Il target terapeutico

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Review

Goal-directed osteoporosis treatment: ASBMR/BHOF task force position statement 2024

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Pragmatic approach to osteoporosis

- *new medical evidence*
- *development of new therapeutic agents*
- *traditional "step therapy" is not optimal for all patients (e.g. common clinical practice to prescribe an oral bisphosphonate as initial treatment for all patients with osteoporosis, unless a contraindication is present)*
- ***goal-directed treatment personalizes therapy based on risk factors***

Cosamn F et al. Journal of Bone and Mineral Research, 2024, 39, 1393–1405

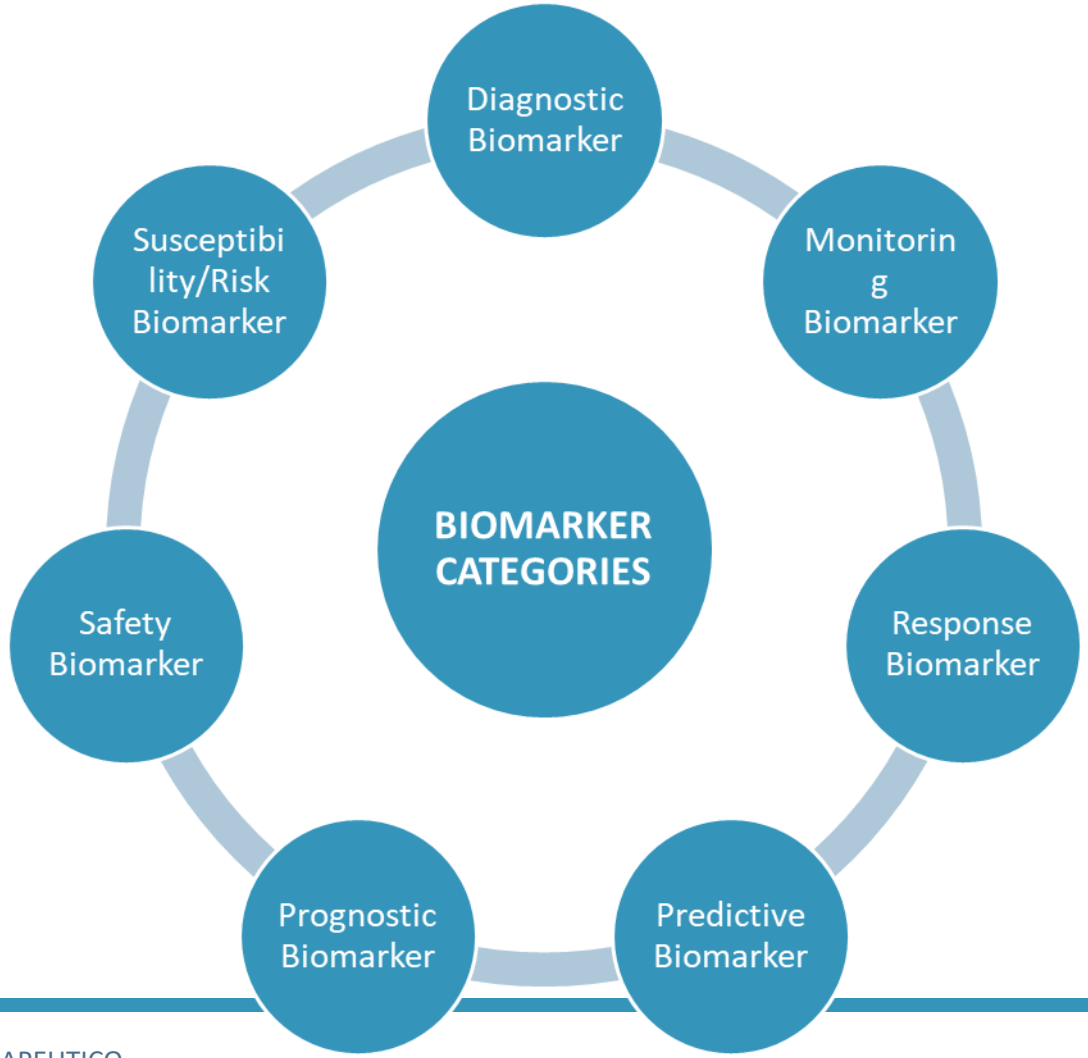
Bone Mineral Density (BMD) as an FDA-Qualified Biomarker

T2T for osteoporosis treatment decisions

Tsoudi E. et al. ECTS position statement

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 1, 264–281
doi:10.1210/clinem/dgaa756
Reports and Recommendations

