ORIGINAL RESEARCH

Use of Mineralocorticoid Receptor Antagonists in Patients With Heart Failure and Comorbid Diabetes Mellitus or Chronic Kidney Disease

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***Background*—**Perceived risks of hyperkalemia and acute renal insufficiency may limit use of mineralocorticoid receptor antagonist (MRA) therapy in patients with heart failure, especially those with diabetes mellitus or chronic kidney disease.

***Methods and Results*—**Using clinical registry data linked to Medicare claims, we analyzed patients hospitalized with heart failure between 2005 and 2013 with a history of diabetes mellitus or chronic kidney disease. We stratified patients by MRA use at discharge. We used inverse probability–weighted proportional hazards models to assess associations between MRA therapy and 30-day, 1-year, and 3-year mortality, all-cause readmission, and readmission for heart failure, hyperkalemia, and acute renal insufficiency. We performed interaction analyses for differential effects on 3-year outcomes for reduced, borderline, and preserved ejection fraction. Of 16 848 patients, 12.3% received MRA therapy at discharge. Higher serum creatinine was associated with lower odds of MRA use (odds ratio, 0.66; 95% confidence interval, 0.61–0.71); serum potassium was not (odds ratio, 1.00; 95% confidence interval, 0.90–1.11). There was no mortality difference between groups. MRA therapy was associated with greater risks of readmission for hyperkalemia and acute renal insufficiency and lower risks of long-term all-cause readmission. Patients on MRA therapy with borderline or preserved ejection fraction had greater risks of readmission for hyperkalemia (P=0.02) and acute renal insufficiency (P<0.001); patients with reduced ejection fraction did not.

***Conclusions*—**Among patients with heart failure and diabetes mellitus or chronic kidney disease, MRA use was associated with lower risk of all-cause readmission despite greater risk of hyperkalemia and acute renal insufficiency. **(*J Am Heart Assoc*. 2017;6: e006540. DOI: 10.1161/JAHA.117.006540.)**

Key Words: chronic kidney disease • diabetes mellitus • heart failure • outcomes research

The mineralocorticoid receptor antagonists (MRAs), spironolactone and eplerenone, are recommended for patients with symptomatic heart failure with ejection fraction of 35% or less.[1] Although the role of MRAs in patients with ejection fraction greater than 35% is unclear,[2,3] they may benefit patients with comorbid hypertension, diabetes mellitus, or renal insufficiency. MRAs can be used for blood pressure management regardless of heart failure status, and addition of an MRA to angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy reduces proteinuria in patients with chronic kidney disease and diabetic nephropathy and can delay progression of renal dysfunction.[3–10]

Despite clinical trial evidence and guideline recommendations, MRA therapy in patients with heart failure with reduced ejection fraction is underused in clinical practice.[11] Risks of hyperkalemia and worsening renal function often limit use of MRA therapy in patients with heart failure.[12–14] Several

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Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/6/12/e006540/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Mineralocorticoid receptor antagonists are often underutilized in clinical practice, possibly because of concerns over risks of hyperkalemia and worsening renal function.
- In high-risk patients with heart failure and concomitant diabetes mellitus or renal insufficiency, mineralocorticoid receptor antagonist use was associated with lower risk of all-cause hospitalization despite increased risk of hospitalization with hyperkalemia or acute renal insufficiency.
- The increased risk of adverse events was mostly confined to patients with borderline or preserved ejection fraction.

What Are the Clinical Implications?

- Because of the overall decrease in the risk of hospitalization for patients treated with mineralocorticoid receptor antagonist therapy, the benefits of therapy may outweigh the risks in a high-risk population.

factors increase hyperkalemia risk, including renal insufficiency and diabetes mellitus.[15–19] Although the presence of renal insufficiency or diabetes mellitus increases the risk of adverse events with MRA therapy in heart failure, these drugs are potentially beneficial in these higher-risk populations.

The landmark clinical trials of MRA therapy in heart failure have had conflicting results with respect to the benefit of therapy in high-risk subgroups. The RALES (Randomized Aldactone Evaluation Study) trial of patients with reduced ejection fraction and severe symptoms showed a mortality benefit for spironolactone in patients with median creatinine of 1.2 mg/dL or greater.[20] Subgroup analyses from EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), which included patients with reduced ejection fraction and mild symptoms, also showed a benefit for the primary end point of cardiovascular death or heart failure hospitalization in patients with an estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2 and in patients with a history of diabetes mellitus.[21] However, in patients with left ventricular dysfunction after myocardial infarction, studied in the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), for the outcomes of all-cause mortality and cardiovascular death or hospitalization, the benefits of eplerenone in patients with serum creatinine of 1.1 mg/dL or greater and those with a history of diabetes mellitus were not statistically significant.[22] Finally, in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, for patients with preserved ejection fraction, spironolactone therapy did not significantly reduce the primary end point. There was no benefit for the subgroup of patients with an estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2 or the group of patients with a history of diabetes mellitus.[2]

Building on past work from registry analyses that examined outcomes and adverse events in patients with reduced ejection fraction who were prescribed an MRA at hospital discharge,[23] we examined MRA use in patients with heart failure who were at greater risk for adverse events and outcomes. Our objective was to describe MRA initiation at discharge from a heart failure hospitalization and to evaluate associations between MRA therapy and short- and longer-term outcomes in a registry-based cohort of older patients with heart failure with concomitant diabetes mellitus or chronic kidney disease.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data Sources

Data were from the American Heart Association's Get With the Guidelines-Heart Failure registry linked to Medicare claims from the Centers for Medicare & Medicaid Services. The registry is an ongoing online registry for patients hospitalized with heart failure.[24] Patients are eligible for inclusion in the registry if they are admitted or discharged with a diagnosis of heart failure (*International Classification of Diseases, Ninth Revision, Clinical Modification ICD-9-CM* codes 402.x1, 404.x1, 404.x3, and 428.x).

The Medicare data include 100% of Medicare Part A claims and associated denominator files from 2005 through 2013. Medicare Part A includes institutional claims from inpatient hospitalizations. Denominator files include information about demographic characteristics, Medicare eligibility and enrollment, and mortality. We linked the registry data to the Medicare data using indirect identifiers, as described and validated previously.[25]

Study Population

The study population included Medicare fee-for-service beneficiaries aged ≥65 years who were discharged from a registry hospitalization for heart failure between January 1, 2005, and December 31, 2013. To be eligible for this study, patients had to have a concomitant diagnosis of diabetes mellitus and/or chronic kidney disease before the index hospitalization, as recorded in the registry. In the medical history section of the registry, diabetes mellitus is recorded as "diabetes—insulin treated" or "diabetes—non-insulin treated" and chronic kidney

disease is recorded as "renal insufficiency-chronic (serum creatinine >2.0)." Patients included in the analysis were required to be new users of MRA therapy, defined as no MRA therapy at admission. We excluded patients with a contraindication to aldosterone antagonists recorded in the registry. Only patients discharged to home were included. If the patient had multiple hospitalizations in the registry, we used the first hospitalization for the analysis.

Treatment

The treatment of interest was MRA therapy prescribed at discharge, as recorded in the registry. Dosage information was unavailable.

