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ORIGINAL RESEARCH ARTICLE

Mineralocorticoid receptor antagonist use following heart failure hospitalization

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Abstract

Aims Patients hospitalized for heart failure (HF) are at increased risk for events post-discharge. Mineralocorticoid receptor antagonists (MRAs) improve the clinical course of patients with HF with reduced ejection fraction. We assessed MRA use in high-risk patients following an HF hospitalization to determine rate of MRA prescription, likelihood of drug continuation post-discharge, reasons for discontinuation, and association between MRA maintenance and outcomes.

Methods and results Patients admitted to our hospital system between 2011 and 2013 were identified retrospectively through automated search of electronic medical records for appropriate ICD 9 and 10 codes. Patients with left ventricular ejection fraction $<$40%, New York Heart Association class III–IV symptoms, $>$1 year of follow-up and no contraindication to MRA use were included. Of 271 patients meeting inclusion criteria, 105 (38.7%) were prescribed an MRA on discharge from index admission. Over a median follow-up of 3.12 ± 0.09 years, 70 (66.7%) continued MRA therapy, while 35 (33.3%) discontinued MRA therapy. Hyperkalemia, which occurred in 43 of the 105 patients (40.1%), was the most frequent cause of MRA discontinuation. Patients who maintained MRA therapy had significantly less all-cause, cardiovascular, and HF hospitalizations and significantly better survival compared with those who discontinued drug.

Conclusions A minority of HF with reduced ejection fraction patients who were eligible for an MRA received them following HF hospitalization and nearly a third of them discontinued drug. Patients who discontinued an MRA were more likely to be hospitalized or die during follow-up. These findings indicate a need for better strategies to increase MRA prescription and maintain therapy following a hospitalization for HF.

Keywords Heart failure; Mineralocorticoid receptor antagonist; Hyperkalemia; Outcomes

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Introduction

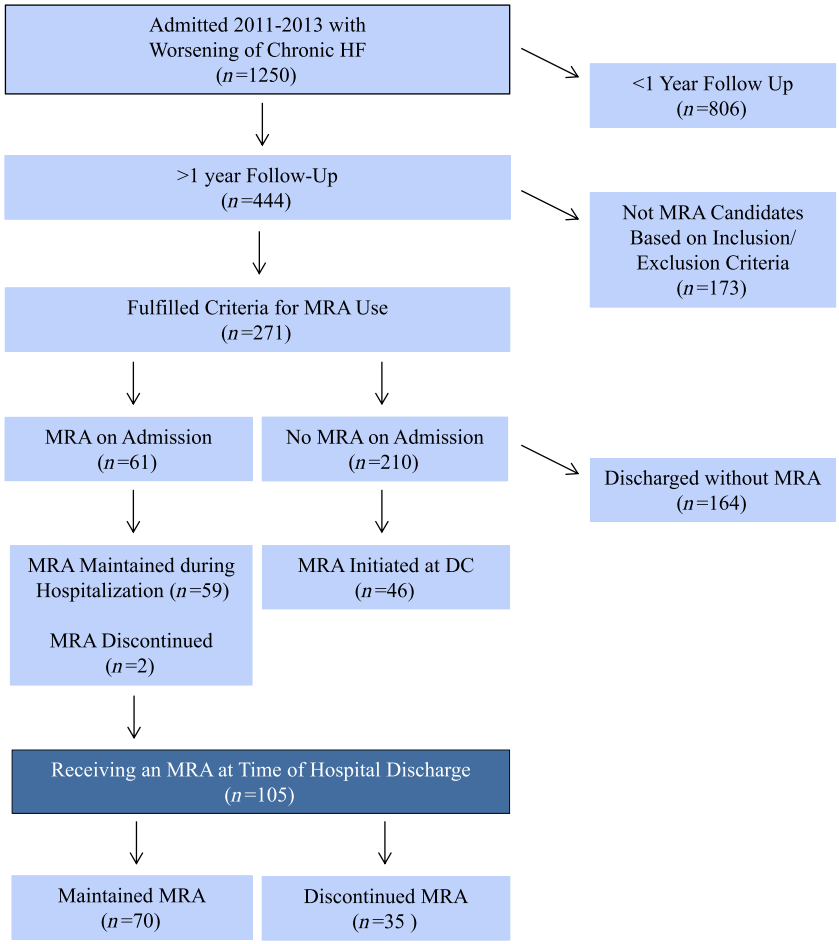
Mineralocorticoid receptor antagonists (MRAs) have been shown in clinical trials to improve outcomes in patients with heart failure (HF).[1–3] Based on compelling evidence from these trials, MRAs received Class I recommendations in both American and European guidelines in patients with HF with reduced ejection fraction (HFrEF).[4–9] Although considerable variability in MRA use has been reported, most studies indicate that a substantial proportion of eligible HF patients are not taking these drugs.[10–20] Hospitalization because of exacerbation of HF is common in HFrEF patients and has been identified as a potent risk factor for subsequent morbidity and mortality. Studies assessing the effects of MRAs on outcomes following HF hospitalization have shown mixed results[10–18,21] and whether or not they improve the clinical course of patients during the post-discharge period remains uncertain. Consequently, we performed retrospectively an analysis of consecutive patients hospitalized with a primary discharge diagnosis of HF over a 3 year period at our institution and identified those who would be considered eligible for an MRA according to contemporary guideline recommendations. Our goal was to determine frequency of MRA prescription at the time of discharge, whether therapy was maintained over time, reasons

