Effect of Patiromer on Reducing Serum Potassium and Preventing Recurrent Hyperkalemia in Patients with Heart Failure and Chronic Kidney Disease on RAAS Inhibitors

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/EJHF.402

Abstract

Aims: We evaluated the effects of patiromer, a potassium (K^+)-binding polymer, in a prespecified analysis of hyperkalemic patients with heart failure (HF) in the OPAL-HK trial.

Methods and results: CKD patients on RAASi with serum K^+ levels ≥5.1-<6.5 mEq/L (n=243) received patiromer (4.2 g or 8.4 g BID initially) for 4 weeks (initial treatment phase); the primary efficacy endpoint was mean change in serum K^+ from baseline to week 4. Eligible patients (those with baseline K^+ ≥5.5-<6.5 mEq/L and levels ≥3.8-<5.1 mEq/L at the end of week 4) entered an 8-week randomized withdrawal phase and randomly assigned to continue patiromer or switch to placebo; the primary efficacy endpoint was the between-group difference in median change in the serum K^+ over the first 4 weeks of that phase. One hundred two patients (42%) had HF. The mean (±SE) change in serum K^+ from baseline to week 4 was −1.06±0.05 mEq/L (95% CI, −1.16,−0.95; *P*<.001); 76% (95% CI, 69,84) achieved serum K^+, 3.8 to <5.1 mEq/L. In the randomized withdrawal phase, the median increase in serum K^+ from baseline of that phase was greater with placebo (n=22) than patiromer (n=27) (*P*<0.001); recurrent hyperkalemia (serum K^+, ≥5.5 mEq/L) occurred in 52% on placebo and 8% on patiromer (*P*<0.001). Mild-to-moderate constipation was the most common adverse event (11%); hypokalemia occurred in 3%.

Conclusion: In patients with CKD and HF who were hyperkalemic on RAASi, patiromer was well-tolerated, decreased serum K^+ and, compared with placebo, reduced recurrent hyperkalemia.

Key words: chronic kidney disease, heart failure, hyperkalemia, patiromer

Introduction

Renin angiotensin aldosterone system inhibitors (RAASi) have been shown to be effective in reducing mortality as well as hospitalizations for heart failure (HF) in patients with chronic HF and a reduced left ventricular ejection fraction (HFREF) and have been accorded a class 1 indication in international guidelines (1-6). In patients with chronic kidney disease (CKD) complicating their HF, renal excretion of potassium (K^+) is compromised and is in part compensated by an increase in colonic excretion, which often is not sufficient to avoid hyperkalemia (7). Patients with CKD and HFREF are therefore at an increased risk of death but paradoxically often receive suboptimal doses of RAASi because of fear of inducing hyperkalemia (serum K^+ >5.0 mEq/L) and its consequences, including sudden cardiac death (8-10). While there are several options for the treatment of acute hyperkalemia, options for the management of chronic hyperkalemia, and thereby maintaining RAASi use in patients with HF, are limited. Agents that have been employed to manage persistently high potassium levels include diuretics (with or without sodium bicarbonate) and the potassium-binding resins, calcium polystyrene sulfonate (CPS) and sodium polystyrene sulfonate (SPS) (11,12). Calcium polystyrene sulfonate and SPS can lead to serious gastrointestinal AEs, including colonic necrosis and perforation (11-14), which has led to warnings in the prescribing information (11,12,15). Additionally, because sodium is the counter exchange ion with SPS, caution is advised when treating patients who cannot tolerate even small increases in sodium load (eg, those with severe congestive heart failure, severe hypertension, or marked edema) (11). Patients

with chronic HF who develop hyperkalemia therefore often have their dose of RAASi reduced or discontinued (8,10,16), thereby exposing them to increased cardiovascular risk.

The active moiety of patiromer is a nonabsorbed oral potassium-binding polymer. It acts primarily in the distal colon, where the concentration of free potassium is the highest, to increase fecal potassium excretion (17,18). Patiromer consists of smooth, spherical beads approximately 100 μm in diameter that are insoluble, free-flowing, and that do not swell appreciably when mixed with water (18). The OPAL-HK study showed patiromer to be generally well tolerated and effective in reducing serum K^+ levels in CKD patients with mild and moderate-to-severe hyperkalemia (serum K^+ ≥5.1–<6.5 mEq/L) (17).

We evaluated patiromer's efficacy and safety in a prespecified analysis of OPAL HK in the subgroup of CKD patients with HF and compared those results to CKD patients without HF.

Methods

Study population

The OPAL-HK study has been described previously (17). In brief, eligible patients were 18 to 80 years of age, had stage 3 or 4 CKD (estimated glomerular filtration rate [eGFR] of 15–<60 mL/min/1.73m^2 of body surface area), serum K^+ 5.1 to <6.5 mEq/L indicative of hyperkalemia, and had been receiving a stable dose of ≥1RAASi for ≥28 days. Patients who were also on anti-hypertensive medication, loop and thiazide diuretics, or beta-blockers, were receiving them at stable doses for ≥28 days.

Patients were excluded if at screening they presented with potassium-related electrocardiographic changes, severe gastrointestinal disorders, uncontrolled or unstable arrhythmias or clinically significant ventricular arrhythmias, type 1 diabetes, New York Heart Association (NYHA) class IV heart failure, acute coronary syndrome, or confirmed systolic blood pressure >180 mmHg or <110 mmHg, or diastolic blood pressure >110 mmHg or <60 mmHg. Patients were also excluded if they underwent recent cardiac surgery, kidney or heart transplantation, had an ischemic attack or stroke within the previous 2 months, or received emergent treatment for type 2 diabetes or acute heart failure within the previous 3 months.

The study (NCT01810939) was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and complied with the Declaration of Helsinki. The study protocols were reviewed and approved by institutional review boards and patients provided written informed consent.

