Real-World Use, Persistence, and Safety of Steroidal Mineralocorticoid Receptor Antagonists Among Patients with Heart Failure in the United States

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Craig J. Beavers[1], Arvind Katta[2], John W. Ostrominski[3], Orly Vardeny[4], Zihe Zheng[2], Mauricio Ferri[2], Keith A. Betts[5], Aozhou Wu[5], Travis Wang[5], Alanna A. Morris[2], Marco Antonio Lavagnino[2], Jacob Earl[2], Yunxun Wang[2], Tszshan Ma[5], Shumin Rui[5], Danni Yang[5], Andrew J. Sauer[6]

[1] University of Kentucky College of Pharmacy, Lexington, KY, USA; [2] Bayer, Whippany, NJ, USA; [3] Brigham and Women's Hospital, Boston, MA, USA; [4] University of Minnesota Medical School, Minneapolis, MN, USA; [5] Analysis Group, Inc., Los Angeles, CA, USA; [6] Saint Luke's Mid America Heart Institute, Kansas City, MO, USA

Background

- Steroidal mineralocorticoid receptor antagonists (sMRAs; spironolactone and eplerenone) are recommended for heart failure (HF) management, with a Class 1 recommendation in HF with reduced ejection fraction (HFrEF) and Class 2b recommendations in HF with mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) in the 2022 AHA/ACC/HFSA guidelines.[1-3]
- Despite demonstrated benefits and guideline recommendations, real-world uptake of sMRAs has been limited, with prior studies reporting high discontinuation and low long-term adherence, partly due to safety and tolerability concerns.[1, 4, 5]
- Contemporary real-world evidence on sMRA persistence, predictors of non-persistence, and safety events after initiation is lacking, limiting efforts to optimize HF management as the treatment landscape evolves.[3, 6]

Objective

- This study characterizes real-world sMRA initiation, treatment patterns, and safety outcomes, as well as identifies the factors associated with sMRA non-persistence.

Methods

Data source

- This retrospective, non-interventional cohort study used the Komodo Research Data (KRD+) (January 1, 2016–April 30, 2025).

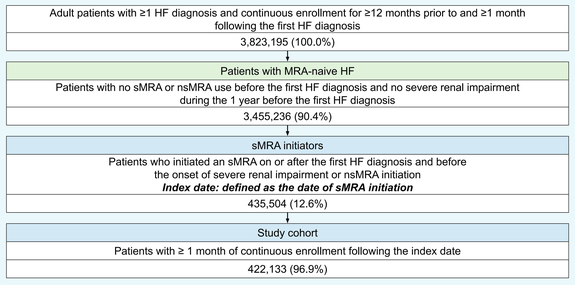
Study design and sample selection

- A total of 3,455,236 patients with MRA-naïve HF were identified. Among them, those who initiated sMRA treatment on or after the first HF diagnosis were included as the study cohort (**Figure 1**).
- **Index date:** the first sMRA prescription fill date.
- **Baseline period:** 12 months before the index date.
- **Follow-up** spanned from index date to the earliest of death, disenrollment, non-steroidal MRA (nsMRA) initiation, or end of data availability.

Outcomes and statistical analysis

- sMRA treatment pattern outcomes
  - Non-persistence: having discontinuation (>90-day gap) or switching to another sMRA or nsMRA.
  - Re-initiation: having a subsequent prescription fill for the same index sMRA drug after a discontinuation.
- Safety outcomes
  - Clinically significant hyperkalemia, AKI, and hypotension were identified from inpatient (IP) or emergency room (ER) encounters. Diagnosed sexual side effects were identified from IP, ER, or outpatient encounters.
- Initiation of sMRA, treatment patterns, and safety outcomes were assessed using cumulative incidence functions (CIFs), accounting for death as a competing risk.
- These outcomes were also assessed in systolic and diastolic HF subgroups at index.
- Factors associated with non-persistence were evaluated using a Cox proportional hazards model including on-treatment safety outcomes as time dependent covariates.

Figure 1. Sample Selection and Cohort Identification



Results

sMRA initiation

sMRA initiation after HF onset was modest, reaching only 13.7% by 3 years.

- The cumulative incidence of sMRA initiation was 9.6% at 12 months and 13.7% at 36 months; among initiators, the median time from diagnosis to initiation was 2.4 months (**Table 1** and **Figure 2**).
- Initiation was more common among patients with systolic HF than among those with diastolic HF (**Figure 2**).
- Among patients who initiated sMRAs, 98.5% initiated spironolactone.

