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Estimated glomerular filtration rate and the risk–benefit profile of intensive blood pressure control amongst nondiabetic patients: a post hoc analysis of a randomized clinical trial

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Abstract. Obi Y, Kalantar-Zadeh K, Shintani A, Kovesdy CP, Hamano T (University of California Irvine Medical Center, Orange, CA, USA; Obi Clinic, Osaka, Osaka, Japan; Fielding School of Public Health at UCLA, Los Angeles, California, USA; Tibor Rubin Veterans Affairs Medical Center, Long Beach, CA, USA; Osaka City University Graduate School of Medicine, Osaka, Osaka, Japan; University of Tennessee Health Science Center; Memphis VA Medical Center, Memphis, Tennessee, USA; Osaka University Graduate School of Medicine, Suita, Osaka, Japan). Estimated glomerular filtration rate and the risk–benefit profile of intensive blood pressure control amongst nondiabetic patients: a post hoc analysis of a randomized clinical trial. *J Intern Med* 2018; **283**: 314–327.

Background. The Systolic Blood Pressure Intervention Trial (SPRINT; ClinicalTrials.gov, NCT01206062) reported reduced cardiovascular events by intensive blood pressure (BP) control amongst hypertensive patients without diabetes. However, the risk–benefit profile of intensive BP control may differ across estimated glomerular filtration rate (eGFR) levels.

Methods. This is a post hoc analysis of the SPRINT. Nondiabetic hypertensive adults ($n = 9361$) with eGFR >20 mL per min per 1.73 m² were enrolled from 102 US facilities between November 2010 and

March 2013 and were followed up until August 2015 (median follow-up, 3.26 years). Patients were randomly assigned to either a systolic BP target of <120 or <140 mmHg (for intensive or standard treatment, respectively). The outcomes of interests were the development of (i) fatal and nonfatal major cardiovascular events and (ii) acute kidney injury (AKI).

Results. The cardiovascular benefit from intensive treatment was attenuated with lower eGFR ($P_{\text{interaction}} = 0.019$), whereas eGFR did not modify the adverse effect on AKI ($P_{\text{interaction}} = 0.179$). Amongst 891 participants with eGFR <45 mL per min per 1.73 m², intensive treatment did not reduce the cardiovascular outcome (54/446 vs. 54/445 events in the standard group, respectively; hazard ratio [HR], 0.92; 95% CI, 0.62–1.38) with an absolute rate difference (ARD) of -0.02 (95% CI, -0.07 to $+0.03$) per 100 patient-years, whereas it increased AKI (62/446 vs. 38/445 events in the standard group; HR, 1.73; 95% CI, 1.12–2.66) with an ARD of $+1.93$ (95% CI, $+1.88$ to $+1.97$) per 100 patient-years.

Conclusions. Intensive BP control may provide little or no benefit and even be harmful for patients with moderate-to-advanced chronic kidney disease.

Keywords: acute renal failure, blood pressure control, cardiovascular clinical research, chronic renal failure, hypertension.

Introduction

Chronic kidney disease (CKD) is an established risk factor for cardiovascular disease [1]. Interestingly, however, traditional cardiovascular risk factors, including hypertension, are paradoxically associated with better outcomes in advanced CKD [2], which is known as ‘reverse epidemiology’ or risk factor paradox [3]. The Modification of Diet in Renal Disease (MDRD) study indicated that the renoprotective effect of intensive blood pressure (BP) control may be attenuated amongst patients with lower kidney function [4]. In this population, an observational study also suggested an increased mortality risk associated with strict BP control [5], and cardiovascular benefit from intensive BP control has not been confirmed by randomized controlled trials (RCTs) [6]. By contrast, the Systolic Blood Pressure Intervention Trial (SPRINT) reported that whilst intensive BP control increased the incidence of acute kidney injury (AKI), the beneficial effect of intensive BP control on fatal and nonfatal cardiovascular events was not modified by the presence of CKD [i.e. estimated glomerular filtration rate (eGFR) <60 mL per min per 1.73 m²] [7, 8].

However, dichotomizing continuous variables often impair the statistical power to detect meaningful differences, which may have resulted in an apparently null effect modification by CKD. The incidence of both cardiovascular events and renal outcomes, including AKI and the progression of CKD, also substantially increases in more advanced stages of CKD in a disproportional manner [1, 9], even between stages 3a and 3b (i.e. eGFR 45–<60 vs. 30–<45 mL per min per 1.73 m²) [10]. Hence, eGFR may change the risk–benefit profile of intensive BP control in terms of absolute risk reduction/increase. Therefore, we conducted a post hoc analysis of the SPRINT to examine whether the effects of intensive BP control on cardiovascular events and adverse events are modified by eGFR, and we examined the relative and absolute effects on these efficacy and safety outcomes across more granular eGFR categories.

Methods

De-identified data from the SPRINT trial were obtained from the National Heart, Lung, and Blood Institute (NHLBI) Data Repository. This post hoc analysis of SPRINT data was approved by the ethics committee of the Japan Primary Care Association

with an exemption of written consent due to the anonymity of the participants and the noninvasive nature of the research.

Details of the study design of SPRINT have been described in the protocol (appears in Supporting information). Briefly, the SPRINT was an open-label RCT that enrolled hypertensive adults with an increased cardiovascular risk (based on a history of clinical or subclinical cardiovascular disease, CKD, a 10-year Framingham general cardiovascular disease risk $\geq 15\%$ or age ≥ 75 years) from 102 facilities in the USA between November 2010 and March 2013. Exclusion criteria consisted of type 2 diabetes, a history of stroke, eGFR ≤ 20 mL per min per 1.73 m², symptomatic heart failure within the past 6 months or reduced left ventricular ejection fraction (<35%), dementia, expected survival of <3 years, unintentional weight loss (>10%) during the preceding 6 months, systolic BP (SBP) of <110 mmHg following 1 min of standing or residence in a nursing home. A total of 9,361 participants were randomly assigned to a SBP target of either <120 mmHg (intensive treatment) or <140 mmHg (standard treatment) and were followed up until August 2015, when the trial was terminated early based on the significant interim finding favouring the study intervention [7].

