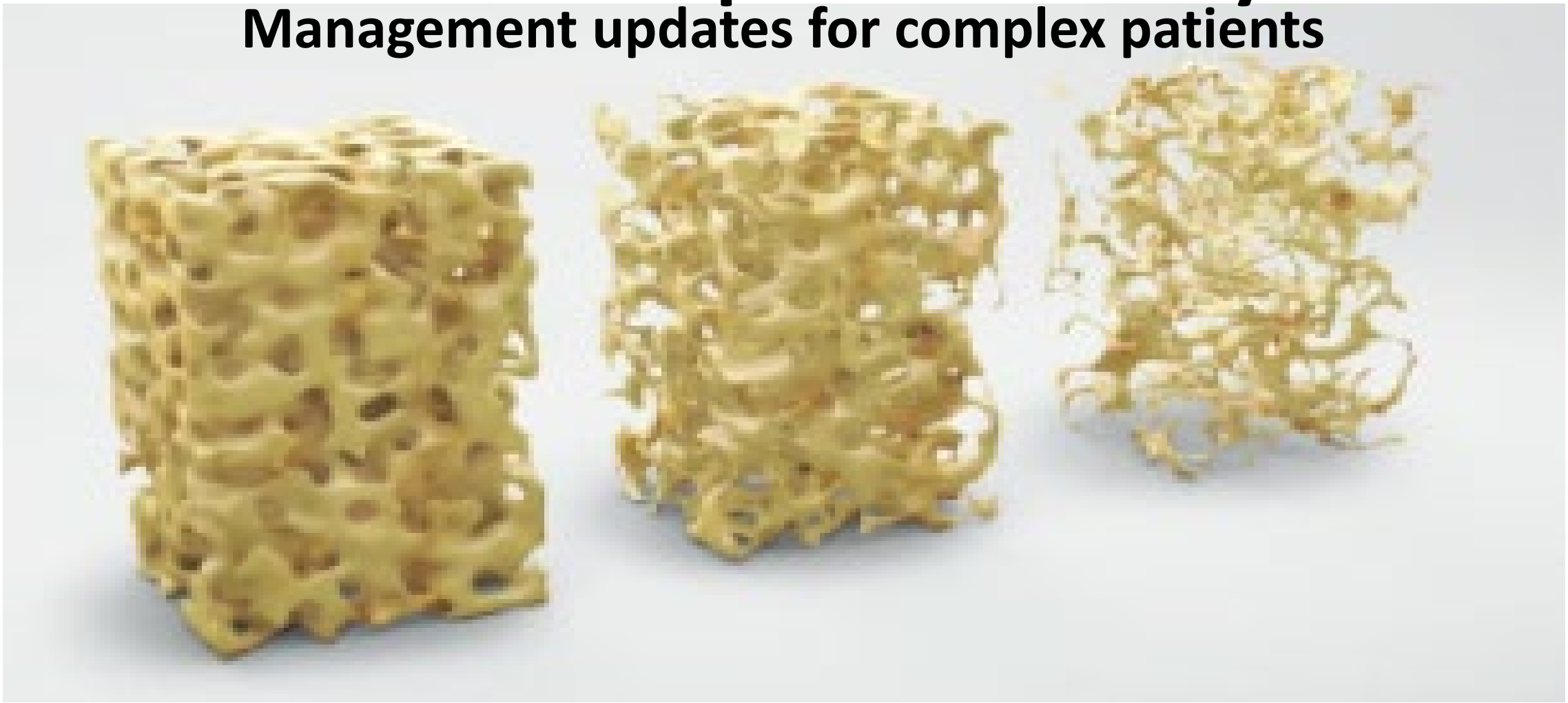
# Don't let osteoporosis break you!

