Factors Associated With Steroidal Mineralocorticoid Receptor Antagonist Use in Newly Diagnosed Heart Failure

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Background

- Heart Failure (HF) is a global epidemic, with approximately 1 in 4 individuals developing HF during their lifetime.[1]
- Steroidal mineralocorticoid receptor antagonists (sMRAs) constitute a key treatment pillar in HF with reduced ejection fraction (HFrEF), alongside renin-angiotensin-aldosterone system inhibitors, beta blockers, and sodium-glucose cotransporter-2 inhibitors (SGLT2is).[2]
- Data for sMRA use in patients with HF with mildly reduced and preserved EF (HFmrEF and HFpEF) are less robust than in HFrEF.[2,3]
- As newer nonsteroidal MRAs (nsMRAs) are introduced for patients with higher EFs, understanding real-world sMRA use, particularly among patients with cardiovascular-kidney-metabolic (CKM) comorbidities, may help identify treatment gaps and inform clinical practice.[4]

Objective

- To describe real-world sMRA initiation among patients with newly diagnosed HF in the US and to identify factors associated with treatment initiation, including CKM-related comorbidities.

Methods

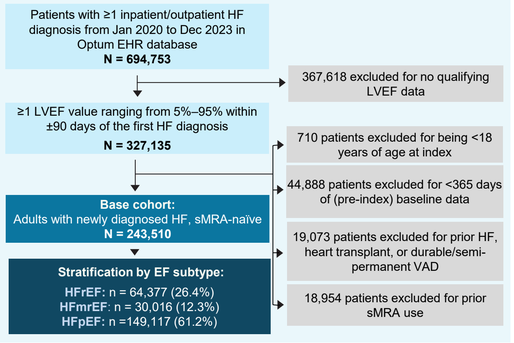
Study Design

- This retrospective cohort study used the Optum® de-identified electronic health record (EHR) database from January 1, 2020, to December 31, 2023.

Study

- Patient selection criteria are summarized in **Figure 1**.
- The index date was defined as the latter of two dates: the first HF diagnosis and corresponding left ventricular ejection fraction (LVEF) measurement.
- Patients were followed from index until December 31, 2023, or censoring due to death, durable / semi-permanent ventricular assist device (VAD) use, or heart transplant.

Figure 1. Stepwise selection of patient population



Study Variables

- **Baseline characteristics**: Sociodemographic and clinical characteristics, comorbidities, and prior HF-targeted therapies assessed at index or during the 365-day baseline (pre-index) period.
- **Treatment initiation with sMRA**: Cumulative incidence, incidence rates (IRs), and factors associated with initiation during follow-up.

Statistical Analysis

- Cumulative incidence of sMRA initiation (unadjusted time to initiation) was estimated using the Aalen–Johansen method for the base cohort and HF subgroups, with death treated as a competing event.
- A Cox proportional hazards model was used to evaluate sociodemographic and clinical characteristics, comorbidities, and prior treatments associated with time to sMRA initiation in the base cohort.
- IRs of sMRA initiation were reported per 100 person-years (PY) with follow-up censored at first sMRA prescription for the base cohort, and subgroups stratified by HF subtype and key CKM-related comorbidities.
- All analyses were conducted using R software (version 4.3.1).

Results

- The study included 243,510 patients with newly diagnosed HF who were sMRA-naïve at index (HFrEF: 26.4%; HFmrEF: 12.3%; HFpEF: 61.2%) (**Table 1**).
- Overall, 15.4% of patients initiated sMRA therapy during follow-up (median follow-up: 7.7 months).
  - Cumulative incidence of sMRA initiation was highest in patients with HFrEF (29.6%; IR: 36.8/100 PY), followed by HFmrEF (14.0%; IR: 13.4/100 PY), and HFpEF (9.5%; IR: 8.6/100 PY).
- Among sMRA initiators, median (Q1, Q3) time to initiation was 10 (2, 144) days.
  - Patients with HFrEF initiated sMRA treatment earlier (median: 6 days) than those with HFmrEF (17 days) and HFpEF (26 days) (**Figure 2**).

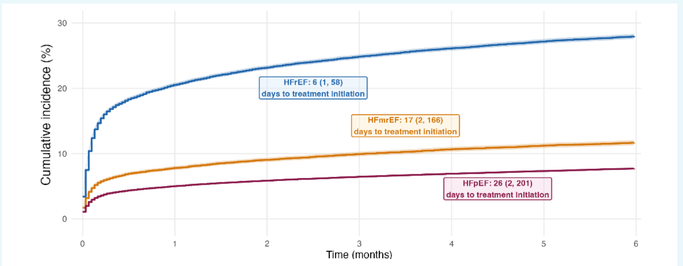
Table 1. Baseline characteristics of patients with newly diagnosed HF who were sMRA-naïve, stratified by HF subtype

