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ORIGINAL RESEARCH

HEART FAILURE

Patiromer for Heart Failure Medication Optimization in Patients With Current or Past Hyperkalemia

DIAMOND Subanalysis

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ABSTRACT

BACKGROUND For heart failure with reduced ejection fraction (HFrEF), suboptimal use of renin-angiotensin-aldosterone system inhibitors (RAASis), including mineralocorticoid receptor antagonists (MRAs), due to hyperkalemia, may be improved by potassium binders.

OBJECTIVES This prespecified analysis of the phase 3 DIAMOND (Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure) trial assessed the effect of patiromer in patients with HFrEF and either current or past hyperkalemia.

METHODS Patients with HFrEF and current or past (within 1 year before enrollment) hyperkalemia (serum potassium [sK^+] >5.0 mmol/L) entered a single-blind, run-in phase to optimize RAASis while receiving patiromer. They were subsequently randomized, double-blind, to continue patiromer or change to placebo.

RESULTS Of the 1,038 patients who completed run-in, 354 (83.9%) of 422 with current hyperkalemia and 524 (85.1%) of 616 with past hyperkalemia achieved RAASi optimization and were randomized to treatment. During the double-blind phase, patiromer lowered sK^+ levels compared with placebo in both the current and past hyperkalemia subgroups: difference in adjusted mean change from baseline: -0.12 (95% CI: -0.17 to -0.07) and -0.08 (95% CI: -0.12 to -0.05), respectively; $P_{interaction} = 0.166$. Patiromer was more effective than placebo in maintaining MRA at target dose in patients with current vs past hyperkalemia (HR: 0.45 [95% CI: 0.26-0.76] vs HR: 0.85 [95% CI: 0.54-1.32]; $P_{interaction} = 0.031$). Adverse events were similar between subgroups.

CONCLUSIONS The use of patiromer facilitates achieving target doses of RAASis in patients with HFrEF with either current or past hyperkalemia. For those with current hyperkalemia before RAASi optimization, use of patiromer may be more beneficial in helping to maintain sK^+ control and achieve MRA target dose. (Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure [DIAMOND]; NCT03888066) (JACC Heart Fail. 2024;12:2026-2037) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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In patients with heart failure with reduced ejection fraction (HFrEF), renin-angiotensin-aldosterone system inhibitors (RAASis), including mineralocorticoid receptor antagonists (MRAs), improve symptoms, reduce the risk of heart failure hospitalization and death, and are recommended by U.S. and European heart failure guidelines.[1,2] However, RAASis, and in particular MRAs, increase the risk of developing hyperkalemia,[3,4] especially in patients who have chronic kidney disease (CKD) and/or diabetes.[5] Because hyperkalemia can have serious clinical consequences,[6-8] clinicians are concerned about both current hyperkalemia and the potential for development of hyperkalemia. Therefore, clinicians may not initiate RAASis or optimize their doses and may even discontinue or reduce the doses of RAASis, in particular MRAs, when hyperkalemia develops.[9-11] However, suboptimal RAASi use can also have adverse consequences.[12-14]

Patiromer is a potassium binder that is indicated for the treatment of hyperkalemia.[15,16] The phase 3 DIAMOND (Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure) trial enrolled patients with HFrEF and either current or a history of hyperkalemia related to RAASi use to assess the ability of patiromer to control serum potassium (sK^+) concentration, prevent hyperkalemia events, increase the proportion of patients achieving guideline-recommended doses of RAASi, and improve outcomes. The results of DIAMOND showed that, for patients with HFrEF and RAASi-related hyperkalemia, patiromer was well tolerated and, compared with placebo, significantly reduced sK^+ and led to fewer hyperkalemia episodes and use of higher doses of MRA and other RAASis.[17]

This prespecified analysis of the DIAMOND trial aimed to investigate whether the effect of patiromer compared with placebo differed in terms of changes in mean sK^+ concentration, recurrent hyperkalemia, and RAASi use within 1 year of trial entry in patients with current hyperkalemia compared with past hyperkalemia.

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin II receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HFrEF = heart failure with reduced ejection fraction

MRA = mineralocorticoid receptor antagonist

RAASi = renin-angiotensin-aldosterone system inhibitor

sK^+ = serum potassium

TEAE = treatment-emergent adverse event

METHODS

TRIAL DESIGN AND PATIENTS. The design of the DIAMOND trial has been previously described;[18] DIAMOND was a prospective, phase 3, multicenter, double-blind, randomized withdrawal, placebo-controlled trial.[17,18] An independent ethics committee for each participating center approved the trial (listed in the Supplemental Appendix). The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice, and local and national guidelines. All patients provided written informed consent.

The study included patients aged ≥18 years with NYHA functional class II to IV heart failure and a left

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ventricular ejection fraction ≤40%. They had either current hyperkalemia (defined as 2 sK^+ values >5.0 mmol/L) while receiving RAASis (angiotensin-converting-enzyme inhibitor [ACEI], angiotensin II receptor blocker [ARB], angiotensin receptor neprilysin inhibitor [ARNI] and/or MRA therapy), or they had past hyperkalemia (defined as normokalemia at screening but with a history of RAASi dose reduction or discontinuation of RAASi therapy due to hyperkalemia in the previous 12 months), as ascertained via investigator reporting/medical record. Complete inclusion and exclusion criteria have been published previously.[18]

Eligible patients were enrolled into a single-blind run-in phase of up to 12 weeks, in which all patients received patiromer (titrated up to a maximum of 3 packs per day [8.4 g/pack]) and were optimized on RAASi therapy; MRAs were titrated up to a maximum of 50 mg/d based on previous clinical trial target doses,[3] and ACEIs/ARBs/ARNIs were titrated to ≥50% of recommended doses. Patients with successful RAASi optimization and normokalemia were randomized 1:1 to continued patiromer or to receive placebo (patiromer withdrawal).

