

RESEARCH ARTICLE

Antihypertensive treatment and risk of cardiovascular mortality in patients with chronic kidney disease diagnosed based on the presence of proteinuria and renal function: A large longitudinal study in Japan

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Data Availability Statement: We used data available upon request due to ethical restrictions on

Abstract

Several recent clinical trials and meta-analyses have shown that lowering blood pressure reduces the risk of cardiovascular disease. However, current evidence that describes general demographics in blood pressure and mortality with chronic kidney disease is sparse in Japan. Using a population-based longitudinal cohort that received annual health checkups in Japan in 2008, hypertensive status, self-reported use of antihypertensive drugs, and prognosis were examined through 2012. Chronic kidney disease was defined as positive proteinuria or estimated glomerular filtration rate <60 ml/min/1.73 m². Subjects were 40 to 74 years old (n = 227,204) with median 3.6 years follow-up period, and patients with and without chronic kidney disease were analyzed separately (n = 183,586 and n = 43,618, respectively). Cardiovascular disease mortality, comprising coronary heart diseases and stroke as entered in the national death registry using ICD-10 coding, was examined. Among all subjects, 346 deaths (96 in chronic kidney disease and 250 in non-chronic kidney disease) due to cardiovascular disease occurred. Compared with cardiovascular disease mortality in chronic kidney disease patients with untreated normal blood pressure, the multi-variable adjusted hazard ratio was 3.08 (95% confidence interval: 1.75–5.41) for those with untreated hypertension, 2.30 (1.31–4.03) for those who became normotensive after treatment, and 3.28 (1.91–5.64) for those who remained hypertensive despite treatment. In non-chronic kidney disease subjects, the ratios were 1.90 (1.33–5.41), 1.95 (1.35–2.80), and 1.77 (1.18–2.66), respectively. These results from a nationwide cohort could be one of

sharing data publicly. The protocol of this project (Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan) determined that analytical data were distributed only to the members of steering committee to avoid any possibility that someone else identify individuals of this cohort. Because the data contain potentially identifying information (i.e. prefectural number and date of health checking), our institutional ethics committee has imposed them. Also, data had been obtained with the protocol approved by the relevant institutional ethical review board. We would like to put the information regarding data access committee; Department of Chronic Kidney Disease Initiatives Fukushima Medical University School of Medicine, Fukushima, Japan (dckdi@fmu.ac.jp).

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representative demographics of controlling blood pressure and cardiovascular disease deaths when treating patients with chronic kidney disease in Japan in recent years. Even after development and spread of anti-hypertensive drugs, preventing development of hypertension is preferable, because any hypertension treatment status comparing untreated normal blood pressure was a risk of cardiovascular mortality at baseline year.

Introduction

High blood pressure (BP) confers a risk of cardiovascular disease (CVD) [1–3]. Compared with the general population, patients with chronic kidney disease (CKD) have a high risk of CVD mortality [4]. Guidelines recommend lower BP targets in the CKD population than in the general population to slow the progression of CKD [5,6]. Antihypertensive therapy is well known to reduce CVD risk in the general population [7,8]. However, there is little evidence regarding BP treatment and CVD death in patients with CKD.

Numerous observational studies focused on general populations have found that, for a given baseline BP, the risk of CVD is higher for people who use antihypertensive medications than for those who do not [1,9–14]. However, most of them failed to consider participants' renal function and proteinuria, which are well-known determinants of cardiovascular risk, because the cohorts were established decades ago, before the current definitions of CKD were developed. A recent meta-analysis of data from randomized, controlled trials showed the effectiveness of BP reduction by antihypertensive medications [15]. However, systematic searches of 123 randomized trials demonstrated that only a few reported the renal function of the cohort. For example, of 31 BP-lowering trials assessing different BP targets, only 6 studies selected cohorts that included CKD patients [16–21], whereas 12 studies defined no-CKD cohorts, and the remaining 13 did not report the renal function of their cohorts. These results also indicate the rarity of longitudinal cohorts that include a well-identified CKD population for assessing CVD mortality.

The present study evaluated a longitudinal, general-population cohort of 227,204 persons who received annual health checkups, including examinations for proteinuria and renal function according to “The Specific Health Check and Guidance in Japan” program in 2008, and followed their prognosis and cause of death through December 2012. In subpopulations with and without CKD diagnosed based on the presence of proteinuria and renal function, risks for all-cause and CVD mortality were examined among various categories of BP control. This analysis provides information about the representative status of BP control and CVD mortality of Japanese people with CKD in recent years.

Methods

Patients and methods

This longitudinal cohort study was conducted according to the guidelines of the Declaration of Helsinki and was granted ethics approval by the relevant institutional review boards (University of Tsukuba for ethical issues approved as No. 999, UMIN: 000019774). Original Ethics Committee approval was obtained from Fukushima Medical University (IRB #1485, #2771).

The study was performed as part of the prospective ongoing “Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance (so-called “Tokutei-Ken-shin”) in Japan” project [22]. Other details, such as the participants' areas of residence, were

reported previously [23–25]. Outliers were deleted through winsorization; they accounted for 0.01%–0.1% of the total. The raw database was solely used and managed by the statistician, and the principal analyses to identify those who died among screened subjects were completed by March 2015 and recently reported [26]. Subsequent analyses were done using a standard analysis file (SAF) without any personal identifiers.

