Concentrazione di calcio nel dialisato, dieta e vitamina D per la prevenzione della CKD-MBD

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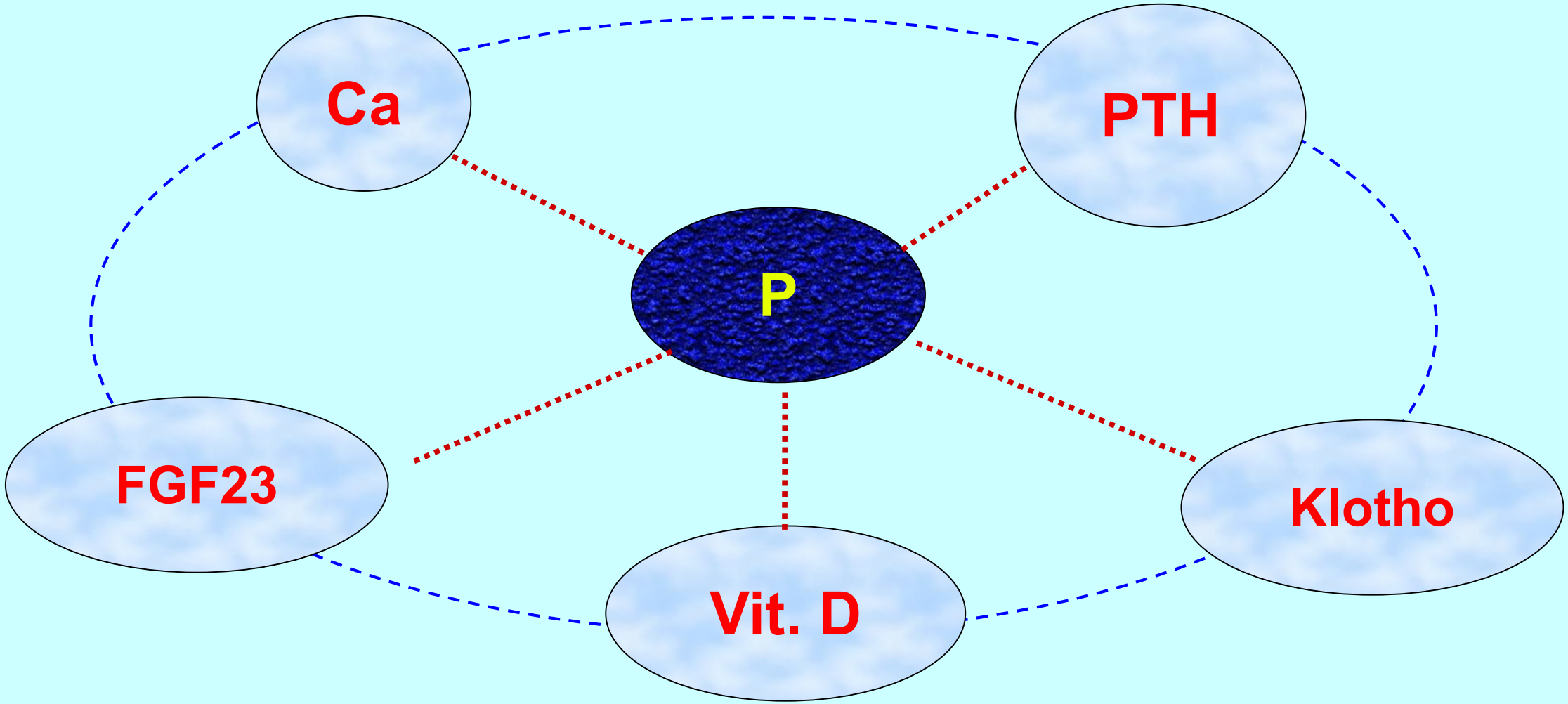
Lecco, 19 Ottobre 2023

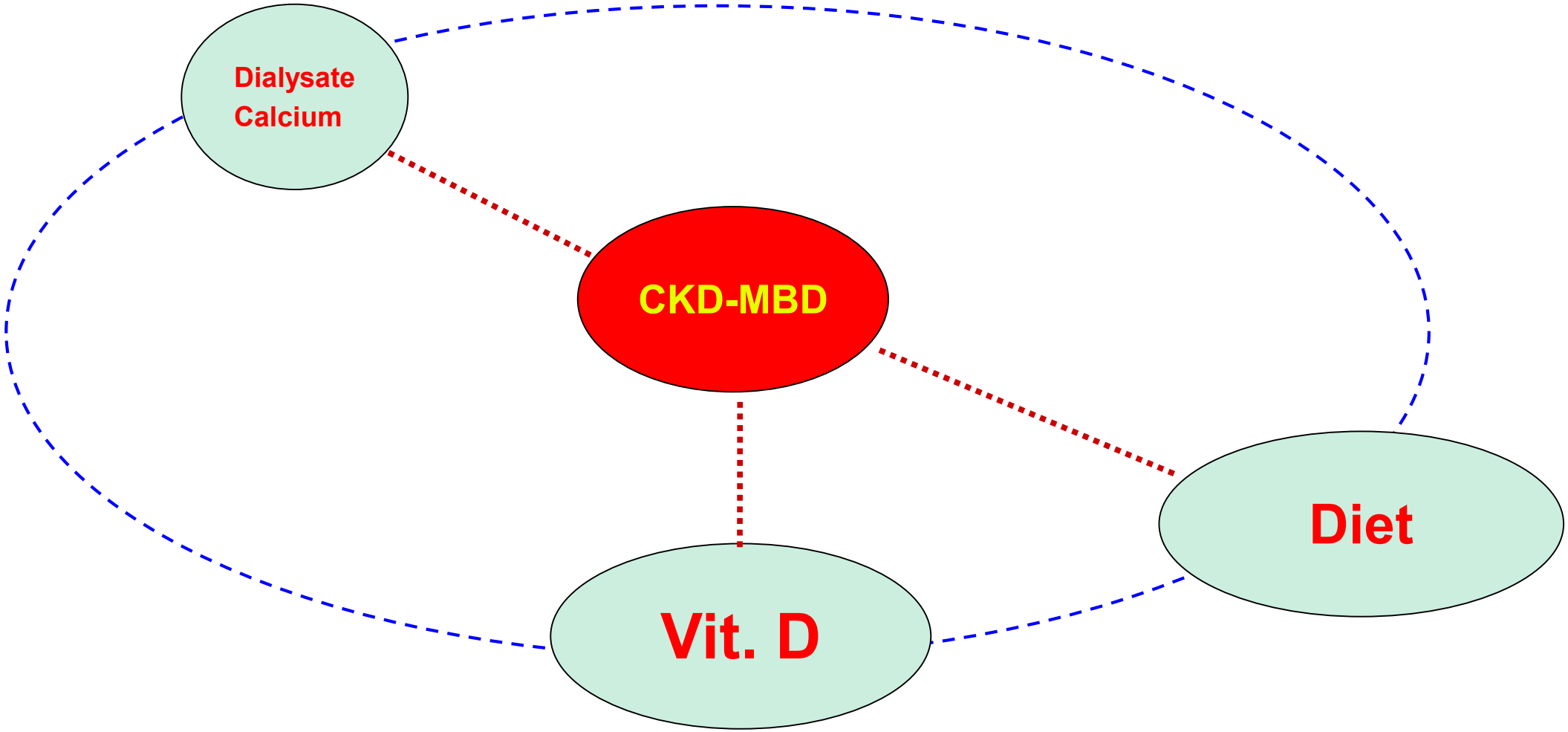
DISS

Phosphate, CKD-MBD, and beyond



Cozzolino M et al. *Clin Kidney J* 2021
Cozzolino M et al. *NDT* 2018

CKD-MBD and beyond…..



Cozzolino M and Mazzaferro S. *Curr Vasc Pharmacol.* 2010
Cozzolino M et al. *NDT* 2020

Dialysate Calcium

Seminars in Dialysis
THIRTY YEARS: LESSONS LEARNED IN DIALYSIS

Dialysate Composition for Hemodialysis: Changes and Changing Risk

Rita L. McGill and Daniel E. Weiner
Division of Nephrology, Tufts Medical Center, Boston, Massachusetts

Dialysate Calcium

4. Potential risks and benefits associated with dialysate calcium choices

	Higher dialysate calcium	Lower dialysate calcium
Potential benefits	• Improved hemodynamic stability • Reduced acute arrhythmia potential • Lower PTH levels • May facilitate cinacalcet use	• Reduced substrate for vascular calcification • May help overcome adynamic bone disease
Potential risks	• Increased vascular calcification, particularly in the presence of other calcification promoters • Suppression of PTH and development of adynamic bone disease	• Increased PTH levels • Requirement for higher vitamin D analog doses with subsequent increased phosphorus • Increased intradialytic hypotension

PTH, parathyroid hormone.

PLOS ONE

Published: July 6, 2020

Dialysate Calcium

RESEARCH ARTICLE

Effects of the dialysate calcium concentrations and mineral bone disease treatments on mortality in The French Renal Epidemiology and Information Network (REIN) registry

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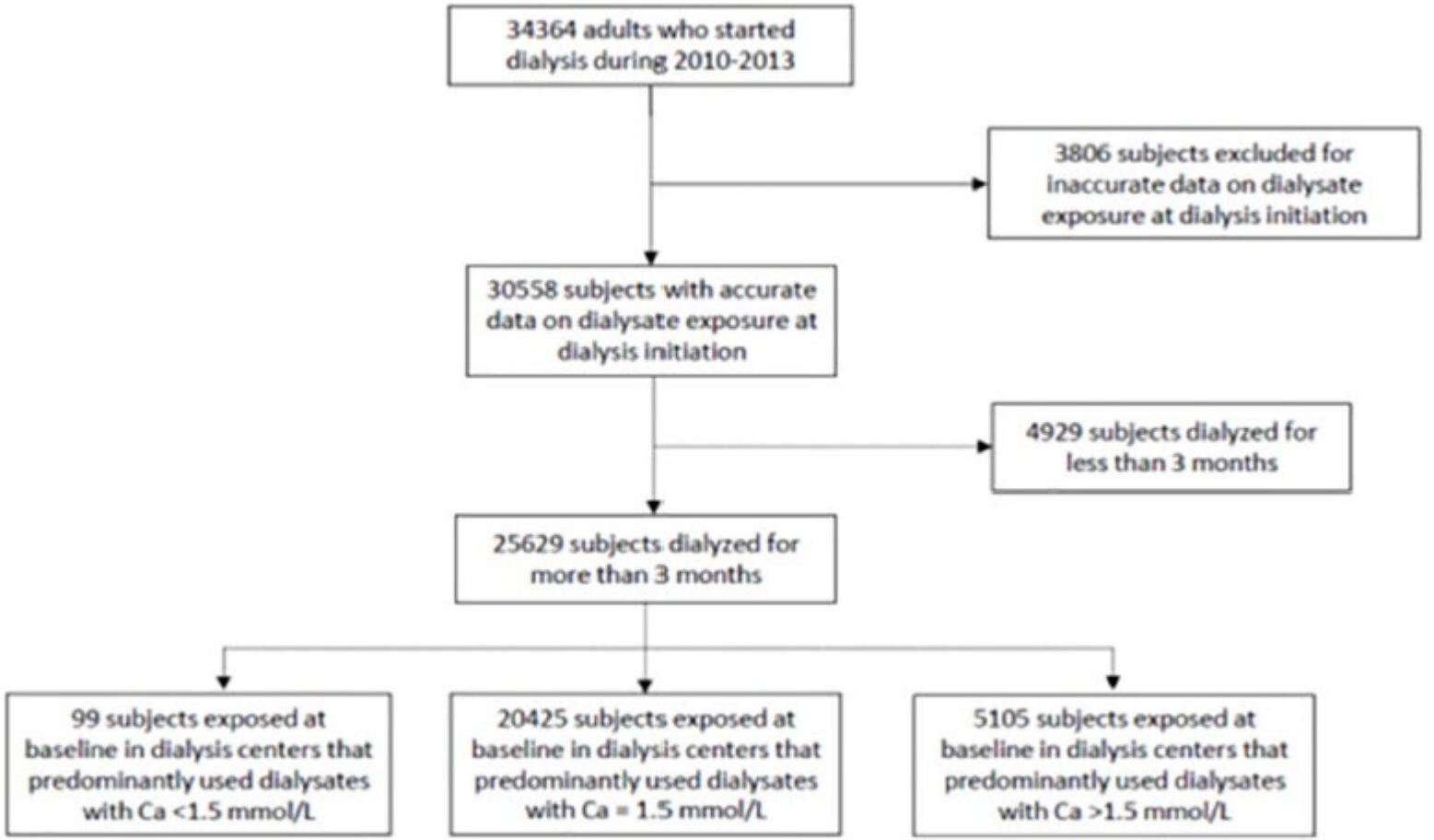
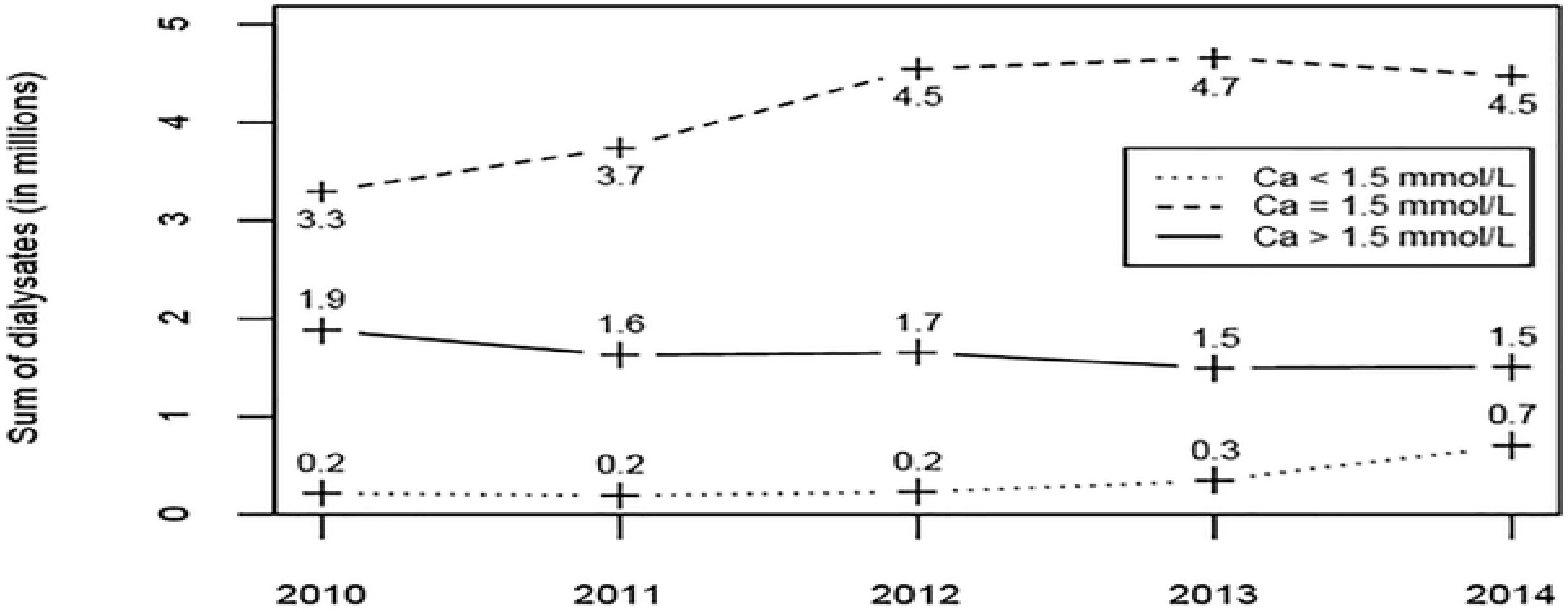


