Mineralocorticoid Receptor Antagonists use pattern in Heart Failure with Reduced Ejection Fraction: findings from BIOSTAT-CHF

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Abstract

Background: Mineralocorticoid Receptor Antagonists (MRAs) are recommended (unless contraindicated) to all patients with heart failure with reduced ejection fraction (HFrEF). However, MRAs are still largely underused in routine clinical practice.

Aims: This study aims to describe the determinants and pattern of use of MRAs in HFrEF.

Methods: BIOSTAT-CHF is an European multicentre, prospective study which enrolled patients sub-optimally treated with ACE-inhibitors/ARBs and/or β-blockers, with the aim of optimizing guideline based use of these agents. From the original 2516 subjects, this retrospective post hoc analysis included the 1325 patients with an indication for MRA therapy (i.e., LVEF≤35%, eGFR≥30 ml/min/1.73m^2, K^+≤5.0 mmol/L).

Results: The mean age was 66.1±12.2 years. At baseline an MRA was prescribed 741 (56%) patients. Patients who were prescribed MRAs at baseline were younger, more often male, had higher BMI, lower sodium, higher proportion of hypertension history and ACEi/ARBs prescription (all p<0.05). Of the 1049 patients who completed the baseline plus the 9-month visit, 585 (56%) had an MRA prescribed at baseline and 662 (63%) patients had an MRA prescribed at 9-months. Among the 585 patients with MRA at baseline, 91 (16%) had discontinued therapy and among the 461 (44%) patients without MRA at baseline 168 (36%) had initiated therapy subsequently. MRA discontinuation was more likely in subjects with higher LVEF and NYHA class III/IV (p<0.05 for both). MRA prescription both at baseline and 9 months was not associated with the outcome of death or HF hospitalization (adjusted HR [95%CI]=1.02 [0.66-1.58], p=0.93).

Conclusions: In this prospective observational study across Europe, MRAs were largely under-prescribed and frequently discontinued. Due to these dynamic changes outcome inferences are inconclusive.

Key-words: Mineralocorticoid receptor antagonists; real-life; observational, adherence, prescription.

Introduction

Mineralocorticoid receptor antagonists (MRAs) improve morbidity and reduce mortality in heart failure with reduced ejection fraction (HFrEF) with severe symptoms (spironolactone)[1], mild symptoms (eplerenone)[2], and in post-myocardial infarction with systolic dysfunction and/or heart failure (eplerenone)[3]. Mortality rates were reduced by 15% to 30% and heart failure (HF) readmissions dropped up to 40% in these landmark trials.

Despite these remarkable improvements in morbidity and mortality and a class IA guideline recommendations, MRAs are still largely underused in routine clinical practice[4, 5]. This may be (at least partly) explained by an undue concern about inducing hyperkalemia or worsening renal function[6-14] and the need of close monitoring of potassium and renal function[7], but also by a lack of education/promotion about these drugs and their indications[8-14].

"Real-life" data suggest that non-compliance and discontinuation of therapy is common, especially with regards to MRAs, with less than 50% of daily doses ingested in some series (i.e., a much lower adherence than that reported for angiotensin converting enzyme inhibitors/angiotensin receptor blockers [ACEi/ARBs] and β-blockers, for example)[15, 16]. Many reports of "real-life" observational data pointed to a lack of association of MRA therapy with clinical benefit, in contrast with the findings of multiple randomised clinical trials. No matter how extensive are adjustment in statistical analyses, such observation data are usually fraught with residual bias[17, 18]. We hypothesize that one of the major and often overlooked biases is the wrong assumption that patients prescribed MRA therapy at baseline keep their medications unchanged throughout the course of the observation period. Hence, the main goals of the present analysis are to study: 1) the rates and determinants of MRA prescription; 2) the characteristics of the population with and without MRAs prescribed; 3) the changes in MRA therapy that occurs after baseline observation and during the 9-month period after the baseline observation, and 4) the determinants of these changes. We took advantage of the European BIOSTAT-CHF program as a multicentre, multinational, prospective, contemporary, observational study which enrolled patients who had suboptimal dosing or no treatment with ACE-inhibitors/ARBs and/or β-blockers, with the aim of optimizing guideline based use of these agents and examining the predictors of optimization. Patients' characteristics are compared at baseline (visit 1) and 9 months (visit 2) follow up. This retrospective post hoc analysis was restricted to patients indicated for MRA therapy.

Methods

Patient population

BIOSTAT-CHF is a European project that enrolled 2516 HF patients from 69 centres in 11 European countries to determine profiles of patients with HF that do not respond to recommended therapies, despite anticipated up-titration. The design of the study and patients

have been described elsewhere[19]. In brief, patients were aged ≥18 years with symptoms of new-onset or worsening HF, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or a BNP and/or NT-proBNP plasma levels >400 pg/ml or >2000pg/ml, respectively. Patients needed to be treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. Patients should not have been previously treated with evidence based therapies (ACEi/ARBs and β-blockers) or were receiving <50% of the target doses of at least one of these drugs at the time of inclusion. Initiation or up-titration of ACEi/ARB and/or β-blocker therapy should have been anticipated by the treating physician. The first three months of treatment were considered to be the optimization phase after which a stabilization phase of 6 months was defined. During the optimization phase, initiation or up-titration of ACEi/ARB and/or β-blocker was performed according to the routine clinical practice of the treating physicians, who were encouraged to follow the ESC guidelines at the time of treatment[20, 21]. There were no inclusion criteria nor optimization strategy specific to MRA therapy, which is assumed to be reflective of "usual care".

The recruitment period was 24 months, starting from December 2010. The last patient was included on December 15, 2012. Median follow-up was 21 months.

From the original 2516 patients enrolled in the BIOSTAT-CHF program, the retrospective analysis only included 1325 patients with a formal indication for the use of an MRA (LVEF ≤35%, estimated glomerular filtration rate [eGFR] ≥30 ml/min/1.73m^2, and K^+ ≤5.0 mmol/L) – **Figure 1**.