Study measurements

Sociodemographic data were collected at baseline, and clinical and laboratory data were obtained at baseline and every 3 months. Medical records and electrocardiograms were obtained for the documentation of events. BP was determined using the mean of three properly sized automated cuff readings taken 1 min apart after 5 min of quiet rest without staff in the room. The 4-variable Modification of Diet in Renal Disease equation was used to calculate eGFR [11]. A structured interview was used in both groups every 3 months to obtain self-reported cardiovascular disease outcomes.

Clinical outcomes

The original efficacy outcome was the composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure and cardiovascular death. The other outcomes of interest in this study were renal outcomes. AKI was coded if listed in the hospital discharge summary and confirmed by the safety officer as amongst the top three reasons for admission or continued

hospitalization. The eGFR-based renal outcome amongst participants with CKD was a composite of a $\geq 50\%$ decrease in eGFR or the development of end-stage renal disease; amongst participants without CKD, the eGFR-based renal outcome was defined by a $\geq 30\%$ decrease in eGFR to a value of < 60 mL per min per 1.73 m². The eGFR-based renal outcome was confirmed by a subsequent test ≥ 90 days later. Incident albuminuria, defined by a doubling of the urinary albumin-to-creatinine ratio from < 10 mg g⁻¹ at baseline to ≥ 10 mg g⁻¹, was also evaluated for all study participants.

Statistical analysis

Given the nature of a post hoc analysis, whereby an established population with a fixed sample size is used, the power to detect the effect modification by eGFR was not calculated. All analyses were conducted with the intention-to-treat approach. We used linear mixed models with an unstructured covariance matrix, assuming random intercept and random slope across participants, to model longitudinal trajectories in SBP and DBP across two treatment groups and four eGFR strata (i.e. < 45 , 45 – < 60 , 60 – < 90 or ≥ 90 mL per min per 1.73 m²). The fixed effects in the model included visit months, a treatment group indicator, eGFR groups and their two-way and three-way interactions. We also computed hazard ratios (HRs) using Cox proportional models with the baseline hazard function stratified by clinic site to compare the time to the first event for each of the four outcomes. Proportional hazards assumptions were tested using log-log against survival plots and Schoenfeld residuals. Except for the eGFR-based renal outcome where different definitions were used between patients with vs. without CKD, the effect modification on outcomes by eGFR was evaluated by an interaction term between an intervention group indicator and eGFR. Additionally, within each eGFR stratum, the consistency of the effects of intensive BP control on the cardiovascular composite outcome and AKI was evaluated by an interaction term between treatment group and each of the prespecified variables plus diastolic BP (DBP) [7], followed by subgroup analyses if applicable. We conducted sensitivity analyses with adjustment for age, sex, race, SBP and DBP and confirmed consistent results (data not shown). When evaluating trends and interactions, we treated eGFR, age, SBP, DBP and log-transformed urinary albumin-to-creatinine ratio as continuous variables without categorization. All analyses were

carried out with two-sided tests at the 5% level of significance using Stata/MP version 13.1 (Stata Corp, TX, USA).

Results

Baseline characteristics

After excluding 37 patients without eGFR data at baseline, we assessed all remaining participants, who were randomly assigned to a SBP target of either < 120 mmHg (intensive treatment group, $n = 4662$) or < 140 mmHg (standard treatment group, $n = 4662$; Figure 1). The mean age of the participants was 68 (SD, 9) years, amongst whom 35% were female, and 31% were Black. Mean SBP and eGFR at baseline were 140 (SD, 16) mmHg and 72 (SD, 21) mL per min per 1.73 m², respectively. Baseline characteristics are summarized according to four eGFR categories in Table 1. Participants with lower eGFR were more likely to be older, male, non-Hispanic White and had a higher urinary albumin-to-creatinine ratio. These individuals also had lower BP and a greater number of antihypertensive medications, had slightly lower cholesterol levels and a higher prevalence of statin use, had a slightly greater 10-year Framingham cardiovascular risk and had a higher prevalence of cardiovascular disease history and aspirin use. There were no clinically meaningful imbalances between groups.

Blood pressure and antihypertensive medications

During the median follow-up period of 3.26 years, participants with lower eGFR showed higher achieved SBP, lower achieved DBP and used more antihypertensive medications ($P_{\text{trend}} < 0.001$ for all). Amongst patients with eGFR of ≥ 90 , 60 – < 90 , 45 – < 60 and < 45 mL per min per 1.73 m², the mean SBP in the intensive (vs. standard) treatment group was 121.2 (vs. 134.8) mmHg, 121.3 (vs. 134.7) mmHg, 122.4 (vs. 135.0) mmHg and 124.7 (vs. 135.7) mmHg, respectively (Fig. 2a), and the mean DBP was 70.3 (vs. 77.7) mmHg, 68.8 (vs. 75.4) mmHg, 66.5 (vs. 73.0) mmHg and 65.7 (vs. 70.8) mmHg, respectively (Fig. 2b). The corresponding between-group difference was 13.6, 13.4, 12.5 and 11.0 mmHg for SBP, and 7.4, 6.6, 6.5 and 5.1 mmHg for DBP, respectively. When compared with participants with eGFR 60 – < 90 mL per min per 1.73 m², decreases in SBP and DBP by intensive treatment amongst those with eGFR < 45 mL per min per 1.73 m² were attenuated by 1.5–4.0 mmHg and 0.8–2.0 mmHg, respectively

