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Patiromer Facilitates Angiotensin Inhibitor and Mineralocorticoid Antagonist Therapies in Patients With Heart Failure and Hyperkalemia

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ABSTRACT

BACKGROUND Hyperkalemia (HK) is associated with suboptimal renin–angiotensin system (RAS) inhibitor and mineralocorticoid receptor antagonist (MRA) use in heart failure with reduced ejection fraction (HFrEF).

OBJECTIVES This study sought to assess characteristics and RAS inhibitor/MRA use in patients receiving patiromer during the DIAMOND (Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure) run-in phase.

METHODS Patients with HFrEF and HK or past HK entered a run-in phase of ≤12 weeks with patiromer-facilitated RAS inhibitor/MRA optimization to achieve ≥50% recommended RAS inhibitor dose, 50 mg/d MRA, and normokalemia. Patients achieving these criteria (randomized group) were compared with the run-in failure group (patients not meeting the randomization criteria).

RESULTS Of 1,038 patients completing the run-in, 878 (84.6%) were randomized and 160 (15.4%) were run-in failures. Overall, 422 (40.7%) had HK entering run-in with a similar frequency in the randomized and run-in failure groups (40.3% vs 42.5%; $P = 0.605$). From start to the end of run-in, in the randomized group, an increase was observed in target RAS inhibitor and MRA use in patients with HK (RAS inhibitor: 76.8% to 98.6%; MRA: 35.9% to 98.6%) and past HK (RAS inhibitor: 60.5% to 98.1%; MRA: 15.6% to 98.7%). Despite not meeting the randomization criteria, an increase after run-in was observed in the run-in failure group in target RAS inhibitor (52.5% to 70.6%) and MRA use (15.0% to 48.1%). This increase was observed in patients with HK (RAS inhibitor: 51.5% to 64.7%; MRA: 19.1% to 39.7%) and past HK (RAS inhibitor: 53.3% to 75.0%; MRA: 12.0% to 54.3%).

CONCLUSIONS In patients with HFrEF and HK or past HK receiving suboptimal RAS inhibitor/MRA therapy, RAS inhibitor/MRA optimization increased during patiromer-facilitated run-in. (JACC. 2024;84:1295–1308)

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HFrEF = heart failure with reduced ejection fraction

HK = hyperkalemia

K^+ = potassium

MRA = mineralocorticoid receptor antagonist

RAS = renin-angiotensin system

Renin-angiotensin system (RAS) inhibitors and mineralocorticoid receptor antagonists (MRAs) are guideline-recommended Class I therapies for patients with heart failure with reduced ejection fraction (HFrEF).[1,2] In routine clinical practice, the use of target doses of renin-angiotensin system (RAS) inhibitors, and MRAs in particular, is suboptimal, which may be due to actual or a concern of inducing hyperkalemia (HK; serum potassium [K^+] >5.0 mmol/L),[3-6] and the associated increased risk of arrhythmias, hospitalizations, and death with HK.[7-9] Patients initiated on MRAs often have their treatment discontinued within the first 6 to 12 months of initiation.[10,11] Suboptimal RAS inhibitor/MRA use may decrease the risk of HK;[12,13] however, not using RAS inhibitor/MRA therapy is associated with an increase in cardiovascular mortality and hospitalizations for heart failure,[13-15] and HK may be harmful, less because of clinical events such as arrhythmia, and more because it causes underuse of RAS inhibitors/MRAs.[9,16]

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Patiromer is a K^+ binder that exchanges K^+ for calcium in the gastrointestinal tract and is indicated for the treatment of HK in adults.[17,18] In the phase 3 DIAMOND (Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure) trial, patients with HFrEF and HK or past HK were treated with patiromer and uptitrated to ≥50% recommended doses of RAS inhibitor and 50 mg/d of MRA therapies during the run-in phase of the study.[19] Patients who could attain specified target doses while achieving or maintaining normokalaemia within 12 weeks were randomized to continue or withdraw patiromer while maintaining their RAS inhibitor and MRA dose. During the randomized phase of the DIAMOND trial, patients who continued on patiromer had significant improvements in serum K^+ control, decreased recurrent HK events, and a decreased need for MRA down-titration compared with patients who were withdrawn from patiromer and received placebo.[19] This post hoc analysis of the run-in phase of the DIAMOND trial aimed to assess patient characteristics, RAS inhibitor/MRA use, and clinical parameters of the patients with HK or past HK (ie, a history of dose reduction or discontinuation of RAS inhibitor/MRA therapy owing to HK in the previous 12 months but had normal levels of K^+ at the start of run-in), who did or did not meet the eligibility criteria for randomization after the run-in phase. This analysis also aimed to explore the RAS inhibitor/MRA dosing during the run-in phase and the reasons for run-in failure in patients who were not eligible for randomization.

METHODS

STUDY DESIGN AND PATIENTS. The design and primary results of the DIAMOND trial were published previously.[19] The study was conducted in accordance with the Declaration of Helsinki and its amendments, and any applicable national guidelines and was approved by local independent ethics committees/Institutional Review Boards (full list is included in the Supplemental Appendix). Briefly, DIAMOND was a prospective, phase 3b, multicenter, double-blind, randomized withdrawal, placebo-controlled trial including male or female patients, aged ≥18 years with NYHA functional class II to IV heart failure and a left ventricular ejection fraction of ≤40%, who either had HK at the start of run-in (2 serum K^+ values of

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>5.0 mmol/L) while receiving a RAS inhibitor (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, angiotensin receptor-neprilysin inhibitor), and/or MRA therapy, or had a history of RAS inhibitor/MRA dose reduction or discontinuation of therapy owing to HK in the previous 12 months but had normal levels of K^+ at the start of run-in (past HK).

Eligible patients were enrolled into a run-in phase of ≤12 weeks in which all patients received patiromer to control serum K^+ levels, while concurrently optimizing RAS inhibitor and MRA therapy, defined as ≥50% of recommended doses of RAS inhibitors and 50 mg/d of an MRA. The starting dose of patiromer was 8.4 g/d and could be uptitrated to 25.2 g/d to control serum K^+ levels. Patients who reached the above specified target doses of RAS inhibitor and MRA therapy while achieving normokalemia were then randomized to either continue patiromer or to withdraw patiromer and receive placebo.

This post hoc analysis assessed differences in patients with HK or past HK at the start of run-in who completed the run-in phase between those patients who met the randomization criteria (randomized group) and those patients who received ≥1 dose of study medication, but did not meet the randomization criteria (run-in failure group). The following parameters were assessed: patient characteristics and disease background (including treatment) at the start of run-in; the reasons for and the time to run-in failure; changes in patiromer and/or RAS inhibitor/MRA dosing (uptitration and downtitration); time to specified target dose of RAS inhibitor/MRA; dose of RAS inhibitor/MRA at the start and end of run-in (dropout dose in patients who did not complete the run-in phase); and laboratory (K^+, magnesium) and clinical changes (blood pressure, weight, and estimated glomerular filtration rate [eGFR]).

