Osteoporosis Management Focus on Medications

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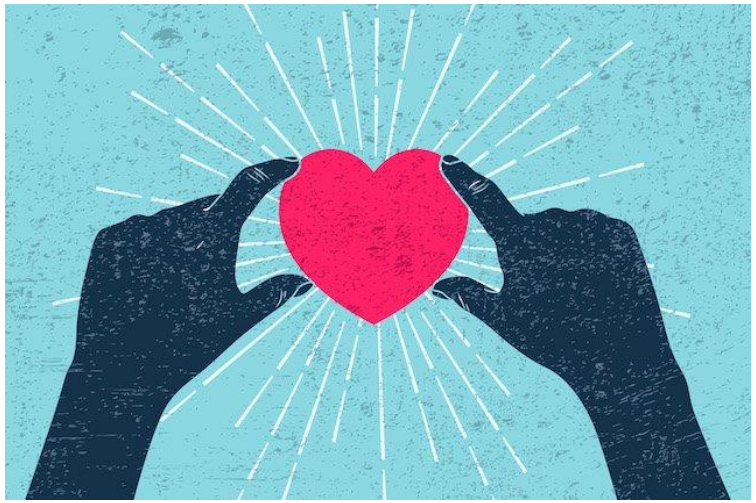


Question – Poll Everywhere

- What is your current comfort level with Osteoporosis Medication Management?

- A) Fuzzy
- B) Somewhat understand and when to refer to Osteoporosis clinicians
- C) Fair level of understanding and looking forward to confirming information
- D) Not sure, need more coffee

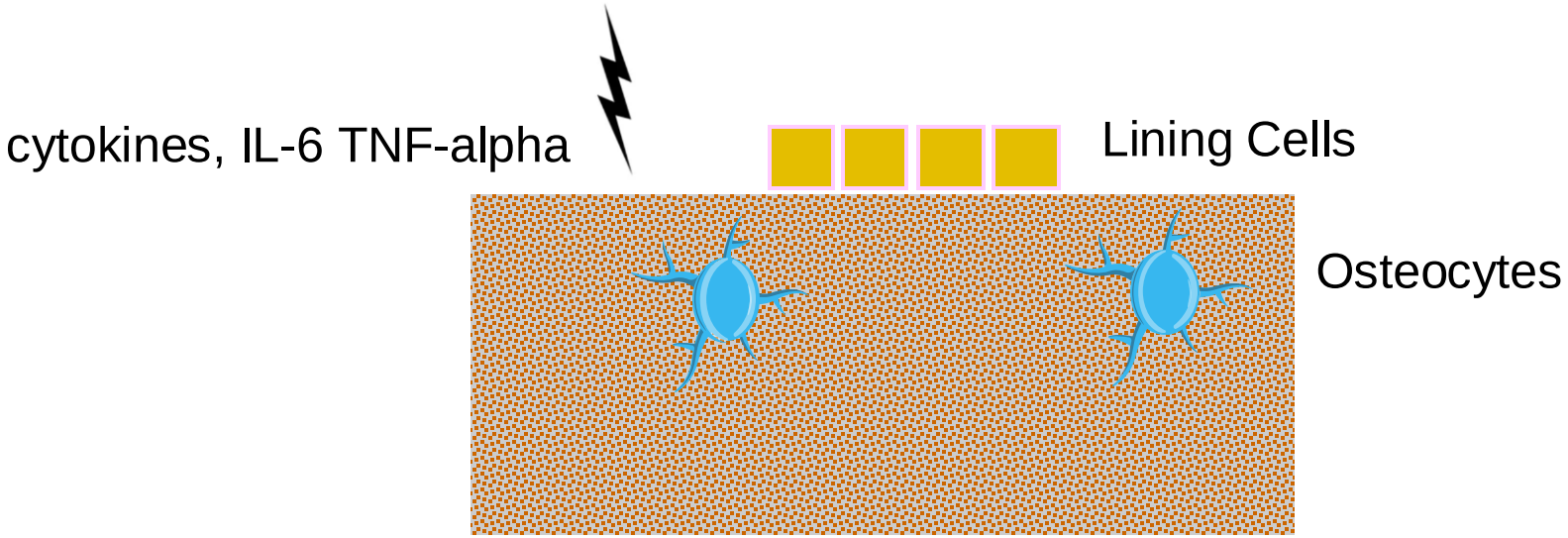
Learning Objectives

1. Describe a Basic Overview of Bone Remodeling
2. Discuss Anabolics
    - Mechanism
    - Sequence Therapy
    - Offer a Practical Approach to Clinical Practice?
        - When? How to utilize?
    - Share concept of Risk Stratification
3. Discuss Bips
    - Share Efficacy
    - Comment and Relate on Side Effects vs Drug Holidays
    - Share concept of Risk Stratification

I have no disclosures

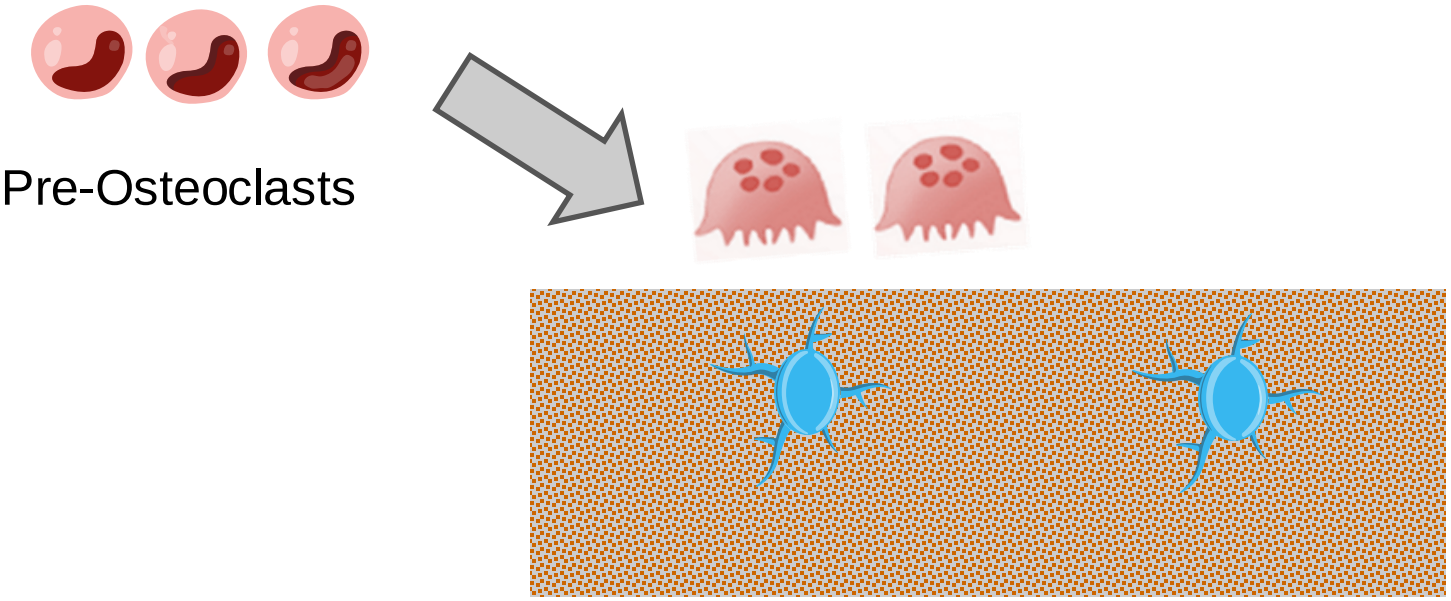
1.Bone Remodeling Concept

Resting Stage

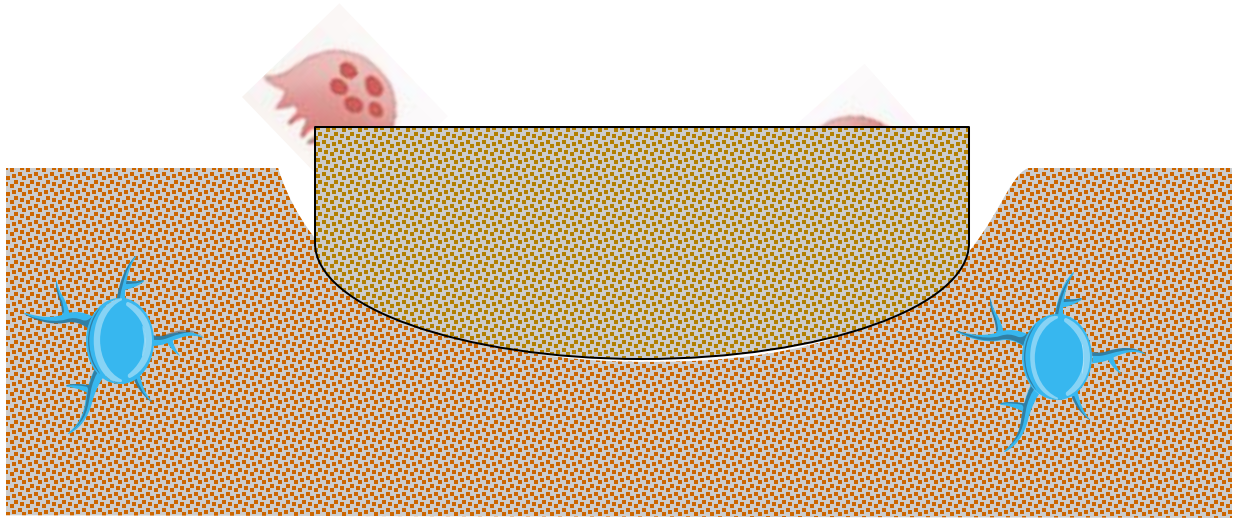


The resting bone surface is covered with lining cells.

