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Author manuscript

*Mayo Clin Proc.* Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

*Mayo Clin Proc.* 2020 November ; 95(11): 2408–2419. doi:10.1016/j.mayocp.2020.03.035.

## Hyperkalemia and Acute Kidney Injury with Spironolactone Use Among Patients with Heart Failure

**Alex M. Secora, PhD,**

Johns Hopkins University Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD

**Jung-Im Shin, MD, PhD,**

Johns Hopkins University Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD

**Yao Qiao, MPH,**

Johns Hopkins University Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD

**G. Caleb Alexander, MD, MS,**

Johns Hopkins University Bloomberg School of Public Health, Division of General Internal Medicine, Department of Medicine, Johns Hopkins Medicine, Baltimore, MD

**Alex R. Chang, MD, MS,**

Division of Nephrology, Geisinger Health System, Danville, PA

**Leslie A. Inker, MD, MS,**

Tufts Medical Center, Department of Internal Medicine, Division of Nephrology, Boston, MA

**Josef Coresh, MD, PhD,**

Johns Hopkins University Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD

**Morgan E. Grams, MD, PhD**

Johns Hopkins University Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD, Division of Nephrology, Department of Medicine, Johns Hopkins Medicine, Baltimore, MD

### Abstract

**Correspondence:** Address to Alex M. Secora, PhD, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205 (asecora1@jhu.edu).

**Potential Competing Interests:** Dr Shin is a principal investigator of a grant provided to the Johns Hopkins Bloomberg School of Public Health from Merck. Dr Alexander is past Chair of the US Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; serves as a consultant and holds equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Dr. Inker has consulting agreements with Tricida and Omeros Corp. The remaining authors report no potential competing interests.

#### SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Objective:** To quantify the risk of hyperkalemia and acute kidney injury (AKI) when spironolactone use is added on to loop diuretic use among patients with heart failure, and to evaluate whether the risk is modified by level of kidney function.

**Methods:** We identified 17,110 patients with heart failure treated with loop diuretics between January 1, 2004, and December 31, 2016 within the Geisinger Health System. We estimated the incidence of hyperkalemia and AKI associated with spironolactone initiation, and used target trial emulation methods to minimize confounding by indication.

**Results:** During a mean follow-up of 134 mo, 3229 of 17,110 patients (18.9%) initiated spironolactone. Incidence rates of hyperkalemia and AKI in patients using spironolactone with a loop diuretic were 2.9 and 10.1 events per 1000 person-months, respectively. In propensity score-matched analyses, spironolactone initiation was associated with higher hyperkalemia and AKI risk compared with loop alone (hazard ratio, 1.69; 95% CI, 1.35 to 2.10;  $P < .001$ , and hazard ratio, 1.12; 95% CI, 1.00 to 1.26;  $P = .04$ , respectively). There were no differences in the relative risk of either outcome associated with spironolactone by level of kidney function.

**Conclusion:** The addition of spironolactone to loop diuretics in patients with heart failure was associated with higher risk of hyperkalemia and AKI; these risks must be weighed against the potential benefits of spironolactone.

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Spironolactone is an aldosterone antagonist indicated for the treatment of New York Heart Association functional class III-IV heart failure with reduced ejection (HFrEF).<sup>1</sup> Concomitant spironolactone and loop diuretic use decreased heart failure hospitalization and mortality among patients with HFrEF in the landmark Randomized Aldactone Evaluation Study (RALES) study.<sup>2</sup> Evidence for spironolactone's effectiveness among patients with heart failure with preserved ejection (HFpEF) is less established,<sup>3</sup> but data from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial suggest a benefit for spironolactone in HFpEF, with a protective effect for heart failure hospitalization but not mortality.<sup>4</sup> Nevertheless, any benefits associated with spironolactone must be weighed in the context of its known serious risks, specifically hyperkalemia and acute kidney injury (AKI).<sup>1,5-13</sup>

Most prior clinical trials of spironolactone focused on patient populations with relatively preserved kidney function. In both RALES and TOPCAT, patients with estimated glomerular filtration rate (eGFR) less than 30 mL/min per 1.73 m<sup>2</sup>, serum creatinine (SCr) greater than 2.5 mg/dL, and serum potassium (K) greater than 5.0 mEq/L were excluded.<sup>2,4</sup> In addition, patients' SCr and K levels were regularly monitored, allowing for dose adjustments and discontinuation that may have mitigated the risk of hyperkalemia and AKI. The risks of spironolactone in less-controlled, real-world settings are not well understood, particularly among those with reduced kidney function who are already at higher risk for hyperkalemia and AKI.

Despite current clinical guidelines recommending aldosterone antagonists only at eGFR greater than 30 mL/min per 1.73 m<sup>2</sup>,<sup>14,15</sup> patients are prescribed spironolactone across all levels of eGFR.<sup>16</sup> Randomized controlled trials are ongoing to better understand whether aldosterone antagonists provide cardiovascular and renal benefit in patients with advanced chronic kidney disease (CKD).<sup>17</sup> Given the existing use, and the potential for expanded use

in patients with HFpEF and lower kidney function, the real-world safety profile of spironolactone must be assured. Because spironolactone is commonly used in addition to loop diuretics and the latter may also modify the risks of hyperkalemia and AKI, we quantified the absolute and relative risks of hyperkalemia and AKI associated with spironolactone use among a population of patients with heart failure on loop diuretics and evaluated for differential risk by level of kidney function.

