GUIDELINES (JSH 2014)

Chapter 7. Hypertension complicated by other diseases

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POINT 7A

Diabetes mellitus

1. The target of blood pressure control in hypertensive patients with diabetes mellitus should be $<130/80$ mm Hg. (Recommendation grade: B, Consensus, Evidence level: I) The target home blood pressure should be $<125/75$ mm Hg. (Recommendation grade: C1, Evidence level: IVa) However, a reduction in organ perfusion related to a decrease in blood pressure must be considered in patients with atherosclerotic coronary artery disease or peripheral arterial disease. Nonclinic blood pressure assessment should be performed (Recommendation grade: C1, Evidence level: IVa).
2. In patients with a blood pressure of 140/90 mm Hg or above, treatment with antihypertensive drugs should be promptly started. If patients with a blood pressure of 130–139/80–89 mm Hg are expected to achieve the target of blood pressure control by lifestyle modifications, lifestyle modifications should be attempted to reduce blood pressure within 3 months. However, if it is considered difficult to achieve the target of blood pressure control by lifestyle modifications, treatment with antihypertensive drugs should be promptly started (Recommendation grade: C1, Consensus).
3. When selecting antihypertensive drugs for hypertensive patients with diabetes mellitus, an angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor is recommended as the first choice (Recommendation grade: A, Evidence level: I). A Ca channel blocker and low-dose thiazide diuretic should be used concomitantly for blood pressure control (Recommendation grade: B, Evidence level: II). In patients with angina on effort or old myocardial infarction, β -blockers, which have a cardioprotective effect, can also be used for blood pressure control (Recommendation grade: B, Evidence level: II).

Dyslipidemia

1. When selecting antihypertensive drugs for hypertensive patients with dyslipidemia, ARBs, ACE inhibitors, Ca channel blockers and α -blockers, which improve or do not exacerbate lipid metabolism, are considered appropriate (Recommendation grade: B, Evidence level: II).

1. DIABETES MELLITUS

In diabetics, blood pressure should be measured in both a recumbent and standing as well as a sitting position, because orthostatic hypotension is observed in some patients. The frequency of hypertension is about two times higher in diabetics than in nondiabetics according to results in Japan.⁷⁴¹ In addition, the frequency of diabetes mellitus is 2–3 times higher in hypertensive patients,⁷⁴¹ and an etiological relationship between the two diseases has been suggested. Briefly, type 2 diabetes and hypertension are major factors of metabolic syndrome (discussed later), having insulin resistance as a common background factor.

Microvascular complications of diabetes mellitus include nephropathy, neuropathy and retinopathy. These conditions may affect not only the quality of life but also prognosis through severe impairment of physical functions. Both diabetes mellitus and hypertension are important risk factors for macrovascular disease related to atherosclerosis. When the two diseases are concomitantly present, the incidences of cerebrovascular disease and coronary artery disease markedly increase.⁷⁴² Therefore, strict blood pressure/glucose control is important for the prevention and treatment of microvascular and macrovascular diseases in hypertensive patients with diabetes mellitus.

With regard to the blood pressure control level in hypertensive patients with diabetes mellitus, the risk of cardiovascular events was significantly reduced in a group managed with a target diastolic pressure of ≤ 80 mm Hg compared with a group managed with a target of ≤ 85 or ≤ 90 mm Hg in HOT,²⁷³ in which antihypertensive treatment was performed primarily using Ca channel blockers. Moreover, the results of UKPDS38²⁵⁷ showing that the risk of macrovascular and microvascular diseases was markedly reduced by lowering mean blood pressure from 157/87 to 144/82 mm Hg and the results of a clinical trial,⁷⁴³ which also indicated the usefulness of antihypertensive treatment in normotensive diabetic patients, suggest that the therapeutic effect can be increased by setting a lower target of blood pressure control for hypertension complicated with diabetes mellitus. On the basis of these results, the JNC-VI, 1999 WHO/ISH Guidelines and JSH2000 Guidelines recommended the initiation of antihypertensive treatment for diabetics with a high-normal blood pressure of $\geq 130/85$ mm Hg. However, the recommendations of the American Diabetic Association in 2003,⁷⁴⁴ JNC7 (2003)¹¹³ and ESH/ESC 2007 Guidelines²⁶⁰ set $<130/80$ mm Hg as a target level of blood pressure control on the basis of the results of the HOT²⁷³ and UKPDS38.²⁵⁷ The JSH2009 Guidelines also set a similar target.

However, in the ACCORD-BP (ACCORD Blood Pressure Trial)²⁸⁵ published in 2010, blood pressure was reduced to 119.3/64.4 mm Hg

in the strict treatment group with a target systolic blood pressure of <120 mm Hg and to 133.3/70.5 mm Hg in the standard treatment group with a target systolic blood pressure of <140 mm Hg. The annual incidences of a primary end point (nonfatal myocardial infarction-/nonfatal stroke-/cardiovascular disease-related death) in the strict and standard treatment groups were 1.87% and 2.09%, respectively. The hazard ratio was 0.88. In the former, the percentage was slightly lower, but there was no significant difference. A meta-analysis of 13 studies²⁵⁸ also indicated that there was no clear reason why blood pressure should be reduced to <130/80 mm Hg. The American Diabetic Association revised the target of blood pressure control in type 2 diabetics to <140/80 mm Hg.⁷⁴⁵ In the ESH/ESC 2013 Guidelines, the target of blood pressure control in type 2 diabetics was also revised to <140/85 mm Hg.¹²⁰ However, in Japan, the incidence of stroke is still higher than in Europe and the United States. In the ACCORD-BP, the incidence of cerebral infarction was about one-quarter that of myocardial infarction. On the other hand, in the Hisayama Study,⁷⁴⁶ the Suita Study⁷⁴⁷ and JDCS,⁷⁴⁸ all of which were conducted in Japan, the incidence of cerebral infarction was 1.5–2.5 times higher than that of myocardial infarction. In the ACCORD-BP Study, the hazard ratio of stroke was 0.59 in the strict control group, showing a significant decrease, although the incidence was low. A meta-analysis of 13 studies involving patients with diabetes/IGT, including more than 100 patients in whom the systolic blood pressure at the completion of the study could be reduced to ≤ 135 mm Hg,²⁵⁸ also compared patients in whom systolic blood pressure was reduced to ≤ 135 mm Hg with those in whom it was reduced to ≤ 130 mm Hg, and indicated that the onset of stroke could be prevented even at a systolic blood pressure of <120 mm Hg, although there were no significant differences in the total mortality rate, cardiovascular mortality rate, incidence of myocardial infarction or incidence of heart failure. Another meta-analysis,⁷⁴⁹ in which the final systolic and diastolic blood pressures in an interventional study and the risks of myocardial infarction and stroke during the course were investigated in diabetics, also showed the preventive effects of reducing systolic and diastolic blood pressures to <130 and <80 mm Hg, respectively, on stroke, although there was no further decrease in the risk of myocardial infarction. In the Tanno–Sobetsu cho Study of Japan,⁷⁵⁰ the mortality rate due to cardiovascular disease was significantly higher in the group with a systolic pressure of ≥ 130 mm Hg and a diastolic pressure of ≥ 80 mm Hg than in the group with an optimal blood pressure of <120/80 mm Hg in borderline diabetics/diabetics. Therefore, the results in Japan also support a target blood pressure of <130/80 mm Hg for hypertensive patients with diabetes mellitus. This is consistent with the results of the CASE-J subanalysis,⁶⁴¹ in which the relationship between the blood pressure achieved and cardiovascular events was assessed. Therefore, in Japan, where the incidence of stroke is higher than that of myocardial infarction, the disease structure differs from that in Europe and the United States, where the incidence of myocardial infarction is higher than that of stroke, and, naturally, evidence is interpreted, focusing on the prevention of stroke. To decrease the incidence of cardiovascular disease including stroke, strict blood pressure control is necessary in hypertensive patients with diabetes mellitus. In Japan, it may be appropriate to establish the target level of blood pressure control as <130/80 mm Hg. In elderly patients, as a rule, blood pressure control should be performed in accordance with their target (65–74 years: <140/90 mm Hg; 75 years or older: <150/90 mm Hg). If they tolerate treatment, a blood pressure of <130/80 mm Hg should be carefully targeted.

