BP Reduction, Kidney Function Decline, and Cardiovascular Events in Patients without CKD

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Abstract

Background and objectives In the Systolic Blood Pressure Intervention Trial (SPRINT), intensive systolic BP treatment (target <120 mm Hg) was associated with fewer cardiovascular events and higher incidence of kidney function decline compared with standard treatment (target <140 mm Hg). We evaluated the association between mean arterial pressure reduction, kidney function decline, and cardiovascular events in patients without CKD.

Design, setting, participants, & measurements We categorized patients in the intensive treatment group of the SPRINT according to mean arterial pressure reduction throughout follow-up: <20, 20 to <40, and ≥40 mm Hg. We defined the primary outcome as kidney function decline (≥30% reduction in eGFR to <60 ml/min per 1.73 m^2 on two consecutive determinations at 3-month intervals), and we defined the secondary outcome as cardiovascular events. In a propensity score analysis, patients in each mean arterial pressure reduction category from the intensive treatment group were matched with patients from the standard treatment group to calculate the number needed to treat regarding cardiovascular events and the number needed to harm regarding kidney function decline.

Results In the intensive treatment group, 1138 (34%) patients attained mean arterial pressure reduction <20 mm Hg, 1857 (56%) attained 20 to <40 mm Hg, and 309 (9%) attained ≥40 mm Hg. Adjusted hazard ratios for kidney function decline were 2.10 (95% confidence interval, 1.22 to 3.59) for mean arterial pressure reduction between 20 and 40 mm Hg and 6.22 (95% confidence interval, 2.75 to 14.08) for mean arterial pressure reduction ≥40 mm Hg. In propensity score analysis, mean arterial pressure reduction <20 mm Hg presented a number needed to treat of 44 and a number needed to harm of 65, reduction between 20 and <40 mm Hg presented a number needed to treat of 42 and a number needed to harm of 35, and reduction ≥40 mm Hg presented a number needed to treat of 95 and a number needed to harm of 16.

Conclusions In the intensive treatment group of SPRINT, larger declines in mean arterial pressure were associated with higher incidence of kidney function decline. Intensive treatment seemed to be less favorable when a larger reduction in mean arterial pressure was needed to attain the BP target.

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Introduction

Hypertension is a major public health issue, and it is expected to affect 1.56 billion people worldwide by 2025 (1). The Systolic Blood Pressure Intervention Trial (SPRINT) was a multicenter, randomized, controlled trial comparing intensive with standard systolic BP control (<120 versus <140 mm Hg) in patients without diabetes and with high cardiovascular risk. It showed lower rates of fatal and nonfatal major cardiovascular events in the intensive treatment group. The trial was stopped earlier (after 3.26 years of follow-up) due to a significantly lower rate of the primary outcome in the intensive treatment group.

However, in patients without prior kidney disease, intensive treatment was associated with an higher incidence of kidney function decline defined by a ≥30% reduction in eGFR to <60 ml/min per 1.73 m^2 on two consecutive laboratory determinations collected at 3-month intervals (hazard ratio, 3.49; 95% confidence interval [95% CI], 2.44 to 5.10; *P* value <0.001) (2). This finding was unexpected, because hypertension control was thought to be associated with a lower rate of kidney function decline (3,4).

We hypothesize that a greater difference between the baseline mean arterial pressure (MAP) and the lowest attained MAP may be associated with a higher risk of kidney function decline. We aimed to test whether there was an association between the magnitude of MAP reduction and the incidence of kidney function decline in the intensive treatment group of the SPRINT.

Materials and Methods

We performed a secondary data analysis of the SPRINT database using the dataset that was released with the SPRINT Data Analysis Challenge (5). The SPRINT was a multicenter, randomized, controlled

trial that included 9361 patients with an age of at least 50 years old, a systolic BP of 130–180 mm Hg, and high risk of cardiovascular events. Patients with diabetes mellitus or prior stroke were excluded (2). Detailed inclusion and exclusion criteria are listed in the supplementary appendix of the SPRINT (3). The study was conducted in accordance with Good Clinical Practice, all applicable subject privacy requirements, and the guiding principles of Helsinki. We submitted our protocol to the ethics committee of one author's institution (Hospital Garcia de Orta) and received an exemption certificate according to the application rules of the National Heart, Lung, and Blood Institute data repository.

