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ORIGINAL ARTICLE

Relationship between the achieved blood pressure and the incidence of cardiovascular events in Japanese hypertensive patients with complications: a sub-analysis of the CASE-J trial

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Various guidelines for hypertension specify that the target blood pressure (BP) should be below 140/90 mm Hg and that strict control is recommended for patients with cardiovascular risk factors. We examined the relationship between the achieved BP and the incidence of cardiovascular events in hypertensive patients with complications as a sub-analysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial. A total of 4703 patients were evaluated for efficacy in the CASE-J trial. In this sub-analysis, 4553 patients had at least one follow-up visit without any cardiovascular events. We examined the relationship between the achieved BP and cardiovascular events in hypertensive patients with type II diabetes mellitus (DM), chronic kidney disease (CKD) or left ventricular hypertrophy (LVH) at baseline. Possible baseline confounders were adjusted by using the multiple Cox regression model. A higher achieved BP was associated with an increased risk of cardiovascular events in hypertensive patients with complications (DM, CKD or LVH). In patients with LVH, who achieved systolic/diastolic BP (SBP/DBP) <130/75–79 mm Hg, the risk of cardiovascular events was reduced to the same level of SBP/DBP <130/75–79 mm Hg in those without LVH. However, the risks of cardiovascular events in patients with DM or CKD, who achieved SBP/DBP <130/75–79 mm Hg, were still significantly higher than in those without DM or CKD. In conclusion, this study extended the significance of BP control in hypertensive patients especially with complications. Further investigation in a large-scale clinical trial is needed to determine the optimal target BP for LVH patients.
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Keywords: CASE-J; CKD; diabetes; LVH

INTRODUCTION

The prognosis of patients with hypertension does not only depend on the blood pressure (BP) but also on other cardiovascular risk factors (smoking, diabetes, advanced age and family history) and co-morbidities, such as hypertensive organ damage and cardiovascular disease. In particular, hypertensive patients with diabetes mellitus (DM) have been reported to have a high risk of suffering from cardiovascular events,[1–3] and aggressive antihypertensive therapy is recommended for such patients in several guidelines.[4–6] Control of hypertension is also required to prevent the progression of renal impairment.[7] Thus, strict BP control is essential for hypertensive patients with DM and/or chronic kidney disease (CKD). Cardiac hypertrophy is often associated with other cardiovascular diseases, such as hypertension and ischemic heart disease, and is one of the independent risk factors that influence the prognosis of hypertensive patients. Owing to cardiac events and heart failure, both mortality and morbidity are increased in hypertensive patients with left ventricular hypertrophy (LVH).[8]

We recently performed the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J trial), which was a large-scale clinical trial in high-risk hypertensive patients that compared an angiotensin II receptor blocker (candesartan cilexetil) and a calcium channel blocker (amlodipine besylate) with respect to the prevention of cardiovascular events.[9] The incidence of cardiovascular events in the CASE-J trial occurred relatively lower compared with previous similar studies, such as the Valsartan Antihypertensive Long-term Use Evaluation trial,[10] and the CASE-J trial showed no significant difference between the candesartan and amlodipine groups.[11] The achieved BP in

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the CASE-J trial was lower than that in large-scale clinical trials reported earlier, suggesting that the strict BP control overcame the differences of pharmacological action between the two antihypertensive agents.

The CASE-J trial provides us with the opportunity to verify the significance of BP control in high-risk hypertensive patients. In this study, we performed a sub-analysis of the CASE-J trial to examine the relationship between the achieved BP and the incidence of cardiovascular events in patients with DM, CKD or LVH.

METHODS

Study population and treatment

The original CASE-J trial was a prospective randomized open-label blinded-end point study. Details of the study protocol and the main results have been reported earlier.[9,11] The subjects of the CASE-J trial were high-risk patients with essential hypertension, who had at least one of the following cardiovascular risk factors: (1) sitting systolic BP (SBP) $\geqslant$180 mm Hg or diastolic BP (DBP) $\geqslant$110 mm Hg; (2) type II DM; (3) a history of stroke or transient ischemic attacks; (4) LVH, angina pectoris or a history of myocardial infarction; (5) proteinuria or renal dysfunction (serum creatinine $>$1.3 mg per 100 ml); or (6) peripheral arterial disease (Fontaine classification grade II or higher). After randomization, the enrolled patients were given one of the two following medications to achieve the targets for control of BP according to the guidelines developed by the Japanese Society of Hypertension (JSH):[12] $<$60 years old, SBP/DBP $<$130/85 mm Hg; 60s, SBP/DBP $<$140/90 mm Hg; 70s, SBP/DBP $<$150/90 mm Hg; and 80s, SBP/DBP $<$160/90 mm Hg. The one of the medication given was candesartan administered orally at a dose of 4–8 mg day^{-1}. When the BP did not reach the targets for the control of BP, the dose was increased up to 12 mg day^{-1}. The other medication was amlodipine administered orally at a dose of 2.5–5 mg day^{-1} and increased up to 10 mg day^{-1} when necessary. Once a patient was given the assigned medication, the use of other angiotensin II receptor blockers, calcium channel blockers and all angiotensin-converting enzyme inhibitors was prohibited. Patients already being treated with diuretics, α-blockers, β-blockers or α- and β-blockers before enrollment were allowed to continue taking these medications.

