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**RESEARCH ARTICLE**

# Mineralocorticoid receptor antagonist initiation during admission is associated with improved outcomes irrespective of ejection fraction in patients with acute heart failure

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**Aims** Heart failure (HF) guidelines recommend initiation and optimization of guideline-directed medical therapy, including mineralocorticoid receptor antagonists (MRAs), before hospital discharge. However, scientific evidence for this recommendation is lacking. Our objective was to determine whether initiation of MRA prior to hospital discharge is associated with improved outcomes.

**Methods and results** We performed a secondary analysis of 6197 patients enrolled in the RELAX-AHF-2 study. Patients were divided into four groups according to MRA therapy at baseline and discharge. At baseline 30% of patients received MRA therapy, which increased to 50% of patients at discharge. In-hospital initiation of an MRA was observed in 1690 (27%) patients, 1438 (23%) patients remained on MRA therapy, 418 (7%) patients discontinued MRA treatment, and 2651 (43%) patients did not receive an MRA during hospital stay. Compared with patients who did not receive MRA therapy, in-hospital initiation of an MRA was independently associated with lower risks of mortality (multivariable hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.60–0.96; $p = 0.02$), cardiovascular death (HR 0.77, 95% CI 0.59–1.01; $p = 0.06$), hospitalization for HF or renal failure (HR 0.72, 95% CI 0.60–0.86; $p = 0.0003$) and the composite endpoint of cardiovascular death and/or rehospitalization for HF or renal failure (HR 0.71, 95% CI 0.61–0.83; $p < 0.0001$) at 180 days. These results were independent of baseline left ventricular ejection fraction.

**Conclusion** In patients hospitalized for acute HF, in-hospital initiation of an MRA was associated with improved post-discharge outcomes, independent of left ventricular ejection fraction and other potential confounders.

**Keywords** Acute heart failure • Mineralocorticoid receptor antagonist • Post-discharge outcome

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# Introduction

Guidelines recommend use of mineralocorticoid receptor antagonist (MRA) therapy to reduce morbidity and mortality in chronic heart failure (HF) patients with reduced ejection fraction (HFrEF). They also recommended consideration of MRAs for treatment of chronic HF patients with mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF).[1–3]

In patients with acute decompensated HF, no established medical therapies improve long-term outcomes.[2] Nevertheless, guidelines recommend to optimize treatment before discharge, to initiate or restart chronic HF therapies, including MRAs.[1] This recommendation was supported by the recent findings of the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial.[4] STRONG-HF showed that early and fast up-titration of chronic HF therapies, within 2 weeks of discharge in patients admitted for acute HF, was associated with a reduced risk of 180-day mortality or HF readmission.

However, no prospective data are available to show that in-hospital initiation of MRAs improve clinical outcomes. A few smaller retrospective analyses provided conflicting results.[5–8] In addition, MRAs are frequently underutilized in patients with chronic HF, mostly due to (perceived) risk of worsening renal function and hyperkalaemia, in particular in patients with a recent hospital admission for acute HF.[9]

We therefore aimed to investigate the association between in-hospital MRA initiation and post-discharge outcomes in a large cohort of patients hospitalized for acute HF.

# Methods

## Patient population

The RELAXin in Acute Heart Failure-2 (RELAX-AHF-2) was a multinational, randomized, placebo-controlled, double-blind trial that investigated the effects of serelaxin versus placebo on clinical outcomes in patients hospitalized due to acute HF. The rationale and design of the study have been published previously.[10,11] In brief, the RELAX-AHF-2 trial included 6545 patients with acute HF, mild-to-moderate renal insufficiency (simplified Modification of Diet in Renal Disease estimated glomerular filtration rate [eGFR] of 25–75 ml/min/1.73 $m^2$), increases in brain natriuretic peptide (BNP) or N-terminal pro-hormone of BNP, of 18 years or older, with dyspnoea, congestion on chest radiograph and systolic blood pressure >125 mmHg. Patients were randomized in a 1:1 ratio to either serelaxin infusion of 30 μg/kg per day continuously in the first 48 h or placebo. All patients provided informed consent. The protocol was reviewed and approved by the local Institutional Review Board prior to study start.

## Study outcomes

The outcomes of interest for the present post-hoc analysis were 180-day all-cause and cardiovascular mortality, hospitalization for HF or renal failure at 180 days, and the composite endpoint of cardiovascular mortality or hospitalization for renal or HF at 180 days.

In-hospital laboratory tests investigated were the occurrence of hyperkalaemia (potassium >4.5 mmol/L, potassium >5.0 mmol/L, potassium >5.5 mmol/L) at any time during admission, and worsening renal function between baseline and day 5 (in-hospital). Worsening renal function was defined as an absolute increase in serum creatinine ≥0.3 mg/dl and a relative increase in serum creatinine of ≥25% or a relative decrease in eGFR (Chronic Kidney Disease Epidemiology Collaboration formula) of ≥25%, between baseline and day 5. According to study protocol, patients had visits at baseline, 6, 12, 24, 48, 72, 96, 120 h, and discharge. Follow-up visits took place at day 14, 60, 120 and 180.

