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Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality

Running Title: *Núñez and Bayés-Genís et al.; Potassium Dynamics and Mortality in Heart Failure*

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Abstract

Background—The prognostic value of long-term potassium monitoring and dynamics in heart failure (HF) has not been characterized completely. We sought to determine the association between serum potassium values collected at follow-up with all-cause mortality in a prospective and consecutive cohort of patients discharged from a previous acute HF admission.

Methods—Serum potassium was measured at every physician-patient encounter, including hospital admissions and ambulatory settings. The multivariable-adjusted association of serum potassium with mortality was assessed using comprehensive state-of-the-art regression methods that can accommodate time-dependent exposure modeling.

Results—The study sample included 2164 patients with a total of 16,116 potassium observations. Mean potassium at discharge was 4.3±0.48 mEq/L. Hypokalemia (<3.5 mEq/L), normokalemia (3.5 to 5.0 mEq/L), and hyperkalemia (>5 mEq/L) were observed at the index admission in 77 (3.6%), 1965 (90.8%), and 122 (5.6%) patients, respectively. At a median follow-up of 2.8 years (range=0.03-12.8 years), 1090 patients died (50.4%). On a continuous scale, the multivariable-adjusted association of potassium values and mortality revealed a non-linear association (U-shaped) with higher risk at both ends of its distribution (omnibus p-value=0.001). Likewise, the adjusted hazard ratios (HRs) for hypokalemia and hyperkalemia – normokalemia as reference - were 2.35 (95% confidence interval [CI]:1.40-3.93; p=0.001) and 1.55 (95% CI:1.11-2.16; p=0.011), respectively (omnibus p-value=0.0003). Furthermore, dynamic changes in potassium were independently associated with substantial differences in mortality risk. Potassium normalization was independently associated with lower mortality risk (p=0.001).

Conclusions—Either modeled continuously or categorically, serum potassium levels during long-term monitoring were independently associated with mortality in patients with HF. Likewise, persistence of abnormal potassium levels was linked to higher risk of death compared with patients who maintained or returned to normal values.

Key Words: potassium; mortality; heart failure; acute heart failure, hyperkalemia, hypokalemia, longitudinal cohort study

Clinical Perspective

What is new?

- This study evaluated the prognostic implications of long-term longitudinal monitoring and dynamics of serum potassium in a prospective and consecutive cohort of patients following a hospitalization for acute heart failure.
- On a continuous scale, the follow-up trajectory of serum potassium levels independently predicted mortality through a U-shaped association, with higher risk at both ends of the distribution, and the same was true for potassium categories.
- Potassium changes were associated with substantial differences in mortality risk; accordingly, transitioning from hypo/hyperkalemia to normokalemia was independently associated with lower risk.
- Potassium normalization from hypo/hyperkalemia was the most prevalent change documented in our cohort.

What are the clinical implications?

- These findings support the need for close monitoring of serum potassium after an episode of acute decompensated heart failure.
- In addition, they suggest that maintaining serum potassium levels within normal range may be considered a therapeutic target.

The risk of mortality after hospitalization for acute heart failure (HF) remains high.[1-3] The most recent European data (ESC-HF pilot study) show that patients hospitalized with HF had 12-month all-cause mortality rates of 17%.[4] Common risk scores only include a one-time (or baseline) assessment, neglecting important changes in risk over time,[5,6] which are especially common after an episode of acutely decompensated HF.[1-6]

Serum potassium disturbances are frequent in patients with HF and, to some extent, associated with common comorbidities and usage of treatments such as diuretic therapy, potassium supplements, and renin-angiotensin-aldosterone system (RAAS) blockers, including the combination of angiotensin II receptor blockers (ARB) and neprilysin inhibitors.[7] The prognostic implications of a single measurement of serum potassium in patients with chronic and acute HF have been evaluated in previous studies with heterogeneous findings.[8-10] However, to the best of our knowledge, no studies have specifically addressed the long-term prognostic significance of serum potassium monitoring and dynamics in a truly longitudinal setting. Accordingly, this study was designed to fill this gap in knowledge by evaluating an unselected cohort of patients discharged after an episode of acute HF.

Methods

Study group and protocol

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

We analyzed 2642 patients consecutively discharged after admission for acutely decompensated HF between January 1, 2008, and July 1, 2016 from a single center. Diagnosis of HF decompensation was defined as the rapid onset of symptoms and signs secondary to

abnormal cardiac function and the presence of objective evidence of structural or functional abnormality of heart at rest (such as cardiomegaly, third heart sound, cardiac murmur, abnormality of the echocardiogram or raised natriuretic peptides). The current study was restricted to patients discharged alive from the hospital and followed long-term in an outpatient HF clinic. After excluding 234 in-hospital deaths during index admission and 244 patients with ambulatory follow-up elsewhere, the final study sample included 2164 patients (Supplementary file 1). Data were collected on patient demographics, vital signs and physical examination at presentation and discharge, medical history, laboratory tests, 12-lead electrocardiogram, echocardiogram, and medications during the index hospital stay and in outpatient visits or subsequent hospitalizations for HF decompensation.

Left ventricular ejection fraction (LVEF) was assessed by echocardiography (Agilent Sonos 5500-Philips and ie33-Philips) during the index hospitalization in all patients. Treatment with angiotensin converting enzyme inhibitors (ACEI), ARB, beta-blockers, mineralocorticoid receptor antagonists (MRA), diuretics, anticoagulants, and other therapeutic strategies were individualized following established guidelines during the study period.

Potassium measurements

Serum potassium was measured by indirect potentiometry using an ion-selective electrode. The first measurement was assessed at discharge with further measurements taken during routine clinical visits and subsequent hospitalizations. Using standard cut-off points, three groups were created (K-3C): hypokalemia (<3.5 mEq/L), normokalemia (3.5 to 5.0 mEq/L), and hyperkalemia (>5 mEq/L). In addition, a 7-category variable ($K\text{-}3C_{ch}$) was created to include the following changes in K-3C among two consecutive observations of the same patient (i.e., using the previous observation as reference): 1) normokalemia-to-normokalemia, 2) normokalemia-to-

hypokalemia, 3) normokalemia-to-hyperkalemia, 4) hypokalemia-to-hypokalemia, 5) hypokalemia-to-normokalemia/hyperkalemia, 6) hyperkalemia-to-hyperkalemia, and 7) hyperkalemia-to-normokalemia/hypokalemia.

Post-discharge follow-up

Patients who died during index admission and those with no further follow-up were excluded from this analysis. For the remaining cohort, patient follow-up continued until death or cardiac transplant. After the index hospitalization, potassium measurements were made under the clinical settings of a new hospitalization (34.7%) or as an outpatient visit (65.3%). The number of visits with a serum potassium measurement, including index admission, was 16,116, and ranged from 2 to 78, with a median of 5. The chronological distribution of the number of measurements was: 14,088 (87.4%) during the first year; 15,495 (96.1%) during the first two years; 15,877 (98.5%) by three years; and 16,077 (99.8%) by five years.

Survival outcome

All-cause mortality was selected as the main endpoint. Secondary endpoints included cardiovascular, HF-related, and sudden death. Cause of death was categorized following the classification used by the American Heart Association. Deaths of cardiovascular etiology included sudden death, progressive HF death, deaths attributable to other cardiovascular causes (such as myocardial infarction, stroke, etc.), and unknown cause of death. Sudden death was defined as the event that occurred unexpectedly in an otherwise stable patient, and progressive HF death when it occurred in the setting of progressive clinical deterioration of HF symptoms with no other apparent cause.[11] Information regarding patients' survival status was ascertained at each hospitalization, during office visits, or through a review of electronic medical records. Investigators in charge of endpoint adjudication were blinded to medical information, including

serum potassium status. This study conforms to the principles outlined in the Declaration of Helsinki and was approved by an institutional review committee.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]). Discrete variables are presented as percentages. Baseline characteristics among hypokalemia, normokalemia, and hyperkalemia were compared by ANOVA, Kruskall–Wallis, or chi-squared tests as appropriate.

Multilevel survival analysis.

