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Systolic Blood Pressure Time in Target Range and Major Adverse Kidney and Cardiovascular Events

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Abstract

Background: Whether time-in-target range (TTR) for systolic blood pressure (SBP) associates with adverse kidney and cardiovascular events remains unknown.

Methods: This study included participants in two clinical trials that compared intensive (<120 mm Hg) and standard (<140 mm Hg) SBP lowering. SBP TTR for months 0–3 was calculated using therapeutic ranges of 110–130 mm Hg and 120–140 mm Hg for the intensive and standard arms, respectively. Adverse kidney events included the composite of dialysis, kidney transplant, serum creatinine >3.3 mg/dL, sustained eGFR <15 mL/min/1.73 m^2 or sustained eGFR decline >40%. Adverse cardiovascular events included myocardial infarction, stroke, heart failure and cardiovascular death. Adjusted Cox proportional hazards regression models were used to estimate the association between SBP TTR and kidney and cardiovascular events.

Results: Participants with higher TTR were younger and less likely to have preexisting cardiovascular disease. Compared to participants with TTR of 0%, the risk of adverse kidney events was lower for participants with TTR of >0%−43% (HR [95% CI]: 0.57 [0.42–0.76]; P<0.001), 43-<70% (0.57 [0.42–0.78]; P=0.001), 70%-<100% (0.53 [0.38–0.74]; P<0.001) and 100% (0.33 [0.20–0.57]; P<0.001) in fully adjusted models. The risk of major adverse cardiovascular events was lower for participants with TTR of >0%−43% (0.66 [0.52–0.83];

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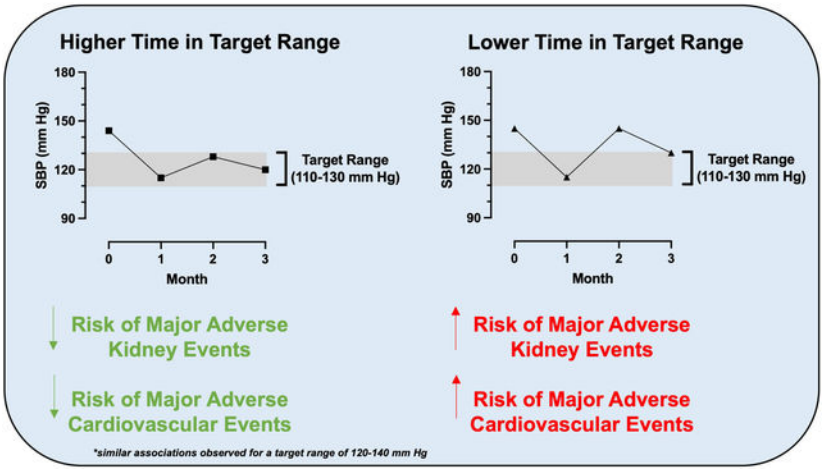
P=0.001), 43-<70% (0.70 [0.55–0.90]; P=0.005), 70-<100% (0.65 [0.50–0.84]; P=0.001) or 100% (0.56 [0.39–0.80]; P=0.001) compared to those with TTR of 0%.

Conclusions: Higher SBP TTR associates with lower risks of adverse kidney and cardiovascular events in adults with hypertension. SBP TTR may be a potential therapeutic target and quality metric.

Graphical Abstract



Keywords

hypertension; time-in-target range; blood pressure control; quality of care; epidemiology

Introduction

Hypertension affects nearly one in every two adults in the United States (approximately 121.5 million persons).[1] Worldwide, over 874 million persons had systolic blood pressure (SBP) of 140 mm Hg or higher in 2015 and the prevalence of hypertension may continue to increase.[2] Persons living with hypertension have an increased risk of death from any cause, as well as coronary artery disease, cerebrovascular disease and heart failure.[3, 4] Intensive SBP lowering to a target of 120 mm Hg or lower reduces the risk of atherosclerotic and non-atherosclerotic cardiovascular disease[5–8] and may reduce the risk of death from any cause.[5]

The prevalence of controlled SBP, defined as less than 140/90 mm Hg, remains less than 43% worldwide.[9] SBP control can also be quantified over time using time-in-target range (TTR), which is the proportion of time with SBP within a defined range. One study estimated the average TTR during the first 12 months after hypertension diagnosis to be 25%.[10] Worse blood pressure control, as measured by TTR, associates with an increased risk of death from any cause and major adverse cardiovascular events.[10–12] It is incompletely understood whether SBP TTR associates with major adverse cardiovascular events in people with and without type 2 diabetes mellitus.

