Current Controversies and New Therapies in Osteoporosis

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Patient Presentation #1

- 60-year-old female referred to MGH Endocrine Associates for osteoporosis management in 2016.
- No personal history of fracture
- Mother with severe osteoporosis, hip fracture
- Bone density:
  - Total Hip T-SCORE -2.1
  - Femoral Neck T-SCORE -2.0
  - Lumbar Spine T-SCORE -2.8

Patient Presentation #1

- Treated with alendronate 70 mg weekly.
- Tolerated
- No fractures.

Patient Presentation #1

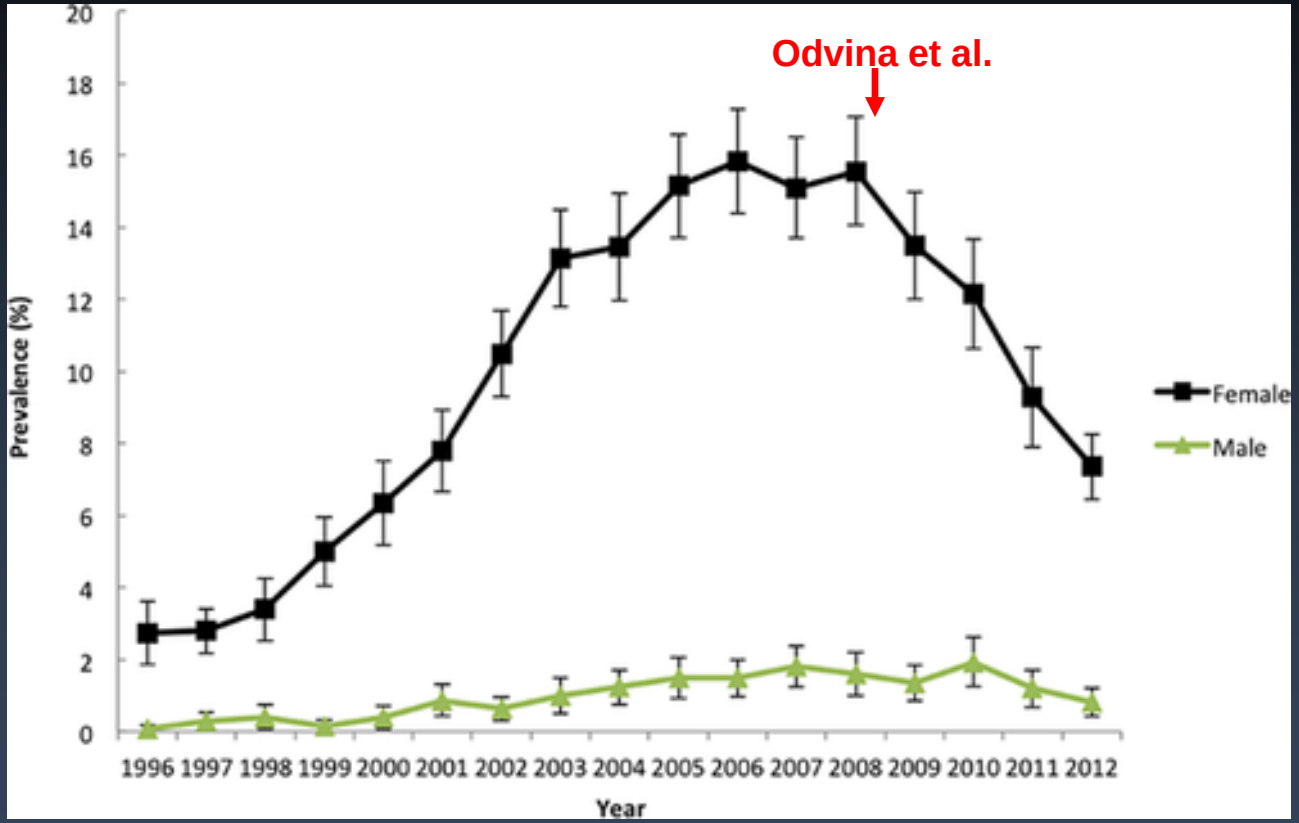
- Returned in 2020 concerned about news reports of bisphosphonate side effects.
- Wants to know if she can safely stop alendronate.
- BMD:
  - Total Hip T-SCORE -1.8
  - Femoral Neck T-SCORE -1.8
  - Lumbar Spine T-SCORE -2.5

How long should patients be treated with osteoporosis medications?

What is the evidence that long-term bisphosphonate therapy is efficacious?

What is the evidence that long-term bisphosphonate therapy is associated with serious adverse events?

Osteoporosis Treatment Rates



Jha et al, JBMR 2015

Limitations in Available Efficacy Data

- Osteoporosis treatment studies are all relatively short (2-4 years).
- Study populations higher risk than most patients.

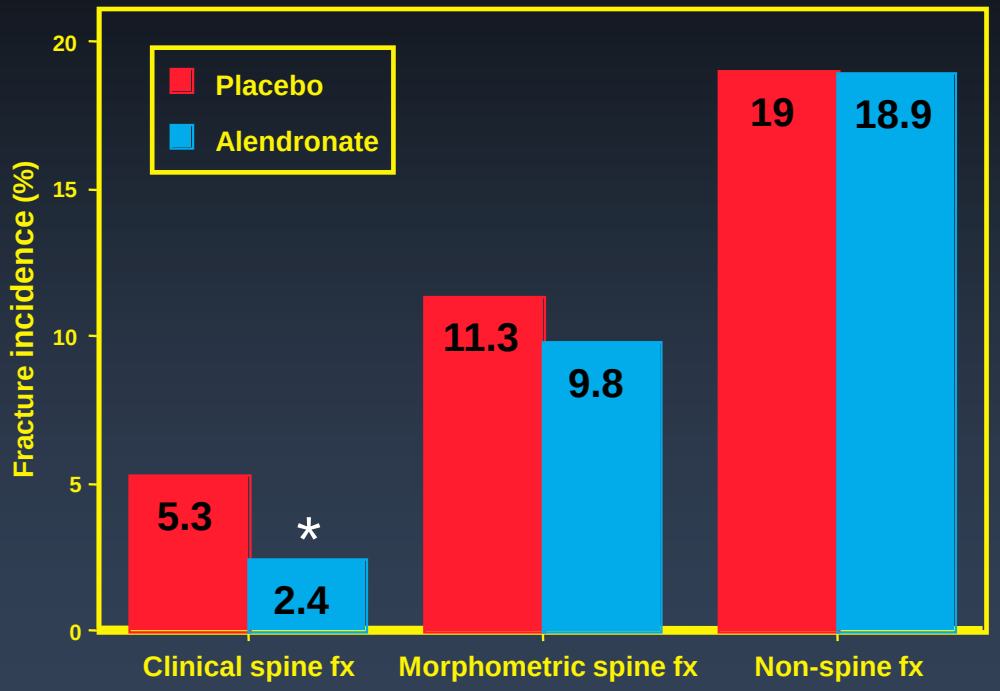
Presented Patient	FIT-1	Horizon

• Age 60
• No Fracture
• Fem Neck BMD
  • 0.62 g/cm^2
• Spine BMD
  • 0.78 g/cm^2
• FRAX 10-year Hip Fracture Risk: **1.3%**
	• Mean age 71
	• 100% with spine fractures
	• Fem Neck BMD
	  • 0.56 g/cm^2
	• Spine BMD
	  • 0.74 g/cm^2
	• FRAX 10-year Hip Fracture Risk: **6.9%**
		• Mean age 73
		• 64% with spine fractures
		• Fem Neck BMD
		  • 0.53 g/cm^2
		• Spine BMD
		  • 0.75 g/cm^2
		• FRAX 10-year Hip Fracture Risk: **8.3%**