With regard to the target of blood pressure control on the basis of home blood pressure, a study indicated that strict antihypertensive

therapy targeting a home blood pressure of <125/75 mm Hg was effective from the perspective of the prevention of organ damage in patients with impaired glucose tolerance or diabetes mellitus showing an HbA1c (NGSP) value of 6.2% or higher.⁷⁵¹ Furthermore, a subanalysis of the HOMED-BP Study involving impaired glucose tolerance patients/diabetics with a fasting blood glucose level of 110 mg dl⁻¹ or higher or an HbA1c (NGSP) value of 5.8% or higher showed that the risk of cardiovascular disease slightly increased in patients with a systolic blood pressure of 125 mm Hg or above, and that it significantly increased in those with a diastolic blood pressure of 75 mm Hg or above. When only diabetic patients were analyzed, more distinct results were obtained than that in impaired glucose tolerance patients (SDC Table 1, <http://links.lww.com/hjh/A259>).²⁸⁰ Therefore, the target of home blood pressure control in diabetics should be <125/75 mm Hg. A home blood pressure of 125/75 mm Hg corresponds to a clinic blood pressure of 130/80 mm Hg, and this also supports a target clinic blood pressure of <130/80 mm Hg in diabetics.

In the INVEST Diabetes Cohort Study,²⁸⁶ in which hypertensive patients with coronary artery disease, aged over 50 years, were assigned to take a combination of sustained-release verapamil tablets and trandolapril or that of atenolol and a thiazide diuretic, the incidence of cardiovascular events was compared among three groups: poor (a blood pressure of 140 mm Hg or above was achieved), standard (a blood pressure of 130–140 mm Hg was achieved) and strict (a blood pressure of <130 mm Hg was achieved) control groups. In the standard control group, the incidence of cardiovascular events was lower than that in the poor control group. There was no significant difference between the standard and strict control groups. In the latter, the total mortality rate was higher than in the former. In addition, when reviewing the data from a cohort study in the United States, in which follow-up was over 5 years, the mortality rate in the strict control group was significantly higher than in the standard control group. However, the study was a retrospective analysis in which the subjects were stratified based on the blood pressure achieved, and it was not a prospective study establishing a target blood pressure; this must be considered. A stratified analysis of the INVEST⁷⁵² showed that a reduction in blood pressure to <130 mm Hg markedly increased the incidence of cardiovascular events in patients with peripheral arterial disease. Therefore, a reduction in organ perfusion related to a decrease in blood pressure should be considered in patients with atherosclerotic coronary artery disease or peripheral arterial disease. Nonclinic blood pressure assessment should be performed.

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

In drug therapy for hypertension with diabetes mellitus, sufficient consideration of the effects of each antihypertensive drug on insulin sensitivity and glucose/lipid metabolism is necessary. Diuretics and β -blockers have been reported to reduce insulin sensitivity and

increase the triglyceride level. Furthermore, β -blockers make symptoms of hypoglycemia in diabetics less perceivable, and disadvantages of both drugs with regard to glucose metabolism have been suggested. On the other hand, some β -blockers that reduce the peripheral vascular resistance have been reported to improve insulin resistance with no adverse effect on lipid metabolism. ACE inhibitors, ARBs^{424,753} and long-acting dihydropyridine Ca channel blockers improve insulin sensitivity and exert no adverse effect on lipid metabolism. A comparison of the three classes of drug showed that ARBs and ACE inhibitors were more effective than Ca channel blockers in suppressing the new occurrence of diabetes mellitus,^{237,424,466} suggesting that ARBs and ACE inhibitors more markedly improve insulin resistance compared with Ca channel blockers. Although α -blockers improve glucose/lipid metabolism, whether they prevent target organ damage is unclear.

With respect to the effects of various antihypertensive drugs on diabetic nephropathy, ACE inhibitors have been shown to prevent decreases in renal function and reduce the frequency of transition to dialysis therapy, even in nonhypertensive patients with type 1 diabetes accompanied by proteinuria.⁷⁵⁴ The J-MIND performed in Japan⁷⁵⁵ showed that Ca channel blockers and ACE inhibitors have comparable effects on proteinuria and renal function in patients with diabetic nephropathy, and the UKPDS39⁷⁵⁶ indicated that ACE inhibitors and β -blockers are equally effective in preventing microvascular disease in hypertensive patients with diabetes mellitus. RENAAL,⁴²⁹ IDNT,^{464,757} IRMA-2⁷⁵⁸ and MARVAL⁷⁵⁹ also suggested the effectiveness of ARBs for the treatment of type 2 diabetic nephropathy. In addition, in Japan, the INNOVATION Study⁴⁶³ also showed the usefulness of ARB. On the other hand, there is no sufficient evidence to compare the efficacy between RA system inhibitors and other antihypertensive drugs in diabetics without proteinuria/albuminuria, but the ROADMAP Study⁷⁶⁰ indicated the preventive effect of ARB on microalbuminuria in type 2 diabetics.

