



Boning Up on Osteoporosis: It's Not Just About the T-score

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Disclosure

I have no financial interests or relationships
to disclose.

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Learning Objectives

- Identify patients at high risk of osteoporosis and osteoporotic fracture and select evidence-based screening and diagnostic modalities
- Recognize the efficacy, risks, and benefits of new and emerging treatments for osteoporosis
- Understand the latest guidelines for the prevention and treatment of osteoporosis

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W.H.O.'s Definition of Low Bone Mass and Osteoporosis

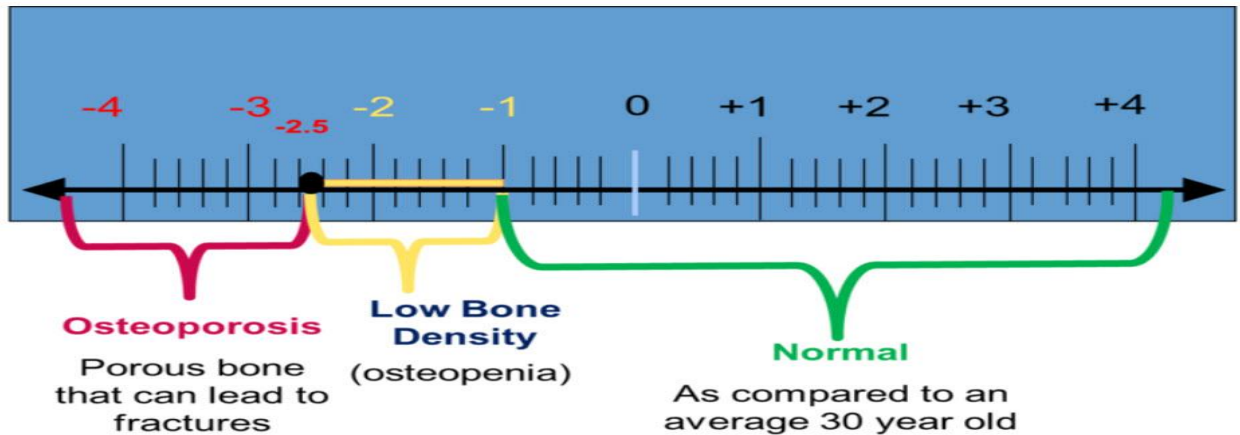
World Health Organization Definition-Criteria:

CLASSIFICATION	T-score
NORMAL BMD (Bone Mineral Density)	> -1.0
Low Bone Mass (Osteopenia)	-1.0 -- -2.49
Osteoporosis	$\leq$ -2.50

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World Health Organization Definition-Criteria

T-score



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W.H.O's Definition of Osteoporosis



"A T score of -2.5 or worse, meaning 2.5 standard deviations below the mean for a normative population of young healthy women".



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Definition of Osteoporosis

Osteoporosis: bone loss which leads to
a decrease in bone strength which
leads to an increased risk of fracture.

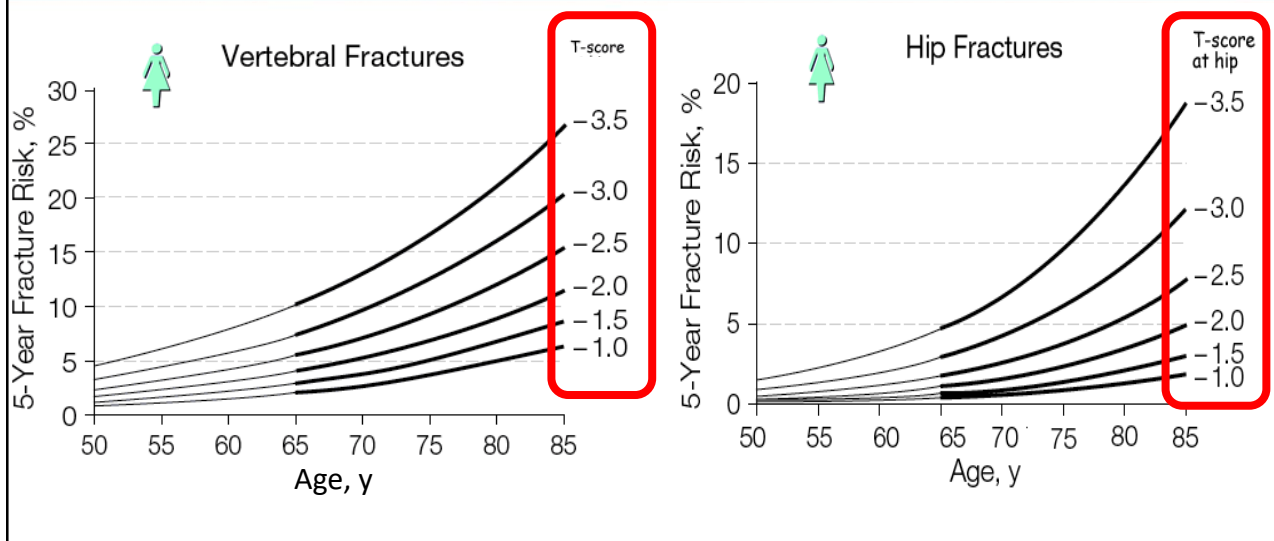
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One More Definition: Severe Osteoporosis AKA “Very High Risk of Fracture” (Disparate Definitions)

- 1. A T-score of ≤ -3.0
- 2. A history of multiple fragility fractures
- 3. One who experienced a fragility fracture while on Rx
- 4. Woman taking ≥ 7.5 mg prednisolone daily (long-term Rx)

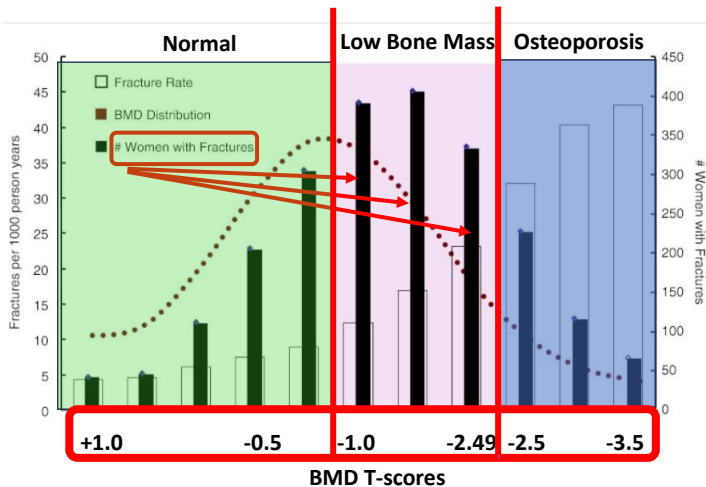
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We've Been Taught to Think Like This



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Your Patient's Absolute Risk of a Fracture (Black Bars)



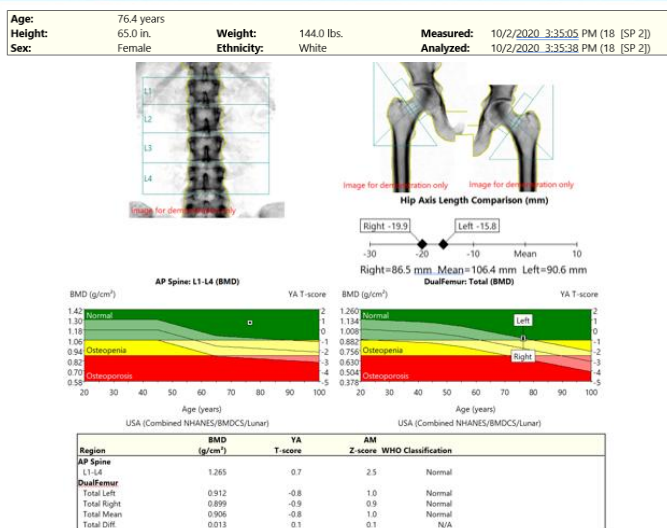
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What We Forget ALL TOO OFTEN

- The definition of osteoporosis is NOT just a T score of ≤ -2.5



Used with permission from GE Healthcare

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Osteoporosis Can Also Be Defined by A FALL, Alone

- A fall from standing height that results in...
 - a fragility fracture of the spine or hip qualifies as defining osteoporosis, irrespective of her T-score
 - AND / OR -----
 - a fragility frx of the proximal humerus or distal forearm/wrist, IF her T-score is any value < -1.0



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We've Been Exposed to a LOT of MYTH-Information

- It is all too easy to focus on T-scores ... and to forget why we are measuring BMD
- Our goal is NOT to achieve improved T-scores
- Our goal IS TO PREVENT the FRACTURES and FALLS that directly result from osteoporosis- called fragility fractures

BMD = bone mineral density

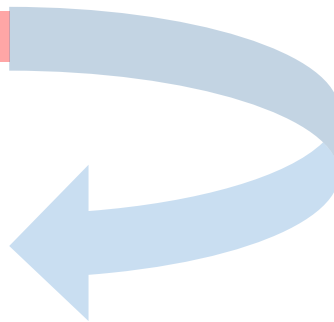
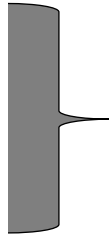