We analyzed patients without prior CKD, defined as eGFR<60 ml/min per 1.73 m^2, in the intensive treatment group and excluded those without any BP measurements during follow-up or lacking baseline eGFR values.

MAP was calculated for each patient (one third of the systolic BP value plus two thirds of the diastolic BP value). We created a new variable (MAP reduction) corresponding to the difference between baseline MAP and minimum MAP achieved throughout follow-up. We categorized patients according to MAP reduction as <20, 20 to <40, and ≥40 mm Hg.

Primary outcome was kidney function decline as defined in the SPRINT protocol (3): a ≥30% reduction in eGFR to <60 ml/min per 1.73 m^2 on two consecutive laboratory determinations collected at 3-month intervals. Secondary outcome was the occurrence of cardiovascular events as defined in the primary composite outcome of the SPRINT (myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, and mortality from cardiovascular causes).

To assess the crude association between MAP reduction and primary and secondary outcomes, we performed Kaplan–Meier curve and log rank tests. We performed a Cox proportional hazards model adjusted for the following potential confounders: age, sex, black race, smoking status, cardiovascular disease (clinical or subclinical), number of antihypertensive agents, statin and aspirin use, ratio of urinary albumin to creatinine, and baseline MAP. A test for trend over categories of MAP reduction was performed where each category median was modeled as a continuous variable in the regression model. Additionally, we also performed the Cox proportional hazards models using MAP reduction as a continuous variable. The proportional hazards assumption was tested, and there was no evidence of violation.

We also performed a supplementary analysis including a Cox proportional hazards model analysis adjusted for the same confounders but categorizing patients according to a 20-mm Hg cutoff of systolic BP and diastolic BP reduction and a 5-mm Hg cutoff of MAP, systolic BP, and diastolic BP reduction. We performed the same analysis according to MAP, systolic BP, and diastolic BP tertiles.

We then analyzed the group of patients in each category of MAP reduction in the intensive treatment group, matching them to patients in the standard treatment group with similar baseline characteristics. We used a propensity score, which included the following baseline covariates: age, sex, black race, smoking status, cardiovascular disease (clinical or subclinical), number of antihypertensive agents, statin and aspirin use, ratio of urinary albumin to creatinine, systolic BP, diastolic BP, eGFR, glucose, total cholesterol, HDL, and triglycerides. We calculated the number needed to treat (NNT) over the course of the trial considering the absolute risk reduction of cardiovascular events between matched groups and the number needed to harm (NNH) considering the absolute risk increase of kidney function decline in matched groups.

We also evaluated the association between kidney function decline and cardiovascular events and the effect modification by treatment group. For this analysis, we used a Cox proportional hazards model with cardiovascular events as outcome and assessed the interaction between intensive treatment and kidney function decline with a likelihood ratio test for the interaction.

Because the degree of missing data was low (described in Results below), patients with missing values in any one of the variables of the adjusted Cox proportional hazards model or the propensity score model were excluded. For those participants lost to follow-up, we used all available information until the time of last assessment.

Continuous variables are presented as means±SD when normally distributed or medians (25th percentiles to 75th percentiles) when not normally distributed. Categorical variables are presented as percentages. A two-sided P value of <0.05 was considered statistically significant. Stata/IC 14.1 was used.

Results

We included 3304 patients in our analysis of the intensive treatment group after excluding 1332 with previous CKD, 34 without any value of BP during follow-up, and eight patients without baseline eGFR. The average follow-up was 3.25 years, with a total of 10,714 person-years of follow-up. Missing data were present in only four of the analyzed variables. Body mass index was missing in 20 (0.6%) patients, ratio of urinary albumin to creatinine was missing in 157 (5%) patients, statin use was missing in 17 (0.5%) patients, and aspirin use was missing in nine (0.3%) patients. Because of missing data in at least one of these four variables, 180 (5.4%) patients were excluded from the adjusted analysis, which included a total of 3124 patients.

