Research Article

Lower Diastolic Blood Pressure was Associated with Higher Incidence of Chronic Kidney Disease in the General Population Only in those Using Antihypertensive Medications

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Keywords

General population · Diastolic blood pressure · Chronic kidney disease · Antihypertensive medication

Abstract

Background/Aims: The association of diastolic blood pressure (DBP) with incidence of chronic kidney disease (CKD) in the general population is not well examined. **Methods:** Using national health check-up database from 2008 to 2011 in the general Japanese population aged 39–74 years, we evaluated the association between DBP and incidence of CKD 2 years later in 127,954 participants without CKD. DBP was categorized by every 5 mm Hg from the lowest (<60 mm Hg) to the highest category (>100 mm Hg) and was further stratified into those with and without antihypertensive medications (BP meds). We calculated the OR for estimating adjusted risk of incident CKD using logistic regression model. **Results:** Participants were 62% female and 25.9% with BP meds, mean age of 76 years with estimated glomerular filtration rate of 78.2 ± 13.4 and DBP of 76 ± 11 mm Hg. Two years later, 12,379 (9.7%) developed CKD. Compared to DBP 60–64 mm Hg without BP meds as reference, multivariate analysis showed no difference in CKD risk at any DBP category among those without BP meds. However, in

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those with BP meds, risk increased according to lower DBP from 95 to 60 mm Hg (p for trend 0.05) with OR 1.51 (95% CI 1.14–1.99) in DBP <60 mm Hg. In subgroup analysis within those with or without BP meds, CKD risk was lower at higher DBP (p for trend 0.02) only in those without BP meds. **Conclusion:** Lower DBP was associated with higher risk of incident CKD only in the general population taking antihypertensive medication.

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Introduction

Hypertension is highly prevalent in the adult population worldwide and has gradually increased affecting approximately 10.1 million people in Japan [1]. It is known to be a risk factor for death [2], cardiovascular disease (CVD) [3], and chronic kidney disease (CKD) [4] in the general population. Indeed, treatment of hypertension has succeeded in lowering the incidence of CVD [5, 6] and death [7] in many studies. In the case of CKD, hypertension treatment has been shown to slow the progression of CKD and incident end-stage kidney disease (ESKD) [8].

Such interventional studies have focused mainly on systolic blood pressure (SBP) and not diastolic blood pressure (DBP) because it has been shown to be an independent risk predictor for coronary events, stroke, heart failure, and ESKD [9–11]. Thus, in clinical practice and in many interventional studies, control of hypertension focuses mainly on SBP [12].

However, previous studies have demonstrated a J-curve for DBP and CVD [13–15] and a negative correlation between DBP and CVD in those with SBP above 120 mm Hg [16]. In a recent study, analyzing the relation between DBP and CVD from the Atherosclerosis Risk In Communities study cohort [17], lowest DBP was also associated with progressive myocardial damage adjusted for antihypertensive medications (BP meds), suggesting a frequent risk of CVD. To date, not much is known about the association between DBP and future incident CKD. Recently, the report of the SPRINT substudy showed that intensive treatment of hypertension leads to higher incidence of CKD than standard treatment regardless of baseline DBP [18]. But it is not known whether the incidence of CKD differs depending on the administration of BP meds. The aim of this study was to clarify the influence of DBP in the incidence of CKD. Furthermore, the association of DBP and incidence CKD was stratified by the use of BP meds.

Methods

The present study was a prospective cohort study based on a nationwide community-based health examination program for adults aged 39–74 years in Japan. This project was approved by the Comprehensive Health Care System for CKD based on the Individual Risk Assessment by Specific Health Checkup, Japan. This annual health check program was initiated in 2008 by the Japanese government in order to promote early diagnosis and intervention strategies for the prevention of metabolic syndrome. All participants completed a self-administered questionnaire that documented medical history, current medications, smoking habit (current smoker or not), alcohol consumption (daily drinker or not), eating habits, and regular exercise habits. Participants' height and weight were measured, and body mass index (BMI) was calculated (kg/m^2). BP measurement and blood and urine sampling were performed as stipulated by the health check program. The BP measurement method was measured in a state of resting by sitting on a chair, putting upper limb at the same height as the heart, rolling up the sleeve so that the arm was bare. Blood samples were collected after participants had

fasted overnight, and blood was analyzed using an automated clinical chemical analyzer within 24 h of sampling. All blood analyses were conducted at a local, rather than a central, laboratory. Methods used for blood analyses were not calibrated between laboratories; however, the Japan Society of Clinical Chemistry has recommended universal methods for laboratory testing, which has been widely adopted by laboratories across Japan. The enzymatic method was used to measure serum creatinine in fresh blood samples.

