Original Article

The Optimal Target Blood Pressure for Antihypertensive Treatment in Japanese Elderly Patients with High-Risk Hypertension: A Subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) Trial

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For hypertensive patients, it has been recommended that antihypertensive treatment strategies be chosen on the basis of the patients' conditions and age. In this sub-analysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, we aimed to compare the effects of candesartan and amlodipine on cardiovascular mortality and morbidity in Japanese elderly patients with high-risk hypertension and to determine their optimal target blood pressures (BPs). The effect of the two drugs on cardiovascular events was compared across different age subgroups (<65, 65–74, and 75–84 years) by use of Cox regression analysis. We also evaluated the associations between the achieved BP and the incidence of cardiovascular events, irrespective of the allocated drugs in multiple Cox regression analyses. The incidence of cardiovascular events was independent of the assigned treatment for each of the age subgroups. For systolic BP (SBP), cardiovascular risk increased steeply when control of SBP was inadequate (higher than 140 mmHg) for patients younger than 65 years old and those between 65 and 74 years old. Patients aged 75 to 84 years old showed a significantly increased risk when their SBP was ≥150 mmHg. For diastolic BP (DBP), the risk significantly increased for the subgroup aged 75 to 84 years when the DBP was ≥85 mmHg. The present results show that candesartan and amlodipine are equally effective in Japanese elderly patients with high-risk hypertension. Moreover, it is important to control BP levels to less than 150/85 mmHg for patients 75–84 years old. (*Hypertens Res* 2008; 31: 1595–1601)

***Key Words*: hypertension, elderly, blood pressure, Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J)**

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Introduction

Diuretics and calcium channel blockers (CCBs) are generally recommended for the treatment of hypertension in elderly patients, and many reports have provided evidence of their efficacy (*1*–*4*). However, the SCOPE trial and a sub-analysis of the LIFE study demonstrated that angiotensin II receptor blockers (ARBs) have beneficial effects for hypertension in the elderly or in patients with isolated systolic hypertension (ISH), which often affects older people (*5*, *6*). Therefore, it is important to compare the efficacy of ARBs and CCBs in senior patients.

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial demonstrated that ARB candesartan and CCB amlodipine equally suppressed total cardiovascular (CV) morbidity and mortality in high-risk Japanese hypertensive patients under strict blood pressure (BP) control (*7*). The ages of the subjects in the study varied widely, from 20 to 84 years of age, with an average age of 63.9±10.5 years.

The target BP for treatment of elderly patients with hypertension (*8*) is generally lower than 140/90 mmHg, although this target is not necessarily supported by direct evidence (*9*). Although lower target BPs are epidemiologically associated with better outcomes, one intervention trial indicated that a systolic BP (SBP) lower than 150 mmHg is optimal (*10*), whereas other results have suggested the existence of a J-shaped phenomenon (*11*, *12*). Thus, a consensus regarding the optimal target BP for elderly hypertensive patients has not yet been determined. Furthermore, it has been reported that, for some senior age categories (>80 or 85 years old), patients with lower BPs have lower survival rates compared with patients with higher BPs (*13*–*15*).

The present sub-analysis of the CASE-J trial was conducted to compare the efficacies of ARB candesartan and CCB amlodipine in high-risk Japanese elderly hypertensive patients, particularly in those aged 75 years or older. Additionally, we sought to determine an adequate target BP for elderly patients by examining associations between the achieved BP and the incidence of CV events.

Methods

Trial Design

The CASE-J trial was a prospective, randomized, open-label study with a blinded endpoint assessment comparing the efficacy of candesartan with that of amlodipine in high-risk Japanese hypertensive patients. The Ethics Committee at the Kyoto University Graduate School of Medicine approved the CASE-J trial protocol according to the principles of the Helsinki Declaration. Details of the primary results from this study have been described elsewhere (*7*).