## Management updates for complex patients




•Alexandra Charlton, BScPharm, PharmD, ACPR
•Pharmacy Clinical Practice Leader, AHS
•Rheumatology Pharmacist, AHS/Cumming School of Medicine

# Disclosures

- **No relevant disclosures for this talk**

- **All photos, unless otherwise noted and attributed are from Shutterstock (User ID 252919591)**

# Objectives

- To identify what makes a patient complex in the world of osteoporosis
- To review the options for treatment of osteoporosis in a complex patient
- To review the potential risks and benefits of each treatment option in a complex osteoporosis patient
- To review guidelines and recommendations for the treatment of a complex osteoporosis patient

# Osteoporosis management in my practice...

- 2018 Study:

  116 RA patients > 50yo, random sample from each physician

  61.2% were moderate or high risk for fragility fracture

  40% had already had a prior fragility fracture

  Only 16% had prescription treatment (bisphosphonate or biologic) in the prior year.

- Division among physicians as to who should be managing fracture risk in these patients

Charlton, A et al. J Rheum 2019 46(7) 843-844

# Typical Patients

- Elderly

- Inflammatory Disease :
  Ex. Polymyalgia Rheumatica/Giant Cell Arteritis, ANCA vasculitis, Rheumatoid Arthritis

- Prior fracture/osteopenia/osteoporosis
  - already on, or recent history of bisphosphonate use

  - glucocorticoid exposure

- Multiple co-morbidities
  - decreased renal function
  - high cardiovascular risk, diabetes etc.

- Limited insurance/ fixed income

# Sample patient

- 73 yo female with relapsing Giant Cell Arteritis
  also: afib, hypertension and hypothyroidism

- Retired admin assistant, husband retired truck driver

- Prior vertebral wedge fractures at T12 and L 3-4;

- Medications:
  prednisone 6mg daily; (Started at 60mg daily 18 months ago, difficulty tapering off completely)
  alendronate 70mg weekly X 6 years, then switched to zoledronic acid X 3 years
  apixaban 5mg bid
  Synthroid 0.125mg daily
  Calcium 500mg daily & Vitamin D 2000IU daily

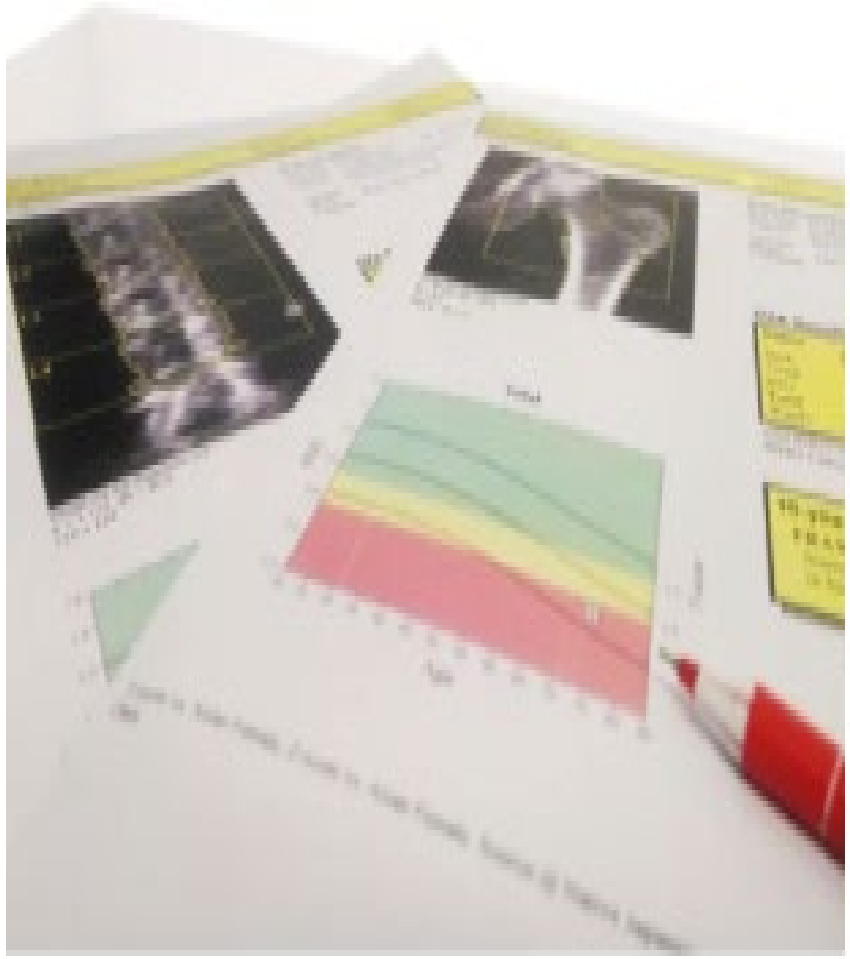
- Relevant labs:
  SCr 105; eGFR 42ml/min/m2;  TSH: 6.92,  CRP 9.1