Multilevel survival analysis was used to combine the longitudinal (repeated-measures) and survival (time-to-event endpoint) aspects of the data. We fit a two-level model with patient identification as random effects and the log (follow-up time) as a random coefficient. For the survival portion of the model, we used a Weibull distribution. The main exposures were: 1) potassium values (continuous), hereafter referred to as cumulative potassium ($K_{cumulative}$), to stress that is not a single measurement but the entire collection of potassium values per patient that are modeled, 2) K-3C categories, and 3) K-3C_{ch} as the temporal category changes in K-3C relative to the previous observation. Regression estimates are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

We selected explanatory variables for the multivariable regression model, with subject-matter knowledge as the main criterion. Starting with this initial (oversaturated) model, backward elimination was applied to exclude variables with $p \geq 0.1$. For our continuous exposure (i.e., $K_{cumulative}$), we determined its appropriate functional form using the multivariable fractional polynomial (FP) method.[12] A 4-df FP of (-2 -1) was the best transformation suggested, which relates the continuum of $K_{cumulative}$ to the risk of mortality through a U-shaped curve with higher

risk observed at both ends. Any decision about the use of random intercept, random coefficient, and the polynomial that best describes the functional form for $K_{cumulative}$ was based on likelihood ratio test comparisons. The type of distribution for the parametric survival function was determined with the AIC/BIC criteria. The same set of covariates was used for the $K_{cumulative}$, K-3C, and K-$3C_{ch}$ models: age (years), systolic blood pressure (mmHg), heart rate (bpm) at baseline, LVEF (<40%, 40-49%, and ≥50%) at baseline, anemia using Centers for Disease Control (CDC) criteria (0/1), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (0/1), lymphocyte count <1500 x 10^3 cells/mL (0/1), serum sodium ≤135 mEq/L (baseline), beta-blockers (0/1, baseline), logNT-proBNP (pg/mL), plasma antigen carbohydrate 125 (CA125) >35 U/mL (0/1), NYHA class (I, II, III/IV) at baseline, Charlson Comorbidity Index at baseline, use of potassium-modifying treatments (none, MRA, ACEI/ARB, and both) at baseline, and the log of follow-up time (years). All model estimates for all-cause mortality are presented in Supplementary file 2. A dynamic discrimination index (DDI) was estimated as a measure of model discrimination index in the setting of data with longitudinally-updated exposure-status.[13] The global DDI of the final model was 0.802, revealing an excellent performance.

Multistate analysis

Using Multistate Markov model (MSM) with continuous time,[14] we determined the instantaneous transition hazards (iTH) - and their respective 95% CI - among K-3C categories. Because the same patient can be in different states at follow-up, the summary data is presented as patient-visits (P-Vs). These transitions were adjusted by gender, eGFR-time-varying <60 mL/min/1.73 m2 (0/1), diabetes mellitus – time-varying (0/1), and the use of potassium-modifying treatments (none, MRA, ACEI/ARB, and both) at baseline. From all possible transitions, we focused on the ratio of the following two: iTHr1 = [hypokalemia-to-

normokalemia] / [normokalemia-to-hypokalemia] as surrogate of the relative frequency of becoming normokalemic (from a previous hypokalemic state) vs becoming hypokalemic from previous normokalemia; and iTHr2 = [hyperkalemia-to-normokalemia] / [normokalemia-to-hyperkalemia] as surrogate of the relative frequency of normalization from a previous hyperkalemic state vs becoming hyperkalemic from previous normokalemia.

We set a two-sided p-value of <0.05 as the threshold for significance. Within Stata 14.2 (Stata Statistical Software, Release 14 [2015]; StataCorp LP, College Station, TX, USA), the main longitudinal analysis was performed with "mestreg", a module that allows multilevel modeling to be combined with a parametric analysis of survival-time outcomes. For the estimation of DDI and the MSM longitudinal transitions analysis, we used the "JM"[13] and "msm"[14] R-packages, respectively [R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org.

Results

The study sample included 2164 patients (50.4% males) with a total of 16,116 potassium observations. The mean age was 73±11 years. Left ventricular systolic dysfunction (LVEF<40%) was present in 31.2% of the patients, mid-range ejection fraction (LVEF 40-49%) in 15.6%, and preserved ejection fraction (LVEF≥50%) in 53.2%. The index admission was the first admission ever for acutely decompensated HF in 38% of the patients. The mean discharge potassium level was 4.3±0.48 mEq/L. At the index hospitalization, hypokalemia, normokalemia, and hyperkalemia were observed in 77 (3.6%), 1965 (90.8%), and 122 (5.6%) patients, respectively. Table 1 shows the baseline characteristics of the studied population relative to these three strata.

Overall, hyperkalemia at baseline was more frequent in association with older age, diabetes, prior dyslipidemia, ischemic heart disease, worse NYHA class, greater comorbidity, lower systolic blood pressure, higher heart rate, greater renal dysfunction, other electrolytic disturbances, and less frequent treatment with ACEI/ARB and beta-blockers. On the other hand, hypokalemia was more frequent in association with HF with preserved ejection fraction (HFpEF), and in patients receiving more intensive depletive regimens.

During a median follow-up of 2.79 years (IQR 1.28, 4.91), 1090 patients died (50.4%), which is a mortality rate incidence of 15% person-years and a median survival of 4.96 years. Of these deaths, 781 (71.7%), 345 (31.7%), and 78 (7.2%) were cardiovascular in origin, HF-related, and sudden deaths, respectively.

Observed K-3C transitions (no adjusted)

Of a total of 16,116 observations (P-Vs), 14,292 (88.7%) 1,260 (7.8%), and 564 (3.5%) corresponded to normokalemia, hyperkalemia, and hypokalemia, respectively. An observation of normokalemia was followed by hypokalemia, normokalemia, and hyperkalemia on 132 (0.92%), 11,899 (83.3%), and 372 (2.6%) occasions. An observation of hypokalemia was followed by hypokalemia (no change), normokalemia, and hyperkalemia on 352 (62.4%), 135 (23.9%), and 8 (1.4%) occasions. An observation of hyperkalemia was followed by hypokalemia, normokalemia, and hyperkalemia (no change) on 3 (0.24%), 293 (23.3%), and 758 (60.2%) occasions.

Long-term potassium monitoring ($K_{cumulative}$)

Risk-gradient trajectory was independently associated with mortality through a U-shaped association (Figure 1). Values at both ends of $K_{cumulative}$ were indicative of higher mortality risk (overall p=0.001). Some snapshot comparisons at the lower side indicated that $K_{cumulative}$ values

of 2.5, 3.0, and 3.5 mEq/L equated with HRs of 7.09 (95% CI:2.31-21.78), 1.86 (95% CI:1.18-2.91), and 1.12 (95% CI:0.93-1.36), respectively. On the upper side, values of 5.0, 5.5, and 6.0 mEq/L were associated with HRs of 1.18 (95% CI:1.00-1.38), 1.39 (95% CI:1.05-1.84), and 1.67 (95% CI:1.12-2.496), respectively. Similarly, the adjusted-association between $K_{cumulative}$ with cardiovascular (Figure 2a) and HF-related mortality (Figure 2b) follows a similar non-linear relationship. For sudden death, however, the association is best described as positive, with higher risk along the continuum of $K_{cumulative}$ (Figure 2c).

Long-term potassium dynamics (K-3C and K-3C$_{ch}$)

Hypokalemia and hyperkalemia – with normokalemia as a reference – were independent predictors of mortality (Omnibus p-value=0.0003) with HRs of 2.35 (95% CI:1.40-3.93, p=0.001) and 1.55 (95% CI:1.11-2.16, p=0.011), respectively. Figure 3 depicts the adjusted survival probabilities for each of these categories. We found no significant interactions between hypokalemia and hyperkalemia among the most important clinical subgroups: age, gender, diabetes, ischemic etiology, renal dysfunction, and LVEF (Figure 4). Similarly, no significant interactions were found among baseline treatments (MRA and/or ACEI/ARB use) or potassium categories (hypokalemia and hyperkalemia, Figure 4).

