset or aggravation of hypertension in the elderly, history of proteinuria or renal diseases, long history of diabetes, history of weakness or paralysis of the limbs, paroxysmal headaches or palpitation, history of drug use, etc. 2. Physical findings moon face, central obesity, striae cutis, weight loss, tachycardia, sweating spells, labile hypertension, asymmetric pulse and blood pressure, upper body hypertension, bruits, etc. 3. Laboratory examinations proteinuria, urinary glucose, urine of low specific gravity, abnormal urinary sediment, increased plasma creatinine, hypokalemia, hypercalcemia, etc.	1. Renal parenchymal hypertension chronic glomerulonephritis, diabetic nephropathy, chronic pyelonephritis, polycystic kidney, etc. 2. Renovascular hypertension atherosclerosis, aortitis syndrome, fibromuscular dysplasia, etc. 3. Endocrine hypertension primary aldosteronism (adenoma, hyperplasia, cancers), hereditary adrenocortical hyperplasia, Cushing syndrome, pheochromocytoma, renin producing tumor, hyperthyroidism, hypothyroidism, acromegaly, etc. 4. Vascular hypertension coarctation of aorta, etc. 5. Drug induced hypertension glucocorticoids, glycyrrhizin, Chinese medicine, estrogen, nonsteroidal anti-inflammatory drugs, catecholamine analogues, tricyclic antidepressants, cyclosporine, erythropoietin, etc.

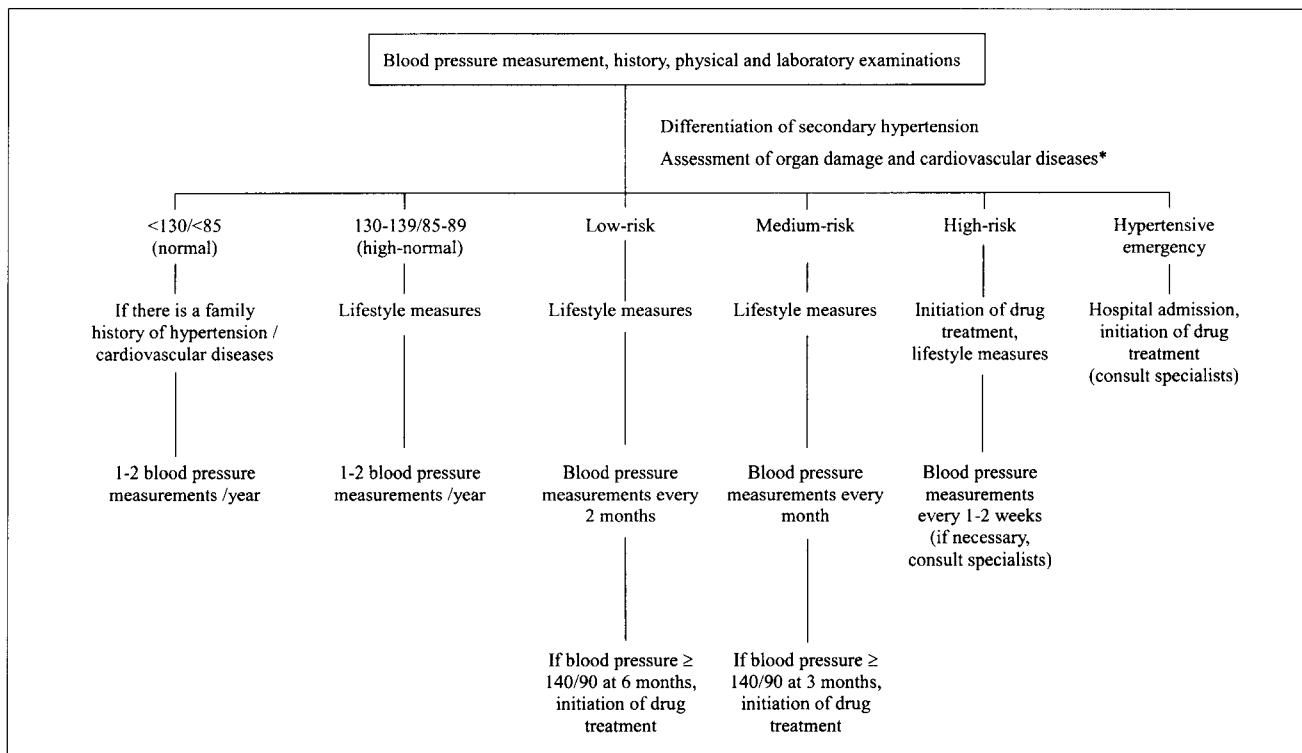
Evaluation and Stratification of Hypertension Risks

The prognosis of hypertensive patients is related to the presence of hypertension, risk factors other than hypertension, organ damage and cardiovascular diseases. Thus, stratifying risks requires the evaluation of the factors listed in Tables 2 and 3. In contrast to the case in Western countries, mortality from cerebrovascular disease in Japan is about twice as high as that from ischemic heart diseases (12), and morbidity resulting from cerebral hemorrhage is also 3 to 5 times higher than that resulting from myocardial infarction (13, 14). Since the cause of stroke is closely related to hypertension, the management of blood pressure is particularly important. In

JSH 2000, hypertensive patients are classified as being in the low-risk group, the medium-risk group or the high-risk group after the presence of the major risk factors shown in Table 4 are considered (diabetes and other risk factors, organ damage associated with hypertension, cardiovascular diseases).

Classification of Hypertension

Hypertension is classified into three categories, *i.e.*, essential hypertension, elderly systolic hypertension and secondary hypertension. Secondary hypertension includes renal parenchymal hypertension, renovascular hypertension, en-



*See Table 2 and Table 3.

Fig. 2. Management strategy.

doctrinal hypertension, vascular hypertension and drug-induced hypertension (Table 5). When a patient is found to have secondary hypertension, clinical and more specialized examinations should be performed.

Treatment Strategy

In order to identify and exclude secondary hypertension, practitioners should take blood pressure measurements, make a record of the patient's history and conduct clinical and laboratory examinations. Risk factors other than blood pressure, including the presence of organ damage and cardiovascular disease, should be evaluated at the same time. As shown in Fig. 2, a treatment plan should be set up based on these conditions.

Selection of Patients and Target Blood Pressure

Patients to Be Treated

Hypertensive patients across a wide range of ages should be treated, although the benefits of treatment for the population over the age of 85 years seem to be less than expected (15, 16). The initiation of antihypertensive treatment should be based on blood pressure levels and the stratification of risk factors (Table 4). A treatment plan should be set up in accordance with the flowchart shown in Fig. 2. Among hyperten-

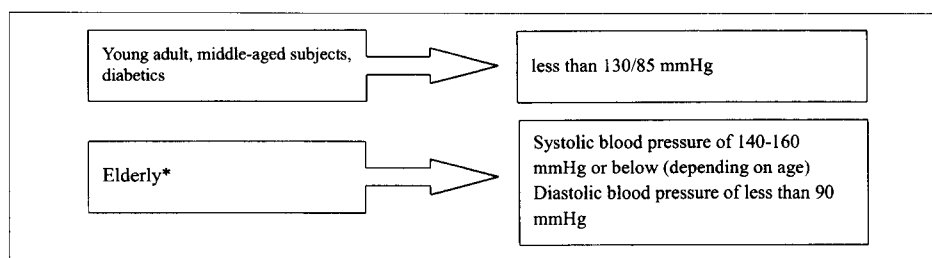
sive patients aged 60 years or older, blood pressure levels for starting treatment and the target blood pressure levels might be different depending on age and SBP (see Hypertension in the Elderly in page 628, and Guidelines for hypertension in the elderly: 1999 revised version (17)).

Target Blood Pressure

Blood pressure levels for young adult and middle-aged hypertensive patients and also for those with diabetes should be lowered to normal blood pressure below 130/85 mmHg and maintained at this level as much as possible (Fig. 3). For hypertensive patients aged 60 years or older, however, the target blood pressure has to be set slightly higher than that for younger and middle-aged patients, because vascular damage to the important organs is commonly observed among elderly hypertensive patients and strict and excessive lowering of blood pressure tends to reduce organ perfusion.

