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ORIGINAL ARTICLE
Atrial fibrillation

Association between serum potassium levels and short-term mortality in patients with atrial fibrillation or flutter co-treated with diuretics and rate- or rhythm-controlling drugs

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Aims We investigated the association between potassium levels and 90-day all-cause mortality in atrial fibrillation or flutter (AF) patients co-treated with diuretics and rate- or rhythm-controlling drugs.

Methods and results During 2000–12, first-time AF patients treated with beta-blockers, amiodarone, sotalol, verapamil, or digoxin combined with any diuretic within 90 days post-AF discharge were included. Following co-treatment, a potassium measurement within 90 days after initiating diuretic treatment was required. Mortality risk associated with potassium <3.5, 3.5–3.7, 3.8–4.0, 4.5–4.7, 4.8–5.0, and >5.0 mmol/L (reference: 4.1–4.4 mmol/L) was assessed using multivariable Cox regression. In total, 14 425 AF patients were included (median age: 78 years; women: 52%). Patients most often received beta-blocker monotherapy (29%), beta-blockers and digoxin combined (25%), digoxin monotherapy (24%), amiodarone monotherapy (3%), and verapamil monotherapy (3%). Increased 90-day mortality risk was associated with <3.5 mmol/L [hazard ratio (HR) 2.05, 95% confidence interval (CI) 1.68–2.50], 3.5–3.7 mmol/L (HR 1.28, 95% CI 1.05–1.57), 4.5–4.7 mmol/L (HR 1.20, 95% CI 1.02–1.41), 4.8–5.0 mmol/L (HR 1.37, 95% CI 1.14–1.66), and >5.0 mmol/L: (HR 1.84, 95% CI 1.53–2.21). Compared with beta-blocker monotherapy, rate- or rhythm-controlling drugs did not modify the association between potassium groups and mortality risk.

Conclusion In addition to hypo- and hyperkalaemia, low and high normal range potassium levels were associated with increased 90-day mortality risk in AF patients co-treated with diuretics and rate- or rhythm-controlling drugs. These associations were independent of rate- or rhythm-controlling drugs.

Keywords Atrial fibrillation • Diuretics • Mortality • Potassium • Rate- or rhythm-controlling drugs

Introduction

Hypo- and hyperkalaemia may induce electrophysiological disturbances of the myocardial function and consequently cause arrhythmias.[1–3] The impact of hypo- and hyperkalaemia may be particularly relevant in patients having ongoing rhythm disorders such as atrial fibrillation or flutter (AF) as this can exacerbate the clinical condition.[1,4] The clinical scenario becomes even more complicated when rate- or rhythm-controlling drugs are used to control AF considering their associated proarrhythmic risk.[4,5] For example, this includes QT prolongation for amiodarone, and another proarrhythmic risk may be observed with digoxin in patients with low serum potassium,

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where mortality risk is considerably increased relative to those with normal ranging serum potassium.[6,7]

While excess mortality risk has been associated with serum potassium both below and above the clinically accepted normal range in patients with heart failure and hypertension,[8–11] it remains unknown whether this U-shaped relationship may be observed in AF. Despite limited evidence, it may be particularly important to manage AF patients within narrower serum potassium levels given that this group may be of older age, have compromised myocardial function, have competing comorbidities, receive diuretics, and receive e.g. amiodarone. Altogether, these factors can increase the likelihood of adverse outcomes including proarrhythmic events, poorly controlled AF, and ultimately death.

Considering this sparse knowledge, we investigated the association between serum potassium levels and short-term mortality risk in a nationwide registry-based AF population co-treated with diuretics and rate- or rhythm-controlling drugs. In particular, AF patients on diuretics are at increased risk of altered serum potassium homeostasis, thus allowing us to examine the impact of different serum potassium levels on mortality risk. In addition, we included only patients who redeemed prescriptions for rate- or rhythm-controlling drugs including beta-blockers, amiodarone, sotalol, verapamil, or digoxin to focus on AF patients in need of symptom-relieving therapy. Demanding that patients were co-treated with these rate- or rhythm-controlling drugs enabled us to additionally examine whether these drugs modified the association between serum potassium levels and mortality risk.

