Chronic Kidney Disease- Mineral Bone Disease KDIGO 2017, CKD-MBD.

Ioannis Griveas, MD, PhD



Liver and Kidney Functions Are Essential for Vitamin D Precursor Activation to Calcitriol

Vitamin D₃ Cholecalciferol 25-Hydroxyvitamin D 25(OH)D (Calcidiol) 1,25-Dihydroxyvitamin D₃

1,25 (OH)₂D₃, Calcitriol (Active Vitamin D)

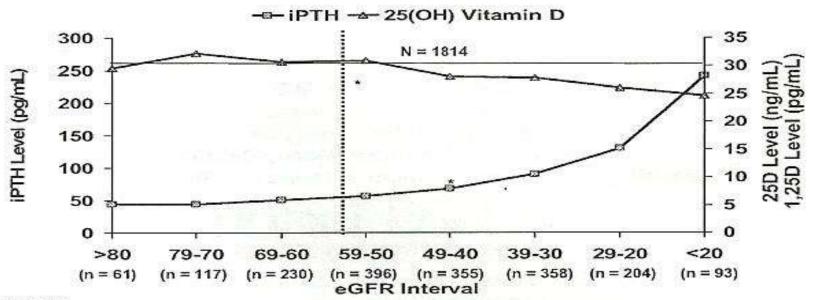
 $25(OH)D_{(2+3)} < 30 \text{ ng/ml is insufficient}$

< 15 ng/ml is deficient

< 5 ng/ml is severely deficient

Brown et al. Am J Physiol. 1999;277:F157-F175.

Mean Values of iPTH, 1,25(OH)₂D₃, and 25(OH)₂D₃ by eGFR



*P<0.001.

Bakris et al. Poster presented at: American Society of Nephrology Renal Week 2005; November 8-13, 2005; Philadelphia, PA. Abstract F-PO732.



2009 KDIGO

Controversies Conference 2013 "CKD-MBD: Back to the Future

2017 update

- Work Group acknowledged the lack of high-quality evidence on which to base recommendations.
- Multíple randomízed controlled trials (RCTs) and prospective cohort studies.
- *KDIGO recognizes the need to reexamine the currency of its guidelines.

A total of

12 recommendations were identified for revision.

2017 updates followed a rigorous process of evidence review and appraisal, based on systematic reviews of results from clinical trials.

GRADE

Where appropriate, the Work Group issued "not graded" recommendations, based on general advice, that were not part of a systematic evidence review.

KDIGO 2017 GUIDELINE UPDATE CONTRIBUTORS

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Table 4 GRADE system for grading quality of evidence for an outcome

| Step 1: starting grade for quality of evidence based on study design | Step 2: reduce grade | Step 3: raise grade | Final grade for quality of evidence for an outcome ^a |
|--|---|--|--|
| High for randomized controlled trials | Study quality 1 level if serious limitations | Strength of association +1 level is strong, ^b no plausible | High |
| Moderate for quasi-randomized trial | -2 levels in very serious limitations | confounders, consistent and direct evidence | Moderate |
| Low for observational study | Consistency 1 level if important inconsistency | +2 levels if very strong, ^c no major threats to validity and direct evidence | Low |
| Very low for any other evidence | | | Very low |
| 5 (6 th 5 1 2 5 th 6 th 1 | Directness | Other | |
| | -1 level if some uncertainty | +1 level if evidence of a dose-response | |
| | 2 levels if major uncertainty | gradient | |
| | | +1 level if all residual confounders would | |
| | Other | have reduced the observed effect | |
| | -1 level if sparse or imprecise data | | |
| | 1 level if high probability of reporting bias | | |

GRADE, grading of recommendations assessment, development, and evaluation; RR, relative risk.

Modified with permission from Uhlig K, Macleod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;70:2058–2065.⁷¹



KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)



Author 1 | 1000 1 | 1011 201

[&]quot;The highest possible grade is "high" and the lowest possible grade is "very low."

 $^{^{}b}$ Strong evidence of association is defined as *significant RR of > 2 (< 0.5)* based on consistent evidence from two or more observational studies, with no plausible confounders.

Very strong evidence of association is defined as "significant RR of > 5 (< 0.2)" based on direct evidence with no major threats to validity.

Table 1 Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

3.2.1. In patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (2B).

3.2.2. In patients with CKD G3a–G5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B). Multiple new prospective studies have documented that lower DXA BMD predicts incident fractures in patients with CKD G3a–G5D. The order of these first 2 recommendations was changed because a DXA BMD result might impact the decision to perform a bone biopsy.

3.2.2. In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (Not Graded). 3.2.1. In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (Not Graded). The primary motivation for this revision was the growing experience with osteoporosis medications in patients with CKD, low BMD, and a high risk of fracture. The inability to perform a bone biopsy may not justify withholding antiresorptive therapy from patients at high risk of fracture.

in case of fracture

| | | (| | | | | | | | |
|-----------------------------------|----------|----------------------|---------|-------------|-------------------------|-------|--------|----------------------|-----------------|----------|
| | Fract | ture Gro | up | Non-Fr | acture Gr | oup | | Mean Difference | Mean Difference | e |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% | CI |
| 1.2.1 Dialysis Patient | S | | | | | | | | | |
| Ambrus 2011 | 0.66 | 0.18 | 21 | 0.72 | 0.14 | 109 | 7.0% | -0.06 [-0.14, 0.02] | | |
| Cejka 2011 | 0.573 | 0.048 | 24 | 0.6764 | 0.037 | 50 | 28.3% | -0.10 [-0.13, -0.08] | - | |
| Fontaine 1999 | 0.62 | 0.13 | 11 | 0.73 | 0.12 | 77 | 7.0% | -0.11 [-0.19, -0.03] | - | |
| limori 2012 | 0.567 | 0.133 | 46 | 0.636 | 0.141 | 416 | 17.9% | -0.07 [-0.11, -0.03] | | |
| Jamal 2002 | 1.3 | 0.23 | 54 | 1.3 | 0.25 | 50 | 5.7% | 0.00 [-0.09, 0.09] | - | _ |
| Jamal 2006 | 0.76 | 0.17 | 27 | 0.79 | 0.14 | 25 | 6.6% | -0.03 [-0.11, 0.05] | | |
| Urena 2003 | 0 | 0 | 21 | 0 | 0 | 49 | | Not estimable | _ | |
| Subtotal (95% CI) | | | 204 | | | 776 | 72.5% | -0.07 [-0.11, -0.04] | • | |
| Heterogeneity: Tau ² = | | | | (P = 0.12) | $(2); ^2 = 439$ | 6 | | | | |
| Test for overall effect: | Z = 4.81 | (P < 0.0) | 0001) | | | | | | | |
| 1.2.2 Non-dialysis pa | tients | | | | | | | | | |
| Nickolas 2010 | 0.621 | 0.0718 | 23 | 0.747 | 0.134 | 59 | 16.0% | -0.13 [-0.17, -0.08] | - | |
| Nickolas 2011 | 0.677 | 0.127 | 32 | 0.755 | 0.154 | 59 | 11.4% | -0.08 [-0.14, -0.02] | | |
| Subtotal (95% CI) | | | 55 | | | 118 | 27.5% | -0.11 [-0.15, -0.06] | - | |
| Heterogeneity: Tau ² = | | | | (P = 0.21) |); I ^z = 389 | 6 | | | | |
| Test for overall effect: | Z = 4.47 | (P < 0.0 | 0001) | | | | | | | |
| Total (95% CI) | | | 259 | | | 894 | 100. | [-0.11, -0.06] | • | |
| Heterogeneity: Tau² = | 0.00; Ch | ni² = 11.3 | 3, df= | 7 (P = 0.1) | 2); $I^2 = 38$ | 3% | | | -0.2 -0.1 0 | 0.1 0.2 |
| Test for overall effect: | | | | | | | | | | |
| Test for subgroup diff | erences: | Chi ² = 1 | .21, df | = 1 (P = 0) | 1.27), $I^2 = 1$ | 17.5% | | BMD | ow | BMD high |