Patients were divided into four groups according to MRA therapy at baseline (hospital admission) and MRA use at discharge. If no information was available on MRA therapy at discharge, the last observation carried forward approach was used, using information at closest visit, which was at 120 h/day 5. The four categories consisted of (1) patients who were not on MRA therapy during admission, (2) patients in which MRA therapy was discontinued during admission, (3) patients where MRA therapy was initiated during admission, and (4) patients in which MRA therapy was continued during hospital admission.

Mineralocorticoid receptor antagonist target dose was defined at discharge as a dose of 50 mg or more of either canrenone, eplerenone, potassium canrenoate, or spironolactone (based on the higher dose of the two most common used MRA spironolactone and/or eplerenone), and below target dose was defined as a dose between 1 and 49 mg. If no information on MRA dose at discharge was available, the last observation carried forward approach was used, using information at closest visit, which was at 120 h/day 5.

## Statistical analysis

Baseline characteristics are presented by MRA categories as mean ± standard deviation, median (interquartile range [IQR]), or numbers (percentages). ANOVA test was used to compare groups for continuous variables normally distributed, Kruskal–Wallis test for not-normally distributed continuous variables, and chi-square tests or Fisher's exact test for categorical variables.

Multivariable predictors at baseline for in-hospital MRA initiation were obtained using logistic regression models. Univariable predictors were transferred to the multivariable model if $p < 0.10$. For multivariable modelling, backward elimination ($p > 0.05$) was performed until all variables remained statistically significant ($p < 0.05$). Multiple imputation was performed in 50 generated imputed datasets as sensitivity analysis with pooled test statistics for all variables.

Incidence rates (IR) were calculated by the total number of events divided by the sum of the individual times at risk, and are presented per 100 patient-years. Cox regression models were used to evaluate association with post-discharge outcome. Multivariable adjustment was performed according to previously published models.[12]

To account for confounding by MRA treatment indication, covariate adjustment using a propensity score was used in Cox regression models. The propensity score was based on variables that were associated with MRA use at discharge and the outcomes investigated.[13–15]

Estimates are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical analyses were performed using R statistical software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

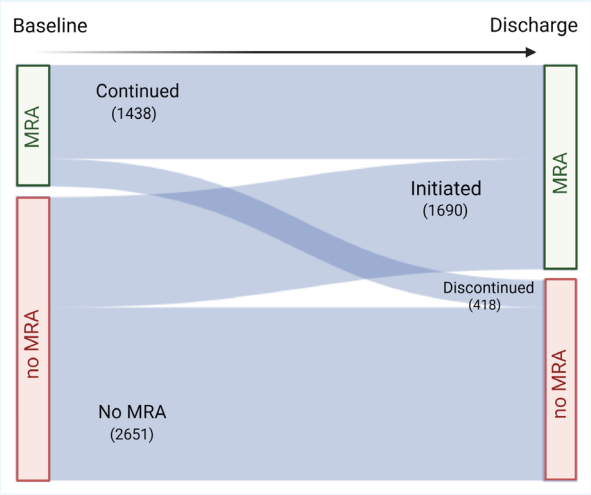


**Figure 1** Sankey diagram representing mineralocorticoid receptor antagonist (MRA) groups.

# Results

## Baseline characteristics

Of the 6545 patients included in the RELAX-AHF-2, 6197 patients had data available regarding MRA use at baseline and discharge. Characteristics of patients with and without available data are presented in online supplementary *Table S1*. Of the 6197 patients who were included in this post-hoc analysis, 1856 (30%) had MRA therapy at baseline, which increased to 3128 (50%) patients at discharge (*Figures 1* and *2*). Of the patients that received MRA therapy at discharge, 975 (31%) were on target dose (*Table 1*).

Patients were divided into four groups based on MRA status: 1690 (27%) of patients were started on an MRA during admission, 1438 (23%) patients were on an MRA at baseline and continued throughout hospitalization, 418 (7%) patients discontinued MRA treatment, and 2651 (43%) patients did not receive an MRA during admission or upon discharge for acute HF (*Figure 1*). Patients with in-hospital MRA initiation had fewer previous HF hospitalizations, lower baseline creatinine, and therefore higher baseline eGFR, lower baseline potassium, lower baseline blood urea nitrogen (BUN), and were less frequently on beta-blocker therapy, when compared to patients in the other three MRA groups (*Table 1*).

