Drugs (2018) 78:1171–1186
https://doi.org/10.1007/s40265-018-0950-2

LEADING ARTICLE

Targeting Gastrointestinal Transport Proteins to Control Hyperphosphatemia in Chronic Kidney Disease

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Published online: 18 July 2018

Abstract

Management of hyperphosphatemia in patients with dialysis-dependent chronic kidney disease remains a major challenge, requiring a multifaceted approach that includes dietary phosphate restriction, dialysis, and phosphate binders. However, these treatments fail to meet serum phosphate targets in many patients, potentially further exacerbating the significant morbidity and mortality burden associated with the disease. Recent advances in our understanding of the mechanisms underlying phosphate homeostasis have shed new light on the issue and suggest that gastrointestinal transport proteins may be promising targets for new hyperphosphatemia treatments. Drugs that inhibit or downregulate these transport proteins, and thus reduce phosphate uptake from the gut, may overcome some of the limitations of existing phosphate-lowering strategies, such as interdialytic rises in serum phosphate levels, poor adherence to dietary and phosphate-binder regimens, and maladaptive responses that can increase gastrointestinal phosphate absorption. Here, we review the latest preclinical and clinical data for two candidates in this novel drug class: tenapanor, a small-molecule inhibitor of the sodium/hydrogen ion-exchanger isoform 3, and nicotinamide, an inhibitor of sodium–phosphate-2b cotransporters. We also discuss how potential synergies in their mechanisms of action suggest that coadministering phosphate binders with sodium–phosphate-2b cotransporter inhibitors may yield additive benefits over traditional phosphate-binder therapy.

Key Points

Hyperphosphatemia is a significant problem in patients with chronic kidney disease, with high serum phosphate levels associated with increased mortality.

Many patients cannot adequately maintain serum phosphate concentrations at recommended levels despite current treatments such as dietary phosphate restriction, dialysis, phosphate binders, and controlling secondary hyperparathyroidism.

Tenapanor and nicotinamide are two promising new treatments for hyperphosphatemia; by inhibiting active gastrointestinal phosphate absorption, these treatments may prove to be useful alternative or additional therapies for hyperphosphatemia in chronic kidney disease.

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1 Introduction

In chronic kidney disease (CKD), glomerular filtration rate (GFR) declines, and phosphate excretion becomes increasingly dependent on the actions of fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH); both inhibit tubular phosphate reabsorption in order to maintain phosphate homeostasis. However, these mechanisms cannot compensate for continual decline in GFR, and hyperphosphatemia develops. This can be further exacerbated by dietary phosphate load, the major contributor to the body's exchangeable pool of phosphate, and by CKD-related bone disease, where bone is resorbed more rapidly than it is formed or where its phosphate absorbing capacity is compromised (Fig. 1) [1, 2]. Here, we review active phosphate transport mechanisms and their potential role as targets for novel hyperphosphatemia treatment strategies in CKD.

2 Overview of Phosphate Transport and Homeostasis

Under normal conditions, serum phosphate levels are governed by gastrointestinal absorption/secretion, bone formation/resorption, and renal reabsorption/excretion [1, 3]. In healthy adults, dietary phosphate is absorbed via the intestines into an exchangeable pool, comprising intracellular phosphate (70%), bone (29%), and serum phosphate (< 1%), with the proportion of phosphate absorption dependent on the ingested phosphate source. Phosphate exits the body predominantly via excretion of phosphate from the kidneys (Fig. 1) [1–3].

Historical views of mineral homeostasis regard the kidneys as the primary organ responsible for dealing with excess phosphate. Because intestinal dietary phosphate absorption was believed to occur by passive diffusion, the intestines were considered of secondary importance. It is now known that intestinal phosphate absorption occurs via two distinct mechanisms: passive paracellular transport

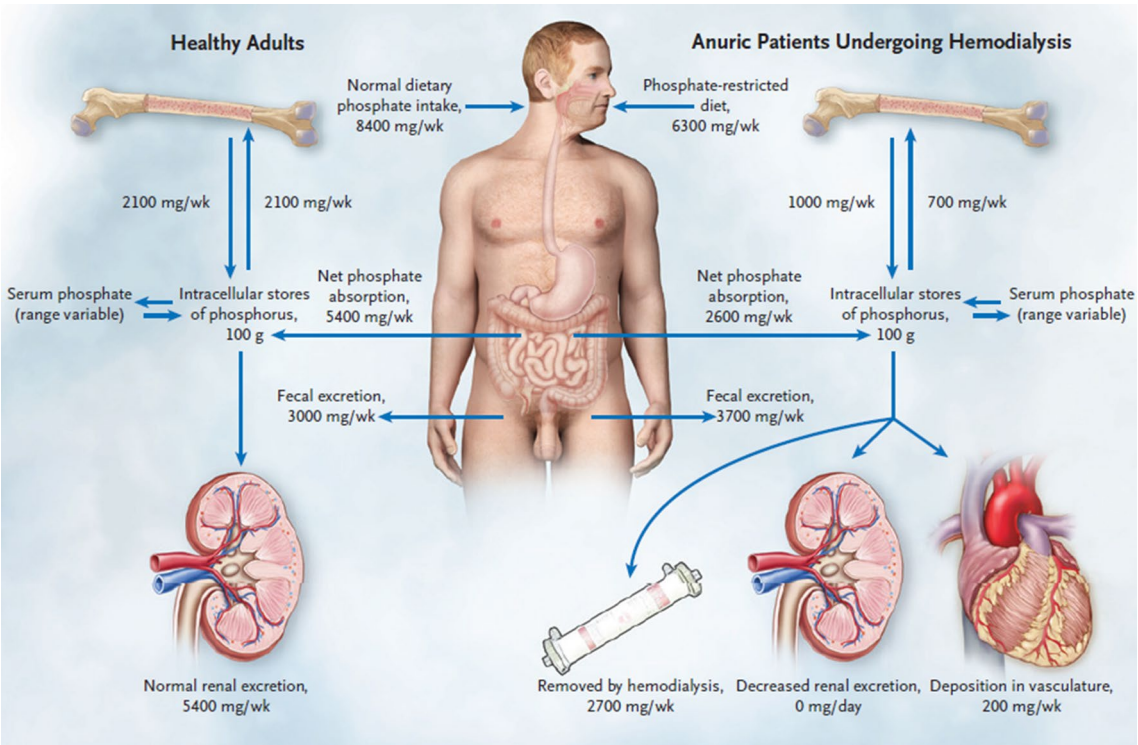

Fig. 1 Mechanisms underlying phosphate homeostasis in healthy adults and in patients with chronic kidney disease [2]. In healthy adults, phosphate intake is matched by phosphate excretion in feces and urine, and the flux of phosphate between the skeleton and the extracellular phosphate pool is approximately the same in both directions. In patients with chronic kidney disease, dietary restriction of phosphate is insufficient to compensate for the decrease in renal phosphate excretion, resulting in a positive phosphate balance. In addition, bone is often resorbed more rapidly than it is formed because of abnormal bone remodeling in kidney failure. Together, these abnormalities may confer a predisposition to vascular calcification, especially when serum phosphate levels are suboptimally controlled. The phosphate values shown are for illustrative purposes only, as these values vary from patient to patient. Reproduced with permission from Tonelli et al. [2]

along concentration gradients, and active sodium-dependent transcellular transport via carrier or transporter proteins. Expression of these gastrointestinal transporters is increased by active vitamin D [4].

A study in patients with CKD showed that the balance between the two mechanisms was affected by vitamin D levels and dietary phosphate intake [5]. Vitamin D deficiency reduced the rate of active phosphate absorption but did not affect passive absorption. Phosphate transport was also affected by luminal phosphate concentration, with absorption dependent on active transport at low concentrations and passive transport predominating at high concentrations; this is commonly the case with Western diets [5].

In passive paracellular transport, substrate movement occurs along a concentration gradient through tight junction complexes formed between adjacent cells [3]. Tight junction complexes function as a selective barrier to restrict paracellular diffusion, and are formed by interactions between complementary adhesive transmembrane proteins, such as occludin and claudins, located in the lateral cell membrane. These complexes interact with the cytoskeleton and signal transduction pathways, and differ in their morphology and permeability characteristics across different tissues. Evidence suggests that occludin and claudins are important for ion specificity. However, specific tight junction proteins associated with phosphate specificity have yet to be identified [3].

Two families of solute carrier (SLC) membrane proteins mediate sodium (Na)-dependent cotransport of inorganic phosphate (Pi) across cell membranes—SLC34 and SLC20 [4, 6]. In the SLC34 cotransporter family, NaPi2b (SLC34A2) is primarily responsible for phosphate absorption in the gut, and the main function of NaPi2a (SLC34A1) and NaPi2c (SLC34A3) is mediation of transcellular phosphate reabsorption in the renal proximal tubule (Fig. 2) [4, 6]. The SLC20 cotransporters, PiT-1 (SLC20A1) and PiT-2 (SLC20A2), are expressed ubiquitously and were considered historically to be "housekeeping" transport proteins [6]. However, PiT-1 is now believed to play a role in intestinal phosphate absorption [4, 7], and PiT-2, which is present in rat renal proximal tubule brush-border membranes [4], is downregulated following administration of a high (1.2%) phosphate-containing diet, suggesting a regulatory role for this transporter on an organism level [8].

Animal data support the notion that renal mechanisms are not the sole effectors of phosphate homeostasis, with evidence suggesting that intestinal NaPi2b cotransporters play a significant role [4]. Studies in adult conditional NaPi2b-knockout mice demonstrated that intestinal NaPi2b cotransporters make up > 90% of active phosphate absorption, contributing up to 50% of total phosphorus uptake. Interestingly, the decreased phosphate absorption in this model was countered by a compensatory decrease in urinary

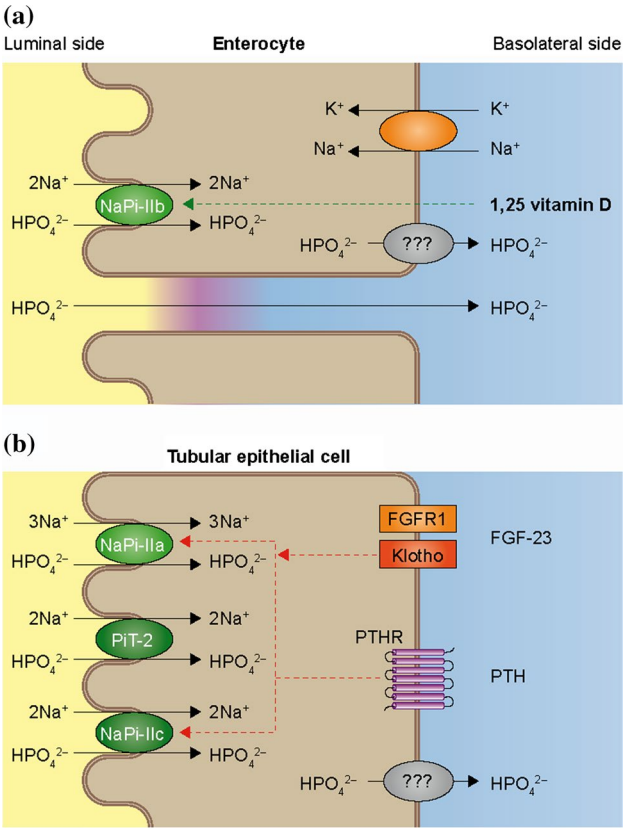

Fig. 2 Role of NaPiII family of sodium–phosphate cotransporters in the intestines and in the kidney [120]. **a** Intestinal phosphate uptake occurs by active transport via sodium–phosphate cotransporters (NaPi-IIb) and is positively regulated (dotted green arrow) by active vitamin D. Phosphate is subsequently transported into the circulation by an as yet unknown mechanism (represented in the figure as '???'). Electrogenic balance is accounted for by the sodium–potassium exchanger in the basolateral membrane. Additionally, passive phosphate transport takes place through a paracellular pathway, which is diffusion-driven and is mostly regulated by dietary phosphate intake. **b** In the kidney, an active transport process takes place that is highly similar to that seen in the intestine. Upon free glomerular filtration, phosphate is reabsorbed by NaPi-IIa and NaPi-IIc transporters, with PiT-2 transporters also contributing to this process. Phosphate is subsequently transported back into the circulation. NaPi-IIa and NaPi-IIc are negatively regulated by PTH and FGF-23, either directly or by enhancing the effect of PTH (dotted red arrow). Reproduced with permission from Baia et al. [120]. *1,25 vitamin D* 1,25 dihydroxyvitamin D_3, *FGF-23* fibroblast growth factor 23, *FGFR1* fibroblast growth factor receptor 1, *PTH* parathyroid hormone, *PTHR* parathyroid hormone receptor

phosphate excretion, mediated by renal NaPi2a upregulation [9]. In the context of an experimental CKD model, where compensatory renal phosphate excretion is lost, mice lacking the NaPi2b cotransporter have significantly lower serum phosphate levels than their wildtype counterparts (8.21 ± 0.56 vs. 10.04 ± 0.51 mg/dL; $p < 0.05$) [10].

Dietary and pharmacological phosphate restriction influences intestinal NaPi2b expression across species. Adaptive

increases in intestinal NaPi transport activity and NaPi2b expression have been observed in rats, mice, goats, and pigs in response to chronic dietary phosphate restriction, conceivably in an attempt to maintain phosphate uptake [7, 9, 11–14]. From an evolutionary perspective, this makes sense in order to save the body from inappropriate phosphate deprivation. Importantly, although vitamin D deficiency in CKD may limit gastrointestinal NaPi2b expression, studies in mice have demonstrated that even in the complete absence of active vitamin D or its receptor, dietary phosphate restriction upregulates NaPi2b [15, 16].

In mice, switching abruptly from a low- to a high-phosphate diet can lead to a maladaptive increase in intestinal NaPi transport activity, inducing transient postprandial hyperphosphatemia [3, 7]. Postprandial hyperphosphatemia also occurs in humans [3, 17, 18]. Phosphate-binder treatment, which essentially mimics the effects of a low-phosphate diet, also enhances intestinal NaPi2b expression in mice [10]. Injecting FGF-23 into normal mice has been shown to lower levels of 1,25-dihydroxyvitamin D_3 and serum phosphate [19]. FGF-23 also has been shown to inhibit intestinal NaPi transport activity and reduce NaPi2b protein in brush-border membranes in a vitamin D receptor-dependent manner [19]. Finally, 1,25-dihydroxyvitamin D_3 can enhance intestinal NaPi2b expression in wildtype mice and rats [12, 20]; this is important because many patients with CKD are prescribed active vitamin D metabolites.

Humans with an NaPi2b loss-of-function mutation do not develop hypophosphatemia [21, 22], likely owing to increased renal NaPi2a expression. Preclinical data indicate that nearly half of intestinal phosphate transport is NaPi2b-mediated [9]. However, this proportion may be smaller in patients with CKD owing to low vitamin D levels, in part a consequence of increased vitamin D catabolism driven by high concentrations of FGF-23 [2]. Alternatively, considering that NaPi2b cotransporters may be upregulated by therapy directed at improving mineral and bone disease in CKD (low-phosphate diet, phosphate binders, vitamin D supplementation) and the postprandial increase in intestinal NaPi activity [3, 10], NaPi2b is a potential target for hyperphosphatemia therapies.

3 Epidemiology and Impact of Hyperphosphatemia in Chronic Kidney Disease

The prevalence of hyperphosphatemia in patients with CKD increases with decreasing kidney function [23–25]. However, following a subtle decline in serum phosphate levels during the earliest stages of CKD, increased serum phosphate levels occur once CKD has progressed [25], suggesting phosphate homeostatic compensatory mechanisms may remain effective up to CKD stage 3.

A link between hyperphosphatemia and mortality was first shown in 1998 [26], but strong evidence demonstrating its independent association with increased morbidity and mortality was not available until 2004 [27]. In a large, retrospective analysis of data from 40,538 US patients with CKD receiving hemodialysis, serum phosphate concentrations > 5.0 mg/dL were found to be associated with a significantly elevated relative risk of mortality ($p < 0.05$), which rose incrementally with each additional 1.0 mg/dL increase in phosphate level [27]. The highest category of serum phosphate concentration (≥ 11.0 mg/dL) was associated with the greatest increase in relative risk of mortality (2.47; 95% confidence interval [CI] 1.90–3.19); hyperphosphatemia was also significantly ($p < 0.05$) associated with all-cause, cardiovascular, and fracture-related hospitalization [27]. A more robust methodological approach accounting for time-dependent variations in clinical and laboratory measures was adopted in a large historical cohort analysis of patients receiving maintenance hemodialysis ($n = 58,058$) [28]. Regardless of the model used, hyperphosphatemia was found to be strongly and independently associated with mortality, supporting a causal role for phosphate [28].

Many observational studies subsequently confirmed this association between hyperphosphatemia and increased risk of mortality, but by their design all these studies precluded definite establishment of causality [29–33]. While no randomized controlled trials to date have demonstrated that reducing serum phosphate concentrations reduces mortality [34], a 3-year study of 1744 patients receiving dialysis identified that having serum phosphate levels above the normal range was associated with a significantly higher risk of death [35]. Additional support for the presumed causal role of hyperphosphatemia in poor outcomes comes from COSMOS (Current Management of Secondary Hyperparathyroidism: a Multicenter Observational Study), a 3-year, European, multicenter, open-cohort, observational study designed specifically to prospectively assess possible links between serum phosphate, calcium, PTH levels, and mortality risk in adults undergoing maintenance hemodialysis ($n = 6307$) [36]. In the study, both high and low serum phosphate levels were associated with increased mortality risk [36]. A serum phosphate concentration of 4.4 mg/dL was associated with the minimum relative risk for mortality, and the range in which patients faced the lowest mortality risk was 3.6–5.2 mg/dL [36]. For patients whose baseline serum phosphate level was greater than 5.2 mg/dL, reductions toward this range were associated with reduced mortality risk [36]. Further evidence comes from a 6-month observational study conducted in the USA in patients initiating hemodialysis ($n = 102,754$). This study showed that, compared

with the reference range (3.5 to < 5.5 mg/dL), higher and lower serum phosphate concentrations were associated with increased risk of all-cause mortality among patients whose serum concentrations did not change during hemodialysis [37]. For patients with phosphate levels above the reference range at baseline, increases in phosphate levels during hemodialysis were associated with an increased risk of mortality. For patients with the highest baseline phosphate levels (≥ 7.5 mg/dL), a reduction in phosphate levels (≥ 0.5 mg/dL) was associated with a decreased risk of mortality [37].

These data suggest a causal link between hyperphosphatemia and increased mortality. The improvements in survival observed when serum abnormalities were close to the lowest risk ranges support the rationale for controlling this parameter in patients with advanced CKD [35, 36]. However, whether this approach improves other clinical outcomes remains unproven. In addition to increased mortality risk, hyperphosphatemia is associated with a number of intermediate cardiovascular outcomes, such as increased arterial stiffness [38], coronary atherosclerosis [39], and vascular calcification [40], which may induce additional morbidity and negatively affect quality of life.

4 Target Serum Phosphate Levels

Several international foundations aim to develop evidence-based clinical practice guidelines for the management of patients with CKD. These include the Kidney Disease Outcomes Quality Initiative and the Kidney Disease: Improving Global Outcomes (KDIGO) Work Groups, both of which have published recommendations for serum phosphate targets; the KDIGO recommendations were updated in early 2017 (Table 1) [41, 42]. Most recent guidelines suggest lowering serum phosphate concentrations toward the normal range. However, attainment of these targets remains poor with current strategies [35, 43–49].

5 Current Phosphate-Lowering Strategies

The main strategies for managing hyperphosphatemia are optimizing dialysis schedules, dietary phosphate restriction, administering phosphate-binding agents, and controlling hyperparathyroidism [50]. Detailed discussions of the current recommendations for these approaches have been published elsewhere [41, 42, 51, 52], but the key limitations of these approaches are summarized in Table 2.

Dietary phosphate restriction is routinely recommended to reduce serum phosphate levels in patients with CKD, although achieving adequate phosphate restriction can prove challenging given the high phosphate content of Western diets [50, 53]. Furthermore, marked restrictions in dietary phosphate can result in protein malnutrition. To date, no randomized controlled clinical trials have evaluated the effects of dietary phosphate restriction on clinical outcomes in patients on dialysis. Evidence from a 3-year observational cohort study in 30,075 patients on maintenance hemodialysis suggested that the risks of controlling serum phosphate levels through dietary protein restriction may outweigh its benefits [54]. This study showed that an increase in normalized protein nitrogen appearance (nPNA), a surrogate for dietary protein intake, together with a decrease in serum phosphate levels was associated with a reduced risk of mortality compared with an increase in both nPNA and serum phosphate levels. By contrast, a decrease in nPNA was associated with an increased mortality risk irrespective of whether serum phosphate levels increased or decreased [54].

Phosphate binders have a well-established efficacy profile in terms of reducing serum phosphate concentrations, but to date no randomized, double-blind,

Table 1 Overview of Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for target serum phosphate levels in patients with chronic kidney disease

Guideline	Target serum phosphate level recommendation
2009 CKD-MBD clinical practice guideline document [41]	*CKD stages 3–5* Should be maintained within the normal range of 2.5–4.5 mg/dL *CKD stage 5D/patients on dialysis* Should be reduced toward the normal range of 2.5–4.5 mg/dL
2017 Clinical practice guideline update on diagnosis, evaluation, prevention, and treatment of CKD-MBD [42]	*CKD stages 3A–5D* Treatment of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together. Serum phosphate levels should be reduced toward the normal range of 2.5–4.5 mg/dL

Conversion factors for units: serum phosphate in mg/dL to mmol/L, × 0.3229

CKD chronic kidney disease, *CKD-MBD* chronic kidney disease–mineral and bone disorder, *PTH* parathyroid hormone

Table 2 Overview of current strategies to lower serum phosphate levels and potential drawbacks of each intervention

Strategy	Potential drawbacks of intervention
Dialysis	Dialysis carries a significant healthcare resource burden and has a marked impact on patients' daily activities Three-times-weekly hemodialysis can remove only about 3 days' worth of ingested phosphate, meaning a relatively large amount must be handled by dietary phosphate binders instead [50]
Dietary phosphate restriction	Achieving adequate dietary phosphate restriction can prove challenging in clinical practice [50, 53] Western diets have a high phosphate content, and marked restrictions can result in protein insufficiency [50] Patients often find they are unable to adhere to these regimens [53] Dietary phosphate restriction can lead to compensatory upregulation of NaPi2b-dependent phosphate transport [7, 9, 11–14]
Phosphate binders	Most effective when dietary phosphate intake is < 1000 mg/day; when phosphate intake is ≥ 2000 mg/day, effectiveness is reduced, and hyperphosphatemia may persist [53] Calcium overload is a serious potential consequence of calcium-based binder use [42]. Non-calcium-based binders can eliminate this risk, but may be associated with other adverse events, such as aluminum accumulation toxicity [114]. They may also be less cost-effective than calcium-based binders [115] High phosphate-binder doses are often required, which may lead to high tablet burdens and issues with gastrointestinal tolerability Phosphate-binder treatment can lead to compensatory upregulation of NaPi2b-dependent phosphate transport [10] High tablet burdens are associated with nonadherence to treatment [116, 117], which, in turn, is associated with poor phosphate control [116, 118, 119]
Controlling PTH levels	Calcimimetics can only lower the amount of phosphate mobilized from bone, limiting their effect to an estimated 3% reduction in serum phosphate concentration for every 10% reduction in PTH level [66]. This intervention is restricted to patients with additional hyperparathyroidism, who only make up about 40% of all patients with CKD stage 5D (dialysis-dependent)

CKD chronic kidney disease, *NaPi2b* sodium–phosphate cotransporter 2b, *PTH* parathyroid hormone

placebo-controlled study has assessed the effects of phosphate binders on hard clinical outcomes, such as mortality or cardiovascular events, in patients on dialysis. However, clinical outcomes were investigated in the observational COSMOS trial [36]. Of the 6297 patients in COSMOS, all-cause mortality and cardiovascular mortality were significantly lower in patients prescribed phosphate binders than in those who were not, with hazard ratios (95% CIs) of 0.71 (0.61–0.82; $p < 0.001$) and 0.78 (0.62–0.97; $p = 0.03$), respectively [55]. Moreover, treatment with phosphate binders was independently associated with improved mortality compared with no phosphate-binder treatment in a prospective cohort study of 10,044 incident patients receiving hemodialysis, even after matching of propensity score for receiving phosphate binders and adjusting for confounders including malnourishment, which may have existed in those not in need of phosphate binders [56]. A second prospective cohort study of patients receiving hemodialysis ($n = 23{,}898$) also showed that prescription of phosphate binders was associated with lower mortality, even after adjustments for nutritional indicators [57]. A randomized, controlled pilot study (TARGET [Two Phosphate Targets In End-Stage Renal Disease Trial]) showed that it was possible to achieve and maintain different target serum phosphate levels in the two groups of patients on dialysis by titrating phosphate binders [58]. Further studies are now required to determine the effect on clinical outcomes of targeting different serum phosphate concentrations in patients on dialysis.

The KDIGO 2017 guidelines mention the potential harm of calcium exposure in patients with CKD [42]. An open-label, randomized controlled trial of calcium-based versus non-calcium-based phosphate binders [59] and two meta-analyses [60, 61] reported lower all-cause mortality with non-calcium-based binders (sevelamer) than with calcium-based binders. However, it is not possible to ascribe this difference to a beneficial effect of non-calcium binders or to harm inflicted by calcium-based binders owing to the lack of a placebo control arm to assess all-cause mortality [60–62] and the significant heterogeneity of this outcome among the trials examined [60, 63]. Indeed, questions regarding the methodology of the key study [59] also limit the conclusions that can be drawn from these analyses [63].

A further limitation of current phosphate-binder treatments is that although they reduce serum phosphate levels, many patients who take them do not reach recommended targets. For example, although 86.4% of the patients included in the COSMOS study received phosphate-binder therapy, only 26.7% attained the KDIGO serum phosphate target range (3.0–4.5 mg/dL) [64]. Poor target attainment may be because of suboptimal adherence to phosphate binders, inappropriate timing of drug-taking or blood sampling, the release of phosphate from bone, or, as discussed earlier, the upregulation of NaPi2b in the gastrointestinal tract following

phosphate binders or dietary phosphate restriction [7, 9–14]. Should these compensatory mechanisms occur in patients, they may reduce the efficacy of phosphate binders, and even exacerbate phosphate uptake if adherence is variable.

Controlling hyperparathyroidism is important because, when severe, it can aggravate hyperphosphatemia via increased mobilization of phosphate from bone [50]. Analyses have shown that treating hyperparathyroidism with the oral calcimimetic agent cinacalcet hydrochloride significantly reduced serum phosphate concentrations [65, 66]. However, patients with secondary hyperparathyroidism represent only 40% (27.9–54.2% globally) [67] of all adult dialysis-dependent patients.

Only a small proportion of patients reach target phosphate levels with dialysis, dietary phosphate restriction, phosphate binders, and calcimimetics. Considering this together with the known impact of elevated phosphate levels on cardiovascular risk and mortality, there remains an unmet need for further treatment options that can safely lower serum phosphate levels more effectively toward normal ranges.

6 Alternative Treatment Strategies for Hyperphosphatemia: Targeting Gastrointestinal Transport

To date, there are no approved treatments for hyperphosphatemia that specifically target the intestinal transepithelial transport of phosphate, although a number of treatments are currently in development. As mentioned earlier, intestinal phosphate absorption occurs by two distinct mechanisms (passive paracellular transport via tight junctions and active sodium-dependent transcellular transport via ion cotransporters). Two investigational compounds affect passive paracellular transport: tenapanor (RDX5791/AZD1722; Ardelyx, Inc., Fremont, CA, USA), a small-molecule inhibitor of the sodium/hydrogen ion-exchanger isoform 3 (NHE3), which has shown promising results in preliminary studies, and TP0469711, another NHE3 inhibitor that is in the early stages of development. In addition, two agents target active sodium-dependent transcellular transport, and represent an alternative mode of action. Nicotinamide, the amide form of vitamin B_3, inhibits NaPi cotransporters, and preliminary studies have yielded promising results; ASP3325 inhibits NaPi2b and is at an earlier stage of development.

6.1 Ion-Exchanger Inhibitors: Tenapanor and TP0469711

Tenapanor is a small-molecule inhibitor of NHE3 that produces reductions in intestinal sodium and phosphate absorption [68, 69]. It is under development for several indications, including hyperphosphatemia in patients with CKD receiving hemodialysis. In the intestine, tenapanor reduced absorption of phosphate with minimal systemic exposure (Table 3) [69–73]. Exactly how tenapanor reduces intestinal phosphate absorption is not well understood, and the underlying mechanisms are being investigated. However, it does not seem to involve direct inhibition of type 1 intestinal transport proteins or the NaPi2b cotransporter [68]. Evidence suggests that NHE3 inhibition by tenapanor temporarily increases the intracellular hydrogen ion concentration of epithelial cells, which reduces the permeability of tight junctions to phosphate, thereby reducing the paracellular absorption of luminal phosphate [74, 75]. This is important because passive paracellular phosphate transport is thought to account for the majority of phosphate absorption in humans.

Results have been published from a phase II, randomized, double-blind, placebo-controlled, dose-finding study that assessed the effects of tenapanor on serum phosphate concentrations in patients receiving hemodialysis ($n = 162$) [76]. After a 1- to 3-week phosphate-binder washout period, patients with hyperphosphatemia (serum phosphate level 6.0–10.0 mg/dL and an increase of 1.5 mg/dL from screening) were randomized equally to receive tenapanor 2, 3, 6, 20, 30, or 60 mg/day or placebo for 4 weeks [76]. Tenapanor induced dose-dependent reductions in mean serum phosphate level from baseline, ranging from −0.47 to −1.98 mg/dL (vs. −0.54 mg/dL with placebo; $p = 0.01$), with the largest reductions occurring in the tenapanor 20 and 60 mg/day groups (both $p < 0.05$ vs. placebo) [76]. Tenapanor was generally well tolerated at the lowest dose (2 mg/day), with a similar incidence of adverse events (AEs) to placebo (43 and 42%, respectively). AEs were more frequent at higher tenapanor doses (57–76%). The most common AEs were gastrointestinal-related, such as diarrhea (tenapanor, 26% at 2 mg/day, 18–68% at higher doses; placebo, 12%) and nausea (tenapanor, no cases at 2 mg/day, 4–9% at higher doses; placebo, 4%). The most common AE causing discontinuation was diarrhea (tenapanor, 9% at 2 mg/day, 0–32% at higher doses; no cases with placebo) [76]. Studies have identified the need to clarify the optimal dosing of tenapanor for patients with hyperphosphatemia [72, 76].

Another NHE3 inhibitor, TP0469711, is under investigation for the treatment of hyperphosphatemia. Early preclinical in vitro and rodent data have demonstrated its phosphate-lowering potential [77].

6.2 Sodium–Phosphate Cotransporter Inhibitors

Given their apparent role in phosphate homeostasis [7, 9–14], targeting intestinal NaPi2b cotransporters is a logical step in the development of novel treatments for hyperphosphatemia.

Table 3 Effects of tenapanor on phosphate excretion and serum phosphate levels in published phase I/II trials

Study	Patients receiving tenapanor	Patient population	Treatment duration	Tenapanor dose (mg)	Baseline/placebo group phosphate measurement	Phosphate measurement after treatment
Phase I trials					*Phosphate excretion (mean mmol/day ± SD)*	
Johansson et al., 2016 [72]	16	Healthy volunteers	4 days	15 (bid) Crossover phase: Tenapanor with SC (800 mg, tid)	31.3 ± 6.7 (urinary; baseline measure)	Tenapanor: 26.1 (23.8–28.3)[a] Tenapanor/SC: 25.2 (23.0–27.4)[a]
					17.1 ± 9.8 (stool; baseline measure)	Tenapanor: 37.4 (33.2–41.6)[a] Tenapanor/SC: 37.7 (33.5–41.9)[a]
Johansson et al., 2017 [71]	54	Healthy Japanese volunteers	7 days	180 (od) 15–90 (bid)	25.5 ± 8.6 (urinary; placebo group)	18.7 ± 4.4 (od) 15.3–19.4 ± 3.5–4.5 (bid)
					16.8 ± 7.9 (stool; placebo group)	31.0 ± 11.5 (od) 17.6–24.8 ± 6.5–8.6 (bid)
Johansson et al., 2017 [73]	18	Healthy volunteers	4 days for each food regimen	15 (bid) taken before food, after food, or when fasting	27.5 ± 13.6 (urinary; baseline measure)	Before food: 21.4 (17.8–25.0)[b] After food: 21.6 (18.0–25.2)[b] While fasting: 25.3 (21.7–28.9)[b]
					23.2 ± 13.9 (stool; baseline measure)	Before food: 27.3 (24.0–30.5)[b] After food: 25.6 (22.3–28.9)[b] While fasting: 22.3 (19.1–25.6)[b]
Phase II trials					*Serum phosphate levels (mean, mg/dL ± SD)*	
Block et al., 2016 [70]	37	Patients with CKD stage 5D and PWV ≤ 2% receiving hemodialysis	4 weeks	32 (bid)	5.2 ± 1.8	−0.8 ± 1.5 (change from baseline)
Block et al., 2017 [76]	136	Patients with hyperphosphatemia receiving hemodialysis	4 weeks	3 or 30 (od), 1–30 (bid)	7.32–7.92	Dose-dependent reductions of 0.47–1.98; significant vs. placebo at 10 and 30 mg (bid), $p < 0.05$

Conversion factors for units: serum phosphorus in mg/dL to mmol/L, × 0.3229

bid twice daily, *CI* confidence interval, *CKD* chronic kidney disease, *od* once daily, *PWV* postdialysis weight variability, *SC* sevelamer carbonate, *SD* standard deviation, *tid* three times daily

[a]90% CI

[b]95% CI

ASP3325 is an inhibitor of NaPi2b and has been shown to reduce NaPi2b-mediated phosphate uptake in vitro and reduce serum phosphate concentrations in a rat model of renal failure [78]. While ASP3325 was well tolerated in patients with end-stage renal disease in a phase Ia clinical trial, no effect was observed on serum phosphate concentrations [79].

Nicotinic acid (niacin) is a water-soluble organic compound with a pyridine ring and a molecular formula of $C_6H_5NO_2$ with a carboxyl group at the 3-position, otherwise known as vitamin B_3. Nicotinic acid can be metabolized to nicotinamide (also known as niacinamide), the corresponding amide [80]. Both forms have demonstrated phosphate-lowering activity [81–83].

While the exact mode of action remains unknown, animal studies have suggested that nicotinamide reduces hyperphosphatemia in an NaPi2b-dependent manner [9]. Nicotinamide lowered sodium-dependent intestinal phosphate absorption and reduced NaPi2b expression [84, 85], while the expression of Pit-1 and Pit-2 transporters remained unchanged [85]. In addition, nicotinamide administration has been shown to produce marked increases in renal phosphate excretion in animal studies, acting via inhibition of sodium-dependent renal phosphate transport [86–89]. Nicotinamide was associated with a reduction in NaPi2a levels in renal cells in some in vitro models, which may also explain this observation [90].

7 Nicotinamide

7.1 Proof-of-Concept Studies

The potential to reduce hyperphosphatemia in humans with nicotinamide has been demonstrated in several small studies conducted in patients receiving dialysis (Table 4) [81, 91–96]. These include a 12-week, proof-of-concept study in patients on long-term hemodialysis ($n = 65$) in which nicotinamide monotherapy was administered at a starting dose of 500 mg/day and was increased thereafter by 250 mg/day every 2 weeks until phosphate control (< 6.0 mg/dL) was achieved [81]. Rapid (from week 3), sustained (up to week 12), and significant reductions in mean serum phosphate levels were observed, decreasing from 6.9 mg/dL at baseline to 5.4 mg/dL during treatment ($p < 0.001$) [81]. Furthermore, mean serum phosphate increased significantly to 6.7 mg/dL following a 2-week post-treatment washout period ($p < 0.001$), suggesting that the phosphate-lowering effect was attributable to nicotinamide [81].

7.2 Head-to-Head Comparator Studies

In a 24-week, multicenter, randomized, open-label, non-inferiority study in patients receiving long-term hemodialysis ($n = 100$), nicotinamide monotherapy (0.5–2.0 g/day) appeared to be as effective as sevelamer (3.2–9.6 g/day) [94]. After 24 weeks of treatment, reductions in serum phosphate from baseline were similar with nicotinamide (6.50–5.57 mg/dL) and with sevelamer (7.12–5.26 mg/dL) [94]. However, the non-inferiority criterion was not met, possibly because a smaller number of patients were included than planned [94]. The treatment discontinuation rate due to AEs was 1.6-fold higher with nicotinamide than with sevelamer, with 55% of patients in the nicotinamide group completing the entire treatment period compared with 90% in the sevelamer group. However, patients previously treated with sevelamer were not excluded from this study, implying a possible selection bias favoring tolerability with sevelamer. Notably, pill burden was much lower with nicotinamide (mean dose 1.3 g/day, equivalent to 2.6 tablets) than with sevelamer (mean dose 8.6 g/day, or 10.8 tablets). Another difference was that FGF23 concentrations declined in the sevelamer arm, while they increased in those allocated to nicotinamide [94].

7.3 Add-On Studies

Coadministration of NaPi2b cotransporter inhibitors and phosphate binders may show greater efficacy in reducing serum phosphate than phosphate-binder monotherapy, owing to the complementary mechanisms of action. Nicotinamide has the potential to overcome limitations of phosphate binders and dietary phosphate restriction by limiting the effect of any NaPi2b upregulation observed upon reducing intestinal phosphate concentrations, and combining nicotinamide with phosphate binders (and/or dietary phosphate restriction) may maximize reductions in intestinal phosphate absorption. The benefits of nicotinamide are that its administration is independent of food intake and that a modified-release formulation may permit once-daily dosing and simple treatment regimens. Additional potential benefits may include reduced phosphate-binder dose and pill burden, reduced dose-dependent AEs, reduced calcification risk (should lower doses of calcium-based binders be needed when coadministered with nicotinamide), and optimized effects of dietary phosphate restriction, although these remain to be proven.

Results from two small studies appear to confirm that coadministering nicotinamide with phosphate binders yields greater reductions in serum phosphate concentration than phosphate-binder monotherapy [92, 93]. In one study, children undergoing hemodialysis ($n = 60$) were randomized 1:1 to receive nicotinamide (100 mg two or three times daily) plus calcium-based phosphate binders, or calcium-based

Table 4 Effects of nicotinamide on serum phosphate levels in published randomized controlled trials to date

Study	Number of patients in nicotinamide arm	Patient population	Treatment duration	Nicotinamide dose (mean ± SD, mg/day)	Nicotinamide combination therapy with phosphate binders?	Change from baseline in serum phosphate level in nicotinamide arm (mean, mg/dL)	Absolute serum phosphate level at end of treatment in nicotinamide arm (mean ± SD, mg/dL)
Cheng et al., 2008 [92]	33	Adults receiving hemodialysis, serum phosphate level ≥ 5.0 mg/dL	8 weeks	Up to 1500	CA, $n=9$; CC, $n=6$; LC, $n=4$; Sev HCl, $n=25$	−0.79 ($p=0.02$ vs. baseline)	5.47
Young et al., 2009 [96]	8	Adults receiving peritoneal dialysis, serum phosphate level > 4.9 mg/dL	8 weeks	Up to 1500	CA or CC, $n=3$; Sev Ac, $n=3$; none, $n=2$	−0.7 ± 0.9 (treatment effect difference vs. placebo, $p=0.037$)	5.20 ± 0.9
Shahbazian et al., 2011 [95]	24	Adults receiving hemodialysis, serum phosphate level ≥ 5.0 mg/dL	8 weeks	Up to 1000	CC	−1.24 ($p=0.0001$ vs. baseline)	4.66 ± 1.06
Allam et al., 2012 [91]	30	Adults receiving hemodialysis, serum phosphate level ≥ 5.0 mg/dL	8 weeks	Up to 1000	CC	−1.28 ($p=0.001$ vs. baseline)	5.47 ± 1.28
Lenglet et al., 2016[a] (NICOREN study) [94]	49	Adults receiving hemodialysis, serum phosphate level ≥ 4.95 mg/dL	24 weeks	1300	No	−0.77 ($p=0.01$ vs. baseline)	5.73
El Borolossy et al., 2016[a] [93]	30	Children receiving hemodialysis, serum phosphate > 5.0 mg/dL	6 months	233	CA or CC	−1.8 ($p=0.0001$ vs. baseline)	5.1 ± 0.9

CA calcium acetate, *CC* calcium carbonate, *LC* lanthanum carbonate, *SD* standard deviation, *Sev Ac* sevelamer acetate, *Sev HCl* sevelamer hydrochloride

[a]Nutritional counseling was provided to patients in these studies to limit/control phosphorus intake. Conversion factors for units: serum phosphorus in mg/dL to mmol/L, ×0.3229

phosphate binders alone [93]. The mean serum phosphate level decreased from 6.9 ± 1.6 mg/dL at baseline to 5.1 ± 0.9 mg/dL at month 6 ($p < 0.0001$) in the group receiving nicotinamide and phosphate binders, and a nominal but statistically significant increase was observed in those receiving phosphate binders alone (baseline, 7.7 ± 1.9 mg/dL; month 6, 8.1 ± 1.4 mg/dL; $p < 0.0001$; between-group comparison, $p = 0.001$) [93]. In a separate prospective, randomized, double-blind, placebo-controlled crossover study, adult patients receiving hemodialysis and phosphate binders ($n = 33$) were randomized to receive add-on nicotinamide (up to 1.5 g/day) or add-on placebo for 8 weeks [92]. The mean serum phosphate fell significantly in the group receiving nicotinamide and phosphate binders (baseline, 6.26 mg/dL; week 8, 5.47 mg/dL; $p = 0.02$), but no change was reported in the group receiving placebo and phosphate binders (baseline, 5.85 mg/dL; week 8, 5.98 mg/dL; $p = 0.73$; between-group difference, $p = 0.05$). The phosphate-lowering effect of nicotinamide was most pronounced in those patients with a treatment compliance level of at least 80% [92].

7.4 Safety/Tolerability Profile

Nicotinamide is a metabolite of nicotinic acid. Thus, some AEs associated with nicotinic acid, such as myalgia, raised glucose concentrations, and elevated liver enzyme levels [97], should be monitored following nicotinamide administration. Nicotinic acid is licensed and is available as an extended-release formulation, ERN [97]. The ERN formulation in combination with laropiprant and/or statins (HMG-CoA reductase inhibitors) has been assessed in several clinical studies in patients with cardiovascular disease [98, 99]. However, further clinical use was stopped due to lack of efficacy (in terms of reducing fatal or non-fatal cardiovascular events) [98, 99] and concerns over safety and tolerability (including increased risks of serious gastrointestinal, musculoskeletal, infection/infestation, bleeding event, and skin-related AEs, and disturbed glucose control/new-onset diabetes mellitus) [99–101]. A subgroup analysis of the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial focused on the effects of ERN on mineral metabolism parameters in patients with cardiovascular disease and concomitant mild-to-moderate CKD [102]. ERN had a modest effect on serum phosphate concentrations over 3 years, with levels 0.08 mg/dL lower per year than placebo ($p < 0.01$), but no corresponding changes in FGF-23 or PTH were observed [102]. In terms of the possible implications of these findings concerning nicotinamide, two issues should be considered. First, it cannot be assumed that the tolerability profile of nicotinamide will be identical to that for nicotinic acid, as both molecules represent unique pharmacological entities. Indeed, nicotinic acid causes flushing via G protein-coupled 109A niacin receptor-mediated prostaglandin release; nicotinamide does not bind to this receptor [103–105]. Second, the combination of nicotinic acid plus statins may have caused drug–drug interactions that led to certain AEs, such as myopathy and rhabdomyolysis [97]. This may also be an issue when nicotinamide is used to treat hyperphosphatemia, as some patients with CKD are also prescribed statins.

According to data from published trials in patients with CKD receiving dialysis, nicotinamide was generally well tolerated. The most frequent AEs occurring with nicotinamide use were gastrointestinal disturbances (including diarrhea) [81, 91–95] and thrombocytopenia [81, 94, 95]. AEs such as flushing [91–93] and rash [91–93] were observed occasionally. In four of these studies, no patients discontinued nicotinamide treatment [81, 92, 93, 95].

The terminal nicotinamide metabolite *N*-methyl-2-pyridone-5-carboxamide (2PY) is known to accumulate in patients with CKD [106–108]. As 2PY exerts biological activity by means of inhibiting poly(ADP-ribose) polymerase (PARP-1) [107], the European Uremic Toxins (EUTox) working group classified 2PY as a low-molecular-weight, water-soluble, non-protein-bound uremic toxin that can be removed by dialysis [109, 110]. PARP-1 is a nuclear enzyme involved in cellular response to DNA damage. Controversially, inhibition of PARP-1 has been shown to exert cytoprotective functions; however, excessive or long-term inhibition may be harmful owing to the impairment of DNA repair mechanisms [106, 108]. Use of PARP inhibitors for the treatment of several types of cancer was shown to induce thrombocytopenia, suggesting that this adverse drug reaction, also reported in patients with CKD receiving nicotinamide, may be linked to 2PY accumulation [108].

For example, in the NICOREN (Nicotinamide Versus Sevelamer Hydrochloride on Phosphatemia Control on Chronic Hemodialysed Patients) trial [94], thrombocytopenia was among the most common AEs, along with nausea and diarrhea. In four of the 49 patients receiving nicotinamide, platelet counts decreased to $< 70 \times 10^3/\mu L$, which resolved within 4 weeks of stopping treatment [94]. Mean platelet concentration exhibited only minor changes with nicotinamide treatment. At baseline, serum 2PY levels were similar for patients in the nicotinamide and sevelamer groups. By week 24, serum 2PY levels had increased significantly with nicotinamide and were fivefold higher than that of patients in the sevelamer group (21,285 ± 17,747 ng/mL vs. 3743 ± 5497 ng/mL, respectively; $p < 0.001$) [94]. Further research is needed to understand how the accumulation of 2PY may trigger thrombocytopenia in individual patients.

7.5 Future Studies

Although these trials show promising phosphate-lowering effects of nicotinamide in patients with hyperphosphatemia, they are limited by the short duration (8–24 weeks) and small participant numbers ($n = 8$–65 in the nicotinamide arms). Accordingly, the 1-year, phase III COMBINE (CKD Optimal Management with Binders and Nicotinamide) study (ClinicalTrials.gov identifier: NCT02258074) will investigate the effects on serum phosphate levels of nicotinamide (750 mg twice daily) in combination with lanthanum carbonate (1000 mg three times daily) in patients with CKD stages 3–4 ($n = 205$). The primary endpoint will be the change in serum phosphate and FGF-23 levels from baseline to month 12 [111]. In addition, the 1-year NOPHOS (Nicotinamide As Add-on Therapy compared to Placebo in Dialysis-Dependent Patients with Hyperphosphatemia; EudraCT Number: 2013-000488-95) phase III study in 700 patients will soon provide important placebo-controlled data on the therapeutic add-on effect of modified-release nicotinamide in combination with phosphate binders. The primary endpoint of this trial will be the change in serum phosphate level from baseline to week 12, with secondary endpoints such as serum phosphate concentrations, serum calcium concentrations, intact parathyroid hormone, high- and low-density lipoproteins, and triglycerides assessed over 1 year [112]. The 8-week, phase II DONATO (DOse-finding trial of NicotinAmide in dialysis-dependenT patients with hyperphOsphatemia; ClinicalTrials.gov identifier: NCT01200784) study compared the effects of nicotinamide modified release (250, 500, 750, and 1000 mg/day) with nicotinamide immediate release (1000 mg/day; $n = 252$) [113], but results have not yet been reported.

In summary, both dietary phosphate restriction and phosphate-binder therapy limit gastrointestinal uptake of phosphate mainly by passive paracellular diffusion, but might cause an undesirable maladaptive increase in phosphate uptake by promoting active phosphate transport through increased expression of gastrointestinal NaPi2b. By blocking NaPi2b cotransporters in the gut, nicotinamide may overcome the limitations of these two interventions while potentially increasing their efficacy and reducing phosphate-binder dose and pill burden.

8 Conclusion

Despite current treatments, many patients with dialysis-dependent CKD do not achieve target serum phosphate levels. Additional therapeutic strategies to those currently used are needed to manage hyperphosphatemia. Potential alternative strategies include the NHE3 ion-exchange inhibitor tenapanor and the NaPi2b cotransporter inhibitor nicotinamide, both of which have mechanisms of action that actively inhibit gastrointestinal phosphate absorption. Preliminary clinical evidence suggests that both agents lower serum phosphate levels and overall have an acceptable tolerability profile in patients with CKD, but more long-term safety data are needed. Although a large body of clinical data documents long-term use of nicotinamide for the treatment of different conditions, the clinical implications of 2PY accumulation in patients with CKD should be the subject of further research.

Clinically relevant outcomes are unknown for tenapanor as well as nicotinamide and need to be examined in clinical trials. If such trials show beneficial effects, drugs that target active gastrointestinal phosphate transport combined with phosphate-binder therapy could optimize the therapeutic effects of both treatments and enhance the effectiveness of dietary phosphate restriction. As optimal phosphate control in advanced CKD remains an unmet need, these developments are promising avenues that may ultimately lead to improved clinical outcomes for patients with CKD.

Acknowledgments Medical writing and editorial support were provided by Dr Ian M. Williams of Oxford PharmaGenesis Ltd (Oxford, UK). Open access fees and medical writing and editorial support were funded by Medice Arzneimittel Pütter GmbH & Co KG.

Compliance with Ethical Standards

Funding Medice Arzneimittel Pütter GmbH & Co KG funded medical writing/editorial support for preparation of the manuscript. The final decision to submit was that of the authors.

Conflict of interest Denis Fouque has received lecture fees from Fresenius Medical Care, Fresenius Kabi, Sanofi, Amgen, and Vifor; travel support from Fresenius Kabi and Vifor; and consulting fees from Fresenius Kabi, Sanofi, and Vifor. Marc Vervloet has received lecture or consulting fees from B Braun, Amgen, Baxter, Otsuka, Medice, and VFMCRP. Markus Ketteler has received lecture or consulting fees from Amgen, Bayer (Japan), BMS, FMC, Kissei, Kyowa Kirin, Medice, Pfizer, Sanifit, Sanofi, Shire, and Vifor Fresenius Medical Care Renal Pharma.

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