MAYO CLINIC

OSTEOPOROSIS UPDATE



Ejigayehu Gigi Abate, MD
Assistant Professor of Medicine
Division of Endocrinology
Mayo Clinic, Jacksonville, Florida

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LEARNING OBJECTIVE

- Discuss diagnostic approaches to osteoporosis
- Discuss secondary workup for patients with osteoporosis
- Discuss current guidelines in the selection of appropriate pharmacologic and nonpharmacologic therapies for the management of osteoporosis
- Explore currently available therapies for the management of bone disorders, efficacy, and safety
- Discuss current guidance on the duration of treatment

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INDICATION FOR BONE MINERAL DENSITY TESTING

- All women 65 year of age or older
- All post menopausal women
  - With a history of fracture(s) without major trauma
  - With osteopenia identified radiographic ally
  - Starting or taking long term systemic glucocorticoid therapy(>3 months)
  - Other perimenopausal or post menopausal women with risk factors for osteoporosis if willing to consider pharmacological intervention
  - Low body weight <127 lbs or BMI <20 kg/m2
  - Family history of osteoporotic fracture
  - Early menopause
  - Current smoking
  - Excessive consumption of alcohol
  - Secondary osteoporosis
    - AACE guidelines endocrine practice 2020; NOF.org; ISCD.org

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DIAGNOSTIC CRITERIA - FROM 1994

World Health organization Criteria for Classification of Osteopenia and Osteoporosis	
Category	T-score
Normal	-1.0 or above
Low bone mass (Osteopenia)	Between –1.0 and –2.5
Osteoporosis	-2.5 or below
Severe Osteoporosis	-2.5 or below with fragility fracture

T score- SDs from the normal young adult mean values
The reference standard from which the T- Score is calculated is the female, white, age 20-29 years, NHANES III database.

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MEN AGE <50 AND PREMENOPAUSAL WOMEN

Z score	category
Less than -2.0	Low bone mass
Greater than -2.0	Normal for age

- Z score represents the number of SD from the expected mean value for age, race or ethnicity and sex-matched control subjects
  - Z score useful in men <50 and premenopausal women
  - Older men and women often suggest secondary osteoporosis and should undergo comprehensive evaluation for these causes

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DIAGNOSTIC CRITERIA FOR OSTEOPOROSIS

- T-score at or below ≤-2.5 at the spine or hip
- Low trauma spine or Hip fracture (regardless of bone mineral density)
- Osteopenia (BMD T-score between -1 and -2.5) **and** fragility fracture of the proximal humerus, pelvis, or distal forearm
- Osteopenia (T score between -1.0 to -2.5) **and** high FRAX score - MOF ≥ 20% and hip fracture ≥ 3%

- **National osteoporosis foundation.org**
- **CDC.gov**
- **AACE guideline ENDOCRINE PRACTICE Vol 26 (Suppl 1) May 2020**

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45-YEAR-OLD PREMENOPAUSAL FEMALE WITH LOW ALKALINE PHOSPHATASE

- 45-year-old premenopausal female with chronic pain, recently diagnosed with fibromyalgia, presents for evaluation of osteoporosis after a shoulder fracture from a fall.
- ROS: diffuse body pain, muscle tension, muscle tenderness, joint pain
- Meds: none
- ANA- positive, but the rest of her serology negative.
- TSH, T4 normal.
- DXA scan – osteopenia of the spine and normal hip.
- Lab: CBC-normal, TSH/T4 normal, CMP- Total alkaline phosphatase 35
- PTH, serum calcium normal. Phosphorus is normal.

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WHAT IS THE DIAGNOSIS?

1. Osteopenia based on DXA
2. Osteoporosis due to fracture
3. Osteomalacia
4. Vitamin D deficiency

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- ANA- positive, but the rest of her serology negative.
- TSH, T4 normal.
- DXA scan – osteopenia of the spine and normal hip.
- Lab: CBC-normal, TSH/T4 normal, CMP- Total alkaline phosphatase 35 u/L (reference range 35-104 u/L)
- PTH, serum calcium normal. Phosphorus is normal.

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HYPOPHOSPHATASIAS

- Low alkaline phosphatase
- Unable to form normal bone
- Poor dentition
- Muscle and bone weakness, bone pain
- Misdiagnosed as fibromyalgia
- Fractures

- Dx: Lifetime low alkaline phosphatase

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WORK UP SECONDARY CAUSES OF OSTEOPOROSIS

Labs	Disease processes
Serum calcium	Hypocalcemia, vitamin D deficiency, hypoparathyroidism
Serum phosphorus	Phosphate wasting diseases (x linked hypophosphatemia, tumor induced osteomalacia)
Total 25 hydroxyvitamin D (D2 +D3)	Vitamin D deficiency
Creatinine/eGFR/cr clearance	
Parathyroid hormone (PTH)	Primary hyperparathyroidism Secondary hyperparathyroidism
TSH, free T4	Thyroid problems (hyperthyroidism)
TTG IgA, IgG, celiac cascade	Celiac disease
Bone specific Alkaline phosphatase	Hypophosphatasia (low) Elevated alka phosphatase (osteomalacia, pagets disease, fibrous dysplasia, etc.)
24hr urine calcium, 24 hr urine creat 24hr urine sodium	Hypercalcuria I(idiopathic or secondary to high sodium diet)
Serum electrophoresis	MGUS or Multiple myeloma screening

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ADDITIONAL WORKUP

Labs	Disease
Tryptase	Mastocytosis
Ferritin	Hemochromatosis
24hr urine free cortisol, creatinine Or 1 mg overnight Dex suppression	Cushing's disease or syndrome
Insulin like growth factor 1	Excess GH (acromegaly) or GH deficiency
Testosterone total and bioavailable (8am) for men	Hypogonadism
Estradiol (men and women)	Hypogonadism

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Labs	Disease processes
Serum calcium	Hypocalcemia, vitamin D deficiency, hypoparathyroidism
Serum phosphorus	**Phosphate wasting diseases (x linked hypophosphatemia, tumor induced osteomalacia)**
Total 25 hydroxyvitamin D (D2 +D3)	Vitamin D deficiency
Creatinine/eGFR/cr clearance	
Parathyroid hormone (PTH)	Primary hyperparathyroidism Secondary hyperparathyroidism
TSH, free T4	Thyroid problems (hyperthyroidism)
TTG IgA, IgG, celiac cascade	Celiac disease
Total or Bone specific Alkaline phosphatase	**Hypophosphatasia (low)** **Elevated alka phosphatase (osteomalacia, pagets disease, fibrous dysplasia, etc.)**
24hr urine calcium, 24 hr urine creat 24hr urine sodium	Hypercalcuria I(idiopathic or secondary to high sodium diet)
Serum electrophoresis	MGUS or Multiple myeloma screening