Outcomes

The primary outcome was all-cause mortality at 30 days, 1 year, and 3 years. Other outcomes of interest included 30-day, 1-year, and 3-year all-cause readmission, heart failure readmission, and readmission with a diagnosis of hyperkalemia or acute renal insufficiency. We identified deaths based on death dates in the Medicare denominator files, and we calculated days to death from the index hospitalization discharge date. We identified all-cause readmission using subsequent inpatient claims except those for transfers to or from another hospital and admissions for rehabilitation. We defined heart failure readmissions by a primary diagnosis of heart failure (*ICD-9-CM* diagnosis code 428.x, 402.x1, 404.x1, or 404.x3) on an inpatient claim. We defined hyperkalemia using *ICD-9-CM* diagnosis code 276.7 and acute renal insufficiency using *ICD-9-CM* diagnosis code 584.x on an inpatient claim.

Subgroups

We assigned patients in the study cohort to prespecified subgroups based on disease history and ejection fraction for interaction analyses, using registry indicator variables for history of diabetes mellitus and history of renal insufficiency. We also categorized patients as having ejection fraction of 35% or less or greater than 35%, because heart failure guidelines recommend MRA therapy in patients with reduced ejection fraction. We defined reduced ejection fraction as documentation of left ventricular ejection fraction of 35% or less or a qualitative assessment of moderate or severe left ventricular systolic dysfunction. We grouped together patients with heart failure with borderline and preserved ejection, defined as ejection fraction greater than 35% or a qualitative assessment of no or mild left ventricular systolic dysfunction. We excluded patients with no documentation of ejection fraction.

Covariates

Covariates in population comparisons and modeling included the following registry variables: age, sex, race, medical history (ie, anemia, atrial fibrillation, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, depression, diabetes mellitus, hyperlipidemia, hypertension, implantable cardioverter-defibrillator, ischemic etiology of heart failure, pacemaker, peripheral vascular disease, renal insufficiency, and smoking in the past year), vital signs at admission (ie, systolic blood pressure, heart rate, and respiratory rate), laboratory tests at discharge (ie, creatinine, ejection fraction, potassium, sodium, and urea nitrogen), discharge medications (ie, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β-blocker, anticoagulant, digoxin, diuretic, and lipid-lowering agent), and discharge year. If discharge laboratory test results were missing, we substituted admission laboratory test results.

Statistical Analysis

We describe baseline characteristics of the study population by treatment group, using frequencies with percentages for categorical variables and means with SDs for continuous variables. We tested for differences between groups using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. We used logistic regression to assess unadjusted and adjusted associations between patient characteristics and MRA therapy at hospital discharge.

We describe observed event rates by treatment group. For mortality, we calculated cumulative incidence at 30 days, 1 year, and 3 years based on Kaplan–Meier estimates. We tested for mortality differences between groups using log-rank tests. For other end points, we calculated cumulative incidence based on estimates from the cumulative incidence function, which accounts for the competing risk of death, a high risk in this population. We used Gray tests to test for differences between treatment groups on these outcomes.

We used an inverse probability-weighted estimator—an extension of the propensity score—to assess differences in outcomes among treatment groups while accounting for confounding by observed covariates. We obtained the weights by fitting a treatment selection model as a logistic regression model with treatment as the dependent variable and the baseline characteristics described above as the independent variables. To evaluate the adequacy of the treatment selection model, we compared the baseline characteristics of each group after weighting. We used weighted chi-squared tests to test for differences on categorical variables and weighted analysis of variance to test for differences on continuous variables. We also calculated standardized differences to

Table 1. Baseline Characteristics of the Study Population

Characteristic	MRA Therapy		*P* Value
	Yes (n=2067)	No (n=14 781)	
Age, mean (SD), y	76.3 (7.4)	77.8 (7.6)	<0.001
Age group, n (%)			<0.001
65 to 79 y	1386 (67.1)	8534 (57.7)	
≥80 y	681 (32.9)	6247 (42.3)	
Men, N (%)	1156 (55.9)	7369 (49.9)	<0.001
Race			0.19
Black	244 (11.8)	1683 (11.4)	
White	1504 (72.8)	11 014 (74.5)	
Other/unknown	319 (15.4)	2084 (14.1)	
Disease state			
Diabetes mellitus	1791 (86.6)	12 154 (82.2)	<0.001
Chronic renal insufficiency	574 (27.8)	5326 (36.0)	<0.001
Medical history			
Anemia	381 (18.4)	3350 (22.7)	<0.001
Atrial fibrillation	762 (36.9)	5231 (35.4)	0.19
Chronic obstructive pulmonary disease	632 (30.6)	4717 (31.9)	0.22
Depression	201 (9.7)	1432 (9.7)	0.96
Heart failure with ischemic etiology			<0.001
No	814 (39.4)	6645 (45.0)	
Yes	1129 (54.6)	7204 (48.7)	
Missing	124 (6.0)	932 (6.3)	
Hyperlipidemia	1227 (59.4)	8478 (57.4)	0.08
Hypertension	1678 (81.2)	12 334 (83.4)	0.01
Implantable cardioverter-defibrillator	306 (14.8)	1200 (8.1)	<0.001
Pacemaker	397 (19.2)	2603 (17.6)	0.08
Peripheral vascular disease	287 (13.9)	2468 (16.7)	0.001
Smoker in the past y	228 (11.0)	1398 (9.5)	0.02
Vital signs at admission			
Heart rate, mean (SD), bpm	84.0 (19.1)	81.8 (18.8)	<0.001
Respiratory rate ≥30, N (%), breaths/min	96 (4.6)	922 (6.2)	0.004
Systolic blood pressure, mean (SD), mm Hg	139.5 (28.4)	145.9 (29.7)	<0.001
Tests at admission/discharge			
Reduced ejection fraction at admission*	1251 (60.5)	5468 (37.0)	<0.001
Serum creatinine, mean (SD), mg/dL	1.5 (0.7)	1.9 (1.3)	<0.001
Serum potassium, mean (SD), mEq/L	4.1 (0.5)	4.1 (0.5)	0.006
Serum urea nitrogen, mean (SD), mg/dL	31.9 (16.8)	34.8 (18.0)	<0.001
Medications at discharge			
ACE inhibitor and/or ARB	1502 (72.7)	9247 (62.6)	<0.001
Anticoagulant	730 (35.3)	4555 (30.8)	<0.001
β-blocker	1810 (87.6)	12 006 (81.2)	<0.001
Digoxin	504 (24.4)	2235 (15.1)	<0.001

Continued

Table 1. Continued

Characteristic	MRA Therapy		*P* Value
	Yes (n=2067)	No (n=14 781)	
Diuretic	1790 (86.6)	11 837 (80.1)	<0.001
Lipid-lowering agent	1441 (69.7)	9885 (66.9)	0.01
Discharge year			<0.001
2005	80 (3.9)	499 (3.4)	
2006	288 (13.9)	2106 (14.2)	
2007	221 (10.7)	1898 (12.8)	
2008	179 (8.7)	1678 (11.4)	
2009	203 (9.8)	1710 (11.6)	
2010	229 (11.1)	1929 (13.1)	
2011	291 (14.1)	1868 (12.6)	
2012	295 (14.3)	1509 (10.2)	
2013	281 (13.6)	1584 (10.7)	

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.
*Reduced ejection fraction is defined as documentation of a left ventricular ejection fraction of 35% or less, or a qualitative assessment of moderate or severe left ventricular systolic dysfunction.

assess balance after weighting. Balanced variables were those with a standardized difference of less than 10%.

