Looking Beyond Diabetes: The Role of SGLT2i and MRAs in Cardiorenal Disease

Disclosures

- **Research Grant**
  - AstraZeneca, Boehringer Ingelheim
- **Consultant/Advisory Board**
  - Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Sanofi, Vifor Pharma
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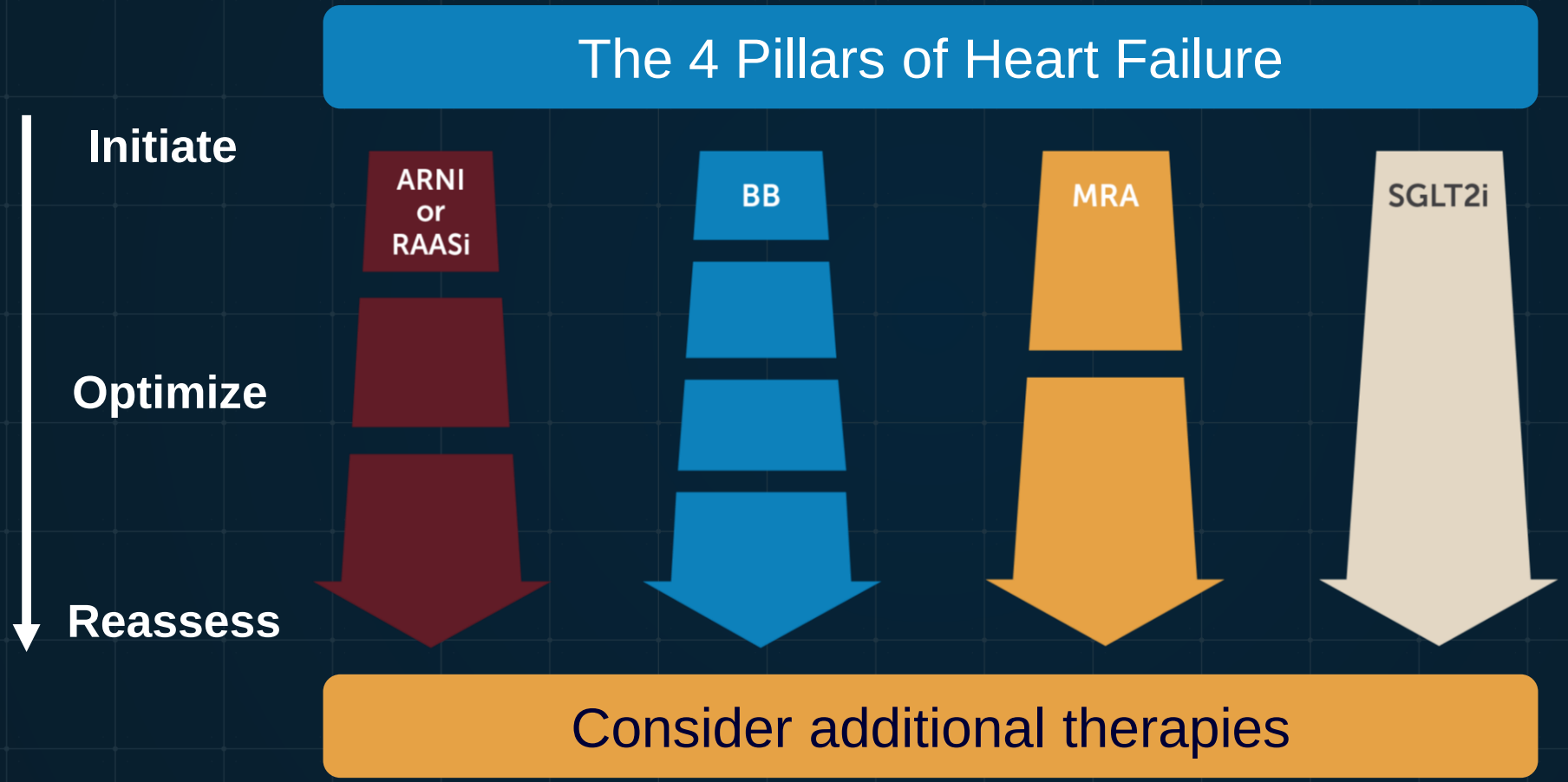
  - AstraZeneca

Initiation and Optimization of the 4 Pillars of Heart Failure



ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium glucose transporter type 2 inhibitor.

Adapted from Straw S, et al. *Open Heart*. 2021;8(1):e001585.

2021 ESC/HFA Guidelines: Pharmacologic Treatments Indicated in Patients with HFrEF

Recommendations	Class	Level
An ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

ACEI, angiotensin-converting enzyme inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

McDonagh TA, et al. *Eur Heart J*. 2021;42(36):3599-3726.