Statistical analysis

In descriptive analyses, continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as frequencies and proportions (%). Population description and comparison of patients with MRA vs. without MRA prescribed was performed using independent samples t-test for normally distributed continuous variables and chi-square test for categorical variables. Normality assumptions were verified by visual binning. No multiple imputation was performed.

To determine predictors of having a MRA prescribed (or not) and discontinued (or not), we developed two logistic regression and two multinomial prediction models. Both models used clinical and laboratory variables with a p-value <0.2 as entry criteria. The first model was a forward conditional model eliminating progressively the variables with weaker association and retaining in the final model those variables with a p <0.05. The second model used a stepwise backward selection process. Both models provided similar final results. Logistic regression assumptions were checked and multicollinearity excluded. Linear relationship between continuous independent variables and the logit transformation of the dependent variable was verified by plotting the means vs. the β estimates in quintiles. If a linear relationship was not present then the variable was dichotomized at the inflexion point.

The primary outcome was a composite of hospitalization for heart failure (HHF) and all-cause death. Cox proportional hazard regression models were used to model long-term event rate both in univariable and multivariable analysis. Cox model's assumptions were verified. An interaction term between the variable of interest (MRA) and time was tested within the Cox model. In the multivariable models, the covariates for adjustment were chosen from demographic (age and gender), clinical (body mass index [BMI], LVEF, European region, congestion signs and symptoms, coronary revascularization, hypertension history, diabetes, medication, and systolic blood pressure), and laboratory (eGFR determined by the CKD-EPI formula[22] and hemoglobin). All parameters were previously found to be independently associated with the outcome of HF hospitalization or all-cause death in the BIOSTAT cohort. These variables were also used to create a propensity score (PS) from a logistic regression model. The PS and its Logit were also used for adjustment as covariate providing similar results[23] (data not shown).

European region was divided in Southern countries (Greece, Italy, Serbia, Slovenia, and France) vs. Northern countries (Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom).

The adjudication of events (heart failure hospitalizations) were done by the treating physician.

All analyses were performed with SAS® software version 9.4 (SAS Institute Inc., Cary, N.C., USA).

Results

Characteristics of the studied population

At baseline, MRAs were prescribed in 741 (56%) patients. Characteristics of the patients according to MRA prescription at baseline and changes in MRA prescription between baseline and 9 months are presented in **Table 1**. Patients with MRA prescription at baseline were younger, more often male, had higher BMI, higher potassium levels, lower SBP, lower NT-pro BNP, were more often from southern Europe, had worse NYHA class, had more often a cardiac device, more coronary interventions, were more often hospitalized for worsening HF in the year before the baseline visit, had ACEi/ARBs prescribed more frequently but achieved ≥50% target dose of such therapies less frequently, had β-blockers prescribed more frequently but also achieved ≥50% target dose of β-blockers less frequently, they also had digoxin prescribed more frequently ($p<0.05$ for all). As compared to patients without any MRA prescription, patients in which an MRA was prescribed both at baseline and 9 months were younger, were more often from southern Europe (but Southern Europe patients were also the ones who had higher proportion of MRA discontinuation at some point between baseline and 9

months), had lower heart rate, lower SBP, higher serum potassium levels, had more often hypertension history, and a loop diuretic prescribed ($p<0.05$ for all) – **Table 1**.

Characterization of patients with and without MRA at baseline

At baseline, MRA recipients had greater odds of having higher BMI, being from Southern Europe, having worse NYHA class, had been hospitalized for worsening HF in the year before the baseline visit, have a device implanted, and hypertension history. Patients not receiving MRA therapy had higher odds of being older, have higher blood pressure, and hypokalaemia – **Table 2**.

Factors associated with MRA therapy change up to 9 months during the post discharge period

From the 1325 patients present at baseline, 276 (21%) were lost to follow-up, from which 169 (61%) died, and 107 (39%) patients did not complete the 9-month visit (data missing). Characteristics of these 276 compared with the remaining 1049 patients are depicted in **Supplementary Table 1**.

Of the 1049 patients who completed both baseline and 9-month visit, an MRA was prescribed at baseline in 585 (56%) patients and at 9 months in 662 (63%) patients. Among the 585 patients with an MRA prescription at baseline, 91 (16%) had discontinued therapy and among the 461 (44%) patients without MRA prescription at baseline, 168 (36%) had initiated therapy subsequently – **Table 3** and **Figure 2**. When looking at the specific drug 448 (42.8%) of the patients were taking spironolactone and 137 (13.1%) eplerenone. The proportion of patients who discontinued spironolactone and eplerenone was similar (15% and 17.5%, respectively), whereas the majority of patients who initiated MRA during the 9-month follow-up were started on spironolactone (23.9% vs. 12.6%) – **Supplementary Table 2**.

Factors associated with MRA discontinuation were a higher LVEF and worse NYHA class. Having a higher heart rate, SBP ≥140 mmHg and K^+ <4 mmol/L at baseline was associated with MRA initiation between baseline and 9 months, whereas patients from Southern Europe were less likely to initiate an MRA between baseline and 9 months – **Table 4**. Of the 1049 patients who completed the two visits, 578 (55%) had an echocardiography performed at both visits (45% missing values). Of these 578 patients, 199 (34.4%) had improved LVEF above 35%. Compared to patients who maintained a LVEF below 35%, subjects with LVEF improvement were less likely to maintain MRA during the 9-month follow-up (55.7% vs. 37.2%, respectively) - **Supplementary Table 3**.

Outcome associations

MRA prescription both at baseline and 9 months was not associated with lower primary outcome event rates as compared to not having an MRA prescription (adjusted HR [95%CI] =1.02 [0.66-1.58], p =0.93). MRA prescribed only at baseline was associated with dismal outcomes in unadjusted models but not after adjustment (unadjusted HR [95%CI] =1.80 [1.07-

3.05], p =0.028 and adjusted HF [95%CI] =1.68 [0.62-3.07], p =0.092). MRA prescription only at 9 months was also not associated with the primary outcome of mortality or heart failure hospitalization (adjusted HR [95%CI] =1.50 [0.89-2.53], p =0.13) – **Table 5**.