We estimated the unadjusted relationship between MRA therapy and each outcome using Cox proportional hazards models in which the treatment indicator was the sole independent variable. Next, we estimated the adjusted relationship between treatment and each outcome using weighted proportional hazards regression models. Finally, we controlled for discharge medications in addition to the treatment indicator using weighted proportional hazards models. We used robust SEs to account for clustering of patients within hospitals.

In addition to estimating an overall treatment effect, we assessed differences between prespecified subgroups by testing the significance of interaction terms between treatment and subgroup variables. This analysis focused on 3-year outcomes. Based on the interaction results, we repeated the main analyses for patients with reduced ejection fraction; we reevaluated the propensity model for these patients only, then estimated associations between treatment and outcomes in this subgroup using ejection fraction–specific weights.

In post hoc exploratory analyses, we used Cox proportional hazards models to examine associations between selected baseline characteristics and the outcomes of hospitalization for hyperkalemia or acute renal insufficiency among patients who were prescribed an MRA at hospital discharge.

Most variables had low rates of missingness. For variables with less than 5% missingness, we imputed continuous variables to the overall median value, dichotomous variables to "no," and multichotomous variables to the most frequent categorical value. For variables with more than 5% missingness, we treated the missing value as a separate category.

We report 95% confidence intervals (CIs) and used α=0.05 to establish statistical significance of tests. All tests were 2-sided. We used SAS software (version 9.4; SAS Institute Inc, Cary, NC) for all analyses. The institutional review board of the Duke University Health System approved the study. Informed consent was waived.

Results

Of 16 848 eligible patients, 2067 (12.3%) were prescribed MRA therapy at discharge. Table 1 shows the baseline characteristics of the study population. A higher proportion of patients on MRA therapy had diabetes mellitus (86.6% versus 82.2%), and a lower proportion had chronic kidney disease (27.8% versus 36.0%). In the overall study population, 6719 patients (39.9%) had reduced ejection fraction, and 10 129 (60.1%) had borderline or preserved ejection fraction. Patients receiving MRA therapy at discharge were more likely to have reduced ejection fraction at admission (60.5% versus 37%), and they had higher rates of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use (72.7% versus 62.6%) and β-blocker use (87.6% versus 81.2%). After weighting by the inverse probability of treatment, baseline characteristics were similar between treatment groups (Table S1).

Among the patient characteristics associated with receipt of MRA therapy in the treatment selection model were age (adjusted odds ratio [OR], 0.98; 95% CI, 0.97–0.99) and sex (adjusted OR for women, 0.89; 95% CI, 0.81–0.99; Table 2).

Table 2. Associations Between Patient Characteristics and Prescription of MRA Therapy at Hospital Discharge

Characteristic	Unadjusted OR (95% CI)	*P* Value	Adjusted* OR (95% CI)	*P* Value
Age, y	0.97 (0.97–0.98)	<0.001	0.98 (0.97–0.99)	<0.001
Women	0.78 (0.71–0.86)	<0.001	0.89 (0.81–0.99)	0.03
Race				
Black	1.06 (0.92–1.23)	0.42	1.14 (0.98–1.33)	0.09
White	1.00 [Reference]		1.00 [Reference]	
Other/unknown	1.12 (0.98–1.28)	0.08	0.97 (0.82–1.14)	0.71
Disease state				
Diabetes mellitus	1.40 (1.23–1.60)	<0.001	1.11 (0.93–1.33)	0.25
Renal insufficiency	0.68 (0.62–0.76)	<0.001	1.03 (0.89–1.20)	0.68
Medical history				
Anemia	0.77 (0.69–0.87)	<0.001	0.96 (0.85–1.08)	0.50
Atrial fibrillation	1.07 (0.97–1.17)	0.19	1.01 (0.92–1.12)	0.80
Chronic obstructive pulmonary disease	0.94 (0.85–1.04)	0.22	0.91 (0.82–1.01)	0.08
Depression	1.00 (0.86–1.17)	0.96	1.00 (0.85–1.17)	0.99
Heart failure with ischemic etiology				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.28 (1.16–1.41)	<0.001	1.08 (0.97–1.19)	0.16
Missing	1.09 (0.89–1.33)	0.42	0.97 (0.79–1.20)	0.78
Hyperlipidemia	1.09 (0.99–1.19)	0.08	1.03 (0.93–1.14)	0.61
Hypertension	0.86 (0.76–0.96)	0.01	0.94 (0.83–1.06)	0.32
Implantable cardioverter-defibrillator	1.97 (1.72–2.25)	<0.001	1.37 (1.18–1.58)	<0.001
Pacemaker	1.11 (0.99–1.25)	0.08	0.96 (0.85–1.09)	0.50
Peripheral vascular disease	0.80 (0.71–0.92)	0.001	0.80 (0.70–0.92)	0.002
Vital signs at admission				
Smoker in the past y	1.19 (1.02–1.38)	0.02	1.00 (0.86–1.18)	0.96
Heart rate	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	0.007
Respiratory rate ≥30 breaths/min	0.73 (0.59–0.91)	0.005	0.74 (0.59–0.93)	0.01
Tests at admission/discharge				
Systolic blood pressure	0.99 (0.99–0.99)	<0.001	1.00 (0.99–1.00)	<0.001
Reduced ejection fraction†	2.61 (2.38–2.87)	<0.001	2.34 (2.11–2.59)	<0.001
Serum creatinine	0.66 (0.62–0.70)	<0.001	0.66 (0.61–0.71)	<0.001
Serum potassium	0.86 (0.78–0.95)	0.002	1.00 (0.90–1.11)	0.98
Serum urea nitrogen	0.99 (0.99–0.99)	<0.001	1.00 (1.00–1.00)	0.87
Discharge year				
2005	0.90 (0.69–1.18)	0.46	0.78 (0.58–1.05)	0.10
2006	0.77 (0.65–0.92)	0.004	0.68 (0.55–0.84)	<0.001
2007	0.66 (0.54–0.79)	<0.001	0.58 (0.47–0.73)	<0.001
2008	0.60 (0.49–0.73)	<0.001	0.52 (0.41–0.66)	<0.001
2009	0.67 (0.55–0.81)	<0.001	0.63 (0.50–0.78)	<0.001
2010	0.67 (0.56–0.81)	<0.001	0.63 (0.50–0.78)	<0.001
2011	0.88 (0.74–1.05)	0.15	0.86 (0.69–1.05)	0.14
2012	1.10 (0.92–1.32)	0.28	1.05 (0.86–1.29)	0.63
2013	1.00 [Reference]		1.00 [Reference]	

CI indicates confidence interval; MRA, mineralocorticoid receptor antagonist; OR, odds ratio.

*Adjustment variables detailed in the Methods section.

†Reduced ejection fraction is defined as documentation of a left ventricular ejection fraction of 35% or less, or a qualitative assessment of moderate or severe left ventricular systolic dysfunction.