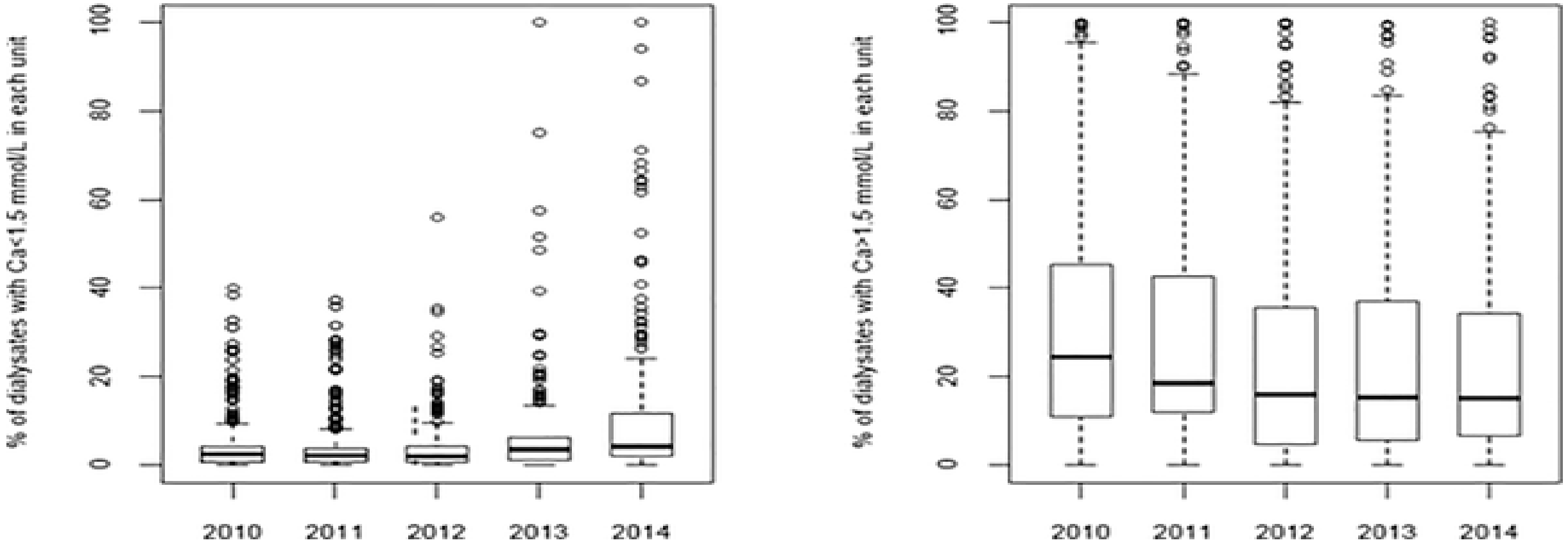
Fig 1. Flow chart.

Fig 2. Overall sales of dialysate in France from 2010 to 2014, as a function of the calcium concentration.



Lambert O, Couchoud C, Metzger M, Choukroun G, Jacquelinet C, et al. (2020) Effects of the dialysate calcium concentrations and mineral bone disease treatments on mortality in The French Renal Epidemiology and Information Network (REIN) registry. PLOS ONE 15(7): e0235135. https://doi.org/10.1371/journal.pone.0235135
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0235135

Fig 3. Boxplots of the dialysis units' percentage use of dialysate calcium concentrations between 2010 and 2014.



Lambert O, Couchoud C, Metzger M, Choukroun G, Jacquelinet C, et al. (2020) Effects of the dialysate calcium concentrations and mineral bone disease treatments on mortality in The French Renal Epidemiology and Information Network (REIN) registry. PLOS ONE 15(7): e0235135. https://doi.org/10.1371/journal.pone.0235135
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0235135

Table 4. First-year medication prescriptions as a function of the primary facility-level dialysate calcium concentration at baseline, for the 21497 patients identified in the French national health database.

		Main facility-level dialysate Ca concentration	
	All (N = 21497)	Ca≤1.5 (N = 17135)	Ca>1.5 (N = 4362)
Active vitamin D			
% of patients exposed	15.8%	15.7%	16%
Dose μg/d	0.23 (0.1–0.35)	0.24 (0.1–0.37)	0.21 (0.08–0.29)
Native vitamin D			
% of patients exposed	56%	57%	51.8%
Dose UI/d	1948 (986–3288)	1953 (989–3288)	1920 (910–3231)
Calcium			
% of patients exposed	42.8%	41.9%	46.4%
Dose mg/d	997 (508–1736)	986 (506–1721)	1035 (530–1779)
Cinacalcet			
% of patients exposed	8.4%	8.5%	7.9%
Dose mg/d	27 (14–37)	27 (15–38)	25 (11–35)
Lanthanum			
% of patients exposed	10.9%	11%	10.4%
Dose mg/d	1098 (506–1849)	1085 (500–1878)	1125 (536–1737)
Sevelamer			
% of patients exposed	30.7%	30.8%	29.9%
Dose mg/d	2526 (1419–3975)	2526 (1412–4012)	2549 (1426–3945)

data are presented as (i) the percentage of patients having received the drug, and (ii) the median [interquartile range] daily dose among patients having received the drug.

https://doi.org/10.1371/journal.pone.0235135.t004

Lambert O, Couchoud C, Metzger M, Choukroun G, Jacquelinet C, et al. (2020) Effects of the dialysate calcium concentrations and mineral bone disease treatments on mortality in The French Renal Epidemiology and Information Network (REIN) registry. PLOS ONE 15(7): e0235135. https://doi.org/10.1371/journal.pone.0235135
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0235135

Table 6. Person-years of exposure and percentages of events, by dialysate group at baseline.

	Main facility-level calcium concentration at baseline	
N = 25629	**Ca ≤ 1.5 mmol/L (N = 20524)**	**Ca >1.5mmol/L (N = 5105)**
Person-years of exposure	36667.4	9764.1
Events% (n)		
At home	0.2% (51)	0.2% (8)
Deceased	27% (5495)	28% (1451)
Loss to follow-up	0.4% (84)	0.4% (19)
Moved out to France	0% (6)	0.1% (7)
Switched to peritoneal dialysis	0.9% (188)	0.7% (35)
Switched to a censored dialysis center	5% (1045)	4% (227)
Transplanted	12% (2475)	12% (598)
Discontinuation of dialysis	4% (767)	4% (208)
Total events	49% (10111)	50% (2553)
Rate for 100 person-years		
Mortality rate	15%	14.9%
Transplantation rate	6.7%	6.1%

https://doi.org/10.1371/journal.pone.0235135.t006

Lambert O, Couchoud C, Metzger M, Choukroun G, Jacquelinet C, et al. (2020) Effects of the dialysate calcium concentrations and mineral bone disease treatments on mortality in The French Renal Epidemiology and Information Network (REIN) registry. PLOS ONE 15(7): e0235135. https://doi.org/10.1371/journal.pone.0235135
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0235135

Conclusions

Dialysate calcium concentration of 1.5 mmol/L was used by 81% of the dialysis centers in 2010 and in 83% in 2014. Most centers were using several formulas in up to 78% for 3 formulas in 2010 to 86% in 2014. In full adjusted Cox survival analyses, the percentage of calcium >1.5 mmol/L and <1.5 mmol/l by center and the number of formula used per center were not associated with survival. Depending on the daily dose used, the MBD therapies were associated with survival improvement for calcium, native vitamin D, active vitamin D, sevelamer, lanthanum and cinacalcet in the second and third tertiles of dose.

Diet

SHPT

On the Pathogenesis of Hyperparathyroidism in Chronic Experimental Renal Insufficiency in the Dog

The Journal of Clinical Investigation Volume 50 1971

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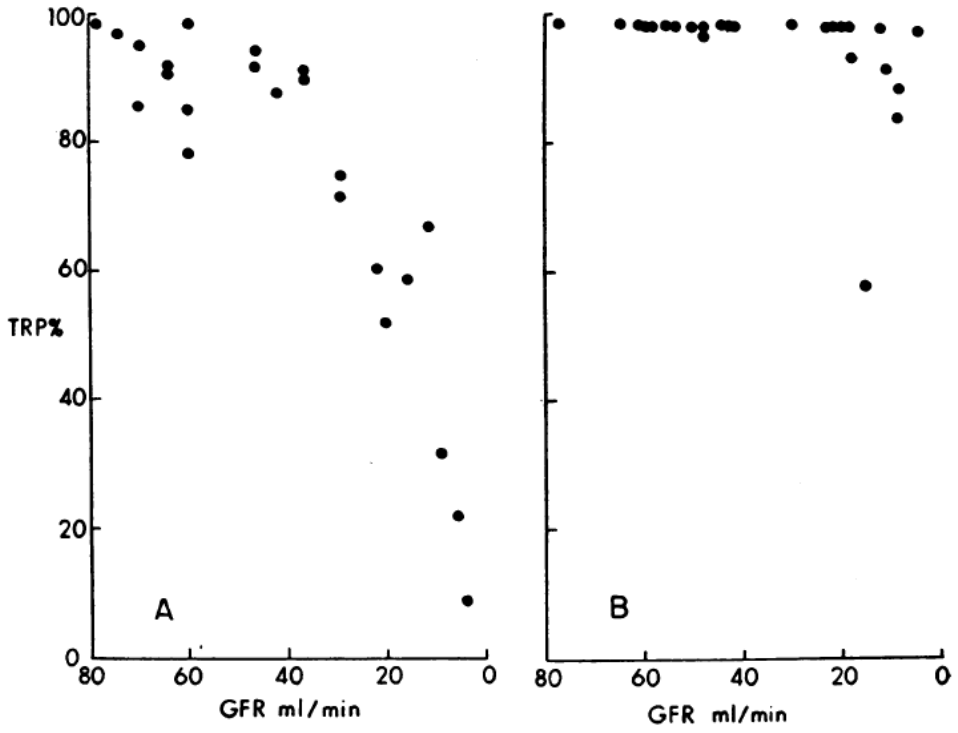
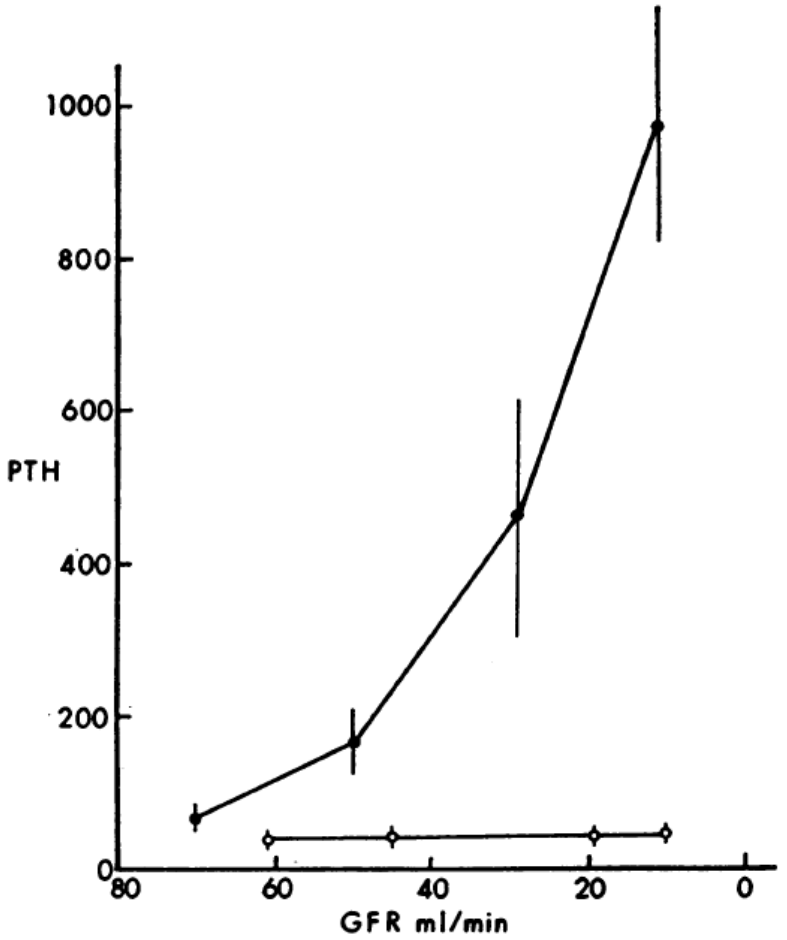
From the Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri 63110, and the Department of Medicine, Michael Reese Hospital and Medical Center and the University of Chicago Pritzker School of Medicine, Chicago, Illinois 60637



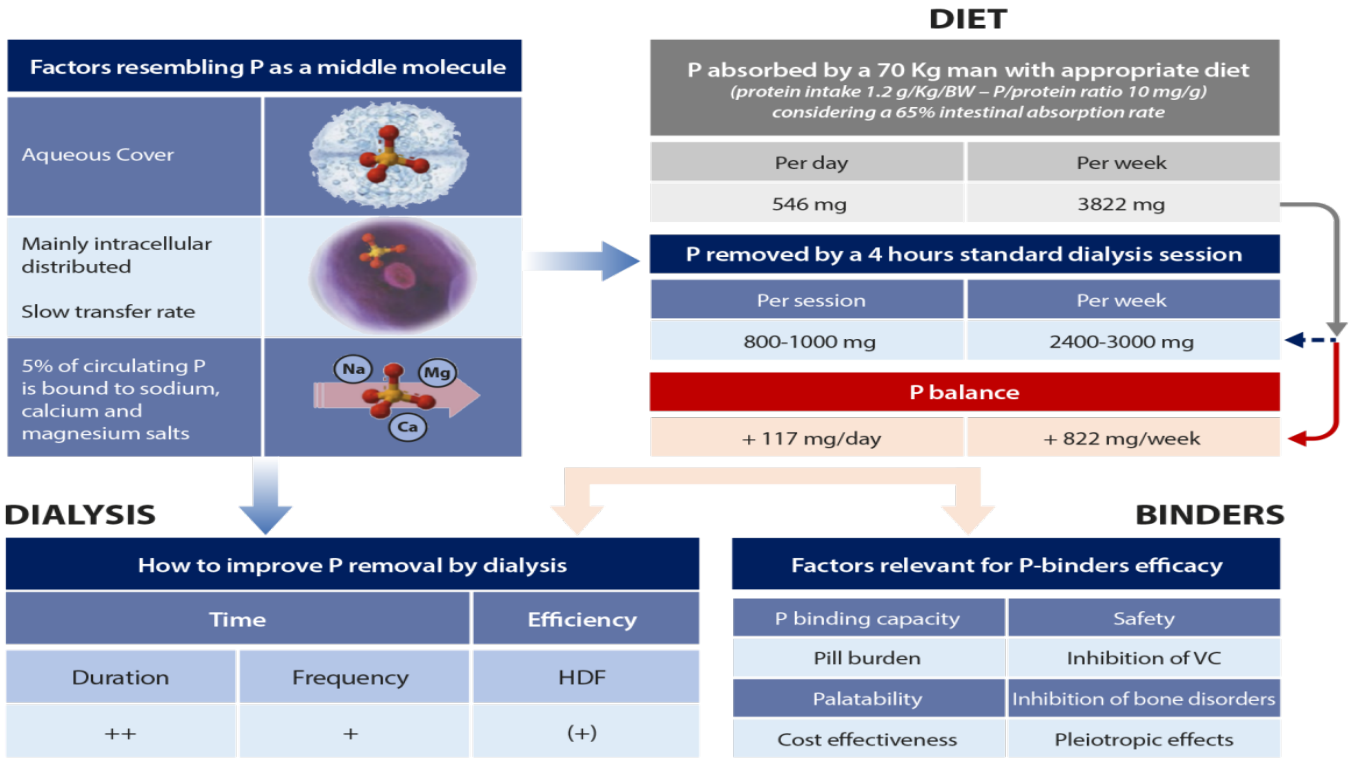


- **Hyperphosphatemia** is a strong predictor of **mortality** in advanced **CKD** and is corrected via diet, phosphorus binders, and dialysis.

