Kidney Medicine

Phosphate Absorption and Hyperphosphatemia Management in Kidney Disease: A Physiology-Based Review

Steven N. Fishbane and Sagar Nigwekar

Phosphate absorption occurs in the gastrointestinal tract through paracellular absorption and transcellular transport. The paracellular pathway does not saturate and has a significantly higher absorption capacity than does the transcellular pathway. Evidence indicates that this pathway is the primary mechanism of intestinal phosphate absorption, particularly with Western diets containing high amounts of phosphorus. Elevated serum phosphorus concentrations are associated with cardiovascular morbidity and mortality but serum phosphorus concentrations > 5.5 mg/dL are highly prevalent despite best efforts with dietary phosphate restriction, dialysis, and the use of phosphate binders. The efficacy of phosphate binders may be inherently limited because the mechanism of action does not target any phosphate absorption pathway. Thus, therapeutic innovations are needed to address the limitations of phosphate binders. Novel therapies leveraging new mechanistic understandings of phosphate absorption and the primacy of the paracellular pathway may improve phosphate control. Phosphate absorption inhibitors that target the pathway are a novel therapeutic class. Tenapanor is an investigational first-in-class nonbinder phosphate absorption inhibitor that inhibits the sodium-hydrogen exchanger isoform 3 to reduce paracellular permeability specific to phosphate. Phosphate absorption inhibitors may represent a new mechanistic approach to phosphate management with the potential to improve clinical outcomes.

Complete author and article information provided before references.

Kidney Med. 3(6):1057-1064. Published online August 27, 2021.

doi: 10.1016/j.xkme.2021.07.003

Systemic phosphate homeostasis is maintained primarily through urinary excretion.[1] As chronic kidney disease (CKD) progresses, kidney function declines, leading to phosphate retention.[2] Elevated serum phosphorus concentrations, or hyperphosphatemia, are seen in most patients with advanced CKD and those receiving dialysis.[3]

NEW UNDERSTANDING OF PHOSPHATE ABSORPTION PATHWAYS

Diet is the primary source of phosphate intake and absorption of dietary phosphate occurs in the gastrointestinal (GI) tract through 2 distinct pathways: paracellular absorption and transcellular transport (Fig 1[4-14]).[4] Paracellular absorption occurs passively along concentration gradients through the tight junction complexes (eg, claudins and occludins) between cell membranes.[5] The paracellular pathway is not limited by a saturation point and has been shown to be responsible for most intestinal phosphate absorption, particularly when luminal phosphate concentrations are high.[4] The transcellular sodium-dependent pathway takes in phosphate primarily through the action of the sodium-dependent phosphate cotransporter 2b (NaPi2b).[6] Evidence suggests that NaPi2b is responsible for phosphate absorption in the presence of low amounts of dietary phosphate[4,6] but because this pathway saturates,[4] it is less relevant for people who consume Western diets, which typically have high amounts of phosphorus.[7]

New studies have found that the paracellular pathway is the primary mechanism of phosphate absorption under typical conditions of phosphate availability in individuals consuming standard Western diets, not the transcellular pathway as previously believed. Although transcellular phosphate transport by NaPi2b plays a significant role in rodents,[8,15] recent clinical evidence shows this pathway to be less physiologically relevant in humans.[16] Furthermore, maximum absorption through the transcellular pathway is reached at a very low luminal concentration of ~2 mmol/L.[4] Based on reported gastric volumes of 750 to 1,500 mL,[17] a typical Western diet of ~2,500 mg of phosphate per day[7,18] translates to luminal concentrations of 18 to 36 mmol/L,[4] far exceeding the maximum concentration that the transcellular pathway can accommodate. Paracellular absorption is biologically favored by the intestinal electrochemical gradient and has much higher capacity for absorption than the transcellular transport system.[5]

CHALLENGES IN ACHIEVING PHOSPHATE GOALS WITH CURRENT THERAPIES

Phosphate is one of the most abundant minerals in the body, and serum phosphorus concentration must be maintained within the normal range (2.5-4.5 mg/dL) for optimal functioning of many biological processes.[19] Elevated serum phosphorus concentrations are associated with significant negative clinical outcomes, and management of phosphate is a guideline-recommended established clinical practice.[9,20] National Kidney Foundation-Kidney Disease Outcomes Quality Initiative/ (NKF-KDOQI) 2003 guidelines recommend targeting phosphorus concentrations of 2.7 to 4.6 mg/dL in patients with stages 3 and 4 CKD and 3.5 to 5.5 mg/dL in patients with stage 5 CKD and those receiving dialysis.[9] These recommendations are based on the association between elevated serum phosphorus concentrations and adverse

