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TABLE 1. Characteristics of osteomalacia patients

patient	age	sex	type	OS/BS (%)	O.Th (μm)	MAR (μm/day)	Calcium (8.4-10.0 mg/dl)	Phosphorous (2.9-4.8mg/dl)	ALP (69-135 IU/L)	$1,25(OH)_2vitD_3$ (20-60 pg/ml)	$25(OH)vit\ D_3$ (10-55 pg/ml)
OM-1	53	F	Oncogenic	83.6	42.8	NC	8.5	1.8	356	12.5	
OM-2	35	F	Fanconi's syndrome	90.2	50.0	NC	8.2	2.4	947	9.2	24
OM-3	53	F	vitamine D-defficiency	97.3	117.5	NC	7.1	2.4	264	23.5	16
OM-4	58	F	Oncogenic	80.1	38.0	NC	8.0	1.6	472	18.0	29

OS/BS, osteoid surface/bone surface; O.Th, osteoid thickness; MAR, mineral apposition rate.

NC, not calculated

TABLE 2. MEPE positivity of osteocytes in normal bone

patient	MEPE(+)OCY(%)
NC-1	100.0
NC-2	97.9
NC-3	86.7
NC-4	92.1
average	94.2±6.0

Values are mean and ±SD.

MEPE(+) OCY, the ratio of MEPE-positive osteocytes/total osteocytes

TABLE 3. MEPE positivity of osteocytes in osteomalacia bone

patient	MEPE(+)OCY in MdB(%)	MEPE(+)OCY in Os(%)
OM-1	75.0	17.3
OM-2	90.6	4.1
OM-3	89.8	4.8
OM-4	94.6	4.8
average	87.5±8.6	7.8±6.4*

Values are mean and±SD.

MEPE(+)OCY, the ratio of MEPE-positive osteocytes/total osteocytes

MdB, mineralized bone; Os, osteoid (non-mineralized bone)

Asterisk indicates statistic significance between MEPE(+)OCY in MdB and in Os, calculated with Mann-Whitney U test (*$p<0.05$)

TABLE 4. MEPE posiivity of osteocytes in osteoporosis bone

patient	MEPE(+)OCY in MdB(%)	MEPE(+)OCY in Os(%)
OP-1	94.9	0
OP-2	96.0	11.1
OP-3	95.1	0
OP-4	95.1	8.3
average	95.3±0.5	4.9±5.7*

Values are mean and±SD.

MEPE(+)OCY, the ratio of MEPE-positive osteocytes/total osteocytes

MbB, mineralized bone; Os, osteoid (non-mineralized bone)

Asterisk indicates statistic significance between MEPE(+)OCY in MdB and in Os, calculated with Mann-Whitney U test (*$p<0.05$).

CASE REPORT

Effects of low-dose quetiapine on psychotic symptoms in elderly patients with physical illnesses: Report of eight cases

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Key words: delirium, elderly, hallucination, quetiapine.

Abstract

Quetiapine, which is a new atypical antipsychotic agent, was administered at low doses (25–50 mg/day) for psychotic symptoms in eight elderly patients with physical illnesses. Delirium and hallucination were alleviated by the administration of low doses of quetiapine, and the cause–effect relationship between the administration and alleviation of symptoms was evident, particularly in one patient with delirium, because delirium was alleviated after administration began, was exacerbated after discontinuation of quetiapine, and was alleviated again after administration was resumed. Little improvement was observed in delusions or mood disorders. None of the patients showed exacerbation of physical symptoms or abnormalities in clinical laboratory tests. The results of this study suggest that quetiapine might be effective in reducing delirium and hallucination that often accompany physical illness in elderly people and could be used without adverse effects.

INTRODUCTION

In elderly patients, psychotic symptoms including delirium, hallucination, delusion and mood disorders frequently accompany physical illnesses, such as congestive heart failure and bone fracture,[1–4] making the treatment and management of the primary disorders difficult. Although these psychotic symptoms have been treated with conventional antipsychotic agents, such as haloperidol, treatment is often hampered in elderly patients by the appearance of adverse events, for example, extrapyramidal signs. In some patients, dysphagia and gait disturbance resulting from extrapyramidal disorders impair the activities of daily living and result in a delay in the cure, or an exacerbation, of the primary disorders.[5]

Recently, atypical antipsychotic agents that have low incidences of adverse effects, such as respiridone[6] and olanzapine,[7] have become available, and their use in elderly patients is anticipated. Quetiapine, which is one such drug, has been reported to be effective for psychotic symptoms associated with dementia and psychiatric disorders in the elderly.[8,9] In previous reports, the total daily dose of quetiapine was 50–400 mg/day and the duration of exposure was 56–87 days. In this paper, we report the use of low doses of quetiapine to control psychotic symptoms in elderly patients with physical illnesses.

SUBJECTS AND METHODS

Quetiapine was administered to eight patients who exhibited psychotic symptoms during their treatment for physical illnesses at the Department of Gerontology, Kanazawa Medical University between January and May 2002 (Table 1). We informed the patients' families that quetiapine was a antipsychotic agent for schizophrenia, but was expected to be effective in reducing the effects of the present illness. In addition, we informed the families of the adverse effects of

Table 1 Profiles and tentative classification of the cases

Case No.	Age	Sex	MMSE	Main illness	Drug for main illness	Psychotic symptom	Maximum dose of quetiapine (mg/day)	Tentative group
1	88	M	0	Pneumonia, multiple cerebral infarction, VD	Antibiotics, anticoagulant	Delirium	25	A
2	91	F	8	Congestive heart failure, AD	Diuretics	Delirium	25	A
3	79	M	22	MK, dumping syndrome, VD	Glucosidase inhibitor	Delirium	50	A
4	88	F	15	COPD, AD	Beta stimulator	Cenestopathy	25	B
5	75	F	20	Rheumatoid arthritis, AD	NSAIDS	Visual hallucination	25	B
6	78	M	20	Osteoarthritis, DM, AD	NSAIDS, insulin injection	Delusion, irratibility	25	C
7	85	F	18	CRF, cerebral hemorrhage, epilepsy, VD	Diuretics, anticonvulsant	Excitation, irratibility	50	C
8	78	F	20	asthma, AD	Beta stimulator	Delusion, depression	50	C

(AD) Alzheimer's disease; (COPD) chronic obstructive pulmonary disease; (CRF) chronic renal failure; (NSAIDS) non-steroidal anti-inflammatory drugs; (VD) vascular dementia.

quetiapine. We obtained agreement from all families before proceeding. During the period of quetiapine administration, which was no longer than 4 months, there was no change to the drugs used for the treatment of the physical illnesses or to the doses given to any of the patients. In addition, no other antipsychotic medication was used concomitantly. Minimal doses of hypnotics were prescribed only when the patients complained of insomnia. In patients with delirium, serial evaluations were made using the delirium rating scale (DRS).[10] In patients who presented with hallucinations or delusions, evaluations were conducted using the brief psychiatric rating scale (BPRS) (18 items, 0–6 points).[11] Table 1 profiles the patients. Patients were tentatively classified into groups A, B and C according to their symptoms (Table 1).

