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Authors

Inampudi, Chakradhari
Parvataneni, Sridivya
Morgan, Charity J
et al.

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Spirolactone Use and Higher Hospital Readmission for Medicare Beneficiaries with Heart Failure, Left Ventricular Ejection Fraction <45% and Estimated Glomerular Filtration Rate <45 ml/min/1.73m²

Chakradhari Inampudi, MD^a, Sridivya Parvataneni, MD^b, Charity J. Morgan, PhD^b, Prakash Deedwania, MD^c, Gregg C. Fonarow, MD^d, Paul W. Sanders, MD^{b,e}, Sumanth D. Prabhu, MD^{b,e}, Javed Butler, MD^f, Daniel E. Forman, MD^g, Wilbert S. Aronow, MD^h, Richard M. Allman, MDⁱ, and Ali Ahmed, MD, MPH^{b,e}

^aUniversity of Iowa, Iowa City, IA

^bUniversity of Alabama at Birmingham, Birmingham, AL

^cUniversity of California, San Francisco, Fresno, CA

^dUniversity of California, Los Angeles, CA

^eVeterans Affairs Medical Center, Birmingham, AL

^fEmory University, Atlanta, GA

^gHarvard University, Boston, MA

^hNew York Medical College, Valhalla, NY

ⁱDepartment of Veterans Affairs, Geriatrics and Extended Care Services, Washington, DC

Abstract

While randomized controlled trials have demonstrated benefits of aldosterone antagonists for patients with heart failure and reduced ejection fraction (HFrEF), they excluded patients with serum creatinine >2.5mg/dl and their use is contraindicated in those with advanced chronic kidney disease (CKD). In the current analysis, we examined the association of spironolactone use with readmission in hospitalized Medicare beneficiaries with HFrEF and advanced CKD. Of the 1140 patients with HFrEF (EF <45%) and advanced CKD (estimated glomerular filtration rate {eGFR} <45 ml/min/1.73m²), 207 received discharge prescriptions for spironolactone. Using propensity scores (PS) for the receipt of discharge prescriptions for spironolactone we estimated PS-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for spironolactone-associated outcomes. Patients (mean age 76 years, 49% women, 25% African American) had mean EF 28%, mean

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Corresponding author: Ali Ahmed, MD, UAB Comprehensive Center for Healthy Aging, 1720 2nd Ave South, CH19-219, Birmingham AL 35294-2041; Telephone: 1-205-934-9632; Fax: 1-205-975-7099; aahmed@uab.edu.

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eGFR 31 ml/min/1.73m², and mean potassium 4.5 mEq/L. Spironolactone use had significant PS-adjusted association with higher risk of 30-day (HR, 1.41; 95% CI: 1.04–1.90) and 1-year (HR, 1.36; 95% CI: 1.13–1.63) all-cause readmission. The risk of 1-year all-cause readmission was higher among 106 patients with eGFR <15 ml/min/1.73m² (HR, 4.75; 95% CI: 1.84–12.28) than among those with eGFR 15–45 ml/min/1.73m² (HR, 1.34; 95% CI, 1.11–1.61; p for interaction, 0.003). Spironolactone use had no association with HF readmission and all-cause mortality. In conclusion, among hospitalized patients with HFrEF and advanced CKD, spironolactone use was associated with higher all-cause readmission but had no association with all-cause mortality or HF readmission.