Patient Characteristics	Base Cohort N = 243,510	HFrEF (LVEF ≤40%) N = 64,377	HFmrEF (LVEF 41%–49%) N = 30,016	HFpEF (LVEF ≥50%) N = 149,117
Age (in years), Mean (SD)	69.9 (13.5)	67 (14.1)	68.8 (13.7)	71.3 (13.0)
Female, n (%)	112,675 (46.3)	22,811 (35.4)	10,987 (36.6)	78,877 (52.9)
Index LVEF,[a] Mean (SD)	50.6 (15.2)	29.6 (8.1)	45.0 (2.2)	60.7 (6.8)
Clinical characteristics[b]				
BNP,[a] Median (IQR), pg/mL	315.0 (681.9)	693.3 (1219.0)	352.0 (728.0)	234.0 (464.0)
NT-proBNP,[a] Median (IQR), pg/mL	1740.1 (4294.0)	3737.1 (7421.0)	2014.0 (4594.0)	1238 (3055.5)
SBP,[a] Mean (SD), mmHg	131.7 (21.8)	128 (21.4)	131.5 (21.6)	133.3 (21.9)
BMI, Mean (SD), kg/m^2	30.5 (7.8)	29.4 (7.1)	30 (7.3)	31.1 (8.2)
BMI ≥30 (obese), n (%)	106,592 (43.8)	24,062 (37.4)	12,339 (41.1)	70,191 (47.1)
eGFR,[a] Mean (SD), mL/min/1.73 m^2	64.0 (27.5)	64.7 (27.8)	65.6 (27.9)	63.4 (27.4)
Serum potassium,[a] Mean (SD), mEq/L	4.1 (0.6)	4.2 (0.6)	4.2 (0.6)	4.1 (0.6)
Charlson comorbidity index, Mean (SD)	2.4 (2.1)	2.4 (2)	2.4 (2.1)	2.4 (2.2)
Baseline prescriptions,[c] n (%)				
ACEi/ARB	81,218 (33.4)	18,176 (28.2)	10,332 (34.4)	52,710 (35.3)
Beta-Blocker	95,475 (39.2)	22,445 (34.9)	12,993 (43.3)	60,037 (40.3)
SGLT2i	5816 (2.4)	1549 (2.4)	866 (2.9)	3401 (2.3)

[a]Data on clinical variables (LVEF, BNP, NT-proBNP, SBP, eGFR, and serum potassium) were obtained during the baseline period (365-day window before the index date), with the most recent value in the baseline period reported. [b]Number and percentage of patients with available clinical variables in the total HF cohort: BNP (88,490; 36.3%), NT-proBNP (48,909; 20.1%), eGFR (220,606; 90.6%), serum potassium (220,316; 90.5%), SBP (237,251; 97.4%), and BMI (230,030; 94.5%).[c]Medications approved for HF and prescribed in the baseline period (365-day window before the index date).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Figure 2. Initiation of sMRA in newly diagnosed patients with HF, overall and by EF subtype

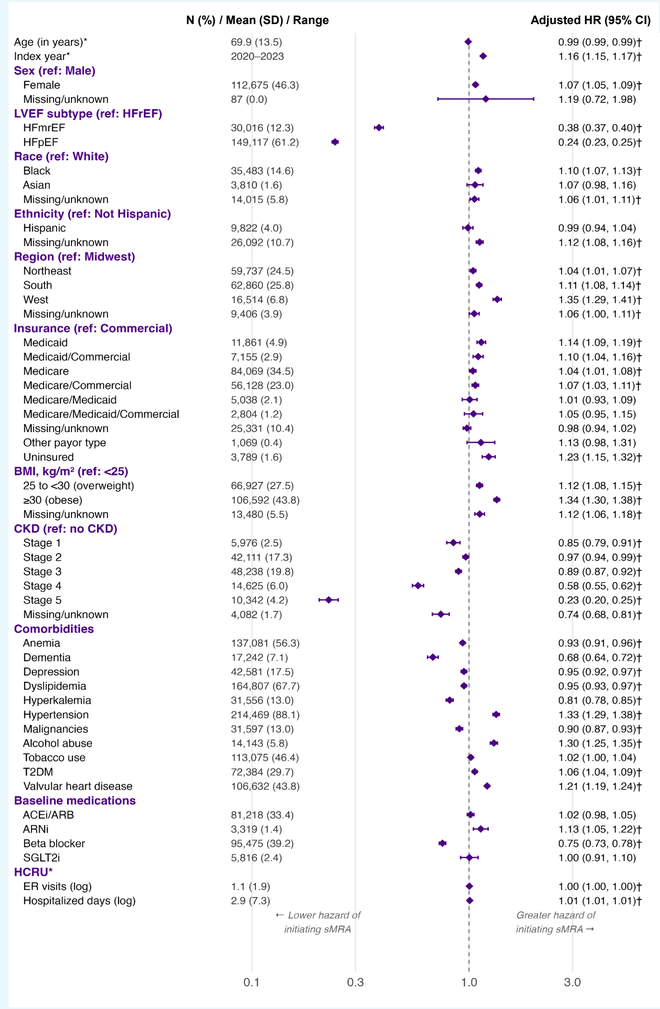
Treatment initiation outcomes	Base cohort	HFrEF	HFmrEF	HFpEF
Patients initiating sMRA during follow-up, n (%)	37,399 (15.4)	19,028 (29.6)	4,195 (14.0)	14,176 (9.5)
sMRA initiation rates per 100 PY	15.1	36.8	13.4	8.6



