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Serum Potassium in the PARADIGM-HF trial

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ABSTRACT

Background: We studied the association between potassium and outcomes, the effect of sacubitril/valsartan on potassium, and whether potassium level modified the effect of sacubitril/valsartan in patients with heart failure and a reduced ejection fraction in PARADIGM-HF.

Aims: We examined several outcomes including cardiovascular death, sudden-death, pump-failure death, non-cardiovascular death and heart failure hospitalization.

Methods: 8399 patients were randomized to either enalapril or sacubitril/valsartan.

Potassium at randomization and follow-up was examined as a continuous and categorical variable (≤ 3.5 , 3.6-4.0, 4.1-4.9, 5.0-5.4, and ≥ 5.5 mmol/L) in various statistical models.

Hyperkalemia was defined as $K^+ \geq 5.5$ mmol/L and hypokalemia as $K^+ \leq 3.5$ mmol/L.

Results: Compared to potassium 4.1-4.9 mmol/L, both hypokalemia (HR 2.40, 95%CI 1.84-3.14) and hyperkalemia (HR 1.42, 1.10-1.83) were associated with a higher risk of cardiovascular death. However, potassium abnormalities were similarly associated with sudden death and pump failure death, as well as non-cardiovascular death and heart failure hospitalization. Sacubitril/valsartan had no effect on potassium overall. The benefit of sacubitril/valsartan over enalapril was consistent across the range of baseline potassium.

Conclusions: Although both higher and lower potassium were independent predictors of cardiovascular death, potassium abnormalities may mainly be markers rather than mediators of risk of death.

Key words: potassium; outcomes; hypokalaemia; hyperkalaemia; sacubitril/valsartan; mineralocorticoid receptor antagonists.

INTRODUCTION

Potassium is essential for normal cellular function and alterations in potassium regulation can lead to gastrointestinal, neuromuscular and cardiac abnormalities, some of which can be life-threatening¹. The treatments used in patients with heart failure and reduced ejection fraction (HFrEF) commonly cause potassium disturbances with hypokalaemia induced by loop and thiazide diuretics and hyperkalaemia resulting from use of renin-angiotensin aldosterone system inhibitors^{2,3}. Even though the clinical significance, and even the definition, of hyperkalaemia is a matter of debate, higher potassium concentrations often lead to the withholding or withdrawal of renin-angiotensin aldosterone system inhibitors, which are life-saving therapies in patients with HFrEF⁴. However, hypokalaemia may be of as much concern as hyperkalaemia in HFrEF, as in other groups of individuals (e.g. the general population and patients with myocardial infarction, hypertension, and chronic kidney disease⁵⁻⁹), the relationship between potassium concentration and clinical outcomes is U-shaped, with both low and high potassium levels associated with worse outcomes¹⁰⁻¹².

The effects of sacubitril/valsartan on potassium have not been described in detail and may differ from enalapril as sacubitril/valsartan reduces aldosterone - a key regulator of potassium¹³. Sacubitril/valsartan likely lowers aldosterone because natriuretic peptides are powerful inhibitors of aldosterone secretion and neprilysin inhibition (sacubitril) increases natriuretic peptide levels^{14,15}. The Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF)¹³ also represents one of the largest and most contemporary HFrEF cohorts, in which most patients received each of the aforementioned drugs known to affect potassium levels.

The aims of the present study were to examine the range of plasma potassium concentrations found in patients with HFrEF, the relationship between potassium concentration and outcomes and the effect of sacubitril/valsartan on potassium.

METHODS

PARADIGM-HF

The design, methods, and principal results of the PARADIGM-HF trial have been previously reported¹³. In brief, the trial was a randomized, double-blind, prospective comparison of the effect of sacubitril/valsartan (97/103 mg twice daily [LCZ696, 200 mg twice daily]) vs. enalapril (10 mg twice daily) among 8,399 patients with chronic HF (New York Heart Association [NYHA] classes II-IV) and a left ventricular ejection fraction (LVEF) of 40% or less. Prior to randomization, all participants underwent single-blind, sequential run-in periods to ensure tolerability of both study drugs at target doses. Eligible patients were those treated with an appropriate regimen of background HF medications at stable doses for at least 4 weeks, including an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) (with dose equivalent to enalapril 10 mg daily or greater) and a beta-blocker (unless not tolerated). The use of MRAs was left to the discretion of the investigators but encouraged if tolerated. Key exclusion criteria included symptomatic hypotension; a systolic blood pressure (SBP) lower than 100 mmHg at screening or 95 mmHg at randomization; an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m² at screening/randomization or a decrease in the eGFR higher than 25% (amended to 35%) between screening and randomization, and a serum K⁺ level higher than 5.2 mmol/L at screening or higher than 5.4 mmol/L at randomization. The serum K⁺ was measured at every study visit (*Supplementary Table 1*). The protocol recommended that any patient with a serum potassium >5.3 mmol/L after randomization required regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern

(≥ 5.5 and < 6.0 mmol/L) or potential danger (≥ 6.0 mmol/L)¹³. No recommendation for dose adjustment in the setting of hypokalaemia was given. The primary composite end point was death from cardiovascular causes or first hospitalization for HF (CV death/HF hospitalization). In the present analysis we also study CV, all-cause and sudden cardiac death (or resuscitated cardiac arrest). The median follow-up time was of 810 (564-1069) days or 116 (81-153) weeks. The trial was approved by the institutional review board or ethics committee at each participating site, and all participants provided written informed consent prior to participation.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation or median (percentile₂₅₋₇₅). Categorical variables are presented as absolute numbers (n.) and percentages. The baseline characteristics were compared between the following K⁺ categories of ≤ 3.5 , 3.6-4.0, 4.1-4.9, 5.0-5.4, and ≥ 5.5 mmol/L, using ANOVA or Kruskal-Wallis tests as appropriate. We examined potassium levels below and above the optimal range of 4-5 mmol/L in order to better understand what patient characteristics were associated with “non-optimal” potassium concentrations and how clinical outcomes related to potassium levels above and below the optimal range. The additional categories created were ≤ 3.5 mmol/L and 3.6-4.0 mmol/L, as well as 5.0-5.4 mmol/L and ≥ 5.5 mmol/L, as these included a sufficient number of patients and events to allow for valid statistical analysis. Several models were used to study the association of K⁺ with the outcomes. For the baseline K⁺ Cox proportional hazards models were used with K⁺ as categorical or continuous variable (using a fractional polynomial “spline” with 5 knots as described by Harrell¹⁶). For K⁺ throughout the follow-up, time-updated (“repeated measures”) Cox models were used with “start” and “stop” times