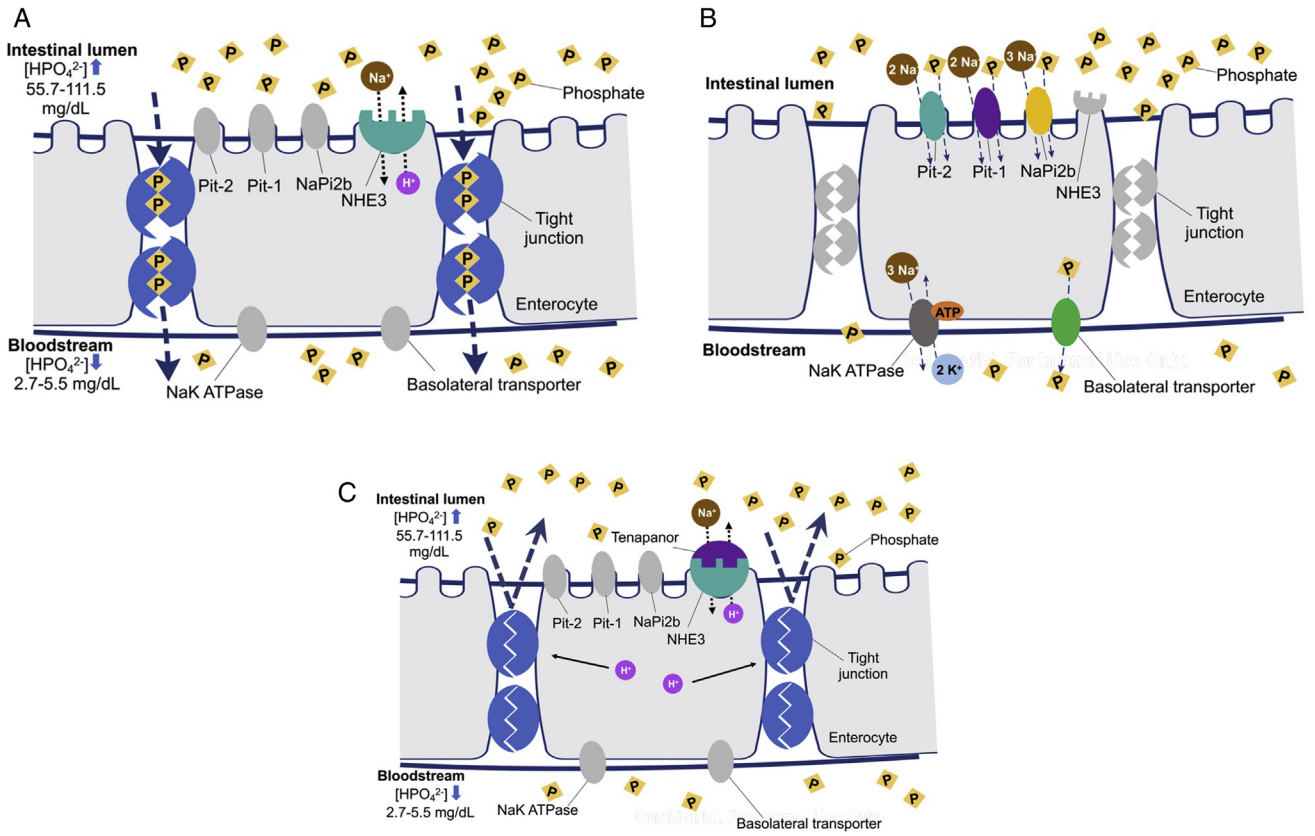

Figure 1. (A) Illustration of the transcellular phosphate absorption pathway.[11] The sodium-dependent phosphate cotransporter 2b (NaPi2b) is responsible for transcellular phosphate absorption.[6] This phosphate transporter saturates at phosphate concentrations well below those associated with conventional Western diets.[4,7] There is evidence that NaPi2b plays a larger role in intestinal phosphate absorption when luminal phosphate concentrations are low,[4] which is likely to occur during dietary privation. (B) Illustration of the paracellular phosphate absorption pathway[5,9-14] Paracellular phosphate absorption is characterized by passive diffusion along concentration gradients through tight junction complexes of claudins and occludins between cell membranes.[5] The paracellular route does not saturate[5] and is the dominant intestinal phosphate absorption pathway.[4,8] (C) Illustration of the paracellular phosphate absorption pathway with tenapanor. Tenapanor blocks paracellular absorption of phosphate in the GI tract by local inhibition of the sodium/hydrogen exchanger isoform 3 (NHE3).[10] NHE3 inhibition directly reduces sodium absorption, leading to modest intracellular proton retention that is proposed to induce conformational changes in tight junction proteins.[10] These changes directly reduce permeability specific to phosphate through the paracellular pathway.[10]

clinical outcomes, as well as the expert opinion of the KDOQI working group.[9] The KDIGO (Kidney Disease: Improving Global Outcomes) 2017 guideline recommends that patients with CKD stages 3A-5D lower elevated phosphate levels toward the normal range.[20]

Phosphate binders, which reduce the quantity of absorbable phosphate by binding to dietary phosphate to create insoluble compounds, are currently the only US Food and Drug Administration–approved treatment for hyperphosphatemia[21] and are prescribed to ~80% of US patients receiving dialysis (Table 1[8,15-18]).[22] Although phosphate binders are widely used, a disturbingly large proportion of patients are unable to consistently achieve and maintain phosphate levels ≤ 5.5 mg/dL.[23] A total of 77% of dialysis patients receiving binders are unable to maintain levels ≤ 5.5 mg/dL over a 6-month period.[23] An even greater proportion of patients receiving dialysis are unable to achieve more normal phosphate levels.[24,25] Modern diets are high in phosphate, primarily from phosphate additives,[26] which makes it challenging for patients to take sufficient binders to consistently maintain target phosphate levels.[27,28]

As evidenced by these data, current phosphorus management strategies that include phosphate binders, reduction in phosphorus dietary intake, and dialysis are insufficient to achieve and maintain phosphate levels ≤ 5.5 mg/dL (or more normal levels) for most patients. Phosphate binders have a fundamentally inefficient mechanism of action that potentially explains the continuing clinical challenge of consistently achieving and maintaining target serum phosphorus concentrations. Instead of directly acting on phosphate absorption pathways,[29-33] either the secondary transcellular pathway or the primary paracellular pathway, phosphate binders "scavenge" particles of dietary phosphate in the GI tract. To scavenge and bind the phosphorus before it is absorbed, the binders must be in the gut

Table 1. Overview of Available Phosphate Binders

Drug	Initial US Approval	Mechanism
Calcium acetate (PHOSLO[15])	1990	Combines with dietary phosphate to form an insoluble calcium phosphate complex, which is excreted in feces, resulting in decreased serum phosphate concentration
Sevelamer carbonate (RENVELA[8,19])	2000	By binding phosphate in the GI tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration in serum (serum phosphate)
Lanthanum carbonate (FOSRENOL[16])	2004	Reduces absorption of phosphate by forming insoluble lanthanum phosphate complexes that pass through the GI tract unabsorbed Reduces both serum phosphate and calcium phosphate product by reducing dietary phosphate absorption
Sucroferric oxyhydroxide (VELPHORO[17])	2013	In the GI tract, phosphate binding takes place by ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and phosphate in the diet. The bound phosphate is eliminated with feces. Reduces both serum phosphate and calcium phosphate product by reducing dietary phosphate absorption
Ferric citrate (AURYXIA[18])	2014	Ferric iron binds dietary phosphate in the GI tract and precipitates as ferric phosphate. This compound is insoluble and is excreted in the stool By binding phosphate in the GI tract and decreasing absorption, ferric citrate lowers the phosphate concentration in the serum

Abbreviation: GI, gastrointestinal.

at the same time as the dietary phosphorus. Thus, most patients are instructed to take phosphate binders with every meal and snack,[29-33] resulting in a high dosing frequency. Moreover, in vivo, each pill can only bind a discrete amount of phosphorus.[27,23] Thus, patients typically require many large pills every time they eat (Fig 2[7,8,15-18,27-34]) in an effort to bind a meaningful amount of dietary phosphate. Studies have shown that on average, patients receiving dialysis are prescribed 10.8 phosphate-binder pills per day, accounting for ~50% of their total daily pill burden (Fig 3[27-33,35]).[36]

Furthermore, as a class, phosphate binders have been associated with clinically significant GI tolerability issues, including abdominal pain, constipation, diarrhea, nausea, and vomiting (Table 2[16,29-33,37,38]).[20,29-33] In clinical trials with phosphate binders, between 14% and 27% of patients discontinued treatment due to adverse reactions, with GI events being the most common reason.[29-33] Furthermore, serious cases of GI obstruction, some requiring surgery or hospitalization, were identified in postmarketing reports of patients taking lanthanum carbonate.[31] Some of these were reported in patients without a history of GI disease.[31] Calcium-based phosphate binders can lead to calcium loading and vascular calcification, further exacerbating negative clinical outcomes.[39] Together, these factors likely contribute to the inability of most dialysis patients to achieve and maintain serum phosphorus concentrations ≤ 5.5 mg/dL, indicating an opportunity for therapeutic innovations, particularly given the association between elevated phosphorus levels and cardiovascular (CV) mortality.

ASSOCIATION OF PHOSPHATE WITH CV DISEASE IN CKD

Mortality rates in patients receiving dialysis are unacceptably high (~160 deaths/1,000 patient-years) and have not improved in the last 5 years.[40] The 5-year survival probability of patients receiving dialysis (~50%) is lower than those of some cancers (prostate cancer, 83%; colorectal cancer, 56%; and breast cancer, 82%).[41] CV disease (CVD) is the primary cause of death in patients receiving dialysis.[42] In 2017, CVD was the cause of death for ~62% of patients with CKD receiving dialysis,[40] and CV mortality in patients receiving dialysis is approximately 20 times higher than that in a general population.[42,43] Novel approaches may provide a much-needed avenue to further improve clinical outcomes and quality of life in patients receiving dialysis, especially considering that mortality and hospitalization data have changed very little since 2014.[44]

Hyperphosphatemia is associated with numerous negative consequences (eg, vascular calcification,[45,46] CVD,[47] and secondary hyperparathyroidism[48]) and may be an independent risk factor for progression of CKD.[49,50] The population-attributable risk percentage for disorders of mineral metabolism was 17.5%, largely due to the high prevalence of hyperphosphatemia.[51] The population-attributable risk for CKD mortality is much higher for elevated phosphate levels (12%) than for hypercalcemia (4%), hyperparathyroidism (2%), low urea reduction ratio (5%), or anemia (6%).[51] Thus, serum phosphorus concentrations are an important remaining modifiable contributor to mortality in patients with CKD.

Hyperphosphatemia is linked to an increased risk for CVD through multiple physiologic mechanisms. First, high phosphate concentrations may increase vascular calcification by inducing the permanent transformation of vascular smooth muscle cells into osteoblast-like cells.[49] Fibroblast

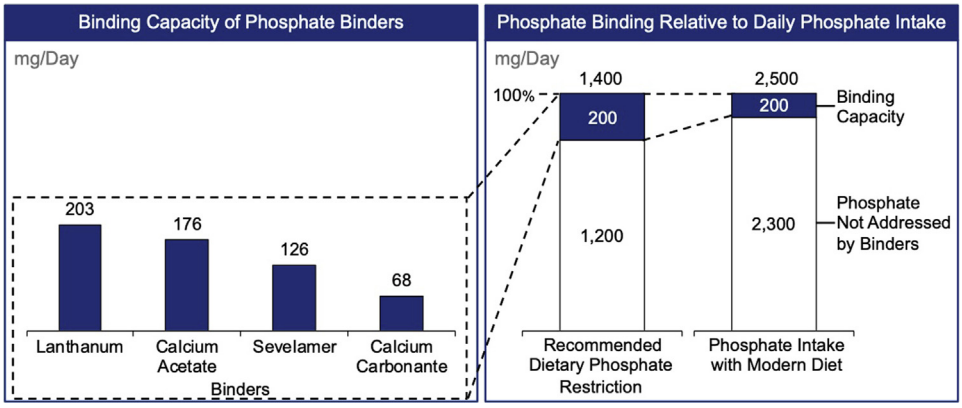

Figure 2. Phosphate binders' binding capacity relative to daily phosphate intake.[27,28,34] In vivo binding capacities of phosphate binders are limited,[27,28] requiring patients to take numerous binders each time they eat in an effort to bind a meaningful amount of dietary phosphate.[29-33] However, phosphate binders can only bind up to ~200 mg[27-33] of the total daily dietary phosphate intake (~1,400 to 2,500 mg).[7,18]

growth factor 23 (FGF-23) and parathyroid hormone (PTH) concentrations, which have been associated with direct pathogenic CV effects,[52,53] increase in response to elevated phosphate or phosphate retention.[54] Increased FGF-23 levels directly target the heart to promote left ventricular hypertrophy,[53] a condition observed in ~70% of patients receiving dialysis,[55] and congestive heart failure.[56] Excess PTH is associated with proinflammatory effects,[57] hypertension,[58] impaired myocardial energy production,[59] cardiac fibrosis,[60] left ventricular hypertrophy,[61] and heart failure.[62] Poor phosphate control over a 6-month period was strongly associated with CV mortality but not all-cause mortality, and more normal phosphate levels were correlated with improved survival.[25]

Declining kidney function causes disruptions in mineral homeostasis (eg, calcium and phosphate) in addition to changes in hormone concentrations (eg, PTH and FGF-23).[20,63] Phosphate retention is an initiating factor and driving force for CKD mineral and bone disorder.[20] CKD mineral and bone disorder is a broad clinical syndrome that describes systemic laboratory abnormalities, bone abnormality, and vascular calcification, which are directly associated with increased risk for CVD, fractures, and mortality.[64] Interactions between increasing phosphate, increasing PTH, and decreasing calcium concentrations drive feedback loops that create a worsening cycle,[65,66] causing mineral and hormone homeostasis to deteriorate as CKD progresses.[66] Calcium-phosphate deposition in the

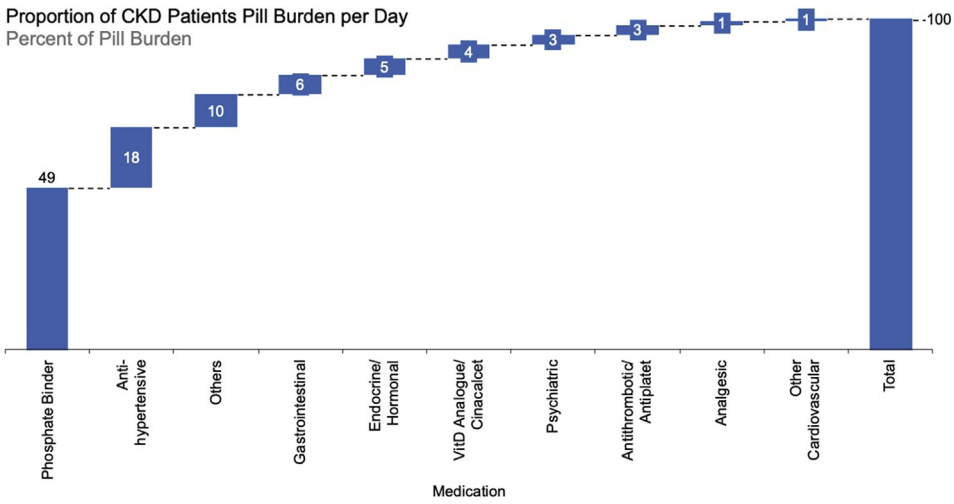

Figure 3. Percent of dialysis patients pill burden per day by medications.[29-33,35] Labeled dosing instructions require patients to take 1 to 4 binders with each meal or snack (~3 to 5 times per day).[29-33] On average, phosphate binders account for almost half the daily pill burden for patients receiving dialysis.[35] Patients are prescribed about 11 phosphate-binder pills per day, and the pill burden from this single medication category is about equivalent to that of 9 other therapy types combined.[35] Abbreviation: CKD, chronic kidney disease.

Table 2. Summary of Adverse Events for Hyperphosphatemia Treatment

Drug Type	Source for Data (population)	Diarrhea	Discolored Feces	Constipation	Vomiting	Nausea	Dyspepsia	Abdominal Pain
Phosphate binders								
Calcium acetate[29]	Label (n = 167)				2.4%	3.6%		
Sucroferric oxyhydroxide[30]	Label (n = 707)	24%	16%			10%		
Sevelamer[33]	Label (n = 99)	19%		8%	22%	20%	16%	9%
Lanthanum carbonate[31]	Label (n = 180)				9%[a]	11%[a]		5%[a]
Ferric citrate[32]	Label (n = 190)	21%		18%		10%		5%
Transcellular pathway inhibitors[b,c]								
ASP3325[16]	Phase 1 trial (n = 19)	11%			11%			
Paracellular pathway inhibitor								
Tenapanor[38]	Label (n = 637)	47%[d]						

[a]Most common reactions that were more frequent (≥5% difference) in the lanthanum carbonate population.
[b]Gastrointestinal adverse event data for EOS789 are not included in this table because trial publications did not provide rates for specific events (eg, diarrhea and nausea), only rates for overall adverse events.
[c]A phase 3 trial of nicotinamide in dialysis patients reported gastrointestinal adverse events in 4% of patients.[37] These data are not included in the main table because no detailed data on rates for each type of gastrointestinal adverse event were published.
[d]Most diarrhea events were mild-to-moderate and transient in nature.

media of the arterial wall leads to increased media thickness and vascular stiffening,[67,68] and high serum phosphorus concentrations induce calcification of vascular smooth muscle cells.[69] Serum phosphorus concentration increases, even within the normal range, are known to be associated with the risk for death, CV events, and vascular calcification even in individuals without CKD.[47,70-73]

PHOSPHATE ABSORPTION PATHWAYS: A MORE TARGETED THERAPEUTIC APPROACH

The goal of hyperphosphatemia treatment should be to reduce serum phosphorus concentrations to ≤5.5 mg/dL (or closer to normal levels) and alleviate negative clinical outcomes for patients with CKD, especially CV mortality. To reflect the latest understanding of phosphate absorption, clinicians could consider implementing new hyperphosphatemia treatment paradigms to achieve phosphate goals, incorporating targeted phosphate absorption inhibitors.

Several inhibitors of the sodium-dependent transcellular pathway have been developed (Fig 4). The novel compound EOS789 interacts with sodium-dependent phosphate transporters (NaPi2b, PiT-1, and PiT-2) and effectively reduced serum phosphate, FGF-23, and PTH concentrations in rats with hyperphosphatemia.[74] A phase 1 study of EOS789 in patients receiving intermittent dialysis found no significant difference in serum phosphate concentrations between patients treated with EOS789 and patients who received a placebo.[75] To our knowledge, no phase 2 or 3 trials have been conducted for this therapy. The NaPi2b inhibitor ASP3325 reduced serum phosphate concentrations in an animal model[15] but had no effect in healthy volunteers or patients with end-stage kidney disease.[16] Nicotinamide suppresses sodium-dependent phosphate transporter activity and effectively reduced phosphate concentrations in animal models.[76] In a trial of patients receiving maintenance dialysis, the mean reduction in phosphate concentrations from baseline was smaller in patients treated with nicotinamide sevelamer (0.25 vs 0.40 mmol/L), and noninferiority was not established.[37] Patients' tolerance of nicotinamide was much lower than that of sevelamer; treatment discontinuation due to adverse events in patients who received nicotinamide was 160% higher than for patients who received sevelamer.[37]

Tenapanor is an investigational first-in-class nonbinder phosphate absorption inhibitor that targets the primary paracellular absorption pathway, providing a novel approach to treating hyperphosphatemia[10] (Fig 1). Tenapanor has a unique mechanism of action that blocks paracellular absorption of phosphate in the GI tract by local inhibition of the sodium/hydrogen exchanger isoform 3.[10] Sodium/hydrogen exchanger isoform 3 inhibition has the effect of directly blocking sodium absorption, triggering an intracellular signaling cascade that induces conformational changes in tight junction proteins and directly reducing the permeability of the paracellular pathway specifically to phosphate.[10] By blocking the primary pathway for phosphate absorption, tenapanor acts more directly to reduce serum phosphorus concentrations.[10]

High pill burdens are common in dialysis patients[35] and paracellular phosphate absorption inhibitors may improve

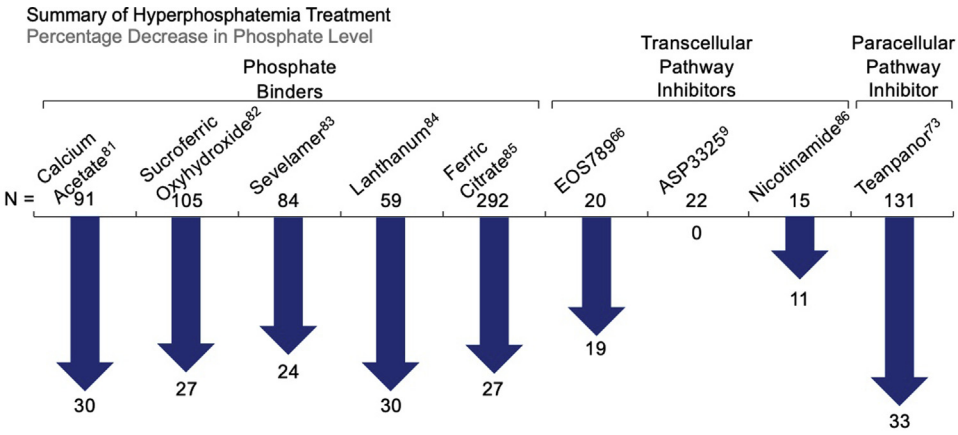

Figure 4. Summary of existing trials for hyperphosphatemia treatment. The percent decrease in phosphate levels of existing trials for hyperphosphatemia treatment are summarized.

patients' quality of life by reducing the total number of pills needed each day. Akizawa et al[77] investigated tenapanor's potential for reducing pill burden in dialysis patients with hyperphosphatemia. Patients who were taking at least 2 phosphate-binder pills 3 times per day received treatment with 30 mg of tenapanor twice daily, and 71.6% of patients achieved a 30% decrease in the total number of phosphate-binder and tenapanor pills ($P < 0.001$).[77] Of those, 52.2% achieved a 50% decrease in total pill burden and 26.9% no longer required any phosphate binders at week 26.[77]

Tenapanor effectively reduced phosphate levels in multiple clinical trials with a dosing regimen of 1 pill twice daily and was generally well tolerated. Tenapanor has been evaluated for efficacy as monotherapy (vs placebo) in separate 12- and 52-week trials. At 12 weeks, tenapanor administration lowered serum phosphorus concentrations in patients from baseline of 8.1 to 5.5 mg/dL in the efficacy analysis set.[78] In the long-term phase 3 study, at 26 weeks, tenapanor administration lowered serum phosphorus concentrations in patients from baseline concentrations of 7.7 to 5.1 mg/dL in the efficacy analysis set.[79] A recent trial that compared the effectiveness of a combination of tenapanor and binder versus placebo and binder showed that tenapanor plus binder resulted in more significant serum phosphate concentration reduction from baseline compared with placebo plus binder (0.84-1.21 vs 0.14-0.21 mg/dL; $P < 0.001$).[80] Additionally, almost twice as many patients treated with tenapanor and binder achieved phosphate concentrations < 5.5 mg/dL compared with patients treated with placebo and binder (37%-50% vs 18%-24%; $P < 0.05$).[80]

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Steven N. Fishbane, MD, and Sagar Nigwekar, MD.

Authors' Affiliations: Department of Medicine, Zucker School of Medicine at Hofstra, Hempstead (SNF); Northwell, Great Neck, NY (SNF); and Department of Medicine, Harvard Medical School, Boston, MA (SN).

Address for Correspondence: Steven N. Fishbane, MD, Kidney Diseases and Hypertension, Department of Medicine, Long Island Jewish Medical Center, Department of Medicine, Zucker School of Medicine at Hofstra, Northwell, Great Neck, NY 11021. Email: sfishbane@northwell.edu

Support: None.

Financial Disclosure: Dr Fishbane is a paid consultant for Ardelyx, Inc and provides research and consulting support for Ardelyx, AstraZeneca, Fibrogen, Akebia, and Gilead. Dr Nigwekar is a paid consultant for Ardelyx, Inc. Writing support was provided by Xelay Acumen Group and funded by Ardelyx, Inc.

Peer Review: Received March 11, 2021. Evaluated by 2 external peer reviewers, with direct editorial input by an Associate Editor and the Editor-in-Chief. Accepted in revised form July 11, 2021.

REFERENCES

1. Turner NN, Lameire N, Goldsmith DJ, Winearls CG, Himmelfarb J, Remuzzi G. Oxford Textbook of Clinical Nephrology. Oxford University Press; 2015.
2. Shaman AM, Kowalski SR. Hyperphosphatemia management in patients with chronic kidney disease. *Saudi Pharm J*. 2016;24(4):494-505.
3. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31(4):607-617.
4. Davis GR, Zerwekh JE, Parker TF, Krejs GJ, Pak CY, Fordtran JS. Absorption of phosphate in the jejunum of patients with chronic renal failure before and after correction of vitamin D deficiency. *Gastroenterology*. 1983;85(4):908-916.
5. Knöpfel T, Himmerkus N, Günzel D, Bleich M, Hernando N, Wagner CA. Paracellular transport of phosphate along the intestine. *Am J Physiol Gastrointest Liver Physiol*. 2019;317(2):G233-G241.
6. Sabbagh Y, O'Brien SP, Song W, et al. Intestinal npt2b plays a major role in phosphate absorption and homeostasis. *J Am Soc Nephrol*. 2009;20(11):2348-2358.
7. McClure ST, Chang AR, Selvin E, Rebholz CM, Appel LJ. Dietary sources of phosphorus among adults in the United States: results from NHANES 2001-2014. *Nutrients*. 2017;9(2):95.
8. Marks J, Lee GJ, Nadaraja SP, Debnam ES, Unwin RJ. Experimental and regional variations in Na+-dependent and Na+-

independent phosphate transport along the rat small intestine and colon. *Physiol Rep*. 2015;3(1):e12281.
9. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4)(suppl 3):S1-S201.
10. King AJ, Siegel M, He Y, et al. Inhibition of sodium/hydrogen exchanger 3 in the gastrointestinal tract by tenapanor reduces paracellular phosphate permeability. *Sci Transl Med*. 2018;10(456):eaam6474.
11. Fouque D, Vervloet M, Ketteler M. Targeting gastrointestinal transport proteins to control hyperphosphatemia in chronic kidney disease. *Drugs*. 2018;78(12):1171-1186.
12. Saurette M, Alexander RT. Intestinal phosphate absorption: the paracellular pathway predominates? *Exp Biol Med*. 2019;244(8):646-654.
13. Walton J, Gray TK. Absorption of inorganic phosphate in the human small intestine. *Clin Sci (Lond)*. 1979;56(5):407-412.
14. Davis JS, Alkhoury F, Burnweit C. Surgical and anesthetic considerations in histrelin capsule implantation for the treatment of precocious puberty. *J Pediatr Surg*. 2014;49(5):807-810.
15. Taniguchi K, Terai K, Terada Y. Novel NaPi-IIb inhibitor ASP3325 inhibits phosphate absorption in intestine and reduces plasma phosphorus level in rats with renal failure. *J Am Soc Nephrol*. 2015;26(Abstract Edition):582A:FR-PO936.
16. Larsson TE, Kameoka C, Nakajo I, et al. NPT-IIb inhibition does not improve hyperphosphatemia in CKD. *Kidney Int Rep*. 2018;3(1):73-80.
17. Fordtran JS, Locklear TW. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. *Am J Dig Dis*. 1966;11(7):503-521.
18. Bell RR, Draper HH, Tzeng DY, Shin HK, Schmidt GR. Physiological responses of human adults to foods containing phosphate additives. *J Nutr*. 1977;107(1):42-50.
19. Bansal VK. Chapter 198. Serum inorganic phosphorus. In: Walker HK, Hall WD, Hurst JW, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3 ed. Butterworths; 1990:895-899.
20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7(1):1-59.
21. Sawin DA, Ma L, Stennett A, et al. Phosphates in medications: impact on dialysis patients. *Clin Nephrol*. 2020;93(4):163-171.
22. Phosphate binder use, last 3 months. DOPPS Practice Monitor. Accessed December 3, 2020. https://www.dopps.org/DPM-HD/Files/maxPBINDER_use_c_overallTAB.htm
23. RealWorld Dynamix: Dialysis US. Spherix Global Insights. Accessed December 3, 2020. https://www.spherixglobalinsights.com/reports/nephrology-reports/dialysis-us/
24. Serum phosphorus (3 month average), categories. DOPPS Practice Monitor. Accessed December 3, 2020. https://www.dopps.org/DPM-HD/Files/meanphosphmgdl_c_overallTAB.htm
25. Lopes MB, Karaboyas A, Bieber B, et al. Impact of longer term phosphorus control on cardiovascular mortality in hemodialysis patients using an area under the curve approach: results from the DOPPS. *Nephrol Dial Transplant*. 2020;35(10):1794-1801.
26. Ritz E, Hahn K, Ketteler M, Kuhlmann MK, Mann J. Phosphate additives in food–a health risk. *Dtsch Arztebl Int*. 2012;109(4):49-55.
27. Daugirdas JT, Finn WF, Emmett M, Chertow GM. The phosphate binder equivalent dose. *Semin Dial*. 2011;24(1):41-49.
28. Martin P, Wang P, Robinson A, et al. 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;57(5):700-706.
29. PhosLo gelcaps (calcium acetate): 667 mg [prescribing information]. Fresenius Medical Care North America; 2011.
30. VELPHORO (sucroferric oxyhydroxide) [prescribing information]. Fresenius Medical Care North America; 2013.
31. FOSRENAL (lanthanum carbonate) [prescribing information]. Shire US Inc; 2016.
32. AURYXIA (ferric citrate) tablets [prescribing information]. Keryx Biopharmaceuticals Inc; 2017.
33. RENVELA (sevelamer carbonate) [prescribing information]. Genzyme Corp; 2020.
34. Cupisti A, Kalantar-Zadeh K. Management of natural and added dietary phosphorus burden in kidney disease. *Semin Nephrol*. 2013;33(2):180-190.
35. Chiu Y-W, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol*. 2009;4(6):1089-1096.
36. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol*. 2009;4(6):1089-1096.
37. Lenglet A, Liabeuf S, Esper NE, et al. Efficacy and safety of nicotinamide in haemodialysis patients: the NICOREN study. *Nephrol Dial Transplant*. 2017;32(5):870-879.
38. XPHOZA (tenapanor) tablets for oral use [prescribing information]. Ardelyx; 2021.
39. Bolasco P. Effects of the use of non-calcium phosphate binders in the control and outcome of vascular calcifications: a review of clinical trials on CKD patients. *Int J Nephrol*. 2011;2011:758450.
40. US Renal Data System. USRDS 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 2019. Accessed December 3, 2020. https://usrds.org/2019/ref/ESRD_Ref_H_Mortality_2019.xlsx
41. Naylor KL, Kim SJ, McArthur E, Garg AX, McCallum MK, Knoll GA. Mortality in incident maintenance dialysis patients versus incident solid organ cancer patients: a population-based cohort. *Am J Kidney Dis*. 2019;73(6):765-776.
42. Tong J, Liu M, Li H, et al. Mortality and associated risk factors in dialysis patients with cardiovascular disease. *Kidney Blood Press Res*. 2016;41(4):479-487.
43. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant*. 2018;33(suppl 3):iii28-iii34.
44. Collins A, Weinhandl E. Chronic Cardiovascular Disease Management in the Dialysis Population. Fresenius Medical Care; 2019.
45. Reynolds JL, Joannides AJ, Skepper JN, et al. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. *J Am Soc Nephrol*. 2004;15(11):2857-2867.
46. Moe SM, Chertow GM. The case against calcium-based phosphate binders. *Clin J Am Soc Nephrol*. 2006;1(4):697-703.
47. McGovern AP, de Lusignan S, van Vlymen J, et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. *PLoS One*. 2013;8(9):e74996.
48. Nielsen PK, Feldt-Rasmussen U, Olgaard K. A direct effect in vitro of phosphate on PTH release from bovine parathyroid

tissue slices but not from dispersed parathyroid cells. *Nephrol Dial Transplant*. 1996;11(9):1762-1768.
49. Zhang D, Bi X, Liu Y, et al. High phosphate-induced calcification of vascular smooth muscle cells is associated with the TLR4/NF-κb signaling pathway. *Kidney Blood Press Res*. 2017;42(6):1205-1215.
50. Zoccali C, Ruggenenti P, Perna A, et al. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J Am Soc Nephrol*. 2011;22(10):1923-1930.
51. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15(8):2208-2218.
52. Wannamethee SG, Welsh P, Papacosta O, Lennon L, Whincup PH, Sattar N. Elevated parathyroid hormone, but not vitamin D deficiency, is associated with increased risk of heart failure in older men with and without cardiovascular disease. *Circulation Heart Fail*. 2014;7(5):732-739.
53. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest*. 2011;121(11):4393-4408.
54. Qadeer HA, Bashir K. *Physiology, Phosphate*. StatPearls. StatPearls Publishing; 2020.
55. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int*. 1995;47(1):186-192.
56. Ix JH, Katz R, Kestenbaum BR, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). *J Am Coll Cardiol*. 2012;60(3):200-207.
57. Cheng SP, Liu CL, Liu TP, Hsu YC, Lee JJ. Association between parathyroid hormone levels and inflammatory markers among US adults. *Mediators Inflamm*. 2014;2014:709024.
58. Goldsmith DJ, Covic AA, Venning MC, Ackrill P. Blood pressure reduction after parathyroidectomy for secondary hyperparathyroidism: further evidence implicating calcium homeostasis in blood pressure regulation. *Am J Kidney Dis*. 1996;27(6):819-825.
59. Smogorzewski M, Perna AF, Borum PR, Massry SG. Fatty acid oxidation in the myocardium: effects of parathyroid hormone and CRF. *Kidney Int*. 1988;34(6):797-803.
60. Rodríguez-Ayala E, Avila-Díaz M, Foyo-Niembro E, Amato D, Ramirez-San-Juan E, Paniagua R. Effect of parathyroidectomy on cardiac fibrosis and apoptosis: possible role of aldosterone. *Nephron Physiol*. 2006;103(3):112-118.
61. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. *Eur Heart J*. 2003;24(22):2054-2060.
62. Li Y, Chen C, Liu HL, Qian G. Vitamin D, parathyroid hormone, and heart failure in a Chinese elderly population. *Endocr Pract*. 2015;21(1):30-40.
63. Goyal R, Jialal I. Hyperphosphatemia. StatPearls. StatPearls Publishing; 2020.
64. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2009;(113):S1-S130.
65. Shemin D. Anemia and bone disease of chronic kidney disease: pathogenesis, diagnosis, and management. *R I Med J*. 2014;97(12):24-27.
66. National Kidney Foundation. An Update on CKD-Mineral and Bone Disorder: State-of-the-Art Considerations for Evaluation and Risk Assessment. *National Kidney Foundation*. 2014.
67. Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int*. 2009;75(9):890-897.
68. Ho CY, Shanahan CM. Medial arterial calcification: an overlooked player in peripheral arterial disease. *Arterioscler Thromb Vasc Biol*. 2016;36(8):1475-1482.
69. Crouthamel MH, Lau WL, Leaf EM, et al. Sodium-dependent phosphate cotransporters and phosphate-induced calcification of vascular smooth muscle cells: redundant roles for PiT-1 and PiT-2. *Arterioscler Thromb Vasc Biol*. 2013;33(11):2625-2632.
70. Eddington H, Hoefield R, Sinha S, et al. Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(12):2251-2257.
71. Dhingra R, Sullivan LM, Fox CS, et al. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med*. 2007;167(9):879-885.
72. Foley RN. Phosphate levels and cardiovascular disease in the general population. *Clin J Am Soc Nephrol*. 2009;4(6):1136-1139.
73. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*. 2005;16(2):520-528.
74. Tsuboi Y, Ohtomo S, Ichida Y, et al. EOS789, a novel pan-phosphate transporter inhibitor, is effective for the treatment of chronic kidney disease-mineral bone disorder. *Kidney Int*. 2020;98(2):343-354.
75. Hill Gallant KM, Stremke ER, Trevino LL, et al. EOS789, a broad-spectrum inhibitor of phosphate transport, is safe with an indication of efficacy in a phase 1b randomized crossover trial in hemodialysis patients. *Kidney Int*. 2021;99(5):1225-1233.
76. Eto N, Miyata Y, Ohno H, Yamashita T. Nicotinamide prevents the development of hyperphosphataemia by suppressing intestinal sodium-dependent phosphate transporter in rats with adenine-induced renal failure. *Nephrol Dial Transplant*. 2005;20(7):1378-1384.
77. Akizawa T, Kanda H, Takanuma M, Kinoshita J, Fukagawa M. P1404A phase 2 open-label, single-arm, first Japanese study of tenapanor, a novel phosphate absorption inhibitor, focusing on pill burden decrease in patients with hyperphosphatemia undergoing hemodialysis. *Nephrol Dial Transplant*. 2020;35(suppl 3):gfaa142.P1404.
78. Block GA, Rosenbaum DP, Yan A, Chertow GM. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: a randomized phase 3 trial. *J Am Soc Nephrol*. 2019;30(4):641-652.
79. Chertow GM, Yang Y, Rosenbaum DP PO0384 Long-term safety and efficacy of tenapanor for the control of serum phosphorus in patients with chronic kidney disease on dialysis. American Society of Nephrology (ASN) Kidney Week. Virtual. October 22-25, 2020.
80. Pergola PE, Rosenbaum DP, Yang Y, Chertow GM. A randomized trial of tenapanor and phosphate binders as a dual-mechanism treatment for hyperphosphatemia in patients on maintenance dialysis (AMPLIFY). *J Am Soc Nephrol*. 2021;32(6):1461-1473.