Steroidal mineralocorticoid receptor antagonist use and all-cause mortality in patients with heart failure: insights from the HEROES study

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Mineralocorticoid receptor antagonists (MRAs) are a cornerstone of heart failure (HF) management, particularly for patients with reduced ejection fraction (HFrEF) [1]. According to European Society of Cardiology (ESC) guidelines, MRAs are recommended in patients with HFrEF (Class I, Level of Evidence A), and can be considered in patients with mildly reduced ejection fraction (HFmrEF) (Class II, Level of Evidence B) [1, 2]. Current ESC guidelines do not issue a specific recommendation for MRAs in the heart failure with preserved ejection fraction (HFpEF) cohort [2]. Spironolactone and eplerenone are recommended for HFrEF to reduce mortality and hospitalisation. They have shown significant efficacy in reducing cardiovascular death and HF hospitalisations in HFrEF patients [1, 3]. Most studies have concentrated on HFrEF, leaving a gap in data for HFmrEF and HFpEF. The efficacy of MRAs in these subtypes remains less clear and inconsistent across studies [3, 4]. On the other hand, the risk of hyperkalaemia and renal function deterioration is a significant concern, especially in patients with chronic kidney disease, which limits the broader application of steroidal MRAs [4, 5].

The aim of the study was to collect contemporary clinical data on prescription of steroidal MRAs in all HF patients and across HF phenotypes and to examine the association between baseline steroidal MRA use and long-term all-cause mortality.

Methods. The Heart Failure Observational Study (HEROES), which is a prospective, multicentre observational registry coordinated by the Polish Society of Cardiology, enrolled consecutive inpatients and outpatients with HF. Recruitment began in February 2022, closed in February 2024, and follow-up ended in May 2024. The HEROES study included 1422 patients who provided informed consent. For the present analysis, 12 patients who died during the index hospitalisation were excluded, resulting in a final cohort of 1410. Baseline MRA exposure was ascertained from the treatment established at the index encounter: for inpatients, the medication prescribed at discharge; for outpatients, the regimen

recorded at the index outpatient visit. The corresponding time origin ($t = 0$) was the completion of that encounter (hospital discharge for inpatients; the visit date for outpatients). The 12 patients who died during the index hospitalisation could not be assigned a discharge regimen and were therefore excluded; the inpatient analysis is consequently conditioned on survival to discharge, and the target population is restricted to patients surviving the index encounter. Comprehensive details regarding the study design and baseline patient characteristics have been reported in the earlier publication [6].

All statistical tests were two-sided, and a significance level of $\alpha = 0.05$ was adopted throughout unless otherwise specified. Continuous variables were tested for normality using the Shapiro-Wilk test and visual inspection of histograms and quantile–quantile plots. Because most of the continuous variables exhibited non-normal distributions, they are presented as medians with interquartile ranges (IQR: 25th–75th percentile); observed ranges are reported in the text where informative. Categorical variables are expressed as absolute frequencies and percentages, with corresponding 95% CIs for proportions computed using the Jeffreys method. For two-group comparisons (MRA-treated versus no MRA) continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using Pearson's χ^2 test of independence when expected cell frequencies were adequate (all expected counts ≥ 5). In situations where expected cell frequencies were small (below 5 in any cell of the contingency table), Fisher's exact test was employed as a conservative alternative.