Discussion

Our study based on a symptomatic HFrEF population with suboptimal ACEi/ARB and/or β-blocker therapy showed that MRAs were largely under-prescribed and frequently changed (i.e., discontinued or initiated) in a short follow-up of 9 months. In this population, only ≈56% of patients with HFrEF with a formal indication for MRA treatment were actually receiving a MRA and within 9 months more than 15% of patients receiving an MRA discontinued, while another 36% without MRA at baseline initiated. We identified common features and determinants for MRA prescription and discontinuation. To the best of our knowledge, this is the first report on treatment initiation and cessation in only 9 months' time. It is, therefore, very difficult to categorize patients in observational studies in MRA vs. non-MRA, since receiving an MRA therapy is a highly unstable condition and moving target. Consequently, reports of observational data, emphasizing lack of association of MRA therapy with clinical benefit, are in contrast with the findings of multiple randomised clinical trials. These reports are usually fraught with residual biases but are also critically invalidated because all are based on the wrong assumption that patients prescribed MRA therapy at baseline keep their medications unchanged throughout the course of the observation periods[17, 18].

Previous observational reports confirmed that MRAs are under-prescribed. In the "Get With The Guidelines-HF quality improvement registry"[4], only about one-third of patients with a formal MRA indication (and no compelling contra-indication) had the corresponding prescription, that varied widely across United States (US) regions and clinicians. In that registry, MRA prescription was also less common among elderly patients, those who have worse renal function, and lower blood pressure. In our study patients with higher and improved LVEF and worse NYHA class were more likely to have MRAs discontinued between baseline and 9 months. Interestingly, patients with hypertension history more often received MRA therapy, whereas patients not receiving MRAs had more often SBP ≥140 mmHg and hypokalemia, which is consistent with the anti-hypertensive and potassium-sparing effects of MRA therapy[24].

More frequent use of MRA therapy in patients with highest BMIs suggests that clinicians may intuitively perceive that MRA therapy is more effective in overweight patients. Actually, experimental and clinical data suggest that this may be the case[25]. Interestingly, we have also recently reported data from the Eplerenone for Heart Failure with Mild Symptoms (EMPHASIS-HF) trial suggesting that patients with abdominal obesity derive the largest benefit from eplerenone therapy[26, 27].

The EURObservational Research Programme: Heart Failure Pilot Survey (ESC-HF Pilot), enrolled 5118 patients admitted for acute HF from 136 cardiology centres in 12 European countries in 2009-2010. In this survey, the rate of MRA therapy at hospital discharge was ~25% prior to hospitalization and ~50% after hospitalization[28]. The use of MRAs in the US is even lower than in Europe[29, 30]. Our data suggest that MRA use in the periods between 2009-2010 did not improve much up to 2010-2012, with only about half of the patients with compelling indication actually receiving the drug. In the 2008 HF guidelines of the European Society of Cardiology (ESC) is stated that "aldosterone antagonists should be considered in all patients with a LVEF ≤35% and severely symptomatic HF"[21], hence most patients included in our study had formal indication for MRAs. It should be noticed that the results of EMPHASIS-HF trial[2] expanding the recommendation of use of MRA therapy to all symptomatic HFrEF patients was only integrated in the 2012 ESC guidelines[20] and subsequently in the 2016 ESC guidelines[31].

Despite guideline indication, other factors may be responsible for the persistently low prescription rate, and these include the excessive concern raised by the publication of population-based studies associating MRA therapy to the increase of hyperkalemia-associated morbidity and mortality[32, 33]. As subsequently recognised, patients enrolled in these studies commonly received inappropriate dosing, or had formal contra-indications to MRA therapy, and had below trial and guideline recommended serum potassium and renal function monitoring[34-36]. It is also noticeable that there is a poor understanding of the mechanisms of action of MRAs beyond their "diuretic with potassium sparing properties" heading[37], lack of pharmaceutical company–sponsored drug marketing and education for clinicians[4], and lack of guidance on how to initiate MRAs on a background of ACEi/ARBs and β-blockers up-titration[13, 38]. The educational gap must be recognized and specifically addressed. Spironolactone is a generic drug, orphan from any industry promotional or educational support. Eplerenone is hardly supported by its single sponsor because of quick loss of patent short after its market launch.

In our study, a high rate (more than 15%) of MRA discontinuation during a short period of follow-up (≈9months) was observed. However, an even higher rate of MRA initiation (in patients without baseline MRA prescription) was observed (36%), possibly reflecting the guidance to up-titrate HF therapies in the BIOSTAT program. Patients at the highest end of the guideline recommended HFrEF range (<35%) or with LVEF improvement above 35%, and with worse NYHA class were more likely to have MRA treatment discontinued. Moreover, being older was associated with having no MRA prescribed at all. Our data do not provide granularity on why patients have stopped the drug, but they may suggest that clinicians` perception of patients` status is likely to play a role in these decisions and are a potential target for intervention[39]. Patient compliance cannot be assessed from our data, and compliance with treatments is a major issue[40], especially concerning MRAs[41, 42]. Notwithstanding, we may

observe that potassium levels were higher in the group of patients with MRA prescription, which is an indirect sign of treatment adherence.