In hypertensive patients with diabetes mellitus, CAPPP⁷⁶¹ showed the usefulness of ACE inhibitors, and the HOT²⁷³ and Syst-Eur⁷⁶² studies reported the usefulness of Ca channel blockers for the prevention of cardiovascular accidents. UKPDS39⁷⁵⁶ also indicated that treatment using an ACE inhibitor or a β -blocker was similarly useful. In IDNT,^{464,757} ARBs induced a 4/3 mm Hg greater decrease in systolic/diastolic pressures than did the placebos, and although no difference was noted in the preventive effect against myocardial infarction or stroke it was significantly more effective in the prevention of congestive heart failure. In addition, Ca channel blockers showed an antihypertensive effect 3/3 mm Hg greater than the placebos, and although no difference in the preventive effect against heart failure was noted they showed a significantly stronger preventive effect against myocardial infarction and a more marked preventive effect against stroke. These results suggest a difference between ARBs and Ca channel blockers in the preventive effect on cardiovascular disease. With regard to the outcome of macrovascular diseases in type 2 diabetics, LIFE⁴²⁸ reported that ARBs were significantly more effective than β -blockers in preventing cardiovascular disease. Thus, ACE inhibitors, ARBs and Ca channel blockers have been confirmed to be useful for the prevention of cardiovascular accidents in hypertensive patients with diabetes mellitus. As for a comparison between ACE inhibitors and Ca channel blockers, their preventive effects were evaluated in the smaller studies ABCD⁷⁶³ and FACET,⁷⁶⁴ and the results suggest that ACE inhibitors are more useful than Ca channel blockers. However, no difference was observed by a subanalysis of ALLHAT,⁷⁶⁵ and further evaluation is necessary to clarify the

differences between the effects of ACE inhibitors and Ca channel blockers on macrovascular disease. Thus, with regard to the selection of antihypertensive drugs for hypertensive patients with diabetes mellitus, RA system inhibitors (ARBs and ACE inhibitors) are recommended as a first-choice drug based on evidence regarding the influence on glucose/lipid metabolism and effects on diabetic nephropathy.

If the hypotensive effects of an RA system inhibitor are insufficient, a Ca channel blocker or a low dose of a thiazide diuretic should be combined as a second-choice drug; if a further decrease in blood pressure is necessary, three drugs should be used simultaneously. In GUARD,⁴³⁶ in which Ca channel blockers and diuretics were compared as a drug to be combined with an RA system inhibitor for the treatment of diabetic nephropathy, combination therapy with a diuretic was more effective for controlling proteinuria, but combination therapy with a Ca channel blocker was more effective for maintaining the estimated glomerular filtration rate. The diabetes subanalysis of the ACCOMPLISH Study,⁷⁶⁶ in which the usefulness of combination therapy with an ACE inhibitor and a long-acting Ca channel blocker or a thiazide diuretic was compared in hypertensive patients with coronary artery disease, left ventricular hypertrophy, peripheral arterial disease or renal dysfunction, showed that a Ca channel blocker was more useful than a diuretic for preventing cardiovascular events. Further investigation should be carried out to decide which of the two classes of drugs should be predominantly used as a second-choice drug. In the OSCAR Study,⁴³³ ARB therapy at an increased dose was compared with combination therapy with a Ca channel blocker in hypertensive patients with a history of cardiovascular disease or those with type 2 diabetes mellitus who had undergone antihypertensive treatment with an ARB. With regard to fatal or nonfatal cardiovascular diseases (including diabetic complications, deterioration of the renal function and noncardiovascular death) as a primary end point, there was no significant difference in the incidence, overall, but it was significantly lower in the Ca channel blocker-combined group among patients with a history of cardiovascular disease. However, among diabetics without a history of cardiovascular disease, the incidence was slightly lower in the ARB dose-increased group, although there was no significant difference between the two groups. In patients with angina on effort or old myocardial infarction, β -blockers can also be used for blood pressure control because of their cardioprotective effects. Figure 7-1 shows a therapeutic flowchart for hypertension treatment in patients with diabetes mellitus.

In the ONTARGET Study involving diabetics and nondiabetics, the results were compared between monotherapy with an ACE inhibitor or ARB and combination therapy. In the combination therapy group, hyperkalemia, renal dysfunction and an excessive decrease in blood pressure were more frequent.⁴⁴⁴ In the ALTITUDE Study, in which combination therapy with a renin inhibitor (aliskiren) or placebo was introduced in high-risk diabetics taking an ACE inhibitor or ARB, adverse events such as hyperkalemia, renal dysfunction and an excessive decrease in blood pressure more frequently occurred in the aliskiren-combined group, and this combination therapy was discontinued.⁴⁹⁰ On the basis of this, aliskiren is contraindicated for diabetics taking an ACE inhibitor or ARB as a rule. However, it is recommended that, when blood pressure control is markedly unfavorable despite other antihypertensive treatments including the administration of an ACE inhibitor or ARB, aliskiren may be used carefully. Therefore, a combination of two or more classes of RA system inhibitors, including direct renin inhibitors, is not recommended. When combining them, careful follow-up is needed.

Figure 7-1 Treatment plan for hypertension complicated by diabetes mellitus. *However, a reduction in organ perfusion related to a decrease in blood pressure must be considered in patients with atherosclerotic coronary artery disease or peripheral arterial disease and elderly patients. A full color version of this figure is available at the *Hypertension Research* journal online.

2. DYSLIPIDEMIA

As shown by the J-LIT of Japan,⁷⁶⁷ the risk of atherosclerosis clearly increases when hypertension is complicated by hypercholesterolemia. The results of recent clinical studies, including ASCOT-LLA,⁷⁶⁸ suggest that the occurrence and recurrence of coronary artery disease and stroke can be prevented by serum low-density lipoprotein (LDL)-cholesterol-reducing treatment in patients with hypertension with hyper-LDL cholesterol, and the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012 also propose a stricter control of LDL-cholesterol level if it is complicated by risk factors including hypertension. For patients with hyper-LDL cholesterol and hypertension, lifestyle modifications, that is, correction of obesity, restriction of saturated fatty acid, cholesterol and alcohol intake, and an increase in the amount of exercise should be strongly advised. If hypercholesterolemia cannot be resolved by lifestyle modifications, drug therapy primarily using an HMG-CoA reductase inhibitor should be performed simultaneously. In patients with hypertension and hypercholesterolemia, the cholesterol level should be controlled to an appropriate therapeutic target level by lifestyle modifications and the use of antihypercholesterolemic drugs. If hypertriglyceridemia or hypo-high-density lipoprotein (HDL) cholesterol is concurrent with hypertension, the presence of insulin resistance or metabolic syndrome should be considered, and this type of dyslipidemia should be corrected by lifestyle modifications and the use of drugs such as fibrates, in principle. If no improvement is noted in dyslipidemia even after practicing lifestyle

modifications for 6 months or longer, drugs such as fibrates should be used to correct it.

A subanalysis of the J-LIT¹¹⁰ showed that, when blood pressure exceeded 140/90 mm Hg in a group in which a normal cholesterol level was maintained under statin administration, the incidence of cardiovascular disease significantly increased in comparison with normotensive patients. In the hypercholesterolemia group, with a total cholesterol level of ≥ 220 mg dL⁻¹, the incidence of cardiovascular disease significantly increased when blood pressure was $\geq 130/80$ mm Hg; the lower blood pressure than in the normal cholesterol group was a risk factor for cardiovascular disease. A recently published subanalysis of the MEGA Study also indicated that the risks of stroke and cardiovascular disease significantly increased when blood pressure exceeded 130/85 mm Hg in hypercholesterolemia patients with a total cholesterol level of ≥ 220 mg dL⁻¹.⁷⁶⁹ If future epidemiological studies yield similar results, the target of blood pressure control for hypertensive patients with hypercholesterolemia may be lowered.