Table 1. Baseline Characteristics of the Study Cohort

	Study Cohort N = 422,133
Demographics	
Age at index (years), mean ± SD	67.2 ± 13.2
Sex, n (%)	
Female	190,683 (45.2%)
Male	224,649 (53.2%)
Unknown	6,801 (1.6%)
Race/ethnicity, n (%)	
White	270,625 (64.1%)
Black or African American	62,143 (14.7%)
Hispanic or Latino	30,767 (7.3%)
Asian or Pacific Islander	8,135 (1.9%)
Other/unknown	50,463 (12.0%)
Subtype of HF diagnosis at index, n (%)	
Systolic HF	258,918 (61.3%)
Diastolic HF only	98,463 (23.3%)
Unspecified or other HF	64,752 (15.3%)
Time from first HF diagnosis to sMRA initiation (months), median (IQR)	2.4 (0.3-14.6)
Selected comorbidities and CCI at baseline and index	
Hypertension	385,331 (91.3%)
Hyperlipidemia	318,467 (75.4%)
Ischemic heart disease	266,094 (63.0%)
T2D	185,812 (44.0%)
CKD	126,436 (30.0%)
Quan-CCI, mean ± SD	3.9 ± 2.1
Other guideline-directed medical therapy (GDMT) medication at index, n (%)	
RAAS inhibitors	301,513 (71.4%)
ACEis/ARBs	250,140 (59.3%)
ARNis	51,373 (12.2%)
Beta blockers	330,925 (78.4%)
SGLT2is	72,113 (17.1%)

Treatment patterns of sMRA

sMRA non-persistence was common and occurred rapidly after treatment initiation, reaching 60% by 3 years.

- Among sMRA initiators, the cumulative incidence of non-persistence was 40.5% at 12 months and 60.3% at 36 months (**Figure 3**). Non-persistence was driven primarily by discontinuation (97.5%).
- Non-persistence was common in both HF subtypes, with similar patterns observed across subtypes.
- Re-initiation of the index sMRA after discontinuation was modest, with cumulative incidence of 28.7% at 12 months and 39.7% at 36 months. Among patients who re-initiated index treatment, non-persistence was common and recurred rapidly, with cumulative incidence of 47.5% at 12 months and 69.2% at 36 months.

Safety outcomes associated with sMRA use

- During sMRA treatment, safety events accrued most rapidly during the first 12 months, with comparable patterns across HF subtypes.
- Clinically significant AKI occurred most frequently, with cumulative incidence of 19.6% at 12 months and 30.5% at 36 months, followed by clinically significant hypotension at 11.9% and 18.6% (**Figure 4**).
- The cumulative incidence of clinically significant hyperkalemia was 6.8% at 12 months and 11.1% at 36 months; corresponding estimates for diagnosed sexual side effects were 6.8% and 10.8%.

Predictors of sMRA non-persistence

Safety events during sMRA treatment were common and were strongly associated with subsequent non-persistence, particularly clinically significant hyperkalemia and AKI.

- Safety events during the sMRA treatment period were strongly associated with subsequent non-persistence: clinically significant hyperkalemia (HR: 1.64), clinically significant AKI (HR: 1.55), clinically significant hypotension (HR: 1.33), and diagnosed sexual side effects (HR: 1.19) were all associated with higher risk of non-persistence (all p-values <0.001) (**Figure 5**).
- Greater baseline GDMT use, reflected by a higher number of drug classes, was associated with better persistence (all p-values <0.001).

Figure 2. Time to sMRA Initiation Among Patients with MRA-Naïve HF Following First HF Diagnosis

	Overall	Diastolic HF	Systolic HF
Total patients with MRA-naïve HF	3,455,236	1,009,259	772,820
Number of patients who initiated sMRA, n (%)	435,504 (12.6%)	107,213 (10.6%)	186,253 (24.1%)
Cumulative incidence, % / number of events, n			
Month 12	9.6% / 313,345	7.6% / 71,595	20.9% / 154,069
Month 36	13.7% / 391,873	11.7% / 94,665	26.0% / 175,710
Month 96	21.0% / 435,353	16.4% / 105,761	31.1% / 184,984

