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Chapter 6. Hypertension associated with organ damage

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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

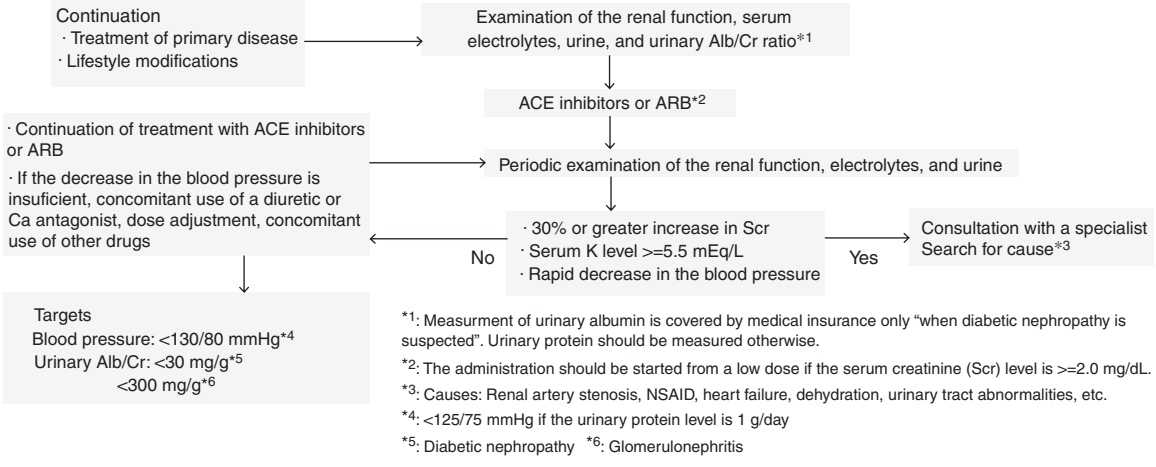

Figure 6-1 Therapeutic plans for hypertension complicated by chronic kidney diseases (CKD).

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

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

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