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Title page

Temporal trends in initiation of mineralocorticoid receptor antagonists and risk of subsequent withdrawal in patients with heart failure: A nationwide study in Denmark from 2003-2017

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Abstract

Aims: Despite landmark heart failure (HF) with reduced ejection fraction (HFrEF) trials showing effect of Mineralocorticoid Receptor Antagonists (MRA) on the risk of death and HF hospitalization, it has been suggested that MRAs are underutilized or frequently withdrawn. This study sought to identify temporal trends in the initiation of MRAs and the subsequent risk of withdrawal and adherence of MRAs in HF patients treated with a renin-angiotensin system inhibitor and a beta-blocker in Denmark from 2003-2017.

Methods and results: From nationwide registries, we identified patients receiving a diagnosis of HF. Use of MRA was identified by at least one prescription within six months after the diagnosis. The absolute risk of withdrawal with treatment was assessed with cumulative incidence, accounting for the competing risk of death. To estimate adherence, we calculated the proportion of days covered (PDC). We included 51,512 patients with incident HF. During the study period 20,779 (40.3%) patients initiated MRA therapy. The incidence of withdrawal of MRA was 49.2% throughout the study period. 48.0 % of the HF patients were adherent with the treatment. Among patients withdrawing treatment with MRA, the cumulative incidence of reinitiating was 36.6 %.

Conclusions: In a nationwide cohort of patients with HF, approximately half of the patients received MRA as third-line therapy within the first six months after diagnosis and approximately half of these withdrew MRA within 5 years. These findings warrant an increasing focus on retention to MRA treatment in a real-life setting.

Keywords: heart failure, adherence, pharmacotherapy

Introduction

Heart failure (HF) is common with substantial morbidity and mortality worldwide. However, major treatment advances have been made during the last decades including renin–angiotensin system (RAS) inhibitors (i.e. angiotensin converting enzyme inhibitors [ACEi] or angiotensin II receptor blockers [ARB]), beta-blockers (BB), mineralocorticoid-receptor antagonists (MRA), sacubitril-valsartan and sodium-glucose co-transporter 2 (SGLT2) inhibitors and implemented in HF guidelines[1,2]. HF guidelines recommend RAS inhibitors and BB and MRA should be applied if patients remain symptomatic with reduced left ventricular ejection fraction (LVEF) and suitable renal function and potassium concentration after initiation of RAS inhibitors and beta blockers. The new ESC guidelines recommend the SGLT2 inhibitors dapagliflozin or empagliflozin for patients with HFrEF to reduce the risk of HF hospitalization and death, and sacubitril/valsartan is recommended as a replacement for an ACEi[1].

MRAs improve the prognosis for patients with HF and a reduced LVEF (HFrEF) significantly. For optimal benefit of the therapy, it is important to ensure long-term adherence to treatment. Despite landmark HF trials showing effect of MRA on the risk of death and HF hospitalization in patients with left ventricular systolic dysfunction[3,4], it has been suggested that MRAs are under-prescribed or frequently withdrawn in guideline-eligible patients with HF[5,6]. The main concerns leading to non-prescription and treatment discontinuation are risk of worsening of renal function and hyperkalemia. These were highlighted after the Randomized Aldactone Evaluation Study (RALES) trial[3] which lead to an enthusiastic and rapid uptake of MRAs but was associated with an increase in the incidence of hyperkalemia in the province of Ontario, Canada[7]. Such observational data were however not confirmed in a survey led in UK[8]. A subsequent trial with eplerenone in patients with patients with less symptomatic HF [4] (a related trial in patients with a myocardial infarction complicated by left ventricular dysfunction and HF or diabetes [9]) were

reassuring with respect to safety and confirmed the efficacy of MRAs. Whether these more recent results and resulting strong guideline-recommendations have affected prescription of MRAs in HF over time has not been investigated.

Therefore, we evaluated the rate of initiation of MRAs over time, risk of withdrawal and adherence in patients with HF in Denmark between 2003 and 2017.