in case of fracture

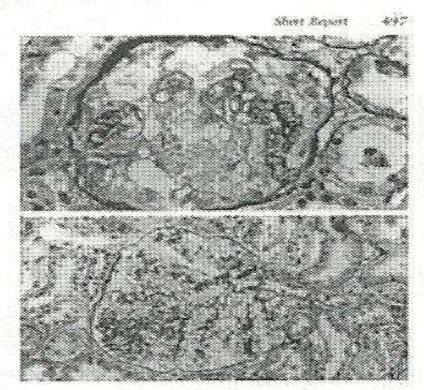
Reduced Bone Density in CKD Stages 2-4

| Вог | ne Mineral Density Mea | surements by | DEXA |
|-------|------------------------------|------------------|------------------|
| Group | Mean GFR (mL/min/1.73 m²) | Spine (g/cm²) | Femur (g/cm²) |
| 1 | 83 | 1.00 | 0.80 |
| 2 | 58 | 1.00 | 0.74* |
| 3 | 39 | 0.98 | 0.72* |
| 4 | 16 | 0.93* | 0.68* |

Bone Mass Falls as CKD progresses

Rix et al. Kidney Int. 1999;56:1084-1093.

Segmental Sclerosis After Pamidronate



Desikan et al. British Journal of Haematology, 2002, 119, 496–499

Fig. 1. Front being received. (Sect. 2017)
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Pamidronate Associated Nephrotic Syndrome with Segmental Glomerulosclerosis

- Five patients with Multiple Myeloma
- Prescribed pamidronate to delay osteolytic lesions
- Each received greater than the recommended monthly dose (>90 mg/monthly) (either 180 mg/month or 90 mg/2 weeks)
- All exhibited nephrotic proteinuria (range 3–24 g/day).
- Dose reduction or discontinuation
 - Resolution in NS in 3
 - Reduction in proteinuria to 4 g/day from a peak of 24 g/day in one patient
 - One required haemodialysis
- One patient continued to have elevated creatinine
- Renal biopsies obtained in two patients revealed focal segmental glomerulosclerosis

Podocyte Injury May Mediate Pamidronate Nephrotoxicity

- Nitrogen-containing bisphosphonates (pamidronate, ibandronate, zoledronate) differ in the mode of action and toxicities from earlier bisphosphonates, as they cause apoptosis of osteoclasts (van Beek et al, 1999; Bergstrom et al, 2000; Coxon et al, 2000).
- This same process may be responsible for the podocyte abnormalities observed in pamidronate nephrotoxicity (Markowitz et al, 2001).
- The dose effect is critical; increased pamidronate dose has been associated with non-linear excretion, increased accumulation in kidneys and proximal tubular damage in animal models (Cal & Daley-Yates, 1999).

Report of Increased Incidence of Renal Failure Following Zoledronic Acid

Renal Failure with the Use of Zoledronic Acid

To the corrost Zeledronic acid (Correct, Novartis Pharmsocutionis) is a potent bisphosphosate dast infelicits basic rescaption. In trials of treatment for bous metastases, the 15 percent of the patients who reschool 4 mg of coledranic acid over a 15-minute period last result describention, defined by circuitons in the serum constraints level. ** With marketed use of the drug, renal deterioration progressing to renal fathers and dishais has been reported. Airborigh the coases of small deterioration are multifactorial, acute tubular necrosis has been described as a potential mechanism associated with caledronic acid.*

We identified 72 cases in the Feed and Drug Administration (FDA) Adverse Event Reporting System from August SRN to March 2016 in which physicians expected renal fullure associated with soledronic acid (Table 1). Our case series combited of a heterogeneous group of putients, including 42 patients with maintiple myeloma, 22 with solid tumors, 2 with benign conditions, and 6 with unbrown diagnoses. The demographic characteristics and outcomes were similar for patients with and these without multiple myeloms. Treatment details, including by deation states, were not uniform.

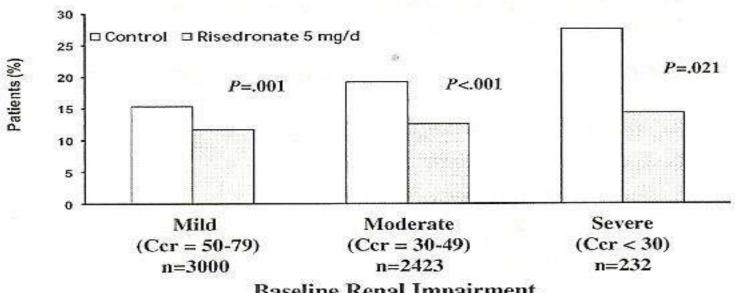
"Because of the serious nature of these events, health care professionals should monitor renal function before each dose of zoledronic acid is administered, provide adequate hydration, and discontinue treatment if renal function deteriorates."

et al. NEJM, 349: 1677, 2003

Summary of Bisophosphonates

- Bisphosphonates appear to cause renal injury, including
 - Nephrotic Syndrome with Focal Segmental Glomerulosclerosis
 - Acute Tubular Necrosis
- The risks appear to be higher with nitrogen containing bisphosphonates (ibandronate, pamidronate, zoledronate)
- The risks appear related to the individual and cumulative dose exposure
- The renal injury usually resolves upon drug cessation

Vertebral Fracture Risk Reduction With Risedronate



Baseline Renal Impairment

n=Patients with evaluable paired spinal radiographs.

Miller et al., J Bone Miner Res 2005;20:2105-2115

Bone Disease in CKD Stage 3 and 4 Bisphosphonates

- Contraindicated when GFR < ~30 ml/min
- May be efficacious in CKD Stage 3/4 patients but long term risks are unclear
- These drugs treat osteoporosis (adynamic low bone turnover)
- These drugs further reduce bone resorption
- May further reduce the calcium and phosphorus buffering capacity of bone in CKD patients

Table 1 Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

4.1.1. In patients with CKD G3a-G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (*Not Graded*).

4.1.2. In patients with CKD G3a-G5D, we suggest lowering elevated phosphate levels toward the normal range (2C). 4.1.1. In patients with CKD G3a–G5, we suggest maintaining serum phosphate in the normal range (2C). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.

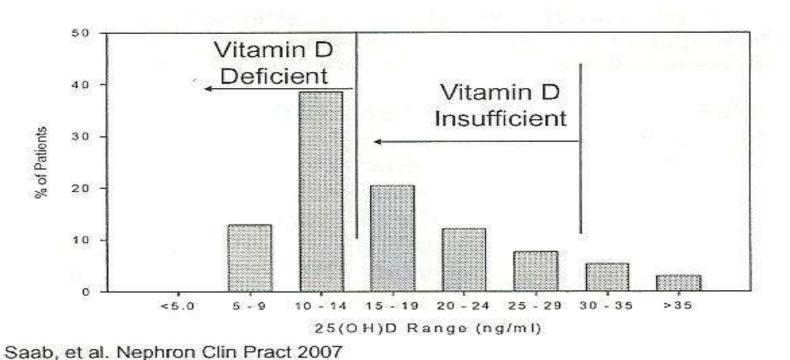
There is an absence of data supporting that efforts to maintain phosphate in the normal range are of benefit to CKD G3a–G4 patients, including some safety concerns. Treatment should be aimed at overt hyperphosphatemia.