GOAL: accetable level of fracture risk



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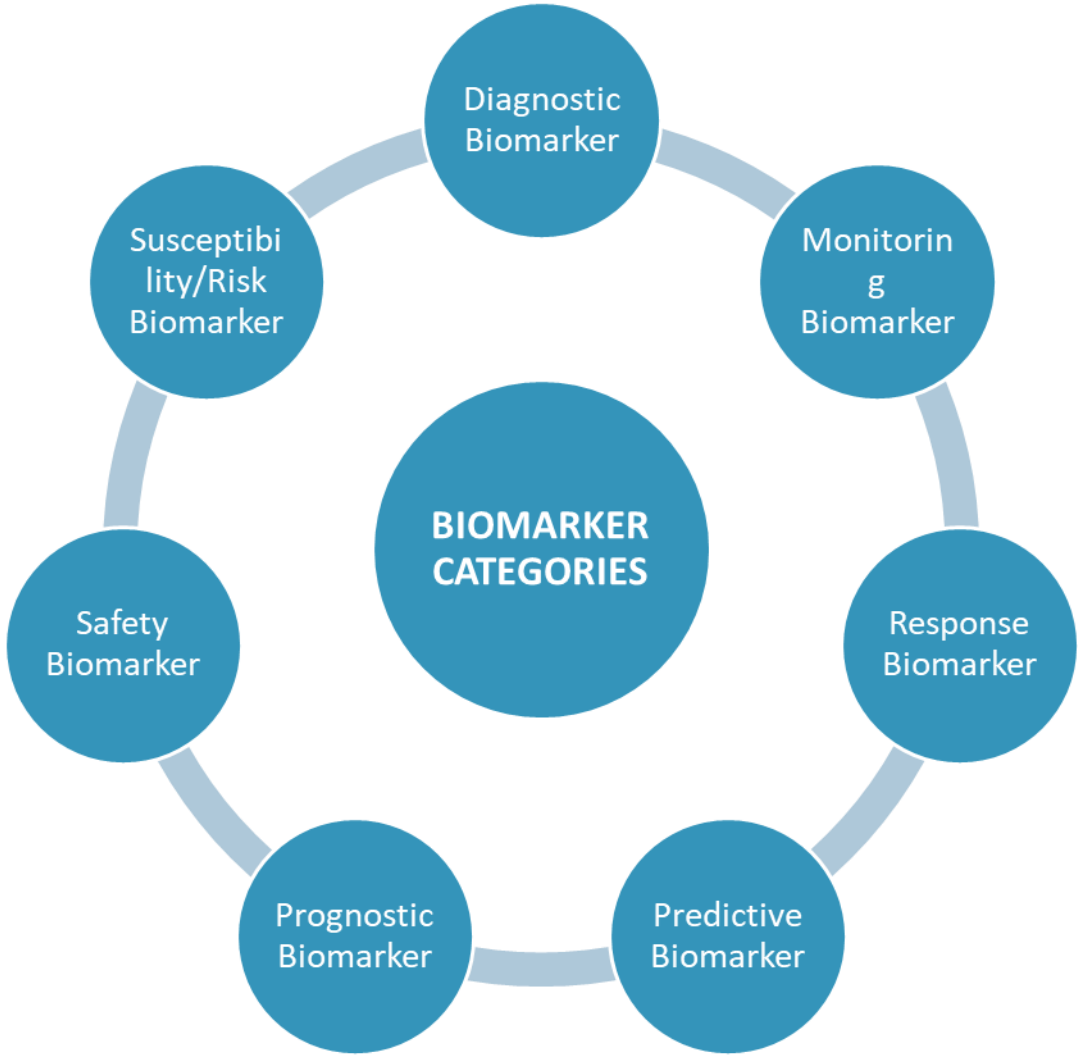

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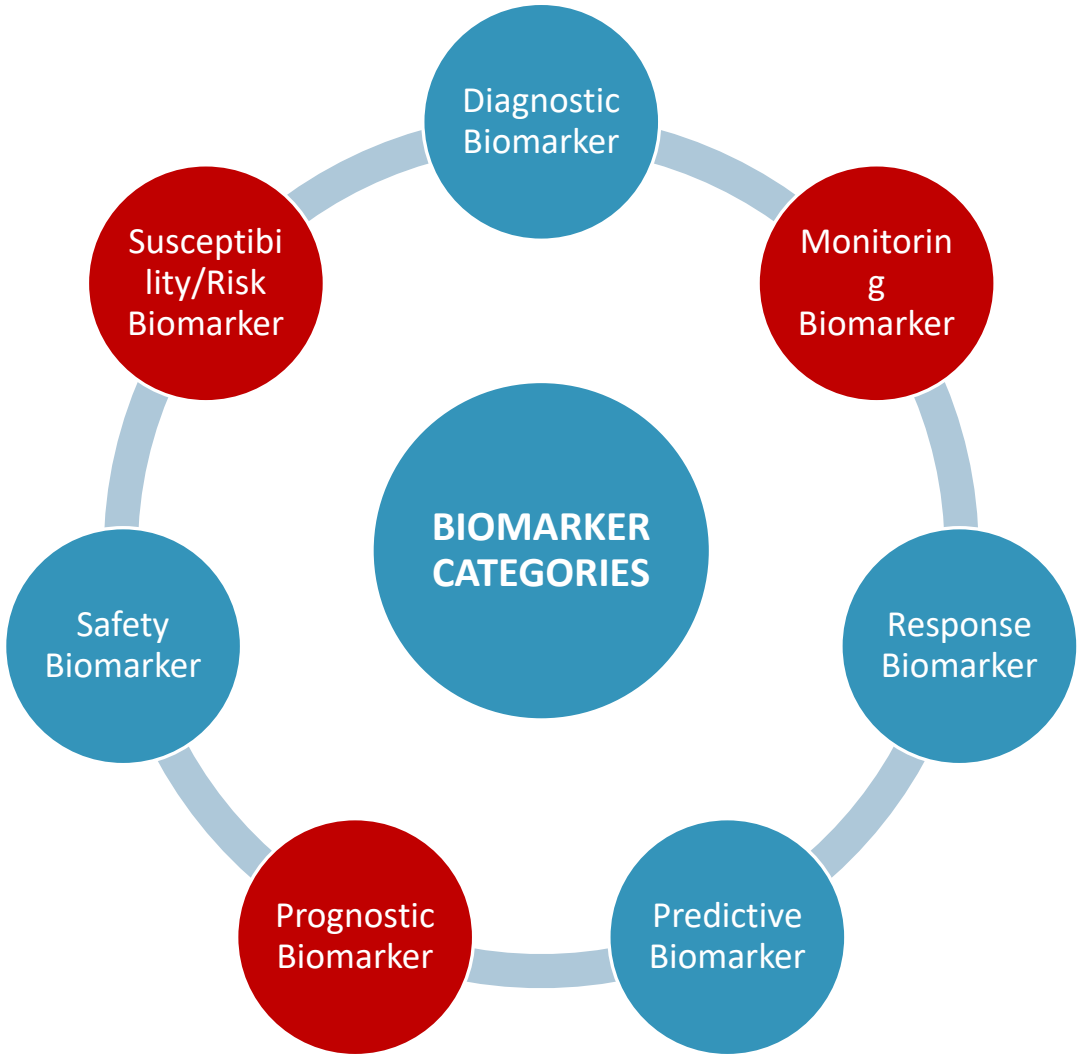

Susceptibility/Risk:

- *Baseline BMD predicts future fracture risk*

Predictive/Monitoring:

- *BMD changes reflect treatment response over time*

Prognostic:

- *Low BMD correlates with higher fracture likelihood*

Key Aspects of BMD

Measurement Standard: Assessed via DXA; requires standardization for regulatory consistency

Limitations: Does not capture bone quality or microarchitecture

- Rapid and sustained fracture risk reduction
- Assessment: fracture history, BMD, and risk factors
- Differentiate **imminent risk** vs. **chronic risk**
- Achieving treatment targets might require intensification of therapy if a fracture occurs or the patient remains far from a BMD target despite osteoporosis treatment
- It must be acknowledged, however, that the BMD effects of switching from antiresorptive to osteoanabolic agents are not as robust as those seen when initiating treatment with an osteoanabolic agent (especially when switching from denosumab)

Rationale for Goal-Directed Therapy

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Selecting treatment to achieve treatment targets

Initial treatment

Selection of initial treatment should consider the probability that a treatment target can be attained over a reasonable period of time, with greater urgency for patients at imminent fracture risk (recent fracture or some multiple prior fractures).

