RESEARCH ARTICLE

Serum potassium in the PARADIGM-HF trial

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Aims	The associations between potassium level and outcomes, the effect of sacubitril–valsartan on potassium level, and whether potassium level modified the effect of sacubitril–valsartan in patients with heart failure and a reduced ejection fraction were studied in PARADIGM-HF. Several outcomes, including cardiovascular death, sudden death, pump failure death, non-cardiovascular death and heart failure hospitalization, were examined.
Methods and results	A total of 8399 patients were randomized to either enalapril or sacubitril–valsartan. Potassium level 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. Hyperkalaemia was defined as $K^+ \geq 5.5$ mmol/L and hypokalaemia as $K^+ \leq 3.5$ mmol/L. Compared with potassium $4.1–4.9$ mmol/L, both hypokalaemia [hazard ratio (HR) 2.40, 95% confidence interval (CI) 1.84–3.14] and hyperkalaemia (HR 1.42, 95% CI 1.10–1.83) were associated with a higher risk for 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 levels.
Conclusions	Although both higher and lower potassium levels were independent predictors of cardiovascular death, potassium abnormalities may mainly be markers rather than mediators of risk for death.
Keywords	Potassium • Outcomes • Hypokalaemia • Hyperkalaemia • Sacubitril–valsartan • Mineralocorticoid receptor antagonists

Introduction

Potassium is essential for normal cellular function and alterations in its regulation can lead to gastrointestinal, neuromuscular and cardiac abnormalities, some of which can be life-threatening.[1] The treatments used in patients with heart failure and reduced ejection fraction (HFrEF) commonly cause potassium disturbances; hypokalaemia is induced by loop and thiazide diuretics, and hyperkalaemia results from the use of renin–angiotensin–aldosterone system (RAAS) inhibitors.[2,3] Although 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 RAAS inhibitors, which are life-saving therapies in patients with HFrEF.[4] However, hypokalaemia may be of as much concern as hyperkalaemia in HFrEF because in other groups of individuals (e.g. the general population and patients with myocardial infarction, hypertension and chronic kidney disease[5–9]) the relationship between potassium concentration and clinical outcomes is U-shaped, and both low and high potassium levels are associated with worse outcomes.[10–12]

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The effects of sacubitril−valsartan on potassium have not been described in detail and may differ from those of enalapril as sacubitril−valsartan reduces aldosterone, a key regulator of potassium.[13] The sacubitril−valsartan combination probably 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] 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 relationships 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 reported.[13] In brief, the trial was a randomized, double-blind, prospective comparison of the effect of sacubitril (97 mg) and valsartan (103 mg) administered twice daily (LCZ696, 200 mg twice daily) and that of enalapril (10 mg twice daily) in 8399 patients with chronic HF [New York Heart Association (NYHA) classes II−IV] and a left ventricular ejection fraction (LVEF) of ≤40%. Prior to randomization, all participants underwent single-blind, sequential run-in periods to ensure the 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) (at a dose equivalent to enalapril 10 mg/day or greater) and a beta-blocker (unless not tolerated). The use of mineralocorticoid receptor antagonists (MRAs) was left to the discretion of the investigators but was encouraged if tolerated. Key exclusion criteria included symptomatic hypotension, a systolic blood pressure (SBP) of <100 mmHg at screening or 95 mmHg at randomization, an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73m^2 at screening/randomization or a decrease in the eGFR of >25% (amended to 35%) between screening and randomization, and a serum K$^+$ level of >5.2 mmol/L at screening or >5.4 mmol/L at randomization. Serum K$^+$ was measured at every study visit (Supplementary material online, *Table S1*). The protocol recommended that any patient with serum potassium of >5.3 mmol/L after randomization required regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it was clear that the potassium concentration was stable and not rising to levels of concern (≥5.5 mmol/L 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 endpoint was death from cardiovascular (CV) causes or first hospitalization for HF (CV death/HF hospitalization). The present analysis also examines CV, all-cause and sudden cardiac death (or resuscitated cardiac arrest). The median follow-up time was 810 (range: 564−1069) days or 116 (range: 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 the mean ± standard deviation or median (percentile$_{25-75}$). Categorical variables are presented as absolute numbers (*n*) and percentages. 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 analysis of variance (ANOVA) or Kruskal−Wallis tests as appropriate. Potassium levels below and above the optimal range of 4−5 mmol/L were examined in order to better elucidate which 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 sufficient numbers of patients and events to allow for valid statistical analysis. Several models were used to study the association of K$^+$ with the outcomes. For baseline K$^+$, Cox proportional hazards models were used with K$^+$ as a categorical or continuous variable (using a fractional polynomial 'spline' with five knots as described by Harrell[16]). For K$^+$ throughout the follow-up, time-updated ('repeated measures') Cox models were used with 'start' and 'stop' times between each K$^+$ measurement. Multi-level survival analysis (a two-stage 'joint model') was also used to combine the longitudinal (repeated-measures) and survival (time-to-event endpoint) aspects of the data. A two-level model with patient identification as a random effect and the log (follow-up time) as a random coefficient was fitted. For the survival portion of the model, a Weibull distribution was used, 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 material online, *Table S1*). Regression estimates are presented as hazard ratios (HR) with 95% confidence intervals (CIs). The models were adjusted for all the characteristics presented in *Table 1*, including age, diabetes, race, region, NYHA class, N-terminal pro brain natriuretic peptide (NT-proBNP), concomitant medications and eGFR (time-updated eGFR whenever appropriate). Potential unmeasured confounding was examined by calculating E-values.[17] All statistical analyses were conducted in STATA® Version 16 (StataCorp LP, College Station, TX, USA). A *P*-value of <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 *Table 1*. Compared with patients with potassium within the normal range (4.1−4.9 mmol/L), those with lower potassium levels were younger, less often White, and had higher SBP and heart rate, better renal function, higher NT-proBNP levels, a higher proportion of prior HF hospitalization, and a lower proportion of treatment with an ACEi/ARB and MRAs. In contrast, those with higher potassium levels were more often White, were of similar age, had similar SBP and heart rate, but had poorer renal function, slightly higher NT-proBNP levels, and were more likely to have diabetes and to be treated with ACEi/ARBs and MRAs (*Table 1*).