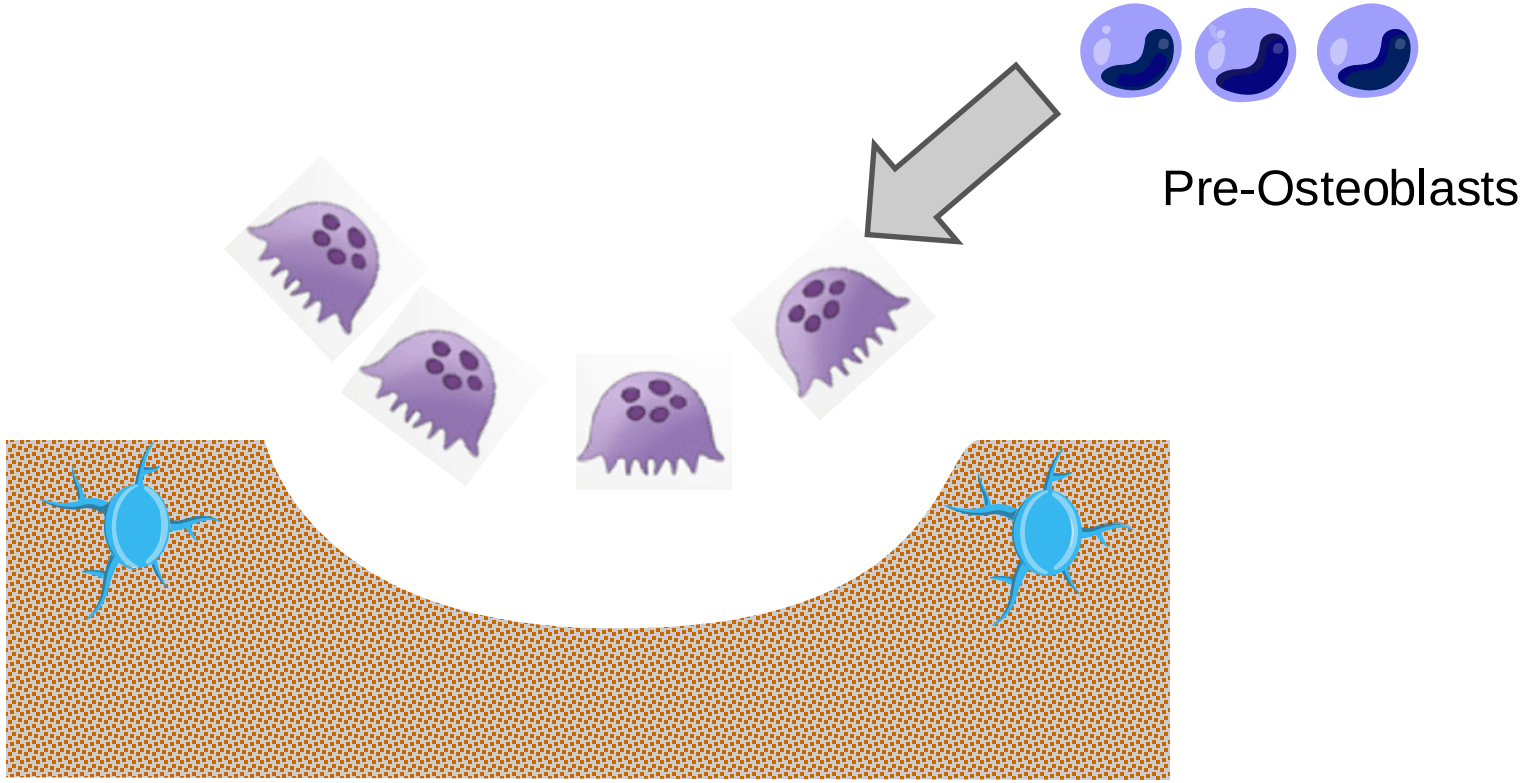
Activation Stage: Osteoclasts Precursors



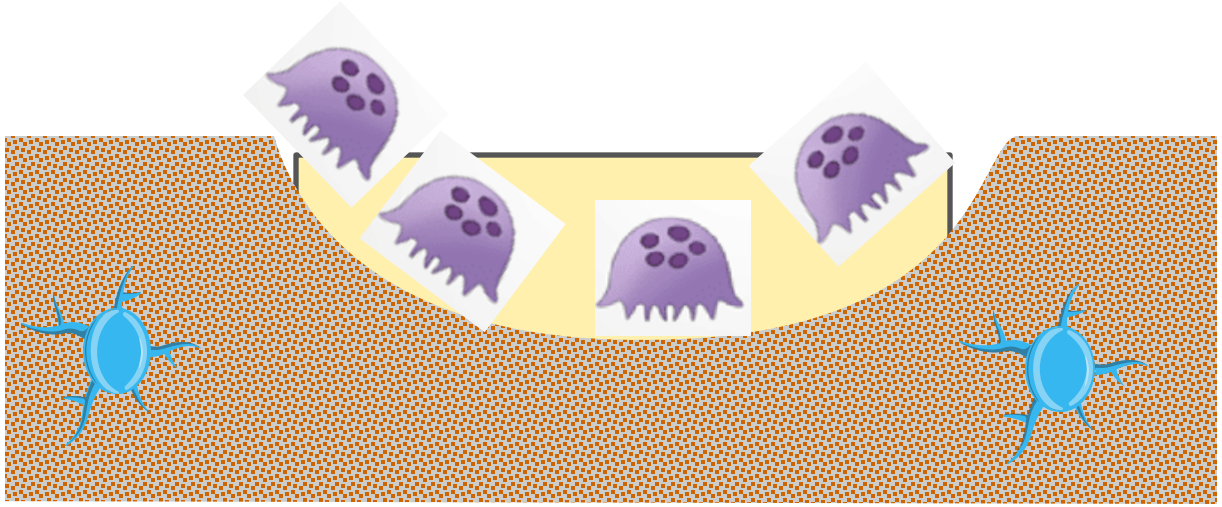
Resorption



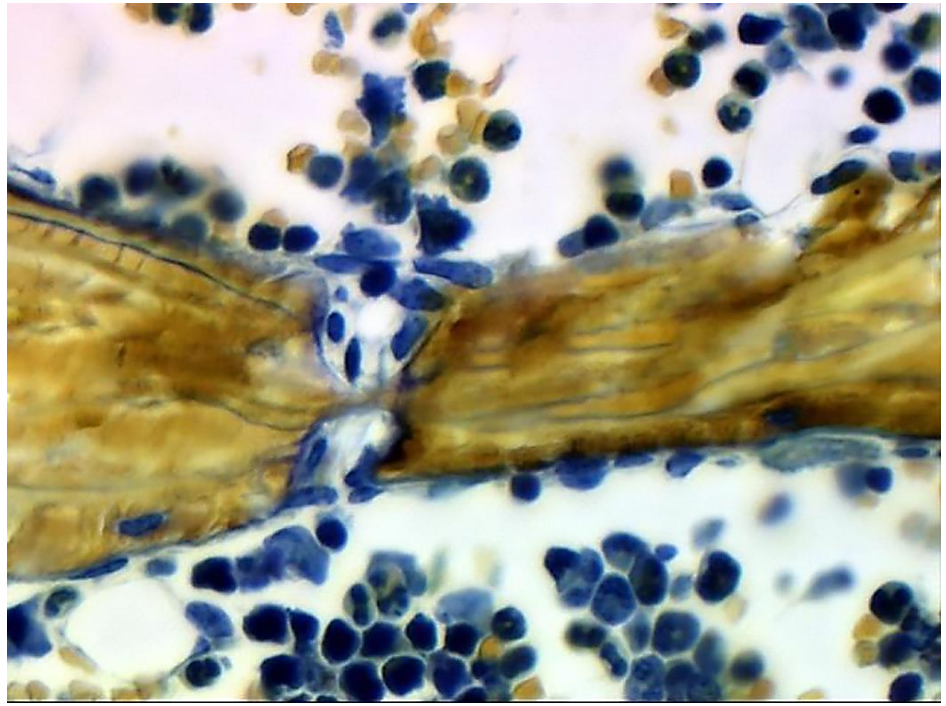
Osteoblasts recruited



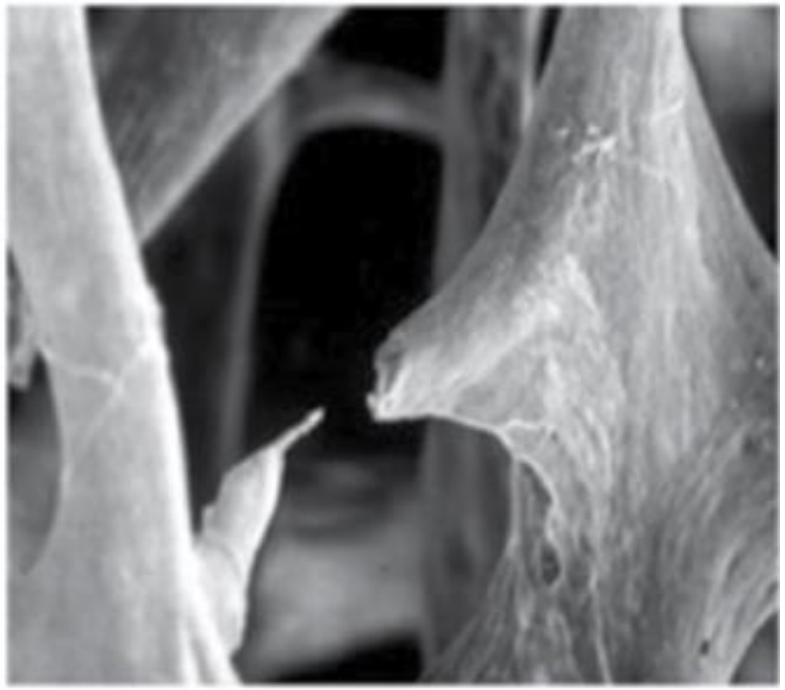
Osteoid Formation/Mineralization



Acceleration of Cancellous bone loss with **Estrogen deficiency in Women**
Decrease in Trabecular number caused by trabecular perforation & loss of connectivity



Microphotograph of a human trabecula perforated by osteoclastic resorption. The image is taken from an iliac crest biopsy specimen. Please note that resorption from either side of the trabecula has left only a thin thread of bone. Almeida M, Physiological reviews January 2017



Isales and Seeman

Question 1

Gary is a 69 yo male (he/him) with prior history of glucocorticoid use for RA. This was in form of oral prednisone and tapers but now off all steroids.

