CẬP NHẬT ĐIỀU TRỊ TĂNG KALI MÁU TRONG BỆNH LÝ NỘI KHOA

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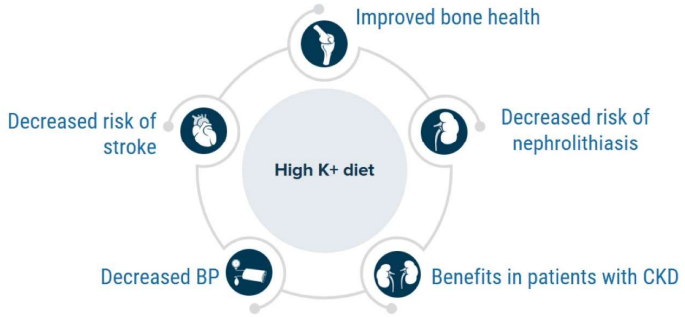
Benefits of High K+ Diet

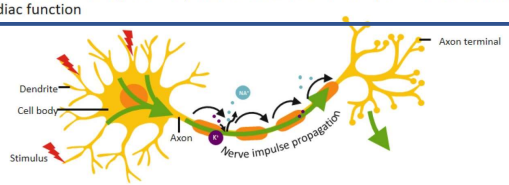


Palmer BF, et al. *Mayo Clin Proc.* 2016;91:496-508.

Potassium Physiology

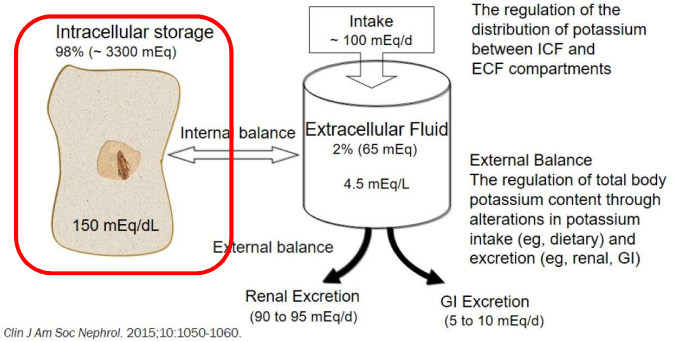
- The most abundant cation in the body
- 98% intracellular (~140 mmol/L), 2% extracellular (3.8 to 5.0 mmol/L)
- Complex regulation of intracellular/extracellular shifts with active uptake and passive leak

Long-term K^+ homeostasis mainly governed by renal excretion -- mainly influenced by aldosterone
Normal plasma K^+ is tightly regulated despite variable intake (40 to 200 mmol/day)
Disorders of K^+ levels profoundly affect membrane excitability and nerve, muscle, and cardiac function



Nyirenda MJ, et al. *BMJ.* 2009;339:b4114.

Regulation of Potassium Balance

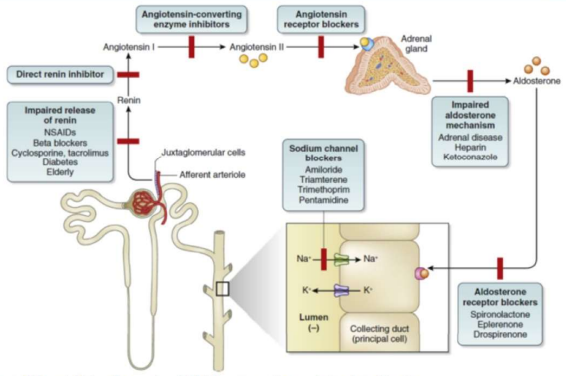


Internal Balance
The regulation of the distribution of potassium between ICF and ECF compartments

External Balance
The regulation of total body potassium content through alterations in potassium intake (eg, dietary) and excretion (eg, renal, GI)

Palmer BF. *Clin J Am Soc Nephrol.* 2015;10:1050-1060.

Renin-Angiotensin-Aldosterone System and Regulation of Renal K^+ Excretion



Reprinted from Clase CM, et al. Kidney International 2019 in press with permission from Elsevier.

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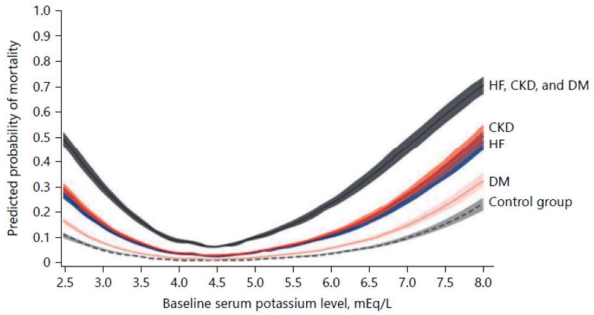
Adjusted Mortality According to Potassium and Comorbid Conditions



Spline analysis adjusted for covariates showing serum potassium as a continuous variable with all-cause mortality in HF, CKD, DM, and combined vs control group.

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

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Who Is at Risk for Hyperkalemia?

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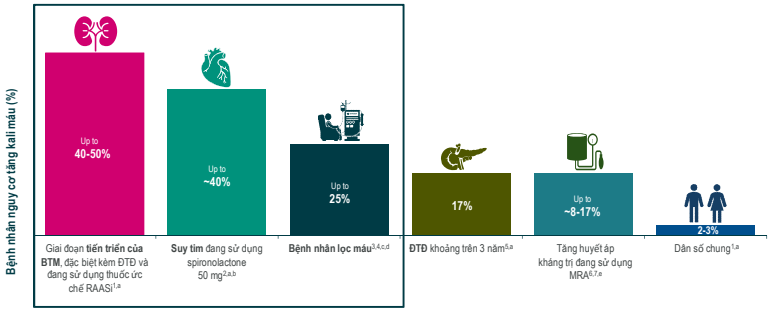
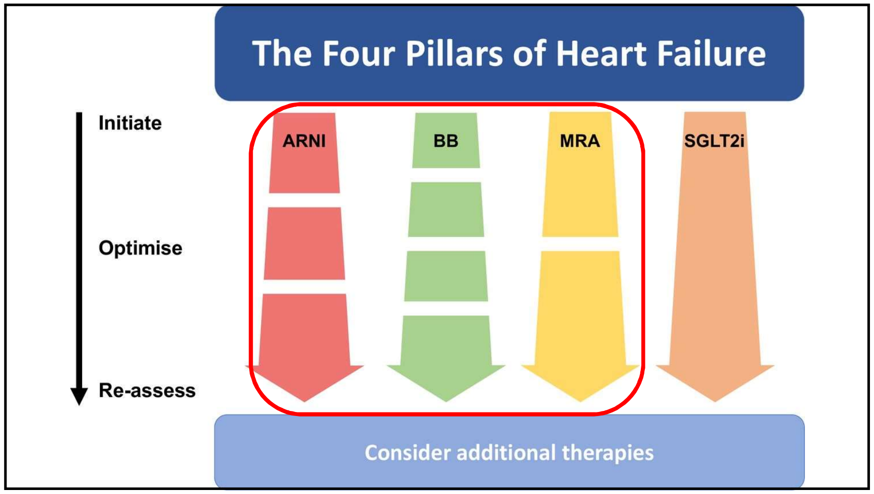
Tăng kali máu thường gặp ở Bệnh thận mạn (CKD), Bệnh thận lọc máu và Suy tim (HF)



[a]Definition of HK varied from K+ >5.0 mmol/L to ≥5.5 mmol/L.[1,2,5] [b]NYHA Class III or IV and LVEF <35%.[2] [c]HK defined as K+ >5.5 mmol/L in patients who received hemodialysis for >120 days.[3,4] [d]When reported, most studies in this systematic review defined HK as kali máu ≥5.5 mmol/L and included patients with end stage kidney disease receiving hemodialysis three times weekly (mean vintage time on hemodialysis, where reported, was 42.3 months).[3,4] [e]HK defined as persistent K+ >5.5 mmol/L (or 1 reading of K+ ≥6.0 mmol/L).[6]

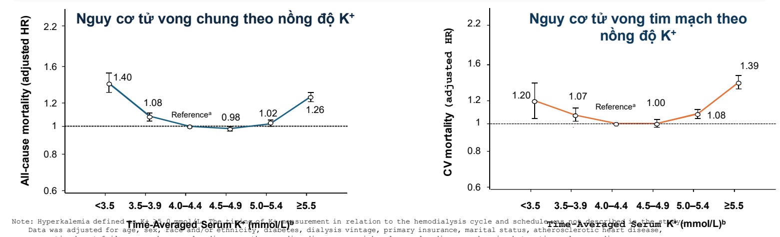
CKD = chronic kidney disease; DM = diabetes mellitus; HK = hyperkalemia; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. Kovesdy CP. *Ital Rev Nephrol.* 2014;1(01):053-062. 2. Vardeny O et al. *Circ Heart Fail.* 2014;7(4):573-579. 3. Xu H, et al. *Poster presented at:* 54th ERA-EDTA Congress; June 3-6, 2017; Madrid, ES; 4. Bem D et al. Article and supplementary material. *Rev Fail.* 2021;43(1):241-254; 5. Nilsson E et al. *Int J Cardiol.* 2017;245:277-284; 6. Chonchol J et al. *J Am Soc Hypertens.* 2014;8(4):245-48. Ata P-10; 7. Khosla N et al. *Am J Nephrol.* 2009;30(5):418-424.



