

ACP Guidelines on Low Bone Density and Osteoporosis

Steven Ing, MD
Associate Professor-Clinical
Department of Internal Medicine
Division of Endocrinology and Metabolism
The Ohio State University Wexner Medical Center

Objectives

- **Review 2017 ACP guidelines on osteoporosis**
- **Discuss guidelines including subsequent studies**

PCP Perspective & Questions

- **Can PCPs have ACP guidelines?**
 - Don't read subspecialty guidelines
- **Too many drugs available; which ones to use?**
 - How to prioritize?
 - How common are side effects
- **How long should osteoporosis drugs continue (without being too complicated)?**
- **How often should bone density monitoring continue during therapy?**
- **Which persons with osteopenia should receive drug?**

ACP Osteoporosis Clinical Guideline (2017)

1. **Offer ALE, RIS, ZOL, DMAb to reduce fracture risk in women with osteoporosis**
(strong recommendation, high-quality evidence)
2. **Treat osteoporotic women with drug therapy for 5 years**
(weak recommendation, low-quality evidence)
3. **Offer bisphosphonate therapy in men with clinically recognized osteoporosis**
(weak recommendation, low-quality evidence)

ACP Osteoporosis Clinical Guideline (2017)

- 4. No DXA monitoring during 5 years of osteoporosis drug therapy**
(weak recommendation, low-quality evidence)
- 5. Recommend against menopausal hormone therapy (E, E&P, raloxifene) for treatment of osteoporosis in women.** (strong recommendation, moderate-quality evidence)
- 6. Treatment of women with osteopenia in women 65+ who are at high risk for fracture based on discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medication**
(weak recommendation, low-quality evidence)

ACP Osteoporosis Clinical Guideline (2017)

- 1. Offer ALE, RIS, ZOL, DMAb to reduce fracture risk in women with osteoporosis**
(strong recommendation, high-quality evidence)

Osteoporosis Medications Reduce Fractures

Drug	Generic	Spine	Non-spine	Hip
alendronate	Yes	Yes	Yes	Yes
risedronate	Yes	Yes	Yes	Yes
ibandronate	Yes	Yes	No	No
zoledronate	Yes	Yes	Yes	Yes
denosumab	No	Yes	Yes	Yes
teriparatide	No	Yes	Yes	*
abaloparatide	No	Yes	Yes	*
romozosumab	No	Yes	Yes	Yes
calcitonin	Yes	Yes	No	No
estrogen	Yes	Yes	Yes	Yes
raloxifene	Yes	Yes	No	No

Adler, J Bone Miner Res 2015;31(1):16-35

Defining “osteoporosis” for drug start

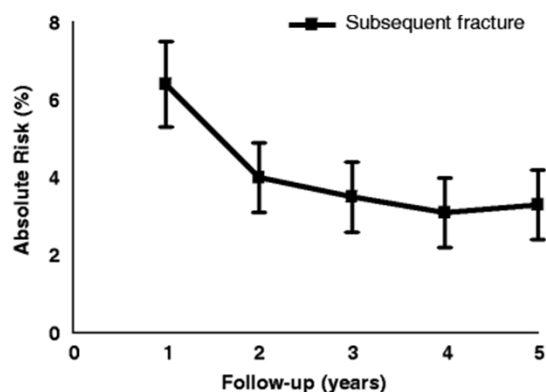
- ACP: T-score ≤ -2.5 or fragility fracture
- NOF: T-score ≤ -2.5 , FRAX Hip $\geq 3\%$, MOF $\geq 20\%$ OR
 - Fragility fracture of hip, spine (clinical or x-ray)
- AACE: T-score ≤ -2.5 , FRAX Hip $\geq 3\%$, MOF $\geq 20\%$ or OR
 - Fragility fracture of hip, spine, proximal humerus, pelvis, or distal forearm with osteopenia
- Endo Society
 - “High risk for future fracture”: recognizes nation-specific guidelines, e.g. NOF
 - Recent fracture (within 2 years) predicts imminent fracture (next 2 years)

Cosman et. al. Osteoporos Int 2014;25(10):2359-2381

Camacho, et. al. Endocr Pract 2016;22(S4):1-42

Eastell, et. al J Clin Endocrinol Metab; 2019;104(5):1595-1622

Risk of Second Fracture after First Fracture



Huntjens, Osteoporos Int 2010;21(12)2075-2082

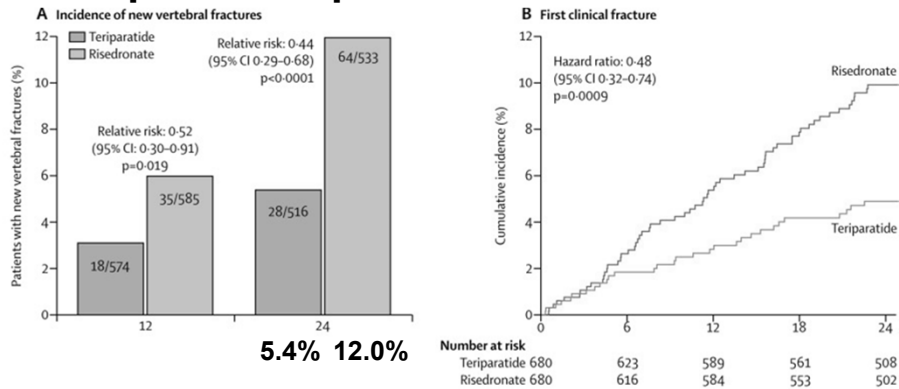
Limitations of Guidelines: Fracture Risk May Vary