The duration of follow-up of the subjects was 1 to 4 years (2008 through 2012, median duration was 3.6 years). The net subject population comprised 227,204 people (59.0% [$n = 134,103$] were women) aged from 40 to 74 years and for whom all of the data necessary for our research purposes were available. The data included information about age, sex, body mass index (BMI), systolic BP, diastolic BP, smoking habit, use of antihypertensive, lipid-lowering, and hypoglycemic drugs (obtained by self-reported questionnaire), and the results of dipstick urinalyses for proteinuria and blood tests for glucose levels, creatinine concentration, and lipid status.

Mortality surveillance

The underlying causes of death were coded according to ICD-10. Follow-up was conducted through December 2012. Incidents of CVD death were defined by ICD coding as I20-29 and I60-69.

Measurement of parameters

Urinalysis by the dipstick method was performed on a single spot-urine specimen collected early in the morning. Urine dipstick results for proteinuria were interpreted by the medical staff at each local medical institution and recorded as –, +/-, 1+, 2+, and 3+. In Japan, the Japanese Committee for Clinical Laboratory Standards (<http://jccls.org/>) recommends that all urine dipstick results of 1+ correspond to a urinary protein level of 30 mg/dl; proteinuria was defined as 1+ or greater. Serum creatinine was measured using the enzymatic method. The glomerular filtration rate (GFR) was estimated using the formula of the Japanese Society of Nephrology [27]. CKD was defined as positive proteinuria or estimated GFR (eGFR) <60 ml/min/1.73 m². Hyperglycemia was defined as HbA1c $\geq 6.5\%$, and hypertension was defined as systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg. Hypercholesterolemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dl, high-density lipoprotein cholesterol ≤ 40 mg/dl, or triglycerides ≥ 200 mg/dl. These comorbid conditions at the baseline year were used for the risk analysis.

Statistical analysis

The primary outcomes for the analysis were all-cause and CVD deaths during the follow-up period. Variables were age, sex, HbA1c, hypertension, renal function, proteinuria, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, cigarette smoking, use of antihypertensive medication, use of lipid-lowering drugs, and treatment for diabetes. The hypertension treatment category was defined according to BP levels (normal, $<140/<90$ mmHg; hypertensive, $\geq 140/\geq 90$ mmHg), as directed in the hypertension guidelines [28]. When the systolic and diastolic BPs were in different categories, the subject was assigned to the hypertension treatment category. After subjects were categorized according to BP, they were allocated to untreated normal, untreated hypertensive, treated normotensive, and treated hypertensive groups. Hazard ratios of the incidence of CVD were estimated using the Cox regression model (SAS version 9.4, SAS Institute, Cary, NC, USA). Other statistical analyses and graphical analyses were performed using Stata version 14 and GraphPad Prism version 6. A P value <0.05 was considered significant.

Results

Table 1 presents the mean ages of the subjects and the means and proportions of risk factors at the baseline year, according to hypertension treatment category. Compared with subjects with untreated, normal BP at baseline, untreated hypertensive subjects were a mean of 2.4 years older, and the treated population was 5.5 years older on average; in addition, BMI was higher in hypertensive subjects, regardless of treatment category. Furthermore, eGFR was 1.3 ml/min/1.73 m² lower in the subpopulation with untreated hypertension and 5 ml/min/1.73 m² lower in subjects who remained hypertensive despite treatment, compared with that of subjects with untreated normal BP. The rate of positive proteinuria was higher in hypertensive than in normotensive subjects, and those with treated hypertension had the highest rate of positive proteinuria. The use of lipid-lowering drugs and of diabetes treatment paralleled that of hypertensive drugs. Finally, the rate of cigarette smoking was lower in treated than in untreated populations.

The characteristics of subjects with and without CKD are shown in Table 2. The trends in mean age, BMI, eGFR, and proportions of positive proteinuria, medication use, and cigarette smoking between subjects with and without CKD (Table 2) paralleled those between hypertension treatment categories (Table 1). Within a hypertension treatment category, subjects with CKD tended to include fewer women and have a higher mean age, higher BMI, worse dyslipidemia and hyperglycemia and a higher rate of positive proteinuria than did those without CKD (Table 2).

During follow-up, 2745 all-cause deaths (2107 non-CKD subjects and 638 CKD subjects) and 346 CVD deaths (250 non-CKD subjects and 96 CKD subjects) occurred in this cohort. The all-cause mortality and CVD mortality in subjects with and without CKD according to proteinuria and renal function are shown in Table 3. Dividing the number of all-cause

Table 1. Study population.