CASE REPORTS

Group A (delirium group)

Case 1

An 88-year-old man had been tube-fed for 5 years because of multiple cerebral infarction and pseudobulbar palsy. He needed total assistance in activities of daily living because of tetraplegia. The patient was admitted to hospital 1 month earlier because of pneumonia. Although the pneumonia subsided, the sleep–awake (day–night) rhythm was inverted, and the patient said 'I see people' and uttered loud monologues during the night. This visual hallucination was alleviated 2–3 days after the beginning of the administration of quetiapine at 25 mg/day (Fig. 1a). No exacerbation of respiratory symptoms was noted during the administration of quetiapine.

Case 2

A 91-year-old woman with congestive heart failure had been suffering memory disturbances for approximately 4 years. Brain magnetic resonance imaging (MRI) demonstrated diffuse cortical atrophy. The patient had recently shown sleeplessness at night, wandering, monologues and visual hallucination. The administration of quetiapine was started at 25 mg/day. Sleeplessness at night and visual hallucinations were alleviated after 1 week. No staggering or falls were observed. Because the condition of the patient improved after 3 months, quetiapine administration was temporarily discontinued, but insomnia and wandering relapsed approximately 3 days after quetiapine administration was discontinued and these symptoms disappeared with its resumption at the same dose (Fig. 1b). No change in electrocardiogram (ECG) or exacerbation of heart failure was noted during the administration period.

Case 3

A 79-year-old man had undergone gastrectomy for stomach cancer 2 years earlier, but had subsequently developed dumping syndrome, which was managed using oral medication. He developed memory disturbance approximately 6 months before admission. A brain MRI disclosed multiple lacunae in the basal ganglia. One month before admission the patient began to complain of sleeplessness at night and Capgras-

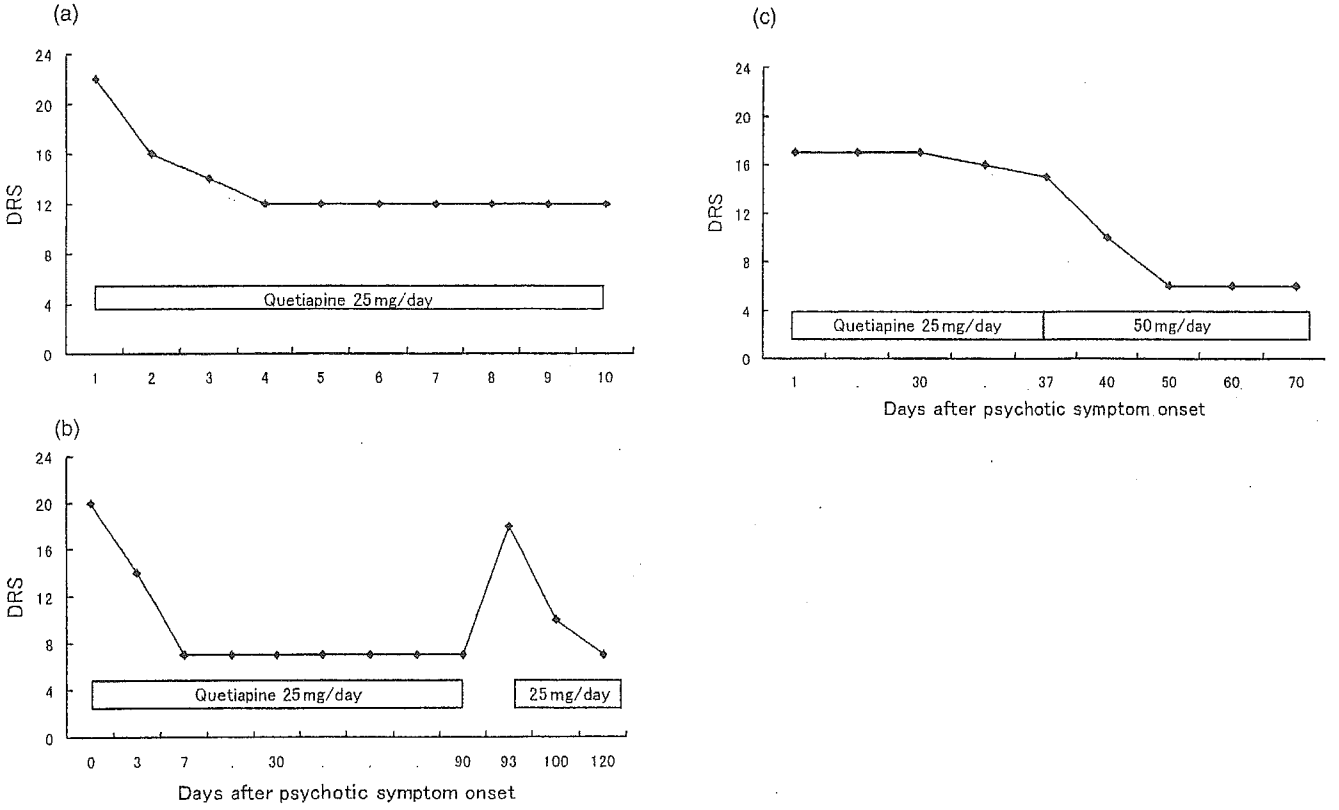

Figure 1 Delirium rating scale (DRS) change after the onset of delirium. (a) Case 1, (b) case 2 and (c) case 3. All delirium cases were alleviated by the administration of low-dose quetiapine, and the cause–effect relationship between the administration and alleviation of symptoms was evident, particularly in case 2, because delirium was alleviated after administration began and was exacerbated after discontinuation of the administration. Delirium was alleviated again after the resumption of quetiapine administration.

syndrome-like delusions, such as insisting that his wife was a substitute and that his house was changed to someone else's. He also showed an exacerbation of wandering. Administration of quetiapine was started at 25 mg/day. However, as results were insufficient, the dose was increased to 50 mg/day, after which time symptoms were alleviated. At present, his gait is slightly unsteady, but no falls have been reported (Fig. 1c).

Group B (hallucination group)

Case 4

An 88-year-old woman required inhalation drug therapy for chronic obstructive pulmonary disease. Her memory had deteriorated gradually over the past 3 years. A brain MRI showed diffuse cortical atrophy. One year before admission, the patient began to insist to her family 'I have a tapeworm in my gut, and part of it comes out with feces.' Initially, donepezil was administered, but it was not effective for the somatosensory hallucination. Complaints regarding a 'tapeworm' disappeared 2 weeks after administration of quetiapine began at 25 mg/day. When asked 'Do you have a worm in your stomach?' she replied 'I am not sure, but I feel it's gone.' No decrease in the arterial oxygen saturation or exacerbation of respiratory symptoms were noted during the administration period. No dizziness on standing up or gait disturbance were recorded (Fig. 2a).

