Update on diagnosis and treatment of osteoporosis

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Overview

I. Introduction

II. Who should receive osteoporosis treatment?

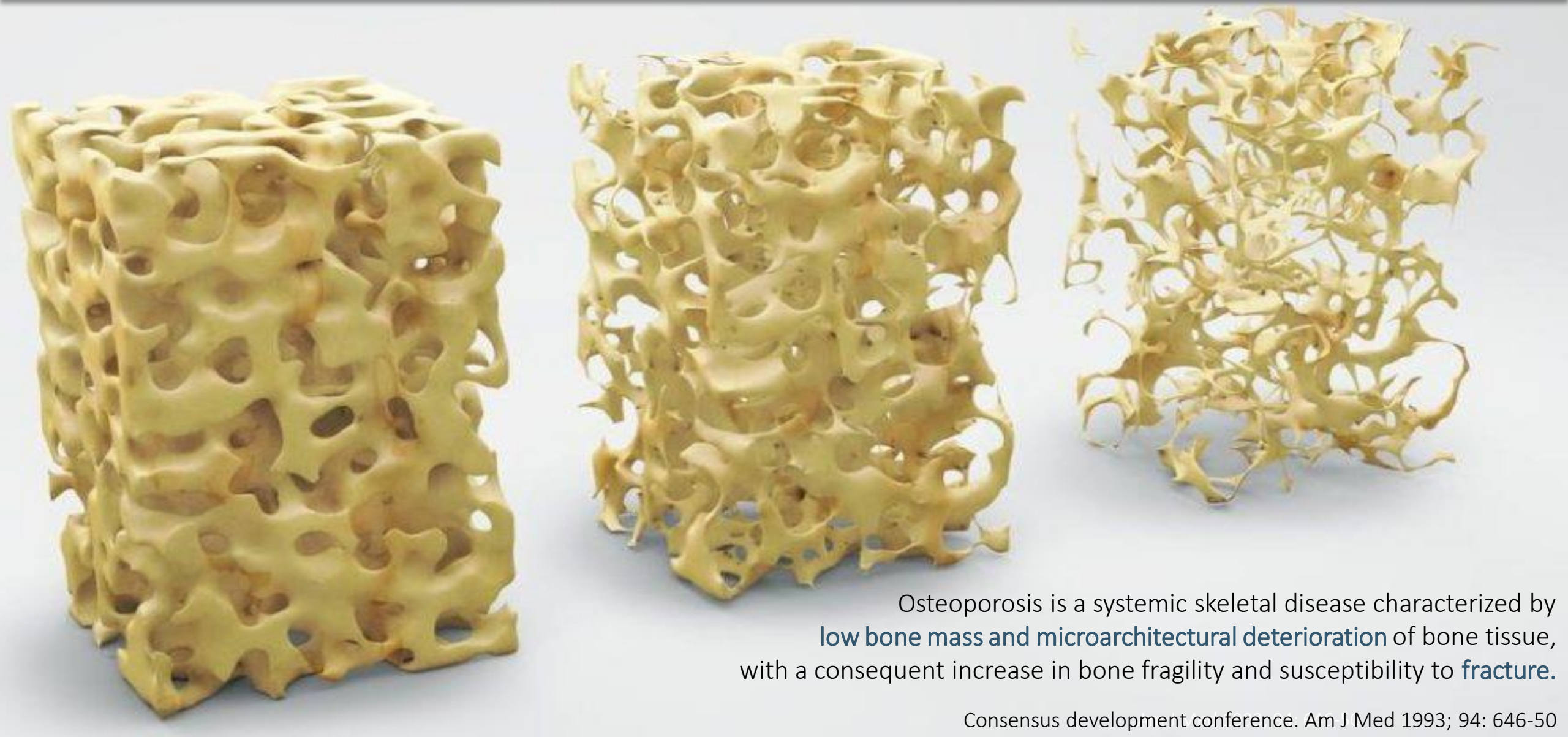
III. How to choose between the drugs for osteoporosis?

IV. Drug holiday & treatment failure

V. Sequential osteoporosis treatment

VI. Conclusion

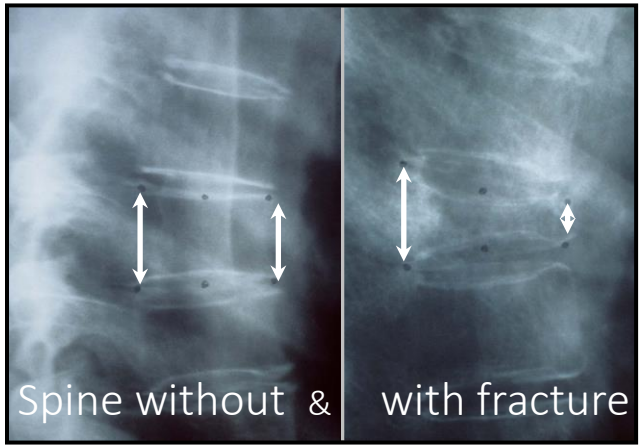
Osteoporosis

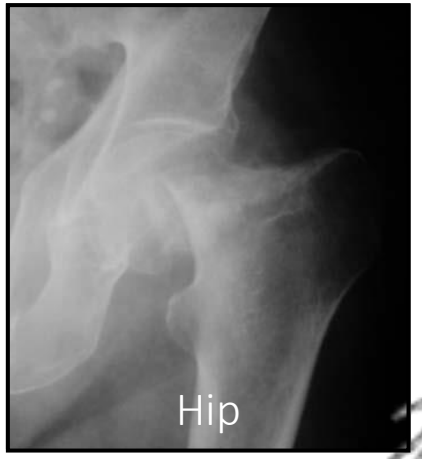


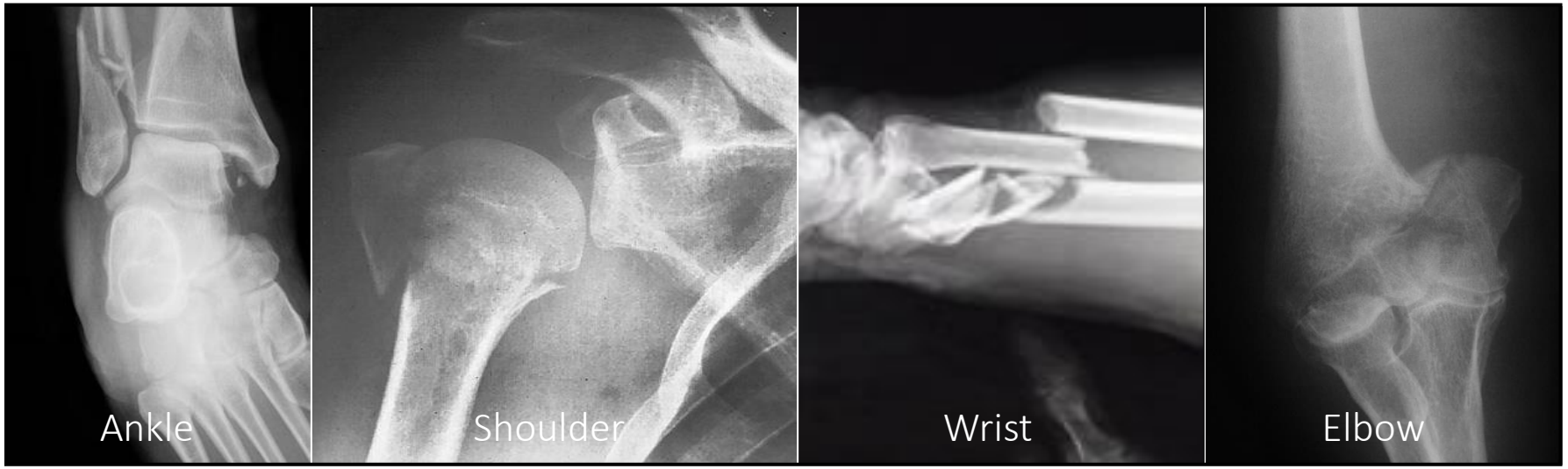
Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.

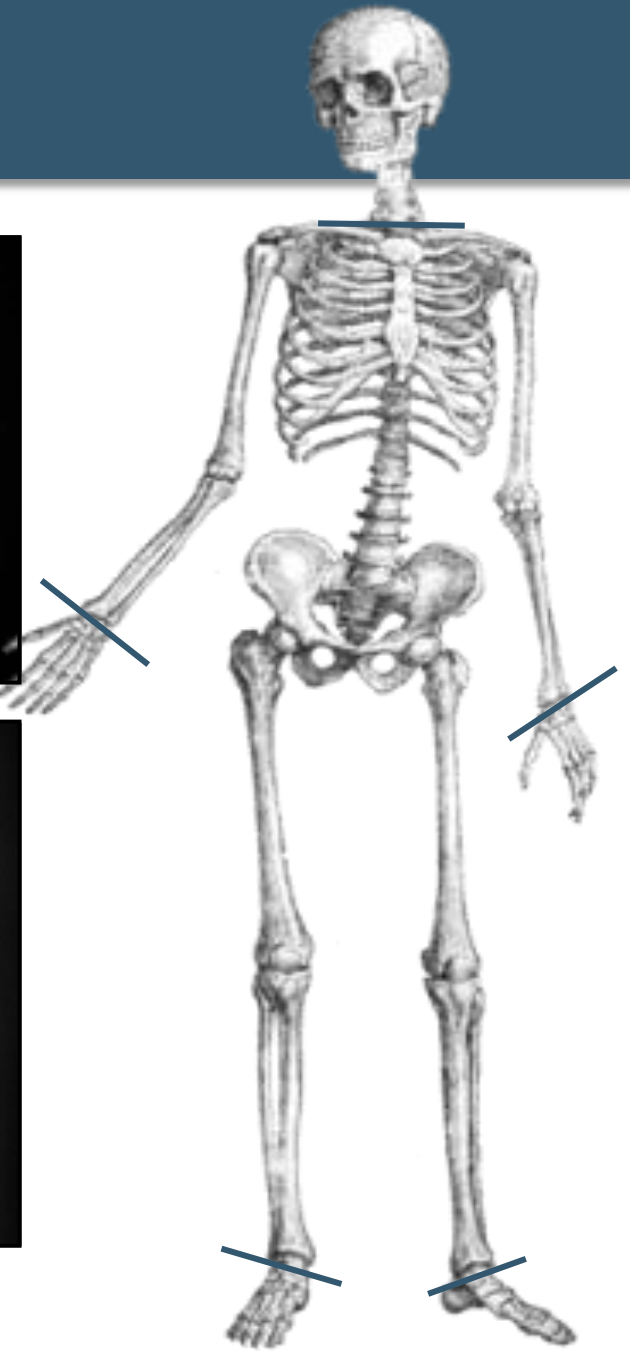
Consensus development conference. Am J Med 1993; 94: 646-50

Osteoporotic fractures



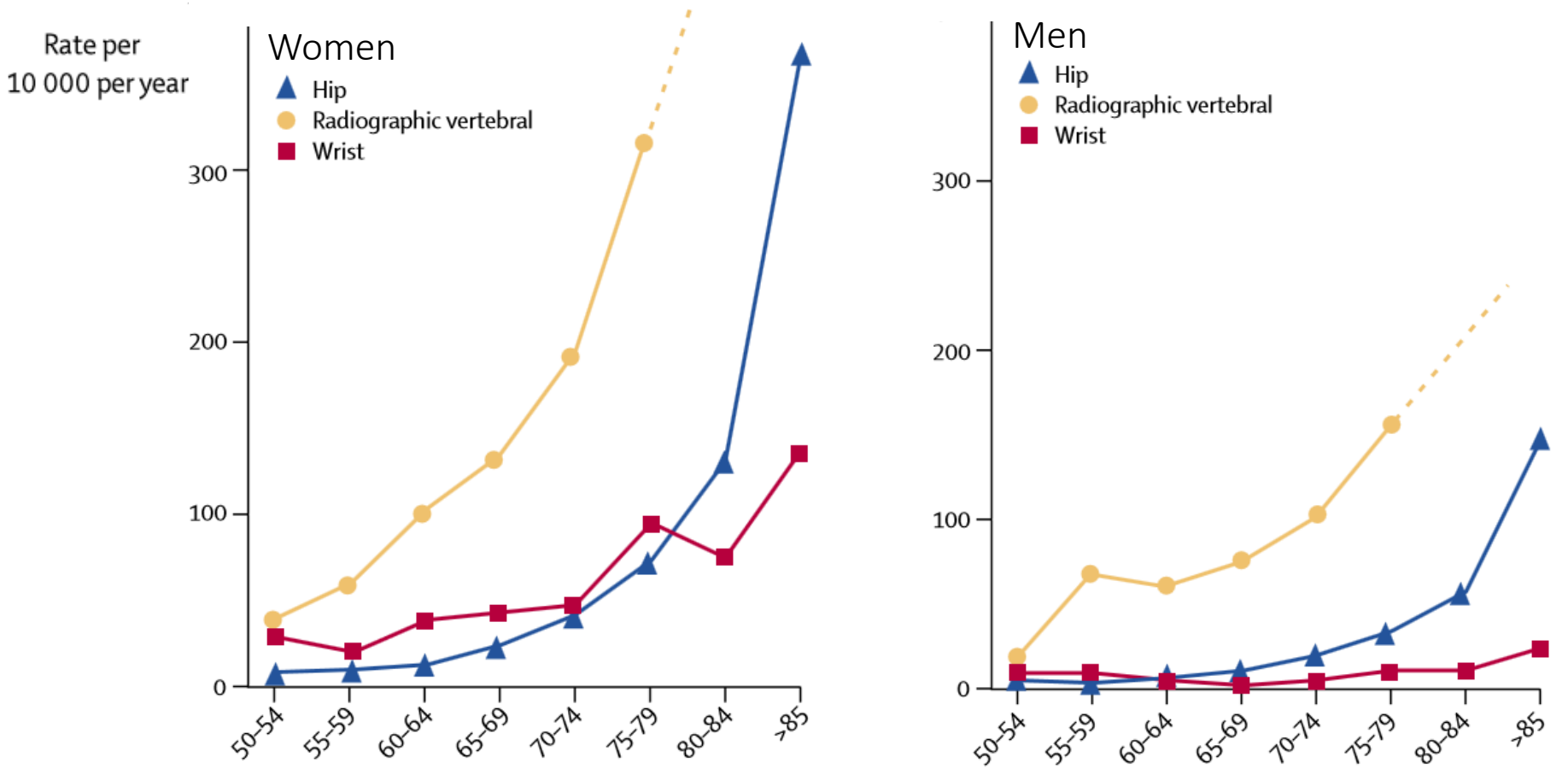






Epidemiology

Age-related exponential increase in incidence of osteoporotic fractures



Sambrook. Lancet 2006;367:2010-2018

Epidemiology

Osteoporosis in old age

- 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 90y, ~ 30% ♀ & 17% ♂ have had a hip fracture [4,5]

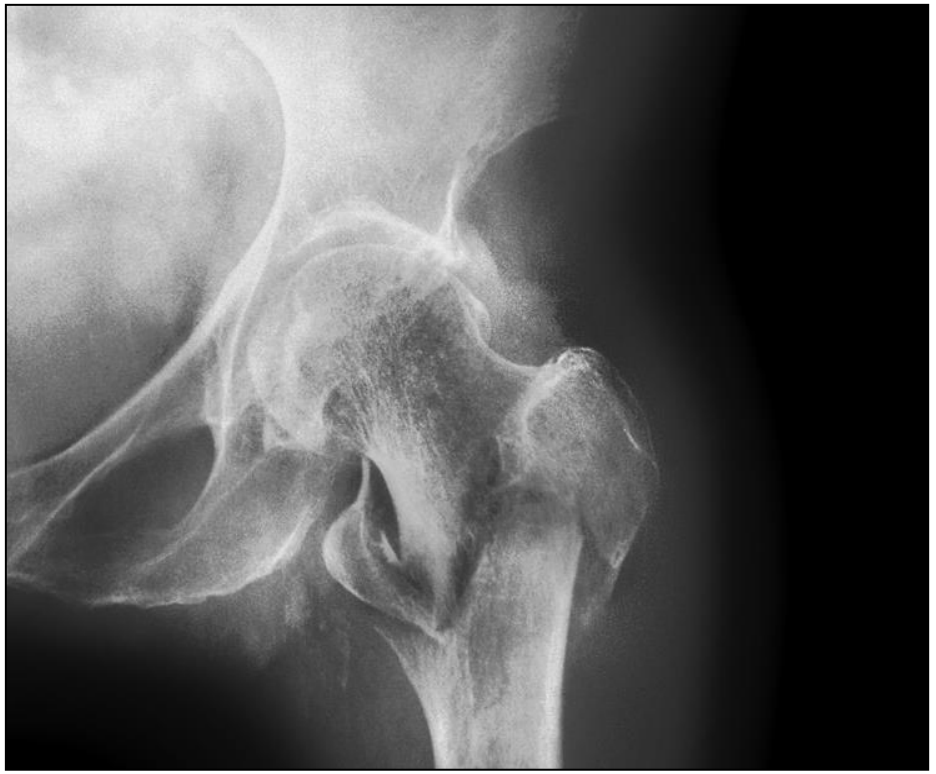
- Remaining lifetime probabilty of hip fracture (%) [6]
  - at 50 years
    - ♀ 18.2
    - ♂ 7.8
  - at 70 years
    - ♀ 18.9
    - ♂ 8.3

[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] Kanis. Arch Osteoporos 2021; 16: 82

Consequences of osteoporotic fractures

Hip fractures

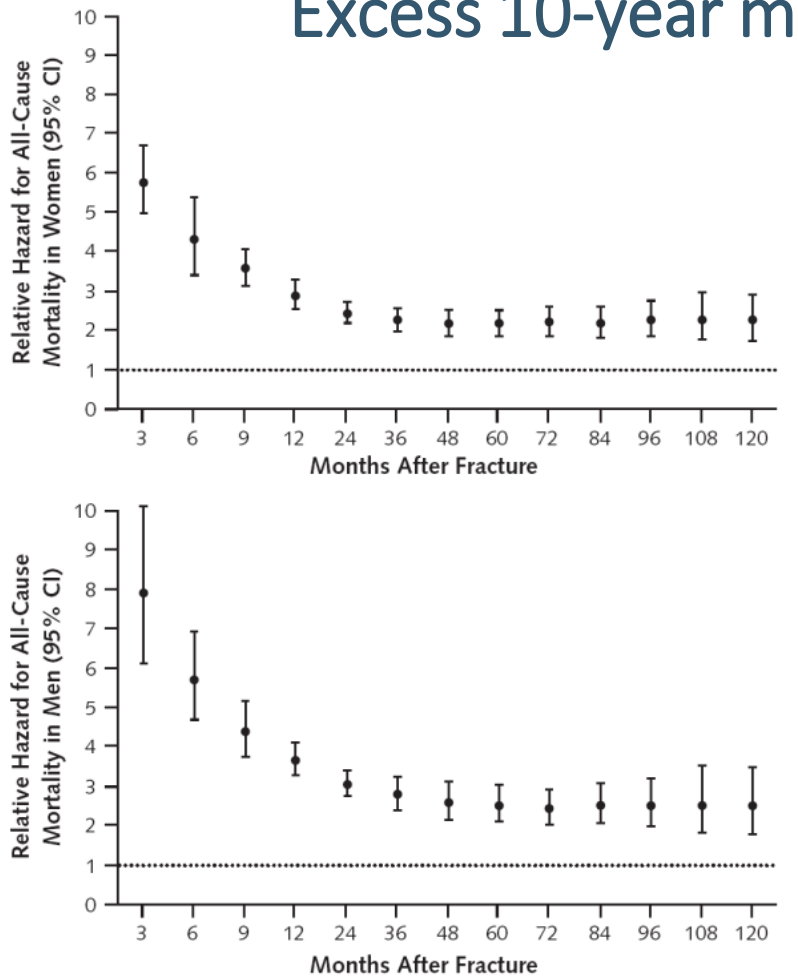
- **Functional decline**: 80% of hip fracture patients still have problems with ADL after 1 year
- **Mobility**: >40% of previously independent hip fracture patients are not able to walk independently after 1 year
- **Institutionalization:** 10-20% of hip fracture patients newly institutionalized over 1 year (up to 35% in ≥ 90 years)
- **Quality of life**: significant loss 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 (in men: 30%)



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 Rheum Reports 2008;10:92-6; Vokó. J Eval Clin Pract 2017;23:1375-1380; Griffin. Bone Joint J 2015;97-B: 372-382

Consequences of osteoporotic fractures

Excess 10-year mortality following hip fracture



Relative hazard of all-cause mortality for (wo)men with hip fracture vs control during FU starting at time of injury

Gebroken heup kondigt de dood aan

Op oudere leeftijd een heup breken is doorgaans geen goed voorteken, leert Belgisch onderzoek onder 750.000 bejaarden.

'Alarmsignaal dat wijst op meer dan alleen een brozer wordend skelet'

BRUSSEL | Elk jaar breken in ons land zo'n achttienduizend mensen hun heup. Twintig procent van hen (dat zijn 3.600 mensen) overleeft dat niet en overlijdt binnen het jaar aan de gevolgen van de breuk. Maar ook de 14.400 Belgen die weer op de been geraken na een heupbreuk, houden er een voorgoed naar beneden bijgestelde levensverwachting aan over, blijkt uit onderzoek aan de universitaire ziekenhuizen van Leuven en Brussel.

Tot dusver werd aangenomen dat een heupbreuk gepaard ging met een kwetsbare periode van een half jaar tot hooguit een jaar. In die periode overlijdt één op de vijf patiënten aan complicaties van de breuk (of van de hersteloperatie), zoals trombose, longembolie of doorligwonden. Maar eenmaal die kritieke periode voorbij, zouden heupbreukpatiënten weer de normale vooruitzichten voor hun leeftijd hebben, zo was het idee.

Die veronderstelling werd evenwel nooit degelijk getoetst in grootschalig bevolkingsonderzoek. Daarin is verandering gekomen met een studie van Leuvense en Brusselse onderzoekers die vandaag verschijnt in het vakblad *Annals of Internal Medicine*.

'Na tien of vijftien jaar ligt de levensverwachting na een heupbreuk nog steeds gevoelig lager dan bij leeftijdsgenoten die niks braken', zegt Steven Boonen, diensthoofd geriatrie in UZ Leuven en hoofd van het osteoporosecentrum van Gasthuisberg.

Samen met Patrick Haentjens van de dienst klinisch wetenschappelijk onderzoek in het UZ Brussel poolde Boonen gegevens over de nasleep van een heupbreuk die waren ingezameld bij 750.000 vooral Amerikaanse bejaarden, om tot de conclusie te komen dat vrouwen tot vijftien jaar na zo'n breuk nog steeds drie tot vier keer meer kans maken om voortijdig te overlijden – ook als de breuk zelf prima is geheeld. 'En als mannen een heup breken, is de prognose nog somberder.'

Het is niet de breuk op zich die mensen voor hun tijd doet overlijden, zegt Boonen. 'Eerder omgekeerd: een kwakkelende gezondheid bestemt tot breuken voor. 'Bejaarden die hun heup breken, zijn doorgaans de kwetsbaarste oudjes. Ze hebben suikerziekte, of hoge bloeddruk, of duizelingen, of hartziekte, waardoor ze vaak een boel medicijnen nemen. Door die broze gesteldheid lopen ze eerder breuken op – een heupbreuk is een alarmsignaal dat wijst op meer dan alleen een brozer wordend skelet.'

Wat betekent de studie voor mensen die hun heup hebben gebroken? Moeten zij de moed opgeven en in een hoekje op Magere Hein gaan zitten wachten?

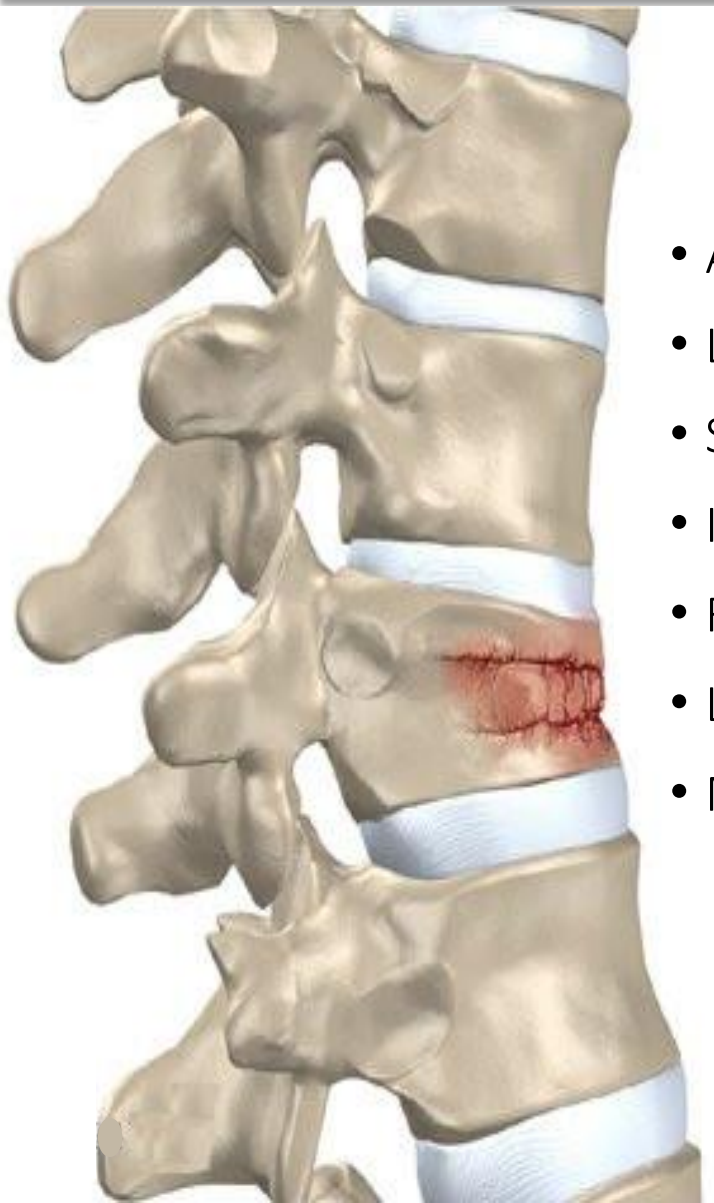
'Neen', zegt Boonen, 'De studie betekent juist dat artsen niet langer mogen denken dat hun werk is gedaan wanneer de breuk is gerepareerd. Een paar heupschroeven zetten volstaat niet, ook de onderliggende kwetsbaarheid van de patiënt moet worden behandeld, zodat levenskwaliteit en levensverwachting weer stijgt.' (hvde)

"A hip fracture announces death -
an alarm signal that means more than just a brittle skeleton"

Hip fracture patients are typically frail elderly

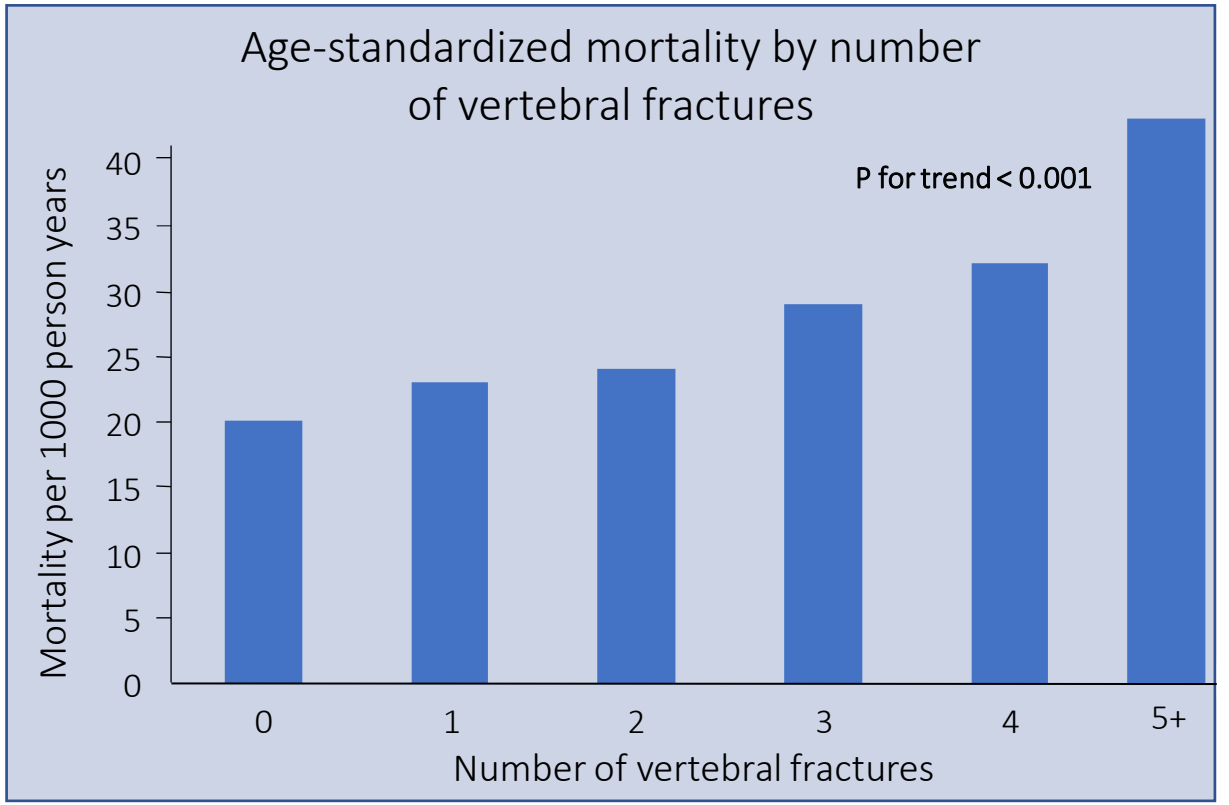
Haentjens. Ann Intern Med 2010; 152: 380-390; Gielen et al. Calcif Tissue Int 2012; 91: 161-177

Consequences of osteoporotic fractures



Vertebral (spinal) fractures

- Acute or chronic back pain
- Loss of height
- Spinal deformity
- Immobility
- Reduced pulmonary function
- Loss of quality of life
- Mortality



Study of Osteoporotic fractures: 9575 postmenopausal women aged ≥65y (mean FU 8.3y), to determine whether women with vertebral fractures have greater mortality than those without fractures.

Kado. Arch Intern Med 1999; 159: 1215-1220

Overview

I. Introduction

II. Who should receive osteoporosis treatment?

III. How to choose between the drugs for osteoporosis?

IV. Duration of treatment, drug holiday & treatment failure

V. Sequential osteoporosis treatment

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Who should receive osteoporosis treatment?

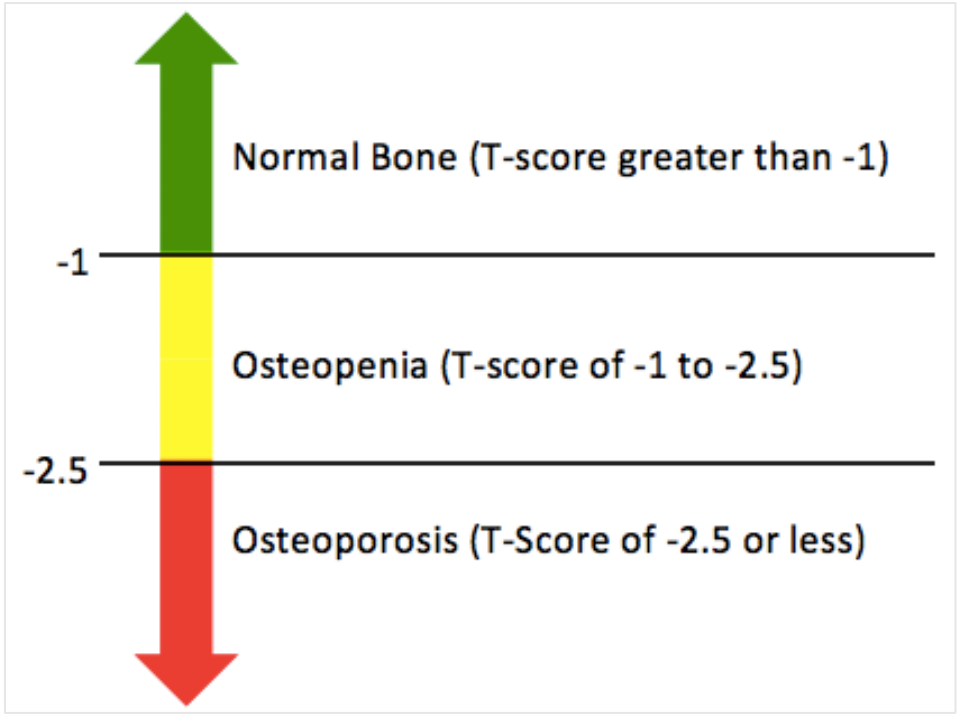
1. WHO BMD-based definition of osteoporosis

- T-score ≤ -2.5 at total hip, femoral neck or lumbar spine (L1-L4)
- Even without prior fragility fractures

➔ Primary fracture prevention

- Cave: no osteoporosis or osteopenia

Who should receive osteoporosis treatment?



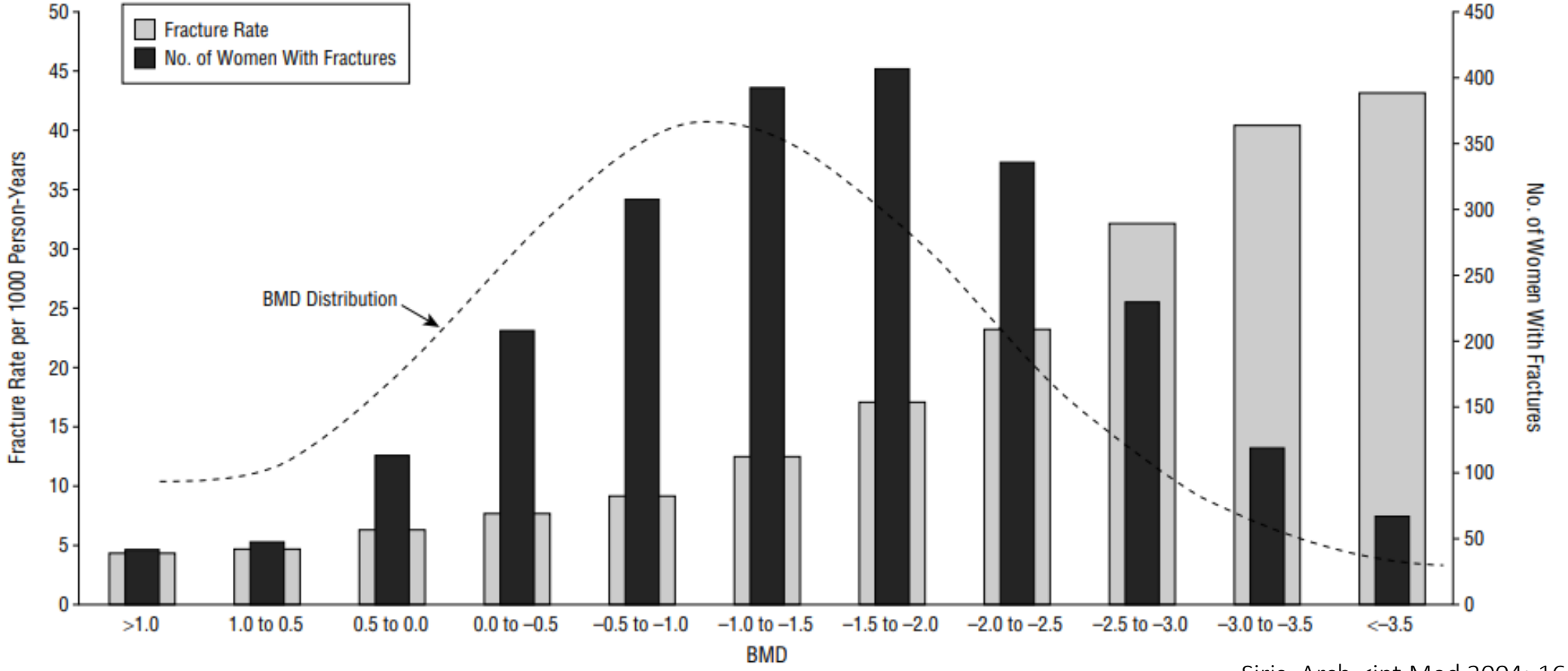
Not to treat?

To treat?

Who should receive osteoporosis treatment?