## METHODS

### Data Source and Population

We used integrated electronic health record (EHR) data from the Geisinger Health System (Geisinger) in Pennsylvania. These EHR data include inpatient and outpatient records for patients receiving their primary care at Geisinger, as well as medication orders, medication reconciliation, and laboratory results. We included patients age 18 years or older with a heart failure diagnosis code from inpatient or outpatient records, and a subsequent outpatient prescription for a loop diuretic from January 1, 2004, to December 31, 2016 (Supplemental Table 1, available online at <http://www.mayoclinicproceedings.org>). We excluded patients with end-stage renal disease, those with spironolactone use before the first loop diuretic order in the data, and patients without an antecedent SCr or K level. This study was approved by the Johns Hopkins University Institutional Review Board and the Geisinger Medical Center Institutional Review Board.

### Study Designs and Exposure Definitions

To determine the incidence of hyperkalemia and AKI during real-world use of spironolactone in heart failure, we performed an as-treated analysis, with patients' time at risk ( $T_0$ ) starting at the first loop diuretic prescription after their initial heart failure diagnosis. We classified time at risk according to time-varying loop diuretic and spironolactone use (single-ingredient spironolactone or combination spironolactone with hydrochlorothiazide). In the continuous use periods, we allowed for a 30-day gap between the end of one prescription and the start of the next for the same medication, and included a 15-day "washout" period at the end of a continuous use episode where outcomes could still be observed. Primary exposure groups in the time-varying, as-treated analysis were thus loop diuretic use without spironolactone (loop alone), spironolactone use without a loop diuretic (spironolactone alone), concomitant use of both a loop diuretic and spironolactone, and no use of either drug.

To strengthen evidence for a causal relationship between spironolactone and hyperkalemia and AKI we performed a target trial emulation with an intention-to-treat (ITT) design.<sup>18–21</sup> This method, particularly when combined with propensity score matching, helps to minimize confounding by indication, allowing for a direct assessment of the risks associated with spironolactone in comparable patients. We used the ITT principle (ie, treatment assignment/status at baseline is carried forward regardless of subsequent changes to treatment) to analyze a series of "trials" where each trial represents a fixed time window when a patient may or may not begin a specific treatment regimen. To mimic a hypothetical trial selection process, enrollment criteria in each trial (cohort years: [1] 2004e2006, [2]

2007e2009, [3] 2010e2012, and [4] 2013e2016) included heart failure diagnosis, loop diuretic prescription order, no prior spironolactone order, and K level less than 5.0 mEq/L. Within each trial, patients who received an initial spironolactone prescription were compared with eligible patients who did not. Time at risk ( $T_0$ ) began on the date of the first spironolactone prescription for spironolactone users (treatment), and a random loop prescription during that trial period for controls. Control patients were eligible to be treatment or control patients in subsequent trials, whereas treatment patients were no longer eligible due to their previous spironolactone use. In the final analysis, the trial cohorts were pooled to create a combined dataset.

### Study Outcomes

In both the as-treated and ITT analyses, patients were followed until the outcomes of interest (hyperkalemia and AKI), death, last recorded health care encounter date (including inpatient, outpatient, laboratory, or medication order dates), or the end of the study period (December 31, 2016), whichever came first. We defined hyperkalemia by inpatient *International Classification of Disease, Ninth Revision (ICD-9)* or ICD-10 codes 276.7 or E87.5, respectively, and AKI by inpatient ICD-9 or ICD-10 codes 584.9 or N17.9, respectively.

### Kidney Function, Potassium, and Other Covariates

We defined eGFR based on outpatient SCr and the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>22</sup> We classified eGFR using four primary categories ( $\geq 90$  mL/min per  $1.73 \text{ m}^2$ ; 60 to 89 mL/min per  $1.73 \text{ m}^2$ ; 30 to 59 mL/min per  $1.73 \text{ m}^2$ ; and  $<30$  mL/min per  $1.73 \text{ m}^2$ ), and as linear splines with a knot at 60 mL/min per  $1.73 \text{ m}^2$ . We classified serum K levels using three categories ( $<3.5$  mEq/L; 3.5 to 4.9 mEq/L; and  $>5.0$  mEq/L), and as linear splines with knots at 3.5 mEq/L and 4.9 mEq/L; in the ITT analysis, only one knot was used (3.5 mEq/L). Baseline SCr and K were considered the closest measurements to  $T_0$  within the window of 365 days before to 7 days after that date. If there was no available outpatient SCr or K, we used available inpatient SCr or K within the same window.

Other medications were captured as prescriptions that overlapped  $T_0$  and were modeled as time-fixed variables; the exception was angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use, which was modeled as a time-varying variable in the as-treated analysis. We defined comorbidities using ICD-9/10 diagnosis codes in the EHR (Supplemental Table 1). We also calculated patients' Charlson comorbidity index (CCI) score.<sup>23,24</sup>

### Statistical Analysis

We calculated frequencies, means, and proportions of the primary analytic cohorts' characteristics at  $T_0$ , including demographics, comorbidities, and prior medication use. We also stratified cohort characteristics by ever/never spironolactone initiators (in as-treated analyses), and cohort "trial" years (in ITT analyses), and we assessed for trends using logistic and linear regression for binary and continuous variables, respectively. We calculated incidence rates for hyperkalemia and AKI (per 1000 PMs) by as-treated exposure groups, both overall and stratified by time-varying eGFR category. We also calculated and

plotted cumulative incidence of hyperkalemia and AKI over 3 years after T<sub>0</sub> in the ITT analyses, incorporating the competing event of death, and stratifying by eGFR.

