Osteoporosis Uncovered: Challenges in Diagnosis and Treatment

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Areas to cover

- Osteoporosis management in the era of treat-to-target
- Diagnosis of osteoporosis; new concepts
- FRAX adjustments and FRAX Plus

No disclosures

Treat-to-target (TTT/T2T)

- Treat-to-goal
- Goal directed treatment
- Treatment decisions are made according to the *likelihood of achieving a measure or composite of measures that represent treatment success (target)*

Key factors in treat-to-target in osteoporosis

- Osteoporosis is a chronic disease with fracture as the major clinical outcome (target)
- Fracture risk increases with age (lifelong treatment)
- Fracture risk is individual
- Management should be individualized

Lewiecki EM, Endocrine and Metabolism, 2021, March

Uncertainties

- How much reduction of fracture risk is desirable and achievable?
- How can we best assess the reduction of fracture risk with treatment?
- How fast can we achieve the clinical end points?
- How can we use this information to individualize treatment decisions?

Lewiecki EM, Endocrine and Metabolism, 2021, March

Standard care vs treat-to-target in osteoporosis

Aim: Stability or increase in BMD and no fracture

1) Begin with low-cost treatment

2) If CI/AE/poor response, change to another low-cost treatment

3) If Step 2 fails, more potent antiresorptive or anabolic

Aim: Achievement of a *target level of BMD (T score)* and no fracture

1) Decide on treatment target at the baseline

2) Initial therapy is selected considering the risk at the baseline and the time taken to reach the target

3) More aggressive and more potent medications

4) Regular monitoring to stop, continue or change medications

Lewiecki EM, Endocrine and Metabolism, 2021, March

Treat-to-target: Steps involved

- Risk categorization at the baseline
- Identification of targets
- Select the best treatment option/s

Align the 3 factors; risk, medications and target

Determinants of fracture risk at the baseline

Major and minor factors

- Prevalent or incident fracture
- T score (BMD)
- Fracture risk (e.g. FRAX)

- Age
- Frailty
- Falls
- Use of medications causing poor bone health

Prior Fracture; the strongest risk factor of future fractures

- **Vertebral fracture**
  - MORE trial: prevalent fx $\rightarrow\uparrow$ 20% new vertebral fx/3 yrs[1]
  - VERT trial: incident fx $\rightarrow\uparrow$ 19% new vertebral fx /1 yr[2]
- **Hip fracture**
  - Rochester: hip fx $\rightarrow$ 29% contralateral hip fx/20 years[3]
- **Any fracture**[4,5]
  - Swedish national dataset; 3,423,320 persons;
    - Recent Fx classified as MOF (70,254) or non-MOF (75,526)
    - Compared with control; recent MOF Hazard ratio for any fracture 2.1 and for recent non-MOF 2.24
  - For a 65-74 year-old, the 5-year risk of any fx following:
    - Forearm fracture = 15% (male) 21% (female)
    - Vertebral fracture = 18% (male) 33% (female)

[1]Ettinger B, et al. JAMA. 1999;282:2189.
[2]Lindsay R, et al. JAMA. 2001;285:320
[3]Melton LJ. Clin Ortho Res. I982;167:131
[4]van Staa TP, et al. Osteoporos Int. 2002:13:624
[5]Axelsson, KF, et al. JBMR, 2023: 38: 851-859

Combining fracture and T score in risk determination (US NOF Guidelines

- Consider initiating pharmacologic treatment in post-MP women and men ≥ 50 years who have the following:
  - T-score −2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
  - Low-trauma spine or hip fracture (regardless of BMD)
  - T-score between −1.0 and −2.5 and a fragility fracture of proximal humerus, pelvis, or distal forearm
  - T-score between −1.0 and −2.5 and high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds

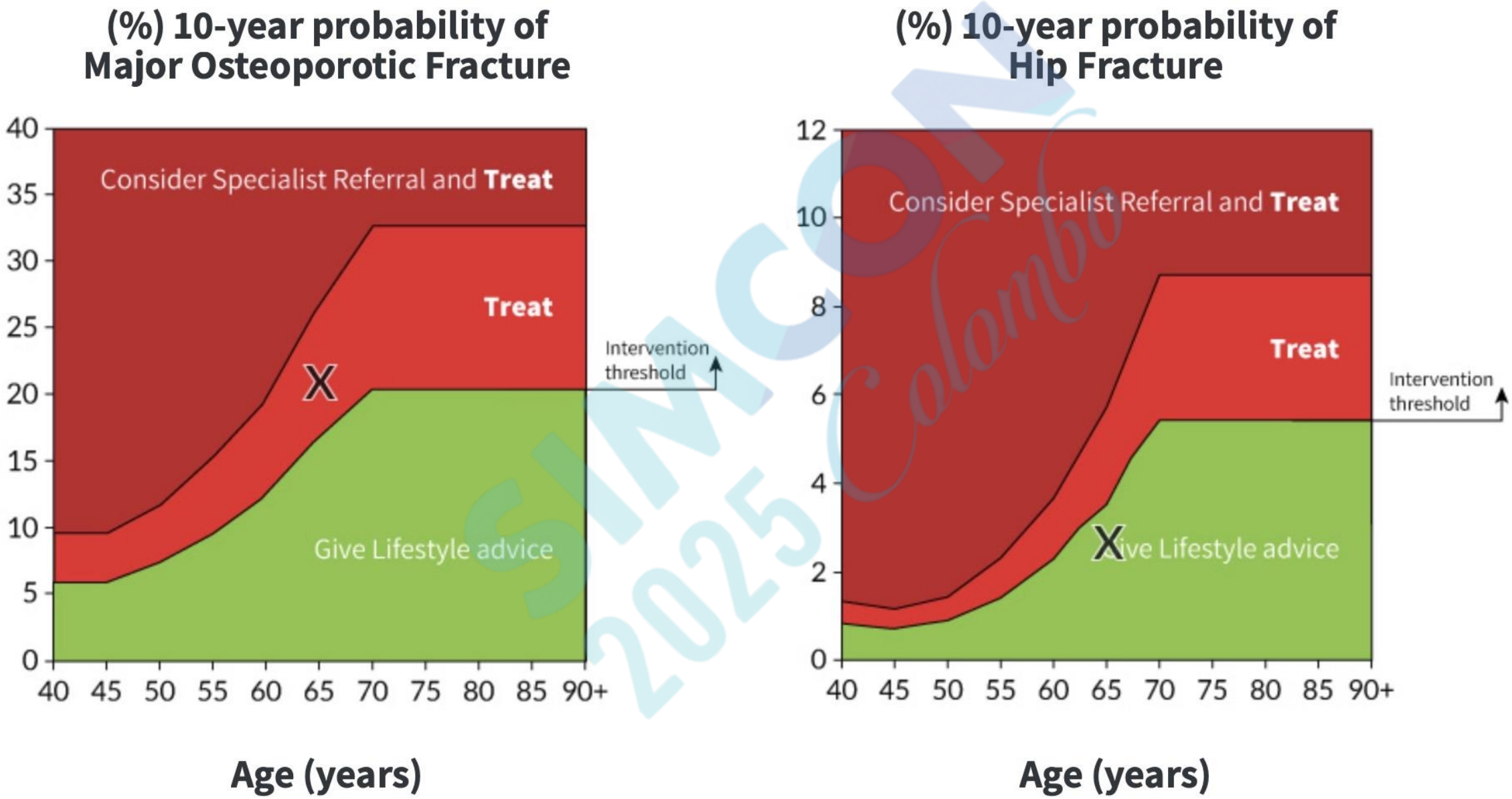
LeBoff, et. al., Osteoporos Int. 2022;

Cosman et al, JBMR, 2024,39, 1393-1305

Applicability of NOF (BHOF) recommendations outside the USA

- Based on economic evaluation
- Access to DXA is unrestricted
- Indications for DXA: strict
- FRAX (USA) model
- IT are applicable only for the USA

