Title

Effect of Intensive versus Standard BP Control on AKI and Subsequent Cardiovascular Outcomes and Mortality: Findings from the SPRINT EHR Study.

Journal

Kidney 360, 3(7)

Authors

Drawz, Paul

Rai, Nayanjot

Lenoir, Kristin

et al.

Publication Date

2022-07-28

DOI

10.34067/KID.0001572022

Peer reviewed

Kidney360

Effect of Intensive versus Standard BP Control on AKI and Subsequent Cardiovascular Outcomes and Mortality: Findings from the SPRINT EHR Study

Paul E. Drawz,[1] *Nayanjot Kaur Rai*,[1] *Kristin Macfarlane Lenoir*,[2] *Maritza Suarez*,[3] *James R. Powell*,[4] *Dominic S. Raj*,[5] *Srinivasan Beddhu*,[6] *Anil K. Agarwal*,[7] *Sandeep Soman*,[8] *Paul K. Whelton*,[9] *James Lash*,[10] *Frederic F. Rahbari-Oskoui*,[11] *Mirela Dobre*,[12] *Mark A. Parkulo*,[13] *Michael V. Rocco*,[14] *Andrew McWilliams*,[15] *Jamie P. Dwyer*,[16] *George Thomas*,[17] *Mahboob Rahman*,[18] *Suzanne Oparil*,[19] *Edward Horwitz*,[20] *Nicholas M. Pajewski*,[2] *and Areef Ishani*[1,21]

Key Points

- Identifying ways to prevent AKI may reduce mortality further in the setting of intensive BP control.
- Creatinine-based ascertainment of AKI, enabled by electronic health record data, may be more sensitive and less biased than traditional serious adverse event adjudication.

Abstract

Background Adjudication of inpatient AKI in the Systolic Blood Pressure Intervention Trial (SPRINT) was based on billing codes and admission and discharge notes. The purpose of this study was to evaluate the effect of intensive versus standard BP control on creatinine-based inpatient and outpatient AKI, and whether AKI was associated with cardiovascular disease (CVD) and mortality.

Methods We linked electronic health record (EHR) data from 47 clinic sites with trial data to enable creatinine-based adjudication of AKI. Cox regression was used to evaluate the effect of intensive BP control on the incidence of AKI, and the relationship between incident AKI and CVD and all-cause mortality.

Results A total of 3644 participants had linked EHR data. A greater number of inpatient AKI events were identified using EHR data (187 on intensive versus 155 on standard treatment) as compared with serious adverse event (SAE) adjudication in the trial (95 on intensive versus 61 on standard treatment). Intensive treatment increased risk for SPRINT-adjudicated inpatient AKI (HR, 1.51; 95% CI, 1.09 to 2.08) and for creatinine-based outpatient AKI (HR, 1.40; 95% CI, 1.15 to 1.70), but not for creatinine-based inpatient AKI (HR, 1.20; 95% CI, 0.97 to 1.48). Irrespective of the definition (SAE or creatinine based), AKI was associated with increased risk for all-cause mortality, but only creatinine-based inpatient AKI was associated with increased risk for CVD.

Conclusions Creatinine-based ascertainment of AKI, enabled by EHR data, may be more sensitive and less biased than traditional SAE adjudication. Identifying ways to prevent AKI may reduce mortality further in the setting of intensive BP control.

KIDNEY360 3: 1253–1262, 2022. doi: https://doi.org/10.34067/KID.0001572022

Introduction

Intensive BP control increased risk for inpatient AKI in the Systolic Blood Pressure Intervention Trial (SPRINT) (1). In observational studies, AKI is associated with increased risk for multiple adverse outcomes, including CKD, progression of CKD, ESKD, cardiovascular disease (CVD), hypertension, and all-cause mortality (2–8). Despite an increased rate of AKI, intensive BP control in SPRINT reduced the risk for cardiovascular morbidity and all-cause mortality, as compared with standard treatment (1).

Adjudication of AKI in SPRINT was based on the International Classification of Diseases diagnosis codes, admission history and physicals, and discharge summaries (9). A similar approach was shown to be only approximately 20% sensitive for AKI in the Atherosclerosis Risk in Communities (ARIC) study (10). In addition to the low sensitivity, AKI was likely selectively ascertained in SPRINT, given that it was an open-label trial. Although blinded adjudicators reviewed the discharge summaries when available, clinicians and patients were not blinded. It is possible that this bias may have led to increased sensitivity to the presence of AKI for patients in the intensive treatment group, increasing the likelihood that AKI would appear on a discharge summary. Finally, in SPRINT, AKI was only

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Paul E. Drawz, Division of Renal Diseases and Hypertension, University of Minnesota, 717 Delaware St. SE, Minneapolis, MN 55414. E-mail: draw0003@umn.edu

assessed in the emergency department (ED) and inpatient settings. However, outpatient AKI is associated with a similar increased risk for adverse outcomes as inpatient AKI, and intensive BP control may increase risk for outpatient AKI (11–14).

The unbiased rate of inpatient AKI and the effect of intensive BP control on outpatient AKI in SPRINT are unknown. Additionally, the effect of creatinine-based inpatient and outpatient AKI on adverse outcomes is also unknown. To evaluate the effect of intensive BP control on creatinine-based AKI, we linked data from SPRINT with electronic health record (EHR) data from 47 participating clinic sites. The objectives of this project were to (*1*) evaluate the effect of intensive versus standard BP targets on the rate of inpatient and outpatient AKI, assessed *via* creatinine values from SPRINT and linked EHR data; and (*2*) evaluate the association of creatinine-based inpatient and outpatient AKI on subsequent cardiovascular events and mortality.

Materials and Methods

SPRINT was a randomized, controlled, open-label clinical trial. Between November 2010 and March 2013, 9361 participants were randomized to intensive versus standard BP control, with target study visit systolic BPs of <120 mm Hg and <140 mm Hg, respectively. The study was stopped after a median follow-up of 3.26 years. EHR data from 47 clinic sites were linked with SPRINT data as part of the SPRINT EHR ancillary study. Institutional review boards approved the original SPRINT study and this SPRINT EHR ancillary study protocol at each site. The SPRINT EHR ancillary study adhered to the Declaration of Helsinki and was conducted under a waiver of informed consent because it only used existing trial and EHR data.

