ESC European Society of Cardiology

European Journal of Heart Failure (2020) **22**, 1390–1398
doi:10.1002/ejhf.1757

RESEARCH ARTICLE

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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Received 4 October 2019; revised 10 January 2020; accepted 16 January 2020; online publish-ahead-of-print 20 February 2020

Aims Hyperkalaemia and hypokalaemia 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 (< 40%) by exploring the relationship between baseline potassium level and short- and long-term outcomes using the Swedish Heart Failure Registry from 1 January 2006 to 31 December 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 3.5–5.0 mmol/L, 3.7% had potassium <3.5 mmol/L, and 3.0% had potassium >5.0 mmol/L. Potassium <3.5 mmol/L and >5.0 mmol/L were more common with lower estimated glomerular filtration rate and heart failure 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 4.2 mmol/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 4.2 mmol/L. After multivariable adjustment, hypokalaemia was associated with increased long-term mortality but hyperkalaemia was associated with increased short-term mortality.

Keywords Heart failure • Potassium • Outcomes

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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, electrolyte abnormalities of hyper- and hypokalaemia are common, often contributing to morbidity and mortality.[4–6] A normal population-reference range for serum potassium is established as 3.5–5.0 mmol/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 (i) the distribution of potassium values and its association with clinical characteristics, and (ii) the association between baseline potassium and short- and long-term all-cause mortality and incident hyperkalaemia.

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 (EF) is included in the registry, though date of echocardiograms 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 hyperkalaemia. Statistics Sweden provided socioeconomic data.

Study population

We identified SwedeHF Registry participants with an index visit between 1 January 2006 (when the Prescribed Drug Registry was introduced) and 31 December 2012. We did not include patients who died during the index hospitalization. Patients with HFrEF (EF < 40%) were included in this study, whereas patients with EF ≥40% or missing EF information were excluded (online supplementary *Figure S1*). We also excluded patients with missing data for New York Heart Association (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 (hypokalaemia <3.5 mmol/L, normokalaemia 3.5–5.0 mmol/L, mild hyperkalaemia 5.1–5.5 mmol/L, and hyperkalaemia >5.5 mmol/L), measured either from serum or plasma, as some centres 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 (online supplementary *Table S1*). Renal function was calculated using the Chronic Kidney Disease Epidemiology Collaboration 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 hyperkalaemia, 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 (<3.5, 3.5–5.0, 5.1–5.5, and >5.5 mmol/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 hyperkalaemia 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 (hazard ratio = 1). Variables adjusted for in the model are noted in *Table 1*, including patient characteristics (age, gender, heart failure 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

Table 1 Baseline characteristics

Variable	Missing %	K^+ < 3.5 mmol/L (*n* = 483)	K^+ 3.5–5 mmol/L (*n* = 12143)	K^+ 5.1–5.5 mmol/L (*n* = 326)	K^+ > 5.5 mmol/L (*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
Male sex[a]	0	61%	74%	78%	73%	<0.001
BMI, kg/m^2[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, bpm[a,b]	1	76 (67–86)	70 (62–81)	70 (62–82)	71 (64–79)	<0.001
Laboratory values						
Glomerular filtration rate, mL/min/1.73 m^2[a,b]	0	61 (43–80)	65 (47–83)	46 (33–66)	37 (27–50)	<0.001
Haemoglobin, g/L[a,b]	0	131 (118–142)	136 (124–147)	132 (118–147)	124 (110–140)	<0.001
NT-proBNP, pg/mL	55	4932 (1979–9759)	2720 (1,200–5988)	3975 (1844–7606)	5818 (2309–8756)	<0.001
Medical history						
Anaemia	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 hyperkalaemia	0	2%	1%	5%	6%	<0.001
Prior hypokalaemia	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%	

Table 1 (Continued)

Variable	Missing %	K^+ < 3.5 mmol/L (*n* = 483)	K^+ 3.5–5 mmol/L (*n* = 12143)	K^+ 5.1–5.5 mmol/L (*n* = 326)	K^+ > 5.5 mmol/L (*n* = 63)	*P*-value
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

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
Patients with missing values for potassium or estimated glomerular filtration rate; ACE inhibitor, ARB, or MRA use; or ejection fraction were excluded. For remaining variables, the % missing is listed.
[a]Variable included in multivariable models.
[b]Data expressed as median (Q1–Q3).

pressure, heart rate), baseline laboratory values (glomerular filtration rate, haemoglobin), 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 hypokalaemia or hyperkalaemia 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 1A*). Patients with eGFR >60 mL/min/1.73 m^2 had potassium levels closely centred in the normal range. Across lower eGFR status, higher and lower potassium values were more common (*Figure 1B*).

