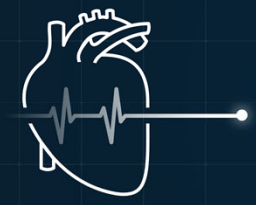


Potassium Management in Patients at Risk for Hyperkalemia

Agenda

- The Benefits of RAASi Therapy in HF and CKD
- RAASi Underuse and Underdosing Is Common
- Hyperkalemia Is a Frequent Side Effect
- Treatments for Hyperkalemia
- Novel Potassium Binders: Facilitators of RAASi Therapy
- Practical Strategies for Dyskalemia Management

The Benefits of RAASi Therapy in HF and CKD

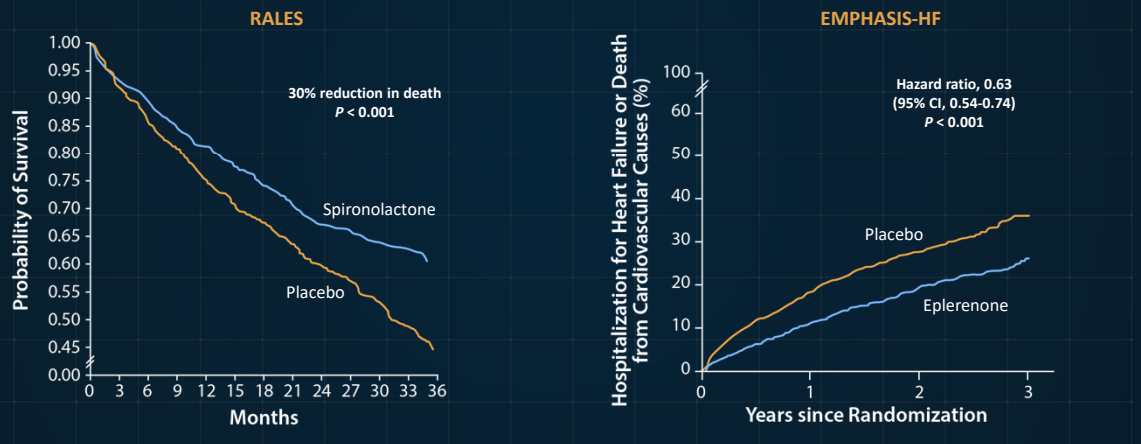
RAASi Therapy Remains a Cornerstone of Guideline-Directed Care

- Cardiology
  - American College of Cardiology/American Heart Association (ACC/AHA)
  - European Society of Cardiology (ESC)
  - Heart Failure Society of America (HFSA)
- Nephrology
  - Kidney Disease Improving Global Outcomes (KDIGO)
  - National Institute for Health and Care Excellence (NICE)
  - National Kidney Foundation (NKF)

RAASi, renin-angiotensin-aldosterone system inhibitor; Yancy CW, et al. *Circulation.* 2013;128(16):1810-1852. Ponikowski P, et al. *Eur J Heart Fail.* 2016;18(8):891-975. Heart Failure Society of America, et al. *J Card Fail.* 2010;16(6):e1-194. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl (2011).* 2013;3(1);1-150. National Institute for Health and Care Excellence. Chronic Kidney Disease in Adults: Assessment and Management. Published July 23, 2014. https://www.nice.org.uk/guidance/cg182. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl (2011).* 2012;2(5);347-356.

Evidence-based treatment guidelines consistent recommend the use of RAASi therapy for patients with heart failure and chronic kidney disease. These agents should be titrated to optimal maximum doses so that patients can derive the greatest benefits from treatment.

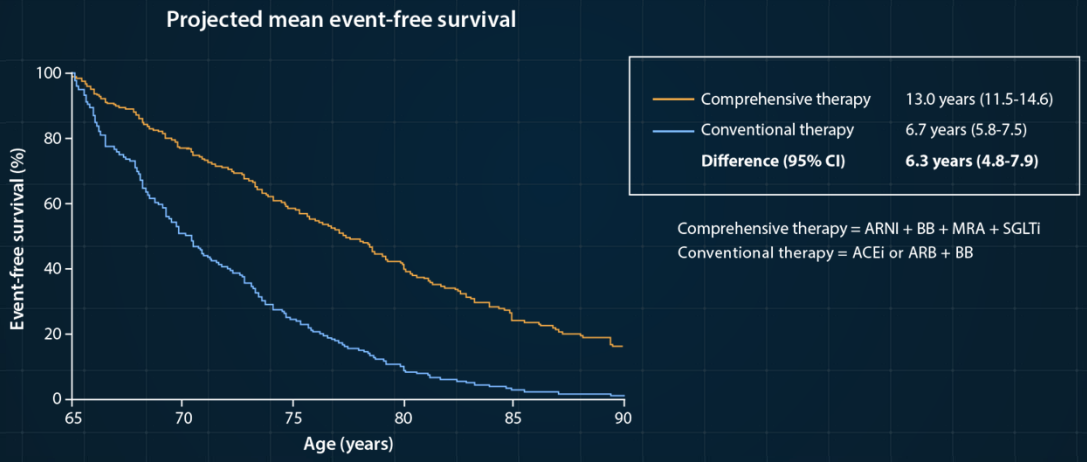
MRA Improves Survival and Reduces Morbidity in HFrEF



HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.
Pitt B, et al. *N Engl J Med.* 1999;341(10):709-717. Zannad F, et al. *N Engl J Med.* 2011;364(1):11-21.

In patients with heart failure, the use of the mineralocorticoid receptor antagonists (MRAs), spironolactone and eplerenone, improves survival and reduces the rate of hospitalization and cardiovascular related death.

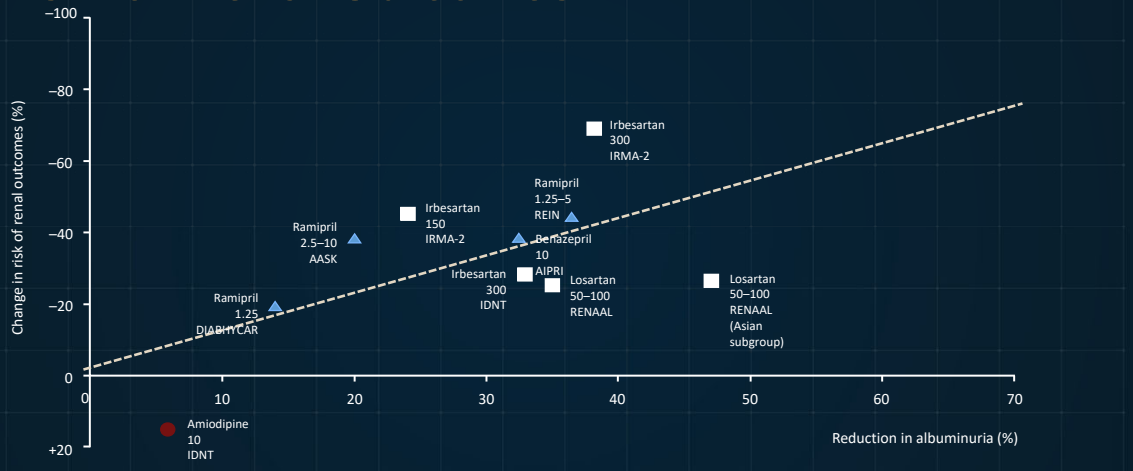
Comprehensive Therapy (ARNI + BB + MRA + SGLT2i) Improves Survival in HFrEF



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium glucose co-transporter 2 inhibitor.
Vaduganathan M, et al. *Lancet*. 2020;396(10244):121-128.

More recently, a cross-trial analysis of data from EMPHASIS-HF, PARADIGM-HF, and DAPA-HF found that comprehensive disease-modifying therapy, consisting of an ARNI, β-blocker, MRA, and SGLT2 inhibitor, provides substantial improvements in survival outcomes of patients with heart failure with reduced ejection fraction (HFrEF). Notably, comprehensive disease-modifying therapy improved survival by more than 6 years compared with conventional therapy.

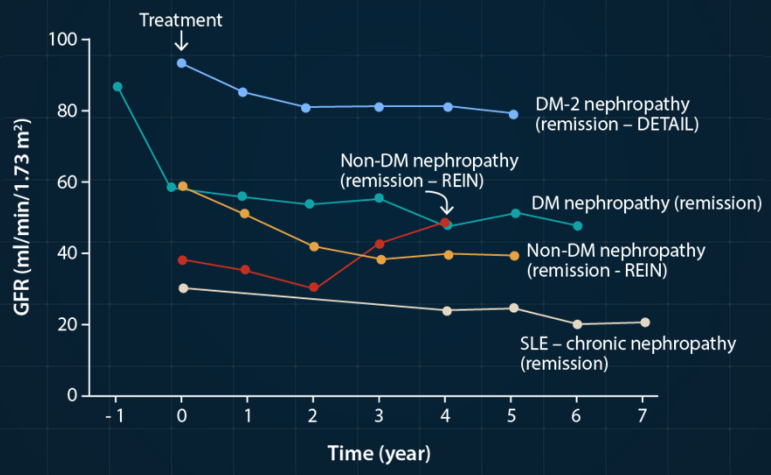
RAASi Therapy Reduces Albuminuria and Risk for Renal Outcomes



White rectangles, ARB; blue triangles, ACEi; red circles, treatment with other classes of antihypertensive drugs; Dotted line, best-fit correlation line determined by linear regression; Study acronyms are presented with the respective active treatment and dose in milligrams per day.
AASK, African American Study of Kidney Disease and Hypertension; AIPRI, Angiotensin Converting Enzyme Inhibition in Progressive Renal Insufficiency; ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; DIABHYCAR, Diabetes, Hypertension, Cardiovascular Events and Ramipril; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria-2; REIN, Ramipril Efficacy in Nephropathy; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (Asian Subgroup). Basi S, et al. *Am J Kidney Dis.* 2006;47(6):927-946.

RAAS inhibition with ACE-inhibitor or ARB therapy is effective at decreasing both albuminuria and risk for renal outcomes. In general, greater decreases in albuminuria have been associated with a lower risk for renal outcomes.

