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ORIGINAL RESEARCH

Treatment Patterns, Adverse Events, and Clinical Outcomes with Steroidal Mineralocorticoid Receptor Antagonists: A Retrospective Analysis of Administrative Claims Data (RELICS)

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Purpose: This study aimed to describe the characteristics, treatment patterns, adverse events (AEs), and clinical outcomes of patients starting steroidal mineralocorticoid receptor antagonists (sMRAs) in real-world settings.

Methods: The RELICS study, complementing the survey-based RELICS-PS study, was a retrospective cohort study conducted using the Healthcare Integrated Research Database (HIRD®), a single-payer healthcare database with medical and pharmacy claims from health insurance plans across the United States. A cohort of adults initiating sMRAs from January 2016 to June 2021 was divided into six subgroups: three mutually exclusive heart failure (HF) subgroups, two mutually exclusive chronic kidney disease (CKD) subgroups, and "all other patients" subgroup, which included those without documented HF or CKD. Outcomes assessed from the first sMRA fill until death, health-plan disenrollment, or June 2022 (whichever came first) included analysis of treatment patterns, AEs, and clinical outcomes. Factors associated with sMRA discontinuation were evaluated with multivariate logistic regression.

Results: Of the 224,100 sMRA initiators identified, 76.4% did not have documented HF or CKD (ie, "all other patients" subgroup). This subgroup was younger and primarily female. Across all initiators, 72.3% were nonadherent, and 73.0% discontinued treatment within a median of 90 days of initiation. Of these discontinuers, 44.2% restarted treatment within a median of 91 days of discontinuation. Factors decreasing odds of discontinuation across most subgroups included a higher comorbidity burden, use of other cardiovascular medications, and cardiologist prescribing. These findings were consistent across subgroups. AEs and clinical outcomes varied across subgroups in line with baseline comorbidity profiles. Patients with a higher comorbidity burden, such as those with both CKD and T2D rather than CKD alone, experienced worse outcomes.

Conclusion: High rates of treatment discontinuation and subsequent restart were observed across all subgroups, implying fluctuating sMRA use. However, heightened cardiovascular risk may decrease the odds of discontinuation.

Keywords: steroidal mineralocorticoid receptor antagonists, treatment patterns, adverse events, clinical outcomes, real-world data, administrative claims

Introduction

Steroidal mineralocorticoid receptor antagonists (sMRAs), including spironolactone and eplerenone, are a class of medications primarily approved for managing various cardiovascular (CV) and endocrine conditions.[1–3] Spironolactone was the first available sMRA in the United States (US), approved in 1960.[2] Eplerenone was approved over four decades later, in 2002.[3] In the US, approved indications for sMRAs include primary hyperaldosteronism, heart failure (HF), hypertension, and edema in patients with cirrhosis or nephrotic syndrome.[2,3]

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Both spironolactone and eplerenone have been shown to have beneficial CV effects, including reducing CV-related hospitalization and all-cause mortality.[4–6] However, the use of sMRAs is linked with adverse drug reactions (ADRs) such as worsening renal function, hyperkalemia, and reactions impacting the reproductive system, such as male gynecomastia, breast tenderness, impotence, loss of libido, and amenorrhea.[6–10] The most common ADRs reported with the use of spironolactone, according to the US Food and Drug Administration (FDA) ADR Reporting System (1969–2018), were hyperkalemia, acute kidney injury (AKI), drug interaction, hyponatremia, dehydration, and hypotension.[9] This safety profile of sMRAs illustrates the necessity for careful patient monitoring to minimize potential risks and maximize therapeutic benefits.

As the landscape for treating CV conditions is continuously changing, it is vital to clearly understand sMRAs, including their use, adverse events (AEs), and discontinuation trends. To investigate these questions, two companion studies were conducted to better understand the use of sMRAs in a real-world setting. This retrospective cohort study, RELICS, was conducted using a large US claims database to gain deeper insight into the demographics, clinical characteristics, treatment patterns, AEs, and clinical outcomes of new users of sMRAs. The companion study, RELICS-PS, was conducted to describe sMRA treatment patterns and side effects from the patient perspective. The findings presented here from the claims study and in the companion short report on the survey study provide important insights for healthcare providers and policymakers to facilitate informed decision-making for the treatment of patients with CV disease.

Methods

Study Design and Data Source

The RELICS study was a retrospective cohort study using the Healthcare Integrated Research Database (HIRD®), a large, geographically diverse healthcare database containing administrative claims and integrated clinical data, for over 80 million people from commercial and Medicare Advantage health insurance plans in the Northeastern, South, Midwest, and Western regions of the US since 1 January 2006. sMRA initiators were identified from the HIRD during the intake period, defined as 1 January 2016 to 30 June 2021. The index date was defined as the date of the first fill of an sMRA. Two baseline periods were used in this study: the 12-month pre-index period, defined as the 12 months before the index date, and the full pre-index period, defined as any time before the index date going back to the earliest data available in the database (1 January 2006). The follow-up period was defined as the time between the index date and the date of health-plan disenrollment, death, or the end of the study period (30 June 2022), whichever came first. This study was reviewed and approved by the Western Institutional Review Board-Copernicus Group (WCG® IRB). This study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided informed consent prior to enrollment.