We used time-to-event Fine and Gray regression models to estimate subdistribution hazards ratios (sHR) accounting for the competing risk of death.<sup>25</sup> Comparing exposure groups in as-treated analyses, we used unadjusted and fully adjusted models with time-fixed covariates, as well as adjusted models where eGFR, K, and ACEi/ARB use were included as time-varying covariates. In as-treated analyses, we tested for an interaction between time-varying eGFR (linear spline) and exposure group. In ITT analyses comparing treatment with control groups, we used unadjusted and fully adjusted models, as well as adjusted models weighted by the inverse probability of treatment weighting (IPTW), and 1:1, “nearest-neighbor” propensity score (PS) matched analyses using calipers of 0.014 (0.2 times the standard deviation of log-transformed PS); after matching, all standardized mean differences were less than 0.10. In the ITT analyses, we also tested for an interaction between T<sub>0</sub> eGFR (linear spline) and treatment. We used robust variance estimators to account for within-person correlation. To assess for heterogeneity of effect among cohort trial years in the ITT analyses, we tested for an interaction between trial and treatment status, and found no statistically significant interaction.

We adjusted final models for age, sex, race (non-white), eGFR (linear splines), K (linear splines), time with heart failure, year of first loop order, CCI, history of hyperkalemia, history of AKI, cardiovascular disease (CVD), peripheral artery disease (PAD), diabetes mellitus, cancer, cirrhosis, ascites, atrial fibrillation, proteinuria, and prior use of anticoagulants, ACEi, ARB, other antihypertensives (combined: beta-blocker, calcium channel blockers, vasodilators), antiarrhythmics, cardiac glycosides, statins, thiazide diuretics, and potassium-sparing diuretics (excluding spironolactone). ITT analyses were additionally adjusted by time between the first loop order and T<sub>0</sub>. We used the same covariates to calculate the propensity scores, and we calculated stabilized weights for IPTW analyses.

All analyses were conducted using Stata 15.1 (StataCorp; College Station, TX) and SAS 9.4 (SAS Institute Inc; Cary, NC).

## RESULTS

### Study Population

There were 17,110 patients with heart failure who used loop diuretics during the study period; 50.5% were female (n=8635), 2.4% were non-White (n=414), and the mean  $\pm$  SD age was 73.2  $\pm$  13.0 years (Table 1). Diabetes (46.6%; n=7977) and CVD (66.3%; n=11,347) were common, as was the use of ACEi/ARB (80.2%; n=13,726), statins (66.2%; n=11,331), anticoagulants (59.8%; n=10,233), and other antihypertensives (89.5%; n=15,308). Roughly 19% (n=3229) went on to initiate spironolactone over a mean follow-up of 134 months; these patients were younger and had higher mean eGFRs at baseline compared with never initiators ( $P<.001$  for both).

## Real-World Incidence of Hyperkalemia and AKI

There were 995 hyperkalemia events (7287 deaths) in 681,944 PMs of observation time. Overall, incidence rates (IRs) per 1000 PMs were highest for those on spironolactone without a loop diuretic (IR, 3.3), followed by concomitant loop and spironolactone (IR, 2.9), loop without spironolactone (IR, 1.4), and no use of either (IR, 1.3) (Table 2). In adjusted models with time-varying eGFR, K, and ACEi/ARB use, both concomitant loop and spironolactone, and spironolactone alone, were associated with a more than two-fold increase in the risk of hyperkalemia (sHR, 2.06; 95% CI, 1.70 to 2.49;  $P<.001$  and sHR, 2.28; 95% CI, 1.40 to 3.69;  $P<.001$ , respectively) compared with loop use without spironolactone (Table 3).

There were 4212 AKI events (5387 deaths) in 620,094 PMs of observation time. In contrast with trends in hyperkalemia, IRs per 1000 PMs for AKI were highest for those on concomitant loop and spironolactone (IR, 10.1), followed by loop without spironolactone (IR, 7.4), spironolactone without a loop (IR, 5.3), and no use of either (IR, 4.6). In adjusted models with time-varying covariates, concomitant loop and spironolactone was associated with a 37% increase in the risk of AKI (sHR, 1.37; 95% CI, 1.23 to 1.53;  $P<.001$ ) compared with loop use without spironolactone, but there was no statistically significant difference in risk with spironolactone alone without the use of a loop diuretic (sHR, 0.77; 95% CI, 0.52 to 1.13;  $P=.18$ ).

The absolute risks of hyperkalemia and AKI were higher in lower eGFR categories, but there were no consistent differences in the relative risks associated with spironolactone/loop diuretic therapy versus loop therapy alone by eGFR level in the as-treated analysis (hyperkalemia:  $P$  for interaction  $P=.63$ , and  $P=.61$  for eGFR levels below and above 60 mL/min per 1.73 m<sup>2</sup>, respectively; AKI:  $P$  for interaction  $P=.33$ , and  $P=.92$  for eGFR levels below and above 60 mL/min per 1.73 m<sup>2</sup>, respectively).