Overall, the mean age was 71 years and 27% were women (*Table 1*). Patients in the hypokalaemia (K^+ <3.5 mmol/L) group were older and more likely female than those with normokalaemia or hyperkalaemia. Patients with normokalaemia 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).

Association 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 hyperkalaemia and hypokalaemia (*Figure 2*). In exploratory analyses further stratifying by narrower categorical potassium levels, patients with K^+ ≥6.0 mmol/L had the lowest survival compared to the other groups at all time points (*Figure 3*). 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^+ 4.2 mmol/L, with a steep increase in risk with both higher and lower potassium levels (*Figure 4A–C*). In unadjusted strata analyses, patients with K^+ <3.5 mmol/L had an increased

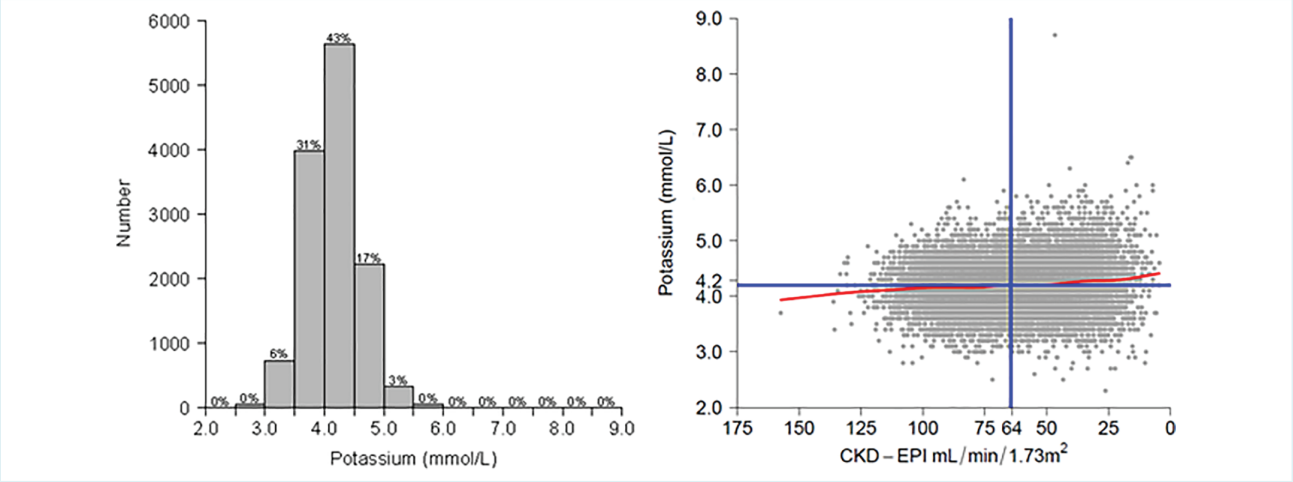

Figure 1 Distribution of baseline potassium values of the study population. (*A*) Overall distribution of baseline potassium. (*B*) Distribution of baseline potassium by estimated glomerular filtration rate. Note: blue line represents median potassium and estimated glomerular filtration rate values; red line represents cubic smoothing spline. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

