

به نام خدا



CKD – MBD

(MINERAL AND BONE DISORDER)

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supplements

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



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تعریف

CKD-MINERAL AND BONE DISORDER

اختلال سیستمیک متابولیسم مواد معدنی و استخوان به علت بیماری مزمن کلیه که به صورت یک یا بیشتر از علائم زیر بروز می کند:

- اختلالات متابولیسم کلسیم ، فسفر ، پاراتورمون و ویتامین D
- اختلالات **turnover** ، مینرالیزاسیون ، حجم ، رشد خطی یا قدرت استخوان
- کلسیفیکاسیون عروقی و سایر بافت نرم

تعریف استئودیستروپی کلیه

- استئودیستروپی کلیه تغییرات مورفولوژی استخوان در بیماران مبتلا به بیماری مزمن کلیه می باشد.
- قسمت اسکلتی اختلال سیستمیک **CKD-MBD** می باشد که سنجش آن با هیستومورفومتري بیوپسی استخوان است.

تشخيص CKD-MBD:

اختلالات بیوشیمیائی

تشخیص CKD-MBD: اختلالات بیوشیمیائی

- در مراحل اولیه CKD توصیه به کنترل سطح سرمی کلسیم ، فسفر ، پاراتورمون و الکالین فسفاتاز می شود.
- در CKD مرحله ۳ به بعد تکرار انجام آزمایش بستگی دارد به :
 - سرعت پیشرفت CKD
 - وجود و شدت اختلال
- در بچه ها توصیه می شود از مرحله ۲ این بررسی ها شروع شود.

تشخیص CKD-MBD: اختلالات بیوشیمیائی

- در CKD مرحله ۳ به بعد پیشنهاد می شود:
- اندازه گیری سطح ویتامین D
- تکرار انجام آزمایش بسته به :
 - مقدار اولیه
 - درمان های انجام شده
- اصلاح کمبود ویتامین D مانند افراد عادی جامعه.

Table 13 | Sources and magnitude of the variation in the measurement of serum calcium, phosphorus, PTH, and vitamin D sterols

Variable	Calcium	Phosphorus	PTH	Vitamin D sterols
Coefficient of variation	+	+	++	++
Diurnal variation	+	++	++	-
Seasonal variation				++
Variation with meals	+	+	+	-
Variation with dialysis time	+	+		
Assay validity	+++	+++	+	+

تعریف مقادیر نرمال

Phosphorus	2.5 – 4.5 mg/dl
Calcium	8.5 – 10 (or 10.5) mg/dl
iPTH (بسته به روش آزمایش متفاوت است)	10 - 65 pg/ml [CDC recommendations]

EVALUATION OF CKD-MBD: BIOCHEMICAL ABNORMALITIES

CKD Stage	3
Ca & P	Every 6-12 ms
PTH & ALP	Baseline
25(OH)Vit D	Baseline

There is an emphasis on trends, vs treating a number

KDOQI / KDIGO - PTH TARGETS



CKD Stage	Target iPTH (pg/ml) KDOQI	
3	35 - 70	
4	70 - 110	
5 ND	150 - 300	
5D	150 - 300	

تشخيص CKD-MBD:

استخوان

تشخیص CKD-MBD: استخوان

در CKD مرحله ۳ به بعد در موارد زیر انجام بیوپسی استخوان عاقلانه است:

- شکستگی غیر قابل توضیح
- درد استخوانی مداوم
- هیپرکلسمی غیر قابل توضیح
- هیپوفسفاتیسم غیر قابل توضیح
- احتمال مسمومیت آلومینیوم
- درمان قبلی با بیس فسفونات در بیماران با CKD-MBD

علائم

- شکستگی استخوان
- پارگی تاندون
- درد استخوان
- درد و ضعف عضلانی
- دردهای اطراف مفصل
- کلسیفیکاسیون متاستاتیک

تشخيص CKD-MBD: كل سيفيكاسيون عروقي

تشخیص CKD-MBD: کلسیفیکاسیون عروقی

در CKD مرحله ۳ به بعد گرافی نیمرخ شکم و اکوکاردیوگرافی می تواند جهت تعیین وجود یا عدم وجود کلسیفیکاسیون عروقی و درجه قلب استفاده شود.

بیماران مرحله ۳ به بعد با کلسیفیکاسیون عروقی و یا درجه قلب بیشترین خطر قلبی عروقی را دارند.



Periosteal resorption and arterial calcification

(a) before PTx; (b)





Periarticular Calcification



Slide courtesy of D. Sherrard.

In Summary ...

**Treat P & Ca to normal
PTH to Goal**

کلسیفیلاکسی

○ سندرم متشکل از :

● کلسیفیکاسیون عروقی

● ترومبوز

● نکروز پوستی

○ فقط در بیماران مرحله ۵ CKD دیده می شود.

○ منجر به زخم های مزمن بهبود نیافتنی شده و معمولاً کشنده است.

CALCIPHYLAXIS



CASE

- 60 ys man, ESRD due to hypertensive nephropathy on HD 2 times/w since 1 m ago
- Hx: TIA 1 y ago
- Daily DHx: Furosemide 80 mg, Amlodipine 5 mg, Nephrotonic.
- PE: BP:140/80 PR:74 RR:16 T:36 W:78 H:170 BMI:27
- 1⁺ pitting edema in lower extremities

سوال

Ca: 7.2 P: 6 Alb: 3.8 25(OH)D: 21 ng/mL
PTH: 139 pg/mL (15-65)

What is your recommendation in treatment of his CKD-MBD?

CaCo3 × 3 /d with meals + Vit D 50000 IU/week

درمان CKD-MBD هدفمند در جهت کاهش فسفر و حفظ کلسیم



مواد غذائی فسفردار

- لبنیات
- حبوبات
- آجیل
- نان سبوس دار
- نوشابه های گازدار بخصوص انواع کولا
- شکلات

درمان CKD-MBD : کلسیم و فسفر

در بیماران تحت دیالیز پیشنهاد می شود:

- کاهش سطح فسفر به سطح نرمال
- استفاده از مایع دیالیز با غلظت کلسیم بین ۲/۵ و ۳ میلی اکی والان در دسی لیتر
- افزایش خارج کردن فسفات از طریق دیالیز در درمان هیپرفسفاتیسمی مداوم

Current Phosphate Binders

- **Phosphate Binders**
 - **Ca Carbonate**
 - **Ca Acetate**
 - **Al Hydroxide**
 - **Renagel (Sevelamer Hydrochloride)**
 - **Renvela (Sevelamer Carbonate)**
 - **Fosrenol (Lanthanum Carbonate)**
 - **Osvaren (Ca Acetate Mg Carbonate)**
 - **Mg Carbonate**



MANAGEMENT OF SECONDARY HYPERPARATHYROIDISM

- Among patients receiving ca-containing buffers, the total dose of elemental ca (including dietary sources) **should not > 2000 mg/d**
- The amount of elemental ca contained in the ph binder **should not > 1500 mg/d.**

درمان اختلالات سطح پاراتورمون در **CKD-MBD**

درمان CKD-MBD: سطح غیر طبیعی پاراتورمون

- در بیماران تحت دیالیز و افزایش PTH ،
کلسی تریول ، مشتقات ویتامین D ،
کلسیمیمتیک ها یا ترکیب آنها تجویز می شود.
- انتخاب نوع دارو بر اساس سطح کلسیم و فسفر
پلاسما و سایر مشخصات CKD-MBD است.

درمان CKD-MBD: سطح غیر طبیعی پاراتورمون

در بیماران با هیپرکلسمی یا هیپرفسفاتمی ،
کلسی تریول یا سایر ترکیبات ویتامین D باید
کم یا قطع شود.

TREATMENT OF CKD-MBD: ABNORMAL PTH LEVELS

- Continued:

- If the iPTH levels fall **below 2 times** the upper limit of normal for the assay, calcitriol, vit D analogs, &/or calcimimetics be reduced or stopped.
- In patients with CKD stages 3–5D with severe HPT who fail to respond to medical/pharmacological therapy, we suggest **parathyroidectomy**.