1. WHO BMD-based definition of osteoporosis

Majority of osteoporotic fractures occur in individuals with T-score > -2.5



Siris. Arch <int Med 2004; 164: 1108-1112

Who should receive osteoporosis treatment?

1. WHO BMD-based definition of osteoporosis

Majority of osteoporotic fractures occur in individuals with T-score > -2.5

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

54% of hip fracture patients 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

Who should receive osteoporosis treatment?

1. WHO BMD-based definition of osteoporosis

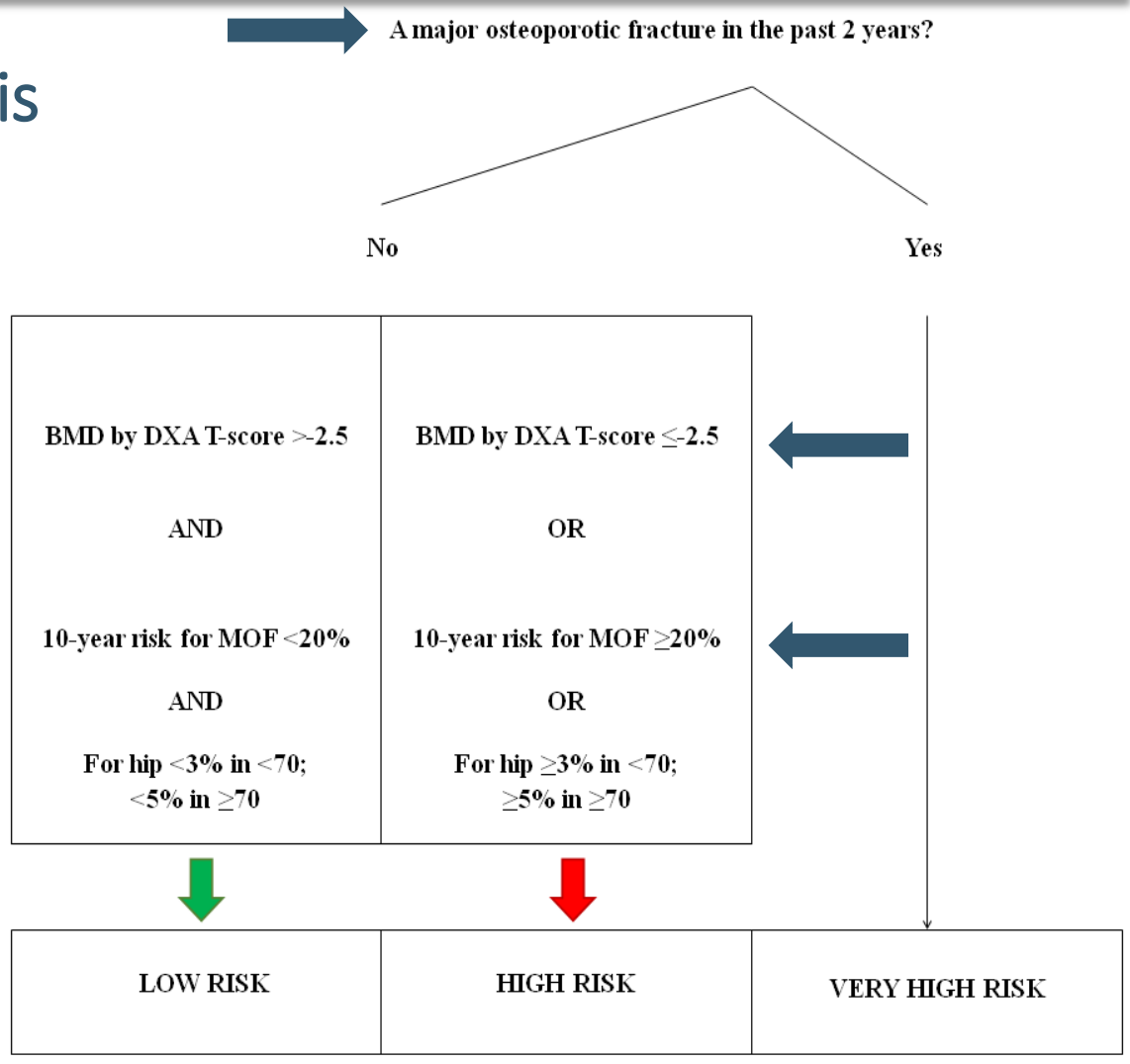
- T-score ≤ -2.5 at TH, FN or LS

2. Low-energetic fracture

- In postmenopausal women or men > 50 years
- Other causes excluded (e.g. Kahler's disease)
- Even without T-score < -2.5

➔ Secondary fracture prevention

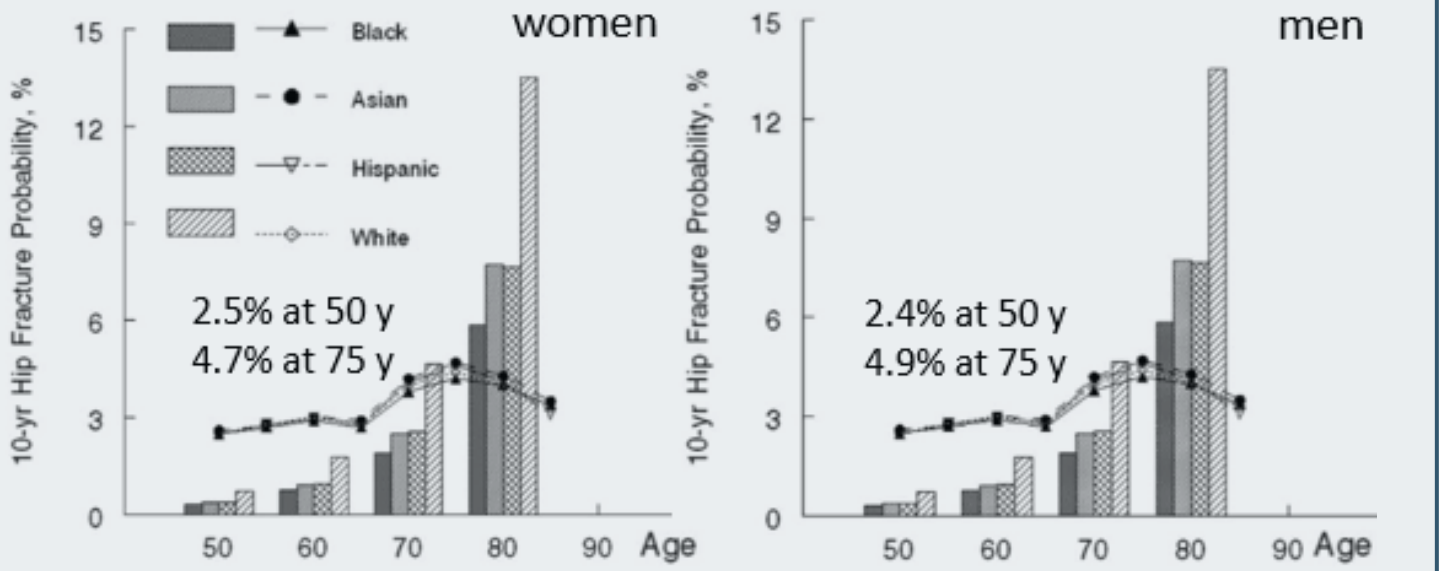
3. Increased fracture risk based on clinical risk factors (e.g., FRAX®)



BBC 2020 guidelines on postmenopausal osteoporosis

Sanchez-Rodriguez. Maturitas 2020; 139: 69-89

❖ Increased fracture risk by FRAX® as threshold for intervention



Absolute 10-year hip fracture risk by age and race at which it is cost-effective to treat (shown by lines) and average 10-year hip fracture risk by age and race shown by vertical bars) for US women and men

FIXED intervention threshold

National Osteoporosis Foundation, USA

- Determined as the 10-year probability of fracture at which it is cost-effective to treat
- Needs to be determined for each individual country
- Treatment is indicated when:

  10-year FRAX probability of fracture:
  - ≥ 20% for MOF
  - ≥ 3% for hip fracture

BBC 2020 guidelines on postmenopausal OP

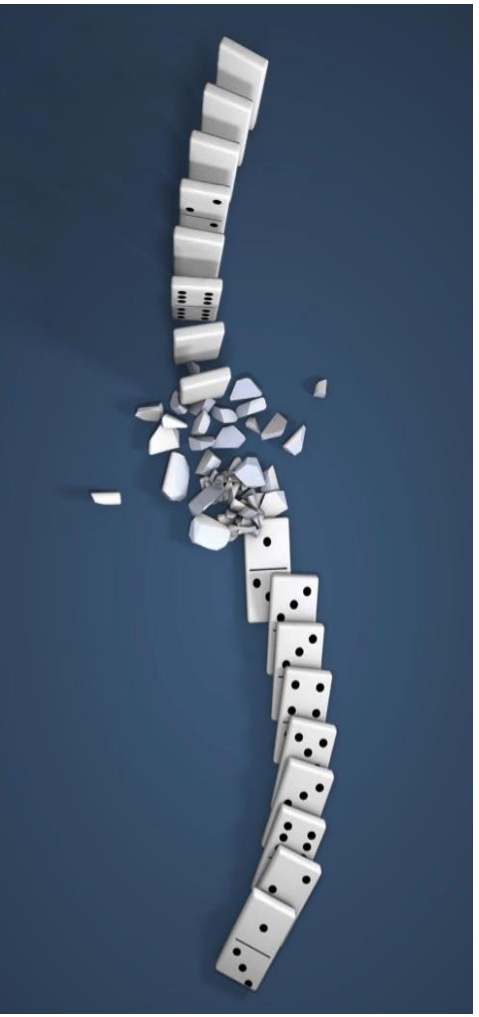
- Treatment is indicated when:

  10-year FRAX probability of fracture:
  - ≥ 20% for MOF
  - ≥ 3% for hip fracture (age < 70 years)

    ≥ 5% for hip fracture (age ≥ 70 years)

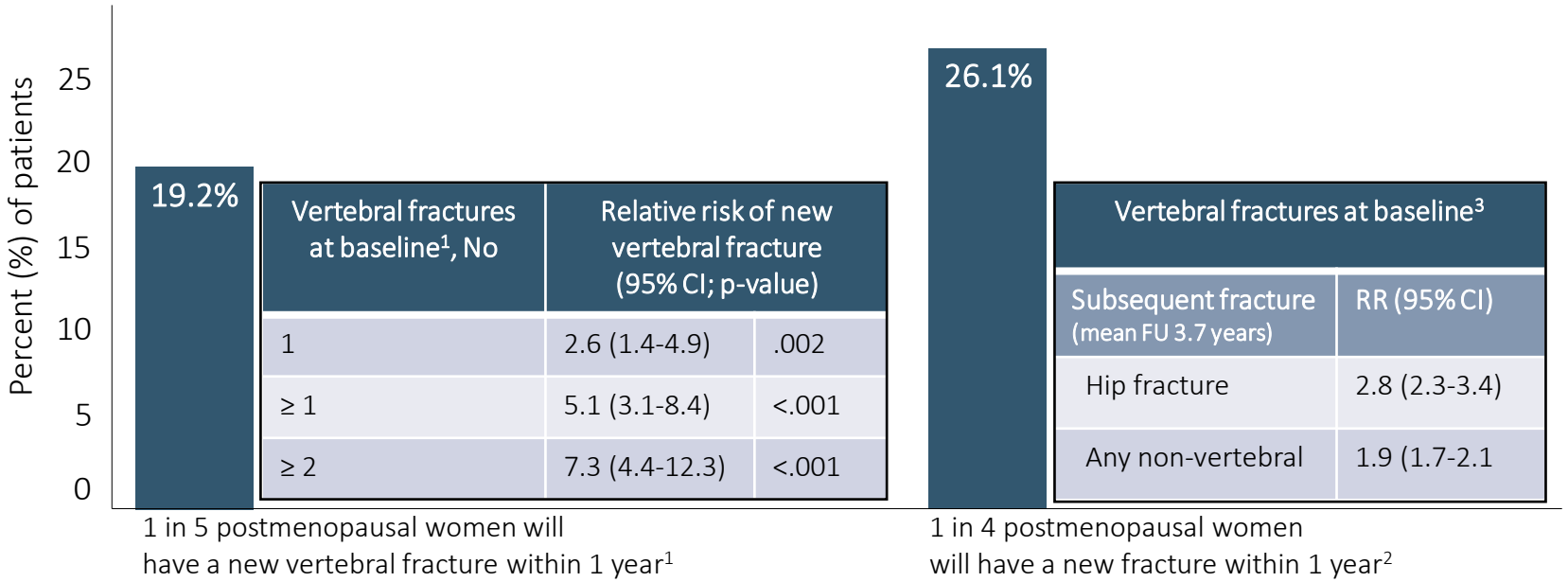
Sanchez-Rodriguez. Maturitas 2020; 139: 69-89; Kanis. Osteoporos Int 2008; 19:1395-408; Kanis. Arch Osteoporos 2016; 11; Kanis. Osteoporos Int 2013; 24: 23-57; Dawson-Hughes. J Clin Endocrinol Metab 2008; 93: 2463-2465; Tosteson. OI 2008; 437-447; Kanis. Arch Osteoporos. 2013; 8: 144; McCloskey. OI 2015; 26: 2091-2099

❖ Previous fragility fracture as threshold for intervention



Vertebral (spinal) fractures

Women who develop a vertebral fracture
are at substantial risk for additional fracture

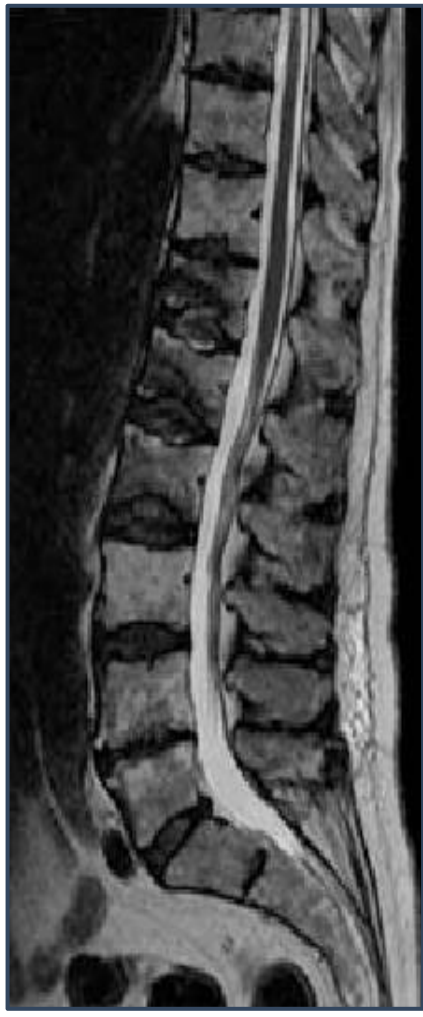


Vertebral fractures at baseline[1], No	Relative risk of new vertebral fracture (95% CI; p-value)	
1	2.6 (1.4-4.9)	.002
≥ 1	5.1 (3.1-8.4)	<.001
≥ 2	7.3 (4.4-12.3)	<.001

1 in 5 postmenopausal women will
have a new vertebral fracture within 1 year[1]

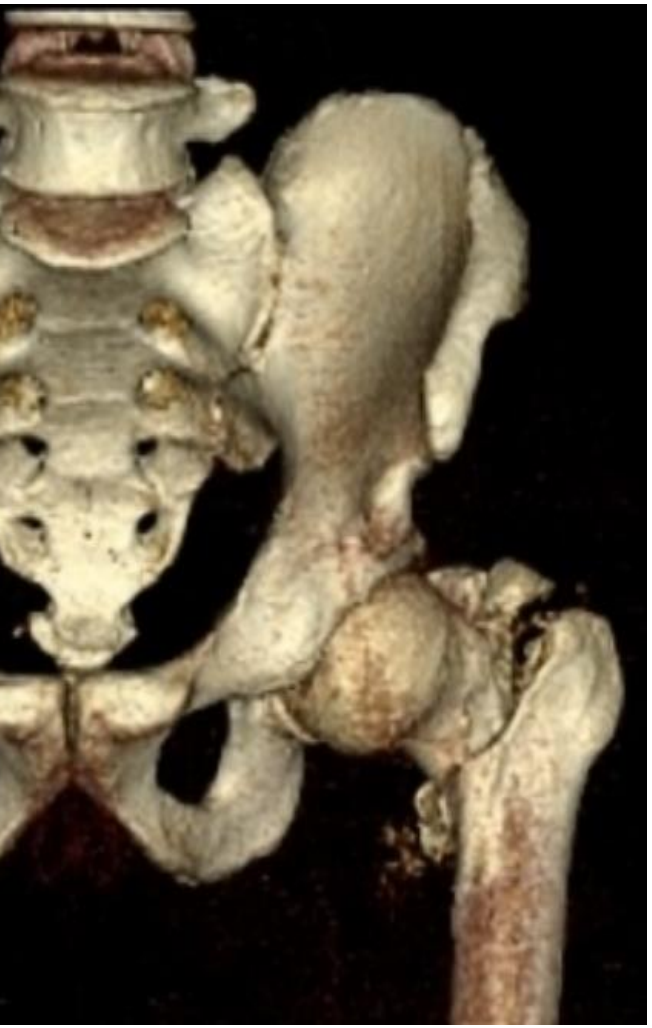
Vertebral fractures at baseline[3]	
Subsequent fracture (mean FU 3.7 years)	RR (95% CI)
Hip fracture	2.8 (2.3-3.4)
Any non-vertebral	1.9 (1.7-2.1

1 in 4 postmenopausal women
will have a new fracture within 1 year[2]



[1]Lindsay. JAMA 2001; 285: 320-23; [2]Lindsay. Osteoporos Int 2005; 16: 78-85; [3]Black. JBMR 1999; 14: 821-828

❖ Previous fragility fracture as threshold for intervention

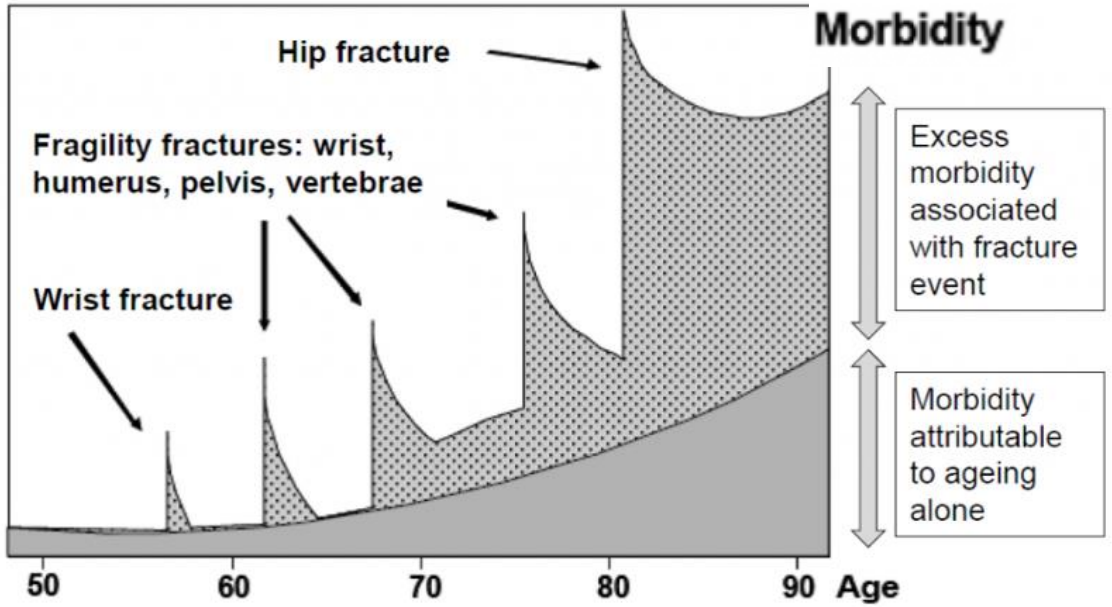


Hip fracture

	Hip fracture admissions, by sex	
	Men, n (%)	Women, n (%)
Number	97	251
Any prior fracture	29 (30%)	113 (45%)
Prior hip fracture	8 (8%)	47 (19%)

All hip fracture admissions in 2 hospitals (Sydney, AU) were identified retrospectively from medical records over 12 months

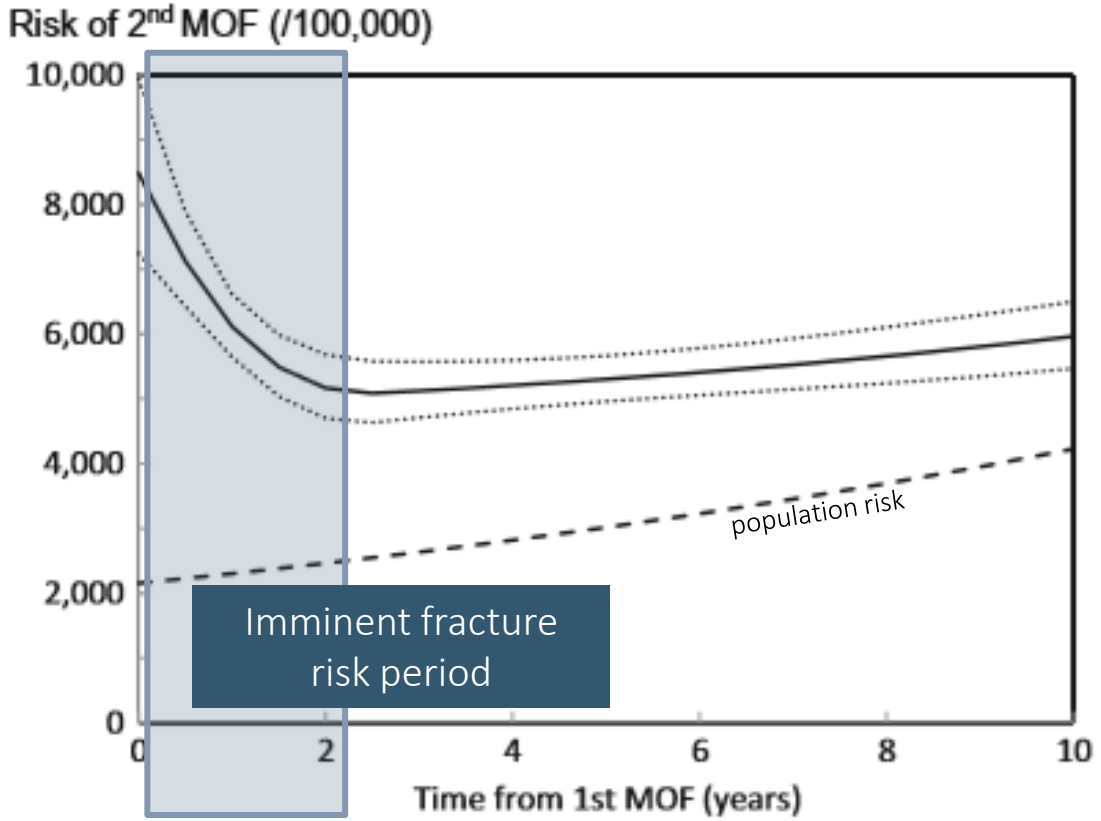
Fragility fracture cycle



Port. Osteoporos Int 2013; 14: 780-784; Kanis. J Endocrinol Invest 1999; 30: 583-8

❖ Previous fragility fracture as threshold for intervention

Imminent fracture 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

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

Risk of second MOF:

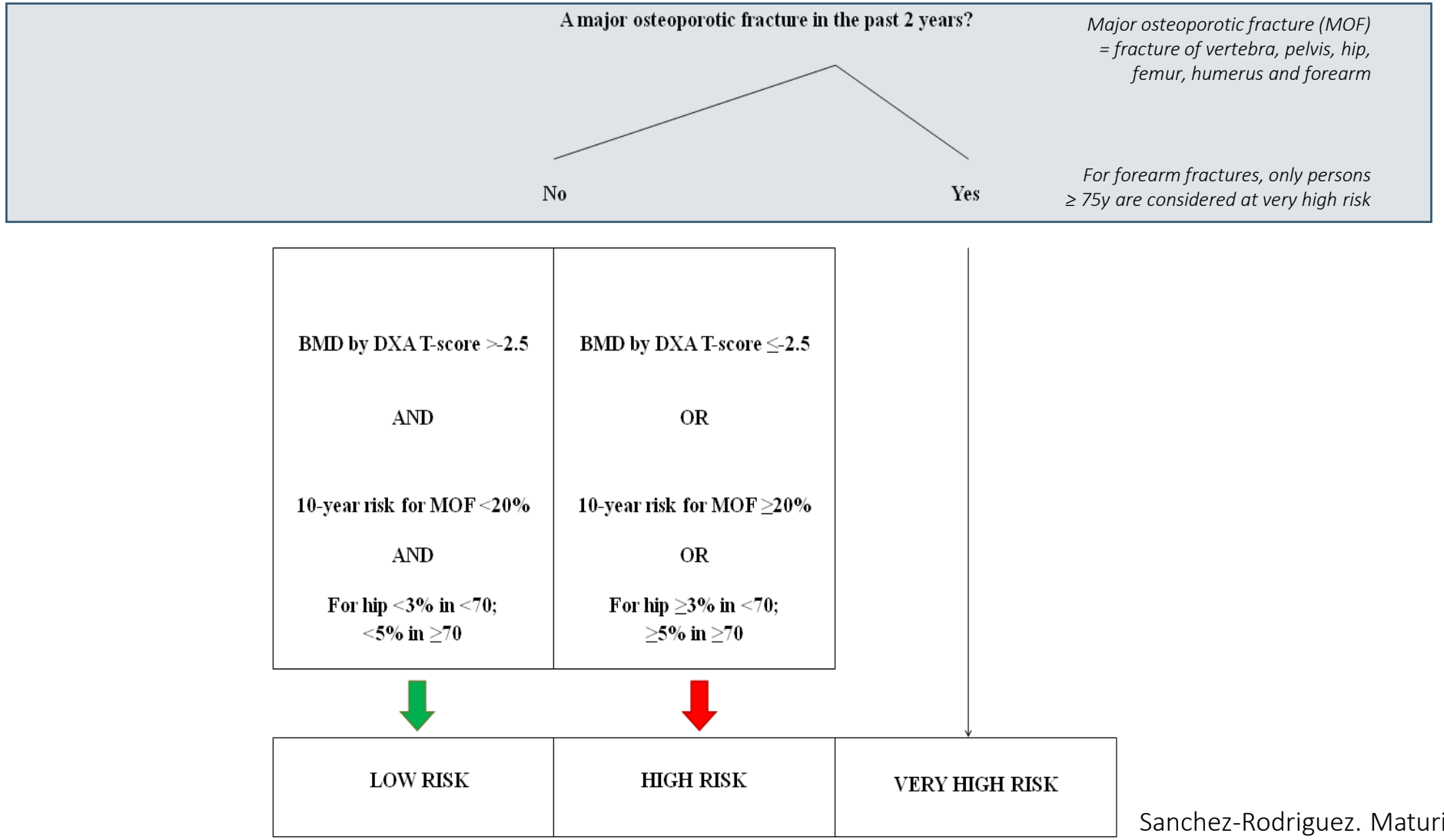
- 1 year after first MOF:
  2.7 (2.4-3.0)x higher than the population risk
- 10 years after first MOF:
  1.4 (1.2-1.6)x higher than the population risk

MOF= major osteoporotic fracture

Johansson. Osteoporos Int 2017; 28: 775-80

Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women

Identification of persons at low, high and very high fracture risk



Sanchez-Rodriguez. Maturitas 2020; 139: 69-89

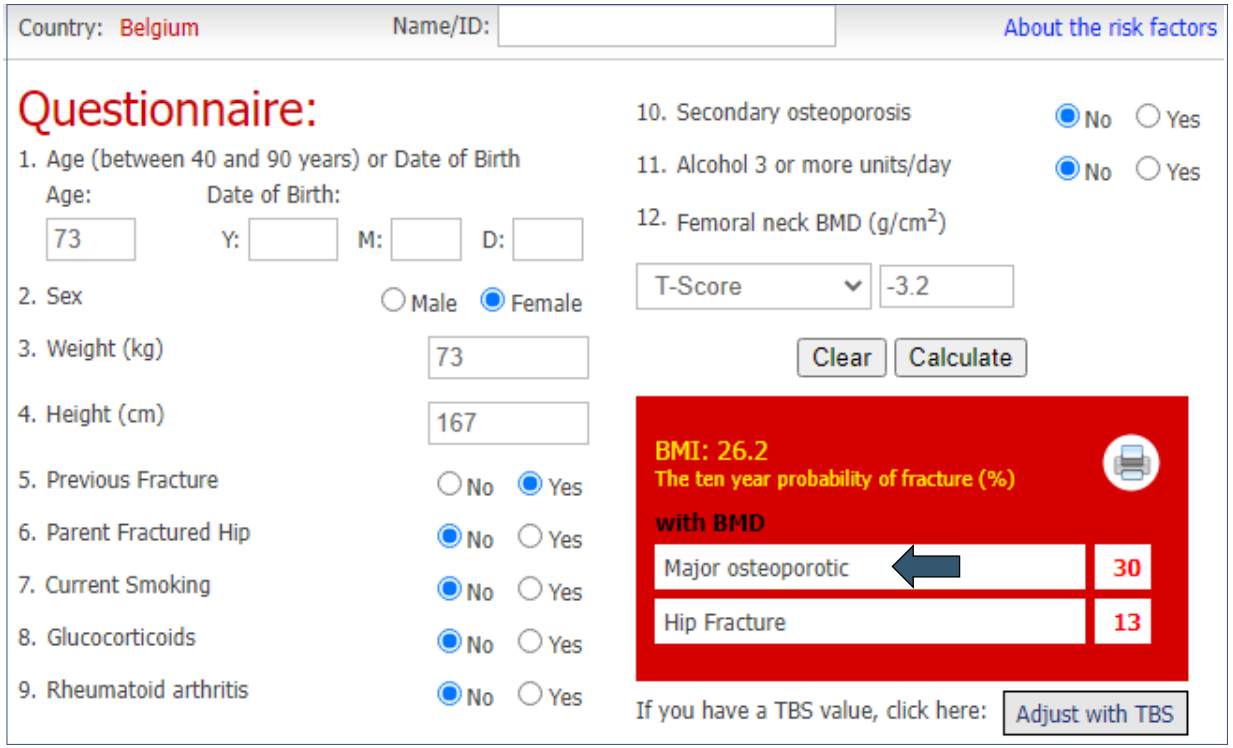
Definition of major osteoporotic fracture (MOF)

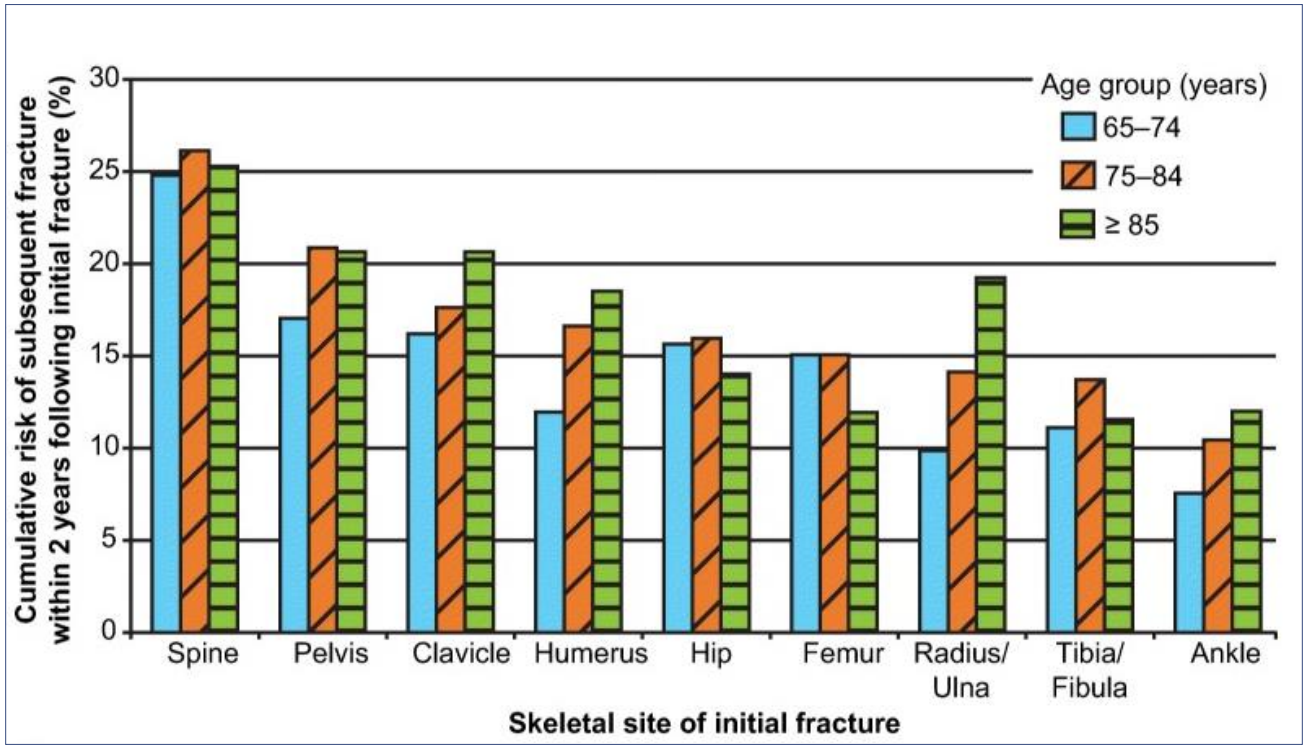
FRAX® Fracture Risk Assessment Tool

hip, clinical spine
proximal humerus
distal forearm

2020 BBC guidelines

hip, vertebral
humerus, pelvis, femur
forearm (if ≥ 75 years old)





Kanis. Osteoporos Int 2008; 19: 385-97; Sanchez-Rodriguez. Maturitas 2020; 139: 69-89; Balasubramanian. Osteopor Int 2019; 30:79-92

Overview

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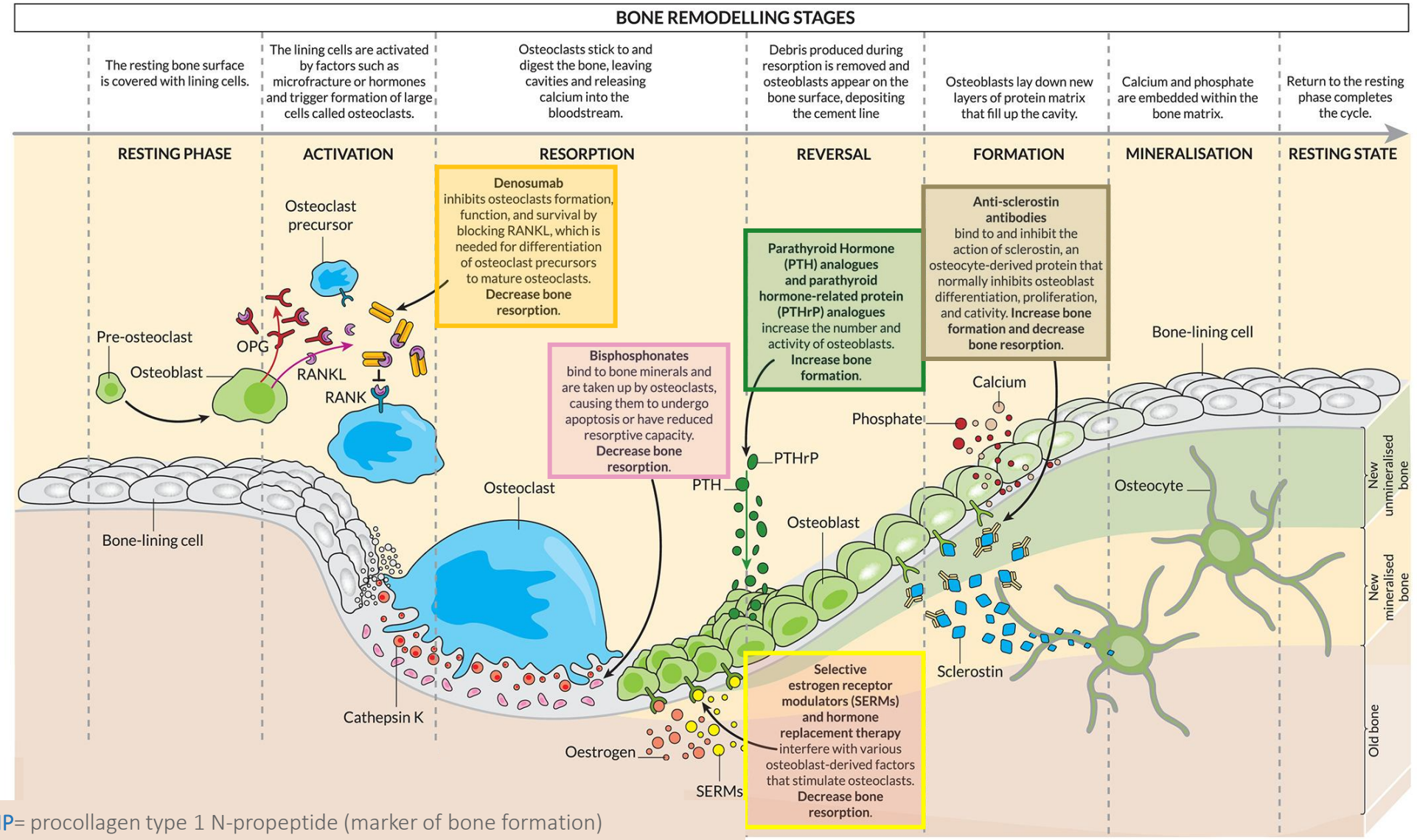
Overview of drugs for osteoporosis*