Table 3. Observed Outcomes of the Study Population

Outcome	MRA Therapy		*P* Value
	Yes (n=2067)	No (n=14 781)	
Mortality			
30 d	72 (3.5)	515 (3.5)	0.98
1 y	521 (27.2)	3887 (28.2)	0.41
3 y	896 (54.4)	7034 (57.5)	0.03
Readmission			
All causes*			
30 d	465 (22.7)	3531 (24.0)	0.20
1 y	1338 (68.2)	10 194 (72.2)	<0.001
3 y	1578 (84.9)	11 939 (88.2)	<0.001
Heart failure*			
30 d	162 (7.9)	1394 (9.5)	0.02
1 y	661 (34.1)	4996 (35.6)	0.09
3 y	854 (48.0)	6477 (49.2)	0.09
Hyperkalemia, primary diagnosis*			
30 d	…†	…†	<0.001
1 y	22 (1.1)	101 (0.7)	0.05
3 y	35 (2.1)	176 (1.4)	0.03
Hyperkalemia, any diagnosis*			
30 d	63 (3.1)	258 (1.8)	<0.001
1 y	200 (10.2)	1227 (8.8)	0.02
3 y	275 (15.7)	1928 (15.3)	0.32
Acute renal insufficiency, primary diagnosis*			
30 d	40 (2.0)	205 (1.4)	0.05
1 y	160 (8.2)	985 (7.1)	0.05
3 y	234 (13.6)	1633 (13.0)	0.34
Acute renal insufficiency, any diagnosis*			
30 d	163 (7.9)	1051 (7.2)	0.19
1 y	619 (31.8)	4255 (30.5)	0.18
3 y	873 (49.5)	6254 (48.5)	0.27

MRA indicates mineralocorticoid receptor antagonist.
*Death treated as a competing risk.
†In accord with the privacy policy of the Centers for Medicare & Medicaid Services, data for cells containing 10 or fewer observations and data for cells that would allow for calculation of cells containing 10 or fewer observations are not reported.

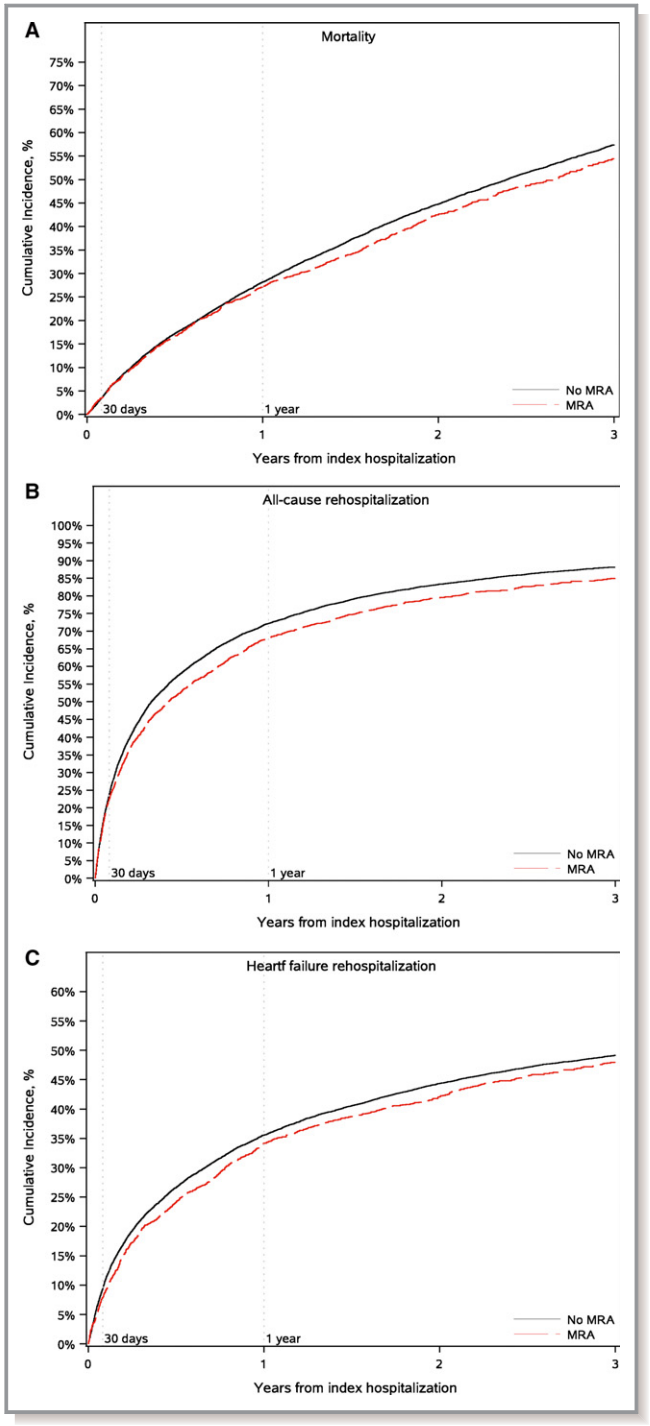

Figure 1. Cumulative incidence of mortality (A), all-cause hospitalization (B), and heart failure hospitalization (C). MRA indicates mineralocorticoid receptor antagonist.

MRA prescription was not associated with a history of diabetes mellitus or renal insufficiency after adjustment. Reduced ejection fraction was strongly associated with MRA prescription (adjusted OR, 2.34; 95% CI, 2.11–2.59). Although discharge serum creatinine was associated with MRA prescription (adjusted OR, 0.66; 95% CI, 0.61–0.71), serum potassium was not (adjusted OR, 1.00; 95% CI, 0.90–1.11).

Patients on MRA therapy had lower observed rates of 3-year mortality (54.4% versus 57.5%), 30-day heart failure readmission (7.9% versus 9.5%), and 1-year (68.2% versus 72.2%) and 3-year (84.9% versus 88.2%) all-cause readmission (Table 3; Figure 1). At 30 days, patients on MRA therapy had higher rates of readmission for hyperkalemia and acute renal insufficiency (Table 3; Figure 2), though overall only 18 patients were admitted within 30 days for hyperkalemia as a primary diagnosis.