between each K^+ measurement. Multilevel survival analysis (a two-stage “joint-model”) was also used to combine the longitudinal (repeated-measures) and survival (time-to-event end point) aspects of the data. A 2-level model with patient identification as random effect and the log (follow-up time) as a random coefficient was fitted. For the survival portion of the model, we used a Weibull distribution, with the continuous K^+ (fractional polynomial) as the main exposure variable. Landmark analyses were performed to assess the association between the cumulative plus K^+ changes at 2 months and subsequent outcomes. The 2-month landmark was chosen to avoid excessive missing K^+ values (*Supplementary Table 1*). The regression estimates are presented as hazard ratios (HR) with 95% confidence intervals (CIs). The models were adjusted for all the characteristics presented in the Table 1, including age, diabetes, race, region, NYHA class, NT-pro BNP, concomitant medications and eGFR (time-updated eGFR whenever appropriate). We examined potential unmeasured confounding by calculating E-values¹⁷. All statistical analyses were conducted in Stata® version 16 (StataCorp LP). 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 analysis.

RESULTS

Baseline characteristics

The clinical characteristics of patients, according to serum potassium category at randomization are provided in the *Table 1*. Compared to patients with potassium within the normal range (4.1-4.9 mmol/L), those with a lower potassium were younger, less often white, with higher systolic blood pressure and heart rate, better renal function, higher NT-pro BNP levels, higher proportion of prior HF hospitalization, lower proportion of treatment with an ACEi/ARB and MRAs. On the other hand, those with a higher potassium were more often white, had similar age, systolic blood pressure and heart rate, had poorer renal function, slightly higher NT-pro BNP levels, had diabetes more often, and were treated with ACEi/ARBs and MRAs more often. *Table 1*.

Change in potassium level

A median of 8.5 (range 1-16) central laboratory potassium measurements were performed per patient after randomization, averaging 13.6 measurements per year of follow-up. During the follow-up, serum potassium was available in 79688 occasions (39699 in the enalapril group and 39989 in the sacubitril/valsartan group); there were 8473 occasions (10.6% of all occasions) when potassium was <4 mmol/L and 1601 (2.0%) occasions when potassium was ≤ 3.5 mmol/L. A potassium value <4 mmol/L was observed on 3942 (9.9%) occasions in the enalapril group and on 4531 (11.3%) occasions in the sacubitril/valsartan group (sacubitril/valsartan vs. enalapril p-value <0.001). A potassium <3.5 mmol/L was observed on 722 (1.8%) occasions in the enalapril group and 879 (2.2%) occasions in the sacubitril/valsartan group (sacubitril/valsartan vs. enalapril p-value <0.001). During the follow-up, a potassium level >5 mmol/L was observed on 5368 (13.5%) occasions in the

enalapril group and 4915 (12.3%) occasions in the sacubitril/valsartan group (sacubitril/valsartan vs. enalapril p-value <0.001). A potassium >5.5 mmol/L was observed on 974 (2.5%) occasions in the enalapril group and on 896 (2.2%) occasions in the sacubitril/valsartan group (sacubitril/valsartan vs. enalapril p-value =0.047). *Figure 1*. In the *Supplemental Figure 1* we present the incidence of both hypo- and hyperkalemia over time by treatment group.

Compared with enalapril, sacubitril/valsartan reduced potassium concentration slightly; mean change, compared with enalapril, at week 80: -0.07 (-0.09 to -0.04), p <0.001.

Patients treated with enalapril and an MRA had slightly higher potassium levels than patients treated with sacubitril/valsartan and an MRA. Patients treated with sacubitril/valsartan and an MRA had similar potassium levels to patients without MRA treatment. *Figure 2*.

Clinical outcomes according to potassium level

There was a U-shaped relationship between baseline potassium level and the clinical outcomes of interest. Patients in the lowest baseline potassium category (≤ 3.5 mmol/l) had higher event rates, as compared to patients with potassium in the normal range (4.1-4.9 mmol/l), even after adjustment for other prognostic variables (*Table 2*). This was also true for those in the highest potassium category (≥ 5.5 mmol/l) in relation to the mortality outcomes, although the magnitude of the elevation in risk was smaller than that seen in the lowest potassium category. *Table 2*.

This overall pattern was generally more pronounced in the time-updated models. For the primary outcome, the HR (95%CI) for a potassium level between 3.6 and 4.0 mmol/L was 1.25 (1.06-1.47) and for a potassium concentration ≤ 3.5 mmol/L the HR was 1.91 (1.41-

2.61), compared with the reference category (potassium 4.1-4.9 mmol/l). For a potassium level between 5.0 and 5.4 mmol/L the HR (95%CI) was 1.08 (0.92-1.27) and for potassium ≥ 5.5 mmol/L the HR was 1.38 (1.06-1.78).

Similar results were obtained for the individual components of the primary outcome, and all-cause death. For sudden death and “pump failure” death the associations were statistically significant for potassium levels ≤ 3.5 mmol/L. For non-cardiovascular death there also appeared to be a U-shaped with potassium, but this was not statistically significant for either potassium ≤ 3.5 mmol/L or ≥ 5.5 mmol/L, possibly due to the small number of events.

Table 2.

The associations between the time-updated potassium, modelled as a continuous variable, and the outcomes of interest are shown in *Figure 3* reinforcing the findings of the categorical analyses described above. The same is shown for baseline potassium in *Supplementary Figure 2* and the landmark analysis and joint models are illustrated in *Supplementary Figures 3 & 4*. To offset the association between hypokalaemia (≤ 3.5 mmol/l) and risk of the primary outcome, an "unmeasured" confounder would have to have an incremental HR ≥ 2.5 on top of the adjusted analysis described. *Supplementary Figure 5.*

Outcomes related to change in potassium category

Landmark analysis, looking at outcomes according to change in potassium category, showed that patients moving from either the lowest or highest potassium category to the normal category, had better outcomes than those remaining in the two extreme categories (*Supplementary Table 2*). For example, persistence of either hypokalemia or hyperkalemia was associated with a higher risk of subsequent cardiovascular death: HR (95%CI) 1.61

(1.25-2.09), $p < 0.001$ for persistence of hypokalemia and HR (95%CI) 1.32 (1.01-1.72),
 $p = 0.041$ for persistence of hyperkalemia.

