Addressing Clinical Inertia in CKD & Heart Failure Management

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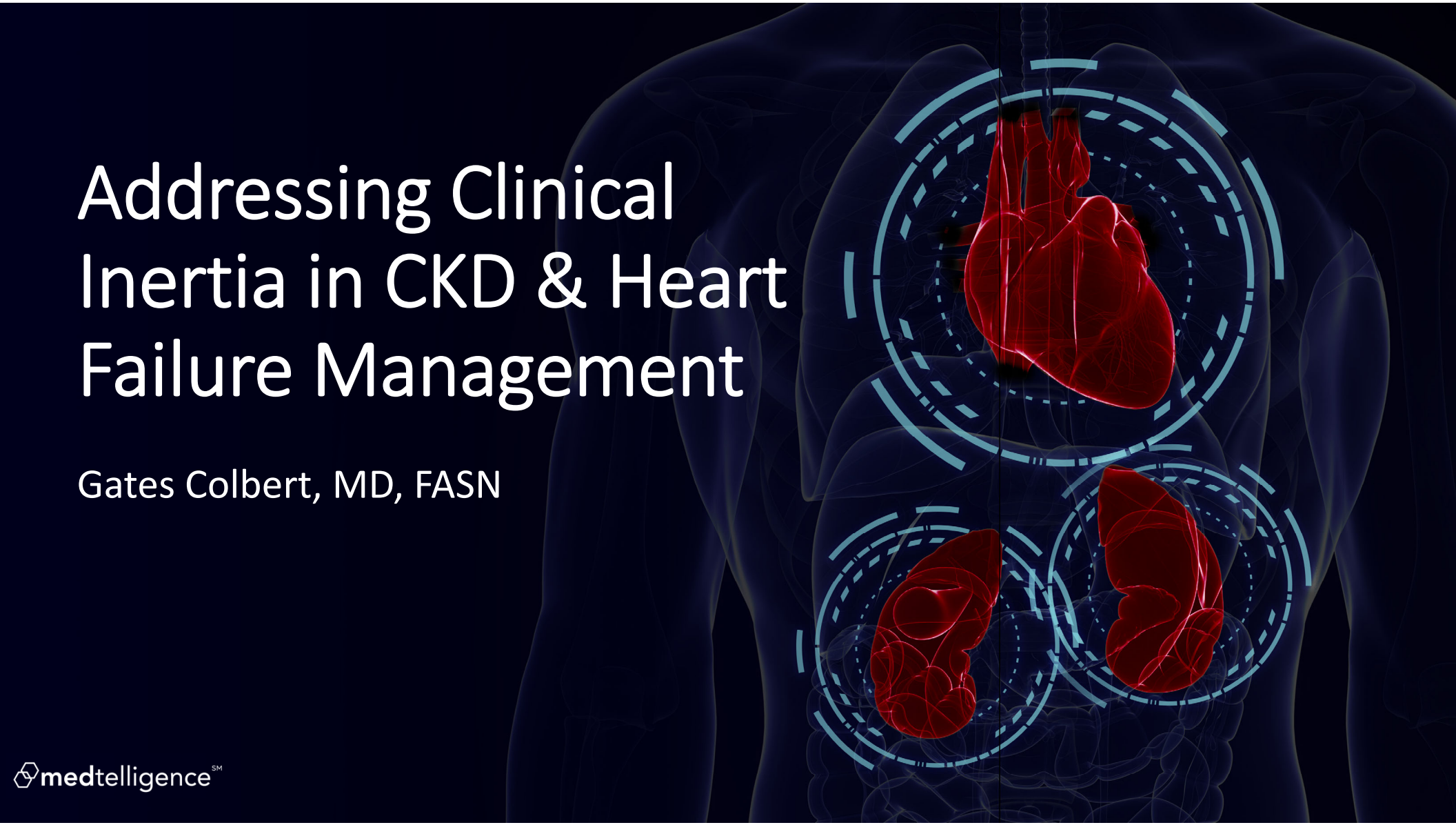

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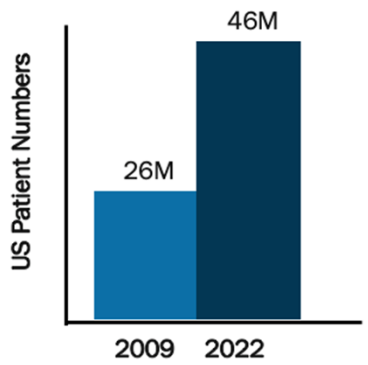
Increasing Incidence of Hyperkalemia

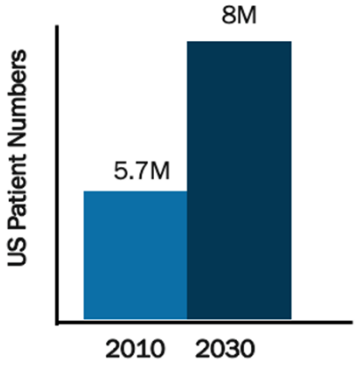
- Incidence of hyperkalemia is increasing, and this is exacerbated by RAAS inhibitor use[a-c]

CKD



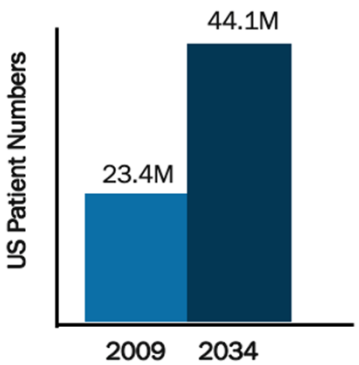
- Reduced kidney function is the most common cause of uncontrolled K^+

HF



- Poor cardiac output leads to renal insufficiency

Diabetes



- Insulin deficiency reduces ability to shift K^+ into cells

a. Einhorn LM, et al. *Arch Intern Med.* 2009;169(12):1156-1162; b. Desai AS. *Curr Heart Fail Rep*. 2009;6(4):272-280; c. Raebel MA, et al. *J Gen Intern Med.* 2010;25(4):326-333.

