Table 8. Therapeutic Goal of Blood Pressure (BP) for Treatment of Hypertension in the Elderly

Age (yr)	60–69	70–79	80 and older
Systolic BP (mmHg)	<140	<150	<160
Diastolic BP (mmHg)	<90	<90	<90

Biological age is more important than chronological age because of the individual difference in elderly subjects.

pressure for initiating drug treatment in the elderly should be a systolic blood pressure of 160 mmHg or greater and a diastolic blood pressure of 90 mmHg or greater (*75*).

Indeed, the large-scale intervention trials performed in groups of elderly subjects in Europe and the USA have shown the beneficial effects of antihypertensive treatment in patients with systolic blood pressure of 160 mmHg or greater and diastolic blood pressure of 90–100 mmHg. In addition, because it has been demonstrated in a cohort study by Hisayama-cho (*24*) and Tanno-Sobetsu-cho (*88*) that a systolic blood pressure of 160 mmHg or greater increased cardiovascular mortality, it is recommended that antihypertensive treatment should be initiated when the systolic blood pressure is 160 mmHg or greater and/or the diastolic blood pressure 90 mmHg or greater.

It has also been reported in a one-year follow-up study that a systolic blood pressure of 140–159 mmHg improved QOL and cardiac hypertrophy (*89*). If more than one complication is present, antihypertensive treatment may be even more strongly indicated. In cases of severe hypertension with a systolic blood pressure of 180 mmHg or greater and/or a diastolic blood pressure of 110 mmHg or greater, antihypertensive treatment should be started immediately.

4-2. Therapeutic Goal of Blood Pressure

In general, the target blood pressure in the elderly should be set at a higher level than that in the young and middle-aged. This recommendation is based on the facts that the elderly tend to already have target-organ damage and to exhibit altered cerebral autoregulation.

According to a meta-analysis of intervention trials of elderly hypertensives treated with diuretics and β-blockers, an average reduction of 12–19 mmHg in systolic and 4–10 mmHg in diastolic blood pressure decreased the morbidity of stroke by 34%, that of coronary artery disease by 21%, and that of heart failure by 15% compared with a placebo group (*90*). In these trials, the reduction of blood pressure from the baseline value was 19–44 mmHg of systolic and 9–21 mmHg of diastolic blood pressure. On the other hand, in recent intervention trials for the elderly utilizing Ca blockers and ACE inhibitors (Table 7), the achieved blood pressure was 144–167 mmHg in systolic and 68–85 mmHg in diastolic. Since the possible existence of a J-curve phenomenon—*i.e.*, a tendency, in some cases, for excessive reduction of blood pressure to increase the incidence of coronary artery disease and cerebrovascular diseases—has been reported (*91–93*), one must be cautious when reducing diastolic blood pressure to below 85 mmHg.

The results of the PATE-Hypertension study in Japan (*11*), in which the incidences of cardiovascular events were compared between patients treated with a Ca blocker and those treated with an ACE inhibitor, indicate that an excessive reduction to less than 130 mmHg in systolic blood pressure may increase the incidences of cardiovascular events. In addition, a case-control study demonstrated that blood pressure under the treatment is low level among hypertensive patients complicated with acute myocardial infarction or recurrence compared to control groups (*94*). However, a Hypertension Optimal Treatment (HOT) trial (mean age, 61.5 yr), designed to study the J-curve phenomenon (*95*) found that the maximum favorable effect was achieved at a systolic blood pressure of 130–140 mmHg and diastolic blood pressure of 80–85 mmHg. In a sub-analysis of elderly subjects aged 65 yr or older (average age, 70.6 yr), patients whose target diastolic blood pressure was less than 85 mmHg (achieved blood pressure, 145/82 mmHg) had a greater reduction in total cardiovascular events compared with those whose diastolic blood pressure was either 90 mmHg or less or 80 mmHg or less (*96*). In addition, the SHEP group showed the relationship of achieved systolic blood pressure to stroke incidence in older patients (average age, 71.6 yr), demonstrating that patients whose systolic blood pressure was lower than 150 mmHg had the greatest reduction in stroke incidence, while those having a systolic blood pressure lower than 140 mmHg had no significant reduction (*97*). These results indicate that a target systolic blood pressure of less than 150 mmHg is appropriate for patients in their 70s. The SHEP study also demonstrated that patients with diastolic blood pressure less than 55 mmHg had a 2 times greater risk of cardiovascular events. Therefore, in individuals having a wide pulse pressure, target diastolic blood pressure should not be set below 55 mmHg.

In light of these facts, the target blood pressure for individuals in their 60s should be systolic blood pressure of below 140 mmHg and diastolic blood pressure of below 90 mmHg, if tolerable, although these values may depend on the pretreatment blood pressure levels. The target systolic blood pressure for individuals in their 70s and 80s should be, respectively, below 150 mmHg and below 160 mmHg, since these patients are more likely to have target-organ damages. Table 8 shows the target blood pressures corresponding to the different age groups. It is possible to improve the prognosis of all age groups by reducing the systolic blood pressure to below 140 mmHg and the diastolic blood pressure to below 90 mmHg, if tolerable. Although there are pros and cons in regard to various blood pressure targets for the different age groups, a number of hypertension specialists in Europe agree with these general targets (*86*, *87*). Recently, based on data from the Framingham study, Port *et al.* demonstrated that

there are no age- or sex-based changes in all-cause mortality and cardiovascular mortality below the 70th percentile of systolic blood pressure, but that such changes increase remarkably over the 80th percentile of systolic blood pressure (*98*). Because blood pressure increases with age, the risk threshold is also expected to increase with age, which would support the use of different target blood pressures for the different age groups.

During antihypertensive drug treatment in elderly hypertensives, postprandial hypotension, orthostatic hypotension and excessive reduction of nocturnal blood pressure may sometimes occur and aggravate ischemia of important organs. Indeed, excessive reductions of blood pressure might be associated with an increased risk for cardiovascular diseases (*79–81*). It is thus useful to confirm the adequacy of drug treatment by means of 24-h blood pressure monitoring with a portable automatic sphygmomanometer. Home blood pressure monitoring is also recommended (*99*).

4-3. Speed of Blood Pressure Reduction

Doses of antihypertensive drugs must be titrated gradually and cautiously in the elderly, because metabolism and excretion of drugs are delayed in such patients due to age-related decreases in the functions of the liver and kidneys (*100*). At the initial stage, antihypertensive treatment should be started at half of the usual dose given to non-elderly patients, and may be increased at intervals of more than 4 weeks with a target blood pressure being achieved in 2–3 months or longer.

5. Lifestyle Modification

Hypertension can be considered a "lifestyle disease." Lifestyle modification is thus useful in the treatment of hypertension in the elderly, although the efficacy of lifestyle change varies among individuals. In the JNC VI (*14*) and WHO/ISH (*52*) guidelines, it is recommended that non-medication therapy be used as the first step for treatment of hypertension, and that it be continued even after antihypertensive drug therapy is started. Mild hypertension can be corrected only by lifestyle modification, but moderate hypertension can be normalized by administration of small doses of antihypertensive drugs. Non-medication therapy is useful for the prevention of side effects of antihypertensive drugs and for the improvement of QOL. However, elderly individuals tend to have firmly established lifestyles and to be resistant to lifestyle modification. For example, family members may not cooperate sufficiently with recommended dietary changes, and other lifestyle modifications may be difficult for practical reasons.

5-1. Diet

1) Salt Restriction

In the INTERSALT study (*101*), a significant correlation between urinary sodium excretion and elevation of blood pressure was recognized with age. In addition, it has been established that blood pressure tends to remain low even in advancing age in communities where urinary sodium excretion is low, and that the relationship between salt intake and blood pressure elevation is important (*102*). Based on the responses to abundant salt intake, patients with essential hypertension can be divided into two groups, a salt-sensitive group showing elevation of blood pressure and a non-salt sensitive group showing no elevation of blood pressure (*103*). In general, elderly individuals show high sensitivity to salt, and thus hypertension can be well corrected by restriction of salt intake.

Accordingly, mild and moderate hypertension in the elderly should be treated first by restriction of salt intake, and by other methods only if salt restriction fails to achieve a favorable response. The TONE trial (*104*), the first large-scale randomized trial, reported that weight reduction and restriction of salt intake were effective for treatment of hypertension in the elderly. The JNC VI recommends restricting dietary salt intake to less than 6 g sodium chloride per day. However, a strict restriction of salt intake from about 13 g/day (the mean salt intake in Japan) down to 6 g/day may cause loss of appetite and deteriorate QOL in the elderly. Therefore, it is recommended that salt intake should be initially restricted to below 10 g/day, and then slowly decreased to below 7 g/day, if possible.

2) Potassium Intake

Potassium itself is not significantly effective for hypertension. However, it is thought that increased potassium intake directly reduces the risk of cerebral stroke (*105*), and that potassium depletion may induce hypertension and ventricular premature beats. Therefore, increased potassium intake seems effective for the prevention of cardiovascular diseases. However, increased potassium intake is more effective for lowering blood pressure in patients with high dietary salt intake than in those with low salt intake. Since it is recognized that the dietary sodium/potassium ratio is well correlated with blood pressure levels, intake of a diet with a low sodium/potassium ratio is recommended. In the elderly, however, careful attention must be paid to cases with renal dysfunction, cases with hyporeninemic hypoaldosteronism complicated with diabetes mellitus, or cases requiring administration of aldosterone antagonists.

3) Calcium and Magnesium Intake

A negative correlation has been recognized epidemiologically between blood pressure and dietary intake of calcium and magnesium (*106, 107*). In Japan, the mean dietary intake of calcium is less than the required 600 mg/day, and in fact is half of the amount (800–1,300 mg/day) taken in Western countries. Therefore, it is recommended that dietary calcium intake be more than 600 mg/day. It has been reported in Japan that magnesium supplements are effective for lowering

blood pressure in hypertensive patients (*108*).

4) Fat

Since fish oil (eicosapentaenoic acid) is said to have anti-atherogenic and anti-hypertensive effects, dietary intake of blue fishes may contribute to the prevention of atherosclerotic diseases. Hyperlipidemia is one of the important risk factors for atherosclerosis, and restriction of dietary fat intake should be recommended for hyperlipidemic patients.

5-2. Exercise

Studies related to exercise and mortality have generally agreed that physical activity is inversely correlated with mortality due to circulatory diseases, and thus adequate exercise is suggested to prevent atherosclerosis (*109*). Exercise treatment is reported to decrease systolic blood pressure by 8–18 mmHg and diastolic blood pressure by 5–16 mmHg (*110*). Exercise treatment is one of the best choices for mild hypertension. However, isometric exercise significantly increases both systolic and diastolic blood pressures, and thus cannot be recommended for treating hypertension. Isotonic and aerobic exercises lower diastolic blood pressure and increase systolic blood pressure during physical activity, and thus can be recommended for treating hypertension. The strength of exercise is recommended to be 40–60% of the maximum oxygen intake; an approximately 10 mmHg depression in systolic blood pressure may be expected by 30–40 min of exercise 3–5 times per week (*111*). Exercise helps not only to lower blood pressure, but also to improve insulin resistance and lower serum triglyceride. While it is not practical to measure the maximum oxygen intake in all patients, a target of 110 beats per min is used for patients aged 60 yr or older, as estimated from the relation between heart rate and physical activity at 50% maximum oxygen intake at various ages. Therefore, it is recommended that exercise treatment consists of isotonic exercise for 30–40 min, 3–5 times a week, and that this regimen be continued indefinitely. However, exercise treatment for hypertension is not suitable for patients with ischemic heart diseases, heart failure, renal failure or orthopedic complications.

