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The association of conventionally medicated systolic and diastolic blood pressure level and mortality from cardiovascular disease: is the lower the better in high stroke population?

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Sirs:

Hypertension has become majority morbidity and a leading factors for the cardiovascular disease mortalities in the current society [1, 2]. While hypertensive managements has improved since the twentieth century [3], the optimal blood pressure (BP) among hypertensive patients remains in question. The new American Heart Association/American College of Cardiology (AHA/ACC) guidelines suggest health benefit for systolic blood pressure (SBP) below 130 mmHg and diastolic blood pressure (DBP) below 80 mmHg [4]. It remains unclear whether this is also favorable for Asian and East-European population where, in contrast to Western countries, mortality from stroke has been higher than that from coronary heart disease (CHD) [2]. We recently

examined an association of the combined category of SBP/DBP with mortality from cardiovascular disease (CVD); the results showed J-curved CVD mortality association among the participants with ongoing antihypertensive treatment but not normotensive participants[5]. However, the individual impact of SBP and DBP on CVD mortality among treated patients for hypertension has not been examined.

We performed an analysis of 10,061 individuals from the Japan Collaborative Cohort (JACC) Study, from 1988 to 1990 at baseline [6], who were on current antihypertensive medication and without history of CVD or cancer, from 45 communities across Japan where recorded mortality from stroke has been higher than from CHD. Informed consent was obtained from participants or community leaders. The ethics committees of the Nagoya University and Osaka University approved the protocol of this investigation. Our primary aim of study was to investigate the conventionally medicated BPs on CVD outcomes. Then, the medicated BP level was assessed by self-report questionnaire. SBP and DBP were categorized into five groups: for SBP (< 130, 130–139, 140–149, 150–159, and ≥ 160 mmHg) and DBP (< 70, 70–79, 80–89, 90–99, and ≥ 100 mmHg). Mortality data were centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded according to the International Statistical Classification of Diseases-10th edition. Participants who died after removal from their original communities were treated as censored cases until the end of 2009. The mortality was categorized as total CVD (I01–I99), stroke (I60–I69), and CHD (I20–I25). The validity of self-BP report was examined with assessed BP at health check-up in 2678/10,061 participants. Baseline characteristics were examined for each of SBP and DBP groups. Normal distribution is displayed as mean or percentage and skewed data as median. The differences between the groups were calculated using one-way analysis of covariance,

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Chi-square, or Kruskal–Wallis test was used when it was appropriate. To investigate the risk of stroke and CHD mortality according to conventionally medicated SBP and DBP levels, the multivariable hazard ratio (HR) and 95% confidence interval (95% CI) were calculated by competing risk analysis, using as reference SBP and DBP levels of < 130 mmHg and < 70 mmHg, respectively. Adjusted variables included sex, age, SBP or DBP level, body mass index, alcohol intake, diabetes, family history of CVD, mental stress, smoking status, activity status, and education level. To address the reverse causality, we excluded early deaths within first 5 years on follow-up period. As for another sensitive analysis, we assessed the association of CVD mortalities per 1000 person-years and assessed BPs. Furthermore, we also confirmed time variability with the impact of BPs on outcomes by Kaplan–Meier analysis.

For 21 years of follow-up, 565 stroke, 275 CHD, and 1,081 total CVD deaths were recorded. The mean age was 62.6 years (men = 35.4%). No difference was observed between distributions of CVD mortality for self-report BP level and assessed BP at health check-up ($P=0.20$ in SBP, 0.50 in DBP), and obtained moderate spearman-rank correlation (SBP = 0.83, DBP = 0.82) and BP distributions of sampled 2678 patients were generally fit into the total 10,061 population.

Table 1 shows the baseline characteristics according to conventionally medicated SBP and DBP levels. In SBP, significant differences were observed in mean age ($P<0.001$), female ($P<0.001$), individuals with diabetes ($P<0.001$), and those with higher education ($P=0.008$). In DBP, the significant differences were found in mean age ($P<0.001$), female ($P<0.001$), BMI ($P<0.001$) and those with higher education ($P=0.008$), median ethanol intake g/

day ($P<0.001$), higher perceived mental ($P<0.001$), current smoker ($P<0.001$), sport > 5 h/week ($P=0.003$), and prevalence of higher education ($P=0.005$).

