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Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes.

Data from 9 222 chronic heart failure patients of the ESC HFA EORP Heart Failure Long-Term HF LT 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 (CV) death in patients with chronic heart failure (CHF). We hypothesized that HK-associated increased death may be related to RAASi withdrawal.

Methods and Results:

The ESC HFA EORP HF Long-Term Registry was used. Among 9222 out-patients (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. ACEi or ARB was used in 88.3%, an MRA in 58.7%, or a combination in 53.2%; of these, at $\geq 50\%$ 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

Inhibitors of the renin-angiotensin-aldosterone system (RAASi) (i.e. angiotensin-converting enzyme inhibitors [ACEs], angiotensin receptor blockers (ARBs), mineralocorticoid-receptor antagonists [MRAs], and angiotensin receptor neprilysin inhibitors [ARNis]), and β 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 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, 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 RAAS inhibitors in patients with HFrEF (2, 3, 5, 7, 8) and at the same time, K is poorly monitored (9), even though benefits of RAASi agents appear as important in patients with severe CKD (10) and older age (11). The ESC HFA EORP Heart Failure Long-Term Registry (HF-LT) identified hyperkalaemia, impaired kidney function and hypotension as the main causes for the non-prescription or underdosing of RAASi (7).

In a recent observational study including all Stockholm citizens initiating MRA therapy, the development of hyperkalaemia 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 hyperkalaemia, 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, hyperkalaemia, beyond its potentially lethal proarrhythmogenic 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 hyperkalaemia-associated increased death may be related to RAASi withdrawal. Therefore, using the ESC HFA EORP Heart Failure Long-Term Registry (HF-LT), we aimed to assess the interplay between hyperkalaemia (and its determinants), RAASi prescription and dosing at baseline, RAASi discontinuation, and associations with outcomes in out-patients 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 out-patients and in-patients 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 (HF-LT) 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. ESC-HF-LT registry enrolled all the out-patients with CHF seen at the clinics and those admitted to hospital for AHF (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 out-patients (i.e. chronic HF) were considered. Compared to the previous publications where 7401 (7) (16) CHF patients were described, 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 equal to or above 50% of the target dosage were compared to those who received less than 50% or no treatment. This threshold was based on the recent observation in the European setting that patients reaching <50% of the recommended ACE-inhibitor/ARB (and beta-blocker) dose displayed an increased risk of death and/or heart failure hospitalisation. Patients reaching 50-99% of the recommended ACE-inhibitor/ARB and/or beta-blocker dose had a comparable risk of death and/or heart failure hospitalisation to those reaching $\geq 100\%$ (17).

Statistical Analyses

Descriptive statistics were used to summarise frequency tabulations (n, %) and distributions [median, interquartile range (IQR)]. 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 MRA use

Because MRAs is the RAASi category most affecting K homeostasis(18) and also the least likely to be started and the most likely to be stopped in HF(19) we assessed predictors of 1) non-use or at low dose at baseline 2) MRA discontinuation during the follow-up. In order to investigate why patients with low doses of MRAs or without MRAs at baseline or with subsequent MRA discontinuation at one-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 one-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 : 1) including ARBs, ACEi and MRA, separately, as use vs. non-use at the baseline; 2) comparing RAASi use at the baseline but not at the follow-up (i.e. discontinued) and, separately, no use of RAASi at the baseline and at the 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 Registry. Of these, 8,290 (43.3%) were in-patients hospitalised with a diagnosis of AHF and 10,846 (56.7%) were out-patients with CHF. Among out-patients, baseline potassium values were available in 9,222 (85.0%) patients (Online supplement Figure), who represented our study population, and of whom 16.6% had hyperkalaemia 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 CV 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 above or equal to 50% (ACEi: 61.8% \geq 50% of the target dose; ARB: 64.7% ; MRA: 90.3%). After one 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 hyperkalaemia at baseline were older, more frequently men, with diabetes and lower eGFR 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 (table1).

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 (SBP), ejection fraction (EF) >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): ≥ 5.5 mmol/L vs. 4 - 5 mmol/L, and patients with renal dysfunction, along with those with higher SBP were more prone to receive lower doses or no MRA at baseline (Figure 1).

In multivariable analyses, lower BP 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 (hyperK ≥ 5.5 mmol/L) were associated with MRA discontinuation, along with other factors such as older age, EF >50 % vs. <40 %, and comorbidities (Figure 2).

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/ for HK and below 4 mmol/L for hypokalaemia. In multivariable analysis, HK ≥ 5.5 mmol/L remained associated with greater risk of death [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)

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 $\geq 50\%$ 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, hyperkalaemia 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. EF < 40 , 40-50, $> 50\%$: data not shown)

In further sensitivity analyses, CV rather than all-cause deaths were considered. In univariable analysis, a U-shaped relationship was observed between baseline potassium and risk of CV death (Figure 3B), with a significant association for HK and for hypokalaemia. However, serum potassium concentrations were not identified as a predictor of CV death in the multivariable models, while use of ACEi or ARB at baseline were associated with better outcomes. (Online data supplement Table 1). 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 (Online data supplement Table 2)

Again, as for all-cause death, ACEI, ARB or MRA discontinuations were all associated with a higher risk also of CV death (online data supplement Table 3). In a sensitivity univariable analysis, ACEI, ARB or MRA discontinuations were found associated with CV death across the ejection fraction strata (i.e. EF <40, 40-50, >50 %: data not shown)

Finally, three multivariable mediation analyses (for ACEi, or ARB, or MRA discontinuation, respectively) were performed. Hyperkalaemia (>5.5 mmol/L) was associated with mortality and CV 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 CV death) (online data supplement Table 4).

Discussion

In this contemporary European out-patient HF cohort, with a high rate of patients treated with RAASi compared to other HF populations, the prevalence of hyperkalemia was high (16.6%), while the 1-year outcome was poor (overall and CV 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 CV death was observed over one-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 CV death, independent from serum potassium at baseline and, importantly, hyperkalaemia was no longer associated with the clinical outcomes. Moreover, in multivariable analyses, hyperkalaemia at baseline was found to be associated with MRA non-prescription at baseline and with its subsequent discontinuation. Additional mediation analyses showed that hyperkalaemia above 5.5 mmol/L was associated with mortality and CV 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 hyperkalaemia is more important through MRA discontinuation than through ACEi/ARB discontinuation.

