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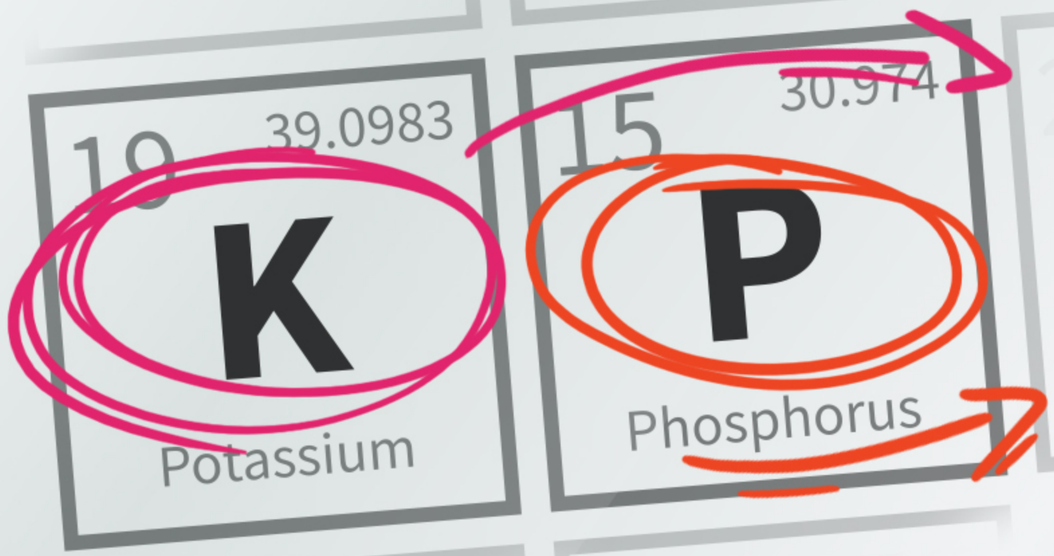

HIT OR MYTH

New Advances in the Management of Hyperkalemia and Hyperphosphatemia

CSN Invites You to a Virtual Accredited Lunchtime Symposium

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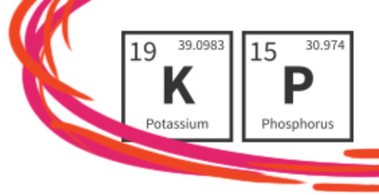

- Thank you Otsuka Canada for providing an unrestricted educational grant to support this symposium.

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University of Calgary

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Disclosures – Relationships with Commercial Interests

	Juliya Hemmett MD MHPE FRCPC	Louise Moist MD MSc CCPE FRCPC	Louis-Philippe Girard MD MBT FRCPC
Financial payments or honoraria	NA	Otsuka, AstraZeneca, Janssen, Ortho, Knight Pharmaceuticals	CPD Network, Alexion, Bayer, BI-Lilly, AstraZeneca, Janssen, Merck, Otsuka, Bausch Health
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Funded grants or clinical trials	NA	EMPA kidney site	Otsuka, Chemocentryx

Learning Objectives

After this program, participants will be better able to:

- Apply the epidemiologic and outcome data of hyperkalemia and hyperphosphatemia to your local practice
- Integrate knowledge of recent clinical trials, practice patterns, and available therapies into your management of hyperkalemia and hyperphosphatemia.
- Apply clinical efficacy and safety data on new potassium and phosphate binders to reduce the impact of hyperkalemia or hyperphosphatemia
- Implement RAASi enablement strategies in patients at risk of or with chronic hyperkalemia

Participation to Earn Section 3 Credits

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- **IMPORTANT:** To claim your Section 3 credits, you must answer ALL the questions and press “submit” once finished.

Pre-Test
Polling Question

Hyperkalemia is prevalent and recurrent in patients with CKD leading to serious clinical consequences

Pre-Test
Polling Question

RAASi dose-titration or discontinuation has a negative impact on HR-QoL and clinical outcomes

Pre-Test
Polling Question

Potassium binders can be used to rapidly and sustainably reduce serum potassium levels while enabling RAASi in patients with chronic hyperkalemia

Pre-Test
Polling Question

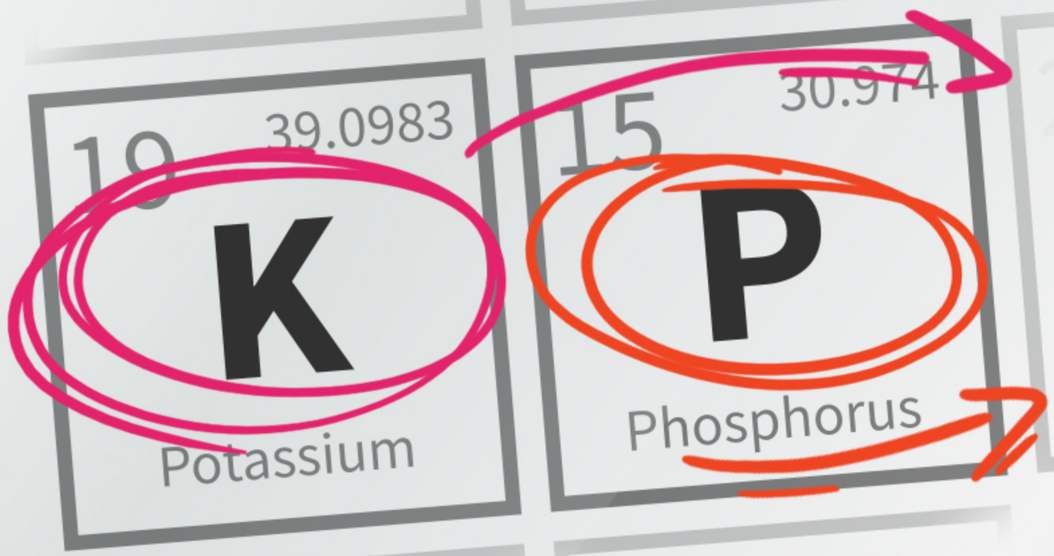
Hyperphosphatemia in advanced CKD is associated with increased risk of morbidity and mortality

Pre-Test
Polling Question

There is conclusive evidence that phosphate-binding agents are effective agents to reduce morbidity and mortality in patients with ESRD

Pre-Test
Polling Question

Phosphate-binding agents have demonstrated phosphate-lowering efficacy in real-world studies, with a substantially lower pill burden compared to traditional phosphate binders



HIT OR MYTH

New Advances in the Management of Hyperkalemia and Hyperphosphatemia

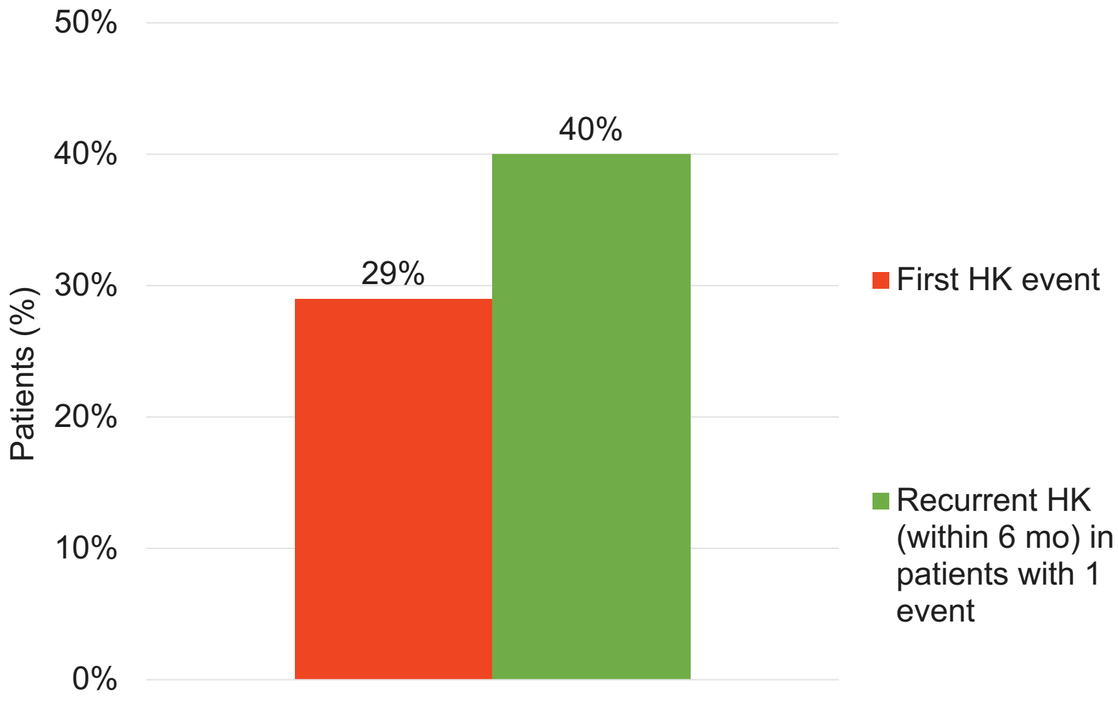
Hyperkalemia

Louise Moist
MD MSc CCPE FRCPC

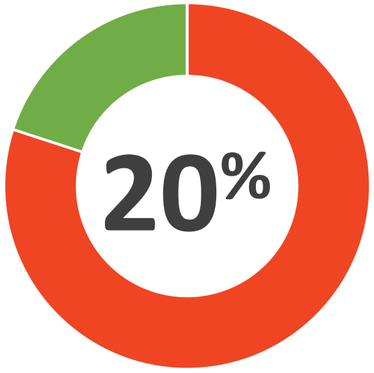
Hyperkalemia is prevalent and recurrent in patients with CKD leading to serious clinical consequences

Hyperkalemia is Prevalent and Recurrent in Patients with CKD

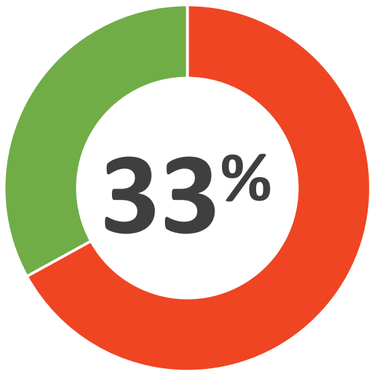
Patients with hyperkalemia (%)[1]



In a large cohort study in the US, data from more than 120,000 dialysis patients, of whom approximately 10,000 were on PD, were analyzed:[3]



of patients on PD had hyperkalemia



of patients on dialysis had hyperkalemia

About half of patients with CKD stage 3–5 with hyperkalemia had ≥2 recurrences within 1 year*[2]

*Hyperkalemia was defined as serum K+ ≥5.5 mmol/L. 70 individuals (0.21%) had more than 20 episodes each in 1 year.
CKD, chronic kidney disease; PD, peritoneal dialysis

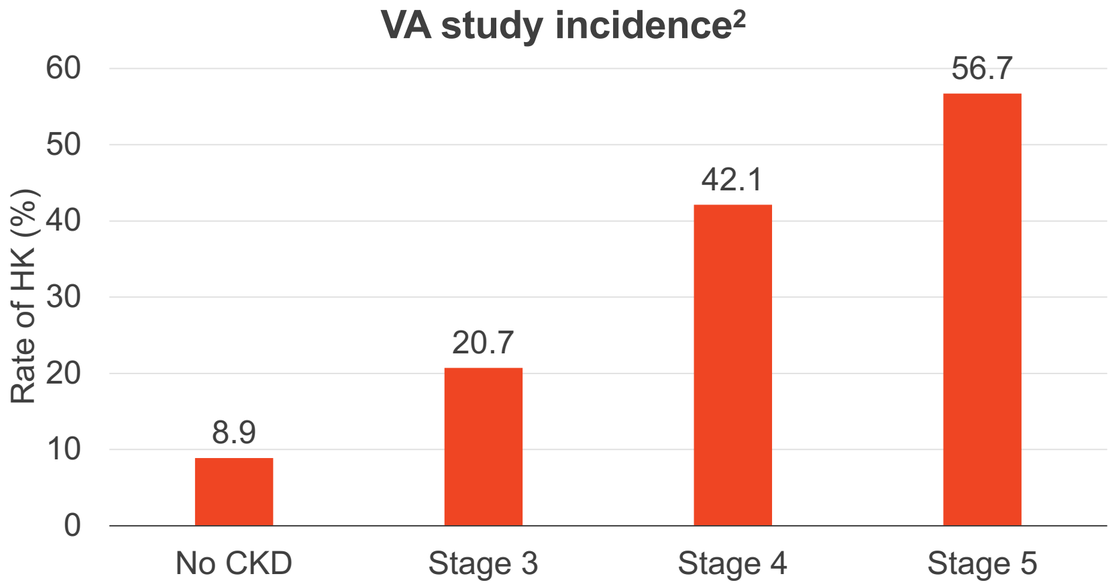
1. Adelborg, K. et al. PLoS One 14(6), e0218739 (2019)
2. Dunn, J. D. et al. Am J Manag Care 21, s307-315 (2015)
3. Torlén, K. et al. Clin J Am Soc Nephrol 7, 1272–1284 (2012)

As Kidney Function Declines, the Risk of Hyperkalemia Increases

The incidence and prevalence of hyperkalemia are high in patients with CKD*

Prevalence[1]

Patient population	Patients (n)	Rate (%)
Pre-dialysis CKD with mean eGFR 14.4 ± 4.6	238	31.5



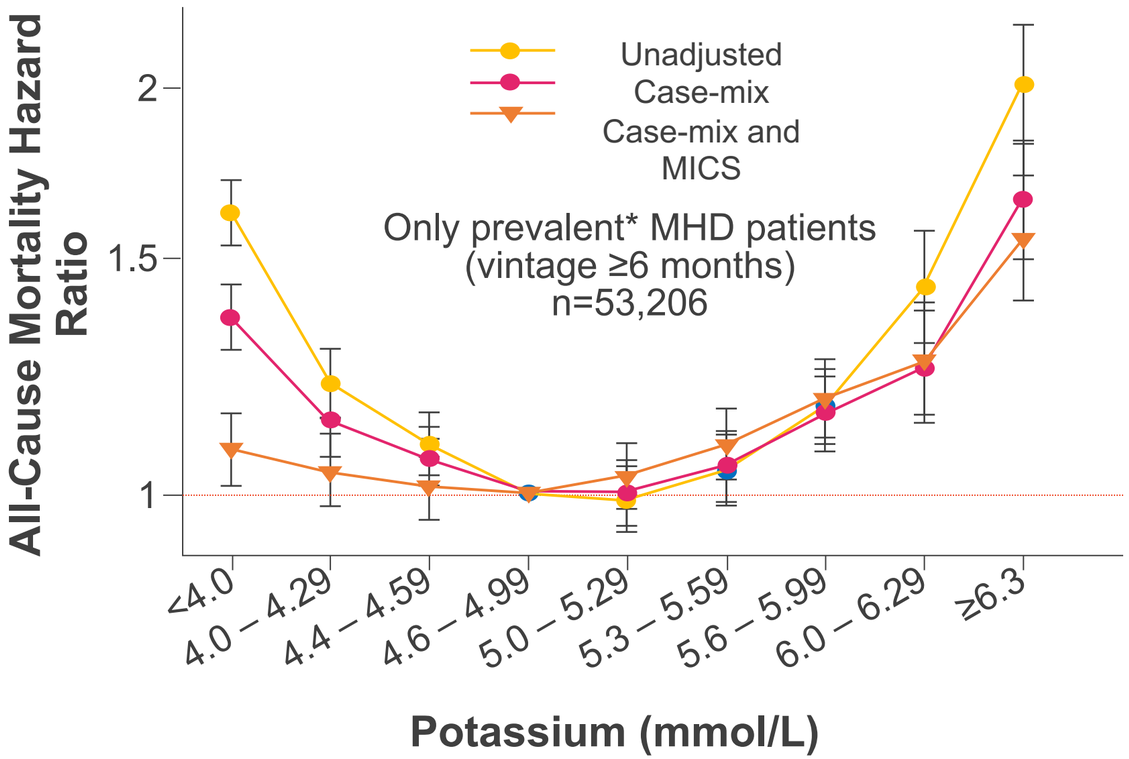
This is a result of the decreased ability to excrete potassium in CKD patients, and the presence of other comorbid/predisposing conditions (e.g., diabetes, CVD)[3]

