

Association Between Mineralocorticoid Receptor Antagonist Use and Outcome in Myocardial Infarction Patients With Heart Failure

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Background—There are no studies of mineralocorticoid receptor antagonist (MRA) treatment examining outcome in unselected real-life patients with myocardial infarction (MI) and heart failure (HF). There is uncertainty regarding effects of MRA in relation to left ventricular ejection fraction (LVEF) and chronic kidney disease (CKD). The aim was to assess MRA use and compare outcomes in MI patients with HF in relation to LVEF and CKD.

Methods and Results—Patients with MI and HF registered in the Swedish myocardial infarction registry, SWEDEHEART, 2005–2014, were included. Associations between MRA use and all-cause mortality up to 3 years were assessed with multivariable Cox regression, stratified by EF groups and presence of CKD (estimated glomerular filtration rate <60 mL/min per 1.73 m²). Of 45 071 patients with MI and HF, 4470 (9.9%) received MRA. Those with HF and LVEF <40% more often had MRA (19.6%) compared with those with LVEF 40% to 49% (9.1%) or LVEF ≥50% (4.7%). 8.6% of patients with CKD received MRA. After adjustment, MRA use was associated with lower mortality in those with LVEF <40% (hazard ratio [95% confidence interval] 0.81 [0.75–0.88]) and LVEF 40% to 49% (0.88 [0.75–1.03]) but not in those with LVEF ≥50% (1.29 [1.09–1.53]), with significant interaction between MRA and LVEF ($P<0.0001$). The association between MRA use and mortality was similar in those without (0.96 [0.88–1.05]) and with (0.92 [0.85–0.99]) CKD.

Conclusions—In patients with MI and HF, MRA use was associated with better long-term survival in patients with LVEF <40% but not in those with LVEF ≥50%, while the mortality risk was similar in MRA-treated patients with or without CKD. (*J Am Heart Assoc.* 2018;7:e009359. DOI: 10.1161/JAHA.118.009359.)

Key Words: ejection fraction • heart failure • mineralocorticoid receptor antagonists • myocardial infarction • prognosis • renal function

Treatment of heart failure (HF) is based mainly on blocking the activation of the renin–angiotensin–aldosterone system.¹ Aldosterone regulates sodium and potassium homeostasis and excessive activation of the mineralocorticoid

receptor may initiate an inflammatory response and cause fibrosis of the heart, fibrosis and remodeling of the vessels, and tubule-interstitial fibrosis in the kidneys.² The mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone, in addition to optimal medical therapy, have been shown in clinical trials to reduce morbidity and mortality among patients with chronic HF with reduced ejection fraction and among patients with acute myocardial infarction (MI) complicated by left ventricular systolic dysfunction and acute HF.^{3,4} There are, however, no studies of MRA treatment examining the outcome in unselected real-life patients with MI and HF.

Since fibrosis and inflammation are believed to be part of the pathogenesis of HF with preserved ejection fraction (HFpEF),⁵ MRA is an appealing treatment also for this patient group. The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) study of spironolactone in HFpEF did not show any positive effects on mortality, although a post hoc regional analysis indicated beneficial effects in the American patients.^{6,7} There is still no study examining outcome of MRA use in patients with HF and

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Accompanying Tables S1 and S2 are available at <http://jaha.ahajournals.org/content/7/14/e009359/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- In patients with myocardial infarction and heart failure, there seem to be no improved survival with mineralocorticoid receptor antagonist (MRA) treatment. In patients with myocardial infarction and heart failure, there seems to be no improved survival with MRA treatment in patients with preserved ejection fraction.

What Are the Clinical Implications?

- Patients with myocardial infarction, heart failure, and reduced ejection fraction should not have MRA treatment withheld, since MRA reduces mortality, while in patients with preserved ejection fraction there should be a clear clinical indication when initiating MRA treatment and in patients with myocardial infarction, heart failure, and chronic kidney disease, MRA may be used with the patients carefully monitored.

normal left ventricular ejection fraction (LVEF) in a MI setting. Moreover, chronic kidney disease (CKD) is common in HF and is an important risk factor for worse outcome.^{8,9} Even though MRAs have been found to reduce left ventricular mass and arterial stiffness in patients with CKD, CKD is a determinant for MRA use in HF by the risk of worsening renal function and hyperkalemia.¹⁰ We lack studies examining outcome of MRA use in unselected MI patients with HF and CKD.

The aim of this study was therefore to assess the use of MRA and association between MRA use and all-cause mortality in patients with MI and HF in relation to LVEF and kidney function.

Methods

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

Registry and Inclusion Criteria

The SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry is a national registry including almost all patients hospitalized for acute MI and admitted to a coronary care unit or other specialized facility.¹¹ The registry covers all hospitals taking care of acute cardiac patients in Sweden (n=72). In the acute coronary care part of the registry, >100 variables are collected prospectively including admission logistics, patient demographics, risk factors, past medical history, medical

treatment before admission, electrocardiographic changes, biochemical markers, clinical investigations, medical treatment in hospital, interventions, hospital outcome, diagnoses, and medication at discharge. Patients receive information about their participation in SWEDEHEART on admission and are allowed to opt out, but individual consent is not required. To ensure correctness of the data, the registry is monitored on a regular basis with visits to ≈30 randomly selected hospitals each year, comparing data entered into SWEDEHEART with the information in the patients' health records, repeatedly showing an agreement of 95% to 96%.

In this study, patients enrolled in the registry from 2005 to 2014 with acute MI and HF were included (Figure 1). HF was defined as either previously known HF or HF that was diagnosed during hospitalization (registered as Killip >1, administration of intravenous diuretics/inotropes, or use of continuous positive airway pressure). Only the first registration for MI and HF was included in these analyses. The use of MRA (spironolactone or eplerenone) was obtained from the Swedish Registry of Dispensed Drugs, which contains all pharmacy-drug dispensations in the country linked to each citizen's unique personal number. Patients with a registered dispensation of spironolactone or eplerenone within 6 months before admission were excluded, as only MRA-naïve patients at admission were included. MRA use after discharge was defined as a recorded dispensation of spironolactone or eplerenone within 2 weeks after discharge. Patients who died during hospitalization or within 2 weeks from discharge were excluded.

