# Pharmacologic treatment of chronic hyperkalemia in CKD



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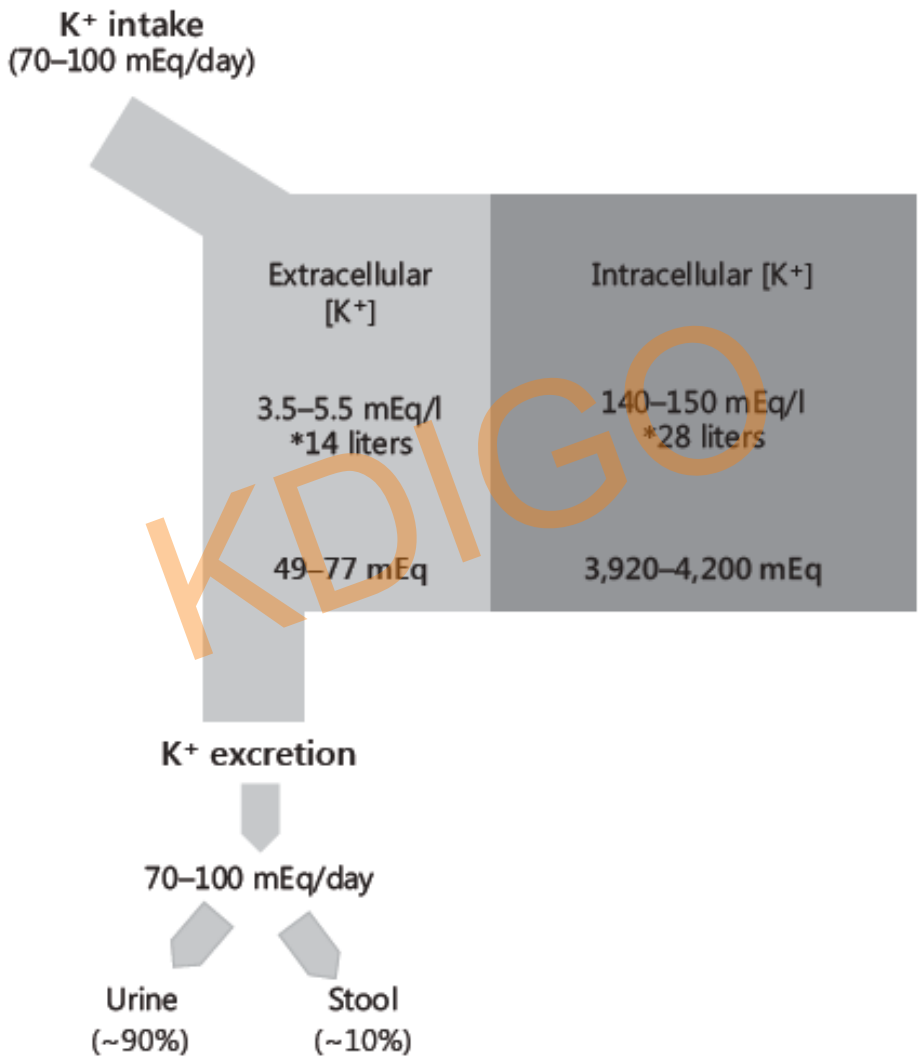
# Potassium homeostasis

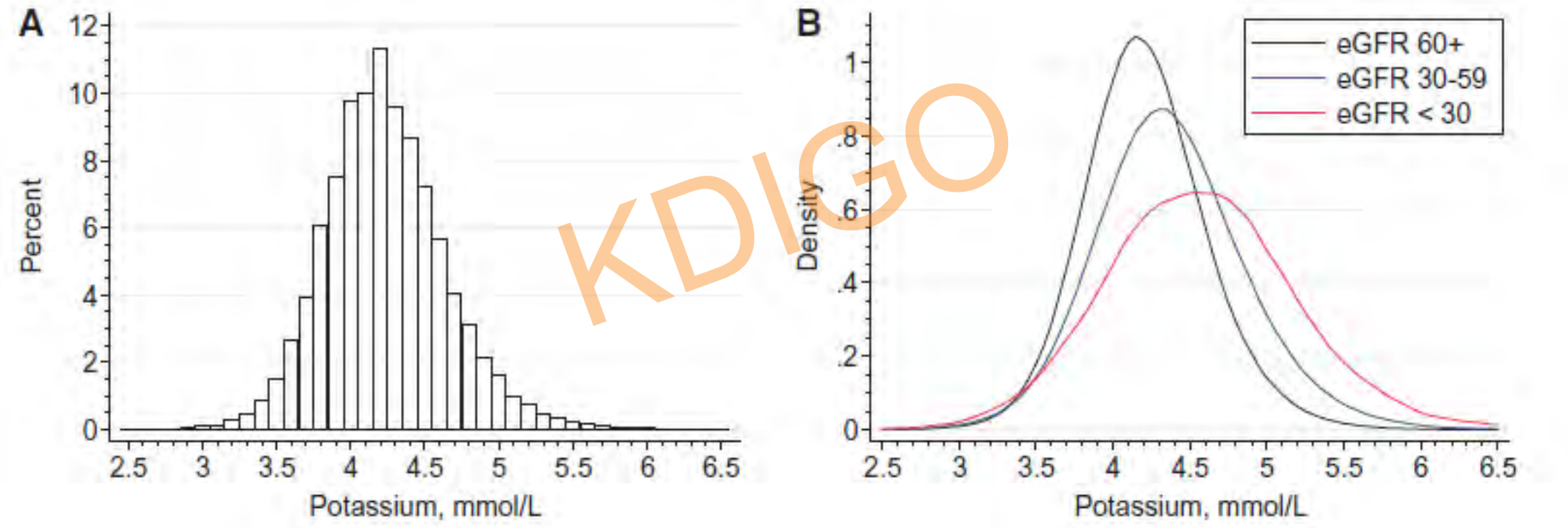





*Kidney Dis* 2016;2:72–79

# Distribution of serum potassium concentrations: from the CKD Prognosis Consortium

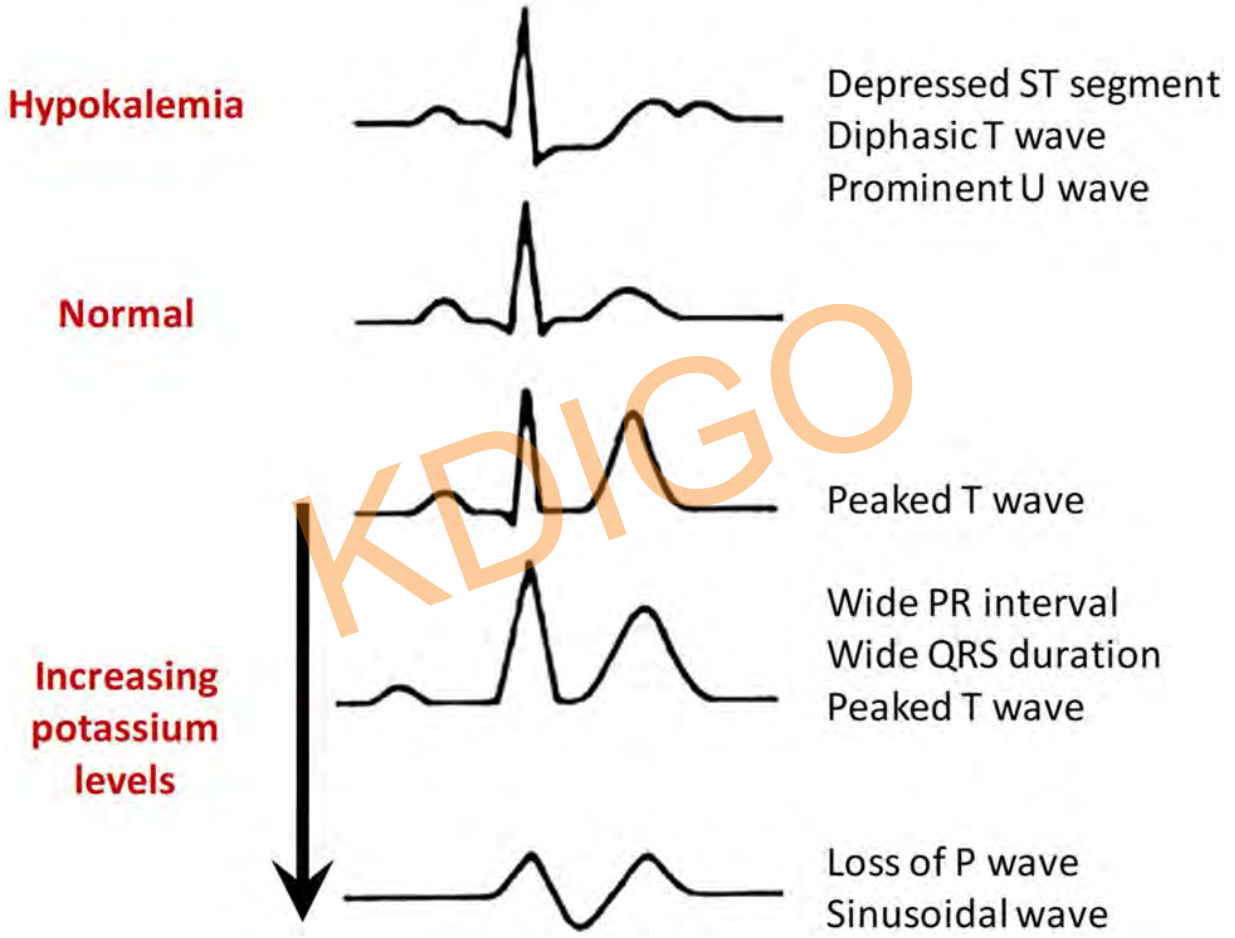
27 international cohorts (n = 1,217,986 participants from 10 general population, 7 high CV risk, and 10 CKD)






*Eur Heart J* 2018;39:1535–1542

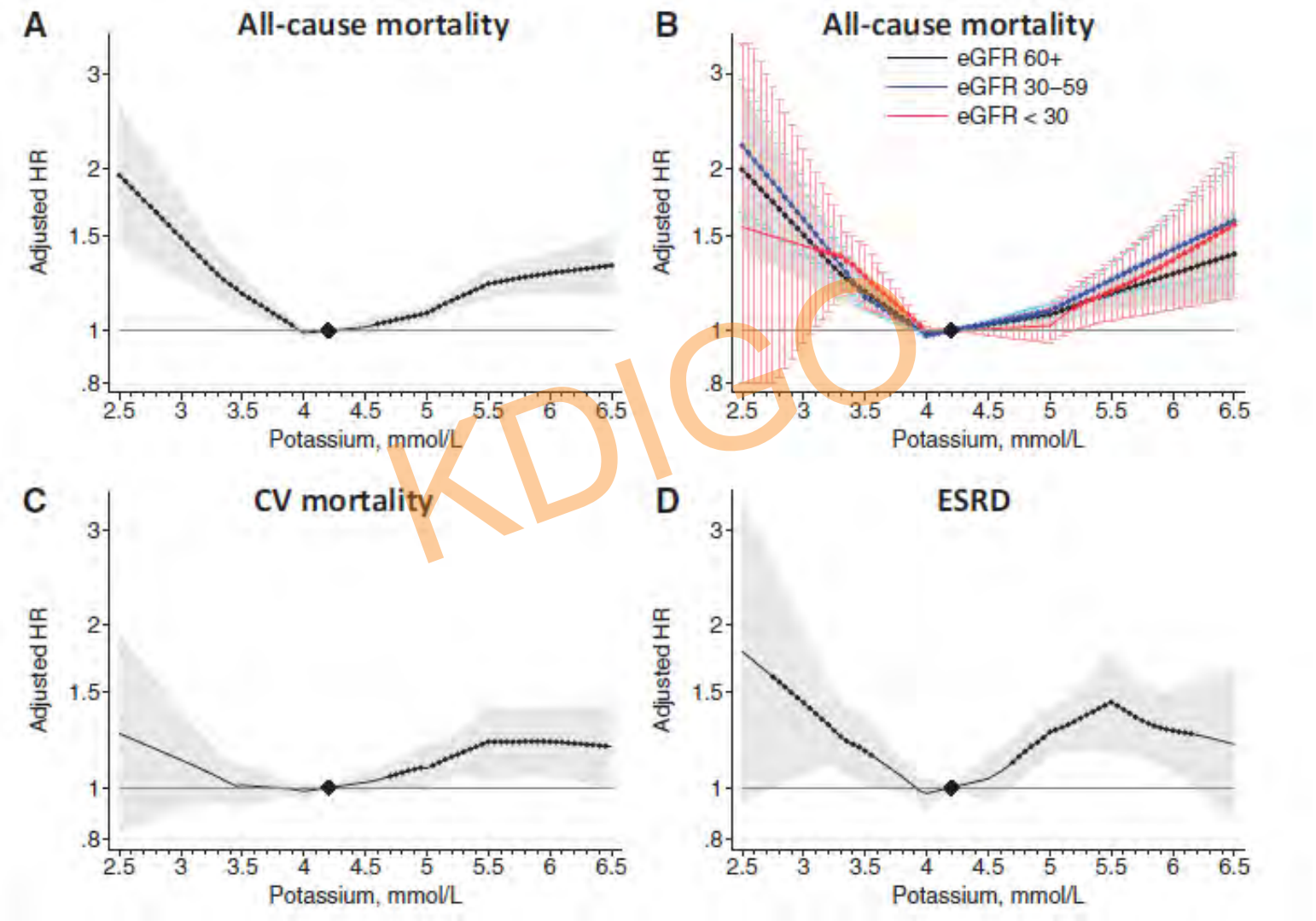
# ECG changes following progressive increases in potassium levels






