OSTEOPOROSIS UPDATE 2021

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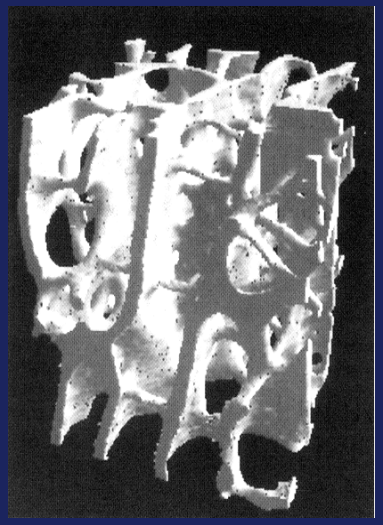
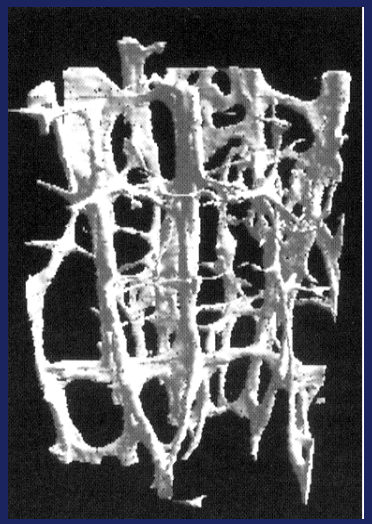
Introduction

- Osteoporosis Updates
- Diagnosis
- Secondary Causes
- Treatments
- Controversies
- Cases from the Bone Clinic



Normal Bone



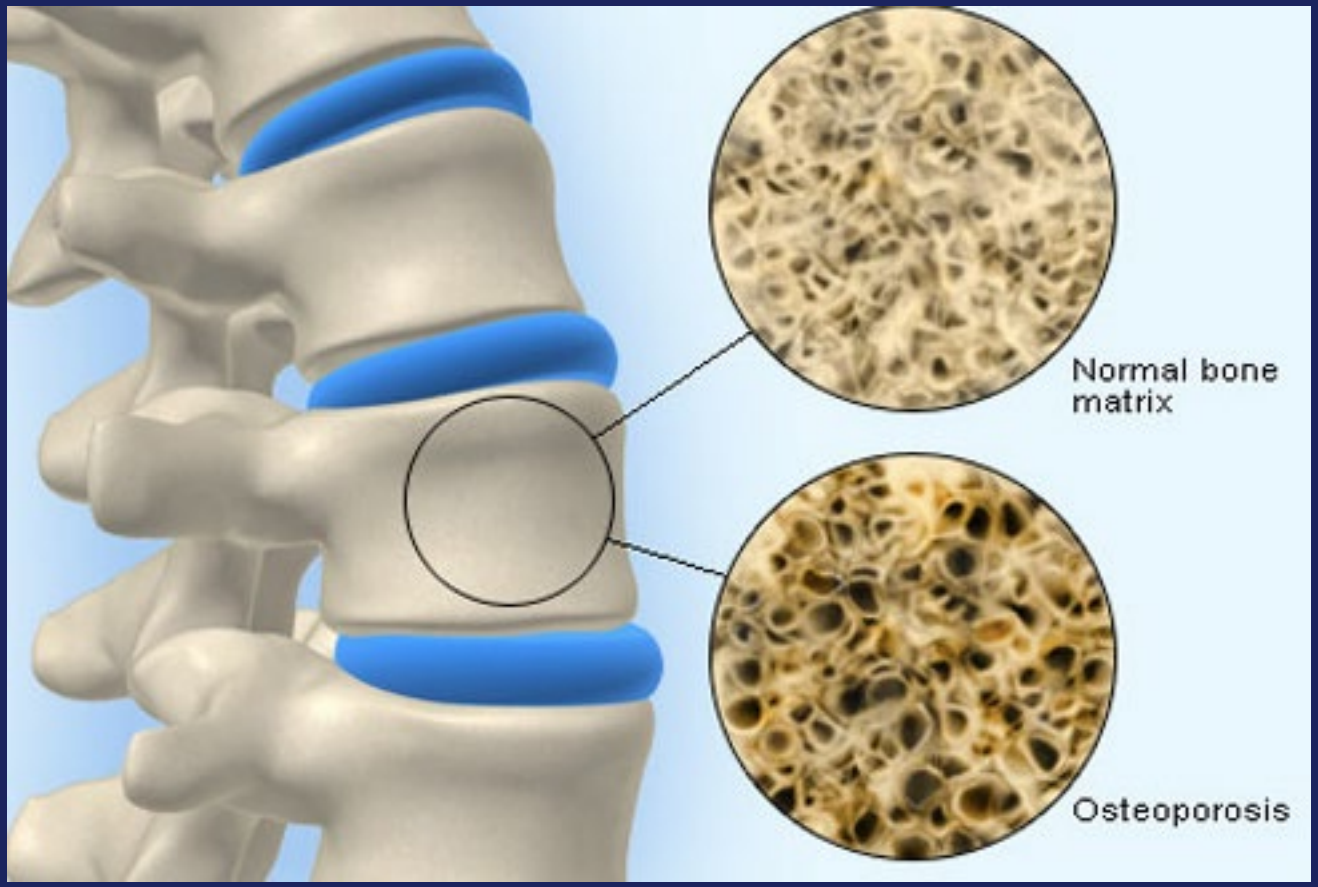
Osteoporotic Bone

Definition of Osteoporosis

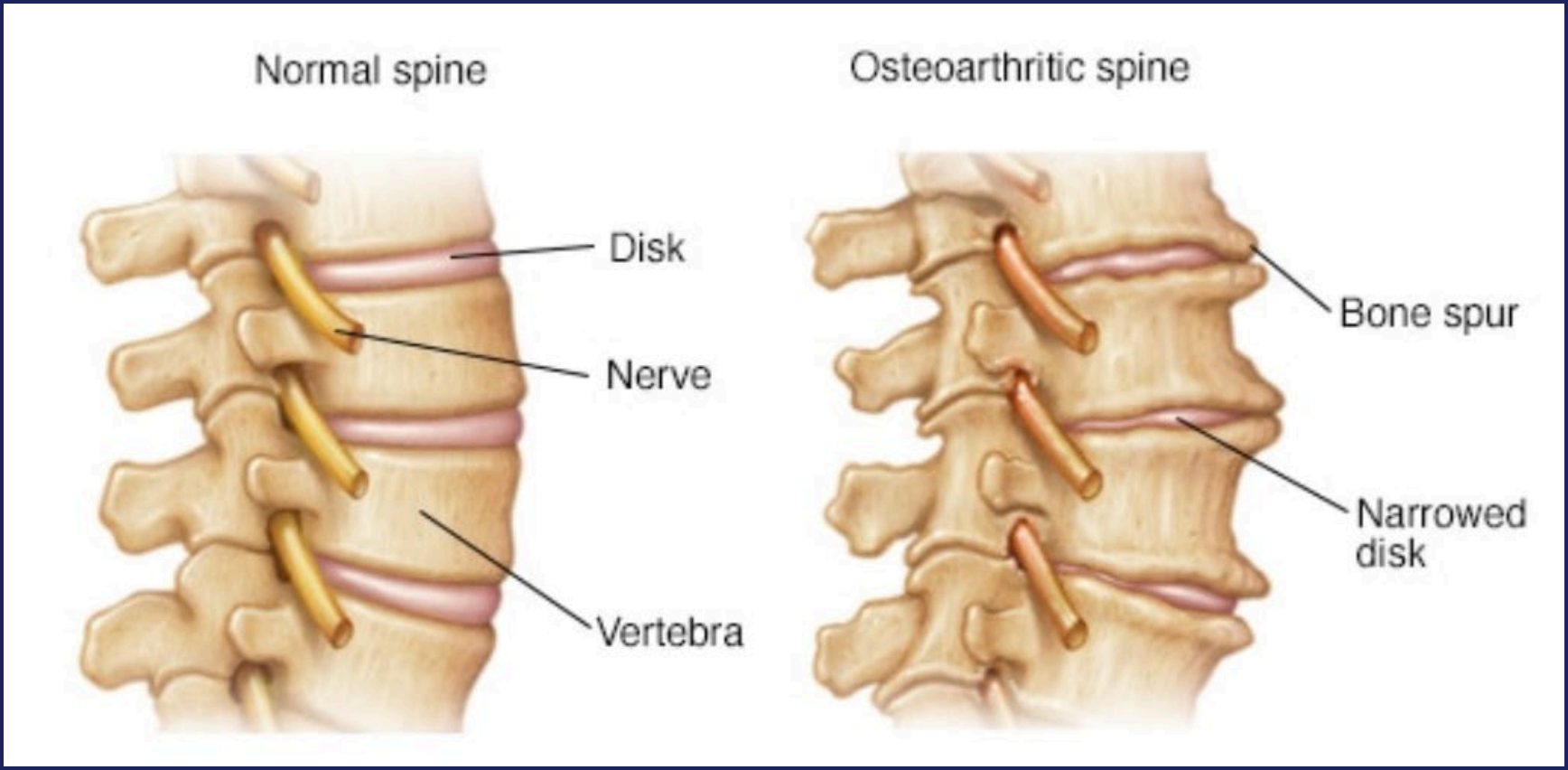
- A skeletal disorder characterized by
  - Compromised bone strength predisposing to
  - An increased risk of fracture
- Bone strength reflects the integration of two main features:
  - Bone density
  - Bone quality

2000 NIH Consensus Development Conference

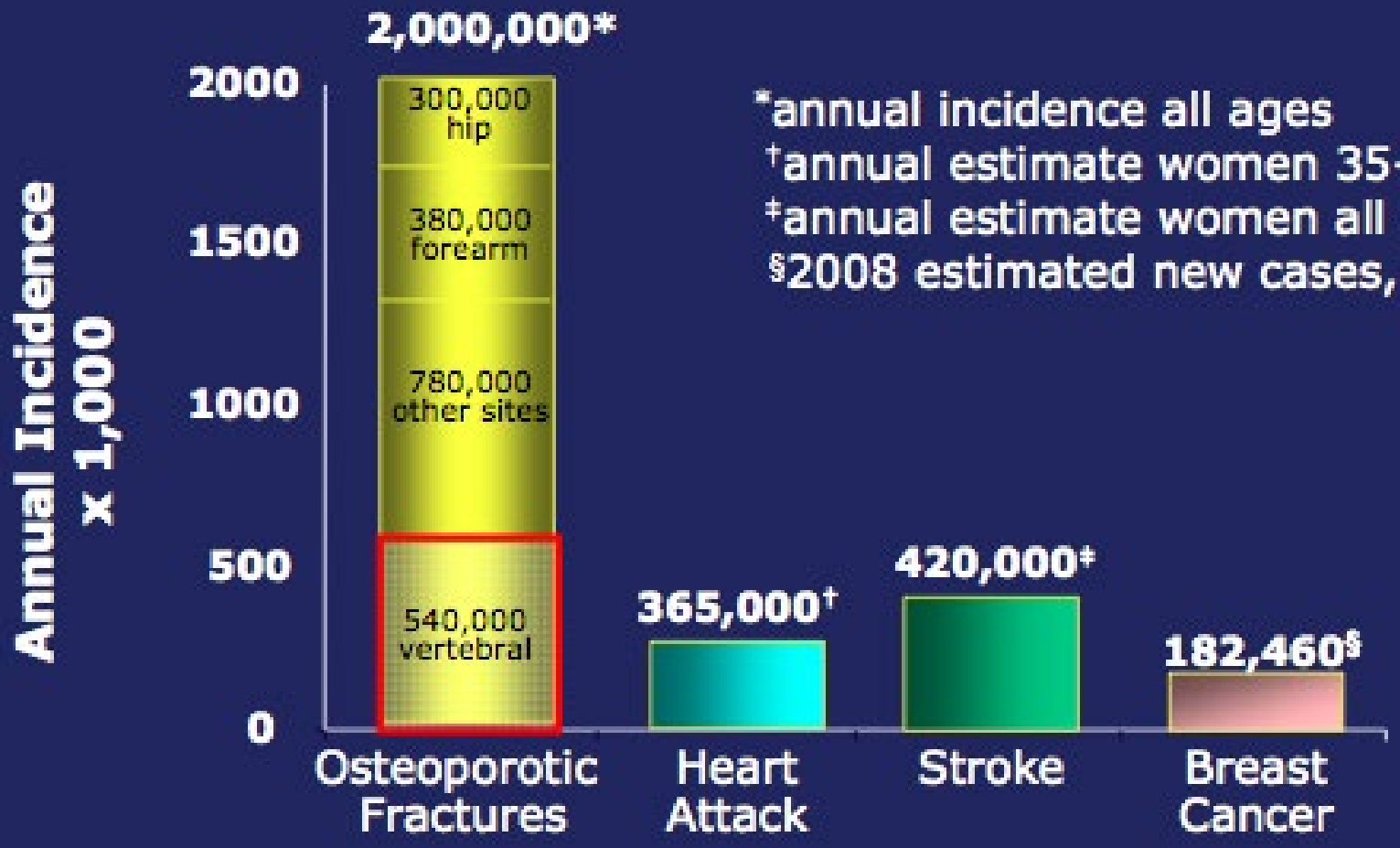
Osteoporosis



Osteoarthritis



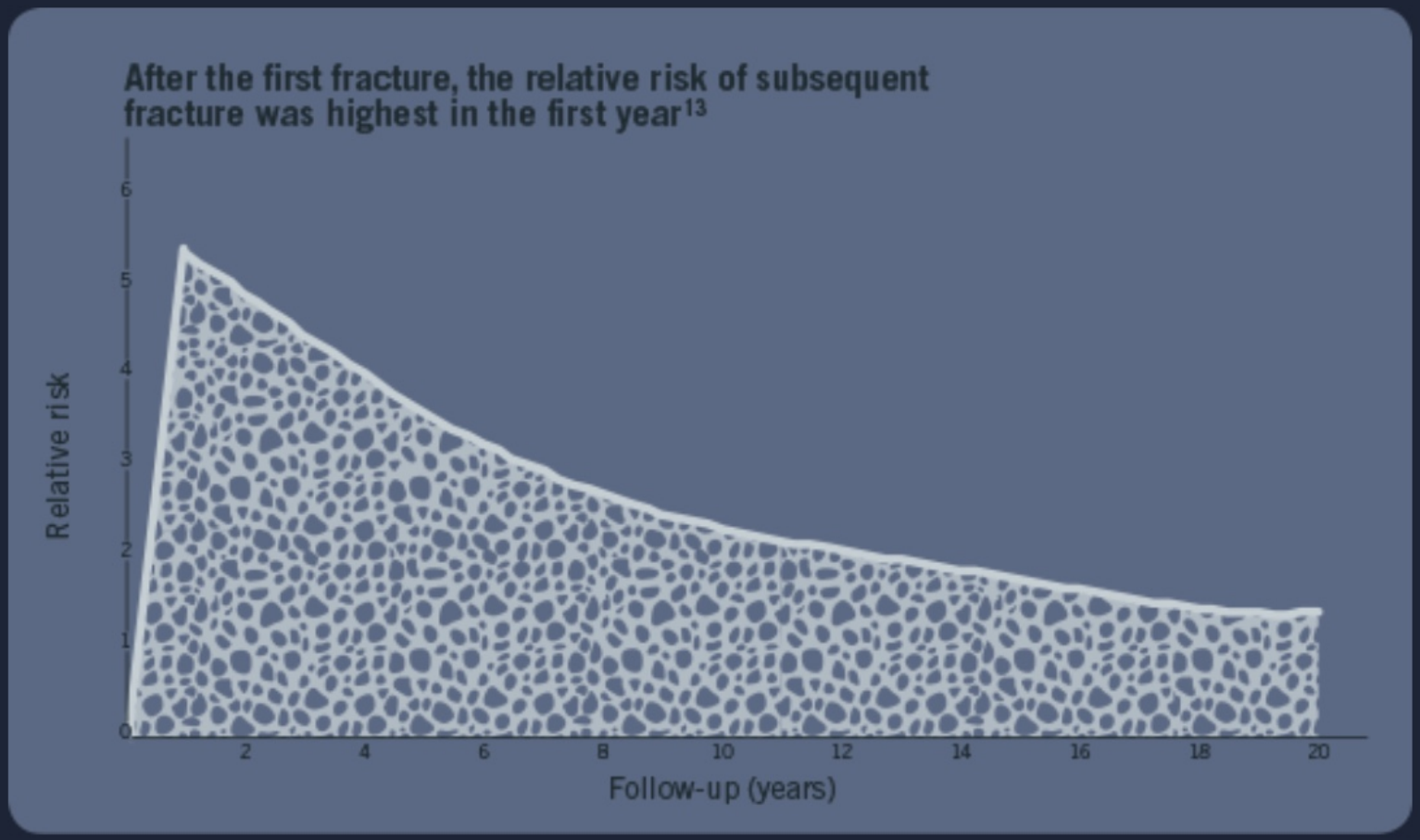
Osteoporotic Fractures in Women: Comparison With Other Diseases



Burge R, et al. *J Bone Miner Res.* 2007;22:465-75.
Riggs BL, et al. *Bone.* 1995;17:505S-511S.
American Heart Association. 2008. Heart and Stroke Facts.
American Cancer Society. 2008. Cancer Facts & Figures.

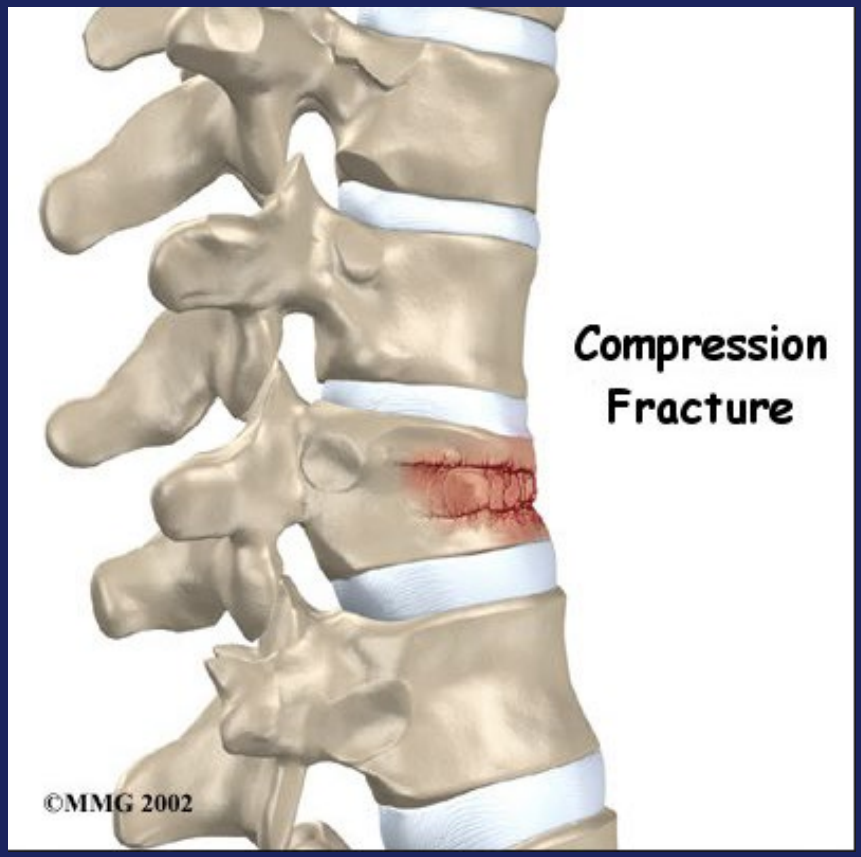
Osteoporosis is Common

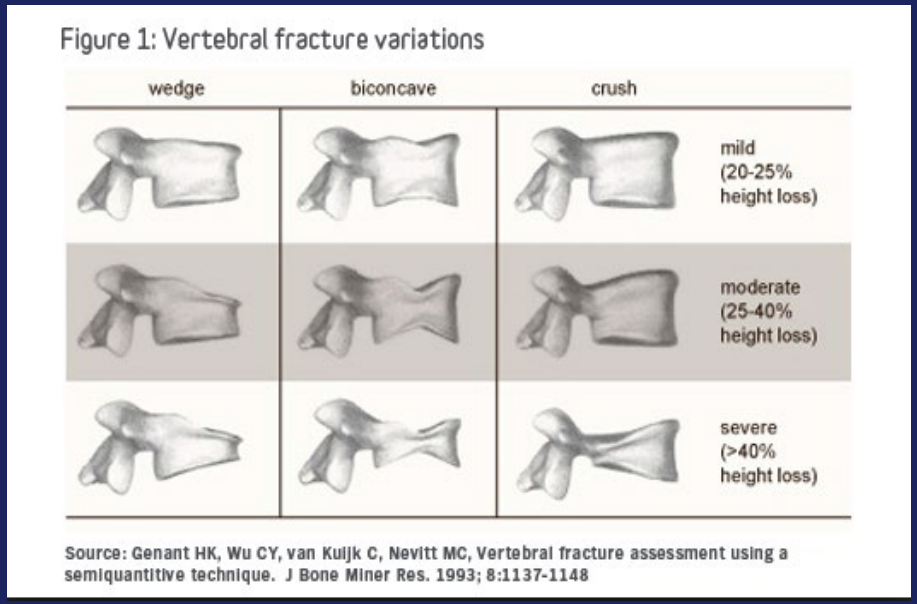
FIRST FRACTURE



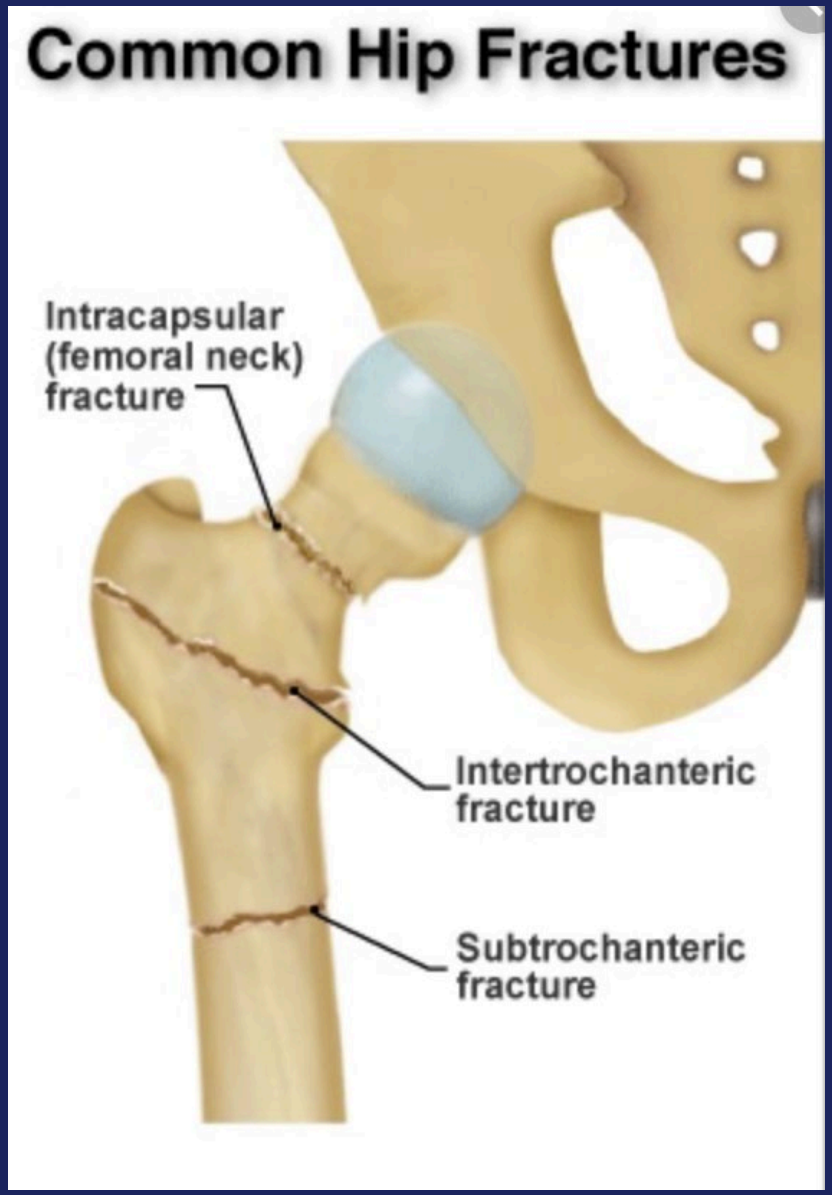
§A cross-sectional study with postmenopausal women aged 50 to 80 (N=4140) who completed a questionnaire on risk factors for osteoporosis, fracture history, and onset of menopause. The time that elapsed between a first and subsequent clinical vertebral and nonvertebral fracture, including low-trauma and high-trauma fractures, was analyzed at various times after the first fracture.[13]

Compression fracture of the Spine





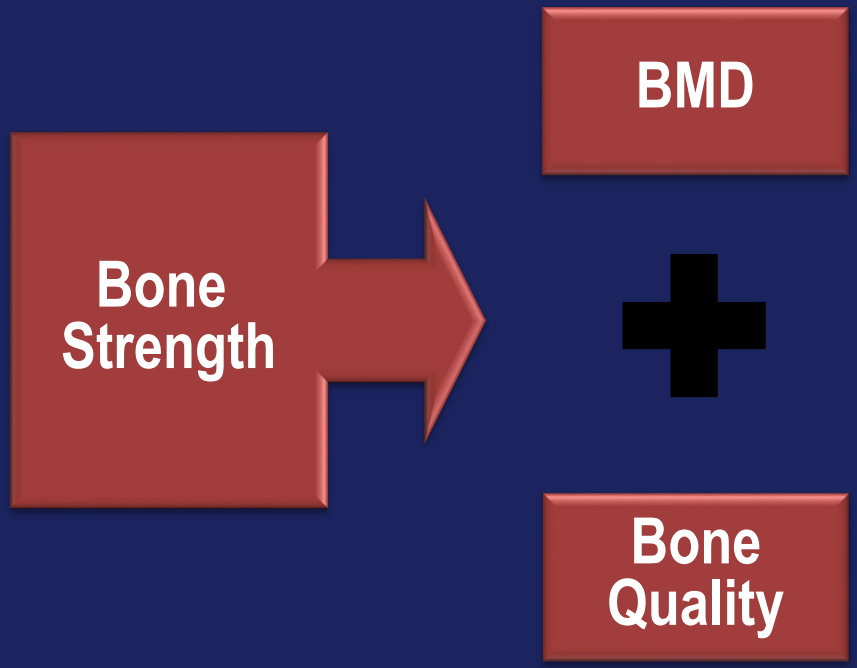
Hip Fracture



Diagnosis of Osteoporosis

Evaluating Bone Strength

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of BMD and bone quality.[1]



Obtain Through a DXA Test

Bone Characteristics[1]

1. Rate of bone remodeling
2. Architecture
3. Degree of mineralization
4. Damage accumulation

Clinical Indicators

1. Increasing age[2]
2. Previous fragility fractures[3]

BMD=bone mineral density DXA=dual-energy x-ray absorptiometry

1. NIH Consensus Development Panel on Osteoporosis Treatment. *JAMA*. 2001;285:785-795
2. Rehman MT, et al. *J Clin Pathol*. 1994;47:529-534.
3. Genant HK, et al. *Osteoporos Int*. 2007;18:69-76.