Key independent predictors of in-hospital MRA initiation were a lower left ventricular ejection fraction (LVEF), higher baseline diastolic blood pressure, Caucasian race, lower baseline potassium, lower baseline creatinine and others described in *Table 2*. Independent predictors of in-hospital discontinuation of MRA were lower systolic blood pressure, lower age, lower baseline sodium, higher baseline BUN, higher baseline potassium, history of myocardial infarction and prior history of HF (online supplementary *Table S2*). Sensitivity analysis performed with multiple imputation yielded similar results (online supplementary *Table S3*).

## Mineralocorticoid receptor antagonist initiation during heart failure hospital admission and hyper- and hypokalaemia

The presence of hyperkalaemia during hospital admission was lower in patients that had an MRA initiated in-hospital, when compared with patients that did not receive MRA therapy, discontinued MRA therapy or remained on MRA therapy during hospital admission (online supplementary *Table S4*). The occurrence of hyperkalaemia at any time during hospital admission, defined as either potassium >4.5 mmol/L, >5.0 mmol/L or >5.5 mmol/L, was similar in patients that did not receive MRA therapy and those that remained on MRA therapy during hospital admission. Patients that discontinued MRA therapy during hospital admission showed more frequent occurrence of hyperkalaemia at any time during hospital admission (online supplementary *Table S4*). The presence of hypokalaemia during hospital admission, defined as potassium <3.5 mmol/L, was more frequently observed in patients that initiated and did not receive MRA therapy during hospital admission (43%), when compared to patients that continued or discontinued MRA therapy (33%). Hypokalaemia at any time during hospital admission defined as potassium <3.0 mmol/L occurred more frequently in patients that had MRA therapy initiated in-hospital (8%), when compared to the other MRA groups (online supplementary *Table S3*).

## Mineralocorticoid receptor antagonist initiation, worsening renal function and post-discharge outcomes

Renal function assessed by eGFR at baseline and day 5 was available in 5520 (84%) patients. Overall, 1009 (18%) experienced worsening renal function between baseline and day 5. Worsening renal function between baseline and day 5 was more frequently observed in patients that did not receive MRA therapy during hospital admission or upon discharge (22%, $p < 0.001$), when compared with patients that discontinued MRA therapy (19%) during hospital admission, patients that had MRA therapy initiated during hospital admission (18%) or patients that remained on MRA therapy during hospital admission and upon discharge (14%) (online supplementary *Table S4*).

In the total study population, worsening renal function between baseline and day 5 was not associated with post-discharge outcomes. In patients that experienced worsening renal function between baseline and day 5, patients that had MRA therapy initiated during hospital admission had lower risks of all-cause mortality at 180 days (HR 0.61, 95% CI 0.39–0.95; $p = 0.03$), rehospitalization for HF or renal failure at 180 days (HR 0.50, 95% CI 0.34–0.74; $p = 0.0004$), and the composite endpoint of CV death and/or rehospitalization for HF or renal failure at 180 days (HR 0.58, 95% CI 0.42–0.79; $p < 0.0001$) in unadjusted models. However, when adjusting for the previously published RELAX model, including serelaxin treatment, associations became non-significant (online supplementary *Table S5*).

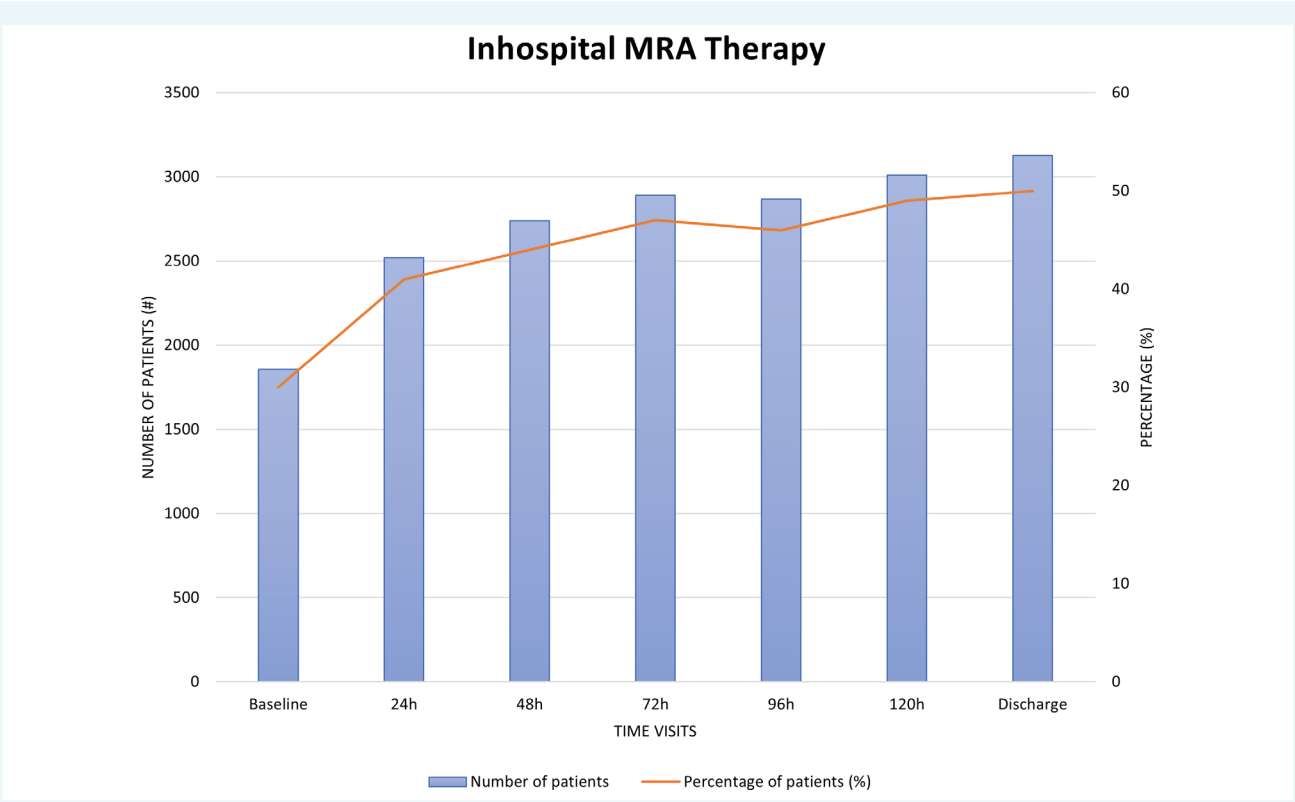


**Figure 2** In-hospital mineralocorticoid receptor antagonist (MRA) therapy.

## Mineralocorticoid receptor antagonist initiation during heart failure hospital admission and post-discharge outcome

The incidence of CV death was lowest for patients in whom an MRA was initiated during admission (IR 14.8 [95% CI 12.2–17.7] per 100 patient-years) when compared with patients who remained on MRA therapy in-hospital (IR 21.2 [95% CI 17.9–25.0] per 100 patient-years), patients who discontinued MRA treatment in-hospital (IR 26.6 [95% CI 19.7–35.2] per 100 patient-years), and who did not receive MRA therapy in-hospital (IR 20.7 [95% CI 18.2–23.5] per 100 patient-years) (online supplementary *Table S6*). These differences between groups were even more pronounced for the other outcomes of hospitalization for HF or renal failure and the composite of CV death and/or HF or renal failure hospitalizations (online supplementary *Table S6*).

In the fully adjusted multivariate models, in-hospital MRA initiation was associated with a lower risk of all-cause mortality at 180 days (HR 0.76, 95% CI 0.60–0.96; $p = 0.02$), when compared with patients that never received MRA therapy (reference category). Similarly, compared with patients that never received MRA therapy during admission, in-hospital MRA initiation was associated with lower risks of CV death (HR 0.77, 95% CI 0.59–1.01; $p = 0.06$), hospitalization for HF or renal failure (HR 0.72, 95% CI 0.60–0.86; $p = 0.0003$) and the composite endpoint of CV death and/or rehospitalization for HF or renal failure (HR 0.71, 95% CI 0.61–0.83; $p < 0.0001$) (*Table 3*, *Figure 3*). In sensitivity analyses using propensity score adjustment, associations remained significant (*Table 3*). The variables included in the propensity score are available in online supplementary *Table S7*.

The association between in-hospital MRA initiation and all-cause mortality, hospitalization for HF or renal failure, and the composite outcome of CV death and/or hospitalization for HF or renal failure was independent of in-hospital LVEF (*Table 3*, online supplementary *Figure S1*).

# Discussion

In this post-hoc analysis of patients with acute HF enrolled in the RELAX-AHF-2 trial, we found that initiation of an MRA during hospitalization for HF is associated with improved clinical outcomes.

The current European Society of Cardiology (ESC) guidelines recommend optimizing chronic HF therapies during a hospital admission for acute HF, despite limited scientific evidence supporting this recommendation. The Efficacy and Safety of Early Initiation of Eplerenone Treatment in Patients with Acute Heart Failure (EARLIER) trial investigated the early initiation of eplerenone in 300 patients with acute HF, and found no significant difference in CV death or CV hospitalization, although results were inconclusive because of inadequate power.[7] The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial found that high-dose spironolactone on top of

