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Effect of Intensive vs Standard Blood Pressure Control on Acute Kidney Injury and Subsequent Cardiovascular Outcomes and Mortality: Findings from the SPRINT EHR Study

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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 EHR data, may be more sensitive and less biased than traditional SAE adjudication.

Abstract:
Background: Adjudication of inpatient acute kidney injury (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 vs. standard blood pressure (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: 3644 participants had linked EHR data. A greater number of inpatient AKI events were identified using EHR labs (187 intensive vs 155 standard) as compared to serious adverse event (SAE) adjudication in the trial (95 intensive vs 61 standard). Intensive treatment increased risk for SPRINT-adjudicated inpatient AKI (HR 1.51, 95% CI 1.09 - 2.08) and for creatinine-based outpatient AKI (HR 1.40, 95% CI 1.15 - 1.70), but not for creatinine-based inpatient AKI (HR 1.20, 0.97 - 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.

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Effect of Intensive vs Standard Blood Pressure Control on Acute Kidney Injury and Subsequent Cardiovascular Outcomes and Mortality: Findings from the SPRINT EHR Study

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Key Points

- Identifying ways to prevent AKI may reduce mortality further in the setting of intensive BP control.
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Abstract

Background: Adjudication of inpatient acute kidney injury (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 vs. standard blood pressure (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: 3644 participants had linked EHR data. A greater number of inpatient AKI events were identified using EHR labs (187 intensive vs 155 standard) as compared to serious adverse event (SAE) adjudication in the trial (95 intensive vs 61 standard). Intensive treatment increased risk for SPRINT-adjudicated inpatient AKI (HR 1.51, 95% CI 1.09 – 2.08) and for creatinine-based outpatient AKI (HR 1.40, 95% CI 1.15 – 1.70), but not for creatinine-based inpatient AKI (HR 1.20, 0.97 – 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.

Introduction

Intensive blood pressure (BP) control increased risk for inpatient acute kidney injury (AKI) in the Systolic Blood Pressure Intervention Trial (SPRINT).[1] In observational studies, AKI is associated with increased risk for multiple adverse outcomes, including chronic kidney disease (CKD), progression of CKD, end-stage kidney disease (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 compared with standard treatment.[1]

Adjudication of AKI in SPRINT was based on International Classification of Diseases (ICD) diagnosis codes, admission history and physicals, and discharge summaries.[9] A similar approach was shown to be only ~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. While 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 assessed in the emergency department 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 EHR data from 47 participating clinic sites. The objectives of the current 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.

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 trial 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 utilized existing trial and EHR data.

SPRINT baseline and follow-up data collection

As previously described, data collected at baseline included self-reported race or ethnicity (as required by the National Institutes of Health) 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 estimated glomerular filtration

rate (eGFR).[16] Trained study coordinators followed an American Heart Association adherent protocol to measure BP.[17] Participant reports of adverse events, including hospitalizations, emergency department visits, and other health outcomes of interest, were ascertained at quarterly visits.[9]

Electronic health record data

We have described this study's methods for linking the SPRINT and EHR data.[15] The current analysis is based on 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 based on names, codes, and result values. Creatinine measurements were classified as outpatient if they were not concurrent with a SPRINT-reported emergency department (ED) or hospitalization serious adverse event, 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 a) the SPRINT definition which utilized serious adverse event reports based on diagnosis codes and review of admission and discharge notes[9] and b) a creatinine-based definition of a 50% or ≥ 0.3 mg/dl increase in EHR creatinine values during an ED visit or hospitalization compared to baseline. Outpatient AKI was defined by a 50% increase in outpatient creatinine using trial and EHR labs. 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 (KDIGO)

criteria.[18] Cardiovascular events were defined per the trial protocol as the first occurrence of fatal or non-fatal myocardial infarction (MI), non-MI acute coronary syndrome (non-MI ACS, sometimes called unstable angina), fatal or non-fatal stroke, fatal or non-fatal heart failure (HF), or death attributable to CVD.[1] Mortality was ascertained in SPRINT using a standard protocol.[19]