Long Term Efficacy

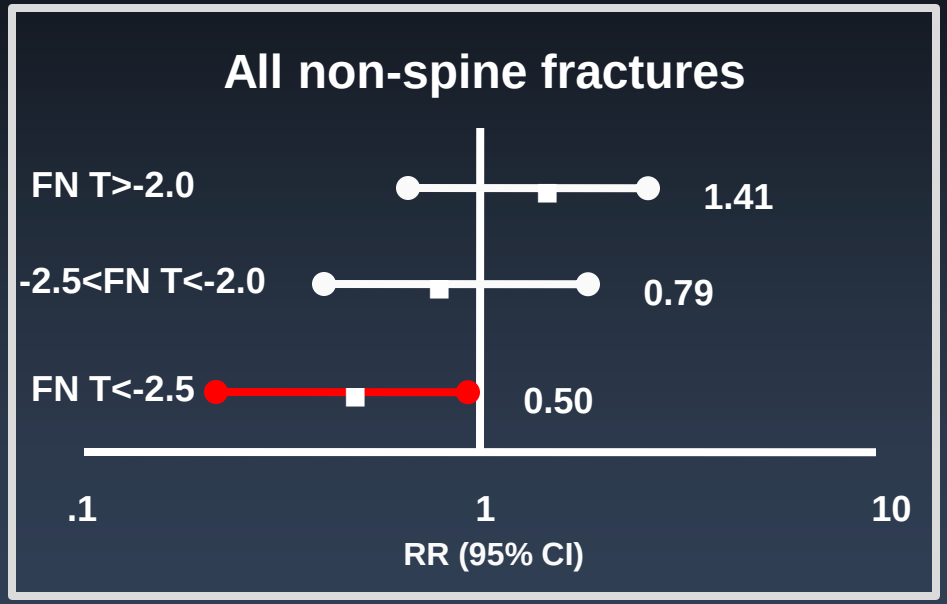
- **FLEX Study**
  - **1099 osteoporotic women assigned to alendronate group in FIT (4 years ALN 5 or ALN 10 QD)**
  - **Re-randomized to ALN 5, ALN 10 or placebo for an additional 5 years**

Long Term Efficacy: Fractures



Schwartz et al., JBMR 2010

Long Term Efficacy: Fractures



Schwartz et al., JBMR 2010

FDA Input

- **FDA's Reproductive Health Drugs Advisory Committee and Drug Safety and Risk Management:**

> **“The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.”**

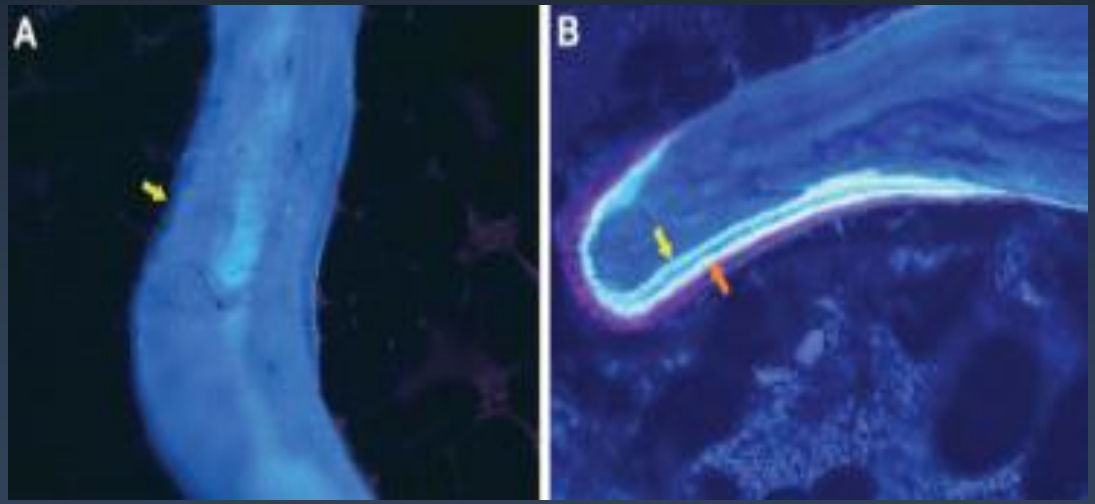
Long-term Bisphosphonate Use: Potential Issues

- Bisphosphonates are taken up by the skeleton where they remain intact for many years.
- Concern that long-term bisphosphonate use might result in accumulation of micro-fractures, increasing skeletal fragility.
  - Increase in micro-fractures but not reduction in bone strength confirmed by animal data

Unusual Fractures and Delayed Healing in Humans

- Series of case reports of unusual fractures (e.g. mid-shaft femur) and delayed or absent fracture healing during long-term bisphosphonate use

- Double tetracycline labeled bone biopsy from a fracture patient (A) and from a normal subject (B)



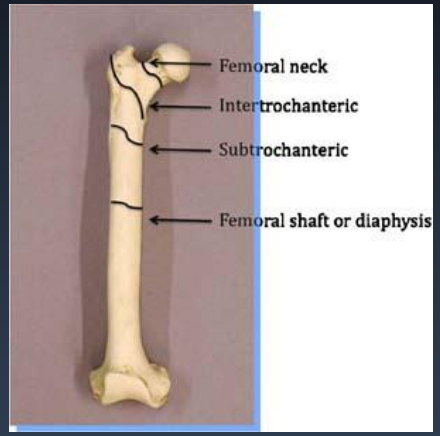
Odvina et al., JCEM 2006

Atypical Femoral Shaft Fractures

2013 Update to ASBMR Task Force Report

- **Major Criteria (4 of 5 necessary)**

1. **Minimal or no trauma**
2. **Fracture line originates at the lateral cortex and is transverse**
3. **Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex**
4. **Noncomminuted or minimally comminuted**
5. **Periosteal or endosteal thickening of the lateral cortex present at the fracture site (“beaking” or “flaring”)**



Atypical Femoral Shaft Fractures

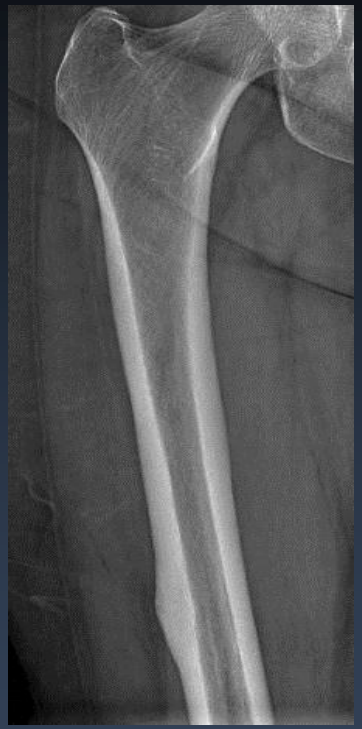
2013 Update to ASBMR Task Force Report

- **Minor Criteria**

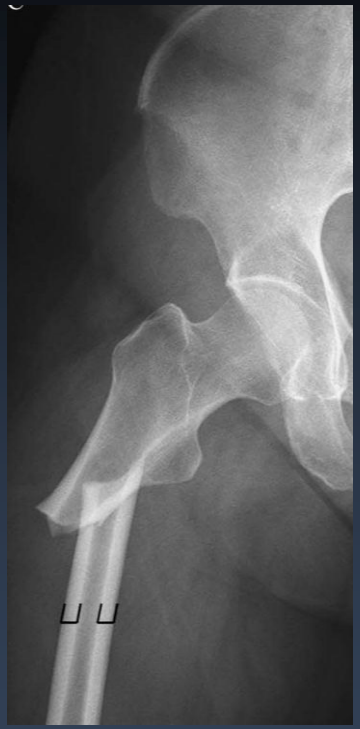
1. **Generalized increase in cortical thickness of the femoral diaphysis**
2. **Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh**
3. **Bilateral incomplete or complete femoral diaphysis fractures**
4. **Delayed fracture healing.**

Radiographic Features

Transverse orientation*



Unicortical beak



Cortical thickening

Atypical Femur Fractures: RCT Data

- Pooled data from the largest fracture prevention trials do not show an increased risk of femoral shaft or subtrochanteric fractures.
- Cannot assess presence of “atypical” features.
- Extremely limited power.

Radiograph-Confirmed Atypical Fractures

National Swedish Patient Registry cohort.