2022 AHA/ACC/HFSA Guidelines: Pharmacologic Treatments Indicated in Patients with HFrEF

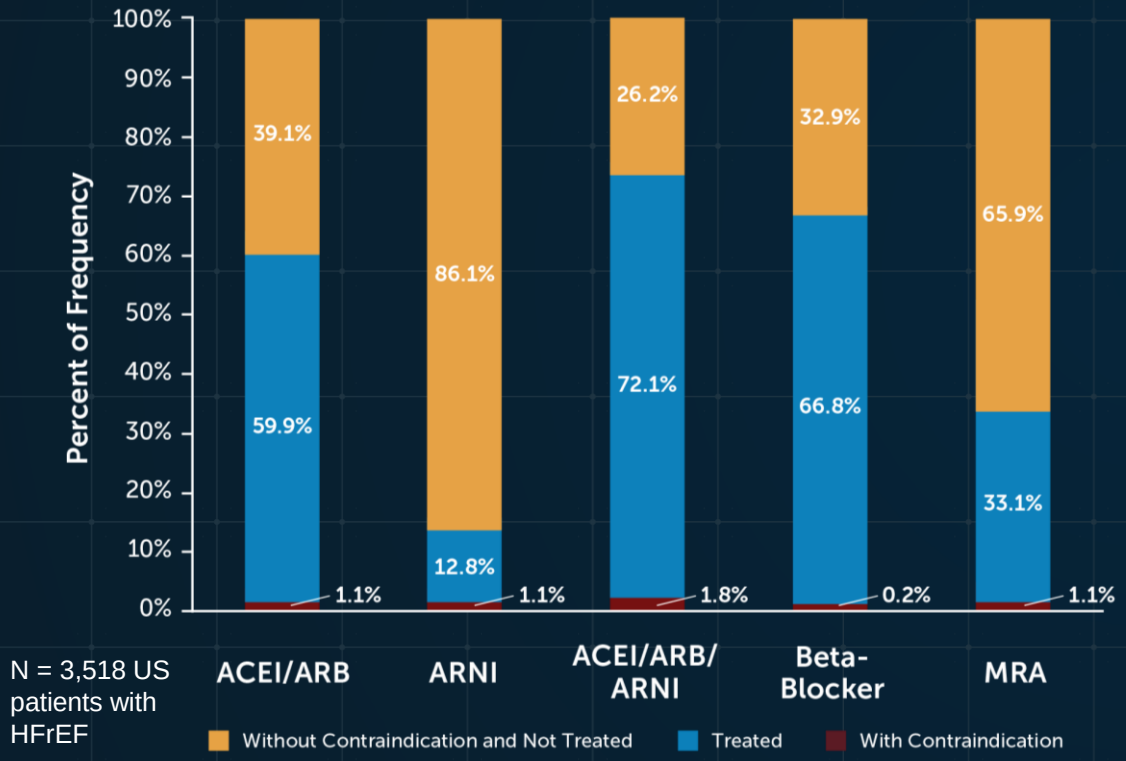
Recommendations	COR	LOE
In patients with HFrEF and NYHA class II to III symptoms, the use of ARNI is recommended to reduce morbidity and mortality.	I	A
In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta-blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.	I	A
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.	I	A
In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.	I	A

ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium glucose transporter type 2 inhibitor.

Heidenreich PA, et al. *Circulation*. 2022;145(18):e895-e1032.

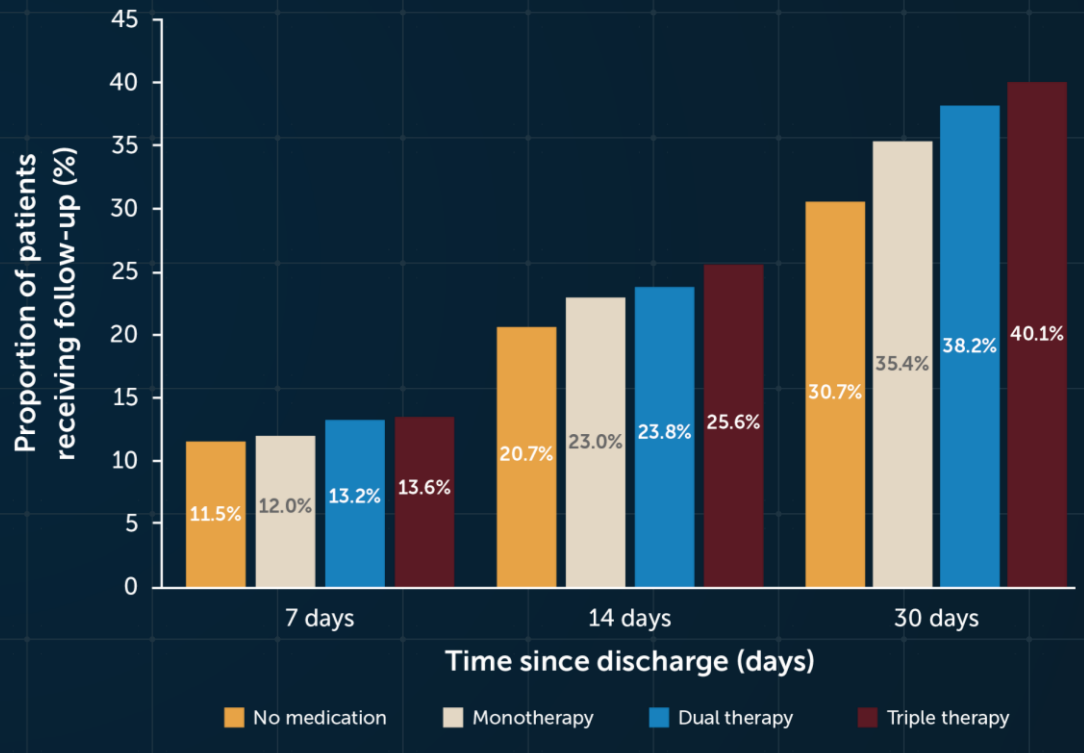
Low Rates of Guideline-Directed RAASi Therapy in HF