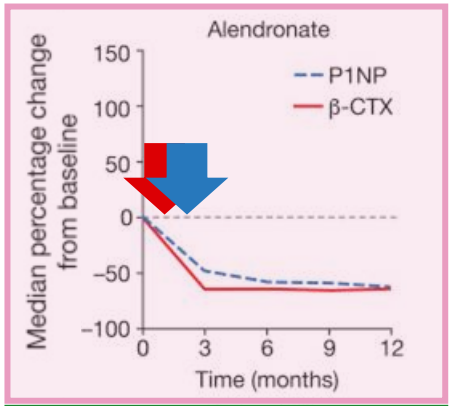
- Antiresorptive medication
  - Selective-estrogen receptor modulator (SERM)
  - Bisphosphonates
  - Denosumab (Prolia®)

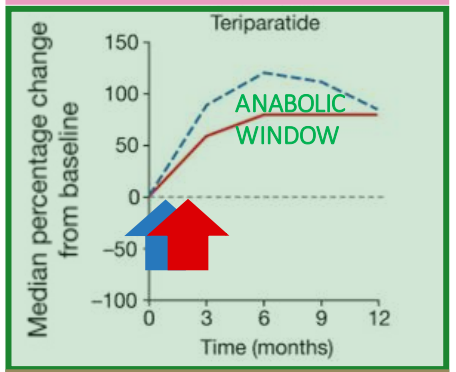
- Anabolic medication
  - Teriparatide (Forsteo®)
  - Romosozumab (Evenity®)

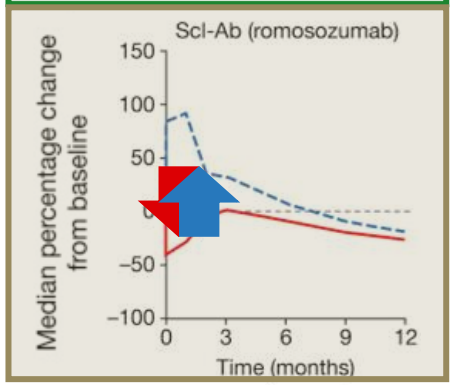
* EMA approved

Overview of drugs for osteoporosis









P1NP= procollagen type 1 N-propeptide (marker of bone formation)

β-CTX = C-terminal cross-linking telopeptide of collagen (bone resorption)

Langdahl. Br J Pharmacol 2021; 178: 1891-906; McClung. N Engl J Med 2014; 370, 412-20

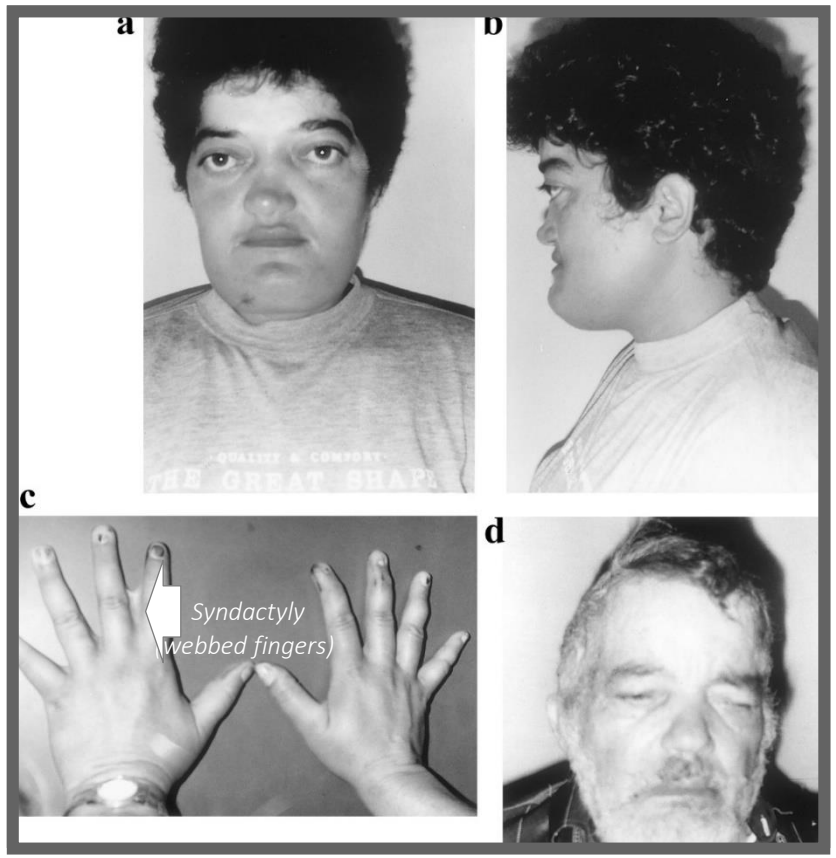
Romosozumab (Evenity®)

① Discovery and mechanism of action of sclerostin and Romosozumab

② Pivotal phase III trials with Romosozumab in postmenopausal women

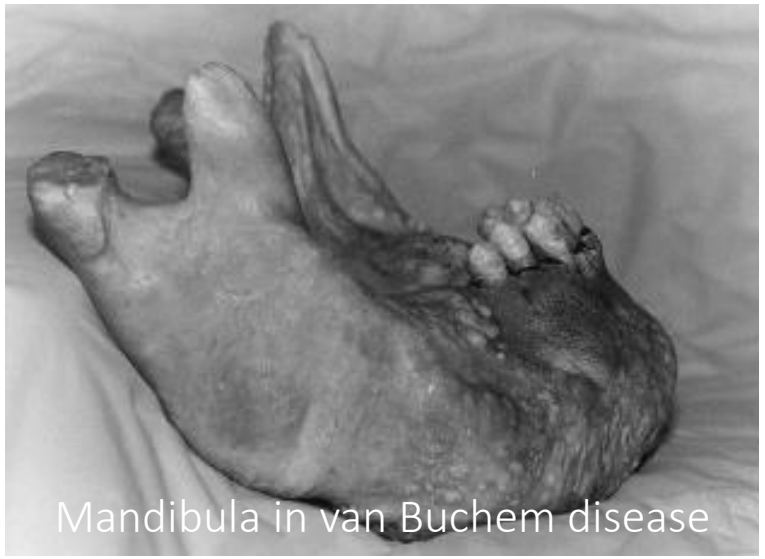
③ Cardiovascular safety of Romosozumab

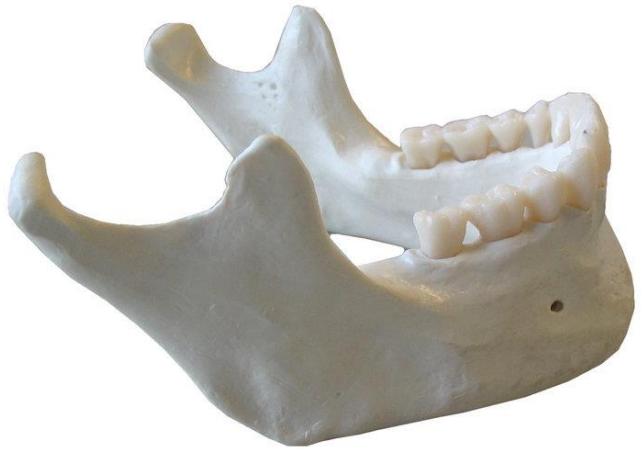
Sclerosteosis
(Truswell-Hansen disease)



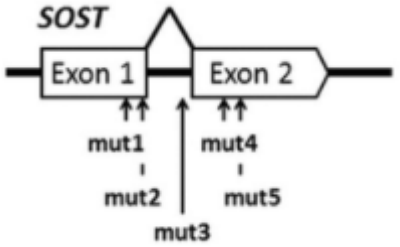
- First described in 1958
- Autosomal recessive disorder
- Most prominent in Afrikaner population in South Africa
- Progressive bone overgrowth, most pronounced in the skull and mandibule
- Increased intracranial pressure and entrapment of cranial nerves (eg. N. II, VII, VIII)
- Variable syndactyly, usually digit II and III
- Fractures have never been reported

Progressive bone overgrowth due to mutation in SOST gene


Mandibula in van Buchem disease

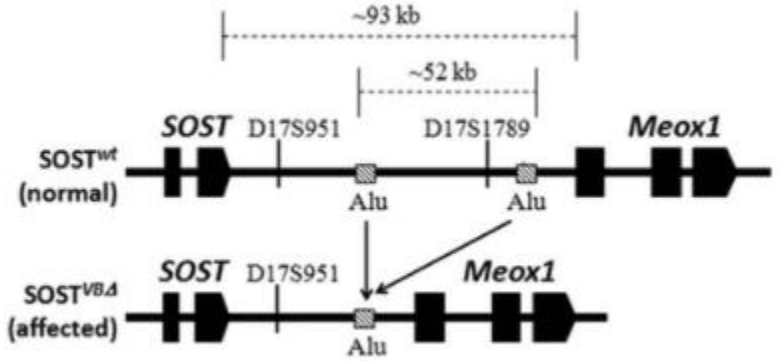

Normal mandibula

Sclerosteosis

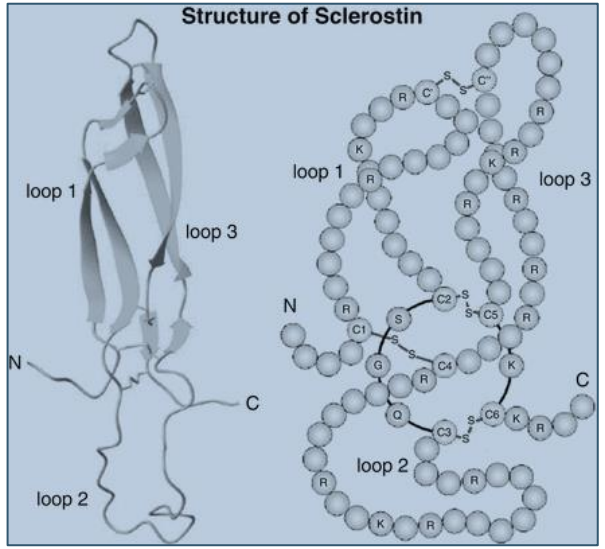


loss of function mutations in SOST gene
➔ *no sclerostin is synthesized*

Van Buchem disease

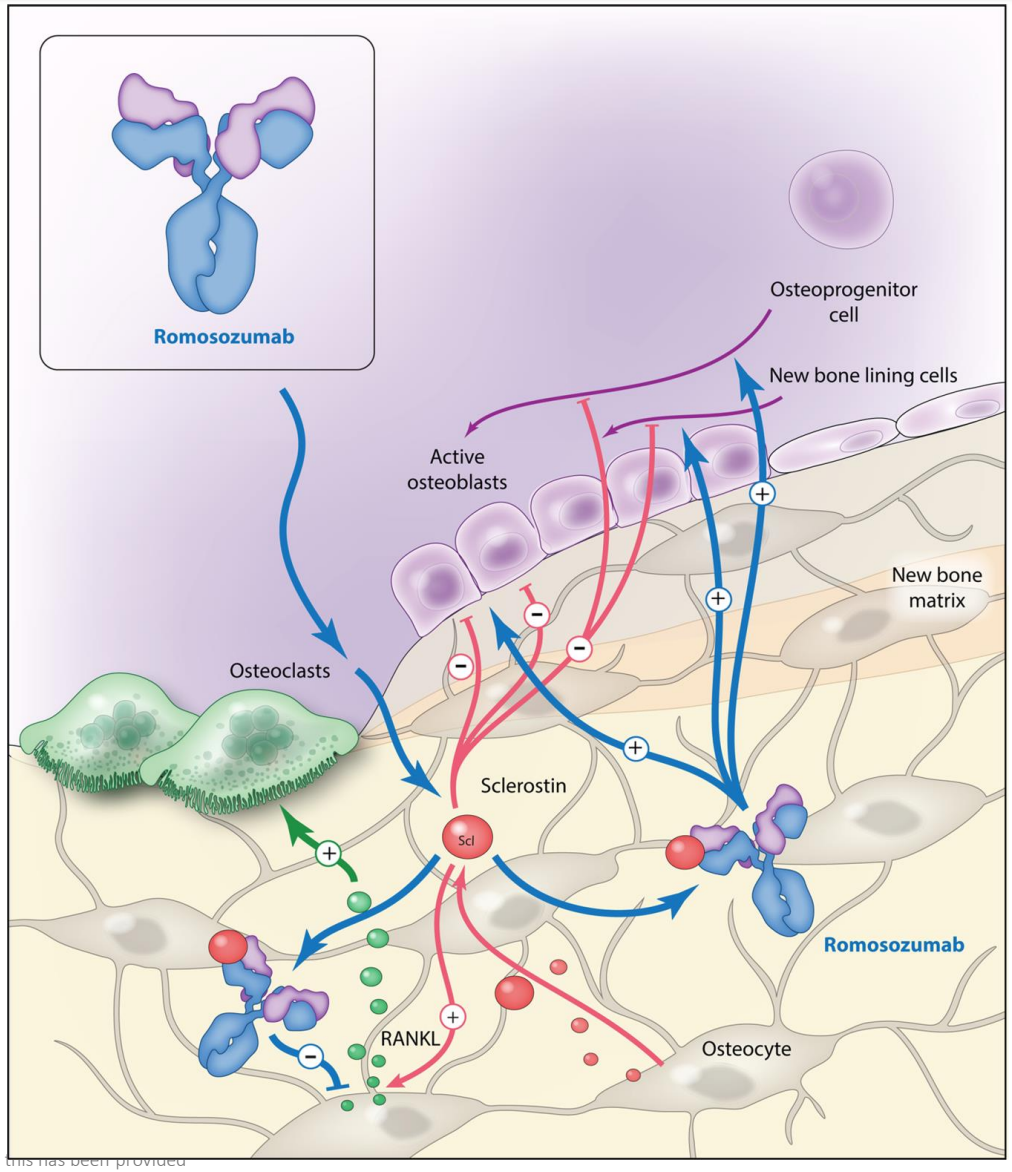


52 kb deletion downstream of SOST gene
➔ *reduced sclerostin production*



Sebastian. Bone 2017; 96: 76-84

Mode of action of Romosozumab



ROMOSOZUMAB

- Monoclonal antibody that binds and inhibits SCLEROSTIN
- Increases bone formation by
  - reactivation of bone lining cells
  - increasing bone matrix production
  - recruitment of osteoprogenitor cells
- Decreases bone resorption by
  - decreasing RANKL production

Uncoupling of bone formation and resorption

Upon request this has been provided

Solling. Ther Adv Musculoskel Dis 2018; 10: 105-15

Romosozumab (Evenity®)

① Discovery and mechanism of action of sclerostin and Romosozumab

② Pivotal phase III trials with Romosozumab in postmenopausal women

③ Cardiovascular safety

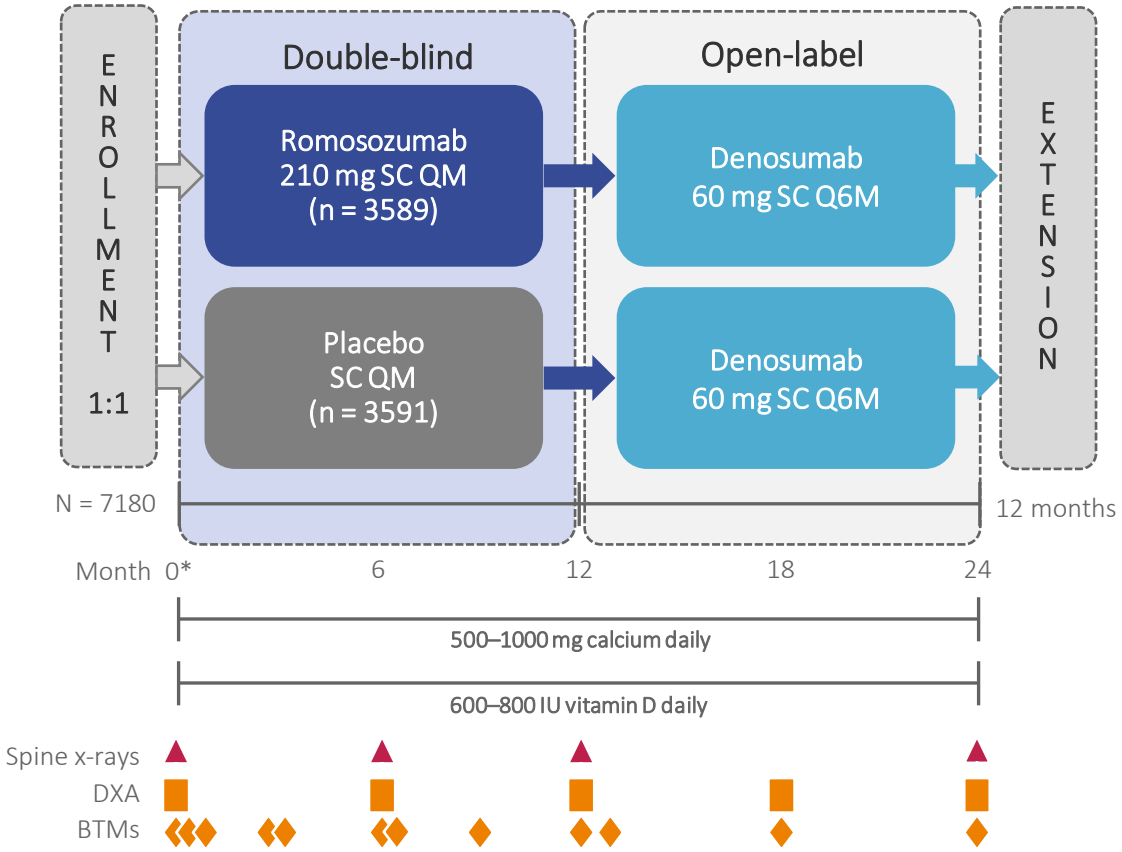
Phase III – FRAME

FRActure Study in Postmenopausal WoMen with OstEoporosis

Romosozumab vs. placebo in postmenopausal women with osteoporosis

FRAME
Study design

FRActure study in postmenopausal woMen with osteoporosis - Phase III, randomized, double-blind, placebo-controlled trial



Inclusion:

- Postmenopausal women aged 55 to 90 years
- BMD T-score ≤–2.5 at the total hip or femoral neck

Exclusion:

- BMD T-score ≤–3.5 at the total hip or femoral neck
- History of hip fracture, or any severe or more than 2 moderate vertebral fractures
- Recent osteoporosis therapy (washout period varied by agent)

➔ Relative low fracture risk population

Co-primary endpoints:

- Subject incidence of new vertebral fracture through 12 & 24 months

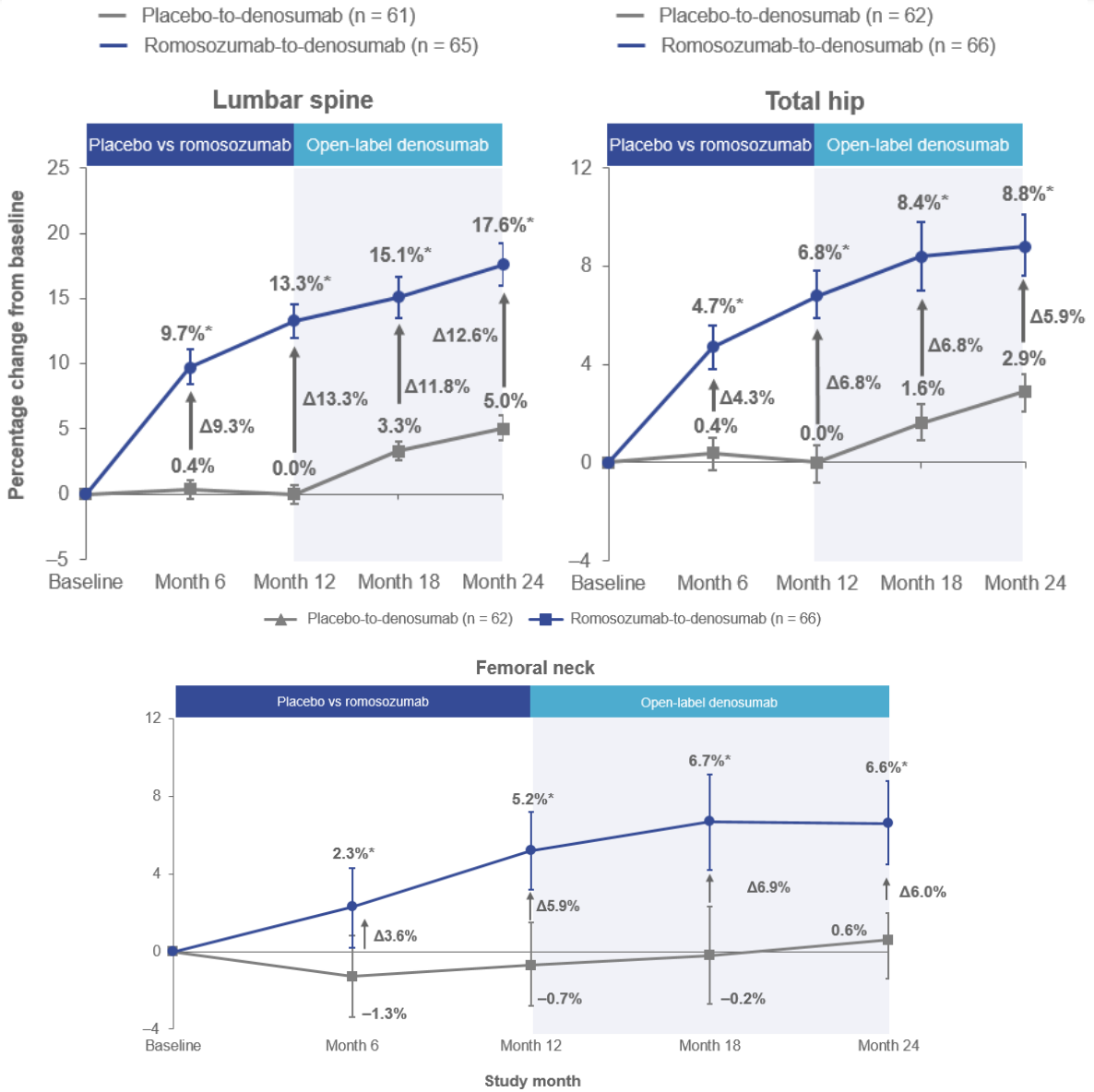
Secondary fracture endpoints:

- Subject incidence of clinical, nonvertebral and other fracture categories through 12 and 24 months

*A loading dose of 50,000–60,000 IU vitamin D was given to subjects with a baseline serum vitamin D 25(OH)D level of ≤40 ng/mL.
BMD=bone mineral density; BTM=bone turnover markers; DXA=dual-energy x-ray absorptiometry; IU = international unit; QM=once monthly; Q6M=every 6 months.

Cosman. N Engl J Med 2016; 375: 1532-43

FRAME: lumbar spine, total hip & femoral neck BMD through month 24

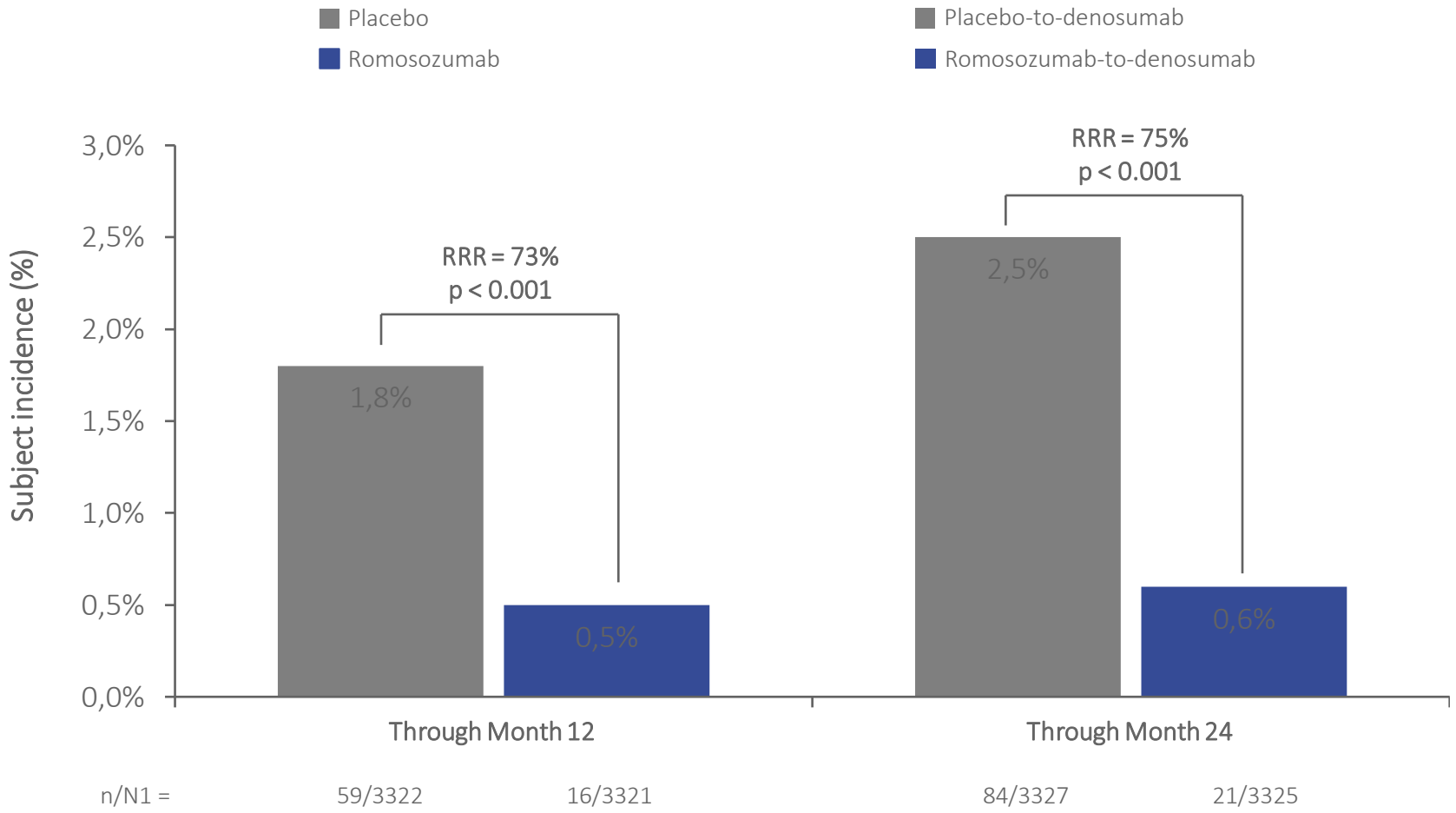


*p < 0.001 compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates.
BMD = bone mineral density; CI = confidence interval; Δ = difference.

Upon request this slide has been provided by UCB.

Cosman. N Engl J Med 2016; 375: 1532-43

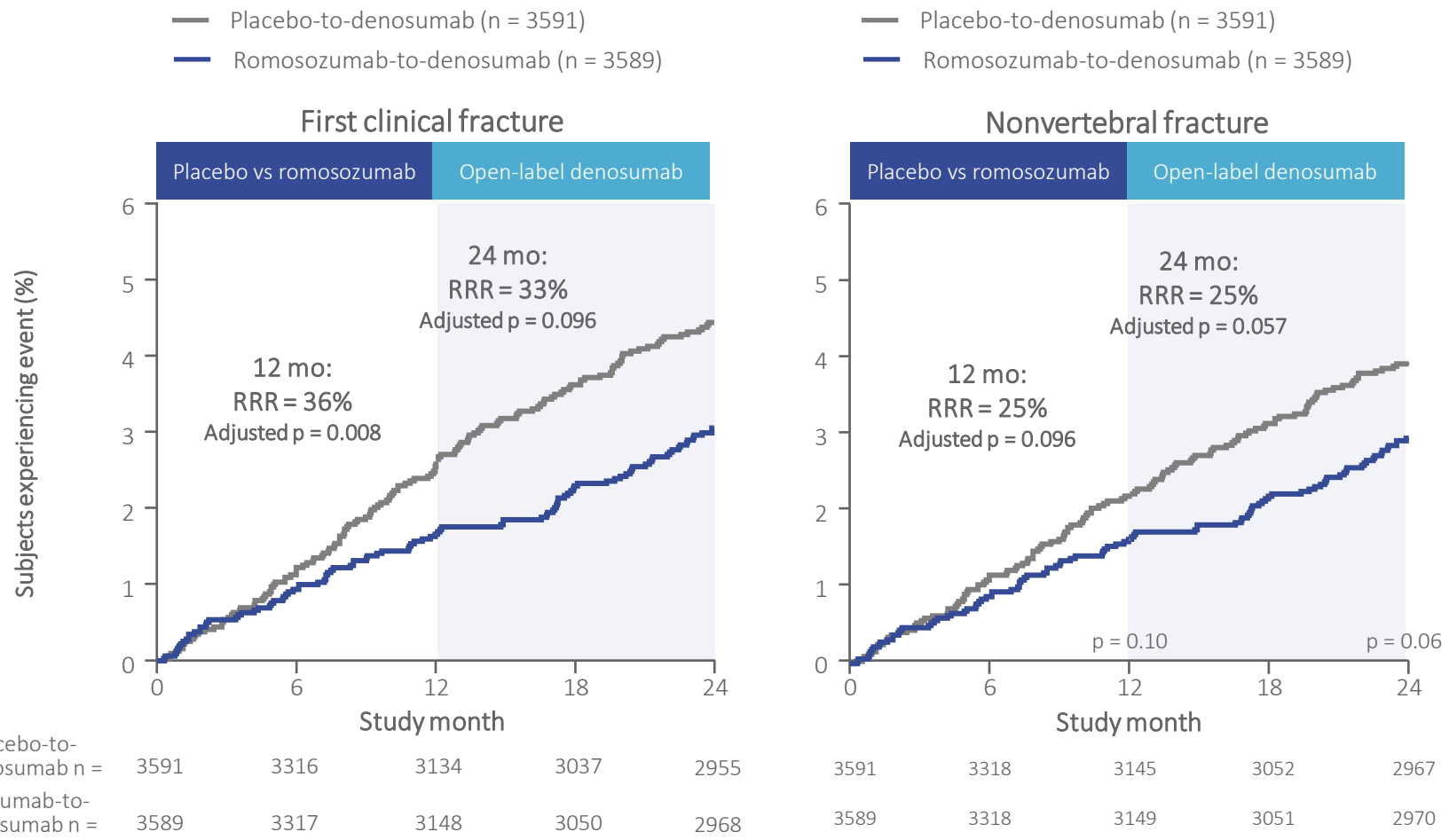
FRAME
Incidence of new vertebral fracture through month 12 and 24



n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures; p value based on logistic regression model adjusted for age (<75, ≥75) and prevalent vertebral fracture.
RRR = relative risk reduction.

Cosman. N Engl J Med 2016; 375: 1532-43

FRAME
Time to first clinical and nonvertebral fracture through month 24

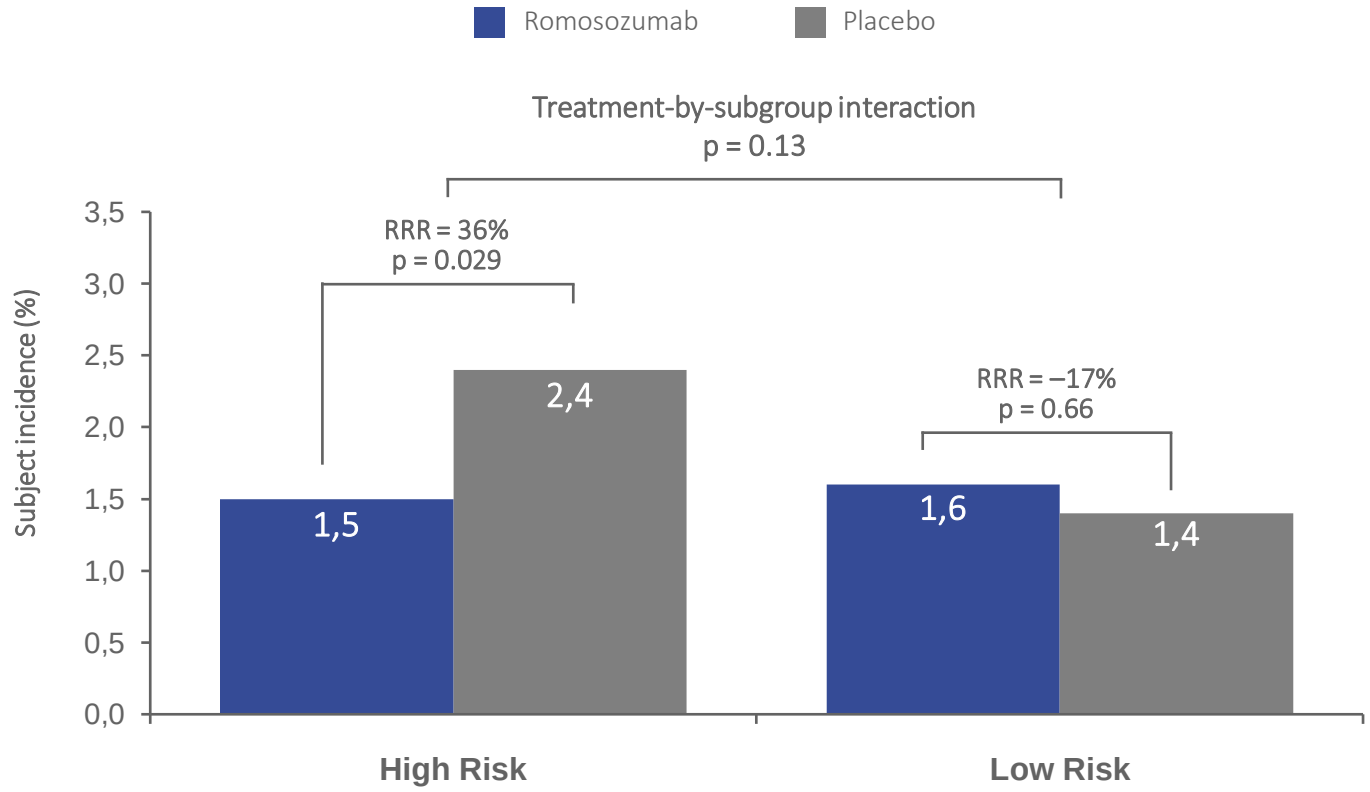


Clinical fractures included all nonvertebral and symptomatic vertebral fractures. Non-vertebral fractures comprised the majority (more than 85%) of clinical fractures and excluded fractures of the skull, facial bones, metacarpals, fingers and toes, pathologic fractures and fractures associated with high trauma. n = number of subjects at risk for event at time point of interest. p value based on RRR. RRR = relative risk reduction.

Cosman. N Engl J Med 2016; 375: 1532-43

FRAME Post-hoc analysis of regional background fracture risk

Nonvertebral fracture efficacy in patients at high vs. low risk based on FRAX in overall study population



High risk defined as 10-year probability of major osteoporotic fracture ≥20% or hip fracture ≥3%

Post-hoc analysis.
High risk: 10-year probability of major osteoporotic fracture ≥20% or hip fracture ≥3%; low risk: 10-year probability of major osteoporotic fracture <20% and hip fracture <3%. HR ratio estimates based on a Cox proportional hazards model, adjusted for age and prevalent vertebral fracture stratification variables. RRR = relative risk reduction. n/N1 = number of subjects with fractures/number of subjects in the analysis set.

