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ORIGINAL ARTICLE
Heart failure/cardiomyopathy

Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction

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Aims Diuretic treatment is often needed in acute heart failure following myocardial infarction (MI) and carries a risk of abnormal potassium levels. We examined the relation between different levels of potassium and mortality.

Methods and results From Danish national registries we identified 2596 patients treated with loop diuretics after their first MI episode where potassium measurement was available within 3 months. All-cause mortality was examined according to seven predefined potassium levels: hypokalaemia <3.5 mmol/L, low normal potassium 3.5–3.8 mmol/L, normal potassium 3.9–4.2 mmol/L, normal potassium 4.3–4.5 mmol/L, high normal potassium 4.6–5.0 mmol/L, mild hyperkalaemia 5.1–5.5 mmol/L, and severe hyperkalaemia: >5.5 mmol/L. Follow-up was 90 days and using normal potassium 3.9–4.2 mmol/L as a reference, we estimated the risk of death with a multivariable-adjusted Cox proportional hazard model. After 90 days, the mortality rates in the seven potassium intervals were 15.7, 13.6, 7.3, 8.1, 10.6, 15.5, and 38.3%, respectively. Multivariable-adjusted risk for death was statistically significant for patients with hypokalaemia [hazard ratio (HR): 1.91, confidence interval (95%CI): 1.14–3.19], and mild and severe hyperkalaemia (HR: 2, CI: 1.25–3.18 and HR: 5.6, CI: 3.38–9.29, respectively). Low and high normal potassium were also associated with increased mortality (HR: 1.84, CI: 1.23–2.76 and HR: 1.55, CI: 1.09–2.22, respectively).

Conclusion Potassium levels outside the interval 3.9–4.5 mmol/L were associated with a substantial risk of death in patients requiring diuretic treatment after an MI.

Keywords Serum potassium • Heart failure after myocardial infarction • Mortality

Introduction

Heart failure is a common and serious complication of acute myocardial infarction (MI), and frequently requires treatment with a diuretic to relieve symptoms and fluid retention. Several studies have demonstrated an interaction between diuretic-induced hypokalaemia and complex cardiac arrhythmias,[1] and patients may present with both ventricular and supraventricular arrhythmias as well as cardiac arrest.[2] Displacement of serum potassium influences resting membrane potentials in cardiomyocytes, which in turn cause cellular hyperpolarity as well as increased excitability and automaticity.

Hypo- and hyperkalaemia following MI are associated with increased mortality,[3,4] but it is important to examine whether specific potassium intervals within the normal range also set patients at risk

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or appear particularly safe. At present, few if any studies provide sufficient evidence regarding the specific cut-off values of serum potassium levels to identify patients with an increased mortality risk.[5]

Using Danish health registries, we aim to examine the possible relationships between serum potassium levels and short-term mortality in patients requiring loop diuretic treatment after acute MI.

Methods

Databases

We used four health databases in this study; one containing hospitalizations, one containing medication dispensations, one containing birthday as well as date and cause of death, and one with blood test results. In Denmark, all residents have a unique and permanent civil registration number that enables linkage on an individual level among nationwide administrative registries. The Danish National Patient Register includes all hospitalizations in Denmark since 1978. At discharge, each hospitalization is coded with one primary and, if appropriate, one or more secondary diagnoses, according to the International Classification of Diseases. Until 1994, the 8th revision (ICD-8) was in use, and from 1994 onwards the 10th revision (ICD-10). The National Register for Medicinal Statistics includes all dispensed prescriptions from all Danish pharmacies since 1995 and is based on the Anatomical Therapeutic Chemical (ATC) System, and the accuracy has been validated.[6] Blood test results were obtained from electronic registries of laboratory data, and we had access to data covering ~1.5 million people. Date of death, date of birth, and vital status were obtained from the Danish Register of Causes of Death and the Central Personal Registry.

Study population

The study population was selected according to following criteria: (i) a first MI episode, (ii) apparent heart failure as indicated by diuretic treatment after MI, and (iii) a measurement of serum potassium level within 90 days after the MI. The date of the first potassium measurement represented time 0 of our study. The patients were censored on 31 December 2012 or after 90 days of follow-up, whichever came first. The primary outcome was all-cause mortality.