Methods

Data sources

Data were obtained from Danish nationwide registries. All Danish citizens are registered in the Civil Registration Registry[10] with a unique personal number that allows identification across several national registries. We utilized data from the following three Danish national registries: (i) The Danish National Patient Registry, which holds information on all hospital in- and outpatient contacts since 1977 coded with one primary diagnosis according to International Classification of Diseases 10th edition (ICD-10) (since 1994) at discharge and if relevant one or more secondary diagnoses,[11] (ii) the National Prescription Registry, which holds information on all medical prescriptions collected at Danish pharmacies since 1995 coded according to the Anatomical Therapeutic Chemical (ATC) classification system,[12] (iii) the National Cause of Death Registry, which holds information on death dates and causes[13].

Study population and outcomes

In the present study, we identified patients aged 18-95 years with a first-time primary in-hospital or out-patient HF diagnosis (ICD-10 I50 and I42) between January 1, 2003 and December 31, 2017. Patients were included if 1) they were alive 6 months after diagnosis and 2) redeemed a

prescription of a RAS inhibitor and BB within 120 days after HF diagnosis. The latter criteria was applied to restrict the HF population to patients with HFrEFand to increase the likelihood of a thorough evaluation of patients in HF outpatient clinics. A previous validation study has shown that this HFrEF definition has a high positive predictive value (95 %), and that the sensitivity and specificity are 85 %[14]. Therefore, some HFrEF patients are overlooked, but only few HFpEF patients included. According to the definition (= + 120 days after the diagnosis HF) the sickest patients might have died before study start. Whether the present HFrEF definition based on administrative codes can be used in other health care systems remains unclear.

Use of an MRA was identified by collection of at least one prescription within the first 6 months of diagnosis. Baseline was correspondingly defined as 6 months from the day of diagnosis, i.e. the first visit to an outpatient clinic or a first admission to hospital for HF (figure A in Supplemental Appendix). We prespecified three subgroups of interest: place of diagnosis (inpatient or outpatient), diabetes status (yes/no) and use of loop diuretic(yes/no). Patients were followed until death, emigration, or end of study (December 31, 2018).

The primary persistence endpoint was defined as withdrawal of treatment for at least 90 days as this has been shown to predict a low probability of later re-initiation[15]. The primary adherence endpoint was defined by the proportion of days covered (PDC), i.e. the total number of days with drug available for each patient divided by number of days in total. To estimate PDC only patients who initiated treatment with the drug and who are alive during the follow up period were included in the analyses. To estimate PDC we used daily dosage for spironolactone of 12.5 mg, 25 mg and 50 mg and for eplerenone of 25 mg and 50 mg. PDC has been shown to more accurately reflect patient behaviour and treatment continuity than other adherence measure[16] and recommended as a gold standard calculation method for long-term treatments. Good adherence was defined as PDC > 80%,

as an 80% adherence level has previously been associated with a reduced risk of death in HF[17]. These methods have been tested and found to be stable in drug dosage calculations[15,18].

Statistical analyses

Baseline characteristics are presented as numbers with percentages for categorical variables and medians with interquartile ranges for continuous variables. Temporal trends in initiation of MRA in HF patients over the first 6 months after HF diagnosis were calculated as proportions for each year of the study period. The primary persistence endpoint was time to a >90-day break in treatment and was estimated with cumulative incidence function taking account for competing risk of death (Aalen-Johansen estimator). Risk of change of MRA type were evaluated likewise. A multivariable Cox proportional hazards regression model was used to evaluate the effect of covariates associated with time to 90 days break. Model assumptions, such as linearity of continuous variables, the proportional hazard assumption, and lack of interactions were tested and found valid, unless otherwise indicated.

All data management and analyses were conducted with SAS, version 9.4 (SAS institute, Cary, NC, USA) and R (R version 3.2.2, R Foundation for Statistical Computing). Two-sided p values <0.05 were considered significant.

Ethics

Retrospective registry-based studies do not need ethical approval in Denmark. The Danish Data Protection Agency has approved the data access (approval number P-2019-393).

Results

From 2003 to 2017, 110873 patients were diagnosed with HF in Denmark. After exclusion criteria were applied, 51512 patients were included in the study (Figure 1).