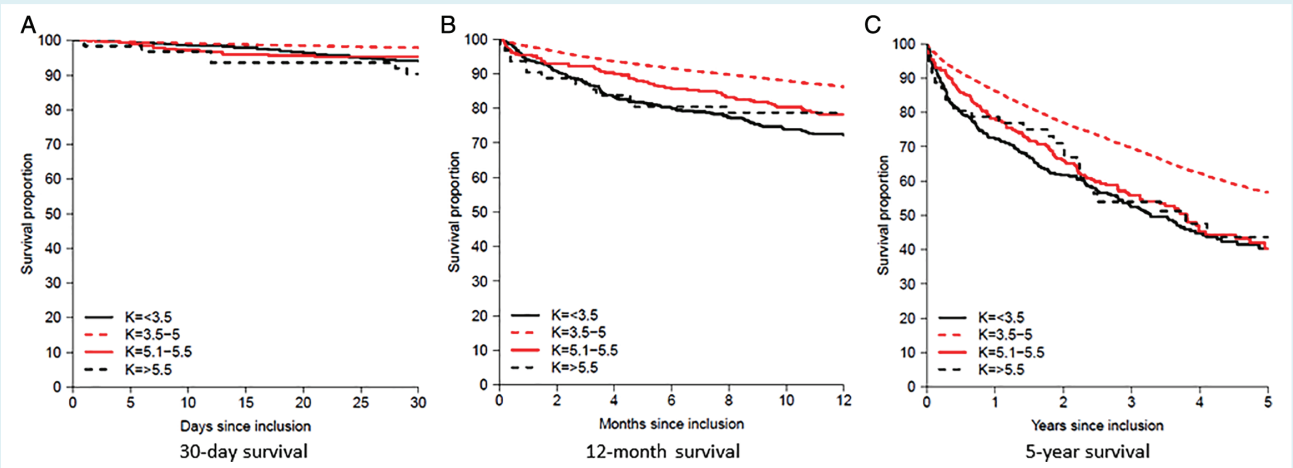

Figure 2 Survival rates from Kaplan–Meier estimates among the study population by baseline potassium level. Thirty-day (*A*), 12-month (*B*) and 5-year survival (*C*) by four groups: K^+ <3.5 mmol/L, K^+ 3.5–5.0 mmol/L, K^+ 5.1–5.5 mmol/L, and K^+ >5.5 mmol/L.

risk of short- and long-term mortality compared with patients with K+ 3.5–5.0 mmol/L (online supplementary *Table S2*). Patients with K^+ >5.0 mmol/L also had an increased risk of short- and long-term mortality compared to those with normokalaemia.

In adjusted spline analyses, the potassium level associated with the lowest hazard ratio for mortality at 30 days was 4.1 mmol/L, and at 12 months and maximal follow-up was 4.2 mmol/L (*Figure 4D–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 4D-F* and online supplementary *Table S2*).

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

In univariate analyses, higher baseline potassium level was visually associated with increased risk of hyperkalaemia at 30 days, 12 months, and maximal follow-up; notably, lower baseline potassium level was also associated with increased risk of hyperkalaemia at all time points (online supplementary *Figure S2*). In multivariate analyses, both lower and higher potassium at baseline were associated

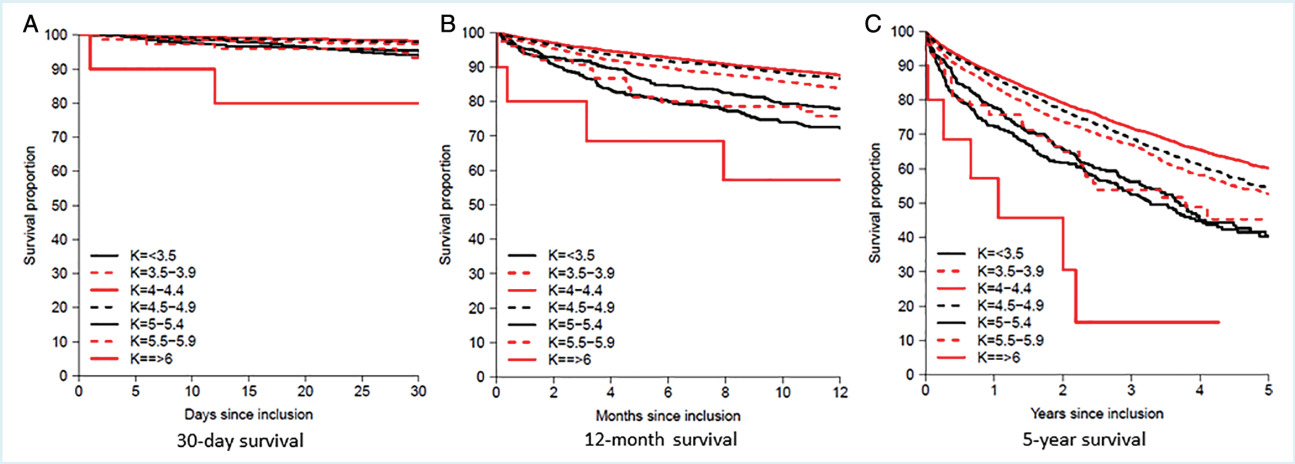

Figure 3 Survival rates from Kaplan–Meier estimates among the study population by baseline potassium level. Thirty-day (*A*), 12-month (*B*) and 5-year survival (*C*) by seven groups: K^+ <3.5 mmol/L, K^+ 3.5–3.9 mmol/L, K^+ 4.0–4.4 mmol/L, K^+ 4.5–4.9 mmol/L, K^+ 5.0–5.4 mmol/L, K^+ 5.5–5.9 mmol/L, and K^+ ≥6.0 mmol/L.

