

The logo for ACoi is displayed within a white circular area. The letters 'A', 'C', and 'i' are rendered in a thin, grey, sans-serif font. The letter 'o' is a solid teal circle. The entire logo is set against a white background that is part of a larger teal circular graphic on the left side of the page.

ACoi

No Disclosures

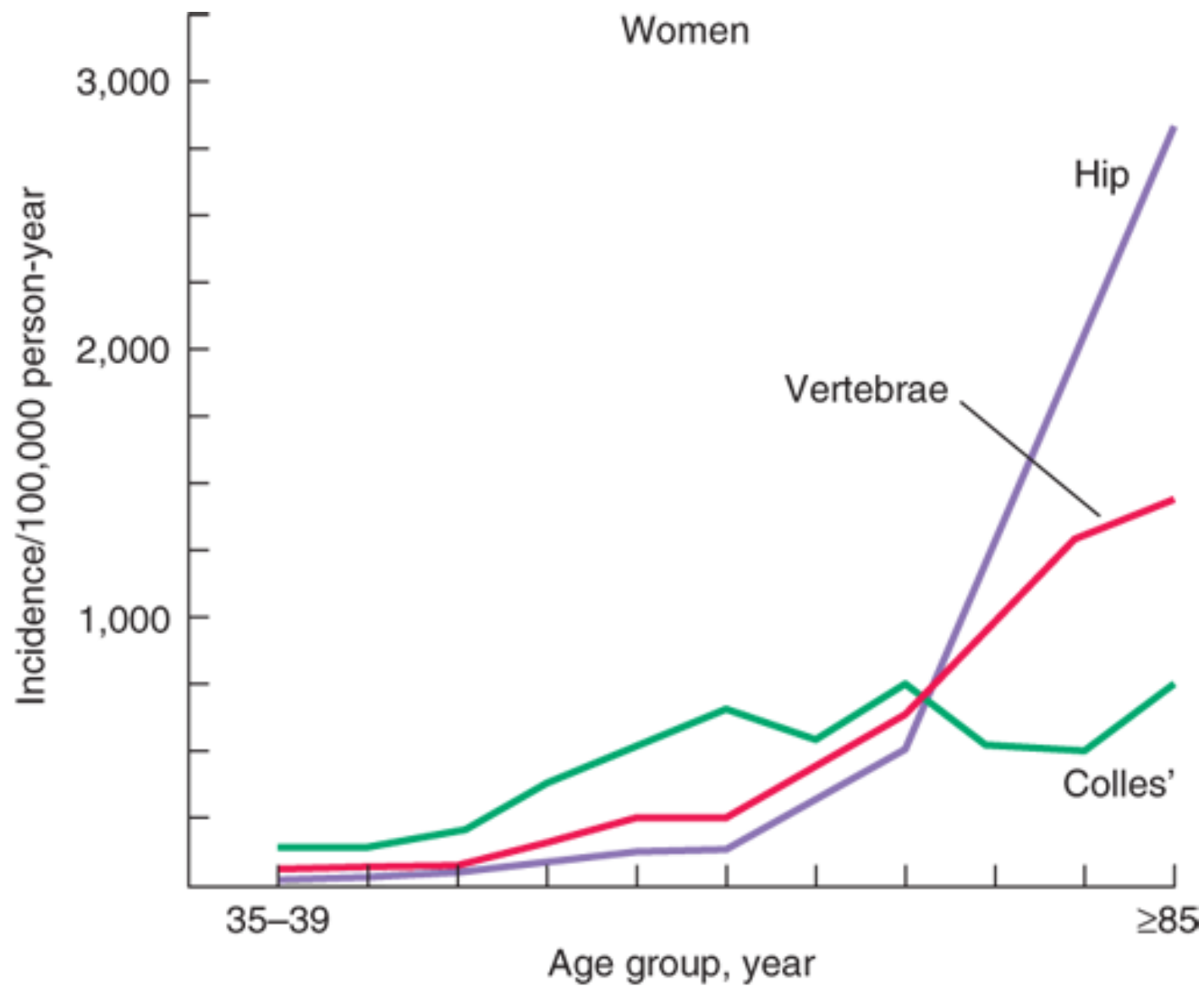
Osteoporosis



Decreased bone strength at the level of microarchitecture resulting in higher rate of fracture

Osteoporosis is a major public health concern

- More than 10 million Americans have osteoporosis, and an additional 43 million have low bone mass
- More than 2 million osteoporosis-related fractures occur each year in the United States, and more than 70% of these occur in women
- For women 55+, costs of caring for osteoporotic fractures exceed the costs of:
 - MI
 - Stroke
 - Breast cancer
- Mortality after hip fracture 12-20% over 2 years



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition Copyright © McGraw-Hill Education. All rights reserved.

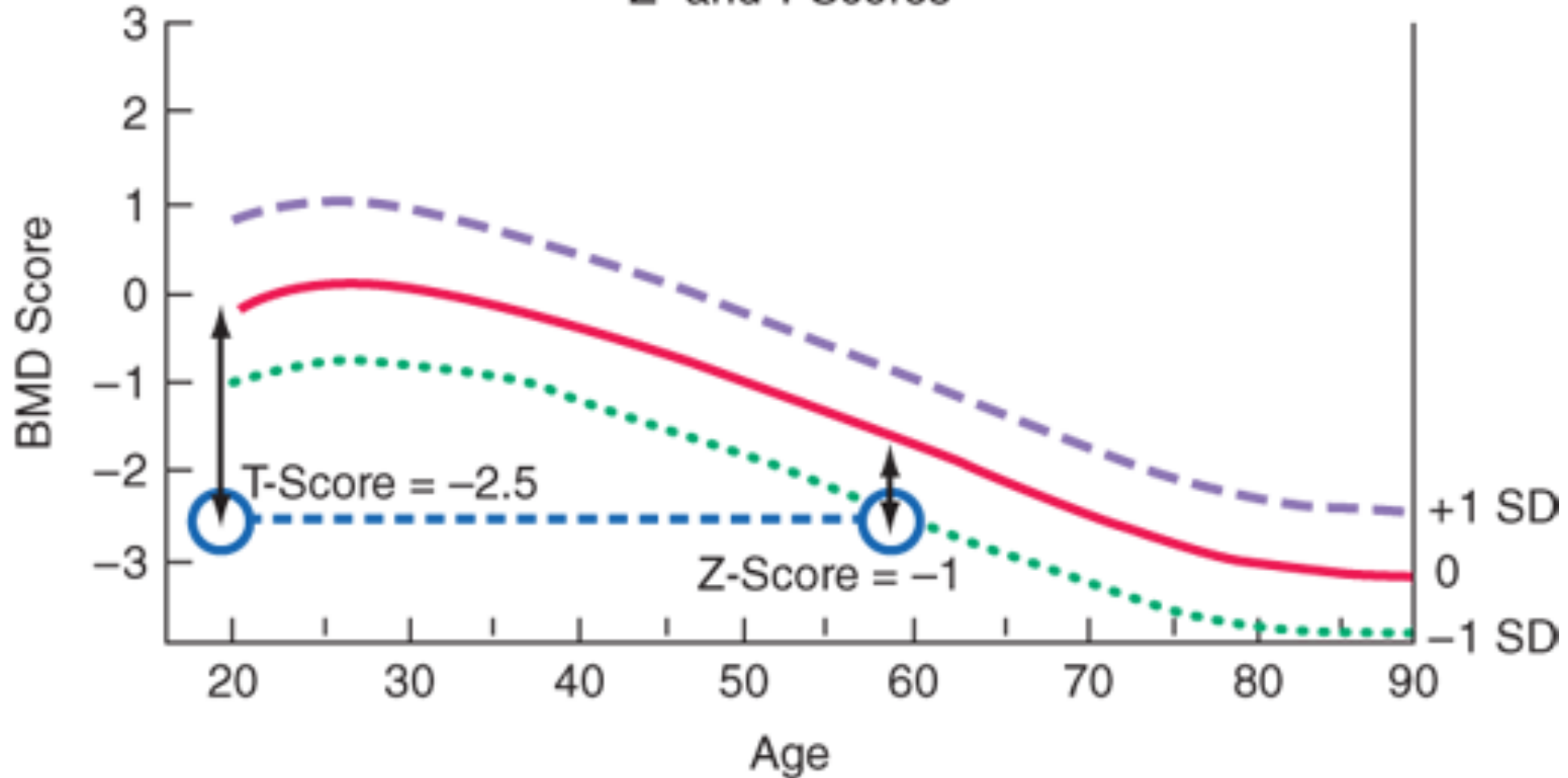
Vertebral fractures

- More than 20% of postmenopausal women have prevalent vertebral fractures
 - As the most common osteoporotic fracture, VF are a hallmark of the disease and indicate a high risk for future fractures
- They are also associated with impaired pulmonary function and increased mortality risk
- However, the majority of VF (2/3) are asymptomatic



- 2.5 standard deviations below the mean bone density g/cm²
- t-score comparison to young adult normal
- z-score comparison to age and sex matched

Z- and T-Scores



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition
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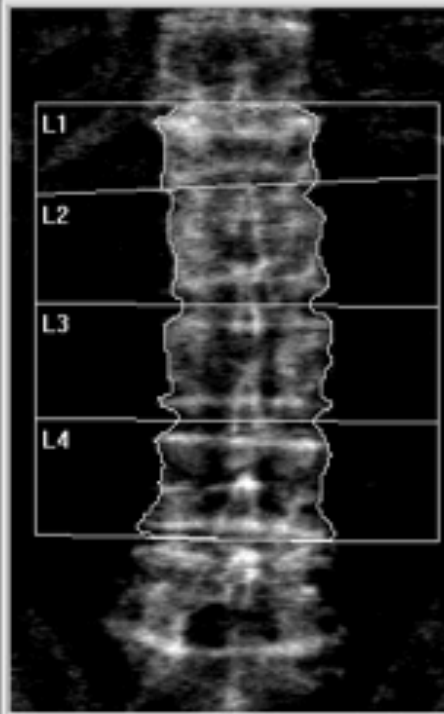
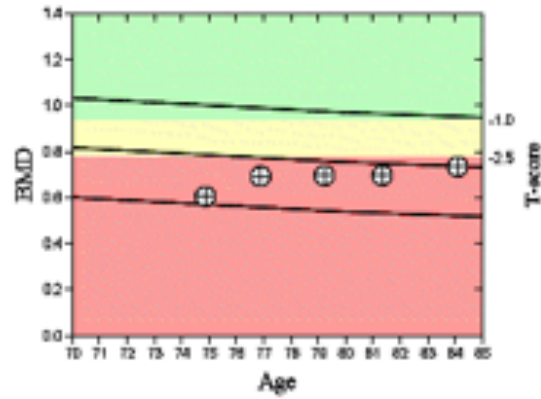


Image not for diagnostic use

116 x 126

k = 1.133, d0 = 50.4

L1-L4



T-score vs. White Female. Source:2012 BMDCS/Hologic
Z-score vs. White Female. Source:2012 BMDCS/Hologic

Results Summary:

Region	Area[cm ²]	BMC[(g)]	BMD[g/cm ²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	10.38	6.95	0.670	-2.3	72	0.2	103
L2	14.76	10.51	0.712	-2.9	69	-0.1	99
L3	15.27	10.78	0.706	-3.4	65	-0.5	93
L4	16.77	13.66	0.814	-2.7	73	0.3	104
Total	57.18	41.90	0.733	-2.9	70	0.0	100

Total BMD CV 1.0%, ACF = 1.041, BCF = 1.006, TH = 6.717



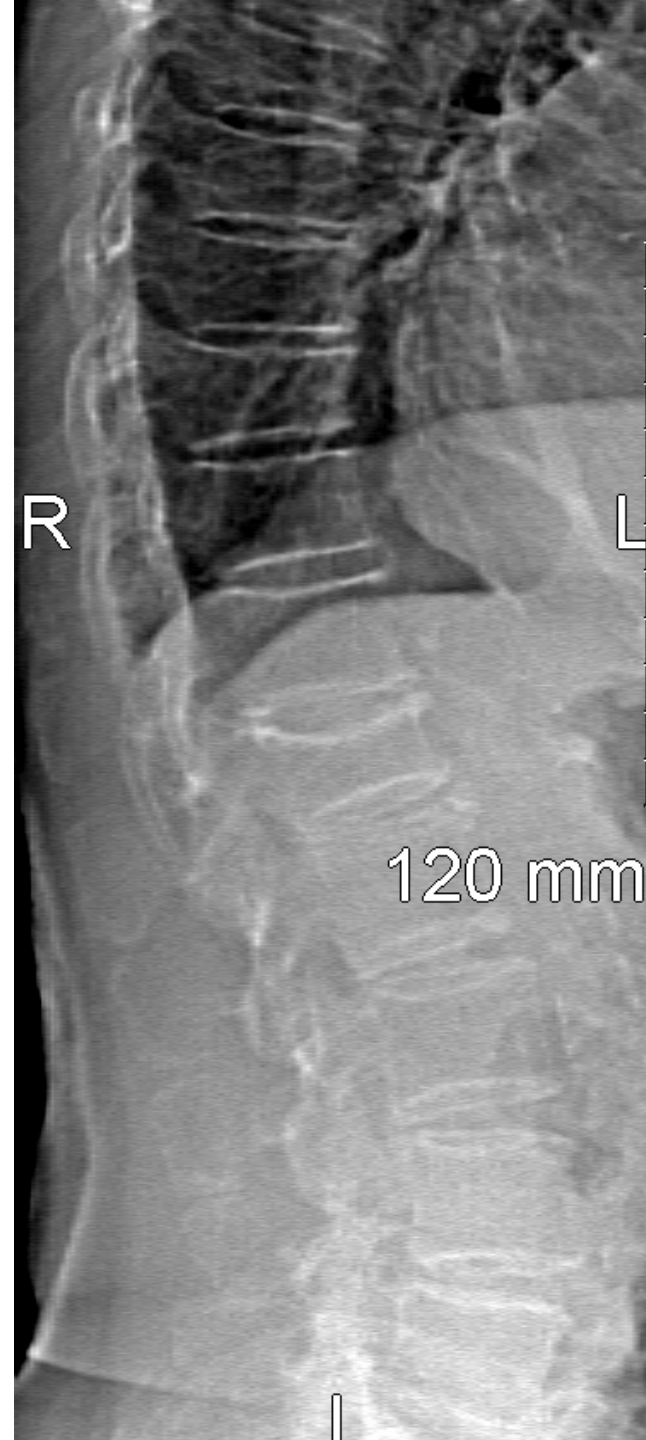
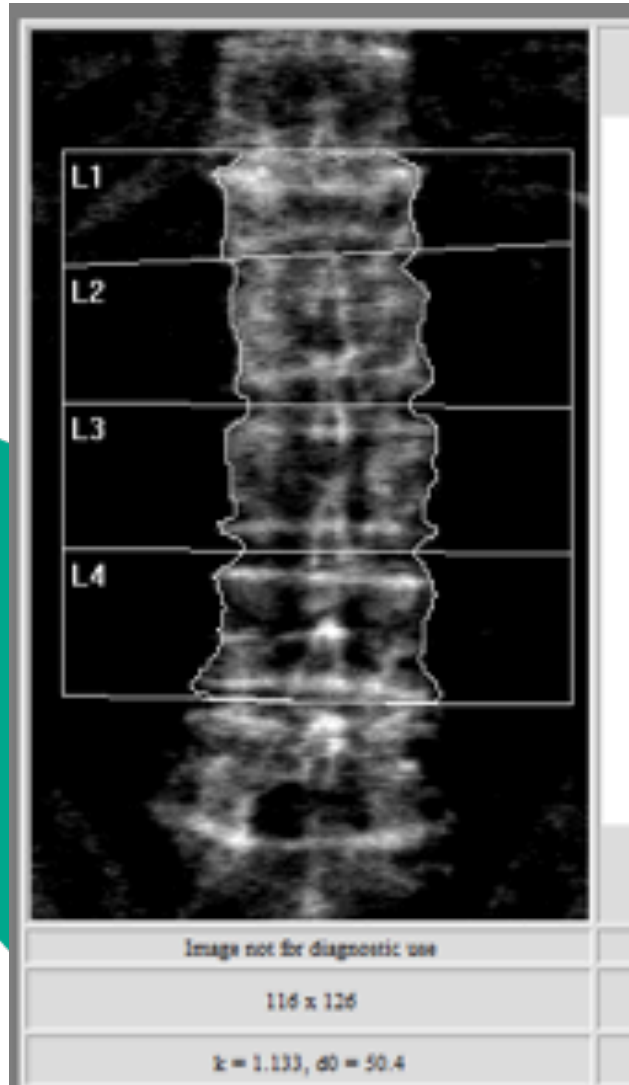
Osteoporosis DXA

- Reconstructed images lateral thoracic and lumbar spine
- Vertebral fracture assessment (VFA)
- Consider with height loss or focal back pain
- Vertebral fractures often without symptoms

Osteoporosis DXA



Osteoporosis DXA



Osteoporosis
by DXA lateral
lumbar view with L1
compression fracture

L
L



ACOi

2021 ACOI Annual Convention
and Scientific Sessions
October 27-30

Calculation Tool

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

Country: **US (Caucasian)**

Name/ID:

[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)

Select BMD

Clear

Calculate



Weight Conversion

Pounds ➔ kg

Convert

Height Conversion

Inches ➔ cm

Convert

09556385

Individuals with fracture risk assessed since 1st June 2011

Osteoporosis FRAX Tool

Age, Sex, Height, Weight
Previous adult fracture
Parental hip fracture
Current smoking
Glucocorticoids
Rheumatoid arthritis
Secondary Osteoporosis
Alcohol
Bone mineral density

Calculation Tool

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

Country: **US (Caucasian)** Name/ID: [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)

Select BMD



Weight Conversion

Pounds kg

Height Conversion

Inches cm

09556385

Individuals with fracture risk
assessed since 1st June 2011



FRAX: 10 year fracture probability

- National osteoporosis foundation
- Cost effective treatment
- Major fracture risk $\geq 20\%$
- Hip fracture risk $\geq 3\%$

Osteoporosis Canada: To Fit to Fracture

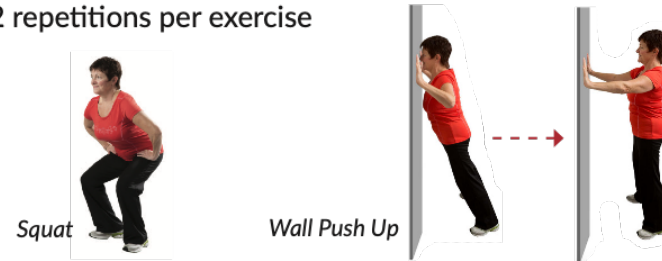
#1 <https://osteoporosis.ca/wp-content/uploads/OC-Too-Fit-to-Fall-or-Fracture-1.pdf>

#2 <https://osteoporosis.ca/wp-content/uploads/OC-Too-Fit-To-Fracture-Osteo-Exercise-Book.pdf>

Too Fit to Fall or Fracture

Strength Training At least 2 days/week

- ▶ Exercises for legs, arms, chest, shoulders, back
- ▶ Use body weight against gravity, bands, or weights*
- ▶ 8 - 12 repetitions per exercise



Try these to get started:

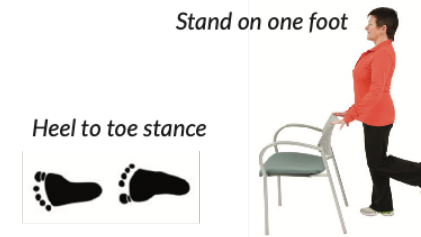
- Classes at YMCA/community centre
- Consult a physical therapist/kinesiologist
- Contact Osteoporosis Canada

Seated Row



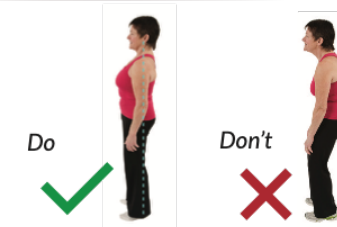
Balance Exercises Every day

- ▶ Tai Chi, dancing, walking on your toes or heels
- ▶ Have a sturdy chair, counter, or wall nearby, and try (from easier to harder): shift weight from heels to toes while standing; stand heel to toe; stand on one foot; walk on a pretend line



Posture Awareness Every day

- ▶ Gently tuck your chin in and draw your chest up slightly
- ▶ Imagine your collarbones are wings - spread your wings slightly without pulling your shoulders back



Aerobic Physical Activity At least 150 mins/week

- ▶ Bouts of 10 mins or more, moderate to vigorous intensity*
- ▶ You should feel like your heart is beating faster and you are breathing harder
- ▶ You might be able to talk while doing it, but not sing

Examples:

- Brisk walking
- Dancing
- Jogging
- Aerobics class

Strength Training (more examples) At least 2 days/week

Other exercises include:

- ▶ Upright row
- ▶ Step up



What are spine sparing strategies?

Spine sparing strategies help “spare” the spine from injury. Injuries to the spine can occur when we bend forward or twist the spine quickly or repeatedly, or if we lift something heavy, bend far forward (e.g., tying shoes) or twist the torso all the way to the side. Bending or twisting while holding a weighted object (e.g., groceries, grandchild) is also risky.

Spine sparing strategies:

- ▶ Bend with your hips and knees, not your spine
- ▶ Turn your whole body rather than twisting your spine



Osteoporosis Canada: To Fit to Fracture

#1 <https://osteoporosis.ca/wp-content/uploads/OC-Too-Fit-to-Fall-or-Fracture-1.pdf>

#2 <https://osteoporosis.ca/wp-content/uploads/OC-Too-Fit-To-Fracture-Osteo-Exercise-Book.pdf>

TREATMENT: Lifestyle modifications

- **Musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures**
- **An adequate intake of calcium and vitamin D**
 - **At least 800-1000 international units (20-25mcg) D daily**
 - Treatment targets is controversial – AACE and Endocrine Society recommend 30
 - IOM sets upper limit of 4000 iu (100mcg) daily
 - **Dietary calcium ~1200mg/day, preferably in diet.**
 - Mixed evidence but recent meta-analysis shows 15% reduced risk of fracture from Ca intake, 30% reduced hip fracture
- **Lifelong participation in regular, weight-bearing, resistance exercise**
- **Balance-improving exercises to minimize falls**
 - Tai Chi

Avoiding tobacco and excessive use of alcohol

Calcium Supplements

- Calcium carbonate (40% elemental Ca)
 - Cheap
 - Needs acid to absorb
 - Comes in pills up to 500mg elemental Calcium (1250mg total)
- Calcium citrate (20% elemental Ca)
 - More expensive
 - No need for acid
 - Pills up to 250mg elemental Ca
- If on more than 500mg elemental calcium daily, split dose

Foods and drinks with calcium

Food	Calcium in milligrams
Milk (skim, 2%, or whole; 8 oz [240 mL])	300
Yogurt (6 oz [168 g])	250
Orange juice (with calcium; 8 oz [240 mL])	300
Tofu with calcium (0.5 cup [113 g])	435
Cheese (1 oz [28 g])	195 to 335 (hard cheese = higher calcium)
Cottage cheese (0.5 cup [113 g])	130
Ice cream or frozen yogurt (0.5 cup [113 g])	100
Soy milk (8 oz [240 mL])	300
Beans (0.5 cup cooked [113 g])	60 to 80
Dark, leafy green vegetables (0.5 cup cooked [113 g])	50 to 135
Almonds (24 whole)	70
Orange (1 medium)	60

Osteoporosis treatment Rx

- Approved agents must yield a decrease in fractures / fracture risk for FDA approval
- Example: There have been historical agents such as Fluoride which increase measured DXA bone density without the same effect on bone quality; This agent does not necessarily decrease fracture risk.
- Patient and community focus on the side effects; Clinician should try to focus on the risks of taking these agents but also on the risks of not taking these agents.

Osteoporosis treatment

- Bisphosphonate: Daily, weekly, monthly dosing on empty stomach, full glass water, otherwise NPO for one hour, do not lie down for one hour = Fosamax / alendronate, Actonel / risedronate, Boniva / ibandronate, Atelvia
- IV Bisphosphonate therapy: Should not be considered a simple substitute for oral bisphosphonate. Not necessarily better than oral treatment.
- Estrogen: Good anti-resorptive action, but
Not to be used for this osteoporosis Tx only
- Evista / raloxifene: SERM = positive to bone negative to breast. Risk of hypercoagulability

- Testosterone = used in the face of male hypogonadism; May not be as helpful in mild male hypogonadism
- Parathyroid hormone (PTH): Subcutaneous injection for severe osteoporosis / fracture & PTHrP anabolic
- Calcitonin: Intranasal and subcutaneous --Limited usefulness
- Denosumab: biological agent subcutaneous twice / yr
- Romazosumab: Anabolic & anti-repsorptive

- Work horse for anti-resorptive therapy, traditional first choice for cost and effectiveness
- Precautions for use based on low absorption and risk of acid reflux potential
- Reflux issues can be circumvented by intravenous bisphosphonates
- Osteonecrosis of the Jaw = low risk
- Joint aches
- Fracture risk = subtrochanteric fractures after years of extended use but uncommon

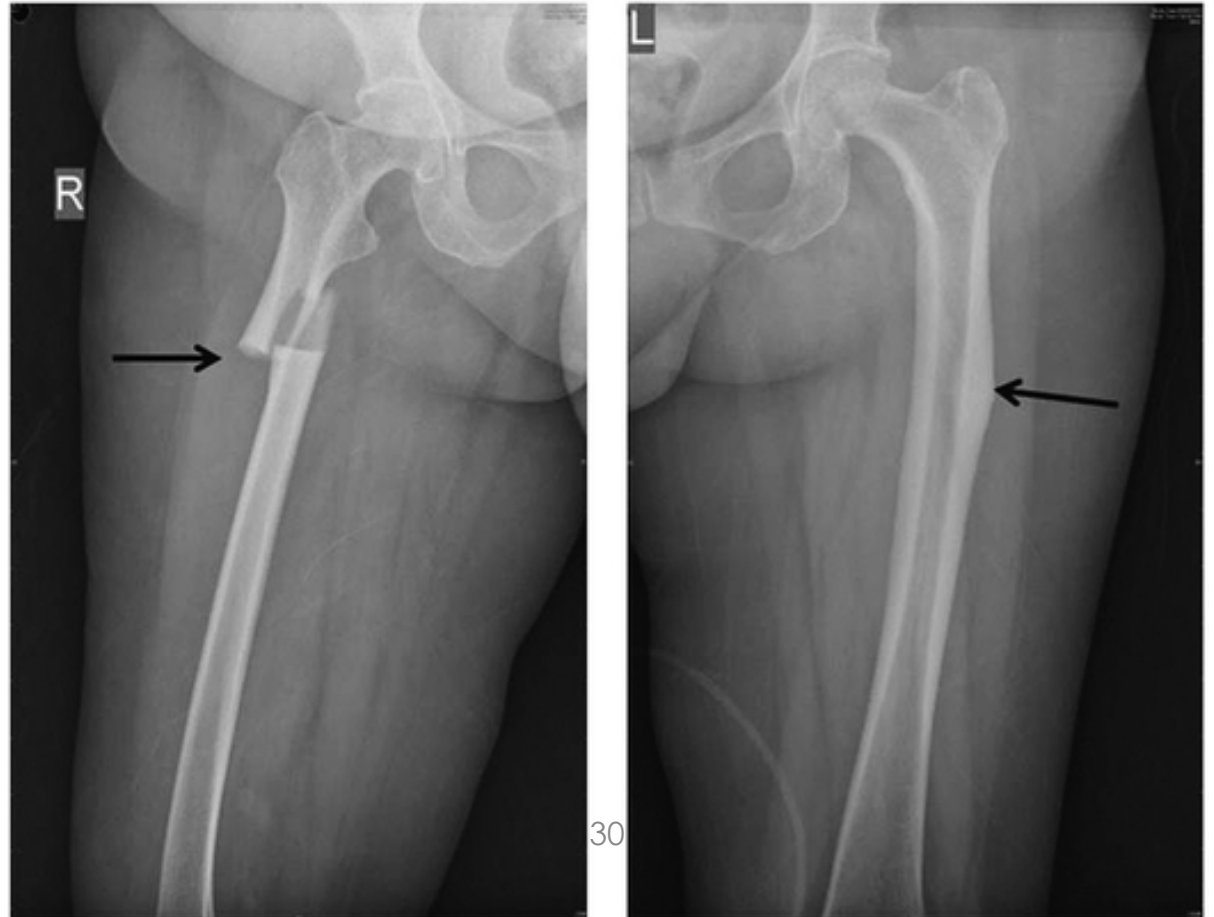
ONJ (Osteonecrosis of the jaw)



- ONJ was first reported in patients with advanced cancer receiving high-dose bisphosphonate / denosumab therapy
- The incidence of ONJ is much lower with oral or IV bisphosphonate therapy for osteoporosis, on the order of 1/10,000 to 1/100,000 patients per year
- Risk factors:
 - dental pathologic conditions
 - invasive dental procedures
 - poor dental hygiene
 - cancer, chemotherapy, radiation
 - antiangiogenic therapies

Subtrochanteric (atypical) femur fractures

- Atraumatic fracture, often with groin/mid-thigh prodromal pain

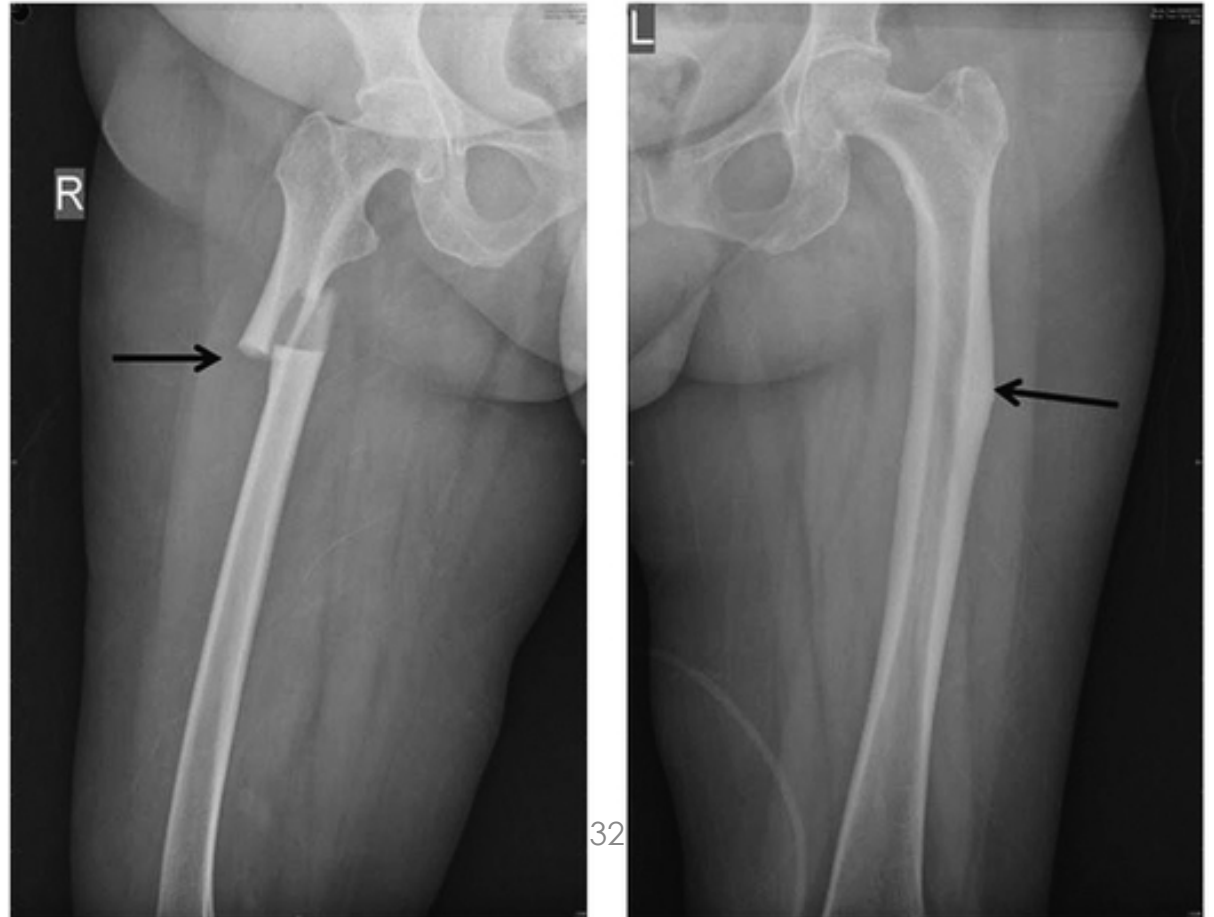


ATYPICAL FEMORAL FRACTURES

- AFF of the subtrochanteric region is rare event that seems to be increased with long-term therapy
- A literature review of AFF cases by the ASBMR reported a history of prodromal groin or thigh pain in approximately 70% of patients with AFF
 - Any patient who presents with persistent thigh or groin pain should interrupt bisphosphonate treatment while appropriate imaging studies are performed
 - In the early stages, a lateral periosteal stress reaction may be seen radiologically