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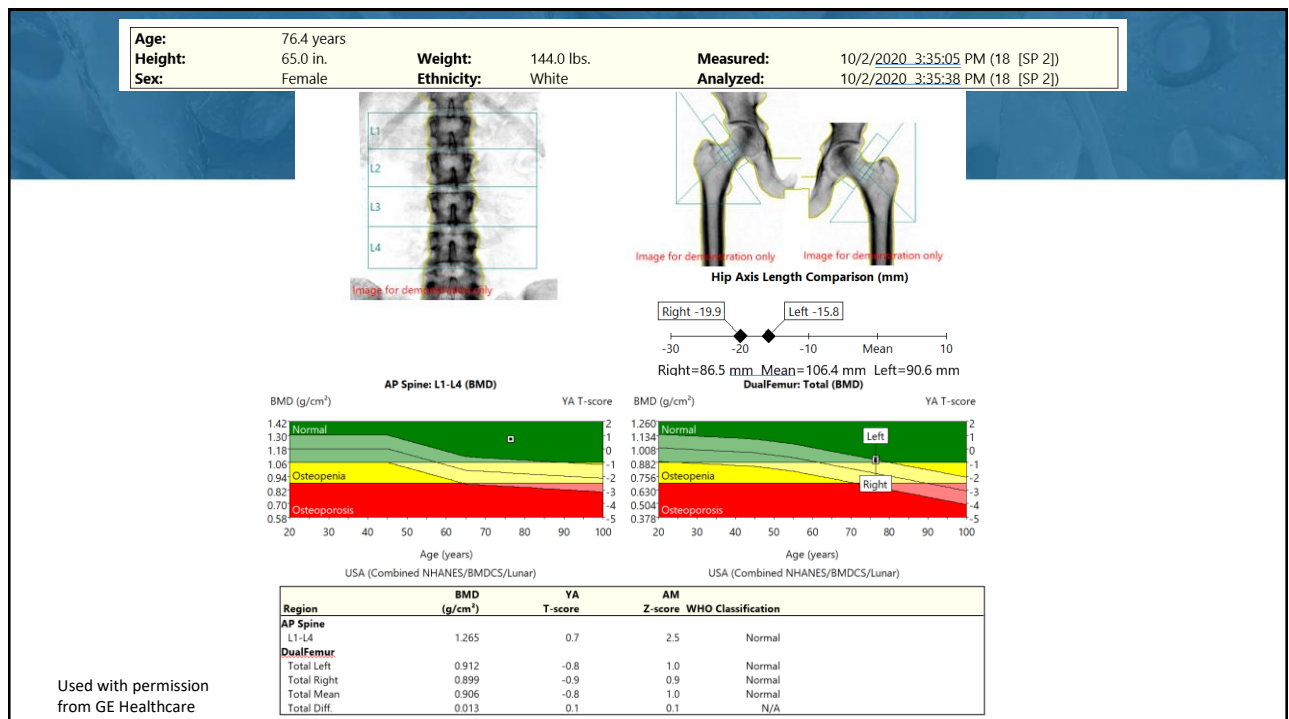
Critically Important Clinically Important...PERSPECTIVE

- There are **more osteoporotic fractures** in the U.S. than the combined total of

- Heart attacks
- Strokes
- Breast cancers
- GYN malignancies



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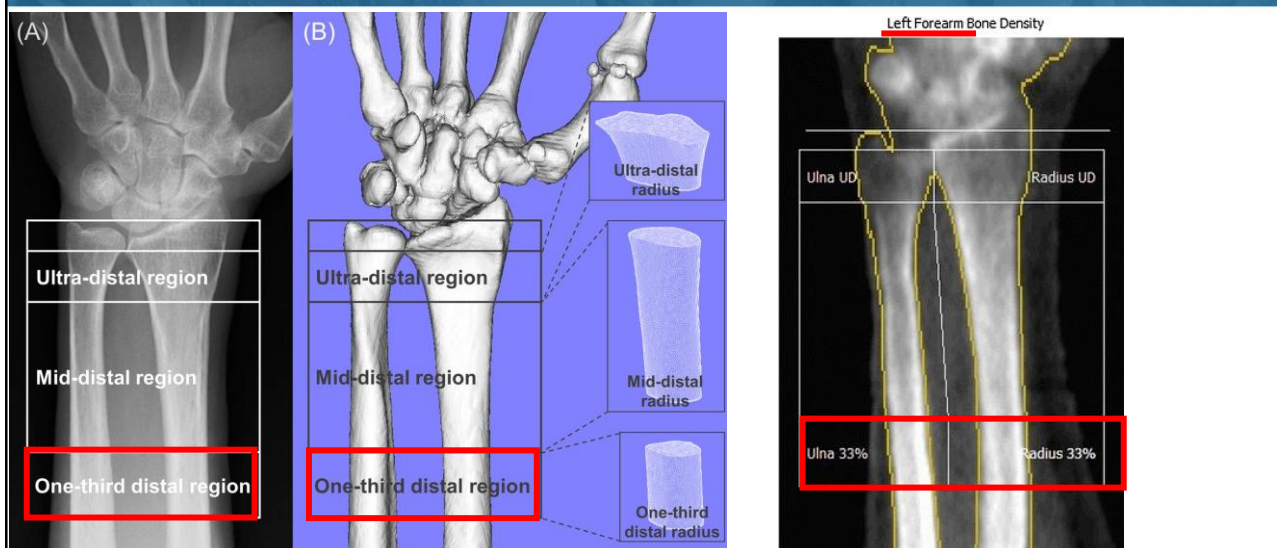
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Peripheral DXA of Distal Radius (or Heel)



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“1/3 Distal Radius” AKA “The 33% Radius” in the NON-DOMINANT Forearm

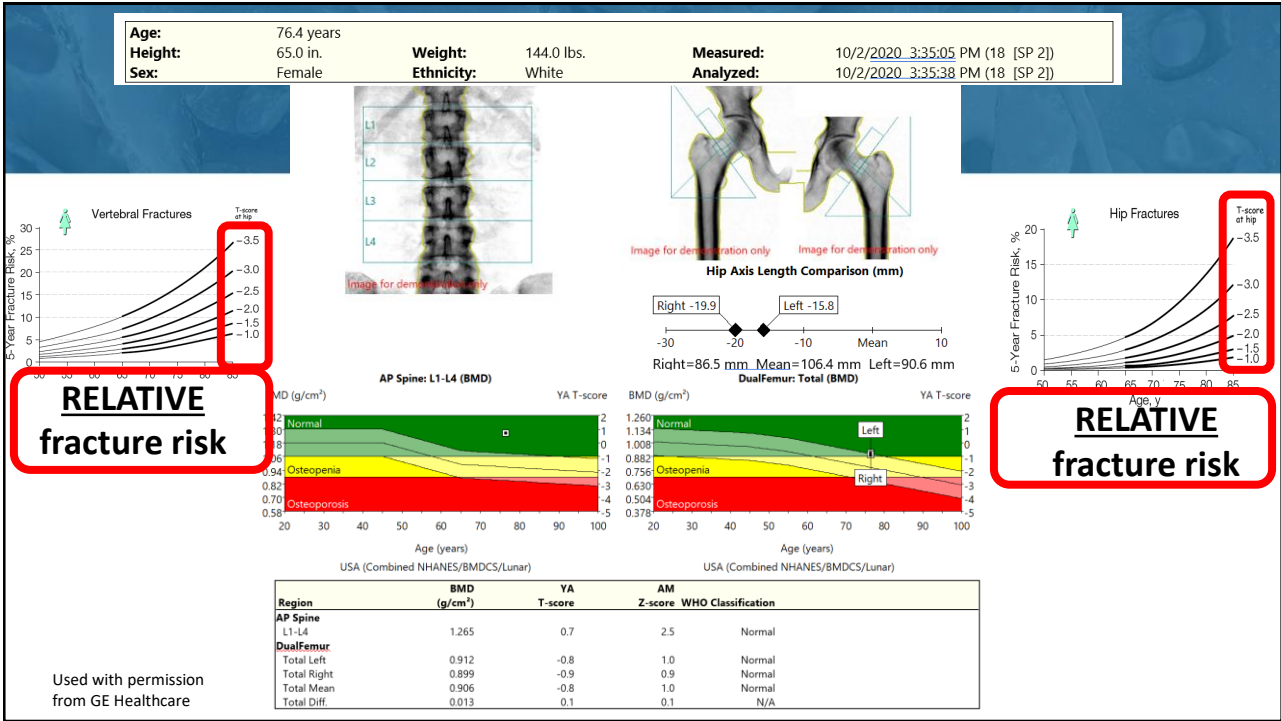


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Peripheral DXA of 1/3 Distal Radius for Patients with Prior Surgery



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We CAN
Do a Better Job
of Predicting...



ACTUAL FRACTURE RISK (Absolute Risk, Not Relative Risk)

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The Optimal Fracture Prediction Profile - 2024

Combination:

- **BMD (central DXA;** peripheral DXA is satisfactory if central DXA testing is not available/reliable)
- **FRAX®**
- +/- Trabecular Bone Score (TBS)

DXA = bone density scanning / dual-energy x-ray absorptiometry

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How Familiar Are YOU with the FRAX Tool?

- A. I've never heard of it
- B. I've heard of it, but never (or rarely) use it clinically
- C. I use it sometimes, but not routinely
- D. I use it routinely



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FRAX® Risk Assessment ACTUAL (Not Relative) Fracture Risk

This patient has a 10-year hip fracture risk of ____%; and a 10-year major osteoporotic fracture risk of ____%

Based upon...

- Age, gender, ethnicity
- **Y N** Hx of fragility fracture, >50 y/o
- **Y N** Rheumatoid arthritis
- **Y N** Family Hx of a hip fracture - parent
- **Y N** Low BMI / body weight
- **Y N** Ever-Hx of steroid Rx $\geq 5\text{mg/d}$ x ≥ 3 mos
- **Y N** Alcohol - ≥ 3 units / day
- **Y N** Current smoking
- +/- BMD @ femoral neck

Lewiecki EM. JBMR. 2007; 22: 1832-41.