Intervention Thresholds : Using FRAX output by NOGG UK



Stratification of fracture risk

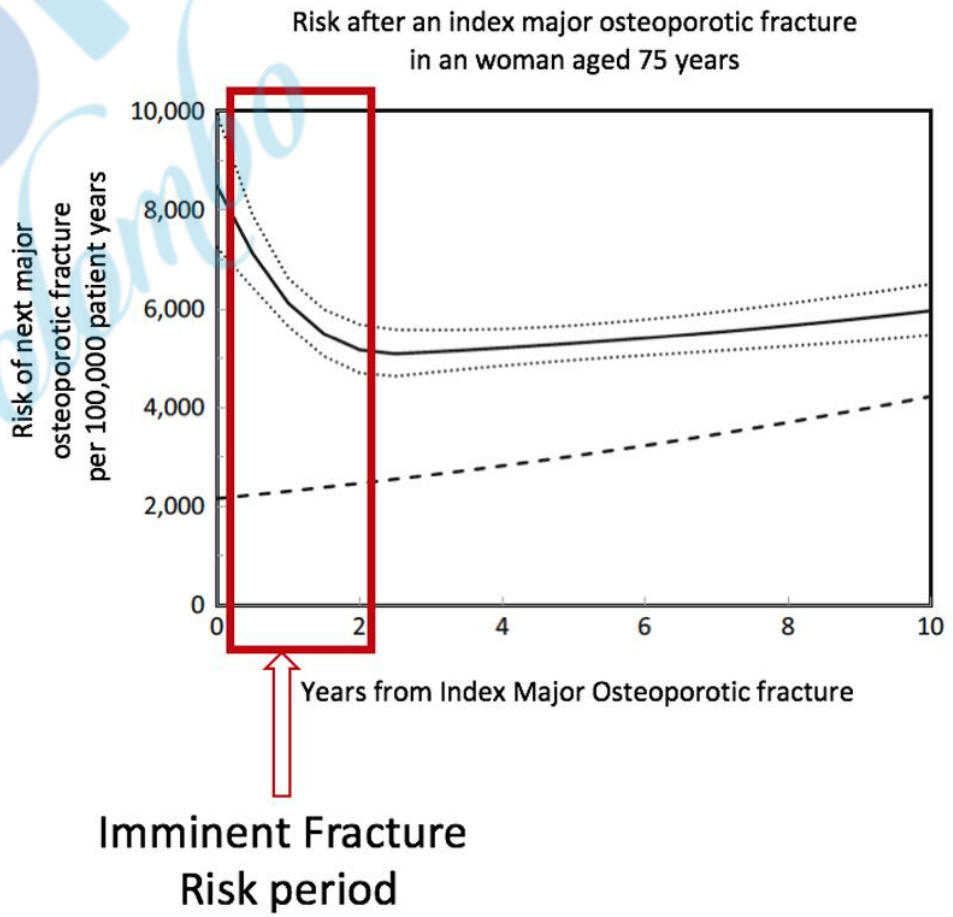
- Very high fracture risk
- High fracture risk
- Imminent fracture risk

Very high fracture risk (AACE 2020)

- Recent fracture (12months)
- Multiple fractures
- Incident fracture while on osteoporosis therapy
- Fracture while on drugs causing skeletal harm (GCs)
- FRAX based MOFR >30% and HFR >4.5%
- T score <-3.0 *(<3.5)*
- H/O injurious falls
- High risk of falls
- Advanced age (>70ys)
- Frailty
- GC >7.5mg/day

Imminent fracture risk (>20% in 2ys)

- Recent fracture (within 2ys)
- Radiographic incident VF
- Multiple fractures
  - 2 prior fracture: risk of recurrent fracture 16% in 2ys
  - >3 prior fracture: recurrent risk 25% in 2 ys



Monitoring osteoporosis therapy; challenges

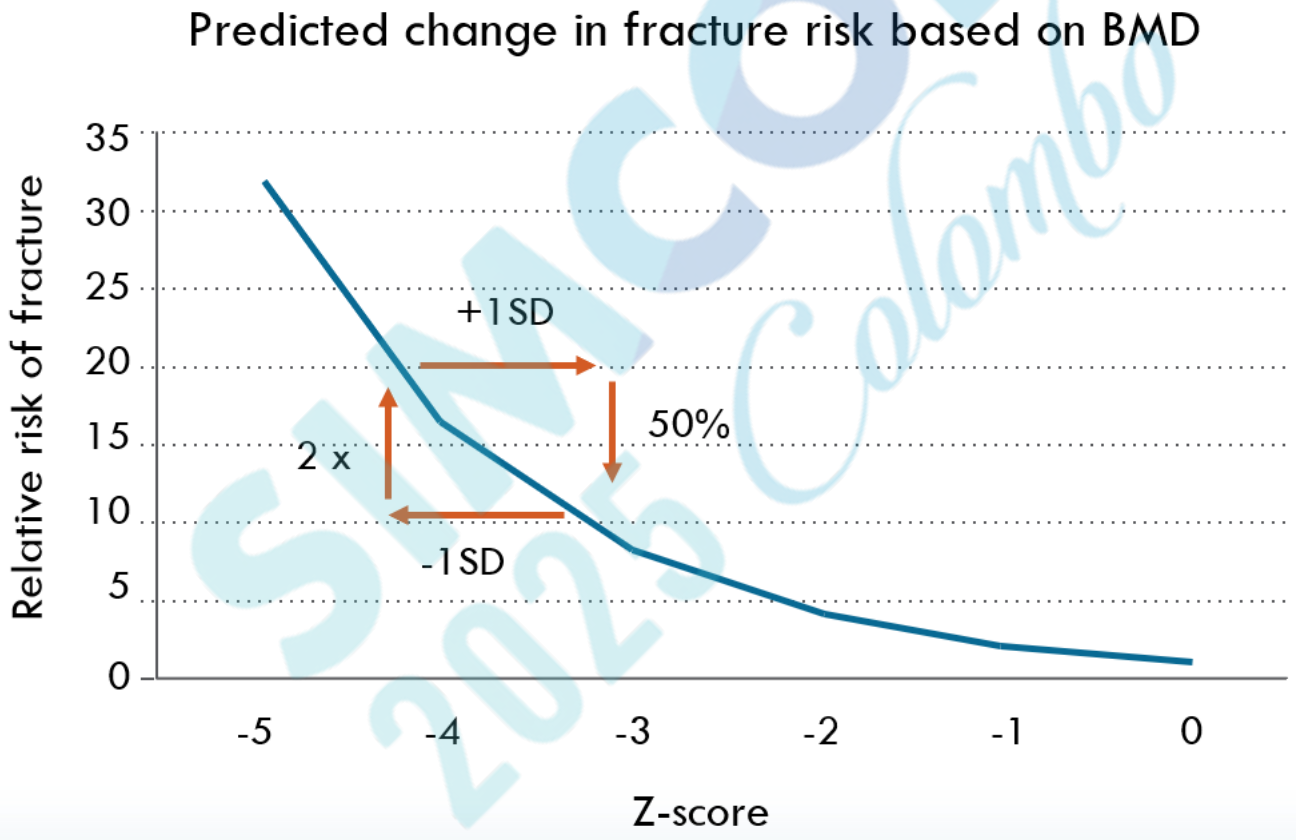
- Goal of treatment = prevent fractures
- Fragility fracture incidence is low, thus absence of fracture during therapy does not necessarily mean treatment is effective
- Fracture occurrence on therapy does not necessarily indicate treatment failure
- The use of surrogates such as BMD to monitor treatment may be useful
- Changes in an ideal surrogate marker during therapy should reflect changes in fracture risk