CLINICAL OUTCOMES AND ASSESSMENTS. Patient disposition and characteristics at screening were recorded at the time the patient signed the informed consent form. The primary endpoint was the adjusted mean change in sK^+ (in millimoles per liter) from baseline (randomization).[17,18] Secondary outcomes included: 1) time to the first hyperkalemic event of >5.5 mmol/L; 2) lack of durable enablement of MRAs at target dose; 3) all investigator-reported adverse events of hyperkalemia (first and recurrent); 4) a win ratio for morbidity- and mortality-adjusted hyperkalemia-related outcomes; and 5) the RAASi use score win-ratio.[17,18] In this analysis, changes in medication use and clinical parameters were compared in the current vs past hyperkalemia subgroups. Severity of hyperkalemia/hypokalemic events labeled here as mild, moderate, or severe are as reported by the investigator.

ANALYSIS. For the primary endpoint, estimates are from analyses based on a mixed model for repeated measures by subgroup including as fixed effects: treatment, geographic region, sex, visit, baseline type 2 diabetes mellitus status, baseline sK^+ value, and baseline estimated glomerular filtration rate (eGFR). Subject was included in the mixed model for repeated measures as a random effect. The error terms assume the data follow multivariate normal distribution with unstructured covariance. For the secondary endpoints, for each subgroup, HRs came from a Cox proportional regression model, and rate ratios came from a negative binomial model; both were adjusted for geographic region, sex, baseline type 2 diabetes mellitus status, baseline sK^+ value, and baseline eGFR. The *P* values for treatment by subgroup interaction came from a model including subgroup and treatment by subgroup interaction as covariates. Event-driven endpoints were also assessed post hoc to determine the absolute risk reduction for patiromer vs placebo and the number needed to treat.

This report focuses on the differences in the placebo-corrected patiromer effect on the primary and secondary endpoints between 2 prespecified patient subgroups: those with current hyperkalemia at screening and those with a history of hyperkalemia but normokalaemia at screening.

RESULTS

TRIAL ENROLLMENT AND PATIENT CHARACTERISTICS AT SCREENING AND BASELINE. Of 1,195 patients who entered the run-in phase, 1,038 (86.9%) patients completed it: 422 (40.7%) of 1,038 patients had current hyperkalemia and 616 (59.3%) had past hyperkalemia. In total, 354 (83.9%) of 422 patients with hyperkalemia and 524 (85.1%) of 616 patients with past hyperkalemia achieved 50 mg/d MRA and other RAASi drugs titrated to ≥50% of recommended doses while maintaining an sK^+ concentration between 4.0 and 5.0 mmol/L and were randomized to treatment. Patient demographic characteristics at screening were generally similar between the subgroups with current and past hyperkalemia (Table 1). At screening, sK^+ concentrations were higher in the current vs the past hyperkalemia subgroup but were similar between subgroups at baseline after the run-in phase with patiromer treatment. The subgroup with hyperkalemia had numerically lower eGFR at screening and baseline than the past hyperkalemia subgroup. Overall, the median duration of follow-up from randomization was 27 weeks (IQR: 13-43 weeks).

PRIMARY OUTCOME IN PATIENTS WITH CURRENT/PAST HYPERKALEMIA. The mean adjusted change in sK^+ level from baseline during the double-blind treatment phase (primary endpoint) favored patiromer vs placebo in both patient subgroups with current and past hyperkalemia. In the current hyperkalemia subgroup, the adjusted mean change was 0.08 mmol/L (95% CI: 0.02-0.14 mmol/L) in the patiromer group and 0.20 mmol/L (95% CI: 0.14-0.26 mmol/L) in the placebo group; there was a between-group difference of −0.12 mmol/L (95% CI: −0.17 to −0.07 mmol/L). In the past hyperkalemia subgroup, the adjusted mean change was −0.01 mmol/L (95% CI: −0.05 to 0.04 mmol/L) in the

TABLE 1 Demographic and Disease Characteristics at Screening and Baseline of Randomized Patients With Current Hyperkalemia and Past Hyperkalemia at Enrollment (Full Analysis Set, N = 878)

	Current Hyperkalemia (n = 354)	Past Hyperkalemia (n = 524)
Demographic characteristics at screening		
Age, y	68.0 (61.0-74.0)	67.0 (60.0-73.0)
Female	100 (28.2)	138 (26.3)
Region		
United States/Canada	34 (9.6)	29 (5.5)
Latin America[a]	25 (7.1)	33 (6.3)
Western Europe and other[b]	18 (5.1)	40 (7.6)
Central/Eastern Europe[c]	277 (78.2)	422 (80.5)
Race		
White	343 (96.9)	517 (98.7)
Black or African American	7 (2.0)	5 (1.0)
American Indian or Alaska Native	4 (1.1)	1 (0.2)
Other	0 (0.0)	1 (0.2)
Ethnicity		
Hispanic or Latino	55 (15.5)	58 (11.1)
Non-Hispanic or Latino	298 (84.2)	462 (88.2)
Unknown or not reported	1 (0.3)	4 (0.8)
Medical history at screening		
RAASi treatment discontinued or decreased in prior 12 months, leading to eligibility for trial	–	515 (98.3)
ACEI	–	211 (41.0)
ARB	–	66 (12.8)
ARNI	–	16 (3.1)
MRA	–	331 (64.3)
Beta-blockers[d]	348 (98.3)	506 (96.6)
Atrial fibrillation	140 (39.5)	201 (38.4)
Diabetes mellitus	156 (44.1)	200 (38.2)
Hypertension	339 (95.8)	463 (88.4)

