Osteoporosis Update

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Topics for discussion

- Case study
- Steroid induced osteoporosis
- Pharmacologic treatment options for Osteoporosis.

Case study

- 65 Year old female
- Evaluated for a cough
- Otherwise normal chest x-ray
- Incidental finding of a vertebral fracture
- She is physically active

More details on hx

- She slipped on her rug a few months ago and had a modest amount of pain.
- She wonders is the xrays finding explain her loss of height
- No previous fracture

FSHx

- 50 year smoking hx
- Menopause at 52
- Weight is stable
- She does not know if her mother had a fragility fracture but does remember mom being hunched over.

ROS

- No hx of kidney stones, malabsorption, No known hx of celiac disease, No hx of seizures or antiseizure medication use, No hx of radiation therapy.

PMHX

- Hyperlipidemia
- Polymyalgia rheumatica treated now on "very low dose of prednisone"

Medication

- Simvastatin 20mg qd
- Prednisone 5mg qd

Vitals are stable

- Mild Cushingoid facies
- No kyphosis
- Minimal discomfort on spine palpation
- No goiter
- No tremor
- No thyroid eye findings

Labs and DEXA

DEXA

- L/s T score –1.6
- Femoral neck T-score -1.5
- Hip T-score –1.3
- Frax analysis: 10 year risk for a major osteoporotic fracture is 19%
- Hip fracture risk is 3.7%

Labs

- SPEP/UPEP, Serum calcium, Phosphorus, 25-OHVitamin D levels, TSH, Free T4, CBC, 24 hour urine calcium/Cr ratio, CMP, celiac antibodies.

What should we recommend.

- Smoking cessation
- Get more details on current prednisone use.
- Life style modification: exercise- weight bearing and strengthening
- Treat with appropriate calcium and Vitamin D
- Counsel on fall prevention- Balance training and Hip strengthening exercises.
- Limitation of alcohol consumption, and the assessment and management of fall risks.

- Do we start treatment with medication

Or

- Do we start with conservative management- No medications

OR – medication and which one.

We need to understand her risk for a fragility fracture

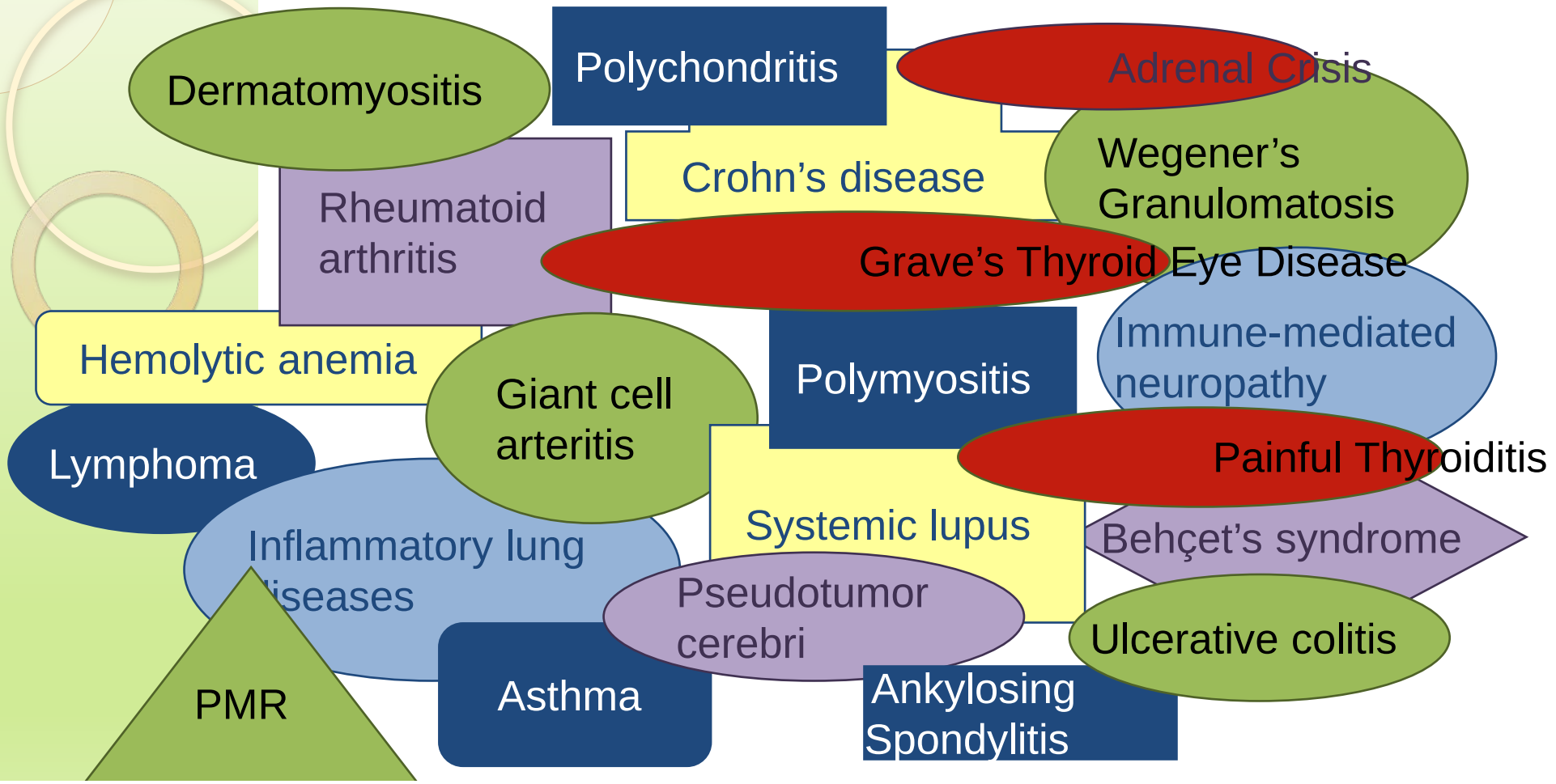
- Smoking
- Prednisone use
- Tobacco
- Maternal Hx of osteoporotic fracture.
- Age
- Postmenopausal

Smoking cessation, and fracture risk in elderly women followed for 10 years -Study in Osteoporosis International

- Smoking increased the risk of all fractures- Femur and vertebral
- Cessation of smoking decreased vertebral fractures
- Using FRAX analysis
- + Smoking 10 year Probability MOF 16% and HF 3.7%
- Smoking discontinuation: 10 year prob of MOF 16% and HF 2.2%