End point and event evaluation criteria

The primary outcome for this sub-analysis was defined as any of the following cardiovascular events (whichever occurred first): sudden death; stroke/transient ischemic attack; acute myocardial infarction, heart failure or angina pectoris; doubling of serum creatinine or an increase to $\geqslant$4.0 mg per 100 ml or end-stage renal disease; dissecting aortic aneurysm; and occlusive peripheral arterial disease.

Occurrence of each event was independently judged by an independent event evaluation committee. The summary of the definition was as follows: (1) sudden death—unexpected abrupt death within 24 h without external cause; (2) cerebrovascular event—new onset or recurrence of stroke, transient ischemic attack (local neurological symptoms completely resolve within 24 h and symptoms develop rapidly) and other cases of stroke that are not classifiable; (3) cardiac event—new onset or recurrence of acute myocardial infarction according to the diagnostic criteria of World Health Organization (WHO)/Monica Project, new onset, exacerbation or recurrence of heart failure assessed by the New York Heart Association (NYHA) classification or angina pectoris; (4) renal event—doubling of serum creatinine (this is not considered as a renal event if the level is $\leqslant$2.0 mg per 100 ml), serum creatinine of $\geqslant$4.0 mg per 100 ml or end-stage renal disease (requiring dialysis or renal transplantation); (5) vascular event—new onset or exacerbation of dissecting aneurysm of aorta or arteriosclerotic peripheral arterial disease; and (6) other cardiovascular events—when the physician reported that his/her patient possibly had a cardiovascular event which did not meet the above criteria, the event evaluation committee assessed the occurrence individually.

In this sub-analysis, CKD was defined as creatinine clearance $<$60 ml min^{-1}, which was calculated by the Cockroft–Gault formulae[13] and/or proteinuria at baseline, whereas LVH was defined as a left ventricular posterior wall or interventricular septal thickness $\geqslant$12 mm on echocardiography or Sv1+Rv5 $\geqslant$35 mm on electrocardiography.

Statistical methods

The association between the achieved BP and the occurrence of cardiovascular events was analyzed in patients who made at least one follow-up visit without any cardiovascular events. The achieved BP was defined as the BP measured at the final study visit. In patients who experienced a cardiovascular event, the achieved BP was defined as that measured within 6 months before the event occurred. The achieved SBP and DBP were classified into five levels (SBP: $<$130, 130–139, 140–149, 150–159 and $\geqslant$160 mm Hg; DBP: $<$75, 75–79, 80–84, 85–89 and $\geqslant$90 mm Hg).

We calculated the crude incidence rates (per 1000 person-years) of cardiovascular events in the subsets of patients with DM, CKD or LVH. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by the multiple Cox proportional hazard model with adjustment for patient characteristics (sex, age, body mass index, treatment group, antihypertensive treatment before starting the CASE-J trial, smoking, drinking, DM, hyperlipidemia, severe hypertension, a history of cerebrovascular events, a history of ischemic heart disease, LVH and renal dysfunction) by setting a reference category at $<$130 mm Hg for SBP and at 75–79 mm Hg for DBP in the subset of patients without DM, CKD or LVH. The interaction between the status of complication and the achieved BP as a continuous variable was also assessed using the interaction term in the multiple Cox proportional hazard model. Statistical tests were two-sided and the level of significance was set at $P\leqslant0.05$. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Demographic profile

A total of 4728 patients with essential hypertension were enrolled in the CASE-J trial. Among them, 4703 patients were evaluated for efficacy, comprising 2354 candesartan-treated patients and 2349 amlodipine-treated patients. The mean follow-up time was 3.2 years and 2.9% of patients were lost to follow-up. In this sub-analysis, 4553 patients (2278 in the candesartan group and 2275 in the amlodipine group) had at least one follow-up visit without any cardiovascular events. The baseline characteristics of the subjects are shown in Table 1. The mean SBP/DBP at enrollment was 162.7/91.6 mm Hg and controlled to 136.2/77.5 mm Hg after 3 years. Since DM, LVH or renal dysfunction is one of the entry criteria, the proportions of other each baseline characteristic were higher compared with the general population in patients without complications.

