CKD-MBD in the 2020s: From Pathophysiology to Practice

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Royal Devon
University Healthcare
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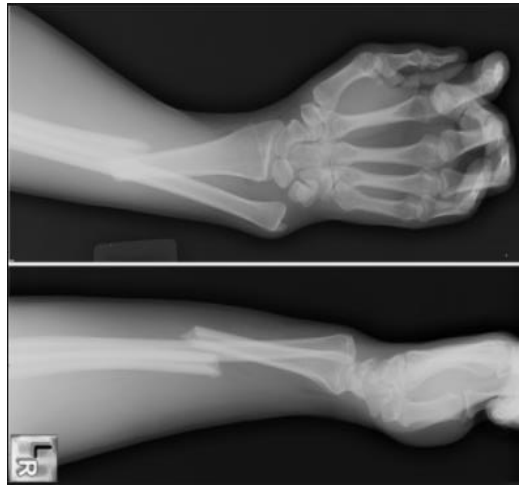
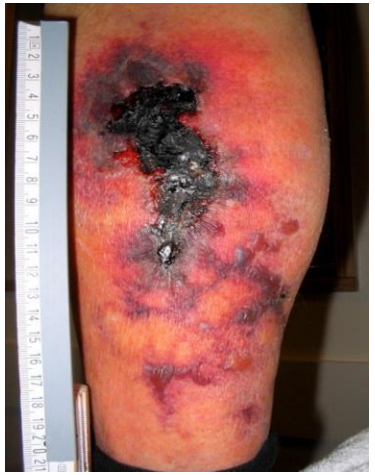
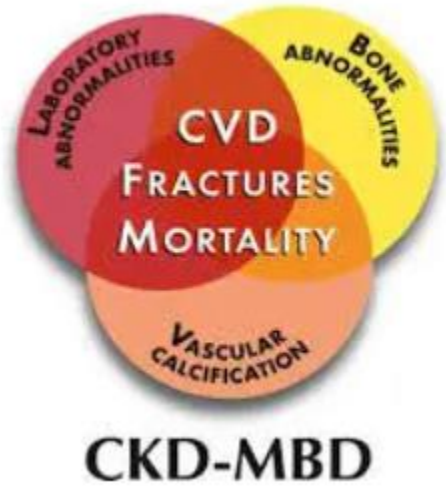
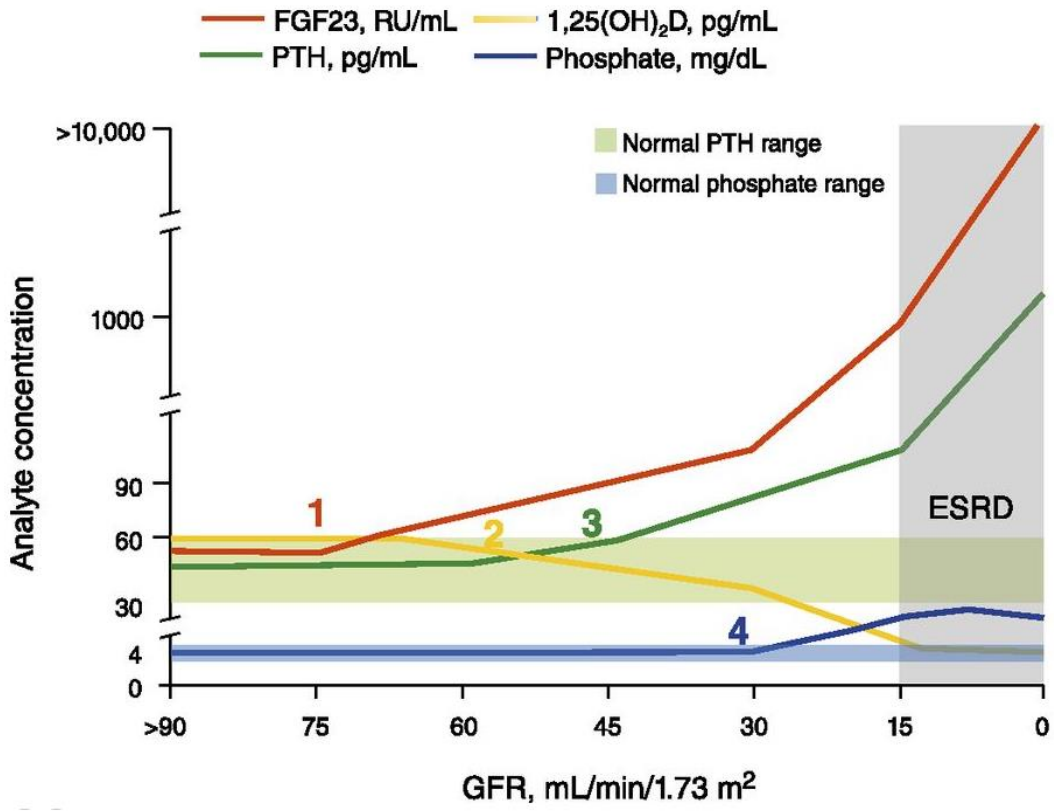
CKD-MBD refers to one or more abnormalities relating to bone health







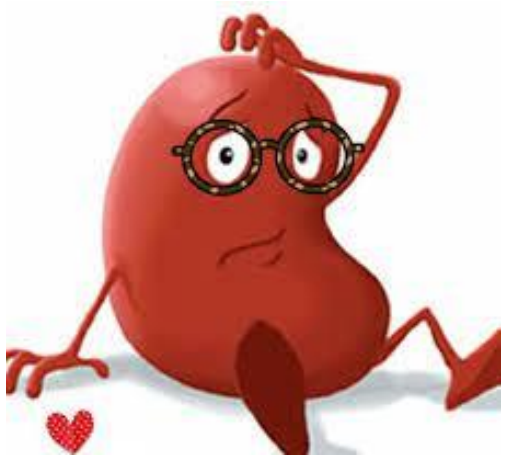


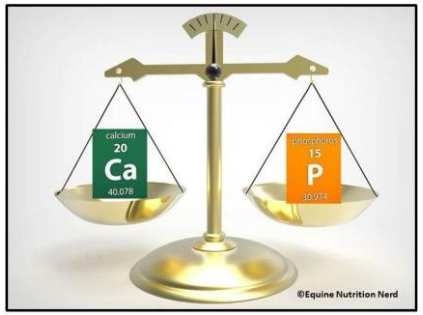
Secondary hyperparathyroidism (SHPT)

A condition where the parathyroid glands secrete excess parathyroid hormone (PTH) due to impaired calcium, phosphate and vitamin D metabolism in chronic kidney disease (CKD).

Pathogenesis of SHPT

PTH

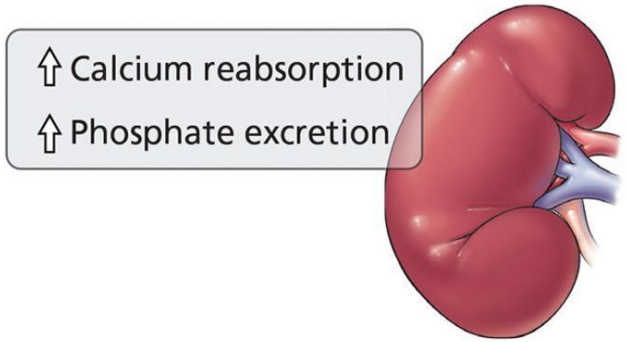




FGF-23

Calcium and phosphate homeostasis

Role of Kidneys:

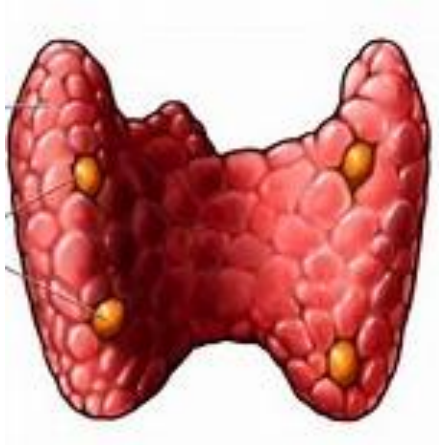


Regulate calcium and phosphate balance through filtration, reabsorption, and excretion

Calcium and phosphate homeostasis

Role of the parathyroid glands (PTH function)

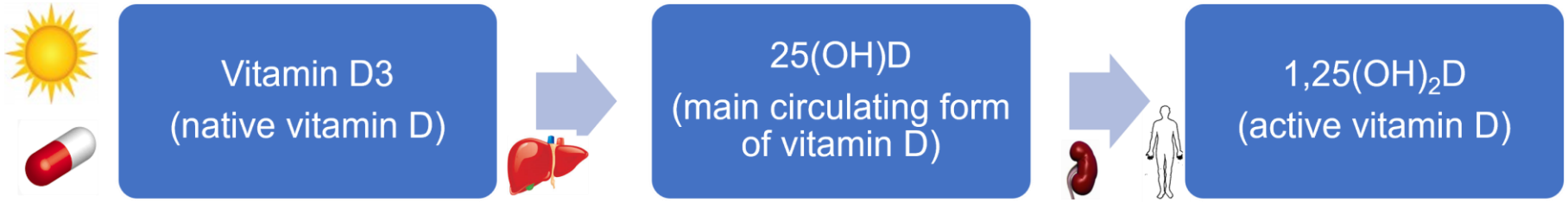
- Increase blood calcium levels by:
  - Stimulating calcium reabsorption in the kidneys
  - Promoting activation of vitamin D
  - Promoting bone resorption