Annual data were obtained from 2008 to 2011. Those without CKD were evaluated for the association between DBP and incidence of CKD 2 years later. So participants who had no health examination at 2008 and 2009, had CKD at the baseline (i.e., 2008 and 2009), and had missing data on covariates such as age, gender, BMI, current smoking, past CVD, diabetes mellitus (DM), SBP, DBP, use of antihypertensive drug, triglyceride, high-density lipoprotein cholesterol, use of lipid-lowering drug and urine protein, or estimated glomerular filtration rate (eGFR) were excluded. CKD was defined as positive dipstick proteinuria (>1+) and/or eGFR below 60 mL/min/1.73 m². Estimated GFR was calculated by the equation for Japanese adults ($194 \times \text{serum Cre} - 1.094 \times \text{Age} - 0.287$ [$\times 0.739$ in females]) [19]. DM was defined as fasting plasma glucose of >126 mg/dL, hemoglobin A1c of >6.5%, or use of antidiabetic medication.

The DBP was categorized by every 5 mm Hg from the lowest (<60 mm Hg) to the highest category (>100 mm Hg) and was further stratified into those with and without BP meds. In addition, analysis by subgroups which was classified by SBP (<120, 120–139, ≥140 mm Hg) was performed.

Statistical Analysis

Continuous variables are presented as average ± SD, and categorical variables are presented as percentages. The comparison between those with and without BP meds was analyzed by Mann-Whitney U test or chi-square test, and the trend between DBP categories were performed using the trend test. To test the association between the risk factors and future diagnosis of CKD, logistic regression models, adjusted for the age, sex, obesity (BMI ≥25 kg/m²), current smoking, past history of CVD, DM, drug for dyslipidemia, high triglyceride (≥150 mg/dL), low- and high-density lipoprotein cholesterolemia (<40 mg/dL), and eGFR, were constructed to calculate the OR and 95% CI. A 2-sided $p < 0.05$ indicated statistical significance. Data were analyzed with SAS version 9.4 (SAS Institute Inc.).

The present study was approved by the Ethics Committee of the Fukushima Medical University (No. 2771), and the study was conducted according to the guidelines of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research (December 1, 2008, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare of Japan). Ethical approval was also obtained from the respective institutional review boards.

Results

A total of 1,120,104 people had health examination between 2008 and 2011 from all-over Japan. Of the whole cohort, 212,684 participants had no CKD at baseline and were followed for 2-years. We then excluded 84,730 participants with any missing data on any covariates. Finally, data from 127,954 participants were analyzed (Fig. 1). Online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000501828) shows the comparison between the final cohort and those without CKD at baseline but were excluded for other missing covariates. Although the differences were statistically significant, by clinical judgment, the differences were small as to be insignificant.

Fig. 1. Study profile. CKD, chronic kidney disease.

Table 1. Baseline characteristics of all subjects and stratification by BP meds use

	Total (n = 127,954)		No medications (n = 94,811)		Medications (n = 33,143)		p value
	value	SD	value	SD	value	SD	
Age, years	62.6	7.84	61.6	8.2	65.3	5.7	<0.001
Female, %	61.6		62.5		58.9		<0.001
BMI	23.1	3.25	22.7	3.1	24.4	3.4	<0.001
Obesity, BMI ≥25, %	24.8		20.2		38		<0.001
Current smoking, %	13.8		14.5		11.7		<0.001
Past CVD, %	7.37		4.77		14.8		<0.001
DM, %	9.82		7.54		16.3		<0.001
SBP, mm Hg	128	17.3	125.2	17	136.7	15	<0.001
DBP, mm Hg	76.1	10.5	74.9	11	79.5	9.7	<0.001
Antihypertensive drug, %	25.9		–		–		
TG, mg/dL	113.7	74.4	110.8	74	122.1	76.2	<0.001
TG ≥150, %	19.2		17.8		23.1		<0.001
HDL cholesterol, mg/dL	62.7	18.6	63.5	16	60.4	15.1	<0.001
HDL cholesterol <40, %	4.42		4.12		5.29		<0.001
Lipid-lowering drug, %	15.4		10.6		29		<0.001
eGFR, mL/min/1.73 m ²	78.3	13.4	78.5	13	77.6	13.4	<0.001

BMI, body mass index; CVD, cardiovascular disease; BP, blood pressure; DBP, diastolic BP; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic BP; TG, triglyceride.

Fig. 2. Comparison of incidence of CKD between those with and without BP meds for each DBP categories. Reference was set at DBP 60–64 mm Hg without BP meds and compared use to no use of BP meds within each DBP categories. * $p < 0.05$ versus reference (DBP 60–64 mm Hg). DBP, diastolic blood pressure.

The characteristics of the final cohort are shown in Table 1. More than half of the final cohort were female (61.6%), and the median eGFR was 78.3 mL/min/1.73 m². Most of the patients were elderly (mean age, 76.1 years), and those with BP meds were more male, elderly, diabetic, hypertensive, dyslipidemia, obese, current smokers, and had CVD history.

Of the incorporated 127,954 people, 33,143 (25.9%) were taking BP meds at baseline and after 2 years follow-up, 12,328 (9.6%) people developed CKD.

Comparison of Incidence of CKD between those with and without BP Meds for each DBP Categories

Those with BP meds were associated with higher incidence of CKD than those without BP meds (13.8 vs. 8.4%; $p < 0.001$), and the differences were significant in most categorical DBP levels (Fig. 2).

Trend for Incidence of CKD According to DBP Categories for those with and without BP Meds

Among the 12,328 people with incident CKD, 4,334 (35.2%) were taking BP meds. Within those taking BP meds, lower DBP showed higher tendency of incidence of CKD, and lower DBP was associated with significantly higher rates of incidence of CKD for those with DBP under 94 mm Hg ($p = 0.03$; Fig. 3a). Meanwhile, those without BP meds showed no correlation of incident CKD with DBP level (Fig. 3b).

Fig. 3. Trend for incidence of CKD according to DBP categories for those with and without BP meds (reference was set at DBP 60–64 mm Hg). **a** With BP medication, $n = 33,143$; incident CKD, $n = 4,334$. * $p < 0.05$ versus reference. **b** Without BP medication, $n = 94,811$; incident CKD, $n = 7,994$. DBP, diastolic blood pressure.

Table 2. Trends in the OR for incident CKD in each DBP categories within those with or without BP meds in SBP subgroups analysis (DBP 60–64 mm Hg was set as reference)

SBP, mm Hg	Incident CKD/ Total, n	DBP, mm Hg									
		<60 OR (95% CI)	60–64 OR (95% CI)	65–69 OR (95% CI)	70–74 OR (95% CI)	75–79 OR (95% CI)	80–84 OR (95% CI)	85–89 OR (95% CI)	90–94 OR (95% CI)	95–99 OR (95% CI)	100≤ OR (95% CI)
Medications (n = 4,334)	SBP <120	382/ 3,149	1.00 (reference)	0.89 (0.62–1.27)	1.01 (0.74–1.38)	0.91 (0.61–1.34)	1.06 (0.68–1.62)	0.66 (0.25–1.49)			
	SBP 120–139	2,023/ 16,219	1.00 (reference)	1.00 (0.89–1.11)	0.96 (0.87–1.05)	1.01 (0.91–1.12)	0.98 (0.89–1.09)	0.98 (0.86–1.11)	1.04 (0.91–1.19)	1.01 (0.83–1.22)	1.02 (0.83–1.25)
	SBP >140	1,929/ 13,775	0.91 (0.36–2.13)	0.52 (0.30–0.90)*	0.74 (0.49–1.15)	0.73 (0.48–1.13)	0.66 (0.44–1.00)	0.60 (0.40–0.93)*	0.60 (0.40–0.93)*	0.60 (0.44–1.08)	0.66 (0.42–1.05)
No Medications (n = 7,994)	SBP <120	2,363/ 33,456	1.00 (reference)	0.94 (0.82–1.07)	0.95 (0.84–1.07)	1.02 (0.87–1.20)	1.04 (0.86–1.26)	1.10 (0.70–1.65)			
	SBP 120–139	3,680/ 43,109	1.25 (0.86–1.77)	1.21 (0.99–1.84)	1.06 (0.90–1.26)	1.15 (0.97–1.37)	1.08 (0.91–1.28)	1.23 (1.01–1.50)*	1.29 (1.03–1.61)	1.18 (0.80–1.71)	
	SBP >140	1,951/ 18,246	0.52 (0.12–1.60)	0.66 (0.37–1.20)	0.80 (0.51–1.29)	0.75 (0.48–1.21)	0.84 (0.55–1.33)	0.71 (0.46–1.13)	0.83 (0.54–1.32)	0.82 (0.52–1.33)	0.93 (0.59–1.49)

* $p < 0.05$ versus reference.
Adjusted for the age, sex, obesity (BMI ≥ 25 kg/m²), current smoking, past history of CVD, DM, drug for dyslipidemia, high triglyceride (≥ 150 mg/dL), low HDL cholesterolemia (< 40 mg/dL), and eGFR.
CKD, chronic kidney disease; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP.

Relationship between Incident CKD and DBP Level According to SBP Subgroups

Among the 33,143 people with BP meds, 3,149 (9.5%) people had SBP under 120 mm Hg, 16,219 (48.9%) people had SBP of 120–139 mm Hg, and 13,775 (41.6%) people had SBP over 140 mm Hg. Among the 94,811 people without BP meds, 33,456 (35.3%) people had SBP under 120 mm Hg, 43,109 (45.5%) people had SBP of 120–139 mm Hg, and 18,246 (19.2%) people had SBP over 140 mm Hg.

In those with BP meds, SBP under 120 and 120–139 mm Hg also showed no correlation of incident CKD with any DBP level, but in those with SBP over 140 mm Hg (Table 2), lower DBP was associated with higher rates of incidence of CKD ($p < 0.05$ in DBP 65–69, 85–89, and 90–94 mm Hg). Such trend was not obtained from those without BP meds that showed higher incidence of CKD in those with SBP 120–139 mm Hg and DBP 85–89 and 90–94 mm Hg ($p < 0.05$; Table 2).

Discussion

Hypertension is an independent risk factor for incident [4, 20] and progressive CKD [21]. Thus, further strict BP control with medication may seem more effective since higher BP even within the normal level has been shown to be a risk for CKD in epidemiological studies [22–27]. From this large study of the general Japanese population, we found that BP meds group is a high-risk population and lower DBP with antihypertensive treatment beyond a certain level may be harmful for the kidney.

Our study shows that those who had BP meds were more susceptible to incidence of CKD at any DBP and also for any SBP levels (online suppl. Fig. 1). The reason why BP meds was associated with higher risk of CKD may be because confounders related to BP meds were not measured. Although treatment of hypertension would be expected to reduce the risk of CKD, epidemiological studies have also suggested that hypertension treatment is a risk factor for CVD [28] and progression of CKD [29]. The reason for this ironical sequence of treatment being a risk factor for organ damage is thought to be due to indication bias that occurs in the real world meaning that those prescribed BP meds may already have advanced atherosclerosis. Possible confounders related to prescription of BP meds are high home BP or type of medication used such as renin-angiotensin-aldosterone inhibiting drug use. Thus, hypertension treatment is a proxy for hypertension and as such is included as a risk factor in the Framingham CVD risk score [28].

Furthermore, our study revealed that lower DBP and susceptibility to incidence of CKD were significant mainly in those with BP meds. Interestingly, we could not find any correlation between lower DBP and incident CKD in those without BP meds. Several studies concerning incident CKD and high BP defined not only by SBP but also DBP in the general population have shown high DBP to be a risk for CKD [27, 30, 31], however, have not made adjustments with BP meds. One prospective study [26] demonstrated that prehypertension was associated with an increased risk of CKD and after adjustment for BP meds showed high DBP was one of the considerable causes of CKD in the general population. In our study, those taking BP meds showed a statistically nonsignificant tendency to incidence of proteinuria and reduction of eGFR below 60 mL/min/1.73 m² (online suppl. Table 2), together defining CKD, especially in those with lower DBP. This raises the possibility that lowering DBP beyond a certain level may provoke incident CKD. Previous studies have shown a positive linear correlation between DBP and onset of ESKD [21, 32]. In those studies, the lowest categorized DBP was less than as high as 80 or 75 mm Hg and did not evaluate lower DBP level with the outcomes. One prospective cohort study [33] from China categorized DBP by every 5 mm Hg setting <68 mm Hg as the lowest category and after

adjustment for BP meds showed a J-curve correlation between the OR of incident CKD and DBP.

Decline in DBP may contribute to organ ischemic damage, especially in case of vessel wall stiffening associated with atherosclerotic progression. Lower DBP, especially in those with BP meds, was associated with higher incidence of CKD in the elderly (online suppl. Table 3) who are assumed to have more atherosclerotic progression. High SBP and low DBP may be interpreted as isolated systolic hypertension. Previous studies have reported a relation of isolated systolic hypertension and atherosclerotic diseases [34], which would not be surprising to be related to the development of CKD. Pulse pressure that reflects the stiffness of the vessel wall [35] was also associated with higher rates of incident CKD (online suppl. Table 4), but in actual clinical practice, DBP is more practical and recognizable than pulse pressure. In line with previous studies [36, 37], the present study confirmed a weak, but significant, relationship between SBP and incident CKD regardless of BP meds (online suppl. Table 5).

There were some limitations that need to be mentioned. First, annual data were obtained on a single measurement at the time of health check-up. Precisely speaking, CKD is defined by at least 2 evaluations 3 months apart, so therefore, annual measurement of eGFR during the observation period may overestimate the incidence of CKD. This limitation will apply to many other retrospective observational studies [38–41]. Second, only limited pre-set information related to health check-up was available. So, unfortunately, urine protein could only be obtained by dipstick, and quantitative evaluation of albuminuria was not available. Third, the cohort was evaluated after only 2 years which may be too short to evaluate the incidence and course of CKD. Finally, type, amount, and duration of BP-lowering medication were not defined.

Conclusions

In conclusion, this study showed that lower DBP was associated with higher risk of incident CKD in the general population only in those taking BP meds. The BP meds group is a high-risk population and that lowering DBP by BP meds may have detrimental effects on the kidney.

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Disclosure Statement

All authors declare that they have no competing interests.

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