SPRINT Baseline and Follow-Up Data Collection

As previously described, data collected at baseline included self-reported race and ethnicity (as required by the National Institutes of Health [NIH]) along with other sociodemographic information (1,15). Serum creatinine was measured at the randomization visit; the 1-, 3-, 6-, 9-, and 12-month follow-up visits; and then every 6 months. The 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study creatinine-based equation was used to calculate eGFR (16). Trained study coordinators followed an American Heart Association–adherent protocol to measure BP (17). Participant reports of adverse events, including hospitalizations, ED visits, and other health outcomes of interest, were ascertained at quarterly visits (9).

EHR Data

We previously described this study's methods for linking the SPRINT and EHR data (15). The current analysis is on the basis of patients with EHR data from 47 clinic sites (out of 102 SPRINT sites). Each site provided all vital signs, laboratory results, and billing/procedure codes for all SPRINT participants within their health system. Creatinine measurements were identified within the laboratory files on the basis of names, codes, and result values. Creatinine measurements were classified as outpatient if they were not concurrent with a SPRINT-reported ED or hospitalization serious adverse event (SAE), with the remaining creatinine measurements classified as inpatient. In secondary analyses, we also classified creatinine measurements on consecutive days as inpatient.

Inpatient AKI was defined using (*1*) the SPRINT definition, which used SAE reports on the basis of diagnosis codes and review of admission and discharge notes (9); and (*2*) a creatinine-based definition of a 50% or ≥0.3-mg/dl increase in EHR creatinine values during an ED visit or hospitalization, as compared with baseline. Outpatient AKI was defined by a 50% increase in outpatient creatinine using trial and EHR laboratory measurements. For both inpatient and outpatient AKI, we defined the baseline as the most recent creatinine measured as part of trial follow-up. AKI stage was defined using the creatinine-based Kidney Disease Improving Global Outcomes criteria (18). Cardiovascular events were defined per the trial protocol as the first occurrence of fatal or nonfatal myocardial infarction (MI), non-MI acute coronary syndrome (sometimes called unstable angina), fatal or nonfatal stroke, fatal or nonfatal heart failure, or death attributable to CVD (1). Mortality was ascertained in SPRINT using a standard protocol (19).

Statistical Analyses

We compared the incidence of AKI between treatment groups using Cox proportional hazards regression with the baseline hazard function stratified by clinic site (20). We examined the proportionality assumption of the Cox model using hypothesis tests on the basis of Schoenfeld residuals (21). We examined the association of incident AKI with subsequent CVD and all-cause mortality. These analyses were also on the basis of Cox regression models with stratified baseline hazard function, treating the occurrence of AKI as a time-varying predictor. Models included treatment group as a covariate, and the following baseline characteristics: age, sex, race and ethnicity, smoking status (current, former, or never smoker), history of CVD, systolic and diastolic BP, eGFR on the basis of the 2021 CKD-EPI study creatinine-based equation (16), log of urine albumin-creatinine ratio (UACR), statin use, and use of either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. To address a small amount of missing data at baseline for eGFR (N=10) and UACR (N=151), we used chained multiple imputation on the basis of random forests as a function of all baseline variables listed above, first imputing eGFR and then imputing log UACR. Recovery after inpatient AKI was previously reported (9). We examined recovery of kidney function after outpatient AKI in two ways. First, we modeled the trajectory of outpatient eGFR in the year preceding and after an outpatient AKI event using linear mixed models. In these analyses, we flexibly modeled eGFR as a function of time using B-splines separated by treatment group. Second, we defined partial recovery as ever having an outpatient serum creatinine within 30% of the pre-AKI serum creatinine concentration (without subsequent elevation >30% of the pre-AKI serum creatinine concentration); full recovery was similarly defined, with a threshold at 20% of the pre-AKI serum creatinine concentration. We compared the incidence of partial and full recovery between the treatment groups using the proportional subdistribution hazards model of Fine and Gray (22), accounting for the competing risk