- Reduce blood phosphate levels by:
  - Reducing phosphate reabsorption (increasing excretion)

Calcium and phosphate homeostasis

Vitamin D:



- 1,25$(OH)_2$D increases calcium absorption in the gut *(also increases phosphate absorption)*
- Production of 1,25$(OH)_2$D is tightly regulated by PTH and calcium

Calcium and phosphate homeostasis

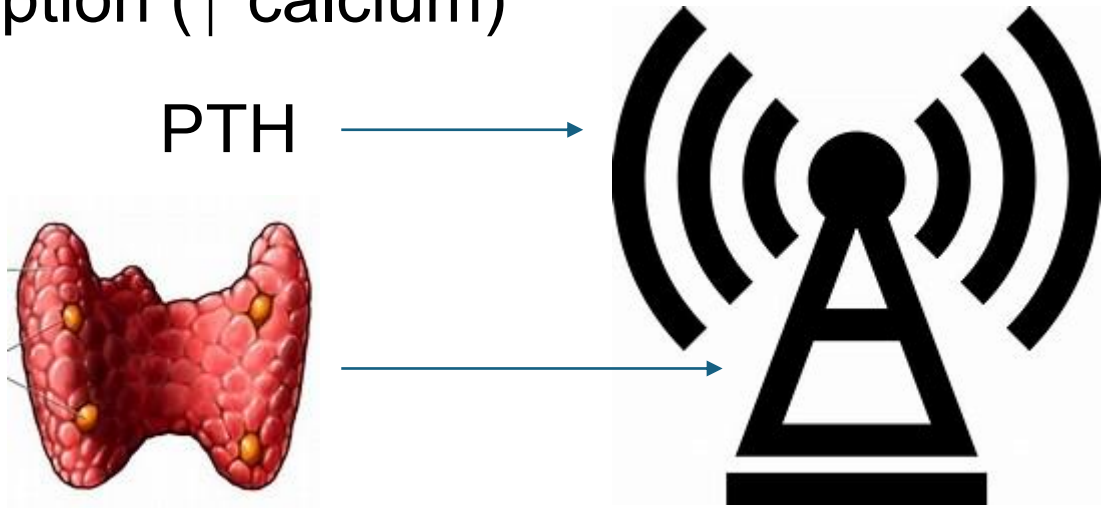
Phosphate:

- Reduced glomerular filtration = less phosphate excreted
- FGF-23 (phosphate and vitamin D regulating hormone) increases to try and normalise phosphate
  - Increases urinary PO4 excretion
  - Decreases 1,25$(OH)_2$D (reduces calcium and PO4 absorption)
- Phosphate levels start to rise at eGFR ~20mls/min/1.73^2

Parathyroid Hormone (PTH)

PTH is released by the parathyroid glands in response to changes in calcium and/or phosphate

- Reduce phosphate reabsorption in the kidney (↓PO4)
- Activate vitamin D (↑ calcium)
- Increase tubular calcium reabsorption (↑ calcium)
- Promote bone resorption



Secondary hyperparathyroidism (SHPT)

In CKD, the kidneys fail to respond to increases in PTH

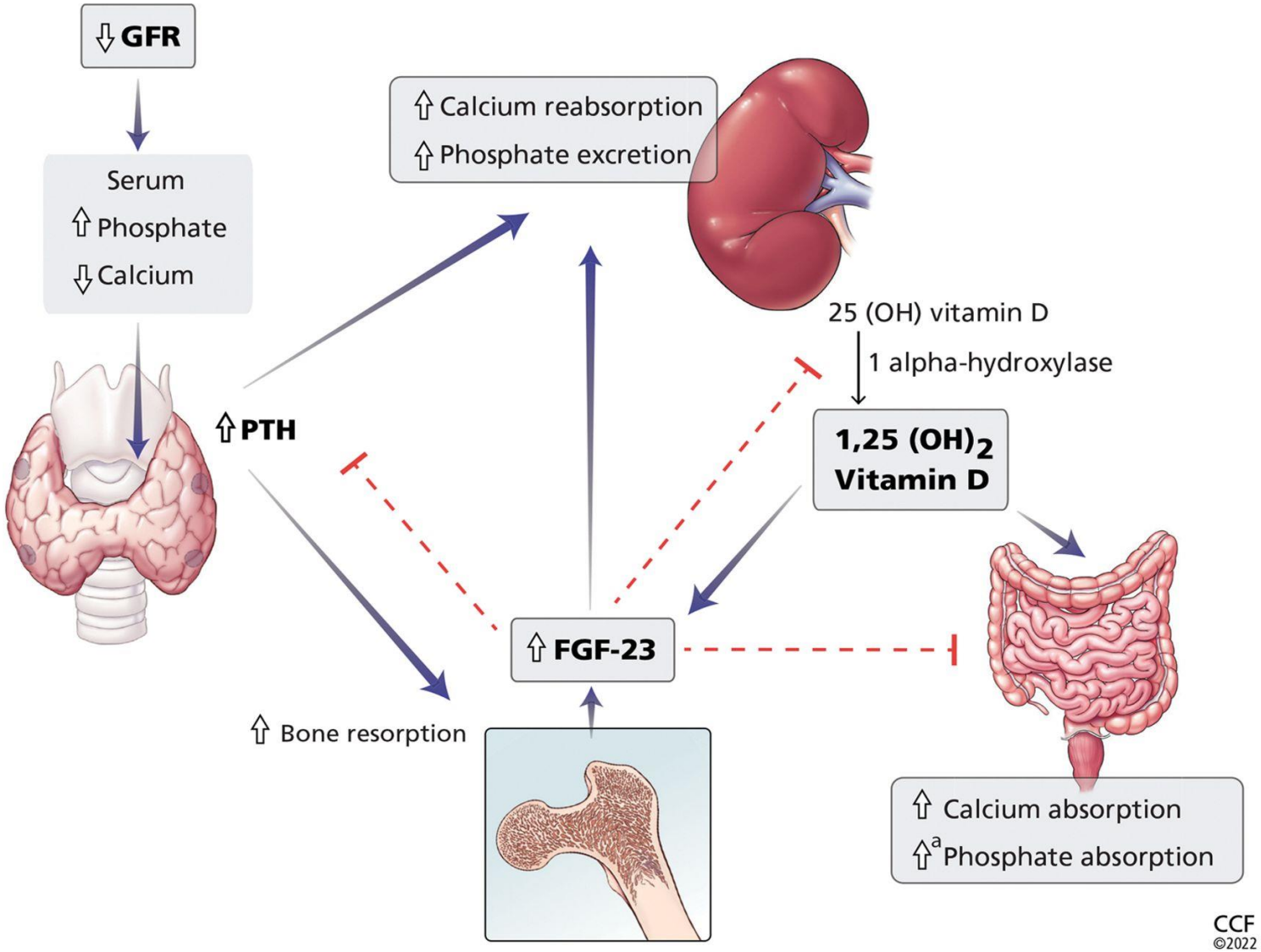
- Normalisation of calcium is more dependent on bone resorption
- PTH and FGF-23 increase (to normalise phosphate)
- PTH secretion becomes excessive

