2022 AHA/ACC/HFSA Guideline for the Management of HF: Recommendations for MRAs

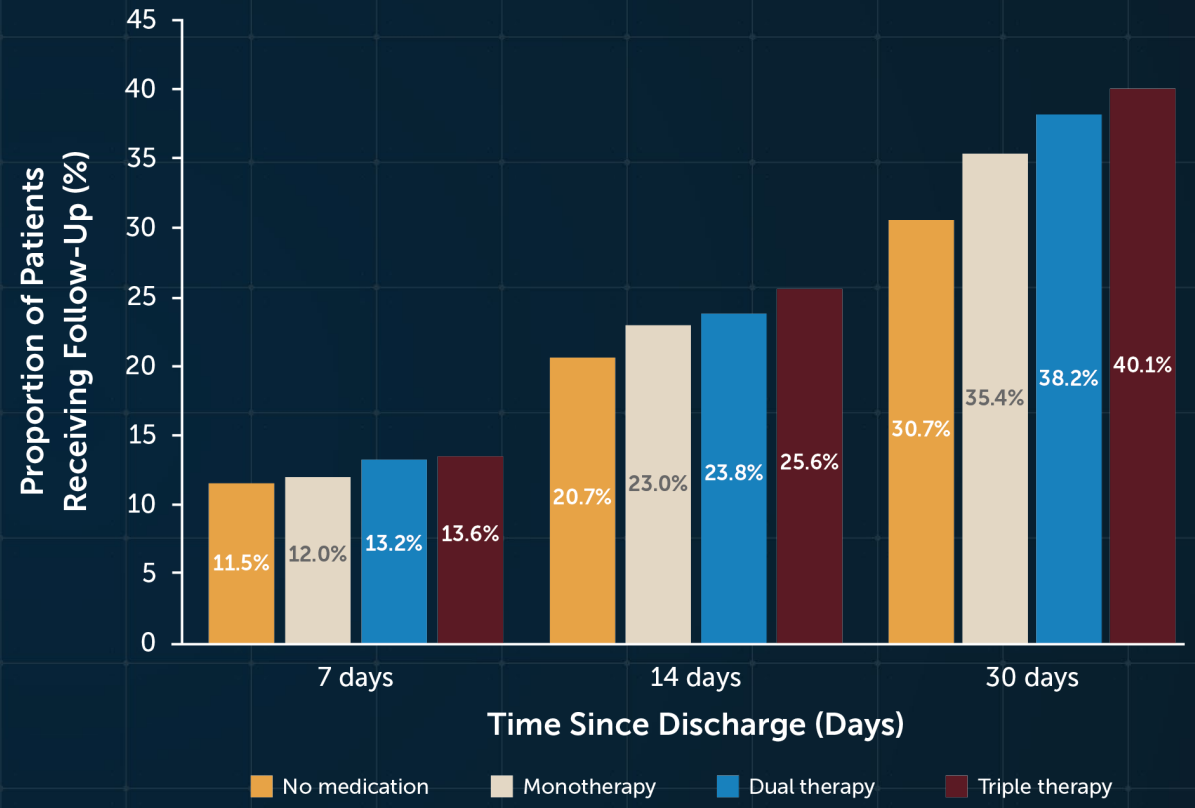
Recommendations	COR	LOE
In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.	1	A
In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value.	**Value Statement: High Value (A)**	
In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia.	3: Harm	B-NR

eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Heidenreich PA, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. Published online April 1, 2022. doi:10.1161/CIR.0000000000001062

GWTG-HF Registry: Low Rates of Guideline-Directed RAASi Therapy in HF

- **Monotherapy:** ACEI/ARB/ARNI *or* BB *or* MRA
- **Dual therapy:** (ACEI/ARB/ARNI + BB) *or* (MRA + BB) *or* (ACEI/ARB/ARNI + MRA)
- **Triple therapy:** (BB + ACEI/ARB/ARNI + MRA)