Cosman. J Bone Miner Res 2018; 33: 1407-16

Phase III – ARCH

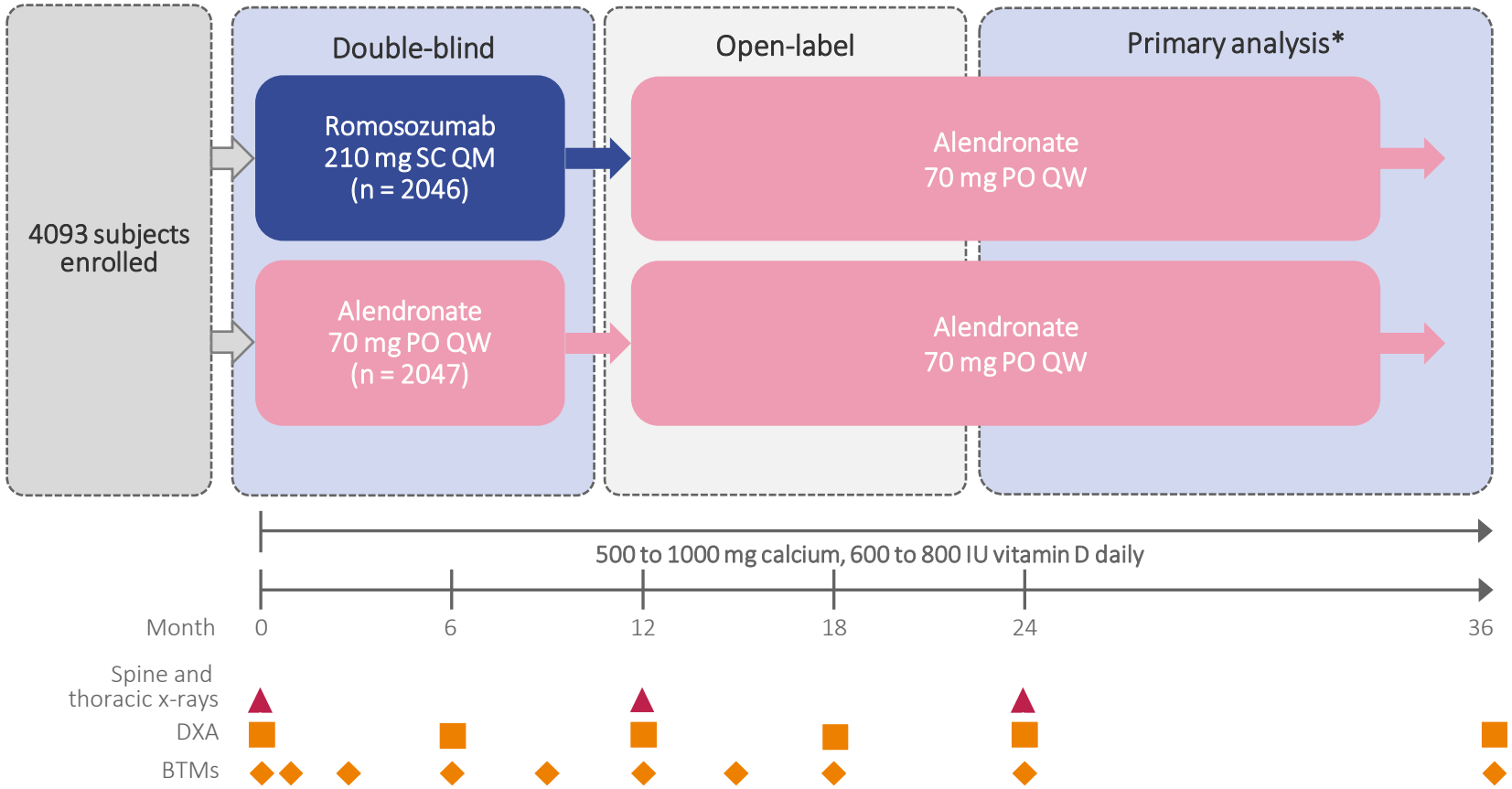
Active-controlled fracture study in postmenopausal women with osteoporosis at High risk of fracture (ARCH)

Romosozumab vs. alendronate in postmenopausal women with osteoporosis at high risk of fracture

ARCH
Study design

Active-contRolled fraCture study in postmenopausal women with osteoporosis at High risk of fracture

Phase III, randomized, double-blind, active-controlled trial



***Primary analysis:** performed when clinical fracture events had been confirmed in at least 330 patients and all patients had completed month 24. Median time on study at primary analysis was 33 months (IQR: 27–40).

BTM = bone turnover marker; DXA = dual-energy x-ray absorptiometry; IQR = interquartile range; IU = international unit; PO = orally; QM = monthly; QW = weekly; SC = subcutaneous.

Saag. N Engl J Med 2017;377:1417-27

ARCH
Key eligibility criteria

Inclusion criteria[1]

- Postmenopausal women aged 55 to 90 years
- BMD T-score and fracture history
  - BMD T-score ≤ –2.5 at the total hip or femoral neck, and
    - ≥ 1 moderate or severe vertebral fractures

    or
    - ≥ 2 mild vertebral fractures

OR

- BMD T-score ≤ –2.0 at the total hip or femoral neck, and
  - ≥2 moderate or severe vertebral fractures

  or
  - hip fracture sustained 3–24 months prior to randomization

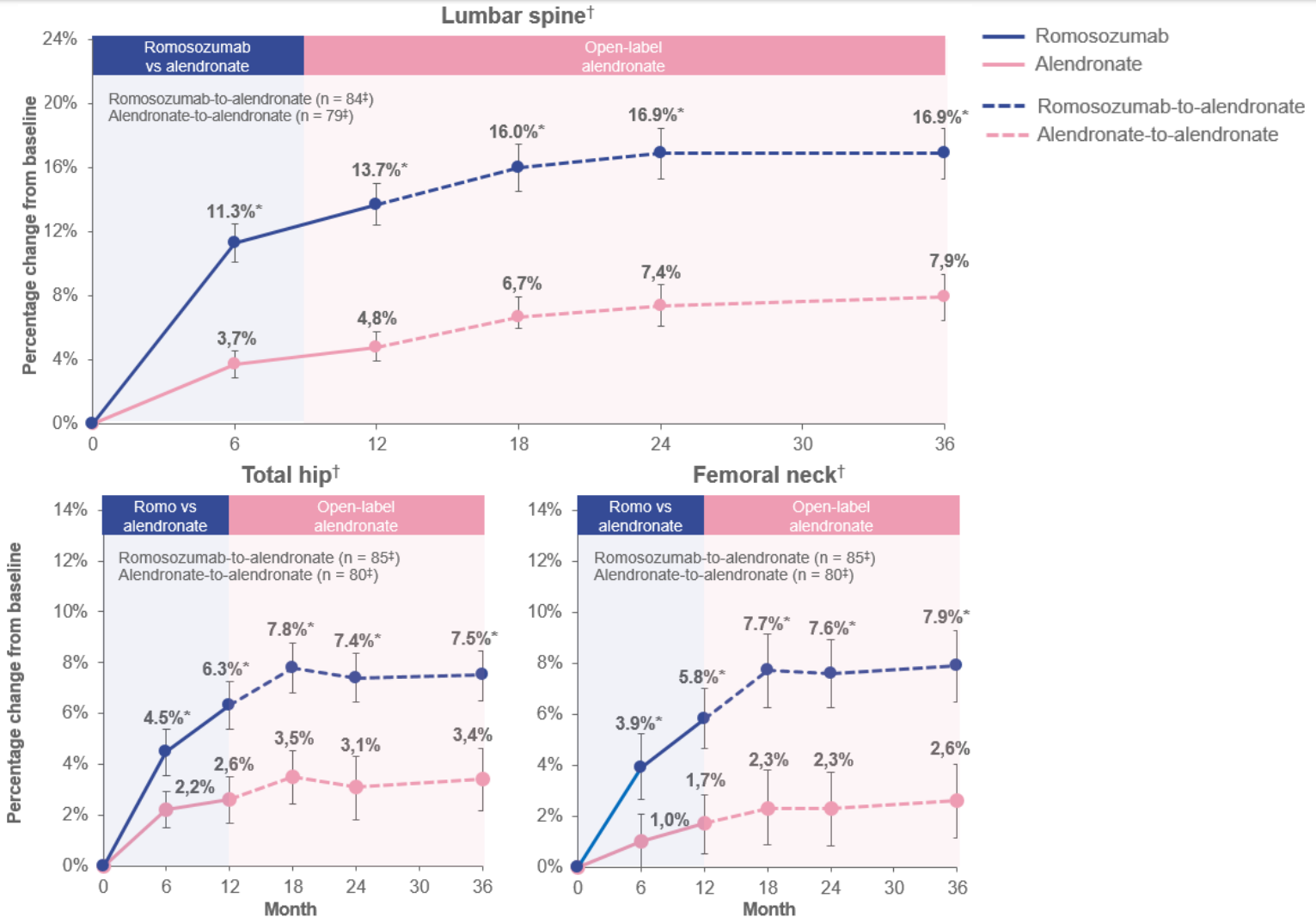
Exclusion criteria[1,2]

- Contraindications or signs of intolerance to alendronate
- Recent use of agents affecting bone metabolism

➔ high fracture risk population

Saag. N Engl J Med 2017;377:1417-27

ARCH
% Change from baseline in LS, TH and FN BMD through Month 36

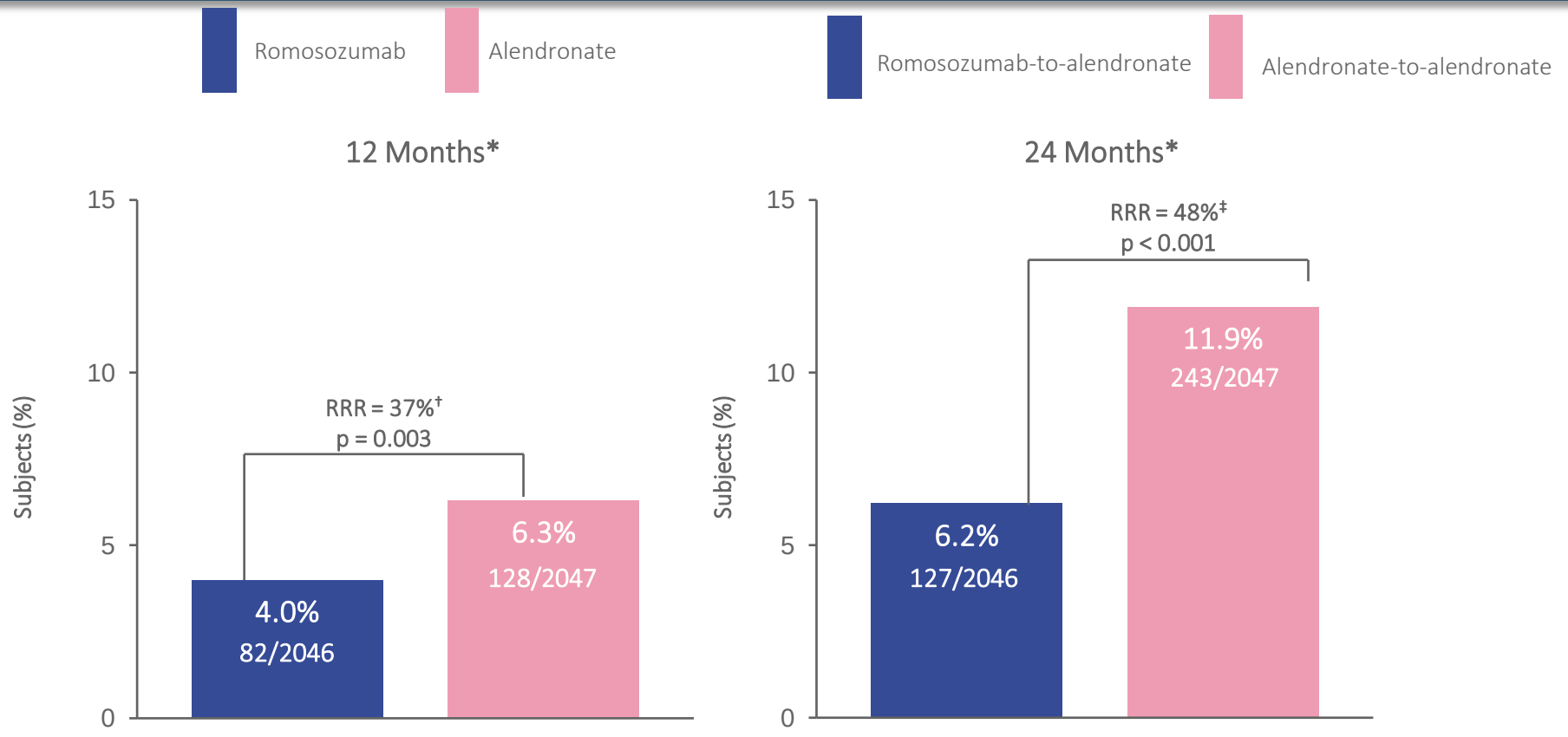


Data are least squares means (95% CI). The substudy population was representative of the overall study (data not shown).
*Nominal p < 0.001 (not-adjusted for multiplicity).
†ANCOVA model using LOCF adjusted for treatment, presence of severe vertebral fracture at baseline, baseline BMD value, machine type and baseline BMD value-by-machine type interaction.
‡Number of subjects with values at baseline and at least one post-baseline visit at Month 6 or Month 18.
ANCOVA = analysis of covariance; LOCF = last observation carried forward.

Upon request provided by UCB.

Saag. N Engl J Med 2017;377:1417-27

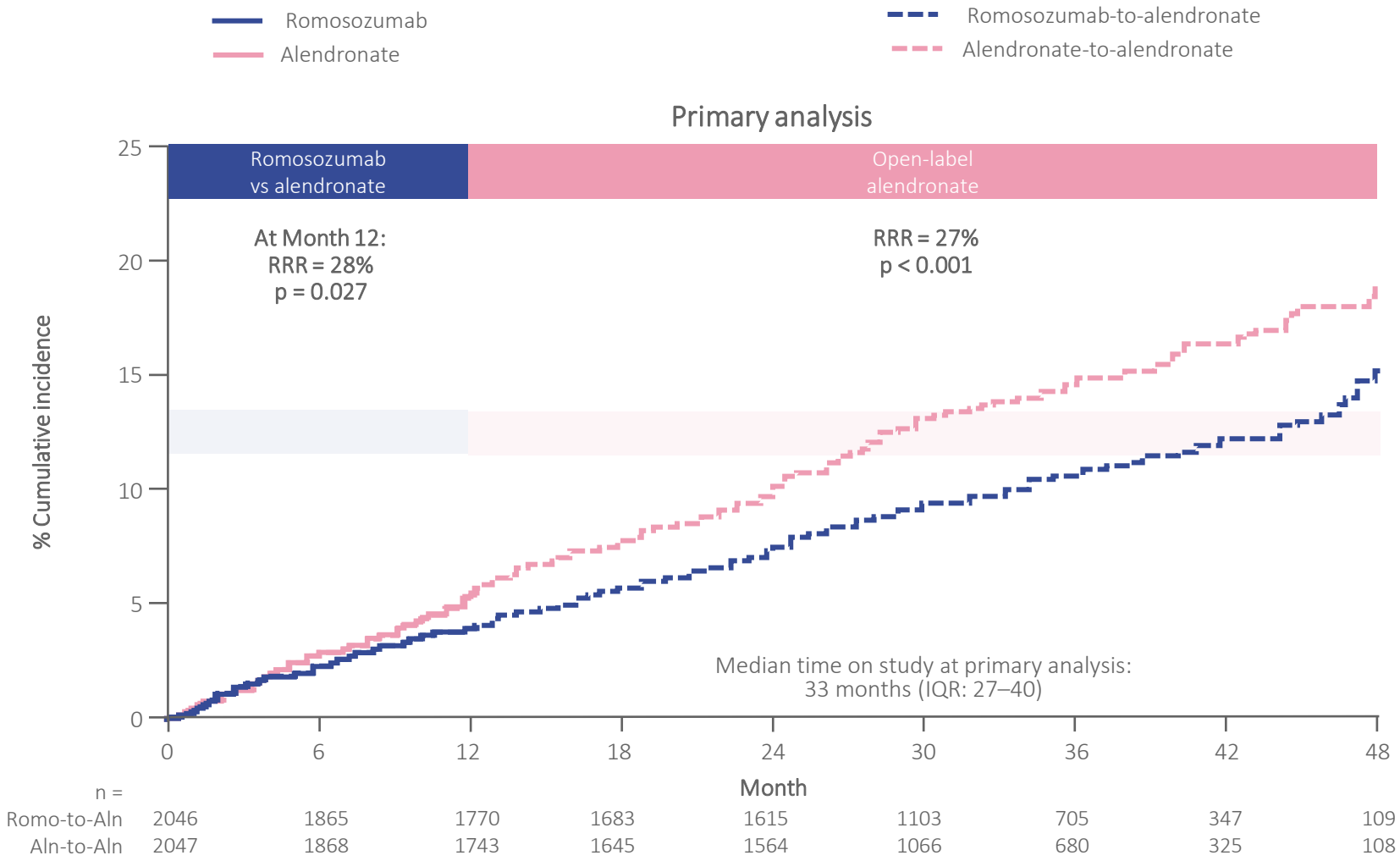
ARCH
Incidence of new vertebral fracture through month 12 and 24



n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures.
*Missing fracture status was imputed by multiple imputation for patients without observed fracture at an earlier time point. n and % are based on the average across five imputed datasets.
†RRR at 12 months by LOCF: 36% (nominal p = 0.008): Romosozumab: 3.2% (55/1696) vs alendronate: 5.0% (85/1703).
‡RRR at 24 months by LOCF: 50% (nominal p < 0.001): Romosozumab-to-alendronate: 4.1% (74/1825) vs alendronate-to-alendronate: 8.0% (147/1843).
LOCF = last observation carried forward; RRR = relative risk reduction.

Saag. N Engl J Med 2017;377:1417-27

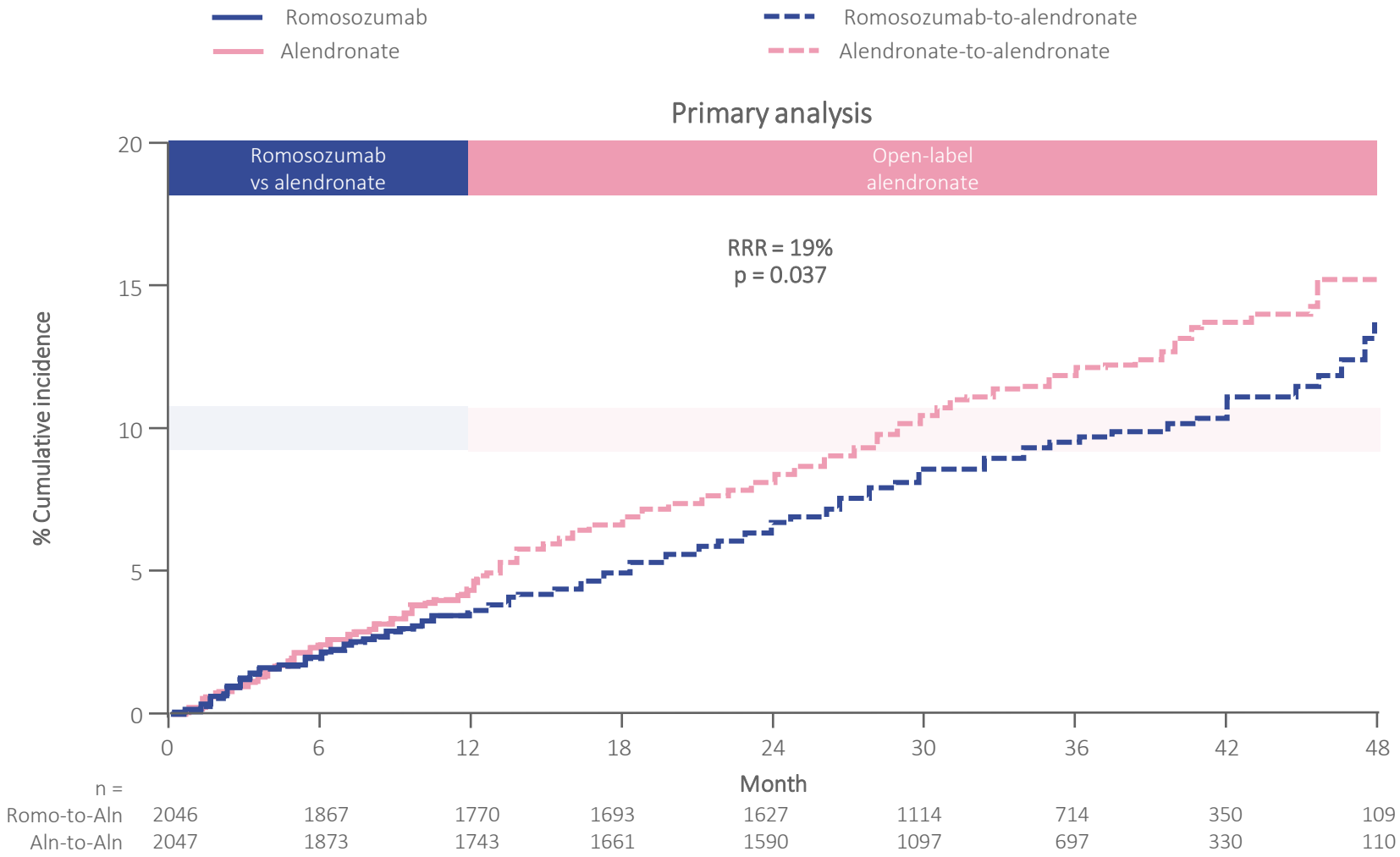
ARCH
Incidence of clinical fracture at primary analysis



n = number of subjects at risk for event at time point of interest.
ALN = alendronate; IQR = interquartile range; Romo = romosozumab; RRR = relative risk reduction.

Saag. N Engl J Med 2017;377:1417-27

ARCH
Incidence of nonvertebral fractures at primary analysis



Non-vertebral fractures = Secondary endpoint. n = number of subjects at risk for event at time point of interest.
ALN = alendronate; Romo = romosozumab; RRR = relative risk reduction.

Saag. N Engl J Med 2017;377:1417-27

Phase III – STRUCTURE

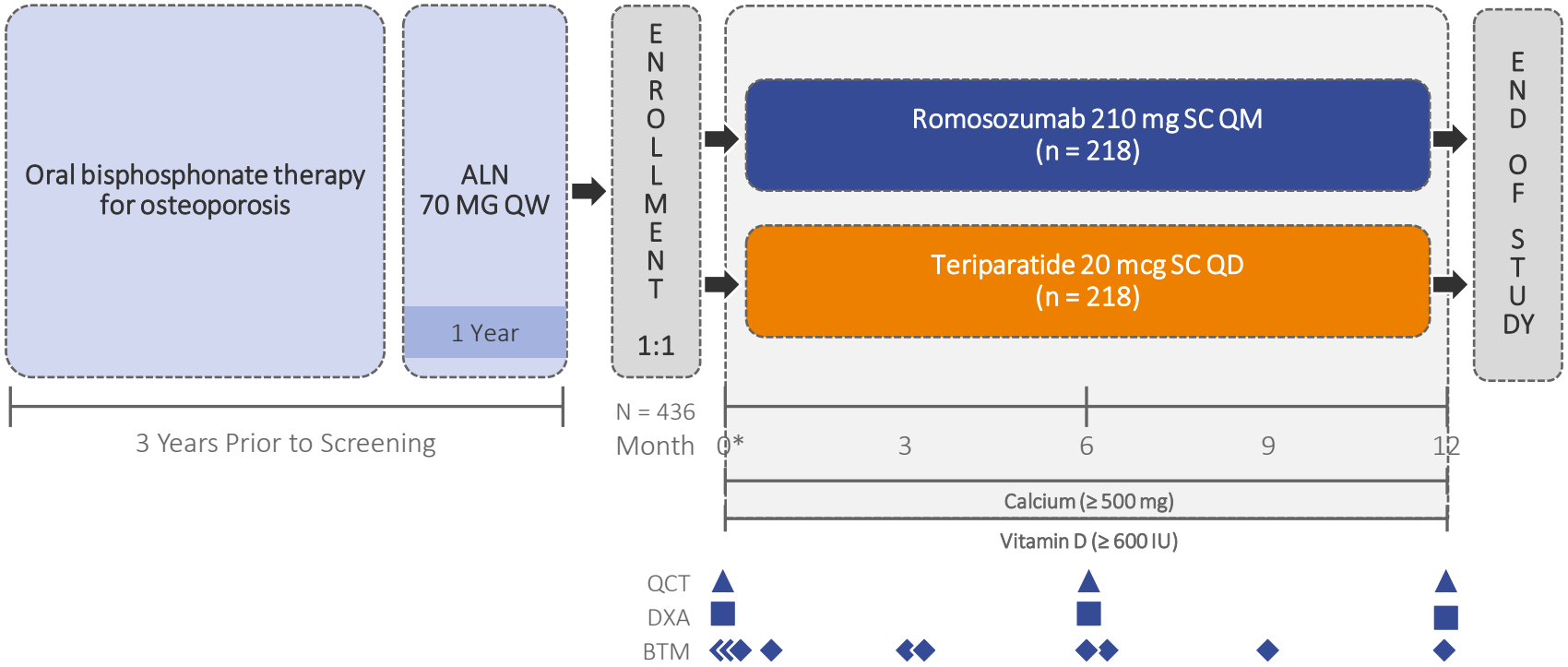
STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy

Romosozumab vs. teriparatide in postmenopausal women with osteoporosis at high risk of fracture previously treated with bisphosphonate therapy

Phase III, randomized, open-label, active-controlled trial

STRUCTURE
Study design

Inclusion criteria	• Postmenopausal women age 55 to 90 years • BMD T-score ≤ –2.5 at the total hip, femoral neck, or lumbar spine • History of nonvertebral fracture after age 50 or vertebral fracture • Oral bisphosphonate for ≥3 years
Exclusion criteria	• Recent use of agents that affect bone metabolism • History of metabolic or bone disease except osteoporosis



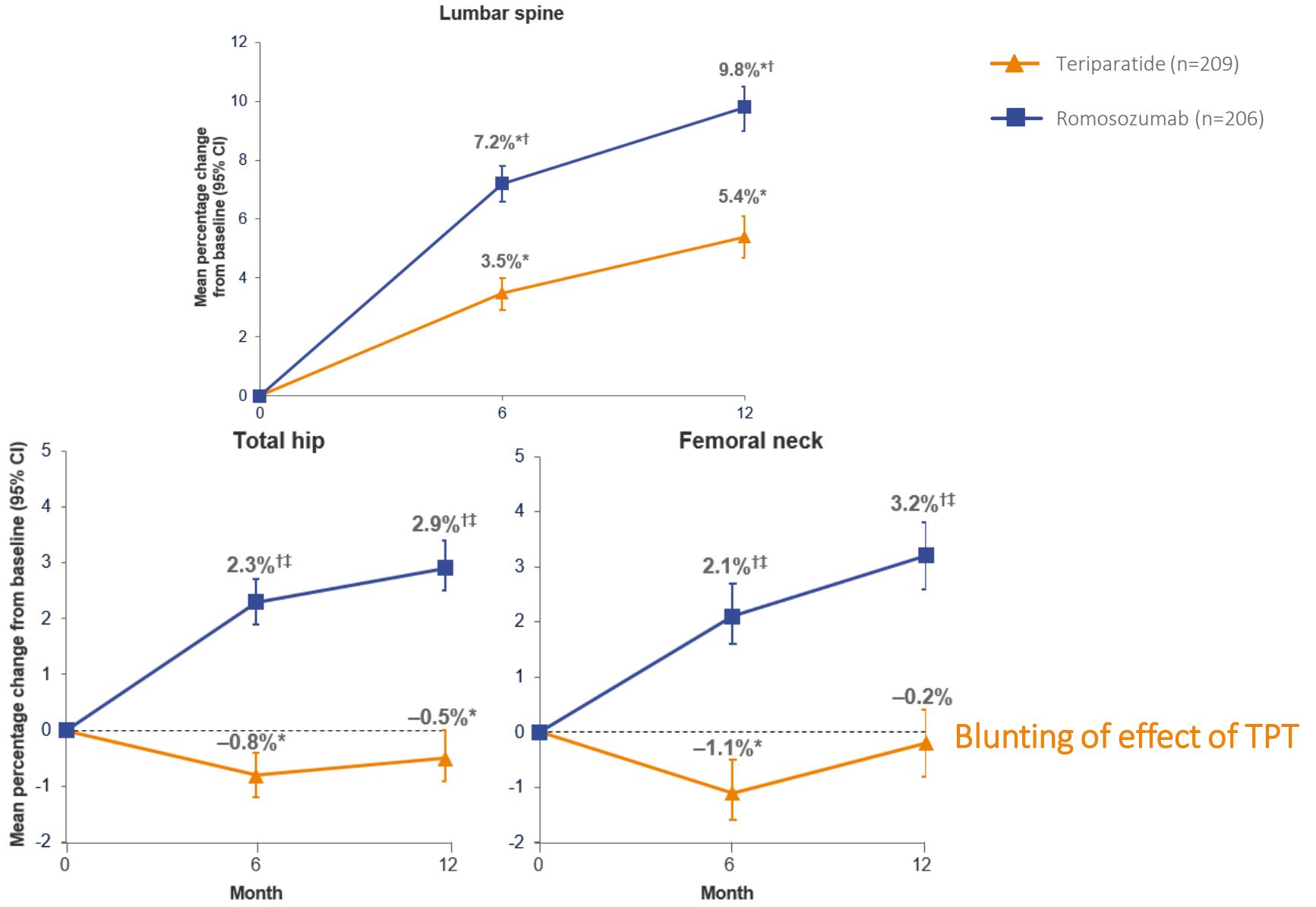
*A loading dose of 50,000–60,000 IU vitamin D was given to subjects in the romo group with a baseline serum vitamin D 25(OH)D level between 50-100 nmol/L
ALN = alendronate; BTM = bone turnover marker; DXA = dual-energy x-ray absorptiometry; IU = international unit; QCT = quantitative computed tomography; QD = daily; QM = once a month; QW = once a week; SC = subcutaneous.

Upon request provided by UCB.

Langdahl. Lancet 2017;390:1585-94

STRUCTURE

Percentage change in LS, TH and FN aBMD by DXA at months 6 and 12



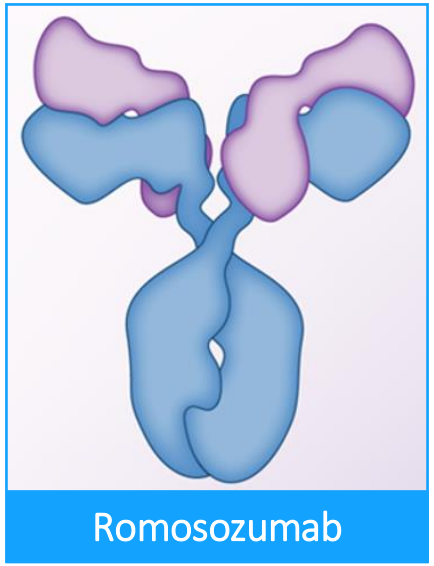
Blunting of effect of TPT

Data are least-squares means and 95% CI. *p < 0.0001 versus baseline. †p < 0.0001 versus teriparatide

Upon request provided by UCB.

Langdahl. Lancet 2017;390:1585-94

Romosozumab (Evenity®)



- Monoclonal antibody that uncouples bone formation and resorption
- Quickly and strongly increases BMD and decreases fracture risk
- Superior to Alendronate in treatment-naive (ARCH) and Teriparatide in pre-treated (STRUCTURE) patients

Romosozumab (Evenity®)

① Discovery and mechanism of action of sclerostin and Romosozumab

② Pivotal phase III trials with Romosozumab in postmenopausal women

③ Cardiovascular safety of Romosozumab

ARCH: adverse events, events of interest and serious adverse events

Event	Month 12: Double-blind period		Primary Analysis: Double-blind and open-label period*	
	Romosozumab (n = 2040)	Alendronate (n = 2014)	Romosozumab-to-alendronate (n = 2040)	Alendronate-to-alendronate (n = 2014)
Adverse event during treatment	1544 (75.7%)	1584 (78.6%)	1766 (86.6%)	1784 (88.6%)
Back pain†	186 (9.1%)	228 (11.3%)	329 (16.1%)	393 (19.5%)
Nasopharyngitis†	213 (10.4%)	218 (10.8%)	363 (17.8%)	373 (18.5%)
Event leading to discontinuation of trial regimen	70 (3.4%)	64 (3.2%)	133 (6.5%)	146 (7.2%)
Event leading to discontinuation of trial participation	30 (1.5%)	27 (1.3%)	47 (2.3%)	43 (2.1%)
Event of interest‡				
Osteoarthritis§	138 (6.8%)	146 (7.2%)	247 (12.1%)	268 (13.3%)
Hypersensitivity	122 (6.0%)	118 (5.9%)	205 (10.0%)	185 (9.2%)
Injection-site reaction¶	90 (4.4%)	53 (2.6%)	90 (4.4%)	53 (2.6%)
Cancer	31 (1.5%)	28 (1.4%)	84 (4.1%)	85 (4.2%)
Hyperostosis‖	2 (<0.1%)	12 (0.6%)	23 (1.1%)	27 (1.3%)
Hypocalcaemia	1 (<0.1%)	1 (<0.1%)	4 (0.2%)	1 (<0.1%)
Atypical femoral fracture**	0	0	2 (<0.1%)	4 (0.2%)
Osteonecrosis of the jaw**	0	0	1 (<0.1%)	1 (<0.1%)
Serious adverse event	262 (12.8%)	278 (13.8%)	586 (28.7%)	605 (30.0%)
Adjudicated serious cardiovascular (CV) event†	50 (2.5%)	38 (1.9%)	133 (6.5%)	122 (6.1%)
Cardiac ischaemic event	16 (0.8%)	6 (0.3%)	30 (1.5%)	20 (1.0%)
Cerebrovascular event	16 (0.8%)	7 (0.3%)	45 (2.2%)	27 (1.3%)
Heart failure	4 (0.2%)	8 (0.4%)	12 (0.6%)	23 (1.1%)
Cardiovascular death	17 (0.8%)	12 (0.6%)	58 (2.8%)	55 (2.7%)
Noncoronary revascularisation	3 (0.1%)	5 (0.2%)	6 (0.3%)	10 (0.5%)
Peripheral vascular ischaemic event not requiring revascularization	0	2 (<0.1%)	2 (<0.1%)	5 (0.2%)
Death of all causes	30 (1.5%)	21 (1.0%)‡	90 (4.4%)	90 (4.5%)‡

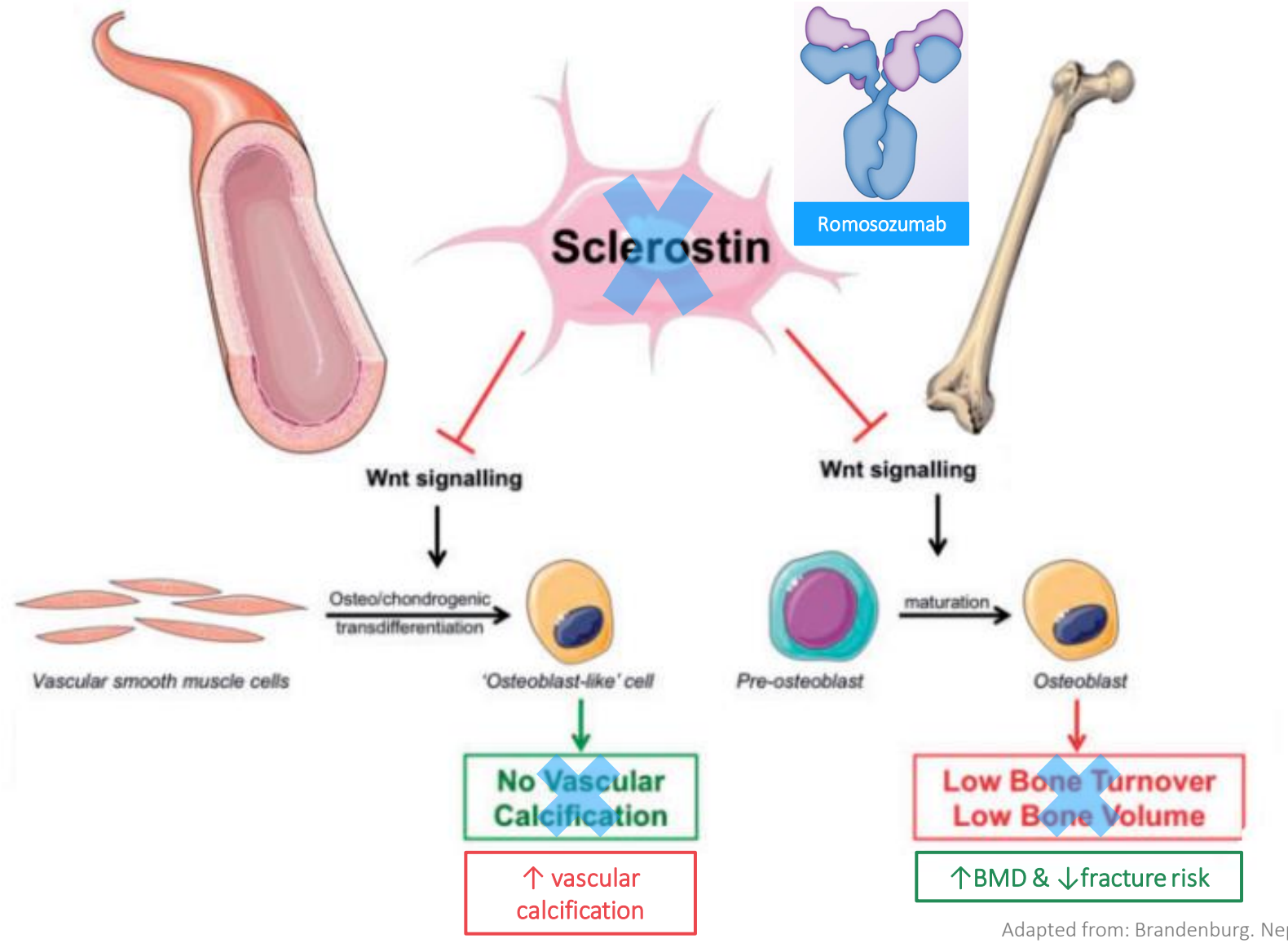
Imbalance was maintained after switching to ALN

*Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label period (to February 27 2017) in patients who received at least one dose of open-label alendronate. †Serious CV adverse events were adjudicated by the Duke Clinical Research Institute. CV deaths include fatal events that were adjudicated as being CV-related or undetermined (and, therefore, possibly CV-related). ‡One patient had a non-treatment-related serious adverse event of pneumonia that was incorrectly flagged as death in the primary analysis snapshot and was not included in the analysis of fatal events.