	Patient 1	Patient 2
Age	58 y.o. woman	78 y.o. woman
Height, weight	67", 130 lbs	63", 115 lbs
Fxr Hx	No	Wrist fxr
Parental Hip Fxr	No	Yes
FN T-score	-2.1	-3.5
MOF risk	9.7%	62%
Hip risk	1.9%	53%

- No discussion of potential use of bone anabolic agents
- Patients continuing to fracture on antiresorptive

VERO Trial

**Double-blind, double-dummy
1360 postmenopausal women**

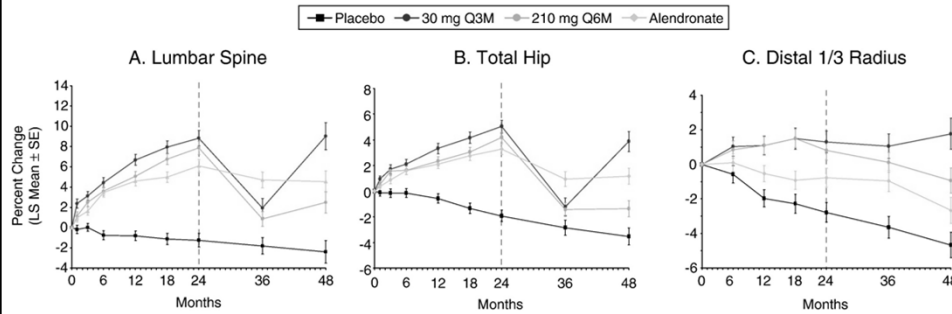


Kendler, Lancet 2018;391:230-40

ACP Osteoporosis Clinical Guideline (2017)

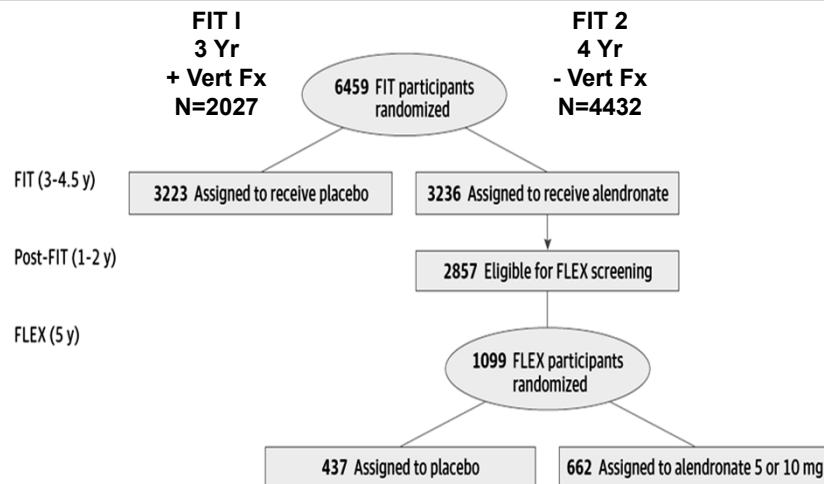
- 2. Treat osteoporotic women with drug therapy for 5 years**
(weak recommendation, low-quality evidence)

Limitations of Guidelines: No “Drug Holiday” after stopping DMAb



Miller et. al. Bone 2008;43:222-9

5 Year Tx Duration based on FLEX FLEX: 5 year extension of FIT



Black JAMA 2006;296:2927-38

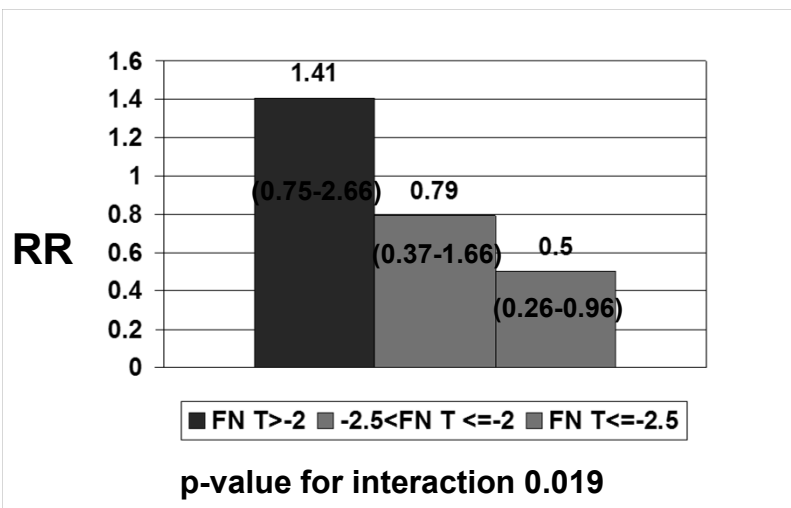
Schwartz AV JBMR 2010;25(5):976-982

FLEX: Fracture Results

Fracture Site	Placebo %	Alendronate %	RR
Morphometric Spine	11.3	9.8	0.86 (0.60-1.22)
Clinical Spine	5.3	2.4	0.45 (0.24-0.85)
Hip	3.0	3.0	1.02 (0.51-2.10)
Forearm	4.3	4.7	1.09 (0.62-1.96)
Nonspine	19.0	18.9	1.00 (0.76-1.32)
Any	21.3	19.9	0.93 (0.71-1.21)