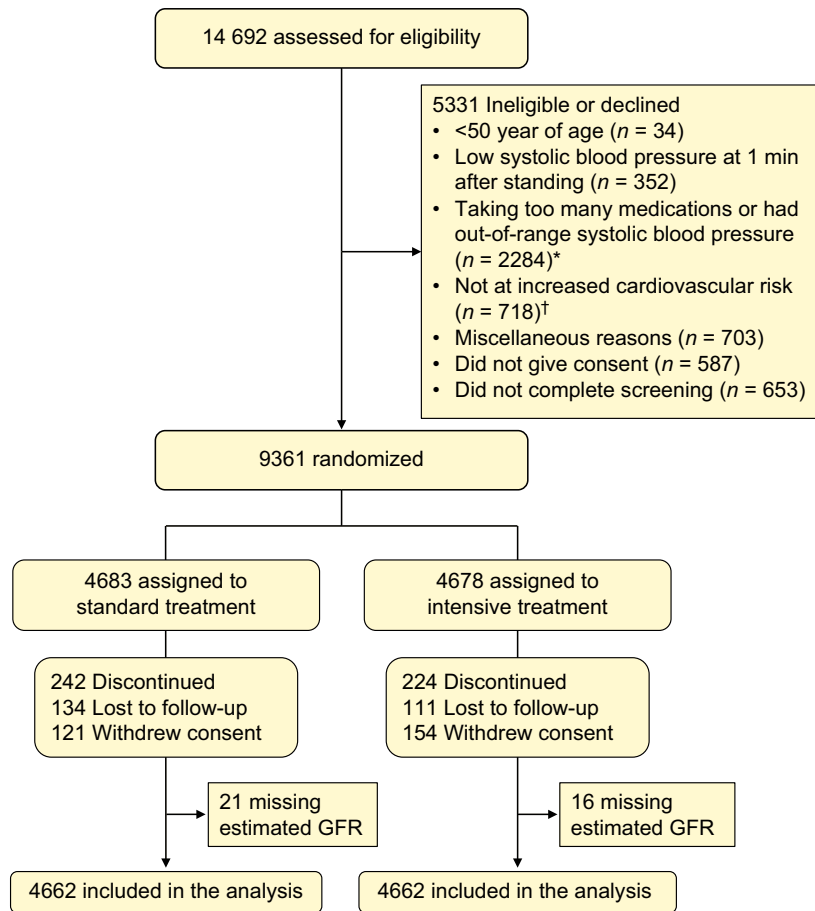


Fig. 1 Eligibility, randomization and follow-up of the study. Note: *systolic blood pressure (SBP) was required to be between 130 and 180 mmHg for participants taking 0 or 1 medications, 130–170 mmHg for participants taking two medications, 130–160 mmHg for participants taking three medications and 130–150 mmHg for participants taking four medications. †Increased cardiovascular risk was defined as the presence of 1 or more of the following: (i) clinical or subclinical cardiovascular disease other than stroke, (ii) chronic kidney disease (defined as an estimated glomerular filtration rate (GFR) of 20 to 59 mL per min per 1.73 m² based on the 4-variable Modification of Diet in Renal Disease equation and the latest laboratory value within the past 6 months), (iii) Framingham risk score for 10-year cardiovascular risk of 15% or greater based on laboratory work performed within the past 12 months for lipids or (iv) age of 75 years or older.

(Fig. 2c and d). The mean number of antihypertensive medications in the intensive (vs. standard) treatment group was 2.7 (vs. 1.7), 2.7 (vs. 1.7), 2.8 (vs. 1.9) and 3.1 (vs. 2.3), respectively, and the difference in the increased number of medications by intensive treatment was small across eGFR groups (Figure S1 in Supporting information).

Clinical outcome events

A total of 562 and 310 participants developed the cardiovascular composite outcome and AKI,

respectively, and 193 participants reached the eGFR-based composite renal outcome. Of the 4619 participants who had a urinary albumin-to-creatinine ratio of <10 mg g⁻¹ at baseline, incident albuminuria was observed amongst 350 participants. Table 2 summarizes the number and incidence rate of each outcome between the intensive and standard treatment group across eGFR categories. The incidence rates of cardiovascular events, AKI and incident albuminuria increased as eGFR declined ($P_{\text{trend}} < 0.001$ for all). In the standard treatment group, those with