Upon request provided by UCB.

Saag. N Engl J Med 2017;377:1417-27

Sclerostin may function as negative regulator of vascular calcification



Adapted from: Brandenburg. Nephrol Dial Transplant; 2019 34: 408–414

ARCH
Comparison of baseline CV risk factors

	Overall study population		Patients with positively adjudicated serious CV AE in the double-blind period	
	Romosozumab (n = 2040)	Alendronate (n = 2014)	Romosozumab (n = 50)	Alendronate (n = 38)
Age (years), mean ± SD	74.4 ± 7.5	74.2 ± 7.5	76.3 ± 7.3	76.3 ± 7.7
Age ≥75 years	1070 (52.5%)	1049 (52.1%)	33 (66.0%)	22 (57.9%)
CV risk score,* median (Q1, Q3)	4 (2, 7)	4 (2, 7)	6.5 (3, 10)	7 (3, 10)
Any history of CV risk factor	1625 (79.7%)	1607 (79.8%)	48 (96.0%)	35 (92.1%)
History of CV disease	1497 (73.4%)	1456 (72.3%)	46 (92.0%)	34 (89.5%)
History of CNS vascular disorder	147 (7.2%)	183 (9.1%)	7 (14.0%)	6 (15.8%)
History of hypercholesterolemia	708 (34.7%)	674 (33.5%)	25 (50.0%)	14 (36.8%)
History of hypertension	1248 (61.2%)	1227 (60.9%)	42 (84.0%)	32 (84.2%)
History of diabetes	664 (32.5%)	658 (32.7%)	24 (48.0%)	18 (47.4%)
Current/former smoker	533 (26.1%)	591 (29.3%)	20 (40.0%)	12 (31.6%)
eGFR 30–<60 mL/min/1.73 m²	508 (24.9%)	476 (23.6%)	17 (34.0%)	12 (31.6%)
eGFR 60–<90 mL/min/1.73 m²	1257 (61.6%)	1189 (59.0%)	27 (54.0%)	22 (57.9%)
Patients with CV-related baseline medications	1229 (60.2%)	1212 (60.2%)	39 (78.0%)	30 (78.9%)
Anti-platelet therapy	471 (23.1%)	455 (22.6%)	16 (32.0%)	11 (28.9%)
Aspirin	437 (21.4%)	421 (20.9%)	15 (30.0%)	11 (28.9%)
Statins	495 (24.3%)	474 (23.5%)	17 (34.0%)	10 (26.3%)
Beta blockers	509 (25.0%)	473 (23.5%)	22 (44.0%)	17 (44.7%)
ACE inhibitors	528 (25.9%)	489 (24.3%)	20 (40.0%)	15 (39.5%)
Angiotensin II receptor antagonists	347 (17.0%)	374 (18.6%)	12 (24.0%)	9 (23.7%)
Anti-coagulants	563 (27.6%)	537 (26.7%)	23 (46.0%)	17 (44.7%)

Data are n (%) unless otherwise noted.
*Modified after Samelson EJ, *et al.*[2] The score was determined as follows: ischaemic heart disease or central nervous system haemorrhages and cerebrovascular conditions (4 points), diabetes mellitus (3 points), age ≥70 years (2 points), age 65 to 69 years (1 point), current/former smoker (1 point), hypertension (1 point) and hyperlipidaemia (1 point); if positive for all three criteria: Smoking, hypertension and hyperlipidaemia, 1 extra point was added (i.e. total of 4 points).
CNS = central nervous system; CV = cardiovascular; eGFR = estimated glomerular filtration rate; Q1 = 25th percentile; Q3 = 75th percentile; SAE = serious adverse event; SD = standard deviation.

Upon request provided by UCB.

Saag. N Engl J Med 2017;377:1417-27

Cardiovascular safety of Romosozumab

- Er geldt een contra-indicatie voor het gebruik van romosozumab bij patiënten die eerder een myocardinfarct of beroerte hebben gehad.

- Wanneer u bepaalt of romosozumab bij een individuele patiënt kan worden gebruikt, moet u rekening houden met het risico dat zij loopt op fracturen in het komende jaar en haar cardiovasculaire risico, op basis van risicofactoren (bijv. vastgestelde cardiovasculaire aandoening, hypertensie, hyperlipidemie, diabetes mellitus, roken, ernstige nierfunctiestoornis, leeftijd). Romosozumab mag uitsluitend worden gebruikt als de voorschrijver en de patiënt het erover eens zijn dat de voordelen opwegen tegen de risico's.

- Als een patiënt een myocardinfarct of een beroerte krijgt tijdens de behandeling, moet de behandeling met romosozumab worden stopgezet.

- Le romosozumab est contre-indiqué chez les patients présentant des antécédents d'infarctus du myocarde (IDM) ou d'accident vasculaire cérébral (AVC).

- L'évaluation de la pertinence d'un traitement par romosozumab doit tenir compte du risque de fracture encouru par le patient concerné au cours de l'année à venir et de son risque cardiovasculaire, déterminé à partir de plusieurs facteurs de risque (par exemple, présence d'une maladie cardiovasculaire établie, hypertension, hyperlipidémie, diabète, tabagisme, insuffisance rénale sévère, âge). Le romosozumab doit uniquement être utilisé si le prescripteur et le patient conviennent que le rapport bénéfice/risque est favorable.

- Si un patient présente un infarctus du myocarde (IDM) ou un accident vasculaire cérébral (AVC) pendant le traitement, le romosozumab doit être arrêté.

Evenity, SmPC

Summary of anabolic treatment in Belgium

	Romosozumab	Teriparatide
Indication	Treatment of severe osteoporosis in postmenopausal women at high risk of fracture	• Treatment of osteoporosis in postmenopausal women and men at increased risk of fracture • Treatment of osteoporosis associated with sustained systemic GC use in women and men at increased risk for fracture
Contraindication	• Hypocalcaemia • History of myocardial infarction or stroke	• Pre-existing hypercalcaemia • Severe renal impairment • Metabolic bone diseases (incl. hyperparathyroidism and Paget's disease of bone) other than primary osteoporosis or GIOP • Unexplained elevations of alkaline phosphatase • Prior external beam or implant radiation R/ to the skeleton • Skeletal malignancies or bone metastases
Posology	210 mg 1x per month SC	20 µg 1x per day SC
Duration	12 months	9 months + 9 months (when ↗ T-score after 9 months)
First line	Yes	No
Second line	Yes: after previous R/ with bisphosphonates, Dmab or SERM	Yes: after previous R/ with bisphopshonate or SERM for ≥ 12 months
Reimbursement criteria	1. MOF (defined by 2020 BBC guidelines) within last 24 months 2. T-score ≤ -2.5 or a moderate VFx	1. 2 moderate VFx (1 while on-treatment with BP or SERM) 2. T-score ≤ -2.5
Follow-on treatment	Bisphosphonates or denosumab	Bisphosphonates or denosumab
Allowed physicians	Rheumatology, physiotherapy, internal medicine (incl. geriatrician)	Rheumatology, physiotherapy, internal medicine (incl. geriatrician)

How to choose between the drugs for osteoporosis? *

- Antiresorptive medication
  - Selective-estrogen receptor modulator (SERM)
  - Bisphosphonates
  - Denosumab (Prolia®)

- Anabolic medication
  - Teriparatide (Forsteo®)
  - Romosozumab (Evenity®)

* EMA approved

How to choose between the drugs for osteoporosis?

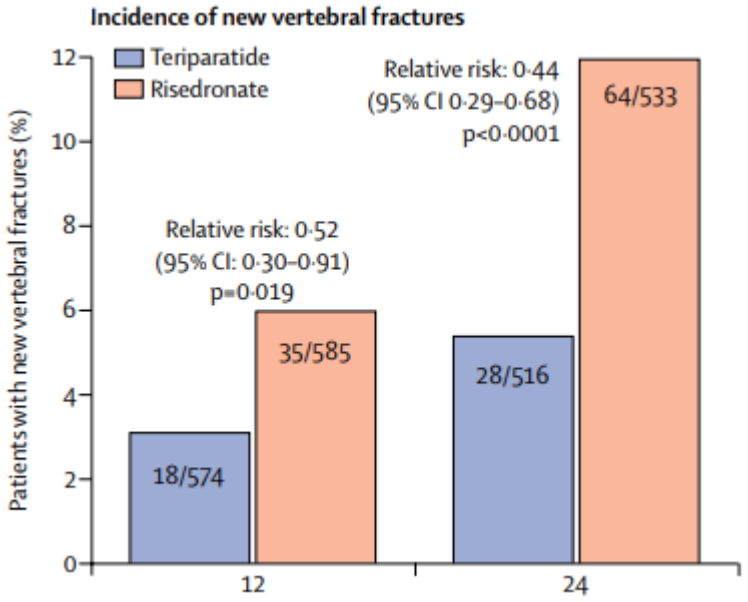
- Efficiency

Crandall. Ann Intern Med 2014;161:711-23

❖ Teriparatide compared to Risedronate (VERO trial)

1366 postmenopausal women

- ≥ 2 moderate or 1 severe vertebral fracture AND T-score ≤ -1.5
- 20 µg Teriparatide + oral placebo *vs.* 35 mg Risedronate + sc placebo, 24 months



	Teriparatide group	Risedronate group	Effect size (95% CI)*	p value
Primary endpoint				
New vertebral fracture†	28 (5%)	64 (12%)	0·44 (0·29–0·68)	<0·0001
Secondary gated endpoints				
New and worsened vertebral fracture†	31 (6%)	69 (13%)	0·46 (0·31–0·68)	<0·0001
Pooled clinical fracture‡§	30 (5%)	61 (10%)	0·48 (0·32–0·74)	0·0009
Non-vertebral fragility fracture§	25 (4%)	38 (6%)	0·66 (0·39–1·10)	0·10
Major non-vertebral fragility fracture§	18 (3%)	31 (5%)	0·58 (0·32–1·05)	0·06
Secondary non-gated endpoints				
New moderate (SQ2) or severe (SQ3) vertebral fracture†	26 (5%)	63 (12%)	0·42 (0·27–0·65)	<0·001
New multiple vertebral fracture†	2 (<1%)	12 (2%)	0·16 (0·04–0·74)	0·007
Pooled fragility and traumatic non-vertebral fracture§	40 (7%)	57 (9%)	0·70 (0·46–1·05)	0·08

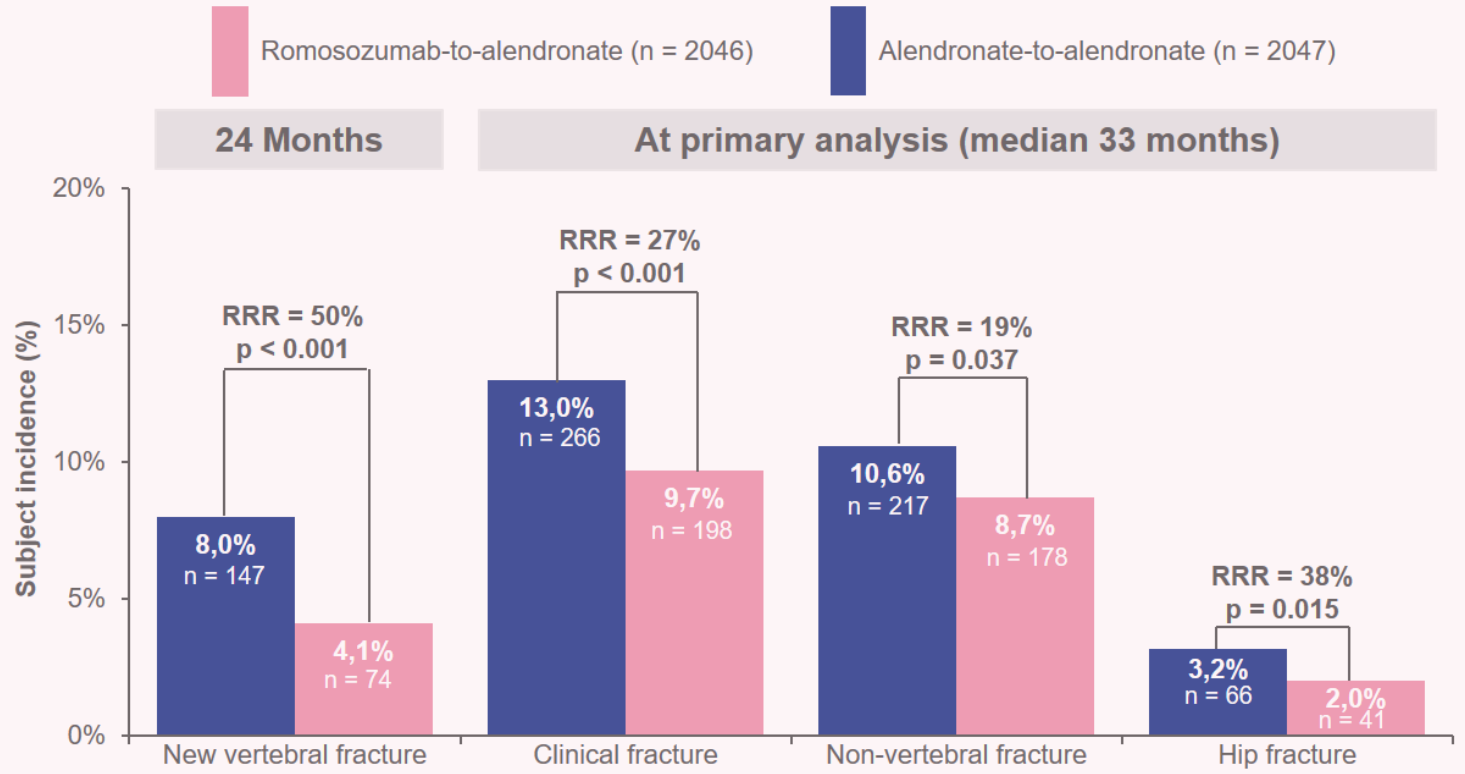
Subgroup analyses of fracture data across subgroups:

- age, previous fractures, GC use, prior/recent osteoporosis R/, baseline BMD

➔ most fracture risk reduction did not significantly differ in any of the subgroups
eg. TPT is superior to RIS in both osteoporosis R/ naïve and previously treated pts

Kendler. Lancet 2018; 391: 230-240; Geussens. J Bone Miner Res 2018; 33: 783-794

❖ Romo + ALN compared to ALN + ALN (ARCH trial)

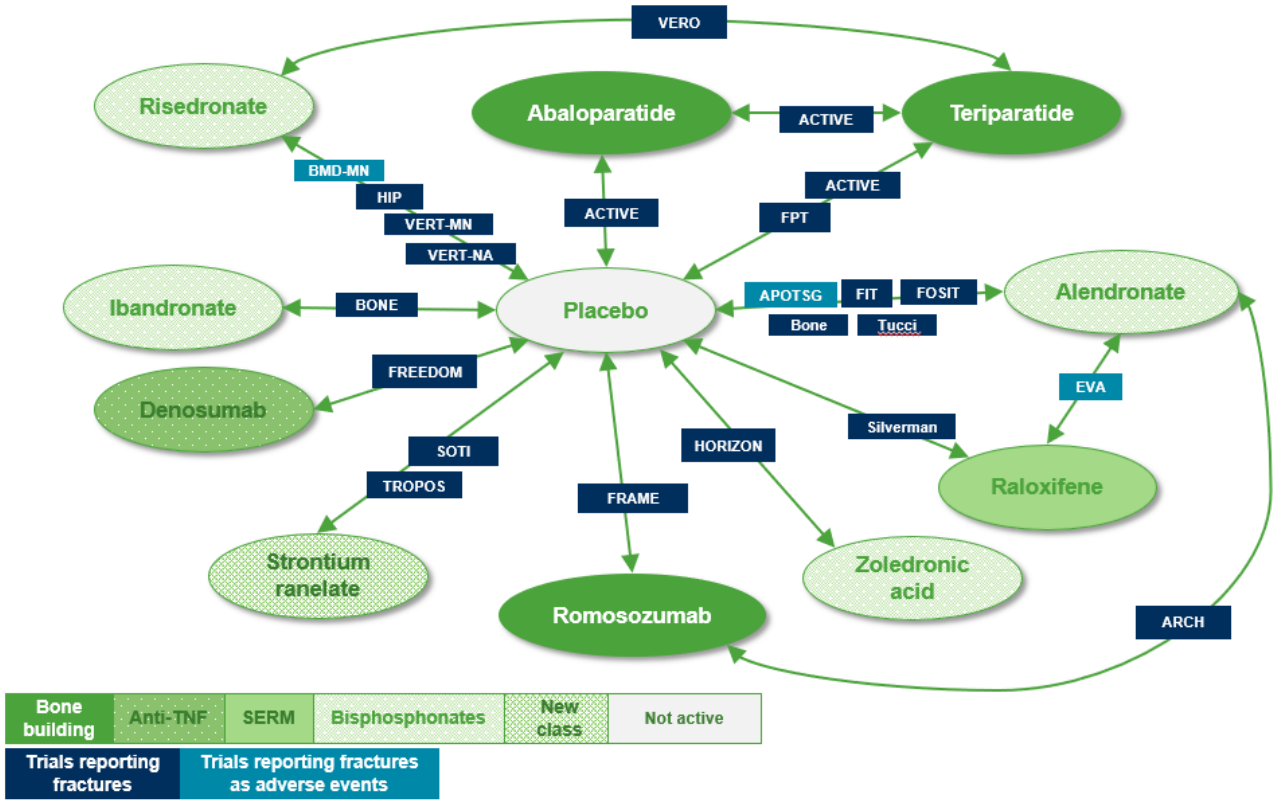


Incidence of fractures through 24 months and at primary analysis

Saag. N Engl J Med 2017; 377: 1417-27

❖ Network meta-analysis

- Lack of direct head-to-head trials to determine the comparative effectiveness of various drugs for OP.
- NMA = statistical analysis that synthesizes information over a network of (direct and indirect) comparisons to assess the relative effects of various drugs for OP.



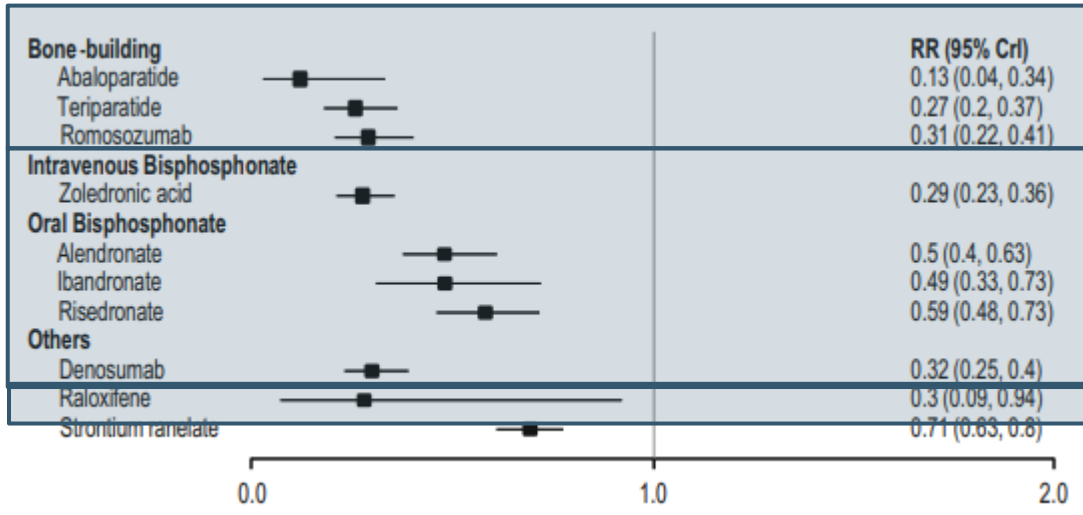
Non-vertebral fracture network

Reginster. Osteoporos Int 2019; 30: 1465–1473

❖ Network meta-analysis

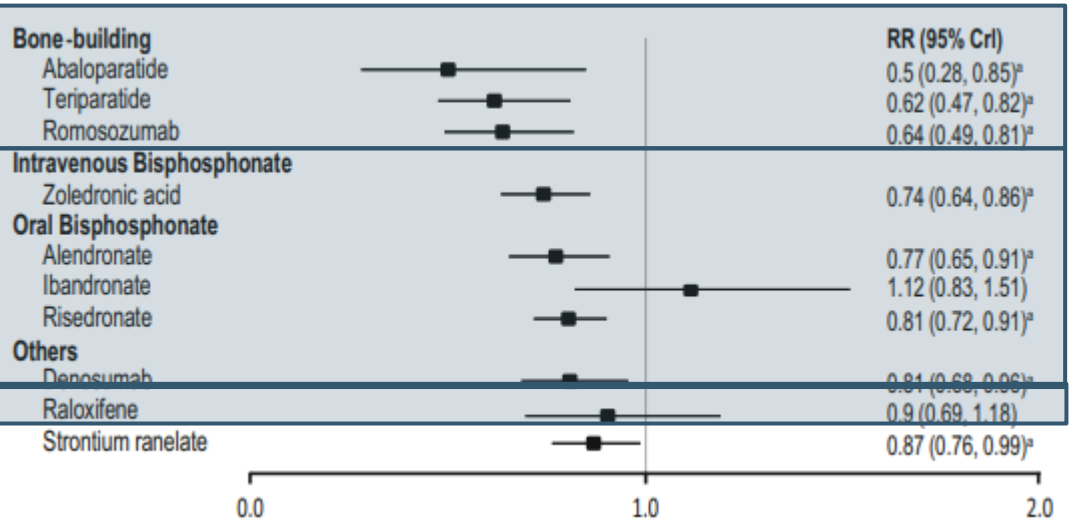
- Lack of direct head-to-head trials to determine the comparative effectiveness of various drugs for OP.
- NMA = statistical analysis that synthesizes information over a network of (direct and indirect) comparisons to assess the relative effects of various drugs for OP.

Relative risk of treatments vs. placebo in the vertebral fractures network



Treatment effects were significantly different for all treatments versus placebo

Relative risk of treatments vs. placebo in the nonvertebral fracture network

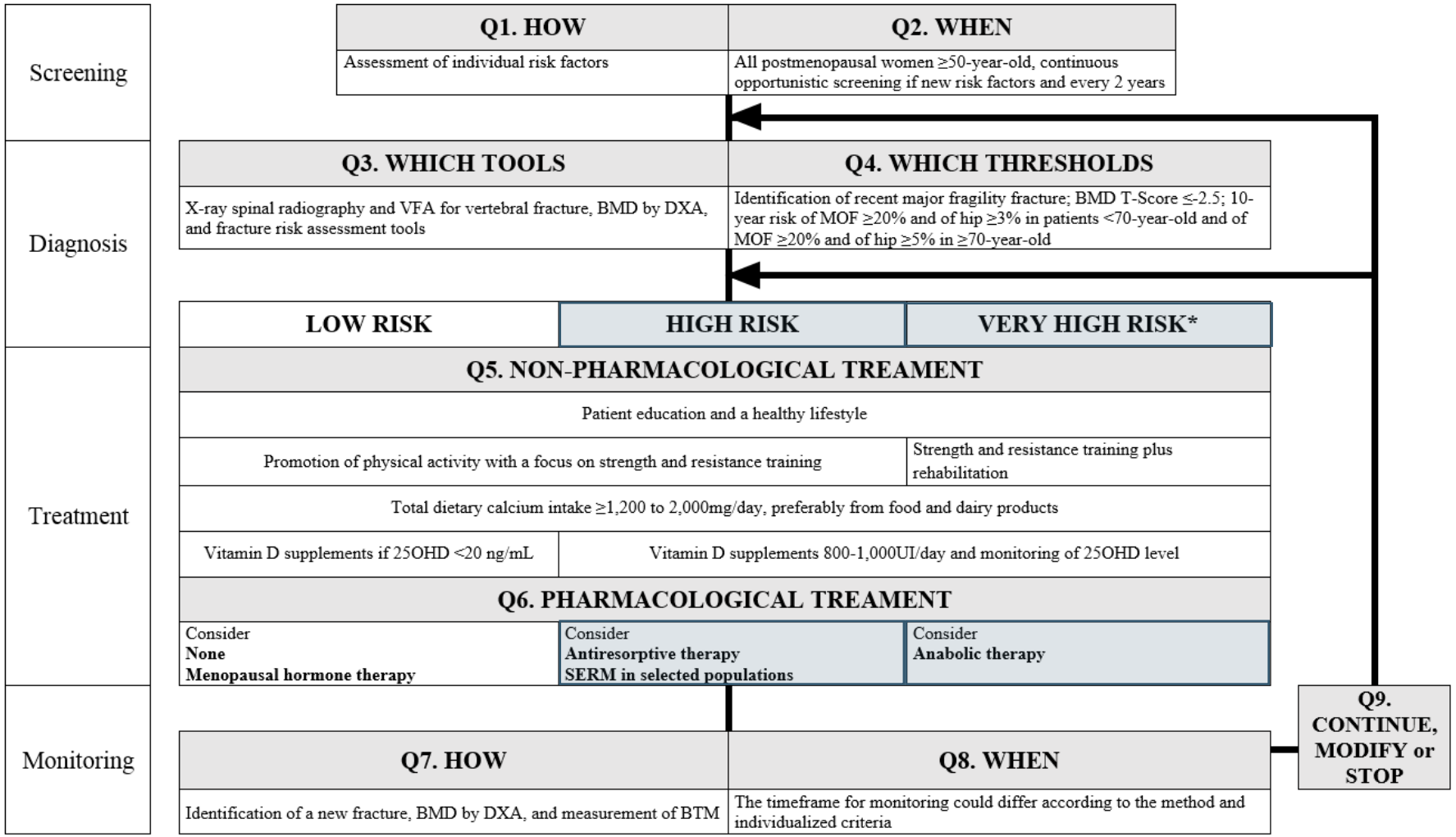


[a] Abaloparatide effect significantly different from network treatment

Reginster. Osteoporos Int 2019; 30: 1465–1473

Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women

Treatment of persons at low, high and very high fracture risk



*For forearm fractures, only women aged ≥75-year-old are considered at very high risk

Sanchez-Rodriguez. Maturitas 2020; 139: 69-89

How to choose between the drugs for osteoporosis?

- **Antiresorptive medication**
  - Selective-estrogen receptor modulator (SERM)
  - Bisphosphonates
  - Denosumab (Prolia®)

For patients at high risk of fractures

- **Anabolic medication**
  - Teriparatide (Forsteo®)
  - Romosozumab (Evenity®)

For patients at very high risk of fractures

* EMA approved

How to choose between the drugs for osteoporosis?

- Efficiency
  - Oral bisphosphonate > Zoledronic acid, Denosumab > Romosozumab, Teriparatide
  - Potential extra-skeletal advantages (eg. SERM)
- Cost & reimbursement
  - Strict reimbursement criteria in Belgium
  - Oral bisphosphonate > Zoledronic acid, Denosumab > Romosozumab > Teriparatide
- Side effects & contra-indications
  - Renal insufficiency, gastric ulcers
  - Frequent: mild side effects (gastro-intestinal, acute-phase reaction)
  - Very rare: medication-related ONJ, atypical femoral fracture
- Compliance, mode of administration and patient preferences
  - Generally low (parenteral > oral)
  - Long-acting bisphopshonates
- Shared-decision making

Crandall. Ann Intern Med 2014;161:711-23

Overview

I. Introduction

II. Who should receive osteoporosis treatment?

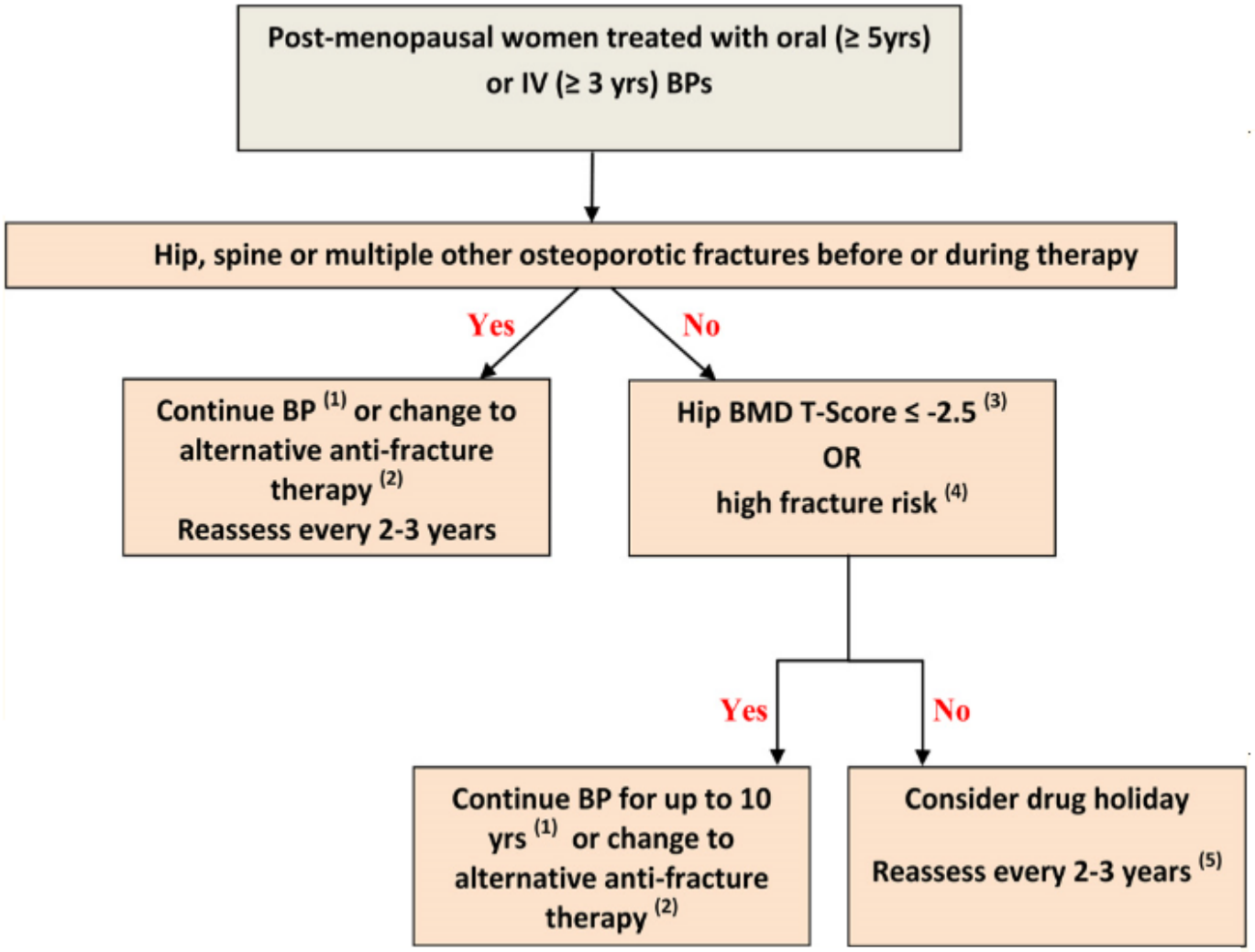
III. How to choose between the drugs for osteoporosis?

IV. Duration of treatment, drug holiday & treatment failure

V. Sequential osteoporosis treatment

VI. Conclusion

Long-term osteoporosis management



After 5 years of po BP or 3 years of ZOL IV

- T-score > -2,5 + no previous #
  [or T > -2,0 + 1 previous vertebral #]
  AND no new # during R/
  ➔ drug holiday + reevaluation after 2-3 years
  (earlier for Ris , NOT for Dmab)

- T-score ≤ -2,5
  OR: previous hip# or ≥ 2 vertebral#
  OR: new # during R/
  ➔ Oral BP: 10 years
  ➔ ZOL: 1x/year for 6 years

➔ After 6x ZOL 1x/y: usually drug holiday possible

➔ What in case of incident osteoporotic fractures?
➔ What if persistent high fracture risk after 6-10 y?
➔ *change to alternative anti-fracture R/ ?*

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

Long-term osteoporosis management

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

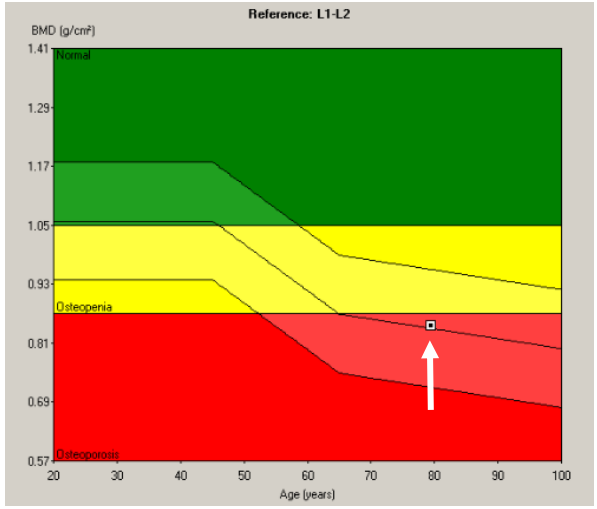
Reference marker	Origin	Further details
s-PINP Serum procollagen type I N propeptide	Precursor molecules of collagen type I synthesised by osteoblasts	Specificity: mostly derived from bone collagen type I Assay: may recognise trimer alone (intact) or trimer and monomer (total PINP) Source of variability: 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)

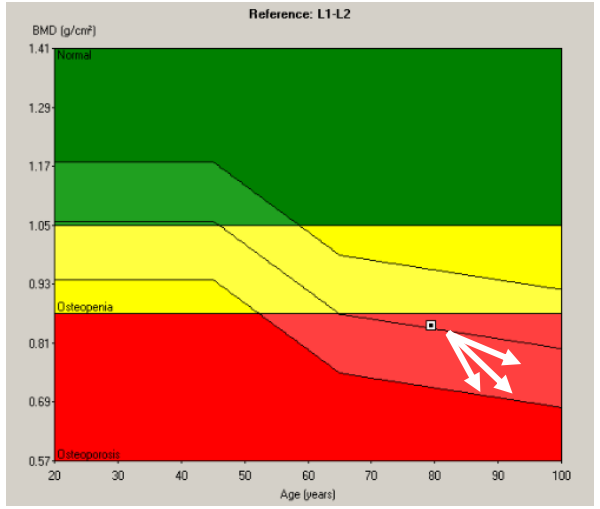
Garnero. J Bone Miner Res 1996; 11: 1531-7

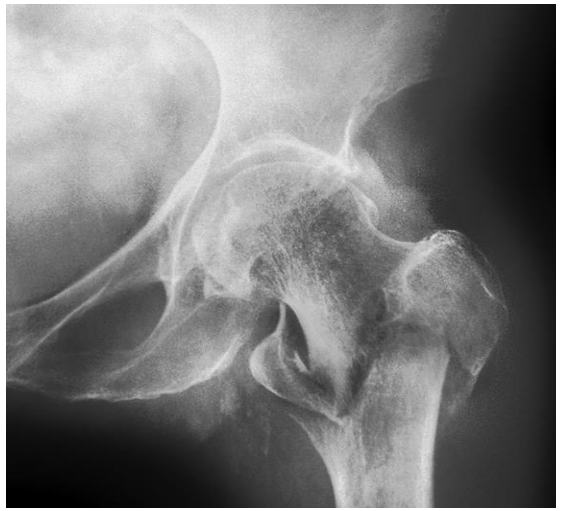
Use of bone turnover markers

❶ No consistent data to support clinical utility of BTMs to

- predict (low) bone mass/osteoporosis
- predict bone loss
- predict fracture risk







Cavalier. Osteoporos Int 2016; Eastell. Lancet Diabetes Endocrinol 2017; 5: 908-23

Use of bone turnover markers

❷ BTMs can be used to monitor the treatment of osteoporosis

ANTIRESORPTIVE TREATMENT

A decrease, greater than least significant change:

- P1NP: decrease of ≥ 20%
- CTX: decrease of ≥ 31%

Value below mean value of healthy young women:

- P1NP < 35 µg/l
- CTX < 280 ng/l

Measured at baseline & 3 months after start of therapy

❸ Can BTMs be used to indicate need to re-start therapy during drug holiday?