RAASi Therapy Slows Declines in Kidney Function

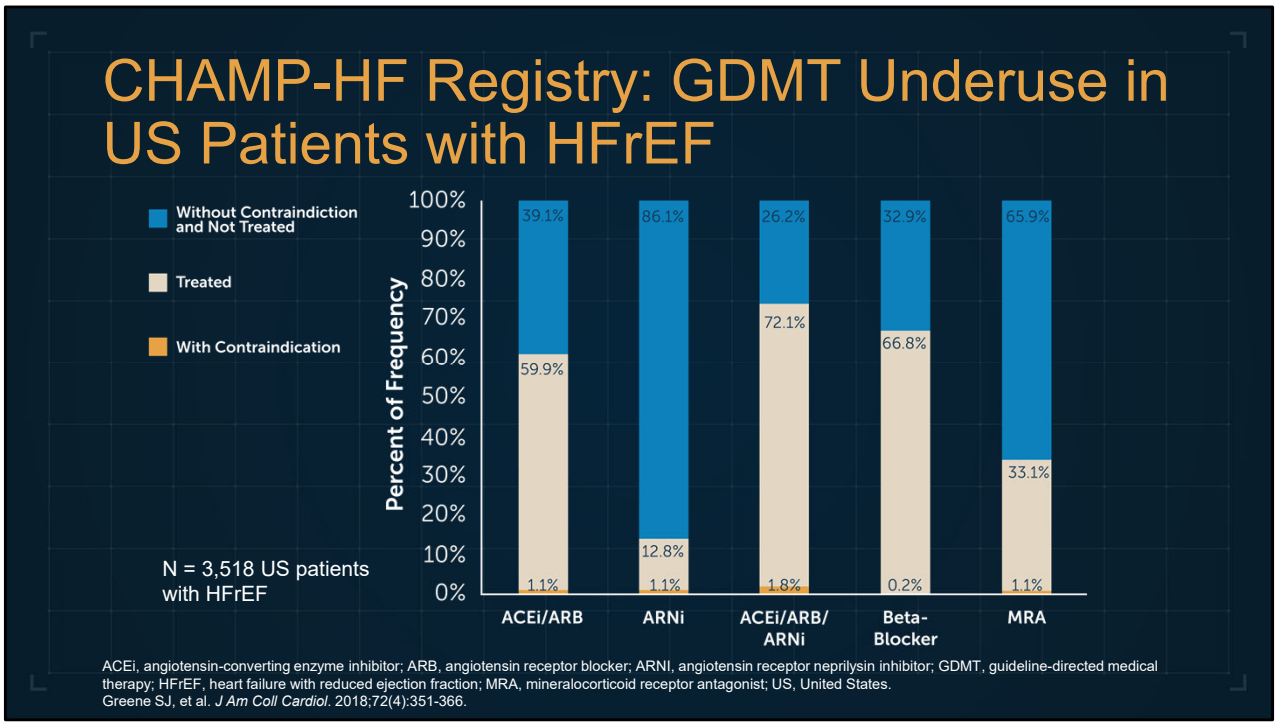


DETAIL, Diabetics Exposed to Telmisartan and Enalapril trial; DM, diabetes mellitus; GFR, glomerular filtration rate; SLE, systemic lupus erythematosus; REIN, ramipril in non-diabetic renal failure. Remuzzi G, et al. *J Clin Invest.* 2006;116(2):288-296.

Treatment with RAASi therapy also stabilizes of glomerular filtration rates (GFRs) and may even improve GFRs in some cases.

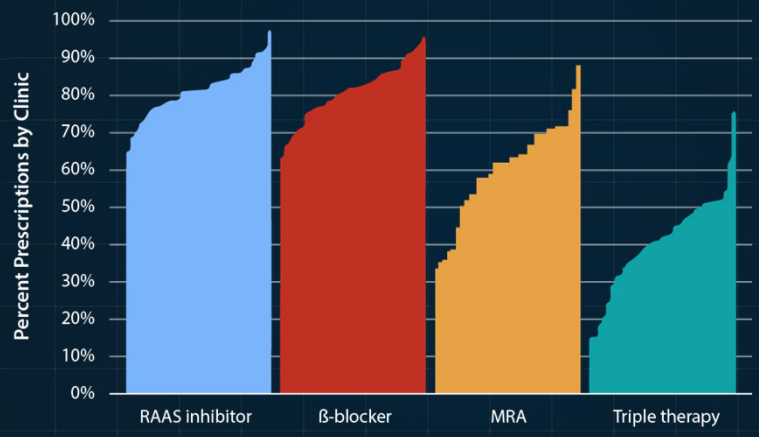
Treatments used in the depicted studies included the following:
DM-2 nephropathy (remission – DETAIL) [blue line]: 250 patients were randomly assigned to either telmisartan (80 mg daily, n = 120) or enalapril (20 mg daily, n = 130).
Non-DM nephropathy (remission – REIN) [red line]: continued ramipril (1.25 to 5 mg daily to achieve a diastolic blood pressure less than 90 mm Hg, n = 26) during the core and follow-up study periods.
Non-DM nephropathy (remission – REIN) [yellow line]: switched to ramipril (1.25 to 5 mg daily to achieve a diastolic blood pressure less than 90 mm Hg, n = 17) during the follow-up study period after completion of the core study period.
DM nephropathy (remission) [green line]: propranolol (40 mg four times daily) [green line]
SLE – chronic nephropathy (remission) [gray line]: the patient was initially treated with an ACE inhibitor to achieve a diastolic blood pressure of 90 mm Hg or less; after three years when severe renal failure developed, the patients was treated with an ACE inhibitor, ARB, statin, and dietary sodium and restrictions.

RAASi Underuse and Underdosing Is Common



Despite survival benefits, guideline-directed medical therapy (GDMT) remains under utilized in patients with heart failure. The CHAMP-HF registry included 3,518 patients with HFrEF from 150 primary care and cardiology practices in the United States. Data showed that among eligible patients, between 26% to 66% were not prescribed ACEi/ARB/ARNi, β-blocker, or MRA therapy. Additionally, only 1.1% of patients eligible to receive all classes of medication received target doses of each of those therapies.

CHECK-HF Registry: GDMT Underuse in Dutch Patients with HFrEF



Prescription rates per clinic ordered by percent of prescription.

n = 5,701 patients with HFrEF at 34 clinics

GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system. Brunner-La Rocca HP, et al. *JACC Heart Fail.* 2019;7(1):13-21.

CHECK-HF registry data from 34 Dutch heart failure clinics also observed that prescribing patterns in guideline recommended therapies varied widely. The variations in prescribing patterns could not be accounted for by differences in patient characteristics. There remains room for improvement in the use of RAASi therapy, including the use of β-blockers, MRA, and combination therapy in patients with HFrEF.

Note that ivabradine had been recently introduced relative to the time of the study period, which was 2013-2016.

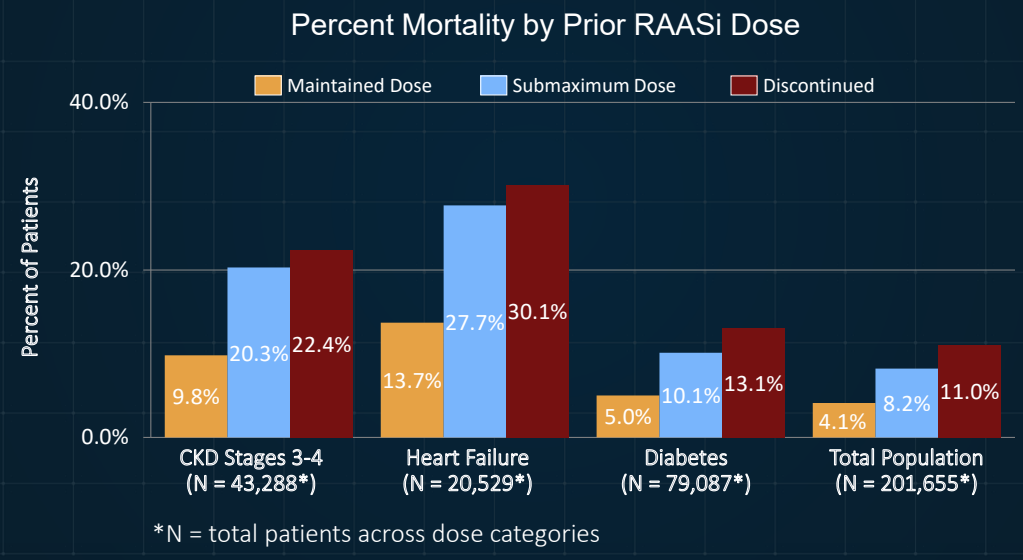
MRA Underuse in HFrEF

Study	MRA use
GWTG-HF (2009)	32% of eligible population
IMPROVE HF (2008)	36% of eligible population
EuroHeart Failure Survey II (2006)	47.5% of patients discharged after hospital admission for HF
ESC-HF Pilot Survey (2010)	~50% of inpatients at discharge 44% of outpatients
BIOSTAT-CHF (2017)	56% of eligible patients *before* HF treatment optimization 63% of eligible patients *after* HF treatment optimization
ESC-HF-LT (2016)	53.9% of patients hospitalized for acute HF receiving treatment at discharge 56.5% of patients hospitalized for acute HF at 1 year from hospitalization
Swedish HF Registry (2018)	40% of eligible population

HF, heart failure; HFrEF, heart failure with reduced ejection fraction. Albert NM, et al. *JAMA*. 2009;302(15):1658-1665. Fonarow GC, et al. *Circ Heart Fail*. 2008;1(2):98-106. Nieminen MS, et al. *Eur Heart J*. 2006;27(22):2725-2736. Maggioni AP, et al. *Eur J Heart Fail*. 2010;12(10):1076-1084. Ferreira JP, et al. *Eur J Heart Fail*. 2017;19(10):1284-1293. Crespo-Leiro MG, et al. *Eur J Heart Fail*. 2016;18(6):613-625. Savarese G, et al. *Eur J Heart Fail*. 2018;20(9):1326-1334.

Several other studies also confirm that underuse of MRA is common among patients with HFrEF.

Low Doses of RAASi Are Less Effective in Preventing Mortality



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

In a US study examining RAASi dose levels and the affect on hyperkalemia found that patients on submaximum doses or who discontinued treatment were more likely to die compared with patients on maximum doses. Of note, the defined disease cohorts are not mutually exclusive. Additionally, comparatively fewer patients were taking maximum doses, and prescribed RAASi therapy declined following hyperkalemia.

Hyperkalemia Is a Frequent Side Effect

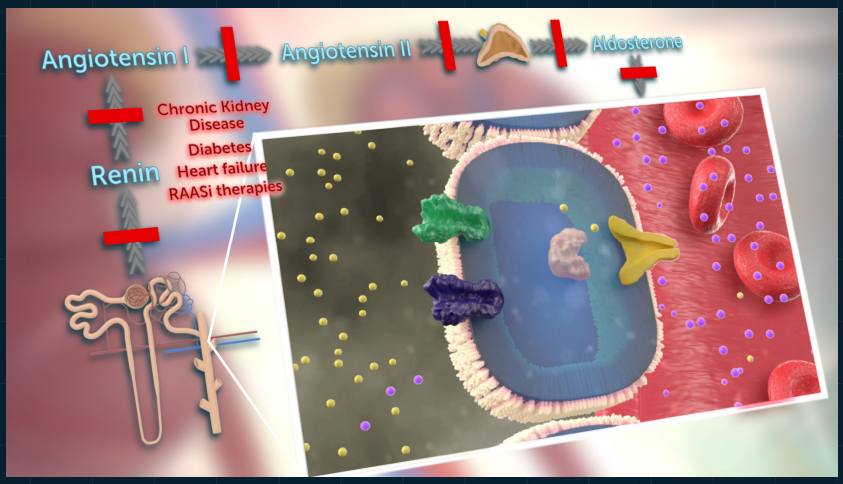
Renin-Angiotensin-Aldosterone System (RAAS) Regulates K^+ Homeostasis

K^+, potassium; RAAS, renin-angiotensin-aldosterone system. Clase CM, et al. *Kidney Int*. 2020;97(1):42-61.

