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Unravelling the interplay between hyperkalaemia, renin–angiotensin–aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry

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Abstract

Aims

We assessed the interplay between hyperkalaemia (HK) and renin–angiotensin–aldosterone system inhibitor (RAASi) use, dose and discontinuation, and their association with all-cause or cardiovascular death in patients with chronic heart failure (HF). We hypothesized that HK-associated increased death may be related to RAASi withdrawal.

Methods and results

The ESC-HFA-EORP Heart Failure Long-Term Registry was used. Among 9222 outpatients (HF with reduced ejection fraction: 60.6%, HF with mid-range ejection fraction: 22.9%, HF with preserved ejection fraction: 16.5%) from 31 countries, 16.6% had HK (≥5.0 mmol/L) at baseline. Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) was used in 88.3%, a mineralocorticoid receptor antagonist (MRA) in 58.7%, or a combination in 53.2%; of these, at ≥50% of target dose in ACEi: 61.8%; ARB: 64.7%; and MRA: 90.3%. At a median follow-up of 12.2 months, there were 789 deaths (8.6%). Both hypokalaemia and HK were independently
associated with higher mortality, and ACEi/ARB prescription at baseline with lower mortality. MRA prescription was not retained in the model. In multivariable analyses, HK at baseline was independently associated with MRA non-prescription at baseline and subsequent discontinuation. When considering subsequent discontinuation of RAASi (instead of baseline use), HK was no longer found associated with all-cause deaths. Importantly, all RAASi (ACEi, ARB, or MRA) discontinuations were strongly associated with mortality.

Conclusions

In HF, hyper- and hypokalaemia were associated with mortality. However, when adjusting for RAASi discontinuation, HK was no longer associated with mortality, suggesting that HK may be a risk marker for RAASi discontinuation rather than a risk factor for worse outcomes.

Keywords

Hyperkalaemia; Hypokalaemia; Heart failure; Renin–angiotensin–aldosterone system inhibitors; Prognosis; Mineralocorticoid receptor antagonists.

Introduction

Renin–angiotensin–aldosterone system inhibitors (RAASi) [i.e. angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor–neprilysin inhibitors], and beta-blockers are the cornerstones of therapy in patients with chronic heart failure (CHF) with reduced ejection fraction (HFrEF). Based on the highest level of evidence, they are strongly recommended in international guidelines (class IA[1]) for improving survival, decreasing sudden death, and preventing heart failure (HF) hospitalisations in patients with HFrEF.[2] International registry data have shown that adherence to guideline recommended medications in HFrEF is associated with improved outcomes.[3] However, guidelines are not being implemented,[4] both in terms of overall use and target doses, often because of actual, or concerns for potential adverse events.[2,5,6] Hyperkalaemia (HK), hypotension, deterioration of renal function, higher age and poor access to cardiologist care are the most frequently cited reasons for underdosing, underuse and discontinuation of RAASi in patients with HFrEF[2,3,5,7,8] and at the same time, potassium is poorly monitored,[9] even though benefits of RAASi appear as important in patients with severe chronic kidney disease[10] and older age.[11]

The European Society of Cardiology Heart Failure Association EURObservational Research Programme (ESC-HFA-EORP) Heart Failure Long-Term (HF-LT) Registry identified HK, impaired kidney function and hypotension as the main causes for non-prescription or underdosing of RAASi.[7]

In a recent observational study including all Stockholm citizens initiating MRA therapy, the development of HK within a year was associated with a four-fold significantly higher risk in overall mortality, with the results being consistent in the subpopulation of patients with HF. Following the occurrence of HK, 47% discontinued MRA whereas only 10% reduced the prescribed dose. Strikingly, when MRA was discontinued, most patients (76%) were not reintroduced to MRA therapy during the subsequent year.[8] Reintroduction of RAASi is less likely the longer the break in therapy.[12] Therefore, HK, beyond its potentially lethal pro-arrhythmogenic properties, may be both a biomarker of RAASi under-use and under-dosing, a barrier to RAASi use, and a trigger for subsequent RAASi discontinuation, with all potentially being associated with poor outcomes in various populations,[13] including HF.[14]

We hypothesize that HK-associated increased death may be related to RAASi withdrawal. Therefore, using the ESC-HFA-EORP HF-LT Registry, we aimed to assess the interplay between HK (and its determinants), RAASi prescription and dosing at baseline, RAASi discontinuation, and associations with outcomes in outpatients with CHF enrolled in the HF-LT Registry.

Methods

Data source and study population

The primary objective of the ESC-HFA-EORP HF-LT Registry is the description of the clinical epidemiology of HF outpatients and inpatients in ESC and affiliated countries, as well as the diagnostic and therapeutic processes used in the care of these patients. All national cardiology societies affiliated to the ESC were invited to participate.[7,15] The ESC-HFA-EORP HF-LT Registry is a prospective, multicentre, observational registry of patients referred to a broad range of cardiology centres in 31 countries. The 31 countries are Belarus, Bulgaria, Croatia, Czech Republic, Georgia, Hungary, Moldova, Poland, Romania, Serbia, Slovakia, Slovenia (Eastern countries), Israel (Middle East), Egypt (North Africa), Denmark, Estonia, Latvia, Lithuania, Sweden (Northern), Bosnia Herzegovina, Cyprus, Greece, Italy, Kosovo, Macedonia, Portugal, Spain, Turkey (Southern), Austria, France, Switzerland (Western). The study design has previously been described.[7,16] Briefly, there were no specific exclusion criteria, with the exception of age, which had to be greater than 18 years. Patients were followed up in accordance with the usual practice of the centres, with the exception of a mandatory follow-up visit at 12 months to collect information on morbidity and mortality. In cases where the patient was unable to reach the clinical centre, a phone survey replaced this follow-up clinical visit. The HF-LT Registry was approved by each local ethics board and written informed consent obtained in accordance with each country's legislation. Random audits were conducted in each participating country. The HF-LT Registry enrolled all the outpatients with CHF seen at the clinics and those admitted to hospital for acute HF (either pre-existing or new-onset HF) for whom intravenous HF therapy (diuretics, inotropes, or vasodilators) was used.[16] Patients were enrolled 1 day per week for 12 consecutive months.[7]

