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RESEARCH ARTICLE

Safety of continuing mineralocorticoid receptor antagonist treatment in patients with heart failure with reduced ejection fraction and severe kidney disease: Data from Swedish Heart Failure Registry

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Aims Mineralocorticoid receptor antagonists (MRAs) improve outcomes in heart failure with reduced ejection fraction (HFrEF) but remain underused and are often discontinued especially in patients with chronic kidney disease (CKD) due to concerns on renal safety. Therefore, in a real-world HFrEF population we investigated the safety of MRA use, in terms of risk of renal events, any mortality and any hospitalization, across the estimated glomerular filtration rate (eGFR) spectrum including severe CKD.

Methods and results We analysed patients with HFrEF (ejection fraction <40%), not on dialysis, from the Swedish Heart Failure Registry. We performed multivariable logistic regression models to investigate patient characteristics independently associated with MRA use, and univariable and multivariable Cox regression models to assess the associations between MRA use and outcomes. Of 33 942 patients, 17 489 (51%) received MRA, 32%, 45%, 54%, 54% with eGFR <30, 30–44, 45–59 or ≥60 ml/min/1.73 m^2, respectively. An eGFR ≥60 ml/min/1.73 m^2 and patient characteristics linked with more severe HF were independently associated with more likely MRA use. In multivariable analyses, MRA use was consistently not associated with a higher risk of renal events (i.e. composite of dialysis/renal death/hospitalization for renal failure or hyperkalaemia) (hazard ratio [HR] 1.04, 95% confidence interval [CI] 0.98–1.10), all-cause death (HR 1.02, 95% CI 0.97–1.08) as well as of all-cause hospitalization (HR 0.99, 95% CI 0.95–1.02) across the eGFR spectrum including also severe CKD.

Conclusions The use of MRAs in patients with HFrEF decreased with worse renal function; however their safety profile was demonstrated to be consistent across the entire eGFR spectrum.

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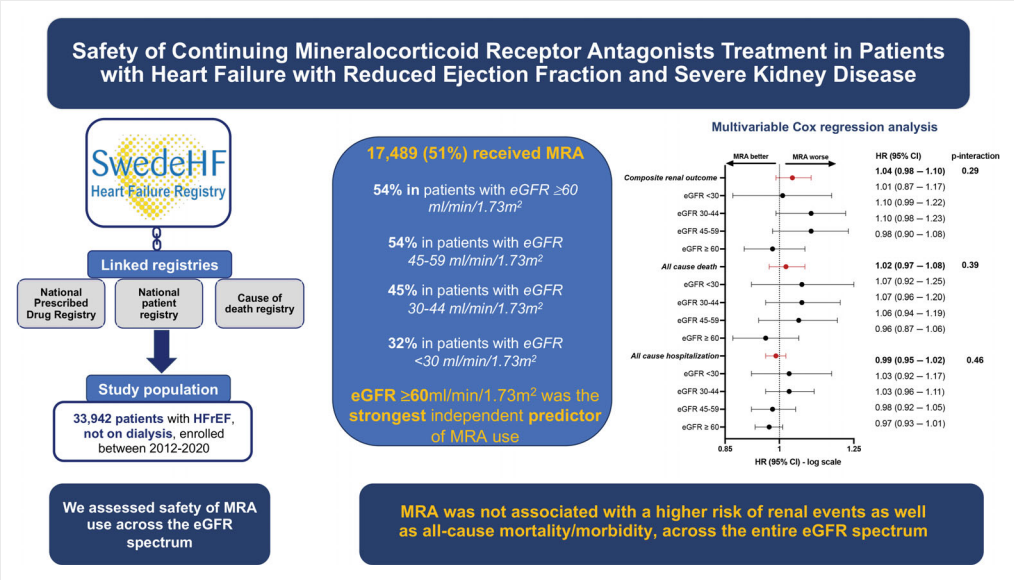
Graphical Abstract



Mineralocorticoid receptor antagonist (MRA) use in severe chronic kidney disease and heart failure with reduced ejection fraction (HFrEF). CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

Keywords Heart failure • Heart failure with reduced ejection fraction • Chronic kidney disease • Mineralocorticoid receptor antagonists • Registry • SwedeHF

Introduction

Chronic kidney disease (CKD) is highly prevalent in patients with heart failure (HF) with reduced ejection fraction (HFrEF), and its presence is a marker of HF severity.[1] CKD has been repeatedly shown as one of the major determinants of under-prescription, under-dosing and discontinuation of HFrEF guideline-directed medical therapies, leading to poorer outcome.[2,3]

Mineralocorticoid receptor antagonists (MRA) (spironolactone and eplerenone) have shown to reduce the risk of death and HF hospitalization in landmark randomized clinical trials (RCTs),[4–6] and therefore have a class I, level of evidence A recommendation in HFrEF international guidelines. American guidelines recommend discontinuation whereas the European guidelines suggest caution together with halving of the dose if the estimated glomerular filtration rate (eGFR) declines below 30 ml/min/1.73 m^2, and discontinuation of MRA when the eGFR reaches <20 ml/min/1.73 m^2.[7,8] Caution/contraindication to MRA use in patients with severe CKD (eGFR <30 ml/min/1.73 m^2) is mainly due to the lack of data on their safety since these patients were not enrolled in previous HFrEF RCTs.[4–6]

Despite the strong level of evidence supporting the efficacy of MRA use in HFrEF, large-scale observational studies highlight their underuse and frequent discontinuation in daily clinical practice.[9] Impaired kidney function, even with an eGFR ranging 30–60 ml/min/1.73 m^2,[10] is a major driver of underutilization likely due to perceived safety concerns, although in post-hoc analyses of RCTs MRAs were safe and effective irrespective of baseline renal function despite the occurrence of worsening renal function and at least until potassium values exceeds 5.5 mEq/L.[11,12]

Recently, the STOP ACEi trial[13] showed that among patients with an eGFR <30 ml/min/1.73 m^2 the withdrawal of renin–angiotensin system inhibitors (RASi), as compared with their continuation, did not prevent the progression to end-stage CKD. While the nephroprotective effect of RASi and sodium–glucose cotransporter 2 inhibitors (SGLT2i) is well established in patients with CKD,[14,15] it is unclear whether also MRAs may play a similar role.[16]

Therefore, we sought to assess the safety of MRAs use in patients with HFrEF and severe CKD (eGFR <30 ml/min/1.73 m^2) by evaluating the risk of renal outcomes, all-cause death and all-cause hospitalization associated with MRA use across the eGFR spectrum in a large, real-world HFrEF cohort, including patients with severe CKD.