Review

Phosphate balance in ESRD: diet, dialysis and binders against the low evident masked pool

A. Galassi, A. Cupisti, A Santoro, M. Cozzolino



P: Phosphorus, HDF: haemodiafiltration, VC: vascular calcification

Galassi A, *et al*. Phosphate balance in ESRD: diet, dialysis and binders against the low evident masked pool. *Journal of Nephrology*. 2015;28;415-429.

- **Dietary counseling** should encourage the consumption of **foods** with the **least amount of inorganic or absorbable phosphorus**, low phosphorus-to-protein ratios, and adequate protein content, and **discourage excessive calcium intake in high-risk patients**.

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 4 June 2019*

doi: 10.2903/j.efsa.2019.5674

Re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as food additives and the safety of proposed extension of use

EFSA Panel on Food Additives and Flavourings (FAF),
Maged Younes, Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul Fowler,
Maria Jose Frutos Fernandez, Peter Fürst, Rainer Gürtler, Trine Husøy, Wim Mennes,
Peter Moldeus, Agneta Oskarsson, Romina Shah, Ine Waalkens-Berendsen, Detlef Wölfle,
Peter Aggett, Adamasco Cupisti, Cristina Fortes, Gunter Kuhnle, Inger Therese Lillegaard,
Michael Scotter, Alessandra Giarola, Ana Rincon, Alexandra Tard and Ursula Gundert-Remy

5. Conclusions

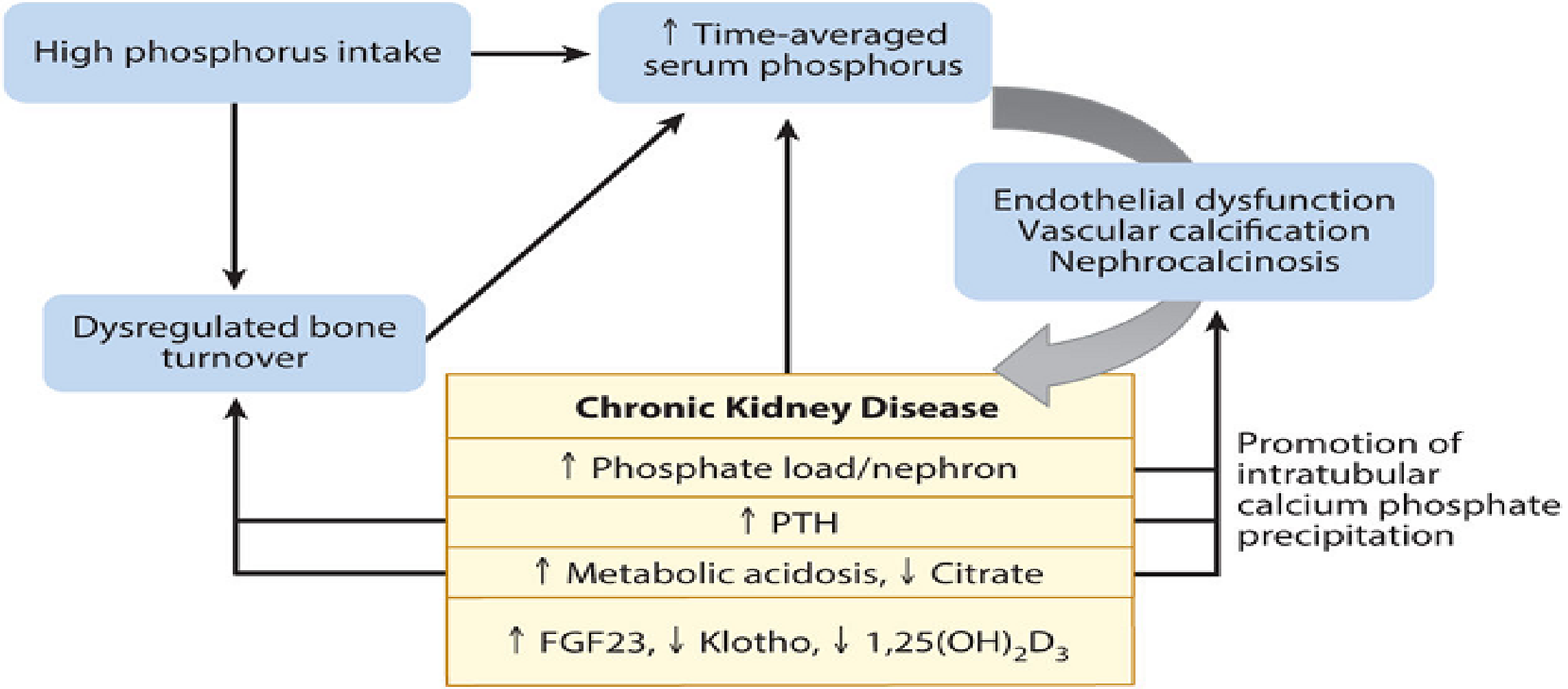
Acceptable Daily Intake = 40 mg/Kg bw per day

Considering the overall database relevant for phosphoric acid–phosphates – di-, tri- and polyphosphates, the Panel derived a group ADI for phosphates expressed as phosphorus of 40 mg/kg bw per day from a chronic study. This ADI corresponds to an acceptable intake of phosphorus of 2,800 mg/day for an adult of 70 kg. This is within the level of 3,000 mg/day indicated by the EFSA NDA Panel (2005) as being tolerated by healthy individuals.

The Panel considers that the group ADI of 40 mg/kg bw per day, expressed as phosphorus, is protective for healthy adults because it is below the doses at which clinically relevant adverse effects were reported in short-term and long-term studies in humans. However, this ADI does not apply to humans with moderate to severe reduction in renal function. Ten per cent of general population might have CKD with reduced renal function and they may not tolerate the amount of P per day which is at the level of ADI. The total phosphorus content of foods (naturally occurring and added as additives) is not mandatory to be reported on food labels.

The Panel noted that the exposure estimates based on analytical data exceeded the proposed ADI for infants, toddlers and children at the mean level and for infants, toddlers, children and adolescents at the 95th percentile. The Panel also noted that P exposure from food supplements exceeds the proposed ADI.

The Panel concluded that the available data did not give rise to safety concerns in infants below 16 weeks of age consuming formula and food for medical purposes. When receiving data on the content of contaminants in formula, the Panel noted that the high aluminium content may exceed the TWI.


High phosphorus intake
↑ Time-averaged serum phosphorus
Endothelial dysfunction
Vascular calcification
Nephrocalcinosis
Dysregulated bone turnover
Chronic Kidney Disease
↑ Phosphate load/nephron
↑ PTH
↑ Metabolic acidosis, ↓ Citrate
↑ FGF23, ↓ Klotho, ↓ 1,25(OH)2D3
Promotion of intratubular calcium phosphate precipitation

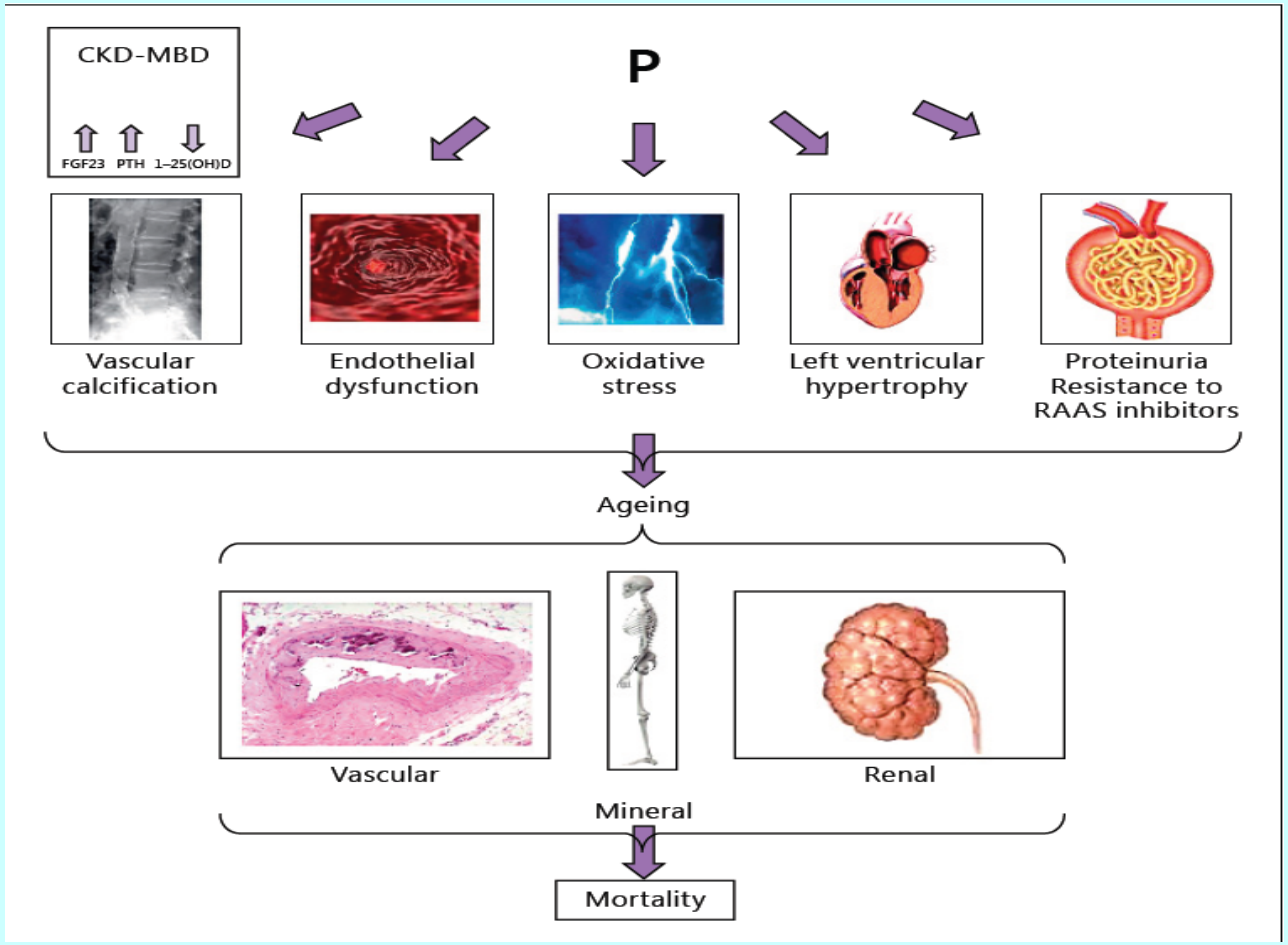
Although phosphorus is an essential nutrient required for multiple physiological functions, recent research raises concerns that high phosphorus intake could have detrimental effects on health. Phosphorus is abundant in the food supply of developed countries, occurring naturally in protein-rich foods and as an additive in processed foods. High phosphorus intake can cause vascular and renal calcification, renal tubular injury, and premature death in multiple animal models. Small studies in human suggest that high phosphorus intake may result in positive phosphorus balance and correlate with renal calcification and albuminuria. Although serum phosphorus is strongly associated with cardiovascular disease, progression of kidney disease, and death, limited data exist linking high phosphorus intake directly to adverse clinical outcomes. Further prospective studies are needed to determine whether phosphorus intake is a modifiable risk factor for kidney disease.

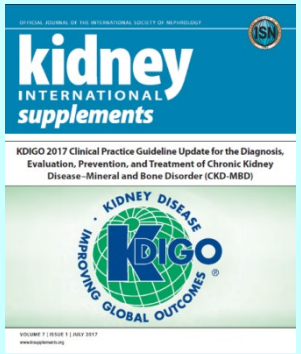
Perspectives in Nephrology and Chronic Kidney Disease

La Manna G, Ronco C (eds): Current Perspectives in Kidney Diseases.
Contrib Nephrol. Basel, Karger, 2017, vol 190, pp 71–82 (DOI: 10.1159/000468915)

Phosphate in Chronic Kidney Disease Progression

Mario Cozzolino[a] · Denis Foque[b] · Paola Ciceri[a] · Andrea Galassi[a]





July 2017

Chapter 4.1: Treatment of CKD-MBD targeted at lowering high serum phosphate and maintaining serum calcium

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*).

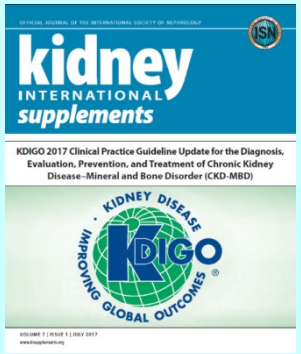
4.1.3: In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (*2C*). In children with CKD G3a–G5D, we suggest maintaining serum calcium in the age-appropriate normal range (*2C*).

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*).

4.1.5: 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*).

KDIGO CKD-MBD Update Work Group. Kidney Int Suppl 2017;7:1–59.



July 2017

4.1.7: In patients with CKD G3a-G5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (*1C*).

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*).

4.1.9: In patients with CKD G5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (*2C*).

KDIGO CKD-MBD Update Work Group. Kidney Int Suppl 2017;7:1–59.

