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Association between Potassium Level and Outcomes in Heart Failure with Reduced Ejection Fraction: A Cohort Study from the Swedish Heart Failure Registry

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Abstract

Aims: Hyperkalemia and hypokalemia are common in heart failure and associated with worse outcomes. However, the optimal potassium range is unknown. We sought to determine the optimal range of potassium in patients with heart failure and reduced ejection fraction (EF <40%) by exploring the relationship between baseline potassium level and short- and long-term outcomes using the Swedish HF Registry from January 1, 2006 to December 31, 2012.

Methods and Results: We assessed the association between baseline potassium level and all-cause mortality at 30 days, 12 months, and maximal follow-up, in uni- and multivariable stratified and restricted cubic spline Cox regressions. Of 13,015 patients, 93.3% had potassium 3.5-5.0mmol/L, 3.7% had potassium <3.5, and 3.0% had potassium >5.0. Potassium <3.5 and >5.0 were more common with lower estimated glomerular filtration rate and HF of longer duration and greater severity. The potassium level associated with the lowest hazard risk for mortality at 30-days, 12 months, and maximal follow-up was 4.2mmol/L, and there was a steep increase in risk with both higher and lower potassium levels. In adjusted strata analyses, lower potassium was independently associated with all-cause mortality at 12 months and maximal follow-up , while higher potassium levels only increased risk at 30 days.

Conclusion: In this nationwide registry, the relationship between potassium and mortality was U-shaped, with an optimal potassium value of 4.2mmol/L. After multivariable adjustment, hypokalemia was associated with increased long-term mortality but hyperkalemia was associated with increased short-term mortality.

Key Words: Heart Failure, Potassium, Outcomes

Abbreviations

ACE: angiotensin converting enzyme

ARB: angiotensin II receptor blocker

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

eGFR: estimated glomerular filtration rate

HFrEF: heart failure with reduced ejection fraction

ICD-10: International Statistical Classification of Diseases, Tenth Revision

MRA: mineralocorticoid receptor antagonist

NYHA: New York Heart Association

RAAS: renin-angiotensin-aldosterone system

Introduction

Heart failure is estimated to affect up to 40 million people worldwide and is associated with high morbidity and mortality. [1-3] Because of the pathophysiology of the syndrome, recommended treatments, and concomitant comorbidities, the electrolyte abnormalities of hyper- and hypokalemia are common, often contributing to morbidity and mortality. [4-6] A normal population-reference range for serum potassium is established as 3.5-5.0mmol/L. [7,8] In hypertension, after myocardial infarction complicated by heart failure, and in chronic heart failure, potassium values outside the normal range but also at the lower and higher ends of the normal range are associated with increased short-term mortality. [9-11] Similar findings have been shown in advanced chronic kidney disease. [12,13] Whether a narrower range of potassium values impacts longer term outcomes in chronic heart failure warrants further investigation.

We used the Swedish Heart Failure Registry (SwedeHF; www.SwedeHF.se) to assess patients with heart failure with reduced ejection fraction (HFrEF) and investigate (1) the distribution of potassium values and its association with clinical characteristics and (2) the association between baseline potassium and short- and long-term all-cause mortality and incident hyperkalemia.

Methods

Data Sources

We used SwedeHF, a nationwide registry funded by the Swedish Federal Government through the Swedish Association of Local Authorities and Regions (www.SKL.se), which started as a pilot in 2000 and was introduced nationwide in 2003. The registry has been described previously. [14] Patients are eligible based on clinician-determined heart failure, and data are entered into the registry by local clinicians at the time of hospital discharge or an outpatient clinic visit. Laboratory data and baseline

prescription drug use at the time of first entry into the registry are included. Ejection fraction is included in the registry though date of the echocardiogram has a high percentage of missingness.

SwedeHF can be linked with several national government-sponsored health and statistical registries through the unique identification number that is given to every permanent resident of Sweden. For this study, the *Population Registry* provided vital status and date of death; the *National Patient Registry* provided information on baseline comorbidities and on the outcomes of hyperkalemia. Statistics Sweden provided socioeconomic data.

Study Population

We identified SwedeHF registry participants with an index visit between January 1, 2006 (when the *Prescribed Drug Registry* was introduced) and December 31, 2012. We did not include patients who died during the index hospitalization. Patients with HFrEF (ejection fraction [EF] <40%) were included in this study, whereas patients with EF ≥40% or missing EF information were excluded (**Supplemental Figure 1**). We also excluded patients with missing data for NYHA class, potassium level, angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) use, or mineralocorticoid receptor antagonist (MRA) use. We excluded patients in whom we were unable to calculate estimated glomerular filtration rate (eGFR), patients on dialysis at the time of registration, and patients who died during the index hospitalization.

Baseline Study Variables

The study population was divided into groups based on baseline potassium level (hypokalemia <3.5mmol/L, normokalemia 3.5-5.0mmol/L, mild hyperkalemia 5.1-5.5mmol/L, and hyperkalemia

>5.5mmol/L), measured either from serum or plasma, as some centers use serum potassium and some use plasma potassium. All baseline data were at the index date, which was at hospital discharge or outpatient clinic visit. Comorbidities were reported in SwedeHF and/or defined by *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* codes, and cause-specific outcomes were defined by ICD-10 codes (**Supplemental Table 1**). Renal function was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. [15] Baseline prescription drug use was recorded as per protocol in SwedeHF.