BMD Testing: treated patient

- Can aid in monitoring response to therapy.
- Should be performed if a fracture has occurred or new risk factors have developed
- Should be used to monitor individuals prior to a temporary cessation of bisphosphonate therapy and during the period of planned interruption of treatment.

Gani, et. al., J Clin Densitom, 2024;27: 101440. doi: 10.1016/j.jocd.2023.101440

Fracture Risk Reduction With Treatment Exceeds that Expected from BMD Gain Alone



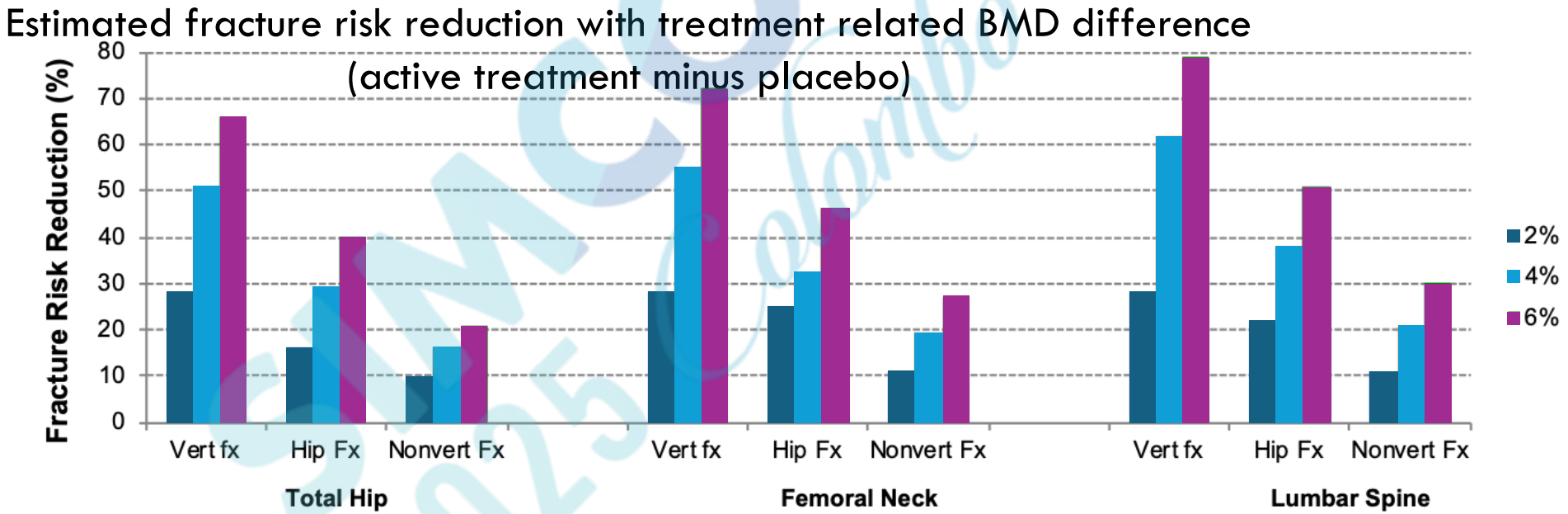
Fracture Reduction is Greater Than Would be Predicted by BMD Increase

Alendronate Fracture Intervention Trial			
	SD ↑ in BMD	Expected ↓ in FX	Observed ↓ in FX
Lumbar spine	~0.5	25%	50%
Femoral neck	~0.2	10%	51%
Forearm	<0.1	0%	48%

Cummings, et al. JAMA 1998:280:2077-2082

Greater BMD increase is associated with greater fracture risk reduction

- Meta-regression of 38 placebo-controlled trials with 19 agents



"In summary, our results confirm and extend prior observations that larger improvements in DXA-based BMD are associated with greater reductions in fracture risk, particularly for vertebral and hip fractures."