Clinical and Research Implications

Our findings, together with other previous observations of under-use and under-dosing of MRA therapy should prompt a vigorous call to action. So many reports have consistently emphasised the lack of adherence with the highest evidence based strongly recommended life-saving MRA therapy in HFrEF, with little proactive action taken, especially in Europe. At least in the US, the Get With The Guidelines initiative (GWTG) is aiming at mitigating the general issue of poor adherence to guidelines, with encouraging results[5]. Actions directed towards clinical education and training (not only in the field of Cardiology, but also Internal Medicine, Geriatrics, Emergency Medicine, Nephrology, Endocrinology, *etc*) should be applied in order to improve the use of MRA therapy, but also to instruct on how to make the best use of it. The main reason for under use, under dosing or frequent discontinuation and no re-initiation of MRAs is the excessive concern about the risk of worsening renal function and of hyperkalemia[9, 43-46]. Although, it has been consistently reported that despite occasional decline in eGFR and rise in potassium after initiating or up titrating an MRA, patients do benefit from life-saving MRA therapy[43]. It also appears that in clinical practice, the rate of monitoring of renal function and serum potassium is suboptimal, and below guideline recommendation[36]. Therefore, emphasizing that both decline in eGFR and rise in potassium are predictable, frequently transient and reversible and also manageable is an important part of education about optimal guideline implementation and disease management programs. Regarding the new potassium binders[7,40,4], rather than increasing the undue concern about hyperkalaemia as a consequence of marketing-based medicine, we should encourage generating appropriate trials evidence that these may indeed improve the use of MRA therapy and consequently maximise clinical benefit. More frequent and guideline-based potassium and renal function monitoring should also be emphasized, given the very low rate of such monitoring associated with the use of MRA in daily practice[47]. Improvement in health-care systems and "HF programmes" such as nurse-led HF care, should be widely implemented since they increase adherence to therapy and improve outcomes while reducing overall costs[48, 49,50]. From a research perspective, the development of point of care home self-monitoring of serum potassium and renal function, together with other congestion assessments, backed by electronic algorithms, and other prescription-helping tools may improve quality care provision while monitoring performance measures.

Future reports of observational data should take into account the prescription changes during the observation period, and these MRA prescription alterations should be included in the analysis in a time-dependent manner in order to mitigate treatment allocation bias and to provide a closer picture of "real-world" clinical practice.

Limitations

Several limitations should be noticed in this study. First, this is a secondary analysis of a prospective non-randomized observational study, therefore all limitations inherent to such analysis are applied herein, including the inability to infer causality (for example, we cannot know if patients with worse NYHA class were more likely to have MRA discontinued because they were "sicker" or if they were more symptomatic because they did not have MRA prescribed). Second, this study was not designed to address MRA prescription with sufficient granularity, hence these data do not allow to assess treatment doses or MRA prescription before baseline visit nor the exact timing where the medication was stopped or initiated. Third, patient selection for the BIOSTAT-CHF study was based on under-prescription of ACEi and β-blockers, therefore MRA under-prescription possibly does not reflect "real life" completely. On the other hand, the MRA prescription increase observed between visits may represent an over-estimation of "real-world" practice, as doctors participating in the BIOSTAT program were clearly instructed to up-titrate HF treatments, hence limiting results generalizability and external validity. Third, the reason(s) why patients have discontinued MRAs are not depicted in the dataset. Medication registry was mandatory at each visit but the reason why a medication was discontinued was not registered. Therefore, we cannot know how many patients discontinued MRA due to hyperkalemia, worsening renal function or gynecomastia, for example. Lastly, association of MRA use with outcome is not possible to be determine due to high rates of discontinuation/initiation during follow up. This may be turned in to a strength of this manuscript, demonstrating that all "real-life" outcome associations (particularly with MRAs) are prone to this type of bias and are therefore potentially misleading.

Conclusion

In this multicenter international European cohort, MRAs were largely underprescribed and frequently discontinued. Only slightly more than half of the patients with indication for MRA therapy received it and more that 15% of patients discontinued therapy in the few months following the baseline visit, while other 36% of patients without MRA prescription at baseline initiated it, reflecting the "up-titration" guidance of the BIOSTAT program. We identified determinants of prescription and therapy discontinuation and we suggest actionable measures to improve prescription and adherence. Given the frequent dynamic changes in therapy, we strongly warn against the use of observational data to infer about association between MRA use at a certain time point and subsequent outcome.

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Figure 1. Study and present analysis flow-chart
Legend: HF, heart failure; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

Figure 2. Percentage (%) of patients with MRAs prescribed in the two study visits relative to the total (n=1049) of the patients who completed the two study visits and changes in MRA prescription between baseline and 9 months
Legend: MRA, mineralocorticoid receptor antagonist.
Total=1046 patients due to 3 (0.3%) missing values.