Data to guide these decisions include the likelihood that a **treatment can provide at least a 50% probability of attaining the T-score target over 3 yr**, depending on the initial BMD.

For some patients, it might be appropriate to select treatment to achieve a higher Tscore target, reach the treatment target faster, or provide a higher probability of achieving the treatment target.

Treatment targets

Patients with baseline T-score ≤ –2.5

Patients with baseline T-score > –2.5

Patients at imminent risk of fracture

Treatment targets

Patients with baseline T-score ≤ –2.5

Patients with baseline T-score > –2.5

Patients at imminent risk of fracture

Treatment targets and selection of treatment for patients with T-scores ≤ −2.5

Why is BMD a good target for osteoporosis treatment and what is the best skeletal site?

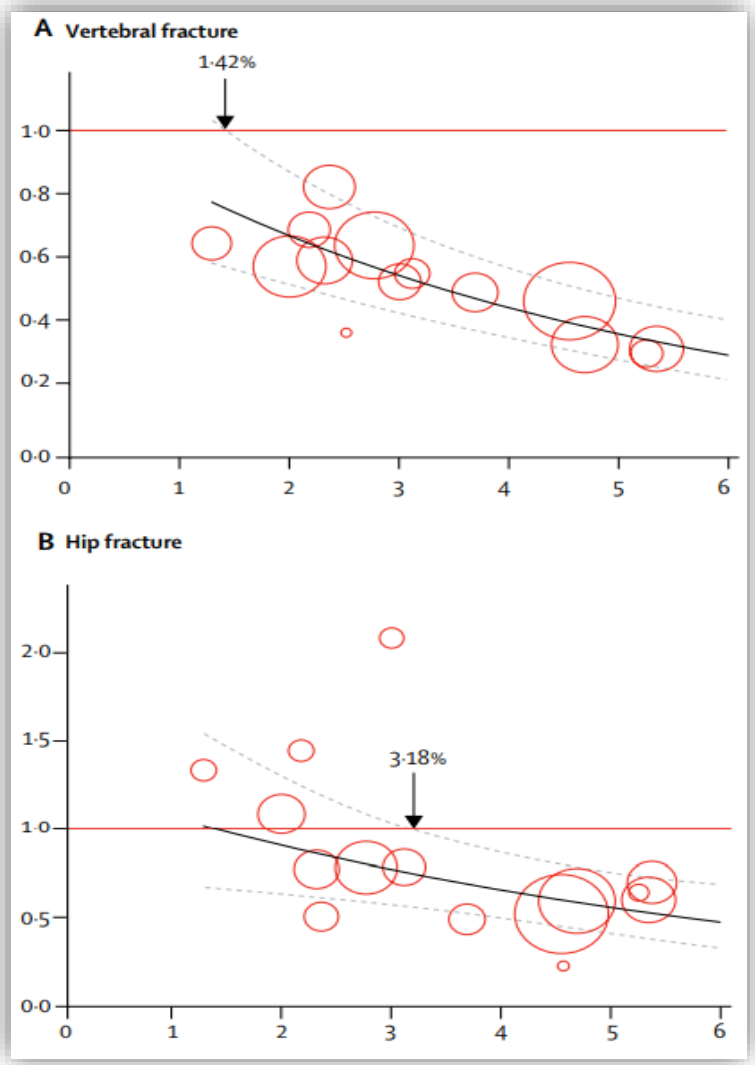
Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials

Dennis M Black, Douglas C Bauer, Eric Vittinghoff, Li-Yung Lui, Andreas Grauer, Fernando Marin, Sundeep Khosla, Anne de Papp, Bruce Mitlak, Jane A Cauley, Charles E McCulloch, Richard Eastell, Mary L Bouxsein*, for the Foundation for the National Institutes of Health Bone Quality Project*

A pooled analysis of individual patient data from multiple randomised placebo-controlled clinical trials.
calculated

1) mean 24-month BMD percent change together with fracture reductions
2) metaregression of the association between treatment-related differences in BMD changes (percentage difference, active minus placebo) and fracture risk reduction

Why is BMD a good target for osteoporosis treatment and what is the best skeletal site?



the **surrogate threshold** effect for total hip BMD indicated that the minimum BMD difference required to show a fracture risk reduction in a future trial was 1.42% for vertebral fractures and 3.18% for hip fractures

	Total Hip	Femoral Neck	Lumbar Spine
Vertebral fracture	59% (50-69)	61% (51-72)	31% (19-44)
Nonvertebral fracture	63% (38-88)	67% (40-95)	52% (23-82)
Hip fracture	48% (21-76)	44% (12-77)	42% (9-75)

Proportion of treatment-related fracture reduction effect explained by BMD increment at the TH, FN, and LS (95% CI).

TH T-score best reflects subsequent fracture risk at both vertebral and nonvertebral sites

Reproducibility is better for the TH than the FN

What is the rationale for choosing the minimum target of > −2.5

- In some countries, a T-score < −2.5 represents an indication for pharmacologic treatment regardless of other risk factors
- Since fracture risk is dependent on other factors, notably age and prevalent fracture a T-score > −2.5 should be considered the minimal target
- Higher T-score targets might also be suggested for patients with advanced age, recent falls history, and poor physical function
- **Setting higher T-score targets in patients with a history of fracture**