1,521,131 women 55+ in 2008, 5% bisphosphonate use

↓

12,777 women 55+ with a femur fracture in 2008

↓

1234 were subtrochanteric

↓

59 had atypical features (0.46%)

Schilcher et al. NEJM 2011

Atypical Femur Fractures: Epidemiologic Data

Risk of fracture in bisphosphonate versus non-bisphosphonate users

	BP user incidence (per 10,000 pt yr)	Non-BP user incidence (per 10,000 pt yr)	Age-adjusted Relative Risk
Any hip	151	74	1.32 (1.25-1.40)
Non-atypical ST/FS	3	1.6	1.27 (0.85-1.90)
Atypical ST/FS	5.5	0.09	47.3 (25.6-87.3)

Schilcher et al. NEJM 2011

Schilcher et al. Update 2014 NEJM

(follow-up cohort and case control analysis through 2010)

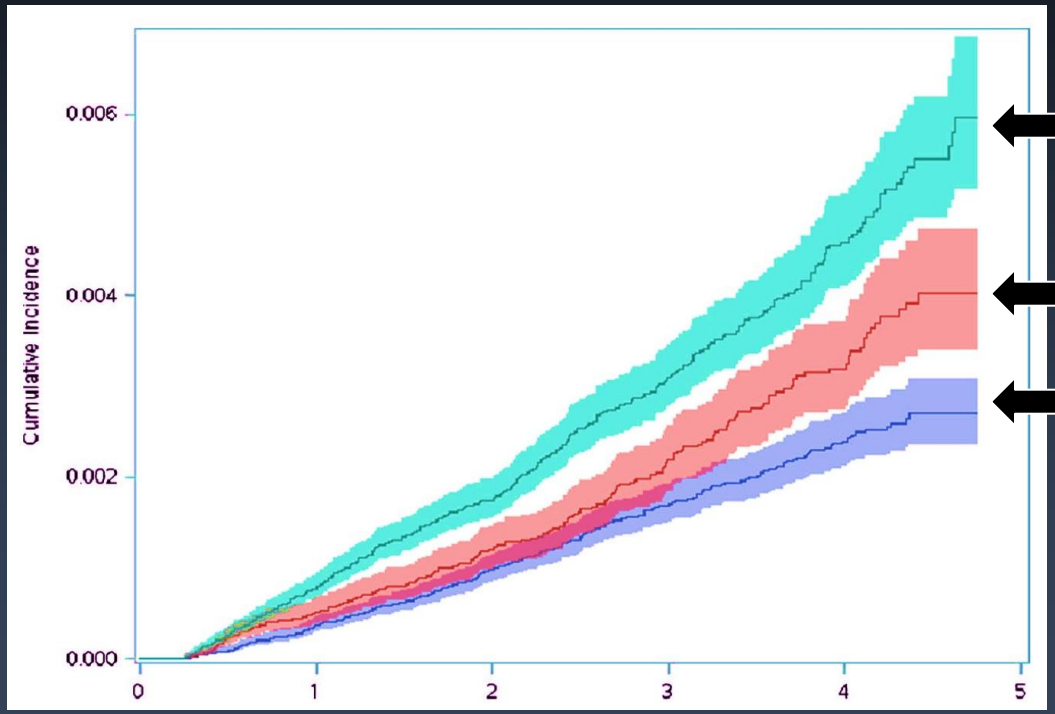
- 5342 radiographs reviewed of femur shaft fractures in men and women >55 years old and 172 atypical fractures were identified (3.2%)

Increasing risk with longer term use.

	Multivariate-adjusted OR
<1 year	1.7 (0.2-18.6)
1-2 years	8.2 (2.5-26.6)
2-3 years	28.7 (25.8-32.0)
3-4 years	39.7 (17.4-90.5)
4-5 years	116.4 (58.0-233.7)

Adherence to Bisphosphonates and Femur Shaft Fractures

- Medicare Study: 537,000 new BP users >65 years old



Wang et al. OI 2014

Atypical Fractures and Other Antiresorptives

- Reports of atypical femur fractures in patient taking the RANKL-inhibitor denosumab
  - Both unilateral and bilateral
  - Often after long term bisphosphonate use
- Reports of atypical femur fractures in patients taking romosozumab.

Atypical Fractures: Conclusions

- While the evidence does indicate an association between bisphosphonates and atypical fractures of the femur, the absolute risk of these fractures is low.
- In patients with established osteoporosis treated for 3 years, the number of fractures prevented far exceeds the number caused.
- With lower fracture risk, the risk/benefit likely rises, as it does with long term use.

Fracture	Number needed to treat
Hip	91
Vertebral	14
	Number needed to harm
Atypical	667

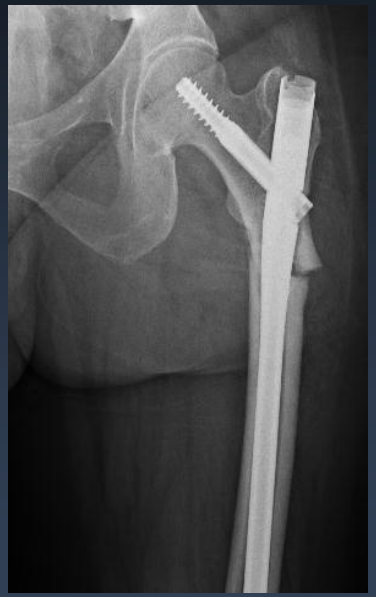
What About Drug Holidays?

- **For each year since last use, the risk of atypical fracture is reduced by 70%.**
- **Consider discontinuing therapy if the patient's BMD and other risk factors no longer meet the criteria for initial treatment.**
- **Continue therapy if the risk of fracture remains high despite a good response (switching to teriparatide also an option).**

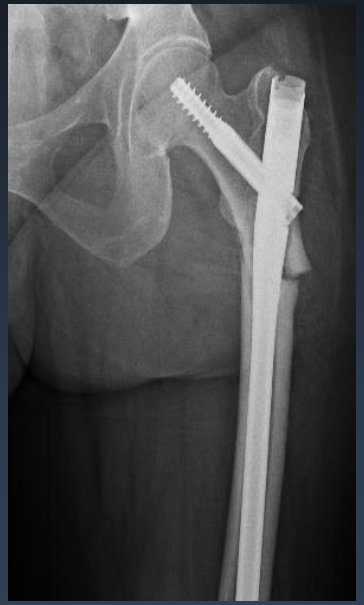
What About Drug Holidays?

- Monitor BMD 2 years after discontinuing antiresorptive medication and consider resuming if rapid bone loss ensues.
- If a patient experiences atypical fracture (or ONJ) and is still at high risk of fracture, consider changing to teriparatide.
  - Very preliminary evidence that teriparatide may be beneficial after atypical fracture, ONJ.

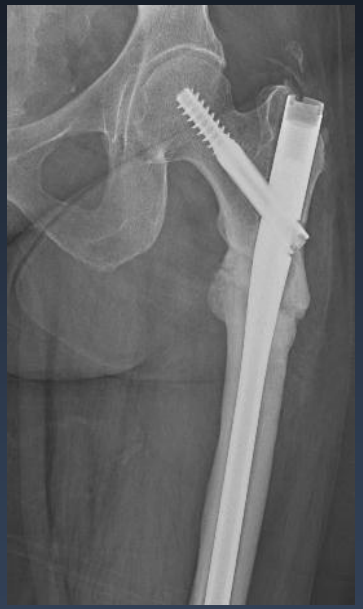
Teriparatide After Non-Healing Atypical Fracture



Fracture 2 weeks
after operative repair



Fracture 6 months
after operative repair



Fracture 4 months
after initiating
teriparatide

Drug Holidays Are Appropriate After Bisphosphonates, Not Denosumab

Patient Presentation #2

- 73 year-old male fell on ice and fractured L femoral neck.
- No glucocorticoid use. No evidence of metabolic bone disease or other endocrinopathy.
- 2/2 sisters with height loss and low BMD by DXA
- Prior to fall, felt well but reported an decrease in erectile function since his 60s and energy in past 3-5 years.
- 5 feet 9 inches, 155 pounds, normal appearance (not Cushingoid), testes 15-20 cc.