DEFINITION OF THE RUN-IN PHASE. The run-in phase was defined as the date that the informed consent form was completed to the day before randomization into the double-blind treatment phase for the randomized group, and to run-in failure date or, if this was not available, to patiromer end date for the run-in failure group. Patients in these 2 groups are considered to have completed the run-in phase.

STATISTICAL ANALYSIS. Descriptive statistics including mean ± SD or 95% CI are presented. *P* values for screening characteristics were from chi-squared test or Fisher exact test if frequency in any category is <5 for categorical variables; from Student's *t*-test to test difference in mean; and from Wilcoxon-Mann-Whitney *U* test for difference in medians. Adjusted mean changes in clinical laboratory and vital sign values during the run-in phase were displayed and based on a model of repeated measures adjusted for the covariates of population, region, visit, and baseline value. The error terms assume to follow multivariate normal distribution with unstructured covariance. The model includes data through the last scheduled visit for which ≥10% of subjects have assessments. HRs and *P* values for time to first achievement of specified target doses of RAS inhibitor and MRA therapies were determined by Cox proportional regression model adjusted for geographic region. A Lasso logistic regression for the binary outcome was used to explore and select the features to model run-in failure (age, body mass index, ejection fraction, eGFR, local serum K^+, NYHA functional class, region, systolic blood pressure, as well as presence of diabetes mellitus and hypertension, and use of cardiac resynchronization therapy, implantable cardioverter defibrillator, angiotensin II receptor blockers, beta-blockers, and MRAs). This used a Lasso with Schwarz Bayesian Criterion for variable selection, with no stopping criterion, and the run-in failure group as the effect to be modeled. For all analyses, SAS version 9.4 (SAS Institute, Inc) was used. *P* values and 95% CIs presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible. All results should be interpreted descriptively.

RESULTS

STUDY COHORTS AND PATIENT CHARACTERISTICS. Between April 24, 2019, and June 24, 2021, a total of 1,642 patients were screened for eligibility, and 1,195 patients were enrolled into the run-in phase of the DIAMOND trial.[19] Overall, 1,038 patients completed the run-in phase; 878 (84.6%) patients met the criteria for randomization, that is, achieving ≥50% recommended dose of RAS inhibitor plus 50 mg/d of an MRA with a serum K^+ level between 4.0 and 5.0 mmol/L (randomized group). In total, 160 patients (15.4%) were not eligible for the randomized phase of the study (run-in failure group). The remaining 157 patients were excluded owing to having not receiving patiromer (n = 13), COVID-19-related stoppages (n = 46), or discontinuations owing to the primary endpoint change (n = 98).[19]

Of patients completing the ≤12-week run-in phase, 422 (40.7%) had HK at the start of run-in, with a similar HK frequency between the run-in failure and the randomized groups (42.5% vs 40.3%; $P = 0.605$). A higher proportion of patients in the run-in failure group than the randomized group had diabetes

TABLE 1 Start of Run-In Phase Demographics and Disease Characteristics

	Hyperkalemia (n = 422)			Past Hyperkalemia[a] (n = 616)		
	Run-In Failure Group (n = 68)	Randomized Group (n = 354)	*P* Value	Run-In Failure Group (n = 92)	Randomized Group (n = 524)	*P* Value
Age, y	69.7 ± 10.2	67.5 ± 10.3	0.108	68.2 ± 10.5	66.5 ± 9.7	0.111
Race						
White	65 (95.6)	343 (96.9)		87 (94.6)	517 (98.7)	
Black or African American	3 (4.4)	7 (2.0)		4 (4.3)	5 (1.0)	
Asian	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Other	0 (0.0)	4 (1.1)	0.372	1 (1.1)	2 (0.4)	0.024
Sex						
Male	46 (67.6)	254 (71.8)		66 (71.7)	386 (73.7)	
Female	22 (32.4)	100 (28.2)	0.494	26 (28.3)	138 (26.3)	0.700
Ischemic HF	52 (76.5)	266 (75.1)	0.816	62 (67.4)	361 (68.9)	0.775
Diabetes	36 (52.9)	156 (44.1)	0.178	46 (50.0)	200 (38.2)	0.033
Hypertension	59 (86.8)	339 (95.8)	0.003	76 (82.6)	463 (88.4)	0.124
Atrial fibrillation	28 (41.2)	140 (39.5)	0.802	33 (35.9)	201 (38.4)	0.650
Local laboratory serum K^+, mmol/L	66	345		84	505	
	5.692 ± 0.550	5.426 ± 0.373	<0.001	4.724 ± 0.336	4.624 ± 0.308	0.007
NT-proBNP, pg/mL	61	313		89	514	
	1611.0 (762.7, 3217.8)	1466.1 (645.0, 3150.0)	0.608	1515.3 (796.6, 3240.7)	1328.0 (776.3, 2524.6)	0.212
eGFR, mL/min/1.73 m^2	64	314	0.022	87	507	0.007
eGFR ≥60 mL/min/1.73 m^2	51.2 ± 18.3	58.1 ± 22.2		59.9 ± 20.6	66.1 ± 19.7	
eGFR ≥45-<60 mL/min/1.73 m^2	20 (31.3)	134 (42.7)		41 (47.1)	297 (58.6)	
eGFR ≥30-<45 mL/min/1.73 m^2	18 (28.1)	80 (25.5)		24 (27.6)	130 (25.6)	
eGFR <30 mL/min/1.73 m^2	21 (32.8)	73 (23.2)		20 (23.0)	77 (15.2)	
	5 (7.8)	27 (8.6)		2 (2.3)	3 (0.6)	
Systolic BP, mm Hg	127.4 ± 16.9	131.8 ± 12.9	0.044	126.3 ± 16.9	128.7 ± 14.1	0.212
Diastolic BP, mm Hg	76.3 ± 9.5	77.6 ± 8.6	0.288	75.2 ± 10.4	77.8 ± 9.4	0.017
Total use of diuretics	53 (77.9)	282 (79.7)	0.748	81 (88.0)	446 (85.1)	0.489
Use of loop diuretics	53 (77.9)	243 (68.6)	0.125	77 (83.7)	426 (81.3)	0.613
Use of supplemental K^+	4 (5.9)	1 (0.3)	0.003	2 (2.2)	3 (0.6)	0.103
ACEI						
No dose	36 (52.9)	176 (49.7)		49 (53.3)	237 (45.2)	
Target (50%-≤100% recommended) dose	24 (35.3)	157 (44.4)		33 (35.9)	200 (38.2)	
Recommended dose	14 (20.6)	76 (21.5)		17 (18.5)	86 (16.4)	
ARB						
No dose	53 (77.9)	230 (65.0)		76 (82.2)	392 (74.8)	
Target (50%-≤100% recommended) dose	6 (8.8)	84 (23.7)		5 (5.4)	70 (13.4)	
Recommended dose	0 (0)	21 (5.9)		0 (0)	20 (3.8)	
ARNI						
No dose	50 (73.5)	307 (86.7)		68 (73.9)	437 (83.4)	
Target (50%-≤100% recommended) dose	5 (7.4)	31 (8.8)		11 (12.0)	49 (9.4)	
Recommended dose	1 (1.5)	10 (2.8)		3 (3.3)	15 (2.9)	
RAS inhibitor (ACEI/ARB/ARNI)						
No dose	3 (4.4)	5 (1.4)		10 (10.9)	22 (4.2)	
Target (50%-≤100% recommended) dose	20 (29.4)	165 (46.6)		29 (31.5)	193 (36.8)	
Recommended dose	15 (22.1)	107 (30.2)		20 (21.7)	124 (23.7)	

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mellitus/type 2 (51.3% vs 40.5%; $P = 0.012$) irrespective of HK status (52.9% vs 44.1% with HK and 50.0% vs 38.2% with past HK). Patients with HK in the run-in failure group had a lower eGFR at the start of run-in than patients with HK in the randomized group (mean: 51.2 ± 18.3 mL/min/1.73 m^2 vs 58.1 ± 22.2 mL/min/1.73 m^2), as did patients with past HK in the run-in failure and randomized groups (mean: 59.9 ± 20.6 mL/min/1.73 m^2 vs 66.1 ± 19.7 mL/min/1.73 m^2).