Hyperkalemia*

Predisposing Risk Factors

- Low eGFR
- Male sex
- White ethnicity
- High proteinuria
- Higher baseline potassium
- DM, CHF, PAD, hyperlipidemia
- Malignancy
- Metabolic acidosis
- Gout
- Tissue breakdown (eg, rhabdomyolysis)
- Use of some medications, such as RAASi

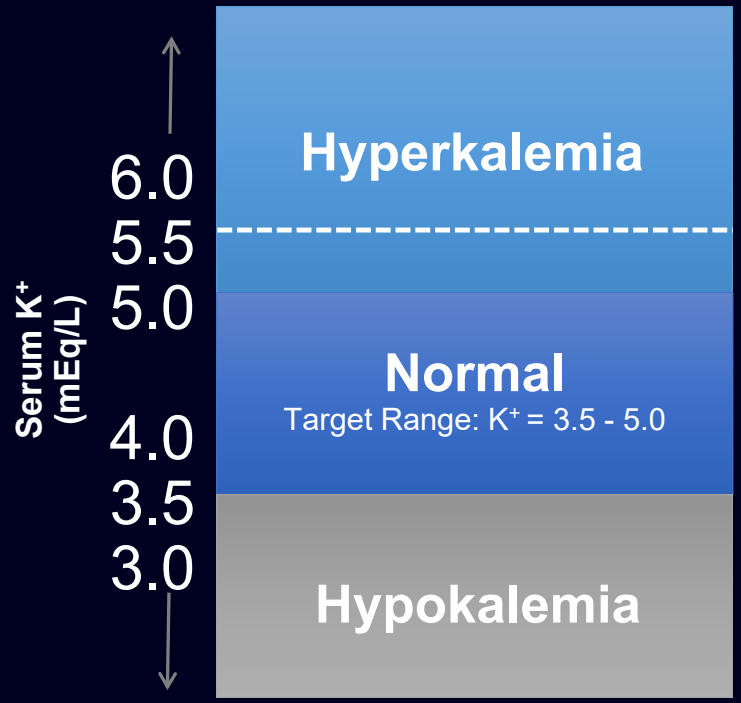
*See publication for complete listing of risk factors and symptoms.

Symptoms/Consequences

- Many patients are asymptomatic
- Muscle weakness
- Paresthesias
- Muscular fasciculations in the arms and legs – early signs
- Paralysis
- Cardiac conduction abnormalities, arrhythmias which can be lethal

Adapted from Lindner G, et al. *Eur J Emerg Med*. 2020;27(5):329-337.

Hyperkalemia Varies Widely in Studies and Guidelines

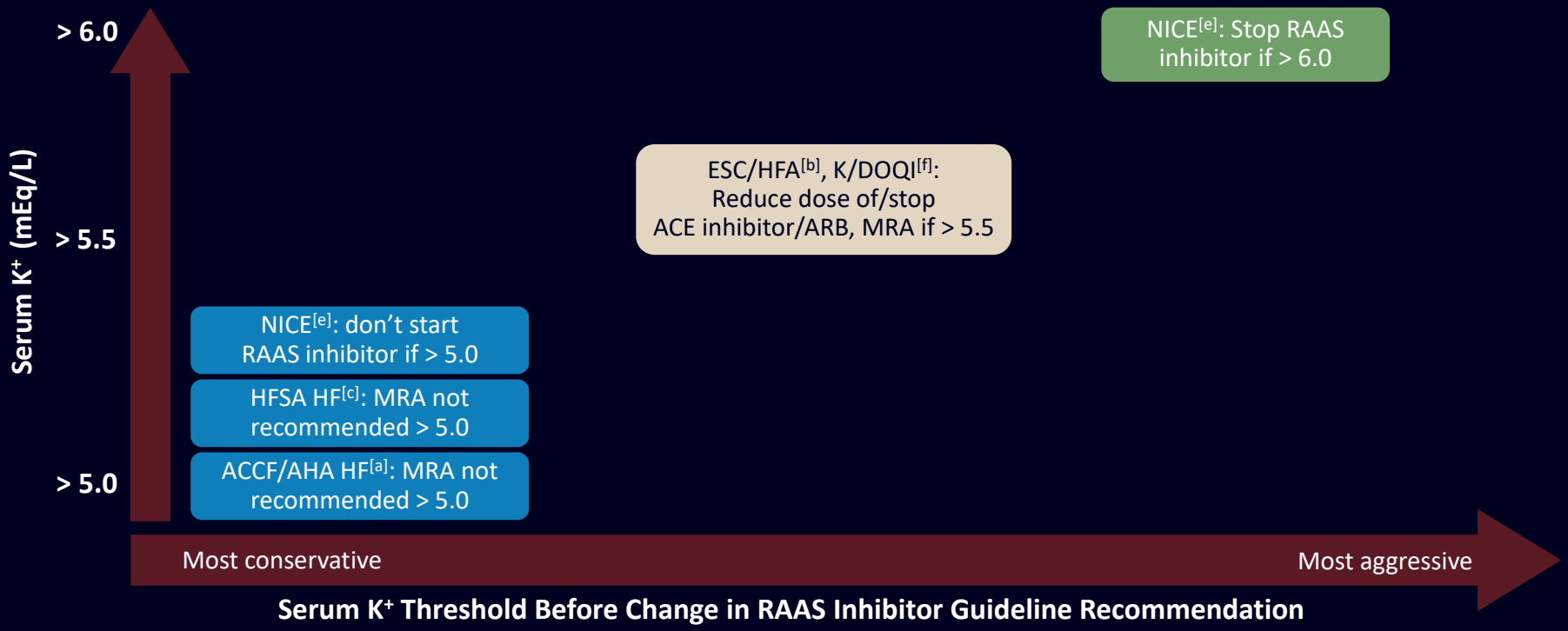


- The upper limit of normal (ULN) for serum K^+ levels varies across guidelines and publications[1-6]
  - Serum K^+ levels of 5.0, 5.5, or 6.0 mEq/L are commonly used cutoffs for ULN
- Some studies differentiate hyperkalemia by severity[1]
  - Serum K^+ levels ≥5.5 - <6.0 mEq/L defined as moderate
 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

K^+, potassium.

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. https://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, Lindenfeld J, et al. *J Card Fail*. 2010;16(6):475-539.

Guidelines Recommend RAAS Inhibitor Dose Modifications with Variable Serum K+



*KDIGO guidelines do not provide recommendations.[d]

a. Yancy CW, et al. *Circulation*. 2013;128(16):1810-1852; b. McMurray JJV, et al. *Eur Heart J.* 2012;33(14):1787-1847; c. HFSA; Lindenfeld J, et al. *J Card Fail*. 2010;16(6):e1-194; d. KDIGO. *Kidney Int Suppl*. 2013;3(1):136-150; e. NICE website. CKD guideline (CG73) 2008; f. National Kidney Foundation website. Guideline 11.