Tăng kali máu làm tăng nguy cơ tử vong do mọi nguyên nhân và tử vong tim mạch ở BN chạy thận nhân tạo

Phân tích dữ liệu 111.434 bệnh nhân chạy thận nhân tạo tại Hoa Kỳ trong giai đoạn từ tháng 7 năm 2001 đến tháng 6 năm 2006



Note: Hyperkalemia defined as K+ ≥5.0 mmol/L. The timing of K+ measurement in relation to the hemodialysis cycle and schedule was not described in the study. Data was adjusted for age, sex, race and/or ethnicity, diabetes, dialysis vintage, primary insurance, marital status, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiac diseases, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, current smoking, body mass index, serum albumin, total iron binding capacity, ferritin, creatinine, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percentage lymphocyte count.

aReference group was patients on hemodialysis with serum K+ between 4.0 and 4.5 mmol/L; bEach patient had K+ measurements performed at least monthly. The average of all repeated measures were done quarterly for 20 calendar quarters to calculate the time-averaged serum K+.

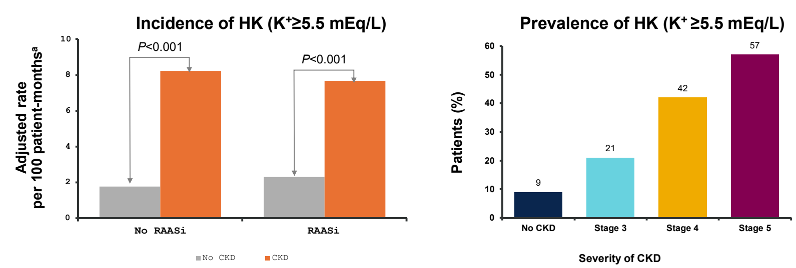
CV = cardiovascular; HR = hazard ratio; US = United States.

Torlén K et al. Clin J Am Soc Nephrol. 2012;7(8):1272-1284.

Hyperkalemia Is a Complex Clinical Challenge

- Aging reduces eGFR and renin levels
- Comorbidities (CKD, DM, HF) place patients at high risk of hyperkalemia
- Comorbidities require therapy (RAAS inhibitors) that increases risk of hyperkalemia
  - Discontinuing therapy places patients at risk of events (eg, CV events, progression of CKD)
- Comorbidities rarely are cured (currently)
  - Lifelong struggle with lifestyle, medications, AEs

Chức năng thận càng giảm, tỷ lệ tăng kali máu càng tăng Đặc biệt trên bệnh nhân G5 và lọc máu



Phân tích hồi cứu trên 245.808 cựu chiến binh có ít nhất một lần nhập viện và có xét nghiệm kali máu trong năm 2005

aAdjusted for confounders; race, gender, age, Charlson comorbidity index, cancer, diabetes, CVD, and RAASi treatment within 30 days.

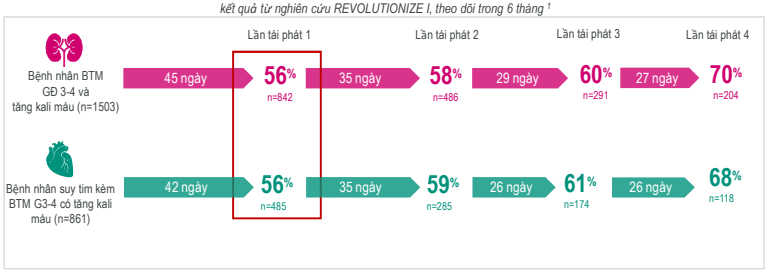
CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; RAASi, renin-angiotensin-aldosterone system inhibitor.

Einhorn LM, et al. Arch Intern Med 2009;169:1156-1162.

Tăng kali máu dễ tái phát trên BN CKD GĐ 3-4 trở lên kèm hoặc không kèm HF:

~60% BN sẽ bị tăng kali máu tái phát trong vòng 45 ngày

*Bệnh nhân đã bị tăng kali máu, sẽ **dễ tái phát hơn với khoảng thời gian giữa các lần tái phát ngắn dần***
kết quả từ nghiên cứu REVOLUTIONIZE I, theo dõi trong 6 tháng [1]



Note: REVOLUTIONIZE I was a retrospective analysis of the US EHRs evaluating HK recurrence following a MNT visit within 30 days of laboratory confirmed HK diagnosis in 2048 adults with CKD Stage 3 or 4 and a subgroup of 1179 patients with a diagnosis code for HF, between January 2019 to October 2022.[1] The index date was the date of MNT visit plus 7 days.[1]
[a]Recurrent HK was defined as post-index lab value of K^+ >5.0 mmol/L that was at least 7 days apart from a prior lab evidence of HK.[1] [b]As reported during the facility-based or outpatient encounters and K^+ measurements between these encounters were unknown.[1]
CKD = chronic kidney disease; EHR = electronic health record; HK = hyperkalemia; HF = heart failure; MNT = medical nutrition therapy; US = United States.
1. Rowan CG et al. *Adv Ther*. 2024;41(6):2381-2398. 2. In House Data, AstraZeneca. DoF 178557.

BN tăng kali máu phải đối mặt với việc tăng thêm 50% nguy cơ Tử vong, đồng thời tăng 3-4 lần nguy cơ nhập viện so với không tăng kali máu

Nguy cơ nhập viện trong 6 tháng:

Mỗi 0,5 mmol/L kali máu tăng thêm làm tăng hơn 50% nguy cơ tử vong[3,a]

So sánh với BN CKD/HF không có tăng kali máu

CKD = chronic kidney disease; HF = heart failure; HR = hazard ratio; K^+ = potassium. a. So với nhóm bệnh nhân có nồng độ kali máu bình thường (4.0-5.0 mmol/L)

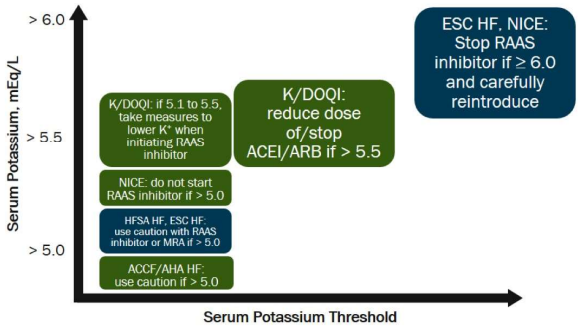
References:
1. Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes-a Danish population-based cohort study. *Nephrol Dial Transplant*. 2018;33(9):1618-1628.
2. Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes. A Danish population-based cohort study. *J Am Heart Assoc*. 2018;7:e008912.
3. Collins AJ et al. Am J Nephrol. 2017;46(3):213-221, Supplement Table #5

