Real world comparison of spironolactone and eplerenone in patients with heart failure

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Highlights

- Treatment with a mineralocorticoid receptor antagonist (MRA) –spironolactone or eplerenone– is indicated to reduce the risk of hospital admission and death in patients with symptomatic heart failure (HF) and reduced left ventricular ejection fraction.
- Despite there are a few differences between spironolactone and eplerenone with regard to their biological properties and safety profile, no randomized clinical trial has compared them directly in patients with HF.
- The present single-center, propensity-score matched study compared the long-term outcomes of 293 real-world patients with HF and reduced ejection fraction treated with eplerenone and 293 propensity-score matched controls treated with eplerenone.
- No significant differences between patients treated with spironolactone or eplerenone were observed with regard to the primary combined end-point cardiovascular death or HF hospitalization.
- Patients treated with eplerenone presented significantly lower risk of cardiovascular mortality and all-cause mortality than patients treated with spironolactone.

Abstract

Aims. In the absence of previous direct comparative studies, we aimed to evaluate the effectiveness of spironolactone and eplerenone in patients with heart failure and reduced ejection fraction (HFrEF) in a real-world clinical setting.

Methods. Using Fine-Gray´s competing risk regression, we compared the clinical outcomes of 293 patients with chronic HF and left ventricular ejection fraction <40% treated with eplerenone and 293 propensity-score matched individuals treated with spironolactone. Study subjects were selected from a prospective cohort of 1404 ambulatory patients with HFrEF seen since 2010 to 2019 in a single specialized HF clinic, among which 992 received a mineralocorticoid receptor antagonist at baseline. Median follow-up was 3.95 years.

Results. No statistically significant differences between patients treated with eplerenone versus spironolactone were observed with regard to the risk of the primary composite end-point cardiovascular death or HF hospitalization (HR 0.95; 95% CI 0.73–1.23; p= 0.677). However, eplerenone use was associated to lower cardiovascular mortality (HR 0.55; 95% CI 0.35–0.85; p= 0.008) and lower all-cause mortality (HR 0.67; 95% CI 0.47–0.95; p= 0.027). The incidence of drug suspension due to side effects (HR 0.58, 95% CI 0.40–0.85; p= 0.005) and drug suspension due to any reason (HR 0.70, 95% CI 0.51–0.97; p= 0.033) were lower among patients treated with eplerenone.

Conclusions. In this observational, real-world, propensity-score matched study of patients with HFrEF, eplerenone was associated to lower cardiovascular mortality and lower all-cause mortality than spironolactone.

Keywords

Heart failure; Reduced ejection fraction; Spironolactone; Eplerenone; Survival; Outcomes

Abbreviations

HF, Heart Failure.

HFrEF, Heart Failure with reduced Ejection Fraction.

HR, Hazard Ratio.

LVEF, Left Ventricular Ejection Fraction.

MRA, Mineralocorticoid Receptor Antagonist.

SD, Standard Deviation.

SMD, Standardized Mean Difference

1. Introduction

Mineralocorticoid receptor antagonists (MRA) play a central role in the therapeutic scheme recommended for patients with heart failure and reduced left ventricular ejection fraction (HFrEF). Three randomized clinical trials support the clinical benefit of MRA in these individuals; spironolactone was associated with increased survival as compared to placebo in patients with HFrEF and severe symptoms [1], while eplerenone showed improved outcomes in patients with HFrEF and mild symptoms [2], and also in patients with reduced left ventricular ejection fraction (LVEF) following an acute myocardial infarction and either symptomatic heart failure (HF) or diabetes mellitus [3].

According to current guidelines [4], the prescription of a MRA is recommended to reduce the risk of HF hospitalization and death in all patients with symptomatic HFrEF and no contraindications for this therapy. A class I recommendation is given indistinctly to spironolactone and eplerenone; however, there are substantial differences between these two drugs with regard to their pharmacokinetics and metabolism [5]. Spironolactone is structurally similar to progesterone and binds to progesterone, androgen and mineralocorticoid receptors [6]. Eplerenone is a selective mineralocorticoid receptor antagonist, so it lacks the anti-androgenic side effects of spironolactone. Previous studies suggested that, at equipotent doses, eplerenone might cause less hyperkalemia than spironolactone in patients with hypertension [7]. Also, eplerenone appears to have a better metabolic profile compared to spironolactone [8]. On the other hand, the cost of spironolactone is substantially lower than the one of eplerenone.

Until now, it is not known whether the pharmacological differences that exist between spironolactone and eplerenone are associated with a different impact of both drugs on the clinical outcomes of patients with HFrEF. Indeed, a well powered, randomized, head-to-head comparison of the efficacy and safety of spironolactone versus eplerenone in the setting of HF has never been conducted. One real world, observational study [9] explored this hypothesis in a small, propensity score matched cohort of Asian patients with acutely decompensated HF, either with reduced or preserved LVEF,

showing no difference between spironolactone and eplerenone with regard to the risk of subsequent readmissions or mortality.

In view of this gap of knowledge, our aim was to compare the effectiveness and safety of spironolactone and eplerenone in a prospective cohort of ambulatory patients with chronic HFrEF treated and observed in a real-world clinical setting.

2. Methods

2.1. Study description

We conducted an observational, single-center study based on the historical cohort of ambulatory patients with HF seen at the HF clinic of the Cardiology Department of the Complejo Hospitalario Universitario de A Coruña (A Coruña, Spain) from January 2010 to December 2019. Data for this investigation were collected from a prospectively maintained database, which is managed by means of an electronic clinical records system developed in our institution, the so-called *Sistema Inteligente de Monitorización* (SiMon®). This database includes clinical information of all consecutive patients with HF who are referred to our clinic since the first encounter; variables collected include those related to past medical history, clinical status, complementary tests and treatments at baseline and at subsequent follow-up visits, as well as vital status and hospital admissions.

The study protocol was approved by the Committee for Ethics in Clinical Research of the Autonomous Community of Galicia, Spain. Informed consent was obtained from studied subjects.

2.2. Outcome variables

Patients were followed since the date of the first visit in the HF clinic until the date of death or until July 31st, 2021, whatever occurred first. In the case of patients who underwent heart transplantation, follow-up was censored at the date of transplant surgery.

The composite outcome cardiovascular death or hospitalization due to HF was selected as the primary end-point of the study. Secondary end-points were cardiovascular death, hospitalization due to HF, all-cause death and the combined outcome cardiovascular death or heart transplantation.

