Hyperkalemia:
Recognition and Management

Incidence/Burden of Hyperkalemia

- Incidence of hyperkalemia in CKD in the US is approximately 50%[1]
  - Incidence may be greater with decreased eGFR and later stages of CKD
- Incidence of hyperkalemia in HF may be 10%-40%[2]
- May be greater in the presence of comorbidities[1,2]
- May be greater in the presence of RAASi and MRA therapies[3]

1. Kovesdy CP. *Kidney Int Suppl (2011)*. 2016:6(1):3-6.
2. Di Lullo L, et al. *Cardiorenal Med*. 2019;9(1);8-21.
3. Palmer BF, et al. *Mayo Clin Proc.* 2021;96(3):744-762.

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

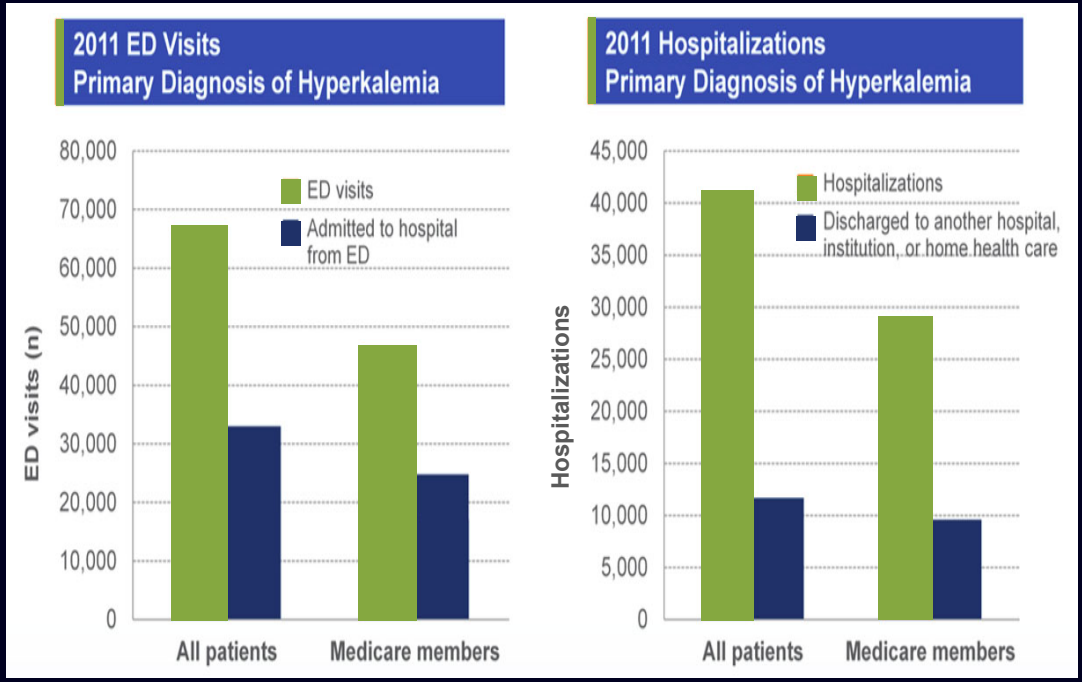
*See publication for complete listing of risk factors and symptoms.

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.

Over 65,000 Hyperkalemia-Related ED Visits and 40,000 Hospitalizations



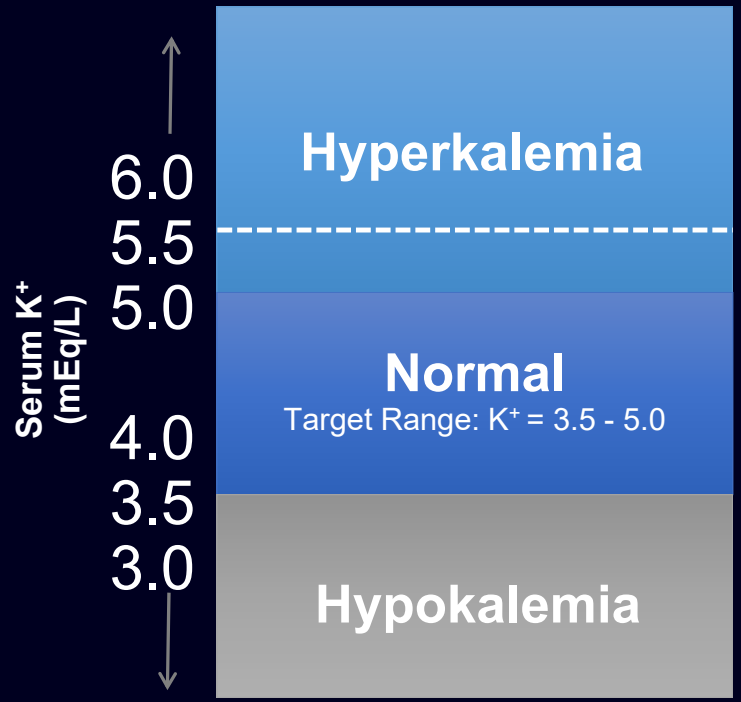
Number of ED Visits and Hospitalizations Due to Hyperkalemia