**Table 1 Baseline characteristics by mineralocorticoid receptor antagonist group ($n = 6197$)**

| | Continued MRA | No MRA | Discontinued MRA | Initiated MRA | *p*-value |
|---|---|---|---|---|---|
| *n* (%) | 1438 (23) | 2651 (43) | 418 (7) | 1690 (27) | |
| **Demographics** | | | | | |
| Age, years | 71 ± 11 | 75 ± 11 | 72 ± 11 | 73 ± 11 | <0.001 |
| Female sex | 538 (37) | 1165 (44) | 162 (39) | 661 (39) | <0.001 |
| Caucasian race | 1378 (96) | 2342 (89) | 386 (93) | 1611 (95) | <0.001 |
| Body mass index, kg/m$^2$ | 29.4 [25.7–33.1] | 28.8 [25.2–33.2] | 29.0 [25.8–33.4] | 29.0 [25.4–33.1] | 0.167 |
| LVEF, % | 35 ± 12 | 43 ± 14 | 37 ± 14 | 38 ± 13 | <0.001 |
| HFrEF | 890 (65) | 929 (38) | 222 (57) | 920 (57) | <0.001 |
| NYHA functional class | | | | | <0.001 |
| I | 28 (2) | 105 (6) | 22 (6) | 47 (4) | |
| II | 488 (36) | 752 (42) | 113 (29) | 463 (41) | |
| III | 679 (51) | 732 (41) | 190 (49) | 525 (46) | |
| IV | 148 (11) | 186 (11) | 61 (16) | 101 (9) | |
| Previous HFH | 1033 (73) | 1274 (52) | 296 (72) | 685 (44) | <0.001 |
| Ischaemic aetiology | 797 (59) | 907 (49) | 239 (60) | 628 (55) | <0.001 |
| Systolic blood pressure, mmHg | 138 ± 13 | 144 ± 17 | 138 ± 13 | 142 ± 14 | <0.001 |
| Heart rate, bpm | 81 ± 16 | 80 ± 16 | 80 ± 16 | 82 ± 16 | <0.001 |
| **Biomarkers** | | | | | |
| Creatinine, mg/dl | 1.33 ± 0.3 | 1.43 ± 0.4 | 1.41 ± 0.4 | 1.29 ± 0.3 | <0.001 |
| eGFR, ml/min/1.73 m$^2$ | 53 ± 13 | 48 ± 15 | 50 ± 14 | 54 ± 14 | <0.001 |
| Potassium, mmol/L | 4.4 ± 0.6 | 4.3 ± 0.6 | 4.5 ± 0.7 | 4.2 ± 0.6 | <0.001 |
| Haemoglobin, g/L | 129 ± 19 | 123 ± 19 | 126 ± 21 | 129 ± 20 | <0.001 |
| Sodium, mmol/L | 139 ± 4 | 139 ± 4 | 138 ± 5 | 140 ± 4 | <0.001 |
| BUN, mg/dL | 25 [19–32] | 25 [20–34] | 28 [21–37] | 23 [18–29] | <0.001 |
| NT-proBNP, ng/L | 6155 [3500–10 231] | 5591 [3340–9331] | 6398 [3963–12 794] | 6330 [3809–9817] | 0.002 |
| **Medical therapy** | | | | | |
| ACEi/ARB | 1079 (75) | 1758 (66) | 312 (75) | 1135 (67) | <0.001 |
| Beta-blocker | 1190 (83) | 1955 (74) | 340 (81) | 1156 (68) | <0.001 |
| Reached MRA target dose of ≥50 mg | 505 (35) | 0 (0) | 0 (0) | 470 (28) | <0.001 |
| Diuretic dose at baseline | 60.0 [40.0–80.0] | 60.0 [40.0–80.0] | 60.0 [40.0–80.0] | 60.0 [40.0–80.0] | 0.97 |

Values are *n* (%), mean ± standard deviation, or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-hormone brain natriuretic peptide; NYHA, New York Heart Association.

usual care for patients with acute HF for 96 h was well tolerated but did not improve efficacy endpoints.[8] In a registry study in older HF patients, the use of MRA at discharge from acute HF hospitalization was not associated with lower mortality but was associated with a lower risk of HF readmission. This finding suggests MRA treatment at discharge may have clinical advantages.[6] Another single-centre retrospective study found no signal for short-term harm after discharge when MRA therapy was initiated during admission, suggesting that hospitalization might represent an opportunity to initiate MRA therapy.[5] This study adds to this knowledge gap, as we show that MRA therapy initiation during hospital admission was associated with lower incidence and risk of all-cause mortality, CV death, hospitalization for HF or renal failure and the composite endpoint of CV death and/or rehospitalization for HF or renal failure.