Statistical Methods

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 based on Schoenfeld residuals.[21] We examined the association of incident AKI with subsequent CVD and all-cause mortality. These analyses were also based on 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, as well as the following baseline characteristics: age, sex, race/ethnicity, smoking status (current, former, or never smoker), history of cardiovascular disease, systolic and diastolic blood pressure, eGFR based on the 2021 CKD-EPI study creatinine-based equation,[16] log of urine albumin to creatinine ratio, statin use, and use of either ACE inhibitors or angiotensin II receptor blockers. To address a small degree of missing data at baseline with eGFR (N=10) and UACR (N=151), we utilized chained multiple imputation based on 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 following outpatient AKI in two ways. First, we modeled the trajectory of outpatient eGFR in the year preceding and following an outpatient AKI event using linear mixed models. In these analyses, we flexibly modeled eGFR as a function of time using B-

splines separately 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 above 30% of the pre-AKI serum creatinine concentration), with full recovery 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 of death. All analyses were performed using the R Statistical Computing Environment, utilizing the *timereg* and *mice* packages.[23, 24]

Results

Of the 5462 participants enrolled at the sites participating in the SPRINT EHR ancillary, 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 age was 69 ± 9 (SD) years, 24% were female, 30% were Black participants, and the mean estimated glomerular filtration rate (eGFR) was 71 ± 20 (SD) ml/min1.73m^2. Compared to the trial participants not included in the current analyses, participants in the current analyses were older, less likely to be female, and more likely to be taking a statin (**eTable 1**).

During a median of 4.01 years of follow-up, the median number of outpatient EHR creatinine measurements from routine care was 6 (Interquartile range: 3 to 11) and similar in the two treatment arms. The median number of trial creatinine measurements was 10 (Interquartile range: 9 to 12). Among the 3644 participants included in the current 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 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 (**eTable 3**).[18]

More inpatient AKI events were identified using EHR creatinine values compared with the number identified through the trial adjudication process (187 vs 95 in the intensive treatment group and 155 vs 61 in the 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 amongst 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 for partial recovery (comparing intensive to standard) is 0.99 (95% CI: 0.78 to 1.24); the subdistribution hazard ratio for full recovery is 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% confidence interval (CI) 1.09 to 2.08; **Table 2**). However, for creatinine-based inpatient AKI, intensive treatment was associated with an attenuated and non-significant 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; **Table 2 and Figure 4**). Results were similar in analyses accounting for the competing risk of mortality (**eTable 2**).

Inpatient AKI was associated with an increased risk for all-cause mortality when defined by SPRINT adjudication (HR 3.57, 95% CI 2.29 to 5.56) and the EHR creatinine-based definition (HR 5.57, 95% CI 3.96 to 7.84; **Table 3**). However, creatinine-based inpatient AKI events were associated with increased risk for cardiovascular events (HR 1.74, 95% CI 1.15 to 2.65), while SPRINT-adjudicated inpatient AKI was not (HR 1.10, 95% CI 0.61 to 2.01). Creatinine-based outpatient AKI was associated with an increased risk for all-cause mortality (HR 2.74, 95% CI 1.87 to 4.02) but not cardiovascular events (HR 1.44, 95% CI 0.97 to 2.13).

Discussion

By linking EHR data with trial data in SPRINT, we were able to utilize 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, multi-center study to evaluate the impact of intensive BP control on AKI based on ICD/document-based adjudication compared to a creatinine-based definition of AKI. Our results demonstrate the under-ascertainment 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 demonstrating chart-based adjudication of AKI has a sensitivity of only ~20%.[10] The increase in creatinine-based inpatient AKI events was relatively greater in the standard treatment group, resulting in a non-significant 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 the current 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 cardiovascular disease 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 to the overall trial due to the inclusion of EHR data from a large number of Veterans Affairs Medical Centers.

Conclusions

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

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Lenoir: Formal analysis; Writing - review and editing. Maritza Suarez: Writing - review and editing. James Powell: Writing - review and editing. Dominic Raj: Writing - review and editing. Srinivasan Beddhu: Writing - review and editing. Anil Agarwal: Writing - review and editing. Sandeep Soman: Writing - review and editing. Paul Whelton: Writing - review and editing. James Lash: Writing - review and editing. Frederic Rahbari-Oskoui: Writing - review and editing. Mirela Dobre: Writing - review and editing. Mark Parkulo: Writing - review and editing. Michael Rocco: Writing - review and editing. Andrew McWilliams: Writing - review and editing. Jamie Dwyer: Writing - review and editing. George Thomas: Writing - review and editing Mahboob Rahman: Writing - review and editing. Suzanne Oparil: Writing - review and editing Edward Horwitz: Writing - review and editing. Nicholas Pajewski: Formal analysis; Methodology; Supervision; Validation; Writing - review and editing. Areef Ishani: Supervision; Writing - review and editing. All authors revised the paper and approved the final version of the manuscript.