Table 1. Characteristics of the BIOSTAT population

Variables	Baseline				Changes between Baseline and 9 months					
	All (N=1325)	No MRA (N=584)	MRA (N=741)	p	All (N=1049)	MRA at both visits (N=494)	MRA discontinuation (N=91)	MRA initiation (N=168)	No MRA (N=293)	p for trend
Age, years	66.1 ± 12.2	68.2 ± 12.2	64.4 ± 12.0	<0.001	65.4 ± 12.2	63.6 ± 11.9	65.7 ± 12.4	64.6 ± 12.4	68.9 ± 12.0	<0.001
Male gender, n (%)	1027 (77.5)	433 (74.1)	594 (80.2)	0.009	811 (77.3)	393 (79.6)	71 (78.0)	130 (77.4)	215 (73.4)	0.25
White caucasian, n (%)	1305 (98.5)	579 (99.1)	726 (98.0)	0.083	1035 (98.7)	484 (98.0)	91 (100.0)	166 (98.8)	291 (99.3)	0.26
Southern Europe countries, n (%)	775 (58.5)	263 (45.0)	512 (69.1)	<0.001	603 (57.5)	345 (69.8)	59 (64.8)	81 (48.2)	115 (39.2)	<0.001
BMI, kg/m²	27.7 ± 5.5	27.1 ± 5.0	28.1 ± 5.8	0.001	27.8 ± 5.4	28.4 ± 5.7	27.6 ± 6.2	28.4 ± 5.0	26.6 ± 4.8	<0.001
Heart rate, bpm	83.2 ± 21.7	86.1 ± 24.3	81.0 ± 19.1	<0.001	83.5 ± 22.3	80.8 ± 18.9	83.8 ± 22.2	90.1 ± 25.3	84.3 ± 24.9	<0.001
SBP, mmHg	123 ± 21	126 ± 23	120 ± 19	<0.001	123 ± 21	121 ± 19	121 ± 17	127 ± 23	127 ± 23	<0.001
Pulmonary rales, n (%)	677 (52.4)	309 (54.7)	368 (50.5)	0.14	514 (50.1)	235 (48.2)	49 (54.4)	89 (54.3)	138 (49.3)	0.45
Peripheral edema, n (%)	609 (56.9)	259 (58.1)	350 (56.0)	0.50	459 (54.4)	217 (52.5)	50 (62.5)	75 (58.6)	114 (52.1)	0.25
Elevated JVP, n (%)	293 (31.7)	135 (35.2)	158 (29.2)	0.052	217 (29.3)	94 (25.0)	21 (34.4)	42 (35.9)	59 (32.1)	0.064
NYHA class III/IV, n (%)	797 (61.4)	322 (56.8)	475 (65.1)	0.002	613 (59.6)	297 (60.7)	68 (75.6)	97 (59.9)	150 (52.6)	0.001
Orthopnea, n (%)	439 (33.2)	184 (31.6)	255 (34.5)	0.27	327 (31.2)	148 (30.0)	38 (41.8)	66 (39.3)	74 (25.3)	0.002
LVEF, %	26.2 ± 6.4	26.5 ± 6.3	26.0 ± 6.4	0.10	26.3 ± 6.2	25.9 ± 6.3	27.4 ± 5.4	26.1 ± 6.1	26.8 ± 6.2	0.078
HHF within 12 months before baseline, n (%)	447 (33.7)	169 (28.9)	278 (37.5)	0.001	346 (31.6)	181 (35.0)	35 (36.1)	44 (25.3)	86 (27.9)	0.032
Primary HF etiology, n (%)	-	-	-	0.12	-	-	-	-		0.12
Ischemic	574 (43.3)	242 (41.4)	332 (44.8)	-	429 (40.9)	216 (43.7)	34 (37.4)	59 (35.1)	118 (40.3)	-
Hypertensive	106 (8.0)	58 (9.9)	48 (6.5)	-	82 (7.8)	30 (6.1)	10 (11.0)	12 (7.1)	30 (10.2)	-
Valvular	73 (5.5)	33 (5.7)	40 (5.4)	-	61 (5.8)	31 (6.3)	4 (4.4)	6 (3.6)	20 (6.8)	-
Other/miscellaneous	572 (43.2)	251 (43.0)	321 (43.3)	-	477 (45.5)	217 (43.9)	43 (47.3)	91 (54.2)	125 (42.7)	-
Hemoglobin, g/dL	13.5 ± 1.8	13.5 ± 1.8	13.5 ± 1.8	0.91	13.7 ± 1.8	13.4 ± 1.8	13.4 ± 1.8	13.8 ± 1.8	13.7 ± 1.8	0.252
eGFR, ml/min/1.73m²	66.2 ± 20.7	65.5 ± 20.7	66.8 ± 20.6	0.23	67.7 ± 20.7	68.4 ± 20.4	66.9 ± 21.9	69.2 ± 20.0	65.8 ± 21.2	0.243
eGFR <45 ml/min/1.73m², n (%)	224 (16.9)	107 (18.3)	117 (15.8)	0.22	153 (14.6)	66 (13.4%)	14 (15.4)	19 (11.3)	53 (18.1)	0.17
Sodium, mmol/L	139 ± 4	140 ± 4	139 ± 4	0.015	140 ± 4	139 ± 4	140 ± 4	140 ± 4	140 ± 4	0.020
Potassium, mmol/L	4.2 ± 0.5	4.1 ± 0.4	4.2 ± 0.4	<0.001	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.5	4.0 ± 0.4	4.2 ± 0.4	<0.001

Potassium <4 mmol/L, n (%)	396 (29.9)	210 (36.0)	186 (25.1)	<0.001	658 (62.7)	114 (23.1)	29 (31.9)	73 (43.5)	88 (30.0)	<0.001
*Log*NT-pro BNP, ng/L	2.97 ± 1.31	3.06 ± 1.34	2.90 ± 1.29	0.031	2.85 ± 1.26	2.74 ± 1.25	2.84 ± 1.23	3.00 ± 1.32	2.94 ± 1.24	0.072
Hypertension, n (%)	756 (57.1)	317 (54.3)	439 (59.2)	0.070	603 (57.5)	301 (60.9)	59 (64.8)	91 (54.2)	152 (51.9)	0.030
Atrial Fibrillation, n (%)	562 (42.4)	249 (42.6)	313 (42.2)	0.88	426 (40.6)	197 (39.9)	39 (42.9)	67 (39.9)	122 (41.6)	0.93
Diabetes mellitus, n (%)	402 (30.3)	163 (27.9)	239 (32.3)	0.088	297 (28.3)	145 (29.4)	31 (34.1)	54 (32.1)	66 (22.5)	0.050
COPD, n (%)	220 (16.6)	97 (16.6)	123 (16.6)	0.99	166 (15.8)	75 (15.2)	13 (14.3)	26 (15.5)	51 (17.4)	0.83
Stroke, n (%)	119 (9.0)	50 (8.6)	69 (9.3)	0.64	86 (8.2)	43 (8.7)	5 (5.5)	10 (6.0)	27 (9.2)	0.46
PAD, n (%)	123 (9.3)	47 (8.0)	76 (10.3)	0.17	88 (8.4)	46 (9.3)	8 (8.8)	15 (8.9)	19 (6.5)	0.57
Device therapy, n (%)	336 (25.4)	116 (19.9)	220 (29.7)	<0.001	255 (24.3)	137 (27.7)	27 (29.7)	32 (19.0)	59 (20.1)	0.020
PCI or CABG, n (%)	411 (31.0)	156 (26.7)	255 (34.4)	0.003	306 (29.2)	165 (33.4)	23 (25.3)	42 (25.0)	74 (25.3)	0.036
Loop diuretic, n (%)	1319 (99.5)	582 (99.7)	737 (99.5)	0.70**	1044 (99.5)	400 (81.0)	59 (64.8)	130 (77.4)	204 (69.6)	<0.001
ACEi/ARB, n (%)	995 (75.1)	421 (72.1)	574 (77.5)	0.025	800 (76.3)	458 (92.7)	79 (86.8)	153 (91.1)	264 (90.1)	0.26
≥50% dose, n (%)*	681 (54.4)	328 (59.7)	353 (50.2)	<0.001	586 (55.9)	263 (53.2)	45 (49.5)	106 (63.1)	270 (58.0)	0.071
Beta-blocker, n (%)	1108 (83.6)	464 (79.5)	644 (86.9)	<0.001	889 (84.7)	473 (95.7)	84 (92.3)	159 (94.6)	274 (93.5)	0.41
≥50% dose, n (%)*	455 (36.3)	220 (40.1)	235 (33.4)	0.015	398 (37.9)	187 (37.9)	32 (35.2)	82 (48.8)	124 (42.3)	0.052
Digoxin, n (%)	250 (18.9)	95 (16.3)	155 (20.9)	0.032	188 (17.9)	90 (18.2)	20 (22.0)	31 (18.5)	36 (12.3)	0.072