Table 1 Baseline characteristics of 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, mean ± SD	62.0 ± 13.0	61.7 ± 12.2	63.9 ± 11.3	65.4 ± 10.7	63.4 ± 10.8	<0.001
Age >70 years, n (%)	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, mean ± SD	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, mean ± SD	75.5 ± 13.3	73.5 ± 12.0	72.1 ± 11.9	72.2 ± 12.3	72.8 ± 12.8	<0.001
BMI, kg/m², mean ± SD	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/1.73 m², mean ± SD	72.4 ± 34.1	72.4 ± 20.8	68.0 ± 19.5	62.6 ± 18.5	60.3 ± 18.9	<0.001
eGFR ≤60, n (%)	62 (37.8)	312 (29.2)	2083 (37.0)	582 (49.8)	108 (54.8)	<0.001
Ischaemic cardiomyopathy, n (%)	90 (54.9)	588 (55.0)	3347 (59.5)	757 (64.8)	135 (68.5)	<0.001
Left ventricular ejection fraction, %, mean ± SD	29.3 ± 6.4	29.4 ± 6.4	29.5 ± 6.2	29.6 ± 6.1	30.1 ± 6.4	0.59
BNP, pg/mL, median (range)	311 (184–717)	291 (169–611)	243 (150–447)	260 (160–468)	271 (171–530)	<0.001
BNP in AF+, median (range)	360 (184–692)	291 (181–544)	245 (157–434)	251 (159–453)	273 (185–588)	<0.001
BNP in AF-, median (range)	302 (183–783)	291 (161–643)	241 (145–455)	269 (160–471)	267 (153–491)	<0.001
NT-proBNP, pg/mL, median (range)	2476 (1199–5093)	1884 (941–4165)	1541 (862–3024)	1705 (946–3380)	1747 (926–3392)	<0.001
NT-proBNP in AF+, median (range)	3019 (1561–6083)	2131 (1114–4520)	1812 (1059–3420)	1961 (1172–3611)	2155 (1412–4781)	<0.001
NT-proBNP in AF-, median (range)	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 (39.2)	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
Randomized to sacubitril–valsartan, n (%)	84 (51.2)	527 (49.3)	2787 (49.5)	605 (51.8)	94 (47.7)	0.63

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; SD, standard deviation.