Selection of Treatment

Genetic and environmental factors are involved in the development of essential hypertension in a complicated manner. Accordingly, modification of a patient's lifestyle, which accounts for a large portion of environmental factors, is essential as part of a treatment regimen. However, relatively few patients are able to reach their target blood pressure level simply by changing their lifestyle, and the majority of pa-



* See Fig. 8 for patients aged 80 years or older.

Fig. 3. Target blood pressure.

tients require additional drug treatment. A specific treatment plan that corresponds to the stratification of risk factors should be tailored to each hypertensive patient (Fig. 2).

Hypertensive patients can be classified into four groups, *i.e.* low-risk, medium-risk and high-risk groups of hypertension, and patients having hypertension emergencies. A major treatment regimen for a patient in the low-risk group should be lifestyle measures; however, if the patient's blood pressure does not reach a level below 140/90 mmHg, drug treatment should be initiated. With those in the medium-risk group, lifestyle changes should be the first therapeutic measure, but if the blood pressure after 3 months does not reach levels below 140/90 mmHg, then drug treatment should be started. With those in the high-risk group, lifestyle measures and drug treatment should be implemented simultaneously. A severely hypertensive patient with hypertensive emergencies or impending symptoms should be immediately admitted to the hospital or referred to a specialist. Treatment of isolated office (white-coat) hypertension should often follow the regimen used for patients in the high-normal blood pressure group, *i.e.*, lifestyle modification and regular blood pressure monitoring.

Compliance of Treatment

In order to achieve good patient compliance, physicians must maintain good communication with patients and provide sufficient information about hypertension, including the importance of treatment, the expected therapeutic effects and the anticipated side effects of the antihypertensive drugs.

Considerations of Quality of Life

Hypertension requires long-term treatment with good patient compliance, so patients' quality of life (QOL) should be considered. The higher the patient's blood pressure, the more likely they will have complications such as emotional disorders, sleep problems and circulatory and digestive symptoms and the accompanying reduction of satisfaction. Furthermore, older patients have reported that their QOL seems more impaired. The QOL includes the patient's subjective perception of somatic symptoms, psychological state, degree of mental and physical satisfaction, feelings of well-being,

work, hobbies, social activities, family, sex life and other factors. Each item should be evaluated in as comprehensive and objective a manner as possible. Moreover, impairment of QOL caused by the side effects of antihypertensive drug used should be carefully observed.

Modifications of Lifestyle

Hypertension is one of the lifestyle-related diseases. Much evidence suggests that changes in lifestyle could not only prevent hypertension but also have blood-pressure-lowering effects (18–24). In principle, education and instructions concerning lifestyle measures should be given to all hypertensive patients. For those with cardiovascular risk factors such as diabetes and hyperlipidemia, lifestyle measures become more important (Table 6). It is difficult to achieve target blood pressure levels by only modifying one's lifestyle; however, such changes may make it possible to reduce the number and dosage of antihypertensive drugs used (25, 26).

Although the antihypertensive effect of restricting dietary salt intake varies among individuals (18), a large-scale clinical trial indicates that reducing salt intake has a blood-pressure-lowering effect. In JSH 2000, a salt intake of less than 7 g/day (seasoning salt intake should be less than 4 g/day) is recommended. Obesity raises blood pressure levels and is one of the important risk factors for cardiovascular diseases. The effect of weight reduction on lowering blood pressure is obvious (19, 20), and patients with weight exceeding the standard weight ($22 \times [\text{height (m)}]^2$) by more than 20% should reduce their weight.

Since long-term drinking habits of large amounts of alcohol cause the consumer's blood pressure to rise (21), alcohol intake in terms of ethanol content should be restricted to less than 20–30 g/day (which corresponds to approximately 180 ml of Japanese sake) for men and 10–20 g/day for women. In order to prevent hyperlipidemia, the dietary intake of cholesterol and saturated lipids should be limited. Reports in the United States and Europe indicate that eating low-fat foods in place of high-fat foods could lower the blood pressure (22).

The effect of aerobic exercise (walking, running, swimming, etc.) on lowering blood pressure has been pointed out (23, 24), and about 30 min of mild exercise with 50% maxi-

Table 6. Desirable Lifestyle Changes

- 1) Salt restriction to less than 7 g/day (this includes 4 g/day of salt used as a spice)
- 2) Maintenance of an appropriate body weight*
- 3) Restriction of alcohol consumption: less than 20–30 g of ethanol per day for men (corresponds to approximately 180 ml of Japanese sake) and less than 10–20 g/day for women
- 4) Restriction of the consumption of dietary cholesterol and saturated fatty acids
- 5) Physical exercise (aerobic exercise) **
- 6) Smoking cessation

* Not exceeding standard body weight ($22 \times [\text{height (m)}]^2$) + 20%. ** For hypertensive patients without cardiovascular diseases.

mal oxygen consumption should be continued every day. Patients with previous cardiovascular disease should consult with physicians before starting exercise. Smoking *per se* does not raise blood pressure but is an important risk factor of cardiovascular diseases, so patients with coronary heart diseases and stroke should be urged to stop smoking. Avoidance of psychological and environmental stress and prevention of constipation also seem to be effective in lowering blood pressure.

Treatment with Antihypertensive Drugs

Principles of Drug Treatment

In addition to the effects of diuretics and β -blockers (27–31), the beneficial effects of calcium (Ca) antagonists (32–38) and angiotensin converting enzyme (ACE) inhibitors (39–42) have been verified in the large-scale clinical trials mostly performed in the United States and Europe in the past 30 years and also in a few trials performed in Japan. Any one of the six classes of drugs including the above-mentioned drugs and α -blockers as well as angiotensin II (AII) receptor antagonists, which have similar effects to the ACE inhibitors, should be used as the first-choice drug. The ALLHAT study (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) has shown that doxazosin, an α -blocker, was less effective than chlorthalidone in preventing congestive heart failure, suggesting that it may not be suitable as a first-choice drug (43, 44).

Determination of the First-Choice Drug

Any of the six drugs, *i.e.*, Ca antagonists, ACE inhibitors, AII receptor antagonists, diuretics, β -blockers (including $\alpha\beta$ -blockers) and α -blockers, should be used as the first-choice drug with an initial low dosage. In the selection of an antihypertensive drug, the following factors should be taken into consideration and the most suitable drug for each individual patient should be used: the patient's cardiovascular risk factor profile (Table 2), the presence of target-organ damages and cardiovascular diseases (Table 3), other complications and, finally, side effects of antihypertensive drugs and their effect on the QOL.

Indications and contraindications of the first-choice anti-

hypertensive drugs are shown in Table 7.

Change and Addition of the Drug

Blood pressure reduction with drugs should be effected in a slow and gradual manner. The target blood pressure should be achieved in 2 months or longer. When the blood pressure cannot be lowered to less than 140/90 mmHg by a low dosage of the first-choice drug, the dose of the same drug can be increased, provided that it has been well tolerated, up to a double dose but not above. If the target blood pressure levels are not achieved, a combination of other drugs with an additive or synergistic hypotensive effect should be used (Table 8). The concurrent therapies commonly used in clinical practice are as follows:

- Ca antagonists and ACE inhibitors or AII receptor antagonists
- dihydropyridine Ca antagonists and β -blockers
- ACE inhibitors or AII receptor antagonists and diuretics
- β -blockers and α -blockers
- diuretics and β -blockers

When the first-choice drug administered does not effectively lower the blood pressure or is poorly tolerated, a different class drug should be used.

Precautions during Drug Treatment

Prior to the administration of any antihypertensive drug, typical side effects should be explained to the patient. Patient blood pressure should be measured every 2 weeks until the target blood pressure levels are achieved. If the target blood pressure levels cannot be achieved after 6 months of treatment, the patient should be referred to a specialist in the treatment of hypertension.