CASE

- **Male, 47 y , ESRD due to FSGS, on HD 3 times/w since 2 y ago**
- **No complaint**
- **PE: BP: 140/90, Right Brachiocephalic AVF, 1+ edema**
- **Medications: CaCo₃ 1-1-1**
- **Lab: Ca: 7.5 P: 5.2 Alb:3.8 PTH: 320 pg/ml(10-65)
25 OH Vit D: 15 ng/ml**

نسخه

1. Tab CaCo_3 500 mg

N: 120/-- ۱ صبحانه ۲ نهار ۱ شام

2. Pearl Vitamin D3 50000 IU

N: 10/-- هفته ای ۱ عدد برای ۸ هفته سپس

هر ۲ هفته ۱ عدد

AFTER 1 MONTH

- **Ca: 7.5 mg/dL P: 5.2 mg/dL PTH: 320 pg/ml(10-65) Alb: 3.8**
- **Ca: 8.5 mg/dL P: 4.2 mg/dL**

36

1. Tab CaCo_3 500 mg

۱ صبحانه ۲ نهار ۱ شام N: 120/--

2. Pearl Vit D3 50000 IU

N: 10/-- هفته ای ۱ عدد برای ۸ هفته سپس

هر ۲ هفته ۱ عدد



AFTER 3 MONTH

- **Ca: 8.5 mg/dL P: 4.2 mg/dL**
- **Ca: 9.6 mg/dL P: 6.1 mg/dL PTH: 790 pg/ml(10-65)**
Alb: 4.1 Vit D: 34

37

1. **Tab CaCo_3 500 mg**
N: 120/--
۱ صبحانه ۲ نهار ۱ شام
2. **Pearl Vit D3 50000 IU**
N: 2/--
هر ۲ هفته ۱ عدد



AFTER 3 MONTH

1. Tab CaCo_3 500 mg

۱ صبحانه ۲ نهار N: 90/--

2. Tab Sevelamer Carbonate 800 mg

۲ شام N: 60/--

3. Pearl Vit D3 50000 IU

هر ۲ هفته ۱ عدد N: 2/--

4. Tab Cinacalcet 30 mg

۱ روی شام N: 30/--

38



AFTER 4 MONTH

Ca: 8.4 mg/dL P: 4.1 mg/dL PTH: 800 pg/ml (18.5-88)

1. Tab CaCO_3 500 mg

۱ صبحانه ۲ نهار N: 90/--

2. Tab Sevelamer Carbonate 800 mg

۲ شام N: 60/--

3. Pearl Vit D3 50000 IU

هر ۲ هفته ۱ عدد N: 2/--

4. Tab Cinacalcet 30 mg

۱ روی شام N: 30/--

39



AFTER 4 MONTH

Ca: 8.4 mg/dL P: 4.1 mg/dL PTH: 800 pg/ml (18.5-88)

1. Tab CaCo_3 500 mg

۱ صبحانه ۲ شام N: 90/--

2. Tab Sevelamer Carbonate 800 mg

۲ نهار N: 60/--

3. Pearl Vit D3 50000 IU

هر ۲ هفته ۱ عدد N: 2/--

4. Tab Cinacalcet 30 mg

۱ روی شام N: 30/--

5. Pearl Calcitriol 0.25 μg

هفته ای ۲ بار هر بار ۲ عدد موقع خواب N: 20/--

40



© 2005 GS

AFTER 5 MONTH

Ca: 8.6 mg/dL P: 4.4 mg/dL PTH: 640 pg/ml (18.5-88)

1. Tab CaCo_3 500 mg

۱ صبحانه ۲ نهار N: 90/--

2. Tab Sevelamer Carbonate 800 mg

۲ شام N: 60/--

3. Pearl Vit D3 50000 IU

هر ۲ هفته ۱ عدد N: 2/--

4. Tab Cinacalcet 30 mg

۱ روی شام N: 30/--

5. Pearl Calcitriol 0.25 μg

هفته ای ۲ بار هر بار ۲ عدد موقع خواب N: 20/--



THERE IS AN EMPHASIS ON TRENDS, VS TREATING A NUMBER

	05.2.13	05.3.14	05.5.15	05.6.15	05.7.14
Ca	7.5	8.5	9.6	8.4	8.6
P	5.2	4.2	6.1	4.1	4.4
Alb	3.8		4.1		
PTH	320 (10-65)		790 (10-65)	800 (18.5-88)	640 (18.5-88)
Vit D	15		34		

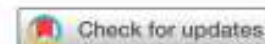
MAXIMUM DOSE/DAY

- **Elemental Calcium**
- **Calcium Carbonate (500mg)**
- **Sevelamer Carbonate**
- **Sevelamer Hydrochloride**
- **Cinacalcet**

LABORATORY RESULT SHEET

Attending Physician: <u>پزشک معالج: دکتر</u>		Ward: <u>بخش: ۱</u>		Name: <u>نام: محمد</u>		Family: <u>نام خانوادگی: محمدی</u>	
Date of Admission: <u>تاریخ پذیرش: ۱۳۹۸</u>		Date of Birth: <u>تاریخ تولد: ۱۳۷۰</u>		Father Name: <u>نام پدر: محمد</u>			
آزمایشات	فروردین	اردیبهشت	خرداد	تیر	مرداد	شهریور	مهر
WBC	۱۰۷	۲۰۹	۲۶۲	۲۱۲	۲۱۶	۲۰۸	۲۰۷
Hgb	۱۰۲	۱۱۵	۱۱۵	۱۱۶	۱۱۱	۱۱۲	۱۱۵
Hct	۳۰	۳۸	۳۸	۳۸	۳۷	۳۷	۳۷
PLT	۲۰	۳۷	۳۸	۳۸	۳۸	۳۸	۳۸
FBS	۸۶	۷۸	۹۴	۹۴	۹۱	۹۲	۹۲
Pre BUN	۵۵	۵۵	۱۰	۱۰	۱۴	۱۲	۱۲
Cr	۸۸	۸۱	۸۹	۹۴	۹۶	۸۵	۹۵
Na	-	-	۱۳۶	۱۳۸	۱۴۱	۱۳۸	۱۳۷
K	۴.۷	۵.۴	۵	۵.۵	۵.۴	۴.۹	۴.۵
Ca	۹.۴	۸.۷	۹	۹.۴	۹.۵	۹.۵	۹.۴
P	۴.۷	۴.۱	۴.۴	۵.۱	۵.۵	۶.۲	۶.۶
آزمایشات سه ماهه			خرداد	شهریور		آذر	
Post BUN			-	-		-	
KT/V			-	-		-	
URR			-	-		-	
✓ HCO3			۱۸.۱	۲۰		۱۹.۸	
AST			۴۴	۲۵		۲۰	
ALT			۵۴	۳۵		۶۵	
Iron			۸۵	۷۶		۷۴	
TIBC			۲۱۰	۲۴۷		۲۴۰	
Ferritin			۸۷۶	۹۶۷		۷۲۰.۸	
CRP			-	-		-	
Alb			۴.۳	-		۴.۴	
PTH			۱۴۰.۶	۸۵.۸ (۷۵-۶۵)		۹۸.۱ (۹-۹۵)	
آزمایشات شش ماهه			شهریور		۹۵-۸۷ (۵۵-۹۵) ۱۵۰.۴ (۹-۹۵)		
HBS Ag			(-)				
HBS Ab			(-)				
HCV Ab			(-)				
HIV Ab			(-)				
Chol							
TG							
HDL							
LDL							
Uric Acid							
آزمایشات دیگر	فروردین	اردیبهشت	خرداد	تیر	مرداد	شهریور	مهر
ALP						۸۶۰.۴۵	۸۶۰.۴۵

Chronic kidney disease–mineral and bone disorder: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference



OPEN

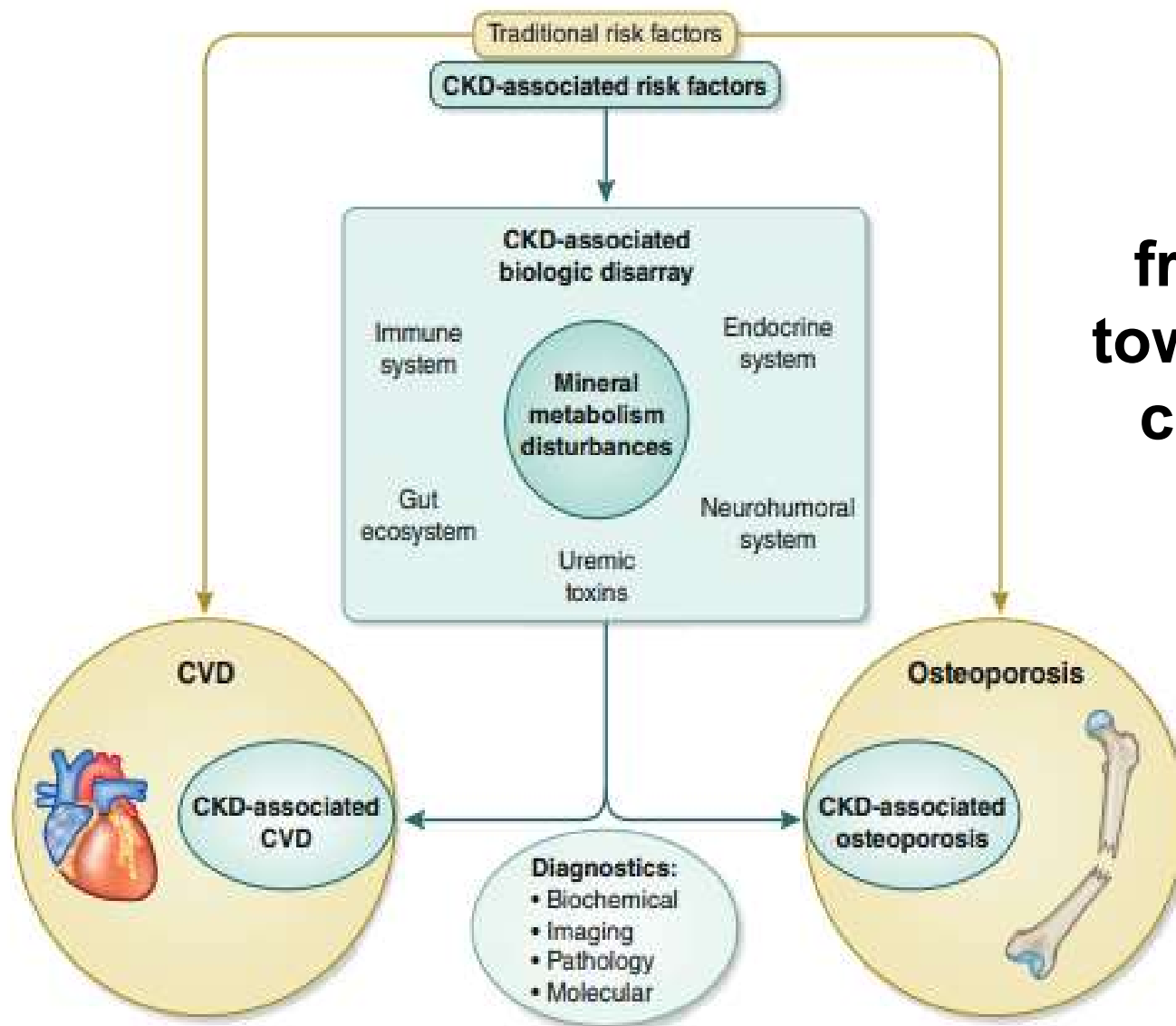
Markus Ketteler¹, Pieter Evenepoel^{2,3}, Rachel M. Holden⁴, Tamara Isakova⁵, Hanne Skou Jørgensen^{6,7}, Hirotaka Komaba⁸, Thomas L. Nickolas⁹, Smeeta Sinha^{10,11}, Marc G. Vervloet¹², Michael Cheung¹³, Jennifer M. King¹³, Morgan E. Grams¹⁴, Michel Jadoul¹⁵ and Rosa M.A. Moysés¹⁶; for Conference Participants¹⁷