Vitamin D in CKD: Stages 3 and 4

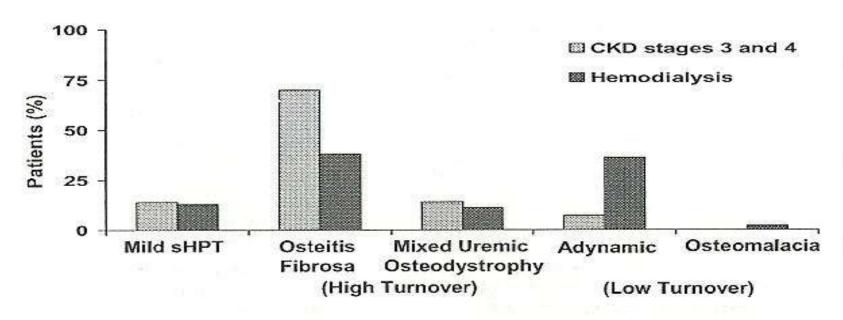
- Measure serum 25-hydroxyvitamin D in patients with ↑ PTH
 PTH target Stage 3 CKD 35 to 70 pg/ml
 Stage 4 CKD 70 to 110 pg/ml
- If 25(OH)D is normal, repeat annually

| Level | | Treatment with Vitamin D ₂ (Ergocalciferol 50,000 IU) |
|-------------|----------------------|---|
| <5 ng/mL | Severe Deficiency | 50,000 IU/wk x 12, then q mo x 6 |
| 5-15 ng/mL | Deficiency | 50,000 IU/wk x 4, then q mo x 6 |
| 16-30 ng/mL | Insufficiency | 50,000 IU/mo x 6 |

Vitamin D Levels are Low in Most Dialysis Patients Distribution of Baseline 25(OH)D Levels n = 132

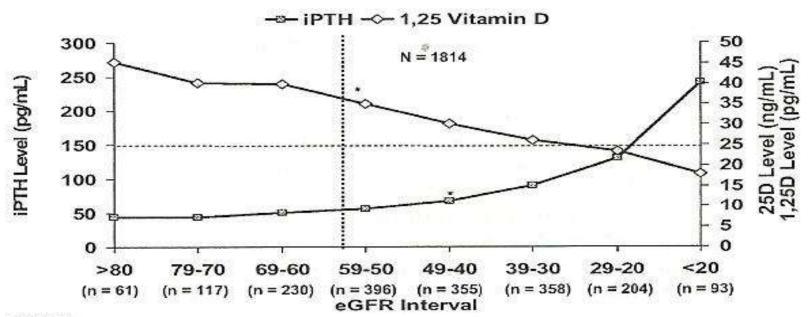


Evidence of High-Turnover Metabolic Bone Disease in CKD



Coen et al. Nephron. 2002;91:103-111. (N = 117); Hamdy et al. BMJ. 1995;310:358-363; Ho et al. Semin Nephrol. 2002;22:488-493. (N = 27); Wang et al. Am J Kidney Dis. 1995;26:836-844. (N = 175).

Mean Values of iPTH, 1,25(OH)₂D₃, and 25(OH)₂D₃ by eGFR



*P<0.001.

Bakris et al. Poster presented at: American Society of Nephrology Renal Week 2005; November 8-13, 2005; Philadelphia, PA. Abstract F-PO732.

Assessment. The previous Recommendation 4.1.1 from the 2009 KDIGO CKD-MBD Guideline¹ provided guidance regarding treatment based on serum phosphate levels in different glomerular filtration rate (GFR) categories of CKD.



2009

The Work Group considered it reasonable to take the context of therapeutic interventions into account when assessing values of phosphate, calcium, and PTH. Further, it is

2017

biochemical parameters. Based on these assumptions, the Work Group also decided to split the previous 2009 Recommendation 4.1.1 into 2 new Recommendations: 4.1.1 (diagnostic recommendation based on accumulated observational evidence) and 4.1.2 (therapeutic recommendation based mostly on RCTs).

PTH Target and Goals of Therapy

- The real goal of treating SHPT is to maintain relatively normal bone turnover
- Low bone turnover is associated with the greatest risk of hypercalcemia, vascular calcification, and death
- The target PTH range is a general area where many patients have relatively normal bone turnover
 - Individuals may be above or below target and have normal bone turnover
 - Individuals may be below, within, or even above target and have LOW bone turnover
- Other indicators of high bone turnover are high alkaline phosphatase and high bone-specific alkaline phosphatase
- It is generally considered better to have somewhat high bone turnover than low bone turnover

Bone Disease in CKD

- Osteitis Fibrosa
 - PTH mediated high bone turnover
 - TREAT by suppressing PTH
- Adynamic Bone
 - Low bone turnover
 - Pathologically the same as osteoporosis
 - Usually due to low PTH
 - TREAT by:
 - avoid Calcium binders
 - Avoid Active Vitamin D and calcimimetics
 - Use low Calcium bath
- Osteomalacia
 - Low bone turnover with large amounts of unmineralized osteoid
 - Usually due to Vitamin D deficiency
 - In past seen commonly due to Aluminum
 - Suspect in dialysis patients with low bone mass and frequent fractures
 - TREAT with Ergocalciferol or Cholecalciferol with or without Active Vitamin D

Bone Disease in CKD

Osteomalacia

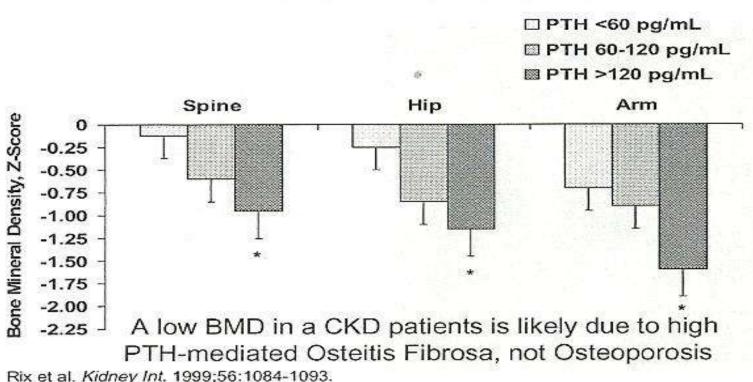
- Low bone turnover with large amounts of unmineralized osteoid
- Usually due to Vitamin D deficiency
- In past seen commonly due to Aluminum
- Suspect in dialysis patients with low bone mass and frequent fractures
- TREAT with Ergocalciferol or Cholecalciferol with or without Active Vitamin D

Indications for Bone Biopsy in CKD and other Tests

- BONE BIOPSY INDICATIONS
- Fractures with minimal or no trauma
- iPTH 100 to 500 pg/ml and <u>unexplained</u> hypercalcemia, severe bone pain or increased bone alkaline phosphatase
- Suspected aluminum bone disease based on symptoms or aluminum exposure
- Bone Mineral Density (DEXA) should be measured in pts.
 with fractures or risk factors for osteoporosis
- Bone Radiographs are not routinely indicated, but can demonstrate vascular calcification or β2-microglobulin amyloidosis

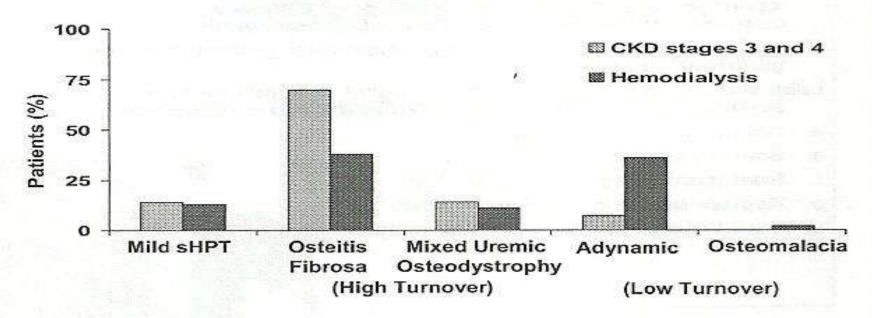
NKF K/DOQI Bone Guidelines 2003

Relationship of PTH to Bone Loss in CKD Stages 2-4



Rix et al. Kidney Int. 1999;56:1084-1093.

Evidence of High-Turnover Metabolic Bone Disease in CKD



Coen et al. Nephron. 2002;91:103-111. (N = 117); Hamdy et al. BMJ. 1995;310:358-363; Ho et al. Semin Nephrol. 2002;22:488-493. (N = 27); Wang et al. Am J Kidney Dis. 1995;26:836-844. (N = 175).

| Table 1 Comparison of the 2013 | and 2009 KDIGO CKD-MBD | Guideline recommendations |
|----------------------------------|------------------------|---------------------------|
|----------------------------------|------------------------|---------------------------|

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

4.1.2. In patients with CKD G3a-G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

4.1.1. In patients with CKD G3a–G5, we suggest maintaining serum phosphate in the normal range (2C). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).

There is an absence of data supporting that efforts to maintain phosphate in the normal range are of benefit to CKD G3a-G4 patients, including some safety concerns. Treatment should be aimed at overt hyperphosphatemia.

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations¹

Brief rationale for updating

4.1.5. In patients with CKD G3a–G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (Not Graded).

4.1.6. In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders (2B).

In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (*Not Graded*).

- 4.1.4. In patients with CKD G3a–G5 (2D) and G5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side effect profile (Not Graded).
- 4.1.5. In patients with CKD G3a-G5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).

In patients with CKD G3a–G5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C). Emphasizes the perception that early "preventive" phosphate-lowering treatment is currently not supported by data (see Recommendation 4.1.2). The broader term "phosphate-lowering" treatment is used instead of phosphate-binding agents since all possible approaches (i.e., binders, diet, dialysis) can be effective.

New evidence from 3 RCTs supports a more general recommendation to restrict calciumbased phosphate binders in hyperphosphatemic patients across all severities of CKD.

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

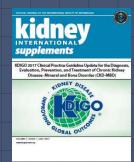
2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations¹

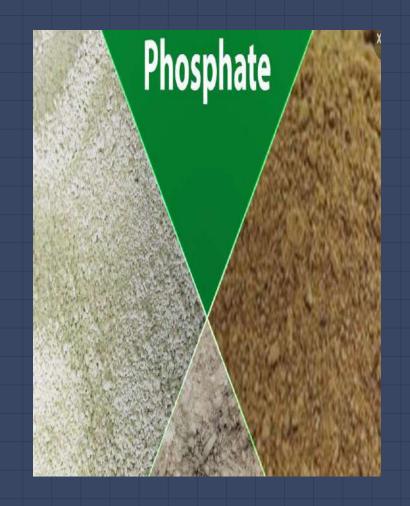
Brief rationale for updating

4.1.8. In patients with CKD G3a-G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D). It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations (Not Graded).

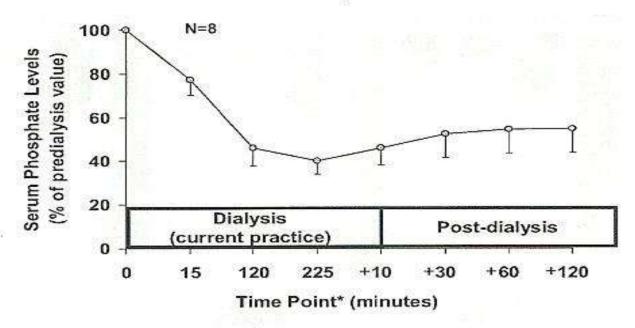
4.1.7. In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D). New data on phosphate sources were deemed important to include as an additional qualifier to the previous recommendation.



the Work Group drew several conclusions: (i) the association between serum phosphate and clinical outcome is not monotonic; (ii) evidence is lacking to demonstrate the efficacy of phosphate binders for lowering serum phosphate in patients with CKD G3a to G4; (iii) the safety of phosphate binders in this population is unproven; and (iv) there is an absence of data showing that dietary phosphate restriction improves clinical outcomes.



Change in Serum Phosphorus during and after a Hemodialysis session



*X axis not drawn to scale.

Musci I et al. Kidney Int. 1998;53:1399-1404.

Mucsi I, Hercz G. Nephrol Dial Transplant. 1998;13:2457-2460.

Effects of Daily Hemodialysis on Mineral and Bone Metabolism

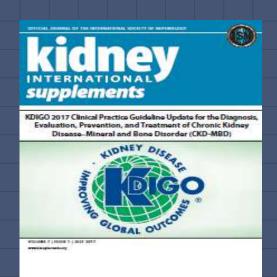
Review of published data on daily dialysis

- Studies with positive results
 - Serum Phosphorus
 - Decrease of 1.2 mmol/L
 - Phosphorus Binder Use
 - Decrease in P binder use of 38%
- Studies with non-significant trends or No effect
 - Serum Phosphorus
 - 2 trend toward decreased P
 - 4 with no change
 - Phosphorus Binder Use
 - 1 decrease use; 3 no change
- Bone Disease: 1 study with trend of less Adynamic Bone

Effect of Time and Nocturnal Dialysis on Phosphorus Control

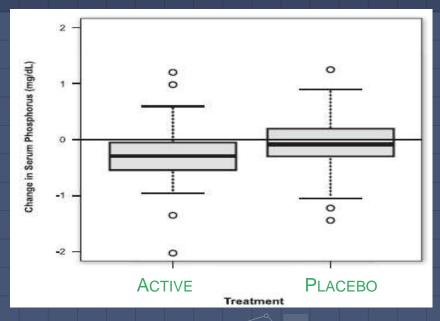
- 9 stable HD patients in random fashion received HD 4h 3x/week or 5h 3x/week (Qb adjusted to keep Kt/V stable)¹
- Weekly phosphate removal
 - 3,007 +/- 641 mg on 4h TIW
 - 3,400 +/- 647 mg on 5 hr; P < 0.02
 - = ~750 mg/hr in 1st 4 hrs, then 400 mg in last hour
- 8 stable HD patients on 5 months 3x/week HD then 5 months of 6x/week Nocturnal HD
 - cumulative weekly phosphate removal was significantly higher with NHD (161.6 +/- 59.0 mumol/week) compared to CHD (75.8 +/-22.5); P < 0.01)
- Vaithilingam I et al. Am J Kidney Dis 2004 Jan;43(1):85-9.

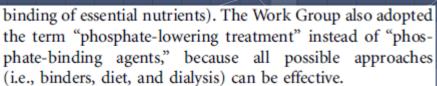
Consequently, the Work Group has abandoned the previous suggestion to maintain phosphate in the normal range, instead suggesting that treatment be focused on patients with hyperphosphatemia. The Work Group recognizes that preventing, rather than treating, hyperphosphatemia may be of value in patients with CKD G3a to G5D, but acknowledges that current data are inadequate to support the safety or efficacy of such an approach.

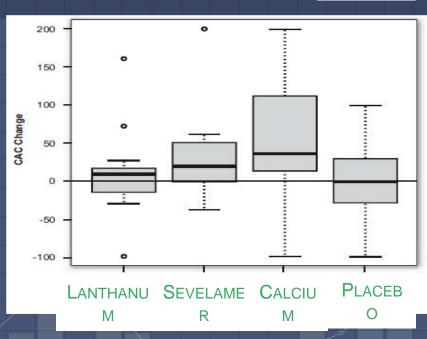


Phosphate Binders in Moderate CKD





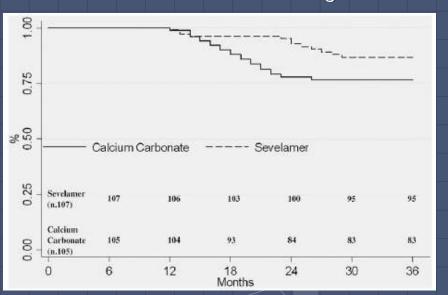




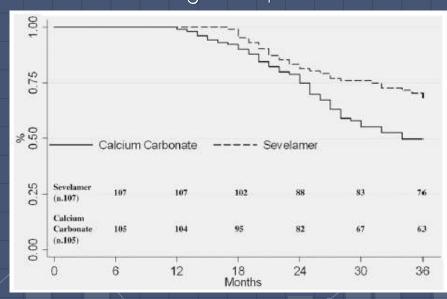
Block G et al. J Am Soc Nephrol. 2012;23:1407-1415

Phosphate Binders and Mortality

All-Cause Mortality



Dialysis Inception



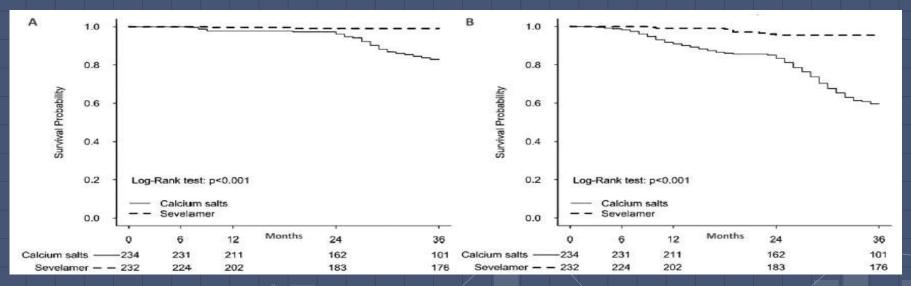




Sevelamer vs. Calcium

Arrythmias

Cardíovascular Mortalíty



Dí Iorío B et al. Am J Kidney Dís. 2013;62:771-778



Foods High in Phospl

Processed Food - Health Risks

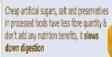
Meat





Fast Food

Food processing removes some of the nutrients, vitamins and fiber present in the food







The salts, phosphates and other processed food leads to kidney and other health problems

requent consumption of processed foods can lead to hormonal problems like menstrual irregularities, premenstrual syndrome, infertility, thyroid dysfunction etc



syndrome etc.

lead to nervous system problem

depression, imitability and inability

concentrate.



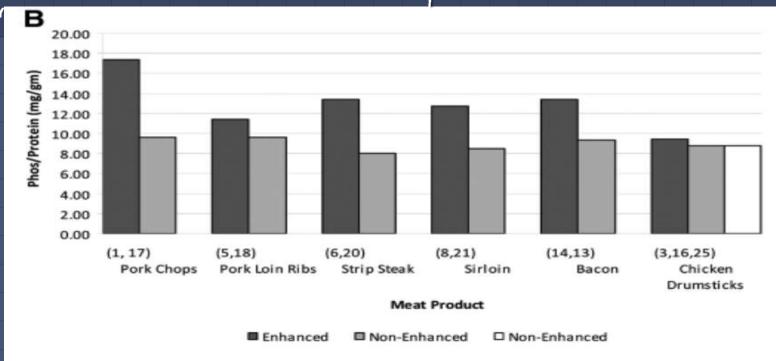




Seeds

Milk Canned Fish

"Hidden" Phosphate



CJASN

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

- 4.1.3. In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (2C). In children with CKD G3a–G5D, we suggest maintaining serum calcium in the ageappropriate normal range (2C).
- 4.1.4. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2C).

4.1.2. In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (2D).

4.1.3. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2D).

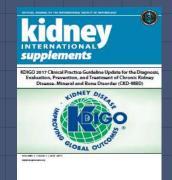
Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.

Additional studies of better quality are available; however, these do not allow for discrimination of benefits and harm between calcium dialysate concentrations of 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l). Hence, the wording is unchanged, but the evidence grade is upgraded from 2D to 2C.

Because mild and asymptomatic hypocalcemia may well be harmless, especially in the presence of calcimimetic therapy, the Work Group emphasized an individualized approach to the treatment of hypocalcemia, rather than recommending the correction of hypocalcemia for all patients. However, significant or symptomatic hypocalcemia should still be addressed.

The 2009 Guideline¹ considered that a dialysate calcium concentration of 1.25 mmol/l (2.5 mEq/l) would yield neutral calcium balance. Based on new evidence, the 2017 Work Group felt that this recommendation remains valid as written in 2009. However, because additional studies of better quality are now available, the evidence grade has been changed from 2D to 2C.





Secondary hyperparathyroidism (SHPT)

Attempt to control the disturbed calcium, phosphorus, and vitamin D metabolism. SHPT causes vascular and soft-tissue calcification and leads to disturbances of mineral metabolism CKD-related mineral and bone disorder (CKD-MBD).

CKD-MBD abnormalities have also been implicated as risk factors for the very rare but devastating calcific and thrombotic arteriolopathy calciphylaxis and lead to reduced health-related quality of life (HRQOL).

The indication for SHPT treatment results from these clinical consequences

sHPT-associated high FGF23 is independently associated with left ventricular hypertrophy, cardiovascular events and premature death.

Consequences of SHPT

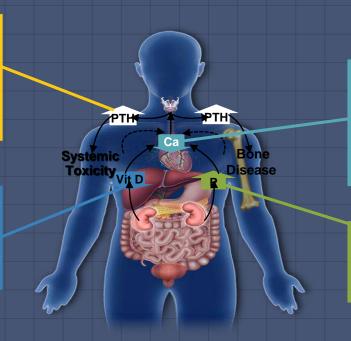
Abnormalities in Metabolic Parameters Are Consequences of SHPT: Management of PTH, Ca, and P

Involved in homeostasis of bone metabolism

- Maintains correct
- balance of Ca and P
- in the body

Increase Vitamin D Levels

 Administer vitamin D sterols to reduce PTH



Control Ca

- Control intake
- Adjust dialysate Ca
- Use Ca supplements or vitamin D therapy (if Ca low)

Lower Elevated Serum P

- Control dietary intake
- Use phosphate binders

Treatment approaches to the management of SHPT include CaxP, PTH, and vitamin D.

Use of vitamin D and phosphate binders alone provide no direct way to control PTH levels without the risk of raising Ca and P levels.

Ca = calcium; P = phosphate; PTH = parathyroid hormone; SHPT = secondary hyperparathyroidism.

Tomasello S. Díabetes Spectrum. 2008;21:19-25

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

4.2.1. In patients with CKD G3a-G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C). 4.2.1. In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).

It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/ or native vitamin D (Not Graded).

The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and has revised this statement to include "persistently" above the upper normal PTH level as well as "progressively rising" PTH levels, rather than "above the upper normal limit." That is, treatment should not be based on a single elevated value.

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations¹

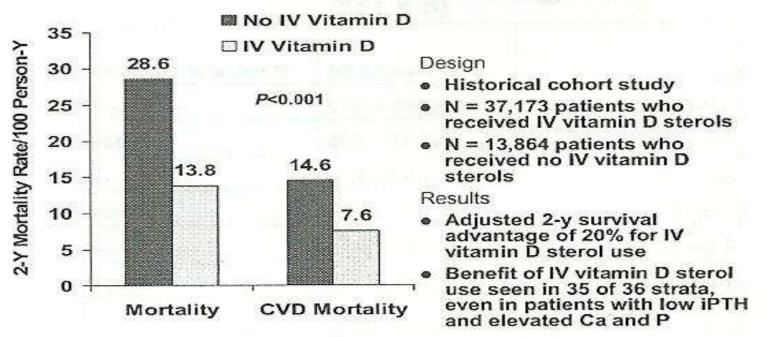
Brief rationale for updating

4.2.2. In adult patients with CKD G3a-G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4-G5 with severe and progressive hyperparathyroidism (Not Graded).

