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RESEARCH ARTICLE

Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry

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Aim

Mineralocorticoid receptor antagonists (MRAs) improve outcomes in heart failure with reduced ejection fraction (HFrEF), but are underutilized. Hyperkalaemia may be one reason, but the underlying reasons for underuse are unknown. The aim of this study was to investigate the independent predictors of MRA underuse in a large and unselected HFrEF cohort.

Methods and results

We included patients with HFrEF (ejection fraction <40%), New York Heart Association (NYHA) class II–IV and heart failure (HF) duration ≥6 months from the Swedish HF Registry. Logistic regression analysis identified independent associations between 39 demographic, clinical, co-treatment, and socioeconomic predictors and MRA non-use. Of 11 215 patients, 27% were women; mean age was 75 ± 11 years; only 4443 (40%) patients received MRA. Selected characteristics independently associated with MRA non-use were in descending order of magnitude: lower creatinine clearance (<60 mL/min), no need for diuretics, no cardiac resynchronization therapy/implantable cardioverter-defibrillator, higher blood pressure, no digoxin use, higher ejection fraction, outpatient setting, older age, lower income, ischaemic heart disease, male sex, follow-up in primary vs. specialty care, lower NYHA class, and absence of hypertension diagnosis. Plasma potassium and N-terminal pro B-type natriuretic peptide levels were not associated with MRA non-use.

Conclusion

Mineralocorticoid receptor antagonists remain underused in HFrEF. Their use does not decrease with elevated potassium but does with impaired renal function, even in the creatinine clearance 30–59.9 mL/min range where MRAs are not contraindicated. MRA underuse may be further related to non-specialist care, milder HF and no use of other HF therapy.

Keywords Mineralocorticoid receptor antagonists • Guidelines • Heart failure with reduced ejection fraction • Hyperkalaemia

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Introduction

Mineralocorticoid receptor antagonists (MRAs; spironolactone and eplerenone) reduce mortality and morbidity in patients with New York Heart Association (NYHA) class II–IV heart failure with reduced ejection fraction (HFrEF)[1,2] and received class IA recommendation in guidelines.[3,4] However, MRAs are underused in the USA[5] and Europe.[6,7] Hyperkalaemia and worsening renal function have been addressed as potential explanations for this phenomenon,[8] although importantly their occurrence does not reduce the benefit of MRAs.[9,10] Furthermore, the independent underlying reasons for MRA underuse in the real world are unknown.

The aim was to measure MRA non-use/use in a large unselected cohort of HFrEF patients, and to investigate the independent associations with MRA non-use.

Methods

Study protocol and setting

The Swedish Heart Failure Registry (SwedeHF; www.SwedeHF.se) has been previously described.[11] The only inclusion criterion is clinician-judged heart failure (HF). Approximately 80 variables are recorded at discharge from hospital or after an outpatient clinic visit on a web-based case report form and entered into a database managed by the Uppsala Clinical Research Center, Uppsala, Sweden (www.UCR.UU.se). The protocol, case report form and annual reports are available at www.SwedeHF.se.

The Swedish Board of Health and Welfare (www.socialstyrelsen.se) administers the Patient Registry that provided additional baseline co-morbidities, defined according to ICD-10 codes. ICD-10 coding in Sweden has been validated, with a positive predictive value ranging between 85% and 95% for most diagnoses.[12] Statistics Sweden (www.scb.se) provided socioeconomic characteristics. Recording of ICD codes and socioeconomic data occurs with a lag time and the procedures around linking to SwedeHF take time. Therefore, this study included SwedeHF registrations between 11 May 2000 (start of SwedeHF) and 31 December 2012, ensuring that all linked ICD code and socioeconomic data up to this date were available.

All Swedish citizens have unique personal identification numbers that allow linking of disease-specific health registries and governmental health and statistical registries.

Establishment of the HF registry and this analysis with linking of the above registries were approved by a multisite ethics committee. Individual patient consent was not required, but patients were informed of entry into national registries and allowed to opt out.

In SwedeHF, ejection fraction (EF) is categorized as <30%, 30–39%, 40–49%, and ≥ 50%. We included <30% and 30–39%. MRAs are indicated with symptoms, so NYHA class II–IV patients were included. MRAs were proven effective in NYHA class III–IV HFrEF in RALES in 1999[2] and in NYHA class II HFrEF in EMPHASIS-HF in 2011.[1] Thus, a consistency analysis including NYHA class III–IV from 2000 (start of the registry) and NYHA class II–IV from 2012 (when EMPHASIS-HF had been published and had time to penetrate the HF community) was performed. Patients with creatinine clearance <30 mL/min or K > 5.0 mEq/L were excluded from trials and do not have MRA indication. In the real world, many patients fluctuate around these cut-offs. If patients are already treated (which many may have been prior to the index date in this study), then worsening renal function or hyperkalaemia unless very severe is not a reason to discontinue MRAs.[3] Therefore, the main analysis included the few patients with creatinine clearance <30 mL/min or K > 5.0 mEq/L, but a consistency analysis was also performed excluding these patients. MRAs are third-line therapy in HFrEF, so patients with HF duration ≥6 months were included to ensure adequate time for initiation of MRA therapy. Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) use was considered as a yes/no variable, but in order to evaluate the possibility that sub-target dosing of ACE-I/ARB may be a reason for MRA non-use, an additional consistency analysis was performed where ACE-I/ARB use was classified as target dose of ACE-I or ARB or use of both ACE-I and ARB vs. non-use or non-target dose of ACE-I or ARB. Registrations with missing data for MRA use, EF, NYHA class and HF duration were excluded.

Statistical analysis

Baseline characteristics

Baseline characteristics of patients receiving vs. not receiving MRA were compared by *t*-test or Wilcoxon–Mann–Whitney to test continuous variables, and by chi-squared to test categorical variables. In a registry setting, patients may have missing baseline data. Excluding these patients from multivariable analyses would introduce bias due to the fact that baseline data are not completely missing at random. Therefore, missing data were managed by multiple imputation using chained equations method ($n = 10$). All analyses, except for descriptive statistics, were performed on imputed data.

Predictors of mineralocorticoid receptor antagonist non-use

In order to identify the independent predictors of MRA non-use, multivariable logistic regression models were performed using MRA non-use as dependent variable. Because predictors of MRA non-use are presently unknown and since the sample size was sufficiently large, we did not perform any stepwise variable selection procedure for choosing the variables to include in multivariable models. Instead, we included all variables from SwedeHF, the Patient Registry, and Statistics Sweden, which were clinically relevant and deemed potentially relevant in directly or indirectly affecting the decision to use MRAs. These added up to 39, marked with an asterisk in *Table 1*. Additional variables were either related and covarying (e.g. creatinine and creatinine clearance, weight and body mass index, etc.) or not deemed relevant, and therefore not included in the model.

Statistical analyses were performed by Stata 14.2 (Stata Corp LLC, College Station, TX, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Between 11 May 2000 (start of SwedeHF) and 31 December 2012, 80 772 registrations were recorded from 51 060 unique patients. Of these, 11 215 were patients with HFrEF, NYHA class II–IV and HF duration ≥6 months who reported no missing data for MRA use; 4443 (40%) patients were receiving MRA and 6772 (60%) were not (*Figure 1*).

Baseline characteristics

In the overall population, the mean age was 75 ± 11 years, 27% were woman. There were numerous differences between

Table 1 Baseline characteristics

Variables	MRA No ($n = 6772$, 60%)	MRA Yes ($n = 4443$, 40%)	*P*-value
Demographics			
Gender[a], *n* (%)			0.085
Male	4932 (72.8)	3301 (74.3)	
Female	1840 (27.2)	1142 (25.7)	
Age[a], years, mean (SD)	74.4 (11.1)	71.9 (11.2)	<0.001
Registration year[a], *n* (%)			<0.001
2000–2008	3330 (49.2)	2385 (53.7)	
2009–2012	3442 (50.8)	2058 (46.3)	
Specialty[a], *n* (%)			0.025
Internal Medicine or Geriatrics	2892 (44.3)	1818 (42.2)	
Cardiology	3631 (55.7)	2494 (57.8)	
Caregiver[a], *n* (%)			0.005
Inpatient	3141 (46.4)	2181 (49.1)	
Outpatient	3631 (53.6)	2262 (50.9)	
Follow-up referral specialty[a], *n* (%)			<0.001
Cardiology or Internal Medicine	4098 (65.6)	2978 (71.5)	
Primary or other care	2151 (34.4)	1189 (28.5)	
Follow-up referral to outpatient HF nurse clinic[a], *n* (%)	2597 (41.5)	1780 (42.9)	0.17
Clinical variables			
NYHA class[a], *n* (%)			<0.001
II	2958 (43.7)	1731 (39.0)	
III	3308 (48.8)	2392 (53.8)	
IV	506 (7.5)	320 (7.2)	
Left ventricular ejection fraction[a], *n* (%)			<0.001
30–39%	3451 (51.0)	1781 (40.1)	
<30%	3321 (49.0)	2662 (59.9)	
Body mass index[a], kg/m^2, mean (SD)	26.4 (5.0)	27.0 (5.5)	<0.001
Systolic blood pressure, mmHg, mean (SD)	124.2 (20.5)	119.0 (19.5)	<0.001
Diastolic blood pressure, mmHg, mean (SD)	72.3 (11.7)	70.7 (11.5)	<0.001
Mean arterial pressure[a], mmHg, mean (SD)	89.6 (12.9)	86.8 (12.5)	<0.001
Heart rate[a], b.p.m., mean (SD)	73.2 (14.9)	72.5 (14.0)	0.011
Laboratory values			
Creatinine clearance, mL/min, mean (SD)	58.3 (30.6)	65.5 (31.7)	<0.001
Creatinine clearance[a], *n* (%)			<0.001
<30 mL/min	991 (15.7)	353 (8.4)	
30–59.9 mL/min	2798 (44.3)	1807 (42.7)	
≥60 mL/min	2526 (40.0)	2070 (48.9)	
Potassium, mEq/L, mean (SD)	4.2 (0.5)	4.2 (0.5)	0.89
Potassium[a], *n* (%)			0.649
<3.5 mEq/L	167 (4.1)	113 (4.5)	
3.5–5 mEq/L	3756 (91.8)	2283 (91.2)	
>5.0 mEq/L	166 (4.1)	106 (4.3)	
Haemoglobin, g/L, mean (SD)	132.0 (17.1)	133.6 (16.9)	<0.001
NT-proBNP[a], pg/mL, median (IQR)	3197.0 (1318.5–7614.0)	3039.5 (1320.0–7200.0)	0.41
Co-morbidities, *n* (%)			
Smoking[a]			0.72
Never	2121 (39.2)	1400 (38.6)	
Previous	2603 (48.1)	1774 (48.9)	
Current	691 (12.8)	452 (12.5)	
Hypertension[a]	4039 (59.6)	2614 (58.8)	0.39
Diabetes mellitus[a]	2104 (31.1)	1533 (34.5)	<0.001
Ischaemic heart disease[a]	4527 (68.9)	2830 (65.3)	<0.001
Coronary revascularization[a]	2684 (39.6)	1753 (39.5)	0.85
Peripheral artery disease[a]	874 (12.9)	519 (11.7)	0.054

Table 1 Continued

Variables	MRA No ($n = 6772$, 60%)	MRA Yes ($n = 4443$, 40%)	*P*-value
Stroke/transient ischaemic attack[a]	1277 (18.9)	767 (17.3)	0.032
Atrial fibrillation[a]	3871 (57.2)	2648 (59.6)	0.010
Anaemia[a,b]	2526 (37.3)	1530 (34.4)	0.002
Valvular heart disease[a]	1793 (27.1)	1214 (27.9)	0.34
Lung disease[a]	1878 (27.7)	1268 (28.5)	0.35
Concomitant medications, *n* (%)			
ACE-I or ARB[a]	5913 (87.5)	4016 (90.6)	<0.001
ACE-I or ARB[c]			<0.001
None or < target dose	4361 (64.7)	2333 (52.7)	
≥ target dose or ACE-I + ARB	2378 (35.3)	2096 (47.3)	
Digoxin[a]	1092 (16.1)	1063 (24.0)	<0.001
Diuretic[a]	5599 (82.8)	4012 (90.5)	<0.001
Nitrate[a]	1463 (21.7)	854 (19.3)	0.002
Platelet inhibitor[a]	3626 (53.7)	2153 (48.6)	<0.001
Oral anticoagulant[a]	2685 (39.8)	2121 (47.9)	<0.001
Statin[a]	3442 (51.0)	2305 (52.0)	0.29
Beta-blocker[a]	6030 (89.1)	4041 (91.1)	<0.001
Heart failure devices[a]			<0.001
None	6113 (91.0)	3736 (84.6)	
CRT-P	199 (3.0)	209 (4.7)	
CRT-D	170 (2.5)	220 (5.0)	
ICD	235 (3.5)	250 (5.7)	
Socioeconomic variables			
Family type[a], *n* (%)			0.86
Living alone	3269 (48.4)	2135 (48.2)	
Married/cohabitating	3492 (51.6)	2296 (51.8)	
Education[a], *n* (%)			0.012
Compulsory school	3329 (49.7)	2062 (46.9)	
Secondary school	2481 (37.1)	1700 (38.7)	
University	882 (13.2)	630 (14.3)	
Income[a], below median, *n* (%)	3487 (51.7)	2092 (47.3)	<0.001
Number of children[a], mean (SD)	2.0 (1.4)	2.0 (1.4)	0.093

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

[a]Variables included in the multivariable logistic regression model.

[b]Anaemia was defined according to haemoglobin levels (<120 g/L in women and < 130 g/L in men).

[c]Included in the consistency analysis. Registration year was included as a continuous variable in the multivariable models.

untreated vs. treated patients, including higher age, more care in and follow-up referral to internal medicine, geriatrics, or primary care vs. cardiology. Notably, potassium and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels were similar in those using and not using MRA. Untreated patients also received less ACE-I or ARB, digoxin, diuretics, oral anticoagulants, beta-blockers and HF devices, and if treated with ACE-I and/or ARB, also lower doses (*Table 1*).

Independent associations with mineralocorticoid receptor antagonist non-use

The differences in *Table 1* are unadjusted and may represent risk markers rather than risk factors for MRA non-use. Adjusted odds ratios (ORs) for MRA non-use after multivariable logistic regression are shown in descending order of magnitude in *Figure 2*, and included e.g. lower creatinine clearance (<30 mL/min but also 30–59.9 mL/min was associated with non-use), no use of diuretics, no cardiac resynchronization therapy (CRT)/implantable cardioverter-defibrillator (ICD), higher blood pressure, higher EF, outpatient setting, older age, lower income, ischaemic heart disease, male sex, lower NYHA class, follow-up in primary care vs. cardiology/internal medicine, absence of hypertension diagnosis and later year of registration. Plasma potassium and NT-proBNP were not associated with MRA non-use. Non-use of digoxin remained associated with MRA non-use, whereas non-use of beta-blockers only approximated a statistically significance, and no association was reported between ACE-I/ARB use and other treatment use (nitrates, platelet inhibitors and statins) and MRA

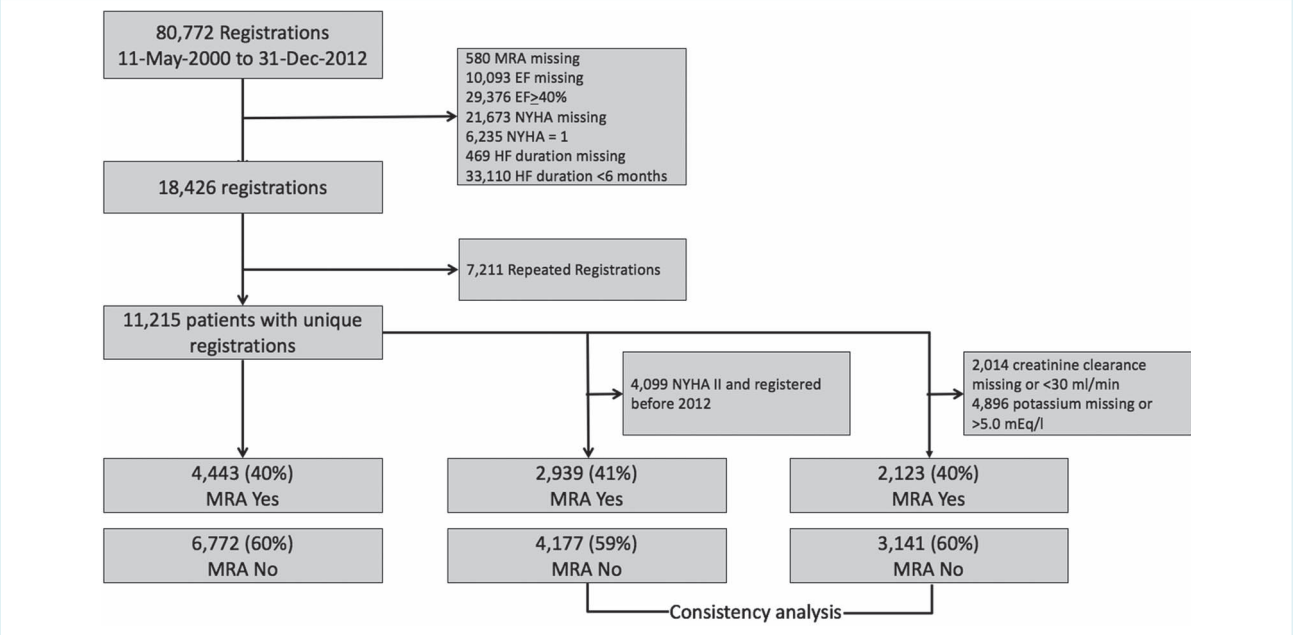

Figure 1 Flow chart of patient selection. EF, ejection fraction; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

non-use. However, when doses of ACE-I/ARB were considered and ACE-I/ARB use was categorized as at (or above) target dose or use of both ACE-I and ARB vs. no use or sub-target dose (target doses for ACE-I and ARB are reported in the supplementary material online, *Table S1*), sub-target doses or no use was significantly associated with MRA non-use (OR 1.61; 95% CI 1.48–1.75) (*Figure 2*).

Other clinical variables/co-morbidities not associated with MRA non-use were body mass index, smoking, history of stroke/transient ischaemic attack, diabetes, lung disease, valvular disease, heart rate, atrial fibrillation, peripheral artery disease, previous coronary revascularization, and anaemia. Demographic/organizational variables not associated with MRA non-use were number of children, education level, living alone vs. being married/cohabitating, being registered in cardiology vs. internal medicine/geriatrics departments, and having a planned follow-up in a HF nurse-led clinic.

Consistency analysis

In the consistency analysis including patients in NYHA class II enrolled from 2012 only plus all the patients in NYHA class III–IV, 2939 (41%) received MRAs and 4177 (59%) did not. All the findings observed in the main analysis were confirmed except for NYHA class and hypertension that were not significantly associated with MRA non-use. We also repeated the analyses excluding patients with creatinine clearance <30 mL/min or missing and K > 5.0 mEq/L or missing. In this cohort, 2123 patients (40%) received MRAs and 3141 (60%) did not. As compared with the main analysis, additional predictors of MRA non-use were heart rate ≥ 70 vs. <70 b.p.m., being registered in cardiology vs. internal medicine/geriatrics departments and higher number of children, whereas ischaemic heart disease, gender, age and year of registration were not associated with MRA non-use (supplementary material online, *Figure S1*).

Discussion

In the large and unselected nationwide SwedeHF, we observed that only 40% of patients with HFrEF, NYHA class ≥II and HF duration ≥6 months received MRA and that low creatinine clearance was a dominant risk factor for MRA non-use, even in the creatinine clearance 30–59.9 mL/min range where MRAs are not contraindicated. Furthermore, MRA use did not decrease with elevated potassium levels. MRA underuse might be further linked to non-specialist care, no use or sub-optimal dosing of ACE-I/ARB, milder HF, and perceived rather than actual risk of hyperkalaemia.

Underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction patients

The MRA underuse observed in the present study confirms previous analyses (*Table 2*).[5,7,13–16] In the US Get With The Guidelines-HF quality improvement registry, only 32% of eligible patients received MRAs between 2005 and 2007, but a trend towards an increase in prescription over time was observed.[5] Similarly, an analysis from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) reported 36% of the eligible population treated

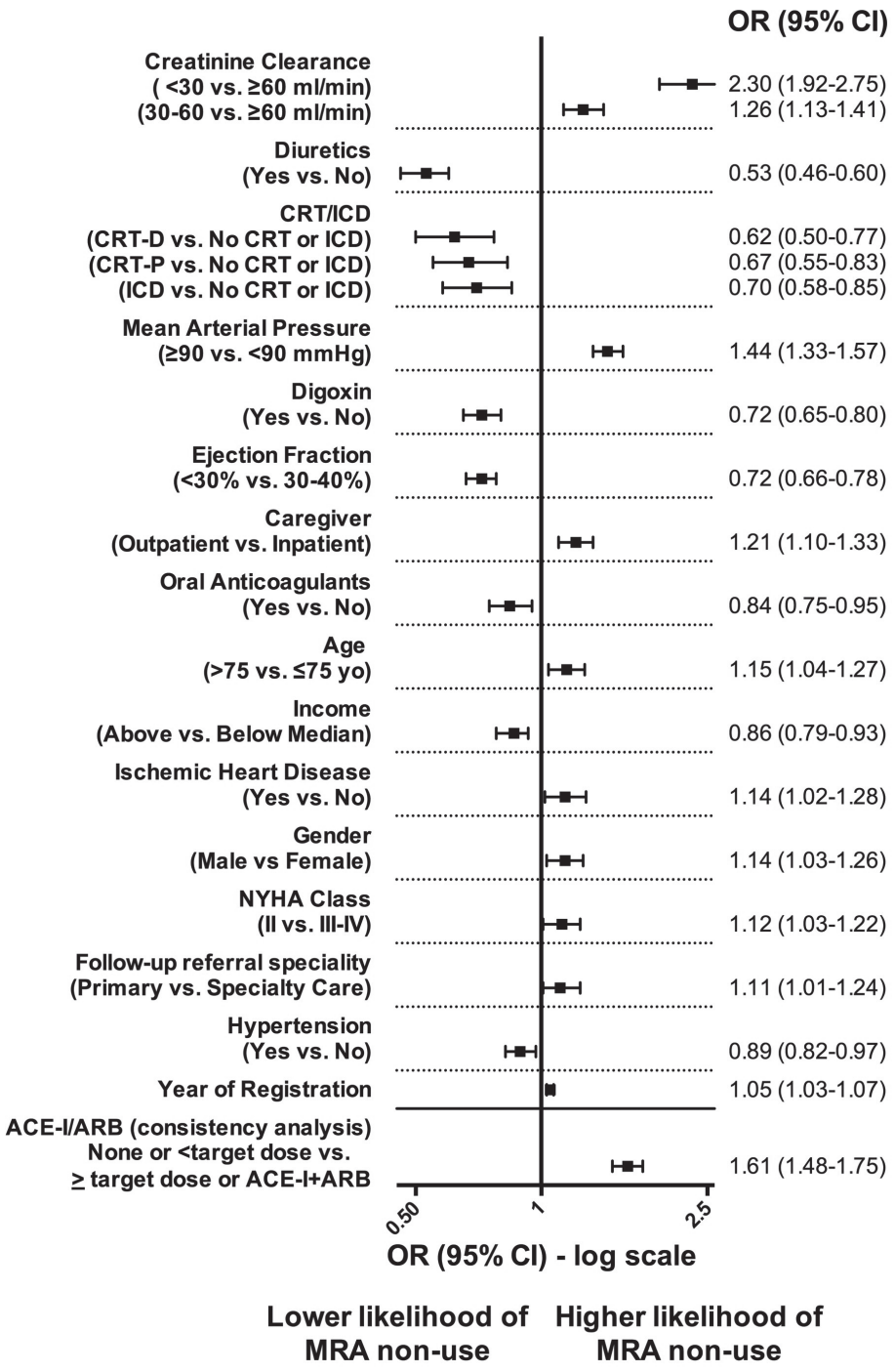

Figure 2 Independent predictors of mineralocorticoid receptor antagonist (MRA) non-use. CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; OR, odds ratio.

by MRA.[13] In Europe, the EuroHeart Failure Survey II showed that 47.5% of patients discharged after a hospital admission for new-onset or decompensated HF received MRAs,[14] whereas in the European Society of Cardiology (ESC) HF pilot survey the rates were ~50% in inpatients at discharge and 44% in outpatients.[15] More recently, in the BIOSTAT-CHF programme enrolling patients with new-onset or worsening of HF who had not been previously treated with evidence-based therapies, 56% and 63% of eligible patients received MRA before and after HF treatment optimization, respectively,[7] whereas in the ESC HF Long-Term Registry

Table 2 Summary of current evidence on mineralocorticoid receptor antagonist underuse in heart failure with reduced ejection fraction

Study	MRA use
GWTG-HF[5]	32% of the eligible population.
IMPROVE HF[13]	36% of the eligible population.
EuroHeart Failure Survey II[14]	47.5% of patients discharged after a hospital admission for HF.
ESC-HF Pilot Survey[15]	~50% in inpatients at discharge and 44% in outpatients.
BIOSTAT-CHF[7]	56% of eligible patients before and 63% after HF treatment optimization.
ESC-HF-LT[16]	53.9% of patients hospitalized for acute HF received MRA at discharge and 56.5% at 1 year from hospitalization.
SwedeHF (current study)	40% of the eligible population.

HF, heart failure; MRA, mineralocorticoid receptor antagonist.

(ESC-HF-LT) 53.9% of patients hospitalized for acute HF received MRA at discharge and 56.5% at 1 year from hospitalization.[16,17] Even when not considering MRAs indicated in NYHA class II until 2012, only 41% received MRAs in the present study. Similarly, when patients with K > 5.0 mEq/L and creatinine clearance <30 mL/min were excluded, again only 40% received MRAs. A previous analysis of SwedeHF has shown high utilization of renin–angiotensin system antagonists and beta-blockers that were prescribed in more than 90% of the population, but modest use of MRA that even decreased over time, from 53% in 2003 to 42% in 2012.[6] However, a major limitation of previous analyses is absence of explanatory factors. Therefore, a common assumption has simply addressed kidney disease and hyperkalaemia as major reasons for non-use.[9]

Patients characteristics independently associated with mineralocorticoid receptor antagonist non-use

Notably, in the present study, plasma potassium levels at baseline were not associated with MRA use decisions at baseline. The cause and effect relationship is of course difficult to establish, but hypokalaemia is likely a reason for use, and hyperkalaemia both a reason for non-use and a consequence of use. However, chronic kidney disease was a strong predictor of MRA non-use, with both creatinine clearance <30 and 30–59.9 mL/min associated with underuse. Creatinine clearance <30 mL/min associated with MRA non-use is expected since MRAs are contraindicated in severe renal disease. However, MRAs are not contraindicated and have been shown to be effective in reducing the risk of all-cause death, cardiovascular death and HF hospitalization in patients with estimated glomerular filtration rate 30–59.9 mL/min/1.73 m^2,[18] thus MRA underuse reported by our analysis in this subgroup is not justified. Similarly, we reported underuse in patients aged >75 years but MRAs have previously been shown to be equally effective also in the elderly.[18] These findings may suggest that a *perceived* risk of worsening renal function may have a role in MRA non-use. Relatedly, diuretic use was the strongest independent predictor of MRA use. One potential explanation for this observation could be that MRAs and loop diuretics were used to balance potassium levels and also in more severe HF. Hypertension was associated with use, whereas high blood pressure was associated with non-use, suggesting but not proving that MRAs have been used and/or tolerated in patients with hypertension, but also have been effective in lowering blood pressure, resulting in lower blood pressure in treated patients. When ACE-I/ARB use was analysed as a yes/no variable, it was not associated with MRA use. However, no use or sub-target dosing of ACE-I/ARB (a larger group than simply non-use) was significantly associated with MRA non-use, which could be explained by similar factors influencing both the choice of MRA non-use and of prescribing no or underdosed ACE-I/ARB (i.e. fear for worsening renal function). Furthermore, non-use, or importantly, failure to reach target doses of ACE-I/ARB (whether fully attempted or not), appears to lead to non-use of MRA. Finally, no referral to cardiology specialists and no use of other HF treatments, as well as lower income were together important associations with MRA non-use, suggesting that organizational, logistical and access to care issues may be relevant, similarly as for other HF interventions.[19,20] Indeed, a willingness and ability to undergo follow-up and monitoring is a requirement for MRAs (and other HF therapy) and although we cannot assess this willingness *per se*, many of the variables assessed may be indirect markers of low willingness or ability to undergo follow-up.

Limitations

Because of the cross-sectional nature of this study, for many associations described, cause and effect relationships cannot be established. We cannot rule out potential effects of unmeasured confounders affecting MRA non-use. We included patients enrolled in the SwedeHF between 2000 and 2012, thus, we cannot exclude any potential improvement in MRA prescriptions following the EMPHASIS-HF trial publication in 2011[1] and the consequent implementation of guidelines. We did not have access to type of MRA, but overall in Sweden, >98% of MRAs prescribed and dispensed are spironolactone.[21] Generalizability of our findings to other countries depends on similarities in population characteristics, health care and HF management. Finally, longitudinal data and time relationship between clinical variables, particularly previous measures of serum potassium levels that might have influenced decisions on whether or not to start an MRA, and medication use represent a major limitation of this and other registry studies.

Conclusions

There are still signals of MRA underuse in HFrEF. Reduced renal function, even in the 30–59.9 mL/min range, was associated with MRA underuse, but elevated potassium levels were not. Thus, we emphasize that the ESC HF guidelines recommend that while estimated glomerular filtration rate < 30 mL/min/1.73 m^2 or K > 5.0 mEq/L are contraindications to MRA initiation, for patients already treated with MRAs, renal function and K need to be considerably worse in order to consider dose reduction or discontinuation of MRAs.[3]

Supplementary Information

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

Table S1. Specific angiotensin-converting enzyme inhibitor and angiotensin receptor blocker agents and doses.

Figure S1. Independent predictors of mineralocorticoid receptor antagonist non-use at consistency analyses.

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References

1. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
2. 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.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 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 J Heart Fail* 2016;**18**:891–975.
4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;**136**:e137–e161.
5. Albert NM, Yancy CW, Liang L, Zhao X, Hernandez AF, Peterson ED, Cannon CP, Fonarow GC. Use of aldosterone antagonists in heart failure. *JAMA* 2009;**302**:1658–1665.
6. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003–2012. *Eur J Heart Fail* 2016;**18**:503–511.
7. Ferreira JP, Rossignol P, Machu JL, Sharma A, Girerd N, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Lang CC, Ter Maaten J, Metra M, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Voors A, Zannad F. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. *Eur J Heart Fail* 2017;**19**:1284–1293.
8. Lachaine J, Beauchemin C, Ramos E. Use, tolerability and compliance of spironolactone in the treatment of heart failure. *BMC Clin Pharmacol* 2011;**11**:4.
9. 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.
10. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD; Randomized Aldactone Evaluation Study (RALES) Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail* 2014;**7**:573–539.
11. Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail* 2010;**12**:25–31.
12. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
13. Fonarow GC, Yancy CW, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. *Circ Heart Fail* 2008;**1**:98–106.
14. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
15. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L; Heart Failure Association of ESC (HFA). EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2010;**12**:1076–1084.
16. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlstrom U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–625.
17. Ferreira JP, Mentz RJ, Pizard A, Pitt B, Zannad F. Tailoring mineralocorticoid receptor antagonist therapy in heart failure patients: are we

moving towards a personalized approach? *Eur J Heart Fail* 2017;**19**: 974–986.
18. 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.
19. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson A, Jernberg T, Dahlstrom U. Association between enrolment in a heart failure quality registry and subsequent mortality – a nationwide cohort study. *Eur J Heart Fail* 2017;**19**:1107–1116.
20. Lund LH, Braunschweig F, Benson L, Stahlberg M, Dahlstrom U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2017;**19**: 1270–1279.
21. Lund LH, Svennblad B, Melhus H, Hallberg P, Dahlstrom U, Edner M. Association of spironolactone use with all-cause mortality in heart failure: a propensity scored cohort study. *Circ Heart Fail* 2013;**6**:174–183.