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Original article

Short-term prognosis of changes in plasma potassium following an episode of hyperkalaemia in patients with chronic heart failure

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ABSTRACT

Background/Aim: There is an increasing prevalence of chronic heart failure (HF). It is well known that patients with HF and disturbances in the potassium level have an increased mortality risk. The aim of this study was to investigate the prognosis of a second plasma-potassium measurement after an episode with hyperkalaemia on short-term mortality in patients with chronic HF.

Methods and results: From Danish national registers, 2,339 patients with chronic HF and hyperkalaemia (>4.6 mmol/L) at first potassium measurement within 14–365 days from concomitant treatment were identified. To be included, a second measurement was required within 6–30 days subsequent to the first measurement and the 60-day mortality was observed. Based on the second measurement, the patients were divided into five groups: <3.5 mmol/L ($n = 257$), 3.5–4.0 mmol/L ($n = 709$), 4.1–4.6 mmol/L ($n = 1,204$, *reference*), 4.7–5.0 mmol/L ($n = 89$) and >5.0 mmol/L ($n = 80$). To assess all-cause and cardiovascular mortality, we used the Cox regression model. The multivariable analysis showed that patients with potassium concentrations <3.5 mmol/L (hazard ratio (HR): 3.03; 95% CI: 2.49–3.70) and 3.5–4.0 mmol/L (HR: 1.81; 95% CI: 1.54–2.14) had a worse prognosis compared to the reference. We observed similar results when calculating the risk of cardiovascular mortality. A restricted cubic spline curve showed a U-shaped relationship between plasma-potassium and all-cause mortality.

Conclusion: Patients with chronic HF and hyperkalaemia who became hypokalaemic after 6–30 days were associated with a higher 60-day all-cause and cardiovascular mortality compared to the reference. This also applied for patients with low normal potassium concentrations (3.5–4.0 mmol/L).

1. Introduction

Chronic heart failure (HF) is an increasing problem in public healthcare and is associated with considerable morbidity and mortality [1]. HF affects approximately 23 million people worldwide, primarily the elderly, and the prevalence of HF is predicted to increase by 46% from 2012 to 2030 [1,2].

Patients with chronic HF are usually treated with loop-diuretics and angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II-receptor blockers (ARBs), which influence potassium homeostasis [3]. Loop diuretics are known to induce hypokalaemia, while treatment with ACE inhibitors and ARBs or treatment with mineralocorticoid receptor antagonists (MRAs) can lead to hyperkalaemia due to impaired or retained potassium excretion, respectively [4].

Hyperkalaemia is defined as plasma-potassium >4.6 mmol/L and is associated with an increased risk of arrhythmias, which can be fatal [5,

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6]. Thus, a well-adjusted potassium homeostasis is fundamental for normal myocardial function, especially in patients with heart disease [6].

Despite the increasing prevalence of HF, there is still little knowledge regarding the effect of changes in plasma-potassium levels in patients with chronic HF and hyperkalaemia. This study aimed to investigate the impact of changes in plasma-potassium after an episode with hyperkalaemia on short-term mortality in patients with chronic HF. For this purpose, Danish national registers were used to examine 60-day all-cause and presumed cardiovascular causes of mortality in patients with HF after a second potassium measurement following hyperkalaemia.

2. Method

2.1. Data sources

The study is a register-based cohort study. In Denmark, several national and regional registers contain personal data on all residents, including information regarding the residents' healthcare.

To obtain information concerning the residents' age and sex, the Danish Civil Registration System was used [7]. The Danish National Patient Register contains information about hospital contacts [8]. This study used the register to obtain information regarding operation and procedure codes, discharge dates, and diagnoses. Discharge diagnoses are divided into primary and secondary diagnoses, according to the WHO International Classification of Diseases (ICD). ICD-8 was used until