First, patients with a first MI were selected from The Danish National Patient Register between 2004 and 2012. Myocardial infarction (ICD-10: I21) has been validated to be accurate.[7,8] Secondly, we identified patients who received a prescription for loop diuretics (ATC: C03C) within 90 days using the National Register for Medicinal Statistics (prescription database). Administration of loop diuretics as a proxy for heart failure has already been associated with increased mortality without being correlated with estimated glomerular filtration rates among heart failure patients. This implies that use of loop diuretics is most likely due to cardiac causes rather than renal pathology.[9–12] Based on several studies which have shown that heart failure following MI frequently develops in the first few months, patients were allowed a window period of 90 days (from MI) to redeem the loop diuretic prescription.[13–16] Finally, we obtained one serum potassium level for each patient within 90 days following heart failure defined as a prescription of loop diuretics following an MI. Potassium measurements from the first day following MI were excluded.

Potassium intervals and comorbidities

Baseline demographics and clinical characteristics were compared among groups of patients stratified according to the following potassium levels: <3.5, 3.5–3.8, 3.9–4.2, 4.3–4.5, 4.6–5.0, 5.1–5.5, and >5.5 mmol/L. The serum potassium interval of 3.9–4.2 mmol/L was used as a reference for statistical analysis. Hypokalaemia was defined as potassium <3.5 mmol/L and hyperkalaemia as >5.0 mmol/L.

Based on the van Deursen *et al.* study on comorbid illnesses in heart failure, we selected 11 covariates prior to the analysis including age, gender, diabetes, chronic obstructive pulmonary disease (J44), stroke (ICD-10: I61, I62, I63, I64), atrial fibrillation (ICD-10: I48), hypertension, drugs with effect on renin–angiotensin system, potassium-sparing diuretics, β-blockers, and potassium supplements.[17] It is important to state that we did not analyse our population's drug administration after measured serum potassium.

Patients with a loop diuretic prescription or diagnosed with heart failure or chronic kidney disease before their first acute MI episode were excluded. Renal insufficiency and anaemia were identified within 1 week from serum potassium measurement. Renal insufficiency was defined as a serum creatinine level of >105 and >90 μmol/L for men and women, respectively (age between 18 and 70 years). Regarding patients over 70 years, renal insufficiency was defined as serum creatinine level >125 and >105 μmol/L for men and women, respectively.[18–20] Anaemia was defined by a serum haemoglobin level of <8.1 mmol/L for men and <7.5 mmol/L for women.[17] Diabetes was defined as administration of glucose-lowering drugs, and hypertension as a prescription of minimum two concomitant classes of antihypertensive drugs.[21]

All comorbidities were defined prior to the MI episode. Drug dispensations included in the analysis had to be prescribed in the period from the MI episode and serum potassium measurement.

Statistical analysis

Kaplan–Meier cumulative mortality curves were plotted for the seven preselected potassium intervals to illustrate trends in mortality over time. Cox proportional hazard regression models were used to determine the risk of death in heart failure patients with different potassium intervals, and adjusted for the defined covariates. To validate this statistical model, we tested the three Cox proportional hazard model assumptions: proportionality, linearity, and interactions.

The association of potassium with mortality was also assessed using restricted cubic splines with knots at the 10th, 25th, 50th, 75th, and 90th percentiles of potassium.

Relative risks are presented as hazard ratios (HRs) with 95% confidence intervals (95% CIs). *P*-values of <0.05 were considered significant. Analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and R statistics (version 3.0.1, R Development Core Team).

Results

Baseline characteristics

From Danish national registries we identified 2596 patients who were discharged after an MI with a prescription of loop diuretics, where a serum potassium measurement was available within 90 days following discharge. The baseline characteristics of the population reported according to each potassium level are presented in *Table 1*. This study population was characterized by advanced age, there were more men than women, and ~40% of the patients had an increased creatinine level post-MI indicating renal insufficiency.

