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Guideline Concordance of Testing for Hyperkalemia and Kidney Dysfunction During Initiation of Mineralocorticoid Receptor Antagonist Therapy in Patients with Heart Failure

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Abstract

Background—Mineralocorticoid receptor antagonists (MRA) reduce morbidity and mortality in heart failure with reduced ejection fraction (HFREF), but can cause hyperkalemia and acute kidney injury. Guidelines recommend measurement of serum potassium (K) and creatinine (Cr) before and serially after MRA initiation, but the extent to which this occurs is unknown.

Methods and Results—Using electronic data from 3 health systems 2005-2008, we performed a retrospective review of laboratory monitoring among 490 patients hospitalized for HFREF who were subsequently initiated on MRA therapy. Median age at time of MRA initiation was 73 years and 37.1% were female. Spironolactone accounted for 99.4% of MRA use. Initial ambulatory MRA dispensing occurred at hospital discharge in 70.0% of cases. In the 30 days before MRA initiation, 94.3% of patients had a K or Cr measurement. Pre-initiation K was >5.0 mmol/L in 1.4% and Cr >2.5 mg/dL in 1.7%. In the 7 days after MRA initiation among patients who remained alive and out of the hospital, 46.5% had no evidence of K measurement; by 30 days, 13.6% remained untested. Patient factors explained a small portion of post-initiation K testing (c-statistic 0.67).

Conclusions—While laboratory monitoring prior to MRA initiation for HFREF is common, laboratory monitoring following MRA initiation frequently does not meet guideline recommendations, even in patients at higher risk for complications. Quality improvement efforts that encourage the use of MRA should also include mechanisms to address recommended monitoring.

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Disclosures
None.

Keywords

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The aldosterone / mineralocorticoid receptor antagonists (MRA)—spironolactone and eplerenone—reduce hospitalization and death among patients with heart failure and reduced left ventricular ejection fraction (HFREF). The Randomized Aldactone Evaluation Study (RALES),[1] Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[2] and Eplerenone in Mild Patients Hospitalization and Survival Study (EMPHASIS)[3] provide strong evidence for the use of an MRA in a broad range of patients with HFREF.

Notwithstanding their overall efficacy in selected patients, MRA carry an increased risk of hyperkalemia and acute renal injury. In RALES, the median increase in serum potassium compared to control was 0.3 mmol/L, with rates of serious hyperkalemia 2% for spironolactone versus 1% for placebo. In EPHESUS, serum potassium ≥ 6.0 mmol/L occurred in 5.5% of eplerenone-treated patients versus 3.9% of placebo. These risks are potentially exacerbated by the presence of cardiorenal syndrome or chronic kidney disease, whose prevalence was underrepresented in trial populations.[4] Frequent abnormalities in serum potassium and kidney function after MRA initiation have been confirmed in observational data,[5] and may translate into increased adverse events.[6,7]

Recognizing these potential dangers, clinical practice guidelines mirror testing protocols from MRA trials. The 2005 American College of Cardiology (ACC) / American Heart Association (AHA) Guideline for the Evaluation and Management of Heart Failure stated, “Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months,”[8] a recommendation that has remained essentially unchanged in the 2009[9] and 2013[10] guideline updates. The European Society of Cardiology guidelines have also consistently recommended “to check blood chemistry 1 week and 4 weeks after starting/increasing dose”.[11,12] The extent to which these recommendations are being followed in routine practice has not been well characterized.[13]

Therefore, we set out to describe laboratory monitoring patterns for patients initiated on MRA in a large, multi-center, community-based cohort of adults with HFREF. Our aims were to 1) characterize patient selection for MRA therapy, 2) describe the frequency and results of pre-initiation monitoring, 3) describe the frequency and timing of post-initiation monitoring, 4) identify factors associated with failure to perform recommended laboratory monitoring after MRA initiation, and lastly 5) explore the association between early post-initiation testing and subsequent clinical outcomes.

Methods

Data Source

Participating health plans for the present study were Kaiser Permanente Colorado, Kaiser Permanente Northwest, and Fallon Community Health Plan.[14,15] These health plans serve an ethnically and socioeconomically diverse population across varying clinical practice settings and geographically diverse areas. A Virtual Data Warehouse (VDW) at each site served as a distributed standardized data resource comprised of electronic datasets, populated with linked demographic, administrative, ambulatory pharmacy, outpatient laboratory test results, and health care utilization data.[16,17] For the present study, laboratory data were limited to

the ambulatory setting, as detailed inpatient clinical data were not consistently captured across study sites. Institutional review boards at participating sites approved the study and waiver of consent was obtained due to the nature of the study.