Risk of Hypokalemia or Hyperkalemia-Associated Mortality in Patients with CKD, HF and DM

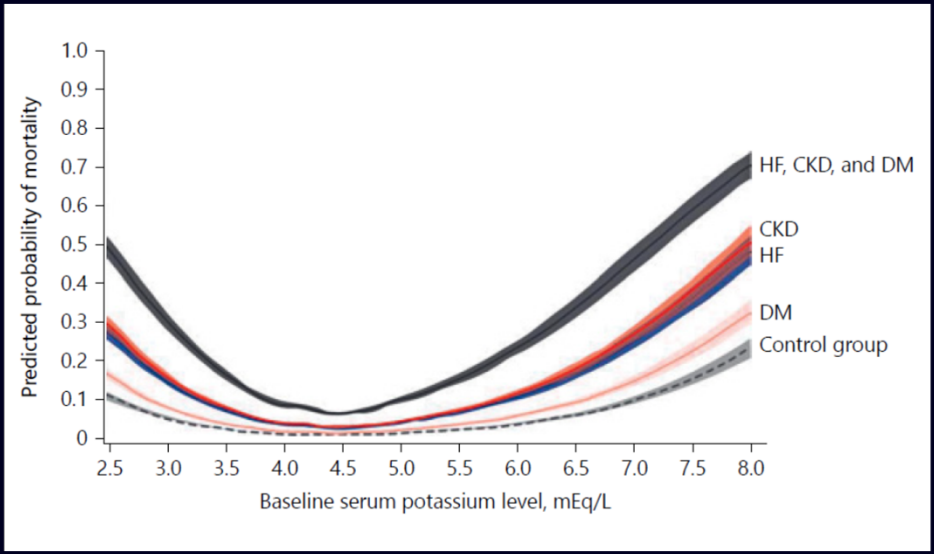
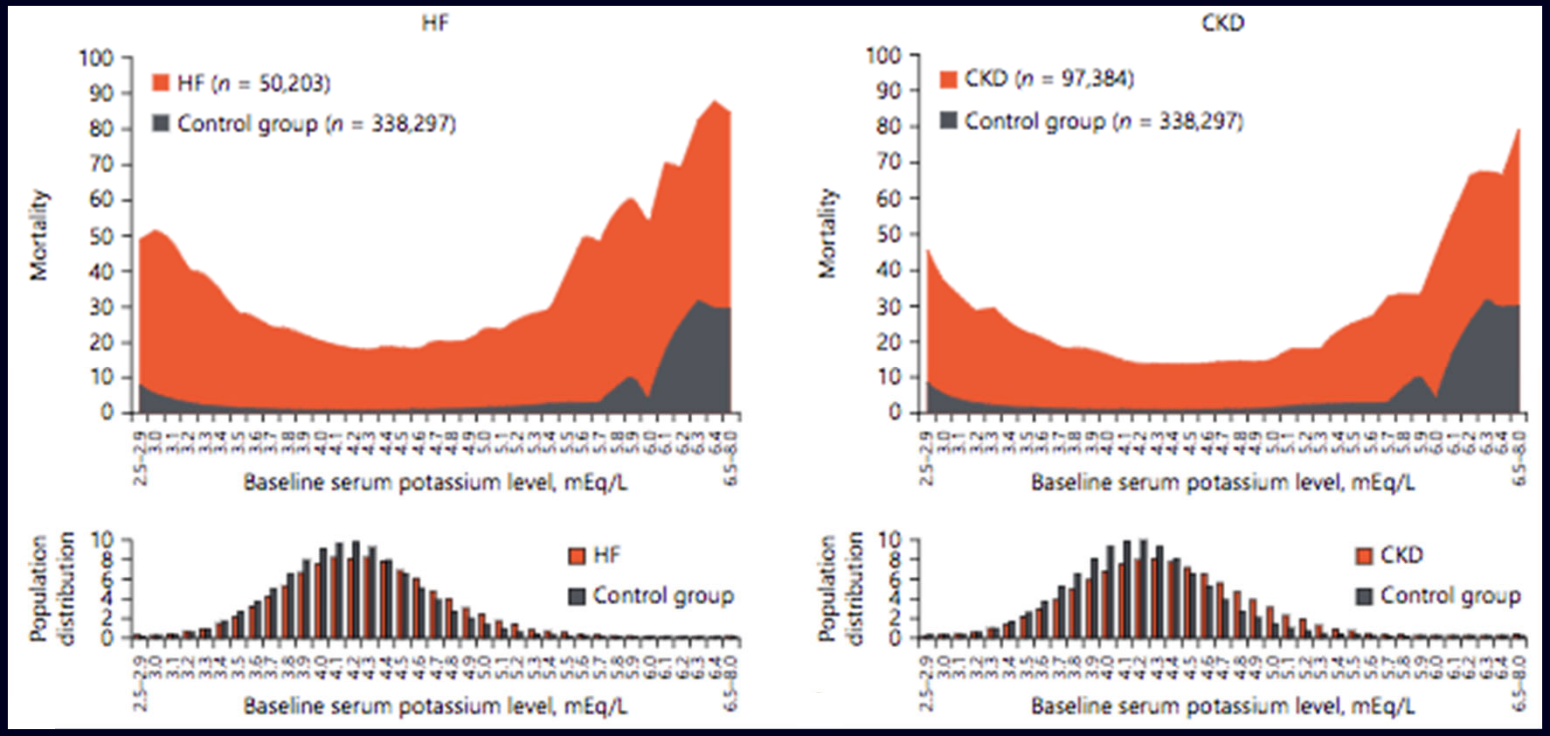


Figure from Collins et al. *Am J Nephrol* 2017;46:213-221

CKD=chronic kidney disease; DM=diabetes mellitus; HF=heart failure.
Palmer et al. *Mayo Clin Proc*. 2021;96(3): 744-762