LVEF was obtained from the measurement obtained during hospitalization and according to local practice (echocardiography in 99% of the cases in SWEDEHEART). Patients were categorized according to LVEF into 3 groups: EF ≥50%, EF 40% to 49%, and EF <40%.

Serum creatinine was obtained at admission and glomerular filtration rate (eGFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).¹² CKD was defined as eGFR <60 mL/min per 1.73 m².

The study conforms to the declaration of Helsinki and was approved by the regional ethical review board in Stockholm.

End Point

The outcome was all-cause mortality up to 3 years of follow-up. Mortality data were obtained by running the registry against the Swedish population registry, which includes the vital status of all Swedish residents.

Statistical Analysis

Descriptive continuous variables are presented as median and interquartile range and categorical variables are presented as counts and proportions (%). Mortality rates per

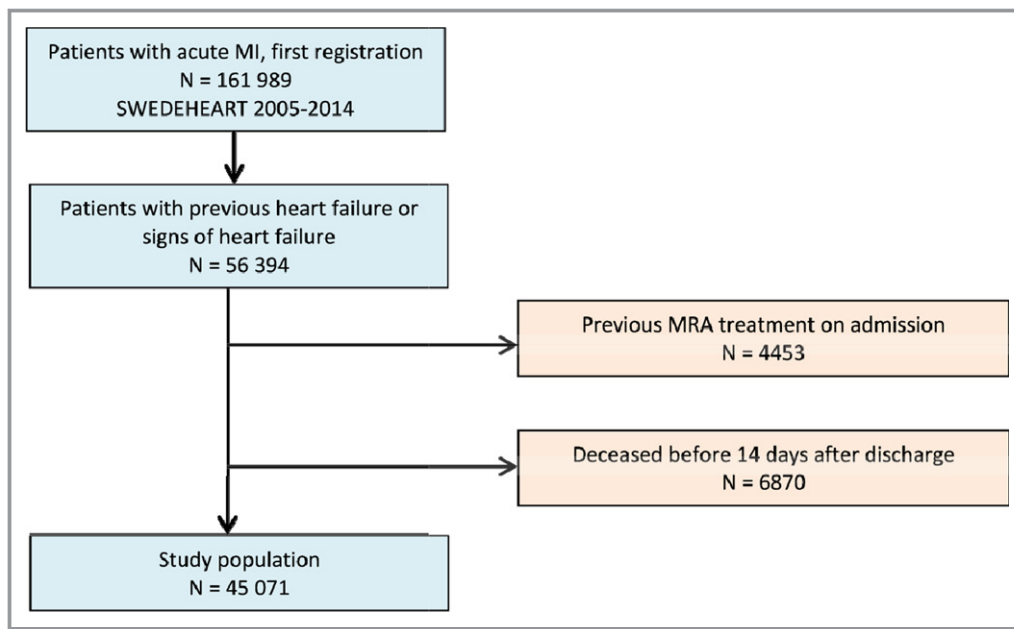


Figure 1. Flow chart of patient inclusion. MI indicates myocardial infarction; MRA, mineralocorticoid receptor antagonist.

100 person-years and Kaplan–Meier survival curves were estimated.

Uni- and multivariable Cox proportional hazards models were used to estimate hazard ratios for the association between the use of MRA and mortality in the different EF groups and in the presence or not of CKD. Adjustments were made for 28 variables: center as random effect, year of admission, age, sex, risk factors (diabetes mellitus, hypertension), previous cardiovascular disease (MI, HF, peripheral vessel disease), previous other diseases (chronic obstructive pulmonary disease, cancer), status at presentation (ST-segment–elevation, Killip >1, atrial fibrillation), intervention and treatment (percutaneous coronary intervention, coronary artery bypass graft, intravenous diuretics, inotropes), medication at discharge (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β -blockers, calcium antagonists, diuretics, digoxin, statin therapy, antiplatelet therapy, and warfarin), atrial fibrillation at discharge, and eGFR. Analyses of interaction between MRA and EF groups and MRA and CKD were performed by creating an interaction term in the Cox regression analysis. For continuous variables, natural cubic splines with 4 degrees of freedom (knots) were used.

The percentage of missing values across the outcome and adjustment variables varied between 0% and 6.8%. Not considering LVEF, 19.6% of the records were incomplete. Multiple imputation was used to create 30 imputed data sets. Incomplete variables were imputed using the random forest-based MICE (Multivariate Imputation by Chained Equations) algorithm.¹³ LVEF was not imputed. The imputation model for

each incomplete variable included all adjustment variables as well as the outcome variable.

A sensitivity analysis of complete cases was performed to validate the robustness of the results.

Results

Treatment With MRA

Out of 45 071 patients with acute MI and HF, 4470 (9.9%) patients had MRA prescribed at discharge, of which 4269 (9.5%) had spironolactone and 204 (0.5%) had eplerenone (Table 1). Compared with patients not treated, those treated with MRA were overall somewhat younger with more often ST-segment–elevation MI on admission, had less often prior MI, HF, and CKD, and were less often treated with antiplatelet treatment, β -blockers, and diuretics on admission (Table 1). Patients treated with MRA had more often severely reduced EF but less often CKD (Table 2). They were more often treated with inotropic drugs, intravenous diuretics, and revascularization. At discharge, patients with MRA had more angiotensin-converting enzyme inhibitor /angiotensin receptor blocker and diuretics, and slightly more often β -blockers compared with patients without MRA.

Out of 30 485 patients with a known LVEF, 9895 (32.5%) had LVEF \geq 50%, 7921 (26.0%) had LVEF 40% to 49%, and 12 669 (41.6%) had LVEF <40% (Table 3). Patients with lower EF were generally older, more often had diabetes mellitus, a history of MI and HF, presented more often with ST-segment–

Table 1. Baseline Characteristics in All Patients and in Relation to Kidney Function