Briefly, the trial involved 4,728 high-risk hypertensive patients. High risk was defined as the presence of any one of the following factors: severe hypertension; type 2 diabetes; history of stroke or transient ischemic attack; history of myocardial infarction, angina pectoris, or left ventricular hypertrophy; renal dysfunction; or arteriosclerotic peripheral artery disease (*16*). The ages of the patients ranged from 20 to 84 years old. After randomization, 2,364 patients were assigned to the candesartan group, and 2,364 patients were assigned to the amlodipine group (the mean of 3.2 years follow-up). The primary endpoint of the CASE-J trial was CV mortality and morbidity, which was a composite of sudden death; cerebrovascular events, including stroke or transient ischemic attack; cardiac events, including heart failure, angina pectoris, or acute myocardial infarction; renal events, including a serum creatinine concentration ≥4.0 mg/dL or a doubling of the serum creatinine concentration; and vascular events, including dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery (*7*, *16*). The CASE-J trial followed the CV events repeatedly until a patient died, and a 97.1% follow-up rate was achieved. BP was measured every 6 months after registration. According to the guideline proposed by the Japanese Society of Hypertension, two consecutive BP measurements were taken from each patient in a sitting position at a clinic (*17*).

Patients were categorized by age into three subgroups (<65, 65–74, and 75–84 years old) in the sub-analysis. Outcome measures were the same as for the CASE-J trial, which was a composite of CV mortality and morbidity. Additionally, each endpoint, which is sudden death, cerebrovascular events, cardiac events, and renal events, was independently assessed.

Statistical Methods

Patient characteristics were reported as mean±SD or percentage for each of three age subgroups. A Cox proportional hazard model stratified by diabetic status at baseline (a stratified factor for the allocation in the CASE-J trial) was used to assess differences between the candesartan and amlodipine groups in the time to a CV event for each age subgroup. The treatment effect of candesartan compared with that of amlodipine was measured using the hazard ratio (HR) and a 95% confidence interval (CI). Only the time to the first CV event was considered for the composite primary endpoint. Similarly, only the first event in each category was counted for each endpoint (sudden death, cerebrovascular events, cardiac events, or renal events).

To determine the optimal target BP levels for each of the three age groups, we targeted patients who had at least one follow-up visit without a CV event. We defined the achieved BP as the BP measured during the most recent visit before the occurrence of a CV event or as the BP obtained at the end of the follow-up. The achieved SBPs and DBPs were classified into five categories (for SBP, <130 mmHg, 130–139 mmHg, 140–149 mmHg, 150–159 mmHg, and ≥160 mmHg; for DBP, <75 mmHg, 75–79 mmHg, 80–84 mmHg, 85–89

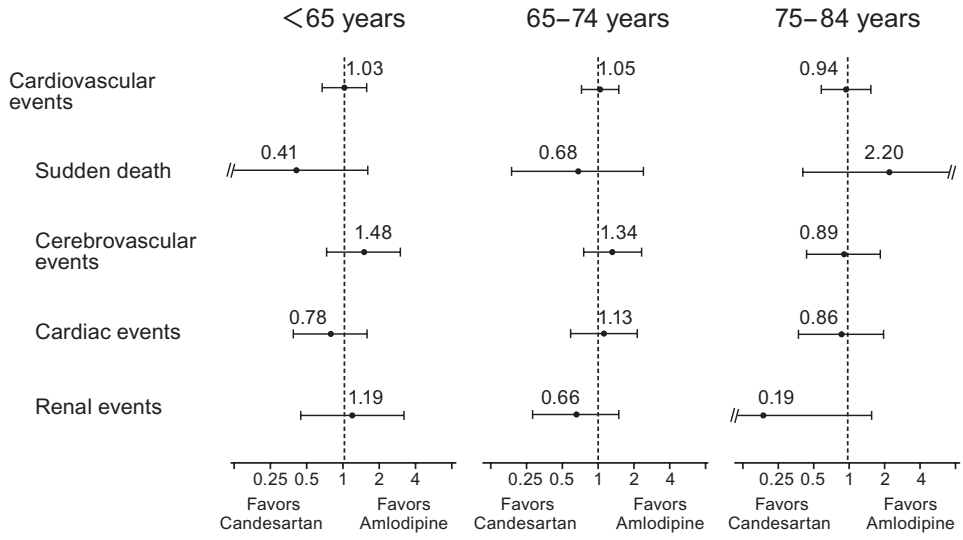

Fig. 1. *Comparison of cardiovascular mortality and morbidity by age between the two treatment-based regimens. The numbers above the circles indicate the HRs. The bars indicate the 95% confidence intervals.*