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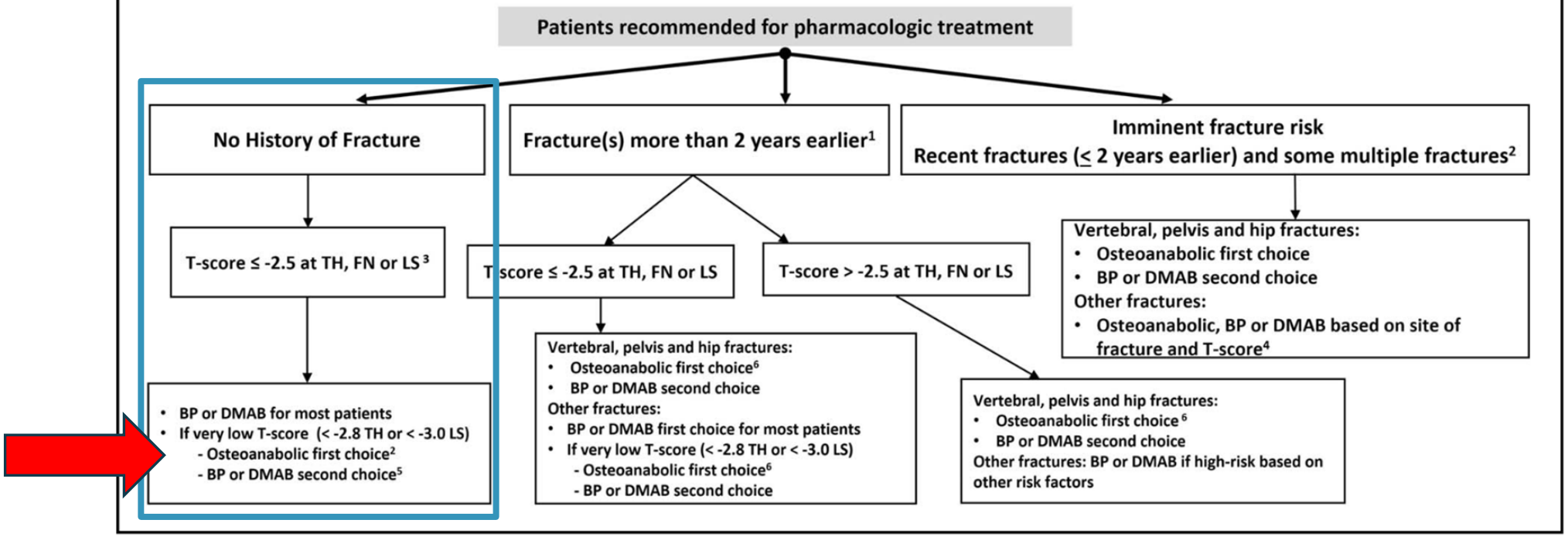
In patients with **TH T-score –2.5 to –2.8** (inclusive) and **LS T-score –2.5 to –3.0** (inclusive)

BMD targets can be attained with a specific treatment over a reasonable period of time

Treatment Targets:

- For imminent risk patients, maximal rapid reduction in fracture risk
- For patients with T-score ≤ -2.5, minimal target is to increase T-score to > -2.5, higher for patients with fracture history, or other major risk factors
- For patients with T-score > -2.5, increase TH T-score by 0.2 (3%) and LS by 0.5 (6%)



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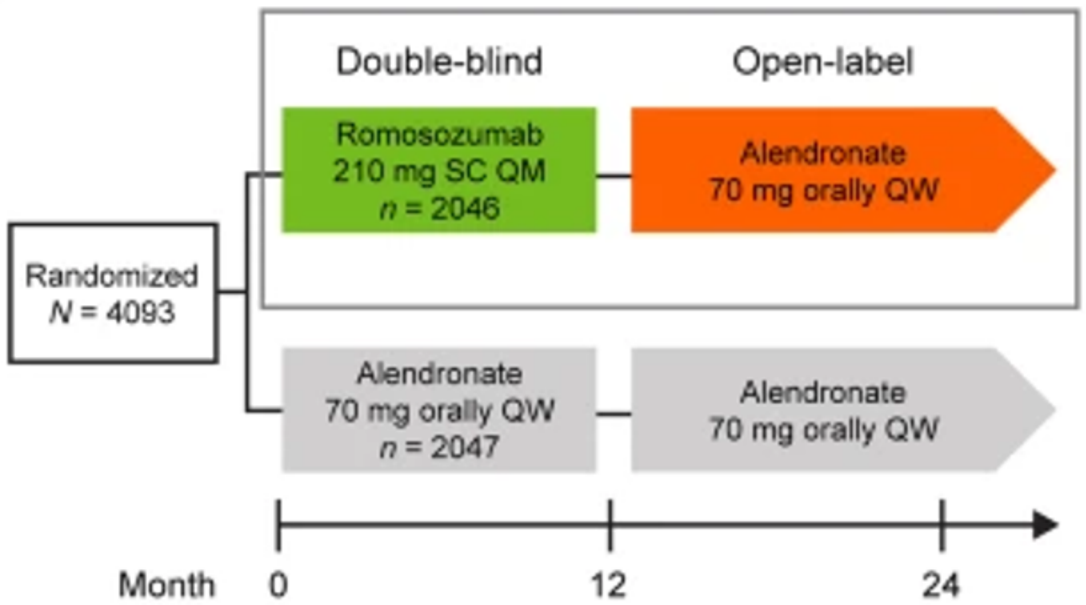
ARCH Trial: post-hoc relationships between T-scores achieved and fracture risk reduction



- Primary endpoints for ARCH were incidence of new vertebral fracture through 24 months and clinical fracture at primary analysis
- This report is focused on results from the post hoc analyses that evaluated mean BMD and corresponding mean T-score changes, and the relationships between T-scores after 1 year of romosozumab or alendronate and subsequent fracture incidence

Cosamn F. et al, J Bone Miner Res, Volume 35, Issue 7, 1 July 2020, Pages 1333–1342

ARCH Trial: post-hoc relationships between T-scores achieved and fracture risk reduction

Characteristic	Romosozumab (n = 1739)	Alendronate (n = 1726)
Age (years), mean ± SD	74.1 ± 7.5	74.0 ± 7.4
BMD T-score, mean ± SD (Total hip)	-2.77 ± 0.67	-2.80 ± 0.65
BMD T-score, mean ± SD (Femoral neck)	-2.88 ± 0.47	-2.90 ± 0.50
BMD T-score, mean ± SD (Lumbar spine)	-2.95 ± 1.23	-3.00 ± 1.22
Previous osteoporotic fracture at ≥45 years of age, n (%)	1718 (98.8)	1709 (99.0)
Prevalent vertebral fracture, n (%)	1671 (96.1)	1651 (95.7)
Moderate	450 (25.9)	476 (27.6)
Severe	1165 (67.0)	1112 (64.4)