In the current analysis only HF outpatients (i.e. CHF) were considered. Compared to the previous publications where 7401 CHF patients were described,[7,16] a total of 9222 patients could now be described at the time the present research question was first addressed (2017). RAASi target doses were defined as in the ESC HF guidelines related to HFrEF.[1] Patients who were receiving a RAASi dose ≥50% of the target dosage were compared to those who received <50% or no treatment. This threshold was based on the recent observation in the European setting that patients reaching <50% of the recommended ACEi/ARB (and beta-blocker) dose displayed an increased risk of death and/or

HF hospitalisation. Patients reaching 50–99% of the recommended ACEi/ARB and/or beta-blocker dose had a comparable risk of death and/or HF hospitalisation to those reaching ≥100%.[17]

Statistical analyses

Descriptive statistics were used to summarise frequency tabulations (*n* , %) and distributions (median, interquartile range). Categorical variables were compared using the Chi-square test or Fisher exact test, and continuous variables with a non-parametric test (Kruskal–Wallis test).

Predictors of mineralocorticoid receptor antagonist use

Because MRAs is the RAASi category most affecting potassium homeostasis[18] and also the least likely to be started and the most likely to be stopped in HF,[19] we assessed predictors of (i) non-use or at low dose at baseline, and (ii) MRA discontinuation during the follow-up. In order to investigate why patients had low doses of MRAs or were without MRAs at baseline or with subsequent MRA discontinuation at 1-year follow-up, logistic regression models were performed with a stepwise procedure, using a *P* -value <0.05 to allow entry in the model and a *P* -value <0.05 to remain in the updated model. Independent variables that were significant at univariable analysis ($P < 0.10$) as well as variables considered of relevant clinical interest were included at the beginning in the multivariable model. Potential interactions between baseline characteristics and baseline kalaemia (as a categorical variable) were tested. For the logistic regression model, MRA discontinuation corresponds to patients with any MRA agent at baseline but not at 1-year follow-up (i.e. stopped during the 1-year follow-up or at the 1-year follow-up visit).

Outcomes

For all-cause and cardiovascular death, Cox regression models including baseline potassium level were performed using the same stepwise procedure as in the logistic regression models. Two different models were performed: (i) including ARBs, ACEis and MRAs, separately, as use vs. non-use at the baseline, and (ii) comparing RAASi use at baseline but not at follow-up (i.e. discontinued) and, separately, no use of RAASi at baseline and at follow-up with RAASi use at baseline and at 1-year follow-up. In addition, natural cubic splines were presented for the unadjusted association between potassium levels and outcomes.

Finally, three mediations analyses were performed[20] for ACEi, ARB or MRA discontinuation, where the ‘direct effect’ was the direct effect of the potassium level on overall/cardiovascular mortality, meaning if significant that the potassium level directly impacts the mortality. The ‘indirect effect’ means that the potassium level has an impact on MRA/ACEi/ARB discontinuation, which has its own impact on mortality.

P -value <0.05 was used as a cut-off for statistical significance. All analyses were performed in SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Between April 2011 and May 2017, 19 136 patients were included in the HF-LT Registry. Of these, 8290 (43.3%) were inpatients hospitalised with a diagnosis of acute HF and 10 846 (56.7%) were outpatients with CHF. Among outpatients, baseline potassium values were available in 9222 (85.0%) patients (supplementary Figure S1), who represented our study population, and of whom 16.6% had HK at baseline (≥5.0 mmol/L). Over a median follow-up of 371 days (363–427), there were 789 deaths (8.6%), 241 (2.6%) patients lost to follow-up, and 410 cardiovascular deaths (4.4%, or 52% of all deaths) as well as 195 deaths (2.1%, or 25% of all deaths) from unknown causes.

Patient baseline features are presented in Table 1. In this mixed population of HFrEF (60.6%), HF with mid-range (HFmrEF) (22.9%) and preserved ejection fraction (HFpEF) (16.5%), with the latter two without any guideline recommendation for RAASi,[2] most patients were treated with an ACEi or an ARB (88.3%), an MRA (58.7%), or a combination thereof (53.2%), mostly at doses ≥ 50% (ACEi: 61.8% ≥ 50% of the target dose; ARB: 64.7%; MRA: 90.3%). After 1 year, the frequency was 57.5%, 23.5%, 79.1% and 54.3% for ACEi, ARB, ACEi/ARB and MRA, respectively.

Factors associated with RAASi prescription and dosing at baseline, or RAASi discontinuation

Patients with HK at baseline were older, more frequently men, with diabetes and lower estimated glomerular filtration rate compared to normokalaemic patients (4.0–5.0 mmol/L). There were no significant differences in the proportion of patients with HFrEF, HFmrEF or HFpEF across the potassium strata (Table 1). ACEi use was more common in mildly hyperkalaemic (5–5.5 mmol/L) patients while MRA use was more common in normokalaemic patients. The co-prescription of ACEi/ARB and MRA was less common in patients with serum potassium ≥5.5 mmol/L. While the percentage of ACEi or ARB target dose at baseline did not differ significantly across the potassium categories, hyperkalaemic patients were 2–3 times more frequently prescribed an MRA at <50% of the target dose at baseline (*Table* 1). Hyperkalaemic patients were also more prone to undergo ACEi/ARB or MRA discontinuation during follow-up (Table 1).