He also has hx of DM II, peripheral neuropathy on MDI and CGM, GERD on PPI and HTN on 3 anti-HTNs. Unfortunately, he sustained a right hip fracture a few months back after a ground level fall.

DXA T score –2.5 L spine, left femoral neck –2.6

EGFR normal, 25OH D 36, PTH normal

Answer Choices- Poll Everywhere

- Based on the best evidence available, you discuss with him:
- A) Aledronate
- B) IV Zoledronic acid
- C) Teriparatide
- D) Romozosumab
- E) Denosumab

2. Anabolics

- Mechanism
- Sequence Therapy
- Offer a Practical Approach to Clinical Practice?
  -When? How?
- Share concept of Risk Stratification

Overview of Osteoporosis Medications

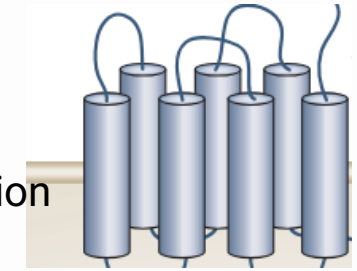
Bisphoshosnates
Denosumab

PTH analogues
Romozosumab

- **Teriparatide PTH 1-34**
- **Abaloparatide PTH-rP**

PTH-Analogue Mechanism

RG Confirmation



PTH Analogue

Pulsatile

Bone Formation

RANKL RANK

Pre-Fusion Osteoclast

Mature Osteoclast

Bone Resorption

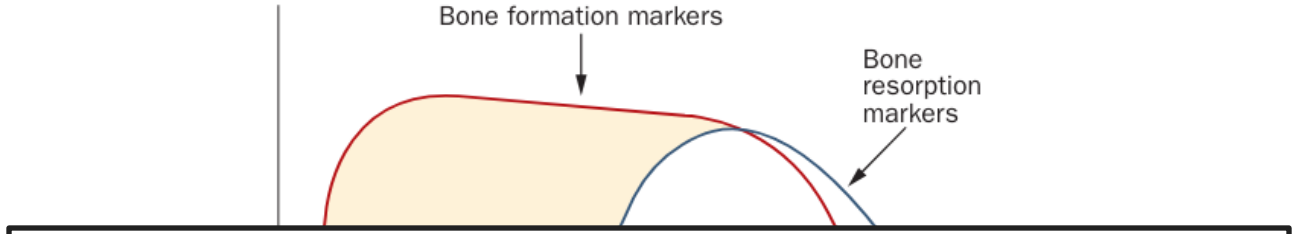
Does Order Matter?

Teriparatide

Abaloparatide

+

Anti-Resorptive

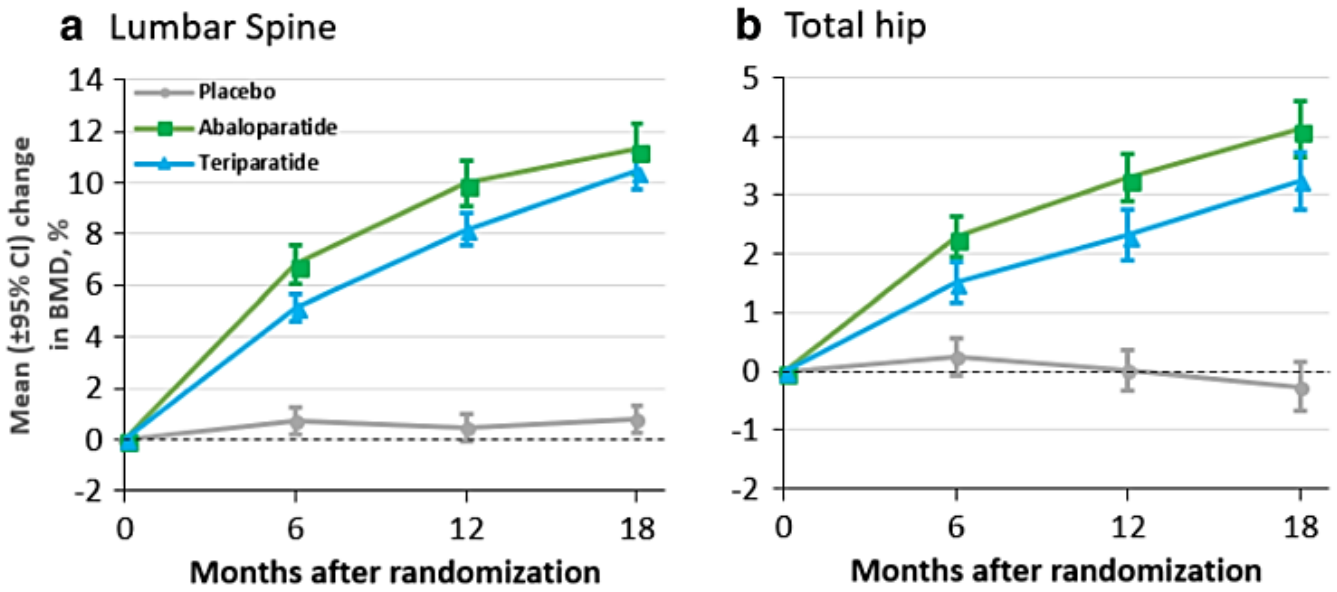


For very-high-risk (imminent) patients, treating with osteoanabolic agents first, followed by antiresorptive agents, produces substantially larger BMD gains than the reverse treatment sequence.

Rubin, M. R. & Bilezikian, J. P. Endocrinol. Metab. Clin. North Am. 32, 285–307 (2003).

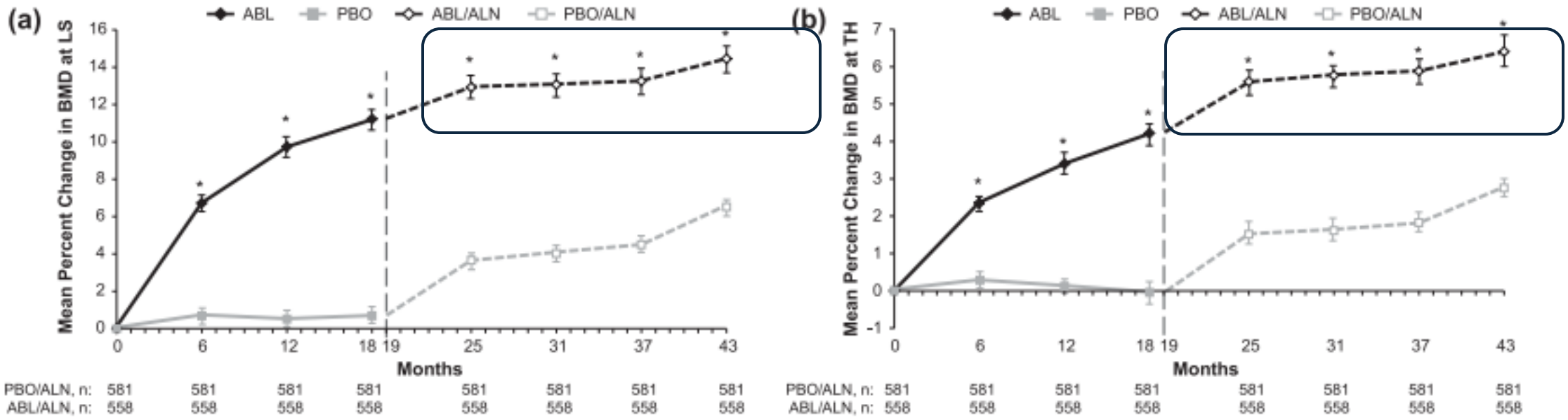
BMD Gains for PTH Analogues: ACTIVE trial

Fig. 2 Mean change (95% CI) in lumbar spine and total hip BMD over time during treatment with placebo, abaloparatide, or teriparatide over 18 months for patients included in the BTM analysis