Mean baseline MAP was 100±11 mm Hg. The distribution of patients according to MAP reduction categories was as follows: 1138 (34%) patients attained <20 mm Hg, 1857 (56%) patients attained 20 to <40 mm Hg, and 309 (9%) patients attained ≥40 mm Hg. There were significant differences among these groups (Table 1): patients with higher MAP reduction were younger, had higher baseline BP (MAP, systolic, and diastolic), and had higher values of urinary albumin-to-creatinine ratio, total cholesterol, and HDL. This group also had a higher proportion of current smokers. Regarding medications, these patients were taking significantly fewer antihypertensive agents, statins, and aspirin.

The average value of the minimum MAP achieved in each group was 78±8 mm Hg for patients with MAP reduction <20 mm Hg, 74±7 mm Hg for those with MAP reduction between 20 and <40 mm Hg, and 69±8 mm Hg for patients with MAP reduction ≥40 mm Hg. MAP, systolic BP, and diastolic BP in the three categories of MAP reduction over the course of the trial are presented in Figure 1.

Table 1. Baseline characteristics of the study participants according to achieved mean arterial pressure reduction: <20, 20 to <40, and ≥40 mm Hg

Variables	Mean Arterial Pressure Reduction		
	<20 mm Hg, *n*=1138	20 to <40 mm Hg, *n*=1857	≥40 mm Hg, *n*=309
Age, yr	67±9	67±9	63±9
Cardiovascular disease, %	19	18	21
Clinical	16	14	18
Subclinical	5	5	5
Women, %	33	34	37
Black race, %	35	31	40
Baseline BP, mm Hg			
Systolic	128±12	143±12	163±14.8
Diastolic	72±10	81±9	94±11
Mean	91±8	102±8	117±10
No. of antihypertensive agents	1.8±1.0	1.7±1.0	1.6±1.1
Body mass index, kg/m^2	30.0±5.7	30.1±5.7	30.4±6.6
Serum creatinine, mg/dl	0.94±0.17	0.92±0.17	0.93±0.19
eGFR, ml/min per 1.73 m^2	81±15	81±16	83±17
Urinary albumin to creatinine, mg/g	7.6 (5.1–14.8)	8.9 (5.6–17.6)	12.5 (7.7–27.0)
Fasting total cholesterol, mg/dl	188±42	192±40	204±47
Fasting HDL cholesterol, mg/dl	52±13	53±14	55±16
Fasting total triglycerides, mg/dl	103 (74–140)	107 (76–150)	110 (77–168)
Fasting plasma glucose, mg/dl	99±14	99±13	99±17
Statin use, %	41	41	31
Aspirin use, %	51	50	44
Smoking status, %			
Never smoked	42	44	43
Current smoker	16	14	25
Former smoker	42	42	33

Baseline characteristics of 3304 Systolic Blood Pressure Intervention Trial participants without CKD at baseline assigned to intensive BP treatment according to achieved mean arterial pressure reduction. Values are percentages for categorical covariates, means±SD for continuous covariates, or medians (interquartile ranges) where appropriate.

In the analyzed population, the incidence rates of kidney function decline among the different subgroups of MAP reduction were as follows: 23 (2%) events for MAP reduction of <20 mm Hg, 77 (4%) events between 20 and <40 mm Hg, and 27 (9%) events for ≥40 mm Hg.

In the unadjusted analysis (Figure 2), the magnitude of MAP reduction was significantly associated with kidney function decline (P value <0.001). Compared with the group of MAP reduction <20 mm Hg, unadjusted hazard ratios for kidney function decline were 1.94 (95% CI, 1.22 to