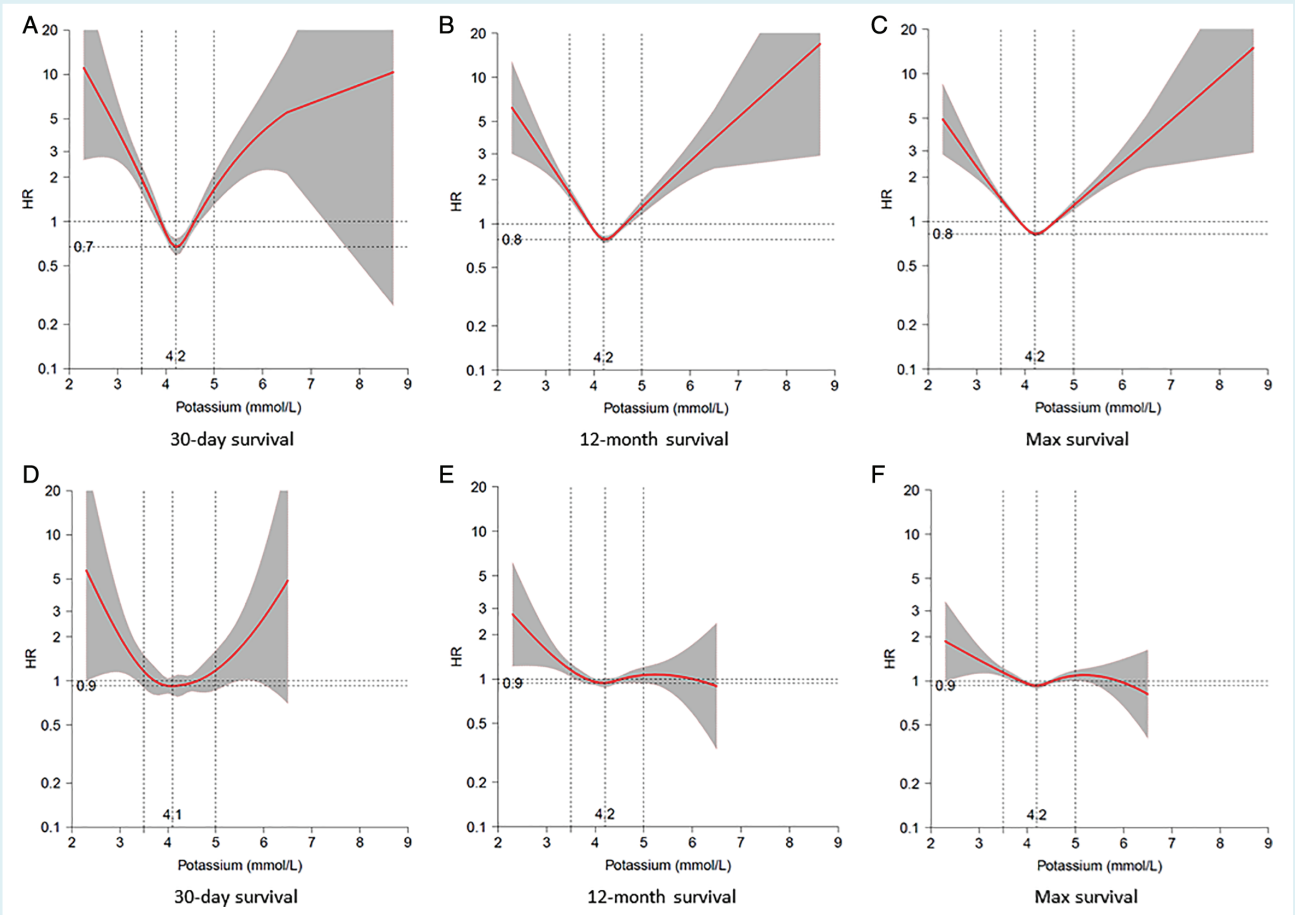

Figure 4 Risk of mortality by baseline potassium level. (*A*–*C*) Unadjusted risk of 30-day (*A*) and 12-month mortality (*B*) and unadjusted risk of mortality at maximal follow-up (*C*): K^+ 4.2 mmol/L was associated with the lowest risk of mortality. (*D*) Adjusted risk of 30-day mortality: K^+ 4.1 mmol/L was associated with the lowest adjusted risk of 30-day mortality. (*E*) Adjusted risk of 12-month mortality and (*F*) adjusted risk of mortality at maximal follow-up: K^+ 4.2 mmol/L was associated with the lowest adjusted risk of mortality.

with increased risk of hyperkalaemia after adjusting for baseline characteristics (online supplementary *Figure S3*).

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; but (iii) after covariate adjustment, hypokalaemia remained associated with increased long-term mortality at all time ranges, whereas hyperkalaemia remained associated only with increased short-term but not long-term mortality; and (iv) the risk of incident hyperkalaemia was potentially associated with both higher and lower potassium levels at baseline.

Optimal potassium levels and mortality

This study confirms what prior analyses from clinical trials and registries have shown, that hyperkalaemia and hypokalaemia are both associated with increased risk of mortality in patients with heart failure.[11,16,18–20] 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^+ 4.2 mmol/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^+ 4.1–4.2 mmol/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]

Hypokalaemia and outcomes

Hypokalaemia was associated with mortality in short- and long-term follow-up. Hypokalaemia may be a risk marker for high or variable diuretic dosing and thus more severe heart failure, congestion, chronic kidney disease, and cardiorenal syndrome. Hypokalaemia is worsened by diuretic therapy and patients with hypokalaemia may be more resistant to diuretic therapy in acute decompensated heart failure.[23,24] Indeed, in this study, baseline hypokalaemia was visually associated with an increased risk of hyperkalaemia, 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, hypokalaemia 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 results in hypokalaemia.[6] The results of the current study, taken together with prior studies, reinforce the importance of avoiding hypokalaemia in patients with heart failure.

Hyperkalaemia and outcomes