Overall survival was described by the Kaplan-Meier product-limit method, and covariate-adjusted survival was displayed as model-adjusted (standardised) survival curves derived from the Cox model and shown with 95% confidence bands. These standardised curves were obtained by marginal (direct) standardisation, whereby each patient's predicted survival under MRA and under no MRA was averaged over the empirical covariate distribution of the cohort, with bootstrap confidence intervals accompanying the resulting standardised absolute risks. Adjusted hazard ratios (aHRs) with corresponding 95% CIs were estimated using multivariable Cox proportional hazards regression models. The confounder set was specified *a priori* as the common causes of both MRA prescription and mortality, on clinical rather than statistical grounds: age, sex, visit type, HF aetiology, hypertension, previous myocardial infarction, chronic kidney disease, and anaemia (219 events; 24 events per variable). Concomitant guideline-directed pharmacotherapy and device therapy were not entered into this clinically selected primary adjustment set. As they were recorded at approximately the same baseline time as MRA use, their causal role – confounder, mediator, or marker of phenotype, severity, or treatment eligibility – cannot be established from these data; models additionally incorporating HF phenotype, disease severity, and background therapy are reported as complementary sensitivity analyses; age was modelled continuously after a spline-based likelihood-ratio test excluded non-linearity ($p = 0.98$). Unrecorded binary comorbidity flags ($n = 12$; 0.9%) were treated as absent, a complete-case analysis being identical; a phenotype-and-severity-adjusted model and a multiple-imputation sensitivity analysis are reported in the Supplementary Material. Crude all-cause mortality rates are reported as percentages with 95% CIs calculated using the Jeffreys method. Because a χ^2 comparison of crude proportions disregards censoring, all-cause mortality was additionally summarised as Kaplan-Meier mortality at 12 months and as incidence rates per 100 person-years. Covariate-standardised absolute risks were derived at 12 and 18 months, each accompanied by a bootstrap 95% confidence interval. The restricted mean survival time (RMST) difference between the treatment groups was estimated to horizons of 12 and 18 months, furnishing a censoring-robust measure that does not presuppose proportional hazards. Follow-up durations are reported as medians with IQRs and were compared between groups using the Wilcoxon rank-sum test to evaluate potential differential follow-up that could introduce informative censoring bias. The multivariable model adjusted for age, sex, visit type, heart failure aetiology, hypertension, previous myocardial infarction, chronic kidney disease, and anaemia; the proportional-hazards assumption was examined using scaled Schoenfeld residuals (treatment term and global test both $p = 0.12$). All-cause mortality was additionally estimated within each ejection-fraction phenotype (HFrEF, HFmrEF, HFpEF); because the within-phenotype event count constrained model complexity, phenotype-specific hazard ratios were adjusted for age and sex, and effect modification was assessed by a treatment-by-phenotype interaction term using a likelihood-ratio test. The interaction model carried age, sex, and the treatment-by-phenotype product term (identical covariates to the phenotype-specific models); phenotype-specific and interaction analyses were restricted to the 1210 patients with classified LVEF, the 200 with unclassified LVEF being retained in the overall and weighted analyses as a distinct phenotype category. The target estimand of the weighted analysis was the average treatment effect (ATE). Propensity scores were estimated by logistic regression on age, sex,

visit type, HF phenotype, aetiology, hypertension, previous myocardial infarction, chronic kidney disease, and anaemia; stabilised weights, SW = P(A = a)/P(A = a|L), were well behaved (mean 1.00, median 0.77, range: 0.45–3.91, no zero weights) and untruncated. No major empirical positivity concerns were identified (propensity-score overlap was acceptable), the maximum standardised mean difference fell from 0.92 to 0.04 after weighting, the effective sample size was 1093, and a weighted Cox model with robust variance was used (Supplementary Material). All analyses were performed in R (version 4.6.1).

Results. The overall study population had a median age of 69.3 years (with interquartile range: 60.3–76.2). Women accounted for 28.4% (n = 400) of the cohort, and 19.8% (n = 279) were managed as outpatients. An ischaemic aetiology of HF was present in 41.1% (n = 579) of the patients. The HF subtype distribution was as follows: HFrEF in 44.5% (n = 627), HFmrEF in 18.6% (n = 262), HFpEF in 22.8% (n = 321), and LVEF not classified in the remaining 200 (14.2%) patients.

In the study cohort of 1410 patients, 899 (63.8%) received MRA therapy: eplerenone was administered to 654 (46.4%) patients and spironolactone to 245 (17.4%) patients. The remaining 511 (36.2%) patients did not receive any MRA. The consolidated Table I presents baseline demographic, clinical, and treatment characteristics of the HEROES cohort, stratified by MRA treatment status.

