Published in final edited form as:

Am J Kidney Dis. 2018 March ; 71(3): 352–361. doi:10.1053/j.ajkd.2017.08.021.

Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT)

Michael V. Rocco, MD, MSCE¹, Kaycee M. Sink, MD, MAS², Laura C. Lovato, MS³, Dawn F. Wolfgram, MD⁴, Thomas B. Wiegmann, MD⁵, Barry M. Wall, MD⁶, Kausik Umanath, MD, MS⁷, Frederic Rahbari-Oskoui, MD, MS⁸, Anna C. Porter, MD⁹, Roberto Pisoni, MD¹⁰, Cora E. Lewis, MD, MSPH¹¹, Julia B. Lewis, MD¹², James P. Lash, MD⁹, Lois A. Katz, MD¹³, Amret T. Hawfield, MD¹, William E. Haley, MD¹⁴, Barry I. Freedman, MD¹, Jamie P. Dwyer, MD¹², Paul E. Drawz, MD, MHS, MS¹⁵, Mirela Dobre, MD¹⁶, Alfred K. Cheung, MD¹⁷, Ruth C. Campbell, MD, MSPH¹⁰, Udayan Bhatt, MD¹⁸, Srinivasan Beddhu, MD¹⁷, Paul L. Kimmel, MD¹⁹, David M. Reboussin, Ph.D.³, and Glenn M. Chertow, MD²⁰ on behalf of the SPRINT Research Group

¹Section on Nephrology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina ²Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina ³Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, Wake Forest University ⁴Zablocki VA Medical Center, Department of Medicine-Section of Nephrology, Milwaukee, Wisconsin and Medical College of Wisconsin, Department of Medicine-Division of Nephrology, Milwaukee, Wisconsin ⁵Clinical Research, Department of Veterans Affairs Hospital, Kansas City, Missouri ⁶University of Tennessee Health Science Center and Department of Veterans Affairs Medical Center, Memphis Tennessee ⁷Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan ⁸Department of Medicine, Renal

Address for correspondence: Michael V. Rocco, MD, MSCE, Vardaman M. Buckalew Jr. Chair in Internal Medicine/Nephrology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1053, Tel: 336-716-4650, Fax: 336-716-4318, mrocco@wakehealth.edu.

N section: Complete author and article information (including a list of the members of the SPRINT Research Group) provided before references

SPRINT Research Group: A list of the members of the SPRINT Research Group appears in the supplementary material accompanying Ambrosius et al¹ and Wright et al².

Authors' Contributions: Research idea and study design: MVR, KMS, GMC, DMR; data acquisition: all authors except DMR and LCL, as these authors were involved with adjudication of AKI events; data analysis/interpretation: MVR, KMS, GMC, LCL; statistical analysis: LCL; supervision or mentorship: MVR, KMS, GMC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the US Department of Veterans Affairs, or the US government.

Financial Disclosure: Barry Dr Freedman: Research support from Novartis Pharmaceuticals and consultant for Ionis Pharmaceuticals. Dr Lewis: Consultant for Sanofi and Acaegen. The other authors declare that they have no other relevant financial interests.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Division, Emory University School of Medicine, Atlanta, Georgia ⁹Department of Medicine, Section of Nephrology, University of Illinois at Chicago, Chicago, Illinois ¹⁰Division of Nephrology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina ¹¹Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, Alabama ¹²Division of Nephrology/Hypertension, Vanderbilt University Medical Center, Nashville, Tennessee ¹³VA New York Harbor Healthcare System and New York University School of Medicine, New York, New York ¹⁴Division of Nephrology and Hypertension, Mayo Clinic, Jacksonville, Florida ¹⁵Division of Renal Diseases & Hypertension, University of Minnesota, Minneapolis, Minnesota ¹⁶Division of Nephrology and Hypertension, Department of Medicine, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio ¹⁷Division of Nephrology & Hypertension, University of Utah and Medical Service, Department of Veterans Affairs, Salt Lake City Healthcare System, Salt Lake City, Utah ¹⁸Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio ¹⁹Division of Kidney Urologic and Hematologic Diseases National Institute of Diabetes, Digestive Diseases and Kidney Disease, National Institute of Health, Bethesda, Maryland ²⁰Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, California

Abstract

Background—Treating to a lower blood pressure (BP) may increase acute kidney injury (AKI) events.

Study Design—Data on AKI resulting in or during hospitalization or emergency department visits were collected as part of the serious adverse events reporting process of the Systolic Blood Pressure Intervention Trial (SPRINT).

Setting & Participants—9361 participants aged 50 or older with one or more risk factors for cardiovascular disease.

Interventions—Participants were randomly assigned to a systolic BP target of <120 (intensive arm) or <140 mm Hg (standard arm).

Outcomes & Measurements—The primary outcome was the number of adjudicated AKI events. Secondary outcomes included the severity of AKI and the degree of recovery of kidney function after an AKI event. Baseline creatinine was defined as the most recent SPRINT outpatient creatinine value prior to the date of the AKI event.