In selecting antihypertensive drugs for dyslipidemia patients, the effects of various antihypertensive drugs on lipid metabolism must be considered. Thiazides at high doses and loop diuretics are known to elevate the serum total cholesterol, triglyceride and LDL-cholesterol levels, but whether thiazides at a low dose also increase lipids is unclear. β -blockers have been reported to increase the serum triglyceride level or reduce the HDL-cholesterol level. α -blockers reduce the serum cholesterol level and increase the HDL-cholesterol level. ARBs, ACE inhibitors, Ca channel blockers and central sympatholytic drugs have no effect on serum lipid levels. For hypertensive patients with dyslipidemia, antihypertensive drugs that improve or have no adverse effect on lipid metabolism, such as ARBs, ACE inhibitors, Ca channel blockers and α -blockers, are desirable from a metabolic point of view.⁷⁷⁰

POINT 7B

Obesity

In hypertensive patients with obesity, weight control by dietary and exercise therapies exhibits hypotensive effects (Recommendation grade: A, Evidence level: I).

As antihypertensive drugs, ARBs and ACE inhibitors are recommended, considering their effects on metabolism (Recommendation grade: B, Evidence level: II).

Metabolic syndrome

Metabolic syndrome is also an important risk factor for cardiovascular disease in Japan. In addition to the management of other risk factors, strict blood pressure control should be performed (Recommendation grade: B, Evidence level: II).

When selecting antihypertensive drugs, the correction of visceral fat-type obesity and improvement of insulin resistance must be considered. ARBs and ACE inhibitors are recommended (Recommendation grade: B, Evidence level: II).

It is recommended that grade I hypertension patients with risk factors for cardiovascular disease on specific health checkups/health guidance should consult a hospital. Information must be given to those without other risk factors. In this case, after being informed of a diagnosis of hypertension, patients should be instructed to modify their lifestyle and undergo additional examination in the hospital after 3 months (Recommendation grade: C1, Evidence level: IVa).

3. OBESITY

In obese patients, the incidence of hypertension is 2–3 times higher than in nonobese persons.⁷⁷¹ In particular, excessive weight gain from a young age is an important risk factor for hypertension. The sympathetic nervous system, sodium retention/salt sensitivity and insulin resistance have been suggested to be involved in the etiology of hypertension accompanied by obesity. Sleep apnea syndrome is occasionally observed in obese patients, and it may be a factor involved in the occurrence and progression of hypertension.

It is known that a 4- to 5-kg decrease in body weight significantly reduces blood pressure.⁷⁷² For antihypertensive therapy in obese patients, weight control through dietary and exercise therapies should be attempted first; however, if the decrease in blood pressure is insufficient even after guidance in weight control, drug therapy should be introduced. In the ACCORD-BP Study, in which the significance of strict blood pressure control in hypertensive patients with diabetes mellitus was investigated, the preventive effects of strict treatment targeting a systolic blood pressure of <120 mm Hg on cardiovascular disease were more marked in obese patients.⁷⁷³ In the future, the target of blood pressure control in obese patients with hypertension should be further examined.

The primary objective of antihypertensive drug therapy is to achieve the target of blood pressure control. However, ARBs and ACE inhibitors are recommended because of their favorable effects on abnormal glucose metabolism and insulin resistance. In CASE-J,⁴⁶⁶ a large-scale clinical study conducted in Japan, the new occurrence of diabetes mellitus, as a secondary end point, in the candesartan (ARB) group was significantly lower than in the amlodipine group. The preventive effect was more marked in obese patients with a BMI of 25 kg m⁻² or greater based on the results of subanalysis. In the ACCOMPLISH Study, in which the usefulness of combination therapy with an ACE inhibitor and a long-acting Ca channel blocker or thiazide diuretic was examined in hypertensive patients with a high risk of cardiovascular disease, the Ca channel blocker significantly prevented cardiovascular events in comparison with the diuretic, but the effects of the two drugs were similar in obese patients with a BMI of 30 kg m⁻² or greater.⁷⁶⁶ Therefore, in the presence of obesity, resistant hypertension is not rare. If a sufficient decrease in blood pressure is not achieved with ARBs or ACE inhibitors, combination therapy with long-acting Ca channel blockers or thiazide diuretics should be considered. Thiazide diuretics do not influence metabolism at a half of the standard dose.

4. METABOLIC SYNDROME

The concurrence of hypertension, dyslipidemia (hypertriglyceridemia and hypo-HDL cholesterolemia), obesity and abnormal glucose metabolism has been shown by many epidemiological studies to synergistically increase the risk of atherosclerotic diseases, including coronary artery disease. As insulin resistance is involved as a common background factor in these risk factors of atherosclerotic diseases, the condition has been referred to by various names including multiple risk factor syndrome, insulin resistance syndrome and visceral fat syndrome, but the term 'metabolic syndrome' proposed by the National Cholesterol Education Program ATP-III (2001) has recently become universal.⁷⁷⁴ The diagnostic criteria of the National Cholesterol Education Program-ATP-III for metabolic syndrome are a high blood pressure ($\geq 130/85$ mm Hg), abnormal glucose tolerance (fasting blood glucose level: ≥ 110 mg dl⁻¹), visceral fat-type obesity (waist circumference: ≥ 102 cm for men and ≥ 88 cm for women), hypertriglyceridemia (≥ 150 mg dl⁻¹) and hypo-HDL cholesterolemia (< 40 mg dl⁻¹ for men, < 50 mg dl⁻¹ for women), and a condition

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

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

Abbreviation: HDL, high-density lipoprotein.

Table 7-2 Treatment plan for hypertension complicated by metabolic syndrome

	Therapeutic strategy
Diabetes mellitus (–)	BP $\geq 140/90$ mm Hg Treatment for hypertension BP 130–139/85–89 mm Hg Lifestyle modifications
Diabetes mellitus (+)	BP $\geq 140/90$ mm Hg The administration of antihypertensive drugs should be started BP 130–139/80–89 mm Hg Blood pressure control should be performed through lifestyle modifications for 3 months or less. If a target blood pressure is not reached, the administration of antihypertensive drugs should be started.
Selection of anti-hypertensive drugs:	Selected primarily from ARBs and ACE inhibitors with a strong insulin resistance-reducing effect

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure.

involving three or more of these five risk factors is regarded as metabolic syndrome.

Diagnostic criteria in Japan were proposed in April 2005 by a joint committee of eight related scientific societies, including the Japanese Society of Hypertension.⁷⁷⁵ According to the criteria shown in Table 7-1, hypertension with metabolic syndrome is accompanied by visceral fat-type obesity concurrent with either abnormal glucose or abnormal lipid metabolism. The main target diseases related to metabolic syndrome are cardiovascular disease and diabetes mellitus. In the Tanno-Sobetsu cho Study, the incidence was 1.87⁷⁵⁰ and 2.17⁷⁷⁶ times higher for cardiovascular disease and diabetes mellitus, respectively, in patients with metabolic syndrome. On the basis of this, patients with metabolic syndrome are classified as risks II or III on cerebrovascular/cardiovascular risk stratification (Table 3-2).