Patient Population

All persons aged ≥21 years with diagnosed HF based on a hospitalization with a primary discharge diagnosis of HF between January 1, 2005 through December 31, 2008 using *International Classification of Diseases, 9th Edition* (ICD-9) codes: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x. Prior studies have shown a positive predictive value of >95% for HF when compared with Framingham clinical criteria.[18-20]

Assessments of left ventricular ejection fraction (LVEF) were ascertained for each HF patient from echocardiograms, nuclear imaging modalities, and left ventriculography test results available from site-specific databases complemented by manual chart review. The measure obtained closest to the index date of study entry was used. We restricted the cohort to HFREF by requiring the summary LVEF to be quantitatively ≤40% or qualitatively described as “moderately” or “severely” reduced.[21] Patients without a documented LVEF measurement were excluded (24.6%).

Patients were required to have a new pharmacy dispensing of either spironolactone or eplerenone at any time after HF hospitalization, with no prior dispensing of these agents (Figure 1). MRA use was determined using filled outpatient prescriptions from health plan databases.

Covariates

Baseline covariates used to describe the cohort and perform multivariate modeling were chosen *a priori* based on presumed interactions with MRA therapy, previously published HF prognostic models, and availability within the VDW. We determined the presence of coexisting illnesses based on diagnoses or procedures using relevant ICD-9 codes, CPT procedure codes, as well as site-specific diabetes mellitus and cancer registries.[17]

Outcomes

Reflecting clinical guideline recommendations, we assessed serum potassium and creatinine measurement in the 30-days preceding MRA dispensing, the 7 days following MRA dispensing, and the 30 days following MRA dispensing. We also used a Kaplan-Meier estimate for time to the first serum potassium measure following MRA dispensing during available follow up. Subjects were censored at the time they were hospitalized, died, disenrolled from the health plan, or reached the end of study follow-up (December 31, 2008). Hospitalizations were identified from each site’s VDW. Deaths were identified from hospital and billing claims databases, administrative health plan databases, state death certificate registries, and Social Security Administration files as available at each site.[15,19]

Statistical Analysis

We described baseline patient characteristics overall and stratified by serum potassium measure, no measure, or death/hospitalization in the 7 days after initial MRA dispensing. Continuous variables were ordinalized using cut points chosen based on clinically meaningful values. Missing covariate data were treated as a separate category. Statistical significance was evaluated using Wilcoxon rank sum tests for continuous variables and chi-square or Fisher’s exact tests for categorical variables.

Step-wise multivariable logistic regression was employed to examine the independent relationship between baseline characteristics and failure to perform laboratory monitoring in the week after MRA initiation, with model performance characterized using c-statistics and Nagelkerek pseudo-R^2. Variable selection included predetermined key variables of clinical interest (age, gender, baseline serum potassium and creatinine), as well as additional variables with significant univariate associations. Missing heart rate and blood pressure measures were imputed to the median.

Cox proportional hazards models were used to assess the relationship between testing 1-7 days after MRA initiation and the outcome of all-cause hospitalization or death 8-90 days after MRA initiation; variables included in the model were taken from the Yale readmission risk calculator.[22]

All analyses were conducted using SAS statistical software, version 9.1 (Cary, NC).

Results

In total, 490 patients with HFREF were initiated on MRA in the ambulatory setting. Median age was 73.6 years and 37.1% were female (Table 1). Spironolactone accounted for 99.4% of MRA use and eplerenone 0.6% of use. The starting dose of MRA was 12.5 mg per day in 33.9%, 25 mg per day in 60.0%, and 50 mg per day in 7.1%. MRA was initially dispensed in 57.8% of patients at the time of a hospital discharge and within 1-7 days of a hospital discharge in an additional 12.2% of the cohort. Concomitant use of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) was 73.5%; concomitant dispensing of both ACEI and ARB in the setting of MRA initiation was 0.6%. Use of an MRA in the absence of a loop diuretic was 23.7%. Use of an MRA with concomitant use of oral potassium supplementation was 40.8%.