Patient Presentation #2

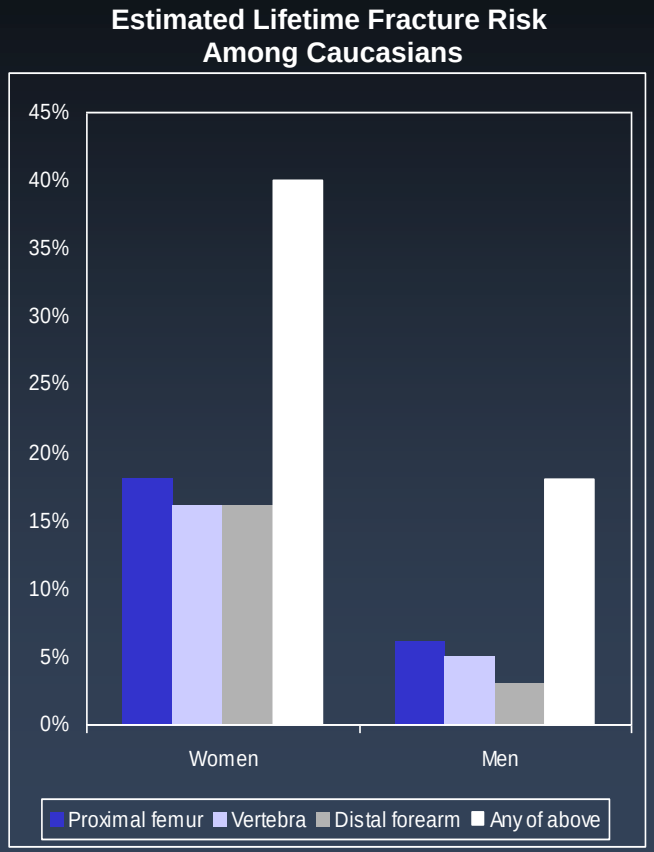
- BMD T scores: Spine= -1.8, Fem Neck=-2.3
- Ca/Phos/Alb = 9.0/3.3/4.0
- TSH =1.80
- PTH = 59 pg/ml
- 25-D = 24 ng/ml
- Testosterone = 205 ng/dl (PM)
- Testosterone (repeated) = 267 ng/dl (AM)
- LH = 7.2, PRL = 8

What is the optimal management of osteoporosis in the setting of hypogonadism (Low-T)?

Osteoporosis in Men

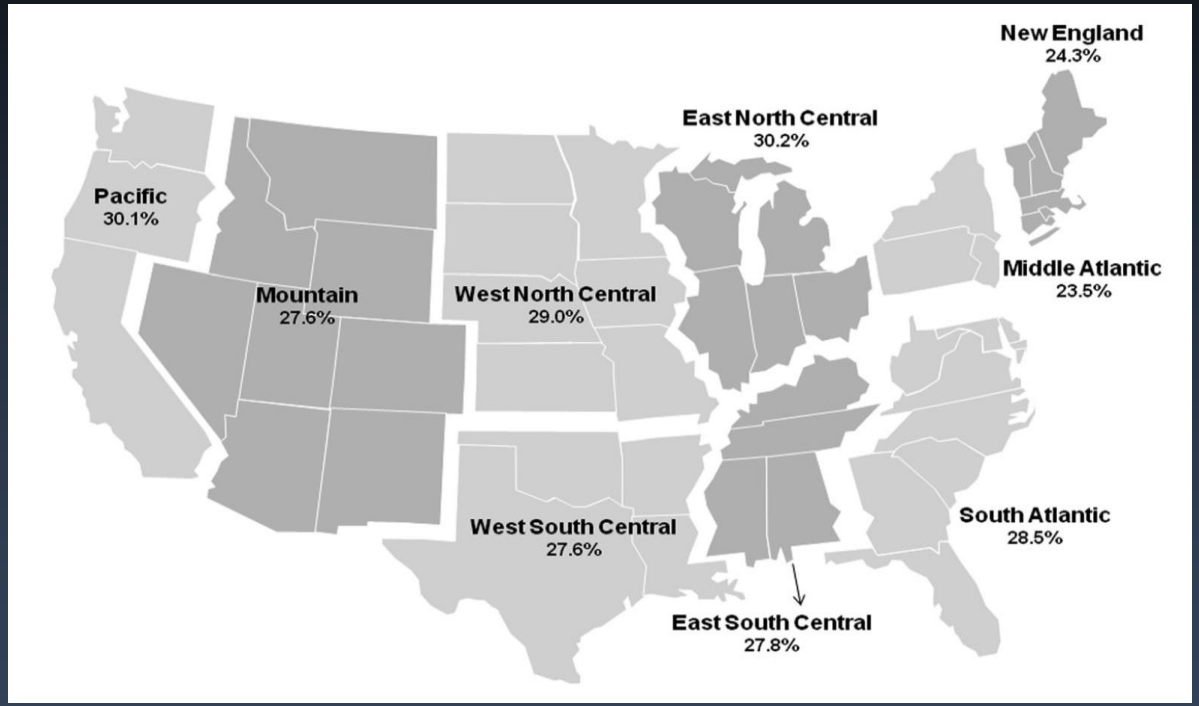
- 1 in 4 men over 50 will experience an osteoporotic fracture in their lifetime
- 30% of hip fractures occur in men
- Mortality is higher in men with hip fracture (30% vs. 10%)

(Johnell et al OI 2006 et al.)



Ignoring Male Osteoporosis:

Rates of Osteoporosis Treatment After Hip Fracture in the US



Solomon et al. JBMR 2014

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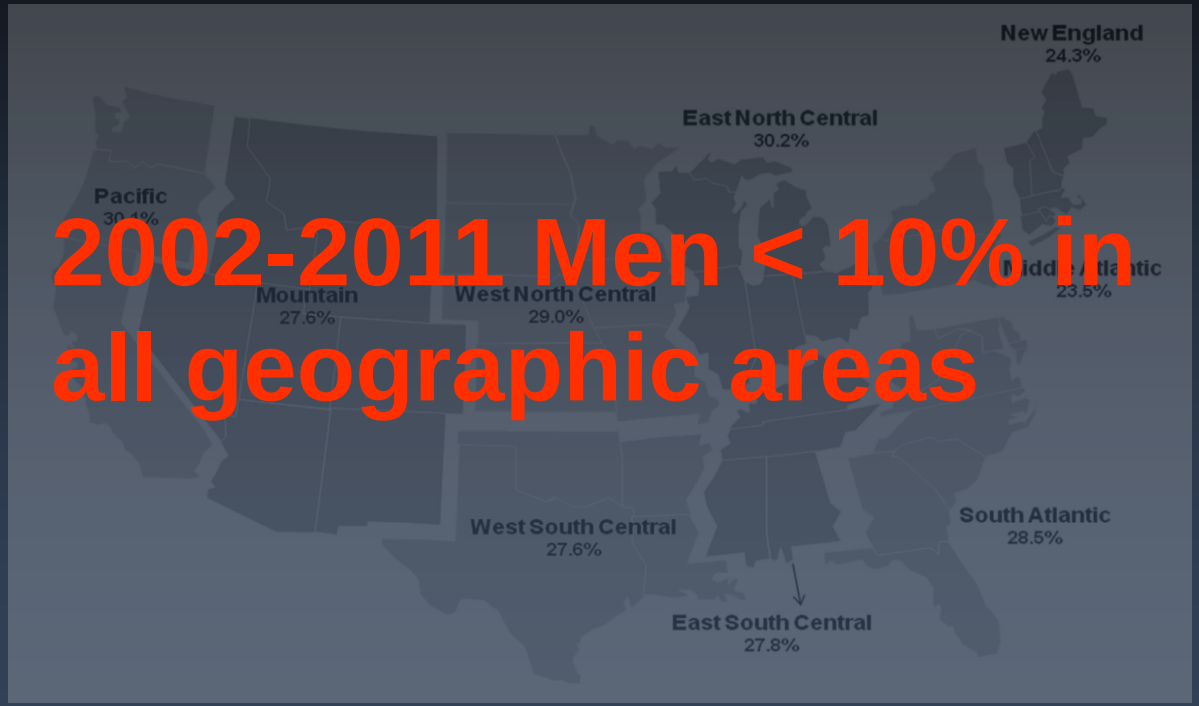
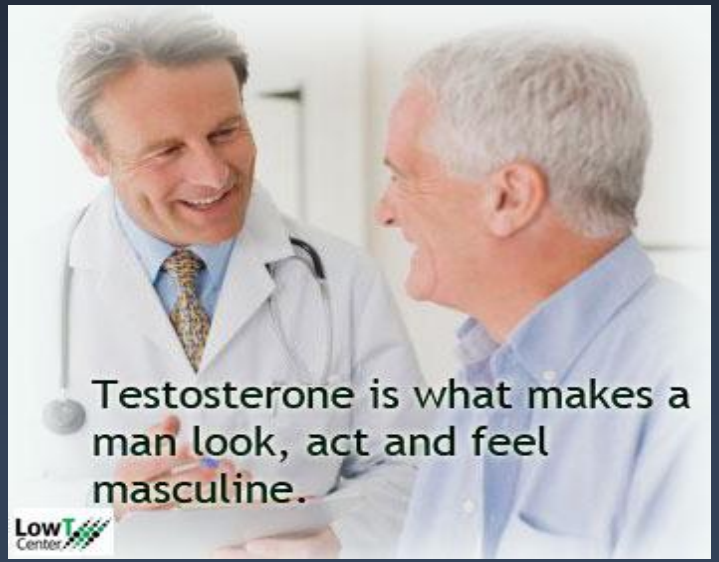


Solomon et al. JBMR 2014

Age-related Decreased Testosterone Production Has Risen

Testosterone prescription increased from 600,000 in 2002 to >3,000,000 in 2015.

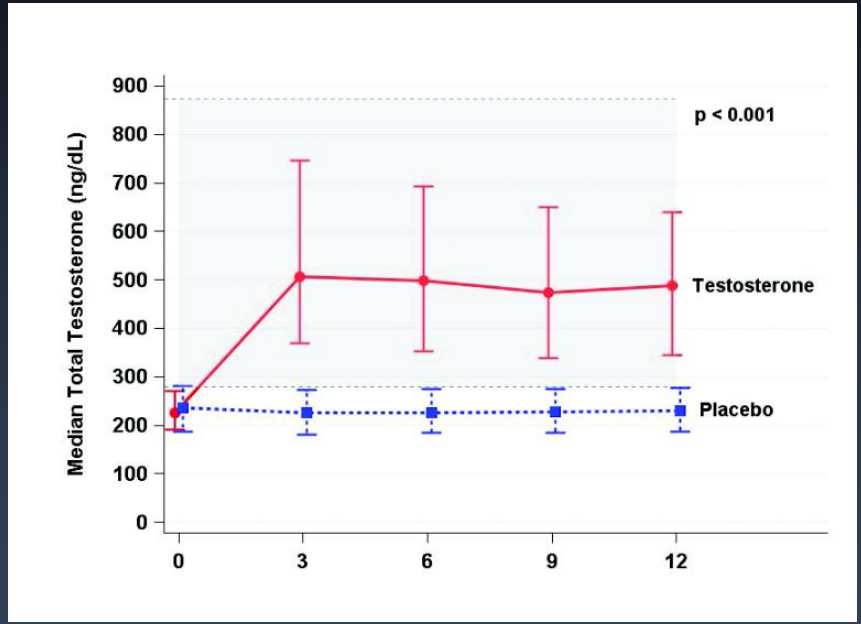


Testosterone Replacement in Older Men: T Trials

790 men 65+ with testosterone <275 ng/dl and symptoms suggesting hypogonadism.

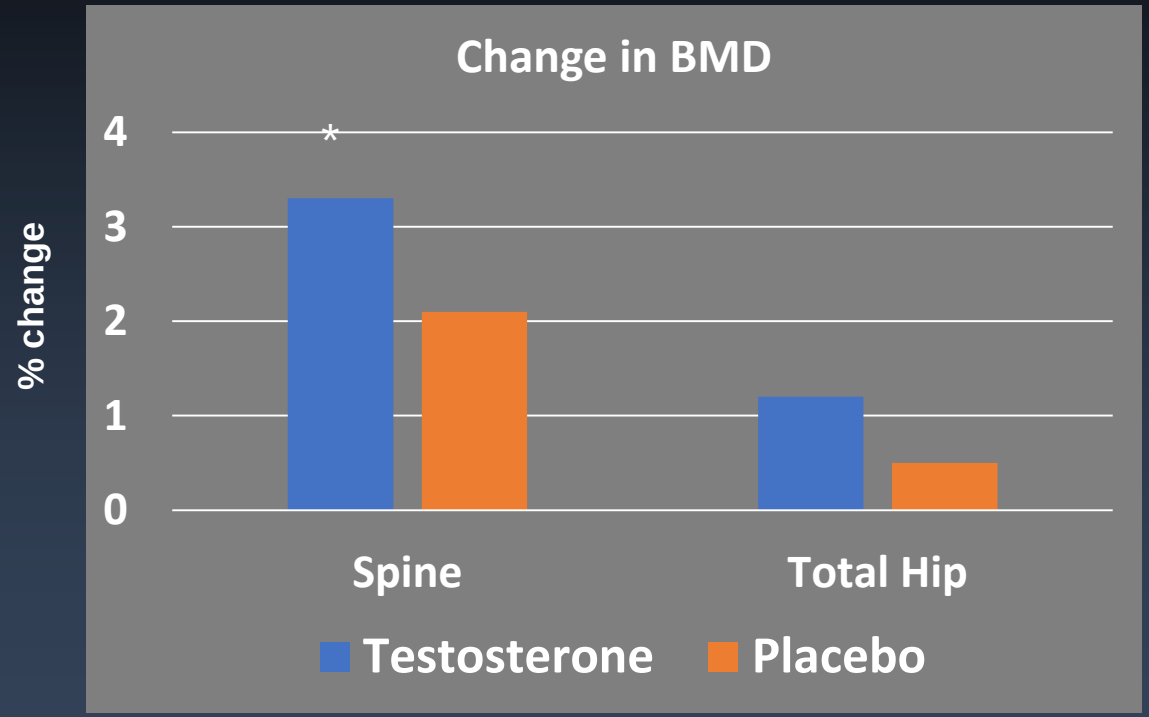
Receive testosterone gel or placebo gel for 1 year.

3 separate trials — the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial.



Snyder et al. NEJM 2016, JAMA 2017, JAMA Int Med 2017

Testosterone Replacement in Older Men: T Trials

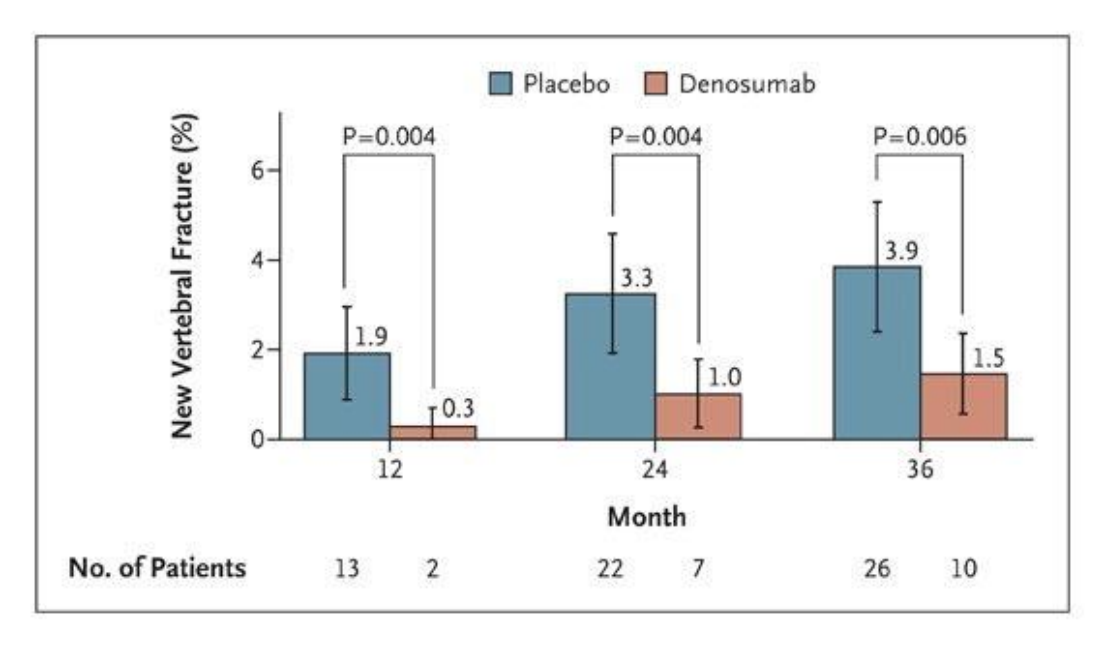


Denosumab in Androgen Deprivation

36-month double-blind, placebo-controlled trial of 1500 men with prostate cancer receiving androgen deprivation therapy

Smith et al. NEJM 2009

Relative Risk of Morphometric Vertebral Fractures

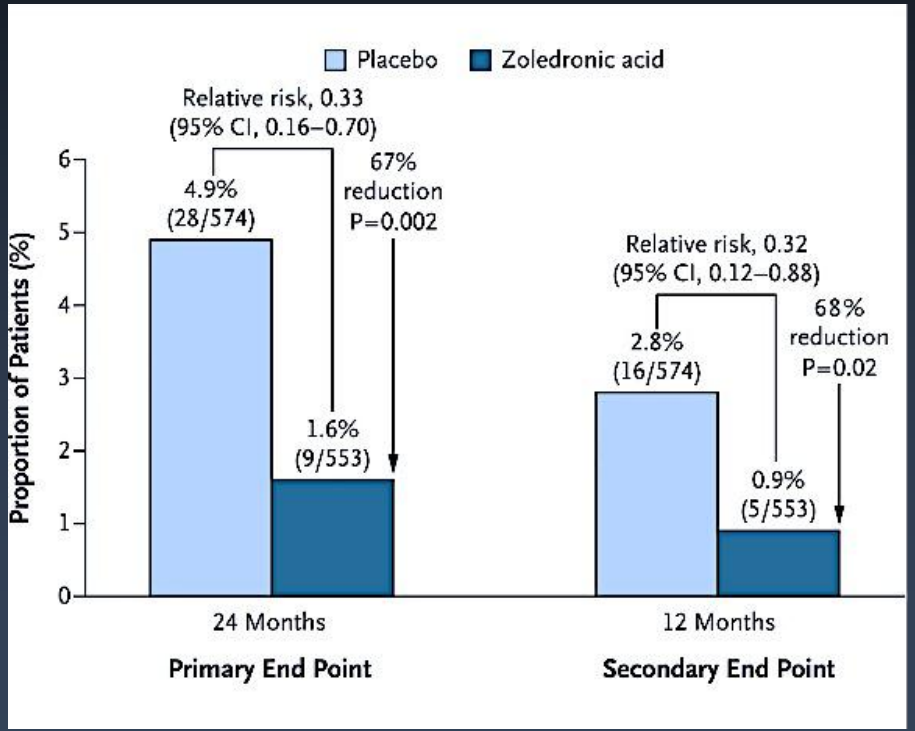


Zoledronic Acid in Idiopathic Male Osteoporosis

24-month double-blind, placebo-controlled trial of 1199 men with osteoporosis

Boonen et al.
NEJM 2012

Relative Risk of Morphometric Vertebral Fractures



Summary

- Osteoporosis in men is under-appreciated and under-treated whereas interest in treating “low T” has expanded beyond what can be supported by data.
- The beneficial skeletal effects of testosterone administration in older men with osteoporosis and moderately low testosterone levels is unproven.
- Testosterone alone should not be considered sufficient therapy for those with established osteoporosis at any testosterone level.
- Bisphosphonates, denosumab, and teriparatide are all effective in treated men with osteoporosis.

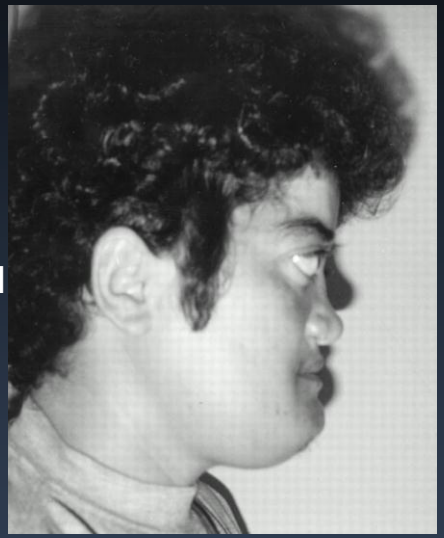
New Therapies in Osteoporosis

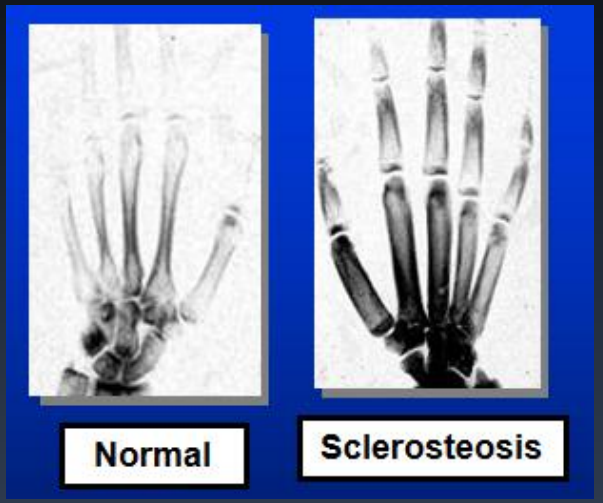
- Approved Osteoporosis Therapies
  - alendronate (antiresorptive): 1996
  - intranasal calcitonin (antiresorptive): 1995
  - raloxifene (antiresorptive): 1997
  - risedronate (antiresorptive): 1998
  - teriparatide (anabolic): 2002
  - ibandronate (antiresorptive): 2005
  - zoledronic acid (antiresorptive): 2007
  - denosumab (antiresorptive): 2010
  - abaloparatide (anabolic): 2017
  - Romosozumab (anabolic/antiresorptive):2021 approval in India – commercialization 2022-2023.

Romosozumab: Sclerostin Inhibition

Human disease: Sclerostiosis

- Good quality, fracture resistant bone
- Bone overgrowth in skull causes clinical problems
- Caused by gene defect in *sost* gene



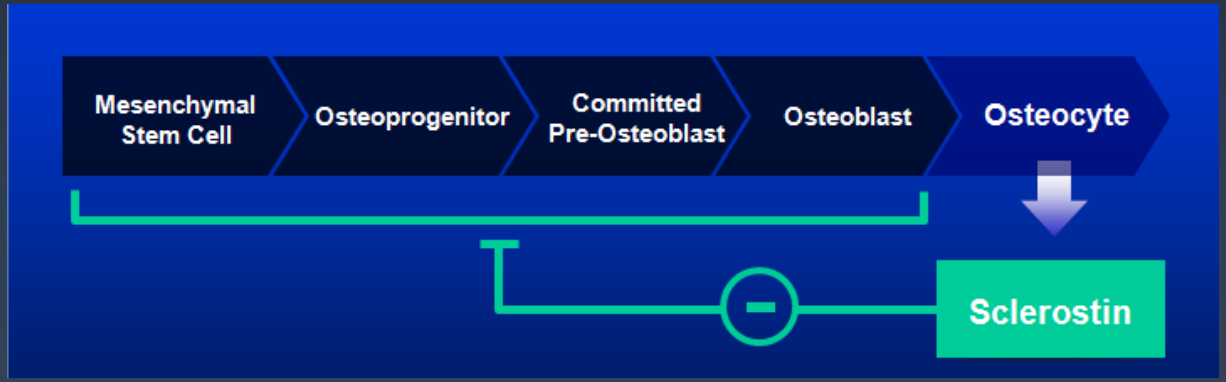


Heterozygote family members have dense, fracture resistant bone but no apparent negative health consequences

