MINERALOCORTICOID RECEPTOR ANTAGONIST (MRA) USE IN UK HEART FAILURE CARE: A NATIONAL PRIMARY CARE COHORT STUDY

AUTHORSHIP

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ABSTRACT

BACKGROUND AND AIMS

Mineralocorticoid receptor antagonists (MRAs) reduce mortality and hospitalisation in heart failure with reduced ejection fraction (HFrEF) but are underused, despite recommendation in key guidelines. Identifying the factors contributing to underuse and addressing adherence are key components of a learning health system. We aimed to evaluate MRA prescription in people with HFrEF who would benefit, based on the UK National Institute for Health and Care Excellence (NICE) HFrEF guideline.

METHODS

We used clinical code lists were used to identify people with HFrEF in primary care electronic health record (EHR) data from The Health Improvement Network (THIN) database. For each calendar year 2014 to 2020, we identified individuals who met the NICE guideline criteria for MRA therapy. We fitted mixed effects logistic regression models to determine the factors contributing to MRA prescription.

RESULTS

Among 24,135 people with HFrEF studied between 2014 to 2020, 12,150 person-years were eligible for MRA treatment. The MRA prescription rate increased from 41 to 55%. MRA prescription was inversely associated with age (odds ratio per one standard deviation, 95% confidence interval) (0.02 [0.01, 0.03]), increasing GFR (0.37 [0.25, 0.55]), hypertension (0.21 [0.40, 0.78]), and prescription of anti-hypertensives (0.03 [0.02, 0.07]). MRA prescription was associated with male gender (6.31 [3.20, 12.4]), dilated cardiomyopathy (25.9 [7.48, 89.4]), calendar year (2.17 [1.85, 2.54] per year after study start), and prescription of sacubitril/valsartan (214 [56, 823]).

CONCLUSIONS

MRAs are underused in people with HFrEF in the UK. Although prescribing increased between 2014 and 2020, half of the cohort still did not receive the therapy. Older age, gender, co-morbidities, and co-prescriptions were linked to MRA underuse. Understanding the factors contributing to under-prescribing at a population level should be used to inform quality improvement strategies.

KEYWORDS

Heart failure with reduced ejection fraction, NICE guideline, quality of care, national audit, mineralocorticoid receptor antagonist

KEY LEARNING POINTS

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Mineralocorticoid receptor antagonists (MRA), such as spironolactone, are under-prescribed in people with heart failure with reduced ejection fraction (HFrEF), despite evidence of efficacy.
- This study aimed to quantify to quantify adherence to guideline-directed MRA prescription in patients with HFrEF and identify factors contributing to MRA under-prescription.

WHAT THIS STUDY ADDS

- This study used electronic health records (EHR) to characterise HFrEF at a national scale and assess guideline-directed treatment.
- Population-scale audits can be implemented retrospectively, using EHR data to evaluate adherence to clinical practice guidelines.
- Older age is associated with MRA under-prescribing.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- At relatively low cost, national audit of electronic health records could be applied across treatment areas, providing insights into guideline-directed treatment.

INTRODUCTION

Heart failure (HF) is a clinical syndrome with current or prior symptoms and signs caused by intravascular fluid overload, associated with structural or functional abnormalities of heart function (1). The ESC long-term registry estimates that 60% of people with HF have left ventricular impairment and reduced left ventricular ejection fraction, termed HF with reduced ejection fraction (HFrEF) (2). Despite sustained progress in the management of HFrEF, mortality remains high in real-world cohorts (3). In a UK observational study, the 5-year mortality for HF was 45%, improving by 5% between 2000 and 2017 (4). The prevalence of HFrEF is estimated to be 5-10% in individuals over 70 years old (5). The management of HF in the older population is complicated by the co-occurrence of cardiometabolic disorders, including atrial fibrillation, chronic kidney disease, hypertension, and diabetes (6).

Mineralocorticoid receptor antagonist (MRA) treatment demonstrates symptomatic and survival benefits (7,8) and is cost-effective (9) . The UK National Institute for Health and Care Excellence (NICE) guideline on the management of chronic HF recommends MRA therapy for people treated with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) (renin angiotensin system inhibitor: RASi) and beta blocker with ongoing HF symptoms. In the European context, the 2021 European Society of Cardiology (ESC) guidelines recommend use of a RASi, beta blocker, and MRA in all people with HFrEF (1). Importantly, the MRA treatment effect is maintained in older age groups, although the risk of reduced renal clearance is greater in older people (10).

Treatment based on HF guidelines leads to improved HF survival (11), yet global evidence indicates that MRAs are under-prescribed in people with HFrEF (12–14). In the UK, the Department for Health reported under-prescribing and regional variation in the use of neurohormonal treatments for HFrEF (15). Following the RALES RCT, there were concerns about MRA adverse events (16). However, subsequent work has argued that MRA therapy is significantly underused, particularly in those with moderately reduced renal clearance or trivial hyperkalaemia (17).

This study aimed to investigate prescribing patterns using national-scale real world data. We hypothesised that MRA therapy would be underused in eligible people, and that individual-level factors would be associated with MRA prescription. Following an audit against national treatment guidelines, we sought to identify factors contributing to under-prescribing. We found evidence of MRA under-prescribing and uncovered explanatory patterns, demonstrating the value of this approach.

METHODS

DATA SOURCE

The Health Improvement Network (THIN) Database (a Cegedim Proprietary Database) is a UK primary care research database of primary care electronic health records since 1994. The data includes the demographics, clinical events (diagnoses, symptoms), test results, and prescription data of around 20 million people across the UK. The dataset has been shown to be representative of the wider UK population (18), and appropriate for studies of prescription use (19).