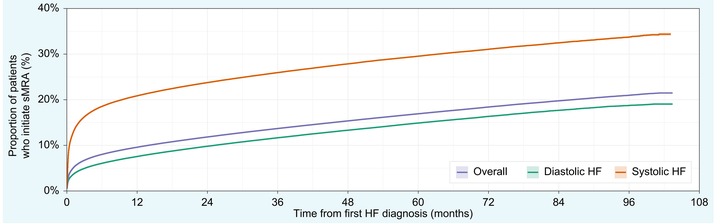


Figure 3. Time to Non-Persistence Following sMRA Initiation

	Overall	Diastolic HF	Systolic HF
Total patients in the study cohort	422,133	98,463	258,918
Number of patients with non-persistence, n (%)	196,765 (46.6%)	46,626 (47.4%)	116,789 (45.1%)
Median time (months) to non-persistence (95% CI)	19.8 (19.6, 20.0)	18.5 (18.2, 18.9)	21.5 (21.2, 21.8)
Cumulative incidence, % / number of events, n			
Month 12	40.5% / 150,367	41.8% / 36,251	38.9% / 88,130
Month 36	60.3% / 190,187	61.0% / 45,161	59.0% / 112,742
Month 96	71.1% / 196,765	69.5% / 46,568	68.2% / 116,609

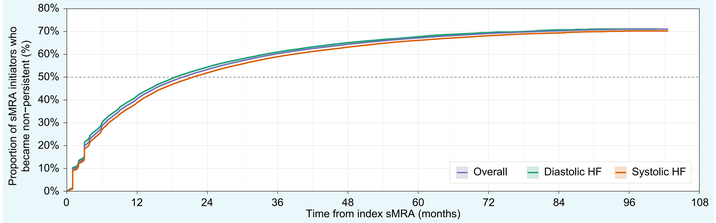


Figure 4. Time to First Safety Event Following sMRA Initiation

	Hyperkalemia	AKI	Hypotension	Sexual side effect
Total patients in the study cohort	422,133	422,133	422,133	422,133
Number of patients with an adverse event, n (%)	27,825 (6.6%)	79,109 (18.7%)	48,212 (11.4%)	26,520 (6.3%)
Cumulative incidence, % / number of events, n				
Month 12	6.8% / 21,690	19.6% / 64,290	11.9% / 38,651	6.8% / 20,914
Month 36	11.1% / 26,794	30.5% / 76,736	18.6% / 46,507	10.8% / 25,858
Month 96	14.2% / 27,824	38.8% / 79,109	24.1% / 48,212	12.4% / 26,519

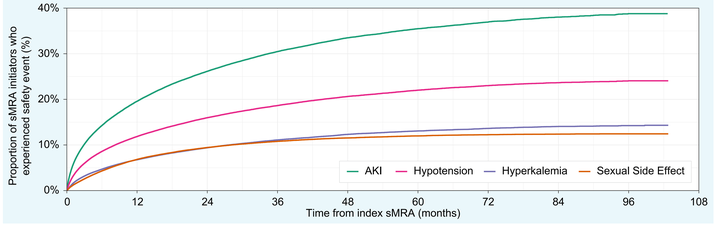
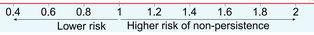


Figure 5. Forest Plot of Predictors of sMRA Non-Persistence Using a Cox Proportional Hazards Model