Over the entire study period, 20,779 patients (40.3%) had an MRA initiated within the first 6 months of their diagnosis of HF, of whom 99% where prescribed spironolactone and 1 % eplerenone. The baseline characteristics of patients prescribed and not prescribed an MRA are depicted in Table 1. There were few differences between patients not started on an MRA and those prescribed an MRA. Patients not prescribed an MRA had their primary diagnosis made in the outpatient setting more often than patients started on an MRA (52.2% versus 43.0%, respectively) and those not prescribed a MRA were slightly more likely to have concomitant kidney disease (5.9% versus 3.7%) and less likely to be treated with a loop diuretic (63.9% versus 79.5%) than patients started on an MRA. For a subpopulation of the study population, available data on serum kreatinine, potassium, sodium and hemoglobin is depicted in Supplementary Table 2.

Temporal trends in initiation with MRA within the first 6 months after HF diagnosis

The proportion of incident HF patients claiming at least one prescription of MRA during each year of the study period is shown in Figure 2a. The time trend analysis indicated that initiation of MRA declined slightly from 2003 to 2010 with a nadir of 29.0 %, whereas it increased again to a value of 48.2 % in 2018. Stratifying the analysis according to diabetes status showed that differences between the two groups which existed in the early years diminished in the more recent years (Figure 2b). Stratifying by place of diagnosis, showed that the difference between MRA initiation in outpatients and inpatients diminished over the study period (Figure 2c). MRA usage was significantly lower in

patients not treated with a loop diuretic, compared to those treated with a loop diuretic, throughout the study period, although the difference became smaller in the latter years (Figure 2d).

Persistence of MRA

The cumulative incidence of withdrawal with MRA was 49.2% by the end of the study period (Figure 3a). This finding was similar whether stratifying by diabetes status, diagnosis setting (outpatient/inpatient) or treated/not treated with a loop diuretic (Figure B in Supplemental Appendix). Using multivariable Cox model, we identified factors associated with withdrawal from MRA (Figure 3b). Several variables were associated with higher rates of MRA discontinuation, including older age, male sex, outpatient HF diagnosis, diabetes, kidney disease, atrial fibrillation, cerebrovascular disease, peripheral arterial disease and COPD. Use/non-use of loop diuretic was not a predictor of discontinuation. Ischemic heart disease was associated with a significantly lower likelihood of discontinuation. The median time to withdrawal was 324 days, with 35.3 % having an early withdrawal defined as withdrawal within 6 months from inclusion. 8.6 % of the patients discontinuing MRA died within 6 months from discontinuation. We conducted a sub analysis of patients surviving the first 365 days after the withdrawal date of MRA to exclude the effect of end of life care and found similar results (data not shown). Conducting a sensitivity analysis excluding patients with history of dementia and cancer showed similar results (data not shown). The withdrawal rate of MRA was significantly higher than those of betablocker and RAS-inhibitor. (Figure 3a-b in Supplemental Appendix). During a median follow-up of 1.4 years after first MRA withdrawal, 3343 patients (36.6%) reinitiated MRA therapy.

Adherence to MRA treatment

In a subgroup of the population who initiated MRA at baseline and survived 5 years consisting of 7,919 patients, good adherence, defined as PDC>80%, was documented in 48.0 % of the subgroup (Figure 4). Adherence to MRA treatment was significantly lower than those of betablocker and RAS-inhibitor. (Figure 3c in Supplemental Appendix). Adherence did not differ among those with/without diabetes, diagnosed as an outpatient/inpatients HF or treated/not treated with a loop-diuretic as shown in the Supplemental Appendix (Figure D in Supplemental Appendix). Adherence to MRA treatment did not improve over the study period (Figure E in Supplemental Appendix).

Changing MRA and initiating MRA after the first 6 months

Overall, 780 patients (4.1%) changed MRA over the study period, more commonly in men compared with women (Figure Fa in Supplemental Appendix). Most of the changes were from spironolactone to eplerenone (98.9 %). Figure Fb shows a multivariable Cox-model showing factors associated with MRA change, showing that elderly had a lower rate of changing MRA type. Among patients not commenced on an MRA within the first 6 months after HF diagnosis, 22.5 % went on to start an MRA at a later time during the 5 years of follow-up (Figure G in Supplemental Appendix).