Outcomes

The primary outcome was all-cause mortality at 30 days, 12 months, and maximal follow-up. Mortality was obtained from the *Population Registry* with virtually no loss to follow-up. Secondary outcomes included hyperkalemia, which were obtained from the *Patient Registry*, and defined by inpatient or outpatient visits with the corresponding ICD-10 codes in any diagnosis position.

Statistical Analysis

Baseline characteristics were summarized by medians with interquartile ranges for continuous variables and percentages for categorical variables. Variables were compared using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. We produced histograms of potassium values, and scatterplots of potassium values by renal function, noting the cubic smoothing spline and the median values.[15]

We used the Kaplan-Meier method to estimate all-cause mortality at 30 days, 12 months, and 5 years, stratified by baseline potassium categories. In a secondary analysis, we also used Cox proportional

hazard regression models to examine the association between four categorical baseline potassium levels (<3.5mmol/L, 3.5-5.0mmol/L, 5.1-5.5mmol/L, and >5.5mmol/L) and mortality up to 30 days, 12 months, and maximal follow up because these potassium categories are commonly used in trials examining serum potassium. [16-18]. We also used Cox proportional hazard regression models to assess the relationship between baseline potassium levels as a continuous variable, modelled with a restricted cubic spline with four degrees of freedom, and the outcomes of 30-day, 12-month, and maximal follow-up mortality and hyperkalemia and plotted the functional form. The restricted cubic spline curves show the function relating potassium to the respective outcomes where the mean of baseline potassium across all patients is set to the reference value (HR = 1). Variables adjusted for in the model are noted in Table 1, including patient characteristics (age, gender, HF duration, NYHA Class, EF), medical history (presence of defibrillator, pacemaker, or cardiac resynchronization therapy; history of myocardial infarction, revascularization, peripheral artery disease, stroke, atrial fibrillation or flutter, severe bleeding, hypertension, diabetes, malignant cancer, alcoholism, liver disease, lung disease, musculoskeletal problems, mental health problems), baseline vital signs (systolic blood pressure, heart rate), baseline laboratory values (glomerular filtration rate, hemoglobin), and baseline medication use (ACE inhibitor/ARB, MRA, beta-blocker, statin, diuretic, digoxin, nitrates, platelet inhibitor, oral anticoagulant). Adjustment variables were chosen based on clinical relevance and their potential role in associating with hypokalemia or hyperkalemia and/or outcomes. Given the very large sample size and large number of events, we did not employ any statistical variable selection procedure. After the inclusion and exclusion criteria were applied, 33 of the 35 variables included in the multivariable models had 0% missing data and two variables had 1% missing data.

We used R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) for all analyses.

Ethics

Establishment of the SwedeHF Registry and this analysis with linking of the above registries was approved by a multi-site ethics committee. Individual patient consent was not required, but patients were informed of entry into national registries and allowed to opt out.

Results

Distribution of and associations with potassium levels

Of the 13,015 patients included in this analysis, the majority of patients had potassium levels within the normal reference range (K^+ 3.5-5.0 mmol/L, 93.3%) (**Figure 1, Panel A**). Patients with eGFR >60 mL/min per 1.73m^2 had potassium levels closely centered in the normal range. Across lower eGFR status, higher and lower potassium values were more common (**Figure 1, Panel B**).

Overall, the mean age was 71 years and 27% were women (**Table 1**). Patients in the hypokalemia (K^+ <3.5 mmol/L) group were older and more likely female than those with normokalemia or hyperkalemia. Patients with normokalemia were more likely to have a shorter duration of heart failure (<6 months). There was no significant difference between the groups for frequency of EF 30-39% vs. <30%.

A majority of patients in all groups were on an ACE inhibitor or ARB (86% with K^+ <3.5 mmol/L, 93% with K^+ 3.5-5.0 mmol/L, 92% with K^+ 5.1-5.5 mmol/L, and 87% with K^+ >5.5 mmol/L), while a lower percentage of patients in each group were on MRA therapy (39% with K^+ <3.5 mmol/L, 34% with K^+ 3.5-5.0 mmol/L, 41% with K^+ 5.1-5.5 mmol/L, and 40% with K^+ >5.5 mmol/L).

Associations between baseline potassium level and outcomes – event rates

The median follow up was 2.0 years overall. At 30-days, 12-months, and 5-years, crude survival with normal potassium (3.5-5.0 mmol/L) was better compared to those with hyperkalemia and hypokalemia (**Kaplan-Meier curves Figure 2, Panels A, B, C**). In exploratory analyses further stratifying by narrower categorical potassium levels, patients with $K^+ \geq 6.0$ mmol/L had the lowest survival compared to the other groups at all time points (**Kaplan-Meier curves Figure 3, Panels A, B, C**). At 12 months, survival for those with K^+ 4.0-4.4 mmol/L and those with K^+ 4.5-4.9 mmol/L was higher than survival for all other groups. At 5 years, patients with K^+ 4.0-4.4 mmol/L had higher survival than all other groups.

