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Temporal Trends in Heart Failure Medication Use in a Population-Based Cohort Study

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Abstract

Objective: We examined temporal heart failure (HF) prescription patterns in a large representative sample of real-world patients in the UK, using electronic health records (EHR).

Methods: From the CALIBER resource, we identified 85,732 patients with a HF diagnosis between 2002-2015. Almost 50% of HF patients were women and the median age was 79.1 [70.2-85.7] years, with age at diagnosis increasing over time.

Results: We found several trends in pharmacological HF management, including increased beta-blocker prescriptions over time (29% in 2002-2005 and 54% in 2013-2015), which was not observed for mineralocorticoid receptor-antagonists (MR-antagonists) (18% in 2002-2005 and 18% in 2013-2015); higher prescription rates of loop diuretics in women and elderly patients together with lower prescription rates of RAS-inhibitors, beta-blockers, or MR-antagonists in these patients; little change in medication prescription rates after 6 months of HF diagnosis; and lastly, patients hospitalised for HF who had no follow-up in primary care had considerably lower prescription rates compared to patients with a HF diagnosis in primary care with or without HF hospitalisation.

Conclusion: In the general population, the use of MR-antagonists for HF remained low and did not change throughout 13 years of follow up. With large differences between HF patients, with lowest prescription rates observed in women, elderly patients, and those not followed-up in primary care, these findings suggest HF management can be improved by focusing effort and healthcare resources on improving communication between primary and secondary care.

Keywords: Prescription patterns, ACE-inhibitors, ARB, RAS-inhibitors, Beta-blockers, MRA, Loop diuretics, Heart failure, Electronic health records.

Article summary

Strengths and limitations of the study

- Large cohort of HF patients from primary and secondary care
- Long follow-up period of almost 15 years
- Unable to differentiate between HF subphenotypes HFrEF or HFpEF
- Unknown treatment eligibility, contraindications or intolerances that may affect the choice of treatment

Key questions

What is already known about this subject?

Previous studies suggest that many heart failure (HF) patients do not receive guideline recommended therapies. Optimal treatment seems to be particularly challenging in elderly patients, women or patients with multiple comorbidities and contraindications for treatments

What does this study add?

This study shows the prescription trends in HF patients in the general population and medication use in HF patients in the years prior to their HF diagnosis.

How might this impact on clinical practice?

Our findings suggest that HF management could be improved by focusing healthcare resources on improving communication between primary and secondary care. We need to direct more effort towards effective implementation of guideline-recommended therapies in real-world HF care.

Abbreviations

HF	Heart failure
EHR	Electronic health records
CPRD	Clinical Practice Research Datalink
HES	Hospital Episode Statistics
ONS	Office for National Statistics
COPD	Chronic obstructive pulmonary disease
RAS-inhibitors	Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers
MR-antagonists	Mineralocorticoid receptor-antagonists
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction

Introduction

Heart failure (HF) is a common public health burden, with the prevalence of HF estimated at approximately 500.000 patients in the UK.(1, 2) Once diagnosed, initiation and up titration of guideline recommended therapies can reduce morbidity and mortality, however 5-year survival still remains 20% to 50%.(3, 4)

Several observational studies have assessed treatment uptake in HF patients following their diagnosis. These studies suggest that many patients did not receive guideline recommended therapies, or at low doses with sparse attempts for up titration.(5–8) Optimal treatment for effective disease management seems to be particularly challenging in elderly patients, women or patients with multiple comorbidities and contraindications for treatments.(7, 8) At present, few data are available for prescription trends in HF patients in the general population and even fewer data are available that shed light on medication use in HF patients in the years prior to their HF diagnosis.

The CALIBER resource curates primary and secondary care EHR of 5 million individuals in the UK, including HF diagnosis and medication prescriptions.(9) Given the amount of information available, medication use of all HF patients in the community may be investigated – including those which are underrepresented in heart failure disease registries of randomised clinical trials.

Therefore, we sought to examine HF treatment prescription patterns following a HF diagnosis for the overall population as well as specific subgroups based on gender (e.g. women), age (e.g. elderly), social economic status and healthcare setting (e.g. primary care or secondary care), in a large representative sample of real-world patients in the UK, using electronic health records (EHR). (10)

Methods

Data source

Patients were selected from the CALIBER resource, which consists of three linked databases: The Clinical Practice Research Datalink (CPRD) with primary care EHR, Hospital Episodes Statistics (HES) containing coded diagnoses and surgical procedures from inpatient hospital admissions, and the Office for National Statistics (ONS) registry containing cause-specific mortality data.(10) Previous work has shown that these patients are representative of the general population in the UK.(11, 12)

Study population

Patients were included at their first record of HF from CPRD or HES between January 1st 2002 and December 31st 2015. In CPRD, events were defined by a diagnosis of HF based on READ clinical codes and in HES by a diagnosis of HF based on ICD-10 codes. The same HF diagnosis codes were used as in previous papers, with in addition several newer READ codes listed in **Table S1**.(13, 14) All patients were eligible for inclusion if they were aged 18 years or older, were registered with a GP for at least one year prior to diagnosis of HF, in a practice that had at least one year of up-to-standard data recording in CPRD. The first record of HF from CPRD or HES was considered the index date. Individuals were censored at the earliest date from the date of de-registration, the last data collection date, the date of death or at the study end date (31st December 2015). Data from HF patients up to 3 years prior to index date was included in this study.

Patient and public involvement

There was no patient or public involvement in this research.

HR phenotyping variables

Baseline patient characteristics were based on records from CPRD and/or HES prior to index date, including demographics (age, sex, ethnicity, social deprivation) cardiovascular risk factors (smoking, BMI, diastolic blood pressure and systolic blood pressure and estimated glomerular filtration rate, comorbidities (a medical history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, ischaemic heart disease, valvular disease and history of cancer) and medication prescription, classified as: RAS-inhibitors (Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers), beta-blockers, mineralocorticoid receptor-antagonists (MR-antagonists) and loop diuretics. Definitions of these variables could be found online at http://www.caliberresearch.org/portal/.

Medication prescription for RAS-inhibitors, beta-blockers, MR-antagonists and loop diuretics was identified between three years prior to HF diagnosis up to three years after HF diagnosis per the following increments: -36 months to -24 months, -24 months to -18 months, -18 months to -12 months, -12 months to -6 months, -6 months to -3 months, -3 months to HF diagnosis, HF diagnosis to +3 months, +3 months to +6 months, +6 months to +12 months, +12 months to +18 months, +18 months to +24 months and +24 to +36 months.

Healthcare setting was characterised as primary care only (no HF hospitalisation), secondary care only (no HF diagnosis recorded in primary care) or HF diagnosis in both primary and secondary care. Ethnicity records from CPRD and HES were combined and categorised as Caucasian, Asian, Black or Other. Social deprivation was measured as quintiles of the index of multiple deprivation of the geographical area of the primary care practice, a score calculated based on seven indices of deprivation: income, employment, health and disability, education, barrier to housing and services, crime and living environment.(15) Smoking status was classified as never, ex- or current smokers.

Statistical analysis

Patient characteristics were summarised as mean (SD) or median [IQR] for continuous variables and percentages for categorical variables. The percentage of HF patients prescribed pharmacological treatments was calculated per increment and per time period as defined by publication year of previous ESC guidelines (2001, 2005, 2008 and 2012)(1, 16–19): 2002-2005, 2006-2008, 2009-2012 and 2013-2015. In addition to the overall cohort, we investigated several subgroups: age (< vs. ≥ 75 years old), sex (men vs. women), social economic status (lowest quintile of social deprivation vs. the rest) and setting (only follow-up in primary care vs. only in secondary care vs. follow-up in primary care after HF hospitalisation). All analyses were performed using R version 3.6.1.

Results

Baseline characteristics

We identified 85,732 patients with a HF diagnosis. The study flow diagram could be found in **Figure S1**. Median follow-up after HF diagnosis (index date) was 2.1 years [0.6 – 4.5] years. **Table 1** shows the overall baseline patient characteristics and per time period 2002-2005, 2006-2008, 2009-2012 and 2013-2015. Almost 50% of patients were women and the median age was 79.1 [70.2 - 85.7] years, with age at HF diagnosis increasing over time. Overall, many HF patients had comorbidities, most common were hypertension (61%), ischaemic heart disease (44%) and atrial fibrillation (37%), with increasing numbers of patients with comorbidities over time. Approximately 40% (n= 34,489) of patients were followed-up in primary care after a HF hospitalisation, 20% (n= 15,330) of patients were only known in primary

care and never hospitalised for HF and the remaining 40% (n= 35,913) of patients had no follow-up in primary care after HF hospitalisation.

Overall prescription patterns

Overall prescription patterns are shown in **Figure 1**. Many patients were prescribed medication before HF diagnosis, especially RAS-inhibitors (20% in 2002-2005 to 46% in 2013-2015). Over time, beta-blocker prescription after HF diagnosis increased from 30% in 2002-2005 to 55% in 2013-2015. Throughout the follow up of 13 years, there were little observed changes for MR-antagonist uptake, this remained at 20% throughout time after HF diagnosis. The largest observed changes in prescription patterns occurred between 6 months before and after HF diagnosis (**Figure 1**). Approximately 20% of HF patients were prescribed a loop diuretic up to three years prior to HF diagnosis.

Setting-specific prescription patterns

Setting-specific prescription patterns are shown in **Figure 2**. Patients followed-up in primary care after HF hospitalisation had the highest prescription rates for all types of medication. Over time, the prescription for loop-diuretics, RAS-inhibitors and beta-blockers converged together. In these patients the prescription for MR-antagonists increased over time after HF diagnosis from 20% in 2002-2005 to 30% in 2013-2015.

Patients known in primary care but never hospitalised for HF had lower prescription rates for all types of treatment compared to patients with primary care follow-up and at least one HF hospitalisation. Mainly loop diuretics were less prescribed in these patients and the prescription of loop diuretics decreased over time with 65% of patients receiving loop diuretics after HF diagnosis in 2002-2005 compared to just over 40% in 2013-2015.

Patients hospitalised for HF but without a HF diagnosis in primary care, had the lowest prescriptions rates for loop diuretics, RAS-inhibitors and beta-blockers, which remained stable over time (50%, 45%, and 45% in 2013-2015 respectively). MR-antagonists were only prescribed in 13% of patients after HF diagnosis, this was similar for each time period.

Age-specific prescription patterns

Differences in prescription according to age categories are shown in **Figure 3**. The observed increase in prescriptions for RAS-inhibitors, beta-blockers, and MR-antagonists between 6 months before HF diagnosis to 6 months after HF diagnosis was less pronounced in elderly patients. The average increase in elderly patients was 12%, 7%, 8% for RAS-inhibitors, beta-blockers and MR-antagonists respectively, while younger patients had an average increase of 23%, 19% and 13% for RAS-inhibitors, beta-blockers and MR-antagonists respectively. On the other hand, a higher proportion of elderly patients were treated with loop-diuretics compared to younger patients, both before and after HF diagnosis (45% before and 63% after HF diagnosis in elderly compared to 27% before and 47% after HF diagnosis for younger patients in 2013-2015). After HF diagnosis, a higher percentage of younger patients were prescribed with RAS-inhibitors and beta-blockers compared to older patients.

Sex-specific prescription patterns

Differences in prescription between men and women are shown in **Figure 4**. Loop diuretics were prescribed in a higher proportion of women compared to men, this difference was already present prior to HF diagnosis where 6 months before diagnosis 30% of women and 20% of men were prescribed a loop diuretic. After HF diagnosis, the most prescribed medication for women was a loop diuretic, while a higher proportion of men were prescribed

a RAS-inhibitor. Men were also more often prescribed RAS-inhibitors, beta-blockers and MR-antagonists after HF diagnosis compared to women.

Social economic status-specific prescription patterns

Social economic status-specific prescription patterns are shown in **Figure 5**. We did not observe any discernible differences between patients in low vs. high social-economic areas (highest quintile of social economic deprivation).

Discussion

In this large-scale study of 85,732 HF patients we investigated treatment prescription patterns in a representative sample of real-world patients with HF in the UK between 2002 and 2015. We found three important trends in pharmacological HF management: a) increased use of beta-blockers, whereas there was no increased uptake of MR-antagonists over 13 years follow up; b) prescription rates remained almost unchanged after the first 6 months following a HF diagnosis; and lastly, c) higher rates of loop diuretics in women and elderly patients together with lower prescription rates for RAS-inhibitors, beta-blockers, or MR-antagonists.