Discussion

In this nationwide study of MRA use in HFrEF in Denmark, three major findings were yielded. First, 40 % of patients with incident HFrEF initiated MRA within 6 months of their HF diagnosis (in addition to a BB and RAS inhibitor). Second, approximately half of these patients withdrew MRA treatment within 5 years, a discontinuation rate significantly higher than for BB and RAS inhibitor. Third, among those remaining on treatment and alive over the first 5 years only half demonstrated good adherence with MRA, and this was significantly lower than for BB and RAS inhibitor. This is

novel information that adds to previous knowledge on long-term patient adherence with evidence-based HF pharmacotherapy.

Initiation

Only 40 % of patients with HF initiated MRA, and these results are in accordance with previous studies suggesting underuse of MRA for eligible HF patients[19,20] or that only ≈ 50 % of the patients remain symptomatic with a continued low left ventricular ejection fraction. In this study the incidence of MRA initiation within 6 months from diagnosis declined substantially from 2003 to 2010 thereafter increasing again. At the beginning of 2011 Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF) trial was published, showing Eplerenone, as compared with placebo, reduced both the risk of death and hospitalization among patients with systolic HF and mild symptoms[21]. Subsequently, the ESC HF guidelines published in 2012 granted a 1A to MRAs in this clinical setting. We did not observe any increase in the use of MRA after the results of the EMPHASIS-HF trial. We think it reflects underuse of MRA by HF specialists e.g. in elderly patients and patient with eGFR in low normal range, partially remission of left ventricular function and symptoms after up titration in ACE-I and BB or resistant to more drugs by the patients. The exact reason cannot be deduced based on our data and need further investigations.

. Recently a paper showed that patients with comorbid HFrEF and kidney disease are not optimally treated with evidence-based medical therapies including MRA, even at levels of eGFR where such therapies would not be contraindicated by renal dysfunction and the underuse was related to renal function rather than an increase in plasma potassium[22]. In a subpopulation of 1000 patients with HF and available baseline renal function and plasma concentrations of potassium, we observed the same tendency, and patients who had initiated MRA treatment had a higher eGFR. Strategies that can improve the use and persistence of MRAs in patients with HFrEF across the whole spectrum of

eGFR and plasma potassium consist of e.g better communication to patients and health care personals on the mortality and morbidity reducing effects of MRAs and not only the diuretic properties, inform specialized HF nurses and general practitioners that plasma concentrations of 5.5 mmol/L are acceptable and that vertigo and hypotension is frequently not associated to treatment with MRA[23].In our real-life cohort, we only identified that approximately 40 % of the patients received an MRA. Compared to data from The Danish Trial[24] and The NorthStar Trial[25] this number is a little lower. Whether this number should be considered low or high and whether it reflects a poor, acceptable or good level of care is complex. For instance, according to clinical guidelines, MRA should only be initiated if symptoms are present and LVEF maintain </= 0.35. Further, some physicians may believe that MRAs are diuretics for symptomatic use rather than live saving neurohormonal blockade reflecting suboptimal education of healthcare professionals. However, considering the lack of increase in the use of MRA after the publication of the results of landmark trials indicate suboptimal initiation of MRAs in Danish HF clinics. A previous small study showed that only 13% of eligible patients discharged from hospital without a prescription for an MRA later started therapy as outpatients[5]. In our study, 1 in 5 patients not initially prescribed an MRA started this treatment after the first 6 months from diagnosis. These data emphasize the importance of initiating MRA treatment early after diagnosis, as the probability of starting treatment later is lower.

Fewer than 1 in 20 patients changed from one type of MRA to another, primarily men and younger patients changing from spironolactone to eplerenone, presumably because of anti-androgenic adverse effects such as gynecomastia.