Altogether, these data provide insights into the interplay between hyperkalaemia, 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 (hyperkalaemia, 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 heart failure hospitalisation (17). Altogether, these data confirm that hyperkalaemia 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 MRA (3, 26) or to discontinue them in presence of hyperkalaemia (8, 27). In other words, beyond its proarrhythmic properties, hyperkalaemia 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-HF-LT Registry suggests that hyperkalaemia is harmful because it causes RAASi discontinuation and a similar study from the SwedeHF registry suggests that hyperkalaemia is harmful because it causes RAASi avoidance and discontinuation(29). Together with a previous analysis from BIOSTAT suggesting that hyperkalaemia 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 hyperkalaemia (28). Whether the vicious circle surrounding hyperkalaemia, 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 hyperkalaemia warrants prospective CV 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 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 death and CV death across the ejection fraction strata (i.e. EF <40, 40-50, >50 %). Fourth, sacubutril/valsartan was not considered, not being approved at the time of data collection, while its use may be associated with less frequent hyperkalaemia 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 2013-2016, 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).

In conclusion, 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), hyperkalaemia was no longer associated with increased risk, suggesting that hyperkalaemia 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. Hyperkalaemia, 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.

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Conflict of interest

Dr. Anker reports grants and personal fees from Vifor Int, personal fees from Bayer, Boehringer Ingelheim, Novartis, Servier, grants and personal fees from Abbott Vascular, personal fees from Impulse Dynamics, SJM, outside the submitted work;

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Figures legends

Figure 1: Multivariable analysis for clinical predictors of low dosage of MRAs at baseline, considering potassium at baseline

Figure 2: Multivariable analysis for treatment discontinuation of MRA during a one-year follow-up, considering potassium at baseline

Figure 3 A: Relationship between baseline serum potassium and 1-year all-cause death - Natural cubic spline without adjustment

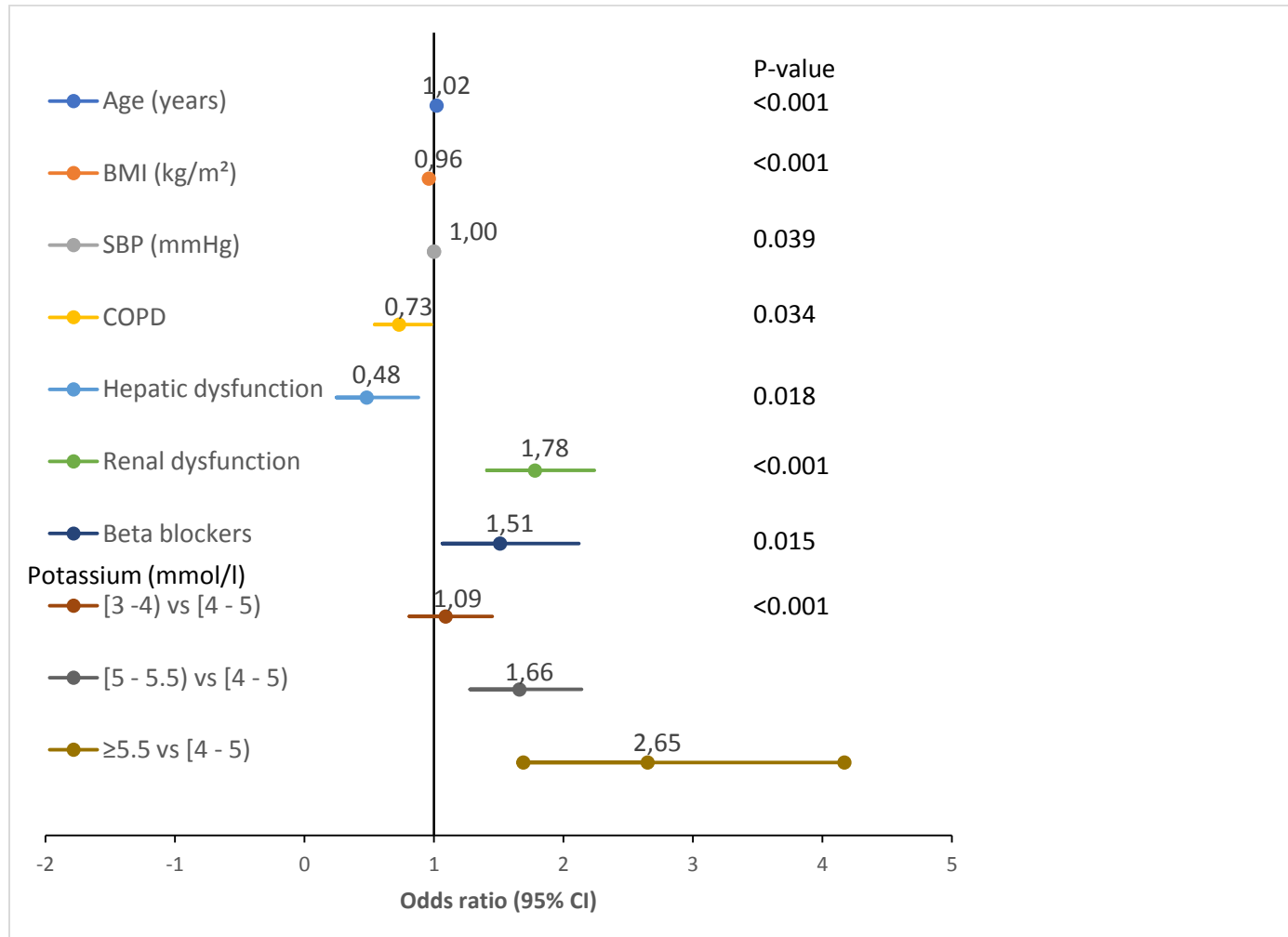
Figure 3 B: Relationship between baseline serum potassium and 1-year CV death - Natural cubic spline without adjustment

Figure 4: Baseline factors associated with all deaths in multivariable analysis considering RAASi prescription

Figure 5: Baseline factors associated with all deaths in multivariable analysis considering RAASi discontinuation during one-year follow-up

Figure 1

Multivariable analysis for clinical predictors of low dosage of MRAs at baseline



Notes:

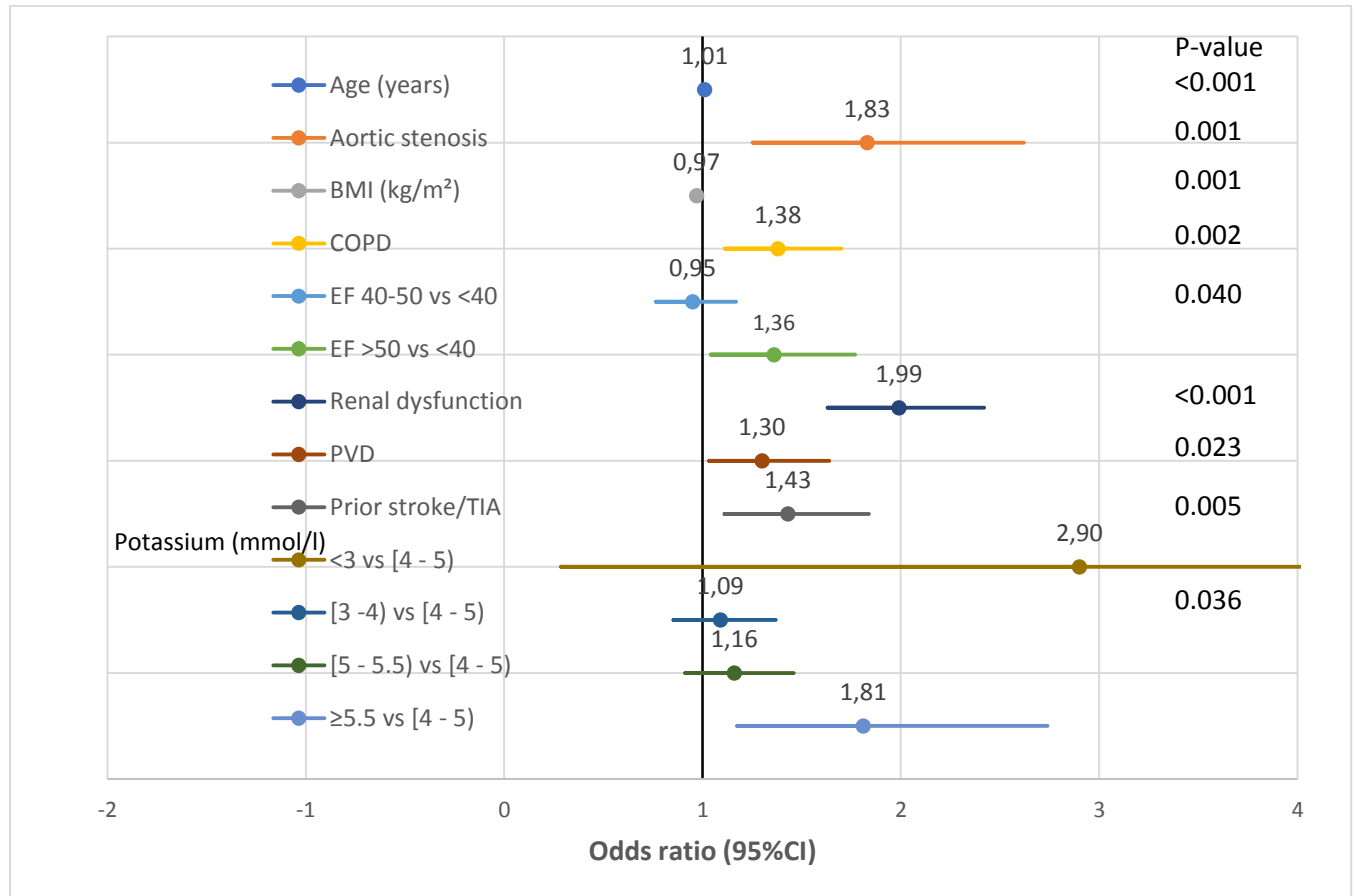
Number of patients with complete data and included in the analysis: 5188 of a total of 5253.

MRA= Mineralocorticoid receptor antagonists; CI= Confidence Interval; BMI= Body Mass Index; SBP= Systolic Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; vs= versus.

Logistic regression with reference $\geq 50\%$ target dose.

Figure 2

Multivariable analysis for treatment discontinuation of MRA during a one-year follow-up



Notes: Number of patients with complete data and included in the analysis: 4408/4748. CI= Confidence Interval; MRA= Mineralocorticoid receptor antagonists; BMI= Body Mass Index; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; PVD= Peripheral Vascular Disease; TIA= Transient Ischemic Attack; vs= versus.

Figure 3 A

Relationship between baseline serum potassium and 1-year all-cause death - Natural cubic spline without adjustment

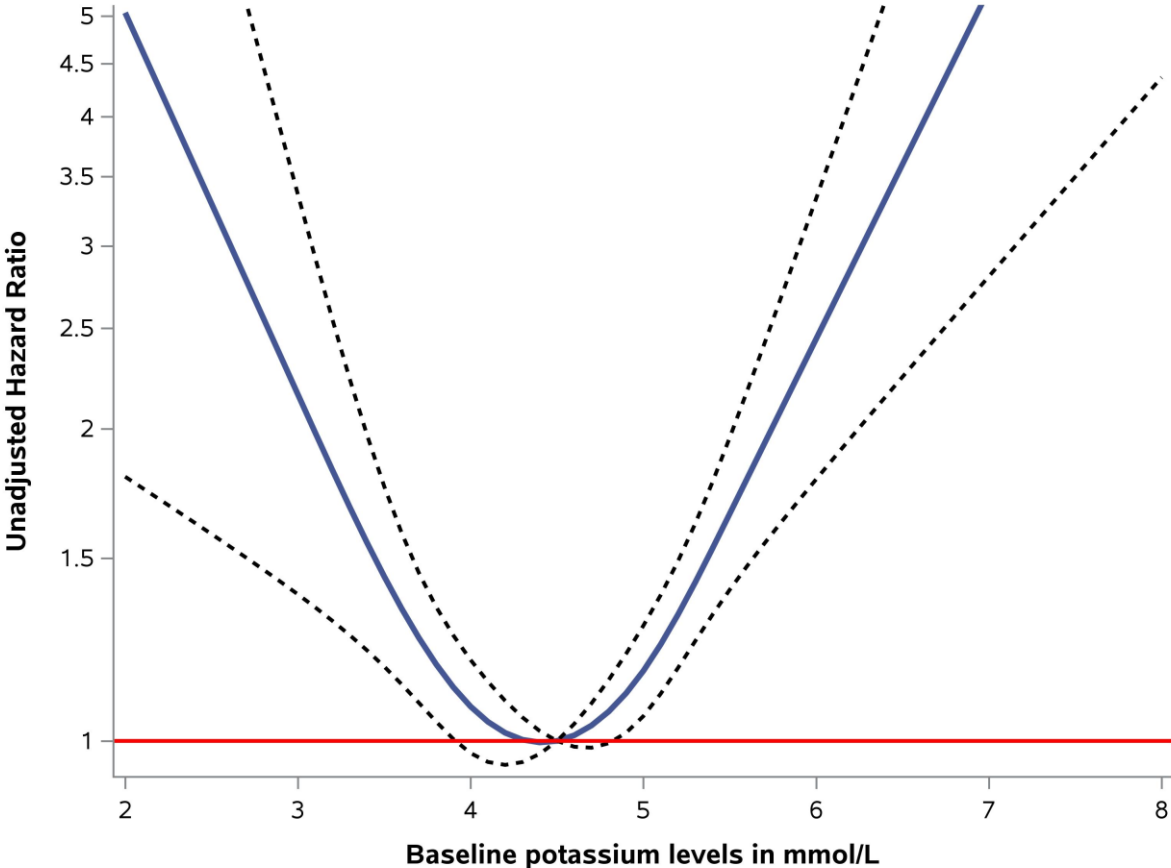


Figure 3 B

Relationship between baseline serum potassium and 1-year CV death - Natural cubic spline without adjustment