# Sample Patient BMD

- last BMD: relatively stable, but very osteoporotic;
  - slight but significant percentage decrease since last BMD

- T-scores:
  - lumbar spine: -2.9
  - femoral neck: - 2.6
  - trochanter: -2.5

- CAROC: HIGH RISK > 20% 10-year risk of fracture



# Options:

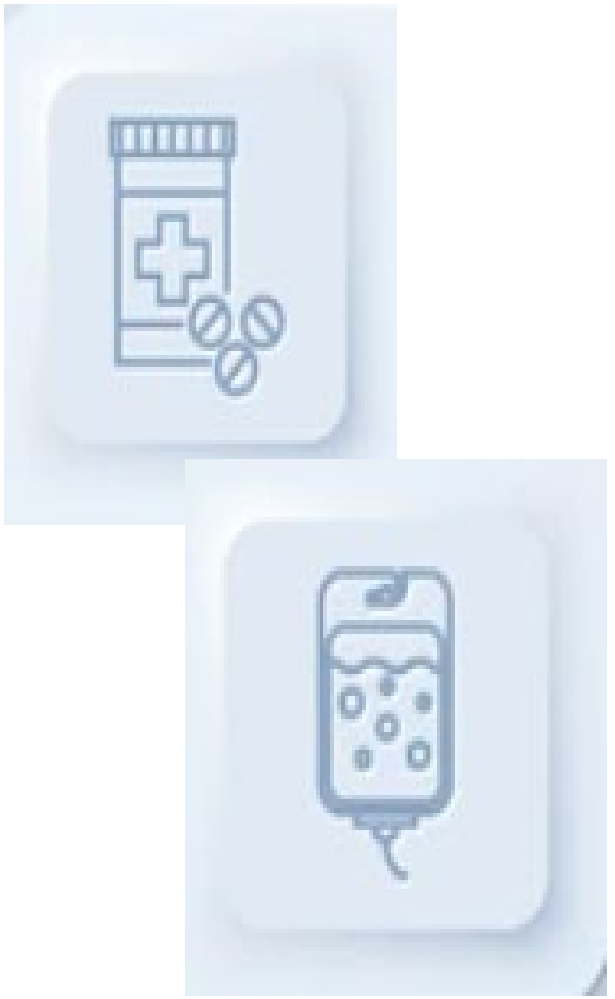
1. Continue with bisphosphonate
2. Switch to denosumab
3. Drug Holiday
4. Switch to teriparatide
5. Switch to romosozumab

# Bisphosphonate continuation

Recommended maximum length of therapy:

10 years of po,  6 years of IV

( our patient: alendronate X 6 years, zoledronate X 3 years)



Risk of continuing bisphosphonate:

Atypical femur fracture

Other risk factors associated with atypical femur fracture:

Asian Ancestry √ (Chinese)

Shorter Height √ (5’1”)

Higher Weight √ (BMI 31.2)

Glucocorticoid use for > 1 year √ (18 months and counting)