* Hyperkalemia was defined as serum K+ >5.5 mmol/L in the pre-dialysis CKD study and ≥5.5 mmol/L in the VA study
CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); VA, Veterans Affairs

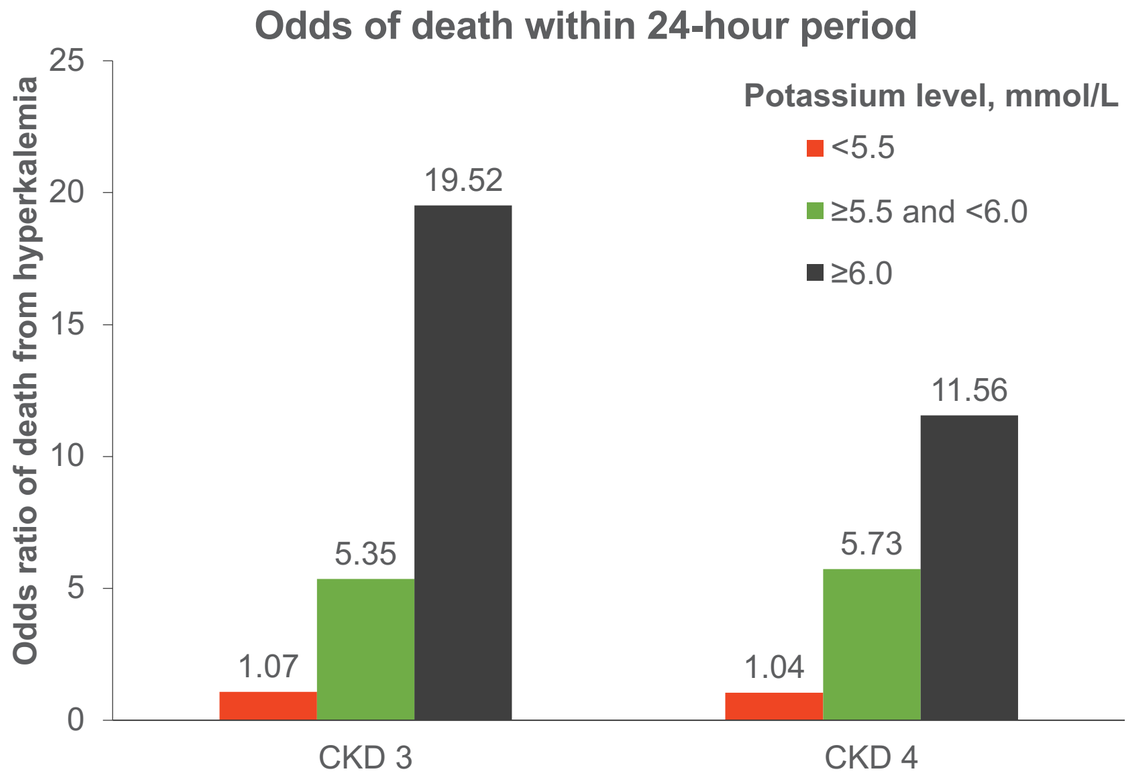
1. Sarafidis PA, et al. Clin J Am Soc Nephrol. 2012;7(8):1234-1241.
2. Einhorn LM, et al. Arch Intern Med. 2009;169(12):1156-1162.
3. Kovesdy, C. P. Nature Reviews Nephrology 10, 653–662 (2014)

Hypo and Hyperkalemia are Associated with Increased Mortality in at Risk Patients

Serum K+ concentrations and survival in hemodialysis patients[1]



Relationship between serum potassium and mortality over an 18-month period (N=911,698)[2]



MHD: maintenance hemodialysis; MICS: malnutrition inflammation complex syndrome

1. Kovesdy, C. P. et al. CJASN 2, 999–1007 (2007)
2. Einhorn LM, et al. Arch Intern Med. 2009;169:1156–62.

Hyperkalemia is Associated with Other Serious Clinical Consequences and Results in Preventable ED Visits in CKD

Clinical consequences[1]

- Ventricular arrhythmias
- Muscle weakness/paralysis
- ED visits and hospitalizations

ED visits for overall CKD-related ACSCs* per 1000 p-y

(hyperkalemia individually by CKD category)[2]

Mean follow-up: 2.4 years, n = 111,087

CKD category (eGFR, ml/min/1.73m²)	Rate per 1000 p-y (95%CI)
3A (45-59)	3.6 (3.3-3.9)
3B (30-44)	8.2 (7.5-8.9)
4 (15-29)	16.3 (14.4 -18.4)
5-ND(< 15)	**22.9 (16.7-29.1)**
5-D(< 15)	**22.4 (17.2 – 27.5)**

*ACSCs are health conditions for which good outpatient care can likely prevent the need for hospitalization and are recognized internationally as a measure of adequacy of ambulatory and primary health care performance

ACSC: ambulatory care sensitive conditions ; CKD: chronic kidney disease; ED: emergency department; eGFR: estimated glomerular filtration rate; ND: not defined; p-y: person years

1. Dunn, J. D. et al. Am J Manag Care 21, s307-315 (2015)
2. Ronksley PE, Tonelli M, Manns BJ, Weaver RG, Thomas CM, MacRae JM, Ravani P, Quinn RR, James MT, Lewanczuk R, Hemmelgarn BR. Clin J Am Soc Nephrol. 2017 Feb 7;12(2):304-314

Post-Test
Polling Question

Hyperkalemia is prevalent and recurrent in patients with CKD leading to serious clinical consequences

Post-Test
Polling Question

Hyperkalemia is prevalent and recurrent in patients with CKD leading to serious clinical consequences

RAASi dose-titration or discontinuation has a negative impact on HR-QoL and clinical outcomes

Rate of Hyperkalemia is High in RAASi-treated Patients

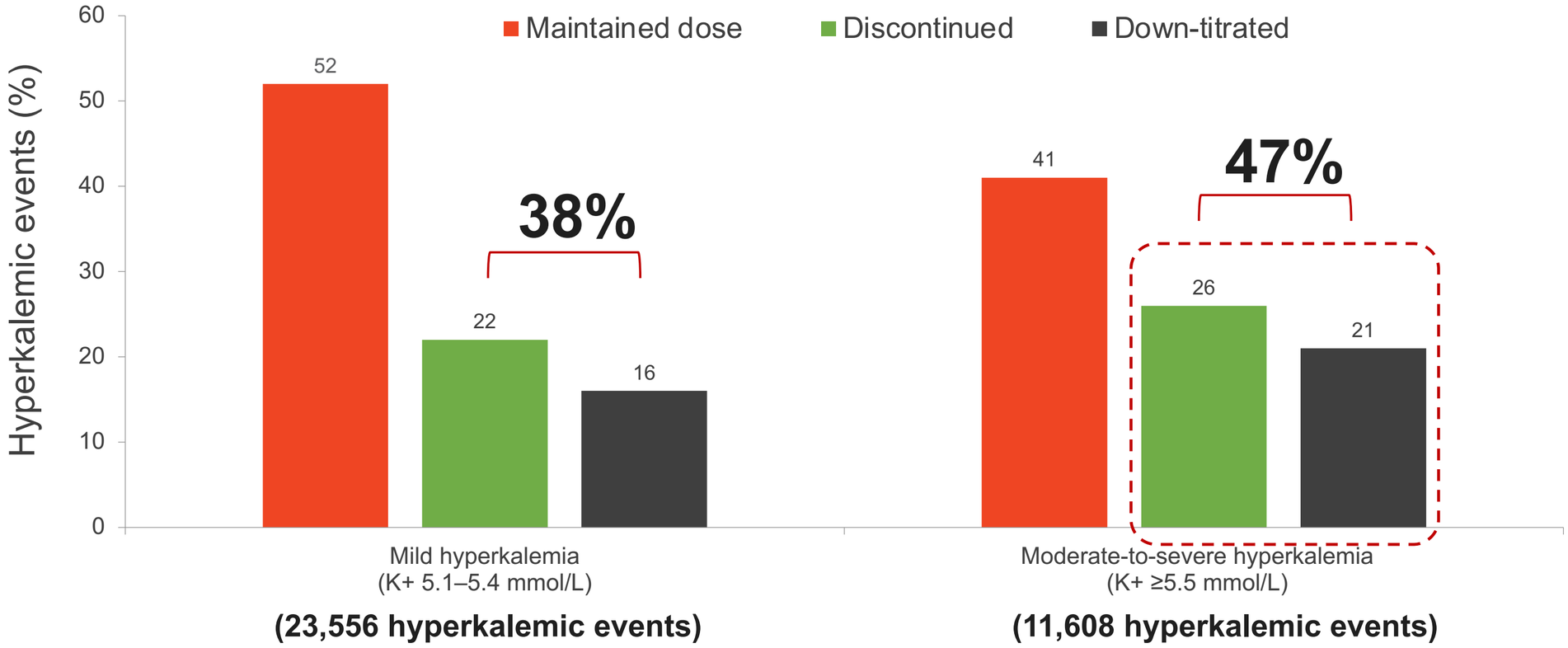
Study (year main results published)	Population	# of Patients	Definition of hyperkalemia (mmol/L)	Mean eGFR (mL/min/1.73m²)	Rate
RENAAL[1] (2001)	Diabetic nephropathy	751	≥ 5.0 ≥ 5.5	40.9 37.0	**38.4%** **10.8%**
IDNT[2] (2001)	Diabetic nephropathy	579	> 6.0	-	**18.6%**
J-LIGHT[3] (2004)	HTN-CKD	58	> 5.1 ≤ 6.9	-	**5.2%**
AASK[4] (2009)	Non-diabetic CKD	417	≥ 5.5	46.6	**7.2%**

CKD, chronic kidney disease; eGFR: estimated glomerular filtration rate; HTN, hypertension; IDNT, Irbesartan Diabetic Nephropathy Trial; J-LIGHT, Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients; RENAAL, Reduction of Endpoints in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan.

1. Miao, Y. et al. Diabetologia 54, 44–50 (2011)
2. AVAPRO® Canadian Product Monograph. Sanofi-Aventis Canada Inc. Date of revision: June 18, 2018.
3. Lino Y, et al. Hypertens Res. 27(1), 21-30 (2004)
4. Weinberg, J. M. et al. Arch Intern Med 169, 1587–1594 (2009)

Elevated Potassium Leads to Suboptimal use of RAASi Therapy

Patients on maximal RAASi dose had their treatment reduced or stopped after a hyperkalemic event nearly half the time*



*Patients with CKD at Stages 3-5 were enlisted within the study. In the remaining events, the data period following the hyperkalemia event was insufficient to determine subsequent RAAS inhibitor dose level.
K+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor.

1. Epstein M, et al. Am J Manag Care 21(11 Suppl), S212–20 (2015)

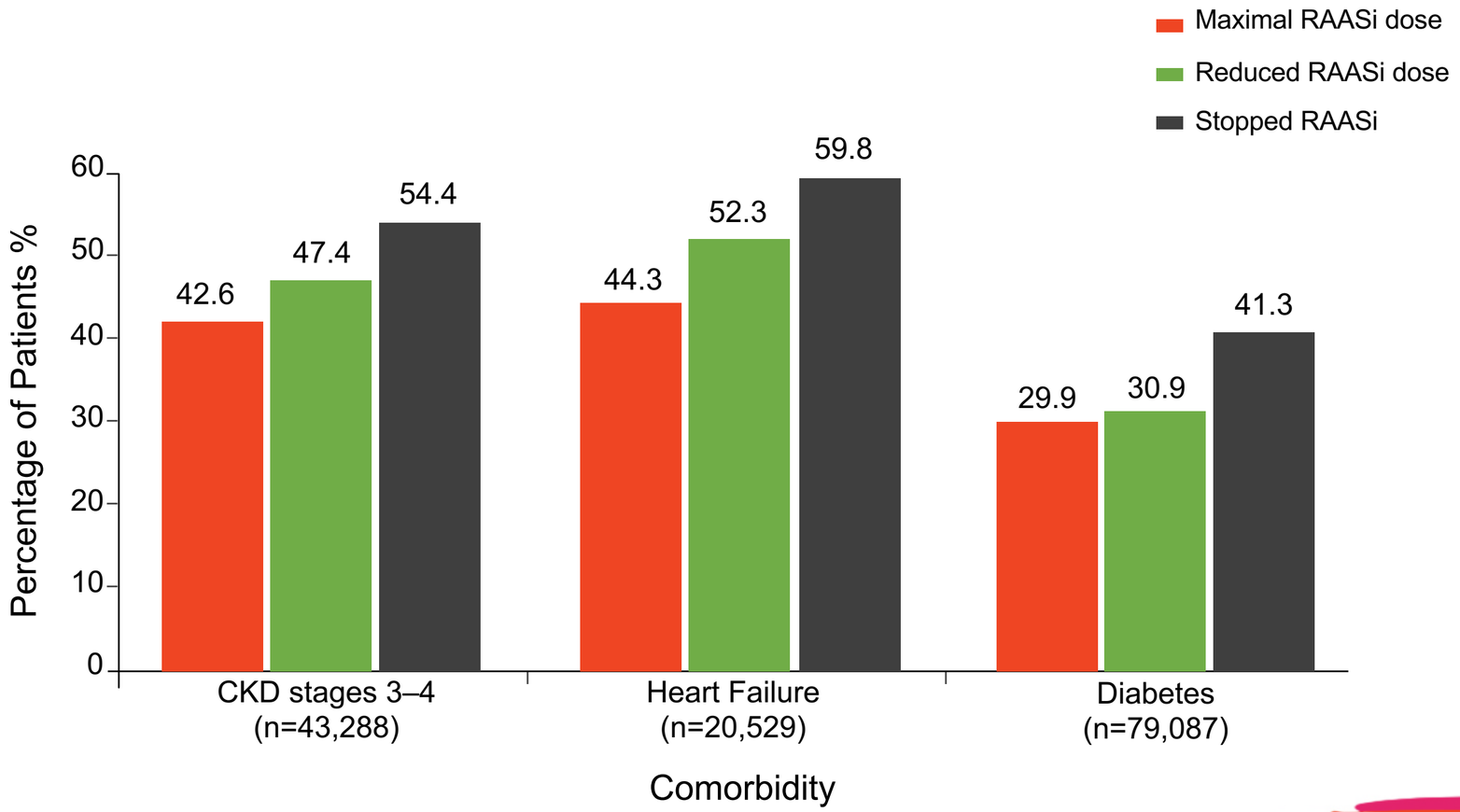
Suboptimal Dosing and Discontinuation of RAASi is Associated with Poor Outcomes[1]