Pre-initiation laboratory testing

In the 30 days before initial MRA dispensing, ambulatory serum potassium measurement was noted for 69.0%; an additional 25.3% of patients had no ambulatory monitoring but were hospitalized during this pre-initiation period, presumably with laboratory monitoring during the hospitalization. Therefore, 5.7% of patients had no direct or indirect evidence of a serum potassium measurement in the 30 days before MRA initiation. Serum creatinine measurements closely paralleled serum potassium measures (absolute differences <1%). Among patients with available measurements, median pre-initiation serum potassium was 4.1 mmol/L (IQR 3.9-4.5); 1.2% [n=6] of patients had a potassium level above the recommended cutoff of 5.0 mmol/L on the measurement immediately preceding MRA initiation. Median pre-initiation serum creatinine was 1.4 mg/dL (IQR 1.1-1.6); 1.6% [n=8] had a creatinine level above the recommended cutoff of 2.5 mg/dL on the measurement immediately preceding MRA initiation (Table 2).

Post-initiation laboratory testing

Among the 443 patients who remained alive and out of the hospital (non-hospitalized and no urgent or emergency care visits) in the 7 days after MRA initiation, 46.5% (n=206) of patients did not have evidence of serum potassium measured 1-7 days following MRA dispensing. For the subset of patients with first ambulatory MRA dispensing occurring at or within 7 days of a hospital discharge, 43.6% (n=136/312) had no evidence of 7-day post-initiation serum potassium measurement; for those with first ambulatory MRA dispensing greater than a week after hospital discharge, 53.4% (n=70/131) had no evidence of 7-day post-initiation serum potassium measurement. After excluding patients (n=75) who were hospitalized, died, or had health plan enrollment termination in the 8-30 days after MRA

initiation,13.6% (n=50/368) of patients had no evidence of serum potassium measurement in the entire 30 days from MRA dispensing. For those patients who were monitored within 7 days and did not suffer death or hospitalization in the 30 days after MRA dispensing, the rate of a second potassium measurement in between days 8-30 was 67.5% (n=127/203). Figure 2 depicts a Kaplan-Meier analysis of time to potassium measurement, with censoring for hospitalization, death, or health plan disenrollment.

Factors associated with failure to monitor

A combination of patient demographics, comorbidities, laboratory testing, vital signs, and medication use explained a relatively small portion of post-initiation K testing patterns (cstatistic 0.67). See Table 3 for details.

Association with post-initiation monitoring and subsequent outcomes

In the 8-90 days after MRA initiation among patients that remained alive and out of the hospital in the first 7 days, death occurred in 6.2% (n=14/225) of those with 7-day serum potassium testing compared to 6.1% (n=12/196) of those without 7-day potassium testing (0.31 versus 0.29 deaths per person years, respectively; p=0.97). All cause hospitalization was also similar, with 1.70 hospitalizations per person years for patients with 7-day post-initiation serum potassium testing compared to 1.61 hospitalizations per person years for patients without 7-day testing (p=0.41). Cox proportional hazards modeling was not statistically significant for the association between testing 1-7 days post MRA initiation and mortality or hospitalization 8-90 days post-initiation, although was underpowered to assess small but clinically meaningful differences (adjusted hazards ratio 1.18, 95% confidence interval 0.83-1.62).

Discussion

In this study of patients with HFREF in managed care plans, laboratory monitoring following initiation of MRA frequently did not meet guideline recommendations. While almost all patients had a baseline serum potassium and creatinine test (or a hospitalization with assumed testing) in the month before initiation of MRA, nearly half of patients had no evidence of a repeat serum potassium and creatinine measurement in the 7 days following initial MRA dispensing. Due to concerns about MRA-mediated hyperkalemia and renal dysfunction, particularly among patients outside of the narrow eligibility criteria and close supervision inherent in randomized controlled trials, such testing has been recommended since 2005, with all major heart failure clinical practice guidelines currently endorsing testing within at least a week of MRA initiation and again at 4 weeks.[8-11,23]. Not only were there gaps between observed and recommended post-initiation testing patterns, testing had little association with risk (i.e., lack of testing was not confined to the lowest risk patients). Finally, MRA initiation appeared to occur at a dose higher than recommended or with concomitant potassium supplementation in a significant minority of patients. These results highlight a need for education and systems of care that enhance appropriate safety monitoring, particularly if quality improvement initiatives[24] and performance measures[25] are implemented to increase the use of MRA in patients with HFREF.