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WHO SHOULD HAVE SECONDARY WORKUP

- Z- score (age-race-sex) matched score <-2.0 regardless of age
- Fractures not matching DXA result
- Premenopausal woman or men <50 with fractures or low bone mass
- Multiple fractures
- Patients not responding to treatment

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CURRENT THERAPY OPTIONS AND HOW TO SELECT THE APPROPRIATE THERAPY

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RISK FACTORS FOR OSTEOPOROSIS

- Low bone mineral density is highly predictive of increased risk of fracture
- Other factors:
  - Age
  - Race
  - Previous fracture
  - Glucocorticoid use
  - Gender
  - History of falling
  - Hyperthyroidism
  - Malabsorption
  - Diabetes mellitus (type 1 and type 2)
  - Chronic diseases (liver disease, heart disease, kidney disease)

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FRACTURE ASSESSMENT TOOLS

- BMD
  - T score <-2.5-→ increased risk of fracture at any site BMD measured by DXA at any skeletal site (lumbar spine, hip, or forearm) can predict osteoporotic (fragility) fracture
  - Overall, there is an approximately twofold increase in the risk of such fractures for each SD decrease in BMD
- Trabecular bone score-
  - Adding Trabecular bone score assessment- measure the microarchitecture of the bone as low, medium, or normal.
- Qualitative CT
- Opportunistic CT

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WHO NEEDS PHARMACOLOGIC THERAPY?

- 1. T-score between −1.0 and −2.5 in the spine, femoral neck, total hip, or 1/3 radius and a history of fragility fracture of the hip or
- 2. Those with a T-score of −2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius
- 3. Those with a T-score between −1.0 and −2.5 in the spine, femoral neck, total hip, or 1/3 radius, if the FRAX (or if available, TBS-adjusted FRAX)10-year probability for major osteoporotic fracture is≥20% or the 10-year probability of hip fracture is ≥3%(in the U.S.)

- **AACE guideline ENDOCRINE PRACTICE Vol 26 (Suppl 1) May 2020**

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T SCORE BETWEEN -1 TO -2.4 + SPECIAL POPULATION- MODIFY FRAX

- Use of glucocorticoids >7.5 mg daily
  - Adjust FRAX by multiplying the unadjusted FRAX risk of major osteoporotic fractures by 1.15, and multiply the unadjusted FRAX risk of hip fractures by 1.20
- Aromatase inhibitor (5 yr. study of AI bone loss 6.2-7% vs tamoxifen 2%) (Eastell. J clin oncol 2008)
  - Check yes for RA in FRAX
- Diabetics type 1 or type 2 - yes for RA
- Organ transplant recipients especially before transplant
  - Shakaib Hayat, MD et al. Cleveland Clinic Journal of Medicine July 2020, 87 (7) 417-426;

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RISK BASED STRATIFICATION FOR OSTEOPOROSIS MANAGEMENT

- High risk – A 10-year probability of hip or combined major osteoporotic fracture of ≥3 and 20 percent, respectively
- •Moderate risk – A 10-year probability of hip or combined major osteoporotic fracture between 1 to 3 percent and 10 to 19 percent, respectively
- •Low risk – A 10-year probability of hip or combined major osteoporotic fracture of ≤1 and <10 percent, respectively

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RISK STRATIFICATION

- Age
- DXA scan result
- FRAX score
- History of fracture

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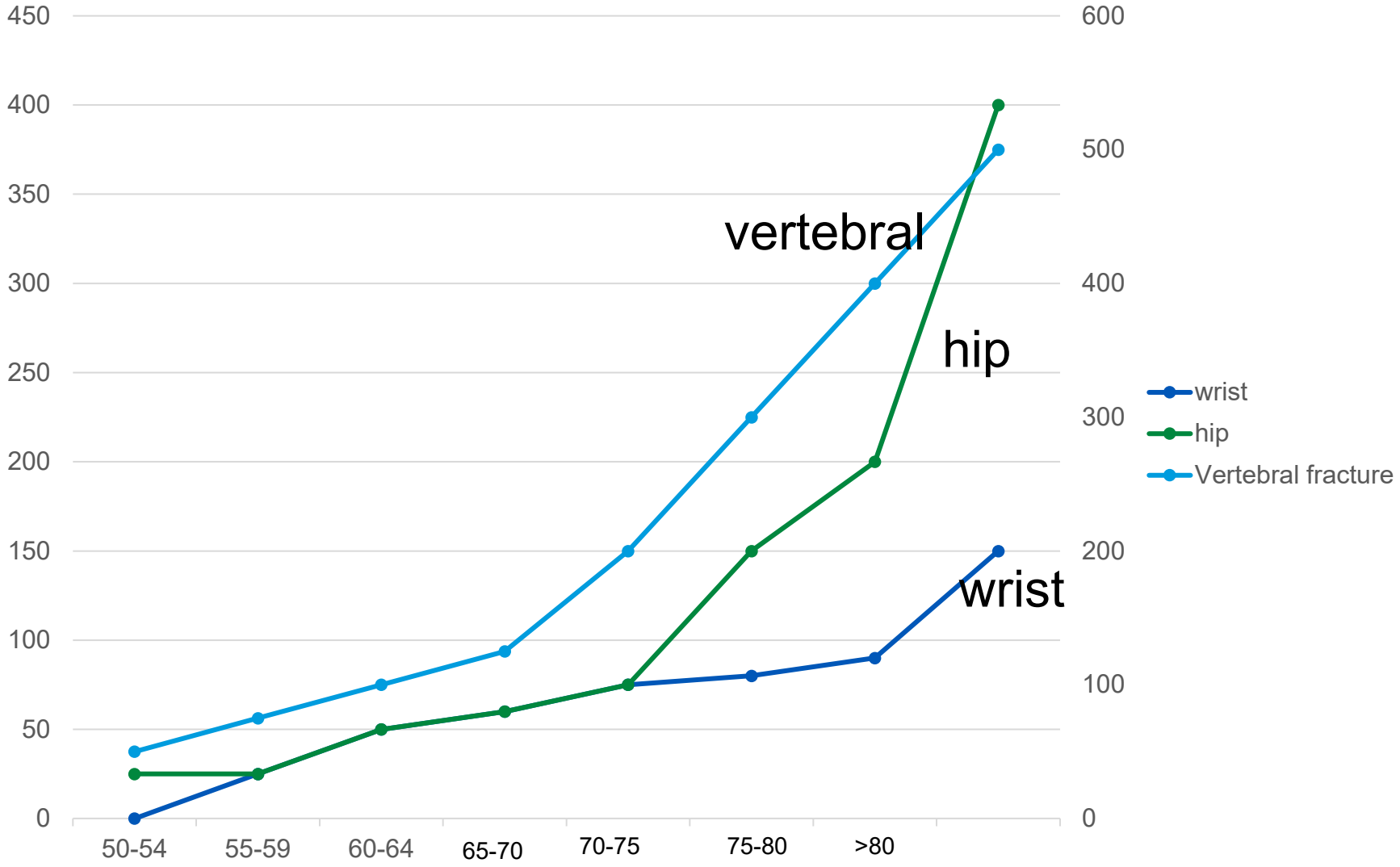
AGE-SPECIFIC INCIDENCE OF FRACTURES