Dose Reduction and Cessation of the Treatment

Once begun, antihypertensive drug treatment can last throughout the patient's life. However, a reduction in dosage or even cessation of the treatment can be achieved by modifying lifestyle patterns. In such a case, the drug dosage should be decreased gradually and eventually drug use can cease if the lifestyle changes are maintained.

Table 7. Selection of Antihypertensive Drugs

	Indications	Contraindications
Ca antagonists	elderly, angina pectoris, cerebrovascular disease, diabetes	heart block (diltiazem)
ACE inhibitors	diabetes, heart failure, myocardial infarction, left ventricular hypertrophy, mild renal dysfunction, cerebrovascular disease, elderly	pregnancy, hyperkalemia, bilateral renal artery stenosis
Angiotensin II receptor antagonists	similar to ACE inhibitors, in particular for patients for whom ACE inhibitors cannot be used because of cough	pregnancy, hyperkalemia, bilateral renal artery stenosis
Diuretics	elderly, heart failure	gout, hyperuricemia
β -Blockers	myocardial infarction, angina pectoris, tachycardia	bronchial asthma, heart block, peripheral arterial disease
α -Blockers	dyslipidemia, prostate hypertrophy, diabetes	orthostatic hypotension

Table 8. Principles of Antihypertensive Drug Treatment

- 1) Be knowledgeable about the characteristics and side effects of antihypertensive drugs, and select the most appropriate drug for each individual patient.
- 2) The drug used as the first choice should be Ca antagonists, ACE inhibitors, Angiotensin II receptor antagonists, low-dose diuretics, β -blockers or α -blockers.
- 3) Choose a single drug among these, and administer it in a low dose to obtain a gentle reduction in blood pressure. If the effect is insufficient, combine with another drug of promising additive or synergistic effects, or change to a different class drug.
- 4) When the target blood pressure cannot be achieved, consult a hypertension specialist.

Characteristics of the Drugs and Main Side Effects

Antihypertensive drugs currently used in Japan can be classified by their mechanisms of action into the following six drug classes: Ca antagonists, which cause vasodilation by inhibiting the inflow of Ca^{2+} from extracellular space into the cells of vascular smooth muscle; ACE inhibitors, which inhibit the production of Angiotensin II; Angiotensin II receptor antagonists, which inhibit the action of Angiotensin II at a receptor level; diuretics, which promote the excretion of sodium and water from kidneys; antiadrenergic drugs, which centrally or peripherally inhibit the sympathetic nervous system; and vasodilators, which dilate blood vessels by directly acting on peripheral blood vessels.

Ca Antagonists

Ca antagonists are effective in lowering blood pressure and are well tolerated, so they are the most common antihypertensive drugs in use in Japan. Ca antagonists of dihydropyridines and benzothiazepines are used as antihypertensive agents; most of the Ca antagonists belong to the former classification, while only diltiazem belongs to the latter. Diltiazem is less effective in lowering blood pressure; however, due to its inhibition of the cardiac conduction system, its action is characterized by decreasing cardiac contractile force and reducing the pulse rate.

The advantages of Ca antagonists are that, in addition to their blood-pressure-lowering effect, they maintain appropri-

ately the cerebral, coronary, renal and peripheral circulations and have no adverse effects on glucose or lipid metabolism. Side effects include facial flushes, headache, palpitation, edema of upper or lower extremities, constipation and gingival hypertrophy. Due to its inhibition of cardiac conduction, diltiazem may cause bradycardia or atrioventricular blocks, so its use is contraindicated for patients with heart block. Among Ca antagonists, it is difficult to obtain stable reduction of blood pressure with short-acting types of Ca antagonists, and they tend to cause side effects such as headache and palpitations, which results in a lower compliance rate. In particular, the activated sympathetic nerve reflex observed during treatment with short-acting Ca antagonists could have adverse effects on ischemic heart disease (45). Therefore, long-acting Ca antagonists are recommended for the treatment of persistent or chronic hypertension.

ACE Inhibitors

In addition to their blood-pressure-lowering effects, ACE inhibitors improve cardiovascular hypertrophy (46, 47) and are useful for the prevention of the progression of atherosclerosis. ACE inhibitors are also effective for insulin resistance without having any adverse effect on glucose or lipid metabolism (48). Other effects include lowering urinary protein and improving prognosis after heart failure or myocardial infarction (49). These drugs also have the effect of improving the hypertension-induced upward shift of the lower limit of

cerebral autoregulation, resulting in maintaining cerebral blood flow in spite of lowered blood pressure. As an adverse effect, coughing is observed in about 20–30% of the patients who are taking ACE inhibitors (50). In rare instances, ACE inhibitors cause dyspnea due to angioneurotic edema, and their use is contraindicated in hypertension in pregnancy. They also should not be used for patients with bilateral renal artery stenosis or hyperkalemia.

Angiotensin II Receptor Antagonists

Since the cardiovascular system has enzymes such as chymase and ACE which produce Angiotensin II from angiotensin I, Angiotensin II receptor antagonists are considered to have more benefits than ACE antagonists with regard to inhibiting the Angiotensin II action. Angiotensin II receptor antagonists have a blood-pressure-lowering effect similar to that of ACE inhibitors; however, patient compliance in taking Angiotensin II receptor antagonists is better because of the absence of coughing, which is the major adverse effect of taking ACE inhibitors (51–53). Indications and contraindications are substantially the same as those for ACE inhibitors.

Diuretics

The most commonly used diuretics are thiazide and thiazide-like diuretics. The side effects of diuretics include potassium depletion, hypomagnesemia, hyperuricemia, hyperlipidemia, impaired glucose tolerance, hemoconcentration and erectile dysfunction, although these side effects are rare when low doses of diuretics are used. In order to prevent hypokalemia, concurrent therapy with other agents such as ACE inhibitors, Angiotensin II receptor antagonists, potassium-sparing diuretics (spironolactone, triamterene) or potassium preparation is recommended. A low-dose diuretic is effective for treating hypertension in the elderly. As a loop diuretic, furosemide is most widely used in hypertensive patients with renal failure whose serum creatinine is higher than 2.0 mg/dl.

Beta-Blockers Including Alpha-Beta-Blockers

The properties of β -blockers vary widely among the different types of agents. According to whether they selectively block β_1 receptors or β_2 receptors, or whether they are fat-soluble or water-soluble, or whether they have an intrinsic sympathomimetic action or not, the β -blockers are classified into several categories. Moreover, β -blockers with vasodilatory effect on the peripheral vessels, which have α_1 -blocking action, Ca antagonist-like effects, or a potassium channel opening mechanism, have been developed recently. β -Blockers are suitable for the treatment of hypertensive patients who have ischemic heart disease and tachycardia and for the primary and secondary prevention of myocardial infarction. Side effects of these drugs are bradycardia, atrioventricular blocks, frequently the aggravation of peripheral vascular disease and obstructive pulmonary disease such as bronchial asthma. These drugs also have adverse effects such as malaise and decreased exercise capacities, and they are not

suitable for the elderly.

Alpha-Blockers

The blood-pressure-lowering effects of α -blockers are based on their arteriolar dilatation, and therefore they are effective for patients with increased vaso-sympathetic tone. They have favorable effects on glucose and lipid metabolism and can improve dysuria in the patients with prostate hypertrophy. Side effects include orthostatic hypotension and postprandial hypotension in the elderly.

Other Antihypertensive Drugs

In addition to the above-mentioned antihypertensive drugs, central and peripheral sympatholytics and classical vasodilators are still currently used as the drugs of second or third choice. They are sometimes used as the first-choice drug in hypertensive patients under specific circumstances.

Methyldopa, clonidine, guanabenz and other drugs in this class are used as central sympatholytics. Methyldopa is comparatively safe for the treatment of hypertension in pregnancy. The side effects commonly observed in this group of antihypertensive drugs are sleepiness, dry mouth, erectile dysfunction and syncope. Although reserpine is comparatively effective in lowering blood pressure, it is seldom used because of the side effects such as nasal congestion, induction of depression and increased gastric secretion. Classical vasodilators such as hydralazine and related drugs have the disadvantage of sympathetic nerve stimulation along with vasodilation and thus induce flushing, palpitation and headaches.