The laboratory testing patterns seen here are concordant with older studies documenting suboptimal monitoring following initiation of MRA[13] and other high-risk medications in general populations.[26] In a study looking at laboratory evaluation among all ambulatory patients dispensed spironolactone in 1999-2000 within 10 health maintenance organizations (regardless of indication), 27.7% of patients had not had a follow-up test for potassium and creatinine over the next 13 months.[13] Contemporary patterns of laboratory monitoring have

not been described in detail for HFREF populations, and speak to the novelty of our findings.

The results presented here do not address the reasons for nonadherence to monitoring recommendations for MRA use in HFREF. Prior study has shown that a computerized system of monitoring alerts managed by pharmacists increased the number of patients who received laboratory safety monitoring of drug therapy;[27] in contrast, laboratory monitoring alerts within a computerized physician order entry system have not improved monitoring.[28] These data suggest that physicians may not be best positioned to order follow up testing. Furthermore, our study assessed the actual performance of laboratory testing, not the intent of prescribing clinicians to obtain such testing in follow-up. The high rate of pre-initiation testing (the absence of which may allow a provider not to prescribe MRA) but subsequently low post-initiation testing (over which a provider has less control) suggest that many gaps in recommended testing may be related to system execution and patient adherence with such testing.

Whether greater monitoring may improve safety and help increase the benefit of MRA use in real-world HFREF patients remains to be determined.[7,29] Theoretically, improvements in adherence to guideline recommended laboratory monitoring can lead to pre-emptive changes in MRA dosing, thereby avoiding some unnecessary adverse events. Yet, interventions that improve laboratory monitoring have not necessarily translated into cost-effective mechanisms to improve clinical outcomes, particularly if not concentrated among high-risk patients[30] and targeted to the health care providers best suited to implement suggested monitoring.[31]

The policy implications of laboratory testing related to MRA use are important. Appropriate MRA use is the lowest of major recommended therapies for HFREF.[24, 32] Yet, a joint report from the ACC/AHA Task Force on Performance Measures and the American Medical Association Physician Consortium for Performance Improvement decided not to include MRA use: "…treatment with aldosterone receptor antagonists was considered but not developed because of the large number of patients excluded from the denominator because of renal insufficiency or hyperkalemia before or during treatment with these agents. In addition, the development of serious renal failure or hyperkalemia in large numbers of patients might be an unintended consequence of the broad implementation of such a measure."[25] Development of effective systems for laboratory monitoring before and after MRA initiation may assuage these concerns, thereby allowing for responsible MRA performance measures that help larger numbers of real-world HFREF patients realize the benefits of MRA seen in randomized trials.

Potential Limitations

Insured populations in our participating health plans may not be fully representative of the general U.S. population or international populations. Nevertheless, the demographic diversity represented across 3 geographically diverse health plans, as well as the community-based nature of health care delivery, suggest that findings from our cohort are likely to be highly generalizable to patients with HFREF in "real-world" practice settings. The data used here to define MRA initiation come from the dispensing date of prescribed MRA, which may misclassify some patients who start their drug at a later date or who do not end up taking it at all. Laboratory testing may occur outside the health plan electronic data capture, either at distant sites or at contract hospitals; however, the potential for such missing data is small as patients are financially discouraged from out-of-system testing and our methods accounted for non-network hospitalizations. Most patients initiating ambulatory MRA within a day of hospital discharge presumably had been started on MRA during hospitalization with laboratory monitoring during the hospital course; regardless, such

patients are relatively high risk for ongoing serum potassium and creatinine changes following discharge, and thus multiple organizations now recommend clinic follow up and laboratory testing within a week after any HF hospital discharge.

Conclusion

Laboratory monitoring following initiation of an MRA in real world practice frequently does not meet guideline recommendations. Given the known risks of MRA, quality improvement efforts that encourage the use of MRA for HFREF should also consider effective mechanisms to ensure appropriate monitoring. The extent to which poor monitoring reduces safety and explains the lack of benefit for MRA seen in observational studies should be further evaluated.

