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Patiromer-Facilitated Renin-Angiotensin-Aldosterone System Inhibitor Utilization in Patients with Heart Failure with or without Comorbid Chronic Kidney Disease: Subgroup Analysis of DIAMOND Randomized Trial

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Keywords
DIAMOND trial · Chronic kidney disease · Mineralocorticoid receptor antagonist · Adverse effects · Adverse events · Hyperkalemia · Renin-angiotensin-aldosterone system inhibitors (RAASis)

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Abstract

Introduction: Renin-angiotensin-aldosterone system inhibitor (RAASi; including mineralocorticoid receptor antagonists [MRAs]) benefits are greatest in patients with heart failure with reduced ejection fraction (HFrEF) and chronic kidney disease (CKD); however, the risk of hyperkalemia (HK) is high. ***Methods:*** The DIAMOND trial (NCT03888066) assessed the ability of patiromer to control serum potassium (sK^+) in patients with HFrEF with/without CKD. Prior to randomization (double-blind withdrawal, 1:1), patients on patiromer had to achieve ≥50% recommended doses of RAASi and 50 mg/day of MRA with normokalemia during a run-in period. The present analysis assessed the effect of baseline estimated glomerular filtration rate (eGFR) in subgroups of ≥/<60, ≥/<45 (prespecified), and ≥/<30 mL/min/1.73 m^2 (added post hoc). ***Results:*** In total, 81.3, 78.9, and 81.1% of patients with eGFR <60, <45, and <30 mL/min/1.73 m^2 at screening achieved RAASi/MRA targets. A greater efficacy of patiromer versus placebo to control sK^+ in patients with more advanced CKD was reported (p-$_{interaction} \leq 0.027$ for all eGFR subgroups). Greater effects on secondary endpoints were observed with patiromer versus placebo in patients with eGFR <60 and <45 mL/min/1.73 m^2. Adverse effects were similar between patiromer and placebo across subgroups. ***Conclusion:*** Patiromer enabled use of RAASi, controlled sK^+, and minimized HK risk in patients with HFrEF, with greater effect sizes for most endpoints noted in patient subgroups with lower eGFR. Patiromer was well tolerated by patients in all eGFR subgroups.

Plain Language Summary

Patients with chronic kidney disease (CKD) can develop high potassium (hyperkalemia) levels in their blood that can lead to complications such as heart issues. Renin-angiotensin-aldosterone system inhibitors (RAASis) are used as treatment for heart failure and CKD, but can also cause hyperkalemia, so are underutilized and used at lower than optimal doses. Patiromer is a potassium binder which was investigated in the DIAMOND trial to identify if it could reduce hyperkalemia in patients receiving RAASis. Lower kidney function (eGFR) has been associated with a greater likelihood of stopping treatment with RAASis; therefore, this analysis assessed the effect of patiromer on patients with varying eGFR levels. Patiromer enabled use of effective RAASi doses, controlled the serum potassium levels and minimized hyperkalemia in patients with heart failure and CKD.

Introduction

An estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 is reported in approximately half of patients with heart failure (HF) [1], owing partially to a bidirectional detrimental effect of chronic kidney disease (CKD) on HF and vice versa, as well as multiple shared risk factors and pathophysiological mechanisms [2]. Renin-angiotensin-aldosterone system inhibitors (RAASis; including mineralocorticoid receptor antagonists [MRAs]) are recommended by the 2020/2021 Kidney Disease Improving Outcomes (KDIGO) guidelines for the treatment of patients with CKD (with or without diabetes) at the highest tolerated approved dose [3, 4].

RAASi therapy in patients with heart failure with reduced ejection fraction (HFrEF) has been reported to be underutilized and underdosed, especially in patients with comorbid/severe CKD [5, 6]. Analysis of the Swedish Heart Failure Registry indicates that patients with HF and CKD are less likely to be prescribed and adhere to evidence-based therapies such as RAASi [7]. In an HFrEF registry, only 25% of patients were receiving target doses of MRA therapy, while <15% received target doses of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), or angiotensin receptor neprilysin inhibitors (ARNis) [5]. Lower eGFR has been associated with a greater likelihood of discontinuing RAASi therapy and a reduced likelihood of receiving an MRA [8, 9]. The underuse of RAASi treatment is evident in patients with the greatest clinical need [5, 7].

The risk of hyperkalemia (HK) increases as eGFR declines, although the absolute benefits of MRA and RAASi may be greatest in patients with concomitant comorbid HF and CKD. The 2020 KDIGO guidelines recommend that reduction or discontinuation of RAASi therapy should be a last resort in patients with HK and measures including low K+ diet, diuretics, and potassium binders should be considered first to maintain RAASi therapy. Unfortunately, diuretics are less effective as eGFR declines and adverse events (AEs), such as orthostatic hypotension and worsening kidney function, can occur [10–13].

Patiromer is a non-absorbed potassium binder that uses sodium-free exchange (which may be of value in patients with CKD and comorbid HF) [14–16]. The DIAMOND trial investigated patiromer for the management of HK in participants receiving RAASi medications for the treatment of HF [17]. This subgroup analysis examined the effect of CKD stages in terms of baseline eGFR on outcomes in the

DIAMOND patient population (eGFR subgroups ≥/<60 and ≥/<45 mL/min/1.73 m^2 had been prespecified, and ≥/<30 mL/min/1.73 m^2 were added post hoc).

Methods

DIAMOND Trial Design and Patients

The rationale and design of the DIAMOND trial (NCT03888066) has been previously published [18]. Briefly, DIAMOND was a prospective, Phase 3, international, multicenter, double-blind, randomized withdrawal, placebo-controlled trial. An independent Ethics Committee at each center approved the trial, which was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice, and local and national guidelines. Written informed consent was obtained from all participants prior to any trial-related procedures.

Participants included in DIAMOND had HFrEF (left ventricular ejection fraction ≤40%) with either current HK (defined as serum potassiun [sK^+] >5.0 mEq/L) or previous RAASi-related HK (within 1 year) at screening. In the initial 12-week, single-blind, run-in phase, all patients received patiromer (titrated up to a maximum of three packs/day; 8.4 g/pack) and were optimized on RAASi therapy, including MRA (spironolactone or eplerenone, titrated to 50 mg/day), and ≥50% of recommended doses of other RAASi drugs (as indicated by practice guidelines and using clinical judgement). Patients with successful RAASi optimization and sK^+ values between 4.0 and 5.0 mEq/L achieved within 12 weeks during the run-in phase were randomized in a 1:1 ratio to receive either continued patiromer (dose maintained or adjusted at investigator discretion) or to withdraw from patiromer and receive placebo in the subsequent double-blind withdrawal phase. During the double-blind treatment phase RAASi medication could also be adjusted according to investigator discretion.

The primary endpoint was the mean difference in sK^+ levels from baseline (immediately prior to randomization) until trial end. Secondary hierarchical outcomes included (1) time-to-first event of HK >5.5 mEq/L; (2) time to discontinuation or reduction of target MRA dose for at least 14 days or less if at the end of study (i.e., lack of durable enablement of MRA at target dose); (3) investigator-reported AEs of HK (first and recurrent); (4) win ratio for HK-related morbidity-adjusted outcomes with the following sequence: time to cardiovascular death, cardiovascular hospitalization, total hyperkalemic events >6.5 mEq/L, >6.0 to 6.5 mEq/L, and >5.0 to 6.0 mEq/L; and (5) win ratio of novel RAASi use score (range 0–8), based on two components: 1/0 to 2 points for all-cause death, occurrence of a cardiovascular hospitalization, or neither; 2/0 to 2 points for each HF medication use and dose of (i) ACEi/ARB/ARNi, (ii) an MRA, and (iii) a beta-blocker (as described previously [17]).

Baseline eGFR Subgroup Analysis

The present prespecified subgroup analysis (in patients eGFR ≥30 mL/min/1.73 m^2 at screening) stratified patients into subgroups based on baseline eGFR, corresponding with CKD stage. Outcomes in patients with eGFR ≥60 mL/min/1.73 m^2 (CKD stage 1–2) were compared with those in patients with eGFR <60 mL/min/1.73 m^2 (CKD stage ≥3a – prespecified analysis), and outcomes in patients with eGFR ≥45 mL/min/1.73 m^2 (CKD stage ≤3a) were compared with those in patients with eGFR <45 mL/min/1.73 m^2 (CKD stage ≥3b – prespecified analysis). Although patients with eGFR <30 mL/min/1.73 m^2 (CKD stage >4) at screening were excluded from the DIAMOND trial because they were unable to be prescribed spironolactone [17, 19], patients could have eGFR <30 mL/min/1.73 m^2 at baseline and then a further post hoc, exploratory subgroup analysis with patients stratified by eGFR ≥30 versus <30 mL/min/1.73 m^2 at baseline was conducted.