Keywords

heart failure; chronic kidney disease; spironolactone; 30 day readmission

The efficacy of aldosterone antagonists in heart failure and reduced ejection fraction (HFrEF) patients has been established in multiple randomized controlled trials.¹⁻³ These randomized controlled trials generally excluded patients with serum creatinine >2.5mg/dl. Although post hoc analyses of randomized trials have suggested that spironolactone and eplerenone may improve outcomes in those with impaired renal function,^{4,5} they did not include patients with advanced chronic kidney disease (CKD). Because these drugs also increase the risk of hyperkalemia and worsening kidney function,^{4,5} the role of these drugs in patients with advanced CKD remains unclear and their use is contraindicated in those with advanced CKD. In one study based on the American Heart Association Get With the Guidelines-Heart Failure data, among real-world HFrEF patients that also excluded advanced CKD, the use of aldosterone antagonists had no association with mortality or cardiovascular readmission.⁶ These findings highlight the need for appropriate patient selection and monitoring so that the efficacy observed in randomized trials may be translated into clinical effectiveness in the real-world. Because HF is the leading cause for hospital readmission and under the new healthcare reform law hospitals are facing billions of dollars of loss in Medicare payments for higher than average 30-day all-cause readmission, in the current analysis, we examined if a discharge prescription of an aldosterone antagonist was associated with lower all-cause readmission in older HFrEF patients with advanced CKD.

Methods

Alabama Heart Failure Project was used for data analysis in the current study, the details of which have been described previously.⁷ Briefly, 9649 charts of fee-for-service Medicare beneficiaries discharged from 106 Alabama hospitals between July 1, 1998 and October 31, 2001 with principal diagnosis of HF were identified and abstracted in 6 different 6-month periods.⁷ Of these, a unique cohort of 8555 patients was identified,⁷ of which 8049 were discharged alive. Of the 5479 with data on EF, 3067 had EF <45%, of which 1142 had estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m². After excluding 2 patients receiving potassium-sparing diuretics other than spironolactone, the final sample consisted of 1140 patients, of which 207 (18%) received a discharge prescription for spironolactone. Extensive data on baseline demographics, medical history including use of medications,

hospital course, discharge disposition including medications, and physician specialty were collected. The primary outcome of the current analysis was 30-day all-cause readmission. Secondary outcomes included 30-day all-cause mortality, HF readmissions and combined end point of all-cause mortality or all-cause readmission. In addition, we also examined the association of spironolactone with these outcomes during longer follow-up. Data on outcomes and time to events were obtained from the Centers for Medicare and Medicaid Services Denominator File, Medicare Provider Analysis and Review File, and Inpatient Standard Analytical File.

Pearson chi-square and one-way ANOVA were used for descriptive analysis as appropriate. We estimated propensity scores (PS) for the receipt of spironolactone for each of the 1140 patients based on 45 variables that were used to estimate PS-adjusted hazard ratios (HRs) for the association of spironolactone with outcomes. All statistical tests were 2-tailed with a *P* value <0.05 considered significant. Statistical analyses were performed using SPSS-21 for Windows (SPSS, Inc., 2012, Chicago, IL).

Results

Mean age of the patients (n=1140) was 76 (\pm 10) years, 49% were women, 25% were African American. The mean EF was 28 (\pm 9)%, mean eGFR 31 (\pm 10) ml/min/1.73m², mean serum creatinine 2.47 (\pm 1.59) mg/dl, mean serum potassium 4.5 (\pm 0.75) mEq/L. Patients receiving vs. not receiving spironolactone at discharge were similar in respect to most baseline characteristics (Table 1). However, patients in the spironolactone group were more likely to have prevalent HF and lower serum creatinine levels, and be prescribed digoxin, diuretics, and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers than those not receiving spironolactone (Table 1).

Within 30 days post-discharge, unadjusted all-cause readmissions rates were 30% and 25% for patients receiving and not receiving spironolactone, respectively. PS-adjusted HR (95% CI) associated with spironolactone use was 1.41 (1.04–1.90; Table 2). There was no association with all-cause mortality or HF readmission during 30 days post-discharge, though there was a near-significant association with 30-day combined end point of all-cause readmission or all-cause mortality (Table 2). The risk of all-cause readmission (PS-adjusted HR, 1.36; 95% CI, 1.13–1.63) and the combined end point of all-cause readmission or all-cause mortality (PS-adjusted HR, 1.30; 95% CI, 1.09–1.54; Table 3 and Figure 1) during one year post-discharge was higher among patients in the spironolactone group. The adverse association of spironolactone use with 1-year all-cause readmission was significantly higher in the 106 patients with eGFR <15 ml/min/1.73m² (HR, 4.75; 95% CI: 1.84–12.28) than in the 1034 with eGFR 15–45 ml/min/1.73m² (HR, 1.34; 1.11–1.61; *p* for interaction is 0.003). Similar differences were observed for 1-year combined end point of all-cause readmission or all-cause mortality (*p* for interaction, 0.007).