Causes of Hyperkalemia

Mechanism	Causes*
Increased K^+ load	• Dietary intake • Drug-induced: potassium supplements, herbal supplements, packed RBC infusions
Altered K^+ distribution	• Metabolic: acidosis, hyperglycemia (in diabetes) • Drug-induced: insulin antagonists, hypertonic solutions, digoxin, β-blockers
Reduced K^+ excretion	• Metabolic: hyporeninemic, hypoaldosteronism, oliguria • Drug-induced: potassium-sparing diuretics, cyclosporine, tacrolimus, pentamidine, trimethoprim, lithium
Impaired renin-aldosterone function	• Drug-induced: ACEIs, ARBs, ARNIs, MRAs, β-blockers, heparin, NSAIDs, COX-2 inhibitors
Reduced GFR/hypovolemia	• Metabolic: acidosis, HF, dehydration • Drug-induced: antihypertensives, diuretics
Laboratory error	• Hemolyzed RBCs, inappropriate sample handling, erroneous reporting, equipment malfunction

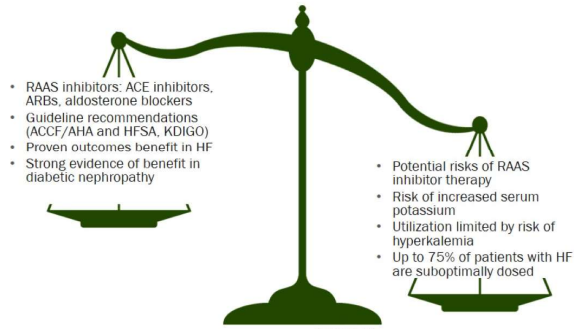
*Table not all-inclusive.
NKF K/DOQI website. Guideline 11: use of ACE inhibitors and ARBs in CKD.

Guideline Recommendations Regarding RAAS Inhibitor Use Based on Serum Potassium Level



Yancy CW, et al. *Circulation*. 2017;136:e137-e161; Lindenfeld J, et al. *J Card Fail*. 2010;16:e1-e194; Ponikowski P, et al. *Eur J Heart Fail*. 2016;37:2129-2200; NICE website. Clinical guideline [CG182]; K/DOQI. *Am J Kidney Dis*. 2004;43:S1-S290.

Challenge of Balancing RAAS Inhibitor Use and Potassium Level



Lindenfeld J, et al. *J Card Fail*. 2010;16:475-539; Yancy CW, et al. *Circulation*. 2013;128:e240-e327; Epstein M, et al. *Am J Manag Care*. 2015;21:S212-S220; Umanath K, et al. *Am J Kidney Dis*. 2018;71:884-895.

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Không tối ưu liều RAASi làm tăng đáng kể nguy cơ tiến triển bệnh thận mạn và tái nhập viện vì suy tim

Bệnh thận mạn

Nguy cơ tiến triển đến ESKD[1,a]

74% Tăng nguy cơ khi **ngừng RAASi** (n=2460)

60% Tăng nguy cơ Khi **giảm liều RAASi** (n=460)

So với nguy cơ khi duy trì RAASi[b] (n=4586)

Suy tim

Nguy cơ tái nhập viện vì suy tim[2,c]

43% Tăng nguy cơ khi **ngừng RAASi** (n=1966)

40% Tăng nguy cơ khi **giảm liều RAASi** (n=430)

So với nguy cơ khi duy trì RAASi[b] (n=3049)

Bệnh nhân CKD/HF **cần tối ưu GDMT (RAASi & MRA)** để giảm tiến triển bệnh và giảm nhập viện, tối ưu hiệu quả bảo vệ tim mạch – thận

Note: An observational study that utilized the US claims and EMR data from July 2019 and September 2021 in 15,488 adult patients with CKD Stage 3 or 4 and/or HF who experienced an index HK event (ICD-10 or ICD-9 diagnosis codes) and had ≥1 filled RAAS prescription within 6 months before the index HK event.[1] RAAS included ACEi, ARB, ARNI, and MRA.[1,3] Subgroups of patients with CKD (n=11,873) identified using diagnosis codes or eGFR) and patients with HF (n=9395; identified using diagnosis codes) were also evaluated after index HK event.[1,2]
Initiation of hemodialysis or a diagnosis of ESKD or CKD Stage 5 in any position recorded in hospital, emergency, or outpatient setting.[1] †p<0.05 for each comparison and adjusted for age, sex, history of hyperkalemia, diabetes, HF, CKD including stage, and baseline use of ACEi, ARB, ARNI, and MRA.[1,2] Hospitalizations with HF or emergency visits for HF.[2,3]
1. Rastogi A et al. Poster presented at: ASN Kidney Week; November 1-5, 2023; Philadelphia, PA. Poster TH-PO1028; 2. In House Data, AstraZeneca. DoF 198652; 3. Kanda E et al. *BMC Nephrol*. 2022;24(1):18.
Abbreviations are provided in slide notes.

Các khuyến cáo nhấn mạnh cần tối ưu mức liều RAASi/MRA trên Bệnh thận mạn và Suy tim

KDIGO ESC

Bệnh nhân Bệnh thận mạn[1-3]	Bệnh nhân Suy tim PSTM giảm[4]
RAASi	**MRA và RAASi**
Được khuyến cáo điều trị nhằm giảm nguy cơ tiến triển của bệnh thận mạn, suy giảm chức năng thận	**Được khuyến cáo nhằm giảm nguy cơ nhập viện và tử vong tim mạch[b]**
❑ ACEi và ARB nên được **điều trị với liều tối ưu dung nạp được** [2,a]	• ACEi nên được **điều trị đến liều tối ưu mà bệnh nhân có thể dung nạp được.**[4]

Khuyến cáo **nên định kỳ đánh giá nồng độ kali máu 2-4 lần/ năm (CKD/HF)** và **định kỳ trên bệnh nhân có tăng kali máu tái phát tùy theo mức kali máu** khi điều trị với RAASi/MRAs[1-5]

*Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB.
†Caution should be exercised when MRAs are used in patients with impaired renal function or serum K+>5.0 mmol/L.[2]
1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl*. 2024;104(5):S117-S314. 2. KDIGO Diabetes Work Group. *Kidney Int Suppl*. 2022;102(Suppl 5S):S1-S127. 3. KDIGO Blood Pressure Work Group. *Kidney Int*. 2021;99(3S):S1-S87. 4. McDonagh TA, et al. *Eur Heart J*. 2021;42(36):3599-3726. 5. Epstein M, et al. *Am J Manag Care*. 2015;21(11 suppl):S212-S220.
5. Renal Association Clinical Practice Guidelines – Treatment of Acute Hyperkalaemia in Adults – July 2020

Hyperkalemia-Related Discontinuation of RAAS Inhibitors and Clinical Outcomes in CKD

HK-related RAAS inhibitor discontinuation is associated with higher mortality and CV events compared with continuation in patients with CKD

HR of Study Outcomes Related to RAAS Inhibitor Discontinuation Using an ITT Approach

	Manitoba Cohort (n = 7200)				Ontario Cohort (n = 71,290)			
Study Outcomes	No. of events	Person-Years at Risk	Rates*	HR† (95% CI)	No. of Events	Person-Years at Risk	Rates*	HR† (95% CI)
All-cause mortality	3228	21,858	14.77	1.32 (1.22, 1.41)	34,087	279,655	12.19	1.47 (1.41, 1.52)
CV Mortality	1156	21,858	5.29	1.32 (1.13, 1.44)	11,049	279,655	3.95	1.32 (1.25, 1.39)
Fatal and non-fatal CV events	2960	17,333	17.08	1.32 (1.11, 1.24)	31,220	226,111	13.81	1.18 (1.15, 1.22)
Dialysis initiation	917	19,310	4.75	1.65 (1.41, 1.85)	22,876	247,965	9.23	1.11 (1.08, 1.16)

*Rate per 100 person-years; †Adjusted for demographics (age and sex), baseline comorbidities (diabetes mellitus, hypertension, heart failure, atrial fibrillation/flutter, stroke/transient ischemic attack, angina), baseline eGFR, serum K+, medication use at baseline (spironolactone, antifungal azoles, cyclosporine, digoxin, beta-blockers, NSAIDs, heparin, K+ supplements, tacrolimus, and trimethoprim).

CKD, chronic kidney disease; ITT, intention-to-treat.

Leon SF, et al. Am J Kidney Dis. 2022. doi: 10.1053/j.ajkd.2022.01.002 (Epub ahead of print).