Among 1131 inpatients, 739 (65.4%; 95% CI: 62.5–68.2%) were treated with MRA (eplerenone 47.4%, spironolactone 17.9%), compared with 160 outpatients (57.4%; 95% CI: 51.4–63.2%; p = 0.013; eplerenone 42.1%, spironolactone 15.0%). Finerenone was not administered to any of the patients.

Among the 899 MRA-treated patients with documented dose status, the target dose was achieved in 422 (47.0%) patients, the maximum tolerated dose (below target) was used in 222 (24.7%) patients, and 255 (28.4%) patients remained on up-titration.

The reasons for not prescribing MRAs were determined by the investigators, and in the group of 511 untreated patients, they were as follows: the absence of an indication (48.7%), renal dysfunction (16.2%), hyperkalaemia (6.1%), gynaecomas-

Table I. Baseline characteristics overall and according to MRA treatment status

Characteristic	Overall (*N* = 1410)	MRA (*N* = 899)	No MRA (*N* = 511)	*P*-value
Age [years] median (IQR)	69.3 (60.3–76.2)	67.6 (58.5–75.0)	71.8 (64.1–79.8)	< 0.001
Female sex	400 (28.4%)	207 (23.0%)	193 (37.8%)	< 0.001
Systolic blood pressure [mm Hg]	127 (113–140)	125 (110–140)	130 (120–145)	< 0.001
Heart failure phenotype				< 0.001
HFrEF	627 (44.5%)	533 (59.3%)	94 (18.4%)	
HFmrEF	262 (18.6%)	157 (17.5%)	105 (20.5%)	
HFpEF	321 (22.8%)	123 (13.7%)	198 (38.7%)	
LVEF not classified	200 (14.2%)	86 (9.6%)	114 (22.3%)	
Ischaemic aetiology	579 (41.1%)	397 (44.2%)	182 (35.6%)	0.002
NYHA III–IV	204 (14.9%)	140 (15.6%)	64 (13.6%)	0.327
Hypertension	953 (68.2%)	590 (65.7%)	363 (72.6%)	0.008
Previous myocardial infarction	482 (34.5%)	339 (37.8%)	143 (28.6%)	0.001
Chronic kidney disease	378 (27.0%)	221 (24.6%)	157 (31.4%)	0.006
Anaemia	178 (12.7%)	93 (10.4%)	85 (17.0%)	< 0.001
Implantable cardioverter-defibrillator	288 (21.4%)	236 (26.3%)	52 (11.5%)	< 0.001
Cardiac resynchronisation therapy	120 (8.9%)	101 (11.3%)	19 (4.2%)	< 0.001
Beta-blocker	1237 (87.7%)	850 (94.6%)	387 (75.7%)	< 0.001
SGLT2 inhibitor	876 (62.1%)	705 (78.4%)	171 (33.5%)	< 0.001
ARNI	325 (23.0%)	297 (33.0%)	28 (5.5%)	< 0.001

Continuous variables are median (IQR) and compared using the Wilcoxon rank-sum test; categorical variables are n (%) and compared using Pearson's χ^2 or Fisher's exact test. Heart failure phenotype percentages are now computed over the full column denominators (1410; 899; 511), and an explicit "LVEF not classified" row has been added, so each column sums to 100%. Available-case denominators for variables with missing data: NYHA class and systolic blood pressure n = 1370; hypertension n = 1398; implantable cardioverter-defibrillator and cardiac resynchronization therapy n = 1348; education and living situation n = 1404. ARNI – angiotensin receptor–neprilysin inhibitor, HFmrEF/HFpEF/HFrEF – heart failure with mildly reduced/preserved/reduced ejection fraction, LVEF – left ventricular ejection fraction, NYHA – New York Heart Association, SGLT2 – sodium-glucose co-transporter 2. Rows unrelated to the reviewer comments are abbreviated here for clarity and are unchanged in the full table.

tia (0.8%), other or unspecified causes (20.2%), and no reason recorded (8.0%, n = 41); the categories now sum to 100%.