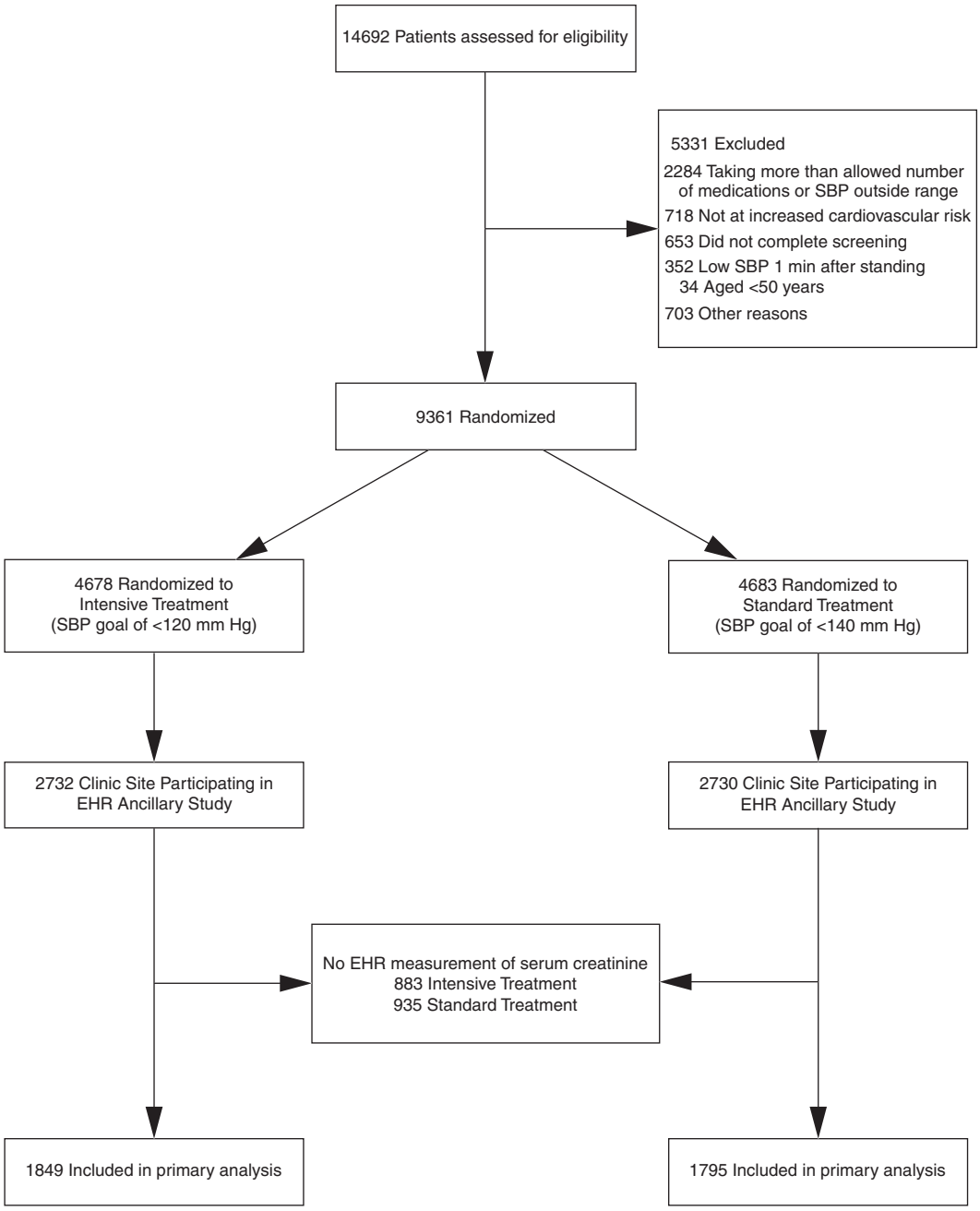

Figure 1. | **Consolidated Standards of Reporting Trials diagram.** EHR, electronic health record; SBP, systolic BP.

of death. All analyses were performed using the R Statistical Computing Environment, using the timereg and mice packages (23,24).

Results

Of the 5462 participants enrolled at the sites participating in the SPRINT EHR ancillary study, 3644 (67%) had at least one creatinine value in their EHR data (Figure 1). The intensive and standard treatment groups were similar with regards to baseline characteristics (Table 1). The mean±SD age was 69±9 years; 24% were female; 30% were Black participants; and the mean±SD eGFR was 71±20 ml/min per 1.73 m^2. Compared with the trial participants not included in these analyses, participants in these analyses were older, less likely to be female, and more likely to be taking a statin (Supplemental Table 1).

During a median of 4.01 years of follow-up, the median number of outpatient EHR creatinine measurements from routine care was six (interquartile range, 3–11), and this was similar in the two treatment arms. The median number of trial creatinine measurements was ten (interquartile range, 9–12). Among the 3644 participants included in these analyses, only 342 (9%) had creatinine-based inpatient AKI, and 416 (11%) had creatinine-based outpatient AKI. The majority of creatinine-based AKI was stage 1

Table 1. Baseline characteristics at trial entry of participants included in the SPRINT electronic health record ancillary study by treatment group

Characteristic	Intensive Treatment (*N*=1849)	Standard Treatment (*N*=1795)
Veterans Affairs site, *n* (%)	919 (50)	907 (51)
Age, yr		
Mean±SD	69.1±9.2	68.7±9.4
≥75, *n* (%)	590 (32)	568 (32)
Female sex, *n* (%)	464 (25)	413 (23)
Race and ethnicity, *n* (%)		
Black	550 (30)	559 (31)
Hispanic	91 (5)	58 (3)
White	1179 (64)	1162 (65)
Other[a]	29 (2)	16 (0.9)
Smoking status, *n* (%)		
Current smoker	239 (13)	237 (13)
Former smoker	898 (49)	878 (49)
Never smoker	712 (39)	680 (38)
BMI, kg/m^2 (mean±SD)	30.1±5.8	30.0±5.7
History of cardiovascular disease, *n* (%)	434 (24)	447 (25)
Blood pressure, mm Hg (mean±SD)		
Systolic	137.8±15.2	137.67±14.9
Diastolic	77.0±11.4	76.9±11.6
Orthostatic hypotension, *n* (%)	124 (7)	120 (7)
eGFR, ml/min per 1.73 m^2 [b]		
Mean±SD	71.0±19.6	71.2±19.3
<60, *n* (%)	548 (30)	518 (29)
Urine albumin-creatinine ratio, mg/g [median (IQR)]	9.9 (5.8–24.9)	9.7 (5.6–23.6)
HDL cholesterol, mg/dl (mean±SD)	51.8±13.8	51.1±13.8
Triglycerides, mg/dl, median (IQR)	106 (76–145)	109 (79–154)
Glucose, mg/dl (mean±SD)	99.5±13.3	99.4±13.4
Antihypertensive agents, *n* (mean±SD)	1.9±1.0	1.9±1.0
Statin use, *n* (%)	905 (49)	951 (53)
Use of ACE inhibitor or angiotensin receptor blocker, *n* (%)	1059 (57)	1066 (59)

SPRINT, Systolic Blood Pressure Intervention Trial; BMI, body mass index; IQR, interquartile range; ACE, angiotensin-converting enzyme.
[a]Includes self-reported American Indian, Alaska Native, Native Hawaiian, Pacific Islander, Asian, and other.
[b]eGFR determined using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

Table 2. Effect of intensive treatment on the incidence of AKI

Population	Outcome	Intensive Events/Rate per 1000 Person-Years	Standard Events/Rate per 1000 Person-Years	Hazard Ratio (95% Confidence Interval)[a]	*P* Value
All participants (*n*=9361)	Inpatient AKI on the basis of SAE	179/10.4	109/6.3	1.65 (1.30 to 2.10)	<0.001
EHR ancillary study (*n*=3644)	Inpatient AKI on the basis of SAE	95/13.6	61/9.0	1.51 (1.09 to 2.08)	0.01
EHR ancillary study (*n*=3644)	Inpatient AKI (creatinine-based)	187/26.9	155/23	1.20 (0.97 to 1.48)	0.10
EHR ancillary study (*n*=3644)	Outpatient AKI (creatinine based)	243/36.0	173/25.8	1.40 (1.15 to 1.70)	0.001

SAE serious adverse event as adjudicated in Systolic Blood Pressure Intervention Trial; EHR, electronic health record.
[a]Hazard ratio determined using Cox proportional hazards regression with the baseline hazard function stratified by clinic site.

for both inpatient (80%) and outpatient (87%) cases. Stage-2 AKI was seen in 13% and 11% and stage 3 in 7% and 3% for inpatient and outpatient AKI, respectively (Supplemental Table 2) (18).