KEY OBSERVATIONS

- ~$697 million estimated total annual hospital charges for Medicare admissions with hyperkalemia as primary diagnosis in 2011
- Average Medicare length of stay was 3.2 days
- Average cost of hospital stay was $24,085

Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. https://www.ahrq.gov/data/hcup/index.html

Hyperkalemia Varies Widely in Studies and Guidelines

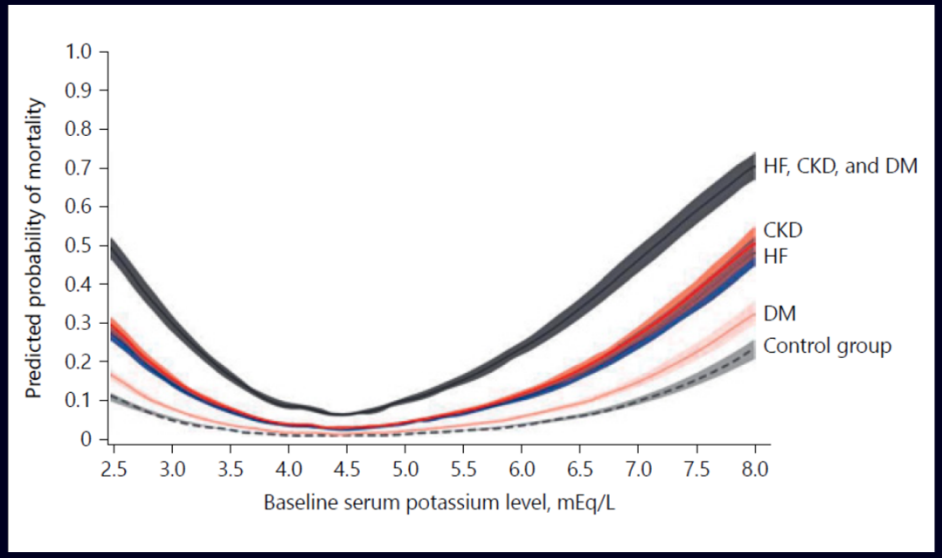


- The upper limit of normal (ULN) for serum K^+ levels varies across guidelines and publications[1-6]
  - Serum K^+ levels of 5.0, 5.5, or 6.0 mEq/L are commonly used cutoffs for ULN
- Some studies differentiate hyperkalemia by severity[1]
  - Serum K^+ levels ≥5.5 - <6.0 mEq/L defined as moderate
 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

K^+, potassium.