*At V1 the up-titration period was the first 3 months. Patients who were lost to follow-up OR who died during the uptitration period were excluded from this analysis. For follow-up purposes only patients who completed the two visits were considered.

** Fisher exact test.

All variables have ≤10% missing values (except peripheral edema and jugular venous pressure, proportion of missing values are 19.2% and 30.3% respectively).

Legend: MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; JVP, jugular venous pressure; NYHA, New York Heart Association; H, hospitalization; HF, heart failure; eGFR, estimated glomerular filtration rate; NT-pro BNP, n-terminal pro brain natriuretic peptide; COPD, chronic pulmonary obstructive disease; PAD, peripheral artery disease; PCI or CABG, percutaneous coronary intervention or coronary artery bypass grafting; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Country location in the BIOSTAT-CHF were considered as follows: Southern Europe: Greece, Italy, France, Serbia, and Slovenia; Northern Europe: Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom.

Table 2. Logistic regression: factors associated with and without MRA prescription at visit 1

Baseline		
Factors associated with MRA prescription	**Odds ratio (95% CI)**	**p-value**
Southern Europe countries	2.39 (1.87-3.05)	<0.001
BMI (per 5 kg/m² increase)	1.14 (1.02-1.28)	0.025
HHF in the 12 months before baseline visit	1.34 (1.04-1.73)	0.024
NYHA class III/IV	1.47 (1.16-1.88)	0.002
Device therapy	1.62 (1.22-2.15)	0.001
Hypertension history	1.30 (1.01-1.68)	0.044
Age (per 10 years increase)	0.79 (0.71-0.87)	<0.001
SBP ≥140 mmHg	0.55 (0.41-0.75)	<0.001
Potassium <4 mmol/l	0.59 (0.46-0.77)	<0.001

A backward conditional model was performed based on variables that have an association with a p-value <0.2 in Table 1 retaining in the final model the variable with a p-value <0.05.

Legend: MRA, mineralocorticoid receptor antagonist; BMI, body mass index; HHF, heart failure hospitalization; SBP, systolic blood pressure; NYHA, New York Heart Association; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Country location in the BIOSTAT-CHF were considered as follows: Southern Europe: Greece, Italy, France, Serbia, and Slovenia; Northern Europe: Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom.

Table 3. MRA prescription drop out and initiation from baseline to 9 months in the 1049 patients who completed the two visits

MRA (yes/no) n (%)	**MRA at Baseline** n=585 (55.9)	**No MRA at Baseline** n=461 (44.1)	**p-value**
MRA at 9 months n=662 (63.3)	494 (84.4)	168 (36.4)	<0.001
No MRA at 9 months n=384 (36.7)	91 (15.6)	293 (63.6)	

Legend: MRA, mineralocorticoid receptor antagonist.
The % presented are relative to the total of 1046 patients due to 3 (0.3%) missing values.

Table 4. Multinomial regression factors associated with MRA prescription change from baseline to 9 months (reference: MRA maintenance from baseline to 9 months)

MRA discontinuation (MRA at baseline but not at 9 months)	**Odds Ratio (95%CI)**	**p-value**
LVEF (per 5% increase)	1.27 (1.04-1.56)	0.020
NYHA class III/IV	2.04 (1.20-3.48)	0.009
PCI or CABG	0.58 (0.33-0.99)	0.047
MRA initiation (no MRA at baseline but prescribed at 9 months)	**Odds Ratio (95%CI)**	**p-value**
Heart rate (per 10 bpm increase)	1.16 (1.07-1.26)	0.001
Potassium <4 mmol/L	2.47 (1.66-3.66)	<0.001
SBP ≥140 mmHg	1.82 (1.16-2.86)	0.010
Southern Europe countries	0.52 (0.35-0.78)	0.001
No MRA (no MRA at baseline neither at 9 months)	**Odds Ratio (95%CI)**	**p-value**
Age (per 10 years increase)	1.37 (1.19-1.59)	<0.001
BMI (per 5 kg/m² increase)	0.78 (0.66-0.91)	0.002
NYHA class III/IV	0.68 (0.49-0.95)	0.022
Hypertension history	0.70 (0.49-1.00)	0.050

A backward was performed according to the type 3 analyses effect (global effect).

Legend: MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association.

Country location in the BIOSTAT-CHF were considered as follows: Southern Europe: Greece, Italy, France, Serbia, and Slovenia; Northern Europe: Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom.