Study Population and Cohorts

Patients were included in the analysis if they were sMRA initiators (ie, ≥1 pharmacy claims for either spironolactone or eplerenone during the intake period with no claims for either sMRA during the full pre-index period), were ≥18 years old as of the index date, and were continuously enrolled in the health plan during the 12-month pre-index period.

From all eligible patients, six subgroups were created based on comorbidities identified through ICD-9/10-CM diagnosis codes in the medical claims during the full pre-index period: three mutually exclusive HF subgroups (HF with preserved ejection fraction [HFpEF], HF with reduced ejection fraction [HFrEF], and undetermined HF [undHF]); two mutually exclusive chronic kidney disease (CKD) subgroups (CKD with type 2 diabetes [T2D] and nondiabetic CKD [ndCKD]); and one subgroup comprising all remaining eligible patients who did not have documented HF or CKD ("all other patients"). While all HF subgroups and both CKD subgroups were mutually exclusive, patients may have been included in both a HF and a CKD subgroup if they had both conditions. (Supplementary Tables 1 and 2 for additional details on subgroup definitions).

Variables and Analyses

Demographics and Clinical Characteristics

Demographics were evaluated on the index date. Baseline comorbidities were assessed over the full pre-index period by the presence of ≥1 medical claim with a diagnosis for the comorbidity of interest. This full pre-index period was used to ensure the capture of chronic conditions across all available data. Baseline medication use was assessed over the 12-month pre-index period by the presence of ≥1 pharmacy claim for the medication of interest. This 12-month pre-index period was used to ensure the capture of medication use most proximate to sMRA initiation.

Treatment Patterns

Steroidal MRA treatment patterns were evaluated over the follow-up period, including the number of sMRA fills, dose change, nonadherence, and discontinuation. Dose change was defined as a dose increase or decrease from the index dose. Nonadherence was evaluated based on the proportion of days covered (PDC), calculated as the number of days with available medication divided by the number of days in the follow-up period, regardless of discontinuation. Patients with <80% PDC were considered nonadherent. Discontinuation was defined as no sMRA refill within two times the days' supply on the previous sMRA fill (eg, 60 days without a fill if the last prescription had a 30-day supply). Multivariable logistic regression was used to explore the predictors of sMRA discontinuation in sMRA initiators overall and by subgroup.

Adverse Events and Clinical Outcomes

AEs were evaluated during the follow-up period by the presence of ≥1 medical claim with a diagnosis for: (a) hyperkalemia, (b) syncope/hypotension, (c) gynecomastia, or (d) amenorrhea. Worsening renal function as an AE during the following up period was defined as (a) ≥1 medical claim with a diagnosis of CKD during the follow-up period, with no claim with a diagnosis of CKD during the full pre-index period, (b) ≥1 medical claim for dialysis during the follow-up period, with no claim for dialysis during the full pre-index period, or (c) ≥1 medical claim during the follow-up period with a diagnosis of an increasing stage of CKD compared to that observed during the full pre-index period. Clinical outcomes were also evaluated during the follow-up period by the presence of ≥1 medical claim with a diagnosis of: (a) end-stage renal disease, (b) acute myocardial infarction, (c) ischemic or hemorrhagic stroke, (d) peripheral arterial disease, (e) AKI, or (f) HF hospitalization. Incidence rates (IRs) per 100 person-years were calculated for each AE and clinical outcome.

Results

Study Population

This study identified 224,100 sMRA initiators. There were three mutually exclusive HF subgroups (HFpEF, 8,553; HFrEF, 19,636; undHF, 20,336), two mutually exclusive CKD subgroups (CKD with T2D, 11,336; ndCKD, 10,134), and one subgroup of patients without HF or CKD ("all other patients", 171,374).

Baseline Demographics and Clinical Characteristics

The mean (standard deviation) age across all sMRA initiators was 46.0 (18.60) years. The mean age of patients in the HF and CKD subgroups was higher (HFpEF, 67.9; HFrEF, 61.0; undHF, 66.6; CKD with T2D, 66.3; ndCKD, 63.8) than the average, whereas the mean age of those in the "all other patients" subgroup was lower (40.6). The majority of sMRA initiators (75.5%) were female. A higher proportion of males was observed in the HFrEF (63.8%), undHF (59.0%), CKD and T2D (57.1%), and ndCKD (52.4%) subgroups, while a lower proportion of males was observed in the HFpEF subgroup (42.6%). The subgroup with the lowest proportion of male patients was the "all other patients" subgroup (14.7%) (Table 1).

