# CKD AND OSTEOPOROSIS

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# LONDON 2019

# Case 1

## Metabolic Bone Clinic Referral

- 75 year old female
- Referred to Metabolic Bone Clinic 2011
- Multiple fracture risk factors
  - Age
  - Early menopause
  - Long-term prednisolone use
  - Low calcium intake
  - CKD stage 4

## Multiple Co-Morbidities

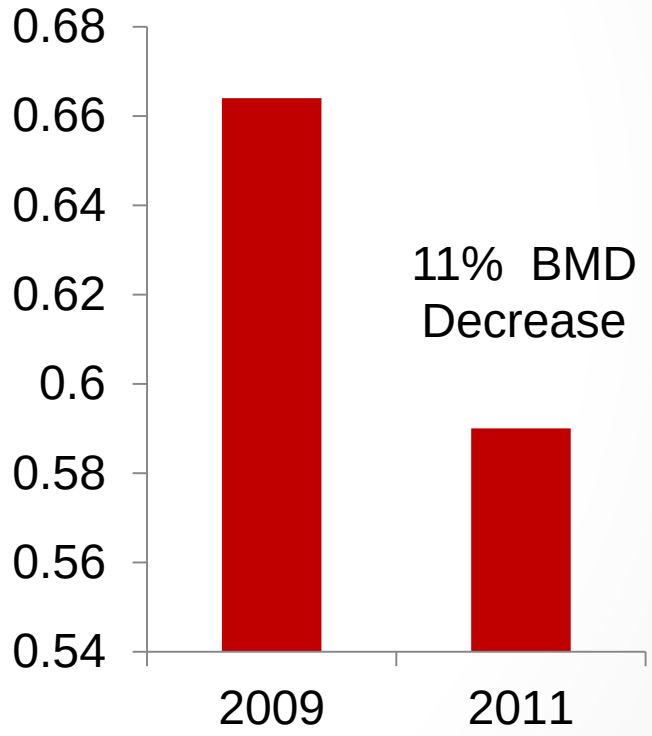
- ESRF from MCGN
- Renal transplant in 1993
  - eGFR 20
- Diabetes Mellitus
- Previous TB
- Hypertension
- Hyperlipidaemia
- Hypovitaminosis D
  - Treated 40,000IU/month for 6 months

# Fracture Risk and BMD Loss

## FRAX Assessment Of Fracture Risk

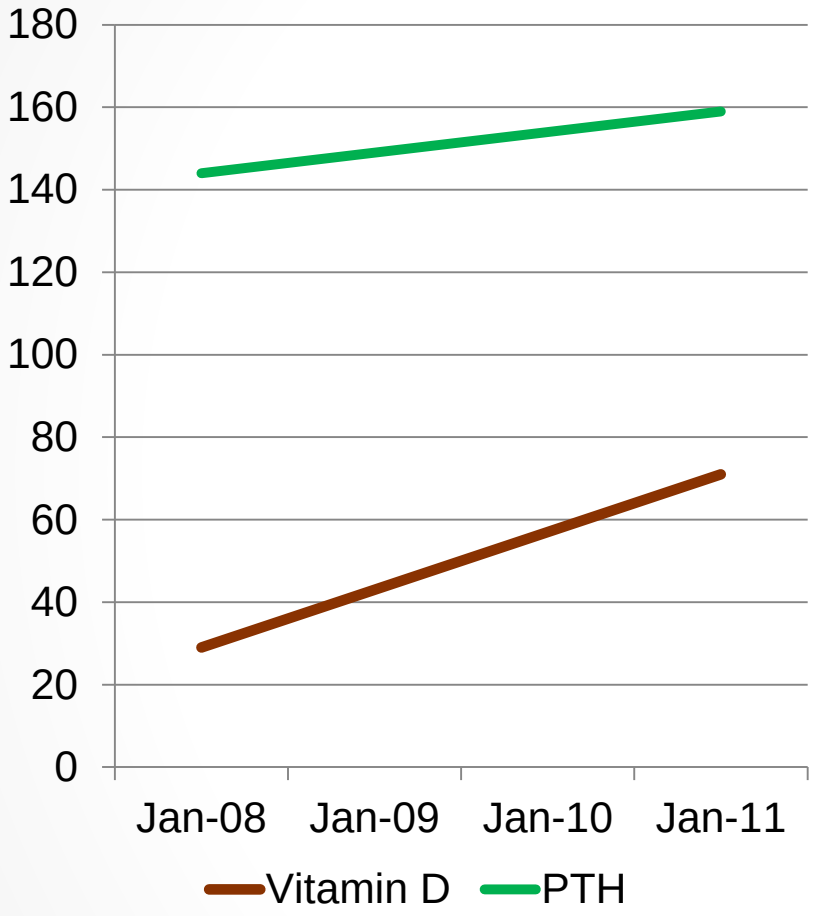
| Risk Type | 10 Year Risk |
|---|---|
| Major Fracture | 28% |
| Hip Fracture | 12% |

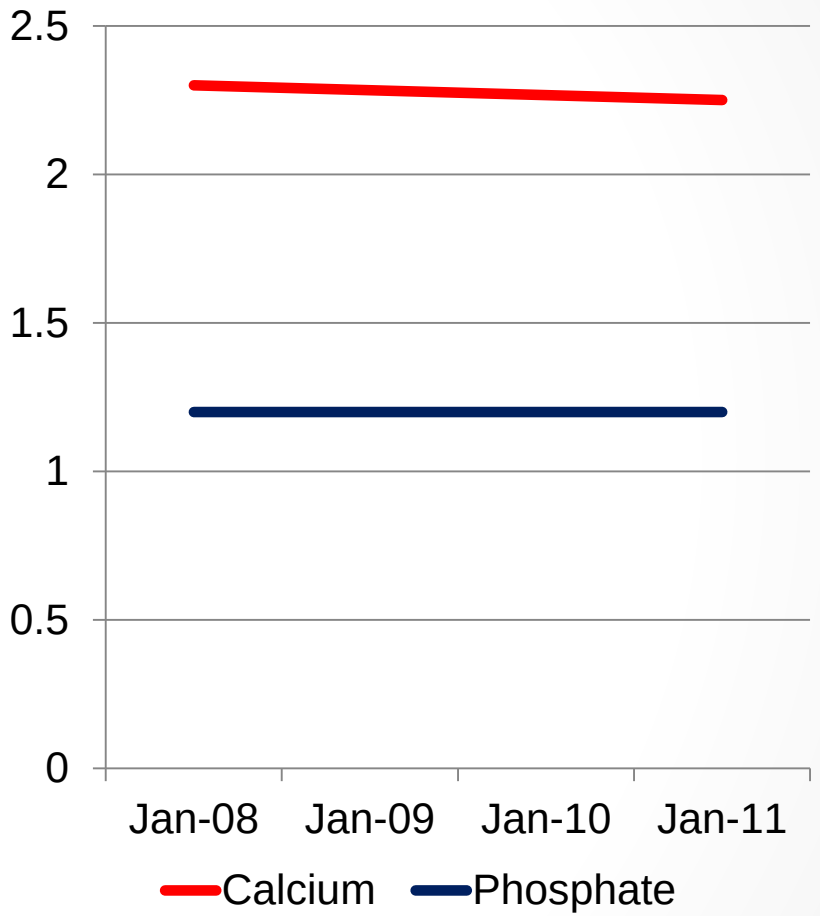
## Bone Mineral Density




**High Risk Of Fragility Fracture**

# Bone Profile




**Despite vitamin D replacement PTH still high**
**Likely both osteoporosis and CKD metabolic bone disease**

## What would you do?

1. Prescribe active vitamin D
   - Lowering PTH may cause adynamic bone disease
2. Prescribe bisphosphonate

   a) Would you use normal or half-dose

   b) For what duration
3. Perform a bone biopsy
   - Exclude adynamic bone disease (unlikely as PTH high)
4. Measure bone specific ALP
   - If high adynamic bone disease unlikely

# What we did

1. Optimised calcium status
   - Adcal D3 one tablet daily (CV risk)
2. Risedronate 35mg once fortnightly
   - As PTH >150 adynamic bone disease unlikely
   - Bone biopsy best practice
3. Discuss with renal physicians regarding active vitamin D
4. Follow-up 3 months

# Case 2

## Metabolic Bone Clinic Referral

- 66 year old female
- Referred metabolic bone clinic 2009
- Renal History
  - ESRF
  - Anti-GBM + ANCA positive cresenteric glomerulonephritis
  - Renal transplant 2003
  - Stable eGFR 32ml/min
- During ESRF had hyperparathyroidism → parathyroidectomy

## Fragility Fracture Risks

- Early menopause
- Post-transplant steroids
- Loss of vertebral body height
- BMD evidence of osteoporosis

## Osteoporosis History

- Osteoporosis diagnosed post-transplant 2003
  - T-score hip -3
- 2005
  - worsening BMD: T-score hip -4.4
  - alendronate started
- 2007
  - 11% improvement in BMD
  - T-score hip -3.9
- When seen as new patient in 2009 BMD improved and stable
  - Continued alphacalcidol + alendronic acid

# Seen January 2010- Deterioration

- Further fractures
  - Metatarsal stress and rib fractures
- Falling BMD
  - 4.1% fall over 12 months
- T score
  - Spine -4.4
  - Hip -2.6

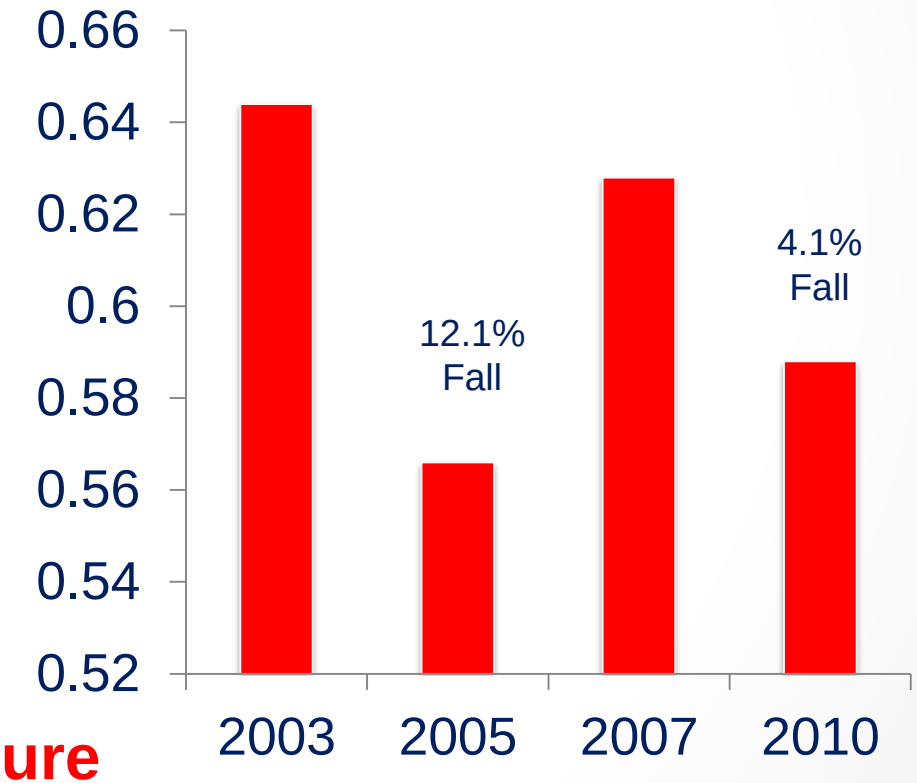
**Summary- 4 years alendronate therapy, previous parathyroidectomy, worsening BMD**

# Fracture Risk And Bone Mineral Density Change

## FRAX Assessment Of Fracture Risk

| Risk Type | 10 Year Risk |
|---|---|
| Major Fracture | 39% |
| Hip Fracture | 19% |

## Hip Bone Mineral Density



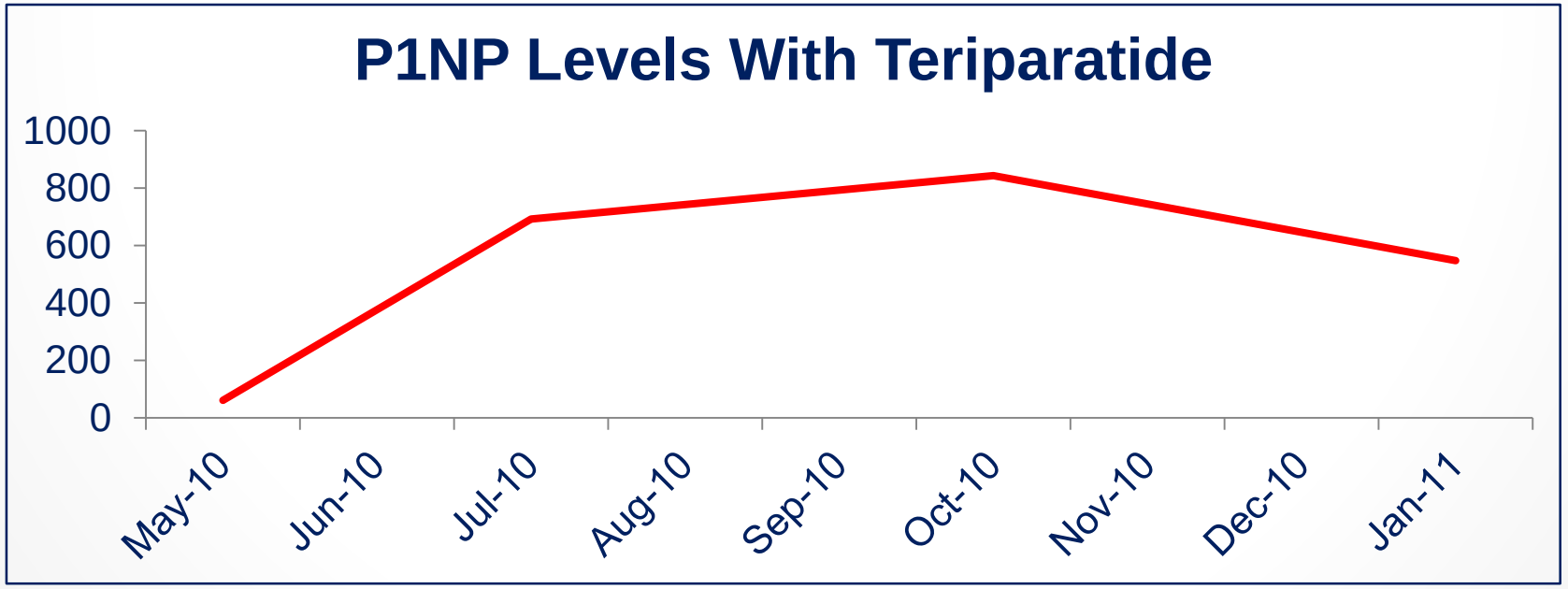

**High Risk Of Fragility Fracture**

# What would you do?

1. Stop alendronic acid
2. Perform bone biopsy
   - Exclude adynamic bone disease
3. What other treatments would you consider