The kidneys play a primary role in potassium homeostasis and are responsible for eliminating up to 95% of potassium from the body. The remaining portion is removed by colonic potassium excretion.

Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.
Clase CM, et al. *Kidney Int*. 2020;97(1):42-61.

RAAS Inhibition Leads to Elevations in Serum K^+

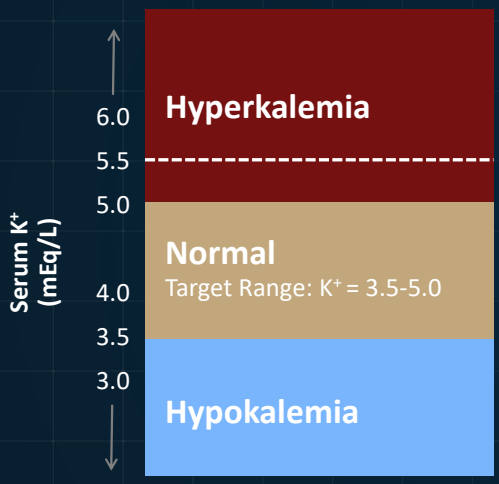


K+, potassium; Na^+, sodium; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system.
Clase CM, et al. *Kidney Int.* 2020;97(1):42-61.

Chronic disease or use of treatments targeting RAAS components can lead to derangements in potassium homeostasis at any point in the pathway. The inhibition of RAAS function can lead to elevations in serum potassium levels.

Definition of Hyperkalemia in Studies and Guidelines

Weir 2017 pg1/ col2/ li 14-18 to pg2/ col1/ li 1-8



- The upper limit of normal (ULN) for serum K^+ levels varies across guidelines and publications[1-6]
  - Serum K^+ levels of 5.0 mEq/L, 5.5 mEq/L, or 6.0 mEq/L are commonly used cutoffs for ULN
- Some studies differentiate hyperkalemia by severity[1]
  - Serum K^+ levels ≥5.5 mEq/L - <6.0 mEq/L defined as moderate
  - Serum K^+ levels ≥6.0 mEq/L defined as severe

1. Einhorn LM, et al. *Arch Intern Med*. 2009;169(12):1156-1162. 2. Yancy CW, et al. *J Am Coll Cardiol*. 2017;70(6):776-803. 3. Ponikowski P, et al. *Eur Heart J*. 2016;37(27):2129-2200. 4. National Kidney Foundation. Guideline 11: Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in CKD. In: *K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease*. 2002. Accessed February 17, 2015. http://kidneyfoundation.cachefly.net/professionals/KDOQI/guidelines_bp/guide_11.htm 5. National Institute for Health and Clinical Excellence (NICE) [UK]. Chronic kidney disease (CG73): Early identification and management of chronic kidney disease in adults in primary and secondary care. 2008. http://www.nice.org.uk/CG73. 6. Heart Failure Society of America, et al. *J Card Fail*. 2010;16(6):e1-194.

The normal range of serum potassium is typically considered to be between 3.5 mEq/L and 5.0 mEq/L. Although definitions of hyperkalemia vary, ≥5.0 mEq/L is generally accepted as the cutoff value for the upper limit of normal of serum potassium.

Sources of Dyskalemia

- Comorbidities
  - Aging
  - Chronic kidney disease (CKD)
  - Diabetes mellitus (DM)
  - Frailty
- Drugs
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin receptor blockers (ARBs)
  - Angiotensin-neprilysin inhibitors (ARNi)
  - Beta-blockers
  - Digitalis glycoside
  - Heparin
  - Loop and/or thiazide diuretics
  - Mineralocorticoid receptor antagonists (MRAs)
  - NSAIDs

Weiner ID, et al. In: Feehally J, et al, eds. *Comprehensive Clinical Nephrology*. 6th ed. Elsevier; 2018:111-123; Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.

Common causes of dyskalemia are chronic kidney disease (CKD), diabetes mellitus (DM), diuretics, and RAASi therapy. The use of diuretics is the most frequent cause of hypokalemia in heart failure while the use of RAASi therapy is commonly associated with hyperkalemia. Clinical outcomes may be influenced directly by the emergence of dyskalemia as a result of these comorbidities and treatments. Reductions in the use of guideline-recommended medical therapy as a result of potassium imbalances may also indirectly affect patient outcomes.

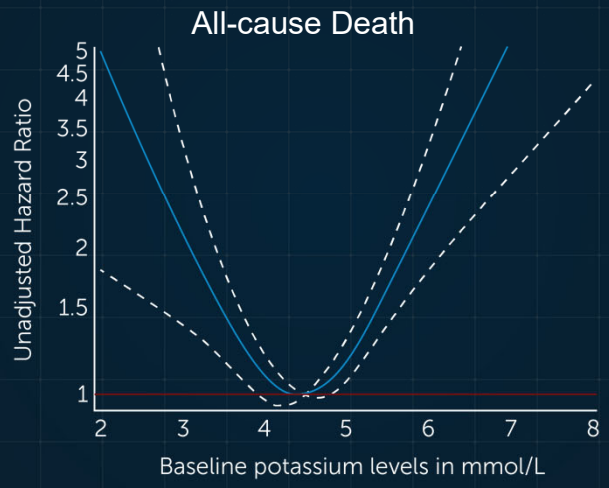
Hyperkalemia Occurs Frequently with RAASi Therapy in Chronic Heart Failure

RAASi Therapy	Study	Publication Year	Treatment	HF Population	Hyperkalemia Rate
ACEi	SOLVD-Prevention	1991	enalapril vs. placebo	HFrEF ≤35%	6.4% >5.5 mmol/L
	CONSENSUS	1987	enalapril vs. placebo	NYHA IV	7.1% elevated serum K^+
MRA	EMPHASIS-HF	2011	eplerenone vs. placebo	NYHA II	11.8% >5.5 mmol/L
	RALES	1999	spironolactone vs. placebo	HFrEF ≤35%	2% ≥6.0 mmol/L
ARB	CHARM	2003	candesartan vs. placebo	NYHA II-IV	3.4% ≥6.0 mmol/L
ARNi	PARADIGM	2014	sacubitril/valsartan vs. enalapril	NYHA II-IV	16.1% >5.5 mmol/L 4.3% >6.0 mmol/L

NYHA, New York Heart Association; SOLVD Investigators, et al. *N Engl J Med*. 1991;325(5):293-302. CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316(23):1429-1435. Zannad F, et al. *N Engl J Med*. 2011;364(1):11-21. Pitt B, et al. *N Engl J Med*. 1999;341(10):709-717. McMurray JJ, et al. *Lancet*. 2003;362(9386):767-771. McMurray JJV, et al. *N Engl J Med*. 2014;371(11):993–1004.

Hyperkalemia is well known and common side effect of RAASi therapy observed in heart failure clinical trials.

Hypo- and Hyperkalemia: Life-threatening Consequences in Chronic Heart Failure



Rossignol P, et al. *Eur J Heart Fail*. Published online April 3, 2020. doi: 10.1002/ejhf.1793

Both hypokalemia and hyperkalemia are associated with an increased risk of all-cause death and extremes in dyskalemia can even be life-threatening. Recently, data from the European Society of Cardiology Heart Failure Association EURObservational Research Programme (ESC-HFA-EORP) Heart Failure Long-Term (HF-LT) Registry the interplay between serum potassium and outcomes of patients with chronic heart failure (CHF) were assessed. Data from 9222 patients with CHF, 20% of whom had CKD, found an increased risk of all-cause death when potassium levels were less than 4 mmol/L and greater than 5 mmol/L.

Dyskalemia in HF Is Associated with Excess Morbidity and Mortality

	Hazard Ratio (95% CI)				
Author (K^+ Level, mmol/L)	**<3.5**	**3.5 - 4.0**	**4.1 - 5.0**	**5.1 – 5.5**	**>5.5**
Aldahl et al. (2017)	3.2	1.6	Ref. (1.00)	1.6	3.3
Nunez et al. (2018)	2.4	1.1[a]	Ref. (1.00)	1.5[a]	2.5[a]
Linde et al.[b] (2019)	2.0	1.3	Ref. (1.00)	1.3	1.5[c]
Hoss et al. (2016)	2.3	1.2	Ref. (1.00)	0.8	0.9
Matsushita et al. (2019)	1.6	1.1[a]	Ref. (1.00)	1.1[a]	1.7
Desai et al. (2018)	1.6	1.3[a]	Ref. (1.00)	1.3[a]	1.7
Cooper et al. (2015)	2.0	1.5	Ref. (1.00)	1.0	1.0

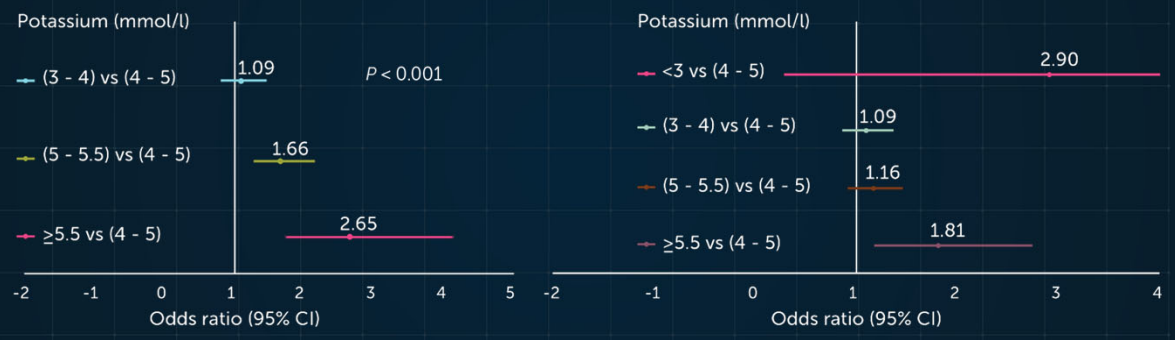
[a]Estimates derived from continuous "spline" curves. [b]Estimates derived from forest plots. [c]The relative risk for patients with K^+ between 5.5 and 6.0 mmol/L was 1.5 (1.3 to 1.8), and for K^+ >6.0 mmol/L was 3.0 (2.0 to 4.0). Patients with K^+ >5.5 mmol/L had higher odds for renin-angiotensin-aldosterone system inhibitor discontinuation.

Aldahl M, et al. *Eur Heart J*. 2017;38(38):2890-2896. Núñez J, et al. *Circulation*. 2018;137(13):1320-1330. Linde C, et al. *ESC Heart Fail*. 2019;6(2):280-290. Hoss S, et al. *Am J Cardiol*. 2016;118(12):1868-1874. Matsushita K, et al. *PLoS One*. 2019;14(8):e0219899. Desai AS, et al. *J Card Fail*. 2018;24(5):313-320. Cooper LB, et al. *JAMA*. 2015;314(18):1973-1975. Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.

Multiple observational studies suggest that dyskalemia is associated with excess morbidity and mortality in heart failure, however further research suggests hyperkalemia-associated risk in these patients is primarily due to avoidance or discontinuation of RAASi therapy.