Methods

Data sources

We analysed data from the Swedish Heart Failure Registry (SwedeHF), a nationwide health quality and research registry started in 2000 that

includes in- and outpatients with HF regardless of ejection fraction (EF).[17] Around 80 variables (online supplementary *Table Appendix S1*) are recorded at discharge from hospital or at the outpatient visit, which is the index date, and entered into an electronic database managed by the Uppsala Clinical Research Center (Uppsala, Sweden). Up to April 2017 the only inclusion criterion was a clinical diagnosis of HF, which was thereafter defined according to the International Classification of Diseases (ICD)-10 codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, I13.2. Informed consent for patients' inclusion is not required, but patients are informed of registration and can opt out. In 2021, 69 of 76 Swedish hospitals enrolled patients in SwedeHF, which had a 32% coverage of prevalent HF.[18] The unique personal identification number held by all Swedish residents enables the linkage across several national administrative and quality registries. Through the linkage of SwedeHF to Statistics Sweden we retrieved data on socioeconomics, that is, income, level of education, living environment (cohabitating vs. living alone). The linkage with the National Patient Registry provided data on additional comorbidities and on the outcomes all-cause hospitalization, hospitalization for renal failure and hyperkalaemia. Through the Cause of Death Registry, we obtained data on the outcomes all-cause and renal death. The National Prescribed Drug Registry provided data on MRA dispensation at a pharmacy. This study including the linkage across the above-mentioned registries was approved by the Swedish Ethical Review Authority and is conform to the Declaration of Helsinki.

Patients

We selected patients with HFrEF, defined as EF <40%, and not as EF ≤40% according to the recent universal definition and classification of HF,[19] since in SwedeHF EF is reported as a categorical variable (i.e. <40%, 40–49%, >50%) in a majority of patients. MRAs were initially proven to be effective in HFrEF patients with a New York Heart Association (NYHA) class III–IV in RALES in 1999 and with a NYHA class II in EMPHASIS-HF in 2011.[4,5] In order to reduce the bias related to the initial restricted indication for MRA in patients with more severe HF, that is, NYHA class III–IV, we included HFrEF patients registered in SwedeHF in 2012 or later, when in the European HFrEF guidelines MRAs received an indication in patients with NYHA class II–IV.[20] The last patient was included by 31 December 2020 and end of follow-up was 31 December 2021. Patients on dialysis at the index visit and registrations with missing entries for eGFR were excluded. If the same patient was registered more than once, we selected the last record as considered more representative of the most recent patient's clinical status and treatment (online supplementary *Figure Appendix S1*).

Definitions

Exposure to MRA and patients' renal function was assessed at the index date. Use of MRA was assessed through the National Prescribed Drug Registry. A patient was considered as receiving MRA if a dispensation was recorded 5 months prior up to 14 days after the index date. Given that a prescription last approximately 3 months and that its duration can be lengthened due to poor patient's compliance or external factors, we defined that MRA was discontinued if there was no drug dispensation in the 5 months prior up to the end of follow-up. eGFR was calculated using the 2021 CKD Epidemiology Collaboration equation from serum or plasma creatinine measurements reported at the SwedeHF registration. eGFR was stratified into four categories according to the Kidney Disease Improving Global Outcomes (KDIGO) classification: normal or mildly decreased kidney function (eGFR ≥60 ml/min/1.73 m^2), mildly to moderately decreased (eGFR 45–59 ml/min/1.73 m^2), moderately to severely decreased (eGFR 30–44 ml/min/1.73 m^2), and severely decreased (eGFR <30 ml/min/1.73 m^2, excluding patients on chronic dialysis).[21]

Main outcome was 1-year risk of a renal composite of dialysis initiation or renal death or renal failure hospitalization or hyperkalaemia hospitalization. We further analysed 1-year risk of all-cause death and 1-year risk of all-cause hospitalization to perform a comprehensive safety analysis and as consistency analysis due to the risk of misclassifying cause-specific hospitalization/mortality by using ICD-10 codes diagnoses. ICD-10 codes used to define the outcome are reported in online supplementary *Table Appendix S1*.

Statistical analysis

Patient characteristics of those receiving versus not receiving MRA were compared in the overall population and within the four KDIGO categories by Wilcoxon rank-sum test for continuous variables, and by chi-squared test for categorical variables.

Multivariable logistic regression models were performed in the overall study population to identify patient characteristics independently associated with MRA use, which was entered in the model as the dependent variable, with 38 variables, labelled with the letter *b* in *Table 1*, as covariates. To assess whether the independent predictors of MRA use differed across the renal function spectrum, additional multivariable models were performed by including an interaction term between each patient characteristic and the eGFR categories. Results were reported as odds ratios (OR) and 95% confidence intervals (CI).

Univariable and multivariable Cox regression models were performed to assess the association between MRA use and outcomes. Models were adjusted for the variables labelled with the letter *b* in *Table 1*. An interaction term between MRA use and eGFR category was included in both, uni- and multivariable models to test whether the association between MRA use and outcomes differed across the eGFR classes. Results were reported as hazard ratios (HR) and 95% CI. The proportional hazards assumption was verified by the assessment of the Schoenfeld residuals and met.

Discontinuation of MRA was evaluated, given the short follow-up, by assessing the dispensation at two time points: at the index date (5 months prior up to 14 days after the index date) and at the end of the study (5 months prior up to the end of follow-up).

Missing data for the variables included in the multivariable models were handled by multiple imputation using the chained equations method ($n = 10$). All analysis, except for descriptive statistics, were performed on the imputed dataset. Variables included in multiple imputation model are labelled with the latter *a* in *Table 1*, whereas online supplementary *Table S2* shows the proportion of missing records for each variable.

Statistical analyses were performed by Stata 17.0 (Stata Corp LLC, College Station, TX, USA). A p-value < 0.05 was considered statistically significant.

