New Potassium Binders in Hyperkalemia

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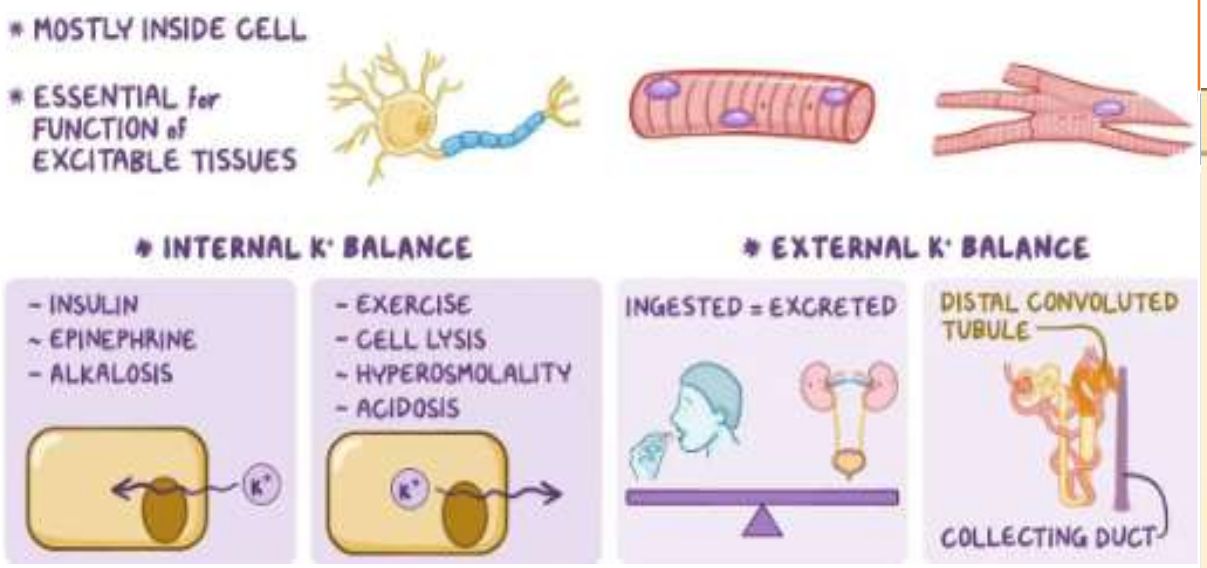
Overview

- Potassium -Major Intracellular Cation
- Hyperkalemia - A potentially life-threatening complication
- Traditional Treatment Strategies
- Evolving strategies
- New K Binding Resins
  - Patiromer
  - ZPCs
  - Combination therapy---Personalised medicine
- Conclusion

-- The Intracellular Cation --



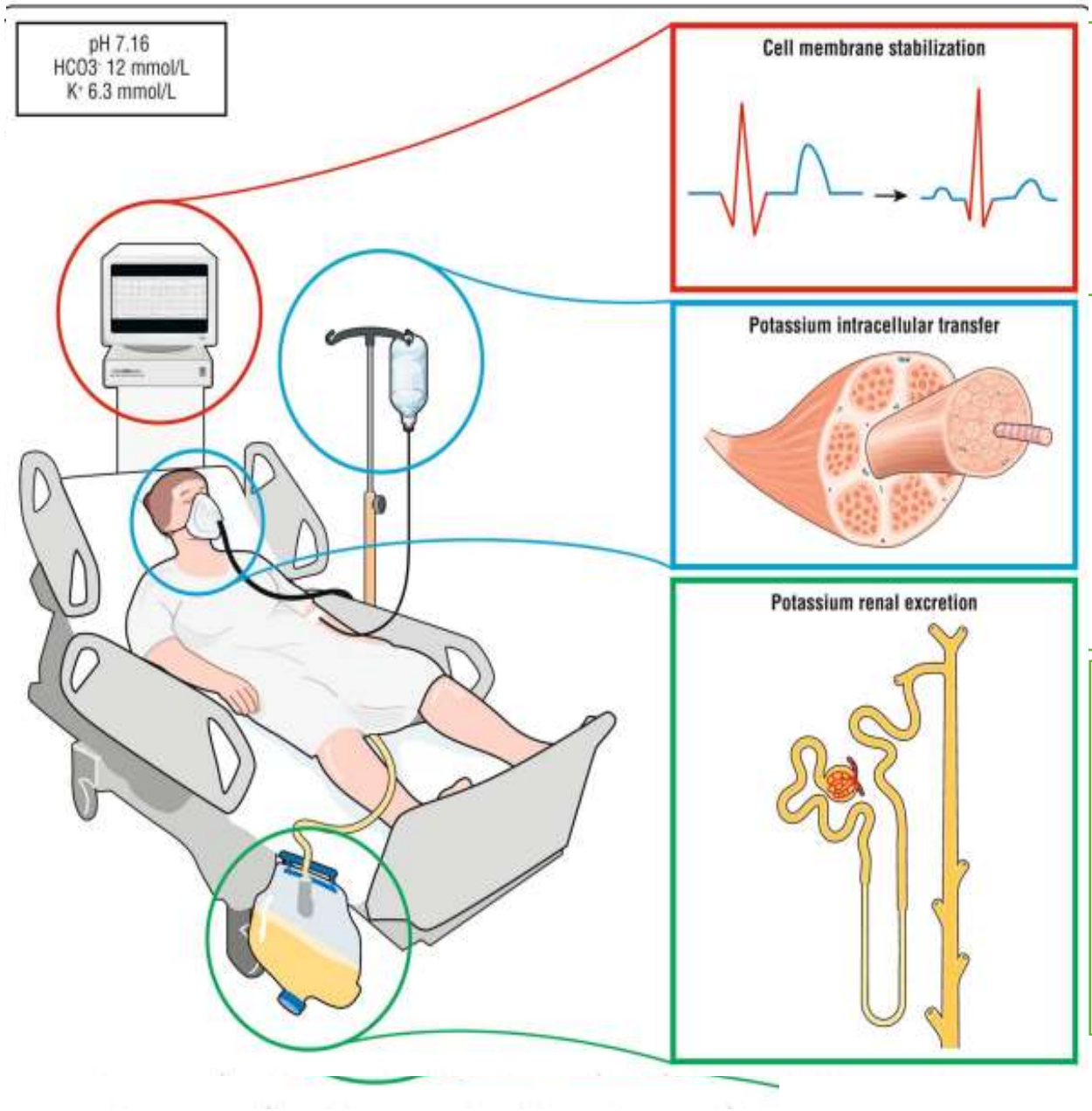
Age	Range (mEq/L or mmol/L)
Premature infant	4 to 6.5
Newborn	3.7 to 5.9
Infant	4.1 to 5.3
Child >1 year old	3.5 to 5