The association of K-3C changes - from previous status – and mortality was determined by estimating and plotting the adjusted survival probabilities of 4 groups of interest: Group 1: persisting hypokalemic; Group 2: normalization from hypokalemia; Group 3: persisting hyperkalemic; and Group 4: normalization from hyperkalemia. Patients at lower risk during follow-up were those that remained within range of normokalemia (groups 2 and 4), whereas patients with persisting hypokalemia (group 1) or persisting hyperkalemia (group 3) had the worse prognosis (Figure 5).

Multistate analysis

The primary result from the multivariable-adjusted multistate analysis is presented in Supplementary Figure 3. Indeed, the instantaneous transition rate from hypokalemia-to-normokalemia is 38-fold the transition from normokalemia-to-hypokalemia; this means that it is 38-fold times more likely that a hypokalemic patient will become normokalemic than the opposite. Similarly, it is 12-fold more likely that a hyperkalemic patient will become normal than the opposite.

Discussion

To the best of our knowledge, this study is the first to evaluate the prognostic implications of the long-term longitudinal monitoring and dynamics of serum potassium in HF. An important finding was that the time-driven history of serum potassium exhibited adequate performance in predicting long-term all-cause mortality, either modeled as a continuous variable or categorized into hypokalemia, normokalemia, or hyperkalemia. This predictive ability remained after adjusting for a comprehensive set of longitudinal and baseline prognosticators. Furthermore, when modeled as a continuous covariable, the prognostic relationship between serum potassium and death exhibited a non-linear association, resembling a U-shaped curve with higher risk at both ends of the distribution. Notably, the association between potassium levels and mortality risk was confirmed for hypokalemia and hyperkalemia when potassium was categorized. When analyzing the associations between potassium dynamics and death, patients who persisted with hypokalemia or with hyperkalemia had significantly higher mortality risk, and the results were similar for cardiovascular and HF-related deaths and consistent in the most representative

subgroups of the disease. In contrast, transitioning from hypokalemia or hyperkalemia to normokalemia was associated with lower risk throughout the follow-up.

Several studies have evaluated the prognostic role of a single measurement of serum potassium in different cardiovascular scenarios. Regarding chronic HF, several studies reported that low serum potassium levels are associated with higher mortality.[15-17] Regarding hyperkalemia, in the Randomized Aldactone Evaluation Study (RALES) trial, the beneficial effect of spironolactone was observed irrespective of potassium levels in the treatment arm (4.54±0.49 mEq/L vs. 4.28±0.50 mEq/L, p<0.001), even though a U-shaped relationship between potassium levels and mortality was reported in both the spironolactone and the placebo group, with higher risk at potassium levels >5.5 mEq/L.[18] In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, worsening renal function and hyperkalemia (>5.5 mmol/L) were interrelated and associated with poor outcomes, and were more frequent when eplerenone (compared to placebo) was added, although their occurrence did not eliminate the survival benefit of eplerenone.[19] In contrast, other recent studies failed to show an independent association between hyperkalemia and the risk of mortality in HF.[20] In the setting of acutely decompensated HF, evidence is even more scarce and conflicting. By combining data from two large cohorts of patients with acute HF (Patients Hospitalized with Acute Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function [PROTECT] trial, and Coordinating Study Evaluating Outcomes of Advising and Counseling Failure [COACH] trial), Tromp, et al. found that patients with higher serum potassium levels had worse baseline risk profiles and outcomes. However, this association was no longer significant after multivariable adjustment.[21] Other authors also reported a neutral prognostic association,[22] and a recent study suggested better outcomes associated with serum

potassium during hospitalization.[23] Most of these studies focused on the prognostic implication of a single measurement or changes occurring during hospitalization, ignoring the potential implications of long-term changes over time.

In the present study, hyperkalemia identified a subset of patients with worse baseline risk profiles and less intense neurohormonal treatment at baseline, similar to the findings from prior studies in acute HF.[21] On the other hand, patients with hypokalemia had more intense diuretic therapy, perhaps indicating greater fluid overload. Therefore, the question of causality arises as to whether risk associated with low or high potassium levels is the result of harm related to disruption of potassium homeostasis or rather the result of confounding factors associated with or having led to serum potassium changes. Although residual confounders may never be completely controlled for in observational studies, one major feature of the present analyses is the extensive state-of-the-art multivariable adjustment that has been performed, including analyses of traditional baseline and time-updated prognosticators. Time-varying potassium values were associated with the risk of mortality in a U-shaped manner. This is consistent with previous reports, although with less extensive adjustments, in patients with acute myocardial infarction and hypertension.[24,25] These findings suggest that both ends of the potassium distribution may play a causative role in the development of clinical complications.[15,16]

Hypokalemia is well-known to lengthen the action potential, increase QT dispersion, and favor a substrate of electrical inhomogeneity.[15] However, we failed to find an association between low potassium levels and the risk of sudden death. The most likely explanation is insufficient statistical power due to the small number of events. Perhaps an alternative, or even contributing factor, may be that half of the patients were categorized as HFpEF and better adapted to chronic hypokalemia.[26] Other evidence supports a causative role of hypokalemia in

processes linked to HF progression, such as peripheral muscle dysfunction, rhabdomyolysis, impaired vasodilation, myocardial diastolic dysfunction, atherosclerosis, and diuretic resistance.[26,27]

On the other side of the spectrum, hyperkalemia is a risk factor for asystole, ventricular fibrillation, and/or cardiac arrest.[24,28] However, we found that hyperkalemia characterizes a subset of patients with more advanced disease and less intense treatment recommended by guidelines.[15,21] Therefore, excess risk is likely to be not only the result of the electrophysiological effects of hyperkalemia per se, but also the result of comorbidities favoring the development of hyperkalemia (such as poor renal function) as well as, possibly, a consequence of under-dosing or discontinuation of RAAS inhibitor lifesaving therapy by physicians faced with the development of hyperkalemia in their patients.

From the clinical perspective, and as suggested by current guidelines, the association between serum potassium and mortality found in our study reinforces the need for its close monitoring in patients with HF. Thus, it seems advisable to include the measurement of potassium in every lab assessment.

Based on our results, we encourage keeping serum potassium levels within normal range as a critical therapeutic target. In patients with hyperkalemia, a complete withdrawal or down-titration of RAAS inhibitor together with dietary potassium restriction should be the first-line treatment choice in non-urgent situations.[15] The use of potassium-binding resins may be recommended, though they are not usually well tolerated.[15] Recently, patiromer (a non-absorbed potassium-binding polymer) and sodium zirconium cyclosilicate (an inorganic oral potassium-binding polymer) have emerged as novel therapeutic agents with demonstrated efficacy and acceptable safety and tolerability profiles with applicability to different cardiovascular

situations.[15] What remains to be demonstrated is the efficacy and safety of these drugs in patients with chronic HF, and whether their preventive use may mitigate the risk of hyperkalemia while enabling RAAS inhibitor therapy optimization. In contrast, when mild hypokalemia is present, up-titration of RAAS inhibitors, especially MRA therapy, and down-titration of loop diuretics and thiazides is recommended in cases with euvolemia. In patients with persistent fluid overload and in those with more severe hypokalemia, the use of potassium supplements may also be an option.[16] However, randomized studies evaluating the safety and efficacy of these different strategies for the treatment of hypokalemia are lacking.

The current report has strengths and limitations that need to be addressed. In contrast to most current evidence based on the assessment of a single potassium measurement, this study is based on truly longitudinal data with repeated potassium measurements. The advantages of this type of design include increased statistical power and, most importantly, a more accurate and real-life approach to the prognostic impact of potassium disturbances in HF. By using all data and not limiting the analysis to a single measurement, we provide a more comprehensive dynamic assessment of the association between serum potassium and mortality.

A number of limitations need to be pointed out. First, an important limitation of this study is that it is observational and, as such, prone to bias due to unmeasured confounding. Second, the potential for ascertainment bias induced by informative drop-out was minimized by using a joint modeling regression approach of the longitudinal and survival portion of the data, but cannot be completely accounted for. Third, as a single center study, the generalizability of these results to other populations needs to be evaluated. This is especially true, given the high baseline risk and mortality found in this registry. Fourth, the lack of follow-up information on several clinical variables, including treatments, precludes their use as covariables in a time-

varying manner; not having all therapeutic changes along the follow-up precludes an accurate evaluation of the interaction between RAAS inhibition/potassium supplements and the exposure. Finally, some performance metrics (reclassification) are lacking because methodology does not yet exist for repeated-measure/survival data.