Across all sMRA initiators, the most common comorbidities were hypertension (49.0%), dyslipidemia (45.0%), and obesity (33.1%). Besides the subgroup-defining comorbidities, hypertension was the most common condition in the HF and CKD subgroups (HFpEF, 95.8%; HFrEF, 88.5%; undHF, 94.9%; CKD with T2D, 98.7%; ndCKD, 92.9%). The most common comorbidity in the "all other patients" subgroup was acne (39.4%). Across all sMRA initiators, the most common medications of

Table 1 Demographic and Clinical Characteristics

Variable	All Eligible Patients	HFpEF	HFrEF	UndHF	CKD with T2D	NdCKD	All Other Patients
N[a]	224,100	8,553	19,636	20,336	11,336	10,134	171,374
Demographics							
Age, mean (SD)	46.0 (18.60)	67.9 (13.48)	61.0 (13.83)	66.6 (14.23)	66.3 (12.86)	63.8 (16.66)	40.6 (16.18)
Female, %	75.5	57.4	36.2	41.0	42.9	47.6	85.3
White, %	77	78	76	76	75	76	77
Insurance type, %							
Commercial	90.1	63.3	79.0	64.1	64.1	73.0	95.9
Medicare Advantage	9.9	36.7	21.0	35.9	35.9	27.0	4.1
Comorbidities over full pre-index period, %							
Acne	30.9	2.6	3.4	2.3	2.5	5.3	39.4
CKD[b]	11.9	36.0	22.8	41.0	87.6	82.2	2.5
Dyslipidemia	45.0	85.0	75.4	84.0	91.5	73.5	34.0
Hemorrhagic stroke	0.6	1.7	1.4	2.0	1.9	1.9	0.3
Hepatic failure	2.0	3.3	2.9	3.4	4.6	5.3	1.4
HF[b]	19.8	81.0	91.0	96.6	52.2	52.2	1.9
Hyperkalemia	3.2	9.8	6.1	12.4	14.8	10.8	1.3
Hypertension	49.0	95.8	88.5	94.9	98.7	92.9	35.6
Ischemic stroke/TIA	6.5	21.1	13.8	22.3	21.4	17.4	3.1
MI	8.9	21.2	33.7	40.9	29.3	21.8	2.3
Nephrotic syndrome	0.4	1.3	0.5	1.1	2.6	3.0	0.1
Obesity	33.1	59.3	43.9	50.6	59.8	39.0	28.0
Medication use over 12-month pre-index period, %							
RAS inhibitors	30.2	63.4	62.1	64.3	74.0	58.7	19.8
ACE inhibitors	16.9	34.0	40.3	40.8	41.6	32.3	10.3
ARB antagonists	15.5	33.5	26.1	28.4	38.0	30.7	10.8
Beta-blockers	27.6	64.5	64.5	73.9	70.0	58.6	15.8
Calcium channel blockers	19.2	48.3	28.3	34.4	49.4	42.7	13.6
Thiazide diuretics	18.0	35.9	22.3	24.6	36.9	31.5	14.8
Loop diuretics	16.4	61.8	41.0	66.4	55.8	44.4	5.8
Statins	22.8	56.1	49.3	58.5	67.4	42.8	13.3
NSAIDs	21.8	24.3	20.4	18.7	20.0	19.4	22.1
Potassium binders	0.1	0.4	0.2	0.4	0.7	0.3	<0.1

Notes: [a]Numbers across subgroups may sum to more than 100% as it is possible for patients to have both HF and CKD simultaneously and therefore be included in both a HF subgroup and a CKD subgroup. However, all HF subgroups are mutually exclusive between them, as are all CKD subgroups. [b]CKD and HF are not 100% across baseline period in respective subgroups. Time periods used to create subgroups (full pre-index to 6 months post-index) and those used to create variables (full pre-index only) differ.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; ndCKD, nondiabetic chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin–angiotensin system; SD, standard deviation; TIA, transient ischemic attack; T2D, type 2 diabetes; undHF, undetermined heart failure.

interest were beta-blockers (27.6%), statins (22.8%), and nonsteroidal anti-inflammatory drugs (NSAIDs) (21.8%). Beta-blockers were the most common medication in the HF and CKD subgroups (HFpEF, 64.5%; HFrEF, 64.5%; undHF, 73.9%; CKD with T2D, 70.0%; ndCKD, 58.6%). The most common medication in the "all other patients" subgroup was NSAIDs (22.1%) (Table 1 and Supplementary Table 3).