Hyperkalemia: A potentially life-threatening electrolyte abnormality and may cause cardiac electrophysiological disturbances in the acutely ill

Serum potassium	Typical ECG appearance	Possible ECG abnormalities
Mild (5.5–6.5 mEq/L)		Peaked T waves Prolonged PR segment
Moderate (6.5–8.0 mEq/L)		Loss of P wave Prolonged QRS complex ST-segment elevation Ectopic beats and escape rhythms
Severe (>8.0 mEq/L)		Progressive widening of QRS complex Sine wave Ventricular fibrillation Asystole Axis deviations Bundle branch blocks Fascicular blocks

EpoMedicine

Traditional Treatment of Hyperkalemia



PROTECT HEART

Cardiac Myocyte stabilization

Calcium Chloride/Gluconate

Hypertonic saline

REDISTRIBUTE

Fast transfer of K from ECF o ICF

- Insulin Glucose infusion
  Severe hyperkalemia >6.5 mmol/L-1st line Rx
- Aerosolized ß2 agonists
- Sodium bicarbonate(if acidosis)

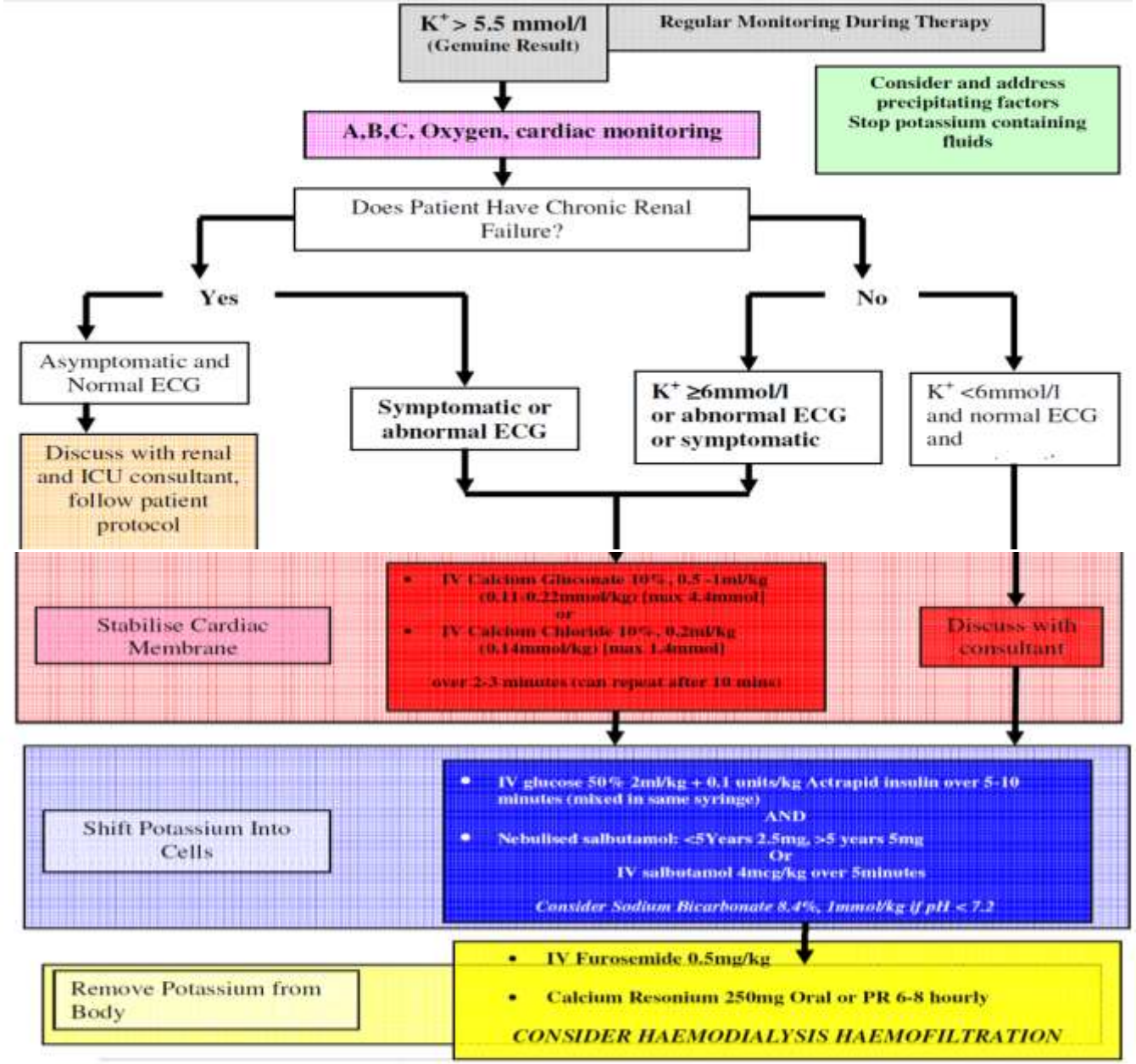
ELIMINATE

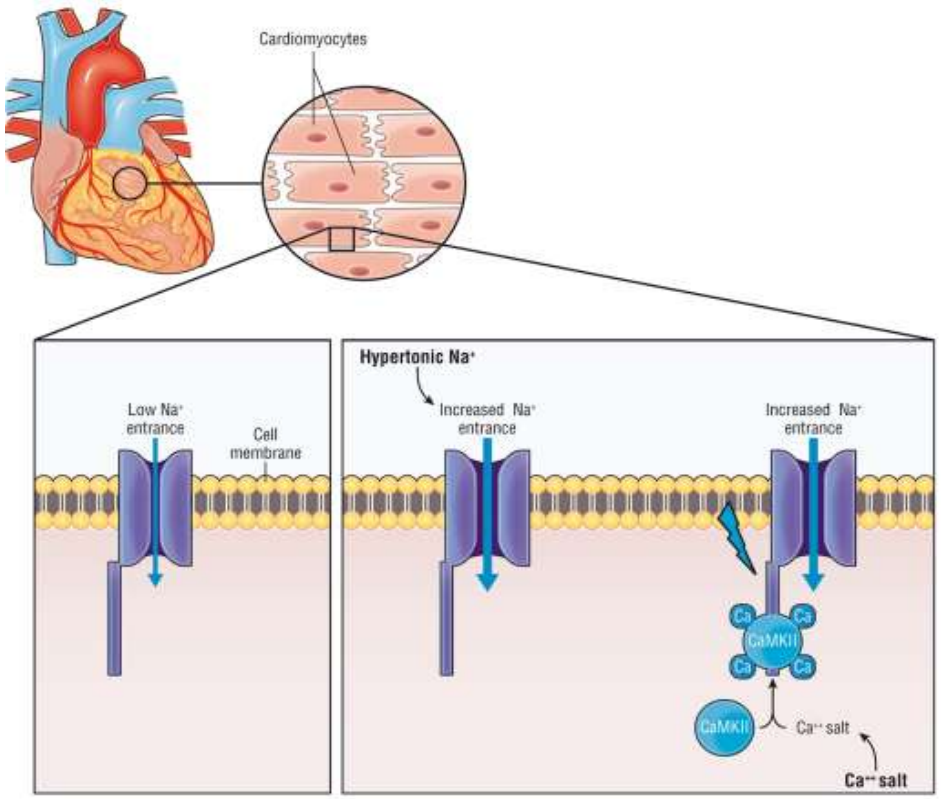
Strategies increasing K excretion

- Renal Excretion
  Loop Diuretics
- GI Excretion
  Exchange Resins
- KRT

Dépret, F., Peacock, W.F., Liu, K.D. et al. Management of hyperkalemia in the acutely ill patient. Ann. Intensive Care 9, 32 (2019). https://doi.org/10.1186/s13613-019-0509-8