Case 5

A 75-year-old woman with rheumatoid arthritis was completely dependent in activities of daily living and had been bed-ridden for 3 years because of multiple cerebral infarction. Approximately 6 months before admission, the patient began to say, 'Someone is standing by the bed,' or 'I see an animal,' during both

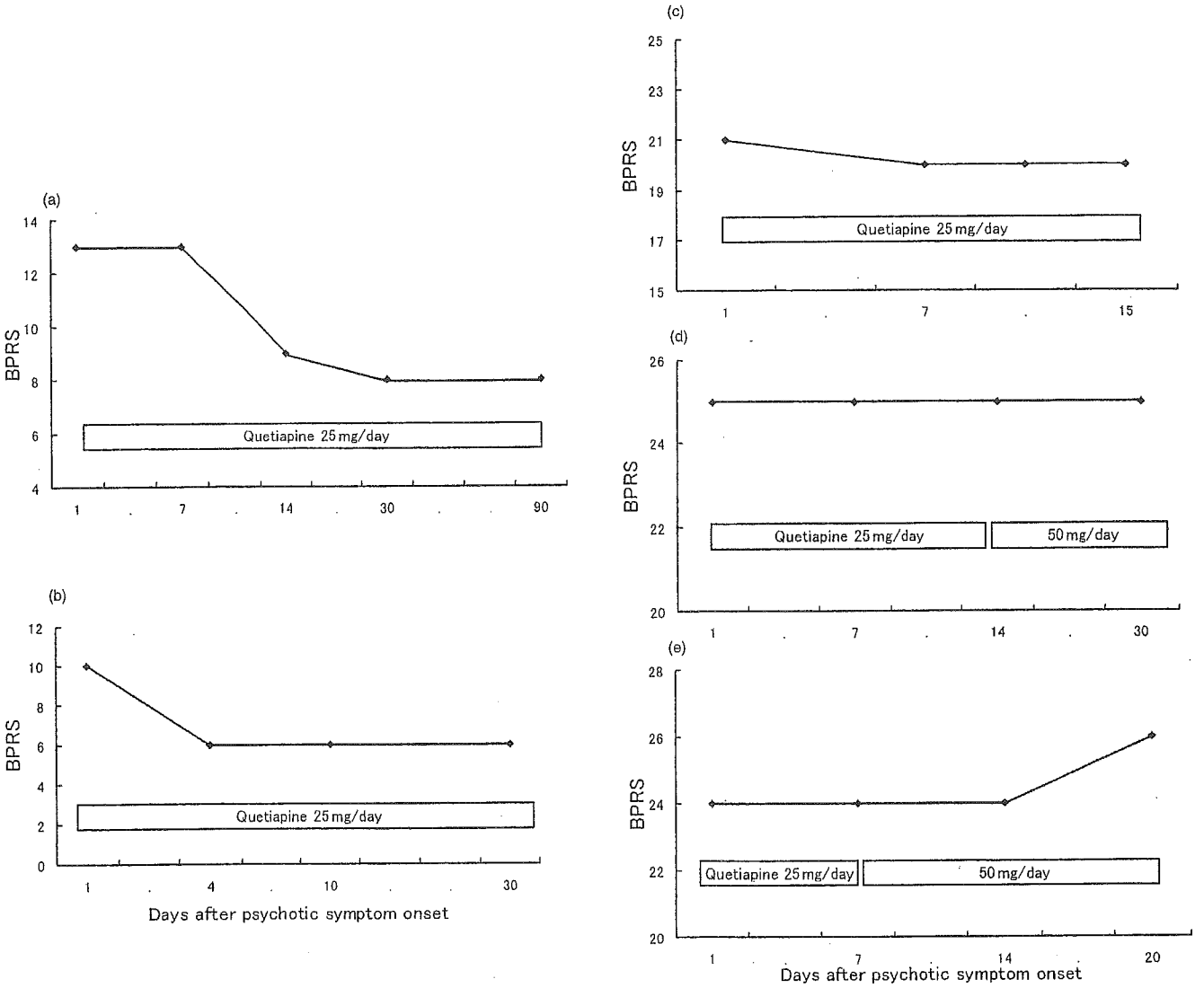

Figure 2 Brief psychiatric rating scale (BPRS) changes after the onset of hallucination, delusion and mood disorder. (a) Case 4, (b) case 5, (c) case 6, (d) case 7 and (e) case 8. The psychotic symptoms of cases 4 and 5 are hallucination, and those of cases 6, 7, 8 are delusion and mood disorder. Symptoms of patients within the hallucination group were all alleviated by the administration of low-dose quetiapine. In contrast, little improvement was observed in the delusion and mood disorders group.

day and night. No drugs that might induce hallucination were being administered. Complaints of visual hallucination decreased within 2–3 days after administration of quetiapine began at 25 mg/day (Fig. 2b).

Group C (delusion and mood disorder group)

Case 6

A 78-year-old man with osteoarthritis of the hips and diabetes mellitus, who was receiving outpatient care for the control of his blood sugar levels, developed memory disturbance, irritability and delusion of theft approximately 1 year prior to admission. The patient was referred to us because he asserted that he had had his money stolen, and shouted and resorted to violence. A brain MRI revealed diffuse cortical atrophy. When quetiapine was administered at 25 mg/day, the irritability was mitigated, but the delusions were unaffected (Fig. 2c).

Case 7

An 85-year-old woman with left hemiplegia as a result of a hemorrhage in the right putamen 5 years previously had a history of epileptic attacks. Symptoms of kidney failure had progressed over the past 3 years. She needed partial assistance in eating and taking a bath. In general, she was reticent and sedate, but became suddenly aroused and rejected assistance because of trivial reasons. She had been prescribed drugs for these conditions, including haloperidol, tiapride and carbamazepine, but adverse effects such as dizziness were noted. She began to take quetiapine at 50 mg/day, but no marked change in her symptoms has been recorded (Fig. 2d).

Case 8

A 78-year-old woamn receiving outpatient care because of asthma developed memory disturbance and complained, 'everybody laughs at me,' and 'my family has given up on me' during the 12 months prior to admission. A brain MRI disclosed diffuse brain atrophy. Quetiapine was administered at 50 mg/day, but as the patient attempted suicide by taking sleep pills, she was transferred to the psychiatric ward for further treatment (Fig. 2e).

SUMMARY OF CASES

No exacerbation of physical symptoms or change in blood pressure was recorded after the beginning of quetiapine administration in any patient. In addition, no abnormalities were indicated on blood tests. One patient who developed delirium developed gait disturbance, which was considered to be an extrapyramidal sign, but no marked impairment of activities of daily living (ADL) was recorded, and quetiapine administration could be continued. In all cases, no cognitive decline was found after quetiapine exposure when measured using the mini-mental state examination (MMSE) and no ADL decline was observed.

DISCUSSION

The eight patients were tentatively divided into three groups according to their symptoms. The effect of low doses of quetiapine differed according to the type of symptoms experienced. In group A, in which the patients primarily showed delirium, all three patients showed good responses to quetiapine. In particular, in case 2, the symptoms improved after quetiapine administration began, deteriorated after its discontinuation, and improved after its resumption. This strongly supports a relationship between quetiapine administration and symptomatic improvements. The results in group B, in which patients showed hallucinations, were also satisfactory. However, in group C, in which patients experienced delusions and mood disorders, low-dose quetiapine administration had little effect.