Results

Between 1 January 2012 and 31 December 2020, 120 199 patients were included in SwedeHF. After applying the selection criteria, 33 942 patients were considered (online supplementary *Figure Appendix S1*). Median age was 74 (interquartile range 65–81), 29% were women. The median eGFR was 68 ml/min/1.73 m^2

Table 1 Baseline characteristics according to estimated glomerular filtration rate classes and mineralocorticoid receptor antagonist use

	Overall				eGFR <30 ml/min/1.73 m²			eGFR 30–44 ml/min/1.73 m²			eGFR 45–59 ml/min/1.73 m²			eGFR ≥60 ml/min/1.73 m²		
	Overall	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value
Patients *n* (%)	33 942	16 453 (49%)	17 489 (51%)		1250 (68%)	584 (32%)		2475 (55%)	2063 (45%)		3110 (46%)	3592 (54%)		9618 (46%)	11 250 (54%)	
Demographic																
Age (years), median [IQR][a,b]	74 [65–81]	75 [66–82]	73 [64–79]	<0.001	81 [74–86]	80 [74–85]	0.028	81 [75–86]	79 [73–84]	<0.001	80 [73–85]	77 [71–82]	<0.001	70 [62–78]	69 [60–76]	<0.001
Female sex, *n* (%)[a,b]	9697 (29)	4952 (30)	4745 (27)	<0.001	425 (34)	249 (43)	<0.001	818 (33)	767 (37)	0.004	1005 (32)	1172 (33)	0.78	2704 (28)	2557 (23)	<0.001
Index year, *n* (%)[a,b]				<0.001			0.009			<0.001			<0.001			<0.001
2012–2016	16 050 (47)	8929 (54)	7121 (41)		776 (62)	325 (56)		1419 (57)	973 (47)		1695 (55)	1536 (43)		5039 (52)	4287 (38)	
2017–2020	17 892 (53)	7524 (46)	10 368 (59)		474 (38)	259 (44)		1056 (43)	1090 (53)		1415 (45)	2056 (57)		4579 (48)	6963 (62)	
Caregiver at registration, *n* (%)[a,b]				<0.001			<0.001			<0.001			<0.001			<0.001
Outpatient	25 079 (74)	11 612 (71)	13 467 (77)		615 (49)	336 (58)		1500 (61)	1474 (71)		2149 (69)	2725 (76)		7348 (76)	8932 (79)	
Inpatient	8863 (26)	4841 (29)	4022 (23)		635 (51)	248 (42)		975 (39)	589 (29)		961 (31)	867 (24)		2270 (24)	2318 (21)	
Location of follow-up, *n* (%)[a,b]				<0.001			0.11			<0.001			<0.001			<0.001
Hospital	26 400 (79)	12 029 (75)	14 371 (84)		754 (63)	379 (68)		1542 (64)	1482 (73)		2082 (68)	2804 (80)		7651 (81)	9706 (88)	
Primary care	6239 (19)	3729 (23)	2510 (15)		402 (33)	161 (29)		800 (33)	494 (24)		895 (29)	649 (18)		1632 (17)	1206 (11)	
Other	629 (2)	324 (2)	305 (2)		49 (4)	20 (4)		64	41 (2)		67 (2)	66 (2)		144 (2)	178 (2)	
Clinical variables																
NYHA class, *n* (%)[a,b]				<0.001			0.021			0.31			0.081			<0.001
I	2666 (10)	1347 (11)	1319 (9)		23	7 (2)		73 (4)	68 (4)		153 (7)	176 (6)		1098 (15)	1068 (12)	
II	12 909 (49)	6143 (50)	6766 (48)		228 (29)	106 (26)		657 (38)	570 (35)		1108 (47)	1272 (44)		4150 (55)	4818 (52)	
III	10 255 (39)	4553 (37)	5702 (40)		457 (58)	270 (66)		935 (53)	929 (57)		1012 (43)	1346 (47)		2149 (29)	3157 (34)	
IV	696 (3)	352 (3)	344 (2)		85 (11)	28 (7)		85 (5)	75 (5)		72 (3)	88 (3)		110 (1)	153 (2)	
EF, *n* (%)[a,b]				<0.001			0.38			0.022			<0.001			<0.001
30–39%	18 828 (55)	9848 (60)	8980 (51)		657 (53)	294 (50)		1380 (56)	1080 (52)		1840 (59)	1833 (51)		5971 (62)	5773 (51)	
<30%	15 114 (45)	6605 (40)	8509 (49)		593 (47)	290 (50)		1095 (44)	983 (48)		1270 (41)	1759 (49)		3647 (38)	5477 (49)	
BMI (kg/m²), median [IQR][a,b]	26 [23–30]	26 [23–30]	27 [24–30]	<0.001	26 [23–29]	27 [24–30]	0.012	26 [23–29]	26 [23–30]	0.001	26 [23–29]	26 [23–30]	<0.001	26 [23–30]	27 [24–31]	<0.001
MAP (mmHg), median [IQR][a,b]	89 [80–97]	90 [82–99]	88 [80–97]	<0.001	87 [80–97]	83 [76–93]	<0.001	87 [80–96]	85 [77–93]	<0.001	89 [80–98]	87 [78–95]	<0.001	92 [83–100]	89 [80–98]	<0.001
Heart rate (bpm), median [IQR][a,b]	71 [62–82]	72 [63–83]	70 [62–80]	<0.001	72 [64–85]	72 [64–82]	0.30	73 [64–83]	70 [63–80]	<0.001	72 [63–83]	70 [62–80]	<0.001	72 [63–83]	70 [62–81]	<0.001
Potassium (mmol/L), median [IQR][a,b]	4.2 [4.0–4.5]	4.2 [3.9–4.5]	4.3 [4.0–4.6]	<0.001	4.3 [3.9–4.7]	4.4 [4.0–4.8]	<0.001	4.3 [3.9–4.6]	4.4 [4.0–4.7]	<0.001	4.2 [4.0–4.5]	4.3 [4.0–4.6]	<0.001	4.2 [4.0–4.4]	4.3 [4.0–4.5]	<0.001
NT-proBNP (pg/ml), median [IQR][a,b]	2340 [965–5578]	2540 [1027–6186]	2223 [920–5131]	<0.001	11 667 [4934–26 570]	6830 [3059–16 410]	<0.001	5235 [2445–10 700]	4183 [2010–8890]	<0.001	3240 [1518–6786]	2934 [1324–5999]	<0.001	1640 [697–3700]	1740 [708–3853]	0.028
Medical history, *n* (%)																
Atrial fibrillation[a,b]	18 612 (55)	8879 (54)	9733 (56)	0.002	778 (62)	410 (70)	<0.001	1548 (63)	1423 (69)	<0.001	1872 (60)	2278 (63)	0.007	4681 (49)	5622 (50)	0.060
Smoking[a,b]				0.001			0.13			0.087			0.080			<0.001
Current	3298 (12)	1670 (13)	1628 (12)		70 (8)	22 (5)		153 (8)	99 (6)		201 (8)	260 (9)		1246 (16)	1247 (14)	
Former	12 360 (46)	5900 (45)	6460 (47)		424 (46)	203 (45)		885 (46)	768 (47)		1125 (45)	1309 (46)		3466 (44)	4180 (47)	
Never	11 427 (42)	5674 (43)	5753 (42)		427 (46)	223 (50)		877 (46)	762 (47)		1184 (47)	1255 (44)		3186 (40)	3513 (39)	
Hypertension[a,b]	22 117 (65)	10 403 (63)	11 714 (67)	<0.001	1047 (84)	466 (80)	0.037	1901 (77)	1598 (77)	0.60	2137 (69)	2676 (74)	<0.001	5318 (55)	6974 (62)	<0.001
Diabetes[a,b]	9236 (27)	4200 (26)	5036 (29)	<0.001	469 (38)	240 (41)	0.14	886 (36)	746 (36)	0.80	898 (29)	1134 (32)	0.017	1947 (20)	2916 (26)	<0.001
Peripheral artery disease[a,b]	3095 (9)	1529 (9)	1566 (9)	0.28	209 (17)	81 (14)	0.12	320 (13)	229 (11)	0.060	332 (11)	396 (11)	0.65	668 (7)	860 (8)	0.053
Ischaemic heart disease[a,b]	18 564 (55)	8828 (54)	9736 (56)	<0.001	853 (68)	410 (70)	0.40	1659 (67)	1410 (68)	0.35	1885 (61)	2227 (62)	0.24	4431 (46)	5689 (51)	<0.001
Valvular disease[a,b]	7978 (24)	3780 (23)	4198 (24)	0.025	407 (33)	222 (38)	0.022	746 (30)	668 (32)	0.10	869 (28)	1009 (28)	0.89	1758 (18)	2299 (20)	<0.001
Cerebrovascular disease[a,b]	5314 (16)	2717 (17)	2597 (15)	<0.001	292 (23)	124 (21)	0.31	503 (20)	404 (20)	0.53	633 (20)	621 (17)	0.001	1289 (13)	1448 (13)	0.26
COPD[a,b]	4215 (12)	2044 (12)	2171 (12)	0.98	191 (15)	97 (17)	0.47	366 (15)	311 (15)	0.79	400 (13)	504 (14)	0.16	1087 (11)	1259 (11)	0.80
Cancer within 3 years[a,b]	4172 (12)	2201 (13)	1971 (11)	<0.001	209 (17)	92 (16)	0.60	434 (18)	298 (14)	0.005	471 (15)	475 (13)	0.024	1087 (11)	1106 (10)	<0.001