Effect of sacubitril/valsartan according to potassium level

The benefit of sacubitril/valsartan over enalapril was consistent across baseline potassium categories and using potassium as a continuous time-updated variable. *Figure 4.*

DISCUSSION

We found that both hypo- and hyperkalemia were associated with a higher risk of adverse clinical outcomes, compared with a normal potassium concentration. Although the risk was stronger for hypokalemia than for hyperkalemia, the associations were largely non-specific, suggesting that the risk related to potassium disturbances reflected disease severity, rather than a direct effect of potassium. Sacubitril/valsartan reduced potassium level slightly, on average, compared with enalapril. The beneficial effect of sacubitril/valsartan over enalapril was consistent across the spectrum of potassium levels studied in PARADIGM-HF.

In keeping with prior studies in patients recently discharged after hospital admission for heart failure and in chronic HFrEF, we found a U-shaped relationship between potassium level and mortality in the well-treated ambulatory patients with chronic HFrEF and mainly mild symptoms in PARADIGM-HF¹⁸⁻²¹. After adjusting for a wide range of clinical predictors, and NT-pro BNP, the elevation in risk of death associated with higher potassium was modest and less pronounced than for hypokalaemia. While prior studies have suggested the elevated risk of death associated with hyperkalaemia might reflect underdosing or even withholding of RAS blockers^{22, 23}, that is likely not the explanation in the present trial given that patients started on maximum dose of study drug and every effort was made to maintain the optimal dose during follow-up. Moreover, the association between higher potassium and fatal outcomes was similar for all subtypes of death examined, including non-cardiovascular death, suggesting a lack of any specific mechanistic direct effect of hyperkalaemia. This perspective is supported by the similar association between hyperkalaemia and risk of heart failure hospitalization, given the lack of obvious pathophysiological link between higher potassium and risk of heart failure hospitalization.

Scrutiny of the baseline characteristics of participants with hyperkalaemia shows them to be older, have more frequent ischaemic aetiology and more comorbidity, including worse renal function. It is possible that our multivariable models did not fully adjust for the measured and unmeasured differences between patients with hyperkalaemia and those with a normal potassium. Higher potassium may, therefore, generally be a marker of a sicker patient, although, in individuals, occasionally, hyperkalaemia may still directly cause a fatal arrhythmia or conduction disturbance²⁴⁻²⁶.

There was also an association between low potassium and higher mortality and the risk associated with low potassium was greater than that found for high potassium and was strengthened in the time-updated model. Although all patients were on a full dose of enalapril or sacubitril/valsartan, as mentioned above, MRA use was less frequent in individuals in the lowest potassium category, in contrast to those with a high potassium. However, MRA use was included in our multivariable adjustment and, therefore, neither lower use of MRAs, nor underuse of ACE inhibitors or ARBs, seem to account for the association between hypokalaemia and higher risk of death. More surprisingly, perhaps, the association between low potassium and outcomes also appeared to lack specificity, with similarly elevated risk of various types of death, as seen with higher potassium concentrations. Moreover, the risk of heart failure hospitalization was elevated to the same degree as overall and cause-specific mortality. This suggests that the association between hypokalaemia and worse outcomes is non-specific in nature and low potassium may also be a marker of disease severity. At first sight, this conclusion may seem at variance with our other finding that “correction” of hypokalaemia (and hyperkalaemia) was associated with a better outcome than a persisting abnormality of potassium. However, the patients who

shifted from an abnormal to a normal potassium category may have been patients who improved their clinical status.

Another interesting observation was that the overall comorbidity profile of patients with hypokalaemia was generally lower risk than that of patients with hyperkalaemia; patients in the lower potassium categories had better renal function less ischemic cardiac disease, diabetes, and atrial fibrillation than patients with higher potassium, although patients with low potassium had higher NT-pro BNP levels, greater use of diuretics and a more frequent history of heart failure hospitalization. One interpretation of these findings could be that low potassium, reflecting greater use of diuretics and less use of MRAs in more recently hospitalized and inadequately decongested patients is a marker of a patient at greater probability of worsening leading to hospital admission or death²⁷. This might suggest that our multivariable adjustment did not fully account for some of the measured confounders discussed or that there was significant unmeasured confounding. For example, there were striking differences in geographic region of enrolment and race across potassium categories. North America was relatively over-represented and Central/Eastern Europe relatively under-represented in the potassium ≤ 3.5 mmol/l category, corresponding to areas of low and high MRA use, respectively, although there are clearly many other demographic, social, cultural and environmental influences on health, and differences in health care provision, across these regions. There was also relative over-representation of Black and Asian individuals in the lowest potassium category, compared with the normal and higher potassium groups. The explanation for this is not obvious. MRA use was not lower in Blacks or Asians and the other factors mentioned in relation to geographical region plus additional genetic variables may be important²⁸. Finally, it remains likely that a general indirect and non-specific association between lower potassium and worse outcome, as discussed,

conceals a true direct, biological link, at least in some patients, between profound hypokalaemia and cardiac mortality.

Compared with enalapril, sacubitril/valsartan had little effect on potassium in PARADIGM-HF, overall. However, in participants treated with an MRA, compared with enalapril, sacubitril/valsartan reduced potassium significantly, maintaining levels within the normal range (and the level similar to patients not treated with MRA)²⁹. One possible (but merely speculative) explanation for the lower potassium levels in the sacubitril/valsartan group is that compared with enalapril, sacubitril/valsartan improved renal function and this may have led to greater distal delivery of loop diuretic and more potassium excretion as a result. In a previous report we have shown that sacubitril/valsartan reduced the risk of hyperkalaemia in patients treated with an MRA³⁰. The present study expands those findings by showing the effect of sacubitril/valsartan vs. enalapril across the full spectrum of potassium. Furthermore, the benefit of sacubitril/valsartan over enalapril was consistent across the range of baseline potassium among the patients randomized in PARADIGM-HF.

