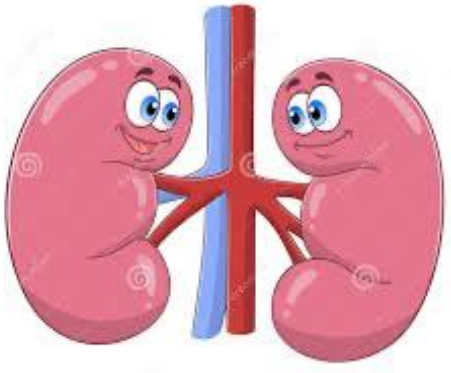
Denosumab of toch maar bisfosfonaat?



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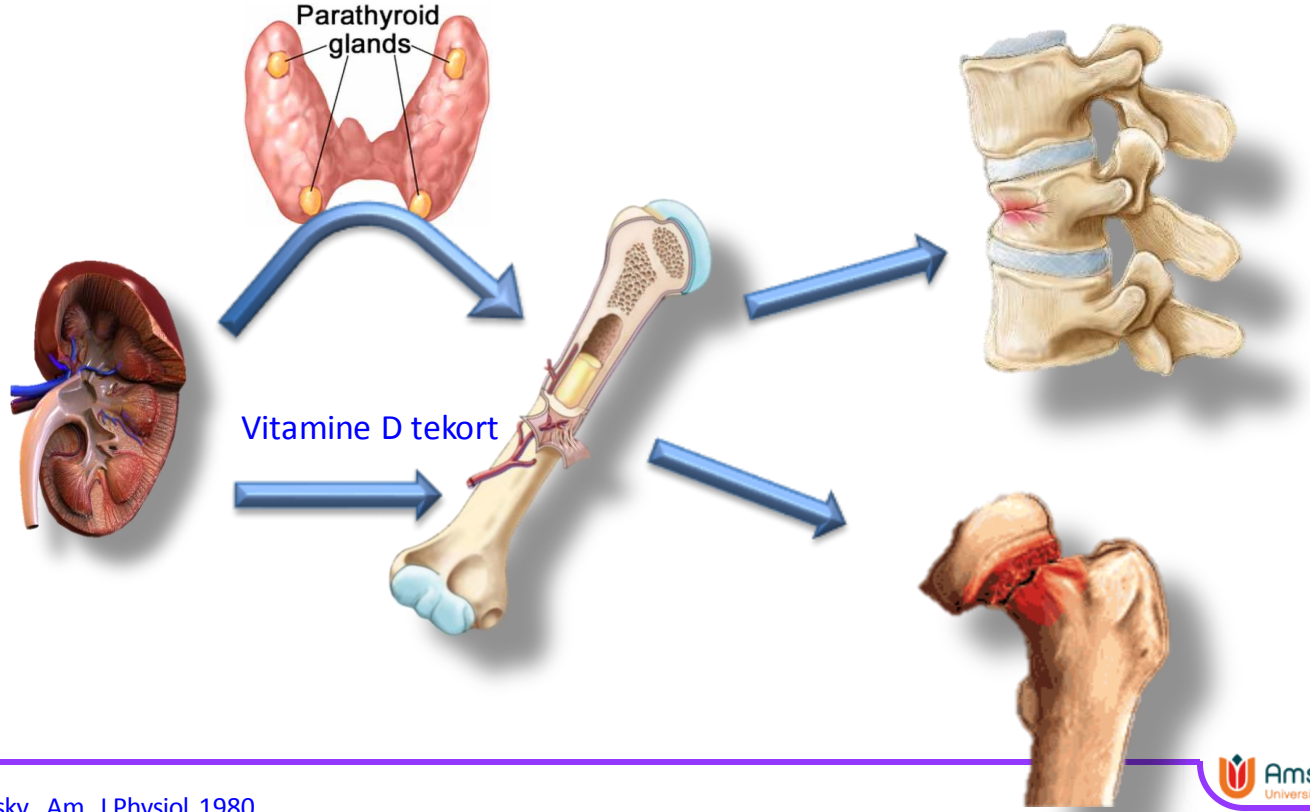
Disclosures

- Pharmaceutical industry
  - Lecture fees, scientific support and advisor for: Amgen, VFMCRP and Vifor, Shire, Medice, Bayer, Kissei, Cablon Medical; all companies involved in marketing or developing phosphate-lowering drugs
  - Scientific support from: AbbVie, Amgen and FMC
  - Advisory board of: Otsuka, Astra-Zeneca, Medice

- Member of
  - ERA-EDTA working group on CKD-MBD
  - KDIGO committee on CKD-MBD

Bone disease: integral part of CKD!



Slatopolsky. Am J Physiol 1980

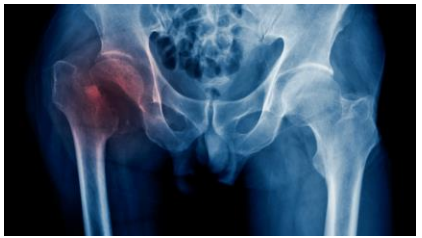
Need to knows:

- Osteoporosis care up to stage 3 (eGFR 30 ml/min/1.73) is the same as in general population
- Applies for both diagnosis and treatment
- Based of trial data (some post-hoc…) from GP

Risk factors for fracture in CKD

As in GP

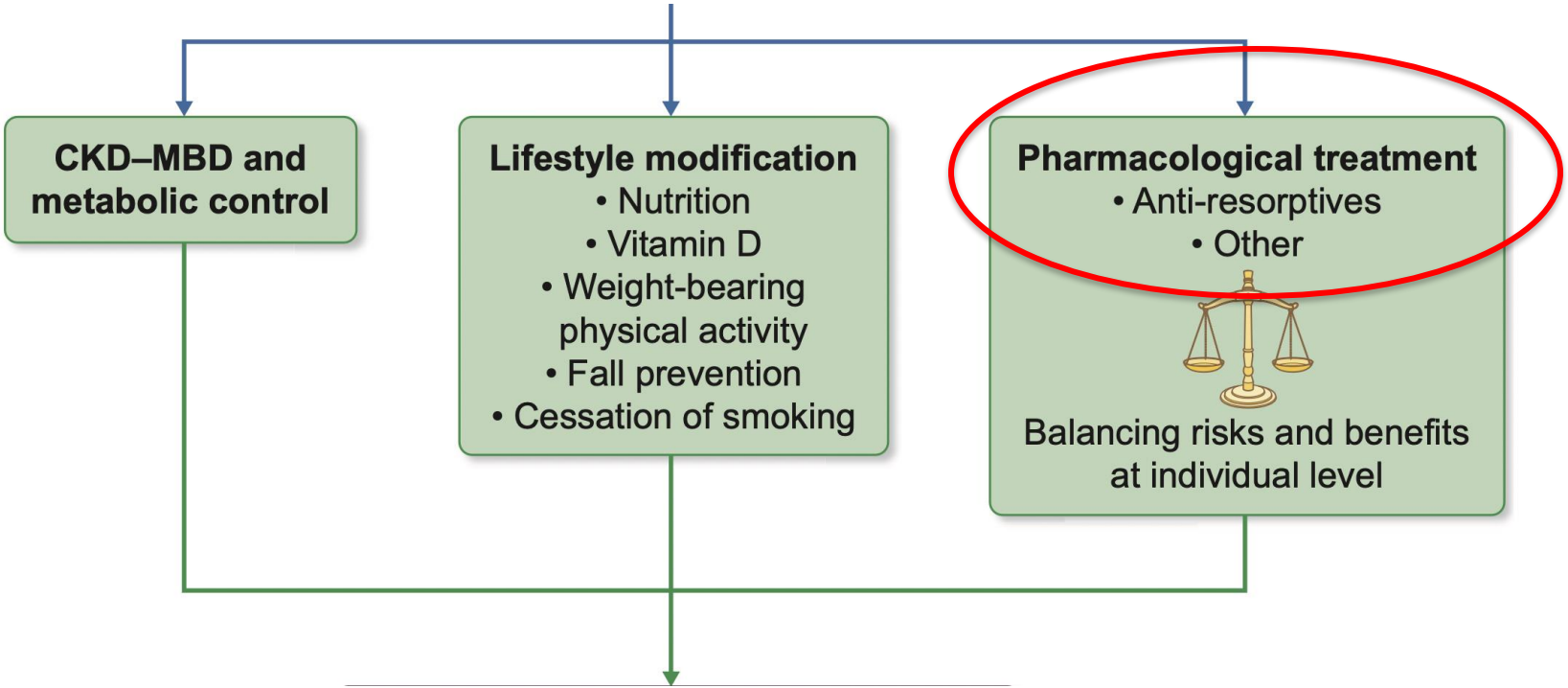
- Age
- Gender
- BMI
- Smoking
- Alcohol use
- Steroid use
- Inflammatie (RA)
- Previous fractures



CKD specific

- Dialysis vintage
- Renal osteodystrophy
- PTH extremes
- Hypogonadism
- Vit D deficiency
- Vitamin K deficiency?

Copy-paste: farma treatment in CKD 4-5D



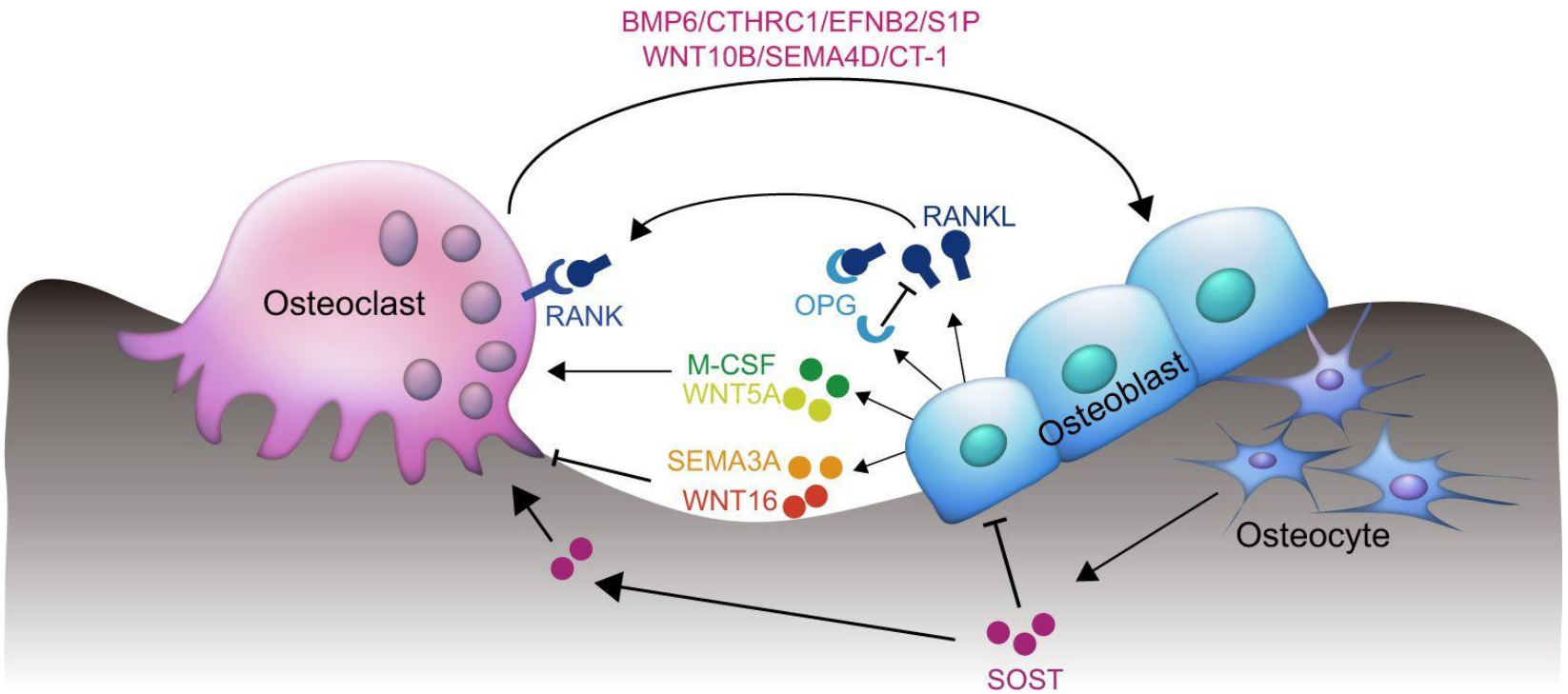
Therapie

- Aandacht voor bot
- Aandacht voor trauma: valrisico
- Incidence-rate = risk/time X time (bij korte levensverwachting laag risico op fractuur)

Treatment principles indicate importance of right diagnosis

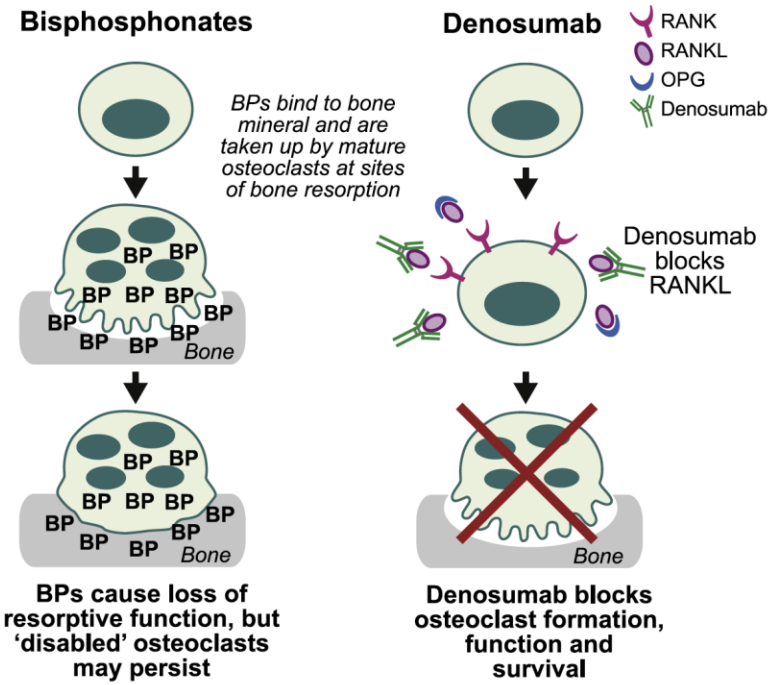
Finding	Action
Abnormal mineralisation	Mineral levels, Ca, vit D, Metal intox?
Low bone volume	Bisphosphonates, Denosumab
Hyperdynamic bone	Calcimimetic, active D, PTX
Adynamic bone	Look for cause; Teriparatide??

Osteoblast-osteoclast coupling



Han, Bone Res 2018

Bisphosphonates vs denosumab



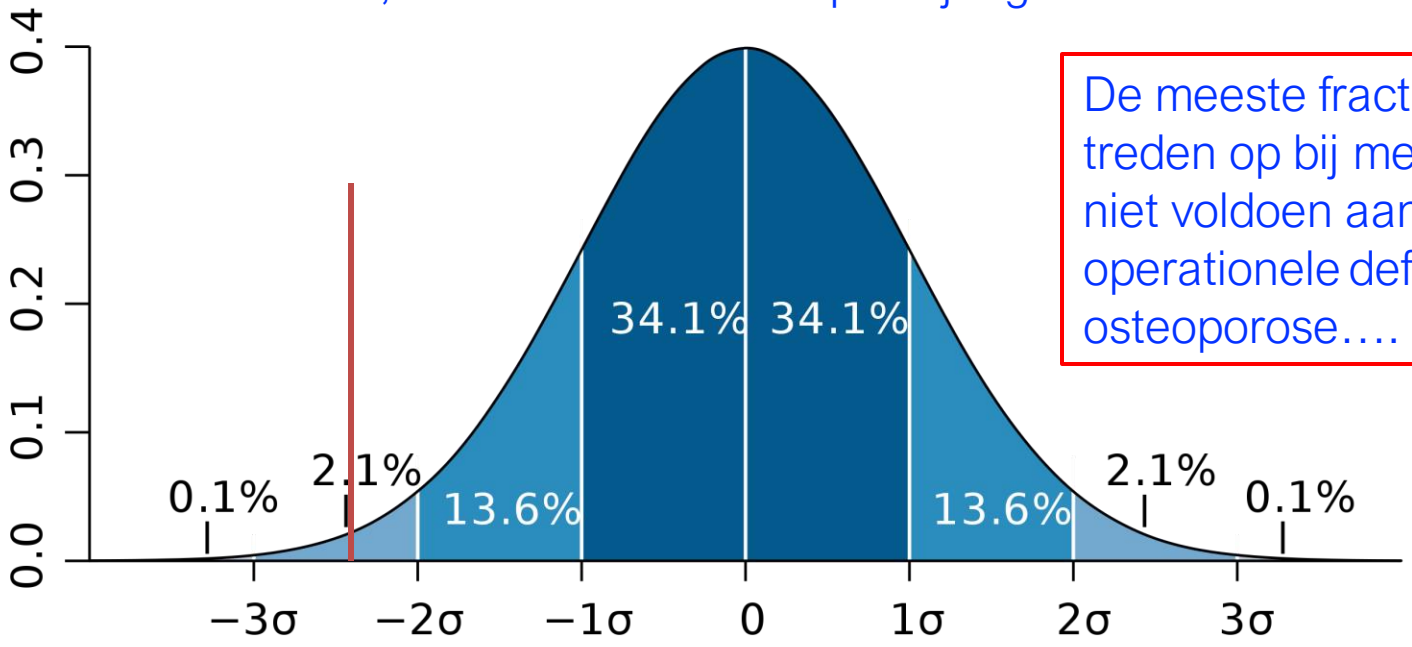
Baron, Bone 2011

Concerns with anti-resorptives:

- Induction of adynamic bone disease
- Osteonecrosis of the jaw
- Acute on chronic kidney injury
- All endpoints: BMD, not fracture incidence (in gevorderd nierfalen dan)

Wie behandelen?

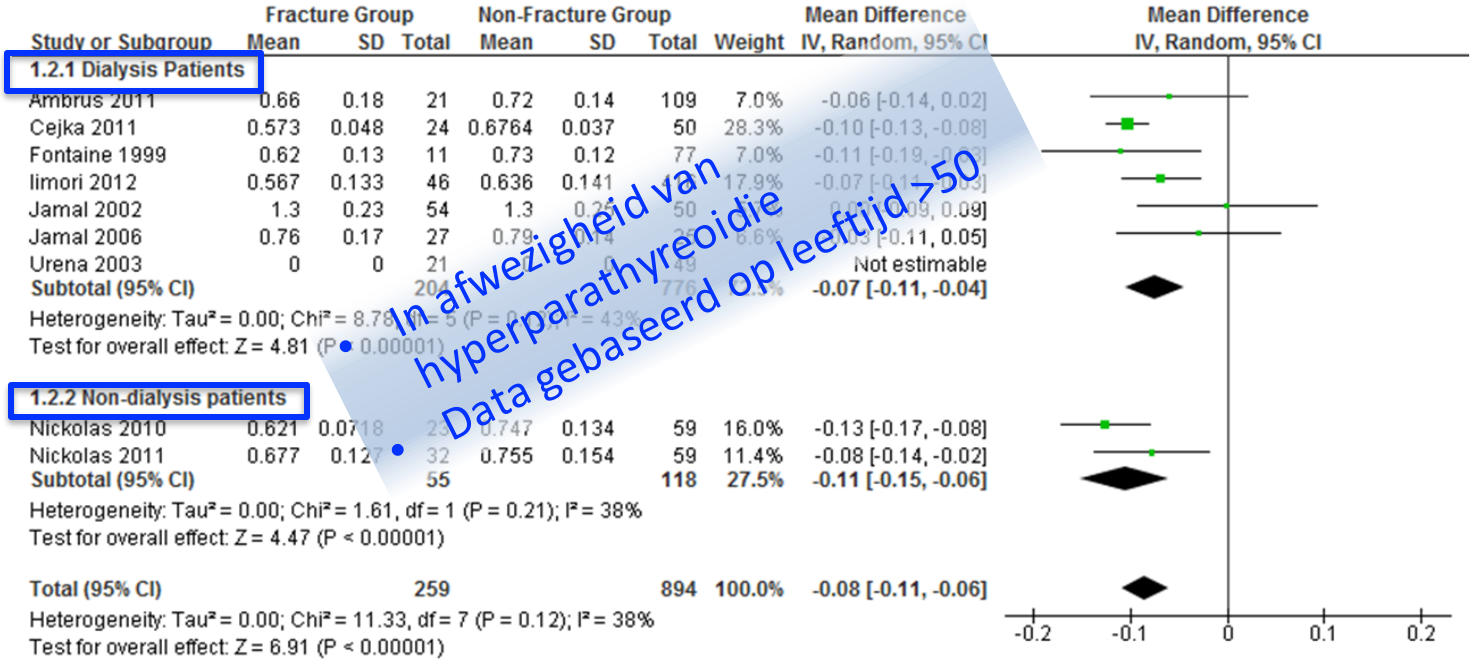
T-score < -2,5 SD van LWK of heup tov jonge vrouwen



De meeste fracturen treden op bij mensen, die niet voldoen aan de operationele definitie van osteoporose….

Meta-Analysis

DEXA-determined femoral BMD

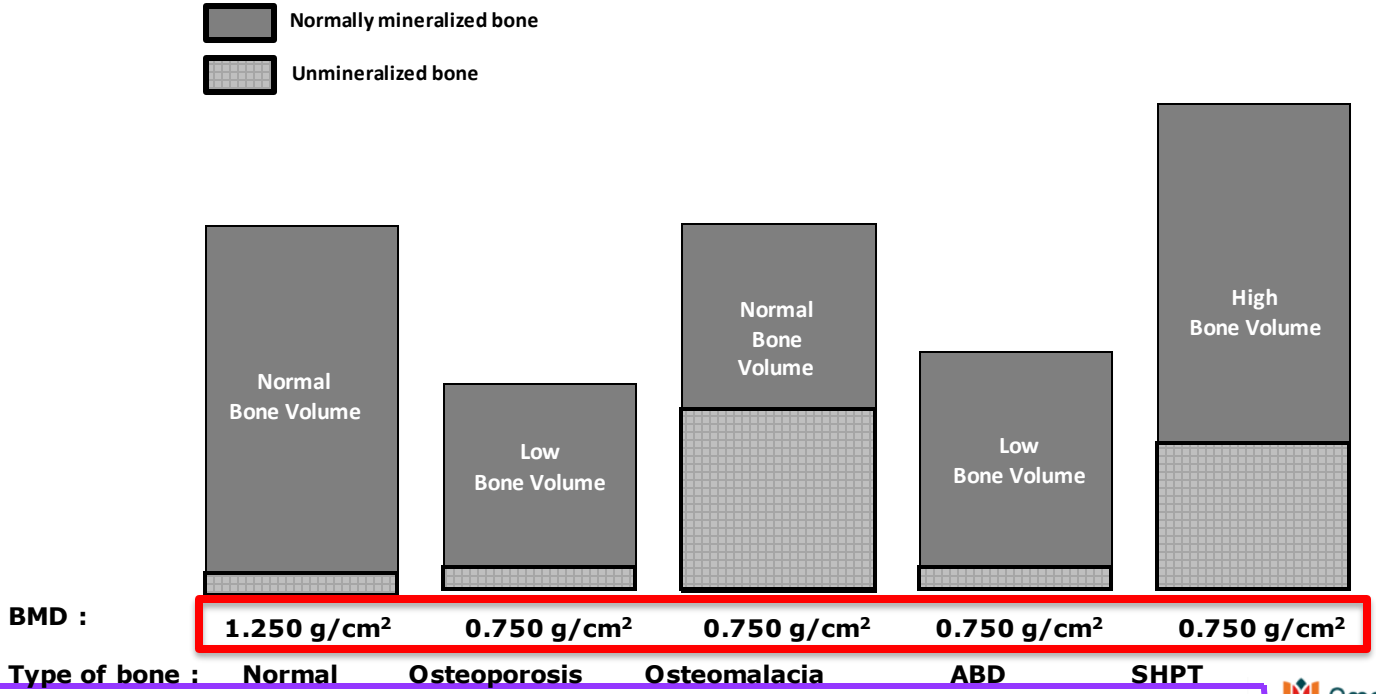


Bucur et al, Osteoporosis 2015:26: 449

Wie behandelen

- Als DXA T-score < -2,5, inclusief mannen?
- FRAX score?
- Of iedereen met een low-impact fracture? (recidief vooral kort na eerste fractuur, een theoretisch voordeel van romososumab)

A problem with DXA in ROD…



Courtesy MH Lafage-Proust

Need-to-know

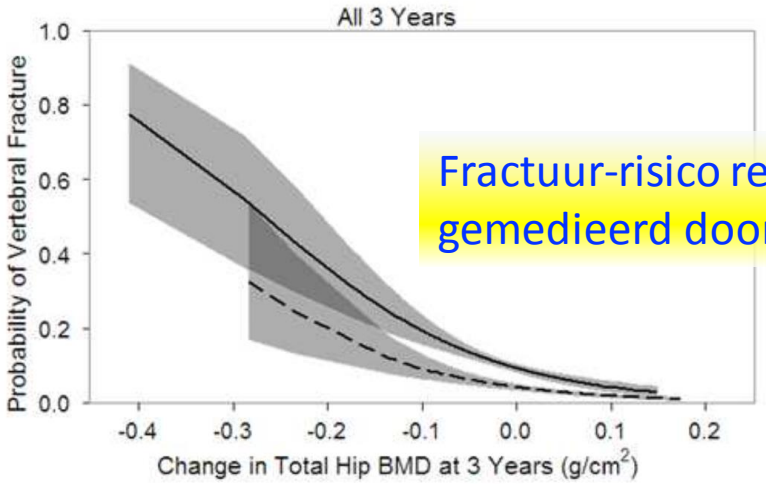
- Botmassa neemt toe door anti-resorptieve therapie onafhankelijk van onderliggende botpathologie
- Onbekend of bot-kwaliteit (=resistentie tegen fractuur) achteruit gaat

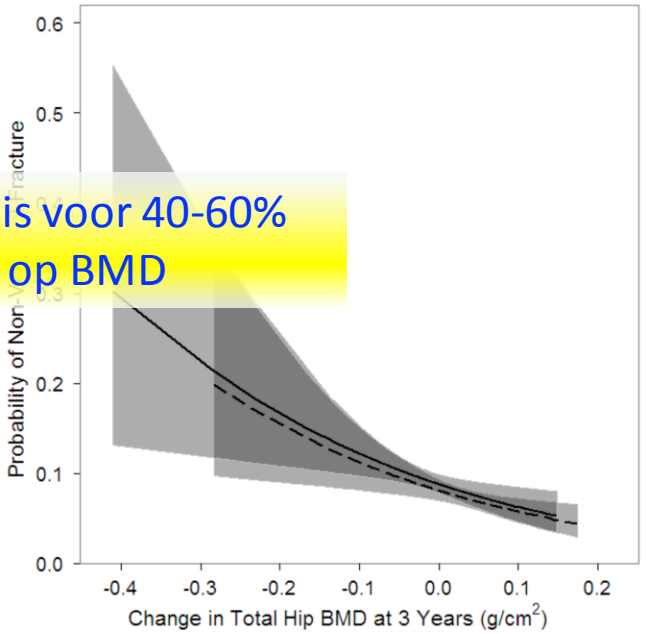
Bisfosfonaten

“Need-to-knows” over bisfosfonaten

- Low oral bioavailability (1% is optimal).
- BTM may indicate adequacy of oral uptake at 3-6 months after initiation
- If no change on BTM: co-medication? Consider iv treatment
- In those without residual kidney function: No risk for AKI of iv BP

Effectiviteit bisfosfonaten





Fractuur-risico reductie is voor 40-60% gemedieerd door effect op BMD

Jacques, JBMR 2012

Subanalyse Fracture Intervention Trial

TABLE 3. FRACTURE RISK WITH ALENDRONATE BY eGFR

Site	*eGFR*	*OR (95% CI)*	*p for interaction*
	All women (n = 6458)		
Clinical fractures	Severely reduced	0.78 (0.51–1.2)	0.90
	Moderately reduced or normal	0.81 (0.70–0.94)	
Spine fractures	Severely reduced	0.72 (0.31–1.7)	0.44
	Moderately reduced or normal	0.50 (0.32–0.76)	
	Women with osteoporosis (n = 3214)		
Clinical fractures	Severely reduced	0.84 (0.45–1.54)	0.72
	Moderately reduced or normal	0.74 (0.61–0.91)	
Spine fractures	Severely reduced	1.01 (0.29–3.6)	0.49
	Moderately reduced or normal	0.62 (0.36–1.10)	

Thyroid hormone past 6 months (%)	11.4	9.97	0.290
Fair or poor self-rated health (%)	10.3	4.7	<0.0001

*All values are means (SD).

Jamal. JBMR 2007

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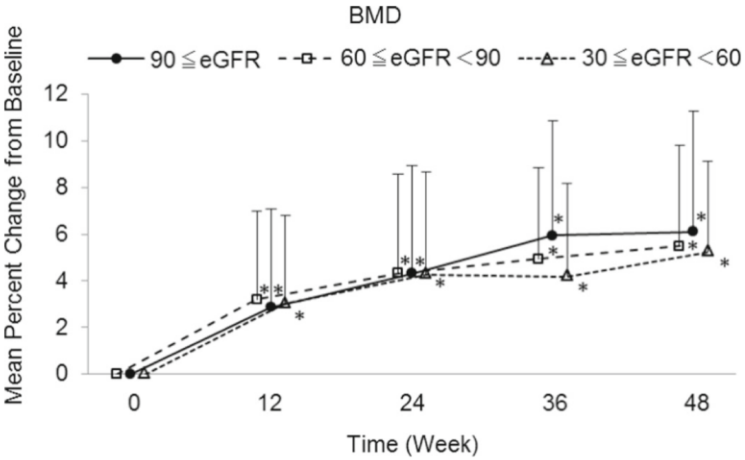
Post-hoc analyse 3 trials (risedronaat)

Table 1 Ba

	P value
Number of su	
Age (years)	<0.0001*
Sex (male/fer	0.5110**
Daily/Weekly	<0.0001**
BMI (kg/m^2)	<0.0001*
Lumbar spine	0.7043*

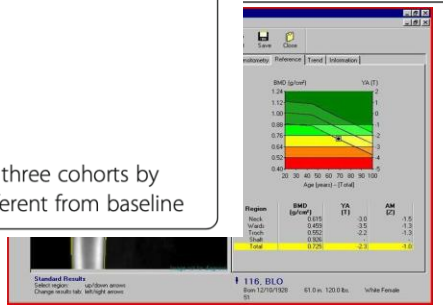
Values are me
*F test, **Chi s



Number of subjects at each measurement time point

90≦eGFR	87	82	79	76	75
60≦eGFR<90	390	375	360	338	329
30≦eGFR<60	119	110	106	104	102

Fig. 2 Mean percent change (± SD) from baseline in lumbar spine BMD in receiving risedronate. Patients were stratified into three cohorts by eGFR in baseline, and the mean percent change in lumbar spine BMD in each cohort was shown. *$p < 0.001$, significantly different from baseline



Shigematsu. BMC Nephrol 2017

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BP and CKD: Alendronate

Denosumab

Denosumab: post-hoc FREEDOM trial

Table 2. Effect of Denosumab, Compared with Placebo, on Fractures—Crude Incidence and Odds Ratios—Over 36 Months, by Stage of

Table 3. Effect of Denosumab, Compared with Placebo, on BMD Over 36 Months, by Stage of Kidney Function Estimated by CG

Outcome	Stage 4 CKD eGFR 15 to 29 mL/min ($N = 73$)	Stage 3 CKD eGFR 30 to 59 mL/min ($N = 2817$)	Stage 2 CKD eGFR 60 to 89 mL/min ($N = 4069$)	Stage 1 CKD/normal eGFR $\geq$ 90 mL/min ($N = 842$)
Lumbar spine BMD, % change	5.0 (−0.8–10.8)	8.9 (8.4–9.3)*	9.0 (8.6–9.4)*	8.1 (7.2–8.9)*
Femoral neck BMD, % change	5.9 (3.3–8.5)*	5.1 (4.7–5.5)*	5.2 (4.9–5.5)*	5.6 (4.9–6.3)*
Total-hip BMD, % change	5.9 (3.0–8.7)*	6.4 (6.1–6.7)*	6.4 (6.2–6.7)*	5.8 (5.2–6.3)*

N = number of randomized subjects. A difference in BMD% change > 0 in favor of denosumab.
*$p \leq .0002$.

(0.67–1.60) (0.60–0.93) (0.42–0.98)

[a]$p \geq .05$ for treatment by subgroup interaction.

Jamal, JBMR 2011

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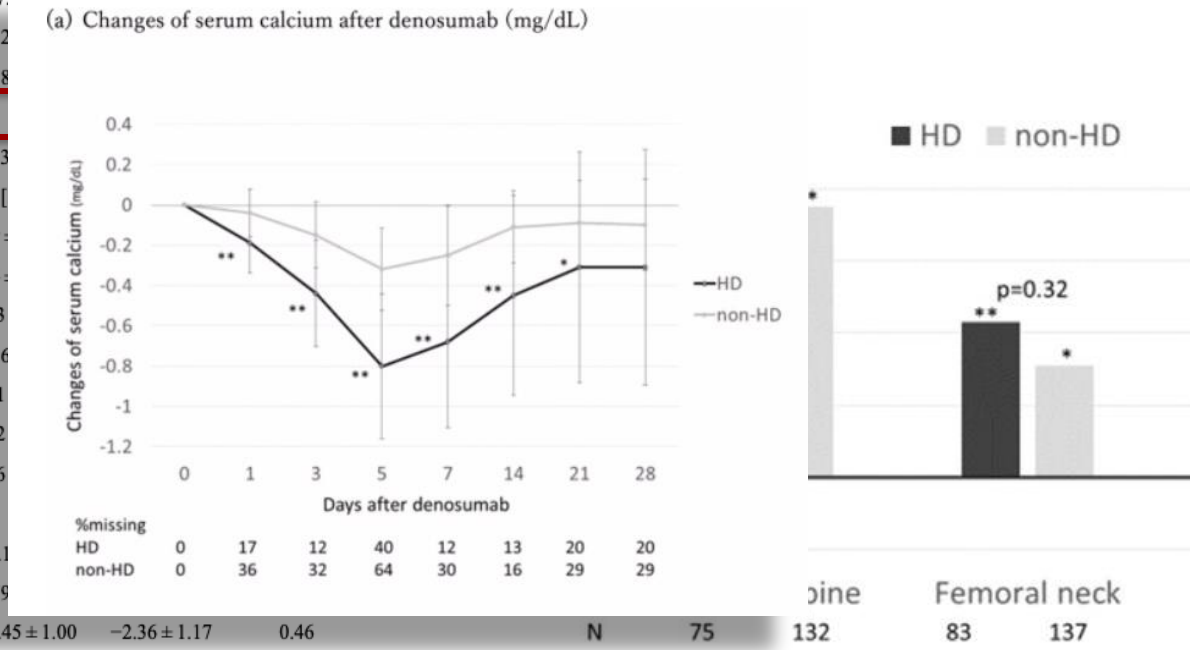
Observationeel: HD Denosumab

	HD (n = 121)	Non-HD (n = 203)	p-value
Age (years)	66.7 ± 10.6	71.2 ± 10.9	<0.001
Female sex (%)	60.3%	85.0%	<0.001
Height (cm)	157.		
Weight (kg)	49.2		
Body mass index (kg/m2)	19.8		
eGFR (mL/min/1.73 m2)			
CKD G1:2:3a:3b:4:5 (%)	11:3		
Dialysis vintage (years)	13 [		
Corrected Calcium	9.9		
Serum Phosphate	4.6		
Alkaline phosphatase (IU/L)	323		
BAP (μg/L)	19.6		
total P1NP (μg/L)	141		
Intact PTH (pg/mL)	132		
TRACP-5b (mU/dL)	496		
Bone Mineral Density (DEXA)			
Lumbar Spine (T score)	−2.1		
(BMD (g/cm2))	0.79		
Femoral Neck (T score)	−2.45 ± 1.00	−2.36 ± 1.17	0.46
(BMD (g/cm2))	0.54 ± 0.12	0.54 ± 0.13	0.90



Kunizawa Sci Rep 2020

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Denosumab versus alendronate in HD

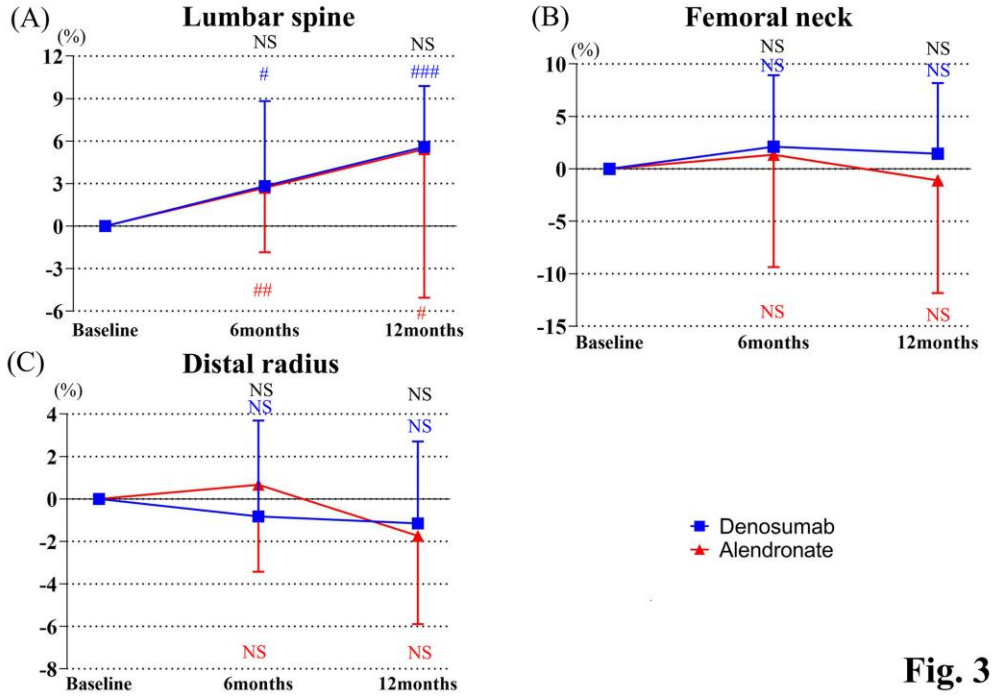
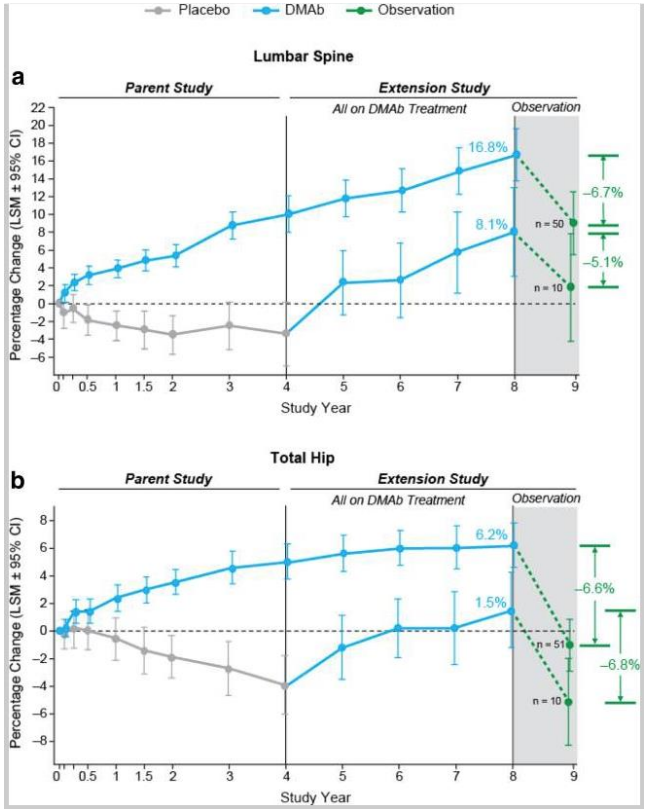


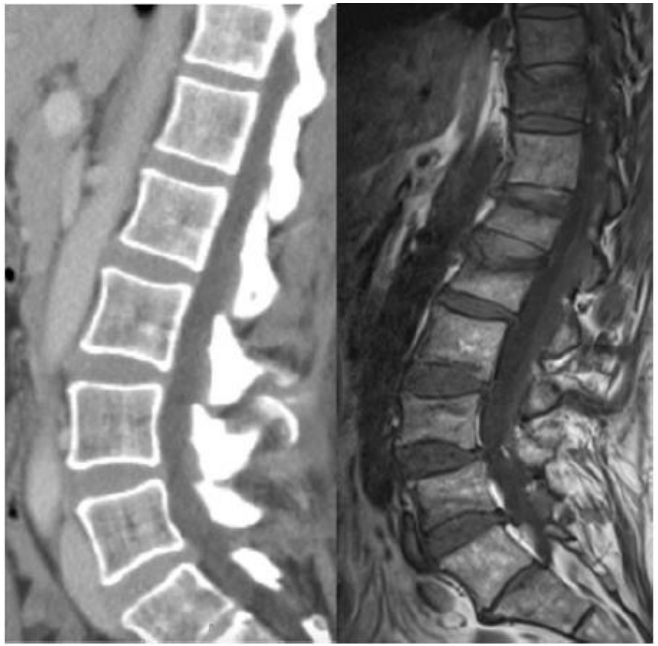
Fig. 3

Iseri, JBMR 2019

Rebound denosumab

Data from phase 2 trial





McClung, Osteoporosis Int 2017

Popp, Osteoporosis Int 2016

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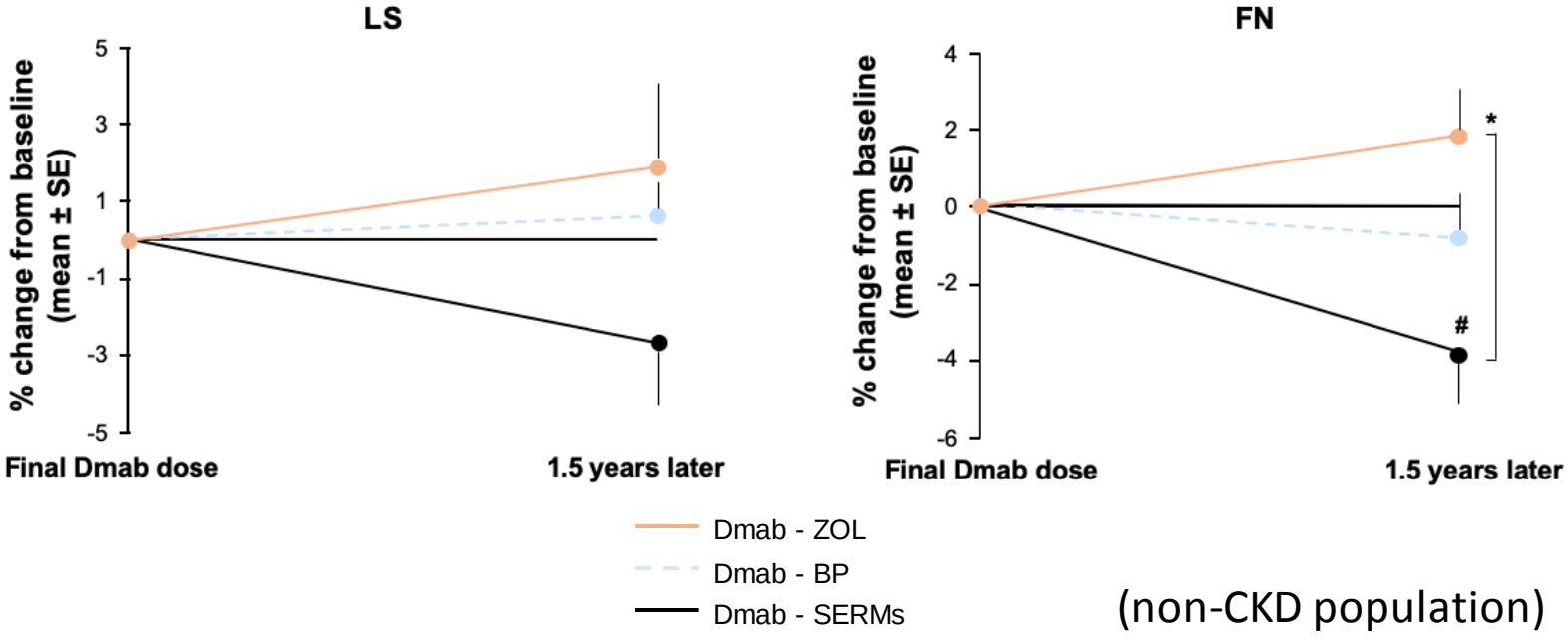
After Dmab discontinuation, switching to BP treatment (especially ZOL) increased BMD more efficiently compared with SERM treatment



(non-CKD population)

Ebina K, et al. Mod Rheumatol 2020;8:1–8.

#P < 0.05 change from final DMAb administration within each treatment group; *P < 0.05 SERMs vs ZOL.

Specifieke aspecten

Bisfosfonaten

- AKI (iv oude middelen non-nitrogen BP)
- Induction of adynamic bone?
- ONJ en atypical fracture
- Renaal geklaard (en dialyse)

Denosumab

- Weinig evidence overall
- Hypocalciemie
- Rebound
- Nabehandelen nodig
- Niet renaal geklaard

Conclusie

- Beide middelen
- Voor DNM én BP heel weinig evidence bij CKD4-5D
- Denosumab:
  - Logischer wat betreft farmacokinetiek
  - Hoger risico hypocalciëmie
  - Rebound: doorgaan of over op BP
- Bisfosfonaat:
  - Accumulatie, off-label gebruik
  - Leidt, net als DNM, heel waarschijnlijk tot bot accruel
  - Geen rebound, veel minder hypocalciëmie