Elderly patients with physical symptoms frequently develop delirium, and low-doses of quetiapine had an excellent effect on delirium and hallucinations. A study showing that quetiapine was effective against delirium in elderly patients has been reported previously.[12] However in this study, responses to low-dose quetiapine administration were insufficient in patients with mood disorders or delusions. In general, atypical antipsychotic agents have relatively weak effects on symptoms such as excitation and offensiveness, and conventional antipsychotic agents are frequently used for their treatment. However, conventional antipsychotic agents are likely to induce adverse effects such as extrapyramidal symptoms, and symptomatic control is extremely difficult.[13]

Quetiapine, the conventional dose of which in adults is 150–600 mg/day, has a strong affinity to 5-HT2A serotonin receptors, H1-histamine receptors, alpha 1-adrenergic receptors and M1-muscarin receptors. However, its affinity to dopamine D2-receptors is weak. Thus, it is considered to be less likely to cause extrapyramidal symptoms. Quetiapine is metabolized in the liver via a pathway mediated by CYP3A4. Therefore, caution is needed in the concomitant use of quetiapine with drugs that have a CYP3A4-inducing activity, such as phenytoin and carbamazepine.[14] Sedation, tachycardia and decreases in blood pressure have been reported as adverse effects associated with its use,[15] but their severity and frequency were reduced compared to the use of conventional antipsychotic drugs and other atypical antipsychotic drugs.[14]

In elderly patients, adverse effects are more likely to occur because of delays in drug absorption, changes in drug distribution within the body and a decrease in drug clearance by the liver and kidneys.[16–18] Also, drug interactions are likely to appear in the elderly because of the high prevalence of physical disorders and the frequent concomitant use of drugs for the treatment of other disorders.[19]

Therefore, it is desirable to treat elderly patients with a minimum number of drugs and at low doses. In particular, in the treatment of psychotic symptoms, high-dose administration is likely to induce oversedation and extrapyramidal symptoms, which may cause falls and aspiration pneumonia and result in impairment of ADL.[20] Therefore, drugs that produce sufficient effects at a low dose are ideal.

In patients in the present study, low-dose quetiapine administration exerted no effect on the cardiovascular system and no change in the results of blood tests during the administration period. Although gait disturbance, which was suspected to be an extrapyramidal symptom, appeared in one patient, discontinuation of administration was unnecessary. The results of this study suggest that it is possible to mitigate hallucination and delirium safely in elderly patients with physical illness without affecting the primary disorders. Low-dose administration of quetiapine is suggested to be useful for the control of at least some of the psychotic symptoms in elderly patients with physical disorders.

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Report

Guidelines for Treatment of Hypertension in the Elderly — 2002 Revised Version —

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(*Hypertens Res* 2003; 26: 1–36)

Introduction

Hypertension is one of the most significant risk factors for cerebrovascular and heart diseases, which rank as the second and third most frequent causes of death in Japan, respectively. The prevalence of hypertension rises as the population grows older, affecting approximately 60% of the Japanese aged 65 yr or older (*1*), and there are currently more patients receiving treatment for hypertension than for any other disease in Japan (*2*). As the size of the elderly population in our country continues to increase rapidly, hypertension has become one of the most important diseases to control and treat, and developing an effective strategy for this disease has become a matter of great social immediacy. Hypertension in the elderly is composed mostly of essential hypertension, but the pathophysiology of essential hypertension in the elderly differs in many respects from that of essential hypertension in the young or middle-aged. In particular, isolated systolic hypertension (systolic blood pressure 140 mmHg or greater, and diastolic blood pressure below 90 mmHg) increases in frequency with age. Isolated systolic hypertension is divided into two types, the so-called "burned-out" and "*de novo*" types. The former generally develops in middle age as essential hypertension, and becomes systolic hypertension as the diastolic blood pressure is reduced due to the aging process, while the latter develops in old age due to reduced vascular compliance in the large arteries. In addition, there are some cases with secondary hypertension due to identifiable causes such as renovascular hypertension.

In the elderly, it has been reported that systolic blood pressure is more strongly related with cardiovascular complications—especially stroke, ischemic heart disease, heart failure, end-stage renal disease, and all-cause mortality—than is diastolic blood pressure (*3*). Furthermore, it has been demonstrated that increased pulse pressure (the difference between systolic blood pressure and diastolic blood pressure) is correlated with an increased risk of such complications (*4*).

The pathophysiology of hypertension in the elderly is characterized by increased total peripheral vascular resistance, decreased compliance of large and middle arteries, a tendency toward decrease in cardiac output and circulating blood volume, increased lability of blood pressure due to age-related decrease in baroreceptor function, decreased blood flow, and dysfunction of autoregulation in important target-organs such as the brain, heart, and kidney. Therefore,

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hypertension in the elderly must be treated with special caution, taking the above-mentioned pathophysiological characteristics into consideration. In addition, as with other diseases in the elderly, it is necessary for the physician to pay close attention to the activities of daily living (ADL), quality of life (QOL) and drug compliance of the patient.

Based on the results of numerous clinical intervention trials, treatment of hypertension in the elderly—including treatment of systolic hypertension—has generally been of great benefit (*5–11*). However, the efficacy of treatment of so-called very old hypertensive patients aged 85 yr or older is still controversial (*12*). It has already been demonstrated that the incidence of cerebrovascular disease, ischemic heart disease and cardiac failure, in addition to all-cause mortality, are decreased by treatment with diuretics or long-acting dihydropyridine Ca antagonists. Although treatment of hypertension in the elderly with β-blockers significantly decreases morbidity and mortality of cerebrovascular disease, it has not been shown to significantly decrease those of ischemic heart diseases or all-cause mortality (*13*). In the United States, the therapeutic guidelines of hypertension in the elderly were published by the National High Blood Pressure Education Program Working Group in 1994 (*3*). In most cases, however, information on the treatment of hypertension in the elderly is not released under separate cover, but is provided only as a constituent part of more general guidelines. For example, in the sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) (*14*), the issue of hypertension in the elderly is described in Section 4, "Special Populations and Situations."

The treatment guidelines for hypertension published in the USA and Europe are essentially guidelines for individuals in Western countries, primarily Caucasians. These guidelines provide a detailed summary of the extensive results of hypertension studies throughout the world, and they are also expected to be a useful reference for the control and treatment of hypertension in Japan. However, it is not appropriate to adopt these guidelines indiscriminately to Japanese hypertensive patients without consideration of the differences in genetic and social background. To address this problem, the present report constitutes a revised version of the "A Guideline for Treatment of Hypertension in the Elderly, 1995" (*15*) prepared by the Comprehensive Research Projects on Aging and Health of the Ministry of Health and Welfare, the Research Group for "Guidelines on Treatment of Hypertension in the Elderly" (Chair: Prof. Toshio Ogihara, Osaka University), and the "Guideline for Hypertension in the Elderly—1999 Revised Version" (*16*) prepared by the Research Group on "Long-Term Prognosis of Hypertension in the Elderly" (Chair: Prof. Kunio Hiwada, Ehime University) of the above project. Thus, this report is the third edition of the guideline. As a first step in developing this revision, a questionnaire was sent to numerous hypertension specialists in Japan, asking their opinions on the 1999 version of the guidelines (*17*). The fundamental concept of this report is the same as in the original version: that is, the report presents guidelines for the control and treatment of the elderly in Japan based not only on the evidences from many recent studies in Western countries and Japan, but also on a consideration of the unique lifestyle of Japanese. Based on the responses to the above-mentioned surveys, the opinions and criticisms of the Japanese hypertension experts were incorporated into the present revision (*17*).