Association between baseline potassium level and mortality – stratified and spline Cox regressions

In unadjusted spline analyses, there was a sharp U-shaped relationship between potassium level and mortality risk at 30 days, 12 months and maximal follow-up; the lowest hazard ratio for mortality was at K^+ 4.2mmol/L, with a steep increase in risk with both higher and lower potassium levels (**Figure 4, Panels A, B, C**). In unadjusted strata analyses, patients with K^+ <3.5 mmol/L had an increased risk of short- and long-term mortality compared with patients with K+ 3.5-5.0 mmol/L (**Supplemental Table 2)**. Patients with K^+ >5.0 mmol/L also had an increased risk of short- and long-term mortality compared to those with normokalemia.

In adjusted spline analyses, the potassium level associated with the lowest hazard ratio for mortality at 30 days was 4.1mmol/L, and at 12 months and maximal follow-up was 4.2mmol/L (**Figure 4, Panels D, E, F**). Visually, at all time periods, the risk of mortality increases with lower potassium levels.

However, higher potassium levels were associated with increased risk of mortality only at 30 days, not at longer follow-up intervals. In the secondary adjusted strata analyses (adjusted for variables listed in Table 1), K^+ <3.5 was associated with increased risk of mortality at 12 months and maximal follow-up, but not at 30 days. K^+ 5.1-5.5 was not significantly associated with adjusted risk of mortality at 30 days, 12 months, or maximal follow-up. At 30 days, K^+ >5.5 was associated with increased adjusted risk of mortality. (**Figure 4, Panels D, E, F and Supplemental Table 2**).

Association between baseline potassium level and incident hyperkalemia during follow-up

In univariate analyses, higher baseline potassium level was visually associated with increased risk of hyperkalemia at 30 days, 12 months, and maximal follow-up; notably, lower baseline potassium level was also associated with increased risk of hyperkalemia at alltime points (**Supplemental Figure 2, Panel A, B, C**). In multivariate analyses, both lower and higher potassium at baseline were associated with increased risk of hyperkalemia after adjusting for baseline characteristics (**Supplemental Figure 3, Panel A, B, C**).

Discussion

In this comprehensive analysis examining potassium levels in patients with HFrEF in a large population-based registry, we showed that (i) most patients had a potassium level in the historically used normal reference range of 3.5-5.0 mmol/L; (ii) the relationship between potassium level and short- and long-term mortality was U-shaped, with an optimal potassium range much narrower than the range considered normal in routine clinical practice; (iii) but after covariate adjustment, hypokalemia remained associated with increased long-term mortality at all time ranges, whereas hyperkalemia remained

associated only with increased short-term but not long-term mortality; and (iv) the risk of incident hyperkalemia was potentially associated with both higher and lower potassium level at baseline.

Optimal Potassium Levels and Mortality

This study confirms what prior analyses from clinical trials and registries have shown, that hyperkalemia and hypokalemia are both associated with increased risk of mortality in patients with heart failure. [11,16,18, 19,20] While some prior studies examined outcomes for potassium values above and below a "normal range," we sought to identify a more "optimal range" for potassium in heart failure. Our results showed a narrow U-shaped relationship between potassium and mortality with K^+ 4.2mmol/L having the lowest risk of mortality, with worse short- and long-term survival with potassium above and below this value, confirming the results of prior analyses with respect to short-term mortality [11], and extending, for the first time, these findings to longer-term mortality. In multivariable analyses, K^+ 4.1-4.2mmol/L was associated with the lowest mortality for short- and long-term follow up. Our findings suggest that for patients with HFrEF, clinicians should be aware of the increased risk outside a much more narrow range of potassium values than the traditionally defined normal potassium levels of 3.5-5.0 mmol/L. This is particularly relevant in light of data suggesting that in clinical practice, potassium levels are not monitored according to guidelines. [21, 22]

Hypokalemia and Outcomes

Hypokalemia was associated with mortality in short- and long-term follow-up. Hypokalemia may be a risk marker for high or variable diuretic dosing and thus more severe heart failure, congestion, chronic kidney disease, and cardiorenal syndrome. Hypokalemia is worsened by diuretic therapy and

patients with hypokalemia may be more resistant to diuretic therapy in acute decompensated heart failure.[23,24] Indeed, in this study, baseline hypokalemia was visually associated with an increased risk of hyperkalemia, consistent with renal dysfunction and electrolyte disturbances that are more difficult to manage or predict. This study demonstrates that patients with abnormal potassium, either low or high levels, are more likely to present with metabolic derangements in the future.

Furthermore, after adjustment for eGFR and other covariates, hypokalemia remained associated with increased long-term mortality suggesting that in addition to a risk marker, it may also represent a risk factor. This association may be potentially mediated via increased risk of ventricular arrhythmias and sudden cardiac death. In addition, activation of the renin-angiotensin-aldosterone system (RAAS) results in hypokalemia.[6] The results of the current study, taken together with prior studies, reinforce the importance of avoiding hypokalemia in patients with heart failure.