5-3. Weight Reduction

Obesity is closely associated with blood pressure elevation, most likely due to insulin resistance and sympathetic nervous system involvement. It is well known that weight reduction in obese patients effectively lowers blood pressure. In fact, weight reduction has been shown to lower blood pressure in 80% of cases, regardless of the extent of obesity, and thus should be widely applied as a useful antihypertensive treatment (*112*, *113*). Hypertension is also related to distribution of body fat. Fat distribution mainly in the upper body, namely a waist/hip ratio of 1.0 or more for males or 0.8 or more for females, has been reported to increase mortality due to hypertension, hyperlipidemia, diabetes mellitus or coronary artery diseases.

5-4. Alcohol, Caffeine, and Smoking

1) Alcohol

Alcohol intake is positively correlated to blood pressure (*14*). Moderate and heavy drinkers (30 ml ethanol or more per day) tend to be significantly more hypertensive than non-drinkers.

2) Caffeine

It has been reported that caffeine can have the acute effects of increasing blood pressure and decreasing arterial stiffness (*114*).

3) Smoking

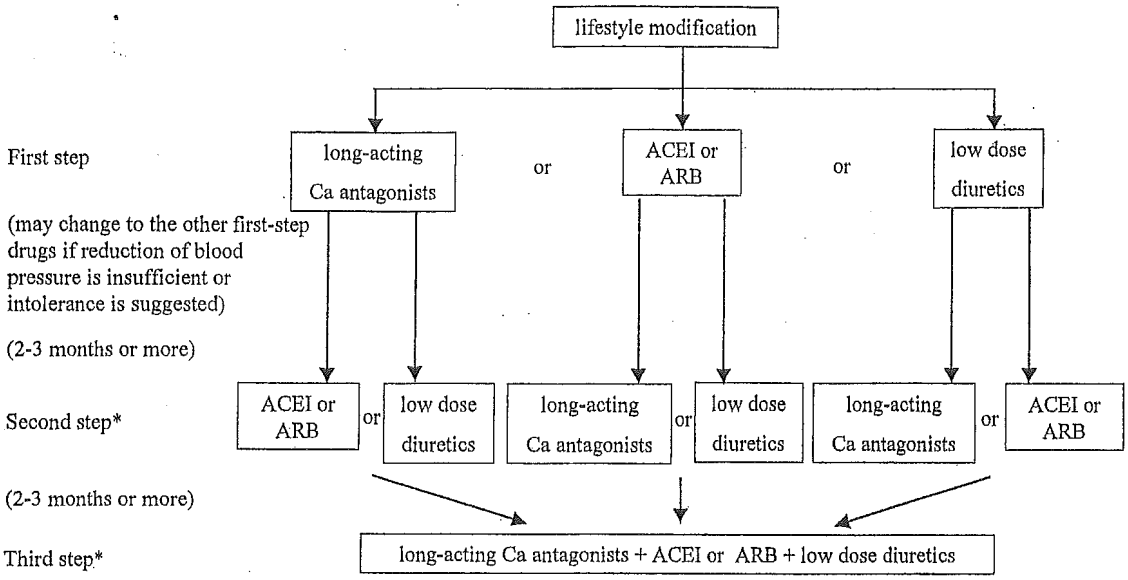
Smoking itself may not be directly implicated in raising blood pressure, but it is one of the major risk factors of cardiovascular diseases. It is, therefore, advised that hypertensive patients avoid cigarette smoking, given that treatment of hypertension is aimed mainly at preventing cardiovascular diseases.

6. Antihypertensive Drug Therapy

Hypertension in the elderly is a major risk factor for cerebrovascular disease, coronary artery disease, cardiac failure, end-stage renal disease, arteriosclerosis obliterans and all-cause mortality (*3*), and systolic blood pressure is a better predictor of these events than is diastolic blood pressure. It has become clear that increased pulse pressure is a good indicator for risk of cardiovascular disease (*4*). Since the late 1980s, several large intervention trials have been performed on hypertension in persons aged 60 yr or older, and all have demonstrated the effectiveness of antihypertensive drug therapy. However, antihypertensive drug therapy has not been definitely confirmed to be effective in very old hypertensive patients (85 yr or older), and thus its effectiveness may be limited after a certain age (*74*). Considering these limitations, guidelines for antihypertensive drug therapy are presented as follows.

6-1. Antihypertensive Drugs Used in Large-Scale Intervention Trials for Hypertension in the Elderly

The major antihypertensive drugs conventionally used in large-scale intervention trials for hypertension in the elderly are diuretics and β-blockers. Diuretics are considered standard drugs for use in trials evaluating long-acting Ca antagonists and ACE inhibitors. In addition, long-acting Ca antagonists have been used as a first step in several recent large-scale intervention trials for hypertension in the elderly (*8–10*). ACE inhibitors were used as a first choice in addition to long-acting Ca antagonists in the STOP Hypertension-2



ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin II receptor blocker
* β-blockers, α-blockers, or $\alpha\beta$-blockers, may be indicated if necessary.

Fig. 1. *Flow chart for treatment of hypertension in the elderly without complications.*

study (*115*).

In the Medical Reserch Council (MRC) trial, the use of β-blockers resulted in no significant reductions in stroke, coronary events or death from all causes compared with the placebo group (*7*). Messerli *et al.* (*13*) analyzed the results of the randomized controlled trials using diuretics and β-blockers for hypertension in the elderly, and reported that diuretics are effective for reduction of cerebrovascular events, stroke mortality, coronary artery disease, cardiovascular mortality, and all-cause mortality in comparison to the placebo group, but β-blockers are not effective for reduction of coronary artery disease, cardiovascular mortality or all-cause mortality. In the Syst-Eur trial (*9*) and Syst-China trial (*10*), a long-acting Ca antagonist significantly reduced the morbidity of stroke, non-fatal cardiac disease, total cardiac disease, and fatal and non-fatal cardiovascular disease. A long-term treatment trial (NICS-EH) of hypertension in Japanese patients (68), although utilizing a relatively small number of participants, reported that a dihydropyridine Ca antagonist was as effective as a diuretic for the prevention of cardiovascular diseases. ACE inhibitors showed similar effects on cardiovascular mortality and morbidity compared with diuretics or β-blockers in STOP Hypertension-2 (*115*).

The PATE-Hypertension study indicated that both an ACE inhibitor and a dihydropyridine Ca antagonist were equally beneficial for reducing cardiovascular mortality and morbidity in elderly hypertensive patients in Japan (*11*).

6-2. Antihypertensive Drugs for Treating Hypertension in the Elderly, Selected by Hypertension Specialists in Japan

In 1993, 123 hypertension specialists in Japan (84% response rate) responded to a questionnaire survey (*75*), and two years later, the results of this survey were used to establish the "A Guideline for Treatment of Hypertension in the Elderly, 1995" (*15*). In 1996, a follow-up questionnaire with items about the 1995 Guidelines was sent to the previous respondents. Among the responding physicians, 65% selected long-acting Ca antagonists (Ca antagonists) and ACE inhibitors as the first choice for hypertension without complications in the elderly, while diuretics and β-blockers were selected by only 17%.

The 1995 Guidelines indicated that β-blockers and α-blockers were relatively contraindicated for the treatment of hypertension in the elderly, but in the second questionnaire about one half of the respondents recognized both blockers as safe for use in the elderly.

Reflecting the changes surrounding antihypertensive drug therapy in the elderly, a "Guidelines for Hypertension in the Elderly—1999 Revised Version" was published (*16*). A follow-up questionnaire survey was carried out to evaluate these guidelines as well. The guidelines adopted Ca antagonists, ACE inhibitors, and low-dose diuretics as the first-line antihypertensive agents for elderly hypertensives without complications. Out of the 122 respondents, 80 (65%) agreed with this proposal. However, the proposal met with a negative response from 40 clinical specialists for hypertension (34%). Ten percent of the respondents recommended re-

moval of diuretics from the first-line drugs, and 15% recommended inclusion of β-blockers in the first-line drugs. One hundred (82%) of the 122 respondents, an overwhelming majority, approved the adoption of angiotensin II receptor blockers (ARBs) as a first-line antihypertensive agent (*17*).

6-3. Selection of Antihypertensive Drugs

Generally, drugs which meet the following criteria are recommended as first-choice drugs.

a. The possibility of administration once or twice a day in order to maintain good compliance.

b. Long-acting effects (a T/P ratio of at least 50%) of 24 h or longer, in order to be effective for rapid elevation of blood pressure in early morning.

c. Low price as compared with comparable drugs of the same efficacy.

1) Patients without Complications

First-choice drug: Ca antagonists, ACE inhibitors, ARBs or a low dose of diuretics. A therapeutic flow chart is shown in Fig. 1. In the event that one of these first-choice drugs is ineffective or intolerable, one of the other drugs in the list can be tried.

a. Ca antagonists

Ca antagonists are usually classified into two groups: dihydropyridines and benzothiazepine (diltiazem). The antihypertensive effect of dihydropyridine Ca antagonists depends on the decrease in peripheral vascular resistance, and these drugs achieve an excellent blood pressure reduction, accompanied by a reflex increase in heart rate and cardiac output. Improved versions of these drugs that act more slowly and for a longer period of time, and that have little stimulatory effect on the sympathetic nerve system and renin-angiotensin system, are now on the market.

Based on the results obtained in a randomized-double blind trial, the NICS-EH trial (*68*) in Japan, a dihydropyridine Ca antagonist, is as effective as a thiazide diuretic in reducing the risks of cardiovascular events, and is superior in terms of tolerability. A prospective, randomized, open, blinded endpoint study has proved that diltiazem is effective in preventing stroke (*116*). In some patients, diltiazem shows inhibitory effects on the sinus node and atrioventricular conduction system, resulting in conduction disturbance and bradycardia.

Benefits of Ca antagonists: Summarizing the benefits of Ca antagonists for the treatment of hypertension in the elderly, these drugs demonstrate excellent effects in blood pressure reduction, and according to the Syst-Eur (*9*), Syst-China trials (*10*), and STOP Hypertension-2 study (*115*), they clearly reduce the morbidity and mortality of cardiovascular disease. Ca antagonists are expected to be effective for hypertensive patients complicated by such conditions as angina pectoris (dihydropyridines and diltiazem), atrial fibrillation (diltiazem), and diabetes mellitus with proteinuria (both Ca antagonists) (*14*). Neither type of Ca antagonist has any effects on the metabolism of carbohydrates, lipids, or uric acid. They have few contraindications, and can be used in combination with other classes of antihypertensive drugs.