Adverse outcomes evaluated:

- CKD progression and progression to ESKD
- Stroke and acute myocardial infarction
- Coronary artery bypass and percutaneous coronary intervention

Doubling of all-cause mortality

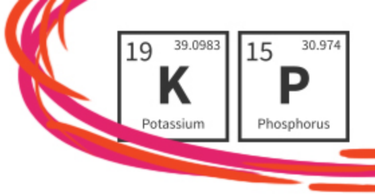
Patients who experienced adverse outcomes or mortality by prior RAASi dosing*



*This was a retrospective database analysis, and therefore cannot detect casualty and can only provide associations in the real-world setting.
CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor; ESKD, end-stage kidney disease

1. Epstein M, et al. Am J Manag Care 21(11 Suppl), S212–20 (2015)

Other Strategies to Manage Hyperkalemia[1]



Remove or manage any ongoing contributors to hyperkalemia

- Diet
- Medications
- Co-morbid conditions

Increase potassium distribution and excretion

- Loop and thiazide diuretics
- Sodium bicarbonate
- Potassium binders

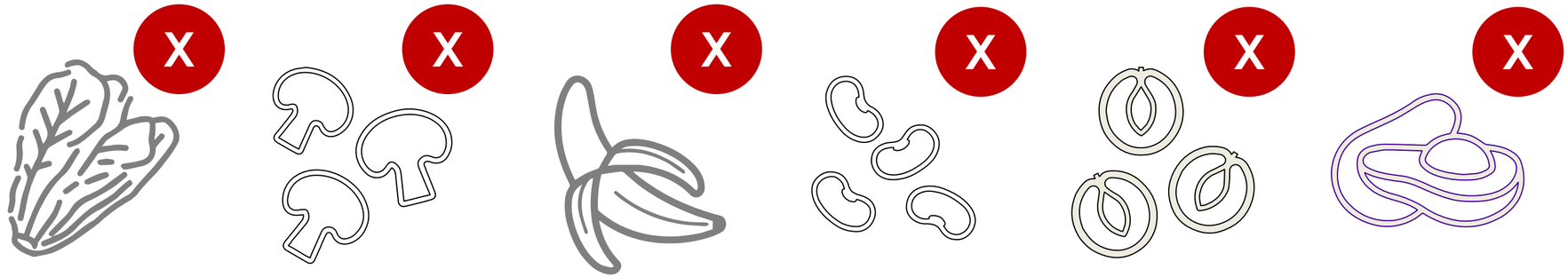
1. Dunn, J. D. et al. Am J Manag Care 21, s307-315 (2015)

Restricting Dietary Potassium is Difficult and has Disadvantages

Many cardio-renal patients already have restricted diets[1]

- Track fluid intake (edema)
- Low carbohydrate (T1 and T2DM)
- Low sodium (hypertension)
- Low protein (severe CKD)
- Avoid alcohol
- Limit caffeine

Low potassium diet further restricts consumption of healthy, affordable foods[1]



CKD, chronic kidney disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

1. Sanghavi, S. et al. Seminars in Dialysis 26, 597–603 (2013)

Modifiable Lifestyle Factors for Primary Prevention of CKD

Recent review of 104 observational studies (n=2,755,719), demonstrated:[1]

Increased dietary potassium intake

22% reduced odds of preventing CKD onset

Other evidence suggests that:[2,3]

Increased dietary potassium intake

Lower risk of all stroke and ischemic stroke

CKD, chronic kidney disease

1. Kelly, J. T. et al. JASN, ASN.2020030384 (2020)
2. Hunt BD, Cappuccio FP. Stroke. 2014;45(5):1519-1522.
3. Seth A, Mossavar-Rahmani Y, Kamensky V, et al. 2014;45(10):2874-2880.

Post-Test
Polling Question

RAASi dose-titration or discontinuation has a negative impact on HR-QoL and clinical outcomes

Post-Test
Polling Question

RAASi dose-titration or discontinuation has a negative impact on HR-QoL and clinical outcomes

Potassium binders can be used to rapidly and sustainably reduce serum potassium levels while enabling RAASi in patients with chronic hyperkalemia

Overview of the New Potassium Binders

	Patiromer[1]	Sodium Zirconium Cyclosilicate (SZC)[2]
Mechanism	Nonabsorbed cation-exchanger polymer that binds K+[3]	Inorganic cation exchanger with a crystalline structure that entraps K+[4]
Site	Colon[3]	Entire GI tract[5]
Exchange ion for potassium	Calcium/magnesium	Sodium
Onset of action	4–7 h[1]	1 h[2]
Adverse events[6]	Mild to moderate gastrointestinal effects, hypomagnesemia, hypokalemia (3–5.6%)	Mild to moderate gastrointestinal effects, edema, and hypokalemia (0–11%, dose dependent)
Recommended dose	8.4 g QD; dose can be titrated at ≥1-wk intervals in 8.4 g increments to a maximum of 25.2 g QD	10 g TID for 48 h; then 5–10 g QD. No more than 10 g QD for maintenance therapy

SZC: sodium zirconium cyclosilicate

1. VELTASSA® Canadian Product Monograph. Otsuka Canada Pharmaceutical Inc. Date of revision: February 28, 2020.
2. LOKELMA™ Canadian Product Monograph. AstraZeneca Canada Inc. Date of revision: July 23, 2019.
3. Li, L. et al. Journal of Cardiovascular Pharmacology and Therapeutics 21, 456–465 (2016) 1 Stavros, F. et al. PLoS One 9, (2014)
4. Stavros, F. et al. PLoS One 9, (2014)
5. Kosiborod, M. et al. JAMA 312, 2223–2233 (2014)
6. Vijayakumar, S. et al. Eur Heart J Suppl 21, A41–A47 (2019)

Patiromer Studies Investigating Potential to Enable RAASi

Trial	Design	Population	Key endpoints	Conclusions

Weir MR et al., 2015 (OPAL-HK)[1]	Phase III
	Phase A (treatment phase): single-bind, single-arm (4 weeks)
	Phase B (withdrawal phase): placebo-controlled, single-bind (8 weeks)
		Phase A: N = 243
		Phase B: N = 107
		
		CKD with hyperkalemia receiving RAASi therapy
			- Part A:
			  - Mean change in K+ from baseline to Week 4
			  - Proportion of normokalemic patients (K+: 3.8 to <5.1 mmol/L) at Week 4
			- Part B:
			  - Treatment group differences in median change in K+ from start of Part B to Part B Week 4 or first visit where K+ was <3.8 or ≥5.5 mmol/L
			  - Proportion of patients with mild (K+: ≥5.1 mmol/L) or moderate/severe (≥5.5 mmol/L) hyperkalemia
				- Significant and clinically meaningful serum K+ reduction
				- Maintenance of serum K+ control
				- **Ability to keep patients on RAASi medications**

Pitt B et al, 2011 (PEARL-HF)[2]	Phase II, double-blind, placebo-controlled, randomized, parallel-group (4 weeks)	N = 105 HF, K+ of 4.3–5.1 mmol/L at screening and **CKD or history of HK that led to RAASi discontinuation**	- Mean change of serum K+ from baseline to the end of the study (Day 28) - Proportion of patients with serum K+ 5.5 mmol/L at any time during the trial and the proportion of patients whose spironolactone dose could be increased to 50 mg/day	- Significantly reduced mean K+ levels - Prevented hyperkalemia - **Allowed a significantly greater percentage of patients to increase spironolactone doses to 50 mg/day**
Agarwal R et al., 2019 (AMBER)[3]	Phase II, multicenter, double-blind, placebo-controlled, randomized (run-in: 4 weeks; treatment: 12 weeks)	N = 295 **CKD and resistant hypertension**	- Difference between treatment groups in the proportion of patients remaining on spironolactone at week 12 - Difference between treatment groups in the change in systolic AOBP from baseline to week 12	- **Enabled more patients to continue treatment with spironolactone with less hyperkalemia**

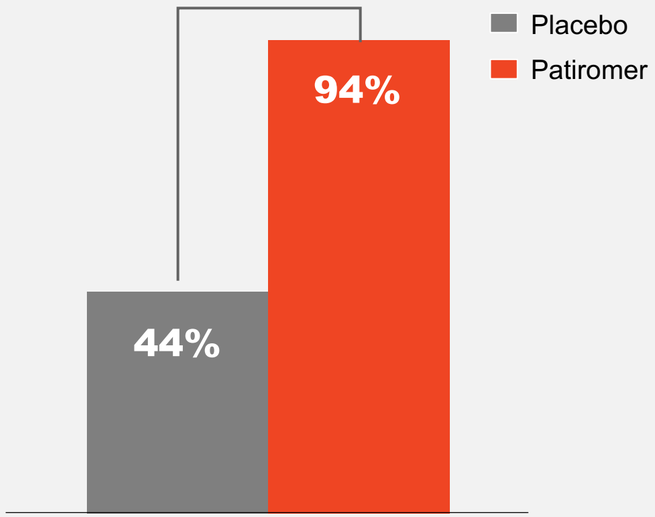
CKD, chronic kidney disease; K+: potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; T2D, type 2 diabetes

1. Weir, M. R. et al. New England Journal of Medicine 372, 211–221 (2015)
2. Pitt, B. et al. Eur Heart J 32, 820–828 (2011)
3. Agarwal, R. et al. The Lancet 394, 1540–1550 (2019)

Patiromer Studies Demonstrating Potential to Enable RAASi

OPAL-HK[1]

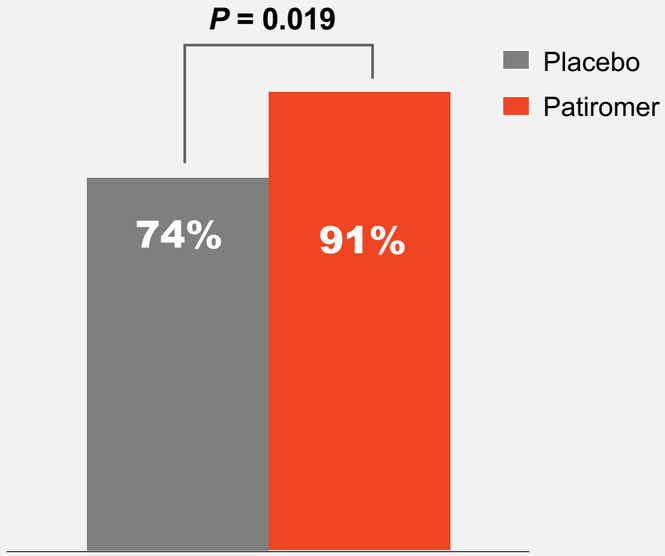
eGFR 15–59 mL/min/1.73 m^2; K^+ 5.1–6.4 mmol/L; RAASi



Exploratory endpoint:
Patients receiving any RAASI dose

PEARL-HF[2]

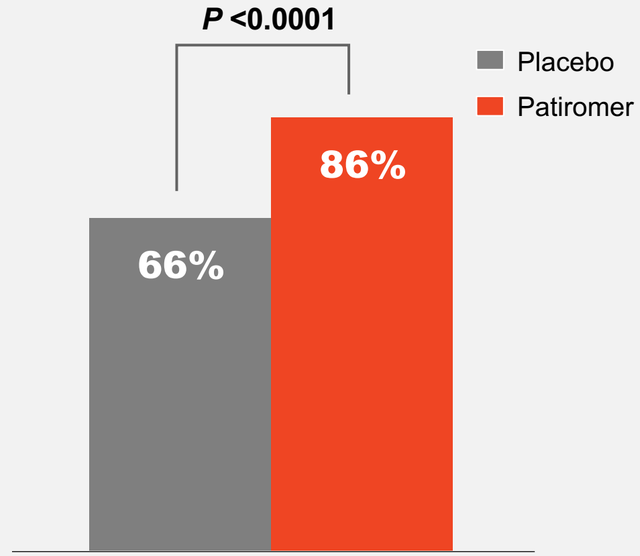
HF + (K^+ requiring d/c RAASi) or (eGFR<60 mL/min/1.73 m^2)



Secondary endpoint:
Increase of spironolactone dose to 50 mg

AMBER[3]

RHTN; eGFR 25–45 mL/min/1.73 m^2;
K^+ 4.3–5.1 mmol/L



Primary endpoint:
Patients who remained on spironolactone at Week 12

Patiromer enabled substantially more patients to:

- Remain on their RAASi medications at the end of the study, compared with those given placebo[1]
- Initiate and up-titrate spironolactone in patients with HF and advanced CKD with RHTN[2,3]

CKD, chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HTN: hypertension; RAASi, renin-angiotensin-aldosterone system inhibitor; T2D, type 2 diabetes

1. Weir MR, et al. N Engl J Med 2015;372:211–21
2. Pitt B, et al. Eur Heart J. 2011;32:820–8
3. Agarwal R, et al. Lancet. 2019;394:1540–50

Patiromer Safety and Tolerability Profile[1]

Most common adverse reactions were GI disorders and hypomagnesemia

System Organ Class	Adverse Reaction	Incidence (%)	Comments
GI disorders	Constipation	6.2	• Generally mild-to-moderate • Generally resolved spontaneously or with treatment • None reported as serious
	Diarrhea	3.0	
	Abdominal pain	2.9	
	Flatulence	1.8	
Metabolism and nutrition disorders	Hypomagnesemia	5.3	• Mild-to-moderate • No patient with serum level <0.4 mmol/L • Serum magnesium should be monitored for at least 1 month after initiating treatment and magnesium supplementation considered in patients who develop low serum magnesium levels
	Hypokalemia	1.5	

AE: adverse event; GI: gastrointestinal tract

1. Veltassa® Product Monograph, 2020.

Main Studies Evaluating Sodium Zirconium Cyclosilicate (SZC)