More inpatient AKI events were identified using EHR creatinine values compared with the number identified through the trial adjudication process (187 versus 95 in the intensive treatment group and 155 versus 61 in the

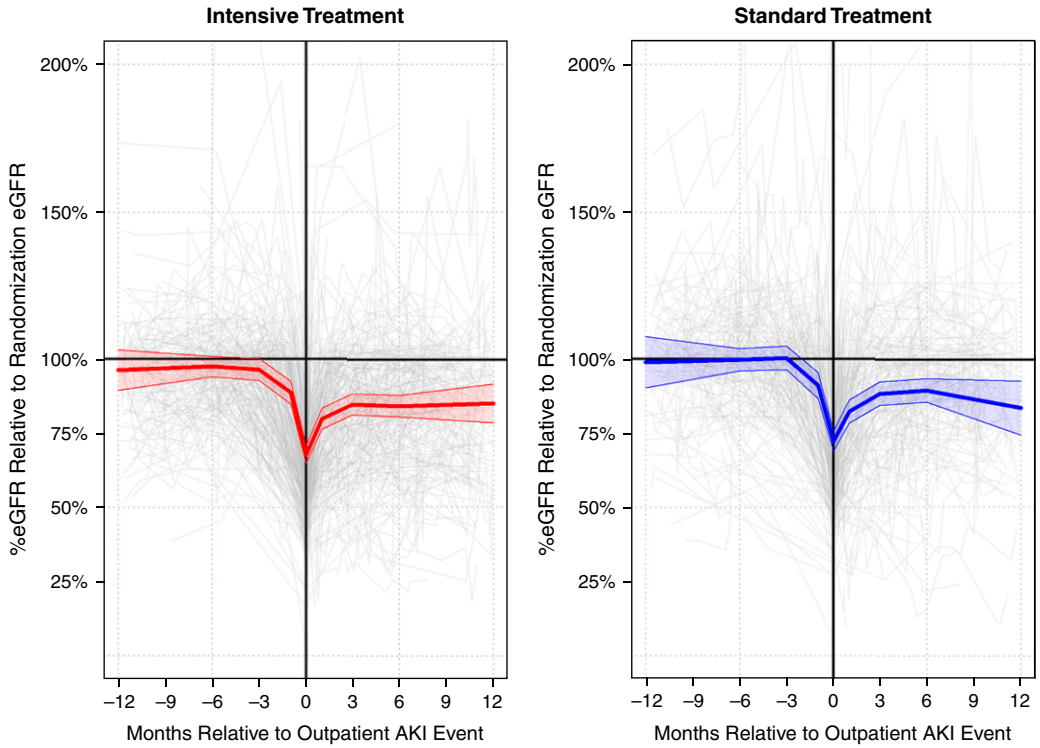

Figure 2. | **The relative reduction in eGFR after AKI was similar between the treatment groups.** eGFR was determined using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation. Estimates determined on the basis of a linear mixed model with random intercepts for participant and clinic site. Time relative to outpatient AKI event was modeled flexibly using B-splines. Shaded areas denote 95% pointwise CIs.

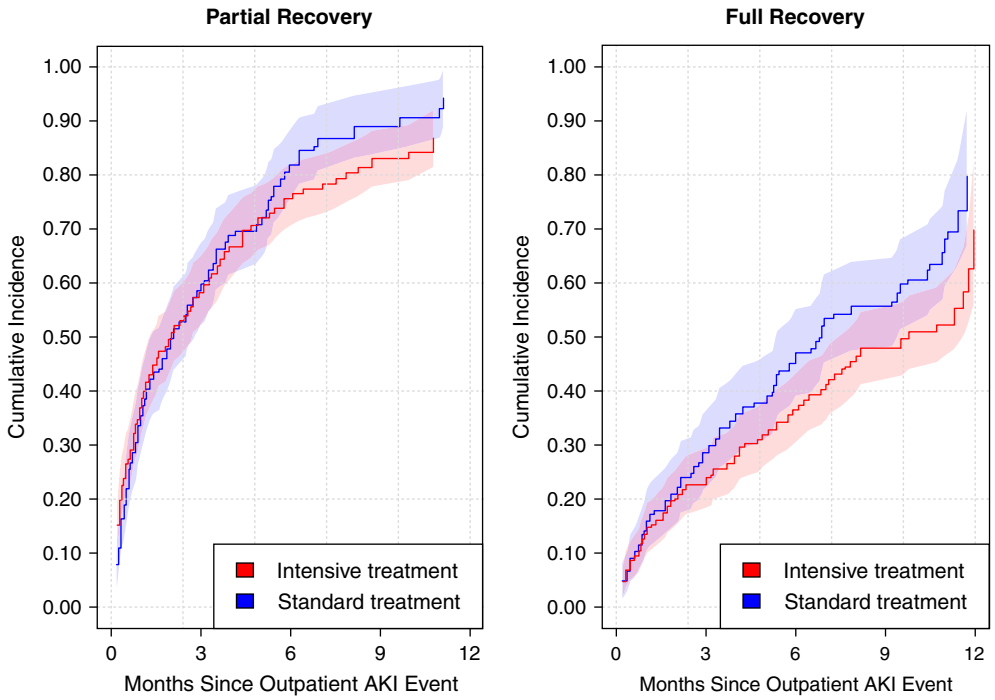

Figure 3. | **Recovery of kidney function after outpatient AKI was similar between treatment groups.** Partial recovery was defined as having a serum creatinine within 30% of the pre-AKI serum creatinine concentration, with full recovery similarly defined as being within 20% of the pre-AKI serum creatinine concentration. Curves denote cumulative incidence estimates, with shaded areas representing pointwise 95% CIs.