Drug Interactions

When several antihypertensive drugs are used in combination, attention should be paid to drug interaction, namely a combination of Ca antagonists such as diltiazem with action of bradycardia and β -blockers, or a combination of ACE inhibitors or Angiotensin II receptor antagonists having hyperkalemic effects and potassium-retaining diuretics. Moreover, Ca antagonists may raise the blood concentration of digitalis. On the other hand, H_2 -blockers such as cimetidine, ranitidine, sildenafil citrate (Viagra®) and grapefruit juice may enhance the action of Ca antagonists. In addition to the above-mentioned drug interactions, non-steroidal anti-inflammatory agents attenuate the action of various hypotensive drugs.

Treatment of Hypertension under Special Conditions

Refractory Hypertension

Hypertension may be termed refractory or treatment-resistant when a combination therapy of more than three antihypertensive drugs including diuretics in adequate doses has failed to lower the blood pressure below the target levels. In

Table 9. Factors of Refractory Hypertension

1) Problems of blood pressure measurement
use of too small cuffs
“white-coat” hypertension
2) Insufficient compliance
3) Excessive body fluid volume
excessive salt intake
inadequate use of diuretics
progression of renal dysfunction
4) Problems of lifestyle
increasing body weight
excessive alcohol consumption
5) Inappropriate use of drug
combined use of drugs with similar class of action
combined use of other drugs counteracting the hypotensive
drugs or raising blood pressure <i>per se</i>
6) Secondary hypertension

such a case, the factors listed in Table 9 should be examined to take appropriate measures.

If lack of compliance is not the problem and the blood pressure level does not decrease, adjustment of the drugs is required, and the dosage and types of diuretics should be modified. Thiazide diuretics should be started at half of the standard dose and may be increased up to a maximum of double the standard dose. When other drugs are used in combination with the diuretics, two or three drugs should be selected from different classes, *i.e.*, either β -blockers or $\alpha\beta$ -blockers, Ca antagonists, or either ACE inhibitors or AII receptor antagonists, while drugs from the same class should not be used concurrently. When a large number or large doses of drugs are administered, side effects and excessive reduction of the blood pressure should be carefully observed. If a sufficient reduction of the blood pressure cannot be achieved, the possibility of secondary hypertension should be suspected, and referral to a specialist should be considered.

Hypertensive Emergencies

Hypertensive encephalopathy, hypertension associated with acute aortic dissection, hypertensive left ventricular failure with pulmonary edema, acute myocardial infarction or unstable angina pectoris with hypertension, pheochromocytoma crisis and eclampsia are termed hypertensive emergencies, for which an immediate blood-pressure-lowering treatment is required. Meanwhile, malignant hypertension and accelerated hypertension with hypertensive retinopathy such as soft exudates or optic edema at the fundus are termed conditions of hypertensive urgency, and hypotensive treatment should be initiated within a few hours. If untreated, these conditions may lead to irreversible cardiovascular diseases in the near future and even be fatal. Any patient diagnosed should be

immediately admitted to the hospital or referred to a specialist, because their treatment requires the selection of appropriate drugs corresponding to pathogenesis and the determination of blood-pressure-lowering rate. In principle, sublingual administration of short-acting nifedipine is not appropriate.

Treatment of Hypertension in Pregnancy

Hypertension in pregnancy is defined as blood pressure of 140/90 mmHg or greater, or a rise in SBP by ≥ 25 mmHg or in DBP by ≥ 15 mmHg from blood pressure levels at preconception or first trimester (9). Hypertension in pregnancy is classified as chronic hypertension, pre-eclampsia, pre-eclampsia superimposed on chronic hypertension, transient hypertension or eclampsia. In any event, the treatment should be carried out in close cooperation with the obstetricians. Eclampsia should be treated as a hypertensive emergency. In pre-eclampsia, blood pressure rises after the 20th week of gestation, associated with proteinuria and edema. The patient should be hospitalized for treatment and rest in bed. Methyldopa is used as the first-choice drug because of its safety for the fetus. Hydralazine, labetalol, atenolol, metoprolol and similar drugs are also effective. The safety of β -blockers has been almost confirmed, but fetal growth retardation when β -blockers are used in the early stage of pregnancy has been reported. Methyldopa and labetalol may rarely induce serious liver damage. If a combination of these drugs does not lower the blood pressure, the use of dihydropyridine Ca antagonists may be considered. However, β -blockers and Ca antagonists cannot be used in pregnant women in Japan, by law. Diuretics should not be newly administered in pregnancy, and ACE inhibitors and AII receptor antagonists are absolutely contraindicated.

Regarding hypertension that was already present and treated prior to the pregnancy, the preceding therapy may be continued. When ACE inhibitors or AII receptor antagonists have been used prior to the pregnancy, they should be immediately replaced by other drugs. When diuretics have been used, they do not have to be discontinued.

Blood Pressure Management at Pre- and Post-Surgery

Hypertension *per se* is generally not a contraindication for palliative surgery. However, since hemodynamics in patients with hypertension tend to fluctuate widely (54), surgery at an outpatient clinic should be avoided. Moreover, the degree of target-organ damage should be checked in advance, and complications, if found, should be treated thoroughly. Anti-hypertensive drug treatment could be continued until just before the operation. β -Blockers, characterized by their high cardiac selectivity, promise easy management of hemodynamics at the time of anesthesia induction and during a surgery. α -Blockers or $\alpha\beta$ -blockers are used for patients with pheochromocytoma.

The hemodynamics in most patients remain unstable for a

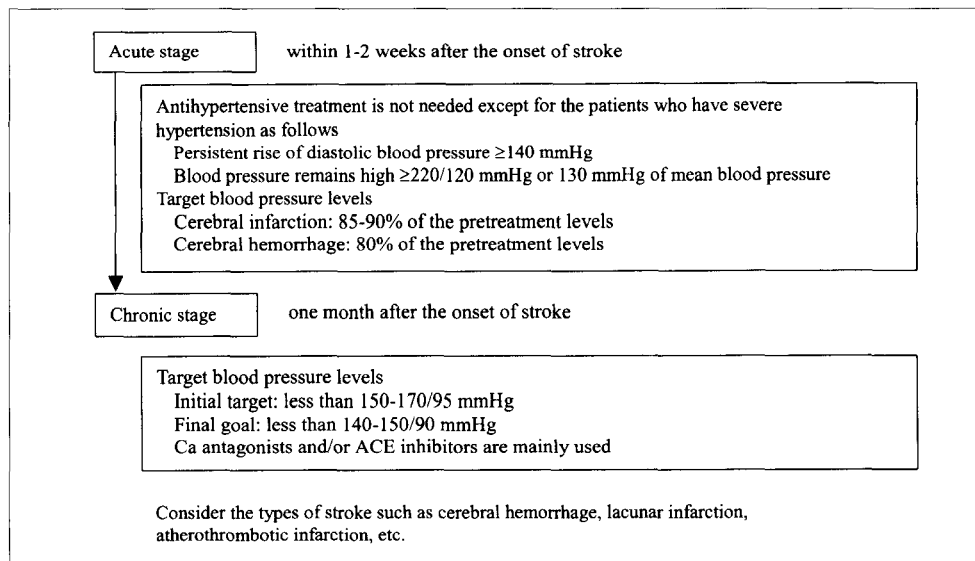


Fig. 4. Treatment of hypertension in patients with stroke.

few hours to several days after surgery. If the oral administration of antihypertensive drugs is not possible during this period, either nitrates or Ca antagonists could be intravenously administered to maintain the blood pressure at the appropriate levels. Hemodynamics should be stabilized through the management of respiration and body fluid by appropriate infusion. When oral administration of the drugs becomes possible, the antihypertensive drug used pre-surgically should be resumed. The use of sufficient analgesics and antianxiety drugs may lessen the fluctuation of blood pressure.