Black DM et. al., JAMA 2006;296:2927-2938

5 year Tx does not account for variable disease severity Nonspine Fracture Risk by BMD



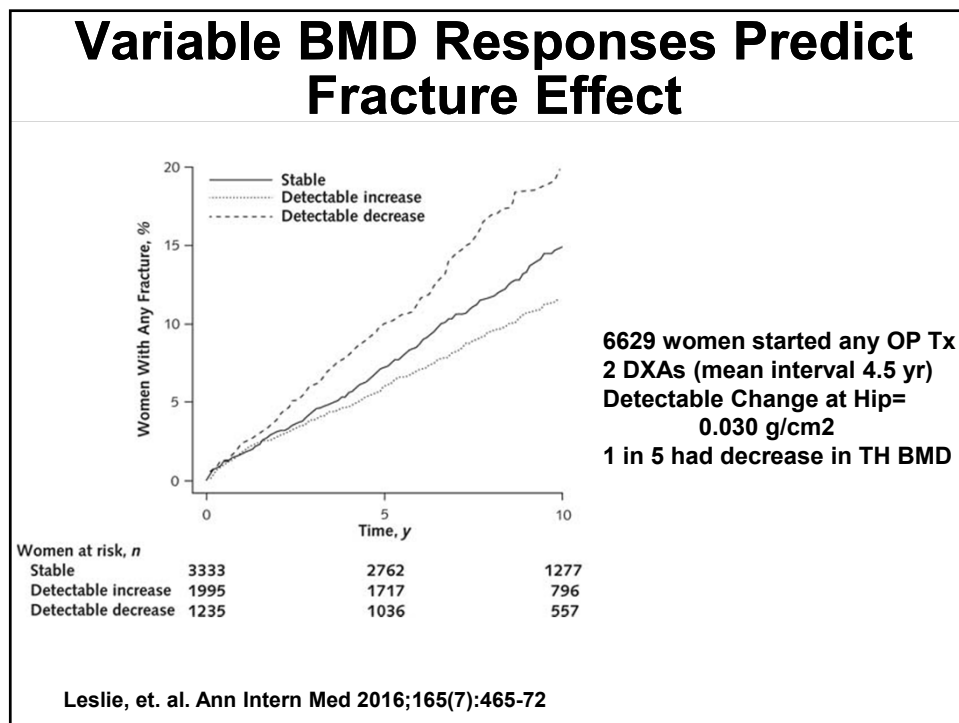
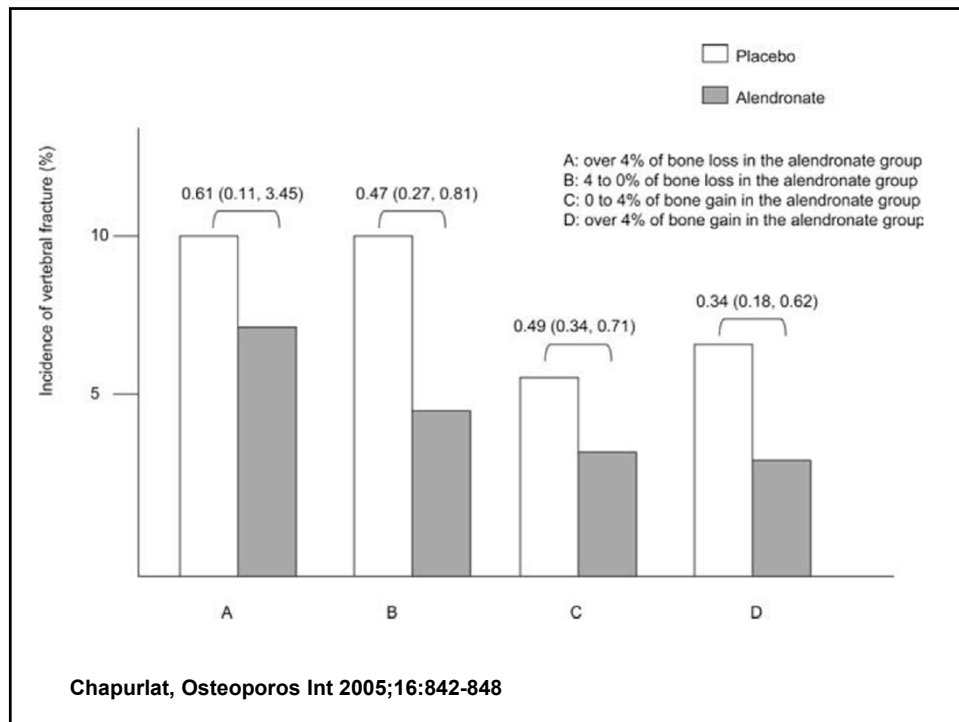
Schwartz AV JBMR 2010;25(5):976-982

ACP Osteoporosis Clinical Guideline (2017)

- 3. Offer bisphosphonate therapy in men with clinically recognized osteoporosis**
(weak recommendation, low-quality evidence)

ACP Osteoporosis Clinical Guideline (2017)

- 4. Recommend against BMD monitoring during 5-year drug treatment period**
(weak recommendation, low-quality evidence)
 - **Patient acceptability to start treatment but not monitor?**
 - **Variability in response**
 - **Determining adherence to medication**



ACP Osteoporosis Clinical Guideline (2017)