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DIAGNOSIS OF THE DISORDERS ASSOCIATED WITH CKD-MBD

- Based on the following:
 - **Biochemical** assessment (ca, ph, 25-(OH)D, PTH, FGF23, & bone formation & resorption markers)
 - **Skeletal imaging** (thoracic/ lumbar spine films & DEXA)
 - **Histomorphometric** assessments (by bone biopsy)
 - **Cardiovascular imaging** (vascular calcification, echocardiogram)



New conceptual framework moving towards personalized care in adults with CKD-MBD

ACTIVATED VIT D

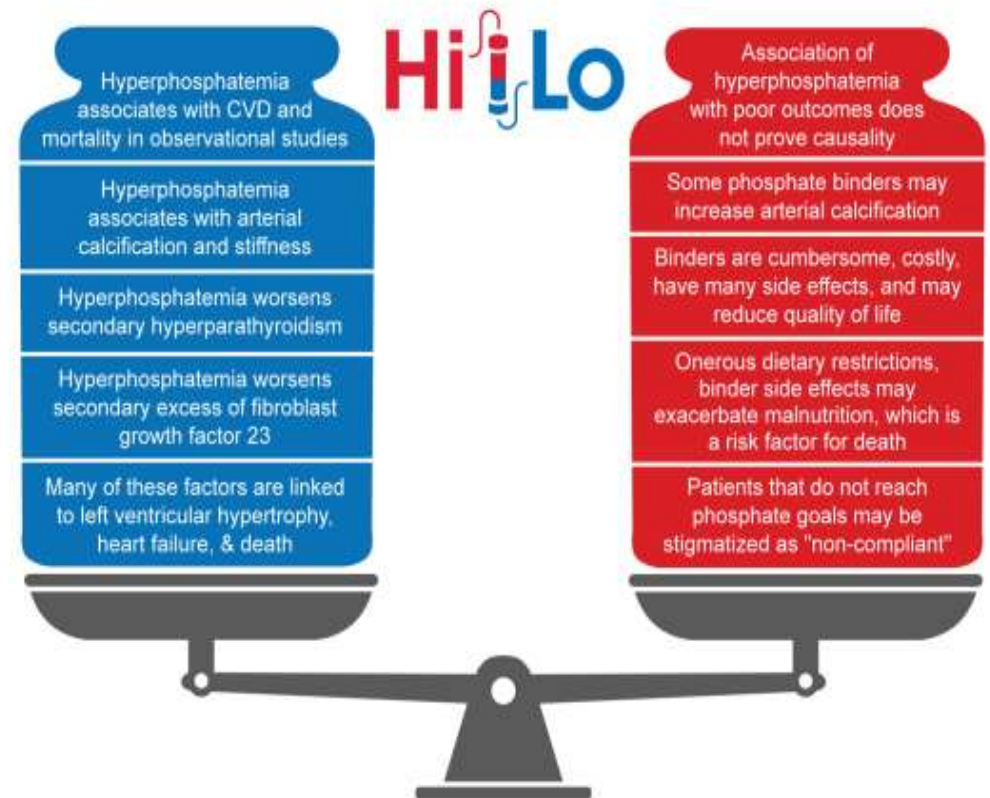
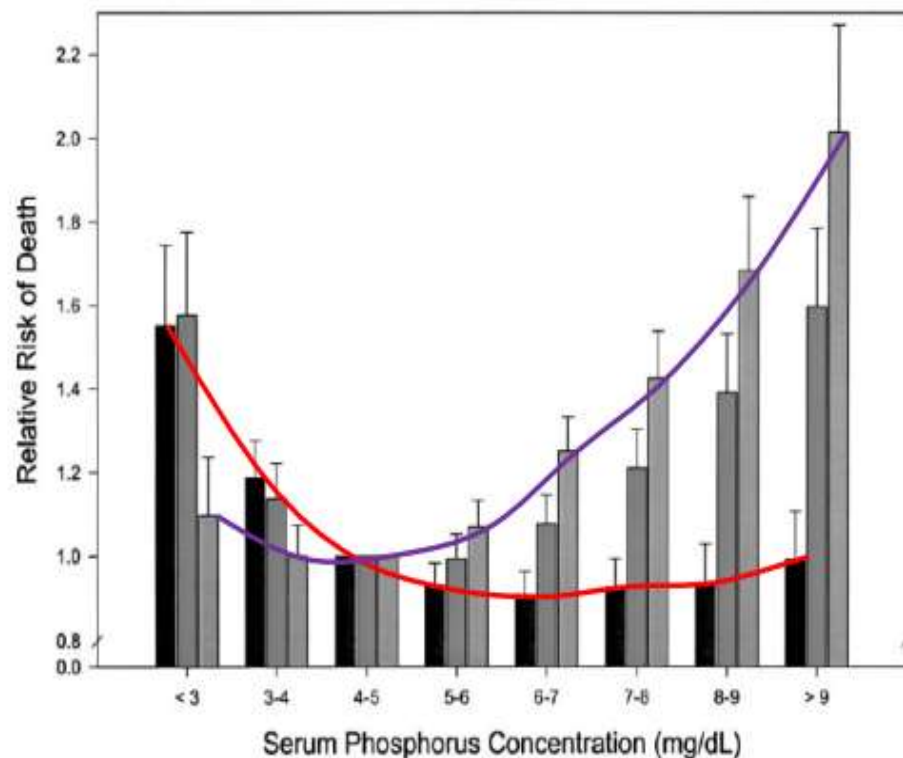
- The 2017 Guideline update made a statement **against routine use of activated vit D in patients with CKD** not on dialysis.
- Indeed, results from the PRIMO & OPERA studies showed activated vit D was associated with an increased risk of hypercalcemia without benefit on cardiac structures.
- However, for controlling PTH, low-dose active vit D could be a helpful supplement to nutritional vit D & dietary phosphate restriction.



TRIALS TO BUILD AN EVIDENCE BASE FOR PHOSPHATE MANAGEMENT IN ESKD

Myles Wolf, MD, MMSc

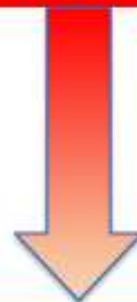
Hemodialysis: serum phosphate & mortality



Block et al. J Am Soc Nephrol 2004; Edmonston D et al. Am J Kidney Dis 2021

Current state

Based on preclinical & observational data, opinion-based guidelines: Maintain P <5.5 mg/dl using binders, diet



But...there is no proof that lowering high phosphate in individual patients helps improve their outcomes!

High-level comparison of trial designs



- Pragmatic
- Targets: <5.5 vs >6.5 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Hierarchical win ratio
 - Death, all cause
 - Hospitalizations, all cause
- No outcome adjudication

PHOSPHATE

- Pragmatic
- Targets: <4.65 vs 6.2 – 7.75 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Time to first event
 - CV death, non-fatal MI, coronary revasc, stroke, PAD event
- Outcomes are adjudicated

KDIGO CONTROVERSIES CONFERENCE ON CHRONIC KIDNEY DISEASE-
MINERAL AND BONE DISORDER: PROGRESS AND KNOWLEDGE GAPS
TOWARDS PERSONALIZING CKD-MBD CARE



ROD and Osteoporosis in CKD

Marie-Hélène Lafage Proust

Osteoporosis in CKD

○ Current Knowledge:

- CKD increases the risk for fracture
- Fractures are osteoporotic (hip, humerus, ..)

○ Combination of Risk factors for fractures

- For primary osteoporosis: Age, low BMI, female gender, falls, prevalent fracture
- From secondary OP : Hypogonadism, diabetes, PP inhibitors, loop diuretics, Glucocorticoids...
- From CKD: KT history, PTX history, dialysis vintage, acidosis, *Phosphate*...

○ Recent data after 2000

- 7566 dialysis patients, 1504 KT patients, Danish background population (4 091 776)

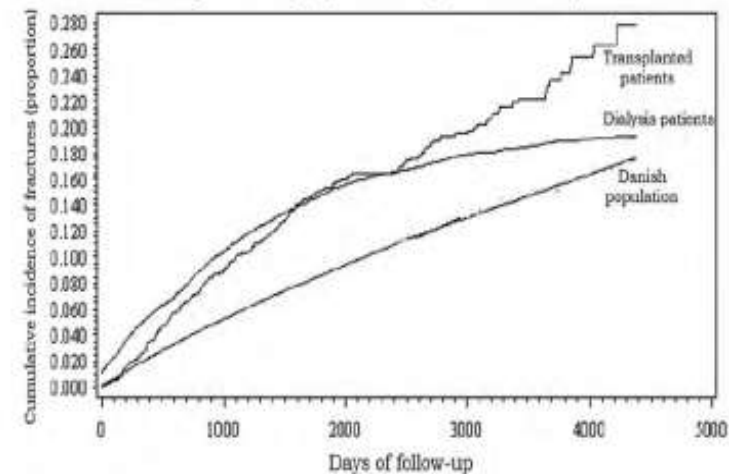


FIGURE 2: Cumulative incidence curves for fractures with death as competing end point.

- (HR) for any fracture:
 - Dialysis: 3.14 (95% CI: 2.97–3.31) 1.85 after adjustment
 - KT: 1.94 (95% CI: 1.72–2.18) 1.82 after adjustment
- Trend for decreased incidence of fractures in KT patients?

Ball AM, et al. JAMA 2002; 288: 3014–3018
 Coco M, Am J Kidney Dis 2000; 36: 1115–1121
 Alem AM, Kidney Int 2000; 58: 396–399
 Covino et al Am J Med Sci 2021

Castro-Alonso et al J. Clin. Med. 2020, 9, 1604;

Hansen D et al Nephrol Dial Transplant (2016) 31: 1654–1662
 Nair S, et al. Am J Transplant, 2014; 14:943–951:
 Perrin et al Transplantation 2016



Which drugs should we use, for whom and when?

• Current Knowledge:

- DXA BMD predicts Fx risk in CKD regardless of CKD stage
- T score <-2.5 discriminant
- Target Population: Pts at high risk Female, age >50...etc
- Sensitivity/ specificity issues

• Better identification of patients at Risk

- TBS, 3D Shaper
- MRI
- FRAX score (or other scores for evaluating the risk for fracture in CKD ?
- Add BTM
- KDIGO (2020, Eval KT candidates)

SECTION 18: BONE AND MINERAL METABOLISM

Disorder (CKD-MBD) guideline (2D).

18.3: Bone mineral density (BMD) should not be measured as part of the transplant evaluation (Not Graded).



Yenchek RH, et al. Clin J Am Soc Nephrol 2012;7:1130–6
West SL, et al. J Bone Miner Res 2015;30:913–9.
VE. Gómez-Islasab et al Bone Rep 2020, 13, 100298
Imori S, et al Nephrol Dial Transplant. 2012;27:345–351.
Prasad B, et al. Can J Kidney Health Dis 2019;2054358119870539

Eun Song et al Transplantation Proceedings, 51, 2704e2709 (2019)
Evenepoel et al Kidney International (2019) 95, 1461–1470



Which drugs should we use?



Treatment of ROD



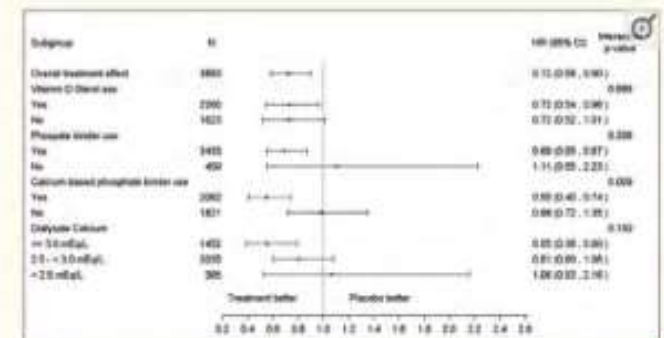
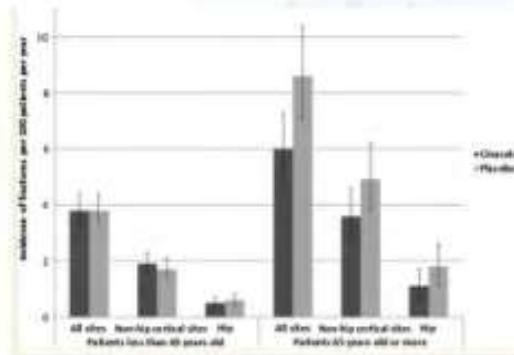
• Current questions:

Effects of SHPT therapy: Differences between calcimimetics and vitamin D analogs on

- BMD
- BTM
- Fractures

↑
Stage 5d.
↓

- Phosphate binders (Ca/non Ca)
- Iron based Phosphate binders
- Vitamin D & derivatives
- Dialysate calcium concentration
- Cinacalcet, Etelcalcetide
- PTX



Which drugs should we use?



Treatment of osteoporosis

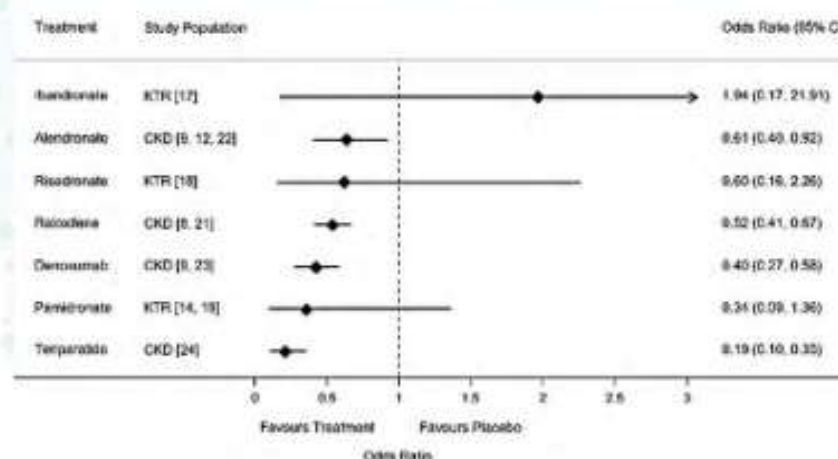


- GFR > 30ml/mn
 - Bisphosphonates,
 - Teriparatide, *abaloparatide*
 - Denosumab
 - Raloxifene
 - Romososumab



- GFR < 30ml/mn
 - Denosumab

17 studies/ 10,214 patients With stage 2–5 CKD, or KT



Forest plots of relative risk of vertebral or clinical fractures

Chen HH et al *Frontiers in Pharmacology* 2022, 822178

Jamal SA, et al. *J Bone Miner Res* 2007;22:503–8; 2. Miller PD, et al. *J Bone Miner Res* 2005;20:2105–15; 3. Ishani A, et al. *J Am Soc Nephrol*, 2008;19:1430, 4; Miller PD, et al. *Osteoporosis Int* 2007;18:59–68; 5-Jamal SA, et al. *J Bone Miner Res* 2011;26:1829–35, Miller et al *JBMR*, 37, 8:2022, 1437–1445.



CONCERNS FOR ADVERSE EFFECTS

- Include the following:
 - (i) **Bisphosphonates**: nephrotoxicity, & osteonecrosis of the jaw, & atypical femoral fractures
 - (ii) **Denosumab**: osteonecrosis of the jaw, atypical femoral fractures, hypoca, rebound bone resorption
 - (iii) **Teriparatide & abaloparatide**: hyperca & hyperuricemia
 - (iv) **Romosozumab**: hypoca, & CV risk.



VASCULAR CALCIFICATION PROGRESSION: NOVEL AGENTS AND FUTURE PERSPECTIVES

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HOW TO MODULATE VC PROGRESSION?



- ❖ CKD-MBD modulation
- ❖ Vitamin K
- ❖ Magnesium
- ❖ SNF472
- ❖ STS



HOW TO MODULATE VC PROGRESSION?



J Am Soc Nephrol. 2022 May; 33(5): 1011–1032.

Published online 2022 May. doi: 10.1681/ASN.2021101327:
10.1681/ASN.2021101327

PMCID: PMC9063901

PMID: [35232774](https://pubmed.ncbi.nlm.nih.gov/35232774/)



- ❖ **CKD-MBD modulation**
- ❖ Vitamin K
- ❖ Magnesium
- ❖ SNF472
- ❖ STS

Interventions To Attenuate Vascular Calcification Progression in Chronic Kidney Disease: A Systematic Review of Clinical Trials

[Chelsea Xu](#), ¹ [Edward R. Smith](#), ^{1,2} [Mark K. Tong](#), ^{1,2} [Irene Ruderman](#), ^{1,2} and [Nigel D. Toussaint](#) ^{1,2}

(...) interventions were compared with placebo, other comparators, or standard of care. *We reviewed 77 heterogeneous clinical trials (63 randomized)* involving 6898 participants. Therapy involving magnesium or sodium thiosulfate appears the most promising, with consistent findings of attenuation of vascular calcification progression, but *evaluable studies were small and of short duration*. Many other studies had inconclusive or conflicting outcomes (...)

HOW TO MODULATE VC PROGRESSION?



Vitamin K1 or K2?

- ❖ *Eelderink et al American Journal of Transplantation 23 (2023) 520–530*: Effect of vitamin K supplementation on serum calcification propensity and arterial stiffness in vitamin K-deficient kidney transplant recipients: A double-blind, randomized, placebo-controlled clinical trial → *no effect on CPP but positive impact on arterial stiffness*
- ❖ *Holden et al Nephrology Dialysis Transplantation (2023) 38: 746–756*: Inhibit progression of coronary artery calcification with vitamin K in hemodialysis patients (the iPACK-HD study): a randomized, placebo-controlled multi-center, pilot trial → *no effect on CAC but higher mortality among treated patients*
- ❖ *Oikonomakiet al International Urology and Nephrology (2019) 51:2037–2044*: The effect of vitamin K2 supplementation on vascular calcification in haemodialysis patients: a 1-year follow-up randomized trial → *no effect on aortic calcification*

.....On going trials.....

- ❖ *Haroon et al. Medicine (2020) 99:36*. Treatment to reduce vascular calcification in hemodialysis patients using vitamin K (Trevasc-HDK). A study protocol for a randomized controlled trial
- ❖ *Krueger et al Nephrol Dial Transplant (2014) 29: 1633–1638*. Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol



Vit K compounds did not consistently attenuate
calcification progression in patients with
advanced CKD

HOW TO MODULATE VC PROGRESSION?



Magnesium

.....*On going trials*.....

Disclosures
VC progression
New treatment
Future perspectives

- ❖ *Leenders et al BMJ Open 2022 Nov 21;12(11):e063524. Magnesium in chronic haemodialysis (MAGIC-HD): a study protocol for a randomised controlled trial to determine feasibility and safety of using increased dialysate magnesium concentrations to increase plasma magnesium concentrations in people treated with haemodialysis*
- ❖ *Vermeulen et al Trials 2022 Sep 12;23(1):769. Reversal Of Arterial Disease by modulating Magnesium and Phosphate (ROADMAP-study): rationale and design of a randomized controlled trial assessing the effects of magnesium citrate supplementation and phosphate-binding therapy on arterial stiffness in moderate chronic kidney disease*

SNF472

- SNF472 is a hexaphosphate phytate usually present in wheat.
- This molecule possesses a pyrophosphate like structure & is being investigated for its potential to inhibit calcification.
- It is minimally absorbed in human intestine, but with parenteral administration, it reaches high plasma concentrations.

HOW TO MODULATE VC PROGRESSION?

CaLIPSO trial

Bellasi et al Clinical Kidney Journal, 2021;14(1):366–374

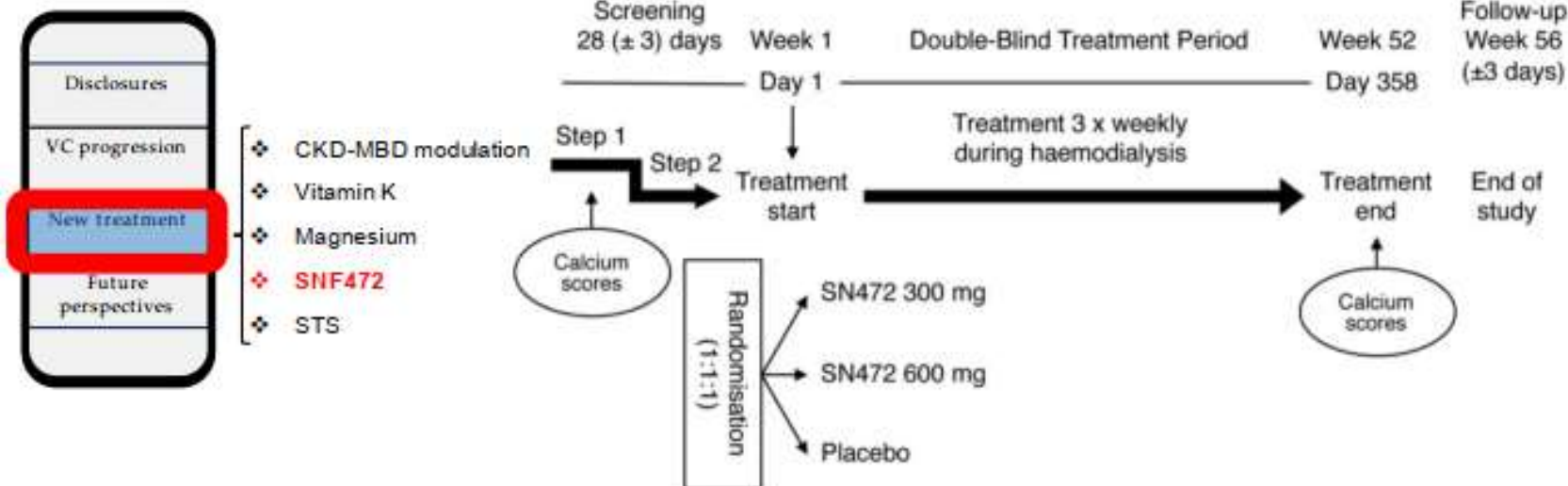


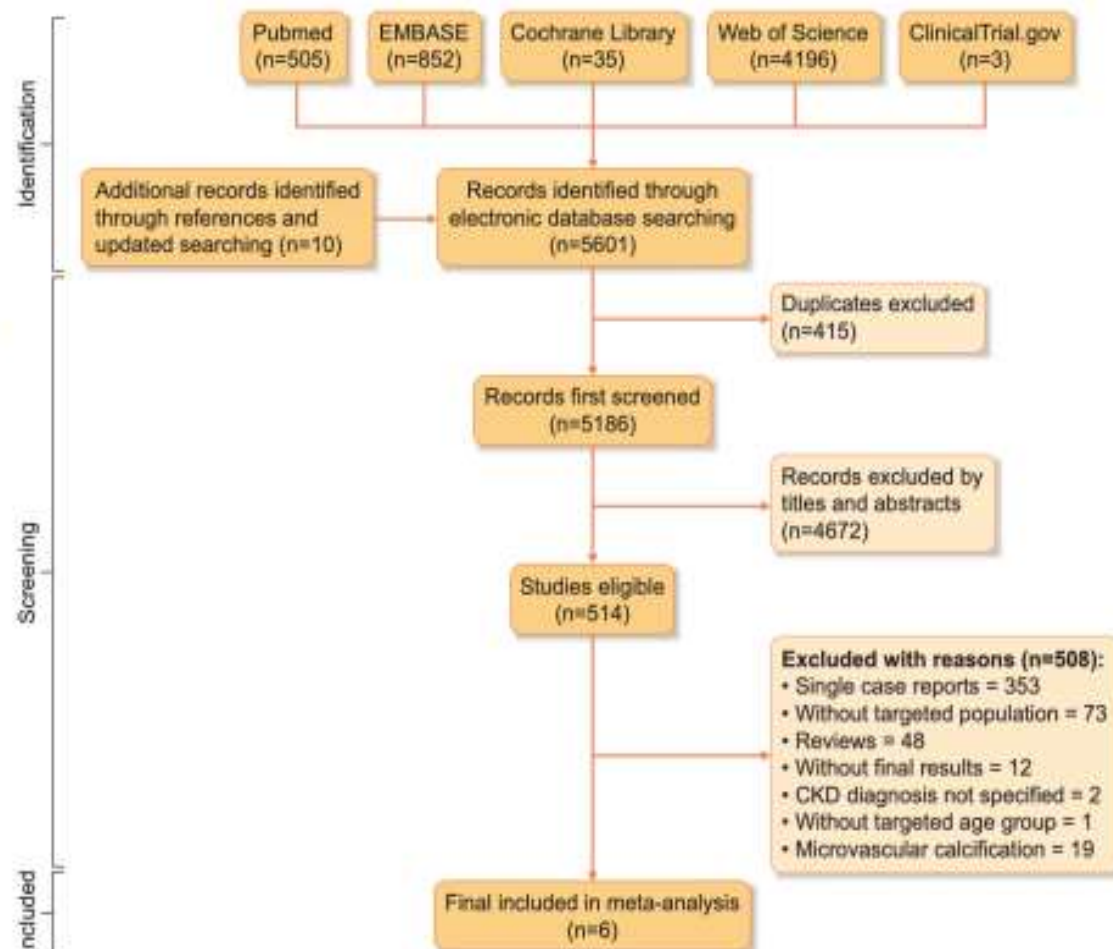
FIGURE 1: CaLIPSO trial flow chart. In Step 1, potential study participants who satisfied the inclusion and exclusion criteria underwent an assessment by MDCT scanner to determine the Agatston score for the coronary artery, as well as dual-energy X-ray absorptiometry for BMD of the total hip and femoral neck. Patients with confirmed calcification of the coronary artery (initially 100–2000 U; later 100–3500 U) at Step 1 entered Step 2 to complete all other screening assessments and confirm all eligibility criteria were met.

HOW TO MODULATE VC PROGRESSION?

Wen et al. Nephrol Dial Transplant (2023) 38: 733–745



- ❖ CKD-MBD modulation
- ❖ Vitamin K
- ❖ Magnesium
- ❖ SNF472
- ❖ **STS**

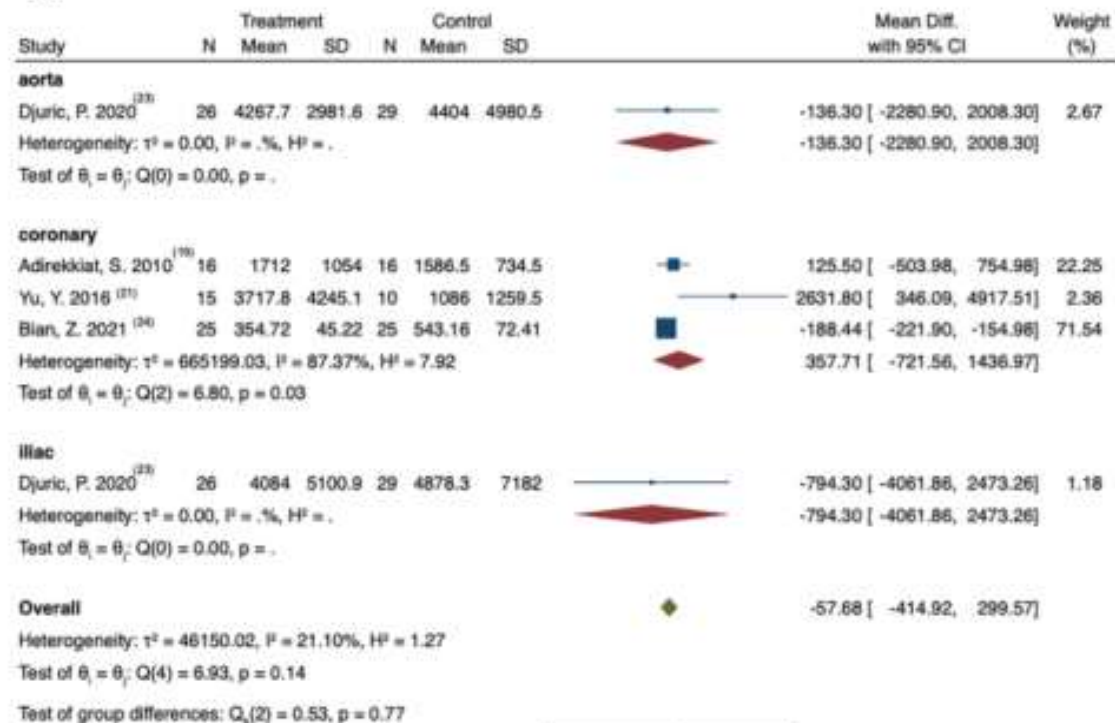


HOW TO MODULATE VC PROGRESSION?

Wen et al. Nephrol Dial Transplant (2023) 38: 733–745

A

Post-interventional Agatston Score



Random-effects REML model
Sorted by: _meta_id

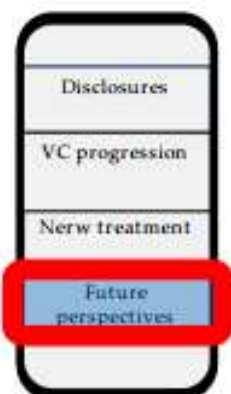
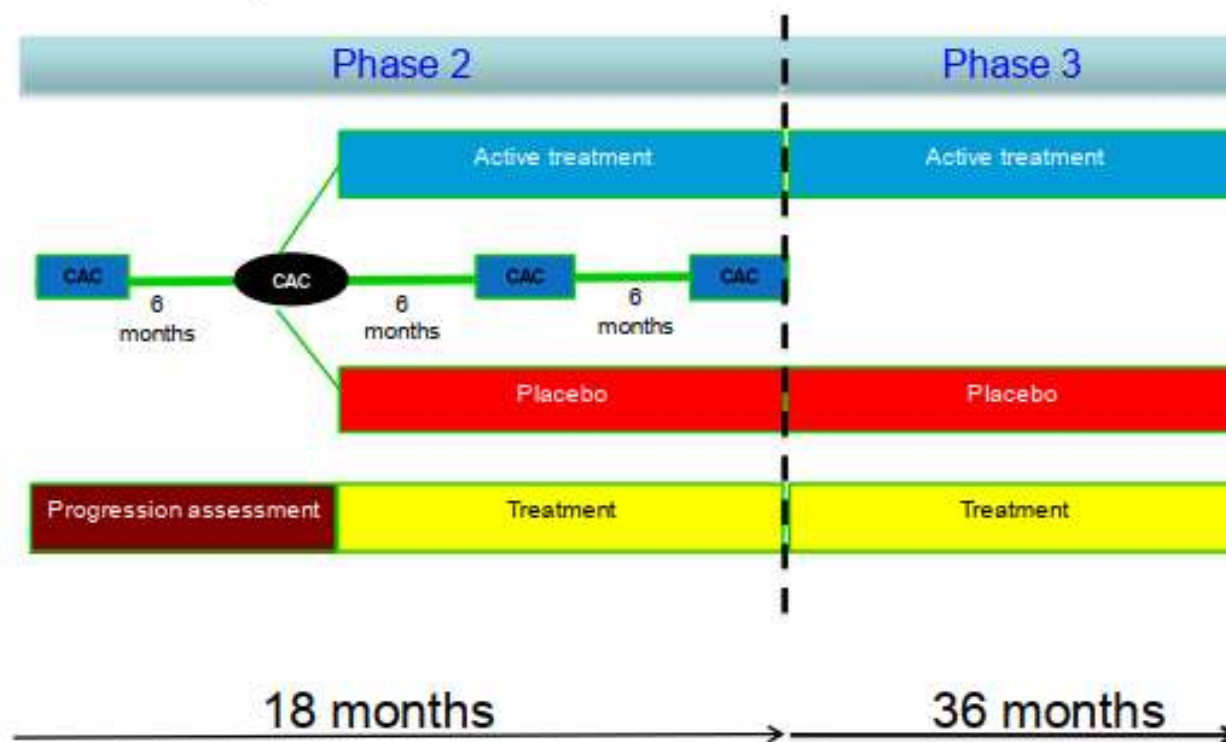
-5000 0 5000



- ❖ CKD-MBD modulation
- ❖ Vitamin K
- ❖ Magnesium
- ❖ SNF472
- ❖ STS

WHAT ARE THE NEXT STEPS?

- Hard outcome study?



TREATMENT

- Since 2017, several randomized controlled trials & observational & post hoc analyses compared lanthanum carbonate or sevelamer carbonate with ca-containing binders or placebo, & overall there was **not a consistent benefit** in terms of reduced progression of vascular calcification associated with the ca-free compounds.



CONTROVERSIES AND TRENDS IN PTH CONTROL (ADULTS) PART 1

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University Hospital Germans Trias i Pujol (Can Ruti)
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Table 1. Different target ranges for dialysis patients

Guideline	Phosphorus	Calcium (corrected)	Intact PTH
KDOQI	3.5–5.5 mg/dL	8.4–9.5 mg/dL	150–300 pg/mL
KDIGO	Normal range	Normal range	2–9 times the upper limit
JSDT*	3.5–6.0 mg/dL	8.4–10.0 mg/dL	60–240 pg/mL

PTH, parathyroid hormone; KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; JSDT, Japanese Society for Dialysis Therapy. * 2013 version.

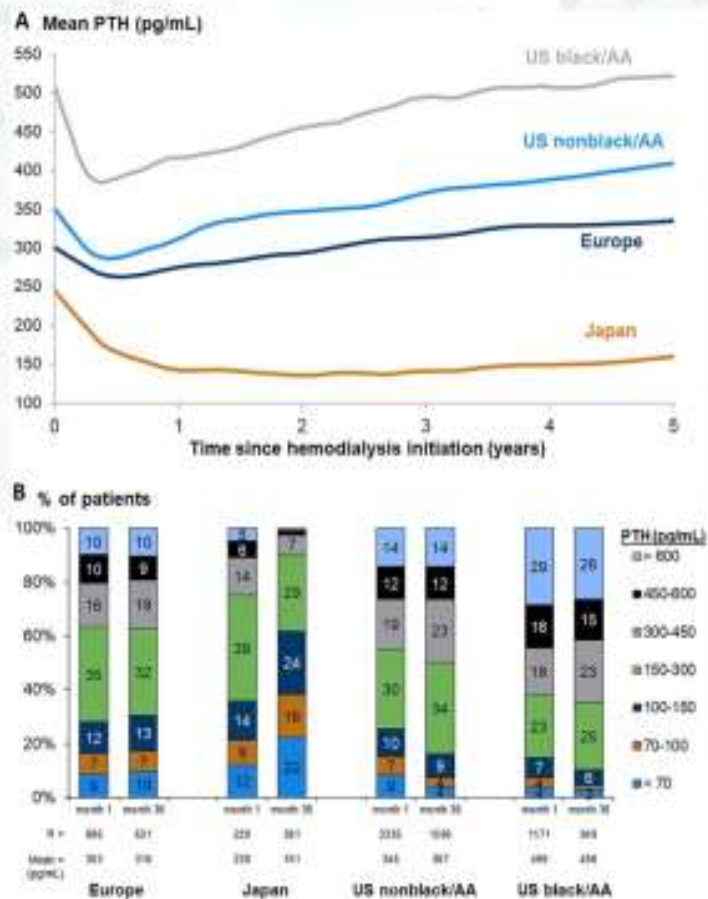
#Japan: Lab at first dialysis session of the week

What are the reasons for such a discrepancy?