Treatment of Hypertension Associated with Organ Damage

Cerebrovascular Disease (Fig. 4)

Acute Stage of Stroke

Antihypertensive treatment for acute stage stroke patients, *i.e.*, those within 1 to 2 weeks after the onset of stroke, should be performed only when the blood pressure rises and remains extremely high. Antihypertensive drugs should be carefully given based on the precise diagnosis on the stroke subtype, and frequent examinations of neurological signs and symptoms are important. If DBP levels of 140 mmHg or greater persist regardless of stroke subtype, urgent blood-pressure-lowering treatment should be initiated by intravenous administration of antihypertensive drugs. Antihypertensive treatment should be started in patients with cerebral infarction who have 220/120 mmHg or greater or mean blood pressure of 130 mmHg or greater. The patients with cerebral hemorrhage who tend to re-bleed or who have enlarged hematomas, drug treatment should be initiated at slightly lower blood pressure levels than in the case of cere-

bral infarction. Short-acting intravenous drugs such as nicardipine, diltiazem, nitroglycerin and nitroprusside should be administered for delicately controlling blood pressure. However, the administration of these drugs should be performed carefully, because they may cause a rise in intracranial pressure. A sublingual administration of nifedipine should be avoided, since it may trigger an excessive fall of blood pressure.

The blood pressure levels should be lowered to the target levels, although the target blood pressures vary depending on the subtypes of stroke, to 85–90% of pretreatment blood pressure levels in cases of cerebral infarction and to 80% in cases of cerebral hemorrhage. More aggressive blood-pressure-lowering treatment is required when hemorrhagic infarction emerges or complication of acute myocardial infarction, heart failure or aortic dissection is observed.

Chronic Stage of Stroke

Antihypertensive treatment should be initiated in the chronic stage, about 1 month after the onset of stroke. While keeping in mind the patient's age and the severity of stroke, blood pressure should be gradually lowered to the initial target levels, *i.e.*, below 150–170/95 mmHg over a period of at least a few months. An appropriate final target blood pressure would be 140–150/90 mmHg or lower. However, the target blood pressure should be slightly lower in patients with cerebral hemorrhage or lacunar infarction (55), while slightly higher in those with atherothrombotic infarction by approximately 5 mmHg (56). Dizziness, fatigue, lightheadedness, numbness, lack of vigor and aggravation of neurological symptoms in patients during hypotensive treatment may each be caused by cerebrovascular insufficiency due to the reduction in blood pressure, and thus a reduced dose or drug substitution is required. When the primary blood pres-

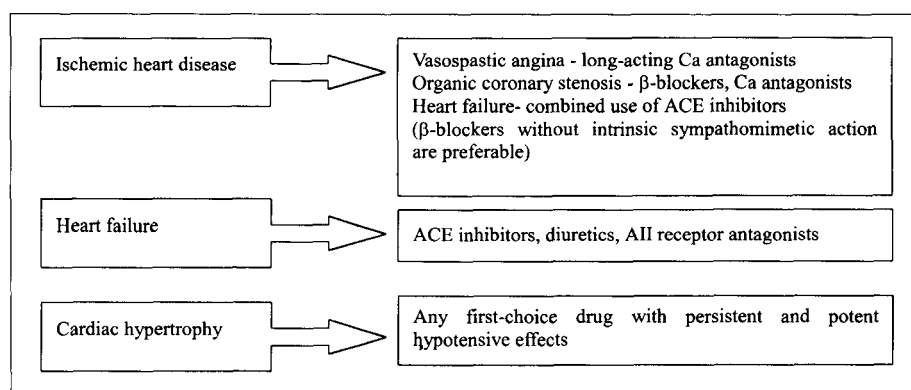


Fig. 5. Treatment of hypertension in patients with heart diseases.

sure target is safely achieved, the necessity for further lowering can be considered. If necessary, the blood pressure should be gradually lowered to the final target over several months. The drugs should be selected in consideration of the effects on cerebral circulation, and either or both Ca antagonists and ACE inhibitors would be effective in the treatment of hypertension with cerebrovascular disease, which may have beneficial effects on cerebral blood flow and cerebral autoregulation as well.

Recently, the Perindopril Protection against Recurrent Stroke Study (PROGRESS) reported that antihypertensive treatment with ACE inhibitors and diuretics effectively prevented the recurrence of ischemic stroke.

Heart Disease (Fig. 5)

Ischemic Heart Disease

In the treatment of hypertension in patients with angina pectoris, Ca antagonists and β -blockers are recommended as the drugs of first choice because of their anti-anginal effects. Angina pectoris is caused by coronary artery stenosis or spasm, the latter of which, so-called vasospastic angina, is more common in Japanese than Caucasians. Ca antagonists are effective for such angina and are used as the first-choice drug. On the other hand, both β -blockers and Ca antagonists are effective against effort angina with organic coronary stenosis. Therefore, when the etiological mechanism of angina is unknown, the use of Ca antagonists or the combined use of Ca antagonists and β -blockers is recommended, because β -blockers may aggravate vasospastic angina. Short-acting Ca antagonists could possibly cause myocardial ischemia in patients with severe coronary artery stenosis as a result of the rapid reduction of blood pressure or reflex tachycardia (45).

The anti-anginal effect of β -blockers is mainly due to bradycardia resulting from the drugs, so β -blockers without intrinsic sympathomimetic actions should be selected for the treatment, although there is no significant difference in the effects between β_1 selective drugs and non-selective drugs. Antihypertensive drugs should be carefully administered to

angina patients with severe coronary artery stenosis, since orthostatic hypotension induced by drugs may trigger anginal attacks.

β -Blockers and ACE inhibitors are known to improve the prognosis of hypertensive patients with myocardial infarction. The results of large-scale clinical trials made in Europe and the United States have shown that β -blockers without intrinsic sympathomimetic actions significantly inhibit the recurrence of myocardial infarction and sudden death in patients who had previously suffered myocardial infarction (57).

However, because of the possible aggravation of coronary vasospasm, β -blockers are not often used in Japan. ACE inhibitors are commonly used, since they reduce morbidity of heart failure and sudden death by suppressing left ventricular remodeling (ventricular dilatation, myocardial hypertrophy, interstitial fibrosis) in patients with low systolic function with an ejection fraction of 40% or less caused by diffuse myocardial infarction (58).

Heart Failure

ACE inhibitors and diuretics are the first-choice drugs for the treatment of hypertension in patients with heart failure. A number of large-scale clinical trials performed in Europe and the United States have shown that ACE inhibitors decrease mortality in patients with heart failure. They also lower the frequency of hospitalization due to the aggravation of heart failure and improve exercise tolerance and the ejection fraction of the left ventricle. Meanwhile, diuretics are used for the treatment and prevention of congestive heart failure. ACE inhibitors have rather significant blood-pressure-lowering effects in heart failure patients, in which the renin-angiotensin-aldosterone system is stimulated. Therefore, ACE inhibitors should be administered in low doses at the initial treatment, *e.g.*, one-fourth or one-half of the standard dose initially, and the dose can be gradually increased as the absence of adverse effects such as hypotension and renal failure is confirmed. A low dose (25 mg) of spironolactone, an anti-aldosterone agent that is used in combination with diuretics, digitalis and/or ACE inhibitors, is effective in lower-

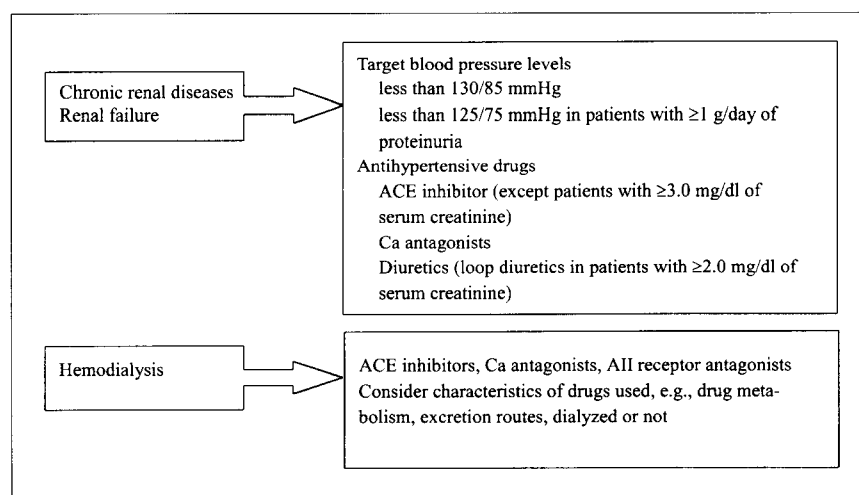


Fig. 6. Treatment of hypertension in patients with renal diseases.

ing mortality rates, including prevention of sudden death (59). Beneficial effects of AII receptor antagonists on heart failure have been reported and verified by clinical trials (60). A recent study has shown that long-acting Ca antagonists do not aggravate the prognosis of patients with heart failure (61). Thus, long-acting Ca antagonists, if necessary, can be used for the treatment of hypertension in patients with heart failure.