Conclusions

In a large non-selected cohort of patients discharged from an episode of acutely decompensated HF, low as well as high serum potassium levels – measured in a time-varying setting - were associated with higher risk of mortality through a U-shaped trajectory. Likewise, when modeling potassium as clinical categories, we found that patients with hypokalemia or hyperkalemia also had a higher risk of mortality. Analysis of potassium dynamics revealed that the persistence of hypokalemia or hyperkalemia at follow-up identified a subset of patients with high mortality risk compared with those who persisted or became normokalemic. Appropriately designed trials of strategies aimed at maintaining normokalemia and not compromising the use of guideline-recommended lifesaving therapy are warranted.

Disclosures

J.N. received board membership fees and travel expenses from Novartis, Roche Diagnostics, Abbott, Rovi, and Vifor. A.B.-G. received board membership fees and travel expenses from Novartis, Roche Diagnostics, and Critical Diagnostics. F.Z. received personal fees (Consultancy; DSMB; Steering Committees; Speaker fees) from: Actelion, Amgen, AstraZeneca, Bayer, Boehringer, Boston Scientific, CEVA, CVRx, Vifor-Fresenius, GE Healthcare, J&J, KBP BioSciences, Livanova, Mitsubishi, Novartis, NovoNordisk, Pfizer, Quantum Genomics, Relypsa, Resmed, Roche, Takeda, ZS Pharma, Founder: CardioRenal, CVCT. PR received

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Table 1. Baseline characteristics

Variables	K <3.5 mEq/L (n=77)	K 3.5 – 5.0 mEq/L (n=1965)	K >5.0 mEq/L (n=122)	All sample (n=2164)	p-value
Demographics and medical history					
Age, years	72 ±12	73±11	76±9	73±11	0.003
Male, n (%)	34 (44.2)	979 (49.8)	77 (63.1)	1090 (50.4)	0.009
Hypertension, n (%)	66 (85.7)	1557 (79.2)	99 (81.1)	1722 (79.6)	0.348
Diabetes, n (%)	37 (48.1)	871 (44.3)	87 (71.3)	995 (46.0)	<0.001
Dyslipidemia, n (%)	46 (59.7)	1007 (51.2)	77 (63.1)	1130 (52.2)	0.016
Smoker, n (%)	9 (11.7)	231 (11.8)	9 (7.4)	249 (11.5)	0.339
Former smoker, n (%)	19 (24.7)	458 (23.3)	43 (35.2)	520 (24.0)	0.011
Ischemic heart disease, n (%)	25 (32.5)	721 (36.7)	72 (59.0)	818 (37.8)	<0.001
Valvular heart disease, n (%)	23 (29.9)	582 (29.6)	34 (27.9)	639 (29.5)	0.917
NYHA class III/IV†, n (%)	6 (7.8)	320 (16.3)	37 (30.3)	363 (16.8)	<0.001
Charlson comorbidity index, n (%) 0 1 - 2 3 - 4 >4	 20 (26.0) 29 (37.7) 22 (28.6) 6 (7.8)	 421 (21.4) 975 (49.6) 409 (20.8) 160 (8.1)	 10 (8.2) 28 (23.0) 47 (38.5) 37 (30.3)	 451 (20.8) 1032 (47.7) 478 (22.1) 203 (9.4)	<0.001
Vital signs on admission					
Heart rate, bpm	99±25	99±28	93±27	99±28	0.064
SBP, mmHg	154±38	149±33	136±30	149±33	<0.001
DBP, mmHg	87±21	82±19	74±18	82±19	<0.001
Electrocardiogram					
Atrial fibrillation, n (%)	40 (51.9)	852 (43.4)	52 (42.6)	944 (43.6)	0.321
LBBB, n (%)	26 (33.8)	607 (30.9)	45 (36.9)	678 (31.3)	0.343
Laboratory data					
Hemoglobin, g/dL	12.3±1.8	12.6±1.9	11.6±2.1	12.5±1.9	<0.001
Anemia (CDC criteria), n (%)	40 (51.9)	994 (50.6)	85 (69.7)	1119 (51.7)	<0.001
Lymphocyte count, x10^3 cells/mL	1517±954	1764±1355	1388±810	1734±1321	0.003
Lymphocyte count <1500 x10^3 cells/mL, n (%)	52 (67.5)	1079 (54.9)	83 (68.0)	1214 (56.1)	0.002
Creatinine*, mg/dL	0.91 (0.78-1.17)	1.10 (0.90-1.40)	1.50 (1.18-2.08)	1.10 (0.90-1.46)	<0.001
eGFR, mL/min/1.73 m^2	71±25	62±25	48±23	62±25	<0.001
eGFR <60 mL/min/1.73 m^2, n (%)	22 (28.6)	963 (49.0)	93 (76.2)	1078 (49.8)	<0.001
Serum sodium*, mEq/L	139 (136-141)	139 (137- 142)	137 (135- 139)	139 (136-142)	<0.001
Serum sodium <135 mEq/L, n (%)	15 (19.5)	356 (18.1)	44 (36.1)	415 (19.2)	<0.001
NT-proBNP*, pg/mL	3149 (1458-6827)	4316 (2318-7735)	6398 (2922-11918)	4342 (2321- 7980)	<0.001
CA125*, U/mL	75 (27-149)	53 (24-124)	59 (28-142)	54 (24-125)	0.115
Echocardiography					
LVEF, %	52±15	50±15	47±15	50±15	0.053
LVEF categories <40%, n (%) 40-49%, n (%) ≥50%, n (%)	 17 (22.1) 11 (14.3) 49 (63.6)	 612 (31.1) 308 (15.7) 1045 (53.2)	 45 (36.9) 19 (15.6) 58 (47.5)	 674 (31.2) 338 (15.6) 1152 (53.2)	0.221
Treatment at admission					
Intravenous furosemide dose at admission, mg/day	62.9±34.3	27.6±45.0	58.2±55.0	30.6±46.2	<0.001
Treatment at discharge‡					
Furosemide, n (%)	65 (84.4)	1497 (76.2)	100 (82.0)	1662 (76.8)	0.093

Torsemide, n (%)	12 (15.6)	445 (22.6)	22 (18.0)	479 (22.1)	0.182
Hydrochlorothiazide, n (%)	10 (13.0)	124 (6.3)	6 (4.9)	140 (6.5)	0.050
Furosemide equivalent dose, mg/day	86±46	74±39	80±36	75±39	0.015
Spironolactone, n (%)	11 (14.3)	395 (20.1)	22 (18.0)	428 (19.8)	0.401
Eplerenone, n (%)	13 (16.9)	263 (13.4)	21 (17.2)	297 (13.7)	0.351
Aldosterone receptor blockers, n (%)	24 (31.2)	658 (33.5)	43 (35.2)	725 (33.5)	0.837
Oral potassium supplements, n (%)	32 (41.6)	131 (6.7)	2 (1.6)	165 (7.6)	<0.001
Beta-blockers, n (%)	63 (81.8)	1275 (64.9)	86 (70.5)	1424 (65.8)	0.005
ACEI, n (%)	28 (36.4)	772 (39.3)	42 (34.4)	842 (38.9)	0.507
ARB, n (%)	29 (37.7)	572 (29.1)	25 (20.5)	626 (28.9)	0.029
ACEI or ARB, n (%)	57 (74.0)	1344 (68.4)	67 (54.9)	1468 (67.8)	0.004

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; LBBB: left bundle branch block; eGFR: estimated glomerular filtration rate; NT-proBNP: amino-terminal pro-brain natriuretic peptide; CA125: carbohydrate antigen 125; LVEF: left ventricle ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Values for continuous variables are expressed as mean ± standard deviation unless otherwise specified.

* Values expressed as median (interquartile range).

† Last NYHA under stable conditions, prior to admission.

‡Administered at discharge or during hospitalization in case of in-hospital deaths.