	Overall (n=45 071)		eGFR \geq 60 (n=22 259)		eGFR <60 (n=20 904)	
	MRA No (n=40 601)	MRA Yes (n=4470)	MRA No (n=19 727)	MRA Yes (n=2532)	MRA No (n=19 102)	MRA Yes (n=1802)
Demographics						
Age (y)	78 (69–84)	76 (67–83)	73 (65–81)	72 (64–80)	82 (75–86)	80 (73–85)
Female	16 915 (41.7%)	1890 (42.3%)	7201 (36.5%)	928 (36.7%)	8921 (46.7%)	898 (49.8%)
University hospital	8035 (19.8%)	1075 (24.0%)	3812 (19.3%)	597 (23.6%)	3422 (17.9%)	416 (23.1%)
PCI center	24 577 (60.5%)	2979 (66.6%)	12 075 (61.2%)	1699 (67.1%)	11 045 (57.8%)	1166 (64.7%)
Risk factors						
Diabetes mellitus	13 065 (32.2%)	1509 (33.8%)	5546 (28.1%)	820 (32.4%)	6977 (36.5%)	643 (35.7%)
Hypertension	25 281 (62.3%)	2790 (62.4%)	10 748 (54.5%)	1441 (56.9%)	13 402 (70.2%)	1260 (69.9%)
Smoking	6688 (16.5%)	890 (19.9%)	4438 (22.5%)	642 (25.4%)	1986 (10.4%)	225 (12.5%)
Prev. cardiovasc dis						
Prior MI	14 398 (35.5%)	1271 (28.5%)	5720 (29.0%)	630 (24.9%)	7965 (41.7%)	594 (33.0%)
Prior HF	15 711 (38.7%)	1287 (28.8%)	5794 (29.4%)	563 (22.0%)	9064 (47.5%)	670 (37.2%)
Prior PCI	5174 (12.7%)	448 (10.0%)	2514 (12.7%)	280 (11.1%)	2394 (12.5%)	147 (8.2%)
Prior CABG	5069 (12.5%)	428 (9.6%)	2159 (10.9%)	227 (9.0%)	2666 (14.0%)	185 (10.3%)
Peripher vasc dis	3924 (9.7%)	343 (7.7%)	1348 (6.8%)	163 (6.4%)	2391 (12.5%)	168 (9.3%)
Prev. comorbidity						
COPD	4689 (11.5%)	425 (9.5%)	2310 (11.7%)	244 (9.6%)	2130 (11.2%)	163 (9.0%)
Cancer	1665 (4.1%)	150 (3.4%)	651 (3.3%)	87 (3.4%)	927 (4.9%)	56 (3.1%)
Status at admission						
ST-elevation	11 331 (27.9%)	1661 (37.2%)	6532 (33.1%)	1085 (42.9%)	4355 (22.8%)	536 (29.7%)
Atrial fibrillation	7522 (18.5%)	897 (20.1%)	2948 (14.9%)	461 (18.2%)	4237 (22.2%)	405 (22.5%)
Killip >1	15 469 (38.1%)	1873 (41.9%)	7071 (35.8%)	986 (38.9%)	7767 (40.7%)	826 (45.8%)
Medication at adm						
ACE inh/ARB	17 085 (42.1%)	1877 (42.0%)	7090 (35.9%)	1005 (39.7%)	9200 (48.4%)	808 (44.8%)
β -Blockers	20 089 (49.5%)	1944 (43.5%)	8226 (41.7%)	988 (39.0%)	10 903 (57.1%)	895 (49.7%)
Diuretics	16 504 (40.6%)	1633 (36.5%)	5358 (27.2%)	691 (27.3%)	10 354 (54.2%)	876 (48.6%)
Digitalis	2126 (5.2%)	246 (5.5%)	862 (4.4%)	117 (4.6%)	1173 (6.1%)	125 (6.9%)
Statins	12 974 (32.0%)	1395 (31.2%)	5926 (30.0%)	744 (29.4%)	6448 (33.8%)	607 (33.7%)
Calcium antagonists	8447 (20.8%)	954 (21.3%)	3449 (17.5%)	497 (19.6%)	4642 (24.3%)	426 (23.6%)
Antiplatelet mono	18 836 (46.4%)	1768 (39.6%)	7791 (39.5%)	910 (35.9%)	10 128 (53.0%)	793 (44.0%)
Antiplatelet dual	2039 (5.0%)	171 (3.8%)	860 (4.4%)	87 (3.4%)	1084 (5.7%)	79 (4.4%)
Warfarin	3588 (8.8%)	398 (8.9%)	1459 (7.4%)	193 (7.6%)	1963 (10.3%)	194 (10.8%)

ACE inh/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; adm, admission; CABG, coronary arterial bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; Prev. cardiovasc dis, previous cardiovascular disease.

elevation MI, and had lower eGFR (Tables 3 and 4). A total of 469 (4.7%) patients with LVEF \geq 50% had MRA, while 722 (9.1%) of patients with LVEF 40% to 49% and 2486 (19.6%) of patients with LVEF <40% had MRA. In patients with EF \geq 50%, baseline characteristics for those treated and not treated with MRA differed from those with EF 40% to 49% or EF <40%. In this group, patients treated with MRA were older, more often had risk factors such as diabetes mellitus and hypertension,

more often atrial fibrillation, and were more often treated with β -blockers and diuretics on admission (Table 3).

Out of 43 163 with known kidney function, 20 904 patients (48.4%) had eGFR <60 mL/min per 1.73 m². These patients were older, more often female, and more often had other risk factors and cardiovascular diseases (Table 1). Patients with eGFR <60 mL/min per 1.73 m² were also less often treated with revascularization and angiotensin-converting enzyme inhibitor/

Table 2. In-Hospital Course and Medication at Discharge in All Patients and in Relation to Kidney Function