ETHICAL APPROVAL

THIN has database-wide ethical approval for purely observational studies conducted using THIN data (South Central – Oxford C Research Ethics Committee 20/SC/0011). This study was approved by the THIN Scientific Review Committee (protocol 20-005).

STUDY COHORT

The study cohort included people actively registered with a participating general practice during the study period. The data extract date was "2020-07-29". For an individual to have adequate data quality, the definition was one year after the first contact date or the start date of data collection and the earlier of the last contact date or the end of data collection. All people included in the study cohort had a diagnosis of HFrEF, determined using Read code lists for heart failure, left ventricular impairment, and dilated cardiomyopathy (Supplemental Material). This was aligned with the NICE CG108 indication for MRA: "Heart failure due to left ventricular systolic dysfunction (LVSD)". An LVEF threshold was not stated (20). The unit of analysis was one person with HFrEF in a one-year period ('person-year').

PHENOTYPING ALGORITHMS

We used validated clinical phenotypes represented as lists of Read codes for diagnoses and clinical findings from the HDR UK phenotype library, updating code lists where necessary (21). Phenotypes included acute coronary syndrome (ACS), unstable angina, stable angina, percutaneous coronary

intervention (PCI), coronary artery bypass grafting (CABG), myocardial infarction (MI), hypertension, diabetes, renal disease, HF symptoms, left ventricular dysfunction, and dilated cardiomyopathy (DCM). Medication data was extracted by Anatomical Therapeutic Chemical (ATC) class: antihypertensives (C02: antihypertensive drugs including alpha-adrenoreceptor antagonists, C08: dihydropyridine and non-dihydropyridine calcium channel blockers), beta blockers (C07), ACE inhibitors / ARB (C09), diuretics (C03), patiromer (V03AE09), sacubitril/valsartan (C09DX04), and SGLT2 inhibitors (A10BK).

MRA ELIGIBILITY

Eligibility for MRA was derived from the NICE guideline CG108 "Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care", published in 2010, in which MRA are a second line treatment for HFrEF, after first line treatment with a beta blocker and a RASi (20). NICE guidance CG108 was replaced by NG106 in 2018, but the criteria for MRA eligibility were unchanged (22). The algorithm implemented in this study was the prescription of an ACE inhibitor or ARB and the prescription of a beta blocker, ongoing heart failure symptoms (breathlessness or prescription of a diuretic) (Supplemental Materials) or myocardial infarction in the preceding 3 months. The exclusions from MRA prescription were based on prescribing guidelines. Exclusions were any single serum potassium value greater than 5.0 mmol/L in the preceding 12 months due to the risk of treatment-related hyperkalaemia, recorded MRA allergy, and any single glomerular filtration rate value (GFR) less than 30 mL/min/1.73m^2 in the preceding 12 months. Missing GFR values were carried forward within each person.

PRIMARY OUTCOME

The audit outcome was the proportion (95% confidence interval) of MRA-eligible people with an active MRA prescription during each year-long time period.

STATISTICAL ANALYSIS

Continuous variables (sodium, potassium, systolic blood pressure, diastolic blood pressure, and GFR) were mean aggregated by person-year. GFR was discretised into GFR groups G1-G3 (>90, 60-90, 30-60 mL/min/1.73m^2). In a data quality assessment, erroneous values were excluded outside the ranges: sodium 100-180 mmol/L (0.041%), potassium 2.0-10.0 mmol/L (0.058%), and GFR 0-200 mL/min/1.73m^2 (0.082%). We calculated eGFR using the four-variable modified MDRD formula (23).

MISSING VALUES

Alcohol, BMI, ethnicity, and smoking status were dropped due to a high proportion of missingness. The remaining categorical variables were complete. Numerical variables with a lower level of missingness (10-15%) (blood pressure, potassium, sodium) were imputed with person-level mean imputation, except for missing GFR values which were carried forward within each person.

MIXED EFFECTS LOGISTIC REGRESSION MODELS

Regression model variables included the time period, demographics (age and gender), laboratory values (sodium, potassium, and GFR), blood pressure (systolic and diastolic), and co-morbidities (ACS, CABG, diabetes, DCM, hypertension, MI, PCI, renal disease, stable angina, and unstable angina). Ischaemic heart disease (IHD) was defined as individuals with any of CABG, MI, PCI, stable angina, or unstable angina. Continuous variables were centred and scaled to one standard deviation. Time period and GFR were modelled both as continuous and discrete variables to assess non-linearity.

Mixed effects logistic regression models with a random intercept (univariable, and multivariable) were fitted using the R package 'lme4', accounting for repeated measures within patients. The intra-class correlation coefficient (ICC) was calculated to validate the use of a mixed model with a random intercept, meaning observations within the same patient are more similar than those from different patients. The ICC value of the null model with random intercept was 0.88, strongly supporting the inclusion of the random intercept. The variance inflation factor (VIF) was calculated to assess collinearity, quantifying if the regression coefficient standard errors were inflated by collinearity, using

the R package ‘performance’. Results were presented as odds ratios (95% CI) and corresponding P value for the null hypothesis of zero effect size.

A LASSO variable selection strategy was used to build the multivariable model. Blood pressure, serum sodium and serum potassium were not included in the multivariable model due to reverse causation. The LASSO logistic regression models were fitted to ten random samples of the longitudinal dataset stratified by participant. The optimal set of regression variables was determined by ten-fold cross-validation, as all variables selected at least once at the LASSO penalty “lambda-1SE”, the highest penalty value within one standard error of the best model fit.