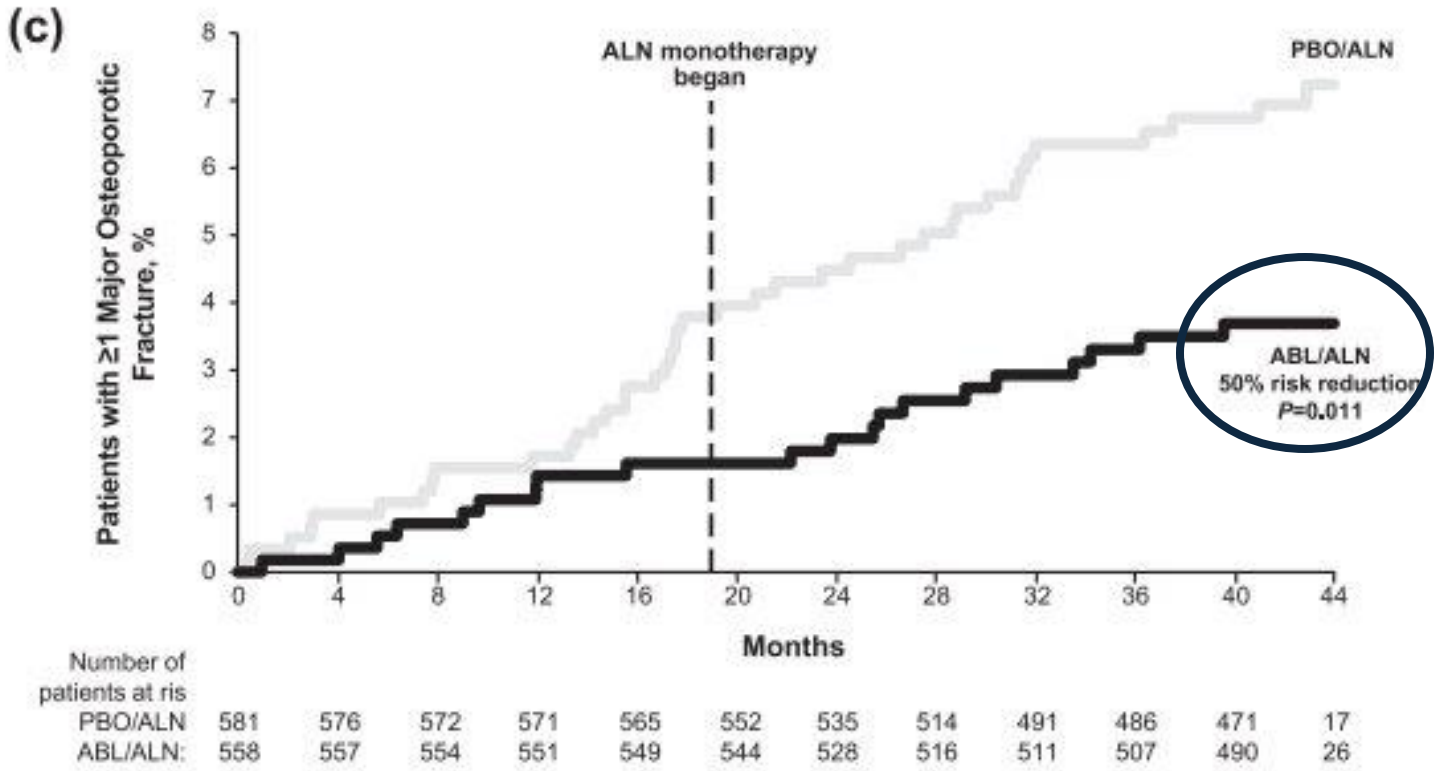
- Osteoporosis Int (2019) 30:667–673

Gains in BMD during ACTIVE with PTH Analogue treatment relative to PBO were sustained during 24 months of Aledronate (ALN)



Bone HG et al ACTIVExtend: J Clin Endocrinol Metab. 2018

ACTIVExtend: 24 Months of Alendronate After 18 Months of Abaloparatide or Placebo for Postmenopausal Osteoporosis



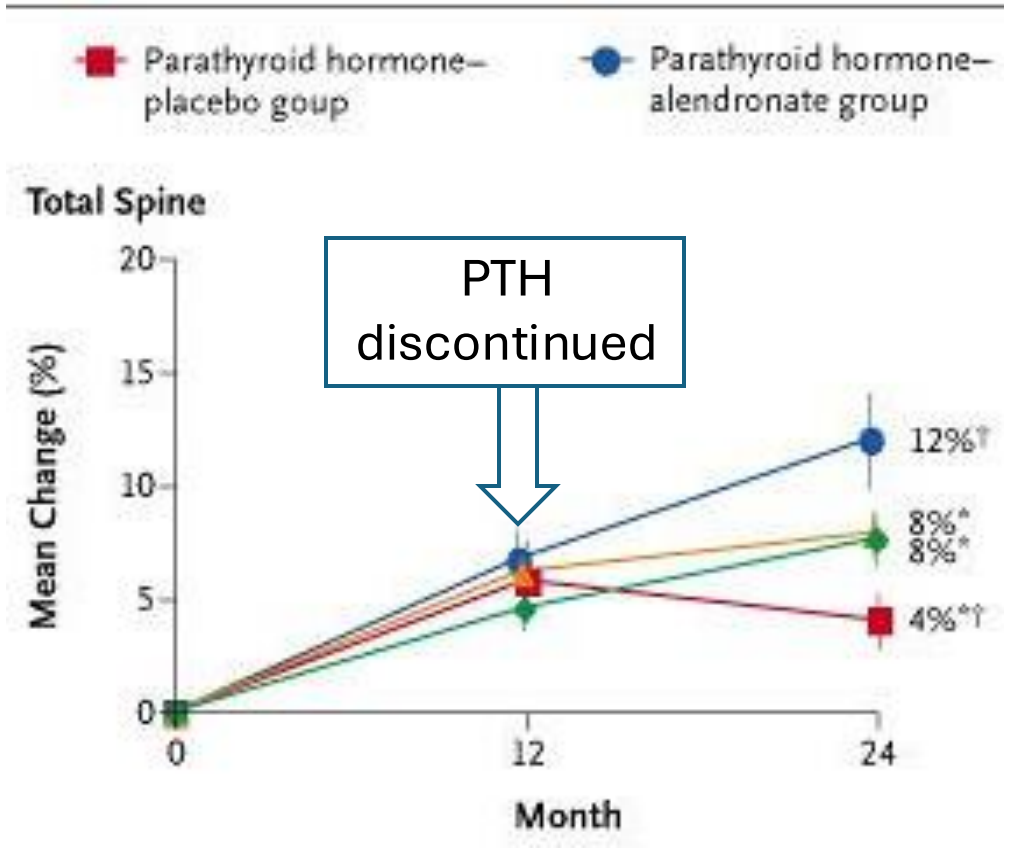
Reduced risk of vertebral, nonvertebral, clinical & major osteoporotic fractures

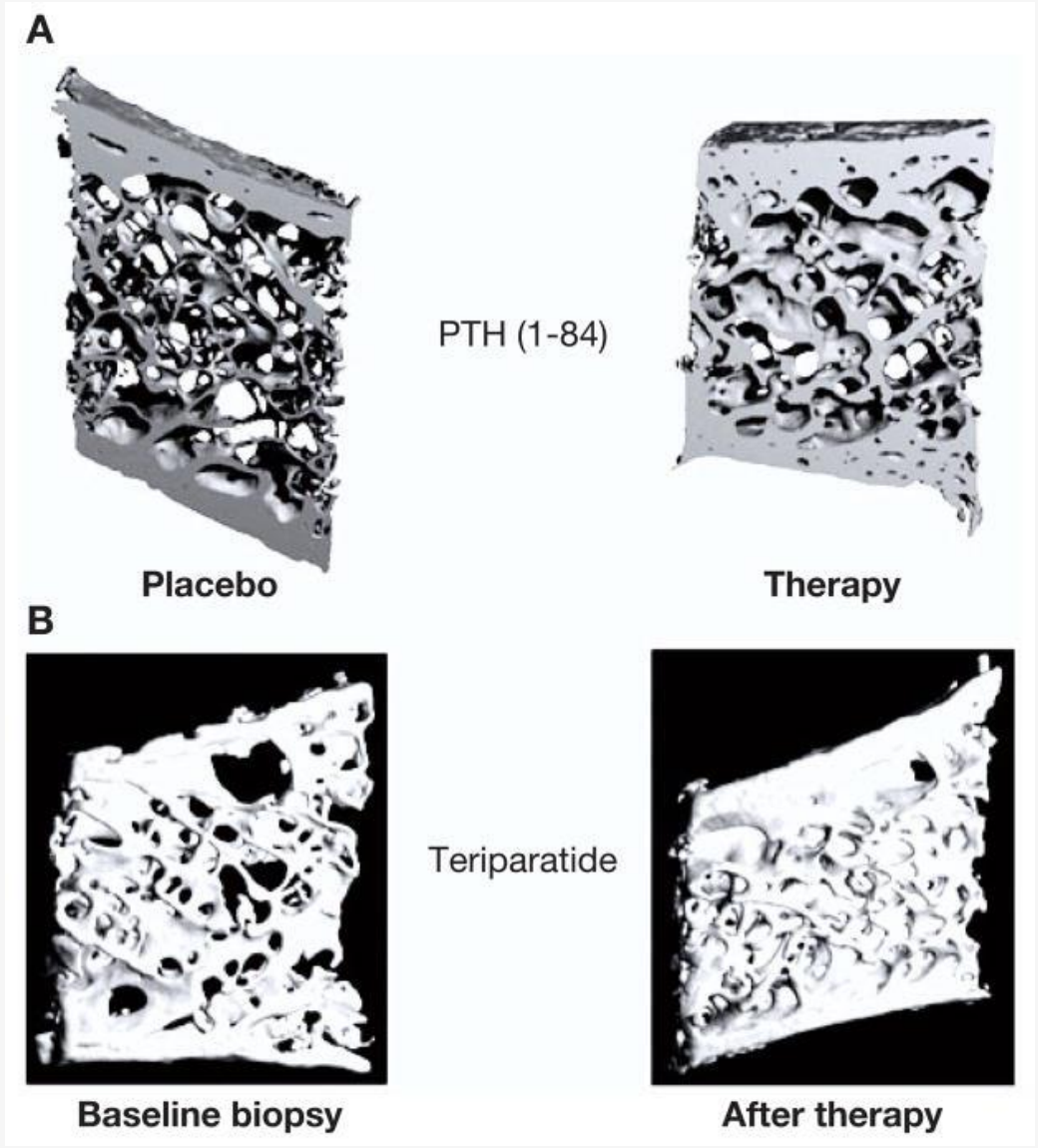
Bone HG et al ACTIVExtend: J Clin Endocrinol Metab. 2018

PATH 2005

PTH -> ALN

PTH -> Placebo





PTH Analogues Improve Trabecular Bone

- Improvements in cancellous bone volume, connectivity, and cancellous bone morphology with more rod-like to a more normal plate-like appearance

- Silva et al. Catabolic and anabolic actions of parathyroid hormone on the skeleton.