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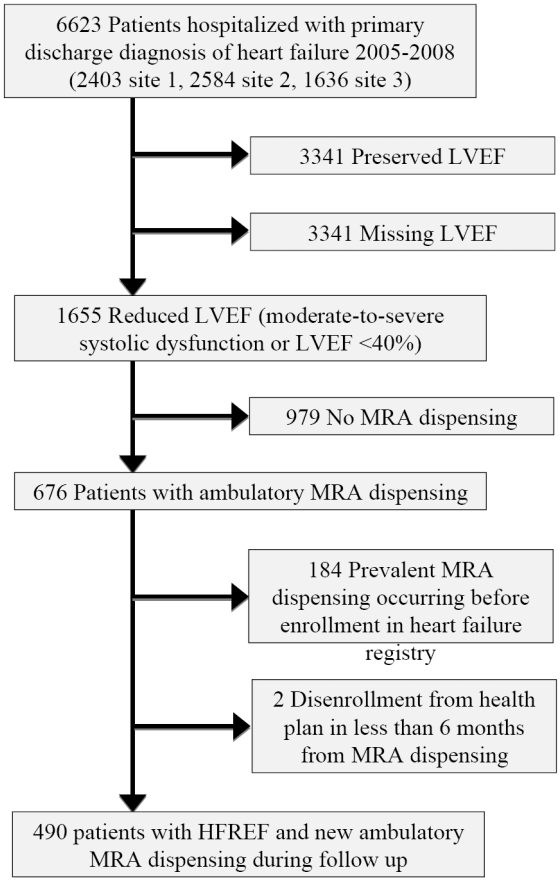

Figure 1.
Cohort selection.

