Effect of Patiromer on Serum Potassium in Hyperkalemic Patients With and Without Obesity: Pooled Results From the AMETHYST-DN, OPAL-HK, and TOURMALINE Trials

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INTRODUCTION

- Obesity (defined as body mass index [BMI] ≥30 kg/m^2) is common in patients with chronic kidney disease (CKD).[1]
- Activation of the renin-angiotensin-aldosterone system may play a causative role in the development of CKD in obese patients along with other factors such as proteinuria and hypertension.[2]
- Renin-angiotensin-aldosterone system inhibitors (RAASi) are beneficial in the treatment of CKD or heart failure patients, with or without obesity.[3,4]
- The risk of hyperkalemia (HK) in CKD or heart failure treated with RAASi, including aldosterone antagonists, is similar in obese and non-obese patients.[3,4]
- Patiromer, a non-absorbed, sodium-free, potassium (K^+) binder, has been shown to effectively reduce serum K^+ levels in hyperkalemic patients with CKD taking RAASi.[5,6]
- The effect of patiromer in obese patients with HK and CKD has not been previously reported.
- The aim of this study was to evaluate the effect of patiromer on serum K^+ in HK patients with and without obesity.

METHODS

- The effect of four weeks of treatment with patiromer on serum K^+ was investigated by combining data from three clinical trials: AMETHYST-DN (NCT01371747), OPAL-HK (NCT01810939), and TOURMALINE (NCT02694744).[5–7]
- Eligible patients had serum K^+ (local lab) >5.0 mEq/L.
- Starting doses of patiromer ranged from 8.4 to 33.6 g/d.
- Patiromer dose was titrated to achieve and maintain normokalemia (serum K^+ upper limit 5.0 mEq/L).
- Patients who took at least one dose of patiromer and had one post-baseline serum K^+ measurement were included in this post hoc analysis.
- Data were pooled and analyzed for:
  - Change from baseline in serum K^+ (primary endpoint in OPAL-HK and AMETHYST-DN; secondary endpoint in TOURMALINE).
  - Proportion of patients achieving target serum K^+ (primary endpoint in TOURMALINE; secondary endpoints in OPAL-HK and AMETHYST-DN).
  - Data were stratified according to BMI (≥30 kg/m^2 obese, and <30 kg/m^2 non-obese) at baseline visit.

RESULTS

Baseline Characteristics

- Of 653 patients included in the analysis, 41% were obese, 62% were men, with a mean (SD) age of 66 (10) years (**Table 1**).
- Mean (SD) BMI was 33.7 (3.4) in patients with obesity, and 26.4 (2.6) in those without obesity.
- Patient characteristics were generally similar among obese and non-obese patients. In the obese group, there was a greater proportion of patients with diabetes mellitus (87% vs. 78% in non-obese). Baseline mean serum K^+ was 5.4 mEq/L in both obese and non-obese patients.
- More than 90% of patients were on RAASi during the studies (**Table 2**).
- More patients with obesity were receiving dual RAASi blockade (21.0% vs. 10.9%) and aldosterone antagonists (10.5% vs. 5.4%).

RESULTS (CONT'D)