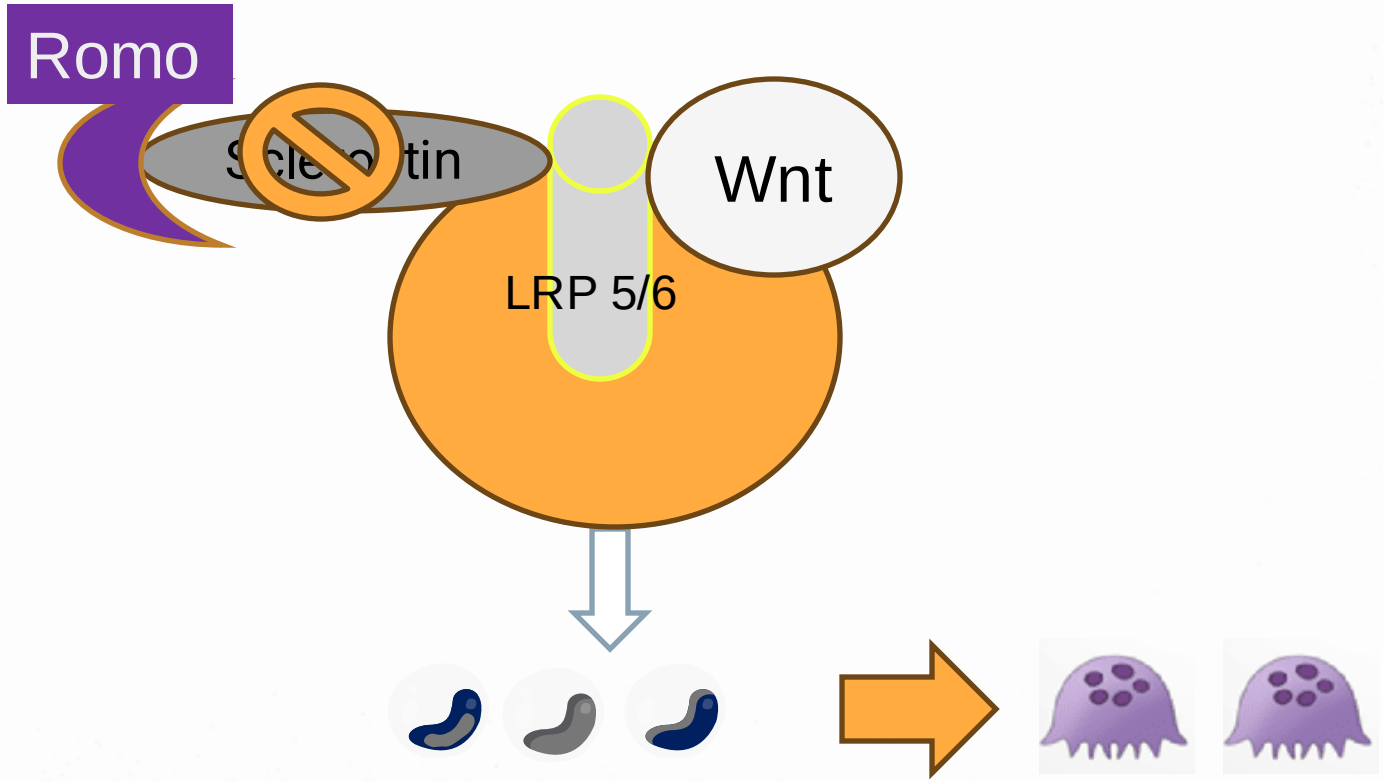
Overview of Osteoporosis Medications

Bisphoshosnates
Denosumab

PTH analogues
Romozosumab

- **Teriparatide PTH 1-34**
- **Abaloparatide PTH-rP**

Romozosumab – Anti-Sclerostin

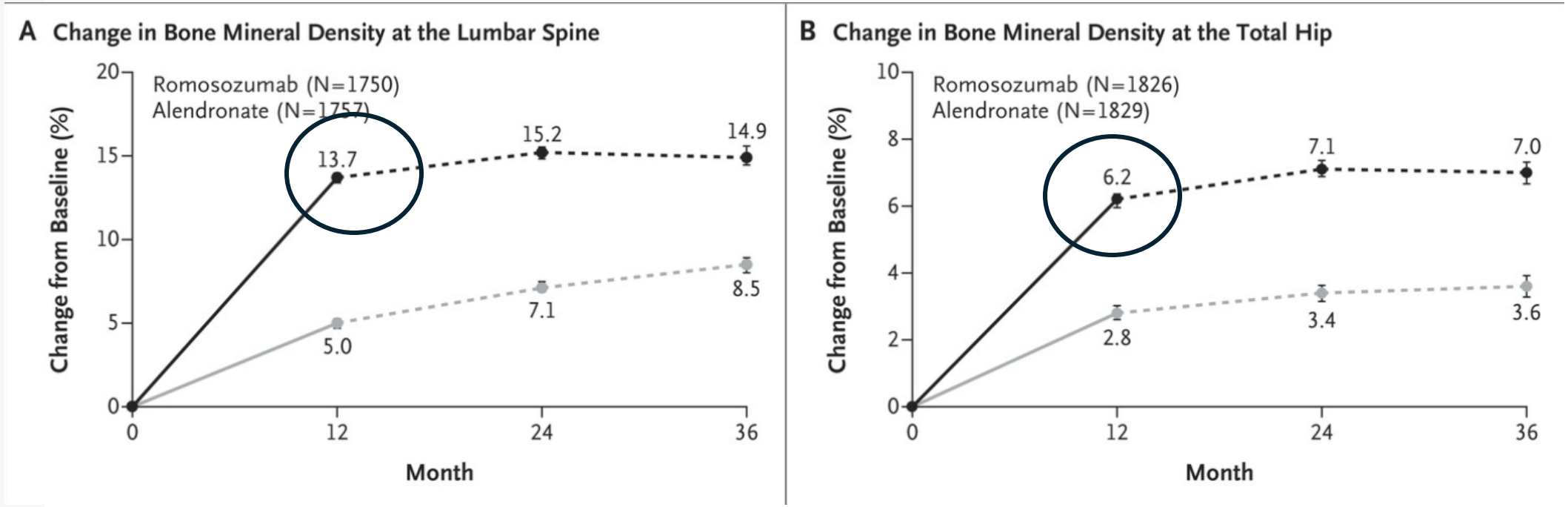


Wnt activation resulting from the inhibition of sclerostin has been associated with decreased bone resorption – but transient.