Persistence

The withdrawal rate of approximately 50 % after 5 years in our cohort is significantly higher than for other HF drugs, especially taking into consideration the significant effect of MRA on improving the

prognosis for HF patients. EMPHASIS-HF reported a discontinuation rate of 16.3 % in the treatment group after a median follow-up period of 21 months[4]. The withdrawal did not differ between different high-risk and low-risk groups. The precise reasons for poor use of MRA therapy are unclear, however likely barriers may include perceived risk of worsening renal function and hyperkalemia. Even though these MRA-associated adverse effects are well recognized, more contemporary evidence supports a relatively good safety profile for in-hospital use of MRA therapy. Notably, the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial found high dose spironolactone to be well-tolerated among patients hospitalized with HF with no significant change in potassium level or renal function, as compared with usual care[26]. Previous studies have shown that non-contraindicated comorbidities such as minimally impaired renal function led to lower prescription rates of MRA[27]. MRAs are a particularly effective treatment for resistant hypertension and therefore a fear of hypotension accompanying dizziness in patients with HFrEF has been raised. A study conducted on HFrEF patients in the RALES and EMPHASIS-HF trials showed that MRA treatment infrequently caused hypotension and the treatment discontinuation rates between MRA and placebo therapy were similar[23]. MRA has diuretic and potassium-sparing effects effect in higher doses, however recommended doses of MRAs for HFrEF patients have additional protective cardiovascular effects[28]. A Swedish study showed that diuretic use was the strongest independent predictor of MRA use[27]. One potential derivation of this could be wrongfully withdrawal of MRA in euvolemic patients. Our study showed re-initiation rate of 36.6 % withing the first 1.4 years, this seemingly dynamic use of MRA is in accordance with other studies showing that MRA therapy is a highly unstable and dynamic condition[29]. However to our knowledge our study is the first to evaluate a re-initiation rate of MRA therapy.

Adherence

In a subgroup of patients initiated with MRA and alive throughout follow-up of 5 years, we found that fewer than 50% demonstrated good adherence to MRA treatment defined as PDC>80 %. This was significantly lower than for other types of HF drugs. Good adherence did not differ between different high-risk and low-risk groups as shown in the supplementary analyses. A smaller study found low adherence in HF with a medication possession ratio (MPR) of 0.63 over 1 year[5]. Directly comparing these numbers with those in our study is difficult as adherence has been defined in different ways. PDC has been recommended as a gold standard calculation method for long-term treatments and is more accurate compared to MPR to assess adherence to treatments in chronic diseases[16]. Good adherence was independently associated with improved clinical outcomes in patients with HF in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) trial, even in the placebo group[17]. Another study in Denmark showed that extended follow-up in an outpatient HF clinic did not improve long-term adherence, and adherence did not deteriorate when patients were shifted from the HF clinic to primary care[25].

Strengths and limitations

The strengths of this nationwide study of HF patients include a large population of HF patients with minimal loss-to-follow up. The Danish registries include all hospital admissions in Denmark from 1978 and therefore not affected by selection bias.

The major limitation is inherent in the observational design of the study, which limits causal inference based on the observed differences. Our study is based on data from administrivia registries and therefore it should be noted that data on LVEF is not available which should be noted. Our used definition of HFrEF is based on a previous published methodological study that proposed that HFrEF patients could be identified in Danish registries with the definition used in present study[14]. Though, we cannot further evaluate the association between mild and severe reduced LVEF and MRA

adherence/persistence, which is an important limitation of our study. Adherence is measured via claims data and not data on the actual intake of medication e.g. through surveys, therefore adherence can be wrongly represented using these calculations. Another methodical consideration to consider is that PDC calculations are based on average intake and cannot distinguish between patients who have a break in treatment or have poor adherence. Furthermore, discontinuation can be caused by several factors not included in the registries including contraindications for treatment or adverse reactions/allergies.

In summary, we noted that in a large population with HF, initiation and long-term adherence to MRA was low. Approximately half of the patients received MRA as third-line therapy within the first 6 months and approximately half of these withdrew MRA within 5 years. Since HF is a major cause of death and disability globally, the need to improve persistence and adherence to effective treatments such as MRA in a real-life setting is obvious.