Temporal trends in heart failure medication

Even though prescription rates increased over time from 2002 to 2015, overall prescription rates remained low. This is in line with previously published studies.(5–8, 20) Low prescription rates could be attributed to the mixed HF cases found in EHR. We were unable to distinguish HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) based on medical records, thereby including known differences in treatment recommendations for these HF phenotypes.(1)

We found no major differences in prescription behaviour after the publication of ESC guidelines, however we did observe the gradual increase of beta-blockers as one of the cornerstones of HF treatment. RAS-inhibitors were prescribed in a high proportion of patients throughout the years of the study, presumably because the first clinical trials in HFrEF showing a beneficial effect were from the late 1980s and early 1990s.(21) Surprisingly, we found lower than expected prescription rates for MR-antagonists, which persisted over the years included in this study. This is in spite of multiple clinical trials which have shown benefit in HFrEF patients.(22) Besides HFrEF trials, a post-hoc analysis of the TOPCAT trial in 2015 (Spironolactone, a MR-antagonist, for HFpEF) reported regional differences between Americas and Russia/Georgia, where the American patients showed clinical benefits.(23) The American College of Cardiology/American Heart Association focused update on HF management in 2017 gave spironolactone a grade IIb recommendation, thereby stimulating that selected HFpEF patients could be treated with spironolactone to decrease re-hospitalisations.(24)

Heart failure medication initiation following diagnosis

Most activity in treatment prescription behaviour was observed between 6 months before to 6 months after HF diagnosis. After the 6 month mark we did not observe many patients starting any of the medication investigated. This is in line with previous studies showing that there are few changes in medication use and little up titration of medication after treatment initiation.(5, 25) This leaves room for improvement in starting treatment longer after HF diagnosis, especially as patients hospitalised with acute HF may not immediately tolerate negative inotropic medication such as beta-blockers.

Impact of heart failure hospitalisation on medication prescription

We found differences in prescription patterns between patients if with HF diagnosis recorded in different settings. Patients with a primary care HF diagnosis without HF hospitalisation had much lower prescription rates of loop diuretics compared to patients with a HF diagnosis recorded in both primary and secondary care. It could be that these patients have less severe fluid overload that requires alleviation by loop diuretics.

Previously it was shown that there are differences in overall five-year survival of patients with HF diagnosis recorded in primary care only, secondary care only and in both, with the worst survival seen in HF patients identified only in secondary care and the best survival for HF patients identified in primary care with or without hospitalisation for HF.(13) Here, we advance current knowledge by showing that there are longitudinal differences in HF care of patients with diagnosis recorded in different settings. Importantly, HF patients with HF hospitalisation and no diagnosis of HF recorded in primary care had the lowest prescription rates, signifying a potential quality of care gap between secondary and primary care, where patients are not treated optimally. Primary care is the basis of many healthcare systems, including the UK. If there is no HF diagnosis recorded in primary care after HF hospitalisation, which is indicative for worse survival, rehospitalisation and severity of disease, this could be detrimental for patients.

Heart failure treatment in women and elderly

Over time, we observed that HF was diagnosed at a later age, with the median almost 80 years old between 2013-2015. This is also seen in many other developed countries where the mean age of HF diagnosis is over 70 years old.(26, 27)

We observed lower prescription rates in elderly patients compared to younger patients for RAS-inhibitors, beta-blockers and MR-antagonists, although the difference in MR-antagonists was less pronounced. Many elderly patients were already using RAS-inhibitors prior to HF diagnosis, therefore the increase in prescription rate is not as steep as compared to younger HF patients who are prescribed less medication prior to HF diagnosis. This could be explained by the presence of comorbidities, such as atrial fibrillation or hypertension, which are much more prevalent among elderly compared to younger patients, and for which these elderly patients could be prescribed RAS-inhibitors.

Remarkably, the difference between prescription of RAS-inhibitors and beta-blockers prior to HF diagnosis was less than 5% for men and women, and only after the diagnosis of HF was a higher proportion of men prescribed a RAS-inhibitor or beta-blocker. This could potentially be related to the fact that elderly women are more likely to develop HFpEF and therefore tend to be treated symptomatically with loop diuretics, rather than with RAS-inhibitors and beta-blockers. However, the literature also shows that there are differences in treatment prescription in men and women with HFrEF, for which there is no obvious explanation.(28)

Both elderly patients and women received more loop diuretics. However, this could potentially be harmful, especially for elderly, since loop diuretics could lead to electrolyte disturbances and acute kidney injury.(29) Elderly patients are often excluded or underrepresented in clinical trials, therefore current recommendations lack convincing evidence in the elderly population. However, recently a large meta-analysis reported a significant effect of beta-blockers on overall mortality regardless of age.(30) These studies indicate that elderly patients also benefit from HF-specific medication and should be a choice of treatment for these patients, besides loop diuretics for symptom alleviation.

Strengths and limitations

Strengths of this study are the large cohort of HF patients and a long follow-up period. Patient records available are representative of the general UK population, which provides evidence for the validity of using these EHR for research.(11, 12) However, we were limited by the inability to differentiate between HF phenotypes based on medical records, since there was no access to detailed echocardiography estimates to assess systolic function. We were also unable to assess patients' symptom class (which would affect their eligibility for treatments such as MRA-antagonists), and contraindications or intolerances that may affect the choice of medication.

Conclusion

The results of this population-based study of over 80,000 patients with heart failure in England shows variable increases in uptake of evidence-based treatments, with no change in prescription of MR-antagonists over 13 years, but an increase in beta-blocker use. Large differences were observed between HF patient groups, with lowest prescription rates in women, elderly patients, and those without a primary care diagnosis. These findings suggest HF management can be improved by focusing effort and healthcare resources on improving communication between primary and secondary care. There is still a need for effective implementation of guideline-recommended therapies in real-world HF care.

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a. Contributor statement

AU has designed the research, analysed and interpreted the data and drafted the manuscript. IV, AH, FA and SK have designed the research, interpreted the data, critically revised the manuscript and supervised AU. SD, HH, AS, JC and DG have interpreted the data and critically revised the manuscript.

b. Competing interests

The authors report no conflict of interest.

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d. Data sharing statement

No additional data available.

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Figure legends

Central illustration Figure 1

Legend Figure 1. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers, MR-antagonists, loop diuretics per months since HF diagnosis. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 2. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by setting (primary care only, secondary care only, both primary and secondary care). RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 3. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by age. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 4. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by sex. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 5. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by social status (highest quintile of social deprivation vs. the rest). RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Table 1. Patients characteristics of heart failure patients between 2002 and 2015

	Overall	2002 - 2005	2006 - 2008	2009 - 2012	2013 - 2015	% missing
n	85732	25366	17715	26114	16537	
Demographics						
Age (Years, median [IQR])	79.1 [70.2, 85.7]	78.7 [70.7, 84.9]	78.7 [69.9, 85.4]	79.5 [71.1, 86.3]	79.7 [70.0, 86.4]	0
Sex (% Women)	48.6	49.3	48.4	48.4	48.0	0
Ethnicity (% Caucasian)	96.5	97.5	96.9	96.1	95.1	3.5
Social deprivation (% lowest quintile)	24.3	25.1	25.0	24.0	22.9	0
Clinical and lifestyle measurements						
SBP (mmHg, mean (sd))	136.2 (20.7)	140.6 (22.3)	135.9 (20.7)	134.4 (20.0)	132.9 (18.7)	13.0
DBP (mmHg, mean (sd))	76.2 (12.0)	78.4 (12.0)	76.2 (12.0)	75.4 (12.0)	74.4 (11.6)	13.0
BMI (kg/m^2, mean (sd))	28.6 (6.6)	28.2 (6.4)	28.4 (6.6)	28.7 (6.8)	28.8 (6.8)	54.0
eGFR (min/m2/1.73mL, median [IQR])	58.4 [45.3, 72.1]	54.7 [43.4, 66.1]	56.5 [44.3, 68.8]	60.5 [46.1, 75.3]	62.9 [47.5, 78.2]	24.0
Smoking status (% Current)	20.8	22.3	20.0	20.4	20.5	38.7
Medical history (%)¶						
Atrial Fibrillation	36.6	28.4	36.3	40.6	43.0	-
COPD	17.9	14.8	17.3	19.5	21.0	-
Diabetes	22.3	18.1	22.2	23.7	26.7	-
Hypertension	60.7	46.0	60.7	67.9	72.0	-
Ischaemic heart disease	44.2	39.0	46.0	46.4	46.8	-
Valvular disease	16.5	9.5	14.9	19.9	23.8	-
Medication prescription up to 3 months after HF diagnosis (%)¶						
RAS-inhibitors	60.8	59.6	63.5	62.0	57.6	-
Beta-blockers	42.5	28.9	41.0	49.3	54.1	-
MR-antagonists	18.0	18.4	17.9	17.6	18.2	-
Loop diuretics	63.0	68.4	63.5	61.1	57.0	-

Legend Table 1. * Assessed by index of multiple deprivation, § denotes prior medical history of given comorbidity, ¤ Medication 12 months prior to index date, Mean (SD) = Mean (Standard deviation), Median [IQR] = Median [Interquartile range], CPRD = Clinical Practice Research Datalink, SBP = systolic blood pressure, DBP = Diastolic blood pressure, BMI = Body Mass Index, eGFR = estimated glomerular filtration rate, COPD = Chronic Obstructive Pulmonary Disease, RAS-inhibitors = ACE-inhibitors and/or angiotensin II receptor blockers, MR-antagonists = mineralocorticoid receptor antagonist. ¶Medical conditions and prescriptions were considered absent if not recorded.

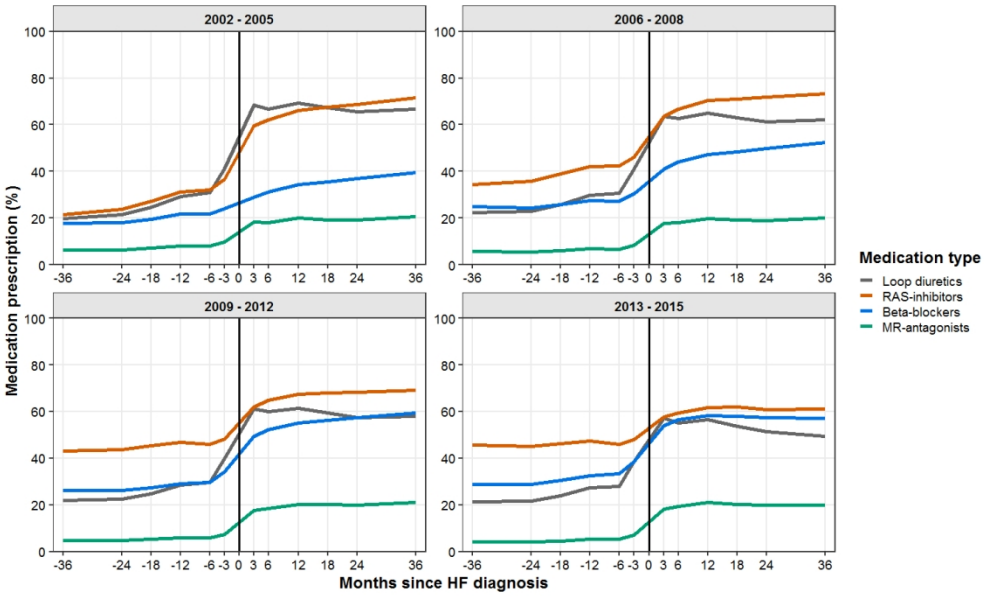

figure 1

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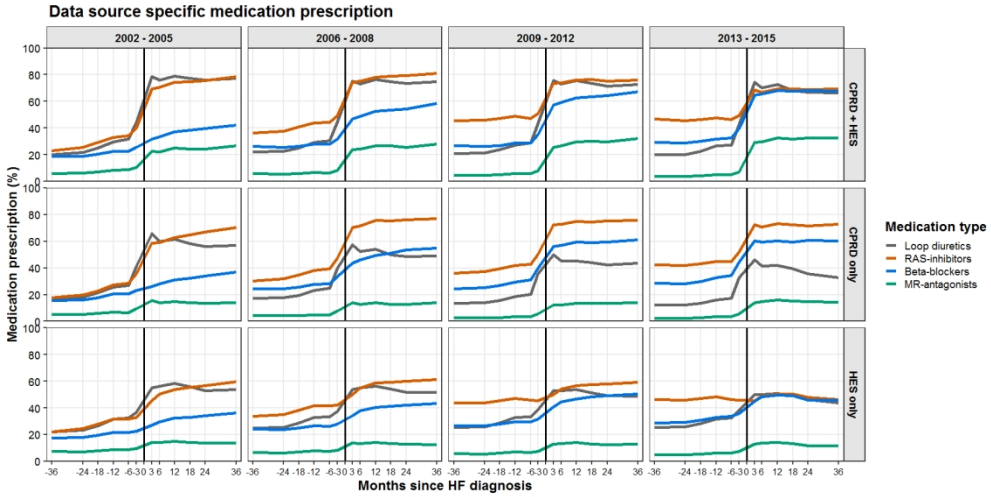