## Target Trial Emulation Assessing Add-on Spironolactone Therapy

In the pooled target trial emulation, there were 24,127 patients (treatment group [concomitant loop and spironolactone] = 2,000; control group [loop without spironolactone] = 22,127). More than half (51.8%, n=12,499) were female, and mean  $\pm$  SD age was 73.8  $\pm$  12.7 y (Supplemental Table 2, available online at <http://www.mayoclinicproceedings.org>).

There were 1197 hyperkalemia events (163 in the treatment group) (Table 4), with a 1-year cumulative incidence of 1.7% and 4.0% in the control and treatment groups, respectively. Cumulative incidence of hyperkalemia at 1 year was lowest for patients with T<sub>0</sub> eGFR greater than or equal to 60 mL/min per 1.73m<sup>2</sup> in the control group (1.2%), followed by those with eGFR greater than or equal to 60 mL/min per 1.73m<sup>2</sup> in the treatment group and those with eGFR less than 60 mL/min per 1.73m<sup>2</sup> in the control group (both 2.1%); those with eGFR less than 60 mL/min per 1.73 m<sup>2</sup> in the treatment group had the highest cumulative incidence (6.3%) (Figure 1). In the fully adjusted model (Figure 2), treatment was associated with an increase in the risk of hyperkalemia compared with control (sHR, 1.75; 95% CI, 1.46 to 2.09;  $P<.001$ ), and this was similar when using IPTW (sHR, 1.58;



95% CI, 1.28 to 1.94;  $P < .001$ ) and 1:1 PS-matching ( $n=1976$  in each group; sHR, 1.69; 95% CI, 1.35 to 2.10;  $P < .001$ ).

There were 5582 AKI events (560 in the treatment group), with a 1-year cumulative incidence of 9.5% and 14.9% in the control and treatment groups, respectively. Similar to hyperkalemia, cumulative incidence of AKI at 1 year was lowest for patients with  $T_0$  eGFR greater than or equal to 60 mL/min per 1.73 m<sup>2</sup> in the control group (5.8%), followed by those with eGFR greater than or equal to 60 mL/min per 1.73 m<sup>2</sup> in the treatment group (10.8%), and those with eGFR less than 60 mL/min per 1.73 m<sup>2</sup> in the control group (13.1%); those with eGFR less than 60 mL/min per 1.73 m<sup>2</sup> in the treatment group had the highest cumulative incidence (20.2%). In the fully adjusted model, treatment was associated with an increased risk of AKI compared with control (sHR, 1.18; 95% CI, 1.08 to 1.30;  $P < .001$ ) and this was similar when using 1:1 PS-matching ( $n=1976$  in each group; sHR, 1.12; 95% CI, 1.00 to 1.26;  $P = .04$ ), and IPTW (sHR, 1.21; 95% CI, 1.08 to 1.36;  $P = .001$ ).

Similar to the as-treated analysis, there were no differences in the relative risks of hyperkalemia or AKI associated with spironolactone/loop diuretic therapy versus loop therapy alone by eGFR in the ITT analysis (hyperkalemia:  $P$  for interaction  $P = .31$  and  $P = .43$  for eGFR levels below and above 60 mL/min per 1.73 m<sup>2</sup>, respectively; AKI:  $P$  for interaction  $P = .93$  and  $P = .46$  for eGFR levels below and above 60 mL/min per 1.73 m<sup>2</sup>, respectively).

## DISCUSSION

In this large, real-world cohort of patients with heart failure prescribed loop diuretics, approximately one in five were prescribed spironolactone. The cohort was at high risk for hyperkalemia and AKI, with the highest rates among patients with eGFR less than 60 mL/min per 1.73 m<sup>2</sup>, and those prescribed spironolactone. In a propensity-matched, target trial emulation, we observed a 69% increased risk of hyperkalemia with the addition of spironolactone compared with using loop diuretics alone, and a 12% increased risk of AKI. The relative risks of hyperkalemia and AKI were not modified by renal function in either analysis. These findings are important because relatively little is known about the real-world safety of spironolactone, particularly among a broader heart failure population (HFrEF and HFpEF) across the spectrum of kidney function.

A more complete understanding of spironolactone-associated hyperkalemia and AKI is critical for utilization to expand to higher risk patients excluded from the clinical trials. In RALES, the pivotal study that established spironolactone's effectiveness in HFrEF, the cumulative incidence of hyperkalemia was very modest (~2% in the spironolactone group vs ~1% in placebo among randomized patients over the study period),<sup>2</sup> likely due to the selection of a lower-risk study population by excluding patients based on their SCr and K, and regular monitoring thereafter. Lee et al (2013)<sup>26</sup> found similar crude rates of both hyperkalemia and AKI when restricting their real-world systolic heart failure study cohort to align with the RALES inclusion. Similar inclusion criteria and monitoring were applied in the TOPCAT trial among patients with HFpEF, but cumulative incidence of hyperkalemia was higher (~19% in the spironolactone group vs ~9% in placebo among randomized

patients over the study period) than what was reported in RALES, and drug discontinuation due to “abnormal renal function” was higher for spironolactone patients versus placebo patients (3.9% vs 2.3%, respectively;  $P=.006$ ).<sup>4</sup> Our study results were more consistent with the TOPCAT trial and other studies that included various heart failure sub-populations such as older women and after an acute myocardial infarction showing more pronounced risks with spironolactone use as compared with RALES, except that AKI was more common in our cohort overall.<sup>10,27,28</sup>