Hypertension also is a major risk factor for progression of chronic kidney disease and end-stage kidney disease, but the effects of intensive SBP lowering on adverse kidney outcomes remains unclear.[13–15] Randomized clinical trials have failed to show consistent differences between lower and higher SBP and mean arterial pressure targets with respect to the risk of adverse kidney outcomes.[16–19] Moreover, the association of SBP TTR with major adverse kidney events is unknown. This study sought to test the hypothesis that worse SBP control, as measured by SBP TTR, associates with a higher risk of adverse kidney and cardiovascular outcomes in adults with hypertension.

Methods

This study was a retrospective, cohort study of participants in the Systolic Blood Pressure Intervention Trial (SPRINT) and the Action to Control Cardiovascular Risk in Diabetes – Blood Pressure (ACCORD BP) trial. The designs and results of SPRINT and ACCORD BP have been reported previously.[5, 20] In brief, participants in SPRINT and ACCORD were randomized to either an intensive SBP target of <120 mm Hg or a standard SBP target of <140 mm Hg. SPRINT included individuals with hypertension and increased cardiovascular risk except those with type 2 diabetes mellitus or prior stroke, whereas ACCORD BP included individuals with type 2 diabetes mellitus.

The National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center provided access to SPRINT and ACCORD BP data, which were altered to protect participant privacy by collapsing categories with few observations, winsorizing extreme continuous variables, and truncating all follow-up at 7 years. Access to the data used for this study may be requested at https://biolincc.nhlbi.nih.gov/home/.

Study Population

All participants in SPRINT and ACCORD BP were eligible for the present study if they had at least 2 systolic blood pressure measurements (including baseline) during the first three months of each study and had available covariate data. Because the ACCORD BP protocol specified blood pressure measurements only at baseline and 1-month for participants in the standard systolic blood pressure lowering arm (additional information on blood pressure measurements below), only ACCORD BP participants in the intensive systolic blood pressure lowering arm were included. Participants who experienced an outcome of interest during the SBP-TTR calculation period (3 months for the primary analysis and 12 months for a sensitivity analysis) were excluded from that analysis.

Exposure

The primary exposure of interest was SBP-TTR during study months 0 through 3. The target ranges for individuals in the intensive and standard SBP target arms were set as 110–130 mm Hg and 120–140 mm Hg, respectively. SBP-TTR was calculated using the linear interpolation method.[10–12, 21] Linear interpolation assumes a linear change in SBP between measured SBP readings and calculates TTR using the measured and linearly imputed changes in SBP. In all SPRINT participants and ACCORD BP participants in the intensive blood pressure target arm, seated blood pressure was measured at baseline,

1-month, 2-months, and 3-months. In-clinic blood pressure measurements were obtained by trained staff as the mean of three measurements on an oscillometric device. Neither study protocol specified whether study staff should or should not be in room with the participant during the measurement. Protocol specifications for SBP management have been reported previously.[22, 23] We performed a sensitivity analysis by calculating SBP-TTR during study months 0 through 12 with the same target ranges as the primary analysis and by calculating SBP-TTR during study months 0 to 3 with target ranges of 100–120 mm Hg for the intensive and 120–140 mm Hg for the standard arms.

Outcomes

The primary outcomes of interest for this study were major adverse kidney events and major adverse cardiovascular events. Major adverse kidney events included chronic dialysis, kidney transplantation, serum creatinine greater than 3.3 mg/dL, sustained CKD-EPI estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73 m^2 (confirmed by a second measurement at least 1 month later), or sustained decline in eGFR of greater than 40% (confirmed by a second measurement at least 1 month later). Outcome follow-up began after study month 3.

Major adverse cardiovascular events included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Each component of the composite kidney and cardiovascular outcomes were evaluated individually.

In SPRINT, end-stage kidney disease was assessed only for the subgroup of participants with chronic kidney disease at baseline. For this analysis, we assumed that none of the participants who were free from chronic kidney disease at baseline developed end-stage kidney disease.

Statistical Analysis

Data were summarized as counts and percentages if categorical, mean ± standard deviation (SD) if approximately normally distributed and median [25^{th}, 75^{th} percentiles] if non-normally distributed. Continuous variable distributions were assessed for approximate normality with quantile-quantile plots. Baseline characteristics were compared across categories of SBP-TTR using the analysis of variance test for continuous variables, Kruskal-Wallis test for non-normally distributed variables and the chi-square test for categorical variables.

The associations between SBP-TTR and adverse kidney and cardiovascular events were assessed using crude incidence rates (per 1,000 person-years) or cause-specific hazard ratios and 95% confidence intervals derived from Cox proportional hazards regression models. Examination of the SBP-TTR distribution revealed a flat distribution across TTR between 0% and 100% but with a large proportion of individuals with SBP-TTR of 0% or 100% (Figure S1). Therefore, SBP-TTR was categorized prior to analysis. Participants with SBP-TTR of 0% or 100% were categorized separately, and the remaining participants were grouped into tertiles. SBP-TTR of 0% was considered the reference category. We assessed non-linear associations between SBP-TTR and adverse kidney and cardiovascular outcomes with restricted cubic spline transformations of SBP-TTR. Models with 3 to 7 knots were

considered and the fit of the model that minimized the Akaike information criterion was compared to the fit of a model with 2 knots using a likelihood ratio test.