Vitamin D

Case report

Name: RA

Age: 62 years **Sex:** Female

Patient notes:

- Hypertension
- CKD Stage 3b (eGFR 38 mL/min)
- Poor adherence with nutritional and medical therapy

Current treatment:

- Warfarin 5 mg qd according to INR
- Levothyroxine 100 µg qd
- Omeprazole 20 mg qd
- Furosemide 25 mg bid
- Lorazepam 1 mg qd
- Polyenoic fatty acids 1 g bid
- Simvastatin 20 mg qd
- Epoetin beta 5000 IU 2 times/week

CKD-MBD diagnosis:

- Calcium: 9.2 mg/dL (2.3 mmol/L)
- Phosphate: 4.1 mg/dL (1.0 mmol/L)
- PTH: 146 pg/mL (15.5 pmol/L)
- 25(OH)D: 12 ng/mL (30 nmol/L)

CKD-MBD treatment:

- Calcium carbonate 1000 mg bid, with meals
- Calcifediol 1.5 mg/mL 20 gtt 2 times/week
- Paricalcitol: 1 µg qd

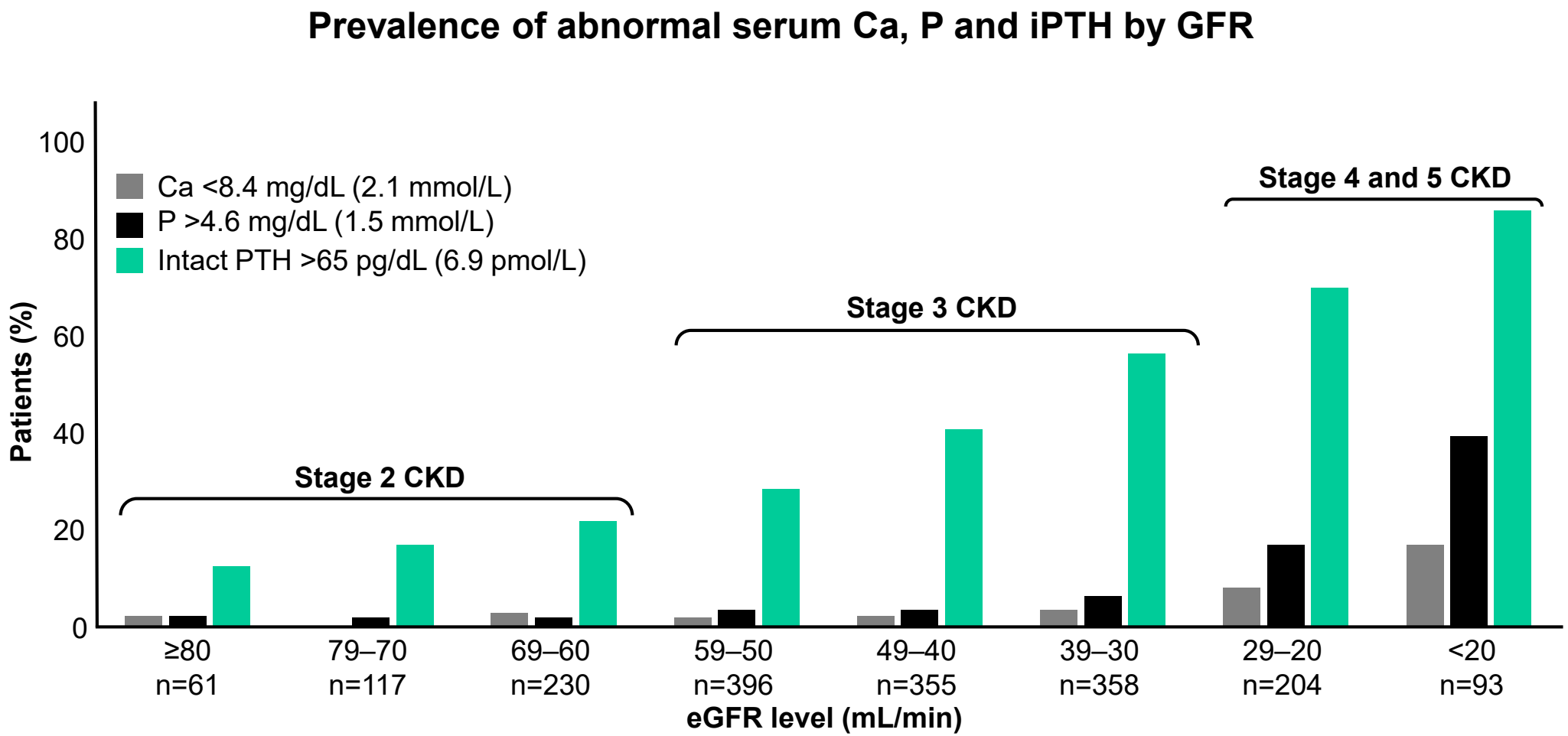
QUESTION 1. Do we need to take care of CKD-MBD?

QUESTION 2. Can we optimise CKD-MBD therapy?

Case provided by Professor Mario Cozzolino, Milan, Italy.

bid, twice a day; CKD-MBD, chronic kidney disease-metabolic bone disease; eGFR, estimated glomerular filtration rate; gtt, drops; INR, international normalised ratio; IU, international unit; PTH, parathyroid hormone; qd, once daily.

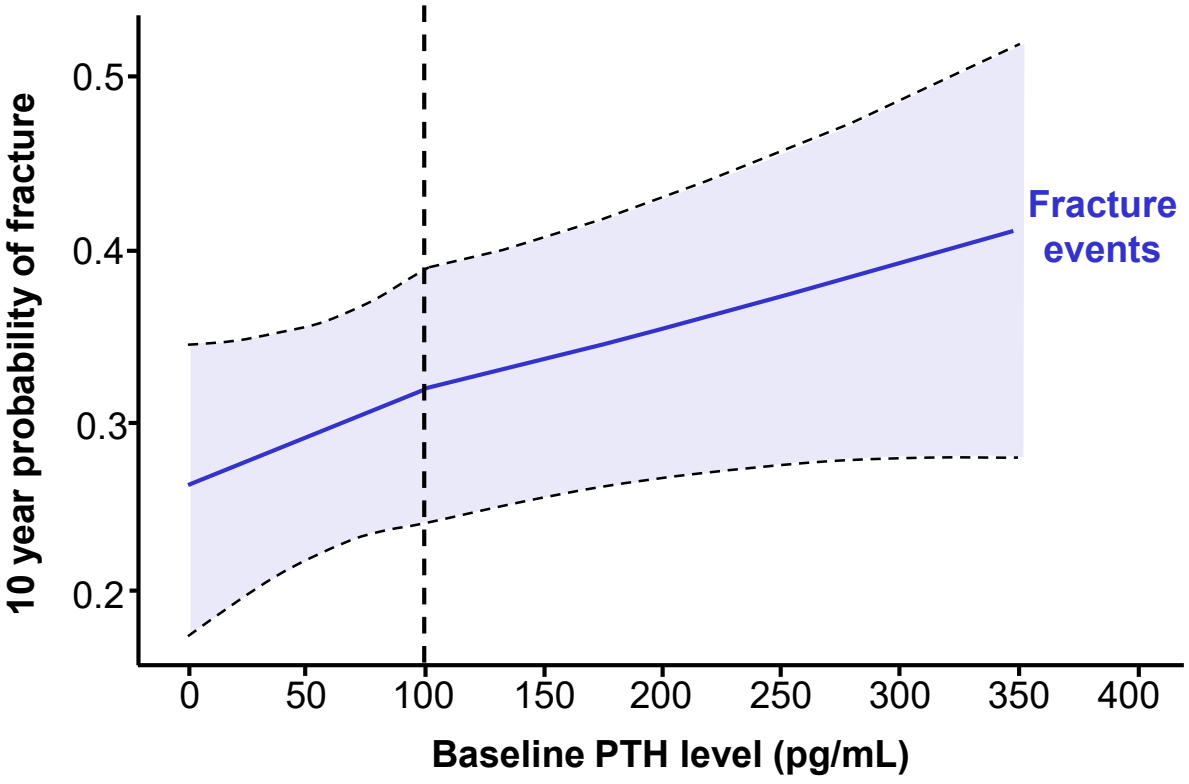
SHPT manifests frequently and early in CKD



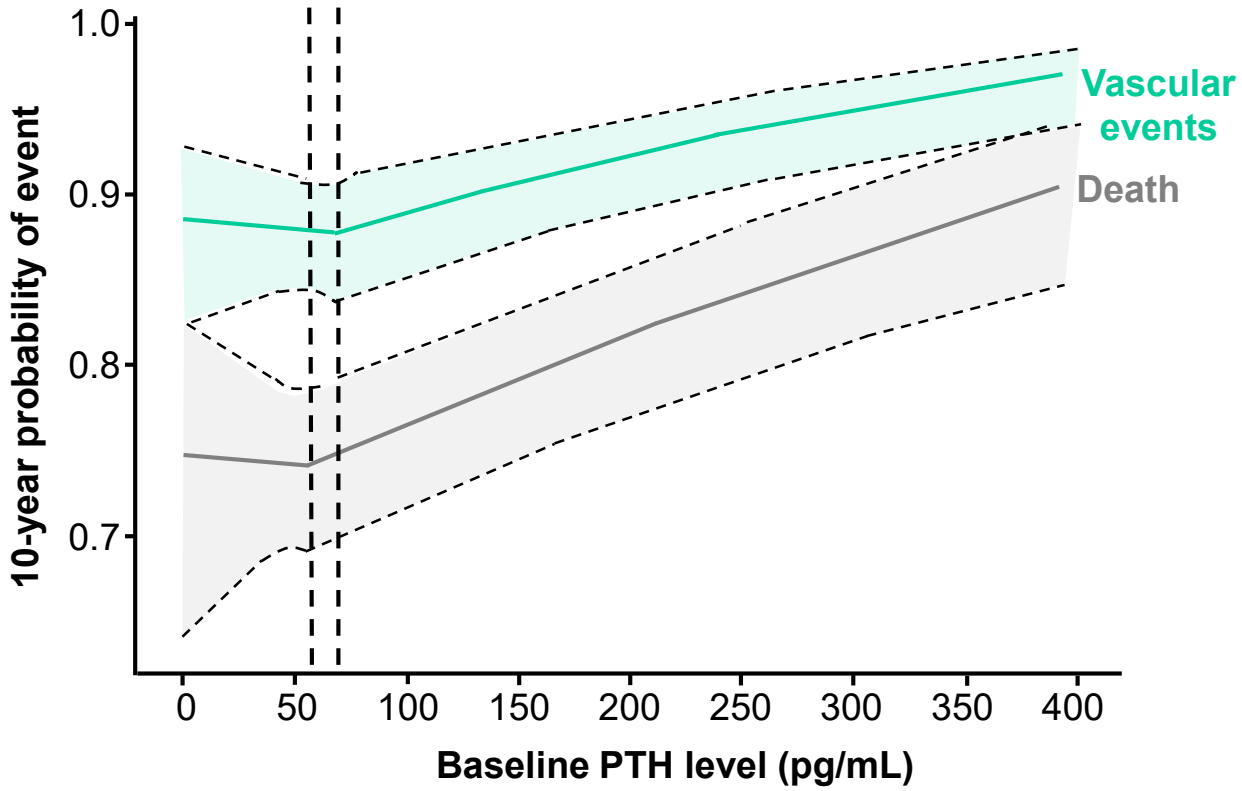
Adapted from Levin A, et al. Kidney Int 2007;71:31–38.

Ca, calcium; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; P, phosphate; SHPT, secondary hyperparathyroidism.

PTH levels independently predict fracture, vascular events and death in stage 3–4 CKD



The hazard of fracture rose steadily with increasing PTH values

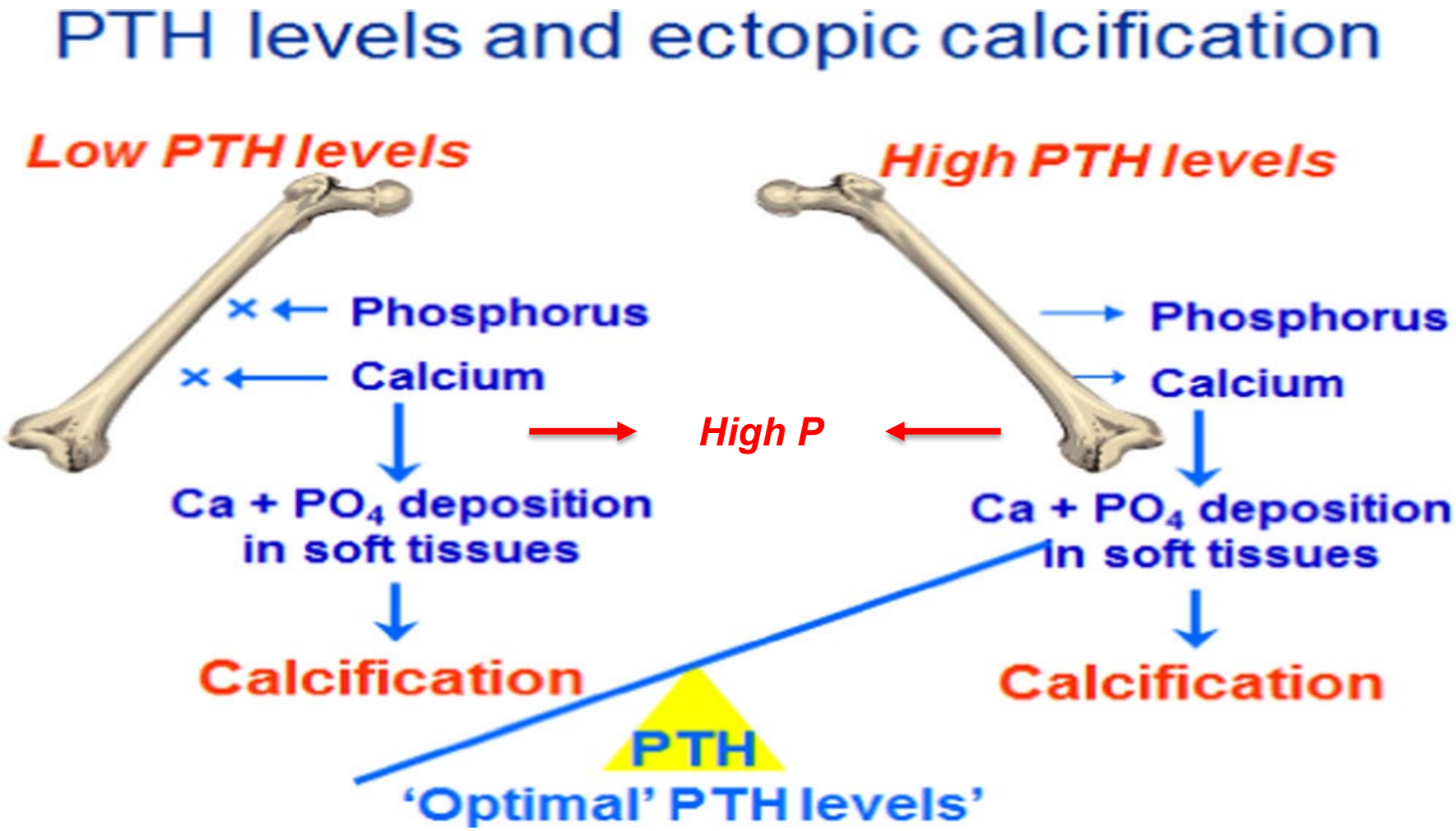


The lowest hazard of vascular events and death was a PTH of 69 pg/mL and 59 pg/mL, respectively

An observational study of 5108 patients with stage 3–4 CKD; multivariate models controlling for age, gender, tobacco use, vascular disease, diabetes, hypertension, hyperlipidaemia, obesity, GFR, and use of osteoporosis medications.
Adapted from Geng S, et al. Osteoporos Int 2019;30:2019-2025.