Discussion

The findings of the current analysis demonstrate that in hospitalized older patients with HFrEF (EF <45%) and advanced CKD (eGFR <45), a discharge prescription of

spironolactone was associated with higher 30-day and 1-year all-cause readmission, and that this risk was higher in those with eGFR <15 than in patients with eGFR 15-45 mL/min/1.73 m². Further, spironolactone had no significant association with all-cause mortality or HF readmission in this subset of high-risk patients. These findings further highlight the need for caution if prescribing spironolactone for hospitalized HFrEF patients with advanced CKD.

Severe hyperkalemia and worsening kidney function are the likely underlying mechanisms for poor outcomes among patients with advanced CKD in our study. Although mean baseline serum potassium in our patients was normal and similar between the two treatment groups, it is possible that patients in the spironolactone group were more likely to develop serious hyperkalemia during follow-up. Findings from a post hoc analysis of EMPHASIS-HF data suggest that those with diabetes and CKD had higher risk of developing hyperkalemia.⁸ Nearly half of the patients in our study had diabetes mellitus. Finally, although similar proportions of patients receiving and not receiving spironolactone received potassium supplements, those in the spironolactone group were more likely to develop life-threatening hyperkalemia. However, incident life-threatening hyperkalemia is unlikely to fully explain an isolated higher hospital readmission without an associated higher mortality among patients in the spironolactone group in our study as deaths associated with hyperkalemia would be expected to be due to cardiac arrhythmias that would also preclude hospital readmission. Spironolactone has also been shown to worsen kidney function,⁹ although it has been suggested to be temporary.^{10,11} Further, patients in the spironolactone group in our study had lower baseline serum creatinine levels. Finally, it is also possible that spironolactone was prescribed to patients with greater HF severity and these findings reflect selection bias and residual measured or unmeasured confounding.

According to the 2013 American College of Cardiology Foundation and American Heart Association Guidelines for the Management of HF, aldosterone antagonists should be avoided in HFrEF patients with eGFR <30 mL/min/1.73 m² and serum potassium >5.0 mEq/L, and both serum creatinine and potassium should be closely monitored (Level of Evidence: A).¹² The guidelines also recommend that the inappropriate use of aldosterone antagonists in these patients is potentially harmful due to risks of life-threatening hyperkalemia or worsening kidney function (Level of Evidence: B).¹² Thus, patient selection is important and it has been suggested that aldosterone antagonists should be used in patients similar to those enrolled in the randomized controlled trials.¹³ Findings from our study suggest that aldosterone antagonists need to be used with caution in HFrEF patients with CKD Stage 3B (eGFR between 30 and 44 mL/min/1.73 m²) and, consistent with guideline recommendations, avoided in those with eGFR <30 mL/min/1.73 m².¹² HF is the leading cause for readmission,¹⁴ and if the findings from the current study can be replicated in other HF populations, it may be reasonable to delay prescriptions of aldosterone antagonists until after hospital discharge. Of note, in the same patient population (EF <45 and eGFR <45), ACE inhibitors and angiotensin receptor blockers have been shown to reduce mortality without increasing all-cause readmission.¹⁵

Several limitations of our study need to be acknowledged. Due to the observational design and small sample size, both bias and chance are alternate explanations and confounding may account for some or all of these findings. We also had no data on the dose of spironolactone

and follow-up data on serum creatinine and potassium. Crossover of treatment during follow-up may have resulted in regression dilution and underestimation of the associations.¹⁶ Finally, these findings based on a single state from an earlier era of HF therapy may limit generalizability. In conclusion, the higher all-cause readmission and lack of mortality benefit associated with spironolactone use among hospitalized HF patients with EF <45 and eGFR <45 highlight the need for caution in the use of aldosterone antagonists in these patients.