Cardiac Hypertrophy

Mortality, morbidity of cardiac events due to ischemic heart disease, and morbidity of heart failure are high in hypertensive patients with cardiac hypertrophy (62). Meta-analyses have demonstrated that ACE inhibitors have the most significant effects on the regression of cardiac hypertrophy (47). However, substantial reduction in blood pressure is the key for stimulating the regression of hypertrophy, which means that any first-choice antihypertensive drug could be expected to regress cardiac hypertrophy if blood pressure is kept low by these drugs (63).

Renal Disease (Fig. 6)

Chronic Renal Diseases and Renal Failure

About 7% of patients with hypertensive nephrosclerosis reach end-stage renal failure in Japan. The number of patients with end-stage renal failure, however, is continuously increasing due to the increase in the number of patients with renal failure caused by diabetes mellitus and/or hypertension. Hypertension is an important risk factor facilitating the progression of renal disease (64, 65), and blood pressure control is crucial for the prognosis of renal failure. Early detection of renal diseases and renal dysfunction is essential for delaying the progression of renal dysfunction, and urinalysis is useful for this purpose. It should be noted that, compared with their serum creatinine levels, elderly patients tend to

have significantly lower renal function.

Lifestyle measures for patients with chronic renal diseases include reduction of dietary salt and protein intake. (See the Guidelines for Lifestyle Measures and Dietary Therapy for Patients with Renal Diseases by the Japanese Society of Nephrology (66)). Patients with renal failure should avoid excessive exercise and extreme fatigue. The target blood pressure is less than 130/85 mmHg (67, 68). Moreover, if patients have urinary protein of 1 g/day or greater, the target blood pressure for these patients should be, if tolerable, less than 125/75 mmHg (69). Clinical trials for the treatment of renal hypertension in Japan have indicated that any of the six classes of first-choice drugs can be useful and safe (70).

ACE inhibitors significantly reduce proteinuria in cases of diabetic and non-diabetic renal disease (71, 72) and have protective effects on the kidney (72–74). Serum creatinine levels often rise during the early phase of the treatment with ACE inhibitors in patients with renal disease; however, renal dysfunction in the early stage is reversible. A slight elevation (10–20%) of serum creatinine levels also needs careful observation. When serum creatinine levels exceed 3.0 mg/dl, ACE inhibitors should be used carefully, since they may aggravate renal dysfunction and induce hyperkalemia. A combination with non-steroidal anti-inflammatory drugs should be avoided to prevent hyperkalemia. Dose adjustment is required for patients with renal failure, since most of ACE inhibitors are excreted through the kidneys.

Ca antagonists are useful and safe, especially for patients with severe renal dysfunction (3.0 mg/dl or greater of serum creatinine), since they do not aggravate the renal function, even though serum creatinine levels are high. Meta-analysis of long-acting Ca antagonists in patients with diabetic nephropathy has shown that Ca antagonists similar to ACE inhibitors reduce proteinuria and delay the reduction of the glomerular filtration rate (75).

Diuretics are essential for patients with expansion of body

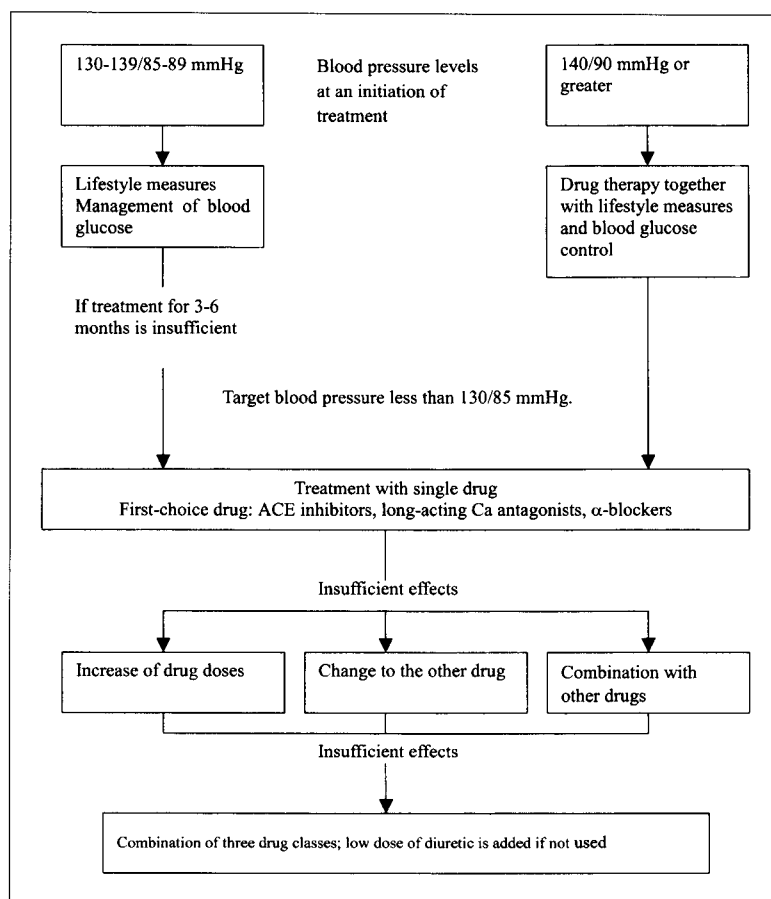


Fig. 7. Treatment of hypertension in patients with diabetes mellitus.

fluid; however, thiazide diuretics are not effective for patients who have serum creatinine of 2.0 mg/dl or greater, in whom loop diuretics are useful. Electrolyte imbalance and dehydration should be carefully observed during treatment with potent diuretics. Potassium-sparing diuretics should not be used for patients with renal failure because of the risk of hyperkalemia.

Angiotensin II receptor antagonists are also expected to have renoprotective action, although their effect remains to be examined in future studies. α -Blockers are widely used, since they have no adverse effects on renal functions and are metabolized in the liver. As far as maintenance of renal blood flow is concerned, β -blockers with intrinsic sympathomimetic actions or α -blocking actions are convenient to use, particularly those metabolized in the liver.

Patients on Hemodialysis

In order to control blood pressure, an adequate dry weight (target weight required in managing body fluid volume) should be determined and excessive weight gain should be suppressed until the next hemodialysis. When the blood pressure does not fall even after the adequate dry weight, antihypertensive drugs are required. In such a case, not only the mechanisms of blood-pressure-lowering action, but also

drug metabolism, excretion route, dialysis property and duration of action should be considered. Calcium antagonists are convenient to use because they are not dialyzed, while many, though not all, ACE inhibitors are dialyzed. When negatively charged dialysis membranes are used, ACE inhibitors sometimes induce a symptom similar to anaphylactic shock. Angiotensin II receptor antagonists have been reported to be useful for hypertension in hemodialysis patients (76). The possible development of orthostatic hypotension and heart failure must be considered during treatment with either α -blockers or β -blockers.