Cardiovascular deaths were those caused by arrhythmia, refractory HF, acute coronary syndrome, cerebrovascular disease, arterial or venous thromboembolism, peripheral artery disease or complications of a cardiovascular procedure, as well as unexplained sudden deaths.

Reasons for permanent discontinuation of spironolactone and eplerenone were collected from clinical records.

2.3. Statistical analysis

In this study, data are presented as absolute and relative frequencies for categorical variables and as mean ± standard deviation (SD) for continuous variables. Between-group differences were analysed using the chi-squared test and the T-student test or the Mann-Whitney test, as appropriate.

Logistic regression was used to construct a propensity score model formed by 28 baseline clinical variables that allowed us to estimate the individual probability of each patient of being treated with spironolactone or eplerenone, according to his/her specific clinical profile. Namely, the baseline variables included in the propensity score model were age, gender, referred patient, current or former smoker, obesity, hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, myocardial infarction, stroke, malignancy, chronic obstructive pulmonary disease, peripheral artery disease, atrial fibrillation or flutter, implantable defibrillator, previous admission due to HF, NYHA class III or IV, LVEF (%), systolic blood pressure (mm Hg), glomerular filtration rate (ml/min/m2), NTproBNP (pg/ml), potassium (mEq/l), hemoglobin (g/dl), use of beta-blockers, use of angiotensin converter enzyme inhibitors or angiotensin-2 receptor blockers, use of sacubitril-valsartan, loop diuretic daily dose (mg of furosemide equivalents).

A nearest-neighbor–matching technique without replacement was used to match patients treated with spironolactone or eplerenone on the basis of their propensity score [10], with a 1:1 ratio and a caliper of width equal to 0.25 of the standard deviation of the logit of the propensity score. Baseline clinical variables were considered as well balanced between both treatment groups if their standardized mean difference (SMD) was <0.10 [11]. *Supplemental Figure 1* shows the distribution of propensity scores both in the unmatched and matched samples.

Fine-Gray´s competing risks regression was used to assess the cumulative incidence of study end-points in the propensity-matched cohort. Non-cardiovascular death was considered a competing event for the assessment of the primary composite end-point, as well as for the analysis of the secondary end-points hospitalization due to HF, cardiovascular mortality, and the composite of cardiovascular death or heart transplantation. Heart transplantation was considered as a competitive event for the assessment of the secondary end-points all-cause mortality and cardiovascular mortality; while it was considered as equivalent for HF hospitalization and so, counted as an event, for the assessment of the primary end-point, as well as for the assessment of the secondary end-point HF hospitalization.

Both heart transplantation and death from any cause were considered competitive events for the assessment of the cumulative incidence of drug discontinuation.

In view of a slight residual disbalance between the two study groups with regard to the baseline daily doses of MRA after propensity score matching, we conducted a sensivity analysis in which we recalculated the HR for primary and secondary end-points by means of a multivariable competing-risk model in which the baseline dose of MRA was entered as an adjusting covariable.

A second sensivity analysis was conducted by including the year of enrollment as an adjusting covariable in the multivariable model. This analysis was intended to rule out a significant era effect on the observed statistical associations, given the known secular improvement of HF prognosis over time [12].

Exploratory analyses of both the primary end-point and the secondary end-point all-cause mortality were performed in several relevant clinical subgroups, according to age, gender, LVEF, glomerular filtration rate, New York Heart Association class, and the presence or absence of diabetes mellitus and coronary artery disease. Subgroup analyses were performed by including interaction terms in the models.

Statistical significance was set as a p-value <0.05. Statistical analyses were performed by means of SPSS 25, R 4.03, and Stata 14.

3. Results

3.1. Study population

Since January 2010 to December 2019, 1404 patients with HF and baseline LVEF <40% were included in our prospective registry, among which 992 (70.7%) were prescribed a MRA, and constituted the population of the present study. Namely, 631 (63.6%) patients with HFrEF received spironolactone and 361 (36.4%) received eplerenone. Fig. 1 shows a flowchart of patients included in this study. A graphical representation of the distribution of study patients according to the year of enrollment is shown in the *Supplemental Figure 2*.

3.2. Baseline clinical characteristics

Baseline clinical characteristics of the unmatched study population are detailed in the Table 1. As shown, there were several baseline clinical variables disbalanced between the two study groups (i.e., those with SMD > 0.10).

Compared with patients who were treated with spironolactone, patients who received eplerenone were younger; more frequently male; more likely to have dyslipidemia, smoking history, coronary artery disease, prior myocardial infarction, an implantable cardioverter-defibrillator, and peripheral artery disease; and less likely to have chronic obstructive pulmonary disease, prior stroke and atrial fibrillation or atrial flutter history.

Patients treated with eplerenone were also less symptomatic, needed lower daily loop diuretic equivalent doses, had higher LVEF, lower serum levels of potassium, higher serum levels of hemoglobin and higher glomerular filtration rate. A higher proportion of patients treated with eplerenone received sacubitril-valsartan and beta-blockers.

By means of propensity-score matching, we selected a sample of 293 patients treated with spironolactone and 293 patients treated with eplerenone. As shown in the Table 1, all relevant baseline clinical variables showed a SMD < 0.10 in the propensity-score matched sample, so as suggesting a good balance of them between the two study groups.

Mean daily dose of eplerenone at baseline was 28.4 mg, while mean daily dose of spironolactone was 26.9 mg (SMD = 0.12).

3.3. Follow-up

Patients of the propensity-matched sample were followed over a median period of 3.95 years (interquartile rank = 2.27 to 5.99 years). In the eplerenone group, 52 (17.7%) patients died and 32 (10.9%) underwent heart transplantation; meanwhile, in the spironolactone group, 76 (25.9%) patients died and 20 (6.8%) underwent heart transplantation. Death was due to a cardiovascular cause in 54 (18.4%) patients of the spironolactone group and in 30 (10.2%) patients of the eplerenone group. Specific causes of death in both study groups are shown in the *Supplemental Table 1*.

During follow-up, at least one hospitalization due to HF was registered in 99 (33.8%) patients of the eplerenone group and in 96 (32.8%) patients of the spironolactone group.

3.4. Effectiveness

The Table 2 shows an evaluation of major clinical end-points of the study. Over follow-up, the primary composite end-point cardiovascular death or hospitalization due to HF occurred in 108 (36.9%) patients of the eplerenone group and 117 (39.9%) patients of the patients of the spironolactone group. The annualized incidence rate of the primary outcome was 10.5% (95% CI 8.6–12.7%) in patients treated with eplerenone and 10.6% (95% CI 8.8%–12.7%) in patients treated with spironolactone.