Subtrochanteric (atypical) femur fractures

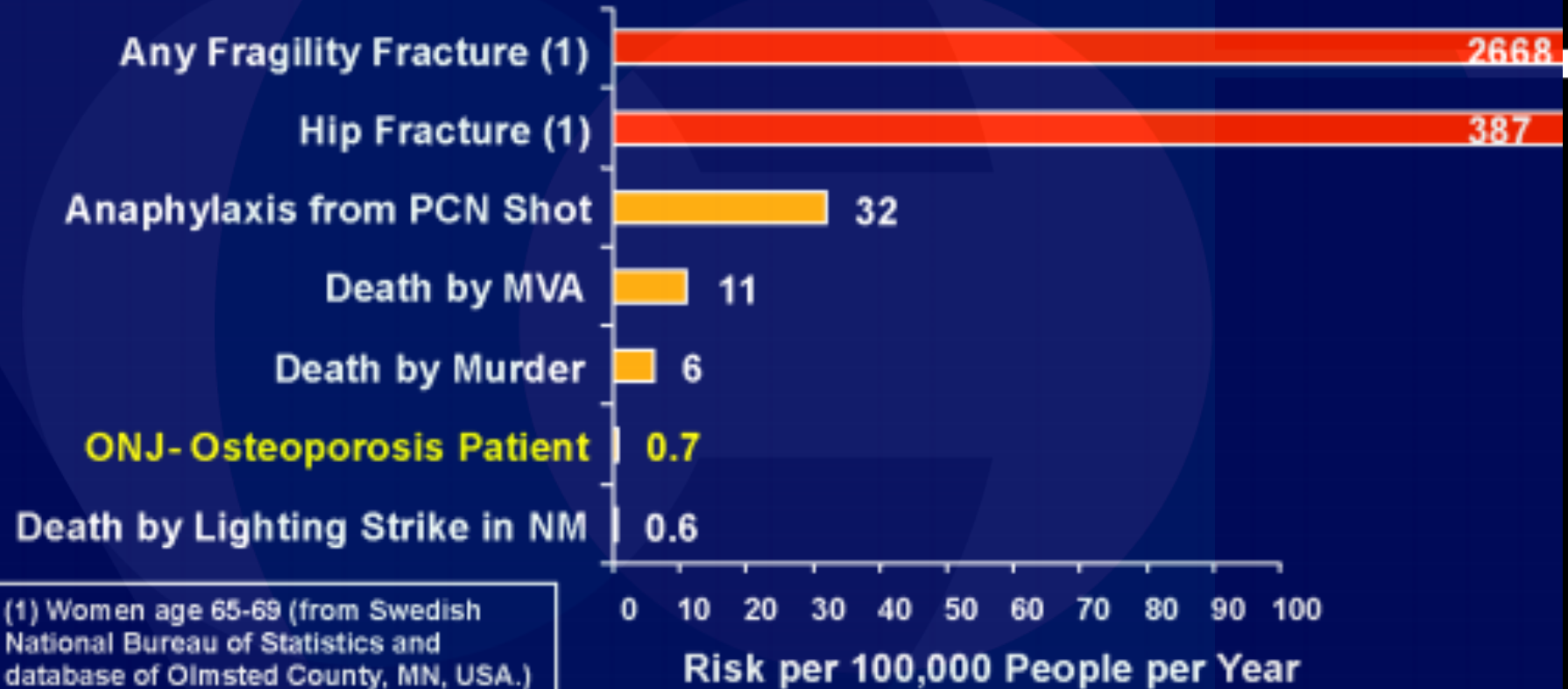
- Atraumatic fracture, often with groin/mid-thigh prodromal pain



A

Comparative Risks

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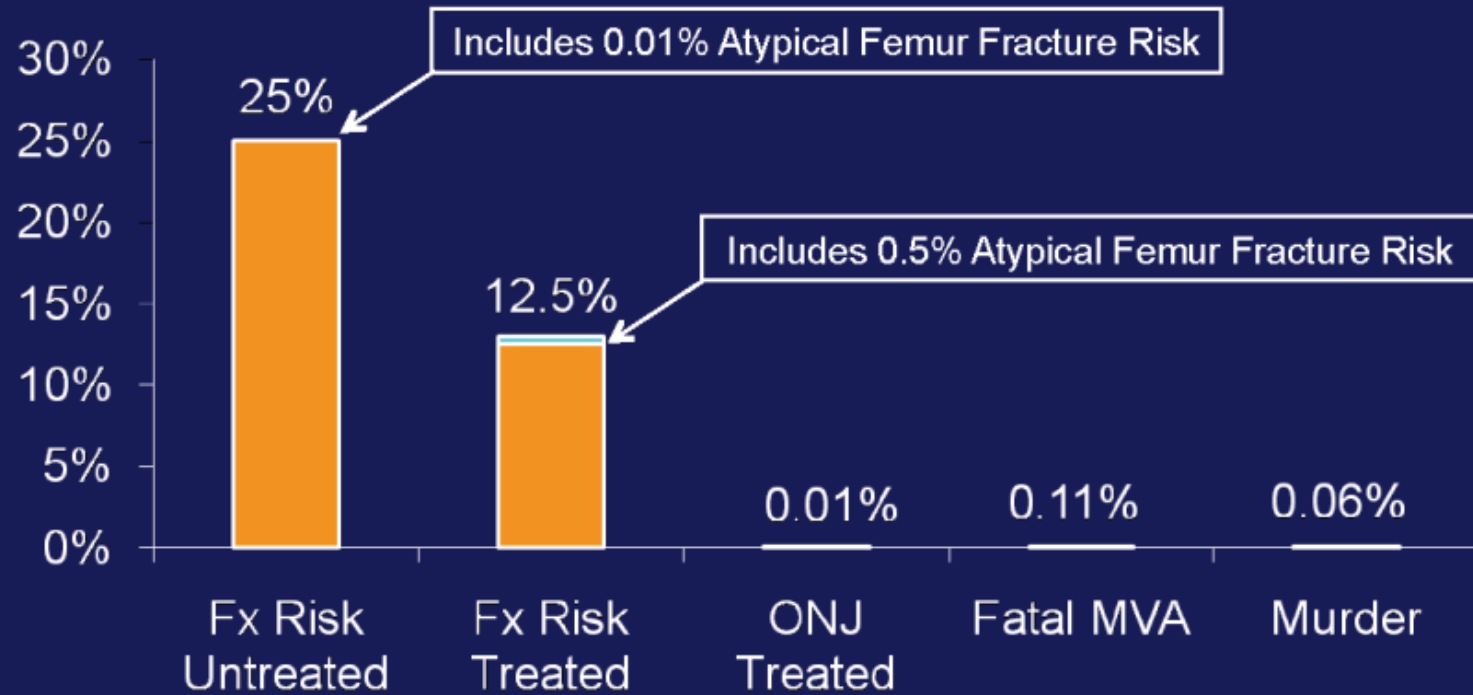


Kanis JA et al. Osteoporos Int. 2001;12:417-427. Pharmcoepidemiol Drug Saf. 2003;12:195-202. National Center for Health Statistics. JADA. 2006;137:1144-1150. www.nssl.noaa.gov/papers/techmemos/NWS-SR-193/techmemo-sr193-4.html

B

10-Year Probabilities

80 year-old woman with FN T-score = -3.3

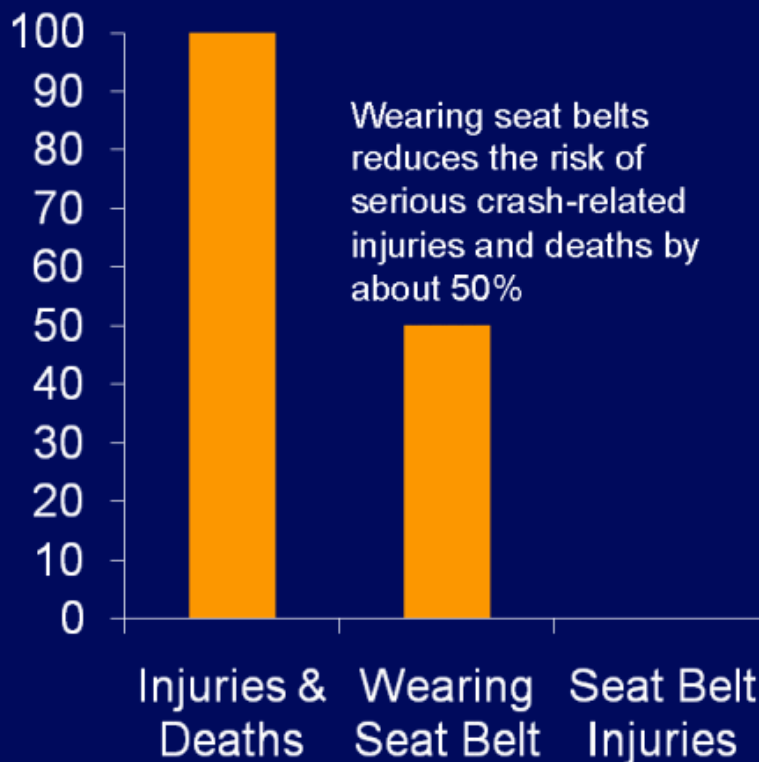


Untreated probability of major osteoporotic fracture calculated by FRAX. ONJ estimate is ~1/100,000 patient-treatment-years from ASBMR Task Force by Khosla S et al. J Bone Miner Res 2007;22:1479-149. AFF estimate untreated is ~0.01/10,000 and treated is ~5/10,000 patient-years from Schilcher J et al. N Engl J Med. 2011;364:1728-1737. Risk estimates assume long-term bisphosphonate therapy resulting in 50% reduction in fracture risk. MVA and murder data from the CDC at http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf. Image copyright © 2011 Lewiecki EM. Slide version.

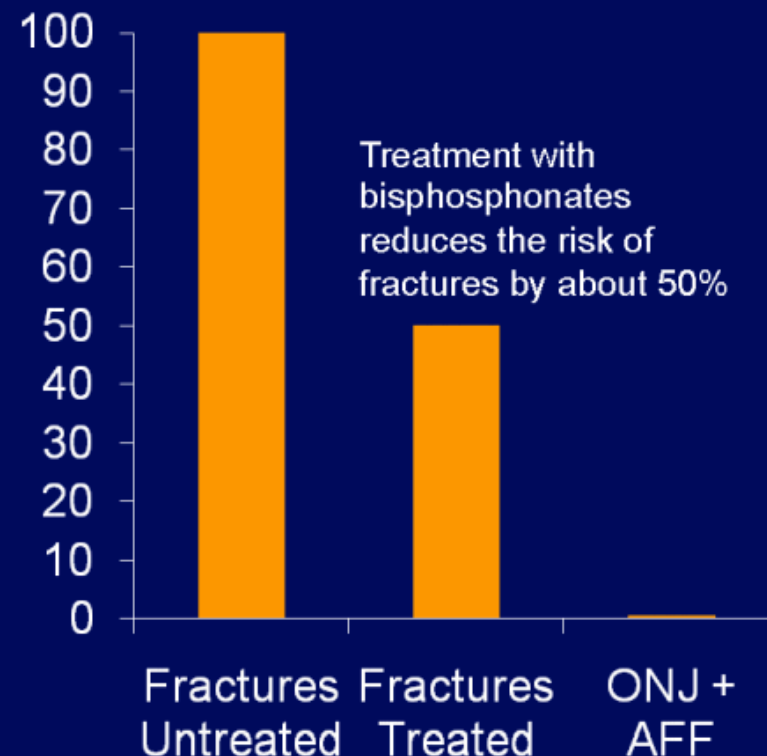
C

Benefits and Risks

Motor Vehicle Accidents



Osteoporosis



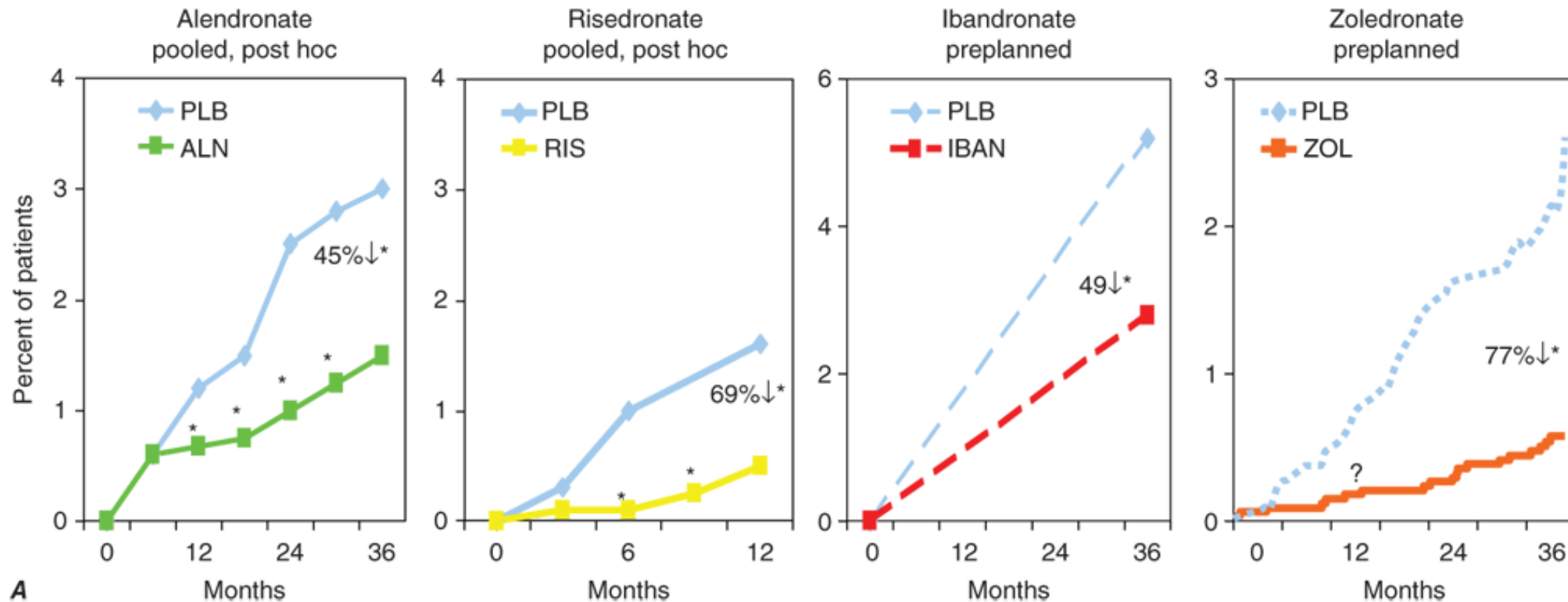
There are about 2.3 million adults treated in ERs each year for injuries from MVAs and about 2 million osteoporotic fractures each year. The risk of seat belt injuries and serious side effects from osteoporosis treatment is very small in proportion to the benefits. Data from multiple sources.

Questions from Dentists

- All cleaning, root canals, etc, are fine on bisphosphonate
- Only extractions and implants are a risk
- If on bisphosphonates long-term >4 years, already in the bone
- Need to be off months-1 year

Holding the week before doesn't make sense

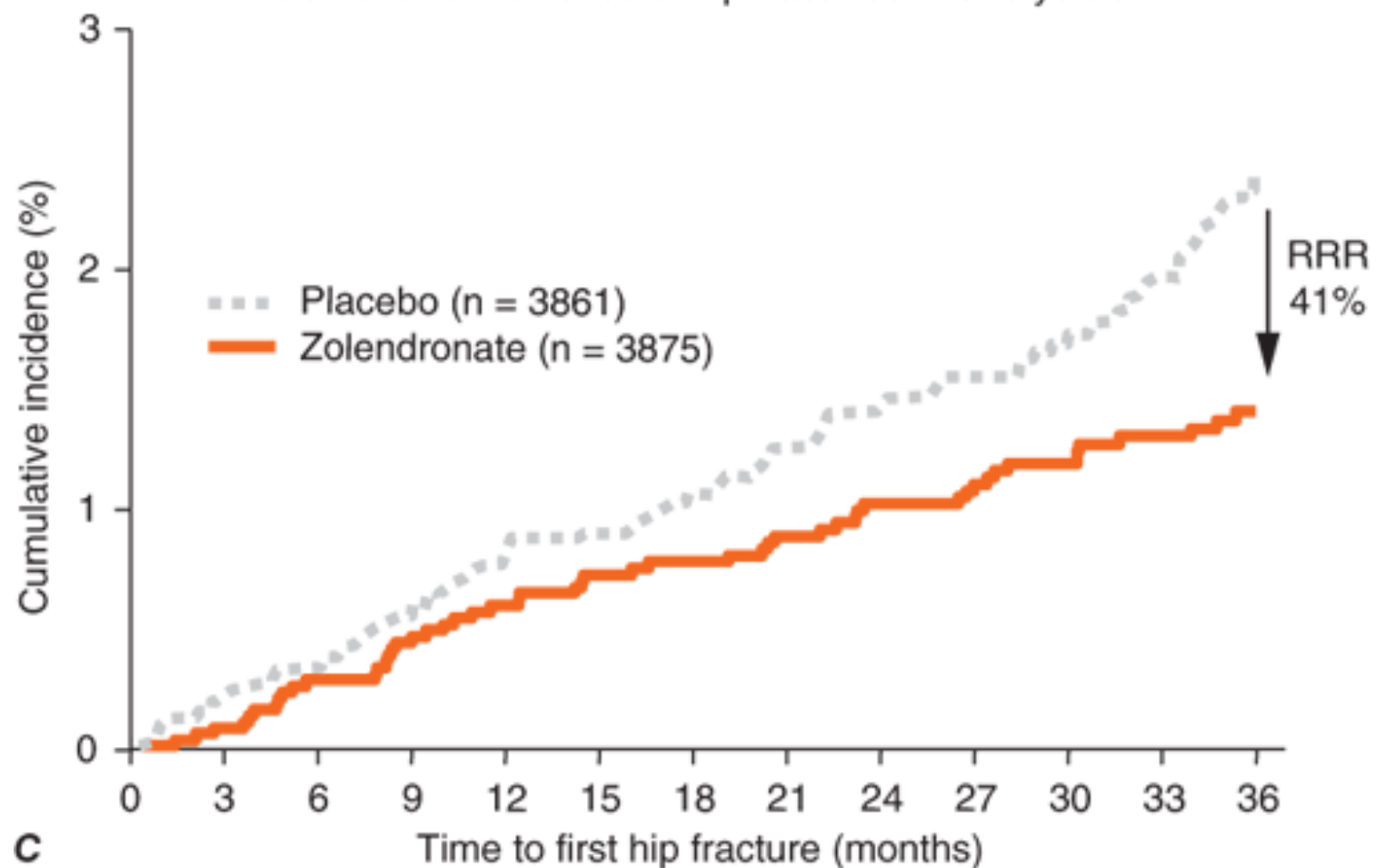
Vertebral fractures



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Hip fractures

Cumulative incidence of hip fractures over 3 years



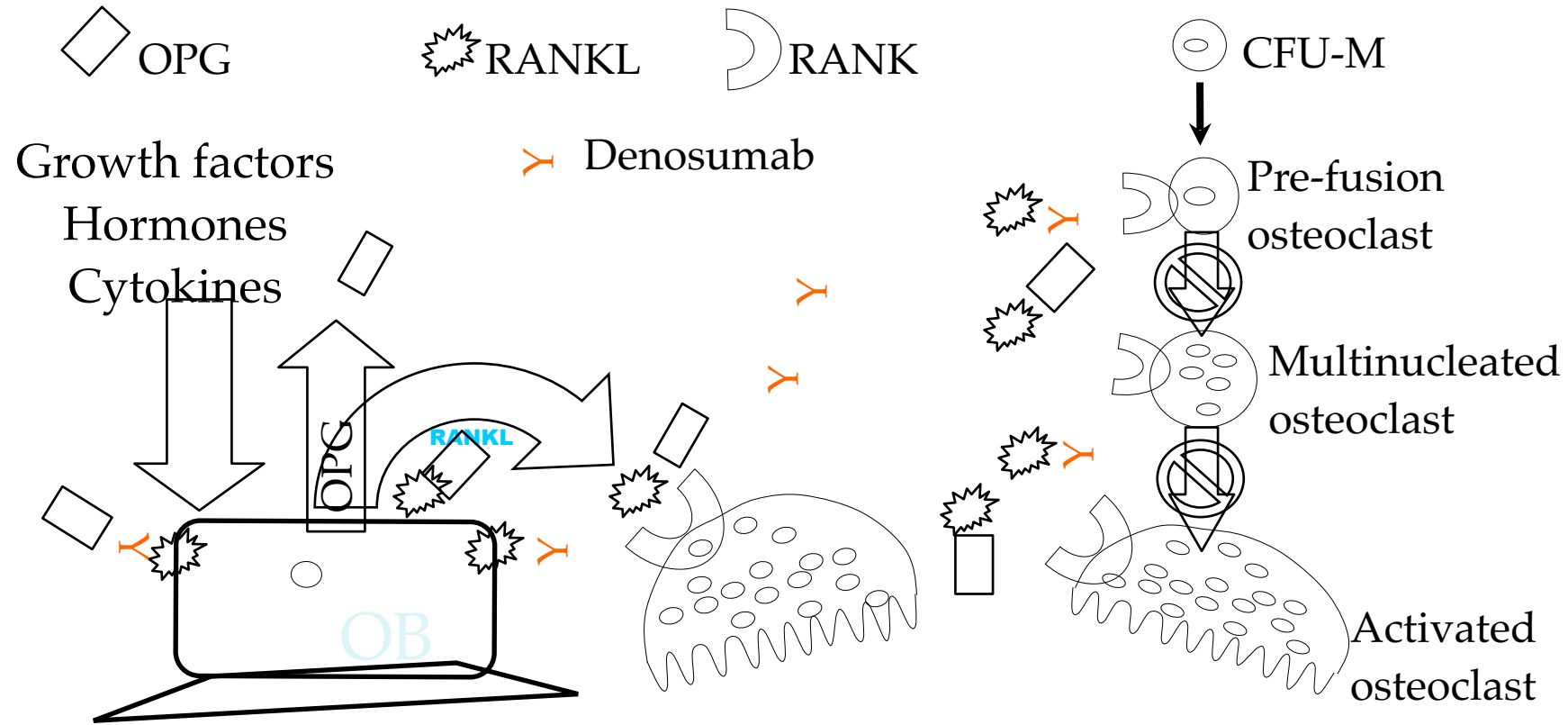
C

Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition
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- Raloxifene: FDA approved to prevent and treat osteoporosis and breast cancer prevention. Not for non-vertebral fracture
- Tamoxifen: Prevention and treatment of breast cancer. Acting like estrogen on bone