POTASSIUM BINDERS

We modelled the potential for the use of potassium binders (such as patiromer or sodium zirconium cyclosilicate) to facilitate MRA therapy in those who would benefit but with potassium at least 6 mmol/L (see NICE TA599 and TA623).

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the design or conduct of this study.

RESULTS

THE COHORT ELIGIBLE FOR MRA PRESCRIPTION

Of 24,135 people with HFrEF during the study period, the cohort eligible for MRA prescription was selected using an algorithm derived from NICE guideline CG108 (Fig. 1). The algorithm required prescription of a RASi and a beta blocker, recent heart failure symptoms or recent prescription of a diuretic, serum potassium ≤ 5.0 mmol/L and GFR > 30 mL/min/1.73m^2 in the preceding year, and no allergy to MRAs. The cohort eligible for MRA prescription included 6,483 individuals and 12,150 person-years across the six time periods. The median age was 73 years (IQR: 65 to 81 years), and the proportion of females was 30% (Table 1). The mean count of observation years per person was 1.87 (SD: 1.21, range 1-6). Geographical coverage represented the UK (England 41%, Northern Ireland: 4.7%, Scotland: 31%, Wales: 24%).

AUDIT OF MRA PRESCRIPTION

In the MRA-eligible cohort, 49.9% were prescribed MRA therapy (Table 1). Over the study time period, prescription of MRA therapy increased significantly from 41% [95% CI: 39%, 43%] to 57% [55%, 60%] (Fig. 2).

REGRESSION MODELS OF MRA PRESCRIPTION

We determined the factors affecting MRA prescription in people who would benefit. The sample size for the regression models was 11,085 person-years. Significant negative associations with MRA prescription were demonstrated for age (0.02 [95% CI: 0.01, 0.03]), blood pressure (SBP 0.24 [0.21, 0.29] and DBP 0.61 [0.53, 0.70]), hypertension (0.07 [0.03, 0.14]), LV impairment (0.04 [0.01, 0.13]), prescription of anti-hypertensives (0.02 [0.01, 0.04]), and serum sodium (0.29 [0.24, 0.35]) (Fig. 3; Table 2). Significant positive associations were demonstrated for dilated cardiomyopathy (DCM) (107 [48.9, 232]), male gender (15.3 [7.21, 32.4]), serum potassium (3.71 [3.12, 4.41]), prescription of sacubitril/valsartan (230 [108, 490]), and progressive time period. The discrete time period variable

demonstrated that the effect of progressive time period was linear (Fig. 3), and therefore the continuous time period variable was used in subsequent analyses.

We sought to model the multiple factors driving MRA prescribing, so fitted a multivariable regression model. We selected variables using a LASSO regression approach and assessed for problematic co-linearity (Supplemental Material). The multivariable model demonstrated inverse associations with MRA prescription for age (0.02 [0.01, 0.03]), prescription of anti-hypertensives (0.03 [0.02, 0.07]), hypertension (0.21 [0.40, 0.78]), and increasing GFR (0.37 [0.25, 0.55]). Significant associations with MRA prescription included prescription of sacubitril/valsartan (214 [56, 823]), DCM (25.9 [7.48, 89.4]), male gender (6.31 [3.20, 12.4]), and progressive year (2.17 [1.85, 2.54]) (Fig. 4; Table 3).

POTASSIUM BINDERS

Using the NICE recommended eligibility criteria for patiromer and sodium zirconium cyclosilicate (NICE TA599 and TA623), we modelled the potential use of patiromer in those who would benefit but have hyperkalaemia of at least 6.0 mmol/L (Supplemental Materials). Over the study period, a total of 114 participants were eligible for patiromer in a year period, compared to 12,150 eligible for MRA with potassium less than 5.0 mmol/L.

DISCUSSION

This study evaluated the use of a guideline-directed medical therapy in a cohort of people with HFrEF using electronic health records at a national scale.

We studied MRA prescription in 6,483 people with HFrEF who would benefit from MRA therapy across six years, computing eligibility for MRA therapy based on NICE HF guidelines. From 2014-2019, MRA prescription increased from 41% to 57%. We discovered factors associated with MRA prescription including age, gender, co-morbidity (hypertension, chronic kidney disease, and DCM), and co-prescriptions (sacubitril/valsartan and anti-hypertensives).

In a recent national study of hospitalised heart failure patients, the proportion of people with HFrEF who were discharged with an MRA prescription was above 50% in 2019, in agreement with this study (24), with the proportion rising to above 60% in 2022.

The UK National Heart Failure Audit (NHFA) includes only patients with an acute hospital admission, whereas our study includes all those known to primary care, who may not have a hospital admission. It can be expected that patients with an acute hospital admission and secondary care input are not the same as those without an acute hospital admission. Electronic health record studies have shown that 26% of people with HF are known only to primary care, 34% are known only to hospital, 27% are known to both, and the remainder only on a death certificate (25). Therefore, both hospital and primary care studies will be required for the purpose of auditing clinical practice. The NHFA has shown increasing MRA prescription between 2014 and 2020 (26), rising more in those with specialist input (55% to 65%) compared to those without specialist input (35% to 40%). Triple therapy of RASi, beta blocker, and MRA was used in 55% (specialist input) and 25% (no specialist input) of people with HFrEF. The NHFA found that "older patients are less likely to access diagnostics, life-saving drugs and specialist care" and that "access to diagnostics, cardiology care and cardiology beds needs to improve for females" (26). This study complements the NHFA in two ways. The primary care focus of this study complements the selection effect of the NHFA inpatient hospital cohort. Secondly, the use in this study of NICE guideline CG108 to identify those who would benefit from MRA therapy provides a stronger basis to assess under-prescribing. Using this approach, factors associated with MRA under-use can inform a strategy to improve guideline-directed prescribing in under-treated groups.