BASELINE HEART FAILURE THERAPY. At the start of run-in, a lower proportion of patients in the run-in failure than randomized groups were on ≥50% recommended doses of beta-blocker (47.5% vs 59.3%), which was irrespective of HK status (47.1% vs 60.5%

TABLE 1 Continued

	Hyperkalemia (n = 422)			Past Hyperkalemia[a] (n = 616)		
	Run-In Failure Group (n = 68)	Randomized Group (n = 354)	*P* Value	Run-In Failure Group (n = 92)	Randomized Group (n = 524)	*P* Value
MRA						
No dose	23 (33.8)	109 (30.8)		40 (43.5)	211 (40.3)	
50%-≤100% target dose	27 (39.7)	103 (29.1)		32 (34.8)	195 (37.2)	
Target (50 mg/d) dose	13 (19.1)	127 (35.9)		11 (12.0)	82 (15.6)	
Beta-blockers						
No dose	5 (7.4)	6 (1.7)		10 (10.9)	19 (3.6)	
≥50% recommended dose	32 (47.1)	214 (60.5)		44 (47.8)	307 (58.6)	
Recommended dose	9 (13.2)	58 (16.4)		13 (14.1)	76 (14.5)	

Vaues are mean ± SD, n (%), n, or median (Q1-Q3). Diuretics are defined as all medications under ATC level 2: C03 with the exception of ATC level 4: C03DA (MRAs). Loop diuretics are defined as all medications under ATC level 3: C03C. Supplemental potassium is defined as all medications under the following ATC 4 levels: A12BA, C03AB, C03BB, C03CB, and (B05XA containing the following ingredients "potassium" or "potassium chloride"). WHO Drug Dictionary Version Global B3 March 2019 is used for medication names. No corrections for multiple testing were applied. [a]History of hyperkalemia before start of run-in.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BP = blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro B-type natriuretic peptide; RASi = renin-angiotensin system inhibitor.

with HK and 47.8% vs 58.6% with past HK). A lower proportion of patients in the run-in failure than randomized groups were also on target (≥50% recommended) doses of RAS inhibitor (52.5% vs 67.1%) and target (50 mg/d) dose of MRA (15.0% vs 23.8%); however, in the randomized group the proportions were higher in patients with HK than past HK (RAS inhibitor: 76.8% vs 60.5%; MRA: 35.9% vs 15.6%), whereas the proportions were more comparable in the run-in failure group with HK and past HK (RAS inhibitor: 51.5% vs 53.3%; MRA: 19.1% vs 12.0%) (Table 1). Conversely, a higher proportion of patients in the run-in failure than randomized groups were not receiving an MRA at the start of run-in (39.4% vs 36.4%), with a lower proportion not receiving an MRA in patients with HK than past HK in the run-in failure group (33.8% vs 43.5%) and the randomized group (30.8% vs 40.3%).

REASONS FOR RUN-IN FAILURE. Reasons for run-in failure and ineligibility for randomization could be pooled into key categories, with some patients having reasons across multiple categories (Table 2, Central Illustration). A higher proportion of patients with HK (n = 68) than past HK (n = 92) did not meet the randomization criteria owing to failing to achieve specified target doses of MRA (17.6% vs 13.0%) or RAS inhibitor (13.2% vs 8.7%) that were or not stable for ≥1 week, or having a serum K^+ measuring outside of 4.0 to 5.0 mmol/L (16.2% vs 13.0%) (Table 2). A higher proportion of patients with past HK than HK failed to receive ≥1 packet (8.4 g) per day of patiromer (19.6% vs 2.9%). Rates of study-related factors for run-in failure (ie, withdrawal by participant, protocol violation, investigator decision, noncompliance with study drug, or withdrawal of consent) were generally similar in patients with HK and past HK.

Lasso regression analysis explored and selected the important variables that could model run-in failure (run-in failure vs randomized groups), identifying older age, lower eGFR, and lower ejection fraction as being prognostic for run-in failure.

CHANGES IN RAS INHIBITOR/MRA AND PATIROMER USE DURING RUN-IN. At the end of the run-in phase, in both randomized and run-in failure groups, including patients with HK and past HK, the proportion of patients with specified target RAS inhibitor and MRA doses had increased vs at start of run-in (Figure 1). The proportion of patients achieving the target (≥50% recommended) RAS inhibitor dose increased from start to the end of the run-in phase in the randomized group with HK (76.8%-98.6%) and past HK (60.5%-98.1%), and in the run-in failure group with HK (51.5%-64.7%) and past HK (53.3%-75.0%; an overall increase in target RAS inhibitor use in the run-in failure group of 52.5% to 70.6%). The proportion of patients achieving target (50 mg/d) MRA dose increased from start to the end of run-in phase in the randomized group with HK (35.9%-98.6%) and past HK (15.6%-98.7%), and the run-in failure group with HK (19.1%-39.7%) and past HK (12.0%-54.3%; an overall increase target MRA use in the run-in failure group of 15.0%-48.1%). The small number of patients who were randomized despite not receiving 100% target dose MRA or ≥50% recommended RAS inhibitor target dose were protocol violations. The proportion of patients not receiving

TABLE 2 Reasons Patients Were Not Randomized at the Start of Run-In (Run-In Failure Group)

Reasons That Patients Were Not Randomized[a]	Hyperkalemia (n = 68)	Past Hyperkalemia (n = 92)[b]	Total (N = 160)
Randomization criteria not met			
MRA below target (50 mg/d) dose and/or not stable for ≥1 wk	12 (17.6)	12 (13.0)	24 (15.0)
RAS inhibitor (ACEI/ARB/ARNI) below target (≥50% recommended) dose and/or not stable for ≥1 wk	9 (13.2)	8 (8.7)	17 (10.6)
Patiromer dose <8.4 g/d	2 (2.9)	18 (19.6)	20 (12.5)
Local serum K^+ level <4.0 or >5.0 mmol/L	11 (16.2)	12 (13.0)	23 (14.4)
Other reasons			
Serum K^+ >5.0 mmol/L 1 wk after maximum 25.2 g/d of patiromer	13 (19.1)	7 (7.6)	20 (12.5)
Serum K^+ <4.0 mmol/L 2 wks after minimum 0 g/d of patiromer[c]	3 (4.4)	9 (9.8)	12 (7.5)
Study-related reason			
Withdrawal by participant	20 (29.4)	24 (26.1)	44 (27.5)
Protocol violation	5 (7.4)	8 (8.7)	13 (8.1)
Investigator decision	2 (2.9)	1 (1.1)	3 (1.9)
Noncompliance with study drug	1 (1.5)	1 (1.1)	2 (1.3)
Withdrawal of consent	0	1 (1.1)	1 (0.6)
Exceeded 12-week run-in window	0	3 (3.3)	3 (1.9)
Adverse event or death			
Adverse event	18 (26.5)	17 (18.5)	35 (21.9)
Death	1 (1.5)	0	1 (0.6)

Values are n or n (%). [a]Only the reasons from the last attempt are summarized. Patients can have >1 run-in failure reasons collected. [b]History of hyperkalemia before the start of run-in. [c]May also be included as an adverse event.