Refractory SHPT

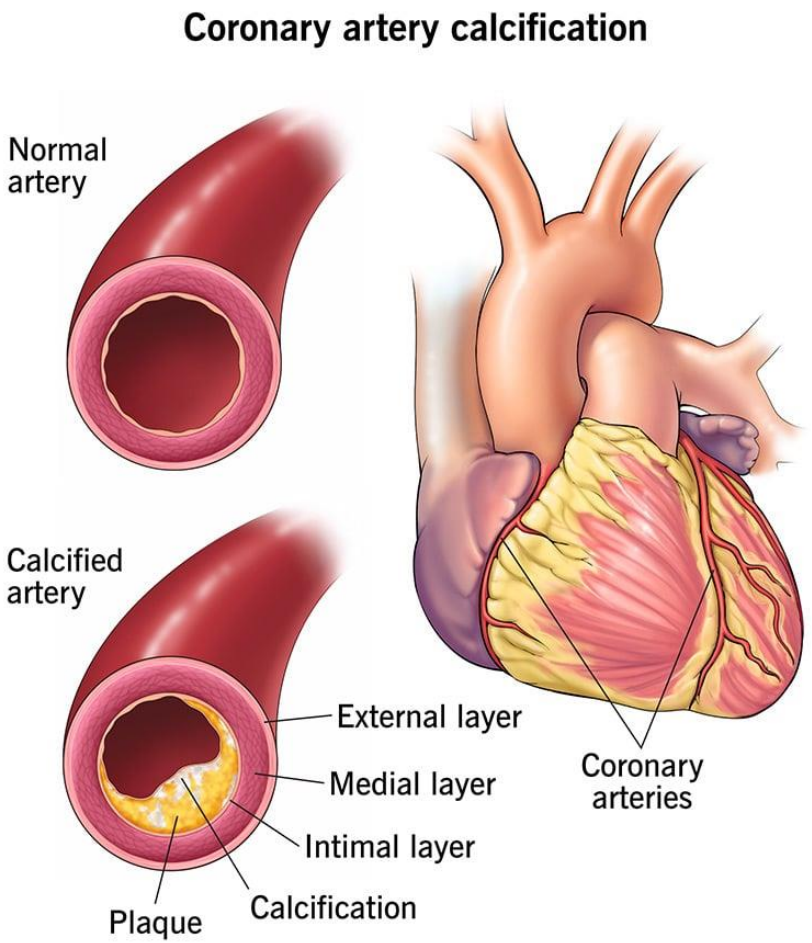
- Very high PTH that doesn’t respond to standard treatments
- Parathyroid hyperplasia
  - Calcium sensing receptor expression is downregulated
- Parathyroid glands function autonomously and continue to secrete PTH even if hypocalcaemia corrected = very high PTH levels (>85pmol/L)

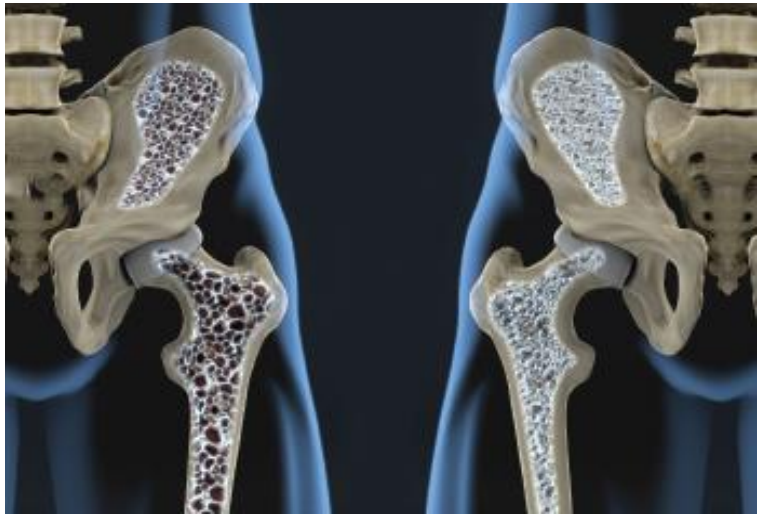
= Surgical parathyroidectomy or calcimimetic

Pathogenesis of SHPT

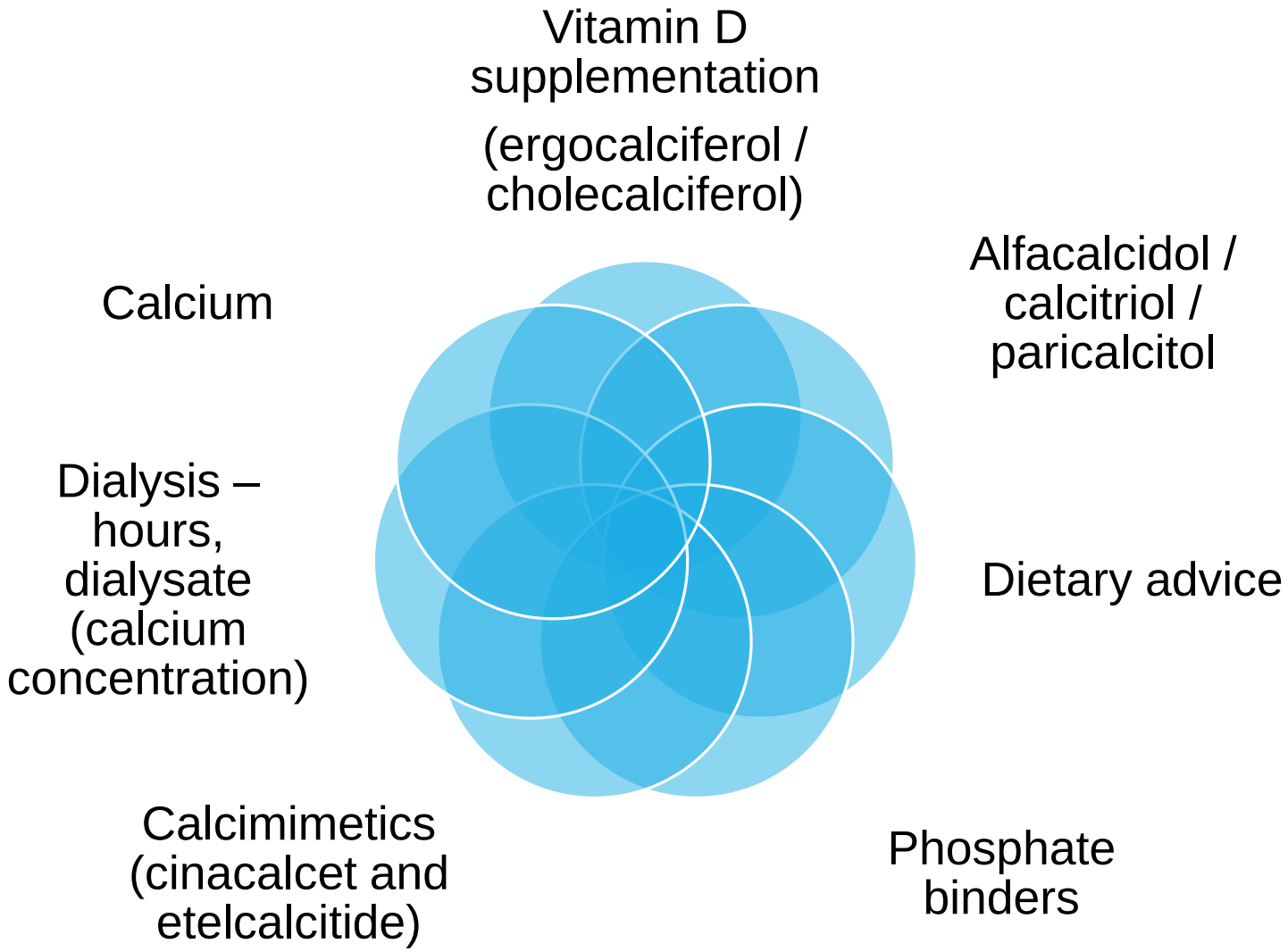


The risks


Coronary artery calcification
Normal artery
Calcified artery
External layer
Medial layer
Intimal layer
Calcification
Plaque
Coronary arteries



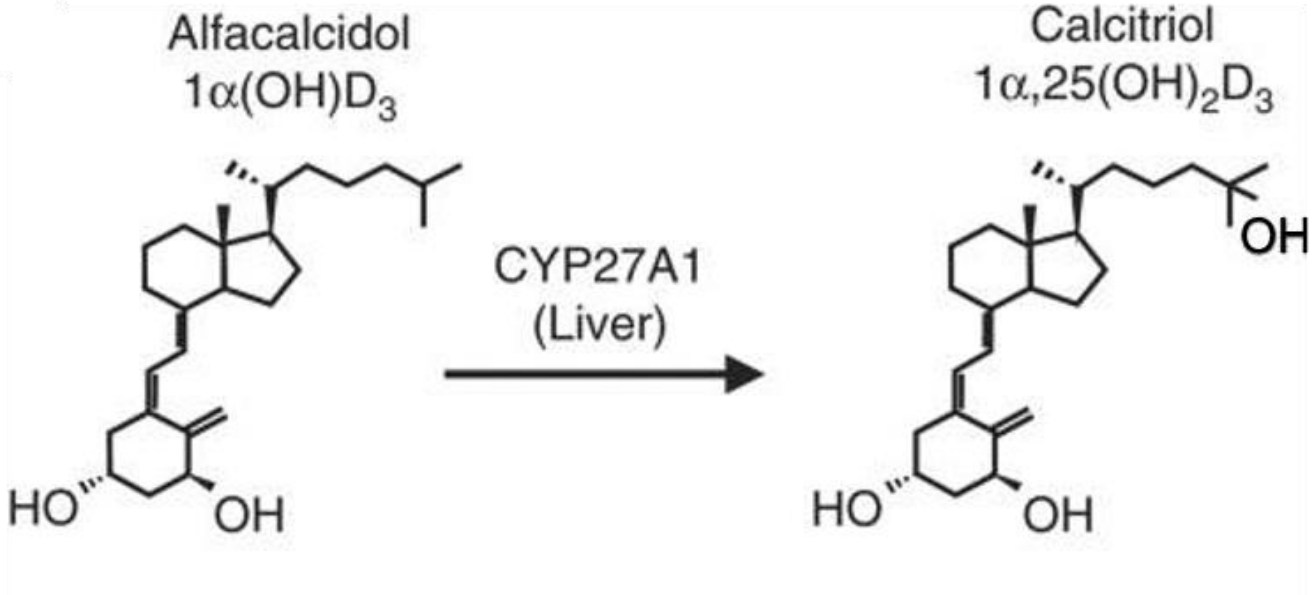
Management


Vitamin D supplementation (ergocalciferol / cholecalciferol)
Alfacalcidol / calcitriol / paricalcitol
Dietary advice
Phosphate binders
Calcimimetics (cinacalcet and etelcalcitide)
Dialysis – hours, dialysate (calcium concentration)
Calcium