Limitations

This was a *post-hoc* analysis of the PARADIGM-HF trial. The patients were highly selected, tolerating recommended doses of enalapril and sacubitril/valsartan in a run-in period. Although this reduces the generalisability of our findings, the trial design also addresses limitations of earlier studies. Regular monitoring of potassium and protocol guided mitigation might have led to correction of potassium abnormalities more frequently, or more quickly, than in routine practice (and perhaps hyperkalaemia more often than hypokalaemia, as only treatment of the former was addressed in the protocol). Moreover, a serum potassium level >5.2 mmol/L at screening (or >5.4 mmol/L at randomization) were

exclusion criteria, which might have led to the selection of patients less prone to develop hyperkalaemia. Although having an independent even adjudication committee was a major advantage of our study, some events, including sudden death and “pump failure” death remain difficult to adjudicate and may be prone to misclassification.

Conclusions

In PARADIGM-HF, both hyperkalaemia and hypokalaemia were associated with a higher risk of death, although the association was stronger for the latter. Although both higher and lower potassium remained independent predictors of death after adjustment in multivariable models, they were also associated with non-cardiovascular death and heart failure hospitalization, suggesting that potassium abnormalities are mainly markers of disease severity. Compared with enalapril, sacubitril/valsartan had no overall effect on potassium in PARADIGM-HF, although reduced potassium significantly in participants treated with an MRA, maintaining it in the normal range in these individuals. The benefit of sacubitril/valsartan over enalapril was consistent across the range of baseline potassium among the patients randomized in PARADIGM-HF.

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Disclosures

None.

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Table 1. Baseline characteristics of the PARADIGM-HF patients by potassium categories at randomization

Characteristics by K+ categories	≤3.5 mmol/L	3.6-4.0 mmol/L	4.1-4.9 mmol/L	5.0-5.4 mmol/L	≥5.5 mmol/L	p-value
N.	164	1069	5625	1168	197	
Age, years	62.0 ± 13.0	61.7 ± 12.2	63.9 ± 11.3	65.4 ± 10.7	63.4 ± 10.8	<0.001
Age >70	42 (25.6%)	258 (24.1%)	1704 (30.3%)	400 (34.3%)	58 (29.4%)	<0.001
Female sex, n. (%)	39 (23.8%)	251 (23.5%)	1213 (21.6%)	251 (21.5%)	45 (22.8%)	0.65
Race or ethnic group, n. (%)						
White	70 (42.7%)	530 (49.6%)	3796 (67.5%)	858 (73.5%)	150 (76.1%)	<0.001
Black	24 (14.6%)	95 (8.9%)	261 (4.6%)	37 (3.2%)	5 (2.5%)	
Asian	44 (26.8%)	294 (27.5%)	988 (17.6%)	152 (13.0%)	23 (11.7%)	
Other	26 (15.9%)	150 (14.0%)	580 (10.3%)	121 (10.4%)	19 (9.6%)	
Region, n. (%)						
North America	26 (15.9%)	132 (12.3%)	379 (6.7%)	45 (3.9%)	6 (3.0%)	<0.001
Latin America	33 (20.1%)	227 (21.2%)	928 (16.5%)	188 (16.1%)	32 (16.2%)	
Western Europe and other	36 (22.0%)	179 (16.7%)	1436 (25.5%)	297 (25.4%)	38 (19.3%)	
Central Europe	27 (16.5%)	243 (22.7%)	1906 (33.9%)	490 (42.0%)	97 (49.2%)	
Asia Pacific	42 (25.6%)	288 (26.9%)	976 (17.4%)	148 (12.7%)	24 (12.2%)	
Systolic blood pressure, mmHg	125.0 ± 17.0	122.5 ± 16.1	121.3 ± 15.3	120.1 ± 14.4	119.9 ± 13.3	<0.001
Heart rate, bpm	75.5 ± 13.3	73.5 ± 12.0	72.1 ± 11.9	72.2 ± 12.3	72.8 ± 12.8	<0.001
Body-mass index, kg/m ²	28.2 ± 7.5	27.9 ± 5.8	28.2 ± 5.4	28.3 ± 5.4	28.0 ± 5.7	0.42
eGFR, mL/min/1.73m ²	72.4 ± 34.1	72.4 ± 20.8	68.0 ± 19.5	62.6 ± 18.5	60.3 ± 18.9	<0.001
eGFR ≤60	62 (37.8%)	312 (29.2%)	2083 (37.0%)	582 (49.8%)	108 (54.8%)	<0.001
Ischemic cardiomyopathy, n. (%)	90 (54.9%)	588 (55.0%)	3347 (59.5%)	757 (64.8%)	135 (68.5%)	<0.001
Left ventricular ejection fraction, %	29.3 ± 6.4	29.4 ± 6.4	29.5 ± 6.2	29.6 ± 6.1	30.1 ± 6.4	0.59
Median BNP, pg/ml,	311 (184, 717)	291 (169, 611)	243 (150, 447)	260 (160, 468)	271 (171, 530)	<0.001
Median BNP in AF+	360 (184, 692)	291 (181, 544)	245 (157, 434)	251 (159, 453)	273 (185, 588)	<0.001
Median BNP in AF-	302 (183, 783)	291 (161, 643)	241 (145, 455)	269 (160, 471)	267 (153, 491)	<0.001
Median NT-pro BNP, pg/ml	2476 (1199, 5093)	1884 (941, 4165)	1541 (862, 3024)	1705 (946, 3380)	1747 (926, 3392)	<0.001