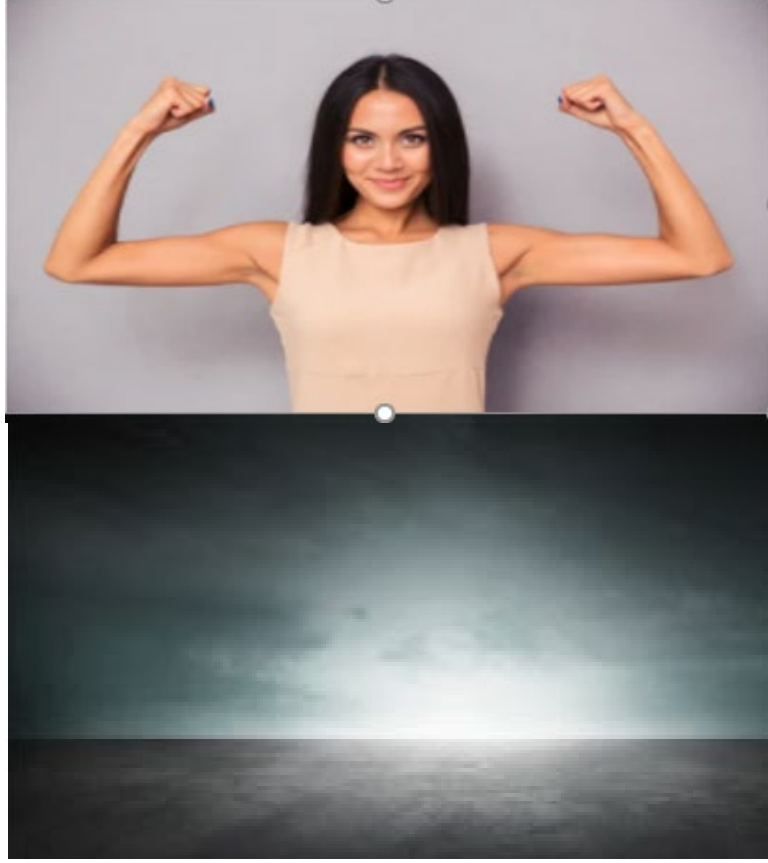
Black et al.  NEJM 2020; 383:743-753

# Evidence for Long Term Bisphosphonate Use

- **Fracture Intervention Trial Long-Term Extension (FLEX)**
  - alendronate vs placebo
  - 10 years alendronate in patients with hip T-score Between -2 and -2.5
  - significantly fewer clinical vertebral fracture compared to placebo

- **HORIZON EXTENSION**
  - 6 infusions of zoledronic acid in patients with hip T-score < -2.5
  - decrease in vertebral fractures compared to placebo, but no difference in non-vertebral fractures.

- **Women's Health Initiative**
  - Cohort study, average age of 80 years; compared subgroups of 2yrs vs 3-5 yrs, 6-9 years and 10-13 years.
  - Improvements over two years of therapy were seen up to 10-13 years, after which the rate of fractures was higher