Vascular Disease

Aortic Dissection

Acute dissection of the aorta is one of the hypertensive emergencies requiring a rapid reduction in blood pressure by intravenous infusion of nitroprusside, diltiazem, nicardipine or nitroglycerin. SBP less than 110–120 mmHg should be maintained, unless there is perfusion impairment in major organs. β -Blockers are also used, if not contraindicated. When the patient's condition has been stabilized, drugs may be orally administered.

Peripheral Arterial Disease

Ca antagonists, ACE inhibitors and α -blockers are suitable for the treatment of hypertension in patients with peripheral arterial disease. When patients are treated with β -blockers, particularly non-selective β -blockers, they should be carefully observed for exacerbation of symptoms, because a relative increase of α -action may induce vasoconstriction and thus decrease perfusion to the affected limbs.

Hypertension with Other Diseases

Diabetes Mellitus (Fig. 7)

Slightly lower blood pressure targets should be set for diabetic patients with hypertension (40, 77, 78). As indicated in JNC VI and the 1999 WHO-ISH guidelines as well, patients who have the high-normal blood pressure level or higher, *i.e.*, 130/85 mmHg or higher, should be subjected to treatment, and the blood-pressure-lowering target should be set at levels lower than 130/85 mmHg. Blood pressure should be rigorously reduced in patients with diabetic nephropathy, particularly in those with proteinuria of 1 g/day or more, with a target blood pressure of less than 125/75 mmHg. Lifestyle measures such as weight reduction and increased physical activities should be initiated in patients with blood pressure of 130/85 mmHg or greater. When blood pressure does not achieve the target level even after 3–6 months of making changes in lifestyle, or when blood pressure remains at 140/90 mmHg or higher, antihypertensive drug treatment should be initiated to accompany the lifestyle measures.

Among antihypertensive drugs for hypertensive patients with diabetes, ACE inhibitors (39, 42, 79–81) or long-acting Ca antagonists (80, 82, 83) are recommended as the first-choice drugs because they have beneficial effects on glucose and lipid metabolism and insulin resistance as well as preventive effects for diabetic complications. β -Blockers can also be used in patients with effort angina or old myocardial infarction. Diuretics at a low dose are used in patients with an excess of body fluid. ACE inhibitors are clearly useful for the treatment of diabetic nephropathy, and thus they are recommended for patients with microalbuminuria regardless of the presence of hypertension (79). AII receptor antagonists might have effects similar to those of ACE inhibitors.

Hyperlipidemia

In hypertensive patients with hypercholesterolemia who thus have a higher risk of atherosclerosis, treatments for both diseases are necessary. Recent clinical trials have shown that lowering serum cholesterol could prevent the incidence and recurrence of ischemic heart disease and strokes as well (84, 85). The guidelines for the treatment of hyperlipidemia in Japan (86) propose tight control of cholesterol in patients with coexisting risk factors such as hypertension. ACE inhibitors, Ca antagonists, α -blockers and AII receptor antago-

nists, which do not aggravate but rather improve lipid metabolism, are preferably used for hypertension in patients with hyperlipidemia.

Obesity

Compared with non-obese individuals, obese people have a 2–3 times higher incidence of hypertension (87). Blood-pressure-lowering regimens for obese hypertensive patients include weight reduction by dietary control and increased physical activity along with drug treatment. ACE inhibitors, α -blockers and AII receptor antagonists are recommended for patients with impaired glucose metabolism and/or insulin resistance. Thiazide diuretics in one-half of the standard dose have little effect on glucose and lipid metabolism, and, therefore, they are useful in combination with other drugs in the treatment of refractory hypertension in obese hypertensive patients.

Bronchial Asthma and Chronic Obstructive Pulmonary Disease

Since β -blockers and $\alpha\beta$ -blockers may aggravate some pulmonary diseases, they should not be used in hypertensive patients with bronchial asthma or chronic obstructive pulmonary disease unless there is a specific reason. When dry cough is developed after the use of ACE inhibitors, they should be replaced with AII receptor antagonists.

Gout

Diuretics should be avoided in patients with gout, since they may elevate serum uric acid levels. Due to uric acid excretion action (88), losartan, an AII receptor antagonist, is considered to be useful for the treatment of hypertensive patients with hyperuricemia.

Liver Disease

Since methyldopa is known to induce liver damage with relative frequency, it should be avoided in hypertensive patients with liver disease. Antihypertensive drugs, which are excreted through kidneys rather than metabolized in the liver, are recommended in cirrhotic patients with severely decreased liver function.

Hypertension in the Elderly

Characteristics

Hypertension in the elderly is characterized by elevated systolic hypertension, widening of pulse pressure, high fluctuation of blood pressure, frequent orthostatic hypotension and postprandial hypotension due to the progression of atherosclerosis with aging. Blood pressure in elderly hypertensive

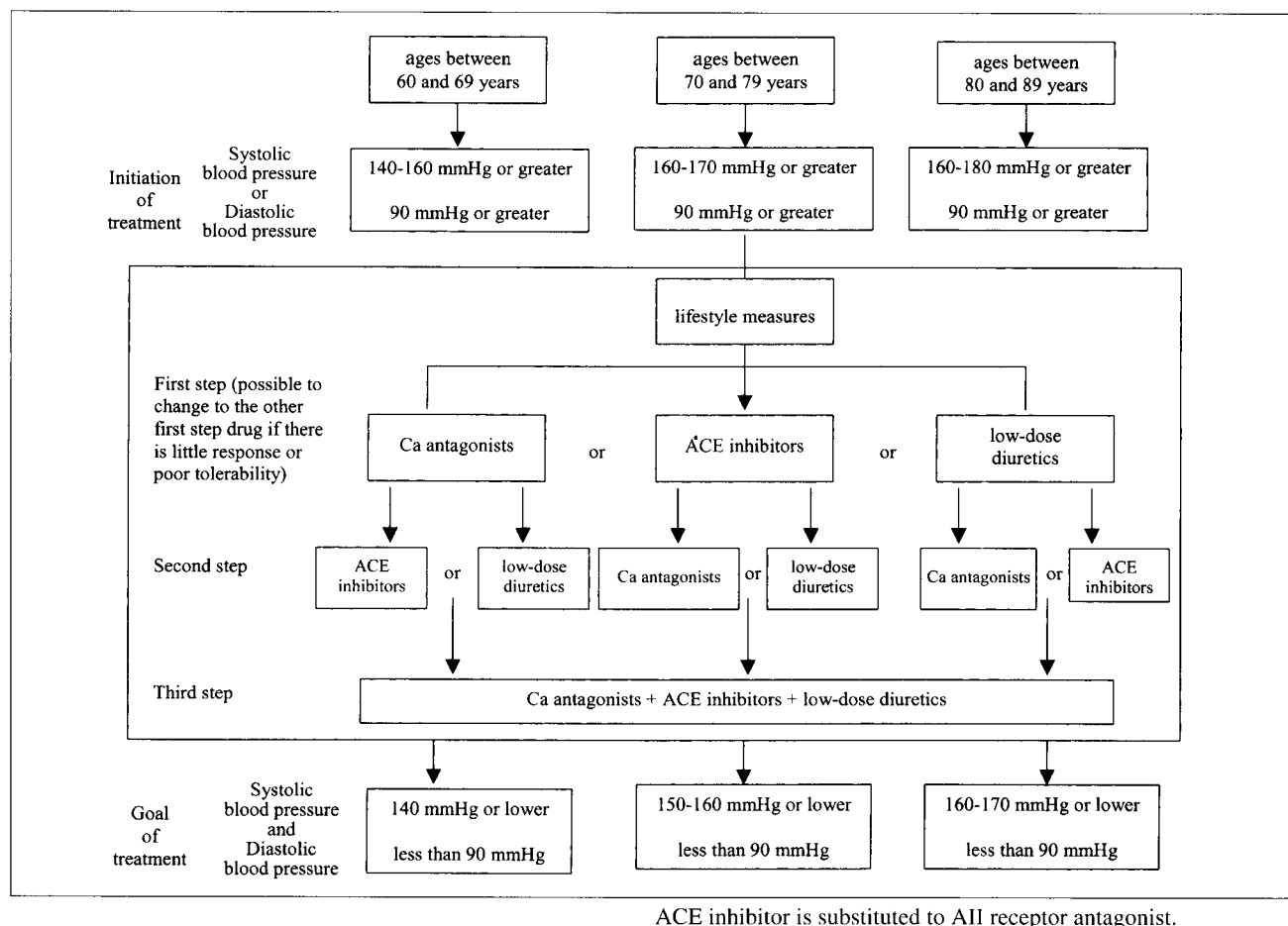


Fig. 8. Treatment of hypertension in the elderly without complications. Guidelines for Hypertension in the Elderly — 1999 Revised Version — Comprehensive Research Project on Aging and Health, Ministry of Health and Welfare of Japan (Chairman, Kunio Hiwada).