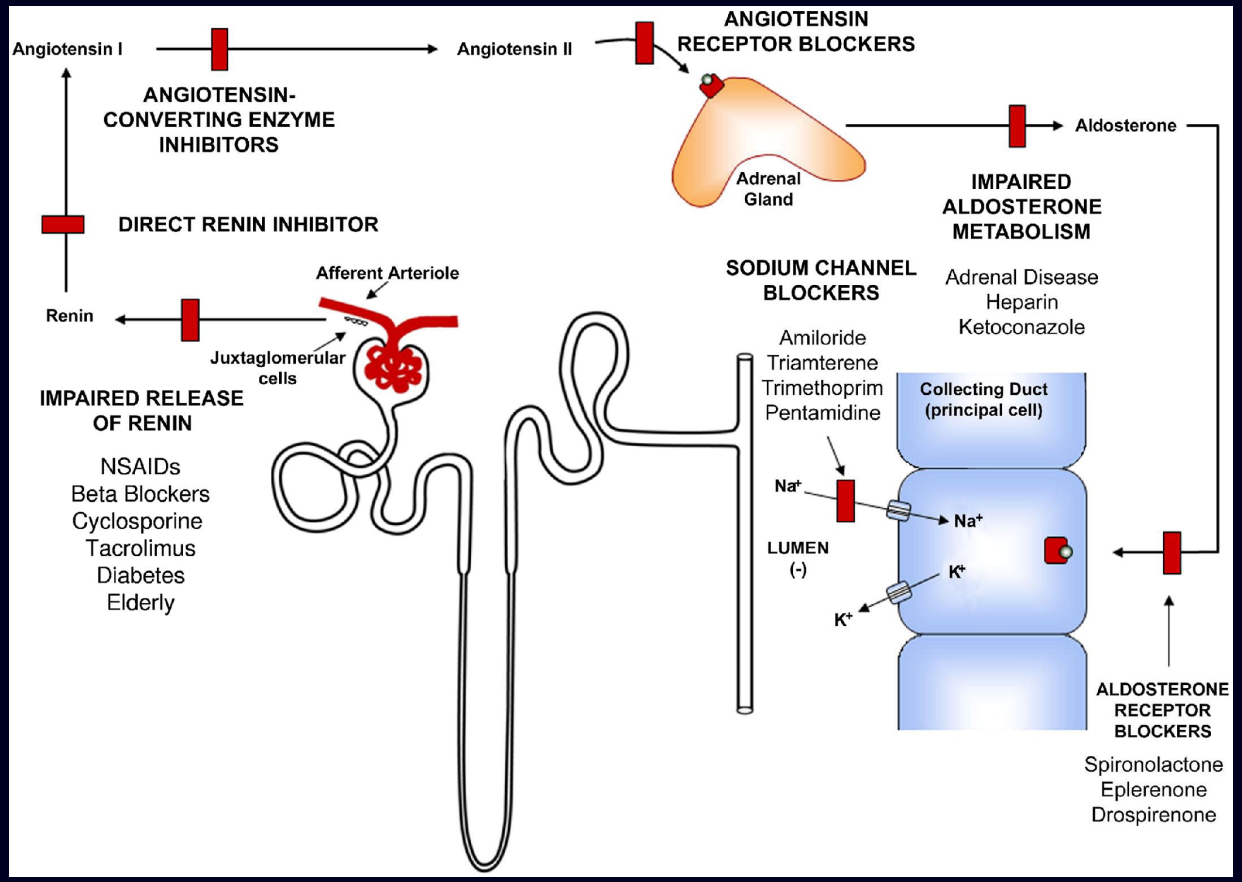
1. Einhorn LM, et al. *Arch Intern Med*. 2009;169(12):1156-1162. 2. Yancy CW, et al. *J Am Coll Cardiol*. 2017;70(6):776-803. 3. Ponikowski P, et al, *Eur Heart J*. 2016;37(27):2129-2200. 4. National Kidney Foundation. Guideline 11: Use of angiotensin-converting enzyme inhibitors and angiotensin receptor 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.

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



CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure.
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

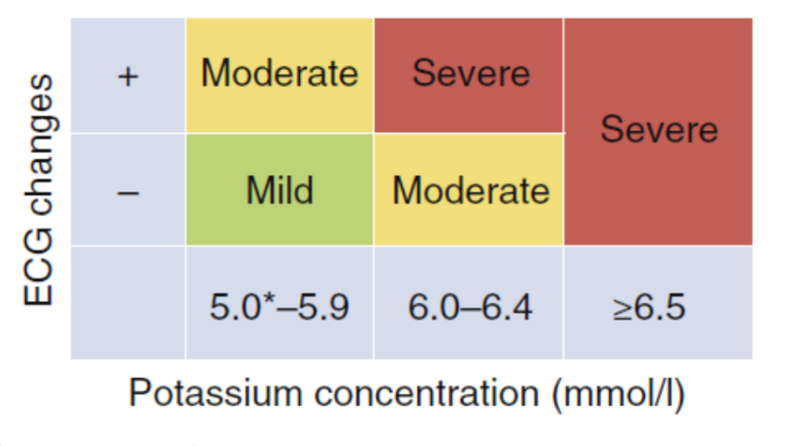
Alternative Remedies:

- 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

Severity of Hyperkalemia: What Level Warrants Concern?



Severity of acute hyperkalemia: expert opinion-based risk classification. *5.0 or upper limit of normal range. (mmol/l = mEq/L)