Currently, MRA therapy is not recommended for patients with HFpEF and HFmrEF by the ESC HF guidelines. This is in line with our observation that patients with a higher ejection fraction were less likely to receive an MRA. Yet, interestingly, we found improved outcomes associated with in-hospital initiation of an MRA were independent of LVEF. Our results are supported by data from the recently published STRONG-HF trial.[4] STRONG-HF was a multinational, open-label, randomized, parallel-group trial, that investigated the effect of up-titration of treatments (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor, MRA, and beta-blocker) to 100% of recommended dose within 2 weeks of discharge versus usual care, in 1078 patients admitted to hospital with acute HF. The trial was stopped early due to overwhelming benefit in the intensive treatment strategy group, where improved quality of life and reduced risk of 180-day all-cause death or HF readmission were observed, when compared with usual care. Notably, there were no inclusion criteria based on ejection

**Table 2 Multivariable predictors of in-hospital mineralocorticoid receptor antagonist initiation (complete case analysis)**

| Variable | Odds ratio (95% CI) | *p*-value |
|---|---|---|
| Baseline characteristics | | |
| Prior HF hospitalization | 0.62 (0.53–0.73) | <0.001 |
| History of ICD implantation | 0.72 (0.55–0.93) | 0.014 |
| Ejection fraction (in-hospital) | 0.99 (0.98–0.99) | <0.001 |
| Diastolic blood pressure | 1.01 (1.00–1.01) | 0.027 |
| Caucasian race | 2.11 (1.57–2.88) | <0.001 |
| Laboratory values | | |
| Baseline potassium | 0.66 (0.59–0.75) | <0.001 |
| Baseline BUN | 0.99 (0.98–1.00) | 0.005 |
| Baseline creatinine | 1.00 (0.99–1.00) | 0.032 |
| Baseline sodium | 1.04 (1.02–1.05) | <0.001 |
| Medical history | | |
| History of CABG | 0.69 (0.55–0.85) | 0.001 |
| History of depression | 0.70 (0.55–0.89) | 0.005 |
| History of HF | 0.77 (0.63–0.92) | 0.005 |
| History of myocardial infarction | 0.77 (0.65–0.92) | 0.004 |
| History of PCI | 0.79 (0.66–0.95) | 0.010 |
| Pulmonary obstructive disease | 0.81 (0.69–0.95) | 0.009 |
| History of myocardial ischaemia | 1.50 (1.26–1.79) | <0.001 |

BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CI, confidence interval; HF, heart failure; ICD, implantable cardioverter-defibrillator; PCI, percutaneous coronary intervention.

fraction, and results were irrespective of LVEF category. This suggests that in-hospital initiation of MRA might not only benefit patients with HFrEF, but those with HFmrEF and HFpEF as well.

Our findings support the results from the post-hoc analysis performed in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT), where in patients from the Americas region spironolactone was associated with reduced risk of HF hospitalizations.[16]

Despite compelling evidence for the benefits of MRAs in chronic HFrEF, they are still underutilized. In our study, 1849 (62%) of HFrEF patients (LVEF <40%) did not use MRA at admission, of which 1316 (71%) had a history of HF. The Change the Management of Patients with Heart Failure (CHAMP-HF) registry described the most common reasons for underutilization of guideline-directed medical therapy,[17] divided into patient and practice characteristics. For MRA therapy, independent factors related to decreased likelihood of MRA initiation were higher ejection fraction (per 10% increase), higher quality of life score (per 10-point increase in Kansas City Cardiomyopathy Questionnaire), and hyperlipidaemia.[18] Specific patient characteristics associated with MRA use at target dose were female sex and history of hypertension. Hispanic ethnicity was associated with not receiving MRA therapy. Furthermore, Greene *et al.*[19] found that more severe New York Heart Association functional class, cardiac resynchronization therapy, atrial fibrillation and high school education, or higher education than high school were associated with MRA therapy discontinuation or dose decrease. Patients with a HF hospitalization within 12 months prior to enrolment were more likely to have MRA therapy initiated or discontinued, and their dose increased or decreased. This corresponds with our findings, where in-hospital MRA initiation was independently associated with lower in-hospital LVEF. We found that independent predictors of in-hospital MRA discontinuation were lower systolic blood pressure, lower age, higher baseline potassium, history of myocardial infarction and prior history of HF.

The most frequently observed hurdle to the initiation or up-titration of MRAs remains hyperkalaemia and renal function. Although hyperkalaemia does occur more frequently with spironolactone, patients with HF receiving spironolactone had lower risk of mortality when compared with placebo, even in the setting of moderate hyperkalaemia.[19] In the Eplerone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), patients with left ventricular dysfunction after myocardial infarction with an early rise in potassium levels at 1 month with eplerenone had decreased risk of CV outcomes.[20,21] Moreover, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study showed maintained survival benefit of eplerenone despite development of hyperkalaemia.[22–24] Recently we provided data to support the concept that the benefits of MRA therapy in patients with HFpEF are preserved, despite a higher incidence of worsening renal function.[25] In this current study, we show that the occurrence of hyperkalaemia at any time during hospital admission, either defined as potassium >4.5 mmol/L, >5.0 mmol/L or >5.5 mmol/L, was consistently lower in patients that had MRA therapy initiated in-hospital, when compared with patients that never received, stopped or remained on MRA therapy during hospital admission. Interestingly, the occurrence of hyperkalaemia at any time during hospital admission was similar in patients that never received MRA therapy and those that remained on MRA therapy during hospital admission. These findings argue against discontinuing an MRA after mild elevations in potassium.