All models allowed different baseline hazards for systolic blood pressure target (intensive or standard) and study (SPRINT or ACCORD BP) by stratifying on these variables. Models were adjusted additionally for age, sex, and race (Model 1) and then history of coronary or peripheral atherosclerotic cardiovascular disease, current smoking status, body mass index, fasting plasma glucose, baseline SBP, baseline eGFR, and urine albumin-to-creatinine ratio (Model 2). All model clinical covariates were selected *a priori* based upon known risk factors for kidney and cardiovascular events (except the spline transformations, as described above).[24] We assessed effect modification of the association between SBP-TTR and adverse kidney and cardiovascular events across SBP targets (less than 120 mm Hg vs. less than 140 mm Hg), between SPRINT and ACCORD-BP participants (i.e., with and without type 2 diabetes mellitus), and between participants with and without chronic kidney disease at baseline (eGFR less than and greater than or equal to 60 mL/min/1.73 m^2) and according to urine albumin-to-creatinine ratio above or below 30 mg/g using multiplicative interaction terms. We conducted a post-hoc analysis that adjusted for mean achieved SBP instead of baseline SBP. All analyses were performed in Stata version 17.0 (Stata Corp, College Station, TX).

Results

Among the 10,047 SPRINT and ACCORD BP participants included in this study (Figure S2), 951 (9%) had zero SBP readings within target range during months 0–3 and 1,178 (12%) participants who had 100% of available SBP readings within target range. The remaining participants were categorized into tertiles: TTR of >0 to <43% (n=2,643), 43% to <70% (n=2,636) and 70% to <100% (n=2,639). Participants with higher TTR were more likely to be men and less likely to have a history of atherosclerotic cardiovascular disease (Table 1). Baseline SBP and mean achieved SBP decreased across categories of increasing TTR (Table 1). Participants with higher TTR had higher eGFR and higher urine ACR than those with lower TTR (Table 1).

Association of Systolic Blood Pressure Time in Target Range with Major Adverse Kidney Events

A total of 395 first major adverse kidney events occurred over 31,438 person-years of follow-up. In models fully adjusted for demographics, risk factors and study characteristics, higher TTR associated with a lower risk of major adverse kidney events (Table 2). The hazard ratio (95% confidence intervals) comparing the reference category of TTR 0% against TTR >0% to 43%, 43% to <70%, 70 to 100% and 100% were 0.59 (0.44–0.80; P=0.001), 0.60 (0.44–0.82; P=0.001), 0.56 (0.40–0.78; P=0.001) and 0.35 (0.21–0.59; P<0.001), respectively. The association between higher TTR and lower kidney risk was non-linear with a decrease in risk between TTR of 0% and 42% and no further changes in risk until TTR exceeded 73%, whereafter risk decreased further (Figure 1).

Similar patterns of association were observed for the individual components of the composite kidney outcome (end-stage kidney disease, sustained eGFR decline of at least

40%, sustained eGFR less than 15 mL/min per 1.73 m^2) and for the composite of death or major adverse kidney event (Table 2). TTR did not associate with death alone (Table 2) in fully adjusted models.

Higher SBP TTR calculated over a 12-month period associated nominally with a higher risk of major adverse kidney events, but the effect sizes were smaller than for SBP TTR calculated over a 3-month period (Table S1). Analyses using target ranges of 100–120 mm Hg for the intensive arm and 120–140 mm Hg in the standard arm were consistent with the primary analyses (Table S2).

Association of Systolic Blood Pressure Time in Target Range with Major Adverse Cardiovascular Events

A total of 726 first major adverse cardiovascular events occurred across 37,486 person-years of follow-up. In fully adjusted models, TTR of 70% to <100% (HR [95% CI]: 0.69 [0.52–0.91; =0.009] and 100% (HR [95% CI]: 0.55 [0.38–0.79]; P=0.001) associated with lower risk of major adverse cardiovascular events compared to TTR of 0% (Table 3). Restricted cubic spline analysis did not support a non-linear association between TTR and major adverse cardiovascular events (Figure 1). Higher TTR associated with a reduced risk of heart failure hospitalization and non-fatal stroke (Table 3). Higher 12-month TTR did not significantly associate with a lower risk of adverse cardiovascular events (Table S3). Analyses using target ranges of 100–120 mm Hg for the intensive arm and 120–140 mm Hg in the standard arm were consistent with the primary analyses (Table S4).