As expected, the absolute risk of both hyperkalemia and AKI with spironolactone use increased with lower eGFR; however, we observed no difference in relative risk for hyperkalemia or AKI associated with spironolactone by level of kidney function (interactions not significant in as-treated or ITT). While differences in risk by kidney function could not be explored in RALES and TOPCAT because those with higher SCr were excluded, other studies have observed relatively infrequent and mild spironolactone-associated increases in SCr and K among those with reduced kidney function.<sup>9,29–34</sup> Similar to ACEi and ARB medications, studies have shown an early reduction in eGFR with spironolactone in the setting of CKD and diabetic nephropathy, but this appears to be transient, with little evidence of a persistent reduction in the context of longer-term use.<sup>9,10,26,35–37</sup> Also, among those with heart failure potentially indicated for spironolactone, there are many other common risk factors which can all contribute to hyperkalemia risk independent of one’s kidney function such as older age, diabetes mellitus, volume-depleting illness, and use of ACEi, ARB, and other medications, making spironolactone’s safety challenging to study, particularly in observational study settings.<sup>5–7,38,39</sup> Of note, several ongoing clinical trials are evaluating spironolactone’s safety and efficacy in patients with CKD, including those with end-stage renal disease.

More data are needed to better understand whether spironolactone’s risks outweigh prospective benefits in patients who are currently exposed. Spironolactone is used among patients with various comorbidities, at many levels of SCr and K, and with exposure to various concomitant medications that can all make hyperkalemia or AKI more likely. In general, aldosterone antagonists are not recommended in heart failure patients with eGFR less than 30 mL/min per 1.73 m<sup>2</sup> by the American Heart Association,<sup>14,15</sup> yet these patients have limited therapeutic options and may derive benefit from its pleiotropic pharmacologic properties. Outside of its cardiovascular benefit,<sup>31–34,40–42</sup> some data suggest spironolactone may also slow the progression of CKD.<sup>29,36,37,39,41,43–47</sup> We observed a marked increase in the incidence of primary safety outcomes in patients with spironolactone use at lower eGFRs, but routine monitoring of SCr and K is warranted at all levels of kidney function. With a better understanding of spironolactone’s safety profile in heart failure, ideal candidates for spironolactone can be chosen with the risks for hyperkalemia and AKI balanced accordingly. Additionally, while K binding therapies are available for the treatment of chronic hyperkalemia, there is still a need for novel therapeutics for the treatment of AKI given its prevalence and complex pathophysiology.



## Strengths and Limitations

Our study has several notable strengths. We used a large, integrated EHR system with access to all primary care patient records across the health system, including laboratory, inpatient, and outpatient data. The Geisinger primary care system generally has little attrition, with many years of detailed records. Mortality data were also available. Our study also had some limitations. Patients were relatively homogeneous with respect to race and ethnicity. We used ICD-9/10 diagnosis codes for comorbidities and outcomes; particularly for hyperkalemia and AKI, these codes are likely to select for the most severe cases.<sup>48,49</sup> Because most heart failure diagnosis codes are for unspecified heart failure, we could not differentiate between reduced or preserved ejection fraction heart failure.

## CONCLUSION

Spirolactone use was relatively uncommon among patients on loop diuretics with heart failure. Concomitant use of spironolactone and a loop diuretic was associated with an increased risk of hyperkalemia and, to a lesser extent, AKI compared with loop diuretic use without spironolactone, with no evidence of risk modification across the spectrum of eGFR. Spirolactone has known benefits and risks in narrower patient populations, and this study offers insight into its safety profile under real-world conditions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

Some data reported here were supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government. The funding sources had no role in the design and conduct of the study, analysis or interpretation of the data, and preparation or final approval of the manuscript prior to publication.

**Grant Support:** Dr Secora was supported by grant T32 HL007024 from the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH). Dr Gram is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (R01 DK100446 and R01 DK115534). Dr Alexander is supported by 1 U01 FD004977-02 from the U.S. Food and Drug Administration (FDA). Dr Chang is supported by a grant from the NIDDK (K23 DK106515). Dr Shin is supported by a grant from the NIDDK (K01 DK121825). Dr Inker is supported by grants from NIDDK (R01DK115534 and U01DK085689), and funding from Retrophin, Omeros, Dialysis Clinics, Inc., and Reata Pharmaceuticals for research and contracts to Tufts Medical Center.