mmHg, and ≥90 mmHg). The HR for the CV event was estimated by comparing the results with those from a reference group, which included patients with a SBP level <130 mmHg and a DBP level of 75–79 mmHg. Differences in baseline characteristics, such as sex, body mass index, treatment group, antihypertensive drug use before starting the CASE-J trial, smoking, drinking, type 2 diabetes, hyperlipidemia, severe hypertension, history of cerebrovascular events, history of cardiac events, renal dysfunction, and the other achieved BP (*e.g.*, the achieved DBP in the analysis of the optimal SBP), were adjusted using multiple Cox regression analysis.

The statistical tests were two-sided, and the significance level was set at 5%. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, USA).

Results

Efficacies of Candesartan and Amlodipine for the Three Age Subgroups

There were 2,247 patients (1,132 patients in the candesartan group and 1,115 patients in the amlodipine group) in the <65-year-old subgroup, 1,705 patients (862 patients and 843 patients, respectively) in the 65–74-year-old subgroup, and 751 patients (360 patients and 391 patients, respectively) in the 75–84-year-old subgroup. Both treatments controlled BP well during the follow-up (for ages 75–84 years old, SBP/DBP at 3 years after enrollment was 137.6/74.7 mmHg in the candesartan group and 136.5/73.3 mmHg in the amlodipine group; for ages 65–74 years old, 136.1/75.5 mmHg and 135.2/75.4 mmHg; and for ages <65 years old, 135.6/79.4 mmHg and 133.0/78.7 mmHg, respectively).

Figure 1 shows the effects of the two treatment–based regimens on CV events and each endpoints. The HR for CV events for ages 75–84 years was 0.94 (95% CI=0.58–1.53; $p=0.808$), for ages 65–74, it was 1.05 (95% CI=0.73–1.51; $p=0.787$), and, for those <65, it was 1.03 (95% CI=0.67–1.56; $p=0.904$). Similarly, there were no significant differences between candesartan and amlodipine on each endpoint among the three age subgroups. Thus, the patients in each age subgroup were considered to form an observational cohort of high-risk hypertensive patients who had received antihypertensive therapy. In this context, in the following section we examine the relationship of the achieved BP levels and the CV events rate for each of the age subgroups irrespective of the allocated drug.

Associations between the Achieved BP and CV Events Rate for the Three Age Subgroups

Table 1 shows the baseline characteristics of patients with at least one follow-up visit without a CV event, and the mean BP during the follow-up. At baseline, older patients had a higher mean SBP, whereas the mean DBP was lower in older patients. There were fewer men in the subgroup for 75–84-year-olds than in the other subgroups. Table 2 shows the crude CV events rates for each BP category in each of the age subgroups, and Fig. 2 shows the corresponding adjusted HR. For patients younger than 65 years old and those 65–74, CV risk increased steeply when control of the SBP was inadequate (SBP≥140 mmHg); in particular, the HRs for SBPs≥160 mmHg were 9.30 (95% CI=4.13–20.95; $p<0.001$) for the patients aged <65 years old and 8.45 (95% CI=4.04–17.66; $p<0.001$) for those aged 65–74 years old. Meanwhile, CV risk in the subgroup of 74–85-year-olds sig-

Table 1. Baseline Characteristics and Mean Blood Pressures during Follow-Up*

	<65 years	65–74 years	75–84 years
n	2,176	1,658	719
Age (years old)	55.0±7.1	69.3±2.8	78.3±2.7
Candesartan	1,097 (50.4)	835 (50.4)	346 (48.1)
Male	1,373 (63.1)	872 (52.6)	272 (37.8)
Body mass index (kg/m^2)	25.1±3.7	24.2±3.4	23.6±3.6
Severe hypertension†	488 (22.4)	267 (16.1)	144 (20.0)
Type2 diabetes mellitus	927 (42.6)	781 (47.1)	250 (34.8)
Cerebrovascular history†	137 (6.3)	218 (13.2)	109 (15.2)
Cardiac history†	922 (42.4)	728 (43.9)	321 (44.7)
Renal dysfunction†	488 (22.4)	402 (24.3)	200 (27.8)
Hyperlipidemia	982 (45.1)	745 (44.9)	301 (41.9)
Antihypertensive drugs before starting the CASE-J trial	1,306 (60.0)	1,245 (75.1)	549 (76.4)
Current smoking	850 (39.3)	465 (28.1)	128 (17.8)
Current alcohol	1,281 (58.9)	677 (40.8)	204 (28.4)
SBP (mmHg)			
Baseline	160.7±14.8	163.2±13.5	167.6±12.2
During follow-up‡	137.6±13.5	138.6±13.7	140.0±13.5
DBP (mmHg)			
Baseline	94.3±10.9	89.3±10.7	88.9±11.4
During follow-up‡	81.2±9.4	77.4±9.1	76.2±9.1

*Data are shown as mean±SD or *n* (%) in each category. †Severe hypertension: blood pressure ≥180 and/or ≥110 mmHg; cerebrovascular history: history of stroke or transient ischemic attack; cardiac history: left ventricular hypertrophy, angina pectoris, or history of myocardial infarction; renal dysfunction: proteinuria or serum creatinine concentration ≥1.3 mg/dL. ‡Mean blood pressures during follow-up; the occurrence of a CV event (excluding baseline). CASE-J, Candesartan Antihypertensive Survival Evaluation in Japan; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, cardiovascular.

Table 2. Cardiovascular Events and Achieved Blood Pressure*

	<65 years		65–74 years		75–84 years	
	Events (*n*)	Rates† (95% CI)	Events (*n*)	Rates† (95% CI)	Events (*n*)	Rates† (95% CI)
SBP (mmHg)						
<130	15 (667)	6.6 (3.7–10.9)	18 (438)	12.0 (7.1–19.0)	8 (161)	15.3 (6.6–30.1)
130–139	21 (780)	7.9 (4.9–12.0)	28 (587)	14.0 (9.3–20.2)	18 (243)	23.0 (13.6–36.3)
140–149	17 (468)	10.8 (6.3–17.3)	28 (419)	20.4 (13.6–29.5)	12 (199)	18.5 (9.6–32.4)
150–159	15 (150)	34.8 (19.5–57.4)	18 (114)	52.2 (30.9–82.5)	9 (50)	58.9 (27.0–111.9)
≥160	18 (111)	58.8 (34.8–92.9)	20 (100)	88.6 (54.1–136.8)	13 (66)	80.1 (42.6–136.9)
DBP (mmHg)						
<75	28 (607)	13.6 (9.1–19.7)	43 (722)	17.8 (12.9–23.9)	21 (339)	19.3 (11.9–29.5)
75–79	6 (341)	5.1 (1.9–11.1)	13 (248)	15.6 (8.3–26.6)	7 (113)	19.5 (7.8–40.1)
80–84	19 (665)	8.4 (5.1–13.2)	22 (438)	14.9 (9.4–22.6)	18 (189)	29.7 (17.6–47.0)
85–89	12 (260)	14.0 (7.3–24.5)	15 (136)	35.5 (19.8–58.5)	8 (46)	57.1 (24.6–112.5)
≥90	21 (303)	22.7 (14.1–34.8)	19 (114)	66.3 (39.9–103.5)	6 (32)	81.1 (29.8–176.5)

*The achieved BP was defined as the BP measured during the most recent visit before the occurrence of a CV event, or as the BP obtained at the end of follow-up. †Rates are given per 1,000 person-years. SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; BP, blood pressure; CV, cardiovascular.

nificantly increased at SBP levels ≥150 mmHg, although the increase was milder than for the other subgroups; the HR for SBPs≥160 mmHg was 3.90 (95% CI=1.44–10.54; $p=0.007$), and for SBPs 150–159 mmHg it was 2.91 (95% CI=1.01–8.39; $p=0.048$). Regarding the DBP, a J-shaped phenomenon was observed in patients <65 years (HR for

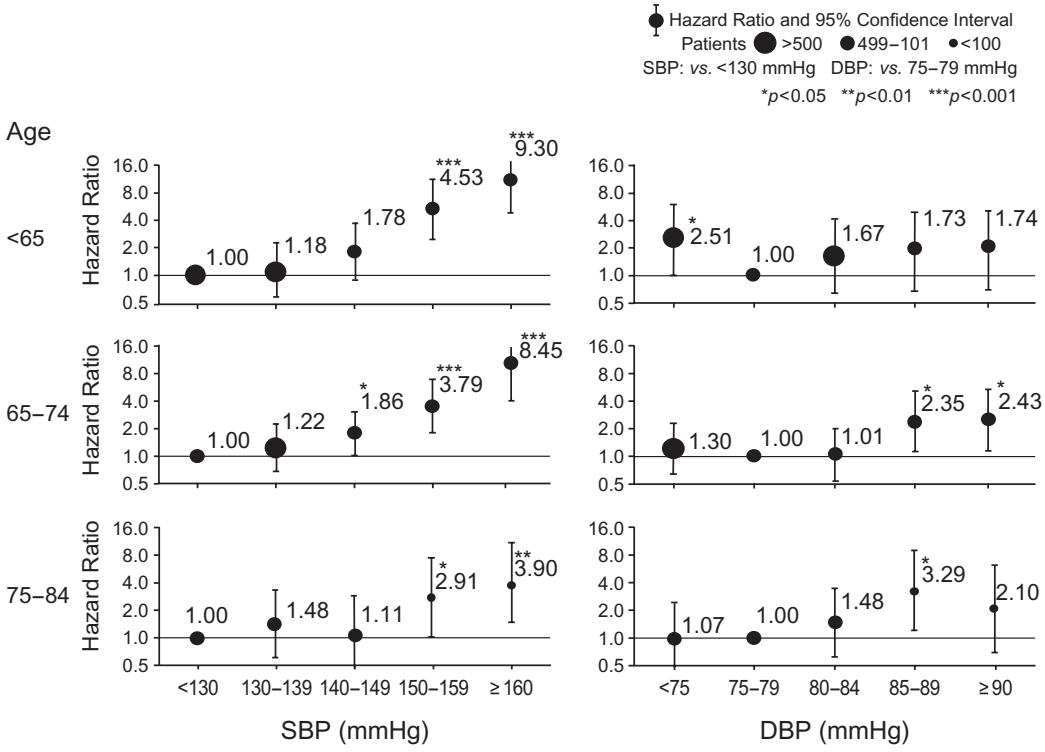

Fig. 2. *Adjusted hazard ratio of cardiovascular mortality and morbidity by age and the achieved blood pressure level. Sex, body mass index, treatment group, antihypertensive drug use before starting the CASE-J trial, smoking, drinking, type 2 diabetes, hyperlipidemia, severe hypertension, history of cerebrovascular events, history of cardiac events, renal dysfunction, and the other achieved BP (e.g., the achieved DBP in case the analysis of the optimal SBP) were adjusted using multiple Cox regression analysis. *p < 0.05, **p < 0.01, ***p < 0.001.*

DBP < 75 mmHg = 2.51; 95% CI = 1.03–6.10; $p = 0.042$), but not in patients aged 75–84 years.

Discussion

CCBs are commonly used for the treatment of elderly hypertensive patients (*1–4*). Recently, ARBs have also been used for elderly patients or patients with ISH (*5*, *6*). Hardly any reported studies, however, have directly compared the effects of CCBs and ARBs in Asian elderly patients (*18*). In the present subanalysis, the effects of lowering BP were comparable in the two treatment groups. When patients were divided into three age subgroups (younger than 65, 65 to 74, and 75 to 84 years old), both treatments exhibited significant antihypertensive effects in each of the subgroups, indicating that the ARB-based and CCB-based regimens are equally beneficial in terms of their hypotensive efficacy as well as in reducing the risk of CV events. Therefore, these data indicate that, similar to CCBs, ARBs are beneficial as first-line agents for elderly patients, because of their wide range of indications in hypertensive patients with co-morbidities, the lack of unfavorable effects on metabolism, and their antidiabetic properties (*19*).

A lower target BP is not necessarily beneficial in senior patients, as was described in the review by August (*9*). Little clear evidence has been reported regarding target BPs for senior patients receiving antihypertensive treatment. Epidemiologically, it is well known that the risks for BP and CV are linearly related and that elderly people with lower BPs are at less risk for CV events (*20*). A sub-analysis of the SHEP study, however, showed that the incidence of stroke was less frequent in patients with SBP levels lower than 150 mmHg compared with those with SBP levels lower than 140 mmHg (*10*) and that the risk of stroke increased in patients with DBP levels lower than 55 mmHg (*21*). Additionally, sub-analysis of the HOT study, which examined patients aged 65 years or older, did not identify any significant differences in the CV risk of groups with different BPs obtained in response to antihypertensive treatment with felodipine (*22*).

The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) was recently conducted to compare the 2-year effect of a strict treatment to maintain SBP below 140 mmHg (group A) with that of a mild treatment to maintain SBP between 140 and 160 mmHg (group B) in Japanese hypertensive patients. Among patients aged 65 years or older, no significant difference was observed

in the incidence of CV events between group A (a mean SBP of 135.9 mmHg after 2 years) and group B (a mean SBP of 145.6 mmHg after 2 years). However, among patients aged 75 years or older, group B had a lower incidence of CV events compared with group A, although the difference was not significant (*23*, *24*). These results suggest that the target SBP should be lower than 150 mmHg, particularly in patients aged 75–84 years old. The Japanese treatment guidelines for hypertension recommend both using an intermediate target BP of 150/90 mmHg for elderly patients over 75 years old and attempting to lower the patient's BP to 140/90 mmHg after reaching this intermediate target, if possible, while closely observing the condition of the patient (*25*).

In the present subanalysis of the CASE-J trial, it is thought that "the lower, the better" applies to the achieved SBP, particularly in younger, Japanese, high-risk hypertensive patients. But, in those aged 75 years or older, the CV risk for an SBP of 140–149 mmHg did not change compared with that for SBPs lower than 130 mmHg. This result is consistent with a rightward shift of risk threshold for SBP with age, which was observed with horizontal spline regression analysis of the data from the Framingham study by Port *et al*. (*26*). Thus, the results of the present sub-analysis support the idea of using SBP targets lower than 150 mmHg for hypertensive patients older than 75 years. In addition, the results of the study for the Hypertension in the Very Elderly Trial (HYVET) were reported recently (*27*). In HYVET, 3,845 patients who were 80 years of age or older and had a sustained SBP of 160 mmHg or more were randomly assigned to either an active treatment group (given indapamide with or without perindopril) or a placebo group. HYVET provided evidence that active treatment in the very elderly, aimed at achieving a target BP of 150/80 mmHg, is beneficial and is associated with reduced risks of heart failure, death from stroke, and death from any cause. This result is compatible with our results. However, since nearly 50% of such patients reached the target BP in HYVET, it is not yet clear whether further reduction is beneficial. A J-shaped phenomenon was observed in patients aged <65, whereas DBPs of 75–79 mmHg yielded the lowest CV risk in the oldest age subgroup. This may indicate that the patients whose DBPs were much lower than expected had advanced arteriosclerosis. However, we think that this remains a matter of future discussion. Oates and his coworkers have previously noted that special attention should be paid to patients aged 80 years or older (*13*) because the prognosis for these patients with lower BPs is poorer than that for patients with higher BPs (*28*).

We must mention some limitations of the present study. First, examination of the optimal target BP for hypertensive patients was post hoc. The CASE-J trial was not designed to determine optimal target BPs. Second, because of the smaller number of CV events in CASE-J trial compared with other trials conducted in Western countries, the statistical power may be limited. Finally, the present study examined the association between the optimal target BP and the rate of CV events in the specific setting of high-risk Japanese hypertensive patients.

Currently, the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study, which compares patients with SBPs lower than 140 mmHg with those with SBPs lower than 150 mmHg, is underway in Japan (*29*). The results of this study may further clarify the appropriate target BPs for elderly patients being treated for hypertension.

In conclusion, the ARB candesartan and the CCB amlodipine are equally effective in Japanese elderly patients with high-risk hypertension. Moreover, it is important to control BP levels to less than 150/85 mmHg for patients 75–84 years old.

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