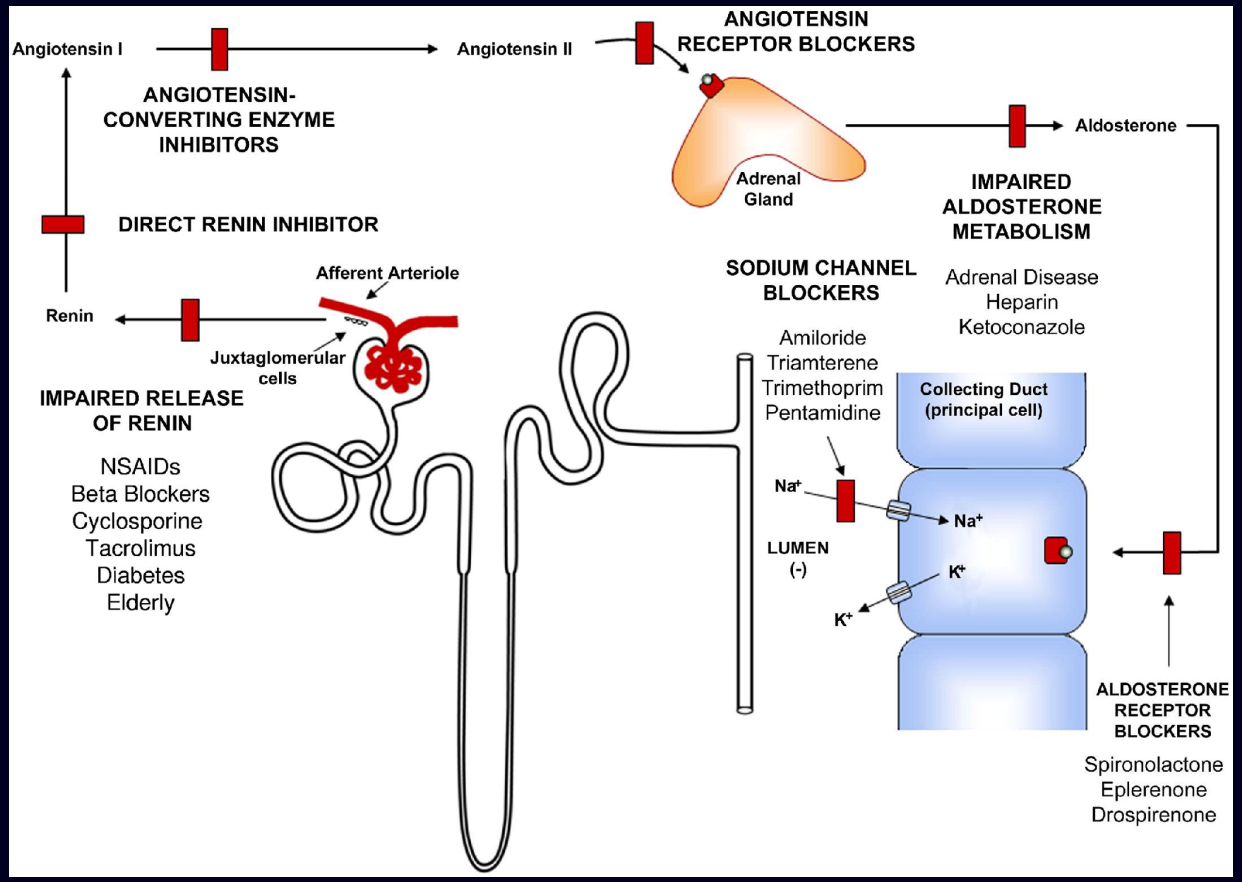
Mortality Related to Potassium in Large Cohorts with HF and/or CKD



Data source de-identified EMR data on approximately 7 million patients collected from multiple US integrated health delivery networks (Humedica, Boston, MA). Covers 2007 to 2012 with a minimum of 2 values of K^+ per patient. Unadjusted mortality (percent) over 18 months and histogram (percent) of serum potassium values.

Collins AJ, et al. *Am J Nephrol.* 2017;46(3):213-221.

Impaired Potassium Secretion



Palmer BF. *Am J Kidney Dis*. 2010;56(2):387-393.

Hyperkalemia-Inducing Medications

- ACE inhibitors & angiotensin receptor blockers (RAASi)*
- Amiloride
- Antifungals
- Beta-blockers
- Cyclosporine, tacrolimus
- Digoxin
- Eplerenone, spironolactone
- Heparin
- Hypertonic solutions: mannitol, glucose
- NSAIDs
- Penicillin, trimethoprim
- Pentamidine
- Succinylcholine
- Blood transfusions
- Triamterene
- Yasmin

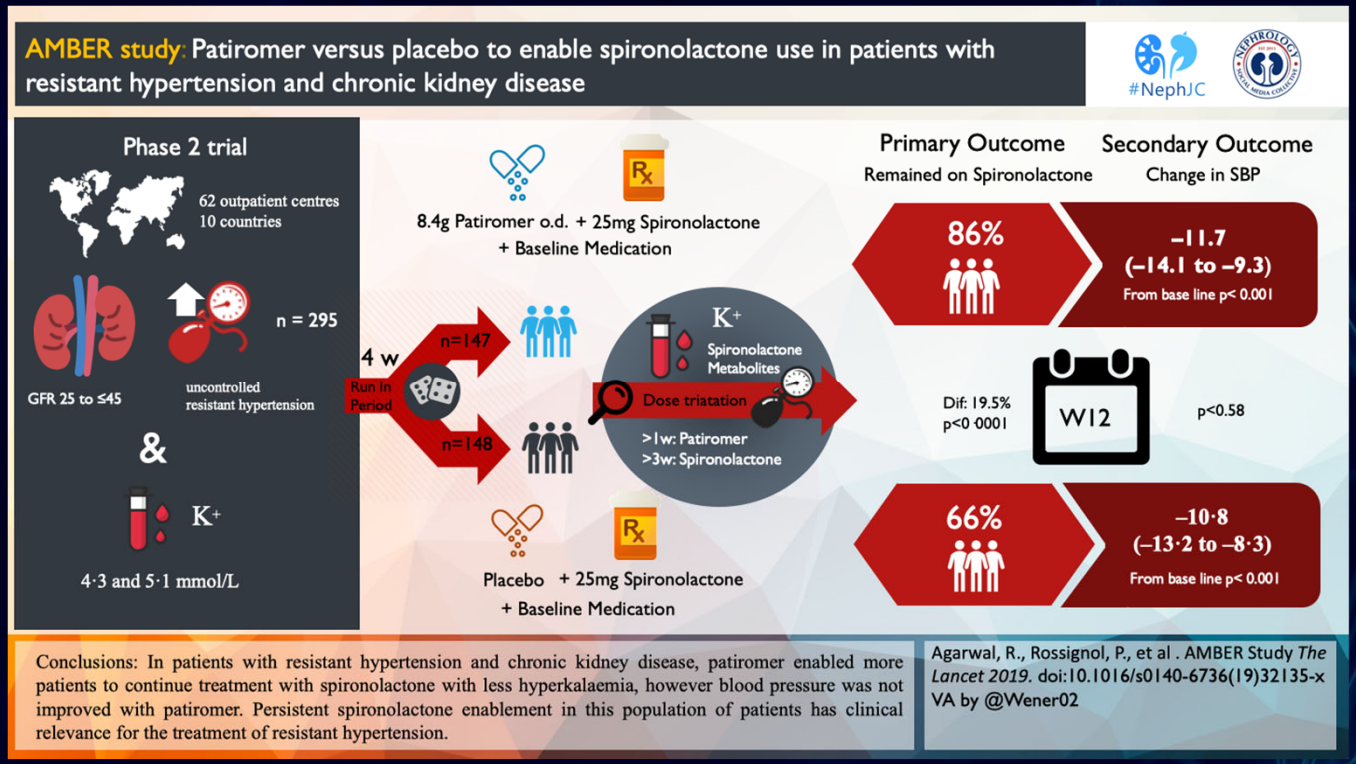
Alternative Remedies:

- Alfalfa
- Amino acids (aminocaproic acid, arginine, lysine)
- Dandelion
- Dried toad skin
- Hawthorn berry
- Horsetail
- Lily of the valley
- Milkweed
- Nettle
- Noni juice
- Siberian ginseng

*Risk of hyperkalemia associated with RAAS inhibition in 2% to 10% of patients with hypertension, heart failure, and chronic kidney disease

Adapted from: Family practice notebook www.fpnotebook.com

AMBER – Utility in Adding Spironolactone



Role of RAAS Inhibitors in HFrEF

Failing heart

RAAS activation

- Water and salt retention
- Adverse ventricular remodeling, etc.

- Worsening of HF symptoms and progression
- Mortality

Inhibition of the RAAS is needed

RAASi therapy

Side effects: hyperkalemia, etc.

MRAs not up-titrated, reduced, or withdrawn even after a single episode of elevated potassium

Management of hyperkalemia

Improved outcomes in HFrEF

RAASi down-titration or withdrawal leads to worsening of HF and increased risk of mortality. Management of hyperkalemia improves outcomes in HFrEF.

MRA, mineralocorticoid receptor antagonist.

Rosano GM, et al. *Card Fail Rev*. 2019;5(3):130-132.

EMPHASIS-HF: Rate of Hyperkalemia

Selected Investigator-Reported Adverse Events and Those Leading to Permanent Withdrawal of the Study Drug, According to Study Group*

Event	Adverse Event			Adverse Event Leading to Study-Drug Withdrawal		
	No. of patients (%)			No. of patients (%)		
	Eplerenone (N = 1,360)	Placebo (N = 1,369)	P Value	Eplerenone (N = 1,360)	Placebo (N = 1,369)	*P* Value
All events	979 (72.0)	1,007 (73.6)	0.37	188 (13.8)	222 (16.2)	0.09
Hyperkalemia	109 (8.0)	50 (3.7)	<0.001	15 (1.1)	12 (0.9)	0.57
Hypokalemia	16 (1.2)	30 (2.2)	0.05	0	3 (0.2)	0.25
Renal failure	38 (2.8)	41 (3.0)	0.82	4 (0.3)	6 (0.4)	0.75
Hypotension	46 (3.4)	37 (2.7)	0.32	0	3 (0.2)	0.25
Gynecomastia or other breast disorders	10 (0.7)	14 (1.0)	0.54	2 (0.1)	2 (0.1)	1.00

*Patients who had received at least one dose of the study drug were included in the safety analysis.
P values were calculated on the basis of the number of patients.

Zannad F, et al; EMPHASIS-HF Study Group. *N Engl J Med*. 2011;364(1):11-21.

Hyperkalemia in PARADIGM-HF

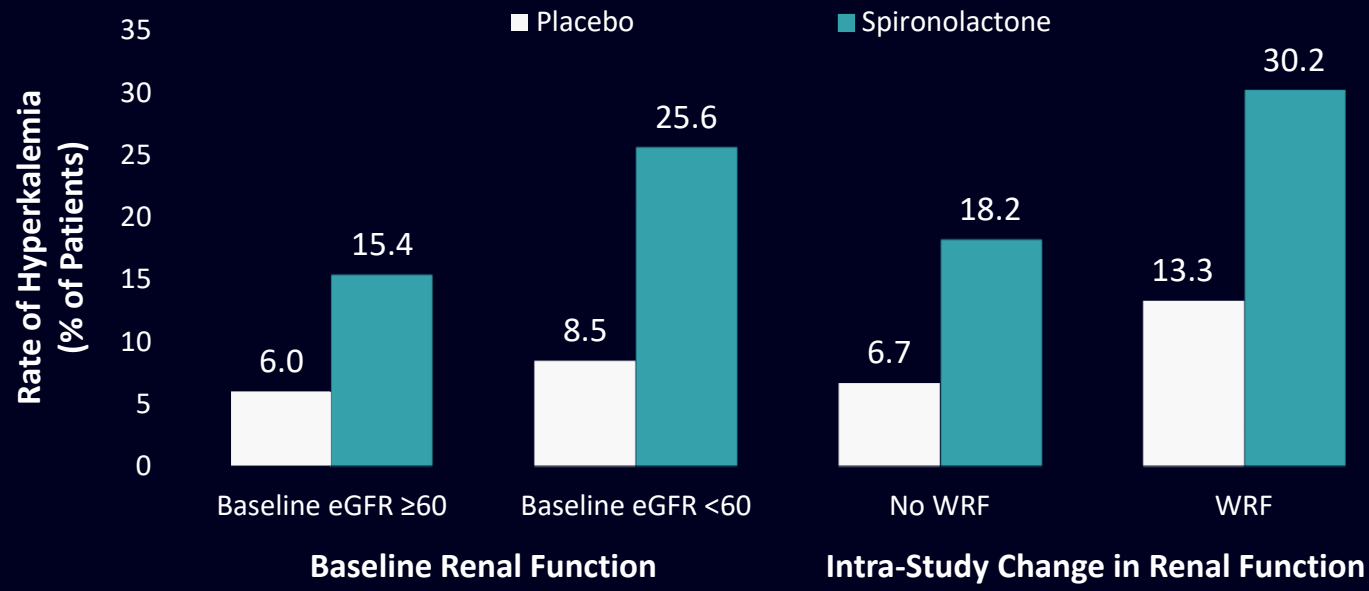
- PARADIGM-HF selected a population at low risk for hyperkalemia prior to randomization
  - Excluded patients with eGFR < 30 mL/min/1.73 m^2, serum K^+ > 5.2 mEq/L at screening (or > 5.4 mEq/L at randomization)
  - Had a run-in phase on ACE inhibitor and then LCZ696; each excluded 6% of patients, which selected a population that would be at low risk for hyperkalemia
  - Hyperkalemia rates remained high despite a carefully selected population
    - **> 5.5 mEq/L: 16.1% LCZ696 vs 17.3% ACE inhibitor (*P* = 0.15)**
    - **> 6.0 mEq/L: 4.3% LCZ696 vs 5.6% ACE inhibitor (*P* = 0.007)**

LCZ696 (sacubitril/valsartan)

McMurray JJV, et al. *N Engl J Med.* 2014;371(11):993-1004.