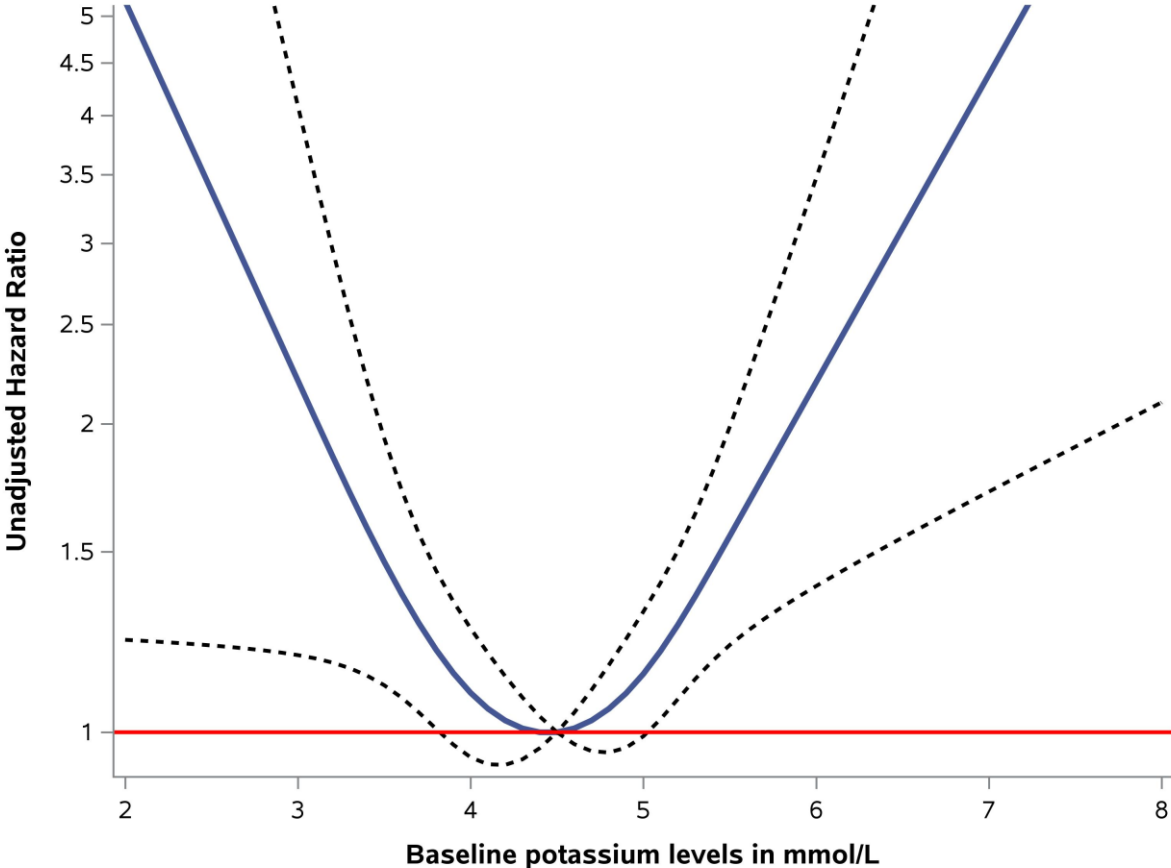
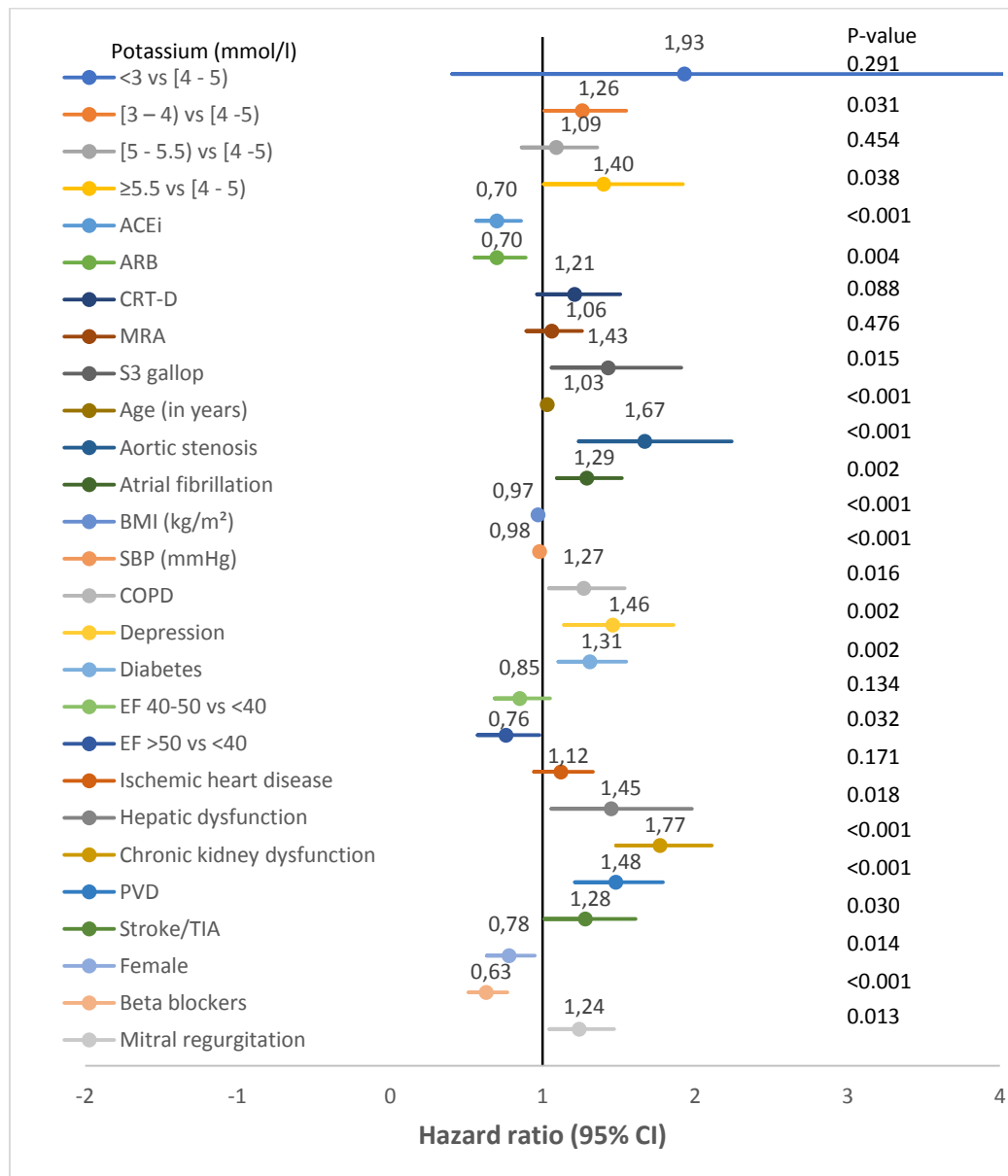