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Figure legends

Figure 1. Flow chart

Figure 2. Time trend of MRA initiation

Figure 2a: Time trend of MRA initiation within the first 6 months from HF diagnosis

Figure 2b: Time trend for MRA initiation stratified according to diabetes status

Figure 2c: Time trend for MRA initiation stratified according to outpatient HF diagnosis

Figure 2d: Time trend for MRA initiation stratified according to use of loop-diuretics

Figure 3: Withdrawal of MRA after the first 6 months. Includes patients in therapy at baseline.

Figure 3a: Cumulative incidence of withdrawal of MRA after the first 6 months

Figure 3b: Covariates associated with withdrawal of MRA

Figure 4: Proportion of days covered for MRA over 5 years

Figure 5: Changing to a different MRA

Figure 5a: Incidence of MRA change stratified according to sex

Figure 5b: Covariates associated with change of MRA

Figure 6: Initiating MRA after 6 months for patients without MRA at baseline

Text tables

Table 1: Baseline characteristics of the study population at inclusion, 6 months after diagnosis

	MRA prescribed at baseline	MRA not prescribed at baseline	P-value
Individuals, No. (%)	20779 (40.3 %)	30733 (59.7 %)	
Age, median [IQR]	69.5 [60.5,77.2]	71.3 [62.3,79.3]	<0.001
Sex, No. ♂ (%)	14274 (68.7 %)	20070 (65.3 %)	<0.001
Outpatient primary diagnosis	8944 (43.0 %)	16043 (52.2 %)	<0.001
Comorbidity, No. (%) *			
Ischemic heart disease	9663 (46.5 %)	14854 (48.3 %)	<0.001
Atrial fibrillation	6802 (32.7 %)	9934 (32.3%)	0.333
Renal disease	760 (3.7 %)	1814 (5.9 %)	<0.001
Diabetes	3451 (16.6 %)	4657 (15.2 %)	<0.001
Cerebrovascular disease	1542 (7.4 %)	2476 (8.1 %)	0.009
Peripheral vascular disease	1171 (5.6 %)	1822 (5.9 %)	0.169
Cancer	1341 (6.5 %)	2160 (7.0 %)	0.012
Dementia	259 (1.2 %)	472 (1.5 %)	0.007
Chronic obstructive pulmonary disease	2284 (11.0 %)	2863 (9.3 %)	<0.001
Pharmacotherapy, No. (%) **			
Loop diuretic	16523 (79.5 %)	19628 (63.9 %)	<0.001
Thiazide diuretic	1569 (7.6 %)	3527 (11.5 %)	<0.001

Glucose-lowering	4232 (20.4 %)	5542 (18.0 %)	<0.001
Statins	12416 (59.8 %)	18820 (61.2 %)	0.001
Antiplatelet	12839 (61.8%)	19691 (64.1 %)	<0.001
Anticoagulant	8011 (38.6 %)	10900 (35.5 %)	<0.001
Potassium supplements	11186 (53.8 %)	16416 (53.4 %)	0.355
Non-medical therapy, No. (%)			
Implantable Cardioverter Defibrillator	276 (1.3 %)	203 (0.7 %)	<0.001
Cardiac resynchronization therapy	69 (0.3 %)	57 (0.2 %)	0.001

Table 1: Baseline characteristics of the study population at inclusion.

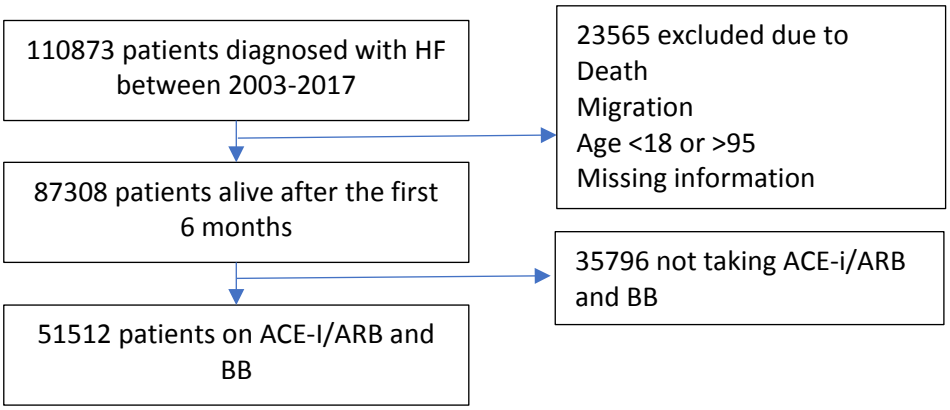
MRA, mineralocorticoid receptor antagonist; No., Number; IQR, Interquartile Range;