	Current Hyperkalemia		Past Hyperkalemia	
	Screening[f]	Baseline[g]	Screening[f]	Baseline[g]
Disease characteristics				
Body mass index, kg/m^2	n = 354 28.3 (25.8-31.9)	n = 354 28.4 (25.8-31.9)	n = 524 28.0 (25.4-31.5)	n = 524 27.9 (25.4-31.3)
Systolic blood pressure, mm Hg	n = 354 132.0 (124.0-140.0)	n = 354 125.5 (120.0-132.0)	n = 524 130.0 (120.0-138.0)	n = 524 125.0 (118.0-131.0)
NYHA functional class	n = 353	n = 352	n = 524	n = 524
I/II	182 (51.6)	202 (57.1)	264 (50.4)	284 (54.2)
III/IV	171 (48.4)	150 (42.3)	260 (49.6)	240 (45.8)
eGFR,[e] mL/min/1.73 m^2	n = 314 55.0 (39.0-75.0)	n = 347 57.0 (42.0-76.0)	n = 507 65.0 (51.0-82.0)	n = 509 64.0 (49.0-83.0)
Chronic kidney disease stage[h]		n = 354		n = 524
Stage 1 (eGFR ≥90 mL/min/1.73 m^2)	–	47 (13.3)	–	86 (16.4)
Stage 2 (eGFR 60-89 mL/min/1.73 m^2)	–	113 (31.9)	–	218 (41.6)
Stage 3a (eGFR 45-59 mL/min/1.73 m^2)	–	86 (24.3)	–	118 (22.5)
Stage 3b (eGFR 30-44 mL/min/1.73 m^2)	–	77 (21.8)	–	91 (17.4)
Stage 4 (eGFR 15-29 mL/min/1.73 m^2)	–	31 (8.8)	–	11 (2.1)
Stage 5 (eGFR <15 mL/min/1.73 m^2)	–	0	–	0
sK^+,[e] mmol/L	n = 298 5.2 (4.9-5.5)	n = 339 4.8 (4.5-5.1)	n = 483 4.6 (4.4-4.9)	n = 481 4.6 (4.4-4,9)
N-terminal pro B-type natriuretic peptide, pg/mL	n = 352 1,313.6 (590.9-2,930.1)	–	n = 524 1,313.6 (766.9-2,516.1)	–

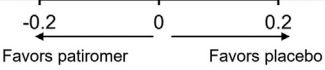
Values are median (IQR) or n (%). [a]Argentina, Brazil, Mexico. [b]Belgium, France, Germany, Israel, Italy, the Netherlands, Spain, and the United Kingdom. [c]Bulgaria, Czech Republic, Georgia, Hungary, Poland, Russia, Serbia, and Ukraine. [d]Safety population, N = 878 (current hyperkalemia, n = 354; past hyperkalemia, n = 524); beta-blocker use with start date before the date of first dose of patiromer in the run-in phase, and for patients who were in the run-in phase twice, their second run-in phase is considered. [e]Central laboratory values. [f]Screening value is defined as the value at screening visit. If this value is not available, the first nonmissing value after first screening date and on or before first run-in dose is used as screening value. [g]Baseline is defined as the value at day 1/baseline visit. If this value is not available, the last nonmissing value within 10 days prior or on the first blinded treatment date is used as baseline. [h]Combined baseline (including central and local laboratory values) was defined as central laboratory baseline and, if not available, as local laboratory baseline. If no baseline estimated glomerular filtration rate (eGFR) value was detected, assessment at the day 3 visit was used. Percentages are based on the number of nonmissing observations.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin-receptor-neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; sK^+ = serum potassium.

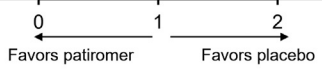
FIGURE 1 Primary and Secondary Outcomes in Patients With Current Hyperkalemia and Past Hyperkalemia at Enrollment (Full Analysis Set, N = 878)

Primary outcome: adjusted mean change in sK^+ (mmol/L) during the double-blind treatment phase

Subgroup	Patiromer (n=439) Adjusted mean change (95% CI)	Placebo (n=439) Adjusted mean change (95% CI)	Difference in adjusted mean change (95% CI)	*P*-value interaction
Hyperkalemia	0.079 (0.015; 0.142)	0.199 (0.135; 0.262)	–0.120 (–0.173; –0.066)	0.166
Past hyperkalemia	–0.007 (–0.052; 0.038)	0.075 (0.030; 0.119)	–0.081 (–0.116; –0.046)	
Overall	**0.029 (–0.007; 0.066)**	**0.127 (0.090; 0.163)**	**–0.097 (–0.128; –0.067)**	



Secondary outcome	Subgroup	Patiromer (n=439) Events, n/N (%)	Placebo (n=439) Events, n/N (%)	Hazard ratio (95% CI)	
sK^+ >5.5 mmol/L	Hyperkalemia	34/182 (18.7)	53/172 (30.8)	0.547 (0.354; 0.845)	0.236
	Past hyperkalemia	27/257 (10.5)	32/267 (12.0)	0.749 (0.445; 1.263)	
	Overall	61/439 (13.9)	85/439 (19.4)	**0.625 (0.449; 0.871)**	
Reduction of the MRA dose below target dose	Hyperkalemia	22/182 (12.1)	42/172 (24.4)	0.446 (0.263; 0.756)	0.031
	Past hyperkalemia	39/257 (15.2)	41/267 (15.4)	0.845 (0.540; 1.323)	
	Overall	61/439 (13.9)	83/439 (18.9)	**0.625 (0.447; 0.874)**	
		Annualized event rate/100 pt-yrs (95% CI)		**Rate ratio (95% CI)**	
Recurrent hyperkalemia adverse events	Hyperkalemia	72.7 (48.8; 108.2)	138.2 (95.9; 199.2)	0.526 (0.373; 0.741)	0.060
	Past hyperkalemia	77.3 (56.8; 105.2)	99.6 (74.1; 133.7)	0.776 (0.606; 0.994)	
	Overall	77.7 (61.2; 98.7)	118.2 (94.5; 147.8)	**0.658 (0.534; 0.810)**	