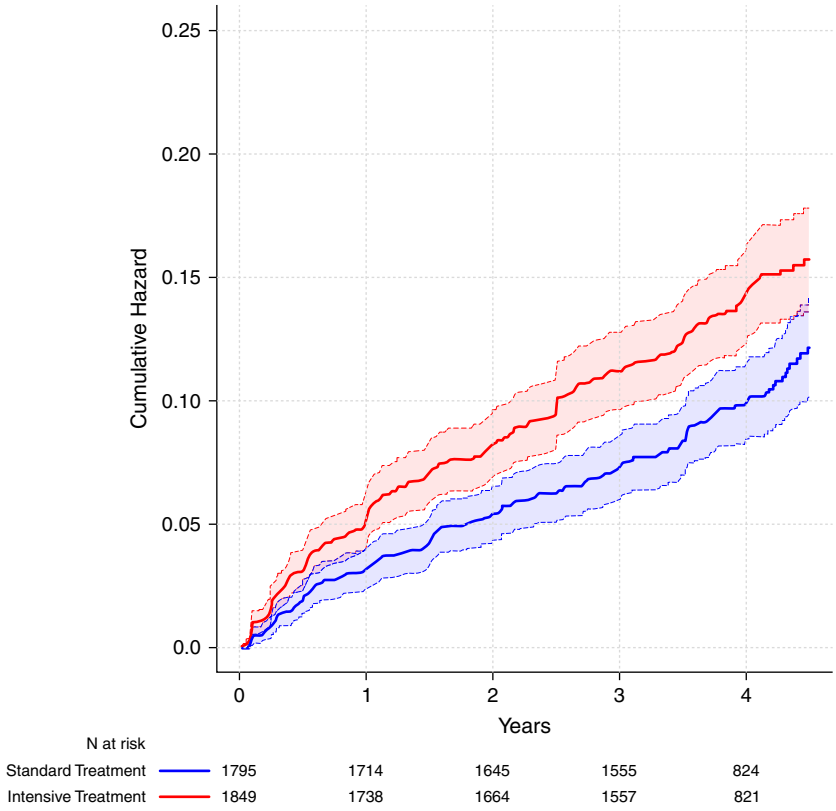

Figure 4. | Intensive treatment increased risk for outpatient AKI**.** Shaded areas denotes pointwise 95% CIs.

standard treatment group; Table 2). There were also more outpatient than inpatient creatinine-based AKI events (Table 2). The change in outpatient eGFR relative to the level at randomization among participants who experienced an outpatient AKI event is shown in Figure 2. In the 12 months after outpatient AKI, approximately 90% of participants had partial recovery of kidney function (creatinine within 30% of pre-AKI SPRINT value) and approximately 70% of participants had full recovery to within 20% of baseline; there was no difference in the incidence of recovery between treatment groups (Figure 3). The subdistribution hazard ratio (HR) for partial recovery (comparing intensive with standard) was 0.99 (95% CI, 0.78 to 1.24); the subdistribution HR for full recovery was 0.78 (95% CI, 0.59 to 1.03).

When the SPRINT-adjudicated AKI definition was applied to this ancillary study population, the results mirrored the risk of AKI seen in the overall trial population: intensive treatment was associated with an increased risk of SPRINT-adjudicated inpatient AKI (HR, 1.51; 95% CI, 1.09 to 2.08; Table 2). However, for creatinine-based inpatient AKI, intensive treatment was associated with an attenuated and nonsignificant increased risk (HR, 1.20; 95% CI, 0.97 to 1.48). For creatinine-based outpatient AKI, intensive treatment was associated with an increased risk (HR, 1.40; 95% CI, 1.15 to 1.70; Figure 4, Table 2). Results were similar in analyses accounting for the competing risk of mortality (Supplemental Table 3).

Inpatient AKI was associated with an increased risk for all-cause mortality when defined by SPRINT adjudication (HR, 3.54; 95% CI, 2.27 to 5.52) and the EHR creatinine-based definition (HR, 5.54; 95% CI, 3.94 to 7.80; Table 3). However, creatinine-based inpatient AKI events were associated with increased risk for cardiovascular events (HR, 1.74; 95% CI, 1.15 to 2.64), whereas SPRINT-adjudicated inpatient AKI was not (HR, 1.10; 95% CI, 0.61 to 2.00). Creatinine-based outpatient AKI was associated with an increased risk for all-cause mortality (HR, 2.73; 95% CI, 1.86 to 4.01) but not cardiovascular events (HR, 1.43; 95% CI, 0.97 to 2.13).

Discussion

By linking EHR data with trial data in SPRINT, we were able to use the gold-standard definition of AKI (change in serum creatinine) to demonstrate that intensive BP control increased the risk for AKI. Notably, the risk for inpatient AKI was attenuated with creatinine-based adjudication versus SPRINT document-based adjudication. Additionally, assessment of outpatient AKI was possible by the availability of EHR creatinine values. The majority of patients with AKI recovered to within at least 30% of their baseline kidney function. Despite the majority recovering, creatinine-based AKI was associated with an increased risk for all-cause mortality and incident CVD, whereas SPRINT-adjudicated AKI was only associated with increased risk for all-cause mortality.

This is the first large, multicenter study to evaluate the effect of intensive BP control on AKI on the basis of International Classification of Diseases/document-based adjudication compared with a creatinine-based definition of AKI.

Table 3. Association of AKI with incident cardiovascular disease and all-cause mortality

AKI Definition	Outcome	AKI, events/*N* (rate per 1000 Person-Years)[a]	No AKI, Events/*N* (rate per 1000 Person-Years)	Hazard Ratio (95% Confidence Interval)[b]	*P* Value
SPRINT SAE	CVD	12/135 (40.4)	289/3488 (22.2)	1.10 (0.61 to 2.00)	0.75
	Mortality	28/155 (82.6)	182/3488 (13.4)	3.54 (2.27 to 5.52)	<0.001
Outpatient creatinine-based AKI	CVD	31/344 (39.1)	255/3228 (21.1)	1.43 (0.97 to 2.13)	0.07
	Mortality	43/384 (49.9)	168/3228 (13.4)	2.73 (1.86 to 4.01)	<0.001
Inpatient creatinine-based AKI	CVD	28/276 (53.1)	242/3302 (19.5)	1.74 (1.15 to 2.64)	0.01
	Mortality	64/340 (101.9)	146/3302 (11.4)	5.54 (3.94 to 7.80)	<0.001

Primary CVD composite outcome includes nonfatal myocardial infarction, acute coronary syndrome, stroke, heart failure, and CVD death. PY, person-years; SPRINT, Systolic Blood Pressure Intervention Trial; SAE, serious adverse event; CVD, cardiovascular disease.

[a]Follow-up time computed from the occurrence of AKI.

[b]Hazard ratio determined using Cox regression model, treating AKI as a time-dependent predictor, adjusting for treatment group, age, sex, race, smoking status, history of CVD, eGFR, urine albumin-creatinine ratio, systolic and diastolic BP, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statin use (all at baseline).