Balemans et al, Hum Mol Gen 2001

Targeting Wnt Signaling

- Sclerostin (*sost*) is a Wnt antagonist
- Wnts are growth factors that bind to a receptor complex (Fz, LRPs) initiating signaling cascades that control osteoblast function
- Wnt signaling is ubiquitous but sost is expressed only in osteocytes



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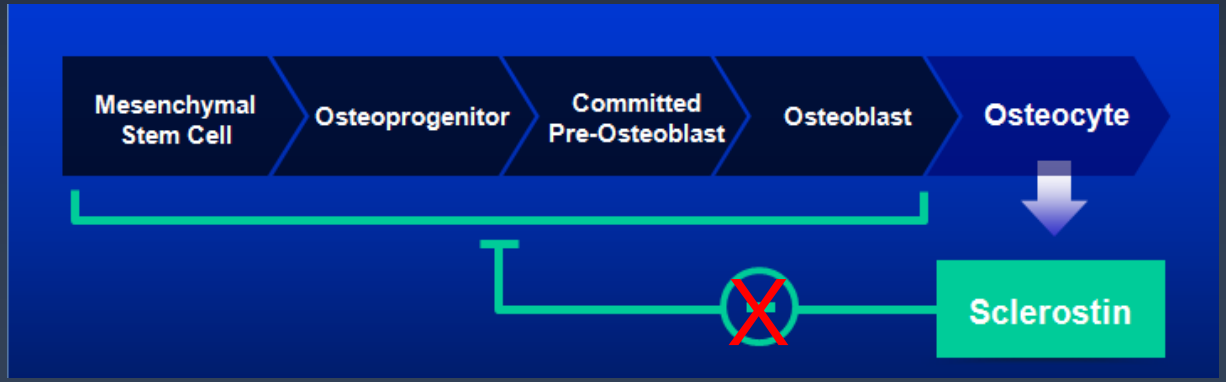
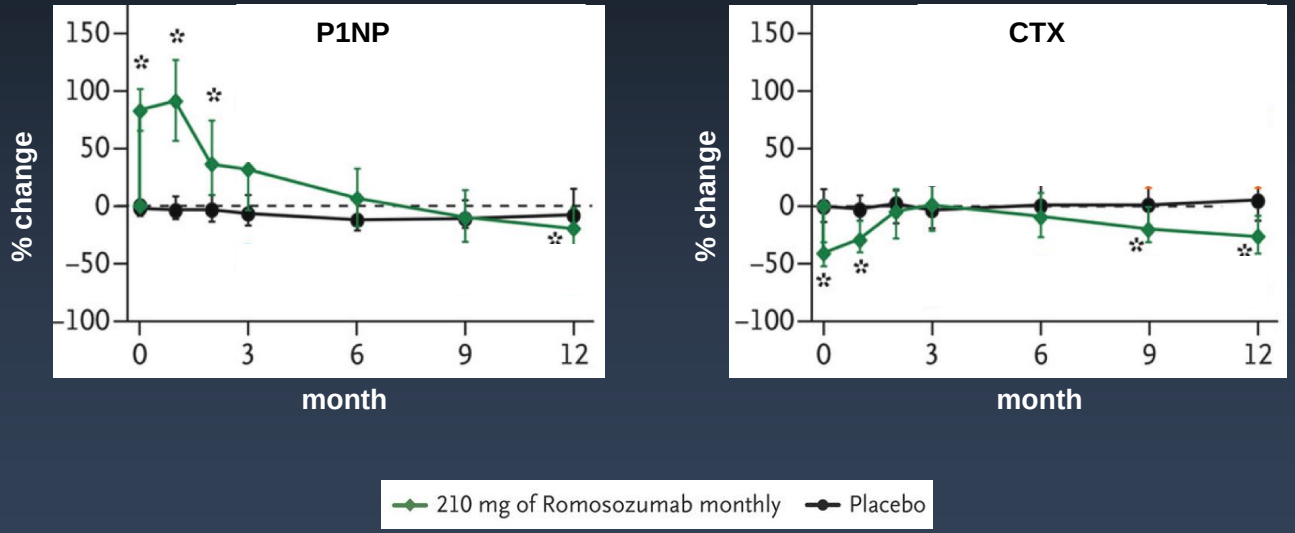


Romosozumab: Bone Turnover

- **1-year trial of sclerostin antibody romosozumab in 419 post-menopausal women.**