Figure Legends

Figure 1. A multivariable-adjusted analysis depicting the non-linear association between the continuum of time-updated serum potassium values and the hazard ratios for all-cause mortality. The shape of the curve was determined by modeling serum potassium with a fractional polynomial with 4 degrees of freedom [-2 -1]. Shaded area represents the 95% CI, and were centered at the median of potassium in the sample (4.3 mEq/l). Thus, any portion of the curve above the y-scale reference line of 1 is statistically significant. The omnibus p-value for the entire trajectory was p=0.0012.

Figure 2. A multivariable-adjusted analysis depicting the non-linear association between the continuum of time-updated serum potassium values and the hazard ratios for specific causes of death as outcome. Shaded area represents the 95% CI, and were centered at the median of potassium in the sample (4.3 mEq/l). Thus, any portion of the curve above the y-scale reference line of 1 is statistically significant. The omnibus p-value associated to each trajectory was included in the figure.

2a. Cardiovascular mortality: fractional polynomial with 4 degrees of freedom [-2 -2]

2b. Heart failure-related mortality: fractional polynomial with 4 degrees of freedom [-2 2]

2c. Sudden death: fractional polynomial with 2 degrees of freedom [-2]

CV: cardiovascular; HF: heart failure.

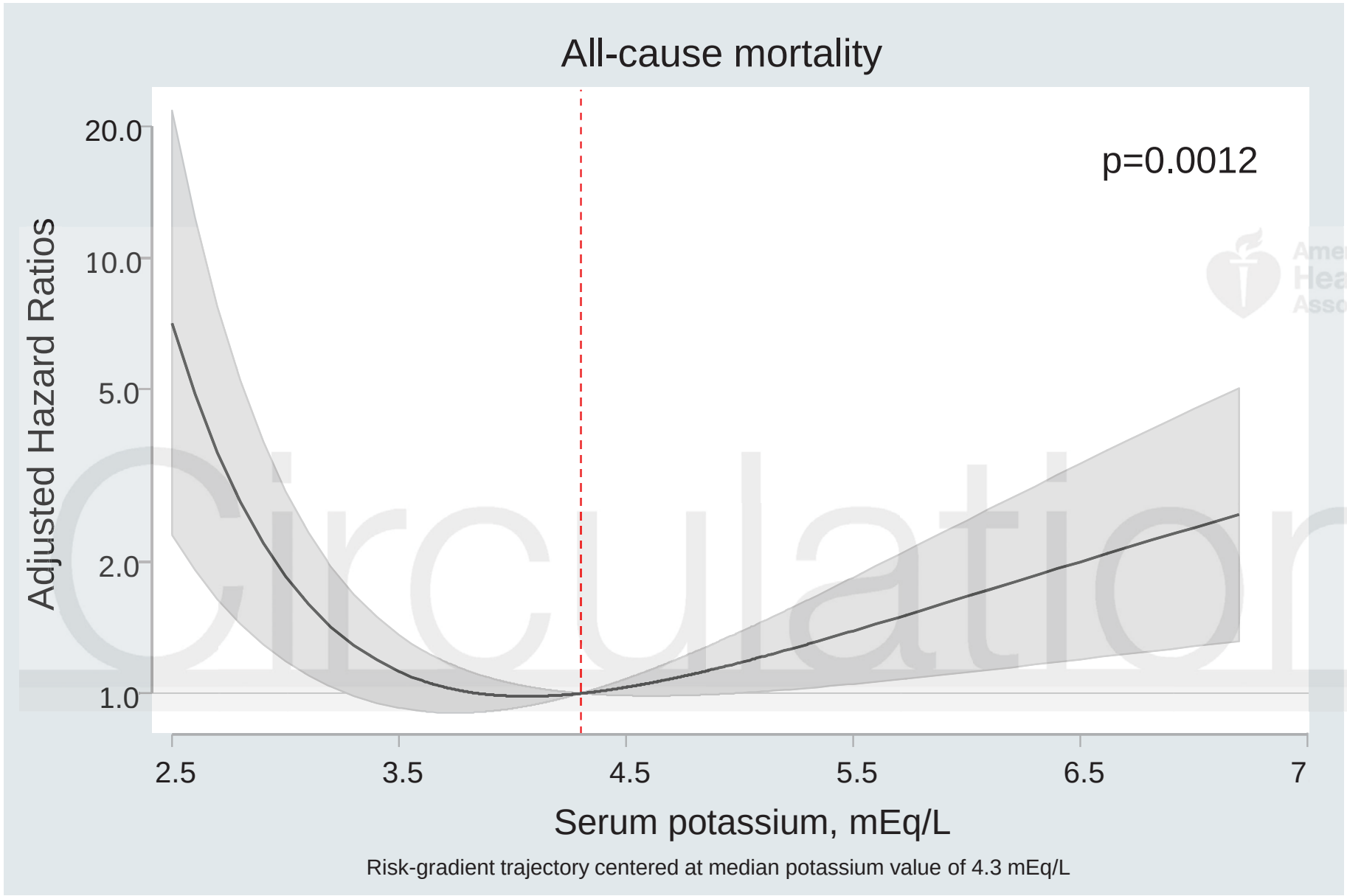
Figure 3. Adjusted survival probabilities associated with potassium categories. Omnibus p-value=0.0003.

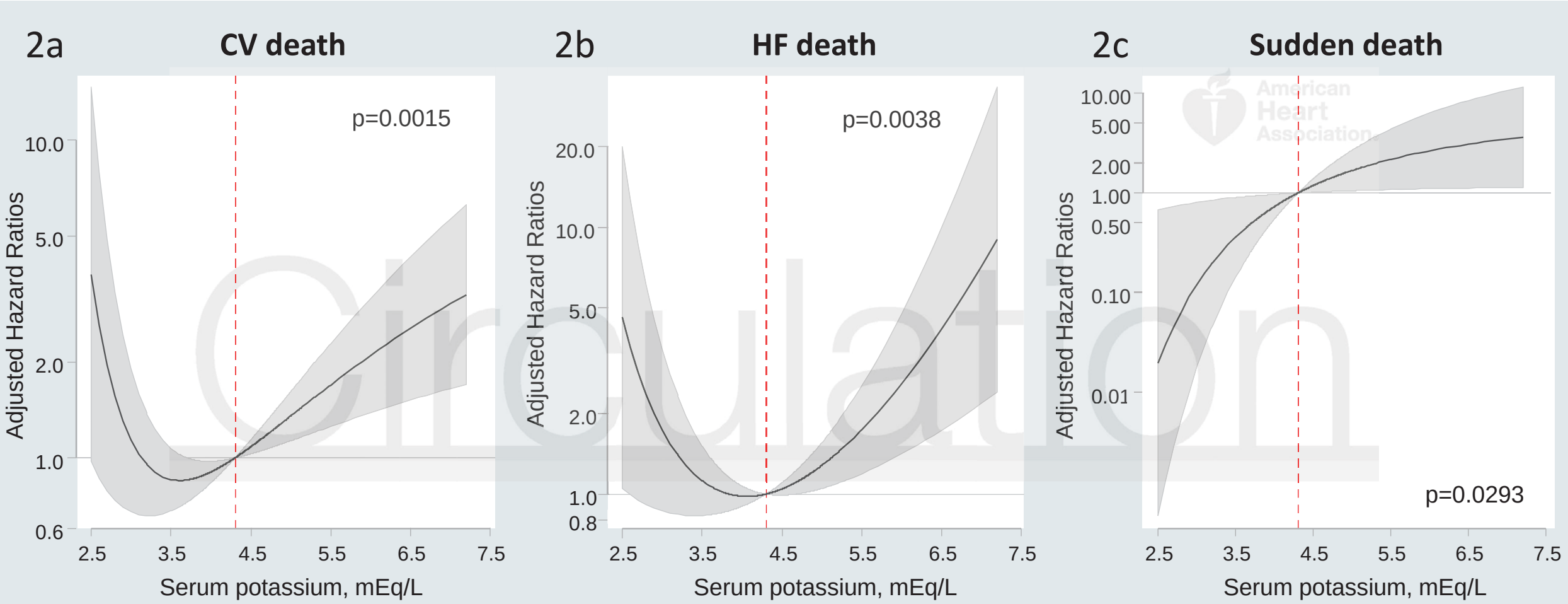
Figure 4. Subgroup analysis of serum potassium and all-cause mortality.

eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonists; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers.