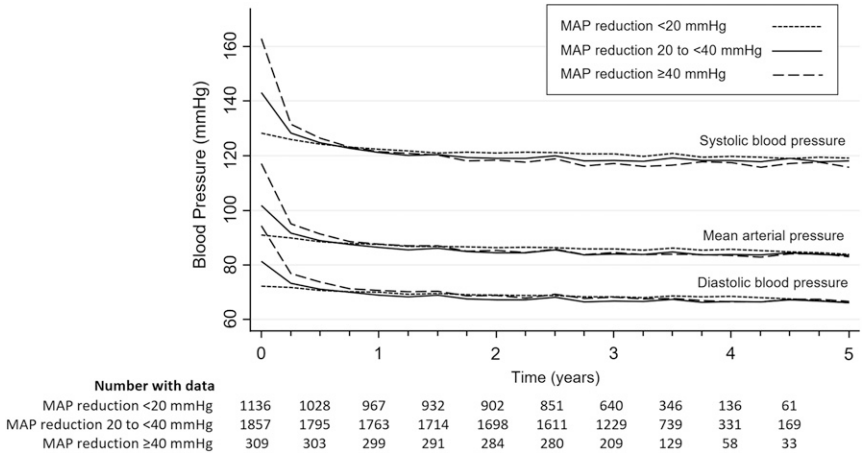

Figure 1. | In the 3304 SPRINT participants without CKD at baseline assigned to intensive BP treatment, mean arterial pressure (MAP), systolic BP, and diastolic BP decreased in a rapid and sustained way, and participants attained similar values in the three categories of MAP reduction.

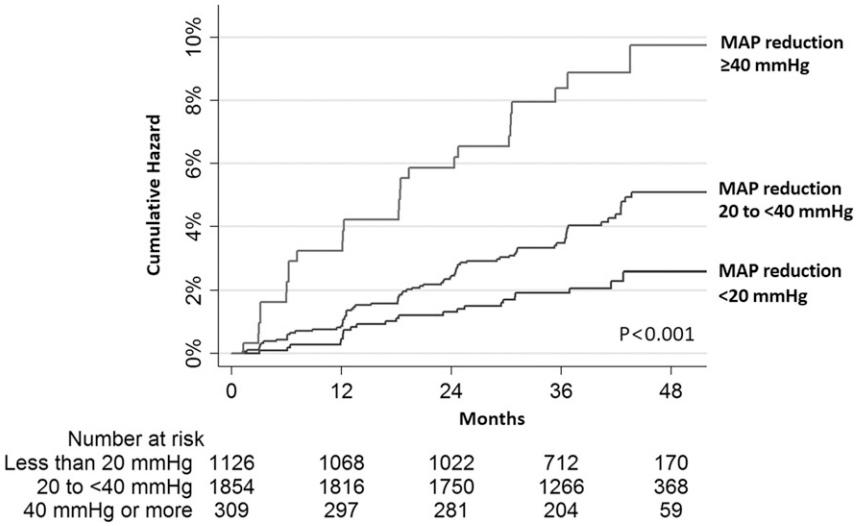

Figure 2. | A larger decrease in mean arterial pressure (MAP) was significantly associated with higher incidence of kidney function decline in the 3304 SPRINT participants without CKD at baseline assigned to intensive BP treatment. Kidney function decline was defined by 30% reduction in eGFR to <60 ml/min per 1.73 m^2 on two consecutive laboratory determinations collected at 3-month time intervals.

3.10) for MAP reduction between 20 and <40 mm Hg and 4.19 (95% CI, 2.40 to 7.30) for MAP reduction ≥40 mm Hg (Supplemental Table 1). This association remained significant after multivariable analysis.

The covariates included in the multivariable analysis are described in Materials and Methods above. Compared with the group of MAP reduction <20 mm Hg, adjusted hazard ratios for kidney function decline were 2.10 (95% CI, 1.22 to 3.59) for MAP reduction between 20 and <40 mm Hg and 6.22 (95% CI, 2.75 to 14.08) for MAP reduction ≥40 mm Hg. Age (P=0.04) and ratio of urinary albumin to creatinine (P=0.002) were also found to be independent predictors of kidney function decline. Unadjusted and adjusted hazard ratios for kidney function decline according to BP reduction tertiles (MAP, systolic, and diastolic) and categories of BP reduction (20- and 5-mm Hg cutoffs) in the intensive treatment group are presented in Supplemental Tables 1–7.

The association with cardiovascular events was also evaluated in the intensive treatment group. The incidence rates of this outcome among the different subgroups of MAP reduction were as follows: 61 (5%) events for MAP reduction of <20 mm Hg, 93 (5%) events between 20 and <40 mm Hg, and 30 (10%) events for ≥40 mm Hg. The unadjusted hazard ratios for cardiovascular events were 1.04 (95% CI, 0.71 to 1.52) for MAP reduction of 20 to <40 mm Hg and 1.52 (95% CI, 0.87 to 2.64) for MAP reduction of ≥40 mm Hg. The adjusted hazard ratios were not statistically significant: 0.93 (95% CI, 0.58 to 1.49) for MAP reduction of 20 to <40 mm Hg and 1.04 (95% CI, 0.47 to 2.31) for MAP reduction of ≥40 mm Hg.