Disadvantages of Ca antagonists: Dihydropyridine Ca antagonists may cause ankle edema, which may be differentiated from congestive heart failure. Care must also be taken also to avoid gingival hypertrophy.

In a meta-analysis of the large available database of randomized controlled trials, Ca antagonists were suggested to be significantly inferior to other types of antihypertensive drugs, *i.e.*, diuretics, β-blockers and ACE inhibitors, in reducing the risks of acute myocardial infarction (*117*). On the other hand, in another meta-analysis of randomized placebo-controlled trials, it was proposed that Ca antagonists are equal to other types of antihypertensive drugs as diuretics, β-blockers, and ACE inhibitors (*118*).

b. ACE inhibitors

In a large, randomized placebo-controlled trial, the STOP-Hypertension 2 trial, ACE inhibitors were shown to be as effective as Ca antagonists and other, older types of antihypertensive drugs, such as diuretics and β-blockers (*115*).

The Heart Outcomes Prevention Evaluation (HOPE) study indicated that ACE inhibitors reduced the rate of cardiovascular events in subjects (55 yr of age or older) who had evidence of cardiovascular disease or diabetes plus at least one other cardiovascular risk factor (*119*). The efficacy of ACE inhibitors in treating elderly patients was proved in the Captopril Prevention Project (CAPPP) randomized trial (*120*) and STOP-Hypertension 2 study, which were based on the results of numerous clinical studies demonstrating the protective effects of these drugs on target organs. The usefulness of ACE inhibitors was reported in the PATE-Hypertension study in Japan (*11*). However, ACE inhibitors also have the major adverse effects of dry cough and, less frequently, angioedema.

Benefits of ACE inhibitors: Elderly individuals generally show low plasma renin activity; however, the antihypertensive effect of ACE inhibitors is almost the same in elderly as in young and middle-aged hypertensives. In elderly patients with mild or moderate essential hypertension, ACE inhibitors effectively lower the blood pressure by about 70%. ACE inhibitors have the compelling indication for hypertensive patients who are complicated with congestive heart failure from systolic dysfunction. ACE inhibitors have been shown to provide beneficial effects in preventing left ventricular remodeling after myocardial infarction, and in regressing left ventricular hypertrophy. ACE inhibitors are compellingly indicated for patients with diabetes mellitus with proteinuria. In addition, they are effective in protecting renal function in patients with renal failure (serum creatinine level, below 2 mg/dl) (*121*). They have few contraindications and can be combined with other classes of antihyper-

Table 9. First-Choice Antihypertensive Drugs and Contraindicated Drugs for the Hypertensive Elderly Patients with Complications

Complications	Ca antagonists (dihydropyridines)	ACE-I /ARBs	Diuretics	β-Blockers	α-Blockers
Cerebrovascular accident, chronic phase	○	○	○*1		
Ischemic heart disease	○	○		○*2	
Heart failure		○	○	△*3	△
Renal insufficiency	○	○*4	○*5		
Diabetes mellitus	○	○	△	△	△*6
Hyperlipidemia	○	○	△	△	○
Gout (Hyperuricemia)	○	○	×		
Chronic obstructive pulmonary diseases				×	
Arteriosclerosis obliterans	○	○	△	×	
Osteoporosis			○*7		
Benign prostate hypertrophy					○

○: Preferable choice, △: Careful in use, ×: Contraindicated. *1 Caution for dehydration. *2 Contraindicated for vasospastic angina pectoris. *3 Start with low dose, and be careful for clinical course. *4 Very cautious for patients with 2 mg/dl or greater serum creatinine. *5 Loop diuretics. *6 Caution for orthostatic hypotension. *7 Thiazide diuretics. ACE-I, angiotensin converting enzyme inhibitor; ARBs, angiotensin II receptor blockers.

tensive drugs. In addition, a recent clinical study has suggested that the use of ACE inhibitors was an independent factor reducing the risk of pneumonia among elderly patients (*122*).

Disadvantages of ACE inhibitors: The major adverse effects of ACE inhibitors are dry cough, which occurs especially in women, and, less frequently, angioedema. ACE inhibitors are relatively contraindicated when the serum creatinine level is 2 mg/dl or greater, and contraindicated for bilateral renovascular hypertension.

c. ARBs

ARBs are now available in Japan, and their antihypertensive effect is equivalent to that of ACE inhibitors, but they do not cause the dry cough or angioedema associated with ACE inhibitors. Based on recent evidence that ARBs show cardiac and renal protective effects, these drugs may be expected to confer the same degree of protection against organ damage as ACE inhibitors. The randomized large-scale intervention trials have demonstrated that there are few adverse effects of ARBs in patients with heart failure (*123–124*).

Benefits of ARBs: Elderly individuals generally show low plasma renin activity, but the antihypertensive effect of ARBs are almost the same in elderly as in young and middle-aged hypertensives (*14*). A comparative study found that the antihypertensive effects of ARBs are equal to those of the standard Ca antagonist, amlodipine (*125*), and that ARBs are highly effective at reducing blood pressure when used in combination with diuretics or Ca antagonists. Recently, it has been shown that the ARB losartan is highly effective in reducing cardiovascular mortality and morbidity in hypertensive patients (*126*). ARBs are recommended as a first-line drug in the JSH 2000 guidelines (*60*). ARBs have the compelling indication for hypertensive patients who are complicated by diabetes mellitus, chronic heart failure, post myocardial infarction, renal failure, or cerebrovascular disease. They have few contraindications and few adverse effects. ARBs are useful owing to high tolerance.

Disadvantage of ARBs: The main disadvantage of ARBs is that their efficacy in elderly hypertensives has not been documented by any large-scale trial, with the exception of the Study on COgnition and Prognosis in the Elderly (SCOPE) trial. ARBs are relatively contraindicated when the serum creatinine level is 2 mg/dl or greater, and are contraindicated for bilateral renovascular hypertension.

d. Diuretics

Large-scale intervention trials for hypertension in the elderly in Western countries have established that low doses of diuretics are useful for prevention of cardiovascular morbidity and mortality (*127*). In the NICS-EH, a diuretic was shown to be as effective as a Ca antagonist in treating hypertension in the elderly, but more patients dropped out from the trial in a thiazide group than in group treated with a Ca antagonist (*68*). Considering the current status of drug prescriptions in Japan and also the results obtained in the NICS-EH trial, diuretics should be used in combination with Ca antagonists and/or ACE inhibitors/ARBs, since monotherapy with a low dose diuretic—*e.g.*, 1 or 2 mg of trichlormethiazide per day—is not successful for reducing blood pressure.

Benefits of diuretics: Diuretics are recommended for treatment of hypertensive patients who have a tendency to retain water. Thiazide diuretics tend to inhibit urinary calcium excretion, and may be useful for the prevention of osteoporosis. Diuretics can be used in combination with other classes of antihypertensive drugs, and may even increase their inherent effects. They also have the advantage of being inexpensive.

Disadvantages of diuretics: Diuretics may cause a variety of unwanted effects, such as hypokalemia, elevation of serum LDL-cholesterol levels, decrease of HDL-cholesterol levels, elevation of blood uric acid levels, reduced glucose tolerance, ventricular ectopic beats and impotence. However, these adverse effects are infrequently recognized with low doses. Because glucose tolerance and renal function decline with aging, blood chemistry examinations should be conducted periodically.

2) Hypertension with Complications

In hypertensive patients with complications, the first-choice drug should be selected according to the complications recognized. Table 9 lists the first-choice and contraindicated drugs for the complications frequently recognized in the elderly.

6-4. Combination Therapy

Combination therapy should be considered when monotherapy is not successful in reducing blood pressure (Fig. 1).

The following combinations of antihypertensive drugs are recommended: Ca antagonist+ACE inhibitor/ARB; Ca antagonist+low dose diuretic (*128*); ACE inhibitor/ARB+low dose diuretic; or a combination of the drugs of first choice. Other antihypertensive drugs, such as β-blockers, α-blockers, or $\alpha\beta$-blockers, may be used if necessary (Fig. 1).

6-5. Antihypertensive Drugs to Be Prescribed with Caution in the Elderly

Drugs acting on the central nervous system, such as reserpine, methyldopa, clonidine are relatively contraindicated for hypertension in the elderly. In Japan, β-blockers and α-blockers have generally not been used for hypertension in the elderly, because elderly hypertensive patients frequently have complications for which these drugs are contraindicated or for which β-blockers are to be used only under special conditions.

(1) Precautions on β-blockers: Because cases of hypertension in the elderly are often complicated by congestive heart failure, bradycardia, arteriosclerosis obliterans, chronic obstructive pulmonary disease, diabetes mellitus, or impaired glucose tolerance, β-blockers are contraindicated or should be prescribed with extreme caution, as indicated above (*13*). These complications may be present in an occult form in the elderly.

(2) Precautions on α-blockers: In elderly hypertensive patients, α-blockers should be prescribed cautiously because they frequently induce postural hypotension due to decreased reflex function of the baroreceptor. Postural hypotension may cause dizziness and syncope, occasionally resulting in falls and bone fracture.

The ALLHAT Collaborating Research Group has indicated that, compared with diuretics, α-blockers significantly increase the risk of congestive heart failure (*129*). Accordingly, α-blockers should not be prescribed alone in elderly hypertensive patients with latent heart failure.

7. Antihypertensive Treatment of Elderly Hypertensive Patients with Complications

7-1. Cerebrovascular Diseases

Treatment of hypertension complicated by cerebrovascular diseases is aimed at preventing the progression of brain ischemia and edema, and re-bleeding or expansion of hematoma in the acute hemorrhagic stroke, and at reducing the recurrence of stroke in the chronic phase. In this regard, it is important that antihypertensive treatment should be made with careful consideration given to cerebral hemodynamics and age.

1) Hypertension and Cerebral Circulation

Autoregulation of the brain keeps cerebral blood flow constant within a certain range against blood pressure alterations. In hypertensive patients, however, the upper and lower limits of autoregulation are shifted to a higher blood pressure level (*130*). When complicated with cerebrovascular diseases, cerebral blood flow at rest is reduced not only in the related lesions but also in other areas of the brain (*131*). Because of advanced arteriosclerotic changes and reduced vasodilator capacity of the brain, antihypertensive treatment has limitations for improving cerebral blood flow and its autoregulation.