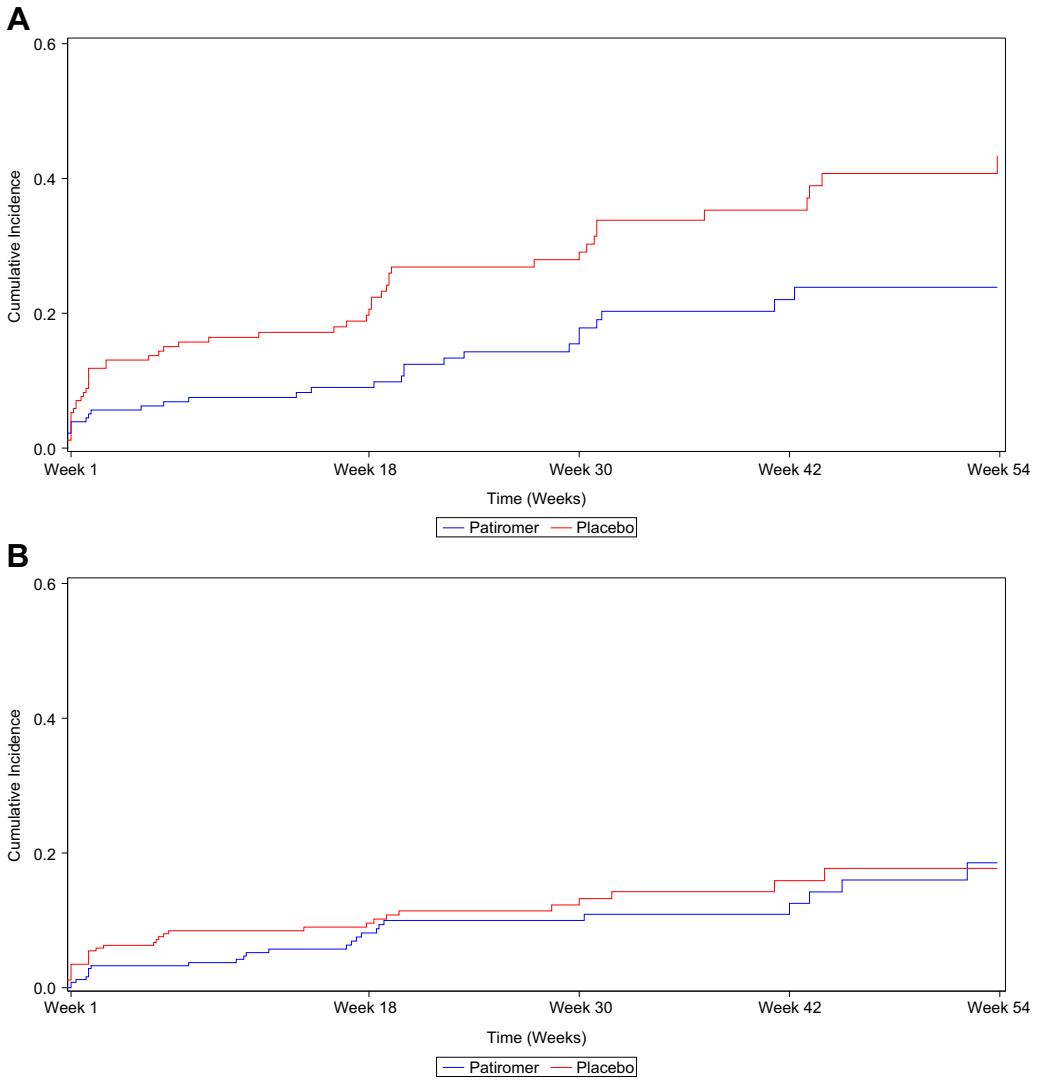
HRs come from a Cox proportional regression model, and annualized event rate ratios come from a negative binomial model. These models are adjusted for treatment, geographic region, sex, baseline type 2 diabetes mellitus status, baseline serum potassium (sK^+), and baseline estimated glomerular filtration rate.
MRA = mineralocorticoid receptor antagonist; pt-yr = patient-year.

patiromer group and 0.08 mmol/L (95% CI: 0.03-0.12 mmol/L) in the placebo group; there was a between-group difference of −0.08 mmol/L (95% CI: −0.12 to −0.05; $P_{interaction} = 0.17$) (Figure 1).

SECONDARY OUTCOMES. For the secondary endpoint of sK^+ >5.5 mmol/L, patiromer was favorable compared with placebo; the *P* value for interaction between current and past hyperkalemia was not significant (Figures 1 and 2). With patiromer vs placebo in patients with current hyperkalemia and past hyperkalemia, the HR of sK^+ >5.5 mmol/L was 0.55 (95% CI: 0.35-0.84) and 0.75 (95% CI: 0.44-1.26), respectively ($P_{interaction} = 0.24$). The absolute risk reduction with patiromer vs placebo for patients with current hyperkalemia was 19.5% (95% CI: 5.6%-33.5%), and the number needed to treat was 5 (95% CI: 3-18) over 54 weeks; for patients with past hyperkalemia, absolute risk reduction was −0.8% (Central Illustration, Table 2).

Patiromer was superior to placebo in preventing the reduction in MRA below the target dose over 1 year overall (13.9% vs 18.9%; HR: 0.62 [95% CI: 0.45-0.87]; $P = 0.01$), but this effect was only observed in the current hyperkalemia subgroup and not in the past hyperkalemia subgroup (Figures 1 and 3). MRA dose reduction below target occurred in a lower proportion of patients receiving patiromer than placebo in the current hyperkalemia subgroup (12.1% vs 24.4%) but in similar proportions of patients in the past hyperkalemia subgroup (15.2% vs 15.4%; HR: 0.45 [95% CI: 0.26-0.76] vs HR: 0.85 [95% CI: 0.54-1.32], respectively; $P_{interaction} = 0.03$). The absolute risk reduction with patiromer vs placebo for patients with current hyperkalemia was 15.3% (95% CI: 4.4%-26.2%), and the number needed to treat was 7 (95% CI: 4-23) over 54 weeks; for patients with past hyperkalemia, absolute risk reduction was 0.8 (95% CI: −10.1% to 11.7%), and number needed to treat was 126 (Table 2). The proportion of patients with target ACEI/ARB/ARNI use (≥50% of the target dose) with patiromer vs placebo was 92.9% vs 87.8% at end of study compared with 98.9% vs 98.8% at week 1 in

FIGURE 2 **Time to First Hyperkalemia Event**



Time to first hyperkalemia event with serum potassium >5.5 mmol/L in patients with current hyperkalemia (n = 354; HR: 0.55 [95% CI: 0.35-0.84]) (A) and past hyperkalemia (n = 524; HR: 0.75 [95% CI: 0.44-1.26]; $P_{interaction} = 0.24$) (B) at enrollment (full analysis set, N = 878). Aalen-Johansen estimators of the cumulative incidence function with death as a competing event. Central and local laboratory results are included. Only data up to week 54 are displayed. Data cutoff on June 24, 2021 is applied.

patients with current hyperkalemia, and 88.7% vs 85.0% at end of study compared with 96.9% vs 98.5% at week 1 in patients with past hyperkalemia (Supplemental Table 1).

