Update on diagnosis and treatment of osteoporosis

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Update on diagnosis and treatment of osteoporosis

1. Introduction
2. Who should receive osteoporosis treatment?
3. How to choose the right osteoporosis treatment?
4. Drug holiday & treatment failure
5. Sequential treatment
6. What about the future?

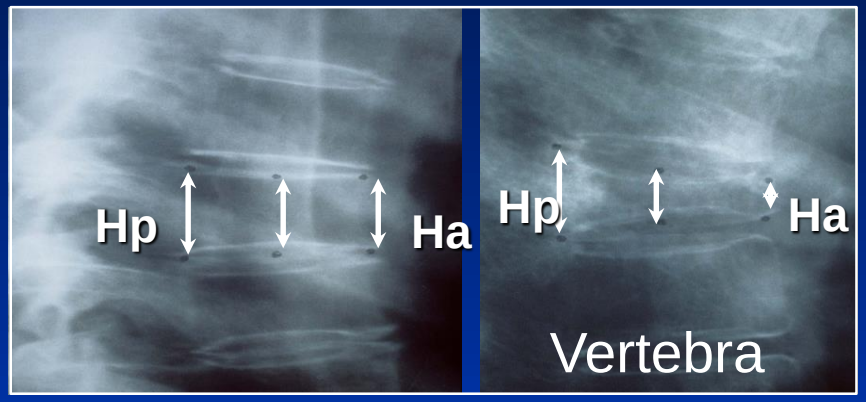
Osteoporosis

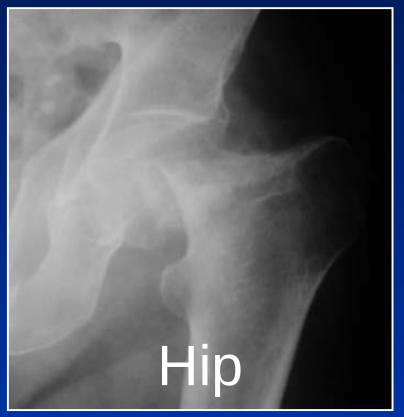
Low bone mass and micro-architectural deterioration of bone tissue

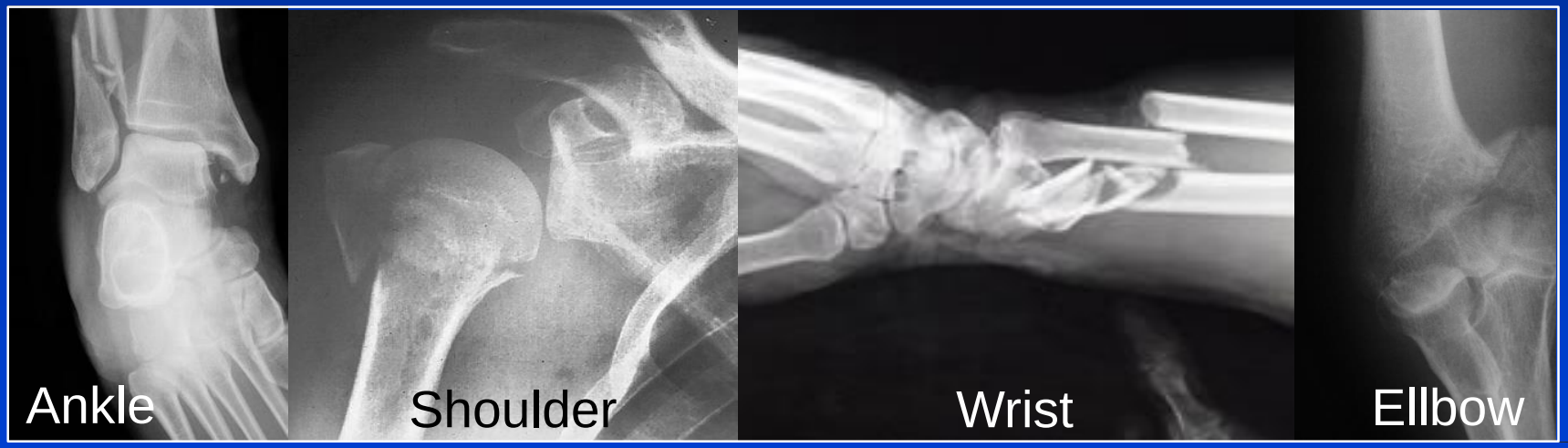
➔ increase in bone fragility and susceptibility to fracture

Am J Med 1993; 94: 646-50

Fragility fractures







Genant. JBMR 1993; 8: 1137-48

Epidemiology of fragility fractures in the elderly

- In ♀, 30% of all fragility fractures occur after 80 years [1]
- In ♀, 60% of hip fractures occur after 80 years [1,2]

- Prevalence of vertebral fractures in ♀

  19% at 75-80y ➔ 22 % at 80-85y ➔ > 40% at ≥ 85y [3]

- By age 90 years, ~ 30% of ♀ & 17% of ♂ have had a hip fracture [4,5]

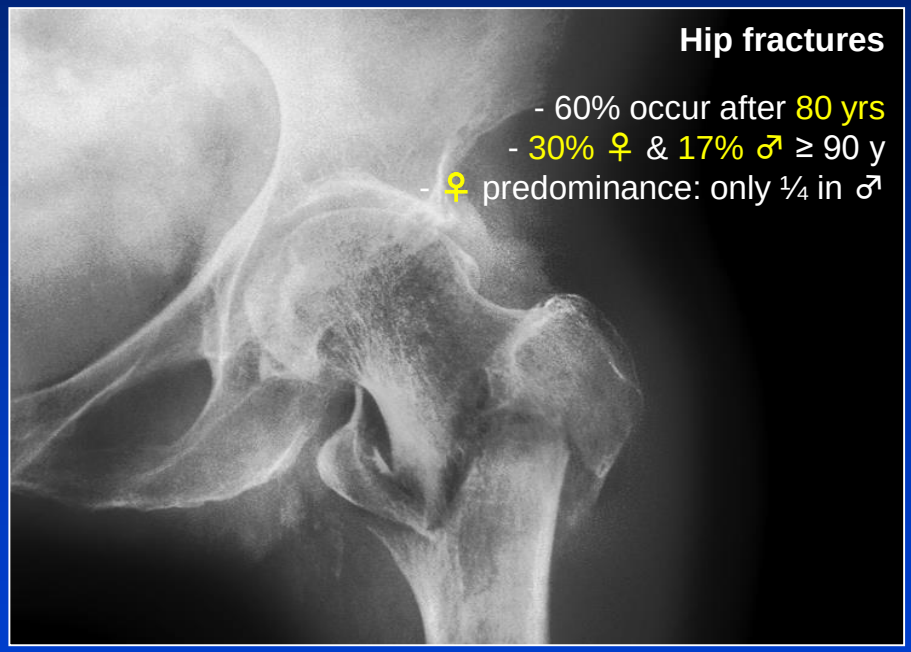
- Remaining lifetime risk at 80 years:
  - Any fracture [6]
    - 28.6% in ♀
    - 9.6% in ♂
  - Hip fracture [6]
    - 12.3% in ♀
    - 3.7% in ♂

[1]Sanders. Med J Aust 1999; 170: 467-470; [2]Chevalley. Bone 2007; 40: 1284-1289; [3]Grados. Bone 2004;34: 362-367; [4]Veronese. Injury 2018; 49: 1458-1460; [5]Gallagher. Clin Orthop Relat Res 1980; 150: 163-71; [6]Van Staa. Bone 2001. 29, 517-22

Consequences of osteoporosis

Impact of hip fractures

- **Functional decline**: **80%** of hip fracture patients still have problems with ADL after 1 year
- **Mobility**: **>50%** of previously independent hip # patients are not able to walk independently after 1 y
- **Institutionalization:** **19%** of hip fracture patients newly institutionalized over 1 year *vs.* 4% of controls
- **Loss of quality of life**: significant in all domains of the SF-36 at hospital discharge and at 1 year
- **Mortality**: **19%** of hip fracture patients over 1 year versus 3% in age- and residence-matched controls



Need for early diagnosis & treatment of osteoporosis to avoid first fracture!

Boonen. Osteoporos Int 2000; 11: 373-80; Haentjens. J Bone Surg Am 2001; 83: 493-500; Boonen. Osteoporos Int 2004; 15: 87-94; Cooper. Am J Med 1997;103:12S-19S; Keene. BMJ 1993;307:1248-50; Cole. Current Rheumatology Reports 2008;10:92-6

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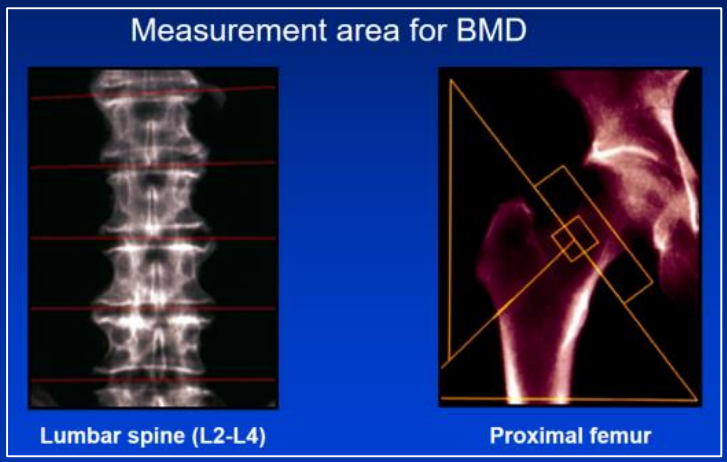
Diagnosis of osteoporosis

Bone densitometry (DXA, dual x-ray absorptiometry)

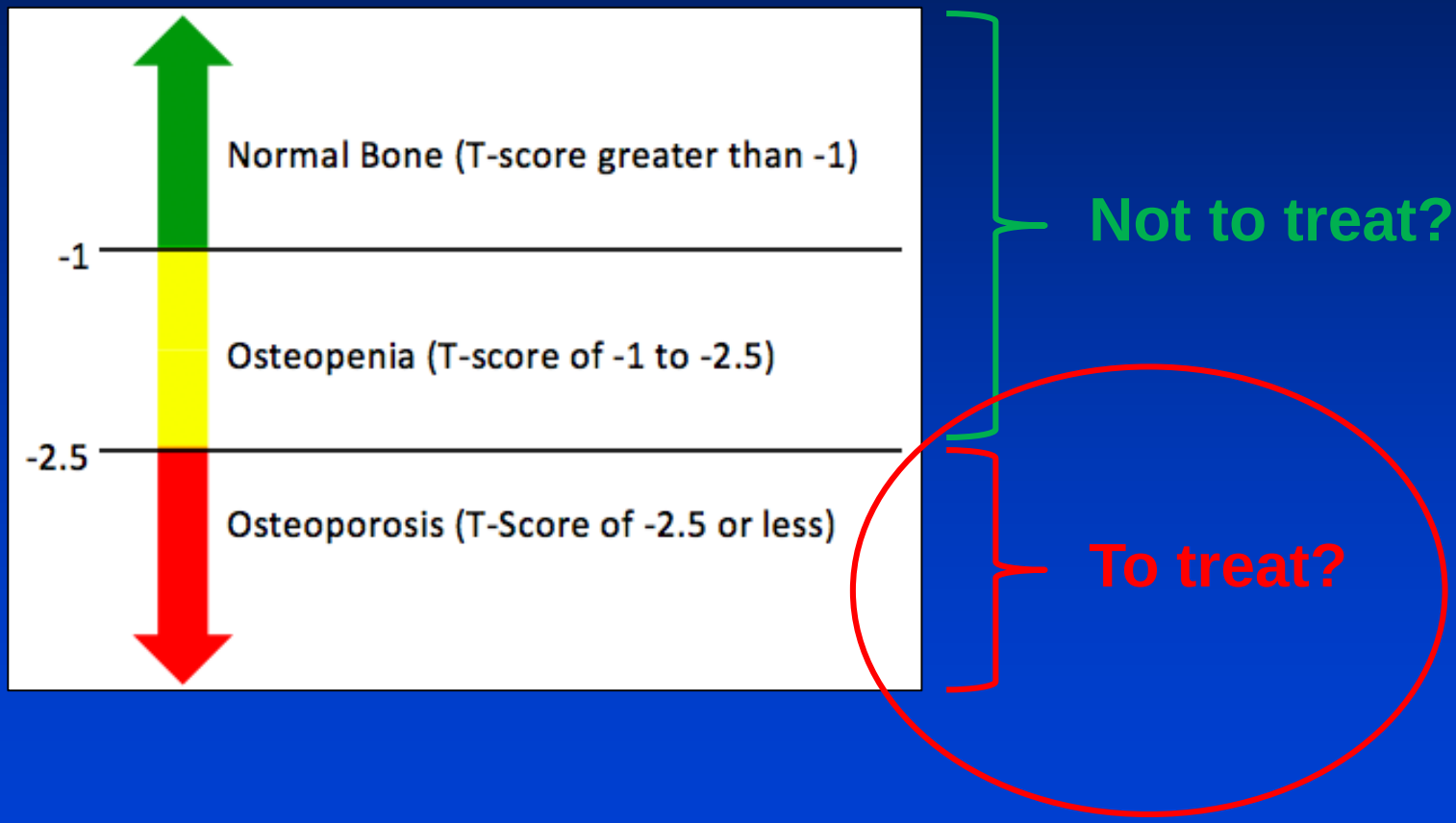


	T-score
Normal	≥ -1
Osteopenia	< -1 and > -2.5
Osteoporosis	≤ -2.5

WHO Tech Rep 1994; 843: 1-129

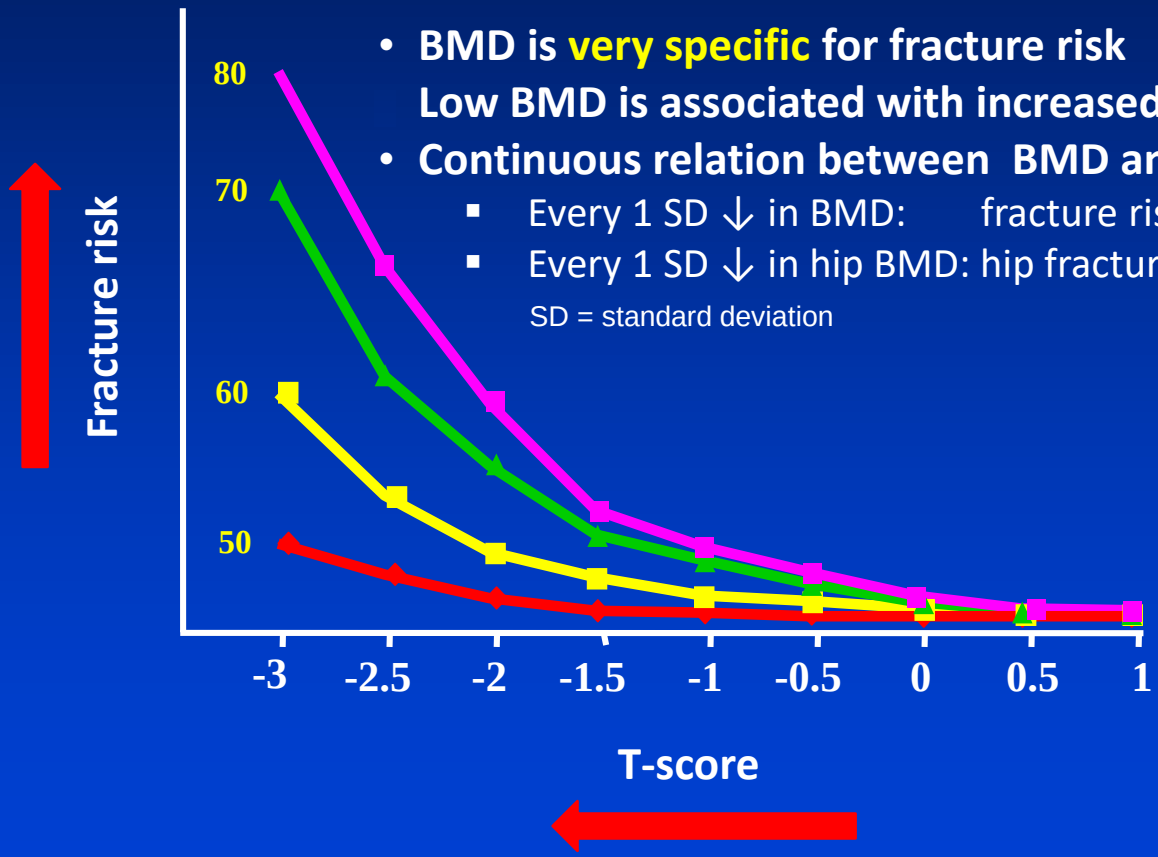
Diagnosis & treatment of osteoporosis

WHO criteria for diagnosis of osteoporosis using BMD



WHO Tech Rep 1994; 843: 1-129

BMD strongly correlates with fracture risk…



- **BMD is very specific for fracture risk**
  Low BMD is associated with increased risk of fracture
- **Continuous relation between BMD and fracture risk**
  - Every 1 SD ↓ in BMD: fracture risk x 1.5-2
  - Every 1 SD ↓ in hip BMD: hip fracture risk x 2.5

SD = standard deviation

Kanis. Osteoporos Int 2001; 12: 989-95; Marschall. BMJ 1996; 312: 1254-59; Johnell. J Bone Min Res 2002; 20: 1185-94

… but normal BMD does not exclude osteoporotic fractures!