**Comorbidity 5 years before inclusion*

***Medication 6 months before inclusion*

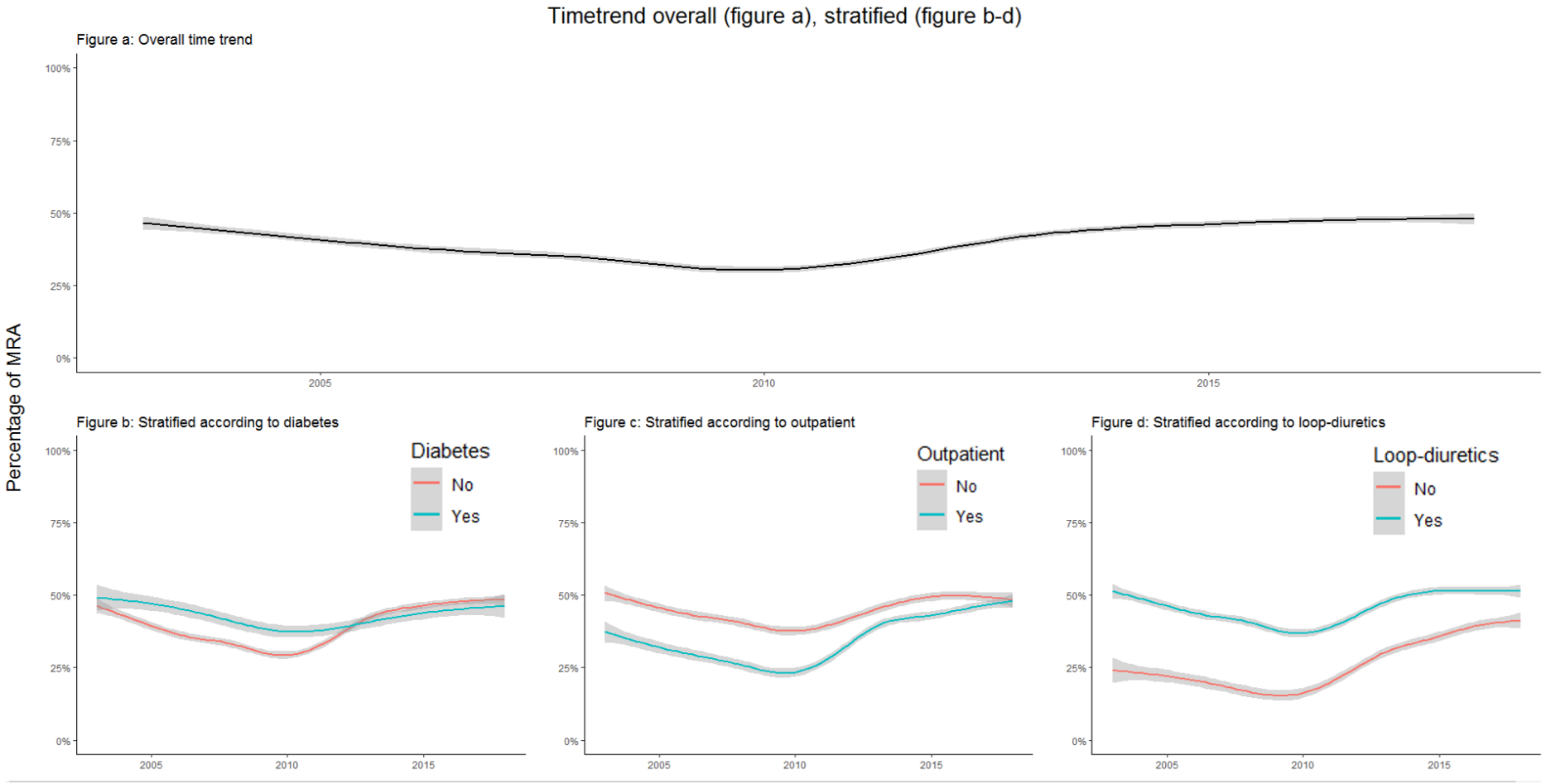
Figures

Figure 1. Flow chart



HF, heart failure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, betablocker