Savarese G, et al. *JACC Heart Fail*. 2019;7(1):65-76.
Lund LH, et al. *Eur J Heart Fail*. 2018;20(5):931-932.
Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.
Rossignol P, et al. *Eur J Heart Fail*. Published online April 3, 2020. doi: 10.1002/ejhf.1793.

ESC-HFA-EORP HF Long-term Registry: K^+ Level Predicts MRA Utilization



Predictors of Low Dosage MRA Usage

MRA Discontinuation During 1-year Follow-up

Rossignol P, et al. *Eur J Heart Fail.* Published online April 3, 2020. doi: 10.1002/ejhf.1793

In the European Society of Cardiology Heart Failure Association Eurobservational Research Programme (ESC-HFA-EORP) long-term registry (N = 9,222) showed that patients with hyperkalemia were more likely to receive lower MRA doses. MRA discontinuation was also associated with potassium levels ≥5.5 mmol/L.

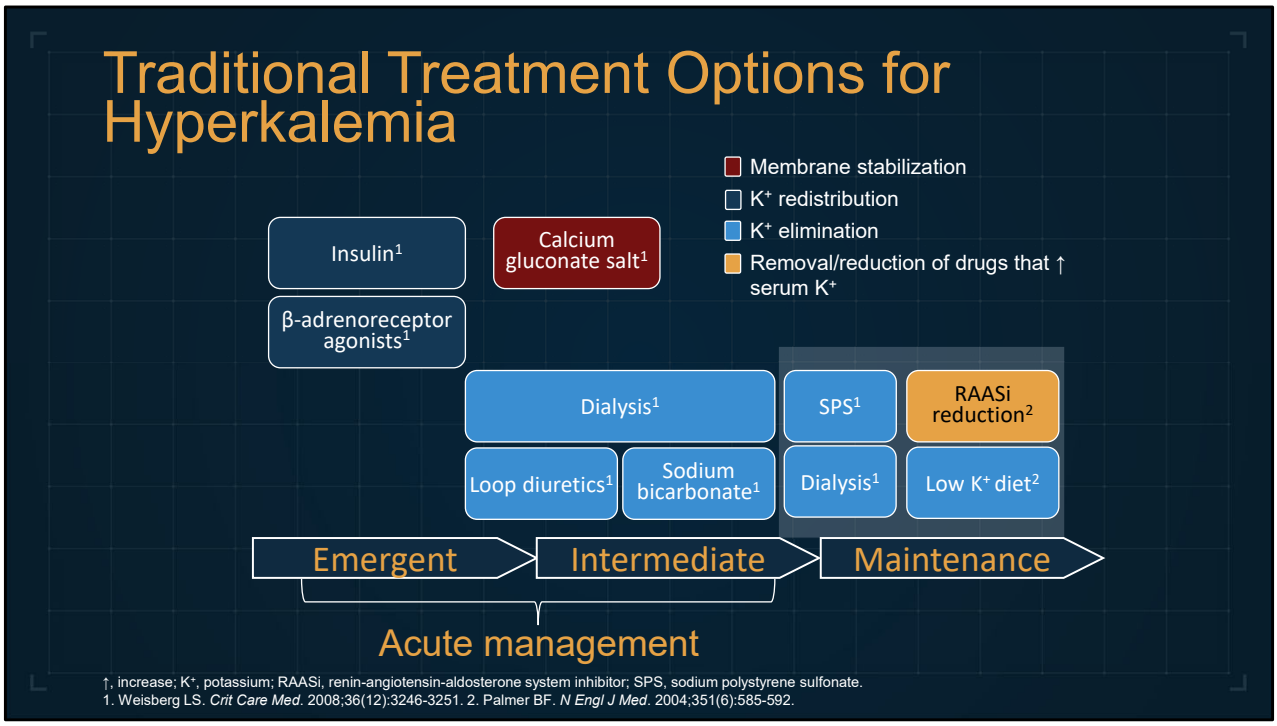
Hyperkalemia Is a Risk Factor for Suboptimal RAASi Therapy

- SCREAM cohort
  - Observational study of Stockholm citizens initiating MRA therapy (N = 13,726)
  - Prescriptions after hyperkalemia:
    - MRA discontinuation 47% (n = 827)
    - MRA dose reduction 10% (n = 92)
    - ACEi/ARB discontinuation 23% (n = 282)
- BIO-STAT CHF
  - International, multicenter, prospective, observational study of the relationship between K^+, uptitration of ACEi/ARB, and outcomes
  - N = 1,666 patients with HFrEF
  - Higher baseline K^+ was an independent predictor of lower ACEi/ARB dosages (OR 0.70; 95% CI, 0.51–0.98; N =2,516)

ACEi, angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; HFrEF, heart failure with reduced ejection fraction; K^+, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor. Trevisan M, et al. *Eur J Heart Fail.* 2018;20(8):1217-1226. Beusekamp JC, et al. *Eur J Heart Fail.* 2018;20(5):923-930.

Observational studies from the Stockholm Creatinine Measurements (SCREAM) healthcare utilization cohort and Biology Study to Tailored Treatment in Chronic Heart Failure (BIO-STAT CHF) show that higher serum potassium levels and episodes of hyperkalemia were associated with reduction and discontinuation of RAASi therapy. Taken together, observational data suggests that hyperkalemia is a marker of suboptimal RAASi therapy and less likely a risk factor for poor outcomes.

Treatments for Hyperkalemia



Several agents are currently used to manage hyperkalemia. In the emergent setting, insulin and beta-adrenoreceptor antagonists are often used to push potassium from serum into the cells. calcium gluconate salt is commonly given, especially in the presence of ECG changes, to stabilize cell membranes. In less urgent situations, dialysis, loop diuretics, and sodium bicarbonate are therapies used to eliminate potassium from the body. Unfortunately, few options are available for longer-term management of persistent hyperkalemia.

- This study is a schematic of various treatment options for hyperkalemia.
- On the far left are the key agents used in the emergency department for hyperkalemia: insulin and beta-adrenoreceptor antagonists. These agents work by pushing potassium from serum into the cells.
- Calcium gluconate salt is commonly given, especially in the presence of ECG changes, to stabilize cell membranes.
- Dialysis, loop diuretics, and sodium bicarbonate are also therapies to eliminate potassium from the body, although I will tell you in a moment why sodium bicarbonate may not be a good option.

- Finally, for longer-term options to manage persistent hyperkalemia, we are left with few options.
- Kayexalate, or sodium polystyrene sulfonate, has a warning related to intestinal necrosis and a precaution related to sodium load.

Previous Challenges with Hyperkalemia Maintenance: Limited Effective Options

- Low-potassium diets
  - Adherence is difficult
  - Many K^+ rich foods are healthy
- High-dose loop diuretics
  - Affects renal hemodynamics
  - Increases counterregulatory hormones
- Sodium polystyrene sulfonate (SPS)
  - Not well tolerated
  - Rare but significant GI side effects including intestinal necrosis
  - Potential for significant sodium load
- Dialysis
  - Limited to patients with advanced CKD
  - Costly
  - Inconvenient
- RAASi reductions
  - Increased mortality risk

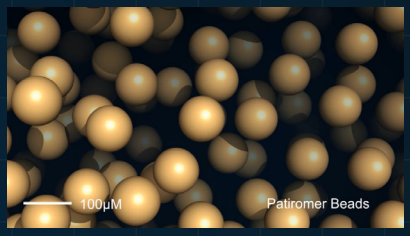
CKD, chronic kidney disease; K^+, potassium; GI, gastrointestinal.
Dunn JD, et al. *Am J Manag Care.* 2015;21(15 Suppl):s307–315.

The above list highlights the important fact that satisfactory long-term management of hyperkalemia is challenging. Asking patients to follow difficult-to-adhere-to low potassium diet or stopping or reducing renoprotective RAASi therapy is often the only option. A need exists for effective and safe treatments that lower serum potassium which patients can tolerate over the long-erm without compromising the benefits of RAASi therapy.

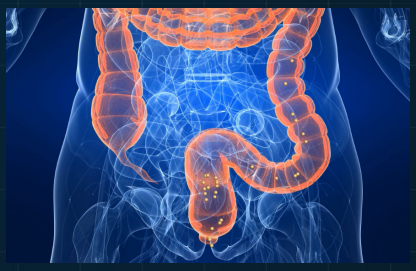
Novel Potassium Binders: Facilitators of RAASi Therapy

Patiromer

- Novel, uniform, spherical, non-absorbed polymer
- Average bead size = 100 µM (too large to be absorbed)
- High-capacity exchange resin
- K^+ exchanged for Ca^{2+}
- Works in the distal colon where K^+ is most abundant



Patiromer beads

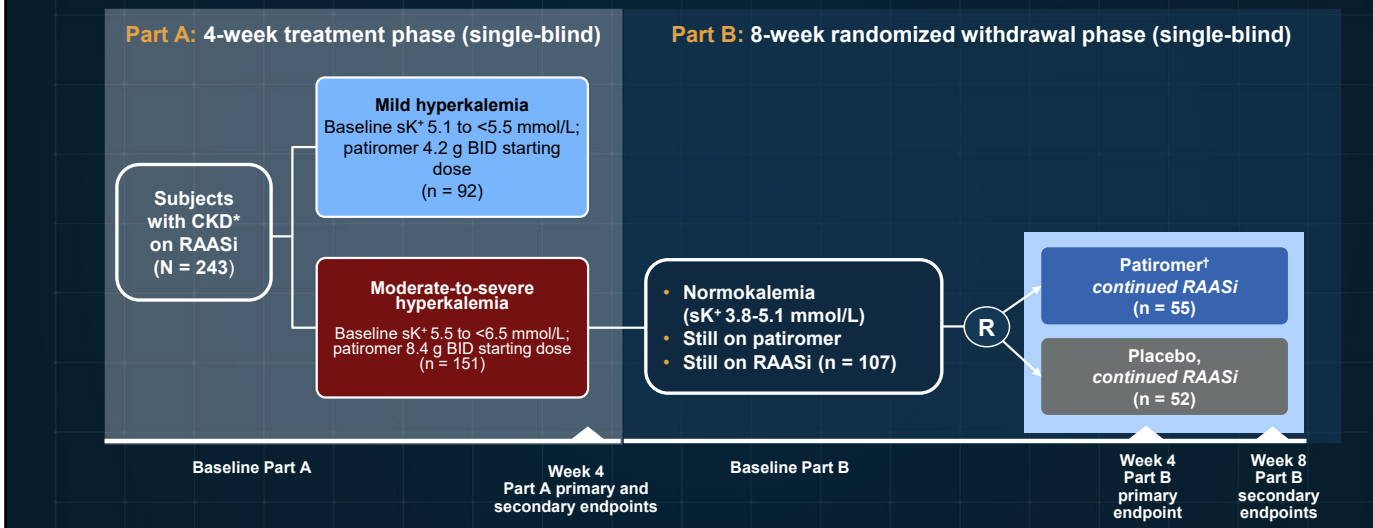


Fully ionized at the physiologic pH of the colon for optimal ion exchange

Ca^{2+}, calcium; K^+, potassium. Li L, et al. *J Cardiovasc Pharmacol Ther*. 2016;21(5):456-465.