## Abbreviations and Acronyms:

<b>ACEi</b>	angiotensin-converting enzyme inhibitor
<b>ARB</b>	angiotensin II receptor blockers
<b>AKI</b>	acute kidney injury
<b>CVD</b>	cardiovascular disease
<b>CCI</b>	Charlson comorbidity index
<b>CKD</b>	chronic kidney disease

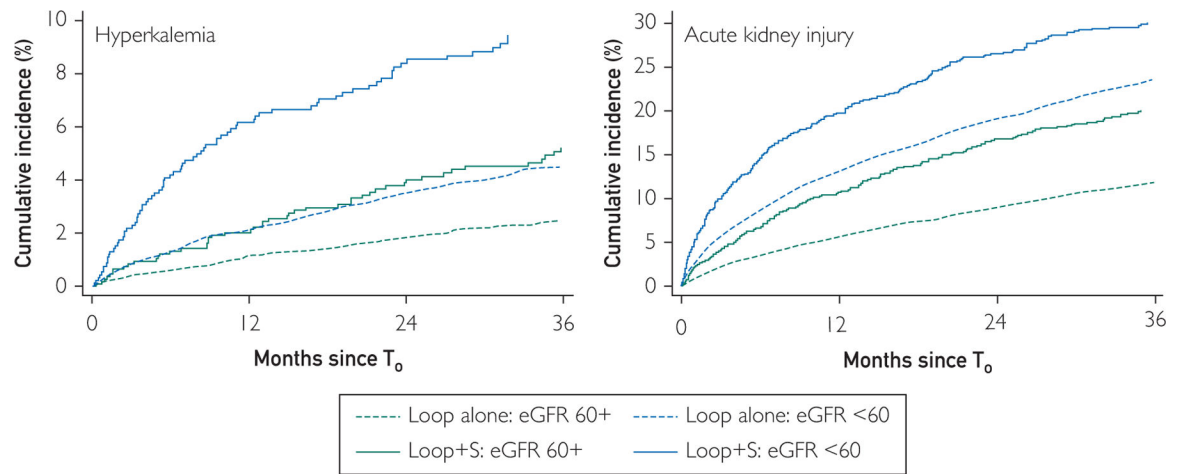
<b>eGFR</b>	estimated glomerular filtration rate
<b>EHR</b>	electronic health record
<b>HFpEF</b>	heart failure with preserved ejection
<b>HFrEF</b>	heart failure with reduced ejection
<b>ITT</b>	intention-to-treat
<b>K</b>	potassium
<b>PAD</b>	peripheral artery disease
<b>PS</b>	propensity score
<b>RALES</b>	Randomized Aldactone Evaluation Study
<b>SCr</b>	serum creatinine
<b>sHR</b>	subdistribution hazard ratios
<b>TOPCAT</b>	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

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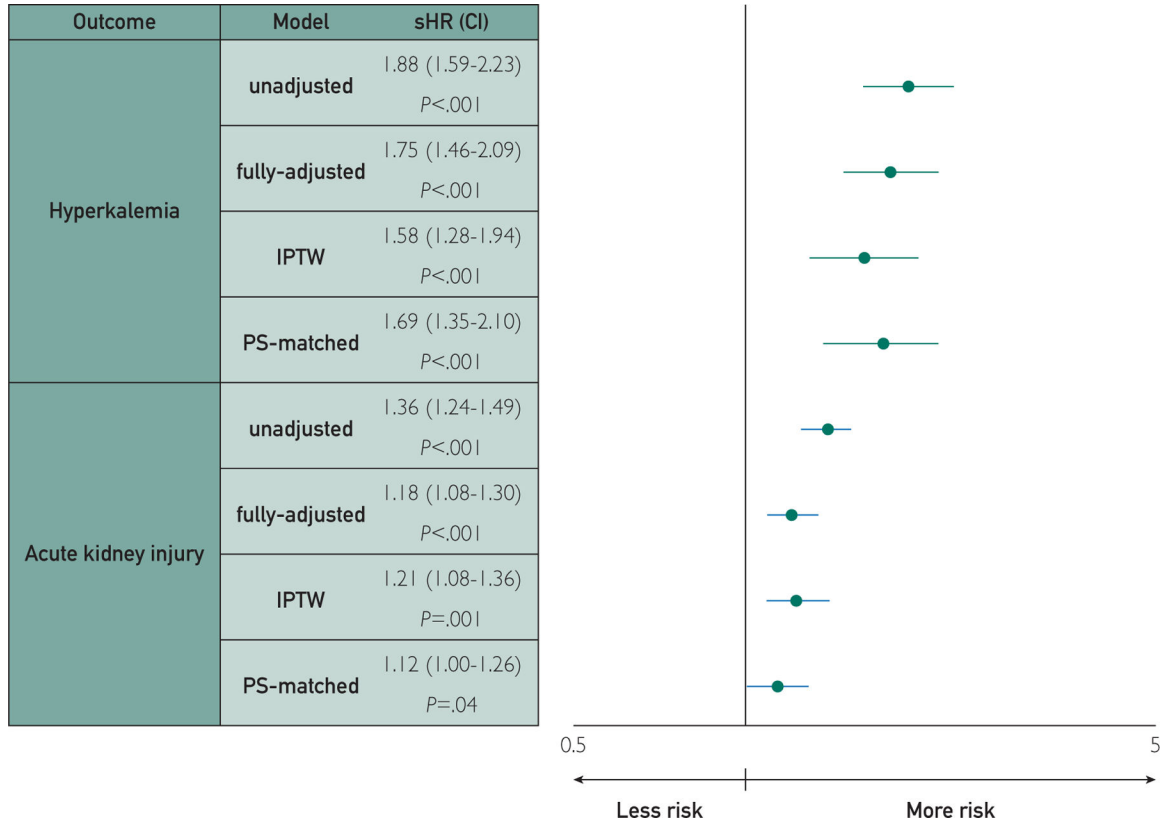
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**FIGURE 1.**

Estimated glomerular filtration rate (eGFR). Cumulative incidence estimates account for the competing risk of death. Loop alone refers to the control group. Loop and spironolactone (Loop + S) refers to the treatment group. eGFR units are mL/min per 1.73 m<sup>2</sup>. T<sub>0</sub> for treatment group = initiation of spironolactone; T<sub>0</sub> for treatment group = random loop order date in relevant cohort “trial” years. For hyperkalemia, 1-year cumulative incidence was 1.7% and 4.0% in control and treatment group, respectively. For AKI, 1-year cumulative incidence was 9.5% and 14.9% in control and treatment group, respectively.