Hyperkalemia (> 5.5 mEq/L) Rates in Patients With HF Increase as Renal Function Declines

RALES

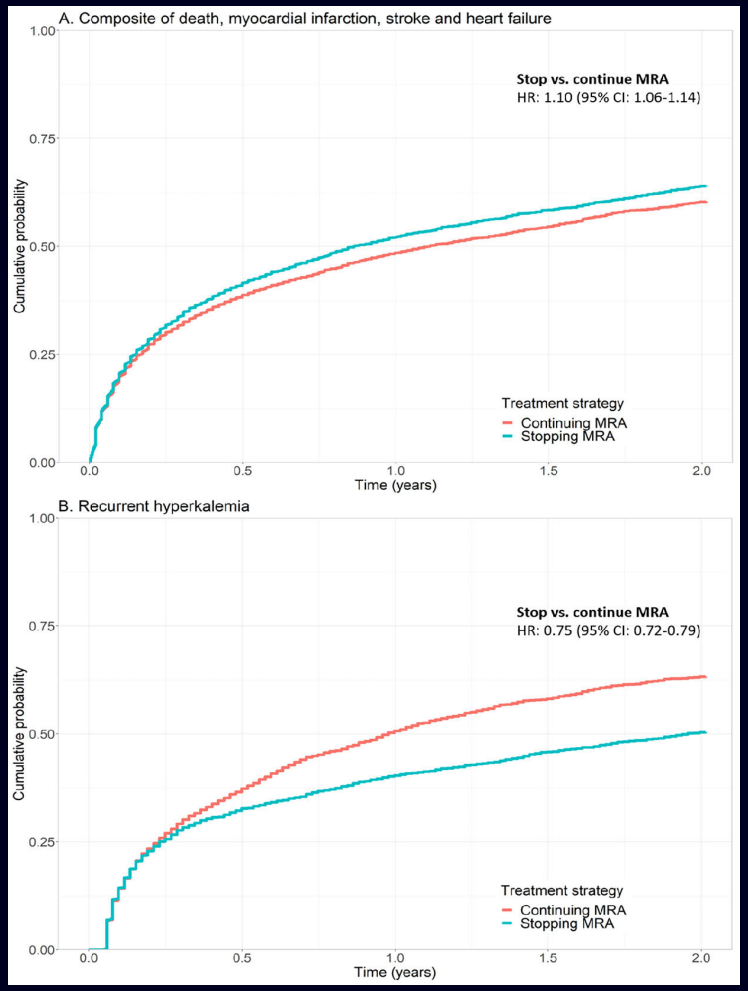


Impaired renal function increases the risk of hyperkalemia in both placebo and MRA-treated patients

RALES, Randomized Aldactone Evaluation Study.

Vardeny O, et al. *J Am Coll Cardiol*. 2012;60(20):2082-2089.

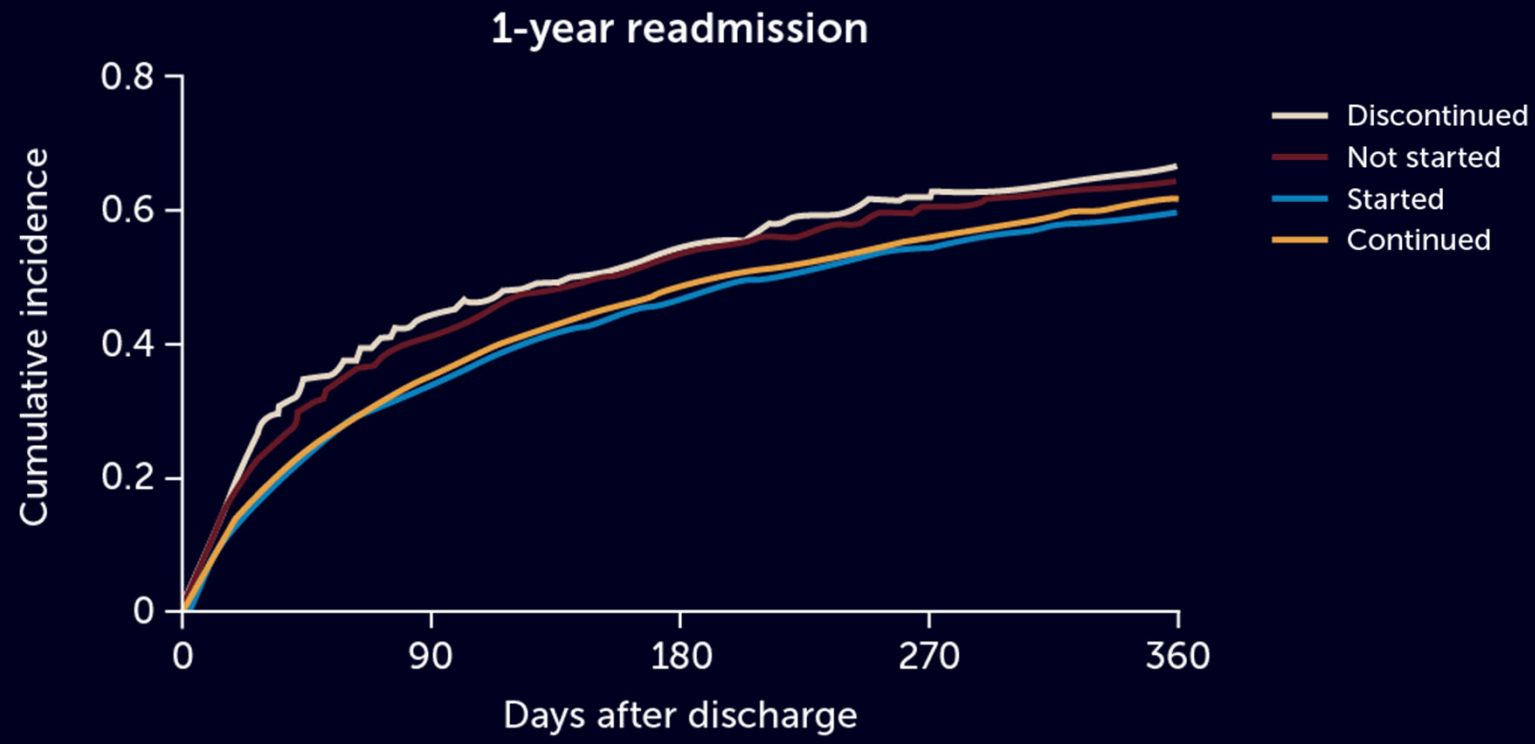
Stopping MRA After Hyperkalemia: Trial Emulation in Data from Routine Care



Weighted cumulative incidence curves for the composite of death, myocardial infarction, stroke, and heart failure outcome (A) or recurrent hyperkalemia (B) associated with continuing or stopping mineralocorticoid receptor antagonists (MRA) after hyperkalemia. CI, confidence interval; HR, hazard ratio.