Wnt–β-catenin signalling
Bone Formation

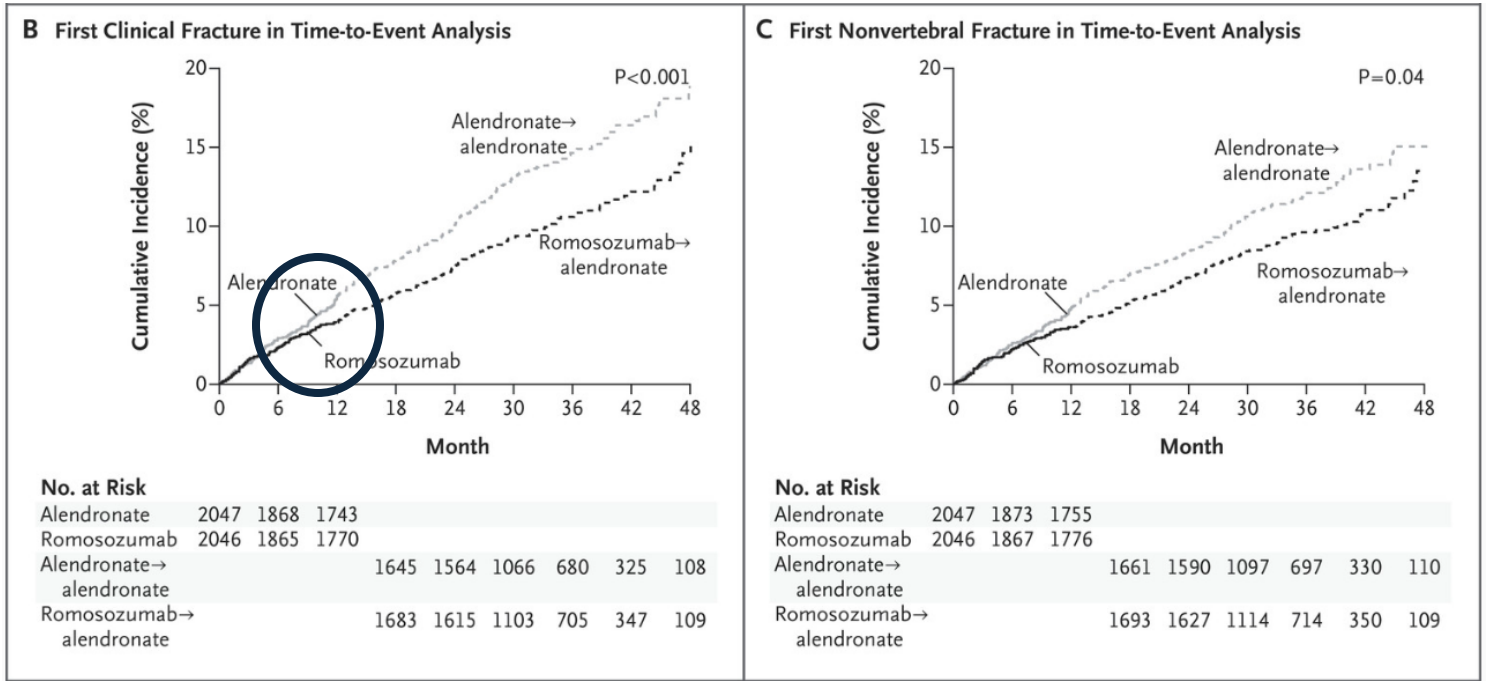
Inhibit bone resorption

ARCH Study: BMD gains



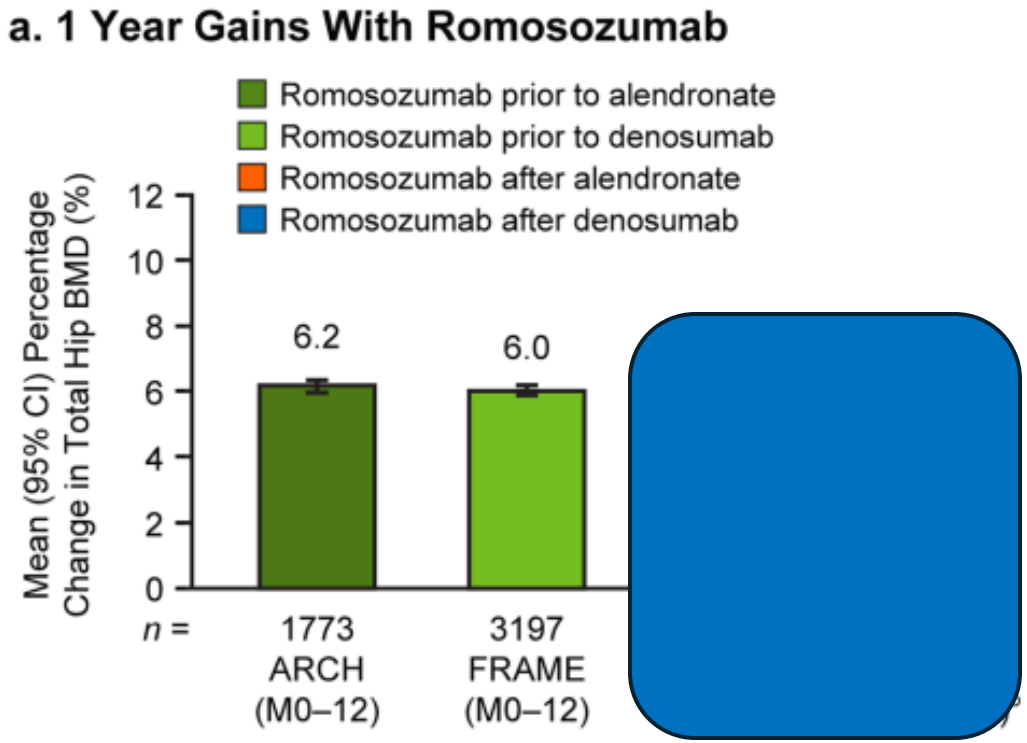
- Saag KG et al, 2017

Incidence for New fracture: Romozosumab



- Saag KG et al, 2017

Does Order Matter?



- Cosman et al. Osteoporosis Int (2022)

Modeling Based Formation with Romozosumab

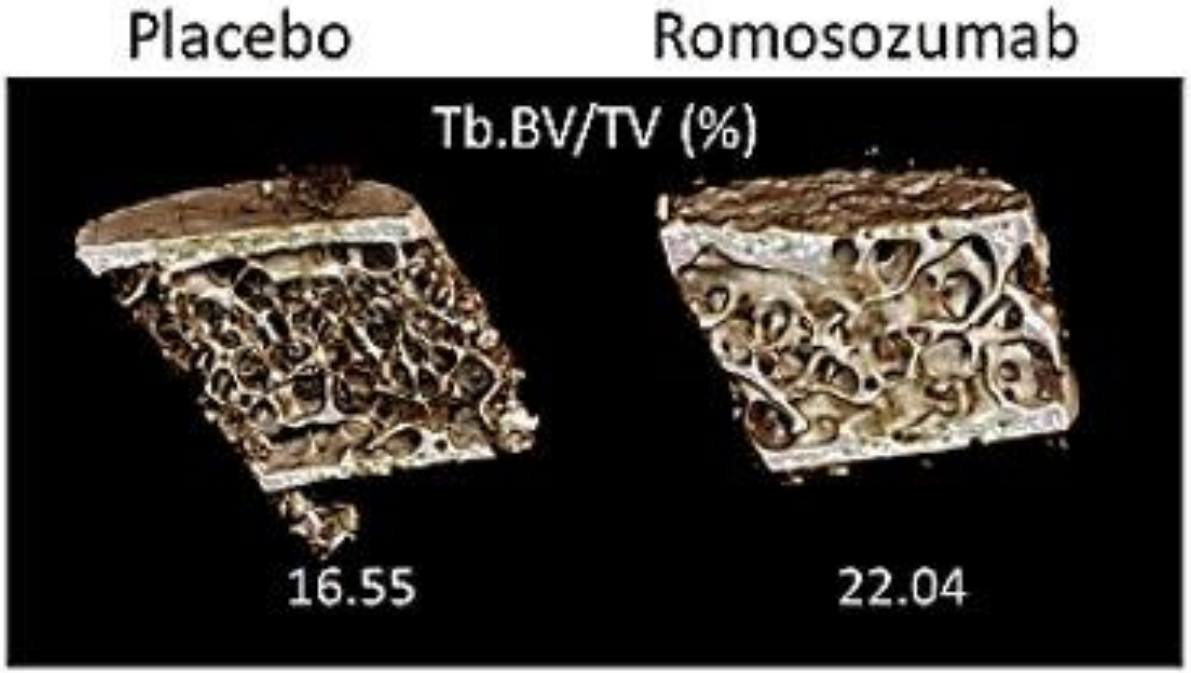


Fig. 3. Effects of romosozumab at month 12 on bone mass and microarchitecture assessed by μCT. Tb.BV/TV = trabecular bone volume per tissue volume

PTH analogues in Clinic

- Concerns: Kidney stones, Hypercalcemia, radiation exposure, bone mets/cancer
- Only if patient remains or at again high risk, could consider recourse (black box warning of osteosarcoma removed)
  - Individualized decision, judicious repeat courses
- Cost:
  - Teriparatide $1,010.06- 1,846 per month
  - Abaloparatide $1671.08 - $2,818
- Need for Daily Injections
  - Teriparatide 24 months vs. Abaloparatide 18 months duration
- Teriparatide needs refrigeration (Abaloparatide doesn't)
- No AFF or ONJ risks

Costs: High variation
Generic: VISN 20 and ACP 2023

Romozosumab in Clinic

- Approved for 1 year
- Cost: $1,4737.27- $2,646 per month
- Injections but in Clinical Settings, Once a month
- Possible MI-CVA risk:
  - Black Box Warning: Not used if had MI or Stroke in past year

Why Choose Anabolic?

Outstanding Fracture Reduction

Different Side Effect Profile

Targets Bone Forming Cells

Who are Candidates for Anabolics?
Per Endocrine Society Guidelines

High
T score ≤ -2.5 OR
Fracture (Hip or VF) OR
FRAX elevated ≥ 20% MOF or ≥ 3% Hip

Very High
T score ≤ -2.5 + Multiple Fragility Fractures and
T score <-3.0 + recent fracture in past 1 year
High Fall Risk
FRAX elevated ≥ 30% MOF or ≥4.5% Hip

Failed Anti-resorptive therapy
Sustain fracture on therapy
BMD declining on DXA

Who are candidates for Anabolics?
New Goal-directed Osteoporosis Treatment: ASBMR/BHOF task force position statement 2024

- **HIGH:** Fracture remote >2 years ago
  - T score ≤ -2.5
    - What was previous fracture? VF/Hip/Pelvic - consider anabolic
    - If another type – consider Anti-resorptive
  - T score > -2.5
    - What was previous fracture? VF/Hip/Pelvic - consider anabolic
    - If another type – consider Anti-resorptive

- **IMMINENT:** Recent fracture <2 years ago, multiple fractures, regardless of T score you wish to reduce future fractures
  - VF, Hip or Pelvic Fracture - Anabolic
  - Maximal reduction in fracture risk

Risk Stratification: My Clinical Practice

Low-Intermediate

No Fracture hx
Anti-resorptives

Very High

T < -2.5 (some guidelines say -3.0 cut off) at TH. LS. FN & Fracture (s) > 2 years earlier
Anabolic first choice

1. Recency of fracture, number & site of prior fractures
2. BMD at the TH, FN, and/or LS
3. Strong risk factors for bone loss & falls

High

No fracture History
T score ≤-2.5-3.0 TH, FN, LS
Anabolic or Antiresorptive

Imminent Risk

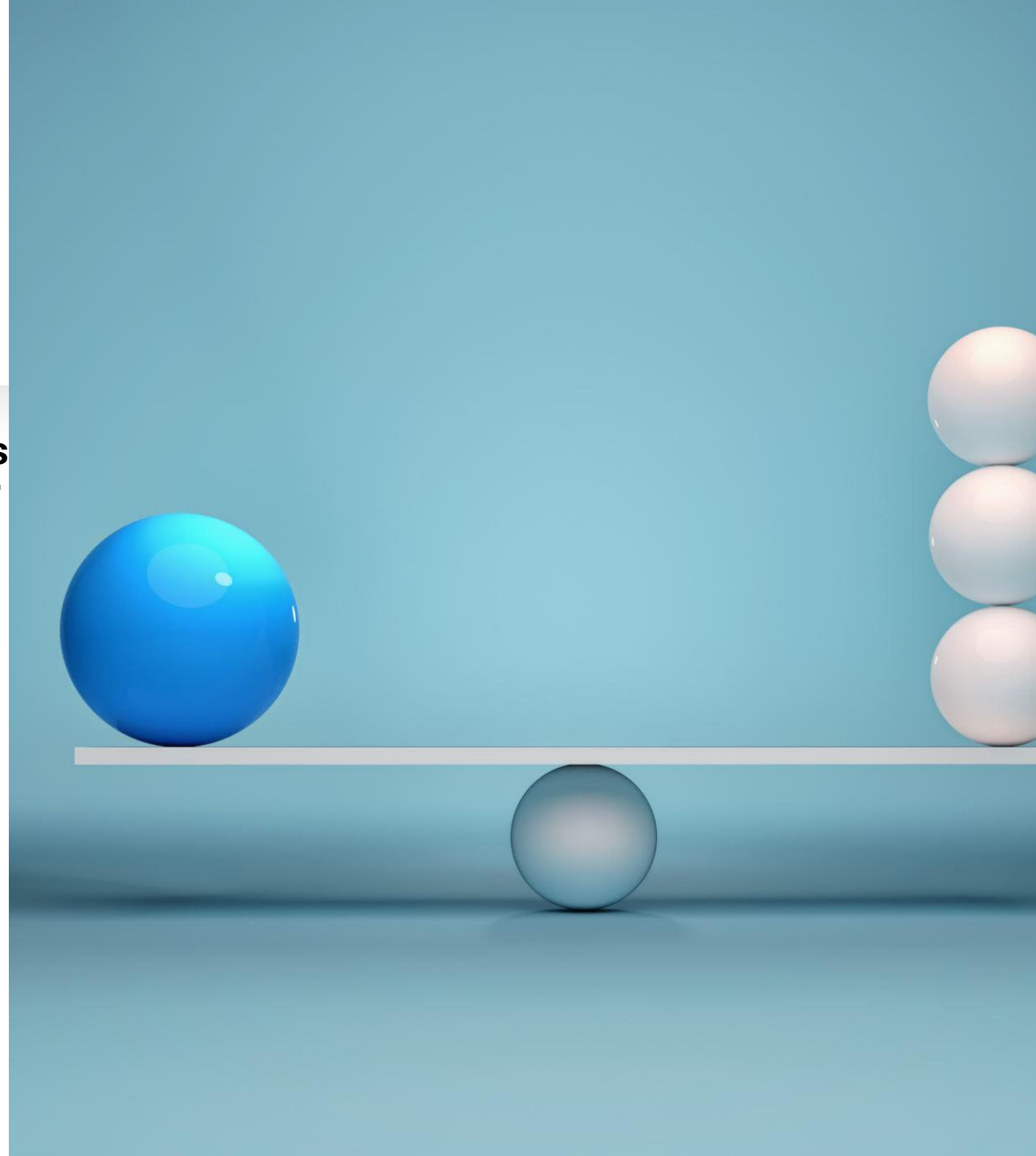
Recent Fractures ≤ 2 yrs earlier or Multiple Fxs; Anabolic first choice