Our results demonstrate the underascertainment of AKI inherent to SAE reporting and potential bias with open-label trials. Given that prior studies reported an increased risk for a rise in creatinine and occurrence of AKI with intensive BP control, providers may have been more likely to identify and mention AKI in their admission and discharge notes—the source of data for the SPRINT adjudication of AKI. Creatinine-based assessment of AKI, made possible by linking EHR data with SPRINT data, indicated a higher incidence of inpatient AKI in both treatment groups. This finding is consistent with a study within ARIC that demonstrated chart-based adjudication of AKI has a sensitivity of only approximately 20% (10). The increase in creatinine-based inpatient AKI events was relatively greater in the standard treatment group, resulting in a nonsignificant increased risk for creatinine-based inpatient AKI with intensive BP control. However, intensive BP control was associated with increased risk for creatinine-based outpatient AKI, an outcome not evaluated in the original SPRINT study.

Similar to prior observational studies, AKI was associated with an increased risk for adverse outcomes (2–8). In our study, both inpatient and outpatient AKI were associated with increased risk for adverse outcomes. Most prior research has focused on the inpatient setting, but at least one study has demonstrated increased risk for all-cause mortality and decline in kidney function with outpatient AKI (14). The effect of AKI on CVD and mortality could be due to short-term effects (*e.g.*, acute health conditions lead to AKI and adverse events) and long-term effects (*e.g.*, AKI results in CKD and elevated BP, which both result in increased risk for cardiovascular events and mortality).

Despite the increased risk for AKI with intensive BP control and the increased risk for adverse outcomes associated with AKI, intensive BP control still reduced overall risk for cardiovascular outcomes and all-cause mortality (1). This is, in part, due to the overall low incidence of AKI. Rather than avoiding intensive BP control, strategies should be developed to lower BP to a clinic target of <120 mm Hg while also reducing risk for AKI. Potential strategies to reduce AKI with intensive BP control could include holding or modifying antihypertensive medications in the setting of illness and more gradual lowering to target. Such strategies may make intensive BP control even more effective at reducing risk for cardiovascular events and all-cause mortality.

Strengths of this study include the linkage of EHR and trial data from SPRINT in a study sample with a relatively large sample size, diverse geographic representation, and formal adjudication of CVD and mortality outcomes. A number of limitations need to be considered. First, the study included a subset of trial sites and only those participants with EHR data. Second, the clinical indication for measuring creatinine in routine practice was unknown and could lead to bias. Third, the study includes a higher percentage of men compared with the overall trial due to the inclusion of EHR data from a large number of Veterans Affairs Medical Centers.

Intensive BP control was associated with increased risk for inpatient and outpatient AKI. Participants with AKI were at increased risk for CVD events and all-cause mortality. Creatinine-based ascertainment of AKI, facilitated by EHR data, may be more sensitive than traditional SAE reporting, particularly for open-label trials and for detecting outpatient AKI events. Routine collection of EHR data should become standard for large explanatory and/or pragmatic trials that include AKI as an outcome. Finally, given that inpatient and outpatient AKI were associated with increased risk for all-cause mortality, identifying ways to prevent AKI in the setting of intensive BP control may reduce cardiovascular events and mortality even further.

Disclosures

A.K. Agarwal reports serving in an advisory or leadership role for American Society of Diagnostic and Interventional Nephrology (ASDIN), *Clinical Nephrology*, *International Journal of Nephrology*, International Society of Nephrology (ISN), *Journal of Vascular Access*, Kidney Self-Assessment Program, National Kidney Foundation (NKF), and *The Open Urology and Nephrology Journal*; having other interests in, or relationships with, the American Society of Nephrology,

ASDIN, ISN, and NKF; serving on a speakers bureau for AstraZeneca; having consultancy agreements with, and receiving honoraria from, AstraZeneca and Otsuka Pharmaceuticals. S. Beddhu reports receiving research funding from Bayer, Boehringer Ingelheim, and Novartis; having consultancy agreements with Bayer and Reata; and serving in an advisory or leadership role for *CJASN* and *Kidney Reports*. M. Dobre reports receiving honoraria from Relypsa and Tricida; and serving in an advisory or leadership role for Relypsa (Resistant Hypertension Working Group) and Tricida (Metabolic Acidosis Working Group). J.P. Dwyer reports having consultancy agreements with Acuta Capital, Akcea, Aleon, Ardelyx, AstraZeneca, Aurinia, Axsome, Bayer, BioRasi, BioVie, Boeringher Ingelheim, Botanix, Caladrius, Cincor, Contrafect, Cumberland, Eli Lilly, ES, Fibrogen, Genentech, Hope Pharma, Icon, Ionis, Innovative Renal Care, Keros, LifeSci Venture, Medpace, MicuRx, PSI, Rarestone, Reata, RenalytixAI, Sanofi, Spero, Tricida, ValenzaBio, and Worldwide Clinical Trials; having ownership interest in BioRasi, Innovative Renal Care, PathEx, ValenzaBio, and Venostent; serving in an advisory or leadership role for Collaborative Study Group (board of directors and president) and The Bolles School (high school in Jacksonville, FL; board of directors); and having other interests in, or relationships with, The Bolles School Board of Visitors. E. Horwitz reports having other interests in, or relationships with, MetroHealth Medical Center, contracted with Fresenius Kidney Care (serving as medical director for inpatient dialysis services). J. Lash reports serving in an advisory or leadership role for *Kidney360*. A. McWilliams reports having ownership interest in iEnroll. S. Oparil reports receiving research funding from Bayer (site principal investigator [PI] in diabetic kidney disease), CinCor Pharma (site PI for primary aldosterone study), George Clinical (site PI for GMRx2 treatment of hypertension), and Higi (site PI for BP validation study); having ownership interest in CinCor Pharma; serving in an advisory or leadership role for CinCor Pharma (scientific advisory board for primary aldosteronism and hypertension) and Preventric Diagnostics (chair medical and technology committee; from March 2019 to present); and serving as editor-in-chief of *Current Hypertension Reports* (journal published by Springer Science Business Media LLC; annual stipend of $5000; editor-in-chief term until December 2022). N.M. Pajewski reports having ownership interest in Eyenovia and Ocuphire Pharma. M.A. Parkulo reports having ownership interest in Apple, Blackberry, Carnival, JPMorgan Chase, Marriott, StitchFix, and Zoom. J. Powell reports receiving research funding from Idorsia (for acting as site PI). F.F. Rahbari-Oskoui reports having consultancy agreements with Astute, Kadmon, Keryx, Phoenix (client Otsuka), Sanofi, and UpToDate; serving in an advisory or leadership role for *BMC Nephrology* (as associate editor), *Journal of Cardiology and Vascular Medicine* (as editorial board member), and PKD Foundation; receiving research funding from Duke University, Kadmon, NIH, Otsuka, Reata, and Sanofi/Genzyme; serving on a speakers bureau for Otsuka (unbranded speakers bureau; only raising disease awareness in autosomal dominant polycystic kidney disease without any reference to commercial products); receiving honoraria from Otsuka and Sanofi; and having other interests in, or relationships with, PKD Foundation (scientific advisory board member) and UpToDate (as author, receiving authorship royalties). M. Rahman reports serving as an editorial board member of *American Journal of Nephrology* and as an associate editor of *CJASN*; having consultancy agreements with Barologics; receiving research funding from Bayer Pharmaceuticals and Duke Clinical Research Institute; and receiving honoraria from Bayer, Reata, and Relypsa. D.S. Raj reports having other interests in, or relationships with, the American Association of Kidney Patients; serving in an advisory or leadership role for National Heart, Lung, and Blood Institute (NHLBI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and Novo Nordisk; receiving research funding from the NIH; having consultancy agreements with, and receiving honoraria from, Novo Nordisk. M.V. Rocco reports having consultancy agreements with Bayer, Baxter, and George Clinical; receiving research funding from Bayer, Boehringer Ingelheim, and GlaxoSmithKline; serving as cochair of the ISN Kidney Care Network Project and as chair of NKF Kidney Disease Outcomes Quality Initiative; and serving in an advisory or leadership role for NKF. S. Soman reports serving in an advisory or leadership role for the American Medical Informatics Association, NKF, and NKF of Michigan; having other interests in, or relationships with, American Medical Informatics Association, Cardiorenal Society of America (CRSA), NKF (education committee), and NKF of Michigan (scientific advisory board); being employed by Henry Ford Hospital; and having ownership interest in Nephroceuticals and Pfizer. G. Thomas reports receiving honoraria from UpToDate. All remaining authors have nothing to disclose.