CHAMP-HF Registry



N = 3,518 US patients with HFrEF

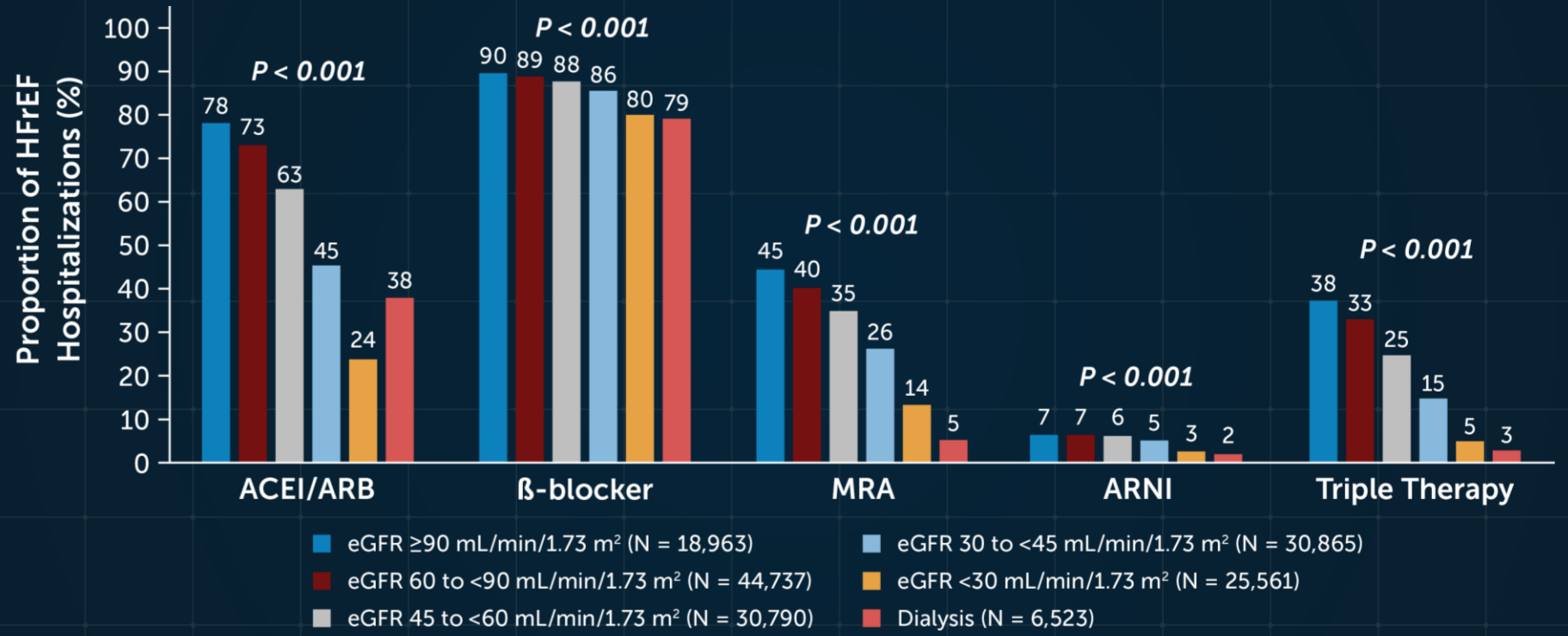
GWTG-HF Registry



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

Greene SJ, et al. *J Am Coll Cardiol*. 2018;72(4):351-366. Wirtz HS, et al. *J Am Heart Assoc*. 2020;9(16):e015042.