CKD, chronic kidney disease; GFR, glomerular filtration rate; PTH, parathyroid hormone.

PTH: the impact on bone, phosphate homeostasis and calcification



Pediatr Nephrol. 2015 Dec;30(12):2061-71.

PTH effects on the cardiovascular system

- PTH receptors are widely expressed throughout the cardiovascular system including the myocardium
- PTH infusions increase blood pressure in healthy volunteers and PTH modifies contractile functions of the myocardium
- PTH levels were highlighted as a cardiovascular risk factor in epidemiological studies

Uppsala Longitudinal Study of Adult Men (ULSAM)

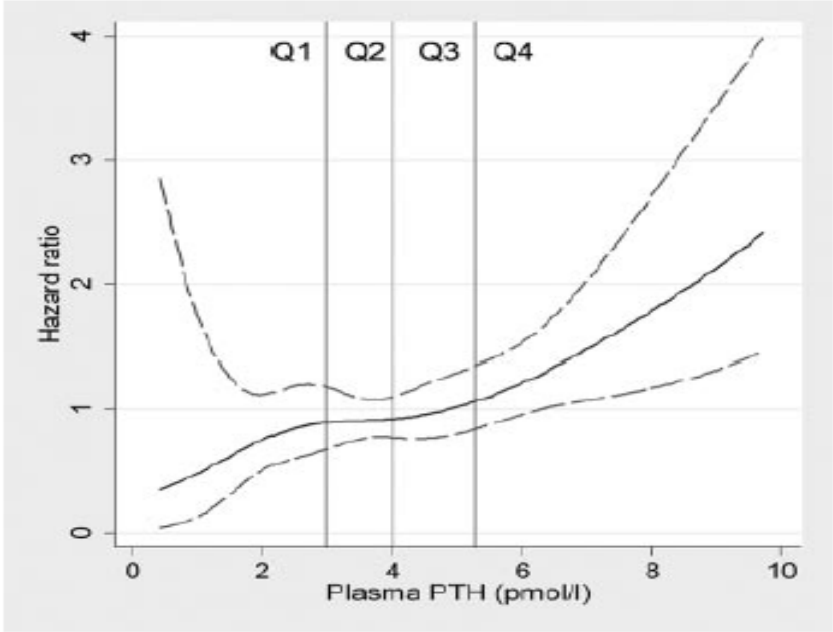


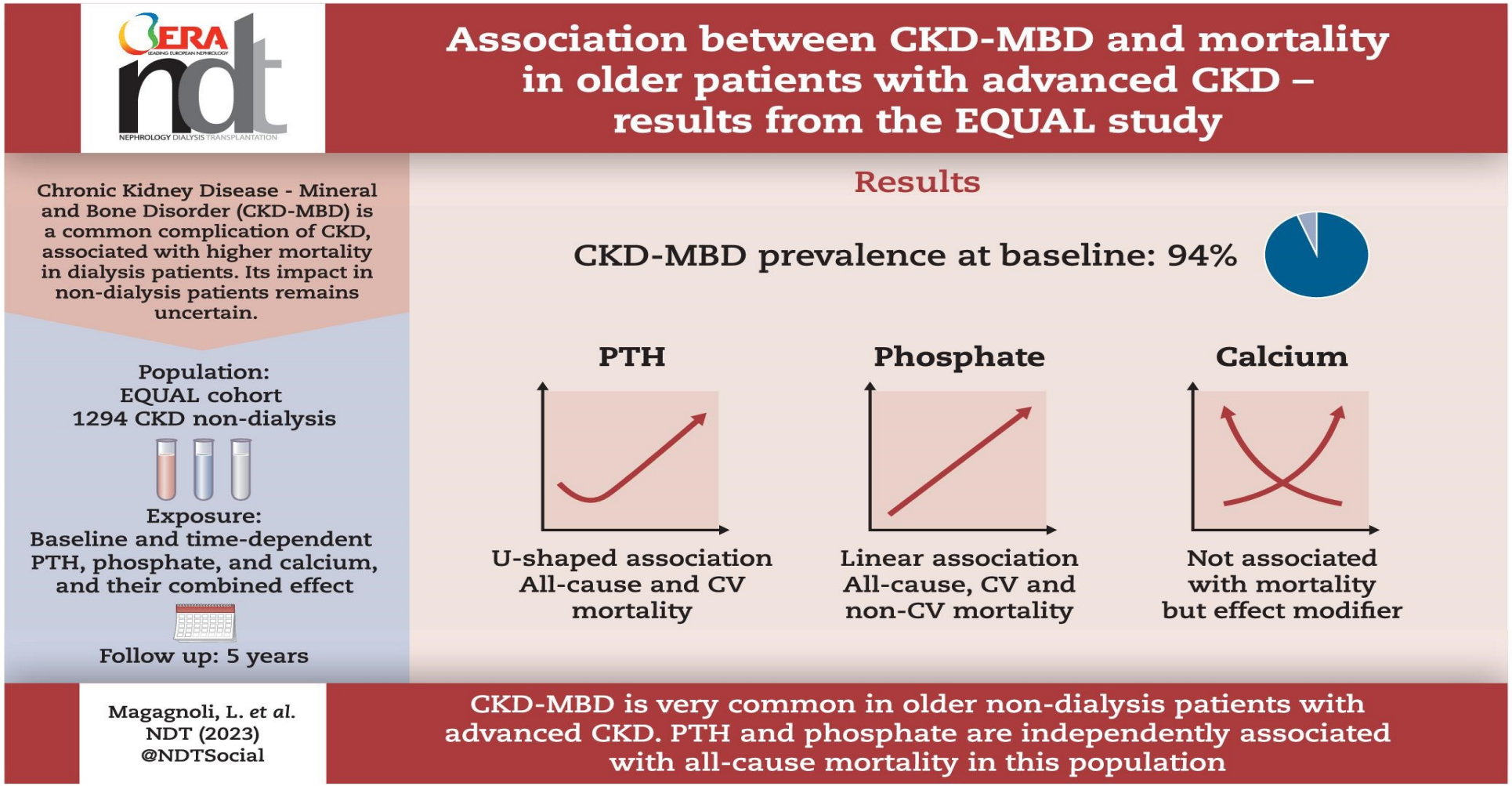
Figure. Association between plasma PTH and cardiovascular mortality in the total sample. Solid line shows estimated hazard ratios (with 95% confidence limits) for cardiovascular mortality in relation to plasma PTH levels as a function of penalized regression splines. Q indicates quartile.

Schlüter KD et al. Cardiovasc Res 1998,37:34-41
Fitzpatrick LA et al. Curr Osteoporos Rep 2008,6:77-83

Nephrol Dial Transplant, 2023, 0, 1–14
https://doi.org/10.1093/ndt/gfad100
Advance access publication date: 25 May 2023

Association between CKD-MBD and mortality in older patients with advanced CKD—results from the EQUAL study

Lorenza Magagnoli[1,2], Mario Cozzolino[1,2], Fergus J. Caskey[3,4], Marie Evans[5], Claudia Torino[6], Gaetana Porto[7], Maciej Szymczak[8], Magdalena Krajewska[8], Christiane Drechsler[9], Peter Stenvinkel[5], Maria Pippias[3,4], Friedo W. Dekker[10], Esther N.M. de Rooij[10], Christoph Wanner[9], Nicholas C. Chesnaye[11,12] and Kitty J. Jager[11,12]; the EQUAL study investigators

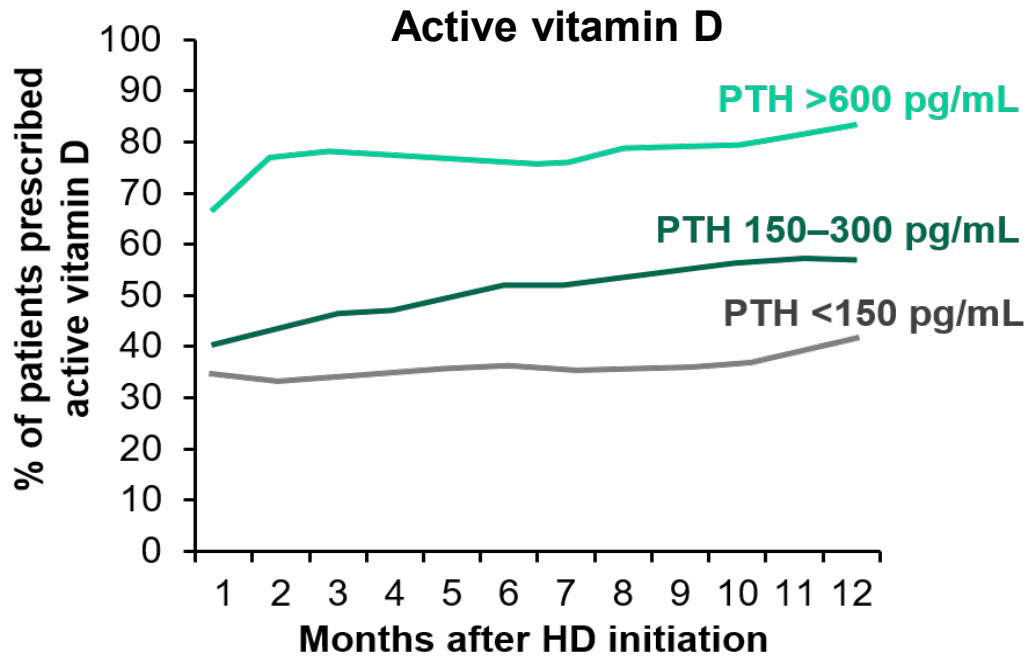


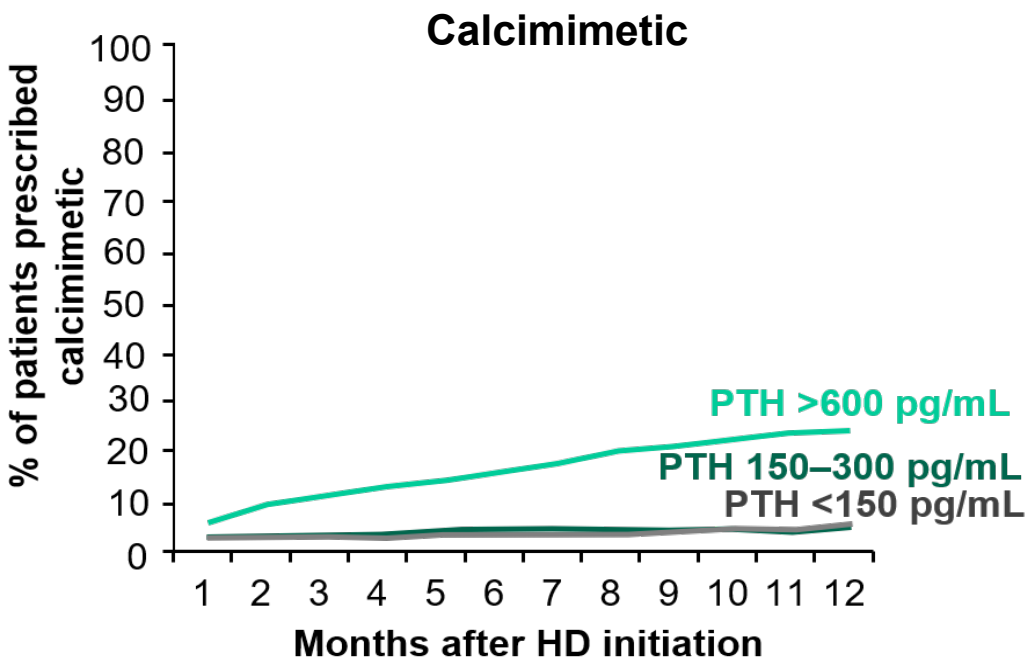
Elevated PTH prior to dialysis is strongly associated with uncontrolled PTH during HD, despite more aggressive SHPT treatment

Risk of PTH >600 pg/mL 9–12 months after HD start, by PTH prior to HD start
(n=2728; DOPPS Phases 4–6 [2009–2018])

PTH (pg/mL) prior to HD start	Adjusted risk difference (95% CI)
50–100	**-3.8** (-8.1, 0.5)
150–300	**0** (Ref)
>600	**19.0** (15.4, 22.7)

PTH-lowering medication prescriptions over the first year of HD, by PTH prior to HD start

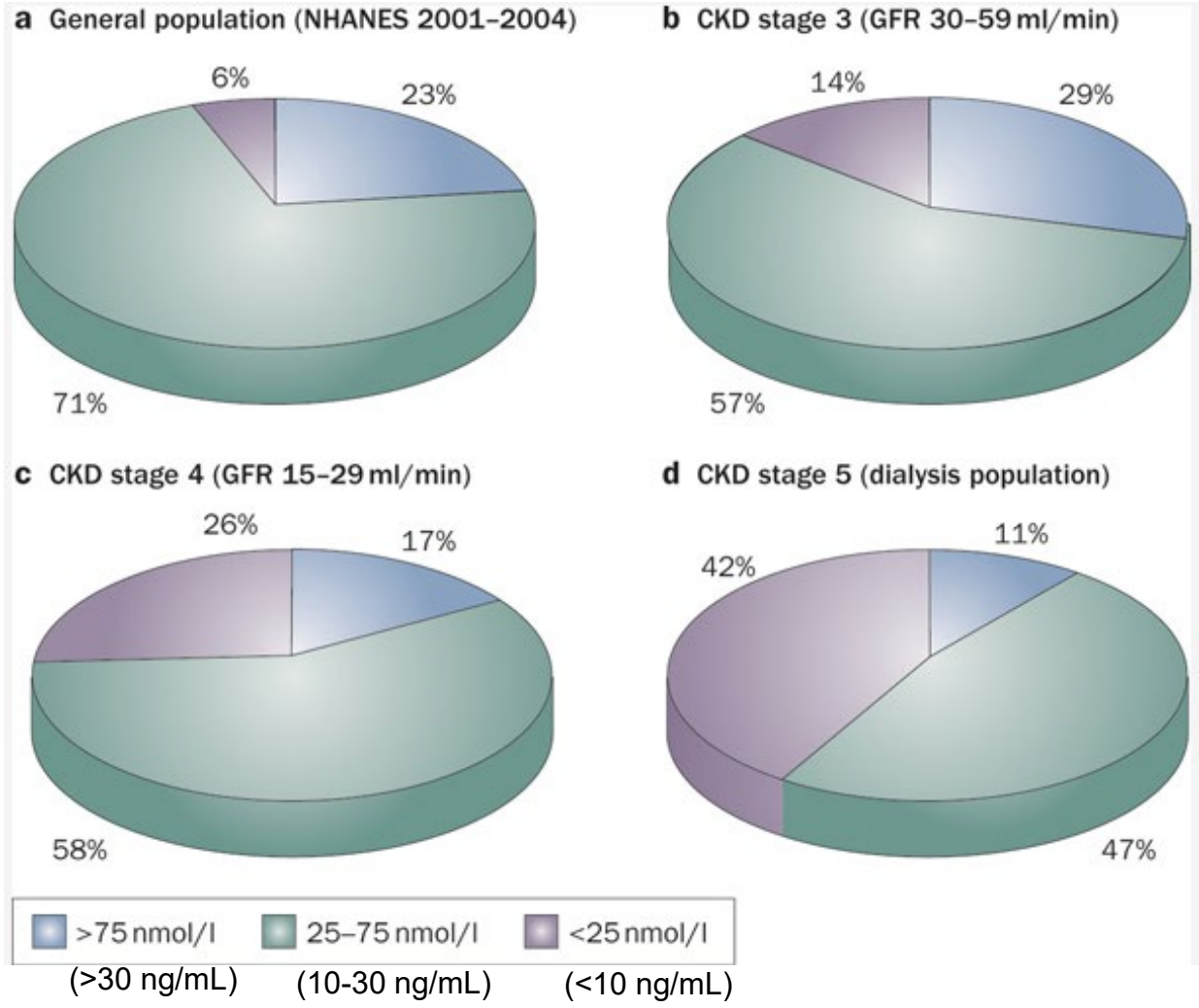




Adapted from Young EW, et al. Abstract FR-PO128 presented at ASN 2019, 5–10 November 2019, Washington DC, USA.