2) Treatment

Treatment of elderly hypertensives with cerebrovascular diseases differs according to the phase (acute or chronic) and type of stroke (cerebral hemorrhage, cerebral thrombosis, cerebral embolism, *etc.*). Before treatment, therefore, it is necessary to determine the type of stroke by means of medical history, clinical findings and brain imagings, including CT and MRI, as well as by other examinations. It is also important to detect stenosis or occlusion of the major arteries by means of non-invasive examinations such as carotid ultrasonography, trans-cranial ultrasonography, or magnetic resonance angiography (MRA), followed by conventional angiography, if necessary. In the case of cerebral embolism, echocardiography is necessary for detecting the embolic source in the heart.

a. Acute phase

Blood pressure is elevated at the acute phase of stroke, regardless of bleeding or infarction, which may be induced by acute stress or reaction to compensate for reduced cerebral perfusion pressure due to increased intracranial pressure. In addition, since the elevation of blood pressure in the acute phase may gradually fall with time even in the absence of treatment, aggressive antihypertensive treatment is not nec-

essary. Cerebral autoregulation is impaired in the acute phase, and then cerebral blood flow becomes dependent on blood pressure, easily resulting in cerebral ischemia due to reduction of blood pressure (*132*). On the other hand, marked elevation of blood pressure may cause aggravation of cerebral edema. Antihypertensive treatment in patients with cerebral hemorrhage should be started with careful monitoring of neurological signs and symptoms in the following cases: when the systolic blood pressure exceeds 180–200 mmHg and persists at that level, or when there is a probability of aggravation of brain edema, expansion of hematoma or re-bleeding, or worsening of cardiac failure, ischemic heart diseases, or aortic aneurysm.

Blood pressure should be controlled gradually by intravenous administration of nicardipine, diltiazem or nitroglycerin. Special care should be given in the use of these drugs, since they may increase intracranial pressure. Short-acting Ca antagonists, such as sublingually administered nifedipine, are not indicated, because of the danger of a rapid, unexpected blood pressure fall. Blood pressure should be lowered to around 80% of the pretreatment blood pressure, but not to normotensive levels. On the other hand, antihypertensive treatment is generally not recommended in the case of cerebral infarction. However, antihypertensive drug treatment may be required when systolic blood pressure is 220 mmHg or greater or the mean pressure exceeds 130 mmHg (*133*). In this case, blood pressure should be lowered gradually to around 85–90% of the pretreatment blood pressure. In patients who receive thrombolytic therapy and have a blood pressure of over 180 mmHg systolic and 105 mmHg diastolic, especially when these blood pressures rise within the first 24 h of thrombolytic therapy, antihypertensive drugs should be administered intravenously for preventing hemorrhagic events while carefully monitoring neurological symptoms (*14*).

b. Chronic phase

When hypertension persists for more than 1 month after acute strokes, antihypertensive treatment should be initiated while taking account of blood pressure level, age and the extent of brain damage and other organ damages irrespective of hemorrhage or infarction. However, when hypertension does not directly aggravate the circulatory system in the very elderly aged 85 yr or older, lifestyle modification alone is indicated. With regard to the secondary prevention of stroke by antihypertensive drug treatment, we refer to the recently published Perindopril Protection against Recurrent Stroke Study (PROGRESS) (*134*). In PROGRESS, over the course of a 4-yr follow-up period, active treatment based on ACE inhibitors reduced blood pressure 9 mmHg in systolic and 4 mmHg in diastolic, and a 28% reduction in the recurrence rate of stroke was observed compared to the placebo group. Moreover, a similar reduction of stroke risk was observed in both the hypertensive and non-hypertensive subgroup. These findings suggest that antihypertensive treatment may reduce the risk of stroke recurrence. Since the mean age in this study was 64 yr, a sub-analysis in the elderly would be of use, as would a sub-analysis in Japanese.

The initial blood pressure target levels for patients with chronic-phase stroke should be set at below 150–170 mmHg systolic and below 90–100 mmHg diastolic. Since cerebral hemorrhage is more closely related with hypertension than cerebral infarction, the target levels of blood pressure should be set slightly lower. Since a J-curve phenomenon between diastolic blood pressure and the recurrence rate of cerebral infarction has been reported (*93*), blood pressure should not be lowered excessively. Rather, blood pressure should be reduced gradually, and drug treatment should be started at half the usual doses and increased at intervals of 4 weeks or greater. Thus 2–3 months will be required to achieve the target blood pressure, and monitoring for the possible onset of cerebrovascular insufficiency should be performed throughout this period. Based on the results of PROGRESS, an appropriate final target blood pressure may be less than 140 mmHg systolic and less than 90 mmHg diastolic. However, the target blood pressure should be slightly lower in patients with cerebral hemorrhage or lacunar infarction, and slightly higher in those with atherothrombotic infarction.

Atherothrombotic cerebral infarction showing a watershed infarct commonly occurs in cases with stenosis or occlusion of the internal carotid or other intracranial major arteries, and thus such patients should be treated more cautiously, by maintaining a slightly higher blood pressure level than in those with lacunar infarction. Antihypertensive drug therapy may have to be reduced in dosage or discontinued if overdose is suggested by clinical symptoms such as dizziness, fainting, a sensation of heaviness in the head, or a decrease in memory and vitality suggesting insufficient cerebral perfusion, and then surgical treatment (carotid endatherectomy, extra- and intracranial bypass) may be considered. The therapeutic target blood pressure must be determined for each individual patient through careful monitoring of symptoms, signs, and laboratory test results. In addition to hypertension, other risk factors for cerebral infarction, such as diabetes mellitus, hyperlipidemia, smoking, alcohol intake, *etc.*, must be controlled.

c. Selection of antihypertensive drugs at the chronic phase

Antihypertensive drugs must be selected in consideration of their direct and indirect pharmacological effects against cerebral vessels and metabolisms. Antihypertensive drugs with adverse effects against cerebral circulation and metabolism (*i.e.*, reduction of cerebral blood flow) or the brain function should be avoided.

Dihydropyridine Ca antagonists have been demonstrated to dilate the cerebral arteries and increase cerebral blood flow in addition to contributing an antihypertensive effect (*135*), and certain long-acting Ca antagonists may improve or shift the lower limit of the autoregulation to the left (*136*). Benzothiazepine Ca antagonists may cause bradycardia,

atrio-ventricular block or reduction of cardiac output due to suppression of cardiac function, any of which may be harmful to the brain. ACE inhibitors shift the lower limit of cerebral autoregulation to the left with a slight increase in cerebral blood flow (*137*). Furthermore, ACE inhibitors improve thickening of vascular walls and have no adverse effects on the metabolic or central nervous system. In PROGRESS, ACE inhibitors were used as the first-line drugs in combination with diuretics and the recurrence of stroke was decreased, so ACE inhibitors can be considered first-line drugs for the chronic phase of stroke (*134*).

Acute administration of classical β-blockers reduces cerebral blood flow; however, chronic administration does not substantially change cerebral blood flow (*138*). β-Blockers should be avoided in patients with congestive heart failure, atrio-ventricular block or bradycardia. They are, however, suitable for patients with old myocardial infarction or effort angina pectoris. β-Blockers with vasodilatory action may increase cerebral blood flow and improve the lower limit of autoregulation (*139*). α-Blockers and $\alpha\beta$-blockers may increase cerebral blood flow by direct effects on cerebral blood vessels richly innervated with sympathetic nerves, and long-acting α-blockers may be used even in the elderly. However, α-blockers often induce orthostatic hypotension by blocking the peripheral sympathetic nerves, and thus they should be started at small doses and titrated with frequent monitoring of standing blood pressure. Since diuretics may cause electrolyte imbalance or metabolic disorders in addition to reduced cerebral blood flow by increased hematocrit, they should be prescribed in small doses to minimize their adverse effects. Sometimes potassium supplementation may be required. Because, in the PROGRESS report, combination therapy with diuretics and ACE inhibitors resulted in a greater reduction in recurrence of stroke than monotherapy, treatment with both drugs should now be considered as a promising option for patients with a history of stroke.

Anti-platelet drugs (aspirin or ticlopidine) or anti-coagulants (warfarin) are also recommended in order to prevent the recurrence of artery-to-artery embolism in atherothrombotic infarction, or cardiogenic embolism with atrial fibrillation.

7-2. Ischemic Heart Diseases

Hypertension is well known as one of the important risk factors for ischemic heart diseases, as demonstrated by the Framingham and many other studies (*140*). Hypertension not only causes acceleration of coronary atherosclerosis, but also frequently causes cardiac hypertrophy due to continuous mechanical overload. In the hypertrophied heart, myocardial oxygen consumption is increased due to an afterload increase, and coronary flow reserve is decreased due to insufficient proliferation of the coronary capillaries and a decrease in reflex vasodilatation of the coronary arteries (*141–143*). Thus, both coronary atherosclerosis and cardiac hypertrophy strongly influence the pathogenesis of ischemic heart disease.

1) Diagnosis

The clinical symptoms of ischemic heart disease in the elderly are often atypical. In addition, the frequency of asymptomatic myocardial ischemia is high in the elderly. Nearly one-half of patients with myocardial infarction do not experience chest pain, and many cases begin with cognitive disorders, disturbance of consciousness or other symptoms suggestive of heart failure. Non-invasive diagnostic procedures for acute myocardial infarction include electrocardiography, echocardiography, blood CPK-MB and troponin-T. Ischemic evidence in cases of effort angina pectoris, unstable angina pectoris and old myocardial infarction can be confirmed by stress electrocardiography, Holter electrocardiography, myocardial scintigraphy, or echocardiographic evaluation of ventricular wall motion, and these laboratory tests are also useful in follow-up studies.

2) Treatment

Treatment of hypertension complicated with ischemic heart diseases is aimed at prevention of angina attacks, development of myocardial infarction, and recurrence of myocardial infarction, and at maintenance of cardiac functions by the prevention of left ventricular remodeling. Therefore, selection of antihypertensive drugs must be based not only on their ability to lower blood pressure, but also on other effects against coronary atherosclerosis, coronary blood flow, cardiac load and myocardial protection.

a. Therapeutic target blood pressure

Antihypertensive drug therapy is given to patients with a systolic blood pressure of 160 mmHg or greater and a diastolic blood pressure of 90 mmHg or greater. The target blood pressures are a systolic blood pressure of below 140 mmHg and a diastolic blood pressure of below 90 mmHg. However, excessive reduction of blood pressure may result in development of ischemic heart diseases, and thus blood pressure must be carefully controlled. Even the PATE-Hypertension report (*11*), in which the incidence of cardiovascular events was compared between patients treated with a Ca blocker and those treated with an ACE inhibitor, suggested that an excessive reduction to less than 130 mmHg in systolic blood pressure may increase the incidence of cardiovascular events. In addition, the occurrence of ischemia could be influenced by a low nocturnal blood pressure value of below 110/70 mmHg in hypertensive patients (*144*).

b. Selection of antihypertensive drugs

β-Blockers and long-acting Ca antagonists are recommended for hypertension complicated with effort angina because these drugs decrease cardiac afterload of the left ventricle and reduce myocardial oxygen consumption. ACE inhibitors/ARBs are the first choice in cases with myocardial

infarction because of their inhibitory action against left ventricular remodeling (*145*).