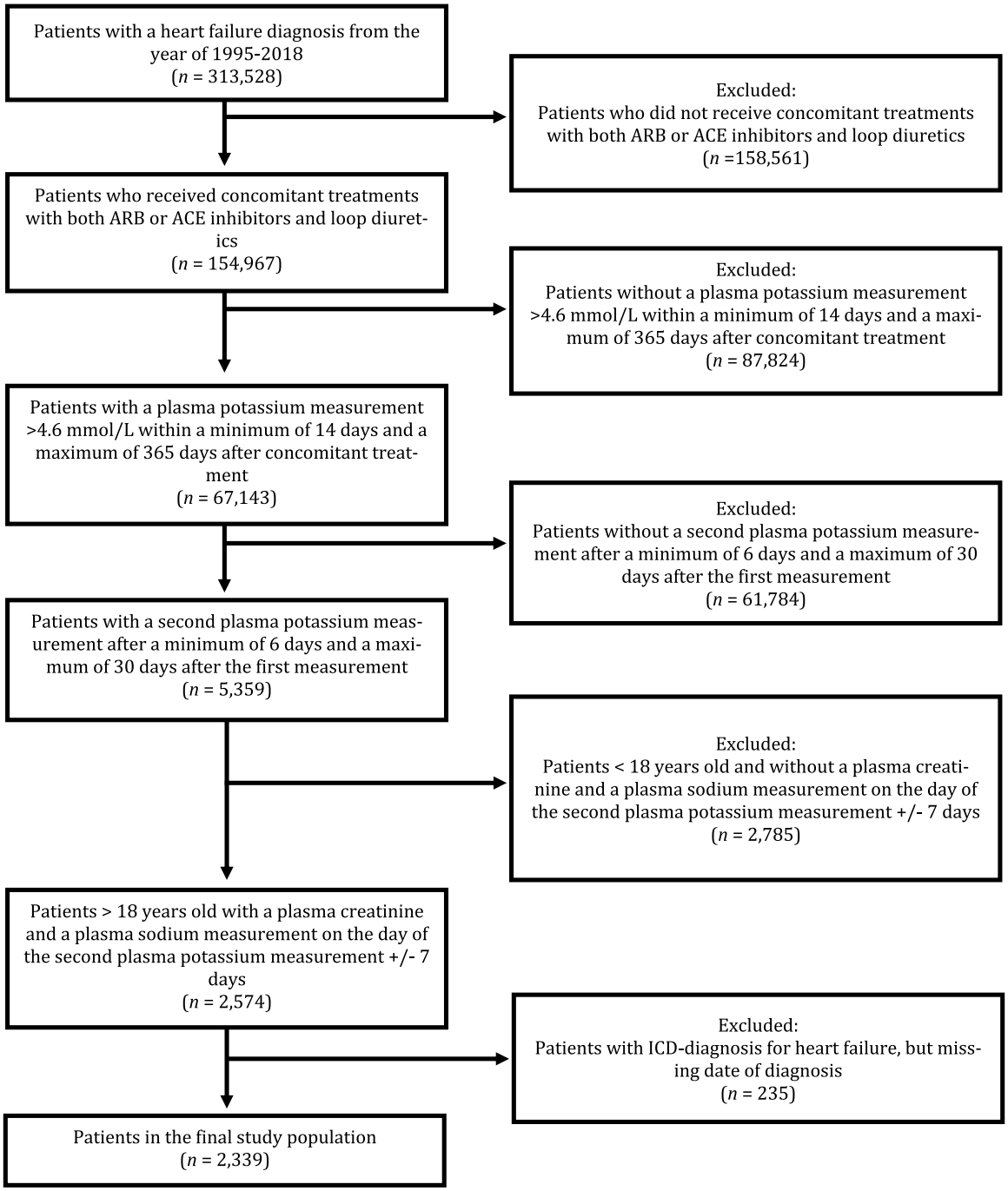

Fig. 1. - Study population flowchart.

1995 and was then updated to ICD-10. Information about survival status was obtained from the Danish Register of Causes of Death [9].

All prescriptions from Danish pharmacies have been registered in Danish National Prescription Registry since 1994 based on ATC codes (Anatomical Therapeutic Chemical codes) [10]. Since the Danish healthcare system partially finances the residents' drug consumption, all pharmacies are obligated by law to register all drug prescriptions, thus providing a reliable register. From this register, information on patients' redeemed prescriptions was retrieved.

Data from laboratories in Danish regions are stored in an electronic register. This study retrieved blood test results from four out of five healthcare regions in Denmark (North Denmark Region, Southern Denmark, Region Zealand, and Capital Region of Denmark). The four regions are covering approximately 4000,000 residents of a total of 5806,015 residents in Denmark (year 2018) [11]. The blood tests were collected from either primary care visit to an outpatient clinic, or during hospitalization in the period 1995–2018.

2.2. Study population

This study population consists of patients over the age of 18 years with a first-time chronic HF diagnosis in the period 1995 to 2018. Chronic HF was defined as patients with a HF diagnosis who also received ACE inhibitors or ARBs and loop-diuretics (see ICD-codes in Table S1 and ATC-codes in Table S2; both in supplementary material).

The first plasma-potassium measurement was retrieved between 14 and 365 days from HF and concomitant treatment. Patients with potassium measurements >4.6 mmol/L (hyperkalaemia) were included in the study. A second plasma-potassium measurement was also required between 6 and 30 days after the first measurement [12]. Generally, the plasma-potassium level tends to rectify within a few days, independent of treatment, for which reason the timeframe has been assessed to be reasonable [13]. Finally, patients with missing measurements of plasma-sodium and plasma-creatinine +/- seven days from the second plasma-potassium measurement were excluded.