Competing-risks regression did not show a statistically significant difference between both study groups with regard to the risk of the primary composite outcome (Hazard Ratio (HR) eplerenone vs. spironolactone = 0.95; 95% Confidence Interval (CI) 0.73–1.23; p= 0.677; Fig. 2). However, patients of the eplerenone group showed statistically significant lower cardiovascular mortality (HR 0.55; 95% CI 0.35–0.85; p= 0.008) and all-cause mortality (HR 0.67; 95% CI 0.47–0.95; p= 0.027) than patients of the spironolactone group (Fig. 3). Even when deaths of an unknown cause were counted as cardiovascular deaths, eplerenone was still associated to lower cardiovascular mortality in comparison to spironolactone (HR 0.59; 95% CI 0.39–0.91; p= 0.018).

In view of the slight disbalance of baseline doses of spironolactone and eplerenone in both study groups, we recalculated the HR for primary and secondary end-points in a multivariable competing-risk model in which the baseline dose of MRA was entered as an adjusting covariable. No relevant change in the sense of the results was observed in this sensivity analysis *(Supplemental Table 2)*. Neither a relevant change in the sense of the results was observed when the year of study enrollment was entered in the multivariable model as an adjusting covariable *(Supplemental Table 3)*.

3.5. Subgroup analyses

Fig. 4 shows the hazards ratios for the primary composite end-point cardiovascular death or hospitalization due to HF (panel A) and the secondary end-point all-cause mortality (panel B) in patients treated with eplerenone vs. spironolactone across several relevant clinical subgroups.

No statistically significant interaction between the type of MRA and the clinical variables explored with regard to the risk of the primary end-point. However, a significant interaction was found between the presence or absence of coronary heart disease and the impact of the type of AMR on all-cause mortality (p for interaction = 0.037). Eplerenone use was associated to statistically significant lower all-cause mortality in patients with coronary heart disease (HR 0.50, 95% CI 0.32–0.77; *p*= 0.032), but not in patients without coronary heart disease (HR 1.08, 95% CI 0.59–2; *p*= 0.795).

3.6. Drug discontinuation

During follow-up, the baseline MRA was permanently discontinued for any reason in 86 (29.4%) patients of the spironolactone group and in 63 (21.5%) patients of the eplerenone group. Switching from spironolactone to eplerenone was done in 35 (11.9%) patients, while the opposite was done in 17 (5.8%).

Drug withdrawal was due to side effects in 69 (23.6%) patients of the spironolactone group and in 42 (14.4%) patients of the eplerenone group. Specific side effects that led to treatment withdrawal are presented in Table 3.

Patients of the eplerenone group showed statistically significant lower incidence of permanent drug discontinuation due to side effects (HR 0.58, 95% CI 0.40–0.85; $p = 0.005$) and lower incidence of permanent drug discontinuation for any reason (HR 0.70, 95% CI 0.51–0.97; $p = 0.033$) than patients of the spironolactone group (Fig. 5).

4. Discussion

We compared the effectiveness and safety of spironolactone and eplerenone in a real world, propensity score matched sample of 586 consecutive ambulatory patients with HFrEF seen at a specialized HF clinic in A Coruña, Spain. We did not find any statistically significant difference between both drugs with regard to the risk of the primary composite end-point death from cardiovascular causes or hospitalization due to HF; however, eplerenone use was associated with a significant reduction of the risk of the secondary end-points all-cause mortality and cardiovascular mortality, as compared to spironolactone use. Permanent drug discontinuation due to side effects was more frequent among patients treated with spironolactone at baseline than among patients treated with eplerenone at baseline, being this observation largely driven by the development of gynaecomastia.

In current practice guidelines, treatment with a MRA, either spironolactone or eplerenone, is indicated to reduce the risk of HF hospitalization or death in symptomatic patients with HFrEF with a class I, level of evidence A, recommendation [4]. Both drugs have demonstrated consistent reductions of mortality and morbidity [1], [2], [3] in different subsets of patients with HFrEF; however, a well-powered, head-to-head randomized comparison between them is still lacking. Indirect pooled analyses of placebo-controlled randomized clinical trials suggested that spironolactone might outperform eplerenone in terms of mortality reduction [13,14]. However, this conclusion may be misleading [5], given the existence of significant variations regarding the baseline risk and background therapy of patients with HFrEF included in different studies. Globally, spironolactone was studied in sicker, less optimally treated patients than eplerenone; it is intuitive that the benefit of MRA in this setting might be greater.

The clinical benefit demonstrated by MRA in randomized controlled trials might not be directly extrapolated to the real-world setting, given the barriers that exist to implement the tight follow-up protocol required to minimize the risk of drug side effects in daily clinical practice, which might reduce the real-world effectiveness of the therapy. A large multicentre cohort-based study failed to demonstrate a significant survival benefit of

spironolactone in real-world Swedish patients with HF, being side effects the most probable reason for this result [15]. Another multicentre, real-life, propensity-score matched, Italian study showed no significant differences between MRA-treated and MRA-untreated patients with HFrEF [16]. No significant difference between spironolactone and eplerenone was found with regard to the risk of the composite end-point cardiovascular death or HF hospitalization or the incidence of sided effects in a real world, single-center study based on a propensity-score matched cohort of 180 Japanese patients with acutely decompensated HF, regardless of LVEF [9].