Figure 5. Adjusted survival probabilities associated with changes in potassium category.

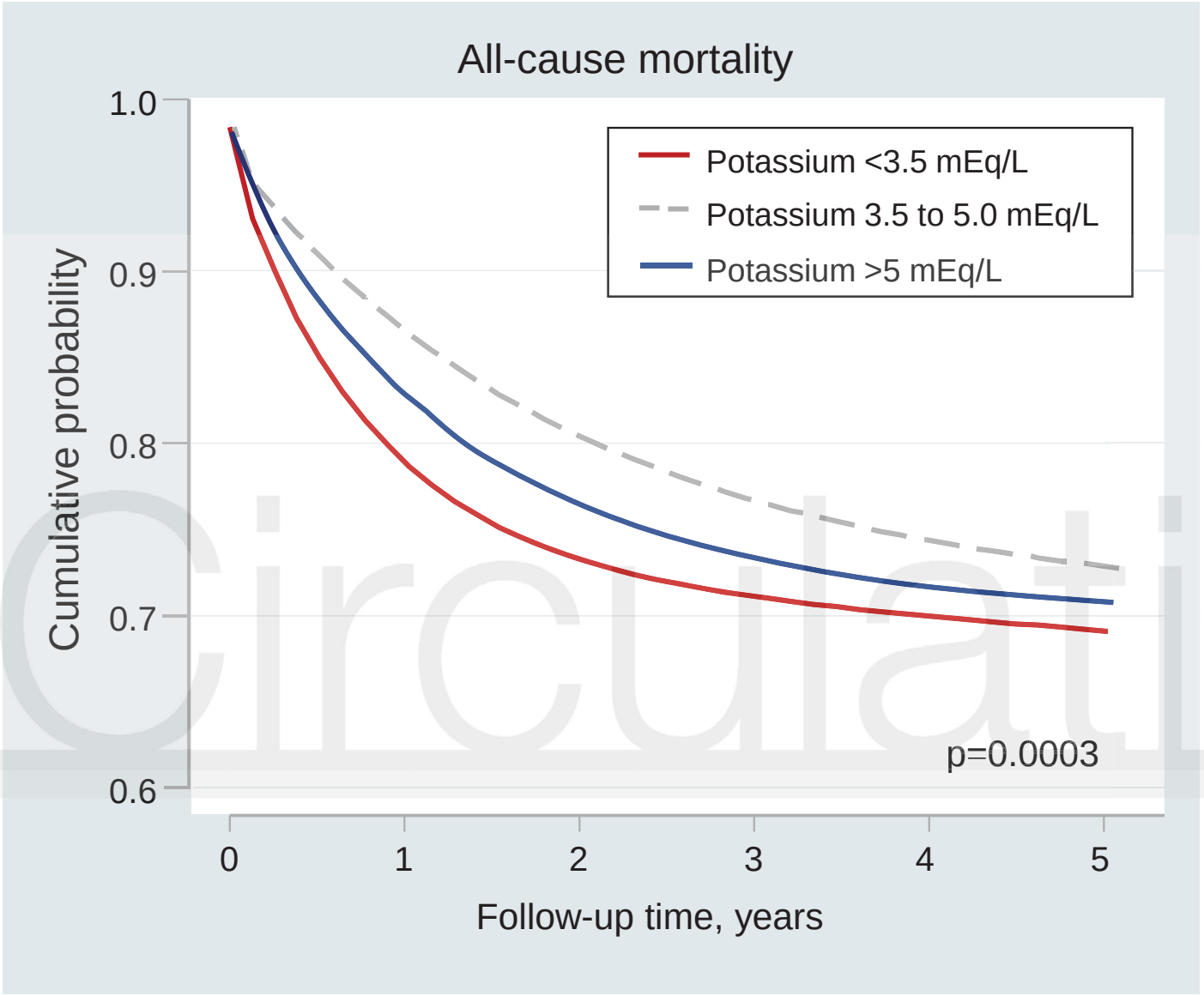
Omnibus p-value<0.0001.