Relationship between the achieved BP and the incidence of cardiovascular events

The event number and crude incidence rate of each achieved BP level with or without any complication (DM, LVH or CKD) are shown in the first row of Table 2. About 85% of patients in the CASE-J trial had DM, LVH or CKD at baseline. Figure 1 depicts the adjusted relative risk of BP levels compared with SBP $<$130 mm Hg and DBP 75–79 mm Hg only in the subgroup with any of the complications. The incidence of cardiovascular events tended to increase when the achieved SBP exceeded 130 mm Hg and increased significantly when the achieved SBP exceeded 140 mm Hg (HR=1.82, 95% CI=1.19–2.77, P=0.006; Figure 1a) compared with SBP $<$130 mm Hg. The incidence of cardiovascular events increased significantly when the achieved DBP exceeded 85 mm Hg (HR=2.61, 95% CI=1.55–4.39, $P<0.001$; Figure 1b) compared with DBP 75–79 mm Hg.

The crude incidence of cardiovascular events stratified by the achieved BP levels and the status of baseline risks are also shown in Table 2. With regard to DM, the hazards of all achieved SBP levels in patients with DM were significantly higher compared with those of the achieved SBP $<$130 mm Hg in patients without DM (Figure 2a).

Table 1 Baseline characteristics*

		DM status		*LVH status*		*CKD status (Ccr<60 or UP)*	
	All	*Non-DM*	*DM*	*Non-LVH*	*LVH*	*Non-CKD*	*CKD*
N	4553	2595	1958	2995	1558	2474	2079
Age (years)	63.9±10.5	63.8±11.1	64.0±9.6	64.3±10.3	63.1±10.8	60.1±9.5	68.3±9.7
Candesartan	976 (49.9)	1302 (50.2)	976 (49.9)	1509 (50.4)	769 (49.4)	1206 (48.8)	1072 (51.6)
Male (%)	2517 (55.3)	1099 (56.1)	1418 (54.6)	1519 (50.7)	998 (64.1)	1536 (62.1)	981 (47.2)
Body mass index ($kg\,m^{-2}$)	24.5±3.6	24.1±3.5	25.1±3.7	24.6±3.7	24.4±3.4	25.2±3.5	23.7±3.6
Severe hypertension[a] (%)	899 (19.8)	785 (30.3)	114 (5.8)	696 (23.2)	203 (13.0)	557 (22.5)	342 (16.5)
Type II diabetes mellitus (%)	1958 (43.0)	0 (0.0)	1958 (100.0)	1499 (50.1)	459 (29.5)	1125 (45.5)	833 (40.1)
Cerebrovascular history[a] (%)	464 (10.2)	339 (13.1)	125 (6.4)	369 (12.3)	95 (6.1)	197 (8.0)	267 (12.8)
LVH[a] (%)	1558 (34.2)	1099 (42.4)	459 (23.4)	0 (0.0)	1558 (100.0)	932 (37.7)	626 (30.1)
Ischemic heart disease history[a] (%)	587 (12.9)	203 (10.4)	384 (14.8)	413 (13.8)	174 (11.2)	335 (13.5)	252 (12.1)
Renal dysfunction[a] (%)	1090 (23.9)	659 (25.4)	431 (22.0)	791 (26.4)	299 (19.2)	27 (1.1)	1063 (51.1)
Vascular disease (%)	52 (1.1)	36 (1.4)	16 (0.8)	43 (1.4)	9 (0.6)	25 (1.0)	27 (1.3)
Hyperlipidemia (%)	2028 (44.5)	1147 (44.2)	881 (45.0)	1344 (44.9)	684 (43.9)	1095 (44.3)	933 (44.9)
Antihypertensive treatment before starting the CASE-J trial (%)	3100 (68.1)	1735 (66.9)	1365 (69.7)	2035 (68.0)	1065 (68.4)	1581 (63.9)	1519 (73.1)
Current non-smoking (%)	3110 (68.3)	1771 (68.3)	1339 (68.4)	2131 (71.2)	979 (62.8)	1572 (63.5)	1538 (74.0)
Current non-alcohol (%)	2391 (52.5)	1319 (50.8)	1072 (54.8)	1681 (56.1)	710 (45.6)	1107 (44.8)	1284 (61.8)
SBP (mm Hg)							
Baseline	162.7±14.1	164.9±14.8	159.8±12.7	163.3±14.2	161.4±12.2	161.7±14.8	163.8±13.3
During follow-up[b]	136.2±13.6	135.4±12.9	137.4±14.4	136.3±13.4	136.1±14.1	135.7±13.3	136.9±13.9
DBP (mm Hg)							
Baseline	91.6±11.2	94.1±11.3	88.3±10.1	91.7±11.4	91.5±10.7	92.6±11.1	90.4±11.1
During follow-up[b]	77.5±9.8	78.1±9.4	76.7±10.2	77.2±9.8	78.1±9.8	78.5±9.7	76.3±9.7