Journal of Nephrology 2018; 31:653–664

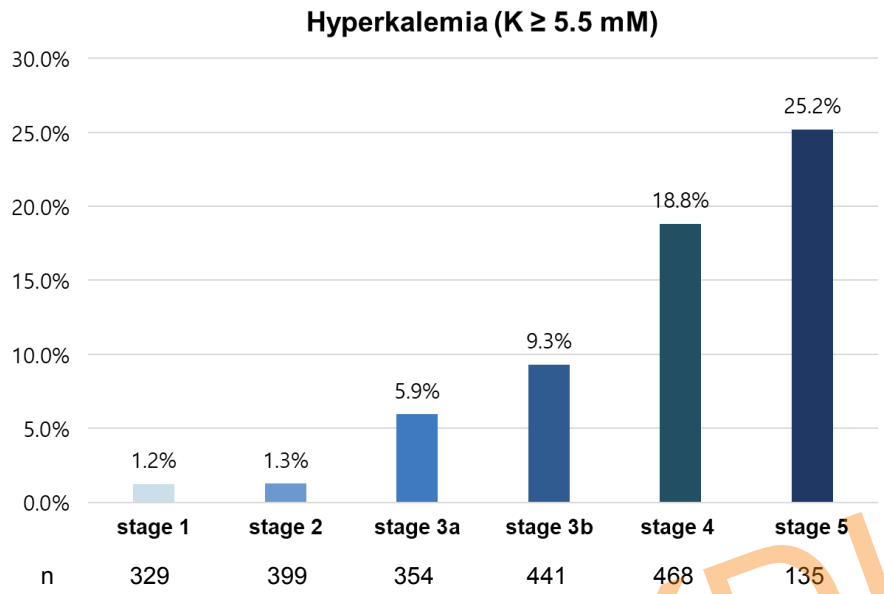
**A meta-analysis of 27 international cohorts** [10 general population, 7 high cardiovascular risk, and 10 chronic kidney disease (CKD)] **in the CKD Prognosis Consortium.**