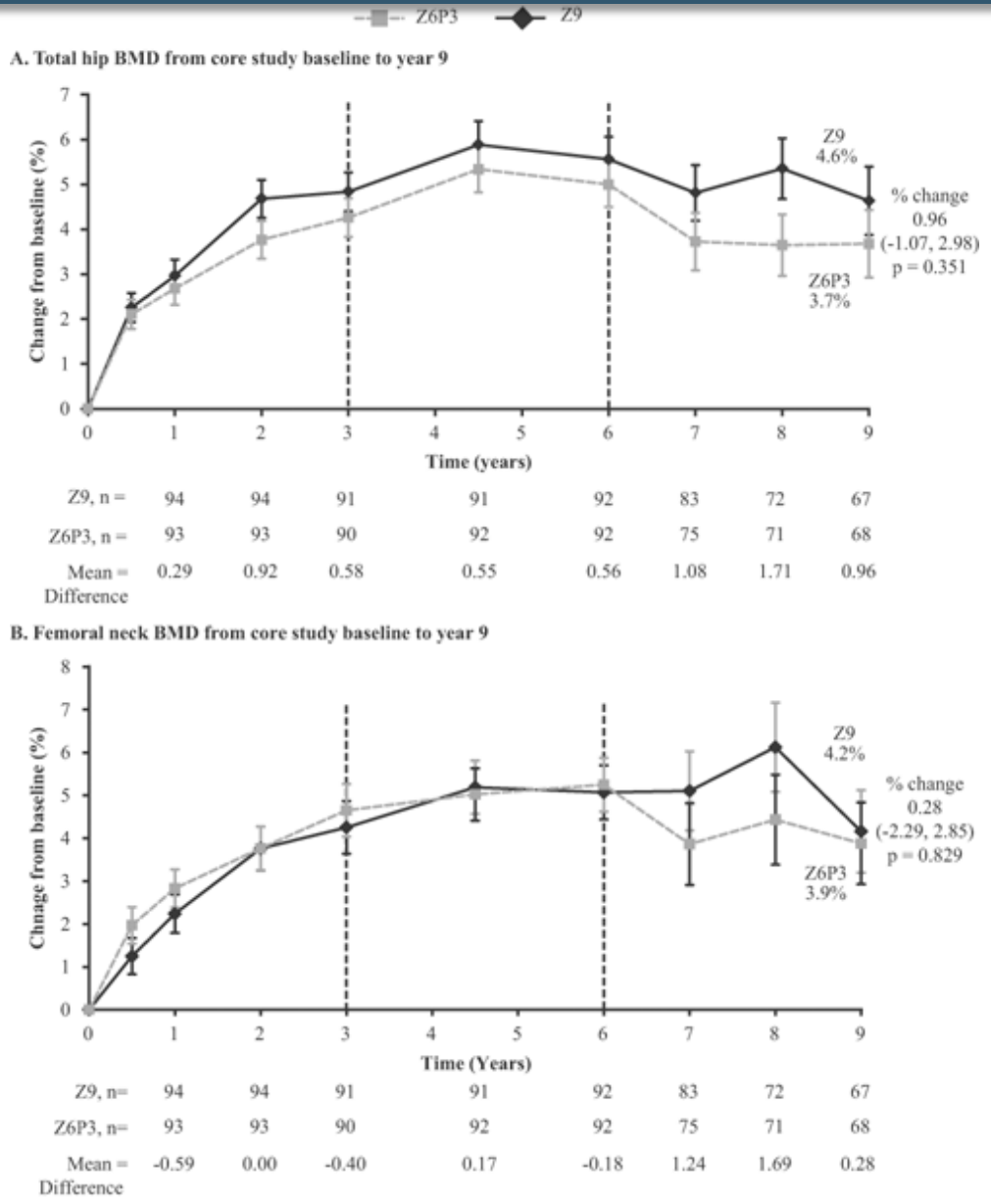
These changes in BTMs could potentially be used to indicate when therapy should be re-started after a drug holiday

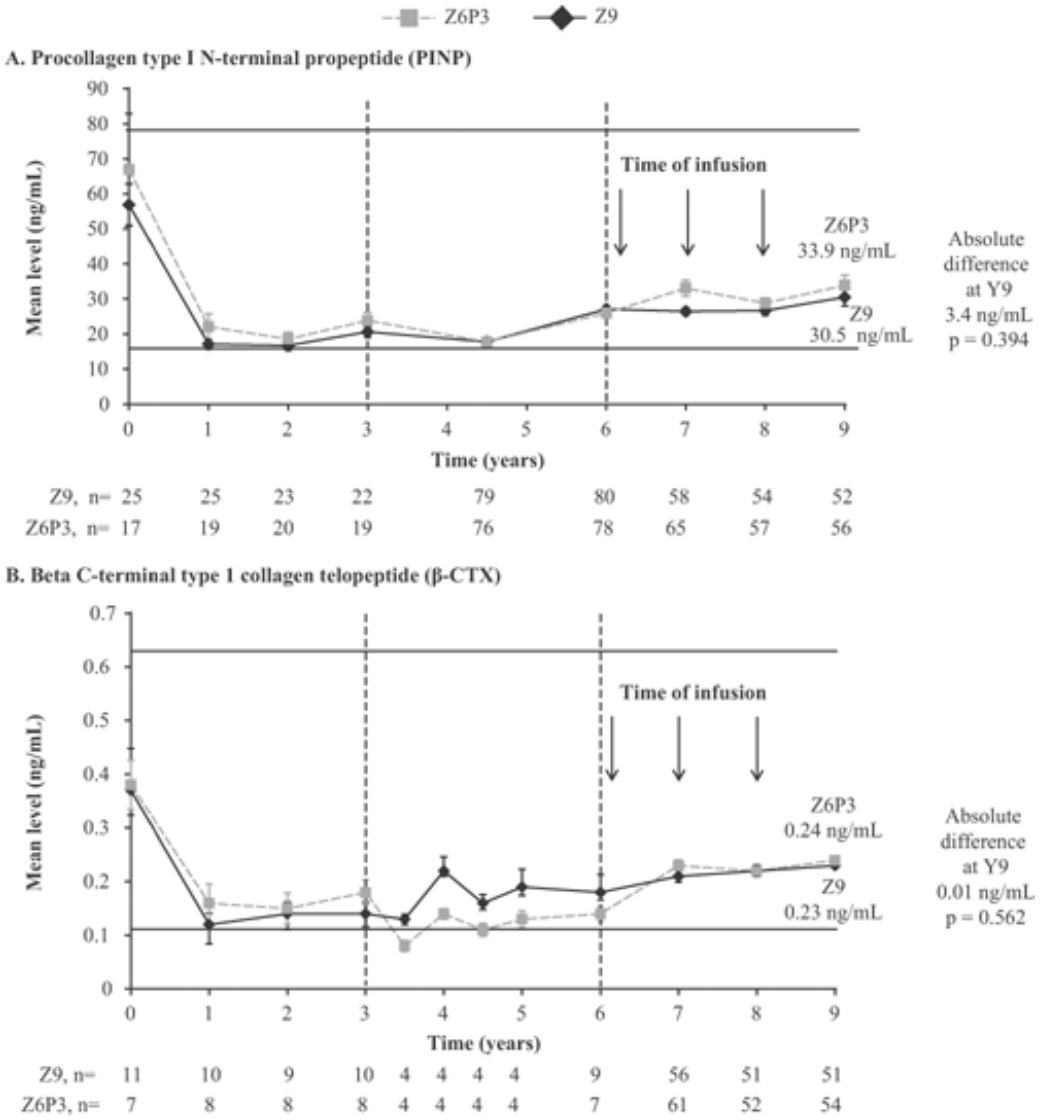
This approach needs further research!

Sanchez-Rodriguez. Maturitas 2020; 139: 69-89;
Cavalier. Osteoporos Int 2020; 31: 1461-70; Eastell. Eur J Endocrinol 2018; 178: 19-31; Eastell. 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

❖ Incident fracture during treatment

- No osteoporosis therapy reduces fracture risk to zero, certainly not in patients at high fracture risk
- Treatment failure is defined as
  - ≥ 2 incident fragility fractures
  - 1 incident fragility fracture AND [no significant decrease in BTM* OR a significant decrease in BMD**]
  - no significant decrease in BTM* AND a significant decrease in BMD**

* **Significant decrease in BTM under antiresorptives:**
decline > LSC (~ 25%) from baseline levels after 6 months
** **Significant decline in BMD under antiresorptives:**
≥ 5% at lumbar spine
≥ 4% at proximal femur

⇔ 1 new fracture during treatment = usually *bad luck*
(~ age, risk of falls, high fracture risk)

- Treatment failure: rare when compliant & no new secondary OP

In osteoporosis speciality center: **10% non-responders**
(50% had previously unrecognized contributing factors)
° Comorbid conditions ° Metabolic factors ° Poor adherence ° Wrong dosing interval
° Malabsorption ° Ca & vit D deficiency ° Wrong dose ° Lack of efficacy

❖ Persistent high fracture risk after 6-10 y

- Lack of data on **treatment** beyond 10 years in persons at high- fracture risk
- Individualized approach:
  - assessment of the patient's individual risk profile
  - risk-benefit analysis
  - shared decision making with the patient
  - careful follow-up

Diez-Perez. Osteoporos Int. 2012;23:2769-74; Lewiecki. J Clin Densitom 2003; 6: 307-14; Adler. J Bone Miner Res 2016; 31: 16-35

❖ Incident fracture during treatment ❖ Persistent high fracture risk after 6-10 y

Expert opinion suggests replacement of

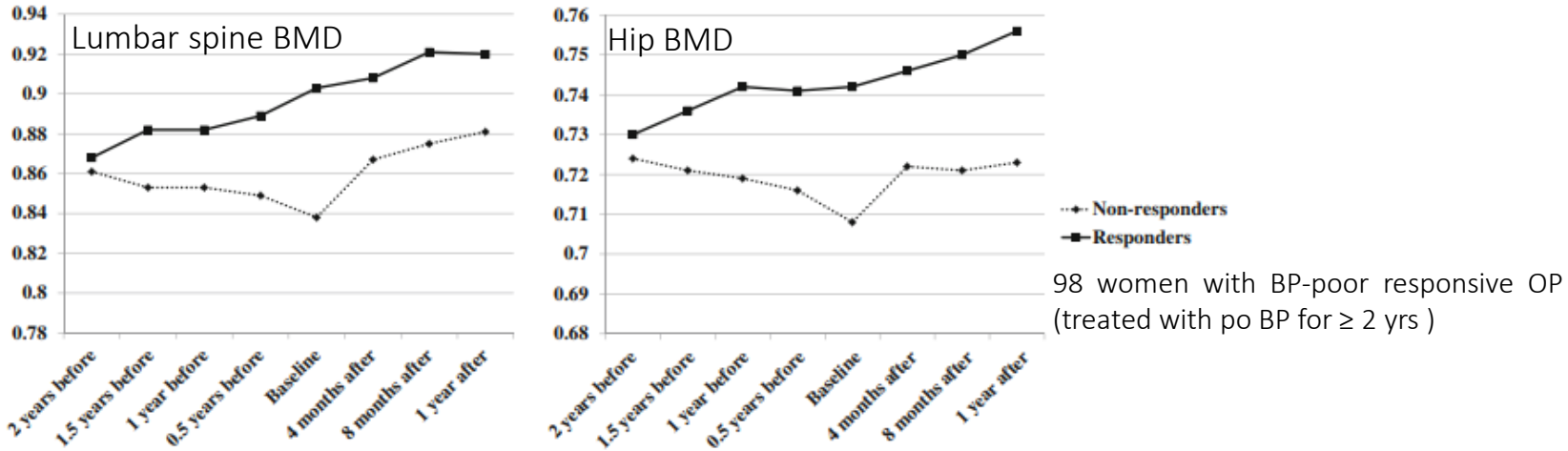
- oral drug by parenteral treatment
- weaker by stronger antiresorptive therapy
- antiresorptive therapy by anabolic therapy

~ Replacement of BP by Dmab ?!

Denosumab versus bisphophonates for the treatment of postmenopausal osteoporosis

- Both in treatment-naïve and BP-pretreated patients: Dmab resulted in a significant increase in BMD at all skeletal sites
- No head-to-head trials with fracture endpoints

- Significant improvement in BMD by Dmab in BP-unresponsive patients



98 women with BP-poor responsive OP (treated with po BP for ≥ 2 yrs)

Diez-Perez. Osteoporos Int. 2012;23:2769-74; Kamimura. Osteoporos Int 2017; 28: 559-66

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Sequential therapy for osteoporosis

① Sequential therapy with Teriparatide (Forsteo®)

② Sequential therapy with Romosozumab (Evenity®)

③ Denosumab (Prolia®): rebound-associated vertebral fractures

① Sequential therapy with Teriparatide

Teriparatide should be followed by treatment with …

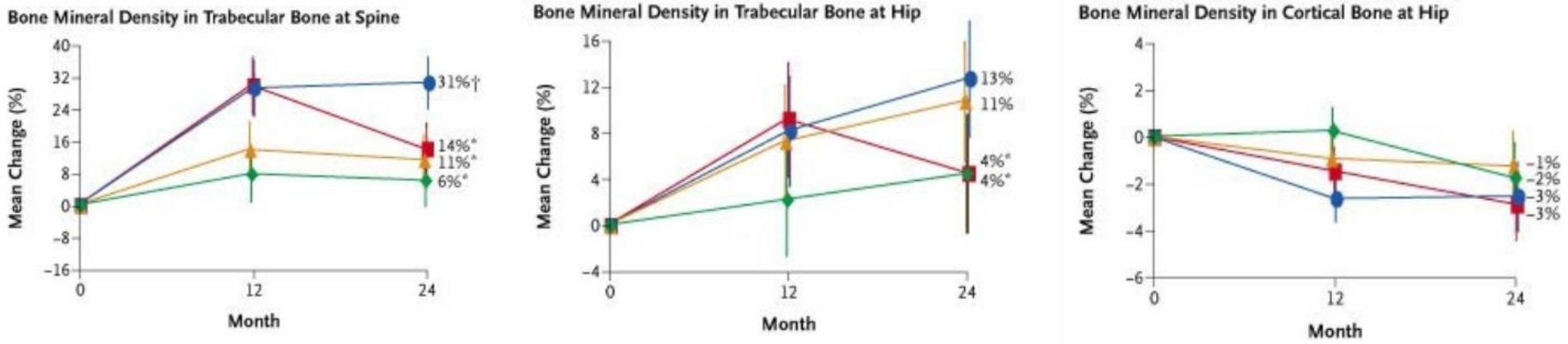
Antiresorptive therapy
- Bisphosphonate

→ Teriparatide →

Antiresorptive therapy
- Bisphosphonate
- Denosumab

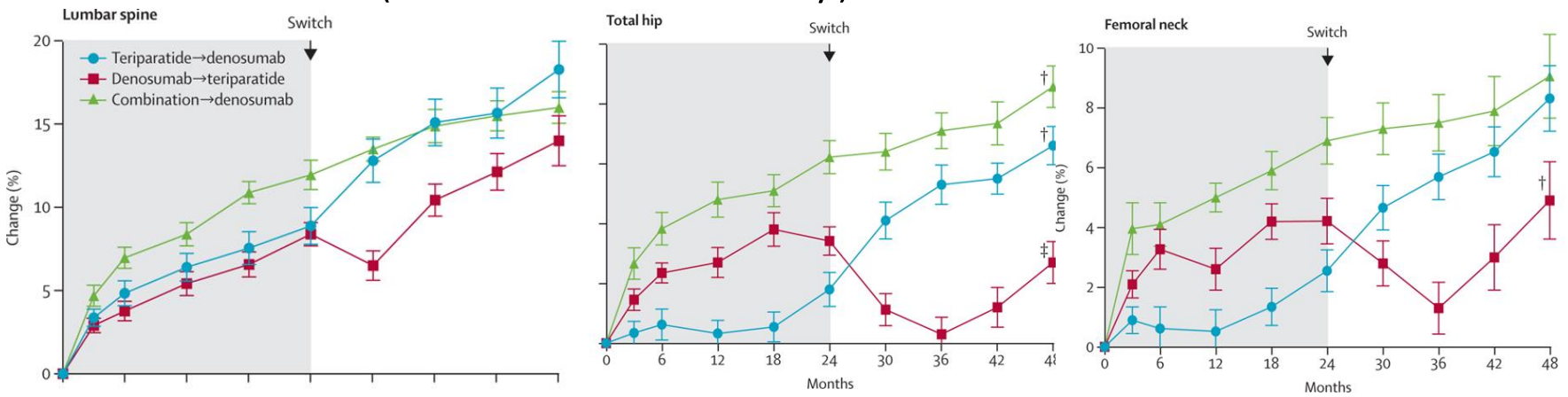
- Bisphosphonates

YES!



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

- Denosumab (DATA –Switch study)



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

YES!

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

Teriparatide (TPT) may follow previous treatment with …

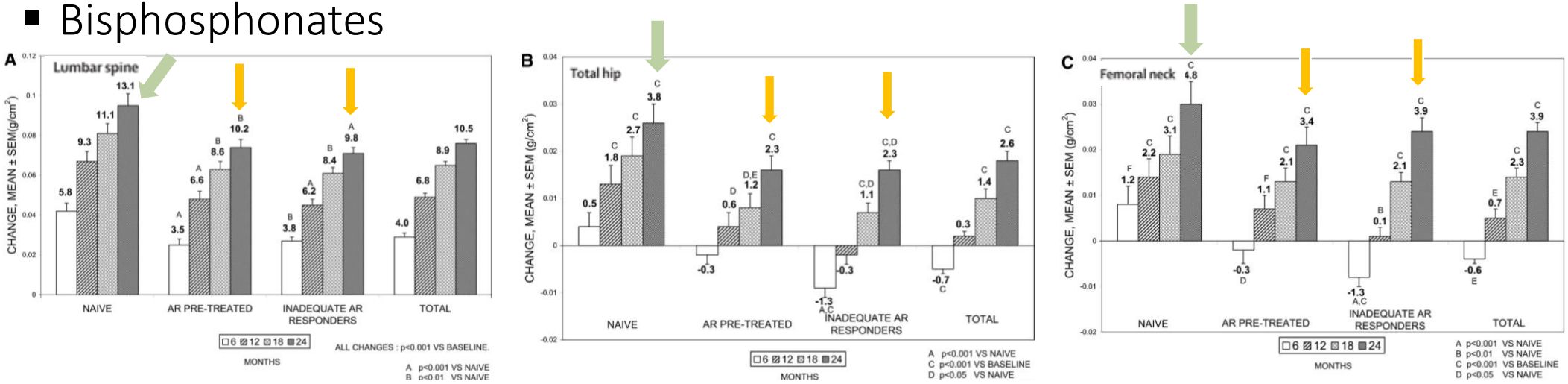
Antiresorptive therapy
- Bisphosphonate

→ Teriparatide →

Antiresorptive therapy
- Bisphosphonate
- Denosumab

- Bisphosphonates

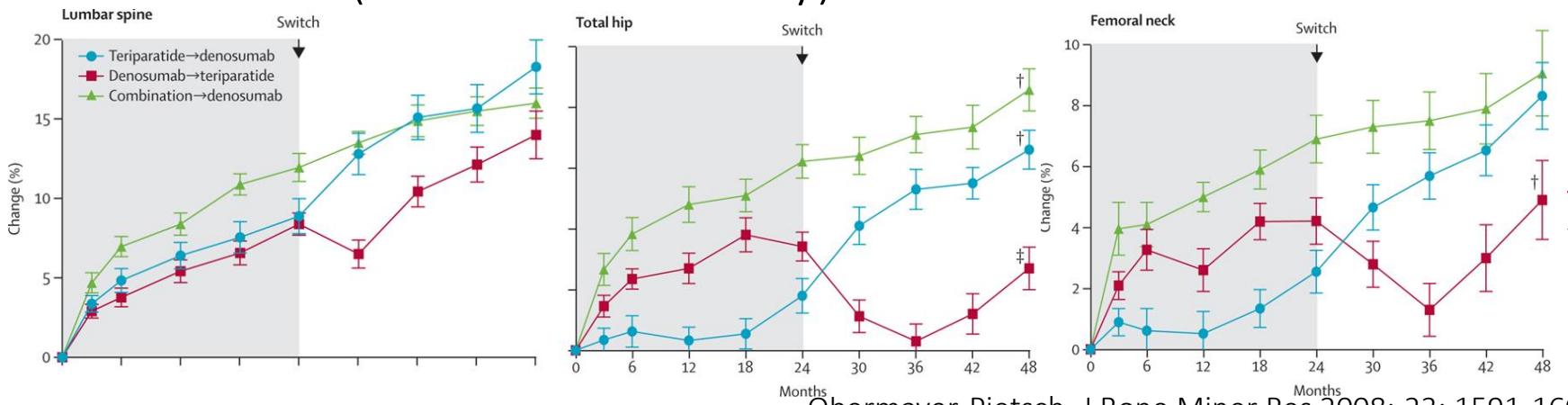
YES!



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)

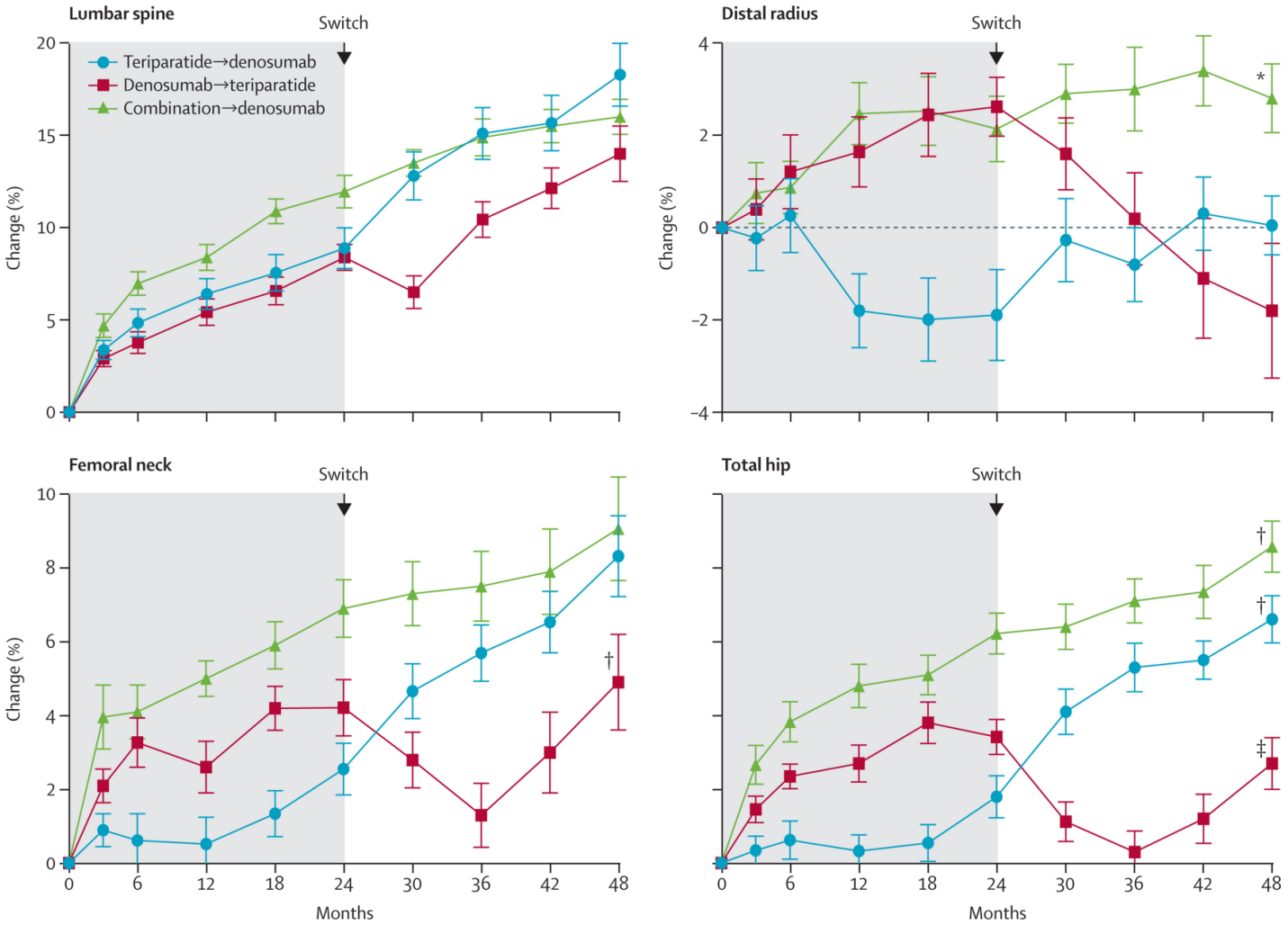
NO!



In postmenopausal 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

Thus, transitioning from TPT to Dmab, but not from Dmab to TPT!



Combinatie ➔ Dmab

Teriparatide ➔ Dmab

Dmab ➔ Teriparatide

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

② Sequential therapy with Romosozumab

FRAME Study
(treatment-naive)

Romosozumab → Antiresorptive therapy
- Denosumab

ARCH Study
(treatment-naive)

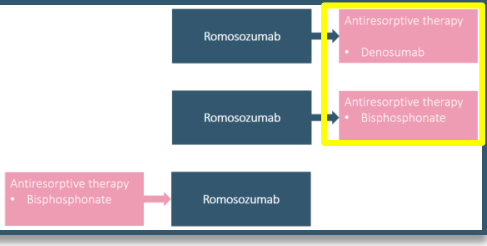
Romosozumab → Antiresorptive therapy
- Bisphosphonate

STRUCTURE Study
(pretreatment ALN)

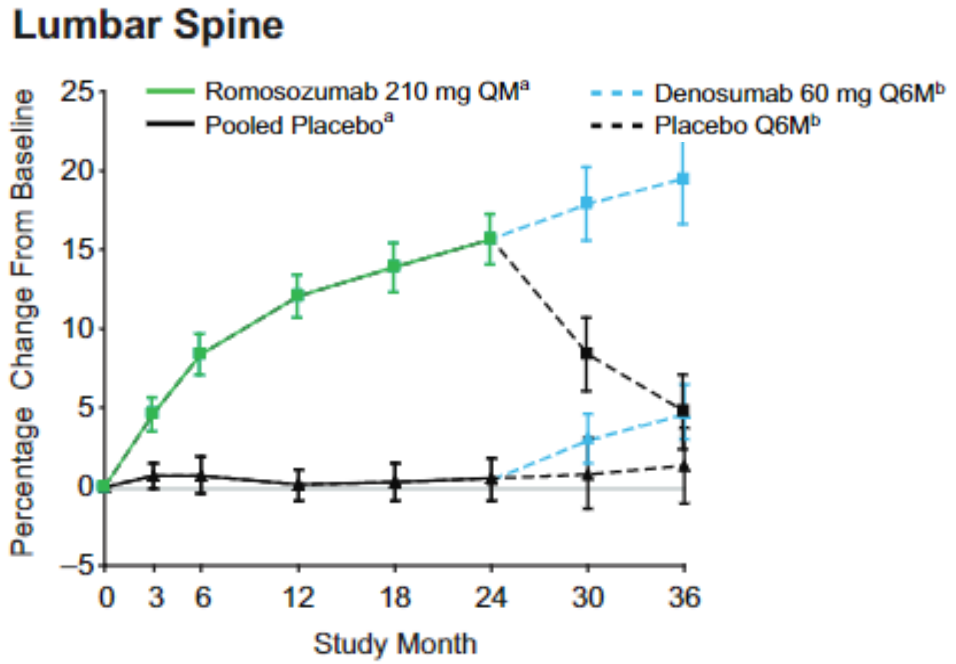
Antiresorptive therapy
- Bisphosphonate

→ Romosozumab

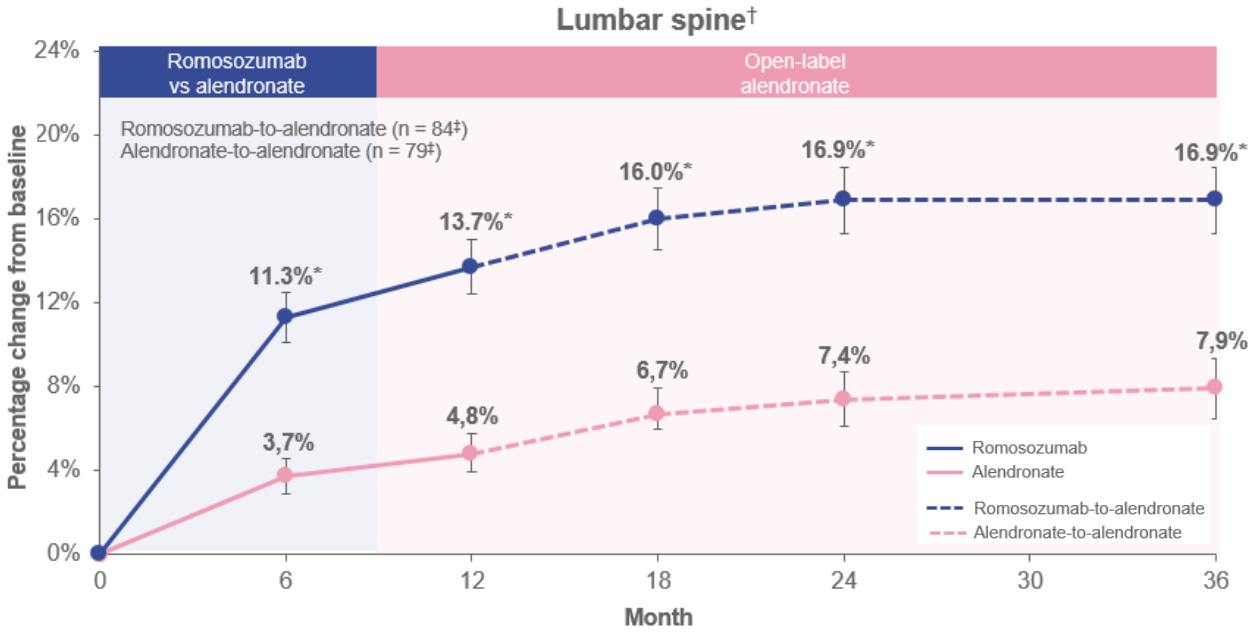
Follow-on treatment after discontinuation of Romosozumab



After discontinuation of Romosozumab, BMD returns to pretreatment levels with placebo
So, consolidation with antiresorptive therapy is needed after 12 months



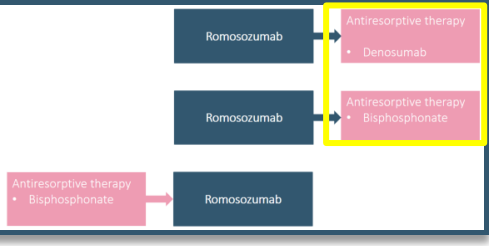
Phase 2 RCT in women aged 55 to 85 years
T-score ≤ –2.0 at LS, TH or FN and ≥ –3.5 at each of these



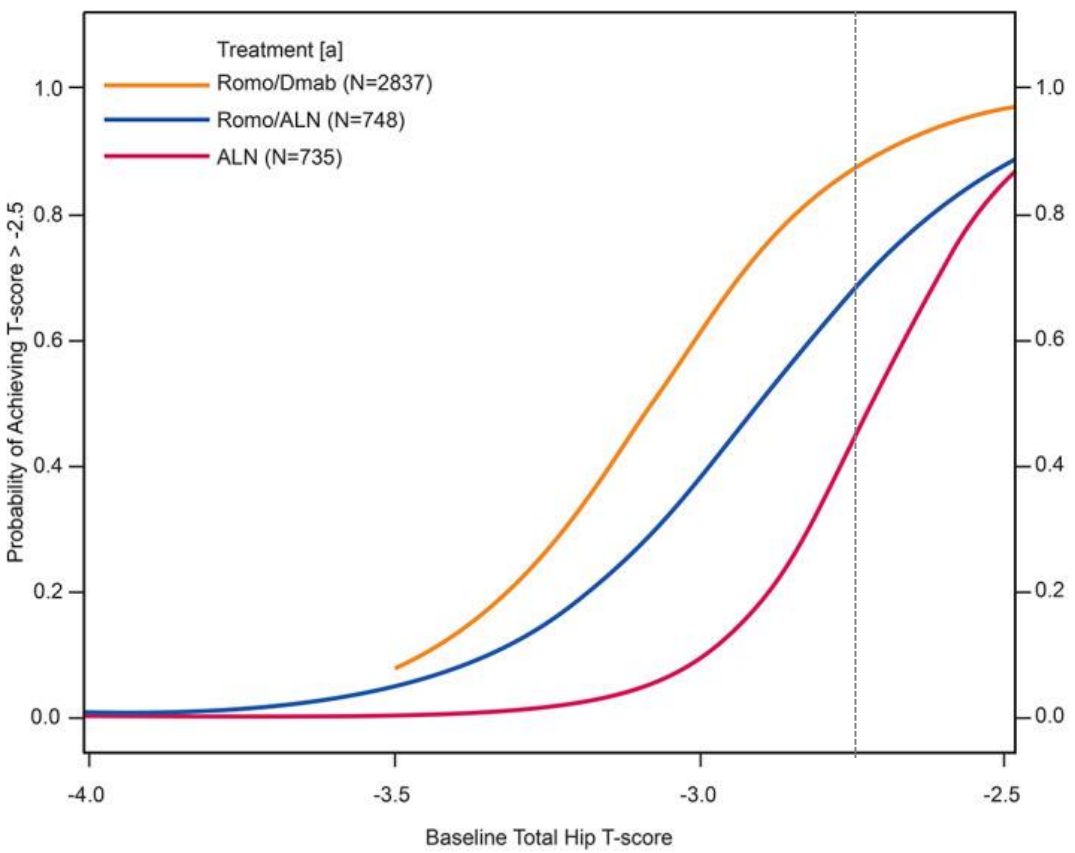
ARCH Study (Romo + ALN vs. ALN +ALN)