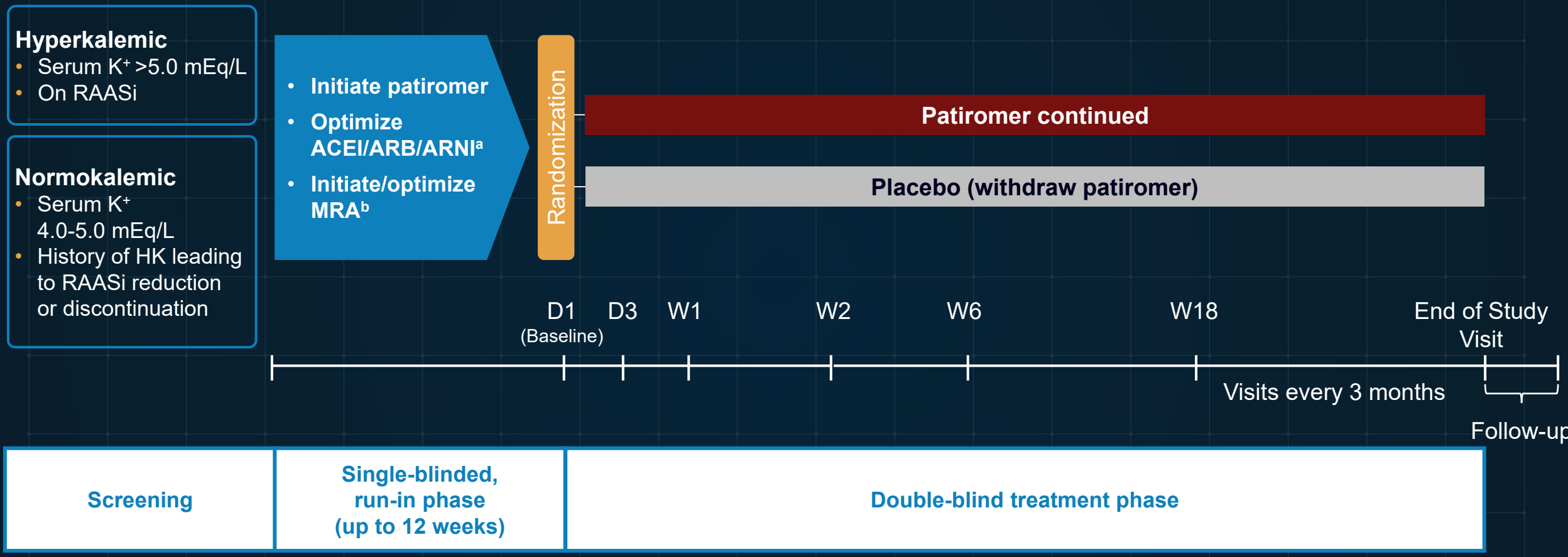


After 30 days post-discharge, 30.7% of patients received no medication and only 40.1% received triple therapy

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist.

Wirtz HS, et al. *J Am Heart Assoc*. 2020;9(16):e015042.

DIAMOND Trial: Study Design



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HK, hyperkalemia; RAASi, renin-angiotensin-aldosterone system inhibitor; W, week.

Follow-up after the end-of-study visit included a K^+ assessment visit within 2 weeks of patiromer/placebo discontinuation and/or follow-up phone call at least 2 weeks after the end-of-study visit.

[a]≥50% recommended dose of ACEI/ARB/ARNI

[b]50 mg of MRA (spironolactone or eplerenone)

Butler J, et al. *Eur J Heart Fail*. 2022;24(1):230-238.

DIAMOND Trial: Impact of COVID-19

Initial Primary Endpoint

Time to CV death or first CV hospitalization

CV, cardiovascular; HF, heart failure.

Butler J, et al. *Eur J Heart Fail*. 2022;24(1):230-238.

DIAMOND Trial: Impact of COVID-19

Initial Primary Endpoint

Time to CV death or first CV hospitalization

Impact of COVID-19 on Clinical Trials

- Slowing of the enrollment rate
- Shift in hospitalization patterns
- Concerns about investigational drug supply
- Concerns about laboratory testing

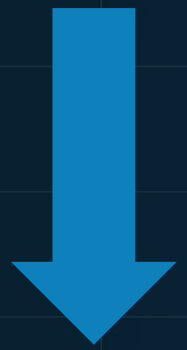
CV, cardiovascular; HF, heart failure.

Butler J, et al. *Eur J Heart Fail*. 2022;24(1):230-238.

DIAMOND Trial: Impact of COVID-19

Initial Primary Endpoint

Time to CV death or first CV hospitalization



New Primary Endpoint

Adjusted mean change in serum K^+ to the end of study (June 24, 2021)[a]

Impact of COVID-19 on Clinical Trials

- Slowing of the enrollment rate
- Shift in hospitalization patterns
- Concerns about investigational drug supply
- Concerns about laboratory testing