Choosing Agents

- **“We advocate for the clinician to risk stratify & encourage shared decision-making with patients choosing the appropriate osteoporosis agent for fracture prevention”**

- Juggling:
  - Risks vs. Benefits
  - Patient Preferences
  - Clinical Evidence

Wysham, Baker, Narla. Osteoporosis evaluation and treatment recommendations in rheumatoid arthritis



Key Takeaways so Far…

- Initial therapy with a Bip may modestly diminish the bone effects of subsequent bone-forming agents but prior antiresorptive *use is not a contraindication to anabolic therapy*
- Following bone-forming agents w/ an antiresorptive is required to maintain the achieved BMD gains.
- This highlights the need to identify and treat patients that may benefit from anabolics before antiresorptives (where all of you come in!)
- If you strongly suspect that patients may risk stratify to Higher Risk Categories– refer to Osteoporosis Clinicians (pending insurance etc).

Question 2

70 year old Jose (he/him) with previous wrist fracture 8 years ago and T score remains -2.5 lowest at L Spine after 3 years of Bip. He is here for follow up and discussion of osteoporosis treatment.

No new clinical risk factors
No new falls
No change in height, weight, medical conditions
reports compliance to Bip

EGFR normal, 25OH D 42

DXA shows stable BMD

Answer Choices- Poll Everywhere

A. Start Anabolic, stop Bip
B. Continue Bip for a few more years
C. Switch to Denosumab
D. Informed discussion of offering drug holiday

3. Bisphosphonates

- Share Efficacy
- Comment and Relate on Side Effects vs Drug Holidays
- Share concept of Risk Stratification

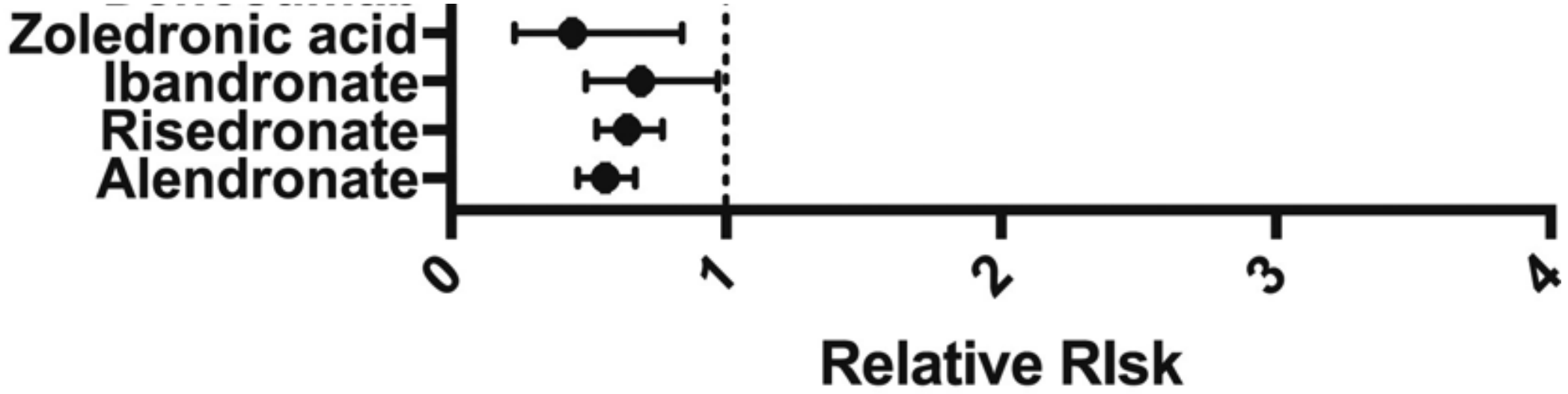
Bisphosphonates

- After how many years of treatment should patients on BP be advised on drug holiday?
- What are some of the characteristics of a “safe” BP drug holiday?
- The answers are complex and lot of unknowns

- Contingent on a range of individual factors, including their fracture profile and side effect risks

Bip and Fracture Risk Reduction: Mean duration of 3-4 years in these trials

Vertebral Fx



Pharmacological Management of Osteoporosis in Postmenopausal Women: Endocrine Society 2019

Long Term Bip Efficacy?

- FIT Long term (FLEX)
  - Randomized women on ALN 4-5 years to either ALN or Placebo for 5 *more* years
- Horizon PFT
  - Randomized women on Zol 3 years to either IV Zol again 3 *more* years or Placebo

Results

- **BMD Changes: -1.9% loss in Placebo groups. BUT higher Hip BMD than baseline so showing long term benefits**

- **Both suggested no increased risk in Non-spine or Hip fractures during drug holiday**
  - May increase spinal (VF) risk if discontinued.
  - There was a statistically significantly lower risk of clinical vertebral fractures among those randomized to ALN (5.3% placebo vs 2.4% ALN; RR, 0.45; 95% CI, 0.24-0.85)
- Two Other observation studies: no increase in Spine or Hip Fracture risk over drug holidays (lasted 4 years)

Balance Safety vs. Risks

Clinically if high risk – previous spinal or hip fracture or very low BMD may not be able to take drug holiday

Versus

Atypical Femoral Fracture (AFF)

Osteonecrosis of the Jaw (ONJ)

What is Osteonecrosis of the Jaw?

- Exposed bone with poor healing in the maxilla-facial region
- Appears as areas of exposed yellow or white hard bone
- May or may not be painful; may or may not be infected or necrotic
- Often in site of prior dental extraction
- More common in cancer patients on high dose/high frequency of IV bisphosphonates
- 1 to 100 cases per 100,000 patient-years for Osteo Dose

Osteoporosis DOSE	Oncology DOSE
Zol 5mg IV Q year	4mg IV Monthly
Dmab 60mg SQ Q6 months	120mg SQ Q monthly

Table 2. MRONJ PREVENTION STRATEGIES

Pretherapy (Nonmalignant Disease)	• Educate patient about the potential risks associated with long-term ART.* • Optimization of dental health can occur concurrent with ART.
Pretherapy (malignant disease)	• Educate patients about the higher risk of MRONJ and the importance of regimented dental care. • Optimization of the dental health *prior* to the initiation of ART if systemic conditions permit (extraction of nonrestorable teeth or teeth with a poor prognosis).
During antiresorptive therapy (nonmalignant disease)	• No alteration of operative plan for most patients. • Considerations include drug schedule, duration of therapy, comorbidities, other medications (especially chemotherapy, steroids, or antiangiogenics), degree of underlying infection/inflammation, and extent of surgery to be performed. Drug holidays are controversial. • BTM† are not a useful tool to assess MRONJ risk.
During antiresorptive therapy/ targeted therapies (malignant disease)	• Educate patients about the higher MRONJ risk in the setting of malignant disease. • Educate the patient about the importance of regimented dental care and prevention. • Avoid dentoalveolar surgery if possible. • Consider root retention techniques to avoid extractions. • Dental implants are contraindicated. • Drug holidays are controversial.

* Antiresorptive therapies.
† Bone turnover markers (CTX).

Ruggiero et al. AAOMS' Position Paper on MRONJ—2022 Update. J Oral Maxillofac Surg 2022.

Suggested Risk Factors in addition to Antiresorptives (American Dental Association)

- Age older than 65 years;
- periodontitis;
- poor oral hygiene;
- dentoalveolar surgery, including tooth extraction;
- Smoking;
- malignant disease (multiple myeloma, and breast, prostate, and lung cancer);
- chemotherapy, corticosteroid therapy, or treatment with antiangiogenic agents;
- denture wearing;
- diabetes

Atypical Femoral Fracture (AFF)

- AFF is very rare; the rate of AFFs for women taking bisphosphonates for <2 years is approximately 1.78 per 100,000

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline, *JCEM*

Atypical Femoral Fracture

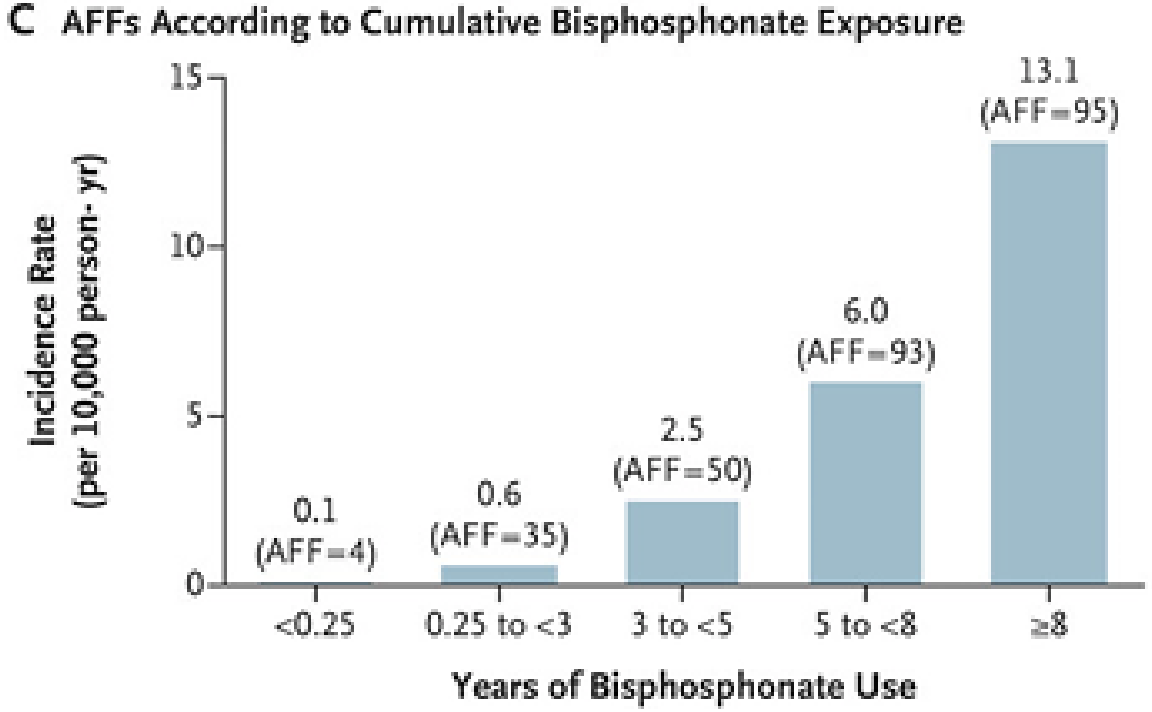
- Mechanism: Unclear
  - Proposed that chronic suppression of bone turnover changes bone quality and impairs micro-crack repair in susceptible patients.
  - Concerns and publicity about AFFs have led to substantial declines in bisphosphonate use, despite their established efficacy.
  - Substantial uncertainty and controversy remain regarding the magnitude of the association between Bip and AFFs.

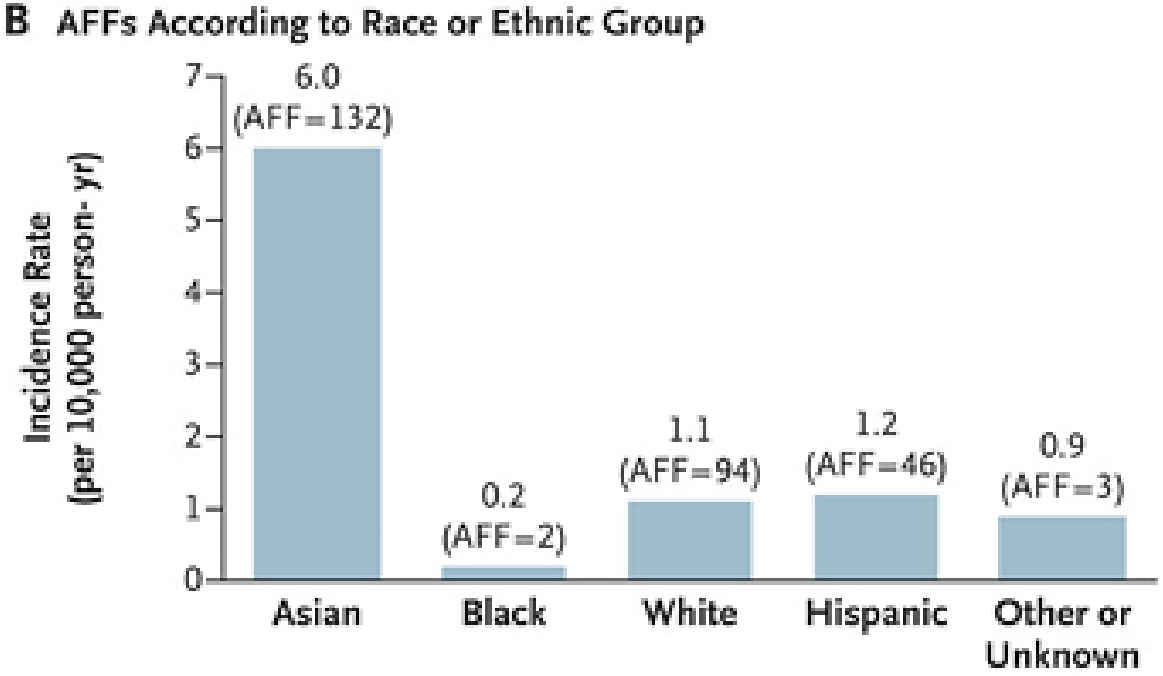
Atypical Femur Fracture Risk versus Fragility Fracture Prevention with Bisphosphonates

- Women 50 years or older who were receiving Bip and enrolled in the Kaiser Permanente Southern California health care system;
- Women followed from January 2007 – November 2017.
- Data on risk factors, including Bip use, were obtained from electronic health records. Adjusted for covariates including BMD. Xrays obtained if suspicion of subtrochantric fracture.

NEJM 2020

Relationship of Duration and AFF





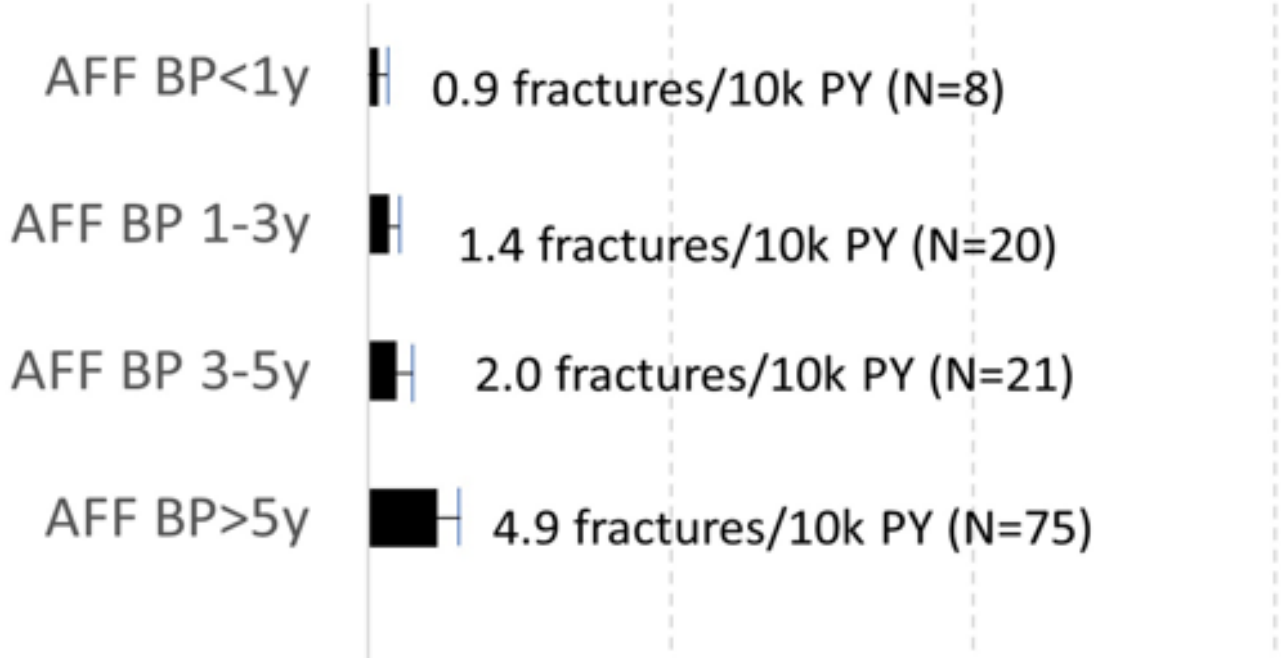
Showed that even after covariate adjustment, the relation between longer duration of Bip use & higher risk of atypical femur fracture remains;

Similarly Asian Race 5X risk even after adjustment

Bauer et al JCEM Jan 2024

- Population-based case-cohort study from Denmark
- Among all 1.9 million Danish adults ≥50, those with subtrochanteric or femoral shaft fractures between 2010 - 2015 (n = 4973) were identified & compared to random sample (n = 37 021).
- Bip use was collected from 1995-2015.
- Fracture radiographs were reviewed by blinded study radiologists to identify AFFs (n = 189) using established criteria.

Bisphosphonate Use and Risk of Atypical Femoral Fractures



- 5-7 years of Bip was associated with a 7-fold increase in AFF

After Bip Discontinuation….

Variable	AFF (n = 189)[a] adjusted HR (95% CI)[b]
Time since last use (y)[d]	
Current use	(ref)
> 0 to 1	1.02 (0.66, 1.55)
> 1 to 3	0.53 (0.22, 1.28)
> 3	0.23 (0.05, 1.01)

After BP discontinuation, the adjusted AFF incidence
-> in year 1 was unchanged
-> 47% lower 1 to 3 years after discontinuation
->77% lower thereafter (*P* for trend = .04).

End Note…

- 1 hip fracture was prevented when 94 individuals were treated with a BP for 3 years, or when 56 were treated for 5 years.

DC Bauer 2024
Image BHOF

Key Pearls on Bips

- Effective in reducing fractures
- Oral and IV options
- Bip 3-5 years; then consider drug holiday if low risk
- Drug holiday duration: The optimal duration of a drug holiday before restarting treatment is unknown. However, some consider 2 to 3 years, some 3-5 years.

- AFF and ONJ rare
- We need more evidence re: second courses of Bip after pause
- Balance benefits vs risks individually

Thank you!