DOPPS, The Dialysis Outcomes and Practice Patterns Study; HD, haemodialysis; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.

Vitamin D insufficiency affects an estimated 71–89% of patients with stage 3–5 CKD vs 30% of the general population

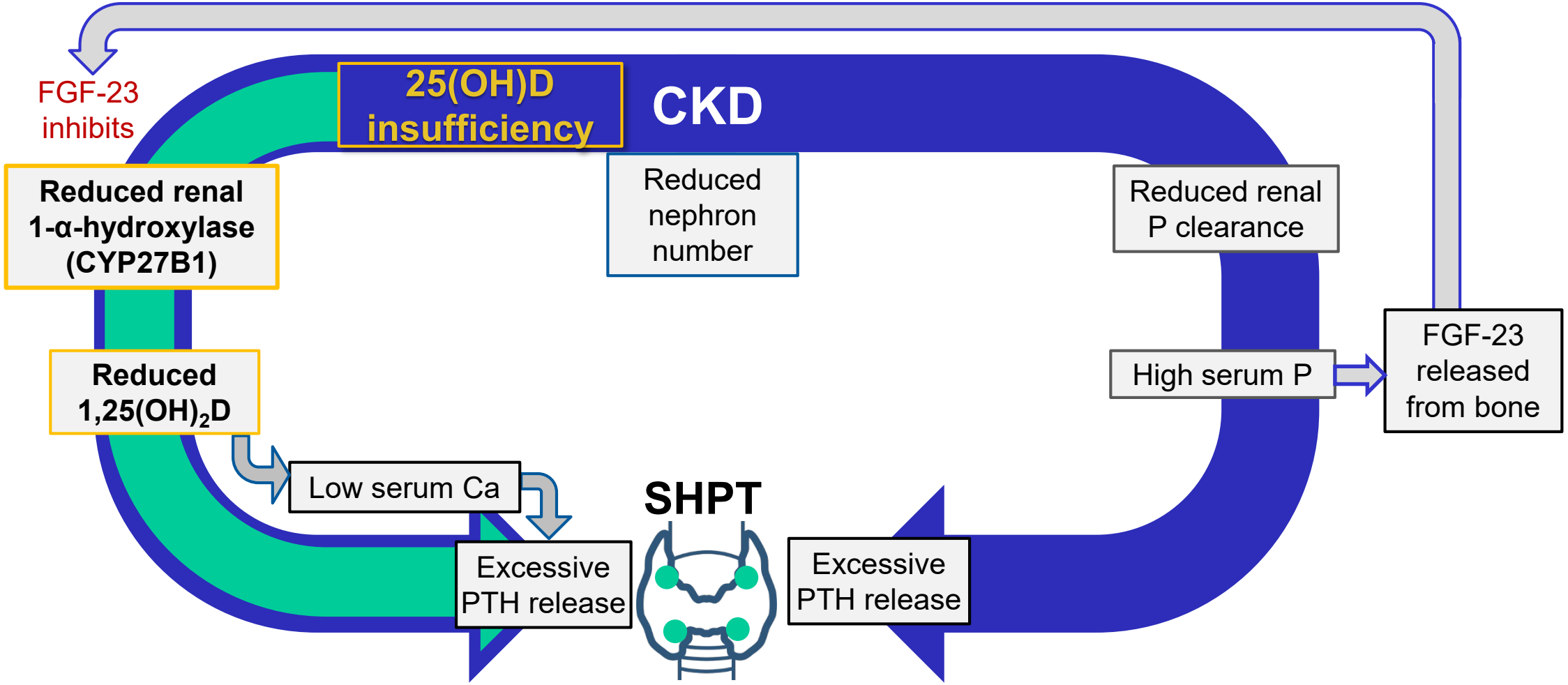


Vitamin D insufficiency defined as ≤75 nmol/L / ≤30 ng/mL

CKD, chronic kidney disease; GFR, glomerular filtration rate; NHANES, National Health And Nutrition Examination Survey.

Doorenbos CR, et al. Nat Rev Nephrol 2009;5:691–700.

Low levels of vitamin D promote the progression of SHPT via multiple pathways[1,2]



Ca, Calcium; CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23; P, phosphate; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D.

1. Cunningham J, et al. Clin J Am Soc Nephrol 2011;6:913–21; 2. Levin A, et al. Kidney Int 2007;71:31–8.

KDIGO: management of bone and mineral parameters remain the therapeutic goal for CKD-MBD

PTH	• ND-CKD (Stages 3a–5): **optimal PTH level not known** – If i**PTH progressively rising** or **persistently above the ULN, evaluate for modifiable factors** (**P, Ca**, high P intake, **vitamin D** deficiency) • CKD G5D: **maintain iPTH levels in the range of ~2–9 x ULN** for the assay – Marked changes in either direction within this range prompt an **initiation or change in therapy** to avoid progression to levels outside of this range
Ca	• Adult CKD Stages 3a–5D: **avoid hypercalcaemia**
P	• CKD Stages 3a–5D: **lower elevated P** levels towards the **normal range**
25(OH)D	• **Correct vitamin D deficiency/insufficiency** using recommended treatment strategies

Ca, calcium; CKD-MBD, chronic kidney disease–mineral and bone disorder; iPTH, intact parathyroid hormone; KDIGO, Kidney Disease Improving Global Outcomes; ND-CKD, non dialysis-chronic kidney disease; P, phosphate; PTH, parathyroid hormone; ULN, upper limit of normal; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

KDIGO 2017 guidelines. Kidney Int (Suppl.);7:1–59.

Available treatment options for SHPT in patients with CKD*

Drug group	Active	Licensed specifically for SHPT	
Nutritional vitamin D	Cholecalciferol[1]	–	
	Ergocalciferol[2]	–	
Vitamin D prohormone	IR calcifediol	–	in Europe
	ER calcifediol[3]	✓	in USA and Canada
Active vitamin D / analogues	Calcitriol[4]	–	
	Paricalcitol[5]	✓	
	Alfacalcidol[6]	–	
	Doxercalciferol[7]	✓	in USA
Calcimimetics†	Cinacalcet[8]	✓	
	Etelcalcetide[9]	†only indicated for HD CKD patients	
	Evocalcet[10]		in Japan

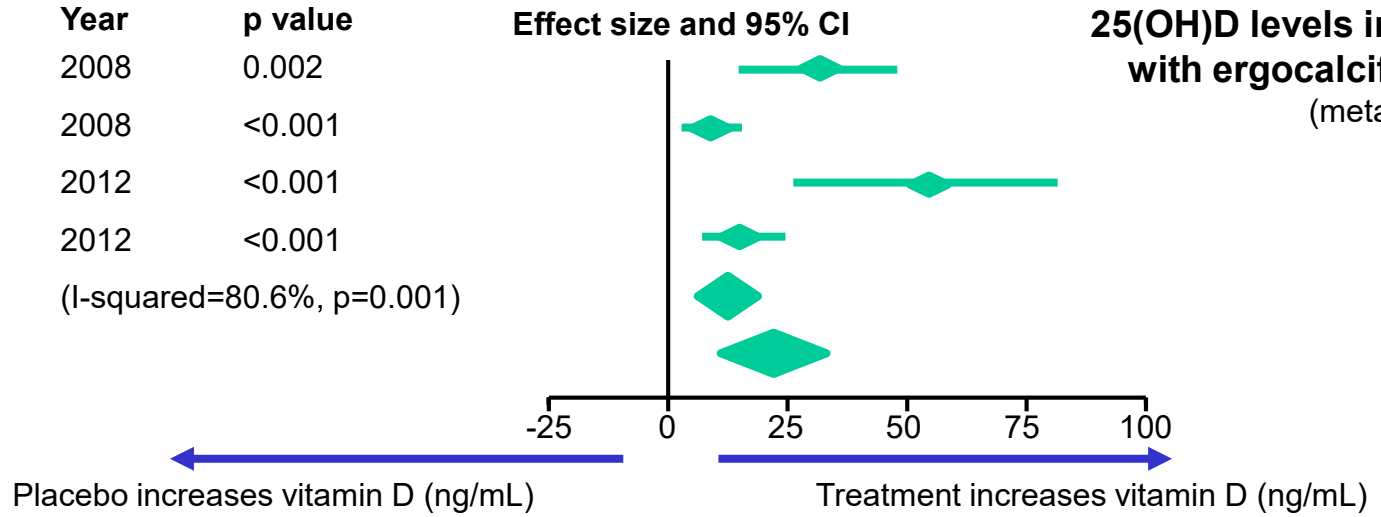
Table adapted from Cozzolino M and Ketteler M. Expert Opin Pharmacother 2019;20:2081-2093.

***Indications may differ between countries; please refer to your local prescribing information.**
ER calcifediol is not licensed in Europe; licensed in the USA and Canada.
ER calcifediol is licensed for the treatment of SHPT in adults with stage 3 or 4 CKD and vitamin D insufficiency (25(OH)D <30 ng/mL)

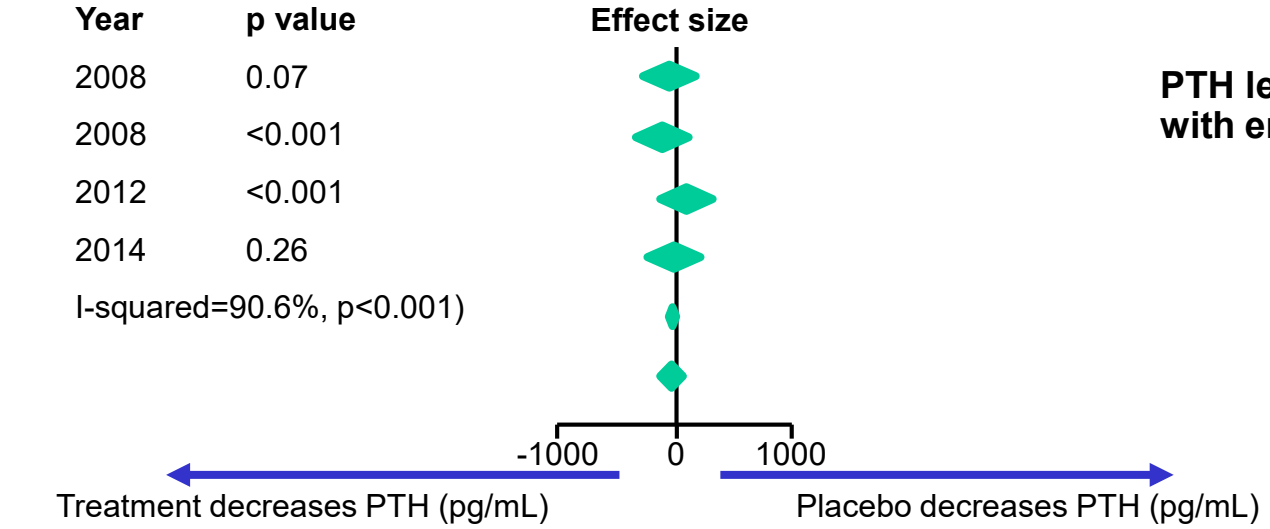
1. Colonis Pharma Ltd. Aviticol SPC. 13 April 2018; 2. RPH Pharmaceuticals. Ergocalciferol SPC. 1 May 2018; 3. OPKO. Rayaldee product information. June 2016;
4. Roche. Rocaltrol SPC. 7 July 2014; 5. AbbVie. Zemplar SPC. 19 April 2018; 6. Leo Laboratories. One-Alpha Summary of product characteristics. 2 May 2017;
7. Genzyme Corporation. Hectorol prescribing information. November 2018; 8. Amgen. Mimpara SPC. 22 August 2019; 9. Amgen. Parsabiv SPC. 29 April 2019;
10. Kyowa Hakko Kirin Co. Ltd press release, available at: https://www.kyowakirin.com/media_center/news_releases/2018/e20180522_01.html [Accessed April 2020].

Ca, calcium; CKD, chronic kidney disease;
ER, extended release; HD, haemodialysis;
IR, immediate release; P, phosphate;
SHPT, secondary hyperparathyroidism.

Nutritional vitamin D increases 25(OH)D, but does not consistently lower PTH levels, in non-dialysis CKD



25(OH)D levels in non-dialysis CKD patients treated with ergocalciferol / cholecalciferol* vs placebo
(meta-analysis of 4 RCTs; n=130)



PTH levels in non-dialysis CKD patients treated with ergocalciferol / cholecalciferol* vs placebo
(meta-analysis of 4 RCTs; n=130)

*Ergocalciferol or cholecalciferol 40,000–300,000 IU/week (4 weeks–6 months).

CI, confidence interval; CKD, chronic kidney disease; IU, international unit; PTH, parathyroid hormone; RCT, randomised controlled trial; 25(OH)D, 25-hydroxyvitamin D.

Adapted from Agarwal R and Georgianos PI. Nephrol Dial Transplant 2016;31:706–13.