Abbreviations as in Table 1.

any dose of an MRA decreased from the start to the end of the run-in phase in patients with HK (31.3%-3.8%) and past HK (40.7%-1.9%). There was an overall decrease in patients not receiving any dose of MRA of 36.9% at start to 2.7% at the end of the run-in phase.

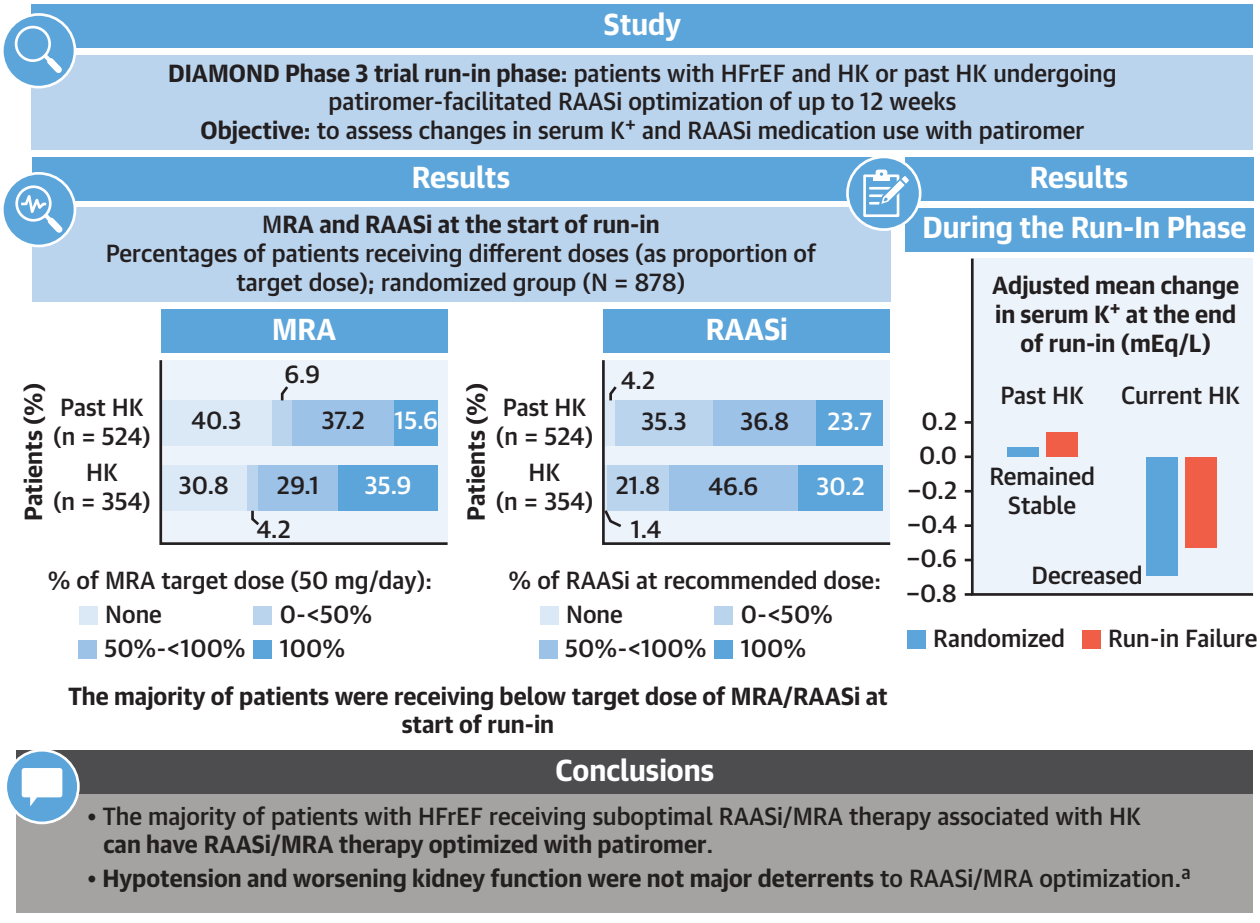
The number of patients receiving downtitrations of RAS inhibitor or MRA was low in both the run-in failure and randomized patient groups, with small numbers of patients overall receiving downtitrations of RAS inhibitor (n = 11) and MRAs (n = 3) (Supplemental Figure 1). Most patients in the run-in failure group had either no titration or uptitration of RAS inhibitor dose (83.1% with HK and 75.9% with past HK, manually calculated) and MRA dose (90.2% with HK and 82.8% with past HK, manually calculated), with no titration of RAS inhibitor/MRA dose more common in patients with HK than past HK (RAS inhibitor 53.8% vs 43.7% and MRA 57.4% vs 41.4%). At the end of the run-in phase, most patients were on 8.4 g/d or 16.8 g/d of patiromer in the randomized group, while a lack of patiromer use in the run-in failure group may reflect discontinuation of patiromer (Supplemental Table 1).

During the run-in, a more rapid time to achieving target (≥50% recommended) RAS inhibitor and target (50 mg/d) MRA doses occurred in the subsequently randomized than run-in failure group (HRs all $P \leq 0.01$) and differences in Kaplan-Meier curves were most marked in the patients with HK than past HK (Figure 2). Time to target MRA dose was shorter for the randomized group than the run-in failure group with HK (median: 1.3 weeks [95% CI: 1.0-2.0 weeks] vs median: 4.0 weeks [95% CI:3.0-8.0 weeks]; HR: 0.43 [95% CI: 0.30-0.62]; $P < 0.001$). This result was also true for the randomized vs run-in failure groups with past HK: median time to target MRA dose was 2.3 weeks (95% CI: 2.0-2.9 weeks) vs 4.0 weeks (95% CI: 2.1-5.3 weeks), respectively (HR: 0.54; 95% CI: 0.40-0.74; $P < 0.001$).

LABORATORY AND CLINICAL CHANGES DURING THE RUN-IN PHASE. At the start of run-in, patients in the run-in failure vs randomized group had a higher serum K^+ (mean: 5.15 ± 0.65 mmol/L vs 4.95 ± 0.52 mmol/L). During the run-in phase, the adjusted mean serum K^+ decreased in the randomized and the run-in failure groups with HK (−0.69 and −0.53 mmol/L, respectively; difference: 0.15 mmol/L; $P < 0.001$), whereas serum K^+ remained more stable during run-in phase in the randomized and run-in failure groups in patients with past HK (0.05 and 0.14 mmol/L, respectively; difference: 0.08 mmol/L; $P = 0.007$) (Table 3, Central Illustration).