Treatment Patterns

Overall, 72.3% of patients were nonadherent to sMRAs. The level of nonadherence varied across subgroups (HFpEF, 62.3%; HFrEF, 58.1%; undHF, 60.7%; CKD with T2D, 65.2%; ndCKD, 65.2%; "all other patients", 75.9%). Dose changes from the index dose were observed in 23.2% of all sMRA initiators. In general, a dose increase (16.0%) was more common than a decrease (7.2%) (Table 2). Dose change did not vary appreciably among subgroups.

Treatment discontinuation was observed in 73.0% of patients and occurred after a median (interquartile range) of 90 (30–203) days (Table 2). Compared with all initiators, discontinuation was observed less frequently in HF and CKD subgroups (HFpEF, 64.2%; HFrEF, 61.0%; undHF, 62.3%; CKD and T2D, 65.6%; ndCKD, 65.8%), and more frequently in "all other patients" (76.3%). Time to discontinuation did not vary appreciably by subgroup. Most discontinuers did so within the first year (63.7%) of treatment, and 44.2% restarted after a median (interquartile range) of 91 (46–185) days. The proportion of patients restarting treatment and the time to restart was similar across subgroups (42.3–46.2%).

Predictors of Treatment Discontinuation

Overall, no specific factors were consistently associated with increased odds of discontinuation across all sMRA initiators (Figure 1). This finding was consistent across subgroups. However, increased comorbidity burden, use of other CV medications, and cardiologist prescribers were associated with lower odds of discontinuation across most subgroups (Supplementary Table 4).

Adverse Events

Worsening renal function was the most common AE across all sMRA initiators, with an IR per 100 person-years of 6.8. Worsening renal function was the most common AE in the HF and CKD subgroups (HFpEF, 20.8; HFrEF, 12.2; undHF, 19.3; CKD with T2D, 29.9; ndCKD, 34.8). Amenorrhea was the most common AE in the "all other patients" subgroup (6.2). In line with the underlying comorbidity profile, syncope or hypotension was the second most common AE in the HF subgroups (HFpEF, 13.4; HFrEF, 11.1; undHF, 17.3), whereas hyperkalemia was the second most common AE in the

Table 2 Treatment Patterns Among All sMRA Initiators and Subgroups

Variable	All Eligible Patients	HFpEF	HFrEF	UndHF	CKD with T2D	NdCKD	All Other Patients
Days of follow-up, median (IQR)	655 (353–1,158)	592 (295–1,058)	640 (317–1,158)	565 (260–1,034)	570 (272–1,026)	584 (263–1,077)	669 (370–1,176)
Dose change, %	23.2	22.8	21.6	22.0	22.9	22.8	23.6
Dose increase, %	16.0	12.5	11.1	11.5	12.7	13.1	17.2
Dose decrease, %	7.2	10.4	10.6	10.5	10.2	9.7	6.3
Number of sMRA fills, median (IQR)	4 (2–10)	5 (2–11)	6 (2–12)	5 (2–11)	5 (2–10)	4 (2–10)	4 (2–9)
Exactly one sMRA fill, %	22.6	19.4	16.3	18.5	19.8	21.2	24.0
Nonadherent, %	72.3	62.3	58.1	60.7	65.2	65.2	75.9
Discontinuation, %	73.0	64.2	61.0	62.3	65.6	65.8	76.3
Days to discontinuation, median (IQR)	90 (30–203)	90 (30–245)	113 (30–299)	95 (30–266)	90 (30–244)	90 (30–221)	88 (30–188)
Restart after discontinuation, %	44.2	43.5	46.2	45.8	42.4	42.3	43.9
Days to restart, median (IQR)	91 (46–185)	96 (49–182)	95 (48–183)	95 (49–181)	96 (48–181)	93 (47–177)	88 (46–186)

Abbreviations: CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; ndCKD, nondiabetic chronic kidney disease; sMRA, steroidal mineralocorticoid receptor antagonist; T2D, type 2 diabetes; undHF, undetermined heart failure.