		Normotensive	Hypertensive	Normotensive	Hypertensive	P
		Untreated	Untreated	Treated	Treated	
Number		127,312	37,867	34,662	27,363	
Sex	%, women	63.4	52.9	56.6	53.2	<0.001
Age	years	60.4 ± 9.4	62.8 ± 8.2	65.9 ± 6.4	65.9 ± 6.5	<0.001
Height	cm	157.2 ± 8.4	157.5 ± 8.8	156.0 ± 8.4	156.4 ± 8.6	<0.001
Weight	kg	56.0 ± 10.0	59.3 ± 10.9	59.4 ± 10.4	60.9 ± 10.8	<0.001
Body mass index	kg/m ²	22.6 ± 3.1	23.8 ± 3.3	24.3 ± 3.3	24.8 ± 3.5	<0.001
Systolic blood pressure	mmHg	118.9 ± 12.0	148.9 ± 12.8	126.2 ± 9.0	149.3 ± 11.5	<0.001
Diastolic blood pressure	mmHg	71.7 ± 8.5	86.9 ± 9.8	74.7 ± 7.8	84.8 ± 9.5	<0.001
Triglycerides	mg/dl	112 ± 76	132 ± 96	125 ± 76	133 ± 89	<0.001
High-density lipoprotein	mg/dl	63 ± 16	61 ± 16	59 ± 15	59 ± 15	<0.001
Low-density lipoprotein	mg/dl	126 ± 31	129 ± 32	120 ± 28	123 ± 29	<0.001
HbA1c	%	5.3 ± 0.6	5.4 ± 0.8	5.5 ± 0.7	5.5 ± 0.8	<0.001
eGFR	ml/min/1.73 m ²	75.8 ± 15.5	74.5 ± 15.9	70.8 ± 16.2	71.0 ± 16.3	<0.001
Proteinuria	%, + or more	3.2	6.7	7.8	11.2	<0.001
Use of antihypertensive drugs	%, yes	0	0	100	100	–
Lipid-lowering drug use	%, yes	8.8	7.4	28.8	26.0	<0.001
Diabetes treatment	%, yes	3.0	3.1	9.4	10.4	<0.001
Cigarette smoking	%, yes	14.4	14.3	10.8	10.6	<0.001

Low eGFR; less than 60 ml/min/1.73 m²

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Table 2. Baseline characteristics of subpopulations with and without chronic kidney disease (CKD).

		Normotensive	Hypertensive	Normotensive	Hypertensive	P
		Untreated	Untreated	Treated	Treated	
CKD (-)						
Number		108653	30341	25236	19356	
Sex	%, women	65.0	55.3	60.4	57.8	<0.001
Age	years	59.7 ± 9.5	62.4 ± 8.3	65.5 ± 6.6	65.4 ± 6.7	<0.001
Height	cm	157.0 ± 8.4	157.2 ± 8.8	155.6 ± 8.4	155.9 ± 8.5	<0.001
Weight	kg	55.7 ± 10.0	58.8 ± 10.8	58.7 ± 10.2	60.1 ± 10.7	<0.001
Body mass index	kg/m ²	22.5 ± 3.1	23.7 ± 3.3	24.2 ± 3.3	24.6 ± 3.5	<0.001
Systolic blood pressure	mmHg	119 ± 12	149 ± 13	126 ± 9	149 ± 11	<0.001
Diastolic blood pressure	mmHg	72 ± 9	87 ± 10	75 ± 8	85 ± 9	<0.001
Triglycerides	mg/dl	111 ± 75	130 ± 95	122 ± 74	129 ± 88	<0.001
High-density lipoprotein	mg/dl	63 ± 16	62 ± 16	60 ± 15	60 ± 15	<0.001
Low-density lipoprotein	mg/dl	126 ± 31	129 ± 32	120 ± 28	123 ± 29	<0.001
HbA1c	%	5.3 ± 0.6	5.4 ± 0.7	5.4 ± 0.7	5.5 ± 0.7	<0.001
eGFR	ml/min/1.73 m ²	78.9 ± 13.9	78.1 ± 13.8	76.6 ± 13.1	76.8 ± 13.1	<0.001
Low eGFR	%, yes	0	0	0	0	-
Proteinuria	%, + or more	0	0	0	0	-
Use of antihypertensive drugs	%, yes	0	0	100	100	-
Use of lipid-lowering drug	%, yes	8.4	7.2	28.0	25.7	<0.001
Diabetes treatment	%, yes	2.8	2.9	8.5	9.0	<0.001
Cigarette smoking	%, yes	14.8	14.3	10.8	10.4	<0.001
CKD (+)						
Number		18659	7526	9426	8007	
Sex	%, women	53.9	43.0	46.4	41.8	<0.001
Age	years	64.0 ± 7.7	64.9 ± 7.2	67.0 ± 5.9	67.0 ± 6.0	<0.001
Height	cm	158.1 ± 8.3	158.6 ± 8.6	157.3 ± 8.4	157.7 ± 8.5	<0.001
Weight	kg	57.7 ± 10.2	61.1 ± 10.9	61.2 ± 10.5	62.9 ± 10.7	<0.001
Body mass index	kg/m ²	23.0 ± 3.1	24.2 ± 3.4	24.7 ± 3.4	25.2 ± 3.5	<0.001
Systolic blood pressure	mmHg	120 ± 12	150 ± 14	126 ± 9	150 ± 12	<0.001
Diastolic blood pressure	mmHg	72 ± 8	88 ± 10	74 ± 8	85 ± 10	<0.001
Triglycerides	mg/dl	121 ± 79	141 ± 102	132 ± 80	142 ± 93	<0.001
High-density lipoprotein	mg/dl	61 ± 16	59 ± 16	56 ± 15	57 ± 15	<0.001
Low-density lipoprotein	mg/dl	128 ± 31	130 ± 33	120 ± 28	123 ± 30	<0.001
HbA1c	%	5.3 ± 0.7	5.5 ± 1.0	5.5 ± 0.8	5.6 ± 0.9	<0.001
eGFR	ml/min/1.73 m ²	58.0 ± 12.6	60.0 ± 15.6	55.2 ± 13.3	56.7 ± 14.7	<0.001
Low eGFR	%, yes	82.8	74.5	82.6	76.8	<0.001
Proteinuria	%, + or more	21.9	33.9	29.0	38.7	<0.001
Use of antihypertensive drugs	%, yes	0	0	100	100	-
Use of lipid-lowering drugs	%, yes	11.0	7.9	31.1	27.0	<0.001
Diabetes treatment	%, yes	4.3	3.9	11.9	13.9	<0.001
Cigarette smoking	%, yes	12.4	14.2	11.0	10.9	<0.001