The proportion of patients with recurrent (more than one) hyperkalemia adverse events with patiromer and placebo, respectively, was 11.0% and 22.1% in those with current hyperkalemia and 13.2% and 13.5% in those with past hyperkalemia. With patiromer vs placebo in patients with current hyperkalemia and past hyperkalemia, the annualized event rate ratio for risk of recurrent hyperkalemia adverse events was 0.53 (95% CI: 0.37-0.74) and 0.78 (95% CI: 0.61-0.99; $P_{interaction} = 0.060$) (**Figure 1**). The absolute risk reduction on patients with at least one hyperkalemia event with patiromer vs placebo for patients with current hyperkalemia was 21.9% (95% CI: 12.1%-31.8%), and the number needed to treat was 5 (95% CI: 3-8); for patients with past hyperkalemia, absolute risk reduction was 8.5% (95% CI: 0.2%-16.8%), and the number needed to treat was 12 (95% CI: 6-532) (**Table 2**).

CENTRAL ILLUSTRATION **The DIAMOND Trial: Patiromer Use for the Management of Hyperkalemia in Patients With Heart Failure With Reduced Ejection Fraction**

DIAMOND Phase 3 Trial (n = 1,195 Enrolled)

Patients with HFrEF + ↑ natriuretic peptides ± CKD (eGFR >30 mL/min/1 .73 m^2) ***and*** HK
or
HK in <12 months leading to RAASi D/C

Single-Blinded Run-In Phase to Optimize RAASi, Up to 12 Weeks (n = 1,038 Completed Run-In)

Patients were randomized if they could achieve patiromer-facilitated RAASi optimization, including 3 key goals:

- ≥50% of target dose of RAASi
- ≥50 mg/day of MRA
- sK^+ ≤5.0 mmol/L while on patiromer

Current HK 84% (354/422)

History of HK 85% (524/616)

Double-Blind Treatment Phase

R (N = 878)

Patiromer continued

Placebo (patiromer withdrawal)

Median 27 weeks (IQR: 13-43 weeks) of follow-up from randomization

Primary Efficacy Endpoint (Adjusted Mean Change in sK^+ [mmol/L] During Double-Blind Treatment Phase)

	Placebo (n = 439)	Patiromer (n = 439)	Difference in Adjusted Mean Change (95% CI)
Current HK	0.20 mmol/L	0.08 mmol/L	−0.12 (−0.17 to −0.07)
Past HK	0.08 mmol/L	−0.01 mmol/L	−0.08 (−0.12 to −0.05)
P interaction			0.17

Secondary Endpoints

	Placebo (n = 439)	Patiromer (n = 439)	
sK^+ >5.5 mmol/L, %			**HR (95% CI)**
Current HK	30.8	18.7	0.55 (0.35-0.84)
Past HK	12.0	10.5	0.75 (0.44-1.26)
P interaction			0.236
MRA ↓ Below Target Dose, %			**HR (95% CI)**
Current HK	24.4	12.1	0.45 (0.26-0.76)
Past HK	15.4	15.2	0.85 (0.54-1.32)
P interaction			0.031
≥1 HK Event Rate/100 Patient-Years			**RR (95% CI)**
Current HK	138.2	72.7	0.53 (0.37-0.74)
Past HK	99.6	77.3	0.78 (0.61-0.99)
P interaction			0.060

Conclusion: The use of patiromer can facilitate achieving target doses of RAAS is in patients with HFrEF with either current or past HK.

For those with current HK prior to RAASi optimization, long-term patiromer therapy may be needed to help maintain sK^+ control and target doses of MRA.

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HRs come from a Cox proportional regression model, and annualized event rate ratios come from a negative binomial model. These models are adjusted for treatment, geographic region, sex, baseline type 2 diabetes mellitus status, baseline serum potassium (sK^+), and baseline estimated glomerular filtration rate (eGFR). CKD = chronic kidney disease; D/C = discontinuation; HFrEF = heart failure with reduced ejection fraction; HK = hyperkalemia; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; R = randomized; RR = rate ratio.

Win ratios for hyperkalemia-related hard outcomes favored patiromer vs placebo in both patient subgroups with current hyperkalemia and past hyperkalemia at enrollment but were not statistically significant (win ratios of 1.92 [95% CI: 1.37-2.71] and 1.28 [95% CI: 0.96-1.73], respectively) (Supplemental Figure 1). Win ratios for RAASi use score favored patiromer vs placebo in both patient subgroups with current hyperkalemia and past hyperkalemia at enrollment (win ratios of 1.24 [95% CI: 0.89-1.78] and 1.26 [95% CI: 0.96-1.71]). Win ratios for cardiovascular death and cardiovascular hospitalization components of hyperkalemia-related hard outcomes with patiromer vs placebo were 0.75 (95% CI: 0.29-1.81) and 1.06 (95% CI: 0.49-2.21) in patients with current hyperkalemia and past hyperkalemia at enrollment.