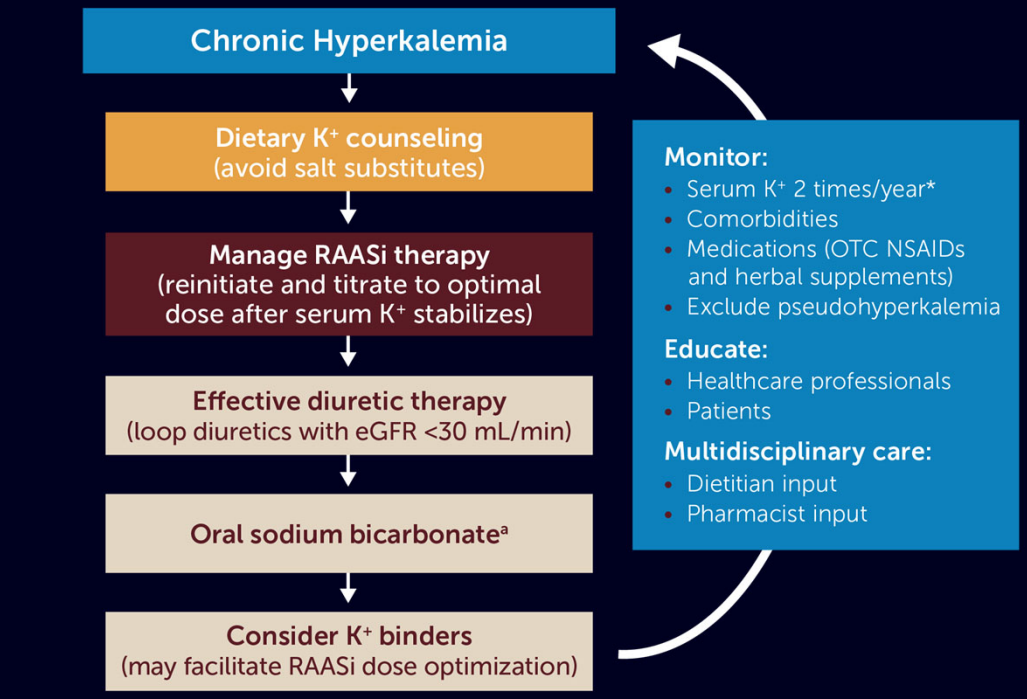
Trevisan M, et al. *Eur J Heart Fail*. 2021;23(10):1698-1707.

Post-HF Discharge Outcomes Based on ACEI Treatment Groups



Oliveros E, et al. *Cardiorenal Med.* 2020;10(2):69-84.

Treatment Options for Management of Chronic Hyperkalemia



Palmer BF, et al. *Mayo Clin Proc*. 2021;96(3):744-762.

Optimizing RAAS Inhibitors with K^+ Binders

- Novel potassium binders: patiromer and sodium zirconium cyclosilicate
  - Effective in treating hyperkalemia
  - Well tolerated
  - Safety and efficacy data for up to 1 year
- Facilitate optimal dosing of RAAS inhibitor therapy
- Decrease ED and urgent care visits
- Reduce the rate of hospitalization
- Reduce cost of care
- Alleviate fear of taking/prescribing RAAS inhibitor therapy
- Liberalize patient diet and improve quality of life

Sarwar CM, et al. *J Am Coll Cardiol*. 2016;68(14):1575-1589.