Table 5. Primary outcome associations for MRA therapy between V1 and V2

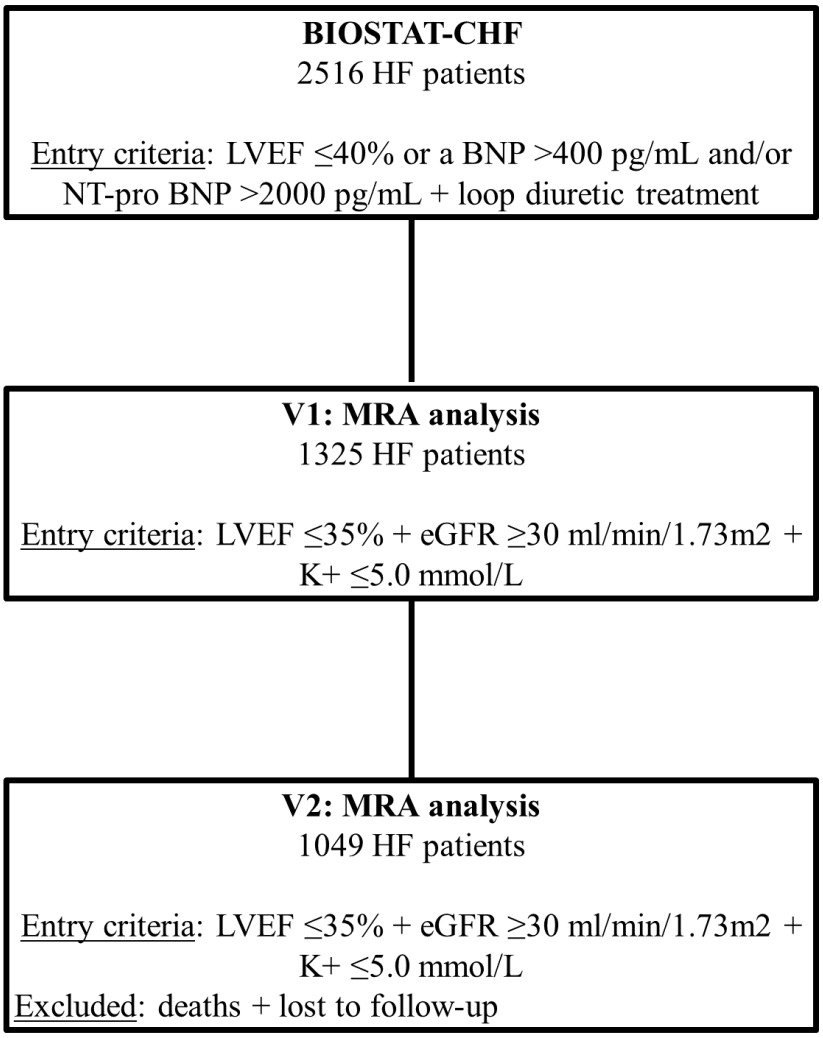
	Unadjusted HR (95%CI)	**p-value**	**Adjusted HR* (95%CI)**	**p-value**
No MRA (reference)	-	0.10	-	0.14
MRA baseline+9 months (yes)	1.00 (0.69-1.46)	0.99	1.02 (0.66-1.58)	0.93
MRA only baseline (yes)	1.80 (1.07-3.05)	0.028	1.68 (0.92-3.07)	0.092
MRA only 9 months (yes)	1.24 (0.78-1.97)	0.36	1.50 (0.89-2.53)	0.13

The 1049 patients who completed the two study visits were included in the analysis. Time was set from 9 months until the end of the study and events previous to 9 months were censored.

*adjusted on the clinical model derived from the BIOSTAT dataset that includes age, heart failure hospitalization in the last year, peripheral edema, systolic blood pressure, estimated glomerular filtration rate, urea, NT-pro BNP, hemoglobin, sodium, and use of beta-blocking agent at baseline.

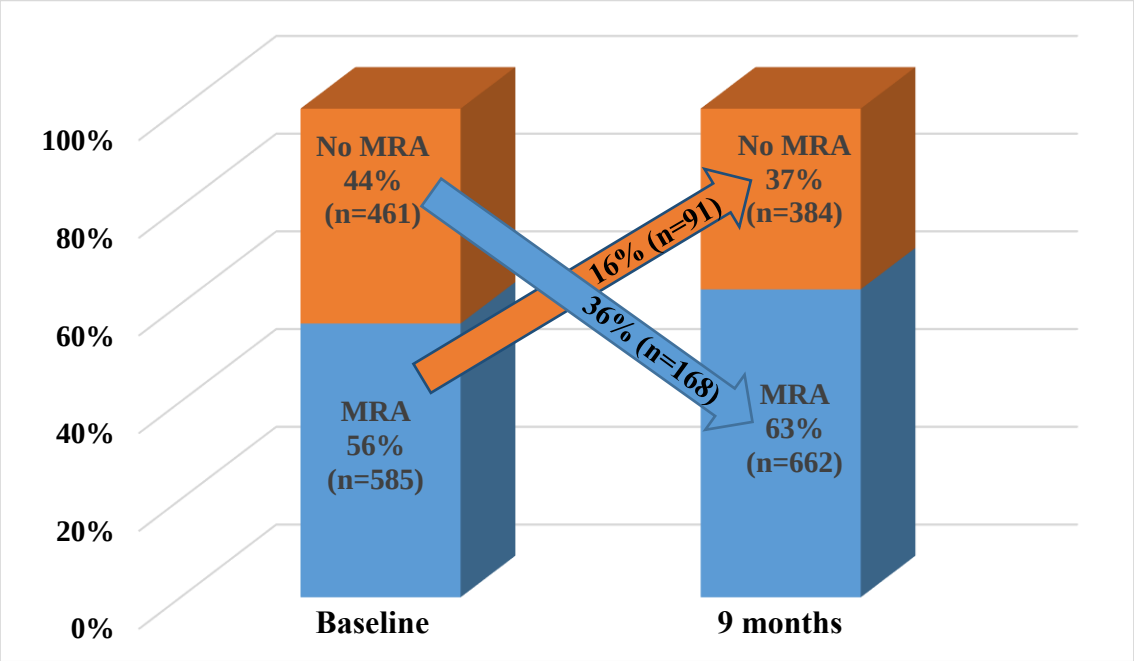
Legend: MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval.