patients should be gradually reduced, because with a lower blood pressure the blood flow to the major organs is decreased, and the autoregulation of organ blood flow to the brain, heart and kidneys can become impaired. The abrupt and excessive reduction of blood pressure tends to reduce blood flow to these organs.

Diagnosis

The indication of elderly hypertension is the same as that of adults, *i.e.*, blood pressure of 140/90 mmHg or higher. When measuring blood pressure in the elderly, practitioners should make multiple measurements to check fluctuations in blood pressure, take measurements at a standing position to check orthostatic hypotension and measure blood pressure by palpation to exclude pseudo-hypertension and auscultatory gap. Home or 24-h blood pressure monitoring is useful for diagnosis.

Among elderly hypertensive patients, renovascular hypertension is sometimes latent and should be ruled out. In order

to determine a treatment strategy and select antihypertensive drugs, it is important to check target organ damage such as brain, heart and kidney or the presence of complications.

Treatment

Effects of Treatment

Large-scale clinical trials have shown that hypertension treatments in elderly patients aged 60 years or older and in those aged 70 years or older significantly reduce the incidence and mortality of cardiovascular diseases (28–30, 32, 33, 89). Comparison studies on antihypertensive treatment in Japanese found a similar beneficial effect (34, 38), although the incidence of stroke is about four times higher than that of myocardial infarction (34).

Patients to Be Treated

In the above-mentioned large-scale trials, therapeutic benefits have been demonstrated among elderly patients with blood pressure levels of 160/90 mmHg or higher, and in

Table 10. Criteria for Hypertension in Children and Adolescence

	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Infants	≥120	≥70
Elementary school children		
Lower grades	≥130	≥80
Upper grades	≥135	≥80
Junior high school students		
Boys	≥140	≥85
Girls	≥135	≥80
Senior high school students	≥140	≥85

those aged up to 80–84 years. Therefore, in the elderly patients aged between 60 and 80 years, high blood pressure can and should be controlled. According to a survey of hypertension specialists in Japan, antihypertensive treatment is initiated at higher blood pressure levels in patients aged 70 and 80 years than in younger and middle-aged patients (90).

Target Blood Pressure

Both the JNC VI and 1999 WHO-ISH guidelines recommended blood pressure levels of lower than 140/90 mmHg as the target for all age groups, including the elderly. However, in JSH 2000, different targets of blood pressure are set corresponding to the age groups. SBP and DBP levels should be lowered to 140/90 mmHg or lower for the patients aged 60–69 years, and slightly higher target levels are set for the patients aged 70 years or older because they are likely to have organ damages, either symptomatic or asymptomatic. Blood pressure should be gradually lowered to the target levels over more than 2 months, with drug intake starting at one-half of the regular dose and increasing or being supplemented with other drugs after 4 weeks or more of administration.

Lifestyle Measures

The first step in the treatment of hypertension in the elderly is lifestyle measures, and the changes needed are substantially the same as those suggested for the younger age group. Dietary salt intake should be reduced to 7 g/day or lower, since elderly patients are sensitive to salt and therefore salt restriction is an effective measure to control blood pressure. Weight reduction is also effective for obese patients. Regular exercises, *e.g.*, mild exercises with pulse rate of about 110/min for 30–40 min, 3–5 times per week, are also effective for elderly hypertensive patients. Alcohol consumption should be restricted to about 20–30 g of ethanol per day, and cessation of smoking is very important.

Selection of Antihypertensive Drugs (Fig. 8)

In patients without major vascular complications or associated diseases, long-acting dihydropyridine Ca antagonists, ACE inhibitors or AII receptor antagonists or a low dose of

either thiazide diuretics or potassium-retaining diuretics are used as the first-choice drug. When the first-choice drug is not sufficient for blood pressure reduction or is not well tolerated, it may be replaced by another drug, or a combination therapy of two or three drugs may be initiated.

Long-acting Ca antagonists or ACE inhibitors are used preferentially for patients with chronic stage of stroke, and β -blockers and long-acting Ca antagonists are used for effort angina and coronary vasospastic angina. ACE inhibitors and diuretics are beneficial in patients with chronic heart failure. ACE inhibitors are used to treat hypertensive patients with renal failure having serum creatinine levels of 2.0 mg/dl or less, and long-acting Ca antagonists are used for those patients having serum creatinine levels of greater than 2.0 mg/dl. Low doses of diuretics are effective in hypertensive patients with a tendency toward volume overload. Rigorous blood pressure lowering is required for hypertensive patients with diabetes mellitus, and ACE inhibitors or long-acting Ca antagonists are preferably selected in cases without advanced renal dysfunction.

Hypertension in Children

Characteristics

Essential hypertension is found in 0.1–1.0% of children aged below 15 years and in 3% of high school students (91, 92). High blood pressure in childhood is not so severe as to require drug treatment, and thus hypertension *per se* is unlikely to cause serious complications of organ damages in patients of this age. However, hypertension is a major risk factor for arteriosclerosis, and tracking the phenomenon of high blood pressure in adulthood has been part of modern medicine. Thus, the prevention of hypertension and the control of blood pressure are essential in childhood. When blood pressure levels in children are elevated to such an extent that drug treatment is required, then secondary hypertension, mostly as a result of renal and renovascular diseases, should be ruled out. Although there are no specific blood pressure criteria for children with hypertension in Japan, the reference values estimated from major reports (93–95) are shown in

Table 11. Sizes of Children's Cuffs

	Around the arm (cm)	Rubber tube	
		Width (cm)	Length (cm)
Newborn	5–7.5	3	5
Infant	7.5–13	5	8
Juvenile	13–20	8	13

In general, bladders of adult's cuffs are used in patients aged 9 years or older.

Table 10.

Lifestyle Measures

Hypertension in children is usually mild; therefore, therapy should start with lifestyle measures such as physical exercises and reduction of dietary salt intake. Body weight reduction is necessary in cases of obesity, and physical exercises such as fast walking, jogging and swimming (isotonic exercises) are effective in reducing weight and lowering blood pressure. In terms of primary prevention of hypertension, adequate lifestyle measures should be started in younger childhood before an unhealthy lifestyle can be established.

Drug Treatment

In the presence of organ damage or when hypertension persists even after 3–6 months of non-drug therapy, drug treatment should be initiated. Antihypertensive drugs should be selected according to the same criteria used for adults.

Note

The sizes of bladders of children's cuffs are defined as follows by the Japanese Industrial Standards (JIS) (Table 11).

Acknowledgements

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The qualities of references were evaluated based on the Agency for Health Care Policy and Research (AHCPR) Guide to Clinical Preventive Services, Second Edition, 1996, and with one of the following indications appended at the end of each article.

- I: Evidence obtained from at least one properly randomized controlled trial.
- II-1: Evidence obtained from well-designed controlled trials without randomization.
- II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III: Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

Well-designed and well-conducted meta-analyses were also considered and were graded according to the quality of the studies on which the analyses were based (e.g., Grade I if the meta-analysis pooled properly randomized controlled trials).

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