Among the study group, MRA prescription rates differed markedly across the HF subtypes. MRA therapy was administered to 85.0% (95% CI: 82.3–87.5%) of patients with HFrEF (533 of 627), 59.9% (95% CI: 53.8–65.8%) of those with HFmrEF (157 of 262), and 38.3% (95% CI: 33.1–43.7%) of those with HFpEF (123 of 321; $p < 0.001$ across subtypes).

During the median follow-up of 14.9 months (IQR: 11.9–18.6; range: 0.1–24.4 months) in the overall cohort of 1410 patients, a total of 219 all-cause deaths occurred, corresponding to a crude mortality rate of 15.5% (95% CI: 13.7–17.5%). In the MRA-treated group, 137 deaths were recorded (15.2%; 95% CI: 13.0–17.7%), compared with 82 deaths in the no-MRA group (n = 511; 16.0%; 95% CI: 13.1–19.4%). Median follow-up duration was slightly longer in the MRA group (14.95 months; IQR: 11.86–18.60) than in the no-MRA group (14.46 months; IQR: 10.94–18.04; p = 0.042). This 0.49-month difference in median follow-up is clinically negligible and is accommodated by the time-to-event analysis, which conditions on differential censoring.

In the HEROES cohort, MRA treatment was not associated with a reduction in all-cause mortality compared with no MRA therapy, as evidenced by an adjusted hazard ratio of 1.08 (95% CI: 0.81–1.44), p = 0.604. The confidence interval remains compatible with a clinically relevant reduction or increase in mortality. The estimate was unchanged when HF phenotype was added to the model (aHR = 0.99; 95% CI: 0.73–1.34) and across every sensitivity specification (Supplementary Table SII), and the estimates were broadly consistent across models. The model-adjusted (standardised) survival curves (Figure 1), shown with 95% confidence bands, overlapped throughout follow-up. Accounting for censoring, Kaplan-Meier mortality at 12 months was 11.8% (95% CI: 9.6–13.9) with MRA versus 13.6% (10.6–16.6) without; incidence rates were 12.4 and 13.7 per 100 person-years (incidence-rate ratio 0.91). Numbers at risk were small beyond 18 months, and survival estimates near 24 months warrant cautious reading. Covariate-standardised absolute risks were consistent with the primary analysis: the 12-month risk was 12.9% under MRA against 12.1% under no MRA (a difference of +0.9 percentage points [95% CI: –2.7 to 4.1]), and the 18-month risk 17.8% against 16.6% (a difference of +1.2 [–3.6 to 5.4]). The restricted mean survival time likewise revealed no meaningful separation, the difference amounting to +0.20 months at the 12-month horizon (95% CI: –0.09 to 0.49) and +0.30 months at 18 months (–0.20 to 0.80). When analysed within each phenotype, no statistically significant association was detected between MRA status and all-cause mortality, and given the limited number of events, clinically relevant benefit or harm cannot be excluded (HFrEF 16.3% versus 20.2%, adjusted HR = 0.84, 95% CI: 0.51–1.39; HFmrEF 14.6% versus 11.4%, adjusted HR = 1.70, 95% CI: 0.83–3.48; HFpEF 13.0% versus 13.1%, adjusted HR = 0.98, 95% CI: 0.53–1.83), and the treatment-by-phenotype interaction was non-significant (p = 0.41) (Figure 1). Estimates were similar under inverse-probability weighting (HR = 0.97, 95% CI 0.70–1.34), and the E-value for the point estimate was 1.38; however, because the confidence interval already includes the null, the corresponding E-value for the interval is 1.00, so no unmeasured confounding is required for the association to be compatible with the null. The E-value is therefore of limited interpretive value here and does not by itself establish robustness against residual confounding. Full phenotype-specific mortality, the sensitivity analyses, and crude mortality by achieved MRA dose are reported in Supplementary Tables SI–SV and Supplementary Figure S1).