Table 7-2 shows the therapeutic approaches for hypertensive patients with metabolic syndrome. Treatment for metabolic syndrome differs according to the presence or absence of diabetes mellitus. Without diabetes, antihypertensive drugs are prescribed when the blood pressure is $\geq 140/90$ mm Hg, and only lifestyle modifications are indicated when it is 130–139/85–89 mm Hg to prevent progression to hypertension or reduce blood pressure to a normal range. If

diabetes is present, antihypertensive drug therapy should also be started when the blood pressure is $\geq 130/80$ mm Hg in patients with metabolic syndrome. The target of blood pressure control is $< 130/80$ mm Hg. The aim of treatment is the correction of visceral fat-type obesity through dietary and exercise therapies. If antihypertensive drugs are used, ARBs, ACE inhibitors, Ca channel blockers and α -blockers that improve insulin resistance are desirable. Prevention of the new occurrence of diabetes mellitus is related to the alleviation of insulin resistance, and this relationship has been established in clinical studies using ARBs and ACE inhibitors. Although Ca channel blockers have also been shown to reduce the occurrence of diabetes, this effect is significantly lower than that of ARBs or ACE inhibitors, as suggested by CASE-J,⁴⁶⁶ VALUE⁴²⁴ and ALLHAT,²³⁷ and thus RA system inhibitors such as ARBs and ACE inhibitors are recommended first. There is no sound evidence that RA system inhibitors are effective in the prevention of cardiovascular disease in hypertensive patients with metabolic syndrome.²³⁷

1) Blood pressure control in specific health checkups/health guidance

In April 2007, a standard program for specific health checkups/health guidance (final version) was proposed by the Ministry of Health, Labour and Welfare. Preparatory procedures were promoted at various insurance corporations and medical facilities associated with outsourcing. This program has been carried out since April 2008. In this program, the entity of metabolic syndrome is introduced, and specific health guidance is indicated for individuals meeting an abdominal circumference of ≥ 85 cm for men and ≥ 90 cm for women or a BMI of ≥ 25 kg m⁻² and having other risk factors, to prevent lifestyle-related diseases by lifestyle modifications through health guidance. For the primary prevention of cardiovascular disease, of which the incidence is increasing in Japan, it is very important to correct abnormal glucose metabolism, a high blood pressure and abnormal lipid metabolism, primarily in patients with visceral fat-type obesity. This may also be useful as a strategy to prevent and treat hypertension. This program will be supported by the Japanese Society of Hypertension to promote specific health checkups/health guidance.

In the program presented as a final draft, the following are the opinions of the Japanese Society of Hypertension submitted complementarily particularly for hypertension management:

(1) *Diagnostic criteria.* Although a blood pressure of 130/85 mm Hg or above is established as a criterion for health guidance, this is the reference value of high-normal blood pressure, and, internationally, the same criterion is also used. In Japan, epidemiologically, evidence that the risk of cardiovascular disease increases at a high-normal or higher blood pressure has also been obtained, supporting this reference value.

(2) *Blood pressure measurement.* Blood pressure measurement should be performed twice, and the mean value should be adopted, as used in the National Health and Nutrition Survey/Basic Survey on Cardiovascular Disease and this program. To measure home blood pressure, the brachial arm cuff/oscillometric method should be used.

(3) *Application of home blood pressure.* As described in the program, blood pressure markedly changes, and the effects of white coat hypertension may also appear on health checkups. To evaluate a true blood pressure level, home blood pressure-based assessment is desirable. Therefore, the Guidelines recommend that the presence or absence of home blood pressure measurement should be confirmed at the time of an inquiry/questionnaire survey or blood pressure

measurement, and that home blood pressure values should be recorded. In the JSH2014 Guidelines, patients with a home blood pressure of 135/85 mm Hg or above are regarded as having hypertension, those with a home blood pressure of 125–134/80–84 mm Hg as showing a high-normal blood pressure and those with a home blood pressure of $< 125/80$ mm Hg as normotensive individuals. Therefore, if the home blood pressure measured in accordance with the method recommended by the Japanese Society of Hypertension is $< 125/80$ mm Hg, even a blood pressure of $\geq 130/85$ mm Hg on a health checkup should be regarded as the white coat phenomenon, and the patient should not be regarded as having high blood pressure. For subsequent health checkups or health guidance, evaluation should be performed with reference to home blood pressure in addition to the blood pressure values measured.

On the other hand, even when blood pressure on a health checkup is $< 130/85$ mm Hg, patients with a home blood pressure of $\geq 125/80$ mm Hg should be regarded as having high-normal blood pressure and meeting the criterion for high blood pressure. In particular, if home blood pressure is $\geq 135/85$ mm Hg, masked hypertension is suggested. Considering that the risk of cardiovascular disease in individuals with masked hypertension is as high as that of hypertension, strategies to treat hypertension should be started by instructing the patient to consult a hospital.

(4) *Recommendations for consultation.* The objective of this health checkup is to select patients with metabolic syndrome, in whom lifestyle-related diseases may be prevented, and stratify the risk of cardiovascular disease. This risk should be evaluated based on the values of checkup items as criteria for health guidance and a questionnaire, and stratified into positive support, motivation support and information provision levels for specific health guidance. Physicians at a medical center should instruct patients to consult a hospital according to each society's guidelines and criteria for recommending a consultation on specific health checkups. Concerning blood pressure, a criterion for health guidance is established as $\geq 130/85$ mm Hg, and that for recommending a consultation as $\geq 140/90$ mm Hg. The latter is the reference value of hypertension, and health practice may be considered.

In the Guidelines for Hypertension Management (JSH2014) in Japan, cerebrovascular/cardiovascular risks are stratified, as shown in Table 3-2. Risk factors for cardiovascular disease are presented in Table 3-1. Strategies to treat hypertension with respect to risk factors are shown in Figure 3-1. Strategies for blood pressure control, including recommendations for consultation, in accordance with the JSH2014 Guidelines, are summarized in Figure 7-2. Grade II or severer hypertension patients with a blood pressure of $\geq 160/100$ mm Hg must be instructed to promptly consult a hospital. Among grade I hypertension patients with a blood pressure of 140–159/90–99 mm Hg, high-risk patients with diabetes mellitus or chronic kidney disease (CKD) should be instructed to promptly consult a hospital. In moderate- or high-risk patients (including those matched to metabolic syndrome) with one or more risk factors for cardiovascular disease (Table 3-1), blood pressure is $\geq 140/90$ mm Hg, which is a criterion for recommending a consultation, and they must be instructed to consult a hospital. For this evaluation, if home blood pressure is $< 125/80$ mm Hg, the above phenomenon can be regarded as white coat hypertension, and it is not necessary to make a diagnosis of hypertension.