Contemporary work has shown that serious hyperkalaemia is rare in the MRA-treated group, and that hypokalaemia is a common problem in the study cohort, which is well-treated with MRA therapy (27). In the case where significant hyperkalaemia limits MRA prescription, potassium-lowering therapies can be considered. Patiromer and sodium zirconium cyclosilicate are approved for use in people eligible for MRA therapy but with hyperkalaemia above 6.0 mmol/L (28). We demonstrated that

individuals can be identified algorithmically from primary care data, and found a modest number who might benefit from this approach.

Older age is associated with reduced MRA therapy (12,14) with 'avoidable undertreatment' and fewer hospital visits (13). In this study, older age was strongly associated with MRA underuse. Meta-analysis of MRA RCTs has shown equal effectiveness for hospitalisation and CVD death in older people, albeit with a greater drop in renal clearance on MRA therapy (10). Factors contributing to under-prescribing are likely to be clinical concerns about deterioration of renal function, frailty, polypharmacy, postural hypotension, and monitoring requirements.

Male gender was associated with increased MRA prescription. The 2022 NHFA found that female people with HFrEF were less likely to have an MRA prescription (26). International studies have found contrasting evidence with lower prescription (13) and higher (12) rates in male people.

Prescription of sacubitril/valsartan was strongly associated with MRA prescription, and likely indicates secondary care input, which is associated with greater MRA prescription (26). Thus, sacubitril/valsartan prescription represents the unmeasured confounder, specialist input. In a Swedish study, patients with HFrEF eligible for MRA prescription but untreated were unlikely to have specialist cardiology follow up (17). Thus, targeted specialist input for those in groups of MRA under-use may improve treatment disparity.

Moderately reduced renal clearance was associated with higher MRA prescription in this study of people with an GFR > 30 mL/min/1.73m^2. Acutely, MRA prescription leads to a modest decrease in renal clearance but multiple RCTs show no long-term effect (29). It may be that renal clearance is moderately reduced by MRA prescription (reverse causation) or that greater HF severity is a common cause of MRA prescription and prescription of diuretics, leading to reduced renal clearance.

A coded diagnosis of hypertension and the prescription of anti-hypertensive drugs (other than ACEi/ARB and beta blockers, which were prescribed in all patients) were associated with lower MRA prescription. Studies have shown that spironolactone is an effective antihypertensive drug (30) and,

for those developing HFrEF, switching to spironolactone should be considered. Lower BP predicts worse outcomes and is associated with higher NYHA severity, lower renal clearance, and lower ejection fraction (31,32). HF severity may be the driver of MRA prescription, possibly linked to specialist care. Male gender, a negative prognostic factor in HF prediction algorithms, was also linked to higher MRA prescription.

STRENGTHS AND LIMITATIONS

The findings from this study are strengthened by several factors. The study cohort is representative of people with HFrEF across UK geography. Routinely collected primary care data mitigates the selection bias induced by the inclusion of only hospital treated patients. Both factors support the generalisability of the findings. However, this dataset was not linked to secondary care data, and so the findings are limited to the group known to primary care.

This study used a treatment eligibility algorithm that mirrors national guidelines. Thus, the findings are directly relevant and applicable to UK practice. This study did not have access to free text GP clinical notes, and so was not able to report on appropriate clinical reasons for non-prescription of MRA, which may be recorded in the clinical notes.

Diagnosis codes for HF in primary care records may not specify the subtype of HF, which complicates HFrEF cohort selection. However, using the same dataset as this study, Sundaram and colleagues validated an approach to HFrEF cohort identification using a combination of HFrEF codes and the prescription of two classes of guideline directed medical therapy (33). We recognise that the HFrEF phenotyping procedure is vulnerable to false negatives, to be balanced against the importance of the positive predictive value of HFrEF case ascertainment.

CLINICAL IMPLICATIONS

This study complements the UK National Heart Failure Audit, bringing a primary care perspective and focusing on guidelines-directed MRA prescribing (26). With six years of longitudinal clinical data (2014-2020), this study provides more than a snapshot of HF care.

To improve guideline-directed MRA prescription, we must understand the factors driving lower use. Prescribing in older age and female gender should be supported, and specialist input is likely to improve appropriate MRA prescription.

There is potential to use potassium-lowering therapies (oral potassium binders) to enable MRA prescription in those with moderate hyperkalaemia, however the number of people with HFrEF meeting these criteria in routine clinical practice remains low.

FUTURE DIRECTIONS

Understanding the factors contributing to prescribing using real world data could improve adherence to guideline-directed therapy and target improvement resources. In a learning health system, data-driven tools, including computable guidelines, could support guideline-directed treatment (34) and be extended to other therapeutic areas. Initiatives to represent clinical practice guideline recommendations in computable formats have the potential to help address the challenges and potential biases in prescribing that are identified in this study. Computable representations enable the faithful translation of guideline recommendations into clinical decision support tools and provide data standards that inform audit and quality initiatives.

