ORIGINAL ARTICLE

Association between blood pressure and disability-free survival among community-dwelling elderly patients receiving antihypertensive treatment

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A reduction of elevated blood pressure (BP) is an important treatment goal in elderly hypertensive patients. However, excessive reduction of systolic BP (SBP) and/or diastolic BP (DBP) might be harmful in such patients. We investigated whether this was the case with regard to risk of incident disability or death in community-dwelling elderly subjects. We analyzed 570 patients receiving antihypertensive treatment aged 65–94 years. The endpoint was the composite outcome of incident disability, defined as first certification of a support/care need or death. Relationships among each of the four classes of SBP or DBP and the risk of incident disability or death were estimated using the Cox proportional hazards model. Over four years, 77 (13.5%) incident disabilities or deaths occurred. After adjustment for age, sex and variables selected according to their univariate analysis P -value <0.20 , the risk of events was significantly higher in subjects with baseline SBP <120 mm Hg (hazard ratio (HR) = 2.81, $P=0.023$) and ≥ 160 mm Hg (HR = 4.32, $P<0.001$), compared with subjects with baseline SBP of 140–159 mm Hg, who showed the lowest incidence of events. This J-curve relationship was observed in very elderly patients (≥ 75 years) but not in younger patients. Patients with SBP <120 mm Hg tended to have a higher risk of incident disability caused by cerebral events, and those with SBP ≥ 160 mm Hg had a higher risk of incident disability caused by falls/bone fractures. These observations indicate that excessive BP reduction could cause discontinuance of disability-free survival in community-dwelling elderly patients.

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INTRODUCTION

Providing high-quality treatment to older adults with elevated blood pressure (BP), which is aimed at both the prevention of cardiovascular/cerebrovascular (CV) morbidity/mortality and the promotion of cognitive/physical function, is growing in importance because of the improved survival of patients with hypertension into old age. Many large-scale intervention trials, including a meta-analysis of eight large-scale intervention trials in elderly hypertensive patients aged ≥ 60 years,¹ recent clinical trials limited to elderly patients aged ≥ 60 years,^{2–7} and Hypertension in the Very Elderly Trial,⁸ which enrolled those aged ≥ 80 years, have revealed significant reductions in CV morbidity/mortality with antihypertensive treatment. By contrast, several long-term interventional trials also have demonstrated J-curve phenomena for the relationships of achieved systolic BP (SBP),^{3,9–11} diastolic BP (DBP)^{12,13} and both¹⁴ with CV morbidity/mortality in elderly hypertensive patients with various CV conditions, including coronary heart disease. Moreover, hypertension is also known to be linked to frailty in the elderly.^{15,16} In Japan, the public Long-Term Care Insurance system provides services to

disabled older adults who have been certified as requiring support (levels 1–2) or care (levels 1–5).^{17,18} However, few studies have examined the association of BP with disability-free survival in community-dwelling elderly hypertensive patients. Therefore, we sought to determine the appropriate BP for elderly patients receiving antihypertensive treatment by examining the associations between baseline BP and the risk of incident disability or death.

METHODS

Subjects

The target area was a town with a population of $\sim 30\,000$ in Ishikawa, Japan. The proportion of elderly people aged ≥ 65 years in the total population was 19.6% (2010). The local government provides a public health center-based annual health check-up to these elderly subjects. In April 2008, of all 4050 community-dwelling uncertified elderly subjects aged ≥ 65 years, 1091 supplied complete information at the time of their health check-ups. Of those subjects, 62.6% were hypertensive, defined as BP $\geq 140/90$ mm Hg or receiving current antihypertensive treatment ($n=683$). Among hypertensive subjects,

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84.8% were receiving antihypertensive treatment ($n=579$)¹⁹ and were included in our study.