At the start of run-in, eGFR was lower in the run-in failure group than the randomized group (mean: 56.2 ± 20.1 mL/min/1.73 m^2 vs 63.0 ± 21.0 mL/min/1.73 m^2; $P < 0.001$) and in patients with HK than

CENTRAL ILLUSTRATION **Patiromer-Facilitated RAAS Inhibitor/MRA Use in Heart Failure: DIAMOND Run-In Phase**



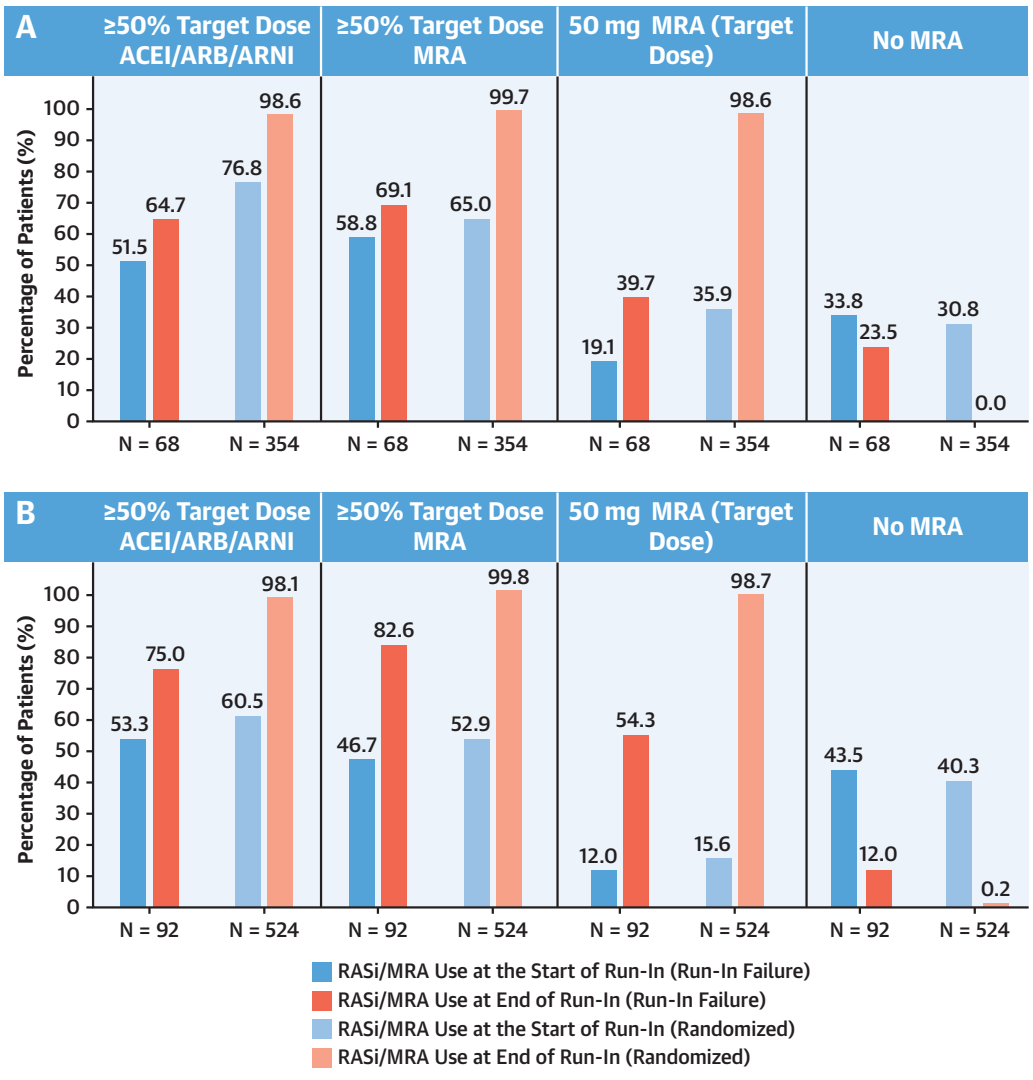
Pitt B, et al. JACC. 2024;84(14):1295–1308.

The DIAMOND phase 3 trial of patients with HFrEF and HK or past HK showed that 84.6% (878/1,038) of patients achieved patiromer-facilitated RAAS inhibitor optimization during run-in. The objective of this post hoc analysis was to assess changes in serum K^+ and RAAS inhibitor medication use with patiromer. The results show that the majority of randomized patients had been receiving a below-target dose of MRA/RAAS inhibitor at the start of run-in. During the run-in phase, serum K^+ remained stable in patients with past HK and decreased in patients with current HK. The majority of patients with HFrEF receiving suboptimal RAAS inhibitor/MRA therapy associated with HK can have RAAS inhibitor/MRA therapy optimized with patiromer. Hypotension and worsening kidney function were not major deterrents to RAASi/MRA optimization. [a]Hypotension and renal impairment were reported in 2 patients and 1 patient, respectively. DIAMOND = Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure; HFrEF = heart failure with reduced ejection fraction; HK = hyperkalemia; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

past HK, with the lowest eGFR in the run-in failure group with HK (Table 2). Changes to the eGFR from the start to end of the run-in phase were small (Table 3). At the start of run-in, mean systolic blood pressures were lower in the run-in failure than randomized group (mean: 126.8 ± 16.9 mm Hg vs 129.9 ± 13.7 mm Hg; P = 0.026). Decreases in the mean systolic blood pressure during the run-in phase were similar between randomized and run-in failure groups with HK and past HK (Table 2). In the randomized group, adjusted mean systolic blood pressure decreased by −8.401 mm Hg (95% CI: −9.749 to −7.053 mm Hg) in patients with HK and −4.873 mm Hg (95% CI: −5.985 to −3.762 mm Hg) in patients with past HK from the start to the end of the run-in phase (Table 3).