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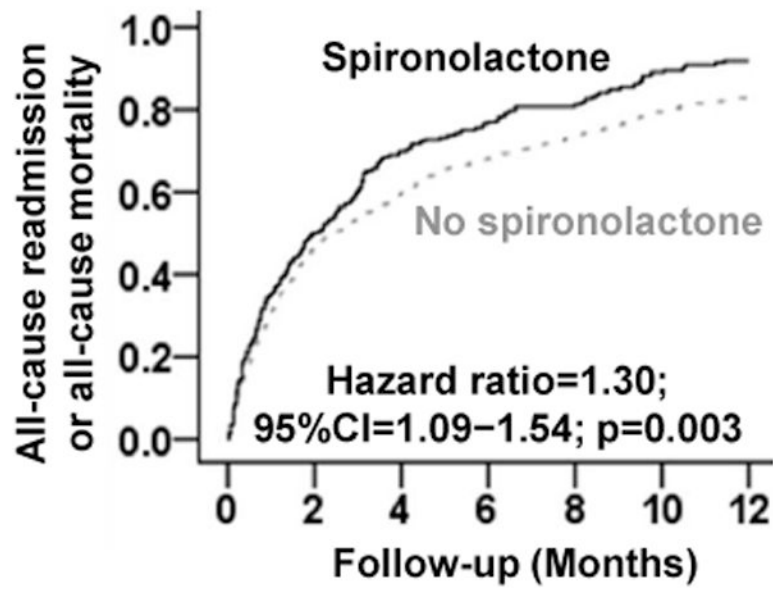


Figure 1.

Propensity score-adjusted 1-year all-cause readmission rates for hospitalized heart failure patients with ejection fraction <45% and estimated glomerular filtration rate <45 ml/min/1.73m² receiving and not receiving spironolactone on discharge (CI=confidence interval)

Table 1
Baseline characteristics of Medicare beneficiaries hospitalized for heart failure who had ejection fraction <45% and estimated glomerular filtration rate <45 mL/min/1.73m² by spironolactone

n (%) or mean (±SD)	Spironolactone on discharge		
	No (n=933)	Yes (n=207)	P value
Age (years)	76 ±10	76 ±8	0.860
Female	451 (48%)	106 (51%)	0.455
African American	228 (24%)	55 (27%)	0.520
Smoker	88 (9%)	17 (8%)	0.583
Admission from nursing home	50 (5%)	9 (4%)	0.552
Past medical history			
Prior heart failure	771 (83%)	186 (90%)	0.010
Coronary artery disease	654 (70%)	158 (76%)	0.073
Myocardial infarction	322 (35%)	72 (35%)	0.941
Percutaneous coronary intervention	165 (18%)	37 (18%)	0.948
Coronary artery bypass graft	323 (35%)	82 (40%)	0.174
Hypertension	682 (73%)	147 (71%)	0.543
Atrial fibrillation	252 (27%)	54 (26%)	0.786
Diabetes mellitus	465 (50%)	97 (47%)	0.438
Stroke	214 (23%)	46 (22%)	0.825
Chronic obstructive pulmonary disease	306 (33%)	61 (30%)	0.354
Dementia	84 (9%)	15 (7%)	0.417
Cancer	21 (2%)	7 (3%)	0.342
Clinical and laboratory data			
Pulse (beats per minute)	91 ±23	90 ±22	0.686
Systolic blood pressure (mmHg)	144 ±33	134 ±30	<0.001
Diastolic blood pressure (mmHg)	79 ±20	76 ±18	0.122
Respiratory rate (breaths/minute)	24 ±6	23 ±5	0.070
Peripheral edema	665 (71%)	164 (79%)	0.020
Pulmonary edema by chest x-ray	679 (73%)	149 (72%)	0.816
Serum sodium (mEq/L)	138 ±4.5	138 ±5	0.040
Serum potassium (mEq/L)	4.5 ±0.76	4.42 ±0.70	0.269
Serum creatinine (mg/dL)	2.6 ±1.7	2.1 ±0.7	<0.001
Glomerular filtration rate (mL/min/1.73m ²)	30 ±11	33 ±8	<0.001
Blood urea nitrogen (mg/dL)	42 ±21	42 ±22	0.720
Hematocrit (%)	36 ±6	37 ±6	0.033
White blood cell (cell/μL)	10 ±9	9 ±5	0.184
In hospital events			
Pneumonia	271 (29%)	52 (25%)	0.257
Acute myocardial infarction	58 (6%)	13 (6%)	0.973
Pressure ulcer	97 (10%)	23 (11%)	0.762