DEXA Machine

DEXA

- DEXA measure only two areas:

$$\frac{\text{BONE MINERAL CONTENT (G)}}{\text{AREA (CM2)}}$$

WHO Criteria for Postmenopausal Osteoporosis

The T-score compares an individual's BMD with the mean value for young adults and expresses the difference as a standard deviation score.

Category	T-score
Normal	-1.0 and above
Low bone mass (osteopenia)	Between -1.0 to -2.5
Osteoporosis	-2.5 and below

Fragility fracture=Osteoporosis
FRAX: using BMI- >20% or 3% for hip

Kanis JA, et al. *J Bone Miner Res.* 1994;9:1137-1141.

GE Lunar Corporation

726 Heartland Trail
Madison, WI 53717-1915

Patient:	Sample, Report		**Facility ID:**		
Birth Date:	10/06/1942	59.6 years	**Physician:**	Dr. Crusher	
Height / Weight:	64.5 in.	133.3 lbs.	**Measured:**	05/14/2002	11:38:30 AM (6.10)
Sex / Ethnic:	Female	White	**Analyzed:**	05/24/2002	8:33:33 AM (6.50)

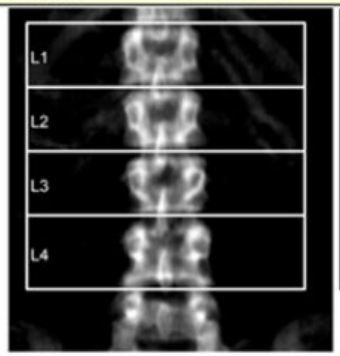


Image not for diagnosis

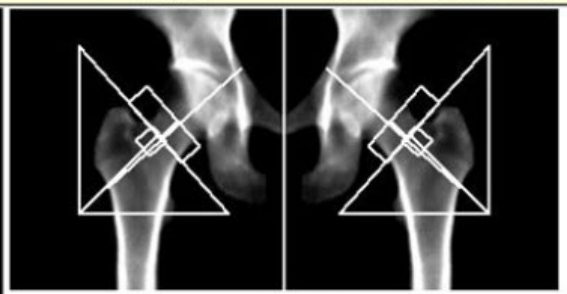


Image not for diagnosis

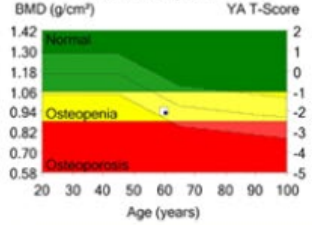
Hip Axis Length Comparison (mm)

Left = 2.9 Right = 3.8

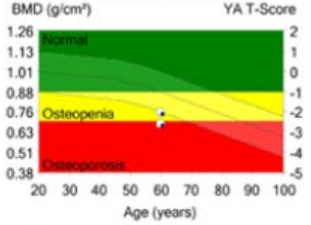
-30 -20 -10 Mean 10 20 30

(Right = 109.5 mm) (Mean = 105.7 mm) (Left = 108.6 mm)

Reference: AP Spine L1-L4



Reference: DualFemur Total



Region	BMD [1] (g/cm²)	Young-Adult [2,7] T-Score	Age-Matched [3] Z-Score	WHO Classification [11]
AP Spine L1-L4	0.946	-1.947	-0.6	Osteopenia
DualFemur Total				
Total Left	0.749	-2.067	-1.1	Osteopenia
Total Right	0.680	-2.609	-1.6	Osteoporosis
Total Mean	0.714	-2.338	-1.3	Osteopenia
Total Diff.	0.068	2.067	-	-

1 -Statistically 68% of repeat scans fall within 1SD (± 0.010 g/cm² for AP Spine L1-L4); (± 0.010 g/cm² for DualFemur Total Mean)
2 -USA/NHANES, AP Spine Reference Population, Ages 20-40; USA/NHANES, Femur Reference Population, Ages 20-40
3 -AP Spine Matched for Age, Weight (females 25-100 kg), Ethnic; DualFemur Matched for Age, Weight (females 25-100 kg), Ethnic
7 -DualFemur Total T-Score difference is 0.5. Asymmetry is None.
11 -WHO - Definition of Osteoporosis and Osteopenia for White Women: Normal = T-Score at or above -1.0 SD; Osteopenia = T-Score between -1.0 and -2.5 SD; Osteoporosis = T-Score at or below -2.5 SD

Printed: 08/12/2002 9:21:29 PM (7.00); Filename: zielsc_gw3xy0akb.dfx; AP Spine; 13.9:%Fat=4.9%; Scan Mode: Standard; Right Femur; 12.8:%Fat=21.2%; Neck Angle (deg)= 53; Scan Mode: Precise; Left Femur; 13.1:%Fat=19.2%; Neck Angle (deg)= 53; Scan Mode: Precise

unar Prodigy P1 - [ef659kceq.dfx]
File Measure Analyze Directory QA Composer Tools Window Help
Analyze Directory QA Imaging ROIs Points Copy Reports Save Close
AP Spine Left Femur Total Body
L1
L2
L3
L4
Image not for diagnosis
CAD Densitometry Reference Trend Information
Reference: L1-L4
BMD (g/cm²)
YA T-Score
1.54
1.42
1.30
1.18
1.06
0.94
0.82
0.70
0.58
3
2
1
0
-1
-2
-3
-4
-5
Normal
Osteopenia
Osteoporosis
20 30 40 50 60 70 80 90 100
Age (years)
Reference
Region | BMD (g/cm²) | YA (%) | YA T-Score | AM (%) | AM Z-Score
L1 1.028 91 -0.9 111 0.8
L2 1.453 121 2.1 146 3.8
L3 1.628 136 3.6 163 5.3
L4 1.274 106 0.6 128 2.3
L1-L2 1.251 107 0.7 130 2.4
L1-L3 1.386 118 1.8 143 3.5
L1-L4 1.354 115 1.5 139 3.1
L2-L3 1.543 129 2.9 155 4.6
L2-L4 1.445 120 2.0 145 3.7
L3-L4 1.441 120 2.0 145 3.7
Standard Results
Select region: up/down arrows
Results tab: left/right arrows
Image tab: tab/shift+tab
Click Here for Patient Info

TBS

BMD= 0.972

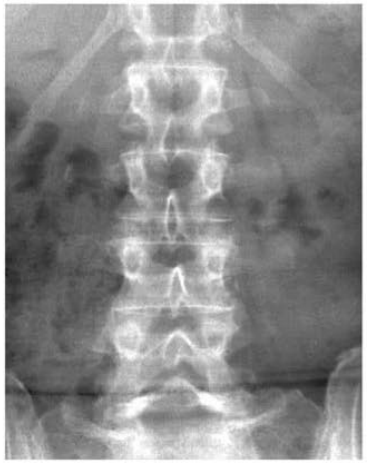
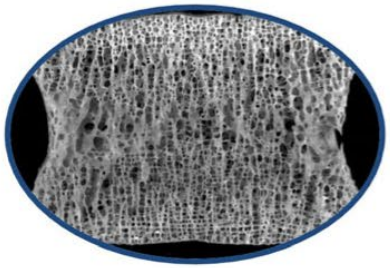
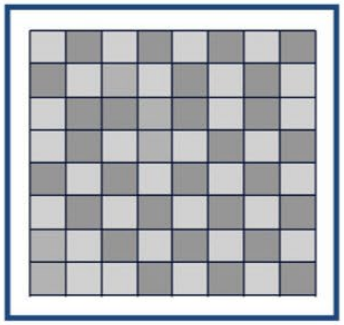
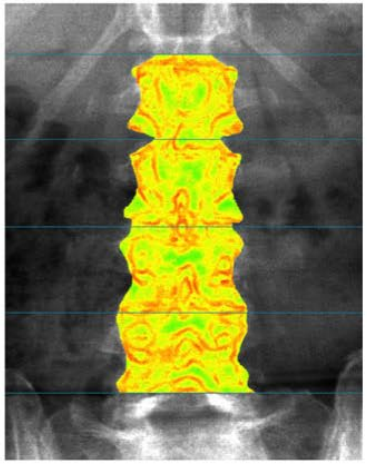


Illustration of Well-structured trabecular bone





TBS= 1.459



BMD= 0.969

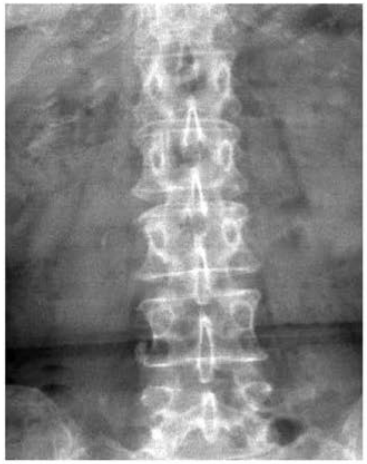
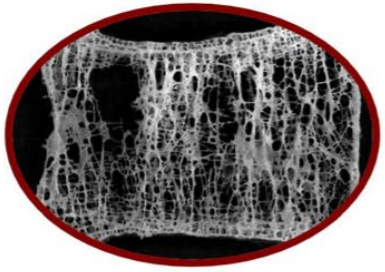
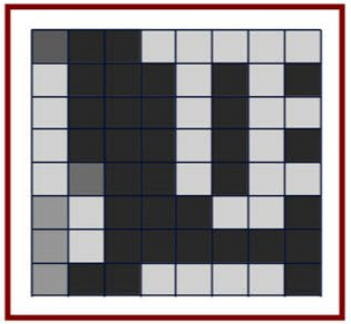


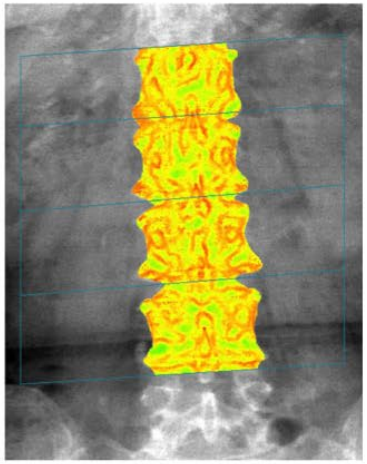
Illustration of Altered trabecular bone



Experimental variogram

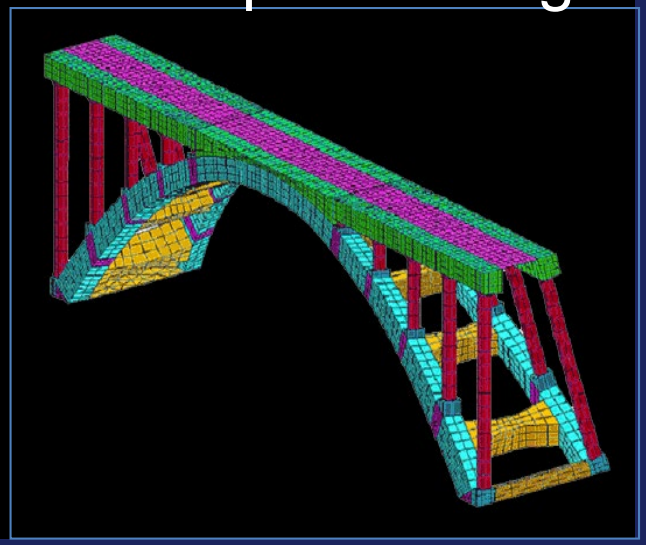


TBS= 1.243



Finite Element Analysis (FEA)

- Well-established method for analysis of complex structures
- Model structure as collection of “finite elements”
- Assign material properties to each element and external forces to whole model
- Compute strength or other structural performance



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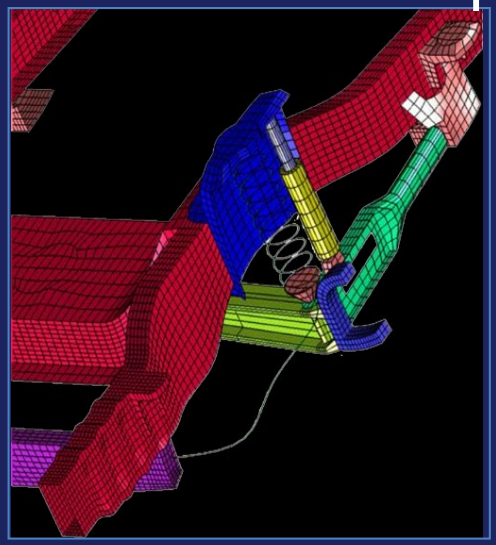
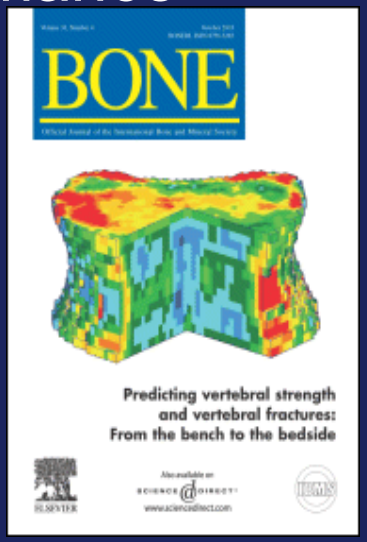
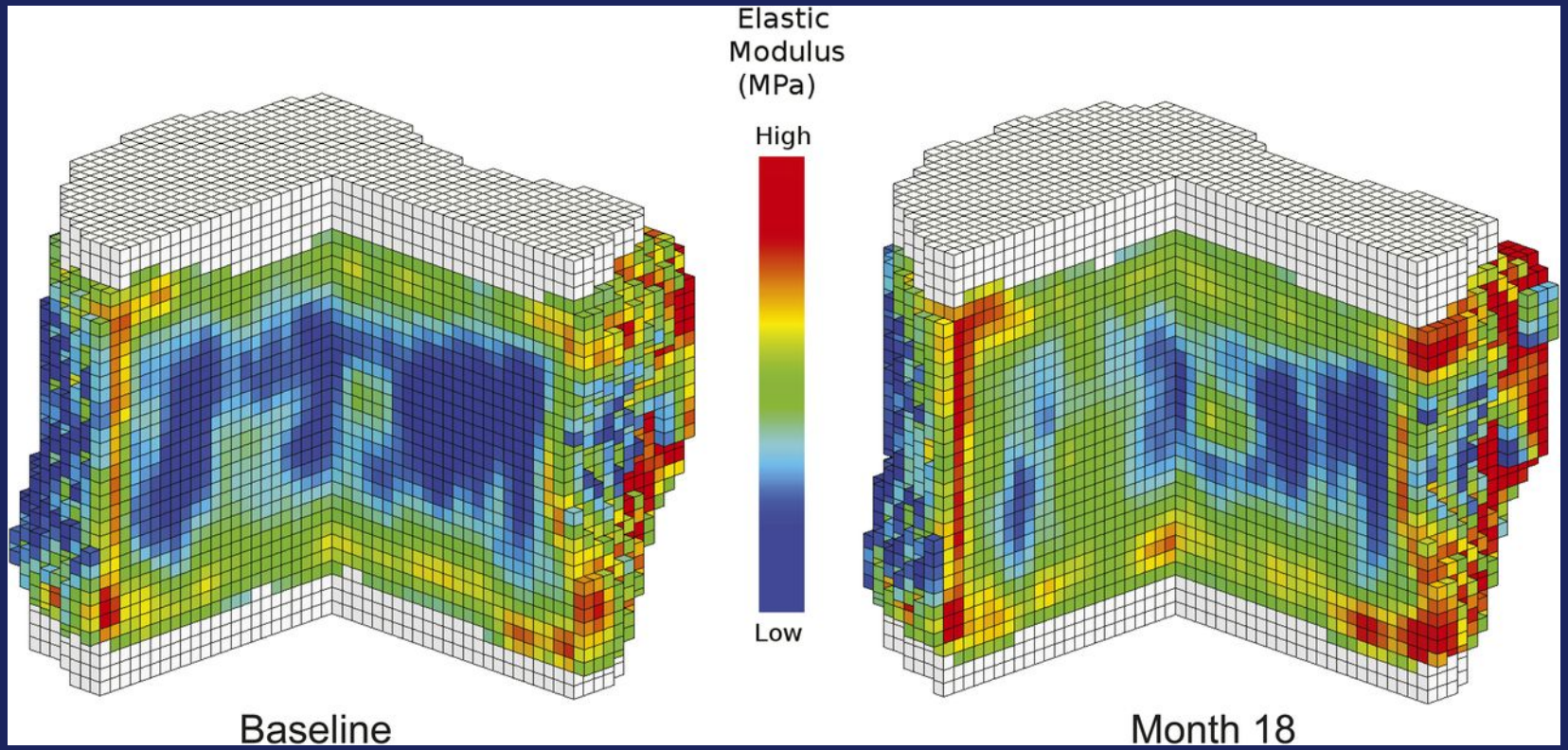


truegrid.com/ gallery/truck2.html



Crawford, Bone 2003

Quantitative CT-based finite element models of the L3 vertebra from a representative study subject before and after treatment with teriparatide.



Kleerekoper M et al. J Bone Joint Surg Am 2014;96:e90

JBJS The Journal of Bone & Joint Surgery
Excellence Through Peer Review

NOF Indications for BMD testing

- Women age 65 years and older
- Men age 70 years and older
- Age 50-69 with risk factor
- Fracture after age 50
- Women >age 50 if a specific risk factor (low body weight, prior low-trauma fracture or high risk medication)

2013 USPTF recommendations for screening for osteoporosis

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Women, 65 and Older	The USPSTF recommends screening for osteoporosis in women aged 65 years and older and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors.	B
Men	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.	I

How Often Should I Have a DXA?

- Important to have DXA on same machine (brand) preferable at same location as prior study
- Every 2 years per medicare
- Recent studies state if osteopenia--?repeat in 5 years or longer
- Postmenopausal women aged 50-64 year without osteoporosis on their first BMD test are unlikely to benefit from frequent rescreening before age 65.
  - Gourlay ML et al. Baseline age and time to major fracture in younger postmenopausal women. Menopause. 2015; 22: 589-97

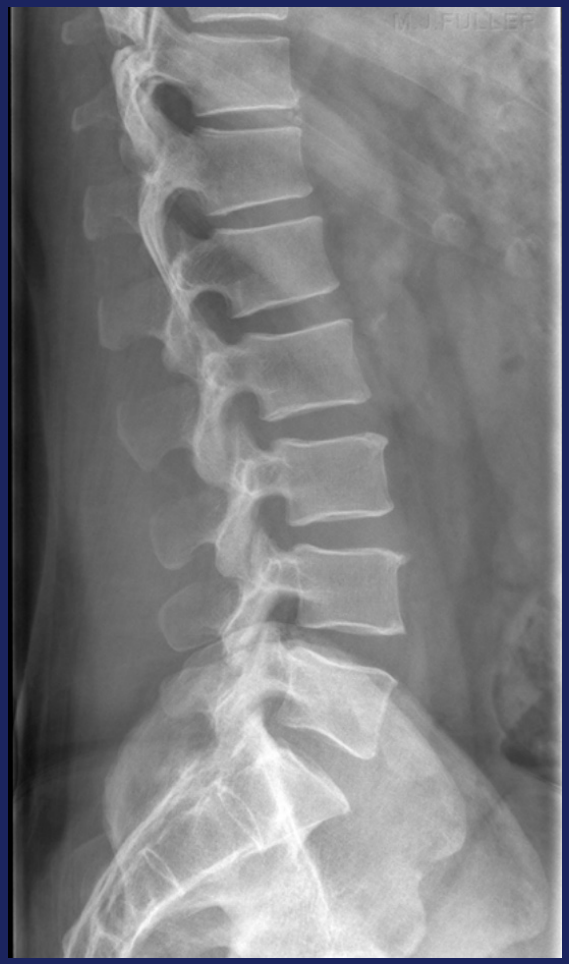
Peripheral DXA

- Order 1/3 distal radius when spine or hips cannot be used due to instrumentation, hardware, osteoarthritis

- This can be used as a guide for treatment as well

Indication for Vertebral Fracture Assessment (VFA)

- Lateral spine imaging or VFA is indicated if T score is -1.0 and one of the following:
  - Age ≥ 70 in female, Age ≥ 80 in males
  - **Height loss >1.5 inches**
  - Documented vertebral fracture
  - Glucocorticoids > 5 mg daily for >3 months



ISCD 2015 guidelines

Ethnic Considerations and DXA

Osteoporos Int. 2016 Dec;27(12):3477-3484. Epub 2016 Jul 28.

Applying ethnic-specific bone mineral density T-scores to Chinese women in the USA.

Lo JC[1,2], Kim S[3], Chandra M[4], Ettinger B[4].

-Caucasian reference data base is currently used

-Using Chinese American BMD data raised t scores by 0.4-0.5 in Chinese American women age 50-79

-Younger, Chinese women may be reclassified from osteoporosis to osteopenia if this database is used.

Premenopausal Osteoporosis

- ICSD recommends NOT using terms osteoporosis/penia
- Z score <-2.0 =LOW BMD for expected age
- Treatment is controversial
  - Munns et al. found adverse pregnancy outcomes
- A history of premenopausal fx increased risk of postmenopausal fx by 35%

JBMR, 2004

Secondary Causes of Osteoporosis

Secondary Causes of Osteoporosis

Table 2
Causes of Generalized Secondary Osteoporosis in Adults*

Endocrine disease or metabolic causes	Nutritional conditions	Drugs	Disorders of collagen metabolism	Other
Hypogonadism	Malabsorption syndromes and malnutrition	Vitamin D toxicity	Osteogenesis imperfecta	Rheumatoid arthritis
Hyperadrenocorticism	Chronic liver disease	Phenytoin	Homocystinuria due to cystathionine deficiency	Myeloma and some cancers
Thyrotoxicosis	Gastric operations	Glucocorticoids	Ehlers-Danlos syndrome	Immobilization
Anorexia nervosa	Vitamin D deficiency	Phenobarbital	Marfan syndrome	Renal tubular acidosis
Hyperprolactinemia	Calcium deficiency	Excessive thyroid medication		Hypercalciuria
Porphyria	Alcoholism	Heparin		COPD
Hypophosphatasia in adults		Gonadotropin-releasing hormone antagonists		Organ transplantation
Diabetes mellitus, type 1				Cholestatic liver disease
Pregnancy				Mastocytosis
Hyperparathyroidism				Thalassemia
Acromegaly				

*COPD = chronic obstructive pulmonary disease.

Adapted from AACE Guidelines on osteoporosis, 2001

Take a Good History

- Height loss
- Family history of hip fx or osteoporosis
- Fracture hx >age 50
- RA, Steroid use
- Medication review
- Menstrual hx/lactation/pregnancy
- ETOH/tobacco/soda

Hx of malabsorption

Hx of bed rest> 1 month

Hx of eating disorder

Hx of chemo/radiation

Hx of kidney stone

Hx of chronic liver/kidney disease

Exercise, nutrition

Diet: cal/vitamin D

Fall hx/balance

Secondary Causes of Osteoporosis

- Hypogonadism
- Hyperthyroidism
- Primary Hyperparathyroidism
- Vitamin D deficiency
- Cushing’s syndrome or SCGH
- Diabetes
- Hypercalciuria
- Celiac Disease

Secondary Causes of Osteoporosis

- GI disease---Malabsorption, bariatric surgery
- Hematological—Bone marrow
- Medications
- Transplantation
- ETOH/tobacco
- Lactation/Pregnancy
- Renal/Liver disease

Medications that cause osteoporosis

- Glucocorticoids (≥ 5 mg/d of prednisone for ≥ 3 months)
- Immunosuppresants (cyclosporines, tacrolimus)
- Heparin/Coumadin
- Anticonvulsants (gabapentin)
- Opioids
- PPI's
- Lithium
- Chemotherapy agents
- Aromatase Inhibitiors
- Androgen Deprivation Therapy
- Depo Provera
- Excess thyroid medication
- SSRI's
- TZD's
- Vitamin A excess/deficiency
- Anti-retroviral therapy

PPI's and Fracture Risk

- Omeprazole was shown to reduce fractional excretion of calcium carbonate in fasting PM women(O'Connell, et al. Am J Med, 2005)
- 2006 study showed possible association btwn hip fractures and chronic PPI use
  - Yang YX etal. . Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006.
- PPI use and increased risk for hip fracture in tobacco users (Khalili H, et al. BMJ. 2012)
- 2011 Meta-Analysis showed assoc. between PPI's and fracture at all sites—but not with H2 blockers. (Yu, et al. Am J Med, 2011)
- **Recommendation: calcium citrate, higher calcium diet if pt requires PPI therapy.**
- **Do benefits of PPI outweigh the risks?**

Laboratory Tests to Assess

- **Comprehensive metabolic panel**
- **CBC**
- **25-OH vitamin D**
- Phosphorus, magnesium
- 24 hour urine for calcium and creatinine
- SPEP/UPEP
- Serum testosterone (male)
- TSH
- PTH
- TTGIgA
- 1 mg dexamethasone suppression test

How often is a secondary cause of bone loss found?

- Population based study in younger patients: 90% found to have secondary cause—Khosla et al., 1994
- Referrals from tertiary center-40-53% found to have secondary causes—Kulak et al. 2000, Tannenbaum et al. 2002 Peris et al. 2003, Cohen et al 2006
- Tannebaum et al. found hypercalciuria was most common secondary cause in 2002

Case Question #1

- 57 yo female with multiple compression fractures
- No past medical history, fam hx, surgical hx . Taking only calcium and vitamin D
- 2010—1st compression fx T8, 2011 second-T4-5, 2015-T-T7
- s/p kyphoplasty 2015—T4-T8
- DXA 2016- t score L femoral neck -3.1 t score LS -3.2
- Xrays reviewed which show pathologic fractures—multiple lesions T4-T8—concern for pathologic process
- Is there a test in the workup for secondary causes that I should order?

Answer-Case # 1

- SPEP/UPEP : negative
- Serum tryptase: 90 (nl< 10)
- What is the diagnosis?

ANSWER

SYSTEMIC MASTOCYTOSIS

Case Question #2

- 55 yo female who presents with a “pop” in her back while lifting heavy boxes.
- On LS xray found to have L2 superior endplate fracture -20% and a sacral alar fracture
- No medications, no pertinent med hx. No family history of osteoporosis
- Alk phos 29 nl (35-140). All other labs normal for secondary causes

Case Question #2

- B6– 282 nmol/L, 313 nmol/L (<125 nmol/L)

- What does she have and what test should I order next?
- What is the treatment of this entity?
  - Could I use bisphosphonates for her osteoporosis medication?

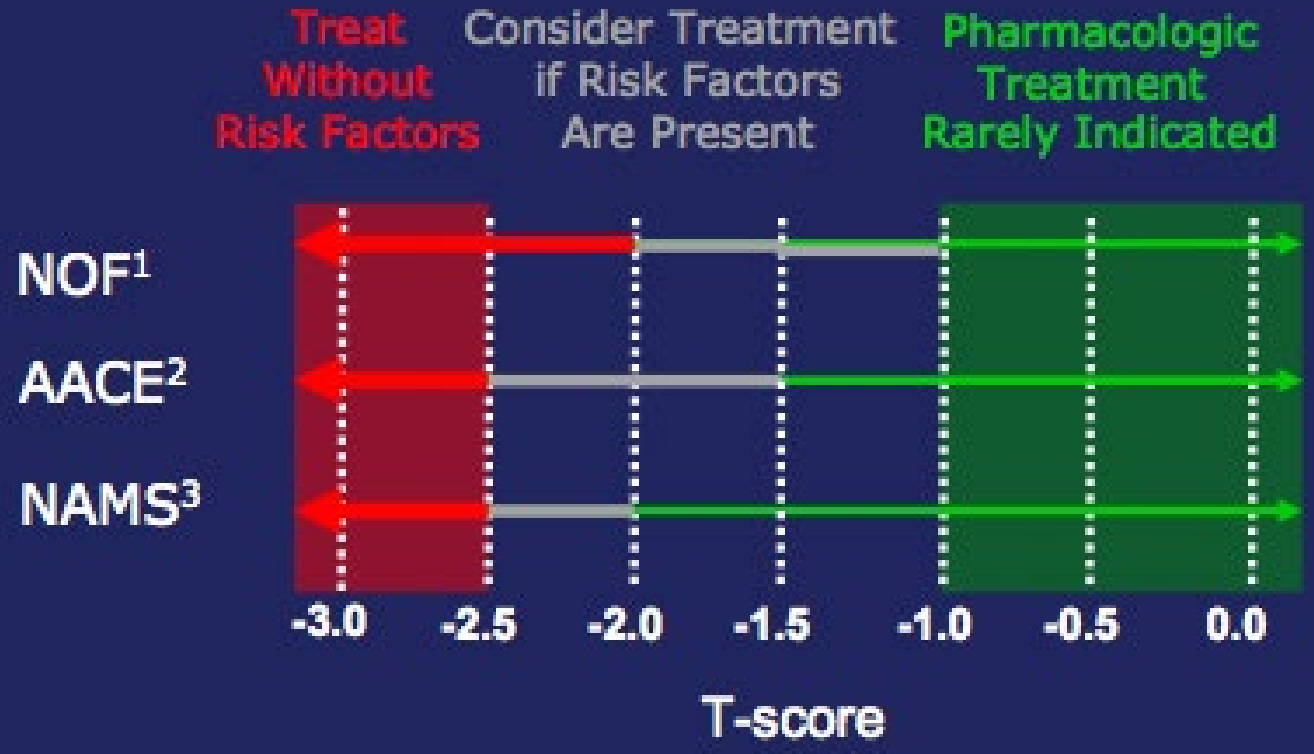
ANSWERS

- Hypophosphatasia (HPP)
  - Rare, genetic disorder loss of fxn mutation of ALPL
  - Autosomal dominant typically in adults
  - Dec levels of TNSALP enzyme
  - Inc substrate levels of phosphoethanolamine (PEA), pyridoxal-5'-phosphate(PLP) and inorganic pyrophosphate (PPi)

- Treatment
  - Asfotase alpha—strensiq
  - Enzyme replacement
  - Do NOT use bisphosphonates (structurally similar to PPi)

Who do we treat?

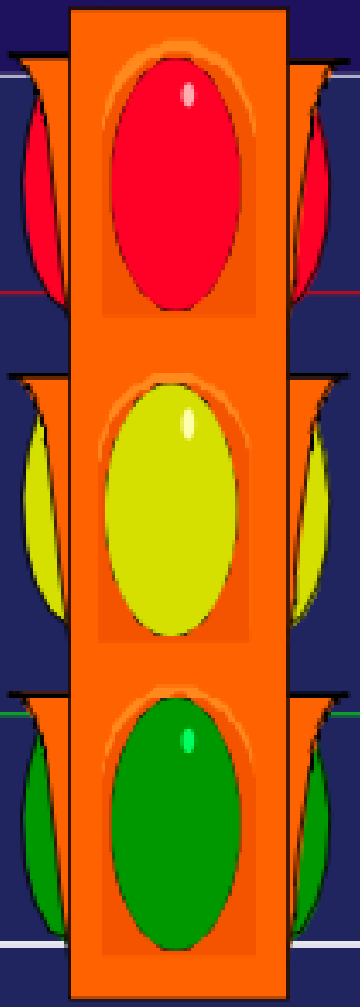
When to Initiate Pharmacologic Therapy



[1] National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. 2008. Available at: http://nof.org/professionals/NOF_Clinicians_Guide.pdf.
[2] American Association of Clinical Endocrinologists. Available at: http://www.aace.com/pub/pdf/guidelines/osteoporosis2001Revised.pdf.
[3] North American Menopause Society. Available at: http://www.menopause.org/aboutmeno/osteo.pdf.

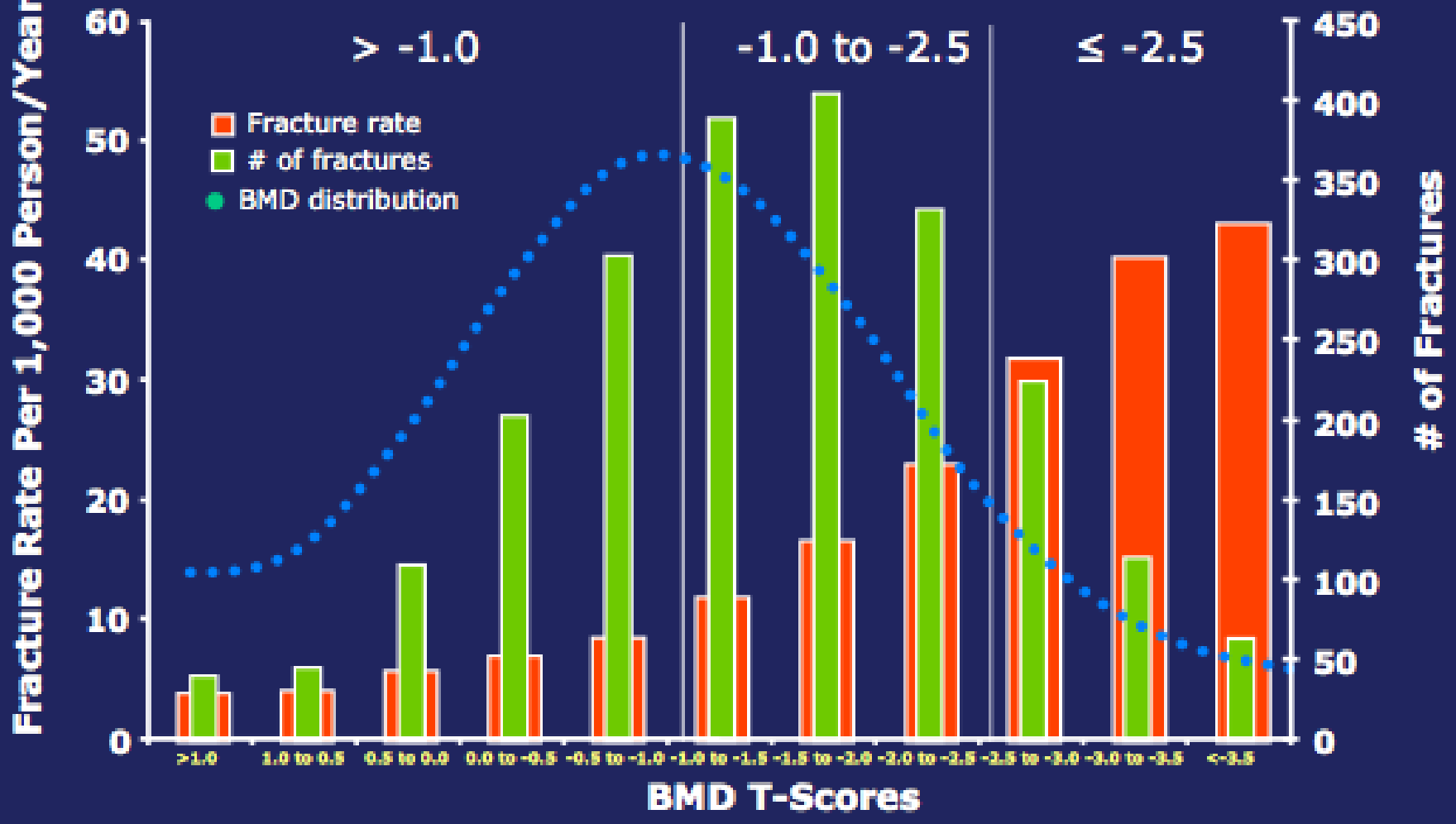
Who Is at Risk?

T-score	Therapy decision
-2.5 or below	High risk Treat
-1.5 to -2.5	Intermediate risk How do we regard these patients? Are they at risk?
Above -1.5	Low risk General preventive measures



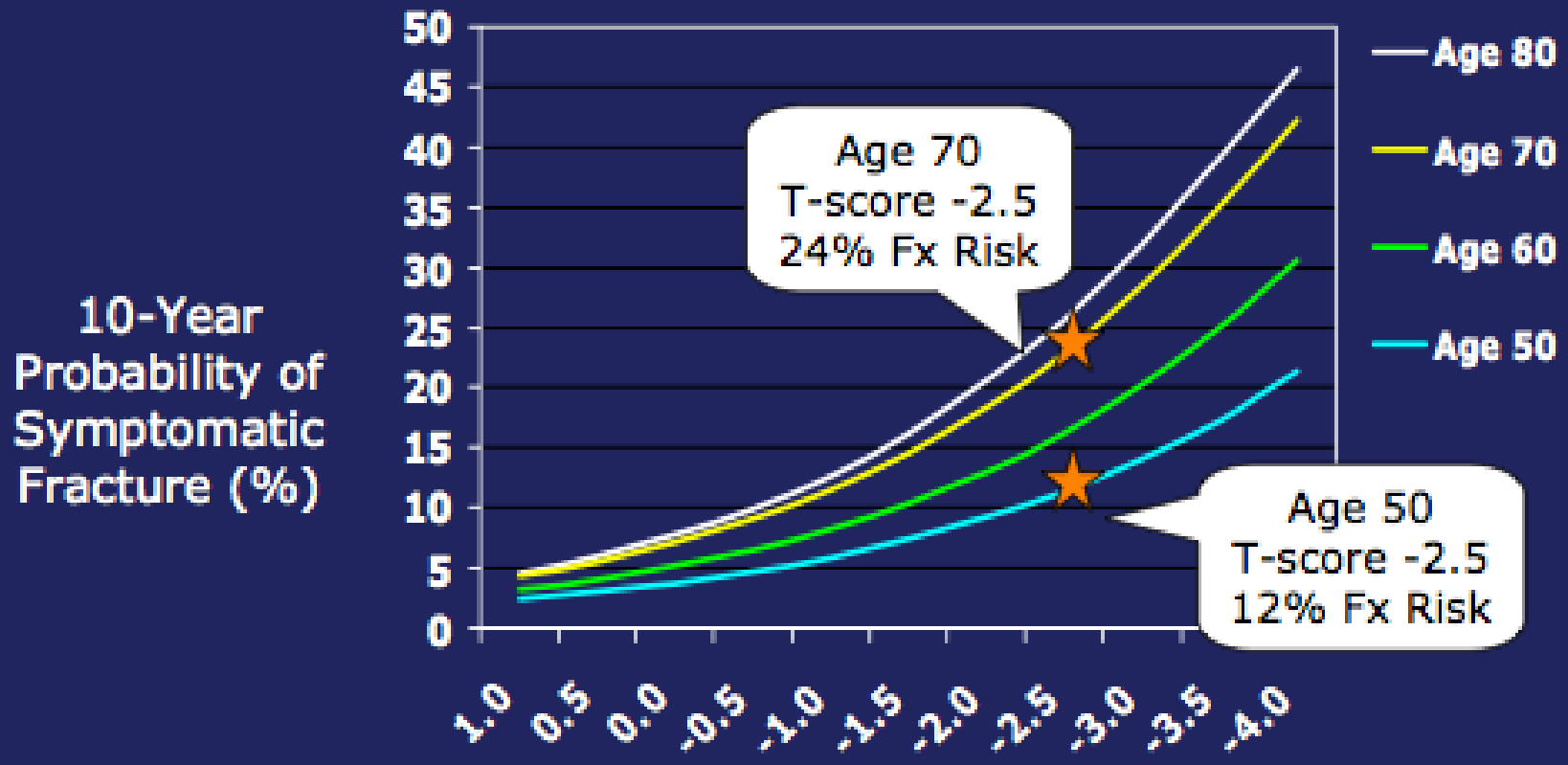
NOF; http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf.
AACE; http://www.aace.com/pub/pdf/guidelines/osteoporosis2001Revised.pdf.

Population BMD Distribution, Fracture Rates, and Number of Women With Fractures



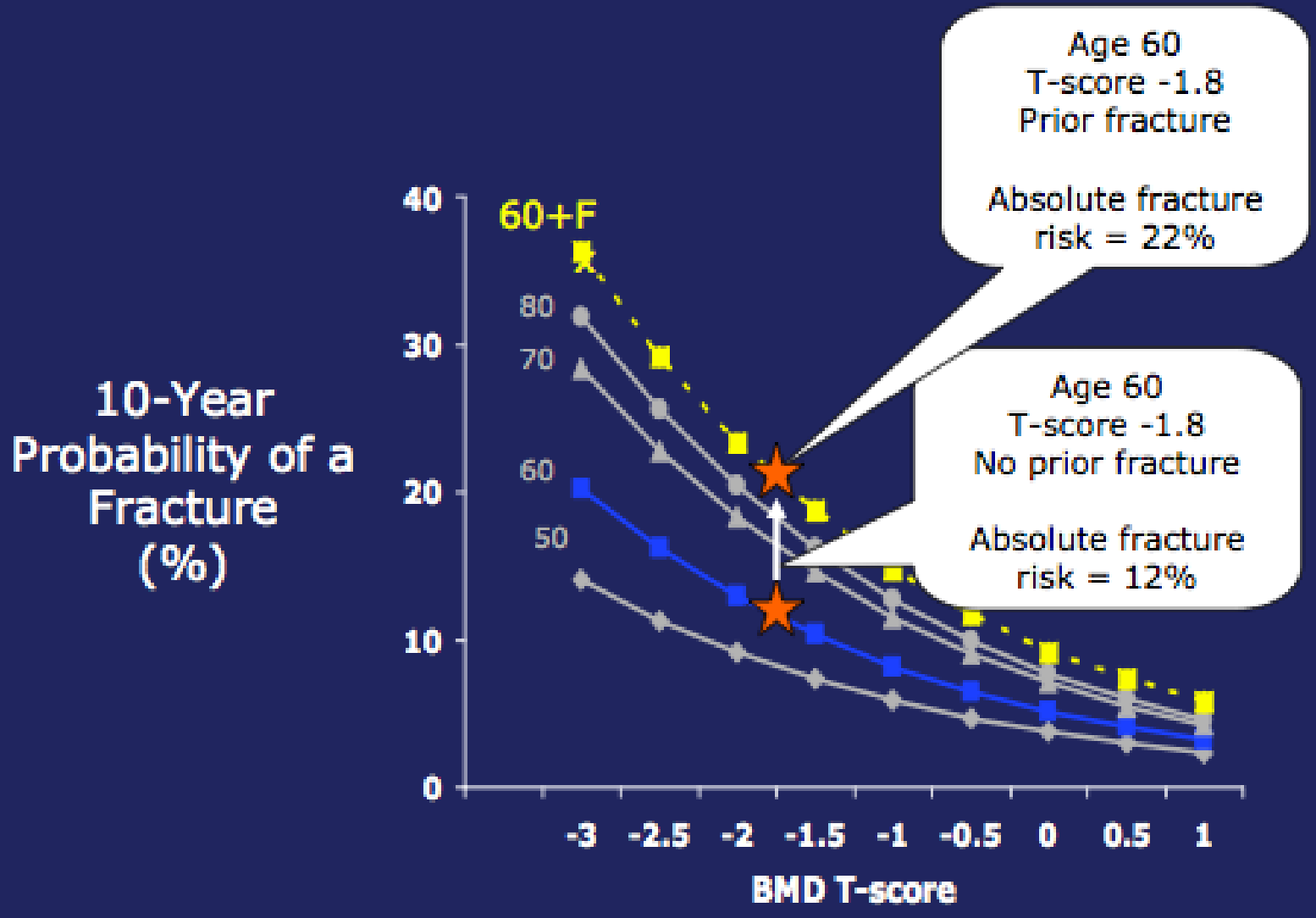
Siris ES, et al. *Arch Intern Med.* 2004;164:1108-12.

Age Is a Risk Factor for Fracture



Adapted from Kanis JA, et al. *Osteoporos Int.* 2001;12:989-95.

The Previous Fracture Increases Risk



Kanis JA, et al. *Osteoporos Int.* 2001:12;989-95.

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

Google

ucsd OsteoEd – O...s Education Google Citrix Access Platform Yahoo! PBS KIDS News (424) Popular Home – Sesame Street

FRAX® WHO Fracture Risk Assessment Tool

HOME | CALCULATION TOOL | PAPER CHARTS | FAQ | REFERENCES | Select a Language

- Austria
- China
- France
- Germany
- Italy
- Japan
- Spain
- Sweden
- Switzerland
- Turkey
- UK
- US (Caucasian)
- US (Black)
- US (Hispanic)
- US (Asian)

Welco

The FRAX® ed by WHO to evaluate fracture risk of patients. It is based on individual patient models that integrate the linical risk factors as well as bone mineral density (BMD) at the femoral neck.

The FRAX® eloped from studying population-based cohorts from Europe, North America, Asia and Australia. In d form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, ba isk factors are also available, and can be downloaded for office use.

The FRAX® year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability o racture (clinical spine, forearm, hip or shoulder fracture).

Dr. John A Kanis
Professor Emeritus, University of Sheffield

Latest Release Notes

Links :

International Osteoporosis Foundation : http://www.iofbonehealth.org/
National Osteoporosis Foundation : http://www.nof.org/
Japan Osteoporosis Foundation : http://www.jpof.or.jp/

FRAX™ WHO Fracture Risk Assessment Tool

HOME | CALCULATION TOOL | PAPER CHARTS | FAQ | REFERENCES | Select a Languag

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Weight Conversion:

pound: [ ]

convert

Height Conversion:

inch : [ ]

convert

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

Questionnaire:

1. Age (between 40-90 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 more units per day ◉ No ○ Yes

12. Femoral neck BMD

    Select [ ]

Clear | Calculate

Country : US(Caucasian) Name / ID : About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age: 70 Date of birth: Y: 1938 M: 2 D: 4

2. Sex ○ Male ◉ Female

3. Weight (kg) 62.59

4. Height (cm) 139.7

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 more units per day ◉ No ○ Yes

12. Femoral neck BMD

T-score -2.0

Clear Calculate

BMI 32.1

The ten year probability of fracture (%)

with BMD

Major osteoporotic	16
Hip fracture	2.3

FRAX Summary

- If t score is between -1.0 and -2.5 treatment is recommended if:

The 10 year probability of a hip fracture is **≥ 3%**

The 10-year probability of a major osteoporosis-related fracture **≥ 20**

10-Year Probability of a Major Osteoporotic Fracture in Average White Women Without Prior Fracture or Other Risk Factors

Age	White women			
	55	65	75	85
Femoral neck T-Score	BMD but no risk factors			
-1.0	7.6	13	22	22
-1.5	8.8	14	24	25
-2.0	10	16	27	28
-2.5	13	20	32	32

1999 Guidelines

Femoral neck T-Score	BMD but no risk factors			
-1.0	7.6	13	22	22
-1.5	8.8	14	24	25
-2.0	10	16	27	28
-2.5	13	20	32	32

2008 Guidelines

Dawson-Hughes B, et al. *Osteoporos Int.* 2008;19:449-58.

FRAX Rules

- FRAX is intended for postmenopausal women and men age 50 and older
- FRAX applies ONLY to previously untreated patients
- Must use only total hip or femoral neck t score or z score in the FRAX
- Only a guideline!

Prevention of Osteoporosis

Non pharmacological approaches to the prevention of osteoporosis

- Adequate intake of dietary calcium
- Regular physical activity
- Minimize alcohol intake—1-2 small glasses/daily
- Encourage smoking cessation
- Minimize risk of fall

Current Calcium Recommendations

- 1200 mg daily for women older than 50
- 1000 mg daily for men older than 50
- 1200 mg daily for men older than 70
- Try and obtain from food sources, then supplement

Calcium and MI association?

- 2010 metanalysis showed possible assoc. btwn MI and >1500 mg of calcium daily
  - Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691
- However, recent study showed no assoc. btwn. calcium and inc. risk of MI
  - Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2012. Epub 2012/12/05.

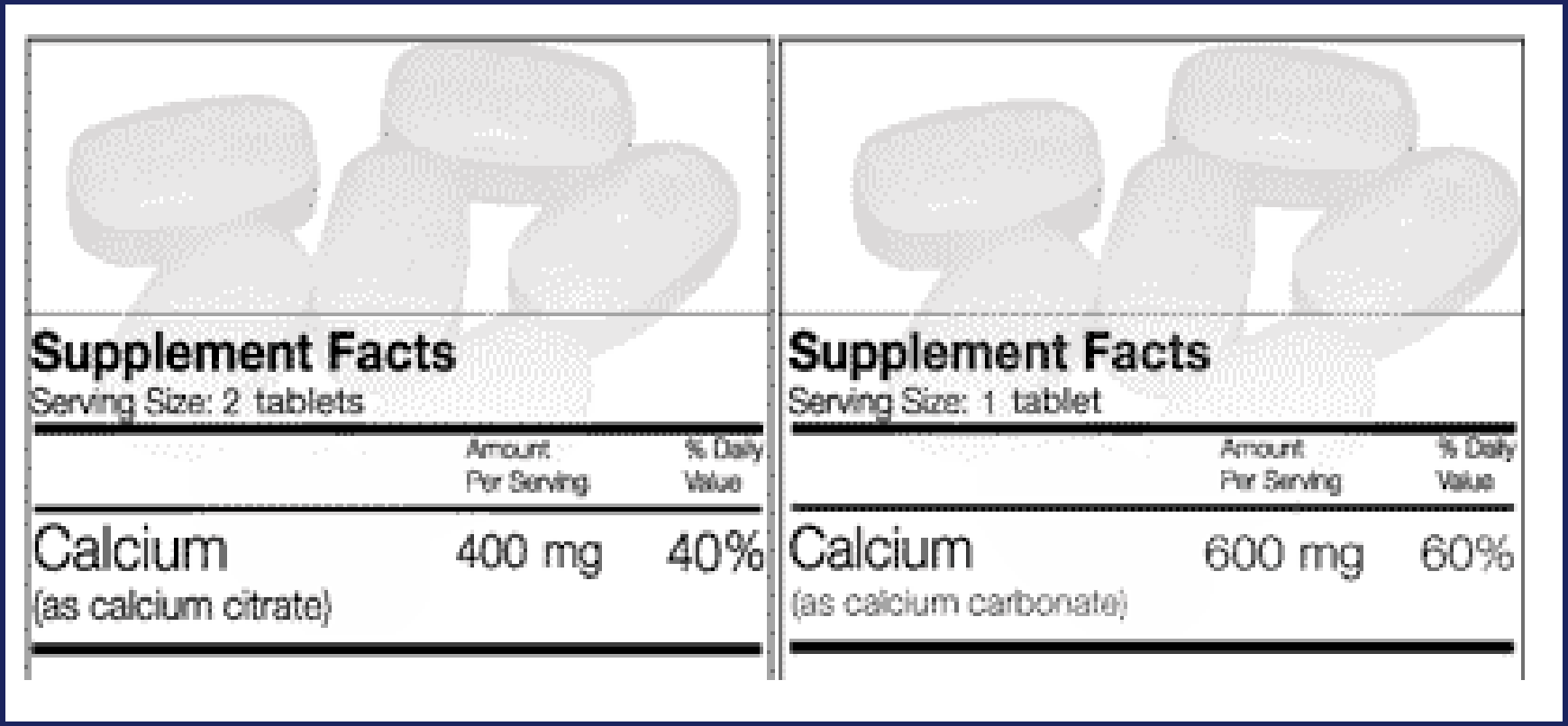
Calcium Calculator

Product	Servings/Day	Calcium (mg)	Total
Milk (8 oz.)		X 300	=
Yogurt (6 oz.)		X 300	=
Cheese (1 oz. or 1 cubic inch)		X 200	=
Fortified Foods/Juices		X 80-1,000	=
Estimated total from other foods			= 250
Total daily calcium intake, in mg			=

Which Type of Calcium?

- Calcium Carbonate---needs to be taken with food for best absorption
- Calcium Citrate—does not need to be taken with food
- Calcium Phosphate
- Calcium Gluconate
- Calcium Lactate

Calcium Supplements



Supplement Facts
Serving Size: 2 tablets

	Amount Per Serving	% Daily Value
Calcium (as calcium citrate)	400 mg	40%

Supplement Facts
Serving Size: 1 tablet

	Amount Per Serving	% Daily Value
Calcium (as calcium carbonate)	600 mg	60%

Vitamin D

- You can get vitamin D from the sun. But, you need sunscreen to protect your skin which also blocks vitamin D.
- Vitamin D food sources: added to milk, OJ. Cod liver oil, fatty fish
- Supplementation is often needed

Vitamin D

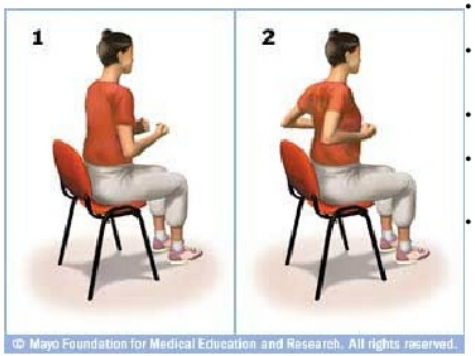
- 800-1000 IU daily
- Max. dose recommended : 4000 IU daily
- Studies have shown no association with cardiovascular disease or reduction in breast cancer

Vitamin D Levels

- This is controversial
  - 25(OH)D level >20 ng/mL = SUFFICIENCY
  - 25(OH) D level 12-20 ng/mL = INSUFFICIENCY
  - 25 (OH) D level <12 ng/mL = DEFICIENCY
  - 25 (OH) D level>100 ng/mL = TOXICITY

EXERCISE

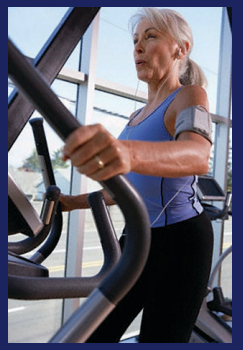
Exercises for Osteoporosis



- **Shoulder blade squeeze**
- To stretch your chest and strengthen your upper back muscles:
- With your feet flat on the floor, sit slightly forward in a sturdy chair, keeping your back and neck straight.
- Look straight ahead, bending your arms at the elbows (1).
- Gently move your elbows and shoulder blades back as far as you can and still be comfortable (2).
- Hold the position for five seconds while breathing normally. Return your arms to the starting position. Repeat this exercise five to 10 times, depending on your ability.

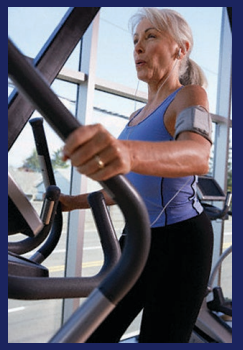
Weight-bearing Exercises

- Which exercise is for you?
  - **Low impact:** walking, elliptical, low impact aerobics, stair-stepper, tai chi
  - **High impact:** jogging or running, aerobic dancing, hiking, jumping rope, stair climbing



Weight-bearing Exercises

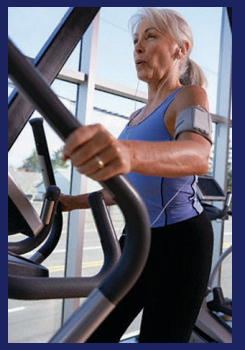
- Which exercise is for you?
  - Try to do the exercises with greatest impact that do not cause problems



- Try to do 30 minutes of weight-bearing exercise, at a moderate pace, most days of the week

Muscle-strengthening Exercises

- Muscle-strengthening exercises make you move your body, a weight or some other resistance against gravity
- Some options include:
  - Lifting weights (machines or free weights)
  - Calisthenics (partial or full push ups, wall slide/wall sits, prone trunk lifts)
  - Using exercise bands or tubes



Fall Prevention

- Ophthalmology check up
- Medication check
- Have patient stay active
- Discuss use of walker, cane or other source to help prevent falls
- Physical therapy

Fall Prevention in the Home

- Use handrails on stairs, in bathrooms
- Keep floors clutter-free
- Keep floors clean but not slippery
- Place skid-proof backing on carpets and rug
- Use rubber mat in shower/tub
- Use 100 watt bulbs in all rooms
- Install ceiling lighting in bedrooms

What about Caffeine?

- Coffee--calcium intake with coffee
- Tea—black tea > 3 cups daily: beneficial
- Soda—Cola—Tufts study showed phosphoric acid did cause significant bone loss (3 cans daily)

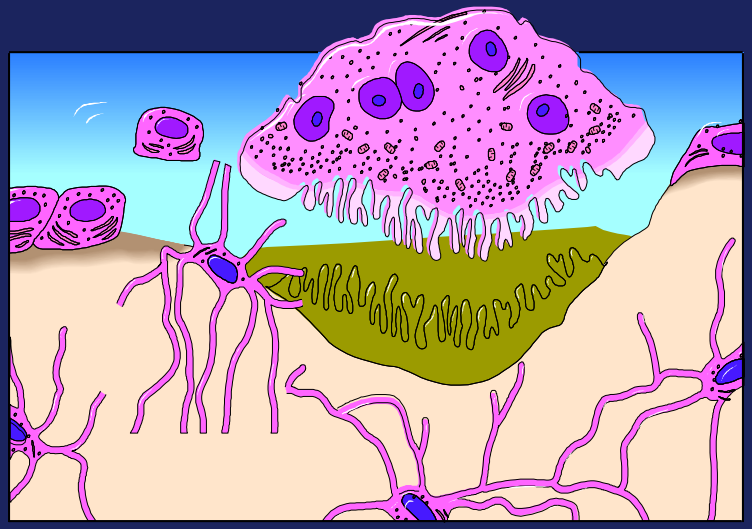
Alcohol and Tobacco

- Minimize ETOH use to <2 glasses daily
- Smoking cessation is key to healthy bones

Therapies for Osteoporosis

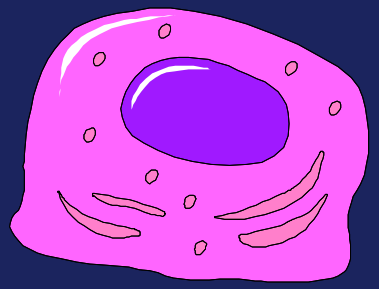
Treatment objectives

Osteoclast



Inhibition of resorption

Osteoblast



Stimulation of formation

FDA Approved Medications for Osteoporosis

Anti-resorptive Agents:

- Bisphosphonates
  - Oral alendronate
  - Oral risedronate
  - Oral ibandronate
  - IV Zoledronic acid
- Denosumab (Prolia)
- Raloxifene (Evista)
- Romosozumab (Evenity)

Anabolic Agents:

- Teriparatide (Forteo)
- Abaloparatide (Tymlos)
- Romosozumab (Evenity)

Case Question

- 78 yo female
- T scores: -2.8 in LS
- T scores: -3.0 in femoral neck
- Patient has concerns about going on therapy and wanted to discuss her risk for ONJ/AFF
- She wants to know if these medications will help you
- WHAT SHOULD YOU TELL THE PATIENT?

Benefits of Osteoporosis Therapy

- Reduction in fracture risk
- Reduction in pain and disability
- Preservation of independence
- Reduction in height loss
- Positive effect on mortality
- Positive effect on BMD

Why bisphosphonates?

- We have years of long term data that they work to reduce fracture compared to placebo
- Only medication with long term safety and fracture efficacy data

Zoledronic Acid Efficacy Summary

HORIZON Pivotal Fracture Trial[1]

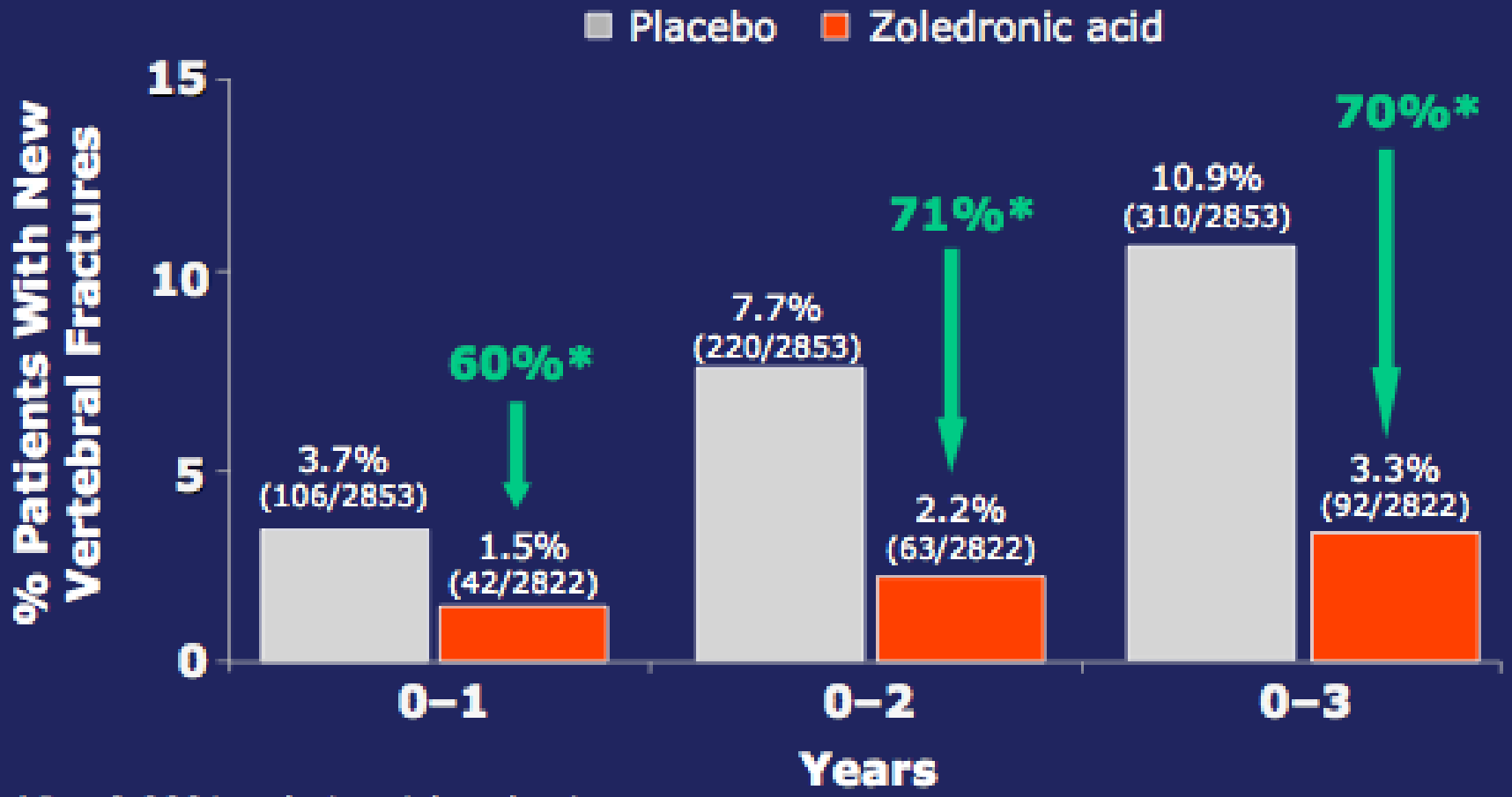
- In postmenopausal women with osteoporosis, once yearly infusion of ZOL 5mg over 3 years significantly reduces:
  - Morphometric vertebral fractures by 70%
  - Hip fractures by 41%
  - Non-vertebral fractures by 25%

HORIZON Recurrent Fracture Trial[2]

- In high risk patients with a recent low-trauma hip fracture, ZOL 5mg IV given within 90 days after a low-trauma hip fracture reduced
  - Risk of any clinical fracture by 35%
  - Risk of clinical vertebral fractures by 46%

1. Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.
2. Lyles KW, et al. *N Engl J Med*. 2007;357:1799-1809.

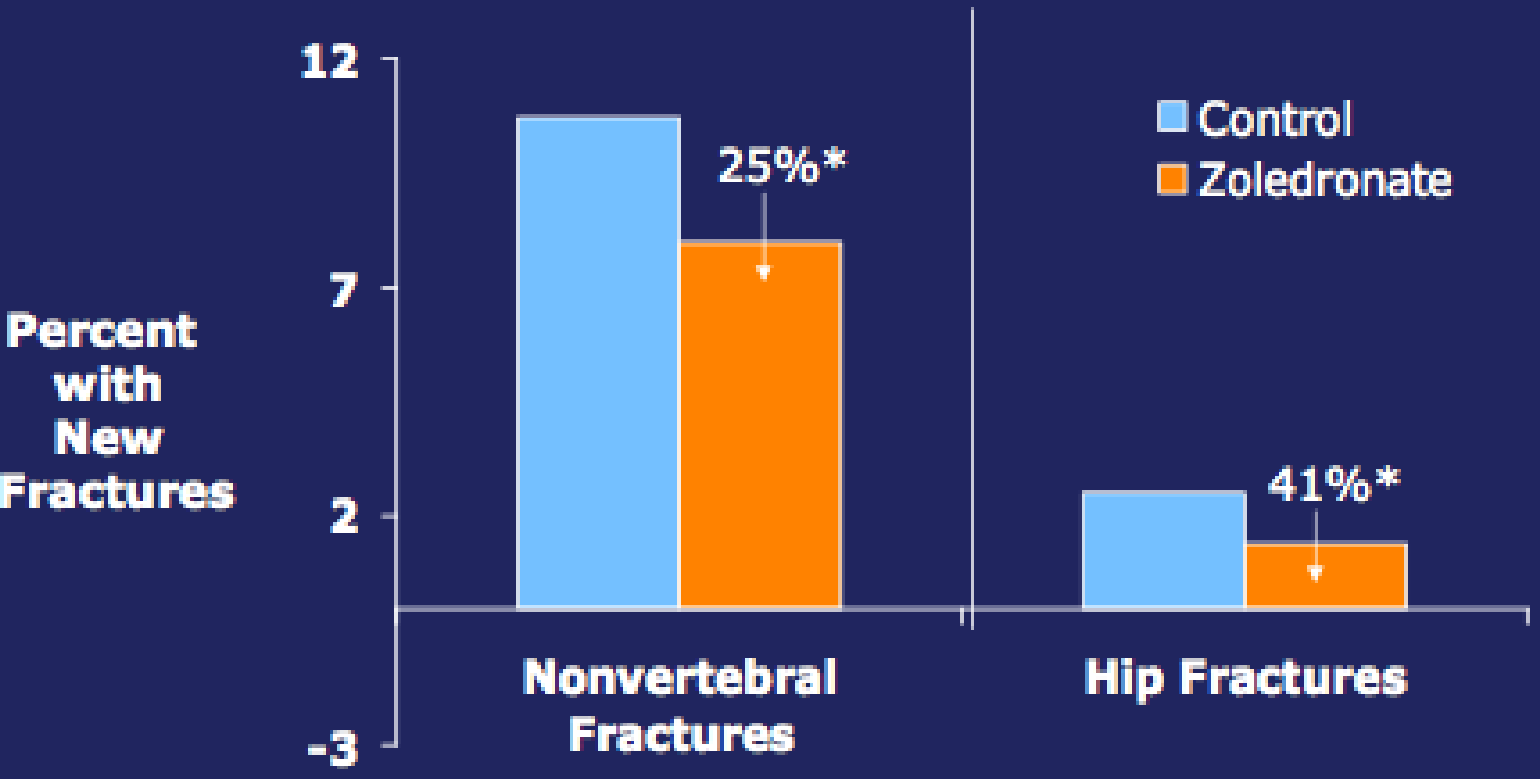
Zoledronate Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)



*$P < 0.0001$, relative risk reduction vs. placebo (95% confidence interval)

Adapted from Black DM, et al. *N Engl J Med.* 2007;356:1809-22.

Nonvertebral and Hip Fractures
Zoledronate HORIZON Trial



140 total hip fractures
NVFX = excluding fingers, toes, and facial bones

*P < 0.05

Black DM, et al. *N Engl J Med.* 2007;356:1809-22

Case Question

- 72 yo female is on oral alendronate for 3 years
- She is going for routine dental cleaning and may have a filling or crown
- She is concerned about her risk for ONJ
- What can you tell her?

Case Question--ONJ

- ONJ is extremely rare----less than 40 cases worldwide on oral bisphosphonates/year
- Cancer patients more at risk—frequent use (ie monthly IV ZA)
- Risk to your patient: 1 in 10,000 to 1 in 100,000
- EXTRACTION or DENTAL IMPLANT

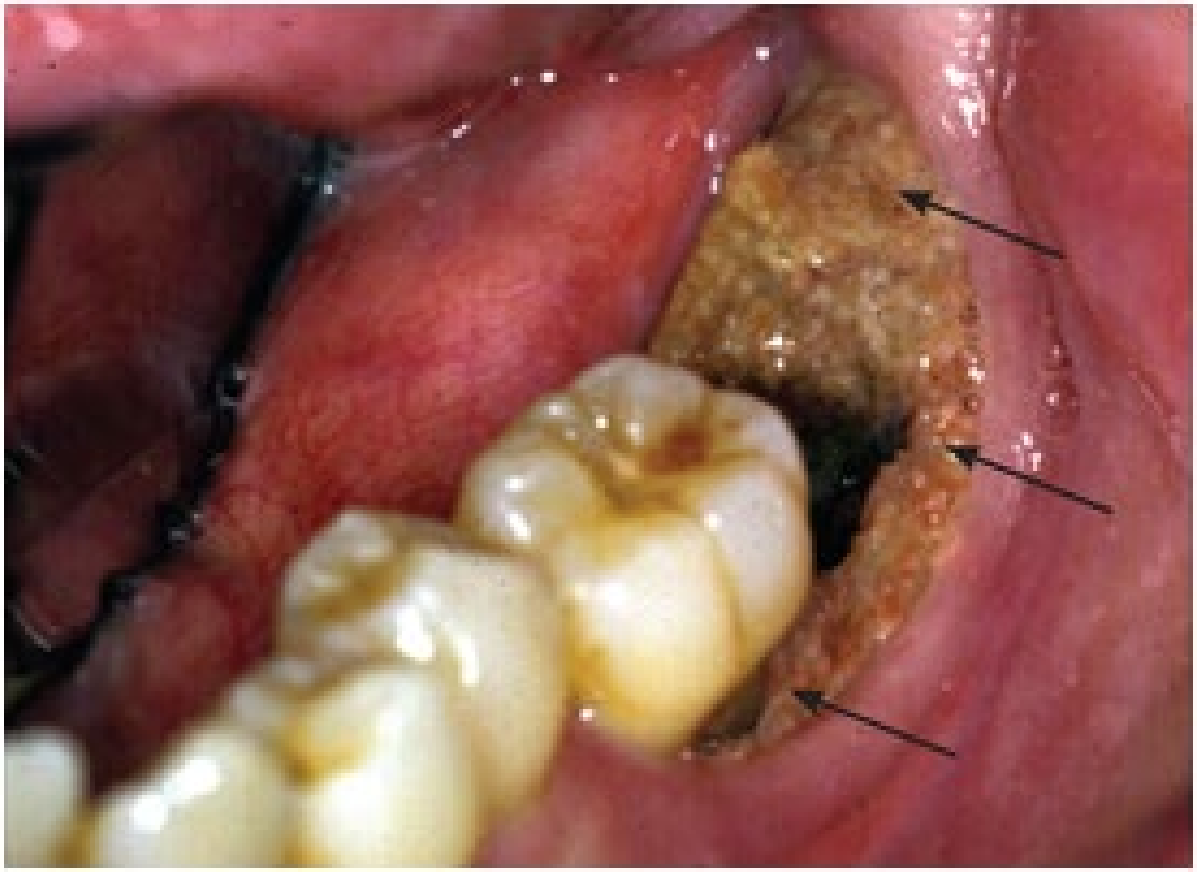
Case Question --ONJ

- The American Association of Oral and Maxial Facial Surgeons suggests continuing bisphosphonate if on less than 4 years prior to extraction/implant if no risk factors. If >4 years of therapy—stop 3 mos prior to surgery
- Risk factors for ONJ:
  - Poor dental hygiene, glucocorticoid use
  - Cancer, smoking, diabetes

Osteonecrosis of the Jaw

- Def: Exposed bone in the maxillofacial region that does not heal within 8 weeks in a patient exposed to an anti-resorptive agent (BP or Dmab)
- Decreased osteoclast activity plays a role
- Typically develops after a tooth extraction or other invasive oral surgical procedure

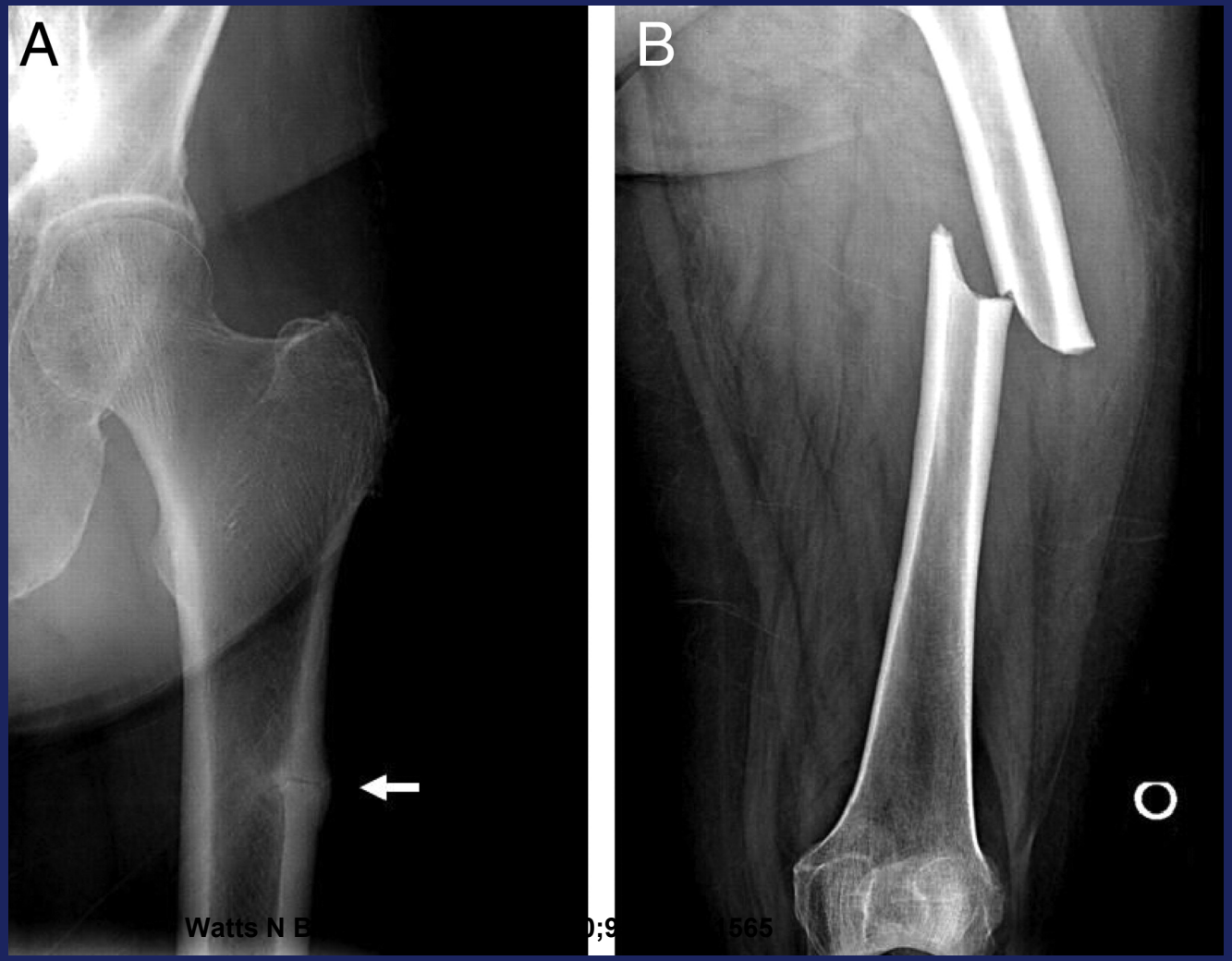
Osteonecrosis of the Jaw (ONJ)



Atypical Femur Fracture

- Patients c/o “dull ache” in groin or thigh”
- Located at diaphyseal area, Lateral cortical thickening
- Transverse Fracture with short oblique extension medially (beaking)
- Often Bilateral
- More common in Asians, prior bisphosphonate use
- Occur with longer term use >5-10 years
- “Frozen bone”

X-rays showing an impending femoral shaft fracture (A) and a representative atypical diaphyseal femoral fracture (B) with thickened cortices and a beak or spike. [Courtesy of J. Lane and A. Unnanuntana, Hospital for Special Surgery, New York, NY.].



Watts N B [illegible] 0;9 [illegible] 565

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Case Question

- 80 yo male with R femoral neck fracture last week. Has never been on osteoporosis medication

- Should this be started today or should you wait to start therapy?

Case Question-Use after Fracture

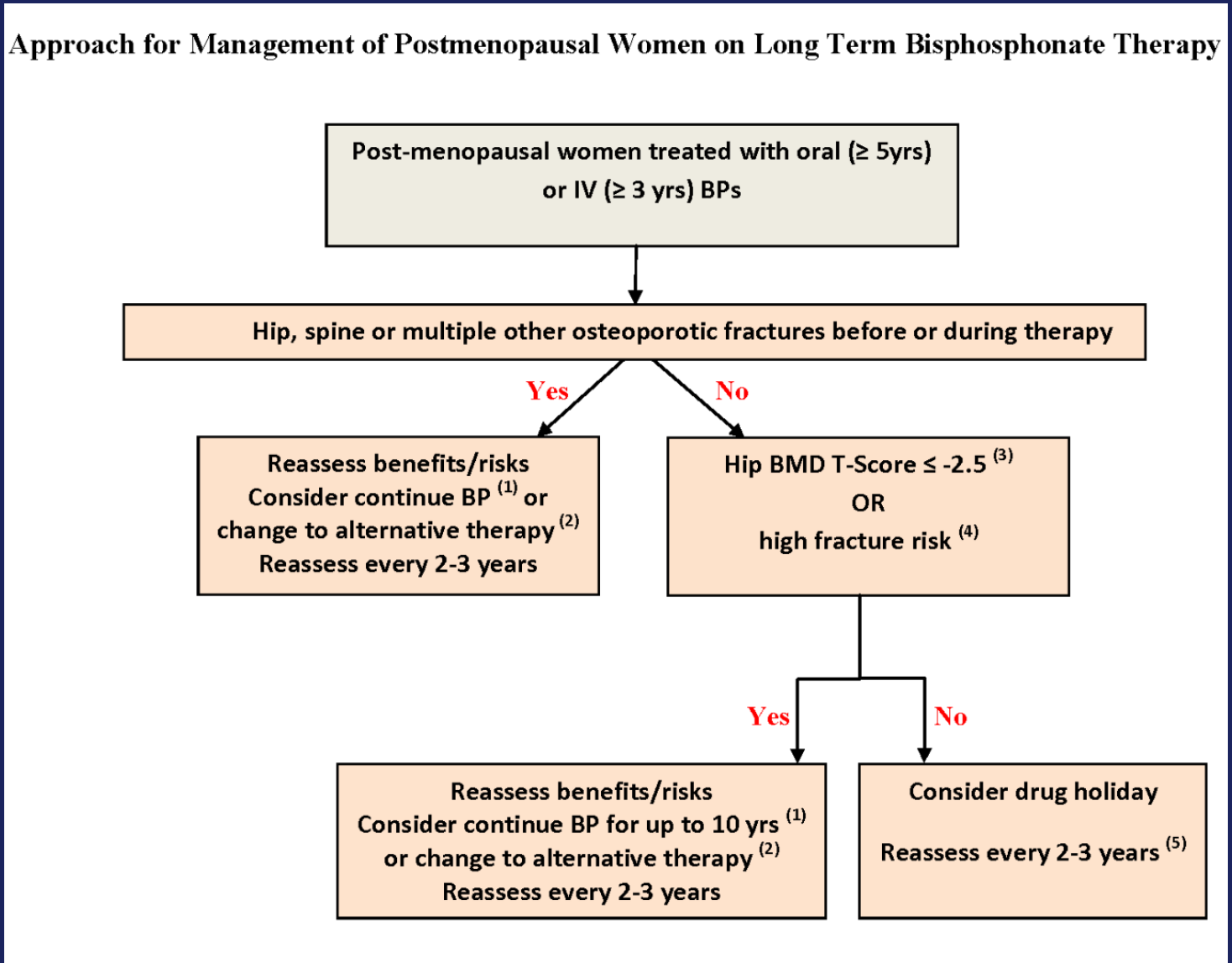
- Bisphosphonates inhibit osteoclast activity. After a fracture we want bone to remodel
- Studies show no difference in fracture healing upon timing of bisphosphonate initiation (2 weeks vs 1 month)
- If patient is already on bisphosphonate therapy <5 years—no need to stop unless AFF

Case Question

- 85 yo female on alendronate for 5 years
- No fracture history
- T score LS -2.6, femoral neck t score -2.8

- Do you take a drug holiday ??

Duration of Bisphosphonate Treatment



JBMR, 2015

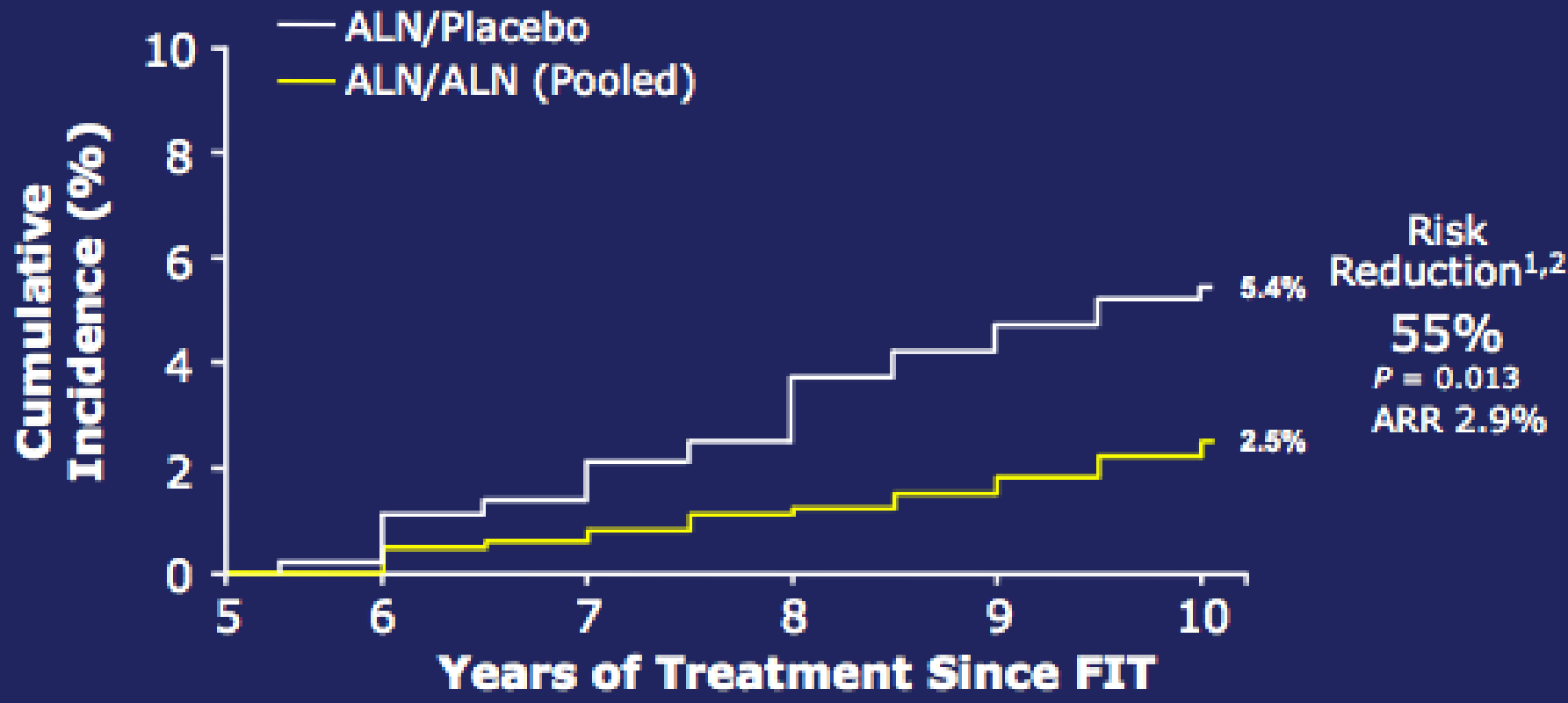
How long to Treat?

- No fracture hx, BMD stable
  - Stop oral at 5 years, IV at 3 years
- T score <-3.5 or FRACTURE/High Risk
  - Continue oral x 10 year, IV x 6 years

Drug Holidays

- No good evidence
- EXPERT opinion:
  - 2-3 years off medication and then can restart if higher risk or osteoporosis
  - If BMD declines by more than 5 % on follow up DXA should restart (statistically significant change)
  - FRACTURE

Cumulative Incidence of Clinical Vertebral Fractures: 10-Year Data



ALN/Placebo, N:	437	436	428	425	419	412	404	398	392	387
ALN/ALN, N:	662	660	651	646	638	631	626	615	606	597

ARR = absolute risk reduction

[1] Black DM, et al. *J Bone Miner Res.* 2004:S45.

[2] Data available on request from Merck & Co., Inc. Please specify 20650700(1)–FOS.

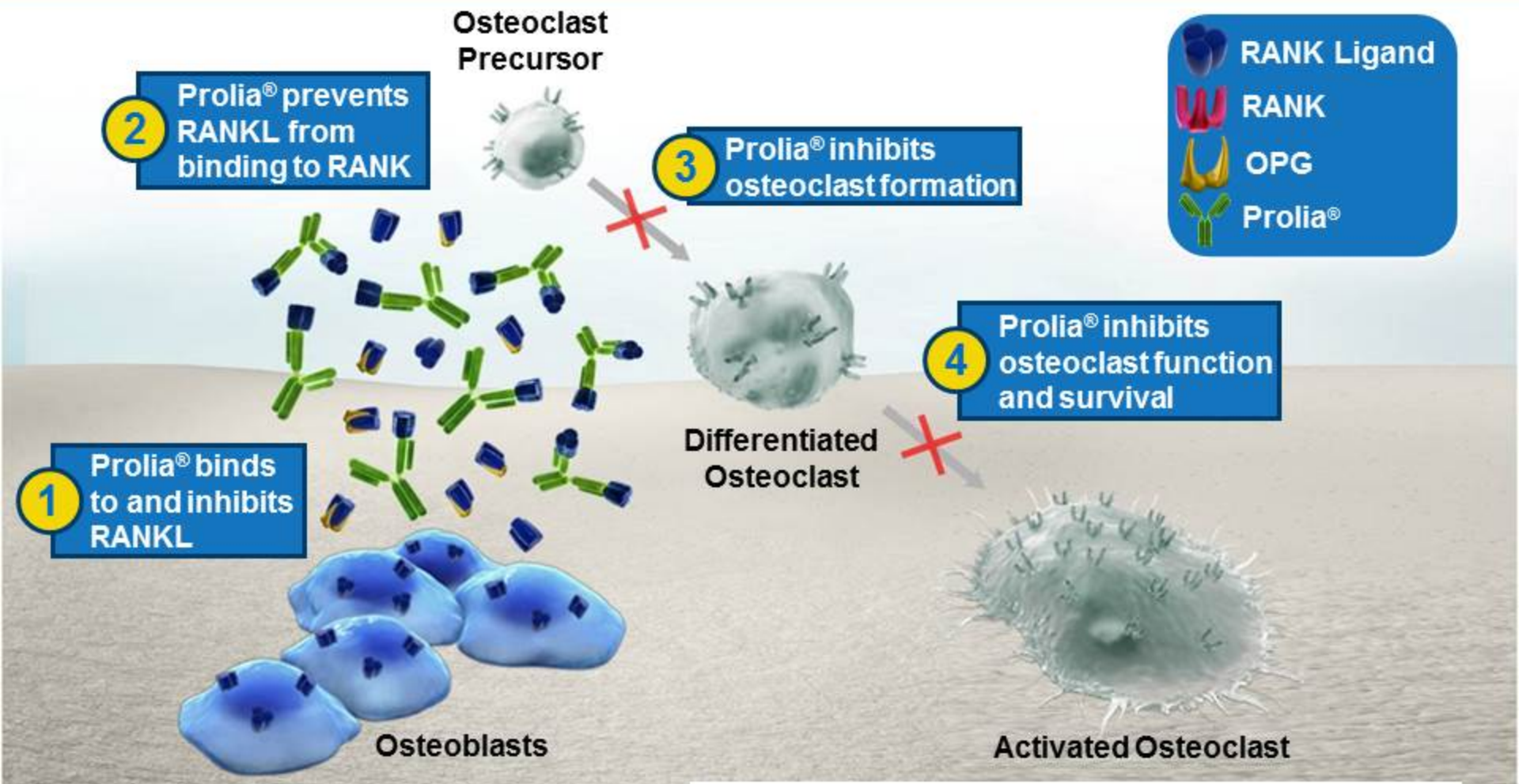
Side Effects of Bisphosophates

- Oral
  - Myalgias
  - Esophagitis
  - arthlagias
  - GERD
- IV
  - Flu-like symptoms
  - Myalgias
  - Hypocalcemia
  - arthlagias
  - Cx: GFR<35

Denosumab

- Human monoclonal antibody
- Binds to Rank-L and prevent it from binding to RANK
- Action: inhibits osteoclasts
- Works like OPG

Prolia® (denosumab), a RANKL Inhibitor, Inhibits Osteoclast Formation, Function, and Survival



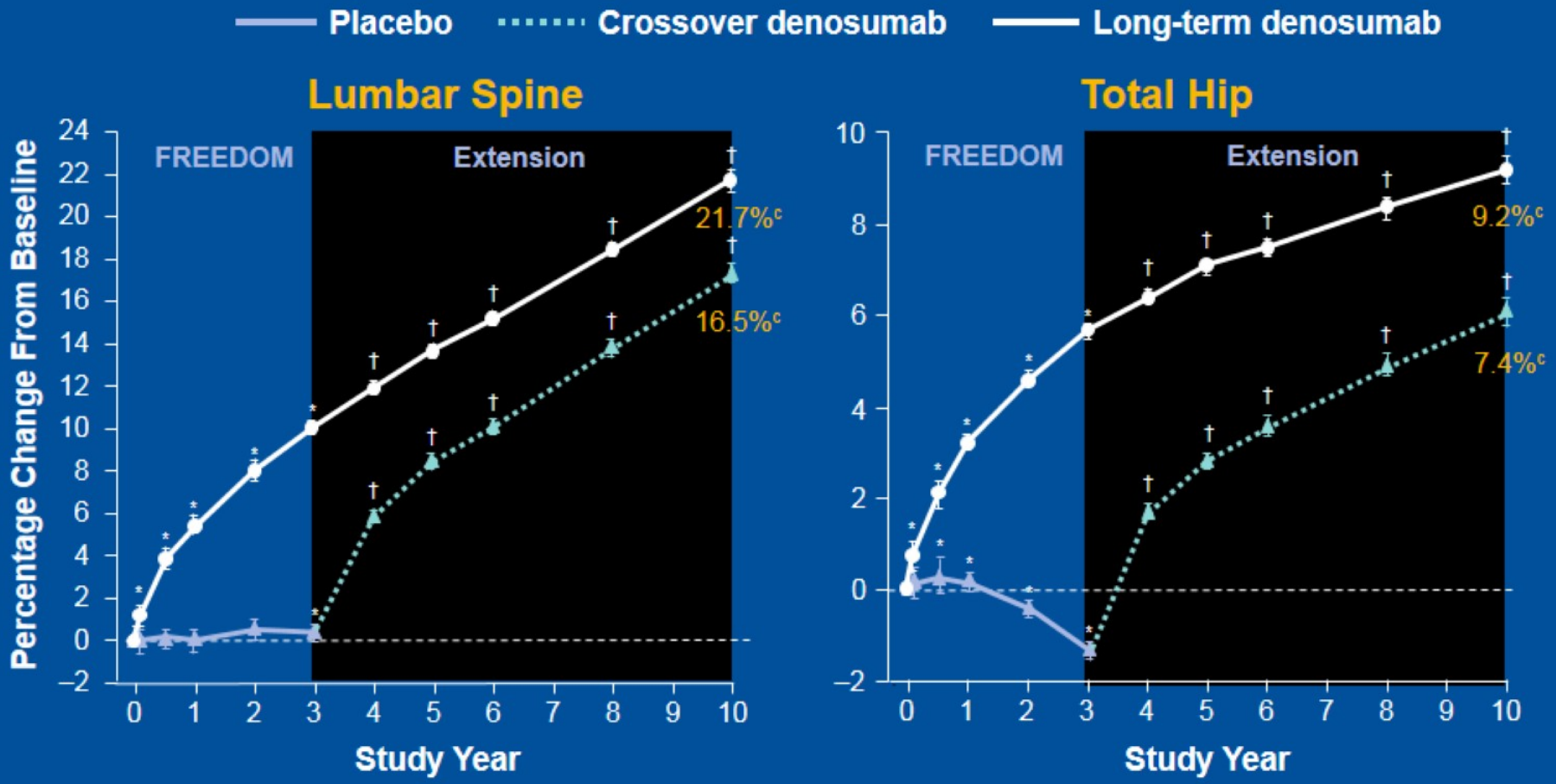
RANKL = RANK Ligand

Prolia® (denosumab) prescribing information, Amgen.

Mechanism of action representations are for illustrative purposes only and are not meant to imply any clinical efficacy.

Change in Lumbar Spine and Total Hip BMD Through 10 Years With Denosumab Treatment

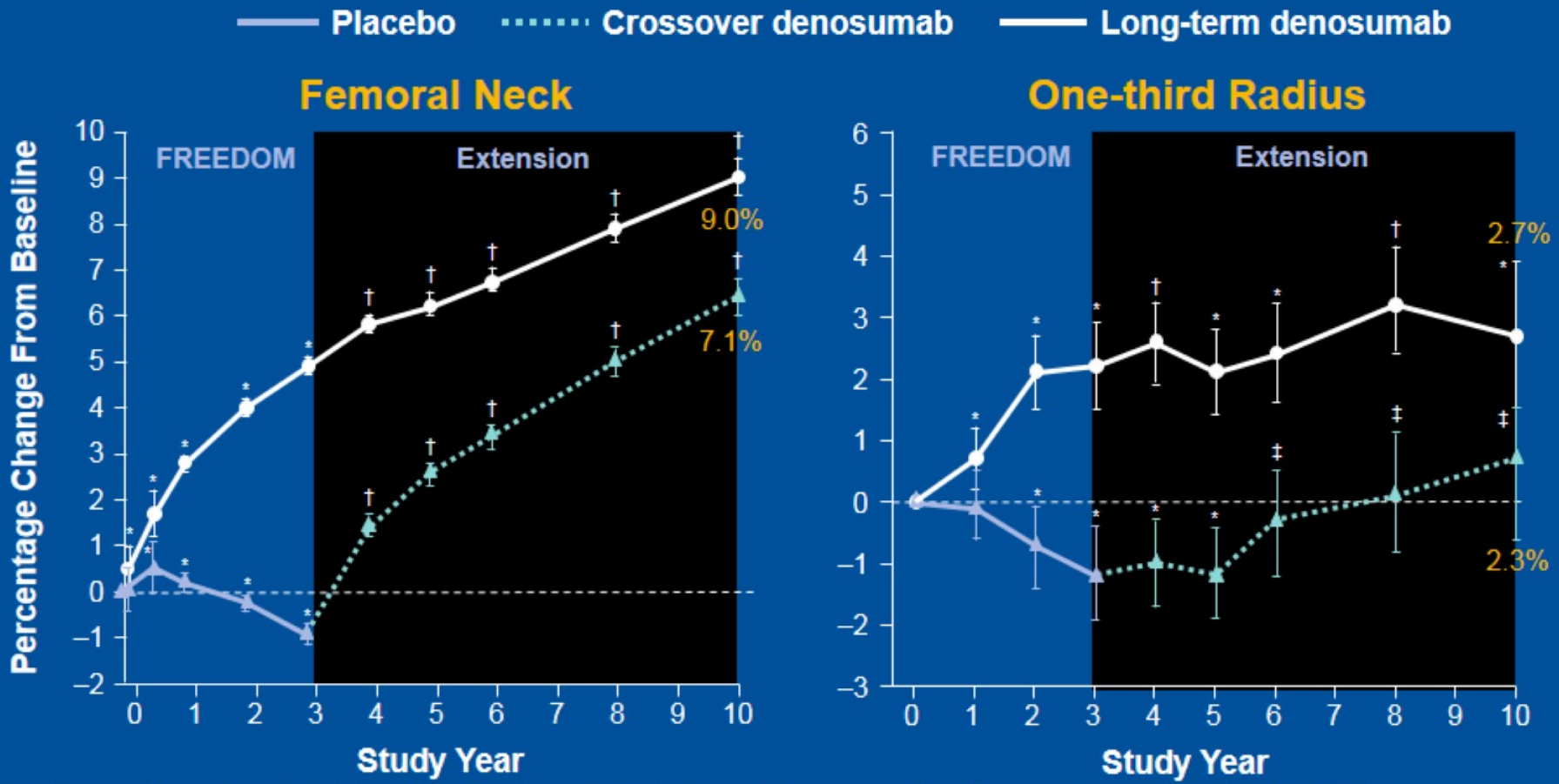
FREEDOM and the Open-Label FREEDOM Extension



Data represent least-squares means and 95% CI.
*p<0.05 compared with FREEDOM baseline. †p<0.05 compared with FREEDOM and extension baselines.
BMD = bone mineral density. Adapted from: Bone, et al. *Lancet Diabetes Endocrinol*. 2017. Published online May 22, 2017.

Change in Femoral Neck and One-third Radius BMD Through 10 Years With Denosumab Treatment

FREEDOM and the Open-Label FREEDOM Extension



Percentage changes from FREEDOM baseline in BMD are shown for the lumbar spine, total hip, femoral neck, and one-third radius. Final number listed at year 10 represents BMD percentage change while on denosumab treatment (from FREEDOM baseline for the long-term group and from extension baseline for the crossover group). Data are least-squares means (95% CI). *p<0.05 compared with FREEDOM baseline. †p<0.05 compared with FREEDOM and extension baselines. ‡p<0.05 compared with extension baseline. BMD=bone mineral density.

Adapted from: Bone, et al. *Lancet Diabetes Endocrinol.* 2017. Published online May 22, 2017.

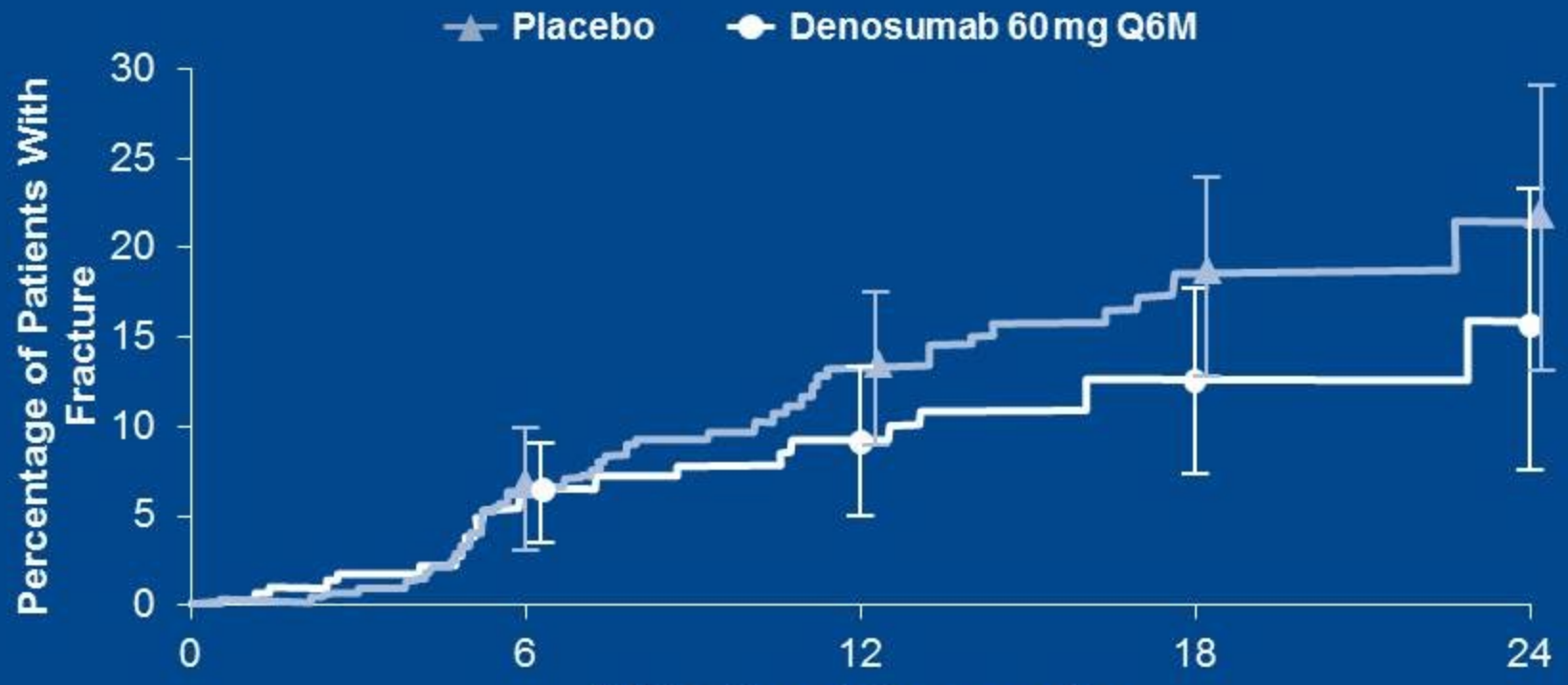
Why are we seeing BMD increasing with a bone resportive agent?

- While not fully understood, the continuous/progressive increases in BMD may be explained by the following potential mechanisms. Clinical data suggest the following:
- Rapid closing of the remodeling space, allowing the formation phase to progress to completion (1)
- Secondary mineralization.(2)
- Decreased cortical porosity and increased cortical mass.(3-5)
- Transient increases in PTH following each dose of dmab on a background of full inhibition of bone resorption (5)

- 1 Seeman E, Delmas PD, Hanley DA, et al. Microarchiterctural deterioration of corticaland trabecular bone: differing effects of denosumab and alendronate. J Bone Miner
- Res. 2010;25(8):1886-1894,
- 2. Bolognese M, Teglberg CS, Zanchetta JR, et al. Denosumab significantly increasesDXA BMD at both trabecular and cortical sites: results from the FREEDOM study. Clin Densit. 2013;16(2):147-153.
- 3. Poole K, Treece GM, Gee A, et al. Denosumab treatment is associated with progressive improvements in cortical mass and thickness throughout the hip. ASBMR
- Annual meeting 2012. Abstract 1133.
- 4 Seeman E, Libanati C, Austin M, et al. The transitory increase in PTH following denosumab administration is associated with reduced intracortical porosity: a dstinctive attribute of denosumab therapy. ASBMR 2011. Abstract 1064.
- 56. Zebaze R, Libanati C, McClung MR, et al. Denosumab reduces hip cortical porosity in women with osteoporosis. ASBMR Annual Meeting 2013. Abstract 1065.

Time to First Osteoporotic Fracture After Discontinuation of Treatment

The Pivotal Phase 3 Trial – Off-treatment Analysis



Patients at Risk, N					
Placebo	470	227	148	51	2
Denosumab	327	154	108	57	1

Adapted from: Brown JP, et al. *J Bone Miner Res.* 2013;28:746-752.

Osteoporos Int. 2017 May;28(5):1723-1732. doi: 10.1007/s00198-017-3919-1. Epub 2017 Jan 31.

Observations following discontinuation of long-term denosumab therapy.

McClung MR[1,2], Wagman RB[3], Miller PD[4], Wang A[3], Lewiecki EM[5].

Calcified Tissue International

October 2017, Volume 101, Issue 4, pp 371–374 | Cite as

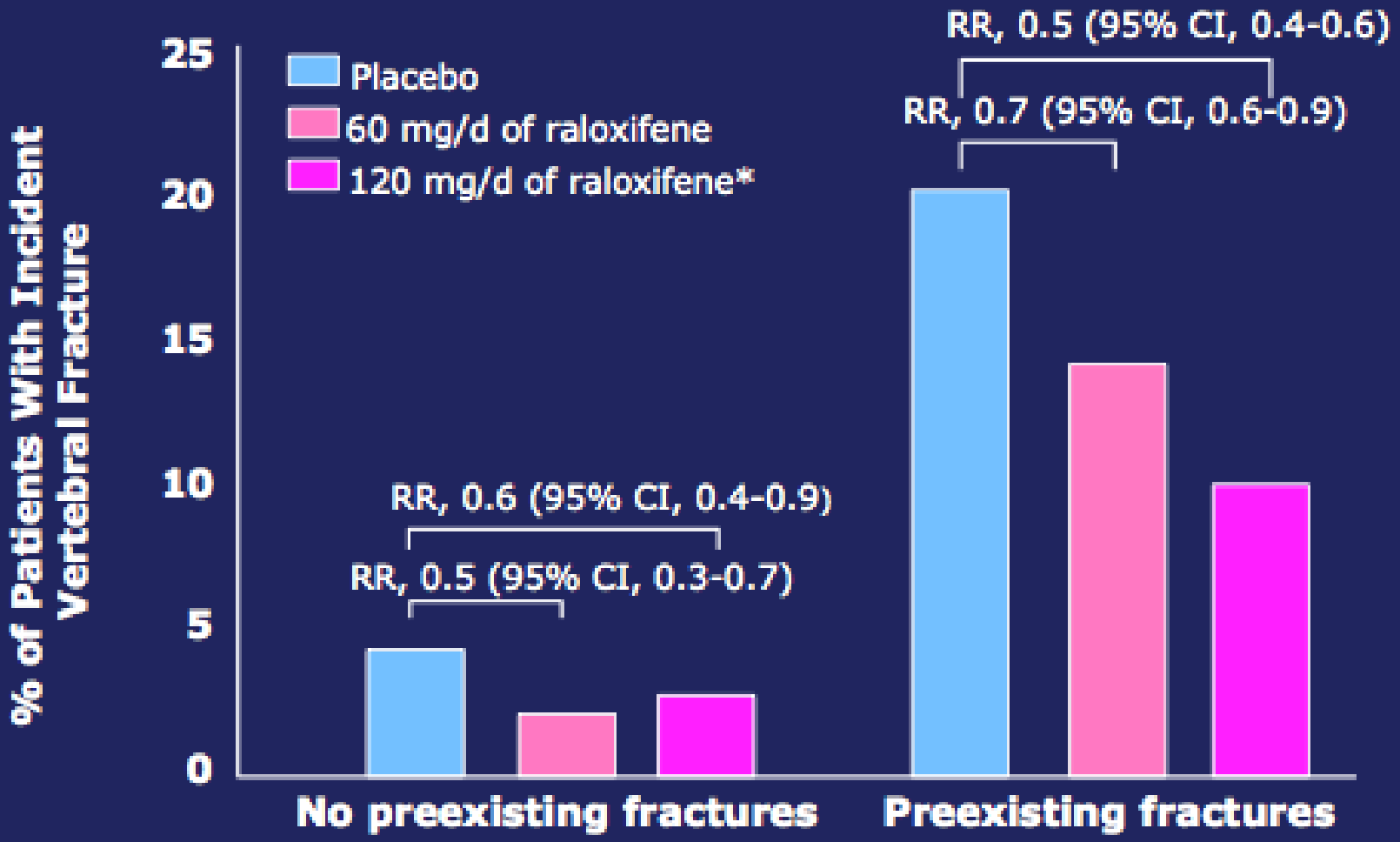
Bone Loss After Denosumab: Only Partial Protection with Zoledronate

Authors | Authors and affiliations

Ian R. Reid ✉, Anne M. Horne, Borislav Mihov, Gregory D. Gamble

Raloxifene (Evista)

Effects of Raloxifene on New Vertebral Fractures: The MORE Trial—36 Months

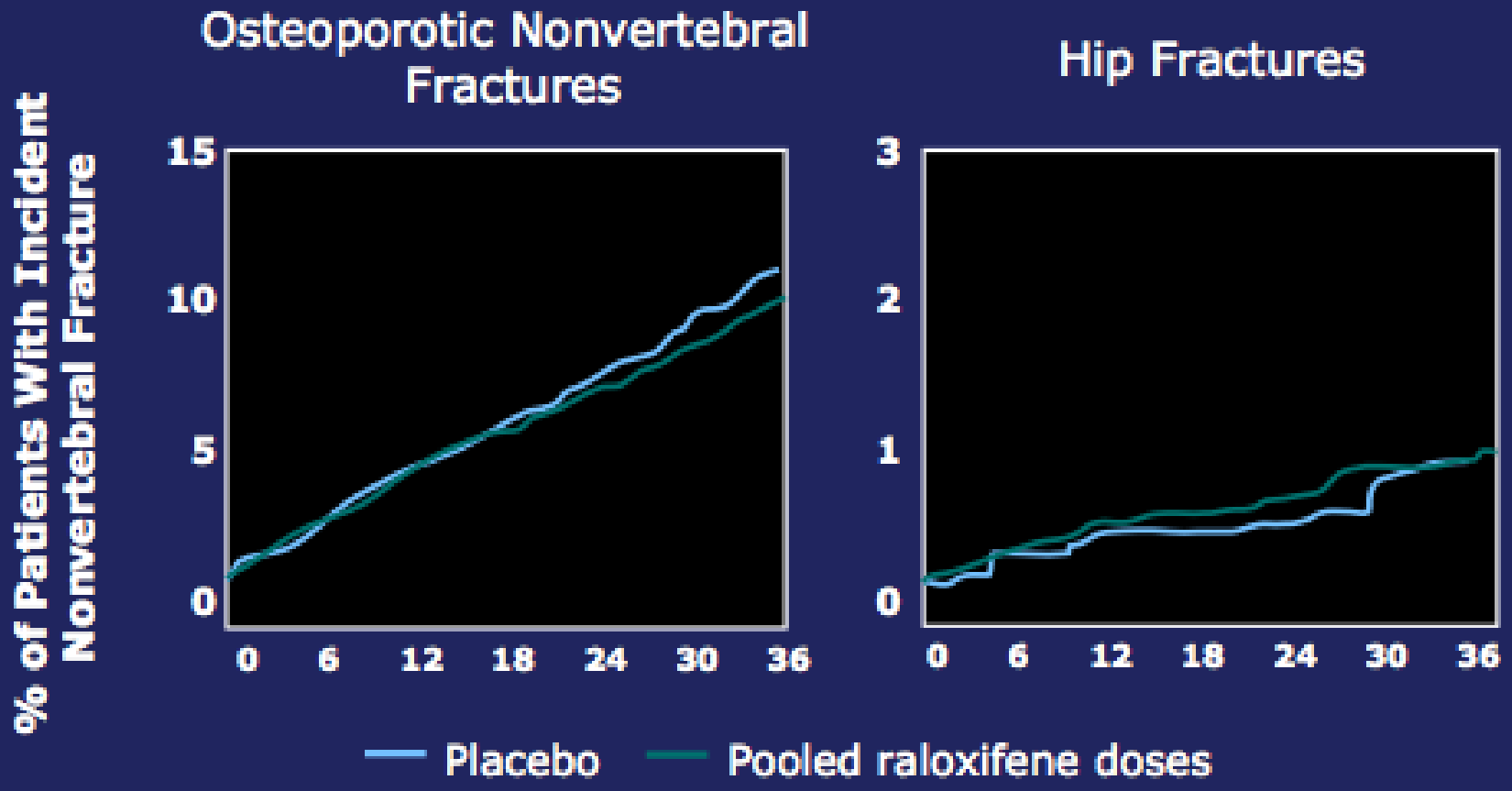


*Not FDA-approved dose

Ettinger B, et al. *JAMA*. 1999;282:634-45.