On the other hand, low-risk, grade I hypertension patients with no risk factor must be instructed to consult a hospital, as a rule, according to the JSH2014 Guidelines. However, as described above,

Figure 7-2 Blood pressure control in specific health checkups/health guidance. ^{*1}Risk factors for cardiovascular disease and organ damage/cardiovascular disease (Table 3-1). ^{*2}To grade I hypertension patients without risk factors, information should be given: the presence of hypertension, necessity of lifestyle modifications and necessity of consulting a hospital if home blood pressure is $\geq 135/85$ mm Hg after 3 months. ^{*3}When providing information or conducting specific health guidance, the significance of home blood pressure measurement must be explained, and patients should be instructed to measure home blood pressure until the subsequent health checkup. ^{*4}Individuals for whom specific health guidance is not indicated can also be covered by the city/town/village's health promotion business. In addition to information provision, physicians should advise them to undergo individualized health education. A full color version of this figure is available at the *Hypertension Research* journal online.

antihypertensive drug therapy should not be promptly introduced in low-risk patients with grade I hypertension, and treatment should be started through lifestyle modifications over 3 months. Thus, in low-risk, grade I hypertension patients with no risk factor, it is desirable to modify their lifestyle and check blood pressure according to the program for specific health guidance. However, low-risk, grade I hypertension patients are not selected for specific health guidance currently because they are not obese. Information should be provided, assuming recommendations for consultation. When providing information, physicians should inform patients of the presence of hypertension, propose lifestyle modifications such as salt restriction and dietary/exercise therapies and instruct them to consult a hospital after 3 months.⁶⁵

If diabetes mellitus or CKD is present in patients with a blood pressure of 130–139/85–89 mm Hg (high-normal blood pressure), they must be instructed to consult a hospital. If diabetes mellitus or CKD is absent, specific health guidance is indicated for patients meeting an abdominal circumference of ≥ 85 cm for men and ≥ 90 cm for women or a BMI of ≥ 25 kg m⁻². Information is given to those who do not meet either criterion. When providing information or conducting specific health guidance, physicians should explain the significance of home blood pressure measurement and instruct patients to measure home blood pressure until the subsequent health checkup.

Finally, the necessity of consulting a hospital is comprehensively evaluated by a physician who assesses the results of a health checkup, with reference to the strategies for blood pressure control proposed by the Japanese Society of Hypertension (Figure 7-2). On the other hand, individuals for whom specific health guidance is not indicated should also be covered by the city/town/village's health promotion business.

5. SLEEP APNEA SYNDROME

POINT 7C

1. In patients with nocturia, nocturnal dyspnea, nighttime cardiovascular events or resistant hypertension in addition to sleepiness during the daytime, obstructive sleep apnea syndrome (OSAS) should be suspected (Evidence level: E-II).
2. In OSAS patients, non-dipper-/riser-type nocturnal hypertension with marked changes in blood pressure is frequently observed. OSAS should be suspected in those in whom home

blood pressure measurement suggests morning hypertension (Evidence level: E-II).

3. In hypertensive patients with OSAS, continuous positive airway pressure (CPAP) therapy should be performed in addition to salt restriction/weight control (Recommendation grade: A, Evidence level: I). Strict antihypertensive treatment involving nighttime blood pressure should be performed (Recommendation grade: C1, Evidence level: IVb).

OSAS is a disease in which hypoxemia occurs periodically during sleep owing to respiratory arrest caused by collapse of the upper airway. It is a risk factor for cardiovascular diseases, such as coronary artery disease and heart failure,^{777,778} and cerebrovascular diseases, including silent cerebral infarction,⁷⁷⁹ in addition to nighttime sudden cardiac death. Moreover, OSAS is the etiology of hypertension, and is the most frequent underlying cause of secondary hypertension that leads to resistant hypertension.⁵¹⁷ OSAS is frequently observed in Japanese patients with hypertension.^{780–783} The diagnosis and treatment of OSAS in hypertensive patients are very important.

OSAS increases with obesity or age, but, in Japan, it is also frequently observed in nonobese individuals with particular skeletal characteristics of the face such as micrognathia, tonsillar hypertrophy or low palatal arch with long low-hanging soft palate (even when the tongue is pushed with a tongue depressor, the uvula or posterior wall of the pharynx cannot be examined).⁷⁸⁴ Although many patients consult a hospital with symptoms such as daytime sleepiness, reduced concentration and a depressive state, symptoms are often absent in hypertensive patients; most patients consult a hospital because of snoring or apnea indicated by the patient's family. In patients with nocturia, nocturnal dyspnea (feelings of suffocation), heart failure, a history of nocturnal cardiovascular events (myocardial infarction, stroke, acute aortic dissection, supraventricular or ventricular arrhythmia), resistant hypertension (particularly resistant morning hypertension) or left ventricular hypertrophy under a normal blood pressure, as well as those with CKD or undergoing dialysis, it is important to suspect OSAS (Table 7-3).^{781,785,786}

OSAS is diagnosed and staged by sleep polygraphy, and it is considered to be mild when the apnea-hypopnea index (AHI: number of apneic or hypopneic periods per hour) is 5–15, moderate when it is 15–30 and severe when it is ≥ 30 .^{777,778,787} In hypertensive patients with symptoms or organ damage showing an AHI of ≥ 15 , treatment must be considered (borderline for the secondary prevention of

Table 7-3 Findings suggesting obstructive sleep apnea syndrome

Symptoms	Sleepiness, reduced concentration, depression, indefinite complaints (headache and malaise) early in the morning, marked snoring, apnea (frequently indicated by patients' families), frequent awakening during the night, nocturia and nocturnal dyspnea (feelings of suffocation)
Physical findings	Obesity, micrognathia, tonsillar hypertrophy and low palatal arch with long low-hanging soft palate
Blood pressure features	Resistant hypertension, morning hypertension and nighttime hypertension
Findings	Left ventricular hypertrophy (especially in patients with normal clinic and home blood pressures), heart failure, nocturnal cardiovascular events (including atrial fibrillation and ventricular arrhythmia), metabolic syndrome, chronic kidney disease and dialysis

cardiovascular disease). In those with an AHI of ≥ 30 , aggressive treatment including CPAP should be performed (borderline for the primary prevention of cardiovascular disease).⁷⁸⁷ In the health insurance system, an AHI of ≥ 20 is a borderline at which CPAP is possible, and an AHI of ≥ 40 is a severe borderline at which treatment can be performed using sleep polygraphy alone.⁷⁸⁷

In patients with OSAS, non-dipper-type nocturnal hypertension is frequently observed in addition to an increase in blood pressure during the daytime, and often detected as morning hypertension by home blood pressure measurement.⁷⁸⁰ OSAS precedes non-dipper-type nocturnal hypertension.⁷⁸⁸ In OSAS patients, non-dipper-type hypertension is also associated with the progression of CKD.⁷⁸⁹ In addition, a marked surge of nighttime blood pressure is observed in the recovery phase after apnea attacks, and such a change in nighttime blood pressure⁷⁸⁰ may induce nocturnal cardiovascular events. Recently, it has become possible to measure nighttime blood pressure^{145,147} and its surge after apnea attacks¹⁴⁶ using a home sphygmomanometer.¹⁴⁷