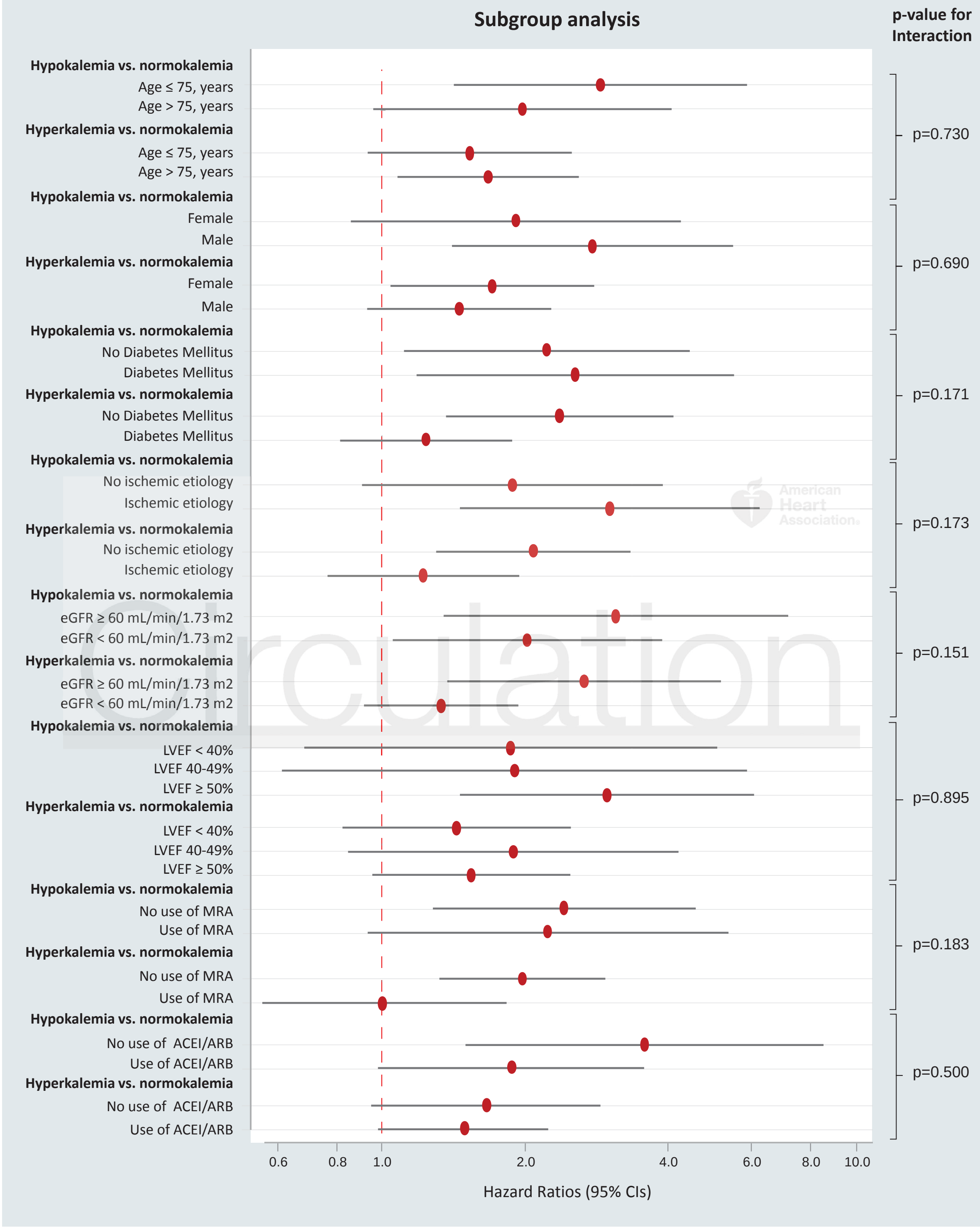


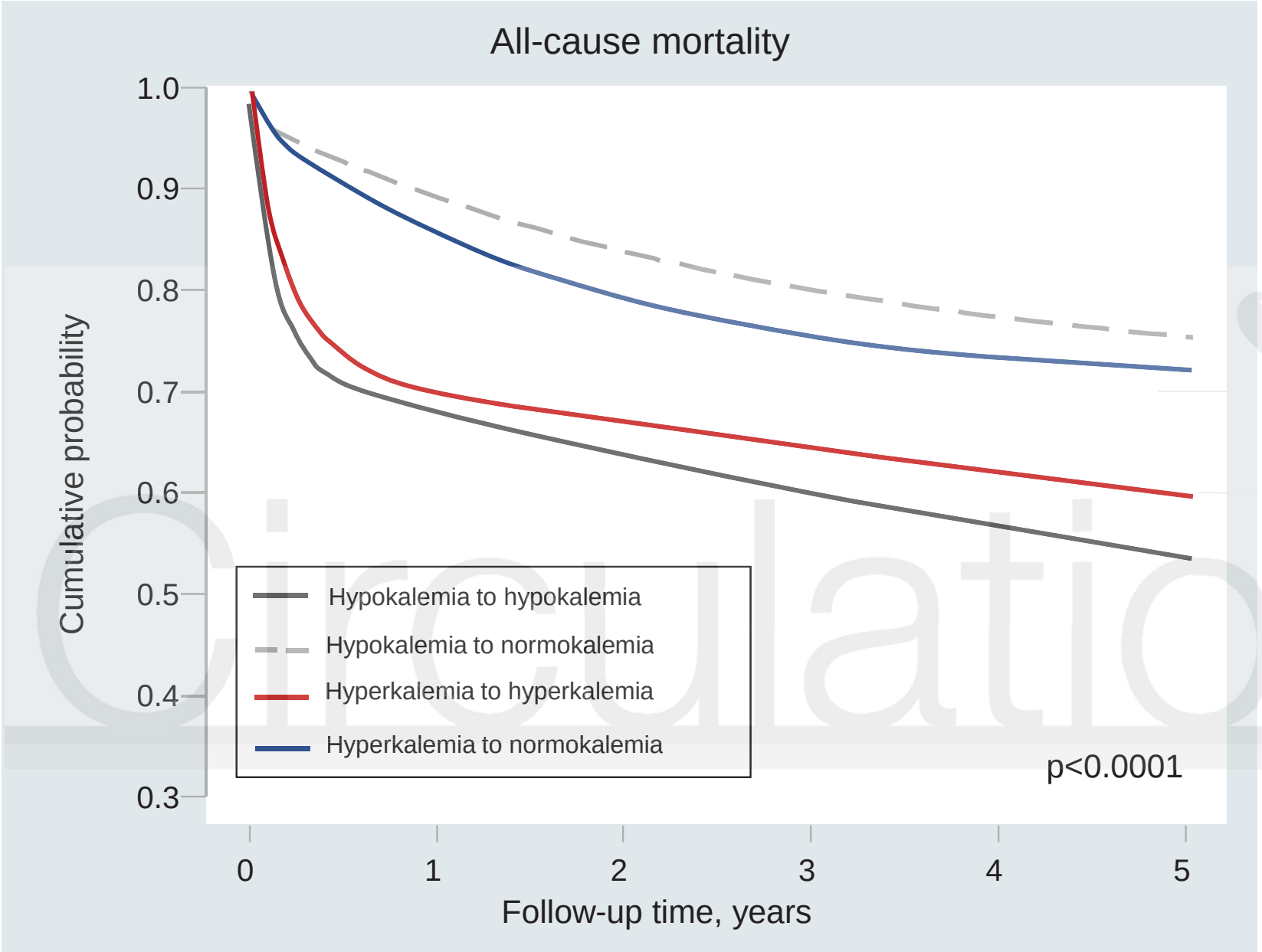


Risk-gradient trajectory centered at median potassium value of 4.3 mEq/L

3







Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality

Julio Núñez, Antoni Bayés-Genís, Faiez Zannad, Patrick Rossignol, Eduardo Núñez, Vicent Bodí, Gema Miñana, Enrique Santas, Francisco J. Chorro, Anna Mollar, Arturo Carratalá, Jorge Navarro, Jose Luis Gorriz, Josep Lupón, Oliver Husser, Marco Metra and Juan Sanchis

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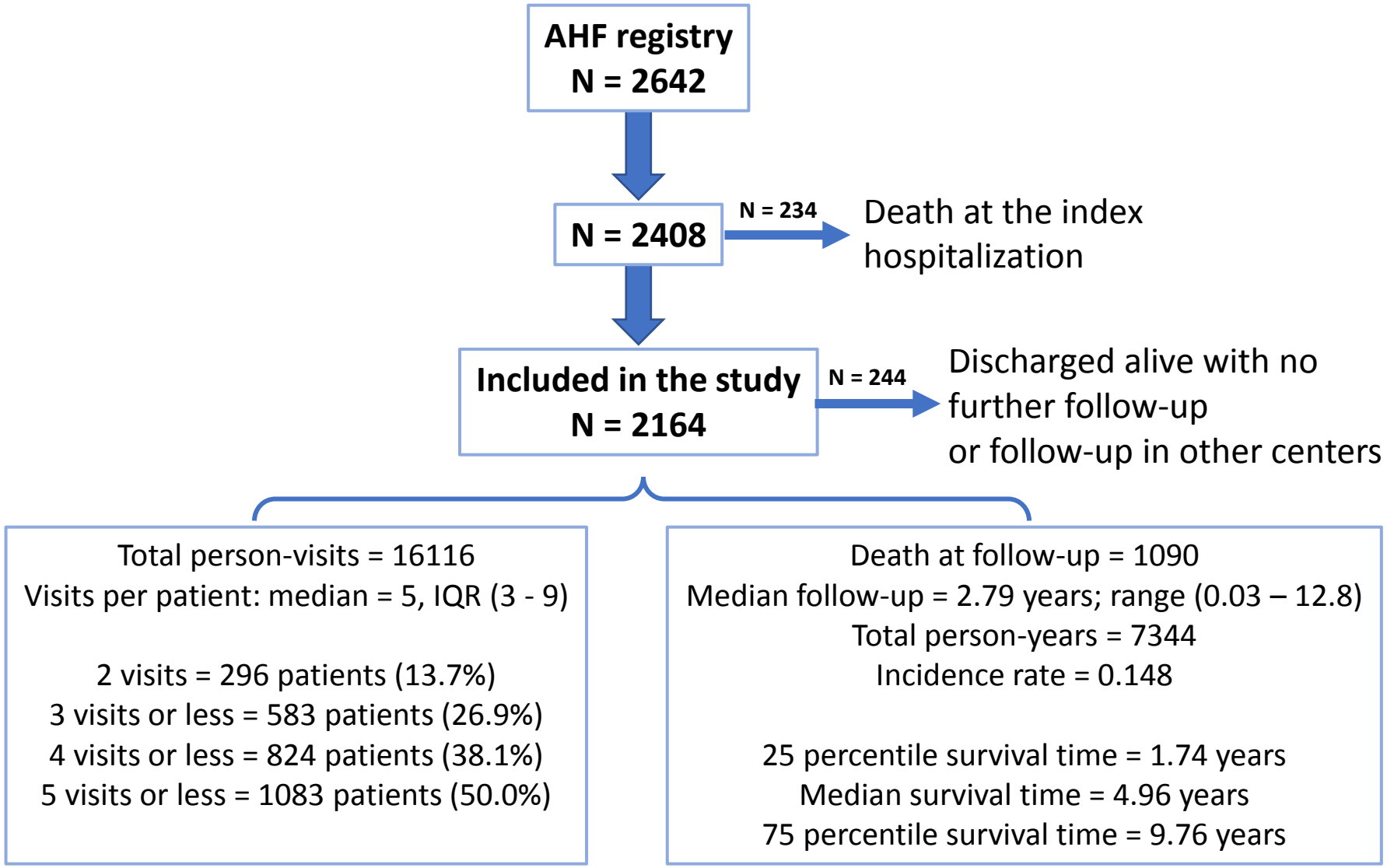
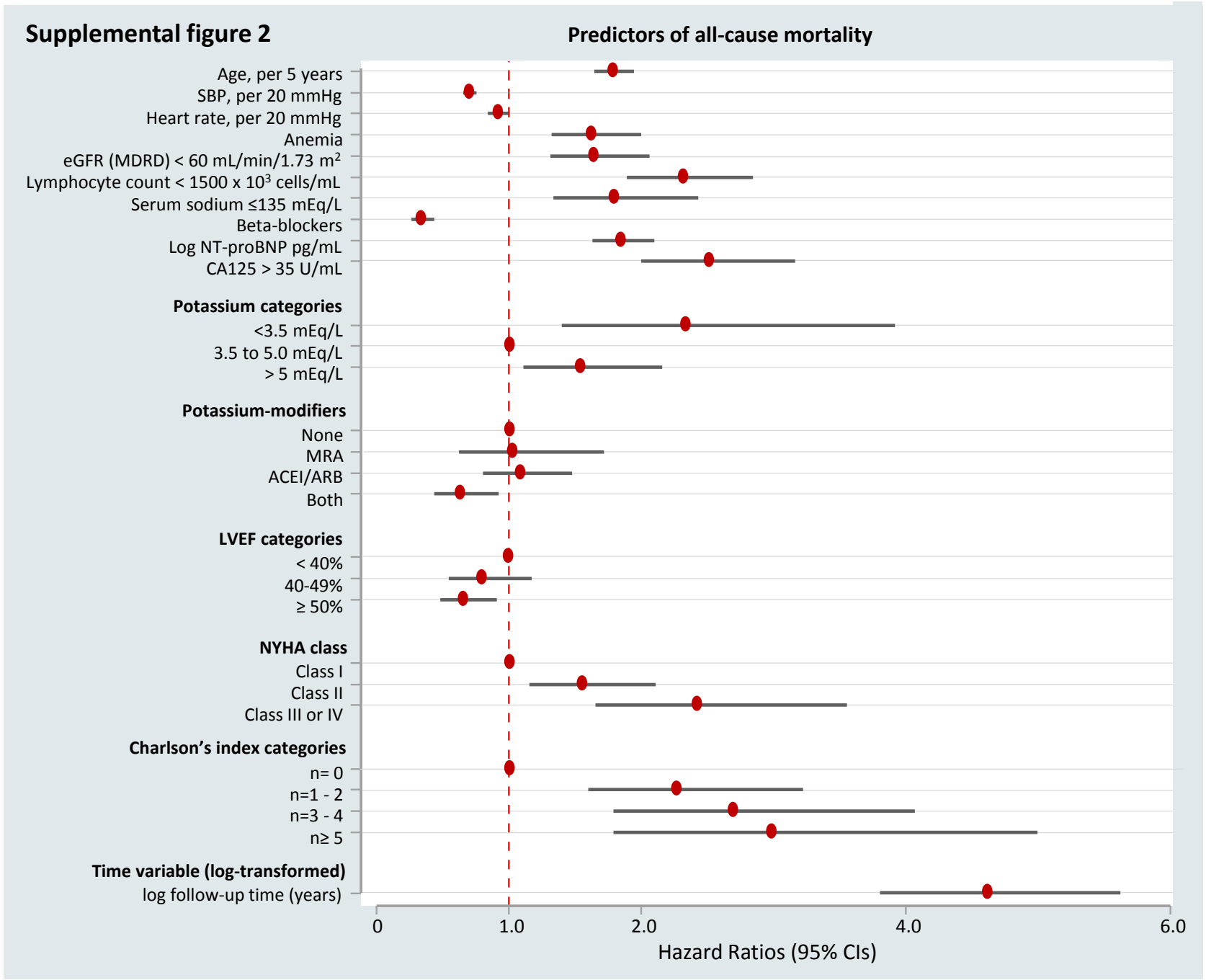
SUPPLEMENTAL MATERIAL