(1) Ca antagonists: Dihydropyridine Ca antagonists lower blood pressure remarkably and increase coronary blood flow with little effects on glucose or lipid metabolisms, and thus they are suitable for cases of hypertension complicated by angina pectoris. Long-acting Ca antagonists are suitable for patients with rest angina and unstable angina, because they inhibit coronary spasms. Benzothiazepine Ca antagonists tend to inhibit cardiac functions and induce bradycardia, and thus should be used cautiously in elderly patients. Ca antagonists usually do not improve the prognosis of hypertension after myocardial infarction (*146*), but may be effective in combination with ACE inhibitors. Amlodipine showed no demonstrable effect on angiographic progression of coronary atherosclerosis but was significantly associated with fewer ischemic events for unstable angina and revascularization compared with the placebo group in the PREVENT study, which was designed to test whether amlodipine would slow the progression of early coronary atherosclerosis in patients with angiographically documented coronary artery disease (*147*).

(2) β-Blockers: β-Blockers have both negative chronotropic and negative inotropic effects, decrease myocardial oxygen consumption caused by decreased heart rate and myocardial contractility, and are effective for angina with improved myocardial ischemia. β-Blockers are especially effective for hypertension complicated with unstable angina and effort angina associated with severe coronary stenosis, because they effectively decrease increased heart rate and elevated blood pressure on physical exercise and increase exertional tolerance. However, they are contraindicated for coronary spasm, because they worsen the clinical symptoms of this disease. β-Blockers without intrinsic sympathomimetic activity (ISA) have superior cardiac protective effects, and are known to effectively prevent the recurrence of myocardial infarction (*148*). They are contraindicated, however, for patients with bronchial asthma or chronic obstructive pulmonary diseases, and should be used cautiously for those elderly patients whose cases are frequently complicated by conduction disorders, bradycardia or cardiac failure.

(3) ACE inhibitors: ACE inhibitors not only decrease cardiac afterload by decreasing total peripheral vascular resistance, but also protect the myocardium, inhibit left ventricular remodeling (*145*), and improve the prognosis of cardiac failure (*149*). Therefore, ACE inhibitors are the first choice for patients with cardiac failure complicated by hypertension after myocardial infarction. ACE inhibitors significantly reduced the rates of heart failure, myocardial infarction, and angina pectoris in a broad range of high-risk patients who did not have a low ejection fraction but showed evidence of vascular diseases in the HOPE trial (*119*). They have also been suggested to exert antiatherosclerotic and vascular protective effects. However, they should be used with special caution for cases with moderate or severe renal failure (serum creatinine over 2.0 mg/dl), and a small initial dose should be prescribed in elderly patients who commonly exhibit latent renal insufficiency.

(4) Diuretics: Diuretics show excellent antihypertensive effects in the elderly, and are expected to inhibit cardiac hypertrophy and dilatation. Interventional megatrials performed in Western countries have also confirmed the efficacy of diuretics for treatment of hypertension in the elderly (*6*, *7*). However, care must be taken with regard to their various side effects, such as hyperlipidemia, glucose metabolic disorders, dehydration and, in cases with cardiac hypertrophy, arrhythmia due to hypokalemia.

(5) α-Blockers: α-Blockers exert vasodilative effects on both arteries and veins, and thus reduce cardiac load; they have no adverse effects on glucose or lipid metabolisms. However, elderly patients administered α-blockers are likely to develop orthostatic hypotension, and thus these drugs should be prescribed cautiously with a small initial dose.

(6) Nitrites: Oral nitrites are effective for preventing anginal attacks. Continuous intravenous infusion of nitrites is most suitable in the acute stage of myocardial infarction associated with hypertension.

7-3. Heart Failure

Hypertension causes cardiac hypertrophy and ischemic heart diseases due to acceleration of coronary atherosclerosis and decreased coronary reserve, and both cardiac hypertrophy and ischemic heart diseases play an important role in the development of heart failure. In elderly patients, distensibility of the left ventricle is decreased in spite of its normal contractility (*150*, *151*), and heart failure will develop as a result of either atrial fibrillation or flutter in the absence of any underlying disease, arrhythmia due to conduction defects or left ventricular diastolic disorder due to cardiac amyloidosis.

1) Diagnosis

Occasionally, heart failure in the elderly may be accompanied by cerebral symptoms such as disturbance of consciousness, disorientation, or delirium. Chest X-ray films can be used to detect cardiac enlargement, increased pulmonary vascularity, changes in pulmonary interstitial tissue or pleural effusion. Cardiac function can be easily evaluated and monitored by means of echocardiography and the determination of peripheral venous pressure (normally 5–10 cmH_2O). Electrocardiography is useful for diagnosing ischemic heart diseases, cardiac hypertrophy, arrhythmia and conduction defects.

2) Treatment

Treatment of heart failure is aimed at reducing cardiac work, correcting over-hydration, and increasing myocardial contractility. Any diseases underlying heart failure should be carefully evaluated.

a. Hypertension associated with acute left-ventricular failure
Acute left-ventricular failure constitutes a hypertensive emergency, and should be corrected with antihypertensive treatment by reducing cardiac afterload and myocardial oxygen consumption and thereby increasing cardiac output. It can be treated effectively by oral administration of ACE inhibitors or continuous intravenous infusion of nitrites or Ca antagonists (nicardipine) in combination with intravenous injection of furosemide. In elderly patients, however, special precautions must be taken to avoid development of reduced blood flow of the coronary arteries, brain and kidneys due to acute reduction of blood pressure. Blood pressure reduction of more than 20% should not be planned at first. Antihypertensive treatment with a target reduction to 160/100 mmHg after 2–6 h is recommended. Treatment with heparin for thrombosis prevention should also be considered (*14*, *152*).

b. Hypertension associated with chronic heart failure
Left ventricular distensibility is decreased even in the healthy elderly, and the elderly with cardiac diseases frequently develop heart failure even though left ventricular contractility remains normal. Cardiac hypertrophy even without coronary stenosis is prone to develop into myocardial ischemia due to decreased coronary flow reserve that is due, in turn, to insufficient coronary vasodilatation and relatively reduced coronary capillary proliferation (*141–143*). Therefore, treatment of hypertension is aimed at first regressing cardiac hypertrophy and then protecting the myocardium, in order to maintain and improve cardiac functions and coronary blood flow. In principle, the therapeutic target blood pressures will be the normal levels (below 140/90 mmHg).

c. Selection of antihypertensive drugs
(1) Diuretics: Hypertension complicated with pulmonary edema, pleural effusion or peripheral edema is treated mainly with loop diuretics, because they decrease venous blood flow and venous blood pressure, resulting in improvement of edema. In addition, they improve pulmonary congestion by decreasing pulmonary capillary wedge pressure. Decrease in end-diastolic volume due to diuresis causes a decrease in preload and hence decreases in cardiac work and myocardial oxygen consumption, enabling the improvement of heart failure. Special care should be given in cases of elderly patients with dehydration, decreased cerebral or renal blood flows due to diuresis, or arrhythmia due to hypokalemia, the latter of which may necessitate administration of an aldosterone antagonist. It has been proved that spironolactone substantially reduces the risk of both morbidity and mortality among patients with severe heart failure (*153*). Diuresis should be attempted gradually, as rapid dehydration may trigger formation of thrombosis.
(2) ACE Inhibitors: ACE inhibitors are effective for vasodilatation in both arteries and veins, resulting in reduced cardiac loading, myocardial protection, and then improvement of the prognosis of heart failure (*149*). Thus, ACE inhibitors are extremely useful antihypertensive drugs, and should be the first-choice drugs in cases with heart failure. In those elderly patients who frequently experience renal dysfunction, a small initial dose is recommended.
(3) ARBs: The ELITE II study showed that ARBs are as effective as ACE inhibitors for improving the prognosis of heart failure (*123*). Furthermore, ARBs have now been made available because they have a lower incidence of adverse effects than ACE inhibitors. The efficacy of combination therapy with both drugs is currently under investigation.
(4) β-Blockers: Carvedilol has been shown to improve the prognosis of chronic heart failure due to left ventricular systolic dysfunction (*154*). Usually, a small initial dose of β-blockers (metoprolol, bisoprolol) is recommended, followed by gradually increased doses, and this regimen could be utilized by many cardiologists. However, the indication of β-blockers in the elderly should be limited, especially for the patients whose cases are complicated with obstructive pulmonary diseases, arteriosclerosis obliterans, diabetes mellitus or bradycardia.
(5) Ca antagonists: Ca antagonists are arterial vasodilators. Their marked peripheral vasodilatation decreases the myocardial oxygen consumption due to decrease in cardiac afterload, and increases coronary blood flow due to coronary vasodilatation. Long-acting Ca antagonists (amilodipine or felodipine) do not aggravate the prognosis of non-ischemic heart failure (*155*).
(6) α-Blockers: Based on the primary outcomes of the ALLHAT, prescription of α-blocker alone should be avoided for the treatment of heart failure (*129*).

7-4. Diabetes Mellitus

Hypertension is commonly complicated with diabetes mellitus or *vice versa* (*156*). In addition, the morbidity of hypertension and glucose metabolic abnormality increase with aging (*157*, *158*), and thus hypertension in the elderly is frequently associated with glucose metabolic abnormality. It has been suggested that essential hypertension and glucose/lipids metabolic disorders belong to so-called insulin-resistant syndrome in cases where there is a background of insulin resistance (*159*), and elderly patients are known to have decreased insulin sensitivity (*156*). Cases of diabetes mellitus associated with essential hypertension are mostly type 2 (non-insulin dependent) diabetes mellitus (NIDDM) both in elderly and non-elderly patients. The pathogenesis of type 2 diabetes mellitus is known to be related to both decreased insulin secretion and increased insulin resistance based on aging and heredity. The etiology and pathogenesis of essential hypertension are likely to be related also to decreased insulin sensitivity and hyperinsulinemia, and the complications of diabetes mellitus and/or obesity decrease insulin sensitivity. The complications of diabetes mellitus in cases of hypertension increase the incidence of atherosclerotic diseases,

and thus hypertension must be more strictly controlled in such cases (*14*). Essential hypertension complicated with diabetes mellitus is pathophysiologically characterized by increased body fluid and decreased renin-angiotensin system and sympathetic nerve activity (*160*). When complicated with diabetic nephropathy, hypertension is more influenced by renal involvement, causing marked increases in body fluid and sodium (*160*). Furthermore, hypertension itself causes aggravation of diabetic nephropathy, prevention of which involves adequate management of hypertension and glomerular hyperfiltration.

1) Diagnosis

Glucose tolerance reduces with aging, but usually remains relatively mild. Therefore, the diagnostic criteria of diabetes mellitus in the elderly may be the same as in the young and middle-aged, *i.e.*, fasting plasma glucose levels of 126 mg/dl or greater, postprandial glucose levels of 200 mg/dl or greater or 200 mg/dl or greater at 2 h after the glucose tolerance test, which levels should be confirmed twice on other days, according to the Japanese Diabetes Association guidelines. However, plasma glucose levels after oral glucose intake will definitely increase with aging, and the diagnosis of diabetes mellitus should be made carefully if diagnosed only by an oral glucose tolerance test.