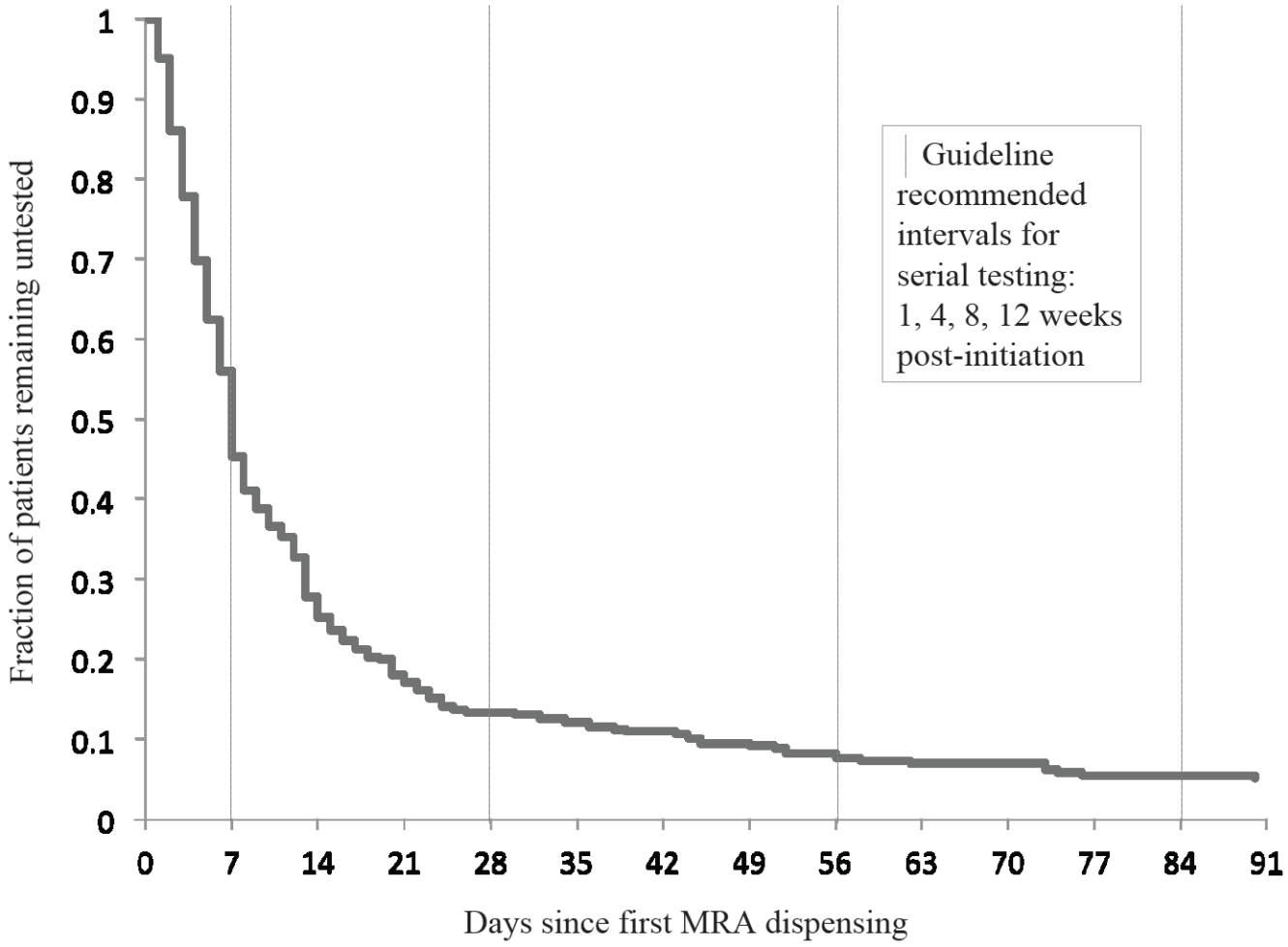

Figure 2.
Kaplan-Meier curve of time to serum potassium measurement from first mineralocorticoid receptor antagonist (MRA) dispensing, with censoring for death, hospitalization, or plan disenrollment.

Table 1

Characteristics of patients with prior hospitalization for heart failure with reduced left ventricular ejection fraction at the time of initiation of a mineralocorticoid receptor antagonist, stratified by death/hospitalization, serum potassium measure, or no measure in the 7 days after initial MRA dispensing.

Characteristic	EXCLUDED due to death or hospitalization within 7 days N=47 (9.6% of 490)	ELIGIBLE for 7 day testing comparisons N=443 (90.4% of 490)		
		TESTING ≤7 days from MRA dispensing N=237 (53.5% of 443)	NO testing ≤7 days of MRA dispensing N=206 (46.5% of 443)	P value*
Age in years, median (IQR)	76 (66, 84)	73 (62, 81)	74 (61, 80)	0.97
Age categories, n (%)				
Age ≤65	10 (21.3%)	76 (32.1%)	64 (31.1%)	0.58
Age 65-74	10 (21.3%)	60 (25.3%)	45 (21.8%)	
Age ≥75	27 (57.5%)	101 (42.6%)	97 (47.1%)	
Female gender, n (%)	22 (46.8%)	87 (36.7%)	73 (35.4%)	0.78
Cardiac History, n (%)				
LVEF, median (IQR)	0.25 (0.20, 0.33)	0.25 (0.20-0.33)	0.25 (0.20-0.30)	0.65
Missing LVEF	8 (17.0%)	82 (34.6%)	56 (27.2%)	0.12
Acute myocardial infarction	7 (14.9%)	39 (16.5%)	23 (11.2%)	0.11
Coronary artery bypass surgery	2 (4.3%)	17 (7.2%)	8 (3.9%)	0.14
Coronary stent or angioplasty	5 (10.6%)	30 (12.7%)	24 (11.7%)	0.75
Atrial fibrillation or flutter	9 (19.1%)	48 (20.3%)	33 (16.0%)	0.25
Ventricular tachycardia	2 (4.3%)	16 (6.8%)	4 (1.9%)	0.02
Rheumatic valvular disease	7 (14.9%)	11 (4.6%)	5 (2.4%)	0.21
ICD	4 (8.5%)	19 (8.0%)	18 (8.7%)	0.78
Pacemaker	5 (10.6%)	23 (9.7%)	18 (8.7%)	0.73
Medical History, n (%)				
Ischemic stroke or TIA	4 (8.5%)	16 (6.8%)	9 (4.4%)	0.28
Peripheral arterial disease	16 (34.0%)	27 (11.4%)	26 (12.6%)	0.69
Dyslipidemia	27 (57.4%)	126 (53.2%)	97 (47.1%)	0.20
Hypertension	22 (46.8%)	117 (49.4%)	100 (48.5%)	0.86
Diabetes mellitus	9 (19.1%)	42 (17.7%)	38 (18.4%)	0.42