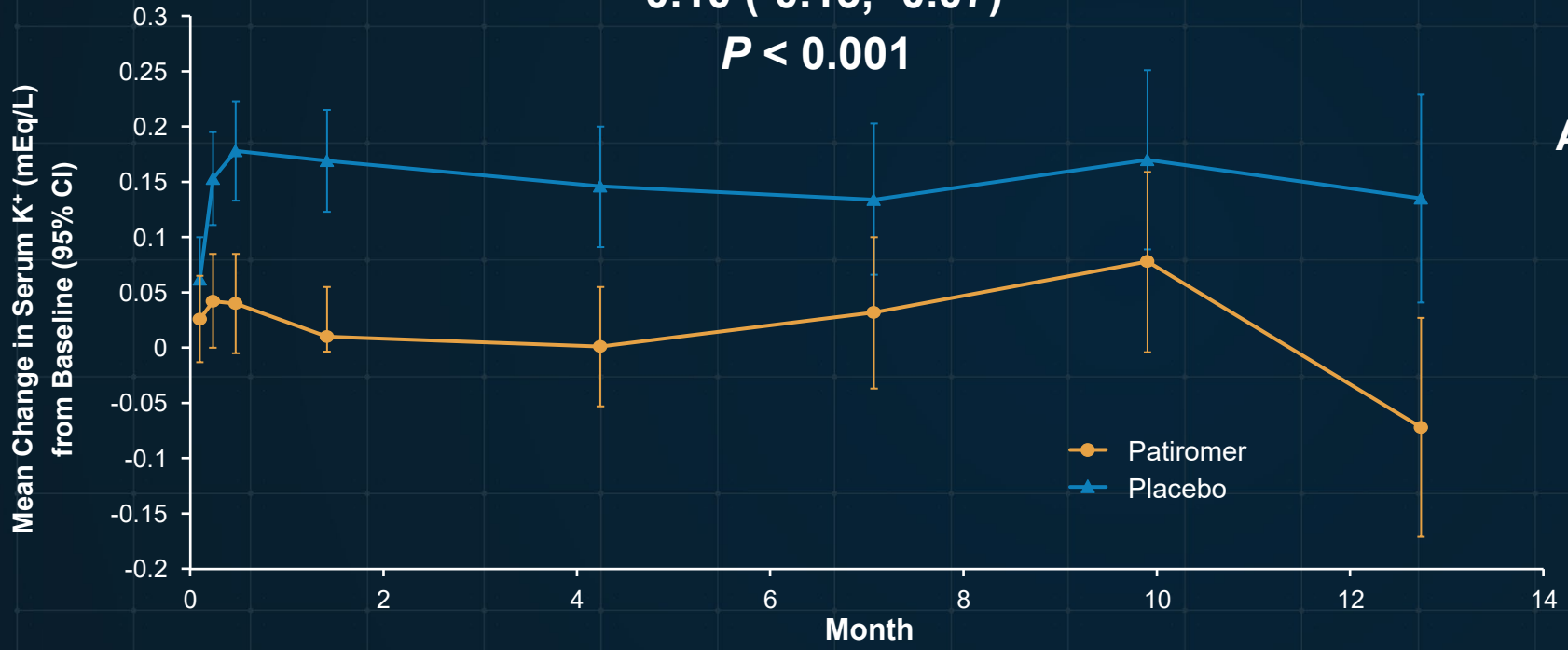
[a]Changed from original endpoint secondary to COVID-19.

CV, cardiovascular; HF, heart failure.

Butler J, et al. *Eur J Heart Fail*. 2022;24(1):230-238.

DIAMOND Trial Primary Endpoint: Change in Serum K^+ Levels from Baseline (Randomization)

Between group difference at EoS:
-0.10 (-0.13, -0.07)
***P* < 0.001**



n	Day 3	Week 1	Week 2	Week 6	Week 18	Week 30	Week 42	Week 54
Patiromer (N = 439)	409	406	402	376	273	183	104	66
Placebo (N = 439)	416	409	397	361	270	184	106	74

Adjusted mean change (95% CI) from randomization to EoS

+0.13 (0.09, 0.16)

+0.03 (-0.01, 0.07)

EoS, end of study.

Butler J, et al. *Eur Heart J*. Published online July 28, 2022. doi:10.1093/eurheartj/ehac401

