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High versus low dose losartan and serum potassium: an analysis from HEAAL

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Abstract

Background: Patients with HF experience frequent alterations of serum potassium. Despite the high risk of events associated with hypokalemia, hyperkalemia is feared by clinicians and often leads to interruption or discontinuation of RAAS inhibitors. Data on serum potassium of patients treated with different doses of RAAS inhibitors are scarce.

Methods: HEAAL randomized 3834 HFrEF patients intolerant to ACEi to losartan 150 (high-dose) vs. 50 (low-dose) mg/day. We studied the associations of serum potassium (baseline and time-updated) with study outcomes and the effect of the randomized treatment on serum potassium.

Results: Patients with higher baseline potassium were older, had diabetes, poorer renal function, and used MRAs more frequently. In time-updated models, hyperkalemia (>5 or ≥ 5.5 mmol/L) was not associated with cardiovascular death nor the composite of cardiovascular death or HF hospitalization. Hypokalemia (serum potassium ≤ 3.5 mmol/L, in particular) was associated with a higher risk of the composite of cardiovascular death or HF hospitalization (HR 1.58, 95%CI 1.19-2.08), all-cause death (HR 1.68, 95%CI 1.26-2.24) and sudden cardiac death or resuscitated cardiac arrest (HR 1.74, 95%CI 1.11-2.73). High-dose losartan decreased the risk of hypokalemia (HR 0.77, 95%CI 0.63-0.92) and increased the risk of hyperkalemia (HR 1.21, 95%CI 1.05-1.39). High-dose losartan reduced the composite of cardiovascular death or HF hospitalizations consistently across the full spectrum of serum potassium at baseline (interaction P-value =0.85).

Conclusions: In HFrEF patients intolerant to ACEi and treated with either high- or low-dose losartan, incident hypokalemia had a stronger association with poor

outcomes than incident hyperkalemia. High-dose losartan reduced the incidence of hypokalemia, and its benefits were maintained across the full spectrum of serum potassium.

Key-words: potassium; losartan; heart failure treatment.

Lay summary

- In patients with heart failure and reduced ejection fraction, the occurrence of hypokalemia was associated with worse prognosis than the occurrence of hyperkalemia.
- High-dose losartan reduced the incidence of hypokalemia.
- High-dose losartan improved outcomes across a wide range of baseline potassium.

Introduction

Patients with heart failure (HF) experience frequent alterations of serum potassium throughout the course of the disease, as these may be caused by HF progression (e.g., fluid retention), comorbidities (e.g., chronic kidney disease) and concomitant medications (e.g., diuretics, ACEi/ARBs, ARNIs, and MRAs).¹ Compared to normokalemia, both hypo- and hyperkalemia have been associated with poor outcomes in HF.²⁻⁴ Despite the high risk of events associated with hypokalemia, hyperkalemia is most feared by clinicians and often leads to interruption or permanent discontinuation of RAAS inhibitors, which may further aggravate HF prognosis.^{5,6} Thus, from observational reports, it is not possible to ascertain if the risk associated with hypo- and hyperkalemia is caused directly by potassium alterations or if the risk is caused by patient's clinical deterioration aggravated by RAAS inhibitors discontinuation (the latter is particularly relevant in the setting of hyperkalemia).⁶

Data on potassium alterations in patients randomized to different doses of RAAS inhibitors are scarce. Despite the potential higher risk of hyperkalemia, higher doses of ACEi/ARB (compared to lower doses) improved outcomes in patients with heart failure with reduced ejection fraction (HFrEF).^{7,8} Thus, it is possible that hyperkalemia is not associated with an increased risk of events when patients are treated with high dose of ACEi/ARB. Supporting this hypothesis, a previous analysis from the HEAAL (effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure) trial showed that high dose losartan improved outcomes despite the more frequent occurrence of hyperkalemia.⁹

HEAAL randomized patients with HFrEF to high (150 mg/day) or low (50 mg/day) dose of losartan, providing an unique setting to study potassium alterations throughout the follow-up and their prognostic associations at different background doses of RAAS inhibition.

Methods

Study design and population

HEAAL was an international, multicentre, double-blind, event-driven trial, comparing the effect of two doses of losartan 150 (high-dose) vs. 50 (low-dose) mg/day among 3834 patients with symptomatic heart failure, a LVEF of 40% or less, stable cardiovascular medical therapy for at least 2 weeks, and known intolerance to ACEi defined as discontinuation of ACE-inhibitor treatment because of one or more of the following adverse effects: cough, symptomatic hypotension, azotaemia, hyperkalemia, taste disturbance, gastrointestinal upset, or rash. Patients with serum potassium <3.5 mmol/L or >5.7 mmol/L at baseline could not enter the trial.⁷ The median follow-up time was 4.7 (pct₂₅₋₇₅, 3.5-5.5) years. Patients assigned to the high-dose group received a mean of 129 ± 39 mg of losartan daily and the patients assigned to the low-dose group received a mean of 46 ± 11 mg/daily. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee or institutional review board of every site. All patients provided written informed consent before randomization. HEAAL is registered with ClinicalTrials.gov, number NCT00090259.

Serum potassium, sodium and creatinine were measured at months 1, 4, 9, and 12 and at every 6-month visit thereafter.

In the present analysis, we studied the associations of serum potassium (both baseline and time-updated) with the outcomes of cardiovascular death or HF hospitalization, cardiovascular death, all-cause death or HF hospitalization, all-cause death, and sudden cardiac death or resuscitated cardiac arrest. The cause of death and the primary cause of admission were determined by an Endpoint Classification Committee, whose members were masked to treatment assignment. Adverse events were reported while patients were taking treatment and for 14 days after the end of treatment. Events were coded with the Medical Dictionary for Regulatory Activities (version 12).

Statistical analysis

The baseline characteristics were compared between the baseline potassium categories of ≤ 3.5 , 3.6-3.9, 4.0-5.0, 5.1-5.4, and ≥ 5.5 mmol/L, using ANOVA or Kruskal-Wallis tests, as appropriate. Continuous variables are expressed as median (percentile₂₅₋₇₅) and categorical variables are presented as absolute numbers and percentages. The association between serum potassium and the study outcomes was studied with potassium both as categorical (using the categories above defined) and continuous (using a fractional polynomial spline with 5 knots¹⁰) covariate, using both the baseline (before any randomized treatment intake) and time-updated values (last available value before the event). Cox models were adjusted for age, sex, race, atrial fibrillation, ischemic HF etiology, hypertension, diabetes mellitus, prior myocardial infarction, NYHA class, LVEF, systolic blood pressure, heart rate, body mass index, eGFR, sodium, hemoglobin, beta-blocker use, MRA use, use of loop diuretics, and randomized losartan dose. eGFR and sodium were treated as time-varying covariates. The effect of high vs. low dose losartan on serum potassium was studied using mixed effects models including baseline potassium levels and

treatment-by-time interaction terms as dependent variables, and random intercept at the patient level. The effect of high- vs. low-dose losartan across the full spectrum of potassium levels at baseline was assessed with a Cox model with a treatment-by-potassium interaction term. The effect of high- vs low-dose of losartan on incident hypo- and hyperkalemia was studied by means of a Cox model with treatment as independent variable and first occurrence of hypo- and hyperkalemia (i.e., first occurrence in a study visit) as outcome variable, in the subset of patients without hypo- and hyperkalemia at baseline using the same potassium thresholds as for the outcomes of interest. No data imputation for missing values was performed. A p-value <0.05 was accepted as the threshold for statistical significance without correction for multiplicity of tests given the exploratory nature of this work. Statistical analyses were conducted in Stata® version 17 (StataCorp LP).

Results

Patient's characteristics by potassium levels at baseline

A total of 3,602 patients (94% of the HEAAL population) with available potassium values at baseline were included in this analysis. The median potassium level was 4.4 (SD \pm 0.5; percentile₂₅₋₇₅ 4.1-4.8) mmol/L with a normal distribution. *Supplemental Figure 1*. Compared to patients with serum potassium between 4.0 and 5.0 mmol/L at baseline (n =2618), those with a serum potassium <4.0 mmol/L (n =471) were younger, less frequently White, with higher eGFR, and using MRAs less frequently. On the other hand, patients with a serum potassium >5.0 mmol/L (n =513) were older, presented diabetes mellitus more frequently, with lower eGFR, and using MRAs more frequently (P <0.05 for all). *Table 1*.

Association of serum potassium with outcomes

In baseline models, compared to patients with a serum potassium between 4.0 and 4.9 mmol/L, those with a higher serum potassium (>5.0 or ≥ 5.5 mmol/L) had a higher risk of cardiovascular death, all-cause death, and sudden cardiac death or resuscitated cardiac arrest ($P < 0.05$ for all). Hyperkalemia was not associated with the composite of cardiovascular death or HF hospitalization nor all-cause death or HF hospitalization. *Table 2.* Baseline hypokalemia (<4 or ≤ 3.5 mmol/L) was not associated with the occurrence of any of the studied outcomes. *Table 2.*

On average, during the follow-up each patient had their serum potassium levels determined on 6 (3-9) visits, with a minimum of 1 and a maximum of 19. A time-updated serum potassium between 5.1 and 5.4 mmol/L was only associated with a higher risk of all-cause death (HR 1.24, 95%CI 1.05-1.44). A time-updated serum potassium ≥ 5.5 mmol/L was not associated with the occurrence of any of the studied outcomes. *Table 2.* Time-updated hypokalemia (serum potassium ≤ 3.5 mmol/L, in particular) was associated with a higher risk of the composite of cardiovascular death or HF hospitalization (HR 1.64, 95%CI 1.23-2.19), all-cause death or HF hospitalization (HR 1.65, 95%CI 1.25-2.19), all-cause death (HR 1.78, 95%CI 1.32-2.41) and sudden cardiac death or resuscitated cardiac arrest (HR 1.77, 95%CI 1.10-2.83). *Table 2.* Analysing time-updated serum potassium as a continuous spline transformed covariate confirmed a higher risk of events with hypokalemia rather than with hyperkalemia. *Figure 1.* No interaction of between randomized losartan dose and serum potassium (either baseline or time-updated) was present (interaction $P > 0.05$ for all outcomes).

Effect of high- vs. low-dose losartan on serum potassium

High-dose (150 mg/day) vs. low-dose (50 mg/day) losartan slightly increased serum potassium over time by ≈ 0.1 mmol/L, on average (P-value for overall effect =0.001).

Figure 2.

High-dose losartan decreased the risk of hypokalemia (10.1% vs. 12.9%; HR 0.77, 95%CI 0.63-0.92 for incident serum potassium ≤ 3.5 mmol/L) and increased the risk of hyperkalemia (22.7% vs. 19.1%; HR 1.21, 95%CI 1.05-1.39 for incident serum potassium ≥ 5.5 mmol/L). *Table 3.*

A total of 6 patients permanently discontinued treatment due to hyperkalemia, 4 in the high-dose group and 2 in the low-dose group.

Effect of high- vs. low-dose losartan across the full spectrum of baseline potassium

High-dose losartan (vs. low-dose) reduced the composite of cardiovascular death or HF hospitalizations consistently across the full spectrum of serum potassium at baseline (interaction P-value =0.85). *Figure 3.*

Discussion

The present study confirms that older age, diabetes, impaired renal function, and MRA use are risk factors for hyperkalemia; however, among HFrEF patients intolerant to ACEi receiving either low or high dose of ARB therapy the development of incident hypokalemia had a stronger association with a higher risk of subsequent events than the development of hyperkalemia, suggesting that hyperkalemia (at least up to 5.5 mmol/L) should not be worrisome in the setting of RAASi inhibition and should not lead to treatment down-titration or discontinuation. Compared with low-dose (50 mg/day), high-dose (150 mg/day) losartan slightly increased serum

potassium by 0.1 mmol/L throughout the follow-up (4.7 years, on average), and decreased the incidence of hypokalemia (≤ 3.5 mmol/L) while increasing the incidence of hyperkalemia (≥ 5.5 and ≥ 6.0 mmol/L), with an absolute difference of 2-3% compared to the low-dose group. Drug discontinuation due to hyperkalemia was low (<1%). High-dose losartan was superior to low-dose for reducing the composite of cardiovascular death or HF hospitalizations across the full spectrum of baseline potassium.

A previous study from the HEAAL dataset, had shown that hyperkalemia was frequent and did not influence the effect of high-dose losartan to improve HF outcomes.⁹ Our study expands these findings by studying the full spectrum of potassium alterations, including time-updated alterations throughout the follow-up which reflect the patient's status closer to the event (whereas the baseline values may be distant in time from the event), suggesting that hypokalemia, which risk may be lowered by high-dose losartan, may have a stronger association with poor outcomes than hyperkalemia in the setting of background ARB treatment. Prior observational studies showing an increased risk associated with hyperkalemia suggested that part of the risk could be related to the stopping of RAAS inhibition in the presence of raised potassium levels; when RAAS inhibitor discontinuation was accounted in the model, hyperkalemia was no longer associated with mortality.¹¹ Of note, it was already reported that Losartan 150 mg daily reduced the rate of death or admission for HF, but was more frequently associated with investigator reported renal impairment and hyperkalemia . However, these reported adverse events did not lead to significantly more treatment discontinuations in the 150 mg group. These findings are supported by those of the PARADIGM-HF trial comparing sacubitril/valsartan to enalapril in HFrEF.¹² PARADIGM-HF also had all patients on

RAAS blockade because an active comparator (enalapril) was used. In this setting, hypokalemia had stronger association with poor outcomes (including HF hospitalizations and mortality) than hyperkalemia.² Of course, above a certain level of serum potassium (which may vary in each individual patient) there may be a risk of arrhythmias and clinicians may reduce the dose or stop RAAS inhibitors. Based on our data there appears to be a slightly higher risk of mortality with serum potassium levels above 5 mmol/L (particularly when considering the baseline potassium values, 11% of the HEAAL population), and clinicians may consider reducing the dose of RAAS inhibitors in such patients. In this setting, potassium binders may be useful to enable the up-titration of RAAS inhibitors. For example, in the recently presented DIAMOND study, patiomer was able to maintain lower serum potassium levels and reduced the incidence of serum potassium (>5.5 mmol/L), allowing more participants to be optimized on guideline-directed medical doses of RAAS inhibitors. However, in DIAMOND patiomer also increased the rates of hypokalemia. The impact of patiomer on HF outcomes remains to be established because the trial was stopped earlier, lacking power to assess morbidity and mortality outcome effects (*presented at ACC 2022*). The use of SGLT2 inhibitors, beyond improving outcomes in HF, may also reduce the risk of hyperkalemia (without increasing the risk of hypokalemia) which may enable the up-titration of RAAS inhibitors.¹³

The mechanism by which hypokalemia is associated with poor outcomes is not fully established. Hypokalemia is known to be associated with ventricular arrhythmias, likely to represent a major cause of death in this population. Hypokalemia also drives muscle weakness, increasing fatigue that may mimic HF worsening and lead to hospitalization.² It is also possible that patients with worsening HF signs and

symptoms receive higher diuretic doses which may cause hypokalemia. In HEAAL, diuretic doses were not recorded throughout the follow-up, and we cannot confirm or exclude this hypothesis. In any case, high-dose losartan reduced the incidence of hypokalemia throughout the follow-up, supporting RAAS up-titration as an effective means of both reducing hypokalemia and improve outcomes.¹⁴

Limitations

Some limitations should be acknowledged in our study. First, this is a post-hoc analysis of a randomized controlled trial which is affected by the biases inherent to observational studies, particularly the impossibility to infer causality. Second, HEAAL had a relatively low proportion of MRA treated patients (38%) and these findings cannot be extrapolated to HFrEF populations with higher frequency of MRA treatment. Third, post-randomization medications including the use of diuretics or the use of potassium binders were not registered in the dataset, and we could not assess medication changes in response to potassium alterations and vice-versa. Diuretic doses or the use of diuretics throughout the follow-up were not available in the dataset; thus, we could not ascertain if diuretic use (or diuretic doses) throughout the follow-up could be associated with incident hypokalemia.

Conclusions

In HFrEF patients intolerant to ACEi and treated with either high- (150 mg/day) or low-dose (50 mg/day) of the ARB losartan, incident hypokalemia had a stronger association with poor outcomes than incident hyperkalemia. High-dose losartan reduced the incidence of hypokalemia, and its benefits were maintained across the full spectrum of serum potassium.

Ethics approval and consent to participate

The study was approved by all relevant ethics committees and regulatory bodies. All participants provided written informed consent prior to study specific procedures.

Consent for publication

There is no data of individual persons included in the manuscript.

Competing interests

JPF is a consultant for Boehringer Ingelheim and receives research support from Astra Zeneca, Bayer, and Novartis through his institution.

References

1. Ferreira JP. Abnormalities of Potassium in Heart Failure. 2020
2. Ferreira JP, Mogensen UM, Jhund PS, et al. Serum potassium in the PARADIGM-HF trial. *Eur J Heart Fail.* Aug 18 2020;doi:10.1002/ejhf.1987
3. Ferreira JP, Claggett BL, Liu J, et al. Serum potassium and outcomes in heart failure with preserved ejection fraction: a post-hoc analysis of the PARAGON-HF trial. *Eur J Heart Fail.* May 2021;23(5):776-784. doi:10.1002/ejhf.2134
4. Nunez J, Bayes-Genis A, Zannad F, et al. Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality. *Circulation.* Mar 27 2018;137(13):1320-1330. doi:10.1161/circulationaha.117.030576
5. Beusekamp JC, Tromp J, van der Wal HH, et al. Potassium and the use of renin-angiotensin-aldosterone system inhibitors in heart failure with reduced ejection fraction: data from BIOSTAT-CHF. *Eur J Heart Fail.* May 2018;20(5):923-930. doi:10.1002/ejhf.1079
6. Rossignol P, Lainscak M, Crespo-Leiro MG, et al. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail.* Apr 3 2020;doi:10.1002/ejhf.1793
7. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet.* Nov 28 2009;374(9704):1840-8. doi:10.1016/s0140-6736(09)61913-9
8. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* Dec 7 1999;100(23):2312-8.
9. Rossignol P, Dobre D, Gregory D, et al. Incident hyperkalemia may be an independent therapeutic target in low ejection fraction heart failure patients: insights from the HEAAL study. *Int J Cardiol.* May 15 2014;173(3):380-7. doi:10.1016/j.ijcard.2014.02.034
10. Harrell F. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis.* New York, Springer; 2001
11. Rossignol P, Lainscak M, Crespo-Leiro M, Laroche C, Piepoli M, et al. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9 222 chronic heart failure patients of the ESC HFA EORP Heart Failure Long-Term HF LT Registry. 2020
12. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* Sep 11 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
13. Ferreira JP, Zannad F, Butler J, et al. Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled. *Eur Heart J.* Jun 10 2022;doi:10.1093/eurheartj/ehac306
14. Rossignol P, Girerd N, Bakris G, et al. Impact of eplerenone on cardiovascular outcomes in heart failure patients with hypokalaemia. *Eur J Heart Fail.* Jun 2017;19(6):792-799. doi:10.1002/ejhf.688

Table 1. Patient's characteristics by baseline potassium levels

Characteristic	Serum potassium (mmol/L)					P-value
	≤3.5	3.6-3.9	4.0-5.0	5.1-5.4	≥5.5	
N.	59	412	2618	409	104	
Age, years	61 (50, 68)	63 (54, 72)	66 (57, 73)	67 (60, 73)	68 (60, 73)	<0.001
Women	15 (25.4%)	124 (30.1%)	787 (30.1%)	117 (28.6%)	27 (26.0%)	0.80
White race	33 (55.9%)	204 (49.5%)	1605 (61.3%)	259 (63.3%)	67 (64.4%)	<0.001
Atrial fibrillation	14 (23.7%)	126 (30.6%)	703 (26.9%)	128 (31.3%)	28 (26.9%)	0.22
Ischemic HF	37 (62.7%)	252 (61.2%)	1670 (63.8%)	275 (67.2%)	71 (68.3%)	0.38
Hypertension	28 (47.5%)	238 (57.8%)	1560 (59.6%)	263 (64.3%)	60 (57.7%)	0.088
Diabetes mellitus	23 (39.0%)	117 (28.4%)	790 (30.2%)	160 (39.1%)	45 (43.3%)	<0.001
Myocardial infarction	6 (10.2%)	25 (6.1%)	259 (9.9%)	35 (8.6%)	12 (11.5%)	0.13
Stroke	7 (11.9%)	37 (9.0%)	205 (7.8%)	30 (7.3%)	8 (7.7%)	0.72
NYHA III/IV	23 (39.0%)	110 (26.7%)	787 (30.1%)	138 (33.7%)	41 (39.4%)	0.027
LVEF, %	30 (25, 35)	32 (26, 37)	33 (27, 37)	33 (29, 37)	35 (26, 38)	0.073
SBP, mmHg	120 (110, 130)	122 (110, 140)	125 (112, 140)	126 (110, 140)	120 (110, 136)	0.14
Heart rate, bpm	72 (65, 84)	72 (65, 82)	72.0 (64, 80)	72 (64, 84)	72 (64, 80)	0.24
BMI, Kg/m ²	26 (23, 31)	27 (24, 30)	27 (24, 30)	27 (24, 31)	27 (23, 30)	0.20
eGFR, ml/min/1.73m ²	75 (59, 95)	70 (58, 87)	68 (55, 83)	60 (48, 75)	55 (43, 72)	<0.001
Potassium, mmol/L	3.5 (3.3, 3.5)	3.8 (3.7, 3.9)	4.4 (4.2, 4.7)	5.1 (5.0, 5.3)	5.6 (5.5, 5.8)	<0.001
Sodium, mmol/L	140 (138, 141)	141 (139, 143)	140 (138, 142)	140 (138, 142)	139 (136, 142)	0.002
Hemoglobin, g/dL	14.2 (13.2, 14.8)	14.1 (12.9, 15.0)	13.9 (12.9, 14.9)	13.8 (12.8, 15.0)	13.9 (12.3, 14.9)	0.53
Beta-blocker	45 (76.3%)	278 (67.5%)	1887 (72.1%)	296 (72.4%)	83 (79.8%)	0.097
MRA	20 (33.9%)	127 (30.8%)	1002 (38.3%)	208 (50.9%)	52 (50.0%)	<0.001
Loop diuretic	52 (88.1%)	335 (81.3%)	2113 (80.7%)	353 (86.3%)	95 (91.3%)	0.003
Statin	26 (44.1%)	142 (34.5%)	1044 (39.9%)	169 (41.3%)	47 (45.2%)	0.14

Legend: HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist.

Table 2. Association of serum potassium with outcomes

Outcome/Potassium levels	Baseline Events, n. (%)	Baseline HR (95%CI) P-value	Time-updated Events, n. (%)*	Time-updated HR (95%CI) P-value
Cardiovascular death or heart failure hospitalization				
≤3.5 mmol/L	25/59 (42.4)	1.22 (0.82-1.82) P =0.32	40/576 (6.9)	1.64 (1.23-2.19) P =0.001
3.6-3.9 mmol/L	159/412 (38.6)	1.00 (0.84-1.18) P =0.98	140/3334 (4.2)	1.06 (0.88-1.27) P =0.55
4.0-5.0 mmol/L	967/2618 (36.9)	Ref.	896/22193 (4.0)	Ref.
5.1-5.4 mmol/L	179/409 (43.8)	1.12 (0.95-1.32) P =0.17	182/3552 (5.1)	1.06 (0.90-1.24) P =0.48
≥5.5 mmol/L	58/104 (55.8)	1.30 (0.99-1.70) P =0.059	71/1082 (6.6)	1.03 (0.81-1.31) P =0.82
Cardiovascular death				
≤3.5 mmol/L	17/59 (28.8)	1.17 (0.72-1.90) P =0.53	26/710 (3.7)	1.44 (0.99-2.11) P =0.058
3.6-3.9 mmol/L	102/412 (24.8)	1.05 (0.85-1.30) P =0.66	88/3801 (2.3)	1.05 (0.83-1.32) P =0.68
4.0-5.0 mmol/L	588/2618 (22.5)	Ref.	565/25108 (2.3)	Ref.
5.1-5.4 mmol/L	124/409 (30.3)	1.26 (1.03-1.53) P =0.023	136/4134 (3.3)	1.13 (0.94-1.37) P =0.20

≥5.5 mmol/L	40/104 (38.5)	1.49 (1.07-2.06) P =0.018	56/1288 (4.4)	1.02 (0.77-1.35) P =0.88
All-cause death or heart failure hospitalization				
≤3.5 mmol/L	26/59 (44.1)	1.12 (0.75-1.65) P =0.58	46/576 (8.0)	1.65 (1.25-2.19) P <0.001
3.6-3.9 mmol/L	185/412 (44.9)	0.99 (0.85-1.16) P =0.93	167/3334 (5.0)	1.10 (0.94-1.30) P =0.24
4.0-5.0 mmol/L	1137/2168 (43.4)	Ref.	1039/22192 (4.7)	Ref.
5.1-5.4 mmol/L	210/409 (51.3)	1.13 (0.97-1.31) P =0.11	222/3553 (6.3)	1.11 (0.96-1.28) P =0.15
≥5.5 mmol/L	62/104 (59.6)	1.20 (0.92-1.55) P =0.17	87/1082 (8.0)	1.08 (0.87-1.34) P =0.49
All-cause death				
≤3.5 mmol/L	20/59 (33.9)	1.00 (0.64-1.56) P =0.99	43/710 (6.1)	1.78 (1.32-2.41) P <0.001
3.6-3.9 mmol/L	143/412 (34.7)	1.04 (0.87-1.25) P =0.65	130/3801 (3.4)	1.17 (0.97-1.41) P =0.099
4.0-5.0 mmol/L	841/2618 (32.1)	Ref.	767/25108 (3.1)	Ref.
5.1-5.4 mmol/L	167/409 (40.8)	1.20 (1.01-1.42) P =0.036	200/4134 (4.8)	1.24 (1.05-1.44) P =0.008
≥5.5 mmol/L	52/104 (50.0)	1.38 (1.04-1.83) P =0.028	83/1288 (6.4)	1.14 (0.91-1.42) P =0.25
Sudden death or resuscitated cardiac arrest				

≤3.5 mmol/L	9/59 (15.3)	1.06 (0.54-2.07) P =0.86	18/710 (2.5)	1.77 (1.10-2.83) P =0.018
3.6-3.9 mmol/L	59/412 (14.3)	1.12 (0.85-1.49) P =0.41	54/3801 (1.4)	1.14 (0.85-1.54) P =0.37
4.0-5.0 mmol/L	314/2618 (12.0)	Ref.	311/25108 (1.2)	Ref.
5.1-5.4 mmol/L	76/409 (18.6)	1.53 (1.18-1.97) P =0.001	62/4134 (1.5)	1.01 (0.76-1.32) P =0.97
≥5.5 mmol/L	20/104 (19.2)	1.52 (0.96-2.41) P =0.074	33/1288 (2.6)	1.26 (0.87-1.81) P =0.22

*Events per number of potassium measurements.

Legend: HR, hazard ratio; CI, confidence interval.

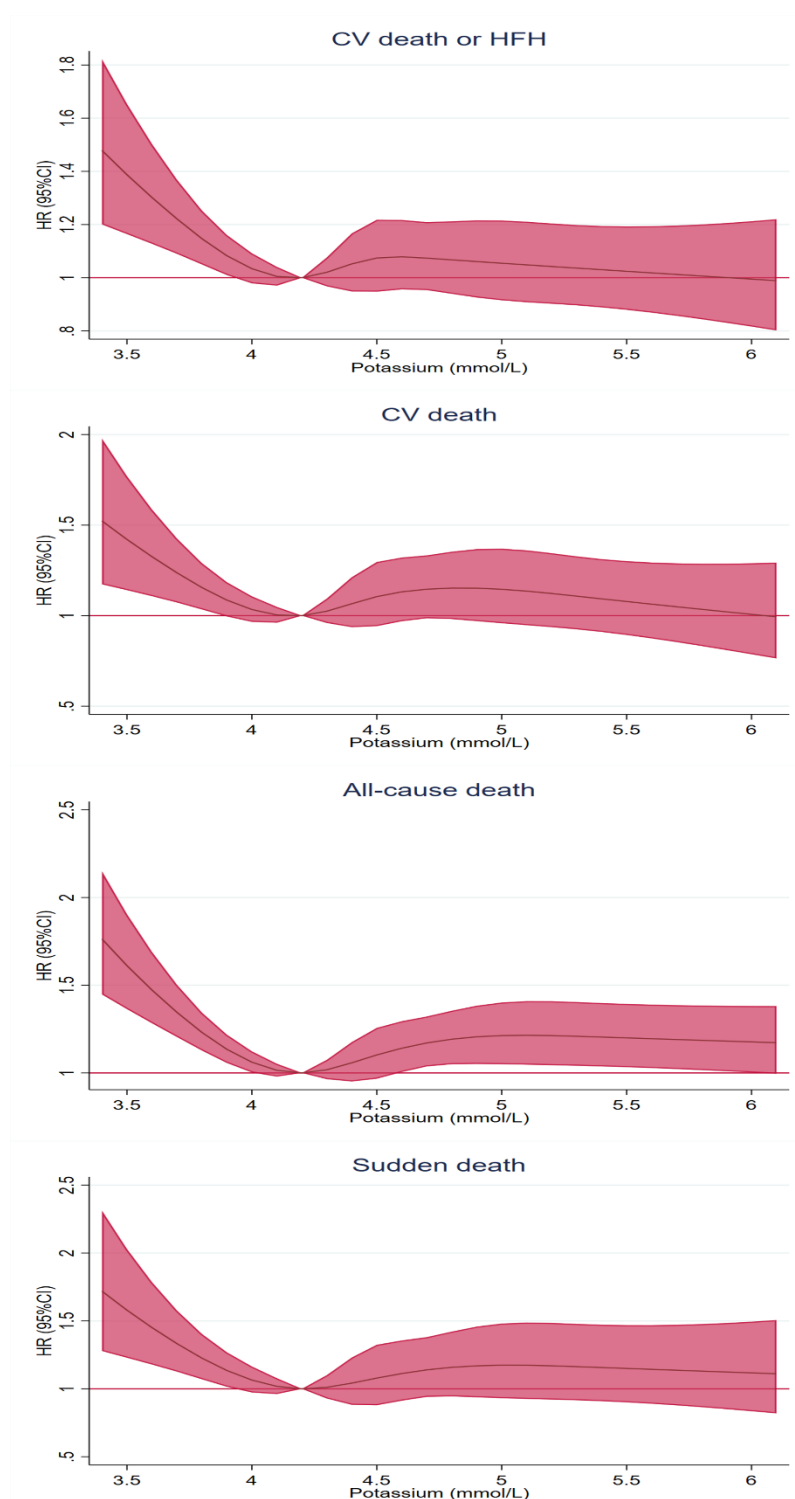
Models adjusted for age, sex, race, atrial fibrillation, ischemic HF etiology, hypertension, diabetes mellitus, prior myocardial infarction, NYHA class, LVEF, systolic blood pressure, heart rate, body mass index, eGFR, sodium, hemoglobin, beta-blocker use, MRA use, use of loop diuretics, and randomized losartan dose. No interaction of between randomized losartan dose and serum potassium (either baseline or time-updated) was present (interaction P >0.05 for all outcomes).

Table 3. Risk of hypo- and hyperkalemia with high- vs. low-dose losartan

Potassium alteration	High-dose losartan n. (%)	Low-dose losartan n. (%)	HR (95%CI) P-value
≤3.0 mmol/L	17/37 (0.9)	20/37 (1.1)	0.83 (0.43-1.58) P =0.56
≤3.5 mmol/L	194/441 (10.1)	247/441 (12.9)	0.77 (0.63-0.92) P =0.005
≥5.5 mmol/L	436/801 (22.7)	365/801 (19.1)	1.21 (1.05-1.39) P =0.008
≥6.0 mmol/L	170/295 (8.9)	125/295 (6.5)	1.36 (1.07-1.71) P =0.010

Legend: HR, hazard ratio; CI, confidence interval.

Figure 1. Visual Take Home graphic: Risk of events with time-updated potassium levels

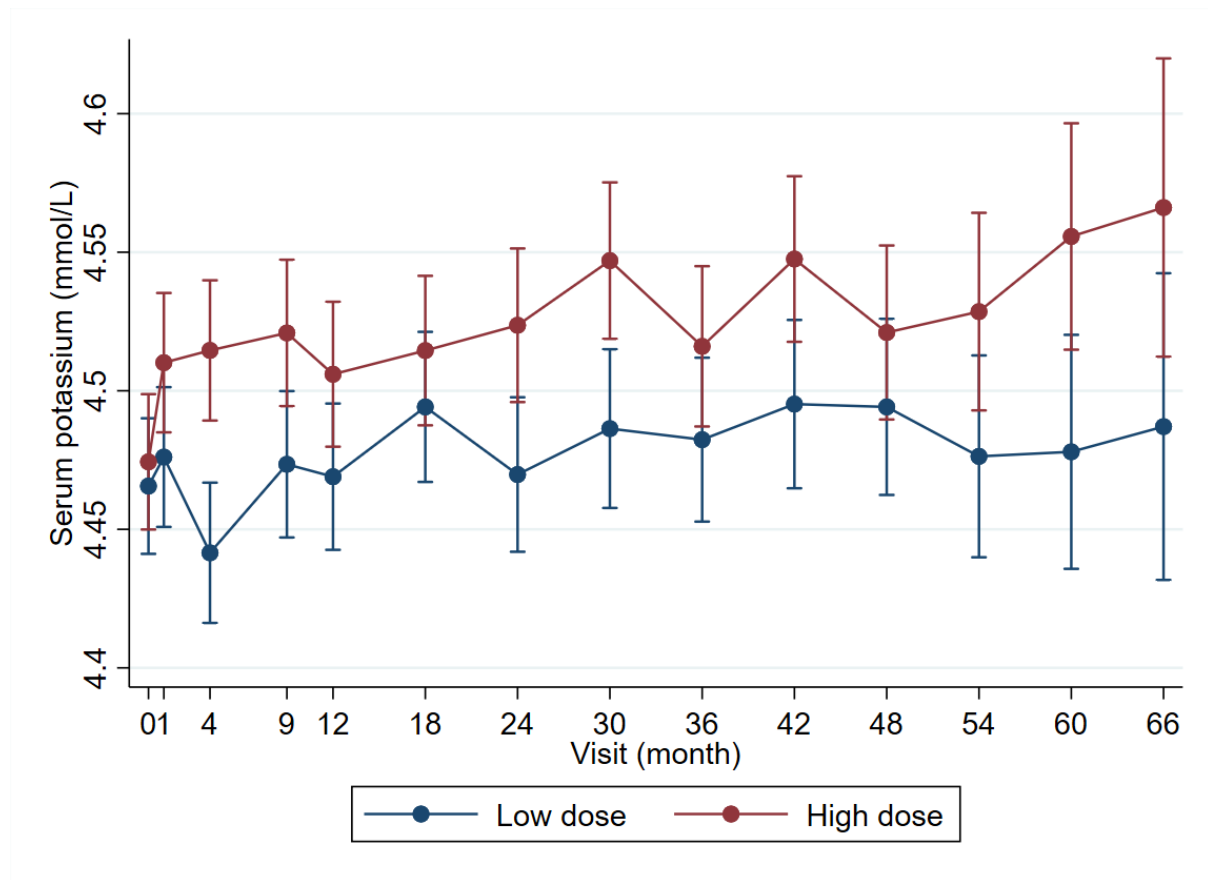


Models adjusted for age, sex, race, atrial fibrillation, ischemic HF etiology, hypertension, diabetes mellitus, prior myocardial infarction, NYHA class, LVEF, systolic blood pressure, heart rate, body mass index, eGFR, sodium, hemoglobin, beta-blocker use, MRA use, use of loop diuretics, and randomized losartan dose.

No interaction of between randomized losartan dose and serum potassium (either baseline or time-updated) was present (interaction P >0.05 for all outcomes).

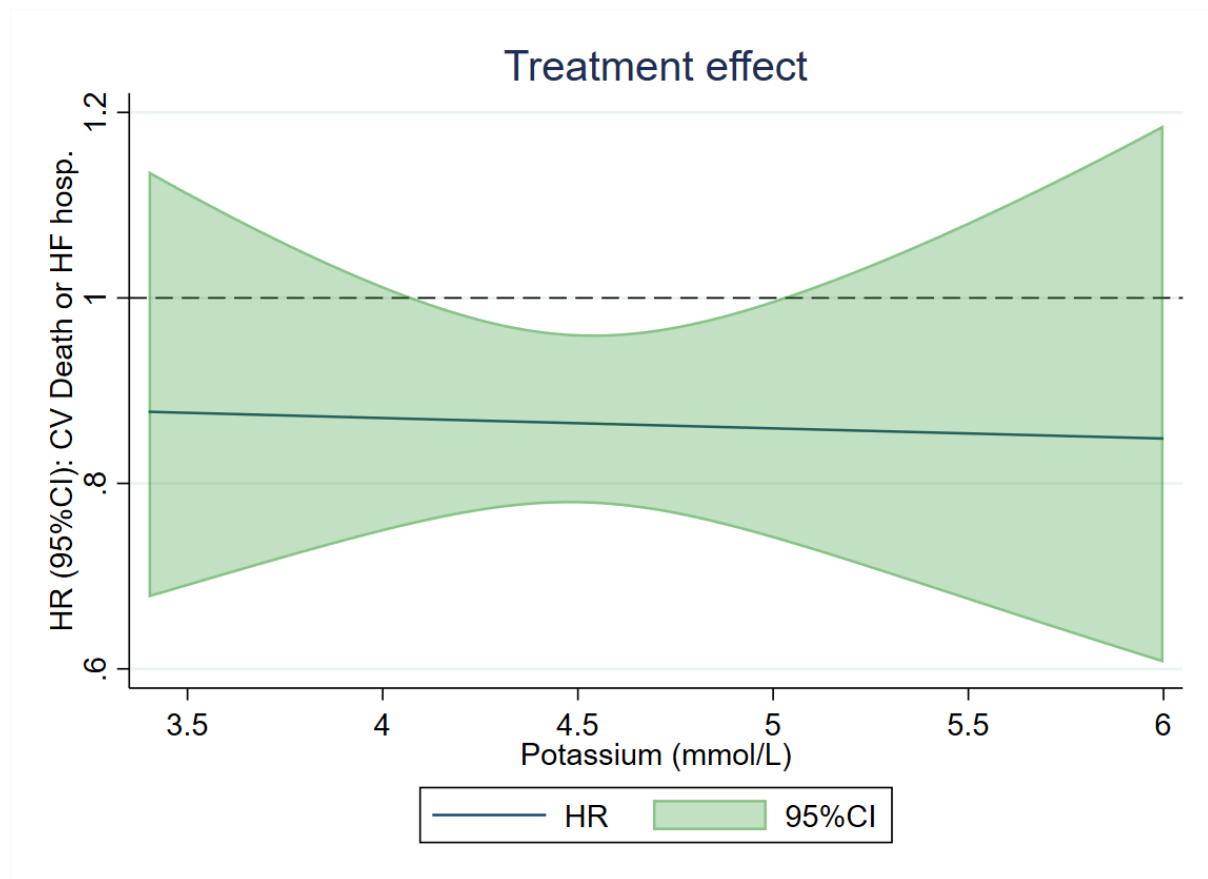
Caption: Overall, the risk of events is higher with hypokalemia than with hyperkalemia.

Figure 2. Effect of high- vs. low dose losartan on serum potassium over time



Caption: High-dose losartan slightly increased serum potassium over time by 0.1 mmol/L, on average (P-value for overall effect =0.001).

Figure 3. Effect of high- vs. low-dose losartan across the full spectrum of potassium



Legend: HR, hazard ratio; CI, confidence interval.

Caption: High-dose losartan (vs. low-dose) reduced the composite of cardiovascular death or HF hospitalizations consistently across the full spectrum of serum potassium at baseline (interaction P-value =0.85).