Figure 4

Baseline factors associated with all-cause death in multivariable analysis considering RAASi prescription at the baseline



Notes:

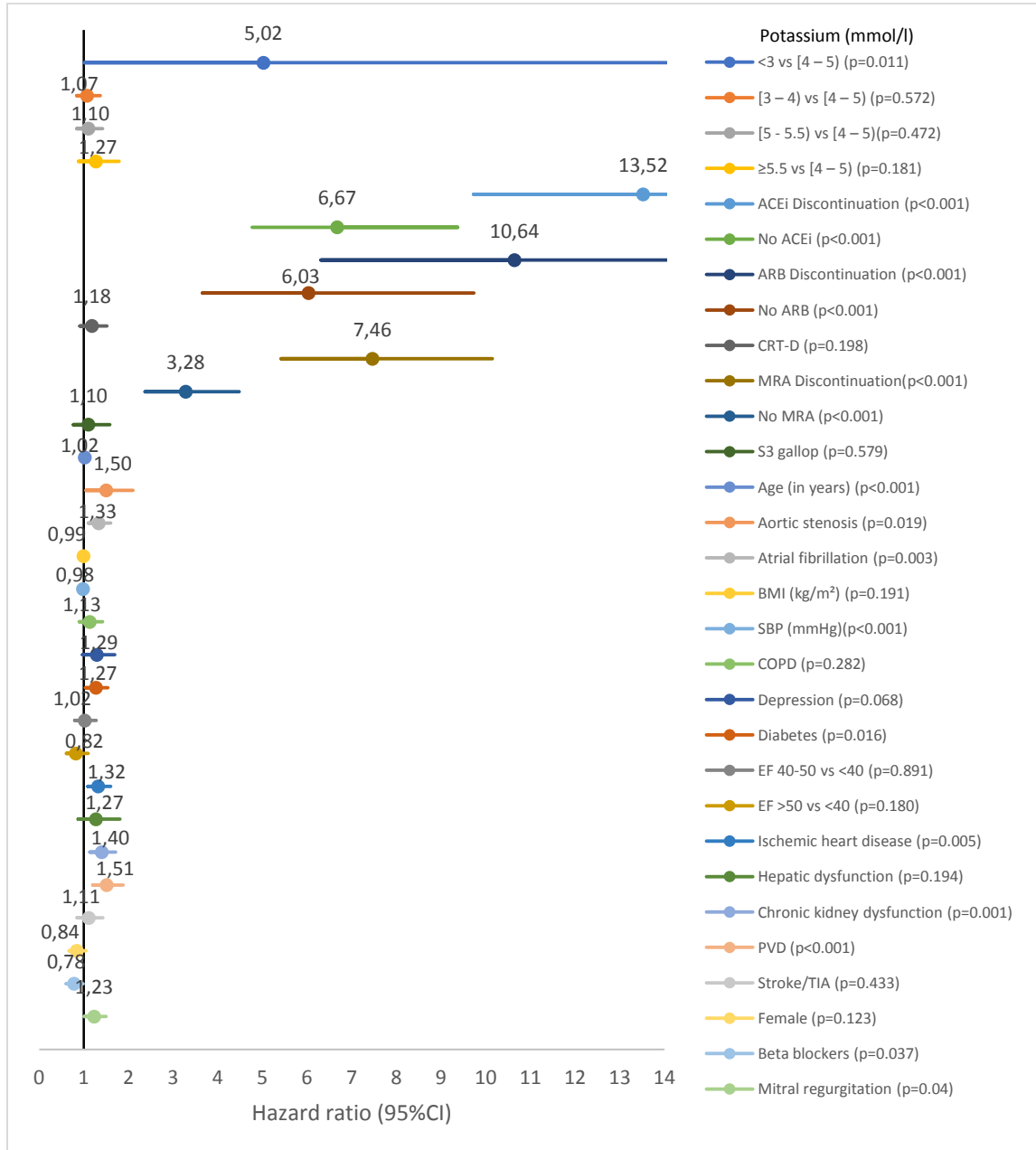
Number of patients with complete data and included in the analysis: 8173/9222.

RAASi= Renin-Angiotensin-Aldosterone System inhibitors; CI= Confidence Interval; ACEi=

Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; MRA= Mineralocorticoid receptor antagonists; CRT-D= Cardiac Resynchronization Therapy with defibrillator; BMI= Body Mass Index; SBP= Systolic Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; PVD= Peripheral Vascular Disease; TIA= Transient Ischemic Attack; vs= versus.

Figure 5

Baseline factors associated with all-cause death in multivariable analysis considering RAASi discontinuation during one-year follow-up



Notes:

Number of patients with complete data and included in the analysis: 7413/9222. RAASi= Renin-Angiotensin-Aldosterone System inhibitors; CI= Confidence Interval; ACEi= Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; CRT-D= Cardiac Resynchronization Therapy with defibrillator; MRA= Mineralocorticoid receptor

antagonists; BMI= Body Mass Index; SBP= Systolic Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; PVD= Peripheral Vascular Disease; TIA= Transient Ischemic Attack; vs= versus.

Variables are the same as in the previous model but instead of RAASi treatment at baseline, RAASi treatment correspond to RAASi treatment during the 1-year follow-up with for each treatment, 3 possibilities: discontinuation – no treatment at baseline – no discontinuation with No discontinuation as reference).