Adapted from Bouxsein M et al, J Bone Miner Res 2019, 34:632-642

Treatment targets of those with high fracture risk

- No fracture while on treatment
- If initial T score was <-2.5; try T score >-2.0 in TH or FN (TH better than FN), those with high VF risk, try LS T Score >-2.0.
- If initial T score was >-2.5; try T score >-1.0 in TH or FN.
- If initial fracture risk was high: try to achieve risk below the ITs

Cosman et al, JBMR, 2024,39, 1393-1305

Aligning risks and targets

Selection criteria at baseline	**Treatment target**
• Fracture	• No fracture
• T score <-2.5	• T score > -2.0
• T score >-2.5	• T score >-1.0
• High fracture risk	• FR below ITs

Cosman et al, JBMR, 2024,39, 1393-1305

Treatment targets of those with imminent fracture risk

- *Rapidly* and maximally reduce the fracture risk
- *Higher BMD gains, initially*
- Long term: no fracture and high BMD (T score >-2.0 TH)

Cosman et al, JBMR, 2024,39, 1393-1305

Selection of initial treatment

- Probability of achieving the treatment target within a reasonable period of time
- Generally, 50% probability over 3ys
- Some needs more rapid gains
- Very high risk at baseline: likely to need sequential therapy
- Anabolic-first or anti-resorptive first??
- Anabolic-first leads to higher BMD gains

Cosman et al, JBMR, 2024,39, 1393-1305

Stopping treatment

- When targets not achieved or unlikely to be achieved: consider sequential treatment
- If targets achieved: maintain BMD is the focus. Continue, change, intermittent or withdrawal of treatment

Cosman et al, JBMR, 2024,39, 1393-1305

Review > Osteoporos Sarcopenia. 2024 Mar;10(1):3-10. doi: 10.1016/j.afos.2024.02.001.

Epub 2024 Mar 16.

Asia-Pacific consensus on long-term and sequential therapy for osteoporosis

Ta-Wei Tai [1], Hsuan-Yu Chen [2], Chien-An Shih [1], Chun-Feng Huang [3 4 5], Eugene McCloskey [6], Joon-Kiong Lee [7], Swan Sim Yeap [8], Ching-Lung Cheung [9], Natthinee Charatcharoenwitthaya [10], Unnop Jaisamrarn [11], Vilai Kuptniratsaikul [12], Rong-Sen Yang [2], Sung-Yen Lin [13 14 15 16], Akira Taguchi [17 18], Satoshi Mori [19], Julie Li-Yu [20], Seng Bin Ang [21], Ding-Cheng Chan [22 23], Wai Sin Chan [24], Hou Ng [25], Jung-Fu Chen [26], Shih-Te Tu [27], Hai-Hua Chuang [28 29 30 31], Yin-Fan Chang [32], Fang-Ping Chen [33 34], Keh-Sung Tsai [23], Peter R Ebeling [35], Fernando Marin [36 37], Francisco Javier Nistal Rodríguez [38], Huipeng Shi [39], Kyu Ri Hwang [40], Kwang-Kyoun Kim [41], Yoon-Sok Chung [42], Ian R Reid [43], Manju Chandran [44], Serge Ferrari [45], E Michael Lewiecki [46], Fen Lee Hew [8], Lan T Ho-Pham [47], Tuan Van Nguyen [48 49 50], Van Hy Nguyen [51], Sarath Lekamwasam [52], Dipendra Pandey [53], Sanjay Bhadada [54], Chung-Hwan Chen [13 14 15 55 56 57 58 59 60], Jawl-Shan Hwang [61], Chih-Hsing Wu [32 62 63]

Affiliations + expand

Recommendations

- For people at very high fracture risk, anabolic agents are recommended as the first-line treatment. Injectable antiresorptive agents can be prescribed as alternatives to anabolic agents.
- Antiresorptive agents should be prescribed after the completion of anabolic therapy as a sequential therapeutic strategy.
- Anabolic therapy should be considered for people who develop new fractures or who have ongoing high fracture risk despite antiresorptive treatment.

Recommendations

- Switching to a more potent BP, denosumab, or anabolic agent is an option for people with inadequate response to initial anti-osteoporosis medications.
- BPs should be prescribed after stopping denosumab to prevent rebound phenomenon with accelerated bone loss and/or multiple vertebral fractures. A SERM is an alternative option for patients who are unable to take BPs.