Abbreviations: CASE-J, Candesartan Antihypertensive Survival Evaluation in Japan; Ccr, creatinine clearance; CKD, chronic kidney disease; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, hazard ratio; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; UP, urinary proteinuria.
*Data are shown as the mean±s.d. or *n* (%) in each category.
[a]Severe hypertension (blood pressure ⩾180 and/or ⩾110 mm Hg), cerebrovascular history (a history of stroke or transient ischemic attack), ischemic heart disease history (angina pectoris or a history of myocardial infarction), Renal dysfunction (proteinuria or serum creatinine ⩾1.3 $mg\,dl^{-1}$).
[b]Mean achieved blood pressure.

Although the lower achieved SBP positively associated with the magnitude of risk reduction for both hypertensive patients with and without DM, the slope in patients without DM was steeper than that in patients with DM in SBP (interaction P=0.019). The patients with SBP 130–139 mm Hg without DM achieved almost same risk as those with SBP <130 mm Hg (HR=1.05, 95% CI=0.56–1.97, P=0.877), whereas the patients with DM still showed a higher risk of cardiovascular events, even in patients who achieved SBP <130 mm Hg (HR=2.31, 95% CI=1.24–4.33, P=0.009). Figure 2b shows the increased risk of cardiovascular events at higher achieved DBP in parallel and there was no interaction between patients with and without DM in DBP (interaction P=0.687).

Figure 3 shows the adjusted HRs in patients with/without LVH. The higher achieved SBP or DBP was associated with an increased risk of cardiovascular events. In detail, the HR of LVH patients who achieved SBP 140–149 mm Hg (HR=2.51, 95% CI=1.45–4.35, P=0.001) was almost the same as that of non-LVH patients with the achieved SBP of 150–159 mm Hg (HR=2.61, 95% CI=1.50–4.56, P<0.001) compared with the reference. A significant interaction was shown between the status of LVH and the achieved DBP (interaction P=0.007). In patients with LVH, who achieved SBP <130 mm Hg or DBP 75–79 mm Hg, the risks of cardiovascular events were reduced to a reference level (HR=0.76, 95% CI=0.38–1.51, P=0.426 for SBP 130 mm Hg with LVH; HR=0.87, 95% CI=0.36–2.07, P=0.750 for DBP 75–79 mm Hg with LVH).

In hypertensive patients with CKD, the increased risk of cardiovascular events was associated with the higher SBP and DBP (Figure 4). Similar to DM, patients with CKD still showed a higher risk of cardiovascular events, even in patients who achieved SBP <130 mm Hg (HR=2.86, 95% CI=1.47–5.58, P=0.002) and DBP <75 mm Hg (HR=4.64, 95% CI=1.99–10.80, P<0.001), compared with those without CKD. There was significant interaction between the status of CKD and of the achieved SBP and DBP.

DISCUSSION

This study verified that strict BP control leads to risk reduction of cardiovascular events in high-risk hypertensive patients with DM or CKD, and is the first to show that risk reduction was also observed in patients with LVH. Interestingly, the adjusted HR indicated that the risk of cardiovascular events increased gradually following a linear regression curve when SBP exceeded 130 mm Hg and DBP exceeded 80 mm Hg in hypertensive patients with these risk factors. In the group without complications, however, the adjusted HR for cardiovascular events increased similar to the report by Port *et al.*,[14] with the threshold being 140–150/85 mm Hg.