Loop diuretics were reclaimed, in average, 20th day after acute MI. Further on, it can be observed that a standard loop diuretic dosage, in the period post-MI until potassium measurement, was of 40.24 mg (±11.66) in a package containing 113.04 (±61.77) pills. A total of 76.4% of the patients received potassium supplement in

Table 1 **Baseline characteristics of patients (*N* = 2596)**

	K <3.5 mmol/L	K: 3.5–3.8 mmol/L	K: 3.9–4.2 mmol/L	K: 4.3–4.5 mmol/L	K: 4.6–5.0 mmol/L	K: 5.1–5.5 mmol/L	K >5.5 mmol/L	Total
Sex								
Female	77 (60.63%)	156 (51.83%)	341 (44.87%)	210 (39.4%)	247 (38.53%)	93 (53.45%)	35 (58.33%)	1159 (44.65%)
Male	50 (39.37%)	145 (48.17%)	419 (55.13%)	323 (60.6%)	394 (61.47%)	81 (46.55%)	25 (41.67%)	1437 (55.35%)
Age								
Mean ± SD	77.40 ± 10.77	75.85 ± 11.48	75.91 ± 11.29	74.42 ± 11.82	75.57 ± 11.36	78.90 ± 9.66	79.96 ± 9.17	75.88 ± 11.33
Renal insufficiency	41 (32.28%)	108 (35.88%)	264 (34.74%)	198 (37.15%)	325 (50.7%)	117 (67.24%)	52 (86.67%)	1105 (42.56%)
Diabetes	19 (14.96%)	46 (15.28%)	123 (16.18%)	89 (16.7%)	159 (24.8%)	39 (22.41%)	21 (35%)	496 (19.11%)
Anaemia	68 (53.54%)	155 (51.49%)	309 (40.66%)	248 (46.53%)	296 (46.18%)	91 (52.3%)	31 (51.67%)	1198 (46.15%)
Atrial fibrillation	18 (14.17%)	37 (12.29%)	87 (11.45%)	50 (9.4%)	69 (10.8%)	22 (12.64%)	7 (11.67%)	290 (11.17%)
COPD	15 (11.81%)	48 (15.95%)	95 (12.5%)	51 (9.57%)	68 (10.61%)	19 (10.92%)	8 (13.33%)	304 (11.71%)
Stroke	26 (20.47%)	52 (17.28%)	122 (16.05%)	83 (15.6%)	109 (17%)	39 (22.41%)	14 (23.33%)	445 (17.14%)
Hypertension	70 (55.12%)	165 (54.82%)	376 (49.47%)	231 (43.34%)	308 (48.05%)	94 (54.02%)	30 (50%)	1274 (49.1%)
Potassium supplements	79 (62.2%)	229 (76.08%)	595 (78.29%)	418 (78.42%)	497 (77.53%)	115 (66.1%)	50 (83.33%)	1983 (76.39%)
ACEIs/ARBs	24 (18.9%)	67 (22.26%)	232 (30.53%)	201 (37.71%)	229 (35.71%)	46 (26.44%)	14 (23.33%)	813 (31.32%)
Beta-blockers	44 (34.65%)	111 (36.88%)	294 (38.68%)	269 (50.47%)	286 (44.62%)	77 (44.25%)	21 (35%)	1102 (42.45%)
Potassium-sparing diuretics	8 (6.3%)	17 (5.65%)	55 (7.24%)	67 (12.57%)	102 (15.91%)	32 (18.4%)	14 (23.33%)	295 (11.36%)
Loop diuretics strength (mg)								
Mean ± SD	39.69 ± 6.03	39.90 ± 6.14	40.80 ± 19.35	40.04 ± 5.85	40.16 ± 6.21	39.43 ± 6.24	41.00 ± 6.56	40.24 ± 11.66
Loop diuretics no. of packages redeemed								
Mean ± SD	1.01 ± 0.09	1.02 ± 0.17	1.03 ± 0.20	1.02 ± 0.17	1.01 ± 0.13	1.01 ± 0.11	1.02 ± 0.13	1.02 ± 0.16
Loop diuretics no. of drugs in a package								
Mean ± SD	113.97 ± 63.27	116.96 ± 62.37	113.65 ± 65.90	108.26 ± 55.67	113.98 ± 60.59	112.57 ± 62.55	117.47 ± 63.67	113.04 ± 61.77
Day at loop diuretic reclaim								
Mean ± SD	24.94 ± 18.71	21.45 ± 17.69	19.86 ± 16.51	19.05 ± 16.09	21.13 ± 16.86	19.33 ± 14.49	20.05 ± 14.15	20.41 ± 16.63
Day at potassium measurement								
Mean ± SD	41.21 ± 21.91	43.17 ± 22.43	41.69 ± 22.07	42.96 ± 22.98	40.83 ± 22.49	38.54 ± 20.14	39.70 ± 21.38	41.63 ± 22.27
Death—90 days								
Alive	107 (84.25%)	260 (86.38%)	704 (92.63%)	490 (91.93%)	573 (89.39%)	147 (84.5%)	37 (61.67%)	2318 (89.3%)
Deceased	20 (15.75%)	41 (13.62%)	56 (7.37%)	43 (8.07%)	68 (10.61%)	27 (15.5%)	23 (38.33%)	278 (10.7%)