Table 1: Patient baseline characteristics and RAASi maintenance after one year

Variable	Modality	Total (N=9222)					[5 - 5.5	≥5.5	P-value
			<3 mmol/L (N=14, 0.2%)	[3 - 4 mmol/L) (N=1431, 15.5%)	[4 -5 mmol/L) (N=6249, 67.8%)	mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)		
Age, 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		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, (%)	<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%)		

Variable	Modality	Total (N=9222)	<3 mmol/L	[3 - 4 mmol/L)	[4 -5 mmol/L)	[5 - 5.5	≥5.5	P-value
			(N=14, 0.2%)	(N=1431, 15.5%)	(N=6249, 67.8%)	mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)	
	>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, (%)	NYHA 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
	NYHA 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%)	
	NYHA 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%)	
	NYHA 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, (%)		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, (%)		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

Variable	Modality	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	≥5.5	P-value
						mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)	
Primary Etiology, (%)	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%)	
	Ischemic 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	3545/9221 (38.4%)	8/14 (57.1%)	604/1430 (42.2%)	2350/6249 (37.6%)	448/1202 (37.3%)	135/326 (41.4%)	

Variable	Modality	Total (N=9222)	<3 mmol/L	[3 - 4 mmol/L)	[4 -5 mmol/L)	[5 - 5.5	≥5.5	P-value
			(N=14, 0.2%)	(N=1431, 15.5%)	(N=6249, 67.8%)	mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)	
Stroke/TIA, (%)		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, (%)		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, (%)		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, (%)		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, (%)		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, (%)		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, (%)		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

Variable	Modality	Total (N=9222)	<3 mmol/L	[3 - 4 mmol/L)	[4 -5 mmol/L)	[5 - 5.5	≥5.5	P-value
			(N=14, 0.2%)	(N=1431, 15.5%)	(N=6249, 67.8%)	mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)	
eGFR (ml/min/1.73m ²)		62.9	64.8	65.0	64.6	55.5	43.6	<0.001
Median [Q1; Q3]		[46.6; 79.9]	[49.3; 77.6]	[49.5; 81.2]	[48.6; 81.5]	[41.0; 73.0]	[29.9; 61.4]	
eGFR (ml/min/1.73m ²) in class	<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, (%)		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, (%)		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, (%)		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

Variable	Modality	Total (N=9222)	<3 mmol/L	[3 - 4 mmol/L)	[4 -5 mmol/L)	[5 - 5.5	≥5.5	P-value
			(N=14, 0.2%)	(N=1431, 15.5%)	(N=6249, 67.8%)	mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)	
Betablockers, (%)		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 (%)		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, (%)		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, (%)		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, (%)		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, (%)		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, (%)		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

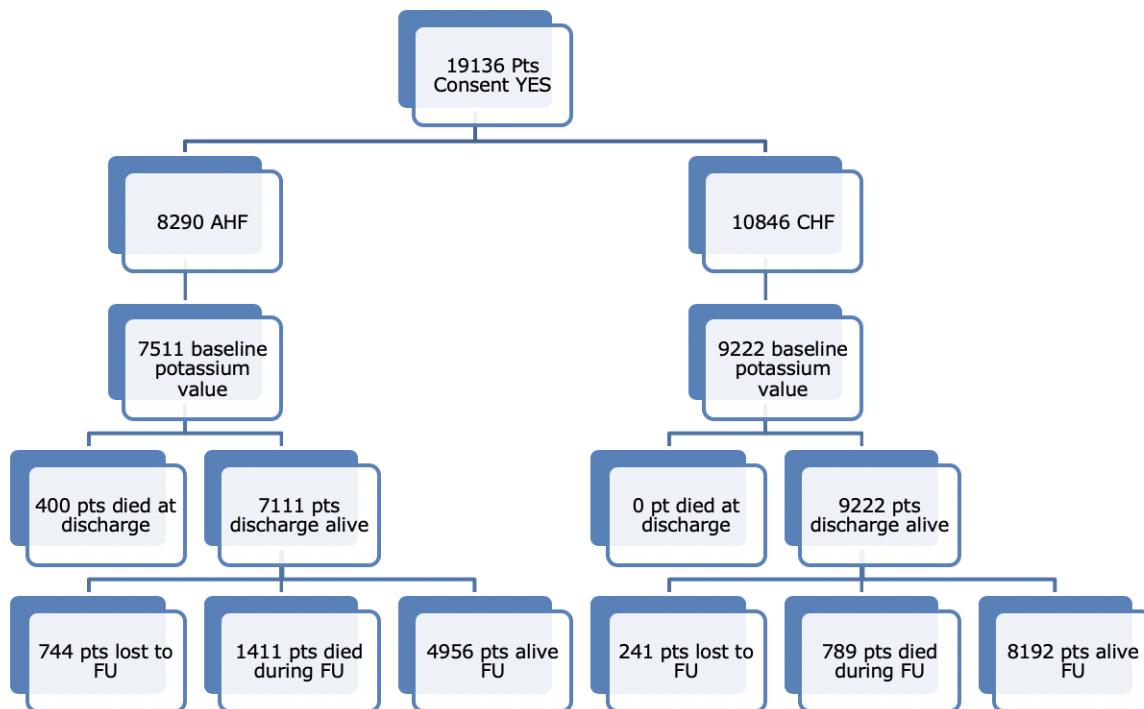
Variable	Modality	Total (N=9222)	<3 mmol/L (N=14, 0.2%)	[3 - 4 mmol/L) (N=1431, 15.5%)	[4 -5 mmol/L) (N=6249, 67.8%)	[5 - 5.5	≥5.5	P-value
						mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)	
ACEi target dose, (%)	< 50% max dosage	2195/5743 (38.2%)	3/4 (75.0%)	338/827 (40.9%)	1483/3937 (37.7%)	296/782 (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, (%)	< 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, (%)	< 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%)	
ACE/ARB Discontinuation, (%)		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

Variable	Modality	Total (N=9222)	<3 mmol/L	[3 - 4 mmol/L)	[4 -5 mmol/L)	[5 - 5.5	≥5.5	P-value
			(N=14, 0.2%)	(N=1431, 15.5%)	(N=6249, 67.8%)	mmol/L) (N=1202, 13.0%)	mmol/L (N=326, 3.5%)	
ACE Discontinuation, (%)		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, (%)		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
BB Discontinuation, (%)		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, (%)		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

RAASi= Renin-Angiotensin-Aldosterone System inhibitors; SBP= Systolic Blood Pressure; HR= Heart Rate; NYHA= New York Heart Association; TIA= Transient Ischemic Attack; ICD= Implantable Cardioverter Defibrillator; CRT-P/D= Cardiac Resynchronization Therapy with or without defibrillator; eGFR= estimated Glomerular Filtration Rate; ACEi= Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; MRA= Mineralocorticoid receptor antagonists; BB= Beta Blocker.