- 5. Recommend against menopausal hormone therapy (E, E&P, raloxifene) for treatment of osteoporosis in women.**

(weak recommendation, low-quality evidence)

ACP Osteoporosis Clinical Guideline (2017)

- 6. In women ≥ 65 with osteopenia at high fracture risk, incorporate patient preferences, fracture risk profile, benefits, harms, cost**

(weak recommendation, low-quality evidence)

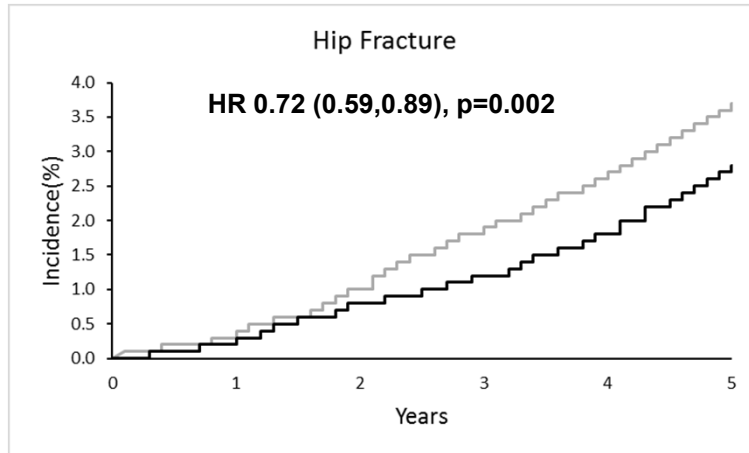
“Although FRAX is widely used, there is no evidence from RCTs demonstrating a benefit of fracture reduction when FRAX scores are used for treatment decision-making.”

SCOOP Study

RCT Women 70-85 years

6250 Usual Care

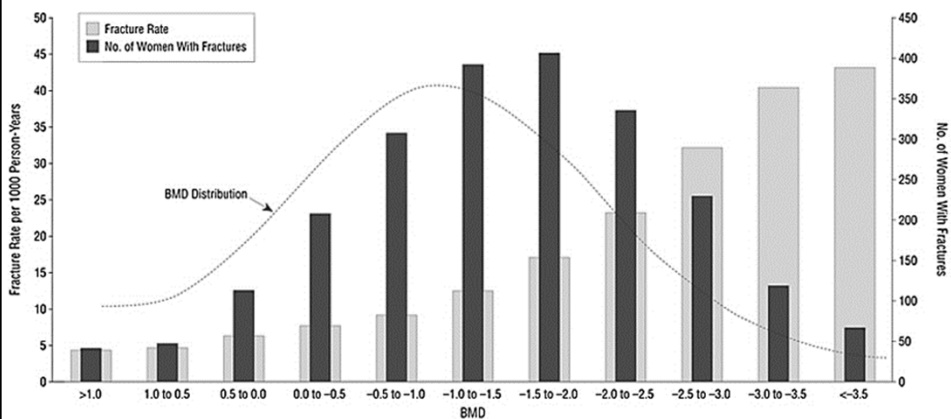
6233 FRAX screening: 14% (898) high risk → 70% started drug



Number need to treat to prevent 1 hip fracture = 111

Shepstone, Lancet 2017; (391)10122:741-7

Fracture Rates vs. # Fractures



Siris ES. Arch Intern Med 2004;164:1108-12

FRAX Limitations

- **Not all known risk factors are incorporated**
 - e.g. Falls, T2DM, CKD, Fam Hx non-hip fragility fracture
- **Dose-response not included**
 - # fractures, dose/duration of glucocorticoid, cigarettes, alcohol, secondary osteoporosis
- **Fracture risk after fracture assumed constant**
- **Valid only in untreated patients**
- **Clinical judgment necessary**

Silverman, Curr Osteoporos Rep 2010;8(4):192-7

My Revisions to Guidelines

- **Most patients can be treated with bisphosphonate or denosumab. Bone anabolic therapy may be considered as first line agent in a patient at very high risk or fracturing on therapy (and may require specialist consultation)**
- **In moderate risk OP: tx BIS x 3-5 years**
 - In high risk OP after 3-5 years consider continuing or switching to anabolic
 - DMAb cannot be stopped without switching to another agent
- **Monitor with DXA**

Conclusions

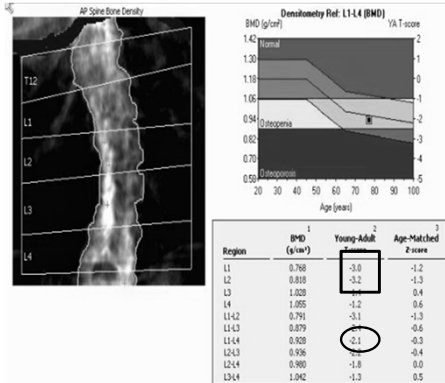
- **ACP Guideline clear, answers key PCP questions**
- **ACP Guideline will hopefully increase the numbers of at-risk persons treated**
- **Consider secondary fracture prevention**
 - Individual patient
 - Set up a program