	Overall (n=45 071)		eGFR ≥60 (n=22 259)		eGFR <60 (n=20 904)	
	MRA No (n=40 601)	MRA Yes (n=4470)	MRA No (n=19 727)	MRA Yes (n=2532)	MRA No (n=19 102)	MRA Yes (n=1802)
Heart function						
LVEF ≥50%	9426 (23.2%)	469 (10.5%)	5421 (27.5%)	280 (11.1%)	3647 (19.1%)	175 (9.7%)
LVEF 40% to 49%	7199 (17.7%)	722 (16.2%)	3886 (19.7%)	429 (16.9%)	3068 (16.1%)	272 (15.1%)
LVEF <40%	10 183 (25.1%)	2486 (55.6%)	4894 (24.8%)	1444 (57.0%)	4981 (26.1%)	978 (54.3%)
LVEF missing	13 793 (34.0%)	793 (17.7%)	5525 (28.0%)	379 (15.0%)	7406 (38.8%)	377 (20.9%)
Kidney function						
Creatinine	94 (76–122)	89 (74–109)	76 (66–88)	77 (67–89)	123 (104–157)	114 (99–136)
eGFR	60 (43–79)	65 (50–81)	79 (69–88)	78 (69–88)	42 (31–51)	46 (38–54)
CKD (GFR <60 mL/min per 1.73 m ²)	19 102 (47.0%)	1802 (40.3%)	0%	0%	100%	100%
Creatinine missing	4.4%	3.0%	0%	0%	0%	0%
Intervention						
PCI	15 772 (38.8%)	2160 (48.3%)	9715 (49.2%)	1425 (56.3%)	5445 (28.5%)	682 (37.8%)
CABG	1487 (3.7%)	151 (3.4%)	909 (4.6%)	101 (4.0%)	492 (2.6%)	46 (2.6%)
Inotropes	2854 (7.0%)	567 (12.7%)	1523 (7.7%)	333 (13.2%)	1211 (6.3%)	213 (11.8%)
IV diuretics	25 794 (63.5%)	3743 (83.7%)	12 353 (62.6%)	2118 (83.6%)	12 474 (65.3%)	1519 (84.3%)
Medication at discharge						
ACE inh/ARB	29 391 (72.4%)	3768 (84.3%)	15 420 (78.2%)	2264 (89.4%)	12 794 (67.0%)	1389 (77.1%)
β-Blockers	35 131 (86.5%)	4074 (91.1%)	17 373 (88.1%)	2335 (92.2%)	16 249 (85.1%)	1615 (89.6%)
Spironolactone	NA	4269 (95.5%)	NA	2381 (94.0%)	NA	1757 (97.5%)
Eplerenone	NA	204 (4.6%)	NA	152 (6.0%)	NA	46 (2.6%)
Diuretics	23 726 (58.4%)	3873 (86.6%)	9272 (47.0%)	2133 (84.2%)	13 447 (70.4%)	1626 (90.2%)
Digoxin	2570 (6.3%)	371 (8.3%)	1141 (5.8%)	201 (7.9%)	1337 (7.0%)	164 (9.0%)
Statins	28 930 (71.3%)	3432 (76.8%)	15 644 (79.3%)	2071 (81.8%)	12 135 (63.5%)	1264 (70.1%)
Calcium antagonists	7098 (17.5%)	551 (12.3%)	2858 (14.5%)	285 (11.3%)	3945 (20.7%)	245 (13.6%)
Antiplatelet mono	13 262 (32.7%)	1322 (29.6%)	5406 (27.4%)	644 (25.4%)	7246 (37.9%)	634 (35.2%)
Antiplatelet dual	23 680 (58.3%)	2803 (62.7%)	12 999 (65.9%)	1722 (68.0%)	9712 (50.8%)	1001 (55.5%)
Warfarin	4488 (11.1%)	738 (16.5%)	2030 (10.3%)	408 (16.1%)	2259 (11.8%)	306 (17.0%)
Atr fib discharge	5323 (13.1%)	640 (14.3%)	2048 (10.4%)	318 (12.6%)	3071 (16.1%)	300 (16.6%)

ACE inh/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; Antiplatelet dual, antiplatelet dual therapy; Antiplatelet mono, antiplatelet mono therapy; Atr fib, atrial fibrillation; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; PCI, percutaneous coronary intervention.

angiotensin receptor blocker, but were more often treated with diuretics (Table 2). A total of 1802 patients (8.6%) with CKD were treated with MRA versus 2532 (11.4%) of the patients without CKD. The relative differences in baseline characteristics and other treatments between patients treated with and without MRA were similar regardless of kidney function.

Mortality

During follow-up, the mortality rate was lower in patients treated with MRA, 14.9 ([95% CI] 14.1–15.6) versus 17.9 ([95%

confidence interval (CI)] 17.6–18.2) per 100 person-years in untreated patients resulting in hazard ratio (HR) (95% CI) of 0.83 (0.78–0.88) (Figure 2A). After adjustment, the association between MRA treatment and mortality was attenuated, but still significant (HR [95% CI] 0.94 [0.89–0.99]).

In the crude analysis when stratifying into different LVEF groups, MRA-treated patients had lower mortality rates compared with the untreated patients in those with reduced LVEF (<40%) (13.2 [12.2–14.2] versus 19.2 [18.6–19.8] per 100 person-years) and LVEF 40% to 49% (10.2 [8.6–11.8] versus 12.2 [11.7–12.7] per 100 person-years). In those with LVEF ≥50%,

Table 3. Baseline Characteristics in Patients in Relation to EF

	EF ≥50% (n=9895)		EF 40% to 49% (n=7921)		EF <40% (n=12 669)	
	MRA No (n=9426)	MRA Yes (n=469)	MRA No (n=7199)	MRA Yes (n=722)	MRA No (n=10 183)	MRA Yes (n=2486)
Demographics						
Age (y)	75 (67–82)	77 (69–83)	76 (67–82)	75 (67–82)	77 (68–83)	75 (66–81)
Female	4166 (44.2%)	261 (55.7%)	2778 (38.6%)	331 (45.8%)	3534 (34.7%)	884 (35.6%)
University hospital	1932 (20.5%)	103 (22.0%)	1562 (21.7%)	151 (20.9%)	2331 (22.9%)	684 (27.5%)
PCI center	6125 (65.0%)	326 (69.5%)	4667 (64.8%)	479 (66.3%)	6535 (64.2%)	1735 (69.8%)
Risk factors						
Diabetes mellitus	2770 (29.4%)	178 (38.0%)	2350 (32.6%)	249 (34.5%)	3440 (33.8%)	884 (33.7%)
Hypertension	6082 (64.5%)	352 (75.1%)	4448 (61.8%)	476 (65.9%)	5786 (56.8%)	1435 (57.7%)
Smoking	1848 (19.6%)	82 (17.5%)	1322 (18.4%)	138 (19.1%)	1928 (18.9%)	575 (23.1%)
Prev. cardiovasc dis						
Prior MI	2389 (25.3%)	95 (20.3%)	2155 (29.9%)	186 (25.8%)	3656 (35.0%)	676 (27.2%)
Prior HF	2728 (28.9%)	115 (24.5%)	2312 (32.1%)	176 (24.4%)	3501 (34.4%)	648 (26.1%)
Prior PCI	1140 (12.1%)	36 (7.7%)	872 (12.1%)	76 (10.5%)	1150 (11.3%)	249 (10.0%)
Prior CABG	917 (9.7%)	42 (9.0%)	831 (11.5%)	79 (10.9%)	1199 (11.8%)	211 (8.5%)
Peripher vasc dis	725 (7.7%)	40 (8.5%)	689 (9.5%)	42 (5.8%)	931 (9.1%)	188 (7.6%)
Prev. comorbidity						
COPD	1135 (12.0%)	40 (8.5%)	760 (10.6%)	71 (9.8%)	1022 (10.0%)	208 (8.4%)
Cancer	384 (4.1%)	20 (4.3%)	271 (3.8%)	20 (2.8%)	342 (3.4%)	81 (3.3%)
Status at admission						
ST-elevation	2572 (27.3%)	122 (26.0%)	2477 (34.4%)	274 (38.0%)	3709 (36.4%)	1085 (43.6%)
Atrial fibrillation	1386 (14.7%)	99 (21.1%)	1198 (16.6%)	137 (19.0%)	1821 (17.9%)	451 (18.1%)
Killip >1	3438 (36.5%)	192 (40.9%)	2553 (35.5%)	291 (40.3%)	3868 (38.0%)	1008 (40.5%)
Medication at adm						
ACE inh/ARB	3798 (40.3%)	217 (46.3%)	2833 (39.4%)	302 (41.8%)	4078 (40.0%)	999 (40.2%)
β-Blockers	4367 (46.3%)	242 (51.6%)	3411 (47.4%)	305 (42.2%)	4563 (44.8%)	970 (39.0%)
Diuretics	3289 (34.9%)	202 (43.1%)	2433 (33.8%)	240 (33.2%)	3602 (35.4%)	751 (30.2%)
Digitalis	363 (3.9%)	35 (7.5%)	278 (3.9%)	27 (3.7%)	451 (4.4%)	116 (4.7%)
Statins	3008 (31.9%)	147 (31.3%)	2301 (32.0%)	236 (32.7%)	3175 (31.2%)	773 (31.1%)
Calcium antagonists	2188 (23.2%)	141 (30.1%)	1582 (22.0%)	187 (25.9%)	1749 (17.2%)	454 (18.3%)
Antiplatelet mono	3873 (41.1%)	201 (42.9%)	3067 (42.6%)	248 (39.3%)	4436 (43.6%)	911 (36.6%)
Antiplatelet dual	417 (4.4%)	14 (3.0%)	336 (4.7%)	26 (3.6%)	435 (4.3%)	79 (3.2%)
Warfarin	748 (7.9%)	47 (10.0%)	592 (8.2%)	62 (8.6%)	876 (8.6%)	208 (8.4%)

ACE inh/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; Adm, admission; CABG, coronary arterial bypass grafting; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; Prev. cardiovasc dis, previous cardiovascular disease.

MRA-treated patients had higher mortality rates compared with the untreated patients (15.1 [12.6–17.5] versus 9.8 [9.3–10.2] per 100 person-years) (Figure 2B). In the adjusted analyses, there was a significant interaction between MRA and LVEF groups ($P<0.0001$), with a lower risk of death in MRA-treated patients with LVEF <40% (hazard ratio [95% CI] 0.81 [0.75–

0.88]) and in patients with LVEF 40% to 49% (0.88 [0.75–1.03]) but not in those with LVEF ≥50% (1.29 [1.09–1.53]) (Figure 3).

When the patients were divided into presence or not of CKD, MRA was associated with a lower mortality rate in patients with CKD (21.5 [20.0–23.1] versus 26.9 [26.4–27.5] per 100 person-years), but not in patients without CKD (10.6

Table 4. In-Hospital Course and Medication at Discharge in Relation to EF

	EF ≥50% (n=9895)		EF 40% to 49% (n=7921)		EF <40% (n=12 669)	
	MRA No (n=9426)	MRA Yes (n=469)	MRA No (n=7199)	MRA Yes (n=722)	MRA No (n=10 183)	MRA Yes (n=2486)
Kidney function						
Creatinine	87 (72–111)	83 (70–103)	91 (75–117)	88 (73–106)	97 (78–126)	91 (75–111)
eGFR	67 (48–84)	66 (51–81)	63 (46–82)	67 (52–84)	59 (42–78)	65 (50–82)
CKD (GFR <60 mL/min per 1.73 m ²)	3647 (38.7%)	175 (37.3%)	3068 (42.6%)	272 (37.7%)	4981 (48.9%)	978 (39.3%)
Intervention						
PCI	4632 (49.1%)	219 (46.7%)	3543 (49.2%)	383 (53.0%)	4454 (43.7%)	1356 (54.5%)
CABG	438 (4.6%)	29 (6.2%)	340 (4.7%)	26 (3.6%)	526 (5.2%)	86 (3.5%)
Inotropes	704 (7.5%)	46 (9.8%)	564 (7.8%)	77 (10.7%)	1167 (11.5%)	408 (16.4%)
IV diuretics	5522 (58.6%)	387 (82.5%)	4809 (66.8%)	615 (85.2%)	7691 (75.5%)	2116 (85.1%)
Medication at discharge						
ACE inh/ARB	6706 (71.1%)	353 (75.3%)	5747 (79.8%)	618 (85.6%)	8365 (82.1%)	2228 (89.6%)
β-Blockers	8238 (87.4%)	417 (88.9%)	6462 (89.8%)	658 (91.1%)	9160 (90.0%)	2319 (93.3%)
Spironolactone	NA	457 (97.7%)	NA	690 (95.6%)	NA	2343 (94.2%)
Eplerenone	NA	11 (2.3%)	NA	32 (4.4%)	NA	146 (5.9%)
Diuretics	4295 (45.6%)	407 (86.8%)	3850 (53.5%)	599 (83.0%)	6705 (65.8%)	2164 (87.0%)
Digoxin	379 (4.0%)	33 (7.0%)	366 (5.1%)	43 (6.0%)	728 (7.1%)	214 (8.6%)
Statins	7635 (81.0%)	353 (75.3%)	5858 (81.4%)	594 (82.3%)	7673 (75.4%)	2040 (82.1%)
Calcium antagonists	2171 (23.0%)	110 (23.5%)	1251 (17.4%)	128 (17.7%)	987 (9.7%)	181 (7.3%)
Antiplatelet mono	2497 (26.5%)	143 (30.5%)	1990 (27.6%)	199 (27.6%)	3167 (31.1%)	671 (27.0%)
Antiplatelet dual	6315 (67.0%)	285 (60.8%)	4770 (66.3%)	482 (66.8%)	6131 (60.2%)	1645 (66.6%)
Warfarin	958 (10.2%)	68 (14.5%)	748 (10.4%)	100 (13.9%)	1371 (13.5%)	469 (18.9%)
Atr fib discharge	908 (9.6%)	70 (14.9%)	856 (11.9%)	91 (12.6%)	1390 (13.7%)	334 (13.4%)

ACE inh/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; Antiplatelet dual, antiplatelet dual therapy; Antiplatelet mono, antiplatelet mono therapy; Atr fib, atrial fibrillation; CABG, coronary arterial bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Dis, discharge; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NA, not applicable; PCI, percutaneous coronary intervention; Prev. cardiovasc dis, previous cardiovascular disease.

[9.7–11.5] versus 10.7 [10.4–11.0] per 100 person-years) (Figure 2C). After adjustment there was no significant interaction between MRA and CKD ($P=0.46$) and there was no difference regarding the association between MRA treatment and outcome in patients with (0.92 [0.85–0.99]) and without (0.96 [0.88–1.05]) CKD (Figure 3).

A sensitivity analysis, including only complete cases in the adjusted analyses, showed similar results with a significant interaction between MRA and LVEF, whereas there was no such sign between MRA and CKD (Table S1). There were even similar results when excluding patients with only prior HF and no acute HF during hospitalization (Table S2).

Discussion

This is to our knowledge the first study on long-term outcome of MRA treatment in nonselected real-life patients

with acute MI and HF. Our study included almost all patients with acute MI and HF for a period of 10 years in an entire country, resulting in highly generalizable results. The main finding was that MRA treatment was associated with a lower mortality in patients with reduced LVEF (<40%) but not in patients with preserved LVEF (≥50%). In patients with CKD there was no difference in mortality risk between treated and untreated patients and no statistical interaction between MRA and CKD.

MRA in Acute MI Patients With HF and Reduced EF

The RALES (Randomized Aldactone Evaluation Study) and the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) firmly established that MRA improves survival and morbidity in patients with HF and reduced ejection fraction (LVEF <30%–35%) and the EPHEUS

(Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) demonstrated similar effects in patients with acute MI complicated by HF and reduced LVEF.^{3,4,14} The present study confirms these findings in a nonselected population by demonstrating a 19% lower (hazard ratio [95% CI] 0.81 [0.75–0.88]) mortality in MRA-treated patients with LVEF <40% and a trend towards lower mortality in those with LVEF 40% to 49% (0.88 [0.75–1.03]), all together strongly supporting the recent ST-segment-elevation MI guidelines with MRA in patients with LVEF ≤40% as a class I recommendation.¹⁵ The low use of MRA in patients with acute MI and LVEF <40% (19.6%) is similar to findings in the United States (14.5%) and should call for actions.¹⁶

MRA in Acute MI Patients With HF and Preserved EF

In this study, there was a significant interaction between MRA and LVEF. In patients with LVEF ≥50%, MRA treatment was not associated with lower mortality. In contrast, after multiple adjustments the MRA-treated patients with preserved LVEF had a significantly higher mortality risk (1.29 [1.09–1.53]). The latter finding should be interpreted with great caution. In the group with LVEF ≥50%, MRA-treated patients were older with more comorbidities. Moreover, the indication for MRA may have been different in those with preserved LVEF compared with those with reduced LVEF. Although we made extensive adjustments for differences in baseline characteristics, we

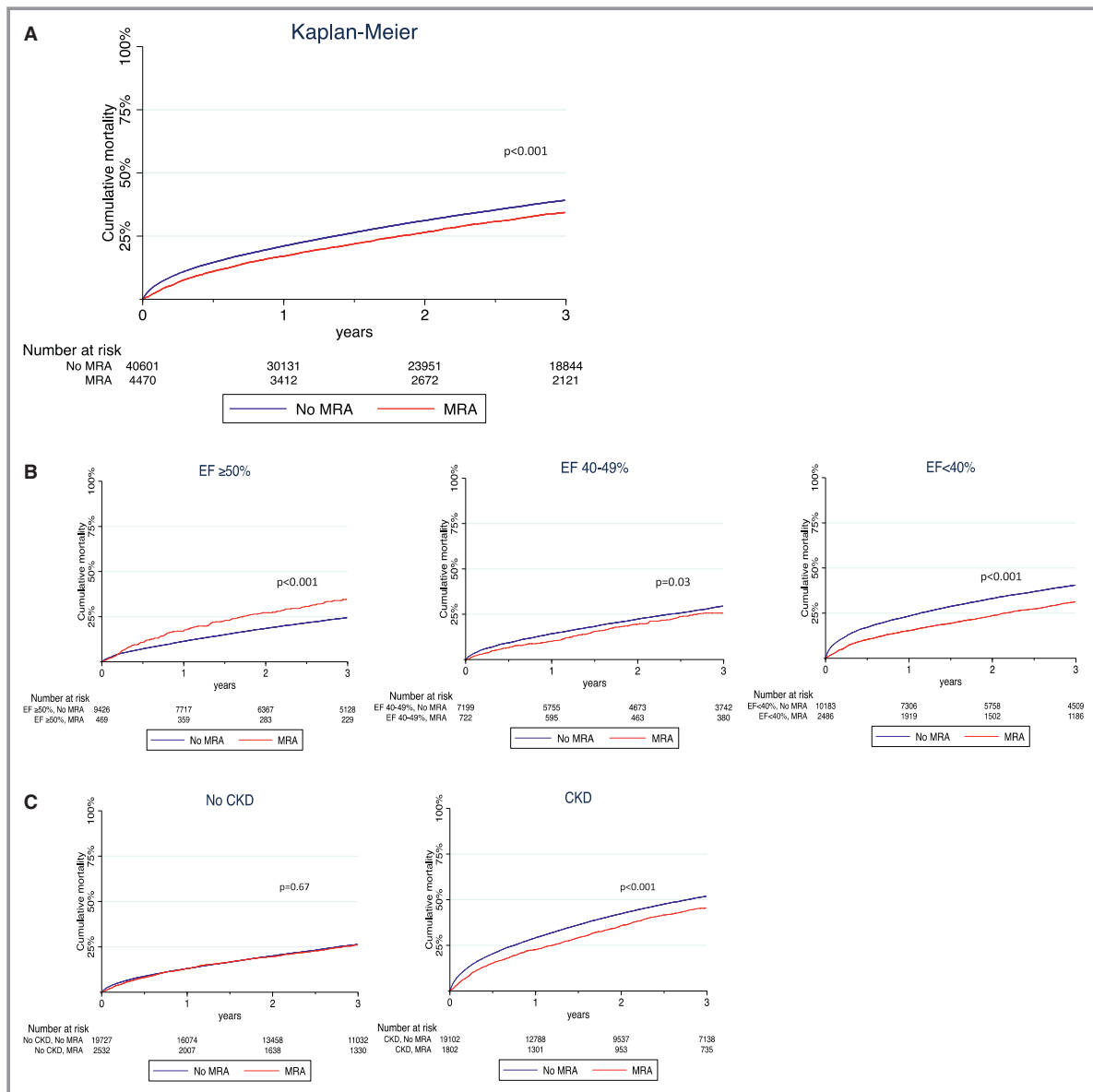


Figure 2. A, Survival curves for all patients with myocardial infarction and heart failure stratified on MRA use. B, Survival curves stratified on EF groups and MRA use. C, Survival curves stratified on presence of CKD and MRA use. CKD indicates chronic kidney disease; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist.

cannot exclude residual confounding, including such by indication. The low number of patients with LVEF $\geq 50\%$ treated with MRA increases the uncertainty of the results. Still, our data indicate that the effect of MRA may be different in patients with and without reduced LVEF and call for more studies in this subgroup of patients.

Although the multicenter randomized study of spironolactone treatment in patients with HF and LVEF $>45\%$ (TOPCAT) did not show a reduction in the incidence of death from cardiovascular cause or hospitalization for HF, a later subanalysis questioned the result because there were regional differences with a possible clinical benefit in the American patients with reduced rate of primary end point.^{6,7} Our results are in contrast to that subanalysis, but in line with a meta-analysis of MRA treatment in HF demonstrating improved outcome in HF with reduced but not with preserved LVEF.¹⁷

It is, however, important to note that patients with acute MI, HF, and preserved ejection fraction (LVEF $\geq 50\%$) are different from patients with chronic HFpEF in several aspects, including pathophysiological mechanisms. In a chronic HFpEF population, a minority will have ischemic heart disease.^{18,19} During acute ischemia, several mechanisms leading to signs of HF will be transient and not permanent as in chronic HFpEF. Therefore, our findings may not be translated into a population with chronic HF. Ongoing trials will examine whether MRA treatment in the HFpEF population improves outcome.²⁰

The HF patients with LVEF 40% to 49% and MRA treatment had a slightly lower mortality risk in the multivariable analysis, although not statistically significant. Because we have little knowledge of treatment of patients with HF and LVEF 40% to 49%, the basis for comparison is limited, although the results are in line with a subanalysis of TOPCAT, which found that EF

modified the spironolactone effect with stronger estimated benefits at the lower end of the EF.^{21,22}

Mechanisms Behind the Interaction Between MRA and LVEF

We still lack knowledge of why there may be a difference in the impact of MRA on survival in the different EF groups. HF with LVEF $\geq 50\%$ and $<50\%$ are structurally different HF phenotypes. Patients with reduced LVEF have been found to have a worse prognosis than HF with preserved LVEF after MI.²³ Patients with HFpEF have more comorbidities and have been shown to die less of cardiovascular death and sudden cardiac death than HF with reduced ejection fraction, which may partly contribute to the lack of positive effect on survival of MRA in HF with LVEF $\geq 50\%$.²⁴ Aldosterone may play a role in the presence of arrhythmia, both atrial and ventricular, which may have a more important role in HF with reduced ejection fraction, because MRA has been found to reduce the risk of atrial fibrillation and sudden cardiac death.^{3,4,14,25}

MRA in Acute MI Patients With CKD

In the present study, the association between MRA treatment and outcome was similar regardless of kidney function. As aldosterone is part of the progressive fibrosis of the heart, vessels, and kidney, MRA is highly interesting as a possible way of preventing renal fibrosis and reducing cardiovascular complications in patients with CKD.^{10,26} A recent meta-analysis of 12 CKD studies and >4000 patients showed that MRA treatment did benefit CKD patients regarding left ventricular muscular mass, all-cause mortality, and cardiovascular events with no increased incidence of severe hyperkalemia.²⁷ MRA treatment may be an alternative even in end-stage renal disease because a small study of hemodialysis patients showed that MRA reduced cardiovascular and cerebrovascular morbidity and mortality.²⁸

MRA and renin–angiotensin–aldosterone system blockade are often withheld from patients with CKD because of fear of hyperkalemia and worsening renal function. Eplerenone, however, was safe in carefully monitored risk patients in a substudy of EMPHASIS-HF.²⁹ In a subanalysis of RALES, the absolute benefit of spironolactone was greatest in patients with reduced kidney function³⁰ and a subanalysis from EMPHASIS-HF showed positive effect on survival despite worsening renal function.³¹ Our findings support that MRA may be used in patients with MI and HF, even in the presence of CKD.

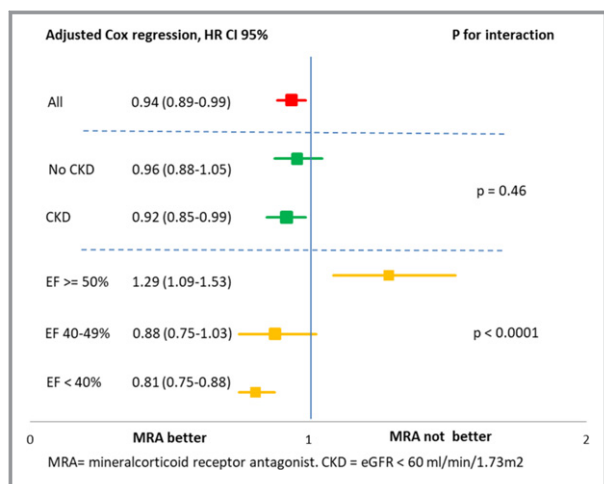


Figure 3. Forest plot depicting adjusted mortality for MRA use overall and stratified for EF and CKD. CI indicates confidence interval; CKD, chronic kidney disease; EF, ejection fraction; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist. CKD, eGFR < 60 mL/min per 1.73 m².

Limitations

This study has limitations. Although this is a nonselective observational study of a contemporary MI population with HF,

there may have been exclusion of some older and less healthy individuals from the cardiac intensive care units. A total of 32% of the included patients lacked data about LVEF and almost 20% did not have complete data in the multivariable analyses, making multiple imputation necessary. The LVEF measurements were according to local practice and not according to a core laboratory. As stated above, given the observational nature of the study, causality cannot be proven and we cannot exclude residual confounding, including such by indication. We only examined the association between MRA and subsequent death. We were not able to study the risk of cardiovascular death, rehospitalization, and quality of life, which are important end points in the present population.

Conclusion

In patients with MI and concomitant HF, MRA was associated with better long-term survival in patients with LVEF <40%, while there was no positive association with survival associated with the use of MRA in patients with LVEF ≥50%. In patients with and without CKD, the association between MRA use and long-term mortality was not significantly different.

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References

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.
- Brown NJ. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nat Rev Nephrol*. 2013;9:459–469.
- Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.
- Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
- Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62:263–271.
- Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.
- Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.
- Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35:455–469.
- Lofman I, Szummer K, Hagerman I, Dahlstrom U, Lund LH, Jernberg T. Prevalence and prognostic impact of kidney disease on heart failure patients. *Open Heart*. 2016;3:e000324.
- Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townend JN. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol*. 2009;54:505–512.
- Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenstrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart*. 2010;96:1617–1621.
- Valente MA, Hillege HL, Navis G, Voors AA, Dunselman PH, van Veldhuisen DJ, Damman K. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. *Eur J Heart Fail*. 2014;16:86–94.
- Shah AD, Bartlett JW, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: a CALIBER study. *Am J Epidemiol*. 2014;179:764–774.
- Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11–21.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
- Rao KK, Enriquez JR, de Lemos JA, Alexander KP, Chen AY, McGuire DK, Fonarow GC, Das SR. Use of aldosterone antagonists at discharge after myocardial infarction: results from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get with the Guidelines (GWTG). *Am Heart J*. 2013;166:709–715.
- Berbenetz NM, Mrkobrada M. Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2016;16:246.
- Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19:1574–1585.
- Patel K, Fonarow GC, Kitzman DW, Aban IB, Love TE, Allman RM, Gheorghiadu M, Ahmed A. Aldosterone antagonists and outcomes in real-world older

- patients with heart failure and preserved ejection fraction. *JACC Heart Fail*. 2013;1:40–47.
20. Lund LH, Oldgren J, James S. Registry-based pragmatic trials in heart failure: current experience and future directions. *Curr Heart Fail Rep*. 2017;14:59–70.
 21. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37:455–462.
 22. Lofman I, Szummer K, Dahlstrom U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail*. 2017;19:1606–1614.
 23. Hellermann JP, Jacobsen SJ, Redfield MM, Reeder GS, Weston SA, Roger VL. Heart failure after myocardial infarction: clinical presentation and survival. *Eur J Heart Fail*. 2005;7:119–125.
 24. Hamaguchi S, Kinugawa S, Sobirin MA, Goto D, Tsuchihashi-Makaya M, Yamada S, Yokoshiki H, Tsutsui H; for the JCARE-CARD Investigators. Mode of death in patients with heart failure and reduced vs. preserved ejection fraction. *Circ J*. 2012;76:1662–1669.
 25. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B; Investigators EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) study. *J Am Coll Cardiol*. 2012;59:1598–1603.
 26. Blasi ER, Rocha R, Rudolph AE, Blomme EA, Polly ML, McMahon EG. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. *Kidney Int*. 2003;63:1791–1800.
 27. Lu R, Zhang Y, Zhu X, Fan Z, Zhu S, Cui M, Zhang Y, Tang F. Effects of mineralocorticoid receptor antagonists on left ventricular mass in chronic kidney disease patients: a systematic review and meta-analysis. *Int Urol Nephrol*. 2016;48:1499–1509.
 28. Matsumoto Y, Mori Y, Kageyama S, Arihara K, Sugiyama T, Ohmura H, Yakushigawa T, Sugiyama H, Shimada Y, Nojima Y, Shio N. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol*. 2014;63:528–536.
 29. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, Pitt B; EMPHASIS-HF Investigators. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *J Am Coll Cardiol*. 2013;62:1585–1593.
 30. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, Solomon SD; RALES Investigators. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol*. 2012;60:2082–2089.
 31. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd N, Bakris G, Pitt B, Zannad F. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail*. 2014;7:51–58.

SUPPLEMENTAL MATERIAL

Table S1. Cox regression: Association MRA and all-cause mortality 0-3 years, complete cases**n = 24 871**

	HR	CI low	CI high	P-interaction
MRA unadjusted	0.83	0.78	0.88	
MRA adjusted	1.01	0.95	1.07	
MRA and eGFR \geq 60 (ml/min/1.73m ²)	0.99	0.90	1.09	
MRA and eGFR<60	1.02	0.94	1.11	0.63
MRA and LVEF \geq 50%	1.35	1.13	1.62	
MRA and LVEF 40-49%	0.92	0.77	1.09	
MRA and LVEF <40%	0.90	0.82	0.99	0.001

eGFR= estimated glomerular filtration rate, LVEF= left ventricular ejection fraction, MRA =mineralocorticoid receptor antagonist

Table S2. Cox regression: Association MRA and all-cause mortality 0-3 years, excluding patients with only prior HF and no acute HF during hospitalization.

	HR	CI low	CI high	P-interaction
MRA unadjusted	0.86	0.8	0.93	
MRA adjusted	0.97	0.9	1.04	
MRA and eGFR \geq 60 (ml/min/1.73m ²)	0.96	0.86	1.07	
MRA and eGFR<60	0.97	0.88	1.08	0.83
MRA and LVEF \geq 50%	1.27	1.02	1.57	
MRA and LVEF 40-49%	0.9	0.74	1.1	
MRA and LVEF <40%	0.8	0.72	0.89	0.0006

eGFR= estimated glomerular filtration rate, LVEF= left ventricular ejection fraction, MRA =mineralocorticoid receptor antagonist