Median NT-pro BNP in AF+	3019 (1561, 6083)	2131 (1114, 4520)	1812 (1059, 3420)	1961 (1172, 3611)	2155 (1412, 4781)	<0.001
Median NT-pro BNP in AF-	2276 (1090, 4565)	1759 (847, 3863)	1383 (804, 2782)	1532 (856, 3161)	1547 (747, 2424)	<0.001
NYHA functional class, n. (%)						
I	6 (3.7%)	50 (4.7%)	270 (4.8%)	46 (4.0%)	9 (4.6%)	0.37
II	120 (73.2%)	774 (72.5%)	3971 (70.7%)	801 (68.8%)	131 (67.2%)	
III	36 (22.0%)	235 (22.0%)	1342 (23.9%)	306 (26.3%)	55 (28.2%)	
IV	2 (1.2%)	9 (0.8%)	36 (0.6%)	11 (0.9%)	0 (0.0%)	
Hypertension, n. (%)	116 (70.7%)	758 (70.9%)	3928 (69.8%)	866 (74.1%)	140 (71.1%)	0.068
Diabetes, n. (%)	54 (32.9%)	334 (31.2%)	1915 (34.0%)	458 (39.2%)	79 (40.1%)	<0.001
Atrial fibrillation, n. (%)	60 (36.6%)	360 (33.7%)	2075 (36.9%)	445 (38.1%)	82 (41.6%)	0.12
Prior HF hospitalization, n. (%)	119 (72.6%)	669 (62.6%)	3542 (63.0%)	715 (61.2%)	119 (60.4%)	0.074
Prior MI, n. (%)	61 (37.2%)	411 (38.4%)	2420 (43.0%)	554 (47.4%)	99 (50.3%)	<0.001
Prior stroke, n. (%)	15 (9.1%)	77 (7.2%)	509 (9.0%)	95 (8.1%)	11 (5.6%)	0.15
Prior use of ACEi, n. (%)	115 (70.1%)	772 (72.2%)	4395 (78.1%)	945 (80.9%)	162 (82.2%)	<0.001
Prior use of ARB, n. (%)	51 (31.1%)	298 (27.9%)	1249 (22.2%)	225 (19.3%)	36 (18.3%)	<0.001
Diuretic, n. (%)	141 (86.0%)	892 (83.4%)	4482 (79.7%)	920 (78.8%)	156 (79.2%)	0.011
Digoxin, n. (%)	50 (30.5%)	334 (31.2%)	1718 (30.5%)	341 (29.2%)	57 (28.9%)	0.84
Beta-blocker, n. (%)	154 (93.9%)	968 (90.6%)	5247 (93.3%)	1098 (94.0%)	182 (92.4%)	0.013
MRA, n. (%)	75 (45.7%)	509 (47.6%)	3179 (56.5%)	704 (60.3%)	117 (59.4%)	<0.001
ICD (incl. CRT-D), n. (%)	18 (11.0%)	139 (13.0%)	868 (15.4%)	176 (15.1%)	18 (9.1%)	0.022
CRT, n. (%)	9 (5.5%)	66 (6.2%)	398 (7.1%)	83 (7.1%)	9 (4.6%)	0.49
Rand. Sacubitril/Valsartan	84 (51.2%)	527 (49.3%)	2787 (49.5%)	605 (51.8%)	94 (47.7%)	0.63

Legend: eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ICD, intra-cardiac defibrillator; CRT, cardiac resynchronization therapy; AF, atrial fibrillation.

Table 2. Events, event-rates, and hazard ratios for the baseline and time-updated potassium levels for the several outcomes

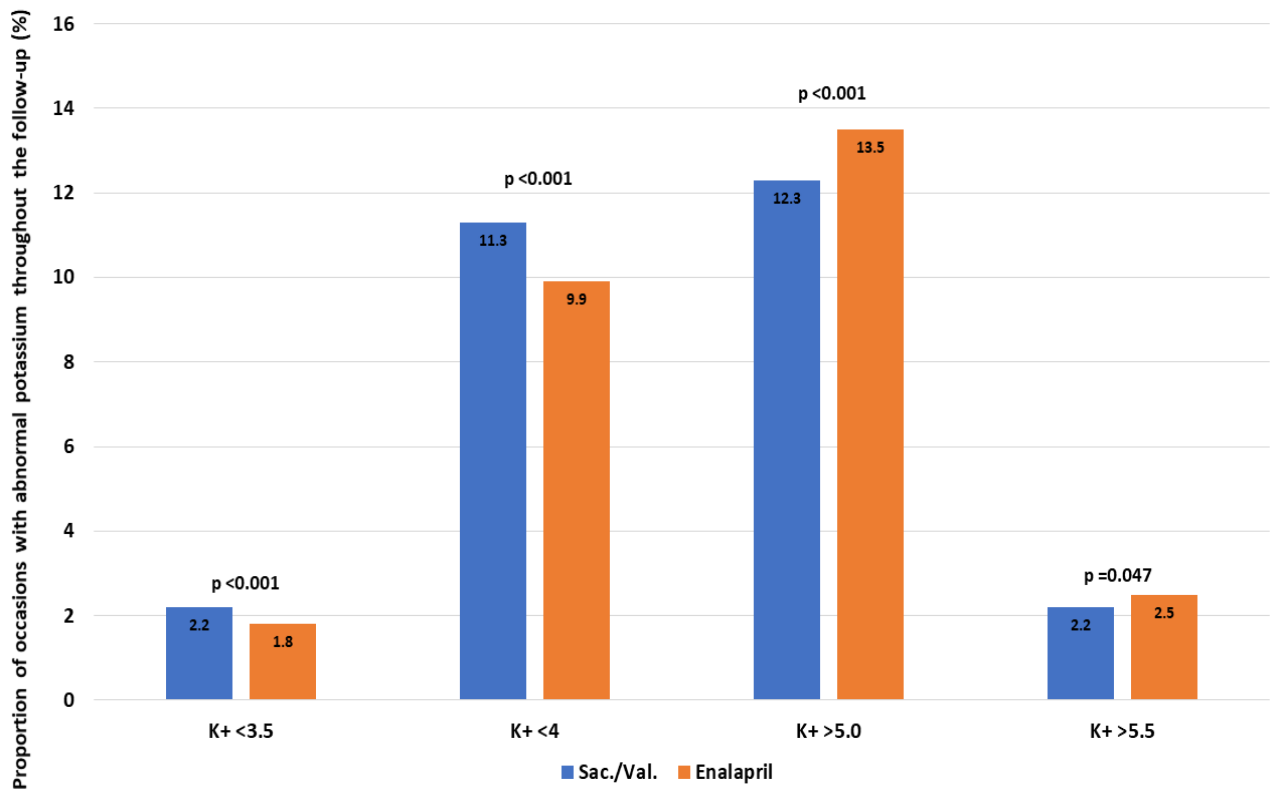
K+ (mmol/L)	Events, n. (%)	Inc. rate, per 100py	Baseline model	P-value	Time-updated model	P-value	K+ by Study Drug Interaction P
Primary outcome							
≤3.5	70 (42.7)	24.8	1.86 (1.46-2.37)	<0.001	1.91 (1.41-2.61)	<0.001	0.20
3.6-4.0	303 (28.3)	14.1	1.25 (1.10-1.42)	0.001	1.25 (1.06-1.47)	0.009	
4.1-4.9	1277 (22.7)	11	Referent	-	Referent	-	
5.0-5.4	292 (25.0)	12.3	1.08 (0.95-1.23)	0.25	1.08 (0.92-1.27)	0.35	
≥5.5	47 (23.9)	12.7	1.11 (0.83-1.48)	0.50	1.38 (1.06-1.78)	0.015	
HF hospitalization							
≤3.5	40 (24.4)	14.2	1.79 (1.29-2.47)	<0.001	2.01 (1.14-3.55)	0.016	0.55
3.6-4.0	192 (18.0)	8.9	1.39 (1.18-1.63)	<0.001	1.32 (9.98-1.77)	0.063	
4.1-4.9	741 (13.2)	6.4	Referent	-	Referent	-	
5.0-5.4	173 (14.8)	7.3	1.08 (0.92-1.28)	0.34	1.35 (1.03-1.77)	0.028	
≥5.5	21 (10.7)	5.7	0.85 (0.55-1.31)	0.45	1.02 (0.50-1.08)	0.95	
CV death							
≤3.5	52 (31.7)	16.1	2.25 (1.69-2.99)	<0.001	2.40 (1.84-3.14)	<0.001	0.45
3.6-4.0	177 (16.6)	7.4	1.14 (0.97-1.35)	0.11	1.27 (1.07-1.49)	0.005	
4.1-4.9	778 (13.8)	6.2	Referent	-	Referent	-	
5.0-5.4	186 (15.9)	7.3	1.13 (0.97-1.34)	0.11	1.19 (1.02-1.40)	0.029	
≥5.5	37 (18.8)	9.6	1.48 (1.06-2.06)	0.021	1.42 (1.10-1.83)	0.007	
All-cause death							
≤3.5	57 (34.8)	17.6	2.00 (1.51-2.62)	<0.001	2.31 (1.80-2.96)	<0.001	0.41
3.6-4.0	215 (20.1)	9	1.14 (0.98-1.33)	0.084	1.26 (1.09-1.47)	0.002	
4.1-4.9	963 (17.1)	7.7	Referent	-	Referent	-	
5.0-5.4	235 (20.1)	9.2	1.15 (1.00-1.33)	0.052	1.26 (1.09-1.44)	0.001	
≥5.5	47 (23.9)	12.2	1.51 (1.12-2.02)	0.006	1.37 (1.09-1.73)	0.007	
SCD or RCA							
≤3.5	21 (12.8)	6.5	1.73 (1.11-2.70)	0.015	2.45 (1.70-3.54)	<0.001	0.064