In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (Not Graded).

4.2.2. In patients with CKD G3a-G5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C). Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but demonstrated increased risk of hypercalcemia.

IV VDRA Therapy and Reduced Mortality for Patients on Dialysis



CLINICAL RESEARCH www.jasn.org.

Effect of Paricalcitol on Left Ventricular Mass and Function in CKD-The OPERA Trial

Angela Yee-Moon Wang,* Fang Fang,† John Chan,* Yue-Yi Wen,† Shang Qing,† Iris Hiu-Shuen Chan, 5 Gladys Lo, 2 Kar-Neng Lai, 2 Wai-Kei Lo, 5 Christopher Wai-Kei Lam, 5 and Cheuk-Man Yut

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Vitamin Disease to protect against cardiovascular disease, but the reported of fects of vitamin Don patie outcomes in CKD are controversial. We conducted a prospective, double blind, randomized, placet controlled trial to determine whether oral activated vitamin Direduces left ventricular (LM) mass in patier with stages 3-5 CKD with LV hypertrophy. Subjects with echocardiographic criteria of LV hypertrop were randomly assigned to receive either oral pariculation (1 up) one time daily (re-30) or matching place. n=30) for 52 weeks. The primary and point was charge in LV mass index over 52 weeks, which w measured by cardiac magnetic resonance imaging. Secondary and points included changes in LV volum echocardiographic measures of systolic and disstolic function, biochemical parameters of mineral bio disease, and measures of renal function. Change in LV mass index did not differ significantly between groups (median linterquartie rangel. - 2591-6.13 to 0.32) g/m² with paricalcito(versus -4.851-9.89 1.10) g/m² with placebo). Changes in LV volume, ejection fraction, tissue Doppler-derived measures. early disatolic and systolic mitrial armular velocities, and ratio of early mitralimflow velocity to early disato mit a annular velocity did not differ between the groups. However, park aight of treatment significan reduced intact parathyroid hormone (P<0.001) and alkaline phosphatase (P=0.001) levels as well as t number of cardiovascular-related hospitalizations compared with placebo. In conclusion, 52 weeks treatment with onal paricalistol (1 µg one time daily) significantly improved secondary hyperparathyrol ambut did not alter measures of LV structure and function in patients with severe CKD. Am Soc Negatival 25: 175-184, 2014. doi: 10.1481/A594.200010103

in patients with CKD and has been attributed to a D exceptor gene resulted in increased cardiomy very high prevalence of left ventricular (IV) hypertrophy 1 as well as traditional Framingham and kidney disease-related risk factors.2 Apart from playing a recognized role in suppressing secondary hyperparathyroidism, vitamin D has been saggested to play a protective role assires cardiovascular disease and exert its effects on the heart and vascular walls through interaction with the vitamin D receptor.34 Experimental studies showed associations between vitamin D deficiency and impairment of cardiac contractile function,5 increased myocardial collagen content, and increase deardiac

Cardiovascular disease is a major cause of mortality mass. 5.7 Similarly, targeted deletion of the vitan cyte size and LV weight.6 Treatment with activat vitamin D attenuated myocardial hypertrophy experimental models of cardiac hypertrophy* a

> Rewind January 20, 2013 American July 9, 2013 Fublished online sheed of print. Publication date available

Correspondence: Dr. Angela Yee-Miron Wang, Department Medicine, University of Hong Kong, Queen May Hospital, 1 Politism Road, Hong Kong, Small: symwong @hispital Copyright @ 2014 by the American Society of Nephrology

J Am Soc Nephror 25: 175-104, 2014

Vitamin D Therapy and Cardiac Structure and Function in Patients With Chronic Kidney Disease

The PRIMO Randomized Controlled Trial

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|-----------------------------------|
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| Yili Pritchott, PhD |
| Yuchiao Chang, PhD |
| Julia Wenger, MPH |
| Hector Tamez, MD, MPH |
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| Daniel Zehnder, MD |
| Amil Shah, MD |
| Ajay Pachika, MD |
| Warren J. Manning, MD |
| Scott D. Solomon, MD |
| Octobron and the Albanda Comments |

LITECUCES PRIMARILY RECOMmended for improving bone health, treatment with vitamin D recently has been suggested or other conditions, including cardiovascular disease (CVD).1-3 Multiple lines of evidence suggest a link between vitamin Dand CVD, including expertmental stud-

For editorial comment see p 722.

674 IAMA, Polymory 15, 2012-4ht 507, No. 7

 Context Vitarrin D is associated with decreased cardiovascular-related morbidity and mortality, possibly by modifying cardiac structure and function, yet firm evidence for

Objective To determine the effects of an active vitamin D compound, paricalcitol, on left ventricular mass over 48 weeks in patients with an estimated glomerular filtration rate of 15 to 60 mL/min/1.73 m2.

Design, Setting, and Participants Multinational, double-blind, randomized placebocontrolled trial amony 227 patients with chronic kidney disease, mild to moderate left. ventricular hypertrophy, and preserved left ventricular ejection fraction, conducted in 11 countries from July 2008 through September 2010.

Intervention Participants were randomly assigned to receive oral participants were randomly assigned to receive oral participants. (n=115), or matching placebo (n=112).

Main Outcome Measures Chango in left ventricular mass index over 48 weeks by cardiovascular magnetic resonance imaging. Secondary end points included echocardiographic changes in left wentricular diastolic function.

Results Treatment with paricalcitol reduced parathyroid hormone levels within 4 weeks and maintained levels within the normal range throughout the study duration. At 48 weeks, the change in left ventricular mass index did not differ between treatment groups (paricalcitol group, 0.34 g/m21 [95%, CL = 0.14 to 0.83 g/m21] vs placebo group, = 0.07 g/m27 [95% CI, -0.55 to 0.42 g/m27]). Doppler measures of diastolic function induding peak early diastolic lateral mitral annular tissue velocity (partcaktiol group, -0.01 cm/s (95% Ct. -0.63 to 0.60 cm/s) vs placebo group, -0.30 cm/s (95% Ct. -0.93 to 0.34 cm/s() also did not differ. Episodes of hypercalcemia were more frequent in the paricalcitol group compared with the placebo group.

Conclusion Forty-eight week therapy with paricalcitol did not alter left ventricular mass Index or improve certain measures of diastolic dysfunction in patients with chronic

Trial Registration clinicaltrials.gov identifier: NCT00497146 JAMA 2012 20101 CM-CM

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tes identifying vitamin D receptors in vascular smooth muscle, endotheltal cells. and possibly cardiac tissue" and observational studies, small clinical trials, and meta-analyses suggesting that vitamin D therapy reduces cardiovascular events. 13 Convincing data demonstrating that vitamin D therapy improves cardiovascu-

lar health, however, are lacking,

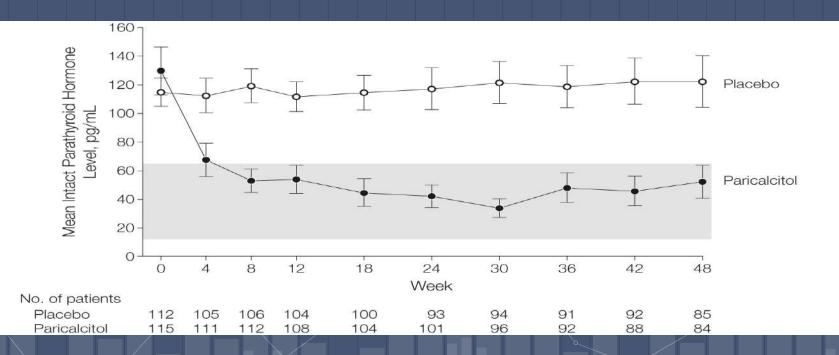
Patients with chronic kidney disease (CKD) frequently develop deficiency of 1.25-difivdroxyvitamin D, (calcirrol) hecause of a lack of its precursor, 25-

Author Affiliations and a list of the PRIMO Investigatom appear at the ord of this article. Corresponding Author: Ray Theritans, MD, MPS, M avautuants Ceneral Hospital 55 Fruit St. Buffrich 13 Boston, MA 02114 (thusbani.nthrogh.harvani.edu).