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Country: **US (Caucasian)** Name/ID: **Jane Doe** [About the risk factors](#)

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
 Age: Date of Birth: Y: M: D:

2. Sex ☐ Male ☒ Female

3. Weight (kg)

4. Height (cm)

5. Previous Fracture ☒ No ☐ Yes

6. Parent Fractured Hip ☒ No ☐ Yes

7. Current Smoking ☒ No ☐ Yes

8. Glucocorticoids ☒ No ☐ Yes

9. Rheumatoid arthritis ☒ No ☐ Yes

10. Secondary osteoporosis ☒ No ☐ Yes

11. Alcohol 3 or more units/day ☒ No ☐ Yes

12. Femoral neck BMD (g/cm²)
 T-Score

BMI: 32.1
 The ten year probability of fracture (%)
 with BMD

Major osteoporotic	11
Hip Fracture	2.1

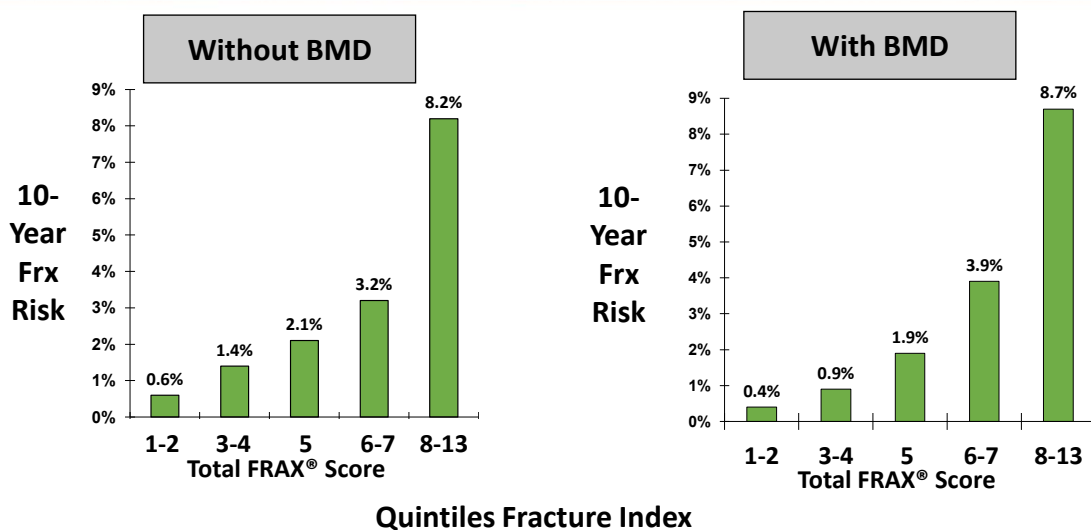
If you have a TBS value, click here:

<https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9>

The U.S. thresholds for High Risk: $\geq 20\%$ major; $\geq 3\%$ hip

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Ten-Year Risk of Hip Fracture



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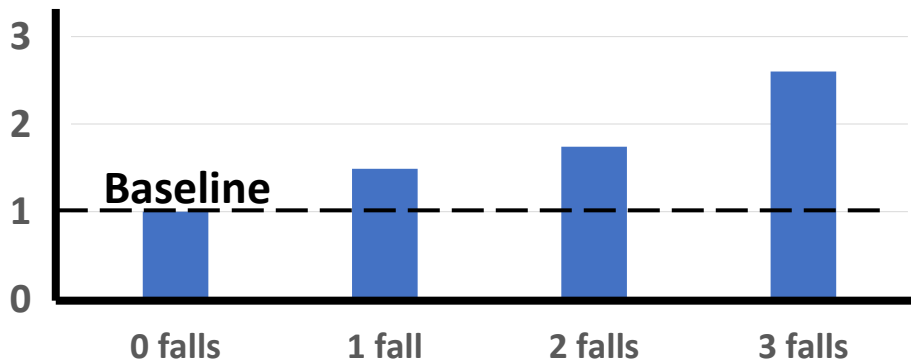


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One Powerful Screening Question in Addition to FRAX®

“Have you fallen in the past year ?”

Risk for a Major Osteoporotic Fracture



Leslie WD. Osteopor Int. 2019. Aug 2. doi: 10.1007/s00198-01905106-3

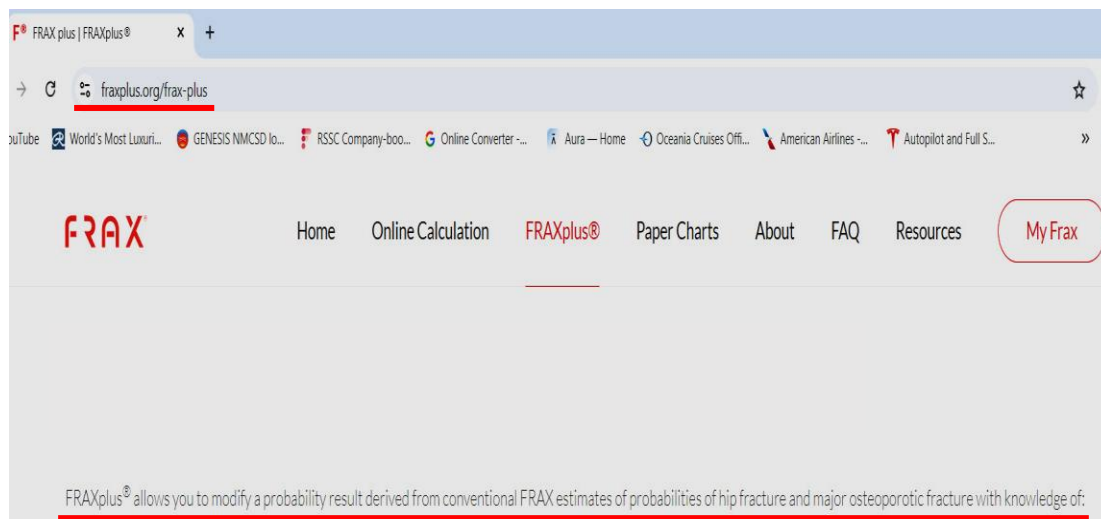
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Limitations of FRAX

- **Valid only given specific conditions:**
- Postmenopausal women > 40 y/o
- ~~Not on Rx~~
 - ~~Cannot follow up/repeat FRAX after beginning Rx~~
- No prior hip or vertebral fracture
- Categorical dichotomous variables
 - Does not allow for degrees of risk-exposure

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FRAXplus® Risk Assessment



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FRAXplus® Risk Assessment

Select the **SINGLE** most dominant factor – most likely to impact the actual risk score. (FRAXplus® provides guidance to clinicians for this)

- Recency of a previous osteoporotic (fragility) fracture
- HIGH-dose glucocorticoids
- Type-2 diabetes
- Concurrent lumbar spine BMD
- Details of falls history – 0, 1, 2, or 3 over the past 12 months
- Trabecular bone score
- Hip axis length

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How to Use FRAXplus® - Step 1

Questionnaire

1. Age (between 40 and 90 years) or Date of Birth: 1956-10-18

2. Sex: ☐ Female ☒ Male

3. Weight: Pounds 170 Pounds / Inch... ▾

4. Height: Inches 72

5. Previous Fracture: ☒

6. Parent Fractured Hip: ☐ X

7. Currently Smoking: ☐ X

8. Glucocorticoids: ☐ X

9. Rheumatoid arthritis: ☐ X

10. Secondary osteoporosis: ☐ X

11. Alcohol 3 or more units/day: ☐ X

12. Femoral neck BMD: Select BMD ▾

Calculate **Clear**

Age: 68 BMI: 23.05 without BMD

THE TEN-YEAR PROBABILITY OF FRACTURE

Major osteoporotic **11.74%**

Hip **3.05%**

Adjust your results, try FRAX plus®

What does FRAX plus® do? Click here

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How to Use FRAXplus® - Step 2

FRAX results

Adjust your results with FRAX plus®

11/7/2024, 10:56:05 AM Country: US (Caucasian)

Age	68	Currently Smoking	No	without BMD	
Sex	Male	Glucocorticoids	No	BMI	23.05
Weight	170 Pounds	Rheumatoid arthritis	No		
Height	72 Inches	Secondary osteoporosis	No		
Previous Fracture	No	Alcohol 3 or more units/day	No		
Parent Fractured Hip	Yes				

THE TEN YEAR PROBABILITY OF FRACTURE

Major osteoporotic	10.22%
Hip Fracture	2.39%

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How to Use FRAXplus® - Step 3

Please select one of the available adjustment algorithms:

Adjust probability according to recent fractures

Adjust probability according to the dose of oral glucocorticoids

Adjust probability according to TBS value

Adjust probability according to duration of diabetes

Adjust probability according to recent falls

Adjust major osteoporotic fracture probability according to differences between femoral neck and lumbar spine BMD T-scores

Adjusting FRAX hip fracture probabilities according to the hip axis length (HAL)

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How to Use FRAXplus® - Step 4

Adjust your results with FRAX plus®

For guidance on choosing a single risk adjustment in an individual with multiple potential adjustments, [please click here](#).

Please select one of the available adjustment algorithms:

Adjust probability according to recent fractures

Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. (only available if previous fracture is yes)

Previous Fracture

- ☐ Vertebral
☒ Hip
☐ Humeral
☐ Forearm
☐ Other

Time since previous fracture

- ☐ 0 to 1 month
☒ 1 to 6 months
☐ 6 to 12 months
☐ 12 to 24 months

Adjust probability

Adjust probability according to the dose of oral glucocorticoids

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How to Use FRAXplus® - Step 4

Adjust your results with FRAX plus®

For guidance on choosing a single risk adjustment in an individual with multiple potential adjustments, [please click here](#).