SAFETY. There were similar proportions of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to withdrawal or death across current hyperkalemia and past hyperkalemia treatment groups during the double-blind treatment phase of the trial (Table 3). There was a lower proportion of hyperkalemia TEAEs in the patiromer subgroup compared with the placebo subgroup in both the current hyperkalemia (42.9% vs 58.1%, respectively) and past hyperkalemia (46.3% vs 51.7%) subgroups, with the highest proportion in the placebo current hyperkalemia subgroup. There were higher proportions of hypokalemia TEAEs in the patiromer vs placebo subgroups in both the current hyperkalemia (11.0% vs 5.8%) and past hyperkalemia (17.9% vs 13.9%) subgroups. Overall, the majority of hypokalemic events were mild (Table 3). Proportions of hypomagnesemia were similar between the treatment and hyperkalemia subgroups. Diarrhea was reported in 5.5% and 1.2% of patients in the current hyperkalemia group (patiromer/placebo) and 3.5% and 4.9% in patients in the past hyperkalemia group (patiromer/placebo). Constipation, nausea, and peripheral edema were reported in <5% of patients in the current hyperkalemia and past hyperkalemia treatment groups.

TABLE 2 Absolute Risk Reduction and Number Needed to Treat for Secondary Outcomes in Patients With Current Hyperkalemia and Past Hyperkalemia at Enrollment (Full Analysis Set, N = 878)

	Current Hyperkalemia		Past Hyperkalemia	
	Patiromer	Placebo	Patiromer	Placebo
sK^+ >5.5 mmol/L[a]	23.9	43.4	18.5	17.7
ARR[b]	19.5 (5.6-33.5)		−0.8	
Number needed to treat	5 (3-18)		–	
MRA reduction below target dose[a]	15.2	30.5	21.9	22.6
ARR[b]	15.3 (4.4-26.2)		0.8 (-10.1 to 11.7)	
Number needed to treat	7 (4-23)		126	
≥1 hyperkalemia event	27.5	49.4	33.9	42.3
ARR[c]	21.9 (12.1-31.8)		8.5 (0.2-16.8)	
Number needed to treat	5 (3-8)		12 (6-532)	

Values are % or HR (95% CI), unless otherwise indicated. Number needed to treat is defined as 1/absolute risk reduction (rounded up to the nearest whole number). [a]The cumulative incidence function estimate at Week 54 (trial day 379) is presented (based on the time to first hyperkalemic event with sK^+ level >5.5 mmol/L and time to reduction of the MRA dose below target dose). Aalen-Johansen estimators of the cumulative incidence function with death as a competing event are used. Data cutoff: June 24, 2021. [b]ARR is the difference between placebo and patiromer using the cumulative incidence function estimate (using nonrounded estimates). [c]ARR is the difference between placebo and patiromer using the proportion of patients with ≥1 hyperkalemic event (using nonrounded proportions). In case of negative ARR, the number needed to treat is not displayed. When the CI for the ARR contains 0 and its lower limit is negative, only the number needed to treat without CI is reported. Normal approximation is used for the 95% CI of cumulative incidence function estimates at Week 54. Wald 95% CI is used for the proportion of subjects with at least one hyperkalemic adverse event.

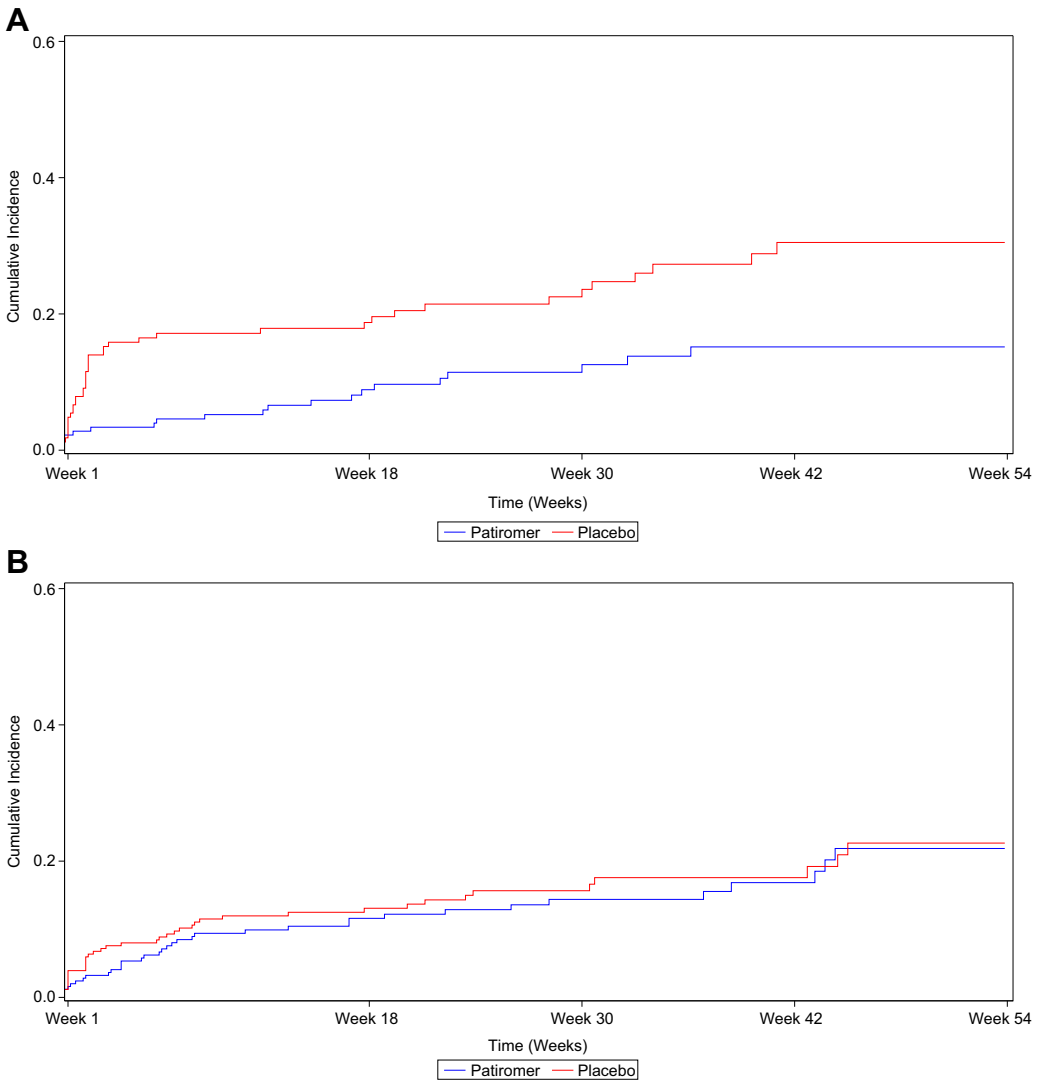
ARR = absolute risk reduction; other abbreviations as in Table 1.