The significant reduction of cardiovascular mortality and all-cause mortality observed in the eplerenone group was the most relevant finding of our study. Despite there is not an evident explanation for this result, a few hypothetical reasons might be discussed. First, spironolactone seems to have a worse metabolic profile than eplerenone, which might carry a differential impact on the cardiovascular risk of treated patients. In a small clinical trial of 107 patients with HF, spironolactone was associated to a significant raise of cortisol levels and glycated hemoglobin, as well as to a significant decrease of adiponectin [7]; however, no significant change was seen in patients receiving eplerenone. This could be of a greater importance in subjects with HFrEF of an ischemic etiology; indeed, we found a significant interaction between the presence or absence of prior coronary artery disease and the effect of the type of MRA on long-term mortality, resulting that the survival benefit of eplerenone over spironolactone was only observed in the subgroup of patients who suffered from this condition. Second, some evidence allows us to hypothesize that the antiandrogenic effect of spironolactone might be deleterious in the setting of HF, especially in men. Anabolic deficiency is frequent in these subjects, and it has been associated with worse outcomes [17]. In experimental models, testosterone appears to have a protective effect against cardiomyocyte apoptosis, which is antagonized by spironolactone, but not by eplerenone [18]. Third, the safety profile of eplerenone appears to have some advantages over spironolactone that may increase the effectiveness of treatment in daily clinical practice. Sexual side effects like dysmenorrhea in women and gynaecomastia in men are relatively frequent with spironolactone but rarely seen with eplerenone, and may constitute a barrier for treatment adherence in a real world setting. Moreover, the incidence of hyperkalaemia

appears to be lower in patients treated with eplerenone than in patients treated with spironolactone [19], a fact that might be explained by the longer half-life of the first drug [5]. In our study, the cumulative rate of drug suspension for any cause and drug suspension due to side effects were higher in patients treated with spironolactone than in patients treated with eplerenone; being this result mostly driven by a higher incidence of gynaecomastia in the first group.

We selected the composite outcome cardiovascular death or hospitalization due to HF as the primary end-point of this study, in the line of most recent randomized clinical trials of pharmacotherapy in HFrEF. Despite the statistically significant, clinically relevant, reduction in both cardiovascular and all-cause mortality observed in the eplerenone group, no significant effect of the type of MRA was observed with regard to the primary end-point. To interpret this apparent discrepancy, it must be acknowledged that HF hospitalization accounted for near 90% of these combined events, so limiting the weight of cardiovascular mortality in the primary end-point. Rates of HF hospitalization, indeed, were similar in both study groups.

In our cohort, the baseline dose of MRA was, in absolute terms, slightly higher in the spironolactone group than in the eplerenone group. Given that the affinity of spironolactone for the mineralocorticoid receptor is higher than the one of eplerenone [5], one can expect a higher intensity of neurohormonal modulation in the group of patients treated with the first agent. Thus, the observed survival advantage of eplerenone over spironolactone observed in our study does not seem to be justified by differences in the baseline doses of drug used. Moreover, no relevant change in the survival advantage of eplerenone over spironolactone was observed in a sensivity analysis in which the baseline dose of AMR was included in the multivariable statistical model as an adjusting covariate. A second sensivity analysis that used the year of enrollment as an adjusting covariate ruled out a significant era effect on the major results of the study.

This study has a few limitations. It is a real-world, observational investigation, so it may be affected by selection, information, and confusion bias. Even though propensity score matching is a useful method to balance multiple baseline variables among study groups in observational studies [10], unmeasured residual confounding may still exist outside randomized controlled trials. Also, this was a single-center study conducted in a specialized HF unit, so its external validity in other clinical settings cannot be assured. The primary end-point of the study assessed the time to the first hospitalization due to HF or death for cardiovascular causes, but repeated hospitalizations were not considered; this might have jeopardized the capacity of the study to detect significant differences between study groups. Reliable information regarding the doses of AMR prescribed were only available at baseline, but follow-up modifications were not assessed. Finally, data were extracted from a general prospective registry of patients followed in a single institution, but it was not designed specifically for the primary intention of the present study; so, drug dose titration and drug discontinuation were made according to local protocols and clinical judgment of attending physicians.

In conclusion, in this real-world, single-center, observational, propensity-score matched study, the cumulative incidence of the primary composite end-point death from cardiovascular causes or HF hospitalization was not statistically significant different between patients with HFrEF treated with spironolactone or eplerenone. However, patients treated with eplerenone showed statistically significant lower cardiovascular mortality and all-cause mortality than patients treated with spironolactone, being the survival benefit of the first drug mainly achieved at the expense of the subgroup of patients with HFrEF and a prior history of coronary artery disease. The cumulative incidence of drug suspension due to side effects was significantly higher among patients treated with spironolactone. Larger multi-institutional studies are warranted to confirm these findings, which may be of relevance for clinical practice.

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Disclosures

None.

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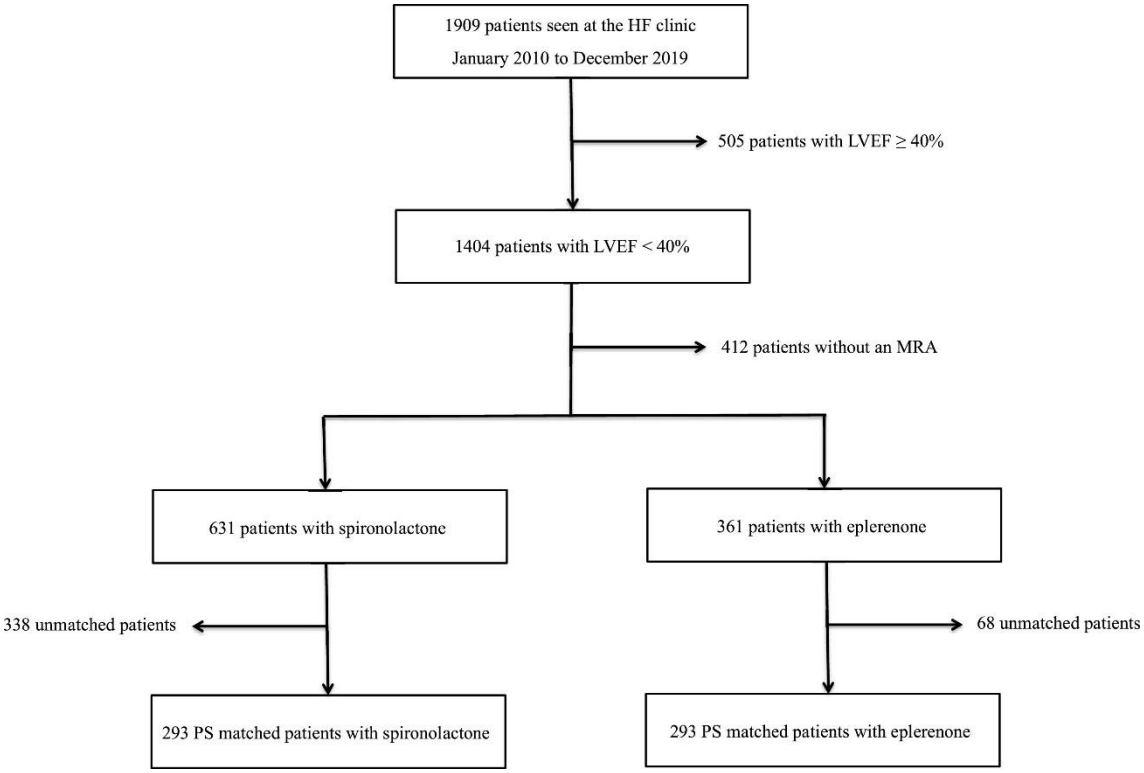


Fig. 1. Flowchart of study patients. HF, Heart Failure. LVEF, Left Ventricular Ejection Fraction. PS, Propensity Score.