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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 (49.7)	907 (50.5)
Age, yr		
Mean ± SD	69.1 ± 9.2	68.7 ± 9.4
≥75, n (%)	590 (31.9)	568 (31.6)
Female sex, n (%)	464 (25.1)	413 (23.0)
Race/Ethnicity, n (%)		
Black	550 (29.7)	559 (31.1)
Hispanic	91 (4.9)	58 (3.2)
White	1179 (63.8)	1162 (64.7)
Other	29 (1.6)	16 (0.9)
Smoking status, n (%)		
Current smoker	239 (12.9)	237 (13.2)
Former smoker	898 (48.6)	878 (48.9)
Never smoker	712 (38.5)	680 (37.9)
BMI, mean ± SD, kg/m^2	30.1 ± 5.8	30.0 ± 5.7
History of cardiovascular disease, n (%)	434 (23.5)	447 (24.9)
Blood pressure, mean ± SD, mm Hg		
Systolic	137.8 ± 15.2	137.67 ± 14.9
Diastolic	77.0 ± 11.4	76.9 ± 11.6
Orthostatic hypotension, n (%)	124 (6.7)	120 (6.7)
eGFR, ml/min/1.73 m^2		
Mean ± SD	71.0 ± 19.6	71.2 ± 19.3
<60, n (%)	548 (29.7)	518 (28.9)
Urine albumin to creatinine ratio, median [IQR], mg/g	9.9 [5.8 to 24.9]	9.7 [5.6 to 23.6]
HDL cholesterol, mean ± SD, mg/dL	51.8 ± 13.8	51.1 ± 13.8
Triglycerides, median [IQR], mg/dL	106 [76 to 145]	109 [79 to 154]
Glucose, mean ± SD, mg/dL	99.5 ± 13.3	99.4 ± 13.4
No. of antihypertensive agents, mean (SD)	1.9 ± 1.0	1.9 ± 1.0
Statin use, n (%)	905 (48.9)	951 (53.0)
Use of ACE inhibitor or Angiotensin receptor blocker, n (%)	1059 (57.3)	1066 (59.4)

Note. “Other” race/ethnicity includes self-reported American Indian, Alaska Native, Native Hawaiian, Pacific Islander, Asian, and Other. Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; eGFR, estimated glomerular filtration rate based on the 2021 CKD-EPI creatinine equation; HDL, high-density lipoprotein; IQR, interquartile range; SD, standard deviation.

TABLE 2. Effect of intensive treatment on the incidence of acute kidney injury

Population	Outcome	Intensive Events / Rate per 1000 PY	Standard Events / Rate per 1000 PY	Hazard Ratio (95% CI)	P value
All participants (n=9361)	Inpatient AKI based on SAE	179 / 10.4	109 / 6.3	1.65 (1.30, 2.10)	<0.001
EHR Ancillary Study (n=3644)	Inpatient AKI based on SAE	95 / 13.6	61 / 9.0	1.51 (1.09, 2.08)	0.01
EHR Ancillary Study (n=3644)	Inpatient AKI (creatinine-based)	187 / 26.9	155 / 23	1.20 (0.97, 1.48)	0.10
EHR Ancillary Study (n=3644)	Outpatient AKI (creatinine-based)	243 / 36.0	173 / 25.8	1.40 (1.15, 1.70)	0.001

CI, confidence interval; EHR, electronic health record; PY, person-years of follow-up; SAE serious adverse event as adjudicated in SPRINT. Hazard ratio based on Cox proportional hazards regression with the baseline hazard function stratified by clinic site.

TABLE 3. Association of acute kidney injury with incident cardiovascular disease and all-cause mortality

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

AKI, Acute Kidney Injury; CI, confidence interval; CVD, cardiovascular disease; PY, person-years; SAE, serious adverse event. *Follow-up time computed from the occurrence of AKI. Primary CVD composite outcome includes non-fatal myocardial infarction, acute coronary syndrome, stroke, heart failure, and CVD death. Hazard ratio based on 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 to creatinine ratio, systolic and diastolic blood pressure, use of ACE inhibitors or angiotensin receptor blockers, and statin use (all at baseline).

Figure legends

FIGURE 1. CONSORT Diagram

FIGURE 2. Trajectory of Outpatient estimated Glomerular Filtration Rate amongst Participants who Experienced an Outpatient Acute Kidney Injury Event by Treatment Group

Abbreviations: AKI, acute kidney injury; eGFR, estimated Glomerular Filtration Rate based on the 2021 CKD-EPI creatinine equation. Estimates based on 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 confidence intervals.

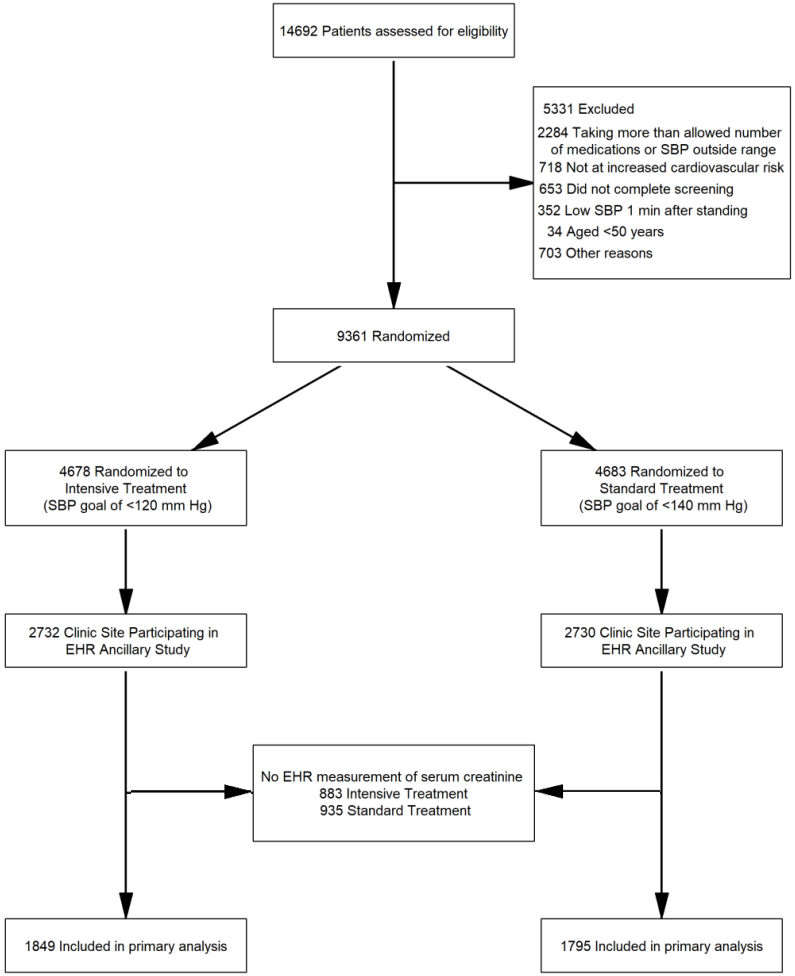
FIGURE 3. Recovery of Kidney Function Following Outpatient Acute Kidney Injury Accounting for the Competing Risk of Death

Abbreviations: AKI, acute kidney injury. 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 point-wise 95% confidence intervals.

FIGURE 4. Incidence of Outpatient Acute Kidney Injury by Treatment Group

Shaded areas denotes point-wise 95% confidence intervals.