Discussion. The HEROES study, a contemporary multicentre Polish registry, provides a comprehensive overview of HF management in Poland. As was expected, the use of MRAs differed across the various HF subtypes. Steroidal MRAs were administered in 85% of patients with HFrEF, 59.9% of those with HFmrEF, and 38.3% of those with HFpEF. Similarly, the CAN-HF (Canadian Heart Failure) Registry showed that MRAs were most often prescribed to patients with HFrEF [7]. In many studies, despite a strong level of evidence, MRAs remain underused for HFrEF, most likely for reasons including hyperkalaemia and gynecomastia related to the blockage of the androgen receptor. The analysis of the guideline-directed medical therapy in the European Society of Cardiology Heart Failure III Registry showed that MRAs were prescribed in HFrEF, HFmrEF, and HFpEF in 78%, 64%, and 65%, respectively [8]. Interestingly, MRAs were used in patients with HFmrEF and HFpEF in a relatively high proportion, despite the absence of clear clinical trial data supporting the benefits of their administration and the lack of strong recommendations from scientific societies. Although the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with Aldosterone Antagonist) trial did not show a significant benefit of spironolactone compared with placebo in the overall cohort of patients with HFpEF, the results of this trial were difficult to interpret due to substantial regional variations, and subgroup analysis demonstrated a clinical benefit of MRA administration in the selected patients with HFpEF. The hopes for expanding the indications for the use of spironolactone in patients with HFpEF and