Time to treatment initiation reported as median (Q1, Q3).
HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IR, initiation rate; IQR, interquartile range; PY, person-years; Q1, first quartile; Q3, third quartile; sMRA, steroidal mineralocorticoid receptor antagonist.

- Factors **positively associated** with sMRA initiation included later index year, female sex, Black race (vs White), living in the West, Northeast, or South (vs Midwest), higher BMI, valvular heart disease, type 2 diabetes mellitus (DM), hypertension, history of alcohol abuse, and being uninsured (**Figure 3**).
- Factors **negatively associated** with sMRA initiation included HFmrEF and HFpEF (vs HFrEF), hyperkalemia, dementia, advanced CKD, anemia, cancer, dyslipidemia and depression; LVEF subtype and CKD stage showed the strongest negative associations with initiation (**Figure 3**).

Figure 3. Descriptive characteristics and factors associated with sMRA initiation in newly diagnosed HF patients who were sMRA-naïve (N=243,510)

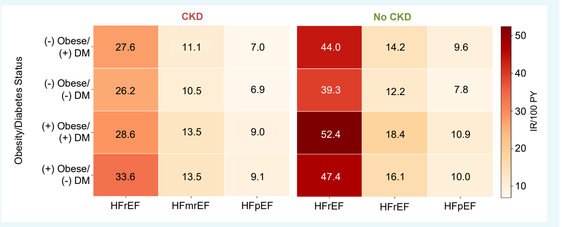


Cox proportional hazard models were used. Significance tested at a 2-sided α of 0.05. Time to treatment initiation is reported as median (Q1, Q3).
*Modeled as a continuous variable.†P<0.05. ACEi, angiotensin-converting enzyme inhibitor; adj, adjusted; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; ER, emergency room; HCRU, healthcare resource utilization; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; ref, reference; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus.

Results (continued)

- The most common CKM subgroup was HFpEF with CKD and without obesity or DM (n=28,117), followed by HFpEF without CKD, DM, or obesity (n=27,135).
- sMRA initiation varied markedly across HF subtype and CKM-related comorbidity profiles, with the highest IRs in HFrEF without CKD (39.2–52.4 per 100 PY) and the lowest in HFpEF and CKD (6.9–9.1 per 100 PY), regardless of obesity or DM status (**Figure 4**).

Figure 4. Steroidal MRA initiation rate by comorbidity profile and CKD versus no CKD



Note: Diabetes includes both type 1 or type 2 DM, as defined by the Sun & Hernandez-Boussard phenotype algorithm.[5] CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IR, incidence rate; MRA, mineralocorticoid receptor antagonist; PY, person-years; sMRA, steroidal mineralocorticoid receptor antagonist.

Discussion

- sMRA initiation rates were low across the HF spectrum, with patients with HFrEF initiating therapy more frequently and earlier than those with HFmrEF or HFpEF.
- Initiation patterns varied by clinical phenotype, insurance coverage, geographic region, and comorbidity burden, underscoring persistent gaps in equitable and timely adoption.

Study limitations

- While the large study population featuring a diverse array of patients from across the US is a strength of our study, findings may not be generalizable to healthcare settings outside the US.
- Persistence and adherence to treatment following sMRA initiation could not be assessed due to a lack of longitudinal pharmacy dispensation data in Optum EHR.
- Contraindications and tolerability-related factors influencing sMRA prescriptions could not be evaluated, potentially resulting in underestimation of guideline recommended use.
- LVEF values were extracted from unstructured notes using natural language processing; therefore, information on diagnostic tests used to ascertain LVEF were unavailable.

Conclusions

- Overall, sMRA initiation was low among patients with incident HF, particularly those with HFpEF and comorbid CKD, which comprised the largest CKM subgroup.
- These findings underscore the importance of early recognition of CKM profiles and patient-centered implementation of GDMT to improve real-world MRA use in line with evolving guidelines.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; adj, adjusted; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EHR, electronic health record; ER, emergency room; HCRU, healthcare resource utilization; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; IQR, interquartile range; IR, incidence rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PY, person-years; Q1, first quartile; Q3, third quartile; ref, reference; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; sMRA, steroidal mineralocorticoid receptor antagonist; T2DM, type 2 diabetes mellitus; US, United States; VAD, ventricular assist device.

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Disclosures

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