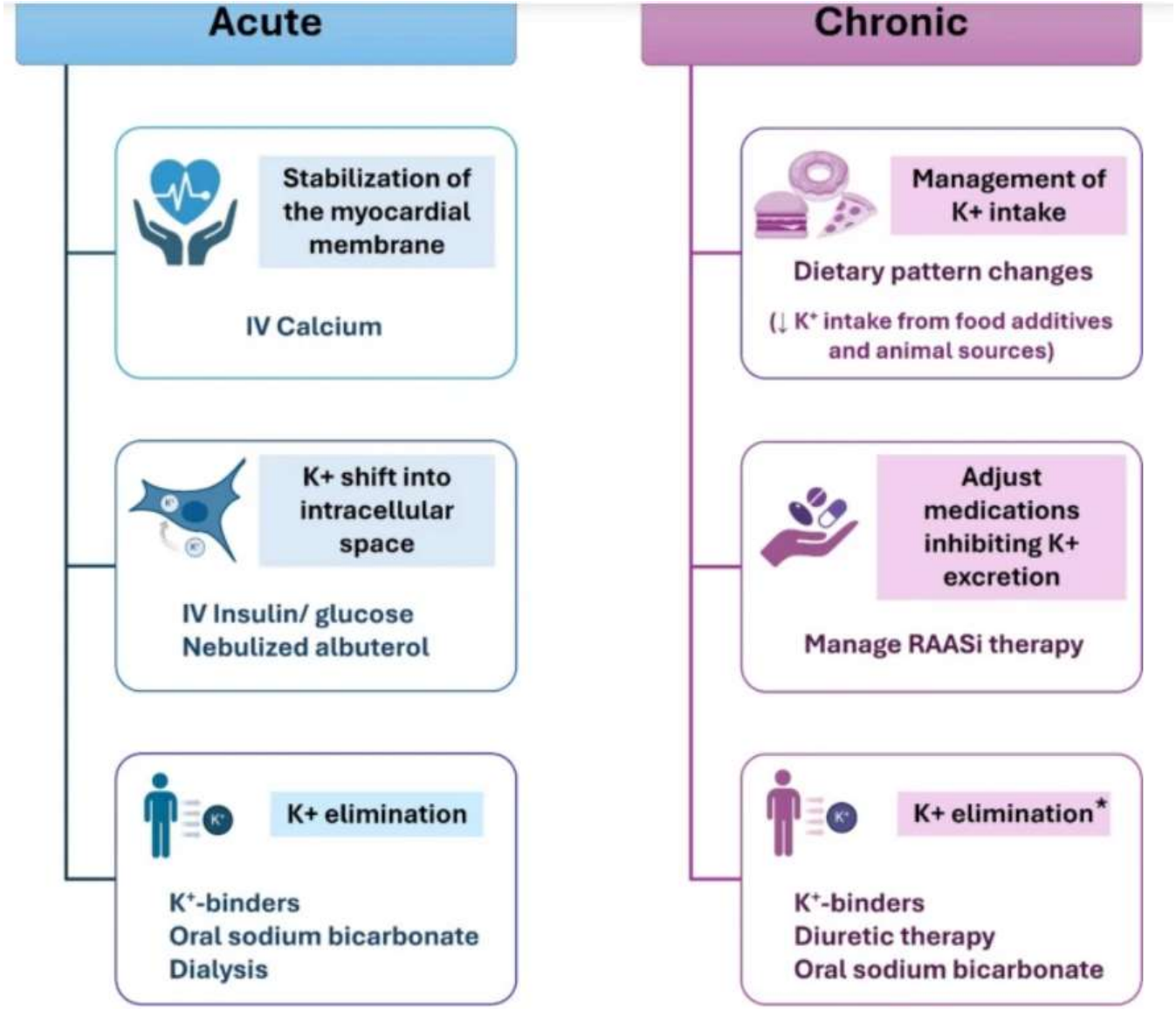
Traditional Approach to Hyperkalemia





Kurzinski KL, Xu Y, Ng DK, Furth SL, Schwartz GJ, Warady BA; CKiD Study Investigators. Hyperkalemia in pediatric chronic kidney disease. Pediatr Nephrol. 2023 Sep;38(9):3083-3090.

Hyperkalemia concerning in acute & Chronic Situations



Traditional Treatment of Hyperkalemia

Limitations & Potential Complications

Modality	Limitations	Complications
Dietary potassium restriction	Adherence difficult	Not sufficient for acute management or in severe cases.
Insulin and glucose infusions	Requires monitoring for hypoglycemia	Hypoglycemia—needs monitoring
Beta-2 agonists	Less effective and reliable than insulin therapy	Tachycardia or exacerbate HF
Renal replacement therapy	Resource intensive, requires vascular access	Hypotension and infections.
Cation-exchange resins Sodium polystyrene sulfonate (SPS) Calcium polystyrene sulfonate (CPS)	GI side-effects-Nausea, vomiting, constipation ,sometimes diarrhea CI: Hypercalcemia, GI Obstruction	Bowel obstruction , Colonic necrosis hypomagnesemia Hypercalcemia

We need a mechanism that maintains serum K in normal range long term and not a temporary amelioration in hyper K ---- especially in CKD & CHF ---ACEI and MRA

Wong SWS, Zhang G, Norman P, Welihinda H, Wijeratne DT.Polysulfonate resins in hyperkalemia: a systematic review. Can J Kidney Health Dis. 2020 Jan 1;7:2054358120965838.

Angela Kimberly Tjahjadi, Henry Sutanto, Artaria Tjempakasari,The role of cation-exchange resins in hyperkalemia management, Medical Journal Armed Forces India, Volume 81, Issue 1,2025,Pages 7-14,ISSN 0377-1237,

Have we got the answer?

Newer **Cation-exchange resins**

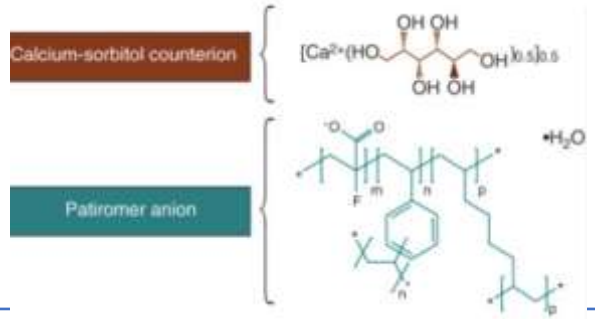
Patiromer & Sodium zirconium cyclosilicate (SZC)

Better safety profile

Fewer gastrointestinal side-effects

Longer Impact

Patiromer Sorbitex Calcium



Patiromer

- Non-absorbed, cation exchange synthetic polymer that contains a calcium-sorbitol counter ion.
- Smooth spherical beads ~100 µm diameter
- Active groups –**Patiromer Sorbitex Calcium** – (Alpha-fluoro carboxylic acids paired with Ca ions rather than Na).
- Increases faecal potassium excretion through binding of K in the colon especially distal colon
  - Onset of action slow, taking ~ 7 hours
  - Decreases serum K by 0.23 mmol/l within 7 hours.
  - Continued effect over long hours– sustained efficacy
- Not used in emergency hyperkalemia treatment.
- Unlike Kayexalate, does not swell when exposed to water
- Does not require a laxative to reach the distal colon.

Only non-sodium containing K exchange resin with no effect on blood pressure or edema.

Favorable side effect profile.
- GI Side effects
- Hypomagnesemia
- Positive calcium balance
- Ectopic calcifications

CKD &CHF

Effectively treats RAAS inhibitor-related hyperkalemia
Well tolerated
But --- concern of drug interactions ? Timing of drugs

Black box warning

2015: Potential drug-drug interactions that could reduce the efficacy of other oral drugs if taken too close to the patiromer dose.
2016: Black box warning removed

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Patiromer Trials

- PEARL-HF trial evaluated the safety and efficacy of patiromer in managing potassium levels in HF patients, revealing its effectiveness in enabling the continued use of vital medications that may increase potassium levels , such as spironolactone.
- AMBER trial highlighted the utility of patiromer in improving treatment outcomes for patients with resistant hypertension. - Patiromer's significant role in enabling these patients to maintain necessary pharmacological treatments without the risk of hyperkalemia.
- AMETHYST-DN randomized clinical trial :Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of patiromer on serum potassium level in patients with hyperkalaemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. JAMA. 2015;314:151.
- DIAMOND trial (Patiromer for the Management of Hyperkalemia in Participants Receiving RAASi Medications for the Treatment of Heart Failure)
- EMERALD Trial -Phase 2, open-label study to assess the pharmacodynamics, safety, and tolerability of patiromer, in children aged 2 to 18 with CKD and hyperkalemia.
- REDUCE study NCT: 02933450:Patiromer for normokalemia in emergency

Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder,in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J. 2011 Apr;32(7):820e828.

Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial.Lancet. 2019 Oct 26;394(10208):1540e1550

Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. JAMA. 2015;314:151.

Can the potassium binder, patiromer powder for oral suspension, be mixed with additional juices, nectars, other liquids, or soft foods for the treatment of hyperkalemia?

Methods

Juice, nectar, other liquid, or soft food

+

Patiromer powder for oral suspension at

- Low ratio ≈ patiromer 8.4 g / 80 mL (1/3 cup)
- High ratio ≈ patiromer 25.2 g / 80 mL (1/3 cup)

Mixed, 45-minute rest period, diluted, and centrifuged → residue and supernatant for testing

Results

- Total potassium-exchange capacity and potassium-binding capacity within the acceptance criterions of 8.4–10.0 mmol/g and 1.7–2.5 mmol/g, respectively
- No adverse impact on appearance
- Released fluoride below the acceptance limit of 135 ppm: no adverse impact on stability

Patiromer powder for oral suspension can be mixed with:

Liquids or juices

✓ Water

✓ Apple or cranberry juice

(demonstrated in previous studies)

Additional juices, nectars, other liquids, or soft foods

✓ Grape, orange, pear, or pineapple juice

✓ Apricot or peach nectar

✓ Milk or thickener

✓ Apple sauce

✓ Chocolate or vanilla pudding

✓ Yoghurt

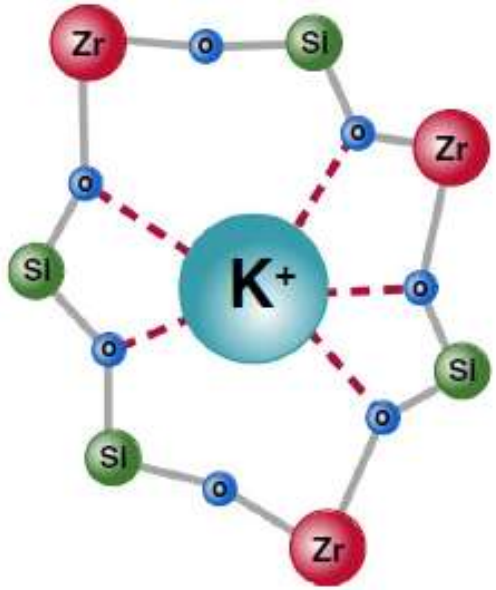
Sodium Zirconium Cyclosilicate in hyperkalemia

Sodium Zirconium Cyclosilicate in hyperkalemia

Insoluble, inorganic, non-polymer zirconium silicate compound comprising units of oxygen-linked zirconium and silicon atoms in the form of a microporous cubic lattice framework

Bonds between the oxygen and zirconium or silicon atoms - covalent, with the octahedral $[ZrO_6]_{-2}$ units conferring the negative charge that enables cation exchange

Pore openings size: ~ 3Å (i.e. approximately the diameter of an unhydrated K ion)



Non-polymer zirconium silicate compound that entraps potassium and ammonium ions and exchanges them for hydrogen and sodium ions in the GIT
Lowers serum potassium levels to within the normal range during the first 48 h of treatment and maintains normokalaemia over the longer term (≤ 12 months)
Effective regardless of chronic kidney disease, diabetes, heart failure and concomitant use of RAAS inhibitors
Low incidence of hypokalemia

Adverse effects:

- Edema-exchange of K for sodium
- Hypokalemia
- Interference with absorption of other oral medications

Rapid Onset of Action (1 hour)

Expensive Drug Interactions

Sodium zirconium cyclosilicate was approved by the FDA in 2018

Angela Kimberly Tjahjadi, Henry Sutanto, Artaria Tjempakasari,The role of cation-exchange resins in hyperkalemia management, Medical Journal Armed Forces India, Volume 81, Issue 1,2025,Pages 7-14,ISSN 0377-1237,

Sodium Zirconium Cyclosilicate Trials

- REALIZE-K: Prospective, double-blind, placebo-controlled trial in patients with HFrEF (NYHA functional class II-IV; left ventricular ejection fraction ≤40%), optimal therapy (except MRA), and prevalent hyperkalaemia (or at high risk).
- REGISTA-K Trial: Efficacy and Safety of Sodium Zirconium Cyclosilicate in the Management of Hyperkalemia in Patients with Heart Failure with Reduced and Mildly Reduced Ejection Fraction and Chronic Kidney Disease Treated with Spironolactone.
- ZS-003 Trial -Multicenter, randomized, placebo-controlled study, assessing SZC in patients with hyperkalemia, including those with CKD, HF, and on RAASi therapy. SZC significantly reduced potassium levels compared to placebo and was effective in both acute and chronic settings
- HARMONIZE Trial: Series of clinical trials in a broader patient population from different geographic regions
- DIALIZE Study: CKD 5 on HD didn't require rescue therapy and maintained pre HD K
- ENERGIZE Trial : Phase 2 RCT double blind trial in ED patients with K above 5.8 mmol/L

KDIGO 2020 Clinical Practice Guideline for diabetes management in CKD recommend the consideration of SZC for patients with CKD and persistent hyper kalemia, highlighting its effectiveness in managing potassium levels and enabling the use of guideline-directed medical therapy

Sodium Zirconium Cyclosilicate in CKD, Hyperkalemia, and Metabolic Acidosis: NEUTRALIZE Randomized Study

KIDNEY360
Accessing Our World From Every Angle

NEUTRALIZE study

229 non-dialysis CKD G3-5

Hyperkalemia sK^+ >5.0 to ≤5.9

Metabolic acidosis $sHCO^-_3$ 16 to 20

Open-label SZC 10g thrice a day for ≤48h

Patients with normokalemia:

SZC 10g daily (n=17)

Placebo (n=20)

End of treatment (EOT) = Day 29

STOP High screen failure led to early study termination

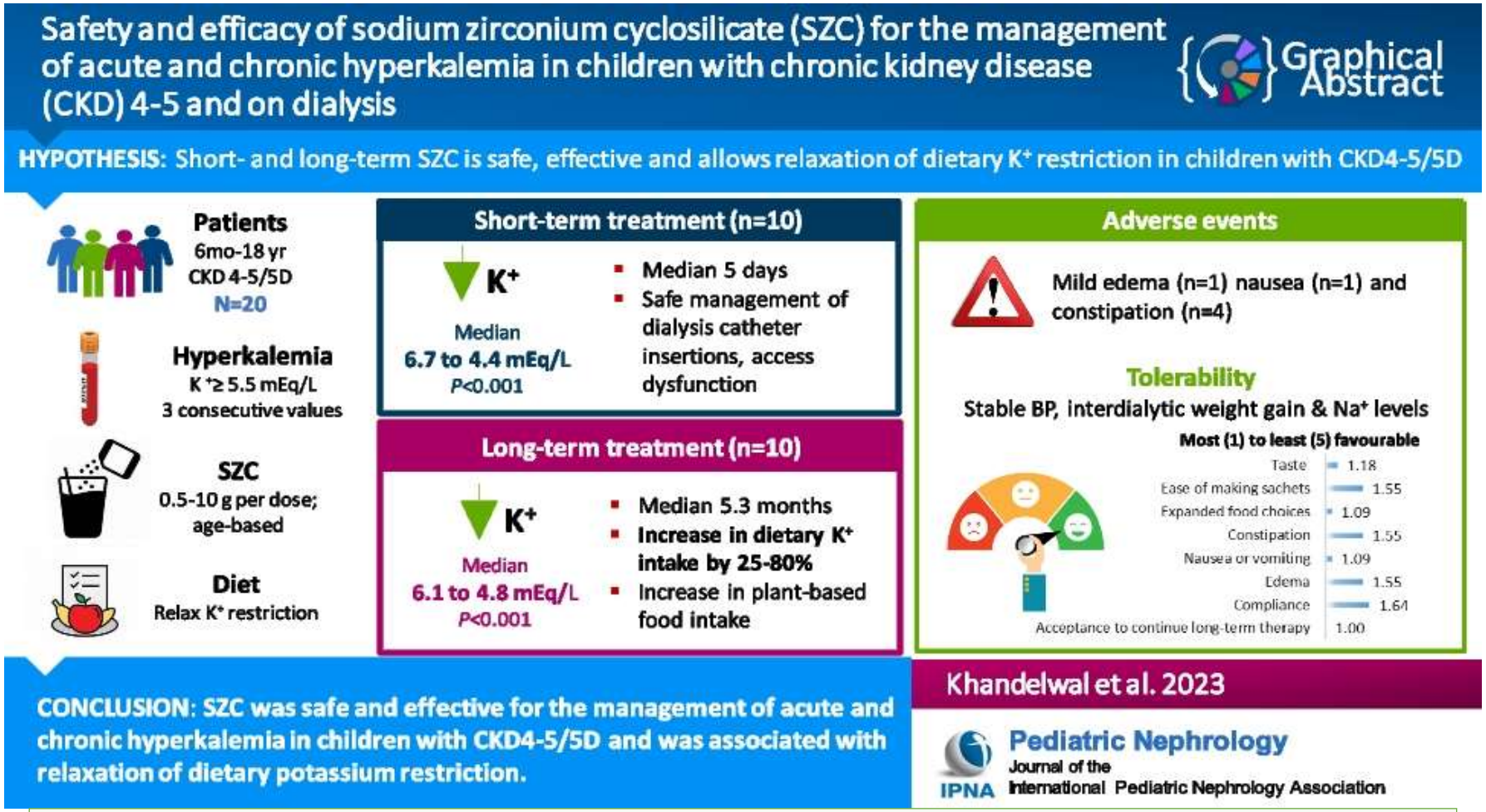
	Normokalemia (K^+ 3.5 to 5.0)	Normokalemia with ≥3mmol/l increase $sHCO^-_3$
SZC	88.2%	35.3%
	OR 56.2 ; p=0.001	p < 0.05
Placebo	20%	5%

SZC treatment provided nominally significant increases in $sHCO^-_3$ in comparison to placebo from Day 15 onwards

Conclusions: SZC effectively lowered sK+ and maintained normokalemia, with nominally significant increases in sHCO3– observed for SZC versus placebo. No new safety concerns were reported.

Stephen R. Ash, Daniel Batlle, Jessica Kendrick, *et al.* ***Sodium Zirconium Cyclosilicate in Chronic Kidney Disease, Hyperkalemia, and Metabolic Acidosis: NEUTRALIZE Randomized Study***. *Kidney360*. DOI: 10.34067/KID.0000000000000446
Visual Abstract by José A. Moura-Neto, MD, FASN, FRCP

Is SZC safe in Children?



- Both Patiromer & SZC more palatable than sodium polystyrene sulfonate
- Promising future treatment options for pediatric patients

Khandelwal P, Shah S, McAlister L, Cleghorn S, King L, Shroff R. Safety and efficacy of sodium zirconium cyclosilicate for the management of acute and chronic hyperkalemia in children with chronic kidney disease 4-5 and on dialysis. Pediatr Nephrol. 2024 Apr;39(4):1213-1219.

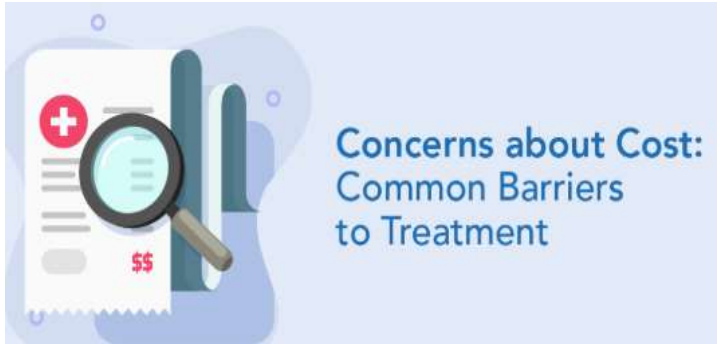
Calcium polystyrene sulfonate, Patiromer, and SZC

Feature	CPS	Patiromer	SZC
Mechanism of action	Exchanges calcium for potassium in the colon.	Binds free potassium in the GI tract, using calcium as a counterion.	Exchanges sodium and hydrogen for potassium in the GI tract.
Efficacy	Effective for chronic management of hyperkalemia.	Effective for chronic management.	Effective for both acute and chronic management of hyperkalemia.
PK	Not systemically absorbed; acts locally in the colon.	Not systemically absorbed; acts locally in the GI tract.	Not systemically absorbed; acts locally in the GI tract.
Drug interactions	May bind to other orally administered medications, reducing their absorption.	Binders like patiromer can decrease the absorption of many oral medications; timing of administration is critical.	May bind to other orally administered medications, reducing their absorption.
Recommended dosage	Initial: 15–30 g orally or rectally 1–4 times a day	Initial: 8.4 g once daily	Initial: 10 g three times a day for up to 48 h
Maintenance dosage	Adjust based on serum potassium levels.	Maintenance: 8.4 g once daily, can adjust based on serum potassium.	For chronic management: 10 g once daily, can be adjusted based on serum potassium levels.
Onset of action	Slow, several hours to days.	Within hours to days, with maximum effect seen within 7 days.	Rapid, within hours.

Calcium polystyrene sulfonate, Patiromer, and SZC

Duration of action	Long-term management, requires continuous use for sustained effect.	Long-term management, requires continuous use for sustained effect.	Both acute and chronic management of hyperkalemia.
Safety and side-effects	Nausea, vomiting, constipation. Rare: intestinal necrosis.	Constipation, hypomagnesemia.	Mild edema, hypokalemia, GI disturbances.
Contraindications	Hypercalcemia, obstructive bowel disease.	Severe GI motility disorders, hypersensitivity to the active substance or any excipients.	Hypokalemia, mechanical bowel obstruction.
Special considerations	Caution in patients with congestive heart failure or renal failure due to calcium load.	Requires separation from other oral medications by at least 3 h.	Monitor for sodium overload in patients with heart failure or hypertension.
Patient preference/ compliance issues	Taste and consistency may affect acceptability; GI side-effects may impact compliance.	Requires mixing with water and has specific administration instructions relative to other medications, which might affect compliance.	Generally well-tolerated, but the need for daily administration in chronic management may affect compliance.
Monitoring requirements	Serum electrolytes, especially calcium and potassium.	Serum potassium and magnesium levels, especially during the	Serum potassium levels, renal function, and signs of edema.

Important Concerns



- Old is Gold : CPS Affordable
- Economically attractive option-A month's supply of CPS is priced between US$20 and US$30
- Patiromer and SZC -significantly more expensive, with monthly costs ranging between US$600 and US$1000.
- CPS : The viable and cost-effective alternative

Is it Available in India?

No official approval:

Not been approved by Indian regulatory bodies, making it unavailable for sale and prescription to patients

Regulatory differences:

Drugs approved in US and EU, may not automatically be available in India due to differences in regulatory processes and approval timelines.

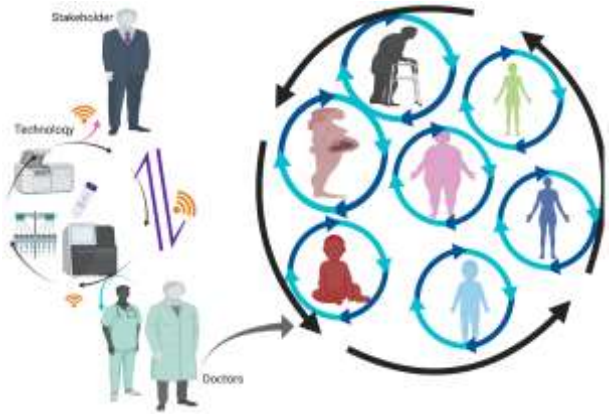
Is it Approved for use in children?

Patiromer-Yes

SZC : NO

Personalized Medicine in management of hyperkalemia

- Tailored to the individual patient's genetic makeup, underlying health conditions, and specific treatment needs, is gaining traction across various medical disciplines, including the management of hyperkalemia.
- Pharmacogenomics and biomarker research :More personalized treatment strategies that could optimize efficacy and minimize adverse effects.



Identifying genetic variants that affect K handling or drug metabolism to predict patient's response to specific treatments, allowing for more targeted therapy choices.

Biomarkers indicative of drug efficacy or risk of side-effects guide treatment selection and dosing, ensuring that patients receive the most appropriate and effective therapy.

Conclusion

- The advent of novel potassium binders such as patiromer and SZC represents a significant advancement in the management of HK, offering new therapeutic options that enhance patient outcomes and safety profiles.
- These agents have demonstrated efficacy in lowering serum potassium levels and maintaining long-term normokalemia, providing critical support in the management of patients with CKD, HF, and other conditions predisposed to HK, as well as optimizing RAASi therapy.
- Despite their efficacy, a pressing need for extensive long-term large head-to-head trials to evaluate their safety profiles, potential side effects, and impacts on patient quality of life.

Thank you!

Question Time ---

All the following drugs are implicated as the cause of hyperkalemia except

A. Ramipril
B. Metoprolol
C. Cotrimoxazole
D. Metolazone

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Which of the following trials lead to the FDA approval for use of Patiromer as an antikallum drug for use in children

A. DIAMOND
B. EMERALD
C. AMETHYST-DN
D. OPAL-HK

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D. OPAL-HK

Anti -Kallum compound that captures potassium in a pH-independent manner throughout the entire gastrointestinal tract, not just in specific areas

A. Sodium Polystyrene sulfonate
B. Calcium Polystyrene sulfonate
C. Patiromer
D. Sodium Zirconium Cyclosilicate

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