Clinical Kidney Journal

Active vitamin D increases the risk of hypercalcaemia in non-dialysis chronic kidney disease patients with secondary hyperparathyroidism: a systematic review and meta-analysis

This study evaluates the effects of active vitamin D therapy on hypercalcaemia in patients with non-dialysis chronic kidney disease (ND-CKD) and secondary hyperparathyroidism (SHPT)

Methods

Systematic search of the PubMed, Embase, and Cochrane Library databases, up to 14 May 2020

RCT
≥ 30 patients per arm
≥ 6 weeks in duration

Outcome: hypercalcaemia

1704 records identified through database searches and screened

20 full-text articles screened for eligibility
10 did not meet criteria; 4 duplicates

6 included: 5 paricalcitol; 1 alfacalcidol

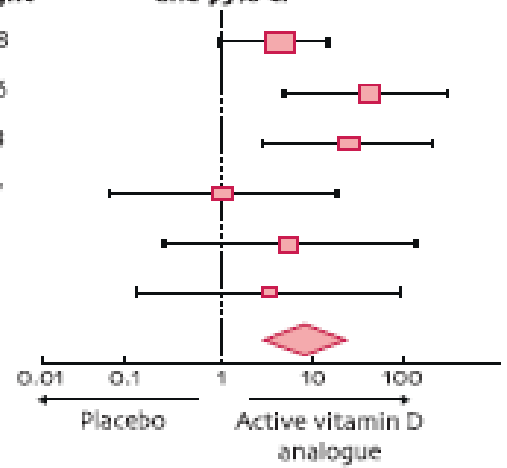
Results

Treatment duration: 16w – 2y

OR 6.6 (95% CI 2.37 – 18.55)

Two separate sensitivity analyses confirmed these results

Study name	Odds ratio (95% CI)	P value	Relative weight
Hamdy	3.54 (0.94, 13.35)	0.061	32.88
Thadhani	32.15 (4.31, 239.74)	0.001	19.26
Wang	22.18 (2.66, 184.80)	0.004	17.78
de Zeeuw	1.00 (0.06, 16.23)	1.000	11.47
Zoccali	5.12 (0.24, 109.63)	0.297	9.75
Fishbane	3.00 (0.12, 76.58)	0.506	8.85
Overall	6.63 (2.37, 18.55)	< 0.001	



Conclusion: Compared with placebo, active vitamin D significantly increased the risk of hypercalcaemia among ND-CKD patients with SHPT

Cozzolino, M., et al
Clinical Kidney Journal (2021)
@CKJsocial

KDIGO guidelines no longer recommend routine use of calcitriol and active vitamin D analogues in non-dialysis CKD G3a–G5

2017 update

In adult patients with CKD G3a–G5 not on dialysis, **do not routinely use calcitriol and vitamin D analogues** (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogues for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (Not Graded). …

KDIGO 2017 Guidelines. Kidney Int 2017;7:1–59.

CKD, chronic kidney disease; G, grade; KDIGO, Kidney Disease Improving Global Outcomes; PTH, parathyroid hormone.

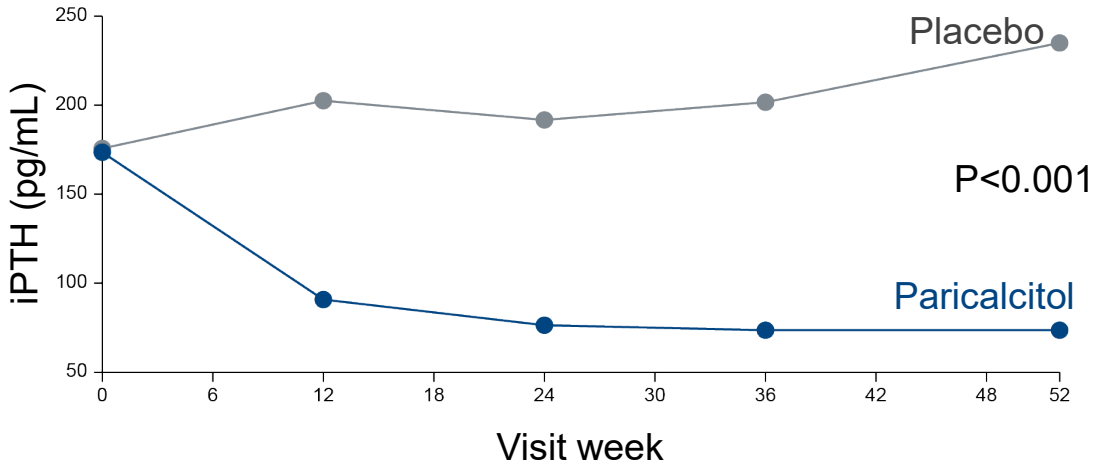
PRIMO and OPERA studies: Paricalcitol reduces PTH but significantly increases risk of hypercalcaemia[1,2]

PRIMO study (n=227):[1]

- Paricalcitol **reduced iPTH within the first 4 weeks**, and maintained levels in the normal range throughout the study[1]
- **85.7% vs 16.5%** of patients in the paricalcitol vs placebo groups had **>30% reduction in iPTH levels** from baseline by week 48 (P<0.001)[1]

OPERA study (n=60):[2]

Effects of paricalcitol vs. placebo on iPTH levels[2]



Rates of hypercalcaemia in PRIMO and OPERA[1,2]

	% patients with hypercalcaemia		P
	Paricalcitol	Placebo	
PRIMO[1*]	22.6%	0.9%	<0.001
OPERA[2†]	43.3%	3.3%	<0.001

Both studies had no significant effect of paricalcitol on surrogate cardiac endpoints.

1. Thadhani R, et al. JAMA 2012;307:674–84; 2. Wang A, et al. J Am Soc Nephrol 2014;25:175–86.

*Defined as 2 consecutive measurements of serum Ca >10.5 mg/dL [corrected to serum albumin of 4.0 g/dL]).
†Defined as serum Ca >2.55 mmol/L.
Ca, calcium; iPTH, intact parathyroid hormone.

Currently available SHPT treatments may not meet medical needs

Effect of current treatment options on MBD parameters

	Drug	Active	25(OH)D	Ca	P	PTH	FGF-23
Non-dialysis / dialysis CKD	**Nutritional vitamin D**	Cholecalciferol[1] Ergocalciferol[1]	↑	–	–	– ↓	–
	Prohormone	IR calcifediol[2]	↑	–	–	– ↓	↑
	Active vitamin D / analogues	Calcitriol[1] Paricalcitol[1]	↓	↑	↑	↓	↑
	Ideally, SHPT treatment in non-dialysis CKD would:[1]		↑	–	–	↓	–
Dialysis CKD	**Calcimimetics**	Cinacalcet[3–5] Etelcalcetide[5]	–	↓	↓	↓	↓

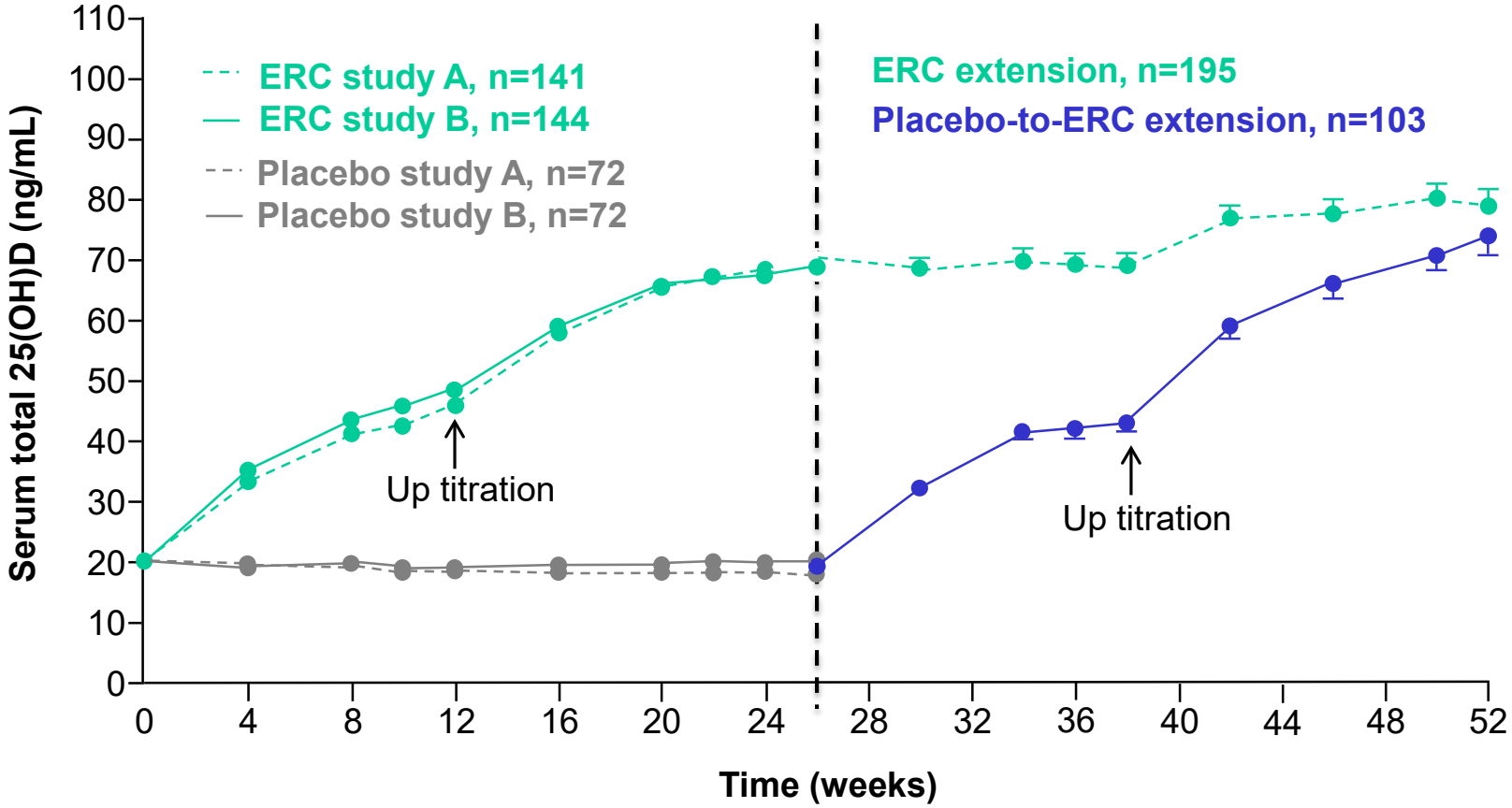
1. Sprague SM, et al. Exp Rev Endocrinol Metab 2017;12:289–301; 2. Petkovich M, et al. J Steroid Biochem Mol Biol 2015;148:283–9; 3. Chertow GM, et al. N Engl J Med 2012;367:2482–94 & Supplementary Appendix; 4. Moe SM, et al. Circulation 2015;132:27–39; 5. Block GA, et al. JAMA 2017;317:156–64.

Ca, calcium; CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23; IR, immediate release; MBD, mineral and bone disorder; P, phosphate; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism; 25(OH)D, 25-hydroxyvitamin D.

ERC increased serum 25(OH)D levels steadily over time

Mean change over time in serum total 25(OH)D (per protocol population)[1]

(Phase 3/open-label extension: Study A and B pooled results)



Steady-state 25(OH)D levels over time by ERC dose[2]

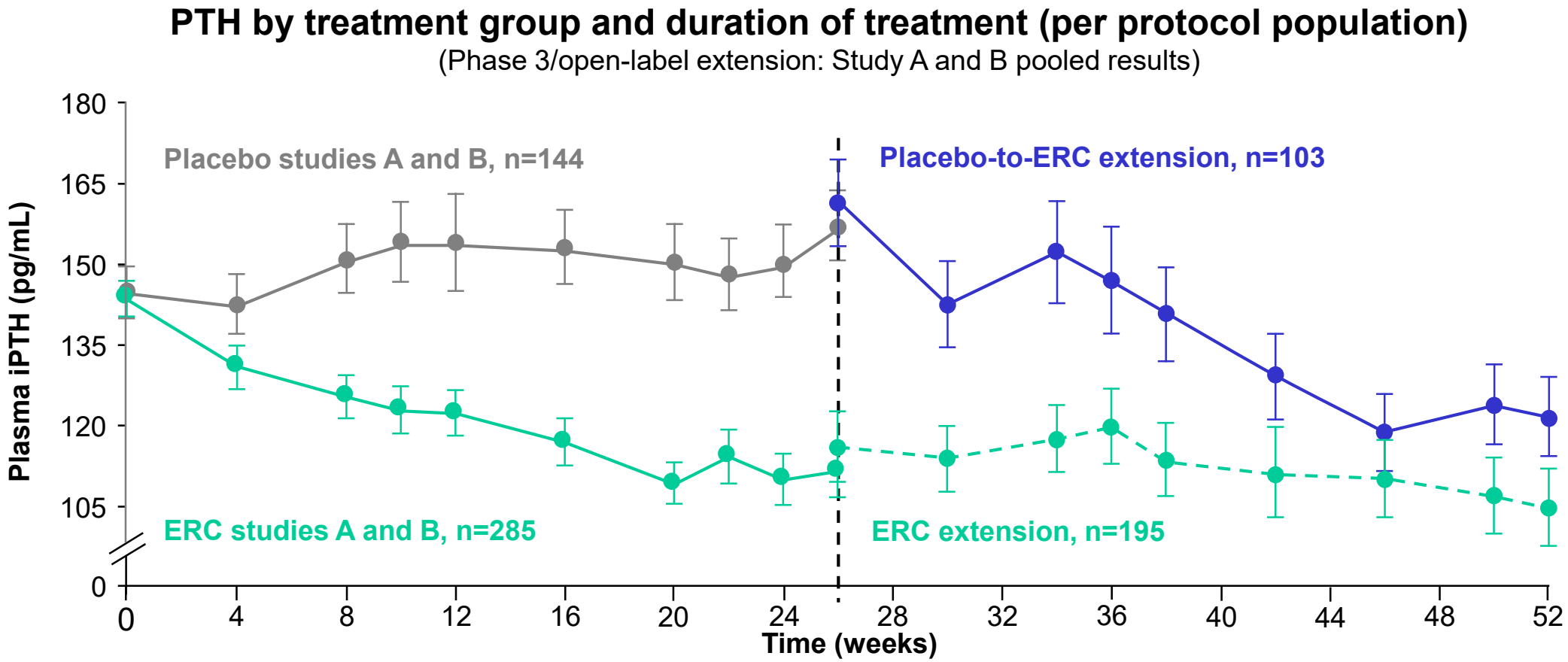
ERC dose	25(OH)D Week 26 (ng/mL)	25(OH)D Week 52 (ng/mL)
30 µg	50	59
60 µg	70	82

ERC is not licensed in Europe (licensed in the USA and Canada).

1. Adapted from Sprague SM, et al. Am J Nephrol 2016;44:316–25; 2. Melnick J, et al. Poster presented at NKF 27 April–1 May, 2016, Boston, MA, USA.

ERC, extended-release calcifediol; 25(OH)D, 25-hydroxyvitamin D.