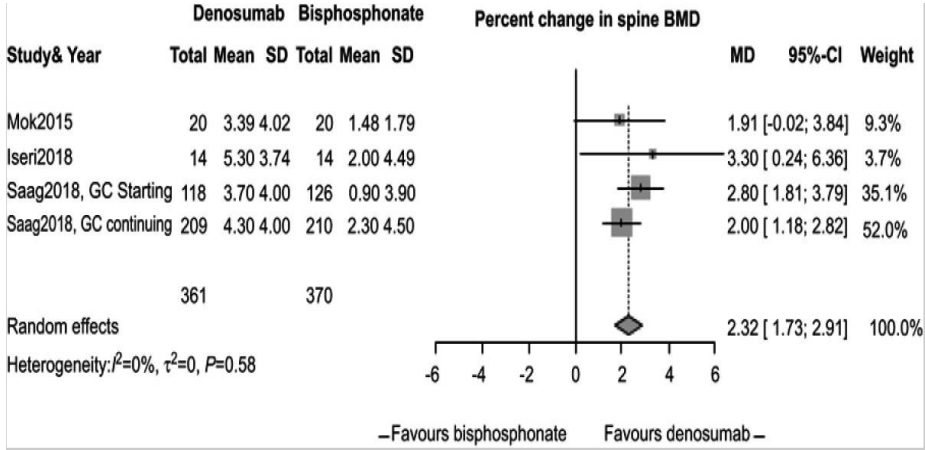


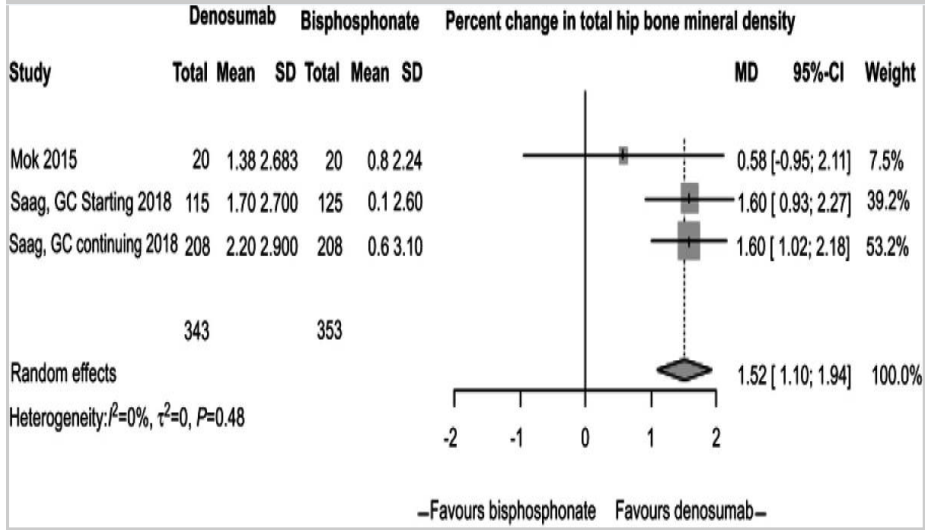
*Black et al. N Engl J Med. 2012;366:2051–2053*
*Black et al. J Bone Miner Res 2012; 7: 243-254*
*Drieling, RL et al. J AM Geriatr Soc 2017 65(9);1924-1931*

# Switch to Denosumab

- Prolia®
- Different MOA, but similar effect on bone resorption, similar risks
- Significantly better in increasing BMD of hip and spine compared to bisphosphonates
- Small study showed switching to denosumab vs staying on bisphosphonates was better
- Denosumab leads to quicker improvement (@ 6 and 12 months) and to a greater extent in patients on corticosteroids
- Non-compliant patients should not use

## Denosumab/Bisphosphonates in GIOP




*Yanbeiy Z, Hansen KE, Drug Des Devel Ther 2019 13: 2843-2852*

*Mok et al Bone 2015 75: 222-228*
*Hsu, Nanes Curr Opin Endocrinol Diab Obes 2018 Dec 24(6)*

# Drug Holiday

- Common practice in those moderate risk after at least 3-5 years of bisphosphonate therapy, little evidence for those at high risk

ASBMR task force on drug holiday (2018):

- Stratified by lowest T-score; there was no statistically significant differences in any fracture, hip or vertebral fracture

- High Risk Group and those with prior fracture: BP holiday group was at reduced risk of any fracture (HR 0.88 CI: 0.78 to 0.99; HR 0.79; CI 0.67 to 0.94) but no difference in hip or vertebral

- Needs careful monitoring for BMD decrease, fracture
  - C-Telopeptide (Serum CTX) to monitor can guide how long to remain off therapy.

Adams et al. JBMR 2018 1252-1259
Ther Adv Musculoskelet Dis 2013 5(3):107-111
Schneider DL, Today's Geriatric Medicine Vol. 8 No. 2 P. 10

