

# Oral Sorbents for Binding Uremic Toxins

Interdisciplinary Nephrology Conference

NKF of Illinois

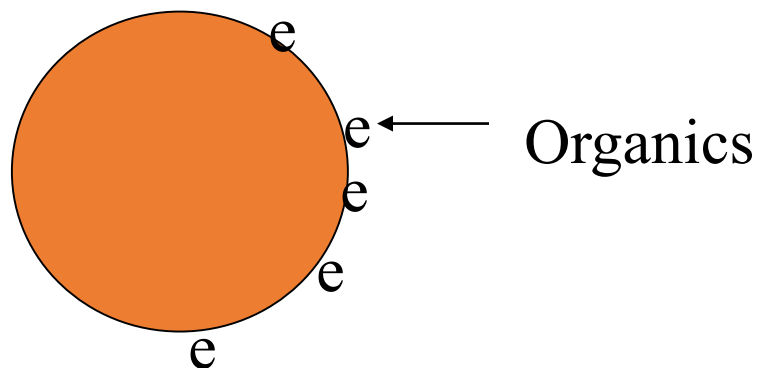
Oak Brook, IL October, 2019

**Stephen R. Ash, MD, FACP**

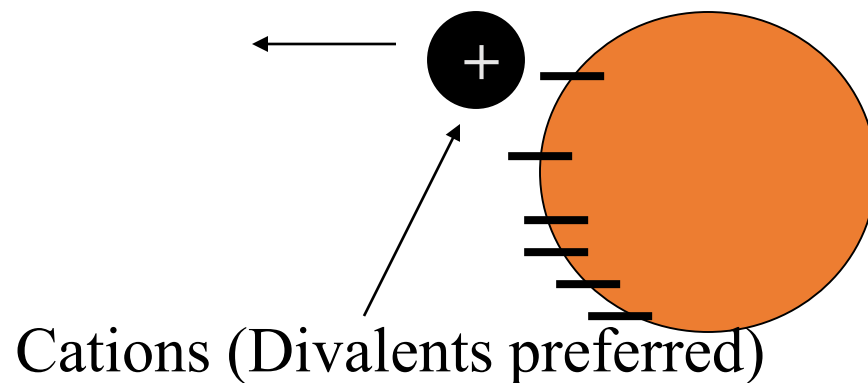
Director of Dialysis: Indiana University Health Arnett and Wellbound  
Chairman of Ash Access Technology and HemoCleanse Technologies, LLC  
Adjunct Associate Professor: Purdue University  
Lafayette and West Lafayette, IN

“Sorbents” are compounds or particles that bind other chemicals. There are Four Classes:

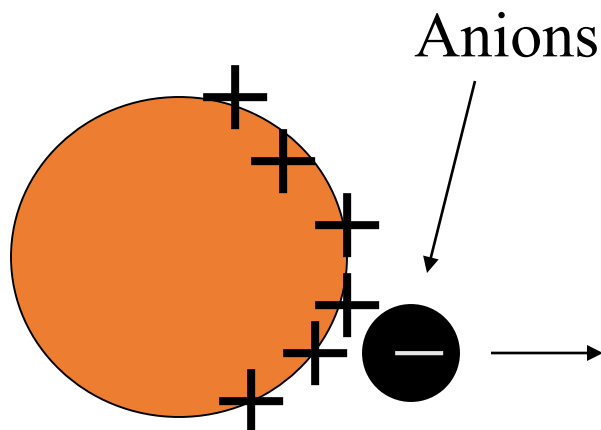
Direct Sorption/  
Hydrophobic or Electrostatic



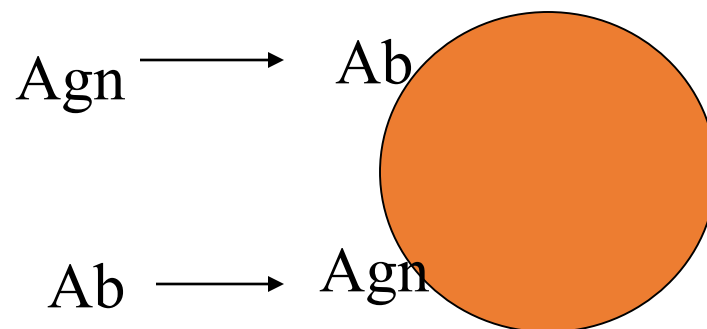
Cation Exchange



Anion Exchange



Antibody/Antigen

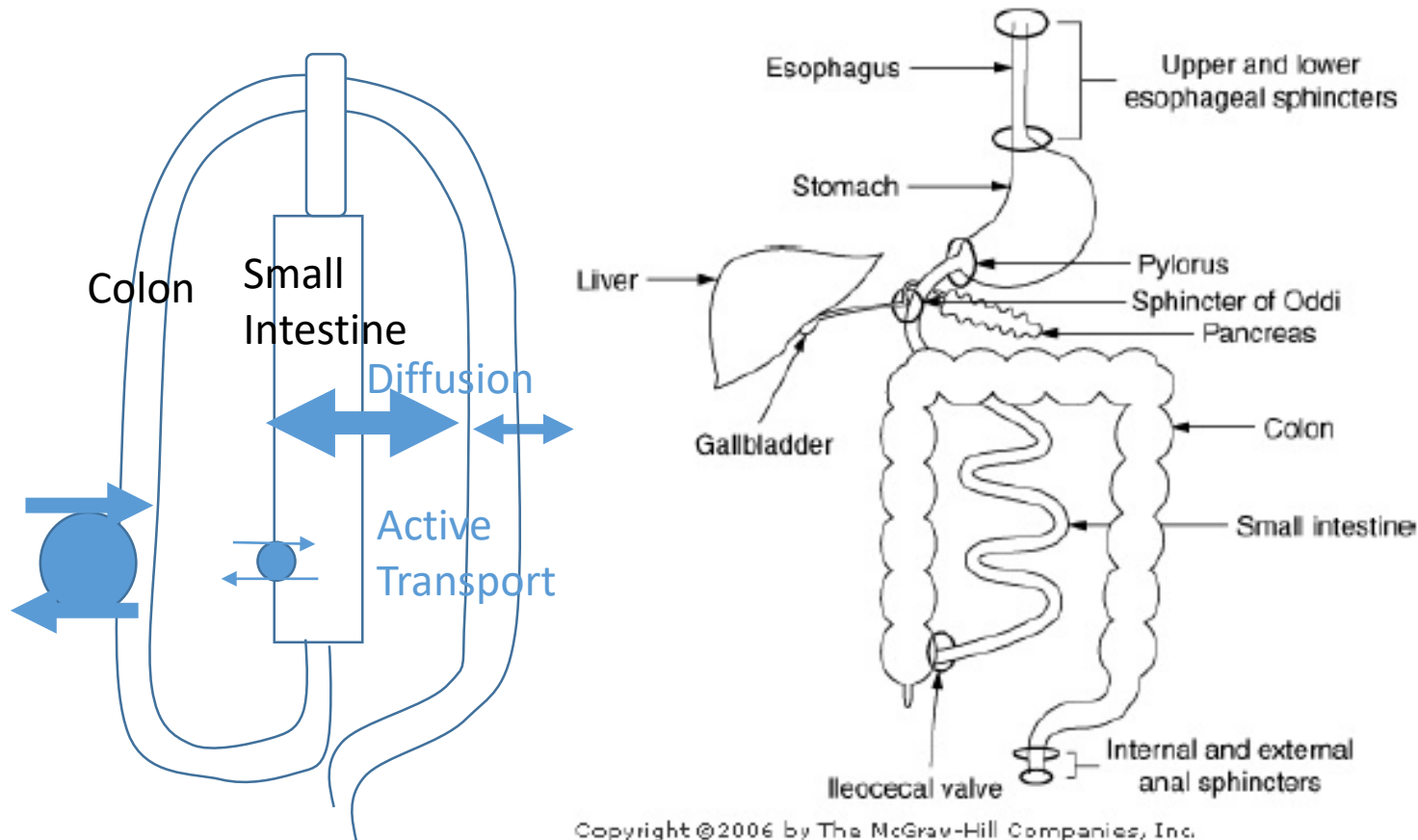


# Overview of the Gut and Absorption for Electrolytes

Author

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Inscience 2019



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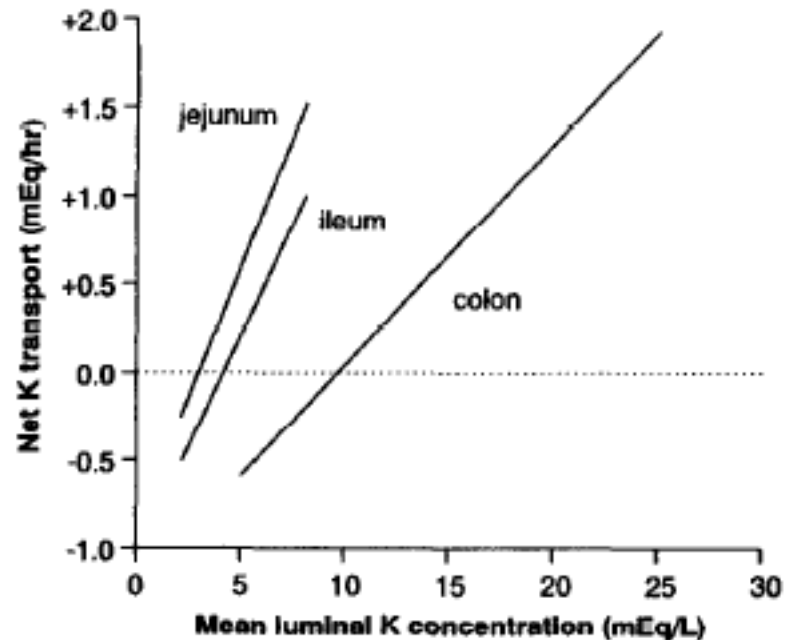
Overall anatomy of the gastrointestinal system and division of the GI tract into functional segments by sphincters and valves.

# Transfer of potassium is passive in the small intestine, active in the colon with passive “back-leak”

## Pathophysiology of Potassium Absorption and Secretion by the Human Intestine

RAJIV AGARWAL, REKHA AFZALPURKAR, and JOHN S. FORDTRAN  
Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas

**GASTROENTEROLOGY 1994;107:548–571**



**Figure 2.** Regression lines for  $K^+$  transport in various regions of the human intestine under experimental steady-state perfusion. Data on  $K^+$  transport in the small intestine represent 30-cm segments of jejunum or ileum<sup>36</sup>; in the colon, the transport rates are for the entire organ.<sup>35</sup> Data on colon  $K^+$  transport were reported as microequivalents per minute but have been mathematically converted to milliequivalents per hour. +, net absorption; –, net secretion.

# Concentration of Electrolytes in Colon

Dr Oliver Wrong  
and Miss Ann Metcalfe-Gibson  
(Department of Medicine,  
Postgraduate Medical School of London)

## The Electrolyte Content of Faeces<sup>1</sup>

<sup>1</sup>Much of the material used in this paper has previously appeared in *Clinical Science* (Wrong *et al.* 1965) and is reproduced here with kind permission

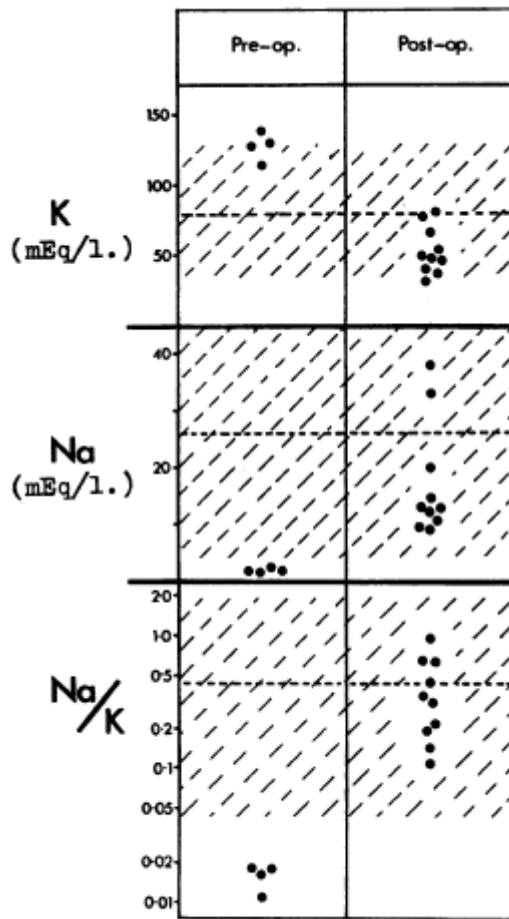


Fig 2 Primary aldosteronism: composition of faecal dialysate before and after removal of adrenal adenoma

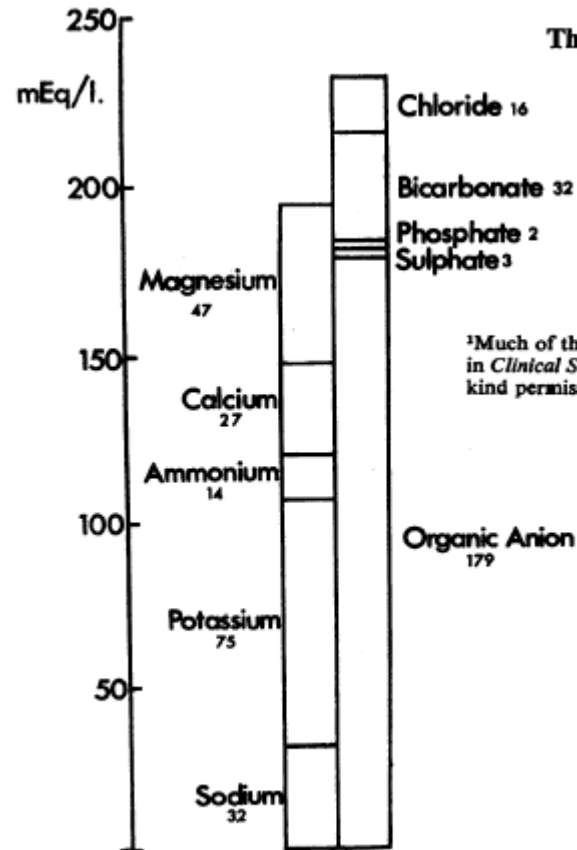
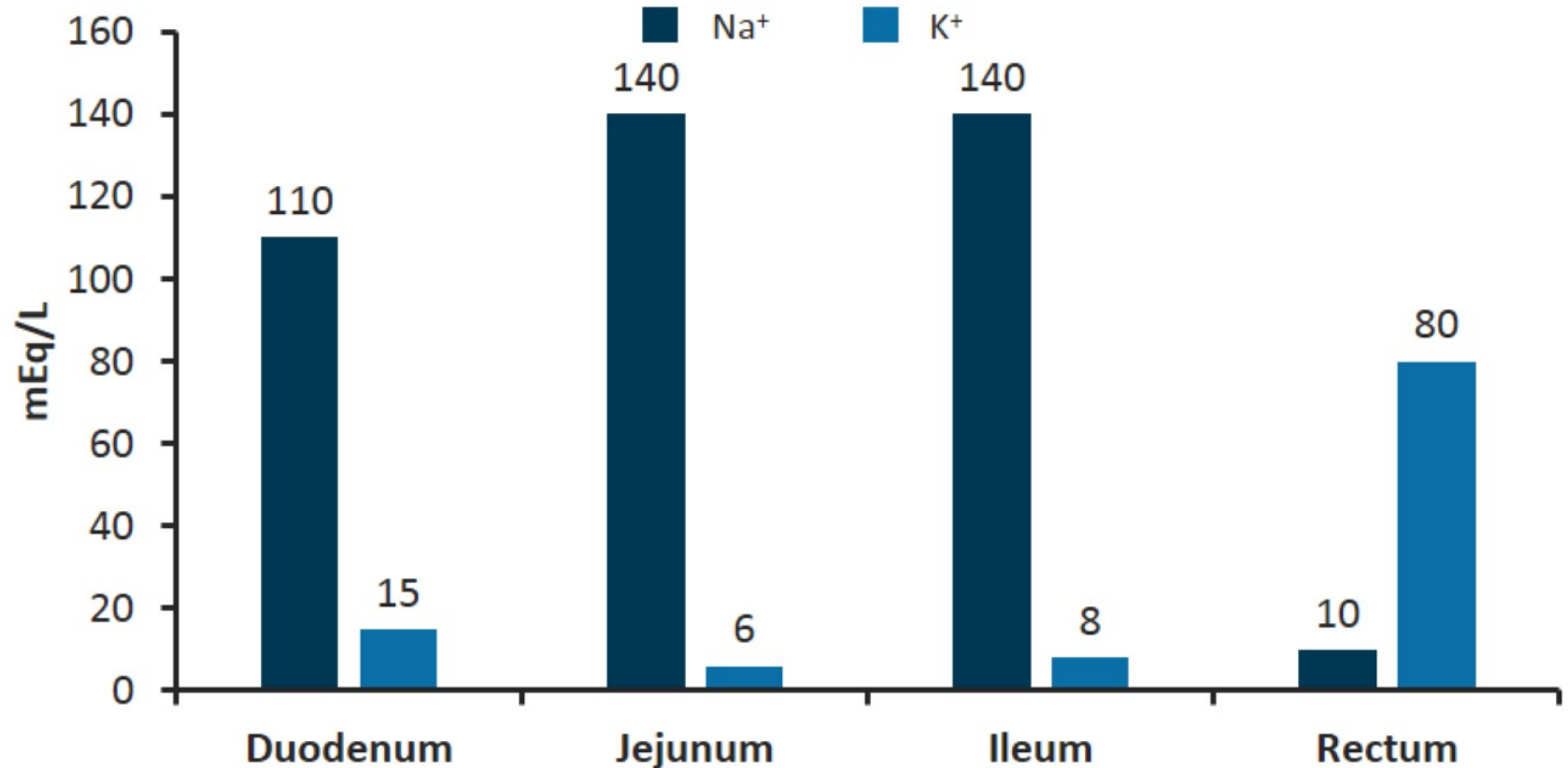
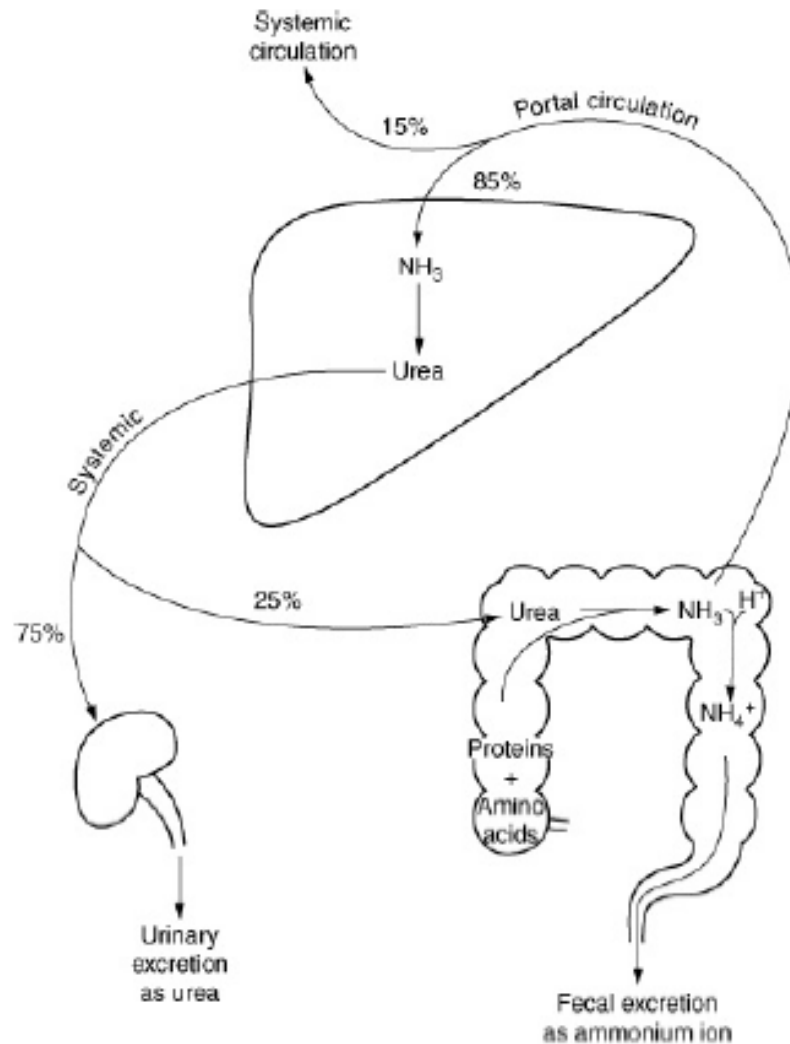


Fig 1 Ionogram of normal faecal dialysate derived from mean concentrations

# K<sup>+</sup> and Na<sup>+</sup> Concentrations in the GI Tract



# Urea Passage from Blood to Gut



## Author

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Whole body ammonia homeostasis in health. The majority of ammonia produced by the body is excreted by the kidneys in the form of urea.

Small and charged uremic toxins that have high abundance in the gut, due to ingestion or transfer from blood

1. Potassium
2. Phosphate
3. Sodium
4. Hydrogen
5. Urea and ammonium



# 1. Potassium

## Panelists

### **Peter A. McCullough, MD, MPH**

Vice Chief of Medicine  
Baylor University Medical Center  
Dallas, Texas

### **Joseph Stephen Alpert, MD**

Professor of Medicine  
University of Arizona Sarver Heart  
Center  
University of Arizona  
Tucson, Arizona

### **Mikhail Kosiborod, MD**

Professor of Medicine  
Saint Luke's Mid America Heart  
Institute  
University of Missouri-Kansas City  
Kansas City, Missouri

# Overview of Hyperkalemia

- Definition<sup>[a]</sup>
  - Serum K<sup>+</sup> concentration greater than 5.0 mEq/L
- Prevalence<sup>[a]</sup>
  - General population: 2% to 3%
  - CKD: up to 50%
- Clinical Effects<sup>[b]</sup>
  - Widening of QRS complex
  - Atrioventricular conduction block
  - Ventricular fibrillation
  - Asystole
- Patients at Risk<sup>[c]</sup>
  - CKD
  - Diabetes
  - Heart failure
  - Advanced age

# RAAS Inhibitor Use and Risk of Hyperkalemia

- RAAS inhibitor therapy benefits:
  - Cardioprotective
  - Renoprotective
  - Antihypertensive
- RAAS inhibitors increase hyperkalemia risk
  - By virtue of their mechanism of action

# Diagnostic Workup

## *Causes of Hyperkalemia*

- Impaired renal excretion of  $K^+$ 
  - Renal insufficiency or failure
  - Mineralocorticoid deficiency
  - Addison disease
  - Type 4 renal tubular acidosis
  - Hereditary enzyme deficiencies
  - Drugs
    - Trimethoprim, pentamidine,  $K^+$ -sparing diuretics (amiloride, triamterene)
    - ACE inhibitors, ARBs, NSAIDs, COX-2 inhibitors, heparin, tacrolimus
    - Spironolactone, eplerenone
    - Cyclosporine
- Shift of  $K^+$  into the extracellular space
  - Insulin deficiency
  - Hypertonicity (uncontrolled diabetes)
  - Acidosis
  - Tumor lysis syndrome
  - Drugs
    - $\beta$ -Blockers, digoxin

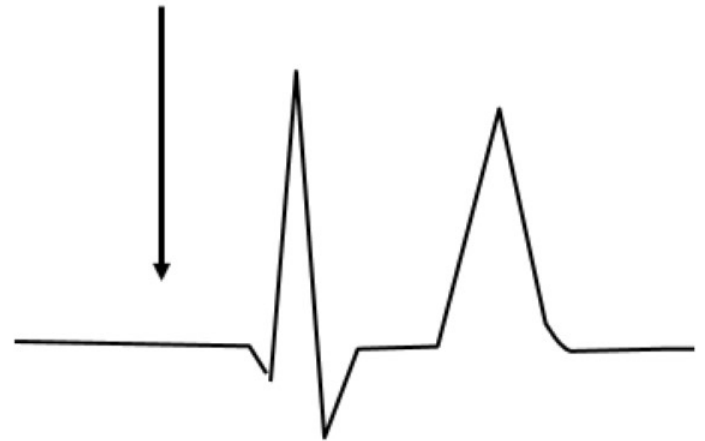
# Diagnostic Workup

## *Electrocardiographic Features*

Tall peaked T wave



Loss of P wave



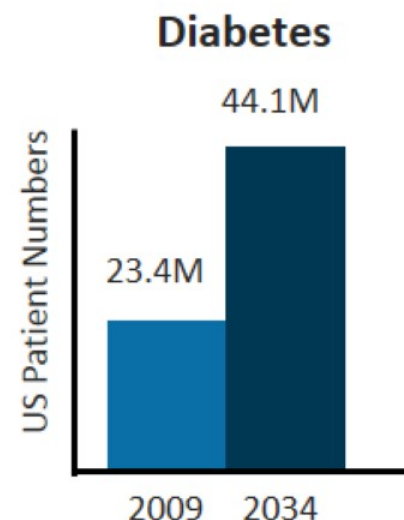
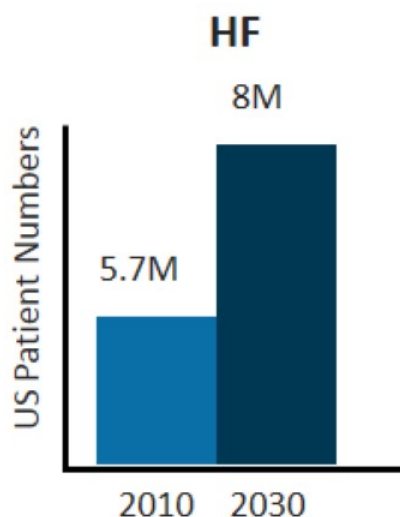
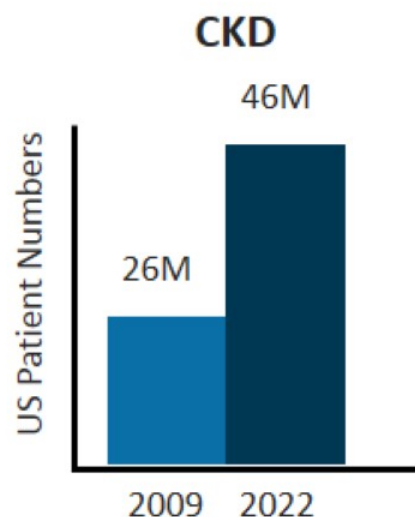
Widening of QRS complex





# Increasing Incidence of Hyperkalemia

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



- Reduced kidney function is the most common cause of uncontrolled K<sup>+</sup>
- Poor cardiac output leads to renal insufficiency
- Insulin deficiency reduces ability to shift K<sup>+</sup> into cells

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

# Acute Treatment of Hyperkalemia

	Calcium	Alkalinization	Glucose and insulin	Loop diuretics	Albuterol
<b>Overview</b>	<ul style="list-style-type: none"> <li>• First-line treatment if ECG is abnormal</li> <li>• Increases threshold potential</li> </ul>	<ul style="list-style-type: none"> <li>• Increases urinary and blood pH and causes temporary K<sup>+</sup> shift from extracellular to intracellular fluid</li> </ul>	<ul style="list-style-type: none"> <li>• Insulin given intravenously</li> <li>• Increases glucose transfer into cells</li> <li>• Brings K<sup>+</sup> with it</li> </ul>	<ul style="list-style-type: none"> <li>• Cause renal loss of K<sup>+</sup></li> </ul>	<ul style="list-style-type: none"> <li>• 10 to 20 mg by nebulizer over 10 min</li> <li>• Shifts K<sup>+</sup> into the cells, additive to the effect of insulin</li> <li>• No effect on total body K<sup>+</sup></li> </ul>
<b>Advantages</b>	<ul style="list-style-type: none"> <li>• Acts quickly, can be life-saving</li> <li>• Rapid onset (&lt;5 min)</li> </ul>	<ul style="list-style-type: none"> <li>• Onset in min, lasts 15 to 30 min</li> </ul>	<ul style="list-style-type: none"> <li>• Onset within 30 min of administration</li> </ul>		<ul style="list-style-type: none"> <li>• Onset in 15 to 30 min of administration</li> </ul>
<b>Disadvantages</b>	<ul style="list-style-type: none"> <li>• Only effective for 30 min</li> </ul>	<ul style="list-style-type: none"> <li>• Likely to work only if underlying acidosis is present</li> <li>• Only effective for 30 min</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of hypoglycemia</li> <li>• Only effective for 2 h</li> </ul>	<ul style="list-style-type: none"> <li>• Lowers K<sup>+</sup> by inconsistent amount</li> <li>• Effects are slow (20 to 60 min to begin)</li> <li>• Does not work in renal failure</li> </ul>	<ul style="list-style-type: none"> <li>• May cause a brief initial rise in serum K<sup>+</sup></li> </ul>

# Dietary Management of Hyperkalemia

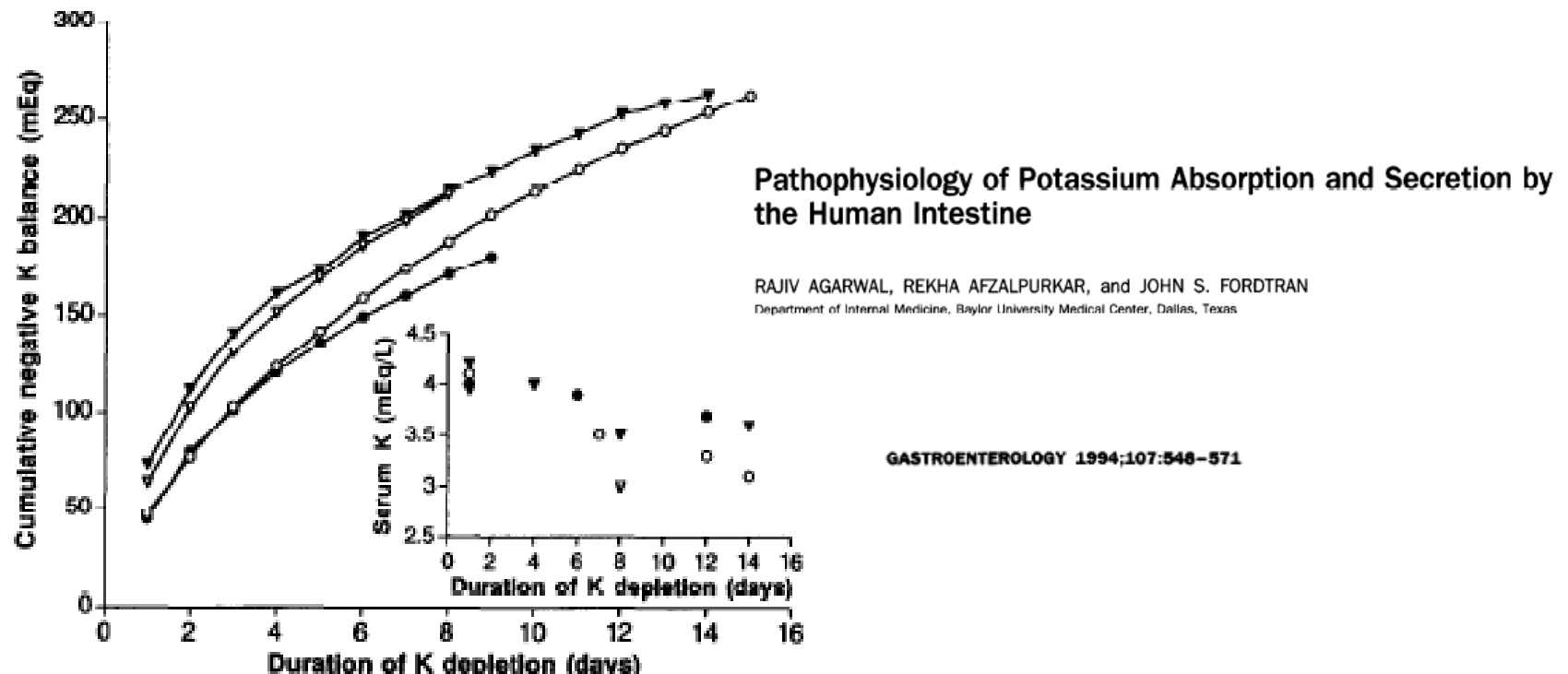
- Dietary K<sup>+</sup> restriction
  - Recommended to less than 2.4 g/d in patients with stage 3 or higher CKD
  - Patients at risk for hyperkalemia should receive comprehensive dietary K<sup>+</sup> education
- DASH diet
  - Overall effects of DASH diet seem beneficial
  - Patients with CKD or diabetes mellitus may be placed at increased risk for hyperkalemia and its consequences



# Management of Chronic Hyperkalemia Before Era of New K<sup>+</sup> Binders

- Assess renal function
- Titrate or discontinue RAAS inhibitors
- Prescribe low-K<sup>+</sup> diet
- Prescribe diuretic therapy

Dietary K restriction does remove significant K from body, but very slowly changes serum K.