In conclusion, in this UK national audit of MRA prescribing in people with HFrEF, MRA prescription increased over the study period, but remained below the target. Major factors affecting prescribing were older age, gender, co-morbidities, and co-prescriptions. Evaluating the factors contributing to under-prescribing points to how to improve care, in the context of clinical complexity.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

This study uses individual patient data from general practice records, and access to data is therefore restricted. Access to the structured data for research from the THIN database can be sought from The Health Improvement Network Ltd. (a Cegedim company). Applications need to be approved by the THIN Scientific Review Committee.

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TABLES

TABLE 1.

Cohort characteristics. N = 12,150 person-years (6,483 individuals) were eligible for mineralocorticoid receptor antagonist prescription. BMI: body mass index, BP: blood pressure, GFR: glomerular filtration rate, LV: left ventricle. Median (IQR); n (%).

Variable	MRA not prescribed	MRA prescribed	Total
n	6,090 (50.1%)	6,060 (49.9%)	12,150
Age (years)	76 (68, 83)	70 (61, 78)	73 (65, 81)
Alcohol consumption (units per week)	7 (2, 14)	8 (3, 14)	7 (2, 14)
Missing (n)	4,979 (82%)	5,007 (83%)	9,986 (82%)
BMI (kg/m^2)	29 (25, 33)	30 (26, 34)	29 (26, 34)
Missing (n)	2,258 (37%)	2,231 (37%)	4,489 (37%)
BP: diastolic (mmHg)	72 (67, 79)	71 (65, 78)	72 (66, 78)
Missing (n)	607 (10%)	669 (11%)	1,276 (11%)
BP: systolic (mmHg)	129 (119, 139)	120 (111, 131)	125 (114, 135)
Missing (n)	607 (10%)	669 (11%)	1,276 (11%)
Country			
England	2,562 (42%)	2,410 (40%)	4,972 (41%)
Northern Ireland	255 (4.2%)	313 (5.2%)	568 (4.7%)
Scotland	2,040 (33%)	1,710 (28%)	3,750 (31%)
Wales	1,233 (20%)	1,627 (27%)	2,860 (24%)
Dilated cardiomyopathy	255 (4.2%)	616 (10%)	871 (7.2%)
Diabetes	1,729 (28%)	1,636 (27%)	3,365 (28%)
Ethnicity			
White	2,489 (41%)	2,260 (37%)	4,749 (39%)
South Asian	34 (0.6%)	86 (1.4%)	120 (1.0%)
Black	23 (0.4%)	49 (0.8%)	72 (0.6%)
Other	20 (0.3%)	14 (0.2%)	34 (0.3%)
Mixed	3 (<0.1%)	17 (0.3%)	20 (0.2%)
Missing	3,521 (58%)	3,634 (60%)	7,155 (59%)
Gender			
Male	3,972 (65%)	4,488 (74%)	8,460 (70%)
Female	2,118 (35%)	1,572 (26%)	3,690 (30%)
GFR (mL/min/1.73m^2)	62 (50, 76)	64 (51, 78)	63 (50, 77)
Missing (n)	777 (13%)	725 (12%)	1,502 (12%)
GFR group (mL/min/1.73m^2)			
G1 (>90)	487 (9.2%)	582 (11%)	1,069 (10%)
G2 (60-90)	2,399 (45%)	2,469 (46%)	4,868 (46%)

G3 (30-60)	2,427 (46%)	2,284 (43%)	4,711 (44%)
Missing (n)	777 (13%)	725 (12%)	1,502 (12%)
Hypertension	3,716 (61%)	2,920 (48%)	6,636 (55%)
Ischaemic heart disease	2,849 (47%)	2,759 (46%)	5,608 (46%)
LV impairment	5,992 (98%)	5,850 (97%)	11,842 (97%)
Myocardial infarction	2,048 (34%)	2,249 (37%)	4,297 (35%)
Potassium max (mmol/L)	4.50 (4.30, 4.80)	4.70 (4.40, 5.00)	4.60 (4.30, 4.90)
Missing (n)	950 (16%)	878 (14%)	1,828 (15%)
Potassium mean (mmol/L)	4.40 (4.15, 4.65)	4.55 (4.30, 4.80)	4.50 (4.20, 4.73)
Missing (n)	950 (16%)	878 (14%)	1,828 (15%)
Prescription: antihyper-tensives	1,513 (25%)	673 (11%)	2,186 (18%)
Prescription: sacubi-tril/valsartan	42 (0.7%)	391 (6.5%)	433 (3.6%)
Prescription: SGLT2 in-hibitor	80 (1.3%)	107 (1.8%)	187 (1.5%)
Smoking status			
Never	1,027 (26%)	957 (25%)	1,984 (25%)
Past	2,372 (59%)	2,221 (58%)	4,593 (59%)
Current	602 (15%)	643 (17%)	1,245 (16%)
Missing (n)	2,089 (34%)	2,239 (37%)	4,328 (36%)
Sodium (mmol/L)	140.00 (138.33, 142.00)	139.20 (137.50, 141.00)	140.00 (138.00, 141.33)
Missing (n)	927 (15%)	865 (14%)	1,792 (15%)
Time period (start)			
2014	1,288 (21%)	903 (15%)	2,191 (18%)
2015	1,052 (17%)	845 (14%)	1,897 (16%)
2016	1,028 (17%)	1,029 (17%)	2,057 (17%)
2017	969 (16%)	1,060 (17%)	2,029 (17%)
2018	982 (16%)	1,182 (20%)	2,164 (18%)
2019	771 (13%)	1,041 (17%)	1,812 (15%)

TABLE 2.

Univariable mixed effects logistic regression model. The outcome was mineralocorticoid receptor antagonist (MRA) prescription in those who would benefit. Odds ratios (OR) are standardised to a one standard deviation change for continuous variables. 95% confidence intervals (CI) are presented. BP: blood pressure, GFR: glomerular filtration rate (units: mL/min/1.73m^2), LV: left ventricle.