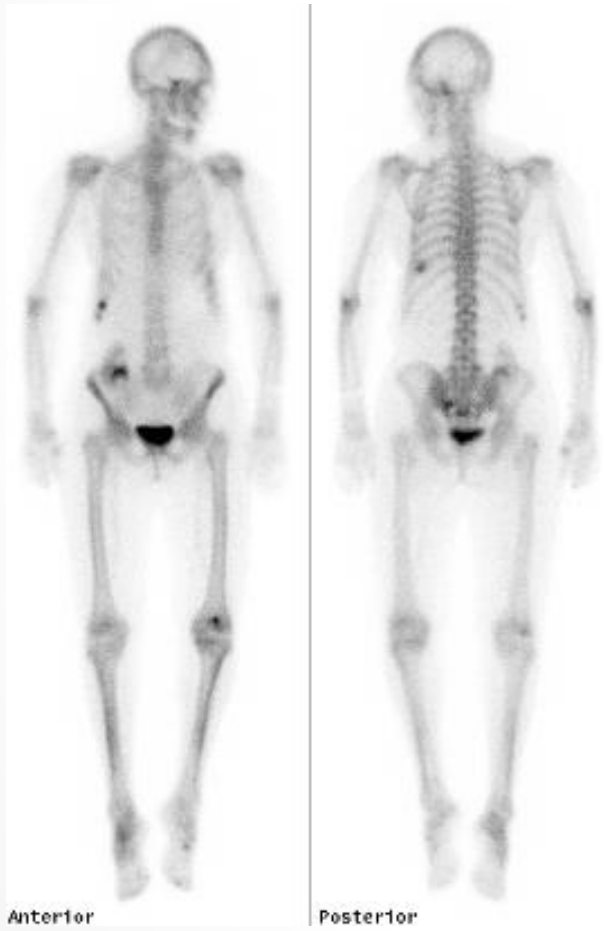
# What we did

1. Stopped alendronic acid
2. Inititated teriparatide

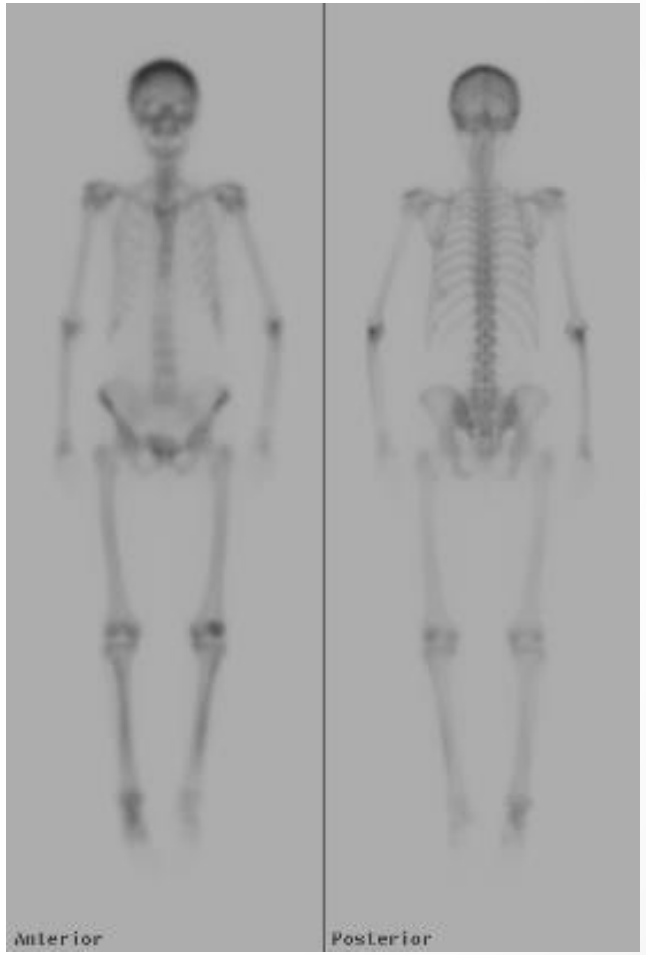


# Isotope Bone Imaging Response

## Pre-Teriparatide

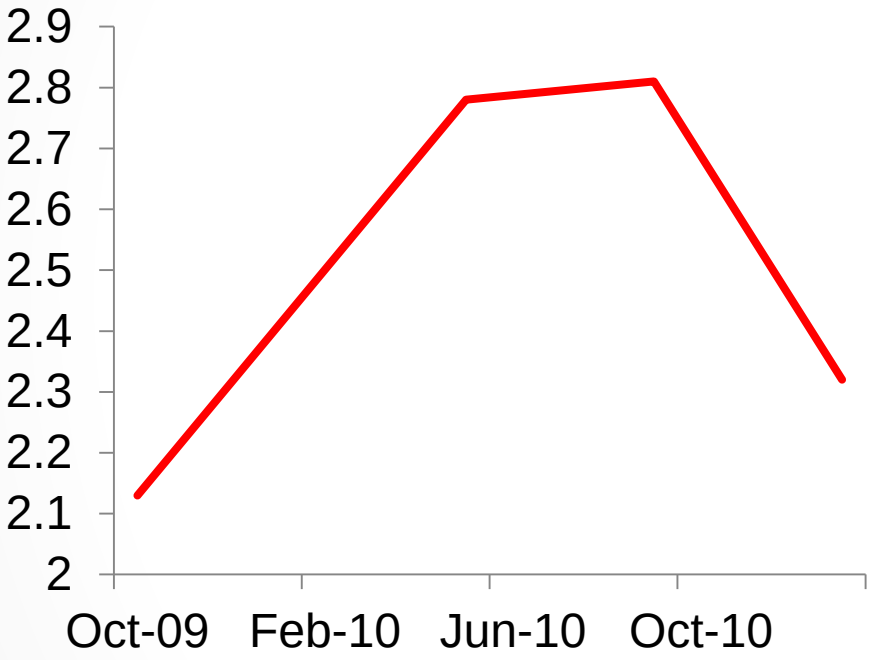



## Post-Teriparatide



# BMD and Calcium Response

## Calcium




## BMD Response

- Increase over 6 months
- 10% at lumbar spine

- Hypercalcaemia with teriparatide initiation
- Responded to alphacalcidol reduction (1mcg to 0.5mcg)

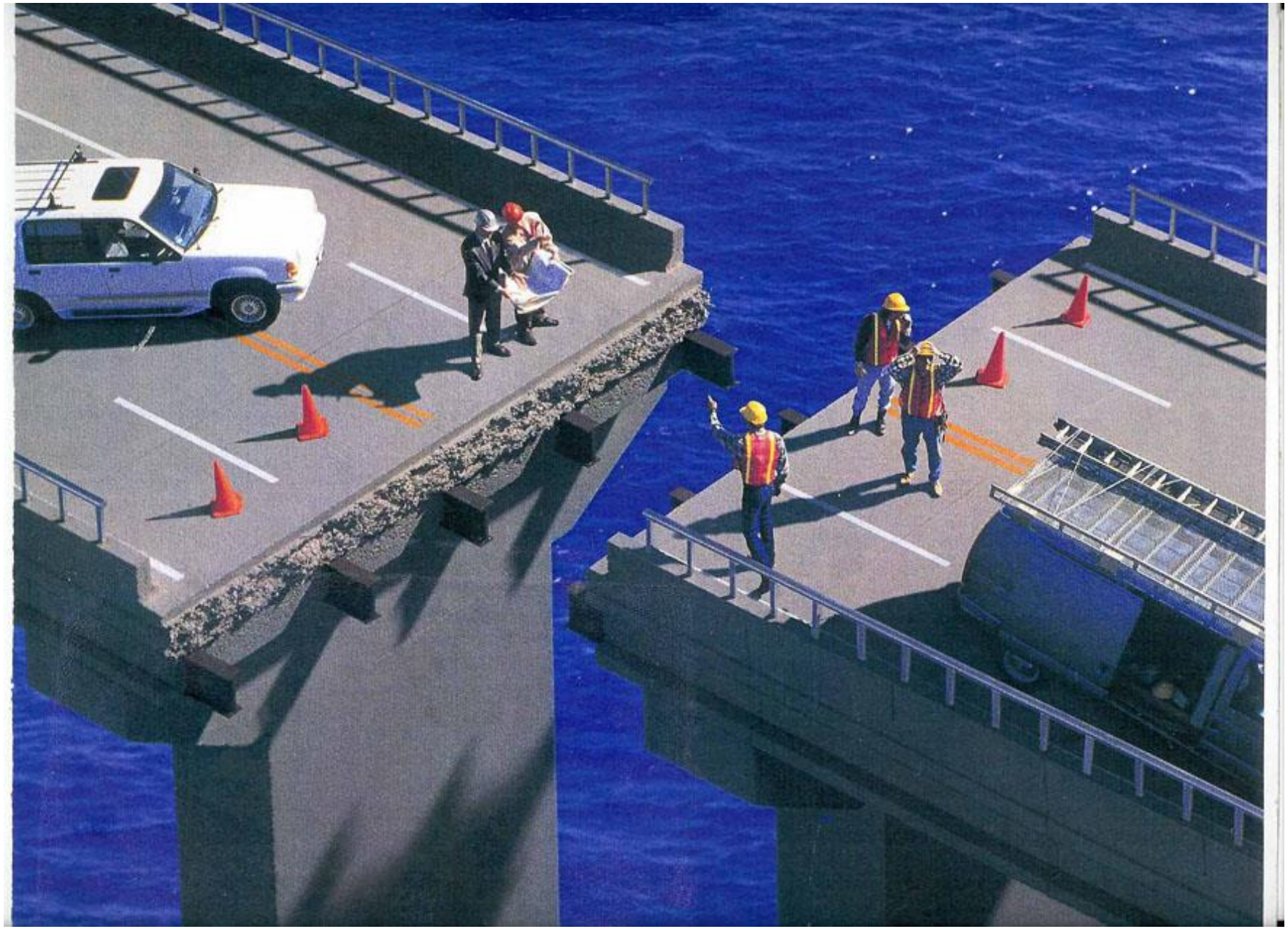
# Siamese Twins – CKD, osteoporosis

- CKD and osteoporosis get much more common with advancing age
  - So “co-localisation” is inevitable
- BUT, CKD has its own important set of skeletal consequences
  - How do these interact with, affect, alter, osteoporosis
    - Diagnostically ?
    - Therapeutically ?

# Are we singing from the same hymnsheet?

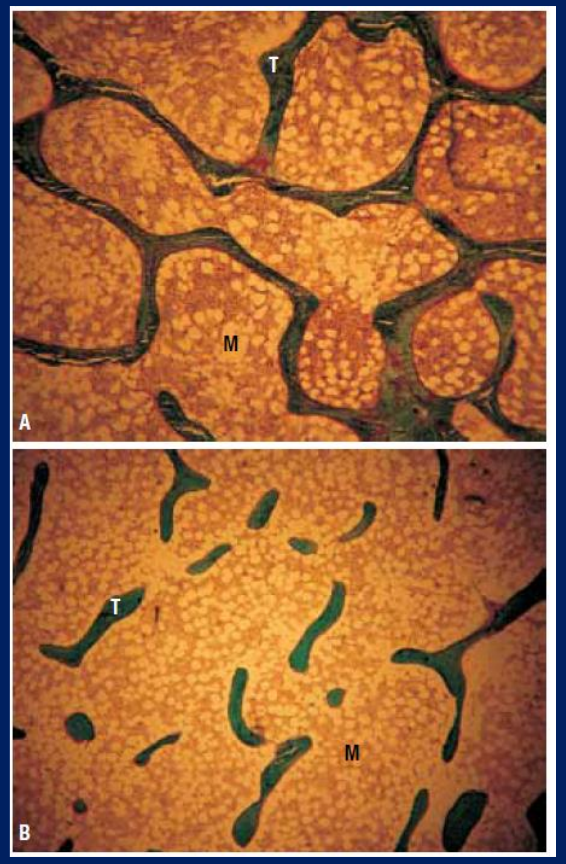
- Rheumatology/Osteoporosis/Care of the Elderly

- Nephrologists
  - CKD, Dialysis, Transplantation

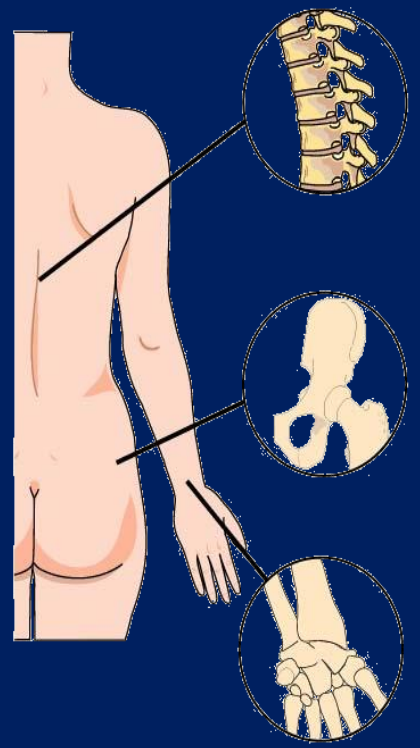


# Osteoporosis

***'…a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fracture'***




## Common sites of fracture



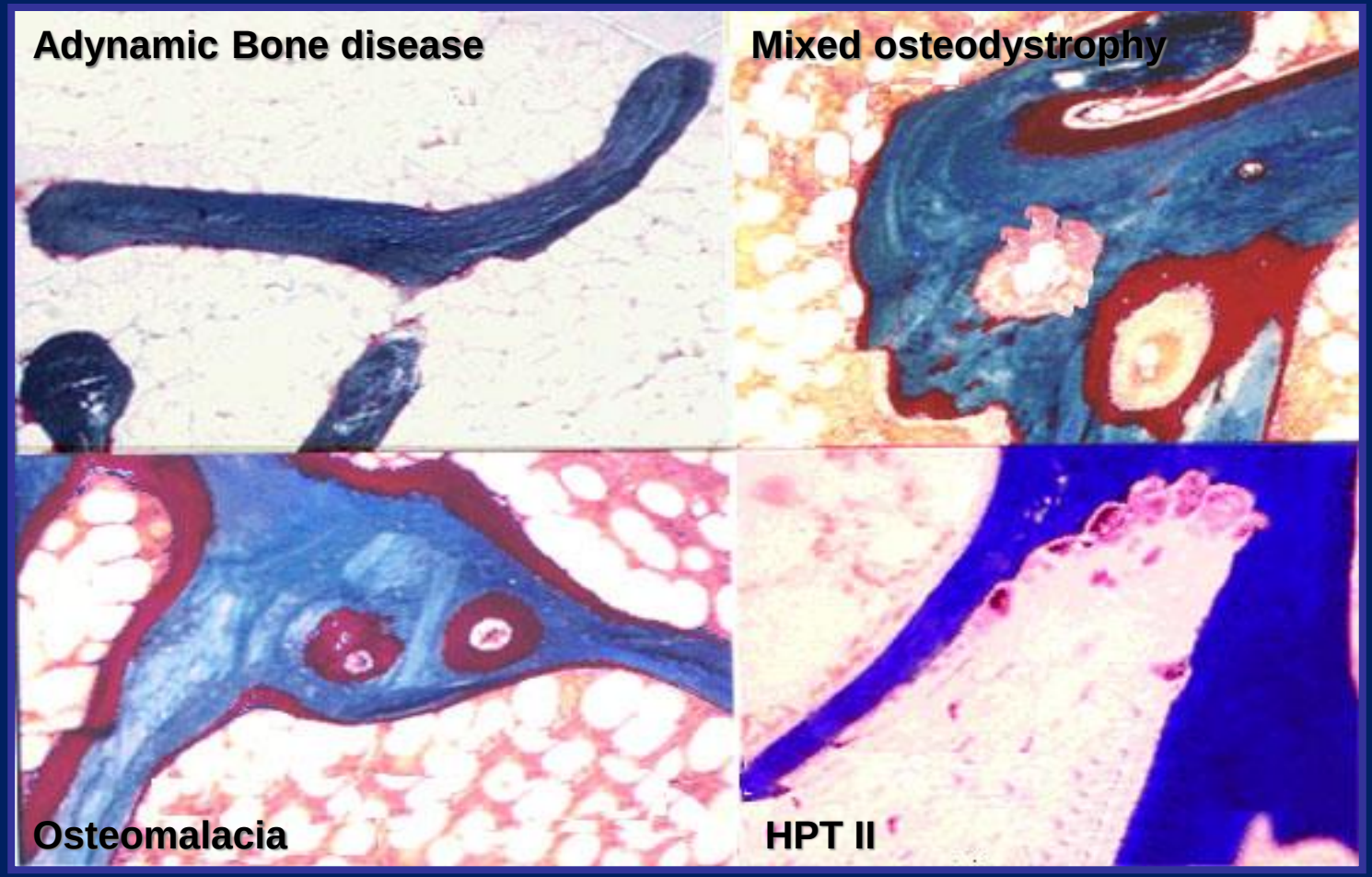
Spine

Neck of femur

Wrist

# Bone disorders in CKD

- ***Systemic dysregulation of bone and mineral metabolism, defined as CKD-MBD (includes biochemical abnormalities and calcification in vascular and soft tissues)***
- ***Renal osteodystrophy : abnormalities in bone histomorphometry that develop as a consequence of CKD-MBD***



# Prevalence of spectrum of bone disorder in CKD-MBD

*Table 1.* Bone biopsies results in predialysis patients[a]

| Reference | No. of Patients | SHPTH (%) | MHPTH (%) | OM (%) | MBD (%) | AMBD (%) | ABD (%) | Normal Bone (%) | Treatment |
|---|---|---|---|---|---|---|---|---|---|
| Eastwood *et al.*, 1982 (23) | 38 | 86.8 | | 44.7[b] | | | NA | 10.2 | No vitamin D |
| Mora Palma *et al.*, 1983 (24) | 327 | 54.0 | | 34.0 | | | NA | 12.0 | NA |
| Dahl *et al.*, 1988 (25) | 60 | 80.0 | | 1.6 | | | NA | 11.0 | NA |
| Hutchinson *et al.*, 1993 (26) | 30 | 27.0 | 23.0 | 7.0 | 13.0 | | 27.0 | | $CaCO_3$ 2 to 10 g/d |
| Hernandez *et al.*, 1994 (27) | 92 | 57.4 | 23.0 | 11.0 | | | | | No vitamin D<br>$CaCO_3$ |
| Torres *et al.*, 1995 (28) | 38 | 30.0 | 10.0 | 2.0 | | 10.0 | 48.0 | | No vitamin D<br>$CaCO_3$ |
| Hamdy *et al.*, 1995 (15) | 87 placebo | 71.0 | | 1.0 | 20.0 | | 3.0 | | |
| | 89 vitamin D | 75.0 | | 0.0 | 18.0 | | 7.0 | | $CaCO_3$ 3 to 8 g/d |
| Coen *et al.*, 1996 (29) | 76 | 2.7 | | 9.0 | 34.2 | 28.0 | 11.8 | 13.0 | No vitamin D<br>No $CaCO_3$ |
| Shin *et al.*, 1999 (30) | 58 | 8.6 | 36.2 | 10.0 | 12.0 | | 24.1 | 8.6 | NA |
| Ballanti *et al.*, 2001 (5) | 27 | 8.0 | | 11.0 | 34.0 | 26.0 | 26.0 | | No vitamin D<br>No $CaCO_3$ |
| Spasovski *et al.*, 2003 (31) | 84 | 9.0 | | 12.0 | | 18.0 | 23.0 | 38.0 | $CaCO_3$ 0.5 g/d<br>No vitamin D |

[a]ABD, adynamic bone disease; AMBD, advanced mixed bone disease; MBD, mixed bone disease; MHPTH, mild hyperparathyroidism; NA, not available; OM, osteomalacia; SHPTH, severe hyperparathyroidism.
[b]Percentage of patients with SHPTH also had OM.

*Clin J Am Soc Nephrol 3 :S 170-174, 2008*

# Osteoporosis and CKD-MBD

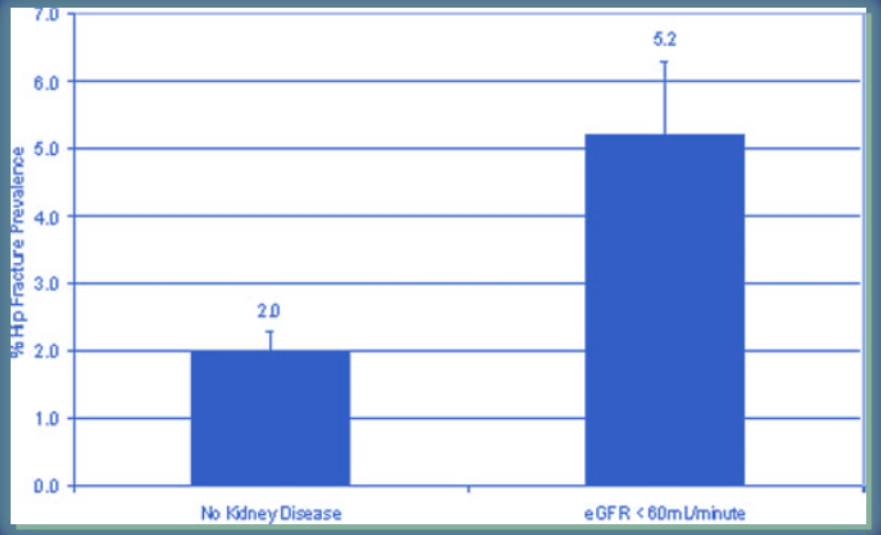
## NHANES III: Renal Compromise & Osteoporosis: GFR <35 ml/min)

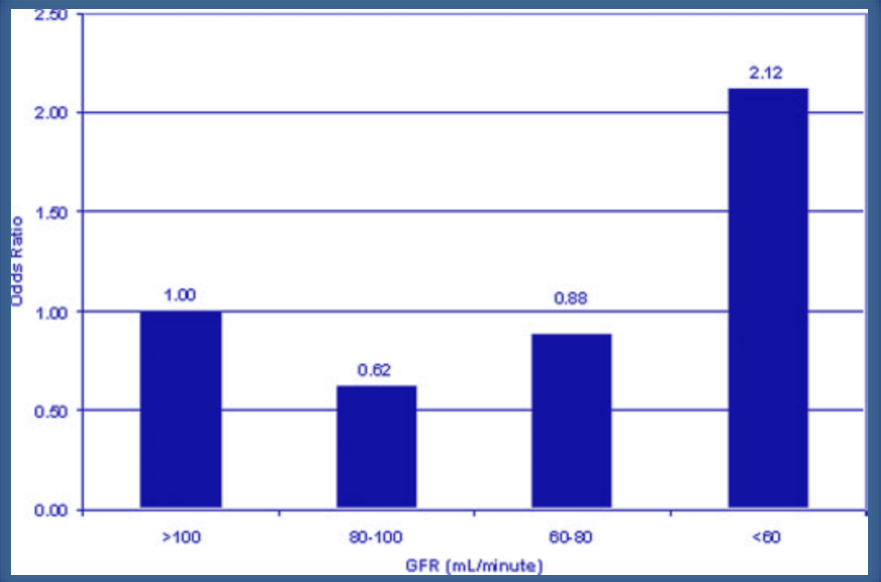
| Age Group | Prevalence |
|---|---|
| 20-29 | 0.0% |
| 30-39 | 0.0% |
| 40-49 | 0.0% |
| 50-59 | 0.0% |
| 60-69 | 7.3% |
| 70-79 | 21.3% |
| 80+ | 53.9% |

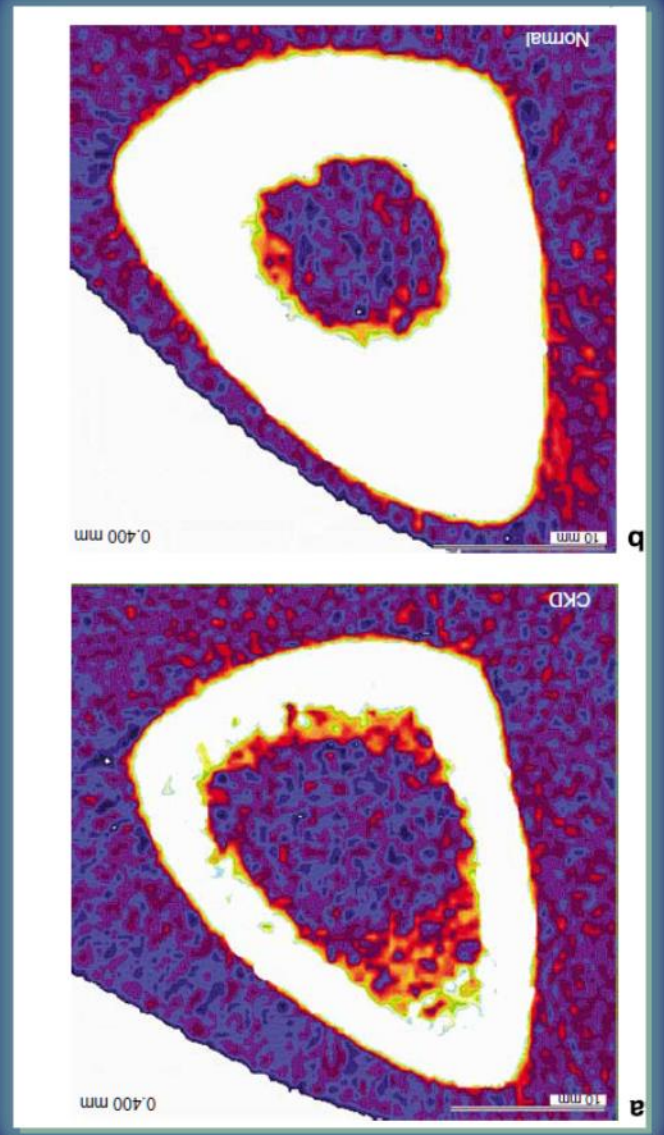
Klawansky et al., Osteoporos Int 2003, 14;7:570-577

- 60% of women with osteoporosis had CKD stage 3 and 23% had CKD stage 4

# Fracture risk in CKD



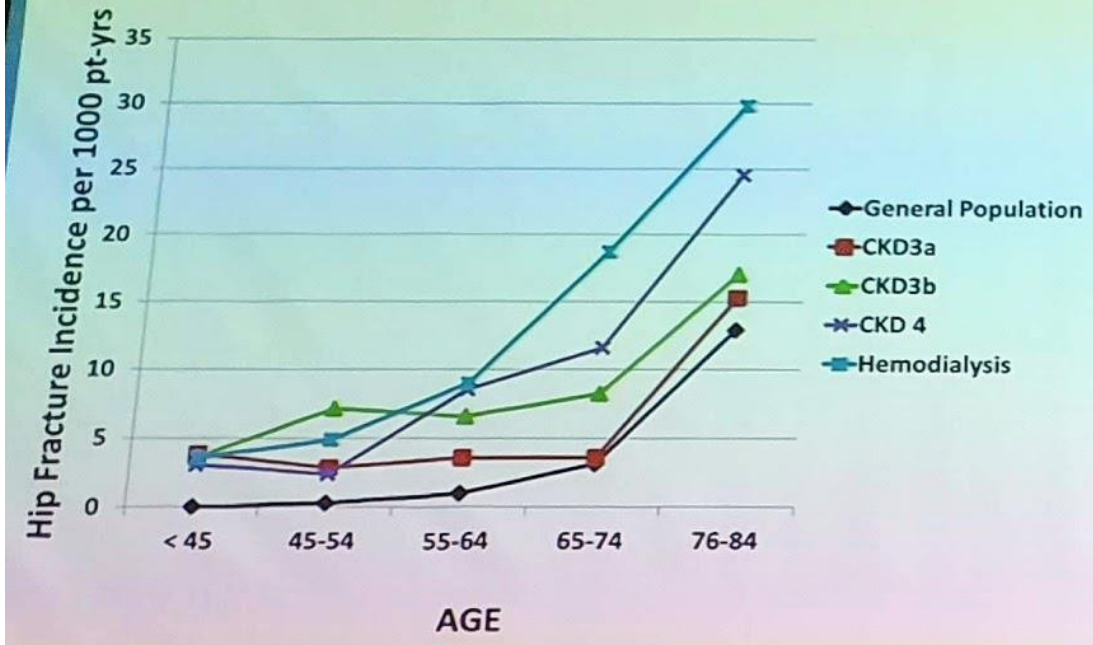

*Association betweeen hip fracture (NHANES III) Participants (Nickolas et al , JASN 2006; 17: 3223-3232*

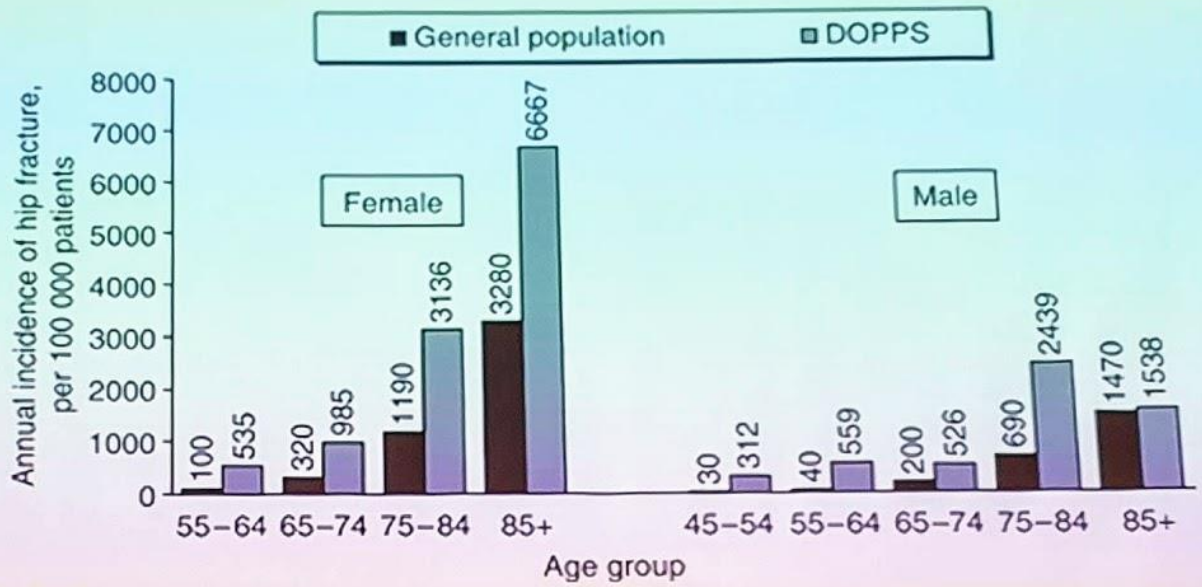
# Overview


Overview
HUNGARIAN SOCIETY OF NEPHROLOGY
Osteoporosis in CKD:
Epidemiology
Pathophysiology
Risk factors
Clinical risk factors
Low Bone Mineral Density
Bone biomarkers ?
Renal osteodystrophy ?
Who to treat?
How to treat?

# Epidemiology

## Epidemiology

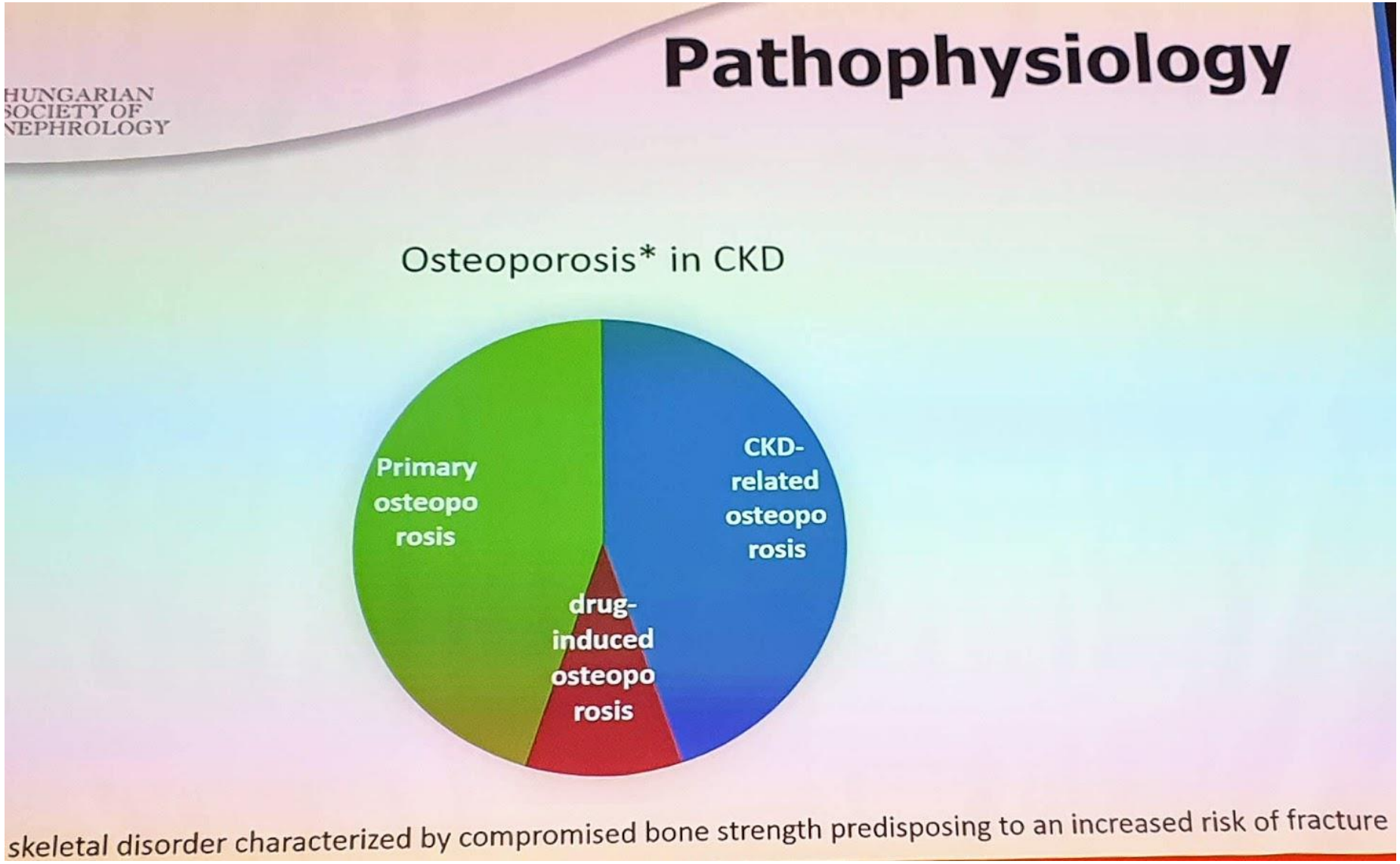


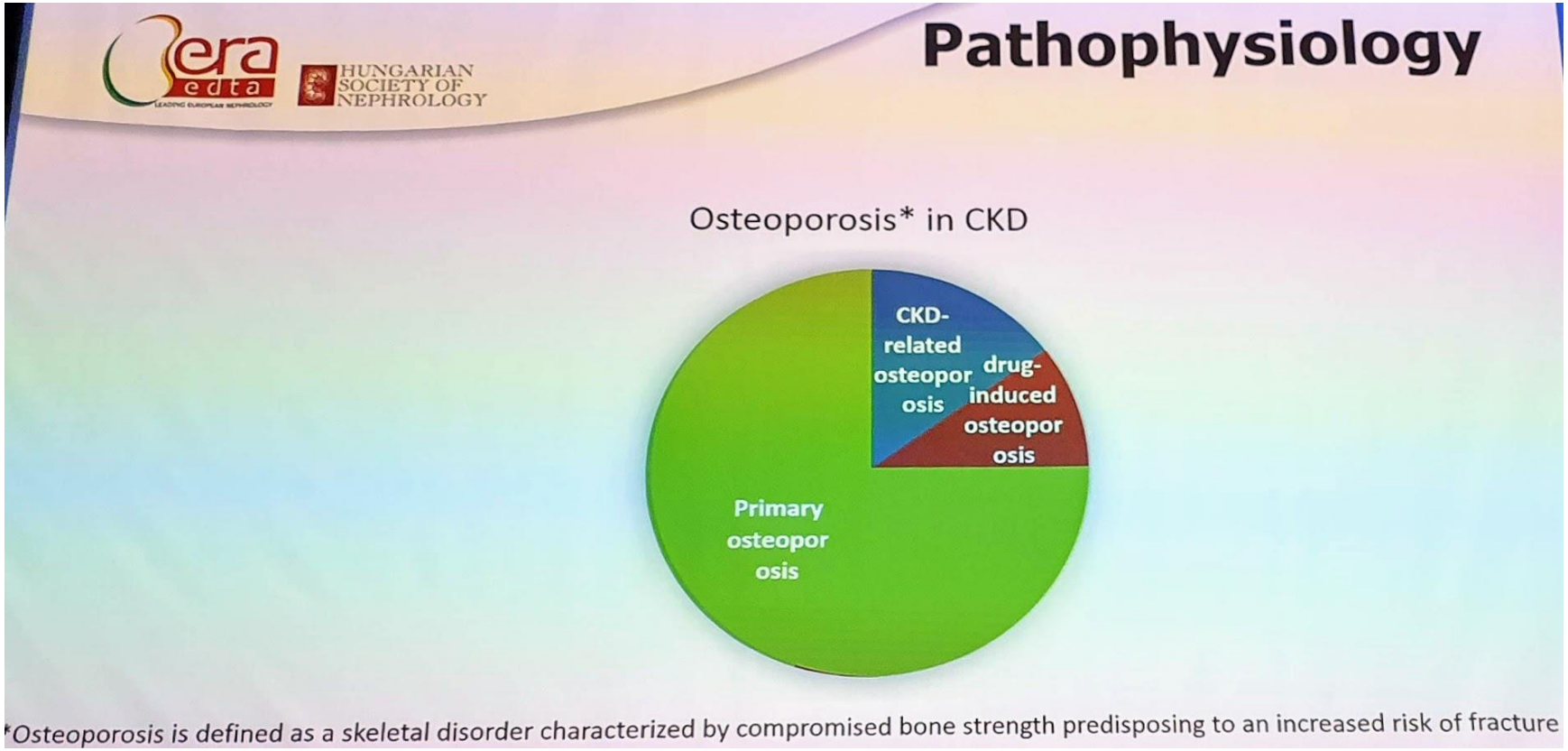

*Moe SM, Nickolas TL. Clin J Am Soc Nephrol 2016;11:1929–31.*

Jadoul M. *et al*. Kidney Int. 2006

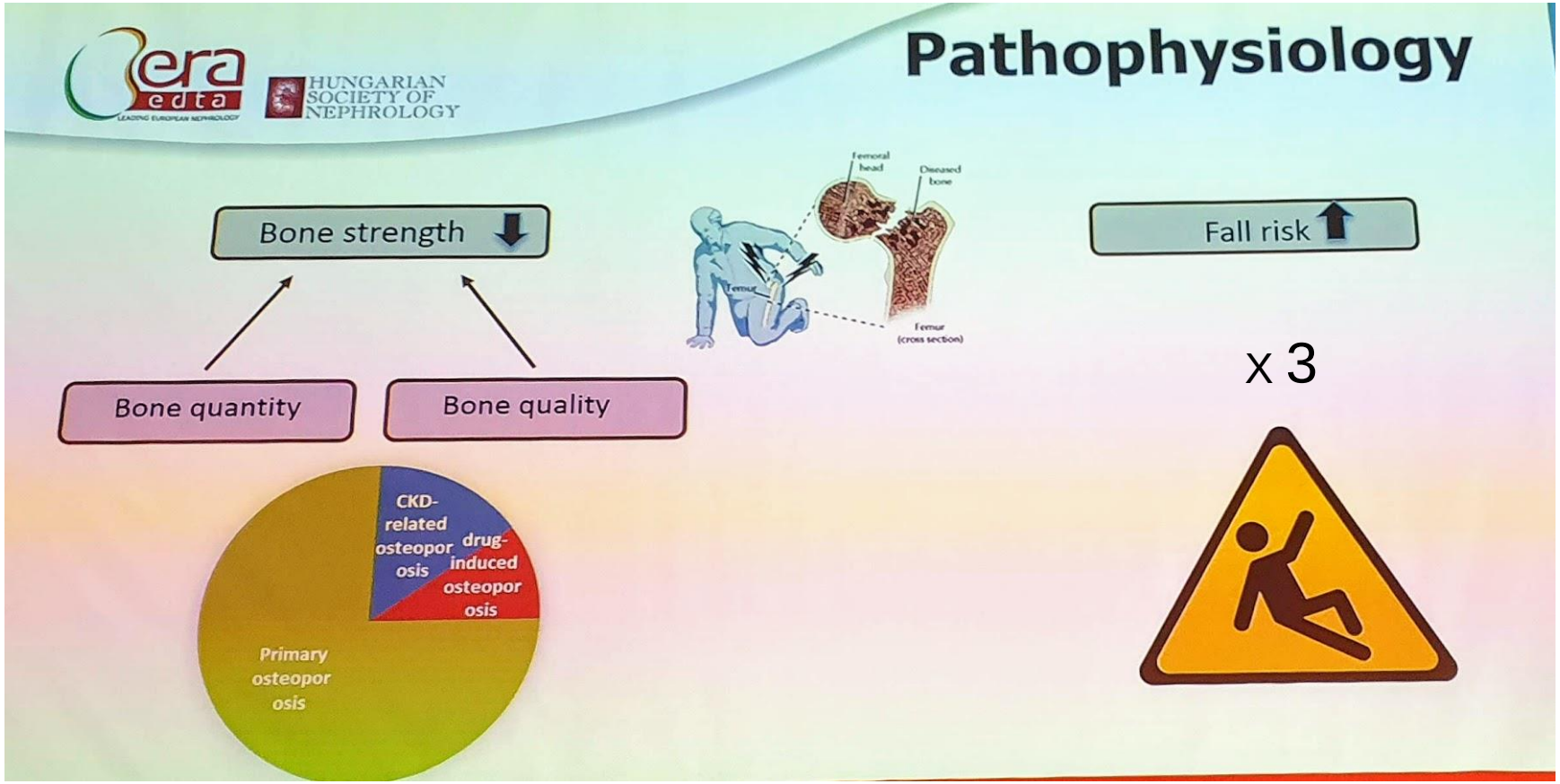
# Pathophysiology



# But maybe in reality….



# Double jeapardy



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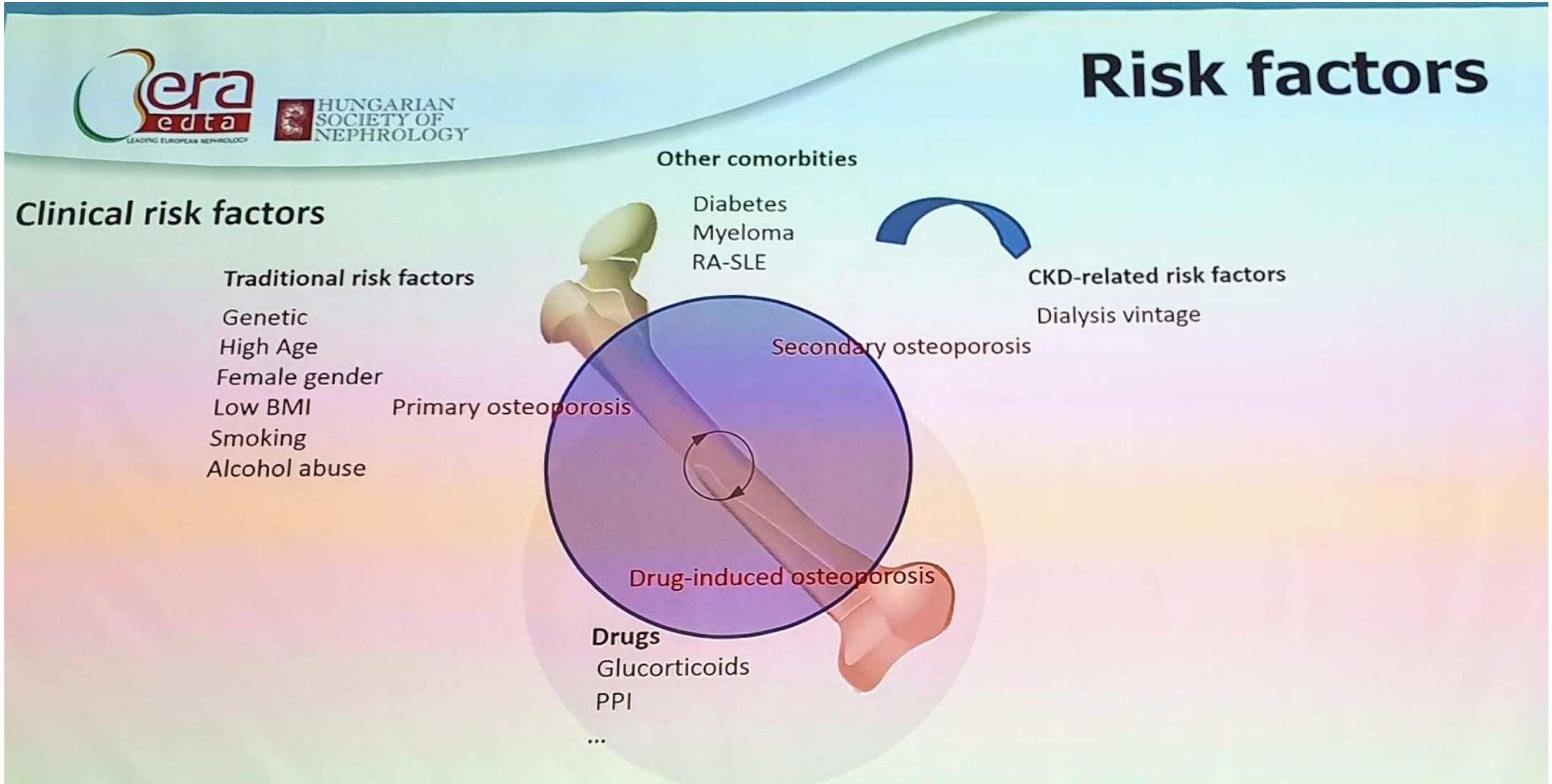
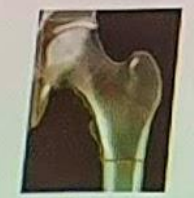
# Clinical Risk Factors



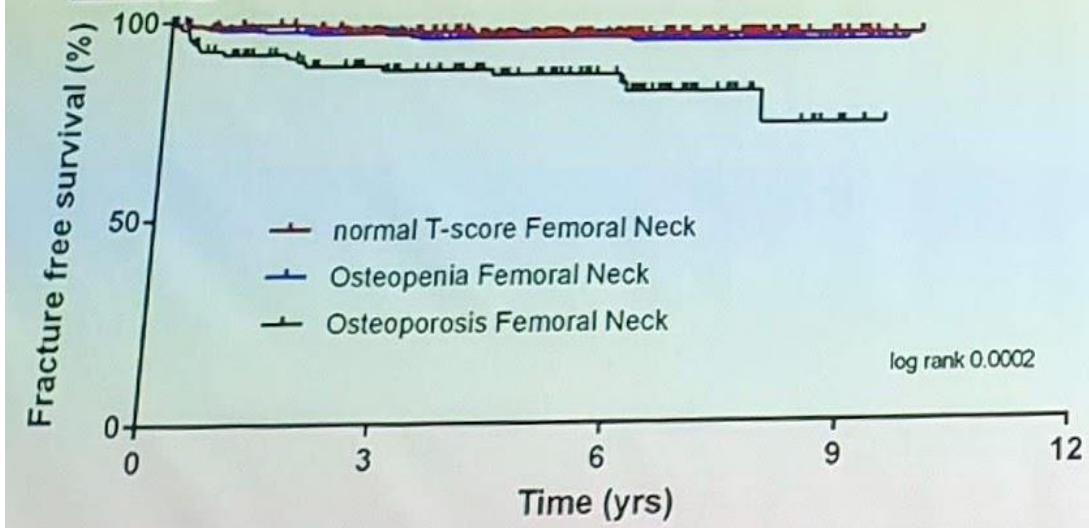
# BMD

## Bone mineral density

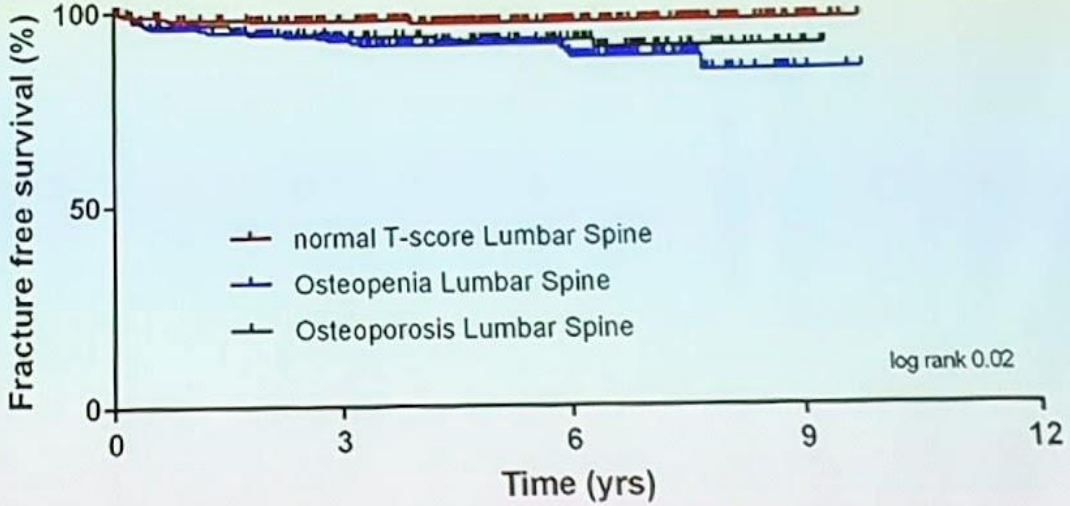
**Fracture-free survival (%) in 518 *de novo* renal transplant patients, categorised according to DXA T-score categories at the time of transplantation**



Femoral neck




Lumbar spine




Evenepoel P, et al. Kidney Int 2019

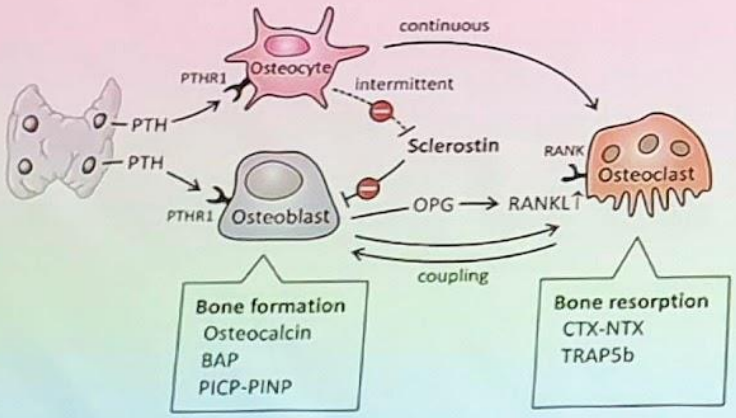
# Bone Turnover

## Risk factors

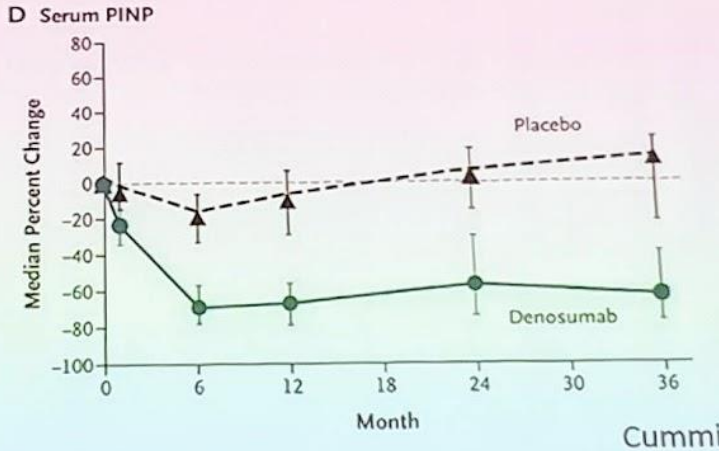
### Bone turnover markers

| Clinical utility | Performance |
|---|---|
| • Diagnosis | Poor, especially on an individual level |
| • Prognostication | |
| • Fractures | Variable, but overall poor |
| • Bone loss | Moderate |
| • Treatment guidance and monitoring | Moderate/good |

Evenepoel *et al.* NDT 2019

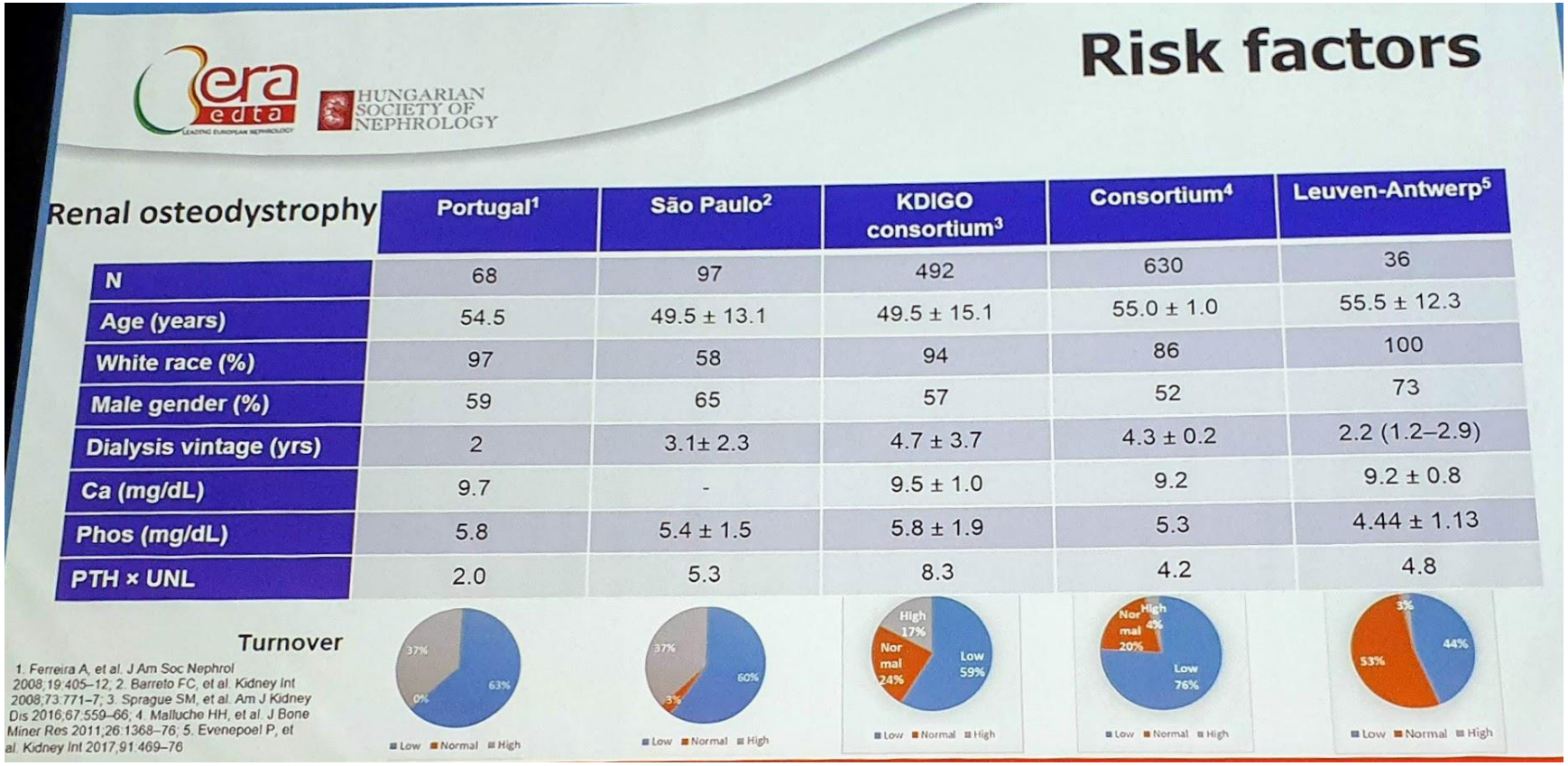



Evenepoel P, et al. Curr Osteoporos Res 2017;15:178–86.

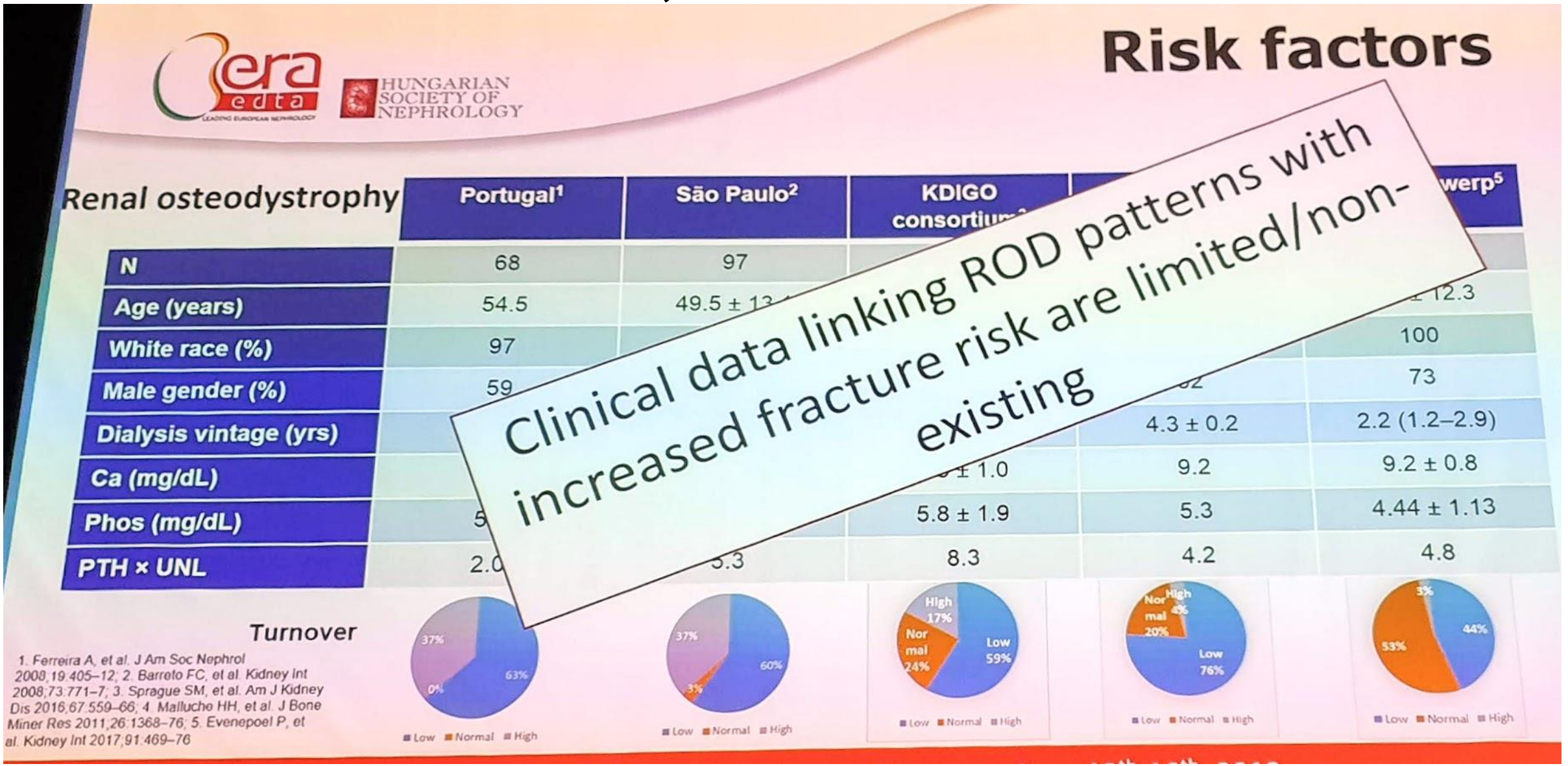



Cummings *et al.* NEJM 2009

# Bone Histomorphometry



# But, caveat….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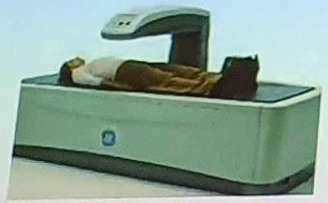
HUNGARIAN SOCIETY OF NEPHROLOGY
Risk factors
Clinical data linking ROD patterns with increased fracture risk are limited/non-existing
Renal osteodystrophy
Portugal[1]
São Paulo[2]
KDIGO consortium
werp[5]
N
68
97
Age (years)
54.5
± 12.3
White race (%)
97
100
Male gender (%)
59
73
Dialysis vintage (yrs)
4.3 ± 0.2
2.2 (1.2–2.9)
Ca (mg/dL)
± 1.0
9.2
9.2 ± 0.8
Phos (mg/dL)
5.8 ± 1.9
5.3
4.44 ± 1.13
PTH × UNL
8.3
4.2
4.8
Turnover
37%
63%
0%
Low
Normal
High
37%
60%
3%
Low
Normal
High
High 17%
Normal 24%
Low 59%
Low
Normal
High
Normal 20%
High 4%
Low 76%
Low
Normal
High
3%
44%
53%
Low
Normal
High
1. Ferreira A, et al. J Am Soc Nephrol 2008;19:405–12; 2. Barreto FC, et al. Kidney Int 2008;73:771–7; 3. Sprague SM, et al. Am J Kidney Dis 2016;67:559–66; 4. Malluche HH, et al. J Bone Miner Res 2011;26:1368–76; 5. Evenepoel P, et al. Kidney Int 2017;91:469–76

# Treatment paradigm - 1

## Who to treat?

HUNGARIAN SOCIETY OF NEPHROLOGY

***BMD centric approach***



### TESTING FOR CKD-MBD

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

**Old 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*).

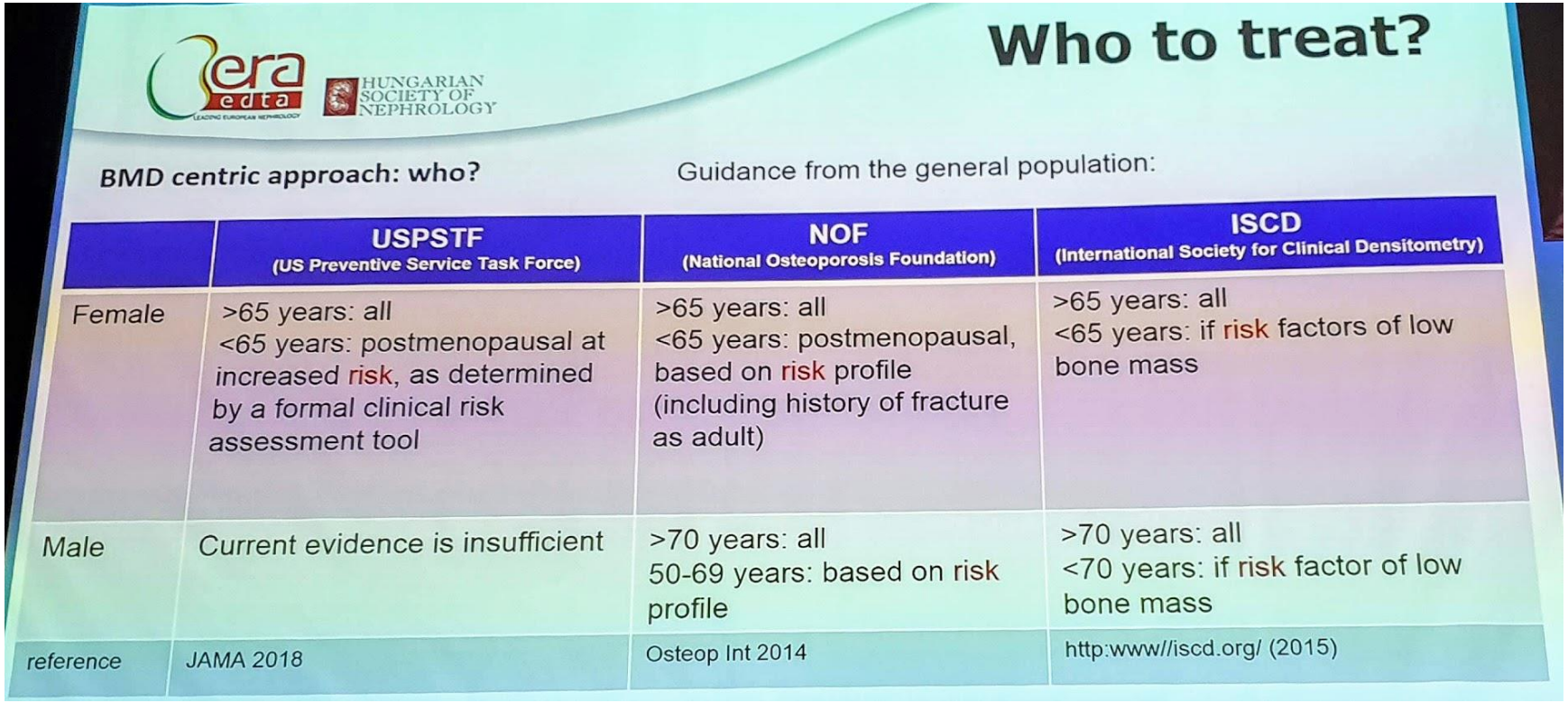
*Kidney Disease: Improving Global Outcomes*

KDIGO recommendations on CKD-MBD Kidney Int 2017

DXA testing:

-Who to test?

# Treatment paradigm 1



## Who to treat?

HUNGARIAN SOCIETY OF NEPHROLOGY

**BMD centric approach: who?**

Guidance from the general population:

| | USPSTF (US Preventive Service Task Force) | NOF (National Osteoporosis Foundation) | ISCD (International Society for Clinical Densitometry) |
|---|---|---|---|
| *Female* | *>65 years: all*<br>*<65 years: postmenopausal at increased risk, as determined by a formal clinical risk assessment tool* | >65 years: all<br><65 years: postmenopausal, based on risk profile (including history of fracture as adult) | >65 years: all<br><65 years: if risk factors of low bone mass |
| *Male* | *Current evidence is insufficient* | >70 years: all<br>50-69 years: based on risk profile | >70 years: all<br><70 years: if risk factor of low bone mass |
| *reference* | JAMA 2018 | Osteop Int 2014 | http:www//iscd.org/ (2015) |

# Pragmatism

## Who to treat?

HUNGARIAN SOCIETY OF NEPHROLOGY

**BMD centric approach: who?**

A pragmatic approach in patients with CKD:

| | CKD 1-3 (+/- transplant) | CKD 4-5D (+/- transplant) |
|---|---|---|
| Female | As in the general population | postmenopausal |
| Male | As in the general population | >50 yrs |

- *Exclude patients with limited life expectancy*
- *Prioritise patients on renal transplant waiting list*

# Dexa distribution

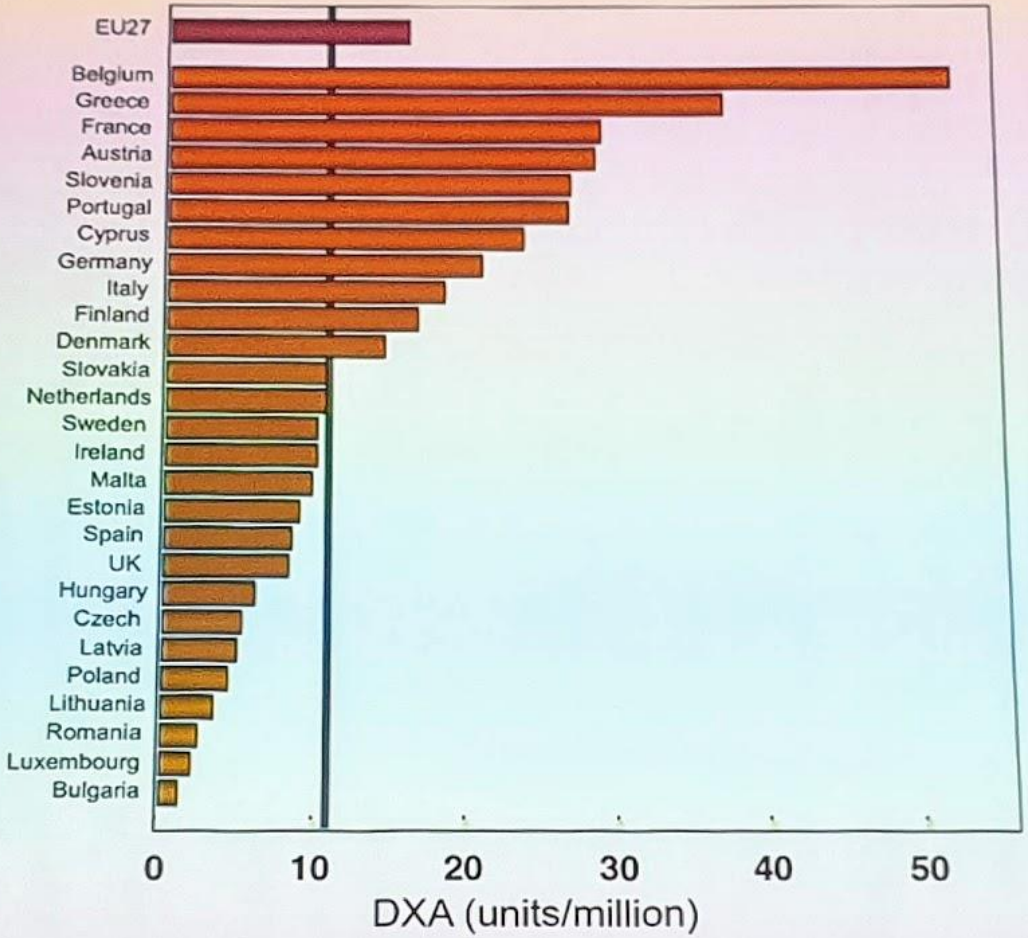
## Who to treat?

HUNGARIAN SOCIETY OF NEPHROLOGY

**BMD centric approach: who?**

Availability

Reimbursement



# Testing – who, where, when

## Who to treat?

***BMD centric approach***

### TESTING FOR CKD-MBD

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

**Old 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*).

*Kidney Disease: Improving Global Outcomes*

KDIGO recommendations on CKD-MBD Kidney Int 2017

DXA testing:

-Who to test?

-Which skeletal site?

-Which intervention threshold?

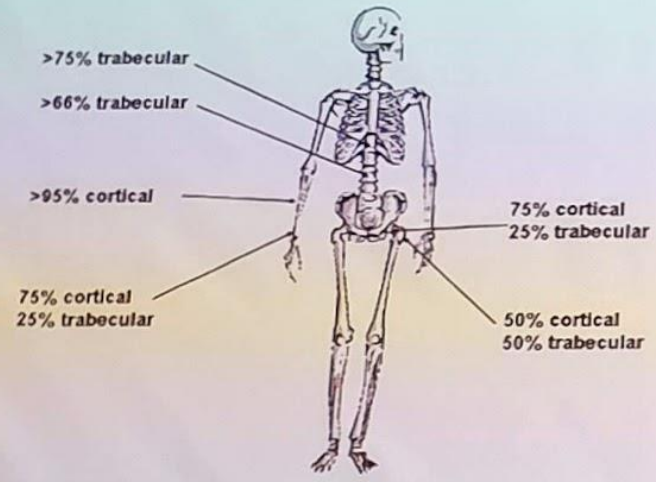
# Biases and error

## Who to treat?

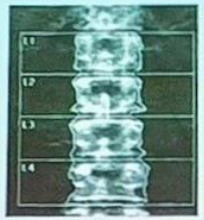
HUNGARIAN SOCIETY OF NEPHROLOGY

### BMD centric approach: which skeletal site?

- *Hip*
- *Lumbar spine*

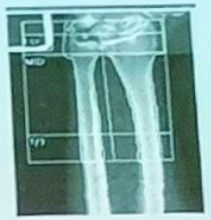



### Sources of Bias



- Aortic calcification
- Scoliosis
- Hypertrophic degenerative disease
- Compression fractures
- Calcium, barium, or lanthanum within the gastrointestinal tract
- Renal lithiasis
- Focal sclerotic bone lesions

Toussaint *et al.* CJASN 2009



- AV fistula
- (measurement bias)

Muxi *et al.* CJASN 2009
Walder *et al.* PlosOne 2018

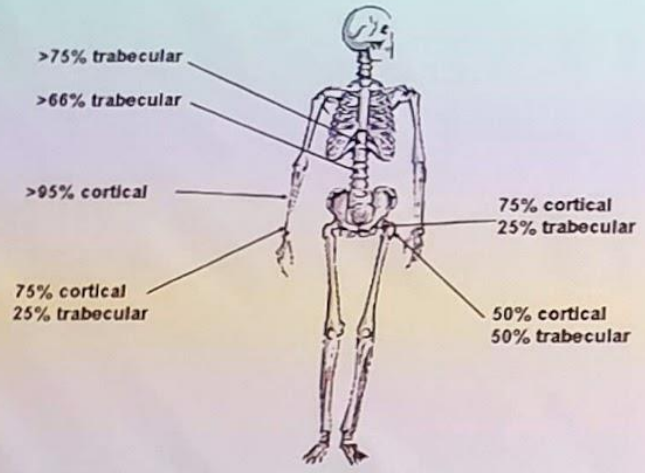
# Treatment Paradigm - 2

## Who to treat?

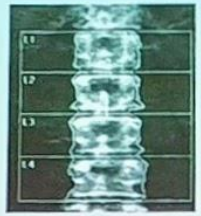
HUNGARIAN SOCIETY OF NEPHROLOGY

### BMD centric approach: which skeletal site?

- *Hip*
- *Lumbar spine*




**Sources of Bias**



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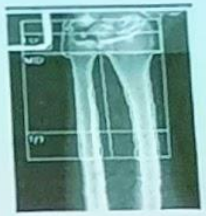

- AV fistula
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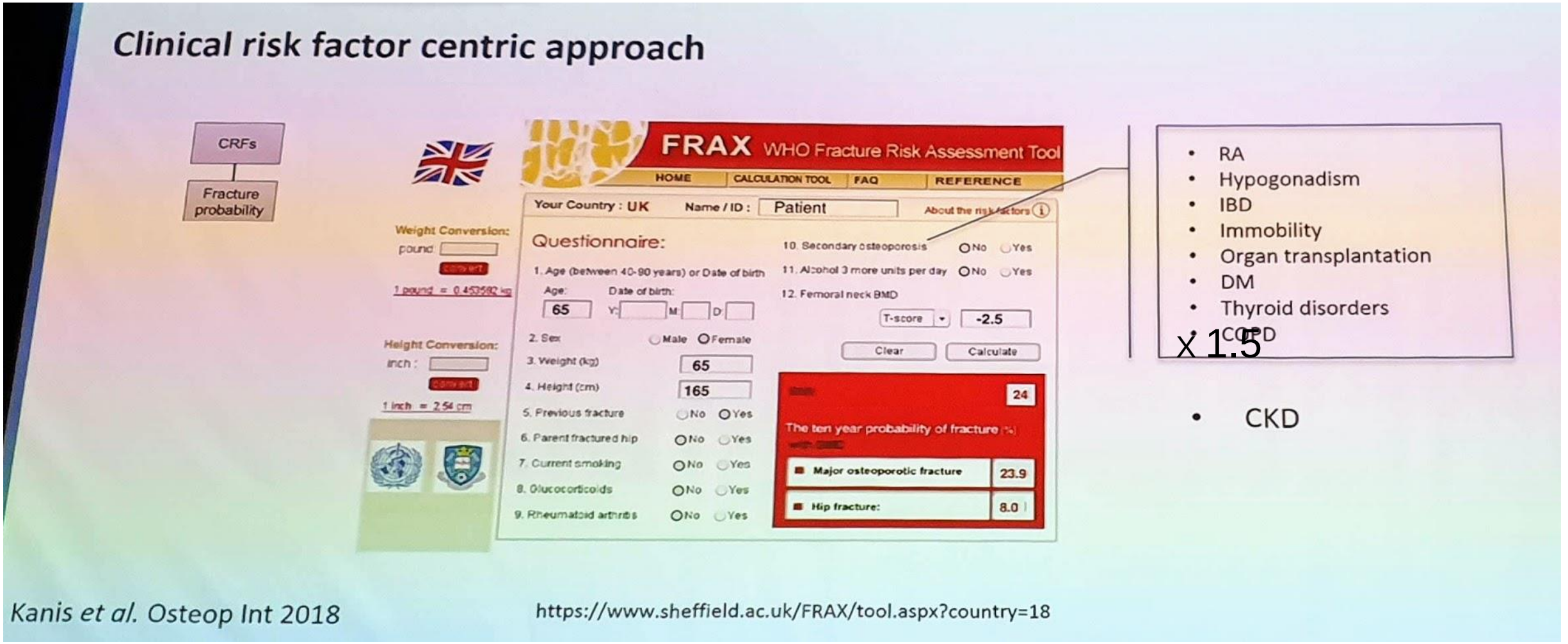
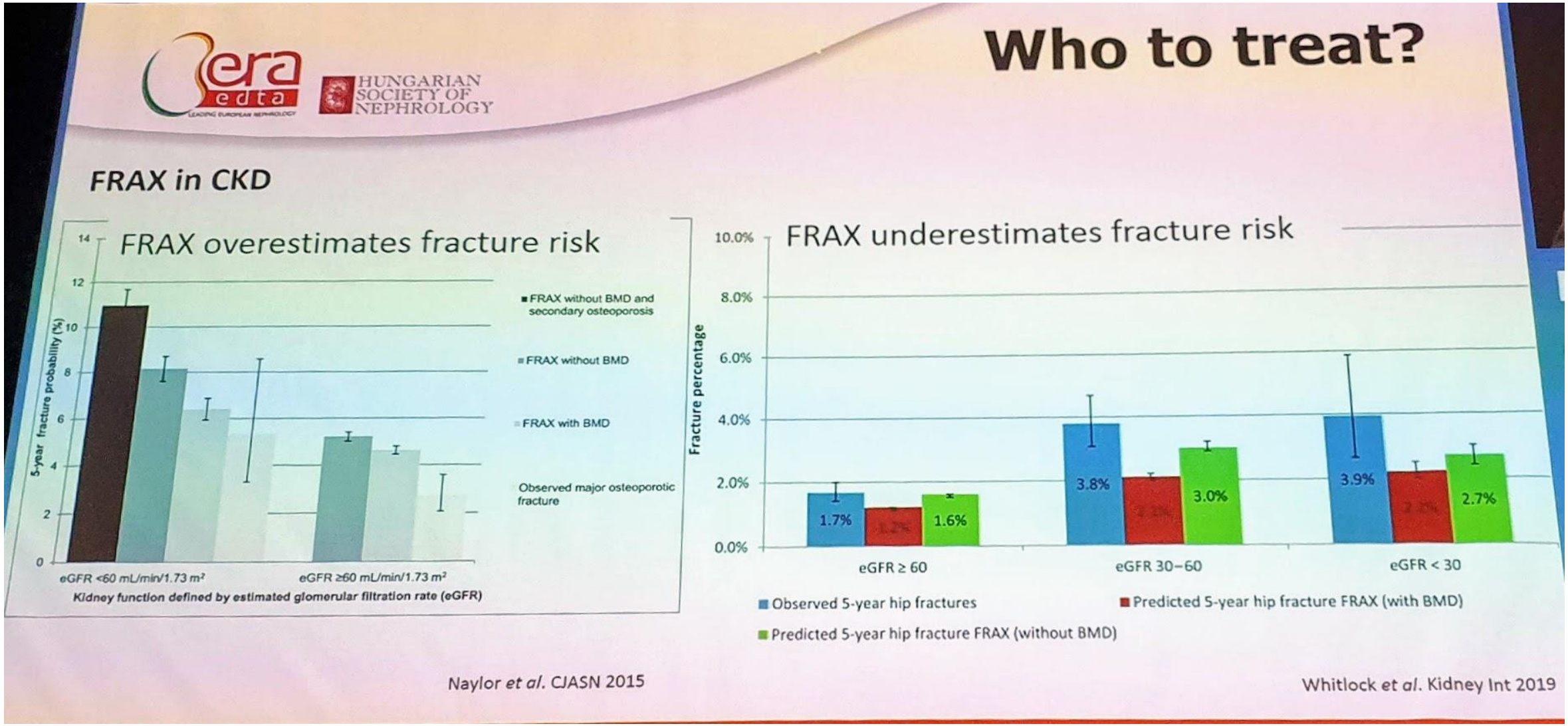
Muxi *et al.* CJASN 2009
Walder *et al.* PlosOne 2018

# Renal relative risk



# Too high, too low…

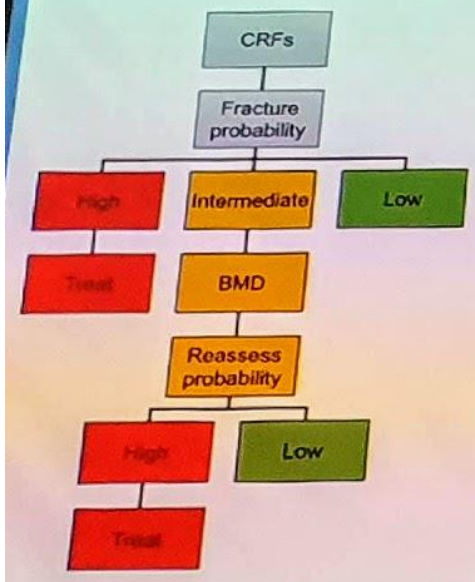


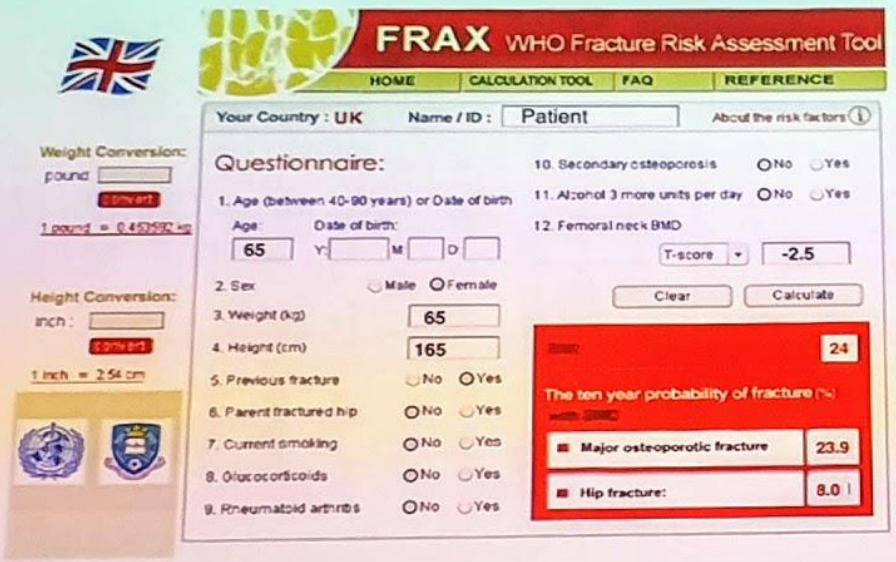
# Composite risk scoring

era edta
LEADING EUROPEAN NEPHROLOGY
HUNGARIAN SOCIETY OF NEPHROLOGY

## Who to treat?

### Clinical risk factors




https://www.sheffield.ac.uk/FRAX/tool.aspx?country=18

- fracture probabilities in CKD remain to be adjusted (upwards)
- intervention thresholds are the same as in the general population

| | Ten-year fracture probability (%) | | |
|---|---|---|---|
| Age range (years) | Intervention threshold | Lower assessment threshold | Upper assessment threshold |
| 40–44 | 5.2 | 2.3 | 6.2 |
| 45–49 | 5.4 | 2.4 | 6.5 |
| 50–54 | 6.3 | 2.9 | 7.6 |
| 55–59 | 7.6 | 3.6 | 9.1 |
| 60–64 | 9.9 | 4.9 | 11.9 |
| 65–69 | 13.4 | 6.9 | 16.1 |
| 70–74 | 17.6 | 9.7 | 21.5 |
| 75–79 | 23.0 | 13.7 | 27.6 |
| 80–84 | 29.1 | 18.7 | 34.9 |
| 85–89 | 31.8 | 20.9 | 38.2 |
| 90–94 | 31.7 | 20.8 | 38.0 |
| 95–99 | 32.2 | 21.1 | 38.6 |
| 100+ | 32.5 | 21.3 | 39.0 |

Kanis *et al.* Osteop Int 2019

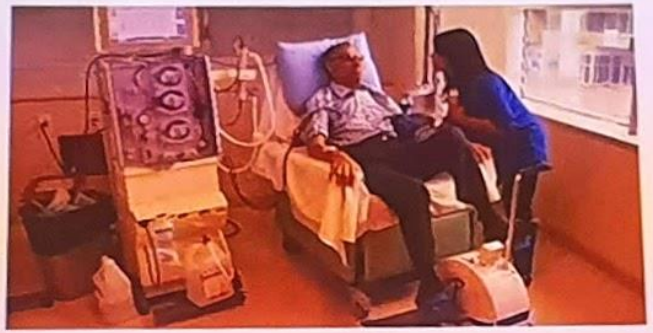
# How to treat – non-drug

## How to treat?

HUNGARIAN SOCIETY OF NEPHROLOGY

***Non-pharmacological management of osteoporosis***

- ***Fall prevention***
- ***Lifestyle modification***
- ***Nutrition***
  - *Vitamin D, RNI 800 U/D*
  - *Calcium, RNI 800-1000 mg/d*



- Regional variability
- Lower intakes in CKD

→ Questionnaires to estimate intake

# Active Rx - primum non nocere

## Pharmacological management of osteoporosis

*CKD 1–3: as in the general population*

*CKD 4–5D: absence of good evidence*

Annals of Internal Medicine

REVIEW

### Benefits and Harms of Osteoporosis Medications in Patients With Chronic Kidney Disease

#### A Systematic Review and Meta-analysis

Lisa M. Wilson, ScM; Casey M. Rebholz, PhD, MPH, MS; Ermias Jirru, MD, MPH; Marisa Chi Liu, MD, MPH; Allen Zhang, BS; Jessica Gayleard, BS; Yue Chu, MSPH; and Karen A. Robinson, PhD

**Background:** Complications of chronic kidney disease (CKD) include weak bones and increased fracture risk.

**Purpose:** To review the benefits and harms of osteoporosis medications (bisphosphonates, teriparatide, raloxifene, and denosumab) compared with placebo, usual care, or active control in terms of bone mineral density (BMD), fractures, and safety in patients with CKD.

**Data Sources:** PubMed and the Cochrane Central Register of Controlled Trials from December 2006 through December 2016.

**Study Selection:** Paired reviewers independently screened abstracts and full-text articles for English-language, randomized, controlled trials that had at least 6 months of follow-up; evaluated osteoporosis medications among patients with CKD; and reported on BMD, fractures, or safety (mortality and adverse events).

**Data Extraction:** Two reviewers serially abstracted data and independently assessed risk of bias and graded the strength of evidence (SOE).

**Data Synthesis:** There were 13 trials ($n$ = 9850) that included kidney transplant recipients (6 trials), patients who had stage 3 to 5 CKD or were receiving dialysis (3 trials), or postmenopausal women with CKD (4 trials). Evidence showed that bisphosphonates may slow loss of BMD among transplant recipients (moderate SOE), but their effects on fractures and safety in transplant recipients and others with CKD are unclear. Raloxifene may prevent vertebral fractures but may not improve BMD (low SOE). Effects of teriparatide and denosumab on BMD and fractures are unclear (very low SOE), and these medications may increase risk for some safety outcomes.

**Limitation:** Unclear rigor of evidence, possible reporting biases, and scant evidence among patients with stage 3 to 5 CKD.

**Conclusion:** Effects of osteoporosis medications on BMD, fracture risk, and safety among patients with CKD are not clearly established.

**Primary Funding Source:** Kidney Disease: Improving Global Outcomes.

*Ann Intern Med.* doi:10.7326/M16-2752 Annals.org

For author affiliations, see end of text.

This article was published at Annals.org on 11 April 2017.

# Treatment - drugs

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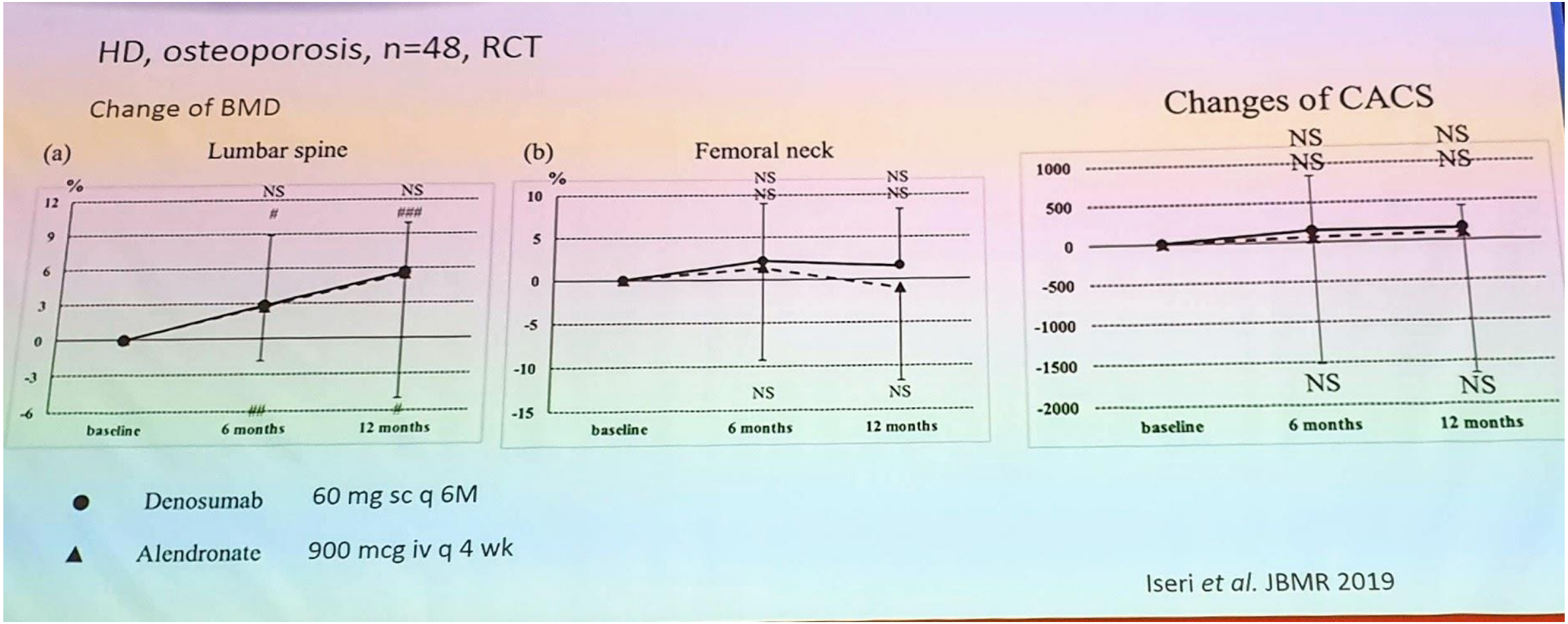
# Treatment – drugs

## Pharmacological management of osteoporosis: antiresorptive agents

| Advanced CKD | | Bisphosphonates | Denosumab |
|---|---|---|---|
| Efficacy | | Evidence from post-hoc analyses of large registration trials do suggest equal efficacy of antiresorptive agents in patients with (advanced) CKD* as in the general population. | |
| Safety (concerns) | Metabolic | Limited risk of hypocalcemia | Substantial risk of hypocalcemia |
| | Skeletal | bone remodeling inhibition | Bone remodeling inhibition. However, steady BMD gains are observed during prolonged remodelling inhibition in GP, while bone strength is preserved |
| | Vascular | No evidence for accelerated vascular calcification | |
| | Renal | Accounting for some precautions, renal risks of BPs are minimal | No renal risks |

*without lab abnormalities of CKD-MBD

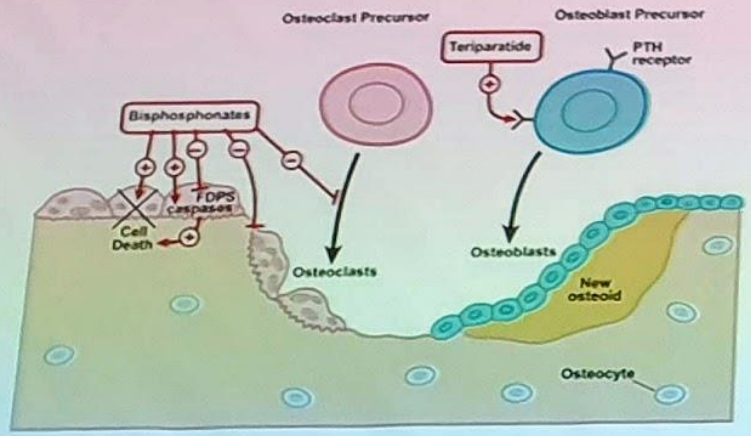
# Treatment in dialysis patients



# Newer drug options (?)

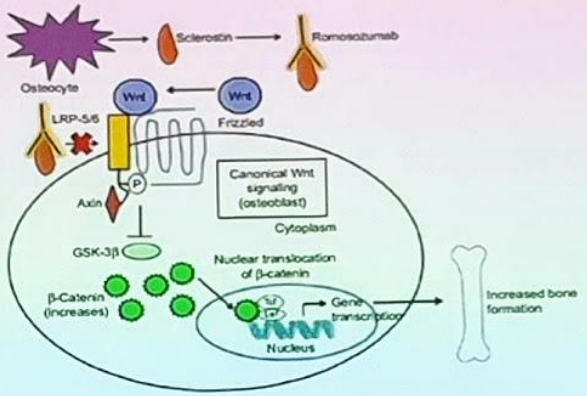
## Pharmacological management of osteoporosis: anabolic agents

### PTH analogs




- *SC only*

### Romosozumab*




- SC only

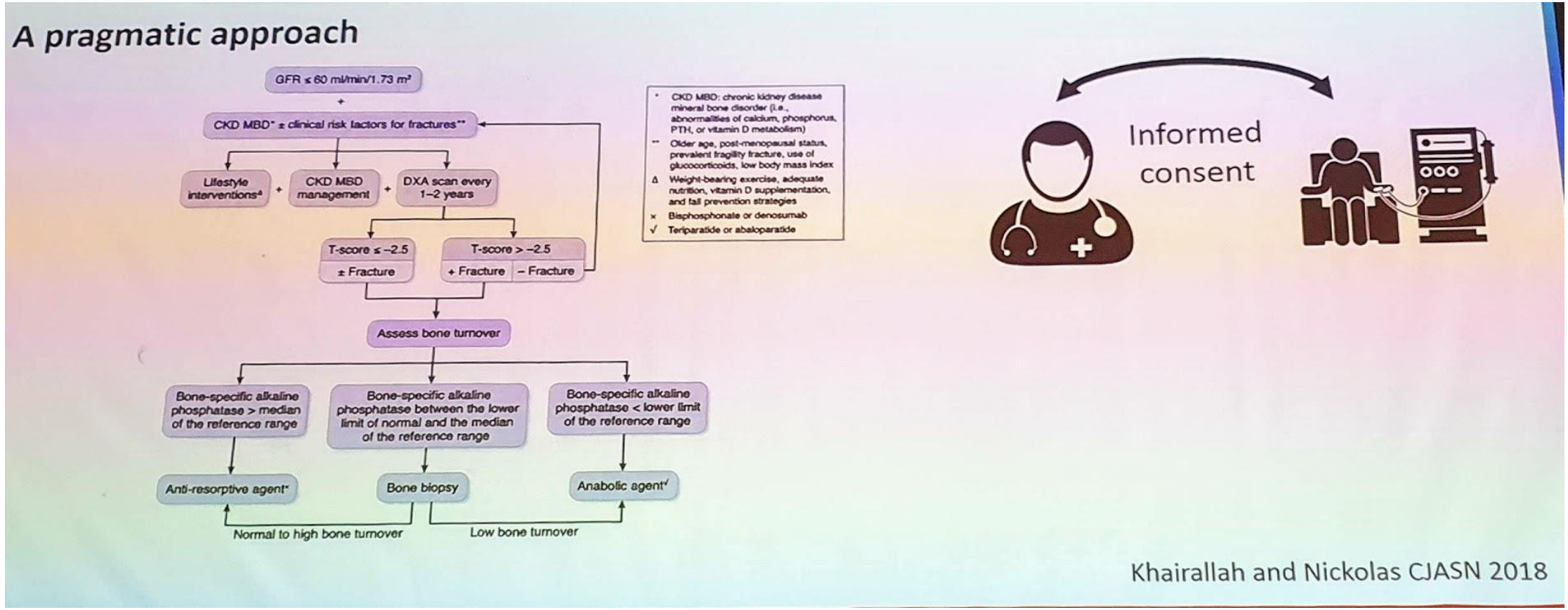
*FDA approved April 9, 2019

# Evidence for newer drugs

**Pharmacological managment of osteoporosis: anabolic agents**

| Advanced CKD | | PTH analogs | Romomosumab |
|---|---|---|---|
| Efficacy | | Post-hoc analysis and small pilot studies show promising results (BMD and biomarker outcomes only) in patients with advanced CKD | No data |
| Safety (concerns) | Metabolic | Limited risk of hypercalemia | hypocalcemia |
| | Skeletal | osteosarcoma | |
| | Vascular | Transient hypotension | More cardiovascular adverse events (odds ratio [OR], 1.31 [0.85 to 2.00]) in postmenopausal women with osteoporosis given 12 months of romosozumab followed by 12 months of alendronate versus 24 continuous months of alendronate |

# Synthesing some themes



# Putting it all together (?)