

# Effect of Chronic Kidney Disease on Cardiovascular Events, An Epidemiological Aspect from SPRINT Trial

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**Keywords.** blood pressure, cardiovascular disease, chronic kidney disease, hypertension, Risk equivalent, SPRINT

**Introduction.** Currently, conflicting evidence exists among community-based studies as to whether chronic kidney disease (CKD) is a cardiovascular (CVD) risk equivalent. We aimed to evaluate the effect of CKD on CVD based on a large trial results. **Methods.** To perform a secondary analysis, we obtained the data of SPRINT trial from NHLBI data repository center. 2646 subjects with baseline CKD and 6715 without CKD were enrolled. A composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes was considered as primary outcome.

**Results.** Throughout the 3.21 years of follow-up, presence of CKD, compared to those without CKD, negatively affected the primary outcome (incidence rate, 2.84% per year vs. 1.55% per year in patients with and without CKD, respectively; Hazard ratio, 1.83; 95% CI, 1.49 to 2.11;  $P < .001$ ). This finding was consistent across all the secondary outcomes. However, the risk was not as great as those with clinical cardiovascular disease (incidence rate, 4.13% per year). Presence of CKD was the strongest predictor of developing AKI with intensive blood pressure reduction, increasing its chance by 215%.

**Conclusion.** SPRINT is the first trial revealing that CKD is an independent risk factor for CVD. However, CKD could not be considered as a CVD risk equivalent. In the presence of CKD, with intensive blood pressure reduction the chance of AKI is dramatically increased.

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## INTRODUCTION

Chronic kidney disease (CKD), characterized by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m<sup>2</sup>, may progress at varying rates (from < 1 to > 12 mL/min/1.73 m<sup>2</sup> each year), depending on blood pressure (BP) management, history of decreased GFR, level of proteinuria, and the underlying factors for CKD (eg. diabetes).<sup>1</sup> In general, 2 strategies can be applied to reduce CKD progression (management of the underlying condition and management of secondary factors) which can predict disease progression such as increased BP and proteinuria.<sup>2</sup>

Currently, the most favorable systolic blood pressure (SBP) target in non-diabetic CKD patients to reduce cardiovascular disease (CVD) is not certain. In a meta-analysis, more intensive BP reduction was related to a decline in the overall mortality rate.<sup>3</sup> According to Systolic Blood Pressure Intervention Trial (SPRINT), a major decline in SBP (to 120 mmHg) could reduce all-cause mortality in non-diabetic individuals with CKD.<sup>4,5</sup> As in SPRINT various groups of patients at increased cardiovascular risk were enrolled (such as: elderly population, patients with high cardiovascular risk, patients with baseline CVD), it may serves as the

first trial which may reveal effect of various risk factor on CVD event.<sup>6</sup> Here, we aimed to perform a secondary analysis of *SPRINT* trial to find out the effect of CKD on cardiovascular outcomes and its role as an important factor for decision making to choose blood pressure targets.

## MATERIALS AND METHODS

### Data Acquisition

We used data from the *SPRINT* trial, obtained from the National Heart, Lung, and Blood institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center with a request ID of 4612.

### Study Design and Population

The rationale and study design for the *SPRINT* trial have been reported in detail elsewhere.<sup>4</sup> Briefly, *SPRINT* trial was a randomized, controlled, open-label trial including 9361 non-diabetic participants with elevated CVD risk and with SBP of  $\geq 130$  mmHg. The participants were randomly assigned to an intensive treatment arm with target SBP  $< 120$  mmHg, or a control arm targeting an SBP  $< 140$  mmHg. The inclusion criteria were SBP of 130-180 mmHg, age of  $\geq 50$  years, and high risk of cardiovascular events. The high risk of cardiovascular events was described according to one or more of the following criteria: 1) CKD (except polycystic renal disease) with eGFR ranging from 20 to  $< 60$ , calculated by the Modification of Diet in Renal Disease (MDRD) formula; 2) presence of clinical or subclinical CVD except stroke; 3) a 10-year risk of  $\geq 15\%$  for CVD, according to the Framingham Risk Score; and 4) age  $\geq 75$  years. Here, we aimed to compare outcomes and adverse events in patients with and without CKD.

### Intervention and Measurements

Medications for the intensive treatment group were prescribed every month to reach an SBP of  $< 120$  mmHg. On the other hand, the drugs were prescribed to reach a target SBP of 135-139 mmHg in the standard treatment group; if SBP was below 130 mmHg in a single visit or below 135 mmHg in 2 successive visits, the dosage was decreased.

The subjects' baseline demographic information was recorded. The clinical and laboratory information of the participants was collected at the beginning of the study and then every 3 months.

In order to identify the CVD outcomes, structured interviews were performed in the 2 groups within 3-month intervals. Serious adverse events were described as fatal or critical events, which caused a major or persistent clinical disorder, requiring a longer hospital stay or the researcher's decision to determine whether the condition poses a major clinical risk to the patient (necessitating treatment to inhibit the adverse outcomes).

### Outcomes

The primary outcome was a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. The primary renal outcomes of CKD patients included reduced eGFR ( $\geq 50\%$  based on the laboratory tests) or ESRD development, necessitating long-term dialysis or renal transplantation. Another specific renal outcome was incident albuminuria, characterized by the doubled urinary albumin (mg)/creatinine (g) ratio (from  $< 10$  at baseline to  $> 10$  in the follow-up).

Prespecified subgroups of interest for primary outcome were defined according to sex, age ( $< 75$  vs.  $\geq 75$  years), baseline systolic blood pressure in three levels ( $< 140$  mmHg,  $\geq 140$  to  $< 160$  mmHg, and  $\geq 160$  mmHg), baseline eGFR in three levels ( $< 30\%$ ,  $\geq 30$  to  $< 45\%$ , and  $\geq 45$ ), and baseline albuminuria in three levels ( $< 30$  mg/g,  $\geq 30$  to  $< 300$  mg/g, and  $\geq 300$  mg/g).

### Statistical Analyses

In this analysis, we used Cox proportional-hazards regression with two sided tests at the 5% level of significance, with stratification according to the clinic. In order to evaluate the interactions between the treatments and groups, the likelihood ratio test was performed. Independent and paired sample t-test was used to compare categorical variables between patients with and without baseline CKD, and for patients who developed or didn't develop AKI. ROC curve analysis was done to find a cut off value for baseline eGFR to predict who will suffer AKI with intensive treatment. All the analyses were performed using the SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Study Participants

A total of 2646 patients with baseline CKD

(1316 in standard treatment group and 1330 in intensive treatment group) and 6715 patients without CKD were enrolled in the *SPRINT* trial (Table 1).

**Comparison Between Blood Pressure in Patients With and Without CKD**

Both treatments caused a rapid and constant difference between the groups in terms of SBP (Figure 1). Intensive blood pressure control was

**Table 1.** Baseline Characteristics of the Study Participants with Baseline CKD\*†

Characteristic	Intensive Treatment (n = 1330)	Standard Treatment (n = 1316)
Other Concomitant High Cardiovascular Risk Features, [no. (%)]†		
Age ≥ 75 y	584/1330 (43.90)	577/1316 (43.84)
Cardiovascular Disease	324/1330 (24.36)	320/1316 (24.31)
Clinical	276/1330 (20.75)	280/1316 (21.27)
Subclinical	80/1330 (6.01)	66/1316 (5.01)
Framingham 10-year Cardiovascular Disease Risk Score ≥15%	592/1330 (44.51)	583/1314 (44.36)
Age, year	71.96 ± 9.00	71.84 ± 9.46
Race or Ethnic Group, [no. (%)]§		
Non-hispanic Black	325/1330 (24.43)	312/1316 (23.70)
Hispanic	94/1330 (7.06)	96/1316 (7.29)
Non-hispanic White	885/1330 (66.54)	893/1316 (67.85)
Other	26/1330 (1.95)	15/1316 (1.14)
Black Race¶	328/1330 (24.66)	316/1316 (24.01)
Baseline Blood Pressure, mmHg		
Systolic	139.14 ± 16.10	139.17 ± 16.03
Diastolic	75.13 ± 12.19	74.76 ± 12.23
Distribution of Systolic Blood Pressure, [no. (%)]		
< 140 mmHg	716/1330 (53.83)	716/1316 (54.40)
≥ 140 mmHg to < 160 mmHg	475/1330 (35.71)	459/1316 (34.87)
≥ 160 mmHg	139/1330 (10.45)	141/1316 (10.71)
Serum Creatinine, mg/dL	1.43 ± 0.39	1.43 ± 0.37
Estimated GFR, mL/min/1.73m <sup>2</sup>	47.83 ± 9.45	47.85 ± 9.49
Ratio of Urinary Albumin (mg) to Creatinine (g)	80.93 ± 236.19	80.33 ± 250.52
Fasting total cholesterol — mg/dl	186.60 ± 40.70	184.94 ± 40.63
Fasting HDL cholesterol — mg/dl	52.88 ± 14.71	52.39 ± 14.76
Fasting total triglycerides — mg/dl	124.88 ± 69.38	133.59 ± 82.02
Fasting plasma glucose — mg/dl	98.21 ± 13.86	98.29 ± 12.36
Statin use — no./total no. (%)	657/1321 (49.73)	697/1306 (53.36)
Aspirin use — no./total no. (%)	754/1330 (56.01)	728/1316 (55.32)
Smoking status — no. (%)		
Never smoked	606/1330 (45.56)	601/1316 (45.66)
Former smoker	617/1330 (46.39)	600/1316 (45.59)
Current smoker	107/1330 (8.04)	114/1316 (8.81)
Missing data	0/1330 (0)	1/1316 (0.07)
Female sex — no. (%)	537/1330 (40.37)	521/1316 (39.58)
Framingham 10-yr cardiovascular disease risk score — %	16.37 ± 10.93	16.28 ± 10.78
Body-mass index <sup>  </sup>	29.49 ± 5.78	29.39 ± 5.73
Antihypertensive agents — no./patient	2.11 ± 1.00	2.09 ± 1.00
Not using antihypertensive agents — no. (%)	61/1330 (4.58)	62/1316 (4.71)

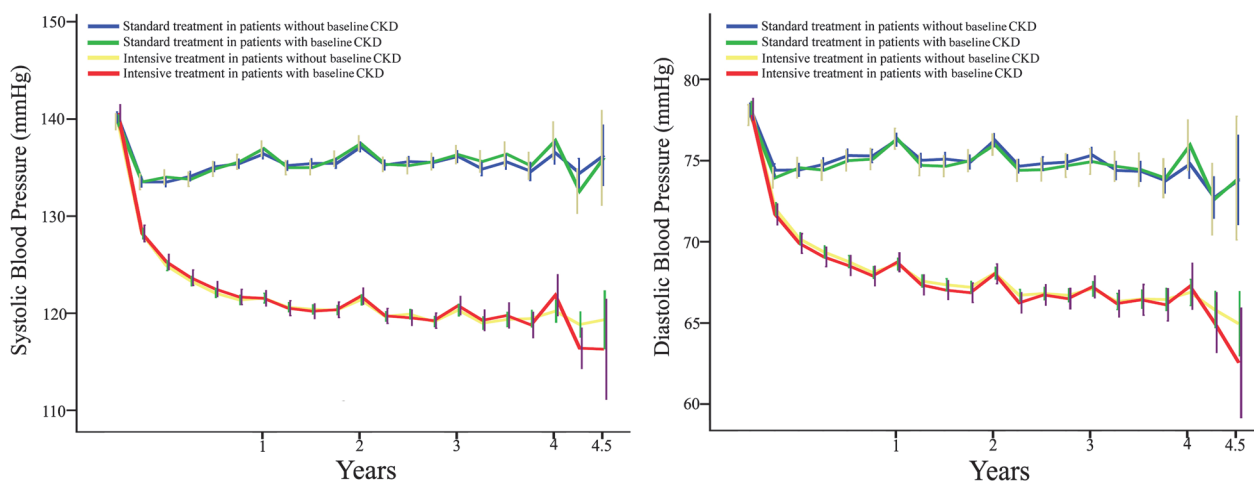
\*Plus-minus values are means ± SD. There were no significant differences ( $P < .05$ ) between the two groups except for statin use ( $P < .05$ ). To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129. To convert the values for glucose to mmol/L, multiply by 0.05551. GFR denotes glomerular filtration rate, and HDL high-density lipoprotein.

†Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73m<sup>2</sup> of body-surface area.

§Race and ethnic group were self-reported.

¶Black race includes hispanic black and black as part of a multiracial identification.

||The body-mass index is the weight in kg divided by the square of the height in meters.



No. with Data	Months of follow up	0	6	12	18	24	30	36	42	48	54
Standard treatment in patients without CKD		3348	3106	3022	2923	2860	2719	2025	1199	548	76
Intensive treatment in patients without CKD		3367	3141	3036	2939	2899	2728	2071	1248	581	84
Standard treatment in patients with CKD		1316	1238	1198	1167	1137	1068	797	480	209	26
Intensive treatment in patients with CKD		1330	1233	1194	1150	1127	1075	816	484	213	31

**Mean No. of Medications**

Standard treatment in patients without CKD	1.83	1.71	1.71	1.69	1.73	1.74	1.73	1.73	1.73	1.73	1.84
Intensive treatment in patients without CKD	2.16	2.64	2.72	2.75	2.77	2.78	2.78	2.77	2.77	2.80	2.84
Standard treatment in patients with CKD	2.17	2	2	2	2.02	1.99	2.04	2.06	2.06	2.07	2.02
Intensive treatment in patients with CKD	2.48	2.89	2.98	2.97	2.96	2.95	2.94	2.92	2.92	2.94	3.10

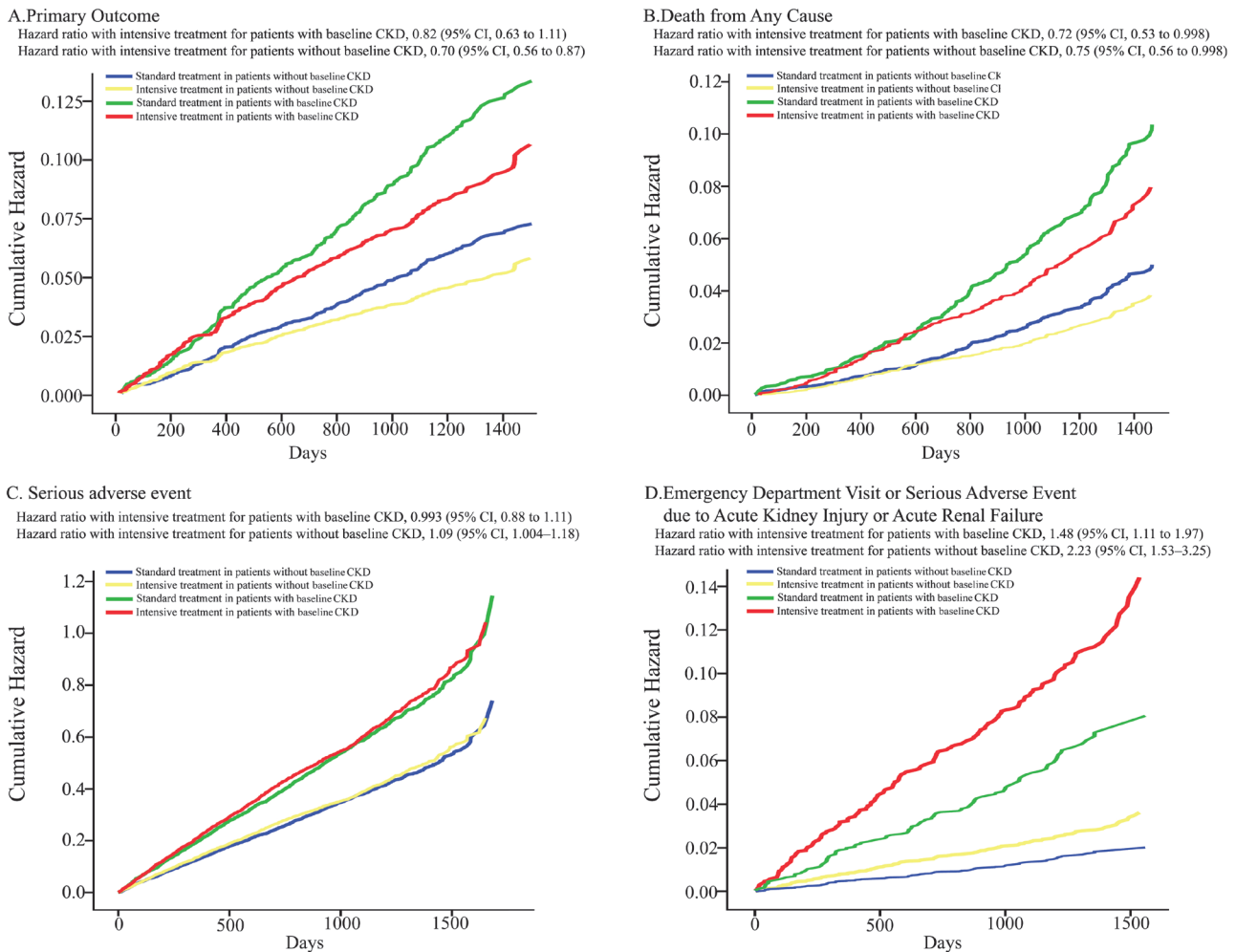
**Figure 1.** It was demonstrated Systolic and diastolic blood pressure in the two treatment groups in patients with and without CKD over the course of the trial in Figure 1. The systolic blood-pressure target in the intensive-treatment group was less than 120 mmHg, and the target in the standard-treatment group was less than 140 mmHg. The mean number of medications is the number of blood pressure medications administered at the exit of each visit. I bars represent 95% CI. CKD denotes chronic kidney disease.

more difficult in patients with baseline CKD as compared to those without CKD. Throughout the 3.02 years of follow-up, the mean systolic blood pressure in the intensive-treatment group was  $124.7 \pm 8.21$  mmHg in patients with baseline CKD and  $123.08 \pm 9.33$  mmHg in patients without baseline CKD (between group difference, 1.68;  $P < .001$ ). For patients in the standard-treatment group, these numbers were  $135.59 \pm 8.01$  mmHg and  $135.17 \pm 6.55$  mmHg; respectively (between group difference, 0.41;  $P < .05$ ). With intensive treatment, systolic blood pressure was reduced for an average difference of 10.82 mmHg in patients with CKD ( $P < .001$ ), and an average difference of 12.08 mmHg for patients without CKD ( $P < 0.001$ ). Controlling blood pressure needed more medications for patients with CKD compared to those without. The mean number of blood pressure medications for patients in the standard-treatment group with and without baseline CKD was 2.04 and 1.74, respectively ( $P < .001$ ); and they were 2.85 and 2.61 for patients in the intensive-treatment group, respectively ( $P < .001$ ).

**Comparison Between Clinical Outcomes in Patients With and Without CKD**

A primary outcome event was confirmed in 234 participants with baseline CKD (108) [2.60% per year] in the intensive-treatment group and 126 (3.09% per year) in the standard-treatment group (hazard ratio with intensive treatment, 0.82; 95% confidence interval [CI] = 0.63 to 1.11;  $P > .05$ ). Patients without CKD showed a treatment benefit with intensive treatment (hazard ratio with intensive treatment, 0.70; 95% CI = 0.56 to 0.87;  $P < .05$ ) (Figure 2). However, among CKD patients, those with micro-albuminuria showed a lower rate of primary outcome events (HR, 0.60; 95% CI, 0.37 to 0.98;  $P < .05$ ) (Figure 3).

Presence of CKD, compared to those without CKD, negatively affected the primary outcome (incidence rate, 2.84% per year vs. 1.55% per year in patients with and without CKD, respectively; Hazard ratio, 1.83; 95% CI = 1.49 to 2.11;  $P < .001$ ). This finding was consistent across all the secondary outcomes, including heart failure (99% higher



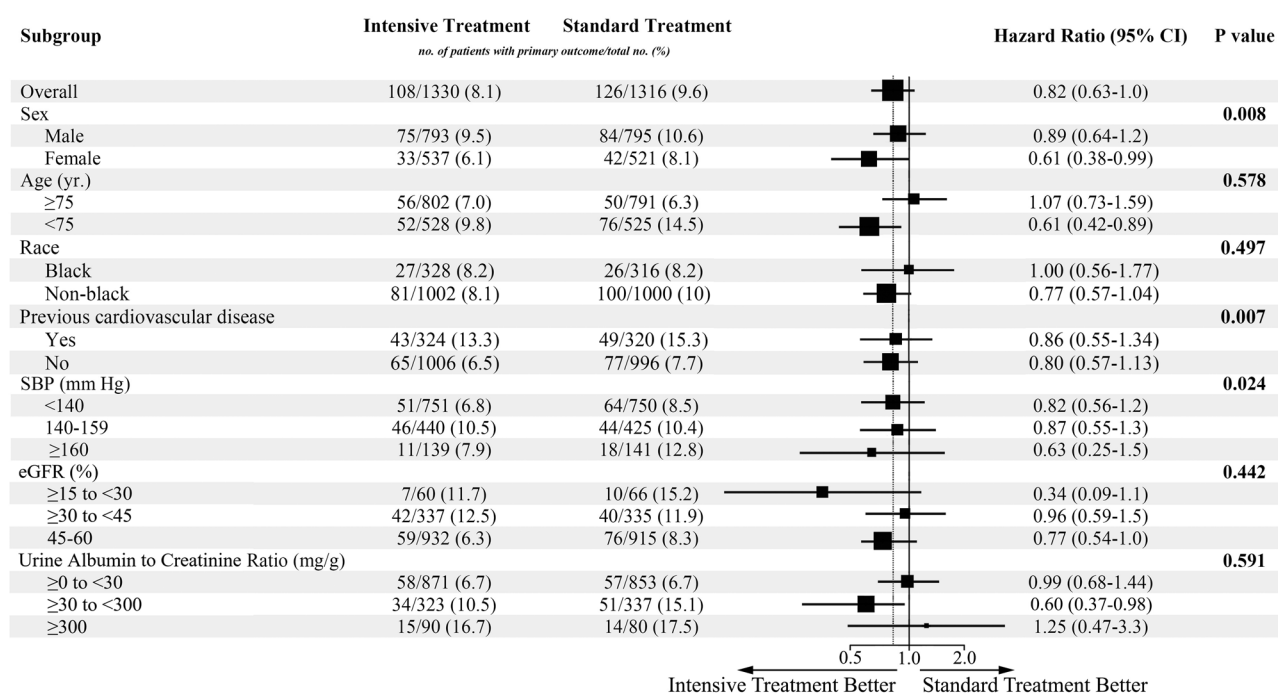
**Figure 2.** It was showed primary outcome, death from any cause, serious adverse events, and emergency department visit or serious adverse event due to AKI or ARF in Figure 2. Shown are the cumulative hazards for the primary outcome (a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) (Panel A), for death from any cause (Panel B), for serious adverse events (Panel C), and for emergency department visit or serious adverse event due to acute kidney injury or acute renal failure (Panel D). AKI denotes acute kidney injury, ARF denotes acute renal failure, CI denotes confidence interval, and CKD denotes chronic kidney disease.

relative risk), myocardial infarction (39% higher relative risk), acute coronary syndrome (11% higher relative risk), stroke (42% higher relative risk), death from cardiovascular causes (64% higher relative risk), and death from any cause (60% higher relative risk). Among other high risk features, the highest event rate was seen in those with clinical cardiovascular disease (incidence rate, 4.13% per year), followed by age over 75 years (incidence rate, 3.18% per year) (Table 2).

**Comparison Between Serious Adverse Events in Patients With and Without CKD**

Serious adverse events occurred in 628 participants in the intensive-treatment group (47.2%) and in

621 participants in the standard-treatment group (48.7%) (hazard ratio with intensive treatment, 0.9;  $P > .05$ ). These numbers for patients without CKD were 1165 (34.8%) and 1095 (32.52%), respectively (hazard ratio with intensive-treatment, 1.09;  $P < .05$ ) (Figure 2). On the other hand, in patients with baseline CKD, AKI or ARF leading to serious adverse events or emergency department visits occurred in 197 participants (117) [2.90% per year] in the intensive-treatment group and 80 (1.98% per year) in the standard-treatment group (hazard ratio with intensive treatment, 1.48; 95% CI = 1.11 to 1.97;  $P < .05$ ) (Figure 2). For patients with CKD, the numbers needed to harm (developing with AKI) was 37. This number for those without CKD was 71.



**Figure 3.** Forest plot of primary outcome according to subgroups was presented in Figure 3. The dashed vertical line represents the hazard ratio for the overall study population. The box sizes are proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision). SBP denotes systolic blood pressure, eGFR denotes estimated glomerular filtration rate, and CI denotes confidence interval.

**Table 2.** Effect of Various Baseline Characteristics on Cardiovascular Outcomes <sup>a</sup>

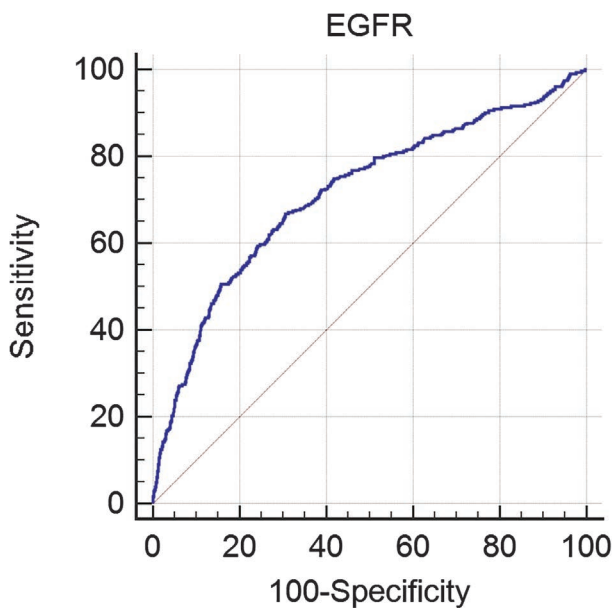
	Incidence Rate (%)	Relative Risk Change (%)	HR	95% CI	P
<b>CKD</b>					
Primary Outcome	2.85	81	1.83	1.49 to 2.11	< .001
CVD Death	0.55	116	2.12	1.41 to 3.19	< .001
Total Death	1.92	109	2.00	1.61 to 2.48	< .001
<b>Clinical CVD</b>					
Primary Outcome	4.13	159	2.64	2.19 to 3.18	< .001
CVD Death	0.83	235	3.09	2.02 to 4.72	< .001
Total Death	2.23	115	2.08	1.64 to 2.63	< .001
<b>Subclinical CVD</b>					
Primary Outcome	2.88	49	1.57	1.14 to 2.18	< .05
CVD Death	0.64	95	2.02	1.00 to 4.04	< .05
Total Death	1.54	26	1.32	0.86 to 1.04	> .05
<b>Age &gt; 75 Years</b>					
Primary Outcome	3.18	97	2.15	1.79 to 2.57	< .001
CVD Death	0.58	118	2.41	1.57 to 3.67	< .001
Total Death	2.21	145	2.73	2.19 to 3.42	< .001
<b>10-year Risk &gt; 15%</b>					
Primary Outcome	2.48	59	1.64	1.38 to 1.95	< .001
CVD Death	0.45	84	2.03	1.34 to 2.07	< .05
Total Death	1.64	84	1.96	1.57 to 2.43	< .001