figure 2

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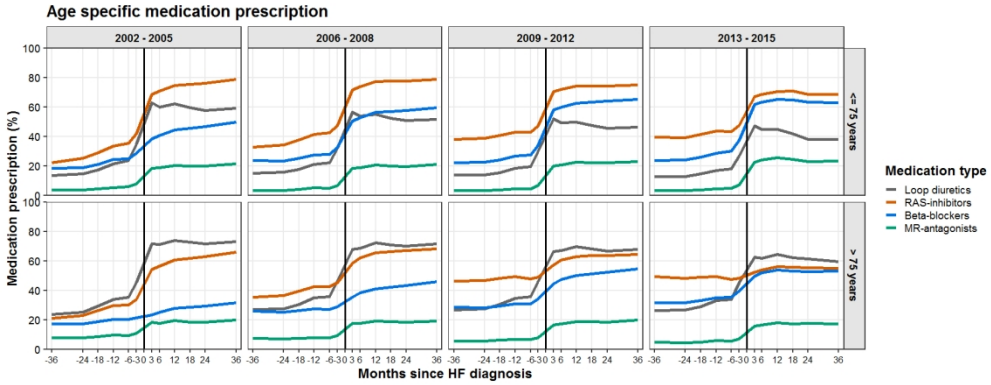

figure 3

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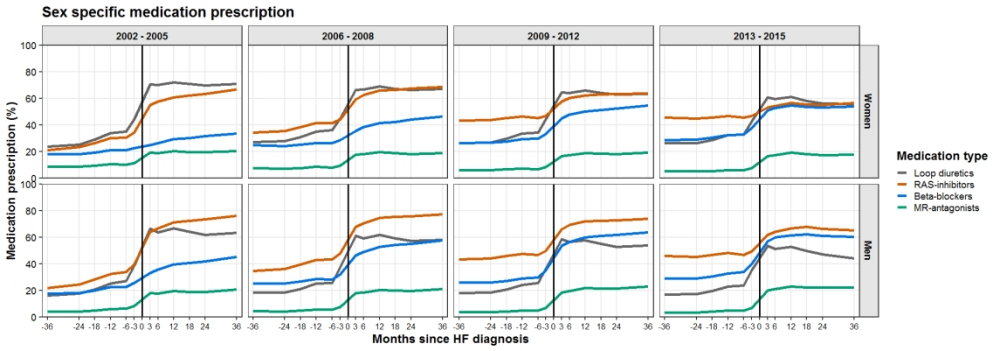

figure 4

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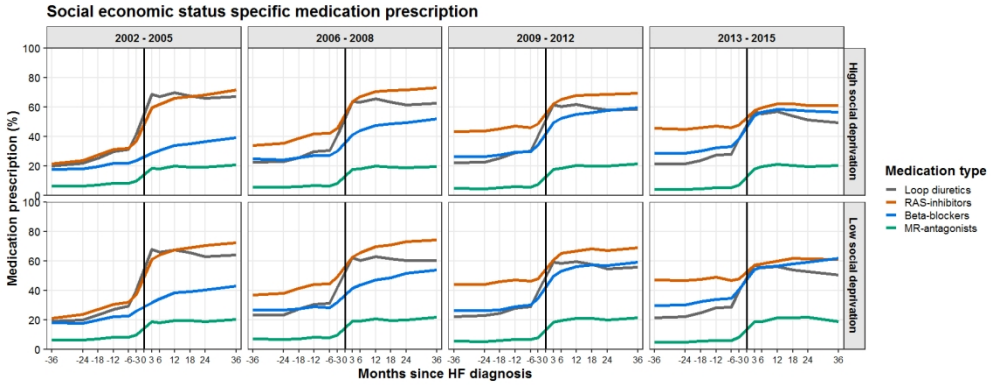

figure 5

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Supplemental material

Figure S1 – study flow diagram

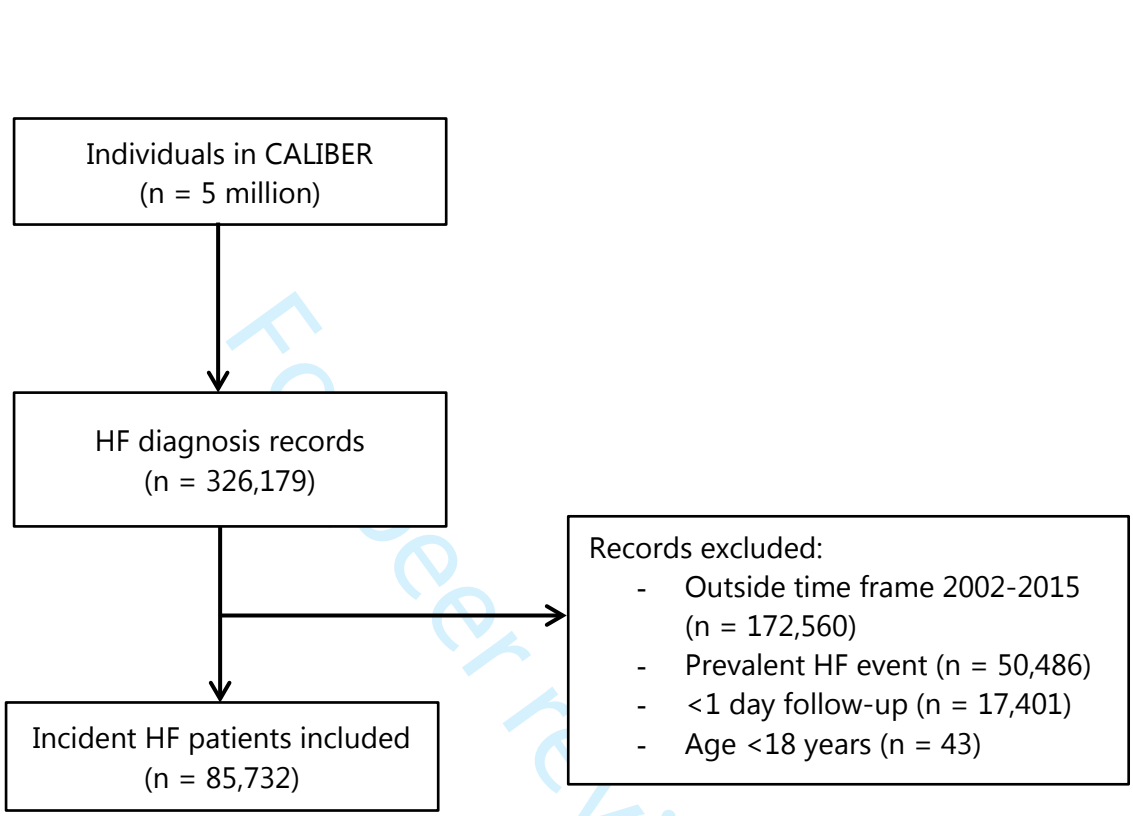

Table S1 – additional READ codes used to identify heart failure in the Clinical Practice Research Datalink

CPRD* Heart Failure READ codes
585g.00, G5yyC00, G5yyA00, G583.12, G583.11, G583.00, G5yy900, 585f.00

Legend Table S1. * CPRD = Clinical Practice Research Datalink

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	-
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 - 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10 - 12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10 - 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13 - 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13 - 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Temporal Trends in Heart Failure Medication Prescription in a Population-Based Cohort Study

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Title: Temporal Trends in Heart Failure Medication Prescription in a Population-Based Cohort Study

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Abstract

Objective: We examined temporal heart failure (HF) prescription patterns in a large representative sample of real-world patients in the UK, using electronic health records (EHR).

Methods: From primary and secondary care EHR, we identified 85,732 patients with a HF diagnosis between 2002-2015. Almost 50% of HF patients were women and the median age was 79.1 [interquartile range 70.2-85.7] years, with age at diagnosis increasing over time.

Results: We found several trends in pharmacological HF management, including increased beta-blocker prescriptions over time (29% in 2002-2005 and 54% in 2013-2015), which was not observed for mineralocorticoid receptor-antagonists (MR-antagonists) (18% in 2002-2005 and 18% in 2013-2015); higher prescription rates of loop diuretics in women and elderly patients together with lower prescription rates of angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers , beta-blockers, or MR-antagonists in these patients; and little change in medication prescription rates occurred after 6 months of HF diagnosis; and lastly, patients hospitalised for HF who had no follow-up in primary care had considerably lower prescription rates compared to patients with a HF diagnosis in primary care with or without HF hospitalisation.

Conclusion: In the general population, the use of MR-antagonists for HF remained low and did not change throughout 13 years of follow up. With large differences between HF patients, with lowest prescription rates observed in women and elderly patients, and those not followed-up in primary care, these findings suggest HF management can be improved by focusing effort and healthcare resources towards these subgroup and communication between primary and secondary care.

Keywords: Prescription patterns, ACE-inhibitors, ARB, RAS-inhibitors, Beta-blockers, MRA, Loop diuretics, Heart failure, Electronic health records.

Article summary

Strengths and limitations of the study

- Large cohort of HF patients from primary and secondary care
- Long follow-up period of almost 15 years
- Unable to differentiate between HF subphenotypes such as HF with reduced, mid-range or preserved ejection fraction.
- Unknown treatment eligibility, contraindications or intolerances that may affect the choice of treatment

Abbreviations

HF	Heart failure
EHR	Electronic health records
CPRD	Clinical Practice Research Datalink
HES	Hospital Episode Statistics
ONS	Office for National Statistics
COPD	Chronic obstructive pulmonary disease
RAS-inhibitors	Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers
MR-antagonists	Mineralocorticoid receptor-antagonists
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction

Introduction

Heart failure (HF) is a common public health burden, with the prevalence of HF estimated at approximately 500.000 patients in the UK.(1, 2) Once diagnosed, initiation and up titration of guideline recommended therapies can reduce morbidity and mortality, although 5-year survival still remains 20% to 50%.(3, 4)

Several observational studies have assessed treatment uptake in HF patients following their diagnosis. These studies suggest that many patients did not receive guideline recommended therapies, or at low doses with sparse attempts for up titration.(5–8) Optimal treatment for effective disease management seems to be particularly challenging in elderly patients, women or patients with multiple comorbidities and contraindications for treatments.(7, 8) At present, few data are available for prescription trends in HF patients in the general population and even fewer data are available that shed light on medication use in HF patients in the years prior to their HF diagnosis.

The CALIBER resource curates primary and secondary care EHR of 5 million individuals in the UK, including HF diagnosis and medication prescriptions.(9) Given the amount of information available, medication use of all HF patients in the community may be investigated – including those which are underrepresented in randomised clinical trials.

Therefore, we sought to examine HF treatment prescription patterns following a HF diagnosis for the overall population as well as specific subgroups based on gender (e.g. women), age (e.g. elderly), social economic status and healthcare setting (e.g. primary care or secondary care), in a large representative sample of real-world patients in the UK, using electronic health records (EHR). (10)

Methods

Data source

Patients were selected from linked EHR in the UK, which consist of three linked databases: The Clinical Practice Research Datalink (CPRD) with primary care EHR, Hospital Episodes Statistics (HES) containing coded diagnoses and surgical procedures from inpatient hospital admissions, and the Office for National Statistics (ONS) registry containing cause-specific mortality data.(10) Previous work has shown that these patients are representative of the general population in the UK.(11, 12)

Study population

Patients were included at their first record of HF from CPRD or HES between January 1st 2002 and December 31st 2015. In CPRD, events were defined by a diagnosis of HF based on Read (version 2) controlled clinical terminology codes (NHS coded clinical terms) and in HES by a diagnosis of HF based on ICD-10 codes. The same HF diagnosis codes were used as in previous papers, with in addition several newer Read codes listed in **Table S1**.(4, 13) All patients were eligible for inclusion if they were aged 18 years or older, were registered with a GP for at least one year prior to diagnosis of HF, in a practice that had at least one year of up-to-standard data recording in CPRD (data quality check). The first record of HF from CPRD or HES was considered the index date. Individuals were censored at the earliest date from the date of de-registration in CPRD, the last data collection date of a practice in CPRD, the date of death or at the study end date (31st December 2015). Data on EHR phenotyping variables from HF patients up to 3 years prior to index date were included in this study.