Figure 1 shows the multivariable HR for stroke, CHD, and total CVD mortalities according to the five categorized SBP and DBP groups. For stroke, J-curve association was observed in both SBP and DBP categories. The nadir HR (95% CI) was 0.65 (0.80–0.91) at SBPs of 130–139 mmHg and 0.81 (0.73–0.89) at DBPs of 90–99 mmHg. For CHD, the HR showed linear association with SBP, but inversed association with DBP. HRs (95%CI) for CHD at SBP of 130–139, 140–149, 150–159, and ≥ 160 mmHg were 1.33 (1.24–1.43), 1.23 (1.17–1.30), 1.24 (1.17–1.32), and 1.27 (1.20–1.35), respectively. Furthermore, HRs (95%CI) for CHD at DBP of 70–79, 80–89, 90–99, and ≥ 100 mmHg were 0.94 (0.86–1.03), 0.78 (0.72–0.85), 0.86 (0.79–0.94), and 0.71 (0.64–0.79), respectively. The total CVD showed a J-curve association, and the nadir HR in this respect was 0.86 (0.80–0.91) at SBP of 130–139 mmHg and 0.71 (0.65–0.80) at DBP of 90–99 mmHg. Those results were not significantly changed, even after excluding early deaths within first 5 years on follow-up period (not shown in table). The Kaplan–Meier curve drafted clear time-dependent association, in a particular the impact of low DBP on outcomes was appeared since > 5 years of follow-up (Supplementary Figure 1).

Our analysis suggested that an achieved SBP of < 130 mmHg was associated with greater benefit for CHD mortality, but not stroke and total CVD, among conventionally medicated hypertensive patients. A, lower DBP associated with stroke, CHD, and total CVD mortality.

The present results of the excess risk of total CVD on SBP < 130 mmHg; this was in contrast of result from

Table 1 Baseline characters according to conventionally medicated systolic and diastolic blood pressure categories

	Systolic blood pressure, mmHg						Diastolic blood pressure, mmHg					
	< 130	130–139	140–149	150–159	≥ 160	<i>P</i> value	< 70	70–79	80–89	90–99	≥ 110	<i>P</i> value
No. at risk	1589	920	3061	2156	2300		340	1566	4225	2931	915	
Person of years	24895	14785	48605	32666	31911		4707	23267	65333	45642	13238	
Age, years	61.8	61.2	62.1	63.2	63.8	<0.001	67.7	65.1	63.2	60.6	59.7	<0.001
Female, %	65.9	65.4	61.1	62.3	61.5	<0.001	70.8	68.5	64.3	58.3	54.9	<0.001
Body mass index, cm/kg ²	23.6	23.9	23.7	23.7	23.7	0.826	22.9	23.3	23.6	24.0	24.3	<0.001
Diabetes, %	8.7	8.9	8.2	9.8	12.4	<0.001	10.4	11.3	9.3	8.2	9.1	0.023
Family history of CVD, %	56.1	53.3	52.6	54.2	54.1	0.740	54.1	51.5	53.9	54.2	55.1	0.422
Ethanol intake, g/day	29.1	26.9	30.1	30.9	30.8	0.090	24.8	27.3	29.1	31.1	34.4	<0.001
High perceived mental stress, %	17.3	20.0	18.9	18.9	21.1	0.349	12.0	15.9	17.9	22.2	29.5	<0.001
Current smoker, %	19.9	22.0	21.6	20.6	22.4	0.512	18.9	19.4	20.1	23.0	24.9	<0.001
Working > 1 h/week, %	44.3	52.3	48.3	49.4	46.2	0.136	46.1	52.0	49.6	45.4	44.0	<0.001
Sport > 5 h/week, %	6.1	8.1	7.8	7.2	6.6	0.530	6.8	8.4	7.5	6.9	4.3	0.003
Education (college or higher), %	7.4	11.9	12.1	11.4	10.4	0.008	5.7	9.3	11.1	12.2	11.8	0.005