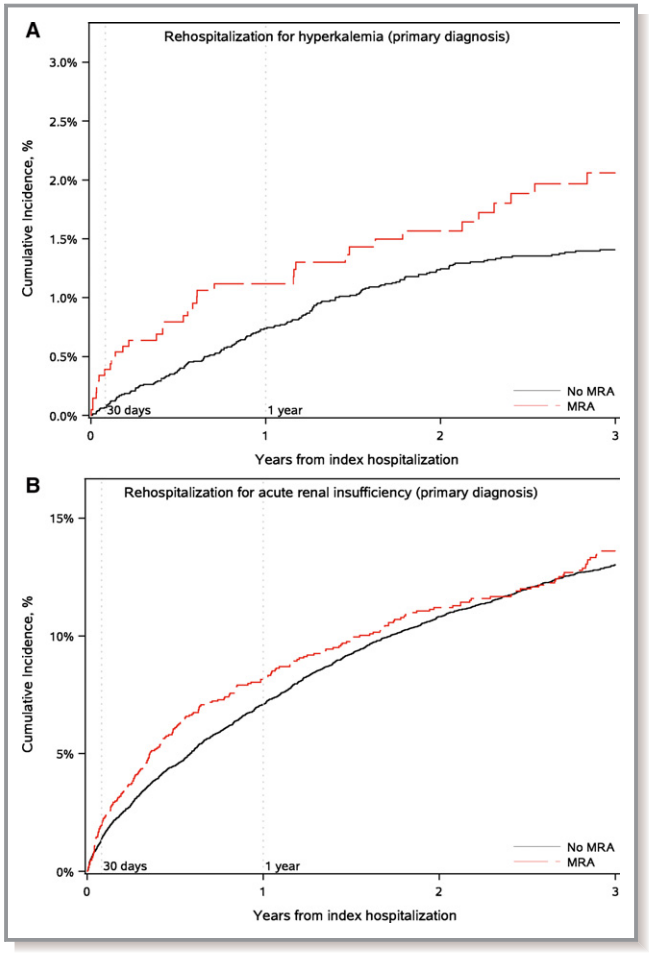

Figure 2. Cumulative incidence of hospitalization for hyperkalemia as the primary diagnosis (A) and acute renal insufficiency as the primary diagnosis (B). MRA indicates mineralocorticoid receptor antagonist.

After inverse probability weighting, MRA use was not associated with 30-day, 1-year, or 3-year mortality (Table 4) or with 30-day all-cause readmission (hazard ratio [HR], 0.97; 95% CI, 0.87–1.09). MRA use was associated with lower risk of readmission at 1 year (HR, 0.92; 95% CI, 0.87–0.98) and 3 years (HR, 0.93; 95% CI, 0.89–0.98). These relationships remained after additional adjustment for discharge medications.

In the weighted analyses, MRA use was associated with a greater risk of 30-day readmission with a diagnosis of hyperkalemia (HR, 2.08; 95% CI, 1.49–2.90) and acute renal insufficiency (HR, 1.31; 95% CI, 1.09–1.56), as well as at 1 and 3 years. MRA use was also associated with greater risk of readmission with a primary diagnosis of hyperkalemia at 1 year (OR, 2.67; 95% CI, 1.54–4.62) and 3 years (OR, 2.20; 95% CI, 1.42–3.41) and acute renal insufficiency at 30 days (OR, 1.65; 95% CI, 1.16–2.34), 1 year (OR, 1.32; 95% CI, 1.11–1.56), and 3 years (OR, 1.18; 95% CI, 1.02–1.38). These relationships remained after additional adjustment for discharge medications.

In the interaction analysis of reduced ejection fraction versus borderline or preserved ejection fraction, there were significant interactions for readmission for acute renal insufficiency as the primary (P=0.01) or any diagnosis (P<0.001), and for hyperkalemia in any diagnosis position (P=0.02; Table 5). Although MRA therapy was not associated with readmission for acute renal insufficiency at 3 years for patients with reduced ejection fraction (HR, 0.94; 95% CI, 0.75–1.18), it was associated with readmission for renal insufficiency among patients with borderline or preserved ejection fraction (HR. 1.34; 95% CI, 1.11–1.62). There were no significant interactions by ejection fraction for mortality, all-cause or heart failure readmission, or hyperkalemia in the primary diagnosis position. There were no significant interactions by disease history (ie, renal insufficiency or diabetes mellitus).

To further explore the role of subtype of heart failure, we restricted inverse probability weighting to patients with reduced ejection fraction (Table 6). MRA therapy was associated with lower risk of all-cause readmission at 3 years (HR, 0.91; 95% CI, 0.85–0.98), but not at 30 days or 1 year. This association remained after adjustment for discharge medications (HR, 0.93; 95% CI, 0.86–1.00). MRA therapy was not associated with greater risk of readmission with hyperkalemia. Unlike the overall analyses, there were no short-term or long-term associations between MRA therapy and hospitalization for acute renal insufficiency in the analysis restricted to patients with reduced ejection fraction.

In post hoc analyses restricted to patients who were prescribed MRA at discharge, we further explored associations between baseline characteristics and readmission for hyperkalemia or acute renal insufficiency by heart failure subtype. Among patients on MRA therapy with preserved ejection fraction, women had a greater 3-year risk of hospitalization for hyperkalemia (adjusted HR, 1.84; 95% CI, 1.28–2.64) and for acute renal insufficiency (adjusted HR, 1.28; 95% CI, 1.05–1.56; Table S2). Serum potassium was positively associated with increased risk of hyperkalemia (adjusted HR, 1.53; 95% CI, 1.02–2.30). Among patients with reduced ejection fraction, women had a greater risk of hospitalization for hyperkalemia (adjusted HR, 1.47; 95% CI, 1.10–1.95; Table S3), but not acute renal insufficiency (adjusted HR, 0.95; 95% CI, 0.76–1.19). Serum potassium was not associated with a greater risk of hyperkalemia in patients with reduced ejection fraction (adjusted HR, 1.33; 95% CI, 0.93–1.90).

Discussion

In this large, retrospective study of patients hospitalized with heart failure and concomitant diabetes mellitus and/or

Table 4. Associations Between MRA Therapy and Outcomes

	Unadjusted*		Weighted*		Weighted and Adjusted*,†	
Events	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Mortality						
30 d	1.01 (0.78–1.30)	0.96	0.94 (0.68–1.30)	0.69	0.97 (0.70–1.34)	0.84
1 y	0.96 (0.90–1.04)	0.31	0.99 (0.91–1.09)	0.89	1.00 (0.91–1.09)	>0.99
3 y	0.93 (0.87–0.99)	0.02	1.02 (0.94–1.09)	0.68	1.02 (0.95–1.10)	0.58
Readmission						
All causes						
30 d	0.94 (0.86–1.03)	0.20	0.97 (0.87–1.09)	0.63	0.98 (0.87–1.10)	0.73
1 y	0.89 (0.84–0.94)	<0.001	0.92 (0.87–0.98)	0.01	0.93 (0.87–0.98)	0.01
3 y	0.88 (0.84–0.92)	<0.001	0.93 (0.89–0.98)	0.006	0.94 (0.89–0.98)	0.01
Heart failure						
30 d	0.83 (0.72–0.96)	0.01	0.83 (0.69–0.99)	0.04	0.83 (0.69–1.00)	0.045
1 y	0.93 (0.86–1.00)	0.05	0.93 (0.84–1.03)	0.15	0.92 (0.83–1.02)	0.11
3 y	0.92 (0.87–0.98)	0.01	0.94 (0.87–1.02)	0.14	0.93 (0.85–1.01)	0.09
Hyperkalemia, any diagnosis						
30 d	1.77 (1.29–2.41)	<0.001	2.08 (1.49–2.90)	<0.001	2.11 (1.51–2.94)	<0.001
1 y	1.19 (1.02–1.38)	0.03	1.42 (1.18–1.71)	<0.001	1.44 (1.20–1.74)	<0.001
3 y	1.04 (0.91–1.21)	0.55	1.28 (1.09–1.51)	0.002	1.30 (1.11–1.53)	0.001
Acute renal insufficiency, any diagnosis						
30 d	1.12 (0.97–1.30)	0.13	1.31 (1.09–1.56)	0.003	1.31 (1.10–1.57)	0.003
1 y	1.05 (0.96–1.14)	0.26	1.17 (1.06–1.28)	0.001	1.16 (1.06–1.27)	0.002
3 y	1.01 (0.93–1.10)	0.78	1.14 (1.05–1.25)	0.004	1.14 (1.04–1.25)	0.005
Hyperkalemia, primary diagnosis						
30 d	...‡		...‡		...‡	
1 y	1.57 (0.97–2.54)	0.06	2.67 (1.54–4.62)	<0.001	2.90 (1.67–5.02)	<0.001
3 y	1.45 (0.97–2.17)	0.07	2.20 (1.42–3.41)	<0.001	2.34 (1.49–3.67)	<0.001
Acute renal insufficiency, primary diagnosis						
30 d	1.40 (1.03–1.90)	0.03	1.65 (1.16–2.34)	0.005	1.62 (1.13–2.31)	0.008
1 y	1.17 (1.02–1.35)	0.03	1.32 (1.11–1.56)	0.002	1.30 (1.10–1.54)	0.003
3 y	1.04 (0.91–1.19)	0.52	1.18 (1.02–1.38)	0.03	1.17 (1.01–1.36)	0.04