This report includes the characteristics of hypertension in the elderly, diagnosis, necessity of treatment, indications, target levels of blood pressure, choice of first antihypertensive drug, treatment and precautions in patients with complications, drug interaction, and consideration of QOL. However, these guidelines are not intended to present uniform therapeutic strategies for hypertension in the elderly, but rather to show the general concepts. All hypertensive drug recommendations presented are considered the best choice currently available. However, the effectiveness of individual drugs, particularly angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors, for hypertension in the elderly should be verified by the results of further intervention trials in Japanese patients.

1. Blood Pressure Levels and Their Circadian Variation in the Elderly

1-1. Aging and Blood Pressure Levels

Blood pressure changes with age. Systolic blood pressure increases and diastolic blood pressure decreases with advancing age, resulting in an increased pulse pressure in the elderly (*18*). Thus, the prevalence of systolic hypertension also increases with advancing age. Pulse pressure, as well as systolic blood pressure, is one of the most important factors to predict the morbidity and mortality of cardiovascular disease (*19–21*). These changes in blood pressure with age are due mainly to an increased arterial stiffness, and thus to decreased compliance of the large elastic arteries (22).

Hypertension in adults is defined as systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more (*14*). However, since blood pressure changes with age, the blood pressure level to be treated by antihypertensive drugs and the therapeutic goal pressure should be established separately for the elderly. Table 1 demonstrates the blood pressure values of each age class obtained in 1992 by the Working Group of the Ministry of Health and Welfare from healthy elderly Japanese who were not taking any antihypertensive drugs (*23*). In the elderly aged 65 yr or older, systolic blood pressure increased and diastolic blood pressure decreased slightly with age. On the whole, the blood pressures of subjects aged 65 to 94 yr were $133 \pm 19/77 \pm 11$ mmHg (mean $\pm$ SD) for men and $134 \pm 19/76 \pm 10$ mmHg for women. According to the Hisayama study (*24*), among those aged 60 yr or older, the cumulative

Table 1. Blood Pressure (BP) of Healthy Elderly Individuals by Age and Sex

	Age (yr)	*n*	Systolic BP	Diastolic BP
Male	63–69	104	127.8±16.3	78.4±7.9
	70–74	75	130.9±20.8	76.4±9.3
	75–79	74	136.9±19.2	75.9±11.8
	80–84	49	140.3±17.4	77.7±12.0
	85–89	16	137.1±17.8	74.1±18.3
Female	65–69	101	134.9±17.5	78.3±10.3
	70–74	92	130.8±18.2	74.4±9.1
	75–79	78	133.6±18.8	74.5±9.8
	80–84	52	139.8±20.8	75.8±10.1
	85–89	19	135.6±19.8	73.4±9.6

BP (mean±SD) of healthy elderly individuals by age (no antihypertensive drug, obesity, emaciation or ECG abnormality) reported by the Ministry of Health and Welfare "Study Group on Normal Values of Laboratory Tests in the Elderly," Subgroup on Blood Pressure (Chairman: Jun Fujii) (*23*).

Table 2. Reference Values of 24-h Blood Pressure (BP) in the Elderly

Investigator	Subjects	Age (yr)	Upper limit	Sex	*n*	24 h BP (mmHg)	Daytime BP (mmHg)	Nighttime BP (mmHg)
Imai *et al.* (*32*)	Japan	60–69		M	54	146/86	153/91	141/82
	Community		Mean+2SD	F	72	150/85	159/91	141/87
	Normotensives	70–79		M	25	151/84	157/90	148/80
				F	26	152/86	162/93	152/80
O'Brien *et al.* (*33*)	Employees	50–79	95 percentile	M	54	151/98	155/103	140/90
				F	72	160/87	177/97	133/75
Kawasaki *et al.* (*34*)	Japan	60–	95 percentile	M	54	149/84	151/87	147/82
	Database			F	49	144/82	145/87	141/79
	Normotensives							
Wendelin-Saarenhovi *et al.* (*35*)	Finland Community	64–87	95 percentile	M	99	145/93	154/99	133/82
				F	112	154/89	158/91	143/85

morbidity of cardiovascular disease was significantly higher in those with systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 80 mmHg than in those with less than 140 mmHg or 80 mmHg, respectively. On the other hand, in the reevaluation of the SHEP study (*25*), the risk for occurrence of cardiovascular diseases was doubled in those with less than 55 mmHg of diastolic blood pressure under antihypertensive treatments (*25*), suggesting that excess lowering of diastolic blood pressure may be harmful in elderly hypertensives.

1-2. Circadian Variation of Blood Pressure in the Elderly

1) Circadian Variation of Blood Pressure in the Elderly

Numerous types of blood pressure variation have been recognized, including short-term blood pressure variations such as cardiac-cycle dependent, respiration-dependent and baroreceptor reflex-dependent variations, 24-h variation, and a long-term seasonal variation. Twenty-four-hour variation, *i.e.*, circadian blood pressure variation, is currently the most extensively studied of these types. Drayer *et al.* (*26*) monitored blood pressure continuously over a 24-h period in hypertensive patients and found nocturnal dipping during sleep; the dipping reached a nadir between 0:00 and 4:00, increased just before awaking, remained elevated throughout the day, and gradually decreased in the afternoon to evening.

Physical activity is the most important among the factors influencing circadian blood pressure variation, though mental activity also plays an important role. Some reports have indicated that circadian variation of blood pressure is mediated by circadian variations of the endocrine and autonomic nervous systems (*27–29*). For example, nocturnal decline in blood pressure disappears in the patients with Cushing's syndrome or with autoimmune disease treated with glucocorticoids (*30*). Lack of nocturnal decline in blood pressure has been seen in patients with autonomic failure, such as in patients with multiple system atrophy, Parkinsonism, spino-

cerebellar degeneration, or diabetic neuropathy, and sometimes nocturnal blood pressure is elevated in such pathophysiological conditions, demonstrating a reversed circadian variation pattern (*28*, *29*).

The circadian variation of blood pressure in healthy elderly is essentially similar to that observed in the elderly with hypertension as described above: *i.e.*, decreases in blood pressure during sleep, increases in the early morning, decreases in the afternoon, and temporary increases again in the evening. The pattern of nocturnal dipping of blood pressure changes with age. Particularly in men, the amplitude of nocturnal dipping decreases with age, and the circadian variation of blood pressure almost disappears in men aged 80 yr and older (*31*). Reference values of 24-h ambulatory blood pressure in the elderly have not yet been established, but several results obtained in cross-sectional studies have been reported (Table 2) (*32–35*).