Supplementary figure 1: Heart Failure Long-Term Registry flow-diagram

HF-LT 1-Year Follow-up – Flow diagram



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Supplementary Table 1

Factors associated with cardiovascular deaths in multivariable analysis considering RAASi prescription at baseline

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Potassium (in mmol/L) at baseline	<3 vs [4 – 5)	2.92 (0.66;12.82)	0.156
	[3 – 4) vs [4 – 5)	1.19 (0.89;1.59)	0.236
	[5 - 5.5) vs [4 – 5)	0.98 (0.71;1.34)	0.882
	≥5.5 vs [4 – 5)	1.08 (0.68;1.74)	0.735
ACEi at baseline	Yes vs No	0.64 (0.49;0.84)	0.001
ARB at baseline	Yes vs No	0.63 (0.45;0.87)	0.006
CRT-D	Yes vs No	1.42 (1.06;1.90)	0.017
MRA at baseline	Yes vs No	1.24 (0.98;1.58)	0.077
S3 gallop	Yes vs No	1.65 (1.12;2.44)	0.011

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Age (in years)		1.03 (1.02;1.04)	<0.001
Aortic stenosis	Yes vs No	1.92 (1.29;2.85)	0.001
Atrial fibrillation	Yes vs No	1.35 (1.08;1.69)	0.009
BMI at baseline		0.96 (0.94;0.99)	0.002
Systolic BP (in mmHg) at baseline		0.98 (0.97;0.98)	<0.001
COPD	Yes vs No	1.28 (0.98;1.67)	0.073
Depression	Yes vs No	1.68 (1.22;2.31)	0.001
Diabetes class	Yes vs No	1.44 (1.14;1.82)	0.002
EF (%)	40-50 vs <40	0.94 (0.70;1.25)	0.651
	>50 vs <40	0.75 (0.51;1.09)	0.129

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
	Ischemic heart disease		
Primary Etiology	vs Non-ischemic heart disease	1.15 (0.91;1.45)	0.249
Hepatic dysfunction	Yes vs No	1.42 (0.92;2.18)	0.110
Chronic kidney dysfunction	Yes vs No	1.82 (1.44;2.32)	<0.001
Peripheral vascular disease	Yes vs No	1.68 (1.29;2.18)	<0.001
Stroke/TIA	Yes vs No	1.36 (1.00;1.84)	0.050
Sex	Female vs Male	0.80 (0.61;1.05)	0.111
Beta blockers (Prior)	Yes vs No	0.61 (0.46;0.80)	<0.001
Mitral regurgitation	Yes vs No	1.16 (0.91;1.47)	0.232

Notes:

Number of patients in the analysis: 8173/9222. RAASi= Renin-Angiotensin-Aldosterone System inhibitors; HR=Hazard Ratio; CI= Confidence Interval; ACEi= Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; CRT-D= Cardiac Resynchronization Therapy with defibrillator; MRA= Mineralocorticoid receptor antagonists; BMI= Body Mass Index; BP= Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; TIA= Transient Ischemic Attack; vs= versus.

Supplementary Table 2

Factors associated with cardiovascular deaths in multivariable analysis considering RAASi target doses prescription at baseline

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Potassium (in mmol/L) at baseline	<3 vs [4 – 5)	2.80 (0.63;12.39)	0.176
	[3 – 4) vs [4 – 5)	1.19 (0.88;1.61)	0.267
	[5 - 5.5) vs [4 – 5)	1.01 (0.72;1.41)	0.959
	≥5.5 vs [4 – 5)	0.97 (0.58;1.63)	0.908
Target dose ACEi	No ACE vs Inferior target dose	1.45 (1.06;1.97)	0.020
	Superior target dose vs Inferior target dose	0.75 (0.55;1.03)	0.077
Target dose ARB	No ARB vs Inferior target dose	1.59 (1.03;2.45)	0.037

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
	Superior target dose vs Inferior target dose	0.96 (0.57;1.62)	0.883
CRT-D	Yes vs No	1.42 (1.05;1.92)	0.025
Target dose MRA	No MRA vs Inferior target dose	1.00 (0.60;1.66)	0.995
	Superior target dose vs Inferior target dose	1.30 (0.79;2.14)	0.292
S3 gallop	Yes vs No	1.75 (1.17;2.63)	0.007
Age (in years)		1.03 (1.02;1.04)	<0.001
Aortic stenosis	Yes vs No	1.99 (1.30;3.03)	0.001
Atrial fibrillation	Yes vs No	1.30 (1.03;1.65)	0.027
BMI at baseline		0.96 (0.93;0.98)	0.001

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Systolic BP (in mmHg) at baseline		0.97 (0.97;0.98)	<0.001
COPD	Yes vs No	1.19 (0.89;1.58)	0.234
Depression	Yes vs No	1.70 (1.22;2.37)	0.002
Diabetes	Yes vs No	1.50 (1.17;1.92)	0.001
EF (%)	40-50 vs <40	0.97 (0.72;1.32)	0.861
	>50 vs <40	0.79 (0.53;1.18)	0.256
Primary Etiology	Ischemic heart disease		
	vs Non-ischemic heart disease	1.20 (0.94;1.54)	0.145
Hepatic dysfunction	Yes vs No	1.45 (0.94;2.26)	0.096
Chronic kidney dysfunction	Yes vs No	1.78 (1.38;2.29)	<0.001
Peripheral vascular disease	Yes vs No	1.66 (1.26;2.18)	<0.001

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Stroke/TIA	Yes vs No	1.25 (0.90;1.74)	0.187
Sex	Female vs Male	0.71 (0.53;0.95)	0.021
Beta blockers (Prior)	Yes vs No	0.62 (0.47;0.83)	0.001
Mitral regurgitation	Yes vs No	1.08 (0.84;1.40)	0.544

Notes:

Number of patients in the analysis: 7514/9222. RAASi= Renin-Angiotensin-Aldosterone System inhibitors; HR=Hazard Ratio; CI= Confidence Interval; ACEi= Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; CRT-D= Cardiac Resynchronization Therapy with defibrillator; MRA= Mineralocorticoid receptor antagonists; BMI= Body Mass Index; BP= Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; TIA= Transient Ischemic Attack; vs= versus.