Table 1. Patient baseline characteristics and renin–angiotensin–aldosterone system inhibitor maintenance after 1 year

Variable	Total (*n* = 9222)	<3 mmol/L (*n* = 14, 0.2%)	3–4 mmol/L (*n* =1431, 15.5%)	4–5 mmol/L (*n* =6249, 67.8%)	5–5.5 mmol/L (*n* =1202, 13.0%)	≥5.5 mmol/L (*n* = 326, 3.5%)	*P* -value
Age (years), median (Q1–Q3)	67 (58–75)	56.5 (46–68)	67 (56–75)	66 (57–75)	69 (60–76)	69 (62–78)	<0.001
Female sex, *n* (%)	2646/9222 (28.7)	5/14 (35.7)	471/1431 (32.9)	1779/6249 (28.5)	305/1202 (25.4)	86/326 (26.4)	<0.001
Body mass index (kg/m^2), median (Q1–Q3)	27.5 (24.6–30.9)	27.3 (25.4–31.1)	27.3 (24.2–30.8)	27.6 (24.6–30.9)	27.4 (24.6–31.0)	26.8 (24.4–30.5)	0.141
SBP (mmHg), median (Q1–Q3)	120 (110–138)	120 (90–144)	120 (110–138)	120 (110–138)	120 (110–139)	120.5 (110–140)	
HR (bpm), median (Q1–Q3)	70 (62–80)	89 (71–105)	70 (63–81)	70 (61–80)	70 (60–79)	70 (63–81)	<0.001
Last known ejection fraction class (%), *n* (%)							
<40%	5073/8369 (60.6)	4/12 (33.3)	749/1236 (60.6)	3445/5685 (60.6)	678/1128 (60.1)	197/308 (64.0)	0.580
40–50%	1918/8369 (22.9)	4/12 (33.3)	275/1236 (22.2)	1315/5685 (23.1)	259/1128 (23.0)	65/308 (21.1)	
>50%	1378/8369 (16.5)	4/12 (33.3)	212/1236 (17.2)	925/5685 (16.3)	191/1128 (16.9)	46/308 (14.9)	
NYHA class, *n* (%)							
I	1512/9197 (16.4)	2/14 (14.3)	198/1420 (13.9)	1058/6236 (17.0)	209/1201 (17.4)	45/326 (13.8)	<0.001
II	5213/9197 (56.7)	7/14 (50.0)	771/1420 (54.3)	3549/6236 (56.9)	695/1201 (57.9)	191/326 (58.6)	
III	2288/9197 (24.9)	4/14 (28.6)	420/1420 (29.6)	1510/6236 (24.2)	278/1201 (23.1)	76/326 (23.3)	
IV	184/9197 (2.0)	1/14 (7.1)	31/1420 (2.2)	119/6236 (1.9)	19/1201 (1.6)	14/326 (4.3)	
Pulmonary rales, *n* (%)	1365/8934 (15.3)	2/14 (14.3)	250/1369 (18.3)	894/6038 (14.8)	166/1189 (14.0)	53/324 (16.4)	0.015
Peripheral oedema, *n* (%)	1859/8945 (20.8)	8/14 (57.1)	354/1371 (25.8)	1216/6047 (20.1)	215/1191 (18.1)	66/322 (20.5)	<0.001
Primary aetiology, *n* (%)							
Dilated cardiomyopathy	2585/9171 (28.2)	3/14 (21.4)	382/1421 (26.9)	1790/6210 (28.8)	324/1201 (27.0)	86/325 (26.5)	0.053
Hypertension	777/9171 (8.5)	1/14 (7.1)	125/1421 (8.8)	516/6210 (8.3)	101/1201 (8.4)	34/325 (10.5)	
Ischaemic heart disease	3956/9171 (43.1)	3/14 (21.4)	588/1421 (41.4)	2670/6210 (43.0)	547/1201 (45.5)	148/325 (45.5)	
Other	931/9171 (10.2)	4/14 (28.6)	149/1421 (10.5)	628/6210 (10.1)	124/1201 (10.3)	26/325 (8.0)	
Tachycardia-related cardiomyopathy	132/9171 (1.4)	0/14 (0.0)	30/1421 (2.1)	85/6210 (1.4)	13/1201 (1.1)	4/325 (1.2)	
Valve disease	790/9171 (8.6)	3/14 (21.4)	147/1421 (10.3)	521/6210 (8.4)	92/1201 (7.7)	27/325 (8.3)	
Atrial fibrillation, *n* (%)	3545/9221 (38.4)	8/14 (57.1)	604/1430 (42.2)	2350/6249 (37.6)	448/1202 (37.3)	135/326 (41.4)	0.006
Stroke/TIA, *n* (%)	860/9213 (9.3)	1/14 (7.1)	127/1428 (8.9)	594/6246 (9.5)	105/1199 (8.8)	33/326 (10.1)	0.853
Diabetes class, *n* (%)	2988/9222 (32.4)	5/14 (35.7)	400/1431 (28.0)	1959/6249 (31.3)	484/1202 (40.3)	140/326 (42.9)	<0.001
Hypertension treatment, *n* (%)	5523/9208 (60.0)	9/14 (64.3)	859/1427 (60.2)	3703/6239 (59.4)	730/1202 (60.7)	222/326 (68.1)	0.034
Peripheral vascular disease, *n* (%)	1149/8936 (12.9)	0/14 (0.0)	161/1370 (11.8)	793/6040 (13.1)	144/1188 (12.1)	51/324 (15.7)	0.139
Chronic kidney dysfunction, *n* (%)	1870/9213 (20.3)	2/14 (14.3)	259/1425 (18.2)	1145/6246 (18.3)	327/1202 (27.2)	137/326 (42.0)	<0.001
ICD, *n* (%)	1468/9203 (16.0)	1/14 (7.1)	223/1425 (15.6)	1018/6237 (16.3)	180/1201 (15.0)	46/326 (14.1)	0.525
CRT-P/D, *n* (%)	1236/9203 (13.4)	2/14 (14.3)	202/1425 (14.2)	828/6237 (13.3)	165/1201 (13.7)	39/326 (12.0)	0.823
eGFR (mL/min/1.73 m^2), median (Q1–Q3)	62.9 (46.6–79.9)	64.8 (49.3–77.6)	65.0 (49.5–81.2)	64.6 (48.6–81.5)	55.5 (41.0–73.0)	43.6 (29.9–61.4)	<0.001
eGFR (mL/min/1.73 m^2) in class, *n* (%)							
<30	604/8583 (7.0)	1/14 (7.1)	79/1281 (6.2)	335/5824 (5.8)	111/1153 (9.6)	78/311 (25.1)	<0.001
30–60	3278/8583 (38.2)	5/14 (35.7)	457/1281 (35.7)	2122/5824 (36.4)	546/1153 (47.4)	148/311 (47.6)	
>60	4701/8583 (54.8)	8/14 (57.1)	745/1281 (58.2)	3367/5824 (57.8)	496/1153 (43.0)	85/311 (27.3)	
ACEi, *n* (%)	6066/9210 (65.9)	4/14 (28.6)	879/1431 (61.4)	4154/6239 (66.6)	822/1201 (68.4)	207/325 (63.7)	<0.001
ARB, *n* (%)	2234/9218 (24.2)	1/14 (7.1)	349/1431 (24.4)	1510/6245 (24.2)	294/1202 (24.5)	80/326 (24.5)	0.680
ACEi/ARB, *n* (%)	8129/9210 (88.3)	5/14 (35.7)	1201/1431 (83.9)	5559/6239 (89.1)	1089/1201 (90.7)	275/325 (84.6)	<0.001