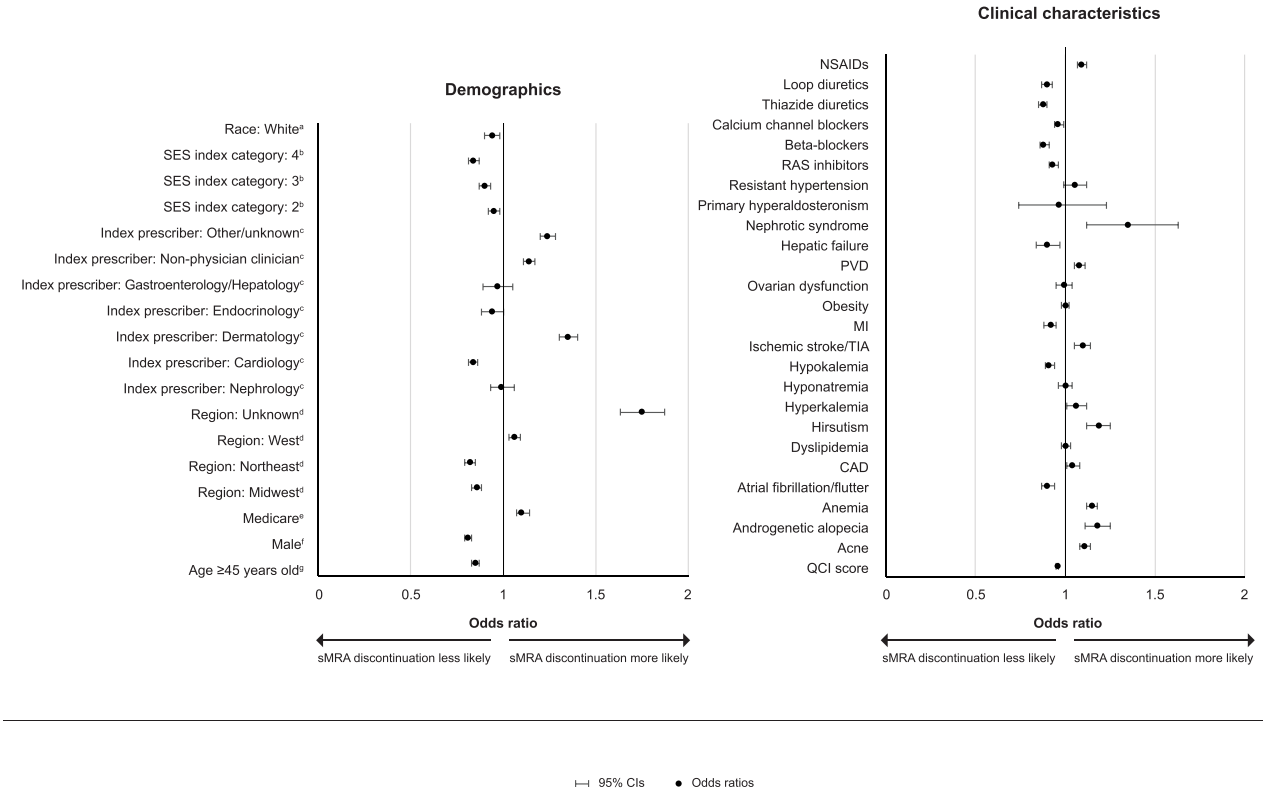

Figure 1 Logistic regression model exploring predictors of sMRA discontinuation among all new sMRA users.
Notes: [a]Reference: Non-white; [b]Reference: SES index category 1; [c]Reference: Primary care provider; [d]Reference: South; [e]Reference: Commercial; [f]Reference: Female; [g]Reference: <45 years old.
Abbreviations: CAD, coronary artery disease; CI, confidence interval; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PVD, peripheral vascular disease; QCI, Quan–Charlson Comorbidity Index; RAS, renin–angiotensin system; SES, socioeconomic status; sMRA, steroidal mineralocorticoid receptor antagonist; TIA, transient ischemic attack.

CKD subgroups (CKD with T2D, 19.5; ndCKD, 14.3). Male gynecomastia was the least commonly documented AE across all subgroups, with an IR per 100 person-years of 1.0 (Figure 2).

Clinical Outcomes

Across all sMRA initiators, AKI was the most common poor clinical outcome, with an IR per 100 person-years of 5.4. In alignment with underlying comorbidities of CKD, AKI was the most common clinical outcome in the CKD subgroups (CKD with T2D, 29.2; ndCKD, 26.2). AKI was also the most common clinical outcome in the "all other patients" subgroup, with an IR per 100 person-years of 2.4. Similarly, in alignment with underlying comorbidities of HF, HF hospitalization was the most common clinical outcome in the HF subgroups (HFpEF, 36.2; HFrEF, 25.8; undHF, 41.6) (Figure 3).

Discussion

This real-world study analyzed a large cohort of sMRA initiators, including individuals with commercial and Medicare Advantage insurance (n = 224,100), to provide contemporary insights into patient demographics, clinical characteristics, sMRA treatment patterns, and AEs.