2) Treatment

The therapeutic target levels of blood pressure are a systolic blood pressure of below 140 mmHg and diastolic blood pressure of below 90 mmHg. In the absence of any urgency, lifestyle modifications are considered first, followed by addition of antihypertensive drug therapy if improvement is insufficient. In the JNC VI, WHO/ISH and JSH 2000, it is recommended that the therapeutic target blood pressure level should be lower than 130/85 mmHg in hypertension complicated with diabetes mellitus, and this target has recently obtained wide acceptance. Accordingly, diabetes mellitus in elderly hypertensives should be treated similarly as in the young and middle-aged (*161*).

a. Lifestyle modification

Obesity is prevalent among hypertensive cases complicated with type 2 diabetes mellitus (*162*). Weight reduction by restriction of dietary calories is indispensable for obese patients, and it is useful not only for improvement of glucose metabolism but also for lowering blood pressure. In practice, patients are advised to reduce their weight by dietary and exercise treatments, and by avoiding foods with high cholesterol and saturated fatty acids. Salt restriction is expected to lower blood pressure, but it should be made cautiously in patients with orthostatic hypotension due to diabetic neuropathy in elderly patients, who are generally prone to blood volume depletion.

b. Antihypertensive drug therapy

Because ACE inhibitors/ARBs or Ca blockers increase insulin sensitivity, these drugs should be used as the first choice in cases of elderly hypertensive patients complicated with diabetes mellitus. In fact, in the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial, which used diuretics or a Ca blocker with a mean follow-up period of four years, the frequency of new diabetic cases among patients treated with Ca blockers was 23% lower than that in the diuretic-treated group (*163*). Both the HOPE (*119*) and CAPPP (*120*) trials have shown that the frequency of new diabetic cases in the ACE inhibitors group was lower than that in the placebo or diuretic/β-blockers group. Diuretics and β-blockers decrease insulin sensitivity and may cause deleterious effects on glucose/lipids metabolism (*164*). Although, α-blockers increase insulin sensitivity and improve lipids metabolism, α-blockers should be used cautiously because they frequently induce postural hypotension.

Recently, several sub-analyses of large-scale intervention trials of diabetic patients with isolated systolic hypertension have been reported—*i.e.*, analyses of the SHEP, Syst-Eur and STOP-Hypertension 2 trials—and have shown that treatment of elderly hypertensive diabetic patients with conventional antihypertensive drugs (low doses of diuretics, β-blockers, or both) is as effective as treatment with newer drugs such as Ca blockers or ACE inhibitors in terms of achieving reductions in cardiovascular events (*165–167*). ACE inhibitors may act to protect the kidneys in diabetic nephropathy, but may deteriorate renal function in the cases with serum creatinine of over 2.0 mg/dl. Special care should be taken when prescribing α-blockers in cases of hypertension with diabetic neuropathy, since they may cause orthostatic hypotension. Diuretics should be prescribed at low dose with careful monitoring of their serum potassium and uric acid levels.

In hypertensive patients with ischemic heart disease, β-blockers may be used if necessary. However, among hypertensive patients treated with oral hypoglycemic agents or especially insulin, β-blockers should be prescribed cautiously because they may mask or prolong hypoglycemic symptoms.

Summarizing the confirmed outcomes of trials and studies, the recommended first-choice antihypertensive agents are ACE inhibitors and Ca antagonists, which may improve glucose metabolism and protect against cardiovascular events. Very recently, ARBs have been reported to be effective in delaying the progression of diabetic nephropathy and reducing cardiovascular events, especially strokes, suggesting the possibility that this class of drug will be one of the first-line antihypertensive drugs (168). α-Blockers, β-blockers or diuretics may be used based on the individual diabetic complications/organ damages and added as the second- or third-line hypotensive drugs.

7-5. Renal Diseases

Hypertension associated with renal diseases is classified into those cases with chronic glomerulonephritis, those with diabetic nephropathy and those with nephrosclerosis (so-called hypertensive renal diseases). Renovascular hypertension may be encountered in association with renal arteriosclerosis in the elderly, especially in bilateral renal arterial stenosis resulting in decreased renal function (ischemic nephropathy). The terminal stage of renal diseases is known as uremia, and the most common reason for hemodialysis in Japan is now diabetic nephropathy. For the past 10 or more years, the number of cases of diabetic nephropathy and nephrosclerosis has nearly doubled (*169*). Cases of mild or moderate hypertension are frequently associated with cerebrovascular diseases and cardiac diseases, but only rarely with renal diseases. However, renal insufficiency may proceed even in cases of mild hypertension (*170*). Hypertension is definitely a risk factor for development of renal insufficiency, regardless of the type of renal insufficiency, and should be treated sufficiently to lower blood pressure.

1) Diagnosis

It is well known that renal function decreases with age even in healthy individuals, and in the very elderly it is thought to decrease to roughly 50% of the level in young individuals (*171*). In hypertension in the elderly, associated renal diseases are closely related to both hypertension and renal arteriosclerosis. Renal function tests necessary at the initial visit include urinalysis and blood chemistry tests (serum creatinine, urea nitrogen, electrolytes and uric acid). In addition, routine examinations, such as chest X-ray, electrocardiography and, if possible, echocardiography and abdominal ultrasonography, should be performed in order to detect any cardiovascular diseases. If necessary, creatinine clearance may also be assessed to evaluate glomerular filtration rate (GFR), since serum creatinine levels, particularly in the elderly, may be within a normal range even though renal insufficiency exists. Renovascular hypertension should be ruled out in hypertensives showing rapid onset, resistance to treatment or progressive renal insufficiency.

2) Treatment

In hypertension with renal diseases, non-pharmacological treatment, particularly dietary treatment, is required. It is most important to reduce salt intake. However, it is risky to reduce salt intake rapidly. Accordingly, the target value for salt intake should be set at about 7 g/day, and reduced gradually, based on monitoring of the serum creatinine value.

Restriction of protein intake (30–60 g/day, 0.5–0.8 g/kg/day) may be required depending on the severity of renal insufficiency and salt intake (3–6 g/day) based on blood pressure levels and edema. Frequency of hypertensive renal diseases in hypertensives is not as high as that of cerebrovascular and cardiac diseases. However, it has been reported that cases with blood pressure higher than 140/90 mmHg promote renal insufficiency faster than those with normal or adequately controlled blood pressure (*172*), and thus even mild hypertension may promote renal diseases. Elevation of intraglomerular pressure might exist from the early stages of diabetic nephropathy, and in such cases relates the progression of renal diseases. Therefore, the therapeutic target blood pressure should be set a little lower, to below 140–150/90 mmHg, in hypertension complicated with renal diseases. The JNC VI guidelines recommend a therapeutic goal of below 130/85 mmHg in the cases with proteinuria below 1 g/day, and of below 125/75 mmHg in those with proteinuria of 1 g/day or more (*172*). The so-called "J-curve phenomenon" has not been recognized between lowering of blood pressure and progression of renal insufficiency, but renal function should be monitored carefully in elderly hypertensives, since elevation of serum creatinine is commonly experienced in association with rapid lowering of blood pressure. A more than 50% decline of renal function may be expected in cases with serum creatinine of over 1.3 mg/dl, and such patients should be monitored by measuring the serum creatinine and electrolytes every 1–6 months.

a. Selection of antihypertensive drugs

Diuretics, ARBs, ACE inhibitors and Ca antagonists are mainly prescribed in cases of hypertension associated with renal insufficiency. A small dose of diuretics is recommended for the cases with body fluid retention, and at a serum creatinine level of over 1.5–2.0 mg/dl, loop diuretics are used instead of thiazide diuretics. ACE inhibitors are used for elderly hypertensives with mild renal dysfunction, and are expected to demonstrate long-term protection of the kidneys by decreasing systematic and intraglomerular blood pressure. Their effectiveness has also been proved clinically in diabetic nephropathy (*173*). However, ACE inhibitors should be carefully used for cases with moderate renal dysfunction (serum creatinine over 2.0 mg/dl), which they may further aggravate, and in such cases should be monitored at most cautiously serum creatinine and potassium levels.

Bilateral renovascular hypertension should be ruled out if a rapid decline of renal function is recognized in an elderly patient. Ca antagonists have a mild diuretic action, and may be widely applicable, regardless of the severity of renal dysfunction, so they could be used in combination with ACE inhibitors or ARBs. Most β-blockers do not significantly influence renal function, although some are reported to decrease renal blood flow (RBF) and GFR; those with trans-hepatic excretion are preferred. Vasodilators and sympatholytic drugs may result in body fluid retention, and may be effective in combination with a small dose of diuretics. α-Blockers are well indicated for elderly patients with prostatic hypertrophy, but should be followed up for orthostatic hypotension in cases with renal insufficiency due to diabetic nephropathy.

7-6. Hyperlipidemia

Hyperlipidemia and hypertension, as well as diabetes mellitus, obesity and smoking, are important risk factors for development of arteriosclerosis, and because the combination of hypertension and hyperlipidemia may aggravate arteriosclerosis, these conditions should be adequately controlled. In the elderly, aging itself is one of the important risk factors for atherosclerosis, and in elderly subjects, hyperlipidemia has been considered less important in arteriosclerosis than in middle-aged or younger subjects. However, many studies have demonstrated that hyperlipidemia in the elderly also synergistically increases the morbidity of ischemic heart diseases (*174*).

Hypo-HDL-cholesterolemia is also considered to be one of the important risk factors for atherosclerosis (*175*). No conclusive report has yet been made as to whether hypertriglyceridemia is an independent risk factor for atherosclerosis. At present, it is reasonable to suppose that hypertriglyceridemia in the elderly would be a risk factor when hypercholesterolemia, hypo-HDL-cholesterolemia, impaired glucose tolerance and obesity are present at the same time.

1) Diagnosis

According to the Practice Guidelines for Hyperlipidemia reported in 1997 (*176*), the diagnostic criteria for hyperlipidemia include a serum total cholesterol of 220 mg/dl or greater, triglyceride of 150 mg/dl or greater, and HDL-cholesterol of below 40 mg/dl. These diagnostic reference values may be applied also for the elderly. Hyperlipidemia should be differentiated into primary and secondary (diabetes mellitus, hypothyroidism, drug-induced, *etc.*) types.

2) Treatment

Because elderly subjects often have multiple pathological disorders, antihypertensive drugs should be used carefully with consideration to each patient's condition. Ca antagonists or ACE inhibitors are recommended for treating hypertensives who also manifest hyperlipidemia, because these drugs are more beneficial for lipid metabolism than other antihypertensive drugs. α-Blockers, which also favor lipid metabolism, should be cautiously used for elderly patients, since they often manifest orthostatic hypotension. Because the ALLHAT trial showed that more heart failure occurred in patients treated with α-blockers than diuretics, α-blockers are better not used for elderly who potentially have decreased cardiac function. ARBs are considered as effective as ACE inhibitors for treating hypertension complicated with hyperlipidemia in the elderly, though the evidence of this parity is still limited.