Table 1. Baseline clinical characteristics of patients with heart failure and reduced left ventricular ejection fraction treated with spironolactone or eplerenone, both in the entire cohort and in the propensity score matched sample. ACE-I, Angiotensin converter enzyme inhibitor. ARB, Angiotensin 2 receptor blocker. BP, Blood Pressure. COPD, Chronic Obstructive Pulmonary Disease. HF, Heart Failure. GFR, Glomerular filtration rate. LVEF, Left ventricular ejection fraction. NYHA, New York Heart Association Class. SD, Standard Deviation. SMD, Standardized Mean Difference.

Variables	Entire cohort			Propensity score matched sample		
	Spironolactone (*N*= 631)	Eplerenone (*N*= 361)	SMD	Spironolactone (*n* = 293)	Eplerenone (*n* = 293)	SMD
Medical history						
Age (years), mean ± SD	63.8 ± 11.5	60.4 ± 10.5	0.30	61.2 ± 11.7	61.5 ± 10.2	0.03
Male, n (%)	436 (69.1%)	298 (82.5%)	0.31	234 (79.9%)	234 (79.9%)	<0.01
Referred patient*, n (%)	188 (29.8%)	138 (39.2%)	0.18	95 (32.4%)	96 (32.8%)	0.01
Hypertension, n (%)	337 (53.4%)	180 (49.9%)	0.07	145 (49.5%)	150 (51.2%)	0.03
Diabetes mellitus, n (%)	203 (32.2%)	113 (31.3%)	0.02	96 (32.8%)	98 (33.4%)	0.02
Obesity**, n (%)	213 (33.8%)	117 (32.4%)	0.03	97 (33.1%)	100 (34.1%)	0.02
Current or former smoker, n (%)	358 (56.7%)	268 (74.2%)	0.36	208 (71%)	209 (71.3%)	0.01
Dyslipidemia, n (%)	327 (51.8%)	215 (59.6%)	0.16	160 (54.6%)	164 (56%)	0.03
Coronary artery disease, n (%)	244 (38.7%)	206 (57.1%)	0.37	145 (49.5%)	146 (49.8%)	0.01
Myocardial infarction, n (%)	167 (26.5%)	174 (48.2%)	0.46	112 (38.2%)	116 (39.6%)	0.03
Atrial fibrillation or flutter, n (%)	157 (24.9%)	68 (18.8%)	0.14	66 (22.5%)	60 (20.5%)	0.05
COPD, n (%)	76 (12%)	31 (8.6%)	0.11	31 (10.6%)	29 (9.9%)	0.02
Malignancy, n (%)	86 (13.6%)	43 (11.9%)	0.05	41 (14%)	38 (13%)	0.03
Stroke, n (%)	65 (10.3%)	23 (6.4%)	0.14	25 (8.5%)	21 (7.2%)	0.05
Peripheral artery disease, n (%)	39 (6.2%)	40 (11.1%)	0.18	25 (8.5%)	29 (9.9%)	0.05
Implantable defibrillator, n (%)	100 (15.8%)	91 (25.2%)	0.24	50 (17.1%)	59 (20.1%)	0.08
Prior admission due to HF, n (%)	343 (54.4%)	191 (52.9%)	0.03	160 (54.6%)	156 (53.2%)	0.03
Clinical status						
Physical signs of congestion, n (%)	134 (21.2%)	73 (20.2%)	0.03	59 (20.1%)	56 (19.1%)	0.03
NYHA class, n (%)			0.10			0.04

I	54 (8.6%)	31 (8.6%)		29 (9.9%)	23 (7.8%)	
II	323 (51.2%)	208 (57.6%)		164 (56%)	168 (57.3%)	
III	226 (35.8%)	108 (29.9%)		88 (30%)	90 (30.7%)	
IV	28 (4.4%)	14 (3.9%)		12 (4.1%)	12 (4.1%)	
Systolic BP (mm Hg)	116 ± 20	116 ± 20	<0.01	116 ± 20	116 ± 19	<0.01
LVEF (%)	27.2 ± 7.1	27.9 ± 6.8	0.11	27.4 ±	27.5 ± 7	<0.01
Laboratory tests						
NTproBNP (pg/ml)	3018 ± 3851	3037 ± 4394	0.01	3020 ± 3778	3125 ± 4516	0.03
Hemoglobin (g/dl)	13.7 ± 1.7	14 ± 1.7	0.13	14 ± 1.7	13.9 ± 1.7	0.03
Bilirubin (mg/dl)	0.8 ± 0.5	0.8 ± 0.4	0.04	0.8 ± 0.5	0.8 ± 0.4	0.03
Potassium (mEq/l)	4.6 ± 0.5	4.5 ± 0.4	0.18	4.5 ± 0.5	4.6 ± 0.5	0.08
Creatinin (mg/dl)	1.1 ± 0.4	1.1 ± 0.3	0.09	1.2 ± 0.3	1.2 ± 0.4	0.01
GFR (ml/min/m2)	76 ± 32	84 ± 32	0.27	82 ± 35	82 ± 31	0.01
Medical therapy						
Loop diuretic, n (%)	560 (88.7%)	313 (86.7%)	0.06	255 (87%)	258 (88.1%)	0.03
Loop diuretic daily dose (mg)***	56 ± 40	51 ± 37	0.06	54 ± 40	53 ± 37	0.03
Beta-blocker, n (%)	587 (93%)	348 (96.4%)	0.15	281 (95.9%)	280 (95.6%)	0.02
ACE-I or ARB, n (%)	497 (78.8%)	276 (76.5%)	0.06	229 (78.2%)	224 (76.5%)	0.04
Sacubitril-valsartan, n (%)	71 (11.3%)	57 (15.8%)	0.14	42 (14.3%)	43 (14.7%)	0.01
Thiazide, n (%)	23 (3.6%)	19 (5.3%)	0.08	14 (4.8%)	15 (5.1%)	0.02
Ivabradine, n (%)	51 (8.1%)	36 (10%)	0.07	26 (8.9%)	23 (7.8%)	0.04
Digoxin, n (%)	58 (9.2%)	34 (9.4%)	0.01	24 (8.2%)	29 (9.9%)	0.06

Baseline variables with SMD < 0.10 were considered well balanced between the two study groups.