Effects of Raloxifene on Nonvertebral Fractures

The MORE Trial—36 Months

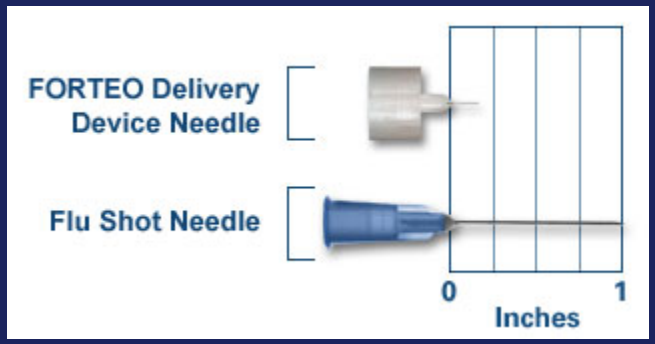


Ettinger B, et al. *JAMA*. 1999;282:634–45

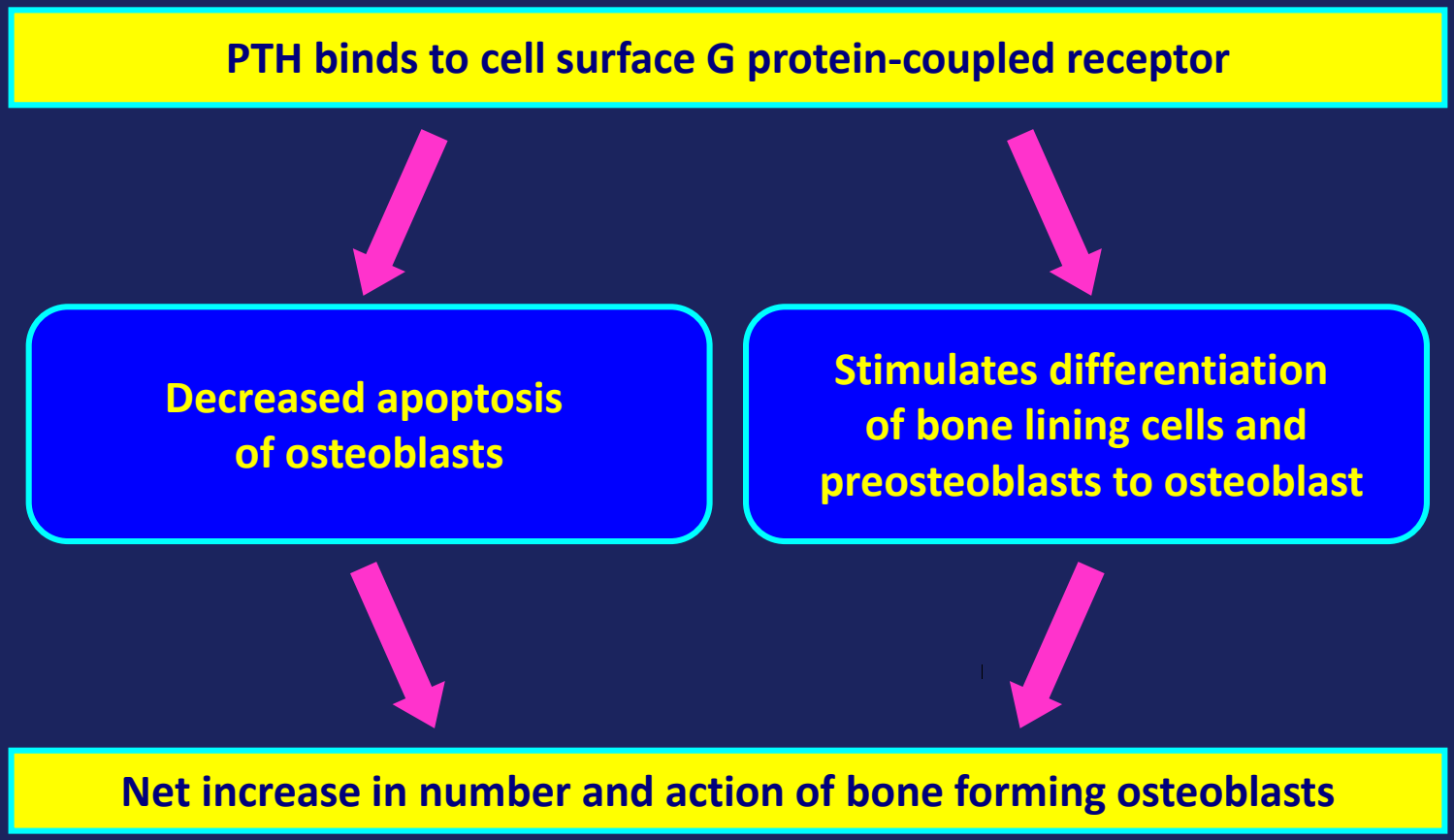
RALOXIFENE

- FDA approved for treatment of osteoporosis in postmenopausal women
- Reduced risk of new vertebral fractures by about 55% and 30% in women with prior vertebral fractures
- Did not reduce fracture risk in hip and nonvertebral in clinical trials
- Increased risk of DVT, hot flashes, and CVA in high risk populations

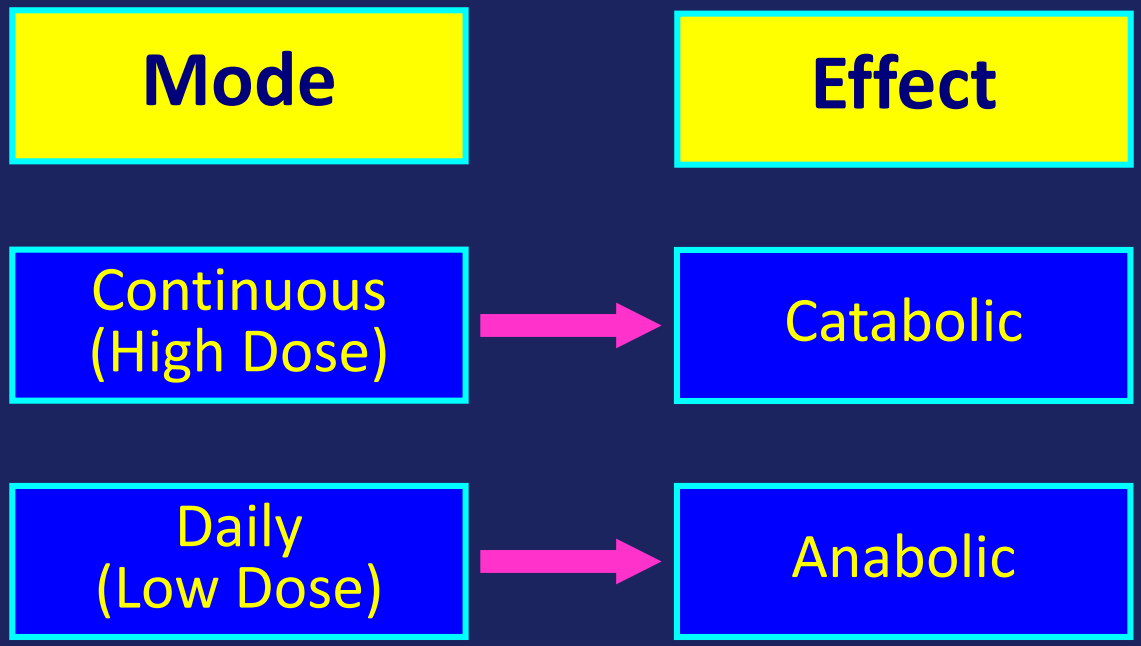
Teriparatide [rDNA origin] injection



Parathyroid hormone (PTH) – Mechanism of action



Administration and dose determine PTH effects on bone



From Dobnig & Turner, Endocrinology, 1997;138:4607-4612.

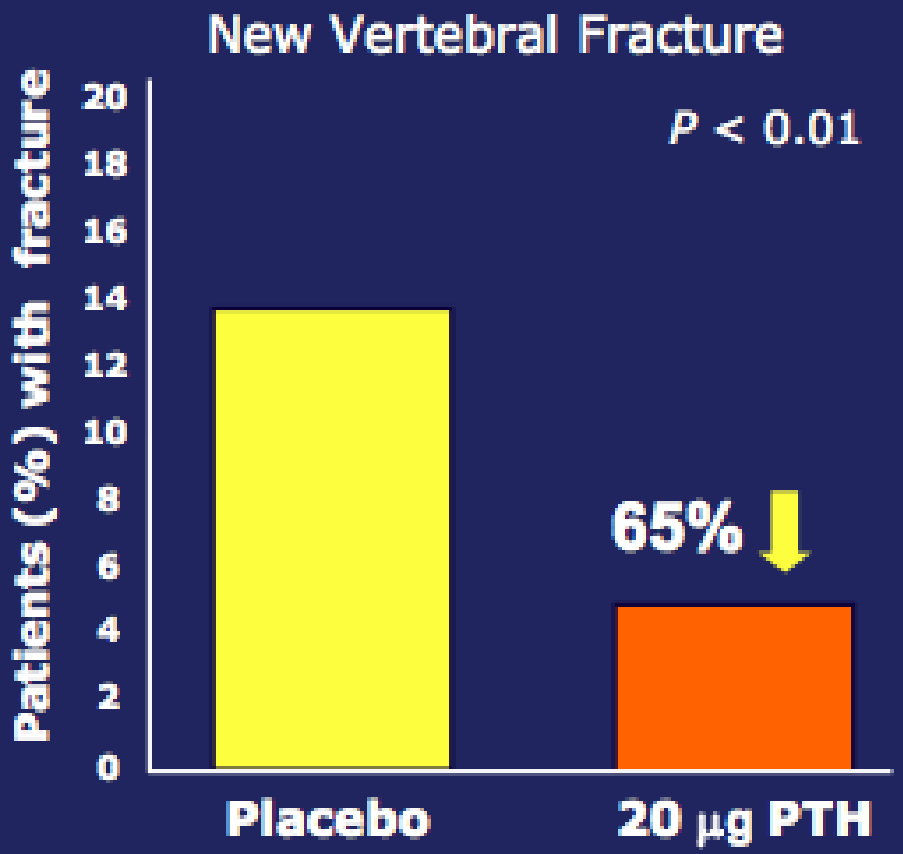
Teriparatide Indications

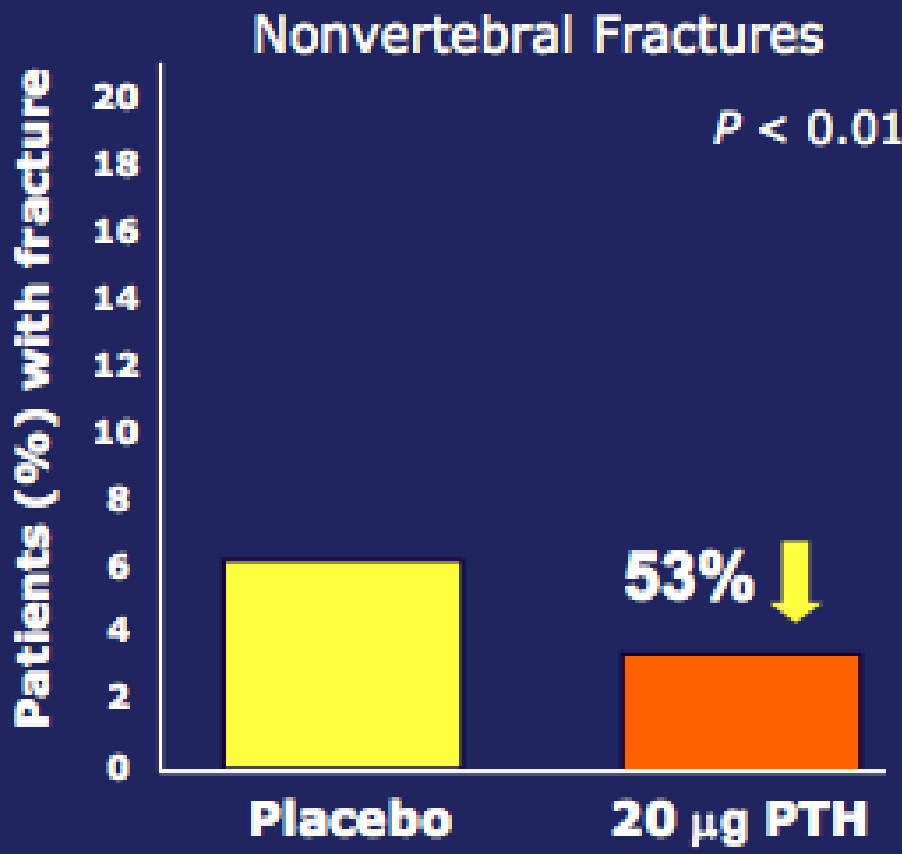
- Previous Adult Fragility Fracture in postmenopausal women and men
- T score: -3.0 without fracture
- Cannot tolerate another therapy
- Bone loss or fracture on another therapy

Teriparatide

- The teriparatide Pen is a prefilled delivery device that can be used up to 4 weeks (28 daily doses)
- Dose: 20 mcg once daily
- Administered as a subcutaneous injection into the thigh or abdominal wall
- Duration of therapy: 18-24 months

Effect of Teriparatide on Incidence of Vertebral and Nonvertebral Fractures in Postmenopausal Women With Osteoporosis





Neer RM, et al. *N Engl J Med*. 2001;344:1434-41.

Side Effects of Teriparatide

- Mild transient increase in serum calcium
- Mean increase in urine calcium of 30 mg in 24 hrs
- Leg cramps
- Dizziness
- Black Box warning-- ↑ incidence of osteosarcoma with high dose longer-term exposure
- Transient tachycardia/HTN after 1st dose

FORTEO® (teriparatide [rDNA origin] injection) Important Safety Information

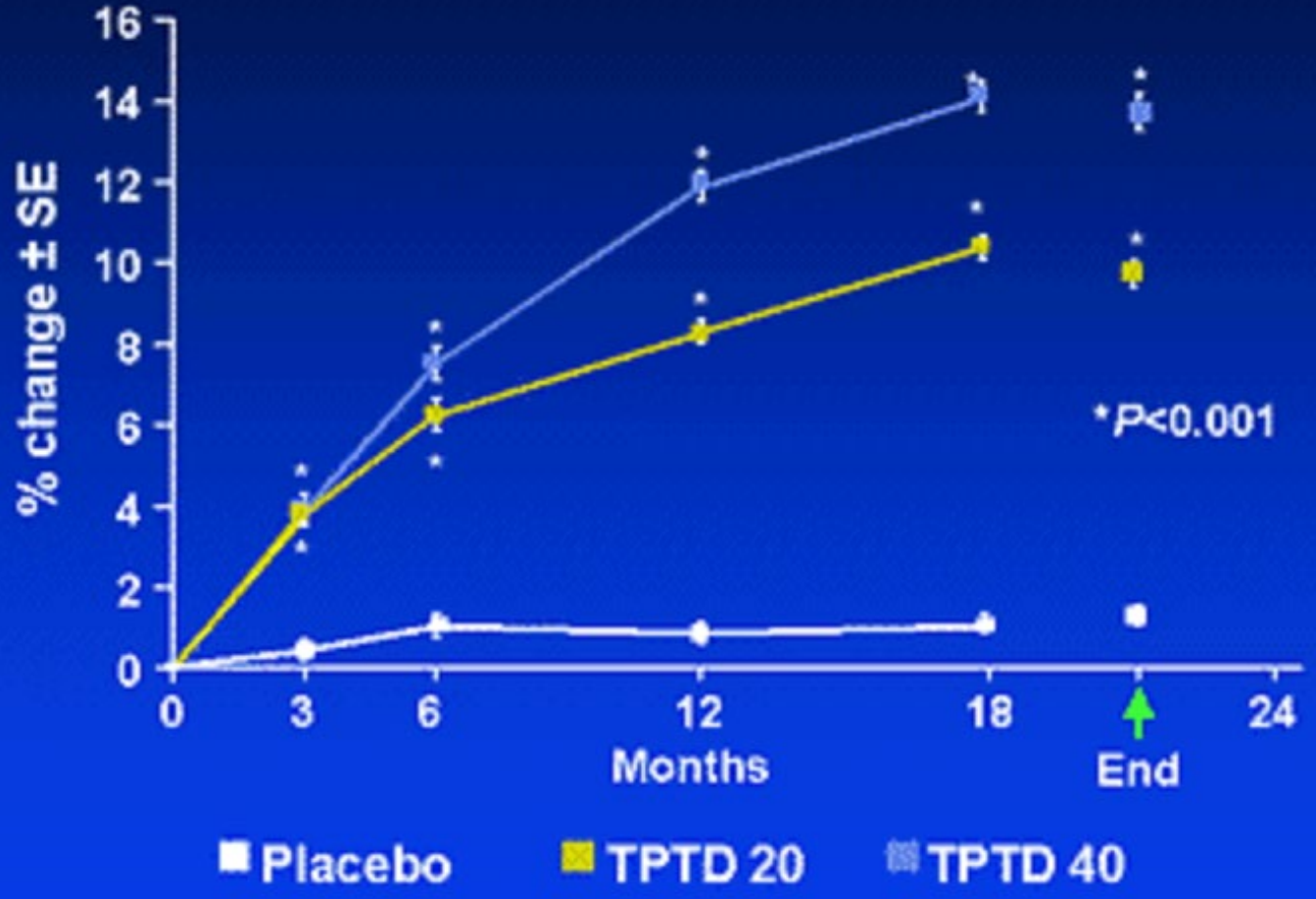
Warning

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor), that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20 mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) (*see* WARNINGS *and* PRECAUTIONS, Carcinogenesis)

Contraindications to Forteo

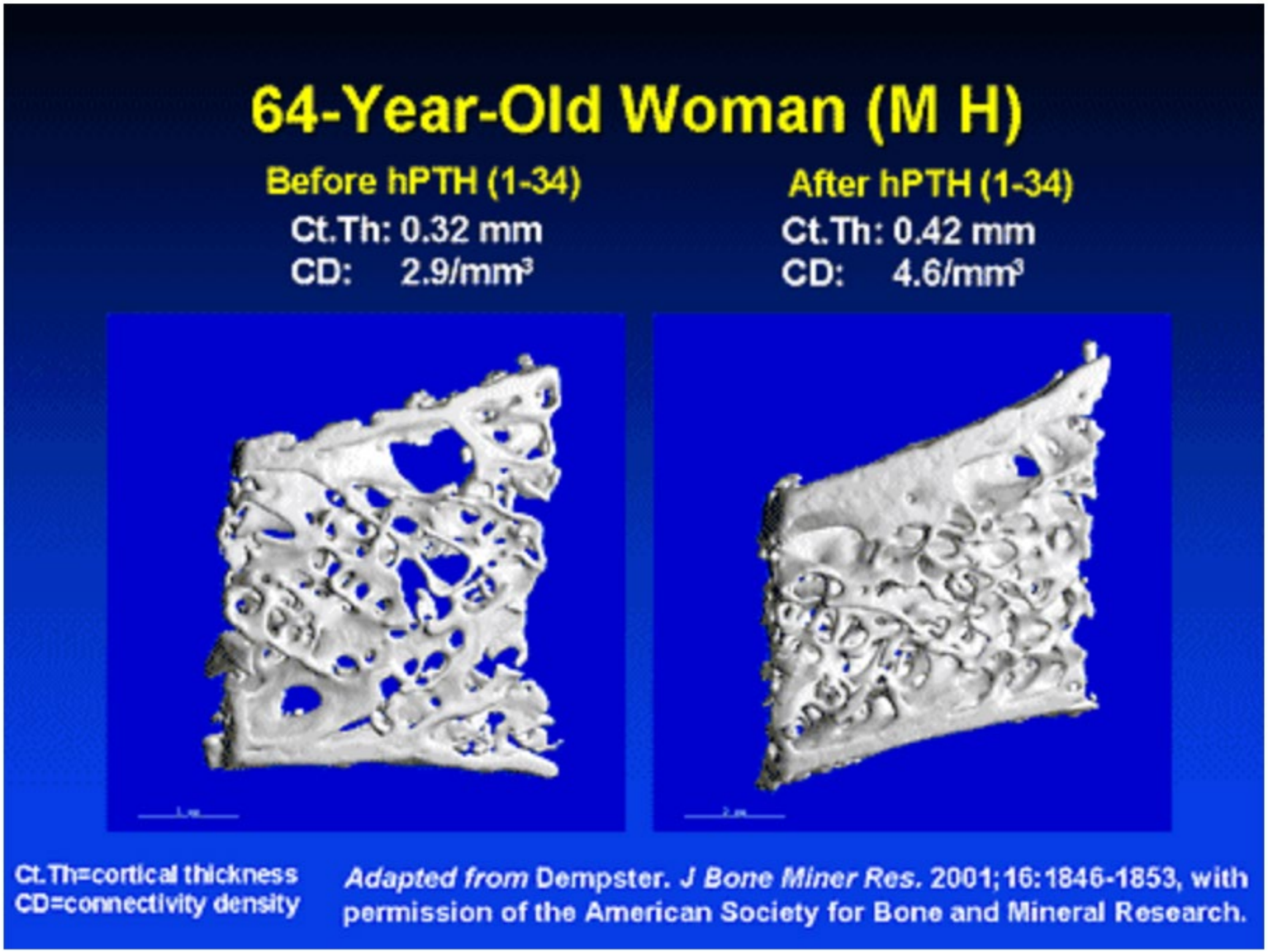
- Paget's disease/↑ alkaline phosphatase
- History of radiation to bone
- Open Epiphyses
- Primary or Metastatic skeletal malignancy
- Hypercalcemia or increased PTH
- Pregnancy/lactation
- Renal insufficiency

Effect of Teriparatide on Lumbar Spine BMD in Postmenopausal Women With Osteoporosis



Data on file. Eli Lilly and Company.