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Previous Fracture

- ☐ Vertebral
☒ Hip
☐ Humeral
☐ Forearm
☐ Other

Time since previous fracture

- ☐ 0 to 1 month
☒ 1 to 6 months
☐ 6 to 12 months
☐ 12 to 24 months

Adjust probability

Adjust probability according to the dose of oral glucocorticoids

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How to Use FRAXplus® - Step 5

Age	68	Currently Smoking	No	without BMD	
Sex	Male	Glucocorticoids	No	BMI	23.05
Weight	170 Pounds	Rheumatoid arthritis	No		
Height	72 Inches	Secondary osteoporosis	No		
Previous Fracture	Yes	Alcohol 3 or more units/day	No		
Parent Fractured Hip	No				

THE TEN-YEAR PROBABILITY OF FRACTURE

Major osteoporotic Hip Fracture **UNadjusted** 11.74% 3.05%

PROBABILITY ADJUSTED ACCORDING TO RECENT FRACTURE

Previous Fracture Hip
Time since previous fracture 1 to 6 months
Adjusted Major osteoporotic 18%
Adjusted Hip Fracture 9.16% **ADJUSTED**

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FRAXplus® - Results

THE TEN-YEAR PROBABILITY OF FRACTURE

Major osteoporotic Hip Fracture **"raw" FRAX** 11.74% 3.05%

PROBABILITY ADJUSTED ACCORDING TO RECENT FRACTURE

Previous Fracture Hip
Time since previous fracture 1 to 6 months
Adjusted Major osteoporotic 18%
Adjusted Hip Fracture 9.16% **FRAXplus®**

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U.S. Preventive Services Task Force (USPSTF) and AACE Recommendations

- Screen all (women and men) >50 with a history and a FRAX® or other fracture risk calculator (e.g. Garvan, CAROC); repeat q 5 years
- Screen all women ≥ 65 years old with BMD testing
- Also do BMD testing for women < 65 who are at increased risk for osteoporosis based upon formal risk assessment tools (e.g. FRAX®)
 - e.g. a FRAX® **score of ≥ 8.2-9.8%** risk for a major osteoporotic fracture (score for a weight-matched 65 y/o without any risk factors)

AACE = American Association of Clinical Endocrinologists

Curry SJ. USPSTF Recommendations JAMA. 2018;319: 2521-31. Guirguis-Blake J. USPSTF Evidence Report. JAMA. 2018; 319(16): 1705-16.
AACE Guidelines for Clinical Practice Guidelines for PMO. Endocrine Practice 2020; 6 (Suppl)

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Which Women Use DXA Before 65 Years Old (But Not Premenopausal Women)

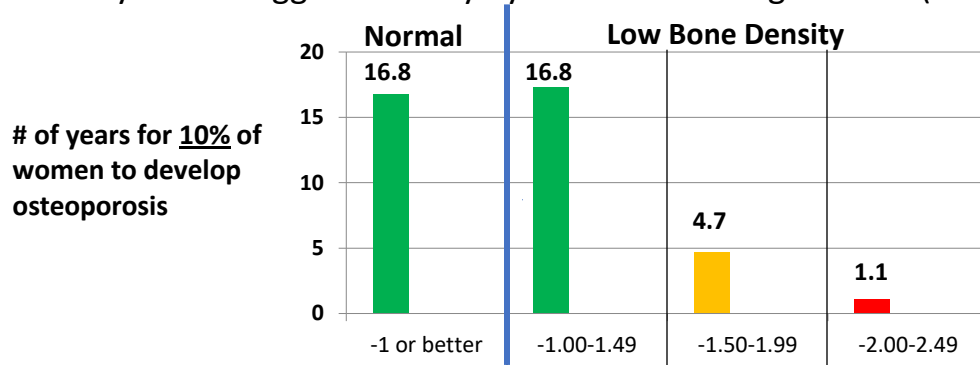
- FRAX®: >8.2—9.8% 10-yr risk of a major osteoporotic fracture
- PMHx fragility fracture
- Radiographically-identified low BMD
- Starting or taking ≥ 3 months of glucocorticoid therapy (esp. if >7.5 mg prednisolone/day)
 - Or aromatase inhibitors long-term
- Any ONE of these risk factors, IF she would be willing to consider Rx:
 - Low body weight (<58Kg (127 lbs) or BMI <20 kg/m²)
 - Low body weight is the single best predictor of low BMD
 - Early menopause
 - Current smoker
 - Excessive ethanol intake (>2 units/day)

PMHx = patient medical history

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When to Repeat DXA ?

- Medicare allows q 24 months
- Gourlay's data suggest: stratify by initial value at age 65--67 (n=4,957)



Gourlay M. NEJM. 2012; 366: 225-33.
Gourlay ML. Am J Med. 2017;130: 862.e15-862.e23

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Conclusions from a Comprehensive Literature Review (Including Gourlay's Data)

- If Normal BMD (>-1.0) → re-screen in 10--15 years
- If T-score -1.0 to -1.4 → re-screen in 5—10 years
- If T-score -1.5 to -1.99 → re-screen in 3--5 years
- If T-score -2.0 to -2.49 → re-screen in 2 years
- If T-score < -2.50 → Recommend treatment

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Most Recent Society Recommendations

American College of OB/GYN:

Repeat DEXA every 1--3 years during Rx, until findings are stable (MODERATE-QUALITY Evidence)

American Association of Clinical Endocrinologists:

Monitor therapy every 1-2 years, or less frequently, as clinically indicated

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Laboratory Testing in Osteoporosis

ALL Patients

- CBC
- CMP (Calcium, renal function, phosphorus, magnesium)
- 25-hydroxyvitamin D level (?)

Selective - As Indicated

- PTH
- TSH
- Serum/urine protein electrophoresis
- tTG antibodies
- Cortisol
- 24-hour urine cortisol
- 24-hour urine for calcium, creatinine

CBC = complete blood count; CMP = complete metabolic panel; PTH = parathyroid hormone;
TSH = thyroid-stimulating hormone; tTG = tissue transglutaminase

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Summary: Predicting Fracture Risk

It's NOT just a DXA T-score

- FRAX® Risk Score (+/- Trabecular Bone Score [TBS])
- Recent falls (esp. in past 12 months)
- Loss of height since age 25 (abnl > 1.6")
 - Morphometric evidence of prior vertebral fracture (even if asymptomatic)
- Impaired visual acuity (over age 65)
- Ability to rise from a chair without use of arms

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Chair Rise Test: SUCCESSFUL



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Chair Rise Test: UNSUCCESSFUL

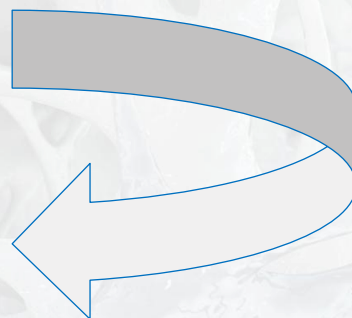


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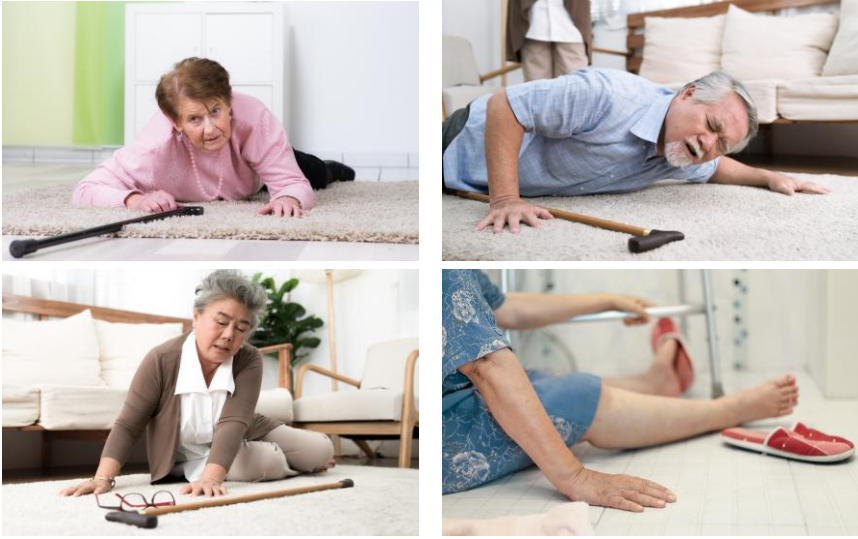
Diagnosis

Treatment



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To Prevent Fractures (esp. Hip Fractures)



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Simple First Steps to Reduce Fall & Fracture Risks

- Assess postural blood pressure and pulse
- If poor eyesight – ophthalmologic/optometry referral
- If poor balance/abnormal gait – define the etiology
 - Consider physical therapy referral
 - Consider Tai Chi for balance
- Minimize sedative/sleep meds
- Exercise
 - Weight-bearing & muscle-strengthening x 30 min 3x/wk minimum
- Household evaluation
 - Lighting, rugs, rails, cords, pet or grandchild toys

Grossman JM. Curr Opin Rheum. 2011; 23: 203-210.

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Calcium & Vitamin D - Dietary Sources Are Preferred AACE Guidelines 2020; ACOG 2022

- Advise adequate dietary Ca++
 - Supplement as needed – to total (dietary + supplement) 1200 mg/d after age 50 (vs. 1000 mg/d ages 19-49)
 - Not to exceed >2,000 mg/day
- Vitamin D3 supplementation (if needed)
 - Goal: maintain @ 30-50 ng/mL (equivalent to 75-125 nmol/L)
 - Supplement with 600 IU/d up to age 70; 800-2000 IU/day after age 70
- Encourage discontinuation of smoking
- Avoid excessive ETOH (> 2 units/day)

ETOH = ethanol

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NAM Recommendations for Calcium & Vit D

AGE	9--18	19--49	50--70	>70
Calcium (mg / day)	1300	1000	1200	1200
Vitamin D (IU / day)	600	600	600	800
				AACE: 1000-2000 IU/day

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How Can We Prevent the Most Fractures...

**Based Upon the Best
Available Evidence
And for the Best Value \$\$**

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Who to Treat – 2025 Consensus Guidelines

- Strongly recommend Rx for patients with a T-score of -2.5 or lower
- Strongly recommend Rx for patients who've had a fragility (low-trauma) fracture of the hip or spine
- Strongly recommend Rx for patients with a T-score between -1.0 and -2.5 if...
 - If they've had fragility (low-trauma) fracture of the pelvis, proximal humerus, or distal forearm
 - If their FRAX® score is high (10-year risk is >3% @ hip or >20% in general)
- Some experts strongly recommend Rx for patients whose FRAX® score is high (10-year risk is >3% @ hip and/or >20% in general)

Grade A; Evidence Level 1

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How Can FRAX® Guide Management?

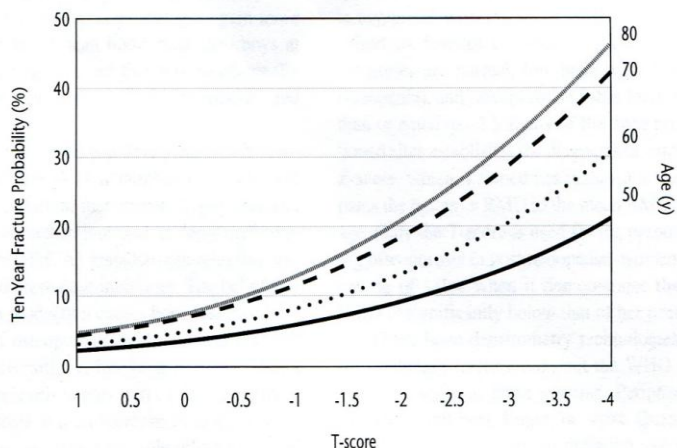


Fig. Kanis et al, Osteopor Int. 2001; 12(12): 989-95.

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How Can FRAX® Guide Management?

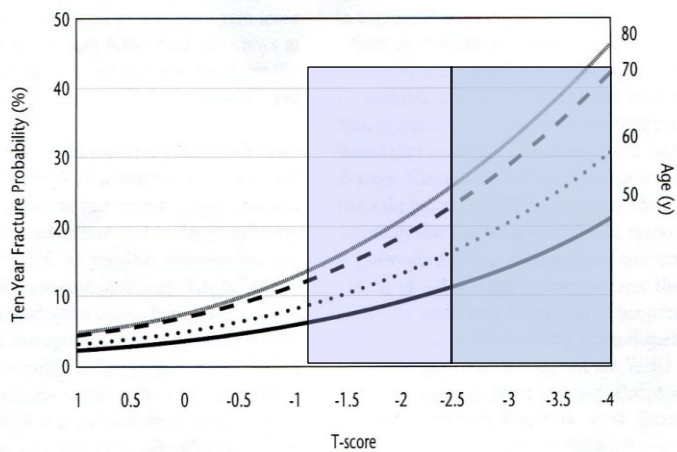


Fig. Kanis et al, Osteopor Int. 2001; 12(12): 989-95.

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How Can FRAX® Guide Management?

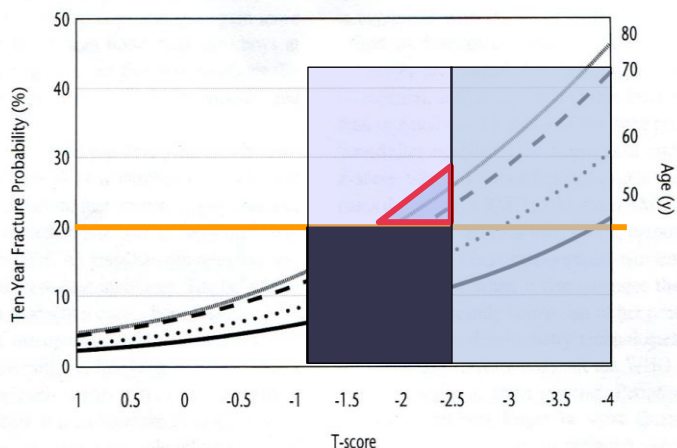
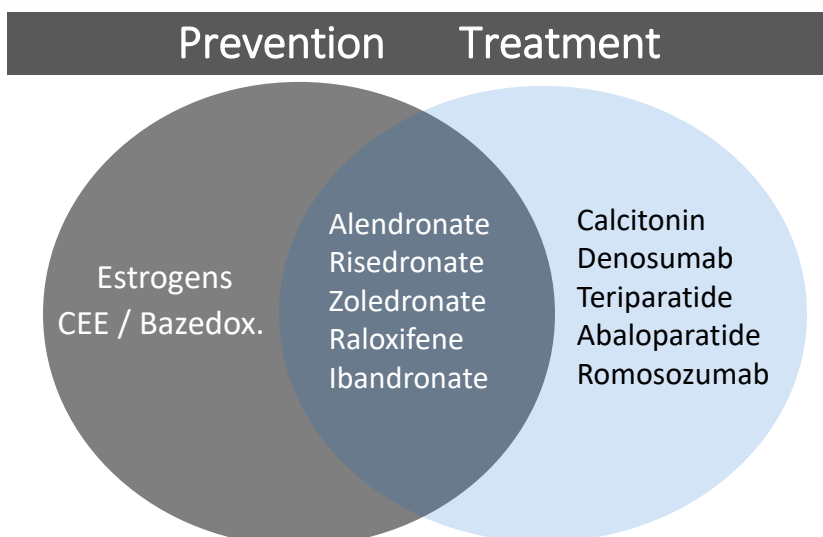


Fig. Kanis et al, Osteopor Int. 2001; 12(12): 989-95.

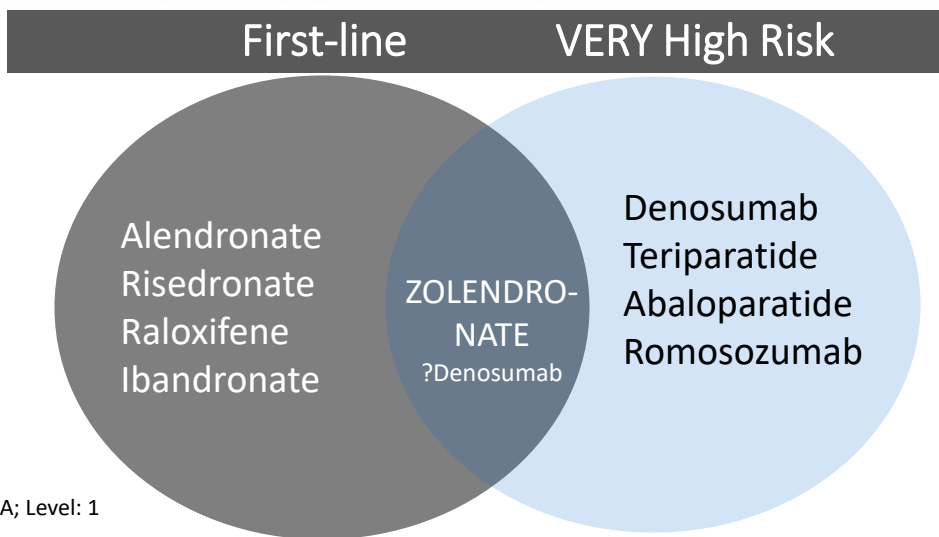
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Postmenopausal Osteoporosis per FDA-approved Labeling



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Treatment of Osteoporosis per AAACE Guidelines 2020; ACOG 2022; ACP 2024



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ACP 2024 Guidelines

[ACP Journals](#) ACP GUIDELINES FOR TX/PREV'N OF PRIMARY OSTEO IN WOMEN (&MEN) 2023 –
UPDATED May, 2024.

Free access

Clinical Guidelines

3 January 2023

Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians

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ACP Recommendations May, 2024

- Use bisphosphonates for first-line pharmacologic treatment for postmenopausal women with primary osteoporosis in order to reduce the risk of fractures (HIGH QUALITY EVIDENCE)
 - Males (LOW QUALITY EVIDENCE)
- Use denosumab for 2nd –line* pharmacologic treatment for postmenopausal women with primary osteoporosis in order to reduce the risk of fractures (MODERATE QUALITY EVIDENCE)
 - Males (LOW QUALITY EVIDENCE)
- *due to (1) cost, and (2) results are not much better than with bisphosphonates

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NAMS - Position Statement

- For women at very high risk for fracture (disparate definitions)
 - Begin with an osteoanabolic agent
 - E.g. teriparatide, abaloparatide, romosozumab
 - More effective than antiresorptive agents (AKA “anti-remodeling agents”)
- No agent “cures” osteoporosis
 - Drug holidays are acceptable/recommended (only for bisphosphonates)
- McClung M. Jnl N Amer Menopause Soc. 2021; 28(9): 973-97

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F.A.C.T. Head-to-Head

Fosamax-Actonel Comparison Trial

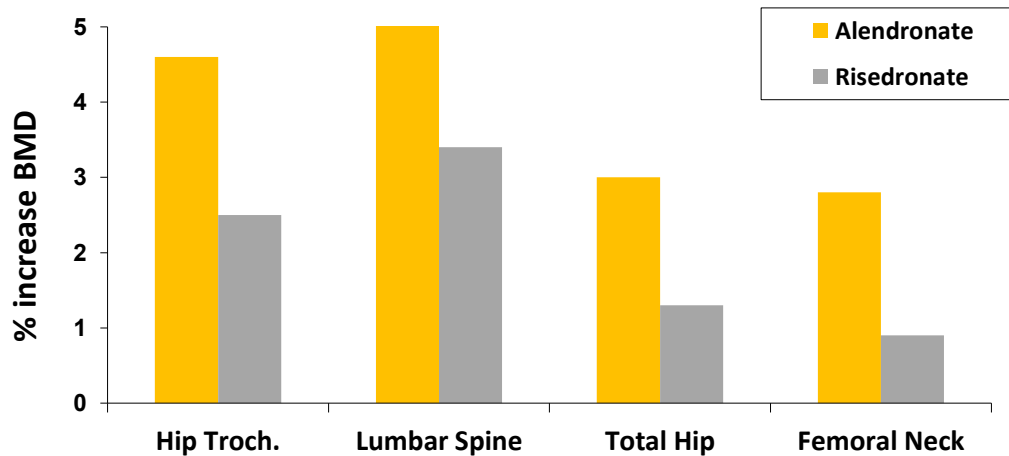
Fosamax 70 mg q wk vs. Actonel 35 mg q wk

- DBDDummyCRT (each pt took two pills – one active and one look-alike dummy to the other)
- N=1,053 women with postmenopausal osteoporosis ($T < -2.5$)
- All women were also given Ca^{++} /Vit D
- F/U DXA BMD at 12 and 24 months

Rosen CJ. JBMR 2005; 20(1): 141-51.