Table 1 (Continued)

	Overall				eGFR <30 ml/min/1.73 m²			eGFR 30–44 ml/min/1.73 m²			eGFR 45–59 ml/min/1.73 m²			eGFR ≥60 ml/min/1.73 m²		
	Overall	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value	MRA no	MRA yes	*p*-value
Liver disease[a,b]	809 (2)	345 (2)	464 (3)	<0.001	37 (3)	17 (3)	0.95	49 (2)	40 (2)	0.92	46 (1)	83 (2)	0.013	213 (2)	324 (3)	0.002
Anaemia[a,b]	9814 (31)	5018 (33)	4796 (30)	<0.001	797 (66)	315 (58)	0.002	1140 (49)	869 (46)	0.094	1040 (36)	1117 (34)	0.17	2041 (23)	2495 (25)	0.007
Concomitant medications, *n* (%)																
Beta-blockers[a,b]	31 628 (93)	15 089 (92)	16 539 (95)	<0.001	1137 (91)	521 (90)	0.23	2271 (92)	1933 (94)	0.015	2849 (92)	3361 (94)	0.006	8832 (92)	10 724 (95)	<0.001
RASi or ARNI[a,b]	30 954 (92)	14 676 (90)	16 278 (93)	<0.001	748 (60)	380 (65)	0.039	2013 (82)	1769 (86)	<0.001	2799 (91)	3316 (93)	0.003	9116 (95)	10 813 (97)	<0.001
Digoxin[a,b]	3896 (12)	1782 (11)	2114 (12)	<0.001	67 (5)	46 (8)	0.037	213 (9)	240 (12)	<0.001	402 (13)	443 (12)	0.44	1100 (11)	1385 (12)	0.050
Diuretics[a,b]	25 270 (75)	11 752 (72)	13 518 (78)	<0.001	1183 (95)	550 (95)	0.70	2268 (92)	1906 (93)	0.30	2554 (83)	3018 (84)	0.074	5747 (60)	8044 (72)	<0.001
Nitrate[a,b]	3274 (10)	1704 (10)	1570 (9)	<0.001	256 (21)	117 (20)	0.85	434 (18)	312 (15)	0.030	399 (13)	425 (12)	0.20	615 (6)	716 (6)	0.94
Antiplatelets[a,b]	12 456 (37)	6462 (39)	5994 (34)	<0.001	526 (42)	179 (31)	<0.001	977 (40)	654 (32)	<0.001	1225 (40)	1168 (33)	<0.001	3734 (39)	3993 (36)	<0.001
Anticoagulants[a,b]	17 350 (51)	7827 (48)	9523 (55)	<0.001	581 (47)	345 (59)	<0.001	1303 (53)	1308 (64)	<0.001	1629 (53)	2157 (60)	<0.001	4314 (45)	5713 (51)	<0.001
Statin[a,b]	17 817 (53)	8248 (50)	9569 (55)	<0.001	602 (48)	316 (54)	0.019	1298 (52)	1158 (56)	0.011	1643 (53)	2036 (57)	0.002	4705 (49)	6059 (54)	<0.001
Procedures, *n* (%)																
Coronary revascularization[a,b]	12 152 (36)	5594 (34)	6558 (37)	<0.001	526 (42)	277 (47)	0.031	1049 (42)	895 (43)	0.50	1205 (39)	1477 (41)	0.048	2814 (29)	3909 (35)	<0.001
Devices[a,b]	5095 (15)	1619 (10)	3476 (20)	<0.001	182 (15)	138 (24)	<0.001	363 (15)	469 (23)	<0.001	354 (12)	760 (21)	<0.001	720 (8)	2109 (19)	<0.001
Socioeconomic characteristics, *n* (%)																
Family type[a,b]				<0.001			0.14			0.036			<0.001			0.004
Cohabitating	18 188 (54)	8567 (52)	9621 (55)		601 (48)	303 (52)		1224 (49)	1083 (53)		1593 (51)	1983 (55)		5149 (54)	6252 (56)	
Living alone	15 707 (46)	7864 (48)	7843 (45)		647 (52)	281 (48)		1251 (51)	977 (47)		1517 (49)	1605 (45)		4449 (46)	4980 (44)	
Education level[a,b]				<0.001			0.56			0.30			0.038			0.15
Compulsory school	12 912 (39)	6454 (40)	6458 (37)		586 (48)	284 (49)		1172 (48)	937 (46)		1353 (44)	1467 (41)		3343 (35)	3770 (34)	
Secondary school	14 258 (43)	6758 (42)	7500 (44)		448 (36)	212 (37)		897 (37)	767 (38)		1179 (39)	1469 (41)		4234 (45)	5052 (46)	
University	6239 (19)	2967 (18)	3272 (19)		194 (16)	80 (14)		356 (15)	323 (16)		526 (17)	607 (17)		1891 (20)	2262 (20)	
Income >median[a,b]	16 951 (50)	7797 (47)	9154 (52)	<0.001	478 (38)	214 (37)	0.50	941 (38)	855 (42)	0.017	1263 (41)	1649 (46)	<0.001	5115 (53)	6436 (57)	<0.001

ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin– angiotensin system inhibitor.

[a]Variables included in multiple imputation together with the primary outcome, MRA use and eGFR.

[b]Variables included as covariates in the multivariable logistic regression models and multivariable Cox regression model, together with eGFR.

Table 2 Changes in mineralocorticoid receptor antagonist use over the follow-up

MRA at index date	MRA at the end of follow-up	Overall	eGFR <30	eGFR 30–44	eGFR 45–59	eGFR ≥60
		33 942	1834 (5%)	4538 (13%)	6702 (20%)	20 868 (62%)
No	No	12 734 (37.5%)	1152 (63%)	2150 (47%)	2533 (38%)	6899 (33%)
Yes	Yes	13 769 (40.5%)	406 (22%)	1378 (30%)	2681 (40%)	9304 (45%)
Yes	No	3720 (11%)	178 (10%)	685 (15%)	911 (14%)	1946 (9%)
No	Yes	3719 (11%)	98 (5%)	325 (7%)	577 (9%)	2719 (13%)

eGFR, estimated glomerular filtration rate (in ml/min/1.73 m^2, calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); MRA, mineralocorticoid receptor antagonist.
MRA at index date yes: if a dispensation was recorded 5 months prior up to 14 days after the index date. MRA at the end of follow-up yes: if a dispensation was recorded 5 months prior up to the end of follow-up. MRA (no−no) = MRA no at the index date−MRA no at the end of follow-up. MRA (yes−yes) = MRA yes at the index date−MRA yes at the end of follow-up. MRA (yes-no) = MRA yes at the index date−MRA no at the end of follow-up = MRA withdrawn. MRA (no-yes) = MRA no at the index date−MRA yes at the end of follow-up = MRA started after index date.

(interquartile range 50–87); 62% had eGFR ≥60 ml/min/1.73 m^2, 20% 45–59 ml/min/1.73 m^2, 13% 30–44 ml/min/1.73 m^2 and 5% <30 ml/min/1.73 m^2 (online supplementary *Table S3*).

A total of 17 489 (51%) patients were on MRA at the index date. The use of MRA decreased with worse renal function, that is, 54%, 54%, 45%, 32% with eGFR ≥60, 45–59, 30–44, <30 ml/min/1.73 m^2, respectively (*Table 1*). During follow-up (10 ± 2.93 months), 11% of patients, consistently across the eGFR spectrum, discontinued MRA. MRA was initiated after the index date in 11% of patients, with an increasing proportions in higher eGFR classes (*Table 2*).

Baseline characteristics according to mineralocorticoid receptor antagonist use at baseline

In the overall population, MRA treated and untreated patients differed for most baseline characteristics (*Table 1*). Those receiving MRA were younger, more likely male, followed up in specialty care and had higher potassium. Although they had characteristics linked with more severe HF (i.e. higher NYHA class, lower EF and higher use of HF medical and device therapy), they had lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. They were more likely to have hypertension, diabetes, atrial fibrillation, ischaemic heart disease and liver disease, but less likely anaemia, history of cerebrovascular disease and cancer. The same discrepancies between MRA users and non-users were found in the subgroup of patients with eGFR <30 ml/min/1.73 m^2, with the exception of beta-blocker (BB) use and EF, which did not significantly differ.

Independent associations with mineralocorticoid receptor antagonist use at baseline

In the overall cohort eGFR ≥60 ml/min/1.73 m^2 was the strongest independent predictor of MRA use (*Figure 1*). MRA use was ∼3- and ∼2-fold more likely, respectively, with an eGFR ≥60 and 30–44 ml/min/1.73 m^2 compared with <30 ml/min/1.73 m^2. Other relevant predictors were potassium >5 mmol/L, more severe HF (i.e. higher NYHA class, use of HF devices, diuretics), use of BB, a later index year, presence of anaemia, history of hypertension, obesity, liver and valvular disease. Patients followed up in primary versus specialty care, with an EF >30%, an age >70 years, hospitalized at the index visit as well as with a history of cerebrovascular disease or cancer were less likely to receive MRAs (online supplementary *Table S4*).

All these associations were consistent across the eGFR spectrum, except for lower EF, use of diuretics, use of BB, presence of anaemia and history of hypertension, which were significantly associated with MRA use only in higher eGFR classes. In patients with eGFR <30 and 30–44 ml/min/1.73 m^2, follow-up location was not associated with the likelihood of receiving MRA; in contrast in those with eGFR 45–59 and ≥60 ml/min/1.73 m^2 a follow-up in primary care was associated with lower likelihood of being treated with an MRA. Ischaemic heart disease and history of coronary revascularization were associated with MRA use only in patients with normal renal function. Higher NT-proBNP levels were associated with more likely MRA use in patients with normal renal function but with lower likelihood in those with eGFR <30 and 30–44 ml/min/1.73 m^2.

Outcomes

In the overall population, 5861 (17%) patients experienced at least one event included in the composite renal endpoint (i.e. dialysis initiation or renal death or renal failure hospitalization or hyperkalaemia hospitalization). The 1-year rate for MRA users was 14.6 versus 17.5 per 1000 patient-years for non-users, with an unadjusted HR of 0.83 (95% CI 0.79–0.88). After adjustments the HR was 1.04 (95% CI 0.98–1.10) which was consistent across the eGFR spectrum (*p*-interaction 0.29; *Figure 2*). Patients with an eGFR <30 ml/min/1.73 m^2 had a crude HR of 0.88 (0.77–1.01) and an adjusted HR of 1.01 (0.87–1.17).