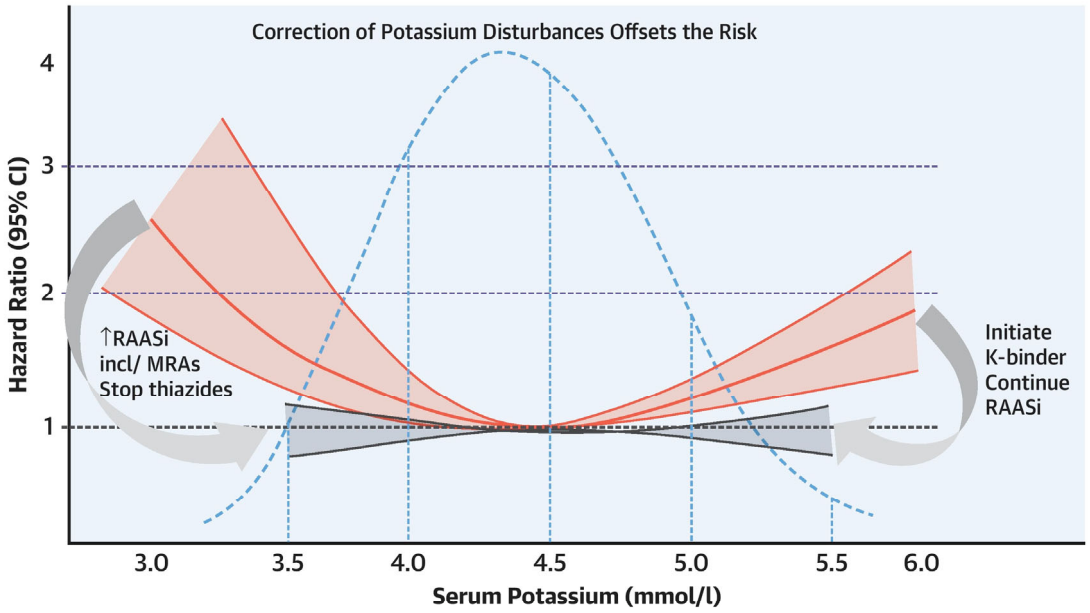
Binding Agents for Hyperkalemia

Characteristic	Sodium Polystyrene Sulfonate (SPS)	Patiromer	Sodium Zirconium Cyclosilicate (SZC)
Approval date	1958	US 2015; EU 2017	US 2018; EU 2018
Mechanism of action	K^+ binding in exchange for Na^+ in GI tract (↑ fecal excretion)	K^+ binding in exchange for Ca^{2+} in GI tract (↑ fecal excretion)	K^+ binding in exchange for H^+ and Na^+ in GI tract (↑ fecal excretion)
Site of action	Colon	Colon	Small and large intestines
Selectivity for K^+	Nonselective; also binds Ca^{2+} and Mg^{2+}	Nonselective; also binds Na^{2+} and Mg^{2+}	Highly selective; also binds NH_4^+
Onset of action	Variable; several hours	7 h	1 h
Na^+ content	1500 mg per 15-mg dose	None	400 mg per 5-g dose
Ca^{2+} content	None	1.6 g per 8.4-g dose	None
Sorbitol content	20,000 mg per 15-g dose	4,000 mg per 8.4-g dose	No sorbitol content
Dosing	15 g 1-4 times (oral); 30-50 g 1-2 times (rectal)	8.4 g QD (oral), titrate up to 16.8 g or 25.2 g QD	10 g TID (oral) for initial correction of hyperkalemia (for ≤48 h), then 5 g QOD to 15 g QD for maintenance
Serious AEs	Cases of fatal GI injury reported	None reported	None reported
Most common AEs	GI disorders (constipation, diarrhea, nausea, vomiting, gastric irritation), hypomagnesemia, hypokalemia, hypocalcemia, systemic alkalosis	GI disorders (abdominal discomfort, constipation, diarrhea, nausea, flatulence), hypomagnesemia	GI disorders (constipation, diarrhea, nausea, vomiting), mild to moderate edema

Palmer BF, et al. *Mayo Clin Proc*. 2021;96(3):744-762.

ACC Recommendations for Hyperkalemia Treatment

CENTRAL ILLUSTRATION: Association of Serum Potassium With All-Cause Death and the Benefits of a Prompt Correction of Dyskalemia



Ferreira, J.P. et al. J Am Coll Cardiol. 2020;75(22):2836-50.

KDIGO DKD and HTN – 2020

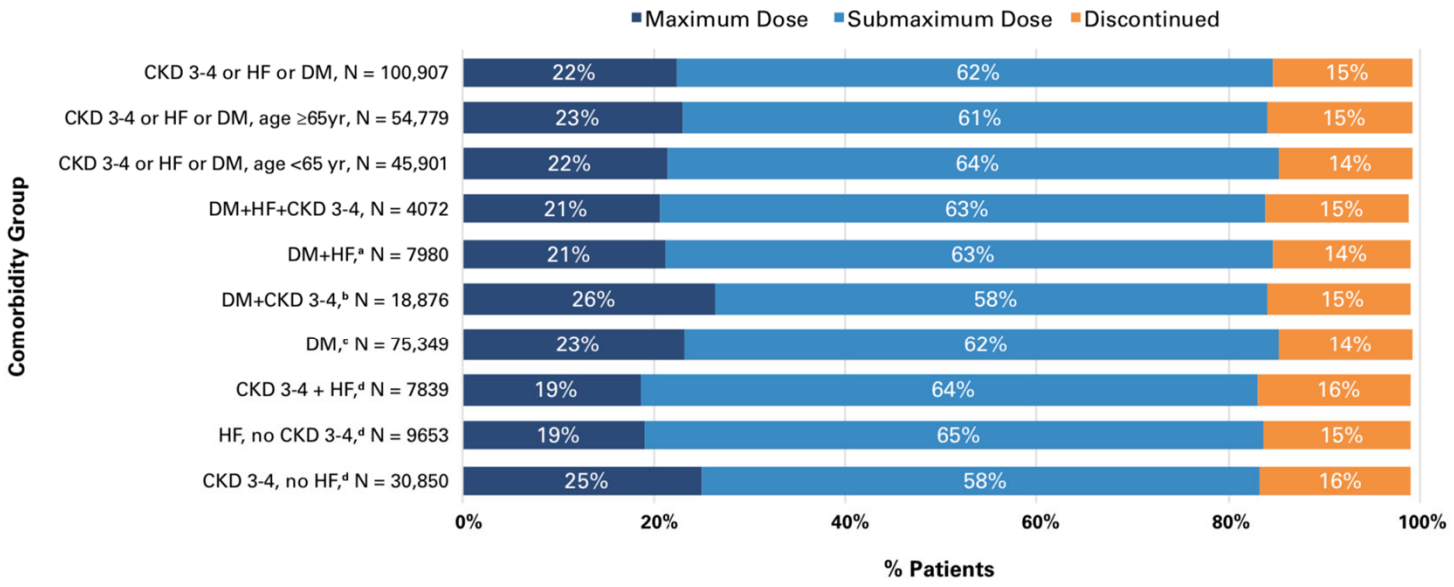
- Practice Point 1.2.5: *Hyperkalemia associated with the use of an ACEI or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping ACEI or ARB immediately*

- "Treatment with gastrointestinal cation exchangers, such as patiromer or sodium zirconium cyclosilicate, where each has been used to treat hyperkalemia associated with RAS blockade therapy for up to 12 months."

de Boer IH, et al. *Kidney Int*. 2020;98(4):839-848.

Suboptimal RAAS Inhibitor Use in Chronic Conditions

Figure 1. Distribution of RAAS Inhibitor Dose Levels by Comorbidity Group



CKD indicates chronic kidney disease; DM, diabetes mellitus; HF, heart failure; RAAS, renin-angiotensin-aldosterone system.
[a]Comorbidity group does not exclude CKD stage 3 to 4.
[b]Comorbidity group does not exclude HF.
[c]Comorbidity group does not exclude CKD stage 3 to 4 or HF.
[d]DM was not excluded from these comorbidity groups.

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

Balancing RAAS Inhibitor Use and Potassium Level

Chronic Management Challenges

RAAS inhibitors: ACE inhibitors, ARBs, aldosterone blockers[a,b]

- Guidelines recommended (ACCF/AHA and HFSA)
- Proven outcomes benefit in HF

Potential risks of RAAS inhibitor therapy

- Risk of increased serum potassium[a,b]
- Utilization limited by risk of hyperkalemia[a,c]
- Up to 65% of patients with HF are suboptimally dosed[c]

Resolve the competing issue (hyperkalemia) so patients can remain on appropriate drugs that lower mortality

a. HFSA; Lindenfeld J, et al. *J Card Fail*. 2010;16(6):e1-194; b. Yancy CW, et al. *Circulation*. 2013;128(16):e240-e327; c. Epstein M, et al. *Am J Manag Care*. 2015;21(11 suppl):S212-S220.

Optimal RAASi Therapy Is Always the Goal

With potassium binders (patiromer and sodium zirconium cyclosilicate) hyperkalemia may be less of a factor, and:

- Patients will have more freedom to eat a healthy diet to improve their quality of life
- Physician and prescriber fear of RAAS inhibitor therapy may be alleviated
- RAAS inhibitor therapy may be initiated and optimally dosed
- Patients will receive guideline-directed medical therapy that will reduce hospitalizations and decrease morbidity and mortality