Hyperkalemia and Outcomes

While hyperkalemia was associated with increased short and long-term mortality in univariable analyses, after adjustment, hyperkalemia was associated only with increased mortality at 30-days, not at 12 months or maximal follow-up. Thus hyperkalemia was a risk factor in the short term, possibly by contributing to metabolic derangements and arrhythmias. In contrast, over time it was merely a risk marker for other risk factors. Prior work shows that predictors of hyperkalemia include renal dysfunction and diabetes, which, together with greater severity of heart failure, cardiorenal syndrome and diuretic resistance, increase the risk of mortality in patients with heart failure. [16,17,25]

Interestingly, in this study, MRA use was greater in patients with hypokalemia—suggesting MRAs may be used in part to increase potassium levels—and hyperkalemia, which may be a consequence

of MRA therapy. Indeed, ACE inhibitors, ARBs, and MRAs are common causes of hyperkalemia and patients with hyperkalemia are more likely to be on these drugs, though prior work shows that mortality benefit of these drugs remains, even with hyperkalemia. [16,26-29] Thus discontinuation of these life-saving drugs may play a role in increasing long-term mortality in these high risk patients. [28] While the actual direct risk of hyperkalemia may be overestimated, the perceived risk leads to avoidance, dose reduction or discontinuation of these drugs, which may play a role in long-term mortality. [30-32]

Future Directions

This study adds to previous studies which examined short-term outcomes in patients with hypertension, with heart failure after myocardial infarction, and with chronic heart failure supporting an "optimal" potassium range that is narrower and on the higher end of what is considered a "normal" range. Krogager and colleagues found that for patients with acute heart failure after myocardial infarction, the risk of death at 90 days was lowest in patients with serum K^+ 3.9-4.5 mmol/L. [10] In advanced chronic kidney disease, 180-day mortality was lowest with plasma K^+ 4.2-4.3 mmol/L. [13] Similarly, in patients with chronic heart failure, serum potassium levels outside the 4.2-4.7mmol/L range were associated with increased short-term risk of death.[11] Our current study shows comparable findings in patients with chronic heart failure with longer term outcomes. Furthermore, our study includes comprehensive adjustment for clinical laboratory and medication variables, with novel results that suggest that hyperkalemia is primarily a risk marker rather than a risk factor.

However, despite these findings, it is unknown if the correction of potassium to an optimal level can attenuate these risks. For hyperkalemia in particular, our study highlights the importance of recognizing underlying factors as well as under-utilization of RAAS inhibitors, particularly MRAs, as

potentially the main drivers of worse long term outcomes. Future studies using potassium supplements for hypokalemia or potassium binders for hyperkalemia are warranted to determine the effect on short- and long-term outcomes and whether they can contribute to optimal use of life-saving heart failure medications.

Limitations

Our study should be taken in the context of some limitations. First, the study population was derived from the Swedish Heart Failure Registry, so the results may not be generalizable to other populations or other geographic regions. Further, the patient population is from 2006-2012, so the results may not be generalizable to current patients. The most notable difference between that era and the current one is the introduction of Sacubitril-Valsartan for patients with HFrEF which was approved in 2015. Second, participation in the registry is voluntary, so while most health care facilities report to the registry, the registry does not capture all care throughout Sweden. In addition, we were limited by data available in the registry. Due to the large scale of this registry, some data were missing. We excluded patients with relevant missing data including patients with missing NYHA Class, potassium level, and renal function. Further, we did not examine mode of death which limits our understanding of the relationship between dyskalemia and outcomes. Third, while most centers in Sweden currently measure potassium in plasma, some of these centers previously or in addition measured potassium in serum and the Swedish Heart Failure Registry database does not differentiate the source of the laboratory value.[33] The mixture of serum and plasma values in this analysis may impact the accuracy of the exact potassium value with the lowest risk, the results still strongly support our main message that the optimal potassium range is narrower than previously described. Fourth, as with all retrospective observational analyses, there is a possibility of

residual unmeasured confounders. Fifth, despite the large sample size, at lower and higher potassium, the confidence intervals were wide and interpretations at the extremes of potassium should be made with caution. In addition, potassium level often fluctuates based on diet, medication, or change in renal function, so there are limitations inherent in using a single potassium value to examine associations with long-term outcomes. Finally, although the spline analyses provide a means to model non-linear risk relationships, the position of the knots may influence both the shape of the curve and the optimal potassium level.

Conclusions

In this nationwide registry, the relationship between potassium level and mortality was U-shaped, with an optimal potassium value of 4.2 mmol/L. After multivariable adjustment, hypokalemia was associated with increased long-term mortality, while hyperkalemia was associated only with increased short-term mortality. This adds to the literature that for select patients, clinicians should be targeting a narrower goal potassium range than what has traditionally been considered within the normal range.

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Figure Legend

Figure 1. Distribution of Baseline Potassium Values of the Study Population

Panel A shows the overall distribution of baseline potassium.

Panel B shows the distribution of baseline potassium by eGFR Note: Blue line represents median potassium and eGFR values. Red line represents cubic smoothing spline.