ERC lowered plasma PTH consistently over time



Primary endpoint met: In the ITT population (n=213), 33% and 34% of patients in study A and B, respectively, achieved ≥30% reduction in iPTH from baseline at Week 26 (vs 8% and 7%, respectively, with placebo)

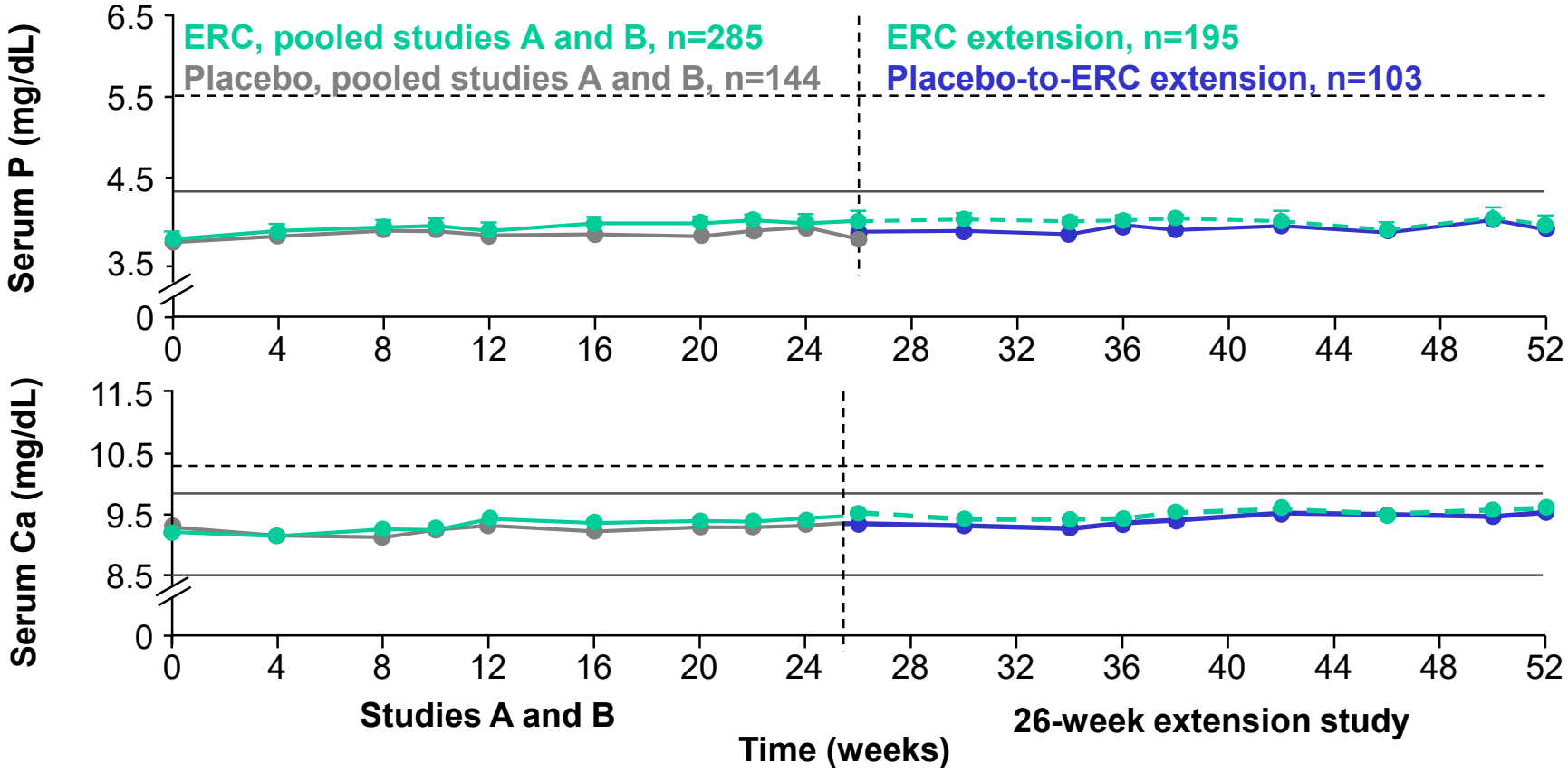
ERC is not licensed in Europe (licensed in the USA and Canada).
Adapted from Sprague SM, et al. Am J Nephrol 2016;44:316–25.

ERC, extended-release calcifediol; iPTH, intact parathyroid hormone; ITT, intention-to-treat; PTH, parathyroid hormone.

ERC led to minimal changes in serum calcium and phosphate

Mean change over time in serum Ca and P (per protocol population)

(Phase 3/open-label extension: Study A and B pooled results)



Hyperphosphataemia:
serum P >5.5 mg/dL

Physiological range:
2.5–4.5 mg/dL

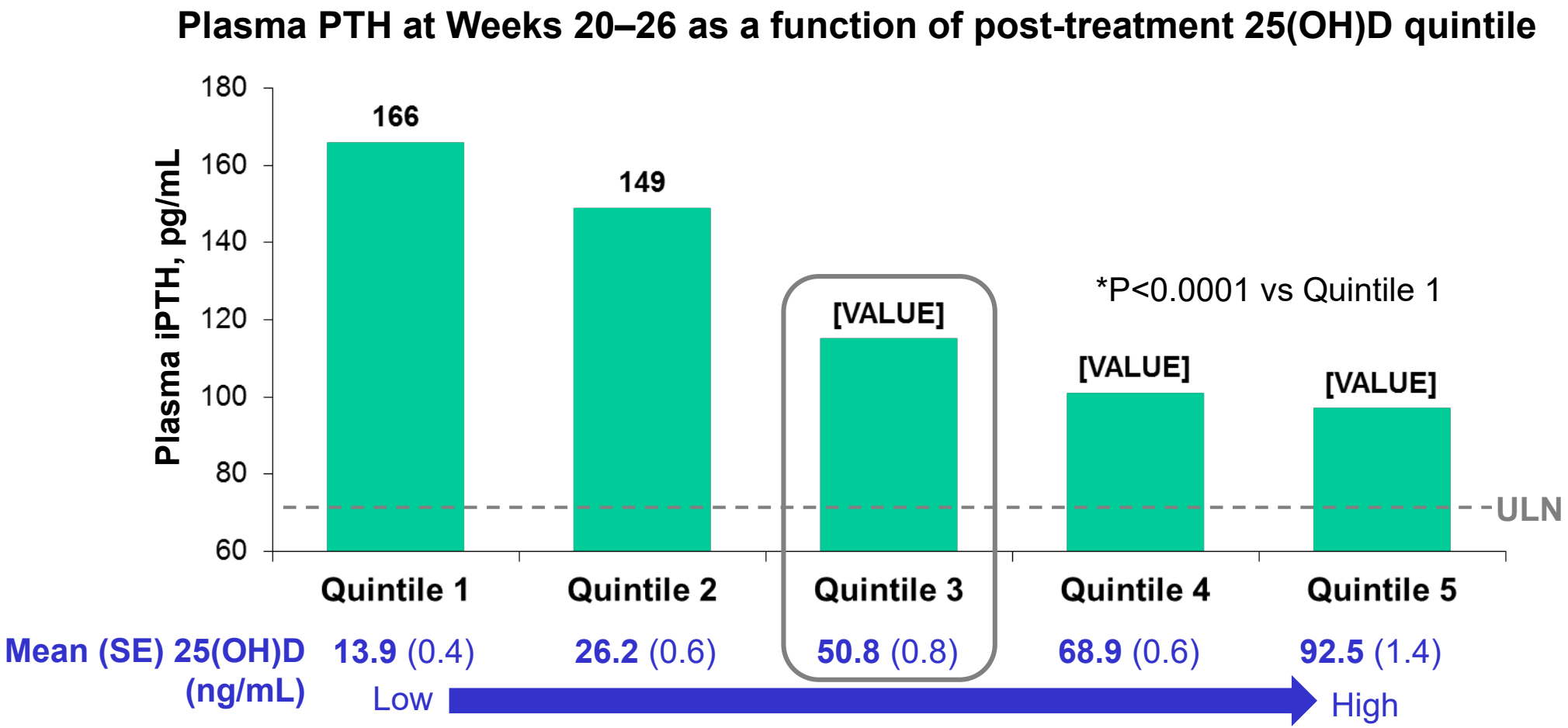
Hypercalcaemia:
serum Ca >10.3 mg/dL

Physiological range:
8.5–10.0 mg/dL
(depending on assay)

ERC is not licensed in Europe (licensed in the USA and Canada).
Adapted from Sprague SM, et al. Am J Nephrol 2016;44:316–25.

Ca, calcium; ERC, extended-release calcifediol; P, phosphate; SHPT, secondary hyperparathyroidism.

25(OH)D levels above 50 ng/mL were associated with significant reductions in PTH



ERC is not licensed in Europe (licensed in the USA and Canada).

Strugnell SA, et al. Am J Nephrol 2019;49:284–293.

ERC, extended-release calcifediol;
iPTH, intact parathyroid hormone; PTH, parathyroid hormone; SE, standard error;
ULN, upper limit of normal; 25(OH)D, 25-hydroxyvitamin D.

No significant differences were observed between 25(OH)D quintile 1 and any of the higher quintiles for safety parameters

Safety parameters by 25(OH)D quintile at 26 weeks

Quintile – mean (SE)	1	2	3	4	5
Serum total 25(OH)D (ng/mL)	**13.9** (0.4)	**26.2** (0.6)	**50.8** (0.8)	**68.9** (0.6)	**92.5** (1.4)
Serum Ca (mg/dL)	**9.3** (0.05)	**9.3** (0.04)	**9.4** (0.05)	**9.4** (0.04)	**9.4** (0.03)
Serum P (mg/dL)	**3.8** (0.06)	**3.9** (0.08)	**3.9** (0.08)	**3.9** (0.08)	**4.0** (0.07)
Serum FGF-23 (pg/mL)	**51.7** (9.6)	**63.3** (16.1)	**50.6** (8.7)	**44.9** (7.5)	**62.8** (7.9)

- No apparent trends in eGFR or urinary Ca:Cr ratio

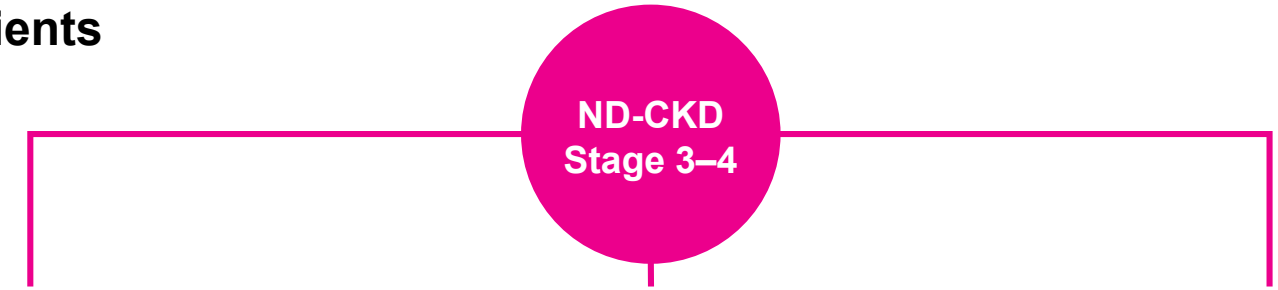
ERC is not licensed in Europe (licensed in the USA and Canada).

Strugnell SA, et al. Am J Nephrol 2019;49:284–93.

Ca, calcium; Ca:Cr, calcium:creatinine; eGFR, estimated glomerular filtration rate; ERC, extended-release calcifediol; FGF-23, fibroblast growth factor-23; P, phosphate; SE, standard error; 25(OH)D, 25-hydroxyvitamin D.

Current treatment options and associated criteria for ND-CKD patients

Flowchart for managing patients with ND-CKD stage 3–4



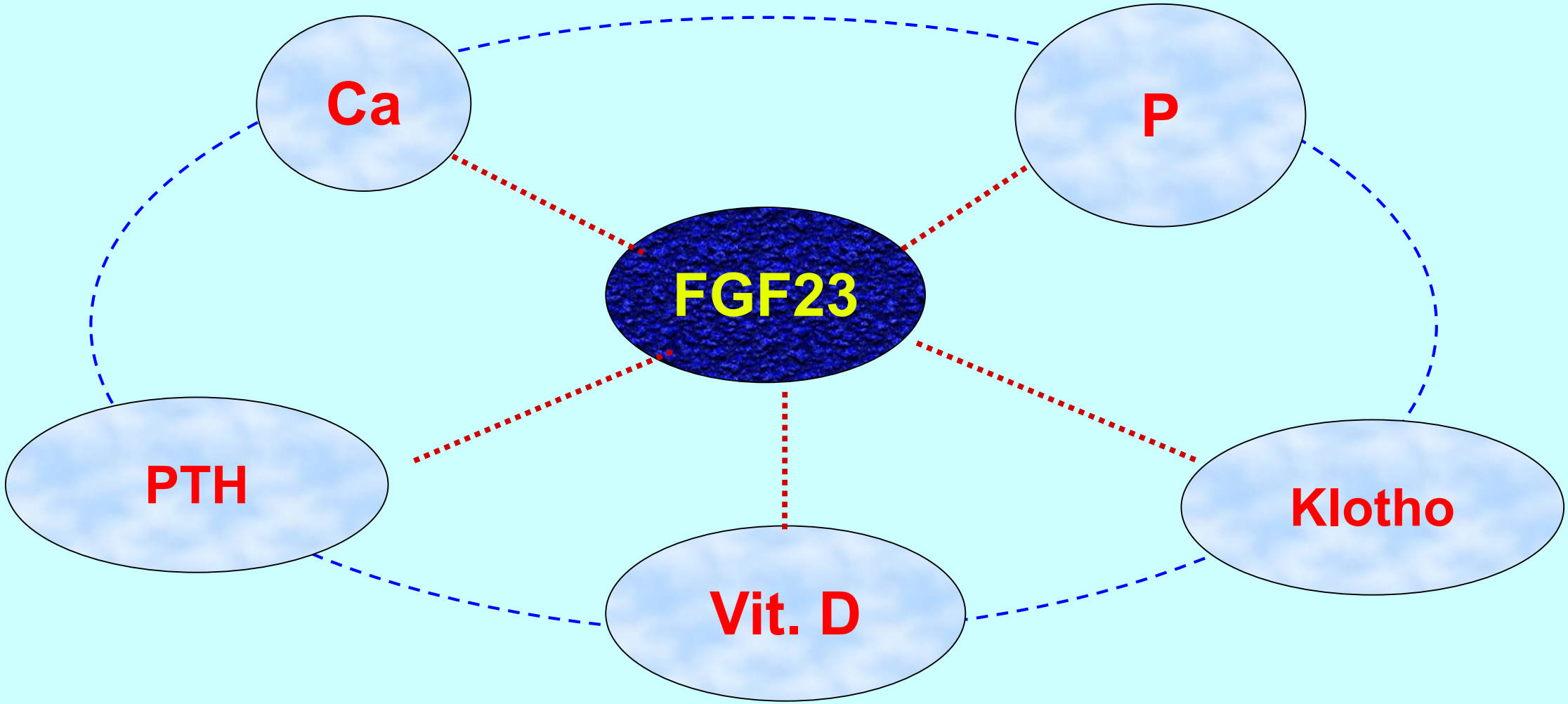
Ca, calcium; ERC, extended-release calcifediol; ND-CKD, non-dialysis chronic kidney disease; P, phosphorus; PTH, parathyroid hormone.

Cozzolino M, et al. J Nephrol 2021;https://doi.org/10.1007/s40620-021-01152-5.

CKD-MBD

CONCLUSIONS & PERSPECTIVES

FGF-23, CKD-MBD, and beyond



Cozzolino M and Mazzaferro S. *Curr Vasc Pharmacol.* 2010
Cozzolino M et al. *NDT* 2020


CKD-MBD:
“The Perfect Storm”

THANKS for your ATTENTION!