Low Rates of Evidence-Based HFrEF Medical Therapies at Discharge by eGFR

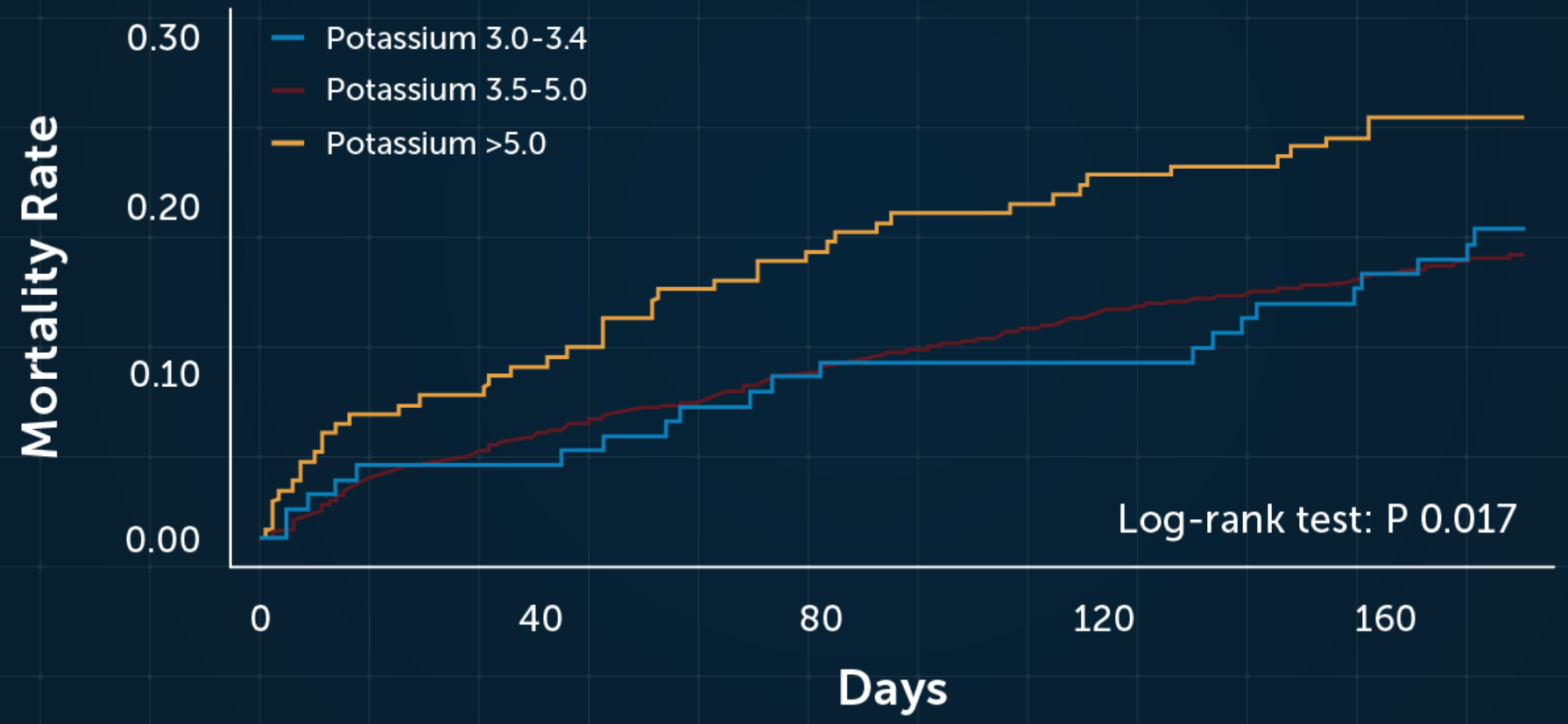


Despite elevated risk of mortality, patients with HFrEF and CKD are not optimally treated with GDMT, even when not contraindicated by severity of kidney dysfunction

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

Patel RB, et al. *J Am Coll Cardiol*. 2021;78(4):330-343.

Association of HK with All-Cause Mortality in HF (PROTECT)



HF, heart failure; HK, hyperkalemia.

Tromp J, et al. *Am J Cardiol*. 2017;119(2):290-296.