CI indicates confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist.

*Proportional hazards assumptions were assessed for 3-y weighted models: It was violated for hyperkalemia readmission, any diagnosis (P=0.02).

†Adjusted for discharge medications.

‡In accord with the privacy policy of the Centers for Medicare & Medicaid Services, data for cells containing 10 or fewer observations and data for cells that would allow for calculation of cells containing 10 or fewer observations are not reported.

chronic kidney disease, prescription of MRA therapy at discharge was not associated with a lower risk of mortality. MRA therapy was associated with lower long-term risk of all-cause readmission, but with greater short-term and long-term risks of readmission with acute renal insufficiency and hyperkalemia. The risk of acute renal insufficiency was limited to patients with borderline or preserved ejection fraction.

Two previous studies using data from the Get With the Guidelines-Heart Failure registry examined MRA therapy in heart failure and risks of adverse events.[11,23] Both studies focused on patients with reduced ejection fraction. Our work expands on previous work by including patients with reduced, borderline, and preserved ejection fraction; focusing on high-risk patients with diabetes mellitus and/or chronic kidney disease; and using more-recent data.

Table 5. Subgroup-Specific Treatment Effects at 3 Years, Based on the Weighted Model

Readmission Event	Hazard Ratio (95% CI)		*P* Value for Interaction
	Ejection Fraction >35%	Ejection Fraction ≤35%	
All-cause rehospitalization	0.96 (0.90–1.03)	0.89 (0.83–0.95)	0.13
Mortality	1.04 (0.93–1.16)	0.99 (0.89–1.08)	0.47
Heart failure rehospitalization	0.99 (0.88–1.12)	0.88 (0.79–0.97)	0.13
Hyperkalemia, any diagnosis	1.44 (1.17–1.78)	1.04 (0.86–1.25)	0.02
Hyperkalemia, primary diagnosis	2.31 (1.29–4.15)	1.96 (1.07–3.60)	0.71
Acute renal insufficiency, any diagnosis	1.29 (1.15–1.44)	0.94 (0.82–1.07)	<0.001
Acute renal insufficiency, primary diagnosis	1.34 (1.11–1.62)	0.94 (0.75–1.18)	0.01

CI indicates confidence interval.

In our study, 12% of patients were prescribed MRA therapy at discharge, and most of these patients had reduced ejection fraction. Using data from 2005 through 2007, Albert et al[11] likewise found that MRA therapy was markedly underused in appropriate patients, though rates of inappropriate and potentially inappropriate use were low. Patient characteristics associated with MRA therapy have not changed substantially, with age, systolic blood pressure, and presence of an implantable cardioverter-defibrillator strongly associated with prescription of MRA therapy. However, in the previous study, history of renal insufficiency was associated with a lower likelihood of receiving MRA therapy, whereas we found no such association.

We also found no association between MRA therapy and lower risk of mortality. Using data from 2005 through 2010, Hernandez et al[23] found that MRA therapy was not associated with lower risks of death or cardiovascular readmission overall, but was associated with a lower risk of heart failure readmission among patients with reduced ejection fraction. We found lower risks of heart failure readmission at 30 days and all-cause readmission at 1 and 3 years. The beneficial long-term association between MRA therapy and all-cause readmission was independent of ejection fraction and the presence of diabetes mellitus and chronic kidney disease. Although the appropriateness of MRA therapy in patients with preserved ejection fraction is uncertain on the basis of clinical trial data, our findings suggest a benefit in high-risk patients. Further study of MRA therapy in patients with heart failure and borderline or preserved ejection fraction is warranted.[2,26]

Although the benefits of MRA therapy are well known, adverse effects have also been documented. Past work showed an greater risk of 30-day and 1-year admission with hyperkalemia in patients with reduced ejection fraction who were treated with an MRA, compared with patients not receiving an MRA; however, there were few hospitalizations with a primary diagnosis of hyperkalemia.[23] Similarly, in our study patients at high risk for adverse events with MRA therapy, the risk of 30-day, 1-year, or 3-year hospitalization for a primary or other diagnosis of hyperkalemia was higher for patients on MRA therapy. In the stratified analyses, however, the association between MRA therapy and increased risk for hospitalization with hyperkalemia in any diagnosis position was limited to patients with borderline or preserved ejection fraction. Ejection fraction type did not significantly alter the positive association between MRA therapy and 3-year risk of hyperkalemia as a primary diagnosis; however, the absolute incidence of hyperkalemia as a primary diagnosis was very low in both groups even at 3 years. Among patients discharged on MRA therapy, women had a greater 3-year risk of hospitalization with a diagnosis of hyperkalemia in any diagnosis position compared with men, regardless of ejection fraction subtype. Notably, higher baseline serum potassium was associated with a greater risk of hyperkalemia among patients with borderline or preserved ejection fraction, but not among patients with reduced ejection fraction.

Similar to the risk of hyperkalemia, the risk of 30-day, 1-year, or 3-year hospitalization for a diagnosis of acute renal insufficiency was higher for patients on MRA therapy; however, this risk was limited to patients with borderline or preserved ejection fraction. In post hoc analyses restricted to patients discharged on MRA, the risk of 3-year hospitalization for acute renal insufficiency in any diagnosis position was greater among women with borderline or preserved ejection fraction, but not among women with reduced ejection fraction. Further research is needed to investigate the mechanisms of increased risk in certain populations.

