Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists

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Background	Concerns for hyperkalaemia limit the use of mineralocorticoid receptor antagonists (MRAs). The frequency of MRA-associated hyperkalaemia in real-world settings and the extent of subsequent MRA discontinuation are poorly quantified.
Methods and results	Observational study including all Stockholm citizens initiating MRA therapy during 2007−2010. Hyperkalaemias were identified from all potassium (K^+) measurements in healthcare. MRA treatment lengths and dosages were obtained from complete collection of pharmacy dispensations. We assessed the 1-year incidence and clinical hyperkalaemia predictors, and quantified drug prescription changes after an episode of hyperkalaemia. Overall, 13 726 new users of MRA were included, with median age of 73 years, 53% women and median plasma K^+ of 3.9 mmol/L. Within a year, 18.5% experienced at least one detected hyperkalaemia ($K^+ > 5.0$ mmol/L), the majority within the first 3 monthsnthsnthsnthsnths of therapy. As a comparison, hyperkalaemia was detected in 6.4% of propensity-matched new beta-blocker users. Chronic kidney disease (CKD), older age, male sex, heart failure, peripheral vascular disease, diabetes and concomitant use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and diuretics were associated with increased hyperkalaemia risk. After hyperkalaemia, 47% discontinued MRA and only 10% reduced the prescribed dose. Discontinuation rates were higher after moderate/severe ($K^+ > 5.5$ mmol/L) and early in therapy (<3 months from initiation) hyperkalaemias. CKD participants carried the highest risk of MRA discontinuation in adjusted analyses. When MRA was discontinued, most patients (76%) were not reintroduced to therapy during the subsequent year.
Conclusion	Among real-world adults initiating MRA therapy, hyperkalaemia was very common and frequently followed by therapy interruption, especially among participants with CKD.
Keywords	Renin−angiotensin−aldosterone system inhibitors • Adverse drug events • Heart failure • Spironolactone

Introduction

Mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, are recommended by hypertension and heart failure clinical guidelines[1−4] owing to their capacity to lower blood pressure and to reduce the risk of cardiovascular complications and mortality in large randomized, placebo-controlled trials.[5−9] However, MRAs may induce hyperkalaemia, and fear of hyperkalaemia likely limits their use.

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Randomized controlled trials of MRAs report rates of hyperkalaemia that may not reflect the heterogeneous reality of clinical practice.[10] 'Real-world' observational studies show suboptimal MRA use, dose titration and poor clinical follow-up[11−13] that may increase hyperkalaemia risk. Current management of hyperkalaemia is most often centred on eliminating modifiable causes, e.g. lowering dietary potassium (K^+) intake, and/or discontinuing or lowering the dose of hyperkalaemia-inducing medications.[14] Some of these measures involve therapeutic compromises, in that the cessation of MRAs deprives patients of their beneficial cardiovascular effects. Understanding the extent of this practice and identifying patients at risk of MRA discontinuation is clinically important. However, rates of MRA discontinuation after hyperkalaemia in real-world settings have been poorly quantified.[15,16]

Studies with broader coverage, such as those derived from healthcare records, may be relevant to inform clinical practice. We constructed a large, contemporary and region-representative cohort of unselected new users of MRA (i) to estimate the 1-year incidence and clinical predictors of hyperkalaemia, and (ii) to describe changes in drug utilization patterns (e.g. MRA discontinuation, switching, or dose adjustment) thereafter.

Methods

Data sources

This study utilizes the Stockholm CREAtinine Measurements (SCREAM) healthcare utilization cohort,[17] which includes all residents in the region of Stockholm, Sweden, undertaking at least one measurement of plasma creatinine in ambulatory or hospital care during 2006−2011. Laboratory data were linked with regional and national administrative databases for complete information on healthcare utilization, diagnoses and procedures, dispensed drugs, and follow-up for death, with no or minimal loss to follow-up. The study was approved by regional institutional review boards and the Swedish National Board of Welfare.

Patient selection and study design

We included all adult (>18 years old) community-dwelling participants initiating MRA therapy (spironolactone and eplerenone) during the study period, irrespective of indication, and with a creatinine and a K^+ test taken on or within a year before the dispensation date. New use of MRA was defined as a first-time MRA dispensation (with no previous dispensation of an MRA recorded) between 1 January 2007 and 31 December 2010. Additional exclusion criteria were non-residence in Stockholm, undergoing dialysis, being semi-institutionalized in elderly or nursing homes, or missing information on age or sex. Information on MRA dispensations was obtained from the Prescribed Drug Registry, a nationwide register with complete information on all prescribed drugs dispensed at Swedish pharmacies. The coverage of this register is considered virtually complete, as outpatient drug prescriptions and dispensations in Sweden are done via each citizen's unique personal identification number.

This report contains two study designs. First, to analyse hyperkalaemia incidence and risk factors, the exposure was MRA initiation with first dispensation of MRA as index date, and hyperkalaemia was the study outcome. Second, to study clinical management after hyperkalaemia, the incident hyperkalaemia was the index date, and the study outcome was MRA continuation/discontinuation (online supplementary *Figure S1*).