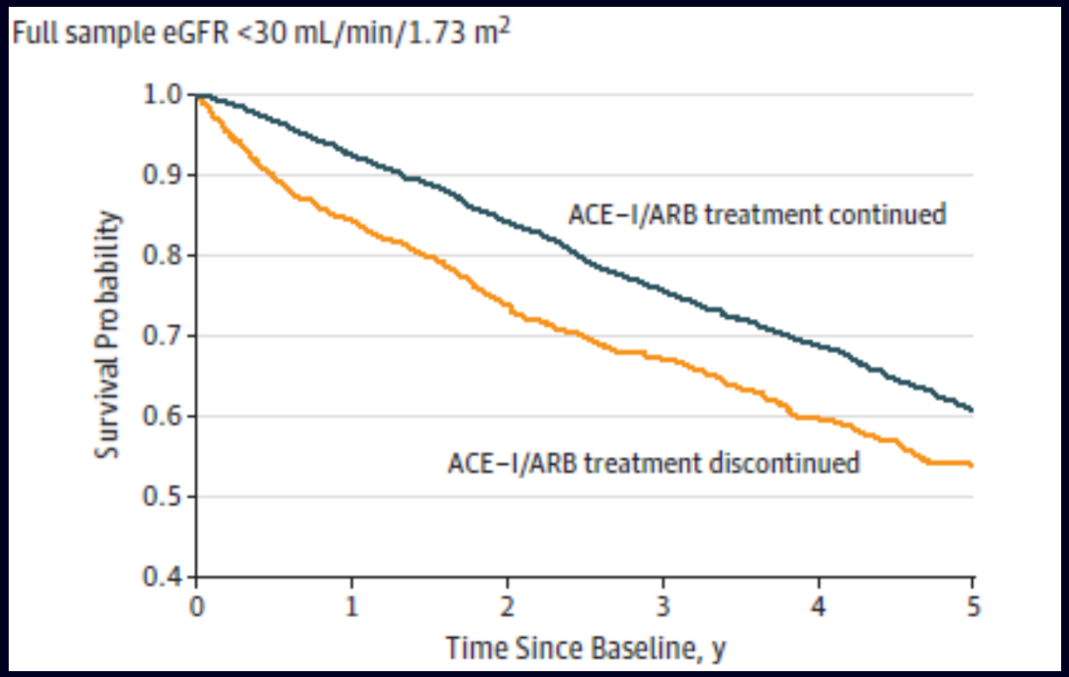
ECG Changes with Acute Hyperkalemia

- Peaked T waves
- Prolonged PR interval and bradycardias
- Progressive widening of QRS complex
- Ventricular fibrillation
- Asystole

ECG, electrocardiogram.

Clase CM, et al. *Kidney Int.* 2020;97(1):42-61.

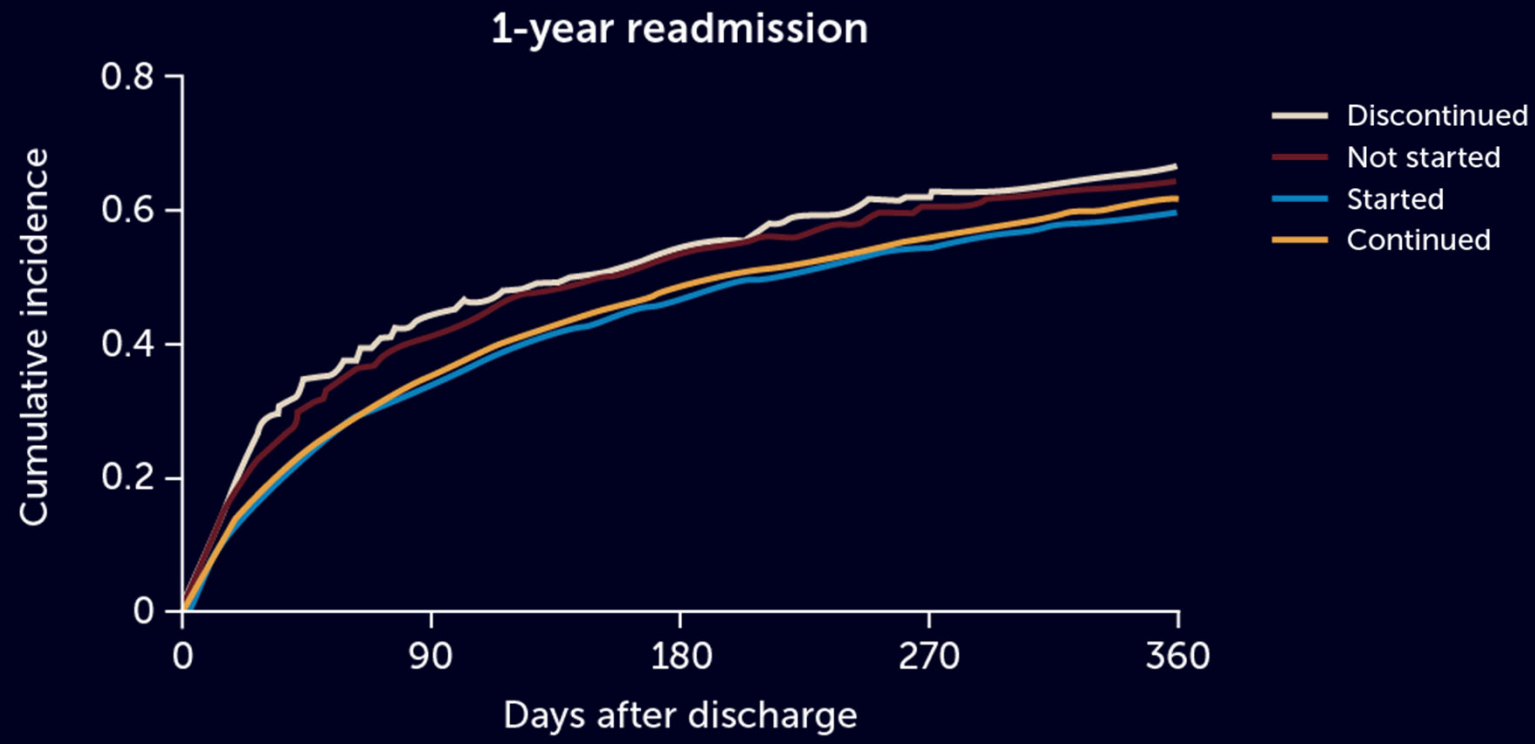
Cumulative Incidence of All-Cause Mortality by ACE-I and ARB Discontinuation Status



Despite a reduction in eGFR, discontinuation of RAASi therapy resulted in decreased survival.