DISCUSSION

This prespecified analysis of the phase 3 DIAMOND trial showed that during the run-in phase of up to 12 weeks (during which all patients received patiromer), a similar proportion of patients with current or past hyperkalemia achieved patiromer-facilitated RAASi optimization while achieving or maintaining normokalemia. In addition, during the postrandomization withdrawal phase, patiromer provided greater control of sK^+ than placebo, and it reduced the risk of sK^+ >5.5 mmol/L and recurrent hyperkalemia adverse events compared with placebo, both for patients with current and past hyperkalemia. However, patiromer had a greater effect on maintaining MRA at target dose in patients with current hyperkalemia than in those with past hyperkalemia.

Prior randomized controlled trials have shown the ability of patiromer, compared with placebo, to enable target doses of MRAs for patients with heart failure and past hyperkalemia (91% vs 74%; $P = 0.019$)[19] and for patients with advanced CKD, resistant hypertension, and sK^+ concentration between 4.3 and 5.1 mmol/L (86% vs 66%; $P < 0.0001$).[20] However, these trials did not include randomized withdrawal of patiromer to assess its longer term effects on sK^+ control and RAASi/MRA use. The OPAL-HK (Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia) trial reported that patiromer achieved normokalemia at week 4 in 76% of patients with CKD taking RAASis, regardless of whether they had mild or moderate to severe hyperkalemia.[21] Subsequently, 94% of patients remained on RAASis if maintained on patiromer compared with only 44% of those randomized to withdrawal and placebo. Recurrent hyperkalemia was reported in 60% of patients receiving placebo vs 15%

FIGURE 3 Time to Mineralcorticoid Receptor Agonist Dose Reduction Below Target Dose



Time to reduction of the mineralocorticoid receptor antagonist dose below target dose in patients with current hyperkalemia (n = 354; HR: 0.45 [95% CI: 0.26-0.76]) (A) and past hyperkalemia (n = 524; HR: 0.85 [95% CI: 0.54-1.32]; $P_{interaction}$ = 0.03) (B) at enrollment (full analysis set, 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 on June 24, 2021 is applied.

receiving patiromer within the following 8 weeks.[21] However, this trial included few patients with heart failure.[22]

The current analysis from the DIAMOND trial of patients with HFrEF and either current hyperkalemia or past hyperkalemia is from the largest randomized trial of patiromer to date, with follow-up extending over a median of 27 weeks (IQR: 13-43 weeks). Patients with heart failure who have experienced hyperkalemia are at high risk of its recurrence;[8] however, the DIAMOND trial showed that most patients can achieve target doses of RAASis,[18] and this analysis further suggests that most patients can achieve target doses of RAASis irrespective of whether patients have ongoing or a past history of hyperkalemia. These findings are consistent with results from the PEARL-HF (Parallel Evaluation of RLY5016 in Heart Failure)[19] and AMBER (Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease)[20] trials and indicate that

patients with hyperkalemia do not need to down-titrate RAASis to control sK^+. Because patiromer was more effective than placebo in maintaining MRA at target dose in patients with current hyperkalemia compared with past hyperkalemia, the need for ongoing sK^+ control with patiromer to maintain target doses of MRAs may be greatest in patients with current hyperkalemia.

There were few differences in TEAEs in patients with current hyperkalemia/past hyperkalemia, and TEAEs were generally similar in the patiromer and placebo groups. There was a higher proportion of hypokalemia TEAEs in patients with current hyperkalemia or past hyperkalemia at enrollment treated with patiromer compared with placebo; however, most of these were mild in severity, and rates align with those of previous studies reporting hypokalemia in 3% to 6% of patients treated with patiromer.[19,23] The rate of hypomagnesemia was low in all subgroups, and constipation occurred in <5% of all patients.

This prespecified subgroup analysis is exploratory, and the results should therefore be interpreted with caution. Patients with an eGFR <30 mL/min/1.73 m^2, systolic blood pressure <90 mm Hg, or symptomatic hypotension at screening were excluded, which influences the generalizability of the results. There were also relatively few sK^+ measurements available at longer follow-up times.

TABLE 3 TEAEs Reported During Double-Blinded Treatment Phase of the Trial in Patients With Current Hyperkalemia and Past Hyperkalemia at Enrollment (Safety Population, N = 878)

	Current Hyperkalemia (n = 354)		Past Hyperkalemia (n = 524)	
	Patiromer (n = 182)	Placebo (n = 172)	Patiromer (n = 257)	Placebo (n = 267)
Any TEAEs	131 (72.0)	130 (75.6)	189 (73.5)	195 (73.0)
Any serious TEAEs	24 (13.2)	22 (12.8)	30 (11.7)	36 (13.5)
TEAEs leading to trial drug withdrawal	4 (2.2)	6 (3.5)	8 (3.1)	5 (1.9)
TEAEs leading to death	10 (5.5)	8 (4.7)	14 (5.4)	10 (3.7)
Treatment-related TEAEs	24 (13.2)	23 (13.4)	35 (13.6)	39 (14.6)
Treatment-related serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common (>5%) TEAEs				
Hyperkalemia[a]	78 (42.9)	100 (58.1)	119 (46.3)	138 (51.7)
Mild	66 (36.3)	78 (45.3)	108 (42.0)	122 (45.7)
Moderate	11 (6.0)	20 (11.6)	9 (3.5)	14 (5.2)
Severe	1 (0.5)	2 (1.2)	2 (0.8)	2 (0.7)
Hypokalemia[a]	20 (11.0)	10 (5.8)	46 (17.9)	37 (13.9)
Mild	17 (9.3)	9 (5.2)	40 (15.6)	33 (12.4)
Moderate	3 (1.6)	1 (0.6)	5 (1.9)	3 (1.1)
Severe	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Hypomagnesemia	8 (4.4)	8 (4.7)	11 (4.3)	14 (5.2)
Diarrhea	10 (5.5)	2 (1.2)	9 (3.5)	13 (4.9)

Values are n (%). [a]Mild, moderate, and severe are as reported by the investigator. Subjects with ≥1 treatment-emergent adverse events (TEAEs) within a level of Medical Dictionary for Regulatory Activities are counted only once in that level, taking the most severe incident. Medical Dictionary for Regulatory Activities (Version 23.0) is used for coding adverse events.