Recommendations

- Drug holidays following BP therapy should be considered only for people who have achieved adequate increases in BMD and remained fracture free.

Denosumab

- Increasingly used now
- Fractures return after withdrawal of treatment
- Sequential therapy plan should be decided very early

- Switching from dmab to teriparatide is associated with adverse effects on BMD, bone microarchitecture, and bone turnover markers, and may increase the risk of fractures.

- BP and romosozumab are recommended

Comparison of Teriparatide and Denosumab in Patients Switching From Long-Term Bisphosphonate Use. J Clin Endocrinol Metab. 2019 Nov

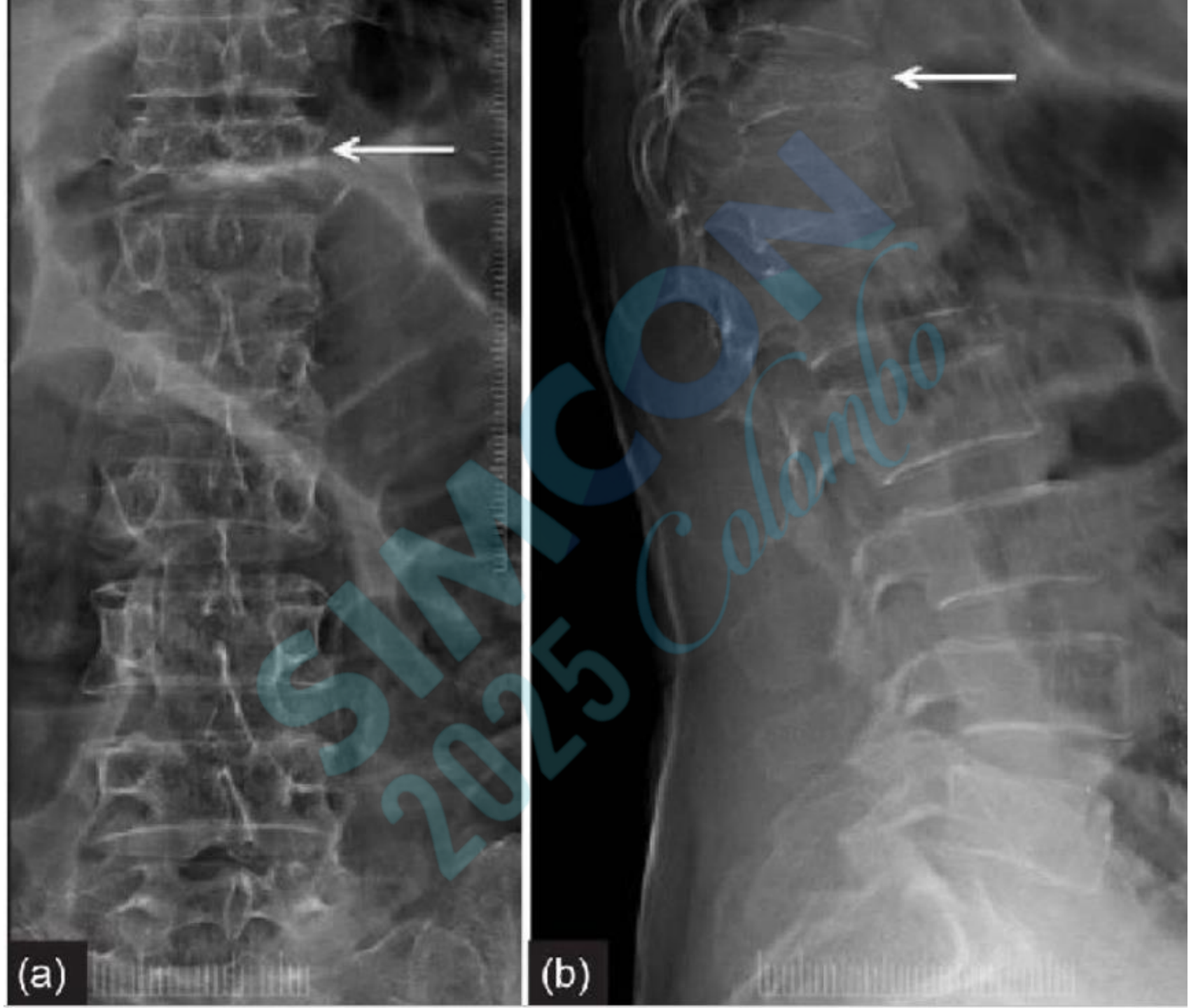
Effects of Teriparatide, Denosumab, or Both on Spine Trabecular Microarchitecture in DATA-Switch: a Randomized Controlled Trial. J Clin Densitom. 2017 Oct-Dec;

Clinical case

- 76y old Ms. B presents with a backpain of 2 days duration. She gives a history of a fall 3ys ago with laceration in scalp (slipped in washroom). Previously well and not on meds. Examination; unremarkable.