To identify patients with conditions relevant to labeled indications, all new initiators were stratified into HF and CKD subgroups (with CKD being a common comorbidity in patients with labeled indications). However, over 75% of all sMRA initiators had neither HF nor CKD. These patients were categorized in the "all other patients" subgroup and appeared to differ substantially from the HF and CKD subgroups. By comparison, the "all other patients" subgroup was, on average, younger, had a higher proportion of females, and a lower comorbidity burden, including comorbidities that are a labeled indication for sMRA use. Previous literature indicates that, beyond their label indications, sMRAs have long

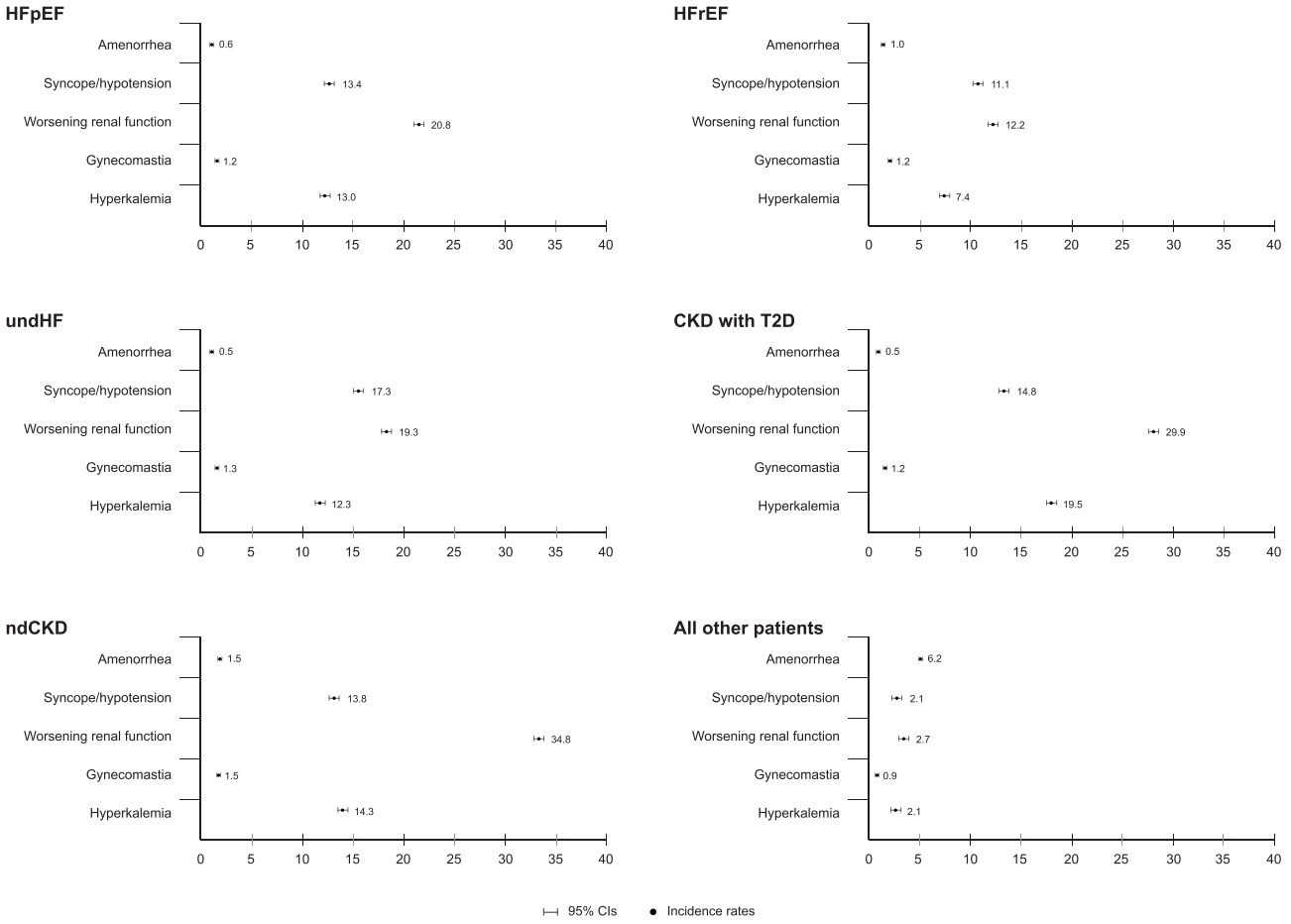

Figure 2 Incidence rates per 100 person-years of potential AEs across new sMRA user subgroups.
Abbreviations: AE, adverse event; CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ndCKD, nondiabetic chronic kidney disease; sMRA, steroidal mineralocorticoid receptor antagonist; T2D, type 2 diabetes; undHF, undetermined heart failure.

been used for their androgen-modulating benefits to treat various dermatological conditions such as acne, female hair loss, hidradenitis suppurativa, and hirsutism.[11–13] Consistent with this evidence, we found that acne was the most common comorbidity in the "all other patients" subgroup. This finding, and the size of the "all other patients" subgroup, suggests substantial sMRA use outside of the main indications in the US.