Figures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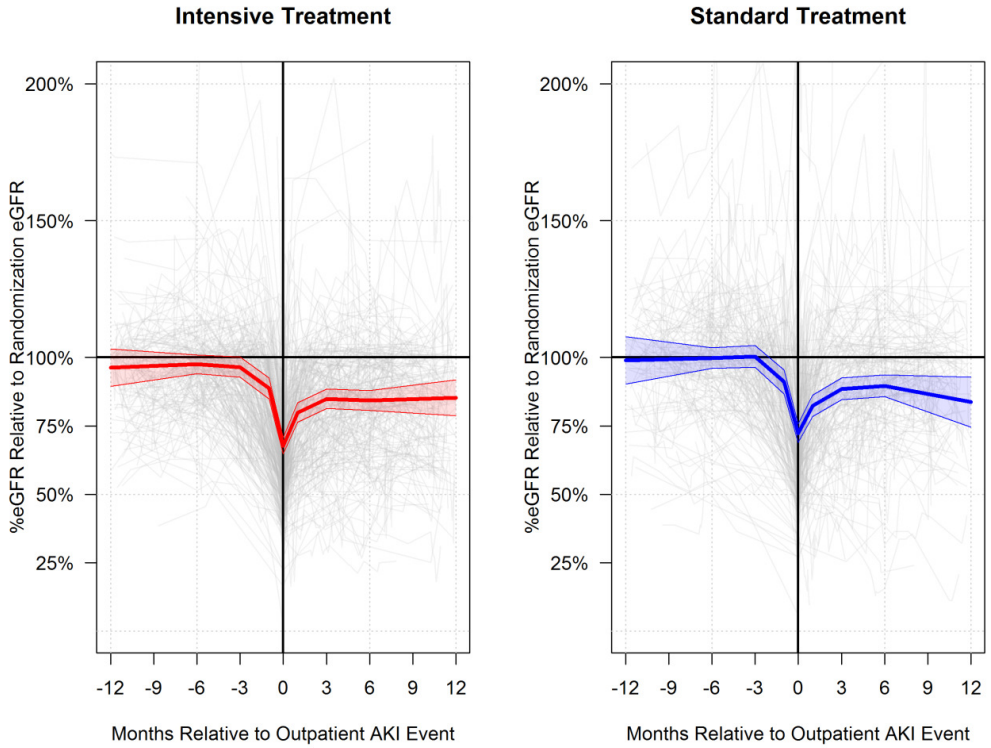
2284 Taking more than allowed number of medications or SBP outside range
718 Not at increased cardiovascular risk
653 Did not complete screening
352 Low SBP 1 min after standing
34 Aged <50 years
703 Other reasons
9361 Randomized
4678 Randomized to Intensive Treatment (SBP goal of <120 mm Hg)
4683 Randomized to Standard Treatment (SBP goal of <140 mm Hg)
2732 Clinic Site Participating in EHR Ancillary Study
2730 Clinic Site Participating in EHR Ancillary Study
No EHR measurement of serum creatinine
883 Intensive Treatment
935 Standard Treatment
1849 Included in primary analysis
1795 Included in primary analysis

Figures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150%
100%
75%
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3
6
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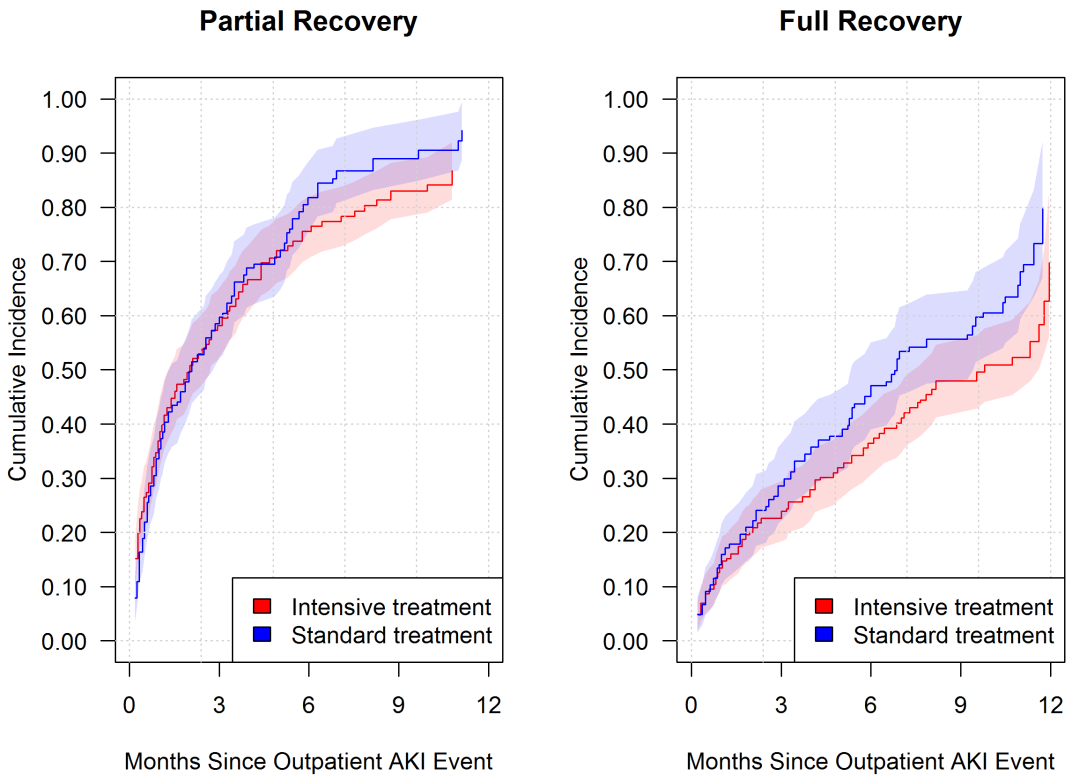
Months Relative to Outpatient AKI Event