Low eGFR; less than 60 ml/min/1.73 m²

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mortalities and CVD deaths in each hypertension treatment category by the total number of subjects in that subpopulation showed increased rates of both all-cause and CVD mortalities in these subjects, regardless of their CKD status, compared to subjects with untreated, normal BP (Table 3).

Table 3. Number, all-cause mortality, and mortality due to cardiovascular disease (CVD) in subpopulations with and without chronic kidney disease (CKD) according to proteinuria (UP) and renal function (eGFR).

		Normotensive	Hypertensive	Normotensive	Hypertensive
		Untreated	Untreated	Treated	Treated
	UP				
Number	(-)	123199	35270	31915	24216
	(+)	4113	2597	2747	3147
All-cause mortality	(-)	1179 (0.96%)	435 (1.23%)	464 (1.45%)	341 (1.41%)
	(+)	79 (1.92%)	78 (3.00%)	83 (3.02%)	86 (2.73%)
CVD mortality	(-)	98 (0.08%)	61 (0.17%)	70 (0.22%)	55 (0.23%)
	(+)	6 (0.15%)	19 (0.73%)	15 (0.55%)	22 (0.70%)
	Low eGFR				
Number	(-)	111868	32290	26892	21230
	(+)	15444	5577	7770	6133
All-cause mortality	(-)	1008 (0.90%)	426 (1.32%)	389 (1.45%)	284 (1.34%)
	(+)	250 (1.62%)	87 (1.56%)	158 (2.03%)	143 (2.33%)
CVD mortality	(-)	87 (0.08%)	62 (0.19%)	57 (0.21%)	44 (0.21%)
	(+)	17 (0.11%)	18 (0.32%)	28 (0.36%)	33 (0.54%)
	CKD				
Number	(-)	108653	30341	25236	19356
	(+)	18659	7526	9426	8007
All-cause mortality	(-)	961 (0.88%)	372 (1.23%)	352 (1.39%)	244 (1.26%)
	(+)	297 (1.59%)	141 (1.87%)	195 (2.07%)	183 (2.29%)
CVD mortality	(-)	83 (0.08%)	51 (0.17%)	52 (0.21%)	36 (0.19%)
	(+)	21 (0.11%)	29 (0.39%)	33 (0.35%)	41 (0.51%)

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The hazard ratio (HR) for all-cause mortality in each hypertensive status is shown in Fig 1. Subjects with and without proteinuria (Fig 1A) or low eGFR (Fig 1B) and those with and without CKD were analyzed separately, regardless of how the condition was defined (i.e., “overall CKD”) (Fig 1C). Using the untreated normotensive subpopulation as a reference, the risk of all-cause mortality among patients with proteinuria was significantly increased among those with untreated hypertension (age- and sex-adjusted HR, 1.38 [95% confidence interval 1.01–1.89]; multivariable-adjusted HR, 1.45 [1.06–1.99]; Fig 1A). However, among subjects with low eGFR (Fig 1B) and those with overall CKD (Fig 1C), the HR for all-cause mortality did not differ significantly between subjects with untreated normotension and those with untreated hypertension, those who became normotensive during treatment, or those who remained hypertensive despite treatment. Overall, analyses for all-cause mortality risk did not identify hypertensive status as an independent risk factor in subjects diagnosed with CKD according to the presence of proteinuria or decreased renal function.

In contrast to all-cause mortality, relative to those for the subpopulation with untreated normal BP, the adjusted HRs for CVD mortality in subjects without proteinuria, without low eGFR, and without CKD showed significance (Fig 2). Moreover, HRs for CVD mortality in subjects with CKD were mostly significant and varied widely in each hypertension treatment category (filled circles in Fig 2): from 2.12 to 4.61 in subjects with proteinuria, from 2.27 to 3.08 in those with low eGFR, and from 2.30 to 3.28 in those with overall CKD. Summarizing the above, these analyses identified every hypertension treatment category as a risk factor for CVD mortality both in non-CKD and in CKD status, independent of well-known CVD risk factors, such as age, sex, BMI, and cigarette smoking.