Figure 2. Survival Rates from Kaplan-Meier Estimates Among the Study Population by Baseline Potassium Level

Panel A shows 30-day survival by 4 groups: K^+ <3.5mmol/L, K^+ 3.5-5.0mmol/L, K^+ 5.1-5.5mmol/L, K^+ >5.5mmol/L

Panel B shows 12-month survival by 4 groups: K^+ <3.5mmol/L, K^+ 3.5-5.0mmol/L, K^+ 5.1-5.5mmol/L, K^+ >5.5mmol/L

Panel C shows 5-year survival by 4 groups: K^+ <3.5mmol/L, K^+ 3.5-5.0mmol/L, K^+ 5.1-5.5mmol/L, K^+ >5.5mmol/L

Figure 3. Survival Rates from Kaplan-Meier Estimates Among the Study Population by Baseline Potassium Level

Panel A shows 30-day survival by 7 groups: K^+ <3.5mmol/L, K^+ 3.5-3.9mmol/L, K^+ 4.0-4.4mmol/L, K^+ 4.5-4.9mmol/L, K^+ 5.0-5.4mmol/L, K^+ 5.5-5.9mmol/L, K^+ ≥6.0mmol/L

Panel B shows 12-month survival by 7 groups: K^+ <3.5mmol/L, K^+ 3.5-3.9mmol/L, K^+ 4.0-4.4mmol/L, K^+ 4.5-4.9mmol/L, K^+ 5.0-5.4mmol/L, K^+ 5.5-5.9mmol/L, K^+ ≥6.0mmol/L

Panel C shows 5-year survival by 7 groups: K^+ <3.5mmol/L, K^+ 3.5-3.9mmol/L, K^+ 4.0-4.4mmol/L, K^+ 4.5-4.9mmol/L, K^+ 5.0-5.4mmol/L, K^+ 5.5-5.9mmol/L, K^+ ≥6.0mmol/L

Figure 4. Risk of Mortality by Baseline Potassium Level

Panel A shows unadjusted risk of 30-day mortality. K^+ 4.2 mmol/L was associated with the lowest risk of 30-day mortality.

Panel B shows unadjusted risk of 12-month mortality. K^+ 4.2 mmol/L was associated with the lowest risk of 30-day mortality.

Panel C shows unadjusted risk of mortality at maximal follow-up. K^+ 4.2 mmol/L was associated with the lowest risk of mortality at maximal follow-up.

Panel D shows adjusted risk of 30-day mortality. K^+ 4.1 mmol/L was associated with the lowest adjusted risk of 30-day mortality.

Panel E shows adjusted risk of 12-month mortality. K^+ 4.2 mmol/L was associated with the lowest adjusted risk of 12-month mortality.

Panel F shows adjusted risk mortality at maximal follow-up. K^+ 4.2 mmol/L was associated with the lowest adjusted risk of mortality at maximal follow-up.

Table 1. Baseline Characteristics

Variable	Missing %	K<3.5 n=483	K=3.5-5 n=12143	K=5.1-5.5 n=326	K>5.5 n=63	p-value
Patient Characteristics						
Age, years[a,b]	0	75 (65-83)	72 (63-80)	73 (65-80)	72 (65-78)	<0.001
Gender, Male[a]	0	61%	74%	78%	73%	<0.001
BMI, kg/m2[b]	50	26 (22-30)	26 (23-30)	25 (22-29)	25 (23-27)	0.02
Duration of HF[a]	0					<0.001
<6 months		43%	49%	35%	38%	
=>6 months		57%	51%	65%	62%	
NYHA Class[a]	0					<0.001
I		5%	9%	4%	6%	
II		34%	45%	37%	33%	
III		50%	41%	47%	51%	
IV		11%	4%	11%	10%	
Ejection Fraction[a]	0					0.28
<30%		57%	53%	54%	54%	
30-39%		43%	47%	46%	46%	
Baseline Assessments						
Systolic BP, mmHg[a,b]	1	125 (110-140)	120 (110-140)	120 (105-130)	110 (100-126)	<0.001
Diastolic BP, mmHg[b]	1	72 (65-82)	70 (65-80)	70 (60-80)	70 (60-75)	<0.001
Heart Rate[a,b]	1	76 (67-86)	70 (62-81)	70 (62-82)	71 (64-79)	<0.001
Laboratory Values						
Glomerular Filtration Rate, mL/min/ 1.73m² [a,b]	0	61 (43-80)	65 (47-83)	46 (33-66)	37 (27-50)	<0.001
Hemoglobin, g/L[a,b]	0	131 (118-142)	136 (124-147)	132 (118-147)	124 (110-140)	<0.001
NT-proBNP pg/mL	55	4,932 (1,979-9,759)	2,720 (1,200-5,988)	3,975 (1,844-7,606)	5,818 (2,309-8,756)	<0.001
Medical History						
Anemia	0	37%	28%	40%	52%	<0.001
Implantable Cardioverter Defibrillator[a]	0	5%	6%	6%	3%	0.39
Cardiac Resynchronization Therapy[a]	0	4%	6%	8%	6%	0.06
Pacemaker[a]	0	9%	7%	10%	10%	0.22
Myocardial Infarction[a]	0	44%	42%	45%	51%	0.23
Revascularized[a]	0	31%	31%	30%	37%	0.75
Peripheral Artery Disease[a]	0	13%	10%	12%	13%	0.04
Stroke/Transient Ischemic Attack[a]	0	17%	14%	18%	19%	0.05
Atrial Fibrillation/Flutter[a]	0	52%	47%	48%	57%	0.09
Any Severe Bleed[a]	0	25%	17%	26%	22%	<0.001
Hypertension[a]	0	55%	48%	53%	46%	0.01
Diabetes[a]	0	28%	25%	36%	32%	<0.001
Malignant Cancer[a] (Past 3 Years)	0	15%	12%	13%	8%	0.22