Patient and public involvement

There was no patient or public involvement in this research.

EHR phenotyping variables

Baseline patient characteristics were based on records from CPRD and/or HES prior to index date, including demographics [age, sex, ethnicity, social deprivation] cardiovascular risk factors [smoking, BMI, diastolic blood pressure and systolic blood pressure and estimated glomerular filtration rate], comorbidities [a medical history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, ischaemic heart disease, valvular disease and history of cancer] and medication prescription.

CPRD includes all prescriptions from the general practice. Prescriptions in CPRD were classified as: RAS-inhibitors (Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers), beta-blockers, mineralocorticoid receptor-antagonists (MR-antagonists) and loop diuretics. Definitions of these variables could be found online at http://www.caliberresearch.org/portal/.

Medication prescription for RAS-inhibitors, beta-blockers, MR-antagonists and loop diuretics was identified between three years prior to HF diagnosis up to three years after HF diagnosis per the following increments: -36 months to -24 months, -24 months to -18 months, -18 months to -12 months, -12 months to -6 months, -6 months to -3 months, -3 months to HF diagnosis, HF diagnosis to +3 months, +3 months to +6 months, +6 months to +12 months, +12 months to +18 months, +18 months to +24 months and +24 to +36 months.

Healthcare setting was characterised as primary care only (no HF hospitalisation), secondary care only (no Read HF diagnosis recorded in primary care) or HF diagnosis in both primary and secondary care. Ethnicity records from CPRD and HES were combined and

categorised as Caucasian, Asian, Black or Other. Social deprivation was measured as quintiles of the index of multiple deprivation of the geographical area of the primary care practice, a score calculated based on seven indices of deprivation: income, employment, health and disability, education, barrier to housing and services, crime and living environment.(14) Smoking status in CPRD was classified as never, ex- or current smokers.

Statistical analysis

Patient characteristics were summarised as mean (SD) or median [IQR] for continuous variables and percentages for categorical variables. The percentage of HF patients prescribed pharmacological treatments was calculated per increment and per time period as defined by publication year of previous ESC guidelines (2001, 2005, 2008 and 2012)(1, 15–18): 2002-2005, 2006-2008, 2009-2012 and 2013-2015. In addition to the overall cohort, we investigated several subgroups: age (< vs. ≥ 75 years old), sex (men vs. women), social economic status (lowest quintile of social deprivation vs. the rest) and setting (only follow-up in primary care vs. only in secondary care vs. follow-up in primary care after HF hospitalisation). All analyses were performed using R version 3.6.1.

Results

Baseline characteristics

We identified 85,732 patients with a HF diagnosis. The study flow diagram could be found in **Figure S1**. Median follow-up after HF diagnosis (index date) was 2.1 years [0.6 – 4.5] years. **Table 1** shows the overall baseline patient characteristics and per time period 2002-2005, 2006-2008, 2009-2012 and 2013-2015. Almost 50% of patients were women and the median age was 79.1 [70.2 - 85.7] years, with age at HF diagnosis increasing over time. Overall, many

HF patients had comorbidities, most common were hypertension (61%), ischaemic heart disease (44%) and atrial fibrillation (37%), with increasing numbers of patients with comorbidities over time. Approximately 40% (n= 34,489) of patients were followed-up in primary care after a HF hospitalisation, 20% (n= 15,330) of patients were only known in primary care and never hospitalised for HF and the remaining 40% (n= 35,913) of patients had no follow-up in primary care after HF hospitalisation.

Overall prescription patterns

Overall prescription patterns are shown in **Figure 1**. Many patients were prescribed medication before HF diagnosis, especially RAS-inhibitors (20% in 2002-2005 to 46% in 2013-2015). Over time, beta-blocker prescription after HF diagnosis increased from 30% in 2002-2005 to 55% in 2013-2015. Throughout the follow up of 13 years, there were little observed changes for MR-antagonist uptake, this remained at 20% throughout time after HF diagnosis. The largest observed changes in prescription patterns occurred between 6 months before and after HF diagnosis (**Figure 1**). Approximately 20% of HF patients were prescribed a loop diuretic up to three years prior to HF diagnosis.

Setting-specific prescription patterns

Setting-specific prescription patterns are shown in **Figure 2**. Patients followed-up in primary care after HF hospitalisation had the highest prescription rates for all types of medication. Over time, the prescription for loop-diuretics, RAS-inhibitors and beta-blockers converged together. In these patients the prescription for MR-antagonists increased over time after HF diagnosis from 20% in 2002-2005 to 30% in 2013-2015.

Patients known in primary care but never hospitalised for HF had lower prescription rates for all types of treatment compared to patients with primary care follow-up and at least one HF hospitalisation. Mainly loop diuretics were less prescribed in these patients and the prescription of loop diuretics decreased over time with 65% of patients receiving loop diuretics after HF diagnosis in 2002-2005 compared to just over 40% in 2013-2015.

Patients hospitalised for HF but without a HF diagnosis in primary care, had the lowest prescriptions rates for loop diuretics, RAS-inhibitors and beta-blockers, which remained stable over time (50%, 45%, and 45% in 2013-2015 respectively). MR-antagonists were only prescribed in 13% of patients after HF diagnosis, this was similar for each time period.

Age-specific prescription patterns

Differences in prescription according to age categories are shown in **Figure 3**. The observed increase in prescriptions for RAS-inhibitors, beta-blockers, and MR-antagonists between 6 months before HF diagnosis to 6 months after HF diagnosis was less pronounced in elderly patients. The average increase in elderly patients was 12%, 7%, 8% for RAS-inhibitors, beta-blockers and MR-antagonists respectively, while younger patients had an average increase of 23%, 19% and 13% for RAS-inhibitors, beta-blockers and MR-antagonists respectively. On the other hand, a higher proportion of elderly patients were treated with loop-diuretics compared to younger patients, both before and after HF diagnosis (45% before and 63% after HF diagnosis in elderly compared to 27% before and 47% after HF diagnosis for younger patients in 2013-2015). After HF diagnosis, a higher percentage of younger patients were prescribed with RAS-inhibitors and beta-blockers compared to older patients.

Sex-specific prescription patterns

Differences in prescription between men and women are shown in **Figure 4**. Loop diuretics were prescribed in a higher proportion of women compared to men, this difference was already present prior to HF diagnosis where 6 months before diagnosis 30% of women and 20% of men were prescribed a loop diuretic. After HF diagnosis, the most prescribed medication for women was a loop diuretic, while a higher proportion of men were prescribed a RAS-inhibitor. Men were also more often prescribed RAS-inhibitors, beta-blockers and MR-antagonists after HF diagnosis compared to women.

Social economic status-specific prescription patterns

Social economic status-specific prescription patterns are shown in **Figure 5**. We did not observe any discernible differences between patients in low vs. high social-economic areas (highest quintile of social economic deprivation).

Discussion

In this large-scale study of 85,732 HF patients we investigated treatment prescription patterns in a representative sample of real-world patients with HF in the UK between 2002 and 2015. We found three important trends in pharmacological HF management: a) increased use of beta-blockers, whereas there was no increased uptake of MR-antagonists over 13 years follow up; b) prescription rates remained almost unchanged after the first 6 months following a HF diagnosis; and lastly, c) higher rates of loop diuretics in women and elderly patients together with lower prescription rates for RAS-inhibitors, beta-blockers, or MR-antagonists.

Temporal trends in heart failure medication

Even though prescription rates increased over time from 2002 to 2015, overall prescription rates remained low. This is in line with previously published studies.(5–8, 19) Low prescription rates could be attributed to the mixed HF cases found in EHR. We were unable to distinguish HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction, and HF with preserved ejection fraction (HFpEF) based on medical records, thereby including known differences in treatment recommendations for these HF phenotypes.(1)

We found no major differences in prescription behaviour after the publication of ESC guidelines, however we did observe the gradual increase of beta-blockers as one of the cornerstones of HF treatment. RAS-inhibitors were prescribed in a high proportion of patients throughout the years of the study, presumably because the first clinical trials in HFrEF showing a beneficial effect were from the late 1980s and early 1990s.(20) Surprisingly, we found lower than expected prescription rates for MR-antagonists, which persisted over the years included in this study. This is in spite of multiple clinical trials which have shown benefit in HFrEF patients.(21) Besides HFrEF trials, a post-hoc analysis of the TOPCAT trial in 2015 (Spironolactone, a MR-antagonist, for HFpEF) reported regional differences between Americas and Russia/Georgia, where the American patients showed clinical benefits.(22) The American College of Cardiology/American Heart Association focused update on HF management in 2017 gave spironolactone a grade IIb recommendation, thereby stimulating that selected HFpEF patients could be treated with spironolactone to decrease re-hospitalisations.(23)

Heart failure medication initiation following diagnosis

Most activity in treatment prescription behaviour was observed between 6 months before to 6 months after HF diagnosis. After the 6 month mark we did not observe many patients starting

any of the medication investigated. This is in line with previous studies showing that there are few changes in medication use and little up titration of medication after treatment initiation.(5, 24) This leaves room for improvement in starting treatment at any time point following a HF diagnosis, for example if patients hospitalised with acute HF do not immediately tolerate negative inotropic medication such as beta-blockers.

Impact of heart failure hospitalisation on medication prescription

We found differences in prescription patterns between patients with a HF diagnosis recorded in different settings. Patients with a primary care HF diagnosis without HF hospitalisation had much lower prescription rates of loop diuretics compared to patients with a HF diagnosis recorded in both primary and secondary care. It could be that these patients have less severe fluid overload or symptoms that requires alleviation by loop diuretics, and thus less severe HF.

Previously it was shown that there are differences in overall five-year survival of patients with HF diagnosis recorded in primary care only, secondary care only and in both, with the worst survival seen in HF patients identified only in secondary care and the best survival for HF patients identified in primary care with or without hospitalisation for HF.(4) Here, we advance current knowledge by showing that there are longitudinal differences in HF care of patients with diagnosis recorded in different settings.

In this study almost 40% of patients did not have a GP record of a HF diagnosis after a HF hospitalisation. One reason could be that GPs do not formally register HF with a Read diagnosis code, but rather in free text descriptions. However, there could also be a potential quality of care gap or failure of communication between secondary and primary care, where patients are not treated optimally. Primary care is the basis of many healthcare systems, including the UK. If there is no HF diagnosis recorded in primary care after HF hospitalisation,

which is shown to indicative for worse survival, rehospitalisation and severity of disease, this could be detrimental for patients.

Heart failure treatment in women and elderly

Over time, we observed that HF was diagnosed at a later age, with the median almost 80 years old between 2013-2015. This is also seen in many other developed countries where the mean age of HF diagnosis is over 70 years old.(25, 26)

We observed lower prescription rates in elderly patients compared to younger patients for RAS-inhibitors, beta-blockers and MR-antagonists, although the difference in MR-antagonists was less pronounced. Many elderly patients were already using RAS-inhibitors prior to HF diagnosis, therefore the increase in prescription rate is not as steep as compared to younger HF patients who are prescribed less medication prior to HF diagnosis. This could be explained by the presence of comorbidities, such as atrial fibrillation or hypertension, which are much more prevalent among elderly compared to younger patients, and for which these elderly patients could be prescribed RAS-inhibitors.

Remarkably, the difference between prescription of RAS-inhibitors and beta-blockers prior to HF diagnosis was less than 5% for men and women, and only after the diagnosis of HF was a higher proportion of men prescribed a RAS-inhibitor or beta-blocker. This could potentially be related to the fact that elderly women are more likely to develop HFpEF and therefore tend to be treated symptomatically with loop diuretics, rather than with RAS-inhibitors and beta-blockers. However, the literature also shows that there are differences in treatment prescription in men and women with HFrEF, for which there is no obvious explanation.(27)

Both elderly patients and women received more loop diuretics. However, this could potentially be harmful, especially for elderly, since loop diuretics could lead to electrolyte disturbances and acute kidney injury.(28) Elderly patients are often excluded or underrepresented in clinical trials, therefore current recommendations lack convincing evidence in the elderly population. However, recently a large meta-analysis reported a significant effect of beta-blockers on overall mortality regardless of age.(29) These studies indicate that elderly patients also benefit from HF-specific medication and should be a choice of treatment for these patients, besides loop diuretics for symptom alleviation. However, elderly patients might have more contraindications or intolerances to RAS-inhibitors, beta-blockers and MR-antagonists and might therefore be more often treated with loop diuretics for symptom control.