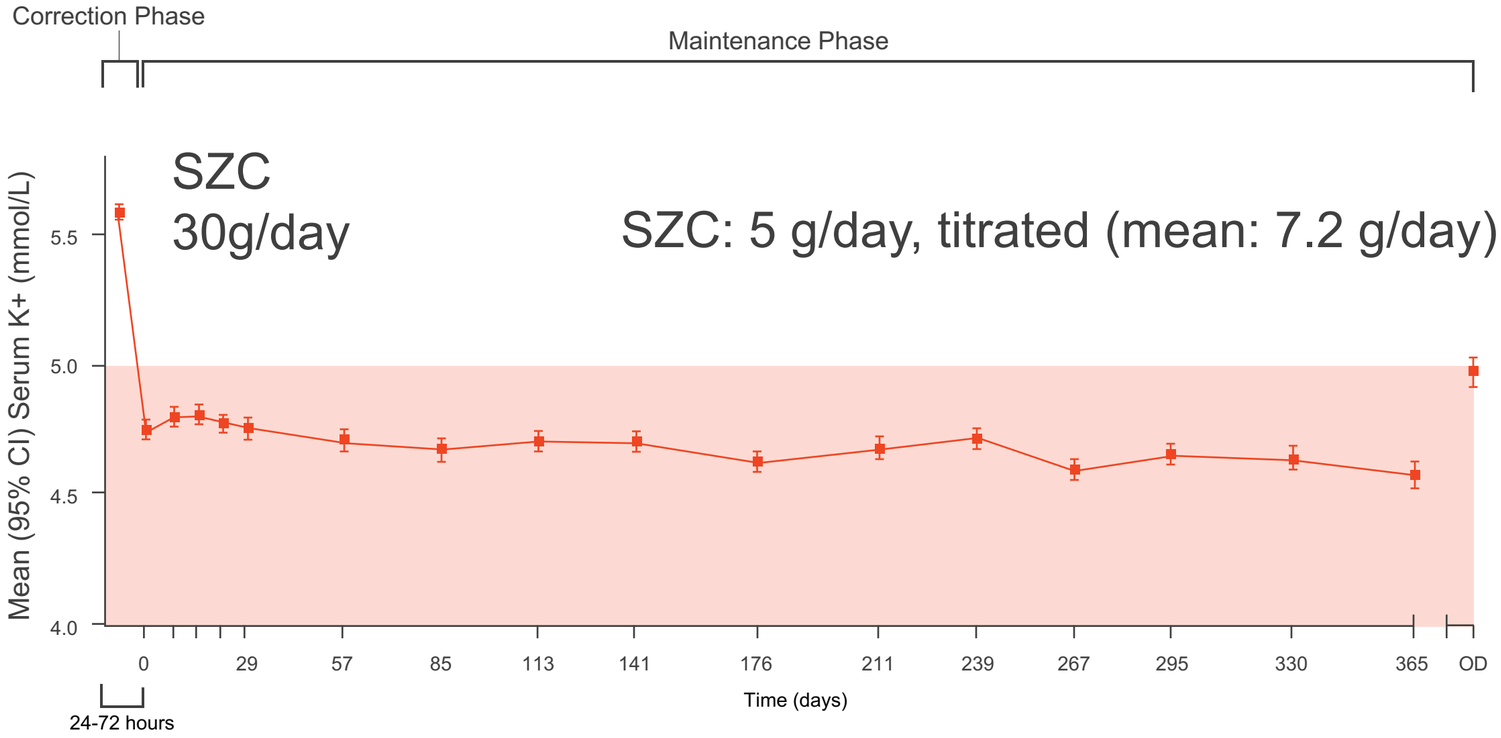
Trial	Design	Population	Objectives	Conclusions
Ash SR et al., 2015 (ZS-002)[1]	Phase II, randomized, double-blind, placebo-controlled, dose-escalating clinical trial (48 hours)	N = 90 Hyperkalemia, CKD 5.0 to 6.0 mmol/L **Stage 3 CKD**	Assess safety and efficacy	- Well-tolerated in patients with stable CKD and hyperkalemia leading to a rapid, sustained reduction in serum potassium
Packham DK et al., 2015 (ZS-003)[2]	Phase III, randomized, double-blind, placebo-controlled, two-stage, dose-ranging clinical trial (14 days)	N = 753 Hyperkalemia regardless of etiology 5.0 to 6.5 mmol/L	Confirm rapid K+ control	- Significant reduction in potassium levels at 48 hours -Normokalemia maintained during 12 days of maintenance therapy
Kosiborod M et al., 2014 (ZS-004: HARMONIZE TRIAL)[3]	Phase III, randomized, double-blind, placebo-controlled clinical trial (1 month + 11-month extension)	N = 258 Hyperkalemia regardless of etiology > 5.1 mmol/L	Establish an extended dose	- All 3 tested doses of SZC resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days
Spinowitz BS et al., 2019 (ZS-005)[4]	Phase III, open-label, two-part (12 months)	N = 751 Hyperkalemia regardless of etiology > 5.1 mmol/L	Establish long-term safety and efficacy	- Maintenance of normokalemia without **substantial RAASi changes for ≤ 12 months**

CKD: chronic kidney disease; RAASi: renin-angiotensin-aldosterone system inhibitor; SZC: sodium zirconium cyclosilicate

1. Ash, S. R. et al. Kidney Int 88, 404–411 (2015)
2. Packham, D. K. et al. New England Journal of Medicine 372, 222–231 (2015)
3. Kosiborod, M. et al. JAMA 312, 2223–2233 (2014)
4. Spinowitz, B. S. et al. CJASN 14, 798–809 (2019)

SZC Among Individuals with Hyperkalemia – A 12-Month Study (ZS-005)[1]

Mean serum potassium over time in the maintenance phase



RAAS Inhibitors

- 74% Continued
- 13% Increased
- 11% Discontinued
- 4% Initiated new

SZC: sodium zirconium cyclosilicate

1. Spinowitz, B. S. et al. CJASN 14, 798–809 (2019)

SZC Safety and Tolerability Across Clinical Trials[1]

The most commonly reported adverse reaction was **edema** related events which were reported in 5.7% of patients treated with SZC; 1.7, 1.8, 5.3 and 14.3% of patients randomized to placebo, SZC 5 g, 10 g, or 15 g once daily up to one month, respectively. SZC 15 g dose is not approved for use in Canada.	**Gastrointestinal:** has not been studied in patients with severe gastrointestinal disorders or history of major gastrointestinal surgery. Avoid use in patients with severe constipation, bowel obstruction or impaction.
	Cardiovascular: During correction of hyperkalemia, QT prolongation can be observed as the physiologic result of a decline in serum potassium concentration.
In clinical trials **4.1%** of patients treated with SZC developed **hypokalemia** with a serum potassium value <3.5 mmol/L, which was resolved with dose adjustment or discontinuation of SZC.	**Interactions:** SZC can transiently increase gastric pH, resulting in changes in solubility and absorption kinetics of co-administered drugs with pH-dependent bioavailability. Therefore, oral medications with gastric pH-dependent bioavailability should be administered at least 2 hours before or 2 hours after SZC.

SZC: sodium zirconium cyclosilicate

1. LOKELMA™ Canadian Product Monograph. AstraZeneca Canada Inc. Date of revision: July 23, 2019.

Considerations with the New Potassium Binders

	Patiromer[1]	SZC[2]
Mechanistic considerations	Uses calcium (as opposed to sodium) as the counter-ion which makes it a more optimal choice in patients with HF and CKD to avoid volume overload and hypertension[3]	Highly selective inorganic, insoluble cation that preferentially exchanges potassium for sodium and hydrogen, thereby entrapping K+ in the intestine[3]
Emergency setting	• SZC starts reducing serum potassium 1 hour after administration[2] • Patiromer results in a statistically significant reduction in serum potassium at 7 hours[1]	
Nonemergent setting	May be considered for the patients prone to recurrence or patients with nonemergent hyperkalemia	
Drug-drug interactions	Administer at least 3 hours before or 3 hours after other oral medicinal products	Oral medications with gastric pH-dependent bioavailability should be administered at least 2 hours before or 2 hours after
Adverse events (of interest)	Hypomagnesemia, gastrointestinal adverse events, and hypokalemia	Edema, gastrointestinal adverse events, and hypokalemia

CKD, chronic kidney disease; HF, heart failure; SZC, sodium zirconium cyclosilicate.

1. VELTASSA® Canadian Product Monograph. Otsuka Canada Pharmaceutical Inc. Date of revision: October 4, 2019.
2. LOKELMA™ Canadian Product Monograph. AstraZeneca Canada Inc. Date of revision: July 23, 2019.
3. Vijayakumar, S. et al. Eur Heart J Suppl 21, A41–A47 (2019)

Post-Test
Polling Question

Potassium binders can be used to rapidly and sustainably reduce serum potassium levels while enabling RAASi in patients with chronic hyperkalemia

Post-Test
Polling Question

Potassium binders can be used to rapidly and sustainably reduce serum potassium levels while enabling RAASi in patients with chronic hyperkalemia

Knowledge Question 1

HYPERKALEMIA

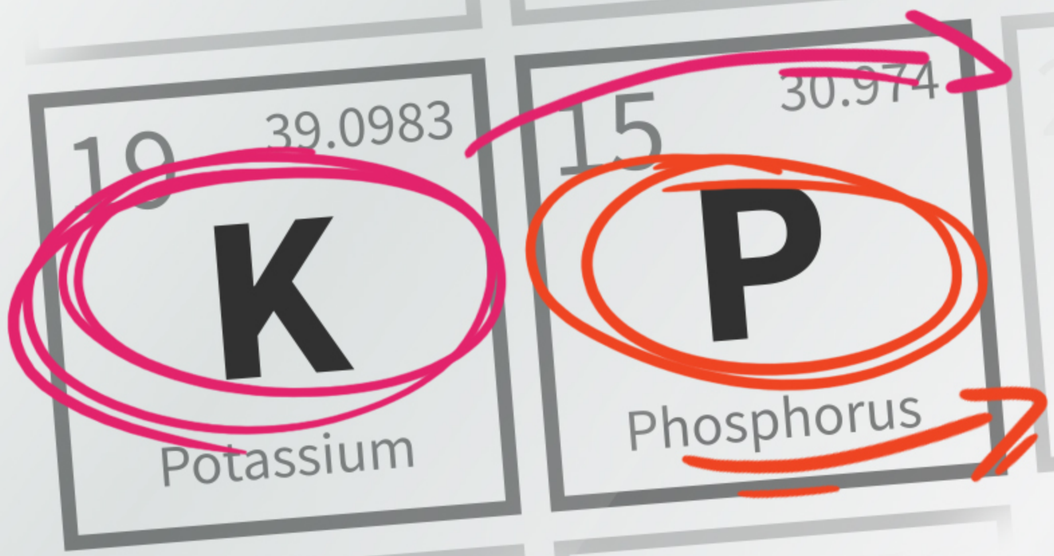
Which of the following statements is correct?

A. About half of patients with CKD stage 3–5 with hyperkalemia had ≥2 recurrences within 1 year

B. The presence of comorbidities does not influence the occurrence of hyperkalemia

C. Suboptimal RAASi dosing does not impact patient outcomes

D. RAASi dose reduction is still required with the new potassium binders



HIT OR MYTH

New Advances in the Management of Hyperkalemia and Hyperphosphatemia

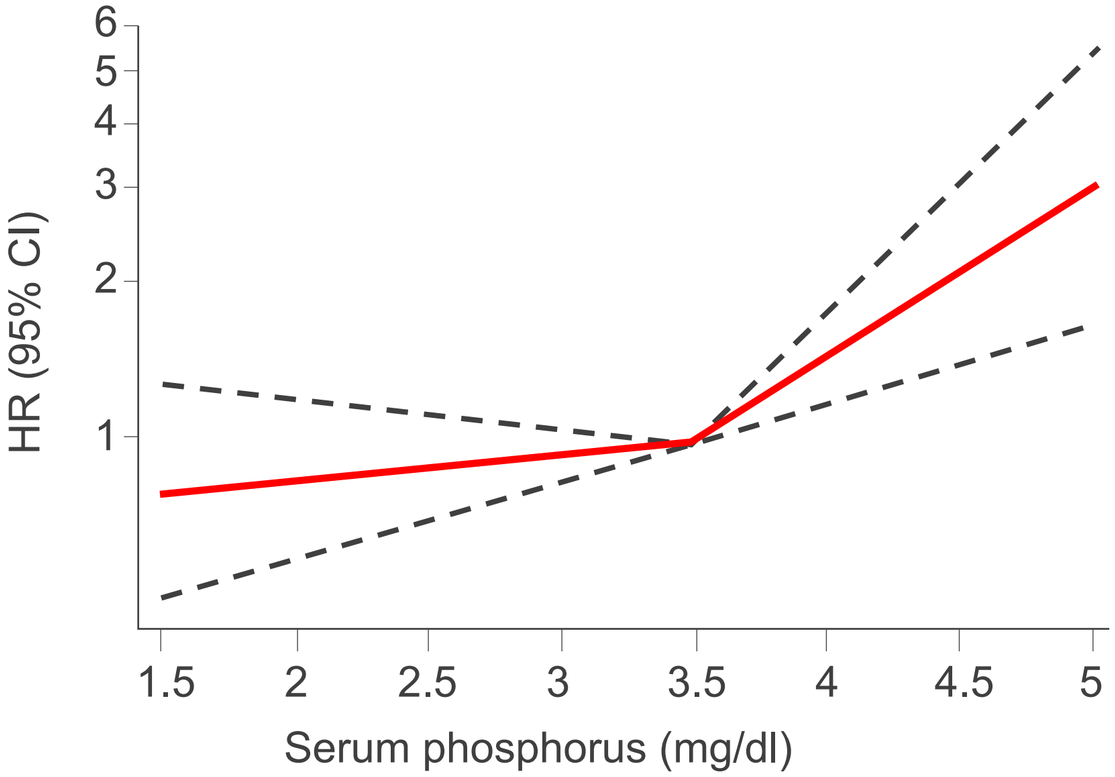
Hyperphosphatemia

Louis-Philippe Girard
MD MBT FRCPC

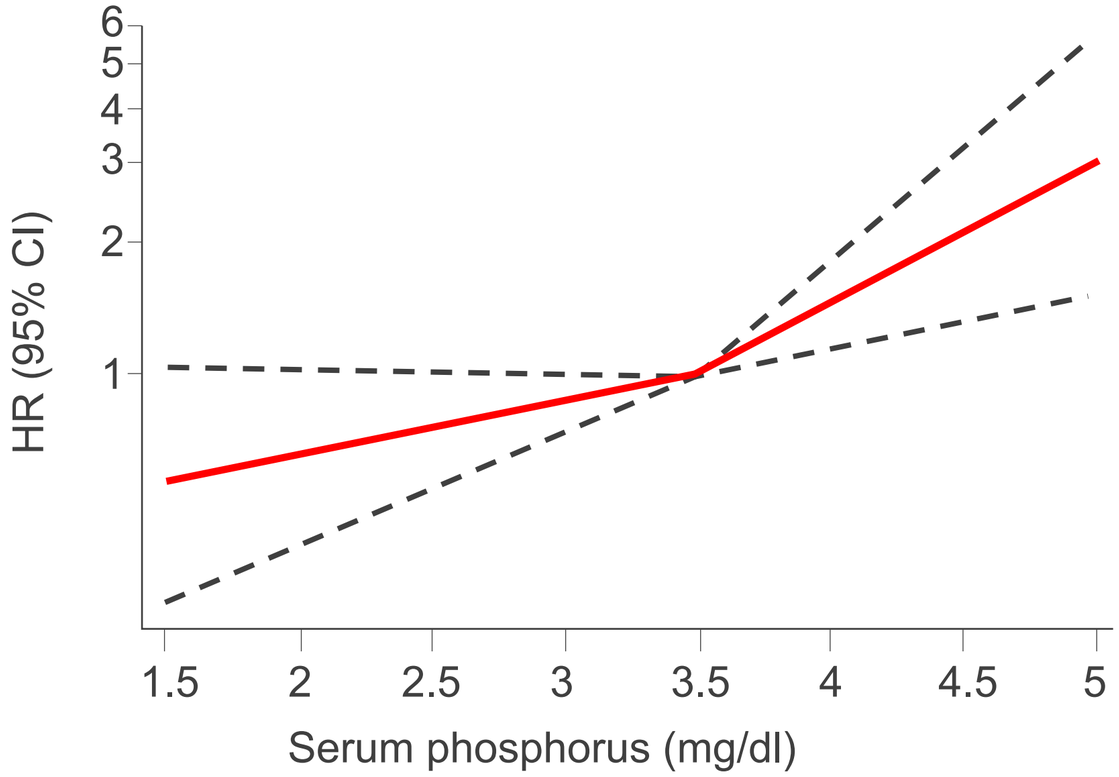
Hyperphosphatemia in advanced CKD is associated with increased risk of morbidity and mortality