Table 1 Baseline characteristics of participants

Variables	Estimated GFR* Allocation							
	<45 mL per min per 1.73 m ²		45–60 mL per min per 1.73 m ²		60–<90 mL per min per 1.73 m ²		≥90 mL per min per 1.73 m ²	
	Standard (n = 445)	Intensive (n = 446)	Standard (n = 873)	Intensive (n = 886)	Standard (n = 2531)	Intensive (n = 2534)	Standard (n = 813)	Intensive (n = 796)
Age, mean (SD), year	73 (10)	72 (9)	71 (9)	72 (9)	67 (9)	67 (9)	63 (9)	63 (8)
Female, No. (%)	204 (45.8)	188 (42.2)	319 (36.5)	349 (39.4)	836 (33.0)	862 (34.0)	280 (34.4)	271 (34.0)
Race/ethnicity, No. (%)								
White	298 (67.0)	278 (62.3)	595 (68.2)	609 (68.7)	1,508 (59.6)	1,513 (59.7)	291 (35.8)	293 (36.8)
Black	111 (24.9)	123 (27.6)	202 (23.1)	202 (22.8)	717 (28.3)	687 (27.1)	385 (47.4)	359 (45.1)
Hispanic	34 (7.6)	38 (8.5)	63 (7.2)	56 (6.3)	263 (10.4)	279 (11.0)	119 (14.6)	127 (16.0)
Other	2 (0.4)	7 (1.6)	13 (1.5)	19 (2.1)	43 (1.7)	55 (2.2)	18 (2.2)	17 (2.1)
Systolic BP, mean (SD), mmHg	139 (17)	139 (17)	139 (16)	139 (16)	139 (15)	140 (15)	141 (15)	141 (16)
Diastolic BP, mean (SD), mmHg	73 (13)	74 (13)	76 (12)	76 (12)	79 (12)	79 (11)	82 (12)	81 (12)
UACR, median (IQR), mg g ⁻¹	25 (10, 102)	24 (9, 118)	11 (5, 32)	10 (6, 29)	8 (5, 16)	9 (5, 17)	9 (6, 19)	9 (6, 18)
History of CVD, No. (%)	118 (26.5)	117 (26.2)	202 (23.1)	208 (23.5)	493 (19.5)	480 (18.9)	118 (14.5)	134 (16.8)
Total cholesterol, mean (SD), mg dL ⁻¹	184 (41)	189 (43)	186 (41)	186 (40)	191 (41)	191 (41)	195 (41)	193 (42)
HDL cholesterol, mean (SD), mg dL ⁻¹	52 (15)	52 (15)	53 (15)	53 (14)	53 (15)	53 (14)	54 (14)	54 (15)
Triglycerides, median (IQR), mg dL ⁻¹	116 (84, 160)	116 (84, 162)	113 (81, 155)	106 (77, 148)	105 (77, 150)	106 (76, 147)	102 (73, 149)	105 (74, 145)

Table 1 (Continued)

Variables	Estimated GFR* Allocation							
	<45 mL per min per 1.73 m ²		45–<60 mL per min per 1.73 m ²		60–<90 mL per min per 1.73 m ²		≥90 mL per min per 1.73 m ²	
	Standard	Intensive	Standard	Intensive	Standard	Intensive	Standard	Intensive
Plasma glucose, mean (SD), mg dL ⁻¹	97 (12)	97 (14)	99 (12)	99 (14)	99 (13)	99 (13)	99 (16)	99 (14)
Statin use, No. (%)	248 (56.4)	224 (50.9)	451 (52.0)	434 (49.2)	1,090 (43.4)	1,049 (41.6)	280 (34.7)	271 (34.2)
Aspirin use, No. (%)	246 (55.5)	248 (55.6)	484 (55.5)	506 (57.1)	1,276 (50.5)	1,319 (52.2)	338 (41.6)	331 (41.6)
10-year Framingham CVD risk, mean (SD), %	21 (13)	22 (13)	22 (12)	21 (11)	20 (10)	20 (10)	19 (10)	19 (10)
Body mass index, mean (SD), kg m ⁻²	29.3 (6.0)	29.0 (5.7)	29.5 (5.6)	29.7 (5.8)	29.8 (5.4)	29.9 (5.7)	30.4 (6.5)	30.4 (6.1)
No. of antihypertensive drugs, median (IQR)	2 (2, 3)	2 (2, 3)	2 (1, 3)	2 (1, 3)	2 (1, 2)	2 (1, 2)	2 (1, 2)	2 (1, 2)

Values are expressed as mean (SD), median (interquartile range) or percentage, appropriately.

*Based on the 4-variable Modification of Diet in Renal Disease equation.

BP, blood pressure; UACR, urinary albumin-to-creatinine ratio; CVD, cardiovascular disease; HDL, high-density lipoprotein; GFR, glomerular filtration rate.

SI conversion factors: To convert HDL and total cholesterol to mmol L⁻¹, multiply by 0.0259; triglycerides to mmol L⁻¹, multiply by 0.0113; and glucose to mmol L⁻¹, multiply by 0.0555.