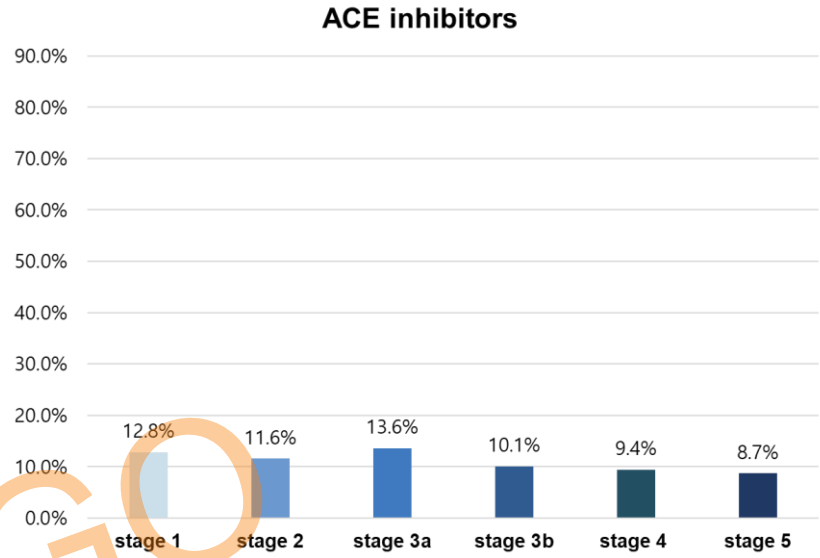


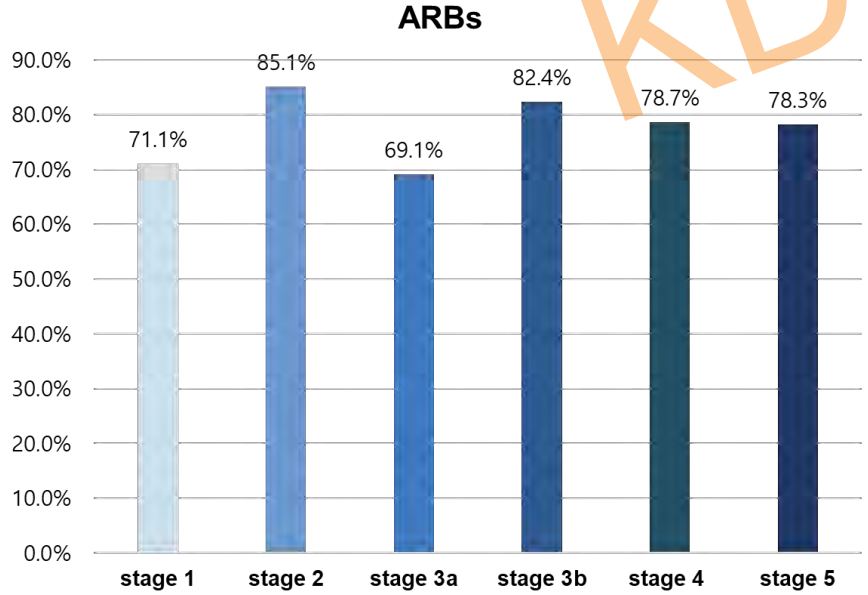


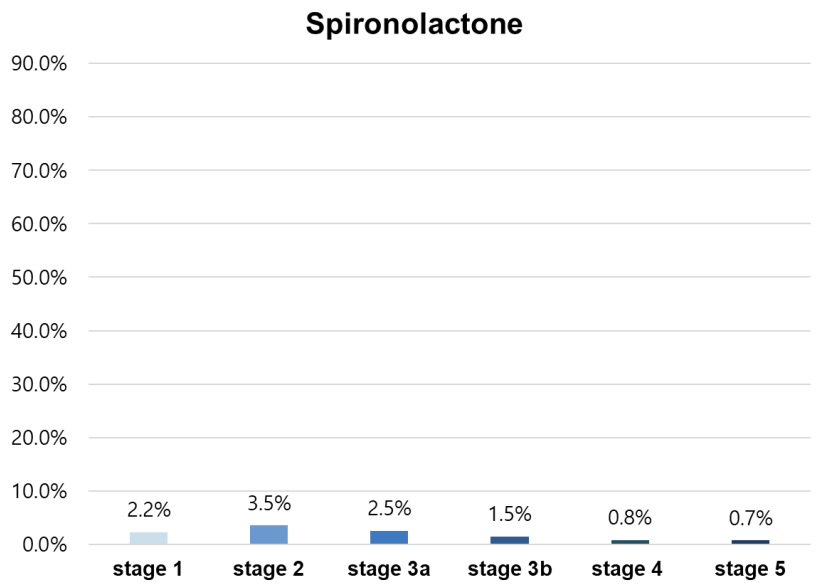

European Heart Journal 2018; 39: 1535–1542

# Prevalence of hyperkalemia and use of RAAS blockades: Data from the KNOW-CKD



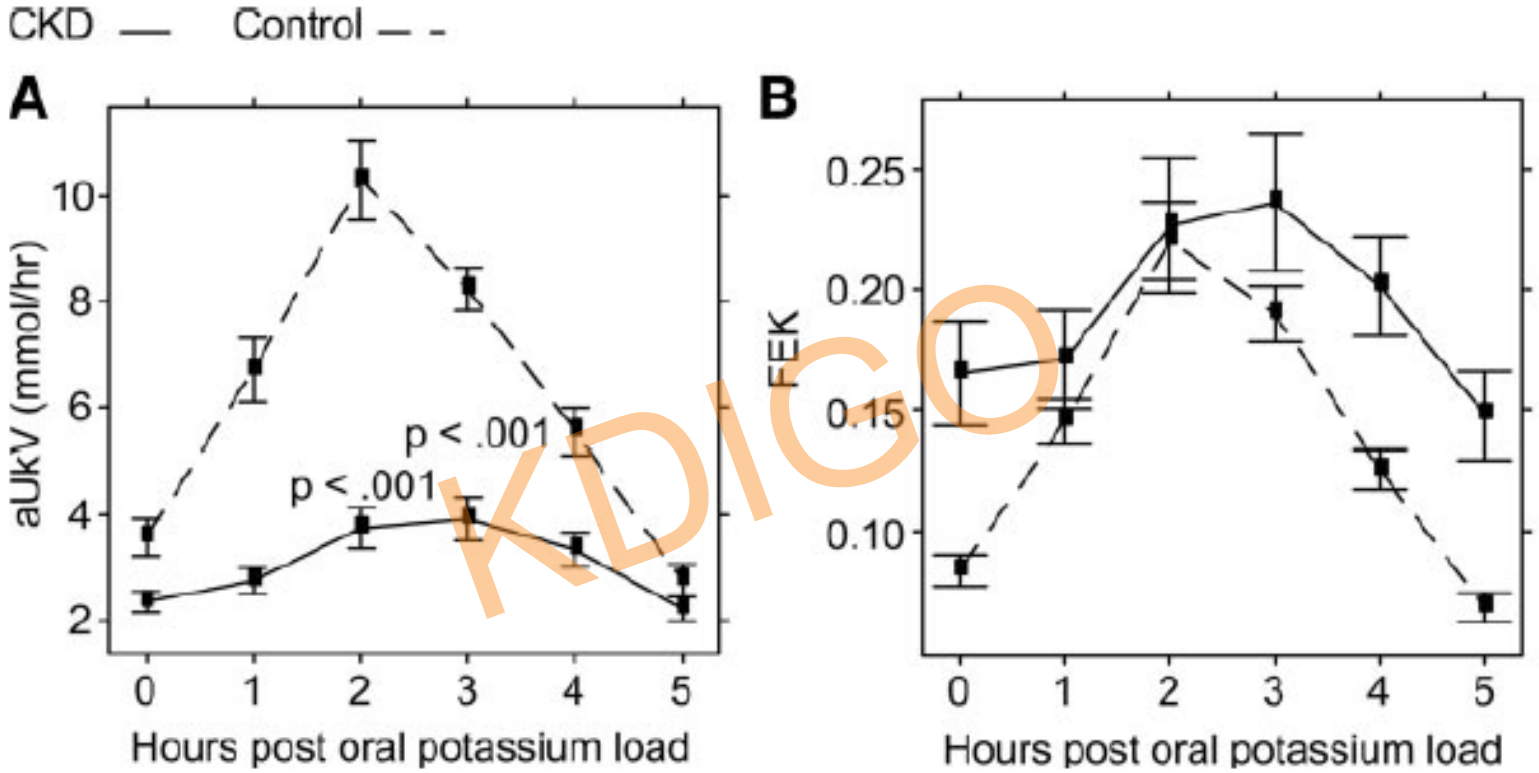






Courtesy of Drs. Eunjeong Kang & Kook-Hwan Oh

# Urinary $K^+$ excretion in CKD

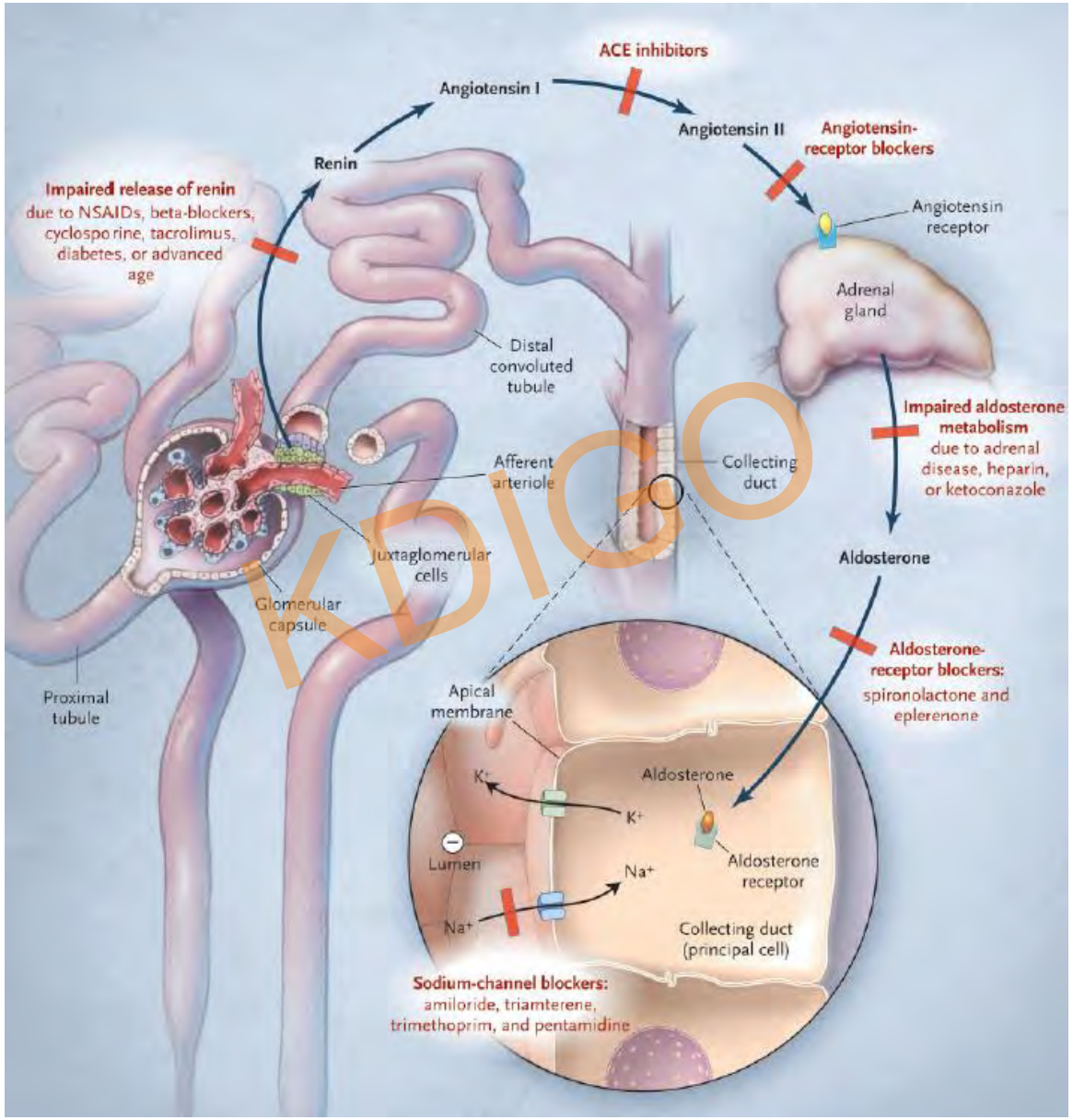





aUkV (mmol/h), hourly determinations of creatinine-adjusted urinary potassium excretion; FEK, fractional excretion of potassium.

*Hypertension* 2009;53;754-760

# RAAS blockades and decreased urinary $K^+$ excretion






*N Engl J Med* 2004;351:585-592

# Major randomized, controlled trials evaluating the effect of RAAS blockade on renal outcomes and the associated risk of hyperkalemia among patients with proteinuric CKD

| Study | Patient characteristics | *N* | Intervention | Follow-up, yr | Effect on renal outcomes | | Associated hyperkalemia risk | | | | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | DScr | ESRD | Definition | Incidence in RAAS group | Incidence in control group | Comparison | |
| Collaborate study group trial | Type 1 DM with overt nephropathy | 409 | Captopril (25 mg 3 times daily) vs. placebo | 3 | ↓ | ↓ | sK ≥6.0 mEq/l | 1.4% | 0% | Nonsignificant | 17 |
| RENAAL | Type 2 DM with overt nephropathy | 1513 | Losartan (50–100 mg/d) vs. placebo | 3.4 | ↓ | ↓ | sK ≥5.5 mEq/l | 24.2% | 12.3% | HR: 2.0; 95% CI 1.56–2.57 | 15 |
| IDNT | Type 2 DM with overt nephropathy | 1715 | Irbesartan (300 mg/d) vs. amlodipine (10 mg/d) vs. placebo | 2.6 | ↓ | ↓ | sK ≥6.0 mEq/l | 18.6% | 6% | $P < 0.001$ vs. placebo | 18 |
| REIN-2 | Nondiabetic, proteinuric CKD | 352 | Ramipril (5 mg/d) vs. placebo | 1.25 | ↓ | ↓ | NR | NR | NR | NR | 14 |
| AASK | African Americans with hypertensive nephrosclerosis | 1094 | Ramipril (2.5–10 mg/d) vs. metoprolol (50–200 mg/d) vs. amlodipine (5–10 mg/d) | 3.0–6.1 | ↓ | ↓ | sK ≥5.5 mEq/l | 2.45 events per 100 patient-months | 1.33 events per 100 patient-months | ACEI vs. CCB, HR: 7.0; 95% CI 2.29–21.39 ACEI vs. BB, HR: 2.85; 95% CI 1.50–5.42 | 19 |
| Benazepril for advanced renal insufficiency | Advanced-stage, nondiabetic, proteinuric CKD | 224 | Benazepril (20 mg/d) vs. placebo | 3.4 | ↓ | ↓ | sK ≥6.0 mEq/l | 5.4% | 4.5% | Nonsignificant | 16 |

AASK, African American Study of Kidney Disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; DScr, doubling of serum creatinine; ESRD, end-stage renal disease; HR, hazard ratio; IDNT, Irbesartan Diabetic Nephropathy Trial; MRA, mineralocorticoid receptor antagonist; NR, not reported; RAAS, renin angiotensin aldosterone system; REIN-2, Ramipril-Efficacy-In-Nephropathy-2; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; sK, serum potassium.
↓, Indicates significant reduction versus control group.



*Kidney Int* 2018; 93: 325–334

# Risk Factors for Chronic Hyperkalemia

**Chronic kidney disease** (eGFR < 30 mL/min/1.73 $m^2$)

**Diabetes mellitus** – hyperglycemia, diabetic ketoacidosis, hypoaldosteronism

**Congestive heart failure** – reduced renal perfusion

**Drugs:** NSAIDs, RAAS blockades, beta-blockers, calcineurin inhibitors, heparin

**Coronary artery and peripheral vascular diseases**

**Advanced age** – decreased plasma renin activity, decreased aldosterone levels

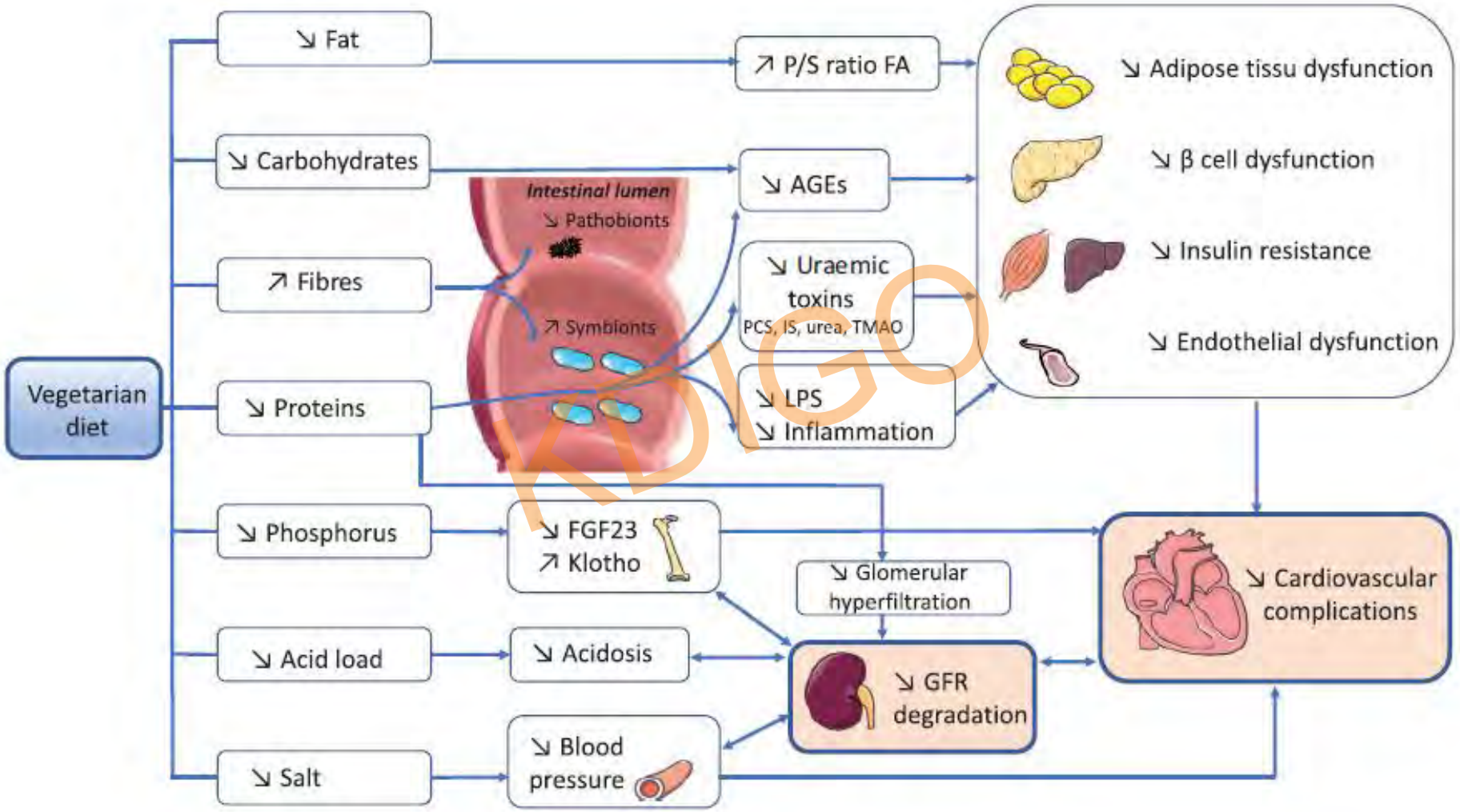
**Potassium intake** – salt substitutes and other dietary sources



*Cardiorenal Med* 2019;9:8-21

*N Engl J Med* 2004;351:585-592

# Hypothesized effects of a vegetarian diet and its components on CKD






*Nephrol Dial Transplant* 2019; 34: 199–207

# Control of potassium load while maintaining the benefit of a high-potassium diet

- In patients with non-dialysis dependent **CKD stages 1–5**, the National Kidney Foundation suggests an unrestricted potassium intake (**90–120 mmol/day**) [*Am J Kidney Dis* 2000; 35:S1–S40].
- Kalantar-Zadeh and Fouque have suggested an intake of **4.7 g/day** in the early stages of CKD without risk of hyperkalemia, while dietary potassium restriction down to **2–3 g/day** (approximately **51–77 mmol/day**) is recommended in CKD patients with **sK > 5.3 mEq/L** [*N Engl J Med* 2017; 377:1765–1776].



The prevention or correction of **metabolic acidosis** as well as **constipation** (by offering vegetarian diets) may well counteract the hyperkalemia-inducing effects of high potassium intake. As renal function declines over time, **colonic potassium secretion** progressively increases [*Trans Assoc Am Physicians* 1967;80:207-16] .

**Cooking procedures** (e.g., soaking or boiling) should be modified in order to remove potassium, and **hidden sources of potassium** (e.g. food additives and low-sodium salt substitutes) should be avoided [*J Nephrol* 2018; 31:653–664].