Alcoholism[a]	0	6%	5%	7%	8%	0.09
Liver Disease[a]	0	2%	2%	1%	3%	0.63
Lung Disease[a]	0	29%	24%	25%	29%	0.06
Musculoskeletal Problems[a] (Past 3 Years)	0	28%	26%	26%	16%	0.18
Mental Health Problems[a] (Past 3 Years)	0	17%	12%	13%	17%	0.01
Prior Hyperkalemia	0	2%	1%	5%	6%	<0.001
Prior Hypokalemia	0	5%	1%	1%	2%	<0.001
Medications						
ACE inhibitor/ARB [a]	0	86%	93%	92%	87%	<0.001
New Prescription		21%	13%	6%	10%	
Old Prescription		65%	80%	86%	78%	
MRA[a]	0	39%	34%	41%	40%	0.01
New Prescription		22%	10%	7%	3%	
Old Prescription		17%	24%	34%	37%	
Beta-Blocker[a]	0	93%	92%	93%	89%	0.55
Statin[a]	0	47%	52%	49%	48%	0.09
Diuretic (loop or thiazide) [a]	0	92%	77%	86%	83%	<0.001
Digoxin[a]	0	19%	17%	14%	11%	0.28
Nitrates[a]	0	16%	14%	17%	13%	0.16
Platelet Inhibitor[a]	0	52%	50%	48%	59%	0.46
Oral Anticoagulant[a]	0	37%	42%	42%	41%	0.11

[a] Variable included in multivariable models
[b] Data expressed as median (q1-q3)
Patients with missing values for potassium or eGFR; ACE inhibitor, ARB, or MRA use; or ejection fraction were excluded. For remaining variables, the % missing is listed.