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 on 79 688 occasions (39 699 in the enalapril group and 39 989 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 of <4 mmol/L was observed on 3942 (9.9%) occasions in the enalapril group
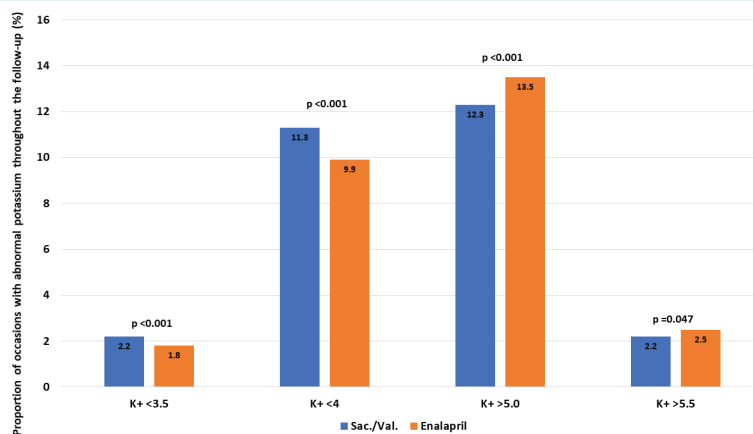
Figure 1 Proportion of occasions/visits in which an abnormal value of potassium was detected separated by treatment group. Sac/Val, sacubitril−valsartan.

and on 4531 (11.3%) occasions in the sacubitril−valsartan group (sacubitril−valsartan vs. enalapril, $P < 0.001$). A potassium level of <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, $P < 0.001$). During the follow-up, a potassium level of >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, $P < 0.001$). A potassium level of >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, $P = 0.047$) (*Figure 1*). Supplementary material online, *Figure S1* presents the incidences of both hypo- and hyperkalaemia over time by treatment group.

Compared with enalapril, sacubitril−valsartan reduced potassium concentration slightly [mean change, compared with enalapril, at week 80: −0.07 mmol/L (range: −0.09 to −0.04 mmol/L); $P < 0.001$].

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 potassium levels similar to those in 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 in comparison with 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*).
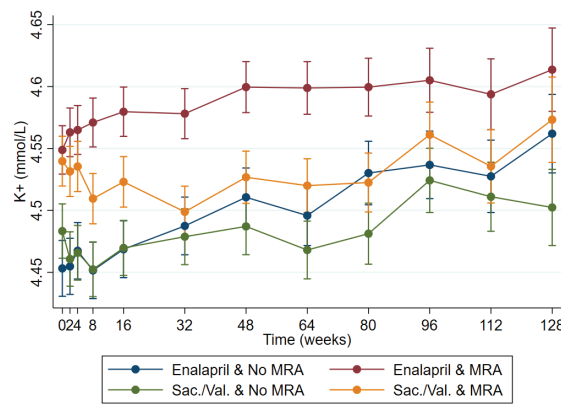

Figure 2 Potassium levels in patients allocated to sacubitril−valsartan or enalapril with or without a mineralocorticoid receptor antagonist (MRA). K^+ change at week 80 sacubitril−valsartan vs. enalapril and no MRA: −0.05 (−0.08 to −0.01), $P = 0.007$. K^+ change at week 80 sacubitril−valsartan vs. enalapril and MRA: −0.08 (−0.11 to −0.04), $P < 0.001$. Sac/Val, sacubitril−valsartan.

This overall pattern was generally more pronounced in the time-updated models. For the primary outcome, the HR for a potassium level of 3.6−4.0 mmol/L was 1.25 (95% CI 1.06−1.47) and the HR for a potassium concentration of ≤3.5 mmol/L was 1.91 (95% CI 1.41−2.61), compared with the reference category (potassium 4.1−4.9 mmol/L). The HR for a potassium level of 5.0−5.4 mmol/L was 1.08 (95% CI 0.92−1.27) and for a potassium level of ≥5.5 mmol/L was 1.38 (95% CI 1.06−1.78).

Similar results were obtained for the individual components of the primary outcome and all-cause death. The associations for sudden death and pump failure death were statistically significant for potassium levels of ≤3.5 mmol/L. Non-CV death also appeared to show a U-shaped association with potassium, but this was not

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

K⁺, mmol/L	Events, n (%)	Inc. rate, per 100 py	Baseline model	P-value	Time-updated model	P-value	K⁺ by study drug interaction P-value
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	

All models are adjusted on age, sex, race, region, systolic blood pressure, heart rate, body mass index, estimated glomerular filtration rate, ischaemic cardiomyopathy, left ventricular ejection fraction, N-terminal pro brain natriuretic peptide, New York Heart Association 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).
CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RCA, resuscitated cardiac arrest; SCD, sudden cardiac death or pump failure death.
The K⁺ group by study drug interaction P-value refers to 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/1.73 m²) was also tested and none was significant (interaction $P \geq 0.1$ for all the studied outcomes).

statistically significant for potassium levels of either ≤3.5 mmol/L or ≥5.5 mmol/L, possibly as a result of the small number of events (*Table 2*).