# Use of Bone Resorption Markers During a Drug Holiday

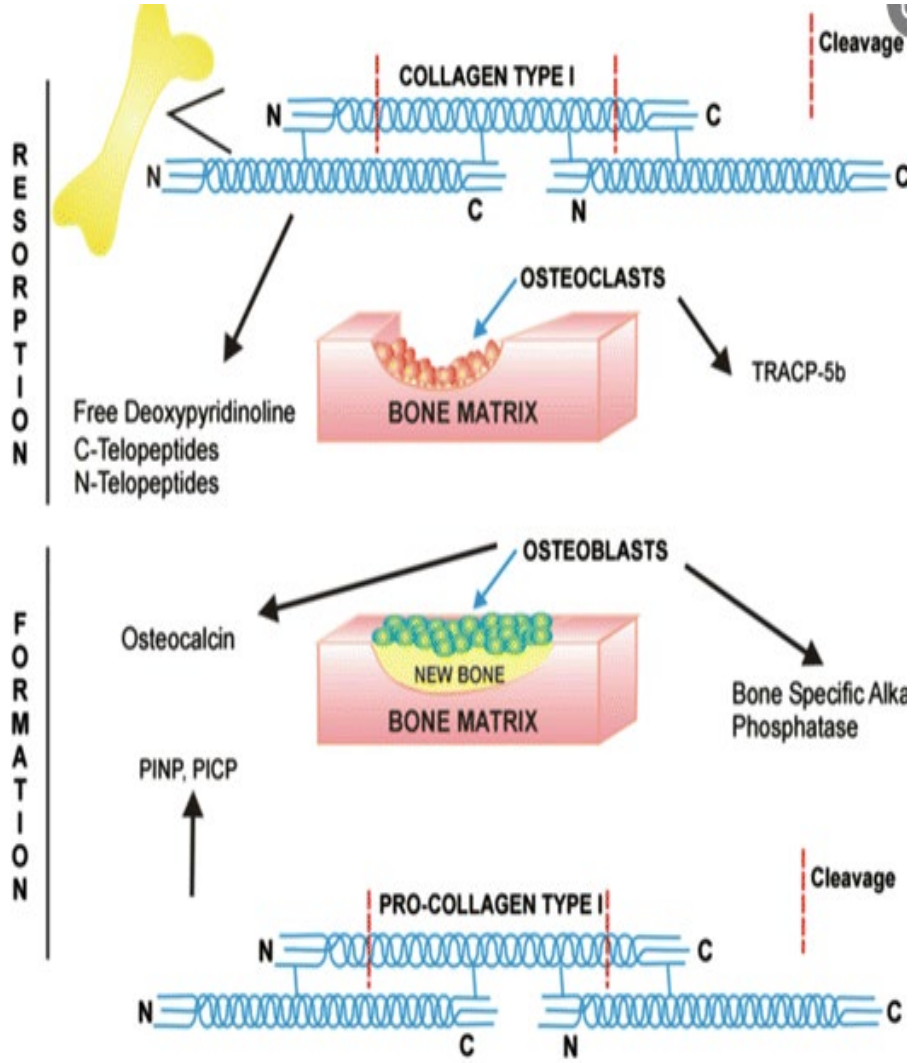
- Most patients on long term bisphosphonates have complete suppression of serum CTX (<400ng/L).

  ~ 25% show increasing levels after 4 months;
  ~ 50% after 1 year

- Those on zoledronic acid remain suppressed longer than other agents

- As bone resorption increases, consider re-start

- NOT appropriate for patients on denosumab or those with a recent fracture




Smith S.Y., Samadfam R. (2017) Biochemical Markers of Bone Turnover

Statham et al Drugs Context 2020; 9: 2020-1-3.

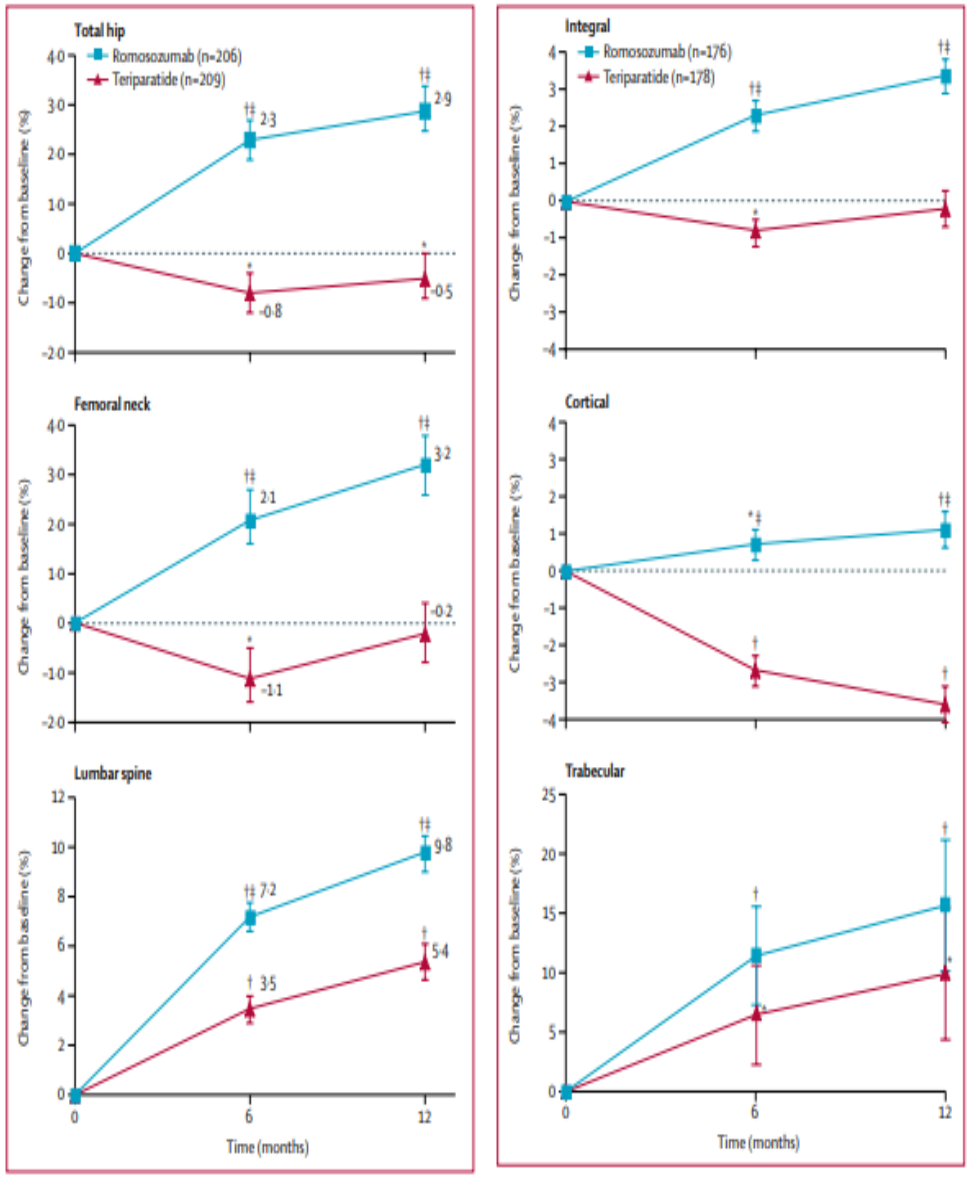
# Switch to Teriparatide

- Forteo®, biosimilars (Apo, Teva, Osnuvo®)
- stimulates osteoblastogenesis and inhibits osteoblast apoptosis, counteracting glucocorticoid action on bones
- Increases bone density and decreases the incidence of vertebral fractures significantly better than bisphosphonates.
- In a study vs denosumab, teriparatide had higher spine BMD change but lower at hip and femoral neck
- Studies of higher dose, once weekly teriparatide for GIOP have been promising (TOWER-GO) may improve compliance

*Saag et al. NEJM 2007 3577: 2028-2039*
*Ameche et al Osteoporos Int. 2016 Jun; 27(6):1989-98.*
*Hsu, Nanes Curr Opin Endocrinol Diab Obes 2018 Dec 24(6)*
*Lyu et al. JCEM 2019 104(11) 5611-5620*
*Tamala.et al. Bone Miner Metab 2021 39(3) 445-455*

# Switch to Romosozumab

- Evenity®
- Mab which binds sclerostin leading to both decreased bone resorption AND increases bone formation
- BMD increases more rapidly and to a greater extent than with teriparatide
- Increases in integral, cortical and trabecular bone were all higher than denosumab in several studies.
    - GIOP particularly effects trabecular bone and increases risk of vertebral fractures
- No studies specifically to GIOP




Langdahl et al. Lancet 2017 390: 1585-1594

So J, Mok CC, JCRI 2020 20(2) 71-79

# Cardiac Issues with Romosozumab

- Carries a warning against using in women at high risk of cardiovascular disease and stroke

**ARCH trial:**
4093 post menopausal women at high risk of fracture
1:1 alendronate: romosozumab with 1 year alendronate follow-up
Incidence of MACE during the first year was 1.9%:2.5%

**FRAME trial:**
7190 postmenopausal women
1:1 romozosumab: placebo with 1 year denosomab follow-up
No difference in serious cardiovascular events at any point.

- The difference in the ARCH trial may be related to a positive benefit of bisphosphonate on cardiovascular risk rather than a negative effect of romosozumab
- Several recent reviews have questioned any cardiovascular risk

Saag et al. NEJM 2017 377: 1417-1427
Cosman et al. NEJM 2016 375:1532-1543
Kerschan-Schindl K, 2020 Wien Med Wochenschr 170(5):124-131

# What the Guidelines Say...

- Canadian Osteoporosis Clinical Practice Guidelines 2010 *...?*

- 2017 American College of Rheumatology GIOP guidelines
  *Continue active treatment (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate [or switch to an OP treatment in another class). Conditional recommendation because of very low-quality data on benefits and harms in GC-treated patients, but moderate-quality data in the general OP literature on benefits and harms of continuing treatment*

- Endocrine Society Update (2020):
  *Romosozumab in those at very high risk of fracture (T-score <-2.5 and fractures) without increased risk of heart attack or stroke*

- ASBMR Task Force on Long Term Use of Bisphosphonates (2015):
  *In those that remain high risk (> 70 yrs, on aromatase inhibitors or glucocorticoids)the Task Force suggests that the provider discuss with the patient the option of continuing BP treatment for another 2 to 3 years with reassessment at that time (after 10yrs po/6 yrs IV) alternative antifracture therapy could also be considered with teriparatide and denosumab as first options.*

*CMAJ 2010 182(17):1862-1873*
*Arthritis & Rheum 2017 69(8): 1521-1537*
*JCEM 2020: 105(3) 587-594*
*JBMR 2016 31(1): 16-35*

# Associated Costs

- **Zoledronic acid** 400.00/dose and year
  - covered by Alberta Health insurance programs

- **Denosumab:** 400.00/dose, 800mg/year
  - covered by Alberta Health insurance programs

- **Teriparatide** 1000.00/dose, 12000.00/ year (for the biosimilar)

  - STEDT criteria: unsatisfactory response to anti-resorptive drug therapy AND denosumab (fragility fracture despite adhering to treatment fully for 1 year and evidence of a decline in BMD below pre-treatment baseline level)
    AND:
    1) Have a T-score of –4.0 SD or below, OR
    2) Have a T-score of –3.5 SD or below plus >2 fractures.
  - All brands have a support program, co-pay assistance, partial coverage available

- **Romosozumab** – $840.00/dose, $10,920/year
  - Under review for coverage- STEDT cannot cover
  - Company will negotiate with family to a maximum of 50%


https://www.osteoporosiscalgary.com/for-health-professionals/medication-access-information.html

# What to choose?....

- **Preferred choices**

  1)teriparatide

  romosozumab

  2) denosumab

  3) drug holiday

  4) continue bisphosphonate

- **In Practice**

  1) denosumab

  2) continue bisphosphonate

  3) drug holiday

  4) teriparatide

  5) romosozumab

*Once you make a decision, the universe conspires to make it happen…*

*Ralph Waldo Emerson*

# Summary:

- Making decisions on OP therapy in high-risk patients is VERY complicated
- Guidelines are often not helpful in elderly, on corticosteroids with multiple co-morbidities
- Often drug choice is financial preference rather than clinical preference & guidelines reflect that
- Drug tolerability and co-morbidities need to be taken into consideration
- Patient MUST be involved in the decision and risks/benefits of each therapy clearly reviewed.