Despite potential differences in the reasons for sMRA use (ie, for labeled vs non-labeled indication), high rates of discontinuation and restart were observed across all subgroups. Other studies have also reported high rates of sMRA treatment flux.[8,14] A single-center retrospective cohort study in Sweden on patients with HFrEF between 2010 and 2018 showed that approximately 50% of them discontinued sMRA treatment, with 42% of discontinuers restarting therapy during the study period.[8] High discontinuation rates among sMRA users were also observed in a multinational real-world study in Sweden, the UK, and the US, although the reported discontinuation rates (~40%) were lower than those observed in the RELICS study.[14] Cross-study differences in discontinuation rates may be associated with context, population, and study design variations. However, this evidence suggests an appreciable amount of flux in sMRA treatment, with patients regularly interrupting and restarting treatment, regardless of the clinical reasons behind treatment initiation.

The established literature highlights that the factors contributing to sMRA discontinuation are complex. A study conducted in the Swedish population suggests that hyperkalemia (a common AE), low estimated glomerular filtration rate, low systolic blood pressure, high left ventricular ejection fraction, and high comorbidity burden are potentially important predictors of treatment discontinuation or interruption.[15] Additionally, our companion survey study, RELICS-

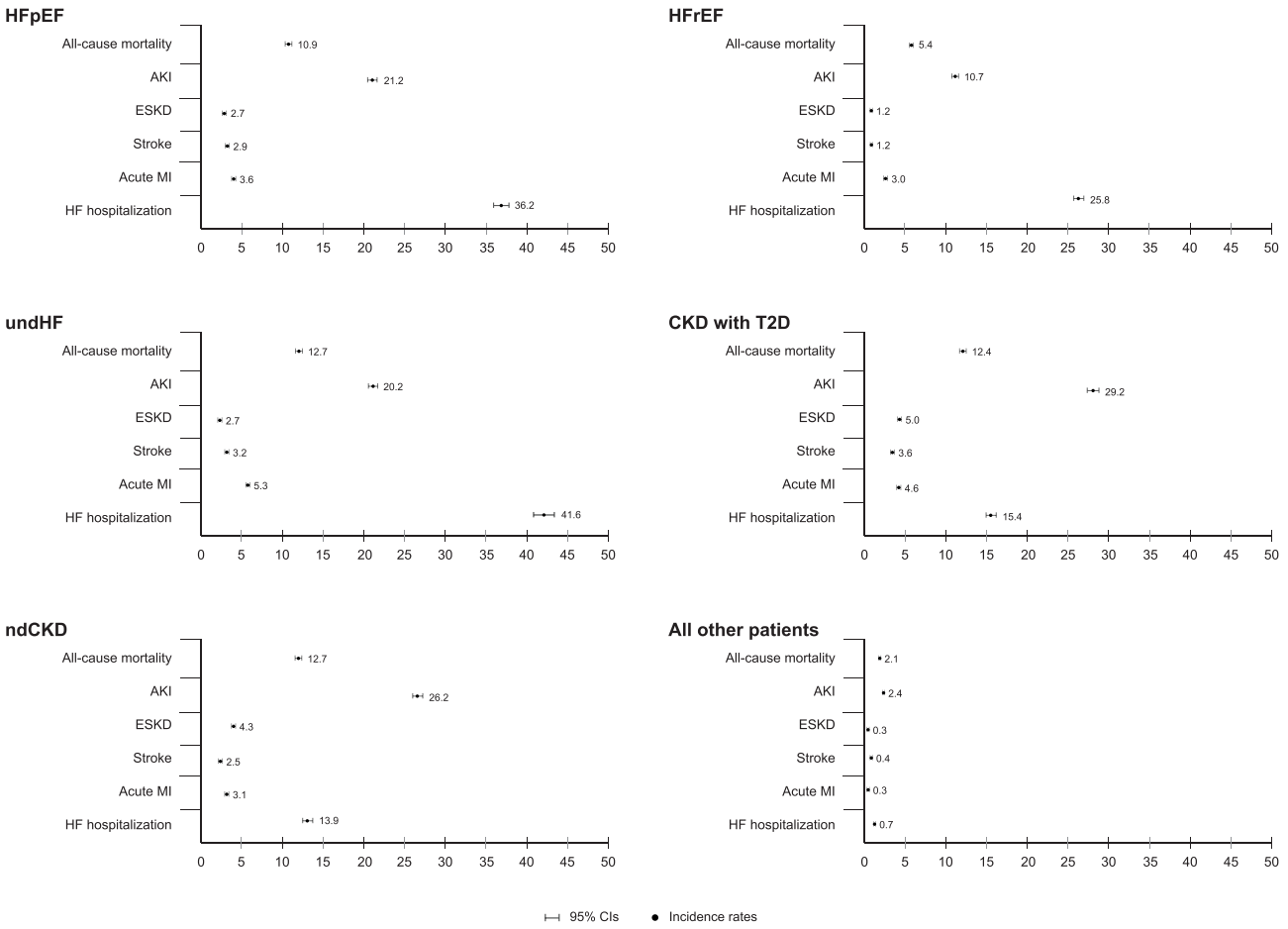

Figure 3 Incidence rates per 100 person-years of clinical outcomes across new sMRA user subgroups.
Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; ESKD, end-stage kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; ndCKD, nondiabetic chronic kidney disease; sMRA, steroidal mineralocorticoid receptor antagonist; T2D, type 2 diabetes; undHF, undetermined heart failure.

