Hypertension Research (2009) 32, 33–39

www.nature.com/hr

GUIDELINES (JSH 2009)

Chapter 5. Treatment with antihypertensive drugs

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

POINT 5A

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

1) BASIC PRINCIPLES FOR THE SELECTION OF ANTIHYPERTENSIVE DRUGS

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

a. First choices

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

b. Use of antihypertensive drugs

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

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

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

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

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

c. Drug interactions

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

d. Dose reduction and withdrawal of antihypertensive drugs

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

2) CHARACTERISTICS AND MAJOR ADVERSE EFFECTS OF VARIOUS ANTIHYPERTENSIVE DRUGS

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

a. Ca channel blockers

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

Table 5-1 Positive indications of major antihypertensive drugs

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

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

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

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

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

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

b. ARBs

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

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

c. ACE inhibitors

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

d. Diuretics

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

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

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

e. β-Blockers (including αβ-blockers)

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

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

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

f. α-Blockers

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

g. Other sympatholytic drugs—centrally and peripherally acting drugs

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

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

h. Classic vasodilators

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

i. Aldosterone antagonists and potassium-sparing diuretics

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

3) COMBINATION THERAPY

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

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

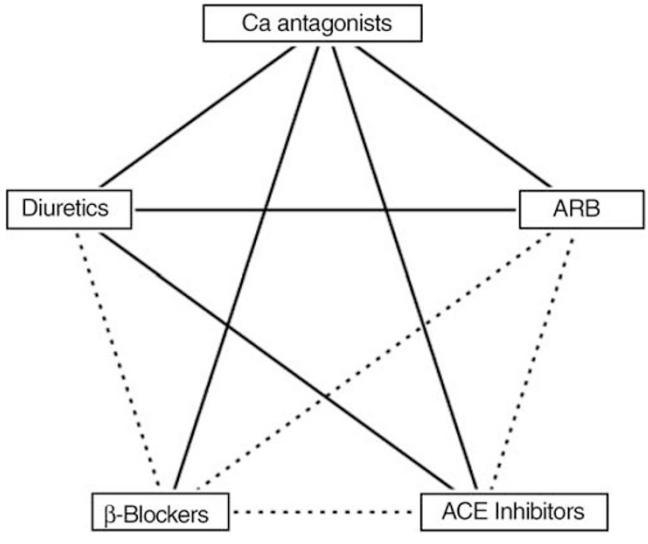

Figure 1 Combination of two drugs.

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

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

4) FIXED-COMBINATION DRUGS

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

POINT 5B

Poorly controlled and resistant hypertension

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

5) MANAGEMENT OF POORLY CONTROLLED AND RESISTANT HYPERTENSION

a. Definition and prevalence

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

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

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

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

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

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

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

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

b. Factors of resistance to treatment and approaches to them

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

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

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

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

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

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

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

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

Citation Information

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

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

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