The results of the continuous analysis were consistent with the analysis of MAP reduction categories. The hazard ratios for each 10-mm Hg of MAP reduction for kidney function decline were 1.49 (95% CI, 1.32 to 1.69; P<0.001) in the unadjusted analysis and 2.27 (95% CI, 1.77 to 2.90; P<0.001) in the adjusted model. The hazard ratios for each 10-mm Hg MAP reduction for cardiovascular events were 1.12 (95% CI, 0.97 to 1.29; P=0.13) in the unadjusted analysis and 0.99 (95% CI, 0.77 to 1.26; P=0.91) in the adjusted model.

To assess the risk-benefit balance of intensive treatment, we compared the categories of patients without previous CKD with different magnitudes of MAP reduction (Table 2) in the intensive treatment group (n=3084) with similar patients in the standard treatment group (n=3084). The MAP reductions were 13±5 mm Hg in the intensive treatment group with <20 mm Hg of MAP reduction and 10±8 mm Hg in the matched standard treatment group, 28±6 mm Hg in the intensive treatment group with MAP reduction between 20 and <40 mm Hg and 19±10 mm Hg in the matched standard treatment group, and 47±6 mm Hg in the intensive treatment group with MAP reduction >40 and 32±11 mm Hg in the matched standard treatment group.

Considering the propensity score analysis, there were 22 (2.1%) kidney function decline events and 38 (3.6%) cardiovascular events in the intensive treatment group with <20 mm Hg of MAP reduction, and there were six (0.6%) kidney function decline events and 62 (5.9%) cardiovascular events in the respective standard treatment group. The hazard ratio with intensive treatment for kidney function decline was 3.83 (95% CI, 1.55 to 9.44; P=0.004), and the hazard ratio with intensive treatment for cardiovascular events was 0.63 (95% CI, 0.42 to 0.94; P=0.02).

In the intensive treatment group with MAP reduction between 20 and <40 mm Hg, there were 72 (4.1%) kidney function decline events and 71 (4.1%) cardiovascular events, and in the respective standard treatment group, there were 22 (1.3%) kidney function decline events and 113 (6.5%) cardiovascular events. The hazard ratio with intensive treatment for kidney function decline was 3.26 (95% CI, 2.02 to 5.26; P<0.001), and the hazard ratio with intensive treatment for cardiovascular events was 0.61 (95% CI, 0.45 to 0.82; P=0.02).

In the intensive treatment group with MAP reduction >40 mm Hg, there were 26 (9.1%) kidney function decline

Table 2. Baseline characteristics of matched groups according to mean arterial pressure reduction in the intensive treatment group: <20, 20 to <40, and ≥40 mm Hg

Variables	Intensive <20 mm Hg, *n*=1046	Matched Standard, *n*=1046	Intensive 20 to <40 mm Hg, *n*=1752	Matched Standard, *n*=1752	Intensive ≥40 mm Hg, *n*=286	Matched Standard, *n*=286
Age, yr	67±9	67±9	67±9	67±9	64±9	64±9
Cardiovascular disease, %	19	19	18	18	22	22
Women, %	34	32	34	33	36	37
Black race, %	35	34	32	30	39	41
No. of antihypertensive agents	1.8±1.0	1.8±1.0	1.7±1.0	1.7±1.0	1.6±1.1	1.7±1.1
Body mass index, kg/m^2	29.9±5.7	30.0±5.7	30.1±5.8	30.1±5.8	30.3±6.3	30.0±5.8
eGFR, ml/min per 1.73 m^2	81±15	81±15	81±16	82±16	82±17	82±16
Urinary albumin to creatinine, mg/g	7.7 (5.0–14.8)	7.8 (5.0–15.1)	9.0 (5.6–17.7)	8.9 (5.6–17.7)	12.1 (7.0–26.9)	12.1 (6.4–28.6)
Fasting total cholesterol, mg/dl	189±43	189±41	193±40	191±39	204±47	202±42
Fasting HDL cholesterol, mg/dl	52±14	52±15	53±14	53±15	55±16	55±16
Fasting total triglycerides, mg/dl	104 (75–140)	108 (77–153)	107 (76–151)	106 (78–157)	111.5 (79–168)	108 (76–160)
Fasting plasma glucose, mg/dl	100±14	100±15	99±13	99±13	100±17	99±13
Statin use, %	41	44	41	42	32	33
Aspirin use, %	51	50	50	50	44	44
Current smoker, %	15	15	14	14	24	26
Baseline BP, mm Hg						
Systolic	129±11	128±11	143±12	143±13	161±13	162±14
Diastolic	72±10	72±10	81±10	81±11	93±10	94±11
Mean	91±8	91±8	102±8	102±10	116±9	116±9

