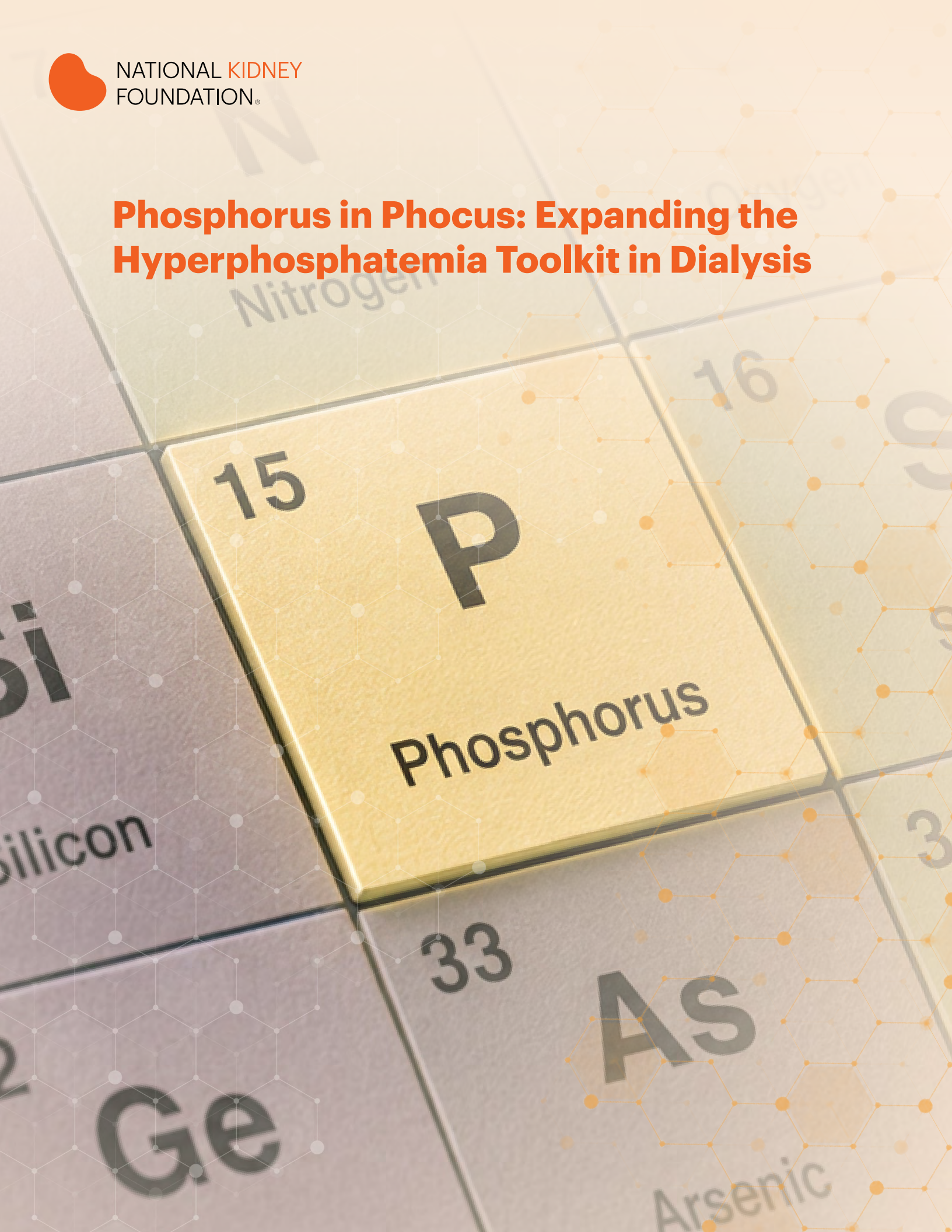
NATIONAL KIDNEY FOUNDATION®

Phosphorus in Phocus: Expanding the Hyperphosphatemia Toolkit in Dialysis



Introduction

Phosphate abnormalities, which may occur in all stages of chronic kidney disease (CKD), increase with the severity of kidney dysfunction. Body phosphate homeostasis is determined by modulation of intestinal uptake of dietary phosphate, phosphate reabsorption and excretion by the kidneys, and the exchange of phosphate between extracellular and bone storage pools.[1,2]

The main regulators of phosphate metabolism include:[1,2]

1) dietary phosphate intake and absorption,

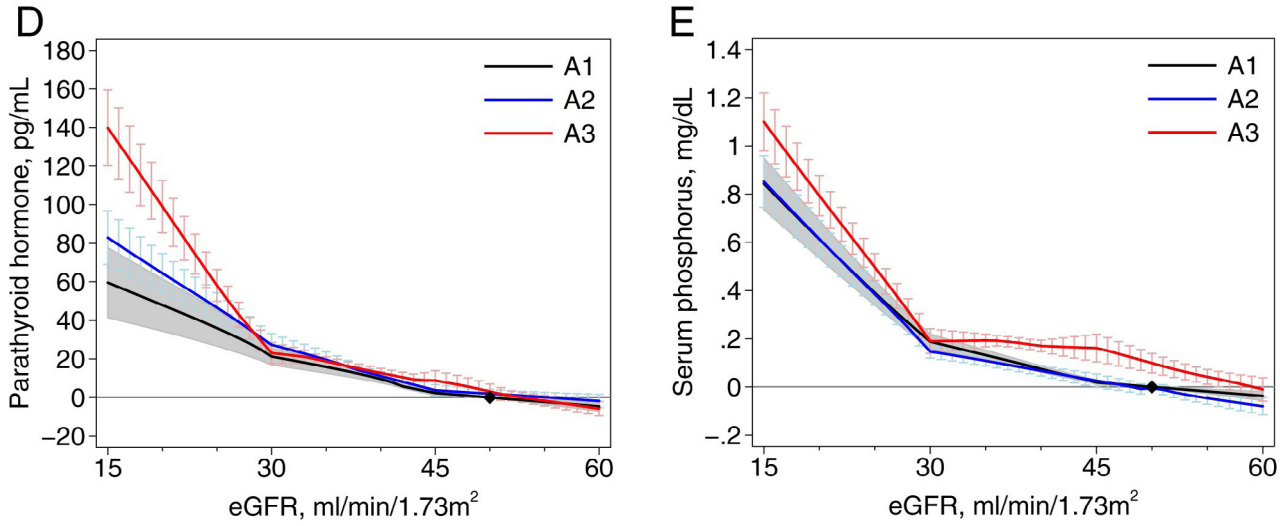
2) calcitriol, which increases phosphate absorption from the intestine,

3) parathyroid hormone (PTH), which directly causes phosphate resorption from bone and decreases its reabsorption in the proximal tubule, and indirectly by stimulating the production of calcitriol, and

4) phosphatonins, such as fibroblast growth factor-23 (FGF-23), which increase phosphate excretion by the kidneys.

As the estimated glomerular filtration rate (eGFR) declines, the kidneys lose the ability to excrete phosphate. Excess phosphate retention occurs even though serum phosphate levels are often maintained within the normal reference range until late stages of CKD.[3,4] Elevated serum phosphate levels do not become evident until GFR approaches 30 mL/min/1.73m^2 or lower (Figure 1).[5,6] This delayed onset of hyperphosphatemia is possibly due to the counter-regulatory actions of FGF23 and PTH, which both stimulate urinary excretion of phosphate to help counteract this excess retention.[6,7] This compensatory mechanism can help continue to manage phosphate homeostasis over the short term, but the progression of CKD eventually makes it unsustainable, especially when the patient has end-stage kidney disease (ESKD).

FIGURE 1: ASSOCIATIONS BETWEEN eGFR, PTH, AND SERUM PHOSPHORUS



Acknowledgement: Inker LA, Grams ME, Levey AS, et al. Relationship of estimated GFR and albuminuria to concurrent laboratory abnormalities: an individual participant data meta-analysis in a global consortium. *Am J Kidney Dis.* 2018;73(2):206-217.

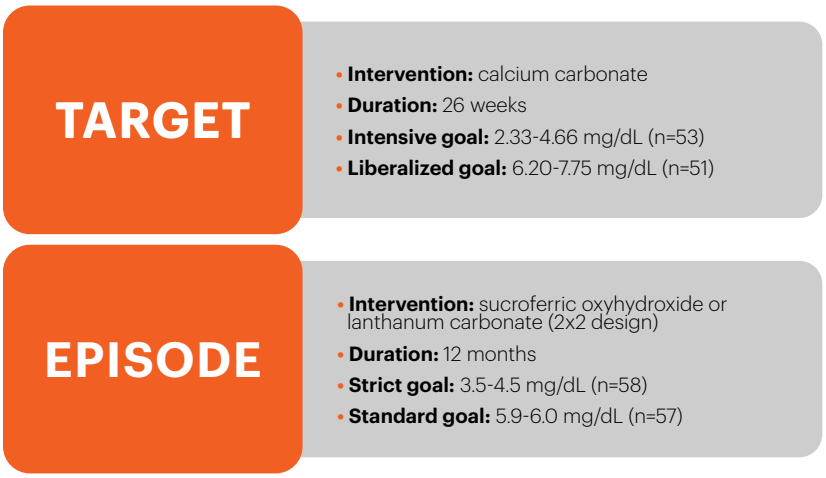
Chronic hyperphosphatemia affects the majority of patients with ESKD on dialysis and is associated with significant negative clinical consequences, including vascular calcification, cardiovascular disease, left ventricular hypertrophy, bone loss, fractures, and mortality.[8–13] Despite decades of clinical awareness and the availability of dietary interventions, phosphate binders, and dialysis-based clearance strategies, phosphate management is steadily worsening, with 25.5% of patients on hemodialysis and 26.3% of patients on peritoneal dialysis having phosphate levels ≥6.5 mg/dL in 2024, up from 19.4% and 20.7%, respectively, in 2016.[14]

Treatment targets in dialysis

For patients with stage G5D CKD, contemporary guidelines recommend **targeting the lowering of serum phosphate levels "toward the normal range" rather than strict normalization, while also avoiding overt hyperphosphatemia and hypercalcemia,** reaffirmed during a 2023 KDIGO controversies conference on chronic kidney disease-mineral and bone disorder (CKD-MBD).[13,15,16]

Two pilot trials established the feasibility of investigating different phosphate target levels in patients with Stage G5D CKD (Figure 2).[17,18] While the TARGET trial was not designed to detect a definitive difference in long-term outcomes given its short duration, the EPISODE trial found lower coronary artery calcium (CAC) scores in the strict group than in the standard group (median 8.52 vs. 21.8; p=0.006). However, both trials were limited by their small sample sizes and relatively short follow-up durations, warranting confirmatory studies.

FIGURE 2: OVERVIEW OF TARGET & EPISODE TRIALS



As a result, two additional trials were initiated to further investigate whether targeting a lower phosphate level in patients on dialysis provides broader clinical benefits (e.g., mortality, hospitalization, cardiovascular events), with both leveraging a pragmatic randomized trial design (Table 1).[19,20] Unfortunately, HiLo was terminated early due to the futility of enrollment and inadequate phosphate separation between groups, precluding inferences about the effects of specific phosphate targets on clinical outcomes.[21] Alternatively, PHOSPHATE is currently underway, with study completion anticipated in late 2028.[22] Of note, all of the study sites are outside the United States, including Australia, Canada, and the United Kingdom (UK).

TABLE 1. OVERVIEW OF HiLo & PHOSPHATE TRIALS

Trial	Pertinent characteristics
HiLo	**Target enrollment:** 4400 adult patients with CKD G5D **Treatment targets:** • "Lo" (<5.5 mg/dL) • "Hi" (≥6.5 mg/dL) **Intervention:** PLT & dietary recommendations at treating physician's discretion **Primary endpoints:** All-cause mortality & all-cause hospitalization
PHOSPHATE	**Target enrollment:** 3600 adult patients with CKD G5D **Treatment targets:** • Intensive (≤4.65 mg/dL) • Liberalized (6.2-7.75 mg/dL) **Intervention:** PLT & dietary recommendations at treating physician's discretion **Primary endpoints:** composite of CV death, non-fatal major CV or peripheral arterial events

Abbreviations: CKD G5D, stage G5 chronic kidney disease on dialysis; CV, cardiovascular; PLT, phosphate-lowering therapies

Traditional approaches to phosphorus management in dialysis

The cornerstone of phosphate management in Stage G5D CKD is managing elevated phosphate levels and secondary hyperparathyroidism concurrently through a combination of limiting dietary phosphate intake, pharmacotherapy (e.g., phosphate-lowering agents, calcitriol/vitamin D analogues, calcimimetics), and customized dialysis settings.[13,15,16,23]

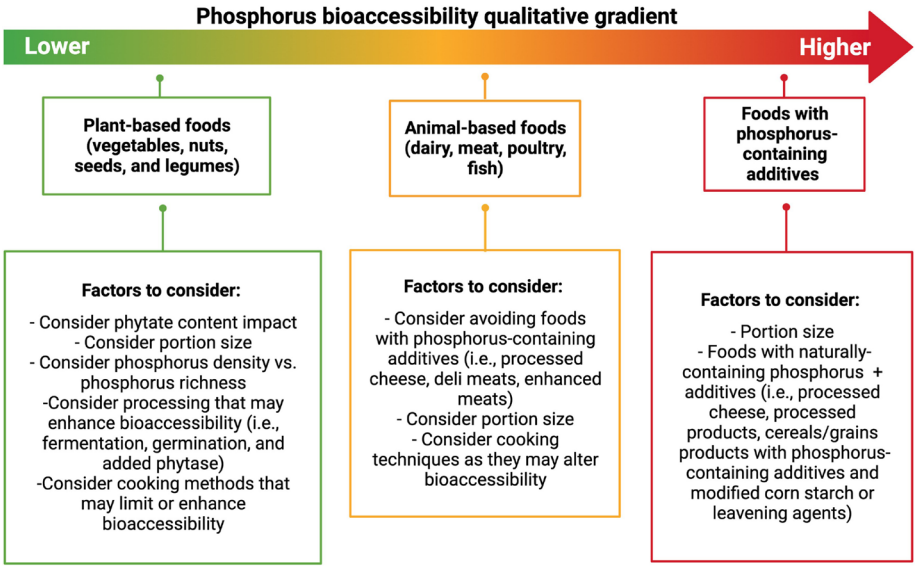
The decision regarding which approach(es) to use is highly dependent upon each patient's individual metabolic status, comorbidities, side effect profiles, personal preferences and circumstances, and potential barriers to access. Additional factors to consider include restricting the dose of calcium-based phosphate binders in adults and basing treatment decisions on serial assessments of phosphate, calcium, and intact PTH levels considered together, rather than focusing on phosphate in isolation.

Dietary modifications

Limiting phosphate intake represents the first-line approach to managing hyperphosphatemia. Recommended strategies include avoiding phosphorus-based preservatives and phosphorus-containing beverages, while also considering the bioavailability of phosphate sources when evaluating dietary intake (Figure 3).[15,16,24–27] To ensure each patient has a meal plan that meets their specific nutritional needs and can be implemented appropriately, the oversight of a kidney dietitian is essential.[25,28–30]

Dietary modifications alone while maintaining adequate protein intake are generally insufficient to control serum phosphate levels in most patients on dialysis, necessitating pharmacologic intervention.

FIGURE 3. FACTORS TO CONSIDER WHEN EVALUATING PHOSPHORUS BIOACCESSIBILITY



Acknowledgement: Biruete A, Hill Gallant KM, Lloyd L, Meade A, Moe SM, S. Jules DE, Kistler BM. 'Phos'tering a clear message: the evolution of dietary phosphorus management in chronic kidney disease. *J Ren Nutr.* 2023;33(6S):S13-S20.

Phosphate binders

While there is insufficient evidence to support intensive phosphate binder use to achieve specific phosphate targets or to favor one agent over another, the risks associated with persistent untreated hyperphosphatemia must also be acknowledged and considered.[31] Phosphate binders remain the primary pharmacologic treatment for hyperphosphatemia in patients on dialysis, with approximately 93% of Medicare-insured patients with ESKD prescribed one in 2019 (Table 2).[31–33]

Among the calcium-free binders, comparative efficacy and effects on hard clinical outcomes remain unclear.[15,34] Overall, these agents demonstrate similar safety and efficacy, but differing side effect profiles, pleotropic effects, and dosage forms.[31,34] These differences allow treatment plans to be individualized based on patient preferences, concurrent conditions, and tolerability using shared decision-making principles.[23]

Overall, phosphate binders are often associated with substantial treatment burden, which contributes to nonadherence. Up to 57% of US patients report skipping at least one dose per month.[35] Many patients also experience inadequate phosphate control despite maximal binder therapy, highlighting the need for alternative or adjunctive approaches.

TABLE 2. OVERVIEW OF PHOSPHATE BINDERS CURRENTLY AVAILABLE IN THE US

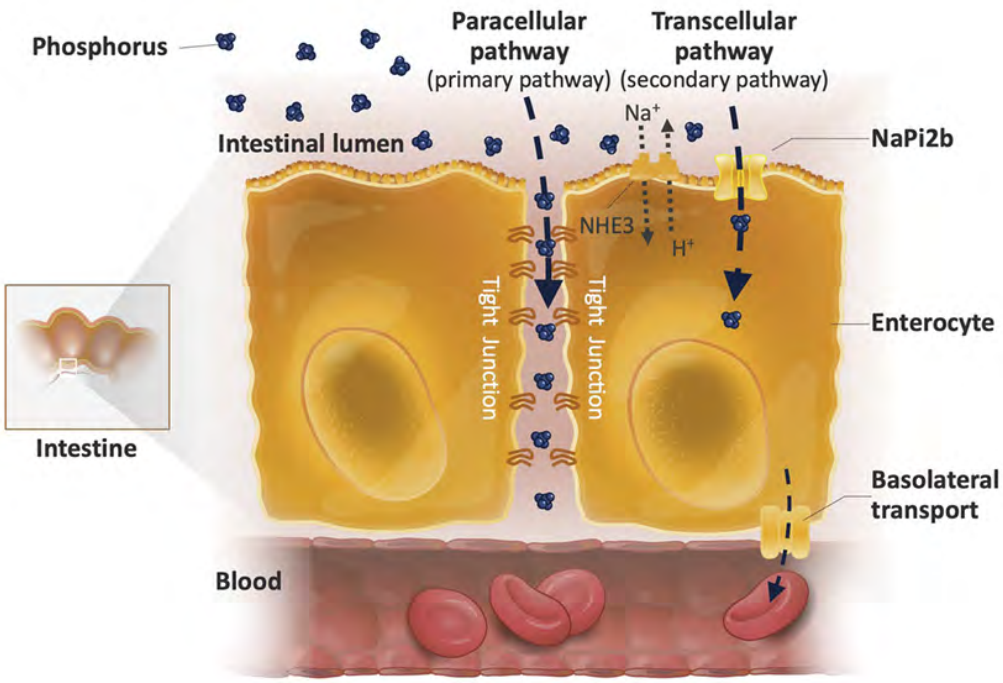
Category	Examples	Potential benefits	Potential risks
Calcium-based binders	• Calcium acetate (Phoslo, Phoslyra, Eliphos. Calphron) • Calcium carbonate (Tums)	• Inexpensive • Comparable efficacy to calcium-free binders	• Positive calcium balance • Hypercalcemia • Adynamic bone disease • May accelerate vascular calcification
Calcium-free binders	• Sevelamer (Renagel, Renvela) • Lanthanum carbonate (Fosrenol) • Ferric citrate (Auryxia) • Sucroferric oxyhydroxide (Velphoro)	• Avoid calcium loading • Theoretical CV benefit from reduced calcium load	• Substantially higher cost • Agent-specific side effects

Introducing the phosphate blocker: Xphozah (tenapanor)

Xphozah (tenapanor) is a first-in-class phosphate absorption inhibitor (PAI) and FDA-approved to reduce serum phosphorus in adults with CKD on dialysis as add-on therapy for patients who have an inadequate response to phosphate binders or are intolerant of any dose of phosphate binder therapy.[36] Xphozah (tenapanor) is administered as one small 30 mg tablet taken twice daily, just before the first and last meals of the day.

While initially developed for irritable bowel syndrome with constipation (marketed as Ibsrela), its phosphate-lowering properties led to its development and approval for hyperphosphatemia management in patients on dialysis at a lower dose (marketed as Xphozah). Rather than bind dietary phosphates to prevent absorption, Xphozah (tenapanor) acts locally in the gut (with minimal systemic absorption) to inhibit the sodium-hydrogen exchanger 3 (NHE3), thereby significantly reducing phosphate absorption via **the nonsaturable paracellular pathway** (Figure 4).[37]

FIGURE 4. DIETARY PHOSPHORUS ABSORPTION VIA TRANSCELLULAR & PARACELLULAR PATHWAYS



Acknowledgement: Yee J, Rosenbaum D, Jacobs JW, Sprague SM. Small intestinal phosphate absorption: novel therapeutic implications. *Am J Nephrol.* 2021;52(7):522-530. CC BY-NC

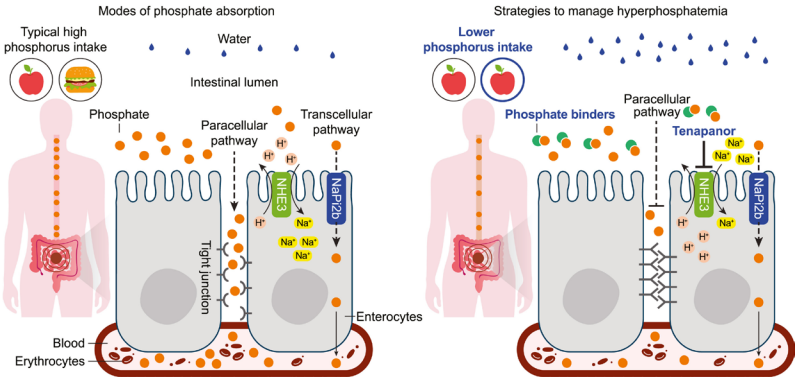
Mechanism of Action

Dietary phosphorus is primarily absorbed through the paracellular pathway, which accounts for approximately 65-80% of total phosphate absorption.[3,38] This passive process occurs along concentration gradients through tight junction complexes between intestinal cells and increases linearly as phosphate concentration rises, rather than reaching a saturation point.[3]

By targeting paracellular phosphate transport, the mechanism of Xphozah (tenapanor) differs fundamentally from phosphate binders, which sequester phosphate within the intestinal lumen. Because Xphozah (tenapanor) acts continuously throughout the day while present in the gastrointestinal tract, it may provide more consistent phosphorus control, especially as an added layer of protection against "hidden phosphorus" in snacks and medications, which can be difficult to address with traditional phosphate binders.[39]

In addition to reducing paracellular phosphate absorption, Xphozah (tenapanor) also decreases expression of sodium-dependent phosphate transporter 2B (NaPi2b), the primary active intestinal phosphate transporter, thereby limiting compensatory increases in active transcellular phosphate absorption (Figure 5).[37,40] Together, these effects on passive and active phosphate transport pathways contribute to the overall phosphate-lowering efficacy of Xphozah (tenapanor).

FIGURE 5. MODES OF PHOSPHATE ABSORPTION & STRATEGIES TO MANAGE HYPERPHOSPHATEMIA



Acknowledgement: Hill Gallant KM, Sprague SM, Rosenbaum DP, Spiegel DM, Kozuka K, Edelstein S, Chertow GM. Tenapanor: a phosphate absorption inhibitor for the management of hyperphosphatemia in patients with kidney failure. *J Ren Nutr.* 2025;35(1):25-34. CC BY-NC-ND 4.0

Clinical trial experience

In the **PHREEDOM trial**, tenapanor administered twice daily (with a phosphate binder washout) significantly lowered serum phosphate in patients receiving maintenance dialysis, resulting in a mean reduction of -1.4 mg/dL from a baseline of approximately 7.4 mg/dL (p<0.0001).[41] In the subsequent **AMPLIFY** trial, patients treated with tenapanor plus binder therapy achieved a larger mean change in serum phosphate compared with placebo plus a binder over 4 weeks (-0.84 mg/dL vs -0.19 mg/dL, p<0.001, both from an average baseline of approximately 6.8 mg/dL).[42] The most commonly reported treatment-related adverse events were diarrhea (40.2% vs. 6.7%) and nausea (5.1% vs. 2.5%).[42] An 18-month open-label extension study **(NORMALIZE)** for patients who completed the PHREEDOM study used tenapanor and sevelamer carbonate (as needed) to maintain serum phosphate levels between 2.5 and 4.5 mg/dL found an overall mean reduction in phosphate level of -2.0 mg/dL from PHREEDOM baseline to the end of NORMALIZE, and 33% of patients achieved phosphate levels within the target range.[43]

Lastly, **OPTIMIZE** was a randomized, open-label study evaluating different strategies for initiating tenapanor in patients on dialysis with uncontrolled hyperphosphatemia. Strategies included switching from phosphate binders to tenapanor (straight switch), reducing phosphate dosage by ≥50% and adding tenapanor (binder reduction), or starting tenapanor monotherapy (binder-naïve). After 10 weeks, 34.4% (straight switch), 38.2% (binder reduction), and 63.3% (binder-naïve) of patients achieved a serum phosphorus ≤5.5 mg/dL. These outcomes were observed despite a median reduction in total daily pill number of 44.4% (straight switch) and 16.7% (binder reduction) from baseline (median 9 pills per day). Among "straight switch" and "binder reduction" patients who completed patient experience questionnaires, 84.4% reported an improved phosphate management routine. Diarrhea was the most common adverse event, affecting 39.9% of patients, leading to tenapanor discontinuation in 6.6% of patients.[44]

In a **2025 meta-analysis** of short-term randomized controlled trials, tenapanor demonstrated a mean reduction of -1.39 mg/dL (95% CI: -1.94, -0.84; p<0.0001) and an increased likelihood of achieving a target serum phosphate level ≤5.5 mg/dL (RR: 2.80; 95% CI: 1.70, 4.61; p<0.0001), both compared with placebo.[45]

Safety considerations

The safety profile of Xphozah (tenapanor) has been evaluated in more than 750 patients with CKD on dialysis across multiple clinical trials, with exposure durations ranging from 4 weeks to over 1 year.[40] Diarrhea is the most common adverse reaction, reported in 43-53% of patients, with severe diarrhea reported in ~5%.[40] This is to be expected, given how inhibiting NHE3-mediated sodium absorption in the intestine increases stool sodium and water content, leading to softened stools or diarrhea.[37] Diarrhea typically occurs soon after treatment initiation but can develop at any time during therapy.[36] Most cases are mild-to-moderate and resolve over time or with dose reduction, while severe diarrhea may lead to dehydration or hyponatremia (<1%). Accordingly, FDA labeling recommends discontinuing Xphozah (tenapanor) in patients who develop severe diarrhea.[36]

Beyond diarrhea, Xphozah (tenapanor) has demonstrated a favorable safety profile with no clinically significant laboratory abnormalities observed other than its intended effects on serum phosphorus.[40,46] Its minimal systemic absorption limits the potential for systemic adverse effects.[36]

Xphozah (tenapanor) is contraindicated in patients with mechanical gastrointestinal obstruction and in patients under 6 years of age.[36]

Practical considerations for clinical use

Mitigating diarrhea risk

Given that diarrhea is the most common adverse effect, proactive management strategies are essential:

- **Patient education:** Inform patients that softened stools or mild diarrhea is expected due to the medication's mechanism of action, and it often improves over time.
- **Stop concurrent laxatives:** Instruct patients to stop using stool softeners or laxatives while taking Xphozah (tenapanor), as these may exacerbate diarrhea. Patients should also be counseled to not start a laxative while using Xphozah (tenapanor).
- **Skip before dialysis:** Ensure patients skip their dose right before a dialysis session and instead take it right before the next meal following dialysis. This helps minimize the inconvenience and potential complications of diarrhea occurring during or immediately after dialysis treatments.
- **Dose reduction or discontinuation:** For moderate diarrhea, consider dose reduction to 20 mg BID. For severe diarrhea, particularly if associated with dehydration or electrolyte abnormalities, discontinue treatment.
- **Consider adding loperamide:** For mild to moderate diarrhea, loperamide may help ameliorate diarrhea associated with tenapanor and facilitate its continued use.[47]
- **Consider a dose titration:** While dose titration is not necessary to initiate Xphozah (tenapanor), patients or clinicians with significant concerns about diarrhea may consider starting at a lower dose (e.g., 20 mg twice daily), increasing to the target dose of 30 mg twice daily as tolerated to maximize its efficacy.
- **Monitoring:** Monitor for signs and symptoms of diarrhea, dehydration, and electrolyte abnormalities, particularly during treatment initiation and dose escalation. Advise patients to report severe diarrhea promptly, as treatment discontinuation may be necessary.

Dosage and Administration

1. The recommended dosage of Xphozah (tenapanor) is 30 mg orally twice daily, taken just prior to the first and last meals of the day. To maximize efficacy, administering Xphozah 5-10 minutes before a meal increases 24-hour stool phosphorus excretion compared to taking the medication in fed or fasting conditions.
2. Monitor serum phosphorus levels and adjust the dosage as needed to manage gastrointestinal tolerability. In clinical trials, starting doses ranged from 3-30 mg twice daily, with some protocols initiating therapy at lower doses and titrating upward based on response and tolerability.
3. Advise patients to skip their Xphozah (tenapanor) dose right before a hemodialysis session, as they may experience diarrhea after taking the medication. Instead, they should take tenapanor right before the next meal following dialysis.
4. If a patient misses a dose, they should skip the missed dose and take the next dose at the regular time before the next meal. Patients should not take two doses at the same time.
5. Store Xphozah (tenapanor) in a dry place, protected from moisture, kept in the original bottle with the desiccant, and keep the bottle tightly closed.

Patient selection

Xphozah (tenapanor) may be most appropriate for patients with:

1. **Inadequate phosphate control despite phosphate binders:** The AMPLIFY & OPTIMIZE trials demonstrated significant additional phosphate lowering when Xphozah (tenapanor) was added to existing binder therapy in patients with persistent hyperphosphatemia.[42,44]
2. **Phosphate binder intolerance:** Xphozah (tenapanor) offers an alternative mechanism for patients who cannot tolerate adequate doses of phosphate binders due to gastrointestinal side effects or other adverse reactions.
3. **High pill burden:** OPTIMIZE demonstrated Xphozah (tenapanor) efficacy in reducing serum phosphate levels while also reducing pill burden by a median reduction in pill number of 16.7% (3 pills/day) and 44.4% (6 pills/day) in the binder reduction and straight switch groups, respectively. Furthermore, 84.4% of patients who completed a patient experience questionnaire reported an improvement in their phosphate management routine, with approximately 35% of respondents citing the size or number of phosphate-lowering pills as the most likely contributing factor.[44]
4. **Constipation:** An additional benefit observed in clinical practice is improvement in constipation, which is common in patients on dialysis. In the OPTIMIZE trial, 25.8% of patients who reported an improvement in their phosphate management routine cited their frequency of bowel movements as a significant contributing factor.[44] This dual benefit may be particularly advantageous for patients on dialysis who often experience constipation from phosphate binders, opioid medications, and reduced physical activity.

Patient access

Unlike phosphate binders distributed by dialysis organizations or traditional prescriptions filled at any local community pharmacy, **Xphozah (tenapanor) is distributed through a specialty pharmacy network.** Prescriptions can be e-prescribed, faxed, or called in to a participating pharmacy within the Xphozah specialty pharmacy network.

When sending the prescription, remember to include the dialysis center name, recent serum phosphorus labs, and brief binder history on the prescription. **Also, inform your patients that they will need to respond to a call or text from the specialty pharmacy or ArdelyxAssist for their prescription to be processed.** This interaction is essential for confirming consent, affordability, and shipping address.

Once submitted, a benefits investigation is conducted to assess insurance coverage, prior authorization requirements, and anticipated out-of-pocket costs. If coverage barriers are encountered, ArdelyxAssist may support prior authorization submissions, appeals, and alternative access pathways (e.g., copay assistance, patient assistance). The manufacturer access team and specialty pharmacies may also assist with troubleshooting delays, resolving denials, and maintaining communication with patients and providers to ensure timely initiation of treatment. Once access is secured, patient onboarding and medication dispensing occur, usually via direct-to-patient shipment from the specialty pharmacy.

More information can be found on the Xphozah website: https://www.xphozah-hcp.com/access-affordability/.

Patient case vignettes

To apply this information through a series of patient case vignettes, scan the QR or visit: http://kidney.org/PhosCases

Case vignette 1

A 58-year-old woman with ESKD on peritoneal dialysis presents for routine follow-up. Her serum phosphorus is 7.2 mg/dL despite taking sevelamer carbonate 2400 mg three times daily with meals (9 tablets per day). She reports difficulty swallowing the large tablets and admits to frequently missing doses because "there are just too many pills." She also takes medications for hypertension, diabetes, peripheral neuropathy, and cardiovascular disease, bringing her total daily pill count to over 20 tablets. Her serum calcium is 9.5 mg/dL, and she has no history of gastrointestinal disorders. She reports chronic constipation requiring daily laxative use.

Case vignette 2

A 33-year-old woman with ESKD on hemodialysis has serum phosphorus levels consistently fluctuating in and out of range over the past year. She reports trying her best with adherence to medications and limiting phosphorus in her diet, while also noting that childcare responsibilities for her 2 young children and juggling competing priorities can often get in the way. Her current serum phosphorus is 8.1 mg/dL despite maximal doses of lanthanum carbonate 1000 mg three times daily. Her serum calcium is 9.3 mg/dL. She reports no diarrhea but does experience occasional constipation. She has no history of bowel obstruction or inflammatory bowel disease.

Case vignette 3

A 71-year-old man with ESKD on hemodialysis presents with worsening hyperphosphatemia (serum phosphorus 7.8 mg/dL) despite taking calcium acetate. He has a complex medical history, including established cardiovascular disease with evidence of vascular calcification, and recurrent episodes of small bowel obstruction (most recent episode was 3 months ago, requiring hospitalization and nasogastric decompression). CT imaging at that time showed multiple areas of small bowel narrowing, likely from adhesions from prior abdominal surgeries. He is currently asymptomatic from a gastrointestinal standpoint but reports taking 15 different medications daily and would like to reduce his pill burden.

Case vignette 4

A 54-year-old woman with ESKD on peritoneal dialysis was started on tenapanor 30 mg twice daily three weeks ago for persistent hyperphosphatemia (baseline serum phosphorus 7.4 mg/dL) despite sevelamer therapy. Her most recent serum phosphorus is 6.1 mg/dL, showing good response. However, she calls the clinic to report loose stools 3-4 times daily for the past two weeks. She describes the diarrhea as bothersome, but "not severe". She has been taking the medication as prescribed (just before breakfast and dinner) and has not been using any laxatives or stool softeners. She denies abdominal pain, fever, blood in her stools, or signs of dehydration.

Case vignette 5

A 38-year-old man with ESKD secondary to IgA nephropathy started hemodialysis 6 weeks ago. His most recent labs show serum phosphorus of 6.2 mg/dL and serum calcium of 9.4 mg/dL. He has not yet started on any phosphate-lowering therapy. He works full-time as a software engineer and is highly motivated to manage his kidney disease. He reports excellent dietary adherence and has been working closely with a kidney dietitian on his low-phosphorus diet. He has a history of chronic diarrhea-predominant irritable bowel syndrome (IBS-D) that has been well-controlled on a low-FODMAP diet for the past year, with 1-2 loose stools daily at baseline. He is concerned about pill burden as he already takes multiple medications and asks about tenapanor, which he read about online as a "low pill burden option."

Conclusion

In conclusion, tenapanor represents a valuable addition to the therapeutic toolbox for managing hyperphosphatemia in patients on dialysis. Its novel mechanism of reducing paracellular phosphate absorption through NHE3 inhibition demonstrated efficacy in lowering serum phosphorus, a favorable long-term safety profile, and the potential to dramatically reduce pill burden make it an important option for patients with inadequate response to or intolerance of traditional phosphate binders. While diarrhea remains a common adverse effect requiring careful patient counseling and monitoring, most patients tolerate the medication well, and many experience the additional benefit of improved bowel function. As clinicians gain more experience with tenapanor, it is likely to play an increasingly important role in personalized approaches to CKD-MBD management.

To learn more, scan the QR or visit:
https://www.kidney.org/professionals/clinician-tools-resources/hyperphosphatemia-dialysis

References

1. Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of Calcium, Phosphorus, and Magnesium Dysregulation in Chronic Kidney Disease. *Semin Dial*. 2015;28(6):564-577.
2. Goretti Penido M, Alon US. Phosphate homeostasis and its role in bone health. *Pediatr Nephrol*. 2012;27(11):2039-2048.
3. Yee J, Rosenbaum D, Jacobs JW, Sprague SM. Small Intestinal Phosphate Absorption: Novel Therapeutic Implications. *Am J Nephrol*. 2021;52(7):522-530.
4. Kates DM, Sherrard DJ, Andress DL. Evidence that serum phosphate is independently associated with serum PTH in patients with chronic renal failure. *Am J Kidney Dis*. 1997;30(6):809-813.
5. Craver L, Marco MP, Martinez I, et al. Mineral metabolism parameters throughout chronic kidney disease stages 1-5--achievement of K/DOQI target ranges. *Nephrol Dial Transplant*. 2007;22(4):1171-1176.
6. Ketteler M. Phosphate Metabolism in CKD Stages 3-5: Dietary and Pharmacological Control. *Int J Nephrol*. 2011;2011:970245.
7. Waziri B, Duarte R, Naicker S. Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): Current Perspectives. *Int J Nephrol Renov Dis*. 2019;12:263-276.
8. Düsing P, Zietzer A, Goody PR, et al. Vascular pathologies in chronic kidney disease: pathophysiological mechanisms and novel therapeutic approaches. *J Mol Med Berl Ger*. 2021;99(3):335-348.
9. Xu C, Smith ER, Tiong MK, Ruderman I, Toussaint ND. Interventions To Attenuate Vascular Calcification Progression in Chronic Kidney Disease: A Systematic Review of Clinical Trials. *J Am Soc Nephrol*. 2022;33(5):1011-1032.
10. Viegas C, Araújo N, Marreiros C, Simes D. The interplay between mineral metabolism, vascular calcification and inflammation in Chronic Kidney Disease (CKD): challenging old concepts with new facts. *Aging*. 2019;11(12):4274-4299.
11. Reiss AB, Miyawaki N, Moon J, et al. CKD, arterial calcification, atherosclerosis and bone health: Inter-relationships and controversies. *Atherosclerosis*. 2018;278:49-59.
12. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*. 2003;18(9):1731-1740.
13. Ketteler M, Evenepoel P, Holden RM, et al. Chronic kidney disease–mineral and bone disorder: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2025;107(3):405-423.
14. United States Renal Data System Annual Data Report. End Stage Renal Disease - Chapter 2: Clinical Indicators and Preventive Care. In: *2025 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2025. Accessed April 14, 2026. https://usrds-adr.niddk.nih.gov/2025/end-stage-renal-disease/2-clinical-indicators-and-preventive-care
15. Isakova T, Nickolas TL, Denburg M, et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). *Am J Kidney Dis*. 2017;70(6):737-751.
16. 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.
17. Wald R, Rabbat CG, Girard L, et al. Two phosphAte taRGets in End-stage renal disease Trial (TARGET): A Randomized Controlled Trial. *Clin J Am Soc Nephrol*. 2017;12(6):965-973.
18. Isaka Y, Hamano T, Fujii H, et al. Optimal Phosphate Control Related to Coronary Artery Calcification in Dialysis Patients. *J Am Soc Nephrol*. 2021;32(3):723-735.
19. Edmonston DL, Isakova T, Dember LM, et al. Design and Rationale of HiLo: A Pragmatic, Randomized Trial of Phosphate Management for Patients Receiving Maintenance Hemodialysis. *Am J Kidney Dis*. 2021;77(6):920-930.e1.
20. National Library of Medicine. Pragmatic Randomised Trial of High Or Standard PHosphAte Targets in End-stage Kidney Disease (PHOSPHATE). Published online May 10, 2024. Accessed September 19, 2024. https://clinicaltrials.gov/study/NCT03573089
21. Edmonston D, Isakova T, Dember LM, et al. Higher versus Lower Phosphate Targets for Patients Undergoing In-Center Hemodialysis: A Randomized Controlled Trial. *J Am Soc Nephrol*. 2025;36(12):2445-2455.
22. University of Queensland. Pragmatic Randomised Trial of High Or Standard PHosphAte Targets in End-stage Kidney Disease (PHOSPHATE) (PHOSPHATE). July 1, 2025. Accessed April 17, 2026. https://clinicaltrials.gov/study/NCT03573089
23. Hu L, Napoletano A, Provenzano M, et al. Mineral Bone Disorders in Kidney Disease Patients: The Ever-Current Topic. *Int J Mol Sci*. 2022;23(20):12223.
24. Ikizler TA, Burrowes JD, Byham-Gray LD, et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am J Kidney Dis*. 2020;76(3 Suppl 1):S1-S107.
25. Kistler BM, Moore LW, Benner D, et al. The International Society of Renal Nutrition and Metabolism Commentary on the National Kidney Foundation and Academy of Nutrition and Dietetics KDOQI Clinical Practice Guideline for Nutrition in Chronic Kidney Disease. *J Ren Nutr*. 2021;31(2):116-120.e1.
26. Biruete A, Hill Gallant KM, Lloyd L, et al. 'Phos'tering a Clear Message: The Evolution of Dietary Phosphorus Management in Chronic Kidney Disease. *J Ren Nutr*. 2023;33(6S):S13-S20.
27. Kalantar-Zadeh K, Gutekunst L, Mehrotra R, et al. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(3):519-530.
28. Naber T, Purohit S. Chronic Kidney Disease: Role of Diet for a Reduction in the Severity of the Disease. *Nutrients*. 2021;13(9):3277.
29. Chan W. Chronic Kidney Disease and Nutrition Support. *Nutr Clin Pract*. 2021;36(2):312-330.
30. Anderson CAM, Nguyen HA. Nutrition education in the care of patients with chronic kidney disease and end-stage renal disease. *Semin Dial*. 2018;31(2):115-121.
31. Scialla JJ, Kendrick J, Uribarri J, et al. State-of-the-Art Management of Hyperphosphatemia in Patients With CKD: An NKF-KDOQI Controversies Perspective. Am J Kidney Dis. 2021;77(1):132-141.
32. Flythe JE, Watnick S. Dialysis for Chronic Kidney Failure: A Review. *JAMA*. 2024;332(18):1559.
33. Natale P, Green SC, Ruospo M, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). Cochrane Central Editorial Service, ed. *Cochrane Database Syst Rev*. 2025;2025(6).
34. Ruospo M, Palmer SC, Natale P, et al. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). *Cochrane Database Syst Rev*. 2018;8(8):CD006023.
35. Fissell RB, Karaboyas A, Bieber BA, et al. Phosphate binder pill burden, patient-reported non-adherence, and mineral bone disorder markers: Findings from the DOPPS. *Hemodial Int*. 2016;20(1):38-49.
36. Xphozah (tenapanor) tablets. Published online June 2025. Accessed April 20, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/213931s005lbl.pdf
37. 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.
38. Saurette M, Alexander RT. Intestinal phosphate absorption: The paracellular pathway predominates? *Exp Biol Med (Maywood)*. 2019;244(8):646-654.
39. Dwyer JP, Kelepouris E. New Directions in Phosphorus Management in Dialysis. *J Ren Nutr*. 2023;33(1):12-16.
40. Hill Gallant KM, Sprague SM, Rosenbaum DP, et al. Tenapanor: A Phosphate Absorption Inhibitor for the Management of Hyperphosphatemia in Patients With Kidney Failure. *J Ren Nutr*. 2025;35(1):25-34.
41. Block GA, Bleyer AJ, Silva AL, et al. Safety and Efficacy of Tenapanor for Long-term Serum Phosphate Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM). *Kidney360*. 2021;2(10):1600-1610.
42. 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):1465-1473.
43. Silva AL, Chertow GM, Hernandez GT, et al. Tenapanor Improves Long-Term Control of Hyperphosphatemia in Patients Receiving Maintenance Dialysis: the NORMALIZE Study. *Kidney360*. 2023;4(11):1580-1589.
44. Sprague SM, Weiner DE, Tietjen DP, et al. Tenapanor as Therapy for Hyperphosphatemia in Maintenance Dialysis Patients: Results from the OPTIMIZE Study. *Kidney360*. 2024;5(5):732-742.
45. Khan LA, Alam B, Ladhwani NK, et al. Efficacy and Safety of Tenapanor in Hemodialysis Patients with Hyperphosphatemia: A Systematic Review and Meta-Analysis of Short-Term Randomized Controlled Trials. *Am J Nephrol*. Published online July 9, 2025:1-12.
46. Akizawa T, Urano N, Ikejiri K, Nakanishi K, Fukagawa M. Tenapanor: A novel therapeutic agent for dialysis patients with hyperphosphatemia. *Ther Apher Dial*. 2025;29(2):157-169.
47. Fishbane S, Zhao S, Edelstein S, Yang Y, Spiegel D. Tenapanor-Treated Patients Using Over-the-Counter Antidiarrheal Agents Saw Decreased Stool Frequency and Improved Stool Consistency. Presented at: 2025 National Kidney Foundation Spring Clinical Meetings; April 2025; Boston, MA. Accessed April 20, 2026. https://cme.kidney.org/spa/app/resource/r649-2025-spring-clinical-meetings/event/home/posters/abstracts?abstractId=6732

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