International Journal of Cardiology 274 (2019) 52–58

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Potassium levels and risk of in-hospital arrhythmias and mortality in patients admitted with suspected acute coronary syndrome

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ARTICLE INFO

Article history:
Received 21 November 2017
Received in revised form 15 May 2018
Accepted 25 September 2018
Available online 28 September 2018

Keywords:
Acute coronary syndrome
In-hospital cardiac arrest
Arrhythmias
Atrial fibrillation
Potassium

ABSTRACT

Background: In acute coronary syndrome (ACS), potassium imbalance at admission has been associated with in-hospital arrhythmias, cardiac arrest, and mortality. However, several important presentation characteristics and subtype of ACS have not been considered.

Methods: Consecutive patients (n = 32,955) admitted with suspected ACS between 2006 and 2011, registered in the Swedish Web-System for Enhancement and Development of Evidence-Based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) and the Stockholm CREAtinine Measurements (SCREAM) project were included. Associations between admission plasma potassium categories (reference 3.5–<4.0 mmol/L) and in-hospital outcomes including mortality, cardiac arrest, new-onset atrial fibrillation, and second- or third-degree atrioventricular block were assessed with logistic regression models. Covariates included demographics, presentation characteristics, comorbidities, estimated glomerular filtration rate (eGFR), main diagnosis, and medication on admission.

Results: U-shaped associations between admission potassium, mortality and cardiac arrest were observed. However, in fully adjusted models, only hyperkalemia (5.0–<5.5 [OR 1.83; 95% CI, 1.34–2.49] and ≥5.5 mmol/L [OR 2.27; 95% CI, 1.57–3.27]) was associated with mortality, while only hypokalemia (3.0–<3.5 [OR 1.63; 95% CI, 1.21–2.19] and <3.0 mmol/L [OR 2.72; 95% CI, 1.56–4.74]) was associated with cardiac arrest. Potassium <3.0 mmol/L (OR 1.93; 95% CI, 1.00–3.76) was associated with new-onset atrial fibrillation. After multivariable adjustment, no association was observed between potassium and second- or third-degree atrioventricular block. Results were not modified by main diagnosis (ACS subtype or non-ACS diagnosis) or eGFR.

Conclusions: Hyperkalemia at admission is associated with in-hospital mortality and hypokalemia with cardiac arrest and new-onset atrial fibrillation in patients admitted with suspected ACS.

1. Introduction

Potassium homeostasis is paramount for normal cell function. Approximately 98% of total body potassium is distributed as an intracellular cation, whereas only a small portion is distributed extracellular with plasma levels normally strictly maintained between 3.5 and 5.0 mmol/L. The ratio of intra- and extracellular potassium concentrations is critical for the resting cellular-membrane potential and for generating action potentials in neuronal, muscular and cardiac tissue [1].

In observational, registry-based studies of acute coronary syndrome (ACS), potassium imbalance has been associated with adverse in-hospital events including ventricular arrhythmias, cardiac arrest and death, with the lowest incidences observed at serum potassium levels between 3.5 and 4.5 mEq/L [2–4]. However, prior studies have not fully adjusted for clinical variables at admission such as blood pressure and heart rate or ACS subtype (ST-elevation myocardial infarction [STEMI] or non-ST elevation ACS [NSTE-ACS]), which may have confounded the results. Further, there is limited data regarding the plausible relationship between potassium levels at admission and the occurrence of new-onset atrial fibrillation and high-degree atrioventricular (AV) block during the hospital course. A better understanding of the prognostic value of electrolyte disorder may aid to the medical decision process and allow implementing preventive strategies.

In this study, we investigated the in-hospital prognostic utility of plasma potassium levels at admission in patients admitted to coronary

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https://doi.org/10.1016/j.ijcard.2018.09.099
0167-5273/

care units (CCU) because of suspected ACS. Study outcomes included mortality, cardiac arrest, new-onset atrial fibrillation, and second- or third-degree atrioventricular (AV) block during the hospitalization. We further studied interactions for final diagnosis (STEMI, NSTE-ACS, and non-ACS) and controlled for important clinical factors. To that end, we used data from the Swedish Web-System for Enhancement and Development of Evidence-Based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry and merged it with the Stockholm CREAtinine Measurements (SCREAM) project, a regional patient laboratory-repository.

2. Methods

2.1. Data sources

This study comprises patients from the region of Stockholm, Sweden, hospitalized in a CCU between 2006 and 2011 and registered in SWEDEHEART [5] and SCREAM [6]. The SWEDEHEART registry includes virtually all patients who are admitted to a CCU in Sweden because of symptoms suggestive of ACS. The registry prospectively collects information on patient demographics, cardiovascular risk factors, medical history, and in-hospital medical treatments including coronary revascularization procedures, hospital outcomes, discharge medications, and diagnoses. SWEDEHEART is regularly linked to the Swedish population registry, which includes information about vital status of all Swedish citizens, and also to the National Patient Register, which includes diagnoses for all patients hospitalized in Sweden. To ensure the correctness and quality of data in the registry, hospitals are monitored on a regular basis. Patients included in the registry are informed about their participation to which they have the right to decline. The SCREAM project is a repository of laboratory analyses performed in connection to healthcare in all citizens from the region of Stockholm during 2006 to 2011. The region of Stockholm is the most populated of Sweden (1.8 out of 9 million citizens in that period) and all centers report to the same healthcare provider (Stockholm County Council). Linkage between SWEDEHEART and SCREAM was made possible thanks to the unique identification number of each citizen. The study protocol was approved by the regional Ethics Committee in Stockholm.

2.2. Study population

All patients registered in SWEDEHEART within the region of Stockholm between January 1, 2006 and July 1, 2011 (n = 36,399) were eligible for entry in the study. Included were those who had a plasma potassium test available on admission (33,366, 91.7%). Given the increased risk of in-hospital adverse events and electrolyte abnormalities at admission, subjects with cardiac arrest before admission (n = 411) were excluded. Hence, 32,955 patients remained for analysis (Supplemental Fig. S1). Of note, patients with cardiac arrest prior to admission, who are not initially admitted to the CCU may not be reported in SWEDEHEART.

2.3. Plasma potassium measurements, covariates and study outcomes

All laboratory measurements were obtained from the SCREAM repository and performed in the clinical laboratories providing services to Stockholm County Council. There are three laboratories involved (Aleris, Unilabs and Karolinska University Hospital), with minimal intra- and inter-individuals variation as ensured by frequent quality and harmonization control programs. Plasma potassium levels were measured by flame photometer or ion-selective electrode, and the values within the range of 3.5 and 5.0 mmol/L were considered as normokalemia. Admission (baseline) potassium was our study exposure and was defined as the first plasma potassium test on the day of CCU admission or during the preceding 24 h. Serum creatinine was also recorded at admission, using standardized to isotope dilution mass spectrometry standards. Estimated glomerular filtration rate (eGFR) was calculated using the 2009 CKD-EPI creatinine-based equation and eGFR strata were categorized as follows: ≥60, 30–59 and below 30 mL/min/1.73 m^2 (including those undergoing chronic dialysis) [7]. We considered eGFR ≥60 mL/min/1.73 m^2 as the reference category.

Other covariates were defined at index date (except for main diagnosis established at discharge) and were recorded as per SWEDEHEART protocol. At the time of data collection, SWEDEHEART protocols did not collect separate information on the use of potassium-sparing diuretics, which was considered within the category of diuretics. Main diagnosis was defined as STEMI, NSTE-ACS, or non-ACS, where the latter is any final diagnosis that is not a confirmed ACS. Our primary study outcome was in-hospital mortality. Secondary outcomes included a) in-hospital cardiac arrest b) new-onset atrial fibrillation during hospitalization, and c) second- or third-degree AV block during hospitalization. All outcomes were documented by the treating physicians and recorded as per protocol in SWEDEHEART. In-hospital cardiac arrest requiring cardiopulmonary resuscitation (CPR) and/or defibrillation is categorized as "ventricular tachycardia or fibrillation" (VT/VF) and "other causes of cardiac arrest", *i.e.* asystole and pulseless electrical activity (PEA). The outcome analysis was conducted using a dichotomized variable defined as in-hospital cardiac arrest "no" or "yes".

2.4. Statistical analysis

We present descriptive values as mean and standard deviation (SD) or count with proportion. Baseline demographics and clinical characteristics were compared among groups of patients stratified according to the following admission plasma potassium levels: <3.0, 3.0–<3.5, 3.5–<4.0, 4.0–<4.5, 4.5–<5.0, 5.0–<5.5, ≥5.5 mmol/L.

Multivariable logistic regression was used to assess the odds of adverse clinical outcomes associated to plasma potassium categories at admission. The category of plasma potassium 3.5–<4.0 mmol/L was considered as the reference. Relative risks are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Three logistic regression models were generated adjusting for: (1) age (per year) and sex; (2) age, sex, eGFR strata, comorbidities (hypertension, diabetes, prior myocardial infarction, history of heart failure, prior stroke, peripheral vascular disease), main diagnosis at discharge (STEMI, NSTE-ACS, non-ACS), and medication on admission (angiotensin converting enzyme inhibitor/angiotensin receptor blocker [ACEI/ARB], dual antiplatelet therapy [DAPT], beta-blocker, calcium channel blocker, statins, diuretics, and nitrates); and (3) including all covariates from model 2 as well as clinical presentation characteristics (systolic blood pressure [mmHg], heart rate [categorized as <50, 50–<100, >100 beats per minute], chest pain at presentation |[yes/no], Killip class ≥2 [yes/no], electrocardiography [ECG] rhythm [sinus rhythm, atrial flutter or fibrillation, other], and ST-T changes on ECG [categorized as no ST-T changes, ST-elevation, ST depression, pathologic T wave changes, and other]). In addition, restricted cubic spline logistic regression including all covariates (those of model 3) was used to graphically model the associations between plasma potassium per mmol/L and study outcomes. Spline knots were set at the 5th, 25th, 50th, 75th, and 95th percentiles of potassium distribution and median plasma potassium of 4.0 mmol/L was used as the reference. A p value for nonlinearity was obtained by testing the coefficient of the second spline transformation equal to zero. Restricted to patients with in-hospital cardiac arrest, additional analyses were conducted with simple logistic regression. Death and type of cardiac arrest were used as outcome variables and admission plasma potassium as the independent variable according to the following categories: <3.5, 3.5–<5.0 (reference), and ≥5.0 mmol/L.

Interaction terms were tested in the following *a priori* strata: eGFR categories (eGFR≥60, 30–59, and <30 mL/min/1.73 m^2), main diagnosis (STEMI, NSTE-ACS, non-ACS,), and single medication use on admission (diuretics [yes/no], ACEI/ARB [yes/no] and beta-blocker [yes/no]). P values <0.05 were considered statistically significant.

Complete data was available for all variables except systolic blood pressure and heart rate, which were missing in 3598 (10.9%) and 3730 (11.3%) patients, respectively. Data was assumed to be missing at random. To account for missing data, multiple imputation by chained equations (MICE) was performed, where all covariates as well as primary and secondary outcome variables were used as predictors, generating 30 imputed data sets. All analyses were performed using STATA version 14.0 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

The study cohort consisted of 32,955 patients (41% women) with a mean age of 67 ± 15 years. Mean plasma potassium at admission was 4.0 ± 0.5 mmol/L. Within each potassium interval the proportions of patients (%) were: <3.0 mmol/L (1%), 3.0–<3.5 mmol/L (9%), 3.5–<4.0 mmol/L (39%), 4.0–<4.5 mmol/L (38%), 4.5 < 5.0 mmol/L (10%), 5.0–<5.5 mmol/L (2%), and ≥5.5 mmol/L (1%). Age and comorbidities generally increased across higher potassium intervals, while the proportion of women and eGFR decreased. Killip class ≥2 was more frequent among patients within the highest potassium intervals. The proportion of patients receiving ACEI/ARB, DAPT, beta-blockers, calcium channel blockers, statins and diuretics on admission tended to increase with higher potassium intervals (Table 1).

About half of the admitted patients (44.6%) had confirmed ACS, and their proportion was similar across potassium intervals. The majority of ACS cases were NSTE-ACS (70.3%). The proportion of events of primary and secondary outcomes across potassium intervals was highest for patients with STEMI followed by those with NSTE-ACS (Fig. 2). Also, the proportion of events of primary and secondary outcomes across potassium intervals was generally inversely proportional to renal function strata (Supplemental Fig. S2).

3.2. Plasma potassium and in-hospital mortality

A total of 886 (2.7%) patients died during the index hospitalization. Most deaths (78%) were attributed to cardiovascular disease. Cause of death (cardiovascular *vs.* non-cardiovascular) according to admission

potassium categories is provided in Supplemental Table S1.When the exposure was treated as a continuous variable, a U-shaped association was observed between plasma potassium and in-hospital mortality (Supplemental Fig. S3). Crude and adjusted relative risks are shown in Table 2 for plasma potassium categories with sequential degrees of multivariable adjustment. The potassium category of 3.5–4.0 mmol/L was associated with the lowest risk. After adjustment for sex, gender, eGFR strata, comorbidities, main diagnosis, and medication on admission (model 2), both hypokalemia and hyperkalemia (<3.0 and ≥5.5 mmol/L) were significantly associated with the odds of dying in hospital. Mortality risk was also elevated among patients with plasma potassium level within the considered upper reference range 4.5–<5.0 mmol/L and also for mild hyperkalemia (5.0–<5.5 mmol/L). In the fully adjusted model, considering presentation characteristics (model 3), the same pattern was present, although the association with in-hospital death was statistical significant only in those with plasma potassium ≥5.0 mmol/L (Table 2, Fig. 1).

3.3. Plasma potassium and cardiac arrest, new-onset atrial fibrillation, and AV block

A total of 494 patients (1.5%) experienced cardiac arrest during the index hospitalization, whereof VT/VF was recorded in 357 (72%). New-onset atrial fibrillation was diagnosed in 804 patients (2.4%) and 361 (1.1%) had second- or third-degree AV block during the hospital course. A U-shaped association between plasma potassium levels and in-hospital cardiac arrest was observed (Supplemental Fig. S3). After adjustment for sex, age, eGFR strata, comorbidities, main diagnosis, and medication on admission (Table 2, model 2), significantly increased odds of in-hospital cardiac arrest were observed for both plasma potassium <3.5 mmol/L and ≥5.5 mmol/L. After further adjusting for presentation characteristics (Table 2 model 3 and Fig. 1) the pattern remained, but the association with cardiac arrest was significant only in those with plasma potassium <3.5 mmol/L.

Table 1
Baseline characteristics stratified by plasma potassium level on admission.

Potassium strata, mmol/L	<3.0	3.0–<3.5	3.5–<4.0	4.0–<4.5	4.5–<5.0	5.0–<5.5	≥5.5	p-Value
No. of patients	335	2908	12,711	12,630	3276	759	336	
Characteristics at presentation								
Age, years, mean (SD)	66.2 (14.5)	65.0 (15.1)	64.5 (14.6)	67.6 (14.1)	72.6 (13.0)	75.0 (12.2)	77.1 (11.7)	<0.001
Women, no. (%)	199 (59.4)	1507 (51.8)	5682 (44.7)	4698 (37.2)	1161 (35.4)	296 (39.0)	123 (36.6)	<0.001
Systolic BP, mmHg, mean (SD) (n = 29,357)	141.3 (30.5)	145.7 (30.0)	146.6 (28.3)	145.6 (27.6)	141.5 (29.5)	137.6 (32.1)	128.8 (33.6)	<0.001
Heart rate, bpm, mean (SD) (n = 29,225)	89.7 (26.9)	84.0 (25.9)	79.6 (22.8)	79.4 (24.1)	82.0 (26.9)	86.3 (29.5)	81.6 (31.4)	<0.001
Heart rate <50 or >100 bpm, no. (%)	78 (23.3)	520 (17.9)	1678 (13.2)	1806 (14.3)	669 (20.4)	185 (24.4)	105 (31.3)	<0.001
Presenting chest pain, no. (%)	191 (57.0)	2031 (69.8)	9671 (76.1)	9498 (75.2)	2229 (68.0)	441 (58.1)	120 (35.7)	<0.001
Killip≥2, no. (%)	55 (16.4)	384 (13.2)	1226 (9.6)	1467 (11.6)	602 (18.4)	216 (28.5)	102 (30.4)	<0.001
ECG rhythm at admission, no. (%)								<0.001
Sinus rhythm	245 (73.1)	2214 (76.1)	10,214 (80.4)	9874 (78.2)	2301 (70.2)	486 (64.0)	175 (52.1)	
Atrial flutter/fibrillation	49 (14.6)	332 (11.4)	1119 (8.8)	1393 (11.0)	538 (16.4)	158 (20.8)	59 (17.6)	
Other	41 (12.2)	362 (12.4)	1378 (10.8)	1363 (10.8)	437 (13.3)	115 (15.2)	102 (30.4)	
ECG ST-T changes, no. (%)								<0.001
No change	85 (25.4)	972 (33.4)	5366 (42.2)	5316 (42.1)	1177 (35.9)	241 (31.8)	89 (26.5)	
ST elevation	72 (21.5)	599 (20.6)	2000 (15.7)	1745 (13.8)	455 (13.9)	112 (14.8)	30 (8.9)	
ST depression	78 (23.3)	485 (16.7)	1662 (13.1)	1729 (13.7)	508 (15.5)	119 (15.7)	60 (17.9)	
Pathologic T wave changes	29 (8.7)	202 (6.9)	1078 (8.5)	1203 (9.5)	306 (9.3)	70 (9.2)	27 (8.0)	
Other	71 (21.2)	650 (22.4)	2605 (20.5)	2637 (20.9)	830 (25.3)	217 (28.6)	130 (38.7)	
eGFR, mL/min/1.73 m^2, mean (SD)	75.7 (25.4)	79.9 (23.6)	82.0 (21.8)	76.4 (23.2)	62.2 (25.7)	47.5 (26.4)	31.0 (20.8)	<0.001
eGFR strata, no. (%)								<0.001
eGFR ≥60	242 (72.2)	2325 (80.0)	10,667 (83.9)	9616 (76.1)	1735 (53.0)	207 (27.3)	36 (10.7)	
eGFR 30–59	74 (22.1)	497 (17.1)	1782 (14.0)	2531 (20.0)	1136 (34.7)	341 (44.9)	105 (31.3)	
eGFR <30	19 (5.7)	86 (3.0)	262 (2.1)	483 (3.8)	405 (12.4)	211 (27.8)	195 (58.0)	
Medical history, no. (%)								
Hypertension	123 (36.7)	942 (32.4)	3340 (26.3)	3664 (29.0)	1307 (39.9)	366 (48.2)	179 (53.3)	<0.001
Diabetes mellitus	55 (16.4)	411 (14.1)	1866 (14.7)	2628 (20.8)	960 (29.3)	299 (39.4)	134 (39.9)	<0.001
Myocardial infarction	26 (7.8)	273 (9.4)	1405 (11.1)	1882 (14.9)	713 (21.8)	212 (27.9)	98 (29.2)	<0.001
Heart failure	35 (10.4)	323 (11.1)	1296 (10.2)	1777 (14.1)	807 (24.6)	298 (39.3)	156 (46.4)	<0.001
Peripheral vascular disease	20 (6.0)	105 (3.6)	436 (3.4)	571 (4.5)	308 (9.4)	75 (9.9)	52 (15.5)	<0.001
Stroke	33 (9.9)	224 (7.7)	942 (7.4)	1030 (8.2)	447 (13.6)	140 (18.4)	61 (18.2)	<0.001
Hospital course								
Main diagnosis, no. (%)								<0.001
Non-ACS	173 (51.6)	1585 (54.5)	7432 (58.5)	6867 (54.4)	1645 (50.2)	388 (51.1)	180 (53.6)	
NSTE-ACS	93 (27.8)	785 (27.0)	3600 (28.3)	4246 (33.6)	1210 (36.9)	258 (34.0)	130 (38.7)	
STEMI	69 (20.6)	538 (18.5)	1679 (13.2)	1517 (12.0)	421 (12.9)	113 (14.9)	26 (7.7)	
PCI, No. (%)	98 (29.3)	834 (28.7)	3360 (26.4)	3435 (27.2)	754 (23.0)	130 (17.1)	34 (10.1)	<0.001
CABG, No. (%)	2 (0.6)	50 (1.7)	255 (2.0)	292 (2.3)	54 (1.6)	9 (1.2)	4 (1.2)	0.012
Medication on admission, no (%)								
ACEI/ARB	95 (28.4)	752 (25.9)	3216 (25.3)	3772 (29.9)	1284 (39.2)	344 (45.3)	165 (49.1)	<0.001
DAPT	5 (1.5)	54 (1.9)	270 (2.1)	309 (2.4)	104 (3.2)	32 (4.2)	19 (5.7)	<0.001
Beta-blocker	110 (32.8)	866 (29.8)	3809 (30.0)	4513 (35.7)	1462 (44.6)	393 (51.8)	176 (52.4)	<0.001
Calcium channel blocker	67 (20.0)	510 (17.5)	1713 (13.5)	1574 (12.5)	501 (15.3)	139 (18.3)	48 (14.3)	<0.001
Statins	70 (20.9)	618 (21.3)	2873 (22.6)	3385 (26.8)	1043 (31.8)	264 (34.8)	108 (32.1)	<0.001
Diuretic	116 (34.6)	837 (28.8)	2335 (18.4)	2474 (19.6)	1001 (30.6)	326 (43.0)	154 (45.8)	<0.001
Nitrates	21 (6.3)	228 (7.8)	1144 (9.0)	1416 (11.2)	498 (15.2)	123 (16.2)	67 (19.9)	<0.001

Abbreviations: BP, blood pressure; bpm, beats per minute; ECG, electrocardiography; eGFR, estimate glomerular filtration rate; ACS, acute coronary syndrome; NSTE, non-ST elevation; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEI/ARB, angiotensin converting enzyme inhibiter/angiotensin receptor blocker; DAPT, dual antiplatelet therapy.

Type of cardiac arrest, as recorded in SWEDEHEART, by plasma potassium categories at admission is provided in Supplemental Table S2. In analysis restricted to patients with in-hospital cardiac arrest and with normokalemia (3.5–<5.0 mmol/L) at admission as the reference, those with hyperkalemia (plasma potassium >5.0 mmol/L) were more likely to have asystole or PEA as compared to VT/VF (OR 2.32; 95% CI, 1.20–4.49). Patients with hypokalemia (plasma potassium <3.5 mmol/L) were less likely to have asystole or PEA as compared to VT/VF (OR 0.53; 95% CI, 0.29–0.97). Patients with hyperkalemia at admission and in-hospital cardiac arrest were more likely to die in hospital than those with normokalemia at admission (OR 2.92; 95% CI, 1.44–5.92). Patients with hypokalemia at admission and in-hospital cardiac arrest were less likely to die in hospital than those with normokalemia (OR 0.56; 95% CI, 0.34–0.93).

In fully adjusted models (Table 2, model 3 and Fig. 1), the risk of new-onset atrial fibrillation was increased in patients with plasma potassium below 3.0 mmol/L. We noted increased risk magnitude for second- or third-degree AV block with plasma potassium ≥5.5 mmol/L but no significant association was observed in the fully adjusted model (Table 2, model 3 and Fig. 1).

3.4. Sensitivity analyses

No statistical interaction was observed between ACS diagnosis, or renal function strata and plasma potassium categories in predicting study outcomes. Statistical interactions were neither observed for plasma potassium and sex, nor presentation characteristics or single medication use (data not shown).

4. Discussion

In this cohort study of nearly 33,000 patients with suspected ACS, we observed that both hyperkalemia and hypokalemia on admission were associated with in-hospital mortality and cardiac arrest, regardless of final diagnosis. In fully adjusted models considering patient clinical characteristics, we found that hyperkalemia at admission was more strongly associated with in-hospital mortality, whereas hypokalemia was more strongly associated with cardiac arrest and also new-onset atrial fibrillation during the hospital course.

The proarrhythmic and potentially lethal effects of severe potassium disturbances are undisputed [8]. Whether, in the setting of

Table 2
Odds ratios (OR) and 95% confidence intervals (CI) for in-hospital mortality, in-hospital cardiac arrest, new-onset atrial fibrillation, and 2nd/3rd degree atrioventricular block by plasma potassium level on admission.

Plasma potassium level on admission, mmol/L	No. of patients	No. of events	Event rate, %	Model 1 adjusted for age, sex		Model 2[a]		Model 3[b]	
				OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
In-hospital mortality									
<3.0	335	14	4.18	2.25**	[1.28,3.96]	1.98*	[1.11,3.52]	1.60	[0.89,2.88]
3.0–<3.5	2908	75	2.58	1.41*	[1.07,1.84]	1.29	[0.98,1.69]	1.15	[0.86,1.52]
3.5–<4.0	12,711	225	1.77	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0–<4.5	12,630	263	2.08	0.95	[0.79,1.14]	0.89	[0.74,1.07]	0.91	[0.75,1.10]
4.5–<5.0	3276	165	5.04	1.74***	[1.41,2.15]	1.30*	[1.04,1.63]	1.22	[0.97,1.54]
5.0–<5.5	759	80	10.54	3.49***	[2.65,4.60]	1.98***	[1.47,2.67]	1.83***	[1.34,2.49]
≥5.5	336	64	19.05	6.29***	[4.58,8.64]	3.05***	[2.16,4.32]	2.27***	[1.57,3.27]
In-hospital cardiac arrest									
<3.0	335	16	4.78	4.27***	[2.52,7.25]	3.21***	[1.86,5.54]	2.72***	[1.56,4.74]
3.0–<3.5	2908	71	2.44	2.10***	[1.58,2.80]	1.83***	[1.37,2.44]	1.63**	[1.21,2.19]
3.5–<4.0	12,711	152	1.2	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0–<4.5	12,630	142	1.12	0.84	[0.67,1.06]	0.83	[0.66,1.05]	0.85	[0.67,1.08]
4.5–<5.0	3276	73	2.23	1.48**	[1.11,1.98]	1.20	[0.89,1.61]	1.11	[0.82,1.50]
5.0–<5.5	759	24	3.16	2.03**	[1.30,3.16]	1.27	[0.80,2.03]	1.20	[0.75,1.92]
≥5.5	336	16	4.76	2.93***	[1.72,5.00]	1.87*	[1.05,3.33]	1.41	[0.78,2.55]
New-onset atrial fibrillation (n = 29,307)									
<3.0	286	10	3.50	2.66**	[1.38,5.11]	2.22*	[1.14,4.32]	1.93*	[1.00,3.76]
3.0–<3.5	2576	41	1.59	1.18	[0.83,1.67]	1.07	[0.75,1.52]	0.98	[0.69,1.40]
3.5–<4.0	11,592	156	1.35	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0–<4.5	11,237	172	1.53	0.98	[0.79,1.22]	0.96	[0.76,1.19]	0.96	[0.77,1.21]
4.5–<5.0	2738	74	2.70	1.43*	[1.07,1.90]	1.23	[0.91,1.65]	1.18	[0.87,1.58]
5.0–<5.5	601	19	3.16	1.54	[0.95,2.52]	1.15	[0.69,1.91]	1.05	[0.63,1.75]
≥5.5	277	9	3.25	1.47	[0.74,2.93]	1.14	[0.56,2.36]	0.88	[0.42,1.83]
2nd/3rd degree atrioventricular block									
<3.0	335	3	0.9	1.09	[0.34,3.45]	0.89	[0.28,2.84]	0.70	[0.22,2.29]
3.0–<3.5	2908	26	0.89	1.07	[0.70,1.65]	0.96	[0.62,1.48]	0.85	[0.55,1.31]
3.5–<4.0	12,711	108	0.85	1.00	[1.00,1.00]	1.00	[1.00,1.00]	1.00	[1.00,1.00]
4.0–<4.5	12,630	131	1.04	1.05	[0.81,1.36]	1.05	[0.81,1.36]	1.03	[0.80,1.35]
4.5–<5.0	3276	60	1.83	1.55**	[1.12,2.14]	1.37	[0.98,1.92]	1.20	[0.86,1.69]
5.0–<5.5	759	18	2.37	1.88*	[1.13,3.14]	1.37	[0.80,2.32]	1.18	[0.70,2.04]
≥5.5	336	15	4.46	3.35***	[1.91,5.86]	2.44**	[1.344.48]	1.54	[0.82,2.90]

Abbreviations: OR, Odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; NSTE, non-ST elevation; STEMI, ST-elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; bpm, beats per minute; ECG, electrocardiography.

[a] Model 2 adjusted for age, sex, eGFR strata (≥60, 30–59, <30), comorbidities (hypertension, diabetes, prior myocardial infarction, history of heart failure, prior stroke, peripheral vascular disease), main diagnosis (non-ACS, NSTE-ACS, STEMI), and medication on admission (ACEI/ARB, DAPT, beta-blocker, calcium channel blocker, statins, diuretics, and nitrates).

[b] Model 3 further adjusted for systolic blood pressure, heart rate category (<50 or >100 bpm), presenting chest pain, Killip ≥ 2, ECG rhythm (sinus rhythm, atrial flutter/fibrillation, other), ECG ST-T changes (no, ST elevation, ST depression, T-wave changes, or other).

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

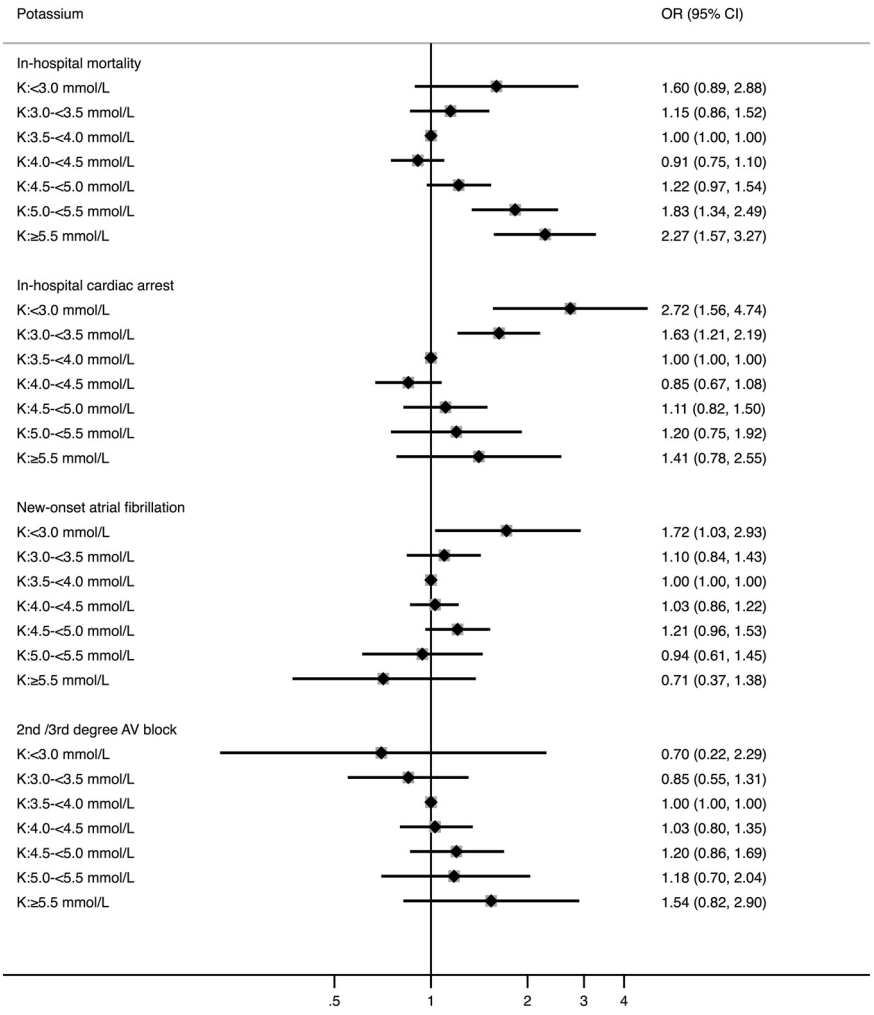

Fig. 1. Odds ratios (OR) and 95% confidence intervals (CI) for in-hospital mortality, in-hospital cardiac arrest, new-onset atrial fibrillation, and 2nd/3rd degree atrioventricular block by plasma potassium categories at admission. Estimates were adjusted for age, sex, systolic BP, heart rate category (<50 or >100 bpm), eGFR strata (60+, 30–59, <30 mL/min/1.73 m^2), comorbidities (hypertension, diabetes, prior myocardial infarction, history of heart failure, prior stroke, peripheral vascular disease), presenting chest pain, Killip ≥ 2, ECG rhythm (sinus rhythm, atrial flutter/fibrillation, other), ECG ST-T changes (no, ST elevation, ST depression, other), main diagnosis (non-ACS, NSTE-ACS, STEMI), and medication on admission (ACEI/ARB, DAPT, beta-blocker, calcium channel blocker, statins, diuretics, and nitrates). The interval of plasma potassium 3.5–4.0 mmol/L was considered as reference.

suspected ACS, even mild or moderate potassium imbalance is a risk factor, a risk marker or a combination of both, remains unanswered. Nevertheless, our results support previous observations that normokalemia on admission is associated with the lowest incidence of adverse events [2–4,9]. In their registry-based study, Goyal and colleagues investigated the impact of mean post-admission serum potassium in patients with myocardial infarction but additionally reported associations for admission potassium [2]. In comparison, our study differed by including a broader population of patients admitted with suspected ACS. Although no interaction was observed, we confirm that patients with STEMI followed by those with NSTE-ACS are generally, at any given potassium level, at the highest absolute risk of any of the adverse in-hospital events, as are patients with lower eGFR. In this study with 44.6% having an ACS, the event rates were lower than those reported by Goyal et al. In contrast, we also adjusted for presentation characteristics, such as Killip class, ECG-changes, blood pressure and heart rate, which may otherwise work as confounding factors. This may in part reflect the differences in results between our study and that of Goyal et al. After multivariable adjustment they observed significantly increased in-hospital mortality for admission serum potassium <3.0 and ≥5.0 mEq/L. For the composite outcome of in-hospital ventricular arrhythmias and cardiac arrest, significantly increased odds were observed for serum potassium levels below 3.5 mEq/L at admission (reference 3.5–4.0 mEq/L) [2]. Our results coincide, to a large extent, with these finding but suggest that hyperkalemia at admission may be an even stronger predictor of in-hospital mortality than hypokalemia.

The association between hyperkalemia and sudden cardiac death has been previously reported [10]. In our study, however, the association between hyperkalemia and cardiac arrest did not remain as strong after multivariable adjustment. This may have several possible explanations. Patients with hyperkalemia were older and had more comorbidities, which may have influenced CPR decisions. Cardiac arrest, where CPR or defibrillation was not initiated, is not registered in SWEDHEART. We also observed that patients with hyperkalemia, as opposed to hypokalemia, and in-hospital cardiac arrest were more likely to have non-VT/VF and to die during the hospital course.

Hypokalemia (plasma potassium <3.0 mmol/L) at admission was associated with new-onset atrial fibrillation during hospitalization, and this association remained after adjusting for all covariates. This finding has been suggested in different clinical settings [11,12] and, in addition, in animal models showing that hypokalemia alters sinoatrial node and pulmonary vein electrical properties [13].

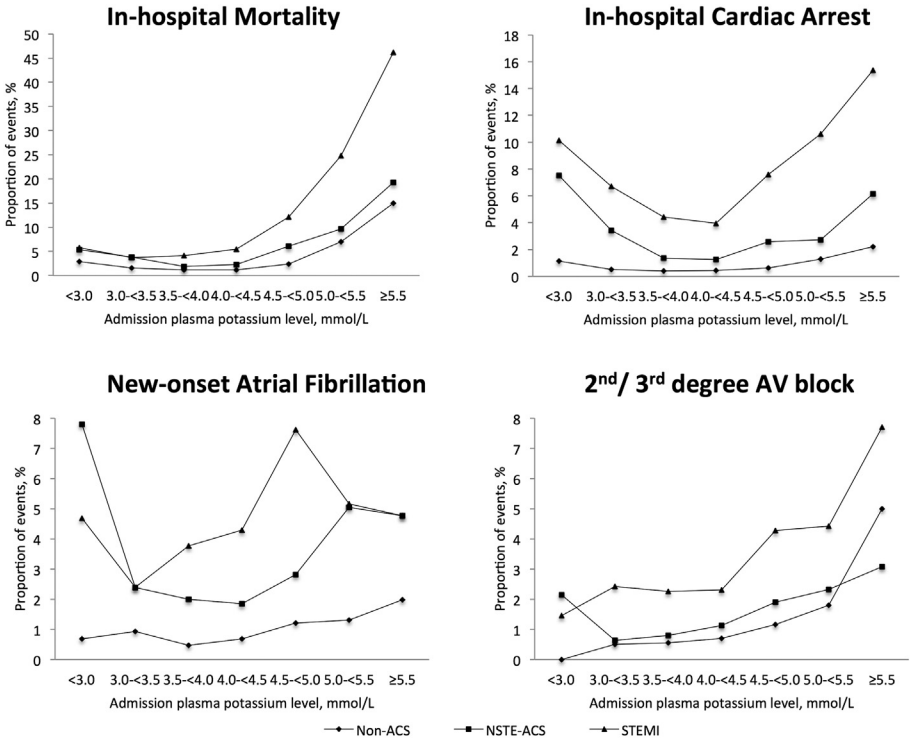

Fig. 2. Proportion of events (in-hospital mortality, in-hospital cardiac arrest, new-onset atrial fibrillation, and 2nd/3rd degree atrioventricular block) by plasma potassium categories at admission and final diagnosis.

Our findings must be interpreted in the light of several strengths and limitations. Strengths are the large sample size, complete regional coverage and a richer characterization of confounders than previous studies. On the other hand, no data on timing of in-hospital events were available and hence no temporal relationships to admission could be investigated. Regarding medication on admission, we could not distinguish between different types of diuretics (*e.g.* loop diuretics and potassium-sparing diuretics). Information on medication during hospitalization was limited. All patients in our cohort, including those with a final diagnosis of non-ACS, were indeed hospitalized in the CCU implicating that these results may not apply to any patient with chest pain in the emergency ward or other non-CCU wards. Additionally, patients with cardiac arrest prior to admission were excluded. The reader is reminded that potassium, in Swedish laboratory testing, is measured in plasma, and values may be systematically 0.1–0.2 mEq/L lower as compared to serum potassium measurements. As with all observational studies, there is a possibility of misclassification and underreporting and importantly, despite multivariable adjustment, association does not imply causation.

To conclude, our study shows that potassium imbalance at admission requires vigilance among treating physicians, as it is associated with in-hospital arrhythmias and mortality among patients admitted with suspected ACS. However, it is unknown whether correction of potassium disturbances at admission would also improve outcome, and this requires further research.

Acknowledgements

This study was supported by the Swedish Heart-Lung Foundation and an institutional grant from Vifor Fresenius Medical Care Renal Pharma to Karolinska Institutet. In addition, we acknowledge grant support from the Swedish Strategic Research Foundation (SSF), Swedish Research Council, Stockholm County Council (including ALF projects), AstraZeneca, as well as Martin Rind's and Westman's Foundations. HX was supported by the Karolinska Institutet faculty for funding of postgraduate doctorial students (KID). KS was supported by the Stockholm County Council (clinical research appointment). ME was funded by the Stockholm County Council post-doc grant.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.099.

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