Funding

The work presented here was supported by NHLBI grant R01HL136679, National Institute on Aging (NIA) grant R01AG0-55606, and funding from the Alzheimer's Association (AA). SPRINT was funded by the NIH (including the NHLBI, NIDDK, NIA, and National Institute of Neurological Disorders and Stroke) grants HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, and HHSN268200900049C, and interagency agreement A-HL-13-002-001. It was also supported, in part, by resources and use of facilities through the Department of Veterans Affairs. Azilsartan and chlorthalidone (combined with azilsartan) were provided by Takeda Pharmaceuticals U.S.A. Additional support was provided through the National Center for Advancing Translational Sciences clinical and translational science awards UL1TR000439 (awarded to Case Western Reserve University), UL1TR000003 (University of Pennsylvania), UL1TR000093 (Stanford University), UL1TR000073 and UL1TR001064 (Tufts University), UL1TR000050 (University of Illinois), UL1TR000005 (University of Pittsburgh), U54TR000017-06 (University of Texas Southwestern Medical Center), UL1TR000105-05 (University of Utah), UL1 TR000445 (Vanderbilt University), UL1TR000075 (George Washington University), UL1 TR000002 (University of California, Davis), UL1 TR000064 (University of Florida), and UL1TR000433 (University of Michigan); the National Center for Research Resources grants UL1RR025755 (Ohio State University), UL1RR024134 (University of Pennsylvania), UL1RR025771 (Boston University), and UL1RR025752 (Tufts University); and by the National Institute of General Medical Sciences Centers of Biomedical Research Excellence award P30GM103337 (awarded to Tulane University).

Acknowledgments

The authors also wish to acknowledge computing support provided the Veterans Affairs Informatics and Computing Infrastructure.

The views expressed in this paper are those of the authors and do not represent the official position of the NIH, the NHLBI, the Department of Veterans Affairs, the US Government, the AA, or the SPRINT Research Group. This paper was not reviewed by the SPRINT Publications and Presentations Committee.

Author Contributions

P.E. Drawz conceptualized the study, wrote the original draft, and was responsible for data curation and funding acquisition;

P.E. Drawz, K.M. Lenoir, and N.M. Pajewski were responsible for formal analysis; A. Ishani and N.M. Pajewski provided supervision; N.M. Pajewski was responsible for methodology and validation; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains supplemental material online at https://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0001572022/-/DCSupplemental.

Supplemental Table 1. Baseline characteristics of participants included in the electronic health record (EHR) ancillary study versus remaining trial participants at EHR ancillary study sites.

Supplemental Table 2. Effect of intensive treatment on the incidence of acute kidney injury accounting for the competing risk of mortality.

Supplemental Table 3. Stage of outpatient and inpatient acute kidney injury events by treatment group.