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval  
<sup>a</sup> Calculations are based on presence of risk factor compared to its absence irrespective of treatment group.

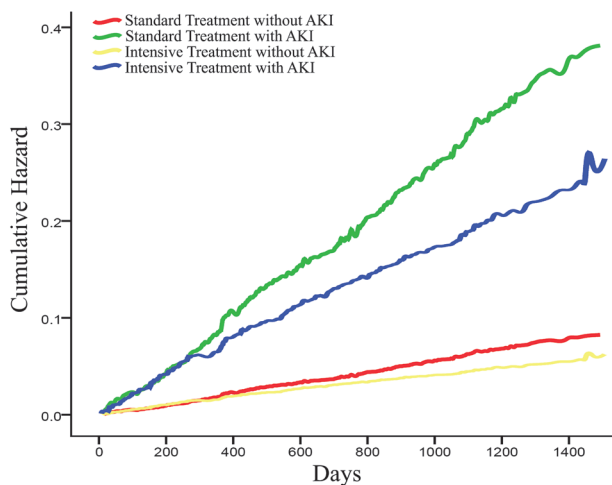
In addition, we performed a retrospective comparison of baseline characteristics between patients who had developed AKI and those who

didn't in the whole study population; those who had developed AKI had a lower eGFR (56.28% vs. 72.50%,  $P < .001$ ) and a higher serum creatinine

level (1.43 vs. 1.05,  $P < .001$ ) compared to those who didn't develop AKI. In fact, presence of CKD increased the chance of AKI by 215%, and an eGFR below 62.04% predicted the occurrence of AKI with 66.77% sensitivity and 69.39% specificity (area under the curve, 0.715;  $P < .001$ ; Figure 4). On the other hand, development of AKI increased the chance of development of cardiovascular events by 378% (Figure 5).



**Figure 4.** ROC curve for prediction of kidney injury based on eGFR was demonstrated in Figure 4. An eGFR below 62% could be defined as a cut off point for predicting AKI development with intensive blood pressure reduction.



**Figure 5.** It was showed primary outcome based on occurrence of AKI or ARF in Figure 5. As it is shown developing AKI significantly increases the chance of CVD.

## DISCUSSION

Our report is the first one from a clinical trial evaluating the impact of CKD on cardiovascular outcomes. We found that CKD is an independent risk factor for CVD; although, it is not a CVD risk equivalent. In CKD population, intensive blood pressure control did not reduce the chance of cardiovascular events or death except for those who had microalbuminuria, although it marginally reduced all-cause mortality. This treatment increased the risk for AKI or ARF. For patients with CKD, the number needed to prevent a death from any causes was 51, and the number needed to harm (developing with AKI) was 37. These numbers are lower than those from the results of the whole population enrolled in the trial because of the higher event rate in CKD population.