Effects of Forteo on BMD



Summary of Teriparatide Effects in Postmenopausal Women

- Increases spinal BMD 10-14%
- Increases femoral neck BMD 3-5%
- Reduces risk of new vertebral fractures by 65-69%
- Reduces risk of non-vertebral fractures by 53-54%
- Decreases fracture risk persisted up to 18 months post-therapy

PTH summary

- Teriparatide produces a more dramatic increase in spinal BMD than with bisphosphonates
- Changes bone geometry, with increase in bone diameter that may increase strength
- Stimulates new bone formation
- Maximum use: 2 years
- But NO EVIDENCE that the fracture protection is superior to bisphosphonates

J Clin Endocrinol Metab. 2016 Aug; 101(8): 3163–3170.
Published online 2016 Jun 6. doi: 10.1210/jc.2016-1801
PMCID: PMC4971333

Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates

P. D. Miller,✉ N. Pannacciulli, J. P. Brown, E. Czerwinski, B. S. Nedergaard, M. A. Bolognese, J. Malouf, H. G. Bone, J.-Y. Reginster, A. Singer, C. Wang, R. B. Wagman, and S. R. Cummings

Author information ► Article notes ► Copyright and License information ►

PERSPECTIVE

JBMR®

Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

Felicia Cosman,[1,2] Jeri W Nieves,[1,3] and David W Dempster[1,4]

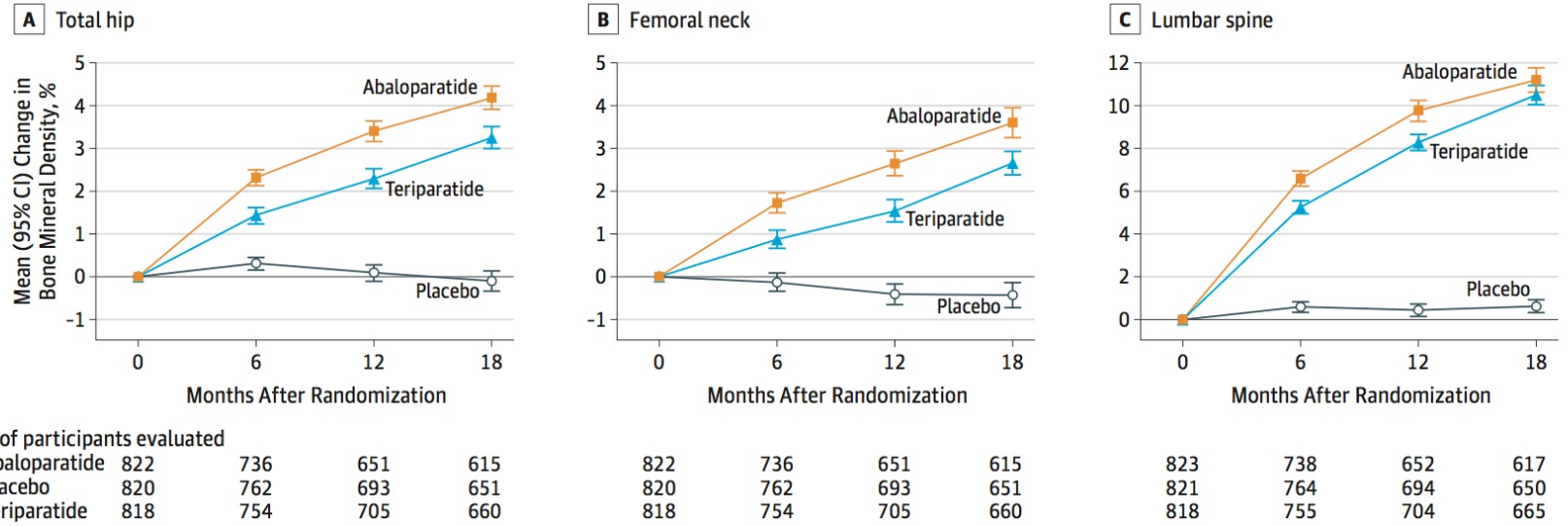
[1]Regional Bone Center and Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, USA
[2]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA
[3]Department of Epidemiology, Columbia University College of Physicians and Surgeons, New York, NY, USA
[4]Department of Pathology, Columbia University College of Physicians and Surgeons, New York, NY, USA

Newer Therapies

- Romosozumab—anti-sclerostin antibodyFDA approved 2019
- Abaloparatide-PTHrP analog—FDA approved April 2017

Abaloparatide

Figure 2. Change From Baseline in Bone Mineral Density



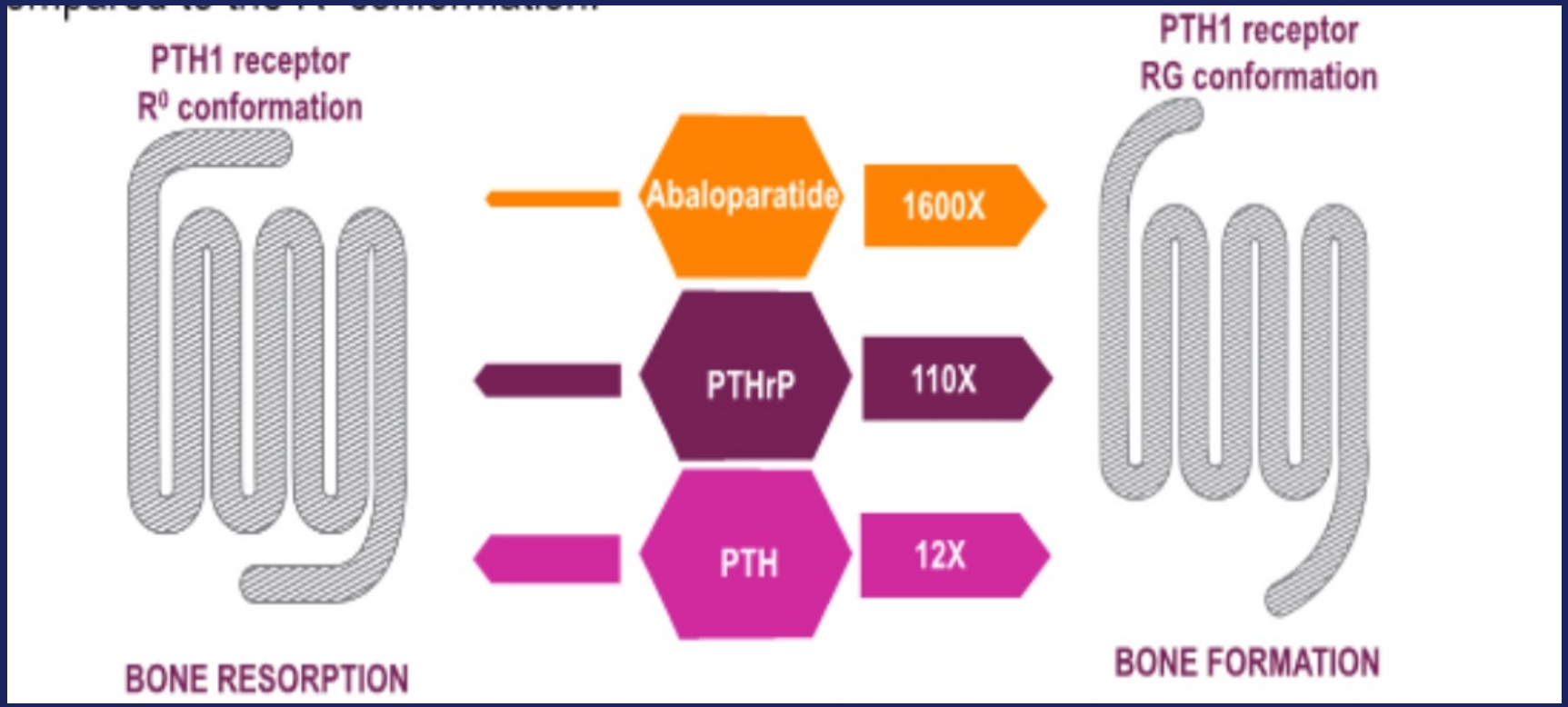
No. of participants evaluated

Abaloparatide	822	736	651	615	822	736	651	615	823	738	652	617
Placebo	820	762	693	651	820	762	693	651	821	764	694	650
Teriparatide	818	754	705	660	818	754	705	660	818	755	704	665

Mean percent changes in bone mineral density at the total hip, femoral neck, and lumbar spine were evaluated using dual-energy x-ray absorptiometry based on the intent-to-treat population. Values shown are mean percent change from baseline using a mixed-effect repeated-measures model. Improvements in bone mineral density associated with abaloparatide were significantly greater than with placebo at all 3 sites and at all time points ($P < .001$). Improvements with teriparatide were significantly greater than with placebo at all 3 sites at all time points ($P < .001$). Improvements with abaloparatide were significantly greater than those with teriparatide at the total hip and femoral neck at all time points ($P < .001$) and at lumbar spine at 6 and 12 months ($P < .001$). Error bars indicate 95% CIs.

Miller, JAMA 2016

Receptor Selectivity



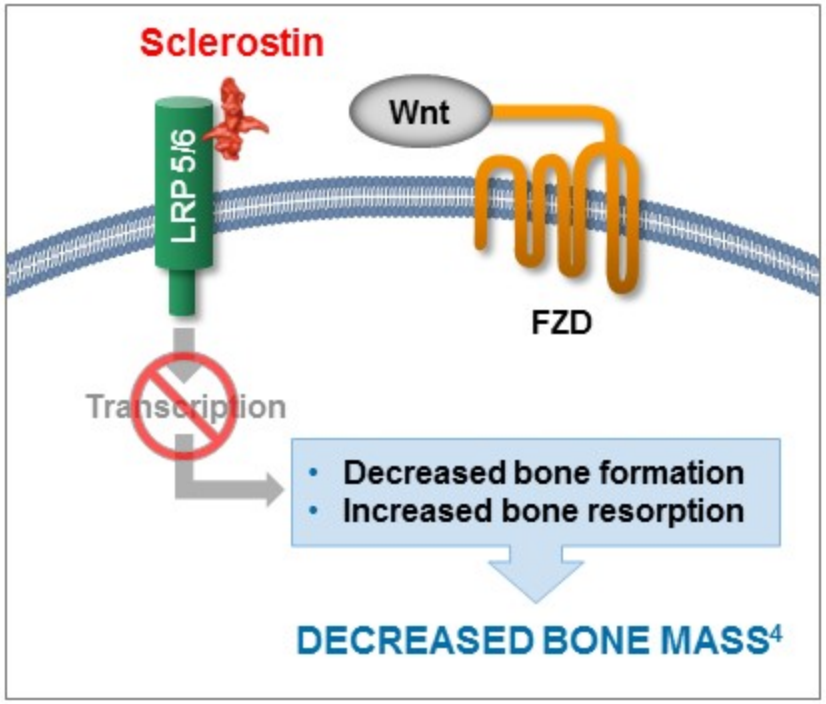
Abaloparatide

- Cannot use if already completed two year course of teriparatide
- Black box warning still exists
- Side effects?

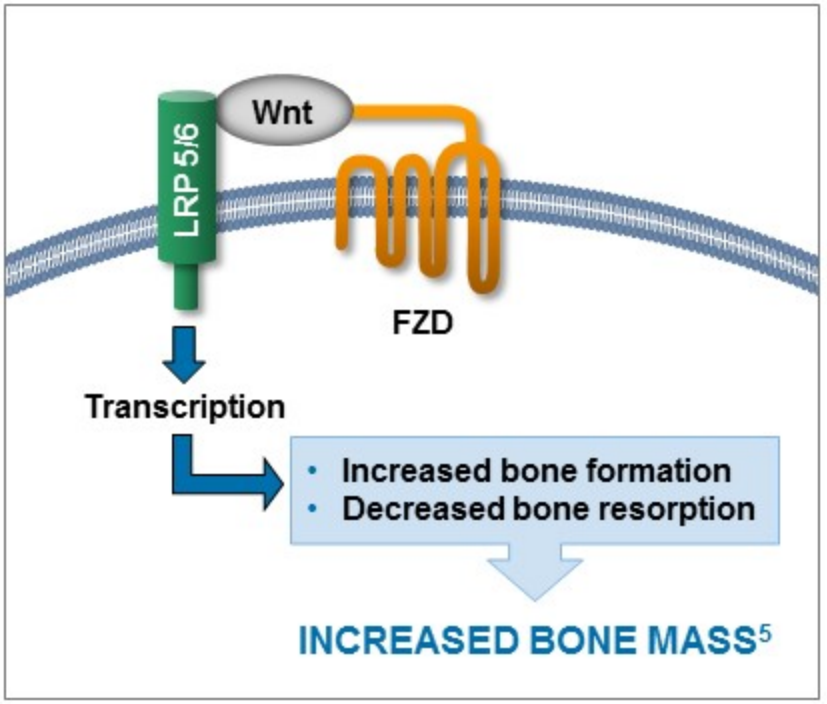
ROMOSOZUMAB

Sclerostin Decreases Bone Formation and Increases Bone Resorption by Inhibiting Wnt Signaling in the Osteoblast Lineage

Sclerostin inhibits Wnt signaling by preventing the assembly of LRP5/6 and FZD, leading to decreased bone formation and increased bone resorption[1-3]



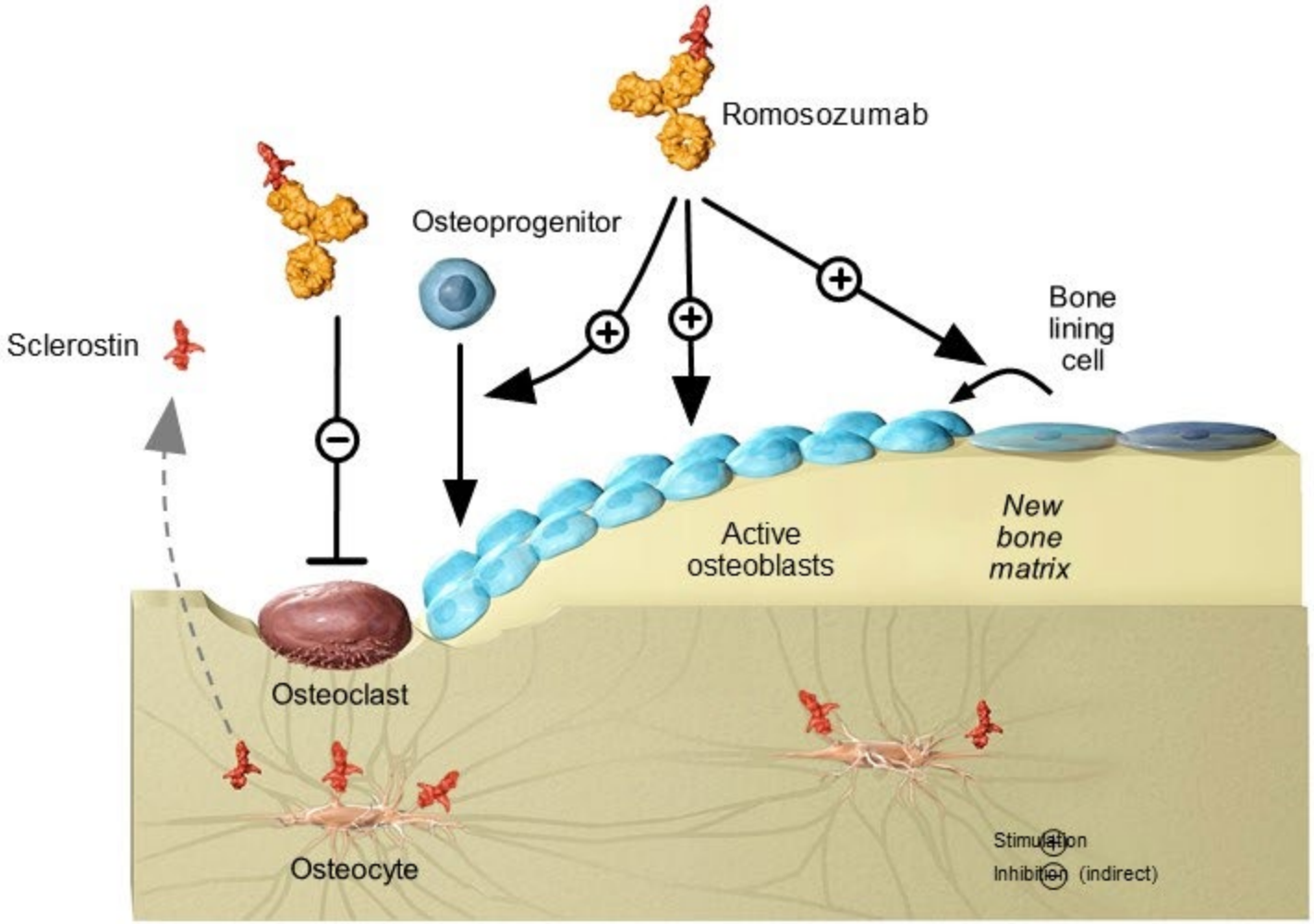
When sclerostin is absent, Wnts can activate signals that increase bone formation and decrease bone resorption[5]



FZD, frizzled coreceptor; LRP5/6, low-density lipoprotein receptor-related proteins 5 or 6.

1. Li X, et al. *J Biol Chem*. 2005;280:19883-19887. 2. Semënov M, et al. *J Biol Chem*. 2005; 280:26770-26775.
3. Wijenayaka AR, et al. *PLoS One*. 2011;6:e25900. 4. Winkler DG, et al. *EMBO J*. 2003;22:6267-6276.
5. Taylor S, et al. *Bone*. 2016;84:148-159.

Romosozumab Exerts a Dual Effect on Bone, Increasing Bone Formation and Decreasing Bone Resorption



1. Baron R, et al. *Nat Med*. 2013;19:179-192. 2. McClung MR, et al. *N Engl J Med*. 2014;370:412-420. 3. Ominsky MS, et al. *J Bone Miner Res*. 2014;29:1424-1430.

Romosozumab

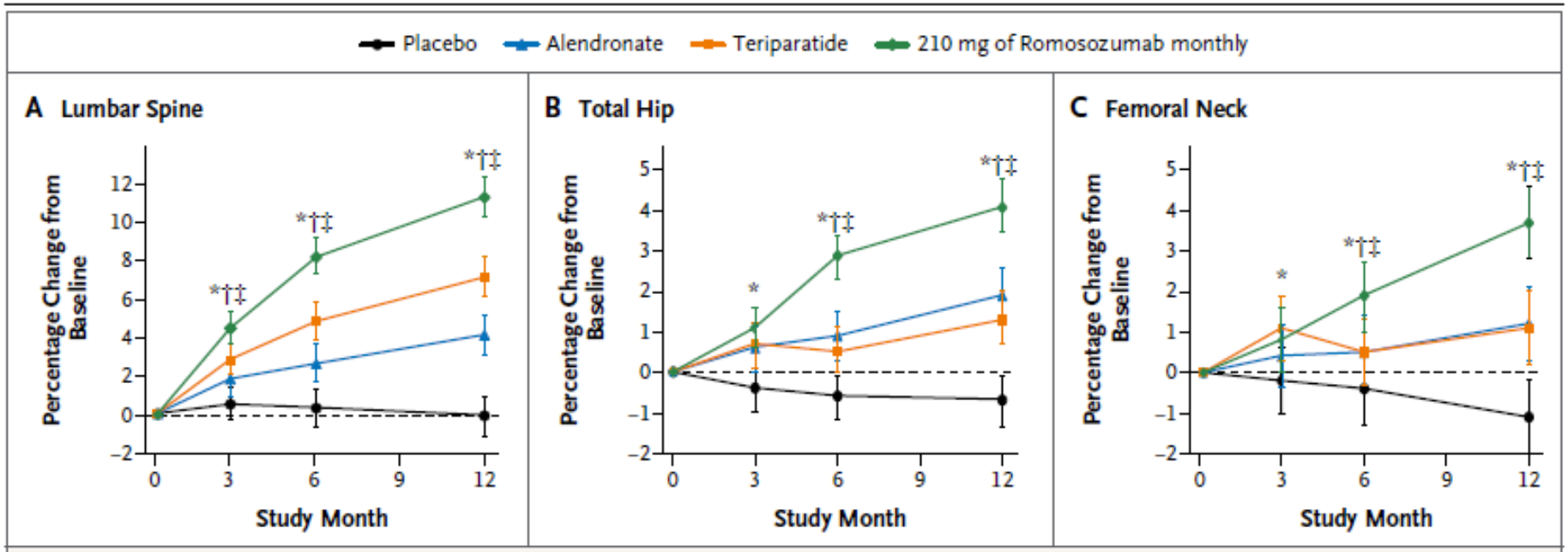
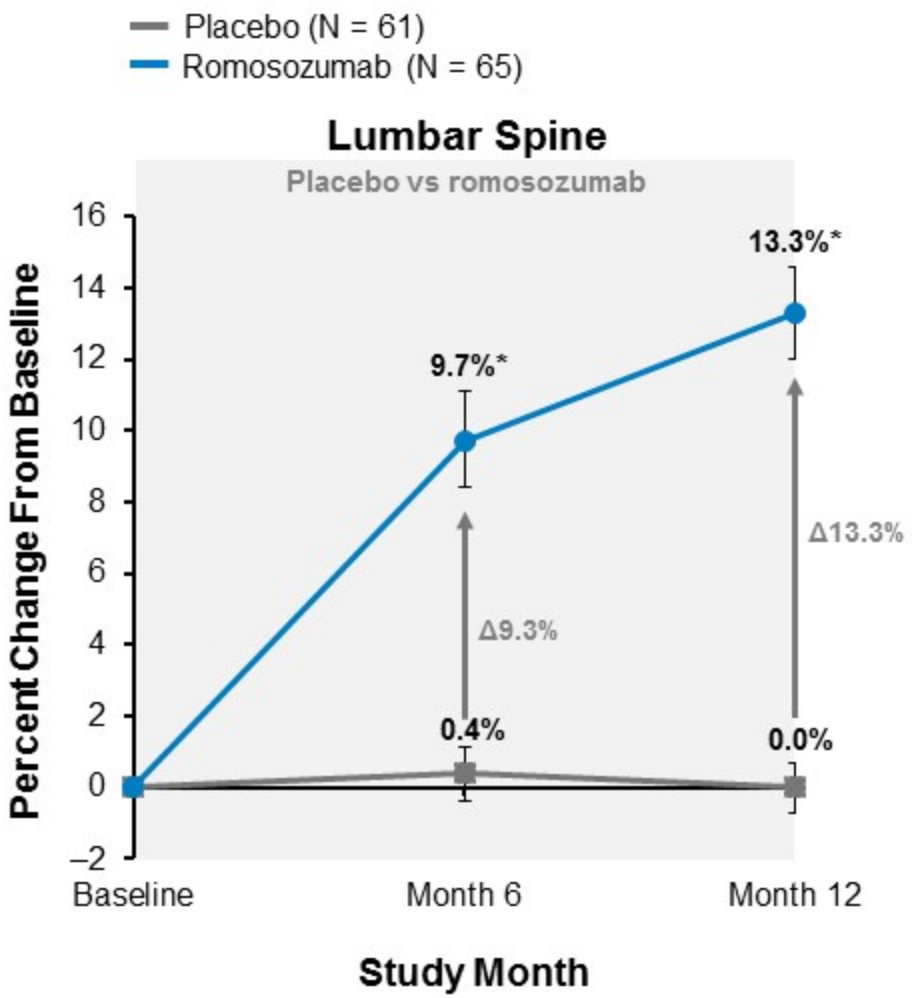


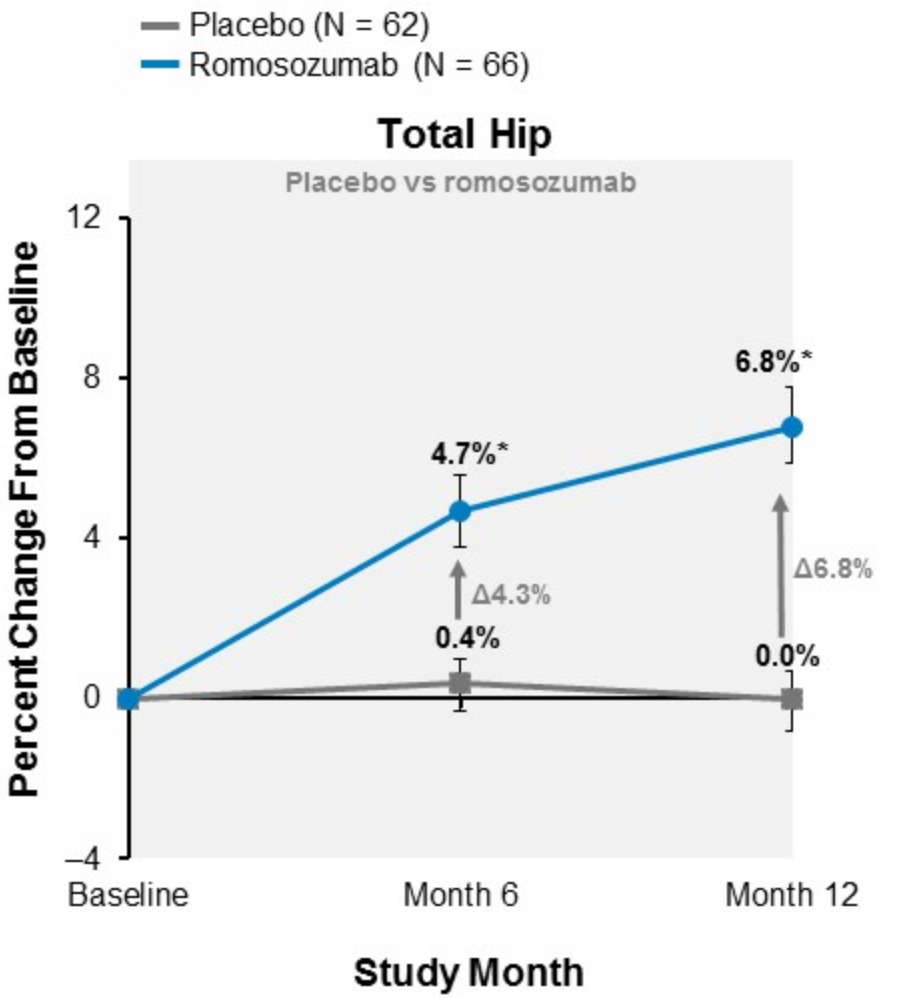
Figure 2. Percentage Change from Baseline in Bone Mineral Density.

Data are least-squares means, and I bars indicate 95% confidence intervals. The asterisk indicates P<0.05 for the comparison of the 210-mg monthly dose of romosozumab with placebo, the dagger P<0.02 for the comparison of the 210-mg monthly dose with alendronate, and the double dagger P<0.02 for the comparison of the 210-mg monthly dose with teriparatide.

NEJM, 2014

Lumbar Spine and Total Hip BMD Through Month 12

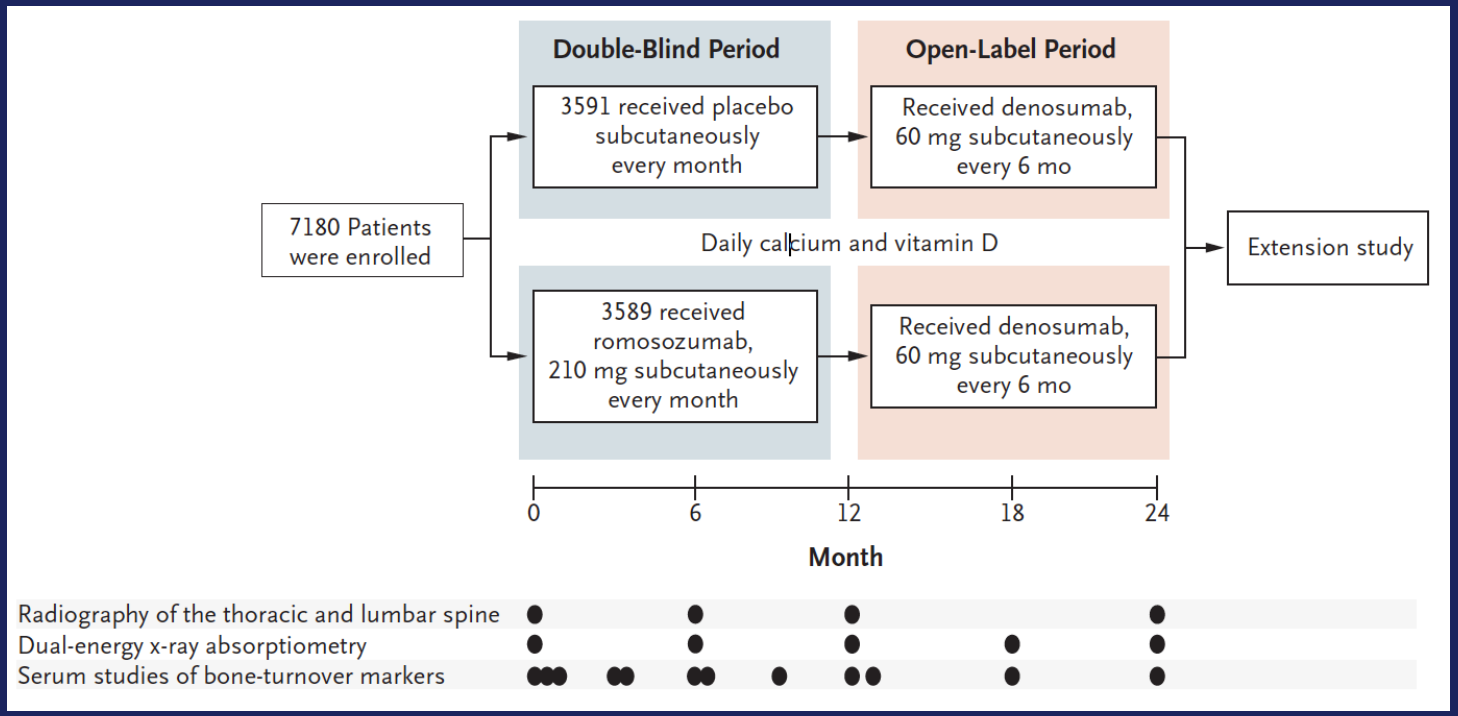




*$p < 0.001$ compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates.
BMD = bone mineral density; CI = confidence interval; Δ, difference
Adapted from: Cosman F, et al; [published online ahead of print Sep 18, 2016]. *N Engl J Med*. doi: 10.1056/NEJMoa1607948.