The enhancement of sympathetic activity, increased pressure receptor/chemoreceptor sensitivity, activation of the renin-angiotensin-aldosterone system and increases in oxidative stress and inflammatory reactions are complexly involved in OSAS-related hypertension or an increase in fluctuation of the blood pressure.⁷⁸¹

As OSAS is closely associated with lifestyle, lifestyle should be initially modified. In addition to salt restriction, weight control must be promoted in obese patients, and smoking and alcohol consumption before retiring should be avoided. CPAP therapy should be predominantly performed in patients with grade I/II hypertension complicated by moderate/severe OSAS.⁷⁸¹ Some patients with grade III hypertension require drug therapy from the initial consultation. In most patients, CPAP therapy lowered blood pressure,^{790,791} allowed a dipper pattern to replace the non-dipper pattern,⁷⁹² reduced a nocturnal surge of blood pressure⁷⁸⁰ and improved the cardiovascular prognosis.⁷⁹³ A long-term follow-up study also showed that CPAP therapy prevented the new onset of hypertension in patients with OSAS.⁷⁹⁴ In OSAS patients without sleepiness, adherence is poor, and the hypotensive effects of CPAP and its preventive effects on cardiovascular events are weak.⁷⁹⁵⁻⁷⁹⁷ In OSAS patients in whom CPAP therapy is impossible or adherence is poor, oral appliances are also useful.⁷⁹⁸ Therefore, patients should be referred to specialists including otorhinolaryngologists and oral surgeons if necessary.

As the risk of cardiovascular disease is high in hypertensive patients with OSAS, the target level of blood pressure control should be established, considering an increase in negative intrathoracic pressure

load on the thoracic aorta and heart during apneic periods (which may reach 80 mm Hg); strict antihypertensive therapy, particularly with the control of nighttime blood pressure, should be performed. However, there is no evidence regarding the usefulness of specific antihypertensive drugs.⁷⁸¹ According to a study, β -blockers more markedly reduced nighttime systolic/diastolic blood pressures compared with Ca channel blockers, ACE inhibitors and ARBs (no significant difference between β -blockers and diuretics), although there were no differences in the rate of decrease in daytime/waking blood pressure among these antihypertensive drugs.⁷⁹⁹ However, another study indicated that monotherapy with antihypertensive drugs, including β -blockers, reduced daytime blood pressure, whereas it was difficult to control nighttime blood pressure during sleep.⁸⁰⁰ A consensus regarding the efficacy of β -blockers has not been reached. In hypertensive OSAS patients with heart failure, the administration of diuretics may reduce laryngeal edema, thereby relieving OSAS.⁸⁰¹ According to several studies, in patients with resistant hypertension, spironolactone administration,⁸⁰² negative-pressure aspiration of the lower limbs⁸⁰³ and renal denervation⁸⁰⁴ decreased blood pressure and the frequency of sleep apnea attacks, although the number of patients was small.

Central sleep apnea syndrome is observed in some patients, showing a poor prognosis. However, it is rare in hypertensive outpatients without severe heart failure.

6. GOUT/HYPERURICEMIA

POINT 7D

Gout/hyperuricemia

1. In hypertensive patients with hyperuricemia, lifestyle guidance such as obesity reduction related to restriction of energy intake, routine practice of aerobic exercise and restriction of intake of a diet with a very high purine content, alcohol and salt/fructose should be started at a serum urate level of $>7 \text{ mg dl}^{-1}$ (Recommendation grade: C1, Evidence level: III).
2. When the serum urate level is $\geq 8 \text{ mg dl}^{-1}$, the initiation of urate-lowering drugs with lifestyle modifications should be considered. The target of control of the serum urate level during antihypertensive treatment should be $\leq 6 \text{ mg dl}^{-1}$ (Recommendation grade: C1, Evidence level: III).
3. Antihypertensive drugs that exhibit effects on urate metabolism should be used. As thiazide and loop diuretics may cause hyperuricemia, changes in the serum urate level must be monitored if these diuretics are required in patients who are likely to develop gout. Ca channel blockers and losartan reduce the risk of gout in hypertensive patients (Recommendation grade: B, Evidence level: II).
4. ACE inhibitors, ARBs, Ca channel blockers and α -blockers have no adverse effect on urate metabolism. Losartan promotes urate excretion, reducing the urate level (Recommendation grade: B, Evidence level: II).
5. Urate-lowering drugs should be selected on the basis of the classification of disease type. However, a drug and its dose should be carefully determined on the basis of the presence or absence of renal dysfunction (Recommendation grade: C1, Evidence level: III).

Urate is the final metabolic product of purine metabolites, and its serum concentration is determined by its production in the body and excretion through the kidney. Urate has a simultaneous antioxidant

action, however hyperuricemia has often been reported to be an independent risk factor for atherosclerosis. No large-scale clinical study has shown a reduction of the occurrence of cardiovascular disease through urate-lowering treatment, and thus whether urate is a risk factor or disease marker is not clear. As hypertensive patients show reduced urate excretion and increased urate synthesis, reflecting anaerobic metabolism of cells, hypertension is often complicated by hyperuricemia.

An increase in the serum urate level in hypertensive patients is correlated with not only the risk of gout but also kidney damage and cardiovascular accidents, although evidence based on an interventional study is lacking. We therefore recommend control of the urate level on the basis of the 6-7-8 rules for comprehensive risk avoidance according to the Guidelines for the Management of Hyperuricemia and Gout (version II)⁸⁰⁵ by the Japanese Society of Gout and Nucleic Acid Metabolism. That is, a serum urate level of $>7 \text{ mg dl}^{-1}$ is defined as hyperuricemia, and a correction of the serum urate level is started by lifestyle guidance if hypertension is concurrent with hyperuricemia. If the serum urate level still increases or is $\geq 8 \text{ mg dl}^{-1}$, urate-lowering therapy should be considered.

The serum urate level during antihypertensive treatment should be maintained at $\leq 6 \text{ mg dl}^{-1}$. As many patients with hypertension complicated by hyperuricemia have obesity or metabolic syndrome, lifestyle modifications such as restriction of energy intake, routine aerobic exercise and restriction of intake of foods and beverages with a markedly high purine content (beer, in particular) are necessary. Lifestyle modifications for hypertensive patients, such as restriction of salt intake,⁸⁰⁶ should be performed. If the urate level cannot be reduced sufficiently through lifestyle modifications alone, the addition of a urate-lowering drug depending on the type of hyperuricemia should be considered. Urate-lowering drugs include inhibitors of urate synthesis (xanthine oxidase inhibitors) and urate transporter (URAT1) inhibitors, which promote urate excretion. In hyperuricemic patients, the urinary pH is often low, and it should be adjusted to ≥ 6.0 and <7.0 to increase the solubility of urate in urine. If alkalinization of the urine is necessary, fixed combination drugs of sodium bicarbonate or those of Na citrate/K citrate may be administered. The latter is adjusted to reduce the Na intake compared with sodium bicarbonate, but attention should be paid to an increase in the serum K level. Allopurinol has been reported to exhibit hypotensive effects,⁸⁰⁷ improve vascular endothelial function⁸⁰⁸ and reduce angina pectoris.^{809,810} Febuxostat is primarily metabolized in the liver and can be relatively safely used even in the presence of renal dysfunction. On the other hand, urate excretion-promoting drugs, probenecid⁸¹¹ and benzbromarone,⁸¹² reportedly reduce blood pressure and improve insulin resistance.