Our study has several limitations that need to be acknowledged. First, as this was a post-hoc and subgroup analysis, the likelihood of type 1 errors and chance findings is increased, and results are hypothesis generating only. It is important to address that, although our findings are derived from a large randomized controlled trial, it did not investigate MRA use primarily, and was therefore not powered or designed to investigate the research question in this current study. We have tried to adjust for confounding by indication by the use of propensity score adjustment in our analyses, however, this does limit the interpretation and translation of our results. The fact that patients that discontinued MRAs have the worst prognosis when compared to the other groups, could be due to selection of predictors of poor outcome that were not captured. Our in-hospital outcomes investigated are associative only, as it is not known whether change in MRA therapy (starting, stopping) caused hyperkalaemia or worsening renal function, as

**Table 3 Mineralocorticoid receptor antagonist initiation and cardiovascular outcomes at 180 days in Cox regression analysis**

| | Hazard ratio (95% CI), *p*-value | | | |
|---|---|---|---|---|
| | **All-cause mortality** | **CV death** | **Hospitalization for HF or renal failure** | **CV death and/or hospitalization for HF or renal failure** |
| Unadjusted | | | | |
| No MRA | Reference | Reference | Reference | Reference |
| Discontinued MRA | 1.28 (0.98–1.66), $p = 0.07$ | 1.28 (0.94–1.74), $p = 0.12$ | 1.25 (1.02–1.54), $p = 0.03$ | 1.29 (1.08–1.55), $p = 0.01$ |
| Continued MRA | 0.90 (0.75–1.09), $p = 0.28$ | 1.01 (0.82–1.25), $p = 0.90$ | 0.95 (0.83–1.10), $p = 0.51$ | 0.95 (0.84–1.07), $p = 0.37$ |
| Initiated MRA | **0.65 (0.54–0.79), $p < 0.001$** | **0.71 (0.57–0.88), $p = 0.002$** | **0.52 (0.44–0.61), $p < 0.0001$** | **0.57 (0.50–0.65), $p < 0.0001$** |
| Age/sex | | | | |
| No MRA | Reference | Reference | Reference | Reference |
| Discontinued MRA | 1.38 (1.06–1.80), $p = 0.02$ | 1.36 (1.00–1.85), $p = 0.05$ | 1.25 (1.02–1.54), $p = 0.03$ | 1.31 (1.09–1.56), $p = 0.004$ |
| Continued MRA | 1.00 (0.83–1.20), $p = 0.98$ | 1.10 (0.89–1.35), $p = 0.39$ | 0.95 (0.83–1.10), $p = 0.50$ | 0.96 (0.85–1.09), $p = 0.53$ |
| Initiated MRA | **0.69 (0.56–0.83), $p = 0.0001$** | **0.74 (0.59–0.92), $p = 0.01$** | **0.52 (0.44–0.61), $p < 0.0001$** | **0.58 (0.50–0.66), $p < 0.0001$** |
| Full model[a] | | | | |
| No MRA | Reference | Reference | Reference | Reference |
| Discontinued MRA | 1.09 (0.79–1.51), $p = 0.60$ | 0.95 (0.65–1.39), $p = 0.80$ | 1.29 (1.03–1.63), $p = 0.03$ | 1.20 (0.98–1.47), $p = 0.08$ |
| Continued MRA | 1.04 (0.84–1.30), $p = 0.70$ | 1.05 (0.82–1.35), $p = 0.68$ | 1.20 (1.02–1.42), $p = 0.03$ | 1.08 (0.93–1.25), $p = 0.29$ |
| Initiated MRA | **0.76 (0.60–0.96), $p = 0.02$** | **0.77 (0.59–1.01), $p = 0.06$** | **0.72 (0.60–0.86), $p = 0.0003$** | **0.71 (0.61–0.83), $p < 0.0001$** |
| Propensity score | | | | |
| No MRA | Reference | Reference | Reference | Reference |
| Discontinued MRA | 1.19 (0.86–1.64), $p = 0.29$ | 1.06 (0.73–1.54), $p = 0.76$ | **1.56 (1.23–1.98), $p = 0.0002$** | **1.42 (1.15–1.76), $p = 0.001$** |
| Continued MRA | 1.03 (0.82–1.31), $p = 0.78$ | 1.03 (0.80–1.34), $p = 0.80$ | **1.35 (1.13–1.61), $p < 0.0001$** | **1.23 (1.05–1.43), $p = 0.01$** |
| Initiated MRA | **0.66 (0.52–0.84), $p = 0.001$** | **0.64 (0.49–0.84), $p = 0.001$** | **0.65 (0.53–0.79), $p < 0.0001$** | **0.66 (0.56–0.78), $p < 0.0001$** |
| Ejection fraction interaction | 0.50 | 0.18 | 0.22 | 0.12 |

CI, confidence interval; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist.