Baseline clinical characteristics of the Systolic Blood Pressure Intervention Trial participants without CKD, including participants assigned to intensive BP control and propensity score–matched participants assigned to standard BP control. The group of patients in the intensive treatment group who attained each mean arterial pressure reduction category was matched with patients in the standard treatment group with similar baseline characteristics according to a propensity score. The following baseline covariates were included: age, sex, black race, smoking status, cardiovascular disease (clinical or subclinical), number of antihypertensive agents, statin and aspirin, ratio of urinary albumin to creatinine, systolic BP, diastolic BP, eGFR, glucose, total cholesterol, HDL, and triglycerides.

events and 17 (5.9%) cardiovascular events, and in the respective standard treatment group, there were eight (2.8%) kidney function decline events and 20 (7.0%) cardiovascular events. The hazard ratio with intensive treatment for kidney function decline was 3.20 (95% CI, 1.45 to 7.07; $P<0.04$), and the hazard ratio with intensive treatment for cardiovascular events was 0.80 (95% CI, 0.42 to 1.53; $P=0.50$).

Considering the absolute risk described above, patients with an MAP reduction of <20 mm Hg presented an NNT of 44 (absolute risk, 3.6% versus 5.9%) and an NNH of 65 (absolute risk, 2.1% versus 0.6%); patients with an MAP reduction between 20 and <40 mm Hg presented an NNT of 42 (absolute risk, 4.1% versus 6.5%) and an NNH of 35 (absolute risk, 4.1% versus 1.3%), and patients with an MAP reduction ≥40 mm Hg presented an NNT of 95 (absolute risk, 5.9% versus 7.0%) and an NNH of 16 (absolute risk, 9.1% versus 2.8%) (Figure 3).

Regarding the association between kidney function decline and cardiovascular events, there was no significant heterogeneity by treatment group (P for interaction =0.22), with a hazard ratio of 2.44 (95% CI, 1.01 to 5.94) in the standard treatment group and a hazard ratio of 1.10 (95% CI, 0.48 to 2.49) in the intensive treatment group (Figure 4).

Discussion

We found that, in patients without CKD, a larger decrease in MAP was significantly associated with higher incidence of kidney function decline. Whereas the benefit-risk balance of intensive treatment became less favorable with greater MAP reduction, the development of kidney function decline did not seem to confer an increase in cardiovascular risk.

Most clinical studies on BP control focus on systolic or diastolic BP instead of MAP. However, many molecular studies of kidney responses to hypertensive stimuli (such as salt intake or volume expansion) use MAP to compare the effect of the interventions being studied on BP (6,7). In critical care patients, MAP is also preferred to systolic or diastolic BP as a measure of kidney perfusion. Several studies show an association between MAP reduction and higher probability of kidney injury (8–10), but most of these studies focus on increasing MAP to a minimum threshold in hypotensive individuals. In general, autoregulation guarantees GFR preservation for an MAP value between 80 and 180 mm Hg (11). However, the ability of the kidney to adapt to BP changes is affected by physiologic and pharmacologic factors. Patients with hypertension and elderly patients are more prone to kidney arteriosclerosis, and they are at higher risk for impaired autoregulation (12). Because patients included in the SPRINT were older and had high cardiovascular risk, they represent a population of increased susceptibility to kidney hypoperfusion with larger decreases in MAP.