# Pharmacologic treatment of chronic hyperkalemia in CKD

| Treatment | Dose | Route of Administration | Onset of Action | Duration of Effect | Mechanism | Comments |
|---|---|---|---|---|---|---|
| Diuretics | 40 mg furosemide or equivalent dose of other loop diuretic. Higher dose may be needed with advanced chronic kidney disease. | IV (acute) or PO (chronic) | Varies with start of diuresis | Until diuresis present or longer† | Excretion | - Loop diuretics for acute intervention<br>- Loop or thiazide diuretics for chronic management |
| Fludrocortisone acetate | 0.1 mg or higher (up to 0.4-1.0 mg/day) | PO (chronic) | N/A | N/A | Excretion | - In patients with aldosterone deficiency<br>- Larger doses may be needed to effectively lower potassium level<br>- Sodium retention, edema and hypertension may occur |
| Cation exchange resins | 25-50 g | PO or PR (acute or chronic), with or without sorbitol | 1-2 hours | 4-6 hours or longer† | Excretion | - Sodium polystyrene sulfonate only approved agent in most countries<br>- Calcium polystyrene sulfonate approved in some countries<br>- New agents in development |



Adapted from *Nat Rev Nephrol* 2014;10:653-662

# Newer potassium-binding drugs

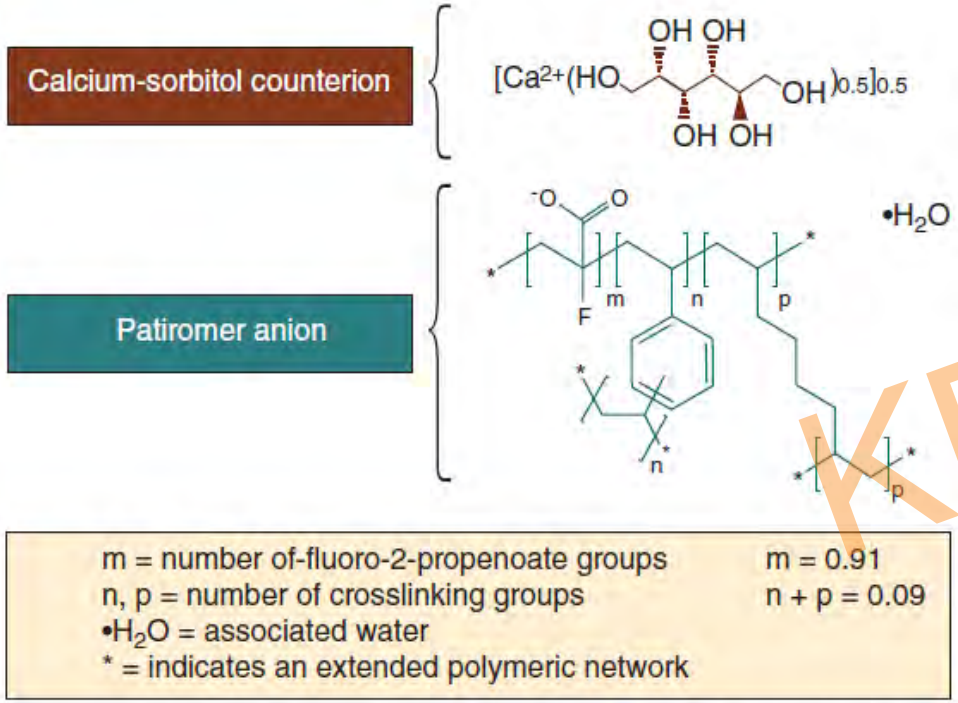



**Figure 1 | Chemical structure of patiromer and the calcium-sorbitol counter ion.** Reproduced with permission from Relypsa, Inc., VELTASSA® Prescribing Information 2016. Redwood City, CA.

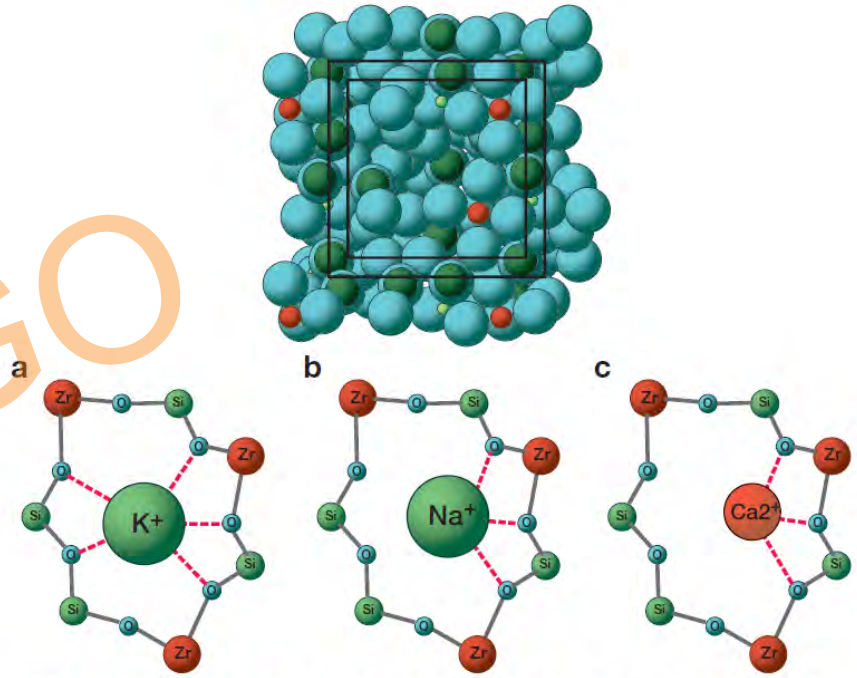



**Figure 2 | Structure of sodium zirconium cyclosilicate.** Pore detail with potassium ion (**a**), sodium ion (**b**), and calcium ion (**c**). Blue sphere indicates oxygen atoms; green spheres, silicon atoms; and red spheres, zirconium atoms. Reprinted from Stavros F, Yang A, Leon A, et al. Characterization of structure and function of ZS-9, a K+ selective ion trap. *PLoS One* 2014;9:e114686.[46] This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



*Kidney Int* 2018; 93: 325–334

Table 1 Baseline comorbidities across Patiromer Phase II-III trials

| Number of patients with the following comorbidities or treatment | Trial 201[44] Haemodialysis subjects ($n=6$) | Trial 202[37,45] PEARL-HF ($n=104$) | Trial 204[46] CKD with HF ($n=63$) | Trial 205[40] AMETHYST-DN ($n=304$) | Trial 301[41] OPAL-HK ($n=243$) |
|---|---|---|---|---|---|
| DT2 (%) | ? | 33 (32%) | 27 (43%) | 304 (100%) | 139 (57%) |
| HF (%) | ? | 100 (100%) | 63 (100%) | 106 (35%) | 102 (42%) |
| HTN (%) | 4 (67%) | ? | 59 (94%) | 304 (100%) | 236 (97%) |
| CKD (%) | 6 (100%) | 57 (55%) | 63 (100%) | 304 (100%) | 243 (100%) |
| Any RAASi | 3 (50%) | 102 (98%) | 63 (100%) | 304 (100%) | 243 (100%) |
| Dual RAAS blockade | ? | ? | 1 (1.6%) | ? | 41 (17%) |

CKD, chronic kidney disease; DT2, diabetes Type 2; HF, heart failure; HTN, hypertension; RAASi, renin angiotensin aldosterone system inhibitor.

Table 2 Baseline comorbidities or treatment across SZC Phase II-III trials

| Number of patients with the following comorbidities or treatment | ZS-002[47] ($n=90$) | ZS-003[43] ($n=753$) | HARMONIZE, or ZS-004[42] ($n=258$) |
|---|---|---|---|
| DT2 (%) | 50 (56%) | 451 (59.9%) | 170 (66%) |
| HF (%) | ? | 300 (39.8%) | 94 (36%) |
| HTN (%) | ? | ? | ? |
| CKD (%) | 90 (100%) | 561 (74.5%) | 169 (66%) |
| Any RAASi | 56 (62%) | 502 (66.7%) | 180 (70%) |
| Dual RAAS blockade | 10 (11%) | ? | ? |

CKD, chronic kidney disease; DT2, diabetes Type 2; HF, heart failure; HTN, hypertension; RAASi, renin angiotensin aldosterone system inhibitor.

# Randomized, controlled trials evaluating the efficacy and safety of newer potassium-binding resins in hyperkalemic patients already treated with RAAS blockers

| Patient characteristics | *N* | Year | Design | Intervention | Follow-up | Effect on sK | Major adverse events |
|---|---|---|---|---|---|---|---|
| **Studies with patiromer** | | | | | | | |
| Outpatients with HF and a history of hyperkalemia or CKD receiving standard therapy and add-on spironolactone | 105 | 2011 | Double-blind RCT | Patiromer (30 g/d) vs. placebo | 4 wk | ↓ | GI disorders (flatulence, diarrhea, constipation, and vomiting) were more frequent in the patiromer than in the placebo group (21% vs. 6%, respectively) |
| Hyperkalemic outpatients with CKD already treated with RAAS blockers | 107 | 2014 | Randomized, placebo-controlled withdrawal | Patiromer (4.2 g or 8.4 g twice daily) vs. placebo | 8 wk | ↓ | Constipation was the most frequently reported adverse event (incidence rate: 11%) |
| Hyperkalemic outpatients with CKD already treated with RAAS blockers | 306 | 2015 | Open-label, dose-ranging RCT | Patiromer (mild hyperkalemia stratum: 4.2, 8.4, or 12.6 g twice daily; moderate hyperkalemia stratum: 8.4 or 12.6 g twice daily) vs. placebo | 52 wk | ↓ | Hypomagnesemia, constipation, and diarrhea had an overall incidence of 8.6%, 6.3%, and 5.6%, respectively |
| **Studies with ZS-9** | | | | | | | |
| Hyperkalemic outpatients with HF, CKD, or diabetes | 237 | 2014 | Double-blind RCT | ZS-9 (5, 10, or 15 g/d) vs. placebo | 4 wk | ↓ | Dose-dependent increase in the incidence of edema |
| Hyperkalemic outpatients with HF, CKD, or diabetes | 753 | 2015 | Double-blind RCT | ZS-9 (1.25, 2.5, 5, or 10 g/d) vs. placebo | 2 wk | ↓ | GI disorders, mainly diarrhea, were the most commonly reported drug-related complications |



*Kidney Int* 2018; 93: 325–334

# Stopping RAAS blockades *vs.* Using potassium binders

KDIGO guidelines recommend **RAAS blockades** in patients with albuminuria > 30 mg/day or proteinuria > 500 mg/day. This recommendation is based on the proven nephroprotective efficacy of these agents in proteinuric patients.

NICE guidelines recommend not to offer RAAS blockades to CKD patients if pre-treatment serum [$K^+$] is **> 5.0 mEq/L**, and to withdraw therapy when serum [$K^+$] increases to **6.0 mEq/L**.

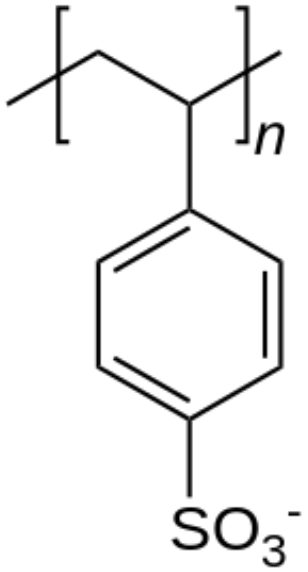


Intensification of **diuretic therapy** in anti-RAAS treated patients is safe and efficacious only in the presence of discrete extracellular volume expansion [Journal of Nephrology 2018; 31:653–664].

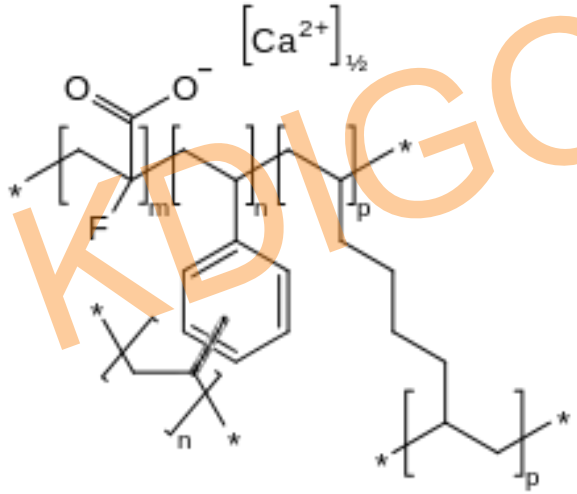
New potassium binding agents (**patiromer** and **ZS-9**) are available that are well tolerated and effective in maintaining the serum [$K^+$] in the normal range without reducing the dose or discontinuing RAAS inhibitors [Clin J Am Soc Nephrol 2018;13:155-157].