02012 American Medical Association. All rishis covered.

The PRIMO Trial

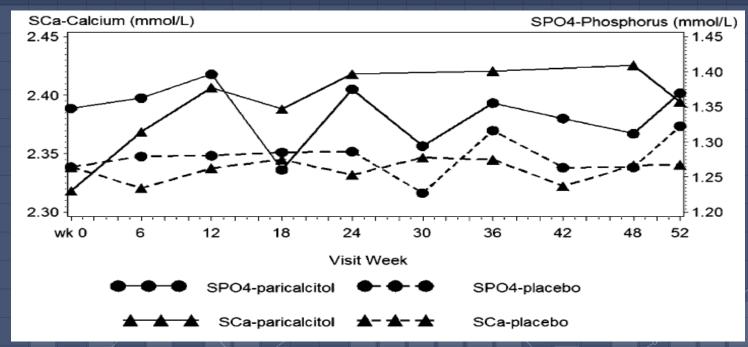




Thadaní R et al. JAMA. 2012;307:674-684

The OPERA Trial





Wang A et al. J Am Soc Nephrol. 2014;25:175-186

Table 1 Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

4.2.4. In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B). 4.2.4. In patients with CKD G5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

- It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphate levels and other aspects of CKD-MBD (Not Graded).
- It is reasonable that calcium or noncalcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphate and calcium (Not Graded).
- We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).
- We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (2D).
- We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D).
- We suggest that, if the intact PTH levels fall below 2 times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/ or calcimimetics be reduced or stopped (2C).

This recommendation originally had not been suggested for updating by the KDIGO Controversies Conference in 2013, However, due to a subsequent series of secondary and post hoc publications of the EVOLVE trial, the Work Group decided to reevaluate Recommendation 4.2.4 as well. Although EVOLVE did not meet its primary endpoint, the majority of the Work Group members were reluctant to exclude potential benefits of calcimimetics for G5D patients based on subsequent prespecified analyses. The Work Group, however, decided not to prioritize any PTH-lowering treatment at this time because calcimimetics, calcitriol, or vitamin D analogs are all acceptable first-line options in G5D patients.

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Effects of Cinacalcet on Fracture Event Receiving Hemodialysis: The EVOLVE T

Sharon M. Moe .* Safa Abdalla *Glenn M. Chertow * Patrick S. Fa Block, Filando Correa-Rotter, Jürgen Floege, Charles A. Herzo Kenneth W. Mahaffay, 1 David C. Wheeler, 12 Bastian Dehmel, 55 W. "Invan B. Drüeke, I for the Evaluation of Cinecalcet HCl Therapy Events (EVOLVE) Trial investigators

"In dans University School of Medicine and Roudebish Visterans Administration Me Indiana; Stanford University School of Medicine, Palo Alto, California; Finally Sca

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ORIGINAL ARTICLE

CLINICAL RESEARCH WWW.perc.com

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigations*

ABSTRACT

Manher of the esting constitue are Distorder of mineral metabolism, including sectorism hyperparts/pyridism, are request to the Clebral. However, the Clebral state of the Constitution of the Clebral state of the Constitution o 780 while tel. have the Per Ahr, on calcimitentic approximation much reduce the first of death or nearfinal cardiovas orar wers in such patients.

In this clinical trial, we randomly assigned \$883 parietrs with moderate-to-severe secondary byperpuraby midden (median level of insign parallyroid burmong, 665 or per million (10th to 90th peromale, 363 to 1694) who were undergoing hemodiciyals to receive either cineralest or placebe. All patients were eligible to receive conventional therapy, including phosphare binders, vitamin D sterois, or both. The parients were followed for up to 64 months. The primary composite and point was the time until death, two caraix infarction, hospitalization for un suffer angina, hear falkin, or a peripheral vacular owns. The primary analysis was per-format on the basis of the locasius to trust principle.

The median duration of study-étus exposure was 31.2 mouths in the cinacalcer group, versus 17.5 mouths in the placeto group. The primary composite and pole was reacted in 198 of 1948 patients (48,2%) in the cinacator group and 952 of 1985 patience (69.7%) in the planetin group (relative hazard in the clean does group vs. the placeso group, 0.91; 99% confidence interval, 0.85 to 1.02; P=0.11). Hypocalcemia strected atteres even were significantly more frequent to partern receiving characters.

Effects of Cinacalcet on Atheroscle

David C. Wheeler, MD; General M. London, MD, Patrick S. Perfley, MD Bastler Dahmol MD: Tilmen & Orlinks, MD: Kireon Roose, MD: Yuni William G. Goodman, MD: Sharon M. Mos, MD: Mario Louise Trot nan Charles A. Hircong, MD; for the EValuation Of Gregolout HG Thorapy

The Evaluation Of Cinacalcet HCLT on Hemodialysis: The Evaluation of Cinacalcet HCL CardioVascular Events [EVOLVE] Tr Therapy to Lower Cardiovascular Events (EVOLVE) Trial

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HHS Public Access Author manuscript

Hemodial Int. Author manuscript; available in PMC 2017 July 01 Published in final edited form as:

Hamodini Int. 2016 July ; 20(3): 421-431. doi:10.1111/lub.12382

Cinacalcet, Dialysate Calcium Concentration, and Cardiovascular Events in the EVOLVE trial

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Abstract

Backgroung-Among patients receiving hemodialysis, abnormalities in calcium regulation have been linked to an increased risk of cardiovaccular ments. Cinacalcut lemme commencious concentrations through its effect on parathyroid hormone secretion and has been hypothesized to reduce the risk of cardiovascrular events. In observational cohort studies, prescriptions of low dialysate calcium comentration and larger observed serum dialysate calcium gradients have been associated with higher risks of in-dialysis facility or peri-dialytic undden cardiac arrest. We performed this study to examine risks associated with dialysate calcium and serum dialysate gradients among participants in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial.

Address for Correspondence: Pariols II Pay, MD, MSSI. Daha University Medical Circles, PO Stor 2797, Darbare, HC, 27710, Nativide passifichabe adu; telephorus (010) 6601.6864; faor (010) 684.4476. Conflict of Interest Discharge Full list of discharges for pullium numbed non-

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Cardiovascular Events in Patients F The Effects of Cinacalcet in Older and Younger Patients EVOLVE Trial

and Survival in Patients Receiving Hemodialysis in the

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Rackground and objectives Patients econoling homodialysis areatrick of cardiovascular events. Arroyal blood test (I₁₀ sec) determines the inclinidual calcin action provention of blood.