Qiao Y, et al. *JAMA Intern Med.* 2020;180(5):718-726.

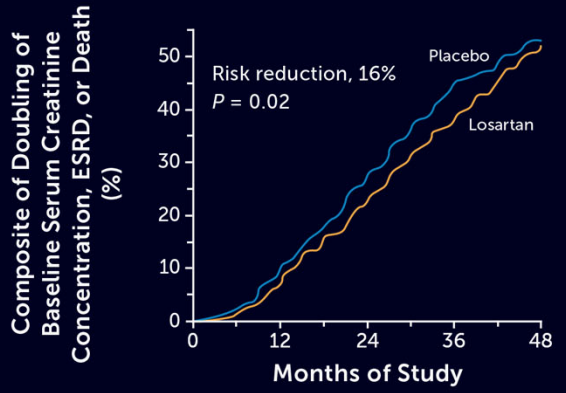
Post HF Discharge Outcomes Based on ACE-I Treatment Groups

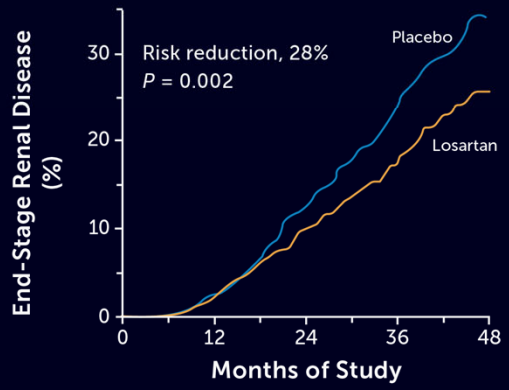


Oliveros E, et al. *Cardiorenal Med.* 2020;10(2):69-84.

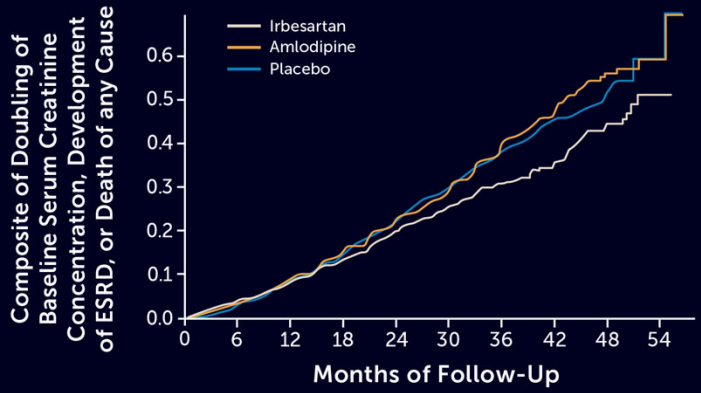
Historical Findings: Clinical Benefits with RAAS Inhibitors in CKD

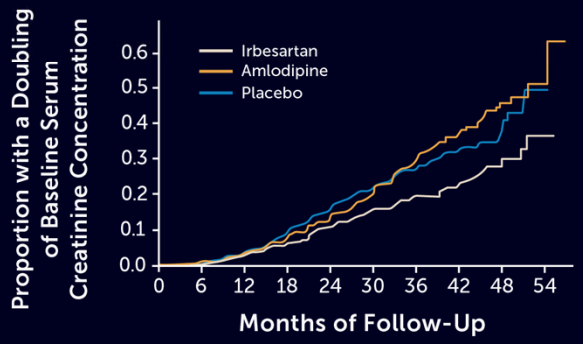
RENAAL Study[1]





IDNT[2]