3.6-4.0	75 (7.0)	3.1	0.90 (0.70-1.15)	0.39	1.20 (0.95-1.52)	0.13	
4.1-4.9	399 (7.1)	3.2	Referent	-	Referent	-	
5.0-5.4	82 (7.0)	3.2	1.03 (0.81-1.31)	0.81	1.41 (1.13-1.75)	0.002	
≥5.5	20 (10.2)	5.3	1.65 (1.05-2.59)	0.03	1.01 (0.64-1.59)	0.97	
“Pump failure” death							
≤3.5	15 (9.2)	4.6	2.75 (1.61-4.70)	<0.001	3.43 (2.15-5.48)	<0.001	0.26
3.6-4.0	56 (5.2)	2.3	1.54 (1.13-2.08)	0.006	1.33 (0.96-1.85)	0.087	
4.1-4.9	194 (3.5)	1.6	Referent	-	Referent	-	
5.0-5.4	51 (4.4)	2.0	1.18 (0.87-1.61)	0.29	1.22 (0.91-1.65)	0.19	
≥5.5	10 (5.1)	2.6	1.54 (0.81-2.92)	0.18	1.49 (0.93-1.37)	0.095	
Non-CV death							
≤3.5	5 (3.1)	1.5	0.83 (0.30-2.24)	0.71	1.86 (0.95-3.66)	0.072	0.46
3.6-4.0	38 (3.6)	1.6	1.15 (0.80-1.64)	0.45	1.24 (0.87-1.77)	0.23	
4.1-4.9	185 (3.3)	1.5	Referent	-	Referent	-	
5.0-5.4	49 (4.2)	1.9	1.22 (0.88-1.67)	0.23	1.54 (1.15-2.08)	0.004	
≥5.5	10 (5.1)	2.6	1.66 (0.87-3.15)	0.12	1.17 (0.66-2.07)	0.59	

Legend: CV, cardiovascular; eGFR, estimated glomerular filtration rate; SCD, sudden cardiac death or pump failure death; RCA, resuscitated cardiac arrest; The K+ group by Study Drug Interaction P is a P-value for the interaction between the time-updated potassium levels and the study drug (sacubitril/valsartan or enalapril). The interaction between the time-updated potassium levels and eGFR (≤60 vs. >60 ml/min/1.73m²) was also tested and none was significant (interaction p≥0.1 for all the studied outcomes).