Characteristic	EXCLUDED due to death or hospitalization within 7 days N=47 (9.6% of 490)	ELIGIBLE for 7 day testing comparisons N=443 (90.4% of 490)		
		TESTING ≤7 days from MRA dispensing N=237 (53.5% of 443)	NO testing ≤7 days of MRA dispensing N=206 (46.5% of 443)	P value*
Diagnosed dementia	8 (17.0%)	25 (10.5%)	22 (10.7%)	0.96
Diagnosed depression	8 (17.0%)	51 (21.5%)	38 (18.4%)	0.42
Chronic lung disease	20 (42.6%)	85 (35.9%)	80 (38.8%)	0.52
Chronic liver disease	2 (4.3%)	9 (3.8%)	13 (6.3%)	0.23
Systemic cancer	12 (25.5%)	16 (6.8%)	18 (8.7%)	0.43
Medications at initial dispensing ambulatory MRA				
Spironolactone	47 (100%)	235 (99.2%)	205 (99.5%)	0.99
Eplerenone	0 (0%)	2 (0.8%)	1 (0.5%)	
Starting MRA dose, mg/24hr				
≤12.5 mg	11 (23.4%)	92 (38.8%)	63 (30.6%)	0.08
25 mg	20 (63.8%)	127 (53.6%)	132 (64.1%)	
≥50 mg	6 (12.8%)	18 (7.6%)	11 (5.3%)	
Potassium supplement	18 (38.3%)	107 (45.1%)	75 (36.4%)	0.06
Loop diuretic	32 (68.1%)	187 (78.9%)	155 (75.2%)	0.36
Thiazide-type diuretic	4 (8.5%)	33 (13.9%)	19 (9.2%)	0.13
ACEI	22 (46.8%)	156 (65.8%)	135 (65.6%)	0.95
ARB	2 (4.3%)	24 (10.1%)	24 (11.7%)	0.61
Beta-blocker	26 (55.3%)	190 (80.2%)	164 (79.6%)	0.88
Digoxin	17 (36.2%)	104 (43.9%)	89 (43.2%)	0.89
Vitals				
Systolic blood pressure, mmHg, median (IQR)	121 (108, 132)	122 (110, 140)	120 (110, 140)	0.90
Missing Systolic BP	5 (10.6%)	11 (4.6%)	17 (8.3%)	0.12
<=90	5 (10.6%)	13 (5.5%)	9 (4.4%)	0.30
91-110	3 (6.4%)	58 (24.5%)	52 (25.2%)	
111-140	13 (27.7%)	103 (43.5%)	89 (43.2%)	
141-160	21 (44.7%)	40 (16.9%)	22 (10.7%)	

Characteristic	EXCLUDED due to death or hospitalization within 7 days N=47 (9.6% of 490)	ELIGIBLE for 7 day testing comparisons N=443 (90.4% of 490)		
		TESTING ≤7 days from MRA dispensing N=237 (53.5% of 443)	NO testing ≤7 days of MRA dispensing N=206 (46.5% of 443)	P value*
>160	3 (6.4%)	12 (5.1%)	17 (8.3%)	
Heart rate, bpm, median (IQR)	80 (64, 96)	83.5 (72, 99)	78 (66, 89)	<0.001
Missing heart rate	5 (10.6%)	11 (4.6%)	18 (8.7%)	0.08
Discharged to a facility location (nursing home, skilled nursing, rehab unit, or another hospital)		9 (3.8%)	12 (5.8%)	

* p values are from Fisher's exact test and chi-square test for categorical variables and Wilcoxon Rank Sum for continuous variables, and compare testing within 7 days to no testing within 7 days.

MRA=mineralocorticoid receptor antagonist; IQR=interquartile range; LVEF=left ventricular ejection fraction; ICD=implantable cardioverter-defibrillator; TIA=transient ischemia attack; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker.

Table 2

Pre-initiation laboratory testing of patients with prior hospitalization for heart failure with reduced left ventricular ejection fraction (HFREF) at the time of initiation of a mineralocorticoid receptor antagonist (MRA), stratified by serum potassium measure, or no measure in the 7 days after initial MRA dispensing.