[a]Rehospitalizazion for heart failure or renal failure at 180 days: creatinine (μmol/L); haemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dl); cerebrovascular accident; depression; asthma/bronchitis/chronic obstructive pulmonary disease; atrial fibrillation/flutter; peripheral arterial occlusive disease; pulse (bpm); respiration rate (breaths/min); systolic blood pressure (mmHg); oedema; intravenous loop diuretics (total dose in furosemide units) at baseline; known history of diabetes mellitus; prior HF hospitalization; actual study treatment; grouped geographical region; composite of N-terminal pro-hormone brain natriuretic peptide or brain natriuretic peptide Z-score; sex; age (years) and left ventricular ejection fraction per 5.

CV death/all-cause mortality outcomes: creatinine (μmol/L); hamoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dl); asthma/bronchitis/chronic obstructive pulmonary disease; cerebrovascular accident; peripheral arterial occlusive disease; respiration rate (breaths/min); systolic blood pressure (mmHg); body mass index (kg/m$^2$); oedema; intravenous loop diuretics (total dose in furosemide units) at baseline; known history of diabetes mellitus; prior HF hospitalization; actual study treatment; composite of N-terminal pro-hormone brain natriuretic peptide or brain natriuretic peptide Z-score; sex; age (years) and left ventricular ejection fraction per 5.

only analysing occurrence was possible in retrospective data. This was also limited by that there were no data available regarding potassium binders. The RELAX-AHF-2 trial included patients with an eGFR between 25 and 75 ml/min/1.73 m$^2$, which could be seen as a limiting factor for the generalization of the use of MRAs in the setting of acute HF. Moreover, the trial consists of mostly Caucasian male patients. No information regarding angiotensin receptor–neprilysin inhibitor therapy was available in the RELAX-AHF-2 study. Whether our results translate to the broader HF population requires further study.

To conclude, in this secondary analysis of a large randomized trial in patients with acute HF, in-hospital initiation of an MRA

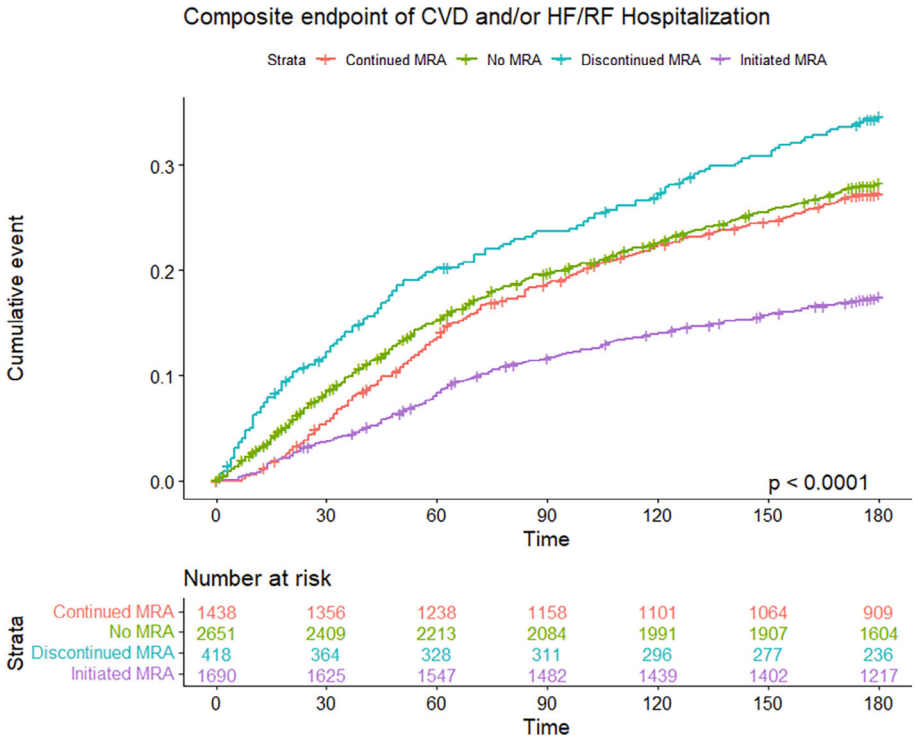


**Figure 3** Cumulative incidence of cardiovascular death (CVD) and/or hospitalization for heart failure (HF) or renal failure (RF) per mineralocorticoid receptor antagonist (MRA) category.

was associated with better post-discharge clinical outcomes, irrespective of ejection fraction and propensity score adjustment. Our findings provide supporting evidence for guidelines recommending initiation of an MRA before discharge in patients who are hospitalized for acute HF.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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