ADVERSE EVENTS. Adverse events leading to study drug withdrawal occurred in 36 patients (22.5%) in

FIGURE 1 RAS Inhibitor and MRA Use at Start and End of Run-In



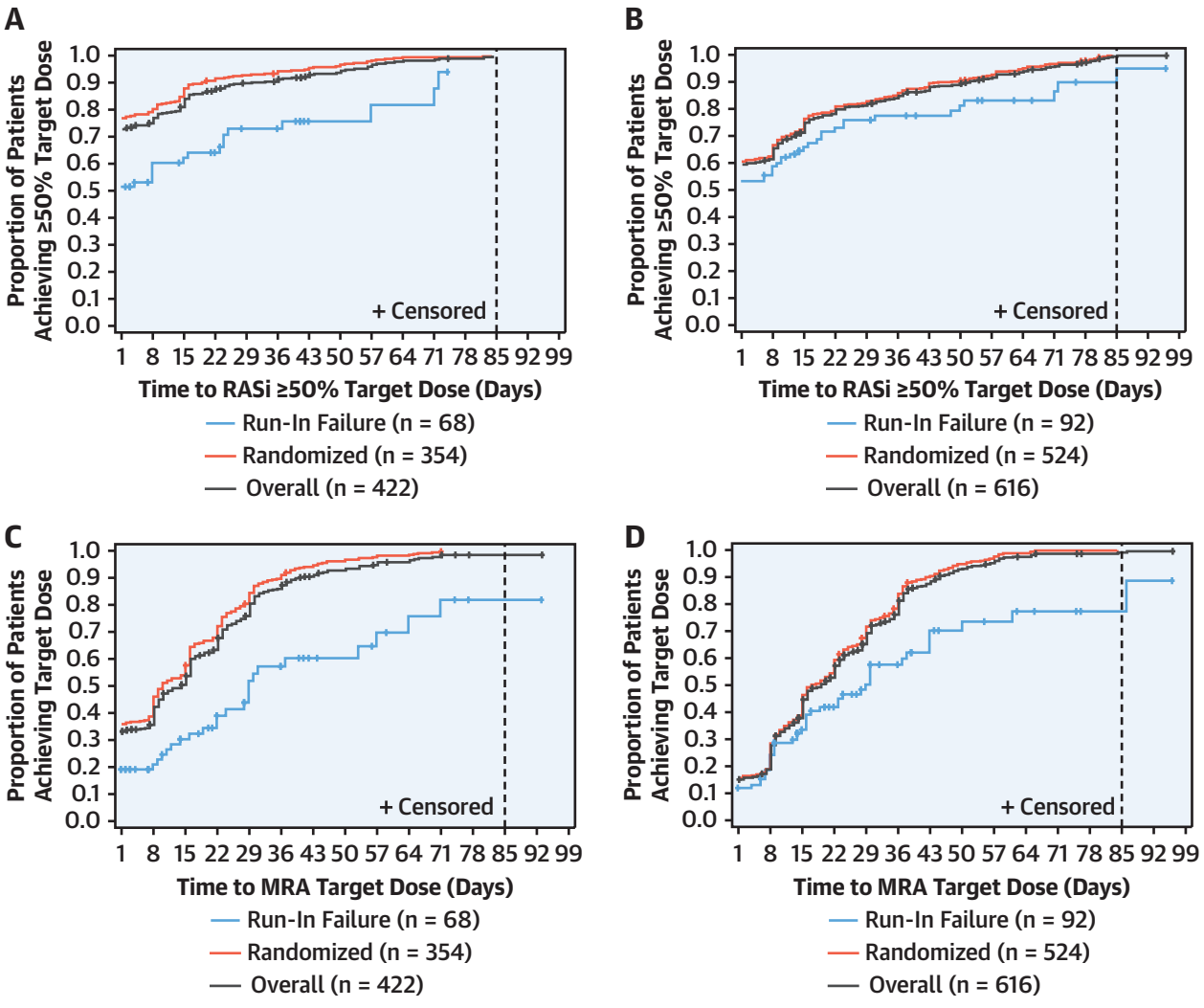
Patients (A) with hyperkalemia or (B) past hyperkalemia at the start of run-in. Doses at the end of run-in phase are displayed: dose taken on the day before the randomization date for the randomized set; and on the run-in failure date or the patiromer end date (if run-in failure date not available) for the run-in failure set. For patients who were in the run-in phase twice, data from their second run-in are summarized. Data cutoff on June 24, 2021 is applied. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; RASi = renin-angiotensin system inhibitor.

the run-in failure group, including 1 death. Overall, HK was reported in 10 patients (6.3%) (more with HK than past HK [7 patients vs 3 patients]) and hypokalemia in 6 patients (3.8%) (more with past HK than HK [4 patients vs 2 patients]), as well as gastrointestinal disorders in 12 patients (7.5%), hypotension in 2 patients (1.3%), and renal impairment in 1 patient (0.6%) (Table 4).

DISCUSSION

In the DIAMOND trial, patients with HFrEF and HK or a history of HK leading to a decrease in RAS inhibitor/MRA treatment, entered a run-in period with patiromer before being randomized to a double-blind withdrawal period. Here we detail that patiromer was able to achieve both normokalemia and ≥50%

FIGURE 2 Time to Target RAS Inhibitor and MRA Use



Proportion of patients with target (≥50% recommended) RAS inhibitor dose in patients (A) with hyperkalemia at the start of run-in and (B) with past hyperkalemia at the start of run-in. Proportion of patients with target (50 mg/d) MRA dose in patients (C) with hyperkalemia and (D) with past hyperkalemia at the start of run-in. Day 1 corresponds to the start of run-in. Patients with events prior and ongoing at ICF date will be considered as having an event on the ICF date. Only events up to last patiromer treatment date during the run-in phase are considered (patients without an event are censored to the last patiromer treatment date during the run-in phase or June 24, 2021, whichever comes first). Data cutoff on June 24, 2021 is applied. Abbreviations as in Figure 1.

recommended dose of RAS inhibitor and 50 mg/d of MRA in 84.6% of patients completing the run-in period, whereas only 17 (1.6%) and 24 (2.3%) of all patients with HK or past HK completing the run-in phase (n = 1,038) were not randomized specifically owing to failing to achieve the specified target doses of RAS inhibitor and MRA therapies (with multiple reasons for run-in failure possible), respectively. The other patients who did not meet the criteria for randomization failed to achieve ≥8.4 g/d patiromer (n = 20 [1.9%]) or normokalemia (n = 23 [2.2%]), withdrew from the study (n = 44 [4.2%]), or owing to adverse events (n = 35 [3.4%]). Patients who entered the randomized phase, including those with HK, achieved the specified target doses of MRA therapy within a median of 2 weeks from start of the run-in

TABLE 3 Adjusted Mean Changes in Clinical and Laboratory Values During the Run-In Phase

Adjusted Mean Change in Clinical Parameter During Run-In	Hyperkalemia			Past Hyperkalemia[a]		
	Run-In Failure (n = 68)	Randomized (n = 354)	*P* Value	Run-In Failure (n = 92)	Randomized (n = 524)	*P* Value
Serum K^+, mmol/L (95% CI)	−0.531 (−0.606 to −0.457)	−0.685 (−0.738 to −0.633)	<0.001	0.139 (0.078-0.199)	0.054 (0.017-0.092)	0.007
eGFR, mL/min/1.73 m^2 (95% CI)	2.051 (−0.118 to 4.220)	0.647 (−0.790 to 2.085)	0.203	−1.331 (−3.277 to 0.615)	−0.999 (−2.215 to 0.216)	0.741
Weight, kg (95% CI)	−0.105 (−0.410 to 0.201)	−0.348 (−0.539 to −0.157)	0.140	−0.036 (−0.313 to 0.242)	−0.084 (−0.260 to 0.092)	0.742
Systolic BP, mm Hg (95% CI)	−7.327 (−9.415 to −5.239)	−8.401 (−9.749 to −7.053)	0.335	−6.266 (−7.980 to −4.553)	−4.873 (−5.985 to −3.762)	0.123
Diastolic BP, mm Hg (95% CI)	−4.540 (−6.059 to −3.021)	−4.326 (−5.312 to −3.341)	0.793	−4.809 (−6.034 to −3.585)	−4.887 (−5.679 to −4.096)	0.903

Start of run-in 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 start of run-in value. Laboratory values recorded as <xx.x are analyzed as xx.x. Laboratory values recorded as >xx.x are analyzed as xx.x. Estimates are from analysis based on model of repeated measures. The error terms assume to follow multivariate normal distribution with compound symmetric covariance structure for weight, systolic and diastolic blood pressures; with unstructured covariance structure for eGFR and serum K^+. The model includes data through the last scheduled visit for which ≥10% of patients have assessments. No corrections for multiple testing were applied. Model: Change = Population + Geographic region + Visit + Baseline value. Data cutoff on June 24, 2021 is applied. [a]History of hyperkalemia before the start of run-in.