Methods

Data source and source population

This study was a registry-based cohort study performed using Danish nationwide registries. All patients hospitalized for first-time AF as the primary diagnosis code [I48 according to the International Classification of Disease (ICD)-10 system] during 2000–12 were identified in the Danish National Patient Registry.[12] The validity of AF in this registry is considered high, with a positive predicted value of 93%.[13] Corresponding data on age, sex, emigration status, and mortality of patients were obtained from the Danish Civil Personal Registry and the Danish Registry of Causes of Death.[14,15]

Study population

From the source population, we included only patients with a redeemed prescription for any diuretic drug [C03 according to the Anatomical Therapeutic Chemical (ATC) system] identified in the Danish National Prescription Registry[16] within 90 days post-AF discharge and a serum potassium measurement within 90 days obtained from electronic registries of laboratory data, as used in other studies.[8–11] The serum potassium measurement represented the baseline in our study. In addition, we included only patients who redeemed prescriptions for rate- or rhythm-controlling drugs including beta-blockers, amiodarone, sotalol, verapamil, or digoxin to focus on AF patients in need of symptom-relieving therapy. We only included the five most frequently prescribed rate- or rhythm-controlling drugs during the study period: (i) beta-blockers (ATC: C07A-B), (ii) amiodarone (ATC: C01BD01), (iii) sotalol (ATC: C07AA07), (iv) verapamil (ATC: C08DA01), and (v) digoxin (ATC: C01AA), both as monotherapy and polytherapy. For a complete overview of the used combinations of rate- and rhythm-controlling drugs, see Supplementary material online, *Table S1A*. We excluded rare combinations of rate- and rhythm-controlling drugs to study a more homogeneous population (Supplementary material online, *Table S1B*).

Serum potassium cut-off levels

We grouped low-risk serum potassium as 4.1–4.4 mmol/L and the remaining as <3.5 mmol/L, 3.5–3.7 mmol/L, 3.8–4.0 mmol/L, 4.5–4.7 mmol/L, 4.8–5.0 mmol/L, and >5.0 mmol/L. This was based on restricted cubic splines, as described in the Statistical Analysis section.

Comorbidities and concomitant drugs

The following comorbidities were included in this study as potential confounding factors: heart failure, ischaemic heart disease including myocardial infarction, hypertension, diabetes, stroke, peripheral artery disease, and chronic obstructive pulmonary disease. All comorbidities were identified within 5 years prior to baseline, and ICD-10 codes are listed in Supplementary material online, *Table S2*. We further defined diabetes from antidiabetic drugs. Moreover, we defined thiazide or loop diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and potassium supplements. Redeemed prescriptions were identified within 90 days prior to baseline, and ATC codes are listed in Supplementary material online, *Table S3*.

In addition, we assessed and adjusted for the kidney function of patients using estimated glomerular filtration rate (eGFR), and we used a cut-off eGFR level <30 mL/min/1.73 m^2 to indicate impaired renal function, in agreement with contemporary literature.[17]

Outcome measure

We studied all-cause mortality within 90 days following baseline. Patients were followed from baseline until event or censoring in case of emigration, end of follow-up, or end of study, whichever occurred first. The main outcome was all-cause mortality, and we performed an additional analysis using death from any cardiovascular cause (ICD-8: 400–451, ICD-10: I00–99) as outcome.

Statistical analysis

Continuous variables were described using medians and 25–75th percentiles, and categorical variables were described using counts and percentages. We used the Kruskal–Wallis test to examine differences in continuous variables, and the χ^2 test to examine differences in categorical variables.

We depicted mortality as a hazard function of serum potassium levels using a restricted cubic spline, as shown in *Figure 1A*. Consequently, we designated serum potassium 4.3 mmol/L as reference and depicted mortality as a hazard ratio (HR) function also using a restricted cubic spline with 95% confidence intervals (CIs), as shown in *Figure 1B*. Here, knots were placed at 10th, 50th, and 90th percentiles of serum potassium levels. Serum potassium groups were formed from the restricted cubic splines and, as mentioned, serum potassium 4.1–4.4 mmol/L represented the reference group, and the remaining groups were formed as follows: <3.5 mmol/L, 3.5–3.7 mmol/L, 3.8–4.0 mmol/L, 4.5–4.7 mmol/L, 4.8–5.0 mmol/L, and >5.0 mmol/L.

Kaplan–Meier estimates were used to depict mortality across serum potassium groups. Assumptions for Cox regression models were tested, and we found deviation in linearity with age using Martingale residuals. Therefore, age was spilt into groups based on 20th percentiles. Furthermore, proportional hazards were tested and visualized with cumulative Martingale residuals for all serum potassium groups according to

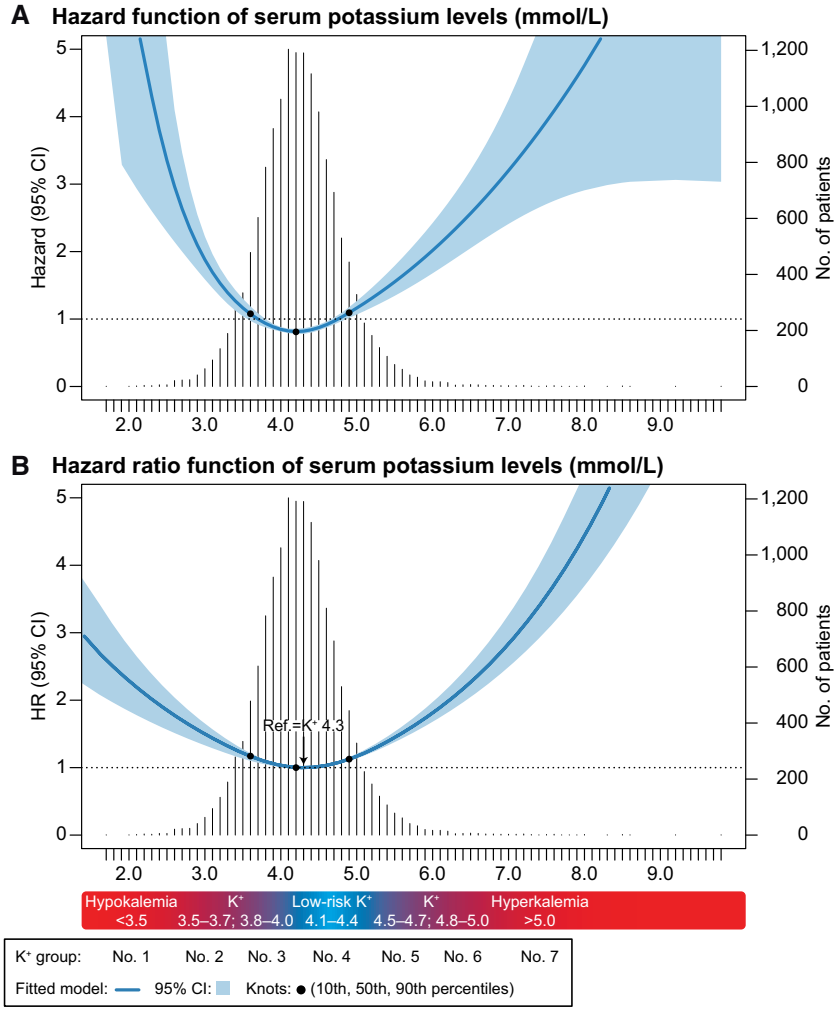

Figure 1 Restricted cubic spline curves showing (*A*) hazard function and (*B*) hazard ratio function according to serum potassium levels. CI, confidence interval; HR, hazard ratio; K^+, serum potassium.

mortality risk and were not violated. Effect modification of rate- or rhythm-controlling drugs on the association between serum potassium groups and mortality risk was tested using a likelihood ratio test. A Cox regression model without an interaction term was compared with a model containing an interaction term, and a *P*-value <0.01 was considered statistically significant. In all other analyses, a *P*-value <0.05 was considered statistically significant.

All restricted cubic splines and Cox regression models were adjusted for age groups, sex, heart failure, ischaemic heart disease including myocardial infarction, hypertension, diabetes, stroke, peripheral artery disease, chronic obstructive pulmonary disease, eGFR <30 mL/min/1.73 m^2, rate- or rhythm-controlling drugs, thiazide or loop diuretics, ACE inhibitors or ARBs, MRAs, and potassium supplements. Of note, rate- or rhythm-controlling drugs, both as monotherapy and polytherapy, were included as one variable, where beta-blocker monotherapy was used as reference.

Data management was performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and analyses were performed using R, version 3.5.0.[18]

Ethics

This study was approved by the Danish Data Protection Agency (reference: 2007-58-0015, internal reference: GEH-2014-013, I-Suite number: 02731). In Denmark, neither informed consent nor ethical approval is required for registry-based studies.

Results

Patient characteristics

A total of 14 425 patients were included in our study. Baseline characteristics of patients according to the seven predefined serum potassium groups are presented in *Table 1*. Flowchart of the selection of the study population is shown in *Figure 2*.

The study population was characterized by advanced age (median age: 78 years) and slightly more women (52%). Around 43% had a diagnosis of heart failure, and around 38% had a diagnosis of

Table 1 **Baseline characteristics of the study population**

	K^+ <3.5 mmol/L (*n* = 888)	K^+ 3.5–3.7 mmol/L (*n* = 1406)	K^+ 3.8–4.0 mmol/L (*n* = 2709)	K^+ 4.1–4.4 mmol/L (*n* = 4668)	K^+ 4.5–4.7 mmol/L (*n* = 2465)	K^+ 4.8–5.0 mmol/L (*n* = 1293)	K^+ >5.0 mmol/L (*n* = 996)	Total (*n* = 14 425)	*P*-value
Demographics									
Age (years)	79.0 [72.0–86.0]	78.0 [70.0–84.0]	78.0 [70.0–84.0]	78.0 [70.0–84.0]	78.0 [70.0–84.0]	78.0 [71.0–85.0]	80.0 [72.0–86.0]	78.0 [70.0–84.0]	<0.001
Sex									<0.001
Female	583 (65.7)	806 (57.3)	1468 (54.2)	2299 (49.3)	1171 (47.5)	611 (47.3)	501 (50.3)	7439 (51.6)	
Male	305 (34.3)	600 (42.7)	1241 (45.8)	2369 (50.7)	1294 (52.5)	682 (52.7)	495 (49.7)	6986 (48.4)	
Rate- or rhythm-controlling drugs									<0.001
Monotherapy									
Beta-blockers	307 (34.6)	433 (30.8)	832 (30.7)	1345 (28.8)	688 (27.9)	319 (24.7)	227 (22.8)	4151 (28.8)	
Amiodarone	28 (3.2)	49 (3.5)	78 (2.9)	133 (2.8)	84 (3.4)	50 (3.9)	23 (2.3)	445 (3.1)	
Verapamil	44 (5.0)	62 (4.4)	99 (3.7)	116 (2.5)	63 (2.6)	23 (1.8)	24 (2.4)	431 (3.0)	
Digoxin	198 (22.3)	306 (21.8)	566 (20.9)	1107 (23.7)	593 (24.1)	356 (27.5)	290 (29.1)	3416 (23.7)	
Polytherapy									
Beta-blockers, amiodarone	19 (2.1)	33 (2.3)	99 (3.7)	150 (3.2)	81 (3.3)	40 (3.1)	31 (3.1)	453 (3.1)	
Beta-blockers, sotalol	15 (1.7)	18 (1.3)	60 (2.2)	80 (1.7)	44 (1.8)	18 (1.4)	12 (1.2)	247 (1.7)	
Beta-blockers, verapamil	11 (1.2)	19 (1.4)	19 (0.7)	24 (0.5)	15 (0.6)	5 (0.4)	6 (0.6)	99 (0.7)	
Beta-blockers, digoxin	186 (20.9)	329 (23.4)	650 (24.0)	1209 (25.9)	633 (25.7)	353 (27.3)	282 (28.3)	3642 (25.2)	
Beta-blockers, amiodarone, digoxin	7 (0.8)	13 (0.9)	21 (0.8)	48 (1.0)	37 (1.5)	14 (1.1)	9 (0.9)	149 (1.0)	
Beta-blockers, sotalol, digoxin	8 (0.9)	11 (0.8)	27 (1.0)	52 (1.1)	26 (1.1)	11 (0.9)	10 (1.0)	145 (1.0)	
Beta-blockers, verapamil, digoxin	9 (1.0)	20 (1.4)	43 (1.6)	61 (1.3)	35 (1.4)	12 (0.9)	11 (1.1)	191 (1.3)	
Amiodarone, digoxin	4 (0.5)	15 (1.1)	34 (1.3)	55 (1.2)	38 (1.5)	23 (1.8)	16 (1.6)	185 (1.3)	
Verapamil, digoxin	52 (5.9)	98 (7.0)	181 (6.7)	288 (6.2)	128 (5.2)	69 (5.3)	55 (5.5)	871 (6.0)	
Comorbidities									
Heart failure	308 (34.7)	487 (34.6)	1042 (38.5)	1977 (42.4)	1180 (47.9)	673 (52.0)	551 (55.3)	6218 (43.1)	<0.001
Myocardial infarction	104 (11.7)	120 (8.5)	254 (9.4)	551 (11.8)	331 (13.4)	179 (13.8)	189 (19.0)	1728 (12.0)	<0.001
Ischemic heart disease	272 (30.6)	353 (25.1)	802 (29.6)	1398 (29.9)	816 (33.1)	453 (35.0)	368 (36.9)	4462 (30.9)	<0.001
Hypertension	367 (41.3)	582 (41.4)	1069 (39.5)	1723 (36.9)	899 (36.5)	481 (37.2)	347 (34.8)	5468 (37.9)	<0.001
Diabetes	148 (16.7)	210 (14.9)	409 (15.1)	766 (16.4)	464 (18.8)	269 (20.8)	237 (23.8)	2503 (17.4)	<0.001
Stroke	127 (14.3)	187 (13.3)	368 (13.6)	585 (12.5)	279 (11.3)	168 (13.0)	142 (14.3)	1856 (12.9)	0.102
Peripheral artery disease	75 (8.4)	91 (6.5)	181 (6.7)	295 (6.3)	188 (7.6)	129 (10.0)	91 (9.1)	1050 (7.3)	<0.001
Chronic obstructive pulmonary disease	149 (16.8)	208 (14.8)	380 (14.0)	685 (14.7)	410 (16.6)	235 (18.2)	218 (21.9)	2285 (15.8)	<0.001
eGFR <30 mL/min/1.73 m^2	62 (7.0)	90 (6.4)	175 (6.5)	372 (8.0)	261 (10.6)	232 (17.9)	337 (33.8)	1529 (10.6)	<0.001
Concomitant drugs									
Thiazide diuretics	416 (46.8)	585 (41.6)	1018 (37.6)	1427 (30.6)	647 (26.2)	303 (23.4)	224 (22.5)	4620 (32.0)	<0.001
Loop diuretics	617 (69.5)	989 (70.3)	1919 (70.8)	3524 (75.5)	1932 (78.4)	1061 (82.1)	829 (83.2)	10871 (75.4)	<0.001
ACE inhibitors or ARBs	321 (36.1)	539 (38.3)	1141 (42.1)	2283 (48.9)	1352 (54.8)	765 (59.2)	606 (60.8)	7007 (48.6)	<0.001
Mineralocorticoid receptor antagonists	89 (10.0)	98 (7.0)	286 (10.6)	757 (16.2)	565 (22.9)	364 (28.2)	376 (37.8)	2535 (17.6)	<0.001
Potassium supplements	522 (58.8)	853 (60.7)	1574 (58.1)	2786 (59.7)	1471 (59.7)	772 (59.7)	590 (59.2)	8568 (59.4)	0.775

Age presented as median with 25–75th percentiles, other variables as *n* (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

hypertension. More patients with higher serum potassium levels tended to have an eGFR <30 mL/min/1.73 m^2 suggestive of chronic kidney disease relative to patients with lower serum potassium levels. Most patients were treated with beta-blocker monotherapy (29%) or digoxin monotherapy (24%), or with a combination of both (25%). This was followed by patients who were either treated with amiodarone monotherapy (3%) or verapamil monotherapy (3%). No patients received sotalol as monotherapy.

Furthermore, most of the study population (75%) was treated with loop diuretics prior to serum potassium measurement and, lastly, 59% were treated with potassium supplements.

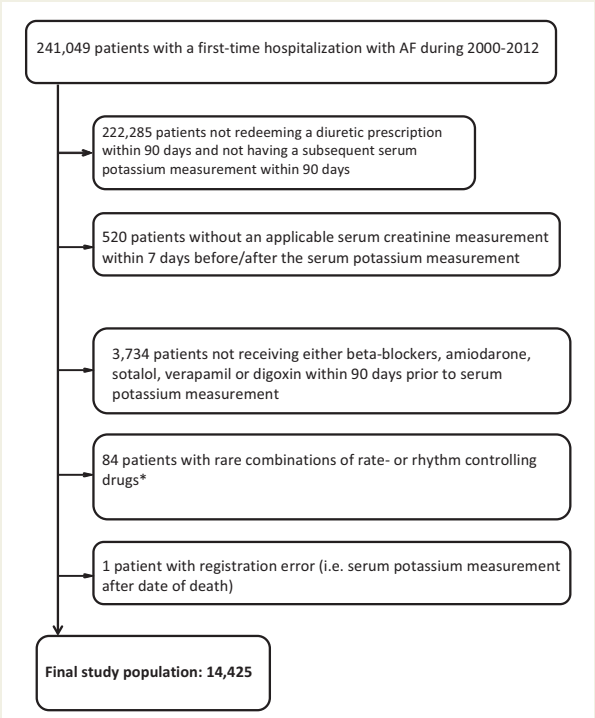

Figure 2 Flowchart showing the selection process of the study population.

Risk of mortality

During 90-day follow-up, mortality occurred in 1460 out of the 14 425 patients (10%). The highest mortality rate was found for serum potassium >5.0 mmol/L (20%), <3.5 mmol/L (15%), and 4.8–5.0 mmol/L (13%), as shown in *Figure 3*.

Compared with reference serum potassium 4.1–4.4 mmol/L, patients with high serum potassium levels had increased all-cause mortality risk (>5.0 mmol/L: HR 1.84, 95% CI 1.53–2.21; 4.8–5.0 mmol/L: HR 1.37, 95% CI 1.14–1.66; 4.5–4.7 mmol/L: HR 1.20, 95% CI 1.02–1.41). A similar association was found for patients with low serum potassium levels (<3.5 mmol/L: HR 2.05, 95% CI 1.68–2.50; 3.5–3.7 mmol/L: HR 1.28, 95% CI 1.05–1.57). The serum potassium group 3.8–4.0 mmol/L did not confer increased mortality risk (HR 1.13, 95% CI 0.96–1.34). Results from the multivariable Cox regression are shown in *Figure 4A*. A similar analysis was made focusing on cardiovascular mortality and showed increased risk with serum potassium levels <3.5 mmol/L: HR 2.04, 95% CI 1.61–2.59; 4.5–4.7 mmol/L: HR 1.25, 95% CI 1.03–1.52; 4.8–5.0 mmol/L: HR 1.32, 95% CI 1.06–1.65 and >5.0 mmol/L: HR 1.66, 95% CI 1.34–2.07, as shown in *Figure 4B*.

Overall, we did not observe that any of the rate- or rhythm-controlling drugs modified the association between serum potassium groups and mortality risk, as shown in Supplementary material online, *Figure S1A–F*. Compared with beta-blocker monotherapy and

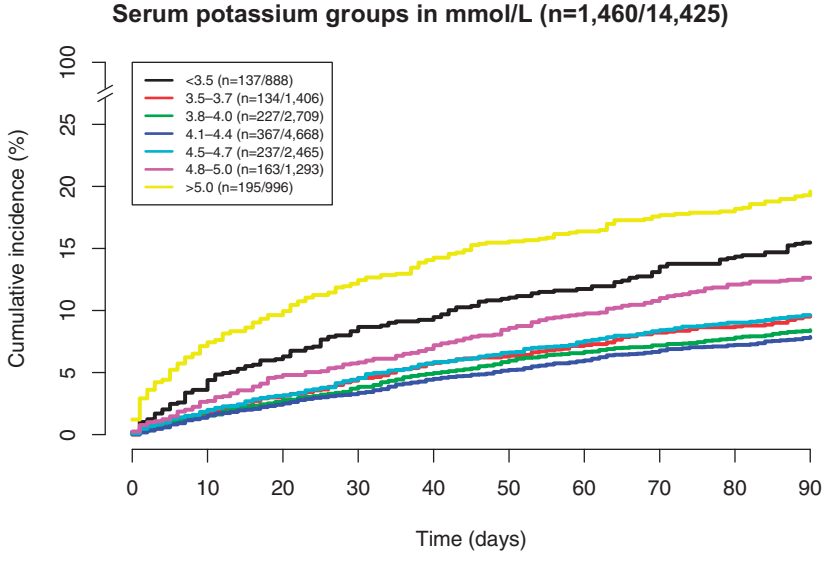

Figure 3 Cumulative incidence of all-cause mortality during 90-day follow-up. Number of events are shown for the total study population and for each serum potassium group.

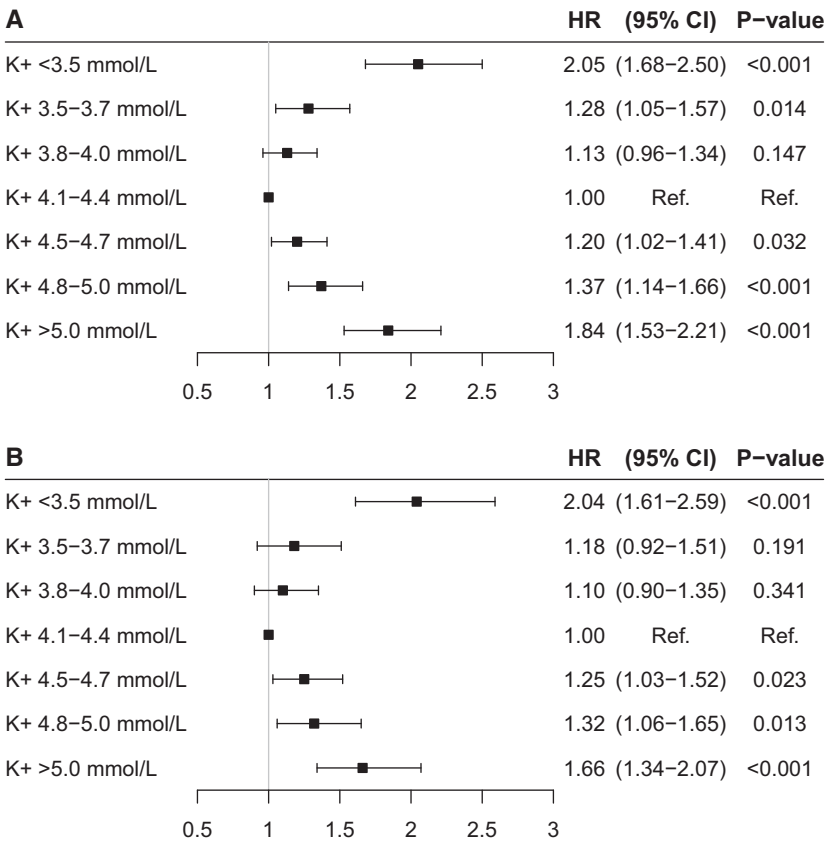

Figure 4 Multivariable Cox regression showing the association between serum potassium levels and (*A*) all-cause mortality and (*B*) cardiovascular mortality during 90-day follow-up. Serum potassium 4.1–4.4 mmol/L served as reference for the analysis. The analysis was adjusted for age groups, sex, heart failure, ischaemic heart disease including myocardial infarction, hypertension, diabetes, stroke, peripheral artery disease, chronic obstructive pulmonary disease, estimated glomerular filtration rate <30 mL/min/1.73 m^2, rate- or rhythm-controlling drugs, thiazide or loop diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and potassium supplements.

reference serum potassium 4.1-4.4 mmol/L, mortality risk was slightly larger particularly with beta-blocker monotherapy and serum potassium <3.5 mmol/L (HR 2.13, 95% CI 1.46–3.10), verapamil monotherapy and serum potassium 3.5–3.7 mmol/L (HR 2.71, 95% CI 1.43–5.14), and amiodarone and serum potassium >5.0 mmol/L (HR 3.93, 95% CI 1.56–8.91). Across all serum potassium groups, digoxin monotherapy conferred increased mortality risk, particularly with serum potassium <3.5 mmol/L (HR 2.23, 95% CI 1.48–3.34) and >5.0 mmol/L (HR 3.22, 95% CI 2.29–4.54). As no patients received sotalol as monotherapy, this analysis could not be performed.

Additional analyses

To test the robustness and consistency of our results, we performed a number of additional analyses:

First, we additionally adjusted for AF hospitalization year during the study period (2000–12), and no changes in results were found. See Supplementary material online, *Figure S2*.

Second, we analysed patients with normal eGFR ≥30 mL/min/1.73 m^2 (*N* = 12 896). This subgroup analysis also showed the same tendencies as the main results. See Supplementary material online, *Figure S3*.

Third, we analysed patients without heart failure (*N* = 8207) and without hypertension (*N* = 8957).

In the subgroup analysis without heart failure, serum potassium <3.5 mmol/L, 4.8–5.0 mmol/L, and >5.0 mmol/L conferred increased mortality risk, and the remaining serum potassium groups were not associated with evidence of differential risk. The subgroup analysis without hypertension, showed the same tendencies as the main results. See Supplementary material online, *Figure S4* and *S5*, respectively. It was not possible to analyse patients without both heart failure and hypertension due to sample size limitations.

Fourth, we performed an additional analysis of AF patients with a serum potassium measurement within 180 days following AF discharge, where no patients had redeemed prescriptions of diuretics prior to the measurement (*N* = 6365). Due to sample size limitations, it was not possible to adjust for rate- or rhythm-controlling drugs, both as monotherapy and polytherapy, as one variable, and the analysis was therefore adjusted for the individual drugs. Otherwise, similar inclusion and exclusion criteria as used in the main study

population were applied. See Supplementary material online, *Table S4* for patient characteristics. The results for this study population showed an increased mortality risk for serum potassium <3.5 mmol/L, 3.5–3.7 mmol/L, and >5.0 mmol/L, as in the main analysis. See Supplementary material online, *Figure S6A,B*.

Discussion

In the present study, we investigated the association between serum potassium levels and short-term mortality risk in more than 14 000 AF patients co-treated with diuretics and rate- or rhythm-controlling drugs. Our key findings were that patients with hypokalaemia (<3.5 mmol/L) and hyperkalaemia (>5.0 mmol/L) had a nearly two-fold increased mortality risk. In addition, patients with low-normal (3.5–3.7 mmol/L) and high-normal (4.5–4.7 and 4.8–5.0 mmol/L) serum potassium groups had increased mortality risk. Of note, rate- or rhythm-controlling drugs did not modify the association between serum potassium groups and mortality risk, meaning that the effect of altered serum potassium homeostasis on mortality risk is more likely to be independent of rate- or rhythm-controlling drugs in AF patients co-treated with diuretics. Overall, these findings were consistent when we studied a control group of AF patients not co-treated with diuretics.

When compared with beta-blocker monotherapy and reference serum potassium 4.1–4.4 mmol/L, we observed slightly changed effect sizes in subgroup analyses, where digoxin monotherapy conferred increased mortality risk across all serum potassium groups, particularly with hypokalaemia (HR 2.23) and hyperkalaemia (HR 2.63). Lastly, patients treated with verapamil monotherapy together with serum potassium 3.5–3.7 mmol/L and amiodarone monotherapy together with hyperkalaemia conferred increased mortality risk (HRs 2.71 and 3.93, respectively).

Knowledge on the prognosis in relation to altered serum potassium homeostasis in the setting of AF is sparse, and whether rate- or rhythm-controlling drugs modify this association remains unknown. Our results of excess mortality associated with hypo- and hyperkalaemia are not surprising, as such associations are also found in other cardiovascular populations.[8–11] However, the result of increased mortality risk associated with low-normal (3.5–3.7 mmol/L) and high-normal (4.8–5.0 mmol/L) serum potassium groups deserves attention. The optimal normal range of serum potassium in AF patients before initiating rate- or rhythm-controlling treatment remains unclear, and current clinical guidelines provide little direction.[19] However, our study suggests that both low-normal and high-normal serum potassium are associated with poor short-term prognosis. These results underscore a need for a more narrow serum potassium normal range, which could possibly improve outcomes in AF patients co-treated with diuretics and rate- or rhythm-controlling drugs.

Two recent studies by Krogager *et al.* also found that low-normal and high-normal serum potassium were associated with increased mortality risk in patients with acute heart failure after myocardial infarction and in patients with hypertension.[8,9] Furthermore, a recent study by Aldahl *et al.* also showed that low-normal and high-normal serum potassium were associated with an increased mortality risk in patients with chronic heart failure. These studies as well as our study suggest that a narrower serum potassium range is associated with a higher survival probability. The serum potassium reference group in the mentioned studies is very similar to the one we used in this study. The study by Aldahl *et al.* used a serum potassium reference group of 4.2–4.4 mmol/L, and the studies by Krogager *et al.* used a serum potassium reference group of 3.9–4.2 mmol/L for patients with acute heart failure and 4.1–4.4 mmol/L for patients with hypertension. The reference group in our study was 4.1–4.4 mmol/L, and the slight deviation between our study and the other studies is not surprising, as our study population is a mixed population of AF patients with hypertension, heart failure, or both. However, when excluding AF patients with either heart failure or hypertension in sensitivity analyses, findings overall resembled the main analysis, meaning that these conditions did not drive the associations.

Low serum potassium, especially hypokalaemia (<3.5 mmol/L), is considered a major risk factor for both ventricular and supraventricular arrhythmias, including AF, which was found in a recent study by Krijthe *et al.* showing that low serum potassium predicted development of AF.[2] As such, we speculate that patients with low serum potassium may have poorer outcomes due to increased risk of new episodes of AF. This speculation is further supported by results of increased stroke risk in AF patients treated with diuretics who demonstrate low serum potassium in a previous study by Green *et al.*[20]

Although, in our study, rate- or rhythm-controlling drugs were not observed to modify the association between serum potassium groups and mortality risk, we know from other studies that especially hypokalaemia should be avoided in patients treated with digoxin, as it can predispose to digoxin toxicity, which can cause fatal ventricular arrhythmias.[6] In our study, we also found that digoxin monotherapy was associated with increased mortality risk across all serum potassium groups, but particularly for hypo- and hyperkalaemia. This could indicate that also elevated serum potassium should be avoided in these patients, which may be attributed to factors such as impaired kidney function. Furthermore, it is known from other studies that amiodarone may have proarrhythmic effects causing QT prolongation, and when combined with hypokalaemia, outcomes may be more adverse.[5,21] However, in our study, relatively few patients were treated with amiodarone monotherapy, thus limiting our results in this patient group.

This study has some limitations. First, our study is observational in nature, meaning that the reported associations may not be causal. Although we have nationwide access to diagnosis codes and redeemed drug prescriptions, we do not have access to important explanatory variables associated with mortality including different lifestyle risk factors. In continuation, we do not know if other unmeasured factors may have influenced our results. Our study focused on AF patients co-treated with diuretics and rate- or rhythm-controlling drugs. Information on precise drug dosage for treatment with thiazide or loop diuretics, ACE inhibitors or ARBs, MRAs was not available from the Danish National Prescription Registry. We did not focus on follow-up serum potassium measurements, although corrected serum potassium together with revision or addition of thiazide or loop diuretics, ACE inhibitors or ARBs, MRAs, or potassium supplements between measurements potentially may affect our findings. Furthermore, data on left ventricular ejection fraction and New York Heart Association class were not available, and it was consequently not possible to subdivide the study population according

to these possible differences. Moreover, it was not possible to know if patients were discharged with paroxysmal, persistent, or permanent AF. Electrocardiogram data were also not available.

Another limitation is that we do not know the indication for measuring the serum potassium level in patients or if patients had symptoms consistent with altered serum potassium homeostasis. In addition, methods for blood potassium analysis have not been consistent in all laboratories during the study period. This includes both serum- and plasma-based tests over the years. The different laboratories were taking precautions to avoid false-positive hyperkalaemia by not reporting results in case of haemolysis, which made false-positive hyperkalaemia a presumably rare case. Lastly, although we included data on cardiovascular mortality, the precise cause of death could not be evaluated due to the retrospective design, meaning that we do not know if patients died from e.g. fatal arrhythmias resulting from altered serum potassium homeostasis.

Conclusions

Besides increased mortality risk in AF patients with hypokalaemia (<3.5 mmol/L) and hyperkalaemia (>5.0 mmol/L), we observed that patients with low-normal (3.5–3.7 mmol/L) or high-normal (4.5–4.7 mmol/L and 4.8–5.0 mmol/L) serum potassium had an increased 90-day all-cause mortality risk. These associations were not modified by any of the rate- or rhythm-controlling drugs, although slightly increased mortality risk was found for all serum potassium groups and digoxin monotherapy, serum potassium 3.5–3.7 mmol/L and verapamil monotherapy, and hyperkalaemia and amiodarone monotherapy. Our results suggest a greater cardiovascular and drug safety with more narrow normal serum potassium levels in AF patients co-treated with diuretic and rate- or rhythm-controlling drugs.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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