2) Mean Values of 24-h Blood Pressure

The clinical significance of ambulatory blood pressure monitoring has been widely recognized (*36*, *37*). The 24-h mean is better correlated than casual-clinic pressure values to prevalence of hypertensive target-organ damages such as left ventricular hypertrophy, fundoscopic changes, renal disorders, and carotid intima-media thickness, as well as to cardiovascular disease morbidity and mortality. In elderly hypertensive patients in Japan, lacunar infarction determined by MRI was observed frequently in the cases with an elevated mean value of 24-h blood pressure (*38*). These studies suggested that the mean value of 24-h blood pressure is more predictive than casual-clinic blood pressure values for the prognosis of hypertension (*39*).

3) Nocturnal Blood Pressure

Recent studies have emphasized the clinical significance of nocturnal blood pressure. Those who have ordinary nocturnal dipping of blood pressure are referred to as dippers, and those without nocturnal dipping are called non-dippers. The frequency of non-dipper status has been reported to increase with advancing age, and to be associated with high prevalence of ischemic heart disease and cerebrovascular disorders (*40*). In asymptomatic hypertensive elderly in Japan, the prevalence of lacunar infarction was reported to increase significantly among non-dippers relative to dippers (*41*). Another study reported that extreme dipping of nocturnal blood pressure was associated with extended periventricular white matter lesions in elderly women (*42*). And recent prospective studies have revealed that both the morbidity and mortality of cardiovascular disease were higher among non-dippers than dippers (*42*, *43*). Extreme dippers who demonstrate nocturnal dipping of more than 20% of the daytime blood pressure have been reported—much like non-dippers—to have more advanced asymptomatic cerebrovascular lesions than dippers, and to run a greater risk of stroke. On the other hand, another study has reported that the prognosis of extreme-dippers is similar to that of dippers (*44–46*).

4) Blood Pressure Elevation in the Morning

Among circadian variations of blood pressure, an increase in blood pressure in the morning is thought to be associated with increased incidence of cardiovascular disease, which is possibly mediated by such mechanisms as increased platelet aggregation due to the rise in sympathetic nerve activity and decreased fibrinolysis accompanied by activation of the renin-angiotensin system. A rapid increase in blood pressure in the early morning is called a "morning surge." In fact, it is well known that acute myocardial infarction, sudden death and cerebral hemorrhage occur frequently in early morning. Morning surge appears to be due to physical activity after wake-up, but it has also been demonstrated in some cases even before wake-up. Morning surge has not been well defined, but an early morning pressure elevation of at least 50 mmHg (corresponding to the 90th percentile of early morning elevation among normotensive individuals) has generally been accepted as a reference, and using this reference, morning surge has been recognized in 52.6% of the elderly with essential hypertension (*47*). An insufficient duration of action of antihypertensive drugs is thought to be closely related to high blood pressure in the morning (*48*).

5) White Coat Hypertension

Measurements of ambulatory blood pressure are useful for diagnosis of so-called "white-coat hypertension." White coat hypertension is defined as reproducible hypertension demonstrated only at the outpatient clinic (or in a medical setting) and not demonstrated in non-medical settings (as determined by ambulatory blood pressure monitoring or home blood pressure measurements) (*49*), and its prevalence increases with advancing age. White coat hypertension (defined as diastolic blood pressure at the outpatient clinic of 90–104 mmHg, and a daytime ambulatory blood pressure mean of 134/90 mmHg or less) is reported to occur in 42% of elderly patients with systolic hypertension aged 65 yr or older (*50*). Patients with white coat hypertension may have excess hypotension in a non-medical setting due to antihypertensive drug treatment. Some investigators have claimed that the left ventricular mass in white coat hypertension is intermediate between those of sustained hypertension and normotension (*51*). In many reports on white coat hypertension, blood pressure in the non-medical setting has been found to be in the borderline hypertensive range. However, the prognosis and target-organ damage in those with white coat hypertension are generally thought to be similar to those in individuals with normotension when blood pressure in the non-medical setting is in the true normotensive range. This is also generally true in elderly white coat hypertension. In this case, "true normotension" at home is defined as less than 125/80 mmHg according to WHO/ISH (1999) (*52*), while hypertension at home is defined as a blood pressure of 135/85 mmHg and over according to JNC-VI (*14*).

6) Indication of Monitoring of Ambulatory Blood Pressure in the Elderly

Measurements of circadian variation of blood pressure can be obtained every 15 min to every 1 h with patients in an ambulatory state using a portable non-invasive sphygmomanometer that is widely available. However, it is difficult to monitor ambulatory blood pressure for all patients with hypertension. In practice, therefore, the monitoring should be applied selectively to only those cases which show: (a) extremely variable casual-clinic blood pressure; (b) no target-organ damage despite the presence of casual-clinic hypertension; (c) a significant difference between home and casual-clinic blood pressure, *i.e.*, suspected white coat hypertension; (d) insufficient control of blood pressure while receiving a sufficient dose of antihypertensive treatment (intractable hypertension or resistant hypertension); (e) autonomic dysfunction such as diabetic neuropathy; (f) signs suggestive of orthostatic or postprandial hypotension; (g) candidates for measurement of nocturnal blood pressure; (h) paroxysmal hypertension. Ambulatory blood pressure monitoring has been shown to be useful to predict cardiovascular risk in elderly patients with systolic hypertension (*53*).

7) Home Blood Pressure Measurements

Blood pressure information other than casual pressure measured at the outpatient clinic is useful for diagnosis and evaluation of therapeutic outcomes, particularly in the management of elderly hypertensive patients with large blood pressure fluctuation. In addition, self-measurement enhances the patient's motivation for treatment of hypertension. To facilitate home measurement, a wide range of devices has recently been marketed. Two of these, the wrist-cuff device and finger-cuff device, are reported to be inaccurate and unreliable, and thus are not recommended for practical use (*54*). Even the arm-cuff device for self-measurement of blood pressure should be regularly calibrated in comparison with the Riva-Rocci-Korotkoff sound method using a mercury sphygmomanometer. Patients should be instructed to consistently measure their blood pressure at similar times of day and under similar conditions. Blood pressure should preferably be measured twice daily, once before antihypertensive medication after getting up in the morning (trough effect) and once in the evening/night at a point when the antihypertensive medication is still expected to exert a sufficient effect (nearly peak effect). Although a reference value of home blood pressure in the elderly has not yet been established, meta-analysis of the international database revealed that the 95th percentile value of home blood pressure in 2,449 normotensives was 135/86 mmHg, and that a home blood pressure of 125/79 mmHg corresponded to an ambulatory blood pressure of 140/90 mmHg (*55*). In a community-based population study, the 95th percentile value of home blood pressure measured in the morning in elderly subjects aged 60 yr who were not taking any antihypertensive drugs was 145/95 mmHg (n=234) (*56*). In a population-based observational study in Japan, home blood pressure measurement was reported to be more predictive of mortality than casual-screening blood pressure measurement (*57*). In addition, both systolic hypertension and wide pulse pressure in home blood pressure measurement have been shown to reflect a poor prognosis (*58*). Although doctors or nurses may sometimes measure blood pressure at the homes of elderly patients, these values differ from those obtained by self-measurement of blood pressure at home. It has been reported that self-measurement of blood pressure at home appears to be useful even in the very old (*59*).