Figures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3
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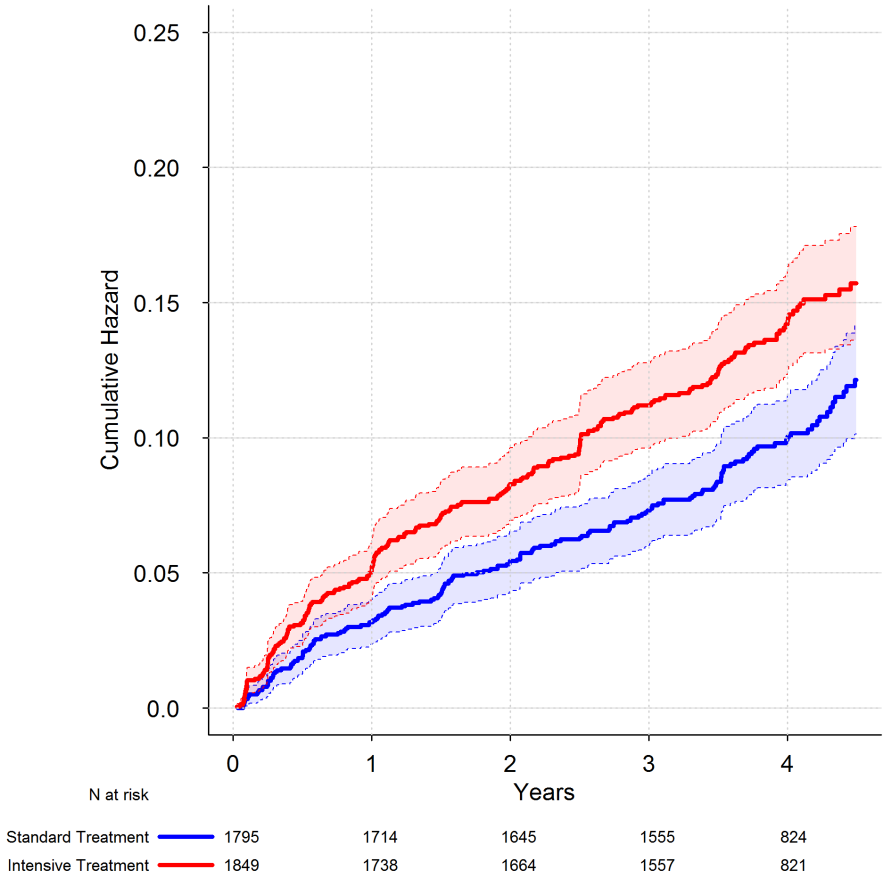
9
12
Months Since Outpatient AKI Event
Intensive treatment
Standard treatment

Figures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0.10
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Cumulative Hazard
0
1
2
3
4
Years
N at risk
Standard Treatment
1795
1714
1645
1555
824
Intensive Treatment
1849
1738
1664
1557
821

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eTABLE 1. Baseline Characteristics of Participants included in the Electronic Health Record (EHR) Ancillary Study versus Remaining Trial Participants at EHR Ancillary Study Sites