While hyperkalaemia was associated with increased short and long-term mortality in univariable analyses, after adjustment, hyperkalaemia was associated only with increased mortality at 30 days, not at 12 months or maximal follow-up. Thus, hyperkalaemia 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 hyperkalaemia 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 hypokalaemia – suggesting MRAs may be used in part to increase potassium levels – and hyperkalaemia, which may be a consequence of MRA therapy. Indeed, ACE inhibitors, ARBs, and MRAs are common causes of hyperkalaemia and patients with hyperkalaemia are more likely to be on these drugs, though prior work shows that mortality benefit of these drugs remains, even with hyperkalaemia.[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 hyperkalaemia 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 4.2–4.7 mmol/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 hyperkalaemia 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 hyperkalaemia in particular, our study highlights the importance of recognizing underlying factors as well as under-utilization of renin–angiotensin–aldosterone system inhibitors, particularly MRAs, as potentially the main drivers of worse long-term outcomes. Future studies using potassium supplements for hypokalaemia or potassium binders for hyperkalaemia 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 SwedeHF 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 dyskalaemia and outcomes. Third, while most centres in Sweden currently measure potassium in plasma, some of these centres previously or in addition measured potassium in serum and the SwedeHF 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, hypokalaemia was associated with increased long-term mortality, while hyperkalaemia 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.

Supplementary Information

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

Table S1. ICD-10 and procedure codes used for baseline comorbidities and outcomes

Table S2. Association between baseline potassium level and mortality.

Figure S1. Study population and exclusion criteria.

Figure S2. Unadjusted risk of hyperkalaemia by baseline potassium level.

Figure S3. Adjusted risk of hyperkalaemia by baseline potassium level.

Funding

The Swedish Heart Failure Registry is funded by the Swedish Federal Government through the Swedish Association of Local Authorities and Regions. This study was supported by grants to Lars Lund's institution from the Swedish Research Council (grants 2013-23897-104604-23, 523-2014-2336 and 2019-01059), the Swedish Heart Lung Foundation (grants 20120321 and 20150557), and the Stockholm County Council (grant 20110120 and 20140220). No funding agency had any role in the design and conduct of the study, in the collection, management, analysis, or interpretation of the data, or in the preparation, or approval of the manuscript.