Target blood pressure for patients with hyperlipidemia should be less than 140/90 mmHg if possible.

In cases in which hypertension has been treated and hyperlipidemia still cannot be corrected by lifestyle modifications such as diet and exercise, antihyperlipidemic drugs are better prescribed. The following drugs should be used carefully for elderly: constipation with cholestyramine, low HDL-cholesterol with probucol, elevated creatine phosphokinase (CPK) and rhabdomyolysis with HMG-CoA reductase inhibitors, and facial hot flush with nicotinates.

7-7. Vascular Complications

1) Arteriosclerosis Obliterans (ASO)

Patients with intermittent claudication, the most characteristic symptom of ASO, complain of weakness and pain in the unilateral or bilateral extremities on walking, and eventually are unable to walk due to painful twitching of the lower extremities. Hypertensive patients complicated with ASO should be treated with antihypertensive drugs which improve blood circulation.

a. Diagnosis

Morbidity of ASO increases with aging, but many elderly patients may not complain of typical intermittent claudication or ischemic symptoms because of their low physical activity (*177*). Therefore, physical examination of elderly hypertensive patients at the first visit should include careful palpation of the upper and lower extremities, especially the femoral, popliteal and dorsal arteries, to rule out ASO. If ASO is suspected, blood flow in the corresponding areas should be measured using a Doppler flowmeter. Together with a careful analysis of the patient's medical history, an ankle brachial systolic blood pressure index (ABI) of less than 0.9 confirms the diagnosis (*178*).

During the follow-up encounters, patients are carefully monitored for any change in subjective complaints, and by palpation of the extremities and non-invasive perfusion pressure measurement. ASO is usually classified by Fontaine's classification as follows: stage I, no symptoms or mild cold flush and numbness; stage II, intermittent claudication; and stage III, cases in which the walking distance is decreased to below 30 m with pains or in which there is pain at rest due to chronic ischemia, and which require surgical treatment.

b. Treatment

All patients should be advised to quit smoking and take regular exercise if possible (*179*). The principal treatment for ASO consists of surgical operation, such as percutaneous transluminal angioplasty (PTA) for patients complaining of advanced intermittent claudication or for Fontaine stage III patients. Drug therapy is supplementary only. Antihypertensive drugs must be selected not to decrease blood circulation, including collateral circulation. In general, diuretics (*177*) and β-blockers (*180*) tend to cause aggravation of ischemic symptoms due to reduction of blood flow of the injured and collateral blood vessels. ACE inhibitors are effective at maintaining or increasing blood flow of the lower extremities and thus improving exercise tolerance capacity (*177–181*). Furthermore, the results of the HOPE study indi-

cate that ACE inhibitor can reduce the risk of cardiovascular complication in patients with ASO (*119*). α-Blockers are also expected to be effective for patients with ASO (*177*), although no clinical evidence has yet been obtained. Dihydropyridine Ca antagonists have strong vasodilatation effects, and are recognized to be effective for patients with ASO (*182*). It has been reported that nicardipine administered to ASO patients with normal blood pressure resulted in worsening of clinical symptoms, probably due to stealing of blood from the injured blood vessels (*181*). Therefore, care must be taken in the administration of short acting drugs that cause rapid vasodilatation. It has been reported that verapamil improves physical movement (*183*). β-Blockers with cardiac selectivity or vasodilatatory action are reported not to aggravate peripheral blood circulation (*184*, *185*), but should be administered cautiously to patients with ASO (*14*).

Blood pressure should be lowered to a level that will not decrease the perfusion pressure of the diseased extremity. It may be necessary to determine this level individually for each patient, depending on the extent of vascular stenosis and development of collateral circulation, but in general the target blood pressure should stay at around 150–160/90 mmHg, slightly higher than that for the elderly non-complicated hypertensives. After the initiation of treatment, patients are monitored by measuring blood pressure routinely at the upper arms and the diseased extremity by Doppler hemodromometer, and also followed-up by subjective complaints and periodically by thermography to determine any clinical aggravation of ischemic symptoms.

For the management of ASO it is important not to overlook any complication, particularly the risk factors for atherosclerosis other than hypertension, such as hyperlipidemia and diabetes mellitus. Patients with ASO frequently have renovascular hypertension (*186*), for which ACE inhibitors should be prescribed very cautiously. Patients with claudication have a three times higher rate of mortality compared with age-matched controls. They also have higher risk for development of myocardial infarction and stroke (*178*). It is important to bear in mind that the prognosis of ASO patients whose cases are complicated by ischemic heart diseases is very poor (*187*), and that antihypertensive drugs must be selected with extreme caution.

2) Aortic Aneurysm

It has been demonstrated that rupture is much more likely to occur when a thoracic aneurysm exceeds 6 cm in diameter and an abdominal aneurysm exceeds 4–5 cm in diameter. Accordingly, surgical treatment is the first choice in such cases.

a. Diagnosis

Presence of aneurysm is confirmed by radiographic examination, such as by CT. In the case of either thoracic or abdominal aneurysms, the prognosis becomes very poor once the aneurysms have ruptured.

The risk of rupture increases with the size of the aneurysm. Surgical intervention is indicated for a thoracic aneurysm more than 6 cm in diameter [5.5 cm in the ascending aorta and 6.5 cm in the descending aorta (*187*)] or for an abdominal aneurysm more than 5 cm in diameter (*189*). The presence of symptoms such as pain and rapid increase in size (10 mm/yr) also indicate surgical intervention. On the other hand, early surgical repair of asymptomatic abdominal aneurysms 4.0–5.5 cm in diameter has been shown not to result in any benefit (*187–190*).

b. Treatment

Hypertension contributes to the degeneration of the aortic wall, and is one of the risk factors for aneurysmal enlargement. The protective effect of β-blockers on rupture is not conclusive (*191*). There is no evidence that other antihypertensive drugs have any effect on the expansion of aortic aneurysm or on postoperative blood pressure control. However, it is generally recommended that blood pressure should be controlled at 140/85 mmHg or below with careful checking for symptoms of other atherosclerotic disease (*60*). Antihypertensive drugs need to be selected based on other concomitant complications. Dissecting aneurysm of Stanford type B is usually managed medically. β-Blockers have been shown to be effective in such cases (*192*). When using other classes of antihypertensive drugs, it is recommended that a β-blocker be added to reduce reflex tachycardia and increase in contractility. The target systolic blood pressure should be maintained at 120 mmHg or below at the chronic stage of rupture or the postoperative period (*60*).

8. Drug Interactions with Antihypertensive Treatment

Elderly hypertensive patients frequently have other diseases, and thus are likely to receive many drugs from other physicians. Accordingly, they tend to encounter various drug interactions with antihypertensive drugs. The age-related decrease in the function of multiple organs, and particularly of the kidneys, may promote accumulation of drugs, resulting in the development of adverse effects, the exaggeration of drug interactions, and the further deterioration of organ functions. The drugs prescribed by other physicians must therefore be confirmed, and patients must be carefully monitored for possible drug interactions. The following are some of the possible drug interactions (Table 10). It should be noted, however, that few interactions with ARBs have yet been reported. And central sympatholytic drugs and peripheral neuronal blockers have been excluded from the following list, because they are rarely prescribed for elderly hypertensive patients.

8-1. Adverse Interactions between Antihypertensive Drugs

The combination of β-blockers and diltiazem may cause

Table 10. Drug Interactions between Antihypertensive and Non-Antihypertensive Drugs

	Increasing antihypertensive effect	Decreasing antihypertensive effect	Possible effects on non-antihypertensive drugs, results of interactions
Ca antagonisits	Cimetidine Macrolide antibiotics, antifungal azole: felodipine, nifedipine Grapefruit juice: some dihydropyridines	Rifampicin Phenobarbital	Digoxin, carbamazepine, triazolam, midazolam: a rise in blood levels with diltiazem Amiodarone: sinus arrest, AV block, cardiac arrest with diltiazem, nifedipine, reported Theophylline: a rise in blood levels with diltiazem Simvastatin, lovastatin: a rise in blood levels with diltiazem Cisapride: QT prolongation, ventricular arrhythmia Cyclosporine, tacrolimus: a rise in blood levels with Ca antagonists Lithium: neurotoxic effects with diltiazem, reported
ACE inhibitors	Diuretics (volume depletion)* Chlorpromazine	NSAIDs* Antacids (Rifampicin: losartan)	Pottasium*: hyperkalemia NSAIDs*: a deterioration of renal function, hyperkalemia Digoxin*: a rise in blood levels in severe heart failure Allopurinol: serum sickness-like syndrome and Stevens-Johnson syndrome with captopril, reported Antihyperglycemic drugs: hypoglycemia Lithium: a rise in blood levels
β-Blockers	Cimetidine, quinidine: β-blockers metabolized in the liver	NSAIDs Rifampicin, phenobarbital, smoking: β-blockers meabolized in the liver Antacids	Antihyperglycemic drugs: masking and prolongation of hypoglycemia Digoxin: marked bradycardia with propranolol, reported Antiarrhythmic drugs: conduction defects, arrhythmia, decreased cardiac function Drugs for cold and nasal congestion containing sympathomimetics: an increase in blood pressure Sildenafil: excessive fall of blood pressure with nipradilol
Diuretics		NSAIDs Steroids Cholestyramine, colestimide: thiazide diuretics	Digoxin: digitalis intoxication by hypokalemia Oral antihyperglycemic drugs: an increase in requirement doses with potassium-losing diuretics Aminoglycosides: an increse in toxicity to kidneys and acoustic nerves with loop-diuretics NSAIDs: renal failure with triamterene, reported Glycyrrhizine: hypokalemia with potassium-losing diuretics Amantadine: a rise in blood levels, reported Lithium: a rise in blood levels
α-Blockers		NSAIDs	Alcohol: augmented fall in blood pressure

Attention should be paid to potential interactions other than those listed in the table. Angiotensin II antagonists are not listed because of paucity of information, but the interactions related to blockade of the renin-angiotensin system may develop as those with ACE inhibitors (indicated by*). Central sympatholitics and peripheral neuronal blockers are excluded.
NSAIDs: non-steroidal anti-inflammatory drugs, ACE: angiotensin converting enzyme.

marked bradycardia, atrioventricular conduction disturbances or heart failure. The combination of potassium-sparing diuretics and either ACE inhibitors or ARBs may cause hyperkalemia, and such combinations are therefore contraindicated for patients with renal insufficiency. In cases in which the renin-angiotensin system is activated by diuretics, additional administration of ACE inhibitors or ARBs may cause excessive reduction of blood pressure. The combination of α-blockers and either diuretics or β-blockers may be likely to cause orthostatic hypotension. (*193*)

8-2. Cardiovascular Drugs

1) Digitalis

Elevation of blood concentrations of digoxin due to diltiazem seems to be mild (*194*), but the possibility of such elevation should be kept in mind when the two drugs are combined for treatment of an elderly patient. Elevation of digoxin concentrations due to captopril has been reported in cases of severe heart failure (*195*). ACE inhibitors are apt to induce renal dysfunction in cases of heart failure, renal arterial stenosis and hypovolemia, and they should be used carefully in combination with digitalis. The combination of digitalis and potassium-losing diuretics may cause digitalis intoxication, and the combination of digitalis with β-blockers or diltiazem may cause severe bradycardia.