**Figure 1.** Cumulative negative  $K^+$  balance induced by a zero  $K^+$  diet.<sup>15</sup> The zero  $K^+$  diet was prepared by treating a milk-based diet with a  $K^+$  exchange resin and fed to four normal volunteers. Each symbol represents one volunteer. The dietary  $Na^+$  content was variable. Data shown represent the combined urinary and fecal  $K^+$  losses. The inset shows the decrease in serum  $K^+$  in each subject.

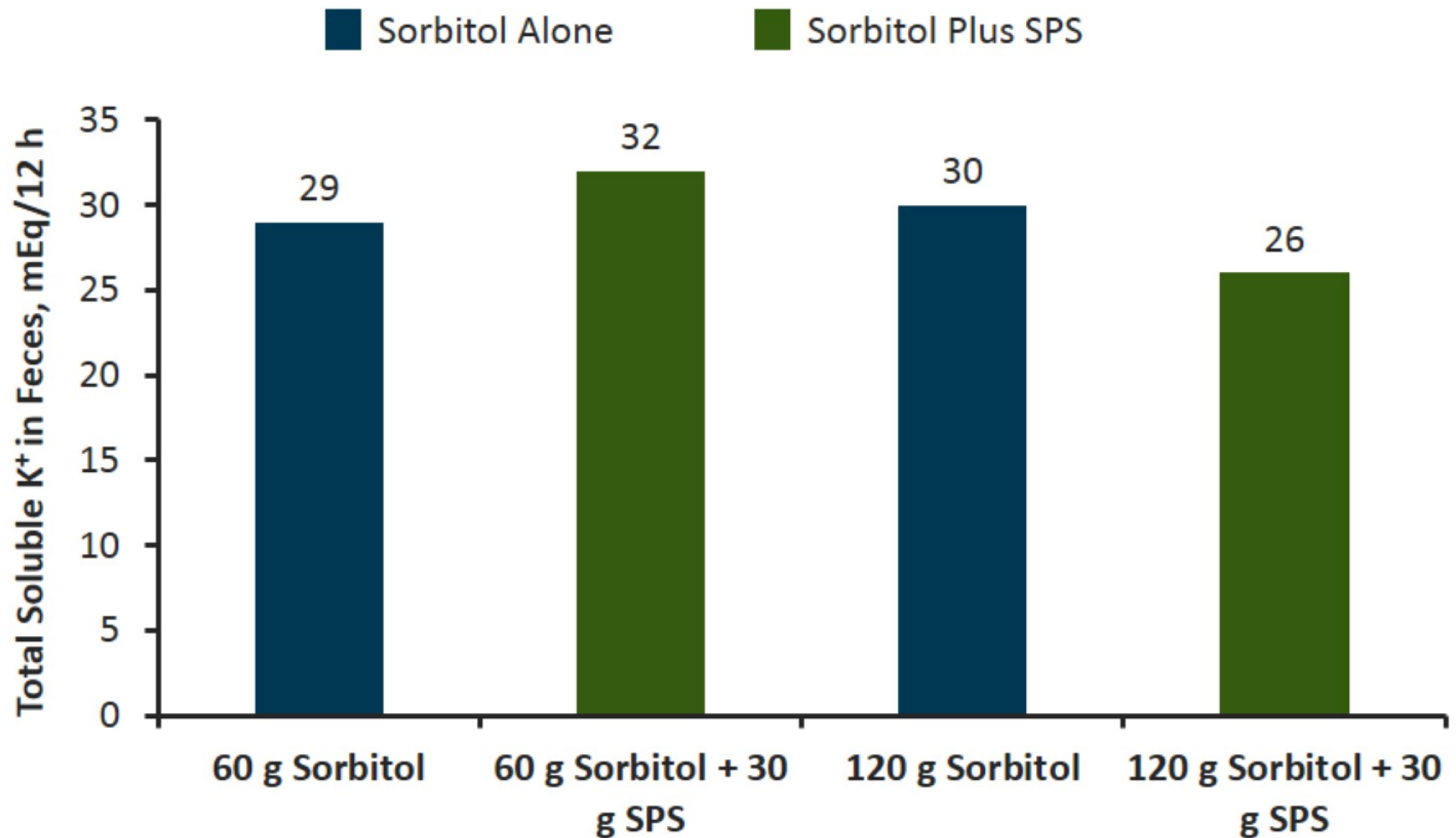
# SPS

- Indicated for the treatment of hyperkalemia
- Cation-exchange resin
  - Exchanges  $\text{Na}^+$  for  $\text{H}^+$  in stomach
  - Then exchanges for  $\text{H}^+$  for other cations in large intestine
- Efficacy
  - Observed decreases in serum  $\text{K}^+$  of 0.82 to 1.14 mEq/L depending on dose
- Safety
  - Risk of acute bowel necrosis, hypernatremia, diarrhea, and GI intolerance

## SPS (cont)

- In use since the early 1960s
- Approved before current era of evidence-based medicine
- Minimal efficacy data
- Safety
  - Reports of highly fatal upper and lower GI transmural necrosis with SPS combined with 70% sorbitol
  - Occurs in 0.1% to 0.3% of patients

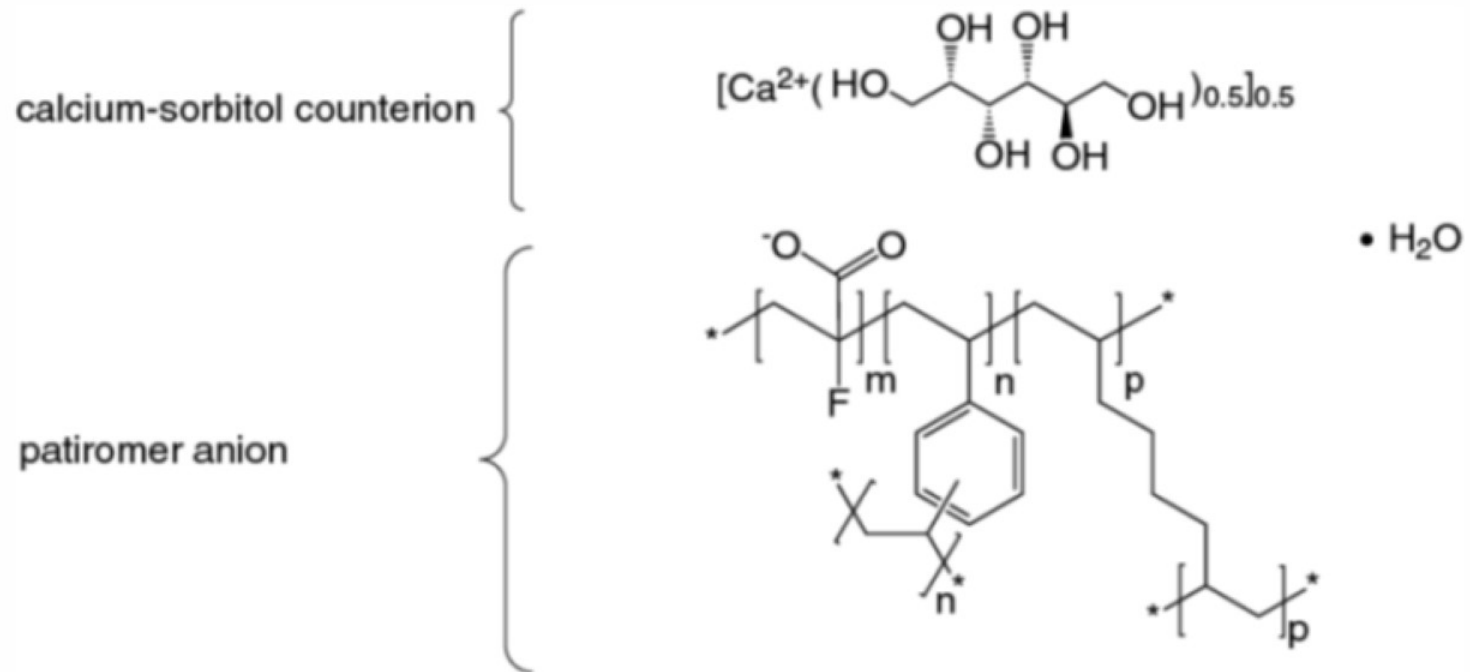
# SPS Plus Sorbitol vs Sorbitol Alone



# New K<sup>+</sup> Binder

## *Patiromer*

- FDA approved for the treatment of hyperkalemia
- Nonabsorbed cation exchange polymer that binds K<sup>+</sup> in exchange for Ca<sup>2+</sup> predominantly in the distal colon and increases fecal K<sup>+</sup> excretion



m = number of 2-fluoro-2-propenoate groups, m = 0.91; n, p = number of crosslinking groups, n + p = 0.09; H<sub>2</sub>O = associated water; \* = indicates an extended polymeric network.

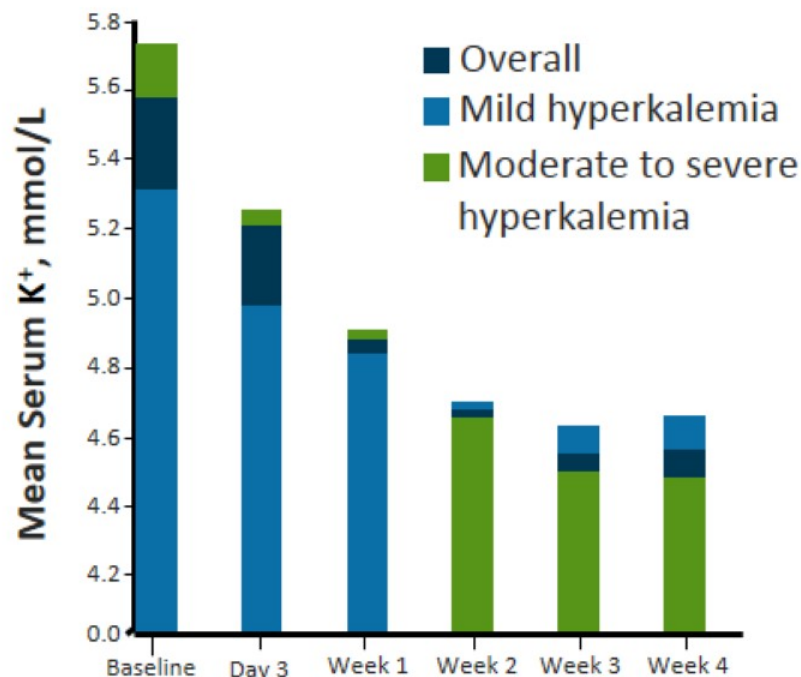
VELTASSA® PI 2016; Pitt B, et al. *Eur Heart J.* 2011;32:820-828.