Inclusion and exclusion criteria are illustrated in a flowchart in Fig. 1.

2.3. Comorbidities and concomitant pharmacotherapy

The Danish National Patient Register was used to identify patients with clinically relevant comorbidities, operations, and procedures (see ICD-codes in Table S1 and operation- and procedure-codes in Table S3, both in supplementary material). We identified relevant comorbidities within five years prior to the second plasma-potassium measurement. The following comorbidities were identified: chronic obstructive pulmonary disease (COPD), atrial fibrillation and atrial flutter, history of second- or third-degree atrioventricular block (AV-block), hypertension, and ischemic heart disease (IHD). IHD was also defined as patients having a history of a previous coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). We also identified patients with an implantable cardioverter-defibrillator and a biventricular pacemaker (+/- implantable cardioverter-defibrillator).

To assess renal function, the estimated glomerular filtration rate (eGFR) was calculated based on the plasma-creatinine measurement by use of the CKD-EPI creatinine equation [14]. Kidney insufficiency was defined as an eGFR<30 mL/min/1.73m^2. In addition, patients on haemodialysis are considered to have kidney insufficiency as well.

Hypothyroidism, stroke, and all malignancies diagnosed five years prior to the second plasma-potassium measurement were also identified. Diabetes mellitus was considered comorbidity if diagnosed with an ICD code, but also if a patient has redeemed any prescription on antidiabetic medication prior to the second plasma-potassium measurement (see ATC-codes in Table S2 in supplementary material).

ATC codes identified the following concomitant pharmacotherapies prior to the second plasma-potassium measurement: digoxin, potassium supplements, beta blockers, calcium channel blockers, thiazides, mineralocorticoid receptor antagonists, and NSAID (see ATC-codes in Table S2 in supplementary material).

2.4. Exposure variable

Based on the first potassium measurement, which was obtained 14–365 days from HF, the patients were divided into two groups: mild hyperkalaemia (4.7–5.0 mmol/L) and moderate-severe hyperkalaemia (>5.0 mmol/L). The second potassium measurement was obtained 6–30 days subsequent to the first measurement. Using the potassium level at the second measurement, the patients were divided into five groups. Based on the normal potassium reference interval (3.5–4.6 mmol/L), the groups were defined as group 1 (<3.5 mmol/L), group 2 (3.5–4.0 mmol/L), group 3 (4.1–4.6 mmol/L), group 4 (4.7–5.0 mmol/L) and group 5 (>5.0 mmol/L).

Plasma-potassium interval 4.1–4.6 mmol/L was used as a reference for statistical analysis, as the group contained the majority of the patients, and the potassium measurements were within the reference interval.

2.5. Outcome measure

In this study, the outcome was cardiovascular mortality and all-cause mortality within a timeframe of 60 days from the second plasma-potassium measurement.

2.6. Statistical analysis

In the descriptive statistics, continuous variables were presented as 25th and 75th percentiles and median. These variables are assumed to be non-parametric, for which reason the Kruskal-Wallis rank sum test was used to evaluate differences in the variables. χ^2-tests was conducted to identify differences in categorical variables, which were displayed as counts and percentages.

A Kaplan-Meier plot was used to illustrate survival in the five plasma-potassium groups. The association between the plasma-potassium groups and mortality within 60 days was examined using a Cox proportional hazard regression model. The assumptions of the Cox regression model were tested, namely proportionality of the hazards, linearity, and possible interactions. Proportionality of the hazards was assessed by looking at plots with Schoenfeld residuals. This assumption was not violated. We tested for interactions on mortality between the variable's plasma-potassium level and age, sex, renal function, and diabetes mellitus. This model was compared to a Cox regression model without an interaction term with a likelihood ratio test. When testing for interactions, a two-sided p-value < 0.01 was deemed statistically significant and a two-sided p-value <0.05 for the other tests. We did not find significant interactions.

Age was divided into five intervals using cut-off values from 20th percentiles: 18–67, 68–74, 75–79, 80–85, and 86–104 and included in the regression models.

Relative risks were displayed as hazard ratio (HR) and absolute risks as percentages, both with a 95% confidence interval (95% CI). The multivariable analyses include age, sex, renal insufficiency, IHD, biventricular pacemaker, diabetes mellitus, cancer, stroke, atrial flutter/fibrillation, COPD, NSAID, potassium supplements, thiazides, mineralocorticoid receptor antagonists, beta blockers, and calcium channel blockers were included as covariates. Multivariable Cox regression was also used to model an average treatment effect of the second potassium measurement in order to estimate the 60-day absolute risks of all-cause and cardiovascular mortality standardised for age and sex. To investigate the association between potassium and mortality within 60 days, we also created a restricted cubic splines curve which showed the absolute risk in a population and was standardised for age and sex. The programs used to process data and perform analyses were SAS, version

9.4 and R, version 4.0.3 [15].

3. Results

3.1. Demographics

This study included 2339 patients, and Table 1 displays characteristics of the study population across second plasma-potassium measurements (<3.5 mmol/L, 3.5–4.0 mmol/L, 4.1–4.6 mmol/L, 4.7–5.0 mmol/L and >5.0 mmol/L). Generally, the groups were characterized by advanced age, and the majority of the patients were men. Approximately 60% of the population was hospitalized at the first measurement and 90% at the second measurement.

At the time of the first potassium measurement, all patients had a plasma concentration >4.6 mmol/L (hyperkalaemia), of which 73.5% had mild hyperkalaemia, and 26.5% had moderate-severe hyperkalaemia. At the second measurement, 7% of the patients still had hyperkalaemia, whilst 11% developed hypokalaemia and 82% had a normalized level within the reference interval.

3.2. Survival analysis

3.2.1. All-cause mortality

The patients included in this study were observed for 60 days following their second plasma-potassium measurement, and the total all-cause mortality events within this period included 793 deaths (33.9%). Survival curves were illustrated in Fig. 2, and the mortality appeared different in each of the five groups. Mortality in the five strata was 62.7%, 42.4%, 24.2%, 15.7%, and 33.8%, respectively.

The results from the univariable and multivariable Cox proportional hazard regression model are illustrated in Fig. 3. The forest plot illustrates, that patients with a potassium level <3.5 and 3.5–4.0 mmol/L had a higher all-cause mortality risk compared to the reference group (HR 3.03 95% CI: 2.49–3.70 and HR 1.81, 95% CI: 1.54–2.14, respectively). Furthermore, the forest plot indicates a lower mortality risk in patients with a potassium level of 4.7–5.0 mmol/L and a slightly higher mortality risk in patients with a potassium level >5.0 mmol/L compared to the reference group. Likewise, the results from the univariable regression indicated an association with higher mortality risk in patients with a potassium level <3.5 and 3.5–4.0 mmol/L.

The standardized 60-day absolute risk of all-cause mortality in relation to plasma-potassium is summarised in Table 2. We found that patients with a plasma-potassium measurement of 4.6–5.0 mmol/L had the lowest risk of mortality and patients with a plasma-potassium measurement <3.5 mmol/L had the highest risk. The linear association between potassium and 60-day mortality was illustrated as a restricted cubic splines curve (Fig. 4). The curve demonstrated a U-shaped relationship, in which the optimal potassium level was estimated to be approximately 4.7 mmol/L. Furthermore, the curve shows a higher mortality at the high and low plasma-potassium levels.

3.2.2. Cardiovascular mortality

During the 60-day period, 553 (69.7%) patients had a cardiovascular cause of death. The cardiovascular mortality in the five strata was

Table 1
The characteristics of the study population at the second plasma-potassium measurement. Data are presented as the number of patients (column percentage) or as median with interquartile range using the 25th and 75th percentiles. [a]eGFR < 30 mL/min/1.73 m^2.

Characteristics of the study population at the second plasma potassium measurement						
Variables	*Plasma potassium groups*					*p-value*
	< 3.5mmol/L	3.5–4.0mmol/L	4.1–4.6mmol/L	4.7–5.0mmol/L	>5.0mmol/L	
Number of patients	257 (11%)	709 (30%)	1204 (52%)	89 (4%)	80 (3%)	
Sex, male	150 (58.4%)	423 (59.7%)	781 (64.9%)	58 (65.2%)	48 (60.0%)	0.105
Age	78.8 [18.1–97.5]	78.1 [20.7–99.2]	76.6 [28.4–103.9]	78.6 [36.9–96.9]	82.9 [49.2–98.1]	<0.001
Plasma-potassium, first measurement (4.7–5.0mmol/L)	172 (66.9%)	523 (73.8%)	933 (77.5%)	58 (65.2%)	34 (42.5%)	
Plasma-potassium, first measurement (>5.0mmol/L)	85 (33.1%)	186 (26.2%)	271 (22.5%)	31 (34.8%)	46 (57.5%)	
Plasma-sodium, first measurement	137 [113–161]	137 [111–156]	138 [116–163]	139 [118–145]	138 [120–146]	<0.001
Missing plasma-sodium	0	0	1	0	0	
Plasma-sodium, second measurement	137 [119–174]	138 [112–170]	138 [106–163]	139 [129–158]	139 [123–153]	<0.001
Renal insufficiency, first measurement [a]	112 (45.0%)	216 (32.4%)	267 (24.2%)	20 (33.9%)	22 (39.3%)	<0.001
Missing plasma-creatinine	8	42	99	30	24	
renal insufficiency, second measurement [a]	111 (43.2%)	212 (29.9%)	276 (22.9%)	30 (33.7%)	36 (45.0%)	<0.001
hospitalization, first measurement	219 (85.2%)	522 (73.6%)	530 (44.0%)	41 (46.1%)	36 (45.0%)	<0.001
hospitalization, second measurement	250 (97.3%)	664 (93.7%)	1107 (91.9%)	65 (73.0%)	66 (82.5%)	<0.001
Comorbidities						
Ischemic heart disease	131 (51.0%)	442 (62.3%)	722 (60.0%)	52 (58.4%)	49 (61.2%)	0.035
Hypertension	175 (68.1%)	476 (67.1%)	700 (58.1%)	48 (58.9%)	40 (50.0%)	<0.001
Hypothyroidism	10 (3.9%)	36 (5.1%)	56 (4.7%)	6 (6.7%)	6 (7.5%)	0.629
Atrial fibrillation or flutter	146 (56.8%)	408 (57.5%)	631 (52.4%)	47 (52.8%)	43 (53.8%)	0.244
2nd and 3rd atrioventricular block	14 (5.4%)	44 (6.2%)	77 (6.4%)	NA	4 (5.0%)	0.787
Stroke	42 (16.3%)	132 (18.6%)	181 (15.0%)	10 (11.2%)	11 (13.8%)	0.182
Diabetes mellitus	95 (37.0%)	268 (37.8%)	464 (38.5%)	34 (38.2%)	30 (37.5%)	0.991
Chronic obstructive pulmonary disease	80 (31.1%)	251 (35.4%)	335 (27.8%)	25 (28.1%)	24 (30.0%)	0.015
Malignancy	64 (24.9%)	166 (23.4%)	259 (21.5%)	18 (20.2%)	22 (27.5%)	0.518
Hemodialysis	13 (5.1%)	25 (3.5%)	36 (3.0%)	9 (10.1%)	6 (7.5%)	0.003
PCI or CABG	36 (14.0%)	124 (17.5%)	206 (17.1%)	17 (19.1%)	13 (16.2%)	0.723
Implantable cardioverter defibrillator	17 (6.6%)	45 (6.3%)	100 (8.3%)	NA	6 (7.5%)	0.292
Biventricular pacemaker	11 (4.3%)	20 (2.8%)	42 (3.5%)	NA	NA	0.571
Pharmacotherapy						
Anti-diabetic prescription	57 (22.2%)	175 (24.7%)	316 (26.2%)	22 (24.7%)	17 (21.2%)	0.607
Digoxin	52 (20.2%)	117 (16.5%)	256 (21.3%)	26 (29.2%)	22 (27.5%)	0.007
Potassium supplements	141 (54.9%)	337 (47.5%)	468 (38.9%)	25 (28.1%)	35 (43.8%)	<0.001
NSAID	36 (14.0%)	85 (12.0%)	132 (11.0%)	9 (10.1%)	14 (17.5%)	0.311
Beta blockers	153 (59.5%)	469 (66.1%)	841 (69.9%)	52 (58.4%)	50 (62.5%)	0.005
Mineralocorticoid receptor antagonists	65 (25.3%)	222 (31.3%)	379 (31.5%)	29 (32.6%)	25 (31.2%)	0.386
Calcium channel blockers	62 (24.1%)	112 (15.8%)	201 (16.7%)	20 (22.5%)	14 (17.5%)	0.023
Thiazides	28 (10.9%)	57 (8.0%)	93 (7.7%)	5 (5.6%)	7 (8.8%)	0.448

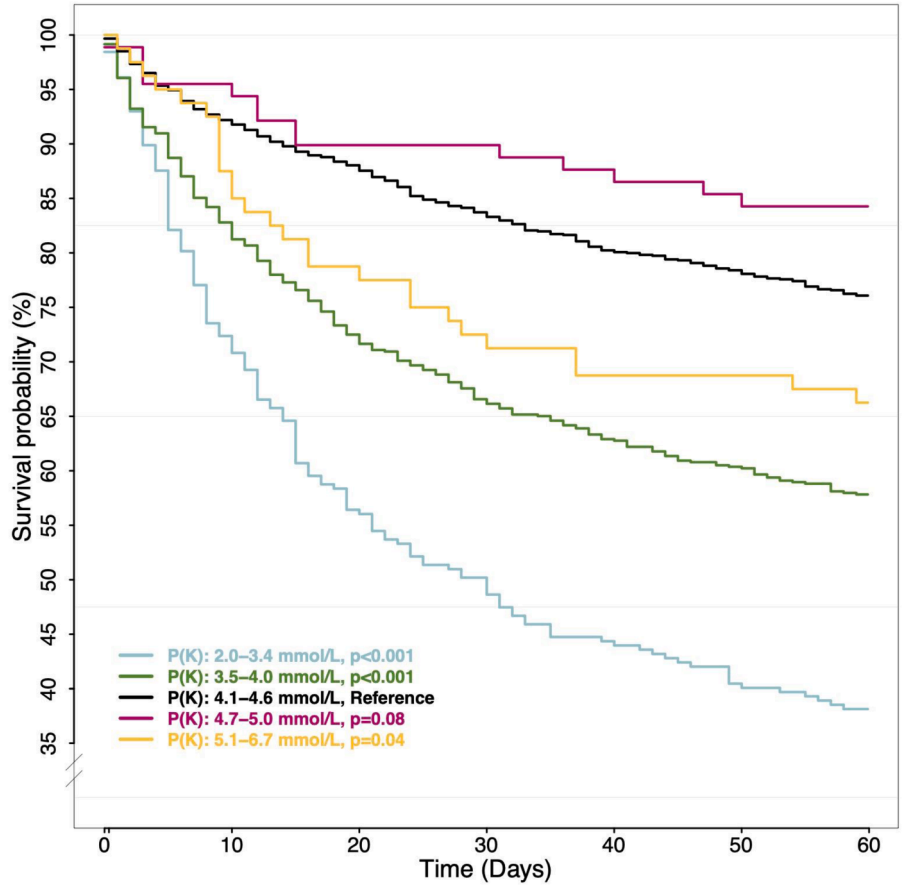

Fig. 2. - Kaplan-Meier survival curves displaying the 60-day survival probability for the five plasma-potassium intervals.

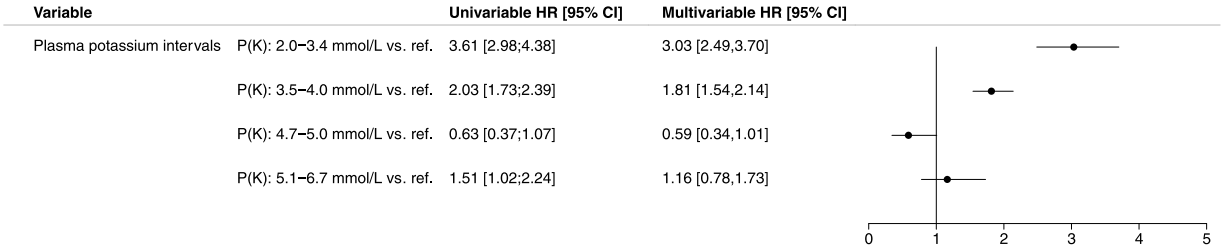

Fig. 3. - All-cause mortality in patients with chronic HF (60-day follow-up, $n = 2339$) after hyperkalaemia according to five potassium intervals. Multivariable analysis adjusted for age, sex, renal insufficiency, IHD, biventricular pacemaker, diabetes mellitus, cancer, stroke, atrial flutter/fibrillation, COPD, NSAID, potassium supplements, thiazides, mineralocorticoid receptor antagonists, beta blockers and calcium channel blockers. Plasma-potassium interval: 4.1–4.6 mmol/L represented the reference group.

Table 2
Standardized 60-day absolute risk of all-cause mortality after hyperkalemia in patients with HF ($n = 2339$). Adjusted for age, sex, renal insufficiency, IHD, biventricular pacemaker, diabetes mellitus, cancer, stroke, atrial flutter/fibrillation, COPD, NSAID, potassium supplements, thiazides, mineralocorticoid receptor antagonists, beta blockers, and calcium channel blockers. Plasma-potassium interval: 4.1–4.6 mmol/L represented the reference group.

	Absolute risk%, (95% CI)	60-d Risk difference%, (95% CI)	*p*-value	Average risk ratio, (95% CI)	*p*-value
P(K) 2.0–3.5mmol/L	56.8% [51.5–62.2]	31.1% [25.1–37.1]	<0.001	0.45 [0.39–0.516]	<0.001
P(K) 3.5–4.1mmol/L	40.7% [37.2–44.3]	15.1% [10.8–19.3]	<0.001	0.63 [0.55–0.71]	<0.001
P(K) 4.1–4.6mmol/L	25.7% [23.1–28.3]	Reference		Reference	
P(K) 4.7–5.0mmol/L	16.2% [8.6–23.8]	−9.5% [−17.4- −1.5]	0.019	0.63 [0.33–0.93]	0.016
P(K) 5.0–6.7mmol/L	29.0% [20.2–37.9]	3.3% [−5.8–12.5]	0.477	1.13 [0.77–1.49]	0.481

43.5%, 28.9%, 17.11%, 13.5%, and 22.5%, respectively.

Results from cause-specific Cox-regression (Fig. 5) showed that a second plasma-potassium measurement <3.5 mmol/L (HR: 3.11; 95% CI: 2.46–3.95) or 3.5–4.0 mmol/L (HR: 1.76; 95% CI: 1.45–2.14) were associated with higher risk of cardiovascular mortality compared to the reference group.

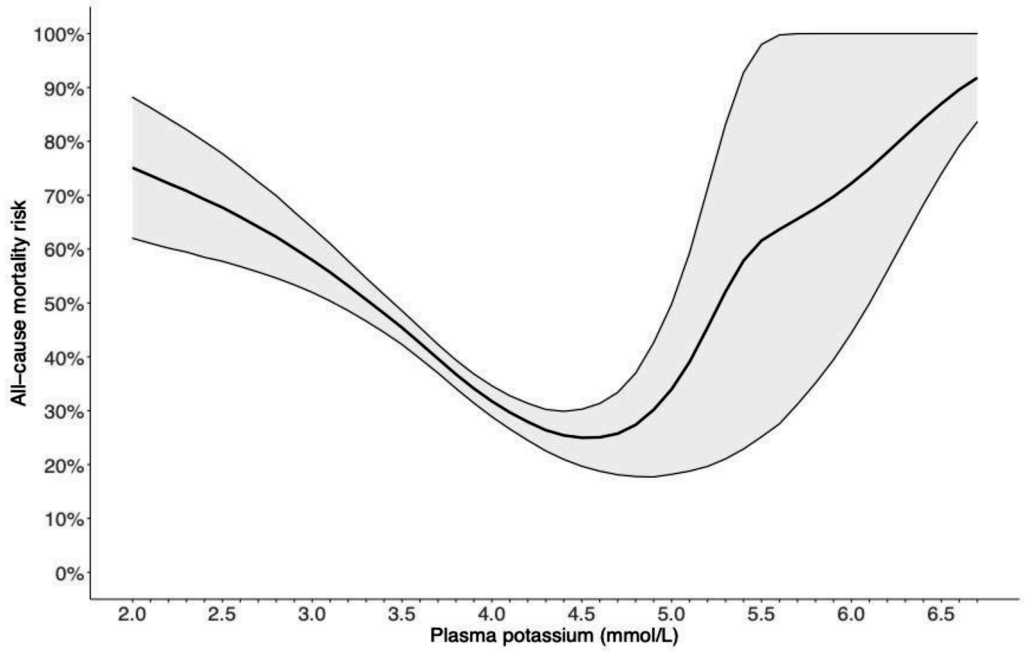

Fig. 4. - Illustrates a restricted cubic splines curve of the standardized 60-day absolute risk of all-cause mortality. Adjusted for age, sex, renal insufficiency, IHD, biventricular pacemaker, diabetes mellitus, cancer, stroke, atrial flutter/fibrillation, COPD, NSAID, potassium supplements, thiazides, mineralocorticoid receptor antagonists, beta blockers, and calcium channel blockers.

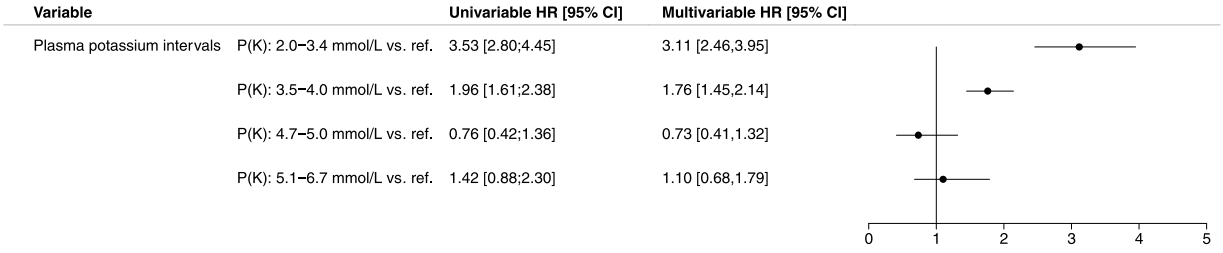

Fig. 5. - Forest plot showing cardiovascular mortality in patients with chronic HF (60-day follow-up, $n = 2339$) after hyperkalaemia according to five potassium intervals. Multivariable analysis adjusted for age, sex, renal insufficiency, IHD, biventricular pacemaker, diabetes mellitus, cancer, stroke, atrial flutter/fibrillation, COPD, NSAID, potassium supplements, thiazides, mineralocorticoid receptor antagonists, beta blockers, and calcium channel blockers. Plasma-potassium interval: 4.1–4.6 mmol/L represented the reference group.