Statistical Analyses

For the primary outcome, the least adjusted change from baseline (95% confidence intervals [CIs]) was reported for each treatment arm within each eGFR subgroup and the estimated treatment difference (95% CI) between placebo and patiromer arms was calculated using a model for repeated measures with adjustment for the following covariates: treatment, visit, geographic region, sex, diabetes, baseline eGFR (continuous), and baseline sK^+; p values for the interaction between eGFR subgroup and treatment effect were calculated for each subgroup pair (eGFR ≥60 vs. <60 mL/min/1.73 m^2; ≥45 vs. <45 mL/min/1.73 m^2; and ≥30 vs. <30 mL/min/1.73 m^2).

Key secondary outcomes were analyzed in a hierarchical manner in the order outlined above. For each key secondary outcome, estimates by treatment arm within each eGFR subgroup were calculated along with 95% CIs for treatment differences; p values for the association between eGFR subgroup and treatment outcomes were calculated for each subgroup pair. Analyses (hazard ratio

Table 1. Baseline characteristics by baseline eGFR subgroup

Characteristic	eGFR ≥60 mL/min/1.73 m^2	eGFR <60 mL/min/1.73 m^2
	N = 464	*N* = 414
Age, mean (SD), years	63.6 (9.7)	70.5 (9.0)
Women, *n* (%)	114 (24.6)	124 (30.0)
Systolic blood pressure, mean (SD), mm Hg	124.3 (10.7)	125.2 (14.1)
Current left ventricular ejection fraction, mean (SD), %	33.4 (6.1)	33.6 (5.2)
NT-proBNP at screening, pg/mL		
n (missing)	464 (0)	412 (2)
Mean (SD)	2,152.2 (4,167.7)	2,644.5 (3,785.0)
Median (Q1, Q3)	1,197.7 (649.2, 2,328.0)	1,430.9 (759.7, 3,083.9)
NYHA class, *n* (%)		
n (missing)	464 (0)	412 (2)
I	6 (1.3)	8 (1.9)
II	225 (48.5)	247 (60.0)
III	230 (49.6)	156 (37.9)
IV	3 (0.6)	1 (0.2)
History of diabetes mellitus, *n* (%)	160 (34.5)	196 (47.3)
Local laboratory sK^+, mEq/L		
n (missing)	454 (10)	396 (18)
Mean (SD)	4.6 (0.3)	4.7 (0.3)
Central laboratory eGFR, mL/min/1.73 m^2		
n (missing)	455 (9)	401 (13)
Mean (SD)	80.2 (14.0)	43.6 (10.2)
ACR, mg/g, *n* (%)		
n (missing)	443 (21)	404 (10)
≥30 mg/g		
Run-in phase week 1	1 (0.2)	15 (3.7)
Treatment phase day 3	2 (0.5)	13 (3.3)
≥300 mg/g		
Run-in phase week 1	0 (0.0)	0 (0.0)
Treatment phase day 3	0 (0.0)	0 (0.0)
At 100% recommended dose, *n* (%)		
ACEi/ARB/ARNi at screening	116 (25.0)	115 (27.8)
ACEi/ARB/ARNi at baseline	304 (65.5)	256 (61.8)
MRA at screening	102 (22.0)	107 (25.8)
MRA at baseline	460 (99.1)	407 (98.3)

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Table 1 (continued)

Characteristic	eGFR ≥60 mL/min/1.73 m^2	eGFR <60 mL/min/1.73 m^2
	N = 464	*N* = 414
At ≥50% recommended dose, *n* (%)		
ACEi/ARB/ARNi at screening	300 (64.7)	289 (69.8)
ACEi/ARB/ARNi at baseline	458 (98.7)	409 (98.8)
MRA at screening	271 (58.4)	236 (57.0)
MRA at baseline	463 (99.8)	413 (99.8)
Number of patiromer sachets at baseline, *n* (%)		
0	0	0
1	329 (70.9)	237 (57.2)
2	103 (22.2)	113 (27.3)
3	32 (6.9)	64 (15.5)
	eGFR ≥45 mL/min/1.73 m^2	eGFR <45 mL/min/1.73 m^2
	N = 668	*N* = 210
Age, mean (SD), years	65.4 (9.9)	71.6 (8.8)
Women, *n* (%)	167 (25.0)	71 (33.8)
Systolic blood pressure, mean (SD), mm Hg	124.4 (11.2)	125.9 (15.7)
Current left ventricular ejection fraction, mean (SD), %	33.4 (5.9)	33.8 (5.5)
NT-proBNP at screening, pg/mL		
n (missing)	668 (0)	208 (2)
Mean (SD)	2,216.8 (4,126.8)	2,919.7 (3,506.7)
Median (Q1, Q3)	1,251.3 (654.2, 2,378.4)	1,594.1 (829.2, 3,675.4)
NYHA class, *n* (%)		
n (missing)	668 (0)	208 (2)
I	9 (1.3)	5 (2.4)
II	339 (50.7)	133 (63.9)
III	316 (47.3)	70 (33.7)
IV	4 (0.6)	0 (0.0)
History of diabetes mellitus, *n* (%)	249 (37.3)	107 (51.0)
Local laboratory sK^+, mEq/L		
n (missing)	649 (19)	201 (9)
Mean (SD)	4.6 (0.3)	4.6 (0.3)
Central laboratory eGFR, mL/min/1.73 m^2		
n (missing)	654 (14)	202 (8)
Mean (SD)	71.6 (17.5)	35.2 (6.8)
ACR, mg/g, *n* (%)		
n (missing)	640 (28)	207 (3)

Table 1 (continued)

	eGFR ≥45 mL/min/1.73 m^2	eGFR <45 mL/min/1.73 m^2
	N = 668	*N* = 210
≥30 mg/g		
Run-in phase week 1	3 (0.5)	13 (6.3)
Treatment phase day 3	6 (0.9)	9 (4.5)
≥300 mg/g		
Run-in phase week 1	0 (0.0)	0 (0.0)
Treatment phase day 3	0 (0.0)	0 (0.0)
At 100% recommended dose, *n* (%)		
ACEi/ARB/ARNi at screening	170 (25.4)	61 (29.0)
ACEi/ARB/ARNi at baseline	436 (65.3)	124 (59.0)
MRA at screening	164 (24.6)	45 (21.4)
MRA at baseline	659 (98.7)	208 (99.0)
At ≥50% recommended dose, *n* (%)		
ACEi/ARB/ARNi at screening	442 (66.2)	147 (70.0)
ACEi/ARB/ARNi at baseline	662 (99.1)	205 (97.6)
MRA at screening	403 (60.3)	104 (49.5)
MRA at baseline	666 (99.7)	210 (100.0)
Number of patiromer sachets at baseline, *n* (%)		
0	0	0
1	465 (69.6)	101 (48.1)
2	148 (22.2)	68 (32.4)
3	55 (8.2)	41 (19.5)
	eGFR ≥30 mL/min/1.73 m^2	eGFR <30 mL/min/1.73 m^2
	N = 836	*N* = 42
Age, mean (SD), years	66.7 (9.9)	70.5 (10.2)
Women, *n* (%)	223 (26.7)	15 (35.7)
Systolic blood pressure, mean (SD), mm Hg	124.5 (12.4)	128.7 (12.2)
Current left ventricular ejection fraction, mean (SD), %	33.4 (5.8)	35.1 (3.9)
NT-proBNP at screening, pg/mL		
n (missing)	835 (1)	41 (1)
Mean (SD)	2,300.2 (3,921.9)	4,085.2 (5,075.9)
Median (Q1, Q3)	1,283.9 (666.1, 2,572.0)	2,805.0 (1,169.5, 4,453.4)
NYHA class, *n* (%)		
n (missing)	834 (2)	42 (0)
I	11 (1.3)	3 (7.1)
II	443 (53.1)	29 (69.0)
III	376 (45.1)	10 (23.8)
IV	4 (0.5)	0 (0.0)