Despite the greater risk of hospitalization for hyperkalemia and acute kidney injury, there was an overall decrease in the risk of hospitalization for patients treated with MRA therapy, suggesting the benefits of therapy may outweigh the risks in this high-risk population. Past analyses from landmark clinical trials of MRA therapy in heart failure had similar conclusions,

Table 6. Associations Between MRA Therapy and Outcomes Among Patients With Heart Failure With Reduced Ejection Fraction

	Unadjusted		Weighted		Weighted and Adjusted*	
Outcome	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Mortality						
30 d	0.99 (0.73–1.35)	0.97	1.08 (0.76–1.54)	0.66	1.15 (0.80–1.65)	0.46
1 y	0.86 (0.77–0.96)	0.007	1.03 (0.87–1.23)	0.71	1.07 (0.91–1.26)	0.40
3 y	0.84 (0.77–0.92)	<0.001	1.06 (0.95–1.18)	0.31	1.10 (0.99–1.22)	0.07
Readmission						
All causes						
30 d	0.87 (0.76–0.99)	0.04	0.89 (0.76–1.05)	0.16	0.91 (0.77–1.07)	0.25
1 y	0.85 (0.79–0.92)	<0.001	0.92 (0.85–1.00)	0.06	0.94 (0.86–1.02)	0.12
3 y	0.83 (0.78–0.89)	<0.001	0.91 (0.85–0.98)	0.01	0.93 (0.86–1.00)	0.04
Heart failure						
30 d	0.79 (0.65–0.97)	0.03	0.84 (0.66–1.06)	0.14	0.87 (0.68–1.10)	0.24
1 y	0.84 (0.75–0.93)	<0.001	0.92 (0.80–1.06)	0.25	0.94 (0.82–1.07)	0.34
3 y	0.81 (0.74–0.89)	<0.001	0.92 (0.82–1.03)	0.13	0.93 (0.83–1.04)	0.19
Hyperkalemia, any diagnosis						
30 d	1.36 (0.85–2.18)	0.20	1.37 (0.83–2.27)	0.22	1.41 (0.84–2.35)	0.20
1 y	1.08 (0.88–1.34)	0.46	1.13 (0.89–1.42)	0.31	1.13 (0.89–1.42)	0.31
3 y	0.94 (0.78–1.14)	0.55	1.08 (0.89–1.31)	0.43	1.09 (0.90–1.32)	0.38
Acute renal insufficiency, any diagnosis						
30 d	0.85 (0.66–1.11)	0.23	0.92 (0.68–1.26)	0.61	0.95 (0.70–1.29)	0.76
1 y	0.91 (0.80–1.02)	0.10	0.98 (0.86–1.13)	0.81	1.00 (0.88–1.15)	0.96
3 y	0.88 (0.79–0.99)	0.03	0.97 (0.85–1.10)	0.62	0.98 (0.87–1.11)	0.80
Hyperkalemia, primary diagnosis						
30 d	…†		…†		…†	
1 y	1.44 (0.68–3.01)	0.34	1.89 (0.86–4.16)	0.11	1.81 (0.83–3.94)	0.13
3 y	1.60 (0.86–2.96)	0.14	2.01 (1.08–3.73)	0.03	2.00 (1.08–3.72)	0.03
Acute renal insufficiency, primary diagnosis						
30 d	1.02 (0.61–1.69)	0.95	1.25 (0.71–2.23)	0.44	1.28 (0.72–2.28)	0.39
1 y	0.99 (0.81–1.22)	0.96	1.13 (0.89–1.45)	0.31	1.16 (0.91–1.47)	0.23
3 y	0.89 (0.73–1.07)	0.22	0.98 (0.78–1.23)	0.86	1.00 (0.80–1.24)	0.99

CI indicates confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist.

*Adjusted for discharge medications.

†In accord with the privacy policy of the Centers for Medicare & Medicaid Services, data for cells containing 10 or fewer observations and data for cells that would allow for calculation of cells containing 10 or fewer observations are not reported.

with sustained benefit of MRA therapy despite increased risk of adverse events.[12,19,27–29] Moreover, past work has shown that MRA therapy is beneficial even at higher serum potassium levels, up to a serum potassium level of 5.5 mmol/L.[19] Maximizing the beneficial effects of MRA therapy in heart failure will depend on minimizing risks of adverse events, particularly in patients at highest risk for adverse events. Novel therapeutic agents, such as potassium binders, may protect against hyperkalemia in patients with heart failure who are at risk of hyperkalemia with MRA use, though additional studies are needed.[30] Furthermore, development of more-selective MRA therapies may achieve the benefits of MRA therapy with fewer adverse events.[31,32] In addition, appropriate patient selection and laboratory monitoring during therapy may decrease the risk of adverse events.[33–35] These considerations warrant further investigation.

Our study has limitations. First, as in all observational studies, unmeasured confounders may have influenced the results. Second, the population was limited to Medicare fee-for-service beneficiaries, so the results may not be

generalizable to other populations. Also, patients were recently discharged from an acute heart failure hospitalization, so the results may not apply to stable outpatients with heart failure. Furthermore, hospital participation in the registry is voluntary, and the practices of participating hospitals may not reflect practices at hospitals that do not participate. Third, we were limited by the data available. For the Get With the Guidelines-Heart Failure registry, we were limited by the fields available in the registry and the completeness of each field, and for outcome data, we were limited to Medicare claims data. We only examined whether MRA therapy was prescribed at discharge, but we did not have information about doses prescribed. Furthermore, we did not analyze outpatient medication initiation, discontinuation, or adherence, though this has been reported in a past Get With the Guidelines-Heart Failure study, which found that eligible patients who were not prescribed an MRA at discharge were less likely to initiate it in the outpatient setting.[36] In addition, we did not have laboratory data with which to further explore the outcomes of hospitalizations for hyperkalemia or acute renal insufficency, so we were not able to comment on the severity of these adverse events. Finally, the results of our subgroup analyses must be interpreted with caution. For patients without quantitative assessment of ejection fraction, we used qualitative assessments, which may decrease the precision of these categories. Furthermore, we were unable to differentiate patients with recovered ejection fraction.

Conclusion

In conclusion, among older patients with heart failure and concomitant diabetes mellitus or renal insufficiency, MRA use was associated with lower risk of all-cause hospitalization despite increased risk of hospitalization with hyperkalemia or acute renal insufficiency. The increased risk of adverse events was mostly confined to patients with borderline or preserved ejection fraction. MRAs may be safe in a selected group of patients with heart failure and concomitant diabetes mellitus or renal insufficiency.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of the Study Population by Study Group After Application of Inverse Probability Weights.