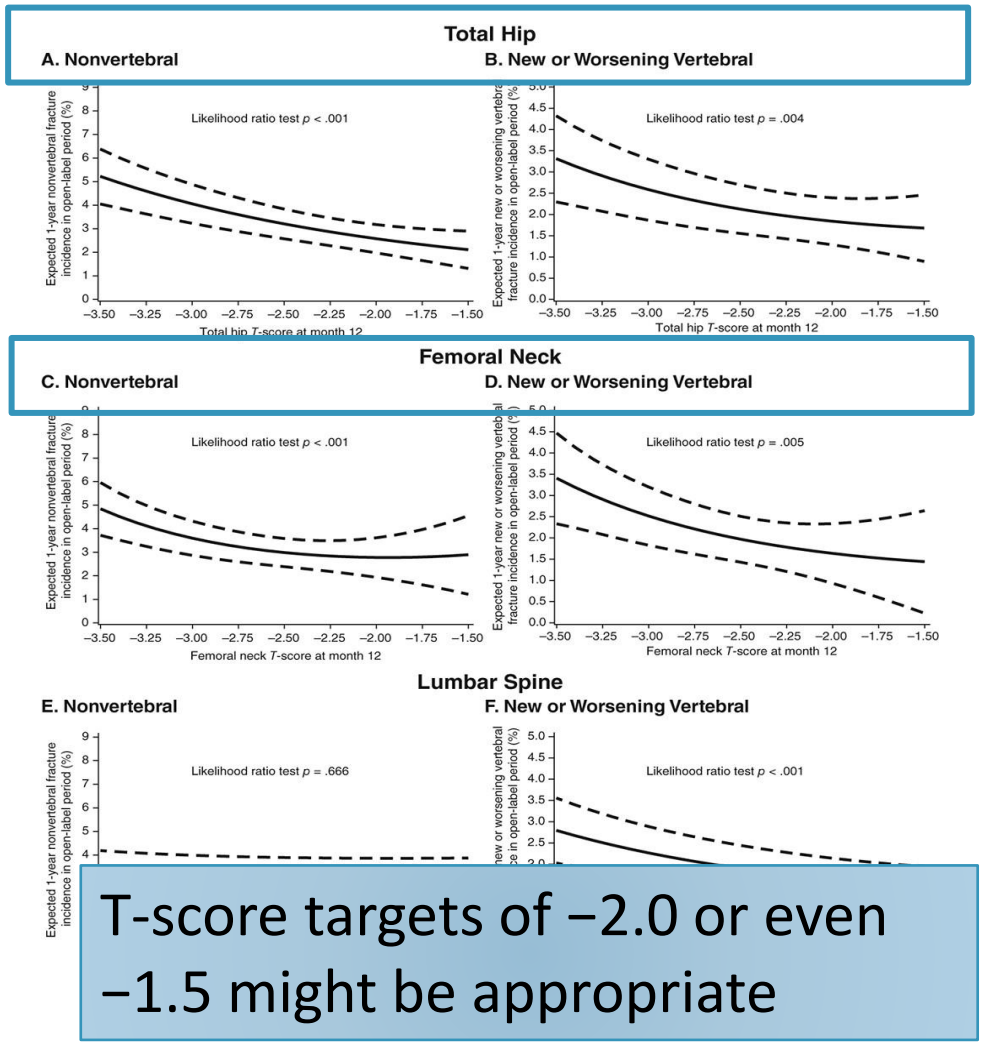
Cosamn F. et al, J Bone Miner Res, Volume 35, Issue 7, 1 July 2020, Pages 1333–1342

	Romosozumab (n = 1739[a])			Alendronate (n = 1726[a])		
Parameter	Mean BMD percentage change	Mean *T*-score change	Mean *T*-score achieved	Mean BMD percentage change	Mean *T*-score change	Mean *T*-score achieved
Total hip	6.3 (6.1–6.5)	0.31 (0.30–0.33)	−2.46 (−2.48 to −2.[illegible])	2.9 (2.7–3.1)	0.15 (0.14–0.16)	−2.63 (−2.64 to −2.62)
Femoral neck	5.0 (4.7–5.3)	0.23 (0.22–0.24)	−2.66 (−2.67 to −2.[illegible])	1.7 (1.5–2.0)	0.09 (0.08–0.10)	−2.80 (−2.81 to −2.79)
Lumbar spine	13.9 (13.6–14.3)	0.90 (0.88–0.92)	−2.07 (−2.09 to −2.05)	5.1 (4.8–5.3)	0.34 (0.32–0.35)	−2.64 (−2.65 to −2.62)

Mean BMD Percentage Changes From Baseline, Mean BMD T-Score Changes From Baseline, and Mean BMD T-Scores Achieved at the Total Hip, Femoral Neck, and Lumbar Spine at Month 12

Cosamn F. et al, J Bone Miner Res, Volume 35, Issue 7, 1 July 2020, Pages 1333–1342

Month 12 total hip (A,B), femoral neck (C,D), and lumbar spine (E,F) T-scores and subsequent nonvertebral and new or worsening vertebral fracture incidence



T-score targets of −2.0 or even −1.5 might be appropriate

1. relationships between T-scores achieved at each of the three skeletal sites at month 12 with subsequent fracture incidence (nonvertebral and new or worsening vertebral fractures)
2. A relationship was observed between month 12 TH T-score and incidence of subsequent nonvertebral fracture (Fig. A; with a likelihood ratio test of p < .001), and new or worsening vertebral fracture (Fig. B; p = .004). Similarly, a relationship was observed between month 12 FN T-score and incidence of subsequent nonvertebral fracture (Fig. C; p < .001) and new or worsening vertebral fracture (Fig. D; p = .005). For LS, a relationship was observed between month 12 T-score and incidence of subsequent new or worsening vertebral fracture (Fig. F; p < .001) but not incidence of subsequent nonvertebral fracture (Fig. E; p = .666)

Cosamn F. et al, J Bone Miner Res, Volume 35, Issue 7, 1 July 2020, Pages 1333–1342

Treatment	Total Hip	Lumbar Spine
Alendronate	-2.7	-3.0
Denosumab	-2.8	-3.1
Romosozumab/Alendronate	-2.9	-3.5
Abaloparatide/Alendronate	-2.9	-3.5
Romosozumab/Denosumab	-3.1	-3.7

Lowest baseline T-score that permits > 50% of women to achieve a T-score > –2.5 in approximately 3 yr

Cosamn F et al. Journal of Bone and Mineral Research, 2024, 39, 1393–1405

Treatment targets

Patients with baseline T-score ≤ –2.5

Patients with baseline T-score > –2.5

Patients at imminent risk of fracture

Treatment targets and selection of treatment for patients with T-scores > −2.5

More than half of all patients who have adulthood fractures have BMD levels above osteoporosis range.