Fukagawa et al: Kidney Dis, 2017



SHPT management among DOPPS countries



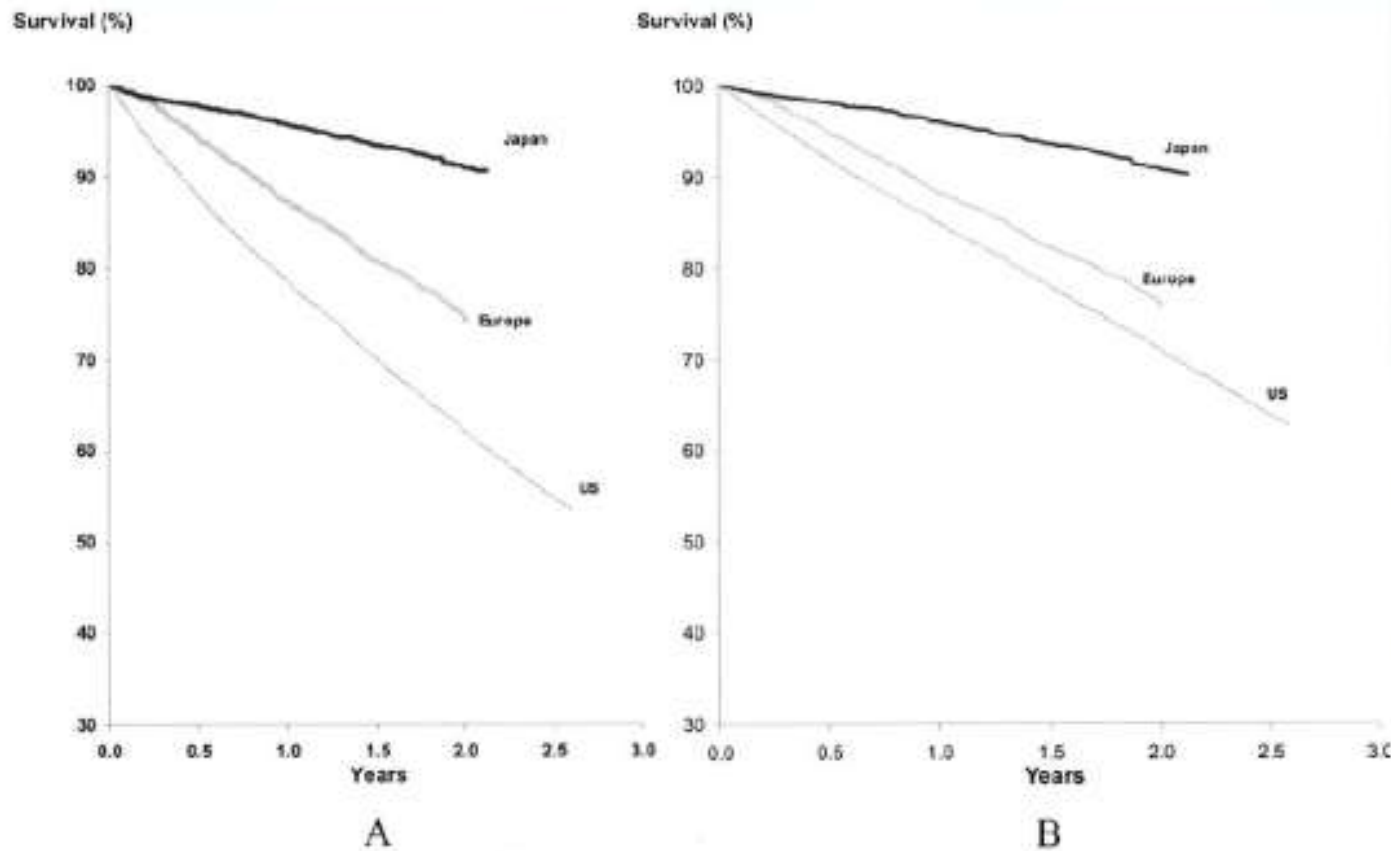
Chan K: Kidney Med . 2019



Reasons for the different targets of PTH control

- Race
- Available drugs
- Medical Care System
- Purposes of PTH Control
- Individualization?

Survival Curve of Dialysis Patients (DOPPS)



Racial Difference

BMI

Food

Adherence

Dialysis Protocol

Time

Methods

Dialysate

Low inflammation

Water purity

Vascular access

More intensive Care

Patient-doctor contact

Routine laboratory tests

Chronic Kidney Disease-Mineral and Bone Disorder in Asia

Masafumi Fukagawa^a Hirotaka Komaba^{a, b}

^aDivision of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, and ^bThe Institute of Medical Sciences, Tokai University, Isehara, Japan

Table 3. Drugs available for chronic kidney disease-mineral and bone disorder in Asian countries and regions

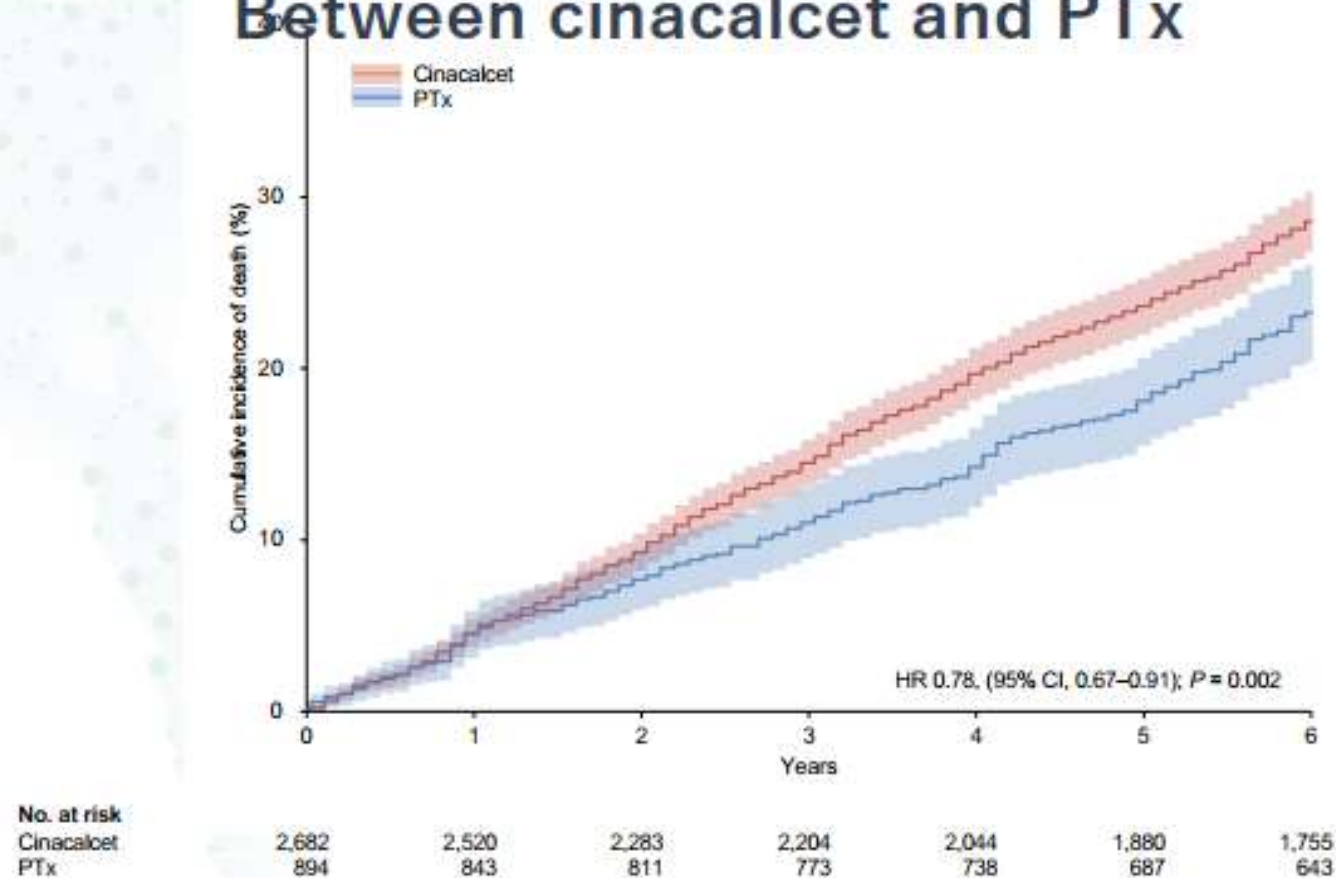
Drug class	Drugs (generic name)	Japan	Korea	China	Taiwan	Hong Kong	Singapore	Malaysia	Thailand
VDRA	Oral	Rocaltriol [®] (calcitriol)	✓	✓	✓	✓	✓	✓	✓
		Alfarol [®] (alfacalcitriol)	✓		✓				
		Horne [®] /Fulstan [®] (falcacalcitriol)	✓						
		Calcitriol generics	✓	✓	✓	✓	✓	✓	✓
	IV	Calcijex [®] (calcitriol)	✓						
		Zemplar [®] (paricalcitol)	✓	✓	✓	✓	✓	✓	
		Oxazol [®] (maxacalcitol)	✓						
		Calcitriol generics	✓	✓				✓	✓
P-binder	Renagel [®] /Phosblock [®] (sevelamar HCl)		✓		✓	✓			
	Renvela [®] (sevelamar CO ₂)		✓	✓	✓	✓	✓	✓	✓
	Kiklin [®] (bicalomer)		✓						
	Riona [®] /Nephoxil [®] (ferric citrate)		✓		✓				
	P-Tol [®] /Velphoro [®] (sacrosferric oxyhydroxide)		✓	✓*			✓		
	Calcium-based phosphate-binder generics		✓	✓	✓	✓	✓	✓	✓
Calcimimetics	Begpara [®] (cinacalcet)		✓	✓	✓	✓	✓	✓	✓
	Parabiv [®] (etelcalcetide)		✓*						

IV, intravenous. Shaded lines, no reimbursement. * Approved but not yet launched, as of December 2016.