Results—There were 179 participants with AKI events in the intensive arm and 109 in the standard arm (3.8% vs 2.3%; HR, 1.64; 95% CI, 1.30–2.10; $p < 0.001$). Of the 288 participants with an AKI event, 248 (86.1%) had a single AKI event during the trial. Based on modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria for severity of AKI, the number of AKI events in the intensive versus standard arm by KDIGO stage was 128 (58.5%) versus 81 (62.8%) for AKI stage 1, 42 (19.2%) versus 18 (14.0%) for AKI stage 2 and 42 (19.2%) versus 25 (19.4%) for AKI stage 3 ($p = 0.5$). For participants with sufficient data, complete or partial resolution of AKI was seen for 169 (90.4%) and 9 (4.8%) of 187 AKI events in the intensive arm and 86 (86.9%) and 4 (4.0%) of 99 AKI events in the standard arm, respectively.

Limitations—The trial results are not generalizable to patients with diabetes mellitus or without risk factors for cardiovascular disease.

Conclusions—More intensive BP lowering resulted in more frequent episodes of AKI. Most cases were mild and the majority of participants had complete recovery of kidney function.

TRIAL REGISTRATION—www.ClinicalTrials.gov; study number: NCT01206062.

Keywords

acute kidney injury (AKI); adjudicated AKI episode; systolic blood pressure (SBP); BP lowering; hypertension; cardiovascular disease (CKD); elderly; chronic kidney disease (CKD); kidney function

Introduction

The Systolic Blood Pressure Intervention Trial (SPRINT), sponsored by the National Institutes of Health (NIH), was a study of blood pressure (BP) control in persons without diabetes mellitus at increased risk of developing cardiovascular disease (CVD).¹ The relative hazard of the primary composite end point in SPRINT, which included myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes, was significantly lower in the intensive arm (goal systolic BP [SBP] <120 mm Hg) compared with the standard arm (goal SBP <140 mm Hg).² In addition, all-cause mortality was significantly lower in the intensive BP-lowering arm of the trial.

The frequency of serious adverse events (SAEs) in SPRINT was not significantly different between the two arms of the trial. The SAEs that were anticipated to be higher in the intensive arm of the trial were *a priori* ascertained by the clinical sites and by the SPRINT Safety Officer. Conditions of interest that were more frequent in the intensive arm included hypotension, syncope, electrolyte abnormalities and acute kidney injury (AKI), typically noted in association with hospitalization.² The goals of our detailed examination of AKI in SPRINT were to 1) identify predictors of AKI resulting in either a hospitalization or emergency room visit; 2) adjudicate each of the reported AKI events; 3) determine severity of, and recovery from, these events; and 4) explore effect modification of intensive *versus* standard BP lowering on AKI within each of the six predefined participant subgroups. Changes in kidney function that were noted based on SPRINT clinic laboratory results that did not result in a hospitalization or emergency room visit will be described in two other SPRINT studies.^{2a,2b}

METHODS

Study Population

SPRINT was a randomized, controlled, open-label trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI), with co-sponsorship by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Diseases and Stroke, and the National Institute on Aging. The trial was approved by Institutional Review Boards at participating study sites; all participants provided written informed

consent. Participants from 102 clinical sites were randomly assigned to a target goal SBP of <120 mm Hg (intensive arm, n=4678) or <140 mm Hg (standard arm, n=4683). The design, eligibility, full trial protocol, sample size calculations and interim analysis and stopping rules have been previously reported.^{1, 2} The SPRINT trial cohort included participants 50 years or older with SBP $\geq$ 130 mm Hg, without a history of diabetes or stroke, with an increased risk of cardiovascular events, defined by one or more of the following: clinical or subclinical CVD other than stroke; chronic kidney disease (CKD), excluding polycystic kidney disease; a 10-year risk of CVD of 15% or greater on the basis of the Framingham risk score; or an age of 75 years or older. Persons with diabetes mellitus, polycystic kidney disease, screening urine protein level of >1 g/day or equivalent, symptomatic heart failure, ejection fraction <35% or stroke were excluded from the trial. Participant enrollment into SPRINT occurred November 2010 to March 2013.