Romosozumab

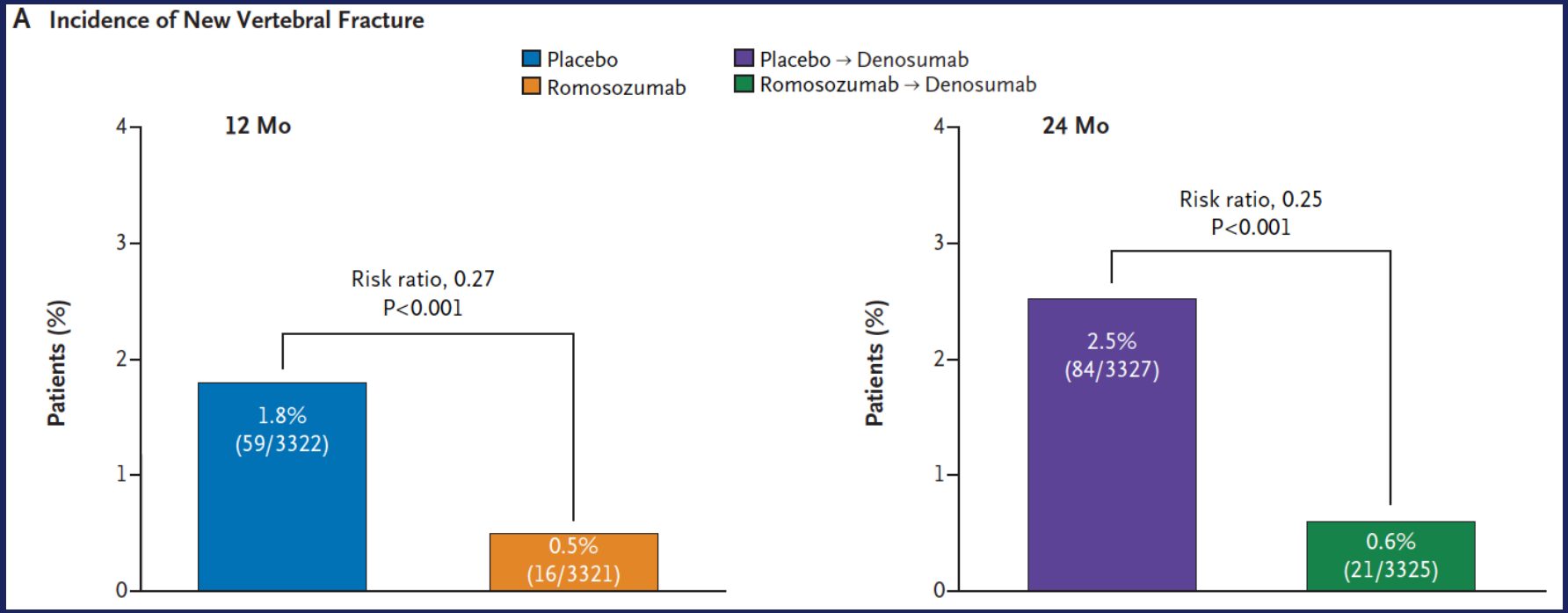
- FRAME Study: 7,180 women, aged 55-90, with a T-score -2.5 to -3.5 at the total hip or femoral neck. Treated with Romosozumab vs. PBO followed by Denosumab



Cosman F et al, NEJM 2016

Romosozumab

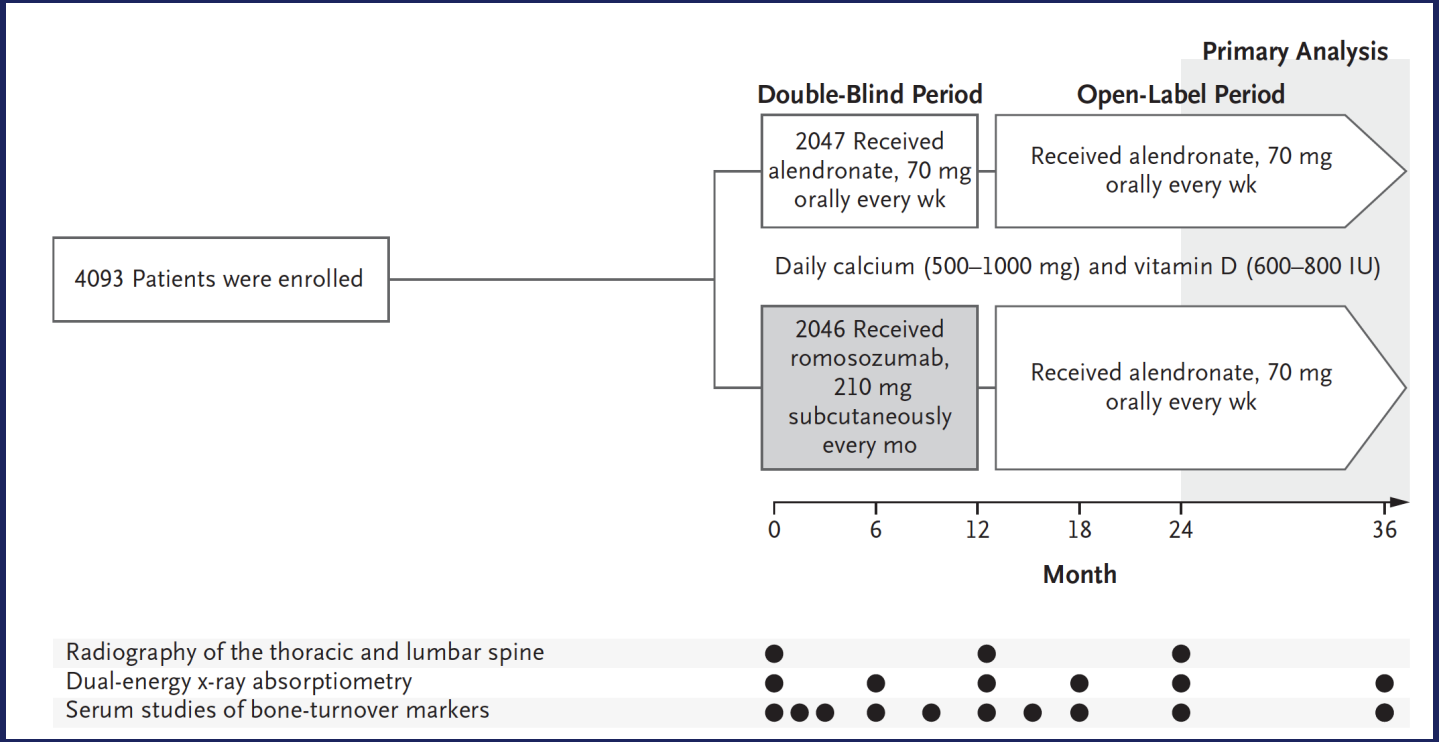
- FRAME Study Results
  - Risk of new vertebral fracture 73% lower at 12 months, effect was rapid
  - Risk of clinical fracture was lower by 36% at 12 months (p = 0.008)



Cosman F et al, NEJM 2016

New Therapeutics: Romosozumab

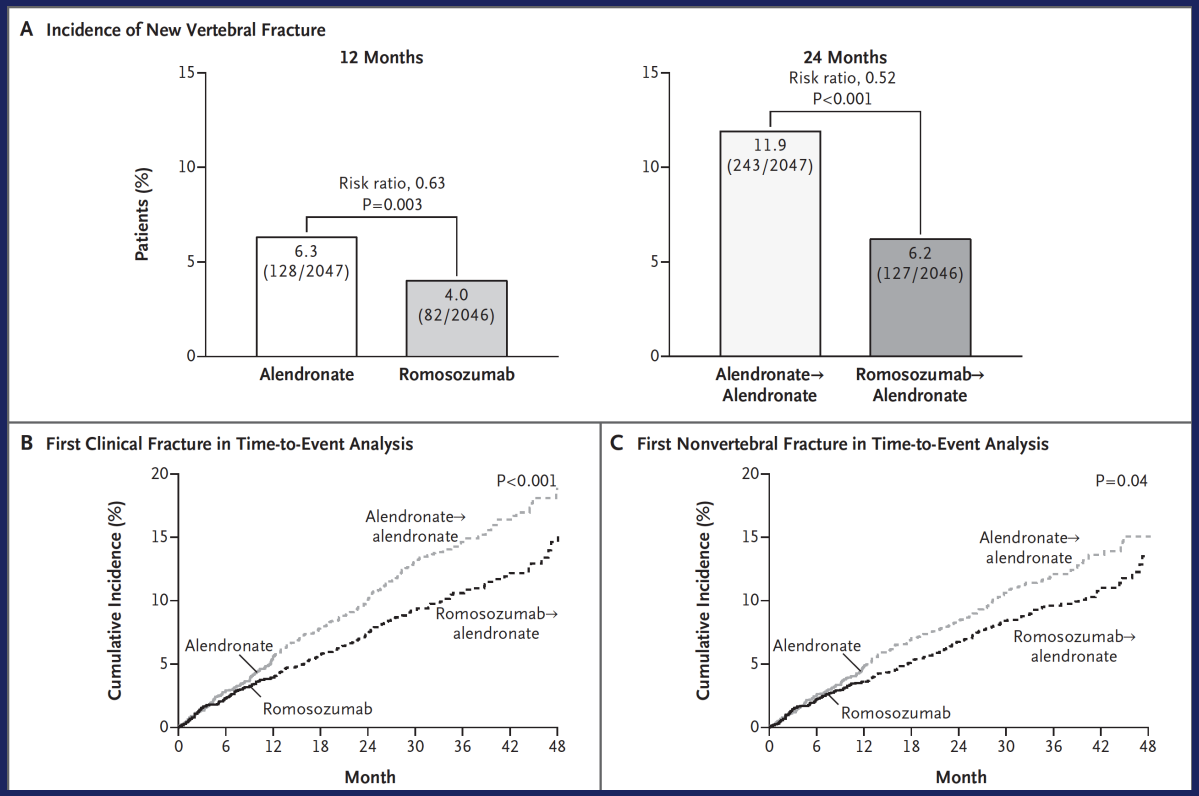
- ARCH Trial – Romosozumab versus alendronate, followed by alendronate
- 4093 women aged 55-90 with T-score of ≤-2.5 and ≥1 moderate or severe vertebral fracture or ≥2 mild vertebral fractures or proximal femur fracture and T-score -≤2.0



Saag K et al, NEJM 2017

New Therapeutics: Romosozumab

- ARCH Trial Results: Women aged 55-90



BENEFITS:
- 37% risk reduction in new vertebral fractures at one year
- 27% risk reduction in clinical fractures
- 38% risk reduction in hip fractures

Saag K et al, NEJM 2017

Romosozumab

- Adverse events reported in 3 trials
  - "Events of interest"
    - Osteonecrosis of the jaw (ONJ)
      - 2 cases in FRAME: 1 in romo group (1st 12 months) and 1 case in romo/dmab group (2nd 12 months)
      - 2 cases in ARCH: 1 case in alen/alen group and 1 case in romo/alen group during open label period (12-36 months)
    - Atypical femoral fracture (AFF)
      - 1 case in FRAME in romo/dmab group (2nd 12 months)
      - 6 cases in ARCH (4 in alen/alen group and 2 in romo/alen group)

Romosozumab

- Summary of adverse events reported in 3 trials:
  - Most concerning:
    - Cardiac ischemic events
      - FRAME trial: 44 in romo vs. 41 in PBO at one year*
      - FRAME trial: 82 in romo/dmab vs. 79 in PBO/dmab at 2 years
      - ARCH trial: 16 romo vs. 6 alen in at one year
      - ARCH trial: 30 romo/alen vs. 20 alen/alen during open label period
      - BRIDGE trial: 3 romo vs. 0 PBO in 12 months
    - Cerebrovascular events
      - ARCH trial: 16 romo vs 7 alen at one year
      - ARCH trial 45 romo/alen vs. 27 alen/alen during open label period
      - BRIDGE trial: 3 romo vs. 1 PBO in 12 months
- **FDA approved April 2019, with cautionary statement with regards to CVD risk**

*FRAME combined all adjudicated serious cardiovascular events into one category

Any questions or comments?

Case Question

- 74 yo female with CKD stage III. GFR 28-30
- Patient had a R distal radius fracture. Had a LS compression fracture in her 60's. DXA shows t score of -2.6 in LS and -2.7 R femoral neck
- What to do?

Case: Osteoporosis and CKD

- Difficult to diagnose osteoporosis in setting of CKD
- CKD get manifest as many bone disorders: Renal osteodystrophy (CKD-MBD): PTH medidated high bone turnover, osteitis fibrosa cystica, adynamic bone disease, osteomalacia, mixed uremic osteodystrophy
- There is no data to suggest an approach to making a diagnosis of osteoporosis in CKD stage 4 or 5

Osteoporosis and CKD

- If GFR between 30-60 ml/min with osteoporosis on DXA or fragility fracture:
  - Measure Calcium, PTH, phos and 25-on vit D
  - If all normal—treat as osteoporosis patient without CKD
  - If abnormalities present that show CKD-MBD—referral to nephrology needed prior to mgmt of osteoporosis
  - Also can check alk phos—need to exclude adynamic bone disease first!

Osteoporosis and CKD

- Bone biopsy is gold standard to evaluate this—but is not necessary if can be determined via biochemistry
- A diagnosis of renal osteodystrophy EXCLUDES osteoporosis
- Current recommendation: GFR<30 and no fragility fracture = no osteoporosis medications

Osteoporosis and CKD

- If GFR 15-30 and no evidence of CKD-MBD then can oral bisphosphonates. Dmab option (hypocalcemia) pt should be seen and followed in specialty clinics
- GFR 15-30 and CKD-MBD = No treatment.
- Not much evidence in CKD patients
- Teriparatide may be useful in adynamic bone disease

Bone Markers

- Bone formation: osteocalcin, P1NP, bone specific alk phos
- Bone resorption: C-telopeptide, N-telopeptide
- Use in individual patients not established
- Variability—fasting, time of day
- Insufficient data on their use in determining start of therapy, when to stop, fracture risk

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background Bisphosphonates have profound effects on bone physiology, and could modify the process of metastasis. We undertook collaborative meta-analyses to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer.

Methods We sought individual patient data from all unconfounded trials in early breast cancer that randomised between bisphosphonate and control. Primary outcomes were recurrence, distant recurrence, and breast cancer mortality. Primary subgroup investigations were site of first distant recurrence (bone or other), menopausal status (postmenopausal [combining natural and artificial] or not), and bisphosphonate class (aminobisphosphonate [eg, zoledronic acid, ibandronate, pamidronate] or other [ie, clodronate]). Intention-to-treat log-rank methods yielded bisphosphonate versus control first-event rate ratios (RRs).

Findings We received data on 18 766 women (18 206 [97%] in trials of 2–5 years of bisphosphonate) with median follow-up 5·6 woman-years, 3453 first recurrences, and 2106 subsequent deaths. Overall, the reductions in recurrence (RR 0·94, 95% CI 0·87–1·01; 2p=0·08), distant recurrence (0·92, 0·85–0·99; 2p=0·03), and breast cancer mortality (0·91, 0·83–0·99; 2p=0·04) were of only borderline significance, but the reduction in bone recurrence was more definite (0·83, 0·73–0·94; 2p=0·004). Among premenopausal women, treatment had no apparent effect on any outcome, but among 11 767 postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002), distant recurrence (0·82, 0·74–0·92; 2p=0·0003), bone recurrence (0·72, 0·60–0·86; 2p=0·0002), and breast cancer mortality (0·82, 0·73–0·93; 2p=0·002). Even for bone recurrence, however, the heterogeneity of benefit was barely significant by menopausal status (2p=0·06 for trend with menopausal status) or age (2p=0·03), and it was non-significant by bisphosphonate class, treatment schedule, oestrogen receptor status, nodes, tumour grade, or concomitant chemotherapy. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR 0·85, 95% CI 0·75–0·97; 2p=0·02).

Interpretation Adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival, but there is definite benefit only in women who were postmenopausal when treatment began.

Funding Cancer Research UK, Medical Research Council.

Lancet 2015; 386: 1353–61

This online publication has been corrected. The first corrected version appeared at thelancet.com on Dec 31, 2015. The second appeared on June 22, 2017.

Published Online
July 24, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60908-4

See Comment page 1319

*Full list of members available at http://www.ctsu.ox.ac.uk/research/meta-trials/ebctcg/ebctcg-page

Correspondence to:
EBCTCG Secretariat, Clinical Trial Service Unit, Nuffield Department of Population Health, Richard Doll Building, Oxford OX3 7LF, UK
bc.overview@ctsu.ox.ac.uk

Table 1. Ongoing or Not Fully Reported Trials

Trial Name (NCT or Other Trial ID)	No. of Patients and Characteristics	Arms or Comparison	Outcomes Reported, Notes
SWOG S0307[61,117] NCT00127205	N = 6,097 Age > 18 y	Clodronate (1,600 mg/d PO for 3 years) *v* ibandronate (50 mg/d PO for 3 years) *v* ZOL (4 mg IV every month × 6 then every 3 months × 2.5 years)	DFS (primary) in abstract only ONJ, fracture, adverse events (secondary) in abstract only Early reporting at 4th interim analysis; no realistic chance of statistically significant difference
TEAM IIb[77] BOOG 2006-04	N = 1,116 Postmenopausal, HR-positive, endocrine therapy	Ibandronate (50 mg/d for 3 years)	Ongoing, results not reported DFS (primary); metastasis, recurrence, OS, 5-year DFS, safety (secondary)
HOBOE, version 2 NCT00412022	N = 1,050 Original version (first 500 patients): age ≥ 18 years (triptorelin if premenopausal); letrozole in both arms Version 2 (after March 2010): premenopausal only; triptorelin + letrozole in both arms	ZOL, 4 mg every 6 months for 5 years	Enrollment complete, results not reported for version 2 or combined DFS (primary, version 2) BMD, OS, toxicity; DFS (original version; secondary)
Success A[78] NCT02181101 EUDRA-CT No. 2005-000490-21	N = 3,754 High-risk; adjuvant chemotherapy	ZOL, 2 years *v* 5 years ZOL at 4 mg IV every 3 months for 24 months *v* every 3 months for 24 months followed by every 6 months for 36 months	Ongoing, results not reported DFS (primary) OS, distant metastasis (secondary)
JONIE-1[66] UMIN000003261	N = 188 Age 20-70 years	ZOL (4 mg IV over 15 min, every 3-4 weeks for 6 months)	pCR (primary) DFS (secondary) in abstract only; follow-up to 2017 planned
Z-FAST Study-Japan[71,72] UMIN000001104	N = 204 Postmenopausal, HR-positive, adjuvant letrozole	ZOL Upfront or delayed start; 4 mg IV every 6 months for 5 years	BMD (primary) reported at 12 months Fracture, adverse events, BMD (secondary) at 36 months in abstract only
CHO-BC-039 NCT02595138	N = 430 (planned) Triple-negative	ZOL	Started 2015, ongoing DFS (primary) OS, adverse effects (secondary)
ABCSG-18[62,63] NCT00556374	N = 3,420 Postmenopausal, HR-positive, receiving nonsteroidal aromatase inhibitors	Denosumab (60 mg SC every 6 months) *v* placebo	Time to clinical fracture (primary) DFS (secondary) in abstract only Patients on placebo may switch to denosumab in 2016, follow-up will be ongoing
D-CARE[74] NCT01077154	N = 4,500 High risk	Denosumab (120 mg SC monthly for 6 months, then every 3 months for total of 5 years) *v* placebo	Enrollment completed 2012, ongoing administration of denosumab (5 years) and planned 7.5 years follow-up, no results reported Primary: bone metastasis free survival Secondary: DFS, OS, safety
GeparX[125] NCT02682693	N = 778 (planned) cT1c-cT4a-d BC; HR-; assessed HER2, Ki-67, TIL and RANK status	Neoadjuvant chemotherapy with or without denosumab (120 mg SC every 4 weeks × 6)	Primary: pCR (ypT0 ypN0) Secondary: breast conservation rates, toxicity, compliance, survival

Abbreviations: BMD, bone mineral density; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; HR-, hormone receptor negative; IV, intravenously; NCT, National Clinical Trial number; ONJ, osteonecrosis of the jaw; OS, overall survival; pCR, pathologically complete response; PO, orally; SC, subcutaneously; ZOL, zoledronic acid.

Monoclonal Gammopathy of Skeletal Significance

PERSPECTIVE

JBMR®

Unveiling Skeletal Fragility in Patients Diagnosed With MGUS: No Longer a Condition of Undetermined Significance?

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ABSTRACT

Monoclonal gammopathy of undetermined significance (MGUS) is a common finding in clinical practice, affecting greater than 3% of adults aged 50 years and older. As originally described, the term MGUS reflected the inherent clinical uncertainty of distinguishing patients with a benign stable monoclonal plasma cell disorder from subjects destined to progress to malignancy. There is now clear epidemiologic evidence, however, that patients with MGUS suffer from a significantly increased fracture risk and that the prevalence of MGUS is increased in patients with osteoporosis. Despite this relationship, no clinical care guidelines exist for the routine evaluation or treatment of the skeletal health of patients with MGUS. Recent work has demonstrated that circulating levels of at least two cytokines (CCL3/MIP-1α and DKK1) with well-recognized roles in bone disease in the related monoclonal gammopathy multiple myeloma are also increased in patients with MGUS. Further, recent imaging studies using high-resolution peripheral quantitative CT have documented that patients with MGUS have substantial skeletal microarchitectural deterioration and deficits in biomechanical bone strength that likely underlie the increased skeletal fragility in these patients. Accordingly, this Perspective provides evidence that the "undetermined significance" portion of the MGUS acronym may be best replaced in favor of the term "monoclonal gammopathy of skeletal significance" (MGSS) in order to more accurately reflect the enhanced skeletal risks inherent in this condition.

KEY WORDS: MGUS; OSTEOPOROSIS; FRACTURE; DXA; HRPQCT

The Importance of having a Fracture Liaison Service: Searching for Secondary Causes of Osteoporosis

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BACKGROUND

Osteoporosis is a common disease affecting millions of men and women. Many patients experience an osteoporosis-associated fracture and are never offered screening and treatment for osteoporosis. Fracture Liaison Services (FLS) are currently being established all over the world to help prevent recurrent fractures and adverse health outcomes. In the past, patient and community focused educational approaches have been ineffective. FLS in several countries have proven to be a consistently successful approach by integrating facture care with secondary fracture prevention. This approach has been adopted as national policy in the UK National Health Service and in some centers in the United States, Canada, and Australia. (1) This case demonstrates another reason why it is important to have a patient seen by a FLS following a fracture: to search for secondary causes of osteoporosis.

The current literature estimates that 30-50% of women and 50-60% of men have a secondary cause of osteoporosis and identifying the cause can be vital to helping the patient receive proper treatment. (2) Some of these disorders may be asymptomatic, and simple laboratory testing can detect more than 90% of disorders (Table 1). If medical history, physical findings, or laboratory tests results suggest the presence of a secondary cause, additional laboratory testing may be warranted.

Table 1: Laboratory Tests Recommended for Secondary Osteoporosis Screening (3)
Complete blood cell count
Serum chemistry including calcium, phosphorus, total protein, albumin, liver enzymes, alkaline phosphatase, total protein and electrolytes
Urinalysis (24 hour collection) for calcium, sodium, and creatinine excretion
Serum 25-hydroxyvitamin D

CLINICAL CASE

A 57 year-old healthy female presents with several months of low back pain after lifting a heavy door. Patient denied fevers, chills, numbness, weakness in the legs, or bowel or bladder dysfunction. An MRI of the lumbar spine showed a compression fracture at L1 (Table 2). The patient was treated with conservative measures by the UCSD Orthopedic spine team and referred to the UCSD FLS service for further evaluation.

FLS Evaluation

DXA scan revealed osteopenia (Table 2) with a calculated FRAX score of 15% for 10-year probability of all osteoporotic fractures and 2.5% probability for hip fracture. A complete osteoporosis history was reviewed, and the patient was found to have no risk factors at the initial visit. Appropriate past medical, family and social history were reviewed and negative as per patient.

CLINICAL CASE

Laboratory testing was performed to look for secondary causes of osteoporosis. A CBC, CMP, phosphorus, magnesium, 25-OH vitamin D, TSH, SPEP and tTG-IGA antibodies were ordered. Labs were notable for elevated LFTs and INR 2.2. Abnormal laboratory results are noted in Table 3. SPEP revealed a decrease in alpha-2 globulin fraction, which has been associated with acute hepatic disease or a hemolytic process. Abdominal US was ordered and showed an enlarged echogenic liver consistent with cirrhosis (Table 2). Patient was referred to hepatology and later revealed excessive consumption of alcohol of approximately 3-4 drinks per day since the age of 18. With further testing including a liver biopsy, the patient was diagnosed with alcoholic hepatitis and cirrhosis with MELD 25.

Table 2: Imaging

Study	Results
MRI Lumbar Spine	L1 superior end plate compression fracture at L1 with approximately 30% height loss. Mild retropulsion.
DXA Scan	RIGHT FEMUR: T-score: -1.9. LEFT FEMUR: T-score: -2.1. LUMBAR SPINE (L1-4): T-score: -1.7.
Abdominal Ultrasound	Cirrhosis with sequela of chronic portal venous hypertension. The liver measures 15.3 cm in long axis and is nodular and diffusely echogenic. Multiple collaterals are present and there is recanalization of the umbilical vein. Moderate ascites is present.

SUMMARY

This previously healthy post-menopausal patient presented with a compression fracture and osteoporosis and was ultimately found to have severe liver cirrhosis as a result of investigation for other causes of her osteoporosis. The patient is currently having her underlying liver disease managed as the initial step in treating further progression of bone loss and osteoporosis. The prevalence of osteoporosis varies between 11-58% in patients with chronic liver disease and transplant recipients. The etiology is likely multifactorial and only partially understood but probably is a result of disruption of hormonal regulators of bone formation and resorption. (4,5)

CONCLUSION

The FLS is an important service to offer patients who have sustained a fracture to help reduce the risk of secondary fractures.(1) The FLS can look for causes of fractures that may have previously gone undetected. The search for secondary osteoporosis causes is important for detection of underlying diseases and is essential for improving bone health in these patients.

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Table 3: Laboratory Values

	Patient's Result	Reference Range
MCV	111.0 μm^3	79.0 – 99.0 μm^3
AST	90 U/L	0-32 U/L
ALT	38 U/L	0-33 U/L
Total Bilirubin	3.2 mg/dL	<1.2 mg/dL
PTT	43.5 sec	25.0-34.0 sec
PT	24.4 sec	9.5-12.5 sec
INR	2.2	<1.5