Strengths and limitations

Strengths of this study are the large cohort of HF patients and a long follow-up period. Patient records available are representative of the general UK population, which provides evidence for the validity of using these EHR for research.(11, 12) However, we were limited by the inability to differentiate between HF phenotypes based on medical records, since there was no access to detailed echocardiography estimates to assess systolic function. Nor did we have information on NYHA class or NT-proBNP biomarker levels. Furthermore, we only had medication prescription available in primary care, not in hospital care. However, CPRD includes all prescriptions from community. Treatments administered during a hospital admission or discharge were not reported, such as intravenous inotropic agents. We were also unable to assess patients' symptom class (which would affect their eligibility for treatments such as MRA-antagonists), and contraindications or intolerances that may affect the choice of medication.

Conclusion

The results of this population-based study of over 80,000 patients with heart failure in England shows variable increases in uptake of evidence-based treatments, with no change in prescription of MR-antagonists over 13 years, but an increase in beta-blocker use. Large differences were observed between HF patient groups, with lowest prescription rates of RAS-inhibitors, beta-blockers and MR-antagonists in women, elderly patients, and those without a HF diagnosis in primary care. These findings suggest HF management can be improved by focusing effort and healthcare resources on improving communication between primary and secondary care. There is still a need for effective implementation of guideline-recommended therapies in real-world HF care.

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a. Contributor statement

AU has designed the research, analysed and interpreted the data and drafted the manuscript. IV, AH, FA and SK have designed the research, interpreted the data, critically revised the manuscript and supervised AU. SD, HH, AS, JC and DG have interpreted the data and critically revised the manuscript.

b. Competing interests

The authors report no conflict of interest.

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d. Data sharing statement

All data were provided anonymised and are not publicly available due to their sensitive nature. Data may be obtained from the Clinical Practice Research Datalink (https://www.cprd.com). EHR phenotypes are available from the CALIBER resource (https://www.caliberresearch.org). The protocol may be obtained via the Clinical Practice Research Datalink under protocol reference: 17_015. No additional data is available.

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Figure legends

Central illustration Figure 1

Legend Figure 1. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers, MR-antagonists, loop diuretics per months since HF diagnosis. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 2. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by setting (primary care only, secondary care only, both primary and secondary care). RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 3. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by age. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 4. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by sex. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 5. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by social status (highest quintile of social deprivation vs. the rest). RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Table 1. Patients characteristics of heart failure patients between 2002 and 2015

	Overall	2002 - 2005	2006 - 2008	2009 - 2012	2013 - 2015	% missing
n	85732	25366	17715	26114	16537	
Demographics						
Age (Years, median [IQR])	79.1 [70.2, 85.7]	78.7 [70.7, 84.9]	78.7 [69.9, 85.4]	79.5 [71.1, 86.3]	79.7 [70.0, 86.4]	0
Sex (% Women)	48.6	49.3	48.4	48.4	48.0	0
Ethnicity (% Caucasian)	96.5	97.5	96.9	96.1	95.1	3.5
Social deprivation (% lowest quintile)	24.3	25.1	25.0	24.0	22.9	0
Clinical and lifestyle measurements						
SBP (mmHg, mean (sd))	136.2 (20.7)	140.6 (22.3)	135.9 (20.7)	134.1 (20.0)	132.9 (18.7)	13.0
DBP (mmHg, mean (sd))	76.2 (12.0)	78.4 (12.0)	76.2 (12.0)	75.1 (12.0)	74.4 (11.6)	13.0
BMI (kg/m^2, mean (sd))	28.6 (6.6)	28.2 (6.4)	28.4 (6.6)	28.7 (6.8)	28.8 (6.8)	54.0
eGFR (min/m2/1.73mL, median [IQR])	58.4 [45.3, 72.1]	54.7 [43.4, 66.1]	56.5 [44.3, 68.8]	60.5 [46.1, 75.3]	62.9 [47.5, 78.2]	24.0
Smoking status (% Current)	20.8	22.3	20.0	20.4	20.5	38.7
Medical history (%)[¶]						
Atrial Fibrillation	36.6	28.4	36.3	40.6	43.0	-
COPD	17.9	14.8	17.3	19.5	21.0	-
Diabetes	22.3	18.1	22.2	23.7	26.7	-
Hypertension	60.7	46.0	60.7	67.9	72.0	-
Ischaemic heart disease	44.2	39.0	46.0	46.4	46.8	-
Valvular disease	16.5	9.5	14.9	19.9	23.8	-
Medication prescription up to 3 months after HF diagnosis (%)[¶]						
RAS-inhibitors	60.8	59.6	63.5	62.0	57.6	-
Beta-blockers	42.5	28.9	41.0	49.3	54.1	-
MR-antagonists	18.0	18.4	17.9	17.6	18.2	-
Loop diuretics	63.0	68.4	63.5	61.1	57.0	-

Legend Table 1. * Assessed by index of multiple deprivation, § denotes prior medical history of given comorbidity, ¤ Medication 12 months prior to index date, Mean (SD) = Mean (Standard deviation), Median [IQR] = Median [Interquartile range], CPRD = Clinical Practice Research Datalink, SBP = systolic blood pressure, DBP = Diastolic blood pressure, BMI = Body Mass Index, eGFR = estimated glomerular filtration rate, COPD = Chronic Obstructive Pulmonary Disease, RAS-inhibitors = ACE-inhibitors and/or angiotensin II receptor blockers, MR-antagonists = mineralocorticoid receptor antagonist. ¶Medical conditions and prescriptions were considered absent if not recorded.

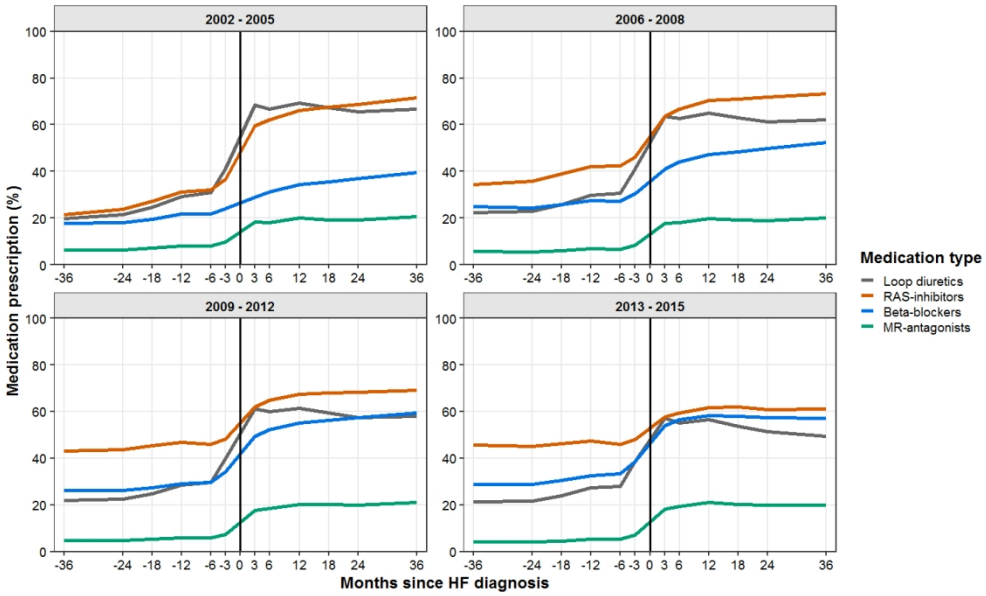

figure 1

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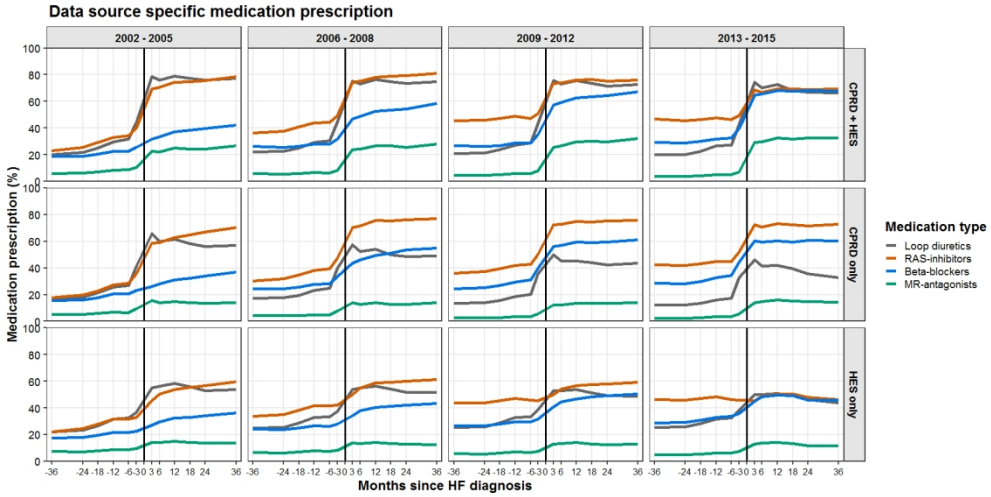

figure 2

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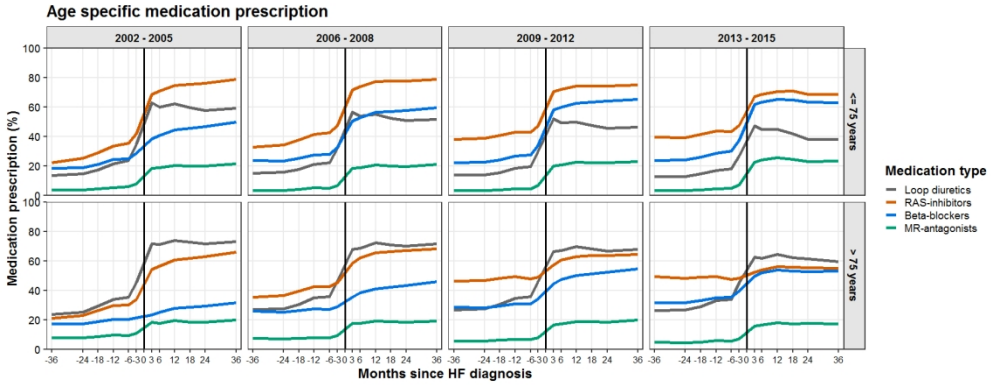

figure 3

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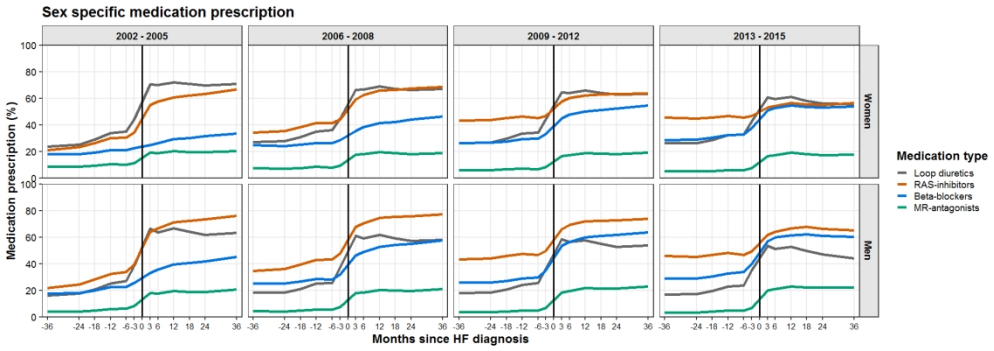

figure 4

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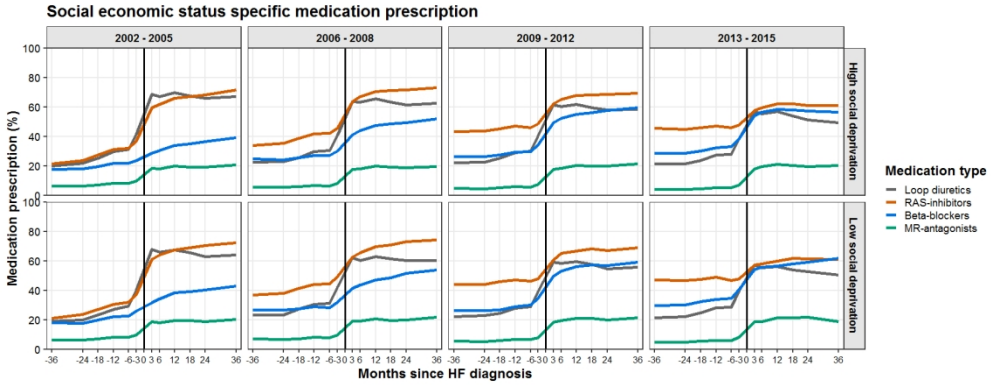