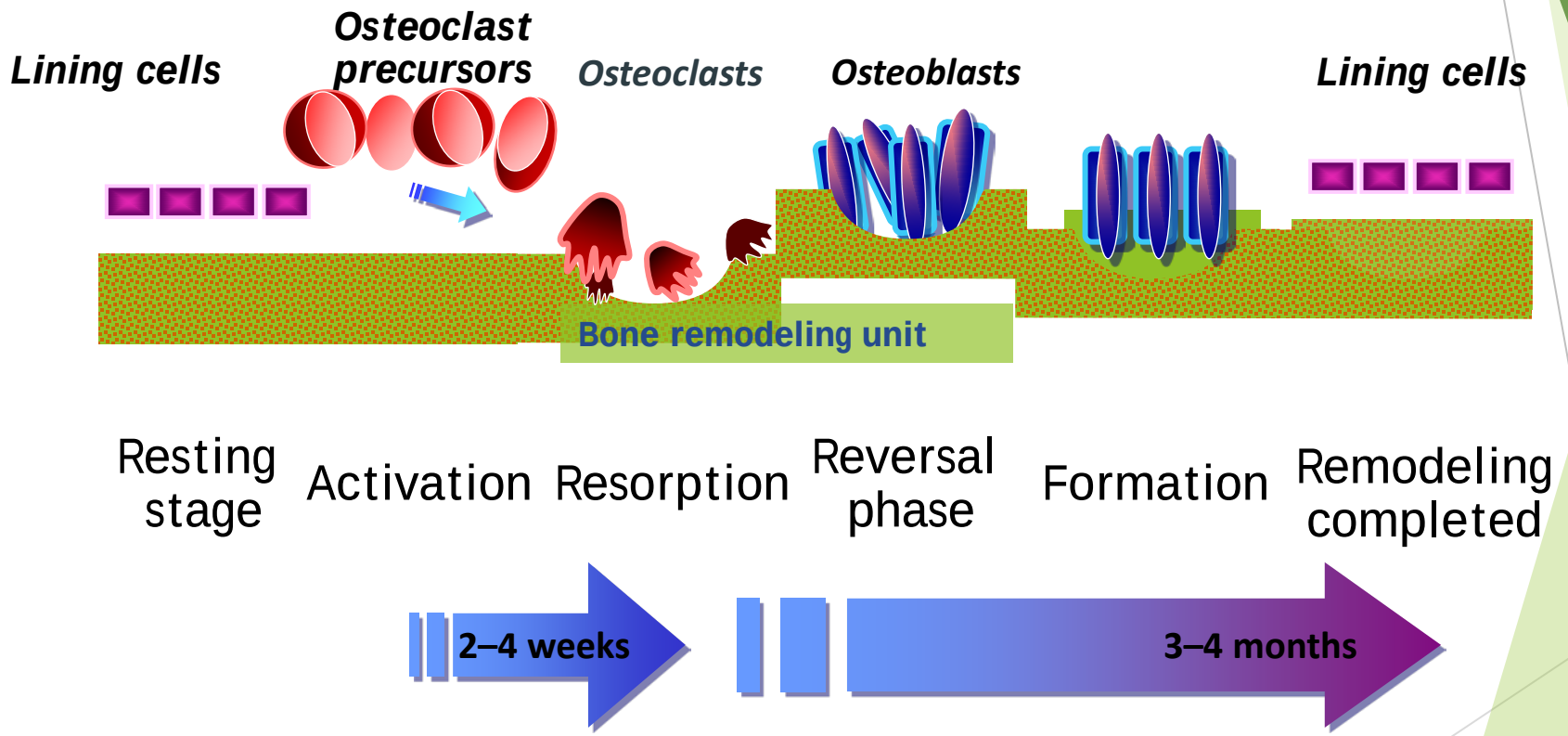
M.H Torin et al. Osteoporosis. Int. 2016 Jan;27(1):249-55.

Approximately 1% of all adults and 3% of adults older than 50 years of age receive Glucocorticoids

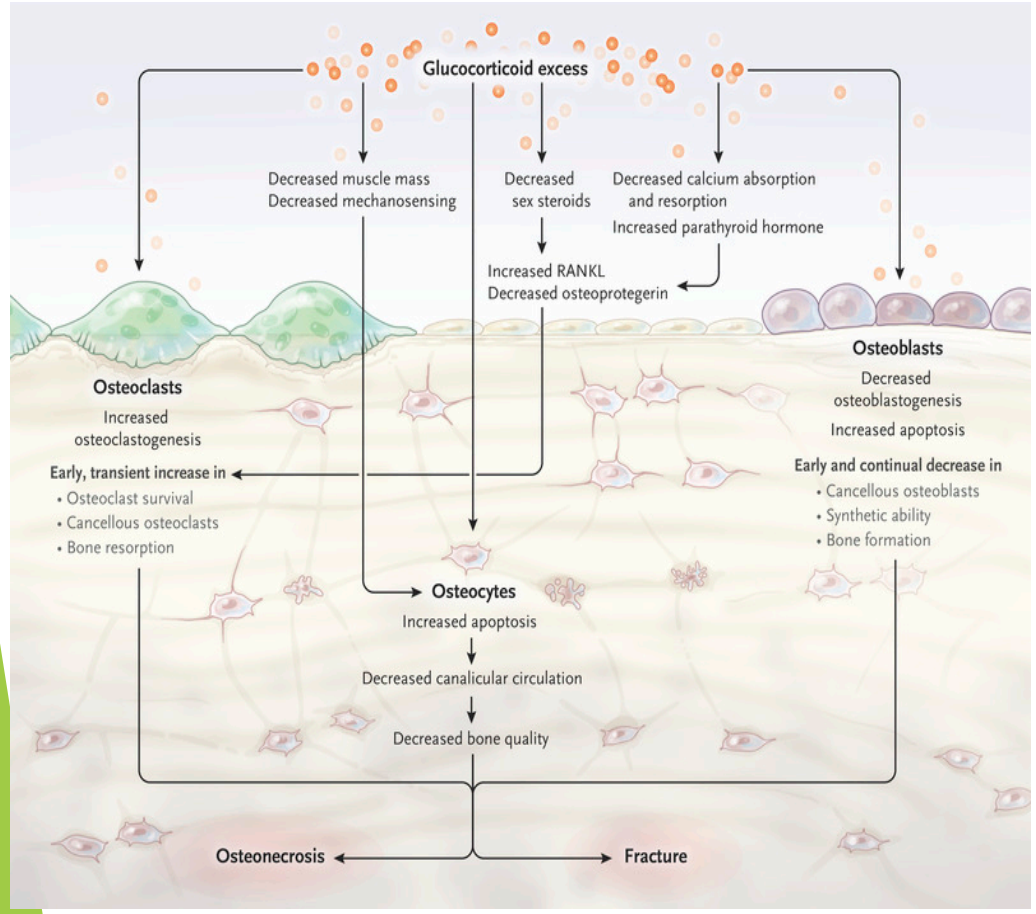


Steroids are Bad for Bone!