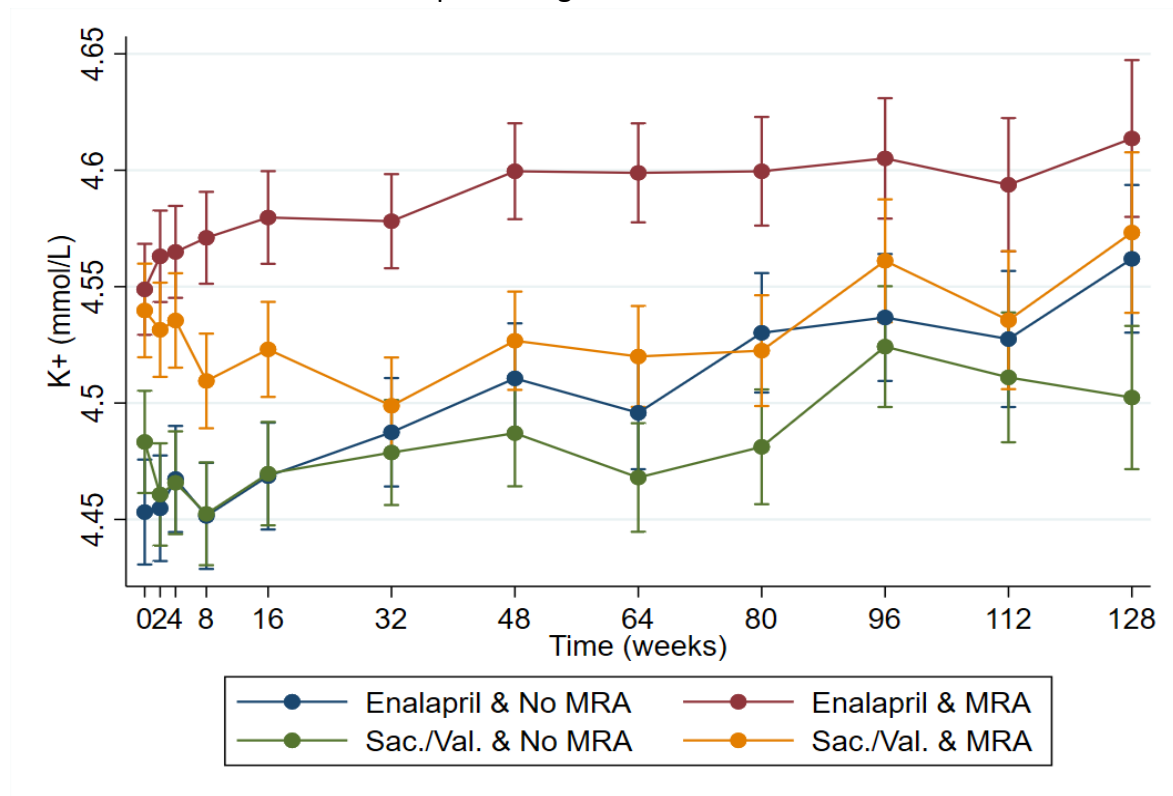
All models are adjusted on age, sex, race, region, systolic blood pressure, heart rate, body mass index, eGFR, ischemic cardiomyopathy, left ventricular ejection fraction, NT-pro BNP, NYHA class, hypertension, diabetes, atrial fibrillation, prior HF hospitalization, prior myocardial infarction, prior stroke, use of diuretics, digoxin, beta-blockers, MRAs, cardiac devices, and treatment group allocation (sacubitril/valsartan or enalapril)

Figure 1. Proportion of occasions/visits in which an abnormal value of potassium was detected separated by treatment group



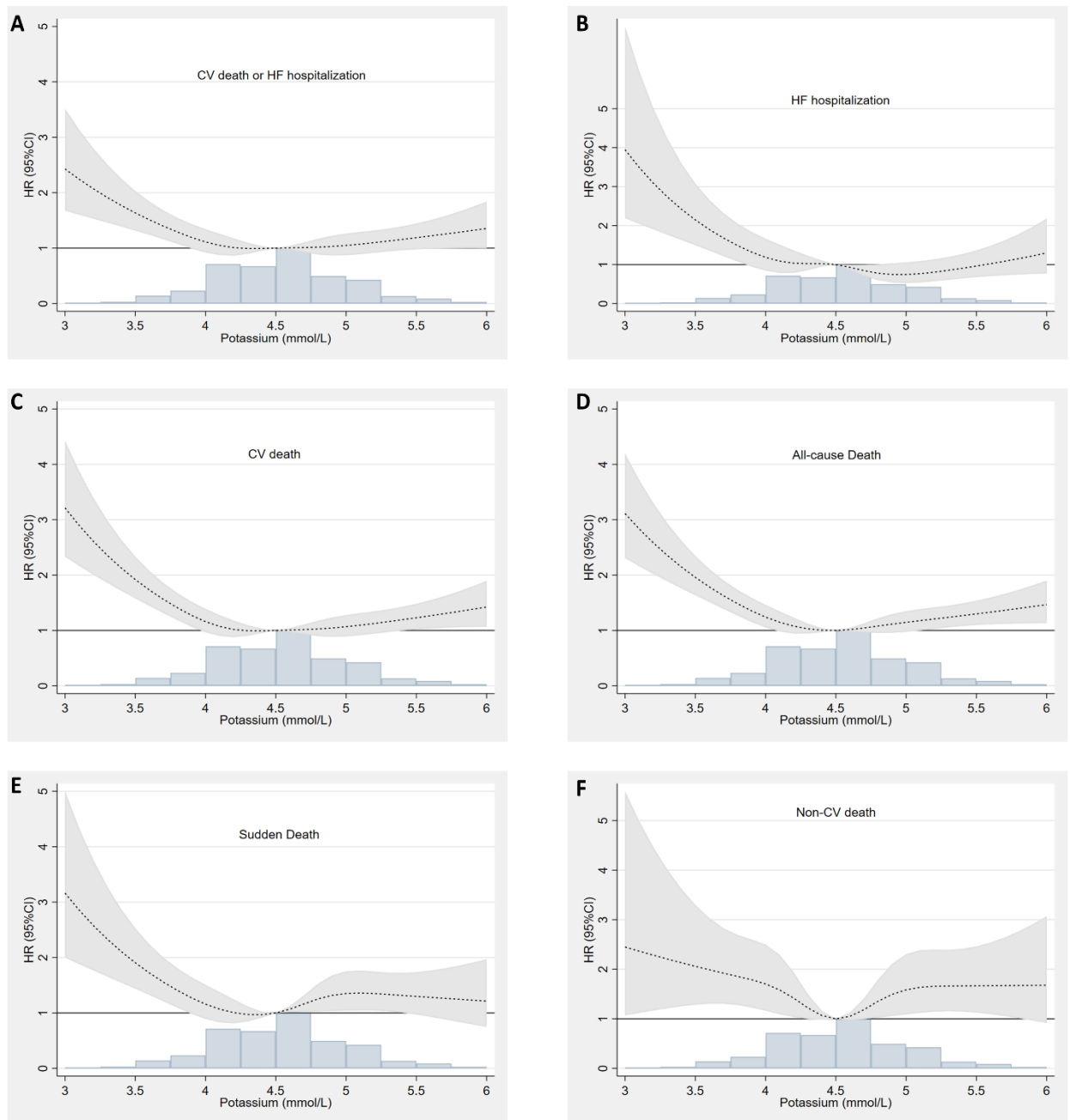
Legend: Sac./Val., sacubitril/valsartan.

Figure 2. Potassium levels in patients allocated to sacubitril/valsartan or enalapril with or without a mineralocorticoid receptor antagonist



Legend: MRA, mineralocorticoid receptor antagonist; Sac./Val., sacubitril/valsartan.
 K⁺ change at Week 80 Sac./Val-Enalapril & No MRA= -0.05 (-0.08 to -0.01), p=0.007.
 K⁺ change at Week 80 Sac./Val-Enalapril & MRA= -0.08 (-0.11 to -0.04), p<0.001.