Therapeutic strategies

Intervention	Rationale	Considerations
Dietary restriction	Lower phosphate	Nutritional adequacy / appetite / preferences
Phosphate binders	Lower phosphate (bind phosphate in GI tract)	Pill burden Preparation – chew / swallow Calcium / non-calcium / Mg
Vitamin D (eg. colecalciferol)	Low 25(OH)D Calcium / PTH management	Baseline level / BMI Concurrent forms are safe
Active vitamin D / analogues (alfacalcidol / calcitriol)	Increase calcium Indirect suppression of PTH	↑ calcium (hypercalcaemia) ↑phosphate Can over suppress PTH
Calcimimetic (cinacalcet / Etelcalcitide)	Direct suppression of PTH ↑ sensitivity of CaSR refractory secondary hyperparathyroidism	Risk of hypocalcaemia Titration of dose Monthly checking of PTH

Alfacalcidol is not active vitamin D - it needs to be made into it…



Structure of alfacalcidol
Alfacalcidol is metabolised to $1,25(OH)_2D_3$ in the liver by CYP2YA1 (25-hydroxylase).

If a patients' calcium does not increase with alfacalcidol, do not keep increasing the dose – consider calcitriol (and ensure adequate calcium intake)

The guidelines

- NICE
  - CG203 (CKD) – details on binders
  - TA117 (cinacalcet)
  - TA448 (Etelcalcitide)

- KDIGO 2017 and commentaries – New controversies conference paper – Ketteler M et al., 2025 *Kidney International*, Volume 107, Issue 3, 405 – 423

Be aware of the level of evidence

The guidelines

- NICE recommend advice is given by registered dietitians, supported by health professionals with the necessary skills and competence.

- KDIGO (2017) states that it is reasonable to consider the phosphate source (e.g. animal, vegetable, additives) in making dietary recommendations, and that efforts to restrict dietary phosphate must not compromise adequate protein intake.

NICE CG203 - Binders

- Optimise diet (and if applicable, dialysis) then…
- First phosphate binder - calcium acetate
- Offer sevelamer carbonate if calcium acetate is not indicated (hypercalcaemia or low PTH) or not tolerated.
- If calcium acetate and sevelamer carbonate cannot be used, consider:
  - sucroferric oxyhydroxide (if needing non-calcium binder)
  - calcium carbonate, if a calcium-based phosphate binder is needed.
- Only consider lanthanum carbonate for adults with CKD stage 4 or 5 if other phosphate binders cannot be used.
- Include the patient when deciding on a binder

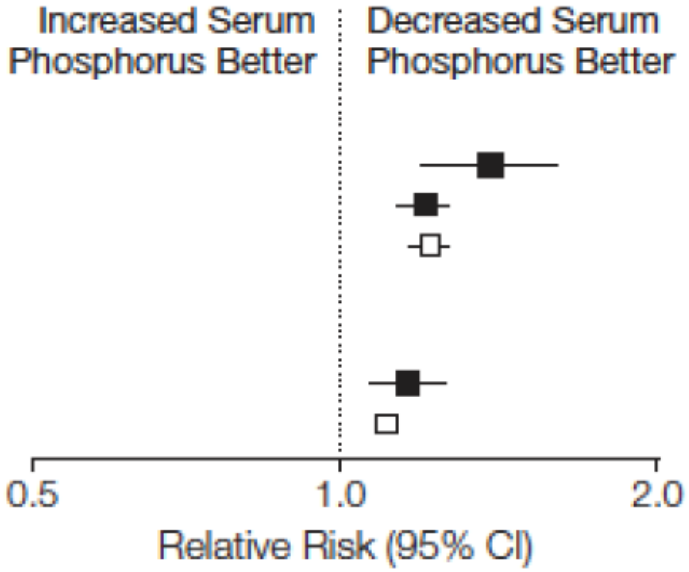
Biomarkers and targets

	Calcium	Phosphate	PTH	25(OH)D
Target range	2.1-2.55mmol/L (or local assay)	0.8-1.5mmol/L Aim towards normal*	1.6-6.9pmol/L** 2-9 times the upper limit of normal	? ≥50nmol/L or ≥75nmol/L

*KDIGO suggest lowering phosphate towards normal.
**PTH target varies according to local assay

Phosphate target

Phosphorus	No. of Cohorts	No. of Participants	Relative Risk (95% CI) Per Unit Increase
All-cause mortality			
Adequate adjustment	3	4651	1.35 (1.16-1.57)
Partial adjustment	10	87 694	1.16 (1.09-1.23)
All studies combined	13	92 345	1.18 (1.12-1.25)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	2	5881	1.14 (1.05-1.24)
All studies combined	3	23 207	1.10 (1.06-1.13)



- 13 *observational* studies, 18% increase in the risk of death for each 0.32 mmol/L increment
- Unclear whether these relationships are causal or mediated by confounders inherent to observational studies

Palmer et al. JAMA. 2011

PHOSPHATE

Investigator-initiated, international, multi-centre, prospective, randomized, open-label, parallel-group, superiority, and pragmatic large simple trial

The United Kingdom: target 2,000 participants

UNIVERSITY OF CAMBRIDGE

NHS Cambridge University Hospitals NHS Foundation Trust

University of Glasgow

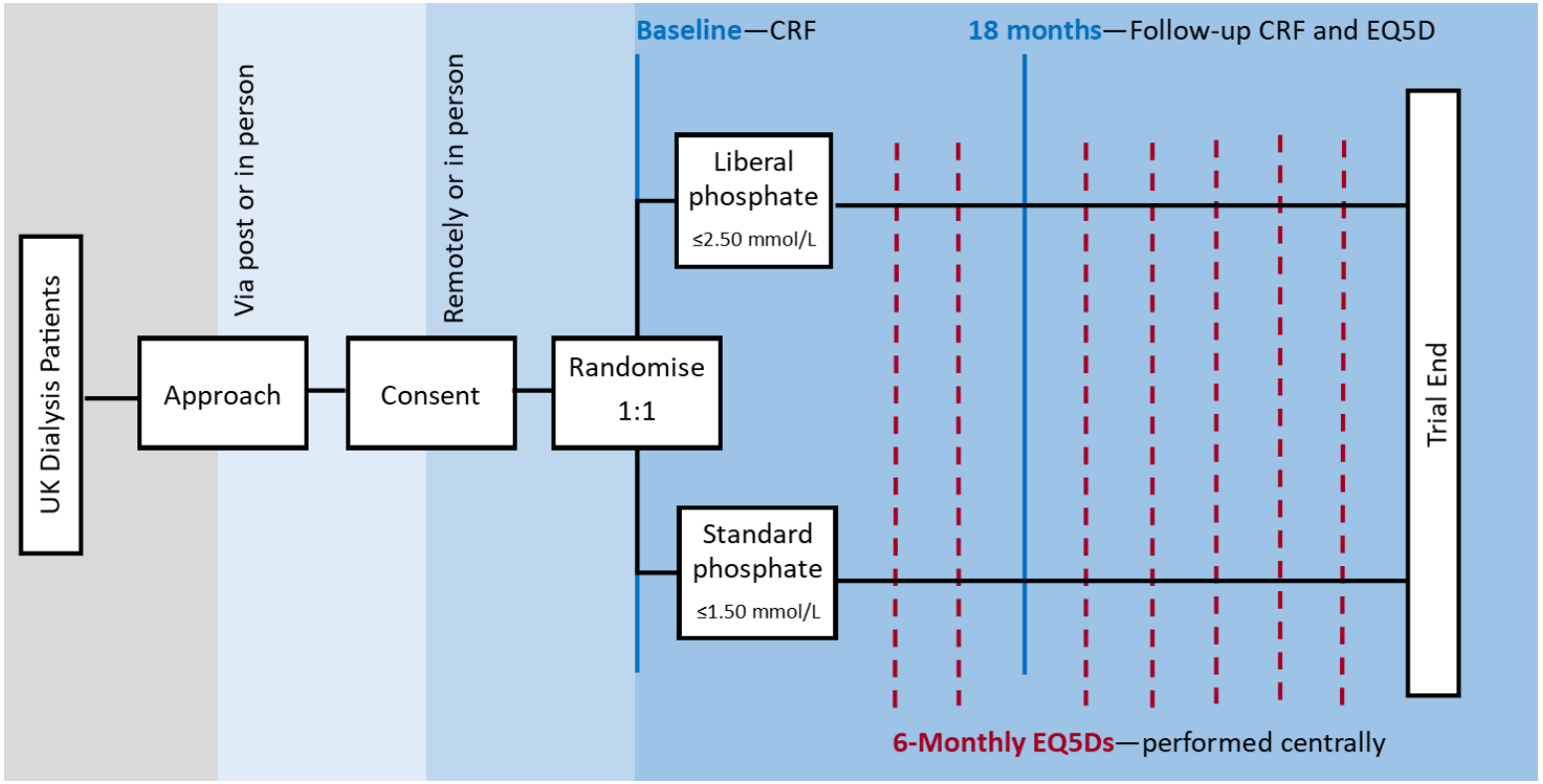
Australia & New Zealand: 600 participants