Patiromer is a novel potassium binder that exchanges one calcium cations for every two potassium cations. This exchange resin works primarily in the distal colon where potassium cations are most abundant in the digestive tract.

OPAL-HK: Study Design



*eGFR 15 to <60 mL/min/1.73 m²; †Dose adjusted as needed by treating physician.
BID, twice daily; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; R, randomization; RAASi, renin-angiotensin-aldosterone system inhibitor; sK⁺, serum potassium.
Weir MR, et al. *N Engl J Med*. 2015;372(3):211–21; Figure adapted from Weir MR, et al. Presented at: the *American Society of Hypertension* 2015 Annual Scientific Meeting.

OPAL-HK was a phase 3 clinical trial designed to evaluate the efficacy and safety of patiromer for the treatment of hyperkalemia. ClinicalTrials.gov number NCT01810939.

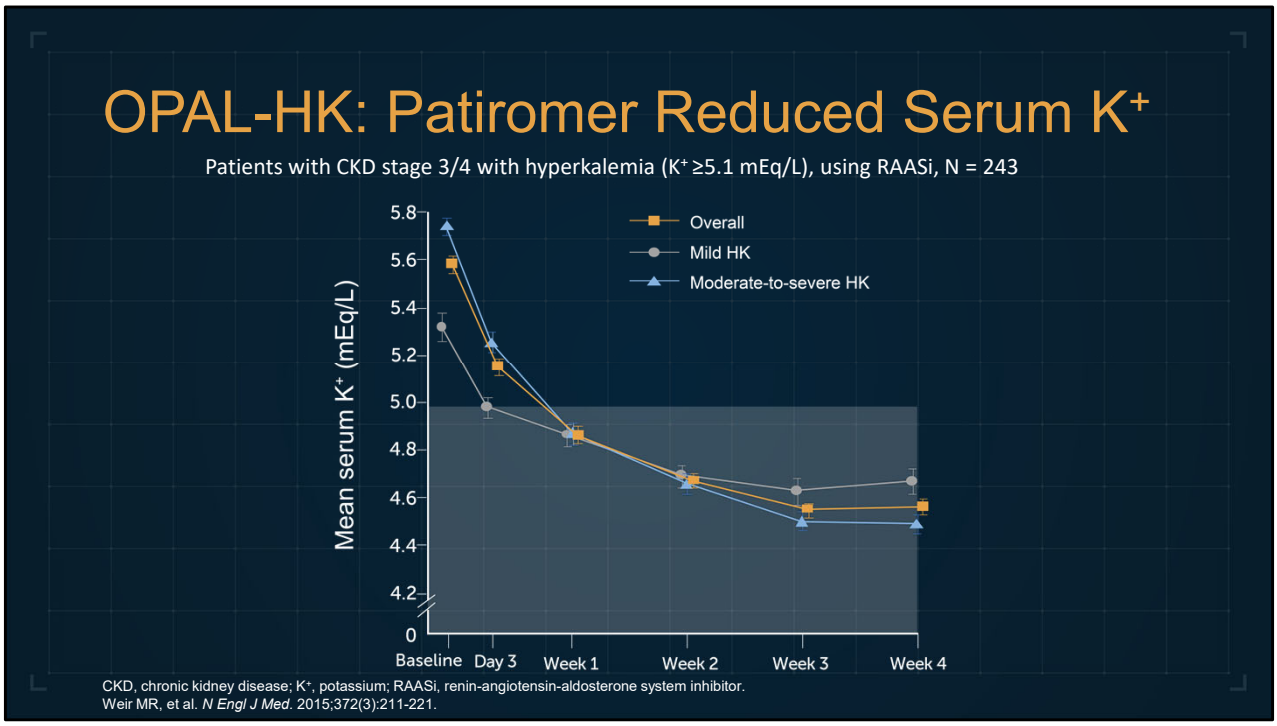
OPAL-HK: Baseline Demographics and Characteristics

Characteristic	Mild HK (n = 92)	Moderate/severe HK (n = 151)	Total (N = 243)
Male, n (%)	49 (53)	91 (60)	140 (58)
Age (yr), mean (SD)	64.6 (11.0)	63.9 (10.2)	64.2 (10.5)
White, n (%)	88 (96)	151 (100)	239 (98)
eGFR (mL/min/1.73 m^2), n (%)			
60 to ≤90 (Stage 2)	6 (7)	16 (11)	22 (9)
45 to <60 (Stage 3a)	22 (24)	27 (18)	49 (20)
30 to <45 (Stage 3b)	24 (26)	39 (26)	63 (26)
<30 (Stage 4/5)	40 (43)	69 (46)	109 (45)
Type 2 diabetes, n (%)	52 (57)	87 (58)	139 (57)
Heart failure, n (%)	39 (42)	63 (42)	102 (42)
NYHA Class I, n (%)	7 (18)	12 (19)	19 (19)
NYHA Class II, n (%)	25 (64)	41 (65)	66 (65)
NYHA Class III, n (%)	7 (18)	10 (16)	17 (17)
Myocardial infarction, n (%)	19 (21)	41 (27)	60 (25)
Hypertension, n (%)	90 (98)	146 (97)	236 (97)

eGFR, estimated glomerular filtration rate; HK, hyperkalemia; NYHA, New York Heart Association; SD, standard deviation.
Weir MR, et al. *N Engl J Med*. 2015;372(3):211-221.

RLY5016 CSR/p136/table 21 and p137-138/table22

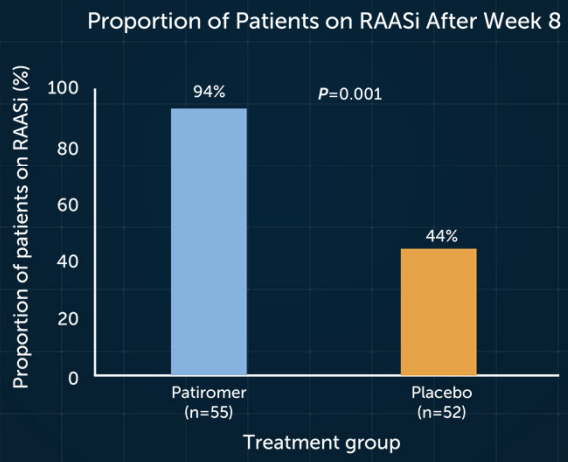
ost of subjects were 65 years or older. There is a distribution of CKD severities: about 40% of patients had stage 3 CKD and about 40% of patients had stage 4/5 CKD. A relatively high proportion of patients (~40%) had heart failure, 60% to 70% of patients had type 2 diabetes, about 25% had a previous myocardial infarction, and almost all patients were hypertensive. From a comorbid perspective, this was a very sick population, reflecting the type of patients that physicians typically treat with regards to hyperkalemia.



Baseline elevations serum potassium levels were reduced with treatment with patiromer in patients with CKD. Similarly, concordant and significant reductions in serum aldosterone and blood pressure occurred in the patiromer group.

Weir MR, et al. *N Engl J Med.* 2015;372(3):211–221.
Weir M, et al. *Kidney Int.* 2016;90(3):696–704.

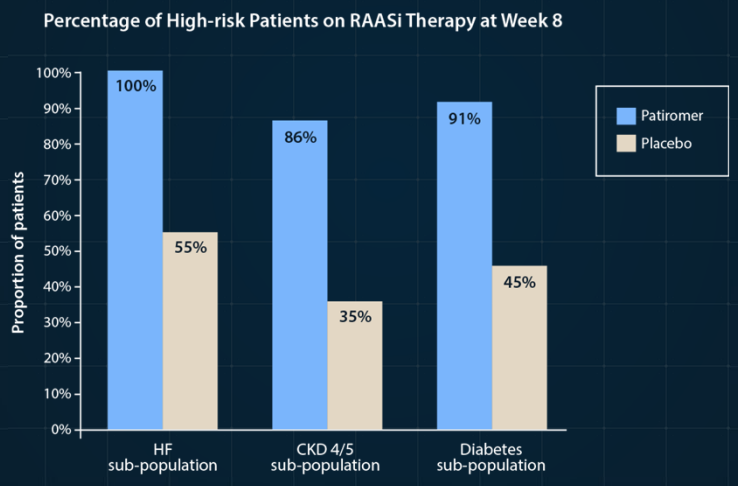
OPAL-HK: Patiromer Enabled RAASi Continuation



RAASi, renin-angiotensin-aldosterone system inhibitor; Weir MR, et al. *N Engl J Med.* 2015;372(3):211-221.

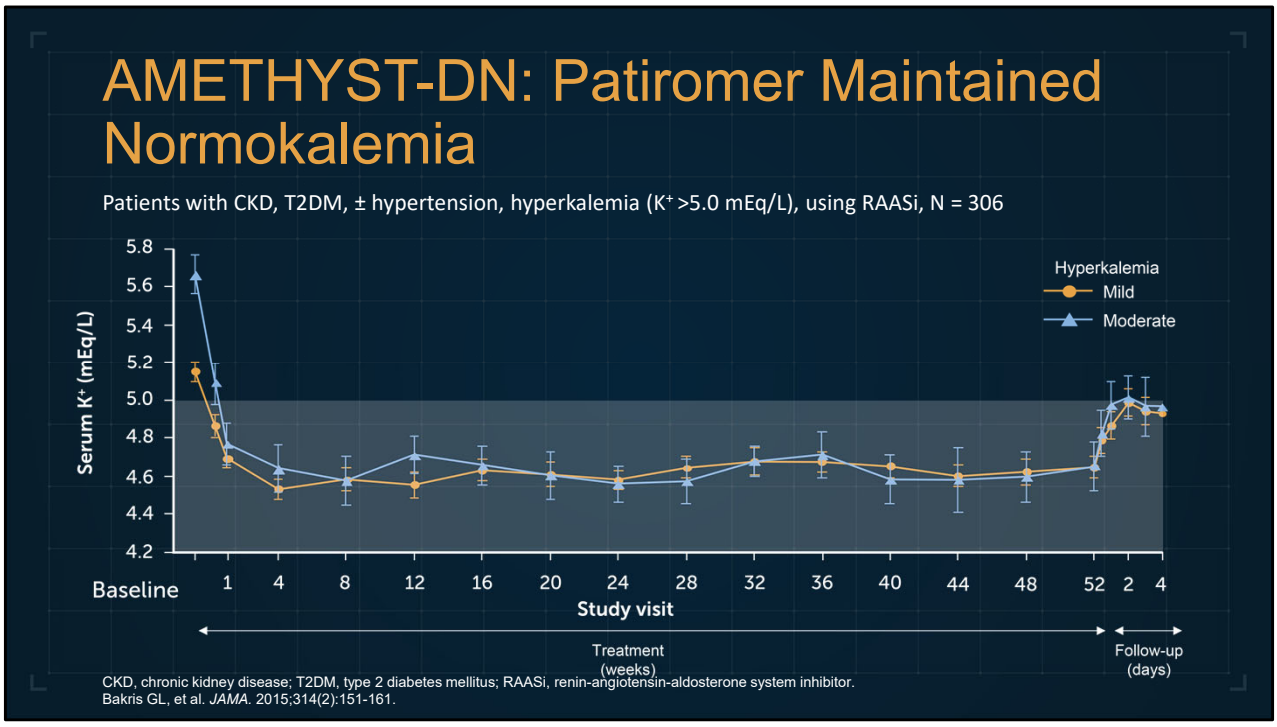
Treatment with patiromer was also associated with a significantly greater percentage of patients receiving RAASi therapy compared with the placebo group at the end of the randomized withdrawal phase. This suggests that patiromer may be used as a tool to facilitate continued treatment with RAASi therapy.