Study Outcomes

Demographic data were collected at baseline, including self-reported race and ethnicity. Six pre-specified subgroups of interest for all outcomes included the following: CVD at baseline (yes vs. no), CKD at baseline (yes vs. no), sex, race (black vs. nonblack), age (<75 vs. $\geq$ 75 years), and tertiles of baseline SBP (<132 mm Hg, $\geq$ 132 to <145 mm Hg, and $\geq$ 145 mm Hg). The presence of CKD at randomization was defined as an estimated glomerular filtration rate (eGFR) of 20–59 ml/min/1.73 m² using the isotope-dilution mass spectrometry (IDMS)-traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation; this definition defined the CKD cohort in SPRINT.³

Clinical and laboratory data were obtained at baseline and every three months thereafter. Serum creatinine concentration was measured in a central laboratory by an enzymatic procedure using a Roche analyzer and was IDMS-traceable for calibration. Urine albumin was measured by an immunoturbidometric method using a Roche analyzer. Urine albumin was quantified along with urine creatinine in random spot urine specimens, with the urine albumin-creatinine ratio (ACR, in mg/g) used to account for urine concentration. AKI was defined using a modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria⁴ incorporating only serum creatinine concentrations to assess for the stage of AKI (ignoring the component of urine output, which was not uniformly measured). These modified KDIGO criteria include the following AKI stages and serum creatinine definitions: stage 1, increase $\geq$ 0.3 mg/dL or increase of 1.5 to 2.0-fold from baseline; stage 2, increase $\geq$ 2.0- to 3.0-fold from baseline; stage 3, increase $\geq$ 3.0-fold from baseline or $\geq$ 4.0 mg/dL with an acute increase of 0.5 mg/dL or need for renal replacement therapy.

At quarterly study visits, a structured interview was used to query participants about hospitalizations in the prior three months as well as specific outcomes of interest, such as initiation of dialysis.² The SAEs were also identified between visits if study staff were informed of them by participant report, electronic medical record notification, or other mechanism. The SAEs were defined as events that were fatal or life threatening, resulted in significant or persistent disability, required or prolonged a hospitalization, or medical events that the investigator judged to be a significant hazard or harm to the participant and required medical or surgical intervention to prevent hospitalization, death or persistent disability. For

selected SAEs, including AKI (either as the primary reason for hospitalization or as a part of the hospitalization), clinic staff were required to obtain medical records of the event for review by the medical safety officer, including Emergency Department (ED) notes for ED visits and the admission history and physical and discharge summary for hospitalizations. The medical safety team at the Coordinating Center reviewed the medical records from hospitalizations and ED visits and from SAE reports, and the team recorded AKI if it was noted on admission or occurred during a hospitalization or ED visit and was reported in the hospital discharge summary as a primary or main secondary diagnosis. If the discharge summary did not list AKI as a primary or secondary diagnosis, the record was not reviewed to determine whether an AKI event may have occurred but was not listed explicitly. In some cases, these records included all laboratory creatinine values obtained during the admission while in other cases only those creatinine values recorded in the discharge summary and/or the admission note and/or progress notes were used to ascertain the occurrence and severity of AKI. The Medical Dictionary for Regulatory Activities (MedDRA) was used to classify the safety events. Coding was performed at the Coordinating Center and up to three codes were assigned to each safety event.

All SAEs and ED visits classified as involving an AKI event by the safety team were reviewed in a blinded fashion by two nephrologists or physician experts in outcomes adjudication to determine the baseline and peak creatinine values, the modified KDIGO stage of AKI, what was the underlying primary cause of the AKI, and whether it was thought that SPRINT study participation caused or contributed to the event. Baseline creatinine was defined as the most recent SPRINT outpatient creatinine value prior to the date of the AKI event. Disagreements regarding the baseline and peak creatinine values, stage of AKI or whether SPRINT study participation caused or contributed to the event were resolved by a single third adjudicator (M.V.R.). After blinded adjudication, 54 of 402 events were not thought to represent AKI by modified KDIGO criteria. Therefore, the remainder of this study reports on the 348 events adjudicated as AKI.

Recovery of kidney function was determined by comparing the peak recorded serum creatinine value with the lowest outpatient SPRINT creatinine value obtained in the subsequent 365 days. Recovery was classified as complete (recovery to within 20% of pre-AKI serum creatinine level),^{5, 6} partial (recovery to within 30% of pre-AKI serum creatinine value)⁷ or “non-recovery” (no decline in serum creatinine or a decline not reaching the “within 30% of baseline value” threshold).

Statistical Analyses

Statistical analyses were conducted at the Coordinating Center using SAS software, version 9.4 (SAS Institute Inc). Baseline characteristics were compared among participants who did and did not have AKI during the trial, with the use of Student’s t-test or the Wilcoxon rank sum test for continuous variables, and the χ^2 test for discrete or categorical variables. Continuous variables are presented as either the mean $\pm$ standard deviation (SD) if normally distributed or the median (25th–75th percentile) if not normally distributed.

Time until first occurrence of AKI was compared between the two study arms with the use of the intention-to-treat approach for all randomized participants. We used Cox proportional

hazards regression, with two-sided tests at the 5% level of significance, with stratification by clinical site.

An assessment for non-proportionality of hazards was made with the addition of the interaction between log (time) and the intervention.⁸ Follow-up time was censored at the time of the final event ascertainment. Interactions between the treatment effect and pre-specified subgroups were assessed using a likelihood ratio test for interaction. Baseline variables thought to be related to the time to development of AKI were assessed first in univariate models, and then added as a group to the primary analysis model.

In exploratory analyses, participants with multiple AKI events were analyzed according to data obtained at the first occurrence of AKI, to determine if these variables were predictive of recurrence. These exploratory analyses used time from first episode of AKI to first recurrence, with censoring time set at the participant's last visit. The association of AKI events with primary and secondary end points was evaluated using the Cox proportional hazards model, with a time-varying covariate for the first AKI episode.

RESULTS

Overview

The SPRINT cohort consists of 9361 participants who were followed up for a mean of 3.26 years before the BP intervention was stopped early on August 20, 2015, after the NIH accepted the recommendation of the Data and Safety Monitoring Board due to benefit in the intensive arm on the primary outcome (Figure 1).² This study reports on AKI events occurring through August 20, 2015.

Incidence and Correlates of Adjudicated AKI events

There were 348 AKI events in 288 (3.0%) participants. Baseline characteristics of the study participants, stratified by the presence or absence of at least one AKI event, are shown in Table 1. Baseline characteristics associated with the time to development of AKI included age 75 years or older, male sex, chronic kidney disease at trial entry, higher urine ACR, presence of CVD, higher Framingham risk score and, in at least one treatment group, also race/ethnicity, smoking status and systolic and/or diastolic BP. Of the 288 participants with an AKI event, 248 (86.1%) had a single AKI event during the course of the trial, 30 (10.4%) had two events, 5 (1.7%) had 3 events and 5 (1.7%) had 4 or more events. AKI events were typically mild, as AKI stage 1 was the most common AKI stage. Based on modified KDIGO criteria, the number of AKI events in the intensive versus standard arm by KDIGO stage was 128 (58.5%) vs. 81 (62.8%) in stage 1, 42 (19.2%) vs 18 (14.0%) in stage 2 and 42 (19.2%) vs. 25 (19.4%) in stage 3 ($p=0.5$ for comparison of stages of AKI by randomized arm; AKI events by CKD cohort in Table 2). Dialysis was required infrequently by participants in the intensive ($n=8$) and standard ($n=6$) arms (Table 3) and end-stage renal disease subsequently developed in 2 intensive-arm and 3 standard-arm participants. No participant underwent kidney transplantation for irreversible AKI.

Etiology and Risk Factors of AKI Events

The most common proximate cause of AKI events in both arms of the trial was dehydration and/or intravascular volume depletion, followed by hypotension (Table 3). In both the CKD and non-CKD cohort, 10.0% of the cases of AKI in the intensive arm and 2.3% of cases in the standard arm were thought to be secondary to the intervention. By multivariable analysis, risk factors for time to development of an AKI event included older age, non-white race, lower baseline eGFR, and presence of CVD at baseline (Table 4).

Effects of Intensive BP Lowering on AKI by Prespecified Subgroups

There were 179 participants with AKI events in the intensive arm and 109 in the standard arm (3.8% vs 2.3%). The hazard ratio (HR) for AKI in the intensive *versus* standard arms was 1.64 (95% CI, 1.30–2.10; Figure 2). The effects of the intervention on the rate of AKI were consistent across the prespecified subgroups (baseline CVD, baseline CKD, sex, race, age, and baseline SBP) (Figure 3). There were no significant interactions between treatment and subgroup (p values range, 0.06–0.9).

Post-AKI events

Among participants with sufficient data to determine recovery, complete or partial resolution of AKI was seen for 169 (90.4%) and 9 (4.8%) of the 187 AKI events in the intensive arm and 86 (86.9%) and 4 (4.0%) of the 99 AKI events in the standard arm, respectively. Only 14 (5.6%) events required dialysis for the treatment of AKI and 50% of these participants subsequently became dialysis independent.

Exploratory analyses were conducted to examine the risk of events following AKI. When including first AKI event as a time-varying covariate in a Cox model accounting for randomized group, AKI events were found to be associated with higher risks of both the primary SPRINT outcome (501 events in the no AKI group [5.5%] vs. 61 events in the AKI group [21.2%]; HR, 2.0; 95% CI, 1.2–3.1; $p = 0.004$) as well as death from any cause (320 events in the no AKI group [3.5%] vs. 45 events in the AKI group [15.6%]; HR, 5.6; 95% CI, 4.0–7.8; $p < 0.001$). Causes of death by randomized arm are shown in Table 5.

DISCUSSION

In SPRINT, participants randomized to the intensive BP-lowering arm had significantly lower rates of the trial's primary composite end point, as well as lower rates of death and no difference in the total number of SAEs compared to participants randomized to the standard arm. These benefits were offset by a *subset* of SAEs that were more common in participants in the intensive treatment arm, including AKI. Of those participants who developed AKI in either arm of the trial, AKI stage, as assessed by modified KDIGO criteria, was in the lowest stage of severity for more than 50% of AKI events. AKI events were mainly attributed to volume depletion and in about 90% of persons in either study arm resulted in complete or partial recovery of kidney function. The need for dialytic therapy for the treatment of AKI was exceedingly rare (0.15%). Moreover, the rate of development of AKI in SPRINT was steady throughout the trial; specifically, AKI was not more common during the initial year, when participants generally experienced the most active titration of anti-hypertensive

medications (Figure 2). We hypothesize that the increased frequency of AKI events in the intensive arm may have been due to the lower baseline SBP that resulted in an increased risk of the BP falling below the autoregulatory threshold for kidney perfusion when a volume depleting illness and/or hypotension occurred.

Episodes of AKI, including those not severe enough to require dialysis, have consistently been shown to associate with an increased risk of in-hospital mortality.^{9–11} Indeed, in this trial, we found that AKI was associated with an increased risk of the primary SPRINT outcome and of death from any cause. Moreover, AKI has the potential to cause significant morbidity, as AKI can contribute to progressive CKD and, in some instances, end-stage kidney disease.^{12–14} Risk factors for AKI include the presence of CKD and older age, subgroups that were specifically recruited into SPRINT. Thus, during protocol development for SPRINT, it was recognized that the acute decrease in eGFR that had been seen in previous hypertension trials^{15,16} could adversely affect kidney function in SPRINT participants, both on a long-term basis, and also by increasing the risk of AKI events. The paucity of AKI events in SPRINT that resulted in longer-term deterioration of kidney function allays this latter concern. In addition, although participants in the intensive arm had an increased risk of AKI events, participants in the intensive arm still had a reduced risk of the primary SPRINT outcome and all-cause mortality compared to those in the standard arm.² These findings help in interpreting the risk-benefit ratio of the SPRINT results and are important to consider when developing clinical guidelines for the management of hypertension.

Comparison of the SPRINT AKI results with other hypertension trials is difficult for several reasons. First, a minority of hypertension trials provide information on the incidence of AKI.¹⁷ Second, persons with CKD, a major risk factor for AKI, have often been excluded from hypertension trials.¹⁸ Furthermore, there is no consensus regarding how to define recovery of kidney function after AKI; a recent meta-analysis demonstrated that there was a broad range of definitions including variability in the timing of post-AKI creatinine measures and in the thresholds used for recovery based on serum creatinine concentrations.¹⁹ We chose to report recovery of kidney function using two different definitions. United Kingdom guidelines adopted a return of serum creatinine to within 20% of baseline as a definition of recovery; the Program to Improve Care in Acute Renal Disease (PICARD) used the same definition.^{5, 6} Other investigators proposed a threshold of recovery to within 30% of the baseline serum creatinine concentration and cite an increased risk of CKD if recovery does not occur.⁷

There are several strengths of these analyses, including the large sample size, inclusion of participants with risk factors for AKI, including CKD at baseline and older age, wide separation between achieved BPs in the trial arms, and capture of major diagnoses from virtually all hospitalizations. There are also important limitations to these analyses. First, serum creatinine data—in hospital and thereafter—were relatively sparse and collected based on the trial protocol (monthly for 3 months, then biannually), rather than based on clinical indications. In other words, post-discharge serum creatinine determinations were not uniformly obtained. Second, site staff were unblinded and could have looked more carefully for AKI events in records of participants randomized to the arm with intensive BP lowering.

Third, although adjudicators were blinded to treatment assignment, in some cases they may have been able to infer the treatment assigned to individual participants. Fourth, AKI events that were managed in the outpatient setting were not captured in this analysis; however, it is likely that these events were not severe enough to warrant either a hospital admission or evaluation in an ED. Note that data on changes in kidney function based on SPRINT laboratory data only will be the subject of two additional studies. Thus, the AKI prevalence reported herein is likely an underestimation of the true AKI incidence in the trial, but does capture all AKI events of sufficient severity to be associated with a hospitalization. Finally, these results are generalizable only to the study population, and thus should be extrapolated cautiously to other patient populations, including those with diabetes mellitus or polycystic kidney disease, persons at low risk for cardiovascular events, and institutionalized patients.

In sum, more intensive BP lowering in persons with hypertension at high risk for CVD resulted in an increase in the risk of AKI, although episodes of AKI were generally mild and largely reversible. Patients and physicians who undertake more intensive BP-lowering strategies should be alert for the risk of AKI, particularly among older patients and patients with CKD. However, for patients thought to benefit in terms of CVD prevention, fear of AKI should not preclude an intensive BP-lowering strategy.

Acknowledgments

Support: Supported by contracts (HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, and HHSN268200900049C) and an interagency agreement (A-HL-13-002-001) from the NIH, including the NHLBI, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke. Several study sites were supported by Clinical and Translational Science Awards funded by the National Center for Advancing Translational Sciences of the NIH (Case Western Reserve University: UL1TR000439; Ohio State University: UL1RR025755; University of Pennsylvania: UL1RR024134 and UL1TR000003; Boston University: UL1RR025771; Stanford University: UL1TR000093; Tufts University: UL1RR025752, UL1TR000073, and UL1TR001064; University of Illinois: UL1TR000050; University of Pittsburgh: UL1TR000005; University of Texas Southwestern: 9U54TR000017-06; University of Utah: UL1TR000105-05; Vanderbilt University: UL1TR000445; George Washington University: UL1TR000075; University of California, Davis: UL1TR000002; University of Florida: UL1TR000064; University of Michigan: UL1TR000433; and Tulane University: P30GM103337 Centers of Biomedical Research Excellence Award National Institute of General Medical Sciences). The trial was also supported in part with respect to resources and the use of facilities by the Department of Veterans Affairs. Azilsartan and chlorthalidone (combined with azilsartan) were provided by Takeda Pharmaceuticals International Inc. The SPRINT Steering Committee was responsible for the design and conduct of the study, including the collection and management of the data. Scientists at the NIH as a group and the principal investigator of the Veterans Affairs clinical network had one vote on the Steering Committee of the trial. There were seven voting members of the Steering Committee. The NIH, the US Department of Veterans Affairs, and the US government had no role in analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

We thank the study participants, without whom this trial would not have been possible.

References

1. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials*. 2014; 11(5):532–546. [PubMed: 24902920]
2. Wright JT Jr, Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015; 373(22):2103–2116. [PubMed: 26551272]
- 2a. Behndu S, et al. Effects of intensive systolic blood pressure lowering on incident chronic kidney disease and cardiovascular outcomes in non-chronic kidney disease subgroup in Systolic Blood

- Pressure Intervention Trial (SPRINT). *J Am Soc Nephrol.* 2016; 27(Abstract Suppl):8A. [PubMed: 26229138]
- 2b. Rahmann M, et al. ASN oral presentation, Intensive blood pressure control and CKD progression in SPRINT. Nov 17.2016
 3. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006; 145(4):247–254. [PubMed: 16908915]
 4. Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Work Group. KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013; 3:1–150.
 5. Lewington A, Kanagasundaram S. Renal Association Clinical Practice Guidelines on acute kidney injury. *Nephron Clin Pract.* 2011; 118(Suppl 1):c349–c390. [PubMed: 21555903]
 6. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* 2009; 76(4):422–427. [PubMed: 19436332]
 7. Grams ME, Sang Y, Coresh J, et al. Candidate Surrogate End Points for ESRD after AKI. *J Am Soc Nephrol.* 2016; 27(9):2851–2859. [PubMed: 26857682]
 8. Therneau, TM., Grambsch, PM. *Modeling Survival Data: Extending the Cox Model.* New York, NY: Springer; 2000. p. 170–174.
 9. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005; 16(11):3365–3370. [PubMed: 16177006]
 10. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis.* 2009; 53(6):961–973. [PubMed: 19346042]
 11. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin J Am Soc Nephrol.* 2014; 9(1):12–20. [PubMed: 24178971]
 12. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int.* 2012; 81(5):442–448. [PubMed: 22113526]
 13. Lo LJ, Go AS, Chertow GM, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. *Kidney Int.* 2009; 76(8):893–899. [PubMed: 19641480]
 14. Hsu, Cy, Iribarren, C., McCulloch, CE., Darbinian, J., Go, AS. Risk Factors for End-Stage Renal Disease: 25-Year Follow-up. *Archives of Internal Medicine.* 2009; 169(4):342–350. [PubMed: 19237717]
 15. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med.* 1994; 330(13):877–884. [PubMed: 8114857]
 16. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA.* 2002; 288(19):2421–2431. [PubMed: 12435255]
 17. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet.* 2016; 387(10017):435–443. [PubMed: 26559744]
 18. Lewis JB. Blood pressure control in chronic kidney disease: is less really more? *J Am Soc Nephrol.* 2010; 21(7):1086–1092. [PubMed: 20576804]
 19. Sawhney S, Mitchell M, Marks A, Fluck N, Black C. Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. *BMJ Open.* 2015; 5(1):e006497.

Figure 1.
CONSORT diagram

Figure 2.
Cumulative Hazard Plot for Acute Kidney Injury (CI denotes confidence interval).

Figure 3.

Forest Plot of Acute Kidney Injury. 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). The subgroup of no previous chronic kidney disease (CKD) includes some participants with unknown CKD status at baseline. Black race includes Hispanic black and black as part of a multiracial identification.

Table 1

Baseline Clinical Characteristics by Occurrence of Acute Kidney Injury (AKI)

Baseline characteristics	Intensive Treatment			Standard Treatment		
	No AKI (n=4499)	AKI (n=179)	P-Value	No AKI (n=4574)	AKI (n=109)	P-Value
Age 75 y	1250 (27.8%)	67 (37.4%)	0.005	1268 (27.7%)	51 (46.8%)	<0.001
Age, y	67.8 ± 9.3	70.7 ± 10.0	<0.001	67.8 ± 9.4	71.4 ± 10.7	<0.001
Female sex	1635 (36.3%)	49 (27.4%)	0.01	1619 (35.4%)	29 (26.6%)	0.06
Race or Ethnic Group			0.002			0.5
African American	1307 (29.1%)	72 (40.2%)		1386 (30.3%)	37 (33.9%)	
Hispanic	493 (11.0%)	10 (5.6%)		474 (10.4%)	7 (6.4%)	
Other	97 (2.2%)	1 (0.6%)		77 (1.7%)	1 (0.9%)	
White	2602 (57.8%)	96 (53.6%)		2637 (57.7%)	64 (58.7%)	
CKD	1233 (27.5%)	97 (54.5%)	<0.001	1245 (27.4%)	71 (65.1%)	<0.001
Serum creatinine, mg/dl	1.1 ± 0.3	1.4 ± 0.5	<0.001	1.1 ± 0.3	1.4 ± 0.5	<0.001
eGFR, mL/min/1.73 m ²	72.2 ± 20.4	59.8 ± 24.4	<0.001	72.1 ± 20.4	55.6 ± 19.9	<0.001
Urinary ACR, mg/g	40.3 ± 161.8	139.1 ± 407	<0.001	37.0 ± 126.7	203.8 ± 544	<0.001
CVD *	889 (19.8%)	51 (28.5%)	0.004	902 (19.7%)	35 (32.1%)	0.001
Subclinical	155 (3.4%)	6 (3.4%)	0.9	151 (3.3%)	3 (2.8%)	0.8
Clinical	734 (16.3%)	45 (25.1%)	0.002	751 (16.4%)	32 (29.4%)	0.003
Smoking Status			0.07			0.002
Never	1986 (44.3%)	64 (35.8%)		2042 (44.8%)	30 (27.5%)	
Former	1892 (42.2%)	85 (47.5%)		1934 (42.4%)	62 (56.9%)	
Current	609 (13.6%)	30 (16.8%)		584 (12.8%)	17 (15.6%)	
BMI, kg/m ²	29.9 ± 5.8	30.0 ± 5.8	0.9	29.8 ± 5.7	29.7 ± 6.3	0.8
SBP, mm Hg	139.6 ± 15.7	142.1 ± 17.1	0.03	139.6 ± 15.4	141.6 ± 16.6	0.2
DBP, mm Hg	78.3 ± 11.8	77.1 ± 13.5	0.2	78.1 ± 12.0	75.8 ± 13.0	0.05
SBP Tertile			0.2			0.1
132 mm Hg	1534 (34.1%)	49 (27.4%)		1522 (33.3%)	31 (28.4%)	
> 132 – < 145 mm Hg	1429 (31.8%)	60 (33.5%)		1518 (33.2%)	31 (28.4%)	

Baseline characteristics	Intensive Treatment		Standard Treatment	
	No AKI (n=4499)	AKI (n=179)	No AKI (n=4574)	AKI (n=109)
145 mm Hg	1536 (34.1%)	70 (39.1%)	1534 (33.5%)	47 (43.1%)
Fasting Glucose mg/dl	98.8 ± 13.6	100.3 ± 16.5	98.8 ± 13.3	99.3 ± 15.1
Statin Use	1896 (42.5%)	82 (45.8%)	2020 (44.6%)	56 (51.4%)
				0.7
				0.2

CKD, chronic kidney disease; CVD=cardiovascular disease, BMI=body mass index, DBP=diastolic blood pressure, eGFR =estimated glomerular filtration rate, ACR, albumin-creatinine ratio; SBP, systolic blood pressure

Note: Values for categorical variables are given as count (percentage); for continuous variables, as mean ± standard deviation. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; glucose in mg/dL to mmol/L, ×0.05551.

* Subclinical CVD includes: 50% stenosis of a coronary, carotid, or lower extremity artery; abdominal aortic aneurysm 5 cm with or without repair; coronary artery calcium score 400 Agatston units; low ankle brachial index (0.90); left ventricular hypertrophy by computer echocardiogram (ECG) reading, ECG report, or other cardiac imaging procedure. Clinical CVD includes: myocardial infarction; acute coronary syndrome with or without resting ECG changes, ECG changes on graded exercise test, or positive cardiac imaging study; coronary revascularization; carotid endarterectomy or carotid stenting; peripheral arterial disease with revascularization

Table 2

Severity of acute kidney injury events in non-CKD and CKD cohorts

	Intensive Arm		Standard Arm	
	Participants*	Events	Participants*	Events
Non-CKD cohort**				
AKI Stage 1	35	42	19	22
AKI Stage 2	19	24	6	6
AKI Stage 3	22	25	13	16
Unknown Stage	6	6	0	0
CKD cohort***				
AKI Stage 1	70	86	52	59
AKI Stage 2	14	18	9	12
AKI Stage 3	13	17	5	9
Unknown Stage	0	1	5	5

Note: Values are given as count (percentage).

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease

* In participants with multiple events, only first AKI event is shown

** p-value = 0.2 for comparison of stages of AKI by randomized arm, excluding unknowns (All Events); p-value = 0.5 for comparison of stages of AKI by randomized arm, excluding unknowns (First Events)

*** p-value = 0.8 for comparison of stages of AKI by randomized arm, excluding unknowns (All Events); p-value = 0.5 for comparison of stages of AKI by randomized arm, excluding unknowns (First Events)

Table 3

Changes in kidney function during and after the AKI event among participants stratified by treatment arm and presence or absence of CKD at baseline

	Intensive Arm		Standard Arm	
	Non-CKD (n= 82)	CKD (n = 97)	Non-CKD (n = 38)	CKD (n=71)
No. of events	97	122	44	85
Participant required RRT	4 (4.1%)	4 (3.3%)	2 (4.5%)	4 (4.7%)
Participant discharged on RRT	4 (4.1%)	1 (0.8%)	0 (0.0%)	2 (2.4%)
Participant developed ESRD	0 (0.0%)	2 (1.6%)	0 (0.0%)	3 (3.5%)
Participant died in hospital during this event	3 (3.1%)	1 (0.8%)	1 (2.3%)	3 (3.5%)
AKI was primary reason for admission	30 (30.9%)	37 (30.3%)	14(31.8%)	22 (25.9%)
AKI developed after admission to hospital	3 (3.1%)	9 (7.4%)	3 (6.8%)	6 (7.1%)
ATN developed or was present during hospitalization	36 (37.1%)	31 (25.4%)	14 (31.8%)	18 (21.2%)
AKI developed during a cardiac event	7 (7.2%)	10 (8.2%)	1 (2.3%)	10 (11.8%)
AKI developed during a CHF event	4 (4.1%)	7 (5.7%)	4 (9.1%)	6 (7.1%)
AKI developed after patient had a fall	9 (9.3%)	13 (10.7%)	2 (4.5%)	11 (12.9%)
AKI developed due to dehydration or intravascular volume depletion	60 (61.9%)	77 (63.1%)	28 (63.6%)	61 (71.8%)
AKI developed due to hypotension	43 (44.3%)	42 (34.4%)	10 (22.7%)	25 (29.4%)
AKI developed post-operatively	1 (1.0%)	4 (3.3%)	1 (2.3%)	2 (2.4%)
AKI developed due to a septic event	7 (7.2%)	15 (12.3%)	7 (15.9%)	11 (12.9%)
AKI developed due to contrast nephropathy	2 (2.1%)	1 (0.8%)	2 (4.5%)	2 (2.4%)
AKI developed due to obstruction	6 (6.2%)	9 (7.4%)	2 (4.5%)	3 (3.5%)
AKI developed due to medications	25 (25.8%)	37 (30.3%)	10 (22.7%)	17 (20.0%)
SPRINT intervention was responsible for this episode of AKI	10 (11.1%)	12 (10.2%)	2 (4.7%)	1 (1.3%)

Note: Unless otherwise indicated, alues are given as number (percentage).

AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; CHF, congestive heart failure; ESRD, end-stage renal disease; RRT, renal replacement therapy

Table 4

Multivariable predictors of time to development of AKI

Baseline Variables	HR (95% CI)	P-value
Male sex	1.86 (1.43 – 2.44)	<0.001
Black Race	2.08 (1.62 – 2.66)	<0.001
eGFR (per 10 ml/min/1.73m ² greater)	0.71 (0.66 – 0.75)	<0.001
CVD Subgroup	1.48 (1.14 – 1.90)	0.003
Senior Subgroup	1.52 (1.18 – 1.95)	0.001
ACE inhibitor use	1.20 (0.95 – 1.51)	0.1
ARB use	1.30 (0.62 – 2.39)	0.4
Diuretic use	0.98 (0.77 – 1.24)	0.9
Randomized to intensive arm	1.64 (1.30 – 2.09)	<0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; CVD=cardiovascular disease, eGFR =estimated glomerular filtration rate, HR, hazard ratio

Table 5

Causes of death for 45 participants with any AKI event who died

Cause of death	Intensive Arm	Standard Arm
CHF	3	2
Cancer	10	3
MI/coronary heart disease	0	1
Other noncardiac/nonstroke death	7	8
Stroke	1	1
Sudden Cardiac Death	0	1
Unclassifiable	2	3
Still under adjudication	1	0
Accident/Injury/Suicide/Homicide	2	0
Total	26	19

Note: Values are given as number of participants.

CHF, congestive heart failure; MI, myocardial infarction