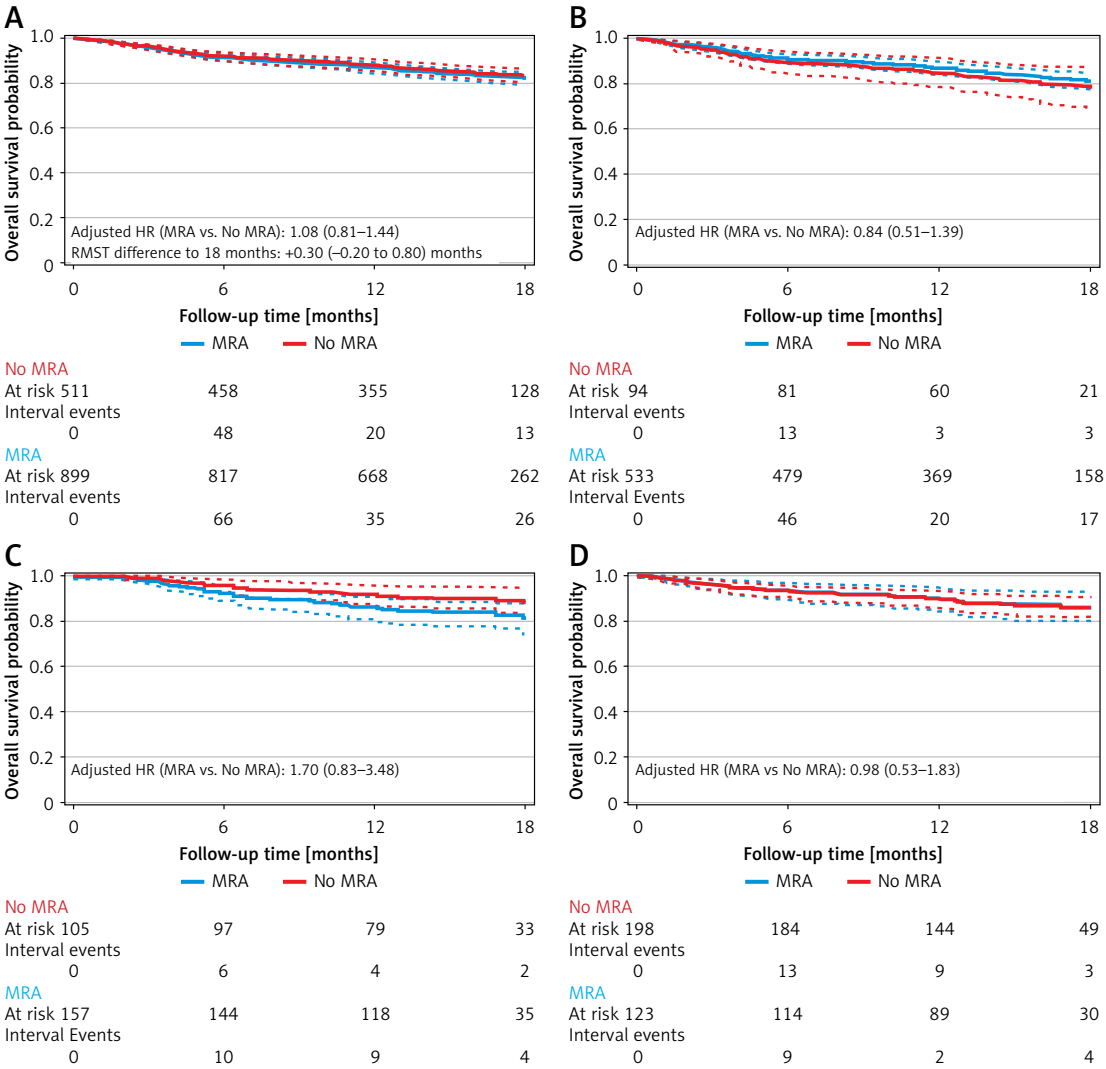

Figure 1. Model-adjusted overall survival according to mineralocorticoid receptor antagonist treatment status. Covariate standardized survival curves (marginal standardization), overall and by heart failure phenotype; follow-up curtailed at 18 months owing 10 sparse numbers at risk thereafter. **A** – Overall cohort, **B** – Heart failure with reduced ejection fraction, **C** – Heart failure with mildly reduced ejection fraction, **D** – Heart failure with preserved ejection fraction

HFmrEF were associated with the results of SPIRIT-HF (Spironolactone in the Treatment of Heart Failure) trial. The trial was affected by a high rate of discontinuation due to the COVID-19 pandemic, with just over half of the patients on spironolactone stopping the study drug, which lowered its ability to conclusively demonstrate differences between the treatment and placebo groups [9, 10]. Research regarding nonsteroidal MRAs such as finerenone and balcinrenone present a promising outlook for the greater use of MRAs, not only for HFrEF, but also for HFmrEF and HFpEF.

Our study, which included 1410 real-world participants, found that steroidal MRA use was not associated with a lower incidence of all-cause mortality compared with patients not receiving an MRA, irrespective of HF phenotypes. In the researched cohort, only 47% of patients reached the target dose of the drug. However, the presented study was not designed to assess the effect of MRA dosing on mortality. In contrast, a systematic review and meta-analysis including 4 trials and 13,846 patients showed that MRAs reduced the risk of cardiovascular death or HF hospitalisation, with an HR of 0.77 (95% CI: 0.72–0.83) in patients with HF [4].

This study is subject to several important limitations that deserve emphasis: its observational nature, the evaluation of only a single endpoint, and the relatively short follow-up. The treatment groups differed substantially at baseline in a pattern consistent with guideline-concordant prescribing, with MRA-treated patients younger, more often being male, and more frequently classified as HFrEF; confounding by indication is therefore likely, and the absence of a mortality difference must not be interpreted as evidence against MRA efficacy, particularly in HFrEF, where randomised

trials have established benefit. No data were available on MRA discontinuation, agent switching, or dose changes during follow-up. The multivariable, inverse-probability-weighted, and phenotype-specific analyses yielded broadly consistent estimates, while residual confounding remains inherent to the observational design. However, it should be emphasised that the HEROES population reflects the wider Polish HF study group, which makes these results especially relevant and distinctive in the national context. In this contemporary, real-world Polish HF registry, steroidal MRA therapy was frequently prescribed, particularly among patients with HFrEF. After multivariable adjustment, baseline MRA treatment was not independently associated with all-cause mortality during mid-term follow-up. Given the observational design and substantial baseline differences between the treatment groups, these findings should not be interpreted as evidence against the established benefits of MRAs in HFrEF. Consequently, further dose-sensitive analyses in larger cohorts are warranted.

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Ethical approval

The Bioethical Committee at the Medical University of Lodz approval No. RNN/316/20/KE (with update No. KE/762/23).

Conflict of interest

The authors declare no conflict of interest.

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