OPAL-HK Sub-analysis: RAASi Continuation in High-risk Patients



RAASi, renin-angiotensin-aldosterone system inhibitor; Weir MR, et al. *N Engl J Med.* 2015;372(3):211-221.

High percentages of patients continuing RAASi therapy at the end of the study period were found across patients with heart failure, chronic kidney disease, and diabetes.



In the longer-term phase 2 AMYTHST-DN study, reductions in serum potassium were maintained throughout the 52-week period following initial treatment. Patients with mild hyperkalemia had a mean serum potassium level of 5.2 mmol/L and patients with moderate hyperkalemia had a mean serum potassium level of 5.7 mmol/L. Compliance throughout the entire study ranged from 86.7% to 95.6% across starting-dose and treatment groups.

AMETHYST-DM: Patiromer Adverse Events

Adverse Event*	Mild Hyperkalemia [>5.0 mEq/L – 5.5 mEq/L] (n = 220)	Moderate Hyperkalemia [>5.5 mEq/L – <6.0 mEq/L] (n = 304)
Worsening CKD	14 (6.4%)	28 (9.2%)
Hypomagnesemia	15 (6.8%)	26 (8.6%)
Worsening hypertension	14 (6.4%)	24 (7.9%)
Constipation	11 (5.0%)	19 (6.3%)
Diarrhea	12 (5.5%)	17 (5.6%)
Hypoglycemia	4 (1.8%)	10 (3.3%)

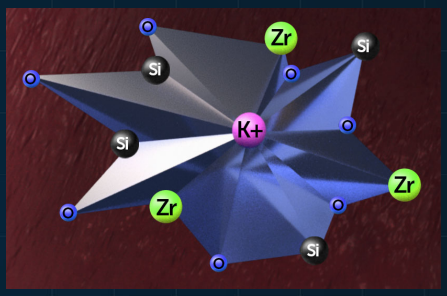
*Occurring in ≥5% of study participants

CKD, chronic kidney disease. Bakris GL, et al. *JAMA*. 2015;314(2):151-161.

Gastrointestinal side effects, such as constipation and diarrhea, were experienced by 5% to 6% of study participants. A subset of patients also experienced hypomagnesemia with patiromer, although the clinical significance of these events remains unclear. Study investigators considered worsening CKD events to be unrelated to the study drug.

Sodium Zirconium Cyclosilicate (SZC)

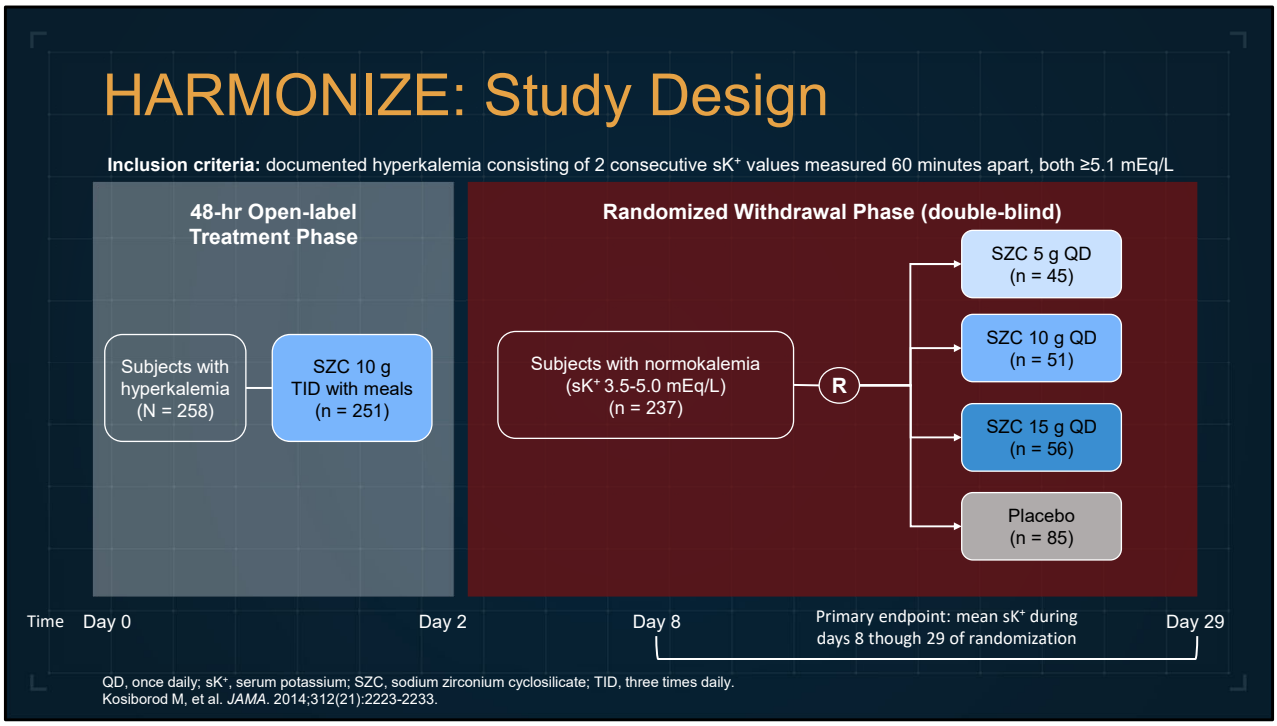
- Formerly known as ZS-9
- Inorganic crystal
- Exchanges K^+ for Na^+ or H^+ in the intestines
  - May bind K^+ in higher portions of the GI tract



SZC crystal

H^+, hydrogen; K^+, potassium; Na^+, sodium; GI, gastrointestinal.
Stavros F, et al. *PLoS One*. 2014;9(12):e114686. Image compliments of M. Kosiborod.

Sodium zirconium cyclosilicate (SZC), also known as ZS-9, is another novel potassium binder. This inorganic crystal exchanges sodium or hydrogen cations for potassium cations. Researchers have observed that SZC has an early onset of action suggesting that the compound works in the upper portions of the gastrointestinal tract. However, potassium concentrations are highest in the colon which is where most of the potassium exchange takes place.



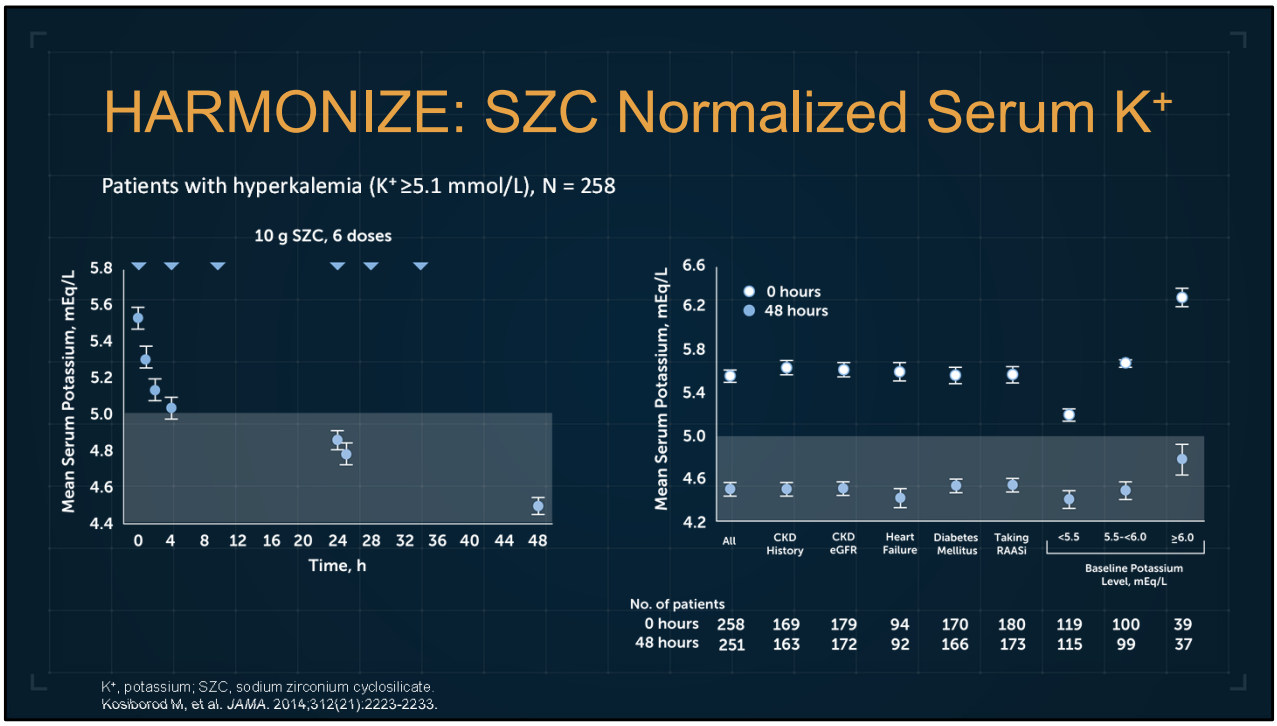
HARMONIZE was a phase 3 clinical trial designed to evaluate the efficacy and safety of SZC in outpatients with hyperkalemia. ClinicalTrials.gov number NCT02088073.