Discussion

When compared with the general population, patients with CKD are at increased risk for CVD mortality [4,29]. General-population-based observational studies have shown that, for a

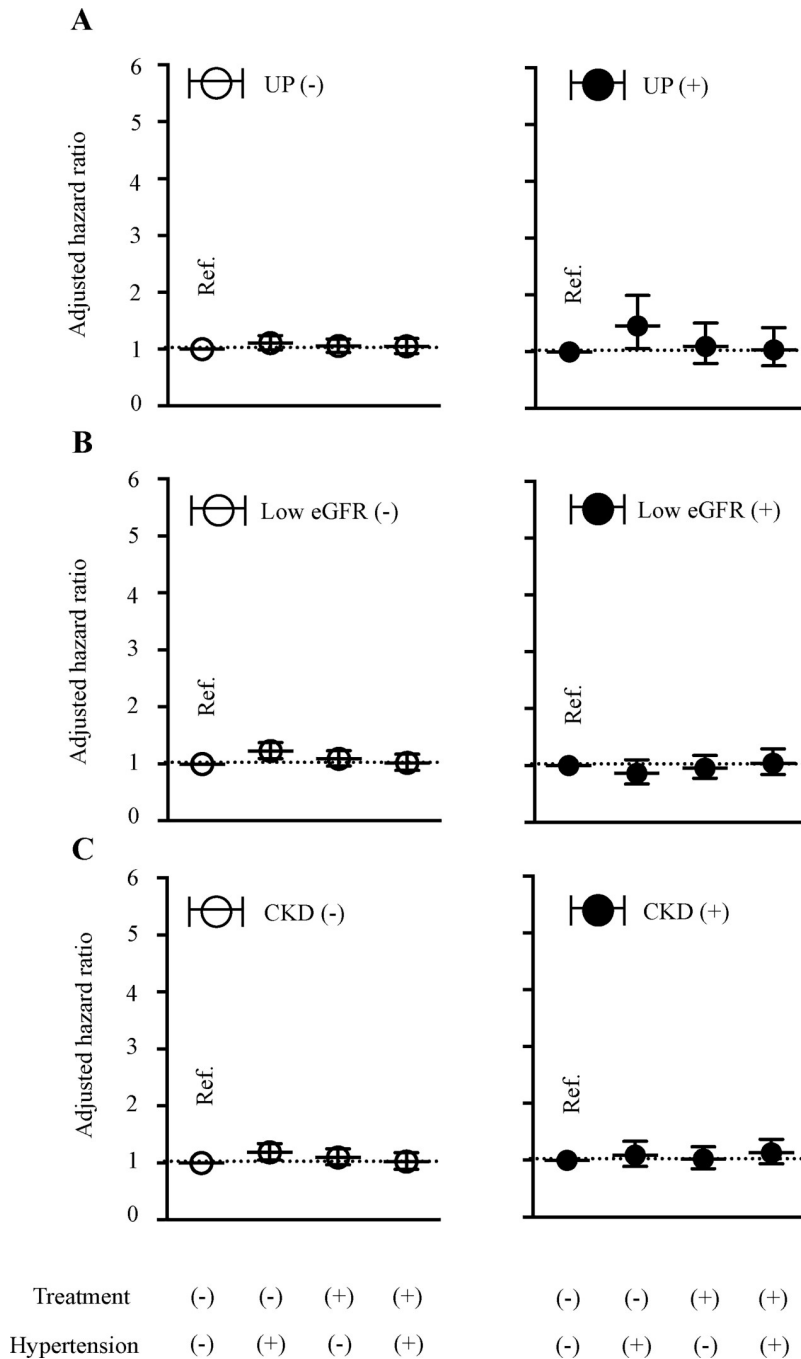


Fig 1. Risk of all-cause mortality in each hypertension treatment category. The multivariable-adjusted hazard ratio and 195% confidence interval for all-cause death in each hypertension treatment category are shown. The reference category is untreated, normal blood pressure. The subgroups reflect the presence (or absence) of proteinuria (A), reduced renal function (B), or chronic kidney disease (C). Adjusted factors for death were: age; sex; cigarette smoking; body mass index; proteinuria; levels of triglycerides, high-density lipoprotein, and low-density lipoprotein; use of lipid-lowering drugs; HbA1c; and treatment for diabetes.