1. Brenner BM, et al. *N Engl J Med*. 2001;345(12):861-869.
2. Lewis EJ, et al. *N Engl J Med*. 2001;345(12):851-860.

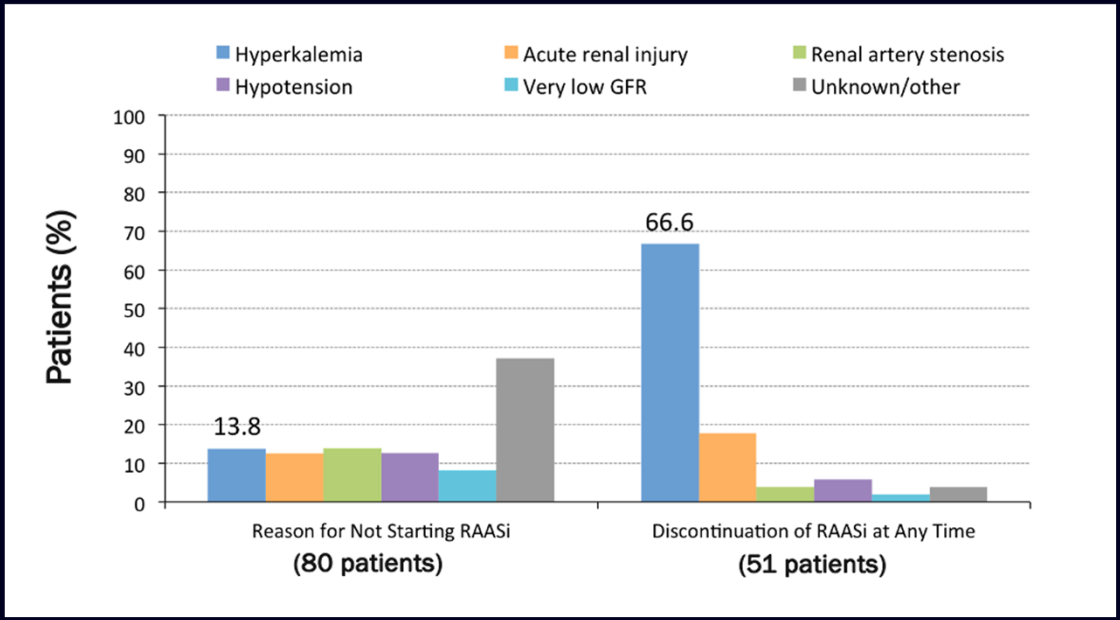
RAASi Therapy in CKD

- KDIGO guideline Class I recommendation (2020)[1]
  - Titrate to “highest approved dose that is tolerated”
- IRMA Trial (2007)[2]
  - Type 2 DM patients with diabetic nephropathy
  - Telmisartan vs placebo
  - Results – Telmisartan induced remission of albuminuria and reduced transition from incipient to overt nephropathy in patients with type 2 DM
- INNOVATION Trial (2001)[3]
  - Type 2 DM patients with microalbuminuria
  - Irbesartan vs placebo
  - Results – Significant renoprotective benefit with irbesartan, independent of BP-lowering effect

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int*. 2020;98(4S):S1- S115.
2. Makino H, et al. *Diabetes Care*. 2007;30(6):1577-1578.
3. Parving HH, et al. *N Engl J Med*. 2001;345(12): 870-878.

Hyperkalemia Is a Leading Reason for Discontinuing or Not Starting RAAS Inhibitors in Patients With CKD

- 279 patients with baseline mean GFR 33.3 mL/min/1.73 m^2 and serum K^+ 4.73 mEq/L



Yildirim T, et al. *Ren Fail*. 2012;34(9):1095-1099.

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.

JACC State of the Art Review: Adjustment of MRAs in the Presence of Hyperkalemia

TABLE 3 Spironolactone and Eplerenone Dose Adjustment Proposal

Serum K^+ (mmol/l)	Dose Adjustment*
	Baseline: eGFR ≥50 ml/min/1.73 m^2 → spironolactone dose = 25 mg/day or eplerenone 50 mg/day eGFR 30-49 ml/min/1.73 m^2 → spironolactone dose = 25 mg every other day or eplerenone 25 mg/day
<4.0	Increase dose: If spironolactone dose = 25 mg/day → increase to 50 mg/day or if eplerenone dose = 50 mg/day → increase to 100 mg/day If spironolactone dose = 25 mg every other day → increase to 25 mg/day or if eplerenone dose = 25 mg/day → increase to 50 mg/day
4.0-5.4	No adjustment recommended
5.5-5.9	Decrease dose: If spironolactone dose = 50 mg/day → decrease to 25 mg/day or if eplerenone dose = 100 mg/day → decrease to 50 mg/day If spironolactone dose = 25 mg/day → decrease to 25 mg very other day or if eplerenone dose = 50 mg/day → decrease to 25 mg/day If spironolactone dose = 25 mg every other day → interrupt treatment and reassess K^+ within 1 week or if eplerenone dose = 25 mg/day → interrupt treatment and reassess K^+ within 1 week
≥6.0	Stop MRA treatment and reassess K^+ levels after 1 week When K^+ levels <6.0 mmol/l, initiate a K^+ binder and reintroduce MRA
	Stop MRA treatment at any case if eGFR ≤30 ml/min/1.73 m^2 and reintroduce upon clinical decision, i.e., upon renal function improvement and K^+ stabilization

Ferreira JP, Butler J, Rossignol P, et al. *J Am Coll Cardiol*. 2020;75(22):2876-2850.