In the overall cohort, 5303 (15%) patients died from any cause. One-year mortality rate was 12.9 per 1000 patient-years for

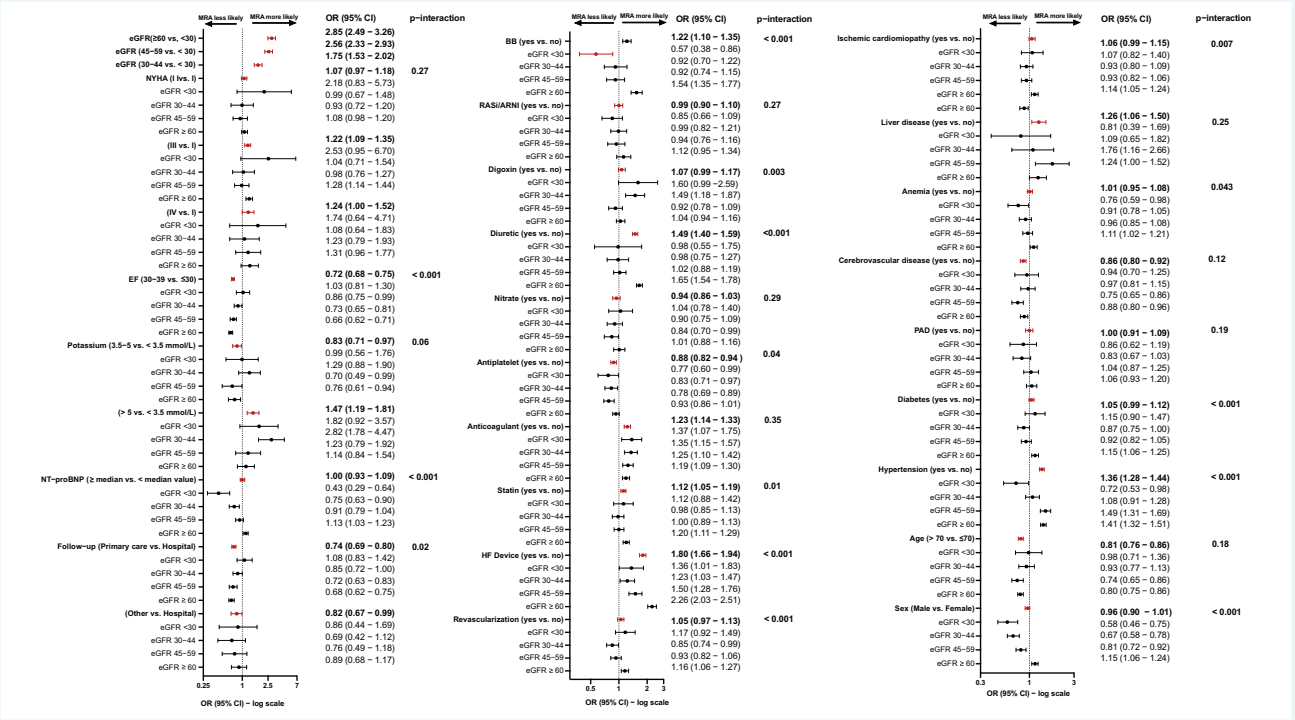


Figure 1 Main independent predictors of mineralocorticoid receptor antagonist (MRA) use across the estimated glomerular filtration rate (eGFR) spectrum. Other independent predictors are reported in online supplementary *Table S4*. ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CI, confidence interval; EF, ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PAD, peripheral artery disease; RASi, renin–angiotensin system inhibitor.

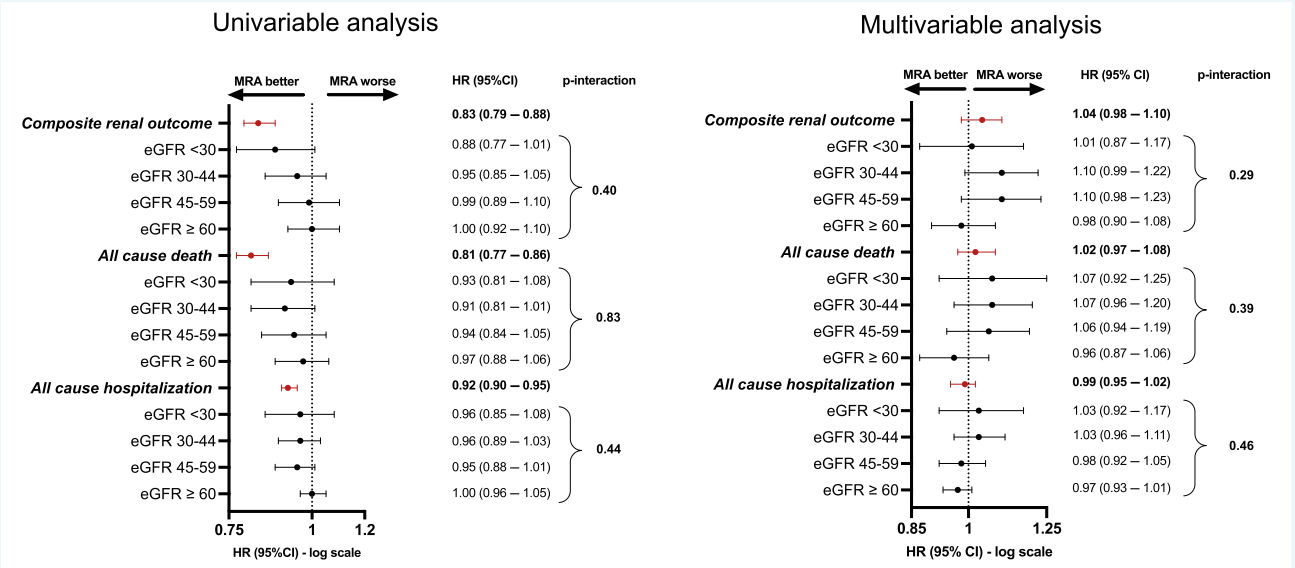


Figure 2 Association between mineralocorticoid receptor antagonist (MRA) use, the composite outcome, all-cause death and all-cause hospitalization across the estimated glomerular filtration rate (eGFR) spectrum. CI, confidence interval; HR, hazard ratio. *Significant *p*-interaction (<0.05). [Correction added on 3 November 2023, after first online publication: The titles of the two plots in Figure 2 have been added in this version.]

MRA users versus 15.9 for non-users, with a crude HR of 0.81 (95% CI 0.77–0.86). After adjustments the HR was 1.02 (95% CI 0.97–1.08), which was consistent across the eGFR classes (*p*-interaction 0.39). In patients with eGFR <30 ml/min/1.73 m^2 crude and adjusted HR were 0.93 (0.81–1.08) and 1.07 (0.92–1.25), respectively (*Figure 2*).

Regarding any hospitalization, in the overall cohort 15 633 (46%) experienced at least one hospitalization for any cause. One-year rate for MRA users was 55.6 versus 60.5 per 1000 patient-years for non-users, with a crude HR of 0.92 (95% CI 0.90–0.95). After adjustments the HR was 0.99 (95% CI 0.95–1.02), which was consistent regardless of renal function (*p*-interaction 0.46). Crude and adjusted HR were 0.96 (0.85–1.08) and 1.03 (0.91–1.17), respectively, in patients with eGFR <30 ml/min/1.73 m^2 (*Figure 2*).

Discussion

In this real-world nationwide HFrEF population, 51% of patients received an MRA. An eGFR ≥60 ml/min/1.73 m^2 was found to be the strongest predictor of MRA use among 38 patient characteristics. In the multivariable Cox regression models, MRA use was not associated with a higher risk of the 1-year composite renal endpoint as well as all-cause death and all-cause hospitalization. The safety profile of MRA was consistent across the different eGFR classes and notably also in patients with severe CKD (*Graphical Abstract*).

Mineralocorticoid receptor antagonist use and its predictors in heart failure with reduced ejection fraction

In our real-world population, 51% of patients received an MRA, which is higher compared with the recent CHAMP-HF registry enrolling patients in 2015–2017 and showing a MRA use of 33%,[22] and consistent with the ∼55% use in the European Society of Cardiology HF Long-Term Registry (ESC-HF-LT) enrolling patients in 2011–2013 as well as in the BIOSTAT-CHF study considering patients between 2010 and 2015.[23,24] Notably, we included patients registered in 2012–2020, with MRA use approximating 60% in Sweden in 2018.[25] In our study, an eGFR ≥60 ml/min/1.73 m^2 was the strongest predictor of MRA use, which is consistent with data from The Get With The Guidelines-HF registry considering patients admitted for HF.[26] We also showed that other independent predictors of use were HF device use, index year >2016, diuretic use and hyperkalaemia. Apart from higher NT-proBNP levels and use of RASi/angiotensin receptor–neprilysin inhibitor (ARNI), variables linked with more severe HF (higher NYHA class, lower EF, and HF devices) were also associated with MRA use. This might be explained by the sequential model for drug initiation recommended by the previous guidelines, where MRA had an indication in patients still symptomatic despite optimal therapy with BB and RASi, which explains also our results of BB being a predictor of use.[20] As previously shown, patient characteristics associated with a better tolerability profile, for example, younger age, hypertension and obesity, were also associated with higher likelihood of receiving MRA.[10,25] Use of diuretics predicted treatment with MRA, which might be explained by the use of diuretics for reducing potassium levels, as well as by the use of MRA as potassium sparing agent in patients in need of diuretics and therefore sicker. Use of MRA was more likely in patients with higher potassium levels, which reflects a consequence rather than a cause of using MRA, that is, reverse causality, and, as expected, in those with later year of registration and follow-up in specialty care, which reflects the natural process of MRA implementation over time and better care in specialty centres, respectively. Some patient characteristics (e.g. lower EF, use of diuretics, use of BB, anaemia, hypertension) which predicted MRA use in the overall population did not consistently perform in patients with severe CKD, which might be explained by their role in MRA prescription being blunted by the impaired renal function.

In agreement with previous studies,[9,27] we found an 11% MRA discontinuation rate at 1 year, which interestingly was consistent across the different eGFR classes. This finding might be explained by more likely prevalent rather than incident use of MRA in our cohort, and therefore MRA might not have been discontinued whether potassium levels were adequate and renal function stable even if reduced over time since not perceived as particularly risky and likely under a stricter monitoring of laboratory tests.

Safety of mineralocorticoid receptor antagonist use in patients with severe chronic kidney disease

Randomized clinical trials have demonstrated the efficacy and safety of MRA in HFrEF patients regardless of baseline CKD status; however, they did not include patients with severe CKD.[4–6]

Real-word studies can provide additional evidence to RCTs for safety purposes, in particular in those subgroups of patients poorly enrolled in RCTs. However, even in previous HFrEF observational studies, the representation of patients with severe CKD was limited and renal outcomes were rarely evaluated. In a Swiss retrospective cohort study including HF ambulatory patients, in the subgroup of patients with CKD, treatment with MRA was not associated with persistent renal function decline, acute kidney injury or serious hyperkalaemia compared with RASi monotherapy.[28] However, of this 1430 patient cohort, only 110 had an eGFR <30 ml/min/1.73 m^2. Similarly, in a single-center Swedish retrospective study, investigating HFrEF patients with impaired renal function, with a majority of them having stage 3 CKD, MRA use was not associated with higher risk of worsening renal function as well as of all-cause mortality.[29]

In the current analysis of a large HFrEF population from the SwedeHF, 1834 patients with eGFR <30 ml/min/1.73 m^2 were included, and 32% of them were on treatment with an MRA, which does represent the largest analysis in this setting. MRA use was associated with a crude lower risk of 1-year renal events (including renal death or need for chronic dialysis or renal failure hospitalization or hospitalization for hyperkalaemia) in the overall population. However, after adjustments no association was observed in the overall population and consistenltly across the eGFR spectrum,

including also patients with severe CKD. The discrepancy between unadjusted and adjusted findings could be explained, among several reasons, by the better use of other HF medications among MRA users, and in particular the better implementation of RASi/ARNI which have a demonstrated nephroprotective effect.