Study covariates

Study covariates included age, sex, laboratory values, co-morbidities and medications. Co-morbid conditions (online supplementary *Table S1*) were defined using diagnostic codes. Medications (online supplementary *Table S2*) included diuretics (both loop and thiazide), angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, and other anti-hypertension medications. Medications were assumed to be concomitant if: (i) there was a pharmacy dispensation at the time of or within the previous 6 months from MRA initiation or after 15 days (part one of the analysis); and (ii) in the 3 months preceding the index hyperkalaemic event (part two of the analysis). Plasma creatinine was measured with either enzymatic or corrected Jaffe method, both methods being traceable to isotope dilution mass spectroscopy standards. Creatinine values <25 and > 1500 μmol/L were considered implausible and discarded. Creatinine tests were used to estimate glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[18] CKD was defined as eGFR <60 mL/min/1.73 m^2, and its severity[18] categorized as eGFR 60−45 mL/min/1.73 m^2, eGFR <45−30 mL/min/1.73 m^2, and eGFR <30 mL/min/1.73 m^2.

Definition of hyperkalaemia

Hyperkalaemia episodes were identified from all plasma and serum K^+ measurements performed in healthcare. K^+ was assessed by potentiometric titration, with laboratory reference ranges of 3.6−4.6 mmol/L for serum K^+ and 3.5−4.4 mmol/L for plasma K^+.[19] Plasma K^+ was the most frequent form of measurement, accounting for 91% of all measurements in the system.[20] Values >10 mmol/L were considered implausible and discarded. Incident hyperkalaemia was defined as the first elevated K^+ exceeding the commonly used clinical thresholds of: (i) 5.0−5.5 mmol/L (mild hyperkalaemia); (ii) 5.5−6.0 mmol/L (moderate hyperkalaemia); (iii) >6.0 mmol/L (severe hyperkalaemia). For simplification of data presentation, the categories of any hyperkalaemia ($K^+ > 5.0$ mmol/L) and moderate/severe hyperkalaemia ($K^+ > 5.5$ mmol/L) were also calculated.

Calculation of mineralocorticoid receptor antagonist exposure

Exposure to MRA was calculated during the follow-up period (post-index date) and was fixed per patient at 365 days. For each patient, duration of MRA exposure during follow-up began on the day after the index date and continued until the first hyperkalaemia occurrence or either discontinuation of MRA exposure, patient's death, or end of study period. At each MRA dispensation, pill supply was calculated as the number of pills contained in the MRA package divided by the prescribed daily dose, allowing a lag-time of 30 days after the estimated pill supply (online supplementary *Figure S2*). Discontinuation of drug exposure was defined as: (i) absence of a subsequent MRA purchase, or (ii) MRA purchase occurring >30 days from the estimated pill supply.

Medication changes after hyperkalaemia

To evaluate changes in drug utilization patterns after hyperkalaemia, we excluded individuals who died within 4 months post-event. We then evaluated the proportion of patients discontinuing MRA, reducing the MRA dose, discontinuing concurrent ACEi/ARBs (absence of dispensation within 120 days of index event), or augmenting therapy [initiation of diuretics or sodium polystyrene sulfonate (SPS) within 120 days of the index event].

Comparison group

To assess whether hyperkalaemia incidence was different in individuals who were not on MRAs, we constructed a parallel cohort of new users of beta-blocker therapy in the same period (1 January 2007 to 31 December 2010), with a creatinine and K^+ test on or within the year before therapy initiation, and who were not on or previously receiving MRAs ($n = 52\,718$). This cohort followed a selection process identical to that of new users of MRAs. We then used propensity score matching to 1:1 match new users of both therapies. The following covariates were used for the calculation of the propensity score: age, sex, diabetes mellitus, history of hypertension, heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease, use of potassium-sparing diuretics, non-steroidal anti-inflammatory drugs, ACEi, ARBs, other hypertension medications, baseline K^+, and eGFR. Of the matched participants, we evaluated the incidence of hyperkalaemia during 1-year follow-up.

Statistical analysis

Descriptive values are presented as median and interquartile range (IQR), or counts with proportions. Multivariable Cox proportional hazards models was used to assess the association between the baseline predictors and the incidence of hyperkalaemia. The main analyses presented follow the 'intention-to-treat' design, censoring for death or end of follow-up (365 days). Sensitivity analyses were done 'on-treatment', that is censoring at time of MRA discontinuation. Time-dependent Cox models were applied to investigate the association between hyperkalaemia and mortality risk during the 1-year follow-up since MRA initiation. In this setting, all covariates were considered as time-dependent at baseline and at first hyperkalaemia ($K^+ > 5$ mmol/L).

Multivariable logistic regression models were used to identify predictors of MRA discontinuation. The number of days since MRA initiation [categorized as early (<3 months) and late events (≥3 months)] and the severity of the index hyperkalaemia were considered *a priori* as covariates influencing clinical decisions. Finally, all analysis was run in the subpopulation of participants with heart failure. All analyses were performed using R (www.r-project.org) and Stata version 14 (www.stata.com).