- Patients were on RAAS inhibitors and had CKD
- At 90 days from initial HK episode, comparisons were made between those with continued and discontinued RAAS inhibitors
- RAAS inhibitor-related HK was defined as $K^+ > 5.5$ mmol/L

Discontinuation of RAAS inhibitor treatment:

- 30% higher risk of death and CV death
- 20% higher risk of fatal and nonfatal CV events
- 10% to 50% higher risk of dialysis

Management of Hyperkalemia

Treatment	Mechanism	Comments
Calcium (chloride or gluconate)*	Membrane potential stabilization	Does not affect K^+ level
Hypertonic saline*	Membrane potential stabilization	Acute hyponatremia
Sodium bicarbonate	Redistribution	Data unclear for acute treatment of dialysis patients
Insulin*	Redistribution	
β_2-receptor agonists*	Redistribution	Effect independent of insulin and aldosterone Caution in patients with CAD
Kaliuretic diuretics (40 mg furosemide or equivalent) Higher doses for advanced CKD	Excretion	Reduces blood pressure and enhances renal excretion of potassium
Fludrocortisone acetate	Excretion	Aldosterone deficiency Sodium retention, edema, and hypertension may occur
Cation exchange resins	Excretion	SPS, patiromer, SZC
Dialysis	Removal	Can affect sodium, bicarbonate, calcium, and magnesium levels

*Treatment for acute hyperkalemia only.
Kovesdy CP, et al. *Nat Rev Nephrol*. 2014;10:653-662.

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Hyperkalemic Emergency

Serum K^+
- Greater than 6.5 mEq/L or approaching 7 mEq/L

Symptoms
- Muscle weakness, paralysis, asymptomatic

ECG findings
- Cardiac conduction abnormalities
- Arrhythmias

Caused by
- Rapidly rising K^+ with tissue breakdown (rhabdomyolysis or tumor lysis syndrome)
- Worsening renal impairment (AKI, acute or chronic kidney disorder)
- Redistribution of potassium (DKA or HHS)

Can be worsened by medications
- ACE inhibitors
- ARBs
- Potassium-sparing diuretics
- Tacrolimus

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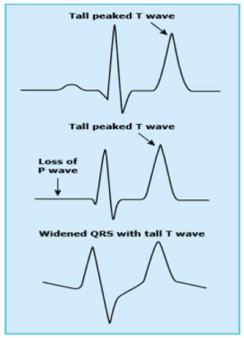
12 Lead - ECG
Typical Features of Hyperkalemia



Serum Potassium (mEq/L)	Major Change
5.5 to 6.5	Tall peaked T waves
6.5 to 7.5	Loss of P waves
7.0 to 8.0	Widening of QRS
8.0 to 10.0	Sine wave, ventricular arrhythmia, asystole

Adapted from Mattu A, et al. *Am J Emerg Med*. 2000;18:721-729.

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Treatment of Hyperkalemic Emergency

Membrane Stabilizer
- Calcium

Potassium Shifters
- Insulin + dextrose
- B2 agonist (albuterol)
- Sodium bicarbonate

Potassium Removers
- Diuretics
- Potassium binders
- HD

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Treatment of Hyperkalemic Emergency

	Agent	Typical Dose	Mechanism of Action	Considerations
Membrane stabilizer	Calcium	Calcium gluconate 1000 mg IV over 2 min (peripheral line ok) Calcium chloride 1000 mg IV over 2 min (central or deep vein)	Raises cardiac threshold potential Stabilizes membrane	Quick onset (1 min) Duration: 30 min Can repeat Does not lower potassium Not used as monotherapy
Potassium shifter	Insulin + glucose	10 U IV push + 25 g dextrose IV over 1 h	Stimulates intracellular K^+ uptake	Only administer glucose or dextrose if glucose < 250mg/dL
	B2-agonist (albuterol)	10 to 20 mg nebulizer over 10 min	Stimulates intracellular K^+ uptake	4 times the dose of bronchodilation May lead to tachycardia May not be effective in patients on β-blockers
	Sodium bicarbonate	50 to 100 mEq IV over 2 min	Raises serum pH allows H^+ exchange for K^+ shift	Considered in metabolic acidosis Limited efficacy

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Treatment of Hyperkalemic Emergency (cont)

Potassium Removers	Agent	Typical Dose	Mechanism of Action	Considerations
Diuretics	Furosemide (Lasix)	20 to 40 mg IV x 1	Loop diuretic increases urinary potassium excretion	Onset: 15 min Duration: 4 to 6 h Should not be used as monotherapy in severe hyperkalemia
Potassium binders	SPS	Not established	Resin exchanges Na+ for K^+	NOT established or approved for severe hyperkalemia (yet)
	Patiromer	Not established	Resin exchanges Ca^{++} for K^+	
	SZC	Not established	Captures K^+ in exchange for H^+ and Na^+	

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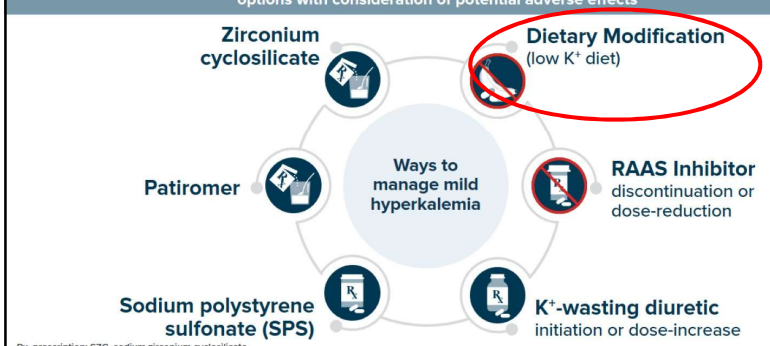
Pharmacologic Treatments for Non-Emergency RAAS inhibitor-Related Hyperkalemia

Management of mild hyperkalemia in the ambulatory setting involves several treatment options with consideration of potential adverse effects



Rx, prescription; SZC, sodium zirconium cyclosilicate.

Hundemer GL, et al. Clin J Am Soc Nephrol. 2021;16:365-373; Weinstein J, et al. CMAJ. 2021;193:E1836-E1841.

Low K+ Diet Is Often the First Step in Chronic Hyperkalemia Management

Foods That Are High in K+ (> 200 mg per portion)

Fruits	Vegetables	Other Foods
▪ Apricot, raw (2 medium) dried (5 halves) ▪ Avocado (¼ whole) ▪ Banana (½ whole) ▪ Cantaloupe ▪ Dates (5 whole) ▪ Dried fruits ▪ Figs, dried ▪ Grapefruit Juice ▪ Honeydew ▪ Kiwi (1 medium) ▪ Mango (1 medium) ▪ Nectarine (1 medium) ▪ Orange (1 medium) ▪ Orange Juice	▪ Acorn Squash ▪ Artichoke ▪ Bamboo Shoots ▪ Baked Beans ▪ Butternut Squash ▪ Refried Beans ▪ Beets, fresh then boiled ▪ Black Beans ▪ Broccoli, cooked ▪ Brussels Sprouts ▪ Chinese Cabbage ▪ Carrots, raw ▪ Dried Beans and Peas ▪ Greens, except Kale	▪ Bran/Bran products ▪ Chocolate (1.5-2 ounces) ▪ Granola ▪ Milk, all types (1 cup) ▪ Molasses (1 Tablespoon) ▪ Nutritional Supplements ▪ Nuts and Seeds (1 ounce) ▪ Peanut Butter (2 tbs) ▪ Salt Substitutes/Lite Salt ▪ Salt-Free Broth ▪ Yogurt

National Kidney Foundation. Potassium and your CKD Diet.