figure 5

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Supplemental material

Figure S1 – study flow diagram

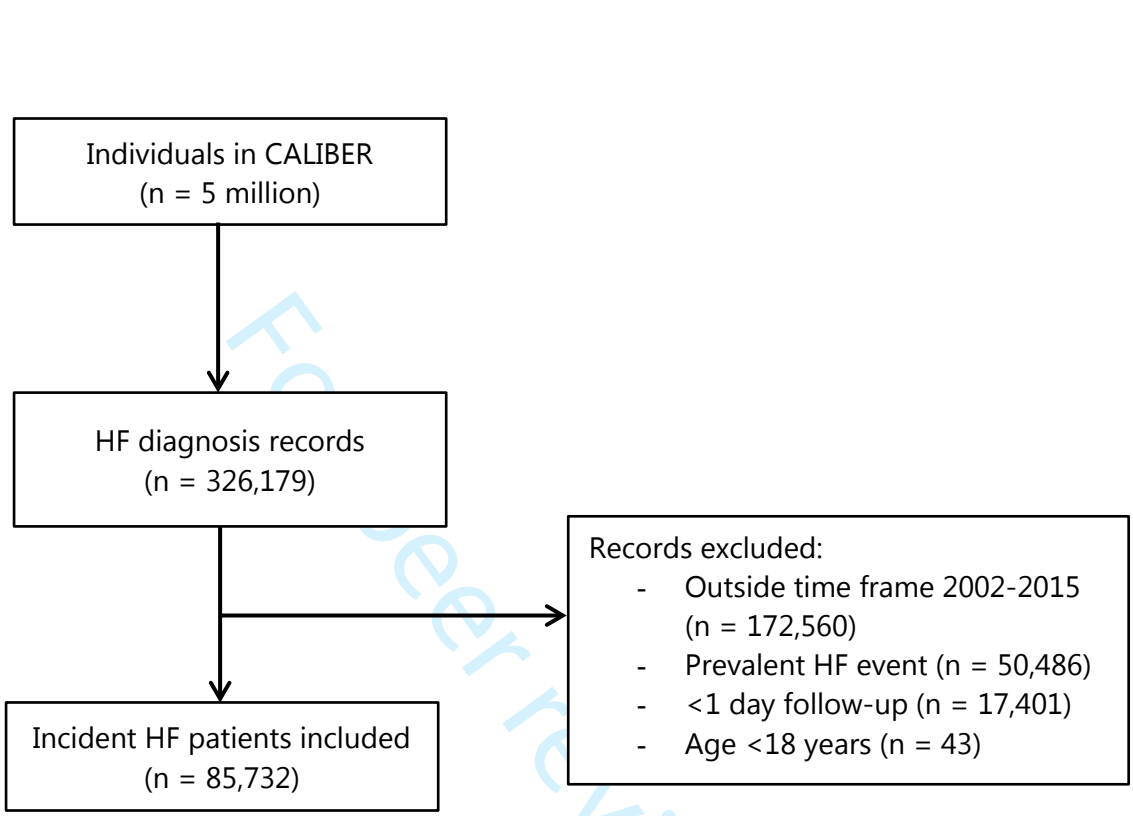

Table S1 – additional READ codes used to identify heart failure in the Clinical Practice Research Datalink

CPRD* Heart Failure READ codes
585g.00, G5yyC00, G5yyA00, G583.12, G583.11, G583.00, G5yy900, 585f.00

Legend Table S1. * CPRD = Clinical Practice Research Datalink

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	-
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 - 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10 - 12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10 - 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13 - 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13 - 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Title: Temporal Trends in Heart Failure Medication Prescription in a Population-Based Cohort Study

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Abstract

Objective: We examined temporal heart failure (HF) prescription patterns in a large representative sample of real-world patients in the UK, using electronic health records (EHR).

Methods: From primary and secondary care EHR, we identified 85,732 patients with a HF diagnosis between 2002-2015. Almost 50% of HF patients were women and the median age was 79.1 [interquartile range 70.2-85.7] years, with age at diagnosis increasing over time.

Results: We found several trends in pharmacological HF management, including increased beta-blocker prescriptions over time (29% in 2002-2005 and 54% in 2013-2015), which was not observed for mineralocorticoid receptor-antagonists (MR-antagonists) (18% in 2002-2005 and 18% in 2013-2015); higher prescription rates of loop diuretics in women and elderly patients together with lower prescription rates of angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers , beta-blockers, or MR-antagonists in these patients; and little change in medication prescription rates occurred after 6 months of HF diagnosis; and lastly, patients hospitalised for HF who had no recorded follow-up in primary care had considerably lower prescription rates compared to patients with a HF diagnosis in primary care with or without HF hospitalisation.

Conclusion: In the general population, the use of MR-antagonists for HF remained low and did not change throughout 13 years of follow up. For most patients, few changes were seen in pharmacological management of HF in the six months following diagnosis.

Keywords: Prescription patterns, ACE-inhibitors, ARB, RAS-inhibitors, Beta-blockers, MRA, Loop diuretics, Heart failure, Electronic health records.

Article summary

Strengths and limitations of the study

- Large cohort of HF patients from primary and secondary care
- Long follow-up period of almost 15 years
- Unable to differentiate between HF subphenotypes such as HF with reduced, mid-range or preserved ejection fraction.
- Unknown treatment eligibility, contraindications or intolerances that may affect the choice of treatment

Abbreviations

HF	Heart failure
EHR	Electronic health records
CPRD	Clinical Practice Research Datalink
HES	Hospital Episode Statistics
ONS	Office for National Statistics
COPD	Chronic obstructive pulmonary disease
RAS-inhibitors	Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers
MR-antagonists	Mineralocorticoid receptor-antagonists
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction

Introduction

Heart failure (HF) is a common public health burden, with the prevalence of HF estimated at approximately 500.000 patients in the UK.(1, 2) Once diagnosed, initiation and up titration of guideline recommended therapies can reduce morbidity and mortality, although 5-year survival still remains 20% to 50%.(3, 4)

Several observational studies have assessed treatment uptake in HF patients following their diagnosis. These studies suggest that many patients did not receive guideline recommended therapies, or at low doses with sparse attempts for up titration.(5–8) Optimal treatment for effective disease management seems to be particularly challenging in elderly patients, women or patients with multiple comorbidities and contraindications for treatments.(7, 8) At present, few data are available for prescription trends in HF patients in the general population and even fewer data are available that shed light on medication use in HF patients in the years prior to their HF diagnosis.

The CALIBER resource curates primary and secondary care EHR of 5 million individuals in the UK, including HF diagnosis and medication prescriptions.(9) Given the amount of information available, medication use of all HF patients in the community may be investigated – including those which are underrepresented in randomised clinical trials.

Therefore, we sought to examine HF treatment prescription patterns following a HF diagnosis for the overall population as well as specific subgroups based on gender (e.g. women), age (e.g. elderly), social economic status and healthcare setting (e.g. primary care or secondary care), in a large representative sample of real-world patients in the UK, using electronic health records (EHR). (10)

Methods

Data source

Patients were selected from linked EHR in the UK, which consist of three linked databases: The Clinical Practice Research Datalink (CPRD) with primary care EHR, Hospital Episodes Statistics (HES) containing coded diagnoses and surgical procedures from inpatient hospital admissions, and the Office for National Statistics (ONS) registry containing cause-specific mortality data.(10) Previous work has shown that these patients are representative of the general population in the UK.(11, 12)

Study population

Patients were included at their first record of HF from CPRD or HES between January 1st 2002 and December 31st 2015. In CPRD, events were defined by a diagnosis of HF based on Read (version 2) controlled clinical terminology codes (NHS coded clinical terms) and in HES by a diagnosis of HF based on ICD-10 codes. The same HF diagnosis codes were used as in previous papers, with in addition several newer Read codes listed in **Table S1**.(4, 13) All patients were eligible for inclusion if they were aged 18 years or older, were registered with a GP for at least one year prior to diagnosis of HF, in a practice that had at least one year of up-to-standard data recording in CPRD (data quality check). The first record of HF from CPRD or HES was considered the index date. Individuals were censored at the earliest date from the date of de-registration in CPRD, the last data collection date of a practice in CPRD, the date of death or at the study end date (31st December 2015). Data on EHR phenotyping variables from HF patients up to 3 years prior to index date were included in this study.

Patient and public involvement

There was no patient or public involvement in this research.

EHR phenotyping variables

Baseline patient characteristics were based on records from CPRD and/or HES prior to index date, including demographics [age, sex, ethnicity, social deprivation] cardiovascular risk factors [smoking, BMI, diastolic blood pressure and systolic blood pressure and estimated glomerular filtration rate], comorbidities [a medical history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, ischaemic heart disease, valvular disease and history of cancer] and medication prescription.

CPRD includes all prescriptions from the general practice. Prescriptions in CPRD were classified as: RAS-inhibitors (Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers), beta-blockers, mineralocorticoid receptor-antagonists (MR-antagonists) and loop diuretics. Definitions of these variables could be found online at http://www.caliberresearch.org/portal/.

Medication prescription for RAS-inhibitors, beta-blockers, MR-antagonists and loop diuretics was identified between three years prior to HF diagnosis up to three years after HF diagnosis per the following increments: -36 months to -24 months, -24 months to -18 months, -18 months to -12 months, -12 months to -6 months, -6 months to -3 months, -3 months to HF diagnosis, HF diagnosis to +3 months, +3 months to +6 months, +6 months to +12 months, +12 months to +18 months, +18 months to +24 months and +24 to +36 months.

Healthcare setting was characterised as primary care only (no HF hospitalisation), secondary care only (no Read HF diagnosis recorded in primary care) or HF diagnosis in both primary and secondary care. Ethnicity records from CPRD and HES were combined and

categorised as Caucasian, Asian, Black or Other. Social deprivation was measured as quintiles of the index of multiple deprivation of the geographical area of the primary care practice, a score calculated based on seven indices of deprivation: income, employment, health and disability, education, barrier to housing and services, crime and living environment.(14) Smoking status in CPRD was classified as never, ex- or current smokers.

Statistical analysis

Patient characteristics were summarised as mean (SD) or median [IQR] for continuous variables and percentages for categorical variables. The percentage of HF patients prescribed pharmacological treatments was calculated per increment and per time period as defined by publication year of previous ESC guidelines (2001, 2005, 2008 and 2012)(1, 15–18): 2002-2005, 2006-2008, 2009-2012 and 2013-2015. In addition to the overall cohort, we investigated several subgroups: age (< vs. ≥ 75 years old), sex (men vs. women), social economic status (lowest quintile of social deprivation vs. the rest) and setting (only follow-up in primary care vs. only in secondary care vs. follow-up in primary care after HF hospitalisation). All analyses were performed using R version 3.6.1.

Results

Baseline characteristics

We identified 85,732 patients with a HF diagnosis. The study flow diagram could be found in **Figure S1**. Median follow-up after HF diagnosis (index date) was 2.1 years [0.6 – 4.5] years. **Table 1** shows the overall baseline patient characteristics and per time period 2002-2005, 2006-2008, 2009-2012 and 2013-2015. Almost 50% of patients were women and the median age was 79.1 [70.2 - 85.7] years, with age at HF diagnosis increasing over time. Overall, many

HF patients had comorbidities, most common were hypertension (61%), ischaemic heart disease (44%) and atrial fibrillation (37%), with increasing numbers of patients with comorbidities over time. Approximately 40% (n= 34,489) of patients were followed-up in primary care after a HF hospitalisation, 20% (n= 15,330) of patients were only known in primary care and never hospitalised for HF and the remaining 40% (n= 35,913) of patients had no follow-up in primary care after HF hospitalisation.

Overall prescription patterns

Overall prescription patterns are shown in **Figure 1**. Many patients were prescribed medication before HF diagnosis, especially RAS-inhibitors (20% in 2002-2005 to 46% in 2013-2015). Over time, beta-blocker prescription after HF diagnosis increased from 30% in 2002-2005 to 55% in 2013-2015. Throughout the follow up of 13 years, there were little observed changes for MR-antagonist uptake, this remained at 20% throughout time after HF diagnosis. The largest observed changes in prescription patterns occurred between 6 months before and after HF diagnosis (**Figure 1**). Approximately 20% of HF patients were prescribed a loop diuretic up to three years prior to HF diagnosis.