Results

Demographic and clinical characteristics of new users of mineralocorticoid receptor antagonists

After applying exclusion criteria (online supplementary *Figure S1*), we studied 13 726 adult community-dwelling individuals who

Table 1 General characteristics of new users of mineralocorticoid receptor antagonists in the region of Stockholm, Sweden, during 2007–2010

N	**13 726**
Spironolactone	13 622 (99.2)
Eplerenone	110 (0.8)
Demographics and laboratory values at therapy initiation	
Age (years)	73 (62–82)
<45 years	682 (4.9)
45–65 years	3403 (24.8)
>65–75 years	3245 (23.6)
>75 years	6396 (46.6)
Women	7291 (53.1)
eGFR (mL/min/1.73 m^2)	76.03 (57.9–90.6)
>60 mL/min/1.73 m^2	9933 (72.4)
45–60 mL/min/1.73 m^2	2264 (16.5)
30–44 mL/min/1.73 m^2	1186 (8.6)
<30 mL/min/1.73 m^2	343 (2.5)
Potassium (mmol/L)	3.9 (3.6–4.2)
Co-morbidities	
Myocardial infarction	2472 (18.0)
Hypertension	8845 (64.4)
Heart failure	6302 (45.9)
Peripheral vascular disease	1504 (10.9)
Cerebrovascular disease	2106 (15.3)
Diabetes mellitus	3438 (25.1)
Concomitant drug use	
ACEi	5203 (37.9)
ARBs	3782 (27.6)
Beta-blockers	8587 (62.6)
Thiazide/loop diuretics	9277 (67.6)
NSAIDs	2443 (17.8)
Other blood pressure-lowering drugs	4248 (30.9)

Values are expressed as counts (%), or median (interquartile range).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug.

initiated MRA therapy in Stockholm during 2007–2010. Descriptive statistics are shown in *Table 1*. The vast majority initiated MRA therapy with spironolactone (99.2%). Median age was 73 years, and 53.1% were women. Median plasma K^+ was 3.9 (IQR 3.6–4.2) mmol/L. Hypertension was the most commonly observed co-morbidity (64.4%), followed by heart failure (45.9%), CKD (27.6%, eGFR <60 mL/min/1.73 m^2), diabetes mellitus (25.1%) and history of myocardial infarction (18%). Concomitant medication included, among others, thiazide/loop diuretics (67.6%), beta-blockers (62.6%), ACEi (37.9%) and ARBs (27.6%).

Mineralocorticoid receptor antagonist exposure time and 1-year incidence of hyperkalaemia

The median time on MRA treatment during the initial 12 months of treatment was 179 (130–346) days. Approximately 42% of
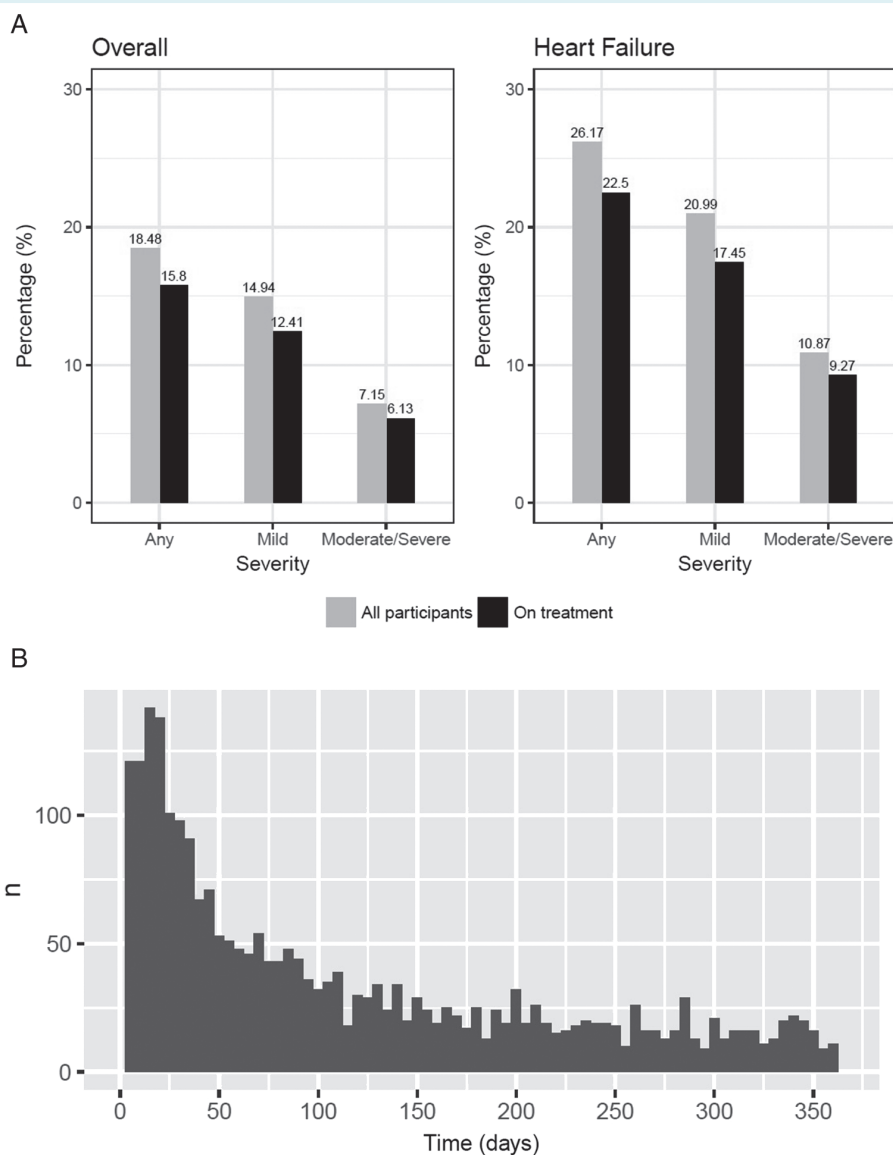
Figure 1 Proportion of hyperkalaemic events overall and in the subpopulation with heart failure (*A*) and time to event distribution (*B*) during 1 year from mineralocorticoid receptor antagonist initiation. In panel *A*, any hyperkalaemia was defined as K$^+$ > 5.0 mmol/L; mild hyperkalaemia was defined as K$^+$ > 5.0−5.5 mmol/L; moderate/severe hyperkalaemia was defined as K$^+$ > 5.5 mmol/L. Please note that mild and moderate/severe events are non-exclusive and a patient can experience both during observation. 'On-treatment' events excluded those hyperkalaemias that occurred after pill supply (plus 30-day lag phase) was exhausted. Panel *B* represents the time distribution to any hyperkalaemia (K$^+$ > 5.0 mmol/L).