Figure 1. Study and present analysis flow-chart



Legend: HF, heart failure; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

Figure 2. Percentage (%) of patients with MRAs prescribed in the two study visits relative to the total (n=1049) of the patients who completed the two study visits and changes in MRA prescription between baseline and 9 months



Legend: MRA, mineralocorticoid receptor antagonist.
Total=1046 patients due to 3 (0.3%) missing values.

Supplemental Material

Supplemental Table 1. Comparison of the characteristics of the patients who died or who were lost to follow-up with the whole baseline population

	Baseline	**Dead or Lost to Follow-up**	**P-value**
Variables	**(N=1325)**	**(N=276)**	
MRA at baseline, n (%)	741 (55.9)	154 (55.8)	0.962
Age, years	66.1 ± 12.2	68.4 ± 11.9	<0.001
Male gender, n (%)	1027 (77.5%)	216 (78.3)	0.737
White caucasian, n (%)	1305 (98.5%)	270 (97.8)	0.309
Southern Europe countries, n (%)	775 (58.5%)	172 (62.3)	0.147
BMI, kg/m²	27.7 ± 5.5	27.1 ± 5.5	0.06
Heart rate, bpm	83.2 ± 21.7	82.2 ± 19.0	0.38
SBP, mmHg	123 ± 21	119 ± 27	0.002
Pulmonary rales, n (%)	677 (52.4%)	163 (60.8)	0.002
Peripheral edema, n (%)	609 (56.9%)	150 (65.8)	0.002
Elevated JVP, n (%)	293 (31.7%)	76 (41.5)	0.001
NYHA class III/IV, n (%)	797 (61.4%)	184 (68.7)	0.006
Orthopnea, n (%)	439 (33.2%)	112 (40.6)	0.003
LVEF, %	26.2 ± 6.4	25.8 ± 6.9	0.23
Primary HF etiology, n (%)	-		0.003
Ischemic	574 (43.3%)	145 (52.5)	
Hypertensive	106 (8.0%)	24 (8.7)	
Valvular	73 (5.5%)	12 (4.3)	
Other/miscellaneous	572 (43.2%)	95 (34.4)	
Hemoglobin, g/dL	13.5 ± 1.8	12.9 ± 1.8	<0.001
eGFR, ml/min/1.73m^2	66.2 ± 20.7	60.8 ± 19.5	<0.001
eGFR <45 ml/min/1.73m^2, n (%)	224 (16.9%)	71 (25.7)	<0.001
Sodium, mmol/L	139 ± 4	138.6 ± 4.3	<0.001
Potassium, mmol/L	4.2 ± 0.5	4.1 ± 0.5	<0.001
Potassium <4 mmol/L, n (%)	396 (29.9%)	107 (38.8)	0.12
*Log*NT-pro BNP, ng/L	2.97 ± 1.31	3.45 ± 1.41	<0.001
Hypertension, n (%)	756 (57.1%)	153 (55.4)	0.541
Atrial Fibrillation, n (%)	562 (42.4%)	136 (49.3)	0.010
Diabetes mellitus, n (%)	402 (30.3%)	105 (38.0)	0.002
COPD, n (%)	220 (16.6%)	54 (19.6)	0.137
Stroke, n (%)	119 (9.0%)	33 (12.0)	0.052
PAD, n (%)	123 (9.3%)	35 (12.7)	0.029
Device therapy, n (%)	336 (25.4%)	81 (29.3)	0.087
PCI or CABG, n (%)	411 (31.0%)	105 (38.0)	0.005
Loop diuretic, n (%)	1319 (99.5%)	275 (99.6)	0.801
ACEi/ARB, n (%)	995 (75.1%)	195 (70.7)	0.055
≥50% dose, n (%)*	681 (54.4%)	121 (43.8)	<0.001

Beta-blocker, n (%)	1108 (83.6%)	219 (79.3)	0.031
≥50% dose, n (%)*	455 (36.3%)	73 (26.4)	<0.001
Digoxin, n (%)	250 (18.9%)	62 (22.5)	0.086
Deaths, n (%)	297 (22.4)	169 (61.2)	<0.001

*At V1 the up-titration period was the first 3 months.

Legend: MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; JVP, jugular venous pressure; NYHA, New York Heart Association; HF, heart failure; eGFR, estimated glomerular filtration rate; NT-pro BNP, n-terminal pro brain natriuretic peptide; COPD, chronic pulmonary obstructive disease; PAD, peripheral artery disease; PCI or CABG, percutaneous coronary intervention or coronary artery bypass grafting; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Country location in the BIOSTAT-CHF were considered as follows: Southern Europe: Greece, Italy, France, Serbia, and Slovenia; Northern Europe: Netherlands, Sweden, Norway, Germany, Poland, and United Kingdom.

Supplemental Table 2. Spironolactone or Eplerenone prescription drop out and initiation from baseline to 9 months in the 1049 patients who completed the two visits

	Spironolactone at Baseline n=448 (42.8)	**Eplerenone at Baseline** n=137 (13.1)	**No MRA at Baseline** n=461 (44.1)	**p-value**
Spironolactone at 9 months n=480 (45.9)	367 (81.9)	3 (2.2)	110 (23.9)	<0.001
Eplerenone at 9 months n=182 (17.4)	14 (3.1)	110 (80.3)	58 (12.6)	
No MRA at 9 months n=384 (36.7)	67 (15.0)	24 (17.5)	293 (63.6)	

Legend: MRA, mineralocorticoid receptor antagonist.

The % presented are relative to the total of 1046 patients due to 3 (0.3%) missing values.

Supplemental Table 3. Patterns of MRA prescription relative to the proportion of patients who improved left ventricular ejection fraction above 35% from baseline to 9 months

	LVEF <35% (n=379)	**LVEF ≥35% (n=199)**	**P-value**
MRA at both visits	211 (55.7%)	74 (37.2%)	<0.001
MRA only at baseline	21 (5.5%)	18 (9%)	
MRA only at 9 months	57 (15%)	31 (15.6%)	
No MRA	90 (23.7%)	76 (38.2%)	

Legend: LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.
From the 1049 patients who completed the 2 visits, 578 (55%) had an echo performed at both visits (45% missing values).