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Increases in BMD with Alendronate vs. Risedronate at 24 Months in F.A.C.T.



Reid D. Int J Clin Pract 2008; 62: 575-84.

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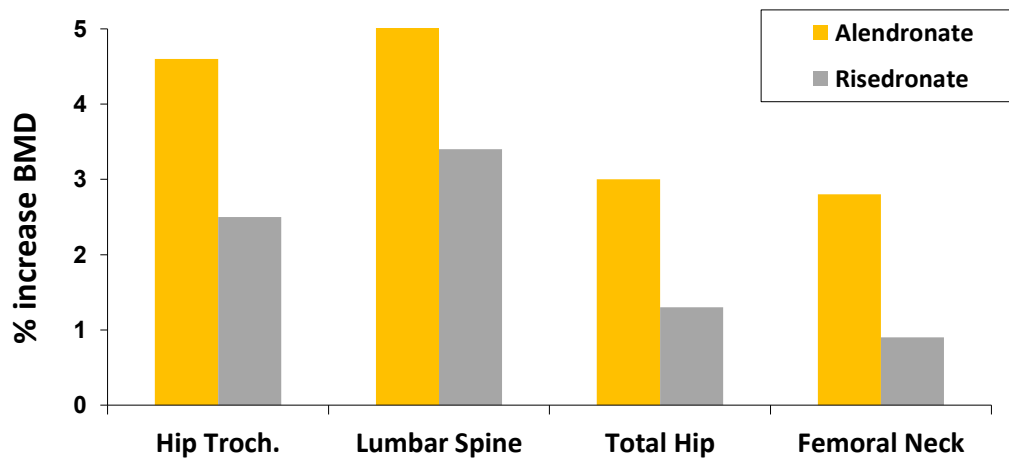
F.A.C.T Clinical Adverse Events Over 24 Months

Number (%) of Patients	Alendronate 70 mg/wk (N=411) n (%)	Risedronate 35 mg/wk (N=414) n (%)
With 1 or more AE	358 (87.1)	356 (86.0)
With serious AE	51 (12.4)	56 (13.5)
With 1 or more UGI AE	102 (24.8)	95 (22.9)
With serious UGI AE	4 (1.0)	6 (1.4)
Death due to serious UGI AE	0 (0.0)	1 (0.2)
Clinical Fractures	34 (8.3)	34 (8.2)

Reid D. Int J Clin Pract 2008; 62: 575-84.

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Increases in BMD with Alendronate vs. Risedronate at 24 Months in F.A.C.T.



Reid D. Int J Clin Pract 2008; 62: 575-84.

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Greater Differences in BMD Do Not Confer Greater Fracture Protection

Antiresorptive Therapy	BMD Increase (3 yr treatment)	Vertebral Fracture Risk Reduction (3 yr treatment)
Raloxifene ¹	2.6	50%
Ibandronate ²	5.2	52%
Risedronate ³	5.9	49%
Alendronate ⁴	8.8	48%

Data are from separate placebo-controlled trials. These are not head-to-head trials in the same patient population, and therefore can not be used to compare clinical efficacy.

1. Ettinger, et al. *JAMA* 1999; 282(7): 637-645.

2. Chestnut, et al. *J Bone Miner Res* 2004; 19(8):1241-9.

3. Reginster, et al. *Osteoporosis International* 2000; 11: 83-91.

4. Liberman, et al. *NEJM* 1995; 333(22): 1437-1443.

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Greater Differences in BMD Do Not Confer Greater Fracture Protection

Antiresorptive Therapy	FN BMD Increase (3 yr treatment)	Non-Vertebral Fracture Risk Reduction (3 yr treatment)
Risedronate ³	1.6	39% (p=0.02)
Raloxifene ¹	2.1	10% (NS)*
Ibandronate ²	2.6	0% (NS)
Alendronate ⁴	5.9	21% (NS)

Data are from separate placebo-controlled trials. These are not head-to-head trials in the same patient population, and therefore can not be used to compare clinical efficacy.

1. Ettinger, et al. *JAMA* 1999; 282(7): 637-645.

2. Chestnut, et al. *J Bone Miner Res* 2004; 19(8):1241-9.

3. Harris, et al. *JAMA* 1999; 282:1344-52.

4. Liberman, et al. *NEJM* 1995; 333(22): 1437-1443.

68

Summary of the Effectiveness of Bisphosphonates

3-year prospective data:

Vertebral Fractures

Δ ~50% (p<0.001) reduction in risk

Hip Fractures

Δ 10--39% (p<0.001) reduction in risk

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Which ONE of the Following Would NOT Be an Appropriate Intervention If a Woman's BMD Worsens After 2 Years on Bisphosphonate Therapy?

- A. Evaluate for causes of secondary osteoporosis
- B. Add a second agent to her existing regimen (begin combination Tx)
- C. Change to a different agent
- D. Refer to an endocrinologist or rheumatologist

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Causes of Secondary Osteoporosis (A Short List)

- AIDS / HIV
- Anorexia nervosa
- Celiac disease
- Diabetes (types 1 and 2)
- Diminished ovarian reserve
- Gastric bypass
- Hyperparathyroidism
- Hypocalcemia
- Premature menopause
 - Including surgical or induced
- Primary ovarian insufficiency
 - Turner's syndrome
- Renal impairment
- Rheumatoid arthritis
- Vitamin D deficiency
- Medications

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Medications Associated with Decreased BMD (A Short List)

- Steroids
- Aromatase inhibitors
- Proton pump inhibitors
- SSRI's
- Anticonvulsants
 - phenytoin, phenobarbital, carbamazepine, and primidone
- GnRH analogues
- heparin

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Zoledronic Acid

- **HORIZON (Health Outcomes Reduced Incidence with Zoledronic Acid ONce Yearly)**
 - Annual IV infusion – 5mg over ≥ 15 min
- 3-yr prospective follow-up data
 - **Vertebral Fractures**
 - 92 frx (Z-arm) [3.2%] vs 310 frx [10.9%]
 - **$\Delta 70\%$** ($p < 0.001$) reduction in risk
 - **Hip Fractures**
 - 52 frx (Z-arm) [1.4%] vs 88 frx [2.5%]
 - **$\Delta 41\%$** ($p < 0.001$) reduction in risk

Black D. NEJM 2007; 356: 1809-22.

73

Zoledronic Acid for Women with Low Bone Mass

- N=1,861
- 6-year F/U
- Placebo (925) $\rightarrow$ 190 fragility fractures
- Zoledronate (936) $\rightarrow$ 122 fragility fractures } **37% reduction**

2018: new indication for zoledronic acid

For osteopenia (low bone mass) T -1.0 to -2.5
5 mg IV infusion over >15 minutes **q 2 years**

Reid I. NEJM. 2018.

74

When Should a Drug Holiday Be Considered AACE 2020; AGOG 2024

- **For bisphosphonates:** after 5 yrs IF THE T-score improves to > -2.5 , and pt remains fracture-free;
 - IF NOT, continue Rx for up to an additional 5 yrs
 - Grade A; Level 2
- **For zoledronate:** after 3 yrs if the T-score has improved to > -2.5 ;
 - if NOT, continue for an additional 3 years
 - For VERY-HIGH Risk women: don't consider a drug holiday until after 6 years
 - Grade A; Level 2

LSC = least significant change

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When to Resume Rx After a Drug Holiday

- **During a Drug Holiday**
 - Repeat DXA (or FRAX®) q 2-4 years
- **Consider resuming therapy after**
 1. a fracture, or
 2. an increase in fracture risk, or
 3. after T-score declines by more than the LSC of the DXA machine
 - Grade A, Level 1

LSC = least significant change

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That Was the Bisphosphonates...

Now, the Monoclonal Antibodies (These Are Also Antiresorptive Agents)

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Denosumab – Pivotal Fracture Trial

- DBPCRT n=7,808 women with postmenopausal osteoporosis
- Randomized 60 mg SQ q 6 mos x 36 mos vs placebo
- Endpoints at 36 months
 - **68%** fewer vertebral fractures
 - 0.32 [0.26-0.41]
 - **40%** fewer hip fractures
 - 0.60 [0.37-0.97]

Cummings S. NEJM. 2009; 361: 756-65.

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Denosumab

PRO's

- Can continue without restriction on the maximum duration of use
- Well-tolerated GI
- OK with renal insufficiency (but not with ESRD or dialysis)
- Q 6-months subQ injection
 - HIGH QUALITY EVIDENCE of benefit -if patient prefers this as 1st line Rx
- No increased risk of ONJ

ESRD = End-Stage Renal Disease

CON's

- A monoclonal antibody – does not reside/linger in bone... so no drug holiday is feasible
 - So if you stop denosumab, must begin another antiresorptive agent
 - AACE 2020 (Grade A; Level 1)
- More AE's – rare anaphylaxis – observe x 15 min

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Summary of the Anti-Fracture Data

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SUMMARY of the DATA: Anti-Fracture Effects

Drug	Vertebral	Hip
Alendronate	50%	20%
Risedronate	50%	40%
Raloxifene	50%	No
Ibandronate	50%	No
Zoledronate	70%	41%
Denosumab	68%	40%
Teriparatide	78%	56%
Abaloparatide	86%	?65%
Romosozumab	73%	38%*

*vs alendronate @ 24 mos in the ARCH Trial

81

Reported Adverse Events of Antiresorptive Agents

COMMON:

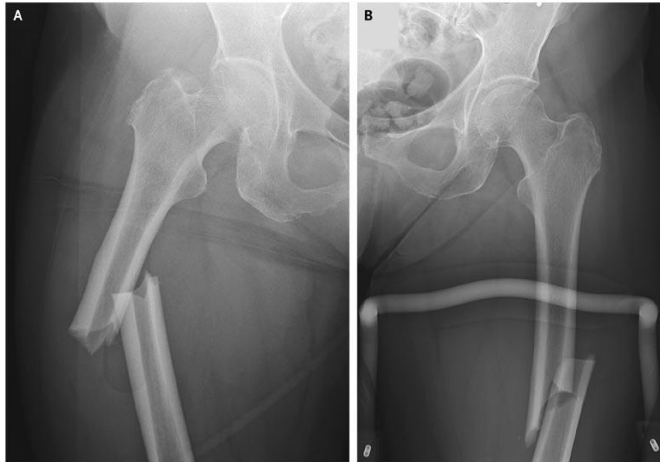
- GI intolerance

RARE:

- Atypical mid-shaft femoral fractures
- Osteonecrosis of the jaw (mandible > maxilla)
- Atrial fibrillation
- Esophageal cancer

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Radiographs of Atypical Mid-Shaft Fractures of the Femur



Lenart B et al. N Engl J Med 2008;358:1304-1306.