participants consumed one MRA package, with an estimated exposure of 130 days. After 3, 6 and 12 months from MRA initiation, the remaining number of participants on therapy was 89%, 50% and 24%, respectively (online supplementary *Figure S3*).

During the 365 days after MRA initiation, 2169 (16%) participants died, and 2536 (18.5%) participants experienced at least one detected hyperkalaemia (*Figure 1A*). Mild hyperkalaemias (observed in 14.9% of participants) were more common than moderate/severe hyperkalaemias (observed in 7.1% of participants). The proportion of hyperkalaemia cases was higher in the subpopulation

of patients with heart failure; specifically, 26.2% heart failure participants experienced at least one detected hyperkalaemia, and 10.87% experienced moderate/severe hyperkalaemia. Development of hyperkalaemia was associated with a significantly higher risk of mortality [hazard ratio (HR) 4.3, 95% confidence interval (CI) 3.8−4.7]. Results were consistent in the subpopulation of patients with heart failure patients (HR 3.3, 95% CI 2.9−3.8) (online supplementary *Table S3*) and after excluding the few participants that initiated MRA with a K$^+$ > 5.0 mmol/L (online supplementary *Table S4*).

Table 2 Baseline predictors of hyperkalaemia risk within 1 year among new users of mineralocorticoid receptor antagonists, overall and by event severity

Variable	Hazard ratios and 95% confidence intervals		
	Any hyperkalaemia (K$^+$ > 5.0 mmol/L)	Mild hyperkalaemia (K$^+$ 5.0–5.5 mmol/L)	Moderate/severe hyperkalaemia (K$^+$ > 5.5 mmol/L)
Age < 45 years	Ref.	Ref.	Ref.
Age 45–64 years	1.56 (1.12–2.16)	1.62 (1.12–2.33)	1.39 (0.82–2.37)
Age 65–74 years	1.75 (1.26–2.42)	1.79 (1.24–2.58)	1.51 (0.88–2.56)
Age > 74 years	2.00 (1.45–2.76)	2.11 (1.47–3.03)	1.57 (0.93–2.66)
Women	0.79 (0.73–0.86)	0.83 (0.76–0.91)	0.73 (0.64–0.83)
eGFR >60 mL/min/1.73 m^2	Ref.	Ref.	Ref.
eGFR 45–60 mL/min/1.73 m^2	1.49 (1.34–1.65)	1.45 (1.29–1.62)	1.73 (1.46–2.04)
eGFR 30–45 mL/min/1.73 m^2	2.08 (1.84–2.33)	1.89 (1.66–2.16)	2.61 (2.18–3.14)
eGFR <30 mL/min/1.73 m^2	2.51 (2.09–3.02)	1.96 (1.58–2.44)	4.03 (3.12–5.19)
Potassium <4.0 mmol/L	0.69 (0.63–0.75)	0.70 (0.64–0.76)	0.68 (0.60–0.78)
Potassium 4.0–5.0 mmol/L	Ref.	Ref.	Ref.
Potassium >5.0 mmol/L	2.78 (2.17–3.58)	2.33 (1.75–3.11)	2.92 (2.06–4.12)
Myocardial infarction	1.00 (0.90–1.10)	1.00 (0.90–1.11)	0.96 (0.82–1.11)
Peripheral vascular disease	1.19 (1.07–1.32)	1.18 (1.04–1.33)	1.34 (1.14–1.58)
Cerebrovascular disease	0.96 (0.87–1.06)	1.03 (0.92–1.16)	0.84 (0.71–0.99)
Heart failure	1.29 (1.17–1.43)	1.26 (1.13–1.41)	1.41 (1.19–1.66)
Diabetes mellitus	1.63 (1.50–1.77)	1.60 (1.46–1.76)	1.86 (1.63–2.13)
Hypertension	0.95 (0.86–1.04)	0.92 (0.83–1.02)	0.97 (0.84–1.13)
ACEi	1.54 (1.41–1.69)	1.56 (1.42–1.73)	1.68 (1.46–1.95)
ARBs	1.17 (1.06–1.28)	1.16 (1.04–1.28)	1.27 (1.09–1.48)
Beta-blockers	1.12 (1.02–1.23)	1.12 (1.01–1.25)	1.19 (1.01–1.40)
Thiazide/loop diuretics	1.52 (1.36–1.70)	1.51 (1.33–1.70)	1.48 (1.23–1.78)
NSAIDs	1.10 (0.99–1.22)	1.13 (1.01–1.27)	1.09 (0.92–1.30)
Other blood pressure-lowering drugs	0.93 (0.85–1.01)	0.97 (0.88–1.07)	0.83 (0.72–0.96)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug.

The characteristics of the propensity score matched cohort of 13 726 new users of beta-blockers are shown in the online supplementary *Table S5*. In them, the 1-year incidence of hyperkalaemia was considerably lower, being found overall in 6.4% of participants (of which 2% were moderate/severe hyperkalaemias) (online supplementary *Figure S4A*). Hyperkalaemia was also less often detected among new beta-blocker users with heart failure (overall in 11.9% of participants, of which 3.7% were moderate/severe) (online supplementary *Figure S4B*).

At first event, hyperkalaemia occurred after MRA pill supply was exhausted (off-therapy, see Methods) in 367 individuals and it was thus deemed not to be associated with MRA therapy. Overall, the distribution of time to first hyperkalaemia shows that most of the events occurred early during the course of therapy, primarily within the first 3 months (*Figure 1B*). This was true for mild as well as for moderate/severe hyperkalaemias when considered separately (online supplementary *Figure S5*).

Multivariable predictors of incident hyperkalaemia

Table 2 describes the baseline risk factors that were associated with the incidence of hyperkalaemia. Overall, increasing age, lower renal function and elevated K$^+$ (>5.0 mmol/L) at MRA initiation were associated with increased hyperkalaemia risk. The presence of various co-morbidities (heart failure, peripheral vascular disease and diabetes mellitus) and concomitant medications (ACEi, ARBs, beta-blockers and thiazide/loop diuretics) were also directly associated with increased hyperkalaemia risk. On the other hand, female sex, low K$^+$ (<4.0 mmol/L) at MRA initiation and concomitant use of other blood pressure-lowering medication were associated with reduced hyperkalaemia risk. In general, predictors of mild and moderate/severe events were similar (*Table 2*), but with some differences in incidence magnitude. For instance, whereas increasing age more strongly predicted mild than moderate/severe events, the association with lower renal function strata was stronger in magnitude for moderate/severe than for mild hyperkalaemias. In a sensitivity analysis where patients were censored according to their exposure to MRA ('on-therapy' design), we found no major deviations from the main results (online supplementary *Table S6*). When analyses were restricted to participants with heart failure, we observed similar predictors and risk magnitudes as in our main models (online supplementary *Tables S7* and *S8*).

Demographic and clinical characteristics of mineralocorticoid receptor antagonist users experiencing hyperkalaemia

For this part of the analysis, we focused on the 2169 participants that experienced hyperkalaemia while still on MRA therapy. Of these, a total of 408 individuals (18%) died in connection to or shortly after hyperkalaemia (within 4 months) and were excluded. Changes in prescription patterns after hyperkalaemia were analysed in the remaining 1761 participants. All of them were spironolactone users and their characteristics at the time of the hyperkalaemia event are shown in the online supplementary *Table S9*. Briefly, the median age was 77 years and 55% were men. Hypertension (74%) was the most common co-morbidity, followed by heart failure (70%), CKD (46%), diabetes mellitus (40%) and myocardial infarction (28%). Thiazide/loop diuretics (68%) and beta-blockers (66%) were the most commonly used concomitant medications. When stratified according to event severity, those with moderate/severe as compared to mild hyperkalaemias were more often men (59% vs. 54%), had lower eGFR (median 57.5 vs. 65 mL/min/1.73 m^2) and higher proportion of diabetes mellitus (44% vs. 38%), hypertension (78% vs. 73%), heart failure (73% vs. 69%) and peripheral vascular disease (21% vs. 17%).

We looked at the prescribed doses in the last spironolactone prescription prior to hyperkalaemia. The most commonly prescribed dose was 25 mg/day (in 65% of participants), followed by 50 mg/day (23% of participants) (*Figure 2A*). Dosages exhibited a weak association with the patient's underlying kidney function (*Figure 2B*). Daily MRA doses of 50 mg were more common among moderate and severe hyperkalaemias compared to mild ones (online supplementary *Figure S6*).

After hyperkalaemia occurrence, 53% of participants continued MRA therapy, 47% discontinued. Among those who remained on therapy, 10% reduced the prescribed MRA dose (*Table 3*). Discontinuation of concomitant ACEi/ARB use occurred in 282 (23%) of cases, being slightly more common among those who discontinued MRA (28%) compared to those who continued (19%). As many as 45% of participants received *de novo* diuretics, and 1.6% started SPS. MRA discontinuation or dose reduction was slightly more common after moderate/severe compared to mild hyperkalaemias (*Table 3*). Likewise, more participants received diuretics or SPS after a moderate/severe event compared to mild events. Timing of therapy also influenced prescription patterns. As compared to late events, hyperkalaemias occurring within the first 3 months of MRA therapy were more often followed by MRA discontinuation, MRA dose reductions and prescription of diuretics, or SPS. Findings were similar in the subpopulation of patients with heart failure (online supplementary *Table S10*).

Multivariable predictors of MRA discontinuation are shown in the online supplementary *Table S11*. Early (<3 months) and more severe events (K$^+$ > 5.5 mmol/L), together with lower kidney function were associated with higher odds of MRA discontinuation. Conversely, concomitant use of ACEi, ARBs or thiazide/loop diuretics was associated with lower odds of MRA discontinuation. Predictors of MRA discontinuation among mild vs. moderate/severe events largely confirmed the overall results, and
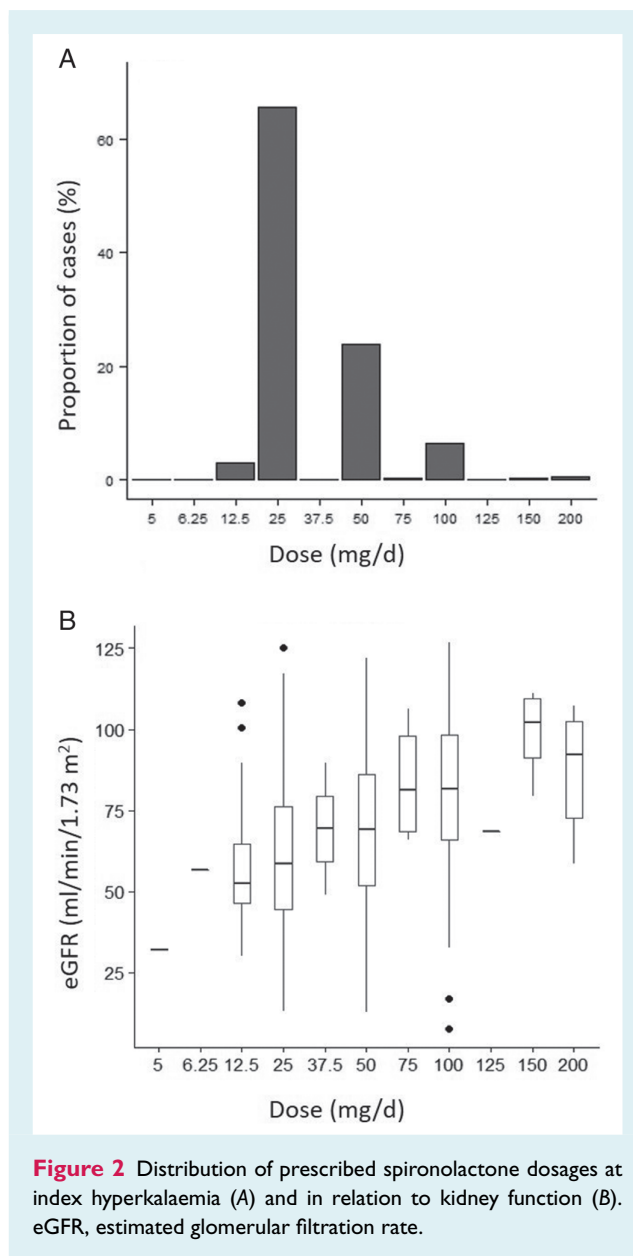

Figure 2 Distribution of prescribed spironolactone dosages at index hyperkalaemia (*A*) and in relation to kidney function (*B*). eGFR, estimated glomerular filtration rate.

findings were similar in the subpopulation of heart failure patients (online supplementary *Table S12*). The decision to discontinue MRA was sustained over time (online supplementary *Figure S7*): 74% of individuals who discontinued MRA after their first hyperkalaemia stayed so during an additional year of follow-up. Only 26% were subsequently reinitiated on MRA. Conversely, only 22% of participants who continued with MRAs were still consuming MRA 1 year post-event, and the remaining 78% interrupted the therapy at some point.

Discussion

In this real-world observational study, 18% of individuals starting MRA experienced one or more hyperkalaemia events during their first year of therapy, a proportion three times higher

Table 3 Matrix of drug prescription patterns after hyperkalaemia overall, by event severity and by time since therapy initiation

	Overall (n = 1761)	By event severity		By timing	
		Mild hyperkalaemia (K$^+$ 5.0–5.5 mmol/L) (n = 1277)	Moderate/severe hyperkalaemia (K$^+$ > 5.5 mmol/L) (n = 484)	<3 mo. of therapy (n = 1084)	>3 mo. of therapy (n = 677)
MRA continuation	934 (53%)	731 (57%)	203 (42%)	535 (49%)	399 (59%)
Same dose	842 (90%)	668 (91%)	174 (86%)	475 (89%)	367 (92%)
Reduced dose	92 (10%)	63 (9%)	29 (14%)	60 (11%)	32 (8%)
MRA cessation	827 (47%)	546 (43%)	281 (58%)	549 (51%)	278 (41%)
Discontinuation of ACEi/ARBs*	282 (23%)	191 (22%)	91 (26.8%)	194 (25%)	88 (20%)
Prescription of new diuretics†	255 (45%)	171 (42%)	84 (53.2%)	133 (47%)	122 (44%)
Prescription of new SPS	28 (1.6%)	10 (0.8%)	18 (3.7%)	19 (1.8%)	9 (1.3%)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SPS, sodium polystyrene sulfonate.
*Proportions based on the number of individuals that were consuming ACEi/ARBs at time of event (n = 1220).
†Proportions based on the number of individuals not consuming diuretics at time of event (n = 562).

than what observed for matched individuals starting beta-blockers. Hyperkalaemia in MRA users occurred primarily within the first 3 months and was moderate to severe in 7% of the participants. CKD, together with old age, and high plasma K$^+$ concentration at MRA initiation were the main independent hyperkalaemia predictors. MRA discontinuation following hyperkalaemia was common (47% of cases), particularly after moderate/severe and early in therapy hyperkalaemias. Participants with CKD were at the highest risk of having MRA discontinued.

Strengths of our analysis include the complete regional coverage of healthcare use in a country with universal healthcare access. The ascertainment of kidney function by eGFR and of hyperkalaemia by K$^+$ tests are also study assets, as these two conditions are not accurately captured by ICD diagnoses.[21,22] The precision of our assessment of MRA treatment length using the estimated pill supply from pharmacy dispensations allowed us to disregard hyperkalaemia not associated with MRA exposure and to assess discontinuation rates accurately. Limitations include the lack of some participant characteristics, such as body mass index, blood pressure or smoking habits, ejection fraction in heart failure patients, and information on dietary interventions to control K$^+$ intake.

We assessed incidence of hyperkalaemia events linked to MRA therapy following a new-user design, which resembles the scenario of trials. The observation that 7% of all MRA users in our region experienced moderate/severe hyperkalaemia (K$^+$ > 5.5 mmol/L) within 1 year is novel, but difficult to compare with preceding studies given the variety of MRA indications. When heart failure patients were studied separately, 9.3% of them experienced moderate/severe hyperkalaemia while on treatment. This incidence proportion is in clear agreement with results from MRA trials in heart failure patients, summarized by a recent meta-analysis showing that 9.3% of patients in those trials experienced hyperkalaemia in the intervention arm.[23] This differs from other real-world analyses from the US[24,25] that report higher hyperkalaemia rates than ours. Several factors may explain the differences between those

and our study, such as differences in the coverage of healthcare use, inclusion period, or differences in clinical practice, for instance the frequency of K$^+$ monitoring. We base our ascertainment of therapy exposure on MRA purchases, which is more accurate than prescription claims. Whereas previous reports assumed all hyperkalaemia events to be linked to MRA therapy, we could differentiate those that occurred on- vs. off-treatment (pill supply exhausted). This represents another strength of our study, but a strength that assumes that all pills from the MRA package were consumed. Finally, our study outcome is based on detected hyperkalaemias, and some participants, for instance, died during the course of therapy without undergoing K$^+$ testing. Such real-world scenario thus differs from randomized controlled trials subjected to programmed study visits and with likely a higher therapy adherence. Thus and altogether, our results are, if any, underestimations of the true hyperkalaemia incidence.

We expand previous evidence with the novel finding that a large proportion of MRA users experience mild hyperkalaemia (15% of all study participants and 21% of heart failure participants). Although guidelines do not currently reach consensus on the need to treat these mild events, K$^+$ concentrations within this range have been associated with an increased risk of death, hospitalizations and emergency room visits.[26−29] Most events occurred within the first 3 months of therapy, which again agrees with the experience of MRA trials: in the Randomized Aldactone Evaluation Study (RALES) trial, the greatest change in K$^+$ occurred within the first 4 weeks following initiation of spironolactone.[30] This finding underscores the importance of early monitoring of K$^+$ after initiation of an MRA, something that despite recommended by current guidelines is not taking place in practice.[12,13]

Characterizing MRA users at high hyperkalaemia risk is important to highlight the need for hyperkalaemia-preventive strategies. This importance is exemplified by our finding that hyperkalaemia development was associated with a three-fold higher risk of mortality. However, some caution is necessary when interpreting the

magnitude of our observed relative risk because of reverse causation bias (i.e. patients at higher risk of dying may have undergone more healthcare explorations and consequently more hyperkalaemias may have been detected). Association does not imply causation, and we note that in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), eplerenone was superior to placebo at all K^+ levels[31] and in RALES, spironolactone with hyperkalaemia up to at least 5.5 mmol/L was more effective than placebo and normokalaemia.[30] Collectively, our results confirm the variety of risk factors for hyperkalaemia and emphasize the central role of the kidneys on K^+ balance. In addition, and alike previous studies, we found that old age, male sex, co-morbidities (heart failure, cerebrovascular disease and diabetes) and concomitant K^+-sparing medications are important hyperkalaemia predictors. A less explored risk factor for hyperkalaemia concerns the prescribed MRA dose. A recent analysis from RALES observed that hyperkalaemia occurred in up to 40% of participants taking spironolactone 50 mg daily, but only in 13.5% of those taking 25 mg.[32] In line with this, our study showed that MRA doses of 50 mg were more common among moderate and severe hyperkalaemias compared to mild ones. Hyperkalaemia related to spironolactone may be dose-related, and this collectively suggest that limiting the maximum dose to 25 mg daily may reduce this risk. As a final consideration, current Food and Drug Administration and product label recommendations suggest to decrease spironolactone dose in individuals with poor kidney function. While our study cannot ascertain the reasons behind prescribed doses, we do observe a relatively weak association (weaker than it would have been anticipated) between eGFR and prescribed dose, with wide inter-individual variation.

Mineralocorticoid receptor antagonist discontinuation after hyperkalaemia has been a matter of concern, but so far poorly quantified. Available reports are few, restricted to heart failure patients and based on prescription claims or self-reports. In our study, we were able to assess MRA discontinuation rates with accuracy and observed a high proportion of individuals discontinuing their medication (47%), as opposed to the relatively low proportion of patients (10%) that followed the recommendation of reducing their MRA dosage.[33–35] The high rate of MRA discontinuations in our study was explained neither by the low prescription of SPS nor by a relatively low discontinuation rate of other concomitant renin–angiotensin–aldosterone system inhibitors (RAASi). However, *de novo* prescription of diuretics seemed to be a recurrent clinical reaction to mitigate chronic hyperkalaemias (45% of cases). We acknowledge the possibility that discontinuation may have been the natural reaction to off-label use. However, the fact that discontinuation rates are essentially the same in the subpopulation with heart failure (the strongest MRA indication) may argue against it. It is also interesting that some clinicians continued MRA without dose modification in patients with moderate/severe hyperkalaemia. However, they may have been given dietary recommendations or initiated/discontinued on other drugs not contemplated in our analysis. Recently, Epstein et al.[36] reported in a US study of healthcare records that RAASi dose was reduced after 16–21% and discontinued after 22–27% of hyperkalaemia events.

We observed that MRA discontinuation was more common after moderate/severe hyperkalaemias and when the event occurred early in the course of therapy. Our data cannot provide an explanation on why patients stopped the drug, but may suggest that clinicians' perception of patients' status and risks are likely to play a role in these decisions.[11] We consistently identified CKD patients as a subpopulation with high risk of hyperkalaemia and high risk of MRA discontinuation, an observation in line with a single-centre study of heart failure patients.[16] Randomized controlled trials and meta-analyses collectively argue against this practice, given that CKD individuals still derive benefit from MRAs in terms of cardioprotection, survival benefit,[31,37] proteinuria reduction and blood pressure control.[38] Another finding in our study is that while the decision of discontinuing MRA was sustained over time, up to 78% of patients who continued with MRA stopped the treatment during the subsequent year. Owing to such dynamic patterns of MRA exposure, cardioprotective effects cannot be anticipated, and may explain why observational real-world studies, under the assumption of treatments being maintained over time, could not observe benefits for this therapy.[39]

To conclude, in an unselected cohort of new users of MRA, we observed that hyperkalaemia events occur frequently. Following the event, a high proportion of participants discontinued. Thus, we provide evidence of the existence of a substantial gap between recommendations in treatment guidelines for hyperkalaemia and real-world prescribing patterns. As proposed by some,[40,41] renewed efforts on education/promotion about these drugs, their indications and need for follow-up and monitoring may positively revert this practice. The novel K^+ binders may also allow the prolonged use of hyperkalaemia-inducing medications,[42,43] but the validity of such approach and the long-term clinical benefit of such strategies are yet to be demonstrated.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Definition of co-morbidities.

Table S2. Definition of medications.

Table S3. Time-dependent association between hyperkalaemia and mortality risk during 1-year follow-up from MRA initiation, overall and in heart failure patients ($n = 13\,726$).

Table S4. Time-dependent association between incident hyperkalaemia and mortality risk in 1-year follow-up from MRA initiation, overall and in heart failure patients (only in participants initiated on MRA with a baseline potassium <5.0 mmol/L; $n = 13\,604$).

Table S5. Baseline characteristics of propensity matched patients who initiated MRA or beta-blocker therapy.

Table S6. Baseline predictors of hyperkalaemia within 1 year among new users of MRA, overall and by event severity, following an 'on-therapy' design.

Table S7. Baseline predictors of hyperkalaemia within 1 year among new users of MRA, overall and by event severity, in the subpopulation of patients with heart failure.

Table S8. Baseline predictors of hyperkalaemia within 1 year among new users of MRA, overall and by event severity, in the sub-population of patients with heart failure, following an 'on-therapy' design.

Table S9. General characteristics at the time of event among those who developed hyperkalaemia (first event detected) within 1 year of MRA use, overall and by event severity.

Table S10. Matrix of drug prescription patterns after hyperkalaemia overall, by event severity and by time since therapy initiation in the subpopulation of patients with heart failure ($n = 1235$).

Table S11. Predictors of MRA discontinuation after hyperkalaemia, overall and by event severity.

Table S12. Predictors of MRA discontinuation after hyperkalaemia, overall and by event severity in the subpopulation of patients with heart failure.

Figure S1. Flow chart and study design.

Figure S2. Graphical explanation of calculations undertaken to estimate MRA exposure based on subsequent MRA purchases.

Figure S3. Distribution of time on MRA treatment and Kaplan−Meier curve of time to stop MRA therapy within 1 year

Figure S4. Proportion of hyperkalaemic events among new users of beta-blockers, overall and in the subpopulation with heart failure.

Figure S5. Distribution of time to mild and moderate/severe hyperkalaemia in an 'intention to treat' design.

Figure S6. Distribution of spironolactone dosages prior to hyperkalaemia according to event severity.

Figure S7. Time (in days) to MRA cessation for those who continued therapy after hyperkalaemia and time to MRA re-initiation for those who discontinued.

Funding

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