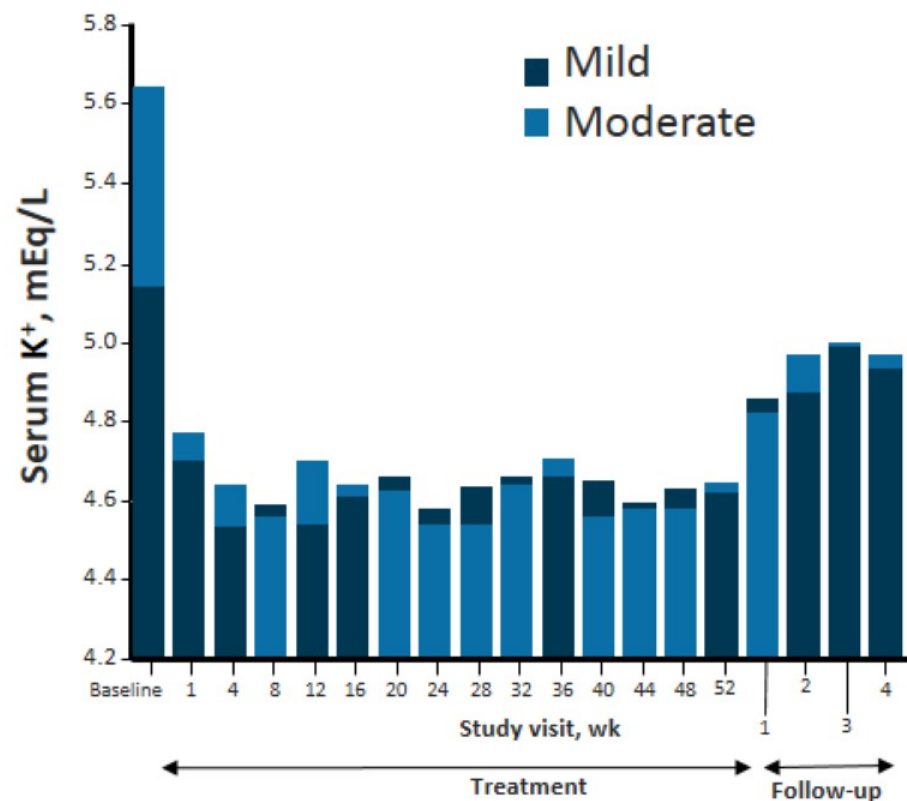
# Efficacy of Patiromer

## *Maintains Normal $K^+$ Levels Up to 1 Year*

OPAL-HK<sup>[a]</sup>



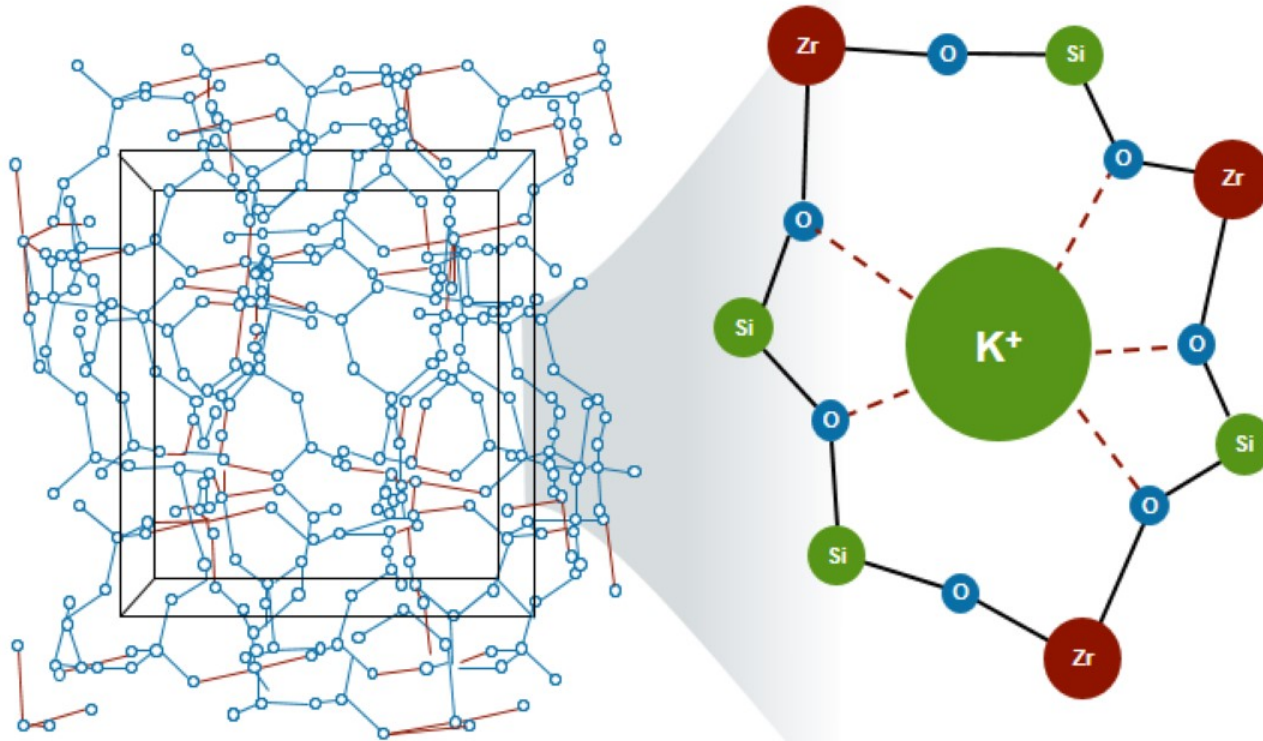
AMETHYST-DN<sup>[b]</sup>



# Emerging $K^+$ Binder

## *Sodium Zirconium Cyclosilicate (ZS-9)*

- Inorganic cation exchanger with a crystalline structure that entraps  $K^+$  along the entire length of the GI tract

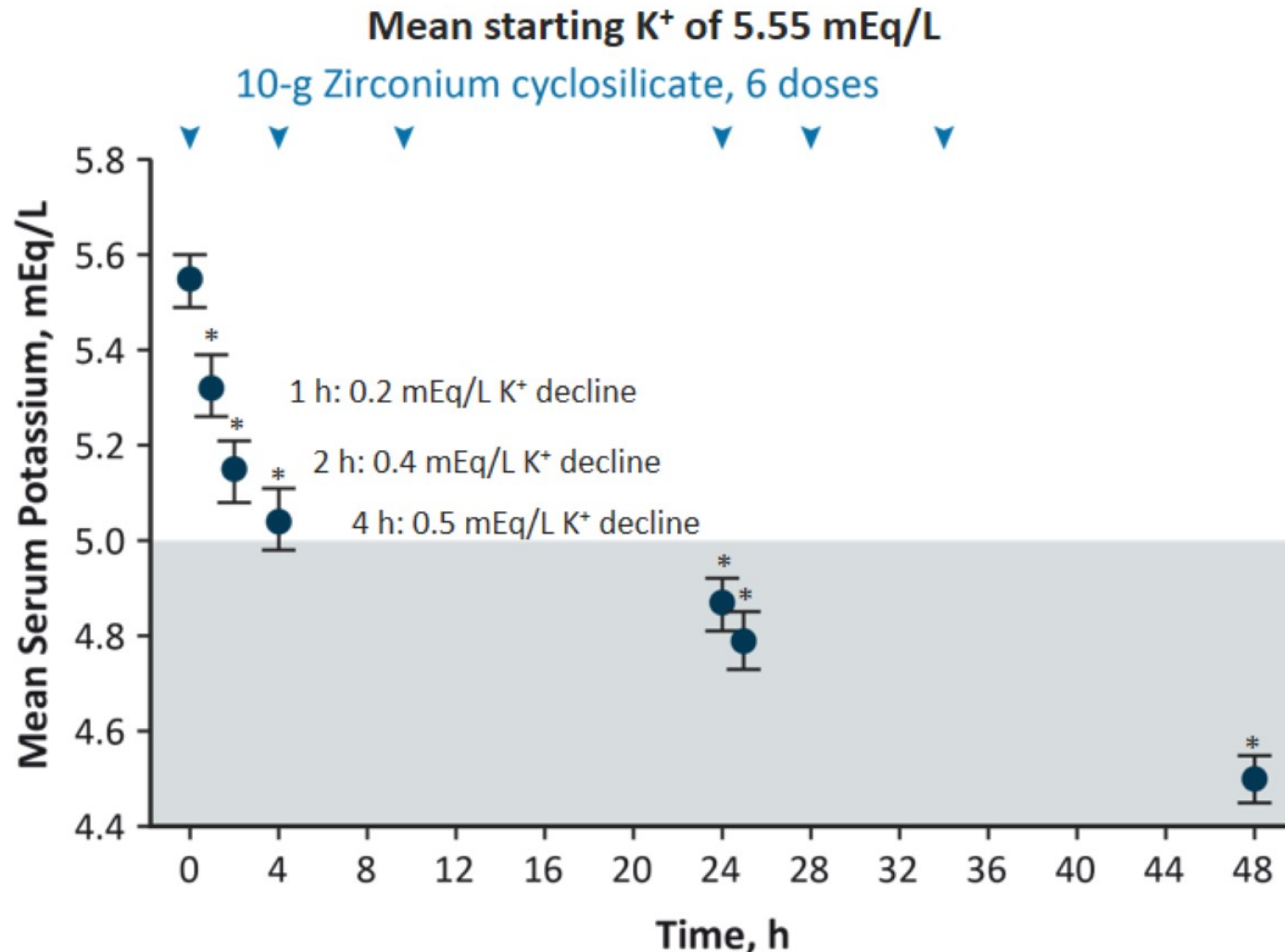


Average width of micropore opening = 3 Å



# Efficacy of ZS-9

## *During 48-h Induction Phase in HARMONIZE*



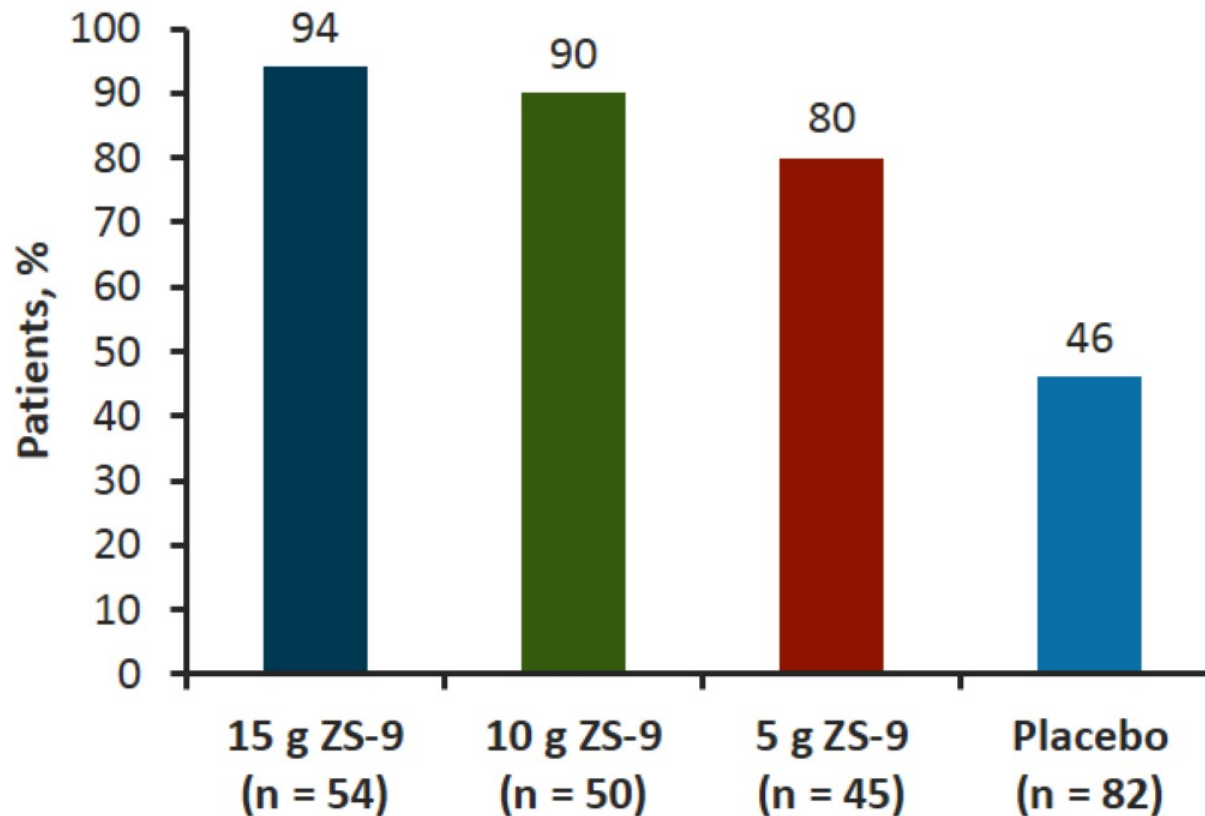
Reproduced with permission from Kosiborod M, et al. *JAMA* 2014;312:2223-2233.

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# HARMONIZE

## *Efficacy During Randomized Phase*

- Proportion of patients with mean serum K<sup>+</sup> less than 5.1 mEq/L during days 8 to 29



\* $P < .001$ .

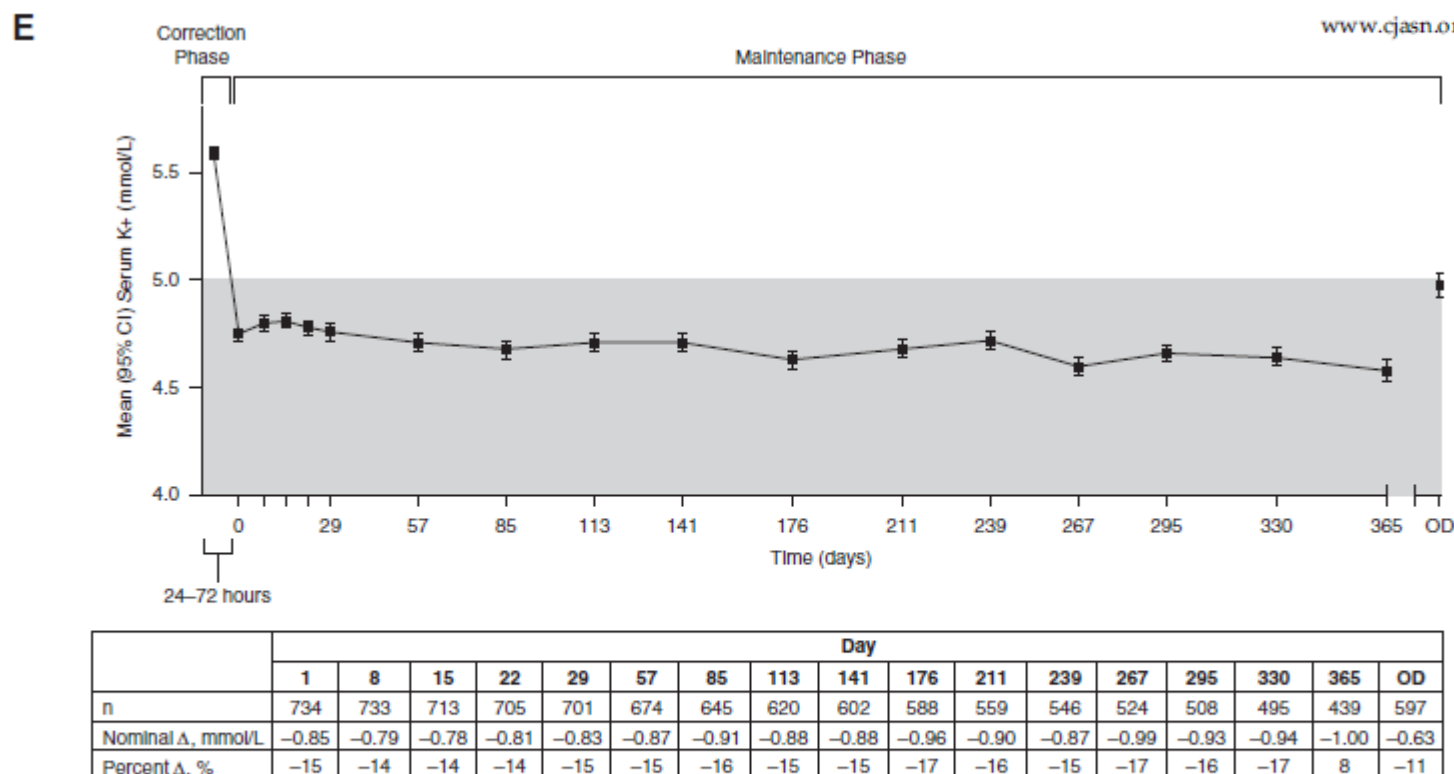
Kosiborod M, et al. *JAMA* 2014;312:2223-2233.

# Maintenance of normal K with daily zirconium cyclosilicate

## Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia A 12-Month Phase 3 Study

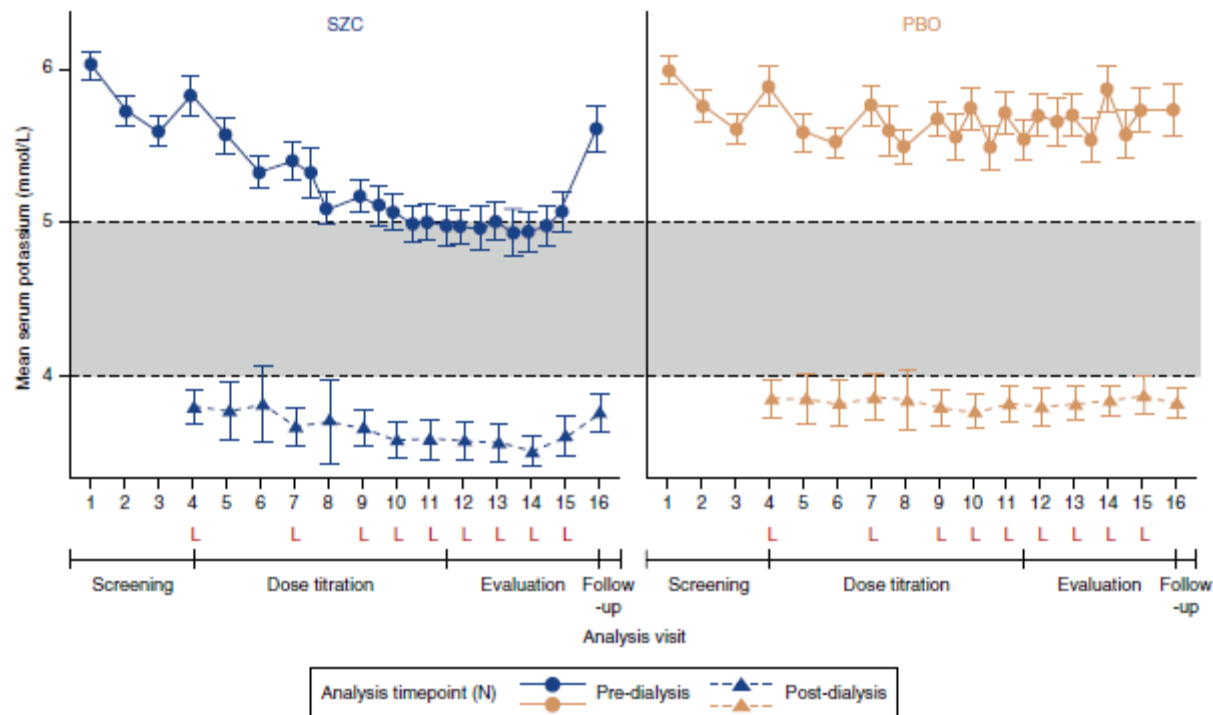
Bruce S. Spinowitz,<sup>1</sup> Steven Fishbane,<sup>2</sup> Pablo E. Pergola,<sup>3</sup> Simon D. Roger,<sup>4</sup> Edgar V. Lerma,<sup>5</sup> Javed Butler,<sup>6</sup> Stephan von Haehling,<sup>7</sup> Scott H. Adler,<sup>8</sup> June Zhao,<sup>9</sup> Bhupinder Singh,<sup>10</sup> Philip T. Lavin,<sup>11</sup> Peter A. McCullough,<sup>12</sup> Mikhail Kosiborod,<sup>13,14,15</sup> and David K. Packham,<sup>16,17</sup> on behalf of the ZS-005 Study Investigators

www.cjasn.org Vol 14 June, 2019



**Figure 3. |** Proportion of participants with mean serum potassium (K<sup>+</sup>) values (A) ≤5.1, (B) ≤5.5, and (C) 3.5–5.5 mmol/L by visit in the maintenance-phase intention-to-treat (ITT) population; (D) box and whisker plots of median, interquartile range, minimum, and maximum serum K<sup>+</sup> values at months 3–12, 6–9, and 9–12 in the maintenance-phase ITT population; and (E) mean serum K<sup>+</sup> over time in the maintenance-phase ITT population. The ITT population included all participants who received sodium zirconium cyclosilicate (SZC) and had any postbaseline

# Reducing pre-dialysis hyperkalemia with zirconium cyclosilicate

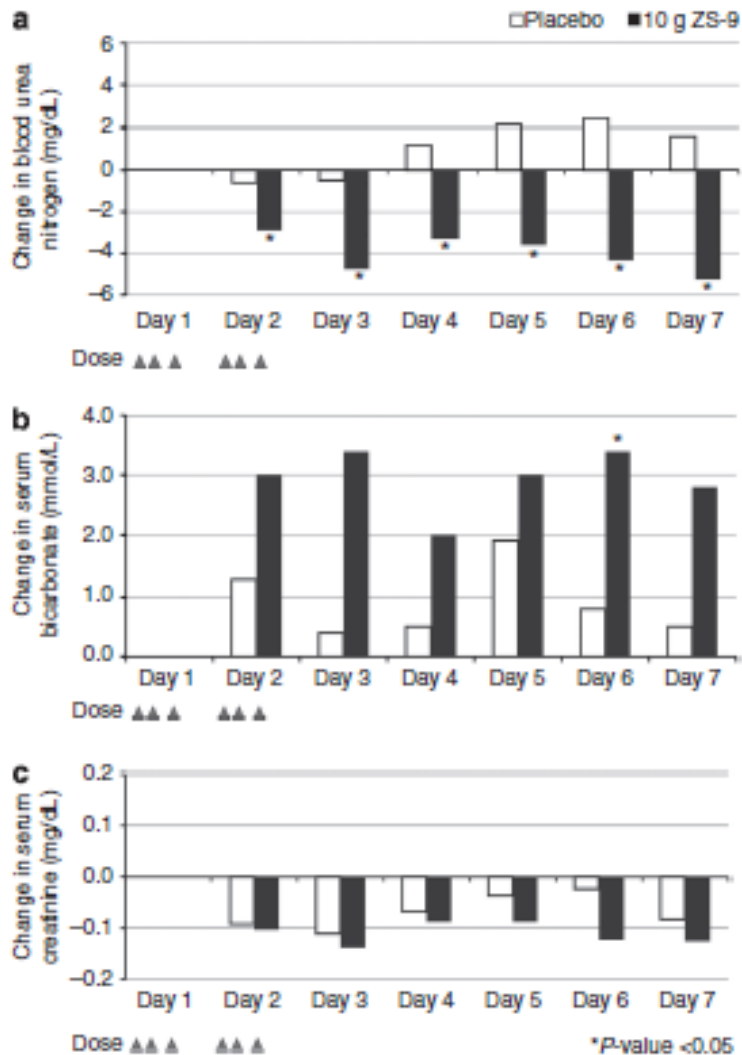


**Figure 3.** Mean pre- and postdialysis  $\text{SK}^+$  values were lower with SZC than with PBO both at the end of the titration period and during the evaluation period. Postdialysis me

## A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study of Sodium Zirconium Cyclosilicate for Reducing the Incidence of Predialysis Hyperkalemia

JASN 30: 1723–1733, 2019.

Steven Fishbane,<sup>1</sup> Martin Ford,<sup>2</sup> Masafumi Fukagawa,<sup>3</sup> Kieran McCafferty,<sup>4</sup> Anjay Rastogi,<sup>5</sup> Bruce Spinowitz,<sup>6</sup> Konstantin Staroselskiy,<sup>7</sup> Konstantin Vishnevskiy,<sup>8</sup> Vera Lisovskaja,<sup>9</sup> Ayman Al-Shurbaji,<sup>10</sup> Nicolas Guzman,<sup>11</sup> and Sunil Bhandari<sup>12</sup>



**Figure 5 | Serum parameters in 10-g ZS-9 ( $n = 24$ ) versus placebo ( $n = 30$ ) over 7 days.** Mean change from baseline in (a) blood urea nitrogen, (b) serum bicarbonate, and (c) serum creatinine. Triangles indicate study drug administration (six doses in 48 h), and \* indicates significant difference compared with placebo,  $P < 0.05$ . ZS-9, sodium zirconium cyclosilicate.

20% drop in urea level means removal of about 20% of daily urea generation through the gut. This is about 140 meq of  $\text{NH}_4$  per day, or almost 5 meq/gm ingested ZS-9, much more than expected.

Bicarbonate increase is beneficial in CKD.

Why creatinine dropped is somewhat of a mystery, it could be from binding on ZS-9.

<http://www.kidney-international.org>  
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clinical trial

OPEN

A phase 2 study on the treatment of hyperkalemia in patients with chronic kidney disease suggests that the selective potassium trap, ZS-9, is safe and efficient

Stephen R. Ash<sup>1</sup>, Bhupinder Singh<sup>2,3</sup>, Philip T. Lavin<sup>4</sup>, Fiona Stavros<sup>3</sup> and Henrik S. Rasmussen<sup>3</sup>

# New K<sup>+</sup> Binders

## *Adverse Events*

- Patiromer and ZS-9
  - Adverse events were similar to those seen in placebo groups
    - Mainly GI effects
    - Transitory hypokalemia
- Patiromer<sup>[a]</sup>
  - Hypomagnesemia
  - Black box warning: administer other oral medications at least 6 h before or 6 h after patiromer<sup>[b]</sup>
- ZS-9<sup>[c]</sup>
  - Edema (dose related)
  - Hypertension
  - Increase in sodium bicarbonate (dose related)

a. Weir M, et al. *N Engl J Med*. 2015;372:211-221; b. VELTASSA® PI 2015;

c. Tumlin J, et al. *J Am Soc Nephrol*. 2015;26:B6.



# Comparison of SPS, Patiromer, and ZS-9

	SPS	Patiromer	ZS-9
<b>Mechanism of action<sup>[a]</sup></b>	Nonspecific cation binding in exchange for Na <sup>+</sup>	Nonspecific cation binding in exchange for Ca <sup>2+</sup>	Selective K <sup>+</sup> binding in exchange for Na <sup>+</sup> and H <sup>+</sup>
<b>Time to normokalemia</b>	Unconfirmed efficacy	Achieves normokalemia within 1 wk <sup>[b]</sup>	84% of patients normokalemic within 24 h <sup>[c]</sup>
<b>Onset of effect</b>	Unknown (generally hours to days)	K <sup>+</sup> levels reduced significantly 7 h after first dose <sup>[d]</sup>	Median time to normalization 2.2 h <sup>[c]</sup>
<b>Drug-drug interactions</b>	Interactions with antacids, laxatives, digitalis, sorbitol, lithium, and thyroxine <sup>[e]</sup>	FDA warning: must be taken 6 h apart from other oral drugs <sup>[f]</sup>	No clinically meaningful drug-drug interactions to date
<b>Location of K<sup>+</sup> binding<sup>[a]</sup></b>	Colon	Distal colon predominantly	Likely to be upper and lower GI tract (not proved)
<b>Safety/tolerability</b>	Poor tolerability/adherence, associated with colonic necrosis, hypokalemia, electrolyte disturbances, and GI effects <sup>[g]</sup>	Well tolerated but may cause hypomagnesemia and GI effects, such as mild-to-moderate constipation <sup>[h]</sup>	Well tolerated but may cause edema and mild-to-moderate GI effects <sup>[i]</sup>

a. Garimella PS, et al. *Am J Kidney Dis*. 2016;67:545-547; b. Weir MR, et al. *N Engl J Med*. 2015;372:211-221; c. Kosiborod M, et al. *JAMA*. 2014;312:2223-2233; d. Bushinsky DA, et al. *Kidney Int*. 2015;88:1427-1433; e. Drugs.com website; f. VELTASSA® PI. 2016; g. Lepage L, et al. *Clin J Am Soc Nephrol*. 2015;10:2136-2142; h. Bakris GL, et al. *JAMA*. 2015;314:151-161; i. Packham DK, et al. *N Engl J Med* 2015;372:222-231.

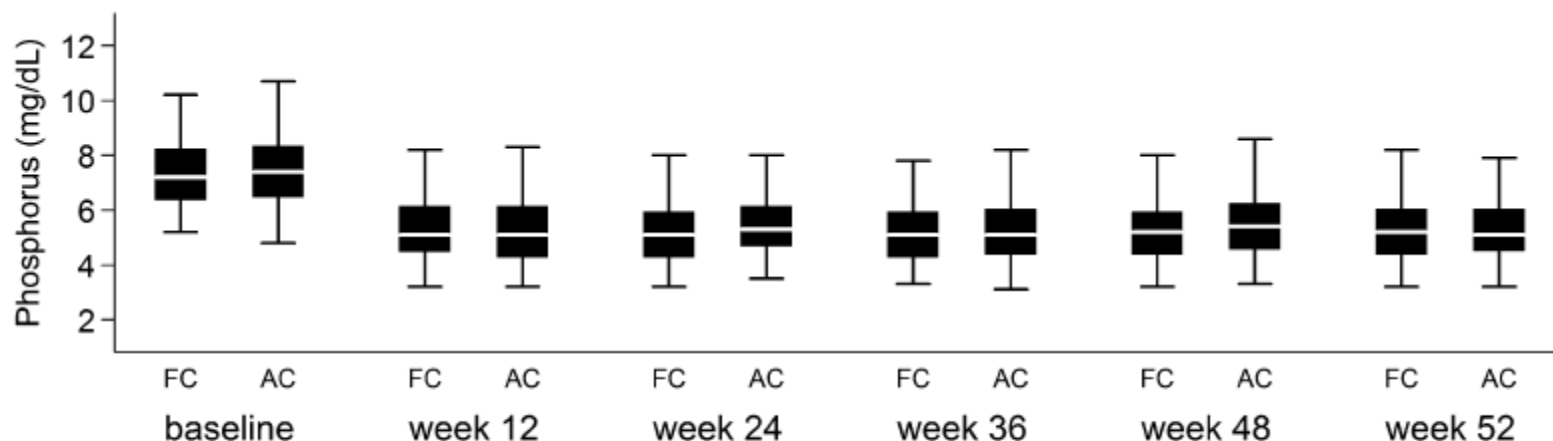
# Closing Comments

- With the new and emerging  $K^+$  binders, hyperkalemia may be less of a factor, and:
  - RAAS inhibitor therapy may be optimally dosed
  - Visits to the ED and urgent care may decrease
  - Fear of taking and prescribing RAAS inhibitor therapy may be alleviated
  - Patients will have more freedom to eat a healthy diet to improve their quality of life



## 2. Phosphate

and **active control** groups (Figure 2). In the **active control** group, 73 subjects were on sevelamer, 36 subjects were on calcium acetate, and 40 subjects were on both. The median daily dose (pill count) of ferric citrate was 8.0 tablets/d versus 7.7 tablets/d for subjects on **active control** taking calcium ac-



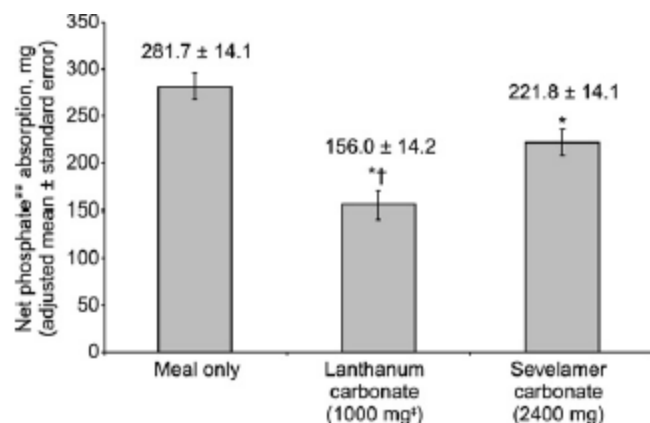
**Figure 2.** Serum phosphorus levels (milligrams per deciliter) by study time point during the 52-week active control period, with missing values imputed using the last follow-up observation carried forward. Box plots display 5th, 25th, 50th, 75th, and 95th percentiles. Under the repeated measures mixed effects model, the mean difference in serum phosphorus between the ferric citrate and active control groups over weeks 12, 24, 36, 48, and 52 was  $-0.0127$  mg/dl (95% confidence interval,  $-0.056$  to  $0.030$  mg/dl). AC, active control; FC, ferric citrate.

### Ferric Citrate Controls Phosphorus and Delivers Iron in Patients on Dialysis

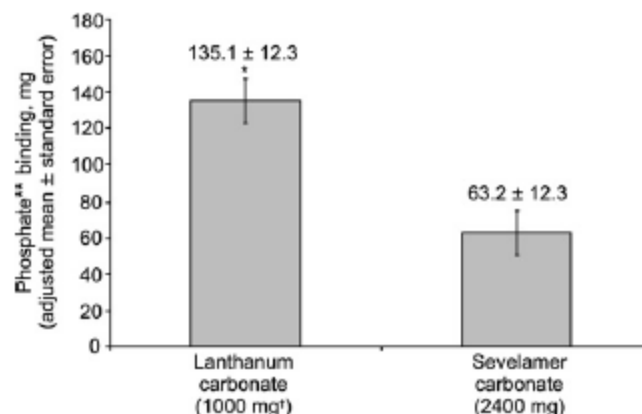
Julia B. Lewis,\* Mohammed Sika,\* Mark J. Koury,<sup>†</sup> Peale Chuang,<sup>‡</sup> Gerald Schulman,\* Mark T. Smith,<sup>§</sup> Frederick C. Whittier,<sup>||</sup> Douglas R. Linfert,<sup>¶</sup> Claude M. Galphin,\*\* Balaji P. Athreya,<sup>††</sup> A. Kaldun Kaldun Nossuli,<sup>‡‡</sup> Ingrid J. Chang,<sup>§§</sup> Samuel S. Blumenthal,<sup>|||</sup> John Manley,<sup>¶¶</sup> Steven Zeig,<sup>\*\*\*</sup> Kotagal S. Kant,<sup>†††</sup> Juan Jose Olivero,<sup>‡‡‡</sup> Tom Greene,<sup>§§§</sup> and Jamie P. Dwyer,\* for the Collaborative Study Group

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# Lanthanum versus sevelamer



**Figure 3.** Lanthanum carbonate significantly decreased net phosphate absorption compared with sevelamer carbonate. \* $P < 0.001$  versus meal only; † $P < 0.001$  versus sevelamer carbonate.  $N = 18$ . †Containing 1,000 mg of elemental lanthanum. \*\*Measured as phosphorus. Conversion factor for phosphorus in milligrams to millimoles,  $\times 0.0323$ .



**Figure 4.** Lanthanum carbonate binds significantly more phosphate than sevelamer carbonate. \* $P < 0.001$  versus sevelamer carbonate.  $N = 18$ . †Containing 1,000 mg of elemental lanthanum. \*\*Measured as phosphorus. Conversion factor for phosphorus in milligrams to millimoles,  $\times 0.0323$ .

## Comparison of Dietary Phosphate Absorption After Single Doses of Lanthanum Carbonate and Sevelamer Carbonate in Healthy Volunteers: A Balance Study

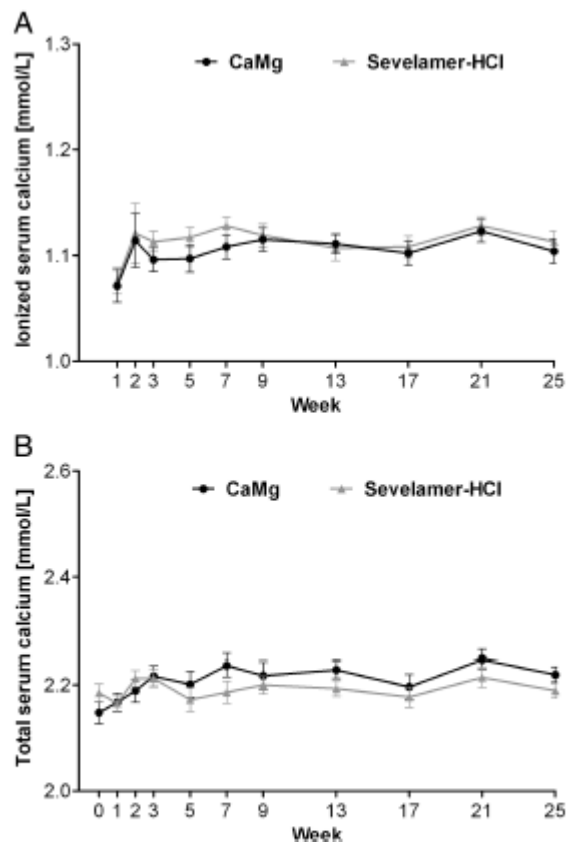
Am J Kidney Dis. 2011;xx(x):xxx

Patrick Martin, MD,<sup>1</sup> Phillip Wang, PhD,<sup>1</sup> Antoine Robinson, MSN, CRNP,<sup>1</sup>  
Lynne Poole, MSc,<sup>2</sup> Jeffrey Dragone, MS,<sup>1</sup> Michael Smyth, FRCS, MRCGP,<sup>2</sup> and  
Raymond Pratt, MD<sup>1</sup>

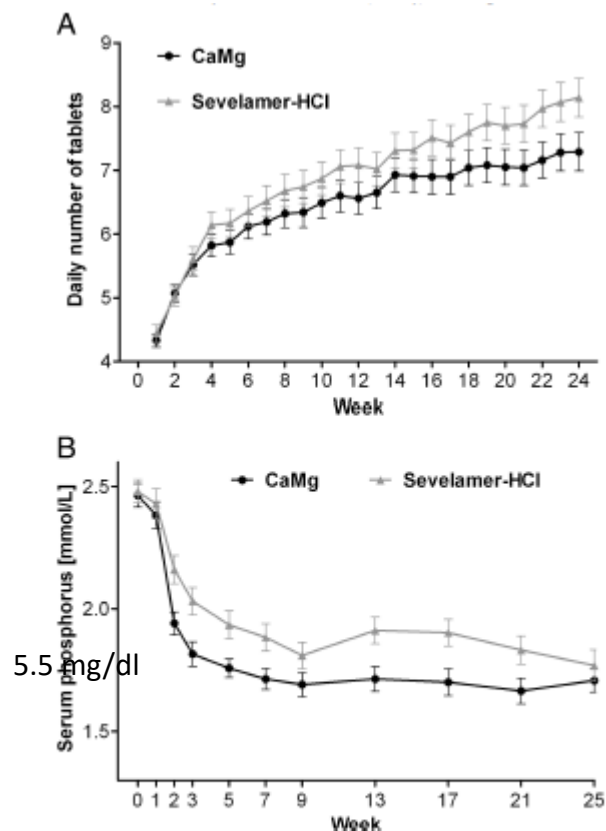
# Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability

Angel L.M. de Francisco<sup>1</sup>, Michael Leijde<sup>2</sup>, Adrian C. Covic<sup>3</sup>, Markus Ketteler<sup>4</sup>, Ewa Benedyk-Lorens<sup>5</sup>, Gabriel M. Mircescu<sup>6</sup>, Cäcilia Scholz<sup>7</sup>, Pedro Ponce<sup>8</sup> and Jutta Passlick-Deetjen<sup>9</sup>

## Ca-Mg Acetate



**Fig. 3.** (A) Time course of ionized serum calcium of the CaMg group ( $n = 120$ ) and of the sevelamer-HCl group ( $n = 119$ ) (FAS;  $P = 0.9173$  (ANCOVA)). (B) Time course of total serum calcium of the CaMg group ( $n = 122$ ) and of the sevelamer-HCl group ( $n = 122$ ) (FAS;  $P = 0.0032$  (ANCOVA)).



**Fig. 2.** (A) Study medication intake per day and group over time in the CaMg group ( $n = 101$ ) and the Sevelamer-HCl group ( $n = 90$ ) (PPS;  $P = 0.0420$  (ANOVA)). (B) Time course of serum phosphorus over 24 weeks for the CaMg group ( $n = 105$ ) and the sevelamer-HCl group ( $n = 99$ ) (PPS).

How about binding of:

3. Sodium

4. Hydrogen

5. Urea and ammonium ?

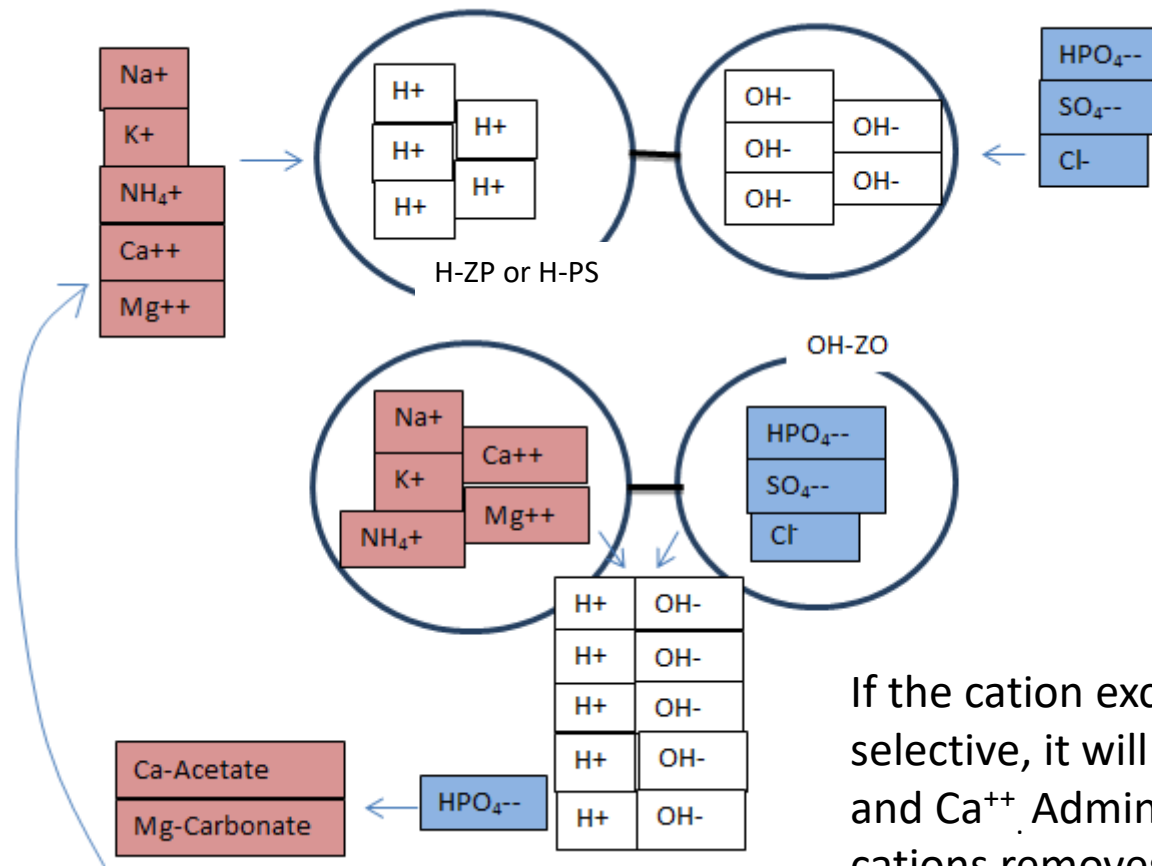
## The Solution?

- An oral sorbent mixture to simultaneously correct abnormalities in serum and total body  $K^+$ ,  $H^+$ ,  $PO_4^{---}$ ,  $Na^+$ , and urea (urea by removing  $NH_4^+$  generated through urease in the gut)
- Implement this oral therapy in late CKD or early ESRD, to correct chemical imbalances
- Implement dialysis when uremic symptoms develop
- Avoid “crash” dialysis and implement home therapies such as PD on a timely basis

# We present a new concept: “Mixed Bed” Ion Exchangers as Oral Sorbent Technology

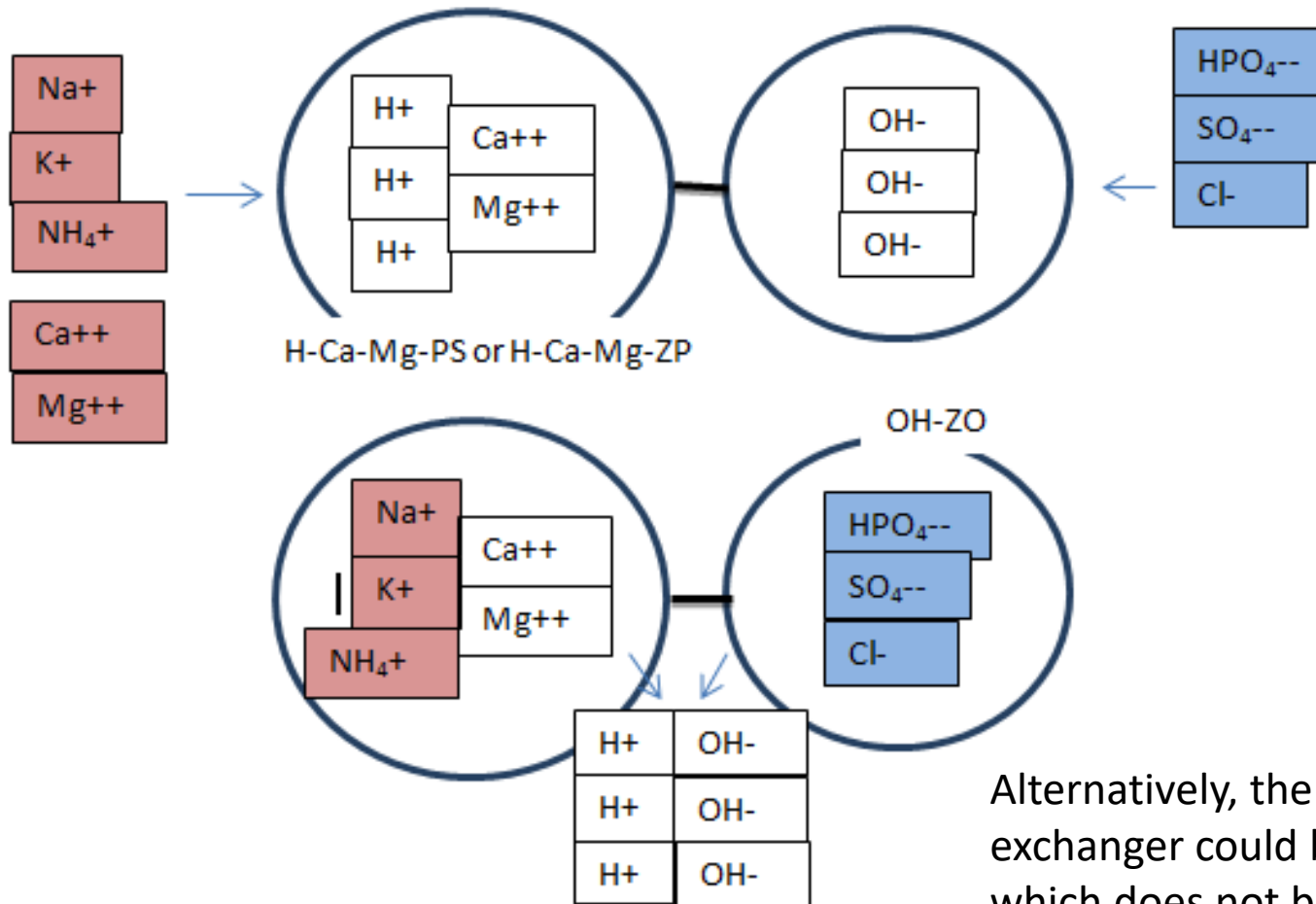
- Some oral sorbents are cation exchangers, such as Kayexelate, Patiromer and ZS-9
- Other oral sorbents are anion exchangers, such as Sevelamer and Cholestyramine
- Others are simple bases or precipitants such as  $\text{NaHCO}_3$  , and CaAcetate or FeHydroxide
- Our new sorbent is a combination of inorganic cation exchangers and anion exchangers, working in the gut as a “mixed bed” ion exchange system
- This results in markedly increased capacity for many uremic toxins, since the released  $\text{H}^+$  and  $\text{OH}^-$  combine to form water

The Cation Exchanger is loaded with Hydrogen and the Anion Exchanger with Hydroxide. The released counter-ions become water and “disappear”. This markedly increases the binding capacity of the sorbents for various uremic toxins:



If the cation exchanger is non-selective, it will remove  $Mg^{++}$  and  $Ca^{++}$ . Administering these cations removes more phosphate while replenishing  $Mg^{++}$  and  $Ca^{++}$ .

To Prevent Removal of  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  the Non-specific Cation Exchanger Can Be Partially Loaded With Divalent Cations



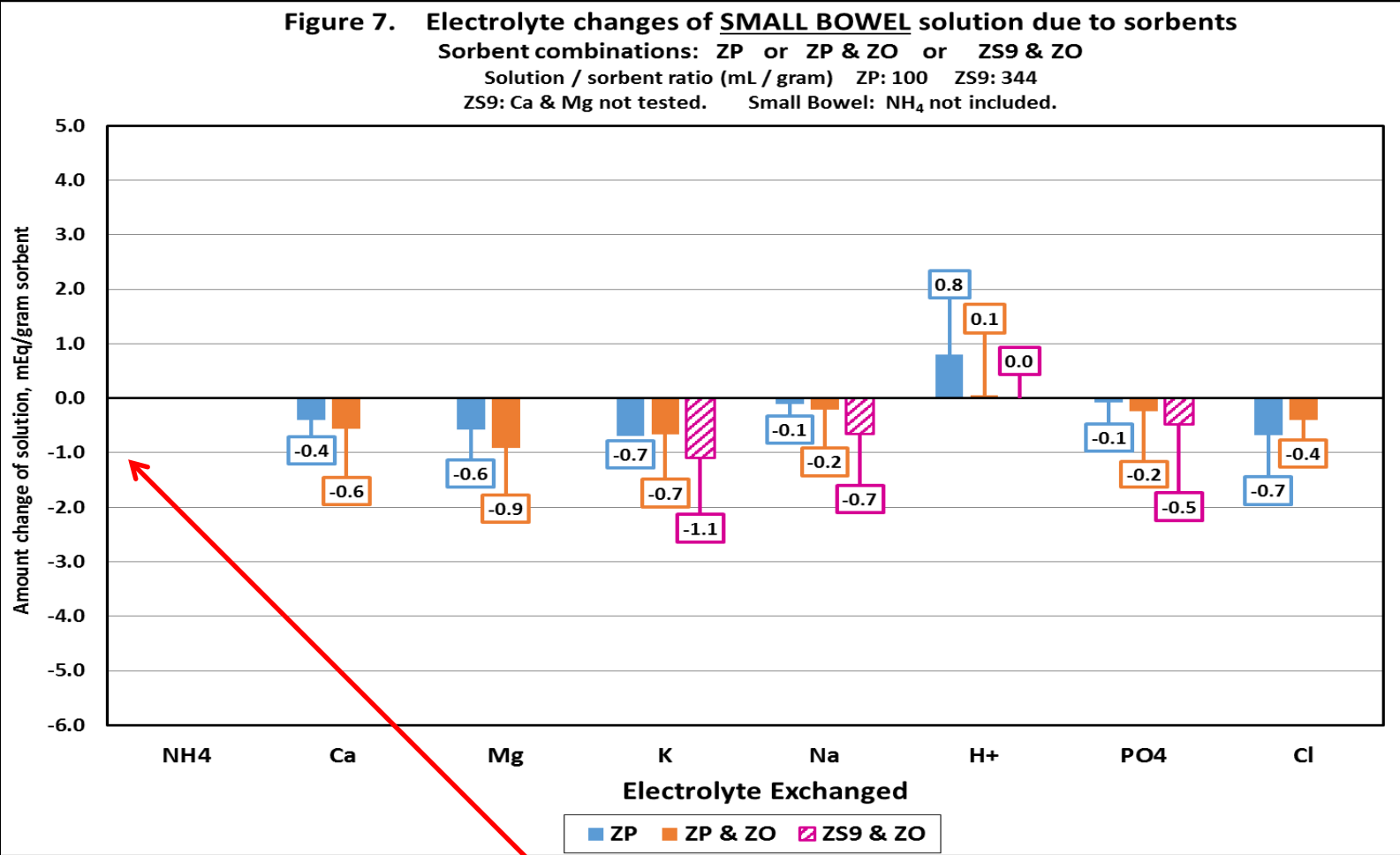
Alternatively, the cation exchanger could be ZS-9, which does not bind  $\text{Ca}^{++}$  or  $\text{Mg}^{++}$ . But, this would make the therapy much more expensive.

Methods: We tested a combination of cation and anion exchangers in solutions that simulated small bowel and colon contents. Literature-reported intestinal fluid concentrations are:

<b>Table 1. Human Physiological Conditions</b>						
	Small Bowel	Colon			Small Bowel	Colon
<b>Cation</b>	mEq/L	mEq/L		<b>Anion</b>	mEq/L	mEq/L
NH <sub>4</sub>		14.0		Bicarb		32.0
Ca	8.0	27.0		Cl	152.0	16.0
Na	138.0	32.0		PO <sub>4</sub>	2.5	2.0
Mg	8.0	47.0		Sulfate		3.0
K	8.5	75.0		Organic		179.0
H	1.0E-05	7.9E-05		<b>Total</b>	<b>154.5</b>	<b>232.0</b>
<b>Total</b>	<b>162.5</b>	<b>195.0</b>				
pH	8.0	7.1				

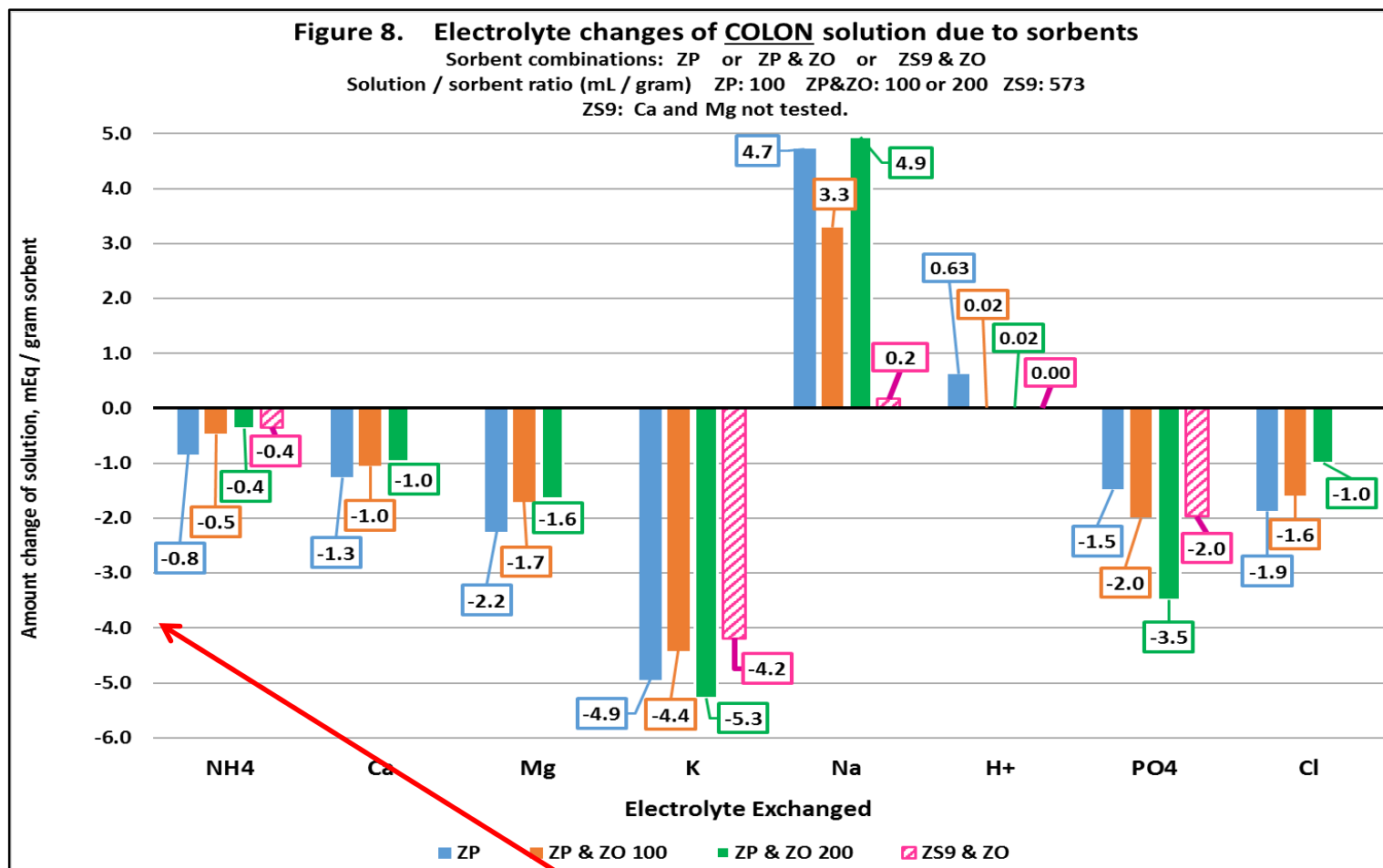


Combination Sorbents in Simulated Small Bowel Solution Effectively Remove  $K^+$ ,  $Na^+$ ,  $PO_4^-$  Without Releasing Significant Amounts of  $H^+$



Note: 1 meq per gram of sorbent is considered effective binding.

Combination Sorbents in Simulated Colon Solution Remove Even More  $K^+$ ,  $PO_4^-$ , and  $NH_4^+$  Without  $H^+$  Release but Some  $Na^+$  Release



Note: 4 meq per gram of sorbent is astronomically high binding.

# Conclusions from Our In-Vitro Tests

- Standard inexpensive ion exchangers (ZP and ZO) when taken orally as a mixed-bed can remove  $\text{PO}_4^-$  and  $\text{K}^+$  very effectively from simulated intestinal contents
- $\text{H}^+$  release is minimal and  $\text{H}^+$  removal can easily be increased by increasing the ratio of ZO to ZP
- $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  removal is modest and can be offset by administration of supplements orally.
- Binding of  $\text{Na}^+$  is lower than desired but binding can be improved by further washing and loading of sorbents with more  $\text{H}^+$
- Binding of  $\text{NH}_4^+$  is also lower than desired, but may be much higher in vivo than in vitro (as seen with ZS-9 in early clinical trials). A simple modification of our AP could greatly increase  $\text{NH}_4^+$  removal (not yet proven for ZP).
- 85 grams of this sorbent mixture ingested daily would remove 1/4 of the total body load of those toxins that are bound to ZP and ZO in the gut. This would be sufficient to normalize serum levels of  $\text{K}^+$ ,  $\text{PO}_4^-$  and  $\text{H}^+$  in patients with some RRF. It would also stabilize levels of other uremic toxins including urea and  $\text{Na}^+$ .

# Potential Clinical Benefits of the Mixed-Bed Oral Sorbent:

1. Patients would NOT start dialysis just because of simple chemical abnormalities such as increased  $K^+$ ,  $H^+$  (acidosis),  $PO_4^{---}$  (phosphate), or high BUN
2. Patients would NOT start dialysis merely for fluid overload and excess  $Na^+$  (edema). An effective sodium sorbent is itself very valuable since it could treat renal failure and heart failure
3. Patients would start dialysis when early uremic symptoms appear, not for simple abnormal chemistries
4. Crash hemodialysis could be avoided, with its risks and those of acute catheters
5. Home dialysis therapies such as PD or frequent home hemodialysis can be implemented on a timely and convenient basis
6. Multiple oral therapies for controlling  $H^+$ ,  $K^+$  and  $PO_4^{---}$  levels in CKD patients are replaced by a single sorbent mixture, and  $PO_4^-$  control will be much better than with current meds
7. Patients would have no dietary restrictions, regardless of the stage of kidney disease. Foods with high  $K^+$ ,  $HPO_4^{---}$ ,  $Na^+$  and protein would be OK. Patients would arrive on dialysis in better nutritional status.
8. Regeneration of dialysate by sorbents will be made much simpler by not having to remove urea and phosphate.

## Five Obvious Questions About This New Therapy

1. Is there a mathematical model to predict chemical function of the mixed sorbents in a complex gut environment?
2. Do we have data to show that small, charged uremic toxins can be sufficiently removed from the gut to normalize or stabilize serum levels of the toxins?
3. How did we calculate the amount of ZP/ZO mixture needed for maximal effect on the toxins?
4. Will zirconium be solubilized and absorbed from the gut?
5. Will this cause any problems in the patients?

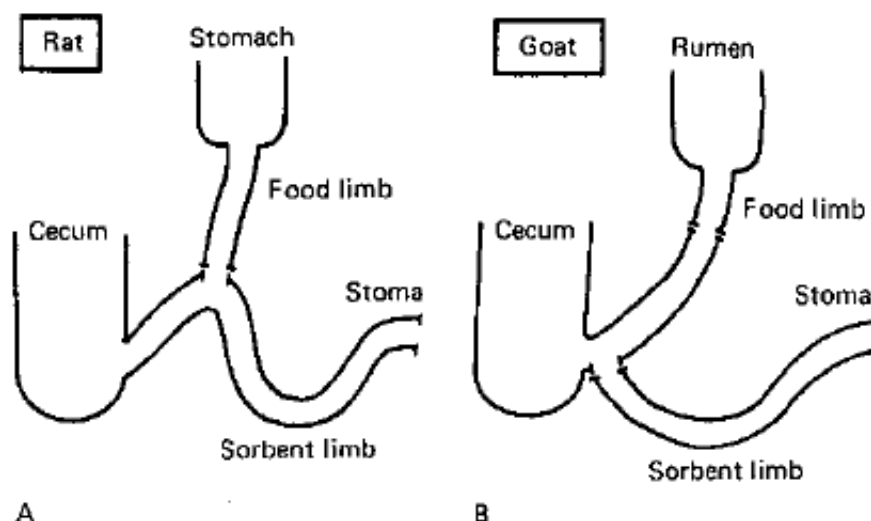
Could we remove all uremic toxins from the gut and not need dialysis for kidney failure? Not really!

- In the 1970s we performed animal studies using large amounts of ZP administered into an isolated gut section. The tests showed stabilization of BUN and  $K^+$  levels in anephric animals (but not creatinine levels)
- Studies in patients taking 30 grams of ZS-9 daily showed rapid normalization of  $K^+$  levels and a 20% decrease in BUN levels
- If taken with food, the ZP/ZO mixture can bind compounds in the food before absorption occurs, increasing efficacy

# Roux-Y intestinal bypass for administration of sorbents in uremia

ANNA SINCLAIR, CHARLES F. BABBS, DEE D. GRIFFIN, and STEPHEN R. ASH

No toxicity was seen in these studies.



**Fig. 1.** Schematic diagram of the Roux-Y operation as performed in a) rats, b) goats.

**Table 1.** Sorbent composition used in uremic animals

	Source	Dose <i>g/kg/24 hr</i>	Putative functions
Urease (400 SU/g)	ICN Pharmaceuticals, Cleveland, Oh.	1.4	Urea breakdown to ammonium carbonate
Zirconium phosphate (90% hydrogen, 10% sodium-loaded)	CCI Life Science, Van Nuys Ca. (donation)	20	Ammonium, potassium, calcium, magnesium, absorption
Charcoal, activated USP	Mallinckrodt, Inc., St. Louis, Mo.	4	Creatinine, uric acid, and unspecified middle molecule absorption
Aluminum hydroxide	Allied Chem. Monistown, N.J.	2	Phosphate absorption
Granulated sucrose	Domino, Amstar Cprp, N.Y.	1 to 20	Water and sodium removal
Polyvinyl pyrrolidone	JCN Pharmaceuticals, Cleveland ,Oh.	0.5	Particle suspension
Water	Tap	30	Particle suspension

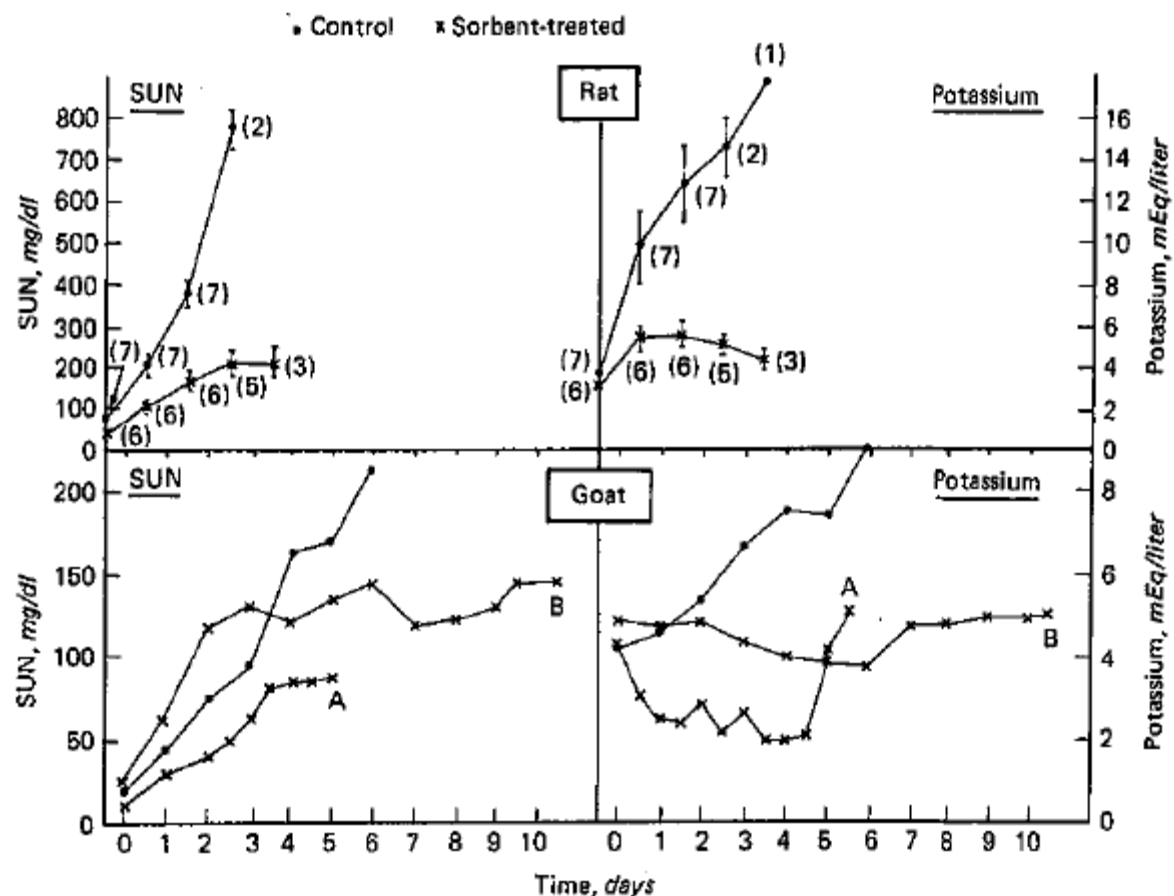
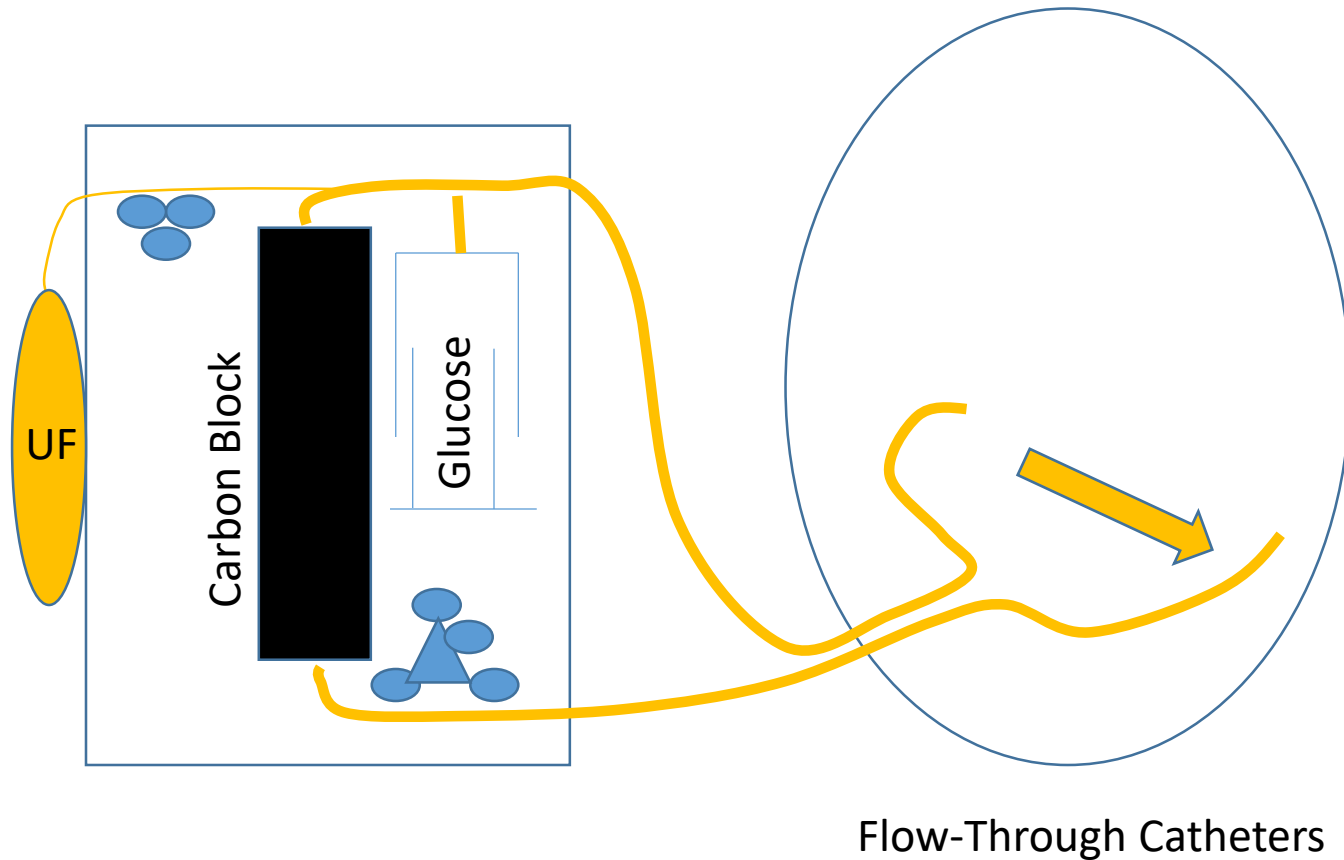


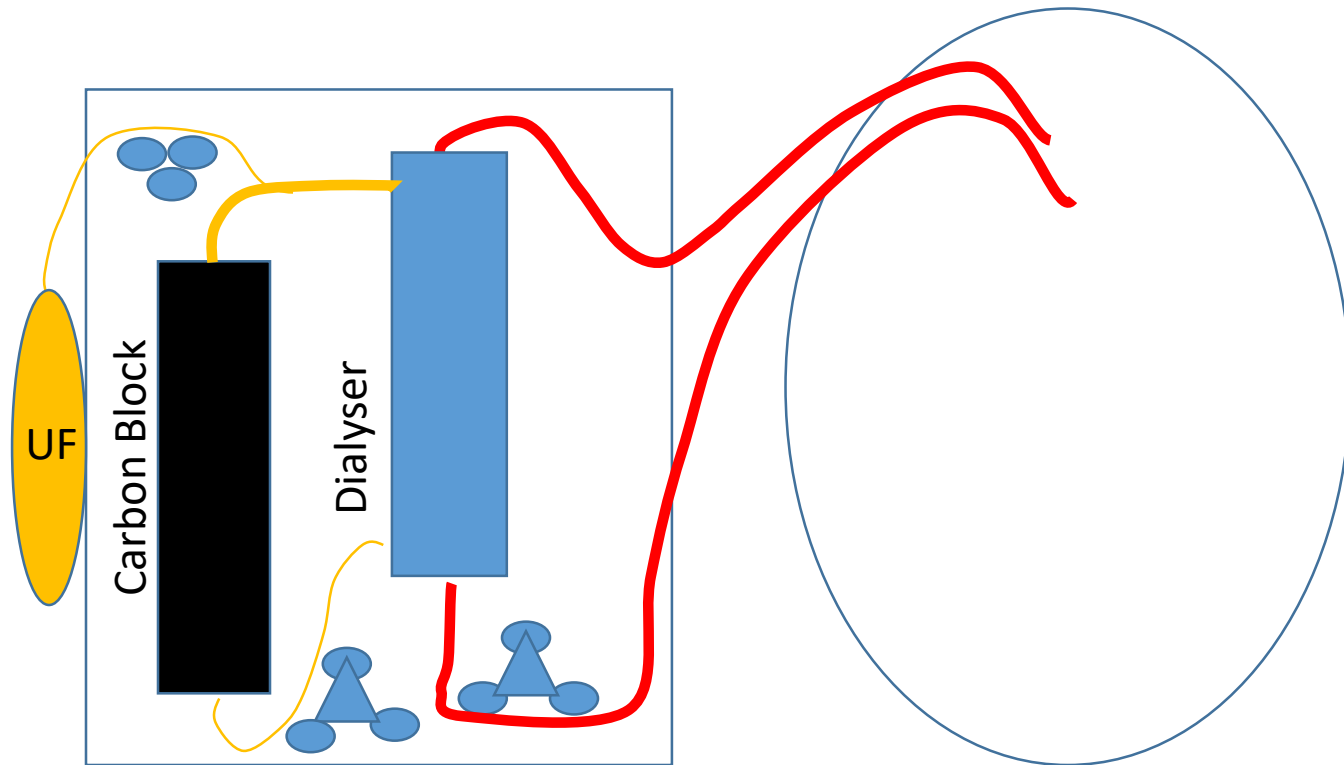
Fig. 4. Effect of Roux-Y sorbent administration on survival, serum urea nitrogen (SUN), and serum potassium in uremic animals vs. controls. The rat data are an average of the 7 control (closed circles) and 6 Roux-Y rats (X's). All other data refer to individual animals.



# PD Therapy Made Simple, Safe and Highly Portable, Using Carbon Block to Regenerate Dialysate

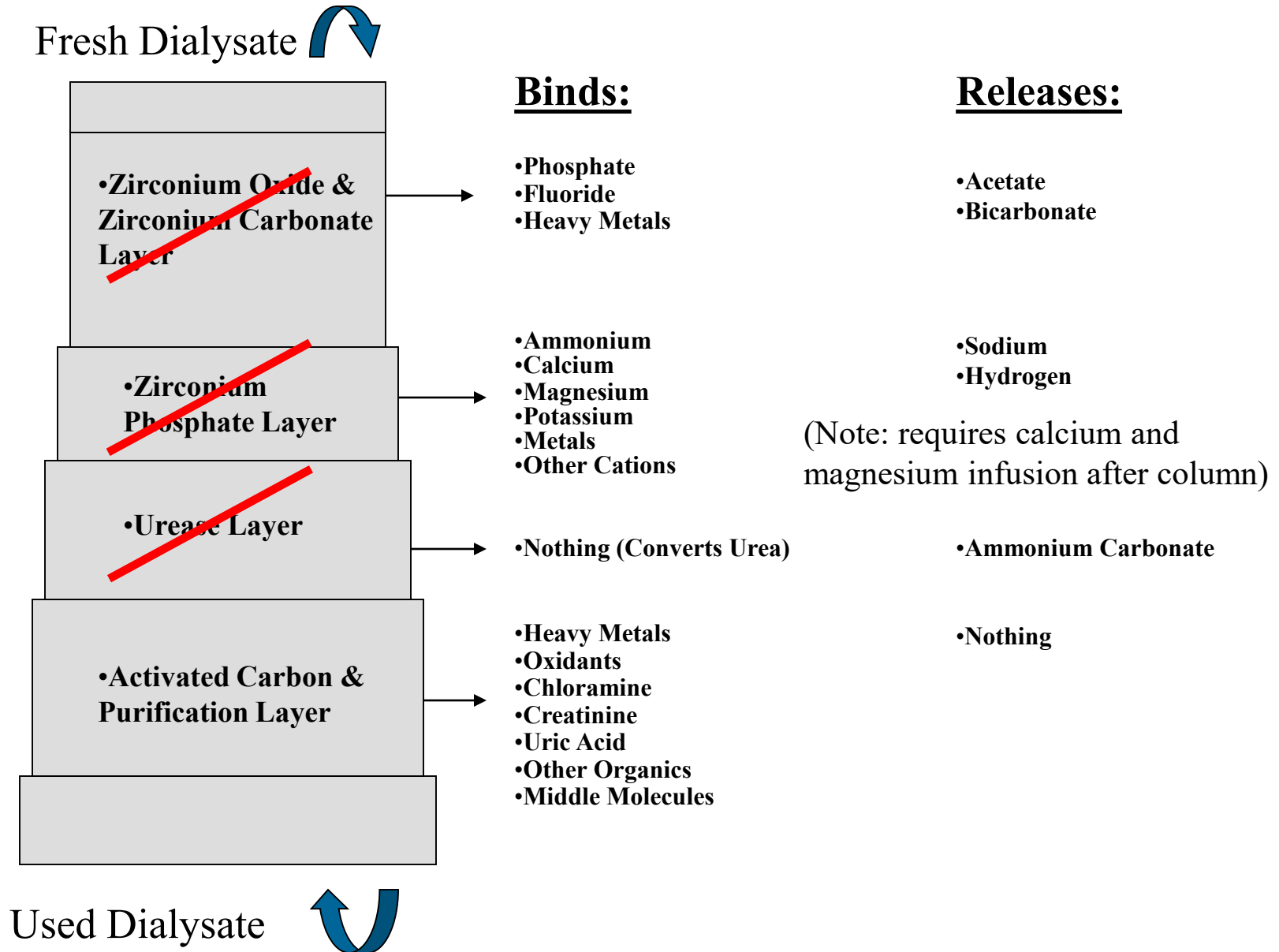


# HD Therapy Made Simple, Safe and Highly Portable, Using Carbon Block to Regenerate Dialysate



Improved Venous Catheters

# If the Oral Sorbent Mixture is Effective, then All That is Needed is Charcoal to Regenerate Dialysate for HD or PD



# Conclusions

- Oral sorbents are an important part of our therapies today for CKD and ESRD
- Improved sorbents for potassium and other toxins are now available.
- With some further development we could have a single sorbent mixture to remove small and charged toxins like potassium, phosphate, sodium, hydrogen and urea.
- Such a sorbent mixture could delay the need for dialysis in many patients
- The use of the mixture could also simplify dialysis by having it focus on removal of larger organic toxins, and regenerating dialysate with carbon.
- This could help to make dialysis therapy simpler, safer and easier to implement in home environments.