DIAMOND Trial: Secondary Endpoints

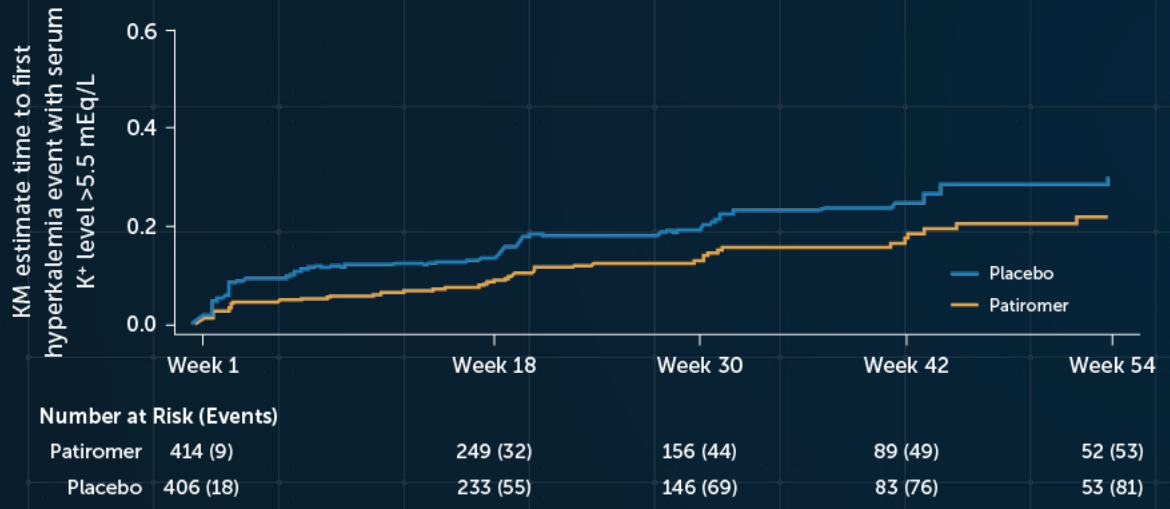
- Time to the first event of hyperkalemia
  - >5.5 mEq/L
- Time to reduction of MRA dose below target
  - 50 mg of spironolactone or eplerenone
- Investigator-reported adverse events of hyperkalemia
  - First and recurrent
- Win-ratio for morbidity and mortality adjusted hyperkalemia-related outcomes:
  - CV death
  - CV hospitalization
  - Total hyperkalemia events >6.5 mEq/L
  - Total hyperkalemia events >6.0 to 6.5 mEq/L
  - Total hyperkalemia events >5.0 to 6.0 mEq/L

Butler J, et al. *Eur Heart J*. Published online July 28, 2022. doi:10.1093/eurheartj/ehac401

DIAMOND Trial: Secondary Endpoints

Time to the first event of hyperkalemia (>5.5 mEq/L)

Patiromer (N = 439) n (%)	Placebo (N = 439) n (%)	HR (95% CI)	*P* value
61 (13.9)	85 (19.4)	0.63 (0.45, 0.87)	0.006

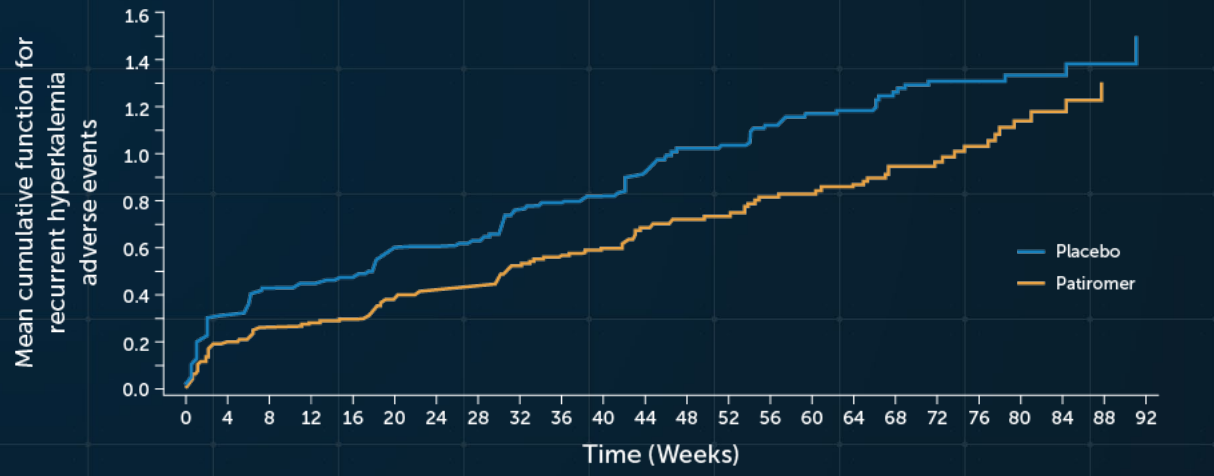


Number at Risk (Events)					
Patiromer	414 (9)	249 (32)	156 (44)	89 (49)	52 (53)
Placebo	406 (18)	233 (55)	146 (69)	83 (76)	53 (81)

HR, hazard ratio; KM, Kaplan-Meier.
Participants without an event are censored at the last K^+ measurement date or at data cut-off, whichever comes first.