*Patient referred to the HF unit of the Complejo Hospitalario Universitario de A Coruña from other institutions.

**Body mass index ≥ 30 kg/m2.

***Expressed as mg of furosemide equivalents. 10 mg of torasemide = 40 mg of furosemide.

Table 2. Hazard-ratio for primary and secondary effectiveness study end-points in patients of the propensity-score matched sample that were treated with spironolactone.

	Eplerenone (*N*;= 293) N (%)	Annualized event rate (%)	Spironolactone (*N*= 293) N (%)	Annualized event rate (%)	HR (95% CI)	P value
Primary end-point						
Death from cardiovascular causes or heart failure hospitalization	108 (36.9%)	10.5%	117 (39.9%)	10.6%	0.95 (0.73–1.23)	0.677
Secondary end-points						
Death from cardiovascular causes	30 (10.2%)	2.4%	54 (18.4%)	4.2%	0.55 (0.35–0.85)	0.008
Heart failure hospitalization	99 (33.8%)	9.6%	96 (32.8%)	8.7%	1.08 (0.82–1.43)	0.590
Death from any cause	52 (17.7%)	4.1%	76 (25.9%)	6%	0.67 (0.47–0.95)	0.027
Death from cardiovascular causes or heart transplantation	62 (21.2%)	4.9%	74 (25.2%)	5.8%	0.85 (0.60–1.18)	0.329

vs. eplerenone. CI, Confidence Interval.

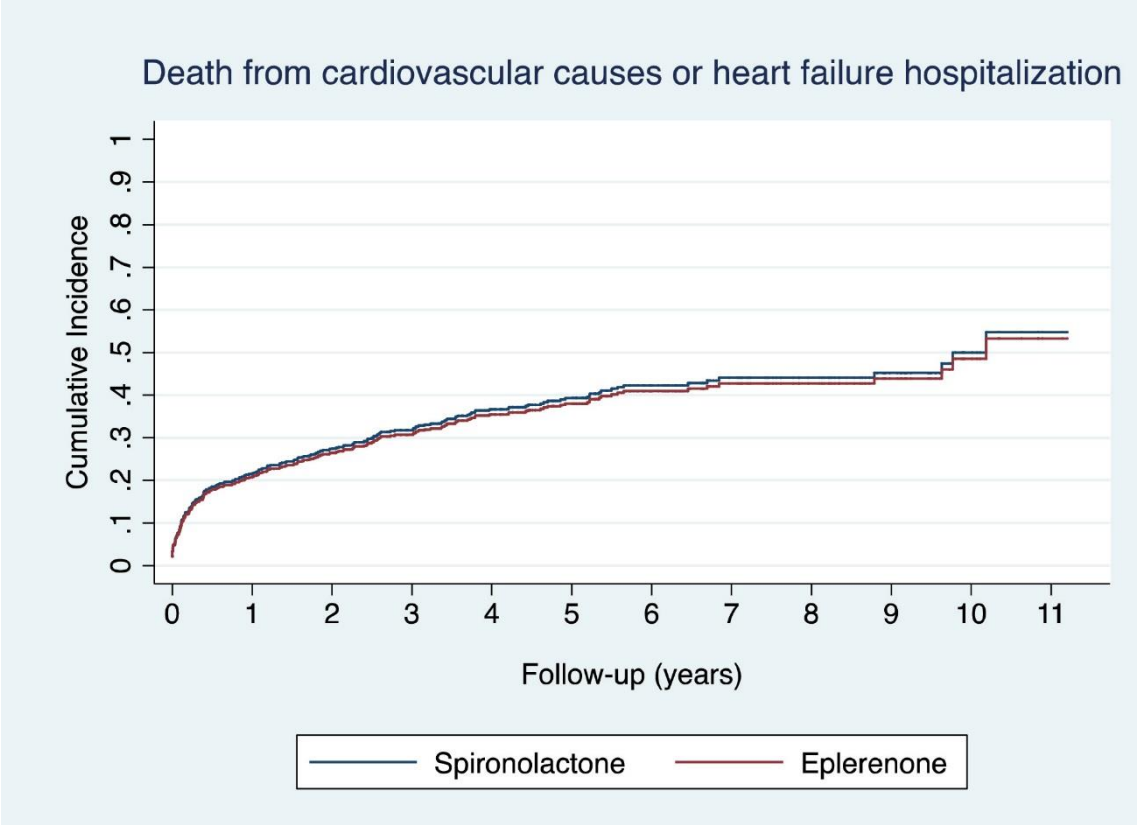
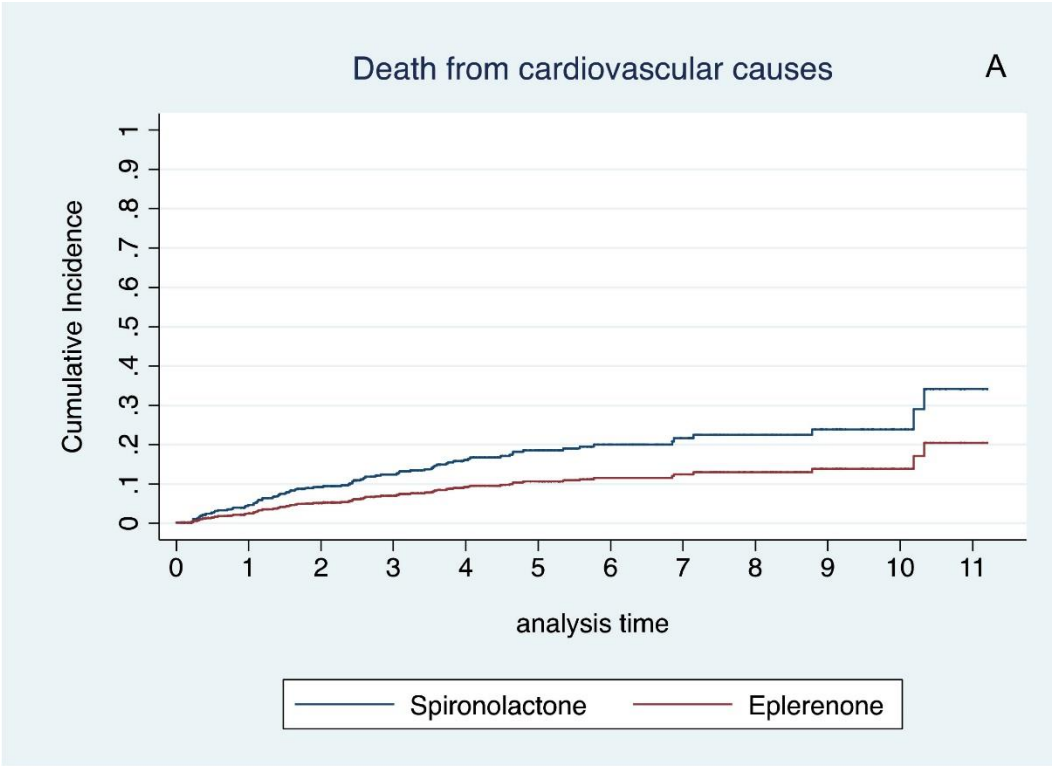