83

~~Oh NO !!!!~~: 25% Increase in Atypical Femoral Fractures with Long-Term Bisphosphonate Use

- Occur mostly after >5 years of Rx
- Rare – background rate: **28/100K** $\xrightarrow{+25\%}$ **35/100K**
 - **7 MORE FRACTURES / 100K women**
- Weigh those 7 more against ~100 less spine frx's; and 30-50 less hip fractures

Oh YES !!!!

After 8+ years of bisphosphonate Rx, risk is **130/100K**

Zhong W. JBMR 2011; 26(3): 553. Black D. NEJM. 2020; 383: 743-53

84

Osteonecrosis Case Definition of “Jaw Rot”

Exposed bone in the maxillofacial region

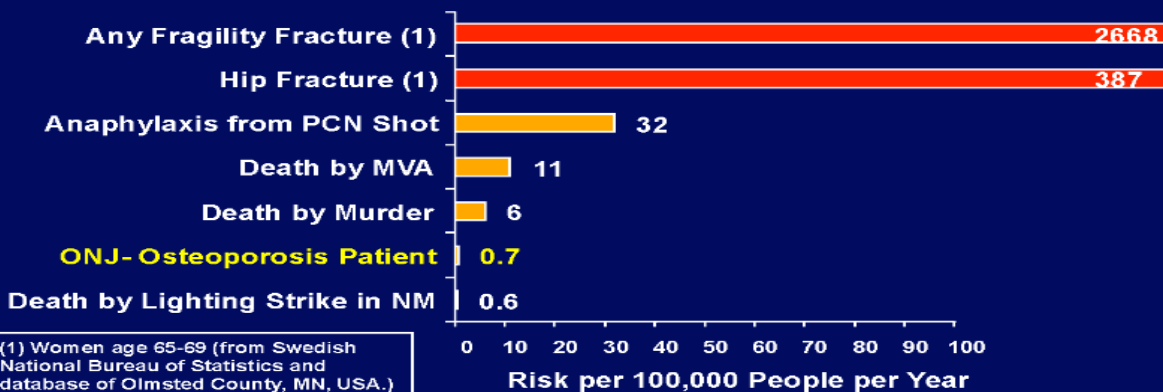
- Remains unhealed > 8 weeks
- No prior hx radiation to the region
- Not osteomyelitis

□ AAOMS

- Khosla S. JBMR. 2007; 22: 1479-91

85

Communicating Risks



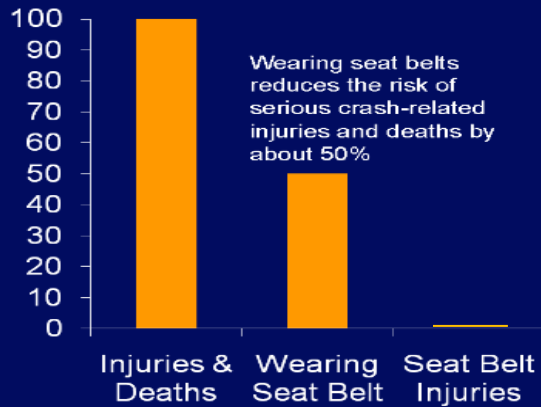
Kanis JA et al. Osteoporos Int. 2001;12:417-427. Pharmcoepidemiol Drug Saf. 2003;12:195-202. National Center for Health Statistics. JADA. 2006;137:1144-1150. www.nssl.noaa.gov/papers/techmemos/NWS-SR-193/techmemo-sr193-4.html

Postmenopausal Osteoporosis Guidelines, Endocr Pract. 2020;26(Suppl 1)

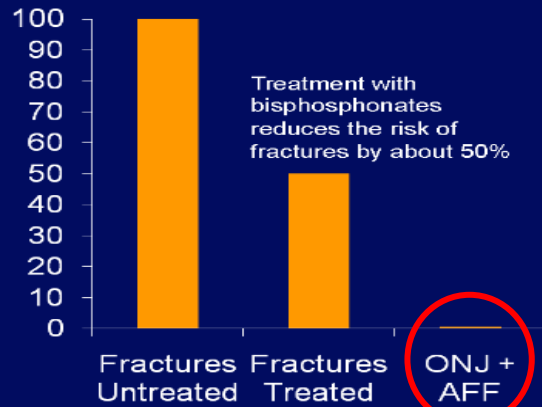
86

SUMMARY: Communicating Risks vs. Benefits

Motor Vehicle Accidents



Osteoporosis



There are about 2.3 million adults treated in ERs each year for injuries from MVAs and about 2 million osteoporotic fractures each year. The risk of seat belt injuries and serious side effects from osteoporosis treatment is very small in proportion to the benefits. Data from multiple sources.

Postmenopausal Osteoporosis Guidelines, Endocr Pract. 2020;26(Suppl 1)

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NOF: Osteonecrosis of Jaw Letter from YOU to Your Patient's Dentist/MFS



Dear Dr. _____,

Our mutual patient _____ (DOB _____) is under my care for his/her diagnosis of osteoporosis and is currently treated with _____ to reduce his/her risk of osteoporotic fracture. I want to take this opportunity to summarize my recent discussion with our patient about his/her high risk of fracture compared to his/her real but very rare risk of MRONJ (Medication-related osteonecrosis of the jaw).

MRONJ is a rare event associated with the following medications: oral alendronate (Fosamax), oral risedronate (Actonel/Atelvia), oral or IV ibandronate (Boniva), IV zoledronic acid (Reclast), SQ denosumab (Prolia*), and SQ romosozumab (Evenity). MRONJ has NOT been associated with oral Raloxifene (Evista), SQ Teriparatide (Forteo*), or SQ Abaloparatide (Tymlos*); therefore, there is NO recommendation for altering your standard dental plan if our patient is on one of these medications.

I know that you may have concerns about the risk of MRONJ; however, in a patient at high risk for fracture, the benefit of an approximate 40-70% reduction in fracture risk far outweighs the rare 1/10,000 to 1/100,000 risk of MRONJ. The most recent scientific summary reports by the ADA, AAOMS and the International Task Force for ONJ support this position. These societies also DO NOT recommend serum CTX testing.

In the publication of the FREEDOM extension trial (Bone HG, et al. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523), the real-world incidence of MRONJ in osteoporosis patients treated with denosumab (Prolia*) for up to 10 years was 5.2 cases per 10,000 subject years. It should be noted that denosumab (Xgeva*) and zoledronic acid (Zometa*) are used in the setting of cancer treatment in significantly higher doses and administered monthly instead of every 6-12 months. The risk of adverse events like MRONJ is much lower in the doses and frequency used for treating osteoporosis patients than in the treatment of oncology patients.

A tooth extraction or invasive jaw surgery may impart additional risk for MRONJ, especially if there is periodontal disease or chronic infection; however, routine cleanings, fillings, scaling/root planing, root canals and even implants do not appear to increase the risk of MRONJ. In all patients, but especially in those with additional risk factors such as diabetes, dry mouth, smoking, periodontal disease, poor fitting dentures or steroid use, the best course of action is appropriate dental hygiene and preventive dental care. You may consider oral antibiotics before and after procedures and/or antimicrobial rinses or local antimicrobial solution application if any of these risk factors are present or where you deem appropriate.

We do not recommend interruption of osteoporosis treatment for dental procedures in patients with high risk of fracture, especially if they are receiving denosumab (Prolia*) where the risk of multiple vertebral fractures is increased if denosumab (Prolia*) is discontinued or dosing is delayed without starting an alternative antiresorptive therapy.

I appreciate being able to care for our patient's bone health and would be happy to address any additional concerns that you may have.