for discontinuation, and the association between discontinuing an MRA and outcomes in this population.

Methods

Collection of all patient data and review of electronic health records was approved and overseen by the University of California, San Diego (UCSD) Internal Review Board, which ensures that this investigation conforms with the principles outlined in the the Declaration of Helsinki. As our study was retrospective, a waiver of consent was granted by the UCSD Internal Review Board as our study poses minimal risk to those patients whose data were collected. Patients admitted to UCSD Hospitals in San Diego and La Jolla, CA from 1 January 2011 to 31 December 2013, for exacerbation of chronic HF were identified retrospectively through automated search of EPIC Systems (Madison, WI) electronic medical records for ICD 9 and 10 codes for systolic HF exacerbation. As shown in *Figure 1*, of the 1250 patients hospitalized for HF over this time, 444 had >1 year follow-up in our clinics (either general cardiology or heart failure clinics). Manual chart review of the medical records of all of these patients was performed to identify patients for whom MRAs were recommended in the available guidelines. Inclusion in this analysis was based on the presence of EF < 40% and history of New York Heart Association class III–IV symptoms and the absence of specific contraindications to MRA use including hyperkalemia or chronic kidney disease according to guideline recommendations[4–7,22,23] or if there were documented provider concerns about a patients' ability to obtain follow-up blood draws to assess potassium levels and kidney function. Patients with New York Heart Association Class II symptoms were not included because a Class 1 recommendation for MRA use in this group became available only during the latter portion of the time period in which patients were identified for this analysis. Patients were also excluded if hospitalization was planned or scheduled for elective procedures (e.g. cardiac catheterizations, pacemaker placement, and device

Figure 1 Consort flow diagram of MRA use following admission for exacerbation of systolic heart failure at the University of California San Diego Health System between 2011 and 2013. HF, heart failure; MRA, mineralocorticoid receptor antagonist.



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generator changes). Overall, 173 of the 444 patients were excluded based on the these criteria, leaving a total of 271 patients who fulfilled the entry criteria described above. Of these, 34 were included in the analysis despite having a left ventricular ejection fraction (LVEF) of 40–50% during index admission if they had documented LVEF <40% on prior studies or LVEF that was sustained at levels <40% on echocardiograms done within 1 year after the index hospitalization.

Baseline patient characteristics were collected from index hospitalization including age (years), gender and patient-designated ethnicity, length of stay during index hospitalization (days), and presenting vital signs from the initial emergency department encounter during index hospitalization (heart rate and systolic and diastolic blood pressure). Values for creatinine and serum potassium obtained prior to discharge were used in this analysis in order to more accurately reflect baseline renal function (as many of the hospitalized patients included in this analysis had evidence of impaired renal function that improved during the course of the hospitalization). The patient's body weight and BMI at first follow-up clinic visit was used as it was considered to be the best indication of the patient's euvolemic baseline weight. Comorbidities were identified from each patient's problem list on the discharge summary from index hospitalization. In 186/271 (69%) of the patients, LVEF measurement from transthoracic echocardiography was performed during index hospitalization. In the remaining 85 patients, the most recent LVEF measurement from either a transthoracic echocardiography performed within the previous 1 year (in 61 patients) or within 30 days after index admission (in 24 patients) was used.

Information regarding use of guideline-directed heart failure medications and the dose prescribed at discharge was extracted from the medical record, including whether the patient was taking an MRA on admission, if it was continued through discharge, or if an MRA was newly initiated prior to discharge. The dose of each guideline heart failure medication was converted to the equivalent of the following medications in each drug class, respectively: angiotensin converting enzyme (ACE) inhibitors, enalapril; angiotensin receptor blockers (ARBs), losartan; beta blockers, carvedilol; and loop diuretics, furosemide.