Beta-blockers, *n* (%)	8197/9217 (88.9)	8/14 (57.1)	1234/1431 (86.2)	5582/6244 (89.4)	1100/1202 (91.5)	273/326 (83.7)	<0.001
MRA, *n* (%)	5412/9218 (58.7)	8/14 (57.1)	838/1431 (58.6)	3725/6245 (59.6)	702/1202 (58.4)	139/326 (42.6)	<0.001
ACEi/ARB and MRA, *n* (%)	4907/9216 (53.2)	4/14 (28.6)	721/1431 (50.4)	3395/6244 (54.4)	661/1202 (55.0)	126/325 (38.8)	<0.001
Diuretics oral, *n* (%)	7684/9217 (83.4)	13/14 (92.9)	1242/1431 (86.8)	5149/6244 (82.5)	1014/1202 (84.4)	266/326 (81.6)	0.001
Ivabradine, *n* (%)	815/8958 (9.1)	0/14 (0.0)	116/1376 (8.4)	560/6052 (9.3)	114/1192 (9.6)	25/324 (7.7)	0.496
Digitalis, *n* (%)	1982/9214 (21.5)	6/14 (42.9)	337/1430 (23.6)	1340/6242 (21.5)	223/1202 (18.6)	76/326 (23.3)	0.007
Statins, *n* (%)	5646/9218 (61.2)	4/14 (28.6)	796/1431 (55.6)	3845/6245 (61.6)	806/1202 (67.1)	195/326 (59.8)	<0.001
ACEi target dose, *n* (%)							
< 50% max dosage	2195/5743 (38.2)	3/4 (75.0)	338/827 (40.9)	1483/3937 (37.7)	296/782 (37.9)	75/193 (38.9)	0.254
≥ 50% max dosage	3548/5743 (61.8)	1/4 (25.0)	489/827 (59.1)	2454/3937 (62.3)	486/782 (62.1)	118/193 (61.1)	
ARB target dose, *n* (%)							
< 50% max dosage	666/1885 (35.3)	0/1 (0.0)	105/290 (36.2)	464/1283 (36.2)	76/250 (30.4)	21/61 (34.4)	0.446
≥ 50% max dosage	1219/1885 (64.7)	1/1 (100.0)	185/290 (63.8)	819/1283 (63.8)	174/250 (69.6)	40/61 (65.6)	
MRA target dose, *n* (%)							
< 50% max dosage	511/5253 (9.7)	0/8 (0.0)	69/807 (8.6)	310/3611 (8.6)	104/690 (15.1)	28/137 (20.4)	<0.001(S)
≥ 50% max dosage	4742/5253 (90.3)	8/8 (100.0)	738/807 (91.4)	3301/3611 (91.4)	586/690 (84.9)	109/137 (79.6)	
ACEi/ARB discontinuation, *n* v(%)	949/7045 (13.5)	1/4 (25.0)	159/1001 (15.9)	600/4830 (12.4)	141/963 (14.6)	48/247 (19.4)	<0.001
ACEi discontinuation, *n* (%)	914/5237 (17.5)	1/3 (33.3)	147/724 (20.3)	580/3599 (16.1)	142/726 (19.6)	44/185 (23.8)	0.002
ARB discontinuation, *n* (%)	418/1962 (21.3)	0/1 (0.0)	69/301 (22.9)	268/1326 (20.2)	53/261 (20.3)	28/73 (38.4)	0.006
Beta-blocker discontinuation, *n* (%)	787/7161 (11.0)	2/7 (28.6)	137/1040 (13.2)	495/4890 (10.1)	110/979 (11.2)	43/245 (17.6)	<0.001
MRA discontinuation, *n* (%)	890/4748 (18.7)	2/7 (28.6)	135/701 (19.3)	583/3295 (17.7)	130/618 (21.0)	40/127 (31.5)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT-P/D, cardiac resynchronization therapy with pacemaker or defibrillator; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