Sincerely,

<http://www.nof.org/wp-content/uploads/Dear-Dr-ONJ-letter-FINAL-FORM1.pdf>

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Resources

- **National Osteoporosis Foundation Healthcare Professionals Toolkit**

- <https://www.bonesource.org/healthcare-professionals-toolkit>

- **FRAX Calculator (& FRAXplus)**

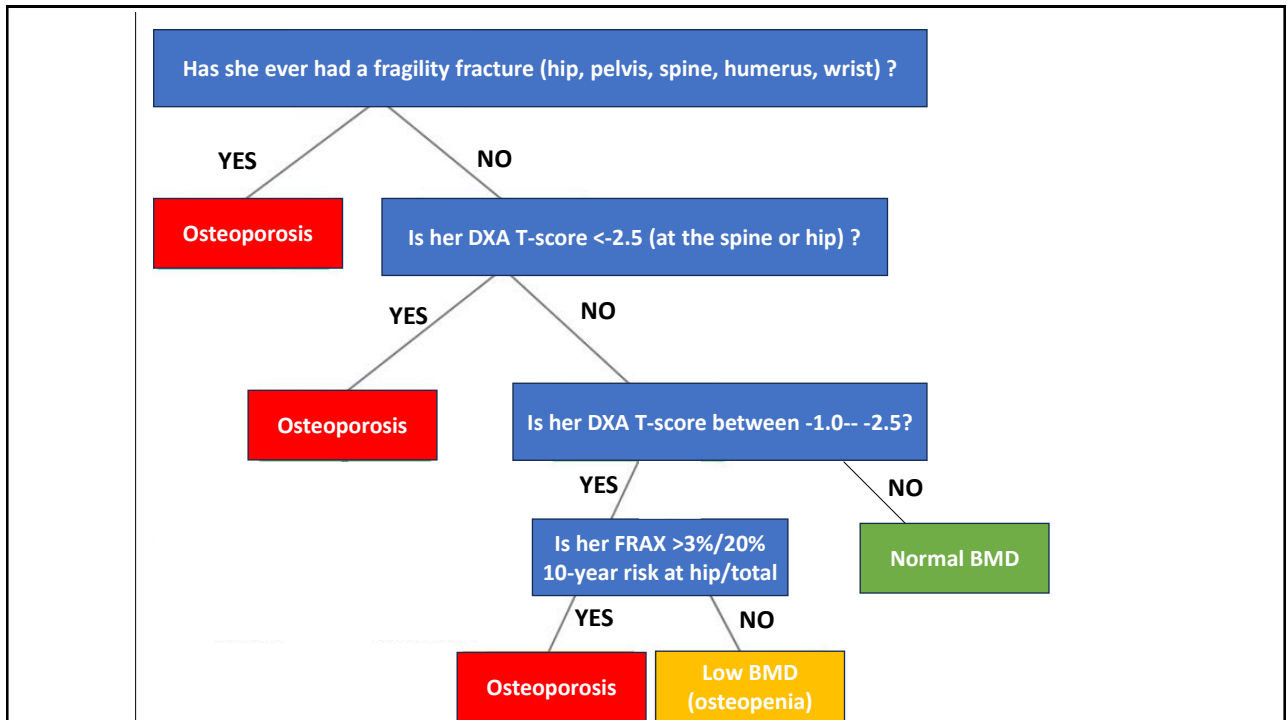
- <https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9>

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Summary

- Osteoporosis and its severe sequelae (fractures) represent a significant health burden to our patients, and a cost burden to the healthcare system
- The best estimate of real-life fracture risk can be achieved by the combination of FRAX® (or similar) screening tool and a central DXA scan
- First-line therapy for osteoporosis is most often a weekly bisphosphonate
- Combination therapy (concurrent agents) are generally not recommended; sequential therapy (e.g., an anabolic agent followed by an antiresorptive agent) is appropriate

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Janice Is a 66-year-old Healthy Non-smoker of Normal Body Habitus. **As a Typical U.S. Woman, Which Condition Would She Have the GREATEST Likelihood of Experiencing During Her Lifetime?**

- A. Heart attack
- B. Stroke
- C. Breast cancer
- D. Osteoporotic fracture

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Which of the Following Is NOT an Appropriate Screening Test for Osteoporosis?

- A. Axial DXA scan (hip, femoral neck, lumbar spine)
- B. Peripheral DXA scan (at distal 1/3 radius)
- C. Bone turnover markers (serum or urine)
- D. FRAX®



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Janice Had Her First DXA Scan Done.
The Result Was Normal (T score = -0.82).
When Should She Expect to Have Her Next DXA Scan?

- A. 1 year later
- B. 2 years later
- C. 10-15 years later
- D. Never again, unless she experiences a fracture



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Just Two Months After Her Normal DXA Scan, Janice Tripped on a Throw Rug in Her Home which Resulted in a Fragility Fracture of Her Hip.

Which of the Following Is TRUE?

- A. She should have another DXA done ASAP to determine if she has osteoporosis of the hip
- B. She should have a bone turnover marker study done ASAP to determine if she has osteoporosis.
- C. She has osteoporosis based upon this fracture alone, even with her recent normal BMD.
- D. She should be aggressively treated with two or more agents, concurrently, for osteoporosis.



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Which of the Following Agents Is NOT Appropriate (FDA-approved) for the Treatment of Osteoporosis?

- A. Conjugated estrogens
- B. Risedronate
- C. Denosumab
- D. Romosozumab



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APPENDIX SLIDES

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ACP Recommendation - May, 2024 ONLY for Women with Primary Osteoporosis and a Very High Risk of Fracture

- Use a sclerostin inhibitor (romosozumab) (only ≤ 12 months) followed by a bisphosphonate or denosumab (MODERATE QUALITY EVIDENCE)...

OR

- or teriparatide or abaloparatide (only up to ≤ 24 months) followed by a bisphosphonate or denosumab (LOW QUALITY EVIDENCE) ...

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**Use a Sclerostin-binding Inhibitor (Romosozumab)
as Rx for Women at VERY-High Risk
ACOG 2022**

- **HIGH-QUALITY EVIDENCE**
 - For women who experience a fracture while on antiresorptive Rx
 - For women NOT at increased risk of cardiovascular disease or stroke
 - For up to 12 months of use

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**Use PTH-analogs (Teriparatide, Abaloparatide)
as Initial Rx for Women at VERY-High Risk
ACOG 2022**

- **HIGH-QUALITY EVIDENCE**
 - For women at VERY high risk
 - For women who experience a fracture while on antiresorptive Rx
 - For women who demonstrate significant further bone loss (beyond the LSC of the DEXA machine/software)
 - For up to 24 months of use

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Use PTH-analogs (Teriparatide, Abaloparatide) as Initial Rx for Women at VERY-High Risk

- Teriparatide
Metanalysis of 23 PCRT's/observational trials:
20µg daily SQ vs placebo
- Endpoints at 18 months (median)
 - **78%** fewer vertebral fractures
 - **56%** fewer hip fractures
- Abaloparatide claims a 17-22% better reduction in hip fractures (publication pending)
 - Eck M. Presented at the World Congress on Osteoporosis. April 11-14, 2024, London, U.K.

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When to Refer to a Subspecialist (Endocrinologist; Osteoporosis Specialist) ACOG 2022

- T-score < -3.0
- Any new fragility fracture
 - New fragility fracture on Rx
 - Fragility fracture with normal BMD
- Progressive decline in BMD while on antiresorptive Rx
- Endocrine or metabolic cause of secondary osteoporosis
 - Hyperthyroidism, hyperparathyroidism, hypercalciuria, elevated prolactin
- Comorbidities that complicate Rx
 - Significantly low GFR, malabsorption syndrome

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Teriparatide (PTH 1-34)

- N=1,637 postmenopausal women w/ prior vertebral fracture(s)
- PCRT – 0, 20, 40 microGm SubQ qd
 - All received Ca++ and Vit D daily supplements
- F/U = 18 months

	Placebo (n=544) # /1000 pt-yrs (%)	20 microGM (n=541)	40 microGm (n=552)	
Vertebral Frx's	136 (14%)	49 (5%)	30 (4%)	78% ↓
Non Vert Frx's	(6%)	(3%)	(3%)	50% ↓

Neer R. NEJM. 2001; 344: 1434-41; . Diez-Perez A. Bone. 2019; 120:1-8

103

Abaloparatide (FDA Approved April 2017)

- Mechanism: binds PTH receptor; Anabolic bone effect
- Regimen: daily subQ injection – 80 micrograms (pen contains 30 doses)
 - Does NOT require refrigeration (unlike TPD)
- **“ACTIVE” Trial : Abaloparatide Comparator Trial In Vertebral Endpoints**
 - DBPCRT: N=2,463 women with postmenopausal osteoporosis
 - Abaloparatide 80 mcg (n=824)
 - vs. teriparatide 20 mcg (n=818)
 - vs. placebo (n=821)
- F/U 18 months – **86% reduction** in vert frx with ABL; vs. 78% with TPD
- CONCLUSION: ABL is slightly superior to TPD in increasing BMD and in reducing major osteoporotic fractures, with a more rapid onset to benefit

Miller PD. Et al for the ACTIVE Study Investigators. JAMA. 2016;316(7):722-733. doi:10.1001/jama.2016.11136

Reginster JY. ACTIVE Trial: Expert Opin Pharmacother. 2017 Dec;18(17):1811-1813. doi: 10.1080/14656566.2017.1395021. Epub 2017 Nov 14

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Monoclonal Antibodies Against Sclerostin

- Sclerostin, produced by osteocytes, inhibits osteoblast activity
- **Romosozumab** – Human monoclonal antibody against sclerostin
FDA approved April 9, 2019

INVESTIGATIONAL DRUG (still in development, December, 2024)

- Blosozumab – Phase III trial; LY2541546 ongoing
- Human monoclonal antibodies against sclerostin

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Romosozumab FRAME Study (PCRT) & ARCH Study (RCT vs. Alendronate)

- n=7,180 women with postmenopausal osteoporosis
- subQ injection 210mg (2 x 105mg prefilled syringes)
q 4 weeks x 12 months
- F/U 12 months
- **73%** fewer vertebral fractures at 12 months (rapid onset benefit)
- **38%** fewer hip fractures at 12 months (rapid onset benefit)

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Limit the Durations of Certain Therapies

- LIMIT TPD & ABPD THERAPIES TO ≤ 24 MONTHS; LIMIT ROMO TO ≤ 12 MONTHS
 - Then follow the anabolic (teriparatide or abaloparatide) with an antiresorptive agent (e.g., a bisphosphonate or denosumab Rx)
 - Grade A; Level 1
 - P.S.
 - R/O Paget's disease (check the serum alkaline phosphatase) before prescribing an anabolic agent
 - Do not prescribe anabolics for patients with untreated hyperparathyroidism
 - Do not switch directly from denosumab to an anabolic agent
 - Do NOT use combination (concurrent) Rx therapies
- LIMIT ROMOSUZUMAB THERAPY TO ≤ 12 MONTHS
 - Then follow with bisphosphonate or denosumab Rx
 - Grade B; Level 1