- Biological agent subcutaneous twice/yr anti-resorptive
- No drug holiday
- Provokes hypocalcemia if marginal calcium balance and abnormal Vitamin D. Need to evaluate Vitamin D and calcium status close to the time of administration
- Prevents maturation of osteoclasts
- Limits mature osteoclasts coming to the bone surface
- Reduce survival of the osteoclast

RANKL Antibody/RANKL: Activation Of Osteoclasts



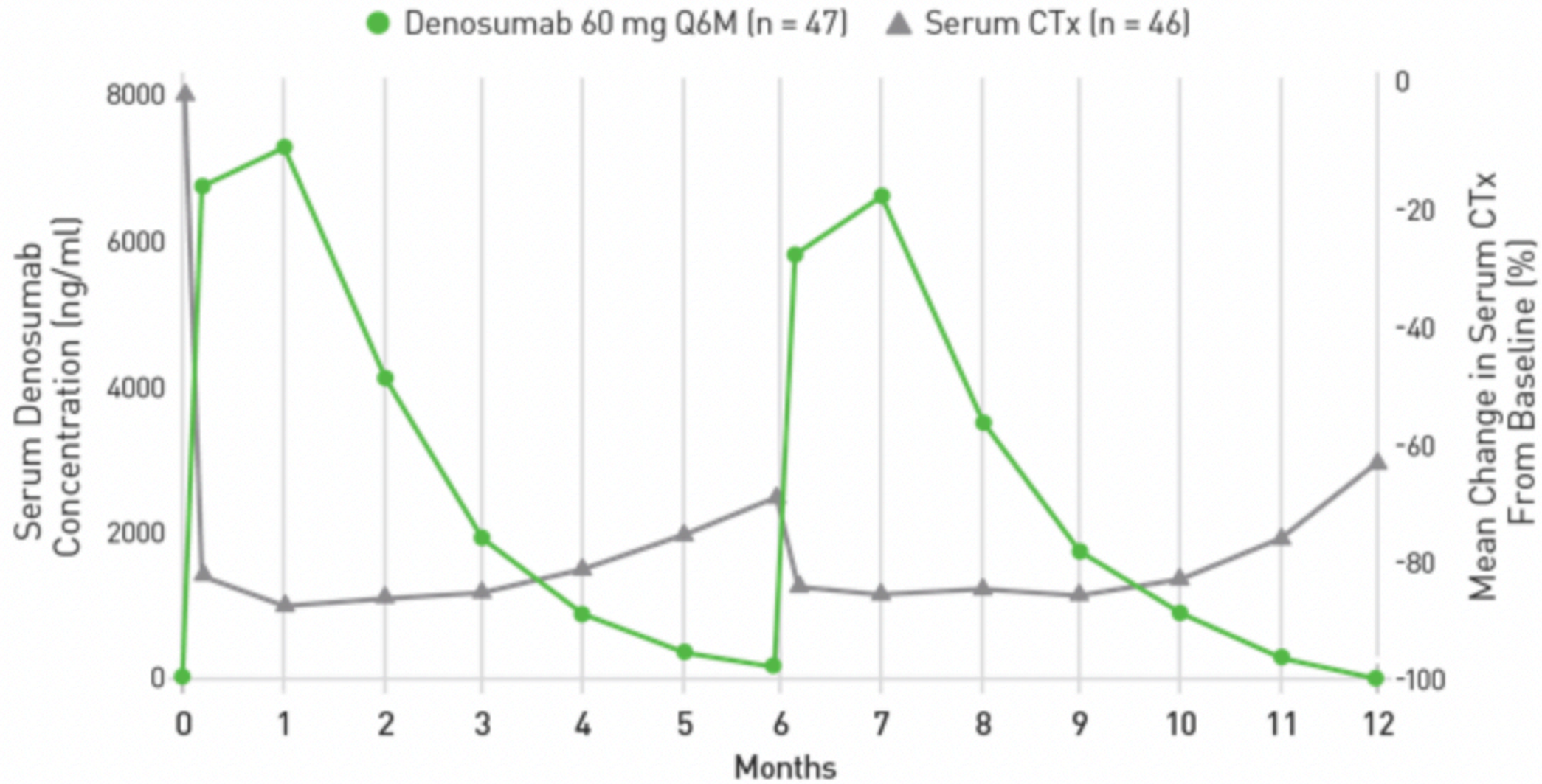
Bone

RANK = Receptor Activator of Nuclear factor Kappa B

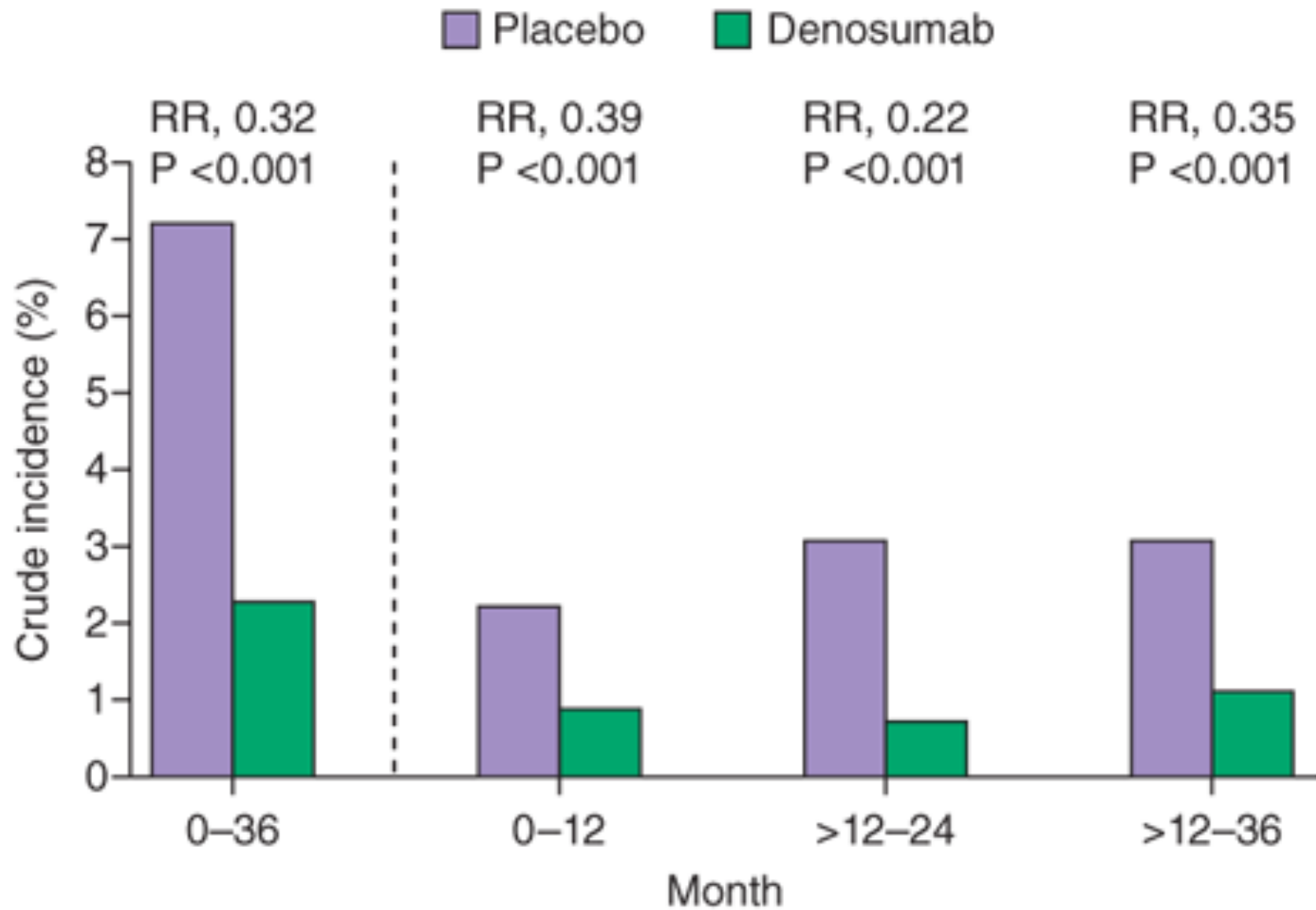
RANKL = RANK Ligand

CFU-M = Colony-Forming-Unit Macrophage

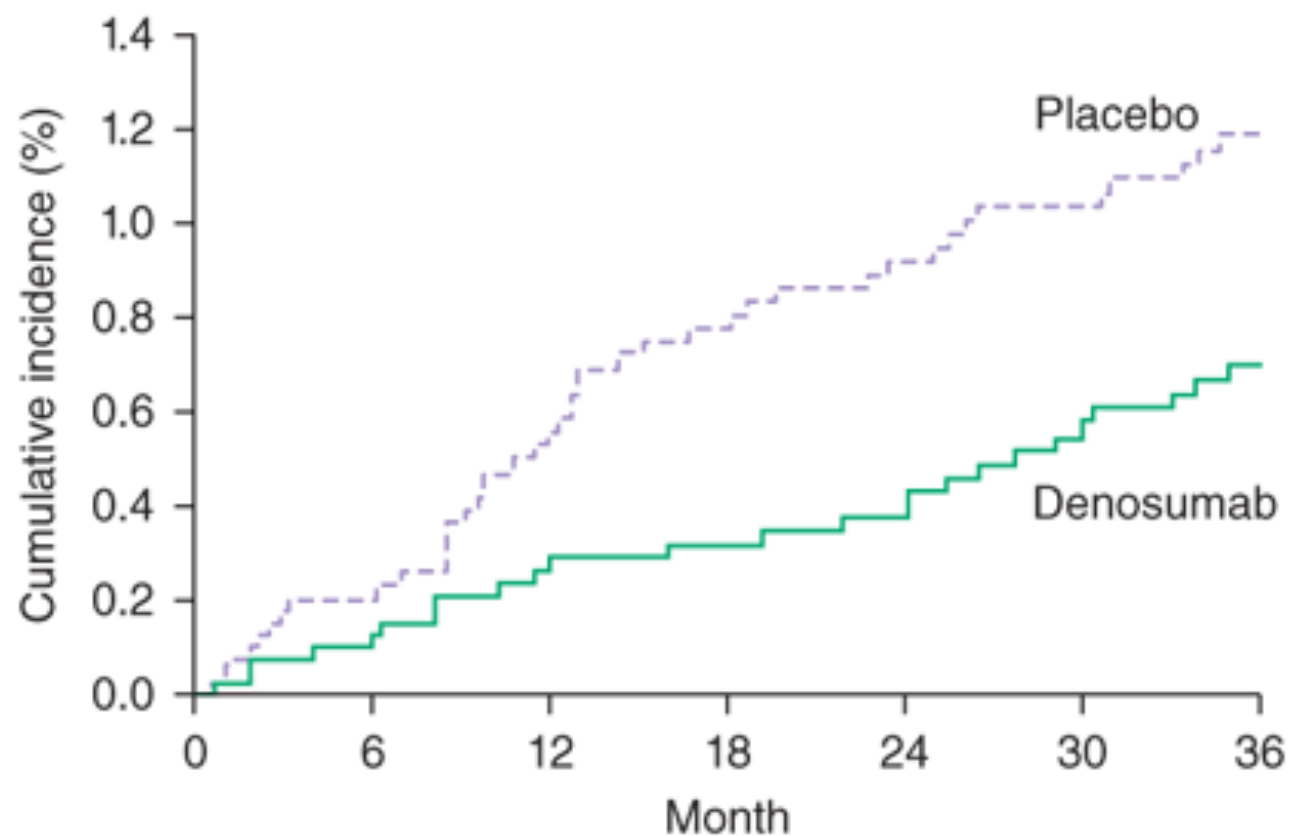
OPG = Osteoprotegerin



A New vertebral fracture



C Time to first hip fracture



No. at risk

Placebo	3906	3799	3672	3538	3430	3311	3221
Denosumab	3902	3796	3676	3566	3477	3397	3311

Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition
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ADVERSE EFFECTS: Hypocalcemia

- One limitation in the use of denosumab is the risk of hypocalcemia due to concomitant medical conditions such as malabsorption or chronic kidney disease
- In contrast to the bisphosphonates, denosumab may be administered to patients with CKD
 - effective at reducing fracture rates and increasing the BMD at all sites in patients with CKD stage 1, 2, or 3
 - stage 4 CKD, compared with placebo, denosumab increased the BMD at hip sites but had no significant effects on fracture rates

- Daily subcutaneous injection
- Promotes increasing bone density DXA
- Promotes increasing bone quality
- Should not be used in patients with current hyperparathyroidism
- Action based on intermittent use of parathyroid hormone
- Should be used only in severe osteoporosis, including consideration in patients with fractures in severe osteoporosis

- Daily subcutaneous injection
- Renal tubular calcium reabsorption
- Minimal effect on intestinal calcium absorption
- Increased bone resorption in continuous exposure, but intermittent use stimulates bone formation
- Should be used only in severe osteoporosis, including consideration in patients with fractures in severe osteoporosis
- PTHrp produced by some cancers. Primary cause of humeral hypercalcemia of malignancy

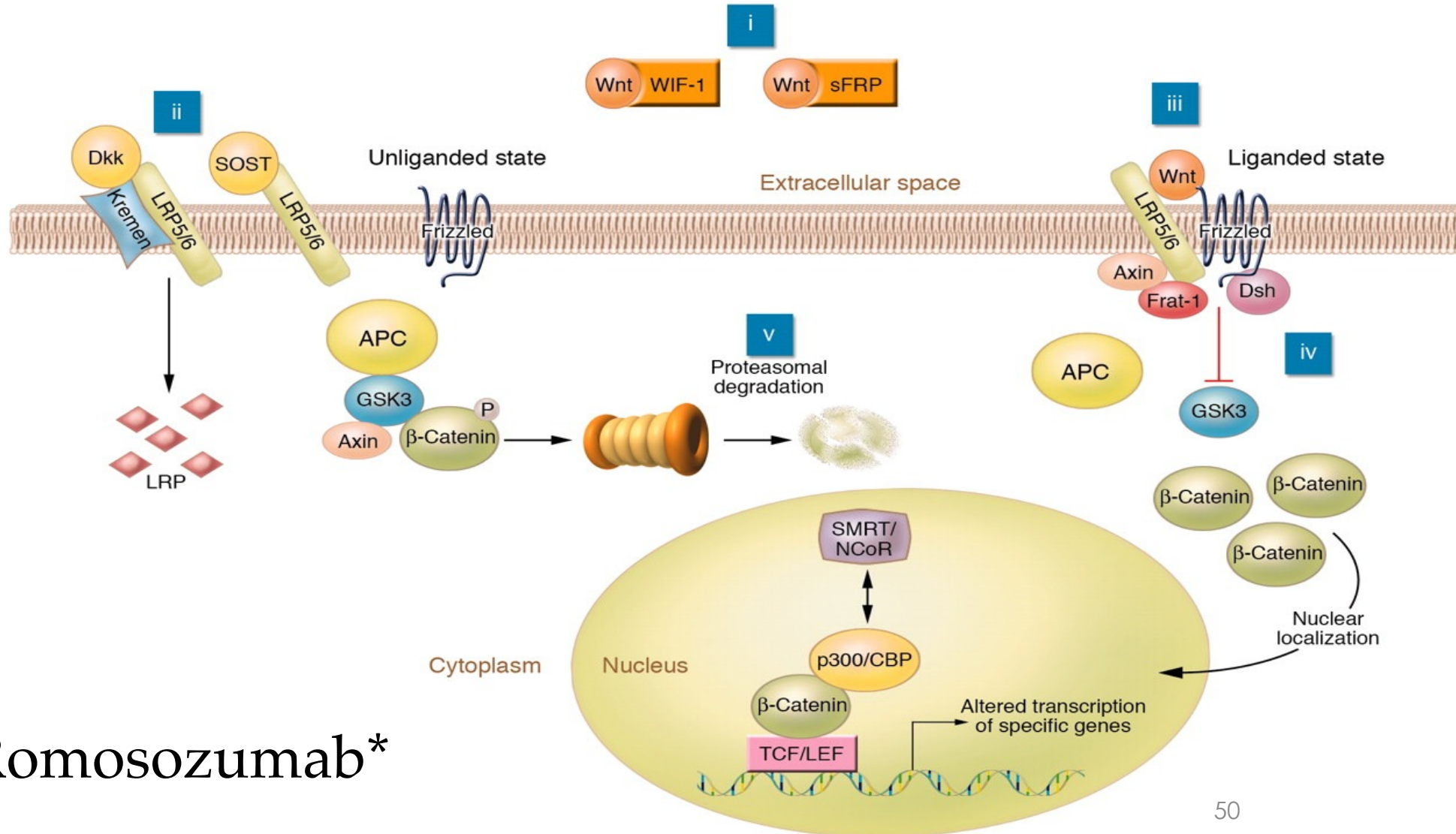
Romosozumab



*Antibody blocking sclerostin
production to increase of
production of bone & decrease of
resorption of bone*

- Increased bone formation, decreased resorption
- 7000+ post menopause women with osteoporosis on Romo for 1 year randomized vs placebo. After one year, open label denosumab every 6 months then for one year. New vertebral fractures lower with Romo at 73% ; Clinical fracture risk reduced but not significant statistics

Wnt, LRP5, Sclerostin Pathway

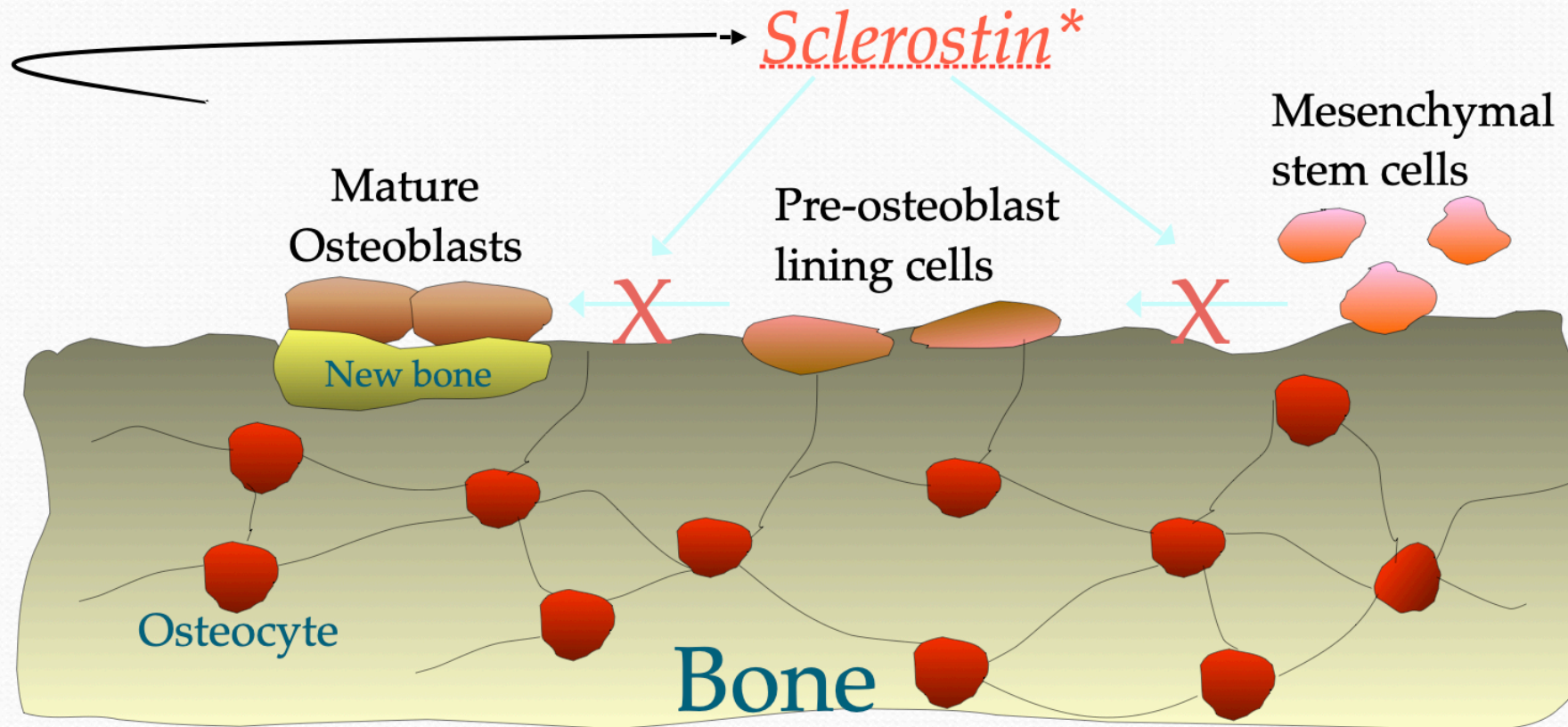


Romosozumab

Osteoblastic gene expression

Sclerostin Secreted by Osteocytes Negatively Regulates Bone Formation

Romosozumab



Ott SM. *JCEM* 2005;90: 6741-6743

Semenov MV, et al. *JBC* 2006;281: 38276

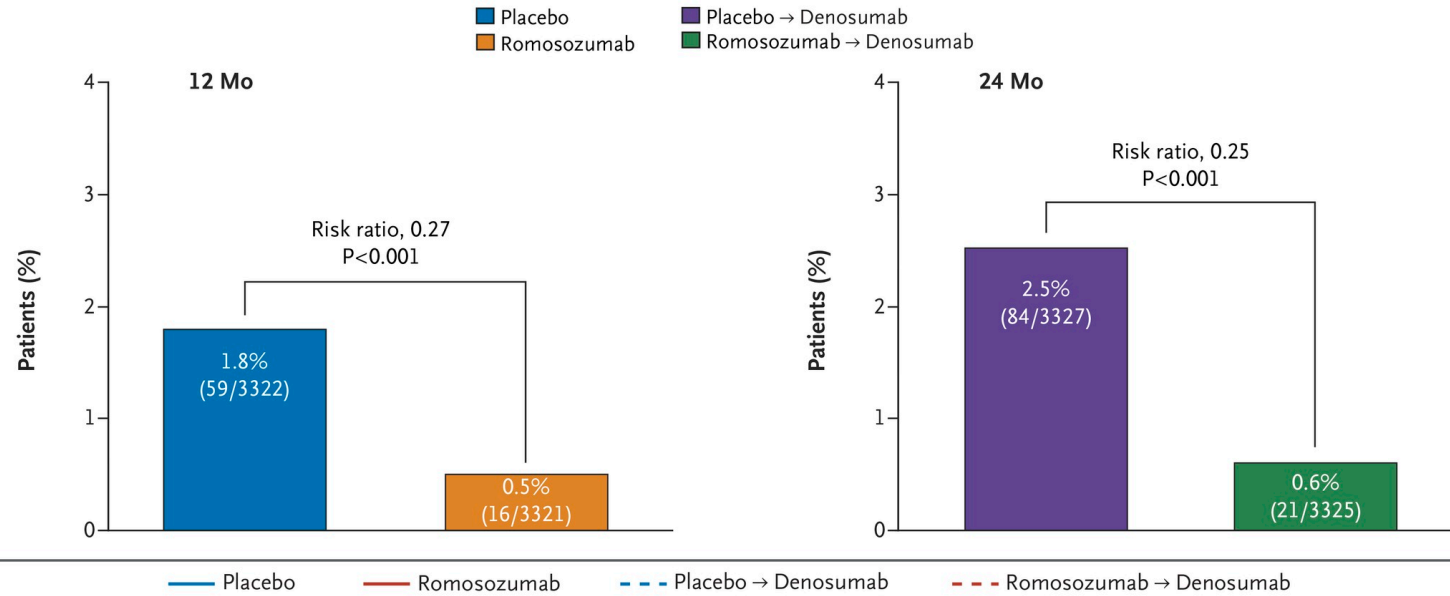
Slide courtesy of Dr. Dolores Shoback

Semenov M, et al. *JBC* 2005;280: 26770

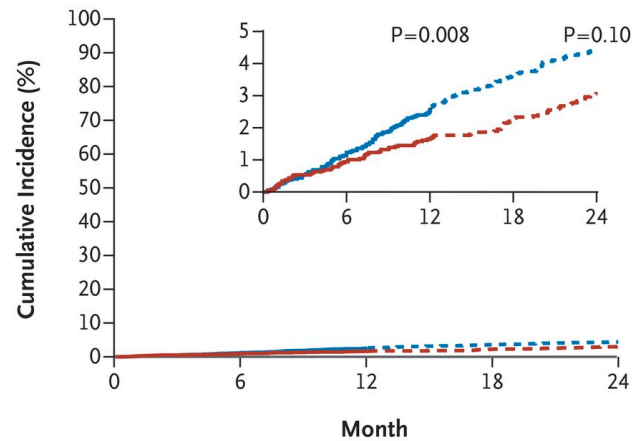
Li X, et al. *JBC* 2005; 280:19883

FRAME: Incidence of New Vertebral, Clinical, and Nonvertebral Fractures.

A Incidence of New Vertebral Fracture

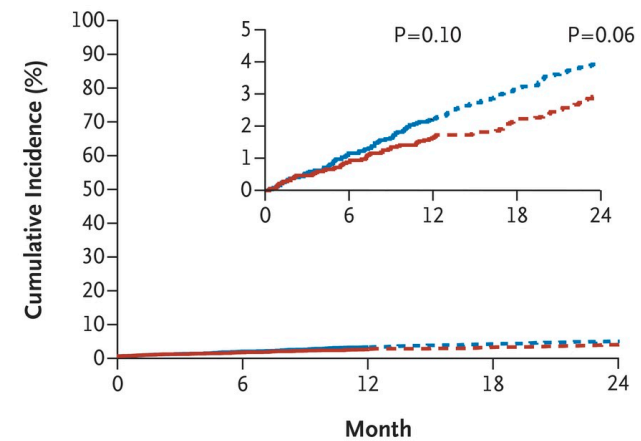


B First Clinical Fracture in Time-to-Event Analysis



No. at Risk	0	6	12	18	24
Placebo	3591	3316	3134	3037	2955
Romosozumab	3589	3317	3148	3050	2968

C First Nonvertebral Fracture in Time-to-Event Analysis

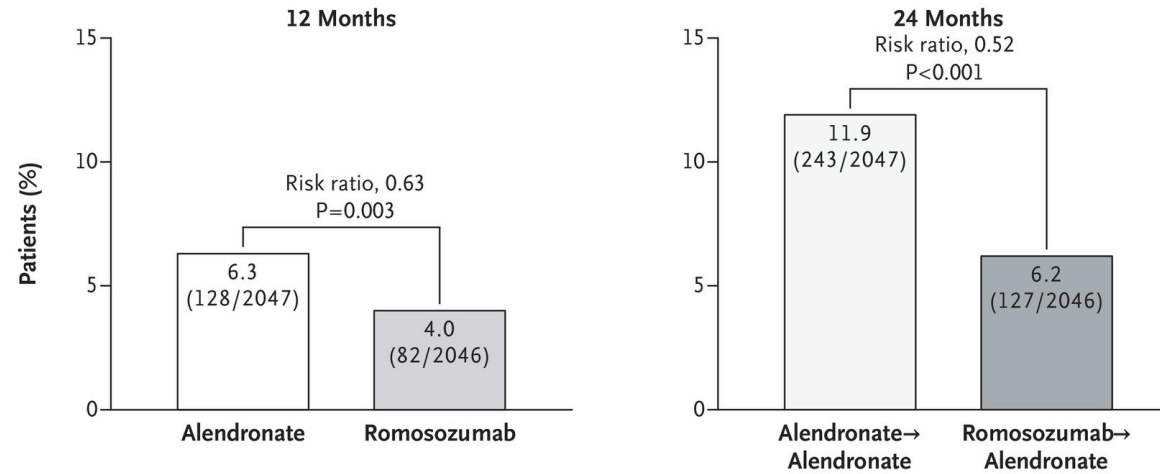


No. at Risk	0	6	12	18	24
Placebo	3591	3318	3145	3052	2967
Romosozumab	3589	3318	3149	3051	2970

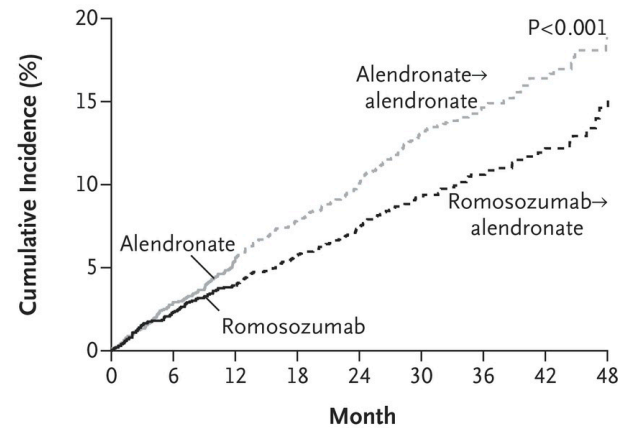
ARCH: Incidence of New Vertebral, Clinical, and Nonvertebral Fracture

Saag KG et al. N Engl J Med 2017;377:1417-14

A Incidence of New Vertebral Fracture



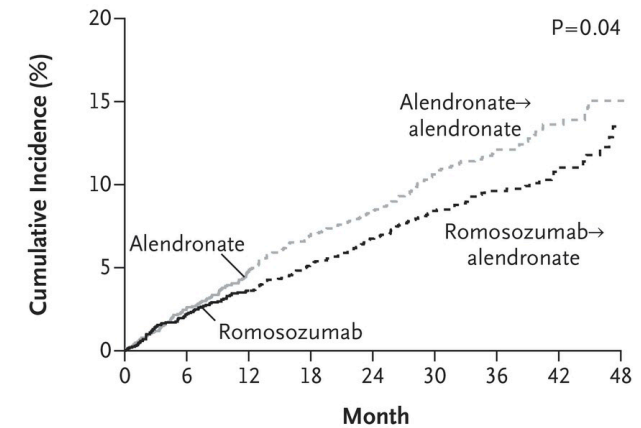
B First Clinical Fracture in Time-to-Event Analysis



No. at Risk

Alendronate	2047	1868	1743					
Romosozumab	2046	1865	1770					
Alendronate→ alendronate			1645	1564	1066	680	325	108
Romosozumab→ alendronate			1683	1615	1103	705	347	109

C First Nonvertebral Fracture in Time-to-Event Analysis



No. at Risk

Alendronate	2047	1873	1755					
Romosozumab	2046	1867	1776					
Alendronate→ alendronate			1661	1590	1097	697	330	110
Romosozumab→ alendronate			1693	1627	1114	714	350	109

Adverse Effects

- No cases of AFF or ONJ in 2 trials, but
- 1 AFF and 2 ONJ cases in a third trial.
- In one trial, more patients in the
- Romosozumab group had serious
- cardiovascular events (cardiac
- ischemic, and cerebrovascular
- accidents [0.8 versus 0.3 percent]).
- No evidence in other trials.
 - Recommended to avoid in patients
 - with recent cardiac events
- 0.2% incidence of hypocalcemia

Osteoporosis



Decreased bone strength at the level of microarchitecture resulting in higher rate of fracture

The logo for ACoi is displayed within a white circular area. The letters 'A', 'C', and 'i' are rendered in a thin, grey, sans-serif font. The letter 'o' is a solid teal circle, matching the teal background of the slide. The letters are positioned horizontally and are slightly overlapping.

ACoi

suttonendo@msn.com