Drug-Induced Hyperkalemia

Medications Associated with Hyperkalemia

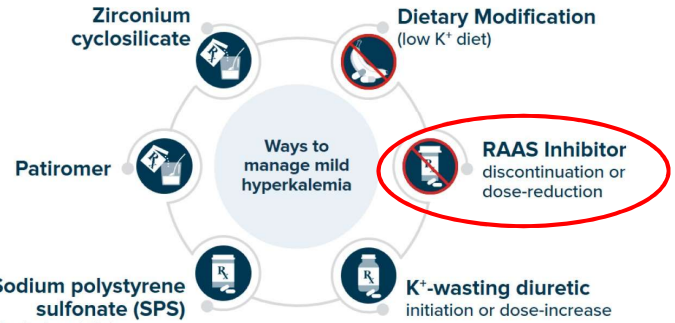
- ACEi and ARB
- K+ sparing diuretics, spironolactone
- Sulfamethoxazole and trimethoprim, trimethoprim, pentamidine
- NSAIDs
- Beta blocker (both non-selective and B_2 selective)
- Heparin
- Digoxin (supratherapeutic levels)
- Succinylcholine (intubation in ICU, Surgery)*
- Calcineurin inhibitors (cyclosporine, tacrolimus [FK506])

*High risk patients include patients with neuromuscular disorders, myopathies, prolonged use of muscle relaxants, muscle trauma or inflammation, thermal trauma, disease atrophy, and severe infection;
ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blocker; NSAID = non-steroidal anti-inflammatory drugs; ICU = intensive care unit

Palmer BF. N Engl J Med. 2004;351(6):585-592.

Pharmacologic Treatments for Non-Emergency RAAS inhibitor-Related Hyperkalemia

Management of mild hyperkalemia in the ambulatory setting involves several treatment options with consideration of potential adverse effects

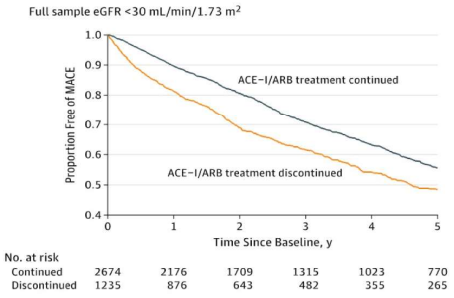


Rx, prescription; SZC, sodium zirconium cyclosilicate.

Hundemer GL, et al. Clin J Am Soc Nephrol. 2021;16:365-373; Weinstein J, et al. CMAJ. 2021;193:E1836-E1841.

Association Between RAAS Inhibitor Discontinuation and All-Cause Mortality in Patients With Low eGFR

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



*Discontinuation of ACE-I or ARB therapy within 6 months after eGFR decreased to < 30 mL/min/1.73m².

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MACE, major adverse cardiovascular event; y, years.

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

Study Specifics:

- N = 3909; initially on ACE-I or ARB therapy
- Patients enrolled had eGFR < 30 mL/min/1.73m²
- RAAS inhibitor discontinuation was associated with increased all-cause mortality
- RAAS inhibitor discontinuation was also associated with increased incidence of end-stage kidney disease within 5 years*

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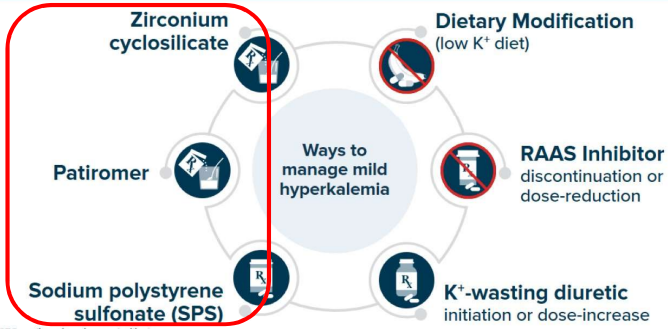

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K^+ Binders for Treatment of Hyperkalemia

	SPS[a]	SZC[b]	Patiromer[c]
Mechanism of action	Nonspecific cation binding in exchange for Na^+	Selective K^+ binding in exchange for Na^+ and H^+	Nonspecific cation binding in exchange for Ca^{2+}
Time to normokalemia	Unconfirmed efficacy	Normokalemia can be achieved typically within 24 to 48 hours of treatment at dosage of 10 g TID	Achieves normokalemia as early as 1 week*
Onset of effect	Unknown (generally hours to days)	1 hour after first dose	K^+ levels reduced significantly 7 hours after first dose
Drug-drug interactions	Interactions with antacids, laxatives, digitalis, sorbitol, lithium, and thyroxine	Oral medications that exibit pH-dependent bioavailability should be administered at least 2 hours before or 2 hours after SZC.	Must be taken 3 hours before or after other oral drugs
Location of K^+ binding	Colon	Likely to be upper and lower GI tract	Distal colon predominantly
Safety/tolerability	Poor tolerability/adherence, associated with colonic necrosis, hypokalemia, electrolyte disturbances, and GI AEs	Well tolerated but may cause edema and mild-to-moderate GI AEs	Well tolerated but may cause hypomagnesemia and GI AEs, such as mild to moderate constipation

There [illegible]

*Depending on severity of HK.

AE, adverse event; FDA, US Food and Drug Administration; SPS, sodium polystyrene sulfonate; SZC, zirconium cyclosilicate.

a. KAYEXALATE [product monograph]. Sanofi Canada Inc. 2018; available online: https://www.astrazeneca.ca/en; b. LOKELMA [product monograph]. AstraZeneca Canada Inc. 2022; available online: https://www.astrazeneca.ca/en; c. VELTASSA [product monograph]. Otsuka Canada Pharmaceutical Inc. 2020; available online: https://otsukacanada.com/.

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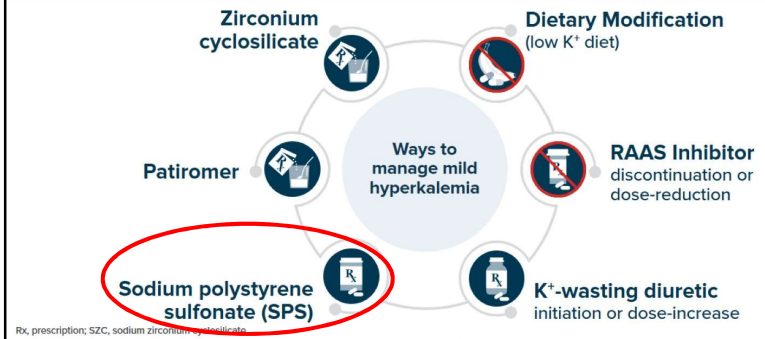

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Sodium Polystyrene Sulfonate

1958

FDA Approval; 1961 in Canada

Four years before requirement to prove safety and effectiveness (Kefauver Harris Drug Amendments)[a,b]

2009

FDA Warning[c]

Cases of colonic necrosis and other serious gastrointestinal AEs...

... concomitant administration of sorbitol is not recommended

2010

Additional Study Findings

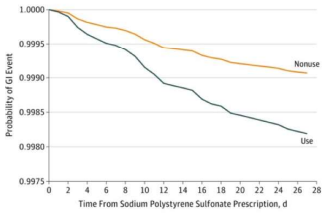
- No convincing evidence that SPS increases fecal K^+ loss in experimental animals or humans[a]
- "Growing concern that suspensions of SPS in sorbitol can be harmful"[a]

a. Sterns Rh, et al. N Engl J Med. 2010;21;733-735; b. Sodium polystyrene sulfonate [PI]. Approved 1958. Revised July 2017; c. FDA warning with kayexalate. Accessed March 24, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/011287s022lbl.pdf.

Risk of Hospitalization for Serious Adverse GI Events Associated With SPS Use in Patients of Advanced Age

Sodium polystyrene sulfonate use was associated with a 1.9-fold higher risk of hospitalization within 30 days of initial prescription for adverse gastrointestinal events compared with nonuse

30-Day Probability of GI Injury Requiring Hospitalization or ER Visit Associated With SPS Use Compared With Nonuse*



Variable	No. of Events (% Total)	Time to Event, Median (IQR), Days	Incidence Rate (95% CI) per 1000 Person-Years	HR (95% CI)
Matched cohort (20,020 with use and 20,020 with nonuse*)				
Use	37 (0.2)	12 (8.2)	22.97 (15.57, 30.37)	1.94 (1.10-3.41)
Nonuse	18 (0.1)	14 (3.2)	11.01 (5.92, 16.09)	

*Matched analysis adjusted for age, sex, diabetes, congestive heart, failure, prior acute kidney injury, chronic dialysis, history of HK, previous nephrologist visit, medication use (β-blocker or renin-angiotensin-aldosterone system blockade), and index date (within 1 year).

d, days; GI, gastrointestinal; IQR, interquartile range.

Noel JA, et al. JAMA Intern Med. 2019;179:1025-1033.