CONCLUSIONS

In patients with HFrEF and either current or past hyperkalemia, patiromer lowered sK^+ concentration and facilitated the optimization of RAASis, with a greater effect observed on maintaining a target dose of MRA in patients with current hyperkalemia than in those with past hyperkalemia. Hyperkalemia does not need to be a barrier to maintaining target doses of RAASis in patients with HFrEF.

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being a DIAMOND Steering Committee member; has received honoraria from Vifor; has received personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, CinCor, Idorsia, KBP Biosciences, Novo Nordisk, Sanofi, Servier, and Vifor; has received support for attending meetings and/or travel from AstraZeneca, Bayer, Boehringer Ingelheim, and Vifor; is a cofounder of CardioRenal; has participated on a data safety monitoring board or advisory board from Bayer, Idorsia, and Sequana Medical; and has stock from Cardiorenal and stock options from G3P. Dr Pitt has received consulting fees, payment or honoraria, support for attending meetings and/or travel, and stock or stock option from Vifor. Dr Weir reports serving on the DIAMOND Steering Committee; and has received personal fees from CSL Vifor, AstraZeneca, Novo Nordisk, Johnson & Johnson, and Care DX. Dr Kosiborod has received research grants from AstraZeneca, Boehringer Ingelheim, and Pfizer; reports consultancy/advisory board activities for 35Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Imbria, Janssen, Lexicon Pharmaceuticals, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, Sanofi, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics; has received other research support from AstraZeneca; has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; has received support for attending meetings and/or travel from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and Vifor Pharma; and reports stock options from Artera Health, and Saghmos Therapeutics. Dr Metra has received honoraria for participation on a DIAMOND trial meeting. Dr Böhm has received research support from Deutsche Forschungsgemeinschaft (DFG, SFB-TTR 219, S-01); has received honoraria for speaking from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Medtronic, Novartis, Servier, and Vifor; and has participated in advisory boards for Amgen, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Pfizer, ReCor, Servier, and Vifor. Dr Ezekowitz has received research support for trial leadership or grants from American Regent, Applied Therapeutics, AstraZeneca, Bayer, Cytokinetics, Merck and Co, Novo Nordisk, and Otsuka; and honoraria for consultancy from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk, and Otsuka. Dr Bayes-Genis has received consulting and/or lecturing fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Roche Diagnostics, and Vifor. Dr Mentz has received honoraria from Vifor and research support and honoraria from AstraZeneca. Dr Ponikowski has received grants or contracts, consulting fees, and payment or honoraria from Abbott Vascular, Amgen, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Cibiem, Bristol Myers Squibb, Impulse Dynamics, Merck, Renal Guard Solution, Novartis, Servier, and Vifor. Dr Senni reports consultancy with Novartis, Merck, Bayer, Vifor Pharma, Abbott, Boehringer Ingelheim, AstraZeneca, BioVentrix, Servier, Novo Nordisk, Cardurion Pharmaceuticals, and AnaCardio. Dr Cleland has received personal fees from Abbott, Amgen, AstraZeneca, Idorsia, Innolife, Medtronic, Novartis, Respicardia, Servier and Torrent, and grants and personal fees from Bayer, Bristol Myers Squibb, Cytokinetics, Johnson & Johnson, MyoKardia, Pharmacosmos, Stealth Biopharmaceuticals, Vifor, and VisCardia; and personal fees and nonfinancial support from Boehringer Ingelheim outside the submitted work. Dr Merkely has received personal fees from Abbott, AstraZeneca, Biotronik, Boehringer Ingelheim, CSL Behring, Daiichi Sankyo, DUKE Clinical Institute, Medtronic, Novartis, and institutional grants from Abbott, AstraZeneca, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CSL Behring, Daiichi Sankyo, DUKE Clinical Institute, Eli Lilly, Medtronic, Novartis, Terumo, and Vifor Pharma. Dr Wächter, Mr Budden, and Dr Perrin report being paid employees and having stock/stock options in CSL Vifor. Dr Butler has received personal consulting fees from Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva Pharma, Lexicon, Lilly, LivaNova, Janssen, Medtronic, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, PharmaIN, Roche, Sequana, SQ Innovation, 3live, and Vifor; and payment from AstraZeneca, Boehringer Ingelheim-Lilly, Janssen, and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This analysis suggests that administration of patiromer helps manage sK^+ and RAASis in patients with HFrEF who have, or are at high risk of, hyperkalemia, and is of greatest benefit to patients with active hyperkalemia. Long-term patiromer therapy may be needed to maintain sK^+ control and achieve target doses of MRA.

TRANSLATIONAL OUTLOOK: The DIAMOND trial was not powered to assess the impact of patiromer-enabled RAASi optimization on cardiovascular outcomes in patients with HFrEF and current or past hyperkalemia. Further trials are warranted to determine whether enhanced use of RAASis facilitated by patiromer improves prognosis.

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KEY WORDS heart failure with reduced ejection fraction, hyperkalemia, patiromer, potassium binder, renin-angiotensin-aldosterone system inhibitor

APPENDIX For a supplemental figure and table and list of Independent Ethics Committees/Institutional Review Boards, please see the online version of this paper.