In the Hypertension Optimal Treatment trial, the optimal target BP for prevention of cardiovascular events was analyzed in hypertensive patients with DM. This analysis revealed that the incidence of cardiovascular events was significantly lower in the group with the achieved DBP set at ⩽80 mm Hg than those with the achieved DBP

Table 2 Event number and crude incidence rate for each subgroup

	N	Event	Incidence rate[a] (95% CI)	N	Event	Incidence rate (95% CI)		N	Event	Incidence rate (95% CI)	N	Event	Incidence rate (95% CI)
	DM, LVH or CKD							*DM, LVH or CKD*					
Achieved SBP (mm Hg)	*Without any complication*			*With any complication*			*Achieved DBP (mm Hg)*	*Without any complication*			*With any complication*		
<130	221	5	6.8 (2.2–15.7)	1045	36	10.2 (7.1–14.1)	<75	220	6	8.0 (2.9–17.4)	1448	86	17.8 (14.3–22.1)
130–<140	239	5	6.1 (2.0–14.3)	1371	62	13.4 (10.3–17.2)	75–<80	105	2	5.5 (0.7–19.9)	597	24	12.0 (7.7–17.9)
140–<150	145	2	4.0 (0.5–14.4)	941	55	17.8 (13.4–23.1)	80–<85	207	4	5.7 (1.6–14.6)	1085	55	15.2 (11.4–19.7)
150–<160	36	1	8.9 (0.2–49.8)	278	41	50.2 (36.0–68.1)	85–<90	60	0	—	382	35	28.8 (20.1–40.0)
160–	21	1	17.2 (0.4–96.0)	256	50	78.6 (58.3–103.6)	90–	70	2	9.2 (1.1–33.1)	379	44	41.3 (30.0–55.4)
	DM status							*DM status*					
Achieved SBP (mm Hg)	*Non-DM*			*DM*			*Achieved DBP (mm Hg)*	*Non-DM*			*DM*		
<130	771	17	6.5 (3.8–10.4)	495	24	14.4 (9.2–21.4)	<75	894	29	9.6 (6.4–13.8)	774	63	24.8 (19.0–31.7)
130–<140	926	23	7.3 (4.6–10.9)	684	44	19.2 (13.9–25.7)	75–<80	405	12	8.8 (4.6–15.4)	297	14	14.0 (7.6–23.4)
140–<150	617	19	9.2 (5.6–14.4)	469	38	24.7 (17.5–33.9)	80–<85	784	26	9.8 (6.4–14.4)	508	33	19.5 (13.4–27.4)
150–<160	143	21	50.7 (31.4–77.6)	171	21	40.8 (25.3–62.4)	85–<90	241	15	19.2 (10.8–31.7)	201	20	31.3 (19.1–48.4)
160–	138	17	51.0 (29.7–81.6)	139	34	94.2 (65.3–131.7)	90–	271	15	19.2 (10.7–31.6)	178	31	61.8 (42.0–87.7)
	LVH status							*LVH status*					
Achieved SBP (mm Hg)	*Non-LVH*			*LVH*			*Achieved DBP (mm Hg)*	*Non-LVH*			*LVH*		
<130	805	30	11.1 (7.5–15.8)	461	11	7.0 (3.5–12.5)	<75	1104	61	16.5 (12.6–21.2)	564	31	16.6 (11.3–23.5)
130–<140	1059	40	11.1 (7.9–15.2)	551	27	14.6 (9.6–21.2)	75–<80	468	19	12.2 (7.3–19.0)	234	7	8.8 (3.5–18.0)
140–<150	748	34	13.6 (9.4–19.1)	338	23	20.9 (13.3–31.4)	80–<85	859	33	11.5 (7.9–16.1)	433	26	17.9 (11.7–26.2)
150–<160	210	22	34.9 (21.9–52.8)	104	20	67.2 (41.1–103.8)	85–<90	307	17	17.0 (9.9–27.2)	135	18	43.1 (25.6–68.2)
160–	173	26	58.2 (38.0–85.3)	104	25	100.8 (65.2–148.8)	90–	257	22	29.6 (18.6–44.8)	192	24	44.4 (28.4–66.0)
	CKD status							*CKD status*					
Achieved SBP (mm Hg)	*Non-CKD*			*CKD*			*Achieved DBP (mm Hg)*	*Non-CKD*			*CKD*		
<130	719	13	5.3 (2.8–9.0)	547	28	15.3 (10.2–22.2)	<75	805	27	9.8 (6.5–14.2)	863	65	23.2 (17.9–29.5)
130–<140	918	18	5.7 (3.4–9.0)	692	49	21.5 (15.9–28.4)	75–<80	395	6	4.4 (1.6–9.6)	307	20	20.0 (12.2–30.9)
140–<150	534	18	10.0 (5.9–15.8)	552	39	21.8 (15.5–29.7)	80–<85	732	19	7.7 (4.6–12.0)	560	40	21.6 (15.4–29.4)
150–<160	172	17	33.0 (19.2–52.8)	142	25	60.6 (39.2–89.4)	85–<90	250	9	10.8 (4.9–20.5)	192	26	44.5 (29.1–65.2)
160–	131	15	42.3 (23.7–69.8)	146	36	105.8 (74.1–146.5)	90–	292	20	22.9 (14.0–35.4)	157	26	63.2 (41.3–92.6)

