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Mineralocorticoid Receptor Antagonist Use in Hospitalized Patients with Heart Failure, Reduced Ejection Fraction, and Diabetes Mellitus (from the EVEREST Trial)

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Abstract

Despite the well-established benefits of mineralocorticoid receptor agonists (MRAs) in heart failure with reduced ejection fraction, safety concerns remain in patients with concomitant diabetes mellitus (DM) because of common renal and electrolyte abnormalities in this population. We analyzed all-cause mortality and composite cardiovascular mortality and HF hospitalization over a median 9.9 months among 1,998 patients in the placebo arm of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial by DM status and discharge MRA use. Of the 750 patients with DM, 59.2% were receiving MRAs compared with

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62.5% in the non-DM patients. DM patients not receiving MRAs were older, more likely to be men, with an ischemic heart failure etiology and slightly worse renal function compared with those receiving MRAs. After adjustment for baseline risk factors, among DM patients, MRA use was not associated with either mortality (hazard ratio [HR] 0.93; 95% confidence interval [CI] 0.75 to 1.15) or the composite end point (HR 0.94; 95% CI 0.80 to 1.10). Similar findings were seen in non-DM patients (mortality [HR 1.01; 95% CI 0.84 to 1.22] or the composite end point [HR 0.98; 95% CI 0.85 to 1.13] [p >0.43 for DM interaction]). In conclusion, in-hospital initiation of MRA therapy was low (15% to 20%), and overall discharge MRA use was only 60% (with regional variation), regardless of DM status. There does not appear to be clear, clinically significant in-hospital hemodynamic or even renal differences between those on and off MRA. Discharge MRA use was not associated with postdischarge end points in patients hospitalized for worsening heart failure with reduced ejection fraction and co-morbid DM. DM does not appear to influence the effectiveness of MRA therapy.

Approximately 40% to 45% of patients hospitalized for worsening heart failure with reduced ejection fraction (HFrEF) have coexistent diabetes mellitus (DM).[1–3] DM is an independent predictor of adverse postdischarge outcomes in hospitalized HFrEF patients[4] and may modulate the risk-benefit ratio of certain pharmacotherapies.[5] Mineralocorticoid receptor antagonist (MRA) have been shown to improve clinical outcomes in chronic HFrEF patients with mild-to-severe symptoms and patients with left ventricular dysfunction after myocardial infarction (MI).[6–8] Accruing evidence suggests that the benefits of mineralocorticoid receptor (MR) blockade may be safely extended to the subset of HFrEF patients with DM.[9,10] The widespread use of MRAs has been limited by ongoing clinician concern regarding worsening renal function and hyperkalemia, especially with concomitant use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers.[11] In addition, type 2 DM was among the major risk factors for life-threatening hyper-kalemia in a small case series of HFrEF patients.[12,13] The immediate postdischarge period after hospitalization for HF is a vulnerable period marked by acute perturbations in electrolyte, neurohormonal,[14] and renal function profiles,[15] perhaps further augmenting MRA-associated side effects. Data are limited regarding the overall utilization and safety profile of MRA use in patients hospitalized for HFrEF with co-morbid DM. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial included patients who largely met criteria for prescription of MRA (e.g., HFrEF, mild-to-severe symptomatology, without major baseline renal or electrolyte abnormalities). This trial experience offers an ideal setting to evaluate an in-depth, longitudinal characterization of the clinical profiles and MRA prescription patterns of patients hospitalized for worsening chronic HFrEF with comorbid DM.

Methods

The study design[16]and primary results[17,18] of the EVEREST trial have been previously described. In brief, EVEREST was a prospective, international, randomized, double-blind, placebo-controlled trial designed to explore the short- and long-term impact of tolvaptan, a vasopressin-2 receptor antagonist, when added to standard therapy, in patients hospitalized for worsening HF with an EF ≤40% and presenting with an evidence of fluid overload.

Participants were randomized within 48 hours of hospitalization to receive either oral tolvaptan or matching placebo, in addition to standard therapy. Background HF therapy was left to the discretion of the treating physician, but guideline-based recommendations for optimal medical therapy were included in the study protocol. Significant exclusion criteria included refractory end-stage HF, hemofiltration or dialysis, supine systolic blood pressure (SBP) <90 mm Hg, serum creatinine concentration >3.5 mg/dl, and serum potassium >5.5 mEq/L.