# Three Types of Potassium Binders

**Polystyrene sulfonate**

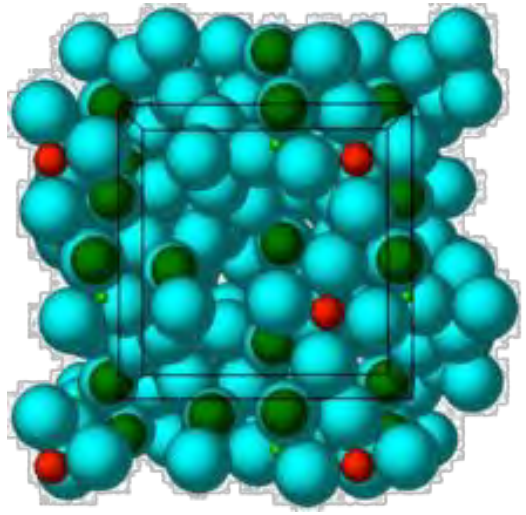



**Patiromer**



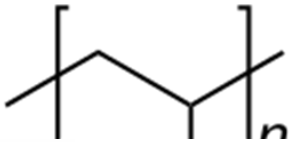



**ZS-9**
**(sodium zirconium cyclosilicate)**



https://en.wikipedia.org/wiki/

**Polystyrene sulfonate**



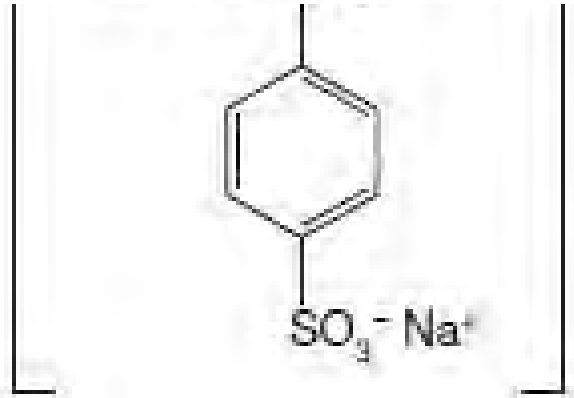
CLINICAL COMMENTARY www.jasn.org

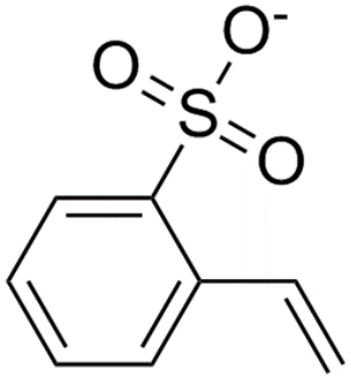
# Ion-Exchange Resins for the Treatment of Hyperkalemia: Are They Safe and Effective?

Richard H. Sterns, Maria Rojas, Paul Bernstein, and Sreedevi Chennupati

Rochester General Hospital and University of Rochester School of Medicine and Dentistry, Rochester, New York





# Sodium polystyrene sulfonate (Kayexalate®)

Kayexalate is a cation exchange resin, first introduced in the **1950s**, before the U.S. Food and Drug Administration was required to establish that drugs are safe and effective before approving them.

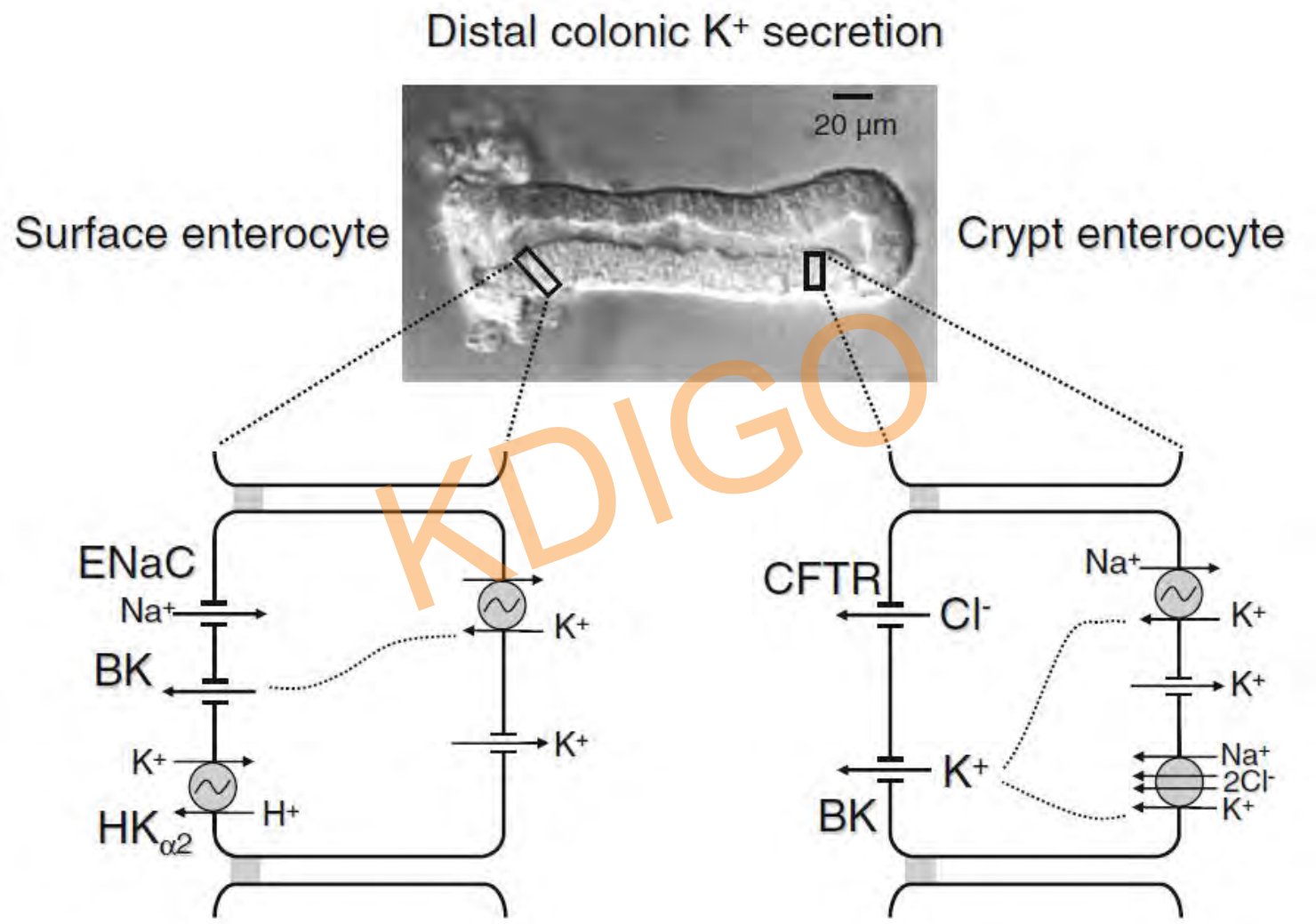
Kayexalate was the name given to the powdered form of SPS, which exchanges **sodium** for calcium, ammonium, and magnesium in addition to **potassium**. At an acid pH, its sulfonate groups are occupied by **hydrogen** ions and are unable to bind potassium.



For this reason, and because of higher potassium concentrations in the **distal colon**, Kayexalate is most effective in binding potassium when it reaches the **rectum**, either by **retention enema** or by oral administration with cathartics. Because the resin swells when it contacts water, large doses of Kayexalate can cause **bowel obstruction**. To avoid this complication and to speed its delivery to the distal colon, Kayexalate has been given together with **sorbitol**, an osmotic cathartic. However, the combination of sorbitol with the resin may result in **colonic necrosis**.

Kidney International 2016; 89: 546–554
The Journal of Emergency Medicine 2018; 55: 192–205

# The apical BK channel ($K_{Ca1.1}$) is the major secretory $K^+$ channel in the distal colon.






Pflugers Arch - Eur J Physiol 2010; 459:645–656

# Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with ESRD

*J Am Soc Nephrol* 1998; 9: 1924-1930

*Table 1.* Treatment regimens

| |
|---|
| Placebo: 8 gelatin capsules with 500 ml of water |
| Sodium polystyrene sulfonate: 30 g of resin with 500 ml of water |
| Phenolphthalein-docusate: 8 tablets[a] with 500 ml of water |
| Phenolphthalein-docusate plus resin: 8 tablets,[a] 30 g of resin with 500 ml of water |
| Sorbitol plus resin: 60 g of sorbitol, 30 g of resin with 500 ml of water |

[a] Given as Correctol®; each tablet contains 65 mg of yellow phenolphthalein and 100 mg of docusate sodium.

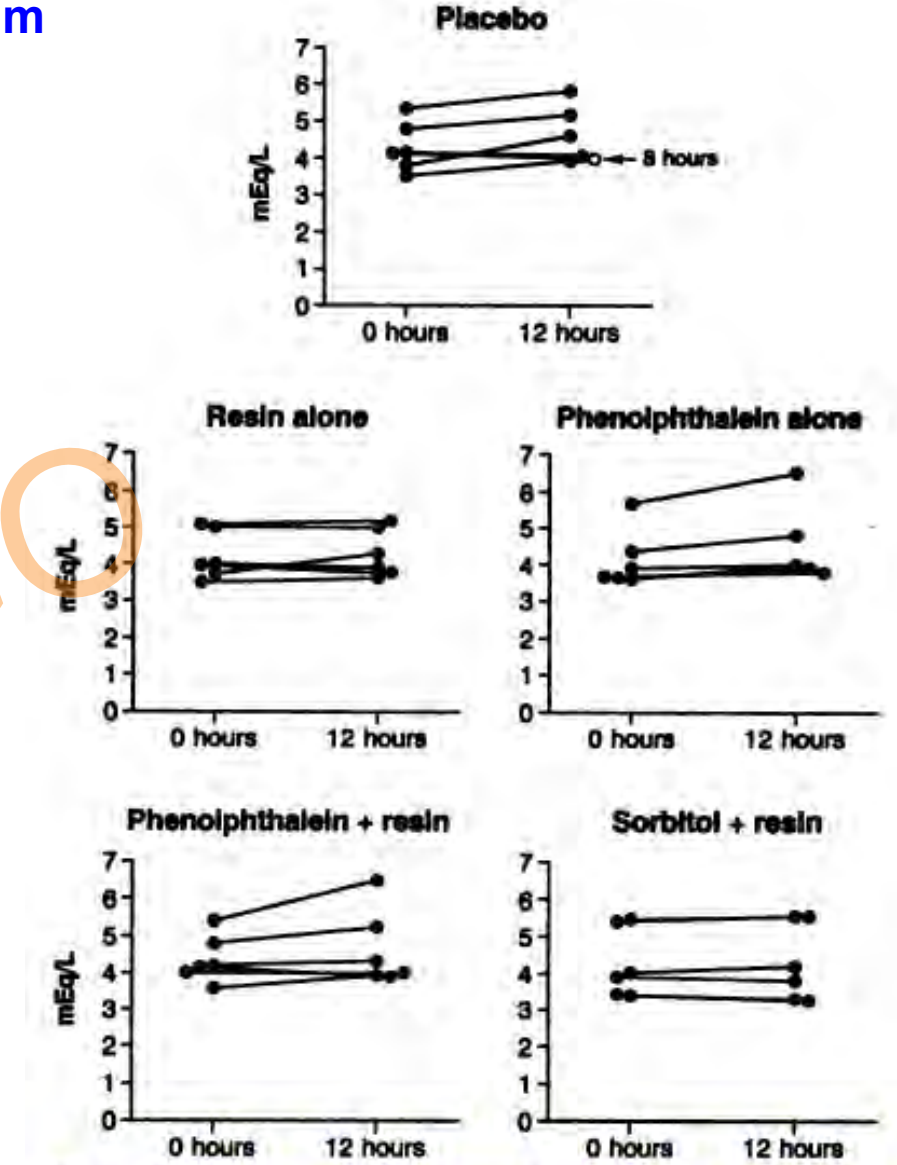



*Figure 1.* Serum potassium concentration (mEq/L) in each patient with end-stage renal failure before and 12 (or 8) h after various treatments.

# Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD

**Sodium polystyrene sulfonate was superior to placebo in reducing serum potassium over 7 days.**

*Clin J Am Soc Nephrol* 2015;10:2136–2142

Table 2. Efficacy outcomes

| Outcomes | SPS ($n$=15) | Placebo ($n$=16) | Difference of Mean Serum Potassium Change (95% CI) | $P$ Value |
|---|---|---|---|---|
| Serum potassium level at baseline, mEq/L[a] | 5.26±0.22 | 5.23±0.22 | | 0.73 |
| Serum potassium level at final follow-up, mEq/L[a] | 3.99±0.56 | 5.03±0.34 | | <0.001 |
| Variation of serum potassium, mEq/L[a] | −1.25±0.57 | −0.21±0.29 | −1.04 (−1.37 to −0.71) | <0.001 |
| Normokalemia, no. (%) | 11 (73.0) | 6 (38.0) | | 0.07 |

Table 3. Safety outcomes

| Outcomes | SPS ($n$=16) | Placebo ($n$=16) | $P$ Value |
|---|---|---|---|
| Nausea, no. (%) | 4 (25.0) | 2 (12.5) | 0.65 |
| Vomiting, no. (%) | 2 (12.5) | 1 (6.3) | >0.99 |
| Constipation, no. (%) | 6 (37.5) | 4 (25.0) | 0.70 |
| Diarrhea, no. (%) | 4 (25.0) | 8 (50.0) | 0.27 |
| **Electrolyte disturbances, no. (%)[a]** | | | |
| Hypokalemia (<3.5 mEq/L) | 3 (18.8) | 0 | 0.23 |
| Hypernatremia (>140 mEq/L) | 0 | 0 | N/A |
| Hypophosphatemia (<2.17 mg/dl) | 0 | 0 | N/A |
| Hypocalcemia (<8.48 mg/dl) | 3 (18.8) | 0 | 0.23 |
| Hypomagnesemia (<1.4 mEq/L) | 5 (31.2) | 1 (6.3) | 0.17 |
| Any adverse event, no. (%) | 12 (75.0) | 10 (58.8) | 0.47 |

**Table 4** Summary of SPS clinical studies for the treatment of hyperkalemia

| Study design | Patient population | Primary end point(s) | Study treatment and duration | Major findings |
|---|---|---|---|---|
| Prospective observational study[36] | Patients with either acute or CKD and hyperkalemia (n=32) | Mean change in potassium concentration over 24 hours | SPS 20–60 g/day PO in four divided doses or 10–40 g rectally and repeated in 4–12 hours if necessary (dosage varied with the degree of hyperkalemia and the course of renal failure) | Mean potassium concentration reduction of –1.0 mEq/L in the PO group and –0.8 mEq/L in the rectal administration group |
| Prospective, randomized, single-blind clinical trial[37] | Patients with CKD (SCr >1.5 mg/dL) and hyperkalemia (>5.2 mEq/L) (n=97) | Mean change in potassium concentration over 3 days | SPS 5 g PO TID or CPS 5 g PO TID for 3 days | Mean ± SD baseline potassium 5.8±0.6 mEq/L in SPS group; potassium concentration decreased to 4.3±0.53 mEq/L by day 3 |
| Prospective, randomized, double-blind, placebo-controlled clinical trial[38] | Outpatients with CKD (eGFR <40 mL/min/1.73 $m^2$) and mild hyperkalemia (5–5.9 mEq/L) (n=33) | Mean change in potassium concentration from baseline to day 7 | SPS 30 g PO once daily or placebo for 7 days | Mean potassium concentration reduction of –1.25±0.56 mEq/L in the SPS group compared to –0.21±0.29 mEq/L in the placebo group (mean difference –1.04 mEq/L, 95% CI –1.37 to –0.71 mEq/L; $P$<0.001) |

**Abbreviations:** CI, confidence interval; CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; eGFR, estimated glomerular filtration rate; PO, per os (by mouth); SCr, serum creatinine; SD, standard deviation; SPS, sodium polystyrene sulfonate; TID, ter in die (three times daily).



The evidence base for SPS is more limited than Patiromer and ZS-9.
**However, use of SPS may continue due to clinical familiarity and lower cost** [Core Evidence 2017:12 11–24].

# Gastrointestinal Adverse Events with Sodium Polystyrene Sulfonate (Kayexalate) Use: A Systematic Review


## ABSTRACT

**BACKGROUND:** Sodium polystyrene sulfonate (Kayexalate; Sanofi-Aventis, Paris, France) is a cation-exchange resin routinely used in the management of hyperkalemia. However, its use has been associated with colonic necrosis and other fatal gastrointestinal adverse events. Although the addition of sorbitol to sodium polystyrene sulfonate preparations was previously believed to be the cause of gastrointestinal injury, recent reports have suggested that sodium polystyrene sulfonate itself may be toxic. Our objective was to systematically review case reports of adverse gastrointestinal events associated with sodium polystyrene sulfonate use.

**METHODS:** MEDLINE (1948 to July 2011), EMBASE (1980 to July 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (1993 to July 27, 2011), bibliographies of identified articles, and websites of relevant drug agencies and professional associations in the United States and Canada were reviewed to identify eligible reports of adverse gastrointestinal events associated with sodium polystyrene sulfonate use. Causality criteria of the World Health Organization causality assessment system were applied to each report.

**RESULTS:** Thirty reports describing 58 cases (41 preparations containing sorbitol and 17 preparations without sorbitol) of adverse events were identified. The colon was the most common site of injury (n = 44; 76%), and transmural necrosis (n = 36; 62%) was the most common histopathologic lesion reported. Mortality was reported in 33% of these cases due to gastrointestinal injury.

**CONCLUSIONS:** Sodium polystyrene sulfonate use, both with and without sorbitol, may be associated with fatal gastrointestinal injury. Physicians must be cognizant of the risk of these adverse events when prescribing this therapy for the management of hyperkalemia.




• *The American Journal of Medicine (2013) 126, 264.e9-264.e24*

**KEYWORDS:** Gastrointestinal adverse events; Hyperkalemia; Intestinal necrosis; Kayexalate; Sodium polystyrene sulfonate

PLOS ONE

RESEARCH ARTICLE

# Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients

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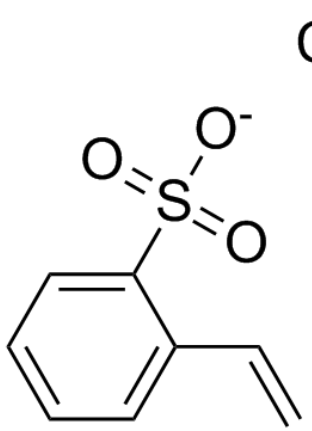
**Calcium polystyrene sulfonate (CPS)**

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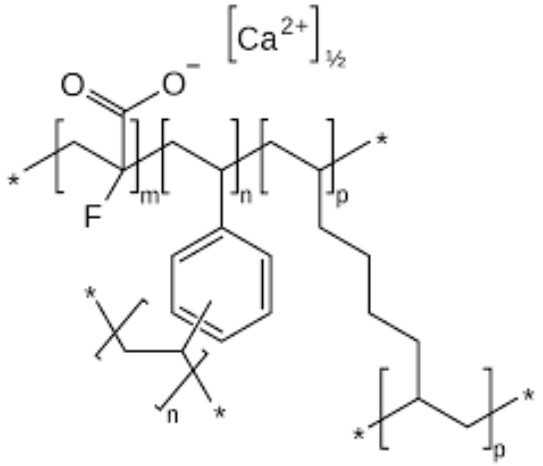

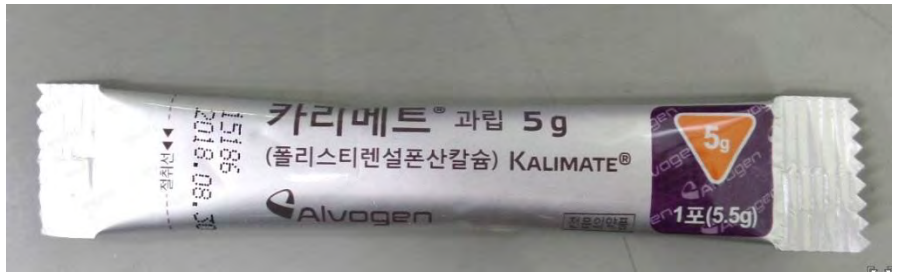
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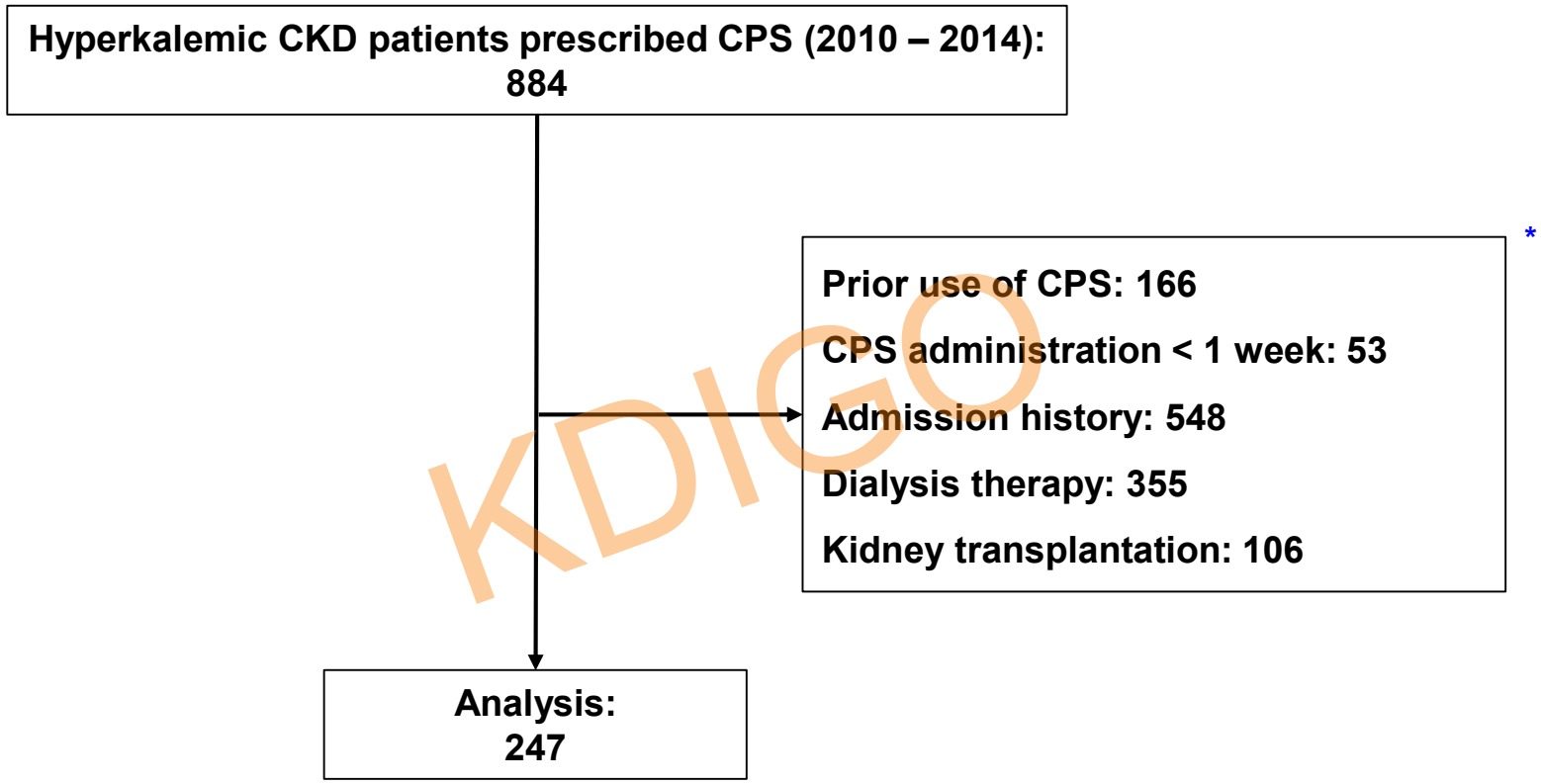
# Patient enrollment






* Patient numbers among categories are overlapped.

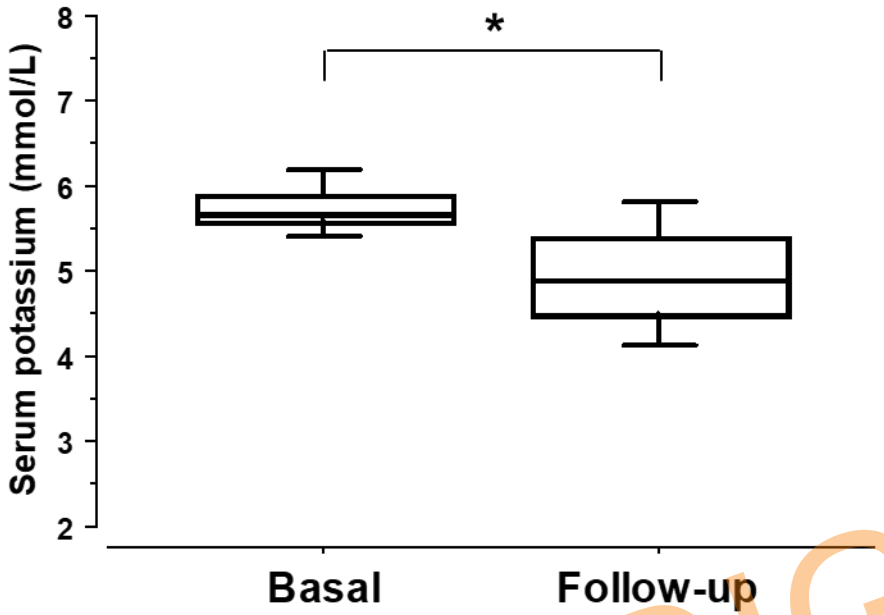
# Patient characteristics at baseline

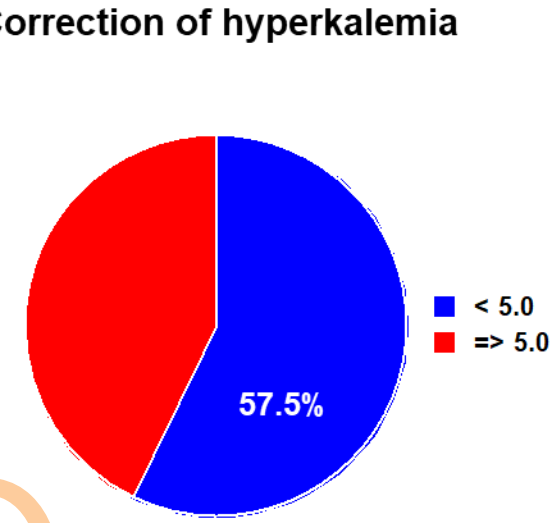
| Variable | Total (n = 247) |
|---|---|
| Age (years) | 64 ± 14 |
| Male | 136 (55.1%) |
| Kalimate® | 169 (68.4%) |
| Daily dose of CPS (g) | 8.0 ± 3.6 |
| Medication duration (months) | 5.6 ± 8.7 |
| Causes of CKD | |
| Diabetic kidney disease | 110 (44.5%) |
| Hypertensive nephrosclerosis | 55 (22.3%) |
| Chronic glomerulonephritis | 35 (14.2%) |
| Polycystic kidney disease | 4 (1.6%) |
| ACEI or ARB use | 155 (62.8%) |
| Hemoglobin (g/dL) | 10.7 ± 1.8 |
| BUN (mg/dL) | 46 ± 22 |
| Serum creatinine (mg/dL) | 2.8 ± 1.8 |
| eGFR (mL/min/1.73 $m^2$) | 30 ± 15 |
| Serum sodium (mmol/L) | 140 ± 3 |
| Serum potassium (mmol/L) | 5.8 ± 0.3 |

Values are expressed as mean ± standard deviation for continuous variables and number (%) for categorical variables.