4. Discussion

In this study, we have investigated the impact of changes in plasma-potassium after an episode with hyperkalaemia on short-term prognosis in patients with chronic HF. Based on Danish registers, 2339 patients were included, of whom 7% still had hyperkalaemia at the second plasma-potassium measurement, whilst 11% had developed hypokalaemia. During the 60-day period, we found that nearly 34% of the patients died of all causes, and nearly 70% of these were due to cardiovascular causes. The main findings of this study were, first, hypokalaemia and low normal potassium concentrations (3.5–4.0 mmol/L) were correlated with a significantly higher mortality risk when compared to the reference. Second, no significant higher mortality risk was seen in patients with moderate-severe hyperkalaemia. Third, no significant difference in all-cause mortality risk was observed in patients with mild hyperkalaemia. These results suggest the clinical importance of the correction of hyperkalaemia; however, it is essential to avoid overcorrection and thereby risk patients getting hypokalaemic or borderline hypokalaemic.

In several studies, hyperkalaemia has been found to be associated with a higher mortality risk in patients with chronic HF [16–18]. To our knowledge, no studies to date have investigated which effect a change in plasma-potassium has on the prognosis in patients with chronic HF subsequent to an episode of hyperkalaemia. Our study found that patients who developed hypokalaemia within 6–30 days were associated with higher risk of all-cause and cardiovascular mortality compared to other groups. This is consistent with other studies which show an association between hypokalaemia and a higher mortality [16,17,19]. Some of the studies used for comparison base their results on serum potassium, while our study was based on plasma potassium. However, the normal reference range for plasma potassium and serum potassium does not vary considerably [13].

In our study, we found that the optimal plasma-potassium level was 4.7 mmol/L in patients with chronic HF. A Swedish study by Cooper et al. investigated the optimal potassium range in patients with chronic HF. Results from the study suggested an optimal potassium level at 4.2 mmol/L [16]. Furthermore, a second study showed an optimal level between 4.2 and 4.7 mmol/L and a level outside this range was associated with a higher short-term mortality risk [17]. These findings are fairly consistent with our results regarding the optimal plasma-potassium level.

At the first plasma-potassium measurement, all patients had hyperkalaemia, and within 6–30 days, 11% of the patients developed hypokalaemia. Approximately two-thirds of these patients had mild

hyperkalaemia at their first measurement, and the relatively rapid shift in potassium could be caused by an overcorrection in treatment or fluid retention. More than half of the patients with moderate-severe hyperkalaemia at their first measurement still had a potassium level >5.0 mmol/L at their second measurement. Approximately half of the patients with high plasma potassium at the second measurement also had renal insufficiency, which could be the reason for the persistent hyperkalaemia in these patients.

Our results indicate that rapid changes in plasma potassium could be considered both a risk factor or a risk marker for a higher mortality in patients with HF. Multimorbidity and advanced age are common in patients with HF. Thus, the treatment of this patient group is complex, including balancing electrolyte concentrations. We believe that potassium plays two roles: a risk factor for a higher mortality and a risk marker for severe disease and multimorbidity, which can lead to overt mortality risk.

4.1. Study limitations

The study is an observational cohort study based on Danish registers, from which all information regarding the study population was obtained. Since the study is based on Danish registers, the results might be difficult to generalize to other populations in different geographical regions.

Although the Danish national registers provide access to great amounts of data about patients in the Danish healthcare system, some important clinical data is still missing: compliance, echocardiographic measurements, including left ventricular systolic function and functional status that may confound the associations between plasma-potassium levels and outcome. Furthermore, any treatment during hospitalization is not registered in the Danish National Prescription Registry and the majority of the patients in this study were hospitalized at the time of potassium measurements. Due to the lack of these data, it is not possible to investigate the effect of possible discontinuation or reduction of drug dose. During hospitalization, patients may have received treatment with e.g. potassium binders which could have affected the potassium level. Lack of these informations may lead to confounding.

The registers used are fairly well validated, but there is a risk that patients with or without chronic HF were misclassified, which could lead to misclassification bias. However, we do not have any indication that the potential misclassification would be differential across different potassium levels. Furthermore, it is not certain that the patients who died had an autopsy performed; thus, some uncertainty is related to the cause of death classification. For this reason, patients' cause of death might have been attributed incorrectly, leading to an overestimation of cardiovascular death.

5. Conclusion

In conclusion, our results indicate that patients with chronic HF and hyperkalaemia who became hypokalaemic after 6–30 days were associated with a higher 60-day all-cause and cardiovascular mortality compared to the reference group (4.1–4.6 mmol/L). This also applied to the lower part (3.5–4.0 mmol/L) of the normal reference interval (3.5–4.6 mmol/L).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.07.031.

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