Phosphate Level is Associated With All-Cause and Cardiovascular Mortality in the General Population[1]

All-cause mortality (fasted ≥12 hours)



Cardiovascular mortality (fasted ≥12 hours)



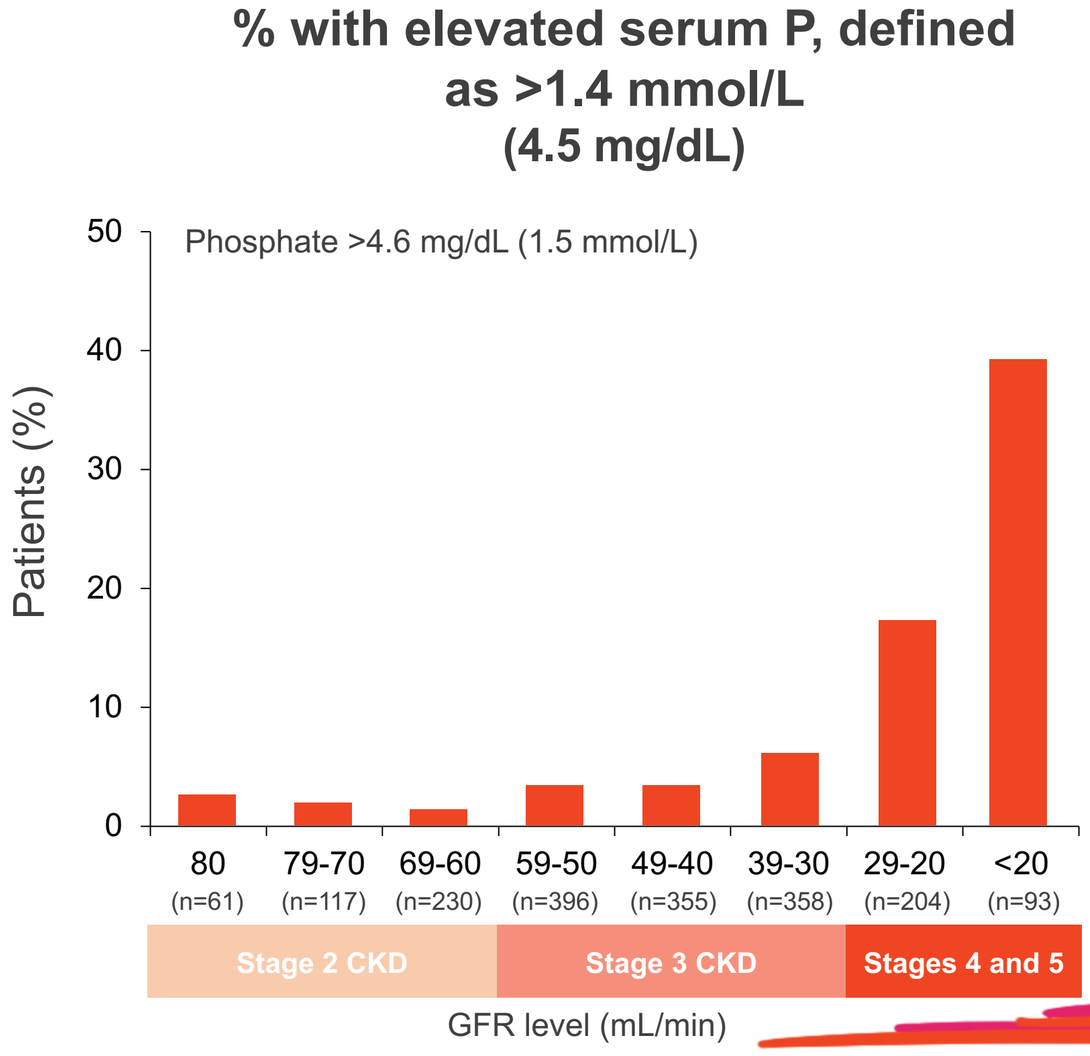
HR: hazard ratio

1. Vervloet MG, Sezer S, Massy ZA, et al. Nat Rev Nephrol. 2017;13(1):27-38.

Hyperphosphatemia Is Poorly Controlled in Advanced CKD[1]

Approximately 20% of patients with CKD stage 4 and 40% of those with CKD stage 5 had hyperphosphatemia

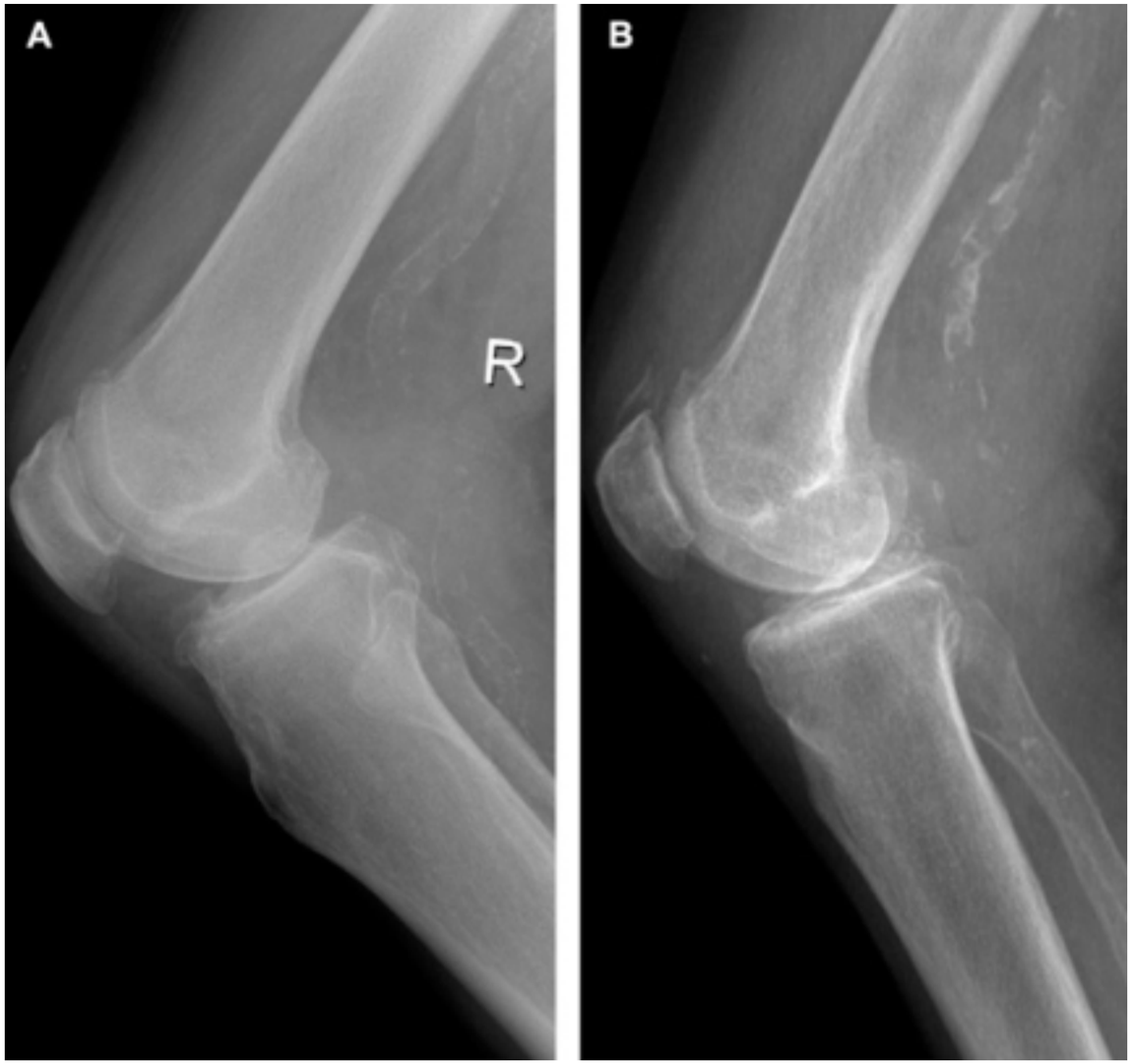
- Prospective, community-based, non-interventional, cohort study
- 1,814 patients with CKD over the age of 40



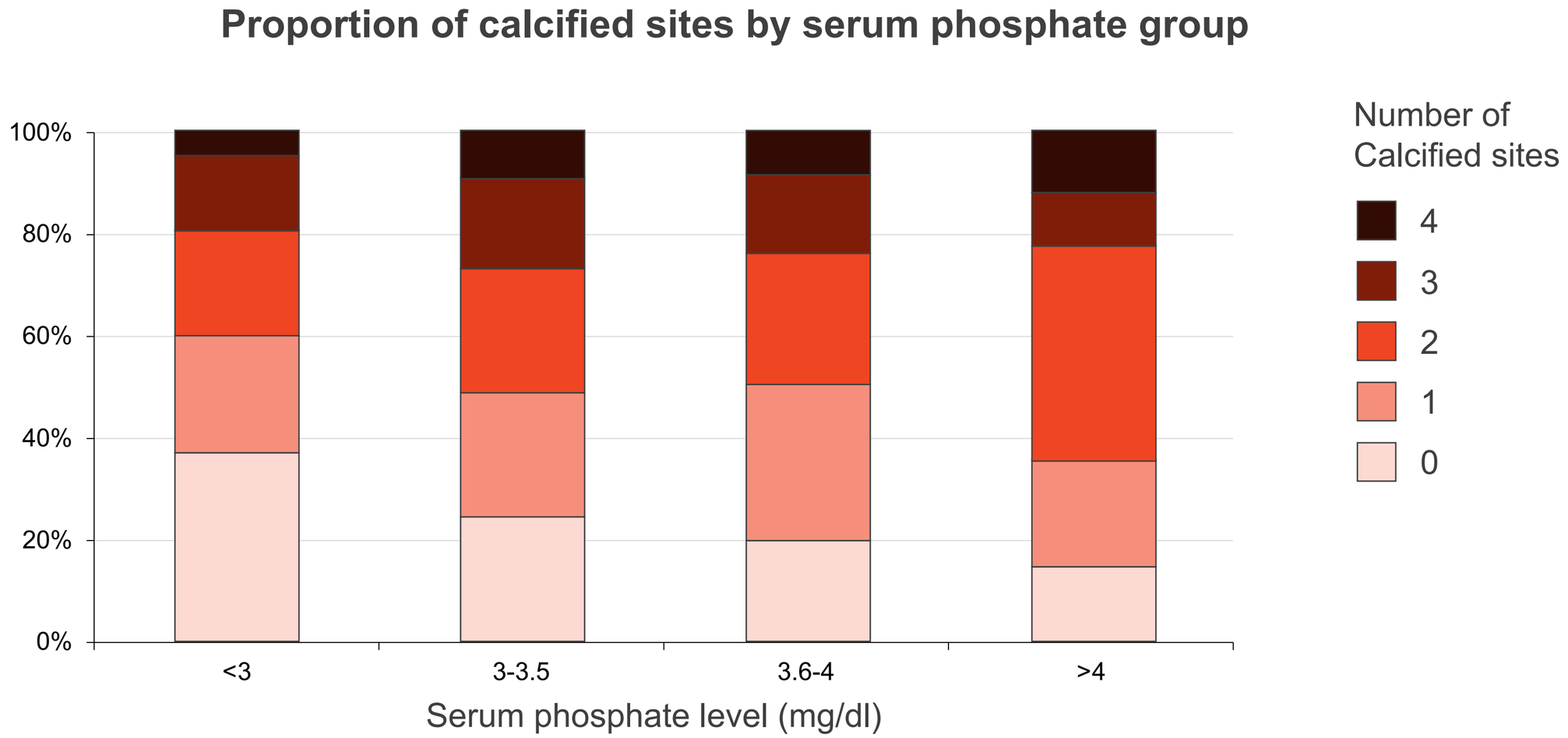
CKD: chronic kidney disease; P: phosphorus

1. Levin A, et al. Kidney Int 2007; 71(1):31–8.

Vascular Calcification



Association of Serum Phosphate with Vascular and Valvular Calcification in Moderate CKD[1]