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Table 1 (continued)

	eGFR ≥30 mL/min/1.73 m^2	eGFR <30 mL/min/1.73 m^2
	N = 836	*N* = 42
History of diabetes mellitus, *n* (%)	340 (40.7)	16 (38.1)
Local laboratory sK^+, mEq/L		
n (missing)	808 (28)	42 (0)
Mean (SD)	4.6 (0.3)	4.7 (0.3)
Central laboratory eGFR (mL/min/1.73 m^2)		
n (missing)	815 (21)	41 (1)
Mean (SD)	65.0 (20.7)	24.4 (3.3)
ACR, mg/g, *n* (%)		
n (missing)	806 (30)	41 (1)
≥30 mg/g		
Run-in phase week 1	12 (1.5)	4 (9.8)
Treatment phase day 3	14 (1.8)	1 (2.4)
≥300 mg/g		
Run-in phase week 1	0 (0.0)	0 (0.0)
Treatment phase day 3	0 (0.0)	0 (0.0)
At 100% recommended dose, *n* (%)		
ACEi/ARB/ARNi at screening	218 (26.1)	13 (31.0)
ACEi/ARB/ARNi at baseline	535 (64.0)	25 (59.5)
MRA at screening	201 (24.0)	8 (19.0)
MRA at baseline	825 (98.7)	42 (100.0)
At ≥50% recommended dose, *n* (%)		
ACEi/ARB/ARNi at screening	558 (66.7)	31 (73.8)
ACEi/ARB/ARNi at baseline	825 (98.7)	42 (100.0)
MRA at screening	485 (58.0)	22 (52.4)
MRA at baseline	834 (99.8)	42 (100.0)
Number of patiromer sachets at baseline, *n* (%)		
0	0	0
1	551 (65.9)	15 (35.7)
2	198 (23.7)	18 (42.9)
3	87 (10.4)	9 (21.4)

All parameters are at baseline and data are available for all patients unless otherwise stated. Percentages are based on the number of non-missing observations. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin creatine ratio; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitors; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quarter; SD, standard deviation.

Baseline eGFR subgroups	Adjusted mean change from baseline (95% CI)		Difference in adjusted mean change from baseline (95% CI)	*P* value for interaction
	Patiromer (N=439)	Placebo (N=439)		
≥60 mL/min/1.73 m² (n1=227;n2=237)[a]	0.05 (–0.01; 0.10)	0.12 (0.07; 0.17)	–0.07 (–0.11; –0.03)	0.027
<60 mL/min/1.73 m² (n1=212;n2=202)[a]	0.002 (–0.05; 0.06)	0.14 (0.09; 0.19)	–0.14 (–0.18; –0.09)	
≥45 mL/min/1.73 m² (n1=321;n2=347)[a]	0.02 (–0.03; 0.06)	0.09 (0.05; 0.13)	–0.08 (–0.11; –0.04)	0.003
<45 mL/min/1.73 m² (n1=118;n2=92)[a]	0.06 (–0.02; 0.14)	0.25 (0.17; 0.33)	–0.19 (–0.26; –0.12)	
≥30 mL/min/1.73 m² (n1=409;n2=427)[b]	–0.03 (–0.06; 0.01)	0.08 (0.04; 0.11)	–0.10 (–0.14; –0.07)	0.027
<30 mL/min/1.73 m² (n1=30;n2=12)[b]	–0.05 (–0.18; 0.09)	0.22 (0.06; 0.38)	–0.27 (–0.42; –0.12)	
Overall	0.03 (–0.01; 0.07)	0.13 (0.09; 0.16)	–0.10 (–0.13; –0.07)	

Fig. 1. Primary outcome: adjusted mean changes in sK^+ level (mEq/L) from baseline to end of study. Estimates are from analysis based on model of repeated measures (MMRM). [a]For the eGFR ≥/<60 and ≥/<45 mL/min/1.73 m^2 subgroups, the error terms assume to follow multivariate normal distribution with unstructured covariance. Model: change = treatment + geographic region + sex + baseline T2DM status + visit + baseline K^+ value + baseline eGFR. Interaction model: change = treatment + geographic region + sex + baseline T2DM status + visit + baseline K^+ value + baseline eGFR + baseline eGFR subgroup + treatment and baseline eGFR subgroup interaction. Regions defined as region A (USA and Canada), region B (Mexico, Argentina, Brazil), region C (France, Germany, Italy, Netherlands, Spain, UK, Israel, Belgium), region D (Bulgaria, Czech Republic, Hungary, Poland, Russia, Serbia, Ukraine, Georgia). [b]For the eGFR ≥/<30 mL/min/1.73 m^2 subgroup, the error terms assume to follow multivariate normal distribution with compound symmetry covariance. Model: change = treatment + geographic region (USA, non-USA) + sex + baseline T2DM status + visit + baseline K^+ value + baseline eGFR. Interaction model: change = treatment + geographic region (USA, non-USA) + sex + baseline T2DM status + visit + baseline K^+ value + baseline eGFR + baseline eGFR subgroup + treatment and baseline eGFR subgroup interaction. CI, confidence interval; eGFR, estimated glomerular filtration rate; K^+, potassium; n1, number of patients in the patiromer group; n2, number of patients in the placebo group; sK^+, serum potassium; T2DM, type 2 diabetes mellitus.

and *p* value) were carried out using a Cox proportional regression model adjusted for treatment, geographic region, sex, diabetes, baseline sK^+, and baseline eGFR for time-to-first event endpoints; a negative binomial regression model (event rate with the logarithm of the individual follow-up time as offset) for investigator-reported HK AEs endpoints adjusted for treatment, geographic region, sex, diabetes, baseline sK^+, and baseline eGFR, and an unmatched win-ratio approach for HK-related outcomes (adjusted for morbid events) and comprehensive RAASi use score. For all analyses, SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA; 2000–2004) was used. Outcomes originally planned to be assessed at the end-of-study visit were instead assessed using the last available data on or before June 24, 2021 (study closure announced) with the exception of safety outcomes, for which all data are reported (no cutoff date was applied). All results should be interpreted descriptively. Event-driven endpoints were also assessed post hoc to determine the absolute risk reduction (ARR) of patiromer versus placebo and number needed to treat (NNT).

Results

RAASi Optimization during Run-in Phase

In total, 1,195 patients entered and 1,038 completed the run-in phase of the DIAMOND trial; of these, 878 (85%) patients were able to achieve target doses of RAASi, including MRA, with normokalemia while on patiromer. These 878 patients were randomized in the withdrawal double-blind treatment phase and 414, 210, and 42 patients had an eGFR at randomization of <60, <45, and <30 mL/min/1.73 m^2, respectively.