PS, found that healthcare-provider recommendations strongly influence discontinuation behavior. In RELICS, no specific demographic or clinical characteristics were associated with increased odds of sMRA discontinuation in any subgroups. Interestingly, higher comorbidity burden, use of CV medications, and being prescribed by a cardiologist rather than a primary care physician were associated with decreased odds of sMRA discontinuation in most subgroups. This finding suggests that patients with higher CV risks may be less likely to stop treatment.

In this study, the incidence of AEs and clinical outcomes varied among subgroups and followed the expected trends, given the underlying comorbidities defining the subgroups. Male gynecomastia was consistently the least common AE reported across all subgroups. Conversely, our findings from the companion survey study found symptoms of male gynecomastia to be the most reported sMRA-associated AE. This finding highlights a potential mismatch between what is documented in administrative claims and in self-reported data. On the other hand, hyperkalemia was one of the most prevalent AEs in the HF and CKD subgroups, which is consistent with previously published literature.[7,8,16] The relatively higher incidence of AEs among patients with HF or CKD suggests that the use of sMRA in these patients may carry an increased risk of AEs.

Considering the introduction of finerenone, a non-steroidal MRA with proven cardio-renal benefits, it will be important to evaluate the impact of this on sMRAs use in a real-world setting.[17] While the present study revealed substantial potential off-label use of sMRAs, future utilization trends may shift as clinicians and patients become more aware of finerenone's clinical profile. As finerenone is integrated into clinical practice, it is crucial to monitor real-world

MRA utilization overall to understand changing treatment patterns. These investigations are essential for optimizing therapeutic strategies and improving patient outcomes in the evolving field of cardio-renal care.

The study findings should be interpreted in the context of potential limitations. First, the study relied on data from commercial and Medicare Advantage insurance plans, which might limit the generalizability of the results to the broader US population not covered by these insurance plans. Additionally, in a claims database, we cannot exclude medical-care coding inaccuracies, both by omission and commission, which could introduce misclassification errors in our descriptive results. Factors such as the use of medication samples, medications that had prescriptions filled but were not consumed, unreported health conditions in the administrative billing data, and inadequate capture of confounding variables in a claims database may also limit results. Finally, the study was not designed to establish causality or statistically compare the subgroups. Thus, it is not possible to ascertain from this study whether the differences in AEs observed across subgroups were due to variations in sMRA use or whether they were linked to the decision to discontinue the medication. Further research is warranted to address these limitations and provide a more comprehensive understanding of sMRA-associated AEs to better inform clinical decision-making and optimize related patient-care strategies.

Conclusion

These findings underscore the need for personalized patient management strategies to effectively navigate the complexities associated with sMRA treatment. The significant proportion of treatment discontinuation and subsequent restarts points to an appreciable amount of flux in sMRA use. Although demographic or baseline clinical factors consistently associated with increased odds of sMRA discontinuation were not identified across the different subgroups, increased CV risk appeared to be associated with increased odds of remaining on treatment in most subgroups. Incidence of AE varied by subgroup, and their incidence aligned with patients' diverse comorbidity risk profiles. Finally, the large proportion of patients initiating sMRA treatment without observed diagnoses of label indications suggests that sMRAs are used for a broad spectrum of conditions. These insights highlight the critical role of real-world data studies in providing valuable information to guide decision making and improve patient care. Continuous monitoring and thorough analysis of real-world data are essential for informing evidence-based clinical practice, refining therapeutic strategies, and delivering better healthcare across various settings.

Abbreviations

ACE, angiotensin-converting enzyme; ADR, adverse drug reaction; AE, adverse event; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; ESKD, end-stage kidney disease; FDA, United States Food and Drug Administration; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIRD, Healthcare Integrated Research Database; IQR, interquartile range; IR, incidence rate; MI, myocardial infarction; ndCKD, nondiabetic chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drug; PDC, proportion of days covered; PPO, preferred provider organization; PVD, peripheral vascular disease; QCI, Quan–Charlson Comorbidity Index; RAS, renin–angiotensin system; SD, standard deviation; SES, socio-economic status; sMRA, steroidal mineralocorticoid receptor antagonists; T2D, type 2 diabetes; TIA, transient ischemic attack; undHF, undetermined heart failure; US, United States.

Data Sharing Statement

The data sets generated during and/or analyzed during the current study are not publicly available due to contractual obligations with the data sources.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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