Baseline examinations

A self-administered questionnaire, which included medical history and time since the last meal,²⁰ was completed at baseline. The blood condition was defined as fasting if blood was collected more than 8 h after the last meal. Chronic kidney disease was defined as an estimated glomerular filtration rate, calculated using the modification of diet in renal disease equation with coefficients modified for Japanese patients,²¹ of $<60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. Diabetes mellitus was defined as fasting blood glucose $\geq 7.0 \text{ mmol l}^{-1}$ (126 mg dl^{-1}), non-fasting glucose $\geq 11.1 \text{ mmol l}^{-1}$ (200 mg dl^{-1}), HbA1c $\geq 6.5\%$ by a standardized method, or the use of hypoglycemic agents and/or insulin.²² Dyslipidemia was defined as fasting serum total cholesterol $\geq 220 \text{ mg dl}^{-1}$, triglycerides $\geq 150 \text{ mg dl}^{-1}$, HDL cholesterol $<40 \text{ mg dl}^{-1}$, or use of the lipid-lowering agents.²³ Hyperuricemia was defined as serum uric acid $\geq 7.0 \text{ mg dl}^{-1}$ in men and $\geq 6.0 \text{ mg dl}^{-1}$ in women or the use of uric acid-lowering agents.²⁴ Hypoalbuminemia was defined as serum albumin $<4 \text{ g dl}^{-1}$.²⁵

Measurements of baseline BP were performed based on the guidelines for the management of hypertension,²⁶ by trained observers using a mercury sphygmomanometer.

Analysis

The primary endpoint of the present study was the composite outcome of incident disability, defined as the first certification for any level of support/care need, or death. Support/care need was judged by the Regional Comprehensive Support Center (RCSC) of the local government, on the basis of the investigation form completed by interview by the RCSC staff and of the doctor's assessment form completed by the physician in charge.¹⁷ We also examined the first disease causing the need for support/care need on the papers of all certificated persons, and we classified the diseases into four categories, namely cerebral events, falls/bone fractures, dementia/depression and other diseases. Baseline SBP and DBP were each classified into four classes (SBP: <120 , 120 – 139 , 140 – 159 and $\geq 160 \text{ mm Hg}$; DBP: <70 , 70 – 79 , 80 – 89 and $\geq 90 \text{ mm Hg}$).^{3,9} The results for continuous variables in baseline clinical characteristics were compared using Mann–Whitney *U*-analysis. Discrete variables were compared by χ^2 -analysis. Comparisons of data among the groups of SBP and DBP were performed by the Kruskal–Wallis test with Bonferroni's correction. Proportional hazards regression (Cox) models²⁷ were used to estimate the unadjusted hazard ratio (HR) of incident disability or death with 95% confidence intervals (CIs) by age, sex, risk factors shown in Table 1, and classes of SBP or DBP. Multivariate models were used to adjust for potential confounding factors at $P<0.20$.²⁸ Using Cox regression, the HR for each baseline BP (SBP: 140 – 159 mm Hg ; DBP: 70 – 79 mm Hg) and the corresponding 95% CI were calculated. Data were analyzed using IBM-SPSS software (v. 18.0, IBM–SPSS, Chicago, IL, USA).

Ethical considerations

The study was formally approved by the Clinical Research Ethics Committee of Kanazawa Medical University. It was also approved by official agreement between the mayor of the town and us. We received baseline data and information of new onset of disability or death, which were irreversibly anonymized, during the follow-up period from the RCSC of the town.

RESULTS

Study population

Out of the 579 treated hypertensive elderly patients, nine moved out of the area during the four-year period and were also excluded. A total of 570 subjects (225 men and 345 women) were included in this analysis. Table 1 shows the baseline clinical characteristics of all of the patients at study entry. The mean $\pm$ s.d. age of subjects was 74.2 ± 6.1 years (65–94 years). The percentage of patients aged ≥ 75 years was 46.3% (Table 1).

Disability and death

A total of 77 subjects (33.8/1,000 person-years) either became disabled or died. These patients included 62 cases of incident disability (27.2/1,000 person-years) and 15 deaths without disability (6.6/1,000 person-years). Seven patients died after incident disability (3.1/1,000 person-years), and a total of 22 died (9.6/1,000 person-years) during the period (Table 1). Compared with patients with disability-free survival, patients with incident disability or death showed a significantly higher mean age and higher female sex rate (Table 1). The incidence rates of the composite outcome of incident disability and death for patients with baseline SBP <120 , 120 – 139 , 140 – 159 and $\geq 160 \text{ mm Hg}$ were 45.9, 34.7, 19.7 and 75.6/1,000 person-years, respectively, while those for patients with baseline DBP <70 , 70 – 79 , 80 – 89 and $\geq 90 \text{ mm Hg}$ were 37.5, 33.3, 33.3 and 32.9/1,000 person-years, respectively. The Kruskal–Wallis test revealed higher incidences of a past history of heart disease in the lower SBP groups and higher incidences of past histories of stroke, chronic kidney disease and diabetes mellitus in the lower DBP groups (Table 2).

Age, female sex, past history of stroke, past history of heart disease, chronic kidney disease, diabetes mellitus, hyperuricemia, and hypoalbuminemia were associated with the risk of incident disability or death in univariate analyses and were sequentially included in the final Cox proportional hazards regression model. The relationship between baseline SBP or DBP and the incidence of events is shown in Figure 1. After adjustment for these factors, the HR for disability or death over four years was significantly higher in subjects with baseline SBP $<120 \text{ mm Hg}$ (HR = 2.81, 95% CI = 1.15–6.82, $P=0.023$) and $\geq 160 \text{ mm Hg}$ (HR = 4.32, 95% CI = 1.90–9.83, $P<0.001$), compared with subjects with baseline SBP of 140 – 159 mm Hg , which yielded the lowest incidence of events (Figure 1). After adjustment for the same factors, the HR for disability alone was also significantly higher both in subjects with baseline SBP $<120 \text{ mm Hg}$ (HR = 3.37, 95% CI = 1.18–9.60, $P=0.023$) and in those with baseline SBP $\geq 160 \text{ mm Hg}$ (HR = 4.09, 95% CI = 1.03–8.16, $P=0.043$), compared with control subjects (Figure 1). Compared with the same control group, the HR for all-cause death was significantly higher in those with baseline SBP $\geq 160 \text{ mm Hg}$ (HR = 6.10, 95% CI = 1.33–19.5, $P=0.017$) but not in those with $<120 \text{ mm Hg}$. There was no difference in HR among each of the baseline DBP classes (Figure 1).

In the subgroup of patients aged ≥ 75 years, subjects with baseline SBP $<120 \text{ mm Hg}$ or $\geq 160 \text{ mm Hg}$ had a significantly higher risk of all events (SBP $<120 \text{ mm Hg}$: HR = 3.30, 95% CI = 1.18–9.21, $P=0.023$; SBP $\geq 160 \text{ mm Hg}$: HR = 4.41, 95% CI = 1.62–12.0, $P=0.004$) (Figure 2) and of incident disability alone (SBP $<120 \text{ mm Hg}$: HR = 3.61, 95% CI = 1.12–12.0, $P=0.032$; SBP $\geq 160 \text{ mm Hg}$: HR = 3.67, 95% CI = 1.20–11.2, $P=0.022$), compared with subjects with baseline SBP of 140 – 159 mm Hg . There were no differences in HRs in the subgroup of patients aged 65–74 years (Figure 2).

Among the 62 disabled subjects, 11 patients were disabled owing to cerebral events, 15 owing to falls/bone fractures, 17 owing to dementia/depression, and 19 owing to other diseases. Of the 11 patients disabled owing to cerebral events, 10 did not have a previous history of stroke at the baseline examination. Conditional Cox hazard analysis revealed that the HR for disability owing to cerebral events was increased in subjects with baseline $<120 \text{ mm Hg}$ (HR = 27.3, 95% CI = 1.09–684, $P=0.044$), while that for disability owing to falls/bone fractures was increased in patients with SBP $\geq 160 \text{ mm Hg}$ (HR = 25.0, 95% CI = 1.61–388, $P=0.021$), compared with the control group (Figure 3).

Table 1 Baseline characteristics of the total population with antihypertensive treatment

					Death		
	Total, n = 570	Disability or death, n = 77	Disability, n = 62	Total, n = 22	Death with disability, n = 7	Death without disability, n = 15	Disability-free survival, n = 493
<i>Demographics</i>							
Age (years)	74.2 ± 6.1	79.5 ± 5.6***	80.6 ± 5.1***	78.1 ± 6.9**	84.3 ± 4.9***	75.1 ± 5.7	73.4 ± 5.7
Age > 75: n (%)	264 (46.3%)	63 (81.8%)*	55 (88.7%)*	15 (68.2%)#	7 (100%)*	8 (53.3%)	201 (40.8%)
Females: n (%)	345 (60.5%)	54 (70.1%)#	46 (74.2%)*	10 (45.5%)	2 (28.6%)	8 (53.3%)	291 (59.0%)
BMI (kg m ⁻²)	23.5 ± 3.2	23.5 ± 3.9	23.4 ± 3.8	23.0 ± 4.3	21.0 ± 3.2#	23.9 ± 4.5	23.5 ± 3.1
<i>Complications</i>							
Past history of stroke: n (%)	31 (5.5%)	8 (10.5%)#	4 (6.5%)	5 (22.7%)*	1 (14.3%)	4 (26.7%)*	23 (4.7%)
Past history of heart disease: n (%)	100 (17.9%)	23 (30.3%)*	20 (32.3%)*	4 (18.2%)	1 (14.3%)	3 (20.0%)	77 (15.6%)
Chronic kidney disease: n (%)	216 (37.9%)	37 (48.1%)#	33 (53.2%)*	7 (31.8%)	3 (42.9%)	4 (26.7%)	179 (36.3%)
Diabetes mellitus: n (%)	125 (21.9%)	23 (29.9%)#	22 (35.5%)*	4 (18.2%)	3 (42.9%)#	1 (6.7%)	102 (20.7%)
Dyslipidemia: n (%)	298 (52.3%)	43 (55.8%)	36 (58.1%)	11 (50.0%)	4 (57.1%)	7 (46.7%)	255 (51.7%)
Hyperuricemia: n (%)	114 (20.0%)	17 (22.1%)	12 (19.4%)	7 (31.8%)#	2 (28.6%)	5 (33.3%)#	97 (19.7%)
Hypoalbuminemia: n (%)	30 (5.3%)	12 (15.6%)*	9 (14.5%)*	7 (31.8%)*	4 (57.1%)*	3 (20.0%)*	18 (3.7%)
<i>Blood pressure at entry</i>							
Systolic (mmHg)	137.2 ± 14.3	139.3 ± 16.4	137.6 ± 15.9	141.7 ± 16.7	132.0 ± 11.5	146.2 ± 17.1*	136.9 ± 13.9
< 120: n (%)	49 (8.6%)	9 (11.7%)*	8 (12.9%)*	2 (9.1%)	1 (14.3%)	1 (6.7%)	40 (8.1%)
120–139: n (%)	288 (50.5%)	40 (50.5%)*	35 (56.5%)*	10 (45.5%)	5 (71.4%)	5 (33.3%)	248 (50.3%)
140–159: n (%) ^a	190 (33.3%)	15 (19.5%)	11 (17.7%)	5 (22.7%)	1 (14.3%)	4 (26.7%)	175 (35.5%)
≥ 160: n (%)	43 (7.5%)	13 (16.9%)*	8 (12.9%)*	5 (22.7%)*	0 (0.0%)	5 (33.3%)*	30 (6.1%)
Diastolic (mmHg)	78.4 ± 9.0	78.2 ± 9.4	77.3 ± 9.3	80.1 ± 8.5	76.0 ± 6.2	81.9 ± 8.9	78.4 ± 9.0
< 70: n (%)	80 (14.0%)	12 (15.6%)	11 (17.7%)	2 (9.1%)	1 (14.3%)	1 (6.7%)	68 (13.8%)
70–79: n (%) ^b	203 (35.6%)	27 (35.1%)	22 (35.5%)	8 (36.4%)	3 (42.9%)	5 (33.3%)	176 (35.7%)
80–89: n (%)	211 (37.0%)	28 (36.4%)	23 (37.1%)	8 (36.4%)	3 (42.9%)	5 (33.3%)	183 (37.1%)
≥ 90: n (%)	76 (13.3%)	10 (13.0%)	6 (9.7%)	4 (18.2%)	0 (0.0%)	4 (26.7%)	66 (13.4%)

Abbreviation: BMI, body mass index.

Results are expressed as mean ± s.d., or n (%). Mann–Whitney *U*-analysis or χ^2 -analysis were used. #*P* < 0.20, **P* < 0.05, ***P* < 0.01 and ****P* < 0.001 vs. group with disability-free survival.^aReference SBP.^bReference DBP.**Table 2** Baseline characteristics by each quartile of SBP and DBP pressure.

	SBP				Kruskal– Wallis, P-value	DBP				Kruskal– Wallis, P-value
	< 120, n = 49	120–139, n = 288	140–159, n = 190 ^a	≥ 160, n = 43		< 70, n = 80	70–79, n = 203 ^b	80–89, n = 211	≥ 90, n = 76	
<i>Demographics</i>										
Age (years)	73.3±5.6	74.8±6.2*	73.4±5.7	75.4±6.7 [#]	*	75.6±6.4	74.8±6.3	73.8±5.7 [#]	72.5±5.7**	*
Age > 75 years: <i>n</i> (%)	23 (46.9%)	140 (48.6%) [#]	78 (41.1%)	23 (53.5%) [#]		43 (53.8%)	100 (49.3%)	93 (44.1%)	28 (36.8%) [#]	[#]
Females: <i>n</i> (%)	29 (59.2%) [#]	168 (58.3%) [#]	122 (64.2%)	26 (60.5%)		48 (60.0%)	123 (60.6%)	130 (61.6%)	44 (57.9%)	
BMI (kg m ⁻²)	23.9±2.7	23.2±3.2 [#]	23.7±3.3	24.0±3.3	[#]	23.3±3.6	23.2±3.2	23.8 ±3.0*	23.9±3.1 [#]	[#]
<i>Complications</i>										
Past history of stroke: <i>n</i> (%)	4 (8.2%)	17 (5.9%)	8 (4.2%)	2 (4.7%)		2 (2.5%)	7 (3.4%)	19 (9.0%)*	3 (3.9%)	*
Past history of heart disease: <i>n</i> (%)	14 (28.6%)*	58 (20.1%)*	25 (13.2%)	3 (7.0%)	**	22 (27.5%)*	34 (16.7%)	33 (15.6%)	11 (14.5%)	[#]
Chronic kidney disease: <i>n</i> (%)	23 (45.9%) [#]	117 (40.6%) [#]	61 (32.1%)	15 (34.9%)	[#]	41 (51.3%)**	70 (34.5%)	71 (33.6%)	34 (44.7%) [#]	*
Diabetes mellitus: <i>n</i> (%)	10 (20.4%)	68 (23.6%)	39 (20.5%)	8 (18.2%)		28 (35.0%)*	49 (24.1%)	40 (19.0%)	8 (10.5%)*	**
Dyslipidemia: <i>n</i> (%)	26 (53.1%)	151 (52.4%)	101 (53.2%)	20 (46.5%)		43 (53.8%)	109 (53.7%)	106 (50.2%)	40 (52.6%)	
Hyperuricemia: <i>n</i> (%)	8 (16.3%) [#]	33 (11.5%)	18 (9.5%)	9 (20.9%)*	[#]	7 (8.8%)	26 (12.8%)	23 (10.9%)	12 (15.8%)	
Hypoalbuminemia: <i>n</i> (%)	3 (5.1%)	17 (5.9%)	7 (3.7%)	3 (7.9%)		8 (10.0%) [#]	9 (4.4%)	11 (5.2%)	2 (2.6%)	[#]

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Results are expressed as mean ± s.d., or n (%). Mann–Whitney *U*-analysis or χ^2 -analysis was used.^aReference SBP.^bReference DBP. Comparisons of data among classes of SBP and DBP were performed by Kruskal–Wallis test with Bonferroni's correction. #*P* < 0.20, **P* < 0.05 and ***P* < 0.01.

Figure 1 Relationship between baseline blood pressure (BP) and the hazard ratio of incident disability or death. Data are presented with relative risks and 95% confidence intervals with reference to patients with baseline systolic BP (SBP) of 140–159 mm Hg and patients with baseline diastolic BP (DBP) of 70–79 mm Hg. * $P < 0.05$; ** $P < 0.01$.

DISCUSSION

The present study newly revealed an emerging profile of treated hypertension and the discontinuance of disability-free survival in community-dwelling elderly subjects. The advantages of the present study are as follows: Long-Term Care Insurance system certification is based on strictly established, uniform criteria throughout Japan,^{17,18} and the included information enabled a very high follow-up rate in the present study (98.4%). Another advantage was that having information about the causal disease for incident disability enabled clarification of whether the risk of incident disability owing to particular causal diseases was higher in any of the SBP groups.

Practitioner's trial on the efficacy of antihypertensive treatment in elderly patients with hypertension II (PATE-Hypertension-II)⁹ and ONTARGET¹⁰ revealed that elderly patients with higher achieved BP (≥ 160 mm Hg) had significantly higher incidences of CV events. The present study revealed that patients with baseline SBP ≥ 160 mm Hg had a significantly higher risk not only of total death and also for incident disability, compared with the control group (Figure 1). We also observed an association of baseline SBP ≥ 160 mm Hg with an increased risk of incident disability owing to falls/bone fractures (Figure 3). Although the precise reason for the association are not

clear, one of the possible explanations is hypertension-induced development of white matter lesions,²⁹ which increase the risk for incident bone fracture in community-dwelling elderly subjects.³⁰ Moreover, a sub-analysis of Hypertension in the Very Elderly Trial revealed that sufficient reduction of BP in very old patients with SBP ≥ 160 mm Hg was associated with a significant reduction in fracture rate.³¹ The precise mechanism for the association should be clarified in the future.

The present study clearly detected J-curve phenomena for the risk of incident disability or death, as well as for incident disability alone (Figure 1). The J-curve phenomenon appeared in patients aged ≥ 75 years but not in younger patients (Figure 2). The SBP range at the HR nadir of 140–159 mm Hg observed in the present study was somewhat higher than the target BP recommended for elderly patients aged ≥ 75 years by the Japanese treatment guidelines for hypertension, which include both using an intermediate target BP of $< 150/90$ mm Hg and attempting to lower the patient's BP to $< 140/90$ mm Hg if possible.²⁶ However, a lower target BP is not necessarily beneficial in elderly patients.³² Indeed, in many large-scale clinical studies in elderly hypertensive patients aged ≥ 60 years, the mean BP achieved by antihypertensive treatment was 141–152/77–85 mm Hg.^{2–8} Moreover,

Figure 2 Relationship between baseline blood pressure (BP) and hazard ratio of incident disability or death in patients <75 years or ≥75 years. Keys as in Figure 1.

Figure 3 Relationship between baseline systolic blood pressure (SBP) and hazard ratio of incident disability according to the four categories of first causal disease for support/care need on doctor's assessment form. Keys as in Figure 1.

a sub-analysis of Systolic Hypertension in the Elderly Program (SHEP) (mean age 72 years) showed that participants whose in-trial SBP was lower than 160 mmHg or 150 mmHg experienced

significant reductions in total stroke incidence compared with those with SBP higher than the respective thresholds, although the reduction of stroke incidence in those with SBP <140 mmHg was

not significant compared with that in those with SBP ≥ 140 mm Hg,³³ indicating that reduction of stroke incidence could be achieved most effectively in those with in-trial SBP of 140–159 mm Hg. Furthermore, among the Japanese elderly hypertensive patients (≥ 75 years) in the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS), which compared the two-year effects of strict treatment to maintain SBP less than 140 mm Hg (group A) with those of mild treatment to maintain SBP between 140 and 160 mm Hg (group B), group B had a lower incidence of CV events compared with group A, although the difference was not significant.³⁴ In addition to these findings, elevated BP (≥ 140 mm Hg) is not necessarily associated with a decreased survival rate in frail elderly subjects because elevated BP was independently associated with a lower risk of death (HR, 0.38) in subjects who could not complete a walk test (6 m), but it was associated with greater risk of mortality compared with subjects without elevated BP (HR, 1.35) among faster walkers (≥ 0.8 m s⁻¹).³⁵ Because the mean age of patients certified with disability in the present study was 80.6 years (Table 1), all of these reports might be compatible to the present observation that patients with SBP of 140–159 mm Hg experienced the lowest risk for events.

PATE-Hypertension³ and PATE-Hypertension II⁹ demonstrated J-curve phenomena for CV morbidity/mortality in elderly patients (≥ 75 years) with a J-curve point for SBP of < 120 mm Hg, similar to that in the present study (Figures 1 and 2). A sub-analysis of ONTARGET also demonstrated a J-curve phenomenon for CV morbidity/mortality in high-risk patients with a mean age of 66 years, with a J-curve point for SBP of < 130 mm Hg.¹⁰ The Japanese Survey for Valsartan In Deployment (J-VALID) also demonstrated a significant systolic J-curve phenomenon, with a J-curve point for SBP of < 120 mm Hg in elderly patients (≥ 75 years).¹¹ J-curve phenomena in these studies were observed for cardiac events but not for stroke. In contrast, a sub-analysis of the International Verapamil SR-Trandolapril Study (INVEST) in patients with hypertension and coronary heart disease also showed J-curve phenomena for the primary endpoint in older age groups (70– < 80 years, ≥ 80 years) with SBP and DBP at the HR nadirs of 140 mm Hg and 70 mm Hg, respectively, for the oldest age group (≥ 80 years).¹⁴ The primary endpoint of INVEST included not only all-cause death and nonfatal myocardial infarction but also nonfatal stroke.¹⁴ This result, as well as those of SHEP,³³ are partly compatible with our study, in which a J-curve phenomenon was observed for incident disability at least partly owing to cerebral events (Figure 3). In contrast, another sub-analysis of SHEP¹² and a sub-analysis of the Systolic Hypertension in Europe in patients with concomitant coronary heart disease¹³ also demonstrated J-curve phenomena for the relationship of achieved DBP with J-curve points of < 60 mm Hg and < 70 mm Hg, respectively. However, there were no differences in HR among the baseline DBP classes in the present study. Nevertheless, the observations in these previous reports, as well as in the present study, indicate the importance of avoiding excessive BP reduction because low BP can often be related to the unexpected manifestation of a J-curve paradox in very elderly hypertensive subjects with underlying chronic debilitating illnesses.³⁶ Indeed, higher incidences of CV events and risk factors for CV were observed in the groups with lower SBP or DBP in the present study (Table 2).

This study had several limitations. First, the analyses performed in the present study could not address the causality of excess BP reduction in the increased risk of disability. The patients with baseline SBP < 120 mm Hg might have originally been at high risk for frailty because SBP is known to decrease in years immediately before

dementia onset in community-dwelling hypertensive elderly subjects.³⁷ The risk of excess BP reduction in very elderly hypertensive patients should be assessed in the future in randomized, controlled trials that compare disability-free survival between hypertensive very elderly patients whose SBP is controlled at higher levels than 120 mm Hg and patients whose SBP is sustained at < 120 mm Hg. Second, in light of the single community model, care must be taken in interpreting the results of the present study, and further evaluation in multi-regional trials is needed. Third, stratified sampling of incident disability or death according to the kinds of antihypertensive drugs used, including renin–angiotensin blockers, is also needed in future studies because the renin–angiotensin system is thought to have a crucial role in aging and/or frailty.³⁸ Finally, because of the small number of normotensives and untreated hypertensives in the present study, precise analysis was statistically limited in these groups and should be examined in the future.

In conclusion, the present study clearly identified J-curve phenomena for the risk of incident disability or death in community-dwelling very elderly patients (≥ 75 years) receiving antihypertensive treatment, indicating that having a low target BP could cause exacerbation of frailty in elderly patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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