Benefit of MRA Use Is Independent of Potassium Level

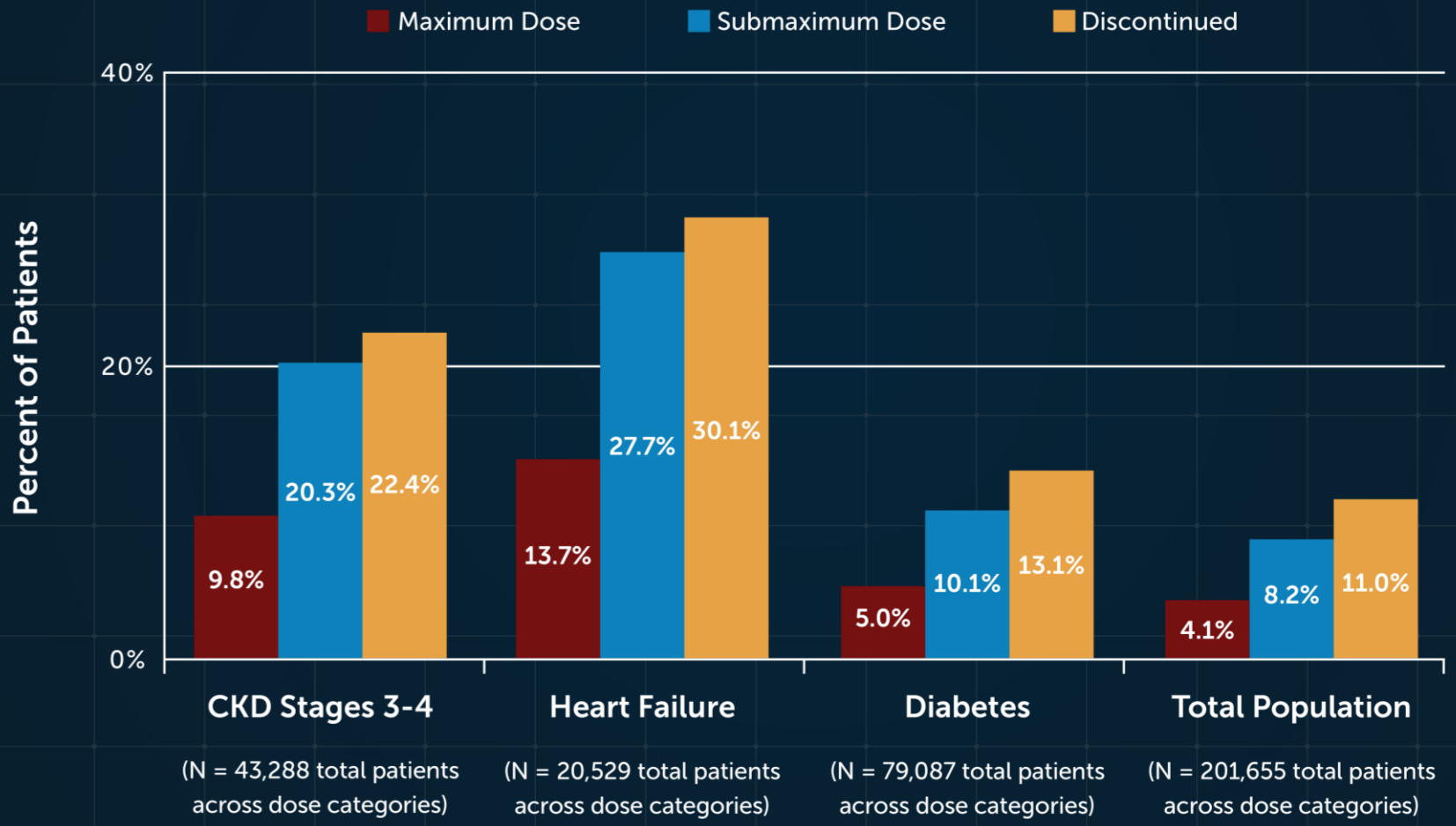
Relationship of Risk of Hyperkalemia, Worsening Renal Function, and Treatment Group (Eplerenone) with Clinical Outcomes Using a Multivariate Cox Model Adjusting for Baseline Covariates

	HF Hospitalization/CV Death (HR, 95% CI)	HF Hospitalization (HR, 95% CI)	CV Death (HR, 95% CI)	All-Cause Death (HR, 95% CI)
HK > 4.5 mmol/L	0.86 (0.72–1.03)	0.86 (0.69–1.06)	0.80 (0.63–1.01)	0.83 (0.66–1.03)
EPL	0.64 (0.55–0.76)	0.60 (0.49–0.73)	0.77 (0.62–0.95)	0.77 (0.63–0.95)
HK > 5.0 mmol/L	1.08 (0.90–1.31)	0.97 (0.77–1.23)	1.08 (0.85–1.39)	1.07 (0.85–1.35)
EPL	0.63 (0.54–0.74)	0.59 (0.48–0.72)	0.74 (0.60–0.93)	0.75 (0.61–0.92)
HK > 5.5 mmol/L	1.20 (0.89–1.61)	1.10 (0.76–1.60)	1.37 (0.95–1.98)	1.40 (1.01–1.96)
EPL	0.63 (0.54–0.74)	0.59 (0.48–0.72)	0.74 (0.59–0.92)	0.75 (0.61–0.91)

Values are hazard ratio (95% confidence interval). CV, cardiovascular; EPL, eplerenone vs placebo; HF, heart failure; HK, hyperkalemia; MRA, mineralocorticoid receptor antagonist.

Rossignol P, et al. *Circ Heart Fail*. 2014;7(1):51-58.

Suboptimal MRA Therapy Is Associated with Increased Mortality



CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist.

Epstein M, et al. *Am J Manag Care*. 2015;21(11 Suppl):S212-S220.

Approaches to Managing Hyperkalemia in HFrEF

- Preventative approach to patients with HF and concomitant CKD
  - Once ACEI is initiated → consider low-potassium diet and eliminate NSAIDs
- ACEI/ARBs, ARNI, and MRA may be maintained
- Monitor K^+ and creatinine closely
- If reliable clinical follow-up and serum K^+ assessment are doubtful, may consider K^+ binder which is preferable to compromising RAASi therapy

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; K^+, potassium; MRA, mineralocorticoid receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; RAASi, renin-angiotensin-aldosterone system inhibitor.

Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.

Guideline Recommendations for Hyperkalemia in HFrEF

2022 AHA/ACC/HFSA

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

2021 ESC/HFA

Guidance
Renal dysfunction and hyperkalemia are the major causes of underuse of RAAS inhibitors, particularly MRA, in clinical practice. Administration of the potassium-lowering agents, patiromer or SZC, may allow RAASi initiation or up-titration in a larger proportion of patients.

HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; SZC, sodium zirconium cyclosilicate.

Heidenreich PA, et al. *Circulation*. 2022;145(18):e876-e894; McDonagh TA, et al. *Eur Heart J*. 2021;42(36):3599-3726; Writing Group. *Eur Heart J*. 2021;ehab368.

DIAMOND Trial: Study Design

Hyperkalemic
- Serum K^+ >5.0 mEq/L
- On RAASi

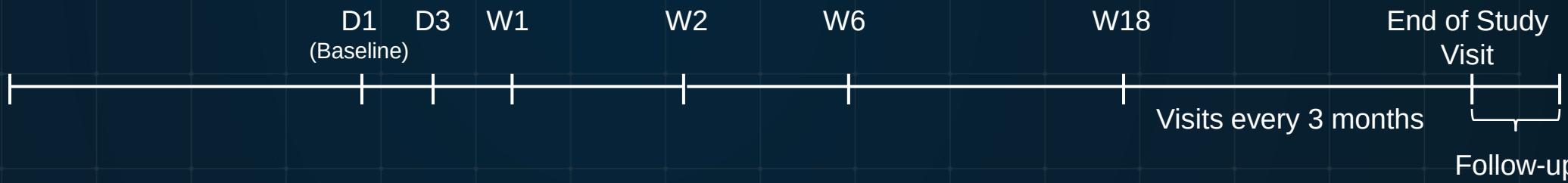
Normokalemic
- Serum K^+ 4.0-5.0 mEq/L
- History of HK leading to RAASi reduction or discontinuation

- **Initiate patiromer**
- **Optimize ACEI/ARB/ARNI[a]**
- **Initiate/optimize MRA[b]**

Randomization

Patiromer continued

Placebo (withdraw patiromer)



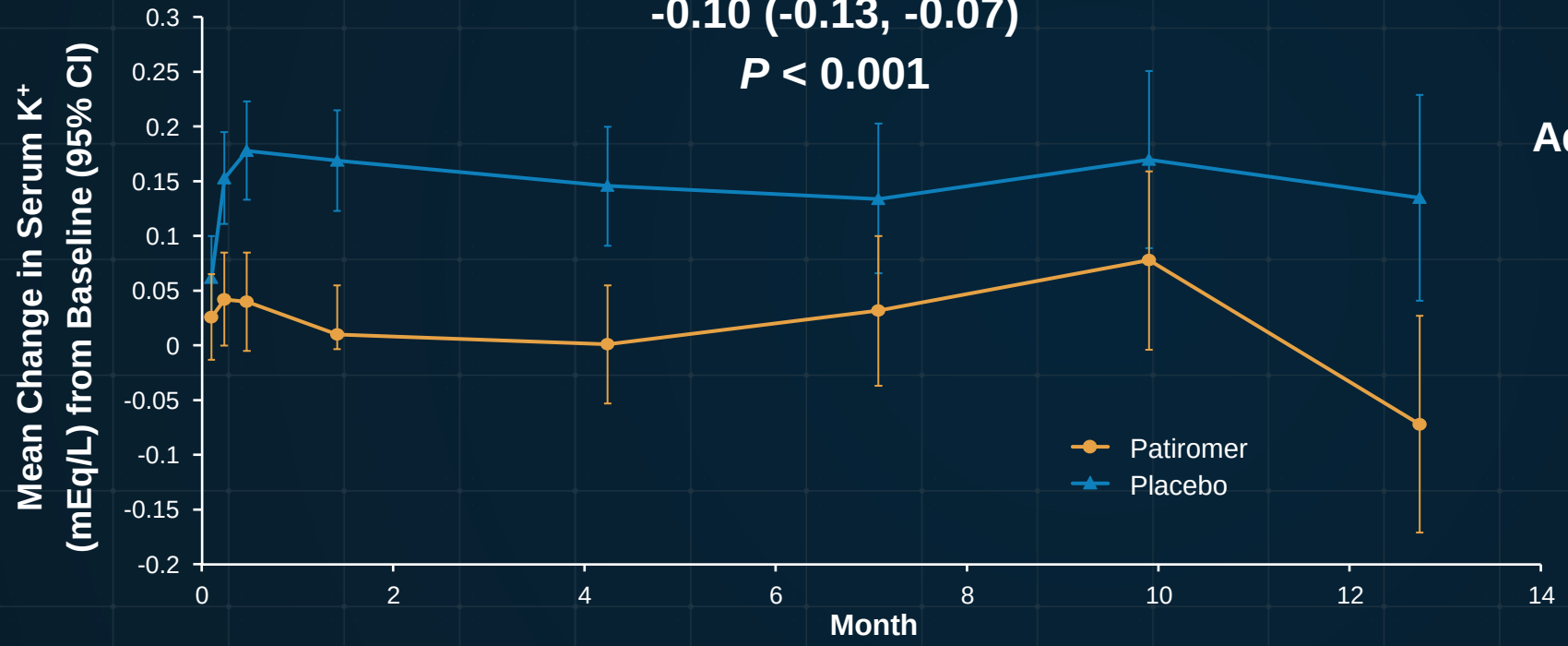
Screening	Single-blinded, run-in phase (up to 12 weeks)	Double-blind treatment phase

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; D, day; HK, hyperkalemia; MRA, mineralocorticoid receptor antagonist; 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 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)

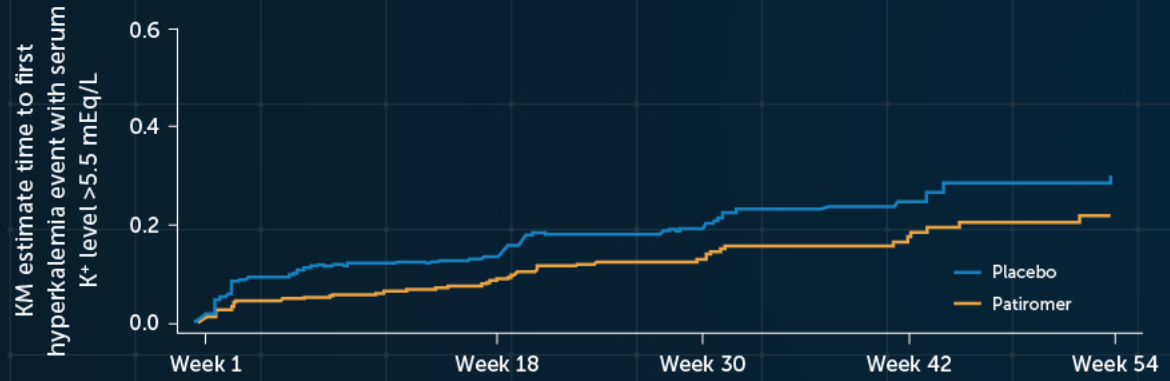
EoS, end of study.

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

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

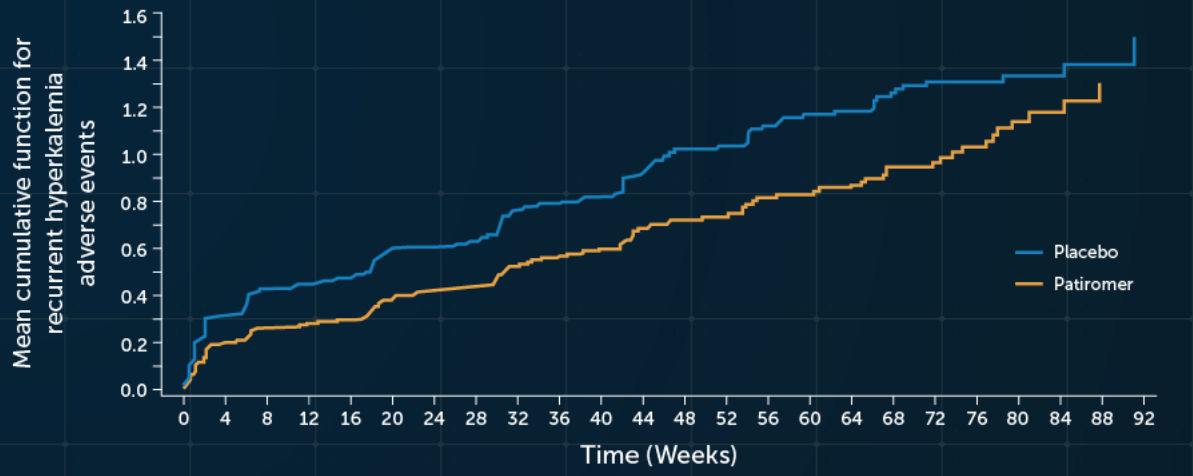


Number at Risk (Events)					
Patiromer	414 (9)	249 (32)	156 (44)	89 (49)	52 (53)
Placebo	406 (18)	233 (55)	146 (69)	83 (76)	53 (81)