Conflict of interest: L.B.C. reported receiving grant support from Abbott and consulting honoraria from AstraZeneca. R.J.M. reported receiving research support from the National Institutes of Health, Akros, Amgen, AstraZeneca, Bayer, GlaxoSmithKline, Gilead, Luitpold, Medtronic, Merck, Novartis, Otsuka, and ResMed; honoraria from Abbott, AstraZeneca, Bayer, Janssen, Luitpold Pharmaceuticals, Medtronic, Merck, Novartis, and ResMed; and has served on an advisory board for Amgen, Luitpold, Merck and Boehringer Ingelheim. G.S. reported receiving grant support from Merck Sharp and Dome, Boehringer Ingelheim, AstraZeneca, Vifor and Swedish Heart and Lung Foundation; speaking honoraria and consulting honoraria from Vifor, Società Prodotti Antibiotici, Servier, AstraZeneca, Genesis, Roche. A.D.D. reported receiving research funding from Amgen, American Heart Association, NHLBI, and Novartis and consulting honoraria from Novartis. J.J.C. reported receiving grant support from AstraZeneca, Viforpharma, Novartis, Merck Sharp and Dome, Astellas, the Swedish Heart and Lung Foundation, and Stockholm County Council. U.D. reported receiving speaking and consulting honoraria from Novartis and Amgen and grant support from AstraZeneca and Boehringer Ingelheim. S.D.A. reported receiving grant support from Vifor and Abbott Vascular and consulting honoraria from Bayer, Boehringer Ingelheim, Servier, Novartis, Vifor,

Impulse Dynamics, and Brahms. M.L. reported receiving speaking and consulting honoraria from Novartis, Relypsa, and Vifor. A.F.H. reported receiving research support from American Regent, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Genentech, GlaxoSmithKline, Merck, Novartis, Verily and consulting honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Merck and Novartis. B.P. reported that he is a consultant to Bayer, AstraZeneca, Sanofi, Relypsa/Vifor, scPharmaceuticals, Sarfez, KBP Biosciences, Tricida, and Stealth peptides; and has a patent for site specific delivery of eplerenone to the myocardium (US patent 9931412). L.H.L. reported grants from AstraZeneca, Relypsa and Novartis and consulting honoraria from AstraZeneca, Relypsa, ViforPharma, Novartis, Bayer, Merck, HeartWare. L.B. has nothing to disclose.