PLoS ONE 2017; 12(3): e0173542




* by Wilcoxon signed-rank test (P < 0.001).

PLoS ONE 2017; 12(3): e0173542



**Table 3. Results from different groups according to the duration of medication administration.**

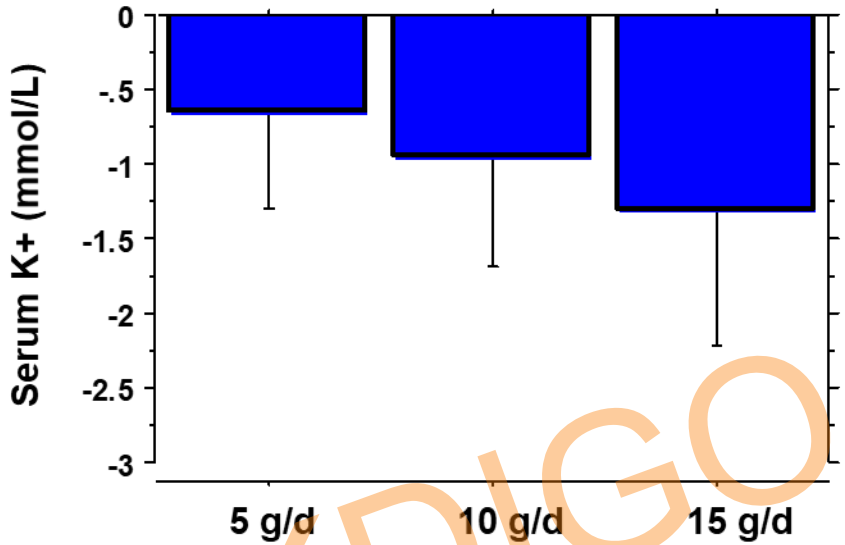
| | < 3 m | 3 – 6 m | 6 – 12 m | ≥ 1 yr |
|---|---|---|---|---|
| | (n = 144) | (n = 35) | (n = 30) | (n = 38) |
| Basal serum $K^+$ (mmol/L) | 5.8 ± 0.4 | 5.7 ± 0.4 | 5.7 ± 0.2 | 5.7 ± 0.3 |
| Follow-up serum $K^+$ (mmol/L) | 4.9 ± 0.7* | 4.9 ± 0.7* | 5.1 ± 0.6* | 4.7 ± 0.6* |
| Daily CPS dose (g/day) | 8.2 ± 3.6 | 7.2 ± 3.6 | 8.7 ± 3.5 | 7.6 ± 3.6 |
| Medication duration (months) | 1.3 ± 0.8 | 4.6 ± 0.8 | 9.2 ± 1.7 | 23.1 ± 10.5 |
| Response (%) | 79.9 | 71.4 | 66.7 | 86.8 |

Values are expressed as mean ± standard deviation.

CPS, calcium polystyrene sulfonate.

*$P < 0.001$ *versus* basal serum $K^+$, comparison with the paired t-test.

## Serum $K^+$ lowering effects with different CPS doses






Significant differences were noted between groups ($P < 0.001$ by Kruskal-Wallis test).

## Safety of long-term CPS use (n=247)

| | |
|---|---|
| Constipation | 19 (8%) |
| Serious adverse events | 0 (0%) |

PLoS ONE 2017; 12(3): e0173542

# Colonic mucosal necrosis following administration of CPS in a Uremic Patient

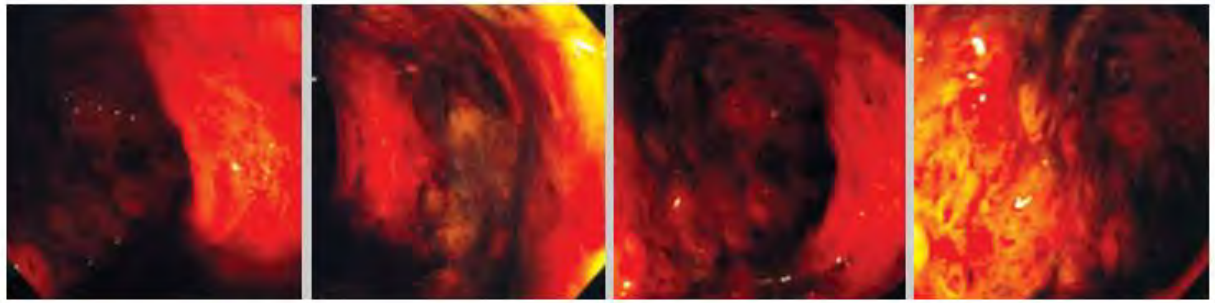


Fig. 1. A sigmoidoscopy shows diffuse ulceration with pseudomembrane formation in the entire sigmoid colon and rectum.

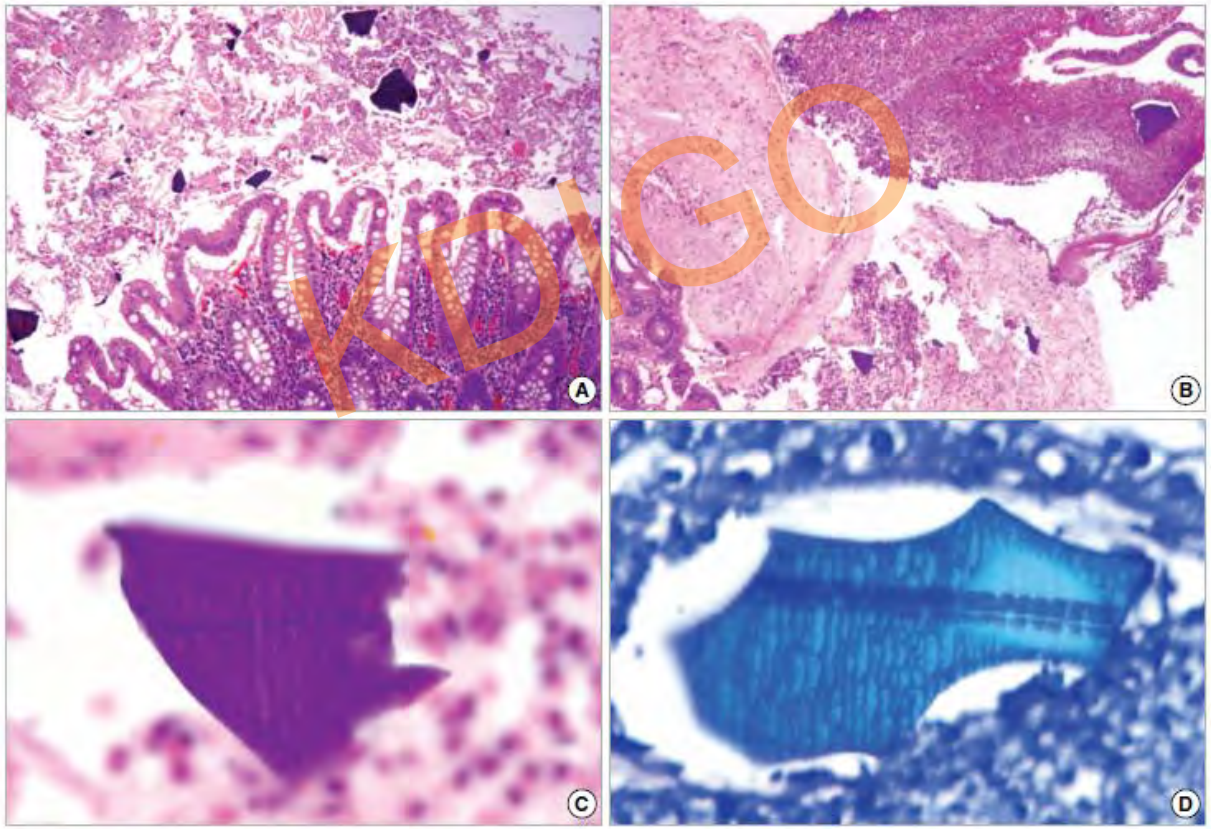





Fig. 2. Microphotographs of Kalimate crystals. (A, B) Angulated crystals are seen on the colonic mucosa and admixed within necroinflammatory exudates (H&E stain, × 100 and × 40). The crystals are basophilic on H&E stain (C, × 1,000) and blue on Diff-Quik stain (D, × 1,000). A characteristic crystalline mosaic pattern is better demonstrated with Diff-Quick staining (D).

*J Korean Med Sci*
2009; 24: 1207-11

# Evaluation of the tolerability and efficacy of sodium polystyrene sulfonate for long-term management of hyperkalemia in patients with chronic kidney disease

**Table 2** Changes in serum electrolytes before and after the initiation of therapy with sodium polystyrene sulfonate

| Parameter | Baseline | Month 1 post-SPS | Mean post-SPS | *P* value (month 1 vs baseline) | *P* value (mean post-SPS vs baseline) |
|---|---|---|---|---|---|
| Serum potassium (mmol/l) | 5.9 ± 0.4 | 4.9 ± 0.7 | 4.8 ± 0.5 | < 0.001 | < 0.001 |
| Serum sodium (mmol/l) | 139.5 ± 2.9 | 140.7 ± 3.6 | 141.2 ± 2.4 | 0.05 | 0.006 |
| Serum calcium (mg/dl) | 9.4 ± 0.5 | 9.3 ± 0.6 | 9.5 ± 0.7 | 0.755 | 0.261 |
| Serum phosphate (mg/dl) | 3.9 ± 0.7 | 4.1 ± 1.1 | 4.0 ± 0.6 | 0.664 | 0.547 |

**Table 3** Adverse effects associated with sodium polystyrene sulfonate use during the follow-up period

| Adverse effects of SPS therapy | Events | Patients |
|---|---|---|
| Electrolyte disturbances | | |
| Hyperkalemia (≥ 5.5 mmol/l) | 10 | 7 |
| Hypokalemia (≤ 3.5 mmol/l) | 0 | 0 |
| Hypernatremia (≥ 145 mEq/l) | 5 | 4 |
| Hypocalcemia (≤ 8.5 mg/dl) | 0 | 0 |
| Hypophosphatemia (≤ 2.1 mg/dl) | 0 | 0 |
| Colonic necrosis | 0 | 0 |
| Discontinuation due to GI intolerance[a] | 1 | 1 |

*GI* gastrointestinal, *SPS* sodium polystyrene sulfonate

[a]Nausea and diarrheic episodes was the reported etiology of SPS discontinuation



In this retrospective, observational study, **26 outpatients with stages 3–4 CKD** were enrolled.

1) Oral therapy with low-dose, sorbitol-free SPS was associated with **significant reductions in serum potassium levels** that were maintained over several weeks and months.

2) This potassium-lowering effect was not accompanied by excess risk of serious **electrolyte disturbances** and other **gastrointestinal side effects**.