The associations between time-updated potassium level, modelled as a continuous variable, and the outcomes of interest are shown in *Figure 3* and reinforce the findings of the categorical analyses described above. The same is shown for baseline potassium in supplementary material online, *Figure S2*. The landmark analysis and joint models are illustrated in supplementary material online, *Figures S3* and *S4*. To offset the association between hypokalaemia
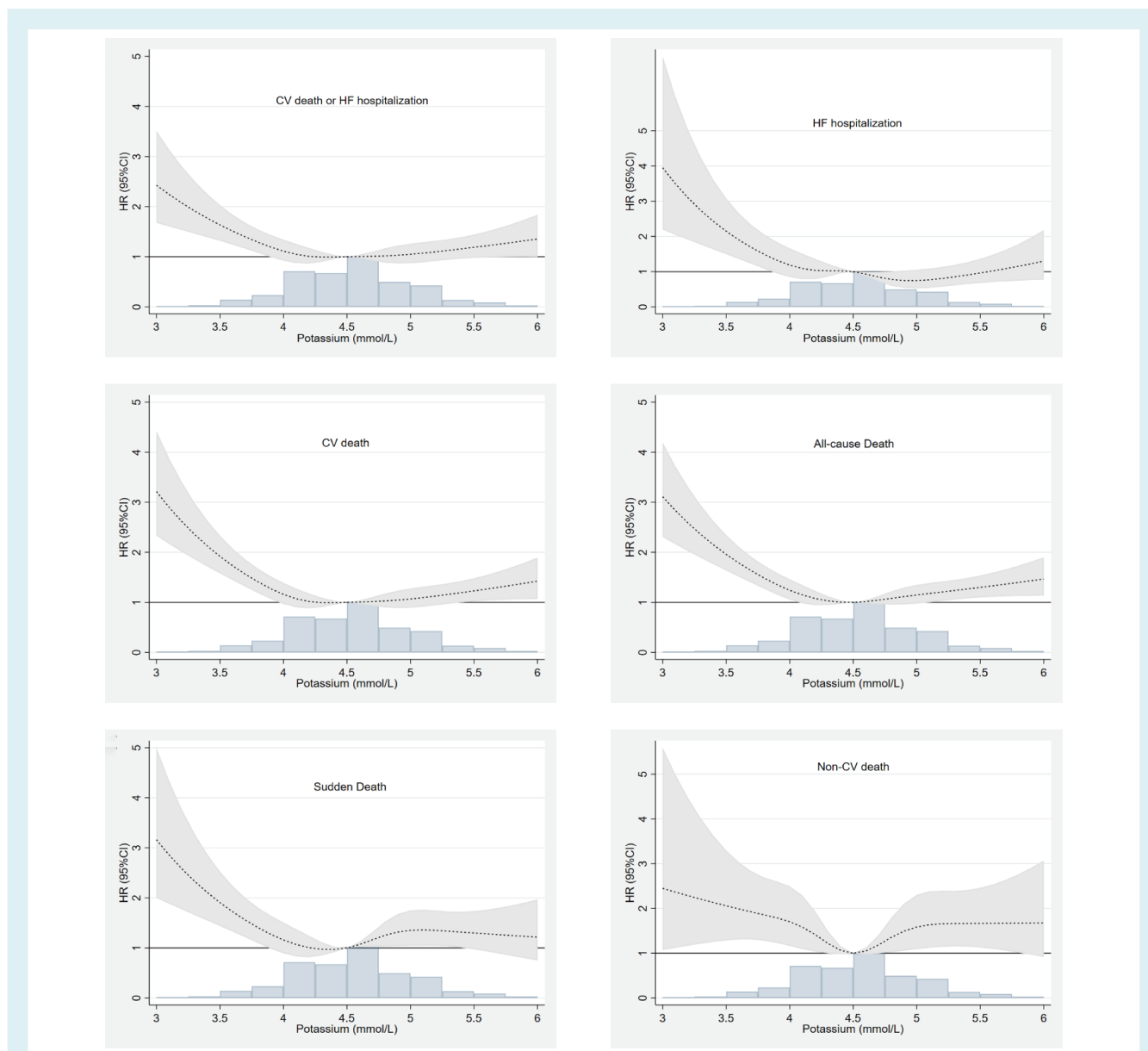
Figure 3 Time-updated potassium and associations with the studied outcomes. The primary outcome was a composite of cardiovascular (CV) death or heart failure (HF) hospitalization. CI, confidence interval; HR, hazard ratio.