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, hazard ratio; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
[a]Incidence rate is calculated per 1000 patient-years.

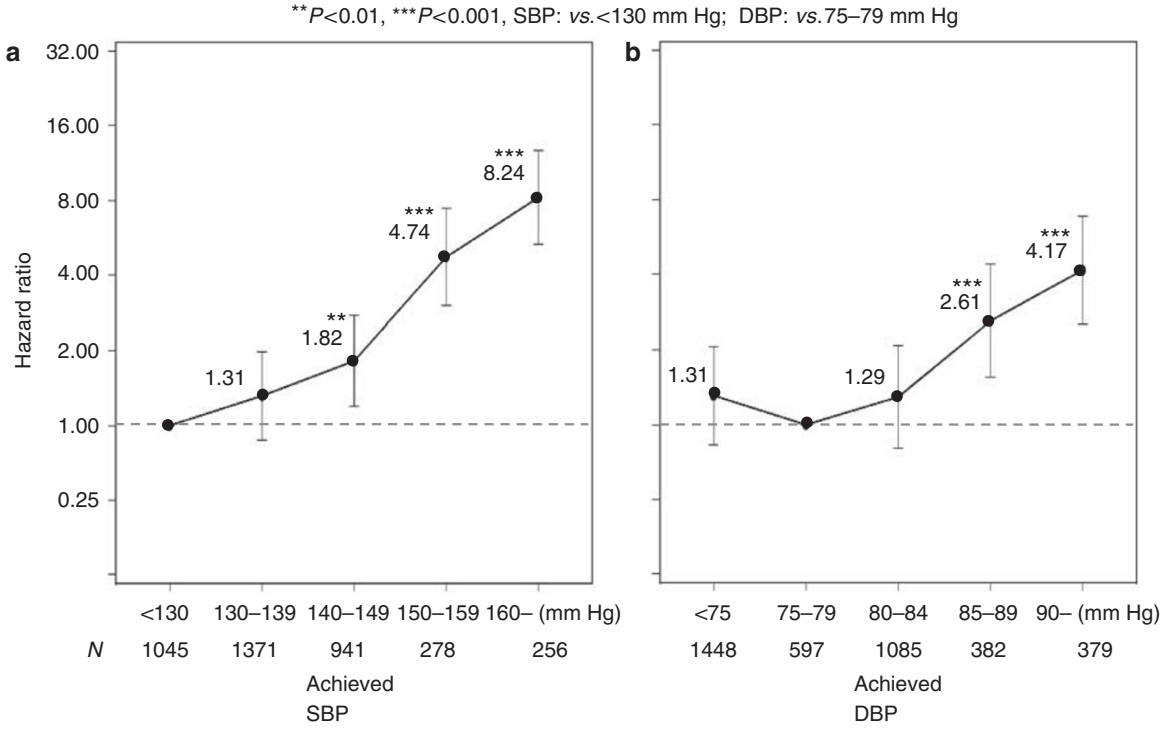

Figure 1 Adjusted relative risk of cardiovascular events and achieved BP in patients with any of the complications (DM, LVH or CKD). (**a**) The relationship between cardiovascular events and the achieved SBP and (**b**) the achieved DBP. A reference category was set at <130 mm Hg for SBP and at 75–79 mm Hg for DBP.