Characteristic	MRA (n = 2067)	No MRA (n = 14,781)	Standardized Difference, %	*P* Value
Age, mean (SD), y	77.9 (7.8)	77.6 (7.6)	4.0	.09
Age group			0.7	.76
65-79 y	58.3	58.7		
≥ 80 y	41.7	41.3		
Men	51.2	50.6	1.1	.64
Race			1.7	.78
African American	11.1	11.4		
White	75.0	74.3		
Other/unknown	13.8	14.3		
Disease state				
Diabetes mellitus	82.4	82.7	1.0	.68
Chronic renal insufficiency	33.9	35.0	2.4	.30
Medical history				
Anemia	22.7	22.1	1.3	.57
Atrial fibrillation	37.3	35.6	3.5	.14
Chronic obstructive pulmonary disease	30.6	31.8	2.6	.28
Depression	9.5	9.7	0.5	.82
Heart failure with ischemic etiology			2.2	.63
No	43.3	44.3		
Yes	50.0	49.5		
Missing	6.7	6.3		
Hyperlipidemia	57.3	57.6	0.6	.81
Hypertension	82.4	83.2	2.1	.36
Implantable cardioverter-defibrillator	8.8	8.9	0.3	.90
Pacemaker	17.7	17.8	0.2	.92
Peripheral vascular disease	16.8	16.4	1.3	.58
Smoker in the past year	9.5	9.7	0.4	.87
Vital signs at admission				
Heart rate, mean (SD), bpm	81.5 (18.4)	82.1 (18.9)	3.1	.19
Respiratory rate ≥ 30 breaths/min, No. (%	5.9	6.0	0.7	.77
Systolic blood pressure, mean (SD), mm Hg	145.4 (31.0)	145.1 (29.6)	1.0	.67
Tests at admission/discharge				
Reduced ejection fraction at admission*	39.1	39.8	1.6	.50
Serum Creatinine, mean (SD), mg/dL	1.8 (1.1)	1.8 (1.2)	1.4	.57
Serum Potassium, mean (SD), mEq/L	4.1 (0.5)	4.1 (0.5)	1.3	.57
Serum urea nitrogen, mean (SD), mg/dL	35.2 (18.8)	34.5 (17.9)	4.0	.08
Discharge year			3.5	.97
2005	4.0	3.4		
2006	14.0	14.2		
2007	13.0	12.6		
2008	11.0	11.0		
2009	11.4	11.4		
2010	12.6	12.8		
2011	12.8	12.8		
2012	10.7	10.7		
2013	10.5	11.1		

*Reduced ejection fraction is defined as documentation of a left ventricular ejection fraction of 35% or less, or a qualitative assessment of moderate or severe left ventricular systolic dysfunction.

Table S2. Associations Between Baseline Characteristics and 3-Year Outcomes Among Patients With Heart Failure With Preserved Ejection Fraction.

	Hospitalization for Hyperkalemia (Any Position)		Hospitalization for Acute Renal Insufficiency (Any Position)	
Characteristic	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age, per 5 years	1.05 (0.92-1.19)	.46	0.98 (0.90-1.07)	.68
Women	1.84 (1.28-2.64)	.001	1.28 (1.05-1.56)	.01
Race				
African American	1.43 (0.85-2.40)	.18	1.00 (0.72-1.39)	.99
White	1.00 [Reference]		1.00 [Reference]	
Other/unknown	0.93 (0.51-1.72)	.83	0.90 (0.64-1.27)	.55
Medical History				
Diabetes mellitus	1.27 (0.61-2.62)	.52	1.06 (0.75-1.50)	.72
Anemia	1.10 (0.72-1.69)	.67	1.02 (0.74-1.38)	.92
Atrial fibrillation	1.28 (0.84-1.95)	.26	1.28 (1.05-1.57)	.01
Chronic obstructive pulmonary disease	1.23 (0.81-1.87)	.32	1.42 (1.18-1.71)	<.001
Depression	1.09 (0.61-1.94)	.77	1.16 (0.85-1.59)	.34
Heart failure with ischemic etiology	1.43 (0.93-2.19)	.10	1.03 (0.84-1.27)	.77
Hyperlipidemia	0.91 (0.58-1.42)	.68	1.06 (0.85-1.34)	.60
Hypertension	0.96 (0.56-1.65)	.89	0.97 (0.73-1.28)	.81
Implantable cardioverter-defibrillator	2.47 (1.05-5.81)	.04	1.33 (0.88-2.03)	.18
Pacemaker	0.71 (0.42-1.21)	.21	0.83 (0.63-1.09)	.17
Peripheral vascular disease	0.93 (0.54-1.58)	.78	1.21 (0.91-1.62)	.18
Smoker in the past year	0.98 (0.49-1.94)	.95	1.34 (0.98-1.84)	.07
Vital signs				
Heart rate	0.97 (0.92-1.02)	.25	0.96 (0.93-0.99)	.01
Respiratory rate ≥ 30 breaths/min	2.00 (0.90-4.44)	.09	1.10 (0.62-1.92)	.75
Systolic blood pressure	1.04 (0.97-1.10)	.29	0.99 (0.94-1.03)	.57
Laboratory tests				
Serum creatinine	1.37 (1.07-1.76)	.01	1.22 (1.03-1.46)	.02
Serum potassium	1.53 (1.02-2.30)	.04	1.13 (0.88-1.46)	.34
Serum urea nitrogen	1.00 (0.99-1.01)	.87	1.01 (1.01-1.02)	<.001

Table S3. Associations Between Baseline Characteristics and 3-Year Outcomes Among Patients With Heart Failure With Reduced Ejection Fraction

	Hospitalization for Hyperkalemia (Any Position)		Hospitalization for Acute Renal Insufficiency (Any Position)	
Characteristic	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age, per 5 years	1.09 (0.96-1.23)	.19	1.08 (1.00-1.16)	.04
Women	1.47 (1.10-1.95)	.008	0.95 (0.76-1.19)	.66
Race				
African American	0.64 (0.39-1.06)	.08	0.97 (0.71-1.32)	.83
White	1.00 [Reference]		1.00 [Reference]	
Other/unknown	0.72 (0.39-1.32)	.28	0.78 (0.59-1.03)	.09
Medical History				
Diabetes mellitus	0.74 (0.49-1.12)	.16	0.80 (0.61-1.05)	.11
Anemia	1.09 (0.72-1.66)	.68	1.06 (0.85-1.32)	.63
Atrial fibrillation	1.14 (0.83-1.56)	.43	1.12 (0.92-1.36)	.25
Chronic obstructive pulmonary disease	1.18 (0.87-1.60)	.30	1.20 (1.01-1.44)	.04
Depression	0.93 (0.53-1.65)	.81	1.33 (1.04-1.70)	.02
Heart failure with ischemic etiology	1.42 (1.00-2.01)	.05	1.18 (1.03-1.36)	.02
Hyperlipidemia	0.94 (0.64-1.39)	.77	1.00 (0.81-1.25)	.97
Hypertension	1.12 (0.72-1.76)	.61	1.11 (0.88-1.39)	.39
Implantable cardioverter-defibrillator	1.47 (0.98-2.19)	.06	1.42 (1.15-1.75)	.001
Pacemaker	0.72 (0.48-1.08)	.11	0.90 (0.72-1.13)	.38
Peripheral vascular disease	1.29 (0.82-2.04)	.27	1.16 (0.89-1.50)	.27
Smoker in the past year	1.32 (0.78-2.24)	.30	1.05 (0.77-1.42)	.77
Vital signs				
Heart rate	1.01 (0.96-1.06)	.72	0.97 (0.95-0.99)	.006
Respiratory rate ≥ 30 breaths/min	0.91 (0.43-1.95)	.82	0.92 (0.57-1.51)	.75
Systolic blood pressure	0.97 (0.91-1.03)	.31	1.00 (0.96-1.04)	.92
Laboratory tests				
Serum creatinine	1.19 (0.99-1.44)	.06	1.12 (0.97-1.30)	.11
Serum potassium	1.33 (0.93-1.90)	.12	1.03 (0.85-1.25)	.75
Serum urea nitrogen	1.01 (1.00-1.02)	.03	1.02 (1.01-1.02)	<.001