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

AUSTRALASIAN KIDNEY TRIALS NETWORK

Canada: 1,000 participants

AHRC APPLIED HEALTH RESEARCH CENTRE



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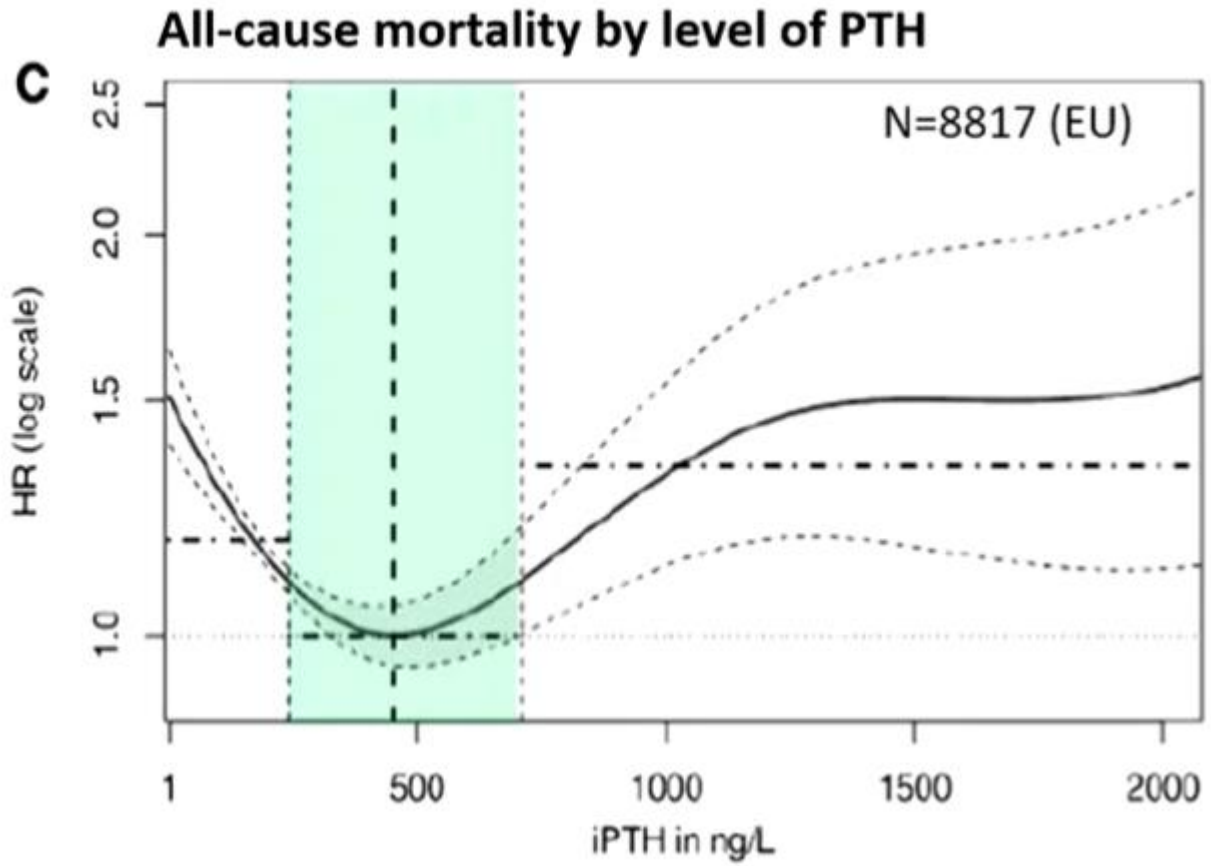
NHS Cambridge University Hospitals NHS Foundation Trust

CCTU Cambridge Clinical Trials Unit

University of Glasgow

PTH target – all cause mortality

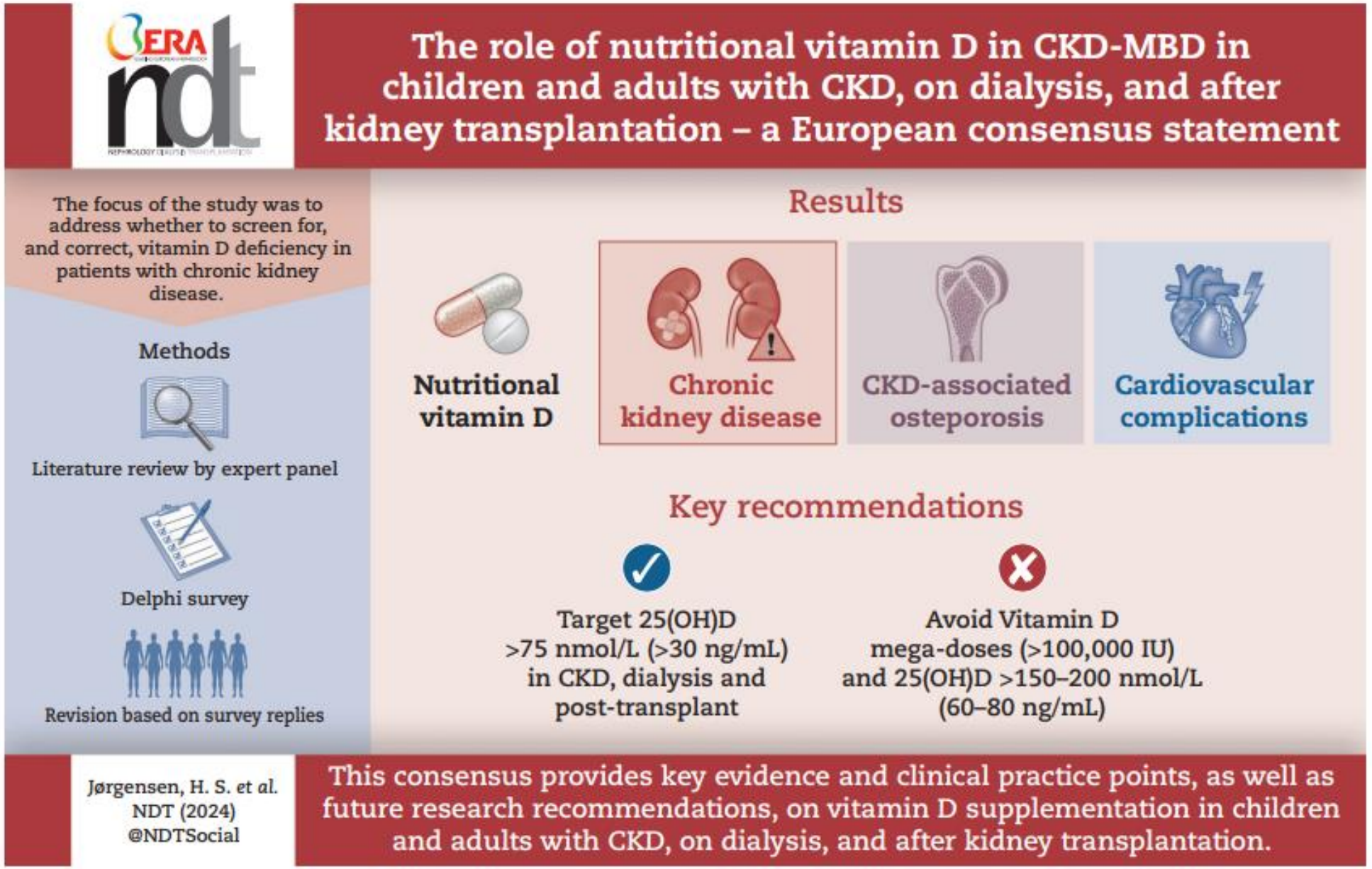


- Absence of data from interventional trials
- Minimum risk 214-981ng/L (23-104pmol/L)
- Increase from low baseline PTH associated with reduced mortality risk

Lamina et al 2020 Nephrol Dial Transplant. 2020 Mar 1;35(3):478-487

To D or not to D?

Does supplementation reduce the risk of cardiovascular events and death? – SIMPLIFIED Trial



Vitamin D – Supplement as per the general population?

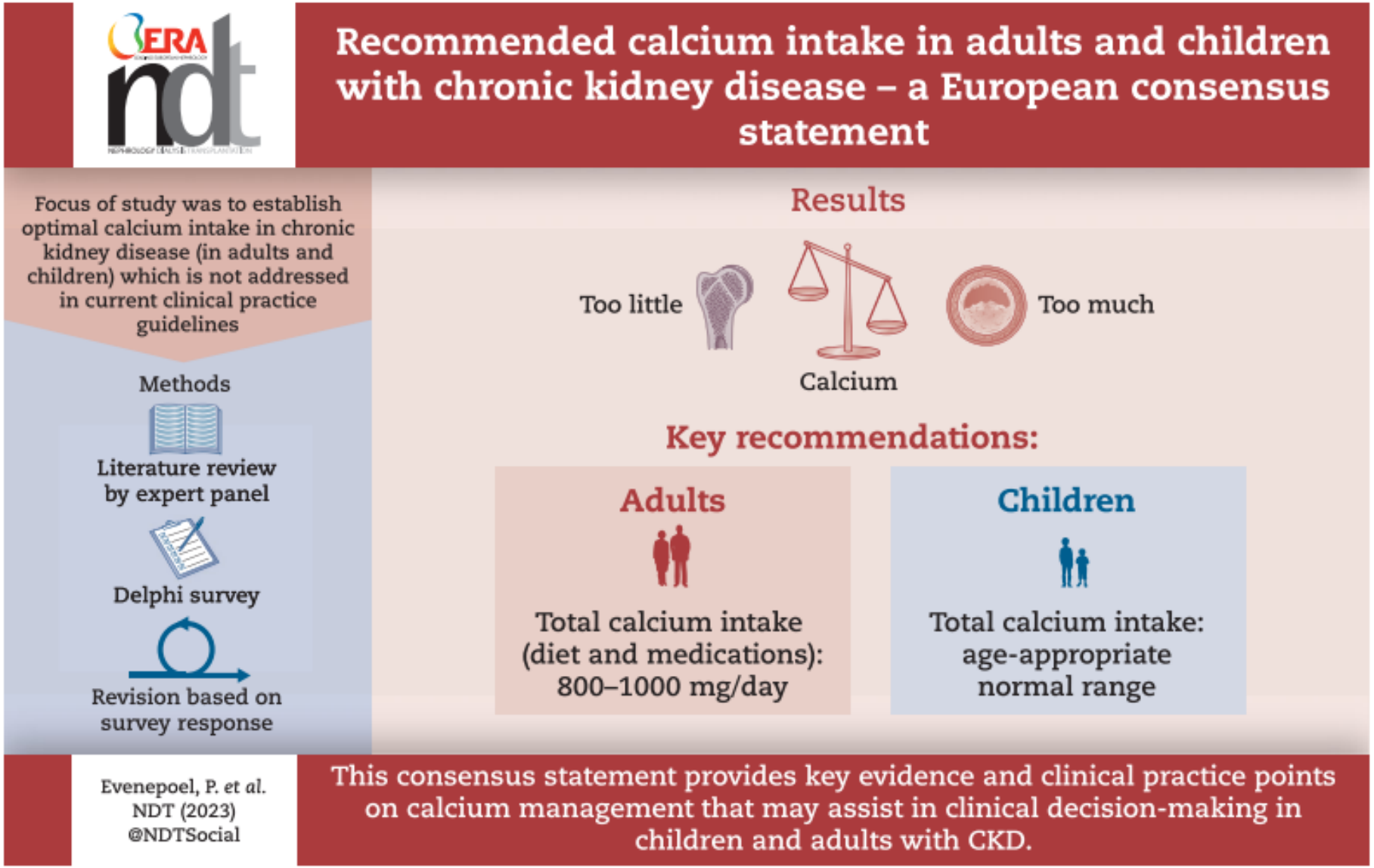
SACN (2016)

- everyone should have 10micrograms (400IU) in the winter months – 25(OH)D ≥25nmol/L

Local formulary guidelines;

- If deficient (<25 or 30nmol/L) – give loading dose 50,000 weekly for 6 weeks (will vary)
- Followed by (or starting with if 25(OH)D 25-50nmol/L) maintenance dose of 800-1000units ~~*(OTC preferred option)*~~

Calcium: friend or foe?



Lack of evidence = limitations in the guidelines/recommendations

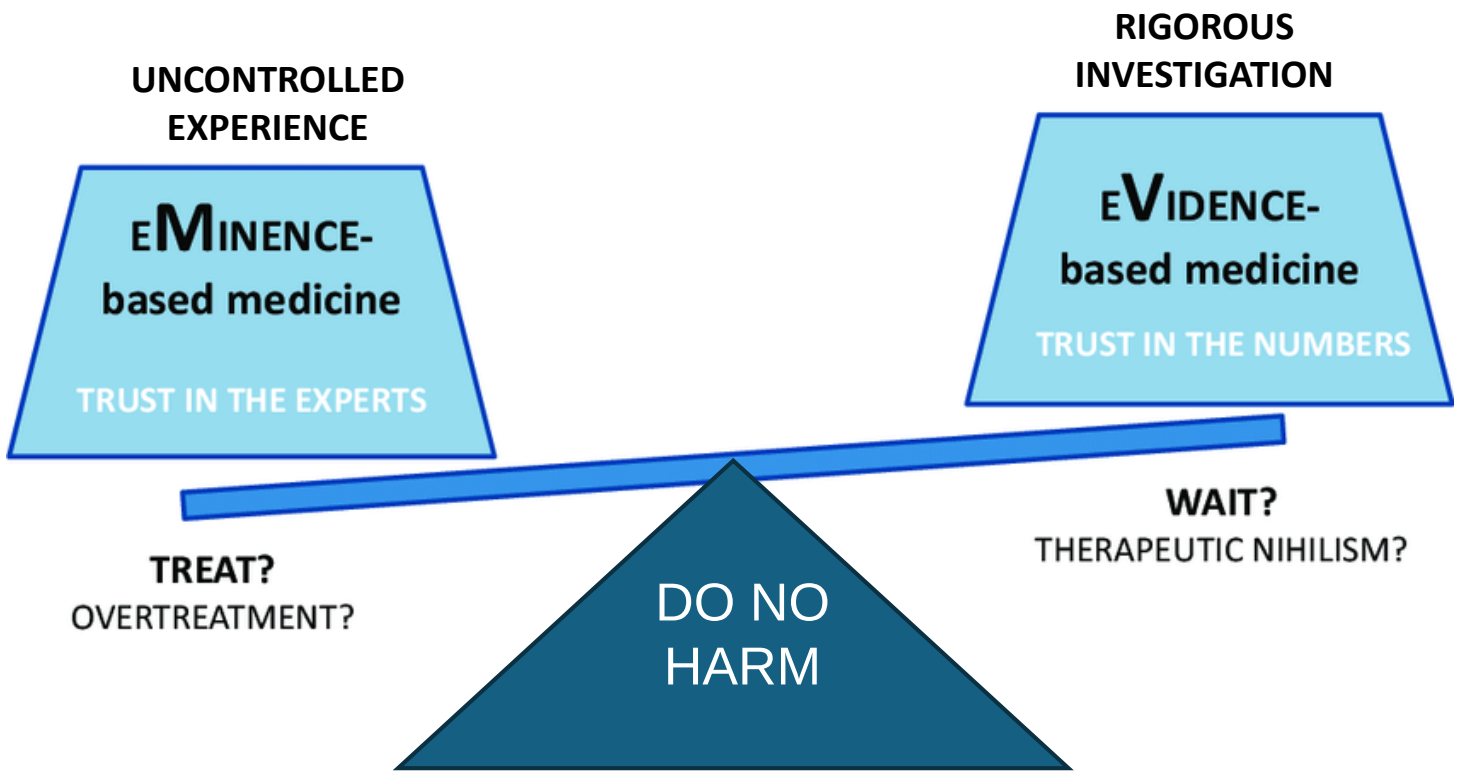
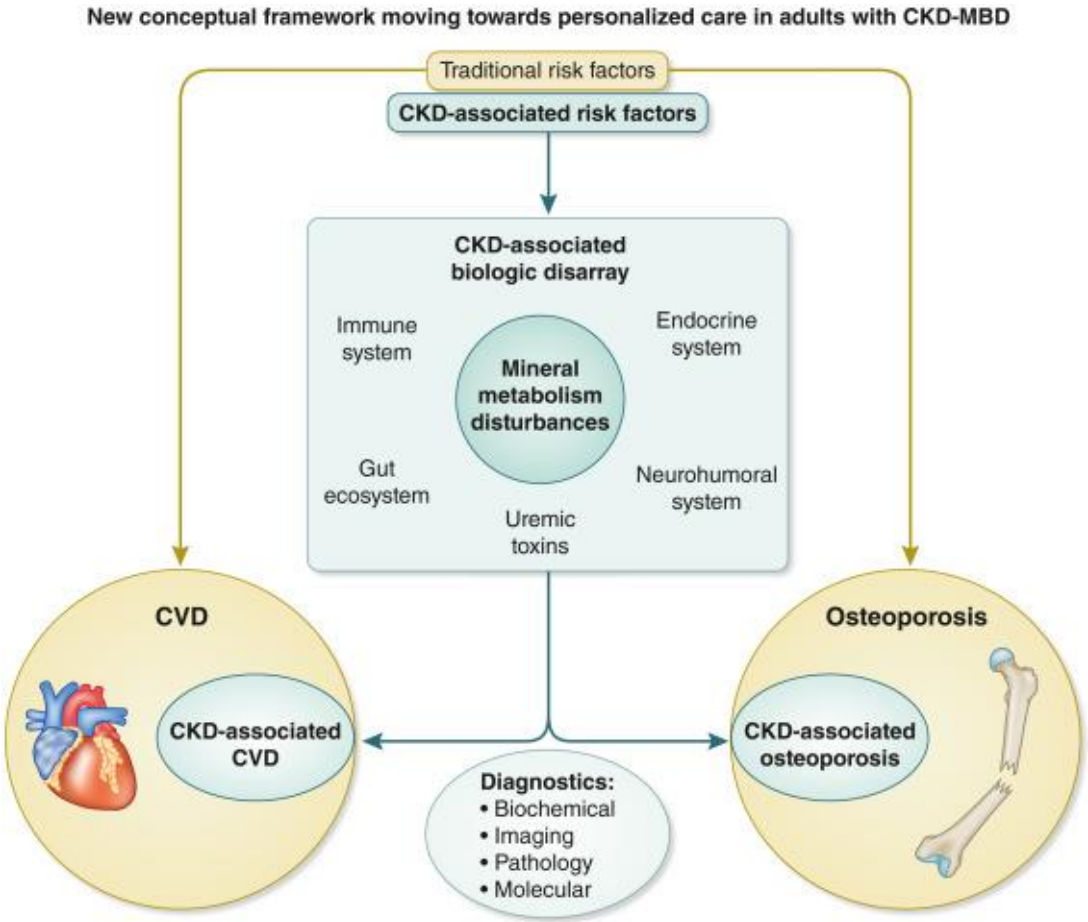
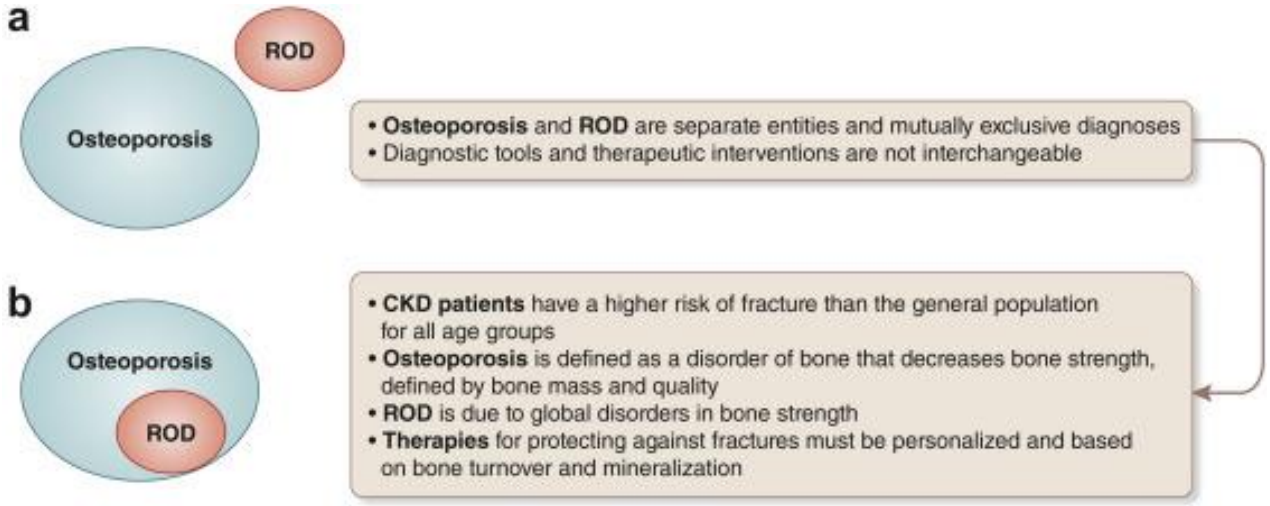


Figure adapted from Bover *et al*., 2020 Clinical Kidney Journal

CKD-MBD
Future directions

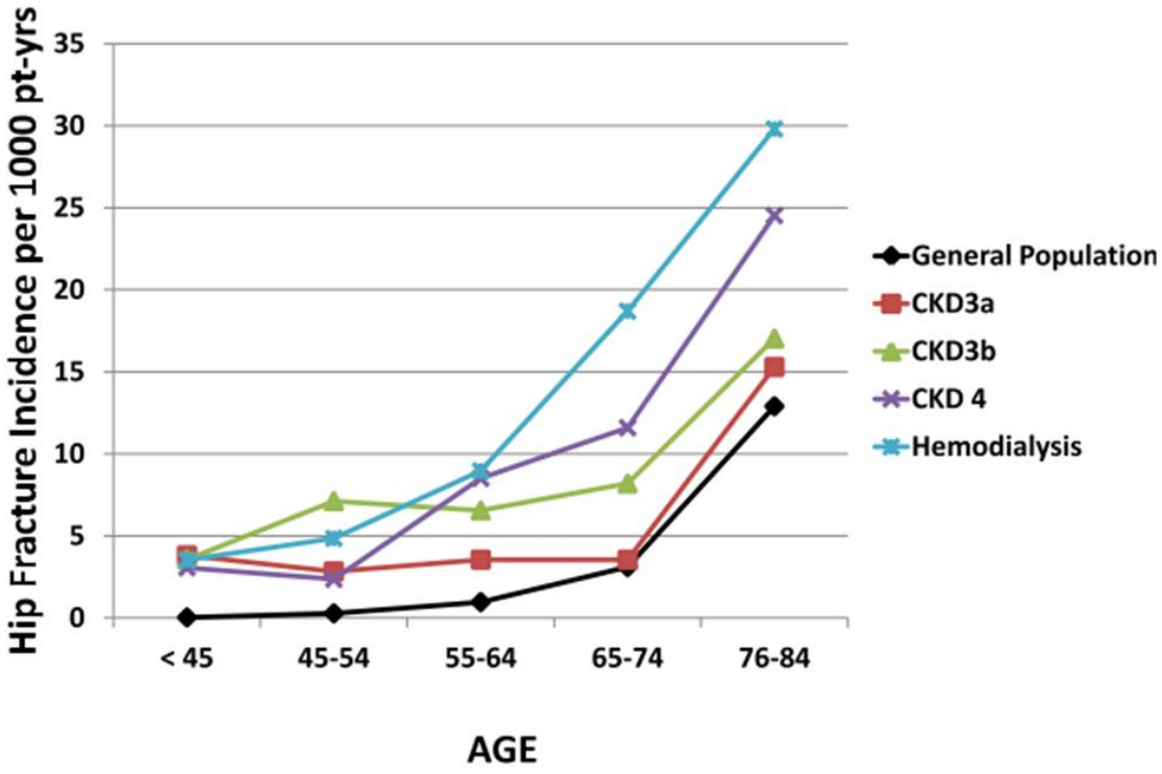
CKD-MBD Controversies Conference





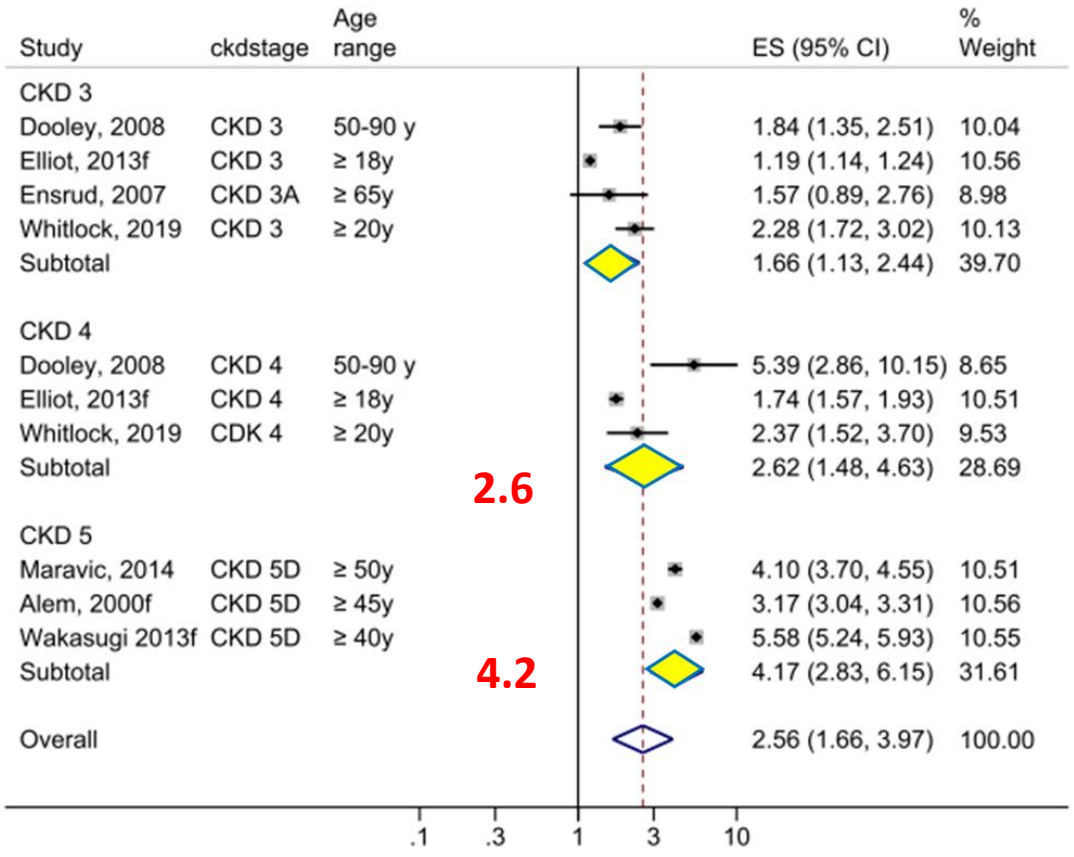
Ketteler M et al. Kidney International 2025, Volume 107, Issue 3, 405 - 423

Hip fracture in CKD



Moe, S; Nickolas, T. Clin J Am Soc Nephrol. 2016

Hip fracture risk in CKD



Vilaca T, Salam S et al. Am J Kidney Dis. 2020 Oct;76(4)

Fracture increases mortality in people having dialysis

IRR = 2.15 compared with no fracture dialysis patients

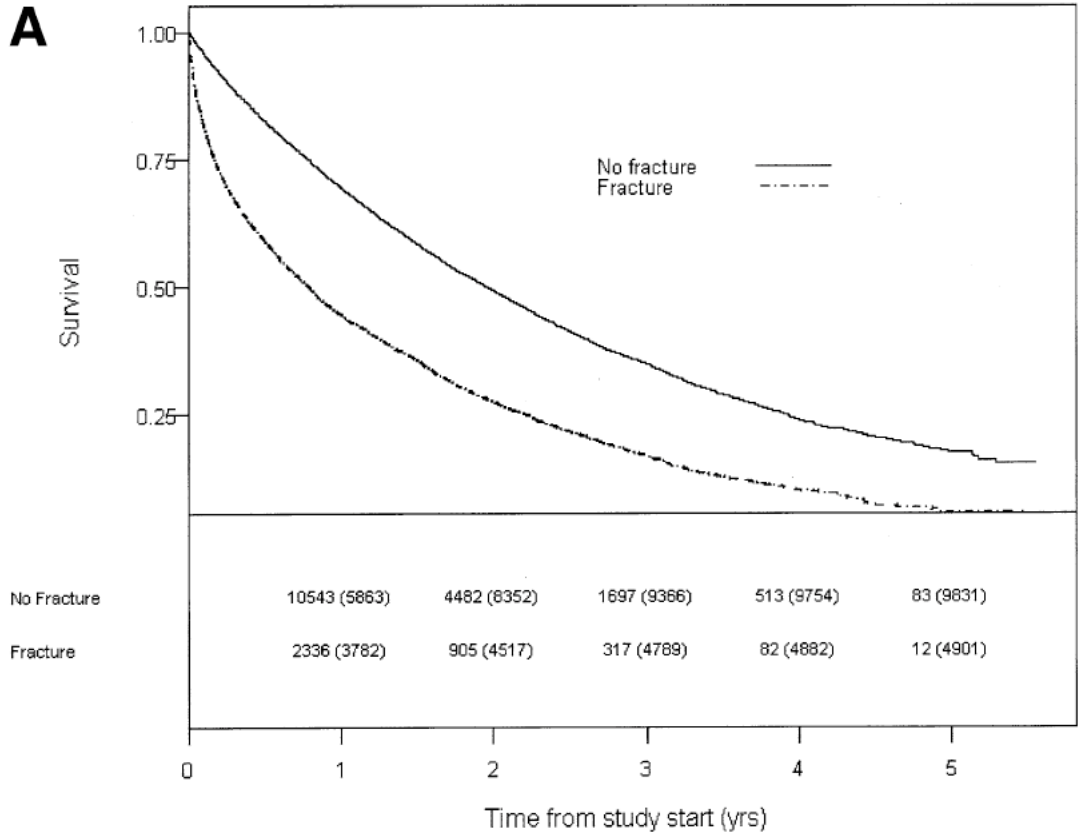
US Renal Data system - Dialysis patients

Medicare – hip fractures

7,626 patients with a hip fracture

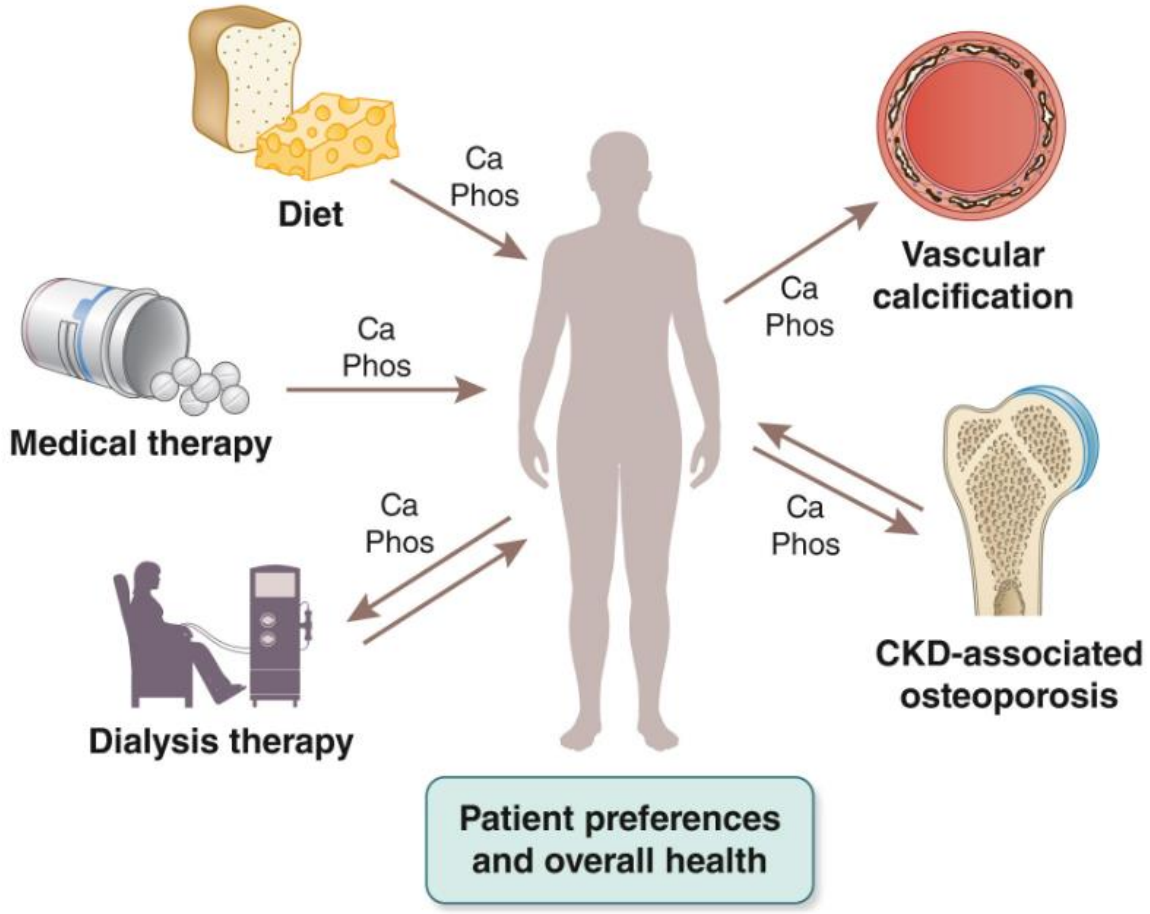
Median survival 289 days

50% mortality at 1 year



Mittalhenkle Am J Kidney 2004

What matters most to the person in front of you?



Ketteler M et al. Kidney International 2025, Volume 107, Issue 3, 405 - 423

Thank you

UK Kidney Research Consortium
CKD-MBD Clinical Study Group