Setting-specific prescription patterns

Setting-specific prescription patterns are shown in **Figure 2**. Patients followed-up in primary care after HF hospitalisation had the highest prescription rates for all types of medication. Over time, the prescription for loop-diuretics, RAS-inhibitors and beta-blockers converged together. In these patients the prescription for MR-antagonists increased over time after HF diagnosis from 20% in 2002-2005 to 30% in 2013-2015.

Patients known in primary care but never hospitalised for HF had lower prescription rates for all types of treatment compared to patients with primary care follow-up and at least one HF hospitalisation. Mainly loop diuretics were less prescribed in these patients and the prescription of loop diuretics decreased over time with 65% of patients receiving loop diuretics after HF diagnosis in 2002-2005 compared to just over 40% in 2013-2015.

Patients hospitalised for HF but without a HF diagnosis in primary care, had the lowest prescriptions rates for loop diuretics, RAS-inhibitors and beta-blockers, which remained stable over time (50%, 45%, and 45% in 2013-2015 respectively). MR-antagonists were only prescribed in 13% of patients after HF diagnosis, this was similar for each time period.

Age-specific prescription patterns

Differences in prescription according to age categories are shown in **Figure 3**. The observed increase in prescriptions for RAS-inhibitors, beta-blockers, and MR-antagonists between 6 months before HF diagnosis to 6 months after HF diagnosis was less pronounced in elderly patients. The average increase in elderly patients was 12%, 7%, 8% for RAS-inhibitors, beta-blockers and MR-antagonists respectively, while younger patients had an average increase of 23%, 19% and 13% for RAS-inhibitors, beta-blockers and MR-antagonists respectively. On the other hand, a higher proportion of elderly patients were treated with loop-diuretics compared to younger patients, both before and after HF diagnosis (45% before and 63% after HF diagnosis in elderly compared to 27% before and 47% after HF diagnosis for younger patients in 2013-2015). After HF diagnosis, a higher percentage of younger patients were prescribed with RAS-inhibitors and beta-blockers compared to older patients.

Sex-specific prescription patterns

Differences in prescription between men and women are shown in **Figure 4**. Loop diuretics were prescribed in a higher proportion of women compared to men, this difference was already present prior to HF diagnosis where 6 months before diagnosis 30% of women and 20% of men were prescribed a loop diuretic. After HF diagnosis, the most prescribed medication for women was a loop diuretic, while a higher proportion of men were prescribed a RAS-inhibitor. Men were also more often prescribed RAS-inhibitors, beta-blockers and MR-antagonists after HF diagnosis compared to women.

Social economic status-specific prescription patterns

Social economic status-specific prescription patterns are shown in **Figure 5**. We did not observe any discernible differences between patients in low vs. high social-economic areas (highest quintile of social economic deprivation).

Discussion

In this large-scale study of 85,732 HF patients we investigated treatment prescription patterns in a representative sample of real-world patients with HF in the UK between 2002 and 2015. We found three important trends in pharmacological HF management: a) increased use of beta-blockers, whereas there was no increased uptake of MR-antagonists over 13 years follow up; b) prescription rates remained almost unchanged after the first 6 months following a HF diagnosis; and lastly, c) higher rates of loop diuretics in women and elderly patients together with lower prescription rates for RAS-inhibitors, beta-blockers, or MR-antagonists.

Temporal trends in heart failure medication

Even though prescription rates increased over time from 2002 to 2015, overall prescription rates remained low. This is in line with previously published studies.(5–8, 19) Low prescription rates could be attributed to the mixed HF cases found in EHR. We were unable to distinguish HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction, and HF with preserved ejection fraction (HFpEF) based on medical records, thereby including known differences in treatment recommendations for these HF phenotypes.(1)

We found no major differences in prescription behaviour after the publication of ESC guidelines, however we did observe the gradual increase of beta-blockers as one of the cornerstones of HF treatment. RAS-inhibitors were prescribed in a high proportion of patients throughout the years of the study, presumably because the first clinical trials in HFrEF showing a beneficial effect were from the late 1980s and early 1990s.(20) Surprisingly, we found lower than expected prescription rates for MR-antagonists, which persisted over the years included in this study. This is in spite of multiple clinical trials which have shown benefit in HFrEF patients.(21) Besides HFrEF trials, a post-hoc analysis of the TOPCAT trial in 2015 (Spironolactone, a MR-antagonist, for HFpEF) reported regional differences between Americas and Russia/Georgia, where the American patients showed clinical benefits.(22) The American College of Cardiology/American Heart Association focused update on HF management in 2017 gave spironolactone a grade IIb recommendation, thereby stimulating that selected HFpEF patients could be treated with spironolactone to decrease re-hospitalisations.(23)

Heart failure medication initiation following diagnosis

Most activity in treatment prescription behaviour was observed between 6 months before to 6 months after HF diagnosis. After the 6 month mark we did not observe many patients starting

any of the medication investigated. This is in line with previous studies showing that there are few changes in medication use and little up titration of medication after treatment initiation.(5, 24) This leaves room for improvement in starting treatment at any time point following a HF diagnosis, for example if patients hospitalised with acute HF do not immediately tolerate negative inotropic medication such as beta-blockers.

Impact of heart failure hospitalisation on medication prescription

We found differences in prescription patterns between patients with a HF diagnosis recorded in different settings. Patients with a primary care HF diagnosis without HF hospitalisation had much lower prescription rates of loop diuretics compared to patients with a HF diagnosis recorded in both primary and secondary care. It could be that these patients have less severe fluid overload or symptoms that requires alleviation by loop diuretics, and thus less severe HF.

Previously it was shown that there are differences in overall five-year survival of patients with HF diagnosis recorded in primary care only, secondary care only and in both, with the worst survival seen in HF patients identified only in secondary care and the best survival for HF patients identified in primary care with or without hospitalisation for HF.(4) Here, we advance current knowledge by showing that there are longitudinal differences in HF care of patients with diagnosis recorded in different settings.

In this study almost 40% of patients did not have a GP record of a HF diagnosis after a HF hospitalisation. One reason could be that GPs do not formally register HF with a Read diagnosis code, but rather in free text descriptions. However, there could also be a potential quality of care gap or failure of communication between secondary and primary care, where patients are not treated optimally. Primary care is the basis of many healthcare systems, including the UK. If there is no HF diagnosis recorded in primary care after HF hospitalisation,

which is shown to indicative for worse survival, rehospitalisation and severity of disease, this could be detrimental for patients.

Heart failure treatment in women and elderly

Over time, we observed that HF was diagnosed at a later age, with the median almost 80 years old between 2013-2015. This is also seen in many other developed countries where the mean age of HF diagnosis is over 70 years old.(25, 26)

We observed lower prescription rates in elderly patients compared to younger patients for RAS-inhibitors, beta-blockers and MR-antagonists, although the difference in MR-antagonists was less pronounced. Many elderly patients were already using RAS-inhibitors prior to HF diagnosis, therefore the increase in prescription rate is not as steep as compared to younger HF patients who are prescribed less medication prior to HF diagnosis. This could be explained by the presence of comorbidities, such as atrial fibrillation or hypertension, which are much more prevalent among elderly compared to younger patients, and for which these elderly patients could be prescribed RAS-inhibitors.

Remarkably, the difference between prescription of RAS-inhibitors and beta-blockers prior to HF diagnosis was less than 5% for men and women, and only after the diagnosis of HF was a higher proportion of men prescribed a RAS-inhibitor or beta-blocker. This could potentially be related to the fact that elderly women are more likely to develop HFpEF and therefore tend to be treated symptomatically with loop diuretics, rather than with RAS-inhibitors and beta-blockers. However, the literature also shows that there are differences in treatment prescription in men and women with HFrEF, for which there is no obvious explanation.(27)

Both elderly patients and women received more loop diuretics. However, this could potentially be harmful, especially for elderly, since loop diuretics could lead to electrolyte disturbances and acute kidney injury.(28) Elderly patients are often excluded or underrepresented in clinical trials, therefore current recommendations lack convincing evidence in the elderly population. However, recently a large meta-analysis reported a significant effect of beta-blockers on overall mortality regardless of age.(29) These studies indicate that elderly patients also benefit from HF-specific medication and should be a choice of treatment for these patients, besides loop diuretics for symptom alleviation. However, elderly patients might have more contraindications or intolerances to RAS-inhibitors, beta-blockers and MR-antagonists and might therefore be more often treated with loop diuretics for symptom control.

Strengths and limitations

Strengths of this study are the large cohort of HF patients and a long follow-up period. Patient records available are representative of the general UK population, which provides evidence for the validity of using these EHR for research.(11, 12) However, we were limited by the inability to differentiate between HF phenotypes based on medical records, since there was no access to detailed echocardiography estimates to assess systolic function. Nor did we have information on NYHA class or NT-proBNP biomarker levels. Furthermore, treatments administered during a hospital admission or discharge were not reported, such as intravenous inotropic agents. However, CPRD includes all prescriptions from general practice to non-hospitalized patients. We were also unable to assess patients' symptom class (which would affect their eligibility for treatments such as MRA-antagonists), and contraindications or intolerances that may affect the choice of medication.

Conclusion

The results of this population-based study of over 80,000 patients with heart failure in England shows variable increases in uptake of evidence-based treatments, with no change in prescription of MR-antagonists over 13 years, but an increase in beta-blocker use. Large differences were observed between HF patient groups, with lowest prescription rates of RAS-inhibitors, beta-blockers and MR-antagonists in women, elderly patients, and those without a HF diagnosis in primary care. Most changes in prescriptions occurred within 6 months prior to or 6 months following a diagnosis of HF, with little change thereafter, suggesting further opportunities to improve HF management.

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a. Contributor statement

AU has designed the research, analysed and interpreted the data and drafted the manuscript. IV, AH, FA and SK have designed the research, interpreted the data, critically revised the manuscript and supervised AU. SD, HH, AS, JC and DG have interpreted the data and critically revised the manuscript.

b. Competing interests

The authors report no conflict of interest.

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d. Data sharing statement

All data were provided anonymised and are not publicly available due to their sensitive nature. Data may be obtained from the Clinical Practice Research Datalink (https://www.cprd.com). EHR phenotypes are available from the CALIBER resource (https://www.caliberresearch.org). The protocol may be obtained via the Clinical Practice Research Datalink under protocol reference: 17_015. No additional data is available.

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Figure legends

Central illustration Figure 1

Legend Figure 1. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers, MR-antagonists, loop diuretics per months since HF diagnosis. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 2. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by setting (primary care only, secondary care only, both primary and secondary care). RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 3. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by age. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 4. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by sex. RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Legend Figure 5. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by social status (highest quintile of social deprivation vs. the rest). RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Table 1. Patients characteristics of heart failure patients between 2002 and 2015

	Overall	2002 - 2005	2006 - 2008	2009 - 2012	2013 - 2015	% missing
n	85732	25366	17715	26114	16537	
Demographics						
Age (Years, median [IQR])	79.1 [70.2, 85.7]	78.7 [70.7, 84.9]	78.7 [69.9, 85.4]	79.5 [71.1, 86.3]	79.7 [70.0, 86.4]	0
Sex (% Women)	48.6	49.3	48.4	48.4	48.0	0
Ethnicity (% Caucasian)	96.5	97.5	96.9	96.1	95.1	3.5
Social deprivation (% lowest quintile)	24.3	25.1	25.0	24.0	22.9	0
Clinical and lifestyle measurements						
SBP (mmHg, mean (sd))	136.2 (20.7)	140.6 (22.3)	135.9 (20.7)	134.1 (20.0)	132.9 (18.7)	13.0
DBP (mmHg, mean (sd))	76.2 (12.0)	78.4 (12.0)	76.2 (12.0)	75.1 (12.0)	74.4 (11.6)	13.0
BMI (kg/m^2, mean (sd))	28.6 (6.6)	28.2 (6.4)	28.4 (6.6)	28.7 (6.8)	28.8 (6.8)	54.0
eGFR (min/m2/1.73mL, median [IQR])	58.4 [45.3, 72.1]	54.7 [43.4, 66.1]	56.5 [44.3, 68.8]	60.5 [46.1, 75.3]	62.9 [47.5, 78.2]	24.0
Smoking status (% Current)	20.8	22.3	20.0	20.4	20.5	38.7
Medical history (%)[¶]						
Atrial Fibrillation	36.6	28.4	36.3	40.6	43.0	-
COPD	17.9	14.8	17.3	19.5	21.0	-
Diabetes	22.3	18.1	22.2	23.7	26.7	-
Hypertension	60.7	46.0	60.7	67.9	72.0	-
Ischaemic heart disease	44.2	39.0	46.0	46.4	46.8	-
Valvular disease	16.5	9.5	14.9	19.9	23.8	-
Medication prescription up to 3 months after HF diagnosis (%)[¶]						
RAS-inhibitors	60.8	59.6	63.5	62.0	57.6	-
Beta-blockers	42.5	28.9	41.0	49.3	54.1	-
MR-antagonists	18.0	18.4	17.9	17.6	18.2	-
Loop diuretics	63.0	68.4	63.5	61.1	57.0	-

Legend Table 1. * Assessed by index of multiple deprivation, § denotes prior medical history of given comorbidity, ¤ Medication 12 months prior to index date, Mean (SD) = Mean (Standard deviation), Median [IQR] = Median [Interquartile range], CPRD = Clinical Practice Research Datalink, SBP = systolic blood pressure, DBP = Diastolic blood pressure, BMI = Body Mass Index, eGFR = estimated glomerular filtration rate, COPD = Chronic Obstructive Pulmonary Disease, RAS-inhibitors = ACE-inhibitors and/or angiotensin II receptor blockers, MR-antagonists = mineralocorticoid receptor antagonist. ¶Medical conditions and prescriptions were considered absent if not recorded.