(≤3.5 mmol/L) and risk for the primary outcome, an 'unmeasured' confounder would need to have an incremental HR of ≥2.5 on top of the adjusted analysis described (Supplementary material online, *Figure S5*).

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 material online, *Table S2*). For example,

the persistence of either hypokalaemia or hyperkalaemia was associated with a higher risk for subsequent CV death [HR 1.61 (95% CI 1.25–2.09), *P* < 0.001 for persistence of hypokalaemia; HR 1.32 (95% CI 1.01–1.72), *P* = 0.041 for persistence of hyperkalaemia].

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*).
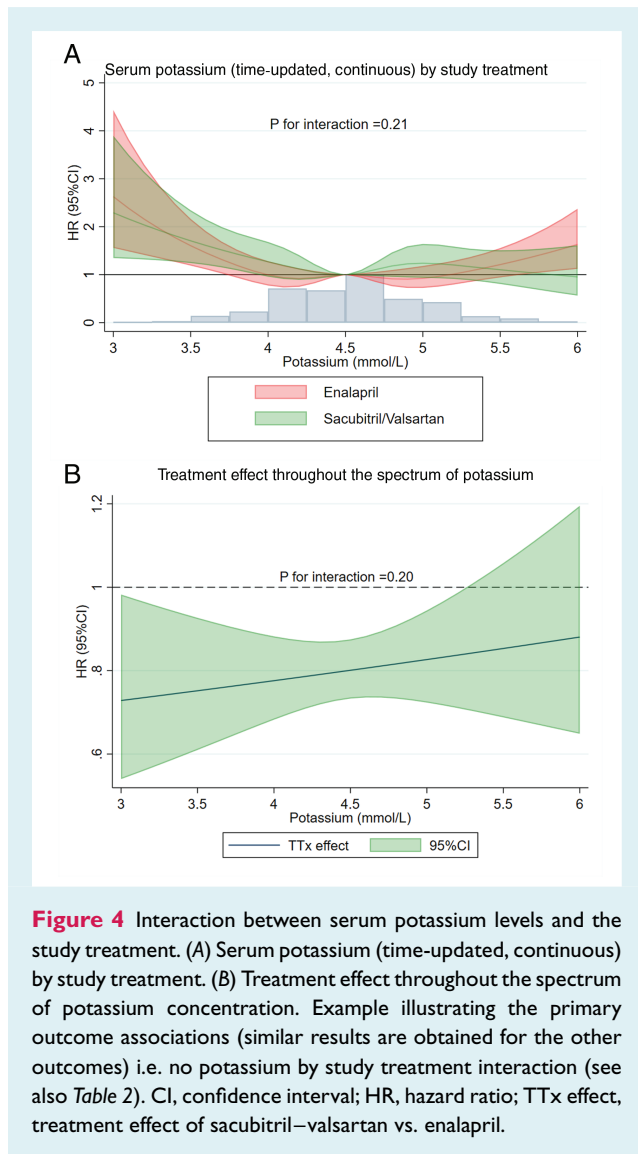
Figure 4 Interaction between serum potassium levels and the study treatment. (*A*) Serum potassium (time-updated, continuous) by study treatment. (*B*) Treatment effect throughout the spectrum of potassium concentration. Example illustrating the primary outcome associations (similar results are obtained for the other outcomes) i.e. no potassium by study treatment interaction (see also *Table 2*). CI, confidence interval; HR, hazard ratio; TTx effect, treatment effect of sacubitril–valsartan vs. enalapril.