McClung et al, NEJM 2014

Romosozumab: BMD

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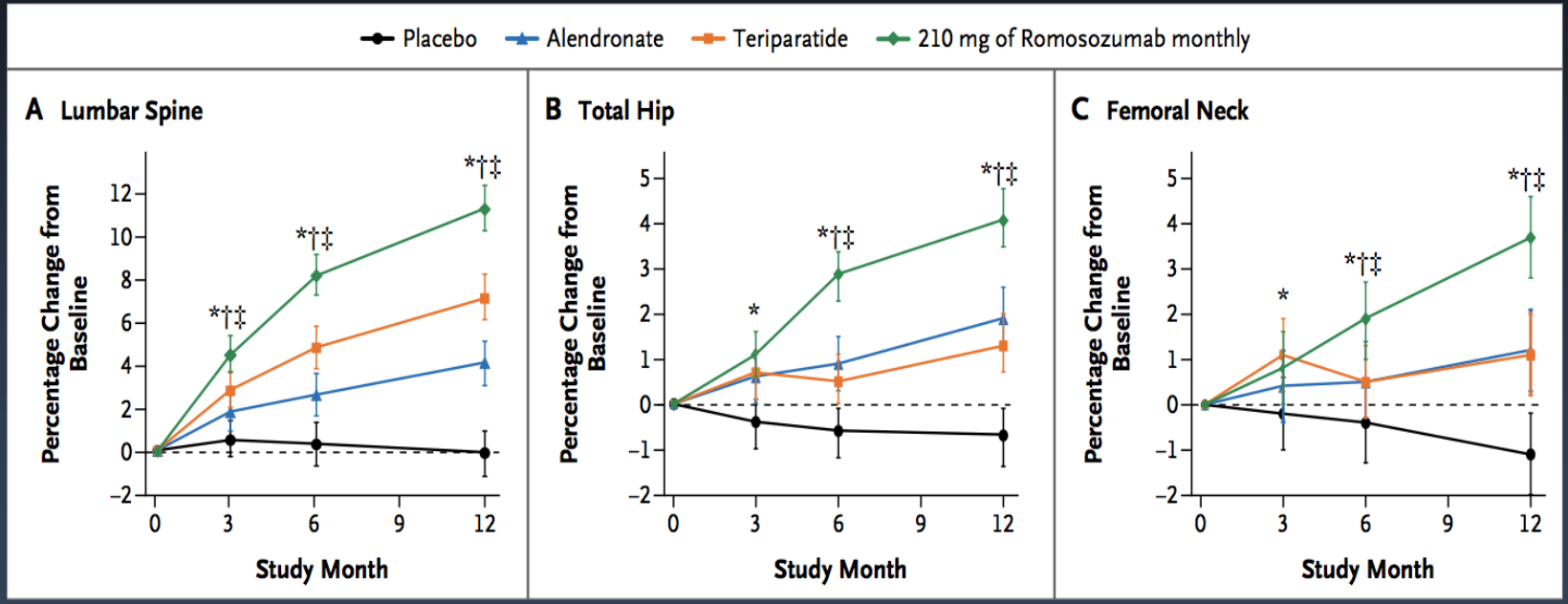
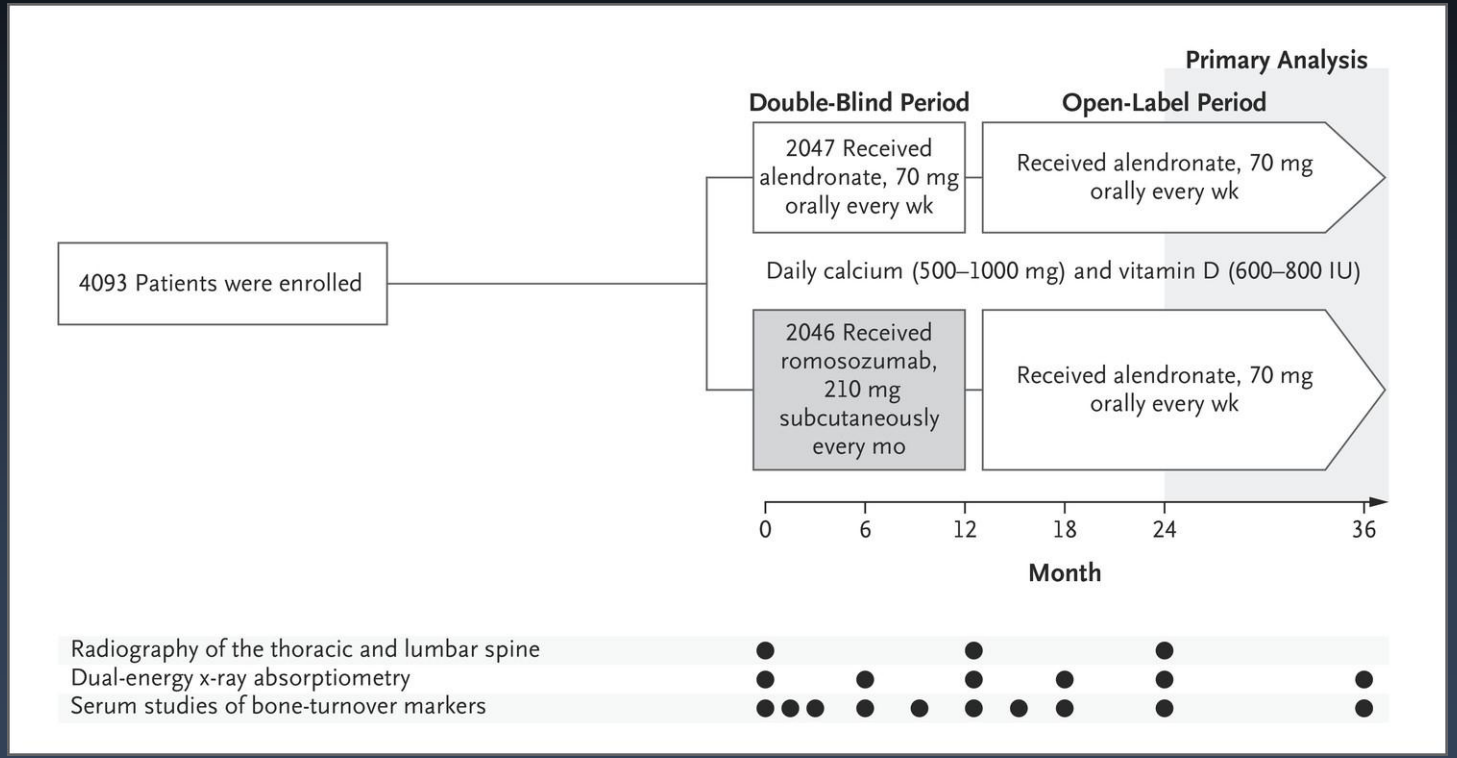


McClung et al, NEJM 2014

Romosozumab: Fracture

- **Active Comparator Phase 3 study**



Saag et al, NEJM 2017

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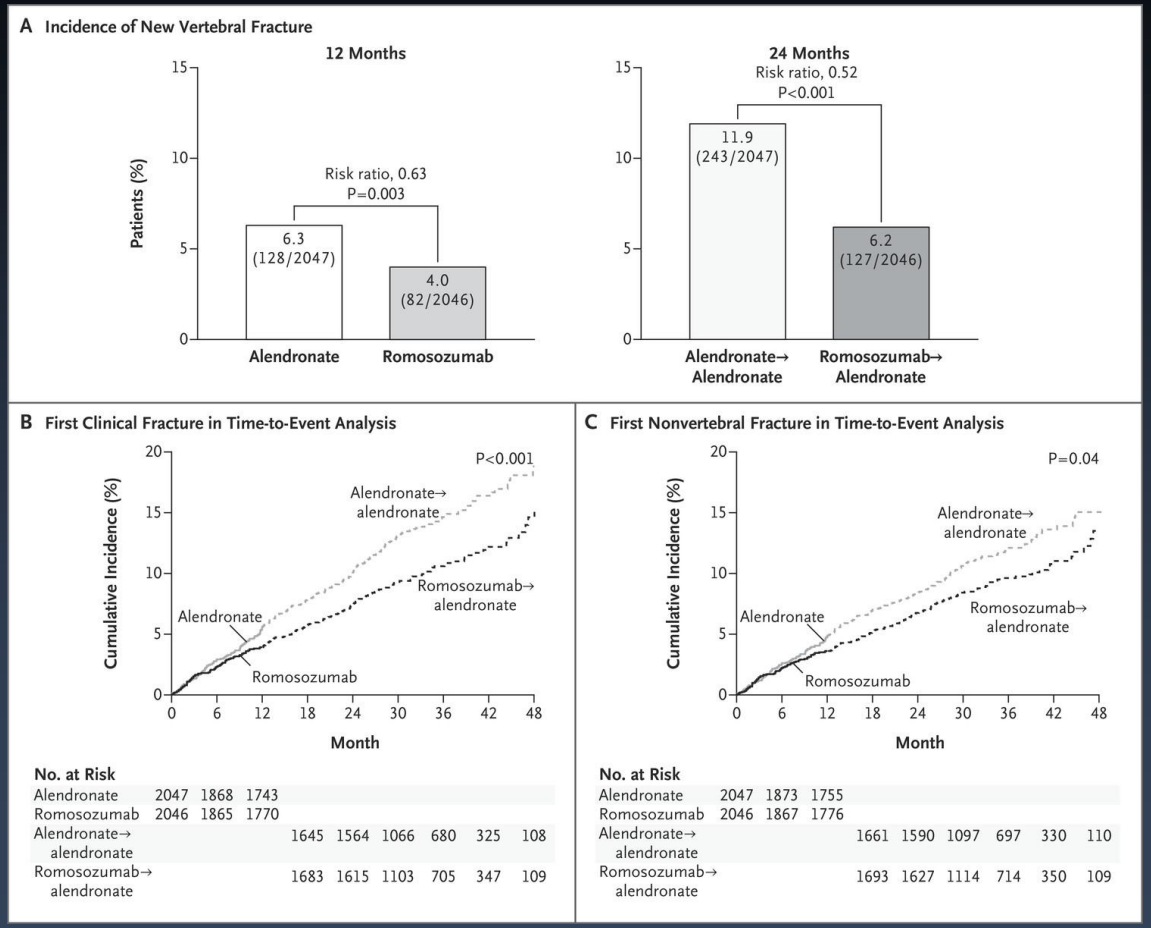

Saag et al, NEJM 2017

Romosozumab: Fracture

Table 2. Adverse Events.

Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period*	
	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate to Alendronate (N=2014)	Romosozumab to Alendronate (N=2040)
	number of patients (percent)			
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Back pain†	228 (11.3)	186 (9.1)	393 (19.5)	329 (16.1)
Nasopharyngitis†	218 (10.8)	213 (10.4)	373 (18.5)	363 (17.8)
Serious adverse event	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Adjudicated serious cardiovascular event‡	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0	5 (0.2)	2 (<0.1)
Death	21 (1.0)§	30 (1.5)	90 (4.5)§	90 (4.4)
Event leading to discontinuation of trial regimen	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Event leading to discontinuation of trial participation	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)

Saag et al, NEJM 2017

Thank You