Data are presented as mean ± SD (age) or number of patients and percentage (all others).
COPD, chronic obstructive pulmonary disease; ACE-I/ARBs, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

the period following MI and before serum potassium measurement. In addition, 19.1% of the participants had a history of diabetes, and 46.1% a history of anaemia. Approximately 30% received drugs with effect on the renin–angiotensin system, and 40% received β-blockers. After 90 days, the mortality rates in the seven strata were 15.7, 13.6, 7.3, 8.1, 10.6, 15.5, and 38.3% respectively.

Univariate analysis of survival

A total of 278 (10.7%) patients died within the follow-up time of 90 days. Survival curves are illustrated in *Figure 1*. Univariate HRs according to potassium levels are shown in *Figure 2*. There was a significantly increased risk of death in hypo- and hyperkalaemic patients. Furthermore, patients with low normal potassium were associated with increased mortality (HR: 1.91, 95% CI: 1.28–2.86, $P < 0.01$].

Multivariate analysis of survival

The results of the multivariate analysis with potassium 3.9–4.2 mmol/L used as a reference are shown in *Figure 3*. After adjusting the model for age, sex, biologically relevant comorbidities and medication, the overall mortality remained significantly increased for patients with hypo- and hyperkalaemia. Furthermore, mortality also remained significantly increased for patients with potassium 3.5–3.8 and 4.6–5.0 mmol/L (HR: 1.84, 95% CI: 1.23–2.76, $P < 0.01$ and HR: 1.55, 95% CI: 1.09–2.22, $P = 0.01$, respectively). Covariates with significant impact on mortality are age, stroke, and drugs with effect on renin–angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin receptor blocker). The results of the analysis of interaction between the predefined potassium intervals and creatinine are shown in Supplementary material online, *Figure S1*.

The U-shaped restricted cubic spline curve is shown in *Figure 4*, indicating that the higher the serum potassium level, the greater the mortality risk. However, the spline curve showed that the HR reached an almost constant increased value when serum potassium <2.7 mmol/L. Additionally, the spline curve indicates a difference in risk within the normal potassium ranges, where a potassium interval 3.9–4.5 mmol/L is associated with the lowest risk of death.

Discussion

We examined the risk of death in patients receiving diuretics after MI depending on serum potassium levels. The main result of this study is that even mild deviation in serum potassium, is associated with increased mortality in patients with heart failure following an MI. It was not surprising that potassium levels outside the normal range (K: <3.5 and >5 mmol/L) were associated with an increased mortality risk. However, the novelty of this study was the association of low and high normal potassium (K: 3.5–3.8 and 4.6–5.0 mmol/L, respectively) with an increased mortality risk in heart failure patients following MI.

Comparison with other studies

MacDonald *et al.* examined the optimal potassium levels in cardiovascular patients through a meta-analysis of four studies. They found that it is desirable to avoid hypokalaemia, and that the recommended serum potassium level in heart failure and MI patients is 4.5–5.5 mmol/L. All of the studies in this meta-analysis included patients with chronic heart failure, and the majority assessed the impact of different treatment regimens on mortality with no direct focus on potassium homeostasis and outcome.[22–28]

Cooper *et al.*[25] demonstrated that patients administrated non-potassium-sparing diuretics suffered from an increased risk for arrhythmic death. In the studies of aldosterone antagonists in chronic heart failure, attempts were made to elucidate on the impact of treatment according to pre-treatment potassium levels.[26,27] Eplerenone was superior in patients with low potassium, using a cut-off value of 4 mmol/L.[26] This is foreseeable since patient with initial higher potassium is more likely to develop hyperkalaemia. However,

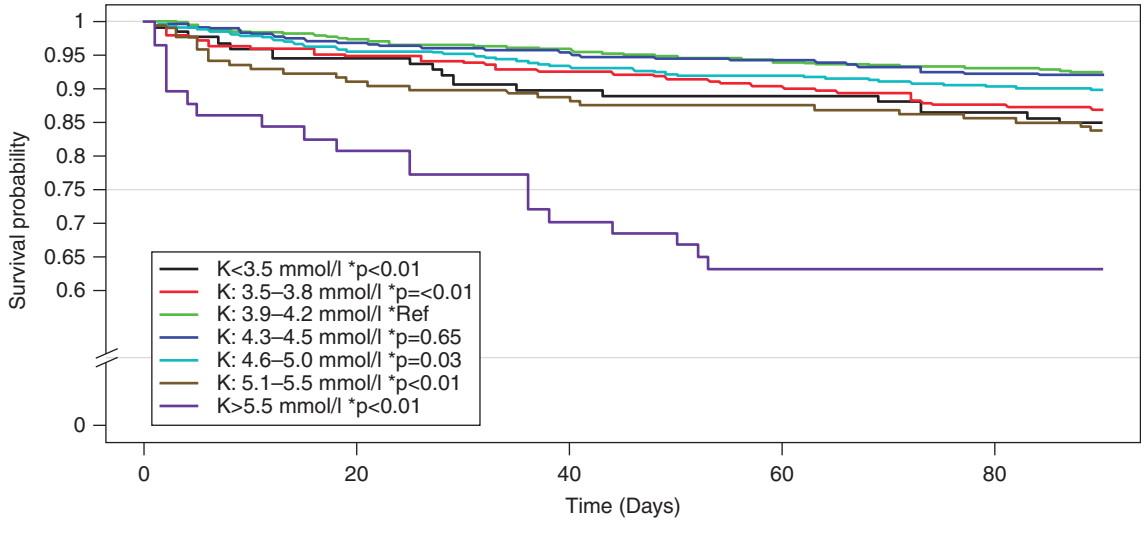

Figure 1 Kaplan–Meier analysis of the survival probability among the different potassium intervals ($N = 2596$).

the same relation could not be confirmed convincingly in a study of spironolactone.[27] Nolan *et al.*[28] provided retrospective data to suggest that a serum potassium level of <4.4 mmol/L was associated with an increased risk of sudden cardiac death.

Overall, none of these four studies provide any direct evidence to select optimum levels of serum potassium in disease or health. Nevertheless, the review recommended a serum potassium level of 4.5–5.5 mmol/L as optimum for patients with heart failure and MI. In contrast to MacDonald's optimal serum potassium level of 4.5–5.5 mmol/L,[5] our study showed a significantly increased risk of death in patients with serum potassium between 5.1 and 5.5 mmol/L (HR: 2.0, 95% CI: 1.25–3.18, $P < 0.01$).

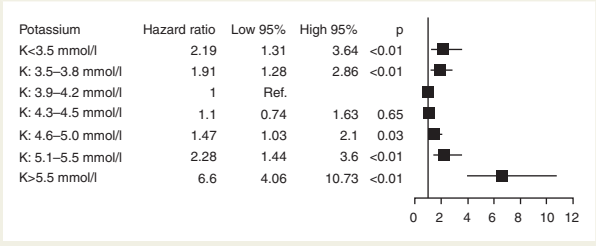

Figure 2 All-cause mortality in heart failure patients following myocardial infarction stratified by potassium intervals. $N = 2596$ (90-day follow-up). Reference interval represented by the interval K: 3.9–4.2 mmol/L.

A substudy from the Digitalis Investigation Group (DIG) trial confirmed that serum potassium levels <4 mmol/L were associated with increased mortality in heart failure patients.[29] This is in agreement with our findings of an association between mortality and K <3.9 mmol/L as are findings from another study where serum potassium levels >5.0 mmol/L predicted short-term mortality (12 weeks).[30]

Several studies have confirmed a link between low potassium and both ventricular arrhythmias and atrial fibrillation and survival.[28,31–34] In a study of atrial fibrillation risk assessment in relation to potassium, there were 11.6% of patients with atrial fibrillation and potassium was measured only at baseline.[32] This is similar to our study where 11.2% of the patients were diagnosed with atrial fibrillation.

Treatment of acute heart failure

As mentioned in the Methods section, the population is selected between year 2004 and 2012. Throughout this period, the pharmacological therapy could be marked by stepwise changes in the international guidelines for heart failure management. Therefore, the baseline characteristics may highlight lower numbers of β-blockers and angiotensin-converting enzyme inhibitors than probably expected and stated in the current guidelines. Though it is essential to have in mind that this study does not observe the pharmaceutical adjustments after the potassium measurement. Thus, some patients may have had only transient heart failure with no further need for chronic heart failure medication.

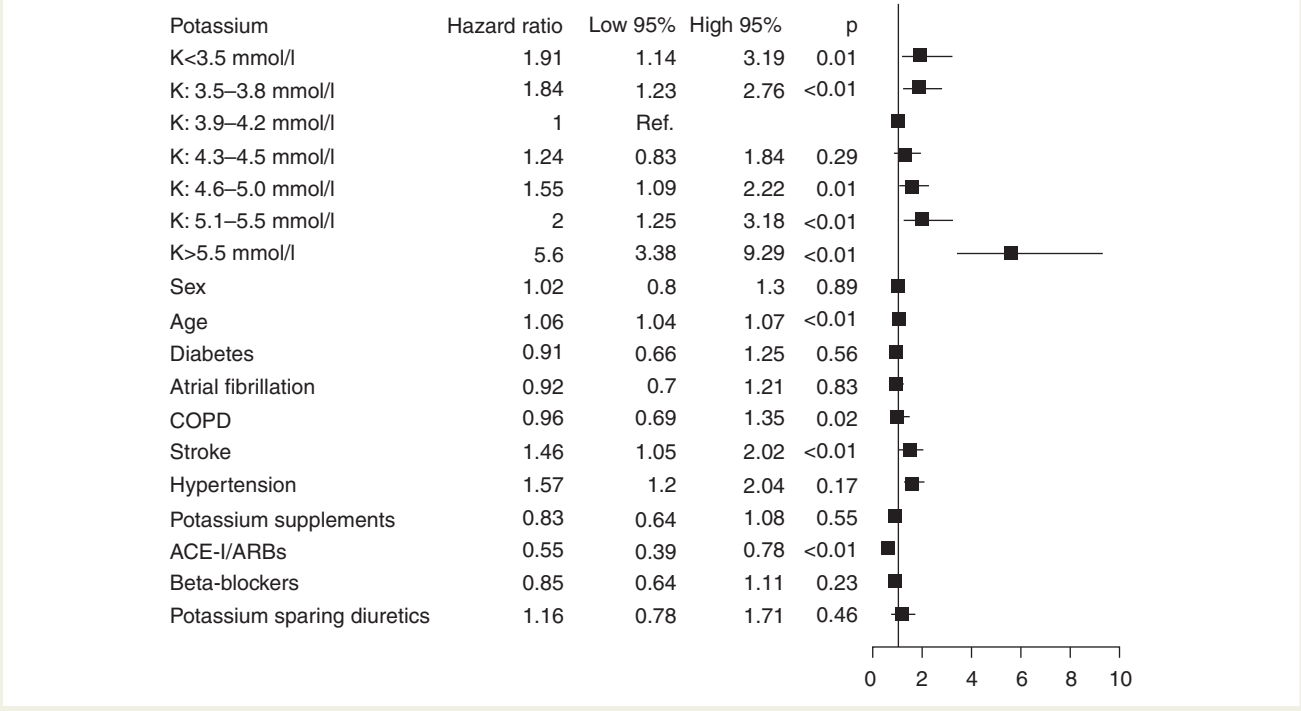

Figure 3 All-cause mortality in heart failure patients following myocardial infarction stratified by potassium intervals. $N = 2596$ (90-day follow-up). Model adjusted for covariates. Reference interval represented by the interval K: 3.9–4.2 mmol/L. COPD, chronic obstructive pulmonary disease; ACE-I/ARBs, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