Characteristic	EHR Ancillary Study N=3644	Not in EHR Ancillary Study N=1818	P value
Randomized to intensive treatment, No. (%)	1849 (50.7)	883 (48.6)	0.14
Age, yr			
Mean ± SD	68.9 ± 9.3	67.3 ± 9.6	<0.001
≥75, n (%)	1158 (31.8)	453 (24.9)	<0.001
Female sex, n (%)	877 (24.1)	709 (39.0)	<0.001
Race/Ethnicity, n (%)			<0.001
White	2341 (64.2)	1018 (56.0)	
Black	1109 (30.4)	652 (35.9)	
Hispanic	149 (4.1)	105 (5.8)	
Other	45 (1.2)	43 (2.4)	
Smoking status, n (%)			<0.001
Current smoker	476 (13.1)	277 (15.2)	
Former smoker	1776 (48.7)	733 (40.3)	
Never smoker	1392 (38.2)	808 (44.4)	
BMI, mean ± SD, kg/m^2	30.0 (5.7)	29.7 (5.6)	0.03
History of cardiovascular disease, n (%)	881 (24.2)	324 (17.8)	<0.001
Blood pressure, mean ± SD, mm Hg			
Systolic	137.7 ± 15.0	140.0 ± 16.6	<0.001
Diastolic	76.9 ± 11.5	78.5 ± 12.3	<0.001
Orthostatic hypotension, n (%)	244 (6.7)	124 (6.9)	0.90
eGFR, ml/min/1.73 m^2			
Mean ± SD	71.1 ± 19.5	74.3 ± 18.7	<0.001
<60, No. (%)	1066 (29.3)	413 (22.9)	<0.001
Urine albumin to creatinine ratio, median [IQR], mg/g	9.8 [5.7 to 24.2]	9.2 [5.6, 20.0]	0.02
HDL cholesterol, mean ± SD, mg/dL	51.5 ± 13.8	53.5 ± 14.9	<0.001
Triglycerides, median [IQR], mg/dL	108 [78 to 150]	100 [73 to 142]	<0.001
Glucose, mean ± SD, mg/dL	99.5 ± 13.3	99.0 ± 14.4	0.25
No. of antihypertensive agents, mean ± SD	1.9 ± 1.0	1.8 ± 1.1	<0.001
Statin use, n (%)	1856 (50.9)	708 (38.9)	<0.001
Use of ACE inhibitor or Angiotensin receptor blocker, n (%)	2125 (58.3)	1024 (56.3)	0.17

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; eGFR, estimated glomerular filtration rate based on the 2021 CKD-EPI creatinine equation; HDL, high-density lipoprotein; IQR, interquartile range; SD, standard deviation.

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

		Intensive	Standard		
Population	Outcome	Events / Cum Inc at 3.8 Yrs	Events / Cum Inc at 3.8 Yrs	Hazard Ratio (95% CI)	P value
All participants (N=9361)	Inpatient AKI based on SAE	179 / 3.8%	109 / 2.4%	1.69 (1.30, 2.20)	<0.001
EHR Ancillary Study (N=3644)	Inpatient AKI based on SAE	95 / 5.2%	61 / 3.4%	1.57 (1.13, 2.19)	0.007
EHR Ancillary Study (N=3644)	Outpatient AKI (Trial+EHR Labs)	243 / 12.4%	173 / 8.9%	1.48 (1.20, 1.82)	<0.001
EHR Ancillary Study (N=3644)	Outpatient AKI (Trial Labs Only)	130 / 6.9%	78 / 4.4%	1.66 (1.28, 2.16)	<0.001
EHR Ancillary Study (N=3644)	Inpatient AKI (EHR Labs)	187 / 9.6%	155 / 8.1%	1.15 (0.91, 1.46)	0.24

CI, confidence interval; Cum Inc, cumulative incidence; EHR, electronic health record, SCr: serum creatinine. Hazard ratio based on the Fine-Gray subdistribution hazard model accounting for the competing risk of death.

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

Outpatient AKI (creatinine-based)			
	Intensive Treatment Events (%)	Standard Treatment Events (%)	P value=0.73
AKI stage 1	208 (85.6%)	152 (87.9%)	
AKI stage 2	29 (11.9%)	16 (9.2%)	
AKI stage 3	6 (2.5%)	5 (2.9%)	
Inpatient AKI (creatinine-based)			
	Intensive Treatment Events (%)	Standard Treatment Events (%)	P value=0.05
AKI stage 1	146 (78.1%)	129 (83.2%)	
AKI stage 2	31 (16.6%)	13 (8.4%)	
AKI stage 3	10 (5.3%)	13 (8.4%)	

AKI, acute kidney injury. AKI stage 1 = serum creatinine ≥0.3 mg/dl or 1.5 to <2.0 times baseline serum creatinine, AKI stage 2 = ≥2.0 but <3.0 times baseline, and AKI stage 3 = ≥3.0 times baseline. Stage 1 outpatient AKI did not include those with only a ≥0.3 mg/dl increase. P values based on Fisher's exact test comparing distribution of AKI severity by treatment group.