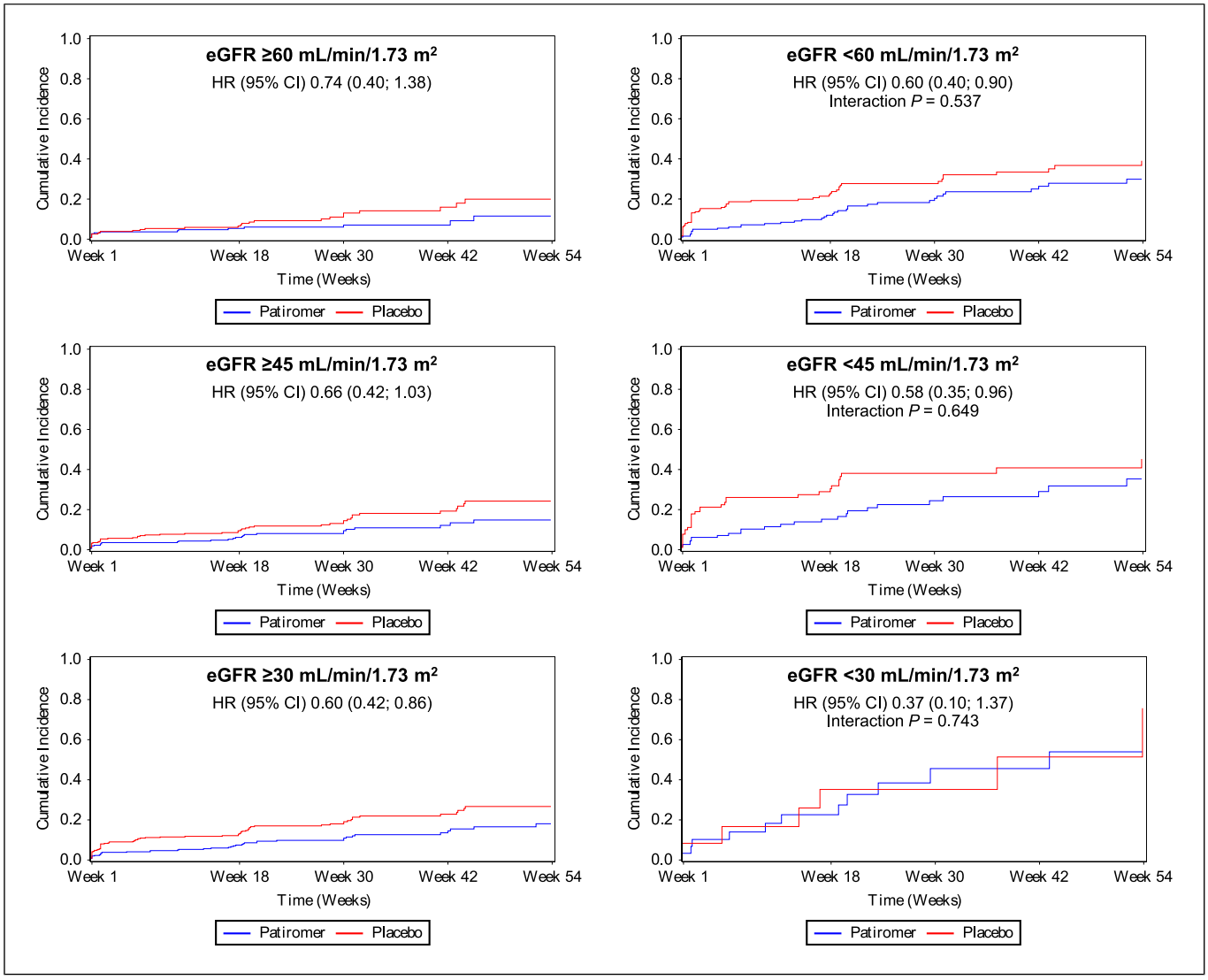

Fig. 2. Time-to-first event of HK of sK^+ >5.5 mEq/L by baseline eGFR subgroup during the randomized double-blind treatment phase, cumulative incidence function – FAS (n = 878). Aalen-Johansen estimators of the cumulative incidence function with death as a competing event. Only data up to Week 54 are displayed. Data cutoff at June 24, 2021. CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HR, hazard ratio; sK^+, serum potassium.

At screening, approximately 70% of patients were not receiving 100% recommended dose of ACEi/ARB/ARNi (72.2, 71.0, and 69.0% with respective baseline eGFRs of <60, <45, and <30 mL/min/1.73 m^2) and approximately 30% were not on ≥50% recommended doses of ACEi/ARB/ARNi (30.2, 30, and 26.2%, respectively). In addition, the majority of patients were not on 100% recommended dose of MRAs (74.2, 78.6, and 81.0%, respectively). A total of 62.3, 54.8, and 54.8%, respectively, of patients were receiving MRAs. After the run-in phase, the proportion of patients on 100% recommended dose of ACEi/ARB/ARNi increased to approximately two-thirds (61.8, 59.0, and 59.5% with respective baseline eGFRs of <60, <45, and <30 mL/min/1.73 m^2), and the majority of patients were on ≥50% recommended doses of ACEi/ARB/ARNi (98.8, 97.6, and 100%, respectively) and 100% recommended dose of MRAs (98.3, 99.0, and 100%, respectively) (Table 1).

Baseline Characteristics by eGFR Subgroup

For each subgroup pairing, the mean age, proportion of women, median systolic blood pressure, and frequency of diabetes at baseline were greater in the lower than higher

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Table 2. Number needed to treat and absolute risk reduction by eGFR subgroup for each of the event-driven endpoints

	eGFR ≥60 mL/min/1.73 m^2 (*N* = 464)		eGFR ≥45 mL/min/1.73 m^2 (*N* = 668)		eGFR ≥30 mL/min/1.73 m^2 (*N* = 836)		eGFR <60 mL/min/1.73 m^2 (*N* = 414)		eGFR <45 mL/min/1.73 m^2 (*N* = 210)		eGFR <30 mL/min/1.73 m^2 (*N* = 42)	
	patiromer	placebo	patiromer	placebo	patiromer	placebo	patiromer	placebo	Patiromer	Placebo	Patiromer	Placebo
Time to sK^+ >5.5, %[a]	11.5	20.0	14.8	24.3	18.1	26.7	29.9	39.1	35.3	45.2	53.9	75.7
ARR[b], %	8.4		9.4		8.6		9.2		9.9		21.8	
NNT	12		11		12		11		10		5	
MRA reduction below target dose, %[a]	10.7	17.1	17.8	19.9	18.2	25.9	26.1	35.7	22.3	47.0	27.8	25.0
ARR[b], %	6.4		2.1		7.7		9.6		24.7		−2.8	
NNT	16		48		13		10		4		–	
Patients ≥1 HK event, %	27.3	43.5	29.3	42.9	30.6	44.3	35.4	47.0	36.4	53.3	40.0	75.0
ARR[c], %	16.1		13.7		13.7		11.7		16.8		35.0	
NNT	6		7		7		9		6		3	

NNT is defined as 1/ARR (rounded up to the nearest whole number) and not calculated for negative ARR. ARR, absolute risk reduction risk or risk difference; CIF, cumulative incidence function; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; sK^+, serum potassium. [a]The CIF estimate at week 54 (study day 379) is presented (based on the time-to-first HK event with serum K^+ level >5.5 mEq/L and time to reduction of the MRA dose below target dose). Aalen-Johansen estimators of the CIF with death as a competing event are used. Data cutoff on June 24, 2021. [b]ARR is the difference between placebo and patiromer using the CIF estimate (using not rounded estimates). [c]ARR is the difference between placebo and patiromer using the proportion of patients with ≥1 HK event (using not rounded proportions).

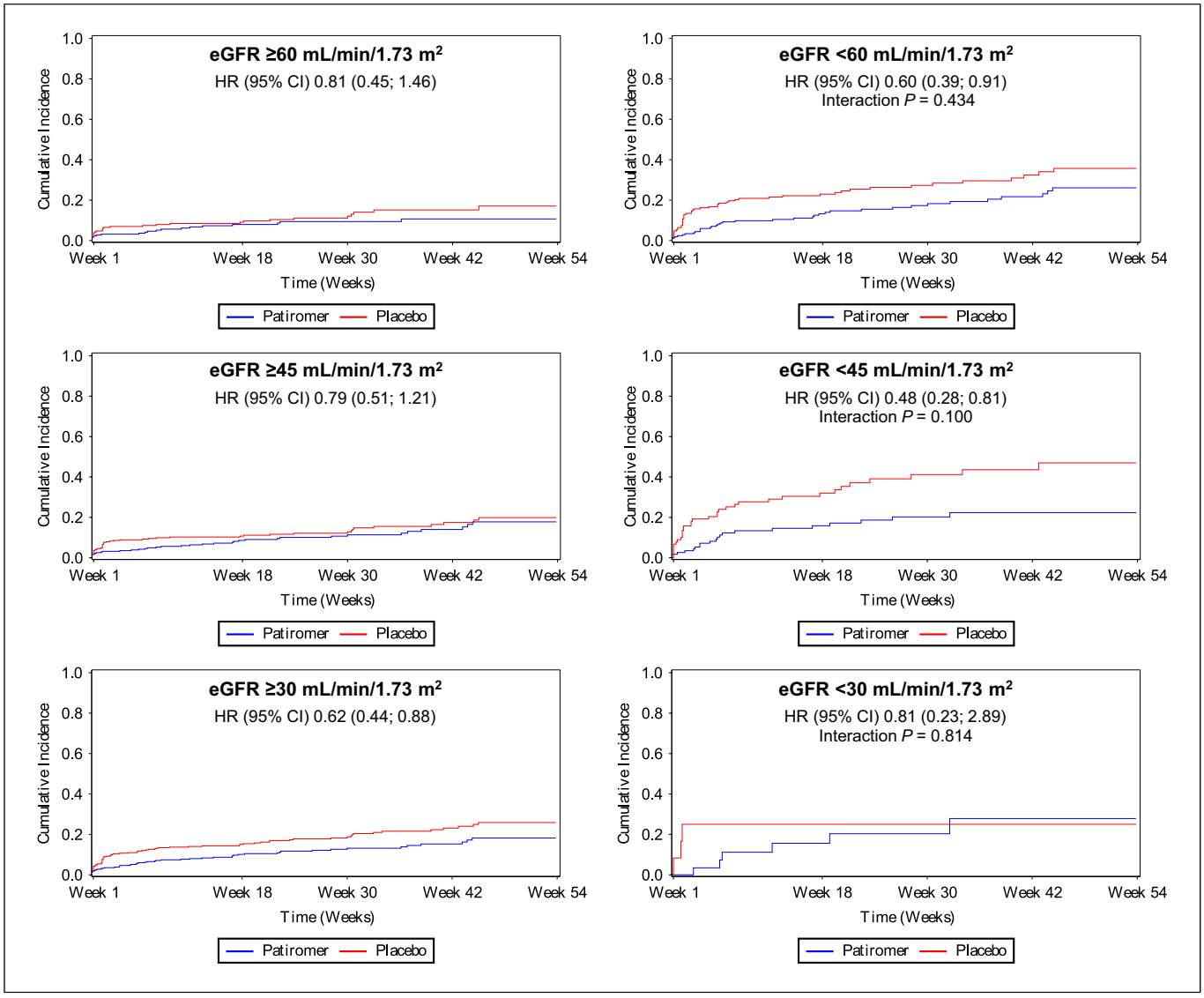

Fig. 3. Time to reduction of MRA dose below target (50 mg of spironolactone or eplerenone) by baseline eGFR subgroup during the randomized double-blind treatment phase, cumulative incidence function – FAS (n = 878). Aalen-Johansen estimators of the cumulative incidence function with death as a competing event. Only data up to Week 54 are displayed. Data cutoff at June 24, 2021. CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist.