HARMONIZE: Baseline Demographics and Characteristics

	Open-Label Phase SZC 10 g (n = 258)	Placebo (n = 85)	SZC 5 g (n = 45)	SZC 10 g (n = 51)	SZC 15 g (n = 56)
Serum potassium					
<5.5 mEq/L	119 (46.1%)	43 (50.6%)	23 (51.1%)	19 (37.3%)	24 (42.9%)
5.5 to <6.0 mEq/L	100 (38.8%)	30 (35.3%)	17 (37.8%)	23 (45.1%)	26 (46.4%)
≥6.0 mEq/L	39 (15.1%)	12 (14.1%)	5 (11.1%)	9 (17.6%)	6 (10.7%)
eGFR					
<60 mL/min/1.73m^2	179 (69.4%)	52 (61.2%)	31 (68.9%)	38 (74.5%)	41 (73.2%)
≥60 mL/min/1.73m^2	72 (27.9%)	28 (32.9%)	12 (26.7%)	13 (25.5%)	15 (26.8%)
Not reported	7 (2.7%)	5 (5.9%)	2 (4.4%)	0	0
Comorbidities					
Chronic kidney disease	169 (65.5%)	50 (58.8%)	29 (64.4%)	36 (70.6%)	37 (66.1%)
Heart failure	94 (36.4%)	26 (30.6%)	18 (40.0%)	18 (35.3%)	25 (44.6%)
Diabetes mellitus	170 (65.9%)	54 (63.5%)	26 (57.8%)	38 (74.5%)	39 (69.6%)
RAASi medication	180 (69.8%)	61 (71.8%)	33 (73.3%)	36 (70.6%)	33 (58.9%)

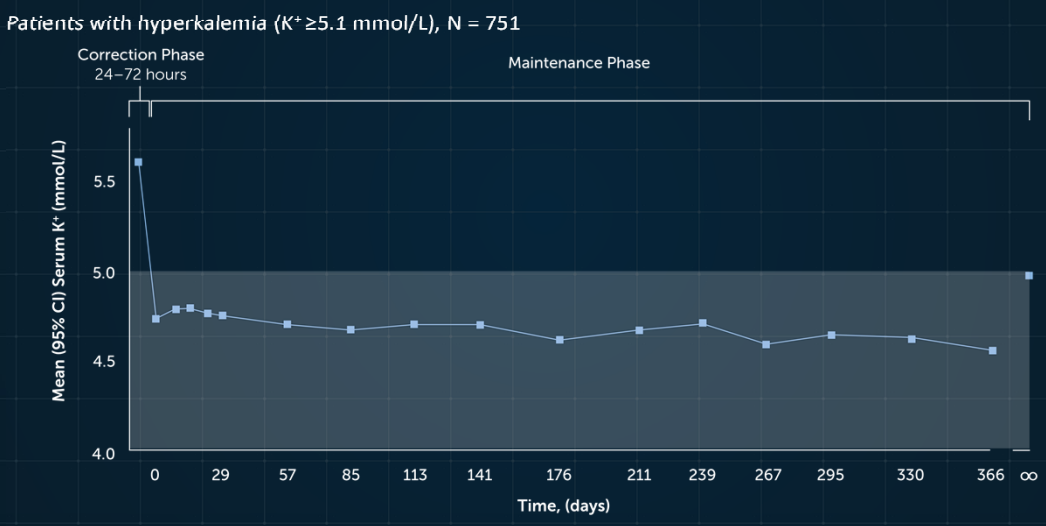
eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate.
Kosiborod M, et al. *JAMA*. 2014;312(21):2223-2233.

The mean age of study participants was 64 years, 42% were women, 83% were white, and 14% were black/African American. A high-proportion of patients had CKD and diabetes mellitus (~65%) while 36% had heart failure. A substantial proportion were using RAASi therapy at the time of the study.



Serum potassium levels were normalized within the first 48 hours of treatment with SZC. This normalization occurred in study participants regardless of comorbidity or severity of hyperkalemia.

ZS-005: SZC Maintained Normokalemia



SZC, sodium zirconium cyclosilicate. Spinowitz BS, et al. *Clin J Am Soc Nephrol*. 2019;14(6):798-809.

In the longer-term ZS—05 study, SZC normalized potassium levels and maintained those over a period of one year in patients with hyperkalemia.

ZS-005: SZC Adverse Events

Adverse Event*	Maintenance Phase (n = 746)
Anemia	44 (6%)
Constipation	48 (6%)
Hypertension	82 (11%)
Hypokalemia	43 (6%)
Nausea	56 (8%)
Peripheral edema	72 (10%)
SMQ edema	113 (15%)
Upper respiratory tract infection	37 (5%)
Urinary tract infection	59 (8%)

*Occurring in ≥5% of study participants

SMQ, standardized Medical Dictionary for Regulatory Activities query; SZC, sodium zirconium cyclosilicate
Spinowitz BS, et al. *Clin J Am Soc Nephrol.* 2019;14(6):798-809.

Gastrointestinal effects (constipation, nausea) and hypokalemia (K^+ ≥2.5 mmol/L to ≤3.4 mmol/L) developed in a small portion of patients. No patients developed severe hypokalemia (K^+ <2.5 mmol/L). Edema was associated with higher doses of SZC and more frequent within the first few months of treatment. Hypertension events were mild to moderate and only one event was attributed to the study drug.

DIALIZE: SZC Treated Predialysis Hyperkalemia in ESRD

- 196 patients with ESRD and persistent hyperkalemia despite hemodialysis
- Randomized to placebo or SZC 5 g once daily on non-dialysis days
  - SZC titrated to maximum of 15 g over 4 weeks
  - Followed by 4-week evaluation period with stable dose
- 41.2% SZC vs. 1.0% placebo maintained predialysis K^+ 4.0-5.0 mmol/L, no rescue therapy required (OR 68.8; $P < 0.001$)
- Fewer SZC subjects required rescue therapy (2.1% SZC vs. 5.1% placebo)
- Interdialytic weight gain was similar (0.2 kg SZC vs. -0.1 kg placebo)
- Serious adverse events were similar (7.3% SZC vs. 8.1% placebo)

ESRD, end-stage renal disease, K^+, potassium; OR, odds ratio; SZC, sodium zirconium cyclosilicate.
Fishbane S, et al. *J Am Soc Nephrol*. 2019;30(9):1723-1733.

The DIALIZE study was a phase 3b, randomized, double-blind, placebo-controlled study that evaluated SZC for the management of persistent hyperkalemia in patients with end-stage renal disease (ESRD) despite hemodialysis. A significantly greater percentage SZC-treated patients maintained predialysis serum potassium levels of 4.0-5.0 mmol/L during at least 3 of 4 hemodialysis treatments after the long interdialytic interval and did not require recuse therapy to lower serum potassium levels. Also, fewer patients receiving SZC required rescue therapy compare with placebo. Interdialytic weight gain and serious adverse events were similar between the study groups.

Upcoming Clinical Trials

Study	Study Arm	# of Patients	Inclusion Criteria	Blinding	Duration	Primary Endpoint	Anticipated Completion
DIAMOND Phase 3	Patiromer	2,388	• HFrEF • β-blocker therapy • Kidney function not more than mild or moderately impaired • K^+ >5.0 mEq/L within the last 12 mo • Hospitalization for HF within the last 12 mo	Double blind	12-week run-in phase optimizing RAASi therapy	Time to first occurrence of CV death or CV hospitalization	March 2022
PRIORITIZE-HF Phase 2	SZC	182	• HFrEF (NYHA class II-IV) • LVEF ≤40% • RAASi therapy • Mild hyperkalemia (K^+ >5.0 mmol/L) or at risk of developing hyperkalemia	Double blind	3 months	Proportion of subjects with: • No ACEi/ARB/ARNI or at less than target dose and no MRA • ACEi/ARB/ARNI at target dose and no MRA • MRA at less than target dose • MRA at target dose	Study completed May 2020 (stopped early due to COVID-19 pandemic)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; HFrEF, heart failure with reduced ejection fraction; K^+, serum potassium; LVEF, left ventricular ejection fraction; SZC, sodium zirconium cyclosilicate. clinicaltrials.gov/ct2/show/NCT03888066; clinicaltrials.gov/ct2/show/NCT03532009

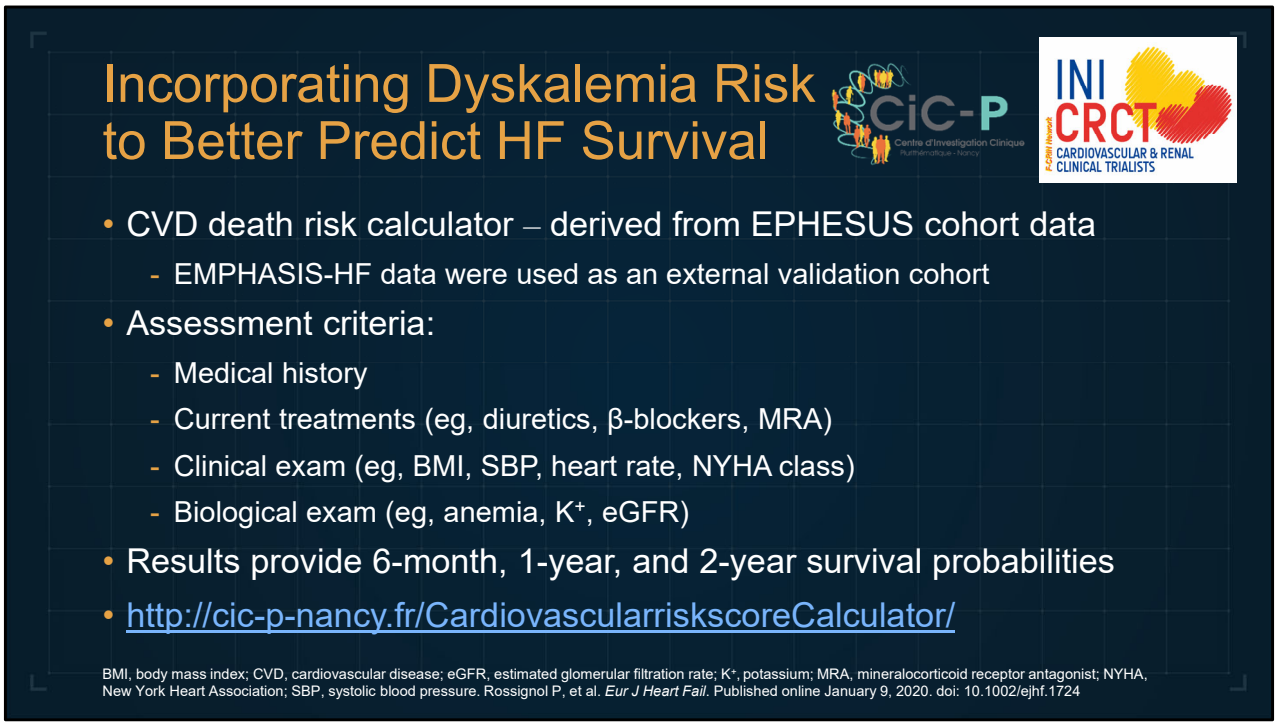
Practical Strategies for Dyskalemia Management

Predictors of Hyperkalemia Prior to Starting RAASi Therapy

- eGFR <45 mL/min/1.73m^2
- Serum potassium of >4.5 mEq/L
- eGFR <45 mL/min/1.73m^2 *AND* serum K^+ >4.5 mEq/L
  - HIGHEST PREDICTOR in the absence of RAASi therapy

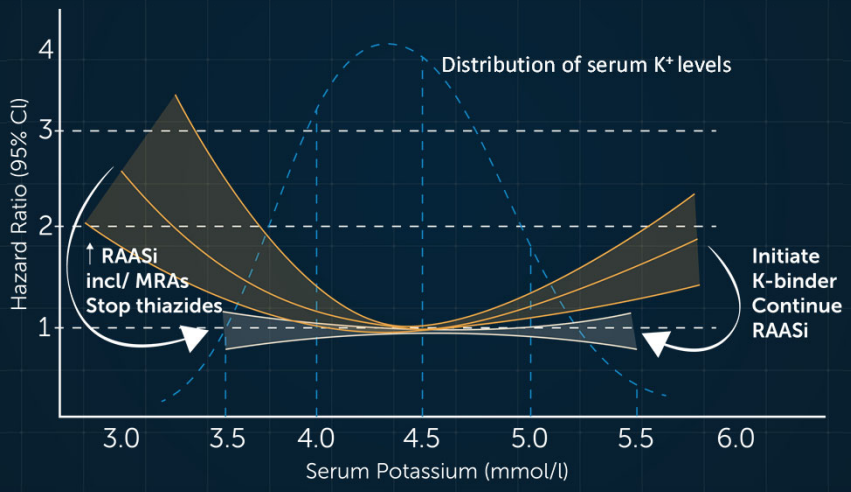
eGFR, estimated glomerular filtration rate; K^+, potassium; RAASi, renin-angiotensin-aldosterone inhibitor
Lazich I, et al. *Sem Nephrol*. 2014;34(3):333-339. Khosla N, et.al. *Am J Nephrol*. 2009;30(5):418-424.