Study protocol

This study was carried out in 2 parts—an initial treatment phase and a randomized withdrawal phase. The initial treatment phase was a 4-week, single-group, single-blind assessment of patiromer in patients with CKD taking RAASi. At the beginning of this phase, patients were assigned 1 of 2 patiromer doses based on their screening serum K^+ levels. Patients with mild hyperkalemia (serum K^+ 5.1–<5.5 mEq/L) received 4.2 g of patiromer twice daily; patients with moderate to severe hyperkalemia (serum K^+ 5.5–<6.5 mEq/L) received 8.4 g of patiromer twice daily. Patiromer was administered as an oral suspension in 40 to 120 mL of water, depending on dose, with breakfast and dinner. Subsequent doses were adjusted to reach and maintain target serum K^+ levels based on a prespecified treatment algorithm (Supplementary Table 1). The target serum K^+ levels were conservative to avoid hypokalemia. The RAASi dose was not adjusted to facilitate interpretation of primary study endpoints during the initial treatment phase. Patients discontinued RAASi and their participation in the study if their serum K^+ was ≥6.5 mEq/L during the initial treatment phase.

Following the initial treatment phase was a randomized withdrawal phase – an 8-week single-blind, placebo-controlled, parallel group assessment of patiromer withdrawal. Patients who completed the initial treatment phase were eligible to start the randomized withdrawal phase if they had moderate to severe hyperkalemia (serum K^+ level of 5.5–<6.5 mEq/L) at baseline of the initial treatment phase and were normokalemic (serum K^+ level within target range of 3.8–<5.1 mEq/L) at week 4 of the initial treatment phase (baseline of the randomized withdrawal

phase). Patients were eligible for continuation to the randomized withdrawal phase if they were still taking patiromer and at least one RAASi. Eligible patients were randomized in a single-blind manner to either continue patiromer at the daily dose they were receiving at week 4 of the initial treatment phase or to switch to placebo, in a 1:1 ratio. The randomization was performed centrally and stratified based on the presence of type 2 diabetes as well as baseline serum K^+ (moderate [5.5–<5.8 mEq/L] vs severe [≥5.8 mEq/L] hyperkalemia).

Use of RAASi and recurrence of hyperkalemia were monitored during the randomized withdrawal phase. Hyperkalemia was defined as a serum K^+ measurement ≥5.5 mEq/L during the first 4 weeks of the randomized withdrawal phase, and ≥5.1 mEq/L during the last 4 weeks of this phase. Recurrences of hyperkalemia were managed with a pre-specified treatment algorithm (Supplementary Table 2) either by increasing the patiromer dose (patiromer group) or by RAASi modification (placebo group) at the time of the first occurrence of hyperkalemia. Subsequent occurrences required RAASi discontinuation. Neither of these interventions was to be used during the first 4 weeks of the randomized withdrawal phase (unless serum K^+ reached ≥5.5 mEq/L) to facilitate the interpretation of the primary efficacy endpoint.

Serum K^+ levels were measured at local and central laboratories at baseline, day 3, and weekly throughout both parts of the study. Safety data were recorded at each of these visits. During the study, site staff counseled subjects to restrict foods high in potassium content (>250 mg/100 g) and to target their potassium intake to ≤2 to 3 g/day (approximately 50–75 mEq/d). Up to 3 safety follow-up visits occurred within 1 to 2 weeks after discontinuation of

patiromer or placebo (including in patients who withdrew from the study or did not qualify for the randomized withdrawal phase) to monitor adverse event (AE) occurrence and serum K^+ levels.

Clinical endpoints

The primary efficacy endpoint of the treatment phase was the mean change in serum K^+ level from baseline to week 4 in patients who received ≥1 dose of patiromer and had at least 1 K^+ measurement after day 3. The secondary endpoint was the proportion of patients whose serum K^+ was within target range (3.8–<5.1 mEq/L) at week 4. The primary efficacy endpoint of the randomized withdrawal phase was the difference between the patiromer and placebo groups in the median change in serum K^+ from baseline to either week 4—if serum K^+ stayed in target range—or the earliest visit when serum K^+ was outside that range. The secondary endpoints were the proportions of patients with a recurrence of hyperkalemia according to 2 definitions: serum K^+ of ≥5.1 or ≥5.5 mEq/L. An exploratory efficacy endpoint of the randomized withdrawal phase was the proportion of patients requiring an intervention to manage a recurrence of hyperkalemia (ie, an increase of the patiromer dose [patiromer group] or RAASi dose reduction [placebo group] at the first occurrence of hyperkalemia; RAASi discontinuation at subsequent occurrences [both treatment groups]). Adverse events were monitored and recorded during both parts of the study and for up to 2 weeks after discontinuation from the study.

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Statistical analysis

The mean change in serum K^+ (primary endpoint) and the associated 95% confidence interval (CI) were estimated using a longitudinal repeated measures model of the centrally measured, weekly postbaseline serum K^+ values. Consequently, only patients with at least 1 weekly postbaseline measurement were included in the analyses. For the subgroups defined by presence or absence of heart failure (HF), the model used 1 binary covariate (presence of type 2 diabetes) and 1 continuous covariate (baseline serum K^+). Patients were included in the HF subgroup based on a history of HF—per the investigator's judgment—which included NYHA class, date of diagnosis (if known), and diagnosis of systolic or diastolic dysfunction (if determined).

To assess the primary efficacy endpoint of the randomized withdrawal phase, changes in serum K^+ from baseline in placebo and patiromer groups were compared using an analysis of variance of rank-transformed data. All patients randomized to enter the withdrawal phase were included in these analyses. The between-group difference in median serum K^+ change from baseline and the associated 95% CI were calculated using a Hodges-Lehmann estimator. The comparison of the treatment groups used rank of change carried forward to account for and include patients who discontinued study drug prior to week 4 of the randomized withdrawal phase. For both secondary endpoint calculations, proportions of patients in the 2 treatment groups were compared using a Mantel-Haenszel test with baseline strata. The analyses for the subgroups defined by the presence or absence of heart failure did not include any adjustment for multiplicity. A more detailed description of the statistical analysis methods is provided in the primary publication describing the overall results of the OPAL-HK study (17).

Comment [A2]: Response Reviewer 2, comment #4

Comment [A3]: Response to Reviewer 2, comment #4

Comment [A4]: Response to reviewer 2, comment #1

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Comment [A7]: Response to Reviewer 2, comment #4

With 240 patients enrolled, this provided more than 99% power to detect a mean change from baseline in serum K^+ of at least 0.3 mEq/L. This calculation was based on a 2-sided, 1-sample, paired t-test, significance level of $\alpha = 0.05$, and the assumption of a standard deviation of 0.55. SAS Version 9.2 was utilized for statistical analyses.

Results

Patients

A total of 243 patients with CKD were enrolled in the initial treatment phase, 102 (42%) with HF and 141 (58%) without HF (Table 1). Of the patients with HF, 39 (38%) entered the study with mild and 63 (62%) with moderate-to-severe hyperkalemia; of the patients without HF, 53 (38%) had mild and 88 (62%) had moderate-to-severe hyperkalemia. All patients received at least 1 dose of patiromer.

A total of 91 (89%) patients with HF completed the initial treatment phase. Of those, 42 patients (46%) were not eligible to continue to the randomized withdrawal phase. The most common reason for ineligibility was a centrally measured baseline serum K^+ of <5.5 mEq/L (40 patients, 44%); 1 patient was ineligible solely because their serum K^+ fell outside of target range at week 4. The remaining 49 patients with HF (54%) eligible for the randomized withdrawal phase were randomly assigned either to continue patiromer (27 patients) or to switch to placebo (22 patients). A total of 12 patients with HF discontinued the randomized withdrawal phase prematurely – 5 (19%) patients in the patiromer group and 7 (32%) patients in the placebo group. Most of the discontinuations were due to an elevated serum K^+ that met the pre-specified withdrawal criteria (5 patients with HF [23%] in the placebo and 0 patients with HF in the patiromer group). Comprehensive disposition information for patients with and without HF can

be found in Supplementary Figure 1 (initial treatment phase) and Figure 2 (randomized withdrawal phase).

At the start of the trial, the proportion of HF patients with stage 3 and stage 4/5 CKD, respectively, was 47% and 44%; in patients without HF, the corresponding proportions were 46% and 45%. In patients with and without HF, 9% had stage 2 CKD based on central laboratory eGFR measurements and were included in the study because they had met entry criteria on the basis of eGFR measurements obtained at local laboratories. The mean serum K^+ (±SD) at baseline was 5.6 ±0.6 mEq/L in patients with HF and 5.5 ±0.4 mEq/L in patients without HF.

Efficacy

Initial treatment phase

The mean (±SE) change in serum K^+ from baseline to week 4 in patients with HF (100 patients who had at least 1 serum K^+ measurement after day 3) was −1.06 ± 0.05 mEq/L (95% CI, −1.16, −0.95, P <.001, Figure 1a). The mean (±SE) change in serum K^+ from baseline to week 4 in HF patients with mild HK (n = 38) was −0.74 ± 0.08 mEq/L (95% CI, −0.91, −0.57), and for patients with HF with moderate-to-severe HK (n = 62) the change from baseline was −1.26 ± 0.07 mEq/L (95% CI, −1.40, −1.12). Figure 1b shows the observed mean serum K^+ over time. By the end of the 4-week initial treatment phase, 76% of patients with HF achieved a serum K^+ in the target range (3.8–<5.1 mEq/L) (95% CI, 69, 84). The primary and secondary efficacy endpoints were similar in patients without HF (Figure 1). The mean daily dose of patiromer received over the 4-week initial treatment phase was 17.8 g for patients with HF and

18.4 g for those without HF, with a similar mean number of dose adjustments in each subgroup (0.8 and 0.9, respectively).

Randomized withdrawal phase

At baseline of the randomized withdrawal phase (week 4 of the initial treatment phase), which included only those patients whose serum K^+ was controlled during the initial treatment phase, mean serum K^+ was 4.52 mEq/L in patients with HF randomized to patiromer and 4.56 mEq/L in patients with HF randomized to placebo. The estimated median change in serum K^+ from baseline to week 4 of the randomized withdrawal phase was 0.74 mEq/L for patients with HF taking placebo and 0.10 mEq/L for those taking patiromer, for a between-group difference of 0.64 mEq/L (95% CI, 0.29, 0.99; *P*<.001; Figure 2).

In patients with HF, 52% (95% CI, 30–74) of those randomized to placebo compared with 8% (95% CI, 1–25) of those randomized to patiromer had at least 1 serum K^+ of ≥5.5mEq/L during the 8-week randomized withdrawal phase (*P* <.001 for placebo-patiromer group difference). A total of 95% (95% CI, 77, >99) of patients with HF randomized to placebo and 36% (95% CI, 19, 57) of those randomized to patiromer had at least 1 serum K^+ of ≥5.1 mEq/L (*P* <.001). Figure 3 shows the time to hyperkalemia (serum K^+ ≥5.1 mEq/L and ≥5.5 mEq/L) recurrence in patients with HF, time to hyperkalemia in patients without HF can be found in Supplementary Figure 3.

In a prespecified exploratory analysis, 13 (59%) patients with HF taking placebo compared with 3 (11%) patients taking patiromer required an intervention to manage their hyperkalemia recurrence; by the end of the randomized withdrawal phase, 55% of HF patients on placebo and 100% of HF patients on patiromer were still receiving RAASi. Figure 4 shows the time to the discontinuation of RAASi. Results were similar in patients without HF (Figures 2-4).

Safety

During the initial treatment phase and its follow-up period, 41% of patients with HF and 51% of patients without HF reported at least 1 AE (Supplementary Table 3A). The most common AEs that occurred during the initial treatment phase are shown in Table 2. The majority of AEs were gastrointestinal. None of the gastrointestinal events that occurred in this phase were severe. Adverse events that led to patiromer discontinuation occurred in 7 (7%) patients with HF and 8 (6%) patients without HF. Three patients (2 with HF and 1 without HF) experienced nonfatal serious AEs during the initial treatment phase; the investigators did not consider the events related to patiromer.

The proportion of patients with and without HF experiencing at least 1 AE during the 8-week randomized withdrawal phase and its follow-up period was similar between the placebo and patiromer groups (HF, 64% and 56%, respectively; non-HF, 40% and 39%; Table 3). The most common gastrointestinal AEs reported in the patiromer group during this phase of the study were diarrhea (HF, 7%; non-HF, 0%) and nausea (HF, 7%; 0% non-HF), all mild or moderate. Cardiac disorders as a class were reported as AEs in 8% of HF and 7% of non-HF patients during

the treatment phase; all individual cardiac AEs occurred in 2 or fewer HF patients in either phase. One HF patient experienced worsening of HF in the treatment phase. In non-HF patients, left ventricular hypertrophy was reported in 6 (4%) patients and first-degree atrioventricular block was reported in 3 (2%) patients in the treatment phase; all other individual cardiac AEs occurred in 2 or fewer non-HF patients in either phase. Study drug discontinuation due to AEs occurred in 2 HF patients (1 [5%] taking placebo and 1 [4%] taking patiromer), and in none of the patients without HF.

Two patients with HF had at least 1 serious AE during the treatment phase. In 1 HF patient, the serious AE was atrial fibrillation leading to hospitalization. However, the patient had a prior medical history of atrial fibrillation and this serious event was deemed not related to patiromer, per the investigator. The other serious AEs occurring during the treatment phase, all of which occurred in the other HF patient, are listed in Supplementary Table 3B. One HF patient on placebo had a serious AE during the withdrawal phase (mesenteric vessel thrombosis leading to death). None of the serious AEs (in either phase) were considered related to patiromer by the investigator.

During the initial treatment phase and its follow-up period, hypokalemia (serum K^+ <3.5 mEq/L) occurred in 3% of patients with and without HF. These patients had serum K^+ in range of 3.2 to 3.4 mEq/L; hypokalemia was most often transient after patiromer dose adjustment. During the randomized withdrawal phase and its follow-up period, hypokalemia requiring withdrawal from the study (serum K^+ <3.8 mEq/L) occurred in 7% and 4% of patients with and

without HF taking patiromer and in none of the patients with HF and one (3%) patient without HF taking placebo.

The mean serum magnesium level remained within normal range throughout both phases of the trial in patients with and without HF. Small mean decreases in serum magnesium were observed at the end of the initial treatment phase in patients with HF (−0.20 mg/dL [−0.16 mEq/L]) and without HF (−0.16 mg/dL [−0.13 mEq/L]), with no apparent dose effect. At the end of the randomized withdrawal phase, a small mean increase from baseline was observed in serum magnesium in placebo patients with HF (+0.19 mEq/L) and without HF (+0.05 mEq/L). There was no significant change in serum magnesium levels in patiromer patients with and without HF during the randomized withdrawal phase. A serum magnesium level of <1.4 mg/dL was observed in 4 HF patients and 3 non-HF patients during the initial treatment phase. During the randomized withdrawal phase, no patient (with or without HF) had a serum magnesium level of <1.4 mg/dL. No patient (with or without HF) had serum magnesium levels <1.2 mg/dL during either phase of the study. Magnesium replacement therapy was prescribed in 9 patients (3 with HF and 6 patients without HF) taking patiromer during the initial treatment phase. No clinically relevant changes in renal function or in levels of serum calcium, fluoride, or other electrolytes (e.g., bicarbonate) were observed in either phase of the study. Two patients in the initial treatment phase (1 with HF and 1 without HF) and 1 patient without HF on patiromer in the randomized withdrawal phase had electrocardiographic changes consistent with hyperkalemia; none had changes consistent with hypokalemia. No clinically relevant changes in renal function were observed (Supplementary Table 4).

Discussion

The results of the present pre-specified analysis of the OPAL-HK trial show that patiromer reduced mean serum K^+ to within the normal range in patents with HF. Additionally, compared with placebo, patiromer reduced the percentage of patients with recurrent HK and importantly, there were no differences in patients with and without HF in regard to these effects of patiromer. Mean serum K^+ level was reduced from 5.6 to <5.0 mEq/L in patients with HF during the initial treatment phase of the study, and 76% of patients with HF achieved normokalemia. Conversely, in the randomized withdrawal phase only 8% of patients on patiromer developed recurrent hyperkalemia (when defined as serum K^+ ≥5.5 mEq/L) compared with 52% on placebo, allowing significantly more patients to remain on guideline-recommended RAASi. This has important implications for patients with HF since RAASi including MRAs have been shown to reduce mortality in patients with HFREF (1-6). Despite the proven efficacy of RAASi and their class 1 indication in guidelines for patients with HFREF, many clinicians have avoided their use, especially MRAs, because of the fear of inducing hyperkalemia (8,10). In those patients with HF in whom MRAs are initiated, they are often discontinued during the first several months due to an increase in serum K^+ or worsening renal function (9,19-21). While many clinicians consider a serum K^+ of ≥5.5 mEq/L as indicative of hyperkalemia and an increased risk for sudden cardiac death, increasing evidence indicates that in patients with HF and CKD a serum K^+ of >5.0 mEq/L is associated with an increase in cardiovascular risk (22). Recurrent hyperkalemia when

Comment [A8]: Editors: Please note we have corrected this error discovered upon re-review. We have also updated Figure 3 to reflect this correction.

defined by serum K^+ ≥5.1 mEq/L occurred in 95% of placebo patients with HF compared with 36% of patiromer patients with HF. The present analysis also suggests that hyperkalemia occurring in a patient with HF can be relatively easily controlled with patiromer as evidenced by the finding that all of the HF patients on patiromer were able to be maintained on their RAASi during the randomized withdrawal phase despite the need for patiromer dose adjustment to manage hyperkalemia in 11%. Importantly, the use of patiromer in patients with HF has the potential to allow titration of RAASi doses to target levels and to maintain these dose levels. Target doses of RAASi appear to be more effective than lower doses in patients with HF as evidenced by the results in the HEAAL study (23).

The tolerability and safety profile of patiromer in CKD patients both with and without HF in the present analysis supports the hypotheses that patiromer can be used to maintain the use of guideline-recommended RAASi. The proportion of patiromer patients discontinuing due to adverse effects was 7% while gastrointestinal intolerance, hypokalemia, and hypomagnesemia were easily managed. This study did not measure intracellular magnesium levels. In this study, no new-onset clinically significant arrhythmias were observed; therefore, it is unlikely that tissue magnesium levels were reduced to critically low levels.

The relatively good tolerability and safety profile of patiromer in the present study, both in patients with and without HF, is supported by the findings in the recent AMETHYST-DN study (24) in which patiromer was administered to patients with hyperkalemia, CKD, type 2 diabetes, hypertension, and receiving RAASi over a 1-year study period. In a study of patiromer

for the prevention of hyperkalemia (PEARL-HF) (25), normokalemia patients with HF with a history of discontinuation of a RAASi or beta adrenergic receptor due to hyperkalemia were randomized to patiromer or placebo and titrated to 50 mg/day of spironolactone. In that study, significantly fewer patients on patiromer developed hyperkalemia (serum K^+ >5.5 mEq/L) compared with patients on placebo (7% vs 25%, $P = 0.015$) (25). In the subgroup of patients with CKD (eGFR <60 mL/min/1.73m^2) in PEARL-HF, hyperkalemia developed in 7% of patients randomized to patiromer compared with a 39% of patients randomized to placebo ($P = 0.041$). While gastrointestinal adverse events occurred more frequently with patiromer than with placebo (21% vs 6%) they were mostly mild-to-moderate in severity, and similar proportions of patients in each group discontinued due to adverse events (25).

There are limitations to the study. No placebo or active control was used in the initial treatment phase of this study, since it was considered unethical to allow patients with hyperkalemia to remain untreated. Although the withdrawal phase was randomized, it was not blinded to the investigators. The sponsor provided treatment algorithms to minimize bias and to standardize interventions when hyperkalemia or hypokalemia occurred. However, it was possible that changes in treatment regimen implemented by the investigator in response to hyperkalemia or hypokalemia may have indicated treatment assignment to the patient. The higher proportion of patiromer patients still receiving RAASi at the end of the withdrawal phase may have been due partly to the treatment algorithm, which allowed investigators to increase the dose of patiromer at the first occurrence of hyperkalemia in the patiromer group. The estimates for mean change from baseline in serum K^+ during the initial treatment phase used only weekly postbaseline

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measurements (ie, 2 HF patients with postbaseline measurements only at day 3 were excluded from the analysis). Since day 3 is not included in the model, our limitations include an inability to estimate day 3 from the repeated measures model. Instead, day 3 was estimated separately using an analysis of variance model with the presence of type 2 diabetes included as a binary covariate and baseline serum potassium as a continuous covariate. In the withdrawal phase, the comparison of the treatment groups used rank of change carried forward to account for and include patients who discontinued study drug prior to week 4 because of hyper- or hypokalemia. Missing serum K^+ values of patients who discontinued study drug prior to week 4 for other reasons were imputed using multiple imputation. Patients were included in the HF subgroup based on a history of HF per the investigator's judgment, therefore inaccuracies in assessing the differences between the groups with and without HF may have occurred because no specific instructions for HF diagnosis were provided. During the study, a low proportion of patients received concomitant aldosterone antagonist therapy, potentially because these agents are contraindicated in patients with hyperkalemia or with reduced renal function (eGFR <30 mL/min/1.73 m^2) (26,27). While this may limit the conclusions that can be drawn regarding the effect of patiromer in CKD patients with HF receiving aldosterone antagonists, the PEARL-HF study previously demonstrated that patiromer prevented hyperkalemia in HF patients with normal serum potassium levels receiving spironolactone (25).

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In conclusion, the efficacy and safety profile of patiromer demonstrated in the present analysis and in the AMETHYST-DN and PEARL-HF studies (24,25) suggests that patiromer may have an important role in initiating and maintaining RAASi in patients with CKD and HF,

with the potential for consequent reduction in cardiovascular death in these high risk patients. Further adequately powered prospective randomized studies will be required to evaluate this hypothesis and to determine the cost-effectiveness of this strategy.

Funding

This work was supported by Relypsa, Inc.

Conflict of Interest

Dr. Pitt has received consulting fees from Pfizer, Inc., Bayer AG, Astra Zeneca plc, Stealth Biotherapeutics, Inc., Sarfez Pharmaceuticals, Inc., and Eli Lilly and Company; and has received consulting fees and holds stock from Relypsa, Inc., Aura Sense Therapeutics, Tricida, Inc., scPharmaceuticals, Inc., and DaVinci BioSciences, LLC; and is on the Data Safety Monitoring Board for Novartis AG, Johnson & Johnson, and Oxygen Biotherapeutics. Dr. Bakris has received consulting fees from Relypsa, AbbVie, Inc., Daiichi-Sankyo LTD, Janssen Pharmaceuticals, Novartis, Bayer, and Medtronic plc; and grants from Takeda Pharmaceutical Company LT. Dr. Weir has received consulting fees from Relypsa and ZS Pharma, Inc. Dr. Bushinsky has received consulting fees from Relypsa. Drs. Berman, Mayo, Garza, and Stasiv are employees of Relypsa. Ms. Christ-Schmidt is an employee of Statistics Collaborative.

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Comment [A12]: This manuscript has now been published

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Figure Legends

Figure 1: Serum Potassium Levels over Time during the Treatment Phase

Figure 2: Effect of Patiromer on Serum K^+ in Patients With and Without Heart Failure During the Randomized Withdrawal Phase

Figure 3: Time to First Recurrence of Hyperkalemia in Patients With Heart Failure During the Randomized Withdrawal Phase

Figure 4: Proportion of Patients Discontinuing RAAS inhibitor Therapy during the Randomized Withdrawal Phase

Tables

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Heart Failure N=102	No Heart Failure N=141
Male, n (%)	56 (55%)	84 (60%)
Age (yr), mean (SD)	67.4 (8.6)	61.9 (11.1)
White, n (%)	102 (100%)	137 (97%)
eGFR (mL/min/1.73m^2), n (%)		
60 to ≤90 [Stage 2]	9 (9%)	13 (9%)
45 to <60 [Stage 3A]	20 (20%)	29 (21%)
30 to <45 [Stage 3B]	28 (27%)	35 (25%)
< 30 [Stage 4/5]	45 (44%)	64 (45%)
Serum K^+ (mEq/L), mean (SD)	5.6 (0.6)	5.5 (0.4)
Type 2 diabetes, n (%)	55 (54%)	84 (60%)
Time since T2DM diagnosis (yr), mean (SD)	12.0 (9.9)	14.0 (8.9)
NYHA HF Class, n (%)		

I	19 (19%)	NA
II	66 (65%)	NA
III	17 (17%)	NA
Myocardial infarction, n (%)	33 (32%)	27 (19%)
Hypertension, n (%)	97 (95%)	139 (99%)
RAASi medication, n (%)	102 (100%)	141 (100%)
ACE inhibitor	70 (69%)	100 (71%)
ARB	37 (36%)	55 (39%)
Aldosterone antagonist	20 (20%)	2 (1%)
Renin inhibitor	2 (2%)	0
Dual RAASi blockade*, n (%)	25 (25%)	16 (11%)
On maximal RAASi dose†, n (%)	42 (41%)	64 (45%)
Other concomitant medication for HF		
Beta blocker	60 (59%)	68 (48%)
Thiazide	27 (26%)	43 (30%)
Loop	44 (43%)	33 (23%)

*Any combination of two or more of the following: ACE inhibitor, ARB, aldosterone antagonist, renin inhibitor.

†As judged of the investigator in accordance with local standards of care.

Table 2. Adverse Events Occurring in at Least 3% of Patients with and without HF during the Initial Treatment Phase and through the Safety Follow-up Period for that Phase*

	Heart Failure N = 102	No Heart Failure N = 141
	No. of Patients (%)	
≥ 1 Adverse event	42 (41%)	72 (51%)
Constipation	11 (11%)	15 (11%)
Diarrhea	4 (4%)	4 (3%)
Nausea	1 (1%)	7 (5%)
Hypomagnesemia	3 (3%)	5 (4%)
Anemia	4 (4%)	3 (2%)
Chronic renal failure	1 (1%)	6 (4%)
Hyperkalemia	3 (3%)	3 (2%)
Left ventricular hypertrophy	0	6 (4%)
Dyslipidemia	0	4 (3%)
≥ 1 Serious adverse event	2 (2%)	1 (1%)

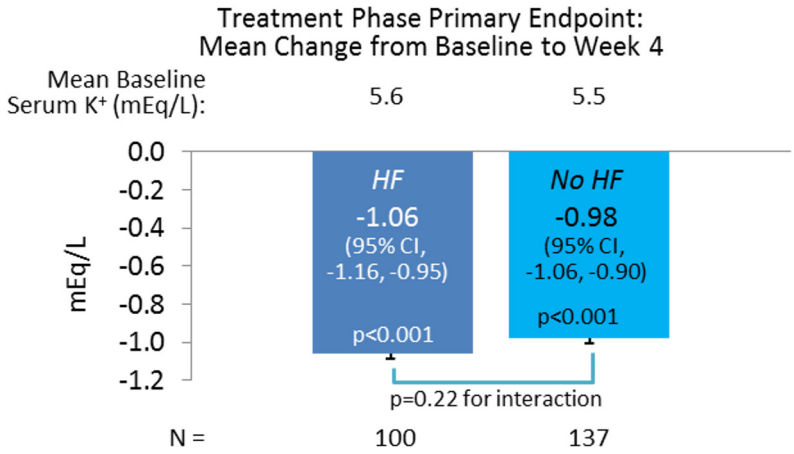
*The safety follow-up period was 1 to 2 weeks after discontinuation of the study drug in the initial treatment phase. Supplementary Table 3A shows adverse events that occurred in at least 2 patients with or without HF in each dose group and Supplementary Table 3B shows all serious adverse events.

Table 3. Adverse Events Occurring in at Least 2 Patients in the Patiromer Group Regardless of HF diagnosis during the Randomized Withdrawal Phase and through the Safety Follow-up Period for That Phase*

	Heart Failure		**No Heart Failure**	
	Placebo (N = 22)	**Patiromer (N = 27)**	**Placebo (N = 30)**	**Patiromer (N = 28)**
	No. of Patients (%)		*No. of Patients (%)*	
≥1 Adverse event	14 (64%)	15 (56%)	12 (40%)	11 (39%)
Headache	3 (14%)	1 (4%)	1 (3%)	1 (4%)
Supraventricular extrasystoles	1 (5%)	1 (4%)	0	1 (4%)
Diarrhea	0	2 (7%)	0	0
Nausea	0	2 (7%)	0	0
Constipation	0	1 (4%)	0	1 (4%)
≥1 Serious adverse event	1† (5%)	0	0	0

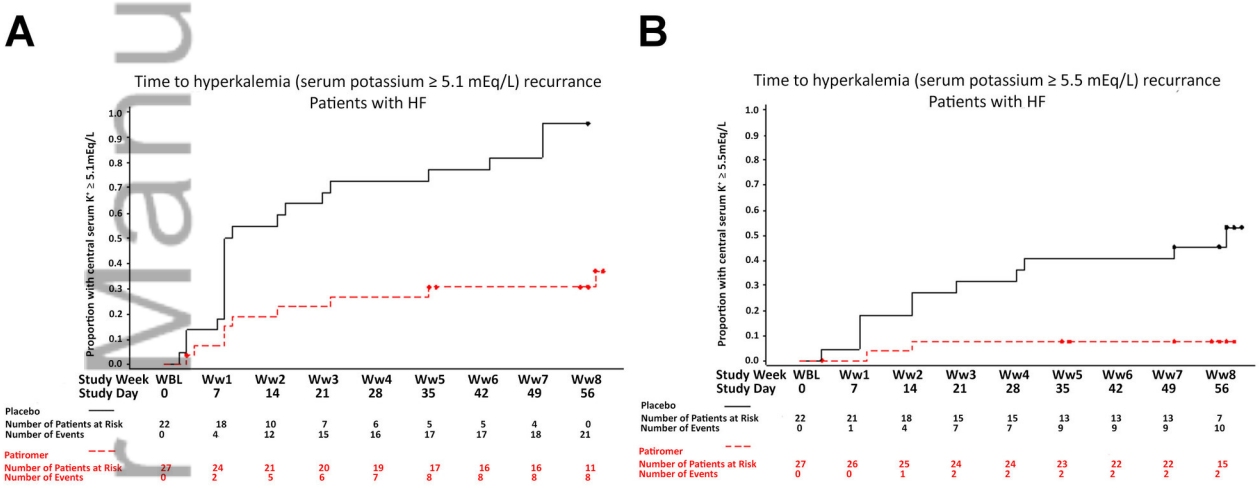
*The safety follow-up period was 1 to 2 weeks after discontinuations of the study drug.

†Mesenteric vessel thrombosis leading to death occurred in one patient.

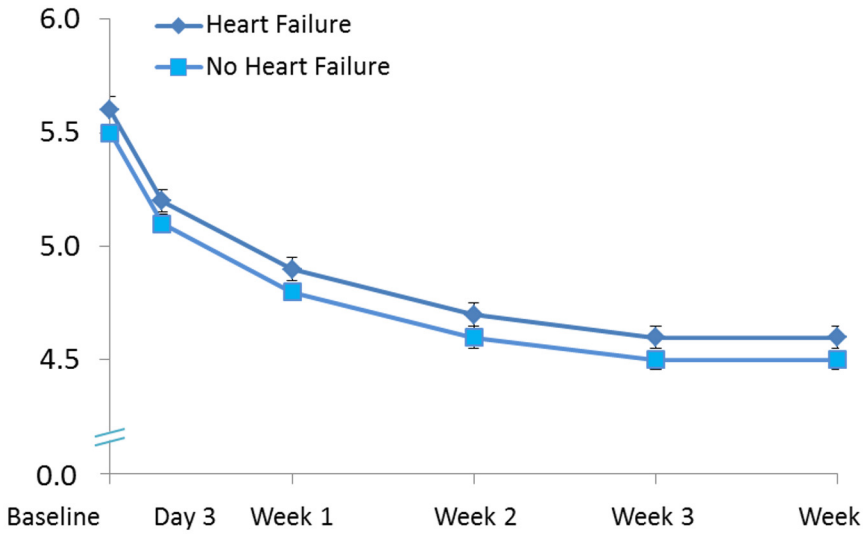


Secondary Endpoint: 76% and 75% of patients with and without HF, respectively, had serum K^+ 3.8 to < 5.1 mEq/L at Week 4