BMD is very specific for osteoporotic fracture risk, but not sensitive

Fracture type	T-score hip < -2.5
Vertebral fractures	27 %
Hip fractures	46 %
Wrist fractures	17 %
All non-vertebral fractures	25 %

54% of hip # pts have hip T-score > -2.5

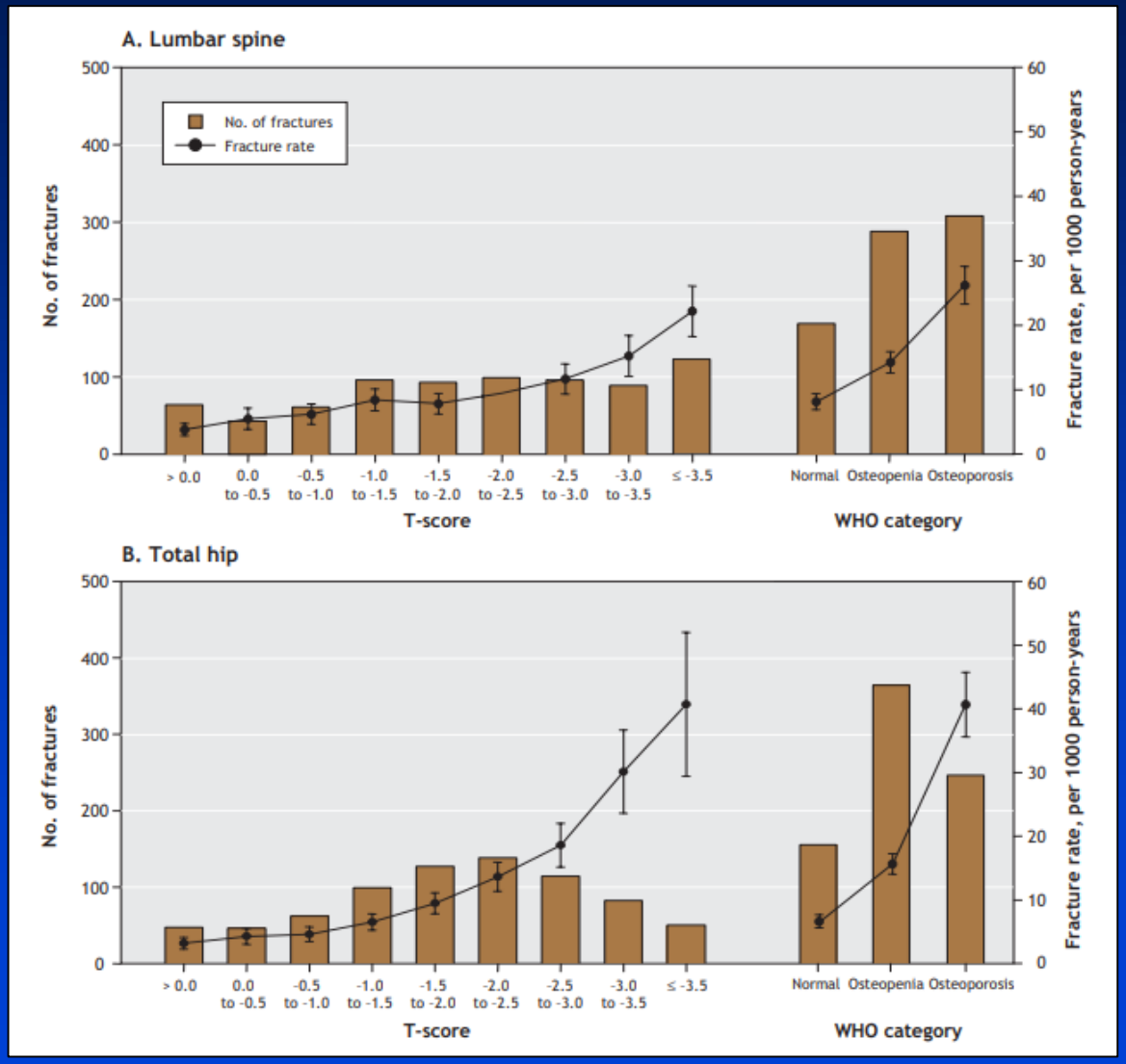
Rotterdam Study, 7806 ♀ & ♂ ≥ 55y
mean follow-up 6.8 years

Schuit. Bone 2004;34:195-202; Wainwright. J Clin Endocrinol Metab 2005; 90: 2787-93

Most fractures occur in persons with osteopenia

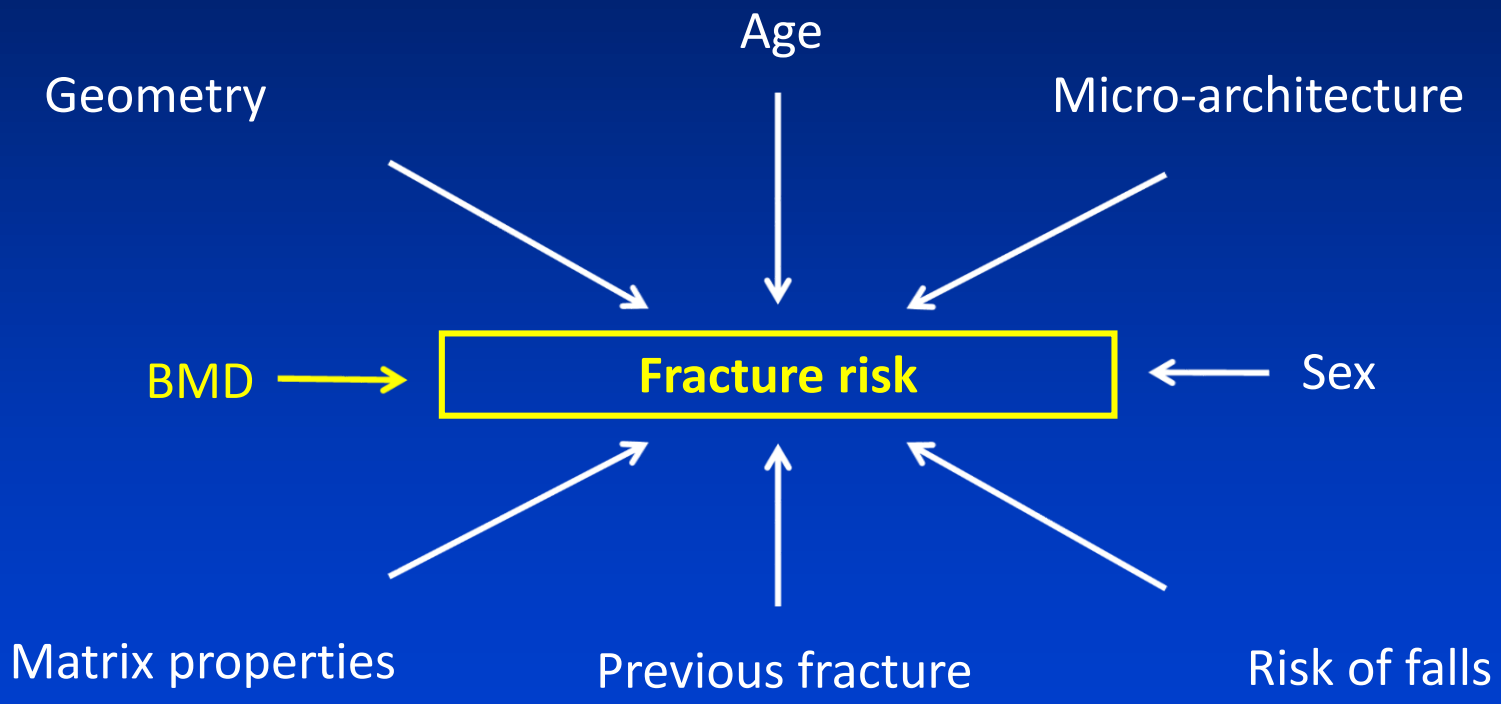
Cohort study of
16.505 women ≥ 50 y
FU 3.2 (SD=1.5) years

Number of fractures and **fracture rate** (per 1000 persons years, with 95% CI) by BMD and WHO category



Cranney. CMAJ 2007; 575-580

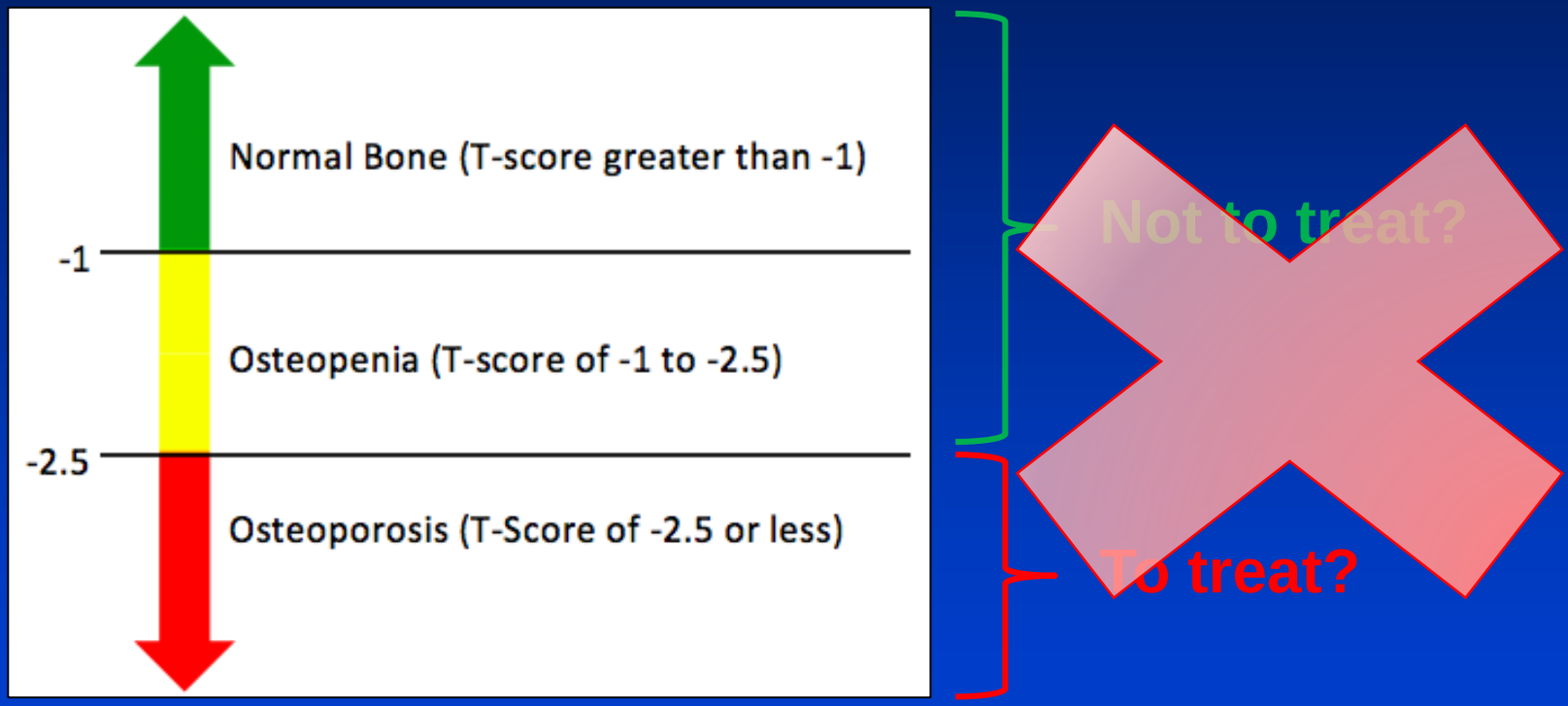
Many risk factors are associated with fracture risk independently of BMD



These risk factors should by taken into account when assessing fracture risk!

Diagnosis & treatment of osteoporosis

WHO criteria for diagnosis of osteoporosis using BMD



Some persons with osteoporosis may not need osteoporosis treatment
Some persons with osteopenia may need osteoporosis treatment

WHO Tech Rep 1994; 843: 1-129

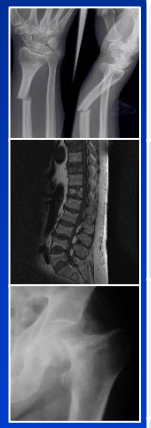
Who are the patients that need osteoporosis treatment?

→ Patients at high risk of fractures

- A. Previous fragility fractures, especially spine or hip
- B. High fracture risk on fracture risk assessment tools
- C. Use of bone turnover markers for fracture risk prediction?

A. Previous fragility fractures

Prior fracture increases the risk of subsequent fracture, independently of BMD



Location of prior fracture	Location of subsequent fractures			
	Wrist	**Vertebral**	**Hip**	**Pooled**
Wrist	3.3 (2.0-5.3)	1.7 (1.4-2.1)	1.9 (1.6-2.2)	2.0 (1.7-2.4)
Vertebral	1.4 (1.2-1.7)	4.4 (3.6-5.4)	2.3 (2.0-2.8)	1.9 (1.7-2.3)
Hip	NA	2.5 (1.8-3.5)	2.3 (1.5-3.7)	2.4 (1.9-3.2)
Pooled	1.9 (1.3-2.8)	2.0 (1.6-2.4)	2.0 (1.9-2.2)	2.0 (1.8-2.1)

Pooled analysis of literature in peri/postmenopausal women, RR (95% CI)

Klotzbuecher. J Bone Miner Res 2000; 15: 721-39

A. Previous fragility fractures

Time since prior fracture is a risk modifier for 10-year osteoporotic fractures

Time since prior fracture	HR (95% CI) incident #	*p*-value
Major fractures (hip, spine, humerus, forearm)		
< 1 year	1.90 (1.60-2.25)	<.001
1 to 5 years	1.75 (1.47-2.08)	<.001
5 to 10 years	1.58 (1.29-1.94)	<.001
> 10 years	1.62 (1.25-2.10)	<.001
Minor fractures		
< 1 year	1.49 (1.13-1.86)	.003
1 to 5 years	1.07 (0.82-1.38)	.632
5 to 10 years	1.32 (1.02-1.71)	.040
> 10 years	1.09 (0.78-1.52)	.633

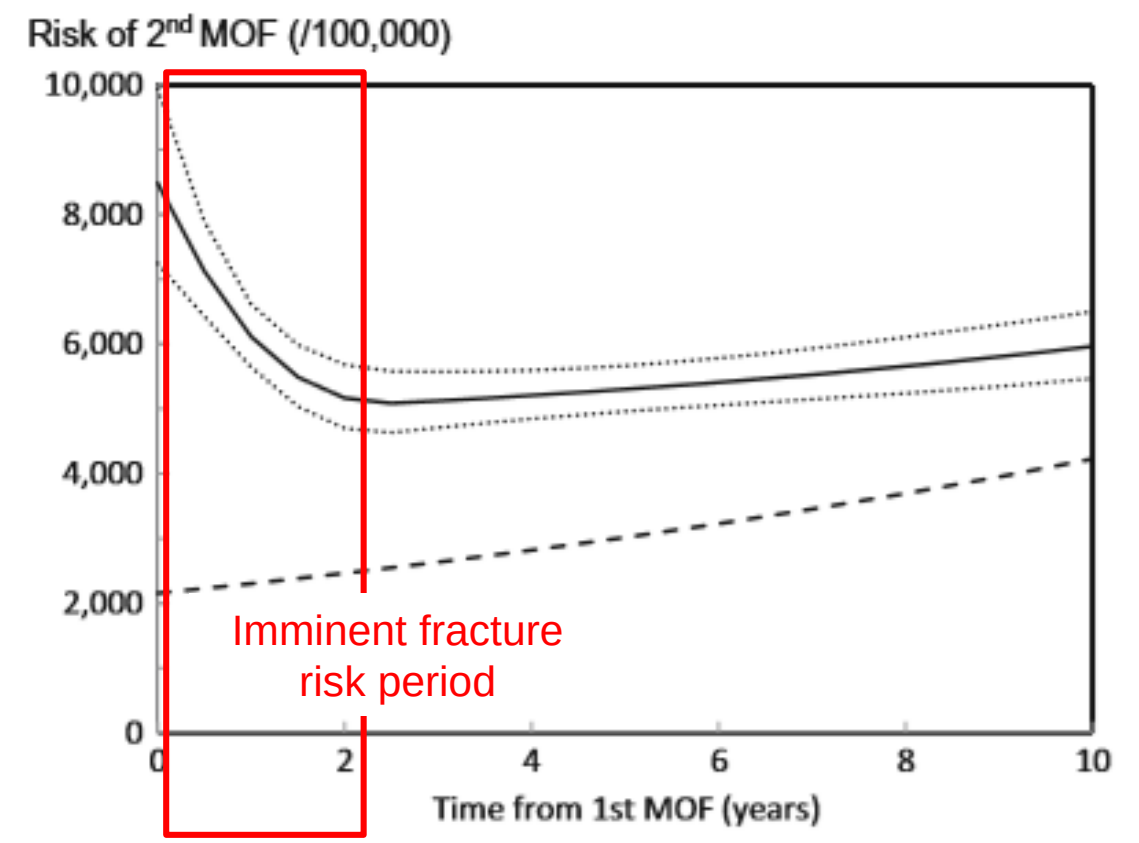
39.991 women ≥ 45y, mean follow-up 4.2 years, maximum 10 years