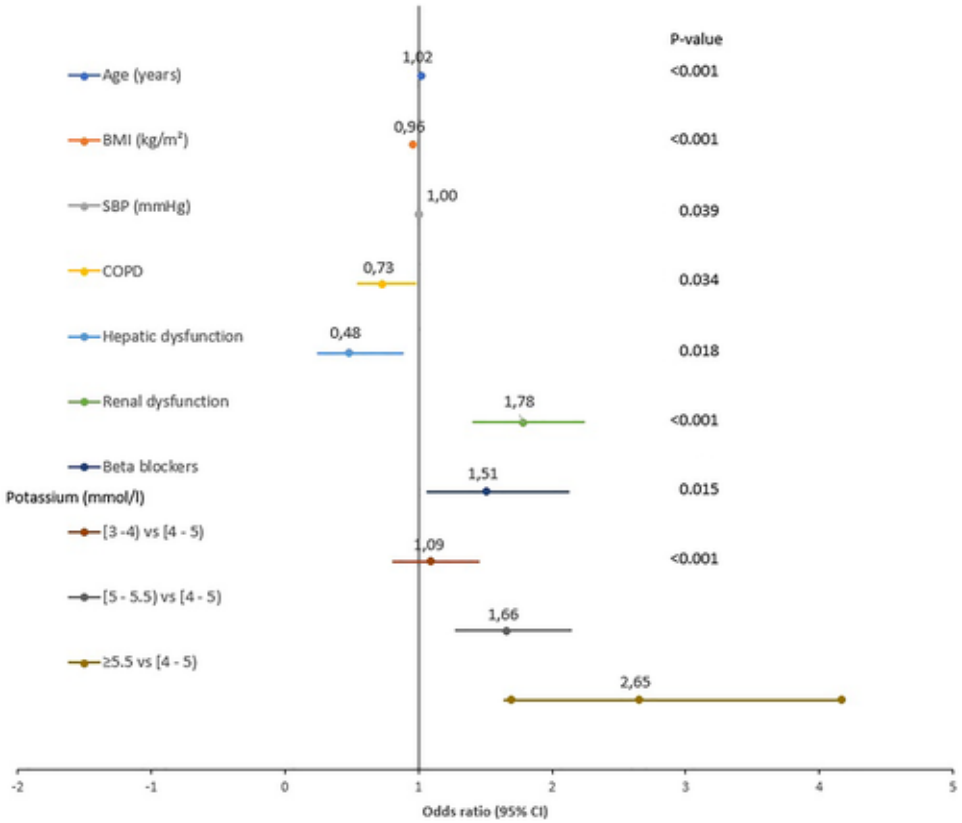

Figure 1 Multivariable analysis for clinical predictors of low dosage of mineralocorticoid receptor antagonists at baseline. Number of patients with complete data and included in the analysis: 5188/5253. Logistic regression with reference ≥50% target dose. BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure.

Multivariable analyses did not confirm an association between baseline potassium categories and no use or low-dose use of ACEi or ARB at baseline, while lower systolic blood pressure, ejection fraction >50% (vs. <40%) (for ACEi drug class) and renal dysfunction (for both drug classes) were found significantly and independently associated with no use or low-dose use at baseline (data not shown). In multivariable analysis, hyperkalaemic patients (5–5.5 mmol/L vs. 4–5 mmol/L) and ≥5.5 mmol/L vs. 4–5 mmol/L) and patients with renal dysfunction, along with those with higher systolic blood pressure were more prone to receive lower doses or no MRA at baseline (*Figure 1*).

In multivariable analyses, lower blood pressure and kidney dysfunction were significantly associated with subsequent discontinuation of ACEi/ARB while potassium levels were not (data not shown). In contrast, renal dysfunction and potassium levels (HK ≥5.5 mmol/L) were associated with MRA discontinuation, along with other factors such as older age, ejection fraction >50% vs. <40%, and comorbidities (*Figure 2).*

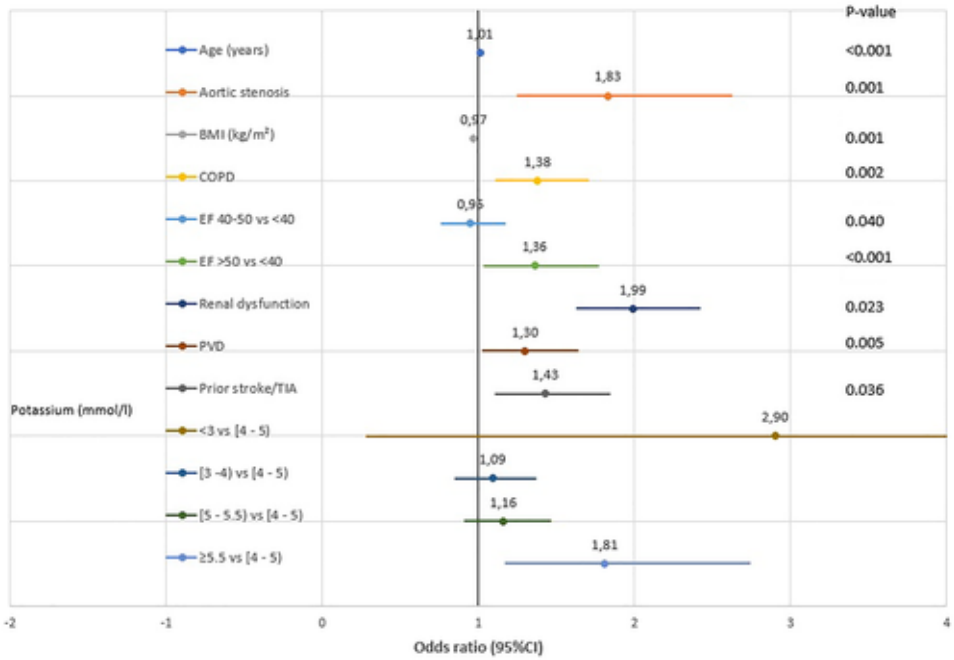

Figure 2. Multivariable analysis for treatment discontinuation of mineralocorticoid receptor antagonists during 1-year follow-up. Number of patients with complete data and included in the analysis: 4408/4748. BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

Factors associated with clinical outcomes

In univariable analysis, a U-shaped relationship was observed between baseline potassium and risk of all-cause death (Figure 3A), with a statistically significant association above approximately 5 mmol/L for HK and <4 mmol/L for hypokalaemia. In multivariable analysis, HK ≥5.5 mmol/L remained associated with greater risk of death [hazard ratio (HR) 1.40 (1.02–1.92), P = 0.038], as was hypokalaemia [3–4 mmol/L; HR 1.26 (1.02–1.55), P = 0.031], while ACEi and/or ARB prescriptions at baseline were associated with better outcomes [HR 0.70 (0.57–0.86), P < 0.001; HR 0.70 (0.56–0.89), P = 0.004]. MRA prescription was not retained in the model (P = 0.476) (Figure 4)

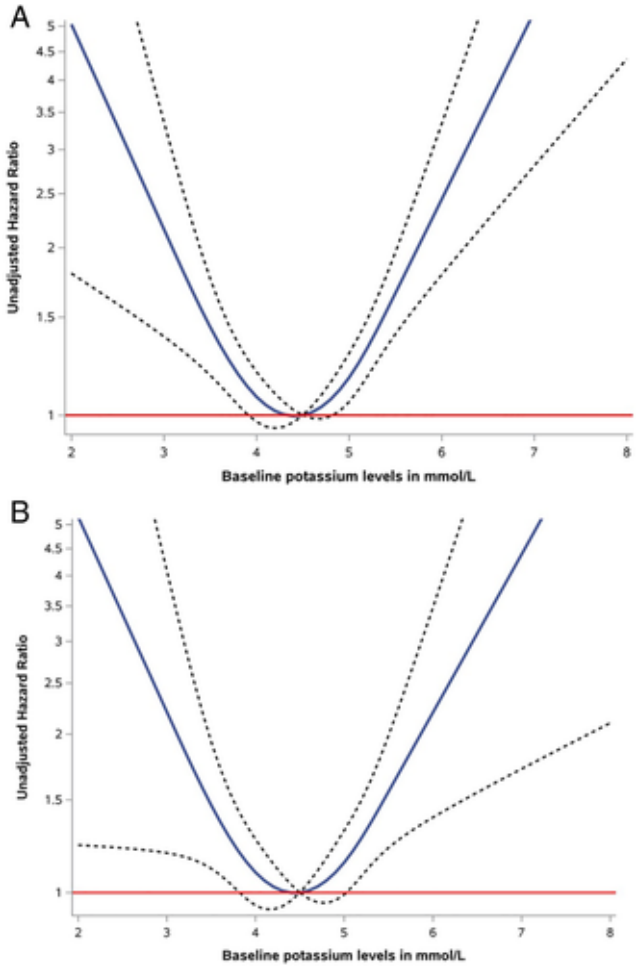

Figure 3. (A) Relationship between baseline serum potassium and 1-year all-cause death – natural cubic spline without adjustment. (B) Relationship between baseline serum potassium and 1-year cardiovascular death – natural cubic spline without adjustment.

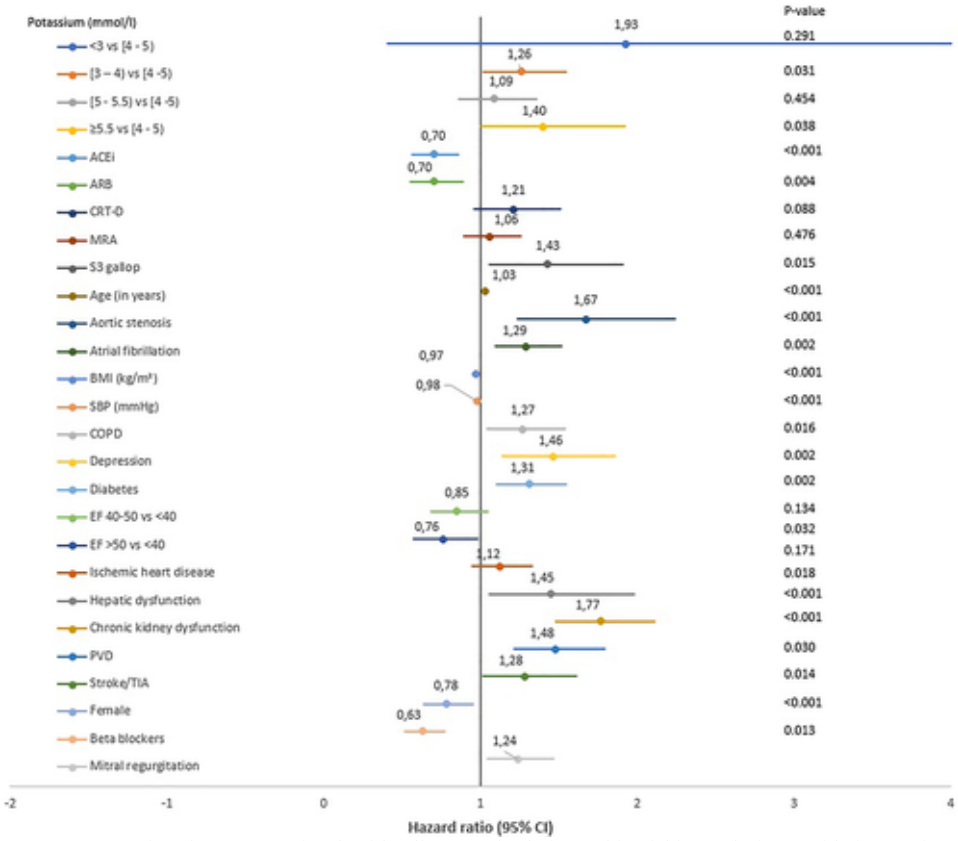

Figure 4. Baseline factors associated with all-cause death in multivariable analysis considering renin–angiotensin–aldosterone system inhibitor prescription at baseline. Number of patients with complete data and included in the analysis: 8173/9222. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

When considering RAASi (ACEi, ARB, MRA) baseline percent of target doses instead of only use vs. non-use, the non-prescription of ACEi performed significantly worse compared to the prescription of ACEi at lower than 50% of the target doses [HR 1.42 (1.13;1.79), $P = 0.003$], while the comparison between <50% and ≥ 50% target doses did not reach statistical significance. In this model, only baseline hypokalaemia was associated with all-cause mortality [HR 1.25 (1.01–1.56), $P = 0.042$].

When considering subsequent discontinuation of RAASi for adjustments (instead of baseline use or dose) and serum potassium at baseline, HK was no longer associated with risk of all-cause death while all RAASi (ACEi, ARB, or MRA) discontinuations, regardless of class, were strongly associated with the outcomes (Figure 5). In a sensitivity univariable analysis, ACEi, ARB or MRA discontinuations were found associated with all-cause death across the ejection fraction strata (i.e. <40%, 40–50%, >50%; data not shown).

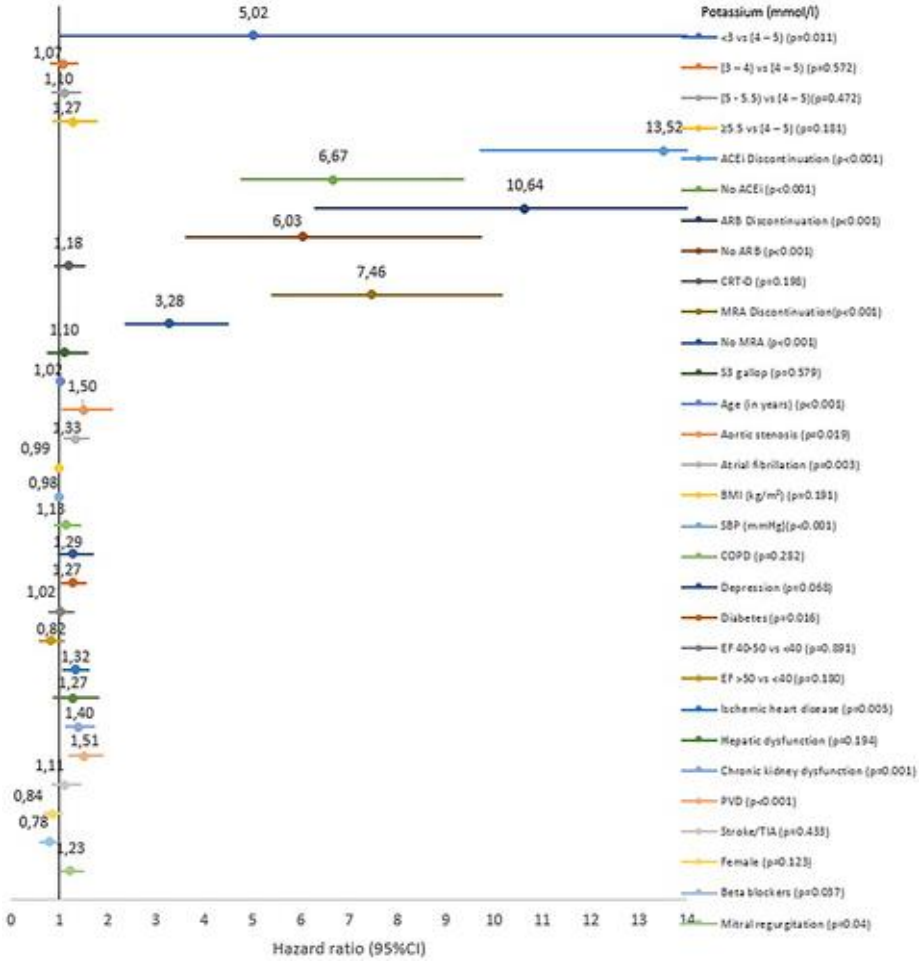

Figure 5. Baseline factors associated with all-cause death in multivariable analysis considering renin–angiotensin–aldosterone system inhibitor (RAASi) discontinuation during 1-year follow-up. Number of patients with complete data and included in the analysis: 7413/9222. Variables are the same as in the previous model but instead of RAASi treatment at baseline, RAASi treatment corresponds to RAASi treatment during the 1-year follow-up with for each treatment (three possibilities: discontinuation – no treatment at baseline – no discontinuation, with no discontinuation as reference). ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

In further sensitivity analyses, cardiovascular rather than all-cause deaths were considered. In univariable analysis, a U-shaped relationship was observed between baseline potassium and risk of cardiovascular death (Figure 3B), with a significant association for HK and hypokalaemia. However, serum potassium concentrations were not identified as a predictor of cardiovascular death in the multivariable models, while use of ACEi or ARB at baseline was associated with better outcomes (supplementary Table S1). When considering RAASi (ACEi, ARB, MRA) baseline target doses instead, only the non-prescription of ACEi or ARB performed significantly worse compared to the prescription of ACEi or ARB lower than 50% of the target doses (supplementary Table S2).

Again, as for all-cause death, ACEi, ARB or MRA discontinuations were all associated with a higher risk also of cardiovascular death (supplementary Table S3). In a sensitivity univariable

analysis, ACEi, ARB or MRA discontinuations were found associated with cardiovascular death across the ejection fraction strata (i.e. <40%, 40–50%, >50%; data not shown).

Finally, three multivariable mediation analyses (for ACEi, or ARB, or MRA discontinuation, respectively) were performed. HK (>5.5 mmol/L) was associated with mortality and cardiovascular mortality by mediating discontinuation of ACEi (marginally significant for all-cause death: P = 0.059), ARB (not statistically significant), and MRA (P = 0.007 for total mortality; P = 0.080 for cardiovascular death) (supplementary Table S4).

Discussion

In this contemporary European outpatient HF cohort, with a high rate of patients treated with RAASi compared to other HF populations, the prevalence of HK was high (16.6%), while the 1-year outcome was poor (overall and cardiovascular death: 8.6% and 4.4%, respectively). Similar to a number of surveys in post-discharge post-acute HF,[21, 22] chronic HFrEF[23] and HFpEF[24] patients, a U-shape relationship between baseline serum potassium and all-cause death and cardiovascular death was observed over 1-year follow-up in univariate analysis

.

In a multivariable model considering all deaths, both hypokalaemia and HK were associated with poor outcomes, while ACEi/ARB but not MRA prescription was found to be independently associated with better outcomes. The absence of association between MRA use and outcomes has been previously described in observational settings and is most likely due to residual unmeasured confounding, such as higher use of MRAs in patients with refractory oedema, ascites, liver disease, diuretic resistance, high-dose diuretic use, and/or other factors associated with poor outcomes. However, in additional multivariable analyses, when considering RAASi doses at baseline or subsequent RAASi discontinuation – instead of considering RAASi prescription at baseline – only RAASi discontinuations (ACEi, ARB, or MRA) were found consistently associated with all-cause and cardiovascular death, independent of serum potassium at baseline and, importantly, HK was no longer associated with the clinical outcomes. Moreover, in multivariable analyses, HK at baseline was found to be associated with MRA non-prescription at baseline and with its subsequent discontinuation. Additional mediation analyses showed that HK ≥5.5 mmol/L was associated with mortality and cardiovascular mortality by mediating discontinuation of ACEi, ARB, MRA, although it was not statistically significant for all. This was actually much more significant for MRA and suggests that the HK is more important through MRA discontinuation than through ACEi/ARB discontinuation.