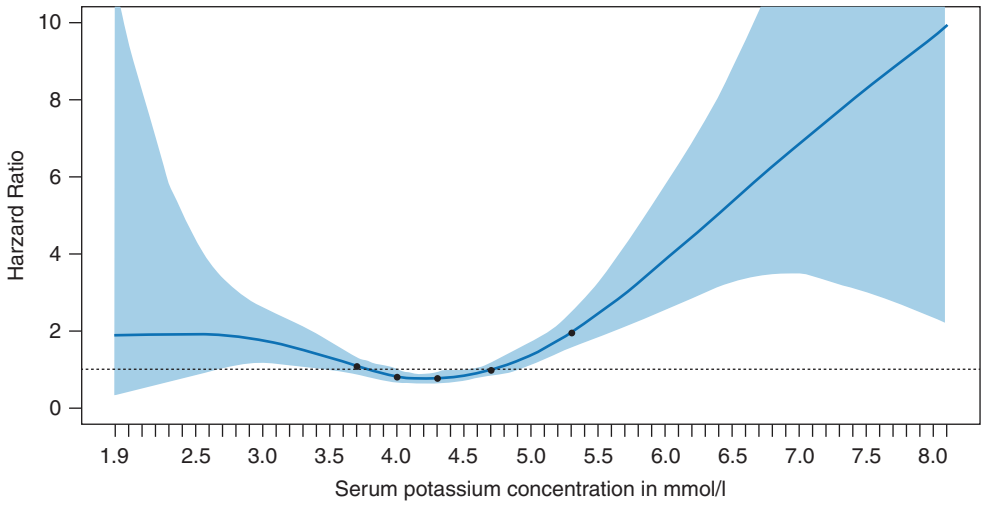

Figure 4 Restricted cubic splines showing the adjusted hazard ratios for all-cause mortality as a function of potassium concentration. Knots at the 10th, 25th, 50th, 75th and 90th percentiles of potassium. Model adjusted for age, sex, COPD, stroke, AF, DM, hypertension, potassium supplement, ACEIs/ARBs, beta-blockers, and potassium-sparing diuretics ($N = 2596$). COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; DM, diabetes mellitus; ACE-I/ARBs, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

Study limitations

This study is not a randomized controlled trial. However, with help of databases, we were able to extract information on comorbid illnesses and concomitant medication use. All factors that were considered possible confounders were included in the Cox multivariable analysis.

Limitations of this study are represented by the lack of information regarding the cause of death. This was not possible due to uncertainty regarding cause of death registry. Based on previous diagnosis, one patient can be attributed one or more causes of death in situations where autopsy is missing.

Last but not least, we did not differentiate between the various types of MI, which means that our population can also encompass patients with type two myocardial infarction. The authors intended to identify serum creatine kinase-MB and troponin-T in order to acknowledge the severity of the MI. We were unable to provide this information due to an increased number of missing values.

Conclusion

Potassium levels outside the interval 3.9–4.5 mmol/L were associated with a substantial risk of death in patients requiring diuretic treatment after an MI.

Clinical implications

This study indicates that low normal potassium levels and mild hyperkalaemia may also be associated with increased mortality, which suggests that a narrower normal interval could possibly improve outcome in heart failure patients following MI. Myocardial changes in heart failure following MI influence potassium homeostasis, which makes standard potassium levels difficult to use in assessment of heart failure patients, as a pathological myocardium does not function as in normal subjects. Potassium imbalance can quickly occur in heart failure patients either due to medication or disease pathophysiology or both. For this reason, closer monitoring of serum potassium in acute heart failure patients would probably be relevant to improve survival.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

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