Supplementary Table 3

Factors associated with cardiovascular deaths in multivariable analysis considering RAASi discontinuation during one-year follow-up

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Potassium (in mmol/L) at baseline	<3 vs [4 – 5)	4.32 (0.97;19.19)	0.054
	[3 – 4) vs [4 – 5)	1.04 (0.75;1.43)	0.817
	[5 - 5.5) vs [4 – 5)	1.03 (0.73;1.46)	0.852
	≥5.5 vs [4 – 5)	0.91 (0.55;1.51)	0.725
ACEi	Discontinuation vs No Discontinuation	12.17 (8.06;18.37)	<0.001
	No ACEi vs No Discontinuation	6.95 (4.51;10.72)	<0.001
ARB	Discontinuation vs No Discontinuation	8.13 (4.35;15.22)	<0.001

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
	No ARB vs No Discontinuation	5.44 (3.00;9.88)	<0.001
CRT-D	Yes vs No	1.43 (1.05;1.96)	0.023
	Discontinuation vs No Discontinuation	6.44 (4.45;9.33)	<0.001
MRA	No MRA vs No Discontinuation	2.51 (1.71;3.68)	<0.001
S3 gallop	Yes vs No	1.54 (1.02;2.32)	0.040
Age (in years)		1.02 (1.01;1.03)	<0.001
Aortic stenosis	Yes vs No	1.51 (0.96;2.37)	0.072
Atrial fibrillation	Yes vs No	1.41 (1.11;1.80)	0.006
BMI at baseline		0.98 (0.95;1.00)	0.100

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Systolic BP (in mmHg) at baseline		0.98 (0.97;0.99)	<0.001
COPD	Yes vs No	1.21 (0.91;1.62)	0.191
Depression	Yes vs No	1.39 (0.99;1.96)	0.059
Diabetes	Yes vs No	1.32 (1.02;1.70)	0.036
EF (%)	40-50 vs <40	0.95 (0.70;1.30)	0.756
	>50 vs <40	0.68 (0.45;1.04)	0.073
Ischemic heart disease			
Primary Etiology	vs	1.34 (1.04;1.73)	0.023
	Non-ischemic heart disease		
Hepatic dysfunction	Yes vs No	1.156 (0.718;1.860)	0.551)

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Chronic kidney dysfunction	Yes vs No	1.380 (1.062;1.793)	0.016
Peripheral vascular disease	Yes vs No	1.755 (1.327;2.322)	<0.001
Stroke/TIA	Yes vs No	1.211 (0.871;1.684)	0.256
Sex	Female vs Male	0.852 (0.634;1.145)	0.288
Beta blockers (Prior)	Yes vs No	0.622 (0.462;0.837)	0.002
Mitral regurgitation	Yes vs No	1.158 (0.891;1.506)	0.273

Notes: Number of patients in the analysis: 7413/9222. RAASi= Renin-Angiotensin-Aldosterone System inhibitors; HR=Hazard Ratio; CI= Confidence Interval; ACEi= Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; CRT-D= Cardiac Resynchronization Therapy with defibrillator; MRA= Mineralocorticoid receptor antagonists; BMI= Body Mass Index; BP= Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; TIA= Transient Ischemic Attack; vs= versus.

Supplementary Table 4: three mediation analyses (for ACEi, or ARB, or MRA discontinuation, respectively), using multivariable* Cox models for the outcomes: all-cause death and cardiovascular death

	All-cause death				Cardiovascular death			
	Type 3 tests		Parameter estimate		Type 3		Parameter estimate	
	Potassium (in mmol/L) at baseline natural direct effect	Potassium level (in mmol/L) at baseline (natural indirect effect via a drug discontinuation mediation)	Potassium (in mmol/L) at baseline natural direct effect	Potassium level (in mmol/L) at baseline (natural indirect effect via a drug discontinuation mediation)	Potassium (in mmol/L) at baseline natural direct effect	Potassium level (in mmol/L) at baseline (natural indirect effect via a drug discontinuation mediation)	Potassium (in mmol/L) at baseline natural direct effect	Potassium level (in mmol/L) at baseline (natural indirect effect via a drug discontinuation mediation)
Models considering ACEI discontinuation	P<0.001	P<0.001	[5; 5.5) vs. [4; 5): HR (CI) 1.03 [0.92; 1.15] P= 0.636	[5; 5.5) vs. [4; 5): 1.03 [0.91; 1.16] P=0.658	<0.044	0.009	[5; 5.5) vs. [4; 5): 0.89 [0.76; 1.05] P= 0.171	[5; 5.5) vs. [4; 5): 1.03 [0.88; 1.21] P=0.703
			>5.5 vs. [4; 5) 1.20 [0.99; 1.44] P= 0.057	>5.5 vs. [4; 5) 1.12 [1.00; 1.26] P= 0.059			>5.5 vs. [4; 5) 0.97 [0.74; 1.27] P=0.814	>5.5 vs. [4; 5) 1.12 [0.96; 1.32] P= 0.151
Models considering ARB discontinuation	P<0.001	P=0.480	[5; 5.5) vs. [4; 5): 1.08 [0.98; 1.20] P= 0.136	[5; 5.5) vs. [4; 5): 1.00 [0.90; 1.12] P=0.953	<0.001	0.734	[5; 5.5) vs. [4; 5): 1.04 [0.90; 1.20] P=0.623	[5; 5.5) vs. [4; 5): 1.00[0.86; 1.17] P=0.974
			>5.5 vs. [4; 5) 1.36 [1.15; 1.60] P<0.001	>5.5 vs. [4; 5) 1.09 [0.97; 1.22] P= 0.136			>5.5 vs. [4; 5) 1.03 [0.79; 1.34] P=0.827	>5.5 vs. [4; 5) 1.09 [0.93; 1.27] P= 0.285
Models considering	P<0.001	P<0.001	[5; 5.5) vs. [4; 5): 1.09 [0.98; 1.22]	[5; 5.5) vs. [4; 5): 1.03 [0.92; 1.16]	0.008	<0.001	[5; 5.5) vs. [4; 5): 0.99 [0.85; 1.15]	[5; 5.5) vs. [4; 5): 1.03 [0.88; 1.21]

MRA discontinuation			P=0.109	P=0.609			P=0.893	P=0.689
			>5.5 vs. [4; 5) 1.21 [1.03; 1.43] P= 0.024	>5.5 vs. [4; 5) 1.18 [1.04; 1.32] P= 0.007			>5.5 vs. [4; 5) 0.85 [0.66; 1.10] P= 0.213	>5.5 vs. [4; 5) 1.15 [0.98; 1.36] P= 0.080

*Age, aortic stenosis, systolic blood pressure at baseline, ejection fraction, primary etiology, chronic kidney dysfunction, peripheral vascular disease, prior beta blockers as covariates in each of the multivariable models