CVD cardiovascular disease

Fig. 1 Forest plots of multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) of stroke, coronary heart disease (CHD), and total cardiovascular disease (CVD) mortalities according to categories of conventionally medicated systolic (SBP) and diastolic

blood pressure (DBP) subgroups. Data were adjusted by age, sex, SBP or DBP level, body mass index, alcohol intake, diabetes, family history of CVD, mental stress, smoking status, activity status, and education level.

meta-analysis that included 42 clinical trials [7]. The previous study showed that low medicated SBP associated with “better” total CVD outcomes. However, those with trials were mostly undertaken in population where the mortality from CHD is higher than from stroke. As such, they may underestimate the impact of low SBP on stroke mortality and morbidity. The mechanism linking low SBP with stroke remains unclear and deserve further study. Because lower limitation of cerebral autoregulation is sub-clinically impaired among adults with longstanding hypertension and/or those with borderline hypertension adults [8], cerebral blood flow may be strongly reduced when BP levels are intensively reduced among hypertensive patients. We may have expected different population characteristics between Asian and Western, particularly in basic BPs level; urinary sodium excretion and serum cholesterol level to determine the different causalities for CVD subtypes [9, 10].

The increased risk of total CVD, stroke, and CHD for low DBP might be due to aggressive antihypertensive medication and/or comorbidity from preclinical heart failure and arteriosclerosis [11–13], which cannot discriminate nor proven in observational study. However, the drop in DBP is likely to cause subclinical harming at circulatory systems and associated with higher risk of CVD among those with longstanding hypertension [13, 14]. Even though SBP has been recognized the stronger predictor compared with DBP [15], careful monitoring for DBP and comorbidities may be necessary. In agreement with this, our study showed the lower SBP, the better in CHD mortality, but not in the case of stroke. Furthermore, Böhm et al. indicated an increased risk of CVD for achieved DBP < 70 mmHg among hypertensive

patients with optimal controlled SBP (120–140 mmHg) [16]. Emmanuelle et al. stated DBP J-curve association with total CVD mortality, which was not solely explained by increased pulse pressure and/or arteries stiffness [12]. Even those study conducted at high CHD population and did not showing a significant difference in excess stroke risk in low-DBP level, it showed the potential of J-curve DBP association for stroke [12, 16]. Although the finding that the impact of low-DBP on CVD outcomes, particularly stroke, was in contrast with the results from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Participants with Cardiovascular Disease (TRANSCEND) trials [16–18], the difference between these findings could be explained by the range in median follow-up period (median range follow-up in JACC: 21.0 years vs. ONTARGET/TRANSCEND: 4.6 years). In our study, the impact of low-DBP on stroke mortality was evident only after > 5 years of follow-up, which was in line with finding of ONTARGET/TRANSCEND of study.

The strengths of the present study included its prospective design. Conducted long-termed following up, large number of participants, over 30 regions in Japan. In addition, using competing risk analysis and excluding the early deaths within first 5 years on follow-up period addressed reversal causality and useful in understanding the essentially impact of individually targeting SBP and DBP level on cardiovascular disease in a population with high stroke mortality. This study is limited by the fact that mortality data were used as an endpoint, which might lead to misclassification in the diagnosis of total CVD, CHD, and stroke. However,

previous validation studies confirm the validity of using death certification referred by non-subjective method such as magnetic resonance imaging, electro-imaging, or ECGs in local hospitals in Japan since 1980s [19]. In addition, conventionally medicated BPs were self-reports. Because misclassification is considered to be non-differential, the real association would be stronger.

In conclusion, conventionally medicated hypertensive patients with SBP of < 130 mmHg showed greater benefit with regard to CHD mortality, but not for stroke and total CVD mortality among a population of hypertensive patients at high risk of stroke. A lower DBP was associated with stroke, CHD, and total CVD mortalities. This suggests necessity for careful monitoring for DBP and inversed risk of stroke, when a low SBP level is achieved through medication. Our results improve knowledge, in this understudied population and for populations where the mortality from stroke has been higher than that from CHD, such as Asians and East-Europeans.

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Compliance with ethical standards

Conflict of interest We declare no competing interests.

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