Adjusted hazard ratios (95% CI) for incident # by time since prior #

Giangregorio. J Bone Miner Res 2010; 25: 1400-1405

A. Previous fragility fractures

Imminent fracture risk



- Population based cohort N=18.872 ♀ & ♂
- Followed for 510.265 person years
  - N=5039: ≥ 1 MOF
  - N=1919: second MOF

Risk of second MOF:

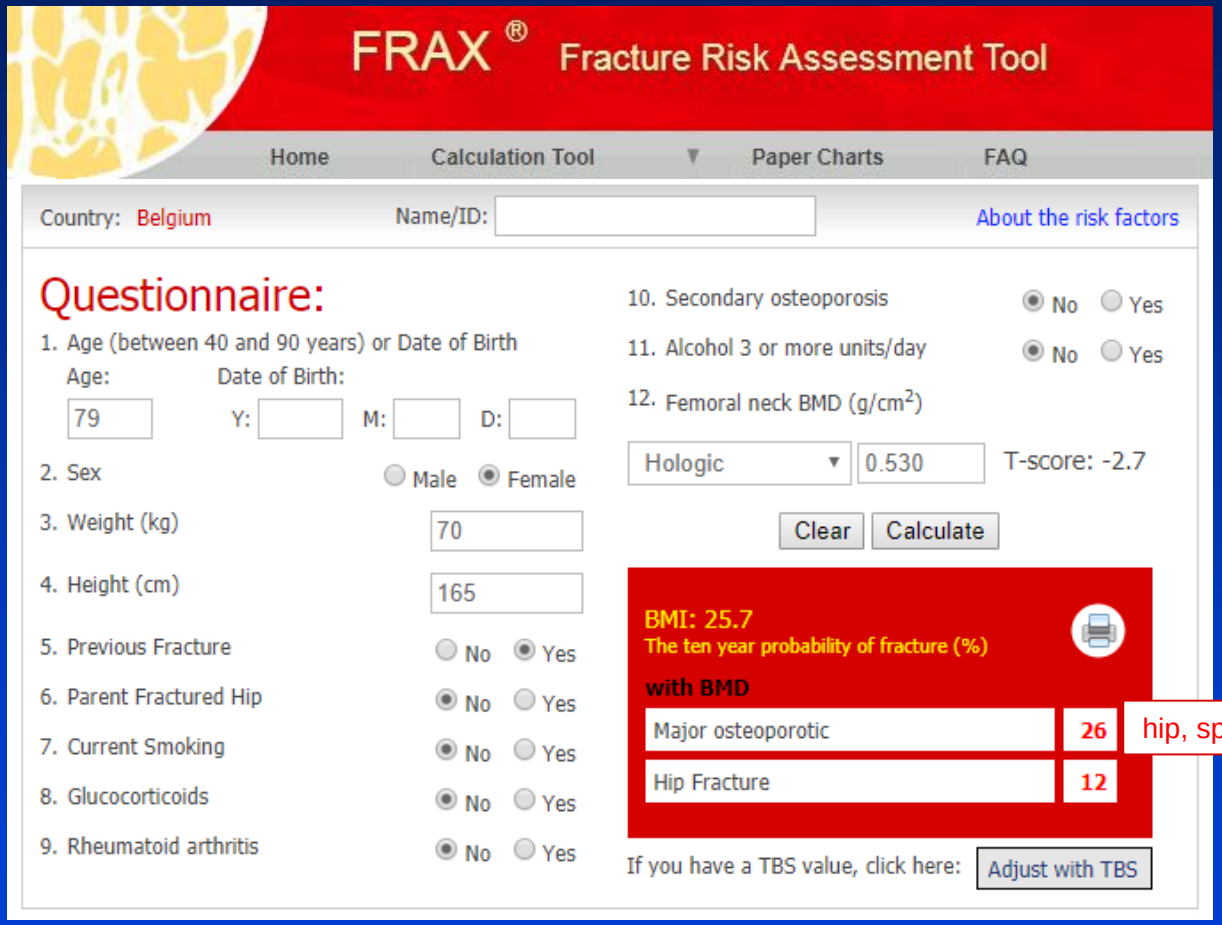
- 1 year after first MOF: **2.7 (2.4-3.0)x** higher than the population risk
- 10 years after first MOF: **1.4 (1.2-1.6)x** higher than the population risk

Time dependency of re-fracture after index fracture
Dashed line is risk of first MOF in whole population for a ♀ 75 years at baseline
MOF= major osteoporotic fracture

Johansson. Osteoporos Int 2017; 28: 775-80

B. High fracture risk on fracture risk assessment tools

- FRAX ® tool
- Garvan fracture risk calculator
- QFracture ®

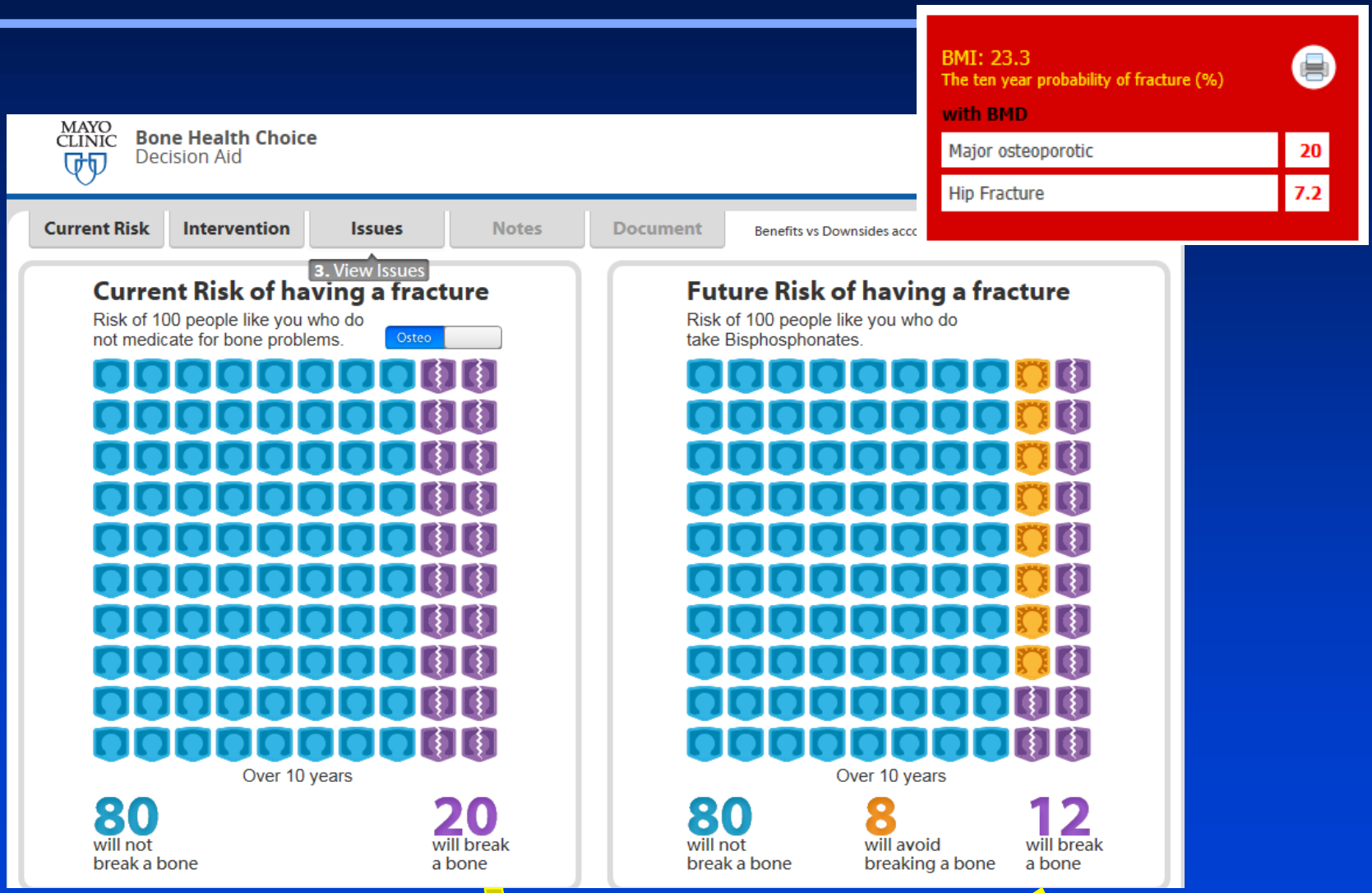


hip, spine, forearm, proximal humerus #

http://www.shef.ac.uk/FRAX/

Kanis. Osteoporos Int 2008; 19:1395-408; Kanis. Arch Osteoporos 2016; 11; Kanis. Osteoporos Int 2013; 24: 23-57; Dawson-Hughes. J Clin Endocrinol Metab 2008; 93: 2463-2465; Tosteson. Osteoporos Int 2008; 437-447; Kanis. Arch Osteoporos. 2013; 8: 144; McCloskey. Osteoporos Int 2015; 26: 2091-2099

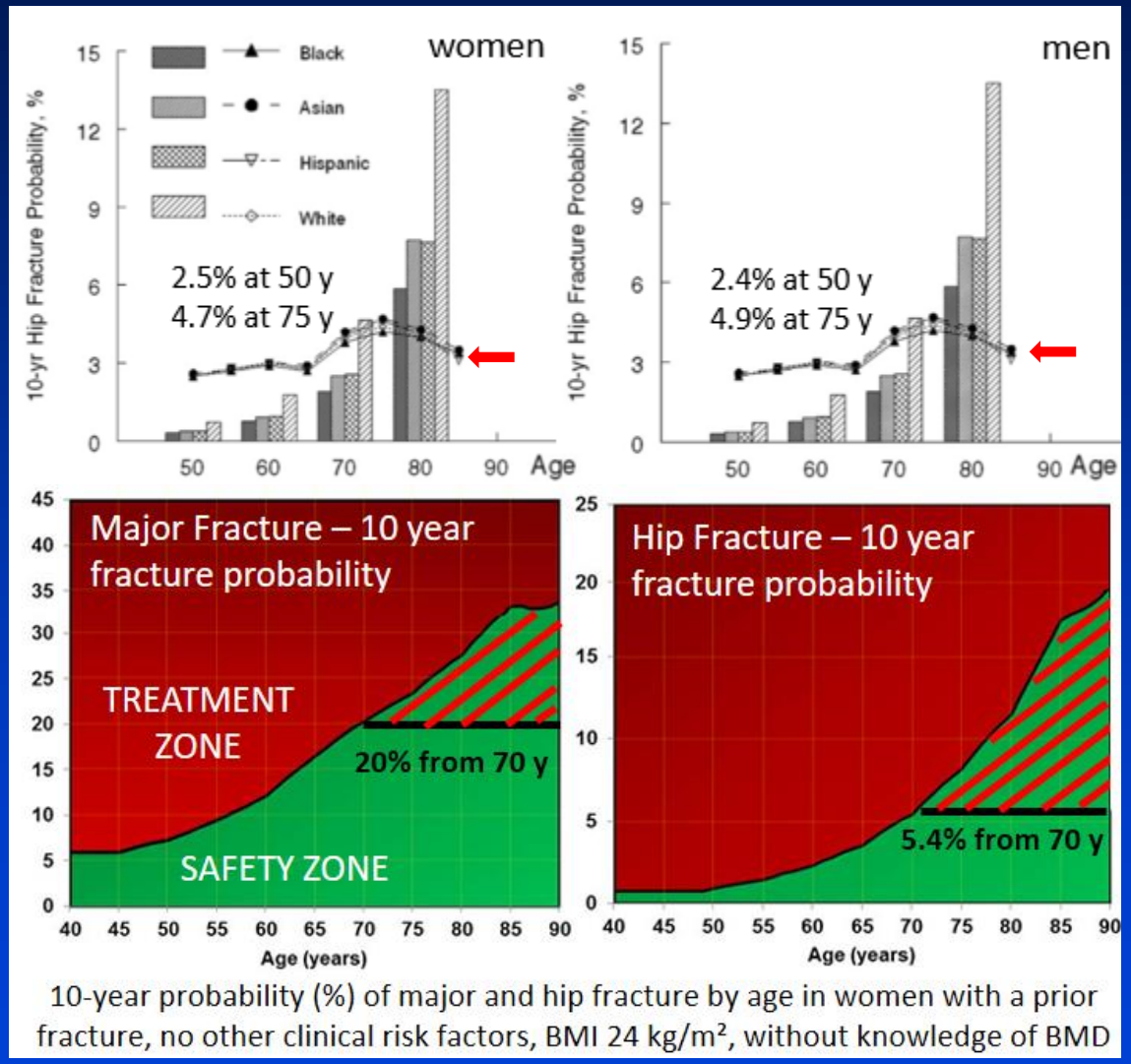
Shared decision making based on FRAX



~ 40% reduction in fracture risk with osteoporosis medication

Maraka S, Kennel KA. BMJ. 2015;351:h3783

Which patients should be treated based on FRAX? ~ intervention threshold



10-year probability (%) of major and hip fracture by age in women with a prior fracture, no other clinical risk factors, BMI 24 kg/m², without knowledge of BMD

Treatment is indicated if:

- **National Osteoporosis Foundation (NOF), USA**

T-score between -1 and -2.5

+ 10-year FRAX probability of fracture:

- ***≥ 3% for hip fracture***
- ***≥ 20% for major fracture***

(10-year probability of fracture at which it is cost-effective to treat, to determine for each country)

- **National Osteoporosis Guideline Group (NOGG), UK**

10-year FRAX probability of fracture

> age-dependent 'fracture threshold'

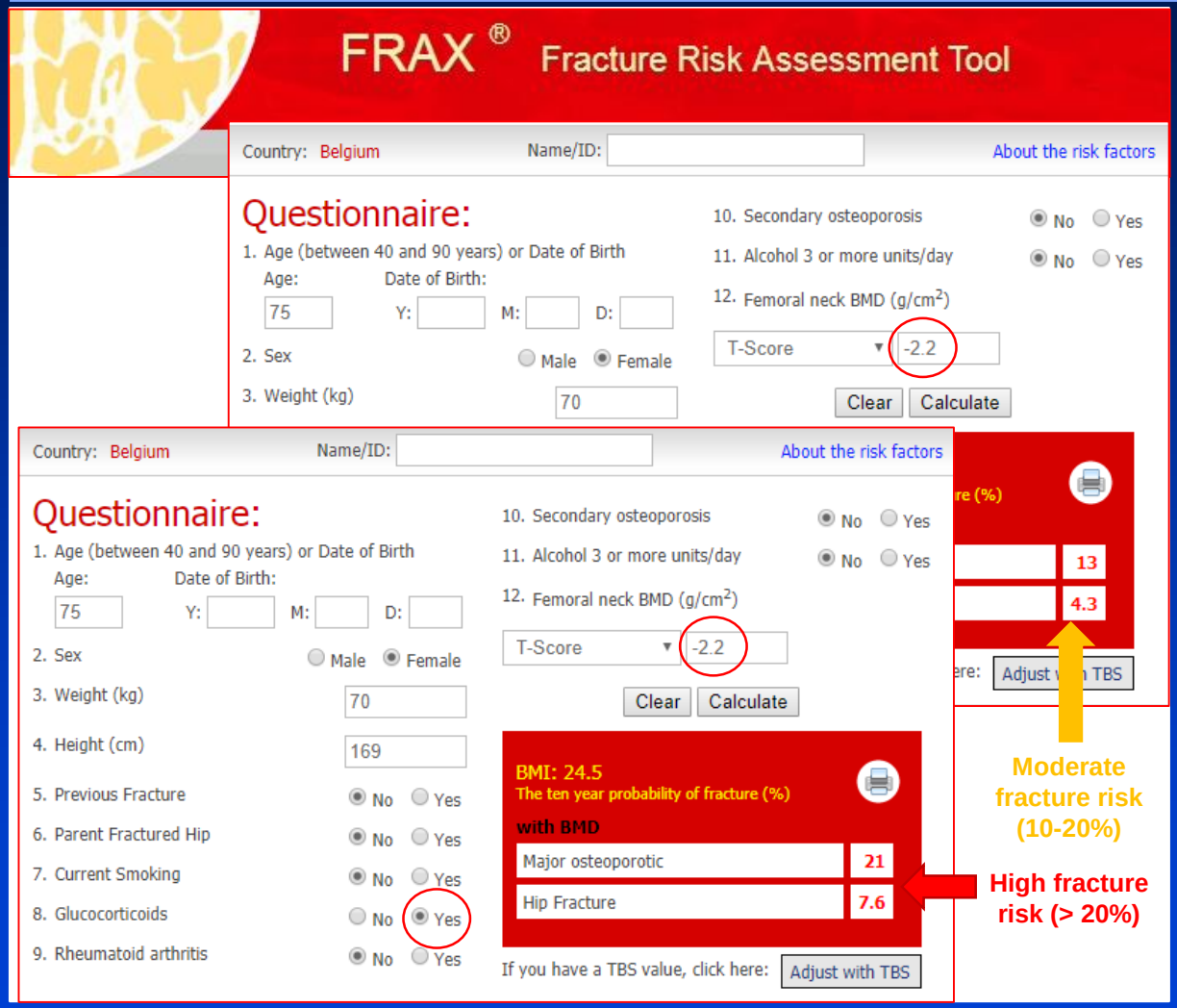
(10-year probability of fracture by age in (wo)men with prior fracture, no other clinical risk factors, BMI 24 kg/m², without knowledge of BMD)

➔ **Hybrid FRAX intervention threshold**

- ***≥ 5.4% for hip fracture (> 70 year of age)***
- ***≥ 20% for major fracture (> 70 year of age)***

Kanis. Osteoporos Int 2008; 19:1395-408; Kanis. Arch Osteoporos 2016; 11; Kanis. Osteoporos Int 2013; 24: 23-57; Dawson-Hughes. J Clin Endocrinol Metab 2008; 93: 2463-2465; Tosteson. Osteoporos Int 2008; 437-447; Kanis. Arch Osteoporos. 2013; 8: 144; McCloskey. Osteoporos Int 2015; 26: 2091-2099

Which patients should be treated based on FRAX?