- ESR, CRP, FBC, creatinine, Ca, phosphate, ALP: normal

- Spine radiograph


(a)
(b)

What is the diagnosis?

- Fragility fracture

- Osteoporosis?

There are Multiple Ways by Which Osteoporosis Can be Diagnosed

- **By DXA:** T-score −2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
- **By Fracture:** Low-trauma spine or hip fracture *(regardless of BMD)*
- **By DXA/Fracture:** T-score between −1.0 and −2.5 and a fragility fracture of proximal humerus, pelvis, or distal forearm
- **By Fracture Risk:** T-score between −1.0 and −2.5 and high FRAX® (or if available, TBS-adjusted FRAX®) (for US: 10-year MOF ≥ 20% or hip ≥ 3%)

*LeBoff, et. al, Osteoporos Int, 2022; 33:2049-2102; Camacho, et. al., Endocr Pract. 2020; 26 (Suppl 1): 36

“Ms. B has osteoporosis with a prevalent vertebral fracture and her risk of subsequent fracture is very high”

FRAX limitations and adjustments

Risk variable	Adjustment to FRAX*	Access
Medium and high dose exposure to oral glucocorticoids ★	Medium doses (2.5–7.5 mg daily) are the assumed minimum requirement for FRAX calculation, and the unadjusted FRAX value is used. For high doses (>7.5 mg daily), MOF probabilities are upward revised by about 15% and hip fracture probabilities by 20% ¥	Automatic adjustment available on FRAX website: www.nogg.org.uk/manual-data-entry. Kanis et al 2011 [85]
Concurrent data on lumbar spine (LS) BMD ★	Increase or decrease the MOF probability by 10% of each rounded T-score difference between LS and FN (see frequently asked question no.4 for worked example)*	Leslie et al 2011 Johansson et al 2014 [86,87]
Trabecular bone score (TBS)	Increase MOF probability by 30% for each standard deviation (SD) decrease in TBS	TBS adjustment can be accessed from the UK FRAX website. McCloskey et al 2016 [88]
Hip axis length (HAL)	Increase or decrease hip fracture probability by 30% for each SD difference in HAL	Leslie et al 2016 [89]
Falls history ★	Increase MOF and hip fracture probability by 30% for a history of recurrent falls (≥2 falls in the last year)	Masud et al 2011 [90] Vandenput et al [93]

Type 1 and 2 diabetes mellitus	Enter 'yes' in the rheumatoid arthritis input to FRAX	Other adjustments in Leslie et al 2018 [91]
Parkinson's disease, and related movement disorders	Enter 'yes' in the rheumatoid arthritis input to FRAX	Schini et al 2023 [92]
Recent MOF	Marked uplift to fracture probabilities (see Section 4h)	Kanis et al 2020 [52]

* downward adjustment to FRAX probabilities should only be made in the context of a very reliable high lumbar spine BMD measurement and not on the basis of a discordant result due to artefact e.g. from degenerative change

¥ See Section 7: 'Glucocorticoid-induced osteoporosis' for further details on glucocorticoid doses and recommendations

Table 8. Adjustment of FRAX derived fracture probability estimates according to daily dose of prednisolone

Dose	Prednisolone equivalent dose (mg/day)	Average adjustment to hip fracture probability	Average adjustment to major osteoporotic fracture (MOF) probability
Low	<2.5	-35%	-20%
Medium	2.5-7.5	None	None
High	≥7.5	+20%	+15%

>7.5 =?? x 1.5
<2.5= ?? x 0.8

Spine-FN T score discordance

- **Spine T score -3.0, FN T score -0.8**
- Difference = 2.2, rounded off to 2
- Difference of 1= 10% increase
- Difference of 2= 20% increase

- **MOFR = 6%**
- MOFR = 6 + (6x20%) = 6+1.2 =7.2%

Variable	Adjustment
Prednisolone >7.5	X1.5 (MOF, HF)
Prednisolone <2.5	X 0.8 (MOF, HF)
Recurrent falls	X 30% (MOF, HF)
Diabetes	Replace Rh arthritis
Spine-FN T score discordance	X 10% for 1 unit difference (MOF)
PD/neurological diseases	Replace Rh arthritis
Recent fracture	Imminent risk
Multiple # at baseline	Imminent risk

FRAX vs FRAX Plus

FRAX vs FRAX Plus

Discover the advantages of FRAXplus®

FRAXplus® allows you to modify a probability result derived from conventional FRAX® estimates of probabilities of hip fracture and major osteoporotic fracture with knowledge of:

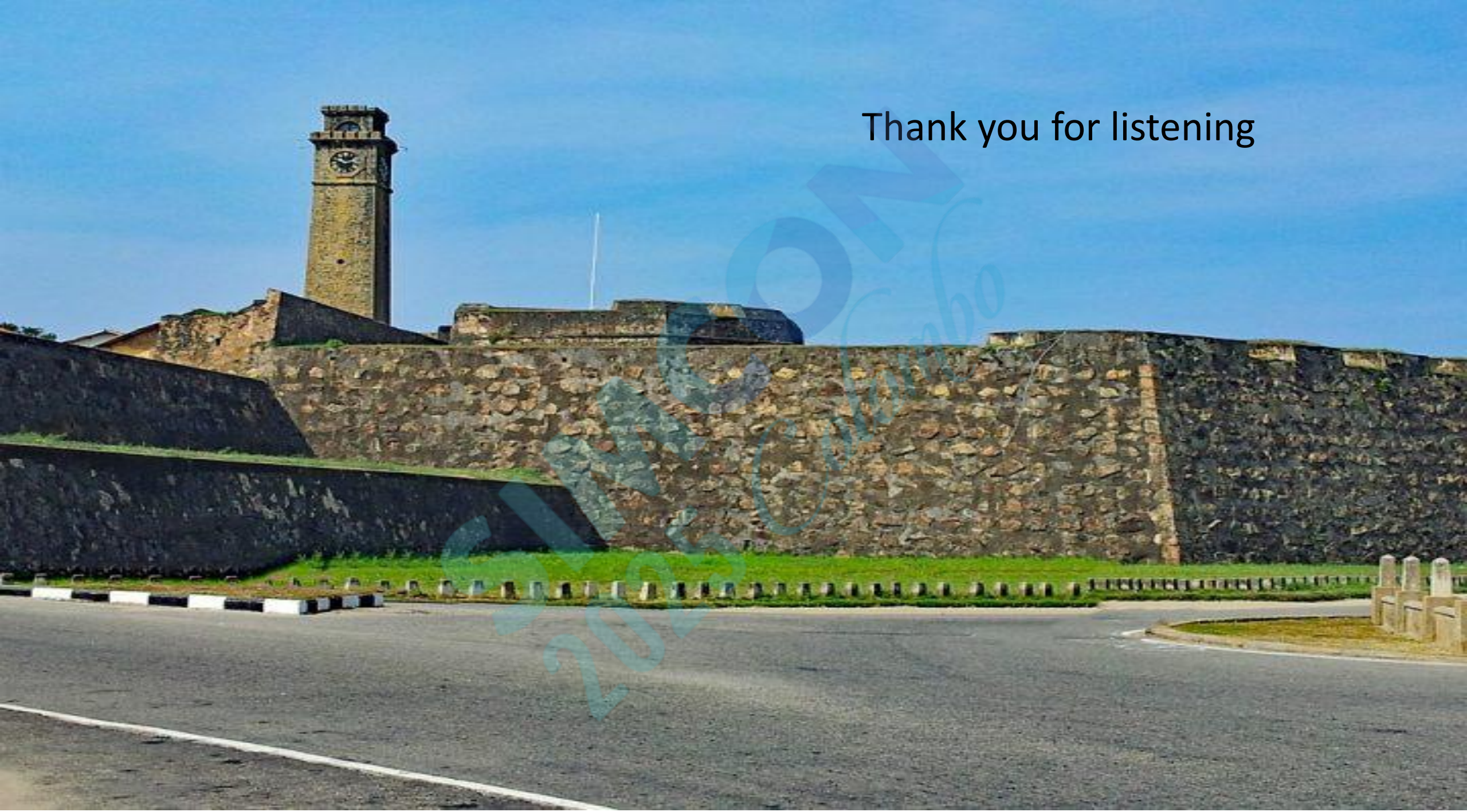
- Recency of osteoporotic fracture
- Higher than average exposure to oral glucocorticoids
- Information on trabecular bone score (TBS)
- Number of falls in the previous year
- Duration of Type 2 diabetes mellitus
- Concurrent information on lumbar spine BMD
- Hip axis length (HAL)
- Primary hyperparathyroidism
- Number of prior fractures

Caveat : There is no evidence base available to inform on the accuracy of multiple adjustments. Pragmatically, any adjustment should be made for the most dominant factor, i.e., that which is likely to have the greatest clinical relevance for the estimated probability.

For guidance on choosing a single risk adjustment in an individual with multiple potential adjustments: please click here.

Summary

- Fracture risk is individual/Treatment should be individualized
- Assessment of baseline fracture risk and determination of treatment targets are crucial
- Different yardsticks are used for the above purposes
- Management plan should be made based on baseline FR and treatment targets
- Sequential therapy is often required
- Diagnostic criteria of osteoporosis is broader
- FRAX output needs adjustments
- Get patient and family involved when making the treatment plan (PCC)


Thank you for listening