2) Nitrates

Nitrates exert vasodilatory effects, and may exert an additive vasodilatory action in combination with various antihypertensive drugs. In cases complicated by coronary artery diseases and treated by nitrates, antihypertensive drugs should be carefully administered to avoid an excessive fall in blood pressure, since the J-curve phenomenon on coronary artery diseases has been reported (*196*). Patients should be informed of the possibility of an excessive reduction of blood pressure and the possible occurrence of orthostatic hypotension upon urgent use of nitrates.

3) Antiarrhythmic Drugs

The combination of β-blockers and diltiazem may cause severe bradycardia, arrhythmia and decreased cardiac function. The combination of antiarrhythmic drugs and potassium-losing diuretics may cause aggravation of proarrhythmic responses due to hypokalemia and hypomagnesemia.

8-3. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs inhibit the synthesis of prostaglandins, and may also inhibit the antihypertensive effects of ACE inhibitors, diuretics, β-blockers, α-blockers and ARBs (*197, 198*). When combined with triamterene, indomethacin has been reported to induce acute renal failure (*199*). In cases with a decreased renal blood flow, the combination of NSAIDs and ACE inhibitors is apt to induce decreased renal function and hyperkalemia. Among NSAIDs, indomethacin and piroxicam have the strongest adverse effects, and sulindac and aspirin have mild ones. Ca antagonists are little affected by NSAIDs.

8-4. Drugs for Metabolic Disorders

1) Antihyperlipidemic Drugs

Diltiazem has been reported to enhance the serum cholesterol-lowering effects of simvastatin (*200*) and to raise the serum levels of lovastatin. The antihypertensive effects of ACE inhibitors may increase in combination with either lovastatin or pravastatin (*201*). Cholestyramine (*202*) and colestimide, anion-exchange resins, inhibit the intestinal absorption of thiazide diuretics. Therefore, diuretics should be administered 1 h before or 4 h after intake of these drugs.

2) Antihyperuricemic Drugs

There has been a single case report of an elderly patient complicated with heart failure and chronic renal failure who died due to hypersensitivity (fever, arthralgia, erythema multiforme, *etc.*) following administration of allopurinol combined with captopril (*203*). Diuretics diminish the effects of uricosuric agents.

3) Antihyperglycemic Drugs

In combination with ACE inhibitors, antihyperglycemic drugs have been reported to induce hypoglycemic attack (*204*). β-Blockers may mask the symptoms consistent with hypoglycemia, which could be prolonged. Potassium-losing diuretics may increase the required doses of oral antihyperglycemic drugs.

4) Potassium

The combination of potassium-sparing diuretics and ACE inhibitors or ARBs may cause hyperkalemia, and this combination is contraindicated in cases of renal insufficiency.

8-5. Drugs Acting on Digestive Organs

1) H_2-blockers

Cimetidine inhibits cytochrome P-450 enzyme in the liver and may cause an increase in serum concentrations of Ca antagonists and β-blockers (propranolol, metoprolol, labetalol, *etc.*) which are metabolized in the liver (*205, 206*). Ranitidine has a mild affinity with the enzyme, but this affinity is dose-dependent.

2) Antacids

Antacids inhibit gastrointestinal absorption of ACE inhibitors and β-blockers (*14, 207*).

3) Cisapride

When combined with diltiazem, cisapride, a promotility agent, has a risk of inducing prolongation of QT interval and ventricular arrhythmia (*208*).

4) Glycyrrhizin

Glycyrrhizic acid enhances hypokalemia in combination with potassium-losing diuretics.

8-6. Drugs for Respiratory Disorder

1) Drugs for Common Cold

During treatment with β-blockers, the administration of drugs for common cold/nasal congestion (many over-the-counter drugs, Dan Rich®) which contain phenylpropanolamine or other sympathomimetic drugs may increase blood pressure due to unopposed α-adrenergic stimulation (*14*).

2) Theophylline

The blood concentration of theophylline rises in combination with diltiazem (*205*).

8-7. Antibiotics and Antifungal Drugs

Rifampicin induces cytochrome P-450 enzyme, and inhibits the antihypertensive effects of Ca antagonists and β-blockers which are metabolized in the liver (*14*). Rifampicin increases oral clearance of losartan and decreases the half-life values of losartan and its active metabolite E3174 (*209*). Macrolide antibiotics such as erythromycin, clarithromycin, *etc.* and antifungal drugs such as itraconazole may increase the blood concentrations of felodipine and nifedipine due to inhibition of the enzymes (*205*, *210*). Fluconazole interacts with losartan by inhibiting its conversion to the active metabolite E3174 (*211*). Combinations of aminoglycosides and loop diuretics increase renal toxicity and acoustic nerve defects (*212*).

8-8. Centrally Acting Drugs

Diltiazem may raise blood concentrations of triazolam (*213*) and midazolam (*214*) and increase their sedative actions. Thiazide diuretics have been reported to increase the anti-Parkinsonism effects of amantadine (*215*). Diltiazem is apt to raise the blood concentrations of carbamazepine, resulting in the development of neurotoxicity. ACE inhibitors, diuretics and losartan may raise the blood concentrations of lithium, an anti-manic drug. Phenobarbital and phenytoin decrease the blood concentrations of Ca antagonists.

8-9. Glucocorticoids

In combination with potassium-losing diuretics, glucocorticoids may enhance hypokalemia. Diltiazem has been reported to increase the blood concentration of oral methylprednisolone and to greatly enhance its adrenal suppressant effects (*216*).

8-10. Immunosuppressants

Diltiazem and nicardipine increase the blood concentrations of cyclosporine (*205*). However, felodipine and nifedipine do not demonstrate such an effect. Carvedilol, a β-blocker, also increases cyclosporine concentrations (*217*). It has been reported that the combination of cyclosporine and enalapril leads to development of renal failure (*218*). Diltiazem, nifedipine (*219*) and nilvadipine increase the blood concentrations of tacrolimus.

8-11. Urogenital Drugs

Sildenafil (Viagra®) is contraindicated for patients with ischemic heart diseases, particularly for those taking nitrates (*220*). It has been reported that, in patients treated with amlodipine, sildenafil decreased blood pressure by 8/7 mmHg, which was similar to the changes in normotensive subjects (*221*). However, patients receiving multiple antihypertensive drugs may experience an excessive reduction of blood pressure with sildenafil (*220*). The combination of sildenafil and nipradilol (Hypadil®), a β-blocker having an NO radical, is contraindicated.

In patients treated with antihypertensive drugs, the α-blocker tamsulosin, which is prescribed for dysuria due to prostate hypertrophy, may induce orthostatic hypotension.

8-12. Beverages

A bitter constituent in grapefruit juice inhibits the metabolism of Ca antagonists such as felodipine, nifedipine, nitrendipine, *etc.*, and thus increases antihypertensive effects (*222*). It has been reported that after a 7-day intake of grapefruit juice the maximum blood concentrations of nisoldipine significantly increased for at least three days (*223*). Prazosin accentuates alcohol-induced hypotension at 2–4 h after ingestion (*224*).

9. QOL Considerations

9-1. Characteristics of QOL in the Elderly

The QOL of patients has been regarded as an important issue in various fields of medical practice. Because uncomplicated hypertension is associated with fewer subjective symptoms than other diseases, QOL in hypertension has been defined in a much broader sense (*225*); *i.e.*, in the management of hypertension, QOL is considered to consist of such components as physical symptoms, psychological state, and functional capacity to perform social activities, which in turn influence such perceptions as life outlook, life satisfaction and sense of well-being (*226*).

Elderly patients have much more complex QOL problems than young or middle-aged patients because of their specific social and psychological circumstances, as well as their mul-

tiple organ disorders whether in the presence or absence of hypertension. The problems pertinent to the QOL evaluation of elderly hypertensive patients, which should be taken into consideration prior to antihypertensive treatment, are 1) depressive tendencies; 2) complication by dementia; and 3) the influence of other diseases.

The psychological state of the elderly is well characterized by a sense of loss in several areas. 1) Physical and mental activities invariably decrease with aging, and losses in social or economic status, as well as the death of a spouse or other family members, are common and highly conducive to depression. 2) In the assessment of QOL in the elderly, dementia is as important as depression. In this regard, it is important that cognitive function in the elderly be evaluated separately from QOL. 3) Finally, elderly patients frequently suffer from chronic diseases that have an undeniable impact on their QOL, particularly in the case of diseases that significantly affect ADL, such as stroke.

9-2. Assessment of QOL in the Elderly

Assessment tools for the QOL of elderly patients, which have been described above, should be able to evaluate not only the direct influence of physical diseases, but also various specific problems pertinent to this age group. For this purpose, a simple and easily understood questionnaire (*227*) is available, which adopts the concept of the five dimensions for QOL assessment developed by Levine and Croog (*226*). This questionnaire is also designed to evaluate general symptoms, willingness to work or daily routines, physical symptoms, quality of sleep, emotional states, sexual activity or interest, life satisfaction, self-control, daily activities, *etc*. A more detailed questionnaire for the assessment of QOL in elderly hypertensives (*228*) was developed in Japan and includes such important subjective and social components as 1) subjectively perceived inconveniences in daily life due to illness; 2) life satisfaction; 3) emotional stability; 4) the sense of life vitality and fulfillment; and 5) the sense of personal independence.

9-3. Antihypertensive Drug Choices Based on QOL Effects

Among the important factors that potentially affect the QOL of elderly hypertensive patients, it is important to consider subjective symptoms or laboratory abnormalities due to the adverse effects of drugs, as well as the expected adverse effects particular to each antihypertensive drug based on its pharmacological properties. ACE inhibitors, long-acting Ca antagonists, small doses of diuretics and some β-blockers are reported to have little or no adverse effect on the QOL of elderly hypertensive patients (*227*, *229–231*). In a HOT study, in which elderly patients were treated with the long-acting Ca antagonist felodipine, it was reported that the QOL was improved in direct proportion to the antihypertensive effects of the drug (*232*). Though the number of reports is still limited, ARBs have been shown to have favorable QOL effects comparable to those of ACE inhibitors in elderly hypertensive patients (*233*), and long-term treatment of elderly patients with an ARB has been shown to result in better reduction of hypertension and better improvement of cognitive function than the use of a diuretic (*234*). In order to maintain or improve the QOL of elderly hypertensive patients, the appropriate antihypertensive drugs should be individually selected for each patient, taking the presence of any complications into account. In terms of QOL, ACE inhibitors, ARBs, and long-acting Ca antagonists are the drugs of choice for the treatment of hypertension in the elderly.

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