Investigator-reported adverse events of hyperkalemia (first and recurrent)

Patiromer (N = 439) n (events/100 patient years)	Placebo (N = 439) n (events/100 patient years)	HR (95% CI)	*P* value
225 (77.7)	316 (118.2)	0.66 (0.53, 0.81)	<0.001

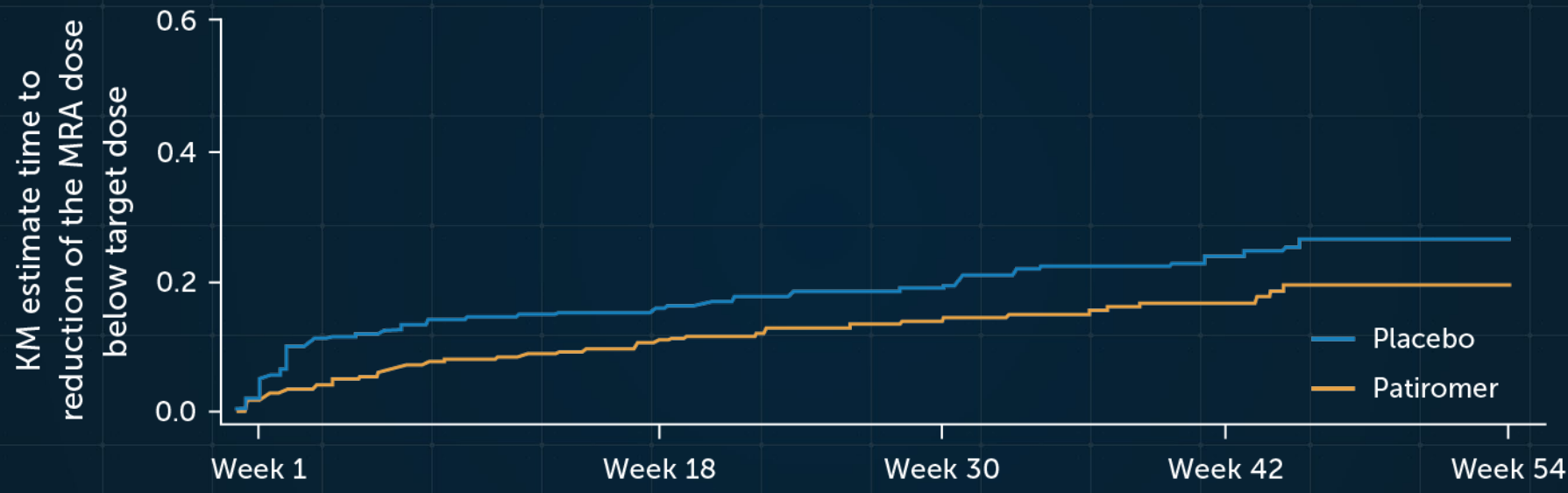


Protocol requested investigators to report K^+ >5.0 mEq/L as an adverse event.

Butler J, et al. *Eur Heart J*. Published online July 28, 2022. doi:10.1093/eurheartj/ehac401 (supplementary data).

DIAMOND Trial Secondary Endpoint:
Reduction of MRA Dose Below Target

Patiromer (N = 439) n (%)	Placebo (N = 439) n (%)	HR (95% CI)	*P* value
61 (13.9)	85 (19.4)	0.63 (0.45, 0.87)	0.006



Number at Risk (Events)					
Patiromer	417 (8)	256 (40)	169 (48)	98 (52)	62 (55)
Placebo	399 (18)	238 (61)	156 (70)	89 (77)	56 (80)

KM, Kaplan-Meier; MRA, mineralocorticoid receptor antagonist.
Target defined as 50 mg of spironolactone or eplerenone.
Participants without an event are censored at end-of-study date or date where MRA target dose could not be determined or at data cut-off, whichever comes first.
Participants not on MRA target dose at baseline are censored on Day 1.

Butler J, et al. *Eur Heart J*. Published online July 28, 2022. doi:10.1093/eurheartj/ehac401 (supplementary data).

2022 AHA/ACC/HFSA Guideline for the Management of HF: Recommendations for Hyperkalemia

Recommendations	COR	LOE
In patients with HF who experience hyperkalemia (serum potassium level ≥5.5 mEq/L) while taking a renin-angiotensin-aldosterone system inhibitor (RAASi), the effectiveness of potassium binders (patiromer, sodium zirconium cyclosilicate) to improve outcomes by facilitating continuation of RAASi therapy is uncertain.	2b	B-R

HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor.

Heidenreich PA, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. Published online April 1, 2022. doi:10.1161/CIR.0000000000001062