A single prior fracture that occurred more than 2 yr earlier, subsequent risk might differ substantially by skeletal site and time since fracture.

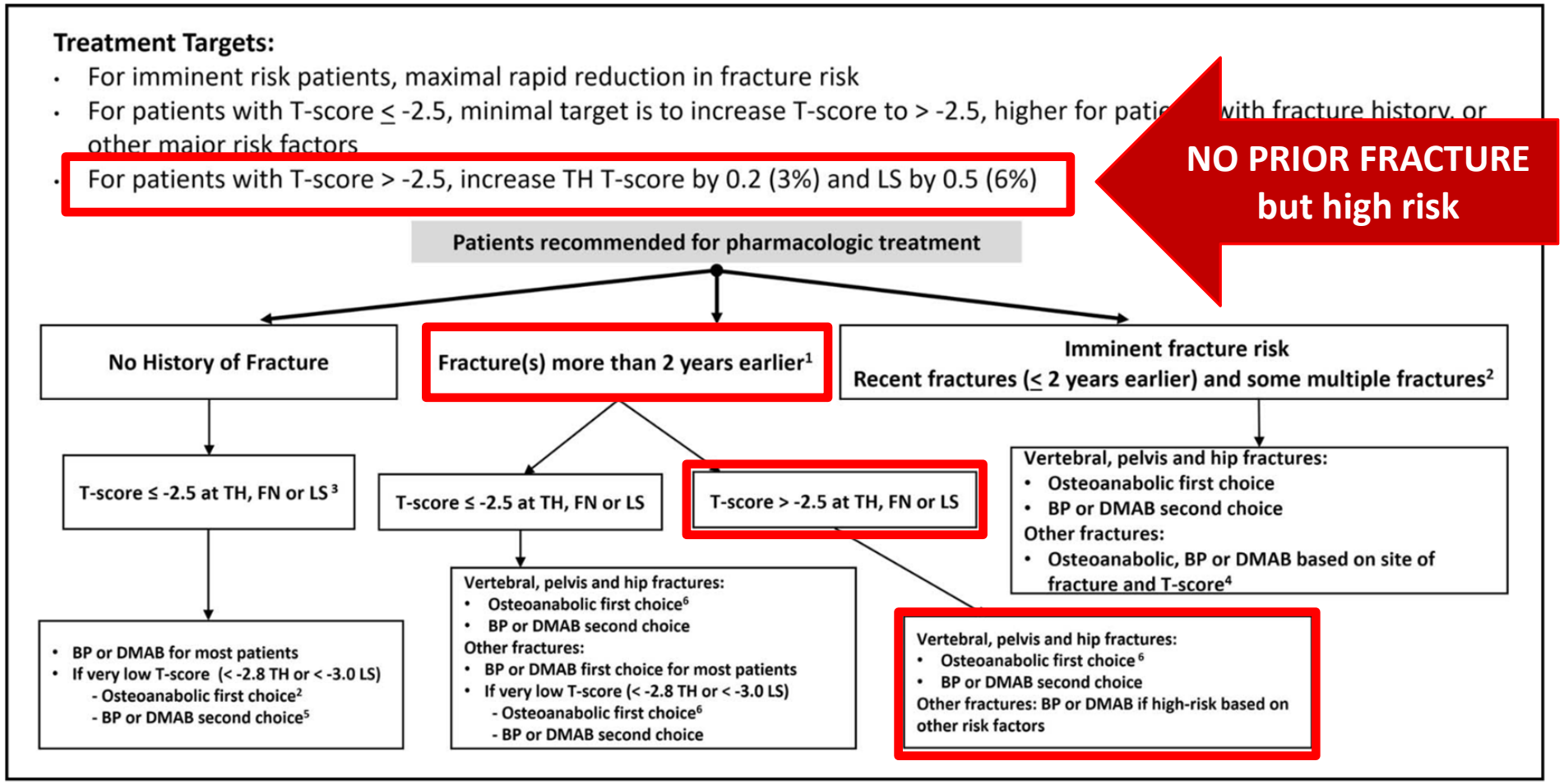
Prior vertebral, hip, and pelvic fractures are associated with higher and more persistent risk than other fractures.

There is a paucity of evidence to guide the actual BMD level to target in these patients.

Percentage increase in BMD is a function of baseline BMD.

Cosamn F et al. Journal of Bone and Mineral Research, 2024, 39, 1393–1405

Treatment targets and selection of treatment for patients with T-scores > −2.5



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Treatment targets

Patients with baseline T-score ≤ –2.5

Patients with baseline T-score > –2.5

Patients at imminent risk of fracture

Selection of treatment for patients at imminent risk

Fracture site, severity, and time from last fracture occurrence remain important determinants of subsequent risk

This risk is largely independent of baseline T-score

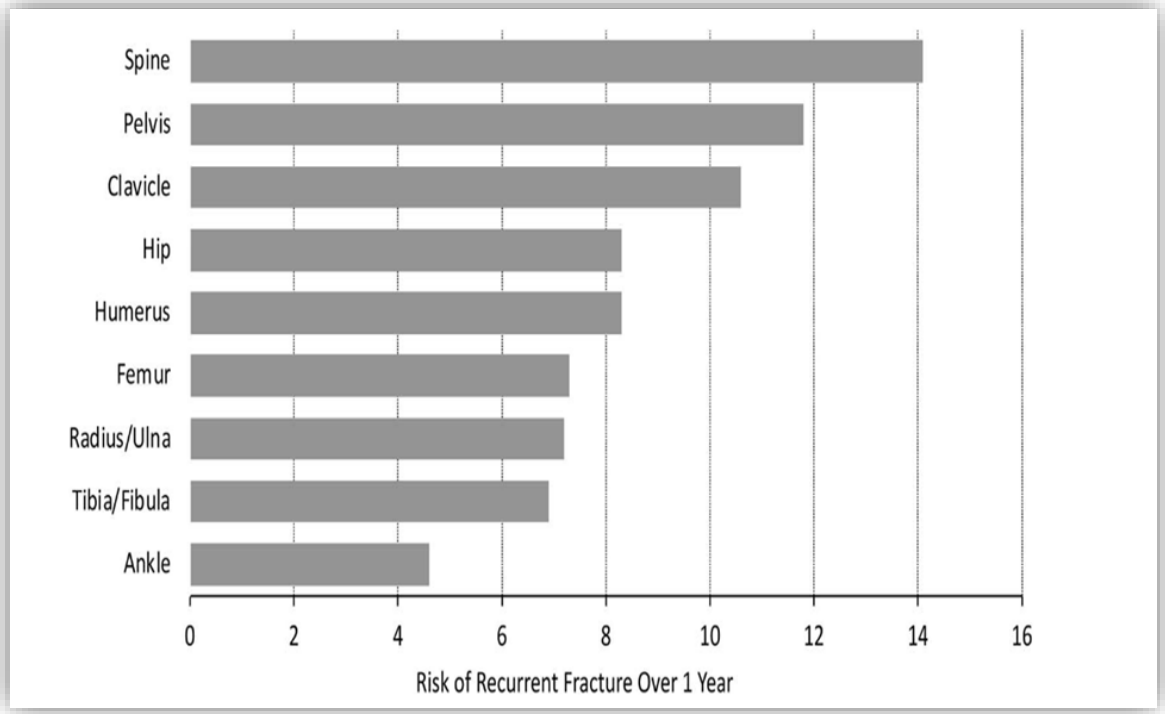
Recent fracture as a predictor of subsequent fracture