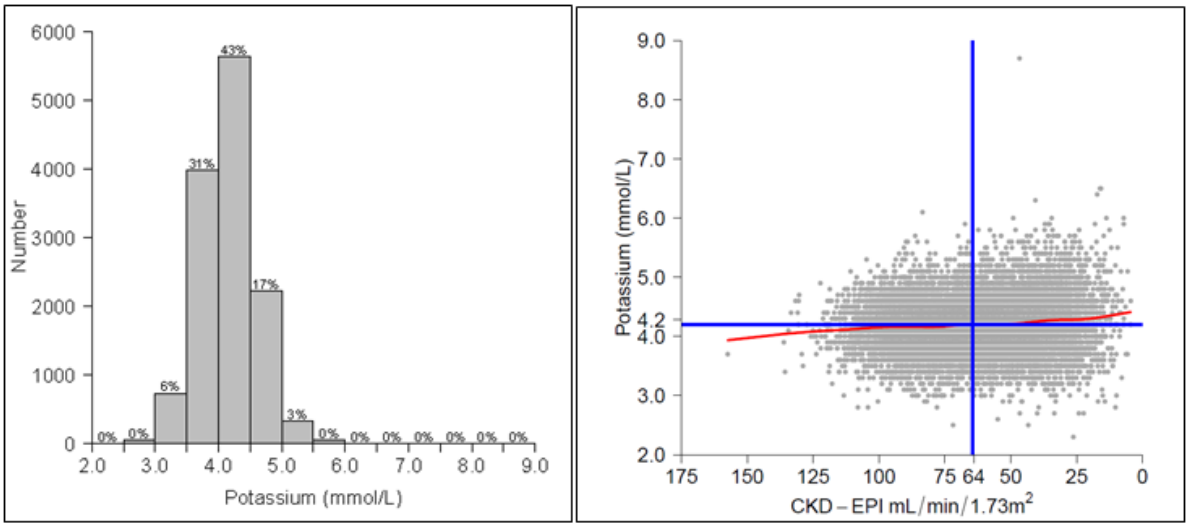
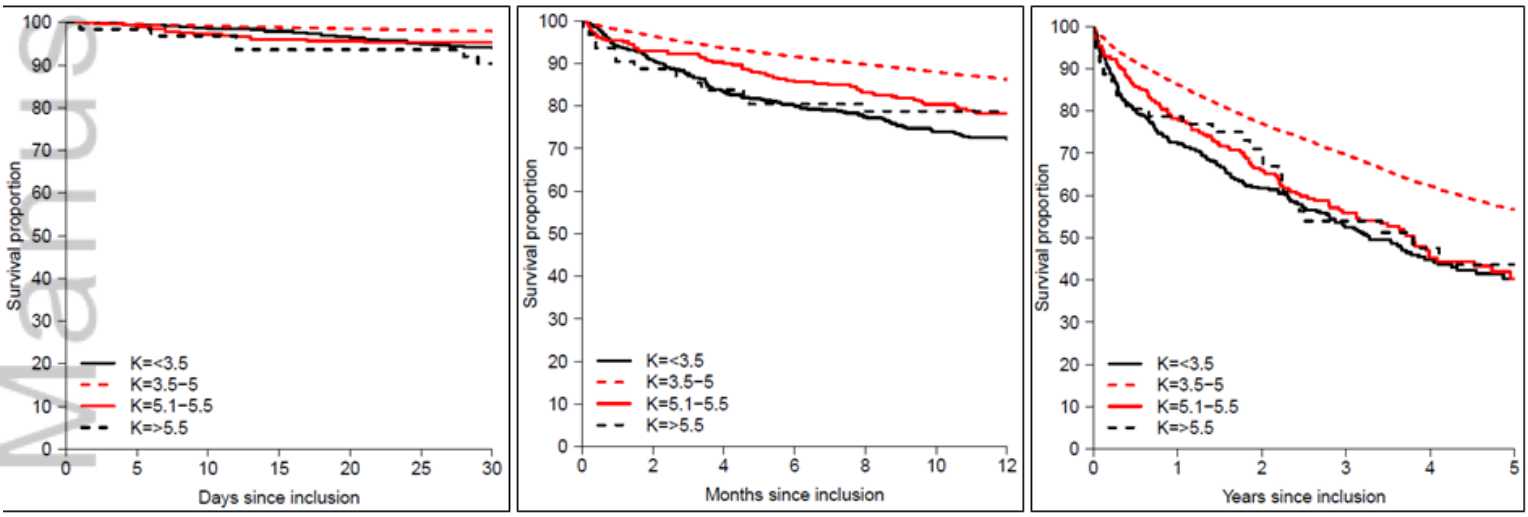
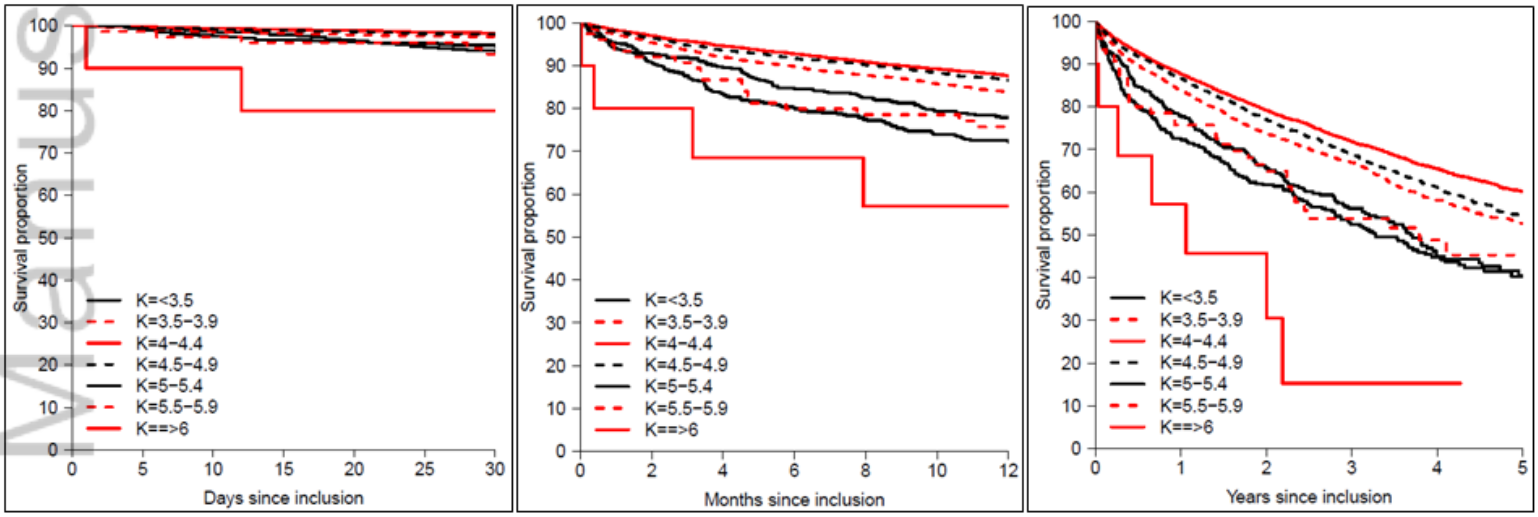