Term	**Odds Ratio (OR)**	**95% CI (lower)**	**95% CI (upper)**	**P value**
Age	0.02	0.01	0.03	<0.001
BP: diastolic (mmHg)	0.61	0.53	0.70	<0.001
BP: systolic (mmHg)	0.24	0.21	0.29	<0.001
Dilated cardiomyopathy	107	48.9	232	<0.001
Diabetes	0.84	0.63	1.12	0.241
Gender: female (reference)				
Gender: male	15.3	7.21	32.4	<0.001
GFR: continuous (mL/min/1.73m^2)	1.03	0.87	1.22	0.756
GFR group >90 (reference)				
GFR group 60-90	1.07	0.77	1.49	0.683
GFR group 30-60	1.15	0.80	1.66	0.448
Hypertension	0.07	0.03	0.14	<0.001
Ischaemic heart disease	0.73	0.55	0.97	0.031
LV impairment	0.04	0.01	0.13	<0.001
Myocardial infarction	1.27	0.94	1.71	0.117
Potassium (max) (mmol/L)	4.99	4.14	6.03	<0.001
Potassium (mean) (mmol/L)	3.71	3.12	4.41	<0.001
Prescription: antihypertensives	0.02	0.01	0.04	<0.001
Prescription: sacubitril/valsartan	230	108	490	<0.001
Prescription: SGLT2 inhibitor	1.71	0.83	3.52	0.142
Sodium (mean) (mmol/L)	0.29	0.24	0.35	<0.001
Time period (continuous)	1.76	1.57	1.97	<0.001
Time period: 2014 (reference)				
Time period: 2015	1.77	1.30	2.40	<0.001
Time period: 2016	2.85	2.05	3.95	<0.001
Time period: 2017	3.39	2.41	4.78	<0.001
Time period: 2018	4.32	3.04	6.13	<0.001
Time period: 2019	5.85	4.00	8.54	<0.001

TABLE 3.

Multivariable mixed effects logistic regression model. The outcome was mineralocorticoid receptor antagonist (MRA) prescription in those who would benefit. Odds ratios (OR) are standardised to a one standard deviation change for continuous variables. 95% confidence intervals are presented. GFR: glomerular filtration rate group (mL/min/1.73m^2), IHD: ischaemic heart disease.

Term	**Odds Ratio (OR)**	**95% CI (lower)**	**95% CI (upper)**	**P value**
Age	0.02	0.01	0.03	<0.001
Dilated cardiomyopathy	25.85	7.48	89.40	<0.001
GFR: continuous	0.37	0.25	0.55	<0.001
Gender: female (reference)				
Gender: male	6.31	3.20	12.43	<0.001
GFR group >90 (reference)				
GFR group 60-90	1.78	0.83	3.83	0.14
GFR group 30-60	2.41	0.85	6.87	0.10
Hypertension	0.40	0.21	0.78	0.01
Prescription: antihypertensives	0.03	0.02	0.07	<0.001
Prescription: sacubitril/valsartan	213.82	55.54	823.21	<0.001
Time period	2.17	1.85	2.54	<0.001

FIGURE LEGENDS

FIGURE 1.

People with heart failure (HF) were identified in a primary care research database using clinical code lists (Supplemental Material) across six calendar years. The selection criteria included a diagnosis of heart failure with reduced ejection fraction (HFrEF), the prescription of an ACE inhibitor (ACEi) or angiotensin receptor antagonist (ARB), the prescription of a beta blocker, symptoms of HF or use of a diuretic, potassium not greater than 5.0 mmol/L in the last year, no known allergy to a mineralocorticoid receptor antagonist, and a glomerular filtration rate (GFR) not less than 30 mL/min/1.73m^2 within the last year.