The risk of fracture is increased dramatically for up to 2 yr after the occurrence of the first fracture

Average risk of subsequent fracture is 10% in the very next year and 18% in the 2 yr following the first fracture.

Patients with ***multiple prior fractures*** may also be at imminent risk for more fractures.

377,500 women age 65 yr and older who had a first clinical fracture



Balasubramanian A et al. Osteoporos Int. 2019;30(1):79–92.

In patients at imminent risk, especially those **with recent fractures of the spine, hip, and pelvis, rapid and maximum fracture risk reduction is the first and most important treatment target**

Treatment Targets:

- For imminent risk patients, maximal rapid reduction in fracture risk
- For patients with T-score ≤ -2.5, minimal target is to increase T-score to > -2.5, higher for patients with fracture history, or other major risk factors
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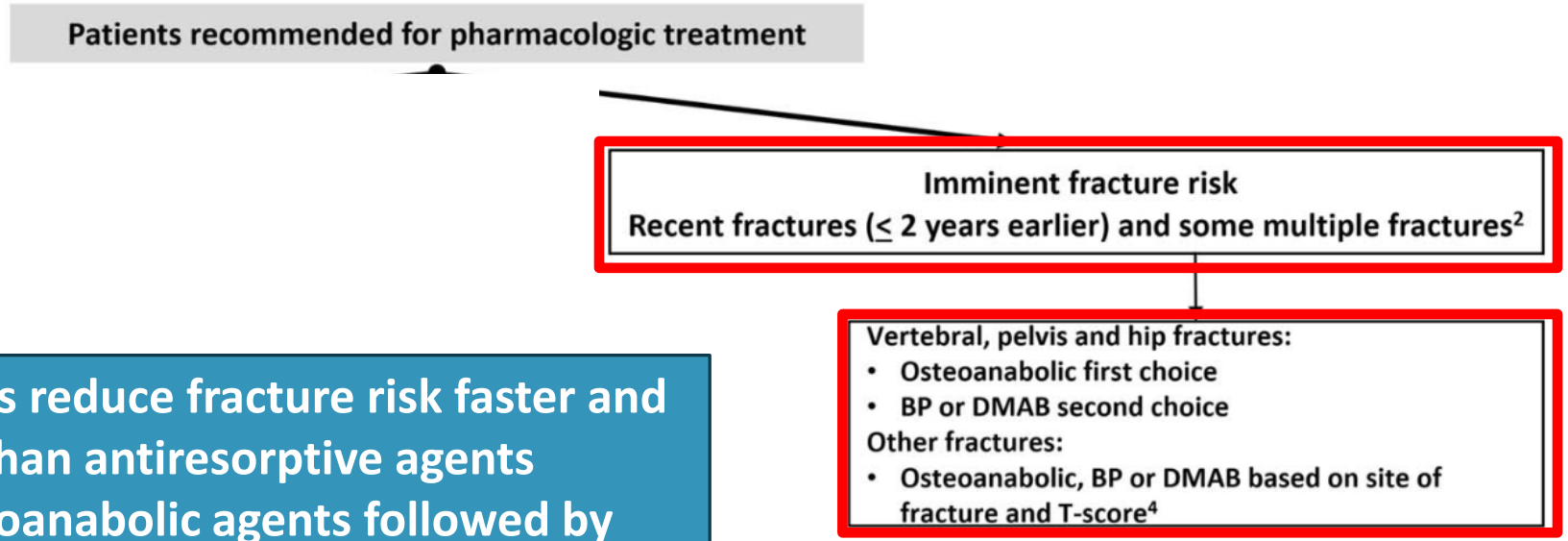


- **osteoanabolic agents reduce fracture risk faster and to a greater extent than antiresorptive agents**
- **treatment with osteoanabolic agents followed by antiresorptive agents also increases BMD more than the reverse treatment sequence**

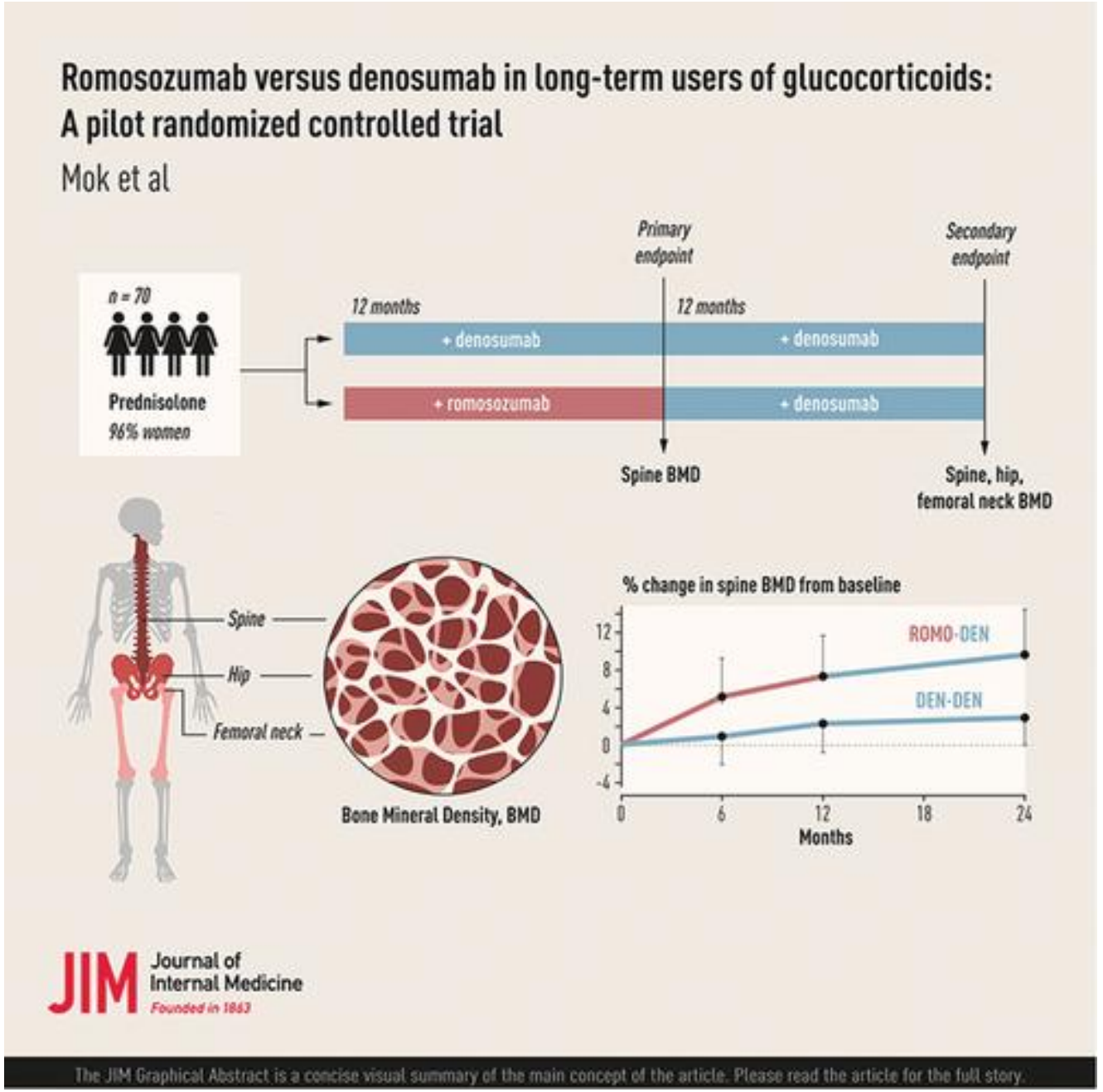
Cosamn F et al. Journal of Bone and Mineral Research, 2024, 39, 1393–1405

Determining if treatment targets have been achieved

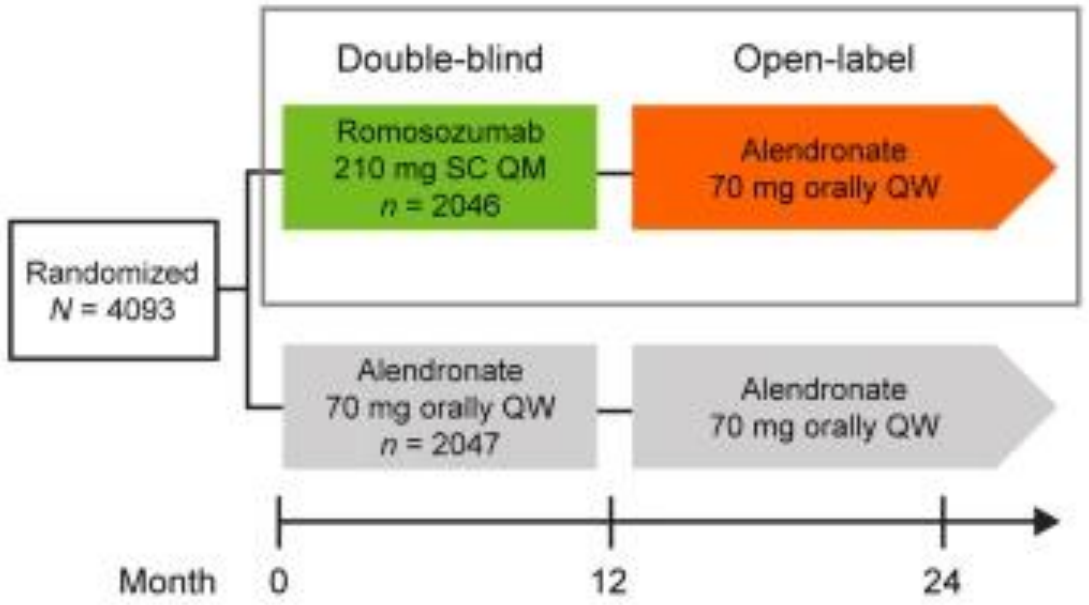
- repeat BMD testing
- assessment for ***new fractures***, including vertebral imaging: ***having a baseline vertebral image before starting treatment*** allows confirmation that an incident vertebral fracture has occurred on follow-up vertebral imaging
- if a patient experiences ***one or more new fractures***, it indicates that the most important treatment ***target has not been met, regardless of the T-scores achieved***
- when a treatment target has not been achieved or is unlikely to be achieved, consider changing to more potent therapy (or continuing the highest potency treatment sequence)

Limits

- evidence used is based almost solely on women self-reporting as White, primarily 60 yr of age and older
- specific BMD levels are associated with a wide variation in absolute fracture risk, depending on ethnicity and geography
- the treatment targets might also differ in patients with secondary osteoporosis conditions such as glucocorticoid-induced osteoporosis or in patients with diabetes mellitus
- consensus is also needed on defining an acceptable level of fracture risk after treatment
- limitations imposed by health systems and insurers


Romosozumab versus denosumab in long-term users of glucocorticoids:
A pilot randomized controlled trial
Mok et al
n = 70
Prednisolone
96% women
12 months
12 months
Primary endpoint
Secondary endpoint
+ denosumab
+ denosumab
+ romosozumab
+ denosumab
Spine BMD
Spine, hip, femoral neck BMD
Spine
Hip
Femoral neck
Bone Mineral Density, BMD
% change in spine BMD from baseline
ROMO-DEN
DEN-DEN
12
8
4
0
-4
0
6
12
18
24
Months
JIM Journal of Internal Medicine
Founded in 1863
The JIM Graphical Abstract is a concise visual summary of the main concept of the article. Please read the article for the full story.

ARCH Trial: post-hoc relationships between T-scores achieved and fracture risk reduction



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