Table 1. Baseline demographics and clinical characteristics

Characteristic	Patients with Obesity[a] (N=267)	Patients without Obesity[a] (N=386)	Total (N=653)
Male, n (%)	139 (52.1)	263 (68.1)	402 (61.6)
Age (yr), mean (SD)	66 (9)	65 (11)	66 (10)
Median (Q1, Q3)	66 (60, 72)	67 (60, 74)	66.0 (60, 73)
White, n (%)	257 (96.3)	372 (96.4)	629 (96.3)
BMI, mean (SD)	33.7 (3.4)	26.4 (2.6)	29.4 (4.7)
Median (Q1, Q3)	32.6 (31.2, 35.7)	26.8 (24.9, 28.4)	29.0 (26.3, 31.9)
eGFR (mL/min/1.73m^2)[b], n (%)			
≥90 [Stage 1]	6 (2.2)	6 (1.6)	12 (1.8)
60–89 [Stage 2]	26 (9.7)	50 (13.0)	76 (11.6)
45–59 [Stage 3a]	60 (22.5)	81 (21.0)	141 (21.6)
30–44 [Stage 3b]	74 (27.7)	105 (27.2)	179 (27.4)
15–29 [Stage 4]	90 (33.7)	122 (31.6)	212 (32.5)
<15 [Stage 5]	10 (3.7)	17 (4.4)	27 (4.1)
Mean (SD)	38.8 (18.7)	39.7 (19.2)	39.3 (19.0)
Median (Q1, Q3)	35.0 (25.0, 50.0)	36.0 (25.0, 49.0)	36.0 (25.0, 49.0)
Serum K^+ (mEq/L)[c], mean (SD)	5.4 (0.38)	5.4 (0.44)	5.4 (0.42)
Median (Q1, Q3)	5.4 (5.1, 5.6)	5.4 (5.1, 5.7)	5.4 (5.1, 5.7)
Diabetes mellitus, n (%)	233 (87.3)	301 (78.0)	534 (81.8)
Time since diabetes mellitus diagnosis (yr), mean (SD)	15.0 (9.1)	13.5 (8.8)	14.2 (9.0)
Median (Q1, Q3)	14.1 (8.2, 20.3)	11.3 (7.0, 19.0)	12.1 (7.1, 20.0)
Hypertension, n (%)	264 (98.9)	375 (97.2)	639 (97.9)
NYHA heart failure class[d], n (%)			
I	20 (7.5)	30 (7.8)	50 (7.7)
II	47 (17.6)	99 (25.6)	146 (22.4)
III	6 (2.2)	12 (3.1)	18 (2.8)
Myocardial infarction, n (%)	41 (15.4)	79 (20.5)	120 (18.4)

[a]Obesity is defined by a body mass index (BMI) ≥30 kg/m^2. [b]Six patients in study 205 did not have a baseline eGFR value and were excluded from this summary. [c]One subject had central baseline serum K^+ value 9.4 mEq/L; this value has been replaced with the value imputed from the local value, 5.6 mEq/L. [d]NYHA class IV heart failure patients were excluded.

Table 2. Baseline concomitant medications of interest

Medication, n (%)	Patients with Obesity (N=267)	Patients without Obesity (N=386)	Total (N=653)
RAASi medication	248 (92.9)	358 (92.7)	606 (92.8)
ACE inhibitors	163 (61.0)	243 (63.0)	406 (62.2)
ARB	117 (43.8)	138 (35.8)	255 (39.1)
Aldosterone antagonist	28 (10.5)	21 (5.4)	49 (7.5)
Renin inhibitor	2 (0.7)	0	2 (0.3)
Dual RAASi blockade[a]	56 (21.0)	42 (10.9)	98 (15.0)
Non-RAASi antihypertensive			
Beta blocker	116 (43.4)	129 (33.4)	245 (37.5)
Non-RAASi diuretic			
Thiazide	20 (7.5)	30 (7.8)	50 (7.7)
Loop	104 (39.0)	121 (31.3)	225 (34.5)

[a]Any combination of two or more of the following: ACE inhibitor, ARB, aldosterone antagonist, renin inhibitor.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

RESULTS (CONT'D)

Efficacy

- The reduction in mean serum K^+ over time was similar in obese and non-obese patients (**Figure 1**).
- At Week 4, least square mean (SE) serum K^+ change from baseline was –0.77 (0.03) and –0.74 (0.03) mEq/L in obese and non-obese patients, respectively (**Figure 2**).
- For those with baseline serum K^+ <5.5 mEq/L, the least square mean (SE) change from baseline at Week 4 was –0.59 (0.04) and –0.48 (0.04) mEq/L in obese and non-obese patients, respectively.
- In patients with baseline serum K^+ ≥5.5 mEq/L, least square mean (SE) serum K^+ decreased by –1.08 (0.07) in the obese group and by –1.03 (0.05) mEq/L in the non-obese group.
- The proportion of patients that achieved any target range K^+ (3.8–5.0 mEq/L) through Week 4 was 96% in obese patients overall, and 97% in non-obese patients overall (**Figure 3**).

Figure 1. Serum K^+ over time

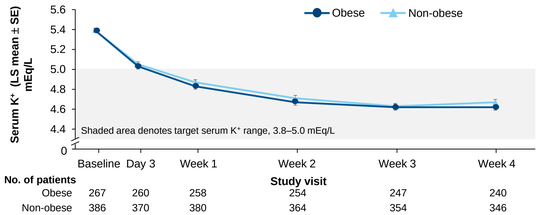


Figure 2. Change in serum K^+ from baseline to Week 4

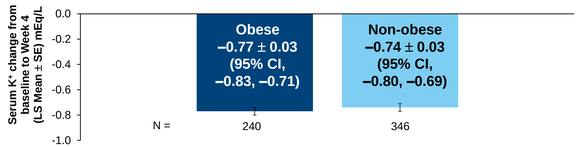
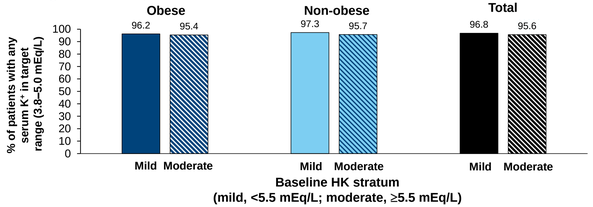


Figure 3. Proportion of patients achieving any serum K^+ in target range through Week 4 by baseline HK stratum



RESULTS (CONT'D)

Safety and Tolerability

Table 3. Safety summary in first 4 weeks of treatment

Patients, n (%)	Patients with Obesity (N=267)	Patients without Obesity (N=386)	Total (N=653)
≥1 AE	101 (37.8)	108 (28.0)	209 (32.0)
Most common AEs (none severe)[a]			
Constipation	19 (7.1)	20 (5.2)	39 (6.0)
Diarrhea	8 (3.0)	11 (2.8)	19 (2.9)
Hypomagnesemia	9 (3.4)	4 (1.0)	13 (2.0)
Patiromer-related AE	42 (15.7)	46 (11.9)	88 (13.5)
≥1 serious AE[b]	10 (3.7)	7 (1.8)	17 (2.6)
AEs leading to study discontinuation	11 (4.1)	13 (3.4)	24 (3.7)
Prespecified laboratory values of interest			
Serum K^+ <3.5 mEq/L	2 (0.7)	8 (2.1)	10 (1.5)
Serum Mg^{2+} <1.4 mg/dL	17 (6.4)	13 (3.4)	30 (4.6)
Serum Mg^{2+} <1.2 mg/dL	0	1 (0.3)	1 (0.2)

[a]AEs occurring in ≥2% of study participants pooled across all 3 studies.
[b]Serious AEs with onset during the first 28 days after the start of patiromer treatment regardless of the date of treatment discontinuation.

- AEs were reported in 101 (38%) obese patients and 108 (28%) non-obese patients (**Table 3**).
- The most common AEs (none severe) were constipation (7.1% in obese, 5.2% in non-obese), diarrhea (3.0% in obese, 2.8% in non-obese), and hypomagnesemia (3.4% and 1.0%, respectively).
- Among patients reporting AEs of hypomagnesemia, baseline serum magnesium was <1.8 mg/dL in:
  - 4 of 9 patients with obesity.
  - 1 of 4 patients without obesity.
- Most AEs (95%) were mild to moderate. AEs led to patiromer discontinuation in 4.1% of obese patients and 3.4% of non-obese patients.

CONCLUSION

- Patiromer reduced serum potassium in hyperkalemic obese and non-obese patients in a manner consistent with overall results in the individual studies.

Declaration of Interest
PR reports honoraria from Astra-Zeneca, Bayer, CVRx, Daichii-Sankyo, Fresenius, Gambro, G3P, HAC, Novartis, Relypsa, Sanofi, Sarfez, Servier, Stealth Peptides, and Vifor Fresenius Medical Care Renal Pharma; research grants from Astra-Zeneca, BG Medicine, BMS and Roche; and travel grants from Astra-Zeneca, Daichii-Sankyo, Gambro, Novartis, Sevier and Takeda; Cofounder: CardioRenal; **CG, MM, SW, JY, and JB** report employment by Relypsa, Inc., a Vifor Pharma Group Company; **EM** has nothing to disclose.

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