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	FRAX	Garvan	Qfracture-2016	
Age	**Yes**, 40-90y	**Yes**, 50-96y	**Yes**, 30-99y	dementia
Gender	**Yes**	**Yes**	**Yes**	cancer
Height	**Yes**	**No**	**Yes**	astma/COPD
Weight	**Yes**	**No**	**Yes**	heart attack, angina, stroke, TIA
Previous fracture	**Yes**	**Yes**, since 50y (0, 1, 2, ≥ 3 #)	**Yes**, fracture of wrist, hip, spine or shoulder	chronic liver disease
Parenteral hip fracture	**Yes**	**No**	**Yes**, or osteoporosis	chronic kidney disease (stage 4/5)
Smoking	**Yes**, current	**No**	**Yes**, non-smoker, ex-smoker, light (< 10), medium (10-19), heavy (≥ 20)	Parkinson's disease
Glucocorticoid use	**Yes**, currently or previously prednisolone ≥ 5mg/d > 3mo	**No**	**Yes**, taking steroid tablets regularly	malbsorption (Crohn, CU, …)
Rheumatoid arthritis	**Yes**	**No**	**Yes**, or SLE	endocrine problem (hyperT,, Cushing, hyperparaT.)
Secondary osteoporosis	**Yes**	**No**	➔	
Alcohol	**Yes**, > 3 units daily	**No**	**Yes**, none, < 1 unit/d, 1-2, 3-6, 7-9, > 9/d	epilepsy or taking anticonvulsants
Femoral neck BMD	**Yes**	**Yes**	**No**	taking antidepressants
History of falls	**No**	**Yes**, last 12 mo (0, 1, 2, ≥ 3 falls)	**Yes**	taking oestrogen only HRT
Living in nursing home	**No**	**No**	**Yes**	

Falls and sarcopenia independently predict fracture risk

- Falls predict fractures independently of FRAX and BMD

HR for fractures	Any fracture	Major osteoporotic	Hip
Falls, adj. for FRAX	1.63 (1.45-1.83)	1.51 (1.29-1.77)	1.54 (1.21-1.95)
Falls, adj. for FN BMD	1.71 (1.51-1.92)	1.58 (1.35-1.85)	1.64 (1.29-2.08)

- Data are hazard ratios (95% CI) adjusted for age and time since baseline
- Meta-analysis of Osteoporotic Fractures in Men (MrOS) Study (N=7857, ≥ 65 y)

- Sarcopenia predicts fractures independently of BMD

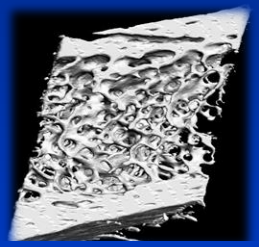
HR for fractures	Any fracture	
Sarcopenia (AWGS)	1.87 (1.26-2.79) (p=.002)	• Data are hazard ratios (95% CI) adjusted for age, hip BMD and other factors • MrOS Hongkong (N=2000, ≥ 65 y)
low RASM (< 7.0 kg/m²)	1.08 (0.77-1.52) (p=.649)	
low grip strength (< 26 kg)	1.75 (1.17-2.61) (p=.007)	
low gait speed (< 0.8 m/s)	1.61 (1.11-2.35) (p=.013)	

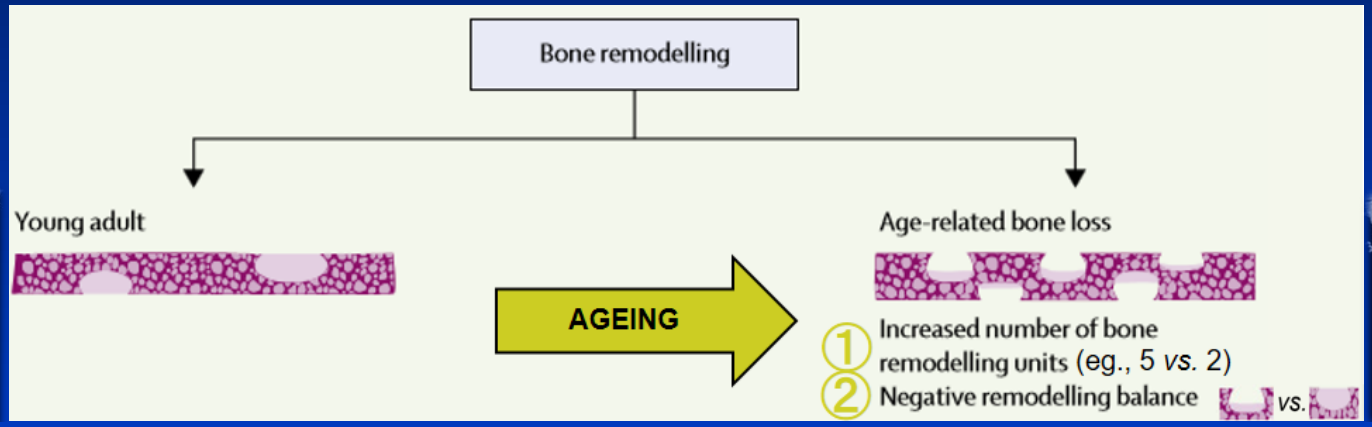
Harvey. J Bone Miner Ras 2018; 33: 510-516; Yu. J Am Dir Assoc 2014; 15: 551-558

C. Use of bone turnover markers for fracture risk prediction?

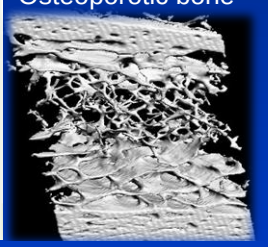
- Osteoporosis occurs with ageing as a result of
  - ① increase in the rate of bone remodeling &
  - ② imbalance between bone formation - resorption

Normal bone

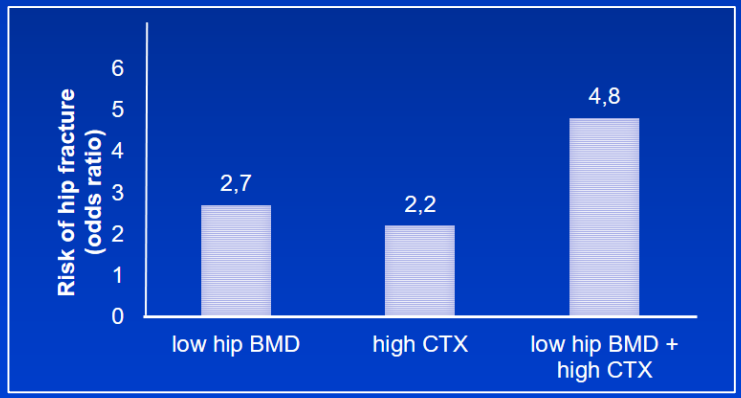




Osteoporotic bone



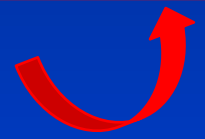
Reference marker	Origin	Further details
s-PINP Serum procollagen type I N propeptide	Precursor molecules of collagen type I synthesised by osteoblasts	Specificity: mostly derived from bone collagen type I Assay: may recognise trimer alone (intact) or trimer and monomer (total PINP) Source of variability: small circadian rhythm Automated ECLIA as well as manual RIA and ELISA available Sample: serum or plasma
s-CTX Serum carboxy-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen, generated by cathepsin K	Standard in assay is well characterised 8-amino acid peptide s-CTX is always isomerised (β) Specificity: collagen type I, with highest contribution probably from bone Sources of variability: very dependent on time of day and food (must be collected after an overnight fast); influenced by renal function, liver function and circadian rhythm Automated ECLIA as well as manual ELISA available Sample: serum or plasma (EDTA preferred)



Nguyen. Osteoporos Sar 2018; 4: 2-10; Garnero. J Bone Miner Res 1996; 11: 1531-7

Who are the patients that need osteoporosis treatment?

- A. Previous fragility fractures, especially spine or hip
- B. High fracture risk on fracture risk assessment tools
- (C. Use of bone turnover markers?)



FRAX MOF > 20%

FRAX MOF 10-20%

+ additional factors that bump patient up to the high risk level

- frequent falls, poor balance
- spine BMD << hip BMD
- multiple fractures
- dosage of CS, smoking
- …

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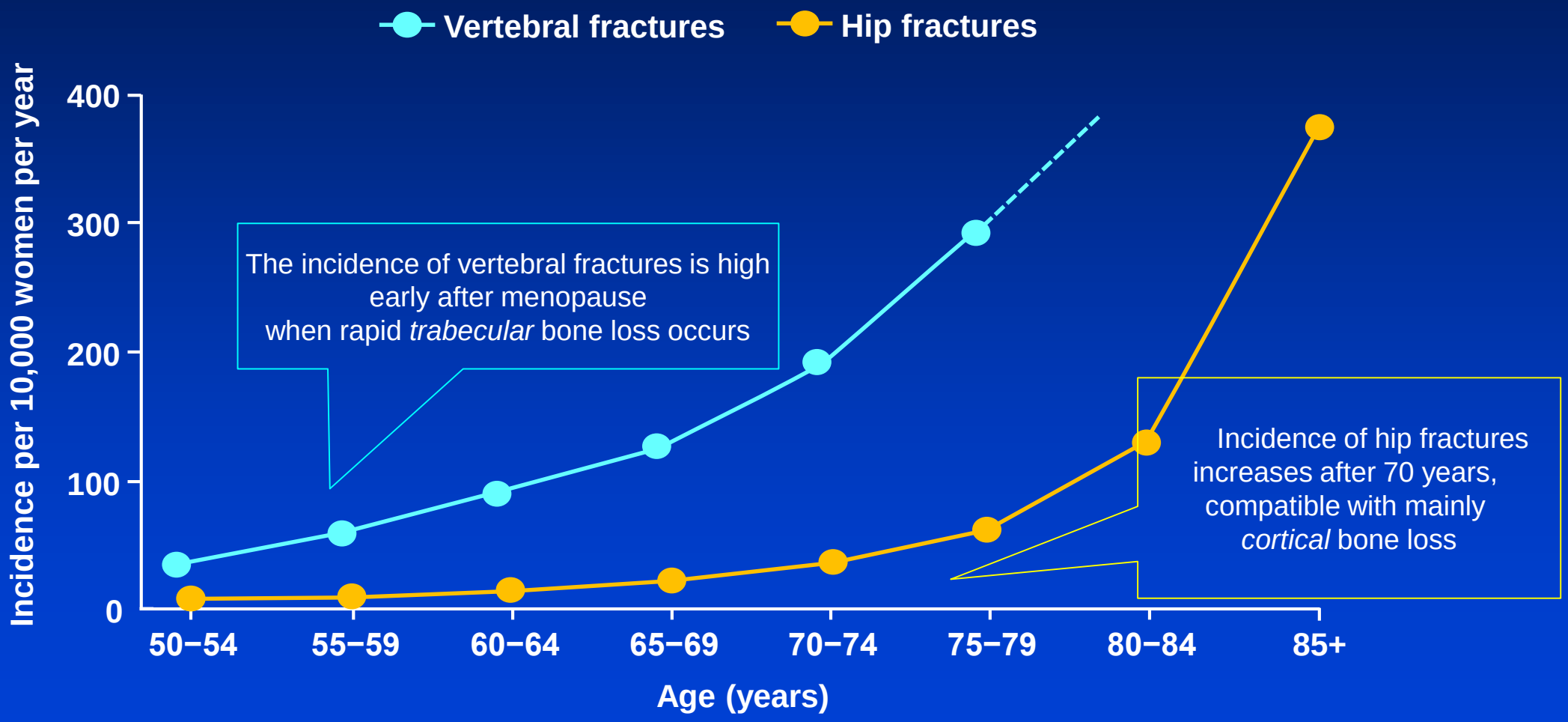
How to choose the right osteoporosis treatment?

EU approved pharmacological interventions				
	Frequency and route of administration	Fracture risk reduction* Vertebral	Hip	Non-vertebral
Bisphosphonates				
• Alendronate (Fosamax ®)	Oral, once daily or weekly	Yes	Yes	Yes
• Risedronate (Actonel ®)	Oral, once daily or weekly	Yes	Yes	Yes
• Ibandronate (Bonviva ®)	Oral, once monthly IV, every 3 months	Yes	ND	ND
• Zoledronic acid (Aclasta ®)	IV, once yearly	Yes	Yes	Yes
RANK ligand inhibitor				
• Denosumab Prolia ®)	SC, every 6 months	Yes	Yes	Yes
Selective oestrogen receptor modulators				
• Raloxifen (Evista ®)	Oral, once daily	Yes	ND	No
• Bazedoxifen (Conbriza ®)	Oral, once daily	Yes	ND	No
Parathyroid hormone receptor antagonist				
• Teriparatide (Forsteo ®)	SC, once daily	Yes	ND	Yes

* Significant fracture risk reduction in primary analysis of clinical trial
ND = studies not powered to observe effect on hip or non-vertebral fracture risk

Age-related exponential increase in fracture incidence



Sambrook. Lancet 2006;367:2010-2018

How to choose the right osteoporosis treatment?

- **Kost – terugbetaling!**
  - Globaal strikte terugbetalingscriteria in België
  - Orale bisfosfonaten ⇔ iv Zoledronaat ⇔ Denosumab ⇔ Teriparatide

- **Nevenwerkingen en contra-indicaties**
  - nierinsufficiëntie, maagulcera
  - Frequent: milde nevenwerkingen (gastro-intestinaal, infusiesyndroom)
  - Zeer zelden:
    - osteonecrose van kaakbeen
    - atypische femurfractuur

Crandall CJ et al. Ann Intern Med. 2014;161(10):711-23

How to choose the right osteoporosis treatment?

- **Efficiëntie? Bisfosfonaten, denusomab en teriparitide**
  - NNT preventie niet-vertebrale fractuur = 50- 60 / 1-3 jaar
  - Weinig verschil tussen producten (geen vergelijkende # studies, uitz. VERO trial)
  - Potentiële extraskeletale voordelen
    - bv. SERMs en borstkankerpreventie

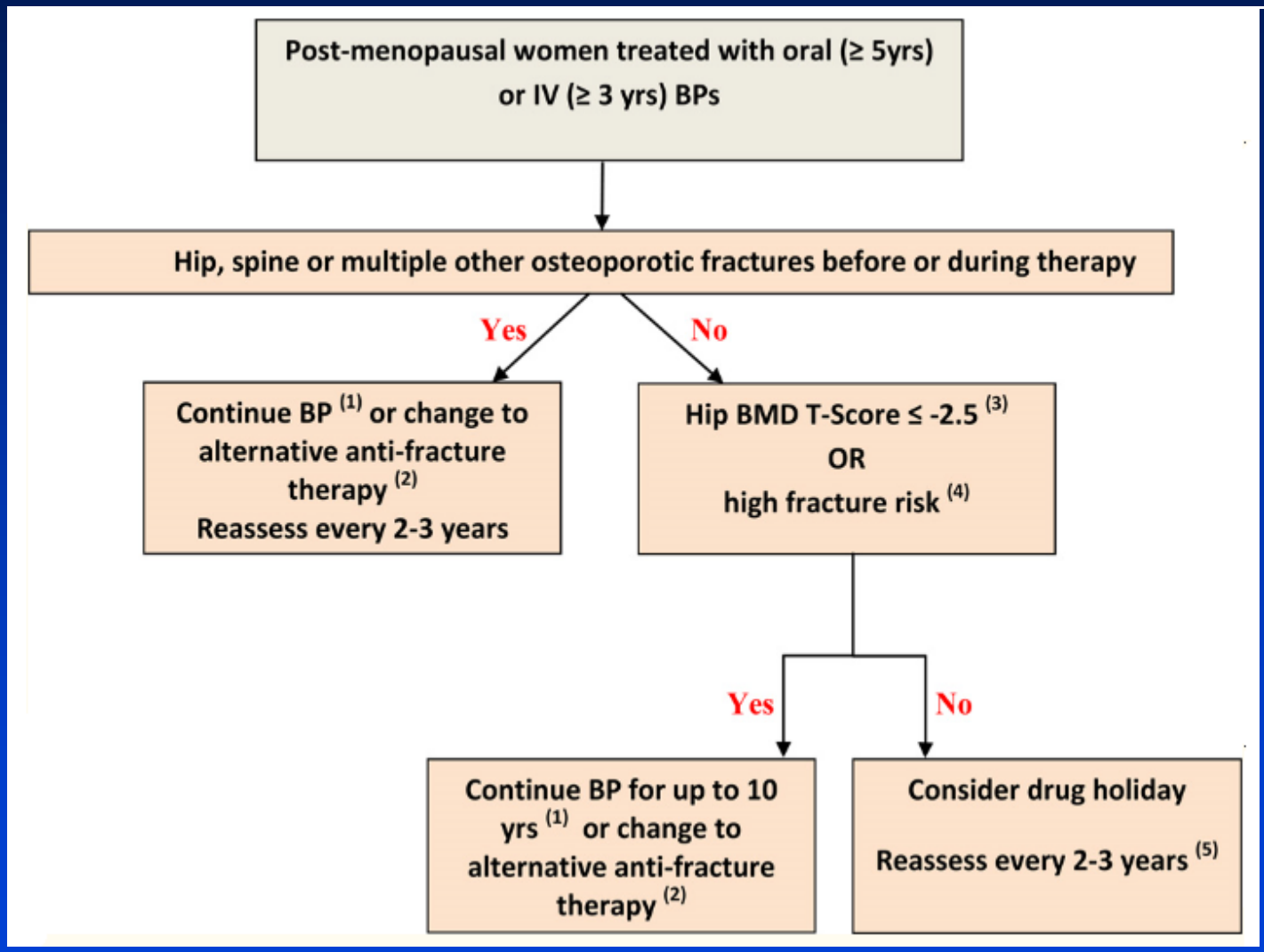
- **Compliantie, toedieningswijze**
  - Globaal laag
    - parenteraal > oraal ?
    - lange werkingsduur bisfosfonaten!

- **Voorkeur patiënt & Shared Decision Making**

Update on diagnosis and treatment of osteoporosis

1. Introduction
2. Who should receive osteoporosis treatment?
3. How to choose the right osteoporosis treatment?
4. Drug holiday & treatment failure
5. Sequential treatment
6. What about the future?

When to stop and restart osteoporosis treatment?



Na 5 jaar po BP of 3j ZOL

– T-scores > -2,5 + vooraf geen #
[of T > -2,0 + vooraf 1 wervel#]
EN geen nieuwe # tijdens R/
➔ **pauze + herevaluatie na 2-3j**
(vroeger voor Ris)

– T-scores ≤ -2,5
OF: vooraf heup# of ≥2 wervel#
OF: nieuwe # tijdens R/
➔ **Orale BP: 10 jaar**
➔ **Zol: 1x/jaar gedurende 6j**

➔ Na 6x jaarlijks zoledronaat:
meestal drug holiday mogelijk

➔ **Wat na 6-10j?**
➔ **Wat met therapiefalen?**
Switch?

When to stop and restart osteoporosis treatment?

Can we use of bone turnover markers to decide when to restart treatment after a drug holiday?

An increase, greater than the least significant change (LSC)

- P1NP: increase of 10 µg/l
- CTX: increase of 100 ng/l

Value above the mean value of a healthy young women

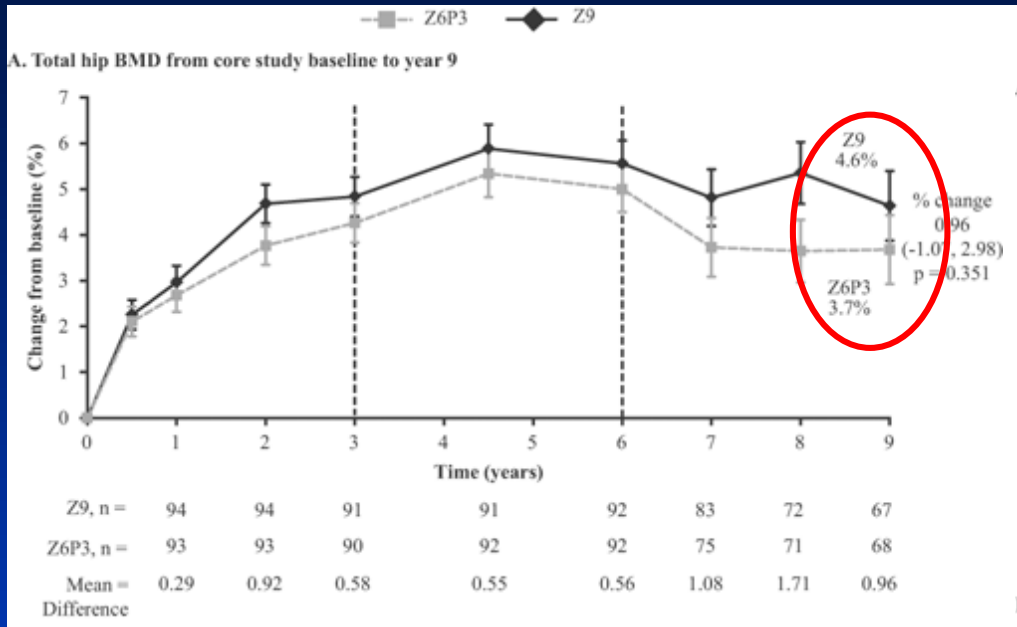
- P1NP > 35 µg/l
- CTX > 280 ng/l

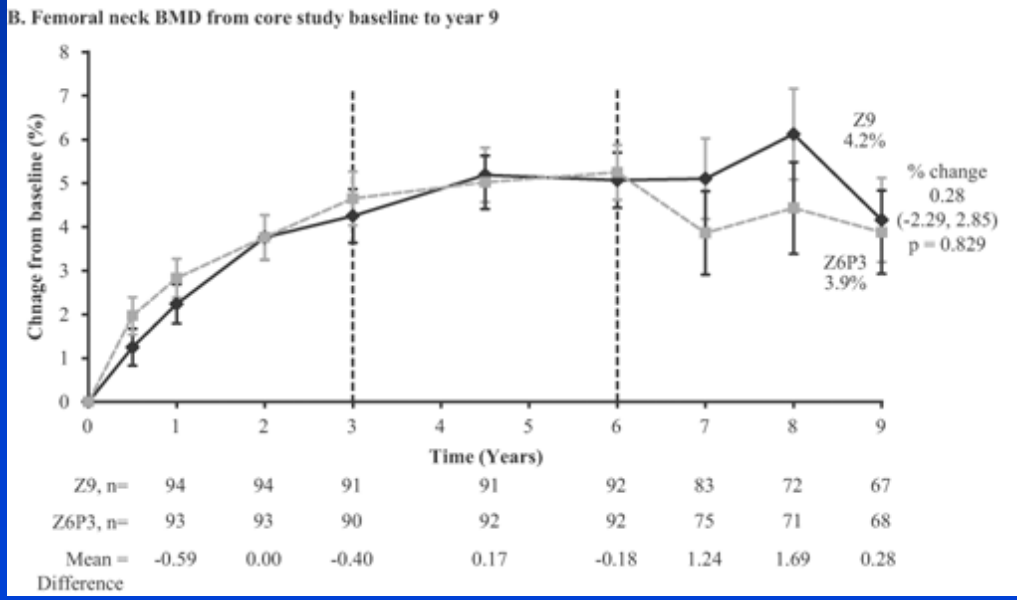
These approaches need further research!

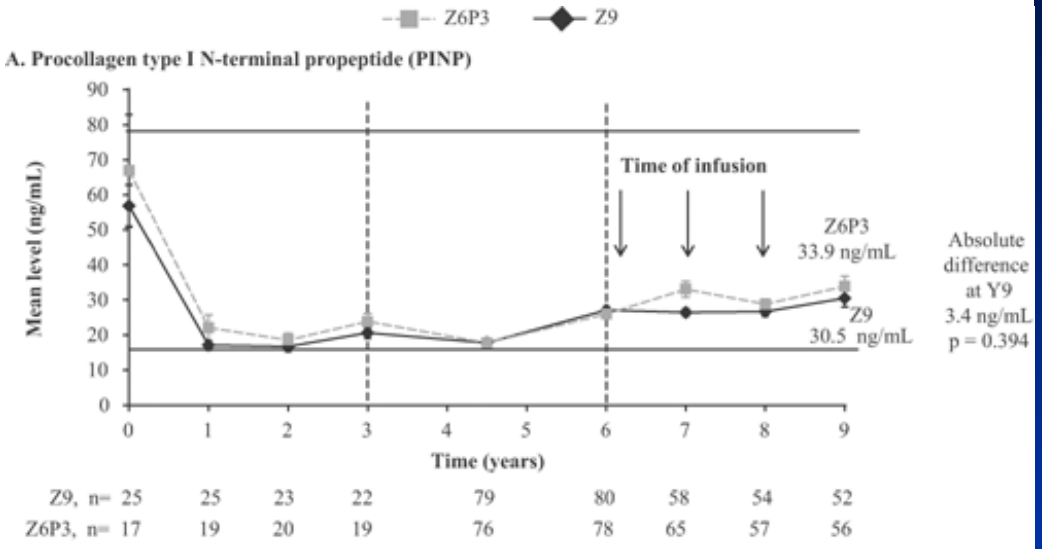
Eastell et al. Eur J Endocrinol 2018; 178: 19-31; Eastell et al. Lancet Diabetes Endocrinol 2017; 5: 908-23

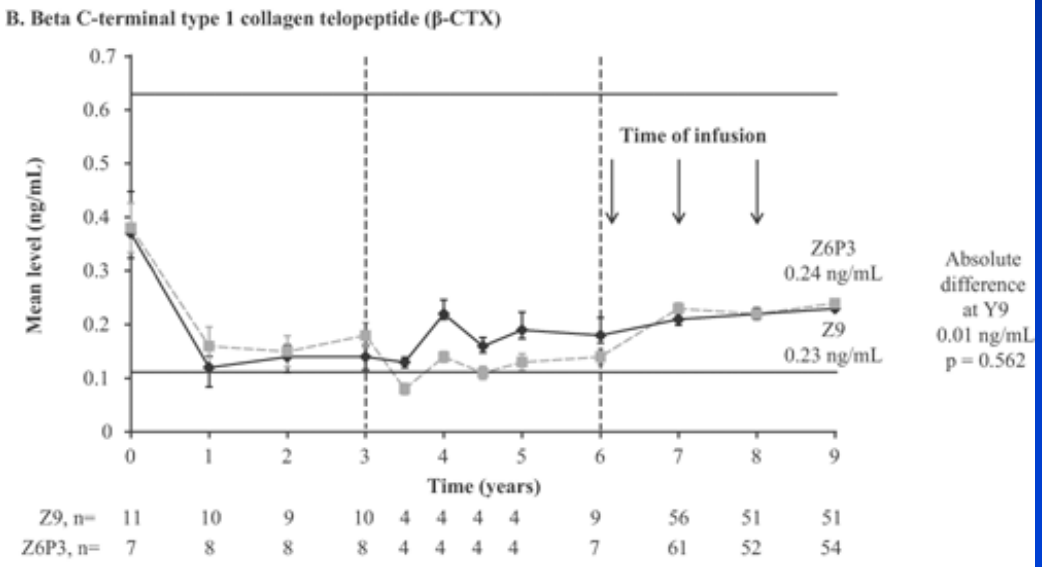
Drug holiday with Zoledronic acid

Z6P3 vs. Z9: no difference in BMD and BTMs









Black. J Bone Miner Res. 2015; 30: 934-944

Therapiefalen

- **Geen enkele beschikbare therapie reduceert fractuurrisico tot nul** én zeker niet bij patiënten met een hoog baseline fractuurrisico!
- Therapiefalen:
  - ≥ 2 fracturen onder behandeling
  - BTM dalen niet met > 25% en BMD daling van > 5% (axiaal) of > 4% (femoraal)
  - 1 fractuur EN geen significante daling van BTM of daling van BMD
- Indien patiënt compliant & afwezigheid van nieuwe secundaire oorzaken botverlies is therapiefalen (=afwezigheid onderdrukken botresorptie) zeldzaam (max. 3-4 %)
  - 1 nieuwe fractuur onder osteoporosemedicatie = meestal *gewoon pech*
  - ~ leeftijd, valrisico
- *Expert opinion* suggereert
  - vervanging oraal door parenteraal alternatief
  - vervanging zwakker door sterker antiresorptivum *(? ALN ➔ Dmab)*

Diez-Perez A et al. Osteoporos Int. 2012;23(12):2769-74.

Denosumab reduces bone turnover markers significantly compared to Aledronate at 12 months

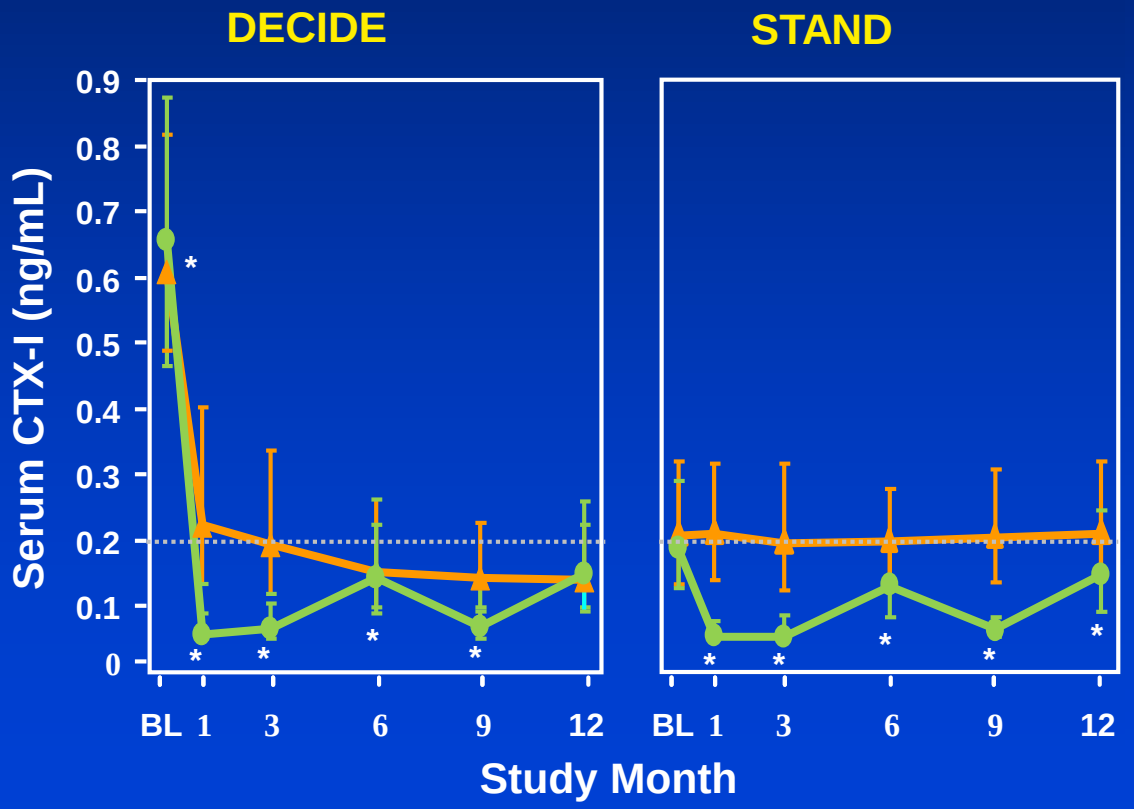
DECIDE: treatment-naïve patients

STAND: previously treated with Alendronate

Alendronate

Denosumab

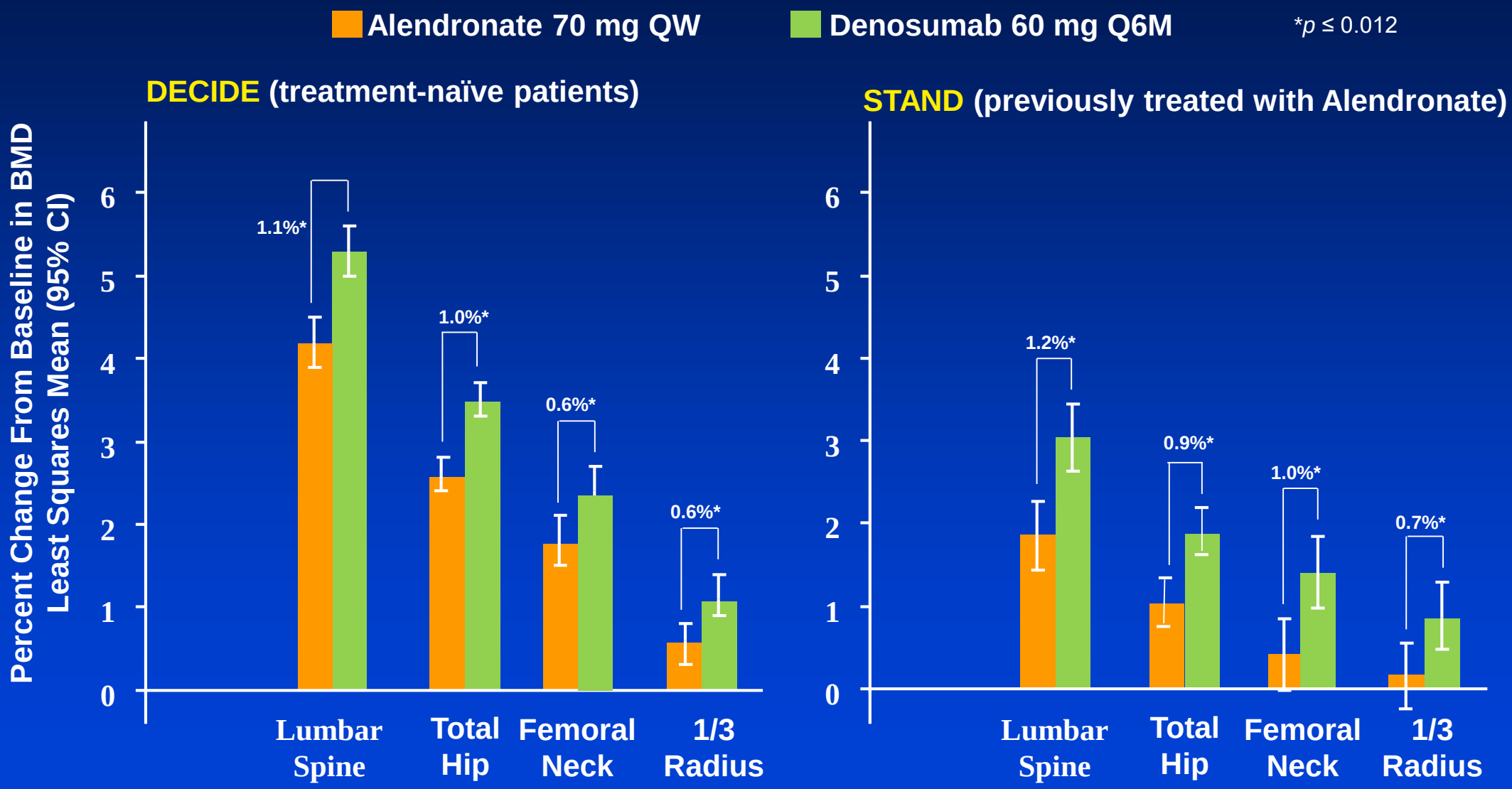
sCTX I (marker of bone resorption)



More profound inhibition of bone remodeling of Denosumab *vs.* Alendronate at any skeletal site.

Brown. JBMR 2009; 24:153-161; Kendler. JBMR 2010; 25:72-81

Denosumab raises BMD significantly compared to Aledronate at 12 months at all key sites measured



Brown. JBMR 2009; 24:153-161; Kendler. JBMR 2010; 25:72-81

Prolonged osteoporosis treatment

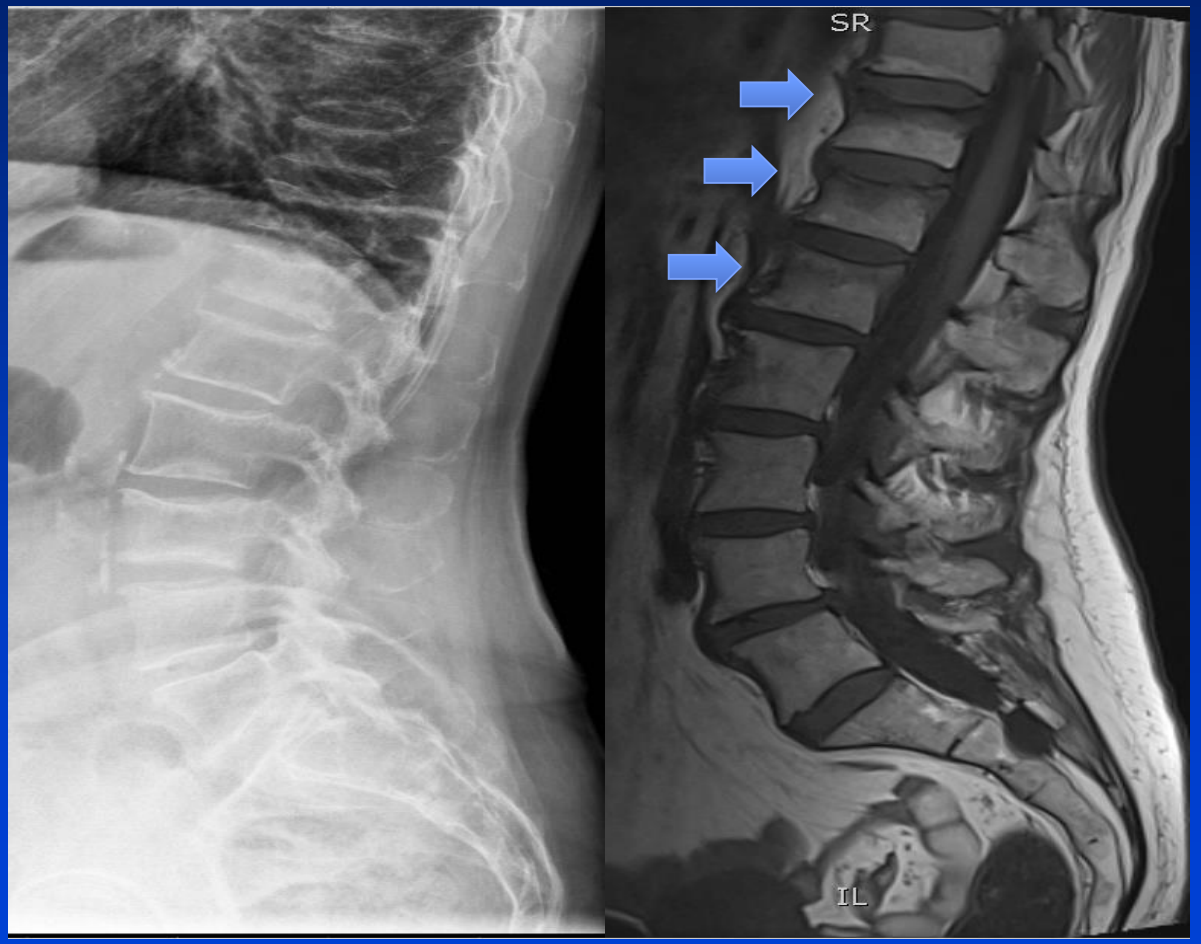
- Lack of any data on BP treatment beyond 10 years in high risk subjects!
- Individual approach:
  - assessment of each patient's individual risk profile
  - risk-benefit analysis
  - shared decision making with the patient
  - careful follow-up
- In clinical practice:
  - sequential therapy with another antiresorptive drug
    - switching from oral to IV BP
    - changing to denosumab

  ➔ no supportive evidence base

Adler. J Bone Miner Res 2016; 31: 16-35

No drug holiday with Denosumab!

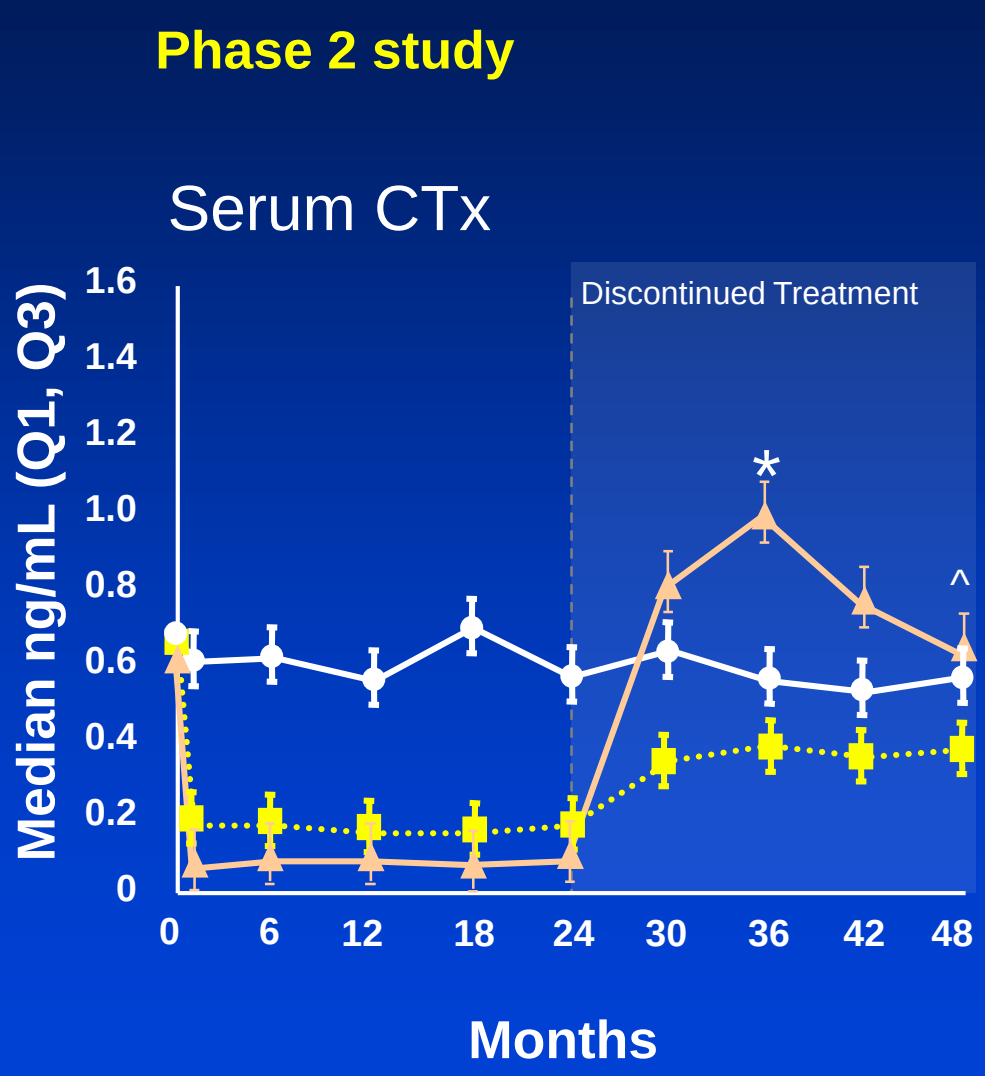
Rebound fracture risk after discontinuation of Denosumab

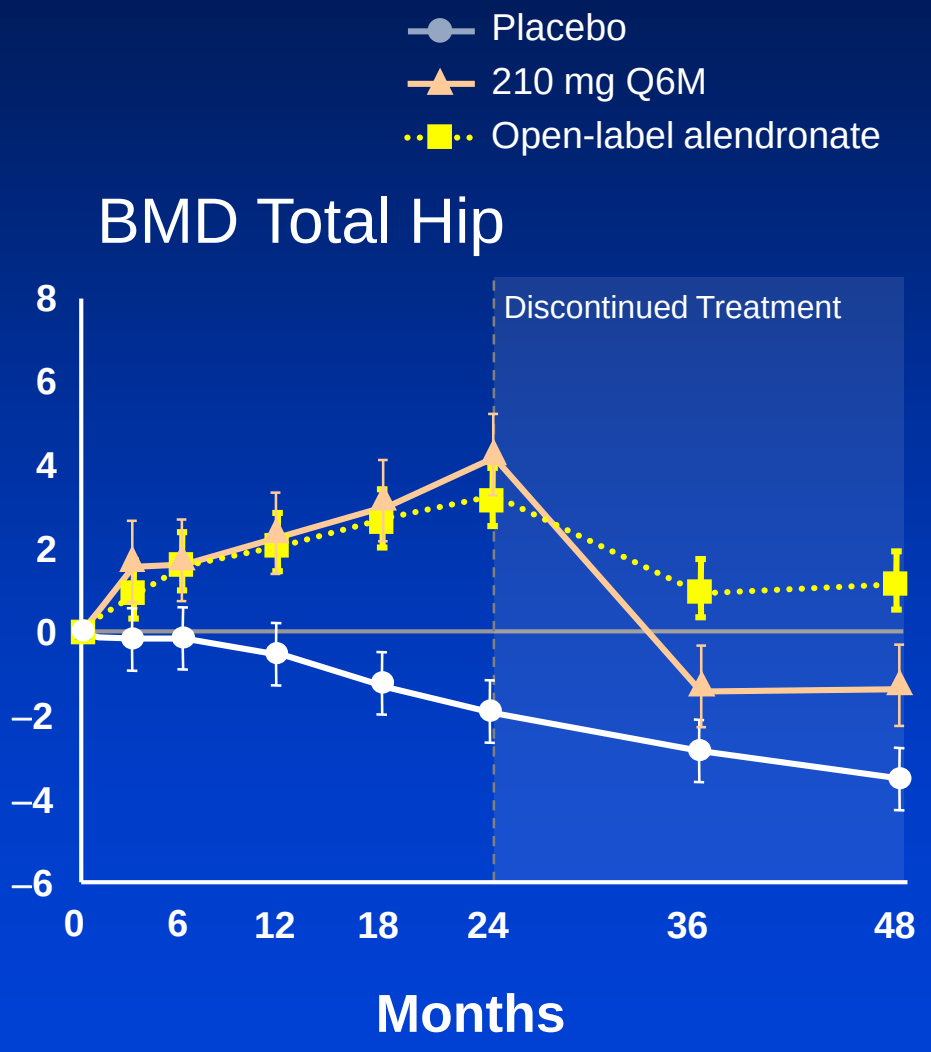


Lamy. J Clin Endocrinol Metab 2017: 102: 354-358

Effect of discontinuation of Denosumab vs Alendronate on bone turnover markers and BMD

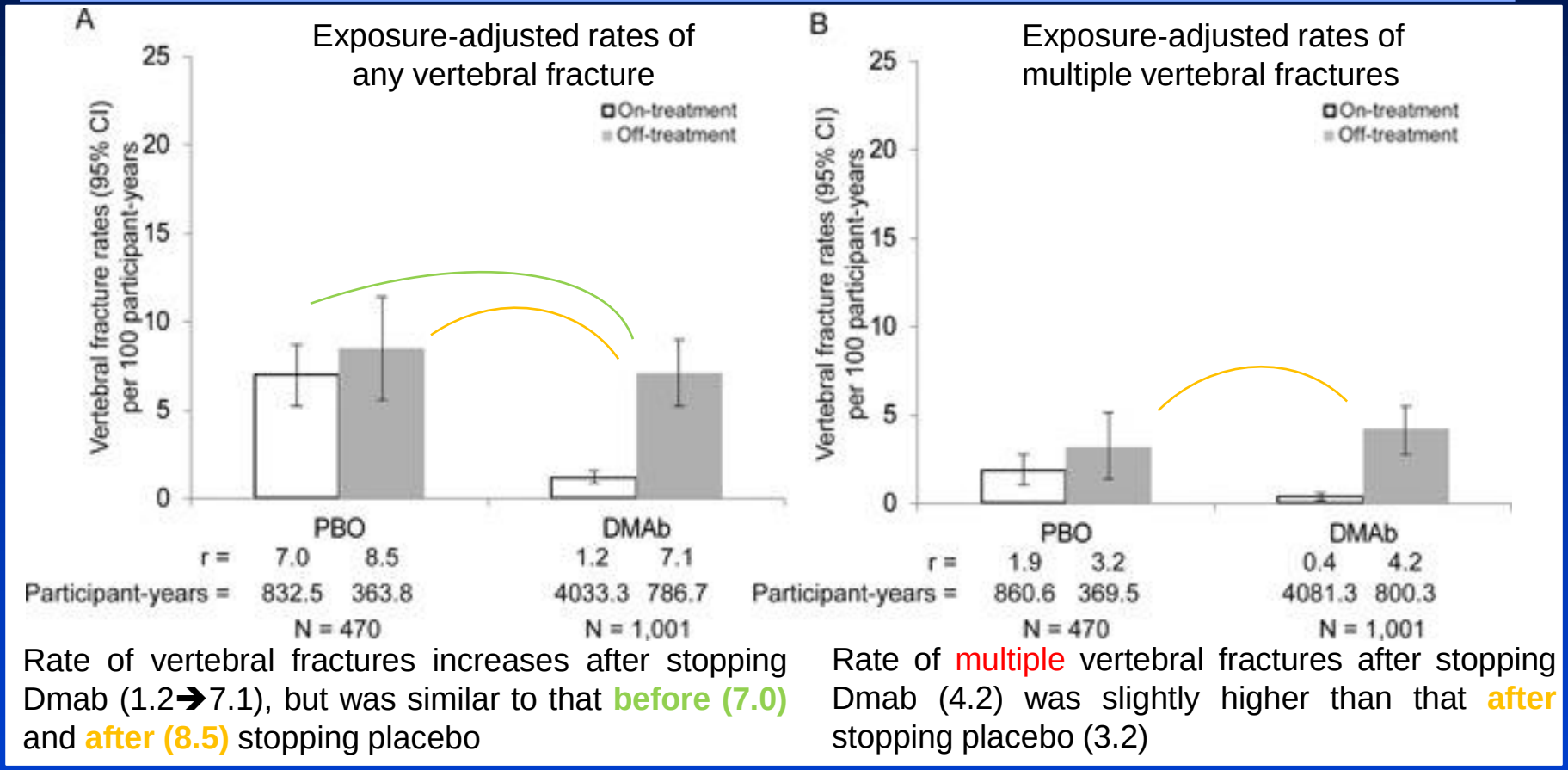
Phase 2 study





Adapted from Miller. Bone. 2008; 43: 222-229

Vertebral fractures after discontinuation of Denosumab



Rate of vertebral fractures increases after stopping Dmab (1.2➔7.1), but was similar to that **before (7.0)** and **after (8.5)** stopping placebo

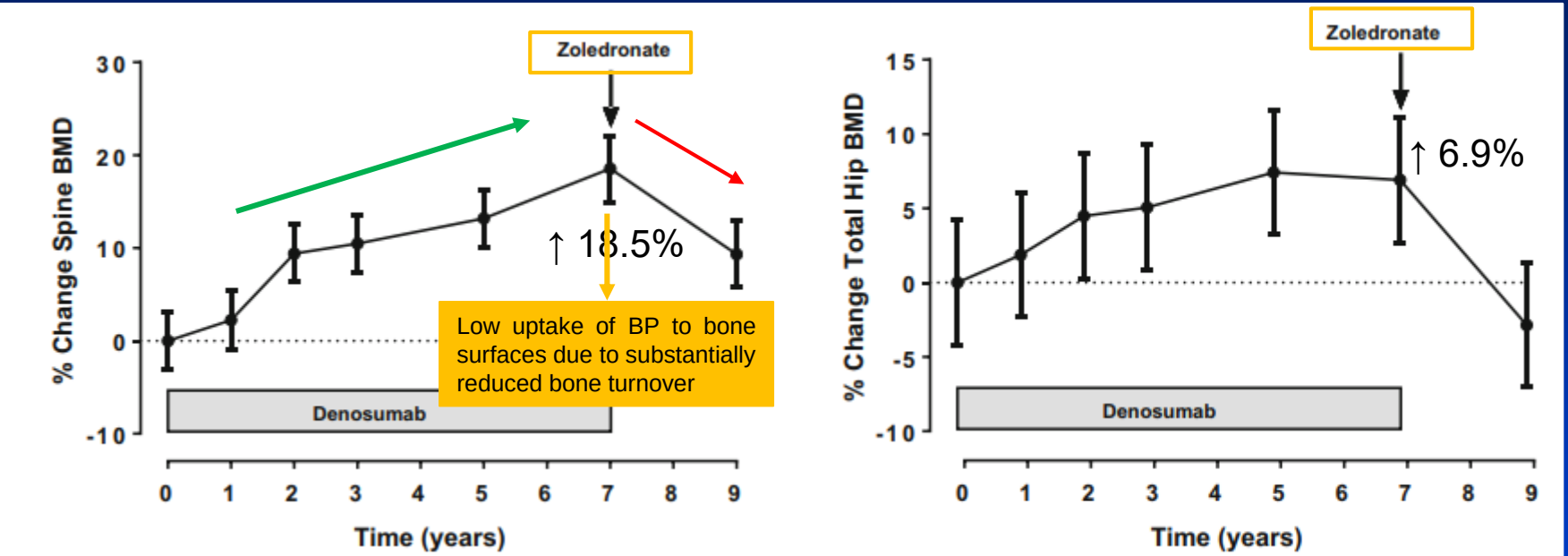
Rate of multiple vertebral fractures after stopping Dmab (4.2) was slightly higher than that **after** stopping placebo (3.2)

- Proportion of multiple vertebral fractures in those who developed 1 or more vertebral fractures: 60.7% in those stopping Dmab ⇔ 38.7% in those stopping placebo (p = 0.049)
- Odds of developing multiple vertebral fractures after stoppping Dmab: 3.9 (2.1-7.2)x higher in those with prior vertebral fractures than those without
- Rates of non-vertebral fractures during off-treatment were similar for placebo (3.8) and Denosumab (2.8)

Cummings. J Bone Miner Res 2017; 33: 190-198

Reduction of bone loss after stopping Denosumab

- Only partial protection with Zoledronate given 6 months after stopping Dmab



Case series of 6 women with postmenopausal osteoporosis

- Oral Alendronate maintains BMD after discontinuation of Denosumab

➔ **To prevent bone loss and rebound vertebral fractures after discontinuation of Denosumab:**

1. Start po Alendronate
2. Zoledronate IV when effects of Dmab start to dissipate (but not delay until risk of rebound vertebral # ↑)

Expert opinion
To investigate!

~ CTx in upper limit of reference range of premenopausal women?

Reid. Calcif Tissue Int 2017; 101: 371-374; Freemantle. Osteoporos Int 2012; 23: 317-326

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Sequential treatment for osteoporosis

① Anabolic treatment should be followed by antiresorptive treatment

- Teriparatide ➔ Bisphosphonate
- Teriparatide ➔ Denosumab

② Anabolic therapy as initial treatment, followed by subsequent antiresorptive is best, since antiresorptive therapy blunts subsequent bone-forming efficacy

③ In real life, most patients considered for bone-forming therapy have had previous antiresorptive therapy ….

- Bisphosphonate ➔ Teriparatide

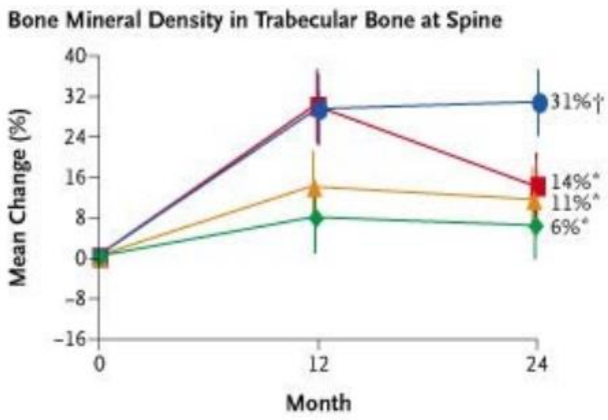
④ … but no transition from Denosumab to Teriparatide

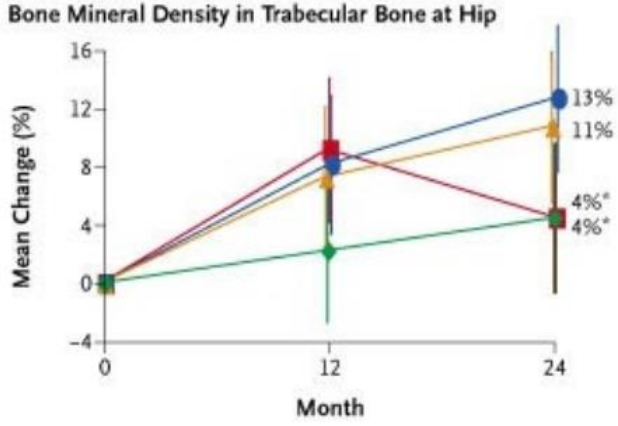
- ~~Denosumab ➔ Teriparatide~~

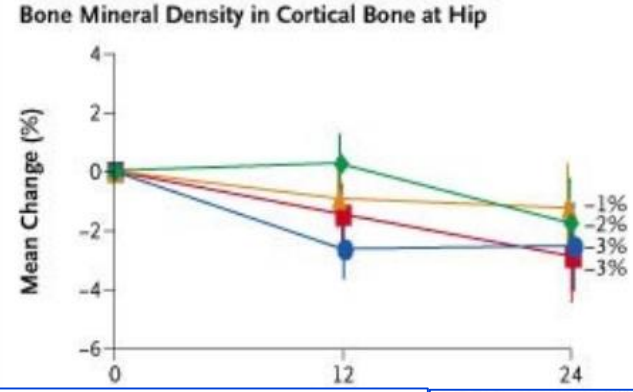
Teriparatide should be followed by treatment with …

TPT➔ xxx

- Bisphosphonates (BP) **YES!**





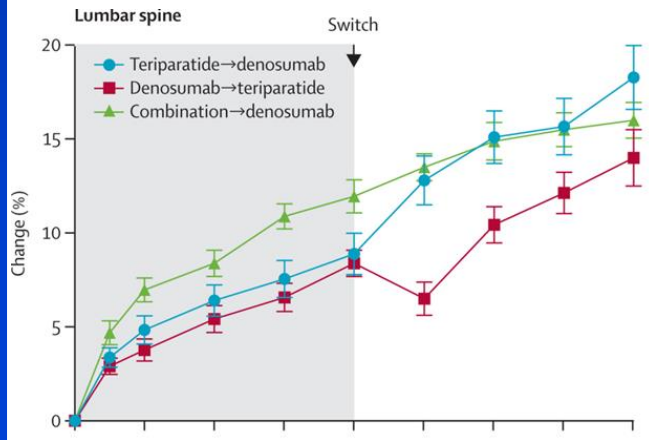


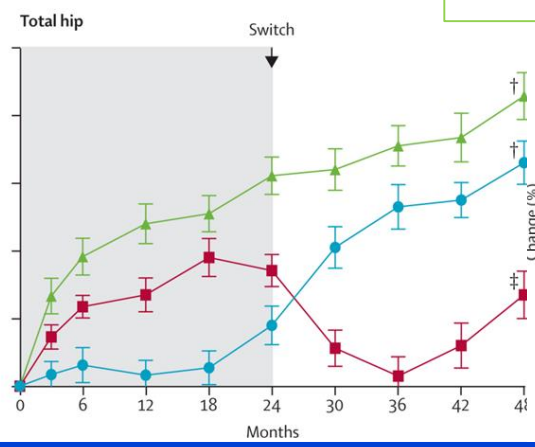
An asterisk: p<0.05 for comparison with TPT➔ ALN at 24 months.
A dagger indicates P<0.05 for the comparison with TPT+ALN

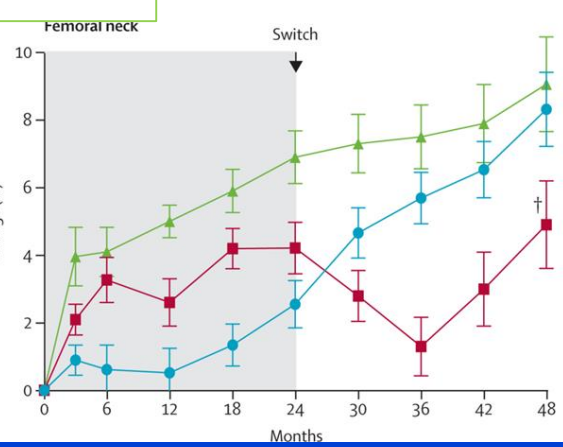
Parathyroid hormone–placebo group
Parathyroid hormone–alendronate group
Combination-therapy–alendronate group
Continued-alendronate group

After one year of TPT, BMD appear to be maintained or increased with alendronate, but lost if TPT is not followed by an antiresorptive agent.

- Denosumab (DATA –Switch study) **YES!**







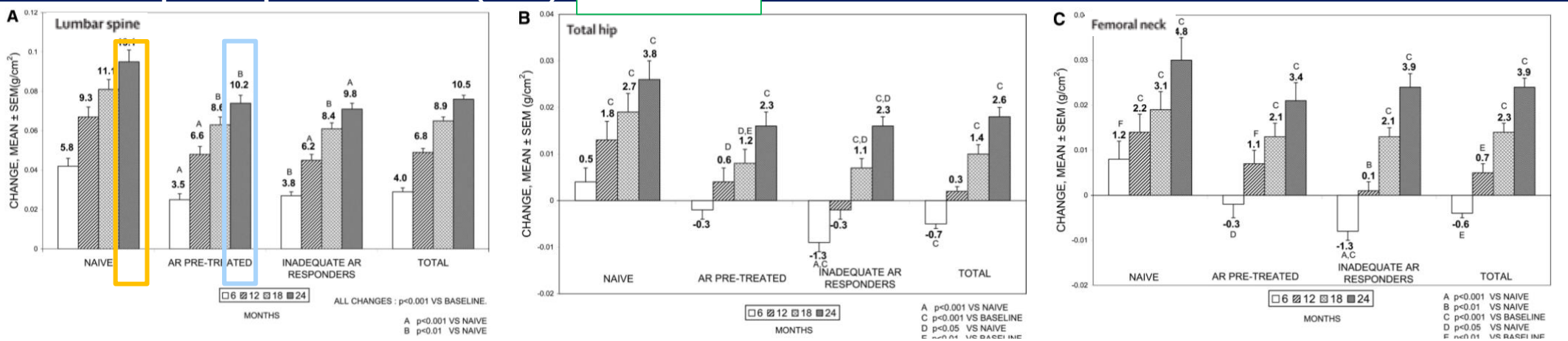
In postmenopausal osteoporotic women switching from TPT to Dmab, BMD continued to increase.

Black. N Engl J Med 2005; 353: 555-565; Leder. Lancet 2015; 3866: 1147-55

Teriparatide (TPT) may follow previous treatment with …

xxx ➔ TPT

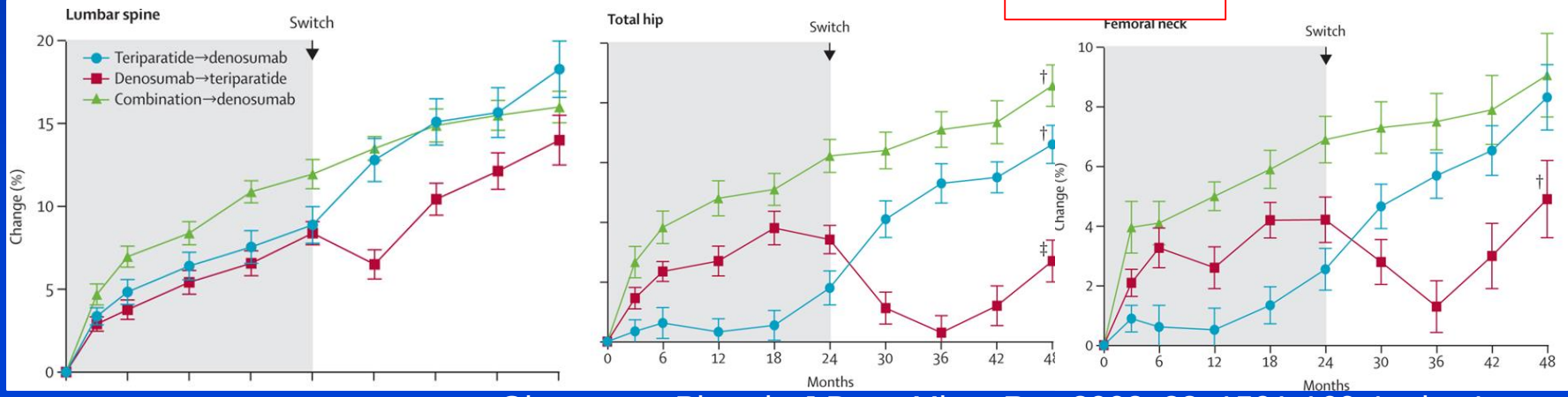
- Bisphosphonates (BP) **YES!**



TPT for 24 months is associated with a significant increase in BMD in patients with and without previous BP use.

Previous BP use modestly blunted BMD response to TPT.

- Denosumab (DATA –Switch study) **NO!**



In postmenopausal osteoporotic women switching from Dmab to TPT, BMD results in transient or progressive bone loss.

Obermayer-Pietsch. J Bone Miner Res 2008; 23: 1591-160; Leder. Lancet 2015; 3866: 1147-55

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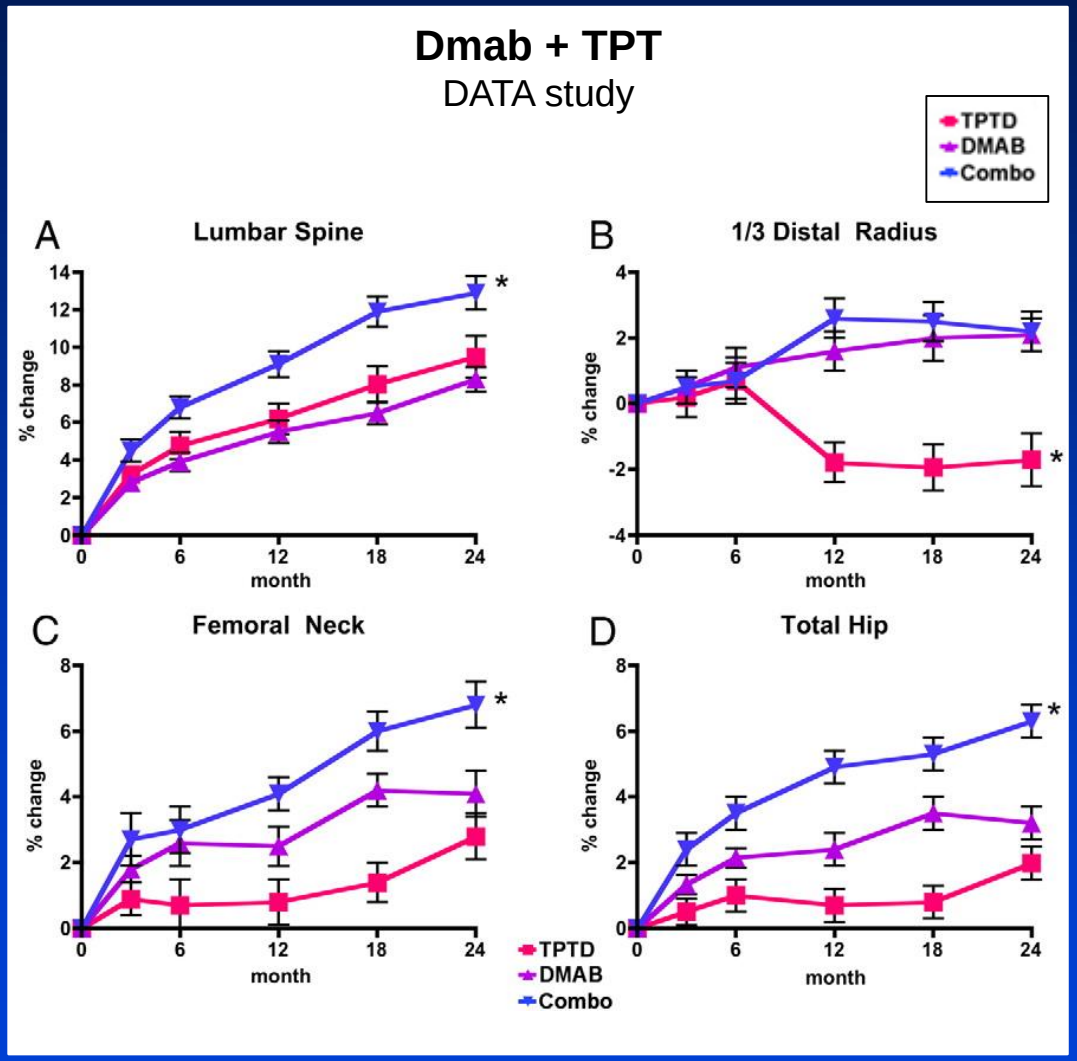
What about the future?

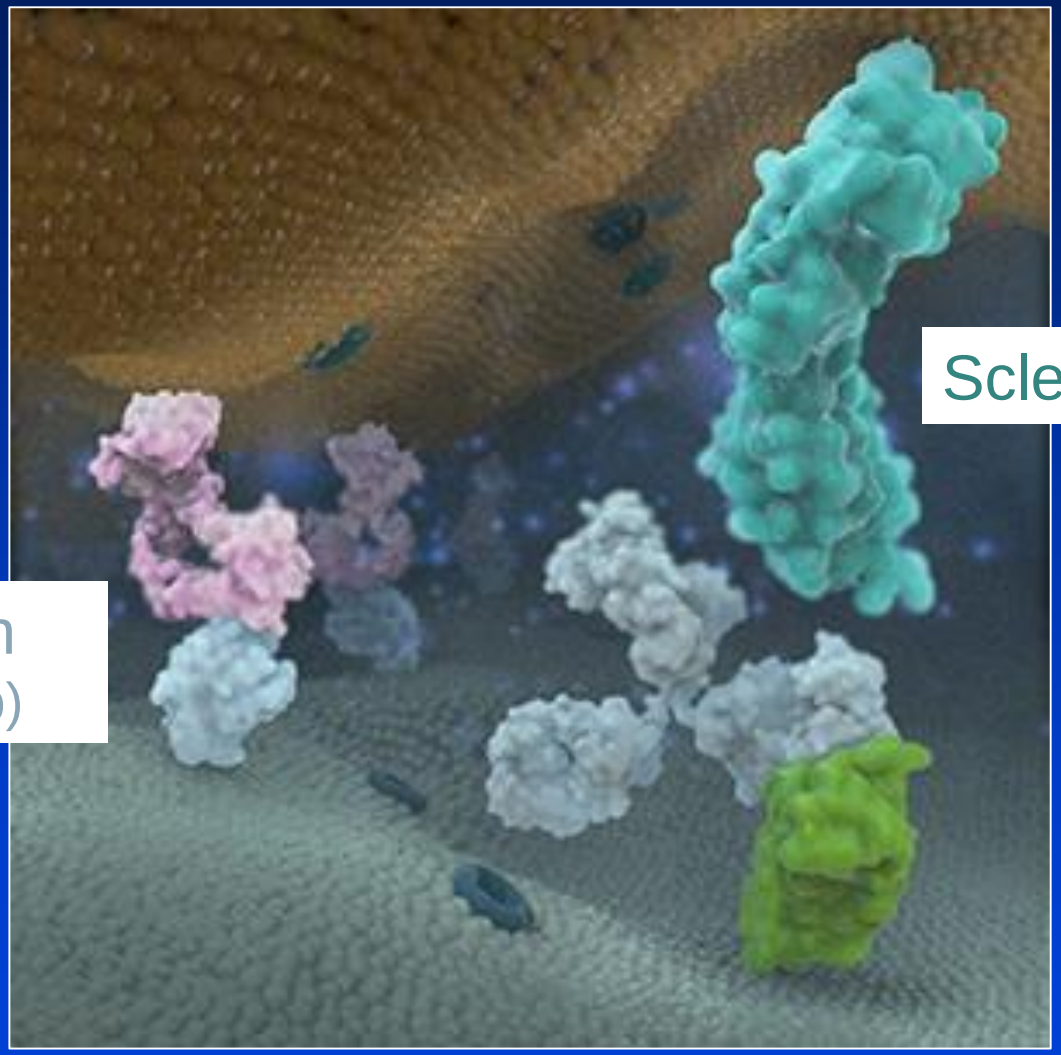
- Combination treatment
- Antisclerostin
- Treatment for sarcopenia

Combination therapy (antiresorptive + Teriparatide)

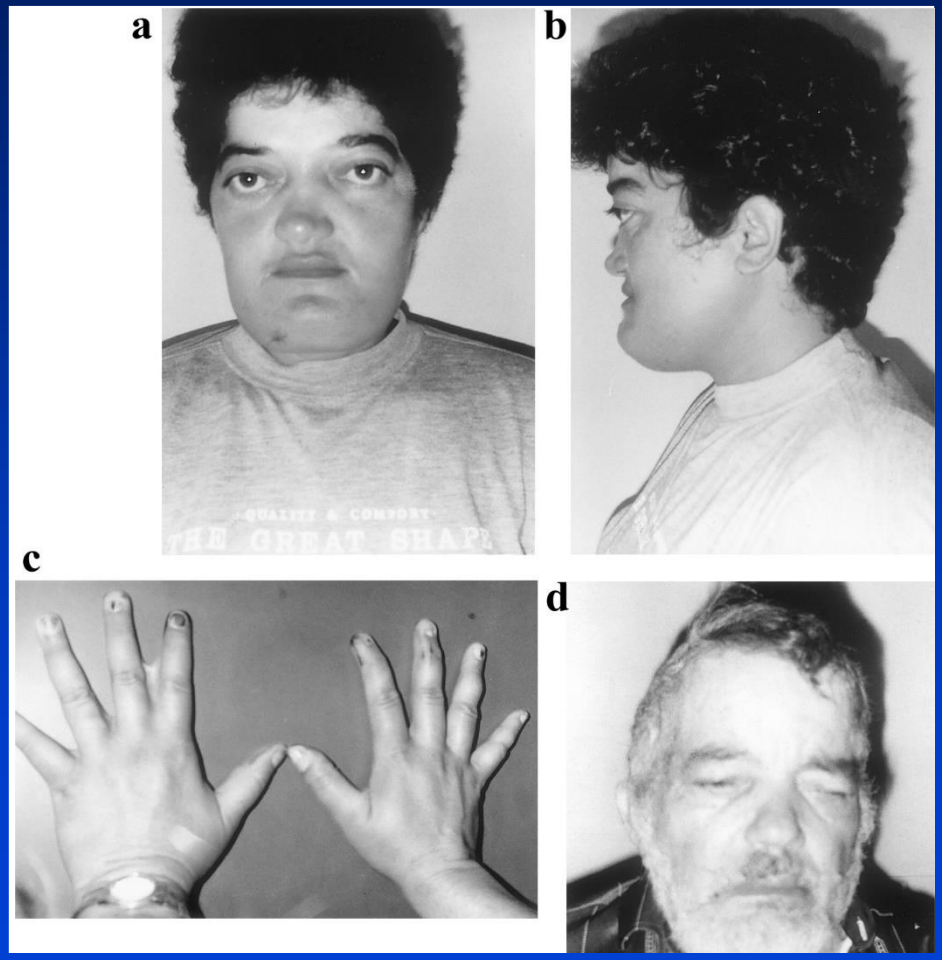


Cosman. J Bone Miner Res 2011; 3: 503–511; Tsai. Lancet 2013; 382: 50-56

Antisclerostin

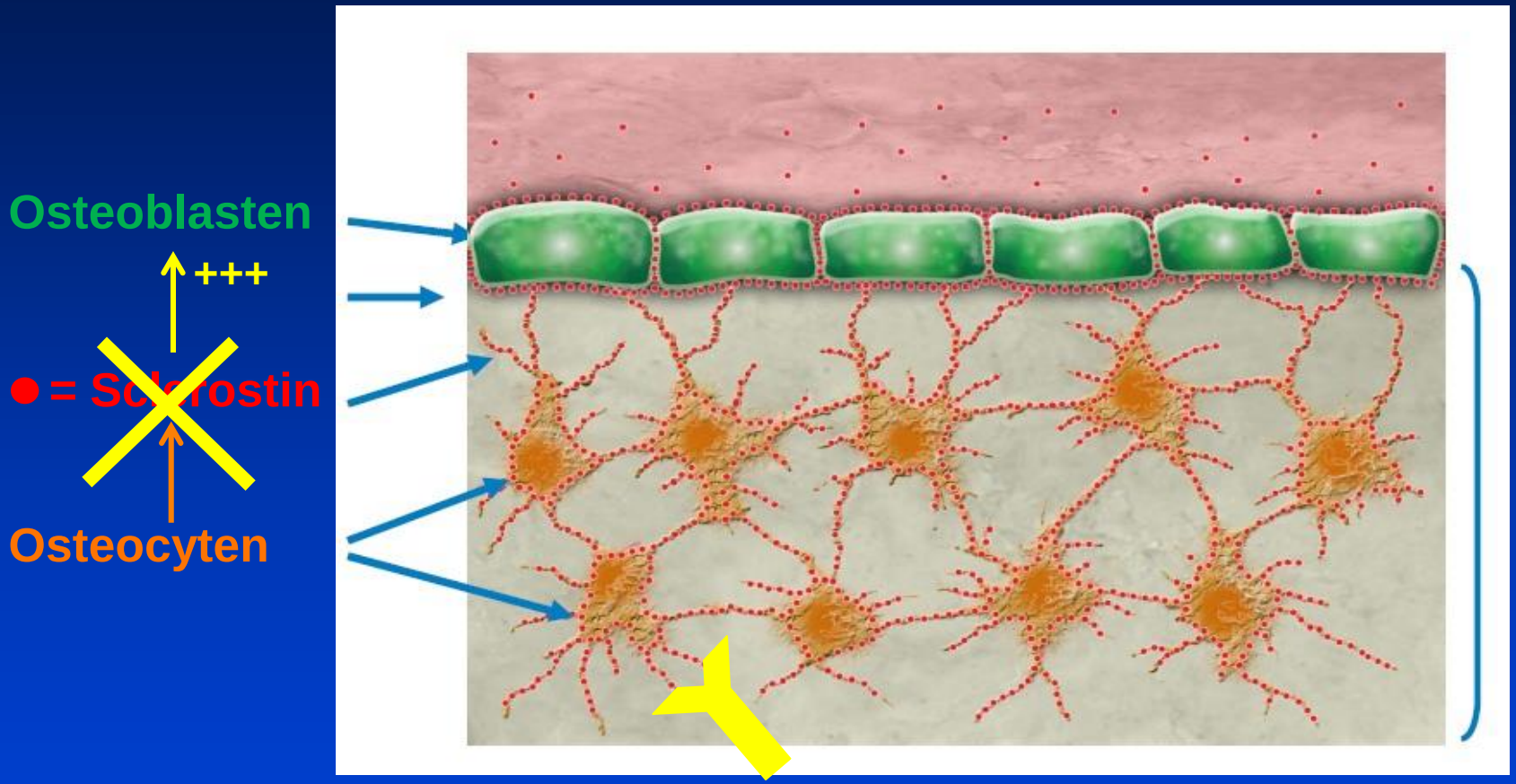


Sclerosteosis (Truswell-Hansen disease)



- Progressieve botaanmaak
- Corticale hyperostose met syndaktylie
- Toegenomen intracraniële druk met zenuwcompressie
- Nooit fracturen
- Relatief frequent bij Afrikaners
- Autosomaal recessief

Dit (d)effect wordt nagebootst door Antisclerostin



Vorming van nieuw bot door de osteoblasten

Sclerostin verhindert de vorming van nieuw bot door de osteoblasten

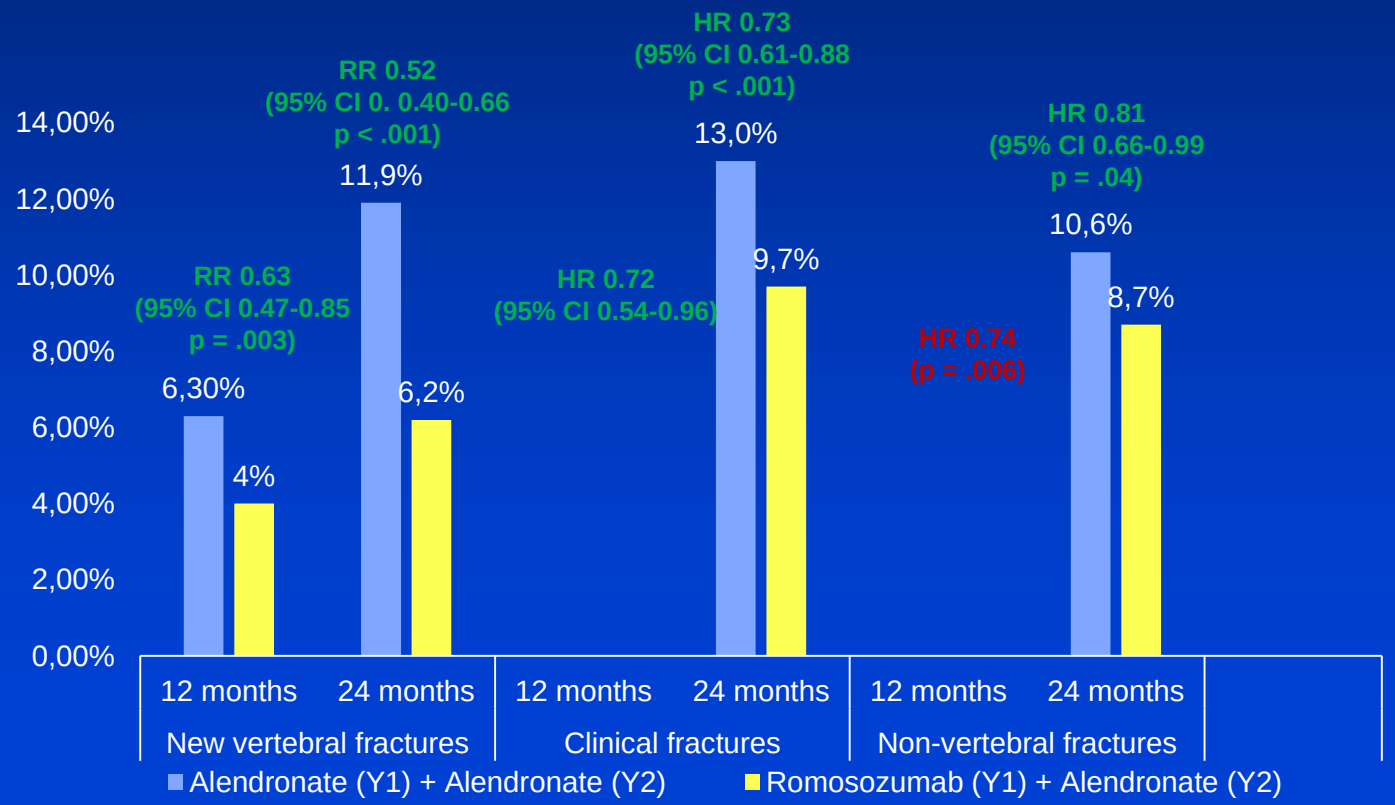
Overdreven botaanmaak door osteoblasten bij een defect in gen voor Sclerostin

Antisclerostin stimuleert de vorming van nieuw bot door de osteoblasten

Romosozumab

4093 postmenopausal women with osteoporosis and a fragility fracture

12 months ➔	12 months
1. Alendronate ➔	Alendronate
2. Romosozumab ➔	Alendronate



Saag. N Engl J Med 2017; 377: 1417-1427

Conclusion

- Fragility fractures are associated with a substantial burden on morbidity, mortality and socio-economic cost
- More accurate assessment of fracture risk (*eg.* FRAX)
- Increased range of therapeutic options for osteoporosis
  - Antiresorptive agents reduce (hip/vertebral) fracture rate by ~ 50%
  - Anabolic therapy for persons at very high or imminent fracture risk
- In high-risk patients, benefit *vs.* risk profile is likely favourable for up to 10 years of treatment with antiresorptive therapy
- In low-risk patients
  - drug holiday may be considered after 3-5 years of bisphosphonates
  - no drug holiday with Denosumab

Update on diagnosis and treatment of osteoporosis

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