Treatment of Postmenopausal Osteoporosis

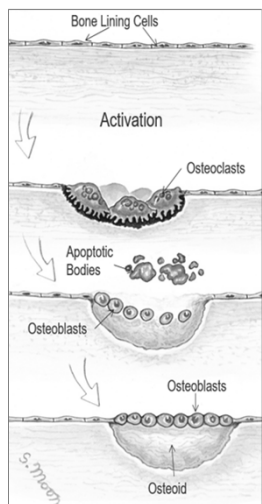
Laura E. Ryan, MD
Clinical Associate Professor of Medicine
Center for Women's Health
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University Wexner Medical Center

Case 1 – Abnormal bone density

- 63yo has screening bone density
 - Osteopenia at the spine and hip
- Has never had a fracture
- Smokes ½ ppd
- Does not require steroids
- No family history of hip fracture
- Has lost 2" of height from her youth
 - Xray shows no compression fracture –
 - but meaningful scoliosis



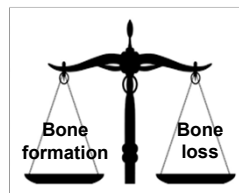
Bone lifecycle



Effects of Aging on Bone:

- Oxidative stress
- Declining autophagy
- Osteoprogenitor and osteoblast senescence
- Estrogen deficiency

In Youth:



With Aging:



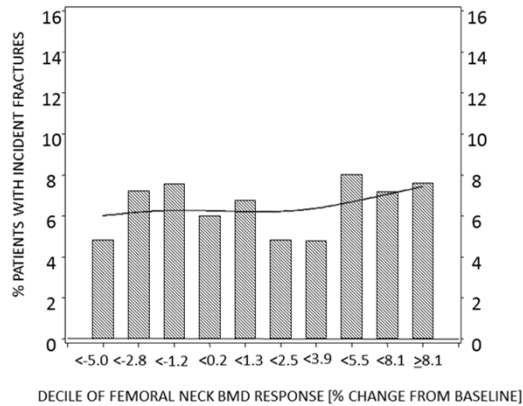
Approach to therapy of osteoporosis

- **Anti-resorptive**
 - Oral bisphosphonates: alendronate, risedronate, ibandronate
 - IV bisphosphonates: zoledronic acid, pamidronate
 - SERMs: risedronate, bazedoxifene
 - Calcitonin
- **Anabolic**
 - Teriparatide (synthetic parathyroid hormone)
 - Abaloparatide (synthetic peptide analog of PTHrP)
- **Dual action**
 - romosozumab

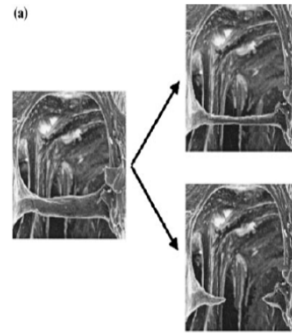
Case 1, continued

- | | |
|--|---|
| <ul style="list-style-type: none">• Secondary evaluation was unrevealing• Recommend smoking cessation• Discuss appropriate calcium and vitamin D supplementation• Begin alendronate, once-weekly<ul style="list-style-type: none">• Reviewing the importance of administration, including timing• Importance of compliance | <ul style="list-style-type: none">• She takes the alendronate and has no difficulty• After four years, she has had no fractures or height loss• She has stopped smoking• Bone density testing reveals stable bone mass – no improvement• What now? |
|--|---|

Relationship between osteoporosis-related nonvertebral fracture risk and increase from baseline in femoral neck BMD in patients treated with risedronate



Watts, et al. AACE abstract May 2005

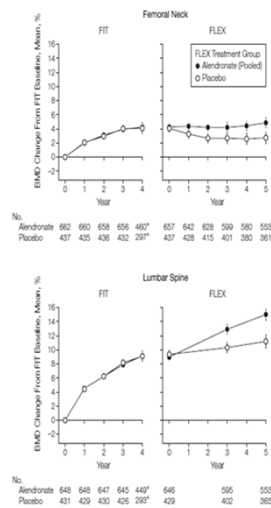


The disparity between Bone Density and Microarchitecture

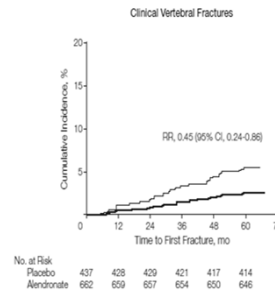
From Wehrli et al, NMR Biomed 2006; 19:731-764

Bisphosphonates: Drug Holiday

Alendronate FLEX BMD Data



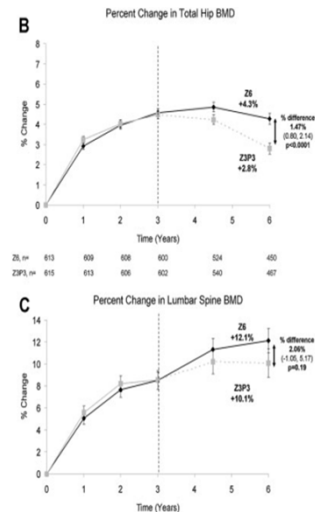
Alendronate FLEX Fx Data



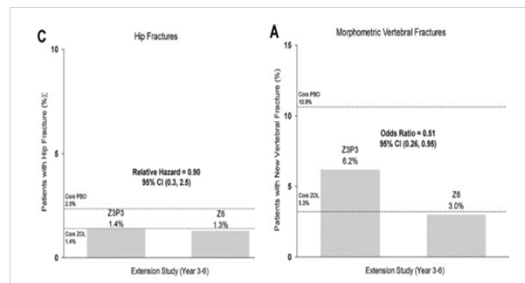
Black DM, Schwartz AV, et al. Effects of Continuing or Stopping Alendronate after 5 Years of Treatment. JAMA 2006;296:2927-2938

Not tolerating Alendronate? Non-compliant?: Zoledronic Acid, 5mg IV yearly – 3 years with holiday vs. 6 years

Zoledronic Acid Extension Trial – BMD Data

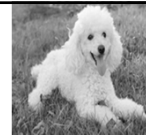


Zoledronic Acid Extension Trial – Hip and Vertebral Fractures



Black DM, Reid IR et al. The Effect of 3 Versus 6 Years of Zoledronic Acid Treatment of Osteoporosis: A Randomized Extension to the HORIZON-Pivotal Fracture Trial. J Bone Miner Res Feb 2012;27(2):243-54

Case 2:

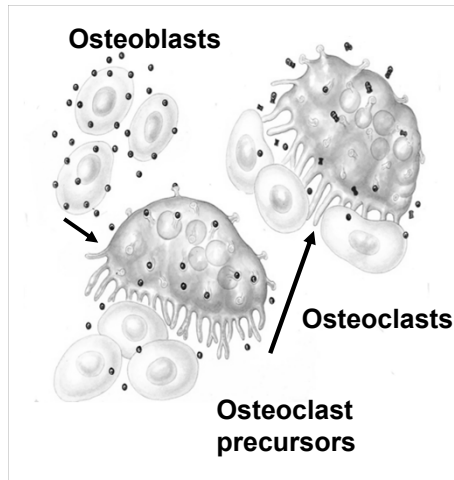


- 73yo presents for further discussion after breaking a wrist when her *poodle* pulled her over while out on a walk
- Bone density testing reveals osteoporosis at the spine, hip and femoral neck
 - *Did she really need to have bone density testing done?*
- She has a history of lupus nephritis
 - Takes prednisone 5mg daily
 - Has CRI Stage III, recent creatinine 1.45
- Secondary evaluation reveals:
 - Vitamin D 27
 - Calcium 9.2
 - PTH 62

What therapy are you considering?

Denosumab, “Prolia”

- Fully human monoclonal antibody to the receptor activator of nuclear factor kb ligand (RANKL) that blocks its binding to RANK
- RANKL is expressed on precursors of osteoblasts, marrow stroma cells and activated T cells
- Inhibits development and activity of osteoclasts
- Decreases bone resorption, increases bone density

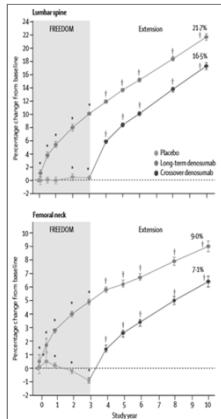


Denosumab

- 60mg subcutaneous injection, given in the provider's office every 6 months
- Well tolerated – see increased incidence of new or worsening musculoskeletal aches/pains
- Can be used in all degrees of renal insufficiency, except for ESRD and those on HD
- Contraindication: hypocalcemia
 - Reported cases of serious, symptomatic hypocalcemia
 - A particular consider for those with secondary hyperparathyroidism
- *Cannot use Drug Holiday*
 - Rapid reduction in bone density, rise in markers of bone turnover and eventually rebound increase in fractures seen with discontinuation

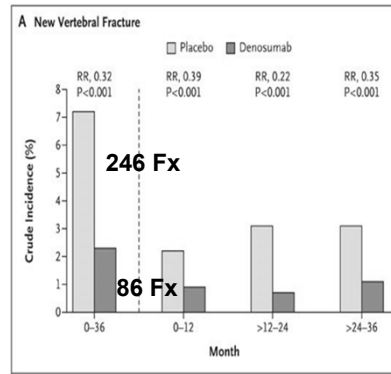
Denosumab

BMD gains show no plateau:



Bone HG, Wagman RB et al. 10 years of denosumab treatment in postmenopausal Women with osteoporosis: results from the phase 3 randomized FREEDOM trial. *Lancet Diabetes Endocrinol.* 2017 Jul;5(8):513-523

Fracture risk reduction is significant:



Cummings SR, Martin JS et al. Denosumab for the prevention of fractures in postmenopausal Women with osteoporosis. *N Engl J Med* 2009 Aug;361:756-765

Case 3

- 65yo female presents to discuss recent abnormal DXA
 - LS T-score -2.8
 - Femoral neck T-score -3.6
 - Total hip T-score -2.7
 - Never had a fracture, has lost 1.5" of height from her college days
 - Has a little bit of back pain – chronic
 - Mother fractured her hip at age 88
- Requires steroids for average of 10 days per year with episodes of sinusitis or bronchitis
- She does not smoke; drinks two glasses of wine per week
- Has started exercising with yoga and walking

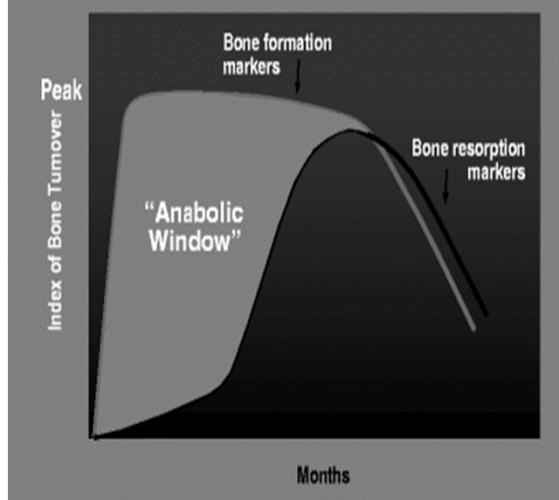
Plain X-ray reveals compression fractures at T10 and L1

Anabolics as first line?

- Those with severe osteoporosis
 - T-score at any site ≤ -3.5 with or without fracture
 - T-score ≤ -2.5 with a low-trauma fracture
- Those who have osteoporosis but cannot tolerate or have contraindications to bisphosphonates
- Second line?
- Those who fracture or who have significantly reduced bone density in spite of compliance with anti-resorptive therapy

Given cost, daily subcutaneous injection, long-term safety concerns and availability of other agents, anabolics still not routinely used as first-line treatment of PMO

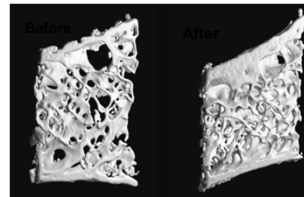
PTH as an Anabolic Agent for Bone: A Kinetic Model



Girotra M Rev Endocr Metab Disord 2006 Jun;7(1-2):113-21

Anabolic Therapy for Osteoporosis

**Osteoblast stimulation,
largely trabecular bone**



Images courtesy David Dempster

Teriparatide (Forteo)

- PTH 1-34, synthetic
- 20mcg daily
- Daily subcutaneous injection
- FDA approved 2002 PMO
 - Also glucocorticoid induced osteoporosis, and OP Men
- Use 18 – 24 months x 1
- FDA warning: osteosarcoma

Abaloparatide (Tymlos)

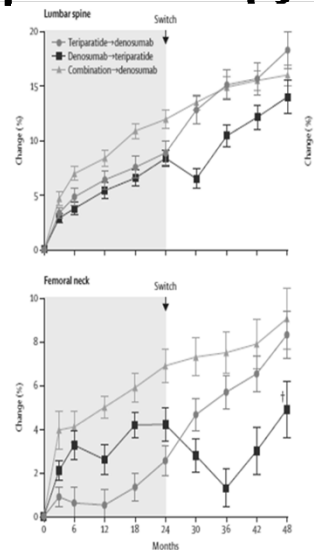
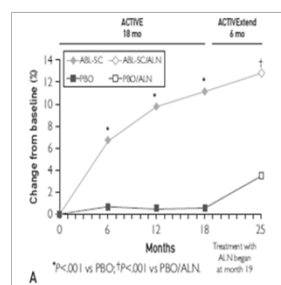
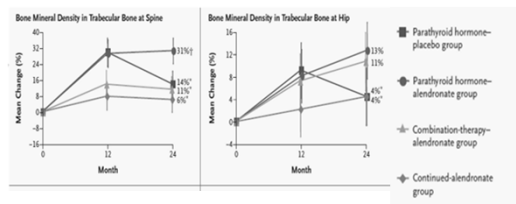
- PTHrP analog, synthetic
 - More rapid binding then unbinding with less hypercalcemia
- 80mcg daily
- Daily subcutaneous injection
- FDA approved 2017, PMO
- Use 18-24 months x 1
- FDA warning: osteosarcoma

Anabolic therapy for osteoporosis: Efficacy

- Increase spine and hip bone density
- Teriparatide and abaloparatide have both been shown to be more rapid and effective in vertebral fracture reduction than oral bisphosphonates
- Significant reduction in vertebral fracture risk and non-vertebral fracture risk, but not hip fracture risk
 - Neither phase III trial was powered to predict significant hip fracture risk
 - See 68- 88% reduction in vertebral fracture risk over 18 months with both
 - 40-50% reduction in non-vertebral fracture risk
 - There is no statistically significant difference in fracture reduction between the two agents, though abaloparatide showed a statistically significant improvement in hip BMD over teriparatide in a 2015 comparison trial

Neer RM, Arnaud CD, et al. N Engl J Med 2001;344:1434-41 Marcus R, JBMR 2003(18):18-23
Miller PD, Hattersley G, et al. JAMA 2016;316(7):722-33 Fontalis A, Kenanidis E, et al. ePub ahead of print, April 2019

When anabolics are complete? Follow up with antiresorptive therapy



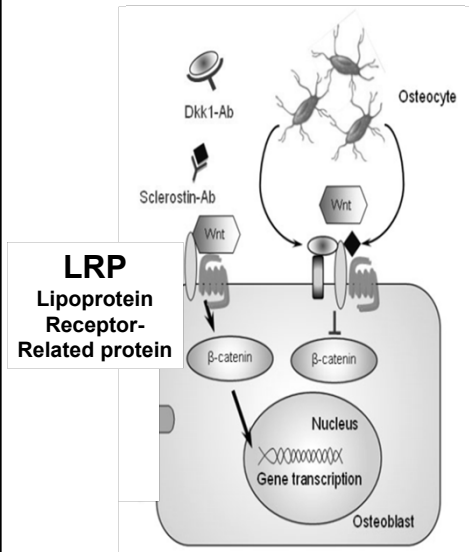
Black DM, Bilezikian JP, et al. N Engl J Med 2005;353:555-65
 Leder BZ, Tsai JN, et al. Lancet 2015;386:1147-55
 Cosman F, Miller PD, et al. Mayo Clin Proc, Feb 2017;92(2):200-10

Case 4: 74 yo with ORIF left hip fracture

- 4 week post operative follow up
 - Has had known osteoporosis by DXA
 - Family history hip fracture in mom
 - Has been on alendronate x 4 years with excellent compliance
 - Excited to finally begin some gardening – tripped over a hose in the yard and broke her hip
 - Secondary evaluation
 - Calcium 9.5mg/dL, normal albumin
 - Vitamin D 28 ng/mL (30-100)
 - PTH 48 pg/mL
 - TSH 2.221; FT4 1.21
 - 24 hour urine cortisol: 19mcg/24hr
 - SPEP: WNL
 - Failure of therapy:
 - Incidence of 2 or more fragility fractures while on treatment for 6+ months
 - OR: One incident fracture plus elevated markers of bone turnover OR decline in BMD
 - OR: Both no sig decline in BTMs and decline in BMD of 5% at LS and/or 4% of total hip
- What next?**

Diez-Perez A, Adachi JD, et al. Osteoporosis International, IOF Inadequate Responders Working Group, 2012;23(12):2769-2774

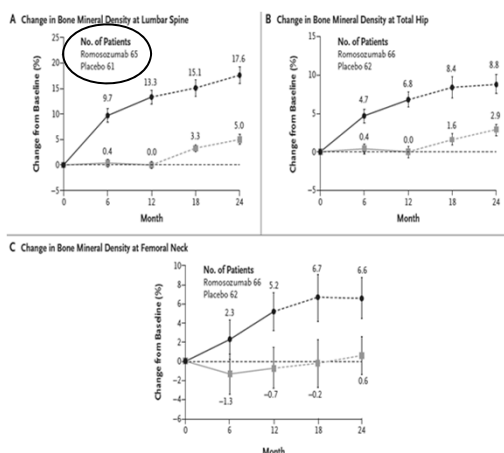
Romosozumab: Anti-sclerostin antibody



- The binding of Wnt to its receptors induces association with LRP, β-catenin is stabilized and target genes are activated, resulting in *osteoblastic formation*
- Sclerostin is a circulating inhibitor of the Wnt-signaling pathway, which binds to LRP 5 and 6
- High bone density was seen in nature with an inactivating mutation in the SOST gene which causes formation of sclerostin by osteocytes

McClung MR. Endocrinology and Metabolism, Sept 2015(30): 429-435
Ng KW, Martin TJ. ASBMR Primer on Metabolic Bone Disease, 8th Ed, Ch 56, 461-467

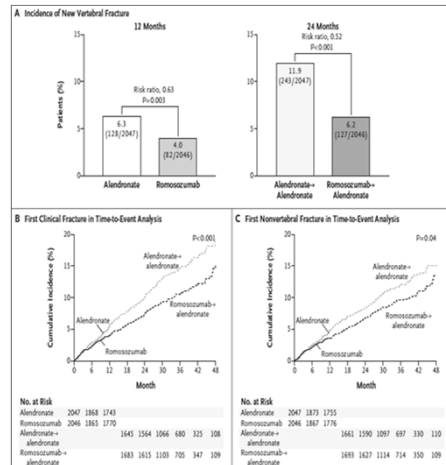
Romosozumab: DXA data



- DXA measured only in a subset of patients
- See increases in bone density as early as 6 months
- Bone density continues to increase after transition to denosumab
- 13% increase at LS BMD seen in one year
- 6.8% increase in total hip BMD seen in one year

Cosman F, Crittenden DB, Adachi JD, et al. N Engl J Med, Sept 2016;375:1532-1543

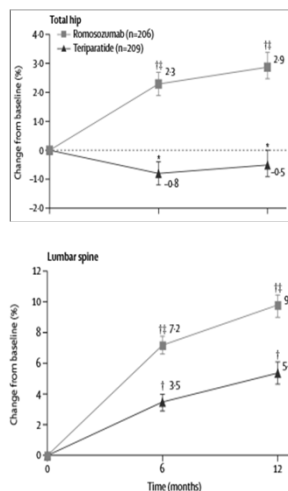
Romozozumab vs. alendronate fracture data



- 12 months romozozumab then 12 months alendronate vs. 12 months alendronate then 12 months alendronate
- At 24 months, see a 48% reduced incidence of new vertebral fractures in the romozozumab group (a)
- 27% lower risk clinical fractures (b)
- 19% lower risk of nonvertebral fractures (c)

Saag KG, Petersen J, et al. N Engl J Med 2017;377:1417-1427

STRUCTURE Trial: teriparatide vs. romozozumab after 3+ years of alendronate



- Small study – 218 patients in each group
- “real-life”: transitioning from bisphosphonate therapy
- BMD data – no fracture data

Langdahl BL, Libanati C, et al. Lancet 2017;390:1585-94

Romosozumab

- FDA approved April 2019
- 210mg (two 105mg injections) monthly in provider's office x 12 months
- Indicated for treatment of postmenopausal osteoporosis
- Follow with antiresorptive therapy
- Contraindication: hypocalcemia
- AR: arthralgia, headache most common
- One case each ONJ AFF

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH
See full prescribing information for complete boxed warning.

- EVENTITY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)
- EVENTITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)
- If a patient experiences a myocardial infarction or stroke during therapy, EVENTITY should be discontinued. (5.1)

Evenity (romosozumab-aqqg) package insert, Amgen, 4/2019

Case 5: Springtime gardener



YIKES!