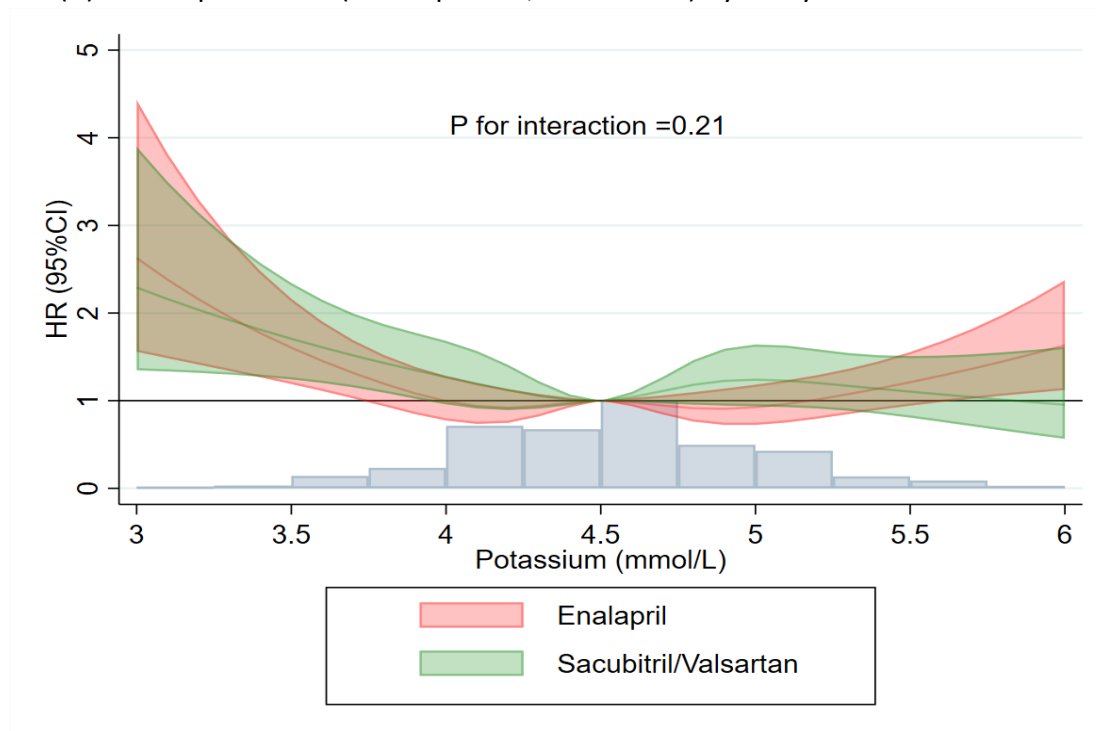
Figure 3. Time-updated potassium and associations with the studied outcomes



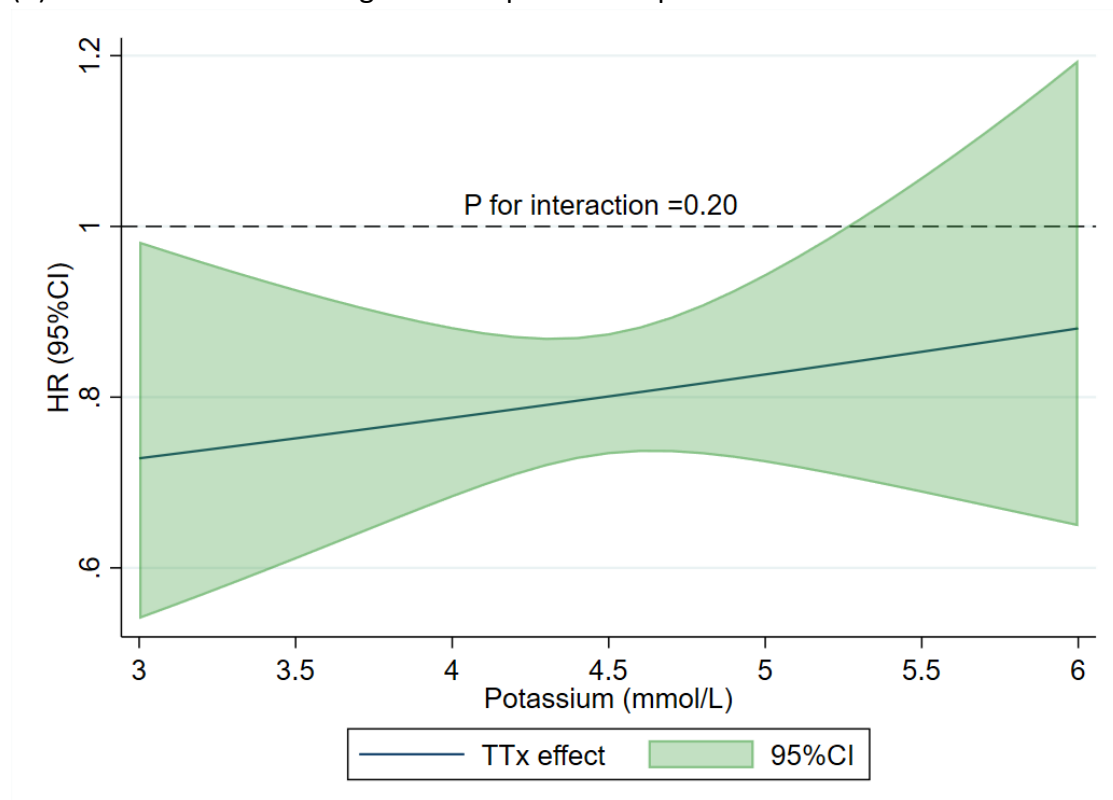
Legend: CV, cardiovascular; HF, heart failure.

The primary outcome was a composite of CV death or HF hospitalization.

Figure 4. Interaction between serum potassium levels and the study treatment
 (A) Serum potassium (time-updated, continuous) by study treatment



(B) Treatment effect throughout the spectrum of potassium



Example illustrating the primary outcome associations (similar results are obtained for the other outcomes) i.e. no potassium by study treatment interaction (see also the Table 2). Legend: HR, hazard ratio; Sac/Val, sacubitril/valsartan; TTx effect, treatment effect of sacubitril/valsartan vs. enalapril.