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

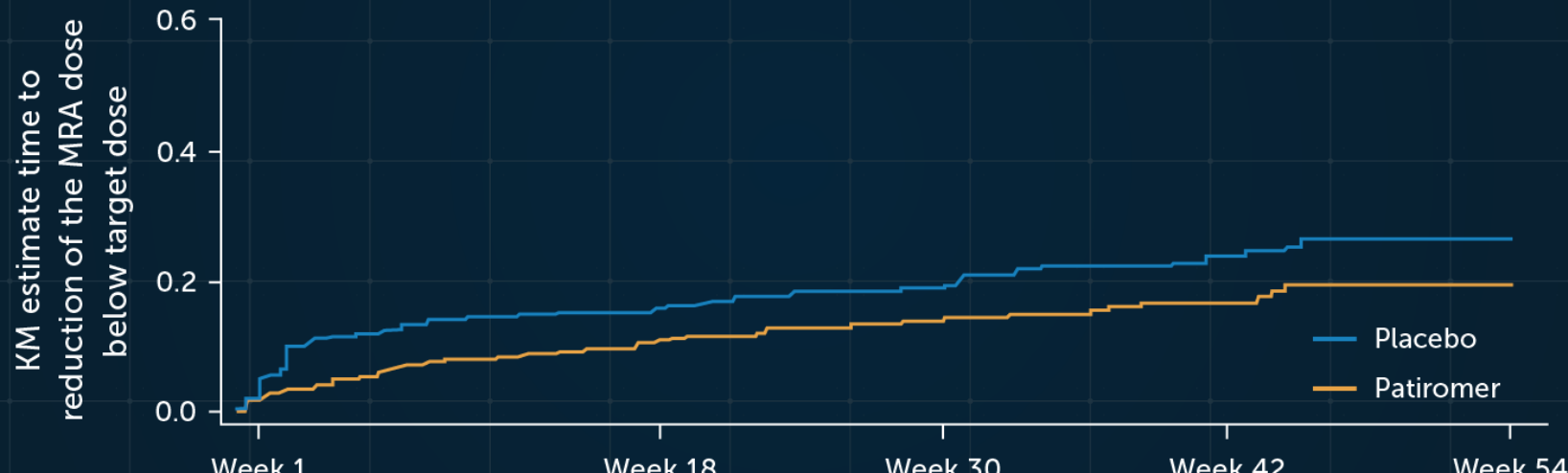


Protocol requested investigators to report K^+ >5.0 mEq/L as an adverse event.

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

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 J Heart Fail*. 2022;24(1):230-238.

Reduction of HK with Use of SGLT2i

Incident Hyperkalemia During Follow-Up by Randomized Treatment in Patients Taking and Not Taking MRA

	Patients Not on MRA		Patients on MRA		
	Placebo (n = 697)	Dapagliflozin (n = 677)	Placebo (n = 1,674)	Dapagliflozin (n = 1,696)	*P* Value for Interaction
Mild hyperkalemia* (potassium > 5.5 mmol/L)					
Events	57/682 (8.4)	63/660 (9.6)	204/1,625 (12.6)	180/1,632 (11.0)	
Rate, per 100 patient-yrs	6.4 (5.0-8.4)	7.2 (5.7-9.3)	10.0 (8.7-11.5)	8.7 (7.5-10.1)	
HR† (95% CI)	1.20 (0.84-1.72); *P* = 0.316		0.86 (0.70-1.05); *P* = 0.144		0.13
Moderate/severe hyperkalemia‡ (potassium > 6.0 mmol/L)					
Events	11/695 (1.6)	13/675 (1.9)	40/1,666 (24)	21/1,683 (1.3)	
Rate, per 100 patient-yrs	1.2 (0.6-2.1)	1.4 (0.8-2.4)	1.8 (1.3-2.4)	0.9 (0.6-1.4)	
HR† (95% CI)	1.17 (0.52-2.62); *P* = 0.707)		0.50 (0.29-0.85); *P* = 0.01		0.08

*Values are n/N (%), unless otherwise indicated. Excluding patients with baseline serum potassium >5.5 mmol/L (n = 145). †Adjusted for baseline potassium and stratified by diabetes status. ‡Excluding patients with baseline serum potassium >6.0 mmol/L (n = 25).

HK, hyperkalemia; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium glucose transporter type 2 inhibitor.

Shen L, et al. *JACC Heart Fail*. 2021;9(4):254-264.

Key Take-Home Messages

- Optimization of guideline-directed medical therapy is critical
- Hyperkalemia can be a rate-limiting step and is an obstacle to GDMT optimization in a large proportion of patients
- The tools in our armamentarium to optimize RAAS inhibition, especially MRAs, are increasing and now include novel potassium binders

Thank You