subset of each eGFR subgroup pairing (apart from the systolic blood pressure and frequency of diabetes for the eGFR ≥30 vs. <30 mL/min/1.73 m^2 subgroup pairing, which were similar in both subsets) (Table 1). Mean current left ventricular ejection fraction and local sK^+ were similar between eGFR subgroups at baseline; however, HK at screening was less common in the higher than lower subset of the eGFR subgroup pairings (for respective eGFR subgroups of ≥60 vs. <60, ≥45 vs. <45, and ≥30 vs. <30 mL/min/1.73 m^2: 34.5 vs. 46.9%, 36.8 vs. 51.4%, and 38.6 vs. 73.8%, respectively).

Primary Outcome by eGFR Subgroup

The adjusted mean changes in sK^+ level from baseline to end of trial (primary endpoint; median follow-up 27 [13–43] weeks) favored patiromer versus placebo across all eGFR subgroups analyzed, with estimated mean treatment differences between patiromer and placebo (95% CIs) of −0.07 (−0.11, −0.03) and −0.14 (−0.18, −0.09) mEq/L in the ≥60 and <60 mL/min/1.73 m^2 subgroups; −0.08 (−0.11, −0.04) and −0.19 (−0.26, −0.12) mEq/L in the ≥45 and <45 mL/min/1.73 m^2

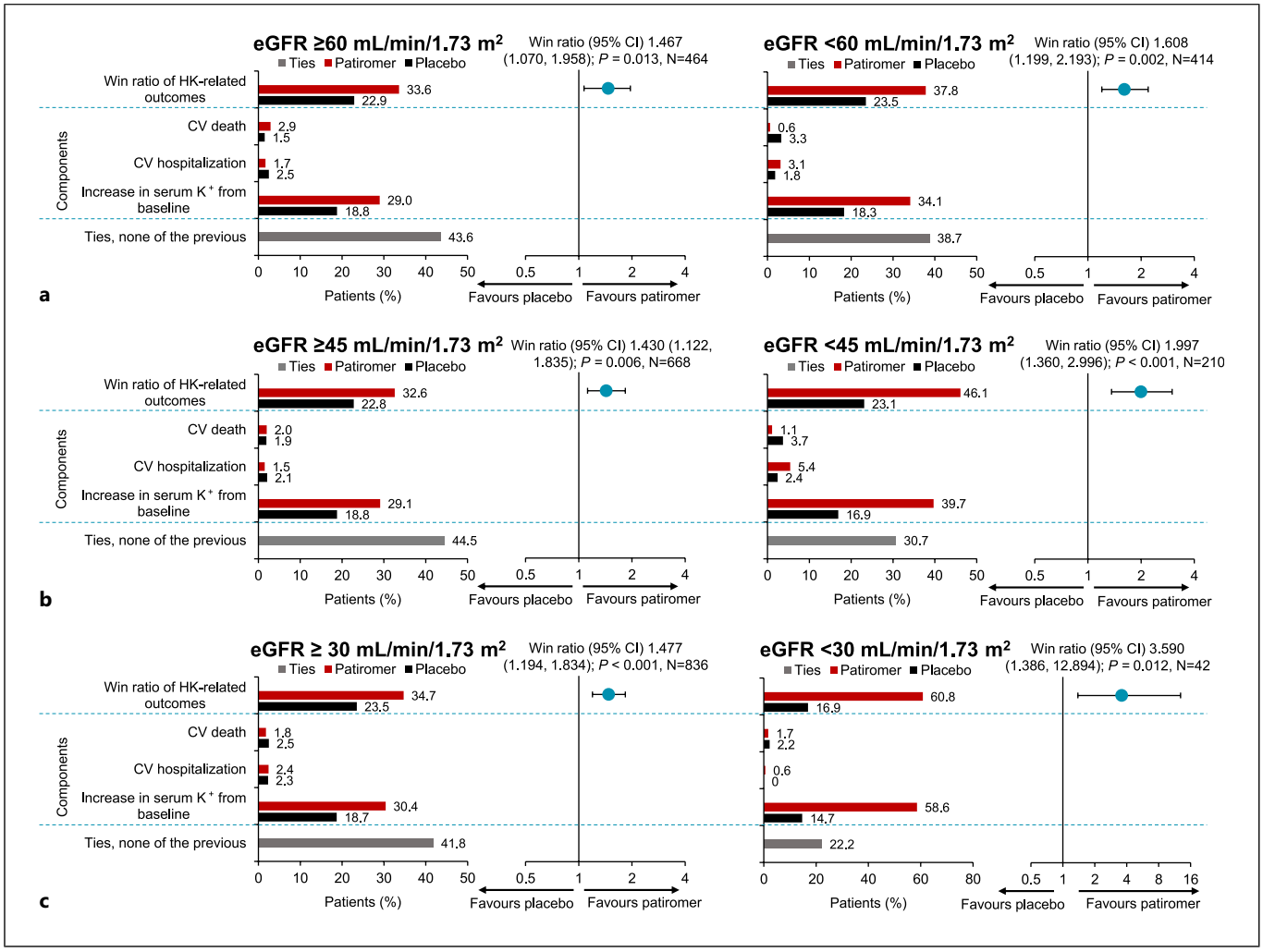

Fig. 4. HK-related outcomes during the randomized double-blind treatment phase – FAS (n = 878): stratified win ratio for baseline (**a**) eGFR ≥60 mL/min/1.73 m^2 versus eGFR <60 mL/min/1.73 m^2, (**b**) eGFR ≥45 mL/min/1.73 m^2 versus eGFR <45 mL/min/1.73 m^2, and (**c**) eGFR ≥30 mL/min/1.73 m^2 versus <30 mL/min/1.73 m^2. Win ratios relate to unmatched pairs. CI, confidence interval; CV, cardiovascular; HK, hyperkalemia; eGFR, estimated glomerular filtration rate; FAS, full analysis set; K^+, potassium.

subgroups; and −0.10 (−0.14, −0.07) and −0.27 (−0.42, −0.12) mEq/L in the ≥30 and <30 mL/min/1.73 m^2 subgroups (Fig. 1). The treatment effect was more pronounced in the lower versus the higher subset of each eGFR subgroup pairing, with p values for interaction of 0.027, 0.003, and 0.027 for the eGFR ≥/<60, ≥/<45, and ≥/<30 mL/min/1.73 m^2 subgroups, respectively. This effect appeared to be primarily driven by smaller increases in sK^+ in the higher than lower subset of the eGFR subgroup pairings with placebo (for respective eGFR subgroups of ≥60 vs. <60, ≥45 vs. <45, and <30 vs. ≥30 mL/min/1.73 m^2: 0.12 vs. 0.14 mEq/L, 0.09 vs. 0.25 mEq/L, and 0.08 vs. 0.22 mEq/L, respectively), that is, in the placebo group, higher baseline eGFR was associated with lesser increases in sK^+, while the change in sK^+ remained similar across subgroups in the patiromer arm (for respective eGFR subgroups of eGFR ≥60 vs. <60, ≥45 vs. <45, and ≥30 vs. <30 mL/min/1.73 m^2: 0.05 vs. 0.002 mEq/L, 0.02 vs. 0.06 mEq/L, and −0.03 vs. −0.05 mEq/L, respectively).

In general, a greater effect of patiromer versus placebo was reported with lower eGFR during the withdrawal phase, with the greatest treatment effect observed in the subset of patients with eGFR <30 mL/min/1.73 m^2 (based on 42 subjects: 30 with patiromer vs. 12 with placebo).

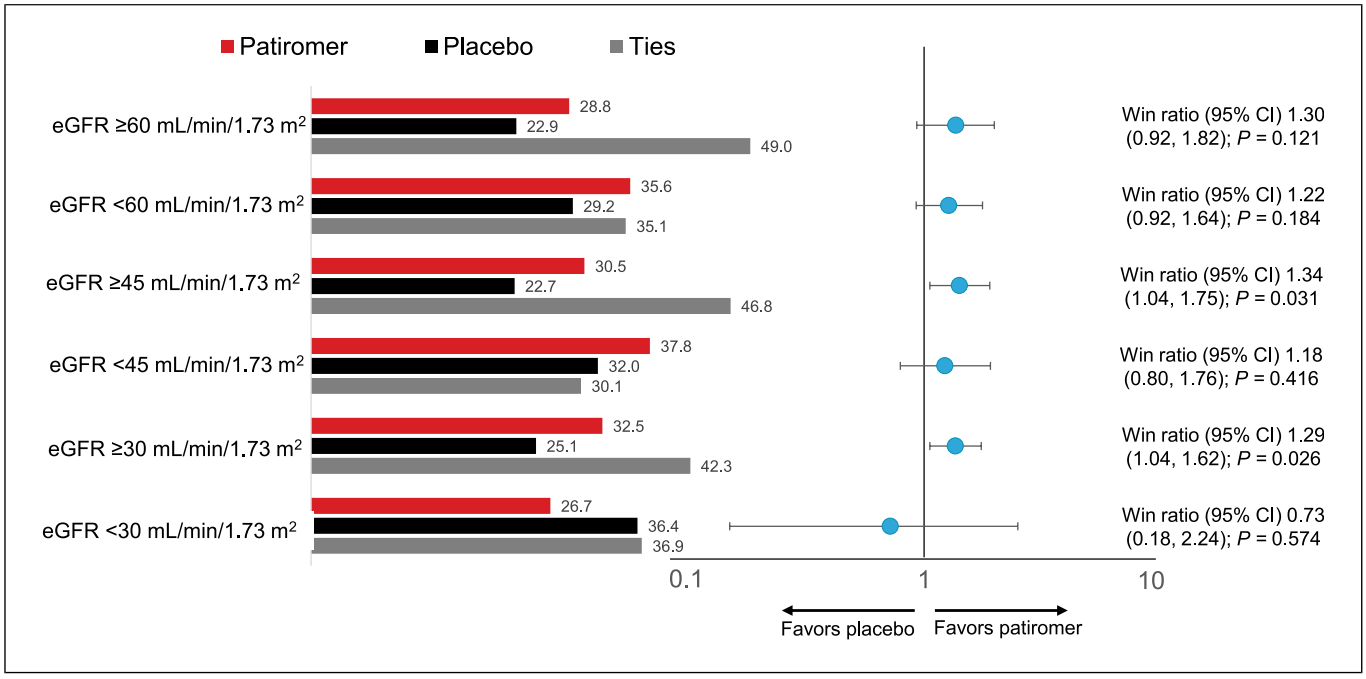

Fig. 5. RAASi use score – FAS ($n = 878$): win ratio by baseline eGFR subgroup. Win ratios relate to unmatched pairs; RAASI used score based on the additive components (0–8 points) at the end of the comparable follow-up period for each subject and each comparison (pair). Higher score will determine the winner (patiromer vs. placebo). Win ratio is defined as the number of unmatched pairs in favor of patiromer divided by the numbers of unmatched pairs in favor of placebo. Ties are not part of the win ratio calculation. CI, confidence interval; eGFR, estimated glomerular filtration rate, RAASi, renin-angiotensin-aldosterone system inhibitor.

Secondary Outcomes by eGFR Subgroup

For the time-to-first hyperkalemic event >5.5 mEq/L endpoint, the effect of patiromer versus placebo was not significantly different between subsets of eGFR subgroup pairings (p values for interaction all >0.05 for the eGFR ≥/<60, ≥/<45, and ≥/<30 mL/min/1.73 m^2 subgroups) (Fig. 2). Similarly, the effect of patiromer versus placebo on time-to-first investigator-reported hyperkalemic AE was not significantly different between subsets of eGFR subgroup pairings (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000540453). However, the ARR in sK^+ >5.5 mEq/L between placebo and patiromer was greatest (21.8%) and the NNT was lowest ($n = 5$) in the subset of patients with eGFR <30 mL/min/1.73 m^2 (Table 2).

The effect of patiromer versus placebo on time to reduction of MRA dose below target was also not significantly different between subsets of eGFR subgroup pairings (p values for interaction of 0.434, 0.100, and 0.814 for the eGFR ≥/<60, ≥/<45, and ≥/<30 mL/min/1.73 m^2 subgroups, respectively) (Fig. 3). For these MRA dose-reduction events, the ARR with patiromer was greater and the NNT was less in the lower subsets of the eGFR subgroup pairings, with the greatest ARR between placebo and patiromer (24.7%) in the subset of patients with eGFR <45 mL/min/1.73 m^2 (Table 2).

HK-related morbidity-adjusted outcome favored patiromer versus placebo across all subgroups (Fig. 4). However, the win ratio was higher as a function of eGFR decreasing (win ratios [95% CIs] of 1.47 [1.07, 1.96] and 1.61 [1.20, 2.19] for eGFR ≥60 and <60 mL/min/1.73 m^2, respectively; 2.00 [1.36, 3.00] for eGFR <45 mL/min/1.73 m^2, and 3.59 [1.39; 12.89] for eGFR <30 mL/min/1.73 m^2). RAASi use score win-ratio point estimates favored patiromer versus placebo across eGFR subsets except the eGFR <30 mL/min/1.73 m^2 subset (Fig. 5).

In general, patiromer was favored over placebo across subgroups for HK-related morbidity and RAASi use score win-ratio point estimates, although some subgroup findings were not significant. The time-to-first hyperkalemic event >5.5 mEq/L and the time to reduction of MRA dose below target were also not significantly different between eGFR subgroups.

Table 3. Treatment-emergent adverse events by baseline eGFR subgroup

	Patiromer (N = 439)		Placebo (N = 439)	
	eGFR ≥60 mL/min/1.73 m^2 (n = 227)	eGFR <60 mL/min/1.73 m^2 (n = 212)	eGFR ≥60 mL/min/1.73 m^2 (n = 237)	eGFR <60 mL/min/1.73 m^2 (n = 202)
TEAEs, n (%)				
Any TEAE	160 (70.5)	160 (75.5)	175 (73.8)	150 (74.3)
TEAEs leading to study drug withdrawal	6 (2.6)	6 (2.8)	5 (2.1)	6 (3.0)
Serious TEAE	24 (10.6)	30 (14.2)	30 (12.7)	28 (13.9)
	eGFR ≥45 mL/min/1.73 m^2 (n = 321)	eGFR <45 mL/min/1.73 m^2 (n = 118)	eGFR ≥45 mL/min/1.73 m^2 (n = 347)	eGFR <45 mL/min/1.73 m^2 (n = 92)
TEAEs, n (%)				
Any TEAE	229 (71.3)	91 (77.1)	253 (72.9)	72 (78.3)
TEAEs leading to study drug withdrawal	7 (2.2)	5 (4.2)	7 (2.0)	4 (4.3)
Serious TEAE	36 (11.2)	18 (15.3)	41 (11.8)	17 (18.5)
	eGFR ≥30 mL/min/1.73 m^2 (n = 409)	eGFR <30 mL/min/1.73 m^2 (n = 30)	eGFR ≥30 mL/min/1.73 m^2 (n = 427)	eGFR <30 mL/min/1.73 m^2 (n = 12)
TEAEs, n (%)				
Any TEAE	297 (72.6)	23 (76.7)	314 (73.5)	11 (91.7)
TEAEs leading to study drug withdrawal	10 (2.4)	2 (6.7)	11 (2.6)	0 (0.0)
Serious TEAE	50 (12.2)	4 (13.3)	57 (13.3)	1 (8.3)

TEAEs are those that occur during the double-blind treatment phase. eGFR, estimated glomerular filtration rate; TEAE, treatment-emergent adverse event.

Adverse Events

The proportions of patients reporting treatment-emergent AEs (TEAEs), TEAEs leading to study drug withdrawal, or serious TEAEs were similar in the patiromer and placebo arms for the eGFR ≥/<60 mL/min/1.73 m^2 and ≥/<45 mL/min/1.73 m^2 subgroups (Table 3). A lower proportion of patients with eGFR <30 mL/min/1.73 m^2 reported TEAEs with patiromer than placebo (76.7 vs. 91.7%); however, a higher proportion of patients reported serious TEAEs (13.3 vs. 8.3%) or TEAEs (6.7 vs. 0%) leading to study drug withdrawal with patiromer than placebo in this subpopulation. A similar proportion of patients with eGFR ≥30 mL/min/1.73 m^2 reported TEAEs in both treatment arms (patiromer: 72.6%; placebo: 73.5%).

Treatment-emergent HK was reported in a higher proportion of patients in the placebo arm than the patiromer arm across all eGFR subgroups (Table 4). HK was most common in patients with lower eGFRs (<60 mL/min/1.73 m^2, <45 mL/min/1.73 m^2, <30 mL/min/1.73 m^2). The proportions of patients reporting TEAEs of hypomagnesemia, diarrhea, constipation, or nausea were similar in all subgroups and for both treatment arms (Table 4). Hypokalemia was reported in a higher proportion of patients in the patiromer arm than the placebo arm within each eGFR subset (eGFR ≥60 mL/min/1.73 m^2: 17.2 vs. 12.2%; eGFR <60 mL/min/1.73 m^2: 12.7 vs. 8.9%; eGFR ≥45 mL/min/1.73 m^2: 15.6 vs. 11.0%; eGFR <45 mL/min/1.73 m^2: 13.6 vs. 9.8%; eGFR ≥30 mL/min/1.73 m^2: 15.4 vs. 11.0% and eGFR <30 mL/min/1.73 m^2: 10.0 vs. 0%). The majority of these hypokalemia events were reported as mild.

Discussion

In the run-in phase of the DIAMOND trial, patiromer treatment facilitated RAASi optimization, including MRA, in the majority of patients even with reduced eGFR. In the double-blind phase, long-term patiromer treatment

Table 4. Most commonly reported treatment-emergent adverse events by preferred term and by baseline eGFR subgroup

Preferred term	Patiromer (N = 439)		Placebo (N = 439)	
	eGFR ≥60 mL/min/1.73 m^2 (n = 227)	eGFR <60 mL/min/1.73 m^2 (n = 212)	eGFR ≥60 mL/min/1.73 m^2 (n = 237)	eGFR <60 mL/min/1.73 m^2 (n = 202)
TEAEs, n (%)				
HK[a]	89 (39.2)	108 (50.9)	122 (51.5)	116 (57.4)
Hypokalemia[a]	39 (17.2)	27 (12.7)	29 (12.2)	18 (8.9)
Hypomagnesemia	7 (3.1)	12 (5.7)	7 (3.0)	15 (7.4)
Hypotension[a]	6 (2.6)	10 (4.7)	4 (1.7)	9 (4.5)
Diarrhea	10 (4.4)	9 (4.2)	8 (3.4)	7 (3.5)
Constipation	3 (1.3)	8 (3.8)	1 (0.4)	4 (2.0)
Nausea	3 (1.3)	1 (0.5)	3 (1.3)	1 (0.5)
	eGFR ≥45 mL/min/1.73 m^2 (n = 321)	eGFR <45 mL/min/1.73 m^2 (n = 118)	eGFR ≥45 mL/min/1.73 m^2 (n = 347)	eGFR <45 mL/min/1.73 m^2 (n = 92)
TEAEs, n (%)				
HK[a]	134 (41.7)	63 (53.4)	183 (52.7)	55 (59.8)
Hypokalemia[a]	50 (15.6)	16 (13.6)	38 (11.0)	9 (9.8)
Hypomagnesemia	14 (4.4)	5 (4.2)	17 (4.9)	5 (5.4)
Hypotension[a]	8 (2.5)	8 (6.8)	10 (2.9)	3 (3.3)
Diarrhea	12 (3.7)	7 (5.9)	9 (2.6)	6 (6.5)
Constipation	7 (2.2)	4 (3.4)	3 (0.9)	2 (2.2)
Nausea	4 (1.2)	0 (0.0)	3 (0.9)	1 (1.1)
	eGFR ≥30 mL/min/1.73 m^2 (n = 409)	eGFR <30 mL/min/1.73 m^2 (n = 30)	eGFR ≥30 mL/min/1.73 m^2 (n = 427)	eGFR <30 mL/min/1.73 m^2 (n = 12)
TEAEs, n (%)				
HK[a]	179 (43.8)	18 (60.0)	229 (53.6)	9 (75.0)
Hypokalemia[a]	63 (15.4)	3 (10.0)	47 (11.0)	0 (0.0)
Hypomagnesemia	16 (3.9)	3 (10.0)	20 (4.7)	2 (16.7)
Hypotension[a]	14 (3.4)	2 (6.7)	12 (2.8)	1 (8.3)
Diarrhea	18 (4.4)	1 (3.3)	15 (3.5)	0 (0.0)
Constipation	10 (2.4)	1 (3.3)	4 (0.9)	1 (8.3)
Nausea	4 (1.0)	0 (0.0)	4 (0.9)	0 (0.0)

MedDRA Dictionary (Version 23.0) is used for coding adverse events. TEAEs are those that occur during the double-blind treatment phase. eGFR, estimated glomerular filtration rate; HK, hyperkalemia; TEAE, treatment-emergent adverse event. [a]Investigator-reported (i.e., not based on laboratory cutoffs).

maintained lower sK^+ levels, reduced the incidence of hyperkalemic events, and enabled a greater proportion of patients to maintain MRA at target dose than placebo across all eGFR subgroups. Although the subgroups were not all prespecified, greater effect sizes were observed in patients with lower than higher eGFRs for most endpoints, suggesting that these high-risk, high-need patients with lower eGFR may derive the greatest benefit from patiromer. This is particularly emphasized by the lower NNT values in the lower eGFR subgroups. Given that patients with CKD who are at risk for HK are frequently excluded from clinical trials, the results of this analysis of the DIAMOND trial, which included patients with current HK or previous HK, highlight that HK does not need to be a barrier to RAASi or MRA use, even in patients with impaired kidney function.

The OPAL-HK study of patients with CKD (46% stage 3; 45% stage 4; 9% stage 2) receiving RAASi showed that patiromer withdrawal had a median increase in sK^+ of 0.72 mEq/L over 8 weeks after withdrawal, versus no change in sK^+ in those randomized to continue patiromer [14]. The AMETHYST-DN study also showed that patiromer could maintain normal sK^+ levels in patients with diabetic kidney disease taking RAASi for 52 weeks [20]. In the DIAMOND study, HK at screening was more frequent in the patients with lower than higher eGFRs at baseline. Withdrawal of patiromer and switch to placebo following the run-in

phase of the trial resulted in a greater rise in sK^+ in the patients with lower compared with higher eGFRs, and the proportion of patients with treatment-emergent HK in the placebo group was highest in patients with eGFR <30 mL/min/1.73 m^2. This suggests that the benefit of patiromer for maintaining stable sK^+ over time may be even greater in those with worse kidney function, in whom the degree of HK is most pronounced.

The STRONG-HF trial of patients hospitalized with acute HF showed that high-intensity care of rapidly uptitrating guideline-directed medical therapy, including ≥50% of maximum MRA dose, within 2 weeks of discharge followed by close monitoring improved outcomes, including risk of all-cause death and HF readmission, compared with usual care [21]. Moreover, the effect was numerically greater in patients with median eGFR ≤59.4 mL/min/1.73 m^2 than those with eGFR >59.4 mL/min/1.73 m^2. Nevertheless, MRAs are only used in approximately 1.2% of patients with CKD [22]; therefore, facilitating doses of RAASi including MRAs, with proven effectiveness in patients with CKD, especially in the presence of HFrEF, is a key unmet need. In DIAMOND, similar numbers of patients with and without CKD (≥ or <60 mL/min/1.73 m^2) achieved RAASi optimization while maintaining an sK^+ level of ≥4.0 to ≤5.0 mEq/L; this suggests that patiromer can help optimize RAASi dose while maintaining normokalemia in patients across the spectrum of eGFR. This is in line with the findings of the much smaller PEARL-HF trial [23].

During the DIAMOND randomized double-blind treatment phase, the win ratio for overall RAASi use score was higher with patiromer than placebo across all eGFR subgroups, except the eGFR <30 mL/min/1.73 m^2 subset. This supports the role of patiromer in allowing maintenance of effective RAASi doses over time, irrespective of eGFR. Future analyses would be beneficial to explore the effect of patiromer versus placebo on RAASi use score in this high-risk subgroup. Patiromer also resulted in a greater maintenance of MRA dose above target dose over time compared with placebo across all eGFR subgroups. This is in line with the findings from the AMBER study in patients with resistant hypertension and CKD (eGFR 25 to ≤45 mL/min/1.73 m^2), which showed that patiromer enabled more patients (86%) to continue treatment with spironolactone than placebo (66%), with less HK [24].

Patiromer was well tolerated by patients in all eGFR subgroups; similar rates of TEAEs were reported by patients in the placebo and patiromer arms across eGFR ≥/<60 mL/min/1.73 m^2, ≥/<45 mL/min/1.73 m^2, and ≥30 mL/min/1.73 m^2 subgroups, with a higher rate of TEAEs in the placebo versus patiromer arm of the eGFR <30 mL/min/1.73 m^2 subset. The higher proportion of patients experiencing hypokalemia in the patiromer than placebo arm in the majority of eGFR subgroups was also seen in the main DIAMOND analysis; however, the majority of hypokalemia events were mild, with only 1 patient per treatment arm reporting severe hypokalemia.

The current subgroup analysis was limited by small patient numbers especially in the exploratory post hoc <30 mL/min/1.73 m^2 subset ($N = 42$ overall; 30 in the patiromer arm and 12 in the placebo arm). This is a limitation of most subgroup analyses, and findings should be interpreted with care. However, these results indicate that patiromer can be used to prevent HK and support RAASi and, in particular, MRA use.

Conclusion

In this DIAMOND subgroup analysis, patiromer enabled use of effective RAASi/MRA doses, controlled sK^+, and minimized HK risk in patients with HFrEF and CKD across a wide range of eGFRs. Patiromer was well tolerated by patients across all eGFR subgroups. A greater treatment effect was observed with lower eGFRs compared with higher eGFRs, indicating that the benefit of patiromer may be more pronounced in patients with more severe renal impairment who have a higher need for RAASi but also a higher risk of HK.

Acknowledgments

The prespecified CKD subgroup data were previously presented at the National Kidney Foundation Spring Clinical Meeting 2022 and 59th European Renal Association Congress 2022. Medical writing support was provided by Rose-Marie Falconer, AXON Communications (London, United Kingdom) and funded by Vifor (International) AG.

Statement of Ethics

The study protocol was reviewed and approved by relevant Institutional Review Boards (IRB) or Independent Ethics Committees (IEC) at each of the sites where the study was conducted. A full list of IRBs and IECs can be found in the supplemental materials. Written informed consent was obtained from all participants prior to any trial-related procedures.

Conflict of Interest Statement

M.R.W. reports serving on the DIAMOND Steering Committee, and personal fees from CSL Vifor, AstraZeneca, Novo Nordisk, Johnson & Johnson, and Care DX. P.R. reports being a DIAMOND Steering Committee member and honoraria from Vifor; personal

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M.R.W., P.R., B.P., L.H.L., A.J.S.C., G.F., M.K., M.M., M.B., S.D.A., and J.B. were responsible for writing (review and editing the manuscript) and were part of the DIAMOND study steering committee involved in the study design and data curation. A.Pe. was involved in writing (reviewing and editing), data analysis and data curation. SW and J. B. were involved in writing (reviewing and editing), study funding and data curation. J.A.E., A.B.-G., R.J.M., P.P., M.S., E.C.-M., J.C.N., A.Pa., P.S. and A.C.-S. were involved in writing (reviewing and editing) and also were involved in the DIAMOND study data collection.

Data Availability Statement

The data that support the findings of this study are not publicly available to protect the privacy of research participants. Data underlying the findings described in this manuscript may be obtained in accordance with CSL Vifor's data sharing policy. Inquiries can be made to medinfo@viforpharma.com.

References

1 Löfman I, Szummer K, Hagerman I, Dahlström U, Lund LH, Jernberg T. Prevalence and prognostic impact of kidney disease on heart failure patients. Open Heart. 2016;3(1):e000324. https://doi.org/10.1136/openhrt-2015-000324

2 Shiba N, Shimokawa H. Chronic kidney disease and heart failure—bidirectional close link and common therapeutic goal. J Cardiol. 2011;57(1):8–17. https://doi.org/10.1016/j.jjcc.2010.09.004

3 Kidney Disease Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98(4S):S1-15. https://doi.org/10.1016/j.kint.2020.06.019

4 Kidney Disease Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3S):S1-87. https://doi.org/10.1016/j.kint.2020.11.003

5 Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. J Am Coll Cardiol. 2018;72(4):351–66. https://doi.org/10.1016/j.jacc.2018.04.070

6 Pecoits-Filho R, Fliser D, Tu C, Zee J, Bieber B, Wong MMY, et al. Prescription of renin-angiotensin-aldosterone system inhibitors (RAASi) and its determinants in patients with advanced CKD under nephrologist care. J Clin Hypertens. 2019;21(7):991–1001. https://doi.org/10.1111/jch.13563

7 Janse RJ, Fu EL, Dahlström U, Benson L, Lindholm B, van Diepen M, et al. Use of guideline-recommended medical therapy in patients with heart failure and chronic kidney disease: from physician's prescriptions to patient's dispensations, medication adherence and persistence. Eur J Heart Fail. 2022;24(11):2185–95. https://doi.org/10.1002/ejhf.2620

8 Luo J, Brunelli SM, Jensen DE, Yang A. Association between serum potassium and outcomes in patients with reduced kidney function. Clin J Am Soc Nephrol. 2016;11(1):90–100. https://doi.org/10.2215/CJN.01730215

9 Linde C, Bakhai A, Furuland H, Evans M, McEwan P, Ayoubkhani D, et al. Real-world associations of renin-angiotensin-aldosterone system inhibitor dose, hyperkalemia, and adverse clinical outcomes in a cohort of patients with new-onset chronic kidney disease or heart failure in the United Kingdom. J Am Heart Assoc. 2019;8(22):e012655. https://doi.org/10.1161/JAHA.119.012655

10 Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet. 2000;356(9227):366–72. https://doi.org/10.1016/S0140-6736(00)02527-7

11 Sica DA. Diuretic-related side effects: development and treatment. J Clin Hypertens. 2004;6(9):532–40. https://doi.org/10.1111/j.1524-6175.2004.03789.x

12 Wang DJ, Gottlieb SS. Diuretics: still the mainstay of treatment. Crit Care Med. 2008;36(1 Suppl):S89–94. https://doi.org/10.1097/01.CCM.0000296272.68078.6B

13 Bruderer S, Bodmer M, Jick SS, Meier CR. Use of diuretics and risk of incident gout: a population-based case-control study. Arthritis Rheumatol. 2014;66(1):185–96. https://doi.org/10.1002/art.38203

14 Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211–21. https://doi.org/10.1056/NEJMoa1410853

15 Li L, Harrison SD, Cope MJ, Park C, Lee L, Salaymeh F, et al. Mechanism of action and pharmacology of patiromer, a nonabsorbed cross-linked polymer that lowers serum potassium concentration in patients with hyperkalemia. J Cardiovasc Pharmacol Ther. 2016;21(5):456–65. https://doi.org/10.1177/1074248416629549

16 Pitt B, Garza D. The tolerability and safety profile of patiromer: a novel polymer-based potassium binder for the treatment of hyperkalemia. Expert Opin Drug Saf. 2018;17(5):525–35. https://doi.org/10.1080/14740338.2018.1462335

17 Butler J, Anker SD, Lund LH, Coats AJS, Filippatos G, Siddiqi TJ, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. Eur Heart J. 2022;43(41):4362–73. https://doi.org/10.1093/eurheartj/ehac401

18 Butler J, Anker SD, Siddiqi TJ, Coats AJS, Dorigotti F, Filippatos G, et al. Patiromer for the management of hyperkalaemia in patients receiving renin-angiotensin-aldosterone system inhibitors for heart failure: design and rationale of the DIAMOND trial. Eur J Heart Fail. 2022;24(1):230–8. https://doi.org/10.1002/ejhf.2386

19 Pfizer. ALDACTONE® (spironolactone) tablets for oral use. US. PI. 2020.

20 Pitt B, Bakris GL, Weir MR, Freeman MW, Lainscak M, Mayo MR, et al. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. ESC Heart Fail. 2018;5(4):592–602. https://doi.org/10.1002/ehf2.12292

21 Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. 2022;400(10367):1938–52. https://doi.org/10.1016/S0140-6736(22)02076-1

22 Blankenburg M, Fett AK, Eisenring S, Haas G, Gay A. Patient characteristics and initiation of mineralocorticoid receptor antagonists in patients with chronic kidney disease in routine clinical practice in the US: a retrospective cohort study. BMC Nephrol. 2019;20(1):171. https://doi.org/10.1186/s12882-019-1348-4

23 Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J. 2011;32(7):820–8. https://doi.org/10.1093/eurheartj/ehq502

24 Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2019;394(10208):1540–50. https://doi.org/10.1016/S0140-6736(19)32135-X