In *SPRINT*, presence of CKD, compared to those without CKD, negatively affected the primary outcome (incidence rate, 2.84% per year vs. 1.55% per year) and this effect was not reduced with intensive blood pressure control. This finding was consistent across all the secondary outcomes. This observation is in agreement with the results of the previous epidemiological studies.<sup>7</sup> In the cohort of 1,120,295 adults from the *Kaiser Permanente Renal Registry*, it was shown that the risk of cardiovascular death and events increased in a graded fashion with reduction of eGFR.<sup>6</sup> The high rate of cardiovascular events could not be entirely attributed to standard risk factors for CKD patients.<sup>8-10</sup> In fact, the association of classical cardiovascular risk factors was attenuated or even reversed at the most advanced CKD stages<sup>11</sup> while the incidence of cardiac events is increased. In CKD patients, a higher risk of plaque formation and rupture has been attributed to higher inflammation and oxidative stress.<sup>12</sup> In addition, presence of mineralocorticoid excess, also, has been linked to development of cardiovascular complications in this population.<sup>13</sup> In *SPRINT*, event rates were higher in patients with previous CVD compared to those with CKD, and CKD could not be considered as a CVD risk equivalent.

Presence of CKD also increased the chance of serious adverse events with treatment of hypertension even when the goals are just below 140 mmHg as compared with those without CKD. However, intensive treatment did not increase this chance except for AKI or ARF. In fact, presence

of CKD increased the chance of AKI or ARF by 216% with intensive treatment. On the other hand, development of AKI increased the chance of development of cardiovascular events by 378%. The variations in adverse renal consequences in the intensive treatment group might be attributed to varying intra-renal hemodynamic changes, caused by the major decline in BP and greater use of medications such as diuretics and ACE inhibitors.<sup>14-18</sup>

Controlling blood pressure in CKD patients was more difficult and needed more medications to reach their targets even for a standard treatment protocol. The addition of antihypertensive medications necessary for intensive blood pressure reduction may increase the cost and decrease the patients' compliance. It has been indicated that medication compliance is negatively correlated with the number of tablets per dose and the number of daily doses.<sup>19</sup> Reduced medication compliance is associated with an increased risk of cardiovascular morbidity and mortality.<sup>20</sup>

Currently, Intensive blood pressure reduction is advised only in patients with gross proteinuria (More than 300 mg in 24 hours).<sup>21</sup> According to the multicenter Modification of Diet in Renal Disease (MDRD) trial, disease progression and antihypertensive treatment efficacy are associated with protein excretion at baseline, which indicates the intensity of glomerular damage.<sup>22</sup> In that study, 2 groups with standard BP control (target mean arterial pressure < 107 mmHg corresponding to 140/90 mmHg) and aggressive BP management (target < 92 mmHg, corresponding to 125/75 mmHg) were assessed during 3 years. Among the 585 participants, only those excreting more than 1 g/d protein showed statistically significant slowing of the renal disease progression with aggressive blood pressure control. In a subsequent study, the long-term outcomes in the first MDRD study were evaluated.<sup>23</sup> The patients were followed-up during 1993-2000 to determine the frequency of renal failure (i.e. frequency of dialysis or renal transplant surgery) and rate of all-cause mortality. Further follow-ups showed that aggressive BP control was only effective for cases with protein excretion > 1 g/d. A major shortcoming of this study was the unavailability of BP analyses in the groups since 1993. Our results, is the first to show that intensive blood pressure reduction is helpful

in reducing CVD events in CKD populations with microalbuminuria.

This secondary analysis of the *SPRINT* involving CKD patients had some limitations. Even though the trial was designed to enhance the recruitment of a prespecified subgroup of CKD patients, it was not clear whether randomization was stratified by the category of CKD or not. In addition, a very small proportion of patients had gross proteinuria (above 300 mg/g) or an eGFR below 30%. Most clinical and epidemiological studies have shown a direct correlation between the degree of urine protein excretion and the likelihood of developing CDV.<sup>24,25</sup>

## CONCLUSIONS

It can be concluded that in non-diabetic patients with an eGFR below 60% (chronic kidney disease), the chance of cardiovascular events is increased. However, CKD could not be considered as a CVD risk equivalent. In CKD population, targeting a systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, does not result in lower rates of fatal and non-fatal major cardiovascular events, unless there is microalbuminuria although it may reduce the rate of death from any cause. This treatment may also be associated with an increased chance of AKI or ARF.

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## CONFLICT OF INTEREST

None declared.

## FUNDING

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## ETHICAL CONSIDERATIONS

The study protocol has been approved by the local



ethical committee and conformed the declaration of Helsinki on working to human subjects. All the subjects have given their written informed consent.

### AUTHOR CONTRIBUTIONS

A. A: study concept and design, drafting of the manuscript, acquisition of data, statistical analysis and interpretation of data; M. S and M.J.Z: statistical analysis, interpretation of data, drafting of the manuscript, critical revision of the manuscript.

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