# Steroidal mineralocorticoid receptor antagonist treatment patterns and predictors of discontinuation

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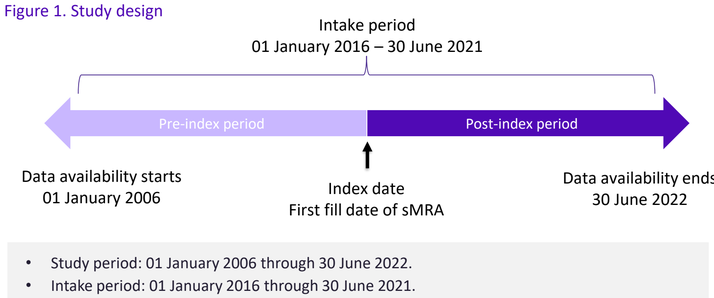
## Background and objectives

- Prior research suggests that steroidal mineralocorticoid receptor antagonists (sMRAs), including spironolactone and eplerenone, have beneficial effects on cardiovascular (CV) outcomes and reduce all-cause mortality, specifically in patients with heart failure (HF).
- While effective at preventing poor clinical outcomes, sMRAs have been associated with a range of adverse drug reactions (ADRs).
- This study aimed to explore possible ADRs, sMRA treatment patterns, and predictors of discontinuation among new users of sMRAs in a US commercially insured and Medicare Advantage population.

## Methods

- This retrospective observational cohort study used the Healthcare Integrated Research Database (HIRD®), a geographically diverse repository of medical and pharmacy claims representing over 60 million lives across the US, to identify adults who initiated sMRAs between 01 January 2016 and 30 June 2021 with at least 12 months of continuous health plan enrollment before initiation (Figure 1).

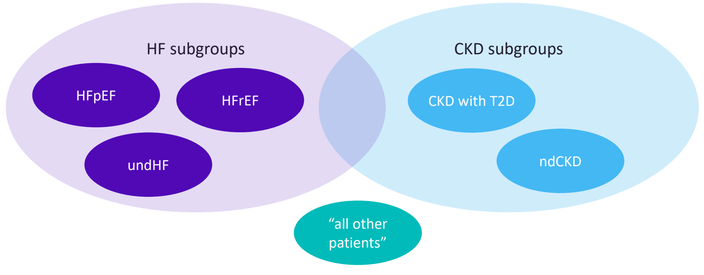
Figure 1. Study design




- Study period: 01 January 2006 through 30 June 2022.
- Intake period: 01 January 2016 through 30 June 2021.
- Index date: The date of the earliest observed fill date for sMRA during the intake period.
- 12-month pre-index period: 12 months prior to index date.
- Full pre-index period: Any time prior to index date going back to 01 January 2006.
- Full post-index period: Index date through the end of the study period, disenrollment, or death (whichever comes first).

- Six subgroups were identified based on comorbidities identified during the full pre-index period to six months post-index:
  - Three mutually exclusive HF subgroups (HF with preserved ejection fraction [HFpEF], HF with reduced ejection fraction [HFrEF], undetermined HF [undHF])
  - Two mutually exclusive chronic kidney disease (CKD) subgroups (CKD with type 2 diabetes [T2D], non-diabetic CKD [ndCKD])
  - One subgroup of the remaining patients without HF or CKD (Figure 2).

Figure 2. Identification of subgroups




- Demographics were described on index. Baseline comorbidities were described over the full pre-index period. Baseline medication use was described over the 12-month pre-index period. Possible ADRs and sMRA treatment patterns, including discontinuation (i.e., no refill within two prescription cycles), were described over the full post-index period.
- Multivariate logistic regression modeling was used to explore predictors of discontinuation.

## Results

- HF and CKD were not identified in the majority (76%) of new sMRA users. This "all other patients" subgroup was younger, more female, and had a lower comorbidity burden than the HF and CKD subgroups (Table 1).
- The incidence rate (IR) per 100 person-years of possible ARDs across all new sMRA users were 0.97 (gynecomastia), 4.42 (hyperkalemia), 4.70 (syncope/hypotension), 4.98 (menorrhagia or breakthrough bleeding), and 6.81 (worsening of renal function). IRs for possible ADRs varied across subgroups (Figure 3).
- Patients with lower CV risk (i.e., "all other patients" subgroup) were more likely to discontinue, while those with higher CV risks (i.e., CKD and HF subgroups) were less likely to discontinue (Table 1). Most discontinuers (87%) do so within one year of treatment initiation.
- No specific factors were consistently associated with increased odds of sMRA discontinuation. However, increased comorbidity burden, use of other CV medications, and cardiologist prescribers significantly decreased the odds of discontinuation across most subgroups (Figure 4).