Characteristic	EXCLUDED due to death or hospitalization within 7 days N=47 (9.6% of 490)	ELIGIBLE for 7 day testing comparisons N=443 (90.4% of 490)		P value*
		TESTING ≤7 days from MRA dispensing N=237 (53.5% of 443)	NO testing ≤7 days of MRA dispensing N=206 (46.5% of 443)	
Potassium, serum, prior to initiation of MRA (mmol/L), median, (IQR) (N=299)	4.1 (3.6, 4.4)	4.2 (3.9-4.5)	4.1 (3.9-4.5)	0.61
Potassium, serum, prior to initiation of MRA (mmol/L), n (%)				
>5.51	0	0	0	0.31
5.01-5.50	0	5 (2.1%)	1 (0.5%)	
4.51-5.00	5 (13.5%)	30 (12.7%)	29 (14.1%)	
4.01-4.50	24 (37.8%)	65 (27.4%)	43 (20.9%)	
3.51-4.00	9 (24.3%)	61 (25.7%)	42 (20.4%)	
<=3.50	9 (24.3%)	10 (4.2%)	13 (6.3%)	
Labs not available: Hospitalized within prior 30 days†	7 (14.9%)	51 (21.5%)	66 (32.0%)	0.012
No labs, no hospitalization within prior 30 days	3 (6.4%)	15 (6.3%)	12 (5.8%)	0.83
Creatinine, serum, prior to initiation of MRA (mg/dL), median, (IQR) (N=307)	1.1 (0.9,1.5) (N=47)	1.2 (1.0-1.4) (N=176)	1.1 (0.9-1.4) (N=131)	0.10
Creatinine, serum, prior to initiation of MRA (mg/dL), n (%)				
>3.00	1 (2.8%)	2 (0.8%)	0 (0%)	0.62
2.51-3.00	0	3 (1.3%)	2 (1.0%)	
2.01-2.50	4 (11.1%)	6 (2.5%)	3 (1.5%)	
1.51-2.00	3 (8.3%)	15 (6.3%)	13 (6.3%)	
1.01-1.50	15 (41.7%)	98 (41.4%)	63 (30.6%)	
<=1.00	13 (36.1%)	52 (21.9%)	50 (24.3%)	

Characteristic	EXCLUDED due to death or hospitalization within 7 days N=47 (9.6% of 490)	ELIGIBLE for 7 day testing comparisons N=443 (90.4% of 490)		P value*
		TESTING ≤7 days from MRA dispensing N=237 (53.5% of 443)	NO testing ≤7 days of MRA dispensing N=206 (46.5% of 443)	
Labs not available, hospitalized within prior 30 days†	8 (17.0%)	48 (20.3%)	63 (30.6%)	0.012
No labs, no hospitalization within prior 30 days	3 (6.4%)	13 (5.5%)	12 (5.8%)	0.88

*p values are from Fisher's exact test and chi-square test for categorical variables and Wilcoxon Rank Sum for continuous variables, and compare testing within 7 days to no testing within 7 days.

†Missing labs prior to MRA initiation are primarily due to hospitalization in prior 30 days from hospital facilities where laboratory data was unavailable; 81% of subjects missing an outpatient serum potassium measure prior to MRA start were hospitalized in prior 30 days. Percentages were not significantly different for subjects with and without potassium monitoring within 7 days of MRA start: 76.9% and 84.6%, respectively; p=0.24.

MRA=mineralocorticoid receptor antagonist; IQR=interquartile range.

Table 3

Performance of baseline factors in predicting serum potassium testing in the 7 days after mineralocorticoid receptor antagonist (MRA) initiation.

Model Covariates	c-statistic	Pseudo R^2
Age, gender	0.50	0.0007
Age, gender, **pre-initiation** serum **potassium and creatinine**[*]	0.56	0.0192
Age, gender, pre-initiation serum potassium and creatinine, **MI, CABG, PCI, V-tach, dyslipidemia**, starting **dose of MRA**, prescription for **potassium chloride**, prescription for **thiazide** diuretic, **heart rate, systolic blood pressure**[†]	0.67	0.1129
Age, gender, K levels, CR levels, MI, CABG, PCI, V-tach, starting dose of MRA, drug indicators for potassium chloride and thiazide diuretic, dyslipidemia, heart rate, systolic BP, **site, year of MRA start**	0.70	0.1620

[*] Pre-initiation serum potassium and creatinine were categorized: potassium missing, ≤4.50 mmol, and > 4.50 mmol; creatinine missing, ≤1.50 mg/dL, and >1.50 mg/dL.

[†] Median used for missing heart rate and systolic blood pressure. Addition of LVEF as continuous covariate for subjects with a quantitative measure did not significantly influence c-statistic or R.