n (%) or mean (\pm SD)	Spironolactone on discharge		
	No (n=933)	Yes (n=207)	P value
Hospital and care characteristics			
Rural hospital	209 (22%)	44 (21%)	0.720
Cardiology care	610 (65%)	156 (75%)	0.006
Intensive care	47 (5%)	11 (5%)	0.870
Length of stay (days)	7.76 \pm 6.5	7.77 \pm 5	0.977
Discharge medications			
Renin angiotensin system antagonists	492 (53%)	133 (64%)	0.003
Beta-adrenergic blockers	235 (25%)	56 (27%)	0.578
Loop diuretics	742 (80%)	192 (93%)	<0.001
Digoxin	429 (46%)	130 (63%)	<0.001
Calcium channel blockers	196 (21%)	28 (14%)	0.014
Potassium supplementation	348 (37%)	78 (38%)	0.918
Anti-arrhythmic drugs	174 (19%)	48 (23%)	0.136
Antidepressants	196 (21%)	38 (18%)	0.393
Non-steroidal anti-inflammatory drugs	62 (7%)	11 (5%)	0.479

Table 2
Associations of discharge prescription for spironolactone with outcomes at 30 days post-discharge among Medicare beneficiaries hospitalized for heart failure with ejection fraction <45% and estimated glomerular filtration rate <45 mL/min/1.73m²

	% (total events / total patients) Spironolactone on discharge		Hazard ratio [†] (95% CI); p-value	
	No	Yes	Unadjusted	Propensity score adjusted
All-cause readmission	25% (237/933)	30% (61/207)	1.19 (0.90–1.57); p=0.233	1.41 (1.04–1.90); p=0.027
Heart failure readmission	12% (116/933)	12% (25/207)	0.97 (0.63–1.49); p=0.872	0.90 (0.57–1.41); p=0.635
All-cause mortality	8% (75/933)	8% (17/207)	1.01 (0.60–1.72); p=0.961	1.05 (0.60–1.82); p=0.866
All-cause mortality or readmission	31% (285/933)	34% (70/207)	1.13 (0.87–1.47); p=0.352	1.31 (0.99 –1.73); p=0.058

[†] Hazard ratios comparing patients receiving spironolactone on discharge with those not receiving it

Table 3
Associations of discharge prescription for spironolactone with outcomes at 1 year post-discharge among Medicare beneficiaries hospitalized for heart failure with ejection fraction <45% and estimated glomerular filtration rate <45 mL/min/1.73m²

	% (total events / total patients) Spironolactone on discharge		Hazard ratio [†] (95% CI); p-value	
	No	Yes	Unadjusted	Propensity adjusted
All-cause readmission	70% (656/933)	77% (160/207)	1.24 (1.04–1.48); p=0.014	1.36 (1.13–1.63); p=0.001
Heart failure readmission	40% (370/933)	44% (91/207)	1.14 (0.91–1.44); p=0.260	1.02 (0.80–1.30); p=0.847
All-cause mortality	46% (432/933)	49% (102/207)	1.09 (0.88–1.35); p=0.441	1.05 (0.83–1.31); p=0.706
All-cause mortality or readmission	84% (779/933)	91% (188/207)	1.22 (1.04–1.43); p=0.014	1.30 (1.09–1.54); p=0.003

[†] Hazard ratios comparing patients receiving spironolactone on discharge with those not receiving it