JACC State of the Art Review: Proposal for Potassium Binder Use Specific to Potassium Level

TABLE 4 Proposal for K^+ Binder Use

Serum K^+ (mmol/l)	K^+ Binder Use
<5.5	Maintain guideline-recommended treatment Do not stop K^+ binder if the patient is taking one Consider initiating K^+ binder between 5.0 and 5.5 mmol/l if reliable patient follow-up is a concern and therefore consideration is given to compromising RAASi dosing
5.5-5.9	Adapt MRA dose as suggested in the Table 3 Do not reduce ACE inhibitors/ARB/ARNi Re-assess K^+ levels after 1 week; if K^+ levels still high add K^+ binder, preferably those with long-term enablement data, i.e., patiromer or SZC Reassess K^+ levels after 1 week (a ≈1 mmol/l K^+ decrease could be expected) If K^+ <5.5 mmol/l, increase MRA dose and maintain K^+ binder for 1 additional week, then continue routine follow-up If K^+ 5.5 to 5.9 mmol/l, do not increase MRA and maintain/uptitrate K^+ binder for 1 additional week reassessing K^+ afterwards
≥6.0	Adapt MRA dose as suggested in the Table 3 Reduce ACE inhibitors/ARB/ARNi in 50% Re-assess K^+ levels after 1 week; if K^+ levels still high add a K^+ binder similar to as recommended for K^+ levels 5.5 and 5.9 mmol/l

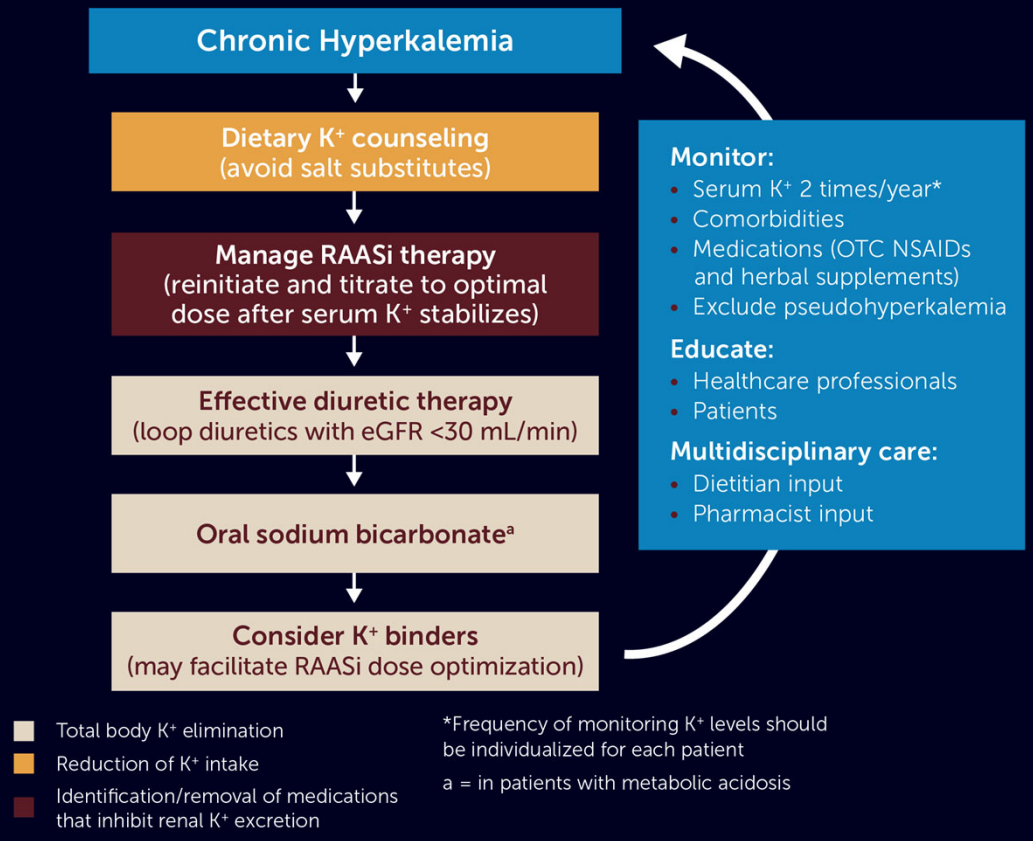
Ferreira JP, Butler J, Rossignol P, et al. *J Am Coll Cardiol.* 2020;75(22):2876-2850.