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Patiromer
Clinical Trials

Study Name; Design (Duration)	Patient Population	Study treatment	Primary Efficacy Outcomes
PEARL-HF Phase 2, randomized, double-blind, placebo-controlled (28 days)	Patients with chronic HF (N = 105) with: 1.) History of HK leading to RAAS inhibitor and/or β-blocker withdrawal or 2.) CKD	Patiromer 15 g or placebo twice daily (plus spironolactone 25 mg/day)	**LS mean change in serum K+:** −0.22 mmol/L with patiromer +0.23 mmol/L with placebo **LS mean difference vs placebo:** −0.45 mmol/L; *P* < .001
AMETHYST-DN: Phase 2, randomized, open-label (28 day)	Outpatients with DKD and mild (K+ 5.0 to 5.5 mmol/L) or moderate (K+ 5.5 to 6.0 mmol/L) HK; N = 306	**Mild HK:** Patiromer 4.2, 8.4, or 12.6 g twice daily **Moderate HK:** Patiromer 8.4, 12.6, or 16.8 g twice daily	**Mild HK:** **LS mean change in serum K+:** −0.35 mmol/L with patiromer 4.2 g −0.51 mmol/L with patiromer 8.4 g −0.55 mmol/L with patiromer 12.6 g **Moderate HK:** **LS mean change in serum K+:** −0.87 mmol/L with patiromer 8.4 g −0.97 mmol/L with patiromer 12.6 g −0.92 mmol/L with patiromer 16.8 g
OPAL-HK **Phase 3; 2 stages:** 1.) Treatment, single-group, single-blind (4 weeks) and 2.) Withdrawal, randomized, single-blind, placebo-controlled (8 weeks)	Patients with CKD on RAAS inhibitor therapy with mild (K+ 5.1 to 5.5 mmol/L) or moderate-to-severe (K+ 5.5 to 6.5 mmol/L) HK; N = 237	**Treatment stage:** Patiromer 4.2 g (mild HK) or 8.4 g (moderate-to-severe HK) twice daily **Withdrawal stage:** Patiromer (at same dosage) or placebo (K+ 3.8 to 5.1 mmol/L)	**Treatment stage:** **Mean change in serum K+ at week 4:** Overall: −1.01 mmol/L (*P* < .001 vs baseline) Mild HK: −0.65 mmol/L Moderate-to-severe HK: −1.23 mmol/L **Withdrawal stage:** **Median change in K+ to week 4:** 0 mmol/L with patiromer +0.72 mmol/L with placebo *P* < .001 vs placebo

Patiromer:

- First "newer" K+ binder approved (2015)
- Calcium-binding resonant; working in the distal colon
- AMETHYST-DN : Largest, longest-term study with daily use

Palmer BF, et al. Mayo Clin Proc. 2021;96:744-762; Patiromer [PI]. Approved 2015. Revised October 2015.

Patiromer
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DKD, diabetic kidney disease; HF, heart failure. Palmer BF, et al. Mayo Clin Proc. 2021;96:744-762.

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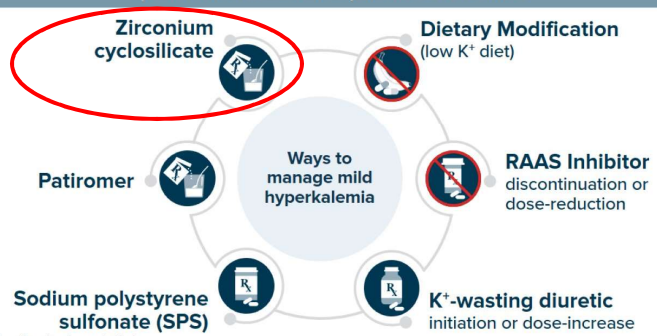

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Hundemer GL, et al. Clin J Am Soc Nephrol. 2021;16:365-373; Weinstein J, et al. CMAJ. 2021;193:E1836-E1841.

Cơ chế tác dụng (MoA)

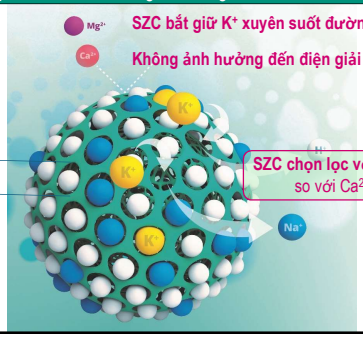
Sodium Zirconium Cyclosilicate

Tinh thể vô cơ, không hấp thu vào máu, không tan, bắt giữ K^+ chọn lọc

Chọn lọc với K^+ >125x so với SPS (thuốc gắn kết kali truyền thống)

Đường kính lỗ trao đổi ion SZC là **3 Å**

Đường kính K^+ ~3 Å, **"Vừa khít"** với các lỗ trên bề mặt của SZC



SZC bắt giữ K^+ xuyên suốt đường tiêu hóa

Không ảnh hưởng đến điện giải Ca^{2+} and Mg^{2+}

SZC chọn lọc với K^+ gấp >25 lần so với Ca^{2+} hoặc Mg^{2+}

GI = gastrointestinal; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate.
Stavros F et al. *PLoS One*. 2014;9(12):e114686

Các thuốc gắn kali mới với một số nghiên cứu trên bệnh nhân lọc máu

Table 3. Summary of studies investigating patiromer and SZC in patients on hemodialysis

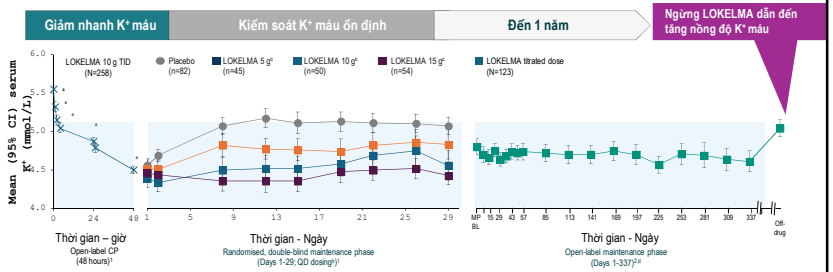
Study, yr (*n*)	Study design	Treatment	Key outcomes
Bushinsky *et al.*, 2016 (6)[89]	Non-R	Patiromer 4.2 g TID for 1 wk vs. 1 wk pretreatment	Mean ± SE serum K^+ difference on patiromer day 7 vs. corresponding pretreatment day: −0.6 ± 0.2 mmol/l ($P = 0.009$) Percent of daily serum K^+ values ≥5.5 mmol/l: 38% on patiromer vs. 69% pretreatment ($P = 0.008$) Fecal K^+ excretion increased by 58% on patiromer vs. pretreatment ($P = 0.02$)
Kovesdy *et al.*, 2019 (10,126)[2]	RW	Patiromer OD ($n = 527$) SPS ($n = 852$) No K^+-binder ($n = 8747$); median follow-up 141 d	Mean change in serum K^+ before vs. after patiromer initiation: 30 d: −0.47 mmol/l ($P < 0.001$) 60 d: −0.49 mmol/l ($P < 0.001$) 90 d: −0.50 mmol/l ($P < 0.001$) Percent of patients with serum K^+ ≥6.0 mmol/l before vs. after patiromer: 30 d: 49% vs. 24% ($P < 0.001$) 60 d: 48% vs. 20% ($P < 0.001$) 90 d: 48% vs. 22% ($P < 0.001$)
DIALIZE, 2019 (196)[90]	R, DB, PC	SZC 5–15 g ($n = 97$) vs. PBO ($n = 99$) OD on nondialysis days for 4 wk	Patients maintaining predialysis serum K^+ 4.0–5.0 mmol/l after long IDI during ≥3 of 4 HD sessions[a] on SZC vs. PBO: 41% vs 1% ($P < 0.001$) Intradialytic K^+ shifts[b] on SZC vs. PBO: At randomization: 2.0 vs. 2.1 mmol/l Wk 3–9: 1.4–1.5 mmol/l vs. 1.9–2.0 mmol/l

DB, double-blind; IDI, interdialytic interval; K^+, potassium; OD, once daily; PBO, placebo; PC, placebo-controlled; R, randomized; RW, real-world; SPS, sodium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate; TID, 3 times daily.
[a]Without the need for rescue therapy.
[b]Difference between pre- and postdialysis serum K^+.

Kidney International Reports (2020) 5, 779–789

Hiện tại, một số thuốc gắn kali đã loại bỏ khỏi cơ thể có thể không có trên thị trường Việt Nam Vui lòng tham khảo thông tin kê toa các thuốc tại Việt Nam trước khi sử dụng.

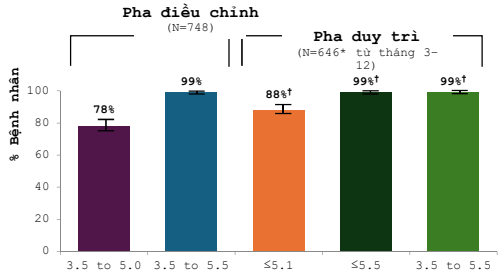
HARMONIZE – SZC **khởi phát tác dụng trong 1 giờ**, đưa **kali máu về mức bình thường trong vòng 4-7 giờ**, kiểm soát **kali máu ổn định đến 1 năm điều trị**



- Nghiên cứu pha III, đa trung tâm, thực hiện trên 258 bệnh nhân bệnh thận mạn, bệnh tim mạch, từ 44 trung tâm ở US, Nam Phi, Úc bị tăng kali máu ≥5,1 mmol/L.
- Mục tiêu đánh giá kali máu khi dùng Lokelma vs placebo tại ngày thứ 8-29 và tỷ lệ bệnh nhân đạt kali máu ≤5,1 mmol/L trong 11 tháng sau đó

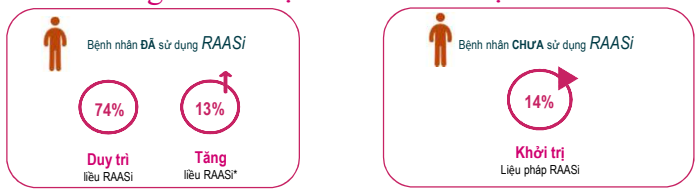
Note: Normokalaemia defined as serum K^+ 3.5-5.0 mmol/L and patients on dialysis were excluded from these studies.[1,2] Error bars indicate 95% CI.
*P<0.001 vs. baseline; [1] #If a patient's K^+ value was between 3.0-3.4 mmol/L at any time during the randomised phase, the dose was reduced from QD to QOD for the remainder of the study; [1] ^P<0.001 vs. placebo during days 8-29; [1] ¶Maintenance LOKELMA dosing was initiated at 10 g QD and titrated in 5 g increments or decrements to maintain i-STAT K^+ 3.5-5.0 mmol/L (minimum 5 g QD); maximum 15 g QD. Off-drug values were recorded at 7±1 days following the last dose of LOKELMA.[1]
1. Kosiborod M, et al. *JAMA*. 2014;312(21):2223-2233. 2. Roger SD, et al. Article and supplementary material. *Am J Nephrol*. 2015;50(6):473-480.

ZS-005 – SZC giúp 88% bệnh nhân duy trì nồng độ kali máu bình thường xuyên suốt 1 năm

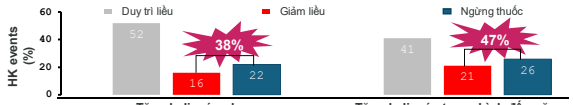


- Nghiên cứu pha III, tiền cứu, đa trung tâm nhãn mở, thực hiện trên 751 bệnh nhân thực hiện trên 56 trung tâm (US, Australia, Europe, South Africa) được xác nhận là tăng kali máu ≥5,1 mmol/L, không thực hiện các liệu pháp ăn kiêng (CKD: 65%, HF: 11%, T2D: 64%, HTN: 83%).
- Tiêu chí chính: % Bệnh nhân đạt được nồng độ kali máu bình thường trong pha điều chỉnh và pha duy trì (Tháng 3-12)

ZS-005 – SZC giúp duy trì RAASi lên đến 74% và tăng ~ 14% bệnh nhân khởi trị RAASi



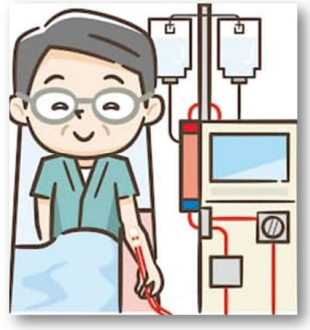
Xóa đi nỗi lo giảm liều/ dừng thuốc RAASi do tăng kali máu gây ra



*Multiple dose increases and decreases.
RAASi = renin-angiotensin-aldosterone system inhibitor.
Roger SD et al. *Am J Nephrol*. 2019;50:473-480.

- HK, hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor
- Epstein M, et al. *Am J Manag Care* 2015;21(Suppl 11):S212–S220

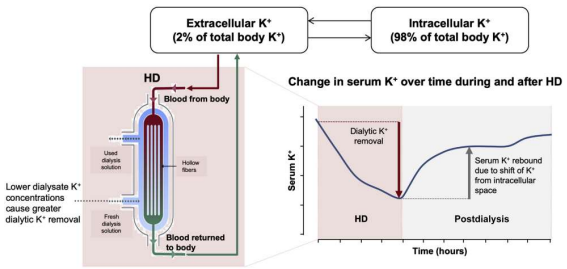
Can potassium binders be used in hemodialysis?



97

Sự dao động của nồng độ kali huyết sau lọc máu có nguy cơ gây tăng rối loạn nhịp tim

Mặc dù trong một buổi lọc máu thông thường kéo dài 3–4 giờ có từ 80–100 mEq kali được loại bỏ, nhưng hiệu quả bị giới hạn do lượng kali từ nội bào nhanh chóng được bù lại sau khi lọc máu



Sự dao động của nồng độ kali huyết thanh liên quan đến chạy thận nhân tạo làm tăng phân cực màng tế bào từ đó dẫn đến nguy cơ tăng rối loạn nhịp tim

Để đo nồng độ kali huyết thanh ở bệnh nhân đang chạy thận nhân tạo, cần phải chờ 3–4 giờ sau khi lọc máu để quan sát giá trị ổn định

1. Sterns R, et al. Kidney Int 2016;89:546-554; 2. Koveady C. Nat Rev Nephrol 2014;10:653-662

Nghiên cứu DIALIZE: SZC giúp kiểm soát ổn định nồng độ kali máu trước lọc trên bệnh nhân chạy thận nhân tạo

Thử nghiệm giai đoạn IIIb có **đối chứng giả dược** để đánh giá hiệu quả và an toàn của SZC trong điều trị tăng kali máu trước lọc máu[a] trên bệnh nhân bệnh thận giai đoạn cuối đang lọc máu ổn định[1]

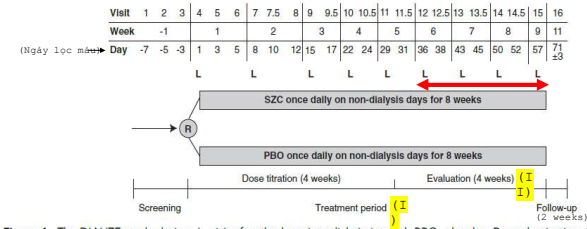


Figure 1. The DIALIZE study design. L, visit after the long interdialytic interval; PBO, placebo; R, randomization; SZC, sodium zirconium cyclosilicate.

Trong giai đoạn điều trị (I), các bệnh nhân được phân ngẫu nhiên 1:1 để uống liều khởi đầu SZC 5 g hoặc giả dược mỗi ngày một lần tại các ngày không lọc máu (n=196)

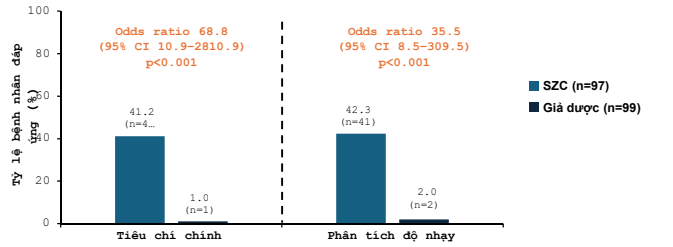
Tiêu chí chính là tỷ lệ bệnh nhân được ghi nhận là "**đáp ứng**", được định nghĩa là những bệnh nhân duy trì được kali máu *4.0-5.0 mmol/L*, tại tối thiểu 3/4 lần đánh giá suốt 4 tuần (II) sau khoảng thời gian giữa các lần lọc máu dài (khoảng cách > 1 ngày) và không cần các liệu pháp cấp cứu

1. Fishbane S et al. Article and supplemental data. J Am Soc Nephrol. 2019;30(9):1723-1733

Hiện tại, một số thuốc gắn kali để loại bỏ kháo cơ thể có thể không có trên thị trường Việt Nam Vui lòng tham khảo thông tin kê toa các thuốc tại Việt Nam trước khi sử dụng.