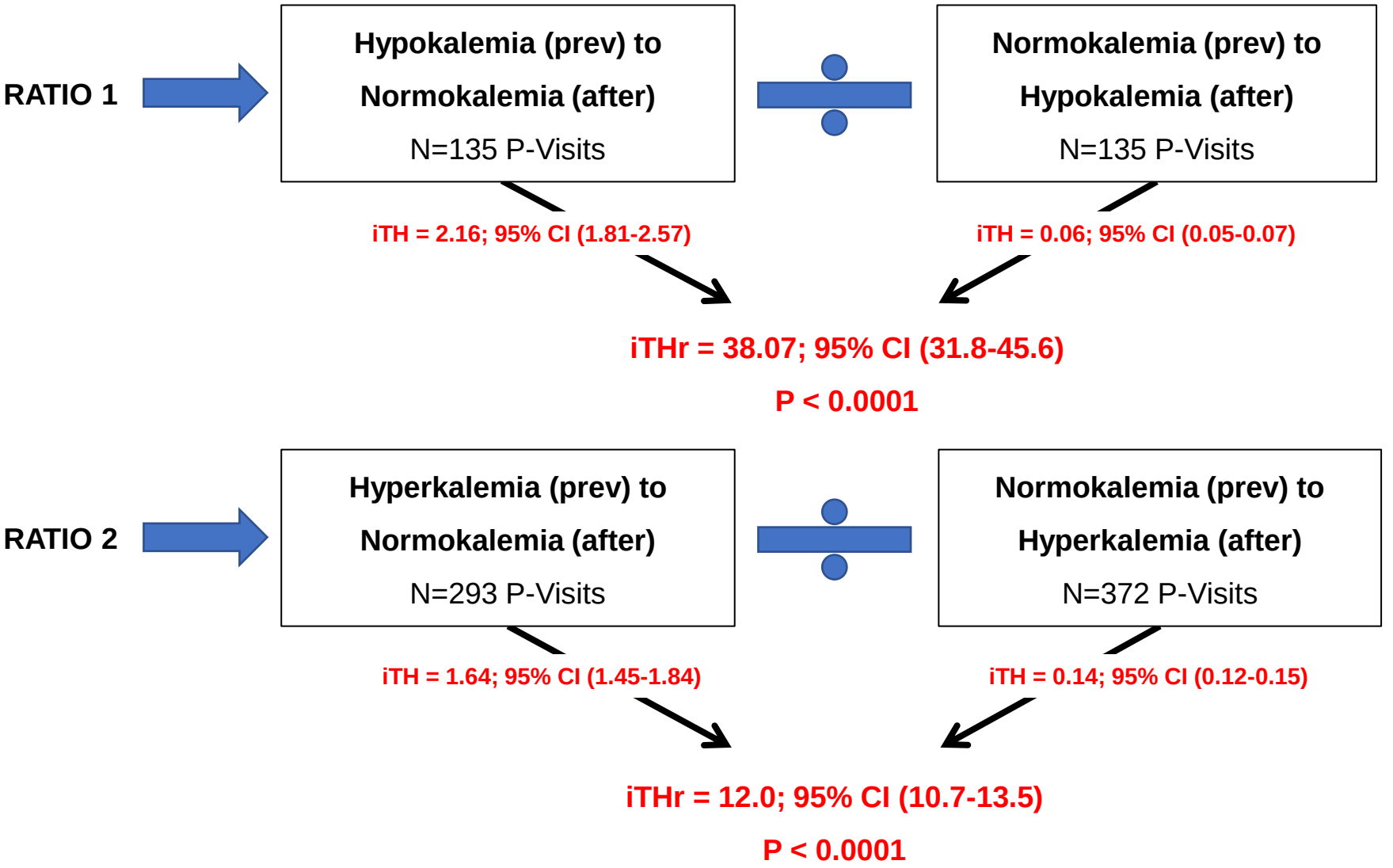
Supplemental figure 1 Flowchart for patient inclusion and follow-up



Supplemental figure 2



Supplemental figure 3 **Instantaneous transitions hazard rates and their respective ratios**



SUPPLEMENTAL FIGURE LEGENDS

Supplemental figure 1. Flowchart for patient inclusion and follow-up.

AHF: acute heat failure

Supplemental figure 2. Model estimates for of all-cause mortality

SBP: systolic blood pressure; eGFR: estimated glomerular filtration rate; NT-proBNP: amino-terminal pro-brain natriuretic peptide; CA125: antigen carbohydrate 125; MRA: mineralocorticoid receptor antagonists; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

Supplemental figure 3. Instantaneous transitions hazard rates and their respective ratios.

iTH: instantaneous transitions hazard rates; CI: confidence interval; P-Visits: patient-visits.