2. Diagnosis of Hypertension in the Elderly

2-1. Diagnostic Criteria and Classifications of Hypertension in the Elderly

One of the characteristics of hypertension in the elderly is a high prevalence of systolic hypertension caused by suppressed Windkessel function and amplification by reflected waves based on arteriosclerosis. No special diagnostic criteria for hypertension in the elderly are stated in the WHO-ISH guidelines (*52*), the JNC VI (*14*), or the guidelines for the management of hypertension by the Japanese Society of Hypertension (JSH 2000) (*60*); systolic blood pressure of 140 mmHg and greater and/or diastolic blood pressure of 90 mmHg and greater is defined hypertension as in general adults. In the intervention trial conducted by the Systolic Hypertension in the Elderly Program (SHEP) (*5*), systolic hypertension was adopted as a systolic blood pressure of 160 mmHg and greater and diastolic blood pressure of below 90 mmHg, which inclusion criteria was different from the criteria for hypertension in general. In many of the epidemiological studies thus far reported, patients with elevated systolic blood pressure demonstrated a significantly higher prevalence of cardiovascular diseases. The importance of managing systolic hypertension has been also emphasized in the therapeutic guidelines published by JNC VI (*14*), WHO-ISH (*52*), and JSH 2000 (*60*).

2-2. Diagnostic Considerations for Hypertension in the Elderly

1) Medical History

Medical history is important in the diagnosis of all diseases, and hypertension is no exception. Thus the medical history should include the duration and level of elevated blood pressure, as well as the subjective symptoms of target organ damage and cardiovascular diseases. To rule out secondary hypertension, patients should be questioned about the presence of weight change, nocturia, and weakness or proteinuria, all of which are highly important in the differential diagnosis of secondary hypertension, as will be discussed later. Since essential hypertension might be related to genetic and environmental factors, symptoms and past history of cardio-

Table 3. Elderly Patients Suspected of Having Renovascular Hypertension

1. Diastolic BP 105 mmHg or greater found after 55 yr of age
2. Drug-resistant hypertension controlled by antihypertensive drugs in the past
3. Hypokalemia
4. Moderate or severe renal dysfunction
5. Abdominal vascular bruits

BP, blood pressure.

Table 4. Risk Factors for Cardiovascular Diseases

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

vascular and renal diseases should be included in addition to family history of hypertension.

2) Measurement of Blood Pressure

Blood pressure should be measured according to JSH 2000 (*60*), taking the mean of two stable pressure values with a difference of no more than 5 mmHg. Hypertension should not be diagnosed by a single measurement of blood pressure at the first visit. If the first blood pressure value is elevated, excluding a systolic blood pressure of 180 mmHg or greater or a diastolic blood pressure of 110 mmHg or greater, or both, blood pressure is measured at two or more consecutive visits within the following 4 weeks. A stable systolic blood pressure mean of 140 mmHg or greater, a stable diastolic blood pressure mean of 90 mmHg or greater, or both may be diagnosed as hypertension (*14*, *52*, *60*).

3) Auscultatory Gap

After the first Korotkoff sound is heard on auscultation, it may disappear for a while and appear again thereafter. In this case, the first sound is considered for systolic blood pressure, but it may be underestimated without careful auscultation. In order to avoid this underestimation in the elderly, a palpation technique should be combined with sufficiently high pressure in the sphygmomanometer cuff.

4) Pseudohypertension

Pseudohypertension is recognized in those cases of advanced arteriosclerosis in which the arteries are not compressed completely by the arm cuff, thereby resulting in a blood pressure reading higher than that measured by a direct method. Osler's procedure (*61*) is reported to be useful for differentiation of pseudohypertension. Upon sufficiently strong compression with the arm cuff, Osler's positive sign is characterized by a palpable radial artery without beats, and it tends to be associated with pseudohypertension. The possibility of pseudohypertension should be considered for the patient with marked elevation of blood pressure not accompanied by target-organ damage, although pseudohypertension is reported to be infrequently recognized in such cases (*62*).

Table 5. Organ Damage and Cardiovascular Diseases

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

5) Fluctuation of Blood Pressure

Blood pressure values fluctuate significantly in all individuals, healthy or otherwise. They vary much more in the elderly than in young individuals, since in the elderly the buffer capacity for controlling blood pressure fluctuation is decreased due to suppression of baroreceptor sensitivity. Blood pressure in the elderly tends to be significantly elevated due to mental stress during conversation with physicians, although in some cases it may become almost normal after several patient/physician encounters. In cases in which elevated blood pressure is seen without target-organ disorders, the possibility of elevated blood pressure due to mental stress or white coat hypertension is suggested, and thus the blood pressure may decrease when measured by an automatic sphygmomanometer in an isolated room. Therefore, a single blood pressure measurement is not sufficient for making any decision during the management of hypertension in the elderly, and several visits at 2–4-week intervals for the measurement of blood pressure may be necessary. It is also important to measure home blood pressure (*63*). Orthostatic hypotension with a decrease in systolic blood pressure of 20 mmHg or greater is frequently encountered in the elderly, and particularly in those with myocardial infarction or transient ischemic attack, or in those who have been bedridden for a long period of time. In addition, it is important to pay attention to such complications as diabetic neuropathy and Shy-Drager syndrome, both of which can cause postural orthostatic hypotension. Therefore, blood pressure should be measured in sitting and standing positions as well as in a supine position. Postprandial hypotension is also frequently

Table 6. Stratification of Risk in Patients with Hypertension

Risk factors other than BP	BP classification		
	Mild hypertension (140–159/90–99 mmHg)	Moderate hypertension (160–179/100–109 mmHg)	Severe hypertension (≥180/≥110 mmHg)
No risk factors	Low risk	Moderate risk	High risk
Presence of risk factors beside diabetes	Moderate risk	Moderate risk	High risk
Presence of either diabetes, organ damage or cardiovascular disease	High risk	High risk	High risk

BP, blood pressure.

encountered in the elderly. In these cases, the time since the last meal should be considered at blood pressure monitoring.