15-377 fig 1A.jpg



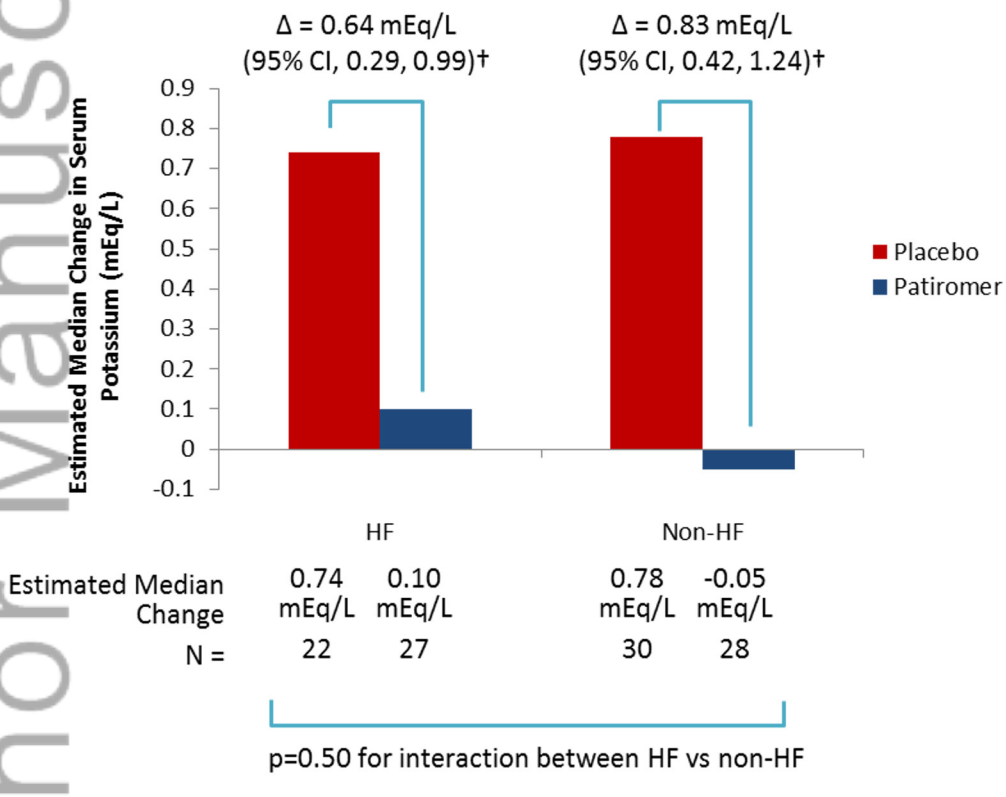
15-377 fig 3.jpg



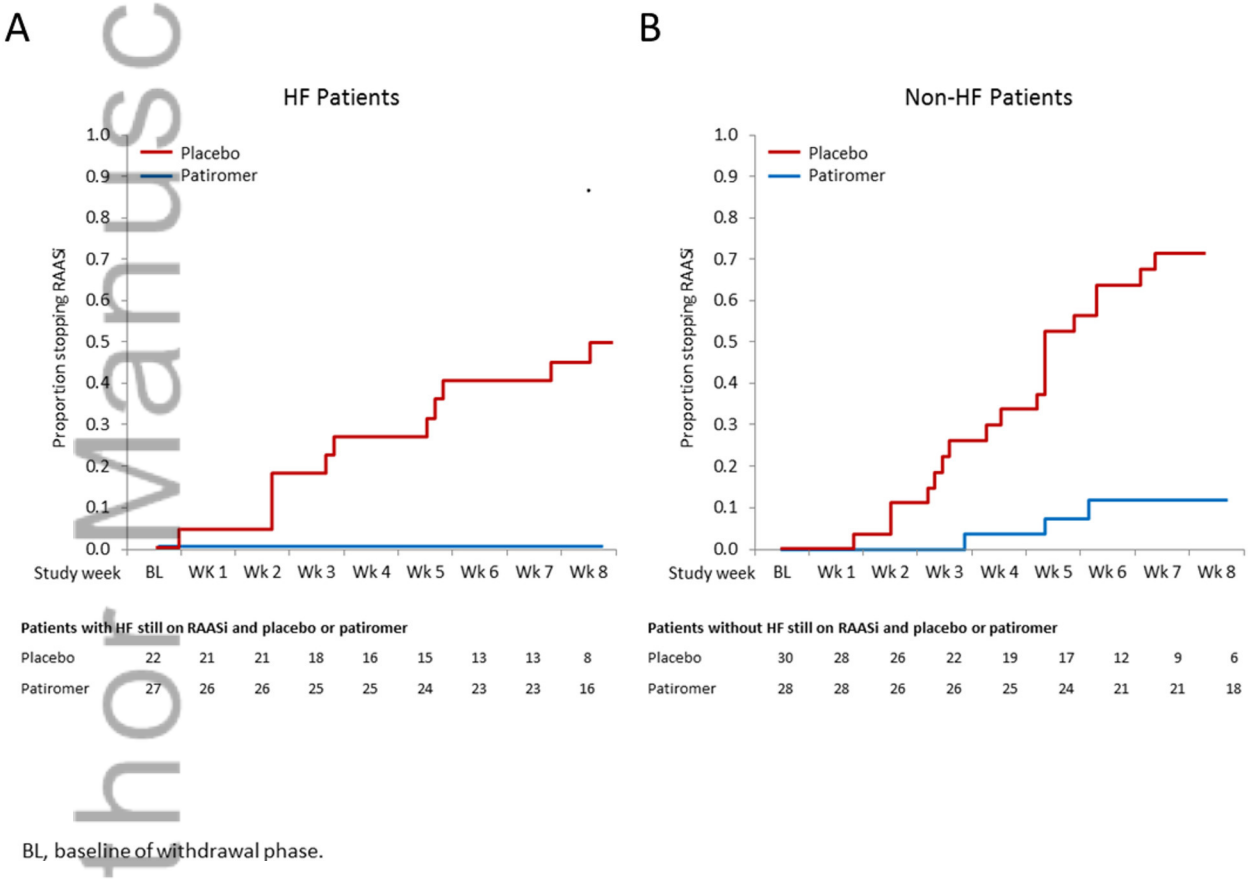
Mean (±SE) Serum K⁺ Change from Baseline (mEq/L)

Heart Failure	-0.5±0.05	-0.8±0.05	-0.9±0.05	-1.1±0.05	-1.1±0.05
No Heart Failure	-0.5±0.04	-0.7±0.04	-0.9±0.04	-1.0±0.04	-1.0±0.04

15-377 Figure 1B.jpg



15-377 Figure 2.jpg



BL, baseline of withdrawal phase.

15-377 Figure 4.jpg