Covariates	HR (95% CI)	*P* value
Demographics		
Age at index (10 years)	0.98 (0.97−0.98)	<0.001*
Sex (ref: Female)		
Male	1.03 (1.02−1.04)	<0.001*
Race (ref: White)		
Black or African American	1.11 (1.10−1.13)	<0.001*
Hispanic or Latino	1.13 (1.11−1.15)	<0.001*
Asian or Pacific Islander	1.10 (1.07−1.14)	<0.001*
Other/Unknown	1.01 (0.99−1.02)	0.418
Region (ref: South)		
Midwest	0.91 (0.90−0.92)	<0.001*
Northeast	0.90 (0.89−0.91)	<0.001*
West	0.99 (0.98−1.01)	0.240
Insurance (ref: Commercial)		
Medicaid	1.26 (1.24−1.29)	<0.001*
Medicare	1.15 (1.13−1.17)	<0.001*
Multiple/Unknown	1.12 (1.09−1.16)	<0.001*
Subtype of HF diagnosis at index (ref: Diastolic only)		
Systolic HF	0.93 (0.92−0.94)	<0.001*
Unspecified or other HF	1.00 (0.99−1.02)	0.537
Care setting of HF at diagnosis (ref: OP)		
IP	1.06 (1.05−1.07)	<0.001*
ER	1.08 (1.06−1.10)	<0.001*
Index year (ref: 2017−2019)		
2020−2022	0.94 (0.93−0.95)	<0.001*
2023−2025	0.76 (0.75−0.77)	<0.001*
Treatment characteristics		
Number of GDMT classes at index (ref: 1)		
2	0.86 (0.85−0.88)	<0.001*
3	0.77 (0.76−0.78)	<0.001*
4	0.66 (0.64−0.67)	<0.001*
Other baseline medication		
Other HF−related medications	0.91 (0.90−0.92)	<0.001*
Other blood pressure−lowering medications	0.95 (0.95−0.96)	<0.001*
Lipid−lowering medications	0.90 (0.89−0.91)	<0.001*
Potassium binders	1.39 (1.27−1.52)	<0.001*
Comorbidities		
CKD	1.13 (1.12−1.15)	<0.001*
T2D	1.07 (1.06−1.08)	<0.001*
Atrial fibrillation	0.98 (0.97−0.99)	<0.001*
Ischemic heart disease	1.02 (1.01−1.03)	0.001*
Chronic obstructive pulmonary disease	1.04 (1.03−1.05)	<0.001*
Hypertension	1.04 (1.02−1.06)	<0.001*
Hyperlipidemia	1.00 (0.99−1.01)	0.809
Obesity/overweight	0.92 (0.91−0.93)	<0.001*
Cerebrovascular diseases	1.07 (1.05−1.08)	<0.001*
Peripheral artery diseases	1.04 (1.02−1.05)	<0.001*
Valvular heart disease	0.96 (0.95−0.97)	<0.001*
CCI	0.99 (0.99−0.99)	<0.001*
Time−varying safety outcomes after index		
Hyperkalemia	1.64 (1.60−1.68)	<0.001*
Hypotension	1.33 (1.31−1.36)	<0.001*
AKI	1.55 (1.52−1.57)	<0.001*
Sexual side effect	1.19 (1.16−1.21)	<0.001*



Conclusions

- **In this large real-world HF population, sMRA initiation after HF diagnosis was modest, and treatment persistence was limited.**
- **Safety events were common during sMRA treatment, and related tolerability issues may represent important barriers to sustained treatment, as these events were strongly associated with sMRA non-persistence.**
- **These findings highlight ongoing unmet needs for durable treatment options that help patients with HF remain on therapy while mitigating safety-related barriers, particularly as the HF treatment landscape expands to include an FDA-approved nsMRA for patients with left ventricular ejection fraction (LVEF) ≥40%.**

Limitations

- Claims data may misclassify or incompletely capture diagnoses, treatments, and outcomes. Pharmacy claims reflect dispensing rather than actual medication use, and inpatient sMRA use may be incompletely captured.
- Clinically significant hyperkalemia, AKI, and hypotension were identified using diagnosis codes from IP or ER encounters, which may capture more severe events and therefore underestimate milder, asymptomatic laboratory-defined events.
- HF subtype was defined by diagnosis codes rather than measured left ventricular ejection fraction.

References

1. Heidenreich PA, et al. *J Am Coll Cardiol.* 2022.
2. Pitt B, et al. *N Engl J Med.* 1999.
3. Jhund PS, et al. *Lancet.* 2024.
4. Chung EY, et al. *Cochrane Database Syst Rev.* 2020.
5. Zahir D, et al. *Eur J Heart Fail.* 2022.
6. Solomon SD, et al. *N Engl J Med.* 2024..

Disclosures

This study was funded by Bayer, which was involved in the study design, data interpretation, and poster preparation. M.A.L., A.A.M., Z.Z., A.K., J.E., M.F., and Y.W. are employees of Bayer, and K.A.B., A.W., T.W., T.M., S.R., and D.Y. are employees of Analysis Group, Inc., a paid consultant to Bayer for this study. C.J.B., O.V., J.W.O., and A.J.S. report research funding, consulting fees, and/or other financial relationships with Bayer and other pharmaceutical companies.

Abbreviations

ACEi, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCI, Charlson Comorbidity Index; CI, confidence interval; CIF, cumulative incidence function; CKD, chronic kidney disease; ER, emergency room; ESKD, end-stage kidney disease; GDMT, guideline-directed medical therapy; 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; IP, inpatient; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; nsMRA, non-steroidal mineralocorticoid receptor antagonist; OP, outpatient; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitors; sMRA, steroidal mineralocorticoid receptor antagonist; T2D, type 2 diabetes.

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