References

1. Lewis CE, Fine LJ, Beddhu S, Cheung AK, Cushman WC, Cutler JA, Evans GW, Johnson KC, Kitzman DW, Oparil S, Rahman M, Reboussin DM, Rocco MV, Sink KM, Snyder JK, Whelton PK, Williamson JD, Wright JT Jr, Ambrosius WT; SPRINT Research Group: Final report of a trial of intensive versus standard blood-pressure control. *N Engl J Med* 384: 1921–1930, 2021 https://doi.org/10.1056/NEJMoa1901281
2. Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int* 81: 442–448, 2012 https://doi.org/10.1038/ki.2011.379
3. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, Slinin Y, Ensrud KE: The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. *Arch Intern Med* 171: 226–233, 2011 https://doi.org/10.1001/archinternmed.2010.514
4. 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* 53: 961–973, 2009 https://doi.org/10.1053/j.ajkd.2008.11.034
5. Wu VC, Wu CH, Huang TM, Wang CY, Lai CF, Shiao CC, Chang CH, Lin SL, Chen YY, Chen YM, Chu TS, Chiang WC, Wu KD, Tsai PR, Chen L, Ko WJ; NSARF Group: Long-term risk of coronary events after AKI. *J Am Soc Nephrol* 25: 595–605, 2014 https://doi.org/10.1681/ASN.2013060610
6. Soto K, Campos P, Pinto I, Rodrigues B, Frade F, Papoila AL, Devarajan P: The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury. *Kidney Int* 90: 1090–1099, 2016 https://doi.org/10.1016/j.kint.2016.07.018
7. Hsu CY, Hsu RK, Yang J, Ordonez JD, Zheng S, Go AS: Elevated BP after AKI. *J Am Soc Nephrol* 27: 914–923, 2016 https://doi.org/10.1681/ASN.2014111114
8. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators: Epidemiology of acute kidney injury in critically ill children and young adults. *N Engl J Med* 376: 11–20, 2017
9. Rocco MV, Sink KM, Lovato LC, Wolfgram DF, Wiegmann TB, Wall BM, Umanath K, Rahbari-Oskoui F, Porter AC, Pisoni R, Lewis CE, Lewis JB, Lash JP, Katz LA, Hawfield AT, Haley WE, Freedman BI, Dwyer JP, Drawz PE, Dobre M, Cheung AK, Campbell RC, Bhatt U, Beddhu S, Kimmel PL, Reboussin DM, Chertow GM; SPRINT Research Group: Effects of intensive blood pressure treatment on acute kidney injury events in the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis* 71: 352–361, 2018 https://doi.org/10.1053/j.ajkd.2017.08.021
10. Grams ME, Waikar SS, MacMahon B, Whelton S, Ballew SH, Coresh J: Performance and limitations of administrative data in the identification of AKI. *Clin J Am Soc Nephrol* 9: 682–689, 2014 https://doi.org/10.2215/CJN.07650713
11. Lafrance JP, Djurdjev O, Levin A: Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. *Nephrol Dial Transplant* 25: 2203–2209, 2010 https://doi.org/10.1093/ndt/gfq011
12. Hobbs H, Bassett P, Wheeler T, Bedford M, Irving J, Stevens PE, Farmer CK: Do acute elevations of serum creatinine in primary care engender an increased mortality risk? *BMC Nephrol* 15: 206, 2014 https://doi.org/10.1186/1471-2369-15-206
13. Sawhney S, Fluck N, Fraser SD, Marks A, Prescott GJ, Roderick PJ, Black C: KDIGO-based acute kidney injury criteria operate differently in hospitals and the community-findings from a large population cohort. *Nephrol Dial Transplant* 31: 922–929, 2016 https://doi.org/10.1093/ndt/gfw052
14. Leither MD, Murphy DP, Bicknese L, Reule S, Vock DM, Ishani A, Foley RN, Drawz PE: The impact of outpatient acute kidney injury on mortality and chronic kidney disease: A retrospective cohort study. *Nephrol Dial Transplant* 34: 493–501, 2019 https://doi.org/10.1093/ndt/gfy036
15. Drawz PE, Agarwal A, Dwyer JP, Horwitz E, Lash J, Lenoir K, McWilliams A, Oparil S, Rahbari-Oskoui F, Rahman M, Parkulo MA, Pemu P, Raj DS, Rocco M, Soman S, Thomas G, Tuot DS, Whelton PK, Pajewski NM: Concordance between blood pressure in the systolic blood pressure intervention trial and in routine clinical practice. *JAMA Intern Med* 180: 1655–1663, 2020 https://doi.org/10.1001/jamainternmed.2020.5028
16. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, Grams ME, Greene T, Grubb A, Gudnason V, Gutiérrez OM, Kalil R, Karger AB, Mauer M, Navis G, Nelson RG, Poggio ED, Rodby R, Rossing P, Rule AD, Selvin E, Seegmiller JC, Shlipak MG, Torres VE, Yang W, Ballew SH, Couture SJ, Powe NR, Levey AS; Chronic Kidney Disease Epidemiology Collaboration: New creatinine- and cystatin c-based equations to estimate GFR without race. *N Engl J Med* 385: 1737–1749, 2021 https://doi.org/10.1056/NEJMoa2102953
17. Johnson KC, Whelton PK, Cushman WC, Cutler JA, Evans GW, Snyder JK, Ambrosius WT, Beddhu S, Cheung AK, Fine LJ, Lewis CE, Rahman M, Reboussin DM, Rocco MV, Oparil S, Wright JT Jr; SPRINT Research Group: Blood pressure measurement in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension* 71: 848–857, 2018 https://doi.org/10.1161/HYPERTENSIONAHA.117.10479
18. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf. Accessed May 24, 2022
19. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT; SPRINT Research Group: A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 373: 2103–2116, 2015 https://doi.org/10.1056/NEJMoa1511939
20. Glidden DV, Vittinghoff E: Modelling clustered survival data from multicentre clinical trials. *Stat Med* 23: 369–388, 2004 https://doi.org/10.1002/sim.1599
21. Grambsch P, Therneau T: Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 81: 515–526, 1994
22. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94: 496–509, 1999
23. Scheike TH, Zhang MJ: Analyzing competing risk data using the R timereg package. *J Stat Softw* 38: i02, 2011
24. van Buuren S, Groothuis-Oudshoorn K: mice: multivariate imputation by chained equations in R. *J Stat Softw* 45: 1–67, 2011

Received: February 23, 2022 **Accepted:** April 18, 2022

See related editorial, "Is There One Best Way to Define AKI?," on pages 1132–1133.

AFFILIATIONS

[1]Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, Minnesota
[2]Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Winston-Salem, North Carolina
[3]Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida
[4]Division of General Internal Medicine, Brody School of Medicine, East Carolina University, Greenville, North Carolina
[5]Division of Kidney Diseases and Hypertension, George Washington University, Washington, DC
[6]Division of Nephrology and Hypertension, Department of Internal Medicine, University of Utah Health, Salt Lake City, Utah
[7]Department of Medicine, Veterans Affairs Central California Health Care System, Fresno, California
[8]Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan
[9]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana
[10]Division of Nephrology, University of Illinois at Chicago, Chicago, Illinois
[11]Renal Division, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia
[12]Case Western Reserve University, University Hospitals Cleveland Medical Center, Cleveland, Ohio
[13]Department of Medicine, Division of Community Internal Medicine, Mayo Clinic, Jacksonville, Florida
[14]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina
[15]Department of Internal Medicine and Center for Outcomes Research and Evaluation, Atrium Health, Charlotte, North Carolina
[16]Division of Nephrology & Hypertension, University of Utah Health, Salt Lake City, Utah
[17]Department of Kidney Medicine, Cleveland Clinic, Cleveland, Ohio
[18]Case Western Reserve University, University Hospitals Cleveland Medical Center, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio
[19]Department of Medicine, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama
[20]Case Western Reserve University, MetroHealth Medical Center, Cleveland, Ohio
[21]Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota