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

Gianluigi Savarese, MD[1]; Juan-Jesus Carrero, Pharm, PhD[2]; Bertram Pitt, MD, PhD[3]; Stefan D. Anker, MD, PhD[4,5]; Giuseppe MC. Rosano, MD, PhD[6], Ulf Dahlström, MD, PhD[7]; Lars H Lund, MD, PhD[1,8]

[1]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[3]Department of Medicine, University of Michigan, Ann Arbor, USA
[4]Division of Cardiology and Metabolism; Department of Cardiology (CVK; and Berlin-Brandenburg Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany.
[5]Department of Cardiology and Pneumology, University Medicine Göttingen (UMG), Göttingen, Germany
[6]Cardiovascular and Cell Sciences Research Institute, St George's University, London, UK; IRCCS San Raffaele Pisana, Rome, Italy
[7]*Department* of Cardiology and Department of Medical and Health Sciences, Linkoping University, Linkoping, Sweden.
[8]Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden

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Corresponding Author:
Gianluigi Savarese, MD
Department of Medicine, Cardiology Unit
Karolinska Institutet
S1:02, 171 76
Stockholm, Sweden
mail. gianluigi.savarese@ki.se

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ABSTRACT

Background. Mineralocorticoid receptor antagonists (MRAs) improve outcomes in heart failure with reduced ejection fraction (HFrEF), but are underutilized. Hyperkalemia may be one reason, but the underlying reasons for underuse are unknown.

Aims. To investigate the independent predictors of MRA underuse in a large and unselected HFrEF cohort.

Methods. We included patients with HFrEF (EF<40%), New York Heart Association (NYHA) class II-IV and 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.

Results. Of 11,215 patients, 27% were women; mean age was 75±11 years; only 4,443 (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 cardiac defibrillator, higher blood pressure, no digoxin use, higher EF, out-patient setting, higher age, lower income, ischemic heart disease, male sex, follow-up in primary vs. specialty care, lower NYHA class, and absence of hypertension diagnosis. Plasma potassium and NT-proBNP levels were not associated with MRA non-use.

Conclusion. MRAs 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. The underuse may be further linked to non-specialist care, milder HF and non-use of other HF therapy.

Keywords: mineralocorticoid receptor antagonists; guidelines; implementation; utilization; heart failure with reduced ejection fraction; hyperkalemia.

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 recommendations in guidelines [3, 4].

However, MRAs are underused in the US [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 HF. Approximately 80 variables are recorded at discharge from hospital or after an out-patient 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 comorbidities, 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 up to 31 Dec 2012, ensuring that all linked ICD code and socieconomic data up to this date was available.

All Swedish citizens have unique personal identification numbers that allows 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, EF is categorized as <30%, 30-39%, 40-49%, and ≥50%. We included <30% and 30-39%. MRAs are indicated with symptoms so we included NYHA II-IV. MRAs were proven effective in NYHA III-IV HFrEF in RALES in 1999 [2] and in NYHA II HFrEF in EMPHASIS-HF in 2011 [1]. Thus, we performed a consistency analysis including NYHA III-IV from 2000 (start of the registry) and NYHA II-IV from 2012 (when EMPHASIS-HF had been published and had time to penetrate the HF community). Patients with creatinine

clearance <30 ml/min or K >5.0 mmol/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 hyperkalemia unless very severe is not a reason to discontinue MRA use [3]. Therefore, the main analysis included the few patients with creatinine clearance <30 ml/min or K >5.0 mmol/L (n and % listed in Table 1), but we also performed a consistency analysis excluding these patients. MRAs are third-line therapy in HFrEF so we included patients with HF duration ≥6 months to ensure adequate time for initiation of MRA therapy. We considered angiotensin converting enzyme inhibitor / angiotensin receptor blocker (ACE-I / ARB) use as a yes/no variable, but to consider the possibility that sub-target dosing of ACE-I / ARB may be a reason for MRA non-use, we performed an additional consistency analysis 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 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 MRA 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 step-wise 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 * in Table 1. Additional variables were either related and covarying (e.g. creatinine and creatinine clearance, weight and BMI, etc.) or not deemed relevant, and therefore not included in the model.

Statistical analyses were performed by Stata 14.2 (StataCorp LLC, College Station, Texas, USA). A p-value <0.05 was considered statistically significant.

RESULTS

Patients (Figure 1)

Between May 11th May 2000 (start of SwedeHF) and December 31th 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; 4,443 (40%) patients were receiving MRA and 6,772 (60%) were not (**Figure 1**).

Baseline Characteristics (Table 1)

In the overall population, the mean age was 75±11 years, 27% were woman. There were numerous differences between 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 anticoagulant, beta-blockers and HF devices, and if treated with ACE-I and/or ARB, also lower doses.

Independent associations with MRA non-use

The differences in **Table 1** are unadjusted and may represent risk markers rather than risk factors for 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 cardiac defibrillator (ICD), higher blood pressure, higher EF, out-patient setting, higher age, lower income, ischemic 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 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 reported in Supplementary Table 1), sub-target doses or no use was significantly associated with MRA non-use (OR: 1.61; 95% CI: 1.48 – 1.75) (bottom row, Figure 1). Other clinical variables/comorbidities not associated with MRA non-use were BMI, smoking, history of stroke/transient ischemic attack, diabetes, lung disease, valvular disease, heart rate, atrial fibrillation, peripheral artery disease, previous coronary revascularization and anemia. Demographic/organizational variable 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 (Supplementary Figure 1)

In the consistency analysis including patients with NYHA II enrolled from 2012 only plus all the patients in NYHA III-IV, 2,939 (41%) received MRAs and 4,177 (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 mmol/L or missing. In this cohort, 2,123 patients (40%) received MRAs and 3,141 (60%) did not. As compared with the main analysis, additional predictors of MRA non-use were heart rate $\geq$70 vs. <70 bpm, being registered in cardiology vs internal medicine/geriatrics department and higher number of children, whereas ischemic heart disease, gender, age and year of registration were not associated with MRA non-use.

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 non-use, even creatinine clearance = 30-59.9 ml/min, where MRAs are not contraindicated. Furthermore, their use does not decrease with elevated potassium levels. The underuse may be further linked to non-specialist care, no use or suboptimal dosing of ACE-I / ARB, milder HF, and perceived rather than actual risk of hyperkalemia.

Underuse of MRA in HFrEF patients (Table 2)

The underuse in the present study confirms previous analyses. In the US Get With The Guidelines-HF (GWTG-HF) quality improvement registry, only 32% of eligible patients received MRAs between 2005 and 2007, but a trend toward an increase in prescription over the 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 by MRA [13]. In Europe, the EuroHeart Failure Survey II showed that 47.5% of patients discharged after a hospital admission for new onset of or decompensation of 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 program enrolling patients with new-onset of 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, whereas in the ESC HF Long-Term Registry (ESC-HF-LT) 53.9% of patients hospitalized for acute HF received MRA at the discharge and 56.5% at 1 year from the hospitalization [16, 17]. Even when not considering MRAs indicated in NYHA II until in 2012, only 41% received MRAs in the present study. Similarly, when patients with K>5.0 mmol/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 been kidney disease and hyperkalemia as major reasons for non-use [9].

Patients characteristics independently associated with MRA 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 hypokalemia is likely a reason for use, and hyperkalemia both a reason for non-use and a consequence of use. However, chronic kidney disease was a strong predictor of 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, they are not contraindicated and have been shown to be effective in reducing the risk of all-cause death, cardiovascular death and HF hospitalization in 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 age>75 years but MRAs have been previously shown to be equally effective also in 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 higher 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 been effective at lowering blood pressure, resulting in lower blood pressure in treated patients. When ACE-I/ARB was analyzed as yes/no, they were not associated with MRA use. However, no use or sub-target doses 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 important, 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 MRAs underuse in HFrEF. Reduced renal function, even in the 30-59.9 ml/min range, was associated with 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/1.73m^2 or K >5.0 mmol/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 of discontinuation of MRAs [3].

CONFLICTS OF INTEREST

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Table 1. Baseline Characteristics

Variables	MRA No (n=6,772; 60%)	MRA Yes (n=4,443; 40%)	p-value
Demographics			
Gender*			
Male	4932 (72.8%)	3301 (74.3%)	
Female	1840 (27.2%)	1142 (25.7%)	0.085
Age, mean (SD), years*	74.4 (11.1)	71.9 (11.2)	<0.001
Registration year*			
2000-2008	3,330 (49%)	2,385 (54%)	
2009-2012	3,442 (51%)	2,058 (46%)	<0.001
Specialty*			
Internal medicine or Geriatrics	2892 (44.3%)	1818 (42.2%)	
Cardiology	3631 (55.7%)	2494 (57.8%)	0.025
Caregiver*			
Inpatient	3,141 (46%)	2,181 (49%)	
Outpatient	3,631 (54%)	2,262 (51%)	0.005
Follow-up referral specialty*			
Cardiology or Internal medicine	4098 (65.6%)	2978 (71.5%)	
Primary or Other care	2151 (34.4%)	1189 (28.5%)	<0.001
Follow-up referral to outpatient HF nurse clinic*	2597 (41.5%)	1780 (42.9%)	0.17
Clinical			
New York heart association*			
II	2958 (43.7%)	1731 (39.0%)	
III	3308 (48.8%)	2392 (53.8%)	
IV	506 (7.5%)	320 (7.2%)	<0.001
Left ventricular ejection fraction*			
30-39%	3,451 (51%)	1,781 (40%)	
<30%	3,321 (49%)	2,662 (60%)	<0.001
Body mass index, mean (SD)*	26.4 (5.0)	27.0 (5.5)	<0.001

Systolic blood pressure, mean (SD), mmHg	124.2 (20.5)	119.0 (19.5)	<0.001
Diastolic blood pressure, mean (SD), mmHg	72.3 (11.7)	70.7 (11.5)	<0.001
Mean arterial pressure, mean (SD), mmHg*	89.6 (12.9)	86.8 (12.5)	<0.001
Heart rate, mean (SD), bpm*	73.2 (14.9)	72.5 (14.0)	0.011
Laboratory values			
Creatinine clearance, mean (SD), ml/min	58.3 (30.6)	65.5 (31.7)	<0.001
Creatinine clearance, ml/min*			
<30	991 (16%)	353 (8%)	
30-59.9	2,798 (44%)	1,807 (43%)	
≥60	2,526 (40%)	2,070 (49%)	<0.001
Potassium, mean (SD), mEq/l	4.2 (0.5)	4.2 (0.5)	0.89
Potassium, mEq/l*			
<3.5	167 (4.1%)	113 (4.5%)	
3.5-5	3,756 (91.8%)	2,283 (91.2%)	
>5.0	166 (4.1%)	106 (4.3%)	0.649
Hemoglobin, mean (SD), g/l	132.0 (17.1)	133.6 (16.9)	<0.001
NT-proBNP, median (IQR), pg/ml*	3197.0 (1318.5, 7614.0)	3039.5 (1320.0, 7200.0)	0.41
Comorbidities			
Smoking*			
Never	2121 (39.2%)	1400 (38.6%)	
Previous	2603 (48.1%)	1774 (48.9%)	
Current	691 (12.8%)	452 (12.5%)	0.72
Hypertension*	4039 (59.6%)	2614 (58.8%)	0.39
Diabetes Mellitus*	2104 (31.1%)	1533 (34.5%)	<0.001
Ischemic heart disease*	4527 (68.9%)	2830 (65.3%)	<0.001
Coronary Revascularization*	2684 (39.6%)	1753 (39.5%)	0.85
Peripheral artery disease*	874 (12.9%)	519 (11.7%)	0.054
Stroke/transient ischemic attack*	1277 (18.9%)	767 (17.3%)	0.032
Atrial fibrillation*	3871 (57.2%)	2648 (59.6%)	0.010
Anemia*+	2,526 (37.3%)	1,530 (34.4%)	0.002
Valvular disease*	1793 (27.1%)	1214 (27.9%)	0.34
Lung disease*	1878 (27.7%)	1268 (28.5%)	0.35
Concomitant medications			
ACE-I or ARB*	5913 (87.5%)	4016 (90.6%)	<0.001
ACE-I or ARB^			
None or < target dose	4,361 (65%)	2,333 (53%)	
≥ target dose or ACE-I + ARB	2,378 (35%)	2,096 (47%)	<0.001
Digoxin*	1092 (16.1%)	1063 (24.0%)	<0.001
Diuretic*	5599 (82.8%)	4012 (90.5%)	<0.001
Nitrate*	1463 (21.7%)	854 (19.3%)	0.002
Platelet inhibitor*	3626 (53.7%)	2153 (48.6%)	<0.001
Oral anticoagulant*	2685 (39.8%)	2121 (47.9%)	<0.001
Statin*	3442 (51.0%)	2305 (52.0%)	0.29
Beta-blocker*	6030 (89.1%)	4041 (91.1%)	<0.001

Heart Failure devices*			
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%)	<0.001
Socio-economic variables			
Family type*			
Living alone	3269 (48.4%)	2135 (48.2%)	
Married/cohabitating	3492 (51.6%)	2296 (51.8%)	0.86
Education*			
Compulsory school	3329 (49.7%)	2062 (46.9%)	
Secondary school	2481 (37.1%)	1700 (38.7%)	
University	882 (13.2%)	630 (14.3%)	0.012
Income, below median*	3,487 (51.7%)	2,092 (47.3%)	<0.001
Number of children, mean (SD)*	2.0 (1.4)	2.0 (1.4)	0.093

NT-proBNP: N-terminal pro b-type natriuretic peptide; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CRT-P: Cardiac resynchronization therapy pacemaker; CRT-D: Cardiac resynchronization therapy defibrillator; ICD: Implantable cardioverter defibrillator; SD: standard deviation; IQR: interquartile range *Variables included in the multivariable logistic regression model. $^{+}$Anemia was defined according haemoglobin levels (<120 g/dl in women and <130 g/dl in men). ^Încluded in the consistency analysis. Registration year was included as a continuous variable.

Table 2. Summary of the 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	~50% in inpatients at the discharge and 44% in outpatients

survey[15]	
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 the discharge and 56.5% at 1 year from the hospitalization
SwedeHF (current study)	40% of the eligible population

FIGURE LEGENDS

Figure 1. Flow chart reporting the patients' selection. MRA: mineralocorticoid receptor blockers; EF: left ventricular ejection fraction; NYHA: New York heart association; HF: heart failure.

Figure 2. Independent predictors of mineralocorticoid receptor antagonist (MRA) non-use. CRT-D: cardiac resynchronization therapy - defibrillator; CRT-P: cardiac resynchronization therapy - pacemaker; ICD: implantable cardioverter defibrillator; NYHA: New York heart association.

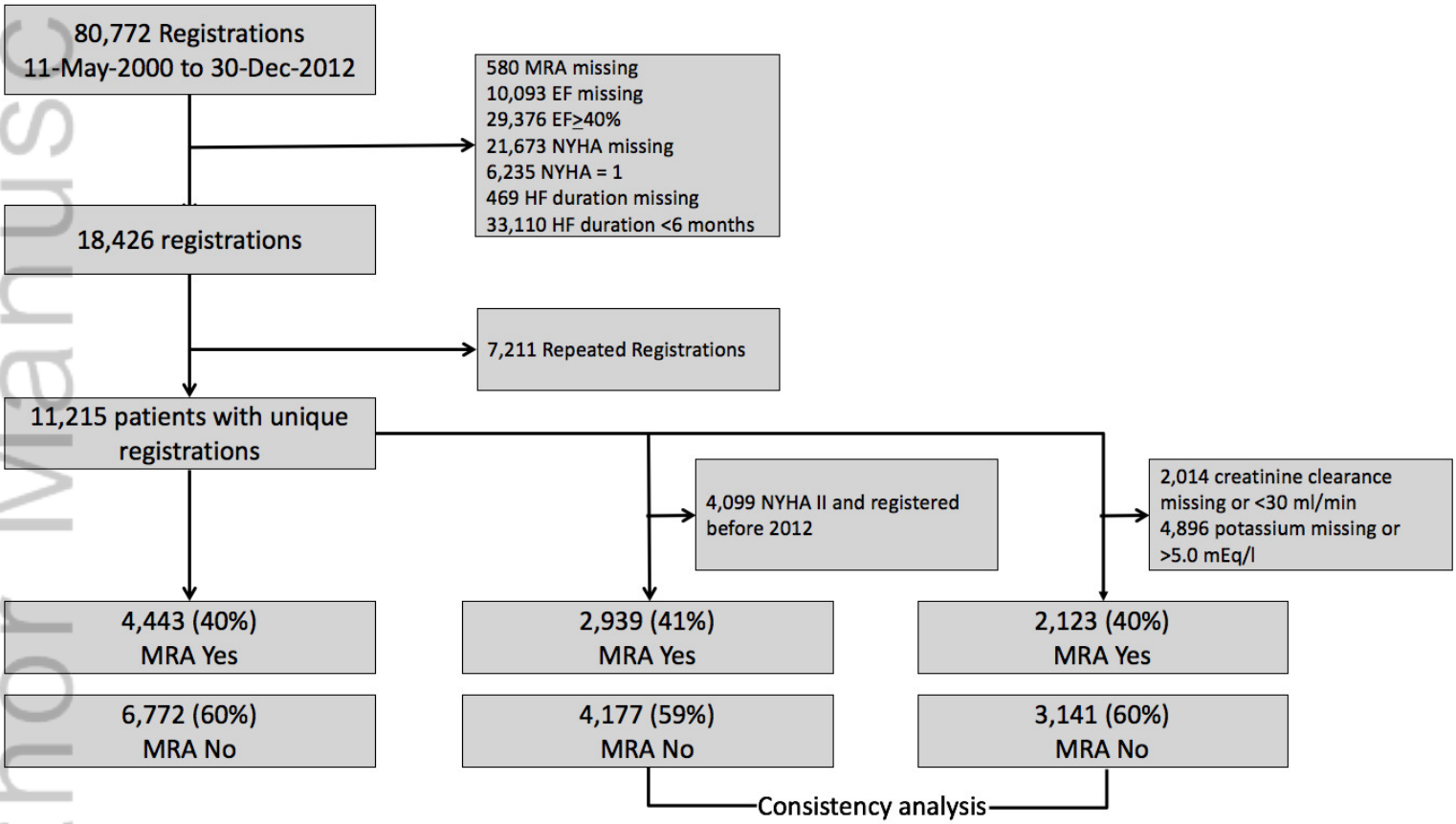

Figure 1.jpg

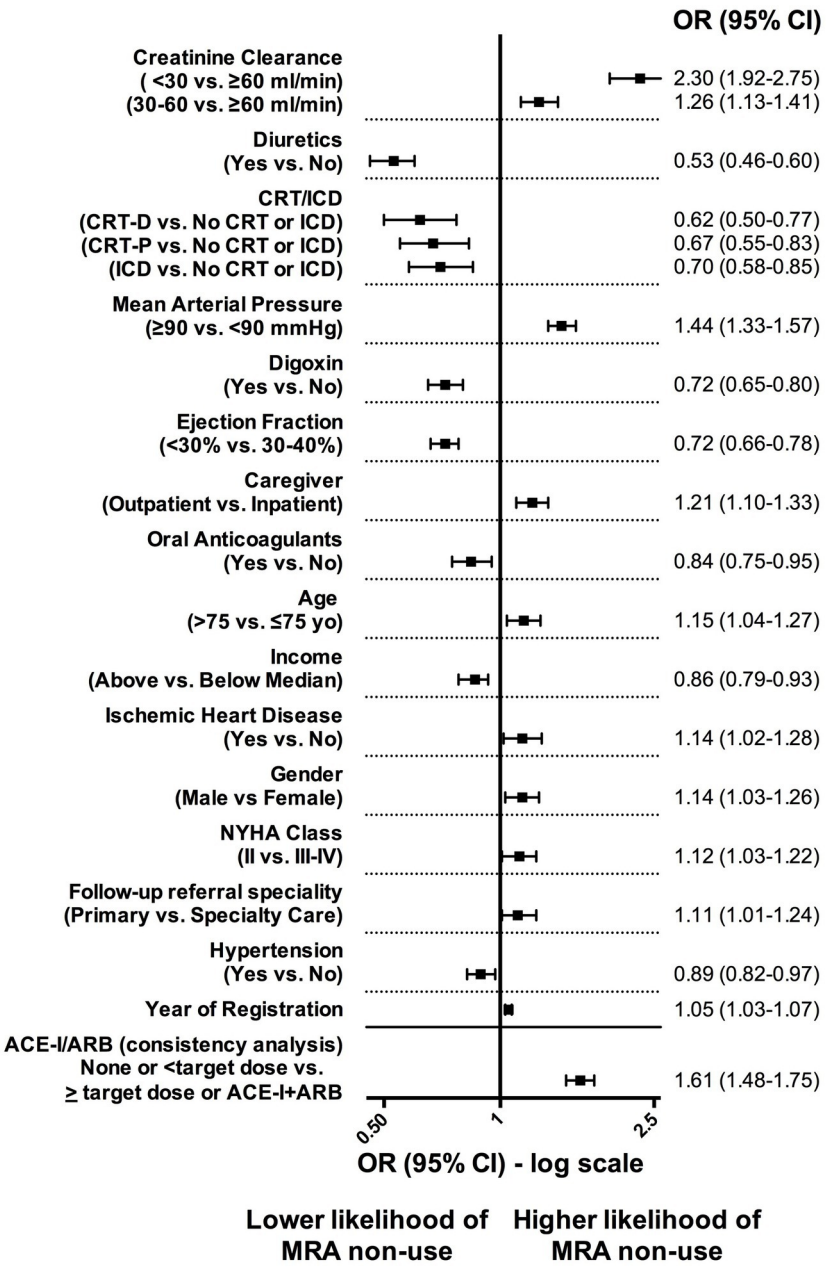

Figure 2.jpg

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