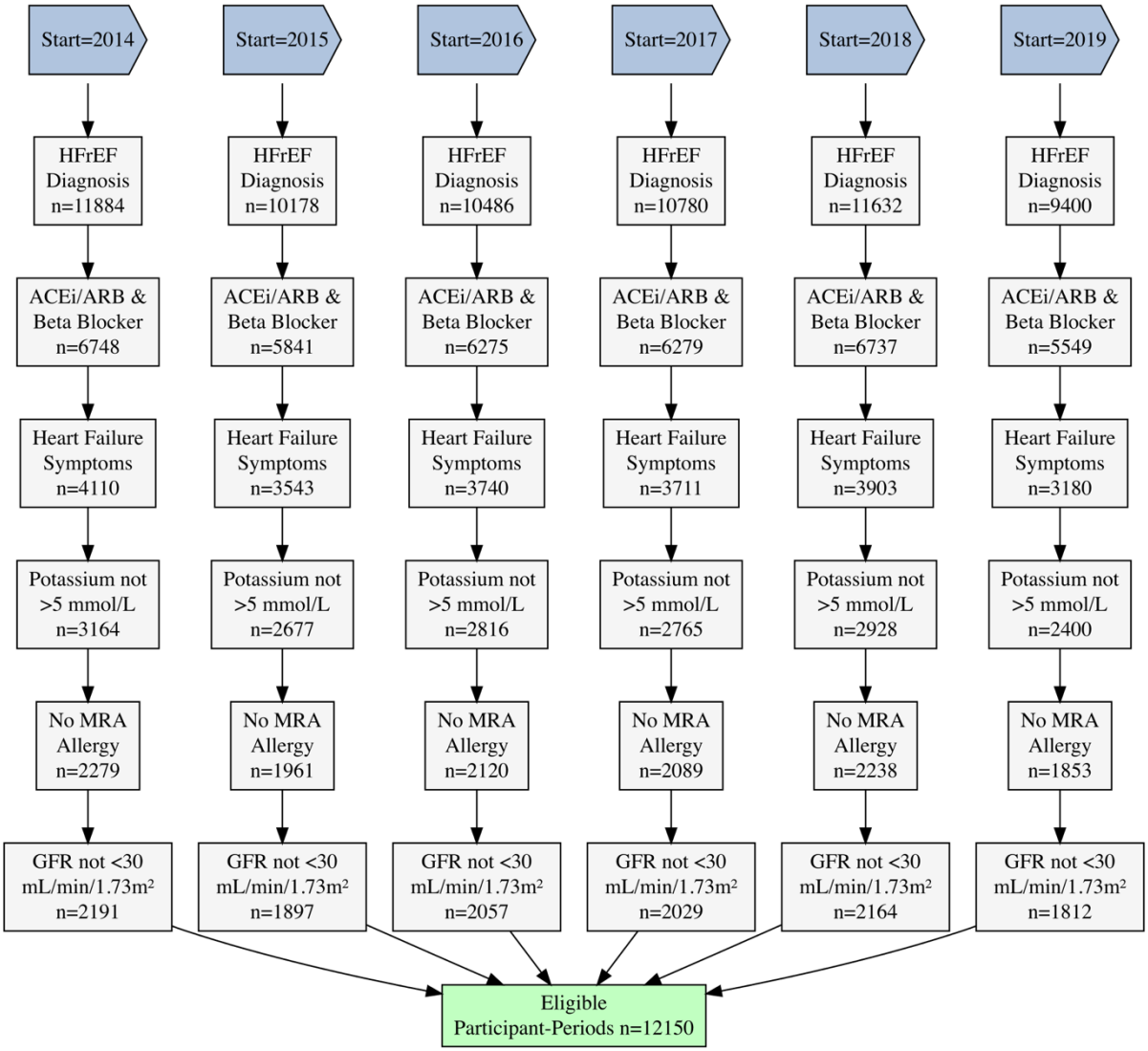

FIGURE 2.

The proportion (95% confidence interval) of people with HFrEF eligible for mineralocorticoid receptor antagonist (MRA) therapy who were prescribed MRA therapy, in a UK national audit of primary care electronic health records.

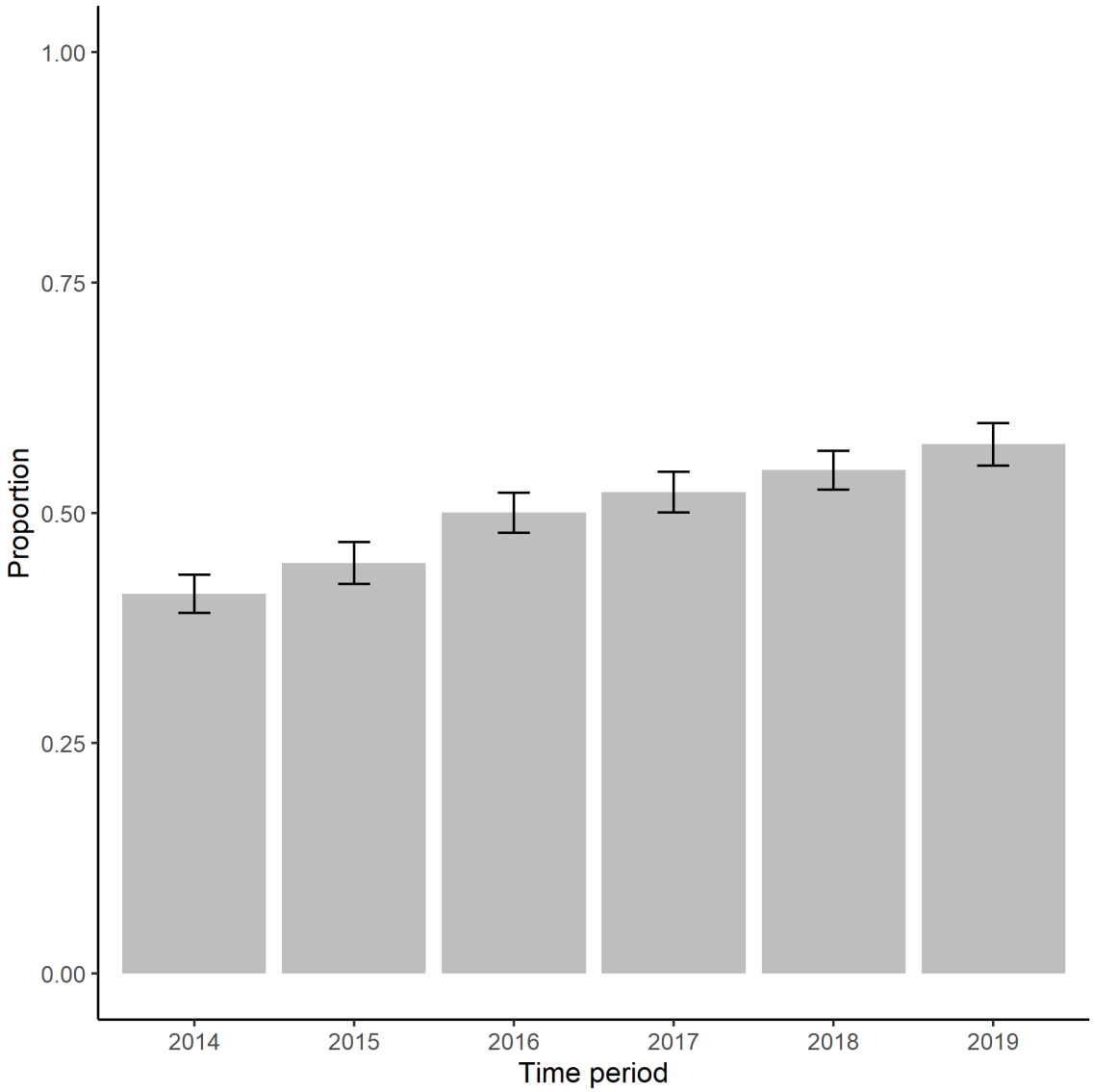

FIGURE 3.