BP reduction has been shown to be renoprotective when it is associated with a decrease in intraglomerular pressure. In those circumstances, the decrease in GFR is expected to be <30%, to improve or resolve on repeated measurements, and to be associated with a slower decline of GFR in the long term (13). In the SPRINT, kidney function decline was >30% and confirmed on repeated measurements (2). Regarding eGFR decline slope, a secondary analysis of the SPRINT by Cheung *et al.* (14) in patients with CKD found that, although the rate of decline in eGFR in the intensive treatment group and the standard treatment group was low, the eGFR decline curve in the intensive treatment group was actually steeper after the initial 6 months. It is

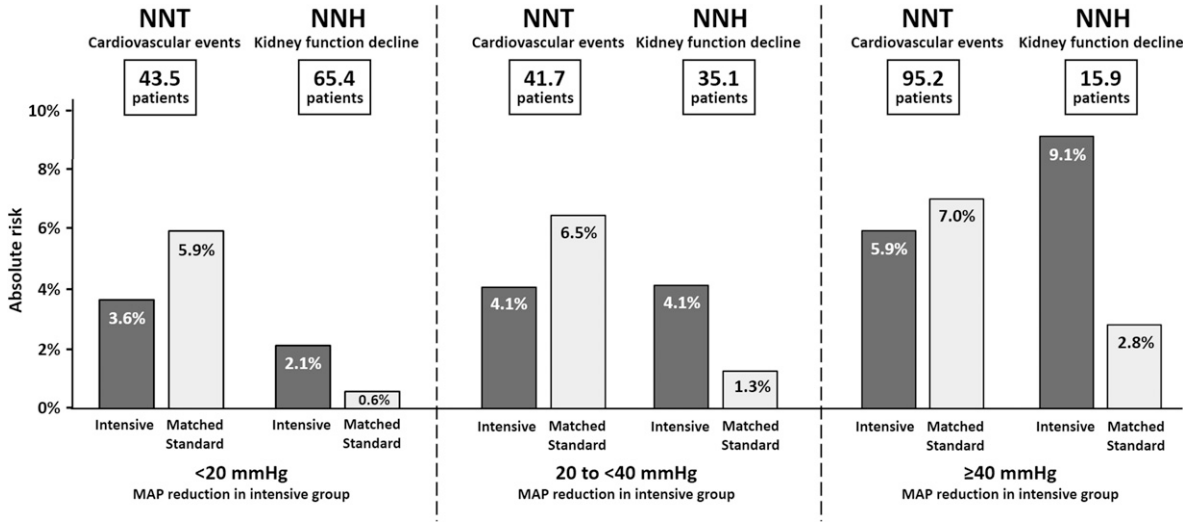

Figure 3. | The balance between benefits and risks becomes less favorable as MAP reduction increases, as shown by the number needed to treat and the number needed to harm of participants assigned to intensive blood pressure control and propensity score–matched participants assigned to standard blood pressure control, according to achieved mean arterial pressure reduction (<20 mm Hg; 20 to <40 mm Hg and ≥40 mm Hg). The following baseline covariates were included: age, sex, black race, smoking status, cardiovascular disease (clinical or subclinical), number of antihypertensive agents, statin and aspirin use, systolic BP, diastolic BP, estimated glomerular filtration rate, glucose, ratio of urinary albumin to creatinine, total cholesterol, high-density lipoproteins, triglycerides. NNT, number needed to treat; NNH, number needed to harm; MAP, mean arterial pressure; BP, blood pressure.

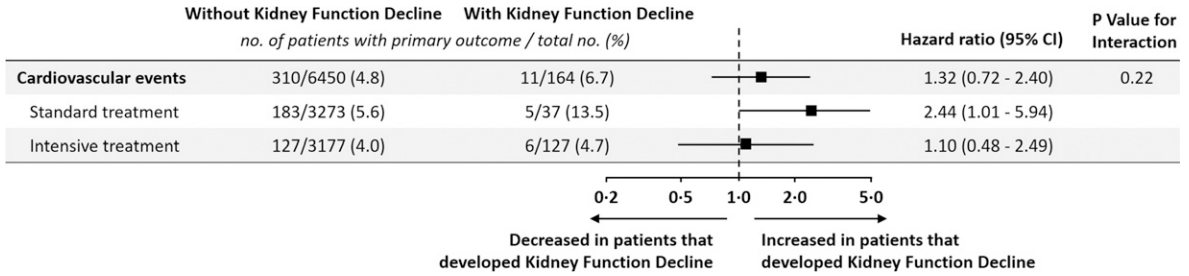

Figure 4. | There was no significant heterogeneity by treatment group for the association between kidney function decline and cardiovascular events of SPRINT participants without chronic kidney disease at baseline. Kidney function decline was defined by ≥30% reduction in eGFR to <60 ml/min per 1.73 m^2 on two consecutive laboratory determinations collected at three-month time intervals. 95% CI, 95% confidence interval.