6) Diagnosis of Secondary Hypertension in the Elderly

The frequency of secondary hypertension in the elderly has been reported as approximately 5%, a rate similar to that in young and middle-aged individuals (*64*). However, the content of secondary hypertension is different for the foremost group; *i.e.*, endocrinological hypertension due to aldosteronism, pheochromocytoma, Cushing syndrome, *etc.*, are infrequent in the elderly, while renal hypertension is most frequently encountered. Renovascular hypertension is a frequently occurring type of secondary hypertension in the elderly (*65*). Symptoms and findings suggestive of renovascular hypertension are listed in Table 3, and the diagnostic criteria for this disease and other types of secondary hypertension in the elderly are discussed below.

a. Renovascular hypertension

Mostly due to atherosclerosis in the elderly, and abnormal findings are recognized usually in bilateral renal arteries. Renovascular hypertension combined with or without essential hypertension should be ruled out when abdominal vascular bruits, rapid elevation of blood pressure during treatment of hypertension, decreased effect of antihypertensive drugs, or deterioration of renal function caused by angiotensin converting enzyme (ACE) inhibitors is recognized. The possibility of the disease should always be considered in new cases of hypertension in the elderly with reference to elevated plasma renin activity and hypokalemia. Special laboratory examinations such as renography, renal scintigraphy and Doppler ultrasonography may also be useful. Angiography of renal arteries and plasma renin activity measurement on samples drawn from bilateral renal veins can be used for a definitive diagnosis.

b. Renal hypertension

In the elderly, caused more frequently by chronic glomerulonephritis, diabetic nephropathy, chronic pyelonephritis, and amyloidosis than it is by those conditions in young and middle-aged hypertensives. Measurements of serum creatinine, endogenous creatinine clearance and urinalysis (hematuria, proteinuria, urinary sediments) are useful for diagnosis, and onsets of hypertension and proteinuria should be confirmed especially in the cases with renal dysfunction.

c. Primary aldosteronism

Elderly individuals frequently take herbal medications, and this can occasionally result in pseudo-aldosteronism. In order to rule out this condition, patients should be asked to describe any regularly taken herbal medications, as well as about the presence of such symptoms as weakness of the extremities, polydypsia and polyuria. Hypokalemia tends to be attributed to diuretics, but differentiation between this disease and primary aldosteronism can often be aided by confirmation of suppressed plasma renin activity and elevated plasma aldosterone level.

d. Pheochromocytoma

Because of the significantly large fluctuation of blood pressure in the elderly, paroxysmal fluctuating hypertension characteristic of pheochromocytoma tends to be overlooked. It should be ruled out when hypertension is complicated with headache, palpitation, tachycardia, perspiration, weight loss, or hyperglycemia. Pheochromocytoma can be definitively diagnosed by assay for increased blood and urinary catecholamines and catecholamines metabolites, along with abdominal CT and ^{131}I-meta-iodobenzylguanidine (MIBG) scintigraphy to confirm the presence of a tumor mass.

e. Cushing syndrome

Rarely encountered in the elderly, and suggested by its characteristic physical signs. An ectopic ACTH-producing tumor associated with lung cancer (small cell carcinoma), pancreatic cancer, *etc.*, may be encountered.

7) Classification of Severity of Hypertension

Prognosis of hypertensive patients is closely correlated not only with hypertension itself, but also with other risk factors for cardiovascular diseases, with degree of target organ disorders, and with cardiovascular complications. In clinical treatment for hypertension, the degree of severity of hypertension should be evaluated for the prognosis assessment, in addition to conducting a differential diagnosis of essential or secondary hypertension. Tables 4 and 5 show risk factors for cardiovascular diseases and organ disorders/cardiovascular diseases, respectively, in JSH 2000 (*60*). The severity of car-

Table 7. Intervention Trials for Hypertension in the Elderly

	EWPHE	HEP	SHEP	STOP	MRC II	STONE
Age (years)	≧60	60–79	≧60	70–84	65–74	60–79
No. of cases	840	884	4,736	1,627	4,396	1,632
BP at entry (mmHg)						
Systolic BP	160–239	170–280	160–219	180–230	160–209	≧160
	&	&	&	&	&	&/or
Diastolic BP	90–119	105–120	<90	≧90 or 105–120	<115	≧96
BP before treatment (mmHg)	180/101	197/100	177/77	195/102	185/91	168/98
Antihypertensives	diuretics methyldopa†	β-blockers diuretics†	diuretics β-blockers† methyldopa†	(1) β-blockers (2) diuretics	(1) β-blockers (2) diuretics	Ca A ACE-I† diuretics†
Study design	double blind	open	double blind	double blind	single blind	single blind
Follow-up period (yr)	4.7	4.4	4.5	2.1	5.8	3.0
BP after treatment (mmHg)						
Active treatment group	150/85	162/77	144/68	167/87	152/77	146/85
Placebo group	171/95	180/88	155/71	186/99	166/83	155/90
Treatment effects (relative risk)						
Cerebrovascular disease	0.64	0.58*	0.67*	0.53*	0.75*	0.43*
Coronary arterial disease	0.82	1.03	0.73*	0.87#	0.81	
Cardiac failure	0.78	0.68	0.45*	0.49*		0.32
Cardiovascular diseases, total	0.71*	0.76*	0.68*	0.60*	0.83*	0.40*

	Syst-Eur	Syst-China	STOP-2	NICS-EH	PATE-Hyp	SCOPE
Age (yr)	≧60	≧60	70–84	≧60	≧60	70–89
No. of cases	4,695	2,394	6,614	414	1,748	4,964
BP at entry (mmHg)						
Systolic BP	160–219	160–219	≧180	160–220	≧160	160–179
	&	&	&/or	&	&/or	&/or
Diastolic BP	<95	<95	≧105	<115	≧90	90–99
BP before treatment (mmHg)	174/86	170/86	194/98	172/94	▲(1) 151/84 ▲(2) 148/82	166/90
Antihypertensives	Ca A ACE-I† diuretics†	Ca A ACE-I† diuretics†	(1) β-blockers/diuretics *vs.* (2) Ca A (3) ACE-I	(1) Ca A *vs.* (2) diuretics	(1) ACE-I *vs.* (2) CaA	ARB HCTZ†
Study design	double blind	single blind	PROBE	double blind	open	double blind
Follow-up period (years)	2.0	4.0	4–6	5	3	5
BP after treatment (mmHg)						
Active treatment group	151/79	150/81	(1) 159/81	(1) 147/81	(1) 142/80	145/80
Placebo or active control group	161/84	159/84	(2) 159/80 (3) 159/82	(2) 147/79	(2) 141/78	149/82
Treatment effects (relative risk)						
Cerebrovascular disease	0.58*	0.62*	Ca A.		● 0.787	■ 0.72*
Coronary arterial disease	0.70#	1.06#	Δ 0.97		●● 0.788	
Cardiac failure	0.71	0.42	ACE-I			
Cardiovascular diseases, total	0.69*	0.63*	Δ 1.01	☆ 0.973	●●● 0.785	■■ 0.89

* Statistically significant, # myocardial infarction only, HEP, MRC: blood pressure (BP) is an estimated value, Δfatal cardiovascular accident *vs.* β-blockers/diuretics, ☆ Ca antagonists *vs.* diuretics, ● cerebrovascular death, ●● death due to heart diseases, ●●● all cardiovascular death, angiotensin converting enzyme (ACE) inhibitors *vs.* Ca antagonists, ▲ under treatment, Ca A: Ca antagonist, ACE-I: ACE inhibitors, ARB: angiotensin II receptor blocker, HCTZ: hydrochlorothiazide, ■ non-fatal stroke, ■■ primary endpoint (cardiovascular death, non-fatal stroke, non-fatal myocardial infarction). STOP, STOP-Hypertension; STOP-2, STOP-Hypertension 2; PATE-Hyp, PATE-Hypertension. †: secondary combined drug