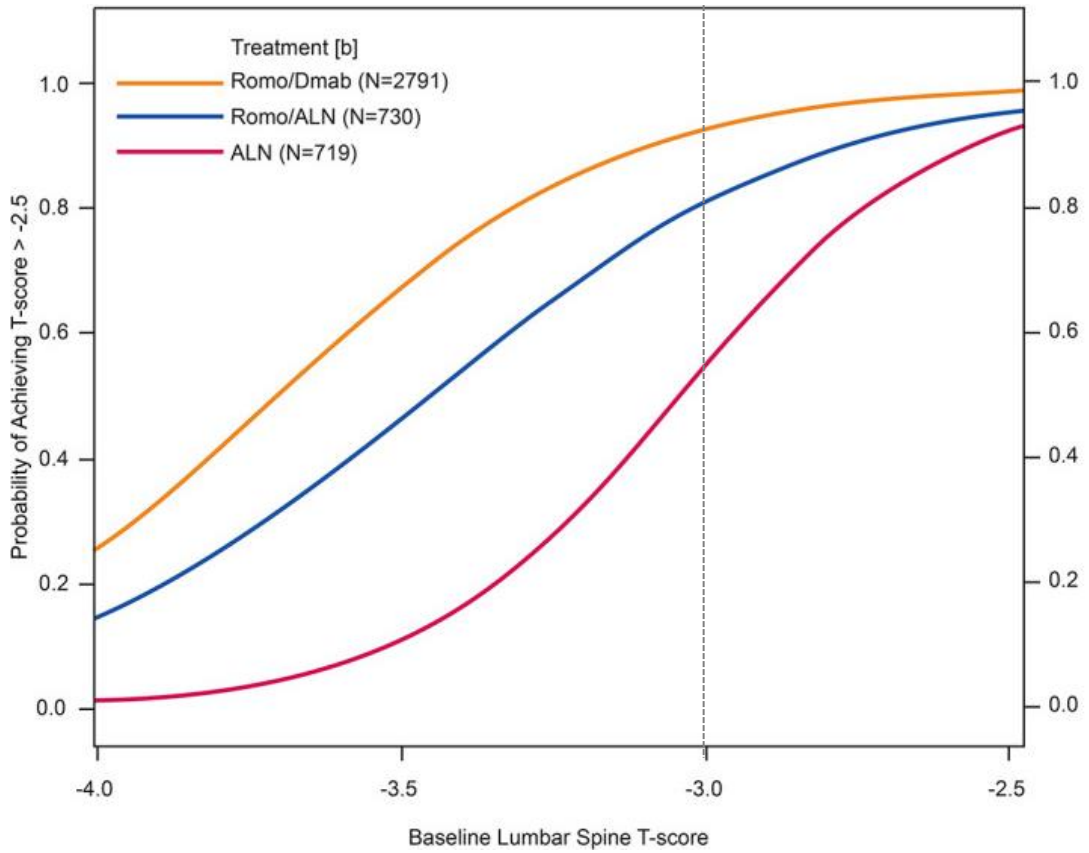
McClung. J Bone Miner Res 2018; 33: 1397-1406; Saag. N Engl J Med 2017;377:1417-27

Follow-on treatment after discontinuation of Romosozumab



Probability of achieving BMD treatment goals

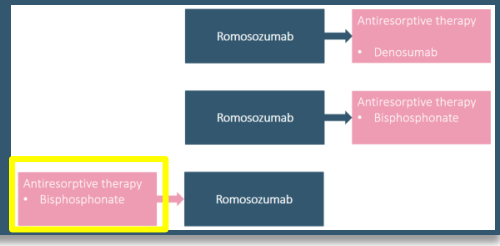




As baseline T-score falls below -2.7 (TH) and -3.0 (LS), ALN has <50% likelihood of achieving a BMD goal above osteoporosis range, whereas these probabilities remain relatively high for regimens beginning with Romo

Cosman. J Bone Miner Res Plus 2021; 5: e10546

② Sequential therapy with Romosozumab



FRAME Study
(treatment-naive)

Romosozumab → Antiresorptive therapy
- Denosumab

ARCH Study
(treatment-naive)

Romosozumab → Antiresorptive therapy
- Bisphosphonate

STRUCTURE Study
(pretreatment ALN)

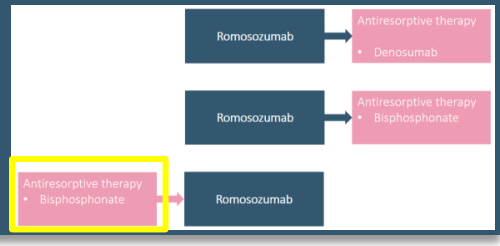
Antiresorptive therapy
- Bisphosphonate

→ Romosozumab

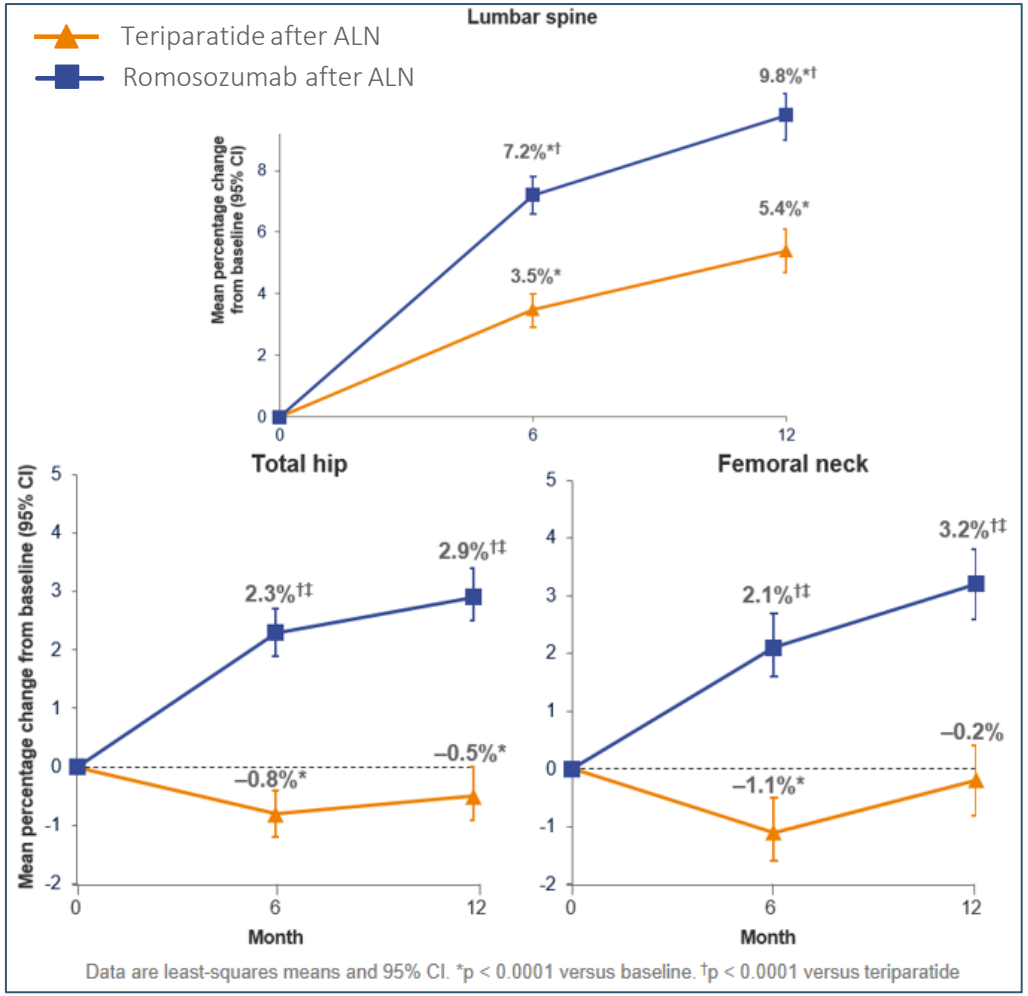
Denosumab?

Blunting (as for TPT)?

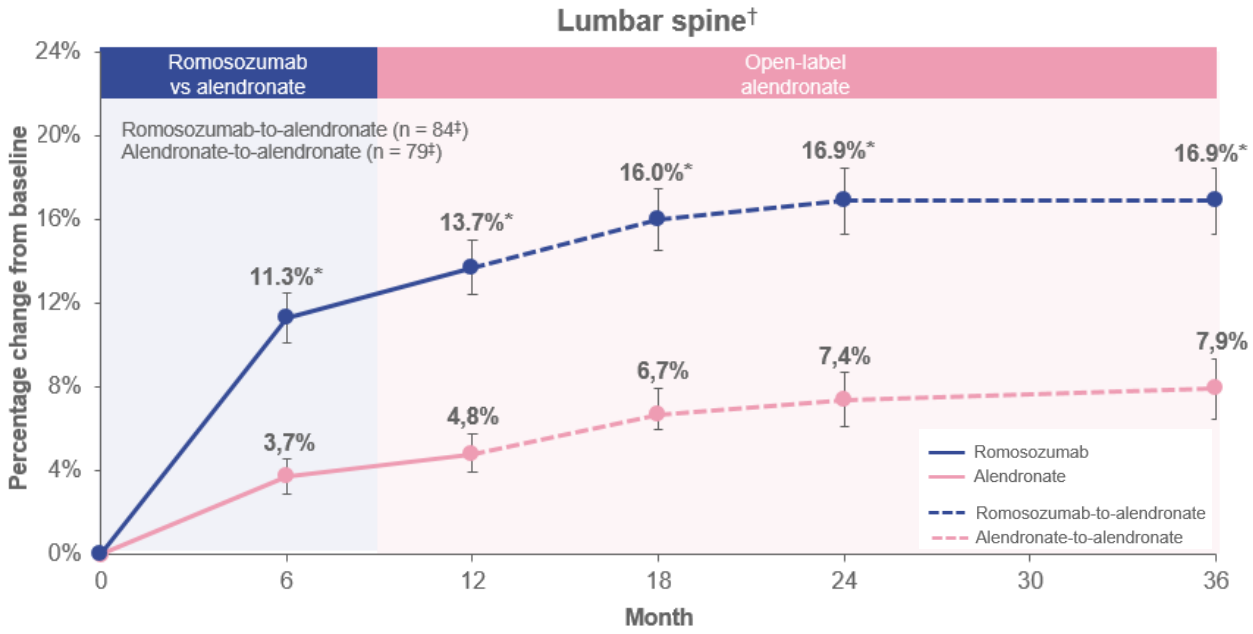
Romosozumab in second line:
previous treatment with bisphosphonate or not in Phase 3 trials



Romosozumab after oral bisphosphonate
STRUCTURE[1]

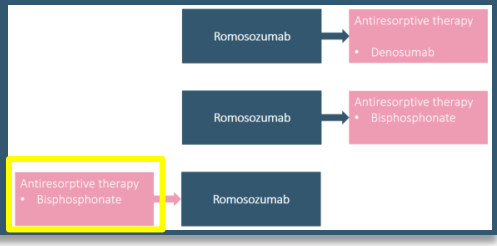


Romosozumab in treatment naive patients
ARCH[2]

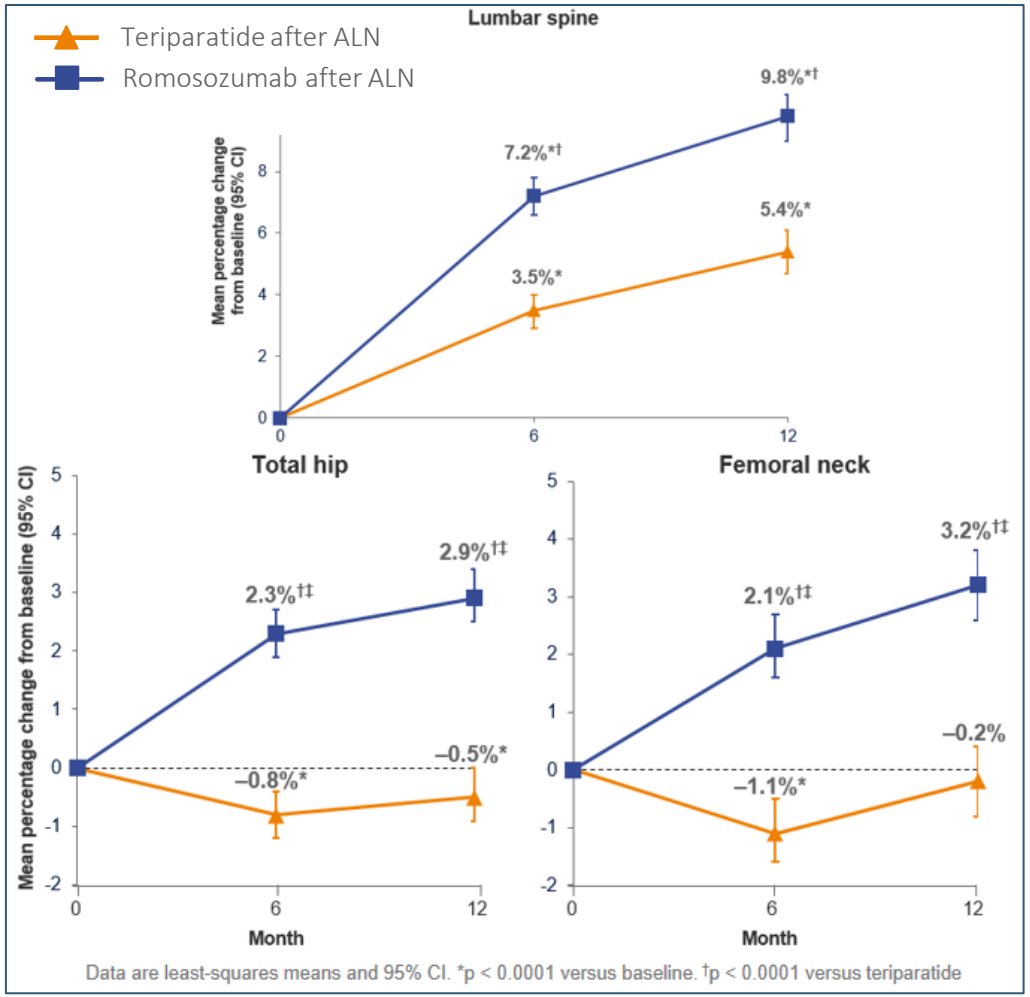


[1]Langdahl. Lancet 2017; 390: 1585-94; [2]Saag. N Engl J Med 2017;377:1417-27

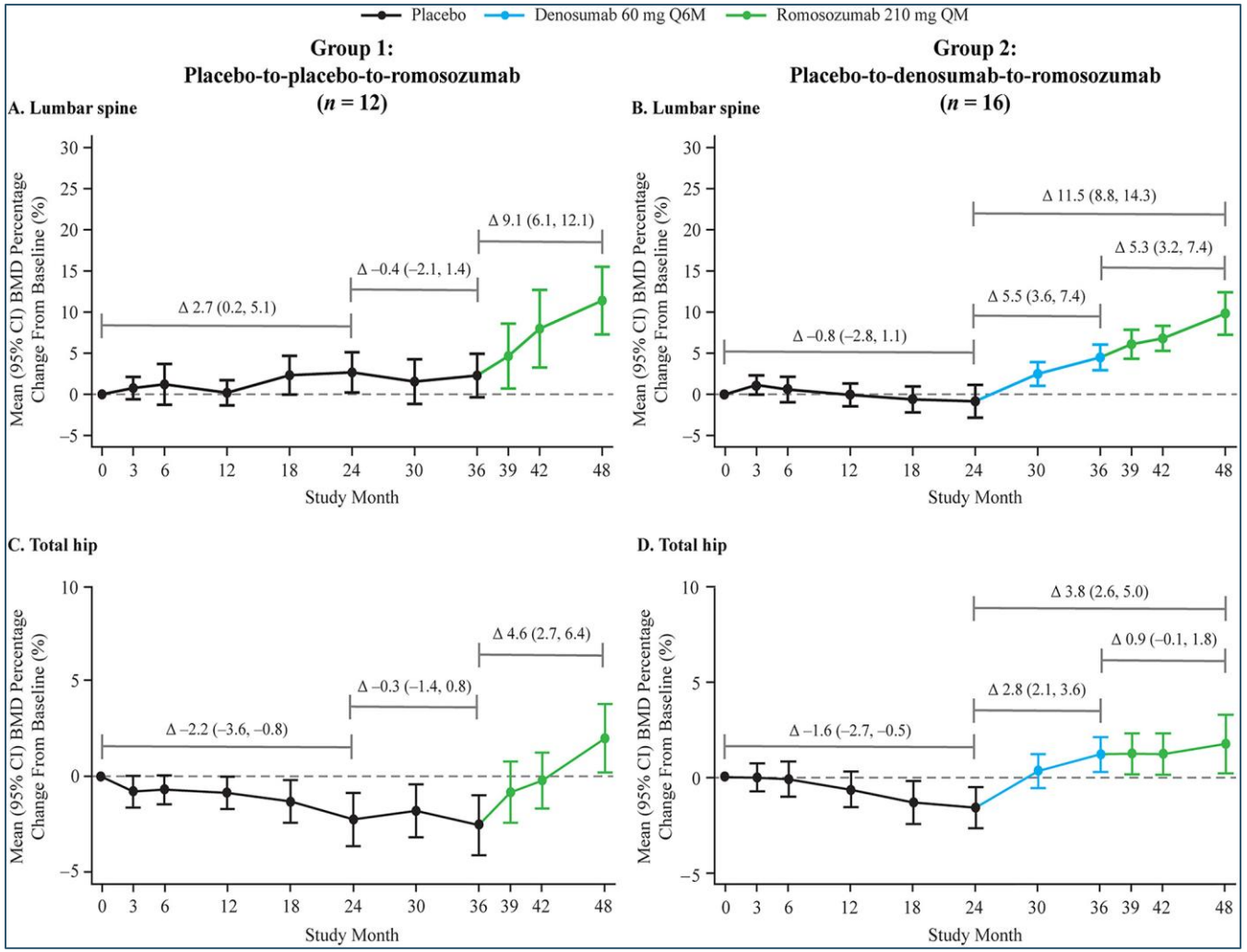
Romosozumab in second line:
previous treatment with bisphosphonate or denosumab in Phase 2 & 3 trials



Romosozumab after oral bisphosphonate
STRUCTURE[1]

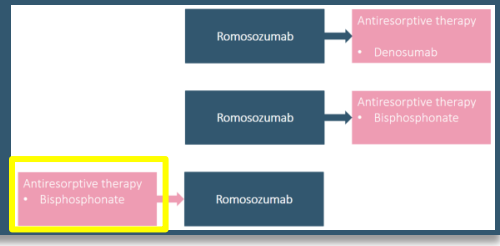


Romosozumab after placebo or denosumab
Phase 2 dose finding study[2]

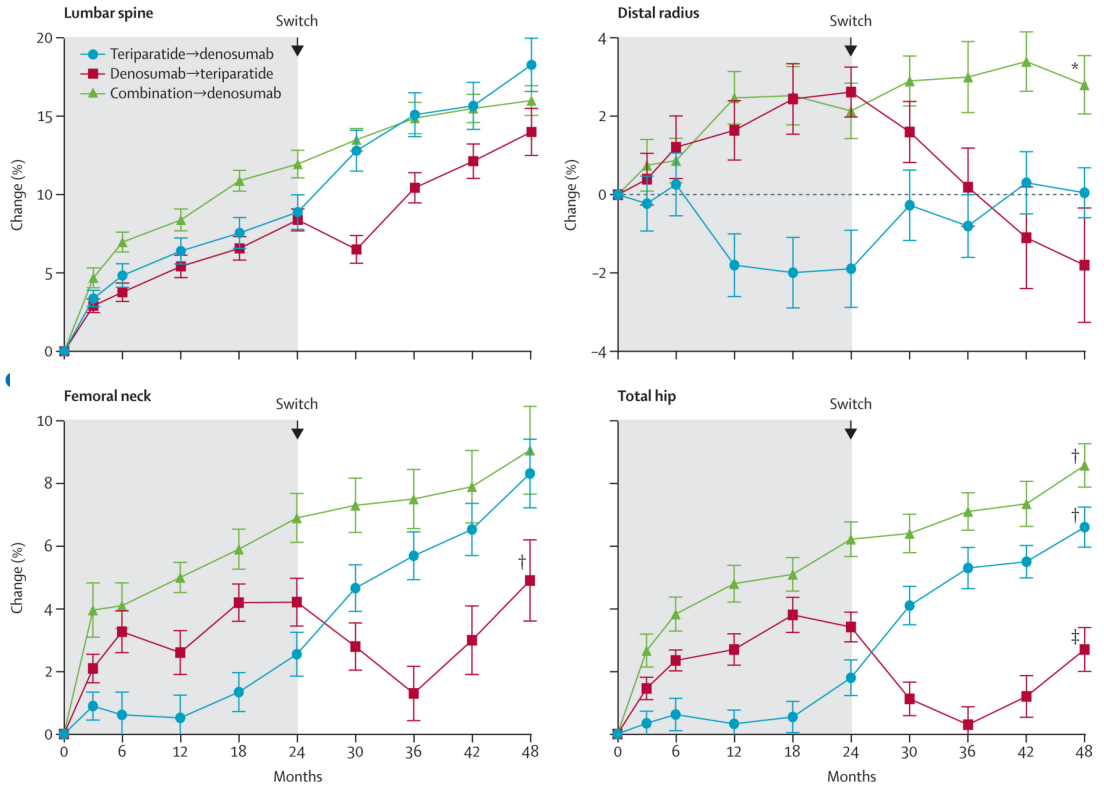


[1]Langdahl. Lancet 2017; 390: 1585-94; [2]McClung. JBMR Plus 2021, e10512

Romosozumab in second line:
previous treatment with bisphosphonate or denosumab in Phase 2 & 3 trials

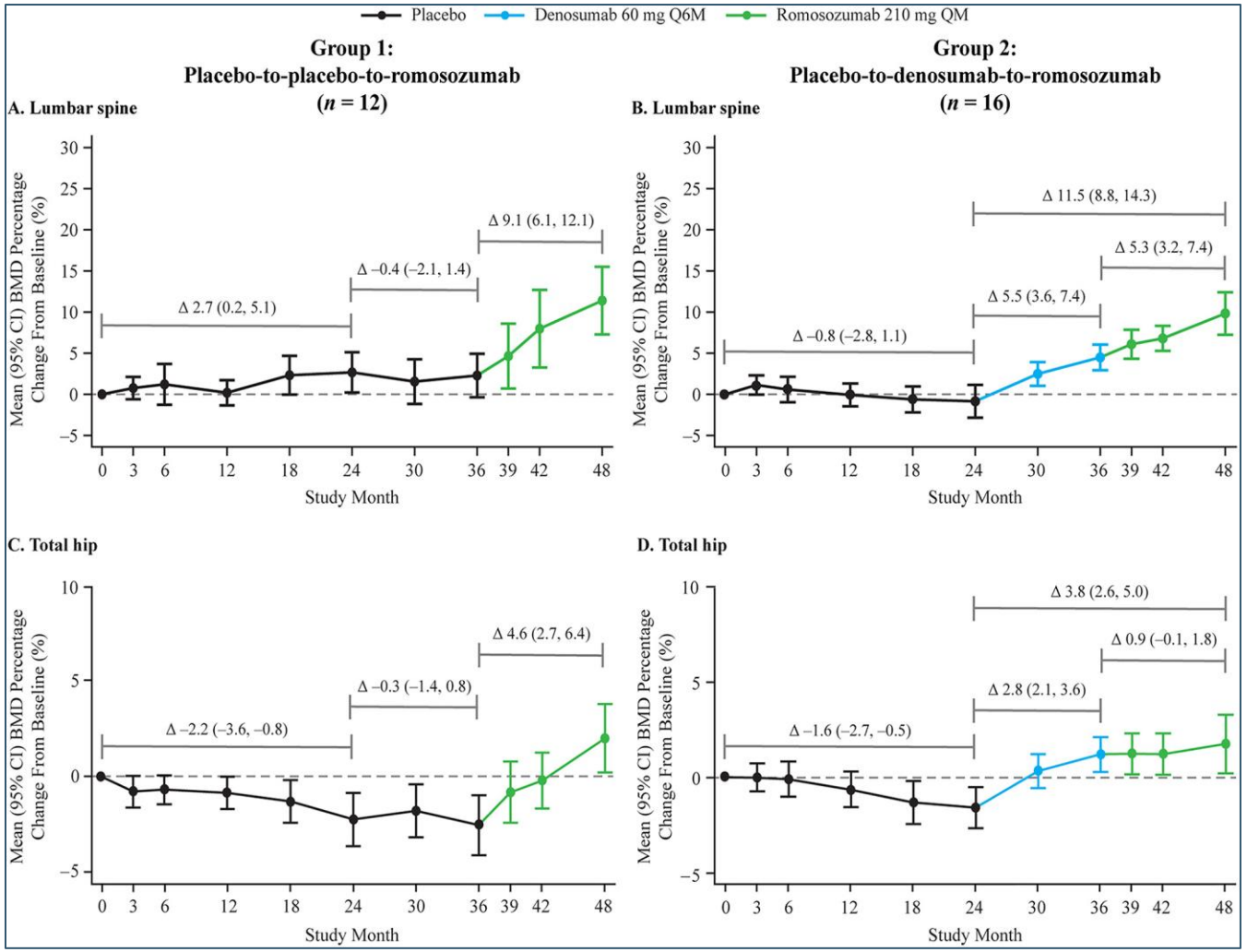


Data Switch Study: no TPT after Dmab!

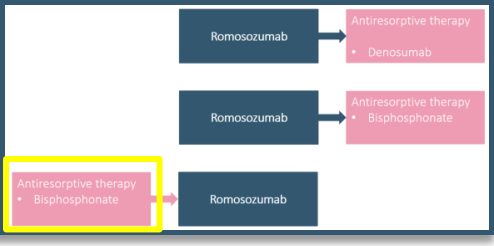


Leder. Lancet 2015; 386:1147-55

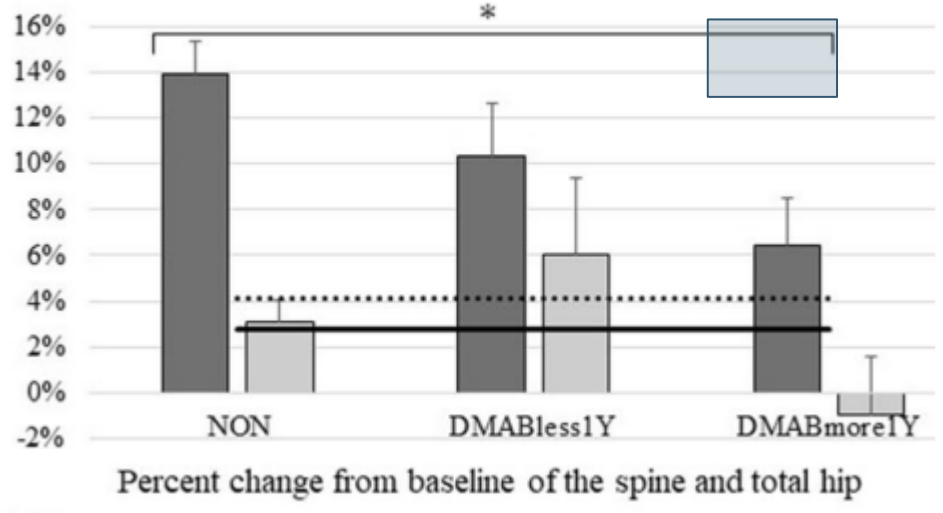
Romosozumab after placebo or denosumab
Phase 2 dose finding study[2]

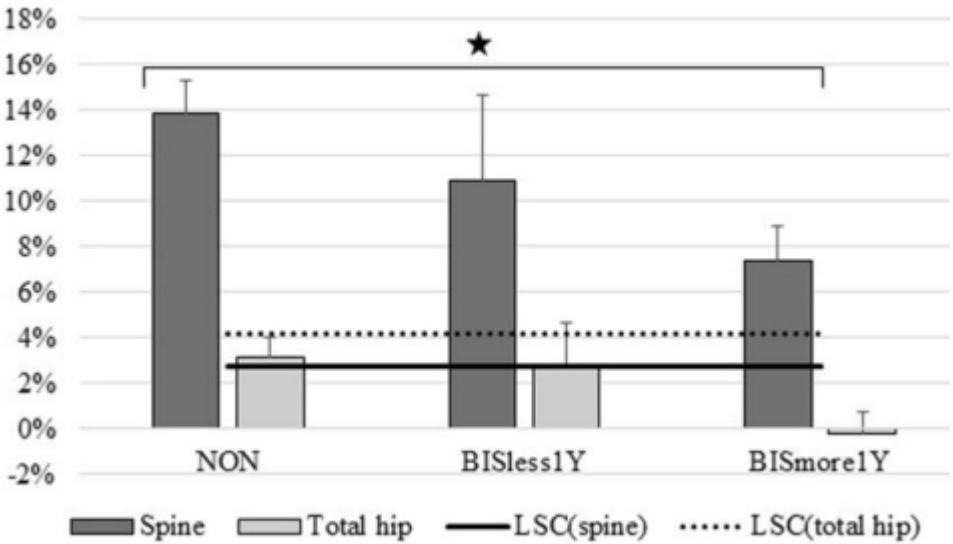


Romosozumab in second line:
real-world data



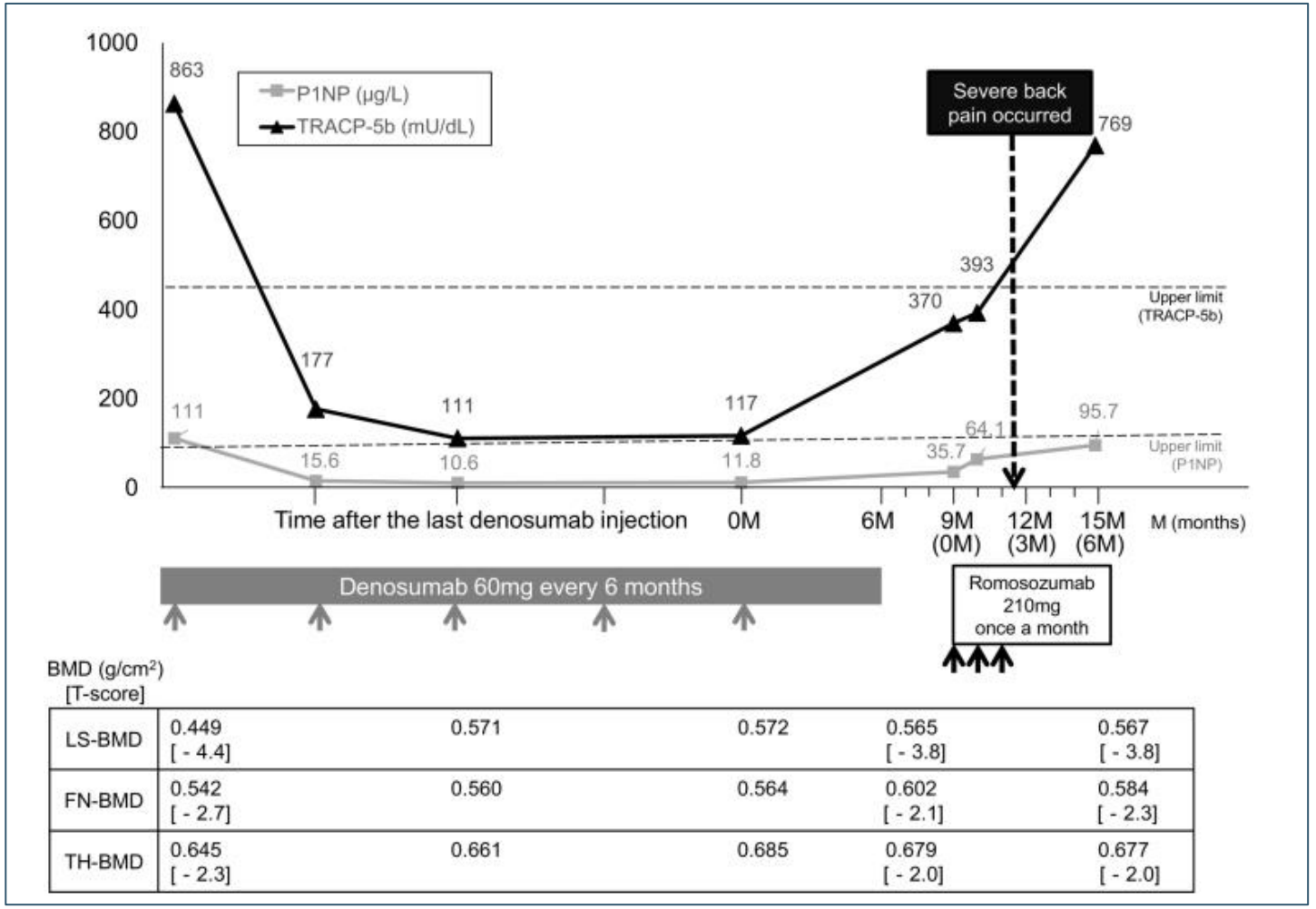
Effect of previous treatment on effect of Romo[1]





N=259 osteoporosis patients receiving Romosozumab

Case report: Romosozumab was not effective in preventing multiple clinical vertebral fractures after denosumab discontinuation (2.5 years)[2]

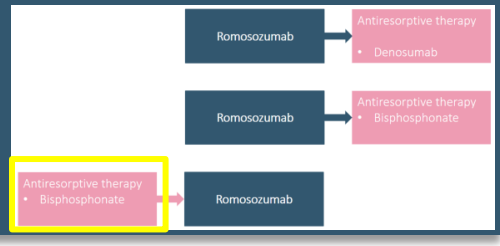


BMD (g/cm²) [T-score]

LS-BMD	0.449 [- 4.4]	0.571	0.572	0.565 [- 3.8]	0.567 [- 3.8]
FN-BMD	0.542 [- 2.7]	0.560	0.564	0.602 [- 2.1]	0.584 [- 2.3]
TH-BMD	0.645 [- 2.3]	0.661	0.685	0.679 [- 2.0]	0.677 [- 2.0]

[1]Tominaga. Osteoporos Int 2022, Online ahead of print; [2]Kashii. Bone Rep 2020 : 100288

② Sequential therapy with Romosozumab



FRAME Study
(treatment-naive)

Romosozumab → Antiresorptive therapy
- Denosumab

ARCH Study
(treatment-naive)

Romosozumab → Antiresorptive therapy
- Bisphosphonate

STRUCTURE Study
(pretreatment ALN)

Antiresorptive therapy
- Bisphosphonate

→ Romosozumab

~~Denosumab?~~

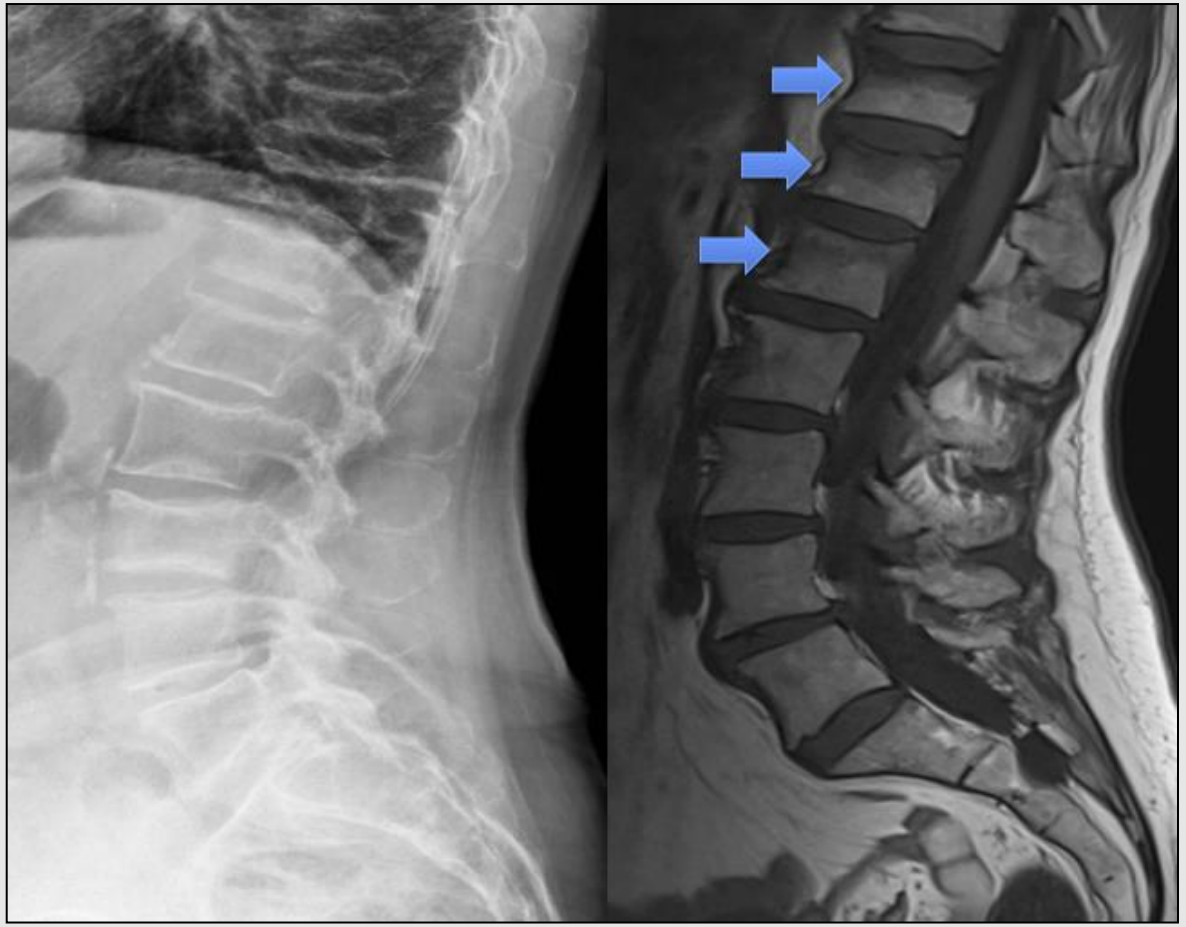
(at least not if long-term treatment with Dmab (> 2.5-3 years))

③ Rebound-associated vertebral fractures (RAVF)

a. How does Denosumab discontinuation affect BTM, BMD and fracture risk?