A further finding of our study was that patients receiving MRA were at lower crude risk of 1-year all-cause death and all-cause hospitalization in the overall cohort. Once again, this result was not confirmed in adjusted analyses, where no statistically significant association was detected in the overall population and across the eGFR spectrum, including also patients with severe CKD. Lack of an association between use of MRA and lower risk of mortality as well as all-cause hospitalization after adjustments in the real-world setting is not surprising and has been previously explained by residual confounding.[30]

Given the results of RCTs in HFrEF showing consistent effect of MRAs in reducing mortality in patients with eGFR 30–60 and ≥60 ml/min/1.73 m^2, our analysis showing that MRA use (prevalent use in most cases) was safe in patients with severe as well as non-severe and no CKD in a large HFrEF cohort might suggest not to discontinue MRA due to impaired renal function because of safety concerns, if close laboratory surveillance is possible. Novel potassium binders could represent a useful strategy to support the continuation of MRA treatments in the setting of CKD.[31]

Limitations

This was an observational study, and although we performed extensive adjustments, causality cannot be established due to likely presence of residual confounding. MRA use was considered at the index date; however, discontinuations over time were limited. We did not consider MRA dose down-titration but only discontinuation since a majority of patients in Sweden receives spironolactone 25 mg.[25] Use of novel potassium binders was not analysed since it is overall very limited in Sweden. Despite ours is the largest analysis that considered the use of MRA stratified across the eGFR spectrum, the generalization of our results to the whole spectrum of CKD is partly limited by the relatively low proportion of patients with severe CKD receiving MRA, and therefore there is chance that only 'healthier CKD' patients were on treatment. Finally, in our analysis we did not consider SGLT2i use as they received indication for HFrEF in Sweden only in 2021.

Conclusions

In a large nationwide cohort of HFrEF patients, use of MRA was safe across the entire eGFR spectrum although decreased with worse renal function. Our findings might suggest not to encourage MRA discontinuation in patients with severe CKD if strict laboratory surveillance is feasible.

Supplementary Information

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

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References

1. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, *et al.* Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014;**16**:103–111. https://doi.org/10.1002/ejhf.30
2. Janse RJ, Fu EL, Dahlström U, Benson L, Lindholm B, van Diepen M, *et al.* Use of guideline-recommended medical therapy in patients with heart failure and chronic kidney disease: from physician's prescriptions to patient's dispensations, medication adherence and persistence. *Eur J Heart Fail* 2022;**24**:2185–2195. https://doi.org/10.1002/ejhf.2620

3. Epstein M, Reaven NL, Funk SE, McGaughey K, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015;**21**:S212–S220. PMID: 26619183.
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717. https://doi.org/10.1056/NEJM199909023411001
5. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, *et al.*; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21. https://doi.org/10.1056/NEJMoa1009492
6. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.*; *Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators*. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321. https://doi.org/10.1056/NEJMoa030207
7. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. https://doi.org/10.1161/cir.0000000000001063
8. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
9. Zahir D, Bonde A, Madelaire C, Malmborg M, Butt JH, Fosbol E, *et al.* Temporal trends in initiation of mineralocorticoid receptor antagonists and risk of subsequent withdrawal in patients with heart failure: a nationwide study in Denmark from 2003-2017. *Eur J Heart Fail* 2022;**24**:539–547. https://doi.org/10.1002/ejhf.2418
10. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlström U, *et al.* Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2018;**20**:1326–1334. https://doi.org/10.1002/ejhf.1182
11. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, *et al.* Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). *J Am Coll Cardiol* 2013;**62**:1585–1593. https://doi.org/10.1016/j.jacc.2013.04.086
12. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, *et al.*; *RALES Investigators*. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol* 2012;**60**:2082–2089. https://doi.org/10.1016/j.jacc.2012.07.048
13. Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, *et al.*; *STOP ACEi Trial Investigators*. Renin-angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med* 2022;**387**:2021–2032. https://doi.org/10.1056/NEJMoa2210639
14. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, *et al.*; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446. https://doi.org/10.1056/NEJMoa2024816
15. House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, *et al.* Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 2019;**95**:1304–1317. https://doi.org/10.1016/j.kint.2019.02.022
16. Chung EYM, Ruospo M, Natale P, Bolignano D, Navaneethan SD, Palmer SC, *et al.*; Cochrane Kidney and Transplant Group. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2020;**10**:CD007004. https://doi.org/10.1002/14651858.CD007004.pub4
17. Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U, Lund LH. The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. *Ups J Med Sci* 2019;**124**:65–69. https://doi.org/10.1080/03009734.2018.1490831
18. RiksSvikt. Årsrapport 2022. https://www.ucr.uu.se/rikssvikt/om-rikssvikt/arsrapporter (last accessed 28 September 2023).
19. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, *et al.* Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380. https://doi.org/10.1002/ejhf.2115
20. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869. https://doi.org/10.1093/eurjhf/hfs105
21. Andrassy KM. Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease'. *Kidney Int* 2013;**84**:622–623. https://doi.org/10.1038/ki.2013.243
22. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al.* Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
23. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, *et al.*; *Heart Failure Association (HFA) of the European Society of Cardiology (ESC)*. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–625. https://doi.org/10.1002/ejhf.566
24. Ferreira JP, Rossignol P, Machu JL, Sharma A, Girerd N, Anker SD, *et al.* Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. *Eur J Heart Fail* 2017;**19**:1284–1293. https://doi.org/10.1002/ejhf.900
25. Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L, *et al.* Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail* 2022;**24**:1047–1062. https://doi.org/10.1002/ejhf.2483
26. Albert NM, Yancy CW, Liang L, Zhao X, Hernandez AF, Peterson ED, *et al.* Use of aldosterone antagonists in heart failure. *JAMA* 2009;**302**:1658–1665. https://doi.org/10.1001/jama.2009.1493
27. Curtis LH, Mi X, Qualls LG, Check DK, Hammill BG, Hammill SC, *et al.* Transitional adherence and persistence in the use of aldosterone antagonist therapy in patients with heart failure. *Am Heart J* 2013;**165**:979–986.e1. https://doi.org/10.1016/j.ahj.2013.03.007
28. Mavrakanas TA, Giannetti N, Sapir-Pichhadze R, Alam A. Mineralocorticoid receptor antagonists and renal outcomes in heart failure patients with and without chronic kidney disease. *Cardiorenal Med* 2020;**10**:32–41. https://doi.org/10.1159/000503223
29. Jonsson Holmdahl A, Norberg H, Valham F, Bergdahl E, Lindmark K. Mineralocorticoid receptor antagonists use in patients with heart failure and impaired renal function. *PLoS One* 2021;**16**:e0258949. https://doi.org/10.1371/journal.pone.0258949
30. Lund LH, Svennblad B, Melhus H, Hallberg P, Dahlström U, Edner M. Association of spironolactone use with all-cause mortality in heart failure: a propensity scored cohort study. *Circ Heart Fail* 2013;**6**:174–183. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000115
31. Butler J, Anker SD, Lund LH, Coats AJS, Filippatos G, Siddiqi TJ, *et al.* Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. *Eur Heart J* 2022;**43**:4362–4373. https://doi.org/10.1093/eurheartj/ehac401