As a rapid decrease in the extracellular fluid volume related to thiazide or loop diuretics may cause hyperuricemia, inducing gout, changes in the serum urate level should be monitored if these drugs are required in patients who are prone to developing gout. Ca channel blockers and losartan reduce the risk of gout in hypertensive patients.⁴⁷⁶ Potassium-sparing diuretics, such as spironolactone, triamterene and eprelone, have no adverse effect on urate metabolism. The administration of a β - or $\alpha\beta$ -blocker at a very high dose increases the serum urate level. ACE inhibitors, Ca channel blockers and α -blockers have been reported to reduce the serum urate level in some reports but have no effect in others. α -Methyldopa has no effect on the serum urate level. With regard to ARBs, some ARBs have been suggested to promote urate reabsorption in the renal tubules, but they exert no clear effect on the serum urate level. Losartan, an ARB, reduces the serum urate level by a mean of 0.7 mg dl^{-1} by inhibiting

the action of URAT1 in the renal tubules.^{471,474,813,814} In LIFE, which showed the superiority of the target organ-protective effect of losartan over a β -blocker, atenolol, in severely hypertensive patients, 29% of the organ-protective effect of losartan, which cannot be explained by its antihypertensive effect alone, was suggested to be derived from an improvement in the urate level.⁴⁷³ In fixed combination drugs of ARB and thiazide diuretics, the type of ARB and dose of the diuretic to be combined are adjusted to avoid an excessive increase in the serum urate level.

In patients with hyperuricemia, the proportion of patients with metabolic syndrome or CKD is high, and, as a rule, strict blood pressure control should be performed in accordance with individual conditions, as recommended for the target of blood pressure control in the general population.

7. BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

POINT 7E

1. In patients with bronchial asthma, β - and $\alpha\beta$ -blockers should be avoided (Recommendation grade: D, Evidence level: I).
2. ACE inhibitors cause dry cough as an adverse effect. As this symptom is sometimes difficult to differentiate from cough related to bronchial asthma, these drugs are not recommended for patients with bronchial asthma (Recommendation grade: C2, Evidence level: IVa).
3. In patients with bronchial asthma, Ca channel blockers, ARBs and low-dose diuretics may be used (Recommendation grade: C1, Evidence level: IVa).
4. In patients with chronic obstructive pulmonary disease (COPD), Ca channel blockers, ACE inhibitors, ARBs and low-dose diuretics may be used (Recommendation grade: C1, Evidence level: IVa).
5. In patients with COPD, the administration of β -blockers is possible (Recommendation grade: C1, Evidence level: III), but selective β_1 -blockers should be used (Recommendation grade: B, Evidence level: II).

Bronchial asthma and COPD are classified as obstructive pulmonary diseases. Bronchial asthma refers to eosinophilic inflammation of the airway, whereas COPD is a systemic inflammatory disease in which neutrophils are involved, and is often complicated by cardiovascular disease. In particular, hypertension is the most frequent complication in patients with COPD.⁸¹⁵

It is unclear whether salt is involved in the enhancement of airway hypersensitivity.⁸¹⁶ However, salt restriction has no adverse effect on bronchial asthma or COPD. Exercise therapy is also recommended for COPD patients, but there are some patients with exercise-induced bronchial asthma.

When selecting antihypertensive drugs, different approaches for bronchial asthma and COPD are necessary. Both α -blockers and Ca channel blockers relieve tension of the bronchial smooth muscle, and they do not affect the respiratory function of patients with bronchial asthma. ACE inhibitors do not influence the asthma symptoms or respiratory function of hypertensive patients with bronchial asthma.⁸¹⁷ However, cough, as an adverse effect, is sometimes difficult to differentiate from the exacerbation of bronchial asthma, and ACE inhibitors should be avoided. ARBs do not exacerbate cough or suppress the respiratory function in patients with bronchial asthma.

Antihypertensive diuretics do not influence the respiratory function, but hypokalemia must be considered in patients orally treated with steroids. As β -blockers increase airway resistance by blocking β_2 -receptors in the bronchial smooth muscle, they must not be administered to patients with bronchial asthma (contraindicated as a rule).⁸¹⁸ In addition, the use of $\alpha\beta$ -blockers should also be avoided. However, when β -blockers are absolutely indicated for patients with ischemic heart disease or heart failure, selective β_1 -blockers should be carefully administered.

In patients with COPD, ACE inhibitors, ARBs, Ca channel blockers and antihypertensive diuretics can be routinely used, because there are no data on the exacerbation of COPD/an increase in the mortality rate. However, antihypertensive diuretics increase the viscosity of bronchial secretions (sputum), and should be used at a low dose while guiding an appropriate water intake. According to several studies, β -blockers were safe and effective in COPD patients with coronary artery disease or heart failure.^{819–822} Currently, β -blockers cannot be positively recommended for hypertensive patients with COPD, but their use is not contraindicated. However, selective β_1 -blockers should be used rather than nonselective β -blockers.⁸²³

8. LIVER DISEASES

POINT 7F

1. **As severe liver dysfunction increases the plasma concentrations of antihypertensive drugs metabolized in the liver, adjustment including a reduction in the dose is necessary (Recommendation grade: C1, Evidence level: IVa).**
2. **β -Blockers may reduce the risks of gastrointestinal bleeding and death in patients with liver cirrhosis (Recommendation grade: C1, Evidence level: IVa).**
3. **RA system inhibitors may prevent fibrosis of the liver (Recommendation grade: C1, Evidence level: III).**

Generally, in patients with advanced liver cirrhosis, blood pressure tends to decrease through changes in the hemodynamics and

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

There have been reports of some meta-analyses that noncardioselective β -blockers such as propranolol lower the risks of gastrointestinal bleeding and death in liver cirrhosis patients by reducing portal pressure.⁸²⁴ However, antihypertensive diuretics such as hydrochlorothiazide, chlorthalidone and furosemide should be used carefully in liver cirrhosis patients, because they may induce hepatic coma through their rapid diuretic action. RA system inhibitors have been suggested by basic studies to prevent fibrosis in the transitional period from chronic hepatitis to liver cirrhosis, but there is no report of results involving a large number of subjects. In nonalcoholic steato-hepatitis, ARBs are reported to be effective for reversing pathological changes such as fibrosis.⁸²⁵

Citation Information

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

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