Fig. 2. Cumulative estimates of the primary end-point death from cardiovascular causes or hospitalization due to heart failure in patients who received spironolactone or eplerenone at baseline, as assessed by means of competing risks regression.



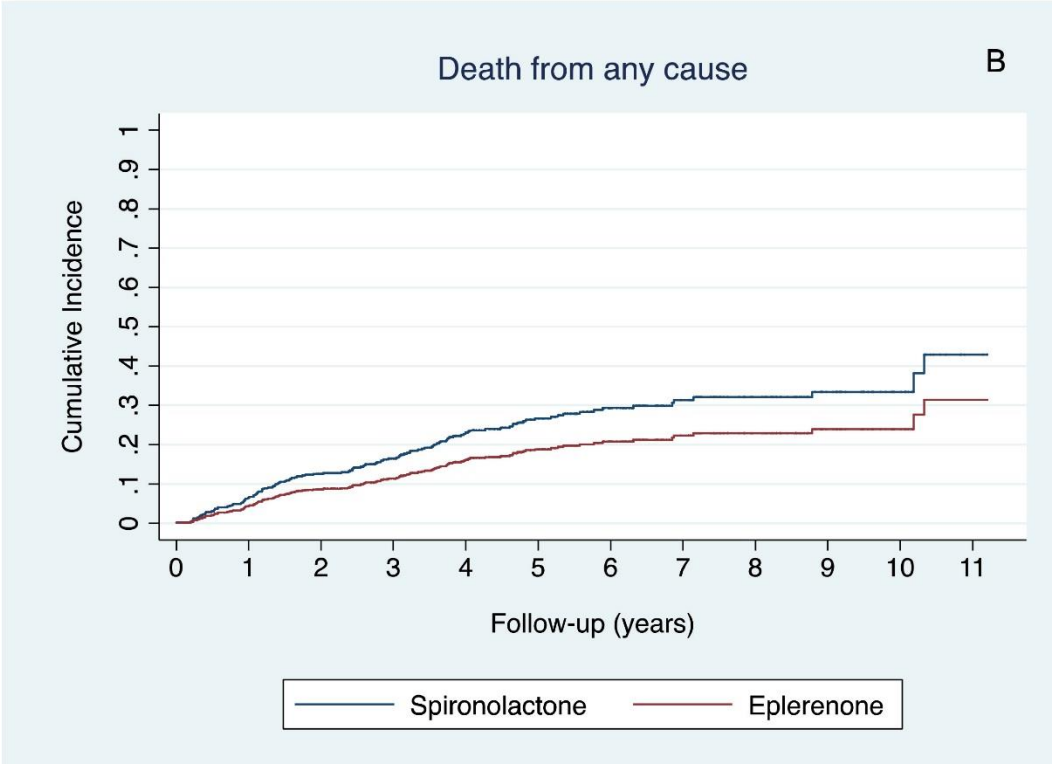


Fig. 3. Cumulative estimates of cardiovascular mortality (panel 3A) and all-cause mortality (panel 3B) in patients who received spironolactone or eplerenone at baseline, as assessed by means of competing risks regression.