Fig 1 1-10-20.tif



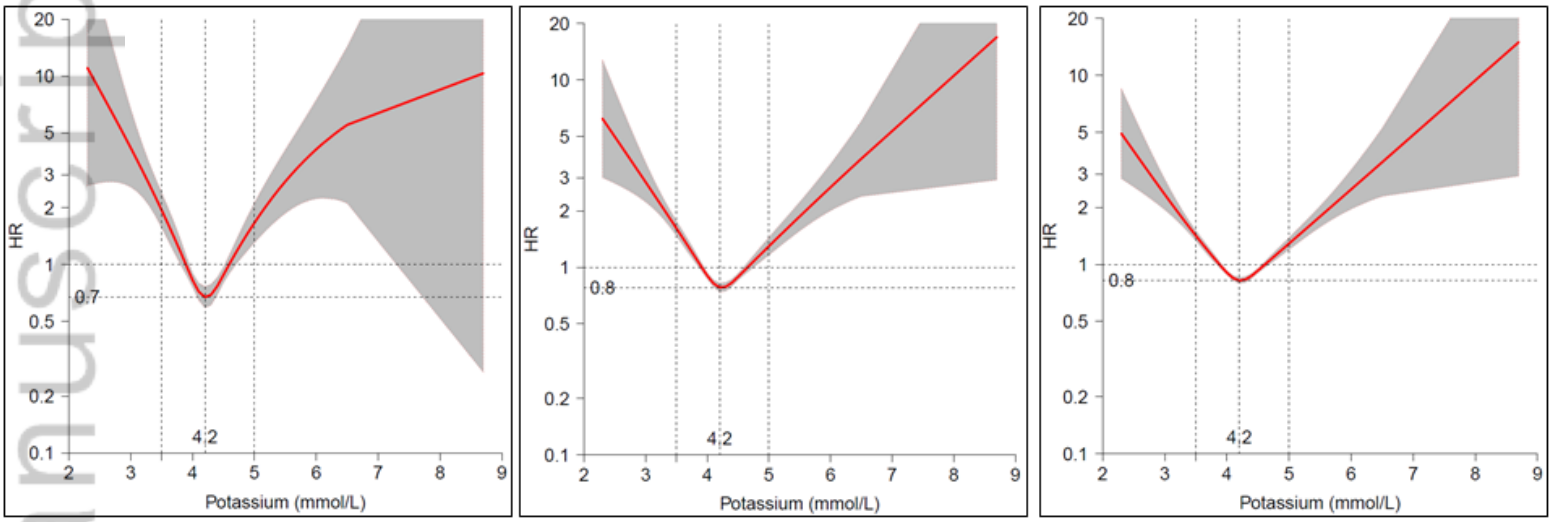
A: 30-day survival B: 12-month survival C: 5-year survival

Fig 2 1-10-20.tif



A: 30-day survival B: 12-month survival C: 5-year survival

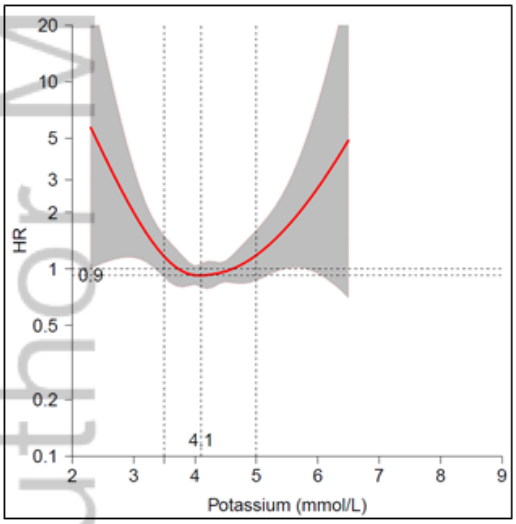
Fig 3 1-10-20.tif



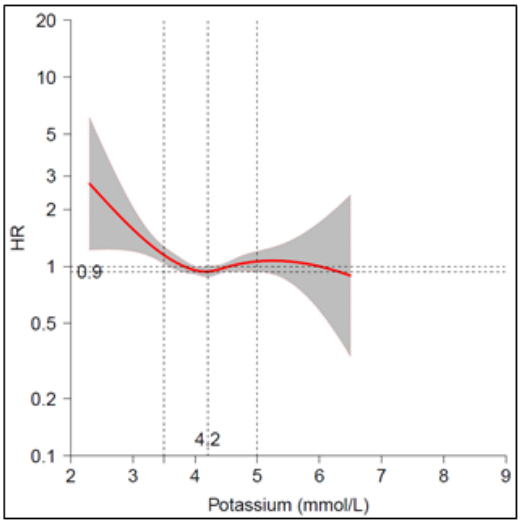
A: 30-day survival

B: 12-month survival

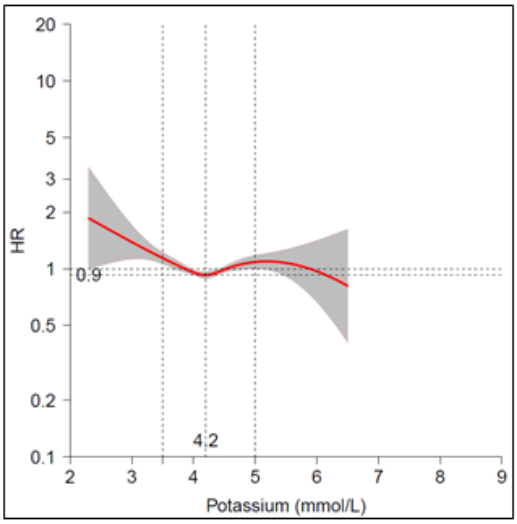
C: Max survival



D: 30-day survival



E: 12-month survival



F: Max survival

Fig 4 1-10-20.tif

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