Normal Bone Remodeling

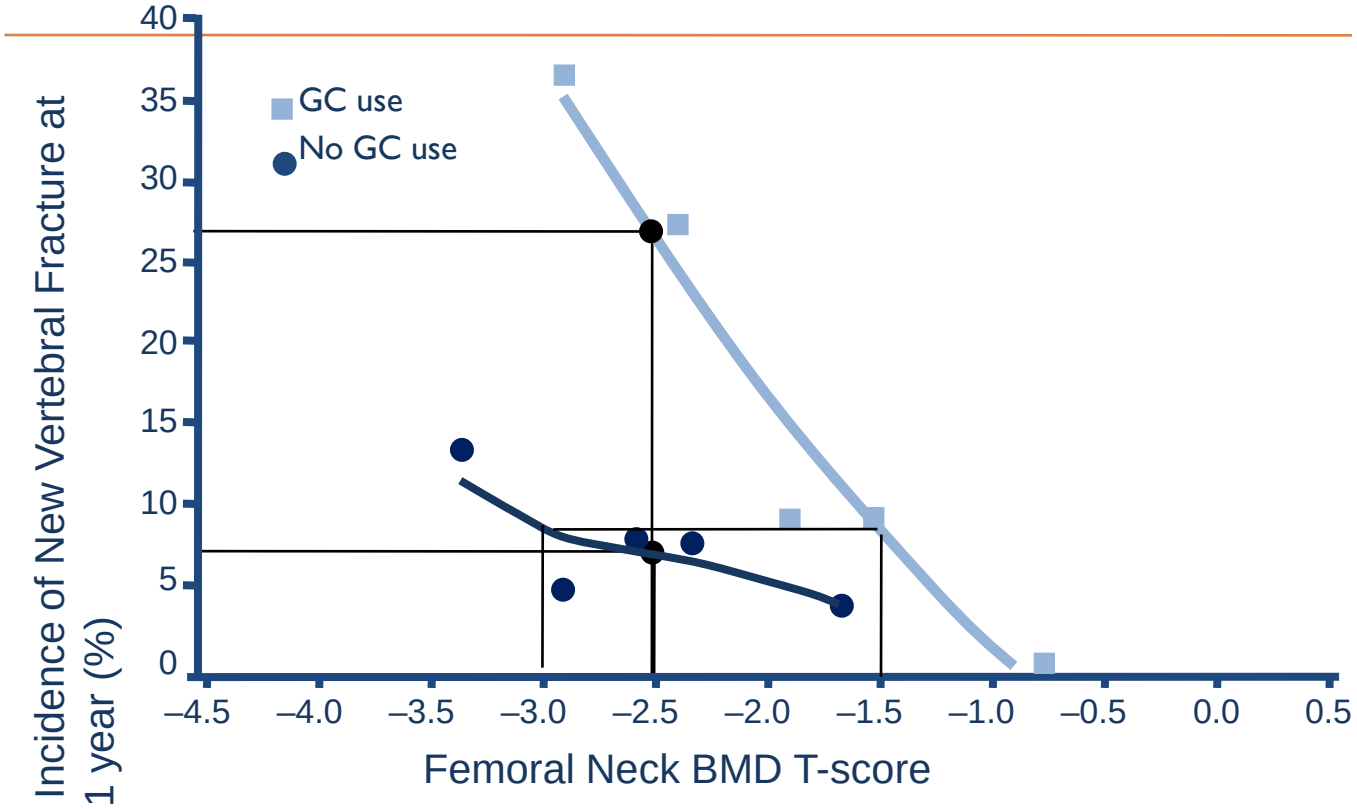


How steroids cause osteoporosis.



- Increase in RankL-osteoclastogenesis
- Increases in Osteocyte and Osteoblast apoptosis
- Decrease in new bone formation
- Decrease in muscle mass
- Decrease in renal absorption of calcium
- Decrease in sex steroids
- Decrease in cannanicular circulation
- Poor quality bone
- Vertebral #s are the most common fractures associated with steroids.
- Risk of vertebral #s start to rise within 3 months after initiation and peaks at 12 months

Steroids Increase Fractures.



*Data were obtained from postmenopausal women from the placebo arms of 2 randomized risedronate clinical trials (n=111).

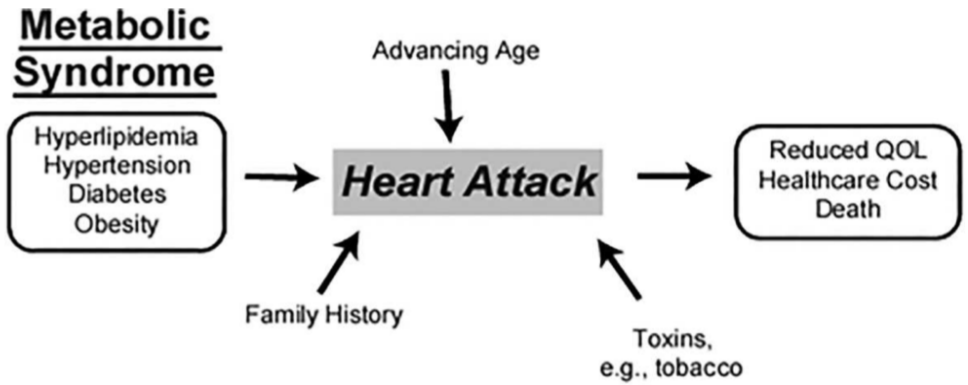
1. Van Staa TP, et al. *Arth Rheum*. 2003;48:3224-3229.

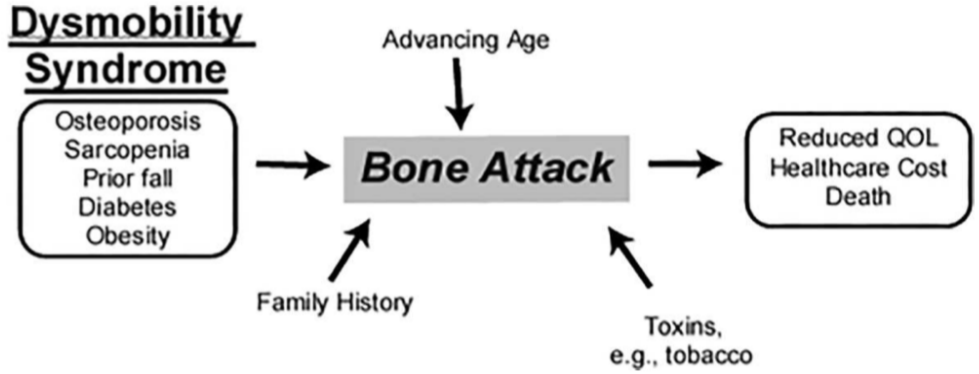
Fracture is a Powerful Risk Factor for Future Fracture

	Relative Risk	
Low BMI	1.3	If BMI <21
Smoking	1.5	If current
Family history	1.6	Sister-Mother

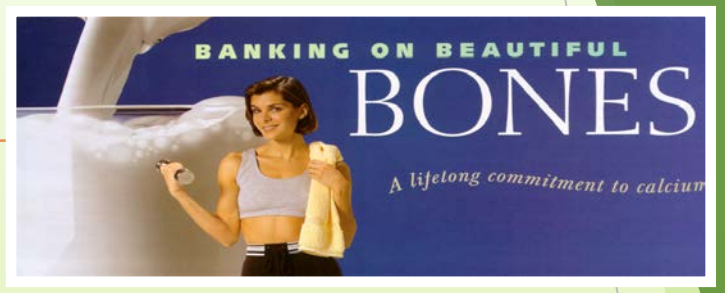
	Spine	Non-Spine
Fractures		
Non-spine	2.2	1.5
Spine		
1 fracture	3.2	1.6
2 fractures	8.0	2.0

Cauley JA, et al. *Osteoporos Int*. 2000;11:556-561





30,000 ft view: Osteoporosis



Calcium 1,000mg/day dietary calcium is best.

Vitamin D @2000iu/day

Exercise

- Weight-bearing impact
- Back strengthening
- Balance and core
- FALL PREVENTION

Medical Therapy

Indication for Pharmacologic Treatment

- Initiate pharmacologic treatment in:
  - **Those with clinical or asymptomatic hip or vertebral fracture**
  - Those with a T score ≤-2.5 at the hip, spine or femoral neck
  - Those with osteopenia and a FRAX 10 yr probability ≥20% of major osteoporotic fracture or >3% of hip fracture

  - For our patient:

The first option would be an oral bisphosphonate vs IV.

Second option if she fails to tolerate this would be Denosumab.