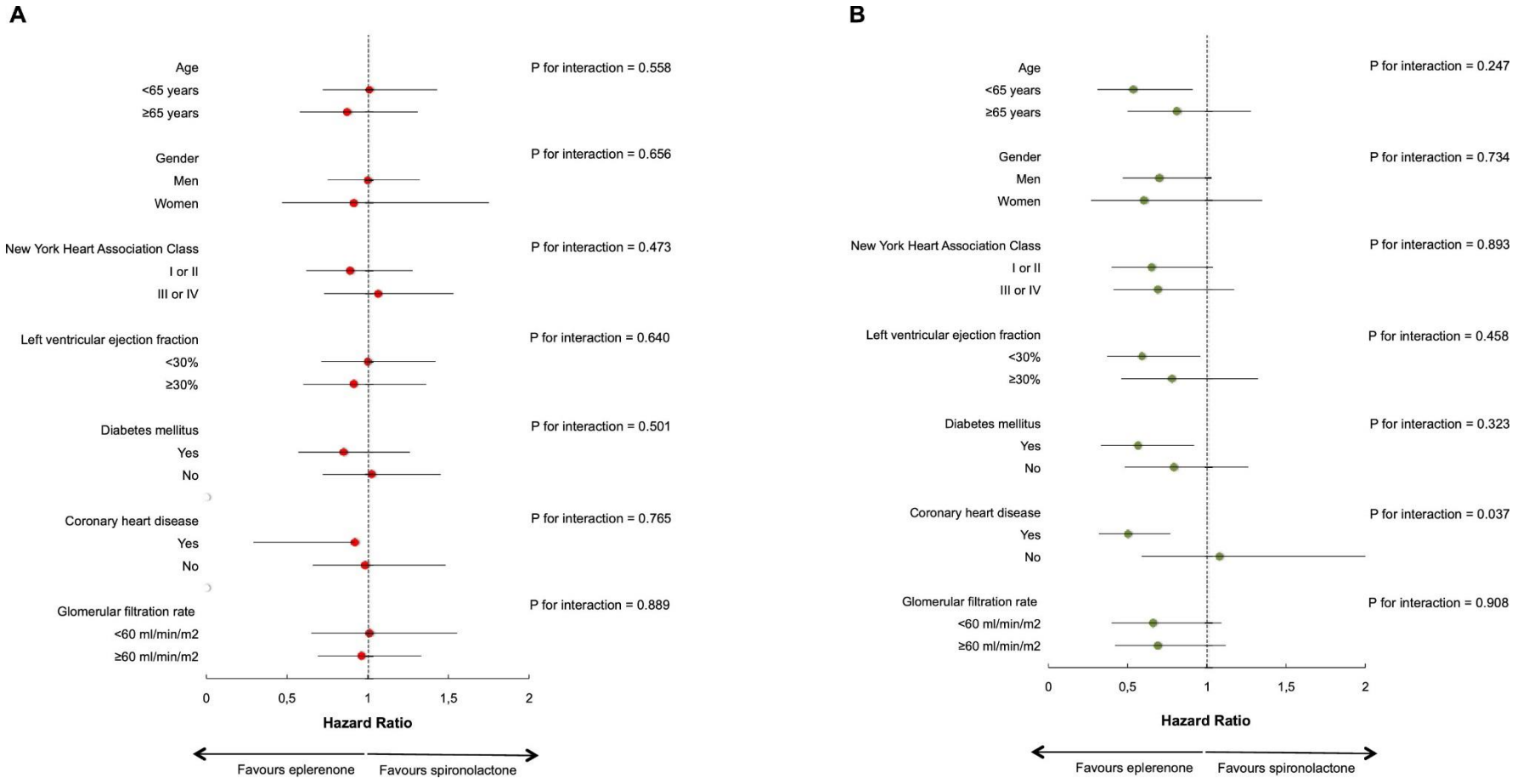


Fig. 4. Hazard ratio of the primary end-point death cardiovascular death or heart failure hospitalization (panel A) and the secondary end-point all-cause death (panel B) for patients treated with eplerenone vs. spironolactone in several relevant clinical subgroups, as assessed by means of competing risks regression.

Table 3. Reasons for mineralocorticoid antagonist receptor discontinuation during long-term follow-up.

	Spironolactone (*N*= 86)	Eplerenone (*N*= 63)
Side effects	69	42
Gynaecomastia	26	0
Hyperkalemia	25	20
Renal dysfunction	9	17
Hypotension	6	3
Cutaneous reaction	3	0
Palpitations	0	1
Erectile dysfunction	0	1
Other reasons	17	21
Physician-related	15	16
Patient-related	2	5

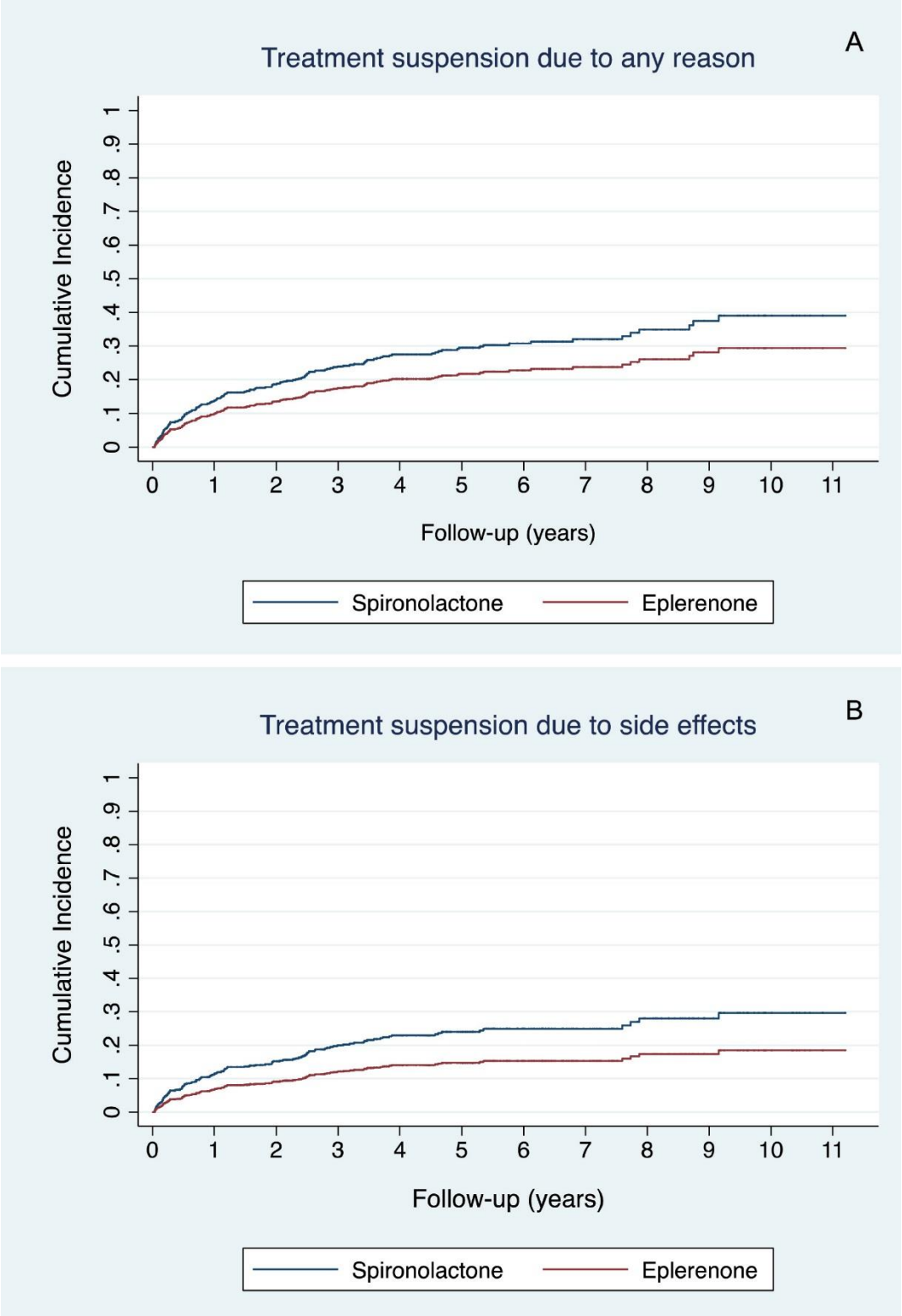


Fig. 5. Cumulative estimates of the incidence of treatment suspension due to any reason (panel 5A) and treatment suspension due to side effects (panel 5B) in patients who received spironolactone or eplerenone at baseline, as assessed by means of competing risks regression.