Because tolvaptan interacts with the renin-angiotensin aldosterone system, we performed a post hoc analysis examining only patients in the placebo arm with available discharge MRA data. All patients who died during hospitalization were, thus, excluded. HFrEF patients were divided by MRA use at the time of discharge in the EVEREST trial and by the presence of DM. MRAs in the EVEREST database included canrenoic acid, canrenone, potassium canreonate, eplerenone, soludactone, and spironolactone. DM status was ascertained by baseline questionnaires obtained by study site coordinators from patient interviews and medical records in accordance to the American Diabetes Association criteria.[19] Patients receiving insulin or oral hypoglycemic agents were also categorized as having DM. Chronic kidney disease was defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2 on the day of enrollment, calculated using the Modification of Diet in Renal Disease Study equation.[20]

The study was approved by the Institutional Review Boards and Ethics Committees of each participating site and was conducted in accordance with the Declaration of Helsinki. Clinical characteristics documented at baseline, with the exception of concomitant therapies that were obtained from discharge records, were used for the present analysis. The first outpatient visit occurred 7 days after discharge for those subjects discharged from the hospital on or before the tenth day or the seventeenth day after randomization for those still in the hospital on day 10. Outpatient assessments were performed after 1, 4, and 8 weeks and every 8 weeks thereafter up to 128 weeks.

An independent, blinded adjudication committee determined the specific causes of death and reasons for rehospitalization. This post hoc analysis used the 2 EVEREST co-primary end points: (1) all-cause mortality (ACM) and (2) the composite of cardiovascular (CV) mortality and HF hospitalization. Median follow-up in the EVEREST trial was 9.9 months (interquartile range 5.3 to 16.1 months).

For descriptive purposes, patients were stratified by discharge MRA use as MRA^+ and MRA^-. Similarly, DM status was defined as DM^+ and DM. Differences between MRA^+ versus MRA^- were summarized separately for DM^+ and DM patients. Baseline characteristics were compared by discharge MRA use in patients with and without DM using chi-square testing, Fisher's exact test, and Kruskal-Wallis tests where appropriate. All continuous variables were reported as mean ± SD if normally distributed or median (interquartile range) if non-normally distributed.

The primary predictor for this analysis was MRA use at the time of discharge. Time-to-event data were analyzed with log-rank test, and hazard ratios (HRs) with corresponding 95%

confidence intervals (CIs) were obtained from Cox proportional hazard models. The proportional hazards assumption (by Kolmogorov-type supremum tests for nonproportionality) was upheld for all end points, except for the composite end point in the non-DM cohort. For this group, the follow-up period was divided into 2 phases at 50 days after randomization (cutoff established by visual inspection of standardized score process plots). All multivariable Cox regression models were adjusted for known baseline predictors of mortality and morbidity: age, sex, region, EF, SBP, sodium, blood urea nitrogen, N-terminal pro-brain natriuretic peptide, QRS duration, discharge medication use (ACE inhibitors, β blockers, digoxin), in-hospital inotrope requirement, New York Heart Association (NYHA) class IV, atrial fibrillation/flutter, history of hypertension, coronary artery disease (CAD), chronic obstructive pulmonary disease, ischemic HF etiology, previous HF hospitalization, and chronic kidney disease. No evidence of significant collinearity between MRA utilization and the covariate set was detected. Testing for interaction between MRA use and outcomes by underlying DM status was performed.

Results

Of the 2,061 patients assigned to the placebo arm in the EVEREST trial, 3.3% (n = 63) of patients died during hospitalization or had missing discharge MRA data. Of those discharged alive with known MRA status, 62.3% (n = 1,245) received an MRA at discharge. Baseline DM was present in 37.5% (n = 750) of patients, and among these, 59.2% (n = 444) were discharged on MRA therapy, compared with 64.2% (n = 801) in patients without DM (Figure 1). Most of these patients had been prescribed an MRA at the time of enrollment, which was continued through hospitalization (76.7% in the DM group and 80.3% in the non-DM group). Spironolactone was the predominant MRA used in the overwhelming majority of patients, regardless of DM status.

Among patients with DM, those not discharged on MRA therapy were generally older ($p < 0.001$) and were more likely to be male ($p < 0.03$), with a higher EF ($p < 0.003$) and better NYHA functional class ($p = 0.024$). Discharge MRA use was less frequent in patients recruited from North America and Western Europe compared with South America and Eastern Europe ($p < 0.001$). Lack of MRA prescription was associated with higher rates of co-morbidities such as hypertension ($p = 0.017$), peripheral vascular disease ($p < 0.001$), and hyperlipidemia ($p = 0.004$) but lower rates of previous HF hospitalization and atrial fibrillation/flutter ($p = 0.009$). The prevalence of CAD and revascularization procedures was also significantly higher (both $p < 0.05$) in DM patients who were not prescribed MRAs at discharge. SBPs were slightly, but nonsignificantly, higher in the non-MRA group (122.1 ± 19.9 vs 119.8 ± 19.3; $p = 0.1$). Serum creatinine was also slightly higher in patients not prescribed MRAs at discharge (1.5 ± 0.6 vs 1.4 ± 0.5; $p = 0.003$). Patients off MRAs at discharge were less likely to receive diuretics, digoxin, β blockers, and inotropic agents and more likely to receive antiplatelet drugs. In general, similar patterns were observed in baseline clinical profiles between patients discharged with and without MRA in both DM and non-DM cohorts (Table 1).

Over a median follow-up period of 9.9 months, 26.5% (n = 199) of patients with DM and 22.8% (n = 285) of patients without DM experienced ACM, whereas 43.9% (n = 329)

patients with DM and 35.8% (n = 447) patients without DM experienced the composite end point (Table 2). In the DM subgroup, patients prescribed MRAs experienced lower rates of composite CV mortality and HF hospitalization (p = 0.002) and non-CV death (p = 0.025) but higher rates of sudden cardiac death (5.9% vs 4.6%; p = 0.030). No other differences in cause-specific outcomes were observed between MRA users and nonusers in patients with and without DM. In unadjusted analyses among DM patients, MRA use was associated with a 31% reduction in ACM (HR 0.69; 95% CI 0.52 to 0.91) and a 19% reduction in the composite end point (HR 0.81; 95% CI 0.65 to 1.01) (Figure 2). MRA use was not associated with either ACM (HR 1.16; 95% CI 0.90 to 1.48) or the composite end point (HR 1.01; 95% CI 0.83 to 1.23) among patients without DM (Figure 3). The unadjusted relation between MRA use and ACM differed significantly by DM status (p = 0.006). There was no significant interaction between MRA use and DM status for the composite end point (p = 0.39).

Among patients without DM, the proportional hazard assumption was violated for the composite end point. Discharge MRA use was associated with improved composite end point in the first 50 days after discharge (HR 0.61; 95% CI 0.43 to 0.87), whereas there was a trend toward a risk of harm after 50 days (HR 1.23; 95% CI 0.97 to 1.56) (p = 0.001 for change in time-dependent hazard).

After adjusting for baseline risk factors, MRA use was not associated with the co-primary end points in either DM^+ or DM^- patients (Table 3). MRA use at hospital discharge was not independently associated with ACM in patients with DM (adjusted HR 0.93; 95% CI 0.75 to 1.15) or in patients without DM (adjusted HR 1.01; 95% CI 0.84 to 1.22). Similarly, MRA use was not associated with the composite end point in patients with DM (adjusted HR 0.94; 95% CI 0.80 to 1.10) or without DM (adjusted HR 0.98; 95% CI 0.85 to 1.13). Testing for interaction for the effect of MRA use on outcomes by DM status was not statistically significant (p >0.43).

Discussion

In a large, international cohort of contemporary patients hospitalized with worsening HFrEF, in-hospital initiation of MRA therapy was low (15% to 20%), and overall discharge MRA use was only 60% (with regional variation), regardless of DM status. Patients with DM who were not prescribed MRAs at discharge appeared to have less severe and symptomatic HF compared with those prescribed MRAs at discharge, as evidenced by a higher left ventricular EF, better NYHA functional class, and lower likelihood of receiving digoxin and intravenous inotropes. Patients who were likely eligible, but not receiving therapy, tended to be older, men, from North America or Western Europe, with a higher overall comorbid burden compared with those receiving an MRA. It is notable that the blood pressure and renal function were only marginally different between patients on and off MRA therapy at discharge, with questionable clinical significance. Discharge MRA use was associated with improved post-discharge morbidity and mortality in the DM subset, but not in the non-DM subset, based on univariate analysis. However, after accounting for baseline risk factors, MRA use was not an independent predictor of postdischarge outcome, in either cohort. After

multivariate adjustment, there was no interaction observed between DM and MRA discharge use on postdischarge outcomes.

EVEREST provides an optimal setting for the analysis of the clinical profiles of discharge MRA utilization since: (1) large, multicenter, globalclinical trial with long-term follow-up and (2) rigorous postdischarge monitoring of electrolyte and renal function parameters. Most patients enrolled in EVEREST were eligible for MRA prescription (e.g., worsening chronic HFrEF, mild to severe symptomatology, without major baseline renal or electrolyte abnormalities). However, compared with contemporary American College of Cardiology/ American Heart Association HF treatment guidelines[21] for the initiation of MRA therapy in patients with NYHA class III to IV symptoms, EVEREST inclusion and exclusion criteria[16] were less stringent, thus potentially altering the expected risk-benefit profile. EVEREST included patients with EF <40% (compared with 35%) and excluded patients with serum creatinine >3.5 mg/dl (compared with 2.5 mg/dl inwomen and 2.0 mg/dl in men) and potassium levels >5.5 mEq/L (compared with 5.0 mEq/L). In addition, EVEREST randomized patients within 48 hours of hospitalization,[16] which may represent a period of fluctuating laboratory and clinical parameters compared with stable outpatients with HF. Current guidelines[21] do not make specific recommendations for MRA therapy based on DM status in this population. Unfortunately, even in this high-risk hospitalized cohort of HFrEF patients enrolled in the EVEREST trial, MRA use at admission and discharge was only modest.

MR activation is maladaptive and increased in both HF[22] and DM[23,24] leading to hypertension, fibrosis, apoptosis, or inflammation with consequent cardiac and renal damage. Even small increases in plasma aldosterone portend a poor prognosis in patients with CAD and DM.[25]

Post hoc analysis of the Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial suggested a greater absolute risk reduction with eplerenone in all-cause death, CV death, or first CV hospitalizationin post-MI HFrEF patients with DM compared with those without DM.[9] Similarly, in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study subgroup analysis, eplerenone was similarly beneficial in patients with and without DM, despite a significant increase in the incidence of potassium >5.5 mmol/L in the DM subgroup.[10] Our data were not able to demonstrate an independent beneficial relation between MRA use and postdischarge outcomes in the setting of hospitalized patients with HFrEF and DM. Similar to other recently published retrospective experiences of the lack of effectiveness of discharge MRA use,[26] our data highlight how retrospective analyses of a nonrandomly allocated drug treatment inherently prescribed to “sicker” patients can conflict with results from definitive prospective randomized trials. With observational study, even with rigorous multivariate modeling, it may be challenging to fully account for this residual confounding. Thus, our findings should not detract from the robust data available from randomized clinical trials to support the use of MRAs in HFrEF patients. Rather, our study highlights the potential differential therapeutic responses in different HFrEF subgroups. These findings warrant future prospective evaluation of this clinically important subgroup in the setting of appropriately powered clinical trials.

DM in patients with worsening HF has emerged as a distinct clinical entity directly influencing clinical outcomes,[4] treatment responses,[5] and attendant side effect profiles. Patients hospitalized for HFrEF and DM experience an exceedingly high rate of postdischarge CV death and HF rehospitalization, approaching 40% despite contemporary guideline-recommended medical therapies.[5] Thus, novel therapies or augmented use of existing proved therapies are urgently required in this high-risk hospitalized cohort. Although, MRAs in our study were slightly less frequently prescribed in HFrEF patients with DM compared with those without DM, overall use in both subgroups was only modest (∼ 60%). These discharge rates in the setting of an HF clinical trial are higher than those reported in national surveys and registry-based studies (∼ 20 to 50%),[27,28] perhaps because of more stringent patient selection and closer laboratory and clinical monitoring during follow-up.

Although univariate analysis in our study suggested that patients with DM stand to benefit more from MRA prescription at discharge compared with their HFrEF counterparts without DM,[28] side effect profiles of these agents in DM pose ongoing clinical concerns. Large, retrospective postrandomization studies may be informative when evaluating drug safety and side effect profiles, especially in high-risk subgroups such as DM. Post hoc analyses of the EPHESUS trial found DM, estimated glomerular filtration rate <60 ml/min/1.73 m^2, and baseline serum potassium above the median to be major predictors of hyperkalemia with eplerenone treatment in post-MI HF patients.[29] Similarly, recent data showed that concurrent use of multiple renin-angiotensin aldosterone system inhibitors may pose a heightened riskofincident hyperkalemia in patients with DM compared with those without.[5] In the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT), prespecified subgroup analyses suggested heterogeneity in post-discharge outcomes with aliskiren by co-morbid DM status, with aliskiren only improving outcomes in the non-DM sub-set.[5] MRA prescription patterns in this cohort of hospitalized HFrEF patients with DM likely reflect clinician attempts to optimize this risk-benefit calculus, selecting patients with severe HF disease burden who are most likely to benefit from therapy. MRAs were also targeted toward patients least likely to experience harm from therapy, for example, those who are relatively young with few disease co-morbidities. Our study revealed a small increase in rates of postdischarge sudden cardiac death in patients with DM prescribed an MRA at discharge, but no excess clinical events were observed in the DM subgroup after risk adjustment. No differences in rates of implantable cardioverter-defibrillator utilization were apparent in DM patients by MRA status at discharge. The ongoing development of novel nonsteroidal MRAs have shown initial promise with similar outcomes as spironolactone with lower rates of worsening renal function and hyperkalemia in high-risk HFrEF subsets.[30]

The primary limitations of this study stems from the post hoc design, with the bias that patients were selected to receive MRAs based on clinical characteristics. Despite stringent multivariate accounting, residual confounding from measured and unmeasured factors may influence the study outcomes. Furthermore, DM status was identified from intake questionnaires only, and cross-verification by medication history, disease duration, and other details were not available. The EVEREST study was a randomized trial, and extrapolation of these results to the general HFrEF population should be done in the context of the study

inclusion and exclusion criteria. Because the publication of the Randomized Aldactone Evaluation Study (RALES) and EPHESUS trials preceded the EVEREST recruitment period, the inherent clinician bias related to these publications and their attendant press is unclear. Because most patients discharged on MRA were prescribed it before hospitalization, the study was not able to evaluate new in-hospital initiation of MRA. Despite these limitations, we believe that our results are representative of the general clinician attitude in prescribing MRAs in hospitalized HFrEF patients with DM.

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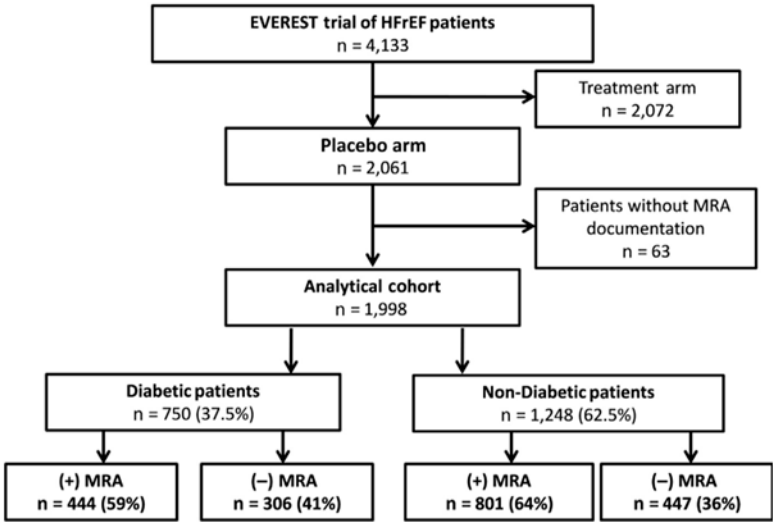

Figure 1.
Selection of analytical cohort.

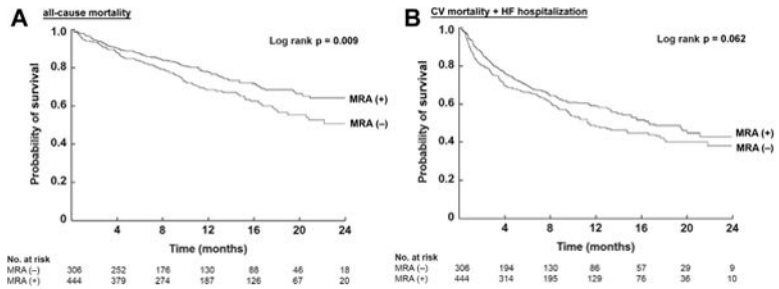

Figure 2.

Unadjusted Kaplan-Meier curves in patients with diabetes. Kaplan-Meier curves for all-cause mortality *(A)* and CV mortality and HF hospitalization *(B)* by MRA use at discharge. Pairwise comparisons by the log-rank test.

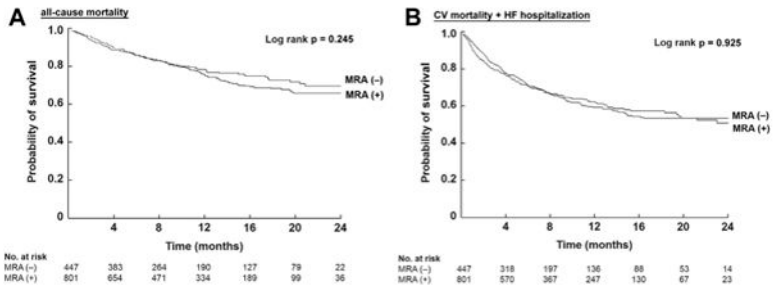

Figure 3.

Unadjusted Kaplan-Meier curves in patients without diabetes. Kaplan-Meier curves for all-cause mortality *(A)* and CV mortality and HF hospitalization *(B)* by MRA use at discharge. Pairwise comparisons by the log-rank test.

Table 1

Baseline characteristics

Variable	Diabetic			Non-Diabetic		
	No MRA (n = 306)	MRA (n = 444)	p	No MRA (n = 447)	MRA (n = 801)	p
Age (years)	67.9 ± 10.7	65.1 ± 10.1	<0.001	67.6 ± 12.6	63.6 ± 12.8	<0.001
Men	242 (79.1%)	320 (72.1%)	0.029	347 (77.6%)	605 (75.5%)	0.403
Non-Hispanic white	259 (84.6%)	373 (84%)	0.3615	387 (86.6%)	691 (86.3%)	0.6121
Black	22 (7.2%)	45 (10.1%)		32 (7.2%)	47 (5.9%)	
Hispanic	18 (5.9%)	19 (4.3%)		18 (4%)	42 (5.2%)	
Other Race/Ethnicity	7 (2.3%)	7 (1.6%)		10 (2.2%)	21 (2.6%)	
Eastern Europe	71 (23.2%)	162 (36.5%)	<0.001	166 (37.1%)	390 (48.7%)	0.337
North America	163 (53.3%)	145 (32.7%)		158 (35.3%)	139 (17.4%)	
South America	23 (7.5%)	73 (16.4%)		61 (13.6%)	176 (22%)	
Western Europe	49 (16%)	64 (14.4%)		62 (13.9%)	96 (12%)	
Ejection fraction (%)	28.6 ± 8.8	26.7 ± 7.8	0.003	28.3 ± 8.2	27.3 ± 8.1	0.039
QRS duration (msec)	122 (95–145)	123 (97–150)	0.677	123 (97–148)	124 (98–152)	0.514
Body mass index (kg/m^2)	29.3 ± 7.1	71.2 ± 856.3	0.078	48.5 ± 448.4	47 ± 623.2	0.962
Atrial fibrillation on electrocardiogram	70 (22.9%)	117 (26.4%)	0.009	130 (29.1%)	253 (31.6%)	0.364
Ischemic heart failure etiology	234 (77%)	301 (68.3%)	0.556	290 (65.9%)	471 (59.7%)	0.032
Prior heart failure hospitalization	237 (78.2%)	375 (84.8%)	0.001	313 (70.5%)	635 (79.4%)	<0.001
Prior myocardial infarction	199 (65.2%)	237 (53.4%)	0.058	226 (50.7%)	357 (44.6%)	0.038
Coronary artery disease*	257 (84.3%)	326 (73.6%)	0.001	325 (72.9%)	497 (62%)	<0.001
Hypertension†	255 (83.3%)	345 (77.7%)	0.017	313 (70%)	508 (63.4%)	0.018
Hypercholesterolemia‡	200 (66%)	254 (57.3%)	0.004	204 (45.8%)	293 (36.7%)	0.002
Peripheral vascular disease	97 (31.7%)	98 (22.2%)	<0.001	84 (18.8%)	155 (19.4%)	0.816
Prior coronary artery bypass graft surgery	112 (36.6%)	108 (24.3%)	0.006	102 (22.8%)	107 (13.4%)	<0.001
Prior percutaneous coronary intervention	90 (29.4%)	92 (20.7%)	0.001	91 (20.4%)	82 (10.2%)	<0.001
Implantable cardioverter-defibrillator	71 (23.2%)	62 (14%)	0.648	73 (16.3%)	76 (9.5%)	<0.001
Pacemaker	62 (20.3%)	84 (18.9%)	<0.001	86 (19.2%)	103 (12.9%)	0.003
Chronic kidney disease	142 (46.4%)	144 (32.5%)	0.797	123 (27.5%)	127 (15.9%)	<0.001

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Variable	Diabetic			Non-Diabetic		
	No MRA (n = 306)	MRA (n = 444)	p	No MRA (n = 447)	MRA (n = 801)	p
Chronic obstructive pulmonary disease	36 (11.8%)	55 (12.4%)	0.556	44 (9.8%)	65 (8.1%)	0.3
Dyspnea	275 (91.4%)	398 (92.6%)	0.629	387 (88.2%)	726 (91.9%)	0.031
Jugular venous distension	76 (25.7%)	116 (27.3%)	0.982	113 (25.9%)	213 (27.1%)	0.638
Rales	241 (80.1%)	344 (80%)	0.061	363 (82.7%)	656 (82.8%)	0.95
Edema§	238 (79.1%)	364 (84.5%)	0.122	325 (74%)	641 (80.9%)	0.005
Systolic blood pressure (mm Hg)	122.1 ± 19.9	119.8 ± 19.3	0.115	122.3 ± 20.4	118.7 ± 18.4	0.002
Heart rate (bpm)	77.5 ± 15	79.4 ± 15.5	0.042	79.7 ± 15.5	80.6 ± 16	0.308
New York Heart Association class IV	121 (39.7%)	185 (41.8%)	0.024	141 (31.6%)	332 (41.4%)	0.001
Albumin (g/dL)	3.6 ± 0.6	3.7 ± 0.5	0.027	3.8 ± 0.5	3.8 ± 0.5	0.745
NT-BNP (pg/mL)	4839 (2079–8567)	3581.5 (1865–7667)	0.001	4820 (2287–10464)	5028 (2462–9483)	0.767
Blood urea nitrogen (mg/dL)	36.5 ± 22	31.6 ± 16.7	0.005	28.5 ± 13.7	27.5 ± 13.9	0.245
Creatinine (mg/dL)	1.5 ± 0.6	1.4 ± 0.5	0.003	1.4 ± 0.5	1.3 ± 0.4	<0.001
Estimated glomerular filtration rate (mL/min)¶	50.3 ± 22.3	54.7 ± 20	0.002	56.1 ± 21.5	59.2 ± 20.1	0.016
Sodium (mEq/L)	139.2 ± 4	139.1 ± 4.8	0.462	140.5 ± 4.5	139.8 ± 4.8	0.008
MRA at enrollment	48 (15.8%)	340 (76.7%)	<0.001	88 (19.9%)	642 (80.3%)	<0.001
Medications at discharge						
Aspirin	176 (57.5%)	251 (56.5%)	0.001	243 (54.4%)	406 (50.7%)	0.213
ACE inhibitor or ARB	237 (77.5%)	385 (86.7%)	0.07	371 (83%)	703 (87.8%)	0.02
Beta-blocker	226 (73.9%)	353 (79.5%)	0.009	325 (72.7%)	582 (72.7%)	0.986
Calcium channel blocker	43 (14.1%)	36 (8.1%)	0.727	53 (11.9%)	39 (4.9%)	<0.001
Warfarin	114 (37.3%)	171 (38.5%)	0.042	173 (38.7%)	317 (39.6%)	0.762
Digoxin	132 (43.1%)	225 (50.7%)	<0.001	177 (39.6%)	421 (52.6%)	<0.001
Diuretics	272 (88.9%)	444 (100%)	0.012	381 (85.2%)	801 (100%)	<0.001
Nitrates	117 (38.2%)	131 (29.5%)	0.374	158 (35.3%)	222 (27.7%)	0.005
Amiodarone	55 (18%)	67 (15.1%)	0.941	101 (22.6%)	139 (17.4%)	0.024
Inotropes	8 (2.6%)	12 (2.7%)	<0.001	7 (1.6%)	9 (1.1%)	0.505
Clopidogrel	54 (17.6%)	40 (9%)	0.113	37 (8.3%)	32 (4%)	0.002
Statins	144 (47.1%)	183 (41.2%)	0.657	155 (34.7%)	190 (23.7%)	<0.001

Note: Data are presented as number (percentage), mean ± standard deviation, or median (interquartile range).

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; MRA = mineralocorticoid receptor antagonist; NT-BNP = N-terminal pro-B-type natriuretic peptide.

*Patient reported history of coronary artery disease.

†Patient reported history of hypertension.

‡Patient reported history of hypercholesterolemia.

§Peripheral edema was defined as slight to moderate to marked pedal or sacral edema.

¶Estimated by the Cockcroft-Gault equation.

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Table 2

Clinical outcomes

	Diabetes			Non-Diabetes		
	MRA (−) (n = 306)	**MRA (+) (n = 444)**	**p**	**MRA (−) (n = 447)**	**MRA (+) (n = 801)**	**p**
Primary endpoints						
All-cause mortality	98 (32)	101 (22.7)	0.172	95 (21.3)	190 (23.7)	0.319
CV mortality + HF hospitalization	147 (48)	182 (41)	0.002	157 (35.1)	290 (36.2)	0.702
Cause of death						
Cardiovascular	66 (21.6)	78 (17.6)	0.443	69 (15.4)	143 (17.9)	0.276
Sudden cardiac death	14 (4.6)	26 (5.9)	0.030	27 (6)	62 (7.7)	0.263
Heart failure	43 (14.1)	40 (9)	0.310	30 (6.7)	67 (8.4)	0.296
Myocardial infarction	3 (1)	1 (0.2)	0.653	6 (1.3)	4 (0.5)	0.181
Stroke	1 (0.3)	4 (0.9)	1.000	0 (0)	2 (0.2)	0.540
Other CV death	5 (1.6)	7 (1.6)	0.154	6 (1.3)	8 (1)	0.581
Non-CV death	16 (5.2)	14 (3.2)	0.025	17 (3.8)	25 (3.1)	0.522
Reason for hospitalization						
Cardiovascular	148 (48.4)	178 (40.1)	0.212	171 (38.3)	282 (35.2)	0.283
Heart failure	107 (35)	136 (30.6)	0.060	115 (25.7)	202 (25.2)	0.843
Myocardial infarction	10 (3.3)	5 (1.1)	0.483	9 (2)	6 (0.7)	0.049
Stroke	2 (0.7)	6 (1.4)	0.486	1 (0.2)	10 (1.2)	0.109
Arrhythmia	11 (3.6)	12 (2.7)	0.319	15 (3.4)	19 (2.4)	0.306
Other CV hospitalization	18 (5.9)	19 (4.3)	0.021	31 (6.9)	45 (5.6)	0.351
Worsening heart failure	141 (46.1)	167 (37.6)	0.056	143 (32)	246 (30.7)	0.640
CV mortality + CV hospitalization	175 (57.2)	203 (45.7)	0.002	191 (42.7)	336 (41.9)	0.789

CV = cardiovascular; HF = heart failure; MRA = mineralocorticoid receptor antagonist.

Table 3

Independent association of MRA use and postdischarge outcomes in HFrEF patients with and without DM

Outcome	Diabetics	Non-Diabetics
	Adjusted HR* (95% CI)	Adjusted HR* (95% CI)
Mortality	0.93 (0.75–1.15)	1.01 (0.84–1.22)
CV mortality + HF hospitalization	0.94 (0.80–1.10)	0.98 (0.85–1.13)

CI = confidence interval; CV = cardiovascular; DM = diabetes; HF = heart failure; HFrEF = heart failure and reduced ejection fraction; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist.

*Adjusted for age, sex, region, ejection fraction, systolic blood pressure, sodium, blood urea nitrogen, N-terminal pro-brain natriuretic peptide, QRS duration, use of angiotensin-converting enzyme-inhibitor, beta-blocker, digoxin, inotrope, New York Heart Association class IV, atrial fibrillation/flutter, hypertension, coronary artery disease, chronic obstructive pulmonary disease, ischemic heart failure etiology, previous heart failure hospitalization, chronic kidney disease.