**FIGURE 2.** Inverse probability of treatment weights (IPTW); propensity score (PS); subdistributional hazard ratio (sHR); figure plotted on log scale; models were adjusted by age, sex, race, estimated glomerular filtration rate, potassium, time with heart failure relative to first loop prescription order, year of first loop order, time since first loop order, Charlson comorbidity index, history of hyperkalemia, acute kidney injury, cardiovascular disease, peripheral artery disease, diabetes mellitus, cancer, cirrhosis, ascites, atrial fibrillation, proteinuria, and prior use of anticoagulants, angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, other antihypertensives, antiarrhythmics, cardiac glycosides, statins, thiazide diuretics, and potassium-sparing diuretics.



**TABLE 1.**

Study Population at T<sub>0</sub>, Stratified by Eventual Initiation of Spironolactone<sup>a,b</sup>

	Overall	Never initiators	Ever initiators <sup>c</sup>	P
N (total)	17,110	13,881 (81.1)	3229 (18.9)	
Female	8635 (50.5)	7189 (51.8)	1446 (44.8)	<.001
Non-White	414 (2.4)	313 (2.3)	101 (3.1)	<.001
Mean age, y	73.2±13.0	74.2±12.6	68.8±13.6	<.001
Mean CCI	7.1±2.8	7.2±2.8	6.5±2.8	<.001
Baseline labs				
Mean K, mg/dL	4.3±0.5	4.3±0.5	4.3±0.6	<.001
Mean SCr, mEq/L	1.2±0.6	1.2±0.6	1.1±0.5	<.001
Kidney function, mL/min per 1.73 m <sup>2</sup>				
Mean eGFR	61.8±23.9	60.9±23.8	65.8±23.8	<.001
90	2404 (14.1)	1821 (13.1)	583 (18.1)	<.001
60–89	6487 (37.9)	518 (37.4)	1302 (40.3)	<.001
30–59	6728 (39.3)	5579 (40.2)	1149 (35.6)	<.001
<30	1491 (8.7)	1296 (9.3)	195 (6.0)	<.001
Comorbidities				
Mean time with HF, mo <sup>d</sup>	177.3±464.5	184.3±476.6	147.0±406.9	<.001
CVD <sup>e</sup>	11,347 (66.3)	9256 (66.7)	2091 (64.8)	.04
Hyperkalemia	1123 (6.6)	937 (6.8)	186 (5.8)	.04
PAD	3755 (21.9)	3086 (22.2)	669 (20.7)	.06
Diabetes	7977 (46.6)	6433 (46.3)	1544 (47.8)	.13
Cancer	3178 (18.6)	2677 (19.3)	501 (15.5)	<.001
Cirrhosis	302 (1.8)	122 (0.9)	180 (5.6)	<.001
Ascites	310 (1.8)	151 (1.1)	159 (4.9)	<.001
AKI	3284 (19.2)	2743 (19.8)	541 (16.8)	<.001
Atrial fibrillation	6745 (39.4)	5481 (39.5)	1264 (39.1)	.72
Proteinuria <sup>f</sup>	1113 (6.5)	915 (6.6)	198 (6.1)	.34
Medications				

	Overall	Never initiators	Ever initiators <sup>e</sup>	P
ACEi or ARB	13,726 (80.2)	10,743 (77.4)	2983 (92.4)	<.001
Other antihypertensive	15,308 (89.5)	12,270 (88.4)	3038 (94.1)	<.001
Anticoagulants	10,233 (59.8)	8126 (58.5)	2107 (65.3)	<.001
Arrhythmic	3776 (22.1)	2821 (20.3)	955 (29.6)	<.001
Cardiac glycoside	3223 (18.8)	2223 (16.0)	1000 (31.0)	<.001
Statin	11,331 (66.2)	9100 (65.6)	2231 (69.1)	<.001
Thiazide diuretic	5605 (32.8)	4260 (30.7)	1345 (41.7)	<.001
Other K <sup>+</sup> -sparing diuretic	567 (3.3)	413 (3.0)	154 (4.8)	<.001

<sup>a</sup> ACEi = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin II receptor blockers; CCI = Charlson comorbidity index; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HF = heart failure; K = potassium; PAD = peripheral artery disease; SCr = serum creatinine; T<sub>0</sub> = baseline is the first loop diuretic order after initial heart failure diagnosis.

<sup>b</sup> Values are n (%); mean values are shown ± SD.

<sup>c</sup> Ever initiators include those who ever took spironolactone, even if it did not overlap with a loop diuretic.

<sup>d</sup> Time with HF is the mean time between initial HF diagnosis and first loop prescription after the initial HF diagnosis.

<sup>e</sup> CVD is a composite category including cerebrovascular disease/stroke, coronary artery disease, and myocardial infarction.