BP = blood pressure; eGFR = estimated glomerular filtration rate; other abbreviations as in Table 1.

phase. Of those in the run-in failure group, most were able to initiate, maintain, and or uptitrate RAS inhibitor (78.9% [120/152]) and MRA (85.8% [127/148]) doses in conjunction with patiromer during the run-in phase. Furthermore, in the run-in failure group, most patients who were not receiving any dose of MRA at the start of run-in were able to initiate and continue with an MRA in conjunction with patiromer (overall, only 16.9% were not receiving any dose of MRA at the end of run-in vs 39.4% at the start of the run-in phase). The primary DIAMOND analysis showed that patients randomized to continued patiromer vs patiromer withdrawal then had significant improvements in serum K^+ control, fewer recurrent HK events, and a lesser need for MRA downtitration.[19] Taken together, these findings suggest that, in addition to achieving and maintaining normokalemia, patiromer can also achieve and maintain significant increases in RAS inhibitor and MRA use, and prevent HK during this time.[19]

Patients in the run-in failure group had a higher serum K^+, lower eGFR and systolic blood pressure, and a higher proportion of diabetes, and a lower proportion received specified target RAS inhibitor and MRA doses at the start of run-in than those who were subsequently randomized. Therefore, patients in the run-in failure group required greater changes in serum K^+, especially in patients with HK, and more adjustments to RAS inhibitor and MRA therapy during the run-in phase than patients in the randomized group. Additionally, a lower proportion of patients with HK were able to achieve uptitration of RAS inhibitor/MRA dose during the run-in phase. This result confirms what is already known in the literature: HFrEF treatment, especially in patients with chronic kidney disease or diabetes, is challenging and HK is a factor that makes it difficult to achieve guideline-recommended medical therapy.[20] Indeed, patients in the run-in failure group, and particularly those with HK, took the longest to achieve the specified target doses of RAS inhibitor/MRA therapy. It is possible that, if the run-in period had been of longer duration, even fewer patients may have been run-in failures.

Adverse events led to patiromer withdrawal in 36 patients during the run-in phase. The most common type of adverse events leading to study drug withdrawal in the run-in failure group were metabolism and nutrition disorders in 17 patients. However, there were only 6 patients with hypokalemia events, which can be managed by appropriate measures to restore serum K^+, such as K^+ binder downtitration or withdrawal, or a K^+ supplement.[17,18] Conversely, there were only 10 patients with an HK event, mainly observed in patients with HK (n = 7). The next most common type of adverse events leading to study drug withdrawal were gastrointestinal disorders in 12 patients, which is in line with the known safety profile of patiromer.[21] In previous studies, initiation of an MRA in patients with chronic kidney disease has been associated with a decrease in systolic blood pressure and eGFR.[22,23] In this study, patients in the run-in failure group had a lower systolic blood pressure and eGFR than the randomized group, and there were decreases in the systolic blood pressure and small changes in the eGFR during the run-in phase. However, there were only a few patients with adverse events of hypotension (n = 2) and renal impairment (n = 1) that led to study drug withdrawal in the run-in failure group.

Although the specified target dosing of RAS inhibitor/MRA therapy could not be achieved in all patients

TABLE 4 Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal During Run-In Phase

	Hyperkalemia (n = 68)			Past Hyperkalemia (n = 92)[a]		
	Patients	Events	Incidence Rate	Patients	Events	Incidence Rate
Run-in failure group						
Patients with any TEAEs	20 (29.4)	27 (100.0)	1.912	16 (17.4)	20 (100.0)	1.190
Metabolism and nutrition disorders	10 (14.7)	10 (37.0)	0.956	7 (7.6)	7 (35.0)	0.521
Hyperkalemia	7 (10.3)	7 (25.9)	0.669	3 (3.3)	3 (15.0)	0.223
Hypokalemia	2 (2.9)	2 (7.4)	0.191	4 (4.3)	4 (20.0)	0.297
Diabetic ketoacidosis	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	6 (8.8)	10 (37.0)	0.574	6 (6.5)	8 (40.0)	0.446
Diarrhea	1 (1.5)	1 (3.7)	0.096	4 (4.3)	4 (20.0)	0.297
Constipation	3 (4.4)	3 (11.1)	0.287	1 (1.1)	1 (5.0)	0.074
Abdominal pain	1 (1.5)	1 (3.7)	0.096	2 (2.2)	2 (10.0)	0.149
Vomiting	3 (4.4)	3 (11.1)	0.287	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (2.9)	2 (7.4)	0.191	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (5.0)	0.074
Cardiac disorders	1 (1.5)	1 (3.7)	0.096	2 (2.2)	2 (10.0)	0.149
Cardiac failure acute	1 (1.5)	1 (3.7)	0.096	1 (1.1)	1 (5.0)	0.074
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (5.0)	0.074
Vascular disorders	2 (2.9)	2 (7.4)	0.191	1 (1.1)	1 (5.0)	0.074
Hypotension	1 (1.5)	1 (3.7)	0.096	1 (1.1)	1 (5.0)	0.074
Peripheral ischemia	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (1.5)	1 (3.7)	0.096	1 (1.1)	1 (5.0)	0.074
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (5.0)	0.074
Renal impairment	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Iron deficiency anemia	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Eye irritation	1 (1.5)	1 (3.7)	0.096	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (5.0)	0.074
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (5.0)	0.074
Randomized group	Hyperkalemia (n = 354)			Past hyperkalemia (n = 524)		
Patients with any TEAEs	0	0	0	2 (0.4)	2 (100.0)	0.041
Nervous system disorders	0	0	0	1 (0.2)	1 (50.0)	0.021
Dizziness	0	0	0	1 (0.2)	1 (50.0)	0.021
Skin and subcutaneous tissue disorders	0	0	0	1 (0.2)	1 (50.0)	0.021
Papule	0	0	0	1 (0.2)	1 (50.0)	0.021

Values are n (%) unless otherwise indicated. AEs reported during run-in phase are AEs with start date on or after first dose date during the run-in phase and before the first dose date during the double-blinded treatment phase where applicable. For patients who were in the run-in phase twice, data from their second run-in are summarized. A TEAE is defined as an AE with an onset or preexisting conditions that worsened on or after the first dose date during the run-in phase. Incidence rate is computed as the number of all patients with an AE divided by the total patient-years of follow-up. MedDRA Dictionary (version 23.0) is used for coding adverse events. [a]History of hyperkalemia before the start of the run-in phase.