Figure 2. Time trend of MRA initiation within the first 6 months



Bands represent 95% confidence intervals

Figure 3: Withdrawal of MRA after the first 6 months of diagnosis. Includes patients in therapy at baseline.

Figure a: Cumulative incidence of withdrawal of MRA

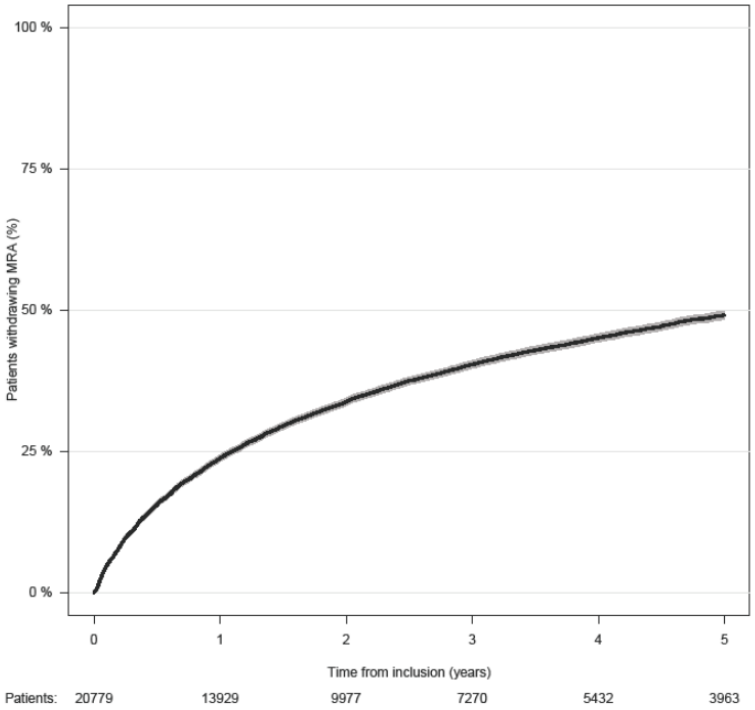


Figure b: Covariates associated with withdrawal of MRA

Variable		N	Hazard ratio	p
Age	<=60 years	4948	Reference	
	60<age<=70	5750	1.16 (1.11, 1.22)	<0.001
	70<age<=80	6617	1.38 (1.32, 1.45)	<0.001
	80<age	3464	1.70 (1.62, 1.79)	<0.001
Sex	Female	6505	Reference	
	Male	14274	1.05 (1.02, 1.09)	0.004
Outpatient diagnosis of HF	No	11835	Reference	
	Yes	8944	1.10 (1.06, 1.14)	<0.001
Ischemic heart disease	No	11116	Reference	
	Yes	9663	0.89 (0.86, 0.92)	<0.001
Atrial fibrillation	No	13977	Reference	
	Yes	6802	1.06 (1.03, 1.10)	<0.001
Cerebrovascular disease	No	19237	Reference	
	Yes	1542	1.14 (1.07, 1.21)	<0.001
Peripheral vascular disease	No	19608	Reference	
	Yes	1171	1.15 (1.08, 1.24)	<0.001
Diabetes	No	17328	Reference	
	Yes	3451	1.13 (1.08, 1.18)	<0.001
Renal disease	No	20019	Reference	
	Yes	760	1.18 (1.08, 1.28)	<0.001
COPD	No	18495	Reference	
	Yes	2284	1.18 (1.12, 1.24)	<0.001
Loop diuretics	No	4256	Reference	
	Yes	16523	1.00 (0.96, 1.04)	0.953

Figure 4: Proportion of days covered for MRA over 5 years