Effect Modification and Sensitivity Analyses

There was no evidence of effect modification of the association between TTR and major adverse kidney or cardiovascular events by type 2 diabetes mellitus status, SBP target (<120 mm Hg vs. <140 mm Hg), chronic kidney disease status or albuminuria status (urine albumin-to-creatinine ratio > or ≤ 30 mg/g) (Tables S5, S6, S7 and S8). SBP-TTR during months 0–3 did not associate with major adverse kidney or cardiovascular events in models that adjusted for mean achieved SBP instead of baseline SBP (Table S9). SBP-TTR associated with heart failure hospitalization whether baseline SBP or mean achieved SBP was used (HR [95% CI] for 70% to <100%: 0.51 [0.29–0.89], P=0.18; for 100%: 0.46 [0.23–0.93], P=0.029) (Table S9).

Discussion

In this study of adults with hypertension, we found that higher levels of SBP control, as measured by TTR, associated with lower risks of adverse kidney and cardiovascular events (Graphical Abstract). The largest changes in kidney risk occurred between TTR of 0%−43% and 70%−100%, with minimal changes in between these ranges. In contrast, cardiovascular risk decreased linearly across the range of TTR. These results support the use of TTR as a hypertension quality metric for use in routine clinical practice and research settings and also provide insight into the relationships between blood pressure lowering and kidney and cardiovascular risk.

Previous studies have demonstrated significant associations between TTR and all-cause mortality and cardiovascular risk.[10–12] The present study shows that TTR associates with cardiovascular risk in individuals with and without type 2 diabetes mellitus and with and without chronic kidney disease. This study also demonstrates a significant association between TTR and kidney risk, an important knowledge gap given the association between hypertension and kidney disease. Future studies should examine the association between TTR and kidney and cardiovascular risk in individuals with a prior stroke, who were excluded from SPRINT and ACCORD BP.

One particularly interesting result in this study is the differential effects of TTR on kidney and cardiovascular risk. In particular, TTR associated linearly with the risk of major adverse cardiovascular events, but non-linearly with the risk of major adverse kidney events. The mechanisms underlying the non-linear relationship of TTR and major adverse kidney events remain unclear, but may relate to kidney auto-regulation.[25] Our observed associations suggest that modest SBP control is sufficient to achieve a reduction the risk of major adverse kidney events, but further risk reduction can be achieved only at very high levels of control. In contrast, reductions in cardiovascular risk can be achieved across the spectrum of TTR. This observation suggests that lowering the risk of adverse kidney outcomes may be achievable through extremely strict SBP control (>70% TTR).[16–19]

SBP-TTR may vary more widely in routine practice settings than in our analysis due to differences in follow-up and adherence between clinical trials and clinical practice. A post-hoc analysis of the CAPTION trial, which compared a 9- and 24-month pharmacist-led blood pressure management intervention to usual care, found that embedding pharmacists within the blood pressure management team was associated with a higher median TTR for the 9-month (32%) and 24-month (30%) intervention groups, respectively, than usual care (19%) (P=.007).[26] Notably, CAPTION included a diverse population and 50% of participants had either diabetes or chronic kidney disease. Pharmacist-led blood pressure management may be one of many possible strategies for improving TTR and blood pressure control and further studies are warranted.

We assessed TTR over a 3-month period in the primary analysis and over a 12-month period in the sensitivity analysis. We expect that TTR calculations using longer durations would provide greater prognostic insight than calculations using shorter durations based upon studies of the associations between cumulative blood pressure exposure and cardio-renal risk.[27] Our results suggest that the early period after the start of intensive blood pressure lowering is an important determinant of future risk of major adverse kidney and cardiovascular events. These results should be interpreted within the context of shorter follow-up and fewer overall events in the 12-month TTR analyses.

Adjustment for mean achieved SBP instead of baseline SBP attenuated the associations of SBP-TTR with adverse cardiovascular and kidney events. These results likely can be attributed to the standard medication titration protocols of ACCORD BP and SPRINT, which would be expected to lead to lower SBP variability than would be observed in routine practice. While SBP-TTR offers an intuitive measure of SBP control, its prognostic value relative to mean SBP should be compared using SBP measurements from routine practice.

Certain limitations of this study warrant discussion. This study included relatively few occurrences of end-stage kidney disease. eGFR-based endpoints, however, do predict end-stage kidney disease risk and we expect that TTR would associate with end-stage kidney disease risk in cohorts with sufficient duration of follow-up for such analyses.[28] SBP was measured in-clinic and whether home or ambulatory SBP-TTR associates with kidney and cardiovascular events remains unclear. Exact visit dates were not available in this dataset and may have altered our SBP-TTR calculations. In this analysis, SBP was measured according to recommended practices. SBP-TTR may not associate with kidney and cardiovascular events if SBP is measured in non-recommended manners as often occurs in routine practice.[29] In SPRINT, ESKD events were ascertained only for participants with CKD at baseline.

