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SHORT COMMUNICATION

Serum potassium level and mineralocorticoid receptor antagonist dose in a large cohort of chronic heart failure patients

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Abstract

Aims Hyperkalaemia is observed frequently in heart failure (HF) patients and is associated with an impaired prognosis and underuse of mineralocorticoid receptor antagonists (MRAs). However, the effects of serum potassium on prescription of the full guideline recommended daily dose of 50 mg in real-world daily practice are unknown. Therefore, we investigated serum potassium and its association with the prescribed MRA dose in a large cohort of chronic HF patients.

Methods and results A total of 5346 patients with chronic HF with a left ventricular ejection fraction ≤40% from 34 Dutch outpatient HF clinics between 2013 and 2016 were analysed on serum potassium and MRA (spironolactone and eplenerone) dose. Data were stratified by potassium as a serum potassium level <4.0, 4.0 to 5.0 or >5.0 mmol/L. Multivariable logistic regression models were used to assess the association between serum potassium and MRA dose and to adjust for potential confounders. Mean serum potassium was 4.4 ± 0.5 mmol/L and hyperkalaemia (serum potassium >5.0 mmol/L) was present in 399 patients (7.5%). MRA was used in 3091 patients (58.1%). Patients with hyperkalaemia significantly less often received ≥100% of the target dose (50 mg) compared with patients with a serum potassium between 4.0–5.0 mmol/L and <4.0 mmol/L (7.7% vs. 9.5% vs. 13.6% respectively, $P = 0.0078$). In the multivariable regression analyses, patients with hyperkalaemia were significantly less likely to receive ≥100% of the target dose compared with patients with serum potassium 4.0–5.0 mmol/L (OR 0.38, 95% CI 0.15–0.97, $P = 0.044$). Additionally, a one unit increase in serum potassium was significantly associated with a lower odds of receiving ≥100% of the target dose (OR 0.69, 95% CI 0.49–0.98, $P = 0.036$).

Conclusions In this large registry of real-world chronic HF patients, both an increase in serum potassium and hyperkalaemia were associated with a lower odds of receiving the guideline-recommended MRA dose.

Keywords Heart failure; Heart failure with reduced ejection fraction; Hyperkalaemia; Mineralocorticoid receptor antagonists; Renin-angiotensin-aldosterone system inhibitors; Guidelines

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Background

Hyperkalaemia, generally defined as a serum potassium level >5.0 mmol/L,[1] is frequently observed in heart failure (HF) patients, with reported incidences between 3.1% and 16.6%.[2–7] Hyperkalaemia is potentially a life-threatening condition and is associated with impaired prognosis, especially in HF patients.[4,6,8–10] Although renin-angiotensin-aldosterone system inhibitors (RAASi) are among the cornerstone therapies for HF patients with a reduced ejection fraction (HFrEF),[11] their use is also an independent risk factor for hyperkalaemia.[12–16] The implementation of guideline-directed medical therapy (GDMT) in HF patients is suboptimal and seems especially challenging for mineralocorticoid

receptor antagonists (MRAs),[10,17–20] which might be due to the increased risk of hyperkalaemia.[21] Hyperkalaemia has been associated with MRA discontinuation and dose reduction[22,23] and, in addition, was found to be a predictor of receiving <50% of the target dose.[7] Because achieving the full target dose is the aim in clinical practice, it is interesting to know the association between serum potassium and prescription of MRA at the guideline recommended daily target dose, especially considering the level 1A recommendation of MRAs and the introduction of potassium binding drugs. However, real-world data on the extent of hyperkalaemia in clinical practice and in relation to MRA use and dose are lacking but important to improve guideline implementation and very relevant for the perspective and future of potassium binding drugs.

Aims

This study aimed to investigate the distribution of serum potassium in a large cohort of chronic HF patients and the association between serum potassium, including hyperkalaemia, and the prescribed MRA (spironolactone and eplerenone) dose relative to the guideline recommended daily target dose of 50 mg.

Methods

For this study, data from the CHECK-HF registry were used. The design and methods of the CHECK-HF registry have been described in detail elsewhere.[24] In short, this cross-sectional registry consisted of 10 910 chronic HF patients from 34 Dutch participating centres with data collected between 2013 and 2016. All patients were diagnosed with HF and were treated according to the 2012 ESC guideline for the diagnosis and treatment of acute and chronic HF.[25] Detailed information was collected on patient characteristics and HF drug prescriptions. The study was conducted in accordance with the Declaration of Helsinki, and ethical approval was provided for anonymously analysing existing patient data by the medical ethical committee of the Maastricht University Medical Center. For this analysis, patients with a left ventricular ejection fraction (LVEF) ≤ 40% were selected (*N* = 6256) (HFrEF).[11] Moreover, patients with missing information on serum potassium were excluded (*N* = 910), and a total of 5346 patients with an LVEF ≤40% were analysed in this study. Data were stratified by serum potassium categories <4.0, 4.0–5.0, and >5.0 mmol/L. For the MRA analyses, only spironolactone and eplerenone were included. A daily MRA dose of 50 mg in real-world was considered 100% of the guideline-recommended dose for both spironolactone and eplerenone, which is in line with the current ESC HF guideline.[11] The proportion of patients treated with an MRA was compared between the different potassium categories. Furthermore, the prescribed dose in categories of <50% (equal to <25 mg), 50%–99% (equal to 25–49 mg), and ≥100% (equal to ≥50 mg) of the guideline recommended target dose (≥50 mg) was compared by potassium category. Multivariable logistic regression analyses with the MRA dose categories as outcome were performed to further assess the association between serum potassium and MRA dose as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Serum potassium was included in the models either as continuous or categorical variable (<4.0, 4.0–5.0, and >5.0 mmol/L). For the latter, the 4.0–5.0 mmol/L serum potassium category was considered the reference group. In the multivariable models, the association between serum potassium and MRA dose was adjusted for age, sex, body mass index (BMI), systolic blood pressure (SBP), New York Heart Association (NYHA) class, QRS time, estimated glomerular filtration rate (eGFR), diabetes mellitus type 2 (DM2), chronic obstructive pulmonary disease (COPD), diuretics use, angiotensin-converting enzyme inhibitor (ACEi) use, and angiotensin receptor blocker (ARB) use.

Results

Of all 5346 patients, 941 patients (17.6%) had a serum potassium <4.0 mmol/L, 4006 patients (74.9%) had a serum potassium 4.0–5.0 mmol/L, and 399 patients (7.5%) had a serum potassium >5.0 mmol/L. Mean serum potassium in the overall cohort was 4.36 ± 0.49 mmol/L (*Figure 1*). The baseline characteristics by serum potassium category are presented in *Table 1*. Patients with a serum potassium >5.0 mmol/L were older, more often male, had worse renal function, were less often treated with diuretics, and more often treated with ACEi. A total of 3091 patients (58.1%) were treated with an MRA, of whom 3075 (99.5%) had complete data on the prescribed dose. Serum potassium in patients with <50%, 50%–99%, and ≥100% of MRA target dose was 4.41 ± 0.47, 4.35 ± 0.49, 4.26 ± 0.51 ($P < 0.001$), respectively (*Figure 2*). The MRA dose overall and by serum potassium category is presented in *Table 2*. There were no significant differences in MRA use between patients with hyperkalaemia as compared with patients with serum potassium between 4.0–5.0 mmol/L and <4.0 mmol/L (55.8% vs. 58.2% vs. 58.6%, respectively). However, patients with hyperkalaemia significantly less often received ≥100% of the target dose compared with patients with a serum potassium between 4.0–5.0 mmol/L and <4.0 mmol/L (7.7% vs. 9.5% vs. 13.6% respectively, $P = 0.0078$).

The results of the logistic regression analyses are summarized in *Table 3*. In the multivariable models, a one unit increase in serum potassium was associated with both a lower

Figure 1 Serum potassium distribution in the overall cohort

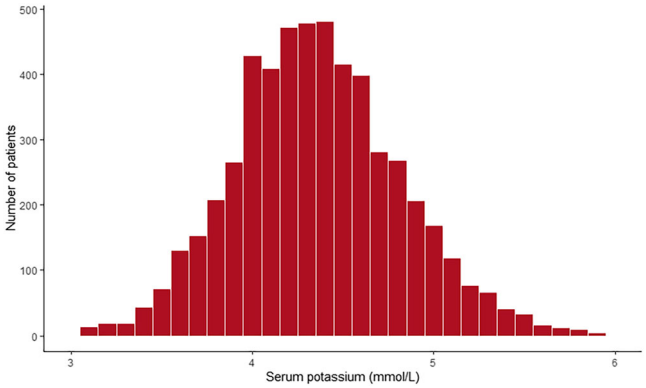

Table 1 Baseline characteristics by serum potassium category

	Missing (*N*, %)	Total (*N* = 5346)	Serum potassium <4.0 mmol/L (*N* = 941)	Serum potassium 4.0–5.0 mmol/L (*N* = 4006)	Serum potassium >5.0 mmol/L (*N* = 399)	*P*-value for difference
Age	7 (0.1)	72.2 ± 11.6	70.8 ± 12.2	72.4 ± 11.5	73.26 ± 10.76	<0.001
Sex (female)	23 (0.4)	1862 (35.0)	372 (39.7)	1358 (34.1)	132 (33.1)	0.0039
BMI	356 (6.7)	27.3 ± 5.1	27.4 ± 5.3	27.3 ± 5.0	27.1 ± 5.1	0.59
SBP	47 (0.9)	123.6 ± 19.7	123.2 ± 20.2	123.7 ± 19.5	123.0 ± 19.6	0.63
DBP	41 (0.8)	70.6 ± 11.0	71.4 ± 11.5	70.6 ± 10.8	69.1 ± 11.6	0.0022
HR	57 (1.1)	71.6 ± 13.7	73.0 ± 13.8	71.2 ± 13.7	72.0 ± 13.4	0.0014
LVEF	928 (17.4)	30.3 ± 9.5	29.6 ± 9.3	30.3 ± 9.5	31.5 ± 9.9	0.012
NYHA						<0.001
Class I	63 (1.2)	612 (11.6)	106 (11.3)	460 (11.6)	46 (11.7)	
Class II		3162 (59.9)	520 (55.6)	2416 (61.1)	226 (57.5)	
Class III		1397 (26.4)	288 (30.8)	1008 (25.5)	101 (25.7)	
Class IV		112 (2.1)	21 (2.2)	71 (1.8)	20 (5.1)	
Atrial fibrillation	61 (1.1)	1279 (24.2)	225 (24.2)	958 (24.2)	96 (24.3)	1.00
LBBB	0 (0.0)	949 (17.8)	172 (18.3)	705 (17.6)	72 (18.0)	0.88
QRS	859 (16.1)	128.1 ± 34.0	130.2 ± 35.2	127.8 ± 33.71	126.3 ± 34.5	0.12
Primary aetiology						0.19
Ischaemic	0 (0.0)	2616 (48.9)	436 (46.3)	1978 (49.4)	202 (50.6)	
Non-ischaemic		2730 (51.1)	505 (53.7)	2028 (50.62)	197 (49.4)	
Hypertension	611 (11.4)	1879 (39.7)	327 (39.4)	1404 (39.6)	148 (40.9)	0.88
Diabetes type 2	611 (11.4)	1234 (26.1)	191 (23.0)	920 (26.0)	123 (34.0)	<0.001
COPD	611 (11.4)	886 (18.7)	152 (18.3)	668 (18.9)	66 (18.2)	0.90
OSAS	611 (11.4)	295 (6.2)	62 (7.5)	211 (6.0)	22 (6.1)	0.27
Thyroid disease	611 (11.4)	340 (7.2)	60 (7.2)	257 (7.3)	23 (6.4)	0.82
eGFR	771 (14.4)	61.0 ± 24.8	65.1 ± 24.3	61.1 ± 24.4	51.0 ± 27.2	<0.001
eGFR						<0.001
<30		476 (10.4)	68 (8.6)	323 (9.4)	85 (23.9)	
30–44		872 (19.1)	110 (13.9)	671 (19.6)	91 (25.6)	
45–60		972 (21.2)	157 (19.9)	749 (21.8)	66 (18.6)	
≥ 60		2255 (49.3)	455 (57.6)	1687 (49.2)	113 (31.8)	
Diuretics	24 (0.4)	4554 (85.2)	839 (89.4)	3368 (84.5)	329 (83.1)	<0.001
ACEi	24 (0.4)	3043 (57.2)	504 (53.7)	2299 (57.7)	240 (60.6)	0.030
ARB	24 (0.4)	1389 (26.1)	229 (24.4)	1055 (26.5)	105 (26.5)	0.42
Beta-blocker	24 (0.4)	4293 (80.7)	729 (77.6)	3238 (81.2)	326 (82.3)	0.030

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; LBBB, left bundle branch block; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnoea syndrome; eGFR, estimated glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Figure 2 Serum potassium distribution by MRA dose. MRA, mineralocorticoid receptor antagonist

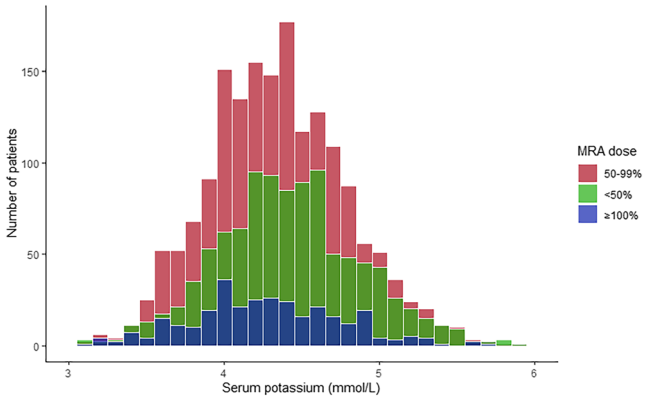

Table 2 MRA dose by serum potassium category

	Missing (*N*, %)	Total (*N* = 5346)	Serum potassium <4.0 mmol/L (*N* = 941)	Serum potassium 4.0–5.0 mmol/L (*N* = 4006)	Serum potassium >5.0 mmol/L (*N* = 399)	*P*-value for difference
MRA use	24 (0.4)	3091 (58.1)	550 (58.6)	2320 (58.2)	221 (55.8)	0.62
MRA dose						
<50% (<25 mg)	16 (0.5)	1018 (33.1)	159 (28.9)	770 (33.4)	89 (40.3)	0.0082
50%–99% (25–49 mg)		1745 (56.7)	316 (57.5)	1314 (57.0)	115 (52.0)	0.34
≥100% (≥50 mg)		312 (10.1)	75 (13.6)	220 (9.5)	17 (7.7)	0.0078

Abbreviation: MRA, mineralocorticoid receptor antagonist.

odds of receiving ≥100% of the target dose (OR 0.69, 95% CI 0.49–0.98, $P = 0.036$) and a higher odds of receiving <50% of the target dose (OR 1.47, 95% CI 1.18–1.83, $P < 0.001$). Furthermore, patients with hyperkalaemia were significantly less likely to receive ≥100% of the target dose (OR 0.38, 95% CI 0.15–0.97, $P = 0.044$) and significantly more likely to receive <50% of the target dose (OR 1.55, 95% CI 1.07–2.26, $P = 0.021$).

Discussion

In this large cohort of real-world chronic HF patients, hyperkalaemia was present in 7.5% of the patients, which is similar to earlier studies.[3–6,8] Interestingly, the use of MRA overall was not associated with serum potassium and hyperkalaemia, but both hyperkalaemia and a one unit increase in serum potassium were significantly associated with a lower odds of receiving ≥100% and a higher odds of receiving <50% of the guideline-recommended target dose.

Earlier studies found hyperkalaemia to be associated with non-use and discontinuation of MRAs,[10,21] and a higher odds of receiving <50% of the guideline-recommended MRA target dose.[7] To the best of our knowledge, serum potassium has not been studied in relation to MRA treatment at the guideline-recommended dose. Compared with the earlier research, our study contained more recent data and also explored the association with ≥100% of the target dose and showed that hyperkalaemia was associated with a 62% lower odds of receiving the guideline-recommended dose. Furthermore, our study showed that an increase in serum potassium itself was significantly associated with a lower odds of receiving ≥100% of the target dose, which is important information in light of the introduction of potassium binding drugs. The current study therefore adds significantly to current literature and indicates that there is room for further improvement of MRA treatment in this subgroup of HFrEF patients.

Maintaining normal serum potassium levels is important but can be especially challenging with MRA use. Although the guideline-recommended target dose for MRAs is 50 mg, a large proportion of patients in the two landmark trials, EMPHASIS-HF and RALES, did not achieve this dose, but nevertheless, a clear benefit from MRAs was shown.[26,27] It therefore may deserve consideration to lower the dose rather than to discontinue the MRA completely, as benefit is still likely to be present even at a lower dose. Two potassium binding drugs, sodium zirconium cyclosilicate (ZS-9) and patiromer, have been shown effective in maintaining normal serum potassium levels and decreasing recurrent episodes of hyperkalemia.[28,29] The recently completed DIAMOND trial reported that the use of patiromer was associated with

Table 3 Logistic regression analysis results

	Univariable model (N = 3075)			Multivariable model (N = 1799)		
Serum potassium	OR	95% CI	*P*-value	OR	95% CI	*P*-value
MRA dose <50% (<25 mg)						
Continuous	1.35	1.15–1.57	<0.001	1.47	1.18–1.83	<0.001
Categorical						
<4.0	0.81	0.66–0.99	0.043	0.80	0.60–1.07	0.13
4.0–5.0	Reference	Reference	Reference	Reference	Reference	Reference
>5.0	1.34	1.01–1.78	0.041	1.55	1.07–2.26	0.021
MRA dose 50%–99% (25–49 mg)						
Continuous	0.90	0.78–1.04	0.17	0.82	0.67–1.01	0.064
Categorical						
<4.0	1.02	0.84–1.23	0.86	1.14	0.88–1.47	0.32
4.0–5.0	Reference	Reference	Reference	Reference	Reference	Reference
>5.0	0.82	0.62–1.08	0.15	0.81	0.56–1.17	0.27
MRA dose ≥100% (≥50 mg)						
Continuous	0.62	0.48–0.80	<0.001	0.69	0.49–0.98	0.036
Categorical						
<4.0	1.50	1.13–1.98	0.0049	1.07	0.71–1.60	0.75
4.0–5.0	Reference	Reference	Reference	Reference	Reference	Reference
>5.0	0.79	0.47–1.32	0.367	0.38	0.15–0.97	0.044

Note: Multivariable models were adjusted for age, sex, body mass Index (BMI), systolic blood pressure (SBP), New York Heart Association (NYHA) class, QRS time, estimated glomerular filtration rate (eGFR), diabetes mellitus type 2 (DM2), chronic obstructive pulmonary disease (COPD), diuretics use, angiotensin-converting enzyme inhibitors (ACEi) use, and angiotensin receptor blocker (ARB) use.
Abbreviations: MRA, mineralocorticoid receptor antagonist; OR, odds ratio; 95% CI, 95% confidence interval.

significantly lower serum potassium, fewer hyperkalaemia episodes, concurrent use of high doses of MRAs, and overall higher RAASi use in patients with HFrEF and RAASi-related hyperkalaemia.[30] Unfortunately, although initially planned to do so, the DIAMOND trial did not completely answer the question whether optimizing RAASi therapy in combination with patiromer improves outcomes.[31,32] Potassium binding drugs have been recommended to maintain normal serum potassium levels during RAASi therapy in two recent expert consensus documents[33,34] but are not included in the current guideline.[11] The future of potassium binding drugs in clinical practice is unclear, especially considering the limited observed recurrent hyperkalaemia and high number needed to treat.[35]

Study limitations

This study has a number of limitations to consider. Due to the cross-section nature of the data, it was not possible to assess any clinical responses to lowering the dose or discontinuing the MRA in patient with hyperkalaemia. However, despite being a cross-sectional study, our findings are relevant and important as they provide insight in the association between serum potassium and MRA dose in a large real-world population. Moreover, the data collection was performed between 2013 and 2016, which was a different period in terms of GDMT with the later introduction of the angiotensin receptor–neprilysin inhibitor (ARNI) and sodium–glucose co-transporter 2 inhibitor (SGLT2i).[11] Nevertheless, we believe the results of this study are still relevant, considering the MRA was the main focus of this study and the recommended target dose for the MRA has remained unchanged.

Conclusions

Our real-world data in a large cohort of HF patients with measured serum potassium are unique and show that both hyperkalaemia and an increase in serum potassium are associated with receiving a lower odds of receiving the full target MRA dose, which adds to the literature that higher serum potassium levels may also be an impediment for reaching the full MRA target dose.

Conflict of interest

None declared.

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