Discussion

The present study found that both hypo- and hyperkalaemia were associated with a higher risk for adverse clinical outcomes, compared with a normal potassium concentration. Although the risk was greater with hypokalaemia than with hyperkalaemia, 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 HF and in chronic HFrEF, the present study 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-HF.[18–21] After adjusting for a wide range of clinical predictors, and NT-proBNP, the elevation

in risk for death associated with higher potassium was modest and less pronounced than in hypokalaemia. Although prior studies have suggested that the elevated risk for death associated with hyper-kalaemia may reflect underdosing or even the withholding of RAAS blockers,[22,23] this is not likely to represent the explanation in the present trial given that patients started on the maximum dose of the study drug and every effort was made to maintain the optimal dose during follow-up. Moreover, the associations between higher potassium and fatal outcomes were similar for all subtypes of death examined, including non-CV death, which suggests a lack of any specific mechanistic direct effect of hyperkalaemia. This perspective is supported by the similar association between hyperkalaemia and risk for HF hospitalization, given the lack of obvious patho-physiological link between higher potassium and risk for HF hos-pitalization. Scrutiny of the baseline characteristics of participants with hyperkalaemia shows them to be older, to have more frequent ischaemic aetiology and greater comorbidity, including worse renal function. It is possible that the multivariable models used in the present study did not fully adjust for the measured and unmeasured differences between patients with hyperkalaemia and those with normal potassium levels. Therefore, a higher potassium concentra-tion may generally represent a marker of a sicker patient, although, in individuals, occasionally, hyperkalaemia may still directly cause a fatal arrhythmia or conduction disturbance.[24–26]

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, MRA use was less frequent in individuals in the lowest potassium category, in contrast to those with high potassium concentrations. However, MRA use was included in the multivariable adjustment and therefore neither the lower use of MRAs nor the underuse of ACEi or ARBs seem to account for the association between hypokalaemia and higher risk for death. More surprisingly, perhaps, the association between low potassium and outcomes also appeared to lack specificity, with similarly elevated risk for various types of death, as seen with higher potassium concentrations. Moreover, the risk for HF hospitalization was elevated to the same degree as that for 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 to be at variance with the finding that the '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 whose clinical status improved.

Another interesting observation was that the overall comorbid-ity profile of patients with hypokalaemia was generally of lower risk than that of patients with hyperkalaemia; patients in the lower potassium categories had better renal function, and less ischaemic cardiac disease, diabetes and atrial fibrillation than patients with higher potassium, although patients with low potassium had higher NT-proBNP levels, greater use of diuretics and a more frequent history of HF hospitalization. One interpretation of these findings

may be that low potassium, reflecting a greater use of diuretics and less use of MRAs in more recently hospitalized and inadequately decongested patients, is a marker of a patient with a greater probability of worsening that will lead to hospital admission or death.[27] This might suggest that the present 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 (a region of low MRA use) was relatively over-represented and Central and Eastern Europe (regions of high MRA use) were relatively under-represented in the potassium ≤3.5 mmol/L category, 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. The use of MRAs was not lower in Blacks or Asians and the other factors mentioned in relation to geographical region plus additional genetic variables may be important.[28] Finally, it remains likely that a general indirect and non-specific association between lower potassium level 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 similar to those in patients not treated with MRAs).[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. A previous report demonstrated that sacubitril−valsartan reduced the risk for hyperkalaemia in patients treated with an MRA.[30] The present study expands those findings by comparing the effects of sacubitril−valsartan with those of enalapril across the full spectrum of potassium concentrations. Furthermore, the benefit of sacubitril−valsartan over enalapril was consistent across the range of baseline potassium levels 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 generalizability of the current findings, the trial design also addresses the limitations of earlier studies. Regular monitoring of potassium and protocol-guided mitigation may have led to the correction of potassium abnormalities more frequently, or more quickly, than in routine practice (and perhaps in hyperkalaemia more often than in hypokalaemia, as treatment of only the former was addressed in the protocol). Moreover, a serum potassium level

of >5.2 mmol/L at screening (or >5.4 mmol/L at randomization) was an exclusion criterion, which may have led to the selection of patients less prone to the development of hyperkalaemia. Although having an independent adjudication committee was a major advantage of the present 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 for death, although the association was stronger for the latter. While both higher and lower potassium levels remained independent predictors of death after adjustment in multivariable models, they were also associated with non-CV death and HF hospitalization, which suggests that potassium abnormalities are mainly markers of disease severity. Compared with enalapril, sacubitril−valsartan had no overall effect on potassium concentrations in PARADIGM-HF, although it 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 levels among the patients randomized in PARADIGM-HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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