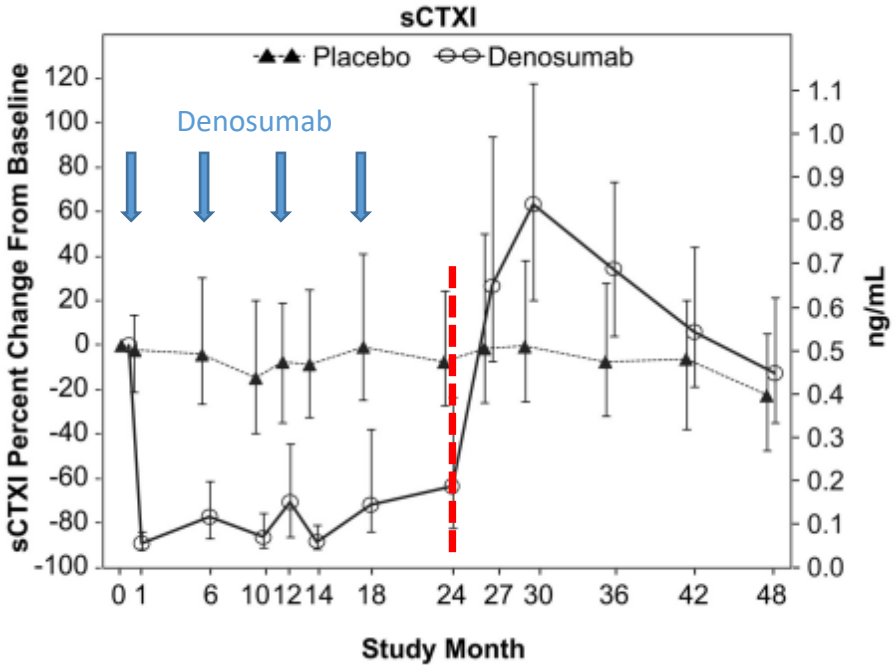
b. How to prevent RAVFs after stopping Dmab?

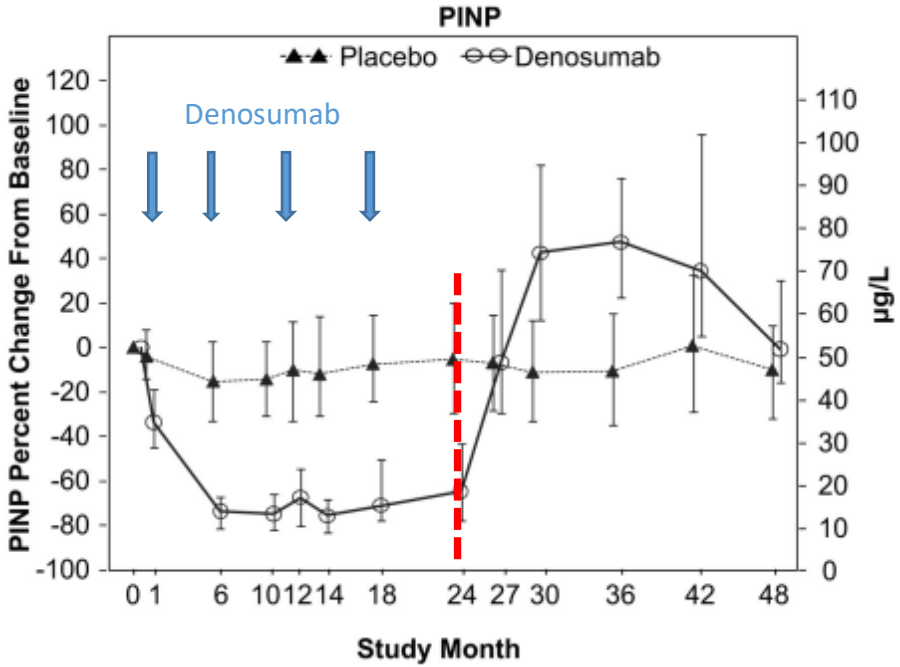
c. How to manage RAVF?



a. How does Dmab discontinuation affect BTM, BMD and fracture risk?

Effect of discontinuation of Denosumab on bone turnover markers





After stopping Densomab (last dose 18 mo), CTX:

- increases above month 0 concentrations within 3 mo
- peaked at 30 months
- returned to month 0 concentrations by month 48

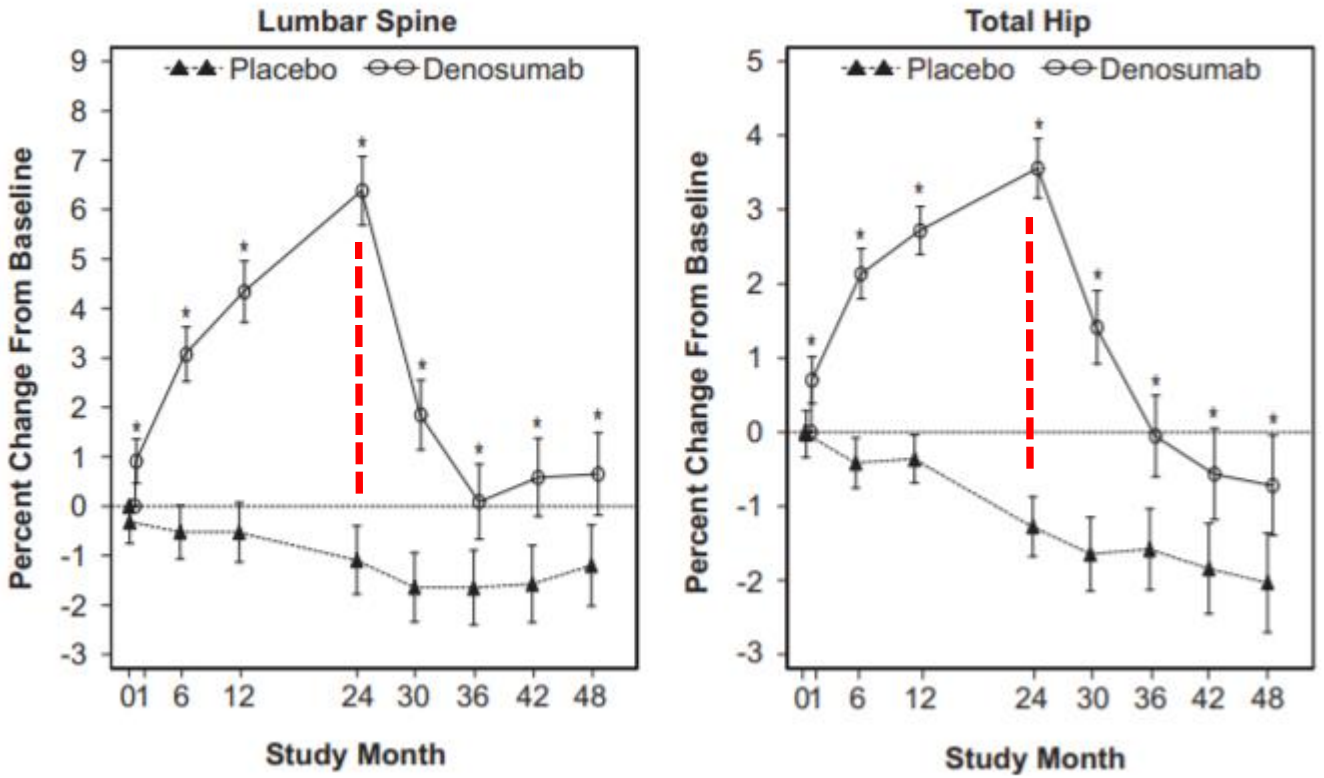
After stopping Densomab (last dose 18 mo), P1NP:

- increases above month 0 concentrations within 6 mo
- peaked at 36 months
- returned to month 0 concentrations by month 48

Bone. J Clin Endocrinol Metab 2011; 96: 972-80

a. How does Dmab discontinuation affect BTM, BMD and fracture risk?

Effect of discontinuation of Denosumab on BMD



After stopping Densomab:

- BMD decreases at all sites, with most of the decrease between month 24 and 36
- Between mo 36-48: BMD measurement in former Dmab groups parallels that of placebo
- At all timepoints, BMD in former Dmab group remains higher than BMD in Pbo group

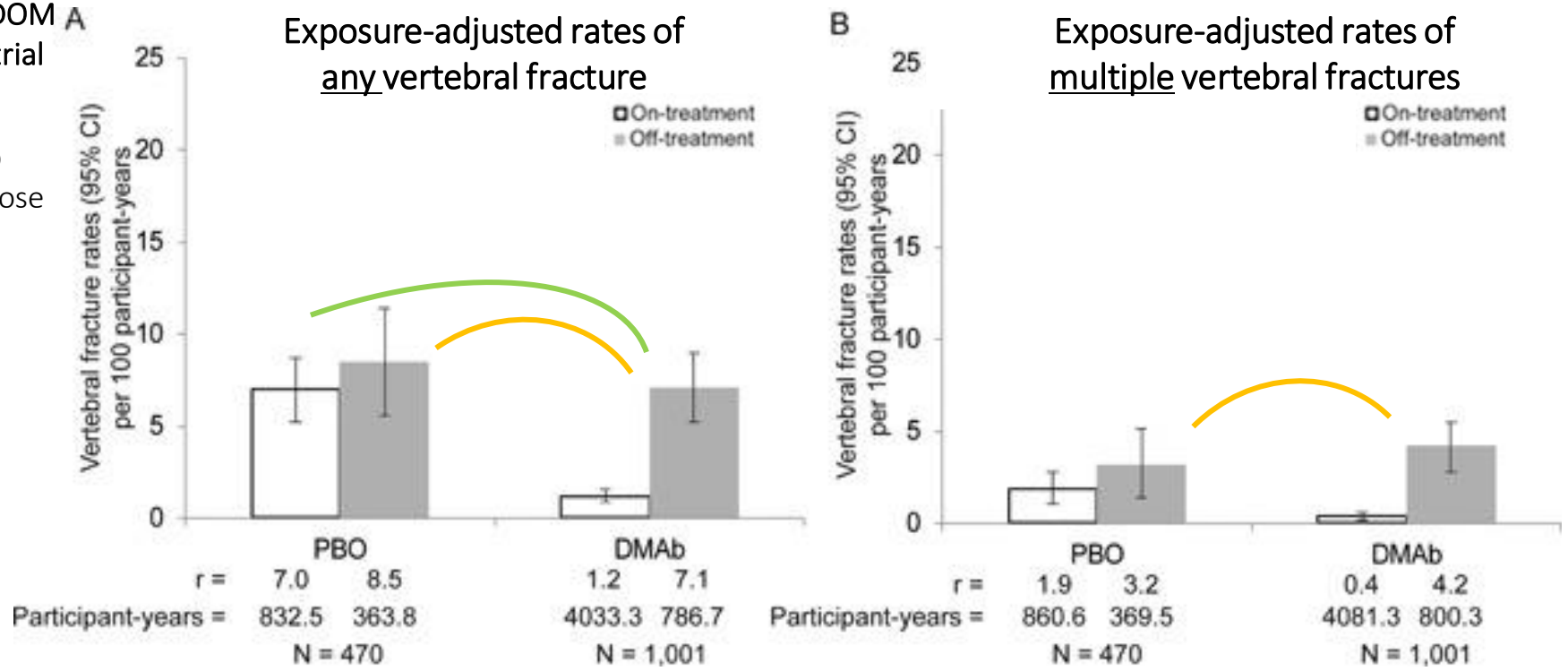
Bone. J Clin Endocrinol Metab 2011; 96: 972-80

a. How does Dmab discontinuation affect BTM, BMD and fracture risk?

Post hoc analysis of FREEDOM and FREEDOM extension trial

470 and 1001 ♀

- stopped Pbo or Dmab
- FU ≥ 7 mo after last dose



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 Pbo

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

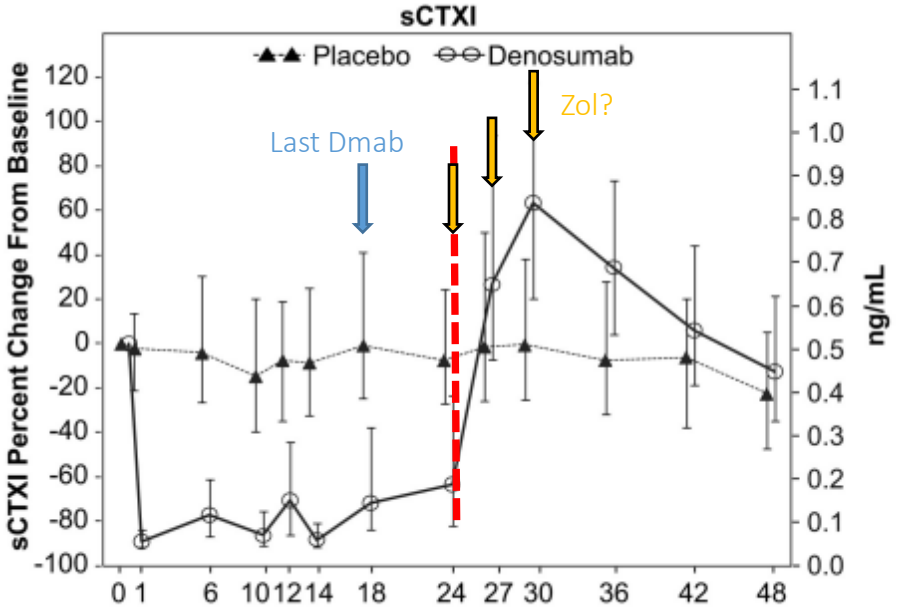
- Proportion of multiple vertebral fractures in those who developed 1 or more vertebral fractures: 60.7% in those stopping Dmab ⇔ 38.7% in those stopping placebo (p = 0.049)
- Odds of developing multiple vertebral fractures after stoppping Dmab: 3.9 (2.1-7.2)x higher in those with prior vertebral fractures 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 2018; 33: 190-198

b. How to prevent RAVFs when stopping Denosumab?

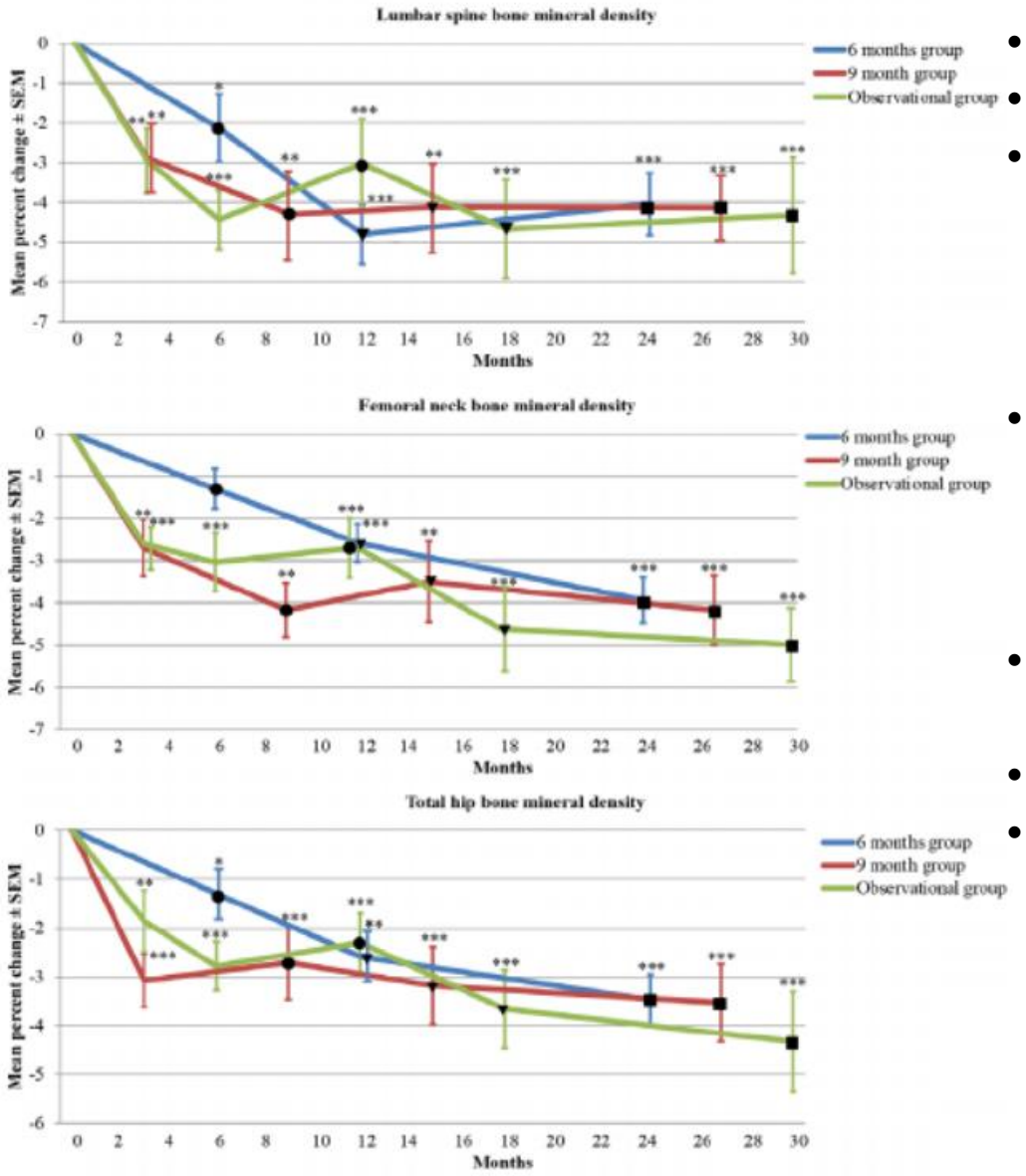
ECTS position statement

- SERMs seem not effective, but limited data so far (2 RCTs ongoing)
- Start potent bisphosphonate to prevent/limit the rebound phenomenon
- Optimal bisphosphonate regimen is not certain
- May be less effective when previous Dmab treatment > 2.5 years



Tsourdi. J Clin Endocrinol Metab 2021; 106: 264-81

b. How to prevent RAFs when stopping Denosumab?



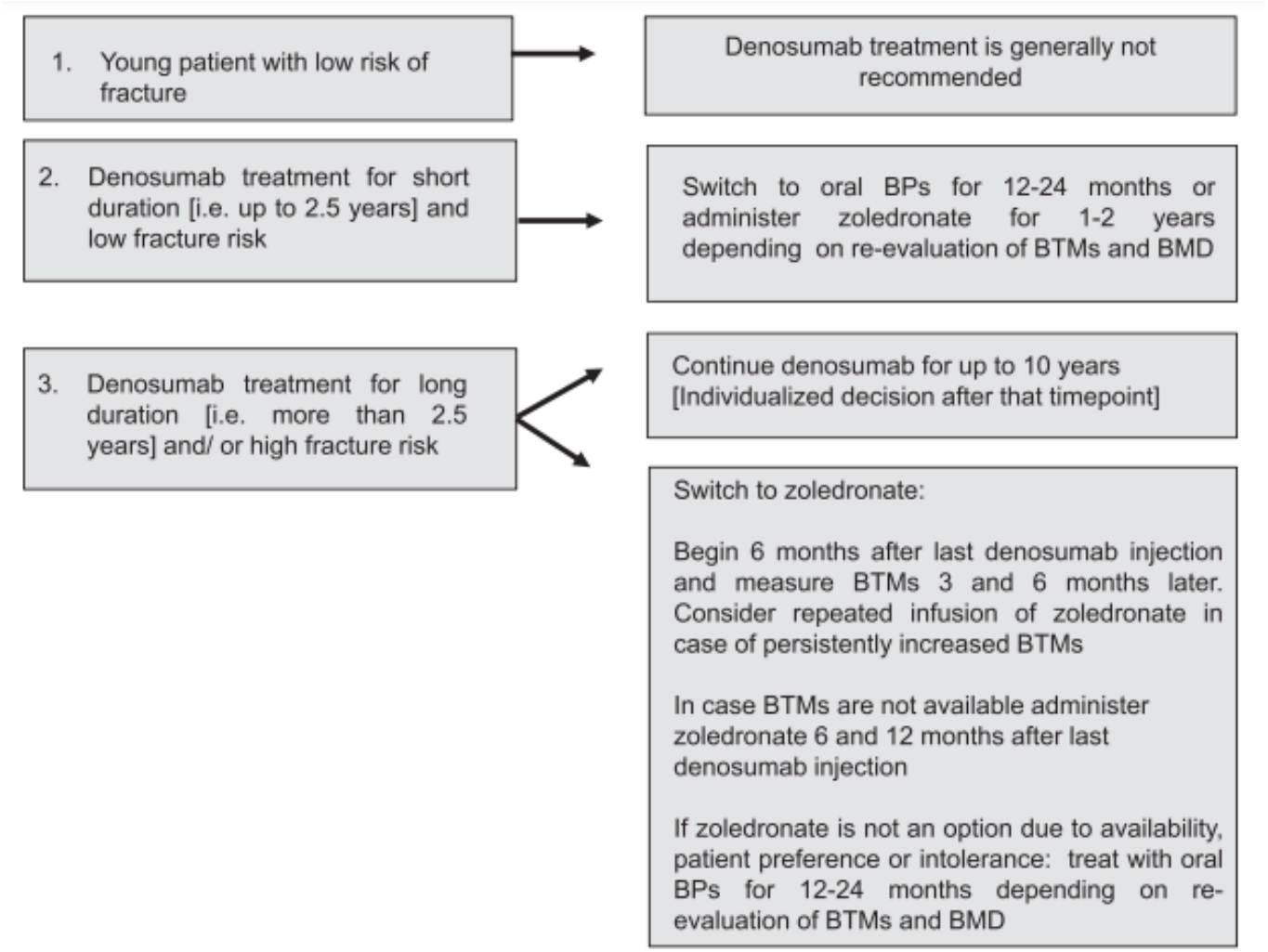
- 61 postmenopausal women and men >50 years
- Mean duration of Denosumab treatment: 4.6 +/- 1.6 years
- Consolidation with 5 mg ZOL IV
  - at 6 months after the last Dmab [6M]
  - *or* at 9 months after the last Dmab [9M]
  - *or* when CTX increased above 1.26 µg/l (50% above reference for elderly), or when BMD decreased > 5% or when fracture (observation group [OBS])
- FU op 12 & 24 months. During 2nd year, retreatment with ZOL when:
  - CTX increased above 1.26 µg/L
  - BMD decreased > 5%
  - VFx or hip fracture
- At 12 months after ZOL: significant decrease of BMD at LS, TH & FN, without difference between 6M, 9M and OBS
- At 24 months after ZOL: no further change in BMD
- From baseline to 24 months after ZOL: significant decrease in BMD
  - LS BMD decreased by 4.0% [6M], 4.1% [9M] and 4.3% [OBS]
  - FN BMD decreased by 3.9% [6M], 4.2% [9M] and 5.0 % [OBS]
  - TH BMD decreased by 3.5% [6M], 3.5% [9M] and 4.3% [OBS]

5 mg ZOL irrespective of timing after stopping Dmab did not fully prevent bone loss

Solling. J Bone Miner Res 2021; 36: 1245-54

b. How to prevent RAVFs when stopping Denosumab?

ECTS position statement



FU BTM: at 3 mo and, if stable, every 6 mo
Target BTM:

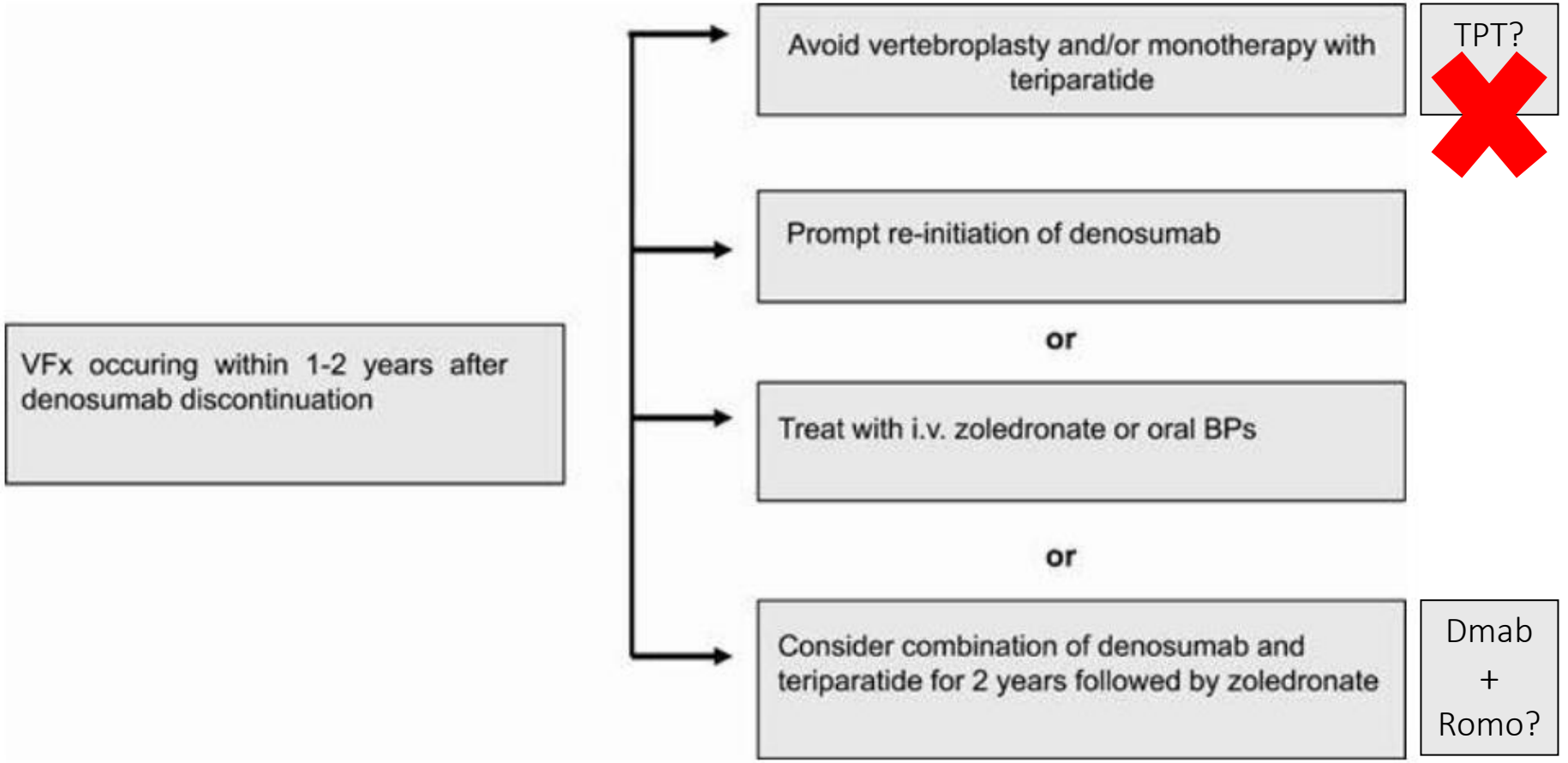
- CTX < 280 ng/l
- PINP < 35 mg/l

Eg. Aclasta 5 mg at 6 months
Zometa 4 mg at 12 months

Tsourdi. J Clin Endocrinol Metab 2021; 106: 264-81

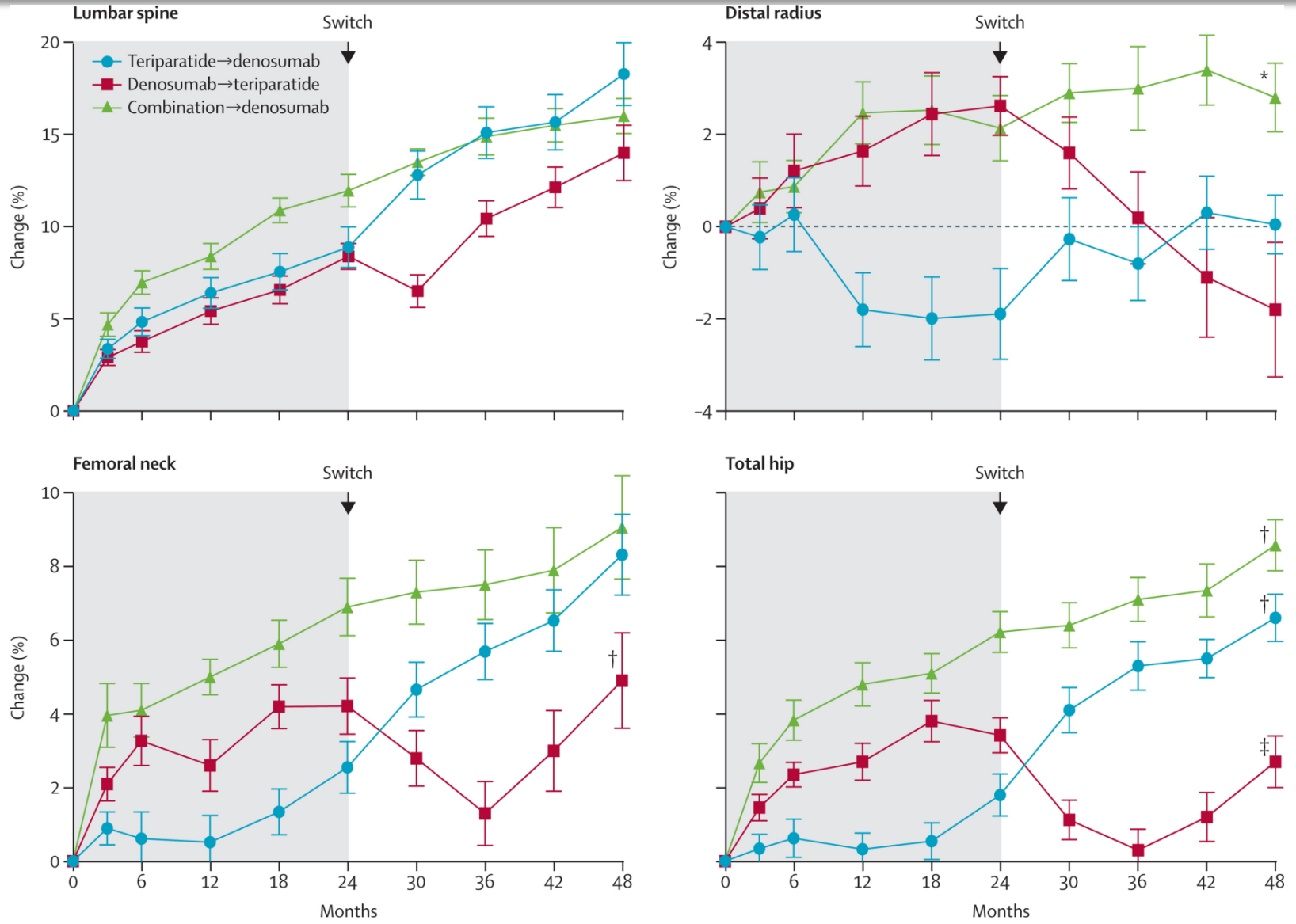
c. How to manage RAVFs?

ECTS position statement



Tsourdi. J Clin Endocrinol Metab 2021; 106: 264-81

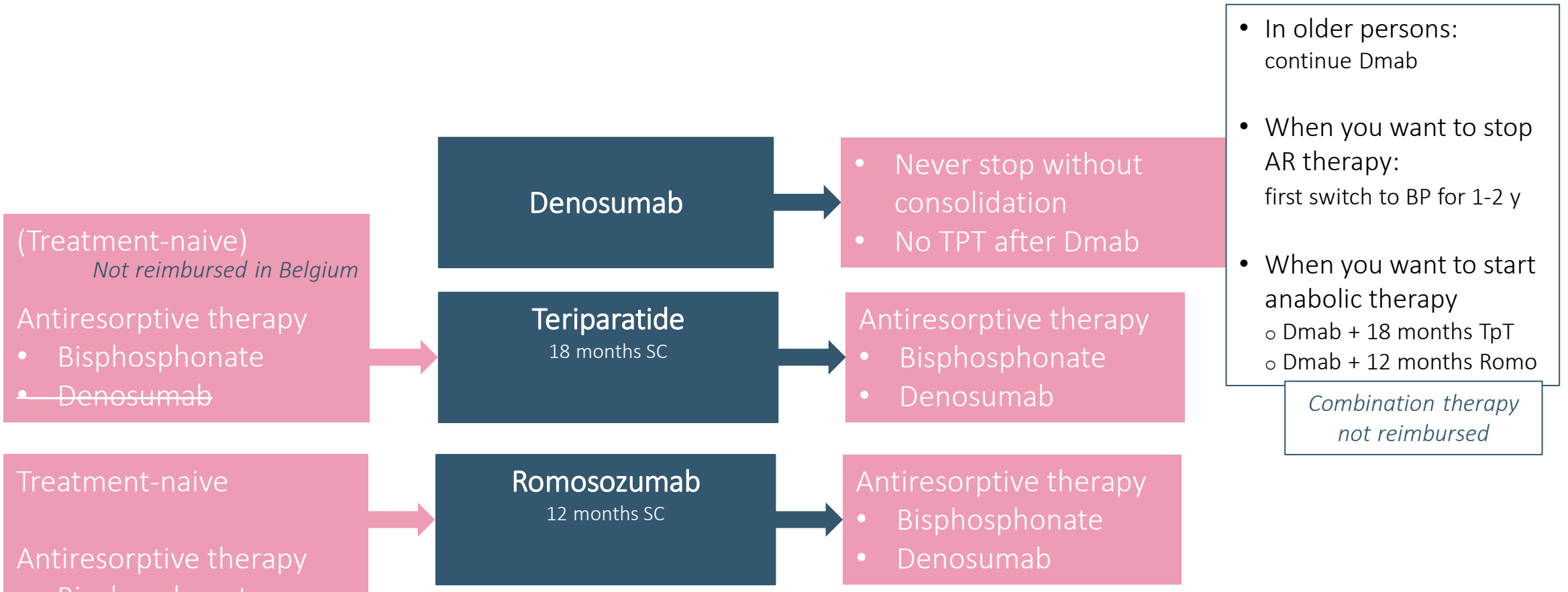
c. How to manage RAVFs?



No Teriparatide alone after stopping Denosumab!

Leder. Lancet 2015; 3866: 1147-55

Sequential therapy for osteoporosis



Overview

I. Introduction

II. Who should receive osteoporosis treatment?

III. How to choose the right osteoporosis treatment?

IV. Duration of treatment, drug holiday & treatment failure

V. Sequential osteoporosis treatment

VI. Conclusion

Conclusion

- Osteoporosis is a major threat to the mobility, quality of life and independence of patients
- Detection and early secondary prevention in fracture patients can prevent the fracture fragility cycle
- Osteoporosis is still too much underdiagnosed and undertreated
- Increasingly better treatment options that can reduce fracture risk

Further reading

THE LANCET

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Drug therapy for osteoporosis in older adults

Prof Ian R Reid, MD • Emma O Billington, MD

Maturitas 139 (2020) 69–89

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journal homepage: www.elsevier.com/locate/maturitas

The Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women

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