After index hospital admission, every follow-up clinic visit to UCSD cardiology clinics was reviewed for the duration of the approved study period (until 31 December 2015). We tracked whether MRAs were continued or discontinued at each clinic visit, verified whether the prescriptions for MRAs were refilled (through the medications tracking tab in EPIC), and recorded the documented reason for drug discontinuation (renal dysfunction, hyperkalemia, etc.) as outlined in cardiology clinic notes. Patients were considered to have continued MRA therapy if they maintained MRA treatment without interruption until the end of the study period (or until the time that they received a left ventricular assist device or orthotopic heart transplant and therefore no longer had a guideline indication for MRA treatment) or if they had no more than one episode of drug discontinuations and had received MRA therapy for at least 180 days (6 months). Patients who received an MRA for less than 180 days were considered to have discontinued drug. The number of hyperkalemic episodes (with documented serum potassium >5.5 mEq/dL) resulting in MRA discontinuation experienced by each patient is reported as the number of these episodes per patient. Patients were followed for the duration of the study period to determine how many times they were rehospitalized because of any cause (all-cause hospitalizations), cardiovascular cause (cardiovascular hospitalizations), or heart failure (heart failure hospitalization). The date of death or survival through the duration of study was also recorded from each patient chart.

Student's *t*-test was used to determine statistical differences between baseline characteristics, guideline-directed drug doses, rates of rehospitalizations after index admission, and episodes of hyperkalemia per patient. Fisher's exact test was used to determine statistical differences between gender distribution and comorbidities and to determine statistical differences between rates of guideline heart failure medication prescription at discharge from index hospitalization. A Kaplan–Meier regression was used to determine survival differences between patients who were or were not tolerant of MRA therapy over the duration of the study, and a log-rank test was used to determine statistical differences in survival between these two groups. To account for the possible influence of confounding factors on the clinical events assessed in this study, multivariable analysis controlling for differences in clinical variables at baseline between patients who continued MRA therapy (ON MRA) and those who did not (OFF MRA) was performed using multiple linear regression for continuous variables (i.e. rates of hyperkalemia, all-cause rehospitalization, cardiovascular rehospitalization, HF rehospitalization, and hyperkalemia) and multiple logistic regression for mortality. Variables were selected for this analysis based on clinical relevance or differences in baseline characteristics with *P* values <0.20. These variables included age, gender, creatinine, use of ACEi/ARB, loop diuretic dose, length of stay, diastolic blood pressure, use of nitrates, and hypertension. The multivariable analysis was conducted in IBM SPSS Statistics v25.0 (IBM Corp. Armonk, NY). For all statistical testing, a *P* value <0.05 was considered statistically significant.

Results

MRA prescription at discharge from HF hospitalization

Of the 271 patients who fulfilled inclusion and exclusion criteria for this analysis, 61 (22.5%) were taking MRA on admission (*Figure 1*). Of these, 59 continued therapy

throughout hospitalization, and an MRA was prescribed on discharge. Two patients who experienced hyperkalemia in the setting of worsening renal function during hospitalization had MRA therapy discontinued. While in hospital, 46 additional patients of the 210 who were eligible (21.9%) were started on an MRA, so that at discharge a total of 105 of 269 (38.0%) patients who were considered eligible for an MRA based on guideline recommendations were prescribed this therapy. For the 164 eligible patients who were discharged without MRA, the rationale for not starting drug was documented in the medical records of only 19 patients (12%). In these patients, although provider notes mentioned concern about renal dysfunction or hyperkalemia as a reason for not prescribing a MRA, documentation of an eGFR <30 mL/min/1.73 m^2 or serum potassium $>$ 5.0 mEq/L (values cited in guideline recommendations as contraindications to MRA use[9,22]) was found in only eight of the patients.

Characteristics of patients discharged with and without an MRA

To gain insight into why patients who were eligible for an MRA were not prescribed one at discharge, the baseline characteristics of the 105 patients who were prescribed an MRA at discharge were compared with the 145 eligible patients who were discharged without MRA (*Table 1*). Patients discharged without an MRA tended to be older, had higher systolic blood pressure and LVEF, and were more likely to be white and to have a history of coronary artery disease and hypertension. They also were less likely to be treated with beta blockers and loop diuretics. Notably, baseline serum creatinine and potassium levels did not differ significantly between patient groups discharged with and without an MRA.

Table 1 Characteristics of patients discharged from index hospital admission with MRAs (105) or without MRA treatment (n = 164)

	No MRA (n = 164)	MRA (n = 105)	P value
Baseline characteristics			
Age (years)	63.75 ± 1.31	54.93 ± 1.44	<0.0001
Body mass index (kg/m^2)	27.64 ± 0.55	29.47 ± 0.88	0.08
Length of stay (days)	5.76 ± 0.47	6.33 ± 0.56	NS
Heart rate (bpm)	89.62 ± 1.99	85.44 ± 1.86	NS
Systolic BP (mmHg)	131.00 ± 1.76	124.60 ± 2.31	0.031
Diastolic BP (mmHg)	79.40 ± 1.50	76.90 ± 1.83	NS
Creatinine (mg/dL)	1.27 ± 0.07	1.22 ± 0.04	NS
Potassium (mmol/L)	4.09 ± 0.04	4.14 ± 0.04	NS
Ejection fraction (%)	31.37 ± 0.79	27.45 ± 0.96	0.0016
Gender	—	—	NS
Female	48 (33.1%)	29 (27.6%)	—
Male	97 (66.9%)	76 (72.4%)	—
Ethnicity	—	—	0.035
White	79 (54.5%)	45 (42.9%)	—
Black	22 (15.2%)	30 (28.6%)	—
Asian/Pacific Island	14 (9.7%)	7 (6.7%)	—
Latino	8 (5.5%)	2 (1.9%)	—
Other	22 (15.2%)	21 (20.0%)	—
Comorbidities			
Arrhythmias	74 (51.0%)	57 (54.3%)	NS
Chronic obstructive pulmonary disease	15 (10.3%)	15 (14.3%)	NS
Coronary artery disease	83 (57.2%)	39 (37.1%)	0.0021
Diabetes mellitus	44 (30.3%)	28 (26.7%)	NS
Hyperlipidaemia	71 (49.0%)	44 (41.9%)	NS
Hypertension	90 (62.1%)	51 (48.6%)	0.039
Malignancy	23 (15.9%)	12 (11.4%)	NS
Substance abuse			
Smoking	74 (51.0%)	66 (62.9%)	0.071
Alcohol	30 (20.7%)	20 (19.1%)	NS
Illicit drugs	33 (22.8%)	27 (25.7%)	NS
Heart failure medications			
ACEi/ARBs	116 (80.0%)	88 (83.8%)	NS
Beta blockers	129 (89.6%)	103 (98.1%)	0.0095
Digoxin	32 (22.1%)	21 (20.0%)	NS
Loop diuretics	119 (82.6%)	98 (93.3%)	0.013
Nitrates	18 (12.4%)	19 (18.1%)	NS

ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; BP, blood pressure; NS, not significant; MRA, mineralocorticoid receptor antagonist.
Values for baseline characteristics are presented as mean ± SEM.

Table 2 Characteristics of patients who discontinued (n = 35) or maintained MRA (n = 70).

	Discontinued MRA (n = 35)	Maintained MRA (n = 70)	P value
Baseline characteristics			
Age (years)	56.20 ± 2.62	54.71 ± 1.70	NS
Body mass index (kg/m^2)	29.98 ± 1.50	29.17 ± 1.09	NS
Length of stay (days)	7.26 ± 0.75	5.48 ± 0.54	NS
Heart rate (bpm)	84.77 ± 3.79	85.46 ± 2.06	NS
Systolic BP (mmHg)	124.30 ± 4.19	124.60 ± 2.80	NS
Diastolic BP (mmHg)	80.89 ± 3.68	74.79 ± 2.02	NS
Creatinine (mg/dL)	1.44 ± 0.09	1.14 ± 0.04	0.0015
Potassium (mmol/L)	4.16 ± 0.08	4.12 ± 0.05	NS
Ejection fraction (%)	26.66 ± 1.71	27.84 ± 1.16	NS
Gender	—	—	NS
Female	10 (28.6%)	19 (27.1%)	—
Male	25 (71.4%)	51 (72.9%)	—
Ethnicity	—	—	NS
White	16 (45.7%)	30 (42.9%)	—
Black	12 (34.3%)	17 (24.3%)	—
Asian/Pacific Island	2 (5.7%)	5 (7.1%)	—
Latino	0 (0.0%)	2 (2.9%)	—
Other	5 (14.3%)	16 (22.9%)	—
Comorbidities			
Arrhythmias	20 (57.1%)	36 (51.4%)	NS
COPD	7 (20.0%)	8 (11.4%)	NS
CAD	12 (34.3%)	27 (38.6%)	NS
Diabetes mellitus	12 (34.3%)	16 (22.9%)	NS
Hyperlipidaemia	18 (51.4%)	26 (37.1%)	NS
Hypertension	21 (60.0%)	20 (42.9%)	NS
Malignancy	2 (5.7%)	11 (15.7%)	NS
Substance abuse			
Smoking	23 (65.7%)	42 (60.0%)	NS
Alcohol	6 (17.1%)	14 (20.0%)	NS
Illicit drugs	6 (17.1%)	20 (28.6%)	NS
Heart failure medications			
ACEi/ARBs	25 (71.4%)	62 (88.6%)	0.052
Beta blockers	35 (100.0%)	68 (97.1%)	NS
Digoxin	5 (14.3%)	16 (22.9%)	NS
Loop diuretics	32 (91.4%)	66 (94.3%)	NS
Nitrates	9 (25.7%)	10 (14.3%)	NS

ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NS, not significant; MRA, mineralocorticoid receptor antagonist.

Table 3 Average dose of heart failure medications. The doses of each class of guideline-directed heart failure medications were calculated and reported as mean dose equivalent for enalpril (ACE inhibitors), losartan (ARBs), carvedilol (beta blockers), furosemide (loop diuretics), or isosorbide mononitrate (nitrates).

Dose equivalent	Discontinued MRA (n = 35)	Maintained MRA (n = 70)	P value
Enalapril	9.55 ± 2.00 (n = 22)	9.00 ± 1.15 (n = 50)	NS
Losartan	54.17 ± 25.34 (n = 3)	68.75 ± 9.80 (n = 12)	NS
Carvedilol	11.43 ± 1.47 (n = 35)	13.42 ± 1.60 (n = 68)	NS
Digoxin	0.15 ± 0.03 (n = 5)	0.14 ± 0.01 (n = 16)	NS
Furosemide	125.00 ± 13.74 (n = 32)	85.00 ± 7.87 (n = 66)	0.015
Isosorbide mononitrate	62.22 ± 12.45 (n = 9)	43.50 ± 7.23 (n = 10)	NS

Mean doses total daily doses of digoxin was reported for each group. Error bars reflect standard error of the mean (SEM).
ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; NS, not significant; MRA, mineralocorticoid receptor antagonist.

Characteristics of patients according to MRA maintenance following discharge

As shown in *Figure 1*, of the 105 patients who were discharged on MRAs, 70 patients (67%) maintained therapy, while 35 patients (33%) discontinued therapy because of permanent or frequent lapses in MRA use. When the characteristics of patients who discontinued MRA use were compared with those who maintained therapy (*Table 2*), the groups did not significantly differ in respect to age, gender, vital signs, comorbidities, or in the frequency of prescription of other HF medications aside from a trend towards lower

Table 4 Beta blocker and ACE/ARB prescription at hospital discharge

	Discontinued MRA (n = 35)	Maintained MRA (n = 70)	P value
Beta blockers			NS
Target dose	8 (22.9%)	14 (20.0%)	—
Below target dose	27 (77.1%)	54 (77.1%)	—
Not taking	0 (0%)	2 (2.9%)	—
ACEi/ARB			NS
Target dose	13 (37.1%)	33 (47.1%)	—
Below target dose	12 (34.3%)	29 (41.4%)	—
Not taking	10 (28.6%)	8 (11.4%)	—

Proportion of patients who were taking target doses as recommended by AHA/ACC heart failure guidelines, patients who were taking these medications but below guideline target doses, or patients not taking these medications at time of discharge from index hospital admission. Contingency analyses were used to calculate statistical significance between groups of patients who discontinued (n = 35) or maintained MRA (n = 70).
ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NS, not significant; MRA, mineralocorticoid receptor antagonist.

likelihood of being prescribed an ACEi or an ARB (71.43% vs. 88.56%; P = 0.05) in patients who discontinued the MRA. The group which subsequently discontinued MRA during follow-up had significantly higher serum creatinine on day of discharge than those who maintained MRA (1.44 ± 0.09 vs. 1.14 ± 0.04 mg/dL; P = 0.0015), but potassium levels were similar in the groups.

Table 3 summarizes the dose of HF medications prescribed at discharge in the groups of patients who subsequently discontinued or maintained MRA therapy. The dose of other HF medications including that of ACEis and ARBs was similar between the groups except for significantly higher daily doses of furosemide at discharge in patients who discontinued MRA therapy (125.00 ± 13.74 vs. 85.00 ± 7.87 mg; P = 0.0146).

As shown in *Table 4*, of the patients who discontinued MRA (n = 35), none were discharged from index admission without beta blocker. However, only 22.9% (8/35) were taking guideline recommended target doses, while 77% (27/35) were receiving doses below target. A similar distribution was seen in the patients who continued MRA (n = 70), where 20% (14/70) were on target dose, 77% (54/70) were on a dose below target, and 2.9% (2/20) were not on a beta blocker. For ACEi/ARB therapy, 28.6% (10/35) of the patients who discontinued MRA (n = 35) were not on one of these drugs, while 37.1% (13/35) and 34.3% (12/35) were on target or below target doses, respectively. This distribution was not significantly different from that seen in the patients who continued MRA of whom 11.4% (8/70) were not taking one of these drugs, while 47.1% (33/70) and 41.4% (28/70) were on target or below target doses.

Occurrence of hyperkalemia and progressive renal dysfunction during MRA treatment

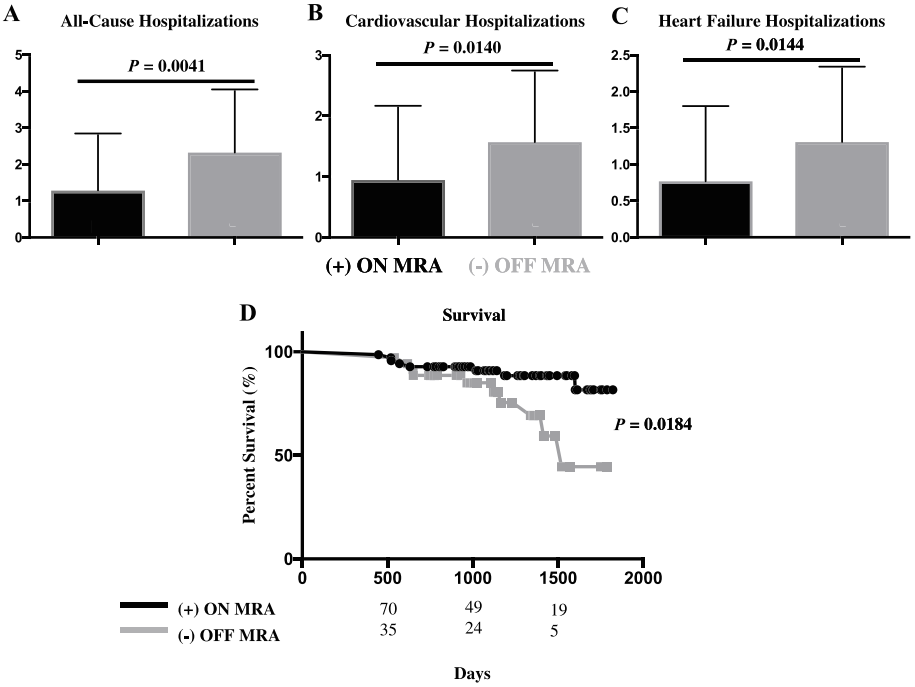
Overall, 61 number of episodes of hyperkalemia occurred in 36 number of the 105 patients discharged from hospital on an MRA. Patients in whom MRA therapy was discontinued experienced significantly more documented episodes of hyperkalemia per patient than those who maintained therapy (1.14 ± 0.20 vs. 0.36 ± 0.08 episodes per patient; P = 0.0006) and this difference persisted when multivariable analysis was performed (β coefficient −0.41; 95% CI −1.1 to −3.5; $P < 0.001$).

These patients also had a numerically greater frequency of discontinuations because of progressive renal dysfunction (acute kidney injury or progression to chronic kidney disease Stage IV–V or end-stage renal disease) than patients who continued on MRA (20% vs. 13%), but this difference was not statistically significant.

Association between maintenance of MRA therapy and outcomes

As shown in *Figure 2*, compared with patients who discontinued MRA therapy, those who maintained MRA therapy experienced significantly lower rates of rehospitalization per year because of any cause (1.29 ± 0.19 vs. 2.32 ± 0.29; P = 0.0041), cardiovascular causes (0.95 ± 0.15 vs. 1.57 ± 0.20; P = 0.0140) or heart failure (0.77 ± 0.12 vs. 1.31 ± 0.18; P = 0.0144). Patients who discontinued MRA also had significantly worse survival than did patients who maintained MRA use. To examine the possible influence of confounding factors on our clinical outcomes, we have performed multivariable analysis of the interaction between relevant baseline characteristics between patients who tolerated MRA (ON MRA) and those who did not tolerate MRA therapy (OFF MRA). Patients who tolerated MRA therapy had significantly lower all-cause mortality, lower rates of all-cause hospitalizations, cardiovascular hospitalizations, heart failure hospitalizations (*Figure 2E*) with adjustments for baseline characteristics (age, gender, creatinine, ACE/ARB, diuretic dose, length of stay, diastolic blood pressure, nitrates, and hypertension).

Figure 2 Outcomes of patients discharged from index admission on MRAs. Number of rehospitalizations during study period for patients ON or OFF MRA therapy because of (A) any cause, (B) any cardiovascular cause, or (C) heart failure. Statistical significance calculated using Student's *t*-test. (D) Kaplan–Meier regression showing survival of patients +ON MRA or –OFF MRA over the course of the study. Number of patients in each group at risk at each follow-up time point listed below the curve. Statistical significance calculated using log-rank test. (E) Multivariable analysis using multiple logistic regression and multiple linear regression for clinical outcomes for patients who were continued ON MRA vs. OFF MRA (reference group) with adjustment for age, gender, creatinine, ACE/ARB, diuretic dose, length of stay, diastolic blood pressure, nitrates, and hypertension. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.



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Outcome	β Coefficient (95% CI)	*P* value
All-Cause Mortality	-1.37 (0.06-0.97)	0.045
All-Cause Hospitalizations	-0.35 (-4.7 - -1.25)	0.001
Cardiovascular Hospitalizations	-0.32 (-3.3 - -0.7)	0.003
Heart Failure Hospitalizations	-0.34 (-2.9 - -0.74)	0.001

Discussion

Although clinical trials have provided strong evidence that MRA therapy favourably affects the clinical course of patients with HFrEF,[1–3] utilization of MRAs has been reported to be suboptimal in many settings.[10-20] In this study, we assessed MRA use in HFrEF patients following hospitalization for HF in order to determine the rate of patients being prescribed an MRA at discharge, likelihood of continuation of post-discharge, reasons for discontinuation, and the association between MRA maintenance and clinical outcomes. We found that well less than half of eligible patients were prescribed an MRA at discharge and that one in three patients who were receiving an MRA at discharge stopped therapy during follow-up, with hyperkalemia being the most common cause of drug discontinuation. Failure to maintain an MRA post-discharge was most commonly because of hyperkalemia and was associated with significantly higher risk of all-cause, cardiovascular, and HF hospitalization and with greater risk of death. These findings suggest that better strategies to initiate and maintain MRA therapy in eligible patients are needed and that increasing MRA utilization in HFrEF patients following a heart failure hospitalization could improve outcomes.

In this study, we identified patients at high risk for future events based on a heart failure hospitalization. After excluding patients for whom therapy was contraindicated, we found that only 38% were discharged on an MRA. Reasons for not prescribing MRAs were not documented in the vast majority of cases. These results are consistent with several previously published retrospective studies examining utilizing of MRAs in patients with systolic heart failure.[10–19] In a large cohort of patients followed in the Swedish HF Registry, only 40% of eligible patients were receiving an MRA. [16] Similar to what was

noted in the Swedish HF Registry, we found that older age, higher systolic blood pressure and ejection fraction, and greater likelihood of CAD were associated with non-MRA prescription. In contrast to the Swedish study, we found that creatinine levels were similar in patients who were and were not discharged with an MRA. Interestingly, differences in potassium levels between the patients who were and were not prescribed an MRA on discharge did not emerge in either the present population or the one included in the Swedish HF Registry. The rate of MRA prescription seen in our population is also similar to that seen in the CHAMP-HF registry of US patients, where 33% of patients were taking an MRA.[20] Of note is the fact that the percentage of patients prescribed an MRA in both our study and the CHAMP-HF registry was considerably lower than the percentage who were taking an ACEi or an ARB, both of which have similar limitations because of creatinine and potassium levels as do the MRAs.

Of the 105 patients who were discharged on MRA therapy in our study, 35 (33%) discontinued therapy over the course of slightly more than 3 years of follow-up. In general, patients who subsequently discontinued MRA therapy had similar characteristics to the patients who maintained therapy with no differences in age, gender, vital signs, EF, comorbidities, and frequency of treatment with other HF medications. The dose of other HF medications, including ACEi and ARB, was similar between the groups, but patients who subsequently stopped drug were receiving higher dose of loop diuretic at the time of discharge compared with those patients who maintained therapy. In addition, the distribution of patients in the two groups between those were receiving guideline recommended target dose, a dose below target, or no drug for both beta blockers and ACEi/ARBs was similar between the groups. The higher creatinine levels at the time of hospital discharge in the patients who subsequently discontinued MRA therapy underscores the well-recognized association between kidney dysfunction and hyperkalemia (which was the major reason for MRA discontinuation). It should be noted that renal dysfunction in this group could also be due to haemodynamic factors that adversely affect kidney function.

Hyperkalemia was the most common documented reason for drug discontinuation, with significantly higher rates of hyperkalemia per patient as well as significantly greater frequency of drug discontinuations attributed to hyperkalemia. The rates of hyperkalemia in patients on MRAs have varied between studies ranging from 0% to 18.7%.[1–3] In the RALES trial, the earliest trial demonstrating efficacy of MRAs in HFrEF, the incidence of hyperkalemia was not increased.[1] This trial, however, had carefully defined entry criteria and follow-up procedures that likely minimized the frequency of hyperkalemia. Both the EPHESUS and EMPHASIS-HF trials demonstrated significantly higher rates of serum potassium (K+) $>$ 5.5 mEq/L in patients treated with eplerenone than with placebo. In the EPHESUS trial, 5.5% of patients taking eplerenone vs. 3.9% of patients taking placebo developed hyperkalemia (P = 0.002)[2] and risk of hyperkalemia was even higher in the EMPHASIS-HF trial, in which 11.8% of patients taking eplerenone vs. 7.2% of patients taking placebo developed hyperkalemia ($P < 0.001$).[3] In the more recent TOPCAT study, which assessed the efficacy of spironolactone in patients with HF with preserved EF (HFpEF),[24] hyperkalemia was reported in over twice as many patients (18.7%) treated with spironolactone compared with placebo (9.1%).[24] Reduction in dose or discontinuation of the MRA was reported in the EMPHASIS-HF trial, where only 60.2% of patients were taking the full 50 mg dose of eplerenone after the initial 5 month dose adjustment phase, and 16.3% of patients discontinued the drug because of hyperkalemia or rise in serum creatinine.[3] High rates of MRA discontinuation have also been reported from HF populations that more closely approximate 'real world' conditions than in clinical trials, where there are more stringent criteria for MRA initiation and patient follow-up than in the usual clinical setting.[25,26]

Hyperkalemia is also associated with the other drugs used in the treatment of HFrEF that block the renin–angiotensin–aldosterone system (RAAS), including ACEis, ARBs, and angiotensin receptor–neprilysin inhibitors. In the recent PARADIGM-HF study, 4.3% of patients treated with the sacubitril–valsartan combination developed serum K+ $>$ 5.5 vs. 5.6% in the enalpril group (P = 0.007), and 16.1% developed serum K+ $>$ 5.0 vs. 17.3% in the enalpril group (P = 0.15).[27] Although use of another RAAS blocker in association with an MRA would be expected to increase the likelihood of hyperkalemia, we found in our study population that although there was a trend for patients who were discontinued MRA to be less likely to be discharged on an ACEi than patients who maintained MRA therapy, the dose of both ACEi and ARB in the patients who stopped their MRA was similar to that given to the patients who continued therapy.

In our study population, discontinuation of MRA therapy was associated with greater likelihood of all-cause, cardiovascular and HF hospitalization, and worse survival. While there is substantial evidence supporting use of MRAs for management of chronic HFrEF patients, the effects of this therapy on outcomes following hospitalization for HF are less clear. The ATHENA-HF trial was a prospective double-blind, placebo-controlled study that assessed the efficacy and safety of short-term treatment with spironolactone in patients hospitalized with acute heart failure in HFrEF patients who would be considered eligible for MRA therapy based on guideline recommendations[19]. The results showed that although addition of high dose spironolactone to standard care was safe, there was no evidence of efficacy over the 96 h period of observation as neither the primary end point of change in NT-proBNP nor changes in any of the secondary clinical endpoints was significantly affected by MRA therapy. It is possible, however, that 96 h may not have allowed adequate time to detect a beneficial effect

of MRA therapy on clinical outcomes in the study population.

A secondary analysis of the COACH study that included patients regardless of LVEF reported that patients discharged on an MRA following a hospitalization for HF had a significant 46% reduction in the risk of combined 30 day all-cause mortality and HF rehospitalization[17]. Benefits were seen with MRA therapy regardless of whether the patient had been receiving the MRA prior to index hospitalization or drug therapy was initiated during the hospitalization. Effects were more prominent in patients with elevated creatinine and also in patients with higher levels of biomarkers during index hospitalization. In contrast, an analysis of the effect of spironolactone on 30 day all-cause readmission rates in patients with HFrEF following a hospitalization for HF in Medicare beneficiaries in Alabama showed no significant improvement associated with prescription of spironolactone at the time discharge from the index hospitalization[19]. Reconciling the differences in post-hospital discharge outcomes between the studies is difficult. Only the short-term ATHEHNA-HF study was prospective and designed to assess the effects of MRAs on outcomes. Differences in the characteristics of the patients between these the studies also likely influenced the findings described above.

Study limitations

Our study is limited by both the relatively small size of the population and the fact that all patients came from a single medical centre. The analysis was retrospective and confounding factors that may have influenced the decision to initiate MRAs during the index hospitalization or that were associated with discontinuation post-discharge may have been overlooked.

Conclusions

Although there is compelling evidence that MRAs improve outcomes in patients with chronic HFrEF, information about their effects following hospitalization for HF is limited. This is unfortunate, given that MRAs are substantially underutilized, and the period of hospitalization offers an excellent opportunity to modify therapy. Initiation of guideline-directed medical therapy during a hospitalization is both recommended[13] and also appears to be safe[19]. Moreover, it is well recognized that the risk of morbidity and mortality increases substantially in HF patients in the period following hospitalization for HF. While our results show an association between the use of MRAs and better outcomes following discharge from a HF hospitalization, they do not provide definitive evidence that MRAs can reduce the risk of adverse events post-discharge. Well-designed prospective trials are required to confirm this possibility. As hyperkalemia is the major reason for discontinuation of MRA therapy, strategies aimed at maintaining drug, and their impact on outcomes should also be assessed in future studies.

Conflict of interest

None declared.

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