Key indicators that patients are at risk for developing hyperkalemia are lower estimated glomerular filtration rates (eGFR) and baseline serum potassium levels that are in the higher-range of normal. The presence of both of these features is the highest predictor of hyperkalemia in the absence of RAASi therapy.



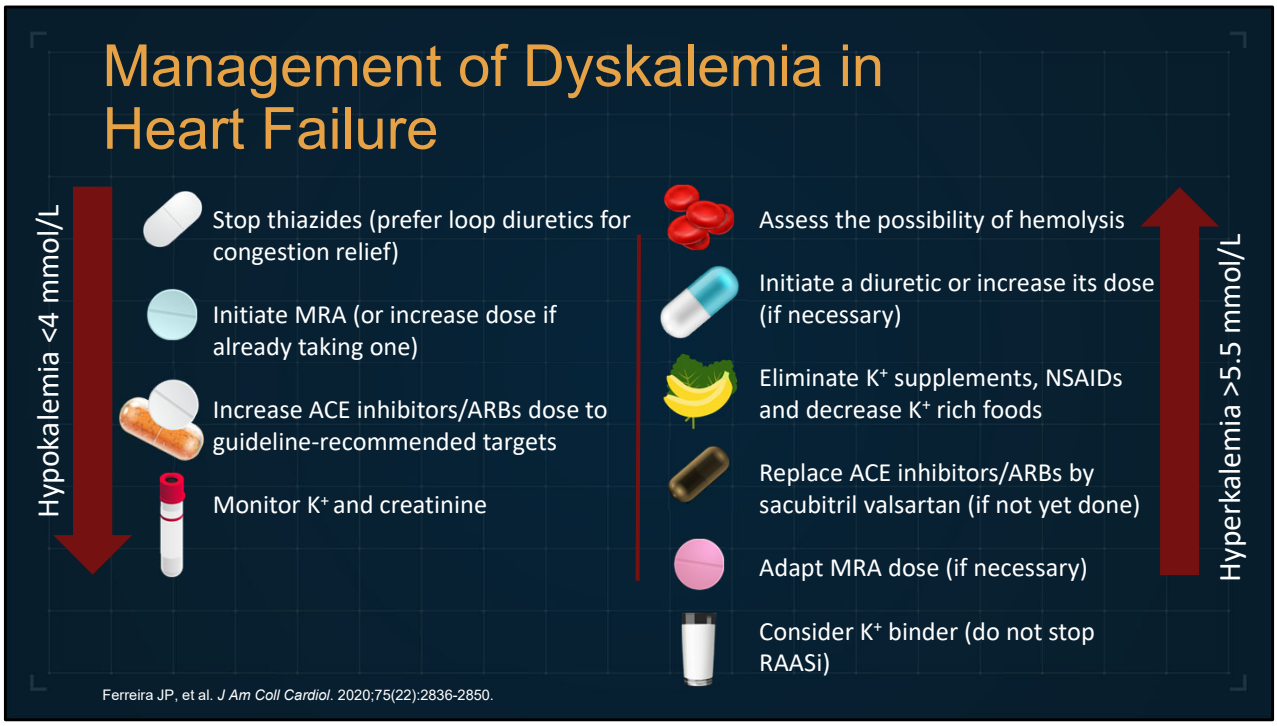
A new online risk calculator is available that incorporates key assessment criteria, including serum K^+ levels, diuretic treatment, and MRA treatment) to predict cardiovascular death in patients with heart failure. The calculator was developed based on a cohort of patients with heart failure post-myocardial infarction (EPHESUS population) and validated in a cohort with chronic heart failure (EMPHASIS-HF population).

Correcting Dyskalemia to Reduce Mortality Risk in Heart Failure



↑, increase; incl, include; K+, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.
Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.

For patients with dyskalemia, management goals should include maintaining serum potassium concentrations within the normal range of 4.0 mmol/L to 5.0 mmol/L. Prompt correction of dyskalemia can offset mortality risks and allow patients to continue RAASi therapy.



Several steps can be taken to increase serum K^+ in patients with hypokalemia including the use of loop diuretics, MRA, ACE inhibitors, and ARBs. In the setting of hyperkalemia, patients should undergo a detailed history of diet and use of supplements, salt substitutes, and medications to identify sources contributing to elevations in K^+ levels. Education by a dietician can help patients learn how to achieve a healthy diet that is low in potassium. RAASi therapies should be adjusted and adapted when necessary with the use of potassium binders in order to facilitate continued treatment.

Monitoring Potassium When Correcting Dyskalemia

- Adjust RAASi therapy and reassess K^+ levels after 1 week until optimal titration
- Monitor K^+ and creatinine at the following times until K^+ is in the "normal" range:
  - 1 week
  - 1 month
  - 2 months
  - 3 months

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

Frequent monitoring of serum potassium is recommended with dose titration of RAASi therapy. Regular monitoring of serum potassium and renal function should continue thereafter once target levels are achieved.

MRA Adjustment* in Heart Failure with Dyskalemia

- Adapt MRA doses according to patient's renal function
  - Use lower doses with impaired renal function
- MRA adjustments according to serum K^+:
  - <4.0 mmol/L → ↑ dose
  - 4.0 mmol/L – 5.4 mmol/L → no adjustment
  - 5.5 mmol/L – 5.9 mmol/L → ↓ dose
  - ≥6.0 mmol/L → Stop MRA and reassess K^+ after 1 week

*Providing renal function is stable with eGFR >30 mL/min/1.73m^2, and BP is stable with systolic BP >100 mm Hg.

eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid antagonist.
Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.

Frequent serum potassium and renal function monitoring is recommended after initiation of MRA therapy. MRA doses may require adjustment in the presence of dyskalemia. In patients with moderate elevations in serum potassium, MRA disruption should be minimized and treatment reintroduced once levels have stabilized provided that other vitals (ie, renal function, blood pressure) are stable. This may require the use of a potassium binder for some patients.

European Society of Cardiology Consensus Recommendation

- An approved potassium-lowering agent is recommended when K^+ >5 mmol/L to initiate, continue, and optimize guideline-recommended target doses of RAASi therapy

Rosano GMC, et al. *Eur Heart J Cardiovasc Pharmacother*. 2018;4(3):180-188.

Consensus by the European Society of Cardiology specifically recommends the use of potassium lowering agents in order to achieve continuous target doses of RAASi therapy.

Guidance for Potassium Binder Use in HF

Serum K^+	Recommendation
<5.5 mmol/L	Maintain guideline-recommended therapy Continue K^+ binder if taking one Consider initiating K^+ binder if 5.0-5.5 mmol/L and patient follow-up is a concern
5.5-5.9 mmol/L	Adapt MRA dose Do not reduce ACEi/ARB/ARNI Reassess K^+ after 1 week; if levels remain high, initiate treatment with novel K^+ binder Reassess K^+ after 1 week: • If K^+ <5.5 mmol/L, increase MRA and maintain K^+ binder for 1 additional week, then continue routine follow-up • If K^+ 5.5-5.9 mmol/L, do not increase MRA and maintain/uptitrate K^+ binder for 1 additional week; reassess K^+ afterwards
≥6.0 mmol/L	Adapt MRA dose Reduce ACEi/ARB/ARNI by 50% Reassess K^+ levels after 1 week; if K^+ levels still high, add a K^+ binder similar to recommendations for K^+ levels 5.5-5.9 mmol/L

ACEi, angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure; K^+, potassium; MRA, mineralocorticoid receptor antagonist. Ferreira JP, et al. *J Am Coll Cardiol*. 2020;75(22):2836-2850.

Potassium binds can help facilitate up-titration of RAASi therapy, including MRAs, and potentially support use of optimal treatment levels over the long-term.

Potassium Binder Prescribing Information

- Patiromer
  - Starting dose = 8.4 g once daily
  - Maximum dose = 25.2 g
  - Adjust dose by 8.4 g daily as needed at one-week intervals to obtain desired K^+ target range
  - Mix package contents with 40 mL (~3T) water, stir, and drink immediately
    - Repeat once or until entire dose is administered
    - Patiromer powder will not dissolve
    - Apple or cranberry juice can be used instead of water
- SZC
  - Starting dose = 10 g three times daily
  - Maximum maintenance dose = 10 g once daily
  - Adjust binder at one-week intervals as needed by 5 g daily to obtain desired K^+ target range
  - Mix package contents with 45 mL (~3T) water, stir, and drink immediately
    - SZC powder will settle quickly
    - If powder remains, add water, stir, and drink immediately

Patiromer. Package insert. Relypsa, Inc.; 2018. Patiromer. Package leaflet. Vifor France; 2019. Sodium zirconium cyclosilicate. Package insert. AstraZeneca Pharmaceuticals, LP; 2020. Sodium zirconium cyclosilicate. Package leaflet. AstraZeneca AB; 2020.

Patiromer and SZC come in powder form and should be mixed with water according to package directions. These binders do not dissolve so stirring thoroughly and drinking immediately are necessary to ensure the entire dose is administered. If powder remains in the glass, additional water, stirring, and drinking may be necessary.

Safety Considerations of Novel Potassium Binders

- Patiromer
  - Can bind other medications
    - *Other oral medications should be taken 3 hr before or 3 hr after patiromer*
  - May worsen gastrointestinal conditions
    - *Avoid use in patients with severe constipation, bowel obstruction, or impaction*
  - Can lead to hypomagnesemia
    - *Monitor serum magnesium*
- SZC
  - Affects absorption of medications whose bioavailability is dependent on gastric pH
    - *Other oral medications should be taken 2 hr before or 2 hr after SZC*
  - May worsen gastrointestinal conditions
    - *Avoid use in patients with severe constipation, bowel obstruction, or impaction*
  - Monitor for signs of edema
    - *Advise patients to adjust dietary sodium, if appropriate*
  - Can lead to hypokalemia in patients on hemodialysis
    - *Adjust dose in these patients with illnesses associated with decreased oral intake, diarrhea*

Clase CM, et al. *Kidney Int*. 2020;97(1):42-61. Patiromer. Package insert. Relypsa, Inc.; 2018. Sodium zirconium cyclosilicate. Package insert. AstraZeneca Pharmaceuticals, LP; 2020.

Conclusions

- Persistent hyperkalemia is a risk factor for RAASi therapy underuse and underdosing that leads to poor outcomes
- Identifying patients at risk and monitoring serum potassium helps to prevent dyskalemia episodes
- Short-term dose adjustments of drugs that increase potassium levels (eg, RAASi therapy) can help stabilize serum levels
- Novel potassium binders can facilitate long-term optimal medical therapy in patients with HF and/or CKD