References

1. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Budi Siswanto B, Sliwa K, Filippatos G. Heart failure: preventing disease and death worldwide. *ESC Heart Fail* 2014;**1**:4–25.
2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016;**13**:368–378.
3. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;**388**:1545–1602.
4. Urso C, Brucculeri S, Caimi G. Acid-base and electrolyte abnormalities in heart failure: pathophysiology and implications. *Heart Fail Rev* 2015;**20**:493–503.
5. Cleland JG, Dargie HJ, Robertson I, Robertson JI, East BW. Total body electrolyte composition in patients with heart failure: a comparison with normal subjects and patients with untreated hypertension. *Br Heart J* 1987;**58**:230–238.
6. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004;**43**:155–161.
7. Burtis CA, Ashwood ER. *Tietz Textbook of Clinical Chemistry*, 3rd ed. Philadelphia, PA: Saunders Company; 1999.
8. *Laurell's Clinical Chemistry in Medical Praxis*, 6th ed. Lund, Sweden: Studentlitteratur; 1991.
9. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur Heart J* 2017;**38**:104–112.
10. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:245–251.
11. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Køber L, Torp-Pedersen C, Søgaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* 2017;**38**:2890–2896.
12. Kovesdy CP, Matsushita K, Sang Y, Brunskill NJ, Carrero JJ, Chodick G, Hasegawa T, Heerspink HL, Hirayama A, Landman GW, Levin A, Nitsch D, Wheeler DC, Coresh J, Hallan SI, Shalev V, Grams ME; CKD Prognosis Consortium. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. *Eur Heart J* 2018;**39**:1535–1542.
13. Gasparini A, Evans M, Barany P, Xu H, Elinder C, Jernberg T, Ärnlöv J, Lund LH, Carrero JJ. Plasma potassium ranges associated with mortality across stages of chronic kidney disease: the Stockholm CREAtinine Measurements (SCREAM) Project. *Nephrol Dial Transplant* 2019;**34**:1534–1541.
14. Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail* 2010;**12**:25–31.
15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–612.
16. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD; Randomized Aldactone Evaluation Study (RALES) Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail* 2014;**7**:573–579.
17. Pitt B, Bakris G, Ruilope LM, DiCarlo L, Mukherjee R. Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation* 2008;**118**:1643–1650.
18. Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, Pitt B. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;**28**:1334–1343.
19. Núñez J, Bayés-Genís A, Zannad F, Rossignol P, Núñez E, Bodí V, Miñana G, Santas E, Chorro FJ, Mollar A, Carratalá A, Navarro J, Górriz JL, Lupón J, Husser O, Metra M, Sanchis J. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. *Circulation* 2018;**137**:1320–1330.
20. Palaka E, Grandy S, Darlington O, McEwan P, van Doornewaard A. Associations between serum potassium and adverse clinical outcomes: a systematic literature review. *Int J Clin Pract* 2019;**74**:e13421.
21. Cooper LB, Hammill BG, Peterson ED, Pitt B, Maciejewski ML, Curtis LH, Hernandez AH. Consistency of laboratory monitoring during initiation of mineralocorticoid receptor antagonist therapy in patients with heart failure. *JAMA* 2015;**314**:1973–1975.
22. Nilsson E, De Deco P, Trevisan M, Bellocco R, Lindholm B, Lund LH, Coresh J, Carrero JJ. A real-world cohort study on the quality of potassium and creatinine monitoring during initiation of mineralocorticoid receptor antagonists in patients with heart failure. *Eur Heart J Qual Care Clin Outcomes* 2018;**4**:267–273.
23. Tromp J, Ter Maaten JM, Damman K, O'Connor CM, Metra M, Dittrich HC, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, van der Wal MH, Jaarsma T, van Veldhuisen DJ, Hillege HL, Voors AA, van der Meer P. Serum potassium levels and outcome in acute heart failure (data from the PROTECT and COACH trials). *Am J Cardiol* 2017;**119**:290–296.
24. Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CR, Hamer J. Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. *Br Heart J* 1979;**42**:316–325.
25. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, Gheorghiade M, Fonarow GC. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail* 2015;**3**:136–145.
26. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd N, Bakris G, Pitt B, Zannad F. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail* 2014;**7**:51–58.
27. Rossignol P, Zannad F, Pitt B. Time to retrieve the best benefits from renin angiotensin aldosterone system (RAAS) inhibition in heart failure patients with reduced ejection fraction: lessons from randomized controlled trials and registries. *Int J Cardiol* 2014;**177**:731–733.
28. Trevisan M, de Deco P, Xu H, Evans M, Lindholm B, Bellocco R, Barany P, Jernberg T, Lund LH, Carrero JJ. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. *Eur J Heart Fail* 2018;**20**:1217–1226.
29. Bandak G, Sang Y, Gasparini A, Chang AR, Ballew SH, Evans M, Arnlov J, Lund LH, Inker LA, Coresh J, Carrero JJ, Grams ME. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm CREAtinine Measurements (SCREAM) Project. *J Am Heart Assoc* 2017;**6**(7):e005428.
30. Beusekamp JC, Tromp J, van der Wal HH, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Metra M, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Rossignol P, Zannad F, Voors AA, van der Meer P. Potassium and the use of renin-angiotensin-aldosterone system inhibitors in heart failure with reduced ejection fraction: data from BIOSTAT-CHF. *Eur J Heart Fail* 2018;**20**:923–930.
31. Lund LH, Pitt B. Is hyperkalaemia in heart failure a risk factor or a risk marker? Implications for renin-angiotensin-aldosterone system inhibitor use. *Eur J Heart Fail* 2018;**20**:931–932.
32. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GM, Dahlstrom U, Lund LH. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2018;**20**:1326–1334.
33. Cooper LB, Savarese G, Carrero JJ, Szabo B, Jernberg T, Jonsson A, Dahlboum C, Dahlstrom U, Larson A, Lund LH. Clinical and research implications of serum versus plasma potassium measurements. *Eur J Heart Fail* 2019;**21**:536–537.