Purposes of PTH Control in CKD

- Easier control of serum phosphorus and calcium level
- Bone turnover
 - Bone fracture
 - Vascular calcification
- Prevent the progression of parathyroid hyperplasia
- Energy wasting
- Survival
- CV risk

Kaplan-Meier cumulative incidence of death Between cinacalcet and PTx



Komaba H et al. J Clin Endocrinol Metab, 2022



CONTROVERSIES AND TRENDS IN ADULT PTH CONTROL

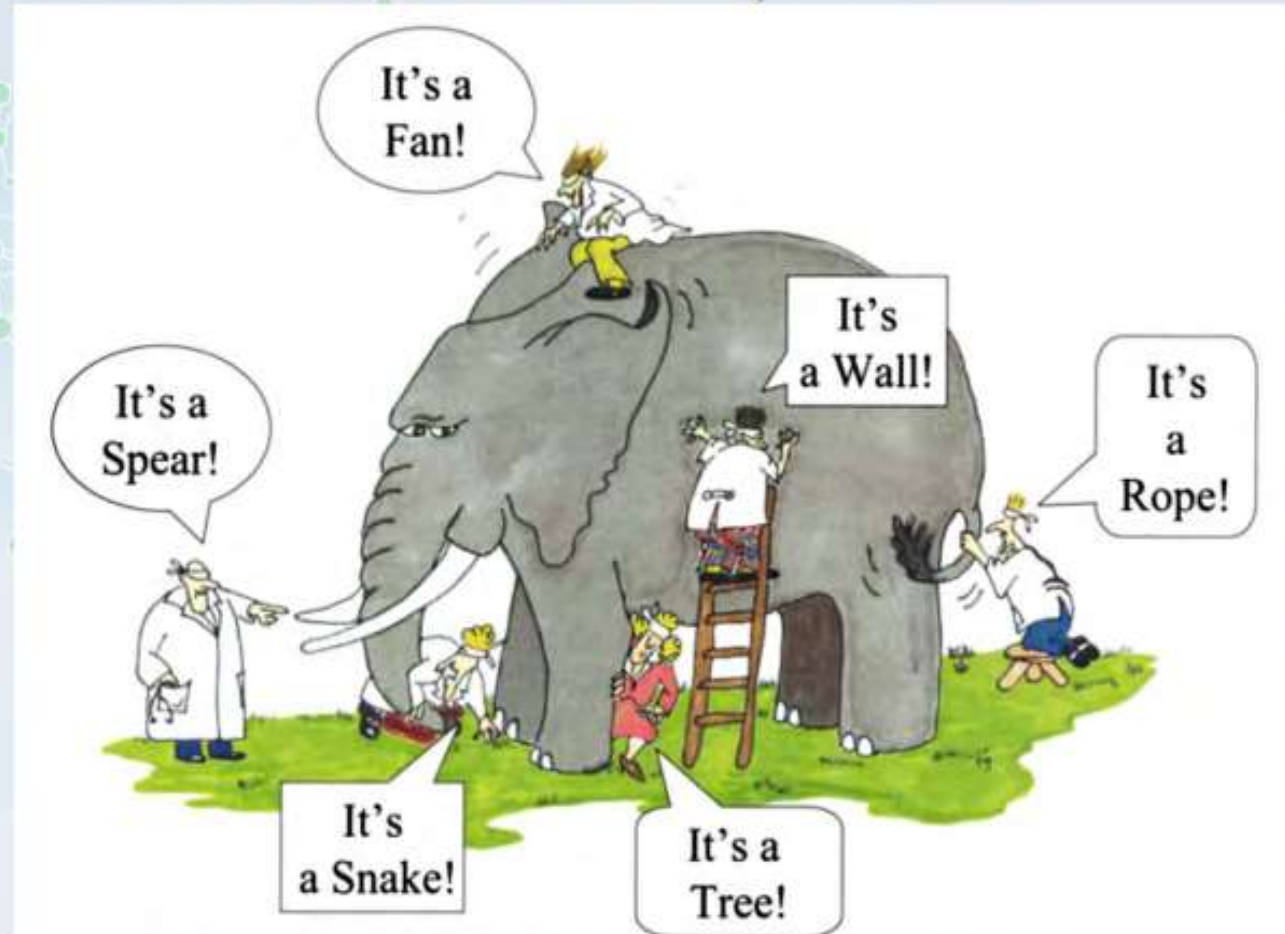
- Should the PTH target ranges be Individually optimized based on the control purposes and patients' backgrounds?

Age
Sex
Race
Diabetes
High risk patients

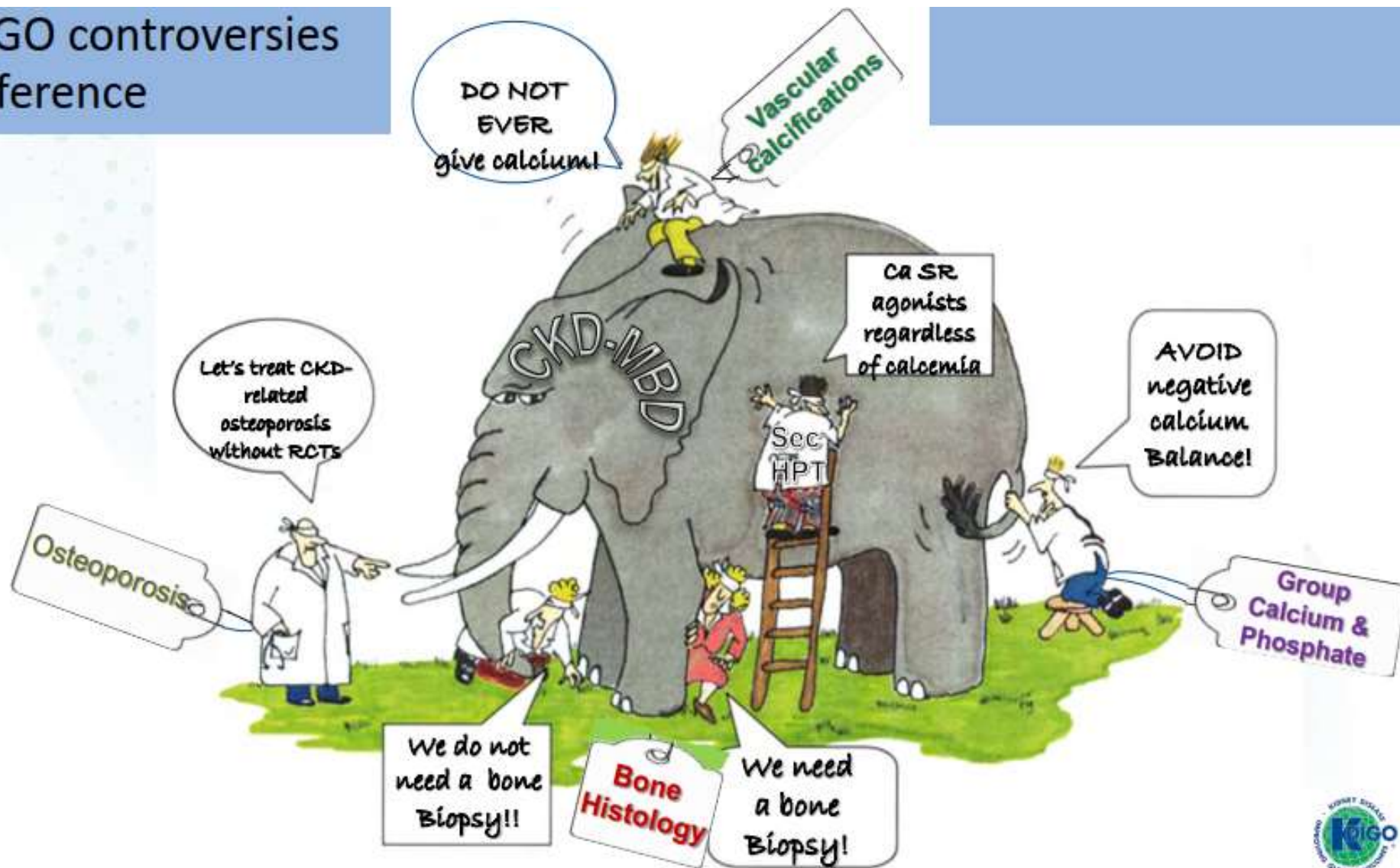
CALCIPHYLAXIS

- Use of vit K antagonists for anticoagulation in patients undergoing dialysis is associated with an up to 11-fold increased risk of developing calciphylaxis.

The tale of the 6 blind men and the elephant



KDIGO controversies conference



[illegible]