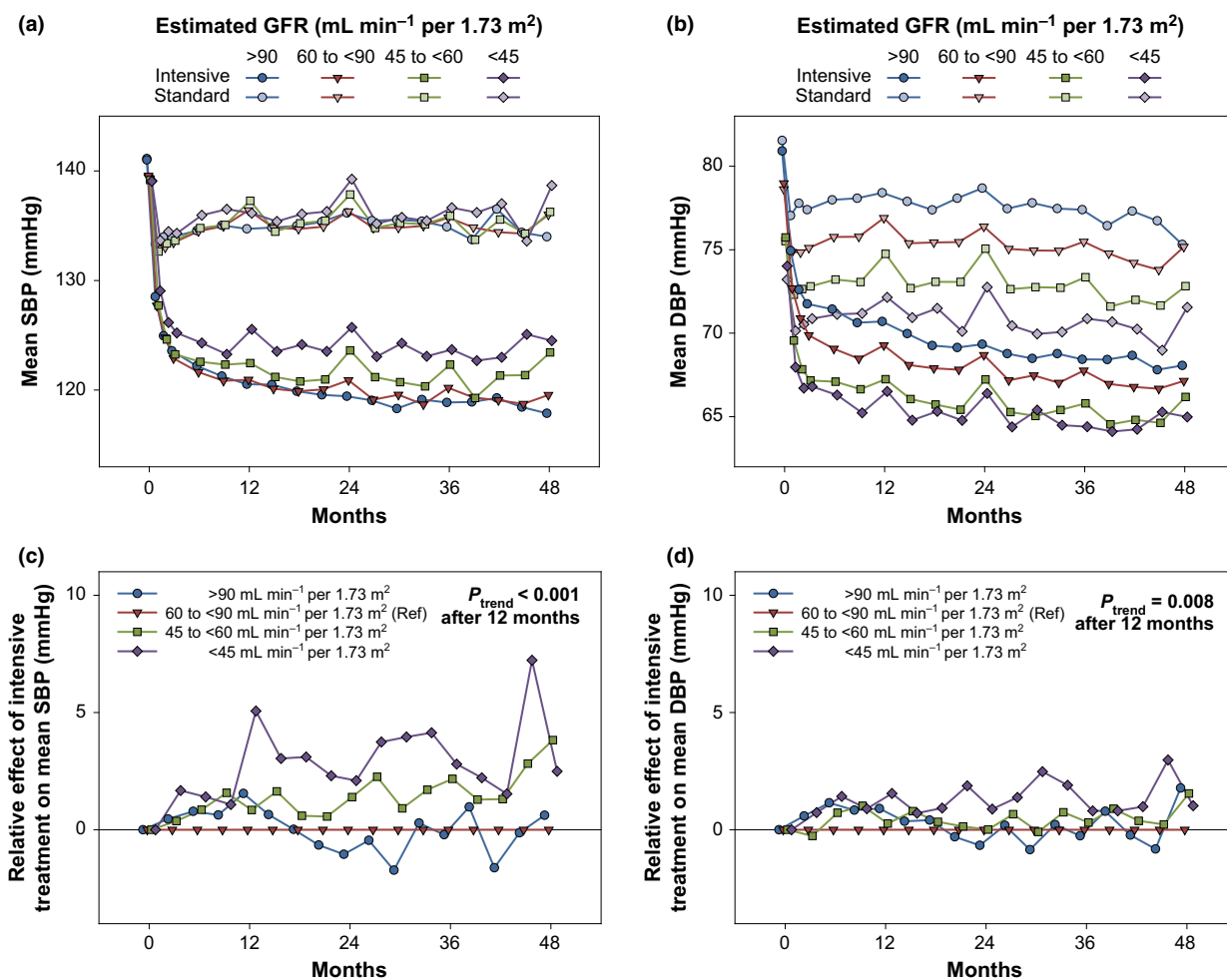


Fig. 2 Trends in SBP and DBP (a and b) and the relative effect of intensive treatment (c and d) over the follow-up period. Estimated GFR of 60–<90 mL per min per 1.73 m² served as reference. Relative effect of intensive treatment was calculated as (decrease in BP from baseline in the intensive treatment group) – (decrease in BP from baseline in the intensive treatment group). SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate. Data were truncated at 4 years, after which <10% patients remained at risk.

eGFR of <45 mL per min per 1.73 m², compared with participants with eGFR 60–<90 mL per min per 1.73 m², had 2.2, 7.5 and 2.3 times higher incidence rates of the cardiovascular outcome, AKI and incident albuminuria, respectively. The incidence rate of the eGFR-based renal outcome was not comparable across eGFR strata due to the different definitions used for this outcome in participants with vs. without CKD (i.e. ≥50% decrease in eGFR or end-stage renal disease, and ≥30% decrease in eGFR to a value of <60 mL per min per 1.73 m², respectively).

The effect of intensive treatment on the cardiovascular outcome was significantly attenuated amongst participants with a lower eGFR ($P_{\text{interaction}} = 0.019$; Fig. 3a and Table 2). Nevertheless, the between-group differences in incidence rate [i.e. absolute rate differences (ARD)] were similarly favourable across groups with eGFR ≥45 mL per min per 1.73 m², likely due to the higher incidence rates in the lower eGFR groups. However, intensive treatment did not show cardiovascular benefit amongst participants with eGFR <45 mL per min per 1.73 m² [i.e. HR (95% CI), 0.92 (0.62 to 1.38), and ARD (95% CI), –0.02 (–0.07 to +0.03) per 100 patient-years].

Table 2 Between-group difference in incidence of each outcome across categories of baseline estimated glomerular filtration rate.

	Standard BP control		Intensive BP control		Absolute rate difference	
	Events/ Total (N)	Incidence rate (95% CI) per 100 PY	Events/ Total (N)	Incidence rate (95% CI) per 100 PY	Absolute rate difference (95% CI) per 100 PY	Hazard ratio (95% CI)
Fatal and nonfatal cardiovascular events						
<i>P</i> _{Interaction} = 0.019						
Estimated GFR						
>90 mL per min per 1.73 m ²	48/813	1.94 (1.46–2.57)	29/796	1.16 (0.81–1.67)	–0.78 (–1.47 to –0.08)	0.59 (0.37 to 0.95)
60–<90 mL per min per 1.73 m ²	144/2531	1.81 (1.53–2.13)	105/2534	1.31 (1.08–1.58)	–0.50 (–0.89 to –0.11)	0.74 (0.57 to 0.95)
45–<60 mL per min per 1.73 m ²	72/873	2.65 (2.10–3.33)	55/886	1.97 (1.51–2.56)	–0.68 (–1.48 to 0.12)	0.79 (0.55 to 1.13)
<45 mL per min per 1.73 m ²	54/445	4.00 (3.06–5.22)	54/446	3.98 (3.05–5.20)	–0.02 (–1.52 to 1.49)	0.92 (0.62 to 1.38)
Acute kidney injury						
<i>P</i> _{Interaction} = 0.179						
Estimated GFR						
>90 mL per min per 1.73 m ²	8/813	0.32 (0.16–0.65)	19/796	0.78 (0.50–1.22)	0.45 (0.04 to 0.87)	2.53 (1.08 to 5.92)
60–<90 mL per min per 1.73 m ²	30/2531	0.38 (0.26–0.54)	60/2534	0.76 (0.59–0.98)	0.38 (0.15 to 0.62)	2.06 (1.33 to 3.20)
45–<60 mL per min per 1.73 m ²	41/873	1.51 (1.11–2.06)	52/886	1.90 (1.45–2.49)	0.38 (–0.31 to 1.08)	1.33 (0.86 to 2.05)
<45 mL per min per 1.73 m ²	38/445	2.85 (2.07–3.91)	62/446	4.78 (3.72–6.12)	1.93 (0.43 to 3.42)	1.73 (1.12 to 2.66)
eGFR-based renal outcome*						
<i>P</i> _{Interaction} : N/A						
Estimated GFR						
>90 mL per min per 1.73 m ²	2/813	0.08 (0.02–0.31)	21/796	0.84 (0.55–1.29)	0.76 (0.39 to 1.14)	11.0 (2.55 to 47.8)
60–<90 mL per min per 1.73 m ²	35/2531	0.43 (0.31–0.60)	106/2534	1.33 (1.10–1.61)	0.90 (0.61 to 1.19)	3.13 (2.13 to 4.60)
45–<60 mL per min per 1.73 m ²	1/873	0.04 (0.00–0.25)	4/886	0.14 (0.05–0.37)	0.10 (–0.05 to 0.26)	3.67 (0.40 to 33.4)
<45 mL per min per 1.73 m ²	14/445	1.00 (0.59–1.70)	10/446	0.71 (0.38–1.33)	–0.29 (–0.98 to 0.40)	0.85 (0.36 to 1.98)
Incident albuminuria						
<i>P</i> _{Interaction} = 0.938						
Estimated GFR						
>90 mL per min per 1.73 m ²	23/427	1.78 (1.18–2.68)	20/393	1.64 (1.06–2.55)	–0.13 (–1.16 to 0.89)	1.07 (0.55 to 2.08)
60–<90 mL per min per 1.73 m ²	110/1399	2.56 (2.12–3.09)	89/1373	2.08 (1.69–2.55)	–0.49 (–1.13 to 0.16)	0.81 (0.61 to 1.07)
45–<60 mL per min per 1.73 m ²	41/395	3.39 (2.49–4.60)	36/408	2.84 (2.05–3.94)	–0.55 (–1.94 to 0.84)	0.79 (0.49 to 1.27)
<45 mL per min per 1.73 m ²	18/106	5.99 (3.78–9.51)	13/118	3.68 (2.14–6.33)	–2.31 (–5.73 to 1.10)	0.68 (0.28 to 1.65)

*≥30% decrease in eGFR to a value of <60 mL per min per 1.73 m² for participants without CKD; and a composite of ≥50% decrease in estimated GFR or the development of end-stage renal disease requiring renal replacement therapy for participants with CKD.
GFR, glomerular filtration rate; PY, person-years.

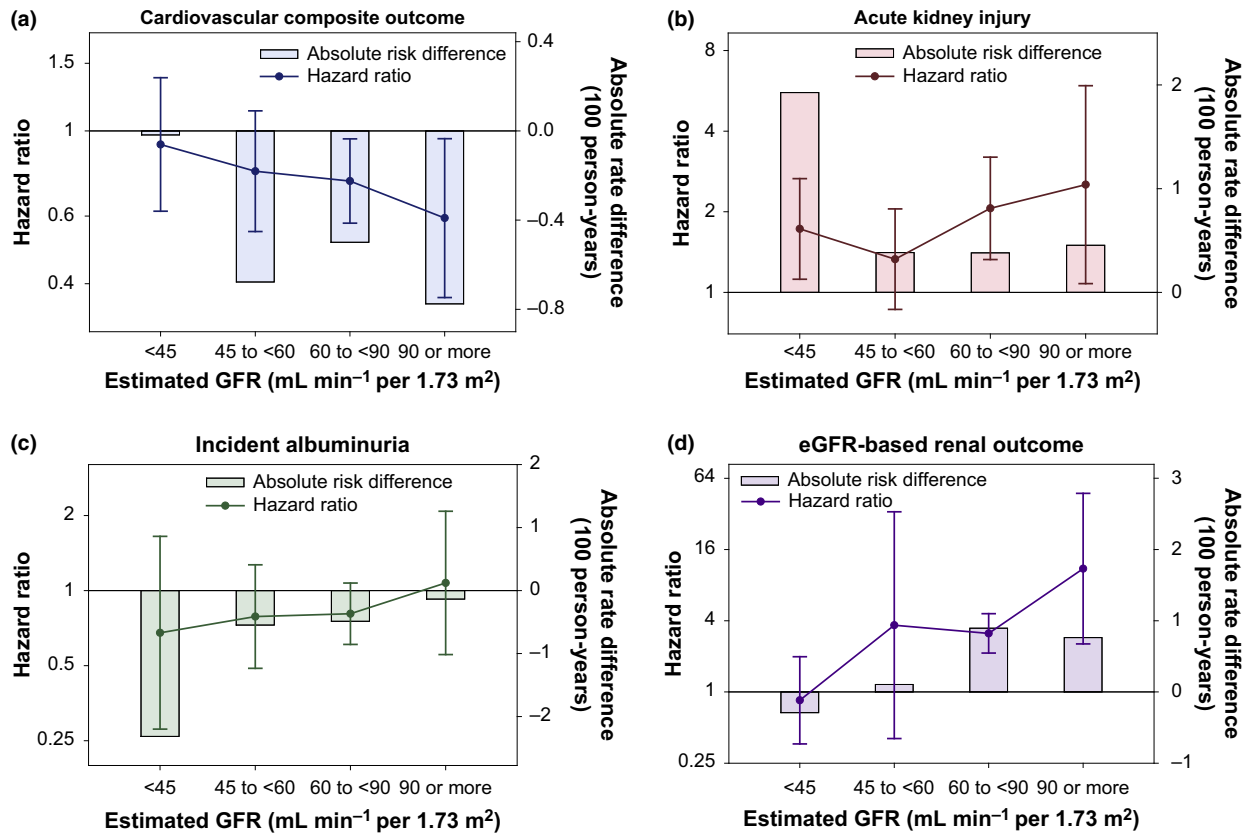


Fig. 3 The hazard ratios of intensive blood pressure control (points and lines) and the absolute rate differences (bars) for (a) the cardiovascular outcome, (b) acute kidney injury, (c) the eGFR-based renal outcome and (d) incident albuminuria across estimated GFR groups. GFR, glomerular filtration rate.

The adverse effect of intensive treatment on AKI was not significantly modified by eGFR ($P_{\text{interaction}} = 0.179$) and was consistently observed across eGFR groups with an overall HR of 1.65 (1.31 to 2.08). The ARD substantially increased along with the increased incidence rate amongst participants with eGFR <45 mL per min per 1.73 m² [i.e. HR, 1.73 (1.12 to 2.66); ARD, +1.93 (+0.43 to +3.42) per 100 patient-years; Fig. 3b and Table 2]. The intervention effect on incident albuminuria was not modified by eGFR ($P_{\text{interaction}} = 0.938$), and the intensive treatment significantly reduced the incidence of incident albuminuria with an overall HR of 0.81 (0.65 to 1.00). The ARD increased along with the increased incidence rate amongst participants with lower eGFR (Fig. 3c). The intensive treatment group experienced the eGFR-based renal outcome more often than the standard treatment group amongst participants without CKD but not amongst those with CKD (Fig. 3d); however, the

number of events was small especially amongst those with eGFR 45–<60 mL per min per 1.73 m².

We further examined the consistency of the intervention effect on the cardiovascular composite outcome and AKI across subgroups of prespecified variables plus DBP within each eGFR stratum (Figure S2 and Table S2 in Supporting information). The intervention effect on the cardiovascular outcome was not significantly modified by these factors in either eGFR strata. Amongst participants with eGFR of <45 mL per min per 1.73 m², the AKI risk associated with intensive treatment was attenuated amongst participants with DBP ≥ 80 mmHg and was pronounced amongst those with lower DBP ($P_{\text{interaction}} = 0.010$). The intervention effect on AKI also appeared pronounced amongst male participants but attenuated amongst female participants in the lowest eGFR stratum ($P_{\text{interaction}} = 0.045$). These effect modifications were not

observed in the other eGFR strata. Race, prior cardiovascular disease and SBP did not modify the effects of intensive treatment on AKI.

Effect modification by the urinary albumin-to-creatinine ratio

The urinary albumin-to-creatinine ratio did not significantly modify the effects of intensive treatment on the cardiovascular composite outcome or AKI ($P_{\text{interaction}} = 0.352$ and 0.301 , respectively).

Discussion

In this study, we demonstrated the modification of the effect of intensive BP control by eGFR. Participants with a lower eGFR in the intensive treatment group showed a higher achieved SBP and lower achieved DBP with more hypertensive medications. Amongst participants with eGFR <45 mL per min per 1.73 m², there was no significant cardiovascular benefit, but an increased risk of AKI was present. Meanwhile, intensive BP control maintained a significant absolute risk reduction for the cardiovascular outcome amongst participants with a higher eGFR, even at the range of ≥ 90 mL per min per 1.73 m², despite their lower incidence of cardiovascular events. Intensive treatment also decreased the incidence of incident albuminuria irrespective of eGFR levels whilst it decreased eGFR amongst participants without CKD.

Higher BP is linearly associated with a greater risk of cardiovascular disease and death in the general population [12–15]. However, several studies of patients with moderate-to-advanced CKD or coronary artery disease have reported J- or U-shaped relationships, in which low-to-normal BP is associated with higher mortality [5, 16–19]. Given the lack of definitive evidence for the benefit of strict BP control in this population [20], there has been a debate regarding whether the relationship between lower BP and greater survival observed in the ‘hypertension paradox’ is causal or confounded by the high burden of comorbid conditions. One suggested pathophysiological mechanism for the risk associated with lowering BP is altered cardiac structure and function amongst patients with cardiovascular disease due to long-standing hypertension [21]. A recent observational study of patients with advanced CKD showed that the association between SBP and cardiovascular risk was linearly incremental when patients did not have cardiovascular disease history [22], supporting intensive BP control for such patients.

However, there remained a U-shaped association for DBP irrespective of cardiovascular disease history, which has made the interpretation of these associations difficult because currently available BP-lowering interventions decrease both SBP and DBP. Observational studies are also subject to potential bias due to residual confounding or unmeasured confounders. Our study used data from a large RCT of intensive BP control, which enabled a direct evaluation of intensive BP control in subgroups, and cardiovascular benefit was not observed in stage 3b or more advanced stages of CKD irrespective of cardiovascular disease history.

Elderly patients with moderate-to-advanced CKD are more likely to have increased vascular stiffness and atherosclerosis, resulting in more severe hypertension and greater pulse pressure [23, 24]. Indeed, we observed that participants in the control group showed similar SBP across eGFR levels but lower DBP with lower eGFR. More importantly, participants with lower eGFR in the intensive treatment arm required more antihypertensive drugs and achieved higher SBP and lower DBP during the trial period, which may partly explain the observed changes in the risk–benefit profile of intensive treatment. Higher achieved SBP might have maintained renal perfusion and mitigated the risk of developing AKI particularly at adverse events that can further lower BP (i.e. cardiac events and sepsis) whilst compromising the long-term cardiovascular benefit. An excessive decrease in DBP may also impair coronary perfusion of the heart in the presence of stenosis as several studies have reported the association of lower DBP with cardiovascular events and mortality [25–27]. The different contributions of SBP and DBP indicate a need for careful consideration against implementing intensive BP control for patients with moderate-to-advanced CKD and high pulse pressure.

The overall effect of intensive BP control on incident albuminuria was significant. However, the intervention did not prevent eGFR decline amongst participants with CKD but decreased eGFR amongst those without CKD, which is consistent with a recently reported secondary analysis of the SPRINT [28]. These apparently conflicting effects in the non-CKD group may be attributed to the acute effect of BP lowering and the greater use of renin–angiotensin system inhibitors in the intensive treatment arm; [29, 30] even a small negative acute effect (i.e. a decline in eGFR in a short term) can result in an increased type 1 error (i.e. false

positive) for harm, especially when 30% eGFR decline was used as a surrogate end-point amongst patients with stage 3 or less advanced CKD (i.e. eGFR >30 mL per min per 1.73 m²) [8, 31]. Given that changes in urinary albumin/protein are considered a good marker of the progression of CKD [32, 33], intensive BP control may actually be renoprotective as suggested in systematic reviews [6, 34]. However, the validity of urinary albumin/protein as a surrogate for treatment effect has not been established in all settings [35, 36]. In a previous RCT that compared mono vs. dual therapy of an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker; [37–39] dual therapy decreased urinary albumin and simultaneously increased the incidence of AKI and a composite renal outcome (i.e. chronic dialysis or doubling of serum creatinine). We also found an increased incidence of AKI by intensive BP control, the extent of which was much greater amongst participants with eGFR <45 mL per min per 1.73 m² than those with higher eGFR. Therefore, the effect of intensive BP control on long-term renal outcomes still remains to be proven across stages of CKD.

One important limitation in our study is the difference in the blood pressure measurement methods in the SPRINT vs. clinical practice. In the SPRINT, blood pressure was measured for three times at 1-min interval with a fully automated device after patients had been seated quietly for 5 min without the presence of observers [40]. Several studies have indicated that this unattended automated office BP technique resulted in 10–20 mmHg lower SBP than conventional auscultatory BP [41, 42], and the target SBP in the intensive treatment group may translate into auscultatory office SBP <130–140 mmHg, which is close to the currently recommended target for most hypertensive patients by all hypertension treatment guidelines [40]. However, there may be heterogeneity in the mean difference in SBP between unattended automated vs. conventional auscultatory office BP depending on the population characteristics as shown in the previous studies comparing different methods for measuring BP [43, 44]. For an extreme example, amongst hypertensive African Americans with eGFR between 20 and 65 mL per min per 1.73 m², clinic SBP was not higher than but similar to 24-h ambulatory SBP (134 ± 20 vs. 137 ± 17 mmHg) [45]. This observation is relevant to our study because approximately 30% of the participants in the SPRINT were

Black [7] and because we focused on patients with CKD. Data regarding the use of unattended automated office BP in CKD are still scarce, if any, and it remains unclear how to translate SBP values in the SPRINT into those in routine office BP measurement across different levels of kidney function, especially amongst patients with moderate-to-advanced CKD.

Several other limitations should also be acknowledged in this study. This study was a post hoc analysis of a RCT; hence, the results should be interpreted as hypothesis generating. Secondly, the SPRINT limited its ability to evaluate the intervention effect on renal outcomes partly due to a lower-than-expected eGFR decline and the early termination of the trial [7] and a lower prevalence of severely increased urinary albumin. Additionally, elderly patients accounted for a majority of participants as per the protocol [46]. Therefore, our results may not be extrapolated to patients with overt albuminuria/proteinuria or younger patients. Lastly, participants with stage 3b or more advanced stages of CKD accounted for only 10% of the study population. Nevertheless, our study included the second largest CKD population to date, next to the African American Study of Kidney Disease and Hypertension (AASK) trial [47] and followed by the MDRD study [4]. Additional strength of the SPRINT over other trials includes its multiethnic and contemporary features.

In conclusion, the eGFR significantly modified the risk–benefit profile of intensive BP control, and intensive BP control may provide little or no benefit and may be harmful for patients with eGFR <45 mL per min per 1.73 m². Further investigation, particularly RCTs with an adequate sample size and a long-term follow-up, is still necessary in moderate-to-advanced CKD.

Author's Contributions

Dr. Yoshitsugu Obi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Obi and Hamano *involved in study concept and design*. Obi, Kalantar-Zadeh, Shintani, Kovesdy and Hamano were responsible for *acquisition, analysis or interpretation of data*. Obi *drafted the manuscript*. Kalantar-Zadeh, Shintani, Kovesdy and Hamano *critically revised the manuscript for important intellectual content*. Obi and Shintani

performed statistical analysis. Obi, Kalantar-Zadeh, Shintani, Kovesdy and Hamano approved the final version of the manuscript.

Conflict of Interest

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Obi reports honoraria and/or support from Ono and Chugai, outside the submitted work. KKZ has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, the American Society of Nephrology, Astra-Zeneca, Aveo, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, the National Institutes of Health, the National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor and ZS-Pharma, outside the submitted work. Dr. Kovesdy reports grants from NIH/NIDDK during the conduct of the study; personal fees from Amgen, Sanofi-aventis, Fresenius Medical Care, Keryx, Bayer, Abbott and Abbvie; and a grant from Shire, outside the submitted work. Dr. Hamano has received honoraria and/or support from Chugai, Otsuka, Torii, Kissei, Kyowa Hakko Kirin, Terumo, Fuso, Eisai and Takeda, outside the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Trends in (A) the number of antihypertensive medications and (B) the relative effect of intensive treatment (reference: estimated GFR of 60 to <90 mL per min per 1.73 m²) over the follow-up period.

Figure S2. Subgroup analyses of the effects of intensive BP control on (A) the cardiovascular

outcome and (B) acute kidney injury across estimated GFR groups.

Table S1. Between-group difference in incidence of acute coronary syndrome, stroke, heart failure, and cardiovascular death across categories of baseline estimated glomerular filtration rate.

Table S2. The hazard ratios (95% CI) of intensive blood pressure control for fatal and non-fatal cardiovascular events and acute kidney injury stratified by estimated glomerular filtration rate (eGFR) and subgroups. ■