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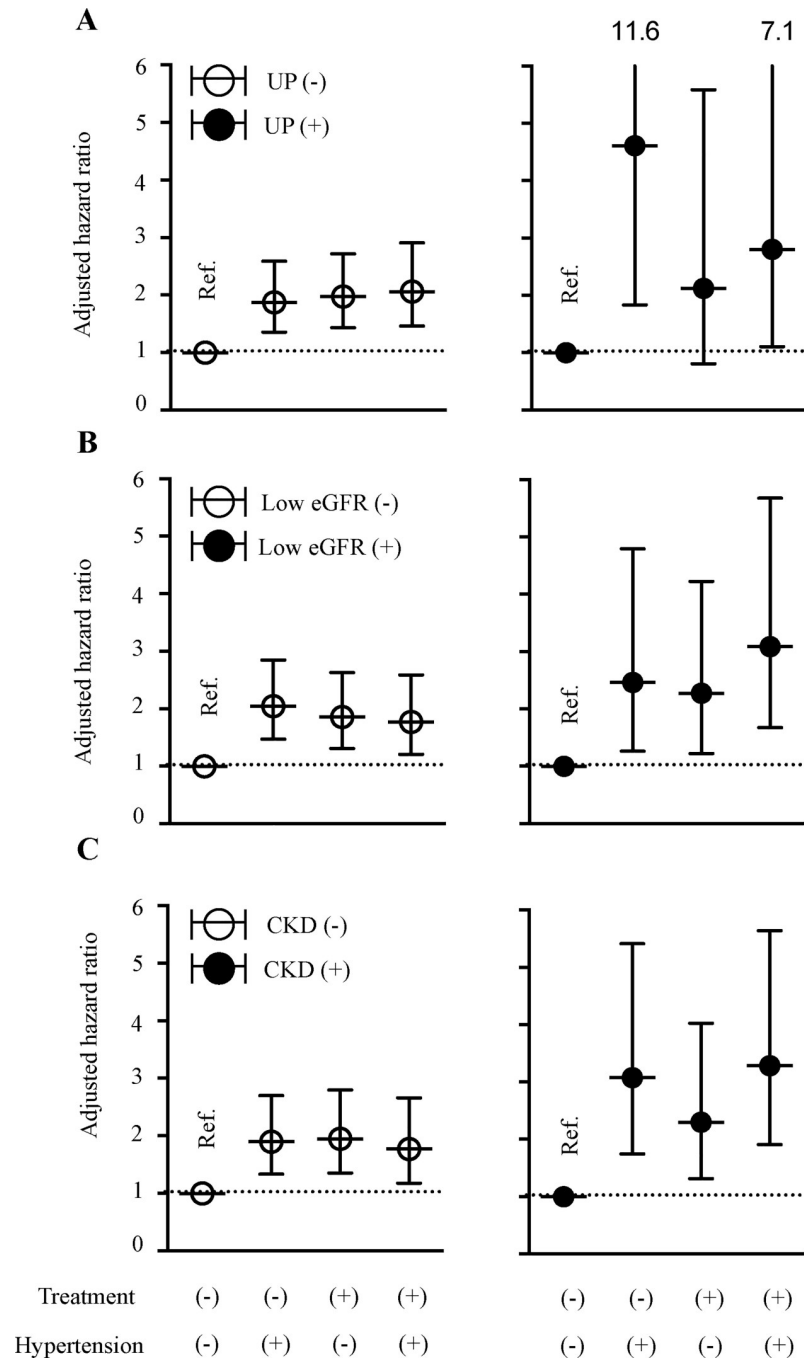


Fig 2. Risk of all cardiovascular mortality in each hypertension treatment category. The multivariable-adjusted hazard ratio and 95% confidence interval for cardiovascular mortality in each hypertensive treatment category are shown. The reference category is untreated, normal blood pressure. The subgroups reflect the presence (or absence) of proteinuria (A), reduced renal function (B), and chronic kidney disease (C). Adjusted factors for death were: age; sex; cigarette smoking; body mass index; proteinuria; levels of triglycerides, high-density lipoprotein, and low-density lipoprotein; use of lipid-lowering drugs; HbA1c; and treatment for diabetes.

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given BP at baseline, CVD risk is higher in subjects who use antihypertensive medications than in those who do not [9–14]. Although the cohorts in the cited studies were well defined and rigorously followed, all of the cohorts were established decades ago (i.e., 1970 [9,10], 1991

through 1998 [11], 1967 through 1996 [13], and 1991 through 1996 [14]). In addition, their results were evaluated in the context of then-contemporary clinical practice. Therefore, most of the evidence [2,30–34] does not take into consideration the renal function of the participants, because the cohorts were also built without the conception of CKD from Kidney Disease: Improving Global Outcomes (KDIGO) in 2002 [6]. Because the timing and breadth of the recruitment might affect the characteristics of cohort subjects because of changes in clinical practice regarding the treatment of hypertension, use of a cohort with well-identified renal function and consistent baseline year data facilitates assessment of the relationship between BP control at baseline and CVD mortality in patients with CKD.

In this analysis, a general-population-based cohort established in 2008 was examined for which data regarding proteinuria, renal function, other CVD risk factors, and ICD-coded cause of death were available. In this cohort, age, risks, and proportions of patients at baseline year differed significantly between subjects with untreated normal BP and those in other hypertension treatment categories. Because ageing is associated with a decline in eGFR and increases in BP and the rate of positive proteinuria [35], the older age and lower eGFR seen in treated or hypertensive subjects are unsurprising (Table 1). Similarly, within the same hypertension treatment category, subjects with CKD tended to be older than those without CKD (Table 2).

Previous Japanese general-population-based cohorts established from 1980 through 1995 [2, 31–34] comprised 27.4% with untreated hypertension. Research and development in anti-hypertensive drugs has been remarkable. As examples, angiotensin-converting enzyme inhibitors began to be prescribed in 1982 to 1998 and angiotensin receptor blockers began in 1998 to 2012, and their market share in Japan continues to grow. Our investigation shows the rate of untreated hypertension was subjects with CKD (17.3%) than those without CKD (16.5%), suggesting successful spread of anti-hypertensive drugs in recent years (Table 2).

A collaborative prospective meta-analysis of randomized trials to examine the cardiovascular effects of lowering BP in people with CKD according to renal function [36], which covers 152,290 participants, including 30,295 with eGFR <60 ml/min/1.73 m². Another [15] performed a meta-analysis of systematic searches of BP-lowering trials to examine the effects of a 10-mmHg reduction in systolic BP on the relative risk of major CVD in 30,766 participants from 18 cohorts. However, neither of these previous studies [15,36] directly showed the effect of BP reduction in patients with proteinuria. Though our study could not show any effect of interventional BP control on CVD mortality in patients with proteinuria, markedly high HR (4.61) in untreated hypertension category for CVD mortality in positive proteinuria population implies importance of BP control in such patients (Fig 2A).

The strength of this study was that it evaluated a large general population (i.e., more than 100,000 subjects) with available data regarding renal function, proteinuria, and CVD (i.e., stroke and cardiac events) mortality according to ICD-10 coding. These features allowed us to perform sub-analyses of the CKD and non-CKD subjects enrolled, showing that the risk of CVD in patients who remained hypertensive despite treatment differed between those with and without CKD, between those with and without proteinuria, and between those with and without low eGFR.

However, this study had several limitations. First, the database did not have details of the types of antihypertensive drugs used, such as renin-angiotensin-targeted drugs, which affect the incidence of CVD [37], because this information was self-reported and not obtained through medical records or claims. Second, the follow-up time (maximum, 4 years) was much shorter than in previous studies. Because this observational study could not show cause/result relationship, evidence for interventional benefit of BP control was not obtained.

Nevertheless, the results from a nationwide cohort could be one of representative demographics of controlling blood pressure and cardiovascular disease deaths when treating

patients with CKD in Japan in recent years. Even after current development and sufficient spread of anti-hypertensive drugs, preventing development of hypertension is preferable, because any hypertension treatment status comparing untreated normal blood pressure was a risk of CVD mortality at baseline year.

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References

1. Asayama K, Ohkubo T, Yoshida S, Suzuki K, Metoki H, Harada A, et al. Stroke risk and antihypertensive drug treatment in the general population: the Japan arteriosclerosis longitudinal study. *J Hypertens.* 2009; 27: 357–364. <https://doi.org/10.1097/HJH.0b013e32831967ca> PMID: 19155790
2. Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, et al. Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med.* 2003; 163: 361–366. <https://doi.org/10.1001/archinte.163.3.361> PMID: 12578518
3. Ikeda A, Iso H, Yamagishi K, Inoue M, Tsugane S. Blood pressure and the risk of stroke, cardiovascular disease, and all-cause mortality among Japanese: the JPHC Study. *Am J Hypertens.* 2009; 22: 273–280. <https://doi.org/10.1038/ajh.2008.356> PMID: 19229210
4. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010; 375: 2073–2081. [https://doi.org/10.1016/S0140-6736\(10\)60674-5](https://doi.org/10.1016/S0140-6736(10)60674-5) PMID: 20483451
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003; 42: 1206–1252. <https://doi.org/10.1161/01.HYP.0000107251.49515.c2> PMID: 14656957
6. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39: S1–266. PMID: 11904577
7. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet.* 2001; 358: 1305–1315. [https://doi.org/10.1016/S0140-6736\(01\)06411-X](https://doi.org/10.1016/S0140-6736(01)06411-X) PMID: 11684211

8. Turnbull F, Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003; 362: 1527–1535. [https://doi.org/10.1016/s0140-6736\(03\)14739-3](https://doi.org/10.1016/s0140-6736(03)14739-3) PMID: 14615107
9. Andersson OK, Almgren T, Persson B, Samuelsson O, Hedner T, Wilhelmsen L. Survival in treated hypertension: follow up study after two decades. *BMJ*. 1998; 317: 167–171. <https://doi.org/10.1136/bmj.317.7152.167> PMID: 9665894
10. Almgren T, Persson B, Wilhelmsen L, Rosengren A, Andersson OK. Stroke and coronary heart disease in treated hypertension—a prospective cohort study over three decades. *J Intern Med*. 2005; 257: 496–502. <https://doi.org/10.1111/j.1365-2796.2005.01497.x> PMID: 15910553
11. Izumi M, Suzuki K, Sakamoto T, Hayashi M. Advantages and limitations of antihypertensive treatment for stroke risk in a general population: the Akita Stroke Registry. *Acta Cardiol*. 2011; 66: 729–735. <https://doi.org/10.1080/ac.66.6.2136956> PMID: 22299383
12. Benetos A, Thomas F, Bean KE, Guize L. Why cardiovascular mortality is higher in treated hypertensives versus subjects of the same age, in the general population. *J Hypertens*. 2003; 21: 1635–1640. <https://doi.org/10.1097/00004872-200309000-00011> PMID: 12923394
13. Gudmundsson LS, Johannsson M, Thorgerirsson G, Sigfusson N, Sigvaldason H, Witteman JC. Risk profiles and prognosis of treated and untreated hypertensive men and women in a population-based longitudinal study: the Reykjavik Study. *J Hum Hypertens*. 2004; 18: 615–622. <https://doi.org/10.1038/sj.jhh.1001725> PMID: 15071487
14. Li C, Engstrom G, Hedblad B, Berglund G, Janzon L. Blood pressure control and risk of stroke: a population-based prospective cohort study. *Stroke*. 2005; 36: 725–730. <https://doi.org/10.1161/01.STR.0000158925.12740.87> PMID: 15746450
15. Etehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016; 387: 957–967. [https://doi.org/10.1016/S0140-6736\(15\)01225-8](https://doi.org/10.1016/S0140-6736(15)01225-8) PMID: 26724178
16. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008; 359: 2417–2428. <https://doi.org/10.1056/NEJMoa0806182> PMID: 19052124
17. Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, et al. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. *Hypertension*. 2008; 51: 393–398. <https://doi.org/10.1161/HYPERTENSIONAHA.107.098475> PMID: 18172059
18. Rakugi H, Ogihara T, Umemoto S, Matsuzaki M, Matsuoka H, Shimada K, et al. Combination therapy for hypertension in patients with CKD: a subanalysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events trial. *Hypertens Res*. 2013; 36: 947–958. <https://doi.org/10.1038/hr.2013.63> PMID: 23864054
19. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003; 290: 2805–2816. <https://doi.org/10.1001/jama.290.21.2805> PMID: 14657064
20. Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005; 36: 1218–1226. <https://doi.org/10.1161/01.STR.0000166048.35740.a9> PMID: 15879332
21. Ogihara T. Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension (The PATE-Hypertension Study) in Japan. *Am J Hypertens*. 2000; 13: 461–467. [https://doi.org/10.1016/s0895-7061\(99\)00215-0](https://doi.org/10.1016/s0895-7061(99)00215-0) PMID: 10826395
22. Iseki K, Asahi K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, et al. Risk factor profiles based on estimated glomerular filtration rate and dipstick proteinuria among participants of the Specific Health Check and Guidance System in Japan 2008. *Clin Exp Nephrol*. 2012; 16: 244–249. <https://doi.org/10.1007/s10157-011-0551-9> PMID: 22057582
23. Yano Y, Sato Y, Fujimoto S, Konta T, Iseki K, Moriyama T, et al. Association of high pulse pressure with proteinuria in subjects with diabetes, prediabetes, or normal glucose tolerance in a large Japanese general population sample. *Diabetes Care*. 2012; 35: 1310–1315. <https://doi.org/10.2337/dc11-2245> PMID: 22474041
24. Sato Y, Yano Y, Fujimoto S, Konta T, Iseki K, Moriyama T, et al. Glycohemoglobin not as predictive as fasting glucose as a measure of prediabetes in predicting proteinuria. *Nephrol Dial Transplant*. 2012; 27: 3862–3868. <https://doi.org/10.1093/ndt/gfs324> PMID: 22859789

25. Nagai K, Yamagata K, Ohkubo R, Saito C, Asahi K, Iseki K, et al. Annual decline in estimated glomerular filtration rate is a risk factor for cardiovascular events independent of proteinuria. *Nephrology (Carlton)*. 2014; 19: 574–580.
26. Iseki K, Asahi K, Yamagata K, Fujimoto S, Tsuruya K, Narita I, et al. (2017) Mortality risk among screened subjects of the specific health check and guidance program in Japan 2008–2012. *Clin Exp Nephrol*. 2017; 21: 978–985. <https://doi.org/10.1007/s10157-017-1392-y> PMID: 28258498
27. Iseki K, Horio M, Imai E, Matsuo S, Yamagata K. Geographic difference in the prevalence of chronic kidney disease among Japanese screened subjects: Ibaraki versus Okinawa. *Clin Exp Nephrol*. 2009; 13: 44–49. <https://doi.org/10.1007/s10157-008-0080-3> PMID: 18854923
28. Subcommittee Guidelines. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens*. 1999; 17: 151–83. PMID: 10067786
29. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004; 351: 1296–1305. <https://doi.org/10.1056/NEJMoa041031> PMID: 15385656
30. Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. *JAMA*. 2006; 296: 1255–1265. <https://doi.org/10.1001/jama.296.10.1255> PMID: 16968850
31. Yasui D, Asayama K, Ohkubo T, Kikuya M, Kanno A, Hara A, et al. Stroke risk in treated hypertension based on home blood pressure: the Ohasama study. *Am J Hypertens*. 2010; 23: 508–514. <https://doi.org/10.1038/ajh.2010.15> PMID: 20186131
32. Nakanishi S, Yamada M, Hattori N, Suzuki G. Relationship between HbA1c and mortality in a Japanese population. *Diabetologia*. 2005; 48: 230–234. <https://doi.org/10.1007/s00125-004-1643-9> PMID: 15650819
33. Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, et al. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke*. 2004; 35: 1836–1841. <https://doi.org/10.1161/01.STR.0000131747.84423.74> PMID: 15166389
34. Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Ueshima H, et al. The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. *Atherosclerosis*. 2006; 184: 143–150. <https://doi.org/10.1016/j.atherosclerosis.2005.03.042> PMID: 15913635
35. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int*. 2007; 71: 159–166. <https://doi.org/10.1038/sj.ki.5002017> PMID: 17136030
36. Blood Pressure Lowering Treatment Trialists C, Ninomiya T, Perkovic V, Turnbull F, Neal B, Barzi F, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *BMJ*. 2013; 347: f5680. <https://doi.org/10.1136/bmj.f5680> PMID: 24092942
37. Kim-Mitsuyama S, Ogawa H, Matsui K, Jinnouchi T, Jinnouchi H, Arakawa K, et al. An angiotensin II receptor blocker-calcium channel blocker combination prevents cardiovascular events in elderly high-risk hypertensive patients with chronic kidney disease better than high-dose angiotensin II receptor blockade alone. *Kidney Int*. 2013; 83: 167–176. <https://doi.org/10.1038/ki.2012.326> PMID: 23051740