DIALIZE: SZC cho thấy tỷ lệ bệnh nhân kiểm soát kali máu ổn định 4.0-5.0 mmol/L trước lọc cao hơn nhiều lần giả dược

Tỷ lệ bệnh nhân đáp ứng[a] (duy trì nồng độ K^+ huyết thanh trước lọc máu trong khoảng 4,0-5,0 mmol/L) cao hơn đáng kể ở nhóm dùng SZC so với nhóm dùng giả dược. Kết quả phân tích độ nhạy phù hợp với phân tích chính[b]

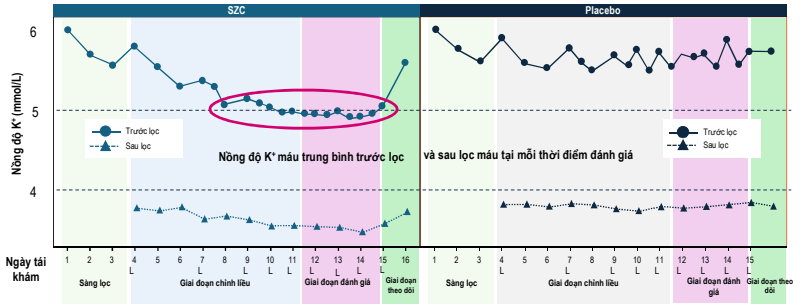


aResponders were defined as patients who, during the evaluation period, maintained a predialysis serum K^+ 4.0–5.0 mmol/L during ≥3 out of 4 HD treatments following the long interdialytic interval and who did not receive rescue therapy; bA sensitivity analysis was conducted to account for nonresponders with missing central laboratory assessment by using adjusted 1-STAT K^+ data.

HD = hemodialysis; SZC = sodium zirconium cyclosilicate.

Fishbane S et al. Article and supplemental data. J Am Soc Nephrol. 2019;30(9):1723-1733.

DIALIZE – Ngày không lọc máu an toàn như ngày được lọc máu

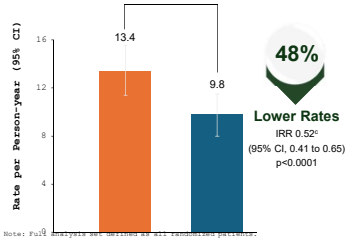


Nghiên cứu pha 3b, ngẫu nhiên, mù đôi, trên 196 bệnh nhân bệnh thận lọc máu 3 lần mỗi tuần, điều trị với SZC 5g 1 lần mỗi ngày vào những ngày không lọc máu hoặc giả dược, sau đó tối ưu liều điều trị từ 5-15g/ ngày

Note: Error bars represent 2 x SE of the mean. Dashed horizontal lines represent the upper and lower limits of normal predialysis serum K^+.
L = visit following the long interdialytic interval; SD = standard deviation; SZC = sodium zirconium cyclosilicate.
Fishbane S et al. J Am Soc Nephrol. 2019;30(9):1723-1733.

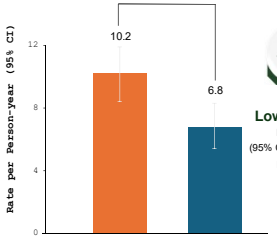
Sử dụng SZC để kiểm soát ổn định nồng độ kali máu trước lọc giúp giảm nguy cơ rung nhĩ và các rối loạn nhịp tim khác

Tỷ lệ rung nhĩ [a] (Tiêu chí chính): Nhịp tim không đều và khoảng R-R không có sóng P xác định trong hơn ≥2 phút



48%
Lower Rates
IRR 0.52[c]
(95% CI, 0.41 to 0.65)
p<0.0001

Tỷ lệ rối loạn nhịp tim có ý nghĩa lâm sàng[b]: Vô tâm thu (Không có dẫn truyền thất ≥3 giây), nhịp tim chậm (≤40 nhịp/phút trong ≥6 giây), nhịp tim nhanh trên thất và nhịp nhanh thất (≥130 nhịp/phút trong ≥30 giây)



53%
Lower Rates
IRR 0.47[c]
(95% CI, 0.38 to 0.58)
p<0.0001

Note: Full analysis set defined as all randomized patients.

aOverall 296 AF episodes (n=9) were recorded, of which, 123 events were in 6 participants on 3.0 mmol/L K^+ dialysate and SZC and 173 events were in 7 participants on 2.0 mmol/L K^+ dialysate; bOverall 217 CSCA events were recorded, of which, 86 events were in 11 participants on 3.0 mmol/L K^+ dialysate and SZC and 131 events in 13 patients on 2.0 mmol/L K^+ dialysate; cModeled rate ratio using Quasi-Poisson model.

AF = atrial fibrillation; BPM = beats per minute; CSCA = clinically significant cardiac arrhythmia; IRR = incidence rate ratio; SZC = sodium zirconium cyclosilicate.

Charytan DM et al. In press, pre-proof. Kidney Int. 2024.

KẾT LUẬN

Các bệnh nhân chạy thận nhân tạo có nguy cơ tăng kali máu cao và dễ tái phát, đặc biệt tại thời điểm trước lọc giữa hai lần lọc máu cách nhau dài ngày, làm tăng nguy cơ tử vong và các biến cố tim mạch

Các liệu pháp xử trí tăng kali máu trên bệnh nhân chạy thận nhân tạo vẫn còn nhiều thách thức:

- Lọc máu vẫn có sự dao động kali máu không ổn định và chệnh lệch kali trước - sau lọc dễ gây rối loạn nhịp tim.
- Chế độ ăn thường khó tuân thủ và có thể trái ngược với chế độ ăn có lợi cho tim mạch
- Giảm liều các thuốc nguy cơ như RASi có thể dẫn đến tăng nguy cơ tim mạch và tử vong

Natri Zirconium Cyclosilicate (SZC) với cấu trúc độc đáo, giúp kiểm soát kali máu nhanh & ổn định. Các bằng chứng cho thấy kiểm soát ổn định kali máu trước lọc trong suốt giai đoạn lọc máu và có thể giảm các biến cố như rung nhĩ và các rối loạn nhịp tim khác

Overview of Novel Potassium Binders

	Patiromer*[a,b]	SZC*[c, d]
Mechanism of action	Nonspecific cation binding in exchange for Ca^{2+}	Selective K+ binding in exchange for Na^+ and H^+
Time to normokalemia†	Achieves normokalemia as early as 1 week, depending on severity of hyperkalemia	84% of patients normokalemic within 24 hours
Onset of effect†	K+ levels reduced significantly 7 hours after first dose	Median time to normalization 2.2 hours
Drug-drug interactions	Other oral drugs administered at least 3 hours before or after patiromer	Other oral drugs administered at least 2 hours before or after SZC
Location of potassium binding	Distal colon predominantly	Likely to be upper and lower GI tract (not proven)
Safety/tolerability	Well tolerated, but may cause hypomagnesemia and GI AEs, such as mild to moderate constipation	Well tolerated, but may cause edema and mild to moderate GI AEs

*There are no head-to-head studies comparing patiromer and SZC; clinical trials were conducted under widely varying conditions.

†These agents should not be used for emergency treatment of life-threatening hyperkalemia because of their delayed onset of action. Patients in the clinical trials were evaluated as outpatients.

a. Veltassa® (patiromer) [PI]. 2021; b. Bakris et al. *JAMA*. 2015;314:151-161; c. Lokelma® (sodium zirconium cyclosilicate) [PI]. 2020; d. Kosiborod M, et al. *JAMA*. 2014;312:2223-2233.