Conclusions

Higher levels of SBP control, as measured by TTR, associates with decreased risks of adverse kidney and cardiovascular events in adults with hypertension regardless of type 2 diabetes mellitus and chronic kidney disease status. SBP-TTR range may be a potential therapeutic target and quality metric.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard abbreviations:

ACCORD BP	Action to Control Cardiovascular Risk in Diabetes – Blood Pressure
SPRINT	Systolic Blood Pressure Intervention Trial
TTR	time-in-target range

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Perspectives

Many guidelines recommend lowering systolic blood pressure to less than 130 mm Hg or less than 120 mm Hg, but mechanisms to monitor blood pressure management control are lacking. Previous studies have demonstrated that time-in-target range provides an intuitive metric of blood pressure control and associates with an increased risk of cardiovascular events. This study builds upon that prior research by demonstrating robust associations between systolic blood pressure time-in-target range and an increased risk of major adverse kidney events. Clinicians and healthcare systems may consider the use of systolic blood pressure time-in-target range as a metric of blood pressure management quality.

Novelty and Relevance

- What is new?
  - Greater blood pressure control, as measured by systolic blood pressure time-in-target range, associates with a decreased risk of adverse kidney and cardiovascular events.
- What is relevant?
  - Modest improvements in blood pressure control may decrease the risk of adverse kidney and cardiovascular events.
- Clinical/pathophysiologic implications?
  - Systolic blood pressure time-in-target range may be useful for monitoring blood pressure control across populations and individuals.

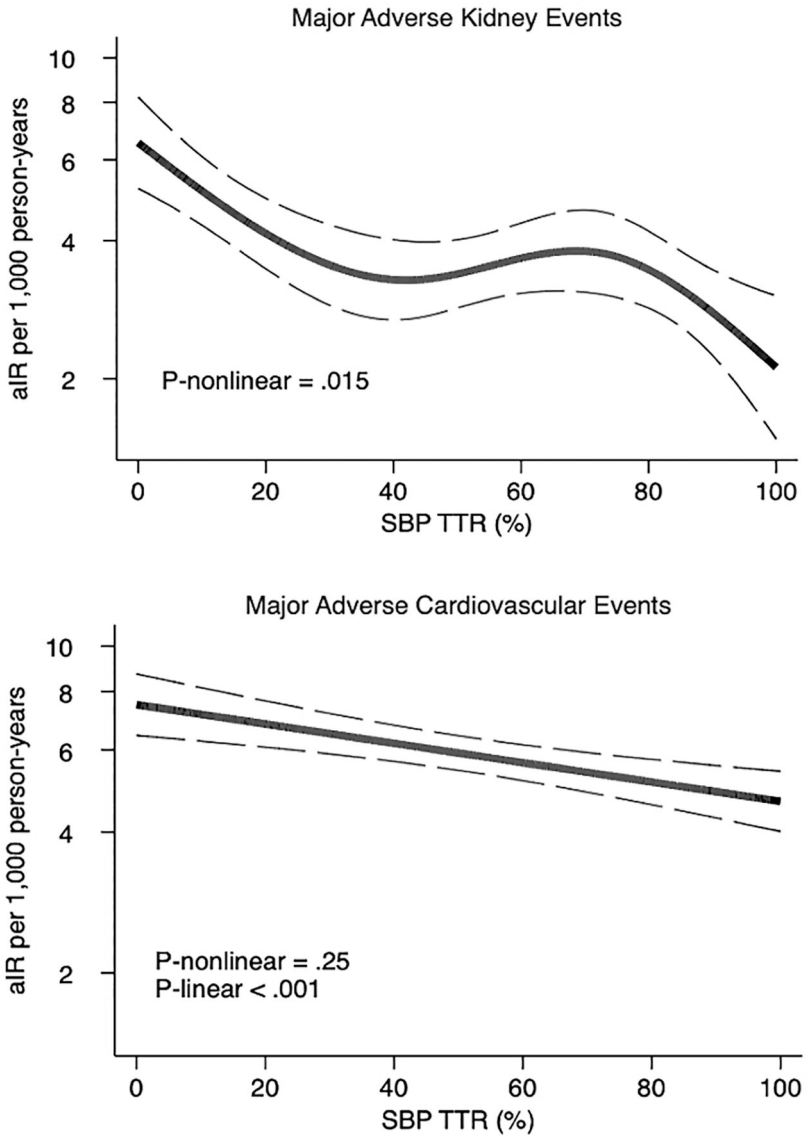

Figure 1. Association between systolic blood pressure time-in-target range and major adverse kidney and cardiovascular events

Restricted cubic splines were used to model the association between systolic blood pressure and adverse kidney and cardiovascular events. Incidence rate was adjusted for age, sex, race, history of coronary or peripheral atherosclerotic cardiovascular disease, current smoking status, body mass index, urine albumin-to-creatinine ratio, fasting plasma glucose, baseline systolic blood pressure and baseline eGFR. Dashed lines indicate 95% confidence intervals. aIR = adjusted incidence rate; SBP = systolic blood pressure; TTR = time-in-target range

Table 1.

Participant characteristics according to systolic blood pressure time-in-target range

	Overall	TTR, 0%	TTR, >0 to <43%	TTR, 43% to <70%	TTR, 70% to <100%	TTR, 100%	
Number of participants	**N=10047**	**N=951**	**N=2643**	**N=2636**	**N=2639**	**N=1178**	**P-Value**
Intensive SBP target, n (%)	6,099 (61%)	750 (79%)	1,663 (63%)	1583 (60%)	1519 (58%)	584 (50%)	<0.001
SPRINT participants, n (%)	7,932 (79%)	634 (67%)	2,061 (78%)	2,098 (80%)	2,152 (82%)	987 (84%)	<0.001
Age, years	67 ± 9	67 ± 9	67 ± 9	67 ± 9	67 ± 9	66 ± 9	<0.001
Women, n (%)	3,764 (38%)	387 (41%)	1103 (42%)	1,000 (38%)	926 (35%)	348 (30%)	<0.001
Race/Ethnicity							0.027
Black	2,828 (28.1%)	304 (32%)	779 (30%)	703 (27%)	714 (27%)	328 (28%)	
Hispanic	980 (9.8%)	82 (9%)	249 (9%)	253 (10%)	276 (11%)	120 (10%)	
Other	349 (3.5%)	44 (5%)	93 (4%)	88 (3%)	92 (4%)	32 (3%)	
Caucasian	5,890 (58.6%)	521 (55%)	1,522 (58%)	1,592 (60%)	1,557 (59%)	698 (59%)	
History of ASCVD, n (%)	2,047 (20.4%)	213 (225%)	557 (21%)	567 (22%)	513 (19%)	197 (17%)	0.003
Current smoking, n (%)	1,262 (12.6%)	110 (12%)	370 (14%)	328 (12%)	307 (12%)	147 (13%)	0.09
Body mass index, kg/m^2	30.4 ± 5.8	30.3 ± 5.9	30.4 ± 5.8	30.4 ± 5.9	30.4 ± 5.7	30.6 ± 5.5	0.79
Prediabetes, n (%)	3,365 (42.4%)	263 (42%)	868 (42%)	861 (41%)	951 (44%)	422 (43%)	0.31
HbA1c, %	8.4 ± 1.1	8.5 ± 1.1	8.4 ± 1.1	8.3 ± 1.0	8.3 ± 1.1	8.4 ± 1.1	0.22
LDL cholesterol, mg/dL	112 ± 35	116 ± 36	112 ± 36	112 ± 36	110 ± 35	109 ± 33	<0.001
SBP, mm Hg	140 ± 16	151 ± 17	144 ± 17	140 ± 15	137 ± 13	128 ± 7	<0.001
Mean achieved SBP, mm Hg	129 ± 12	146 ± 13	131 ± 13	126 ± 9	124 ± 7	125 ± 7	<0.001
eGFR, mL/min per 1.73 m^2	75 ± 21	74 ± 22	73 ± 21	75 ± 20	75 ± 20	78 ± 19	<0.001
Urine ACR, mg/g	10 [6, 25]	15 [8, 54]	11 [6, 28]	10 [6, 25]	9 [6, 20.0]	8 [5, 15]	<0.001

ACR = albumin-to-creatinine ratio; ASCVD = atherosclerotic cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; LDL = low-density lipoprotein; SBP = systolic blood pressure; SPRINT = Systolic Blood Pressure Intervention Trial; TTR = time-in-target range

Table 2.

Estimated associations between systolic blood pressure time-in-target range and major adverse kidney events

			Unadjusted		Model 1		Model 2	
TTR Group	**Events (n)**	**IR (95% CI)[#]**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Composite Adverse Kidney Events								
0%	84	27.9 (22.5–34.5)	Reference		Reference		Reference	
>0% to <43%	107	12.9 (10.7–15.6)	0.54 (0.41–0.72)	<0.001	0.55 (0.41–0.73)	<0.001	0.59 (0.44–0.80)	0.001
43% to <70%	99	12.0 (9.8–14.6)	0.52 (0.39–0.69)	<0.001	0.53 (0.40–0.71)	<0.001	0.60 (0.44–0.82)	0.001
70% to <100%	85	10.4 (8.4–12.8)	0.46 (0.34–0.63)	<0.001	0.48 (0.35–0.65)	<0.001	0.56 (0.40–0.78)	0.001
100%	20	5.5 (3.5–8.5)	0.26 (0.16–0.43)	<0.001	0.28 (0.17–0.47)	<0.001	0.35 (0.21–0.59)	<0.001
Composite Adverse Kidney Events or Death								
0%	125	41.6 (34.9–49.5)	Reference		Reference		Reference	
>0% to <43%	191	23.0 (20.0–26.5)	0.60 (0.48–0.76)	<0.001	0.63 (0.50–0.79)	<0.001	0.69 (0.55–0.87)	0.002
43% to <70%	185	22.4 (10.4–25.9)	0.60 (0.47–0.75)	<0.001	0.64 (0.51–0.80)	<0.001	0.73 (0.57–0.93)	0.010
70% to <100%	159	19.5 (16.7–22.7)	0.52 (0.41–0.66)	<0.001	0.57 (0.45–0.72)	<0.001	0.68 (0.52–0.87)	0.003
100%	52	14.3 (10.9–18.8)	0.40 (0.29–0.55)	<0.001	0.45 (0.33–0.63)	<0.001	0.58 (0.41–0.81)	0.003
Death								
0%	48	13.9 (10.5–18.5)	Reference		Reference		Reference	
>0% to <43%	89	9.7 (7.9–12.0)	0.69 (0.49–0.99)	0.044	0.74 (0.52–1.06)	0.10	0.84 (0.58–1.20)	0.33
43% to <70%	91	10.1 (8.2–12.4)	0.71 (0.50–1.02)	0.062	0.78 (0.54–1.11)	0.16	0.91 (0.63–1.32)	0.62
70% to <100%	79	8.8 (7.1–11.0)	0.63 (0.43–0.90)	0.011	0.69 (0.48–1.00)	0.049	0.86 (0.58–1.27)	0.46
100%	33	8.4 (6.0–11.8)	0.58 (0.37–0.91)	0.019	0.69 (0.44–1.09)	0.11	0.93 (0.57–1.53)	0.78
End-Stage Kidney Disease								
0%	23	7.4 (4.9–11.2)	Reference		Reference		Reference	
>0% to <43%	28	3.3 (2.3–4.8)	0.50 (0.29–0.87)	0.014	0.51 (0.29–0.89)	0.019	0.62 (0.35–1.11)	0.11
43% to <70%	27	3.2 (2.2–4.7)	0.49 (0.28–0.86)	0.014	0.51 (0.29–0.89(	0.018	0.67 (0.37–1.23)	0.19
70% to <100%	24	2.9 (2.0–4.3)	0.45 (0.25–0.81)	0.007	0.46 (0.26–0.83)	0.010	0.67 (0.36–1.27)	0.22
100%	6	1.6 (0.7–3.6)	0.26 (0.11–0.65)	0.004	0.27 (0.11–0.67)	0.005	0.49 (0.18–1.31)	0.16
Sustained eGFR Decline > 40%								
0%	78	22.4 (17.9–28.0)	Reference		Reference		Reference	
>0% to <43%	91	9.8 (8.0–12.1)	0.49 (0.36–0.66)	<0.001	0.49 (0.36–0.67)	<0.001	0.54 (0.39–0.74)	<0.001
43% to <70%	80	8.7 (7.0–10.8)	0.44 (0.32–0.60)	<0.001	0.46 (0.34–0.63)	<0.001	0.53 (0.38–0.74)	<0.001
70% to <100%	71	7.9 (6.3–10.0)	0.41 (0.30–0.56)	<0.001	0.43 (0.31–0.60)	<0.001	0.51 (0.36–0.73)	<0.001
100%	16	4.0 (2.5–6.6)	0.22 (0.13–0.37)	<0.001	0.24 (0.14–0.42)	<0.001	0.31 (0.17–0.55)	<0.001
Sustained eGFR < 15 mL/min per 1.73 m ^{2}								
0%	10	2.8 (1.5–5.2)	Reference		Reference		Reference	
>0% to <43%	6	0.6 (0.3–1.4)	0.17 (0.06–0.48)	0.001	0.18 (0.07–0.50)	0.001	0.22 (0.07–0.68)	0.009
43% to <70%	6	0.6 (0.3–1.4)	0.17 (0.06–0.47)	0.001	0.18 (0.07–0.51)	0.001	0.24 (0.08–0.73)	0.012
70% to <100%	9	1.0 (0.5–1.9)	0.25 (0.10–0.61)	0.003	0.28 (0.11–0.69)	0.006	0.39 (0.14–1.08)	0.071

			Unadjusted		Model 1		Model 2	
TTR Group	**Events (n)**	**IR (95% CI)[#]**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
100%	2	0.5 (0.1–2.0)	0.12 (0.03–0.54)	0.006	0.14 (0.03–0.66)	0.013	0.36 (0.07–1.94)	0.24

[#] per 1,000 person-years, censoring follow-up at death or study exit/end

CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IR = incidence rate; TTR = time-in-target range

Table 3.

Estimated associations between systolic blood pressure time-in-target range and major adverse cardiovascular events

			Unadjusted		Model 1		Model 2	
TTR Group	**Events (n)**	**IR (95% CI)[#]**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Composite Adverse Cardiovascular Events								
0%	89	24.9 (20.2–30.6)	Reference		Reference		Reference	
>0% to <43%	231	23.5 (20.7–27.8)	0.93 (0.73–1.19)	0.57	0.96 (0.75–1.23)	0.76	0.98 (0.76–1.26)	0.89
43% to <70%	202	20.6 (17.9–23.6)	0.81 (0.63–1.04)	0.11	0.85 (0.66–1.09)	0.19	0.89 (0.68–1.15)	0.37
70% to <100%	153	15.5 (13.2–18.2)	0.61 (0.47–0.79)	<0.001	0.64 (0.49–0.83)	0.001	0.69 (0.52–0.91)	0.009
100%	51	11.6 (8.8–15.2)	0.44 (0.31–0.63)	<0.001	0.49 (0.34–0.69)	<0.001	0.55 (0.38–0.79)	0.001
Cardiovascular Death								
0%	20	5.3 (3.4–8.2)	Reference		Reference		Reference	
>0% to <43%	47	4.6 (3.5–6.1)	0.85 (0.50–1.45)	0.56	0.92 (0.54–1.56)	0.75	1.06 (0.61–1.83)	0.84
43% to <70%	36	3.5 (2.6–4.9)	0.66 (0.38–1.14)	0.14	0.71 (0.41–1.24)	0.23	0.87 (0.49–1.57)	0.65
70% to <100%	19	1.9 (1.2–2.9)	0.35 (0.18–0.65)	0.001	0.38 (0.20–0.72)	0.003	0.50 (0.26–0.98)	0.045
100%	12	2.7 (1.5–4.7)	0.48 (0.23–1.00)	0.049	0.59 (0.29–1.23)	0.16	0.88 (0.40–1.96)	0.76
Heart Failure Hospitalization								
0%	38	10.3 (7.5–14.2)	Reference		Reference		Reference	
>0% to <43%	72	7.1 (5.7–9.0)	0.68 (0.46–1.02)	0.060	0.73 (0.49–1.08)	0.12	0.72 (0.48–1.09)	0.12
43% to <70%	71	7.1 (5.6–8.9)	0.68 (0.45–1.01)	0.053	0.72 (0.48–1.08)	0.11	0.74 (0.49–1.12)	0.16
70% to <100%	43	4.3 (3.2–5.8)	0.41 (0.26–0.63)	<0.001	0.44 (0.28–0.69)	<0.001	0.46 (0.29–0.73)	0.001
100%	15	3.4 (2.0–5.6)	0.32 (0.17–0.58)	<0.001	0.38 (0.20–0.69)	0.002	0.39 (0.21–0.75)	0.004
Non-Fatal Myocardial Infarction								
0%	41	11.2 (8.2–15.2)	Reference		Reference		Reference	
>0% to <43%	107	10.7 (8.8–12.9)	0.97 (0.67–1.39)	0.86	0.99 (0.69–1.43)	0.98	1.00 (0.69–1.45)	0.99
43% to <70%	86	8.6 (7.0–10.6)	0.78 (0.53–1.13)	0.19	0.80 (0.55–1.16)	0.24	0.82 (0.55–1.20)	0.30
70% to <100%	74	7.4 (5.9–9.3)	0.67 (0.46–0.99)	0.044	0.69 (0.47–1.02)	0.062	0.73 (0.49–1.10)	0.13
100%	26	5.9 (4.0–8.6)	0.52 (0.32–0.86)	0.010	0.56 (0.34–0.92)	0.021	0.61 (0.36–1.04)	0.067
Non-Fatal Stroke								
0%	20	5.4 (3.5–8.3)	Reference		Reference		Reference	
>0% to <43%	52	5.1 (3.9–6.7)	0.86 (0.51–1.44)	0.56	0.88 (0.52–1.49)	0.64	0.96 (0.57–1.63)	0.88
43% to <70%	50	5.0 (3.8–6.6)	0.82 (0.48–1.38)	0.45	0.85 (0.51–1.44)	0.56	0.98 (0.57–1.68)	0.93
70% to <100%	35	3.5 (2.5–4.8)	0.56 (0.32–0.98)	0.042	0.59 (0.34–1.04)	0.066	0.72 (0.40–1.28)	0.26
100%	8	1.8 (0.9–3.6)	0.28 (0.12–0.63)	0.002	0.30 (0.13–0.70)	0.005	0.41 (0.17–0.97)	0.043

[#] per 1,000 person-years, censoring follow-up at death or study exit/end

CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IR = incidence rate; TTR = time-in-target range