Table 1. Demographics, baseline clinical characteristics, and treatment patterns

| | All eligible | HFpEF | HFrEF | undHF | CKD with T2D | ndCKD | "all other patients" |
|---|---|---|---|---|---|---|---|
| N | 224,100 | 8,553 | 19,636 | 20,336 | 11,336 | 10,134 | 171,374 |
| Duration of full post-index period | | | | | | | |
| Mean (SD) | 793.8 (576.38) | 725.6 (548.95) | 783.4 (587.11) | 707.4 (555.42) | 706.7 (547.85) | 729.0 (573.92) | 807.5 (576.98) |
| Age in years | | | | | | | |
| 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) |
| Sex, % | | | | | | | |
| Male | 25% | 43% | 64% | 59% | 57% | 52% | 15% |
| Female | 75% | 57% | 36% | 41% | 43% | 48% | 85% |
| Payor, % | | | | | | | |
| Commercial | 90% | 63% | 79% | 64% | 64% | 73% | 96% |
| Medicare Advantage | 10% | 37% | 31% | 36% | 36% | 27% | 4% |
| Quan-Charlson Comorbidity Index score (0-24) | | | | | | | |
| Mean (SD) | 1.7 (2.37) | 4.5 (2.63) | 3.8 (2.27) | 4.7 (2.43) | 4.9 (2.65) | 3.9 (2.59) | 0.9 (1.72) |
| Treatment patterns | | | | | | | |
| Dose increase, % | 16% | 13% | 11% | 12% | 13% | 13% | 17% |
| Dose decrease, % | 7% | 10% | 11% | 11% | 10% | 10% | 6% |
| Time to dose change, median days | 249 | 244 | 264 | 246 | 233 | 231 | 248 |
| Discontinue [full post-index period], % | 73% | 64% | 61% | 62% | 66% | 66% | 76% |
| Discontinuers restarting treatment, % | 44% | 44% | 46% | 46% | 42% | 42% | 44% |
| Time to restart, median days | 91 | 90 | 113 | 95 | 90 | 90 | 88 |

Figure 3. Incidence rates per 100-person years of possible adverse drug reactions

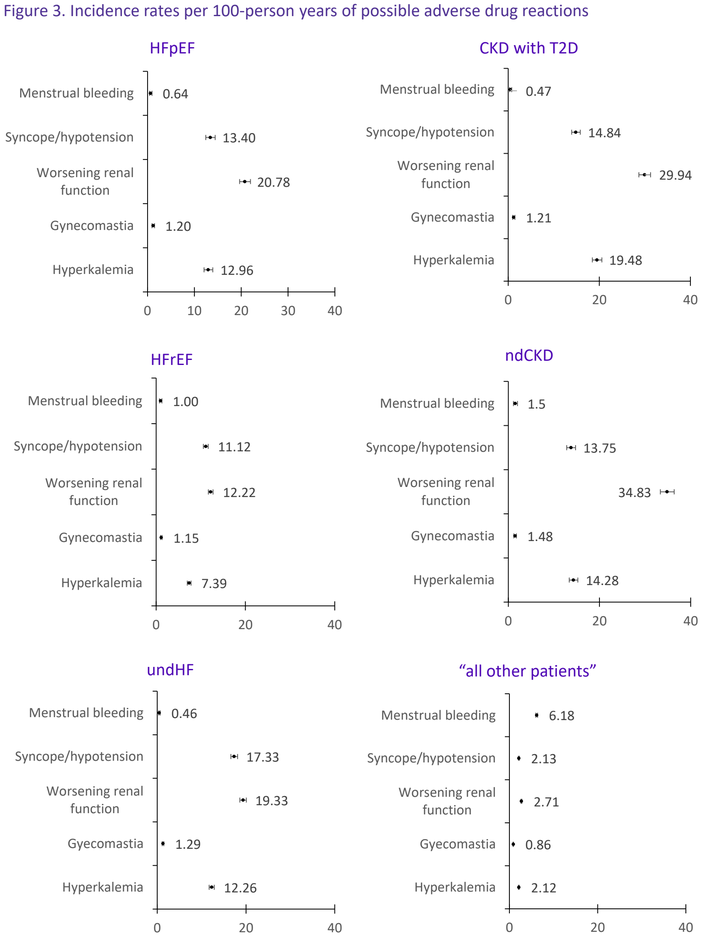



Figure 4. Logistic regression model predicting discontinuation in all new users of sMRAs




## Conclusions

- IR of possible ADRs vary across subgroups but follow expected trends given underlying comorbidities. It is not feasible to determine from this study whether these differences are attributable to differences in sMRA use or to establish a link between these possible ADRs and discontinuation.
- The high proportion of patients discontinuing (73%) and restarting (44%) sMRA treatment suggests an appreciable amount of flux in medication use, with patients regularly restarting treatment. The majority of discontinuation (87%) occurs within the first year of treatment.
- No demographic or clinical characteristic consistently predicted discontinuation. This finding indicates that no single group has a disproportionate burden of discontinuation; however, results suggest that those with higher CV risks are less likely to stop treatment.

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