<sup>f</sup> Proteinuria was defined using diagnosis codes.

Incidence of Hyperkalemia and Acute Kidney Injury Stratified by Exposure Groups and Kidney Function (As-Treated Analysis)<sup>a</sup>

TABLE 2.

eGFR category (mL/min per 1.73 m <sup>2</sup> )	Hyperkalemia		Acute kidney injury	
	Total PM	Incidence rate per 1000 PM	Total PM	Incidence rate per 1000 PM
<b>Loop alone<sup>b</sup></b>				
90	49,638	0.6	48,137	2.9
60–89	153,154	0.7	146,177	4.0
30–59	189,436	1.3	170,912	8.7
<30	41,979	4.8	34,601	21.4
Overall	434,207	1.4	399,826	7.4
<b>None<sup>c</sup></b>				
90	26,176	0.5	24,774	2.0
60–89	73,115	0.6	68,324	2.7
30–59	72,634	1.2	62,737	6.2
<30	20,214	4.7	14,384	10.9
Overall	192,140	1.3	170,220	4.6
<b>Spirolactone alone<sup>d</sup></b>				
90	1161	1.7	1124	3.6
60–89	2701	1.9	2457	2.9
30–59	2743	5.1	2371	7.2
<30	376	5.3	243	20.6
Overall	6980	3.3	6196	5.3
<b>Loop and spironolactone<sup>e</sup></b>				
90	7666	1.6	7335	4.6
60–89	16,420	1.6	15,289	7.7
30–59	21,334	3.3	18,695	11.3
<30	3196	10.3	2531	32.0
Overall	48,617	2.9	43,853	10.1

<sup>a</sup> eGFR = estimated glomerular filtration rate; PM = person-month.

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<sup>d</sup>“Loop alone”, represents use of a loop diuretic without spironolactone.

<sup>e</sup>“None” is no use of either spironolactone or a loop diuretic.

<sup>f</sup>“Spironolactone alone”, represents spironolactone use without a loop diuretic.

<sup>g</sup>“Loop and spironolactone”, represents concomitant use of a loop diuretic and spironolactone.

**TABLE 3.** Risk of Hyperkalemia and Acute Kidney Injury Comparing Diuretic Use Groups (As-Treated Analysis)<sup>a</sup>

	Hyperkalemia			Acute Kidney Injury		
	Unadjusted (95% CI)	Fully adjusted (time-fixed) (95% CI)	P	Unadjusted (95% CI)	Fully adjusted (time-fixed) (95% CI)	P
Loop alone <sup>b</sup>	ref	ref	ref	ref	ref	ref
None <sup>c</sup>	0.59 (0.50–0.70)	0.59 (0.49–0.70)	<.001	0.44 (0.40–0.48)	0.43 (0.39–0.47)	<.001
Spirinolactone alone <sup>d</sup>	2.55 (1.66–3.92)	2.83 (1.82–4.39)	<.001	0.79 (0.55–1.13)	0.81 (0.57–1.17)	.26
Loop and spironolactone <sup>e</sup>	2.30 (1.91–2.77)	2.36 (1.94–2.86)	<.001	1.46 (1.32–1.62)	1.45 (1.30–1.62)	<.001

<sup>a</sup>Data shown are subdistribution hazard ratios with loop as the reference. Models were adjusted by age, sex, race, estimated glomerular filtration rate (eGFR), potassium (K), time with heart failure, year of first loop order, Charlson comorbidity index, history of hyperkalemia, acute kidney injury, cardiovascular disease, peripheral artery disease, diabetes mellitus, cancer, cirrhosis, ascites, atrial fibrillation, proteinuria, and prior use of anticoagulants, angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blockers (ARB), other antihypertensives, antiarrhythmics, cardiac glycosides, statins, thiazide diuretics, and K-sparing diuretics. Time-varying variables in fully adjusted models were eGFR, K, and combined ACEi or ARB use.

<sup>b</sup>“Loop alone” represents use of a loop diuretic without spironolactone.

<sup>c</sup>“None” is no use of either spironolactone or a loop diuretic.

<sup>d</sup>“Spirinolactone alone” represents spironolactone use without a loop diuretic.

<sup>e</sup>“Loop and spironolactone” represents concomitant use of a loop diuretic and spironolactone.

TABLE 4.

Hyperkalemia and Acute Kidney Injury Events for Treatment and Control Groups by Cohort “Trial” Year (Intention-to-Treat Analysis)<sup>a</sup>

Cohort “trial” year	Loop and spironolactone (treated)	Loop alone (control)	Hyperkalemia		Acute kidney injury	
			Total events	Events in treated	Total events	Events in treated
2004–2006	166	1938	125	18	477	45
2007–2009	376	4500	301	39	1274	110
2010–2012	554	6300	371	40	1799	163
2013–2016	904	9389	400	66	2032	242
Pooled	2000	22,127	1197	163	5582	560

<sup>a</sup>Treatment group refers to patients using loop and spironolactone concomitantly (loop and spironolactone). Control group refers to patients using loop without spironolactone. Control group patients can be included in subsequent cohort “trial” years as a treatment or control, but treatment group patients are not eligible for subsequent cohort “trial” years. Patients were excluded if baseline potassium level was greater than 5.0 mEq/L.