Altogether, these data provide insights into the interplay between HK, RAASi use and clinical outcomes in real-life HF settings. Indeed, they clearly depict the current dilemma facing the implementation of these life-saving drugs, in particular MRAs, in routine practice. The present findings complement numerous previous reports from the HF-LT Registry and from the Swedish Heart Failure Registry studying the reasons for non-prescription of RAASi.[5, 7, 19, 25] In the large majority of these cases, reported contraindications, a documented intolerance or concerns about potential intolerance (HK, worsening renal function, hypotension) were the main reasons for the non-prescription of these drugs.[7] From this HF-LT Registry dataset, it was reported that the true rate of under-treatment for ACEi/ARB and MRAs in this well treated population was 3.2% and 5.4%, respectively (compared to others[4]), at least in terms of RAASi use.[7] We also previously reported that, with regard to the target dosages of these drugs, fewer than one-third of the patients were currently prescribed the target dosages suggested by current guidelines: 29.3% for ACEis, 24.1% for ARBs, and 30.5% for MRAs.[7]

For the present study, the threshold of 50% of the recommended ACEi/ARB (and beta-blocker) was selected since in a recent European survey, patients receiving less displayed an increased risk of death and/or HF hospitalisation.[17]

Altogether, these data confirm that HK in itself is a major barrier toward the implementation of, and importantly maintenance of RAASi and more specifically of MRA, since prescribers, in accordance with the guidelines, are not prone to use MRAs[3, 26] or to discontinue them in presence of HK.[8, 27] In other words, beyond its pro-arrhythmogenic properties, HK could also be a risk marker that leads to suboptimal use of RAASi, in particular MRAs, which in turn is causative of poor outcomes, as also suggested by previous surveys,[28] and as shown here for the first time, being a marker of discontinuation. Clinicians may be well served by recognizing the causes of RAASi underuse. The present analysis from the ESC-EORP-HFA HF-LT Registry suggests that HK is harmful because it causes RAASi discontinuation and a similar study from the Swedish Heart Failure Registry suggests that HK is harmful because it causes RAASi avoidance and discontinuation.[29] Together with a previous analysis from BIOSTAT-CHF suggesting that HK is in itself not harmful but prevents RAASi up-titration,[30] it is becoming increasingly clear that the universally poor implementation of RAASi and especially MRA drugs in HFrEF is extensively driven by actual or concerns for HK.[28] Whether the vicious circle surrounding HK, which is an inherent risk factor for RAASi under-use, may be overcome by the availability of new potassium binders[31, 32] and/or novel MRAs less prone to HK warrants prospective cardiovascular outcome trials.

Limitations

As previously acknowledged,[7] there are limitations of this and other registry analyses. All centres were cardiology centres, potentially limiting generalizability to internal medicine and primary care. To mitigate this issue, the centres in HF-LT Registry were selected in proportion to the size of the population of the participating countries, taking into account the different technological levels of the cardiology centres invited to participate.[7]

More specifically in relation to the present analysis, observational data cannot establish causality. This is particularly relevant for the associations between RAASi use and better outcomes, where available randomized trials exist. Secondly, only baseline serum potassium and baseline target doses were considered, whereas we previously reported from this registry that, in approximately one third of the patients not achieving the target doses, a drug up-titration was still ongoing,[7] and neither the timing of RAASi discontinuation nor potassium levels thereafter were recorded. Third, the study population consisted of an amalgamation of HFrEF, HFmrEF and HFpEF patients (in whom target doses were derived from HFrEF recommendations). However, ACEi, ARB or MRA discontinuations were found associated with all-cause and cardiovascular death across the ejection fraction strata (i.e. <40%, 40–50%, >50%). Fourth, sacubitril/valsartan was not considered, not being approved at the time of data collection, while its use may be associated with less frequent HK in MRA recipients.[33] However, findings related to the combined use of ACEi/ARB/MRA match the latest findings in a recently described European dataset. Indeed, the Dutch CHECK-HF registry of HFrEF patients observed that, between 2013 and 2016, 84% of patients were treated with ACEi/ARB and 56% with MRA, and approximately one-half of the HFrEF patients taking the prescribed medication were receiving less than the target dose of MRAs and ACEi/ARB.[34]

Conclusions

In this large, contemporary, international CHF population, hyper- and hypokalaemia, as well as non-use of ACEi/ARB were associated with worse outcomes. Importantly, after adjusting for discontinuation of a RAASi (ACEi/ARB or MRA), HK was no longer associated with increased risk, suggesting that HK may be a risk factor for RAASi discontinuation and through this association becoming a risk marker rather than a risk factor for worse outcomes.[28] This was further confirmed by mediation analyses especially considering MRA discontinuation. HK, also at baseline, represented a major hurdle against MRA use, thus its treatment and/or the prevention of its (re)occurrence under RAASi treatment may represent a potential therapeutic target.

Supplementary Information

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

Appendix S1. EORP Committees and Investigators.

Figure S1. Heart Failure Long-Term Registry flow-diagram.

Table S1. Factors associated with cardiovascular deaths in multivariable analysis considering renin–angiotensin–aldosterone system inhibitor prescription at baseline.

Table S2. Factors associated with cardiovascular deaths in multivariable analysis considering renin–angiotensin–aldosterone system inhibitor target dose prescription at baseline.

Table S3. Factors associated with cardiovascular deaths in multivariable analysis considering renin–angiotensin–aldosterone system inhibitor discontinuation during 1-year follow-up.

Table S4. Three mediation analyses (for angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker, or mineralocorticoid receptor antagonist discontinuation, respectively), using multivariable Cox models for the outcomes all-cause death and cardiovascular death.

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Overall activities were coordinated and supervised by Dr. Aldo P. Maggioni (EORP Scientific Coordinator). All investigators listed in the Supplemental Appendix S1.

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*Conflict of interest***:**

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