AE = adverse event; TEAE = treatment-emergent adverse event.

in this study, the results suggest that even if careful management of patients is needed, clinically relevant RAS inhibitor/MRA use and dosing may still be achievable in the majority of patients. This agrees with the findings of the STRONG-HF (Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure) study, which found when specifically treating patients with the aim of getting them to target dose, most (84% and 54%) were able to achieve target doses of MRA or RAS inhibitor, respectively.[24] Here, most patients in the run-in failure group who did not achieve the specified target doses of RAS inhibitor/MRA were nevertheless able to initiate, maintain, or up-titrate doses of RAS inhibitor and MRA therapies. There were also very few downtitrations of RAS inhibitor/MRA doses overall, including patients in the run-in failure group. Notably, studies have shown

that RAS inhibitor and MRA doses lower than the target doses can still provide a clinical benefit.[15,25-28] STRONG-HF found that patients in the intensively treated (targeting guideline-recommended RAS inhibitor/MRA use) arm had a decreased risk of hospitalizations for heart failure or all-cause death, with improvements in N-terminal pro B-type natriuretic peptide, NYHA functional class, pulse, blood pressure, and body weight.[24] Therefore, although a small number of patients did not meet the criteria for randomization, even these patients had their RAS inhibitor/MRA use increased to a potentially clinically meaningful extent during the run-in phase. Previous studies have shown that patients with HFrEF who do not initiate or who discontinue an MRA are at increased cardiovascular risk.[13-15] However, further study is needed to demonstrate convincingly that an increase in RAS inhibitor/MRA use facilitated by patiromer can result in improvements in cardiovascular mortality and morbidity.

STUDY LIMITATIONS. Because this is a post hoc analysis, the results are not powered to assess the differences between groups. The duration, unblinded nature, and lack of placebo comparison in the run-in phase, as well as the variation in prior medication use of patients entering the study (including low background sodium-glucose cotransporter 2 inhibitor use[19]) and the potential for several parameters to change during the run-in phase, limit the conclusions that can be made about the effectiveness of patiromer. However, this analysis does allow insight into RAS inhibitor/MRA use in conjunction with patiromer in a cohort of carefully clinically and biologically monitored patients for whom many clinicians are hesitant to initiate or maintain an MRA. Although the run-in phase of the DIAMOND study did not include a placebo control, the placebo-controlled PEARL-HF (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) and AMBER (Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease) studies have previously shown significant improvements in the proportion of patients achieving a 50 mg/d dose of spironolactone with patiromer (86%-91% with patiromer vs 66%-74% with placebo).[29,30] A comparable proportion (84.6%) of patients achieved ≥50% of the recommended RAS inhibitor dose and 50 mg/d of an MRA in the DIAMOND study.[19] Whether these results can be translated to other K^+ binders is unknown; the only study of sodium zirconium cyclosilicate, which exchanges K^+ for Na^+, to enable RAS inhibitor/MRA therapy (PRIORITIZE HF [Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure]) was stopped early owing to slow enrollment during the COVID-19 pandemic, and as a result was not powered adequately to assess the effects of sodium zirconium cyclosilicate on RAS inhibitor and MRA optimization.[31] The ongoing REALIZE-K trial is examining the effects of sodium zirconium cyclosilicate vs placebo on optimizing MRA use in patients with HFrEF and HK.

CONCLUSIONS

During the run-in phase of the DIAMOND trial, the majority of patients with HFrEF with HK or a history of HK receiving suboptimal RAS inhibitor and MRA therapy could have their RAS inhibitor/MRA therapy optimized rapidly and safely while achieving or maintaining normokalaemia with patiromer. Neither hypotension nor worsening kidney function were major deterrents for RAS inhibitor and MRA optimization in this high-risk cohort. In this uncontrolled portion of the DIAMOND study, of the patients not able to be randomized, most were still able to initiate, maintain, or uptitrate RAS inhibitor and MRA doses in conjunction with patiromer. These results therefore suggest that patiromer may help to increase and maintain RAS inhibitor and MRA use in patients with HFrEF and HK or a history of HK.

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Study funding was provided by Vifor (International) AG. Dr Pitt has received consulting fees, payment or honoraria, support for attending meetings and/or travel, and stock or stock option from Vifor. Dr Anker has recevied grants from Abbott Vascular and Vifor; has received ad hoc consultancy/advisory board participation from Amgen, AstraZeneca, Bioventrix, Brahms, Cordio, CVRx, Edwards, Novartis, Novo Nordisk, Reparion, Sanofi, and Vectorious; has performed trial/registry steering committee work or consulting for Bayer AG, Boehringer Ingelheim, Cardiac Dimensions, Cardior, Impulse Dynamics, Occlutech, Servier, V-Wave, and Vifor Int; and has received fees for advisory board work from Abbott Vascular. Dr Lund has received grants or contracts from AstraZeneca, Boehringer Ingelheim, Boston Scientific, Novartis, and Vifor Pharma; has received consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Lexicon, MedScope, Merck, Pharmacosmos, Myokardia, Sanofi, Servier, and Vifor Pharma; has received payment or honoraria from Abbott, AstraZeneca, Medscope, Novartis, and Radcliffe; and has been a board member/fellow of ESC Heart Failure Association (HFA), ESC, and Swedish Society of

Cardiology, HF Working Group; and has stock or stock options in AnaCardio. Dr Coats has received consulting fees from Actimed, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, and Respicardia; has received payment or honoraria from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards, Eli Lilly, Menarini, Novartis, Servier, Vifor, and Viatris; and has participated on a data safety monitoring board or advisory board from Impulse Dynamics. Dr Filippatos has been a committee member in trials for the European Commission; has received payment or honoraria from Bayer and Boehringer Ingelheim; has participated on a data safety monitoring board or advisory board from Bayer; has a leadership or fiduciary role from European Academy, Heart Failure Association, and *JACC Heart Failure*; and has received lecture fees, advisory or committee membership in trials from Amgen, Bayer, Boehringer Ingelheim, Cardior, Impulse Dynamics, Medtronic, Novartis, Servier, and Vifor. Dr Rossignol has been a DIAMOND Steering Committee member and has received honoraria from Vifor; has received personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, CinCor, Idorsia, KBP, Novo Nordisk, Sanofi, Servier, and Vifor; has received support for attending meetings and/or travel from AstraZeneca, Bayer, Boehringer Ingelheim, and Vifor; is cofounder of CardioRenal; has participated on a data safety monitoring board or advisory board from Bayer, Idorsia, and Sequana medical; and has stock in Cardiorenal and stock options in G3P. Dr Weir has served 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; has served as a consultant/advisory board member for 35Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Imbria Pharmaceuticals, Janssen, Lexicon Pharmaceuticals, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, Sanofi, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics; has received 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 has stock options in Artera Health and Saghmos Therapeutics. Dr Metra has received honoraria for participation on a DIAMOND trial meeting. 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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, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, 3live, and Vifor; and has received 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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APPENDIX For supplemental tables and figures, please see the online version of this paper.