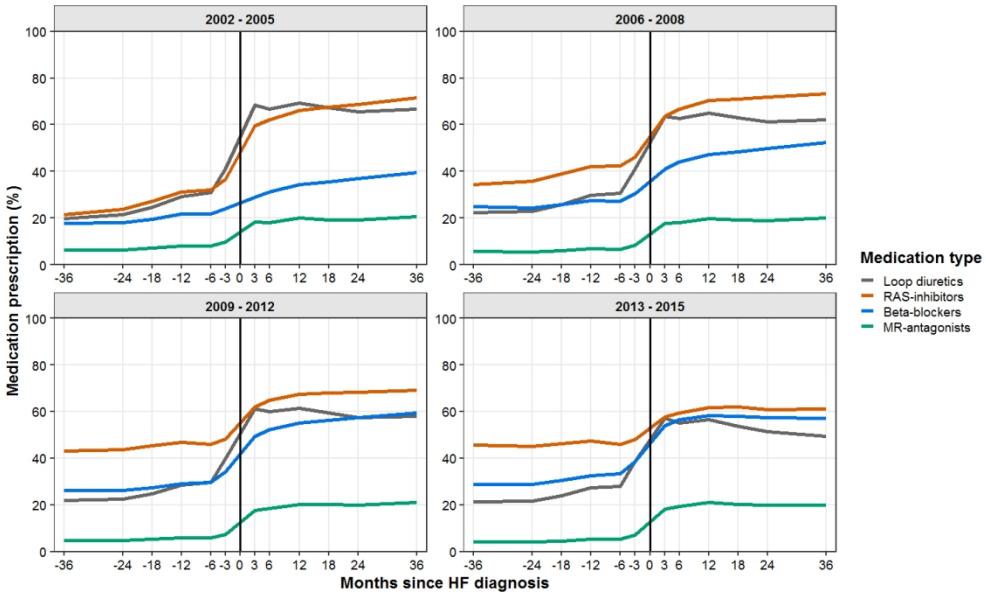

figure 1

127x76mm (300 x 300 DPI)

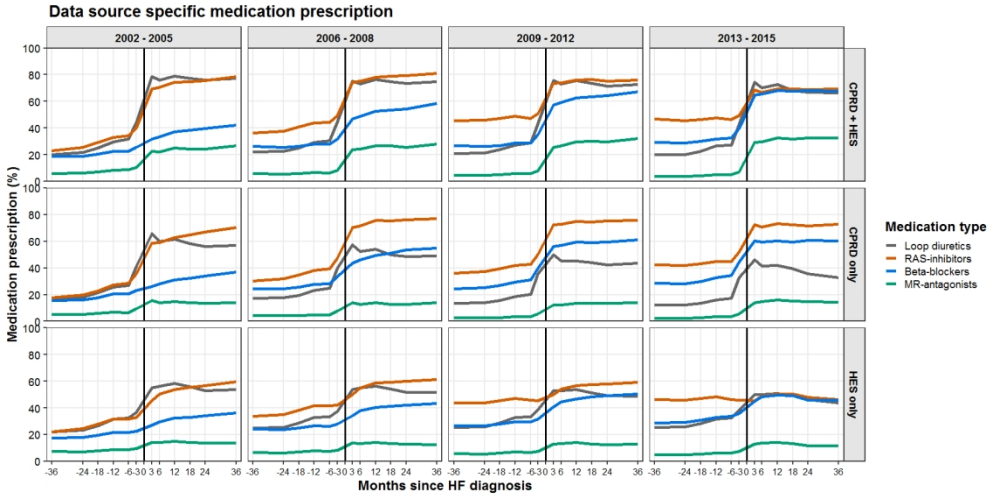

figure 2

152x76mm (300 x 300 DPI)

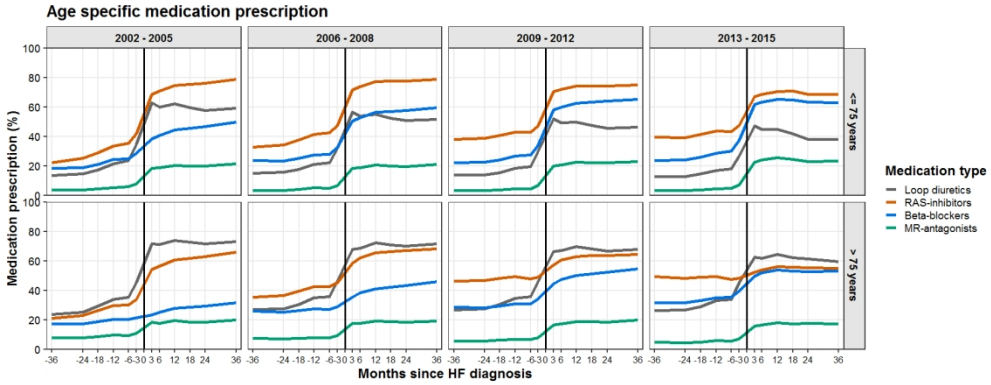

figure 3

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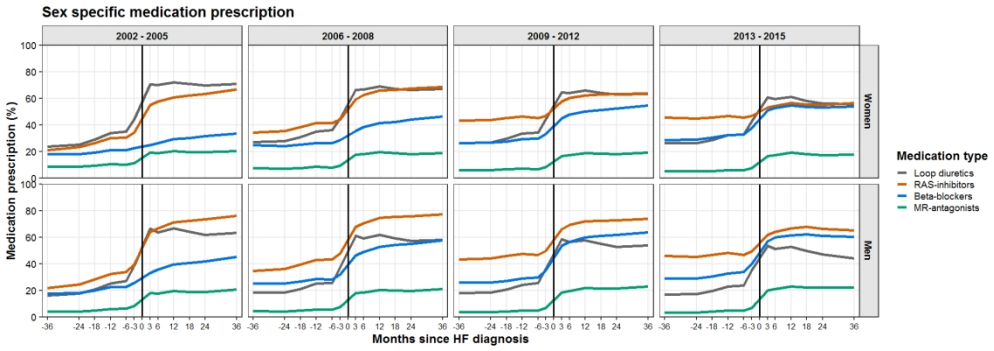

figure 4

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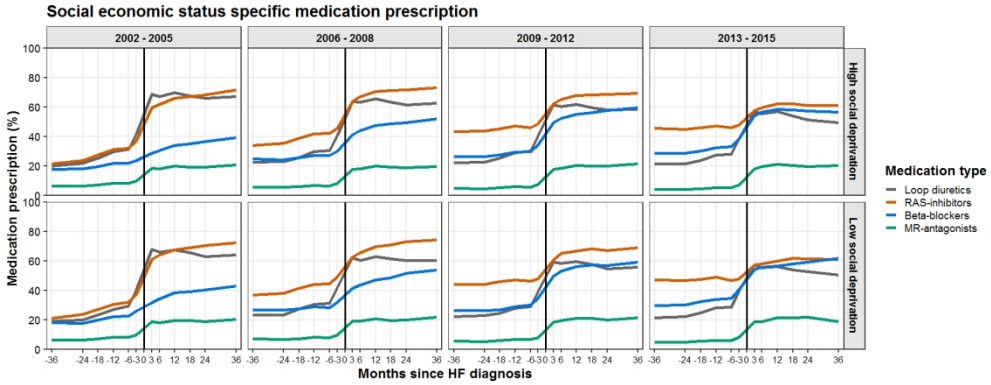

figure 5

152x59mm (300 x 300 DPI)

Supplemental material

Figure S1 – study flow diagram

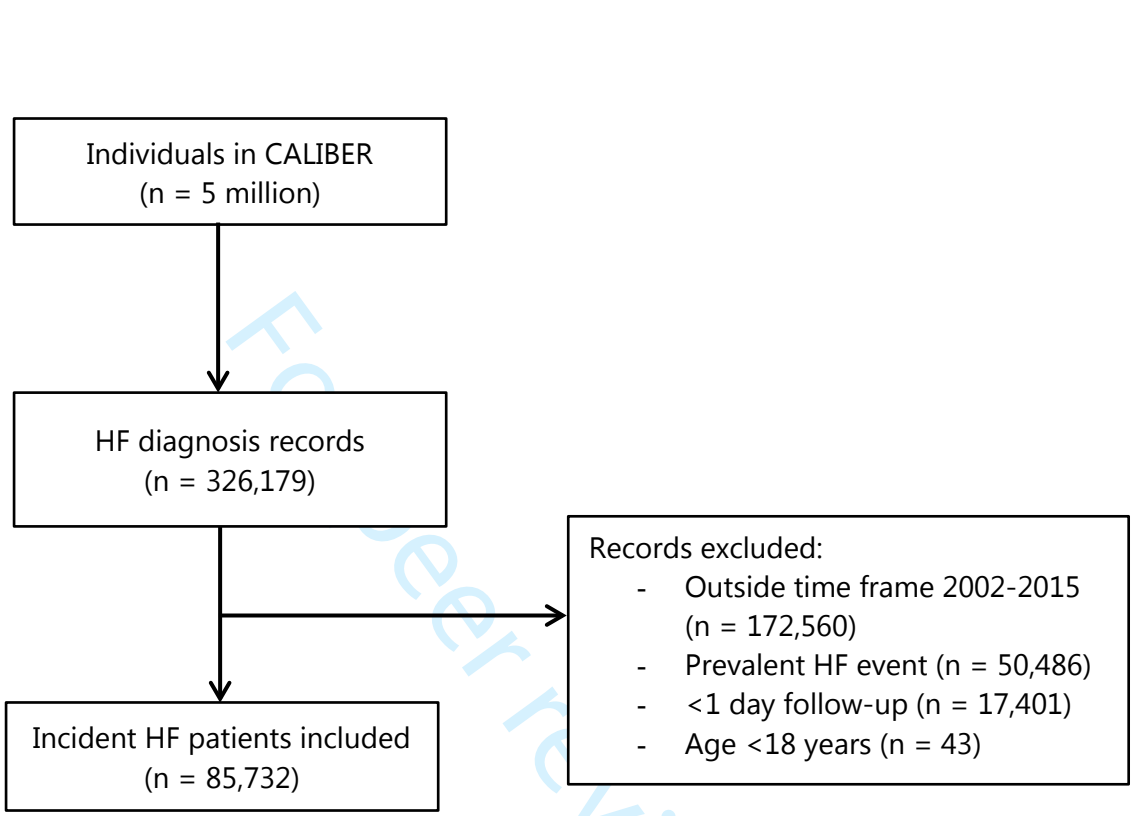

Table S1 – additional READ codes used to identify heart failure in the Clinical Practice Research Datalink

CPRD* Heart Failure READ codes
585g.00, G5yyC00, G5yyA00, G583.12, G583.11, G583.00, G5yy900, 585f.00

Legend Table S1. * CPRD = Clinical Practice Research Datalink

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	-
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 - 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10 - 12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10 - 12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13 - 15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13 - 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.