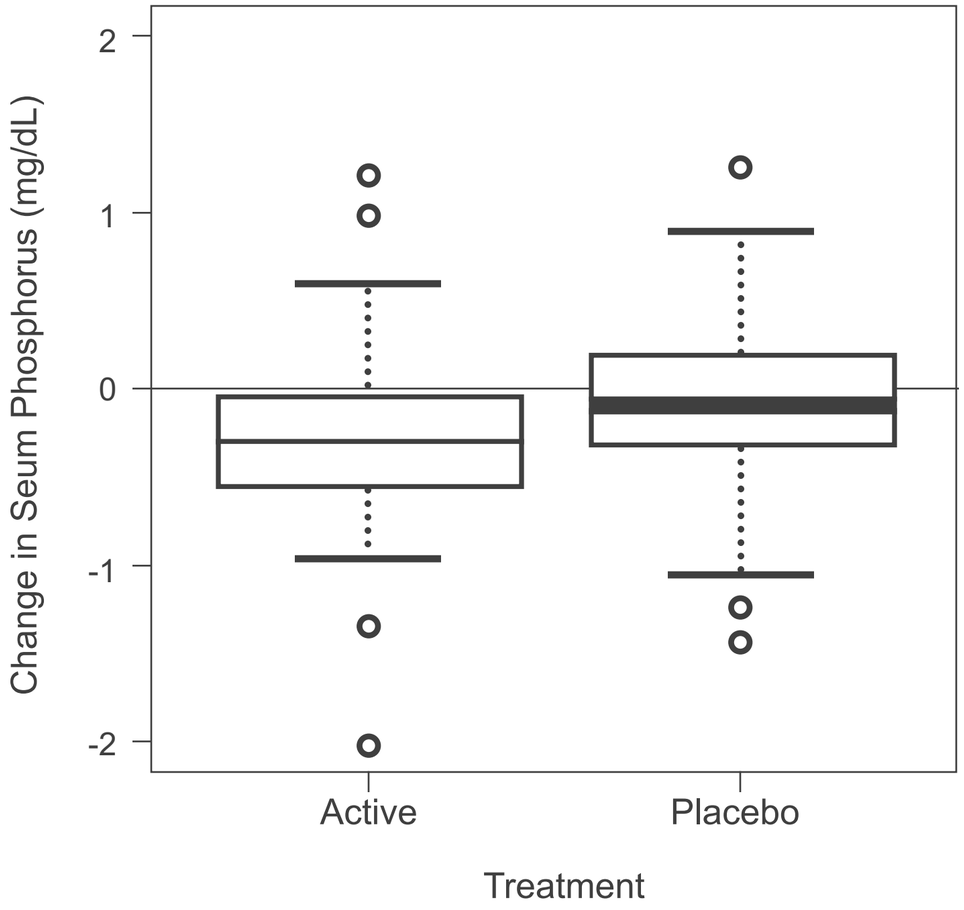


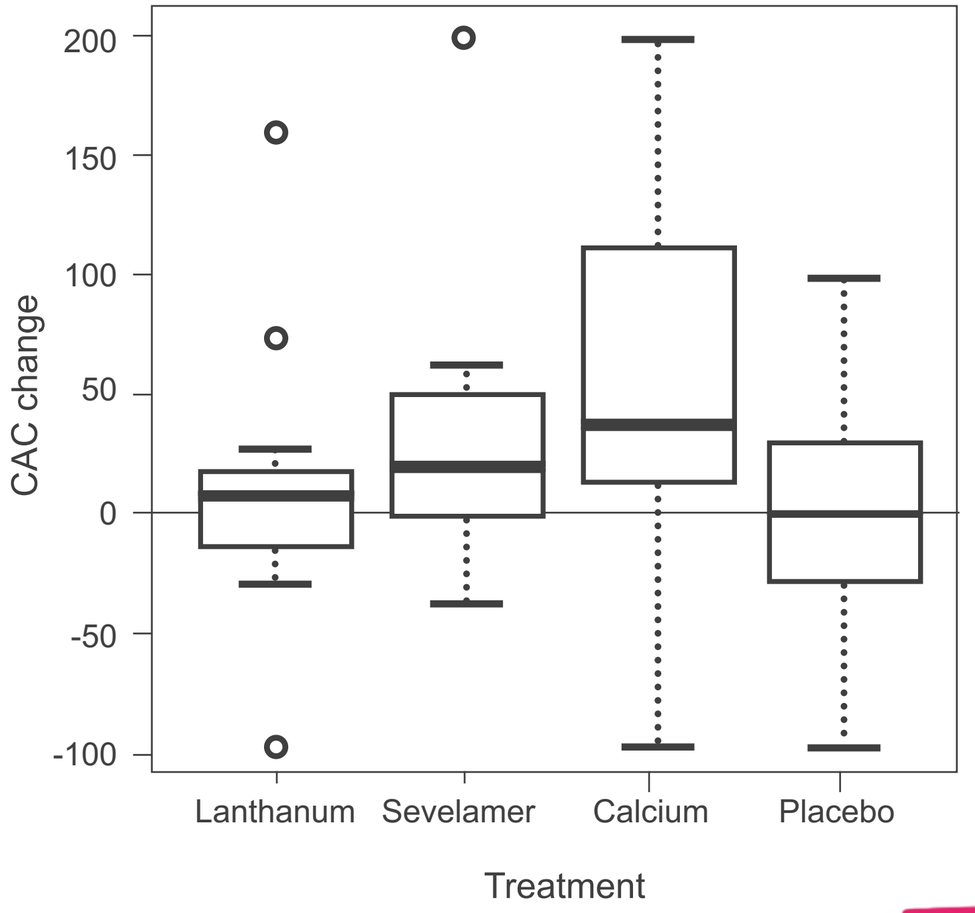
CKD: chronic kidney disease

1. Adeney KL, Siscovick DS, Ix JH, et al. J Am Soc Nephrol. 2009;20(2):381-387.

Vascular Calcification

Biochemical changes on study by treatment arm[1]





CKD: chronic kidney disease

1. Block GA, Wheeler DC, Persky MS, et al. J Am Soc Nephrol. 2012;23(8):1407-1415.

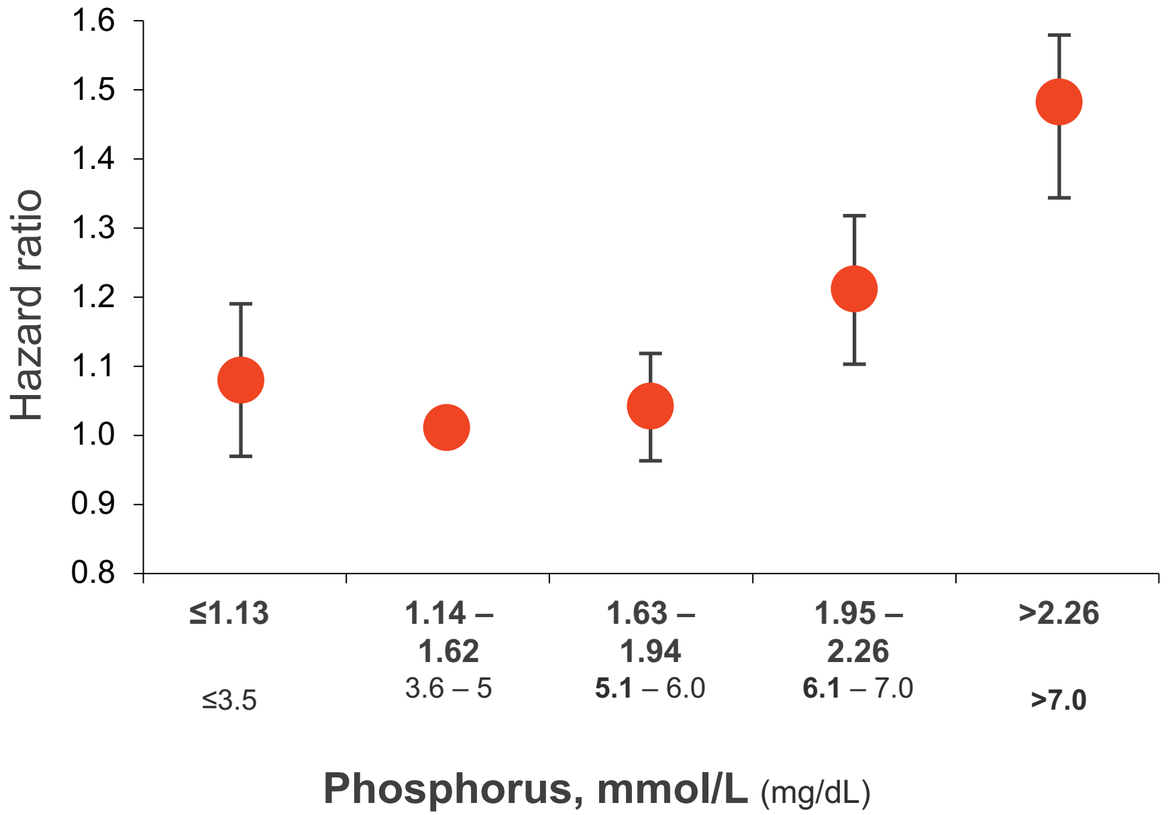
Uncontrolled Hyperphosphatemia is Associated with Increased Cardiovascular and Mortality Risk

Retrospective U.S. database analysis of patients on hemodialysis (N=14,829)[1]

Phosphorus Quintile, mmol/L (mg/dL)	Relative risk of CV event	95% CI	p value
≤1.42 (≤4.4) (Reference)	1.0	NA	NA
1.43 to 1.71 (4.5 to 5.3)	1.06	1.00 to 1.13	<0.05
1.72 to 2.03 (5.4 to 6.3)	1.13	1.06 to 1.19	<0.0001
2.04 to 2.43 (6.4 to 7.5)	1.14	1.07 to 1.22	<0.0001
>2.43 (>7.5)	1.25	1.17 to 1.33	<0.0001
Phosphorus data missing	1.13	0.90 to 1.41	NA

Risk of all-cause mortality[2]

NB. Normal range: 0.8–1.4 mmol/L (2.5–4.5 mg/dL)[3]



CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular

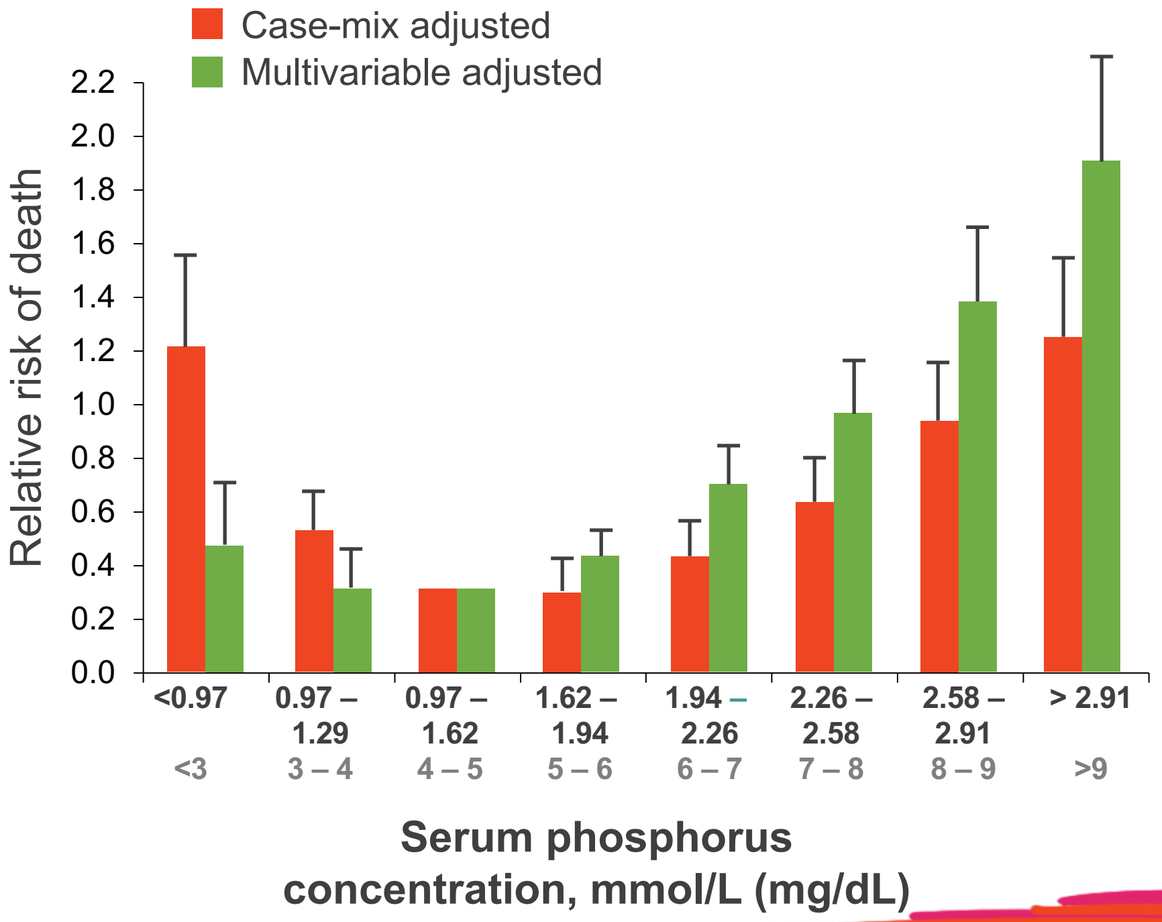
1. Slinin Y, et al. J Am Soc Nephrol 2005; 16(6):1788-93
2. Tentori F, et al. Am J Kidney Dis 2008; 52:519–30.
3. KDIGO. Kidney Int 2009; 76:S1–130.

Uncontrolled Hyperphosphatemia Increases Mortality Risk

Large U.S. observational study of hemodialysis patients with at least 1 determination of serum phosphorus and calcium during the last 3 months (N=40,538)[1]

Serum phosphorus >1.6 mmol/L (5.0 mg/dL) was associated with an ↑ relative risk of death[1]

NB. Normal range: 0.8–1.4 mmol/L (2.5–4.5 mg/dL)[2]



CKD: chronic kidney disease

1. Block GA, et al. J Am Soc Nephrol 2004; 15(8):2208-18.
2. KDIGO. Kidney Int 2009; 76:S1–130.

Post-Test
Polling Question

Hyperphosphatemia in advanced CKD is associated with increased risk of morbidity and mortality

Post-Test
Polling Question

Hyperphosphatemia in advanced CKD is associated with increased risk of morbidity and mortality

There is conclusive evidence that phosphate-binding agents are effective agents to reduce morbidity and mortality in patients with ESRD

Overview of Phosphate Binders[1,2]

Type	Daily dose	Advantages	Disadvantages
Aluminum hydroxide	No safe dose identified	Effective, inexpensive	Associated with cognitive disturbances, osteomalacia, and anemia. Potential for aluminum toxicity. Patient requires careful monitoring
Calcium carbonate	Variable	Effective, inexpensive	Potential for increased hypercalcemia; potential for PTH suppression; could lead to vascular calcification; GI side effects; high pill burden
Sevelamer hydrochloride	3 pills three times daily (9 pills/days)	Effective; lipid-lowering effect; potential cardioprotective effect, no calcium	Cost; high pill burden; GI side effects such as abdominal bloating, diarrhea, and constipation. Potential development of metabolic acidosis
Sevelamer carbonate		Effective; lipid-lowering effect; potential cardioprotective effect; no calcium; available as a powder, which may reduce pill burden	Cost; high pill burden; associated with GI side effects
Lanthanum carbonate	1 pill three times daily (3 pills/day)	Effective; no calcium; low pill burden	Cost; associated with GI side effects such as nausea, vomiting; systemic absorption may be a concern due to potential for accumulation
Sucroferric oxyhydroxide	3 pills per day	Effective; no calcium; reduced pill burden relative to sevelamer; does not lead to iron overload	Cost, discolored feces, diarrhea, nausea

GI: gastrointestinal

1. Umeukeje EM, et al. Patient Prefer Adherence 2018; 12:1175–91
2. Carfagna F, et al. Expert Opin Drug Saf 2018; 17(6):597-607

Systematic Review and Network Meta-Analysis of Phosphate Binders in CKD[1]

Treatment Effect		All-cause Mortality	Mean with 95%CI
Calcium	vs. Sevelamer		1.92 (1,22,3.00)
Lanthanum			1.80 (0.47,6.82)
Iron			1.71 (0.71,4.11)
CalSevMag			0.76 (0.27,2.15)
Placebo			1.38 (0.11,17.44)
Diet			0.95 (0.18,5.11)
Lanthanum	vs. Calcium		0.94 (0.25,3.55)
Iron			0.89 (0.41,1.95)
CalSevMag			0.40 (0.13,1.19)
Placebo			0.72 (0.06,9.10)
Diet			0.50 (0.09,2.77)
Iron	vs. Lanthanum		0.95 (0.26,3.41)
CalSevMag			0.42 (0.12,1.47)
Placebo			0.77 (0.04, 13.22)
Diet			0.53 (0.09, 3.25)
CalSevMag	vs. Iron		0.44 (0.13,1.53)
Placebo			0.81 (0.06,11.46)
Diet			0.56 (0.09,3.25)
Placebo	vs. CalSevMag		1.83 (0.12,28.08)
Diet			1.26 (0.34,4.69)
Diet	vs. Placebo		0.69 (0.03, 14.30)

1. Sekercioglu N, et al. PLoS One 2016; 11(6):e0156891

Mortality Benefit for Non-calcium vs. Calcium Phosphate Binders in CKD[1]

	Non-calcium binders		Calcium binders		Weight	Risk ratio (95% CI)
	Events	Total patients	Events	Total patients		
RCTs						
Barreto et al (2008)[12]	1	52	8	49	0.3%	0.12 (0.02—0.91)
Block et al (2007)[9]	11	60	23	67	3.2%	0.53 (0.28—1.00)
Chertow et al (2002)[5]	6	99	5	101	1.0%	1.22 (0.39—3.88)
Di Iorio et al (2012)[22]	12	107	22	105	3.0%	0.54 (0.28—1.03)
Kakuta et al (2011)[20]	0	91	0	92		Not estimable
Qunibi et al (2008)[13]	3	100	7	103	0.8%	0.44 (0.12—1.66)
Russo et al (2007)[10]	0	27	0	28		Not estimable
Sadek et al (2003)[6]	1	21	3	21	0.3%	0.33 (0.04—2.95)
Suki (2008)[14]	267	1053	275	1050	24.5%	0.97 (0.84—1.12)
Takei et al (2008)[15]	0	22	0	20		Not estimable
Wilson et al (2009)[16]	135	680	157	674	17.9%	0.85 (0.70—1.05)
Subtotal	**436**	**2312**	**500**	**2310**	**50.9%**	**0.78 (0.61—0.98)**
Heterogeneity: τ^2=0.03; x^2=12.35, df=7 (p=0.09); I^2=43%						
Test for overall effect: Z=2.09 (p=0.04)						
Non-randomised studies						
Borzecki et al (2007)[11]	148	608	228	769	20.6%	0.82 (0.69—0.98)
Jean et al (2011)[19]	62	247	109	432	12.7%	0.99 (0.76—1.30)
Panichi et al (2010)[17]	74	242	170	515	15.9%	0.93 (0.74—1.16)
Subtotal	**284**	**1097**	**507**	**1716**	**49.1%**	**0.89 (0.78—1900)**
Heterogeneity: τ^2=0.00; x^2=1.57, df=2 (p=0.46); I^2=0%						
Test for overall effect: Z=1.90 (p=0.06)						
Total	**720**	**3409**	**1007**	**4026**	**100.0%**	**0.87 (0.77—0.97)**
Heterogeneity: τ^2=0.01; x^2=13.88, df=10 (p=0.18); I^2=28%						
Test for overall effect: Z=2.40 (p=0.02)						
Test for subgroup differences: x^2=0.92, df=1 (p=0.34), I^2=0%						

1. Jamal SA, et al. Lancet 2013; 382: 1268–77

Evidence that Phosphate Binders Affect Hard Clinical Endpoints is Inconclusive[1]

When compared amongst phosphate binders, sevelamer reduced all-cause mortality in dialysis patients by 50–60% vs calcium whereas other comparisons* did not reach statistical significance or were not tested

No drug class lowered cardiovascular events or cardiovascular mortality when compared to placebo.

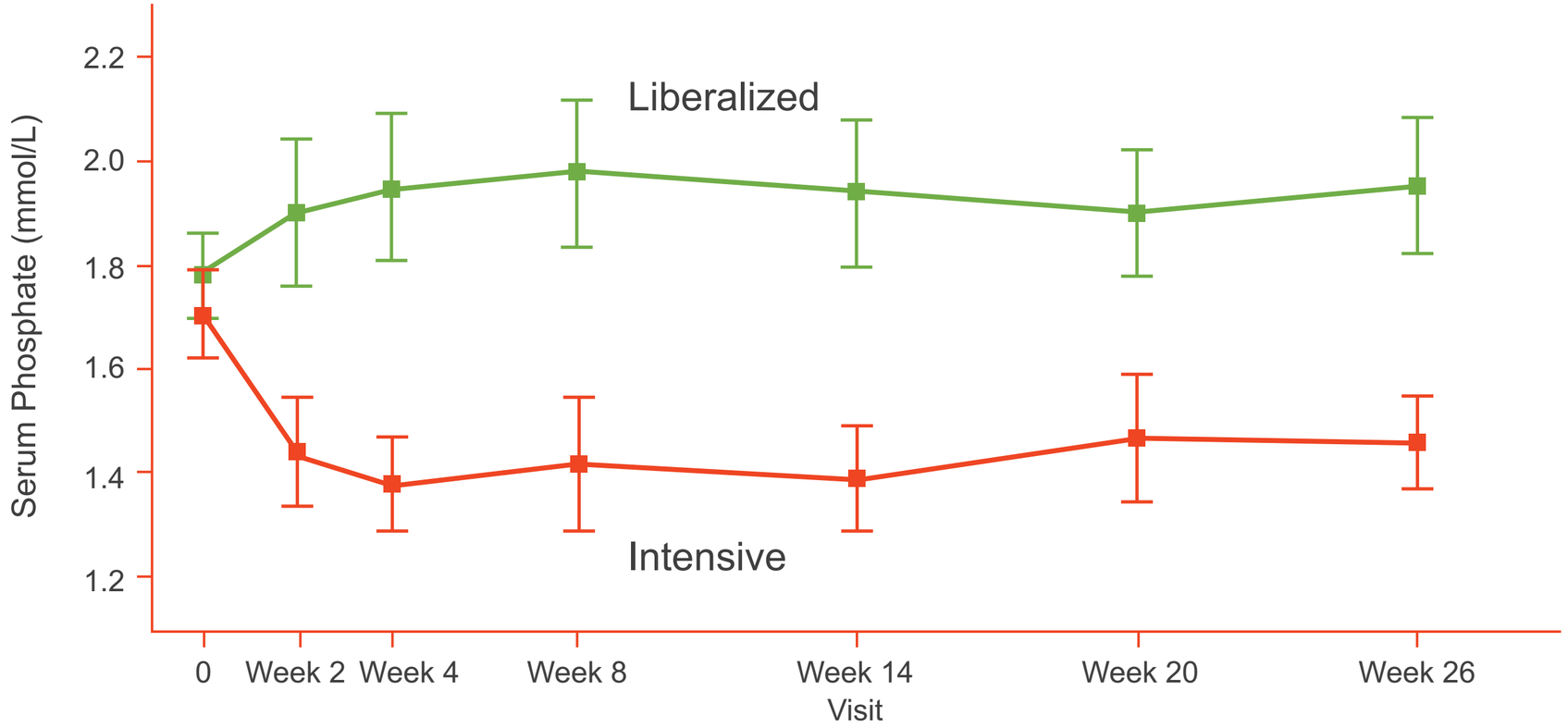
Type	Hard clinical endpoints
Magnesium containing phosphate binders	-
Sevelamer	• No reduction of proteinuria in CKD patients (eGFR > 15 ml/min) • Lower all-cause mortality in CKD patients (stages 3–5D) but not cardiovascular event rate or mortality compared to calcium-containing phosphate binders in most studies
Bixalomer, colestilan	-
Lanthanum carbonate	• Lower all-cause mortality but not cardiovascular event rate compared to other phosphate binders
Ferric citrate	• Fewer hospital admissions and less frequent initiation of dialysis in one small study in non-dialysis CKD patients
Sucroferric oxyhydroxide[2]	• Patients on maintenance SFOH had a significantly lower rate of hospital admissions > 24 hours vs. patients who discontinued SFOH and switched to other phosphate binders

*Comparison between phosphate binders containing sevelamer, colestilan, bixalomer, lanthanum, iron compounds, calcium, nicotinic acid, and calcium plus magnesium
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

1. Floege J. J Nephrol. 2020;33(3):497-508
2. Coyne DW et al. Kidney Med 2020; doi.org/10.1016/j.xkme.2020.01.009

Two phosphAte taRGets in End-stage renal disease Trial (TARGET) – Sustained Separation in Serum Phosphate Concentration[1]

Sustained separation in serum phosphate concentration in patients randomized to a liberalized serum phosphate target or an intensive serum phosphate

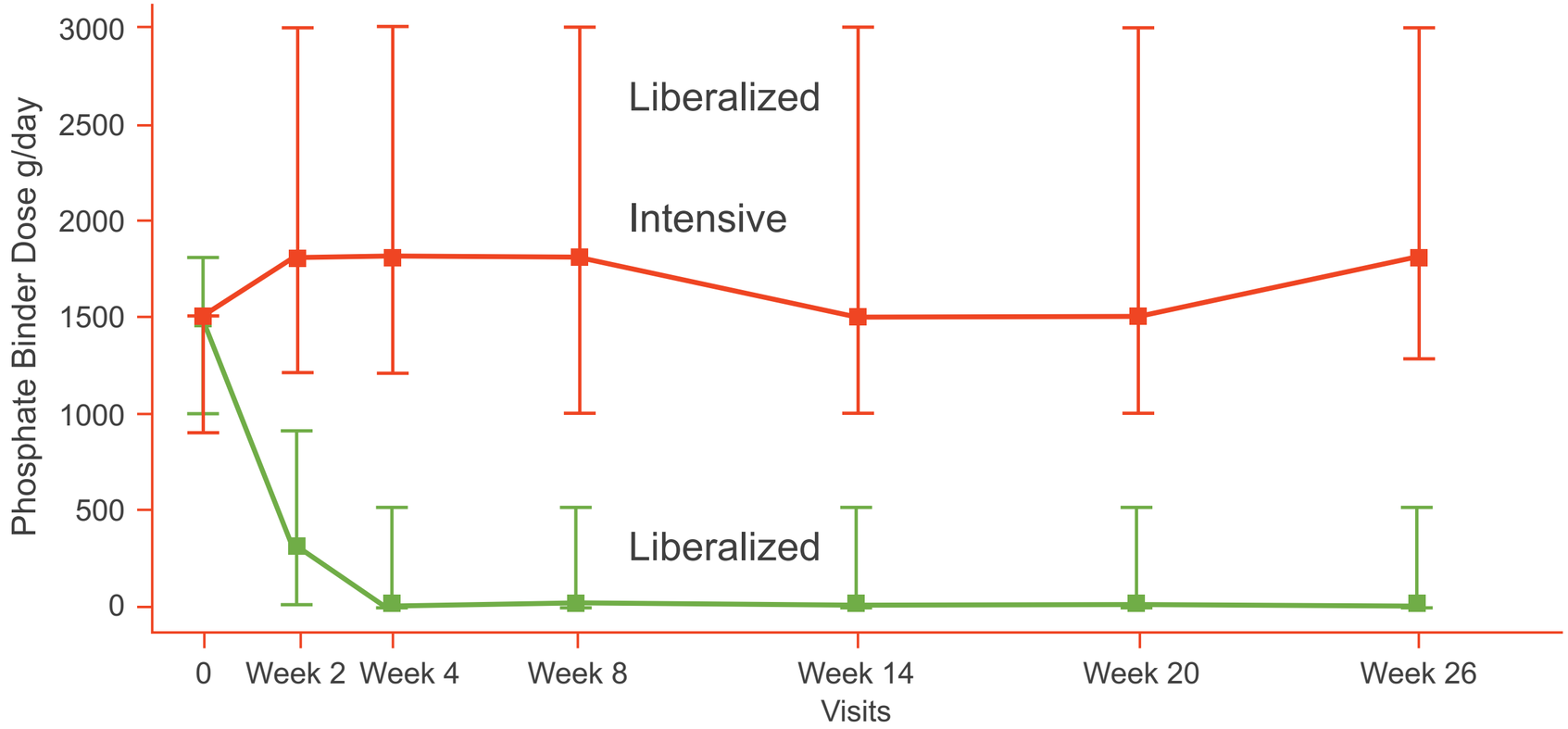


	0	Week 2	Week 4	Week 8	Week 14	Week 20	Week 26
Liberalized	51	50	50	43	47	44	47
Intensive	53	53	53	43	45	44	48

1. Wald R, Rabbat CG, Girard L, et al. Clin J Am Soc Nephrol. 2017;12(6):965-973.

Two phosphAte taRGets in End-stage renal disease Trial (TARGET) – Sustained Separation in the Dose of Elemental Calcium Administered

Sustained separation in the dose of elemental calcium administered in patients randomized to a liberalized phosphate target) or an intensive serum phosphate target



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1. Wald R, Rabbat CG, Girard L, et al. Clin J Am Soc Nephrol. 2017;12(6):965-973.

Two phosphAte taRGets in End-stage renal disease Trial (TARGET) – Outcomes Were Comparable Between Groups[1]

Clinical outcomes by intervention group

Outcome	Liberalized, n=51	Intensive, n=53	Relative Risk (95% CI)
Vascular death or vascular event	3 (6)	5 (9)	0.62 (0.16 to 2.48)
Fracture	3 (6)	1 (2)	3.12 (0.34 to 29.0)
Calciphylaxis	0 (0)	0 (0)	NA
Parathyroidectomy	1 (2)	1 (2)	1.04 (0.07 to 16.2)
Hospitalization (all cause)	18 (35)	14 (26)	1.34 (0.75 to 2.39)
Hospitalization for vascular reason	5 (10)	5 (9)	1.04 (0.32 to 3.38)
Serious adverse event (not listed above)	0 (0)	0 (0)	NA

Data reported as number (%). 95% CI, 95% confidence interval; NA, not applicable

1. Wald R, Rabbat CG, Girard L, et al. Clin J Am Soc Nephrol. 2017;12(6):965-973.

Post-Test
Polling Question

There is conclusive evidence that phosphate-binding agents are effective agents to reduce morbidity and mortality in patients with ESRD

Post-Test
Polling Question

There is conclusive evidence that phosphate-binding agents are effective agents to reduce morbidity and mortality in patients with ESRD

Phosphate-binding agents have demonstrated phosphate-lowering efficacy in real-world studies, with a substantially lower pill burden compared to traditional phosphate binders

Sucroferric Oxyhydroxide

- Calcium-free binder **indicated for the control of serum phosphorus levels** in adult patients with ESRD on dialysis

- **Dosing**
  - Recommended starting dose: 500 mg of iron TID with meals
  - Maximum recommended dose: 3,000 mg of iron (6 tablets)
  - No adjustments needed in elderly

ESRD: end-stage renal disease; TID: three times weekly

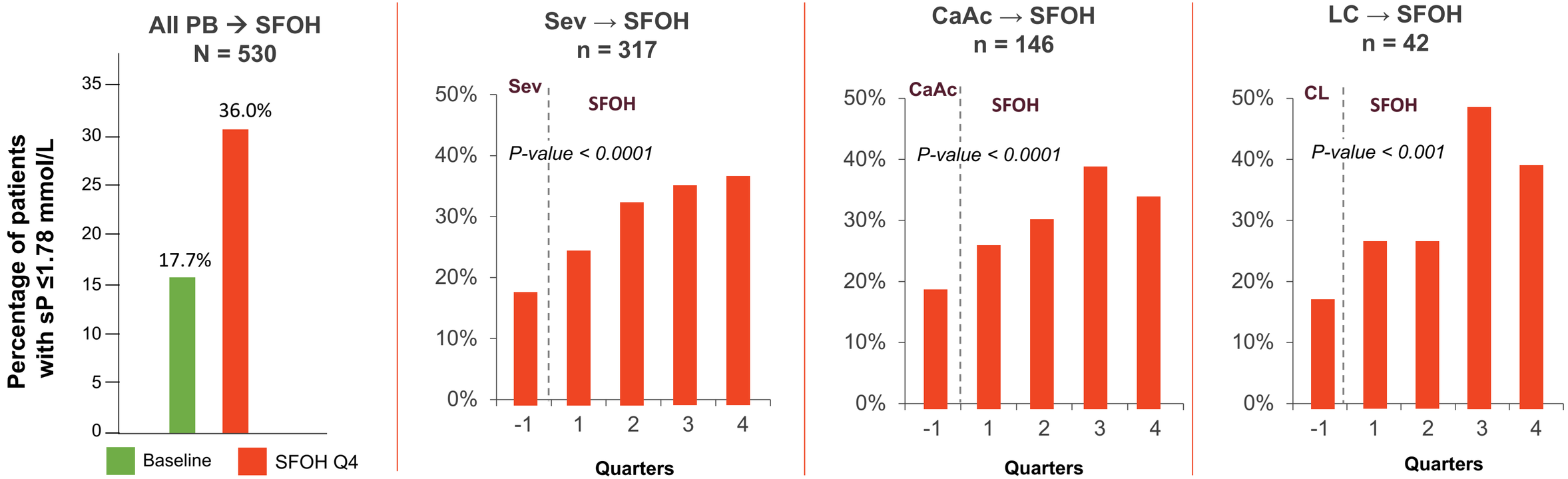
1. VELPHORO® Product Monograph. Date of preparation: October 4, 2019

SFOH Effectiveness in Chronic Hemodialysis Patients – 12-month Follow-up Real-world Data[1]

De-identified patient records for in-centre hemodialysis patients who switched from another PB to SFOH (March 2014-March 2015)

Proportion of patients with phosphorus ≤1.78 mmol/L compared between 3-month intervals (Q1–Q4) of SFOH treatment and baseline

Change in percentage of patients with sP ≤1.78 mmol/L after switching from other PBs



SFOH demonstrated control of phosphorous levels

CaAc: calcium acetate; LC: lanthanum carbonate; PB: phosphate binder; Sev: sevelamer; SFOH: sucroferric oxyhydroxide; Q:quarter

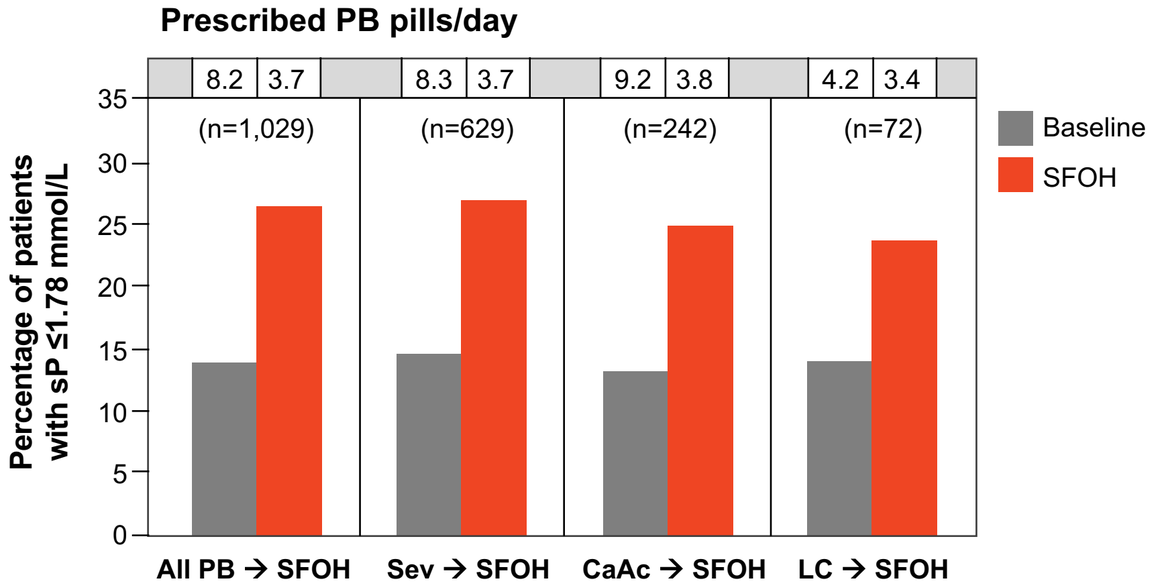
1. Kendrick J, et al. J Ren Nutr. 2019 Sep;29(5):428-437

Retrospective Analysis of Pharmacy Data of SFOH in Patients on Chronic Hemodialysis (≤6 mo)[1]

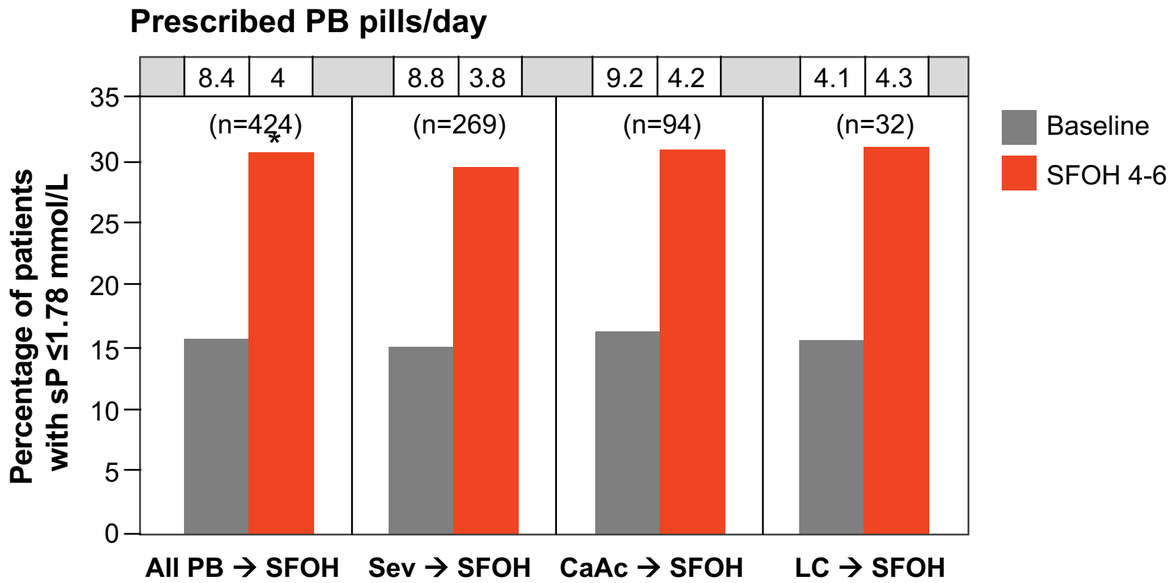
De-identified records for in-centre hemodialysis patients who received their first SFOH prescription between April 2014 and March 2015

Proportion of patients with phosphorus ≤1.78 mmol/L and the mean prescribed PB pills/day were compared

Change in percentage of patients with sP≤1.78 mmol/L after switching from other PBs (Month 1–3 cohort; n=1,029)



Change in percentage of patients with sP ≤1.78 mmol/L after switching from other PBs (Month 4–6 cohort; n=424)



SFOH demonstrated control of phosphorous levels with a low mean prescribed number of pills per day

*p<0.001, †KDOQI recommended phosphorous

CaAc: calcium acetate; LC: lanthanum carbonate; PB: phosphate binder; Sev: sevelamer; SFOH: sucroferric oxyhydroxide; P: phosphorus

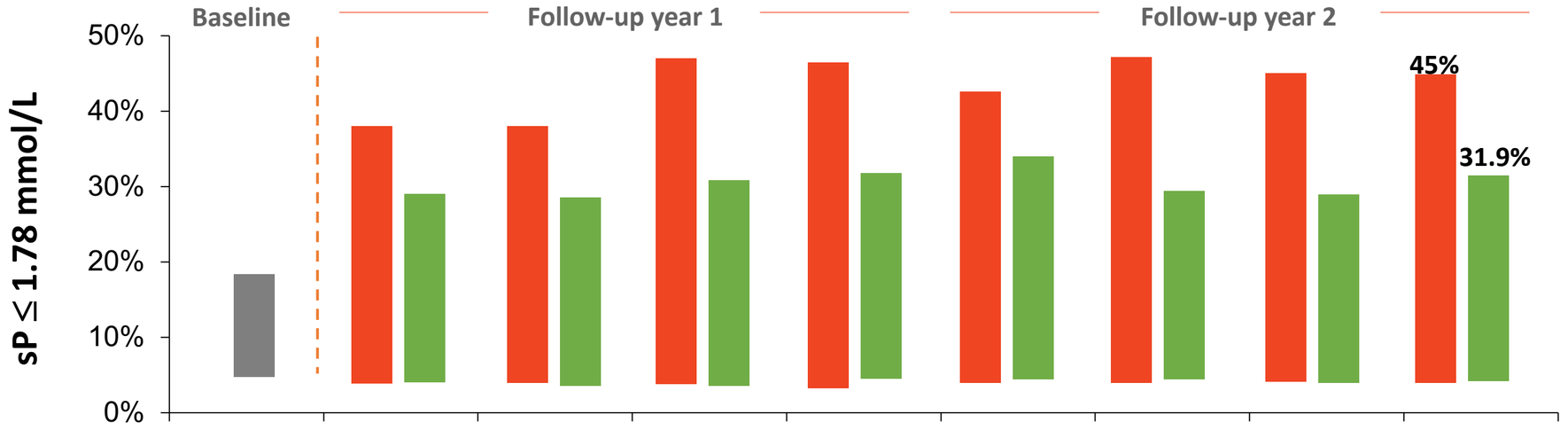
1. Coyne D et al. Clin Nephrol 2017; 2:59–67

Retrospective, Comparative Cohort Study of SFOH in Maintenance Hemodialysis (2 years)[1]

De-identified records extracted from Fresenius Kidney Care electronic records between April 2014 and April 2015

Patients prescribed 2 years of uninterrupted SFOH therapy (maintenance SFOH) were compared with patients who discontinued SFOH therapy within 90 days of initiation and switched to other PB(s) for 2 years

Percentage of patients with sP ≤1.78 mmol/L



	Q1	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Mean Change from baseline*	
sP (mmol/L)	2.18	2.00	1.98	1.93	1.91	1.92	1.90	1.88	1.93	-0.21	P=0.014
		2.08	2.06	2.05	2.03	2.03	2.04	2.05	2.05	-0.15	
# PB pills/day	10.8	4.2	4.4	4.5	4.6	4.9	5.0	5.0	5.1	-3.7	P=0.2
		10.7	10.3	10.4	10.6	10.7	10.8	10.8	10.9	-0.7	

Patients who maintained 2 years of SFOH therapy achieved lower phosphorous levels, were more likely to achieve target serum phosphorus levels of ≤1.78 mmol/L, and were prescribed ~50% fewer phosphate binder pills per day

* Mean change (Q1-Q8) from baseline (-Q1)

PB: phosphate binder; SFOH: sucroferric oxyhydroxide; dSFOH: discontinued SFOH, non-SFOH binder therapy; sP: serum phosphorus

1. Coyne DW et al. Kidney Med 2020; doi.org/10.1016/j.xkme.2020.01.009

Post-Test
Polling Question

Phosphate-binding agents have demonstrated phosphate-lowering efficacy in real-world studies, with a substantially lower pill burden compared to traditional phosphate binders

Post-Test
Polling Question

Phosphate-binding agents have demonstrated phosphate-lowering efficacy in real-world studies, with a substantially lower pill burden compared to traditional phosphate binders

Knowledge Question 2

Hyperphosphatemia

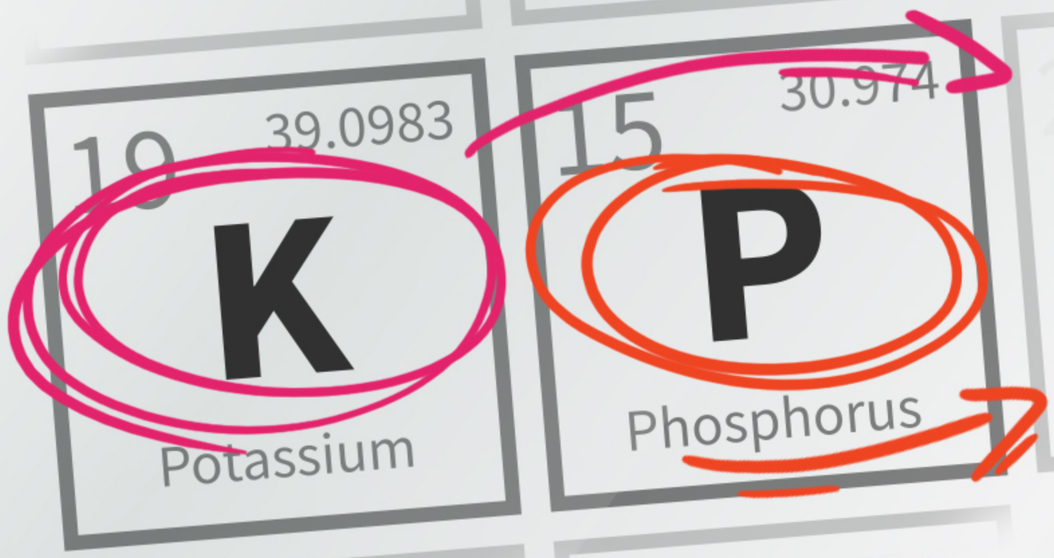
Which of the following statements is correct?

A. Hyperphosphatemia is rare in dialysis patients

B. Serum phosphorus >1.6 mmol/L is associated with an increased relative risk of death

C. There is conclusive evidence that phosphate binders lower cardiovascular mortality

D. SFOH demonstrated control of phosphorous levels with a high pill burden

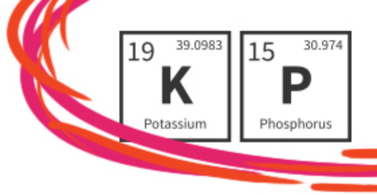


HIT OR MYTH

New Advances in the Management of Hyperkalemia and Hyperphosphatemia

Taking Action

Juliya Hemmett
MD MHPE FRCPC



What changes are you likely to make in the way you manage patients with hyperkalemia based on what you've learned today?

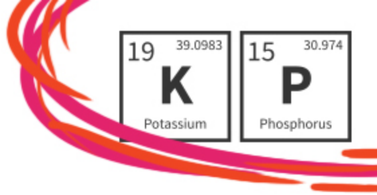
Apply epidemiologic data to identify patients at high risk

Apply clinical efficacy and safety data on new potassium binders to reduce the impact of hyperkalemia

Construct a plan to integrate recent evidence presented today into my practice

I am already successfully implementing the presented strategies into my practice

The topics presented did not apply to my patients and/or practice



What changes are you likely to make in the way you manage patients with hyperphosphatemia based on what you've learned today?

Apply epidemiologic data to identify patients at high risk

Apply clinical efficacy and safety data on new phosphate binders to reduce the impact of hyperphosphatemia

Construct a plan to integrate recent evidence presented today into my practice

I am already successfully implementing the presented strategies into my practice

The topics presented did not apply to my patients and/or practice

Action Plan

Based on what you have seen today, what specific action(s) do you expect to take over the next 6 months? Select all that apply.

- Read/re-read publications and clinical trials on the new potassium and phosphate binders
- Review my charts to determine if my patients with hyperkalemia or hyperphosphatemia would benefit from the latest evidence presented today
- Attend additional CHE events on the optimal management of hyperkalemia and/or hyperphosphatemia
- Discuss strategies with my colleagues to enable RAASi in patients with or at risk of hyperkalemia
- Schedule grand rounds or a journal club to review this data with my colleagues
- Engage with my allied health care colleagues to discuss dietary restriction of potassium and/or phosphate

HIT OR MYTH!

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Questions and Discussion

Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN

HIT OR MYTH

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Thank You!

Please ensure to complete the electronic evaluation.

Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN