



# Chronic Kidney Disease-Mineral and Bone Disorder—Translating Evidence Into Practice

## A CME Activity

### Overview

Joachim H. Ix, MD, and Biff Palmer, MD, provide their perspectives on the clinical impact of 8 recently published studies involving the management of patients with Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Drs. Palmer and Ix will summarize the latest research developments on the pathogenesis of CKD-MBD and assess the clinical implications of recent data and evidence-based research involving various classes of phosphate binders, as well as calcimimetics and other agents for the treatment of secondary hyperparathyroidism, and lowering serum phosphate levels, to manage patients with CKD-MBD in clinical practice.

### Content Areas:

- CKD-MBD pathogenesis
- Intestinal NH3 inhibitors
- Etelcalcetide vs cinacalcet, vs placebo, phase 3 studies
- Sevelamer, and its effects on cardiovascular calcification
- Tenapanor, an NHE3 inhibitor and its effect on serum phosphate
- CKD-MBD 2017 KDIGO guideline

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### Target Audience

This activity was developed for nephrologists, primary care physicians, and other health care professionals who have an interest in chronic kidney disease-mineral and bone disorder (CKD-MBD).

### Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments on the pathogenesis of CKD-MBD
- Assess the clinical implications of recent clinical data and ongoing trials for lowering serum phosphate
- Interpret the clinical implications of recent clinical data and ongoing trials involving calcimimetics and other agents for the treatment of secondary hyperparathyroidism

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## Introduction

Palmer B.

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Biff Palmer, MD

Kidney disease is a pandemic associated with high mortality rates. Because of the severe consequences associated with chronic kidney disease-mineral and bone disorder, it is imperative clinicians are able to classify CKD-MBD. The high number of CKD patients also poses

a challenge for nephrologists and primary care physicians, especially when managing the combination of secondary hyperparathyroidism and mineral bone disease. A 2016 survey conducted by the Annenberg Center for Health Sciences confirmed 47% of physicians surveyed were not confident in their knowledge and understanding of the pathogenesis of CKD-MBD. How confident are *you* in the management of CKD-MBD?

For this activity, we selected 8 articles in which we will summarize the recent research developments on the pathogenesis of CKD-MBD and assess current clinical data and evidence-based research involving various classes of phosphate binders, non-calcium phosphate binders, calcimimetics, and other agents for the treatment of secondary hyperparathyroidism to incorporate into your clinical practice.

In addition, updates to the 2009 KDIGO guidelines are currently in development. These updates aim to align recent studies with more current standards of care in clinical practice. Once available, we will share an executive summary link of the guideline update results.

I'm Dr. Biff Palmer. Please join Dr. Joachim Ix and me to participate in this activity as we discuss and comment on recently published research.



## *The Chronic Kidney Disease—Mineral Bone Disorder (CKD-MBD): Advances in Pathophysiology*

Hruska KA, et al.



Joachim H. Ix, MD

Hello, this is Joe Ix, professor and chief of the Division of Nephrology and Hypertension at UC San Diego. I'll be discussing the publication, *The Chronic Kidney Disease—Mineral Bone Disorder (CKD-MBD): Advances in Pathophysiology*, by

Keith A. Hruska and colleagues. This

study report was published in *Bone*.

I selected this article to discuss because it provides an understanding of the new findings in the pathogenesis of CKD-MBD. New advances on the causes of CKD-MBD are discussed, including the discovery of Wnt inhibitors, as well as the repair and the disease processes in the kidney related to the factors in the circulation that cause the systemic complications of CKD. This recent study demonstrates circulating renal repair and injury factors are a source of the CKD-MBD and CKD-associated cardiovascular disease.

**Key findings:** Studies demonstrating circulating renal repair and injury factors promotes CKD-MBD and CKD-associated cardiovascular disease. Three novel cardiovascular risk factors, which include hyperphosphatemia, vascular calcification, and elevated fibroblast growth factor 23 (FGF23) levels, have been discovered within the CKD-MBD. Various forms of kidney disease increase renal expression of Wnt inhibitors, including Dickkopf 1, or (Dkk1), which is the only critical Wnt inhibitor in the kidney, and known to be stimulated in diabetes. Wnt-inhibitor proteins, nephrogenic-circulating factors reactivated in renal repair, are critical for tubular epithelial reconstruction. Discovery that activin A, second renal repair factor, circulates in increased levels during CKD. Activin A derives from peritubular myofibroblasts of diseased kidneys, where

it stimulates fibrosis and decreases tubular klotho expression, and has been found in the skeleton to be responsible for CKD-stimulation of osteoclastogenesis and bone remodeling, increasing bone turnover.

The review discusses 2 forms of vascular calcification stimulated by CKD: intimal and medial calcification. Klotho expression is significantly reduced by kidney injury, and studies show that the reduction of klotho is, in part, related to activin and activin type IIA receptor, also known as ActRIIA signaling. Klotho deficiency limits its regulation of FGF23 production and leaves hyperphosphatemia as the principal regulator of FGF23 secretion in CKD. In addition, recent mechanistic studies have directly linked klotho deficiency with cardiovascular disease. In CKD, osteoporosis may be observed with either high-turnover or low-turnover renal osteodystrophy. With progressive loss of renal function, bone strength suffers, despite an increase in mass, detected by dual-energy X-ray absorptiometry, or DXA.

FGF23 levels rise prior to changes in calcium, phosphate, or PTH levels, and are now recognized as one of the earliest detectable biomarkers of the CKD-MBD. FGF23 levels are associated with cardiovascular risk in CKD, and kidney transplant loss and mortality. Faul and colleagues did a study showing that FGF23 is a direct pathogenic factor causing left ventricular hypertrophy through activation of the calcineurin-NFAT pathway in cardiac myocytes. Studies by Andrukhova et al have shown that FGF23 promotes calcium reabsorption through stimulation of apical calcium entry channels, TRPV5, in the distal tubule. Vitamin D deficiency is shown through calcitriol deficiency, decreasing intestinal calcium absorption, leading to hypoglycemia and diminished tissue levels of vitamin D receptors, which result in resistance to calcitriol-mediated regulation and

stimulation of PTH secretion, leading to secondary hyperparathyroidism.

In summary, these recent translational discoveries introduce a new paradigm where kidney injury directly leads to skeletal and cardiovascular injury through the production of pathogenic circulating factors during attempted renal repair, including molecules that inhibit the canonical Wnt pathway, and activin, which can lead to chronic allograft injury and cardiovascular disease.

**Here are my thoughts and analysis of this study:**

To highlight the main points of the study from my perspective, this study provides a nice summary of the standard factors that are altered in CKD-MBD, including elevated FGF23, phosphate, PTH, and other factors. Within this known context, the authors describe new discoveries regarding elevated serum levels of Wnt inhibitors, particularly DKK1, which are released into the circulation in CKD animals, and how these factors may promote the CKD-MBD, including vascular and bone effects.

**How do the results of this study impact the current state of patient management?** While the review doesn't directly influence patient management, it gives new insights into cross-talk between the kidney and the vasculature and bone. As DKK1 is elevated in serum, and its neutralization may limit some aspects of the CKD-MBD, this work may lead to new treatment targets in the future.

**How do the results of this study impact the future state of patient management?** The review provides new insights to how signals from damaged kidneys influence vascular calcification and bone morphology. This may provide new targets for treatment to limit the CKD-MBD in future studies.

**What questions remain unanswered?** The exciting findings from this work come from rodent models of CKD. Future studies are required to determine the relevance of these findings in humans with CKD and with acute kidney injury. Future work is also required to determine if blocking DKK1 or other Wnt inhibitors is a viable and safe strategy in humans, and whether such strategies translate into improvements in vascular and bone health in patients living with kidney disease.



## *Nicotinamide and Phosphate Homeostasis in Chronic Kidney Disease*

Ginsberg C, Ix JH.



Joachim H. Ix, MD

Hello, this is Joe Ix, professor and chief of the Division of Nephrology and Hypertension at UC San Diego. I'll be discussing the publication, Nicotinamide and Phosphate Homeostasis in Chronic Kidney Disease, authored by Charles Ginsberg and myself, Joe Ix. This study report

was published in *Current Opinion in Nephrology and Hypertension*.

We selected this article to discuss because it reviews the approach to decreasing Npt2b expression. Although phosphate binders are commonly used to lower phosphate, they have been proven to only be minimally effective in CKD, and meanwhile, the management of hyperphosphatemia remains a major clinical challenge. Because of the associations between hyperphosphatemia with morbidity and mortality in CKD, there is great interest in lowering phosphate in clinical practice, and specifically, using and managing phosphate binders in earlier stages of CKD. Nicotinamide, also known as vitamin B<sub>3</sub>, has been shown to decrease intestinal phosphate transport in animals; however, its efficacy and safety in CKD remain uncertain. This study compares the metabolism and side-effect profile of data differentiating nicotinamide from nicotinic acid, or niacin, in patients with CKD and in the general population. The review focuses on emerging data surrounding the use of nicotinamide and its derivatives for phosphate lowering in patients with CKD and end-stage renal disease.

**From the lead author's perspective, there are several important highlights to this study:** The study summarizes the present literature on the use of intestinal phosphate binders in CKD patients. It highlights the relatively low efficacy in this setting. It also summarizes animal data showing that intestinal

phosphate binders increase expression of the major sodium-phosphate cotransporter in the small bowel (Npt2b). The study summarizes data demonstrating that nicotinamide suppresses Npt2b, and summarizes the experience of use of nicotinamide in patients with kidney disease. The paper lays out a strategy of how nicotinamide may be useful for managing hyperphosphatemia in CKD patients, either in isolation, or, perhaps, in combination with intestinal phosphate binders.

I think the study can have important implications to patients with CKD and MBD. If nicotinamide is found to be effective for phosphate lowering, as well as safe and well tolerated, it would provide a new strategy to treat patients with CKD-MBD.

### **This study has several important key findings.**

Because of limited efficacy of phosphate binders in early CKD, new therapies to lower phosphate in CKD are urgently needed. There is increasing interest in the use of nicotinamide and niacin for inhibiting sodium phosphate cotransporter 2b, or Npt2b, in CKD. Data suggest that nicotinamide may influence transcription or translation of Npt2b, or influence other circulating regulating factors that secondarily impact Npt2b function.

The review differentiates nicotinamide, or vitamin B<sub>3</sub>, from nicotinic acid, or niacin. While although they have similar functions as vitamins, their pharmacologic and toxic properties differ. When niacin is taken orally, it's converted to nicotinamide, and in high doses, it's sufficient to induce flushing and lipid-lowering effects before complete conversion to nicotinamide, metabolism, or excretion. Sodium-dependent absorption is primarily through Npt2b, located in the small intestine; and nicotinamide decreases serum phosphate concentrations by inhibiting sodium-dependent phosphate transport in the small intestine.

In animal models—particularly in rats and mice—studies provide insights into intestinal phosphate handling. Nicotinamide decreases expression of Npt2b cotransporters in the small intestine in animal models, and nicotinamide consistently lowers serum-phosphate concentrations in ESRD patients. Study results show that nicotinamide is a novel potential tool to treat hyperphosphatemia in patients with CKD, but we still need additional data on the safety and efficacy before its widespread clinical use.

**So, here are some highlights of major points of the study from my perspective.** Although widely used, intestinal phosphate binders really have minimal efficacy in lowering phosphate concentrations in CKD patients. This may be, in part, because they upregulate the key sodium phosphate cotransporter Npt2b in the small bowel. In contrast, nicotinamide lowers Npt2b expression.

The study summarizes the effects of nicotinamide on Npt2b in animal models, and in prior studies in patients with CKD and end-stage renal disease. To date, studies consistently demonstrate that nicotinamide lowers serum phosphate concentrations.

The study also highlights the distinct mechanisms of actions of intestinal phosphate binders and nicotinamide, and suggests that the 2 agents may actually have synergistic effects on phosphate lowering. These results may ultimately have impacts on patient management. At present, the study doesn't directly impact patient management; however, randomized clinical trials are ongoing, testing the efficacy and safety of nicotinamide in isolation or when combined with a phosphate binder in CKD patients. These trials will be completed within the next 2 years; thus, the impact on clinical management may be changing in the short term.

In addition, nicotinamide is not marketed as a drug in the US, but rather as a vitamin; thus, it's readily available and inexpensive. It may provide an opportunity to treat patients with CKD-MBD around the world, even in resource-poor settings. With this, though, many questions remain unanswered. In particular, the efficacy and safety of nicotinamide in CKD and dialysis patients is not yet fully established, and trials are ongoing to address these important questions.



## *Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: A Randomized Clinical Trial*

*Block GA, et al.*



Joachim H. Ix, MD

Hello, this is Joe Ix, professor and chief of the Division of Nephrology and Hypertension at UC San Diego. I will be discussing the publication, *Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis with Secondary Hyperparathyroidism: A Randomized Clinical Trial*, by Geoffrey Block and colleagues. The study was published in *JAMA*.

I selected this article because the study evaluates the relative efficacy and safety of the IV calcimimetic etelcalcetide, and the oral calcimimetic cinacalcet, on serum parathyroid hormone, or PTH concentrations, in patients receiving hemodialysis. Secondary hyperparathyroidism is a complication of CKD and end-stage renal disease, contributing to extraskeletal calcification, and associated with cardiovascular mortality. Etelcalcetide is a synthetic peptide, and was shown to be more effective than cinacalcet in lowering PTH concentrations in patients receiving hemodialysis with secondary hyperparathyroidism.

This study was a head-to-head comparison trial evaluating etelcalcetide against cinacalcet, and conducted across 164 sites in the US, Canada, Europe, Russia, and New Zealand. This phase 3, randomized, double-blind, double-dummy, active trial included adult patients receiving hemodialysis with serum PTH levels greater than 500 picograms (pg) per mL. Exclusion criteria included patients who had not received cinacalcet during the 3 months prior to the first screening; and the use of commercial cinacalcet was prohibited during the study. All patients received

standard-of-care with phosphate binders and calcitriol, or active vitamin D analogs.

Etelcalcetide was administered intravenously with oral placebo for 26 weeks. IV study drug was administered 3 times a week, and oral drug was administered daily. Mean average weekly dose of etelcalcetide was 15 milligrams, and median average daily cinacalcet dose was 51 milligrams. The primary endpoint was noninferiority of etelcalcetide achieving a greater than 30% reduction from baseline in mean predialysis PTH concentrations during weeks 20 to 27 of the study. Secondary endpoints included superiority, achieving biochemical endpoints of both greater than 50%, and greater than 30% reduction in PTH, and self-reported nausea or vomiting.

**Key findings:** 683 patients were randomized 1:1 to receive IV etelcalcetide and oral placebo, or, alternatively, oral cinacalcet and IV placebo. The patients had a mean age of 55 years, and 56% were men. There were a number of adverse events: Of the 338 patients treated with etelcalcetide, 62 reported nausea, and 45 reported vomiting. Of the 341 patients treated with cinacalcet, 77 reported nausea, and 47 reported vomiting.

The study showed a greater than 30% reduction in mean PTH concentrations over 27 weeks. Among patients receiving hemodialysis with secondary hyperparathyroidism, use of etelcalcetide was not inferior to cinacalcet in reducing serum PTH concentrations over 27 weeks. It also met superiority criteria. Future studies are needed to assess clinical outcomes, as well as long-term efficacy and safety.

**Here are some of my main thoughts on this important study:** This is the first study to describe the use of a new IV calcimimetic in hemodialysis patients in a head-to-head comparison with cinacalcet. The study was designed as a noninferiority trial for PTH lowering greater than 30% from baseline weeks 20 to 27. Not only did it convincingly show noninferiority, but it demonstrated superiority for this endpoint, with 68% in the etelcalcetide group reaching the primary endpoint, vs 57% in the cinacalcet group. It was also hoped that etelcalcetide would result in less nausea and vomiting relative to cinacalcet, which is a major side effect of cinacalcet, but this was not realized in the present study. Etelcalcetide resulted in more hypocalcemia, and in turn, greater use of calcium-based oral phosphate binders and higher doses of active vitamin D compounds during the trial. And there were numerically more heart-failure events in those treated with etelcalcetide than those with cinacalcet; 10 in the etelcalcetide group vs 2 in the cinacalcet group. These small numbers are, in fact, small, but this important finding should be evaluated in future follow-up studies.

**How will this study impact the current state of patient management?** Management of hyperparathyroidism with cinacalcet in hemodialysis patients is challenging. The PTH has a very short serum half-life; thus, missing even a single dose of cinacalcet often results in large shifts

in PTH concentrations on monthly lab monitoring. This makes managing of PTH in hemodialysis patients quite challenging. Etelcalcetide provides an opportunity to use an IV drug at the end of dialysis. It has a half-life of 48 to 72 hours, and so this may lead to more consistent, and more predictable, changes in PTH. Etelcalcetide is the first IV calcimimetic, and only the second calcimimetic on the market. This may open the door for additional agents targeting CKD-MBD, moving forward. With that said, I also think that there are important remaining questions.

**What questions remain unanswered?** Etelcalcetide binds the calcium-sensing receptor at a unique site relative to cinacalcet. When cinacalcet binds, it requires the presence of calcium to bind and exert its actions in suppressing PTH release. Importantly, this is not the case for etelcalcetide. This may allow more dramatic PTH lowering and hypocalcemia, even when serum calcium concentrations are low.

In the present study, hypocalcemia was more frequent in the etelcalcetide group. As this drug is used in clinical practice, future studies are needed to understand the frequency and severity of hypocalcemia in non-trial settings. As etelcalcetide led to greater use of calcium binders; and active vitamin D compounds, as well as heart-failure events, were numerically higher, future studies are required to evaluate the effects of etelcalcetide on long-time outcomes, include cardiovascular disease.



## *Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: Two Randomized Clinical Trials*

*Block GA, et al.*



Joachim H. Ix, MD

Hello, this is Joe Ix, professor and chief of the Division of Nephrology and Hypertension at UC San Diego. I'll be discussing the publication, *Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis with Secondary Hyperparathyroidism:*

*Two Randomized Clinical Trials.* The manuscript is authored by Geoff Block and colleagues, and the study was reported in *JAMA*.

I selected this article to discuss because this study evaluates the effects of an IV calcimimetic etelcalcetide and compares it with placebo on serum parathyroid hormone concentrations in patients receiving hemodialysis. The study showed that etelcalcetide, a synthetic peptide, was more effective than placebo to have a greater than 30% reduction in PTH concentrations in patients with secondary hyperparathyroidism.

This study evaluated 2 parallel, phase 3, randomized, multicenter, placebo-controlled studies involving adult patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism. The trials were quite similar. Trial A was conducted in 508 patients at 111 sites in the US, Canada, Europe, Israel, Russia, and Australia; and trial B was conducted in 515 patients at 97 sites in the same countries. The trials were identical, except predialysis and postdialysis laboratory data and electrocardiograms were obtained in trial A, and only predialysis measurements were obtained in trial B; thus, they're presented together.

Exclusion criteria included patients who had not received cinacalcet during the 4 weeks prior to the

first screening, and the use of commercial cinacalcet was prohibited during the study. All patients received standard care with phosphate binders and calcitriol, or active vitamin D analogs. Etelcalcetide or placebo was administered IV after each hemodialysis session for 26 weeks. The primary endpoint was the proportion of patients receiving greater than 30% reduction from baseline in mean PTH during weeks 20 to 27. And secondary endpoints were the proportion of patients receiving achieved mean PTH of 300 pg/mL or lower.

One thousand twenty-three patients were randomized 1:1 to receive either placebo or etelcalcetide by an interactive voice and web-based response system. Patients had a mean age of 58 years, and 60% were men. The starting dose was 5 milligrams, and it could be increased by 2.5- or 5-mg increments at weeks 5, 9, 13, and 17, based on PTH and calcium results obtained during the prior week, to achieve predialysis PTH of 300 pg/mL or lower. Investigators were blinded to PTH and phosphate results.

Greater than 50% of etelcalcetide-treated patients achieved the greater than 30% reduction in serum-PTH in less than 6 weeks, compared to only 9% of placebo-treated patients. Reductions in PTH were rapid and sustained over 26 weeks in the etelcalcetide-treated patients.

And treatment with etelcalcetide decreased serum intact FGF23, and decreased bone-specific alkaline phosphatase and collagen type 1 cross-linked C-telopeptide. Most common adverse events were reductions in serum calcium, as well as nausea, vomiting, and diarrhea. Overall, 92% of the etelcalcetide-treated patients experienced adverse events, compared to 80% in the placebo group.

Etelcalcetide was more effective than placebo in lowering PTH concentrations in patients receiving dialysis who had secondary hyperparathyroidism; but future research is needed to assess the clinical outcomes, as well as the long-term efficacy and safety.

**Here are the main points of the study from my perspective:** This is a companion paper to another paper reported previously. Here, etelcalcetide is compared to placebo in hemodialysis patients. This allows one to isolate the biochemical effects of this drug in isolation. Etelcalcetide potently lowered PTH concentrations in hemodialysis patients. It also substantially lowered serum-calcium concentrations, leading to cointervention with more frequent use of calcium-based oral phosphate binders, activated vitamin D compounds, and higher dialysate calcium baths. Etelcalcetide also substantially lowered FGF23 concentrations, and although the number of events was low, there was a numerically higher rate of hospitalization for heart failure in the etelcalcetide-treated group.

**How do these results impact the current state of patient management?** Etelcalcetide is only the second calcimimetic to be brought to the market, and the first to provide an IV route of administration. The half-life is 48 to 72 hours, allowing for intermittent IV dosing after hemodialysis, which should improve compliance and provide more predictable biochemical response laboratories, facilitating better management of CKD-MBD.

**How do the results of this study impact the future state of patient management?** The study shows that etelcalcetide significantly lowers serum PTH concentrations and FGF23 concentrations. FGF23 has been associated with left ventricular hypertrophy and higher risk of heart failure. This study provides an opportunity to test etelcalcetide as a method to lower FGF23 in an effort to lower the risk of heart failure, in future studies.

With that stated, a number of questions remain unanswered. Hypocalcemia was more frequent in the etelcalcetide-treated group, even in the setting of a closely monitored clinical trial. Whether hypocalcemia is more frequent with etelcalcetide in routine clinical care remains unanswered, and clinicians should closely monitor calcium concentrations when this drug is initiated. While suppression of PTH, phosphate, and FGF23 are thought to be beneficial, the cointervention of higher calcium-based binder use, activated vitamin D use, and higher calcium dialysate baths, may have secondary adverse consequences. Future studies are needed to determine the net benefits or harms for CVD events and all-cause mortality associated with etelcalcetide use. Like in the companion study, etelcalcetide-treated patients had numerically higher numbers of hospitalizations for heart failure. And although the number of hospitalizations was small, close monitoring for fluid status and heart failure risk is required in future studies, as well as in clinical practice.



## Effect of Tenapanor on Serum Phosphate in Patients Receiving Hemodialysis

Block GA, et al



Biff Palmer, MD

Hello, this is Dr. Biff Palmer, professor of internal medicine at UT Southwestern Medical Center, Dallas, Texas. I am going to discuss the publication entitled, Effect of Tenapanor on Serum Phosphate in Patients Receiving Hemodialysis, by Geoffrey Block and colleagues.

This study report was published in the *Journal of the American Society of Nephrology*.

I selected this article to discuss because hyperphosphatemia is common among patients with chronic kidney disease stage 5B and is associated with morbidity and mortality. To address this problem, guidelines recommend lowering serum phosphate levels. Tenapanor is a minimally absorbed small-molecule inhibitor of the sodium-hydrogen exchanger isoform 3 that functions in the gut to reduce sodium and phosphate absorption. This trial assesses the effects of tenapanor on serum phosphate concentration in patients with hyperphosphatemia receiving hemodialysis. Results from the study show that tenapanor may reduce serum phosphate concentration effectively, while having no direct effect on the sodium-phosphate cotransporter type 2b (Npt2b). In addition, tenapanor may provide an option to improve adherence, addressing the reduction of pill burden more commonly associated with phosphate binders.

**So, let's discuss the methods.** This was a randomized, double-blind, placebo-controlled, fixed-dose, multicenter, international study involving adult patients with chronic kidney disease stage 5 and hyperphosphatemia, who are receiving hemodialysis. Eligible patients underwent a 1- to 3-week washout of phosphate binders, and then had to have a serum phosphate level of at least 6 mg/dL but not higher

than 10 mg/dL, and show an increase of at least 1.5 mg/dL from screening. Patients were then randomized to 1 of 6 tenapanor doses (3 or 30 mg once daily or 1, 3, 10, or 30 mg twice daily) or placebo for 4 weeks. Patients took 1 tablet in the morning and 1 in the evening, just before breakfast and dinner, respectively. Key exclusion criteria were inflammatory bowel disease, gastrointestinal bleeding or other GI disease, serum parathyroid hormone levels exceeding 1,200 pg/mL, severe metabolic acidosis defined by a bicarbonate concentration less than 18 mmol/L at the last visit before randomization, and clinical signs of hypovolemia at randomization. At the end of the treatment period, patients resumed their prestudy dose of phosphate binders and underwent a follow-up visit 1 to 2 weeks after the last dose of study drug.

**So, what were the key findings?** Well, 162 patients were randomized, of whom 115 received study treatment. Patients' age was 59.1 years, and 64% of the patients were men. Adherence to treatment, assessed by pill count, was generally high, ranging from 85% to 96%. Fifty-eight percent of patients experienced at least 1 adverse event during the study. The incidence of adverse events was similar to placebo at 42%, and tenapanor at 1 mg twice daily (43%), but was higher with other doses of tenapanor (57% to 76%). GI-related adverse events were the most common encountered during the study, reported by 23% to 76% of patients. Of these, diarrhea was the most common adverse event and was most frequent at the highest doses. Nine percent of patients had at least 1 serious adverse event, but none of these were considered treatment-related. The proportion of patients achieving a more stringent serum phosphate level, defined as less than 4.5 mg/dL in a posthoc analysis, was 5% to 23% with tenapanor. The proportion of patients who reached the predefined

serum phosphate goal—which was less than 5.5 mg/dL at the end of the treatment early-termination visit—was numerically higher with tenapanor (9% compared to 43%) than with placebo at 8%. Pharmacodynamic effects of tenapanor included serum phosphate lowering, increased stool frequency, and softening stool consistency, which in fact may be beneficial to a substantial proportion of the patients on dialysis. It will be important to investigate any potential drug-drug interactions with tenapanor in future studies.

**So, what are my thoughts about this study?** Well, this new drug does provide an interesting approach to limit phosphate absorption from the gut, but, indeed, as encountered in the study, diarrhea was problematic. Nevertheless, this could be used as an adjunct to existing therapy, particularly in those who might have some constipation. I don't think the study will change current patient management, but it does introduce a novel therapy to control the serum phosphorus. And it will be interesting to see what future studies show in this regard. Once again, it highlights the idea that we need more effective phosphate binders, and this is at least a study in that right direction.



## *New Conclusions Regarding Comparison of Sevelamer and Calcium-Based Phosphate Binders in Coronary-Artery Calcification for Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials*

Wang C, et al.



Biff Palmer, MD

Hello, this is Dr. Biff Palmer, professor of internal medicine at UT Southwestern Medical Center, Dallas, Texas. I'll be discussing the publication, *New Conclusions Regarding Comparison of Sevelamer and Calcium Based Phosphate Binders in Coronary-Artery Calcification for Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials*, by Wang and colleagues. This study report was published in *PLOS ONE*.

I selected this article to review because it discusses the results of a large meta-analysis of non-calcium phosphate binder sevelamer and its effects on cardiovascular calcification in patients with chronic kidney disease. Patients with chronic kidney disease undergoing dialysis often suffer from mineral metabolism, as well as cardiovascular disease, which is the most common cause of death in these patients. Traditionally, calcium-based agents were used as first-line therapy; however, they can result in hypercalcemia associated with cardiovascular mortality in end-stage renal disease. Sevelamer does not contain calcium, and is a non-calcium, non-magnesium, aluminum-free agent. This meta-analysis of published, randomized, clinical trials of sevelamer showed the impact on cardiovascular calcification, cardiovascular mortality, all-cause mortality, and hospitalization.

**Let's discuss the methods.** A systematic meta-analysis of 31 studies were identified from 1998 to 2013, of which 23 were randomized controlled trials with a total of 4,395 adult participants on dialysis with end-stage renal disease. The average age was 57.9 years. Forty-five percent of the patients in the studies had diabetes. The studies compared sevelamer with

calcium acetate, calcium carbonate, or both, to any calcium-based phosphate binder, and analyzed the effect on phosphate-binders on serum levels of phosphate or calcification of coronary arteries. The primary outcome was cardiovascular calcification, referring to coronary artery calcification scores and aortic calcification scores. The secondary outcomes were serum characteristics, hospitalization, cardiovascular mortality, and all-cause mortality.

**The key findings were as follows:** This was the largest systematic review of randomized controlled trials on dialysis patients to examine the effects of sevelamer compared with calcium-based phosphate binder therapy on kidney-related serum measurements, coronary artery calcifications, arterial calcification score, hospitalization, and other endpoints of clinical safety. In 18 studies, with 3,327 participants, reported serum levels of phosphate showed a significant decrease in serum levels of phosphate with calcium-based phosphate binders by 0.17 mg/dL. Calcium-based phosphate binders were shown to be better than sevelamer for the control of serum levels of phosphate. Compared with calcium-based phosphate binders, sevelamer therapy resulted in a smaller decrease in serum levels of phosphorus and a lower prevalence of hypercalcemia.

This meta-analysis showed a significant difference in coronary artery calcification scores and aortic calcification scores, and suggests sevelamer benefits dialysis patients in terms of these 2 parameters and hypercalcemia. Although sevelamer has less impact in controlling hyperphosphatemia, studies show its use can result in significant reduction in hospitalization. Routine use of sevelamer in dialysis patients is recommended in patients that already have control of

serum levels of phosphate, and if patients may suffer—or already are suffering—from hypercalcemia or cardiovascular disease.

**Here are my thoughts and analysis of this study.**

This meta-analysis is confirmatory of studies in the literature that calcium-based binders have a slight advantage in lowering the plasma phosphate levels as compared to sevelamer. Number 2, calcium-based binders are associated with a higher plasma calcium level, as compared to sevelamer. Calcium-based

binders provide a calcium load to the body that may play a role in increased cardiac calcification in coronary artery calcium scores. There is no obvious difference in mortality in this analysis; however, the sevelamer-treated patients had a trend toward decreased hospitalization and decreased length of hospital stay. I'm not sure that this study will impact practice, but it may confirm this tendency to avoid calcium overload in the management of our patients. The questions that remain are that we clearly need better phosphate binders.



## *The Phosphate Binder Ferric Citrate and Mineral Metabolism and Inflammatory Markers in Maintenance Dialysis Patients: Results from Prespecified Analyses of a Randomized Clinical Trial*

*Van Buren PN, et al.*



Biff Palmer, MD

Hello, this is Dr. Biff Palmer, professor of internal medicine at UT Southwestern Medical Center, Dallas, Texas. I'll be discussing the publication, *The Phosphate Binder Ferric Citrate and Mineral Metabolism and Inflammatory Markers in Maintenance Dialysis Patients: Results*

From *Prespecified Analysis of a Randomized Clinical Trial*, by Peter Van Buren, et al. This study was reported in the *American Journal of Kidney Diseases*.

I selected this article to discuss because it reviews ferric citrate as an option among phosphate binders. End-stage renal disease guidelines recommend phosphate binders to manage hyperphosphatemia. In addition to pill burden, there are undesired side effects of all phosphate binders. This study reviews the effects of ferric citrate, an iron-based compound that binds phosphorus in the intestine and lowers serum phosphorus levels. The study compared ferric citrate to active controls of sevelamer carbonate and/or calcium acetate. Results showed ferric citrate effectively controlled phosphorus levels, while increasing iron stores and reducing intravenous iron and erythropoietin-stimulating agent use, while at the same time maintaining hemoglobin levels compared to active control.

**Let's discuss the methods.** This was a phase 3, randomized, open-label, controlled study involving adult patients with end-stage renal disease with serum phosphate levels greater than 6 mg/dL, after phosphate binders were discontinued during a 2-week washout period. Subjects included those who received prescriptions of 3 to 18 pills per day of phosphate

binders. Serum ferritin levels were less than 1,000 ng/mL. Serum transferrin saturation was less than 50%, and the serum phosphorus levels ranged from 2.5 to 8.0 mg/dL. Patients were randomized in a 2:1 fashion to ferric citrate or active control which, again, was either sevelamer carbonate and/or calcium acetate, for a total of 52 weeks. Key exclusion criteria included parathyroidectomy within 6 months of screening, an absolute indication for oral iron or vitamin C, or prior intolerance to calcium acetate or sevelamer. The study involved 3 phases: (1) measuring serum calcium levels during the 52-week active-control period; (2) measuring the ferric citrate group and active control group following the washout period; and (3) comparing ferric citrate to active control with a subsequent 4-week placebo control period. Pill counts were conducted monthly to assess adherence.

**Let's discuss the key findings.** So again, this was a total of 441 patients. Two hundred ninety-two participants were randomly assigned to ferric citrate, and 149 to active control. Mean changes from baseline phosphorus levels decreased similarly in the ferric citrate and active control groups. And serum calcium levels increased similarly in the ferric citrate and active control groups. Parathyroid hormone levels decreased similarly in the ferric citrate and active control groups. Total and LDL cholesterol levels were lower in participants receiving sevelamer than in those receiving ferric citrate or calcium acetate. The ferric citrate group had less severe adverse events than the active control group (39% vs 49%, with a *p*-value of 0.05). And the number of deaths was similar in the ferric citrate and active control groups (4.5% in the ferric citrate and 5.4% in the active control group). Lastly, ferric citrate effectively decreased serum

phosphorus levels with similar effects on other markers of bone and mineral metabolism as active control in both hemodialysis and peritoneal dialysis patients.

**So, again, what do I think about this study?** First, there was no real difference in the 2 binder studies. The iron contained in ferric citrate did provide exogenous iron and has the potential to lessen the

requirement for erythropoietin. I'm not sure that this study will impact our current state of patient management, but nevertheless it does raise an interesting perspective with regard to the simultaneous binding of phosphorus in the administration of iron. Once again, it highlights the need for better and more effective phosphate binder therapy.



## *Use of Extended-Release Calcifediol to Treat Secondary Hyperparathyroidism in Stages 3 and 4 Chronic Kidney Disease*

*Sprague SM, et al.*



Biff Palmer, MD

Hello, this is Dr. Biff Palmer, professor of internal medicine at UT Southwestern Medical Center, Dallas, Texas. I'm going to discuss the publication entitled, Use of Extended-Release Calcifediol to Treat Secondary Hyperparathyroidism in Stages 3 and 4 Chronic Kidney

Disease, by Stuart Sprague and colleagues. This study report was published in the *American Journal of Nephrology*.

I selected this article to discuss the effects of extended-release calcifediol. Supplementation with ergocalciferol and cholecalciferol is recommended for secondary hyperparathyroidism. However, current guidelines do not provide guidance on how supplements should be best administered. A previous single-dose comparative clinical study showed extended-release calcifediol was more effective than immediate-release calcifediol in lowering elevated plasma intact parathyroid hormone values in chronic kidney disease patients with vitamin D insufficiency. This study extends those findings, demonstrating the safety and efficacy of 30 to 60 µg/day of extended-release calcifediol in the treatment of secondary hyperparathyroidism over a treatment period of up to 52 weeks, and simultaneously correcting the underlying vitamin D deficiency in adult patients with stage 3 or 4 chronic kidney disease.

**Before I analyze the study in more detail, I'd like to discuss or least highlight some of the comments from the lead author, Dr. Sprague.** When asked as to what the 3 most important highlights of the study were, he mentions the following: Extended-release calcifediol effectively and safely corrects vitamin D insufficiency and the associated elevations of plasma immunoreactive parathyroid hormone (iPTH) in

patients with stage 3 or 4 chronic kidney disease, providing an attractive alternative to nutritional vitamin D and vitamin D-receptor activators for treating secondary hyperparathyroidism. Number 2, the effectiveness of extended-release calcifediol in controlling hyperparathyroidism is directly related to the administration dose, the duration of treatment, the degree to which the serum 25-hydroxy vitamin D is raised above 30 ng/mL. He also notes that extended-release calcifediol has minimal impact on serum calcium, phosphorus, fibroblasts growth factor-23 (FGF23) levels, and on urine calcium, suggesting that it does not raise a patient's risk of extraskeletal calcification.

Then I asked, "What impact do you think this study will have on the management of patients with chronic kidney disease-MBD?" (The present treatment paradigm for patients with CKD stage 3 and 4 has been to use nutritional vitamin D—that is cholecalciferol and ergocalciferol—and then, if hyperparathyroidism persists, one would add an activated vitamin D, like calcitriol or an analog.) He comments that this regimen has not been demonstrated to be effective without increasing the risk of hypercalcemia and/or hyperphosphatemia, as well as increasing FGF23 levels. In fact, the proposed, revised KDIGO guidelines for CKD-MBD comment on the ineffectiveness of nutritional vitamin D, and recommend against the routine use of calcitriol or one of its analogs. Thus, as he mentions, these suggest that extended-release calcifediol could become an effective therapy to treat and prevent vitamin-D deficiency and hyperparathyroidism in our predialysis patients.

**So, let me go ahead and discuss the methods, in more detail, of this study.** The study involved 2 identical multicenter, randomized, double-blind, placebo-controlled, trials across 89 US sites, involving

adult patients with either stage 3 or 4 chronic kidney disease, secondary hyperparathyroidism, and vitamin D deficiency. Eligible patients were randomized in a 2:1 fashion to receive oral extended-release calcifediol at 30 or 60 µg, or a placebo, once daily, at bedtime, for a 26-week period. Two hundred ninety-eight or 69% of eligible patients were then entered into a subsequent open-label extension study wherein extended-release calcifediol was administered without interruption for another 26 weeks. Plasma immunoreactive parathyroid hormone and serum calcium, phosphorus, and total 25-hydroxy vitamin D were measured every 2 to 4 weeks in studies A and B and in the subsequent extension. The primary efficacy endpoint in all 3 studies was the number of patients in the intent-to-treat population that attained a mean decrease of greater than 30% in plasma immunoreactive parathyroid hormone from pretreatment baseline in the efficacy assessment period.

**So, what were the key findings in this study?** Well, 429 patients were randomized; 213 subjects were randomized in study A; 72 received placebo; 141 received the extended-release calcifediol. And then 216 patients were randomized in study B; 72 of whom received placebo; 144 received the study drug. Three hundred fifty-four subjects, or 83%, completed both studies A or B. The mean age of the patients was 66 years. About 50% were male.

No significant differences were detected among the 2 treatment groups for both the individual studies A and B and for the pooled data. At baseline, the mean estimated GFR was 31 ml/min. Mean plasma immunoreactive PTH was 130 pg/mL for subjects with stage 3 disease and 166 pg/mL for subjects with stage 4 disease. Mean serum calcium was 9.2 mg/dL. Mean serum phosphorus was 3.7 mg/dL. And the mean serum total 25-hydroxy vitamin D was 20. Mean serum total 25-hydroxy vitamin D increased

gradually and compared with the extended-release calcifediol treatment in both studies, but unchanged with placebo treatment. Levels remained stable throughout the 52-week period.

The most common adverse events were urinary tract infection, diarrhea, and hypertension. Adverse events observed more frequently in the extended-release calcifediol subjects vs placebo subjects were anemia, nasopharyngitis, increased blood creatinine, and dyspnea. The extended-release calcifediol increased serum total 25 hydroxy vitamin D at a slower rate than the immediate-release formulations, and normalized serum total 25-hydroxy vitamin D concentration to a value greater than 30 in greater than 95% of per-protocol subjects, while reducing plasma-intact parathyroid hormone values by at least 10% in 72% of the subjects. The extended-release calcifediol may provide a more reliable and standardized approach to vitamin D repletion than any commonly used regimen of nutritional vitamin D.

**So, what are my thoughts of this study?** Clearly, nutritional vitamin D, as we use it today, poorly restores levels of 25-hydroxy vitamin D. Calcifediol is a prohormone of the active form of vitamin D<sub>3</sub>, and the extended-release form of this compound seems to be more effective at lowering parathyroid hormone and restoring 25-hydroxy vitamin D levels than what we utilize today. It is quite likely that this type of a compound may begin to be utilized more commonly in our stage 3 and 4 chronic kidney disease patients, but is unlikely to be effective in our chronic kidney disease stage 5 [patients] and is not indicated for use in that population.

Does controlling parathyroid hormone level at CKD stage 3 and 4 lead to outcome benefits? This is a question that is currently not known but would be worth examining now that this type of an agent is available for clinical use.



## Summary

Palmer B.



Biff Palmer, MD

Now that you have participated in this program, let us summarize some main points and key findings from this activity, highlighting the potential impact on the management of patients with CKD-MBD in your practice.

As stated earlier, kidney disease is pandemic, associated with high mortality rates. Because of the severe consequences associated with chronic kidney disease-mineral and bone disorder, it is imperative clinicians are able to classify CKD-MBD. The high number of CKD patients also poses a challenge for nephrologists and primary care physicians, especially when managing the combination of secondary hyperparathyroidism and mineral bone disease.

Clinicians need an improved understanding of the mechanisms underlying CDK-MDB to identify the disease and make informed treatment decisions. Health care providers should be aware that management of these patients should include treatment with a combination of dietary phosphorus restriction, phosphate binders, vitamin D analogs, and calcimimetics. From our review of large meta-analysis of calcium-based binders and a non-calcium phosphate binder, we learn the impact of these agents on cardiovascular calcification in patients with chronic kidney disease. Also, studies show that as a phosphate binder, ferric citrate effectively decreased serum phosphorus levels and provides exogenous iron,

which may lessen the requirement for erythropoietin therapy. In addition, a study assessing the effects of tenapanor on serum phosphate concentration in patients with hyperphosphatemia receiving hemodialysis, showed it may provide an option to improve adherence, addressing the reduction of pill burden associated with phosphate binders.

In the recent clinical trial by Sprague and colleagues, the study showed that extended-release calcifediol effectively and safely corrects vitamin D insufficiency in patients with stage 3 or 4 chronic kidney disease, providing an attractive alternative to nutritional vitamin D and vitamin D-receptor activators for treating secondary hyperparathyroidism.

Clinical practice gaps also exist with use of the current KDOQI and KDIGO global guidelines and local clinical practices in CKD-MBD. This may result because implementation on local levels is not always applicable due to medical care and social factors. Furthermore, global CKD-MBD practice guidelines suggest different target levels for serum phosphorus. An attempt to address this important gap will be addressed through updates to the 2009 KDIGO guidelines, which are currently in press. These updates aim to align recent studies with more current standard of care in clinical practice. Once available, we plan to share an executive summary of the guideline update results. A link to this review will be posted, once available.



## 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update

**Newly Added**

Ix J.



Joachim H. Ix, MD

Hello. This is Dr. Joachim Ix, professor and chief of the Division of Nephrology and Hypertension at UC San Diego. I'll be discussing the salient changes to the new CKD-MBD KDIGO guidelines from 2017. These guidelines are available as a resource and a reference tool, and my goal

here is to provide a selection of the most relevant recommended changes to clinical practice.

The 2017 guidelines provide a comprehensive review of research findings since the prior CKD-MBD guidelines in 2009, and how this new literature might influence evidence-based clinical practice. While the new guidelines are too extensive to be fully reviewed here, my goal is to highlight some key aspects of the 2017 CKD-MBD guideline updates, with an emphasis on the rationale for changes made to the original guidelines.

I would also like to bring your attention to a relevant summary article from the working group chairs of the updated guidelines, which provides key points for practice application. This publication, entitled Executive Summary of the 2017 KDIGO Chronic Kidney Disease Mineral and Bone Disorder Guideline Update: What's Changed and Why it Matters, was authored by Dr. Markus Ketteler and his colleagues and was published in July 2017 in *Kidney International*. We have also included a link to this summary article for your access, so please see the downloads associated with this program.

Before beginning my analysis, let's hear about some of the highlights from the working group co-chairs from their perspective. We asked, "What are the 3 most important highlights or findings of the updated guidelines?"

### Dr. Ketteler responded with the following:

"From my point of view, one paradigm shift is the perception that bone mineral density measurements by DEXA is a valuable diagnostic tool in the assessment of fracture risk in all stages of CKD. Nephrologists still need to be aware that such BMD measurements do not identify the type of renal osteodystrophy, and that a low BMD does not necessarily indicate the presence of classic osteoporosis, but results may, indeed, be a help to guide treatment decisions.

A second major point is the growing concern about inappropriate calcium loads in all stages of CKD. Especially in CKD patients not on dialysis, excess exposure to calcium may be harmful. In dialysis patients, it may be more appropriate to tolerate mild and asymptomatic hypocalcemia than with supplementing large amounts of calcium in order to reach normal serum calcium levels when calcimimetic therapy is administered. As a consequence, this limits the use of calcium-based phosphate binders in CKD in a more general way than previously.

Third, the recommendation to avoid routine use of active vitamin D compounds in CKD patients not on dialysis, challenges past concepts. Nevertheless, a moderately elevated PTH may be an adequate compensatory mechanism to counteract phosphate overload and to overcome PTH resistance of the bone in a stage-dependent fashion, while the side effects of drug-induced hypercalcemia may carry patient-related risks. However, autonomous hyperparathyroidism may still be prevented in this group of patients, so progressive rises in PTH levels, especially in the presence of hypocalcemia, will still need to be treated with calcitriol or its analogs."

**We then asked, "What impact do you think these updates will have on the management of patients with CKD mineral bone disorders?"**

Dr. Ketteler responded, "A more frequent use of bone mineral density measurements may provide improved guidance to therapies aimed at bone health in CKD patients. Longitudinal results may allow estimates of therapeutic effectiveness of all available medications, including calcimimetics and active vitamin D analogs, but also in appropriate exceptions at antiresorptive or bone anabolic substances.

The more restriction of calcium exposure may hopefully lead to a more sustained protection from extrasosseous calcification and thus to less cardiovascular complications. The same may be true for a more restricted use of activated vitamin D analogs in earlier stages of CKD. Here, it may be worthwhile to ascertain a solid basal vitamin D status based on a 25-hydroxy vitamin D (25-OH-D) level in order to limit progression of hyperparathyroidism, although the evidence level on this issue still needs to be improved."

**Let's take a look at some of the key guideline changes that clinicians providing best clinical practice should be aware of.**

The first is guideline number **3.2.1**. One major change to the guidelines now suggests that **bone mineral density measurements** may have clinical utility in patients across the spectrum of CKD. Previously, the 2009 guidelines recommended *against* bone mineral density testing in patients with CKD. At that time, there were no data demonstrating that bone mineral density measurement predicted fracture risk in CKD patients, and it did not identify the underlying cause of bone disease. The new guidelines, however, highlight a number of studies published since 2009 that consistently demonstrate that low bone mineral density does indeed predict fracture risk across the spectrum of CKD, including dialysis patients. While it remains true that bone mineral density cannot distinguish between low-turnover or high-turnover bone disease, bone mineral density measurement is now recommended if it might alter diagnostic or therapeutic approaches. For example, a low bone mineral density might lead to a bone biopsy, which

could alter the therapeutic approach. Or, if a patient with an EGFR greater than 30 milliliters per minute per 1.73 meters body surface area, a low bone mineral density may lead to a decision to use bisphosphonates or other therapies.

A second guideline is number **4.1.2**, which relates to the **management of phosphate levels** in CKD patients. Previously, the 2009 guidelines recommended maintaining phosphate levels within the normal range in patients with CKD stage 3-5, and specifically recommended use of intestinal phosphate binders. The implicit assumption was that patients with normal phosphate levels might still benefit from lowering phosphate absorption in an effort to prevent future worsening of the CKD-MBD complex. The revised guidelines recommend targeting normal phosphate levels among patients with hyperphosphatemia. This is in recognition by KDIGO that there is currently an insufficient evidence base to recommend treating patients with normal phosphate levels. Second, the revised guidelines suggest using phosphate-lowering therapy rather than phosphate binding agents. This is because several well-conducted clinical trials have shown only modest reductions in serum phosphate levels with binders and, simultaneously, some evidence of harm. These agents have been linked with worsening of vascular calcium deposition and can cause nausea and other GI symptoms. While still potentially useful, the new terminology of phosphate-lowering treatments encompasses possible other approaches including binders, dietary therapy, and dialysis, that may be more effective, moving the primary focus away from binders alone.

A third guideline is number **4.1.6, restricting calcium exposure** across patients with CKD. While calcium-based intestinal phosphate binders have consistently been associated with worsening vascular calcification deposition in dialysis patients, a number of studies conducted on patients with CKD stages 3-5, that have been published since the 2009 guidelines, now show that calcium-based binders may also worsen calcification in earlier stages of CKD. These guidelines highlight that excess exposure to calcium through diet, medications, or dialysis, may be harmful across all GFR categories of CKD.

Finally, guideline 4.2.2. This guideline recommends that **calcitriol and vitamin D** should not be routinely used in CKD patients. While these drugs are commonly used in CKD stages 3-5 to suppress PTH, the guidelines recognize that the target PTH levels in this stage of CKD are unknown. Moreover, recent clinical trials have shown that active vitamin D analogs did not significantly prevent progression of left ventricular mass, and yet increased the risk of hypercalcemia and other adverse events. Balancing these new insights, the revised guidelines suggest that the use of calcitriol or vitamin D analogs should be reserved for patients with severe or progressive secondary hyperparathyroidism. When initiated, calcitriol or vitamin D analogs should be started at low doses, and titrated based on the PTH response, with the goal of avoiding hypercalcemia.

**I'd like to provide my thoughts and analysis of this important document. The main points of the study from my perspective are as follows.**

Firstly, perhaps the most dramatic shift in practice guidelines is the recommendation to avoid routine use of calcitriol and activated vitamin D analogs in CKD patients. The guidelines highlight the risk of hypercalcemia and the uncertainty of PTH targets. While this seems like a very rational approach in the absence of data, it highlights the need for additional research to define appropriate targets for PTH at different severities of CKDs. Such studies may require bone biopsies and uniformity in regards to PTH assays. It's important for the clinician to

recognize that severe secondary hyperparathyroidism and progressive increases in PTH remain an indication for using vitamin D within the new guidelines.

Second, use of bone marrow density measurements is also an important clinical change recommendation in these new guidelines. Since 2009 there have been a number of studies suggesting that bisphosphonates are useful for fracture prevention and appear to be safe in patients with an EGFR greater than 30. New therapies, such as RANK ligand inhibitors and IV PTH administration are additional new drugs in the armamentarium to address bone disease in select patients. For patients at high risk of fracture, or with low bone mineral density, the recommendation may stimulate use of these medications in individual patients, or referral for bone biopsy, to determine the underlying cause of bone disease to guide further treatment.

Lastly, the subtle changes in wording in the revised guidelines around phosphate management are also quite important. These changes reflect an acknowledgment by the KDIGO panel on potential adverse effects of binders, including worsening of vascular calcification, and a greater focus on other therapies, such as diet and dialysis. In the future, additional research is required to identify therapies that can more potently—but also more safely—lower phosphate levels in CKD patients.

With this, again, my name is Joachim Ix, and I want to thank you so much for participating. Please join us online for the linked articles discussed. Thank you.

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and obtain your CE/CME credit online.  
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