Design, setting, participants, it measurements Tayward elemined in 27th leaving serum samples of parients. serving hemodialysis extelled in the Evaluation of Cinaculast Therapy to Lower Conformation Brents salar (CV) events in EVOLVE) trial and the T_{in} must swere related to patient outcomes.

book Serum albumin, historians, HDL dislosered, and creatinine were the main is does positively (directly sized in older (26) and phophate was the man later required ylorosolly assented with To. The primary composite endopsed fall-case murtality, response a limitation [M.], hospitalisation for contable anging, heart failure, or perioderal worderwere PVE) was reached in CSE pulsers a fera median follow-up time of 65 days. After adjustment for 1 days Gree 11. er Cardiovacralar orderedus, a lover II., secondomordis associated with a lother risk of the persons our courts and court as a Min. Feetendard ortinuas masore fusuel mão [HI] per I SD lover I_{III} I IS: 954 confidence internal (954 CI 108 to 122) urremitting HPT 7:0000. Furthermre, lower T_{co} was associated with a higher risk multi-base morality (HR per I SOlower T_{co} LIG994 CLUE to LIF; P-4001; M. HR per 15D lover T_a, 138,994 Cl, Li9 to LiG; P<0.001; and PVE (HR per ISD lower Tag 172, 995 CI, 165 to 142, 7-101. To improved risk prediction (integrated discrimination other patients and improvement and not reducification improvement, P-(1001) and P-(1001) of the primary composite and point.

shazari 09% Gordalins Fibod calcification propressity was independently associated with they insure composite and point. (0.7) (0.00 to 0.81) ine hazards for all-come mortality. Mr. and FVE in the ENCRYS study and improved risk prediction. Prospective trials should at the day mitting HFT was - clarify election Targacked thempion improve outcomes.

Clin | Am Six Norbell 12:315-311, 2017. doi: 10.2215./CDX.04721416

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nd whos seam manulation of the fied trial (RCT) in

to calcium-sensing sizeal CV risk factors EE, cholesters), an string, budy phosphate scile form. This hads to the insurnaments man index (BMI), and dishere (3.4). Father, so-timestion of primary calciproses particle (CPY). The called normalitional CV risk factors (5p) reflecting timing of the spontaneous transformation of these ar smooth mapels disturbance in horse and indread metabolism appear puriodes into secondary CPP depends on the individis the crossocial to play in important role (1,5). Current the special wall composition of serum, and more openically on patients receiving concept an accordingly sized at lowering devaid. By conceptations and intender of well established the progression of some connectations of phosphas and marketial calcifration-coloring factors, including the present harmone PTHI, which are associated with an in- Stein-A and albumin, and the small materials calprevention of CI creat northly in patients activing herodulysis cium, phosphate, magnetium, pytophosphate, and ation of Circumstates (0,10,11) and with distribute addition within was others (21,22). A sharter transformation time rule wills and contine valves (0,13). Such extract indicates a more capid precipitation of coliners and calcifications are other present even at young age phasp late in the presence of serum and lower Tag (413 and may progress spridy (16). The number whose have been assembled with higher risk of wome of sites with calculat vessels (IT) and the degree of subcone in colors studies. Specifically, the Tip test

alaboriore at specific sites have been associated Patients receiving hemodialysis sofferfrom a thumat- with mortality in this patient population (II-20). ically increased conditionatcher (CV) modelity and . Beautily, a royal functional probes as a (Tighteet for mortality compared with age-matched persons with the determination of calciflation propensity in Napol normal or near normal kidney function (I.M. Allage - was developed (I.D. This see quantifies the calculate parties of this cases risk is attributable to CV casses. See inhibition inherent in bland by challenging the enspor/Mempura, which can only partially be explained by the bath patient's serian with superschanned calcium and

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EVOLVE: Lowering PTH



Chertow GM, et al. N Engl J Med. 2012;367:2482-2494

THE NEW ENGLAND JOURNAL OF MEDICINE

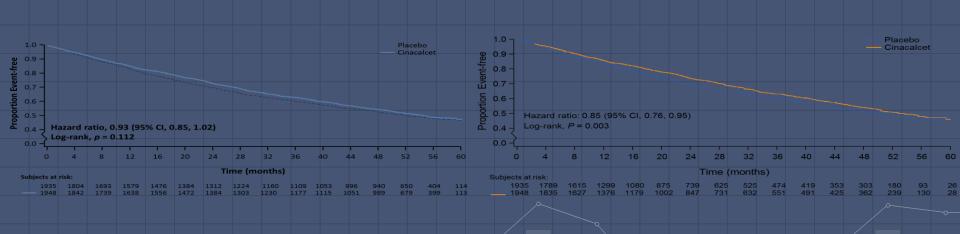
ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

ABSTRACT

EVOLVE Study: Cinacalcet



Chertow GM, et al. N Engl J Med. 2012;367:2482-2494

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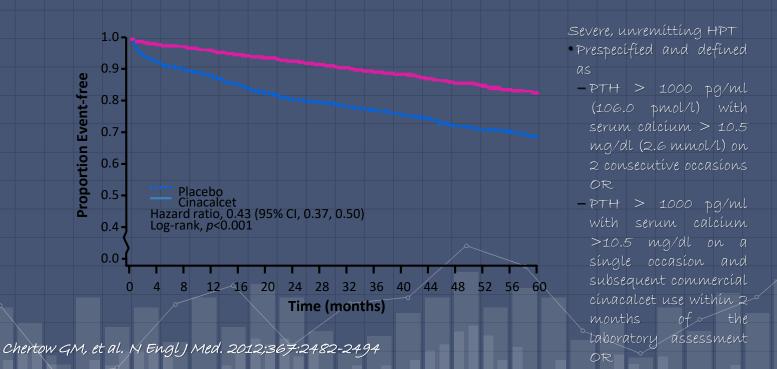
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ABSTRACT

Time to First Episode of Severe Unremitting HPT (Intent-to-Treat Analysis)



– parathyroidectomy

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

4.3.3. In patients with CKD G3a-G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

4.3.3. In patients with CKD G3a–G3b with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).

43.4. In patients with CKD G4–G5D having biochemical abnormalities of CKD-MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (2C). Recommendation 3.2.2 now addresses the indications for a bone biopsy prior to antiresorptive and other osteoporosis therapies. Therefore, 2009 Recommendation 4.3.4 has been removed and 2017 Recommendation 4.3.3 is broadened from CKD G3a–G3b to CKD G3a–G5D.

5.5. In patients with G1T-G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (2C).

5.5. In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m², we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D).

2009 Recommendations 5.5 and 5.7 were combined to yield 2017 Recommendation 5.5.

5.7. In patients with CKD G4T-G5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease (2B).

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations³

2009 KDIGO CKD-MBD recommendations

Brief rationale for updating

5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (2D).

- We suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (2C).
- It is reasonable to consider a bone biopsy to guide treatment (Not Graded).

There are insufficient data to guide treatment after the first 12 months.

5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m² and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered (2D).

- We suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (2C).
- It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (Not Graded).

There are insufficient data to guide treatment after the first 12 months.

The second bullet point is revised, consistent with the new bone biopsy recommendation (i.e., 2017 Recommendation 3.2.2).

- Prospective studies evaluating BMD testing in adults with CKD represent a substantial advance since the original guideline from 2009, making a reasonable case for BMD testing if the results will impact future treatment.
- It is important to emphasize the interdependency of serum calcium, phosphate, and PTH for clinical therapeutic decision-making.

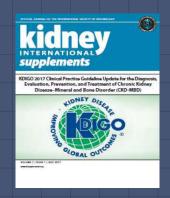
 Phosphate-lowering therapies may only be indicated in the case of "progressive or persistent hyperphosphatemia".

New evidence suggests that excess exposure to exogenous calcium in adults may be harmful in all severities of CKD, regardless of other risk markers.

It is reasonable to limit dietary phosphate intake, when considering all sources of dietary phosphate (including "hidden" sources).

The PRIMO and OPERA studies failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia. Accordingly, routine use of calcitriol or its analogs in CKD 43a-45 is no longer recommended.

4.2.4. In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).



THANKS!

Any questions?