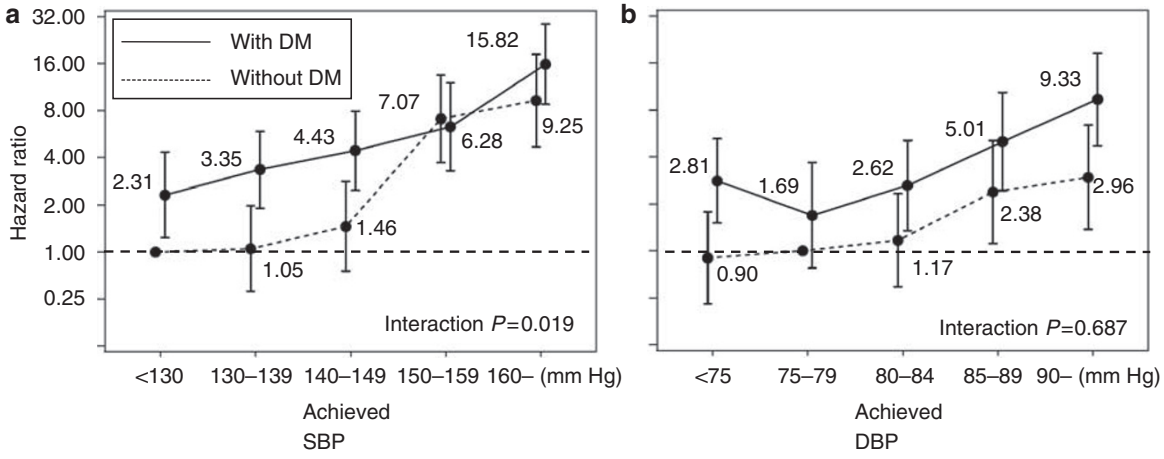

Figure 2 Adjusted relative risks of cardiovascular events and achieved BP in patients with/without DM. (**a**) The relationship between cardiovascular events and the achieved SBP and (**b**) the achieved DBP. A reference category was set at <130 mm Hg for SBP and at 75–79 mm Hg for DBP in the subset of patients without DM.

set at ⩽85 and ⩽90 mm Hg.[15] The results of some other studies in hypertensive patients with DM have also suggested that greater benefit is obtained by setting the target BP at a lower level.[16,17] Therefore, the Joint National Committee (JNC) 7[5] and the European Society of Hypertension-European Society of Cardiology (ESH-ESC) Guidelines,[6] as well as the guideline of JSH 2004,[4] recommend <130/80 mm Hg as the target optimal BP level in hypertensive patients with DM. Our study showed the results consistent with these recommendation for hypertensive patients with DM.

For hypertensive patients with CKD, a meta-analysis of 11 randomized controlled studies revealed that the incidence of end-stage renal failure and doubling of the serum creatinine were reduced by controlling SBP to 110–129 mm Hg in hypertensive patients with urine protein excretion $>1.0\,g\,day^{-1}$.[18] Similar to hypertensive patients with DM, the guideline of JSH 2004 stipulates that the target BP for antihypertensive therapy is <130/80 mm Hg in hypertensive patients with CKD and <125/75 mm Hg in hypertensive patients with urinary protein loss exceeding $1.0\,g\,day^{-1}$. Our results are also consistent with the recommendation of the guideline of JSH 2004.

The first-line antihypertensive agents used in the CASE-J trial were candesartan and amlodipine. On the basis of the meta-analysis of the effects of treatment on the left ventricular mass in patients with

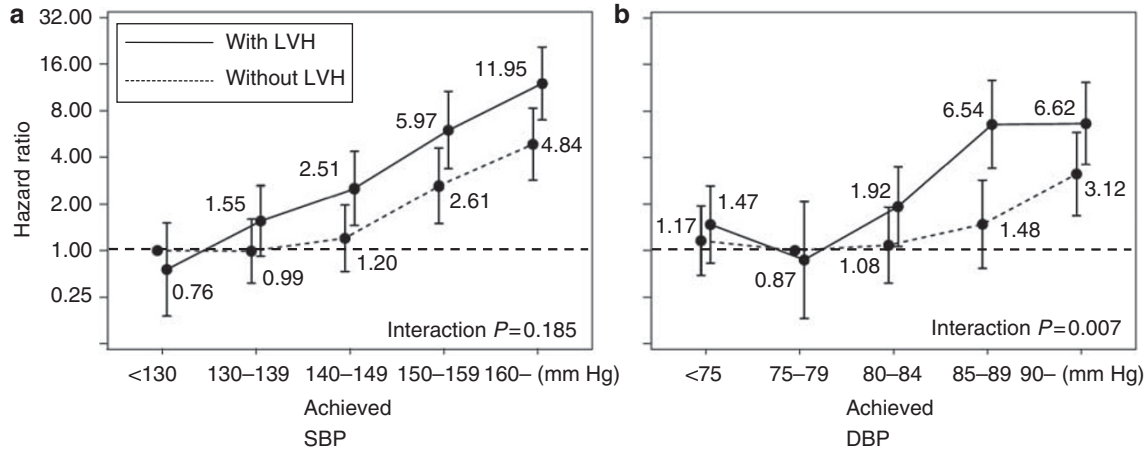

Figure 3 Adjusted relative risks of cardiovascular events and achieved BP in patients with/without LVH. (**a**) The relationship between cardiovascular events and the achieved SBP and (**b**) the achieved DBP. A reference category was set at <130 mm Hg for SBP and at 75–79 mm Hg for DBP in the subset of patients without LVH.

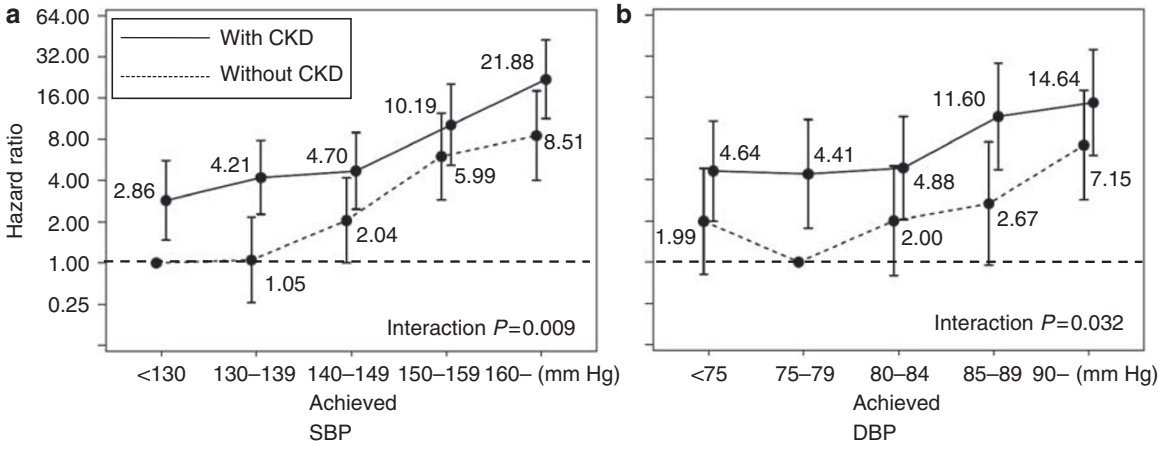

Figure 4 Adjusted relative risks of cardiovascular events and achieved BP in patients with/without CKD. (**a**) The relationship between cardiovascular events and the achieved SBP and (**b**) the achieved DBP. A reference category was set at <130 mm Hg for SBP and at 75–79 mm Hg for DBP in the subset of patients without CKD.

essential hypertension,[19] both agents have been recommended for hypertensive patients with LVH. It was found that strict BP control is more important for reducing the left ventricular mass than the class of antihypertensive agent by comparison of six antihypertensive agents.[20] The most interesting point of this sub-analysis was that the risk of cardiovascular events in patients with LVH, who could achieve SBP <130 mm Hg or DBP 75–79 mm Hg, was reduced to the same level as in those without LVH, but not in patients with DM or CKD. This indicates that hypertensive patients with these complications should be treated with strict BP control, and it is important for DM and CKD patients to receive not only antihypertensive therapy but also sufficient treatment for DM and CKD.

There are some limitations in this study. First, LVH was defined by criteria including electrocardiography, which is inferior in accuracy to echocardiography. Second, as this analysis was *post hoc* and patients were classified into several sub-groups, the population and the number of cardiovascular events in each group might not be enough to analyze the influence of achieved BP on these events. Third, we stratified by post-randomized variables; hence, this might introduce some bias whenever the association with outcome is confounded by more than just a baseline risk factor. Finally, as the CASE-J trial was not designed to determine the optimal BP levels in high-risk hypertensive patients, our results merely give an indication of the optimal BP levels when the patients received an antihypertensive treatment.

In conclusion, this sub-analysis of the CASE-J trial indicates that strict BP control leads to the risk reduction of cardiovascular events in hypertensive patients with DM, CKD or LVH. Further investigation in a large-scale clinical trial is needed to determine the optimal target BP for LVH patients.

CONFLICT OF INTEREST

Our conflict of interest is as follows: Drs T Ogihara, T Saruta, K Ueshima, K Takeda, J Higaki and K Nakao have received lecture fees from Takeda Pharmaceutical Co. and Pfizer Japan Inc. The other authors declare that they have no conflict of interest.

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