JACC State of the Art Review: Treatment of Hyperkalemia

- Assess the possibility of **hemolysis**
- Initiate a **diuretic** or increase its dose (if necessary)
- **Eliminate K^+ supplements,** NSAIDs and decrease K+ rich foods
- **Replace ACE inhibitors/ARBs by sacubitril valsartan** (if not yet done)
- **Adapt MRA dose** (if necessary)
- **Consider a K+ binder (do not stop RAASi)**

Ferreira JP, Butler J, Rossignol P, et al. *J Am Coll Cardiol.* 2020;75(22):2876-2850.

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.

Key Clinical Studies of Patiromer in Patients with Hyperkalemia: OPAL-HK and AMETHYST-DN

Author (year)	Study Design	Treatment	Cohort/Endpoints	Results
Weir MR, et al (2015) OPAL-HK	Two-phase trial: Part A, single-blind Part B, randomized placebo-controlled	Patiromer at 4.2 g, 8.4 g twice daily vs placebo	237 patients in Part A, 107 patients in Part B; mean change in potassium from baseline in Part A and Part B	Patiromer lowered potassium −1.01 mEq/L in Part A. In Part B, 60% of placebo patients had recurrent hyperkalemia vs 15% of patiromer patients.
Bakris GL, et al (2015) AMETHYST-DN	Open label, dose-ranging, randomized	Patiromer at 4.2 g, 8.4 g, 12.6 g, 16.8 g twice daily	306 patients, divided into mild or moderate hyperkalemia; mean change in serum potassium level, adverse events at 52 weeks	Patiromer lowered potassium in all groups over 52 weeks. Higher dosage reduced potassium more. Well tolerated. Most common adverse event was hypomagnesemia 7.2%.

Colbert GB, et al. *Expert Rev Clin Pharmacol*. 2020;13(6):563-570.

Key Clinical Studies of SZC in Patients with Hyperkalemia

Study design	Patient population	Study treatment	Primary efficacy endpoint results
Packham DK, et al Phase 3, 2-wk, randomized, double-blind, placebo-controlled, dose-ranging	Correction phase: serum K^+ 5.0-6.5 mEq/L (n = 754); CKD: n = 463; RAASi: n = 502	Correction phase: SZC 1.25 g, 2.5 g, 5 g, or 10 g TID or placebo for 48 h	Correction phase: between-group difference in exponential rate of serum K^+ change/h in first 48 h: −0.11% for SZC 1.25 g, −0.16% for SZC 2.5 g, −0.21% for SZC 5 g, and −0.30% for SZC 10 g vs −0.09% for placebo ($P < 0.001$ for all except SZC 1.25 g)
	Maintenance phase: serum K^+ 3.5-4.9 mEq/L at 48 h of the initial (correction) phase (n = 543)	Maintenance phase: SZC dose from initial phase (administered QD) or placebo for 12 d	Maintenance phase: between-group difference in mean serum K^+ during 12-d treatment period: SZC 5 g and 10 g were significantly superior to placebo in maintaining normokalemia ($P = 0.008$ and $P < 0.001$, respectively)
Spinowitz BS, et al Phase 3, 12-mo, open-label, single-arm	Correction phase: serum K^+ ≥5.1 mEq/L (n = 751) Maintenance phase: serum K^+ 3.5-5.0 mEq/L (n = 746); CKD: n = 483; RAASi: n = 483	Correction phase: SZC 10 g TID for 24-72 h Maintenance phase: SZC titrated to serum K^+ 3.5-5.0 mEq/L (maximum 15 g QD, minimum 5 g every other day)	Correction phase: proportion of patients with serum K^+ 3.5-5.0 mEq/L: 78% Maintenance phase: proportion of patients with serum K^+ ≤5.1 during 3-12 mo: 88%

Palmer BF. *Mayo Clin Proc*. 2020;95(2):339-354.

Future Hyperkalemia Studies

- Redukx Trial – A study evaluating the safety and efficacy of RDX013 for the treatment of hyperkalemia (cinicaltrials.gov NCT04780841)
- PLATINUM Trial – Patiromer utility as an adjunct treatment in patients needing urgent hyperkalemia management (clinicaltrials.gov NCT04443608)
- DIAMOND Trial – Patiromer for the Management of hyperkalemia in subjects receiving RAASi medications for the treatment of heart failure (clinicaltrials.gov NCT03888066)

Ongoing and Future HF Studies

- CARE-HK in HF Trial – Cardiovascular and renal treatment in heart failure patients with hyperkalemia or at high risk for hyperkalemia [First Patient enrolled April 2021] (clinicaltrials.gov NCT04864795)
- REALIZE-K Trial – Study to assess efficacy and safety of SZC for the management of high potassium patients with symptomatic HFrEF receiving spironolactone (clinicaltrials.gov NCT04676646)
- OPRA-HF Trial – Optimizing aldosterone receptor antagonist therapy by sodium zirconium cyclosilicate in heart failure (clinicaltrials.gov NCT04789239)