FDA-Approved Osteoporosis Medications

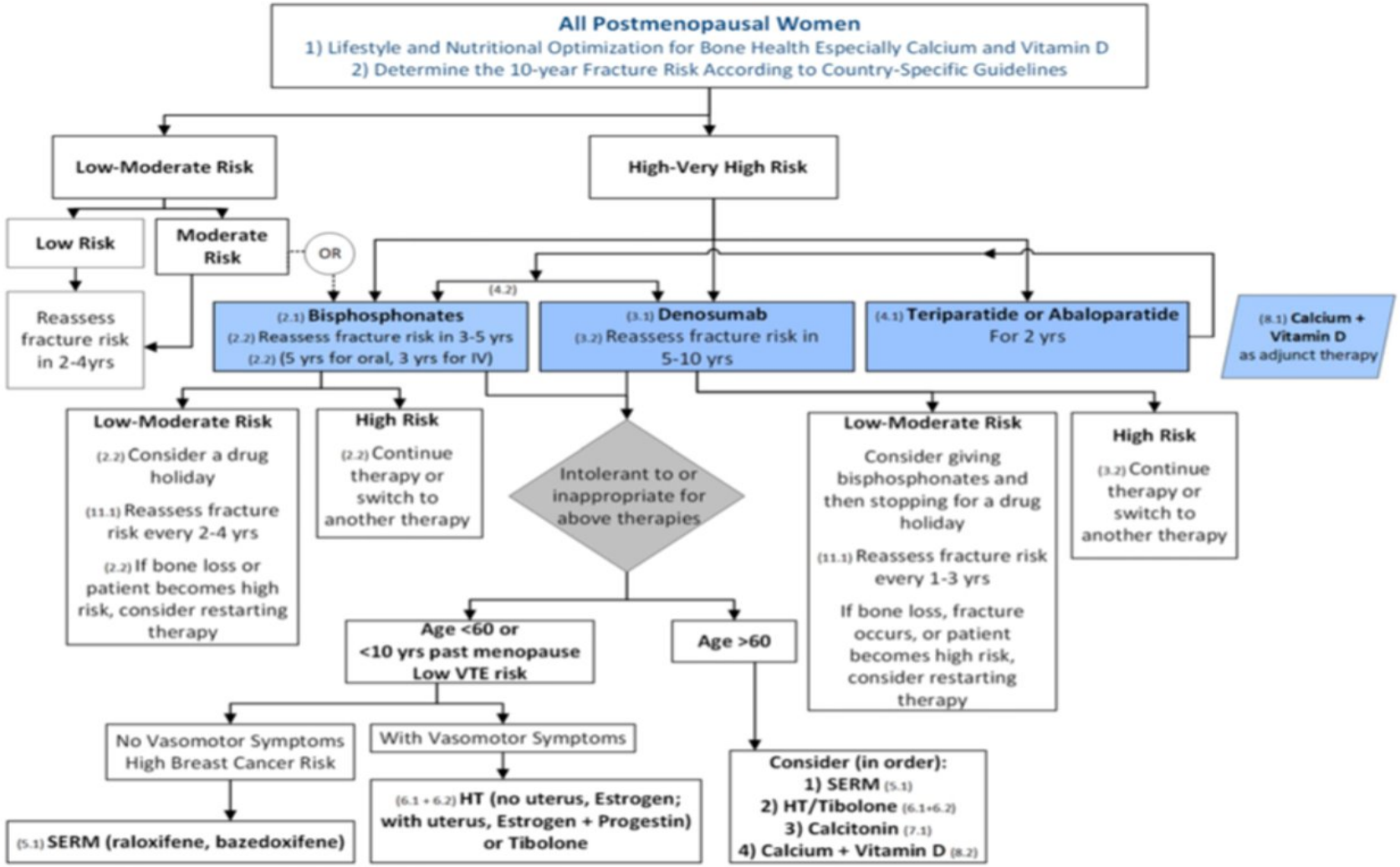
- **Antiresorptives**

- Estrogen/HRT*
- Bisphosphonates
  - Alendronate (Fosamax)*
  - Risedronate (Actonel)*
  - Ibandronate (Boniva)
  - Zoledronic Acid (Reclast)*
- SERMS:
  - Raloxifene (Evista)
  - Bazedoxifene (Duavee)
- Calcitonin (Miacalcin)
- Denosumab(Prolia)*

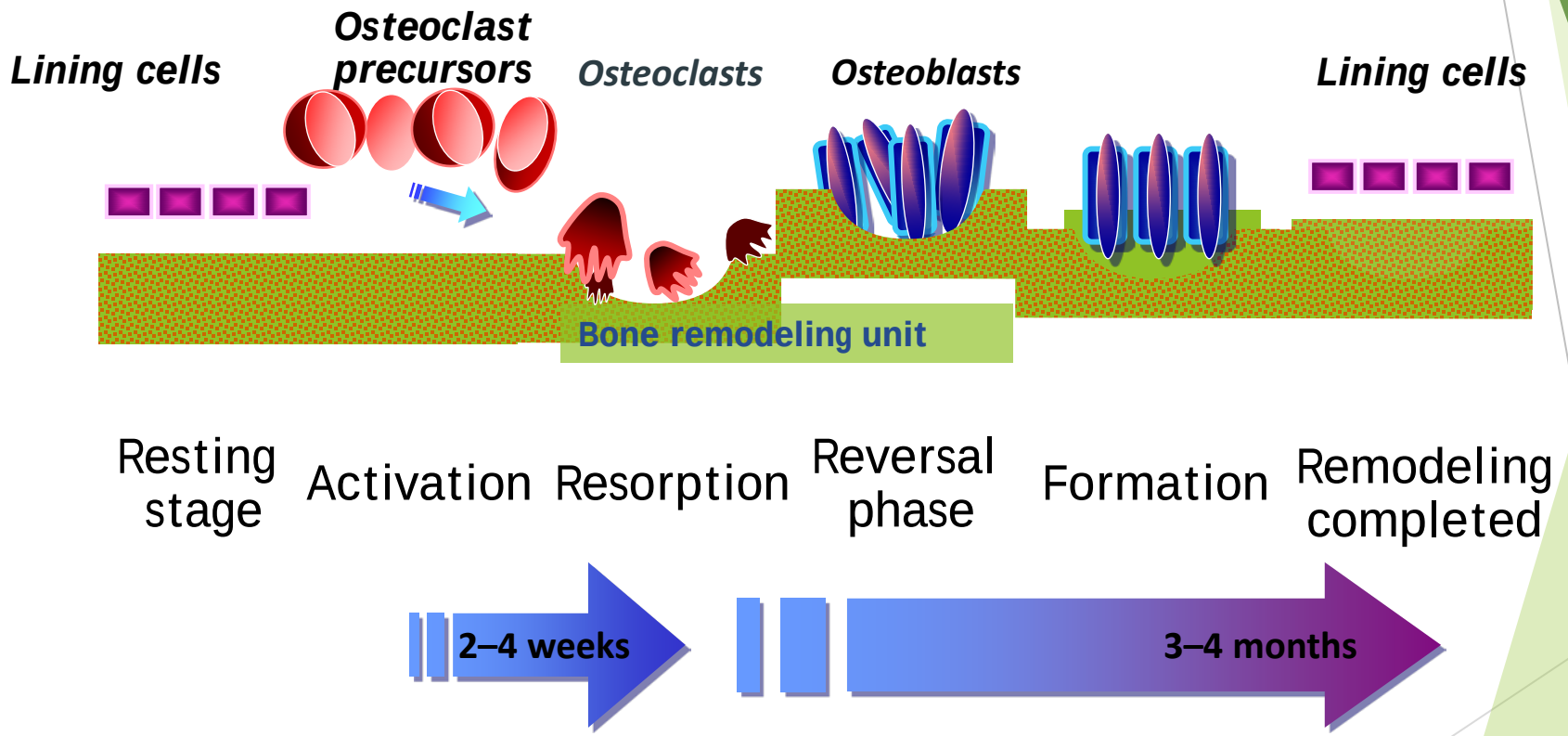
Anabolics

- **Parathyroid Hormone (Teriparatide, Forteo)**
- **PTHrP Analogue (Abalopartide, Tymlos)***
- **Romosozumab(Evenity)**

PHARMACOLOGICAL MANAGEMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE. Eastell, et al. JCEM 104 1595–1622, 2019



Normal Bone Remodeling



There are 18 different osteoporosis guidelines and associations.

- Americal college of Rheumatology
- American college of Physicians
- National osteoporosis foundation
- American association of clin endocrinologist
- US Preventive task force
- Osteoporosis international
- International osteoporosis foundation
- WHO
- To name a few….

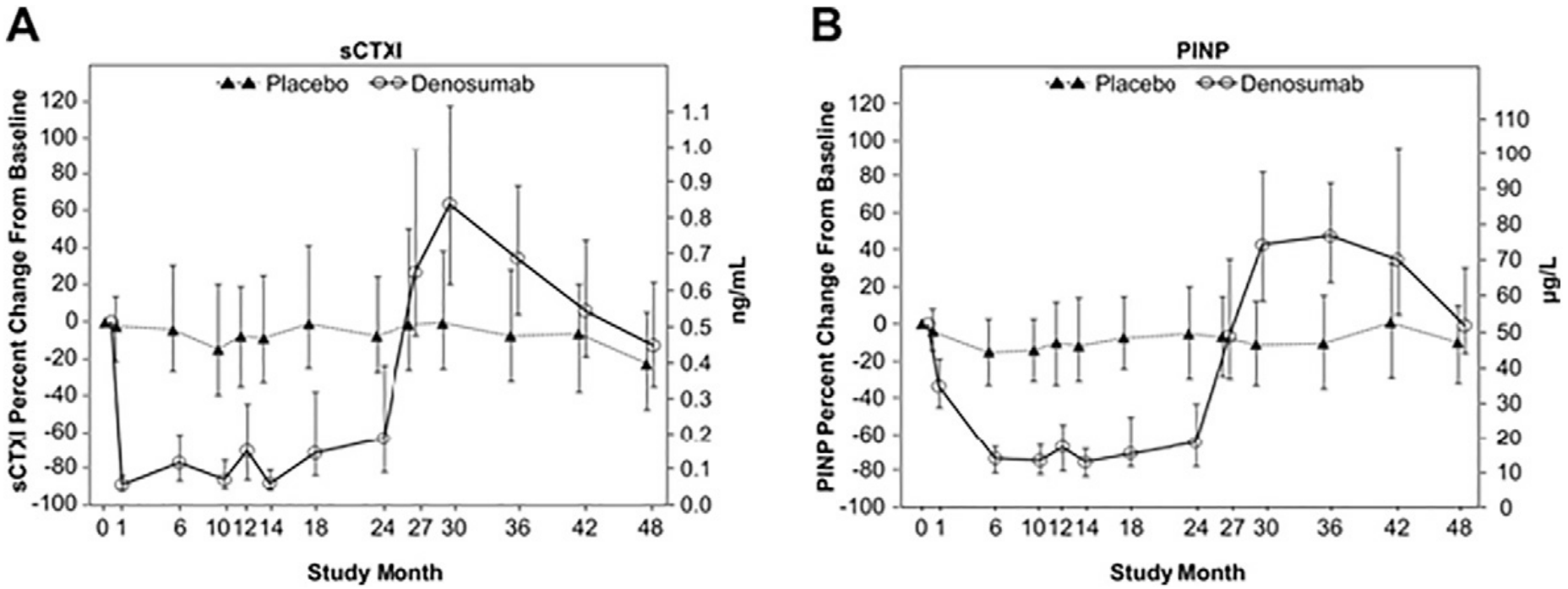
Systemic review by Solomon et al medication use patterns for Osteoporosis an assessment of guidelines treatment rates and quality improvement interventions: Mayo clinic Proc 2005;80(2):194-202

The guidelines are relatively consistent and that any inconsistency is unlikely to contribute to under-treatment of osteoporosis.

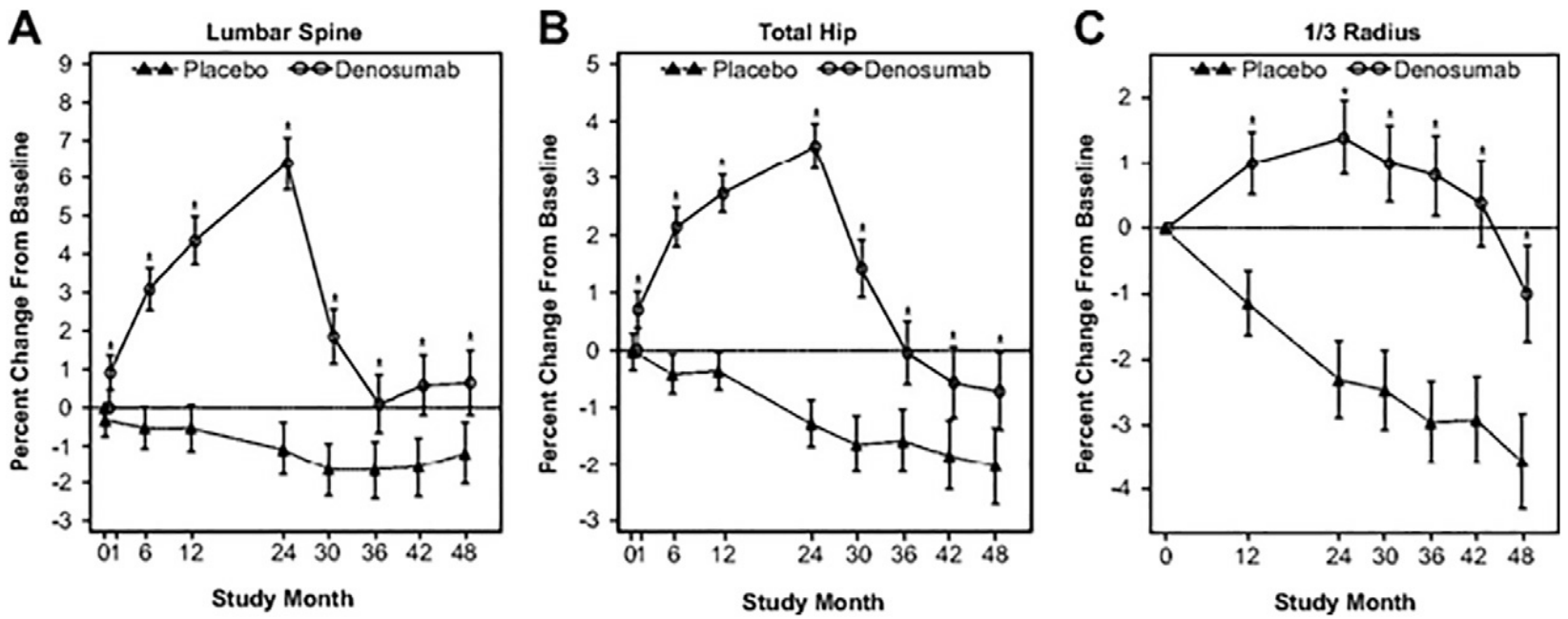
FREEDOM EXTENTION 10 year data

- The FREEDOM trial open-label extension
  - 4,450 women on denosumab- (Prolia) for either 7 or 10 years
- 10 yrs of DMAb was associated with:
  - sustained low fracture rates
  - steadily increasing bone mineral density persistent reduction of bone turnover
  - no increase in adverse events over time
  - There is a concern about the risks associated with Prolia discontinuation.

Bone Markers Rebound within 3 months of Stopping Dmab-Prolia

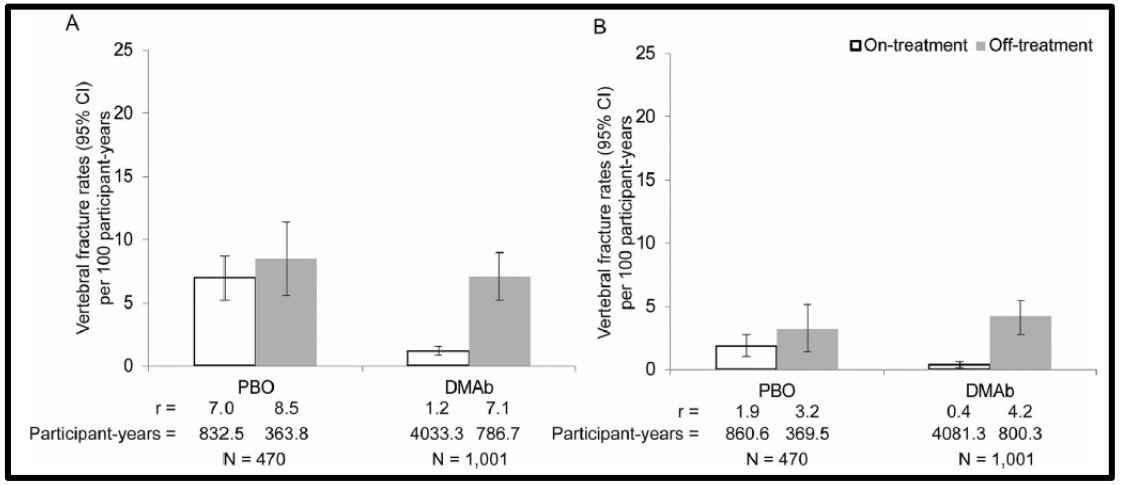


Bone Density Drops within 6 months of Stopping Dmab

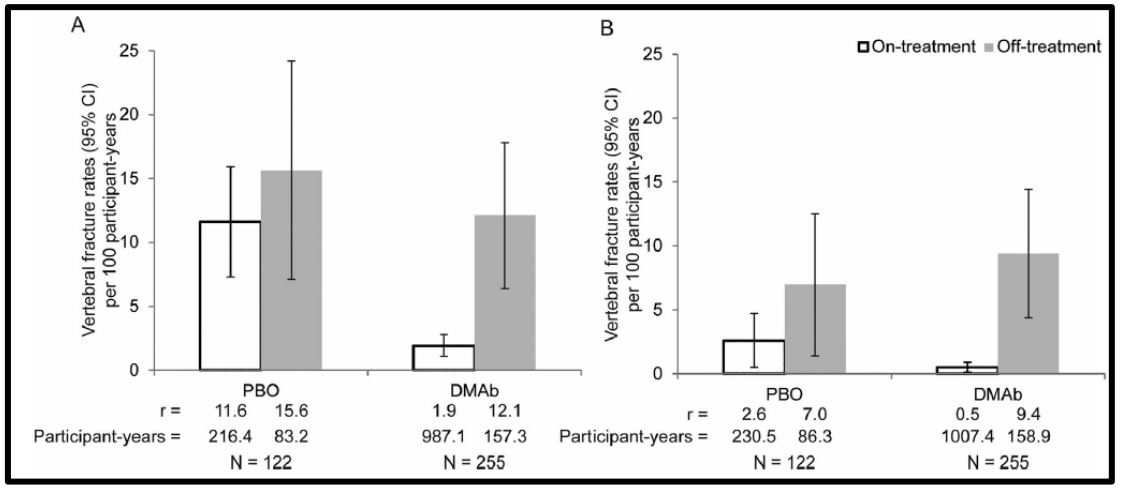


Vertebral Fractures Increase when Dmab is Stopped

ALL



With Prevalent Vertebral Fracture



Cummings, JBMR, 2018

Denosumab must be administered in a timely and continuous fashion

No medication holiday with denosumab

Best practice for transitioning off treatment is being studied

2022- ACR has recommended transitioning for 1-2 years to either a bisphosphonate, PTHrp, PTH, Romosozumab.

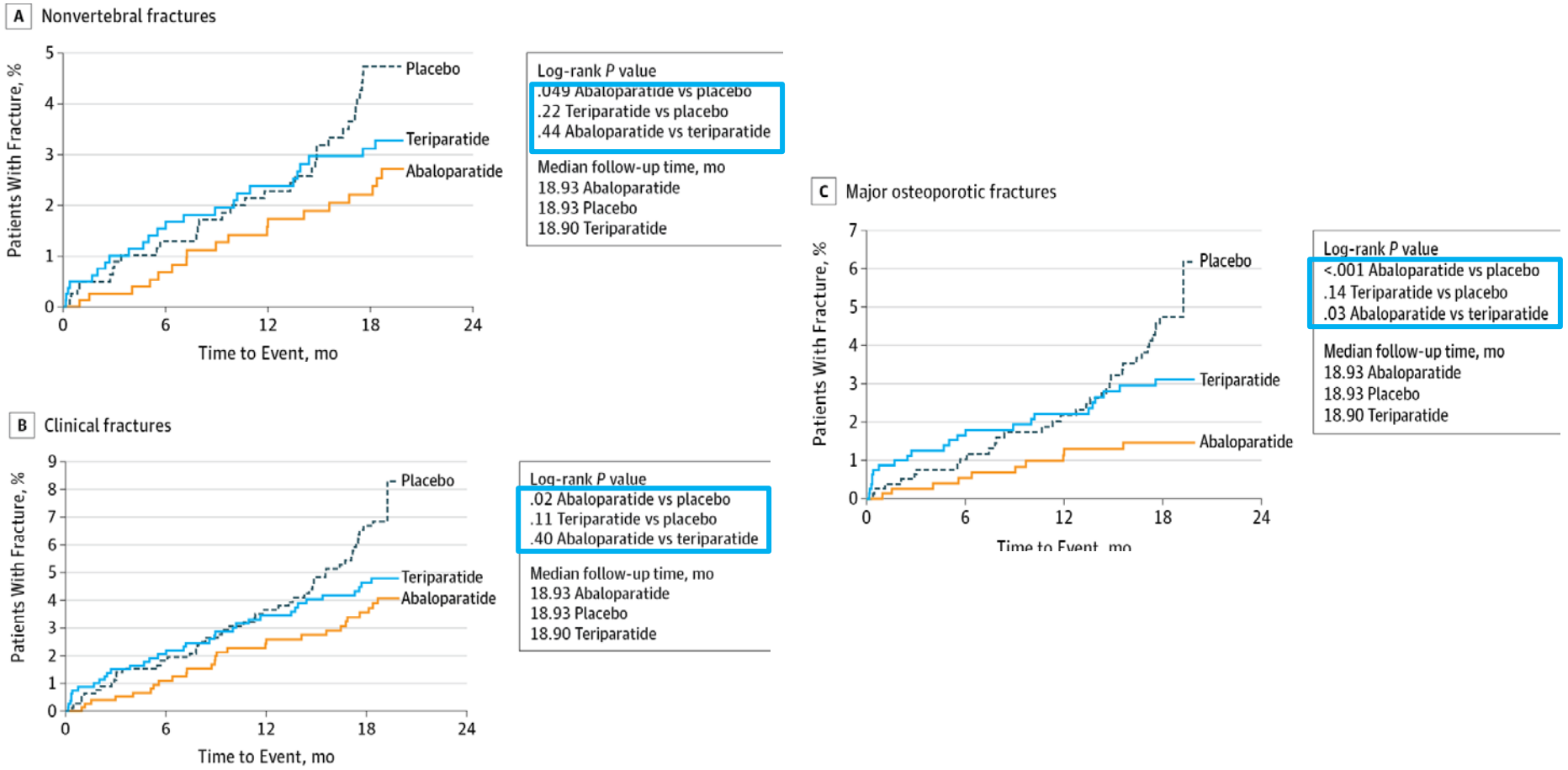
Abaloparatide- Tymlos

- Synthetic peptide analog of human PTHrp
- Potent anabolic agent for the treatment of osteoporosis in PMO
- Daily subcutaneous injection
- 2 years of therapy
- Must be followed by antiresorptive therapy

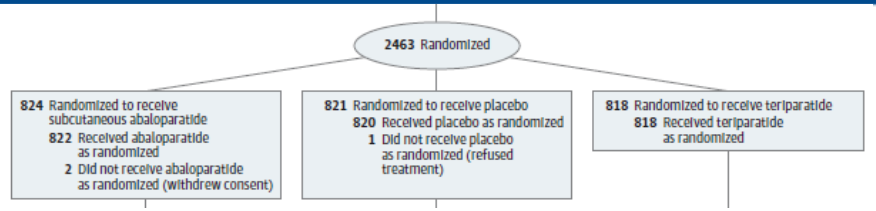
Abaloparatide Comparator Trial in Vertebral End point (ACTIVE)

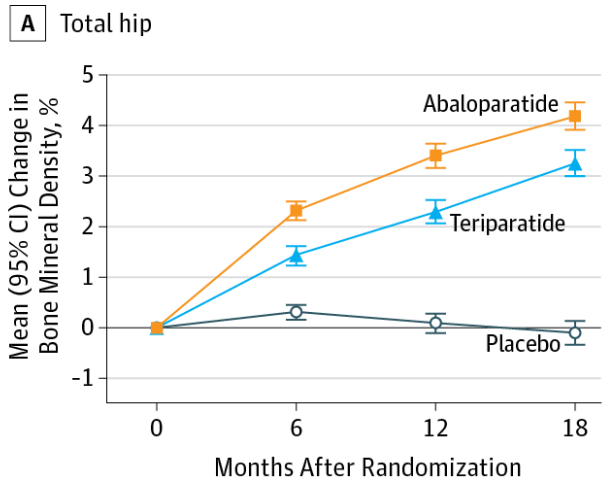
- Randomized controlled and comparator
- 80 mcg abaloparatide, 20 mcg TPTD, injected placebo
- 18 months
- 2463 post menopausal women (1901 completed)

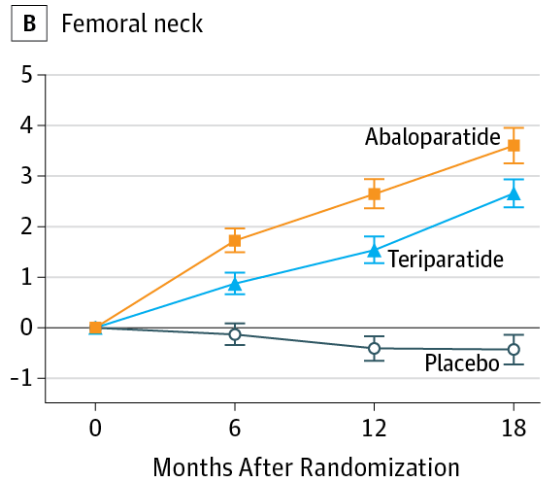
ACTIVE: Fracture

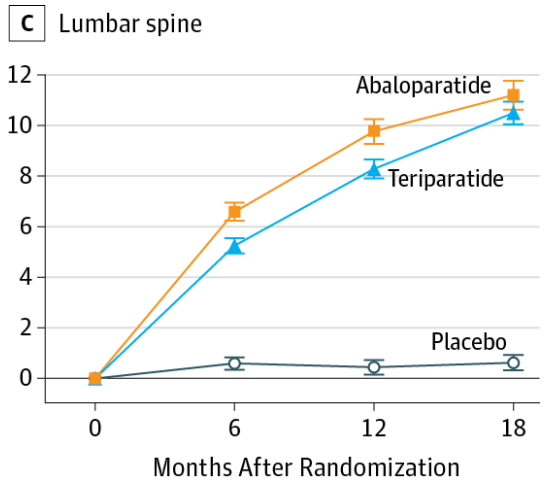


ACTIVE: Abaloparatide v. Teriparatide









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

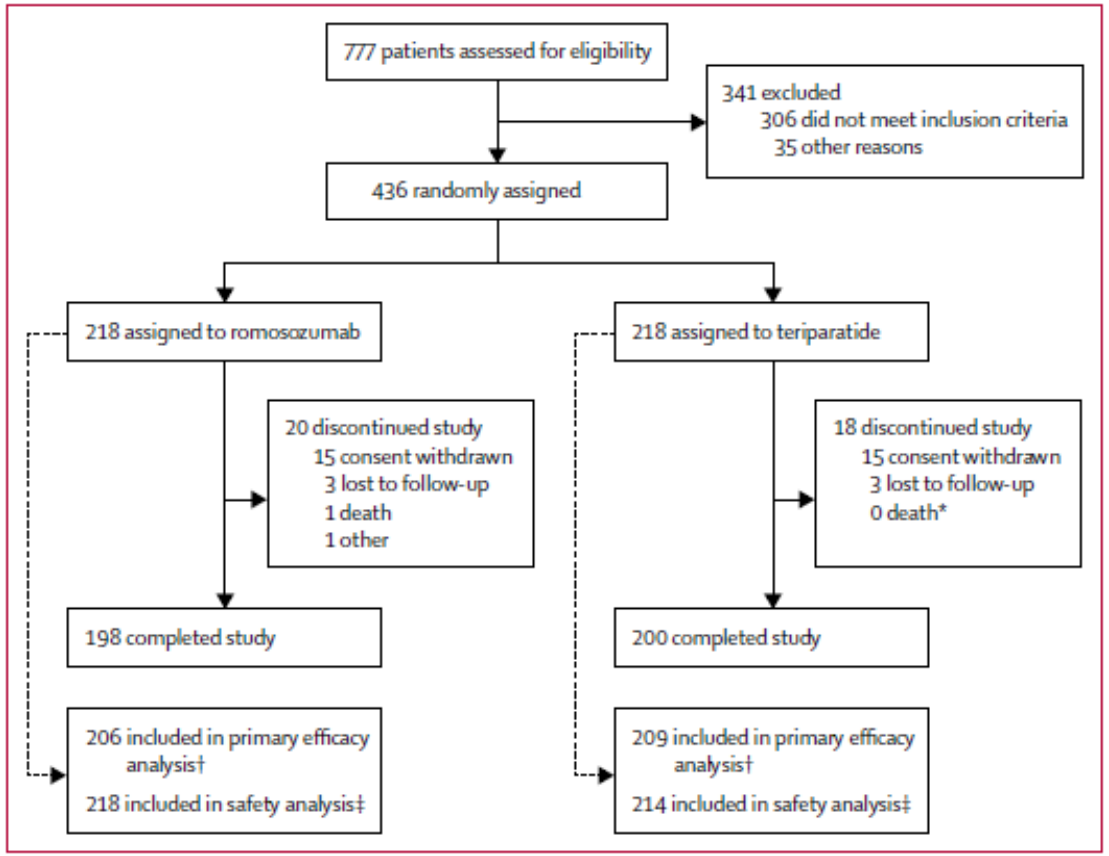
Side Effects of Abaloparatide- Tymlos

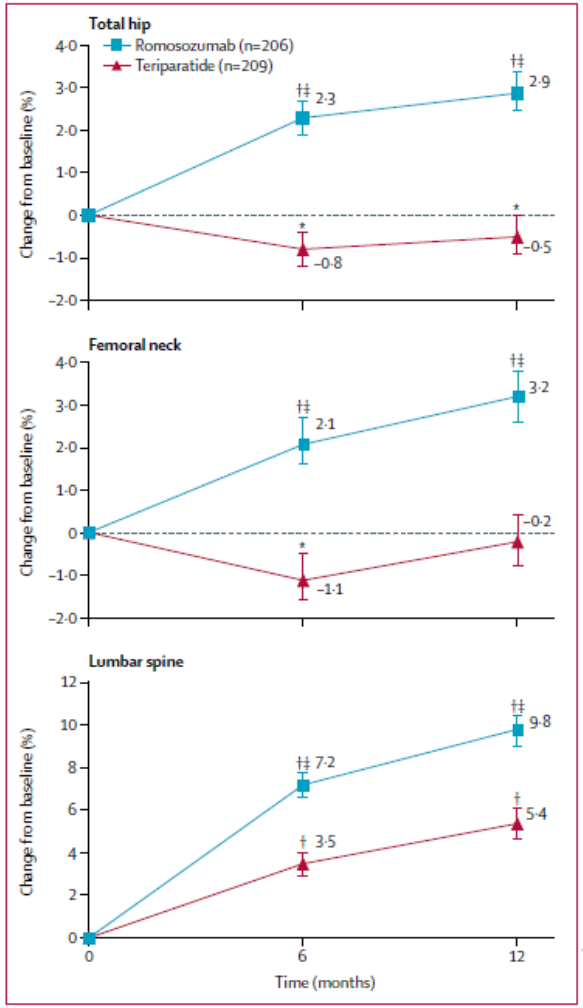
- Black Box: Contraindicated h/o skeletal irradiation, Pagets, mets, open epiphysis
- Hypercalcemia
- Urolithiasis
- Increased Uric acid
- Palpitations
- Hypotension

Romosozumab- Evenity

- Humanized antibody that inhibits Sclerostin.
- Sclerostin is secreted by Osteoclasts to decrease bone formation.
- Administered by a health care professional
- 210mg subcutaneous injections once a month for 12 months
- Must be followed by an antiresorptive
- *Although now approved FDA had initially rejected this due to the cardiovascular risks*.

Romozosumab v. Teriparatide





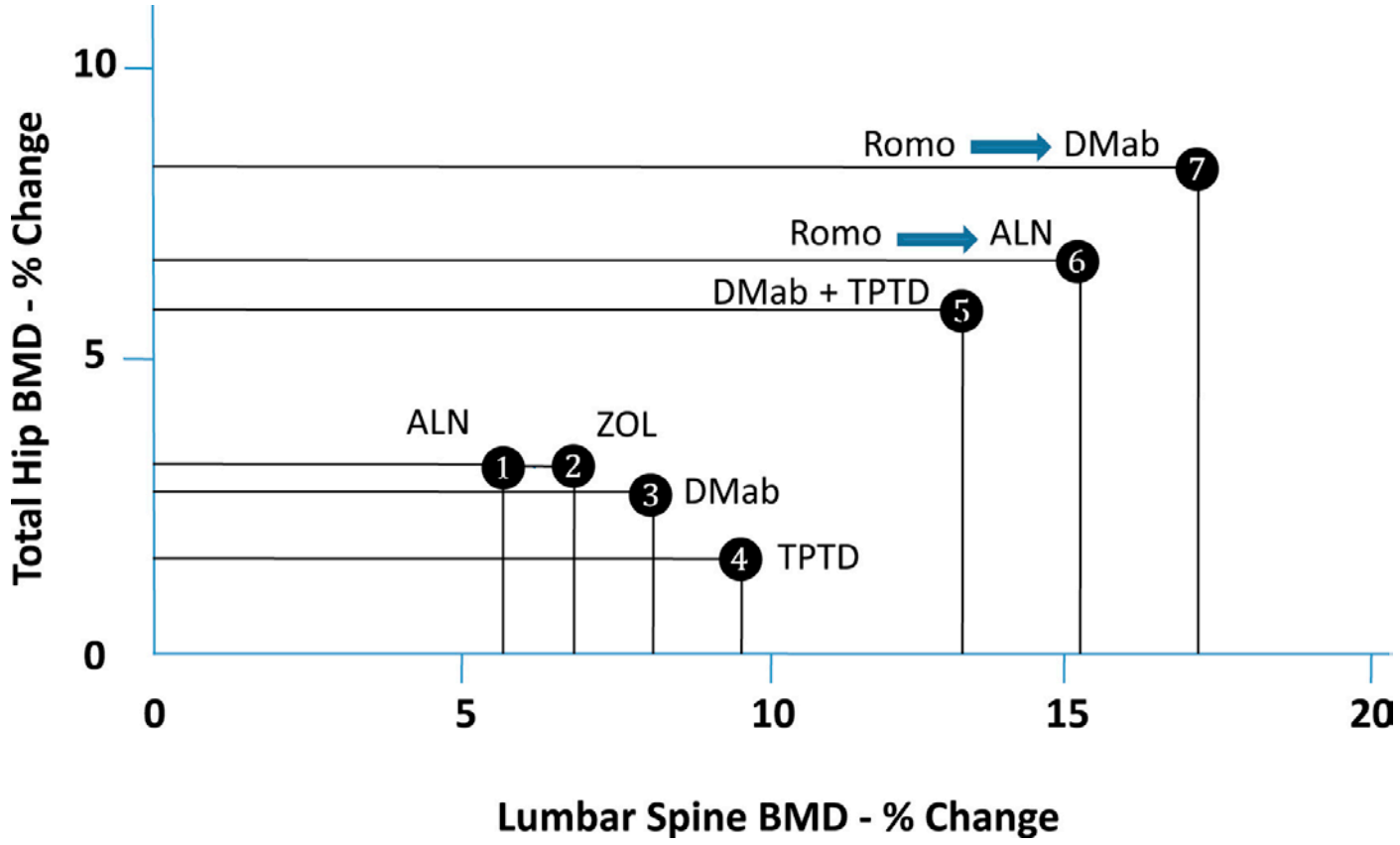
Langdahl, Lancet 2017

Side Effects

- Black Box: CV (contraindicated in those with MI or stroke within a year)
- Arthralgia/myalgia
- Hypocalcemia
- Atypical femoral fracture
- Osteonecrosis of the jaw

- Romosozumab is a potent bone anabolic agent used in severe osteoporosis or those that fail other therapy
- Vertebral fracture reduction>non vertebral
- Romo followed by Dmab is best
- CV side effects seen in clinical trials

Change in BMD at **24 months** in Spine and Total Hip with Various Regimens



McClung Osteo Sarc 2018

- Fragility fracture is skeletal failure and must prompt evaluation and treatment.
- Denosumab use for up to 10 years is safe and effective.
- ACR -2022 recommends that either Prolia forever or Bisphosphonates, ROMO, PTH or PTHrp may be options.
- There are a variety of new treatment options for osteoporosis, that can allow tailoring therapy to the individual patient characteristics.
- “Medication Holiday” applies only to Bisphosphonates other agents including denosumab must be continued or followed by other therapy.

Osteoporosis Update.

Acknowledgements: Thanks to Lynn Kohlmeier,MD Spokane Osteoporosis and Endocrinology and Mayo Clinic