*Int Urol Nephrol* 2017; 49:2217–2221

KI REPORTS
KIReports.org
*Kidney Int Rep* 2018; 3: 47–55
REVIEW

# Treatment of Severe Hyperkalemia: Confronting 4 Fallacies

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[1]Division of Hypertension and Kidney Diseases, Department of Medicine, Rhode Island Hospital and Alpert Medical School of Brown University, Providence, Rhode Island, USA



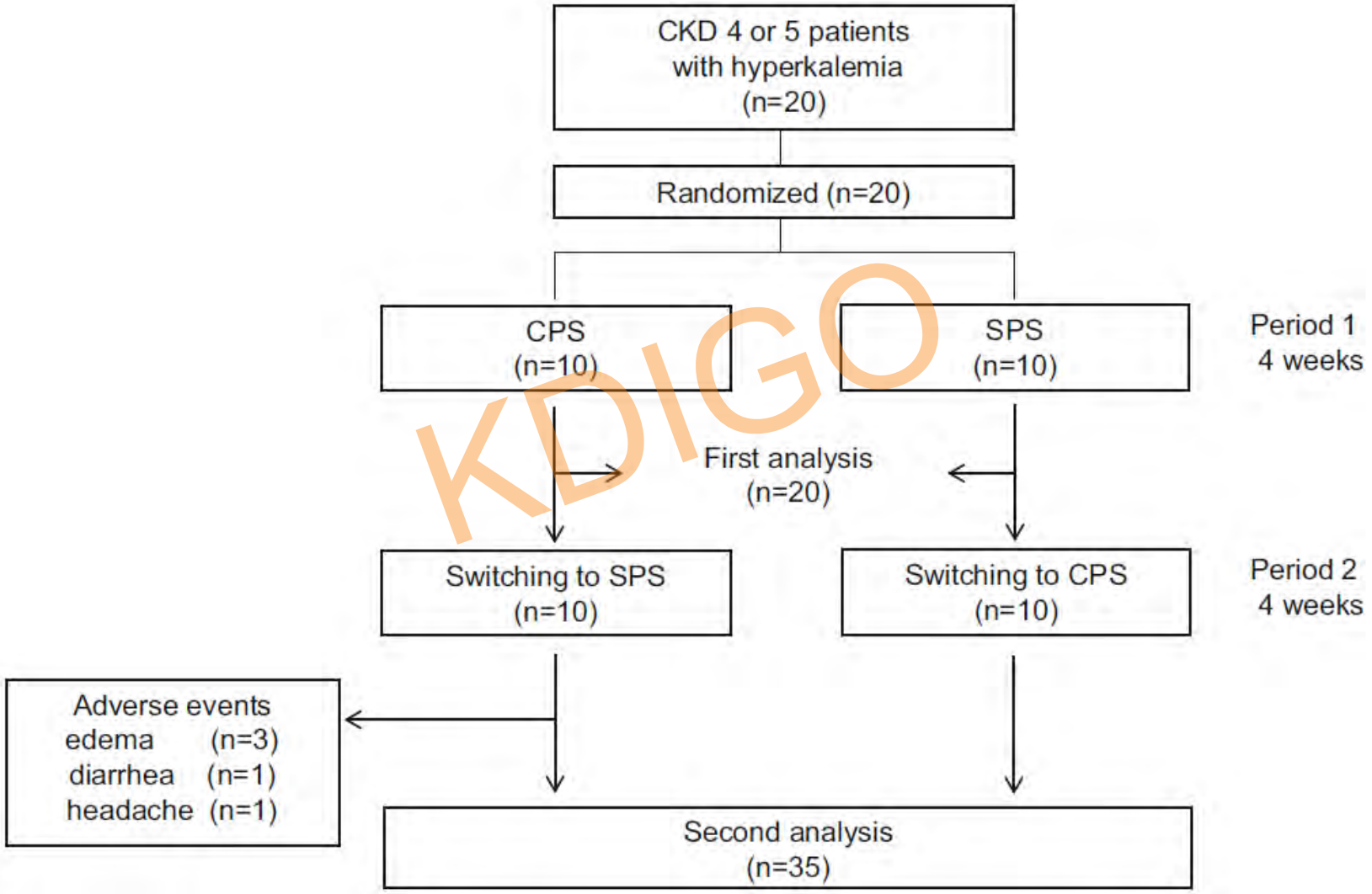
***Fallacy:*** *Sodium polystyrene sulfonate (SPS) is of uncertain efficacy, and if effective, it is only after a delay of several hours, making its usefulness questionable for severe hyperkalemia.*

**Truth:** Recent clinical studies and case series of SPS use confirmed its effectiveness in almost 800 patients; single 60- to 80-g doses were followed by average falls in serum potassium of 0.9 to 1.7 mmol/L. Regarding onset of action, a significant fall of 0.6 mmol/L was noted in potassium concentrations measured from 0 to 4 hours after SPS administration.

***Fallacy:*** *Intestinal necrosis, usually of the colon, is an infrequent, but often fatal complication of SPS.*

**Truth:** It is not clear if SPS causes intestinal necrosis; instead, it may just be a marker for risk factors for intestinal necrosis, such as chronic and end-stage renal disease. Even if SPS with or without sorbitol can rarely produce intestinal necrosis, it is so uncommon (much <1%).

# Comparisons between calcium and sodium polystyrene sulfonate in pre-dialysis patients with hyperkalemia






*Clin Exp Nephrol* 2018; 22:35–44

| Serum K (mmol/l) | 0 week | 4 weeks | Δserum K (95% CI) | *p* |
|---|---|---|---|---|
| CPS ($n = 10$) | 5.39 ± 0.49 | 4.14 ± 0.91 | −1.25 (−1.90 to −0.60) | <0.01 |
| SPS ($n = 10$) | 5.60 ± 0.54 | 4.12 ± 0.64 | −1.48 (−1.88 to −1.08) | <0.0001 |
| *p* | 0.37 | 0.96 | 0.51 | |

| Serum Na (mmol/l) | 0 week | 4 weeks | ΔNa (95% CI) | *p* |
|---|---|---|---|---|
| CPS ($n = 20$) | 142 ± 2.7 | 141 ± 2.8 | −1.25 (−2.33 to 0.17) | <0.05 |
| SPS ($n = 15$) | 141 ± 2.0 | 143 ± 2.7 | 2.07 (0.99–3.14) | <0.001 |
| *p* | 0.19 | <0.05 | <0.001 | |

| Serum Ca (mg/dl) | 0 week | 4 weeks | ΔCa (95% CI) | *p* |
|---|---|---|---|---|
| CPS ($n = 20$) | 8.96 ± 0.46 | 9.09 ± 0.52 | 0.13 (−0.10 to 0.36) | 0.26 |
| SPS ($n = 15$) | 9.09 ± 0.37 | 8.77 ± 0.47 | −0.33 (−0.54 to −0.11) | <0.01 |
| *p* | 0.37 | 0.07 | <0.01 | |

| Serum Mg (mg/dl) | 0 week | 4 weeks | ΔMg (95% CI) | *p* |
|---|---|---|---|---|
| CPS ($n = 20$) | 2.03 ± 0.46 | 2.13 ± 0.34 | 0.11 (−0.01 to 0.22) | 0.07 |
| SPS ($n = 15$) | 2.17 ± 0.45 | 1.93 ± 0.48 | −0.23 (−0.32 to -0.15) | <0.001 |
| *p* | 0.37 | 0.16 | <0.001 | |

# Conclusion

**Chronic hyperkalemia** is a major concern in CKD patients, especially taking RAAS blockades for diabetes and/or cardiac disease.

For the past decades **sodium polystyrene sulfonate (SPS)** and **calcium polystyrene sulfonate (CPS)** were used to treat hyperkalemia in kidney failure, although the issues of their efficacy and safety have not been resolved.



New agents such as **patiromer** and **sodium zirconium cyclosilicate** are promising because of recent RCT results.

Further comparative trials among patiromer, ZS-9, and CPS are required to provide guides to **cost-effective management** of chronic hyperkalemia .


Thank You
Asante
Kiitos
Grazie
Merci
Dankon
Welalin
Terma Kasih
Salamat
Spasibo
Multumesc
Matondo
Nirringrazzjak
Mochchakkeram
Ua Tsaug Rau Koj
Cam on ban
Matur Nuwun
Raibh Maith Agat
Dank Je
Obrigado
Arigato
Kia Ora

# Reducing the risk of hyperkalemia when using RAAS blockades

**Assess renal function to define overall risk of hyperkalemia**

**Discontinue medications that can impair renal potassium excretion,** including herbal preparations and over-the-counter nonsteroidal anti-inflammatory drugs

**Reduce potassium in diet, avoid salt substitutes containing potassium**

**Ensure effective diuretic therapy** (loop diuretics should be used if the estimated glomerular filtration rate is < 30 mL/min/1.73 $m^2$)

**Correct metabolic acidosis when present**

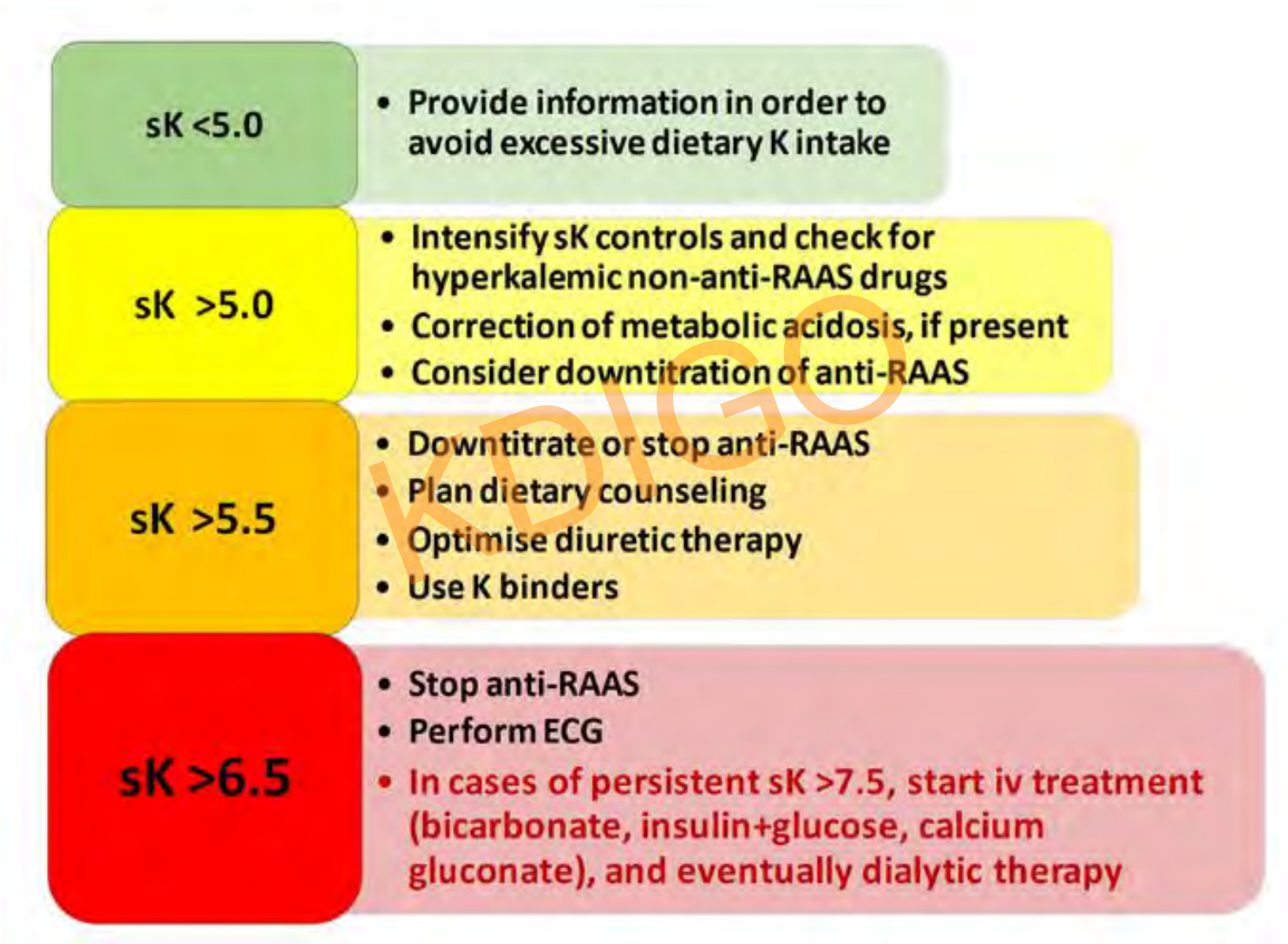
**Start with low doses of renin-angiotensin-aldosterone system blockers and monitor closely**

**Use $K^+$ binders**



Modified from *Cleve Clin J Med* 2017;84:934-942

# Strategies according to the levels of serum [$K^+$] in CKD






Journal of Nephrology 2018; 31:653–664