A univariable mixed-effects logistic regression model. Factors associated with mineralocorticoid receptor antagonist prescription in eligible people with HFrEF. The odds ratio and 95% confidence interval are plotted. BP: blood pressure, DCM: dilated cardiomyopathy, GFR: glomerular filtration rate group (G1 >90, G2 60-90, G3 30-60 mL/min/1.73m^2), LV: left ventricle, IHD: ischaemic heart disease, MI: myocardial infarction.

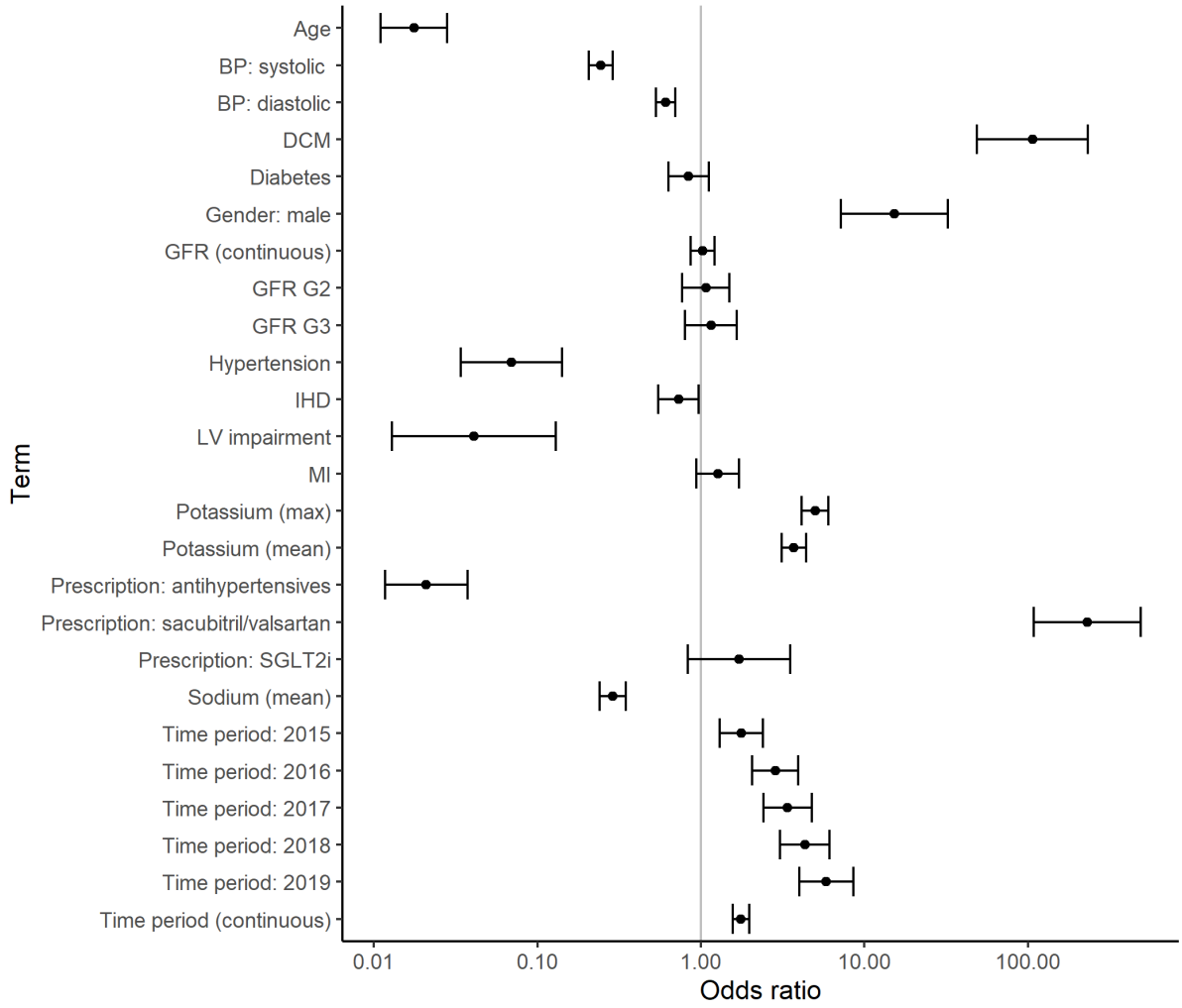

FIGURE 4.

A multivariable mixed effects logistic regression model. Factors associated with mineralocorticoid receptor antagonist prescription in eligible people with HFrEF. The odds ratio and 95% confidence interval are plotted. DCM: dilated cardiomyopathy, GFR: glomerular filtration rate group (G1 >90, G2 60-90, G3 30-60 mL/min/1.73m^2), IHD: ischaemic heart disease.