possible that the decrease in eGFR that we detected corresponds to a structural injury to the kidney caused by a sustained decrease in effective arterial blood volume after institution of antihypertensive agents and as such, does not correspond to a renoprotective reduction in intraglomerular pressure. Previous studies in patients with CKD, including a meta-analysis of 1.7 million patients, showed an association between a 30% reduction in eGFR and a higher long-term risk of ESRD (15,16). Thus, in our population, kidney function decline may be detrimental in the long term. However, this question needs to be examined in detail in this population.

In our analysis, kidney function decline and cardiovascular events were higher in both the intensive and matched standard groups with greater MAP reductions. This finding may be explained by the fact that patients who attained greater decrease in BP also presented higher baseline BP and thus, might present higher cardiovascular (17) and kidney injury risks (18). Although intensive treatment decreases the risk of cardiovascular events across the matched groups, it also greatly increases the risk of kidney function decline. The balance between benefits and risks becomes less favorable as MAP reduction increases.

Furthermore, we evaluated the association between the occurrence of kidney function decline and cardiovascular events in both treatment groups. Although the hazard ratio for cardiovascular events in the standard treatment group was higher among patients with kidney function decline compared with patients without kidney function decline, the interaction between kidney function decline and treatment group was nonsignificant. This analysis must be interpreted as exploratory, because it was limited by the low number of patients who developed both kidney function decline and cardiovascular events over the course of the study. Adequately powered confirmatory studies with a longer follow-up are needed to ascertain the true effect of BP treatment–associated kidney function decline in cardiovascular risk.

Regarding the strengths of our study, we performed a secondary analysis of a large multicenter, randomized, controlled trial, evaluating an unexpected finding of the SPRINT. The definition used for kidney function decline was prespecified in the SPRINT, requiring a 3-month interval between two consecutive laboratory determinations. Because CKD is a major known cardiovascular risk factor (19,20), the identification of patients more likely to develop kidney function decline with intensive BP treatment is clinically relevant.

Considering limitations of our study, longitudinal creatinine values were not included in the SPRINT Data Analysis Challenge dataset, thus not allowing the comparison of eGFR decline rates between groups. Moreover, it is possible that the higher incidence of kidney function decline was due to the unbalanced distribution of cardiovascular risk among categories of MAP reduction. Individuals who had a greater MAP reduction had significantly higher BP at baseline (MAP, systolic, and diastolic), higher total cholesterol, and higher ratio of urinary albumin to creatinine. There was a higher proportion of current smokers, and on average, these patients were taking a smaller number of antihypertensive agents, statins, and aspirin, possibly indicating that they received less medical supervision before trial entry. However, we adjusted for cardiovascular disease, and on the propensity score analysis, we matched the individuals for all of the above-mentioned variables. As in all secondary analyses, our study has an exploratory nature, and patients were not originally randomized for MAP reduction; therefore, it is possible that residual confounding exists due to unmeasured variables. The relationship between benefit and risk of intensive BP lowering must be interpreted with caution. In patients who are hypertensive with lower cardiovascular risk than those included in the SPRINT, the benefit of intensive BP control and the risk of developing kidney function decline may be different (21).

The fact that, in our analysis, the benefit-risk relationship became less favorable with greater MAP reduction may be important for patients and physicians, who aim for the lowest cardiovascular risk with the lowest probability of side effects (19–21). If this association is confirmed by prospective studies, future recommendations for hypertension treatment in this population should consider personalized targets (according to usual MAP) rather than a fixed cutoff for every patient.

In conclusion, MAP reduction >20 mm Hg in patients with a target systolic BP <120 mm Hg was associated with higher incidence of kidney function decline. The benefit-risk balance of intensive treatment seemed to be less favorable with greater MAP reduction. Prospective studies evaluating the effect of MAP reduction in addition to hypertension treatment target on kidney function decline and cardiovascular events are warranted.

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Disclosures

None.

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