Sambrook, P. and C. Cooper, *Osteoporosis*. Lancet, 2006. 367(9527): p. 2010-8.

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Patient M

55-year-old female osteopenia
No prior history of fracture
No prior treatment
BMI 22.5
Mother with osteoporosis and hip fracture at age 85
No tobacco or alcohol use. No steroid therapy.
Bone density:

- Lumbar spine T- score = -2.4
- Total hip T- score= -2.1
- Femoral neck T- score= -2.4

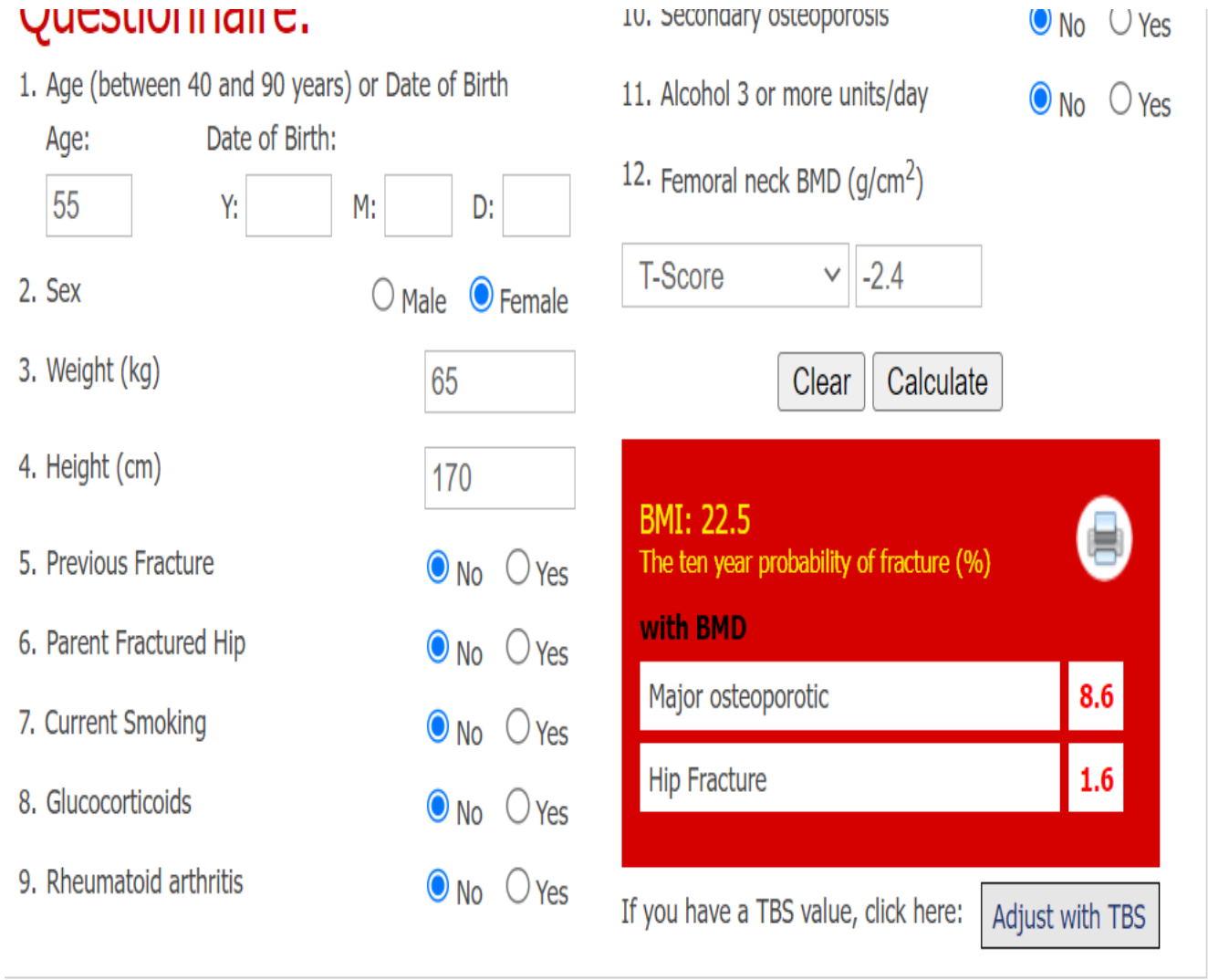
<u>Risk assessment:</u>

- Young age
- No fracture
- FRAX score 10-year risk of MOF 8.6%

Low risk

1. Young women <70
2. BMD T-Score -2.9 to -2.5 without fracture
3. And 10-year hip fracture risk <1% and 10-year risk of major osteoporotic fracture <10%

HRT, Raloxifene, bisphosphonate



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LOW RISK

- Men and women <70
- BMD T-Score -2.9 to -2.5 without fracture
- And 10-year hip fracture risk <3% and 10-year risk of major osteoporotic fracture <20%

Management goal- maintain or improve BMD and reduce fracture

- Menopausal hormone therapy (estrogen, progesterone)- young women with vasomotor symptoms
- Selective estrogen receptor modulator (Raloxifene) (women with strong family or personal history of breast cancer)
- Bisphosphonates (Orals- Alendronate, Ibandronate, risedronate or consider IV- Zoledronic acid if intolerance and/or compliance issue

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MODERATE RISK

- Age >70
- No prior spine or hip fracture
- BMD T score at the hip and spine both ≤ -2.5
- 10-year hip fracture risk <3% or risk of major osteoporotic fracture <20%

Management

- Bisphosphonate
- Teriparatide and abaloparatide (PTH analog)
- Denosumab (RANK ligand antagonists)
- Romosozumab (Sclerostin antibody)

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HIGH RISK

- Those with recent fractures (within two years)
  - Risk of another fracture is about 20% within the first year of the fracture
- Patients with a history of multiple fractures
- individuals with T score <-3.0 with fracture

Management

- #1 Anabolic therapy (teriparatide, abaloparatide, romosozumab)
- #2 Denosumab
- #3 Bisphosphonate (IV zoledronic acid preferably) oral okay if compliant

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SPECIAL POPULATION

- Neurosurgery procedures – consider anabolic therapy as first line agent
- Transplant patients- treat with bisphosphonate prior to transplant
- Diabetics
- Post hip fracture

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CASE

- 52-year-old WF presents with a wrist fracture from a fall one year ago. No prior fractures. LMP age 50. no hormone therapy.
- Risk factors: she is on prednisone 5 mg daily for RA for the past three years. No falls. No alcohol or tobacco use.
- Medications: as above
- DXA: L1-L4 T score -2.0, Left femoral neck: -2.4, and left total hip -2.2

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QUESTION

- What is this patient’s risk of fracture?
- 1. Low risk
- 2. moderate risk
- 3. High risk for fracture

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Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 52 Date of Birth: Y: M: D:
2. Sex ○ Male ◉ Female
3. Weight (kg) 89.2
4. Height (cm) 177
5. Previous Fracture ○ No ◉ Yes
6. Parent Fractured Hip ◉ No ○ Yes
7. Current Smoking ◉ No ○ Yes
8. Glucocorticoids ○ No ◉ Yes
9. Rheumatoid arthritis ○ No ◉ Yes
10. Secondary osteoporosis ◉ No ○ Yes
11. Alcohol 3 or more units/day ◉ No ○ Yes
12. Femoral neck BMD (g/cm^2)
    T-Score -2.4

Clear Calculate

BMI: 28.5
The ten year probability of fracture (%)
with BMD

Major osteoporotic	27
Hip Fracture	7.2

If you have a TBS value, click here: Adjust with TBS

if GC >7.5 mg d
FRAX adjustment
MOF by 1.15
Hip Fx by 1.2

High risk

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Patient 1- 52 y/o WF No fracture

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 52 Date of Birth: Y: M: D:
2. Sex: Male / Female
3. Weight (kg): 89.2
4. Height (cm): 177
5. Previous Fracture: No / Yes
6. Parent Fractured Hip: No / Yes
7. Current Smoking: No / Yes
8. Glucocorticoids: No / Yes
9. Rheumatoid arthritis: No / Yes
10. Secondary osteoporosis: No / Yes
11. Alcohol 3 or more units/day: No / Yes
12. Femoral neck BMD (g/cm^2)
    T-Score -2.4

Clear Calculate

BMI: 28.5
The ten year probability of fracture (%)
with BMD

Major osteoporotic	7.3
Hip Fracture	1.3

If you have a TBS value, click here: Adjust with TBS

Print tool and information

Patient 2- 52 y/o WF with fracture

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 52 Date of Birth: Y: M: D:
2. Sex: Male / Female
3. Weight (kg): 89.2
4. Height (cm): 177
5. Previous Fracture: No / Yes
6. Parent Fractured Hip: No / Yes
7. Current Smoking: No / Yes
8. Glucocorticoids: No / Yes
9. Rheumatoid arthritis: No / Yes
10. Secondary osteoporosis: No / Yes
11. Alcohol 3 or more units/day: No / Yes
12. Femoral neck BMD (g/cm^2)
    T-Score -2.4

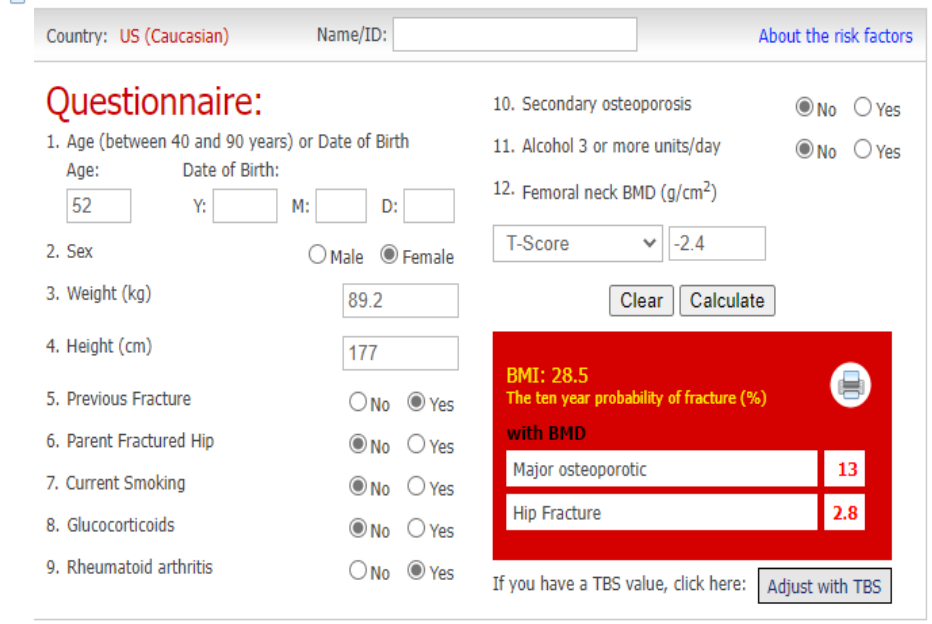
Clear Calculate

BMI: 28.5
The ten year probability of fracture (%)
with BMD

Major osteoporotic	13
Hip Fracture	2.8

If you have a TBS value, click here: Adjust with TBS

Print tool and information



Patient 3- 52 y/o WF with fracture + Aromatase inhibitor use

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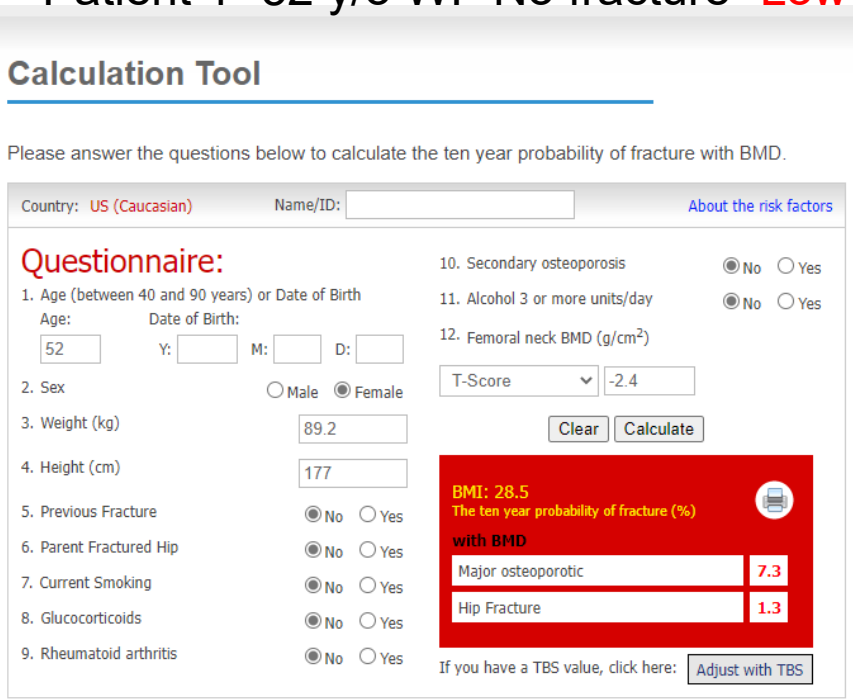
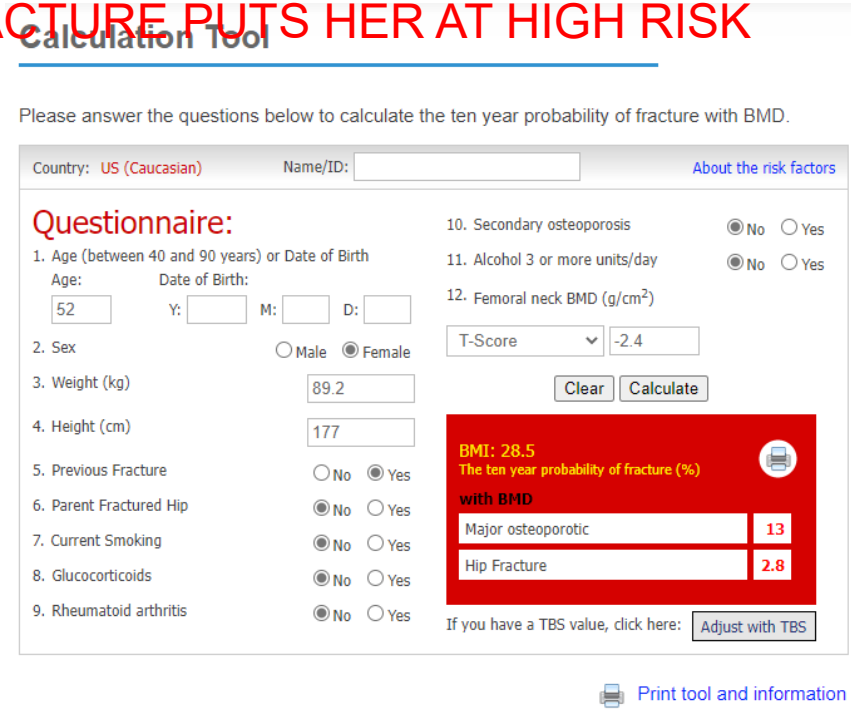
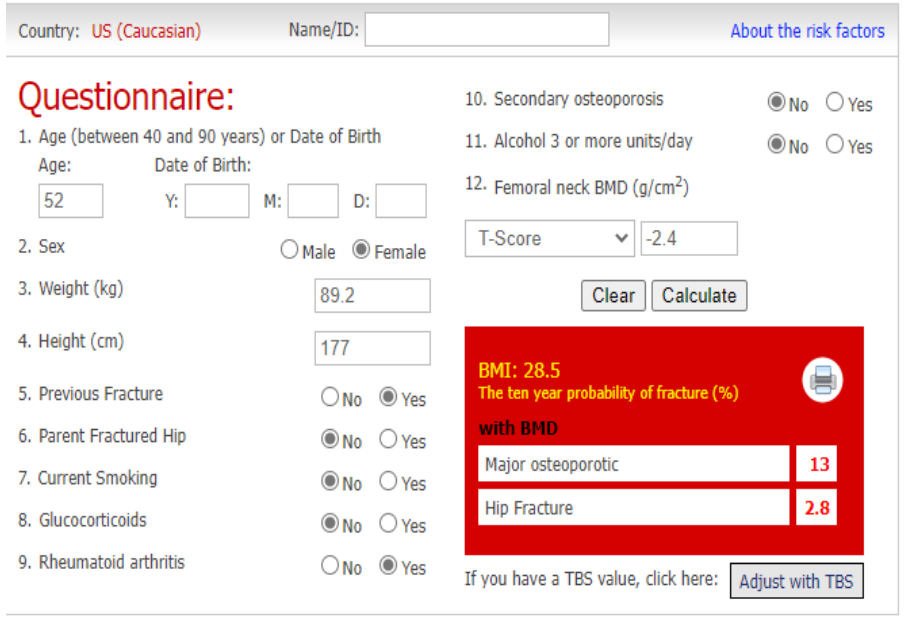
Patient 1- 52 y/o WF No fracture- Low risk

Patient 2- 52 y/o WF with fracture- moderate risk BY frax BUT FRACTURE PUTS HER AT HIGH RISK







Patient 3- 52 y/o WF with fracture + Aromatase inhibitor use - HIGH RISK

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INITIAL TREATMENT CHOICE FOR OSTEOPOROSIS IS BASED ON RISK STRATIFICATION

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MANAGEMENT

- Lifestyle factors contributing to bone loss, including smoking, excessive alcohol, physical inactivity, and poor nutrition, should be addressed. Height and weight should be measured.

- Lifestyle modification alone has never been shown to reduce the risk of fractures, so not appropriate for sole treatment for those with a high risk for fracture

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VITAMIN D

- Vitamin D
  - Plays a role in calcium absorption and bone health
  - Some role in muscle performance, balance, and risk of falling.
  - Moreover, optimal vitamin D status may increase response to bisphosphonate therapy, increase BMD, and prevent fracture
  - AACE and the Endocrine Society recommend serum 25(OH)D ≥ 30 ng/mL
  - Vitamin D 3 1000 to maximum of 4000 iu daily
  - Measure total 25 (OH)D and not 1,25 (OH)2D

    - AACE guidelines endocrine practice 2020

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CALCIUM

- For adults aged 50 years and older, the recommended calcium intake (including diet, plus calcium supplements, if necessary, when dietary intake is insufficient) is 1,200 mg/day.
- Calcium supplementation has been shown to increase BMD slightly
- Some data on fracture reduction but not clear evidence
- AACE, NOF, the IOM (now NAM), and the Endocrine Society recommend that women aged 51 years or older consume 1,200 mg per day of calcium from all sources

- AACE guidelines 2020
- NOF.org
- Endocrine society osteoporosis guidelines

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OTHER

- Magnesium- no randomized controlled study evaluated mg effect on fracture
- It helps our body to absorb calcium but there is no data that adding mg to calcium tablet improves absorption without deficiency
  - Most people get adequate intake
  - Consider checking or replacement in those with gI malabsorption, chronic liver disease (alcoholics), renal tubular acidosis, using PPI, diuretics)
  - Can help in those with constitution from calcium supplement

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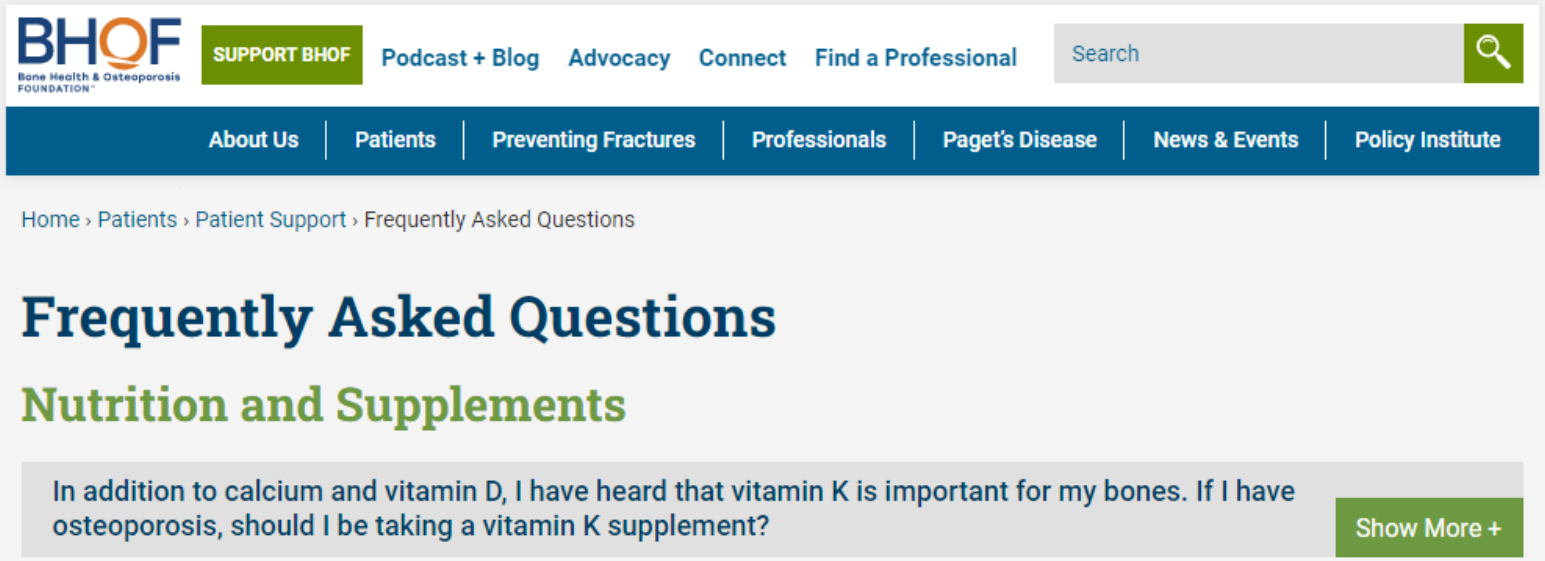

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EXERCISE

- Weight bearing exercise (walking 30-40 minutes per session)
- Back and posture exercises for few minutes, 3-4 times per week
- Strength training-
  - Early post menopausal female
    - 699 subjects showed 2% improvement in the lumbar spine BMD with group exercise than those that did not
    - Elderly
      - Exercise can slow down bone loss, improve balance, muscle strength and ultimately reduce fall risk

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EXERCISE AND SEVERE OSTEOPOROSIS

- Caution with forward spine flex ion, rotation, heavy weights, even side bending of the trunk

- Elder patients with kyphosis, back discomfort and gait instability should be referred to PT for exercise planning
  - Weight bearing, back strengthening and balance training exercise

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WHO NEEDS PHARMACOLOGIC TREATMENT

- a. Those with a T-score between − 1.0 and − 2.5 in the spine, femoral neck, total hip, or 1/3 radius and a history of fragility fracture of the hip or spine
- b. Those with a T-score of − 2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius .
- c. Those with a T-score between − 1.0 and − 2.5 in the spine, femoral neck, total hip, or 1/3 radius, if the FRAX® (or if available, TBS-adjusted FRAX®) 10-year probability for major osteoporotic fracture is ≥ 20% or the 10-year probability of hip fracture is ≥ 3% (in the U.S.) or above the country-specific threshold in other countries or regions

  - AACE osteoporosis guideline 2020

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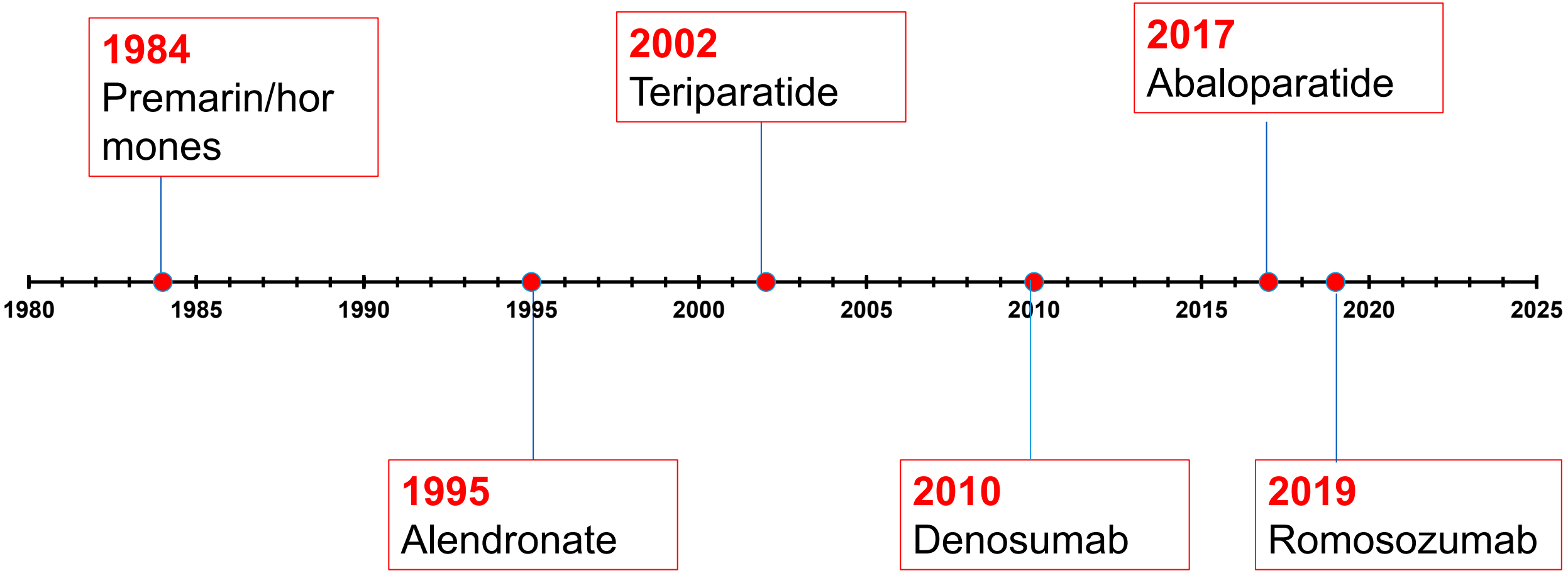

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	Mechanism of action	3yr increase spine BMD	3 yr increase total hip BMD	RRR of spine fracture	RRR of non spine fracture
Estrogen/progestin	Hormone replacement				30%
Raloxifene	Antiresorptive-SERM	2-3%	1%	50%	--
Oral BPs Alendronate, risedronate, ibandronate	Antiresorptive-bisphosphonate	3-5%	2-3%	40-53%	0-20%
IV zoledronic acid	Antiresorptive-bisphosphonate	5-6%	3-4%	70%	25%
SC Denosumab	Antiresorptive-RANKL-inhibitor	6-10%	3-4%	68%	20%
Teriparatide	Anabolic-PTH analog	8-10%	1.5-2%	65-70%	35%
Abaloparatide	Anabolic- PTH analog	10%	2-3%	70-80%	40%
Romosozumab	Anabolic/antiresorptive	11% 1 year	4% (1 year)	48% vs. alendronate	20% vs. alendronate

Black et al. Lancet. 1996, Black et al. NEJM. 2007, Cummings et al. NEJM. 2009, Neer et al. NEJM. 2001, Miller et al JAMA 2017, Saag et al NEJM 2017

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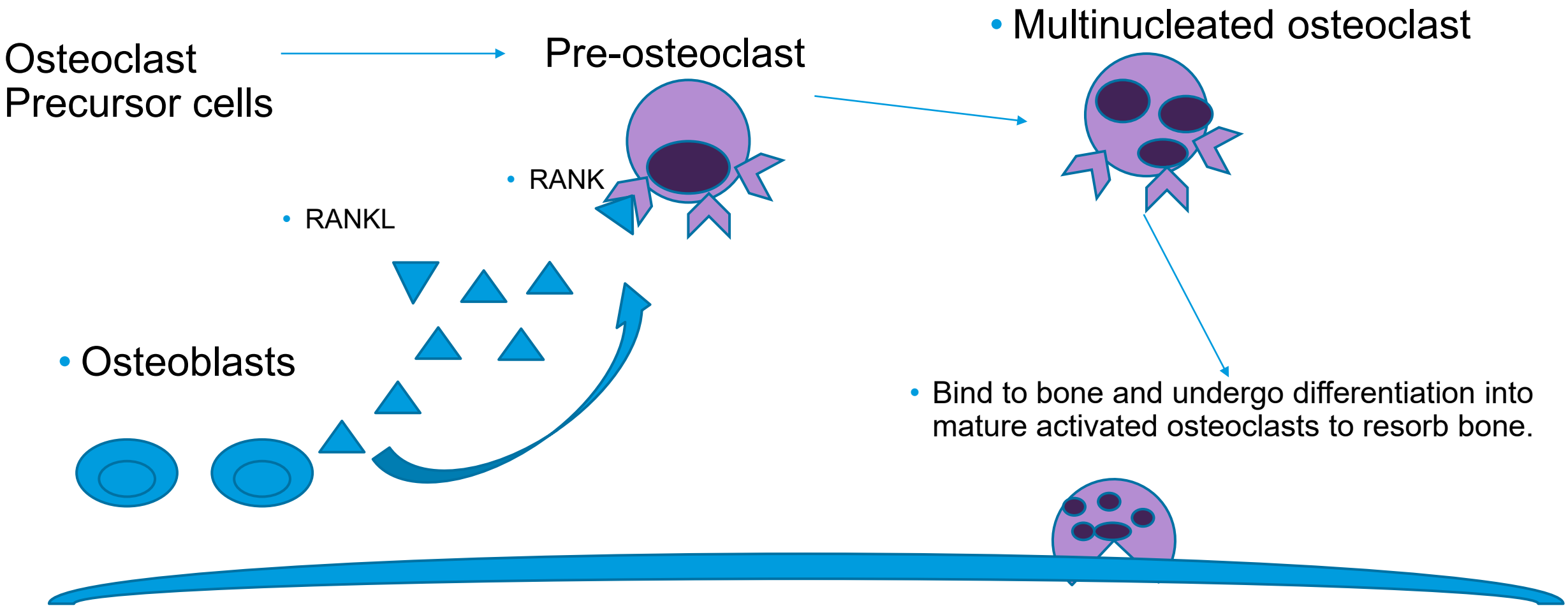
Antiresorptive reduce Osteoclast survival and formation



Osteoclasts develop from osteoclast precursor cells when the receptor activator of nuclear factor kB (RANKL), produced by osteoblasts, binds to the receptor RANK on Pre osteoclasts. Multinucleated osteoclasts adhere to bone, where they undergo differentiation into mature activated osteoclasts, which resorb bone

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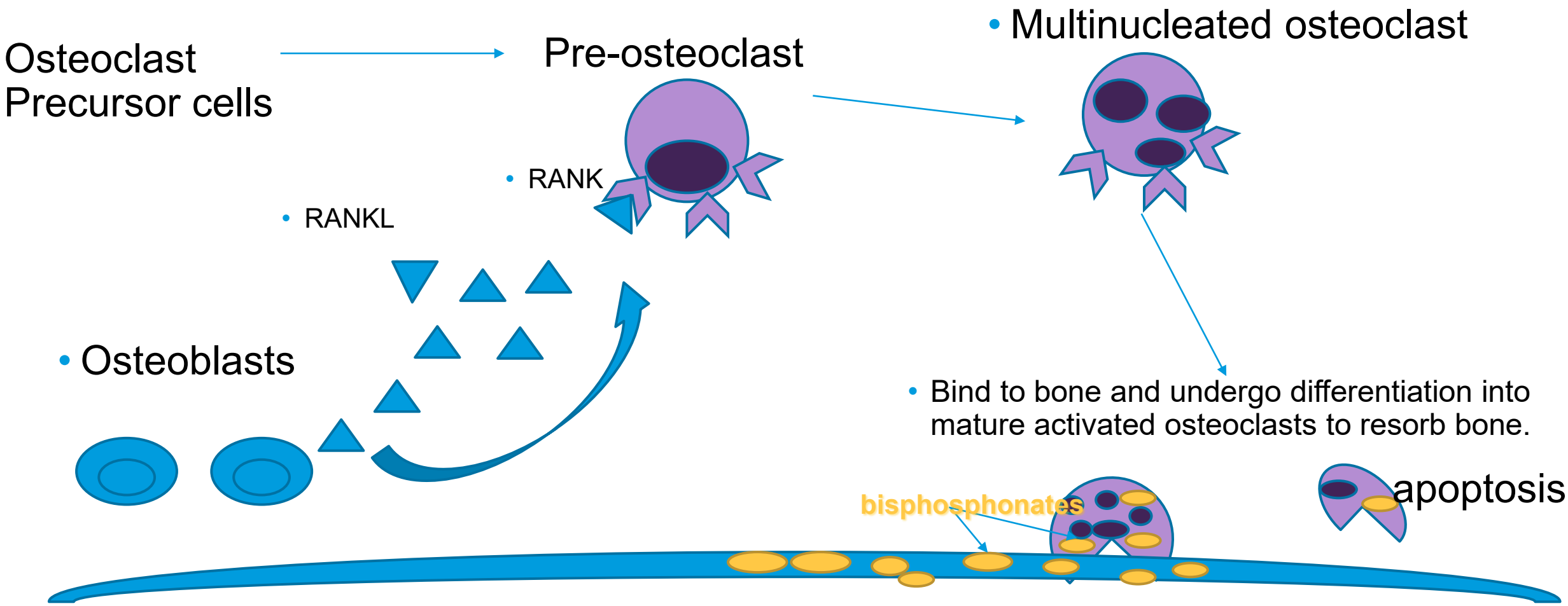
Osteoclast formation and pharmacologic inhibition by bisphosphonates



bisphosphonates adhere to the mineral content of bone and during the resorption process, mature osteoclast endocytosis bispshphonates, resulting In osteoclast inactivation and apoptosis

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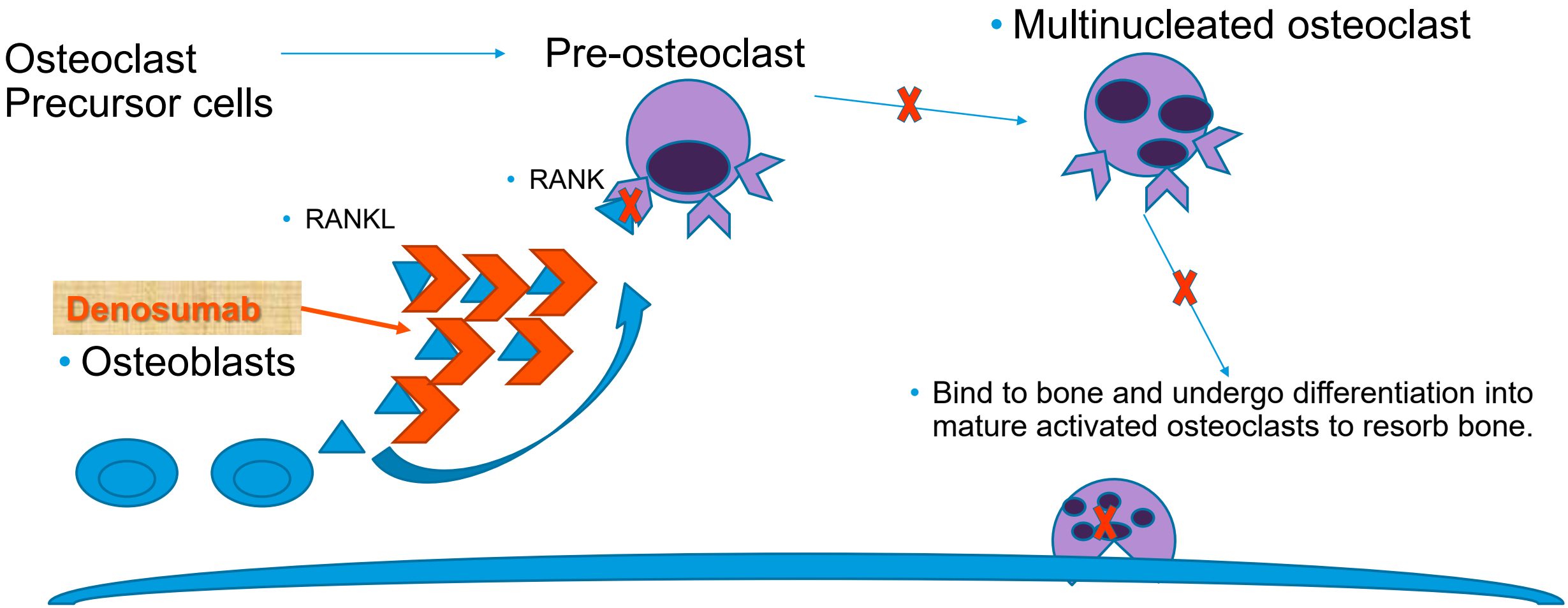
Osteoclast formation and pharmacologic inhibition- Denosumab



humanized monoclonal ab bids to RANKL to block RANK/RANKL binding resulting in inhibition of osteoclast formation, Function and survival

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ANABOLIC- INCREASE BONE FORMATION, PTH ANALOG AND PTH RECEPTOR

- Teriparatide
- Abaloparatide

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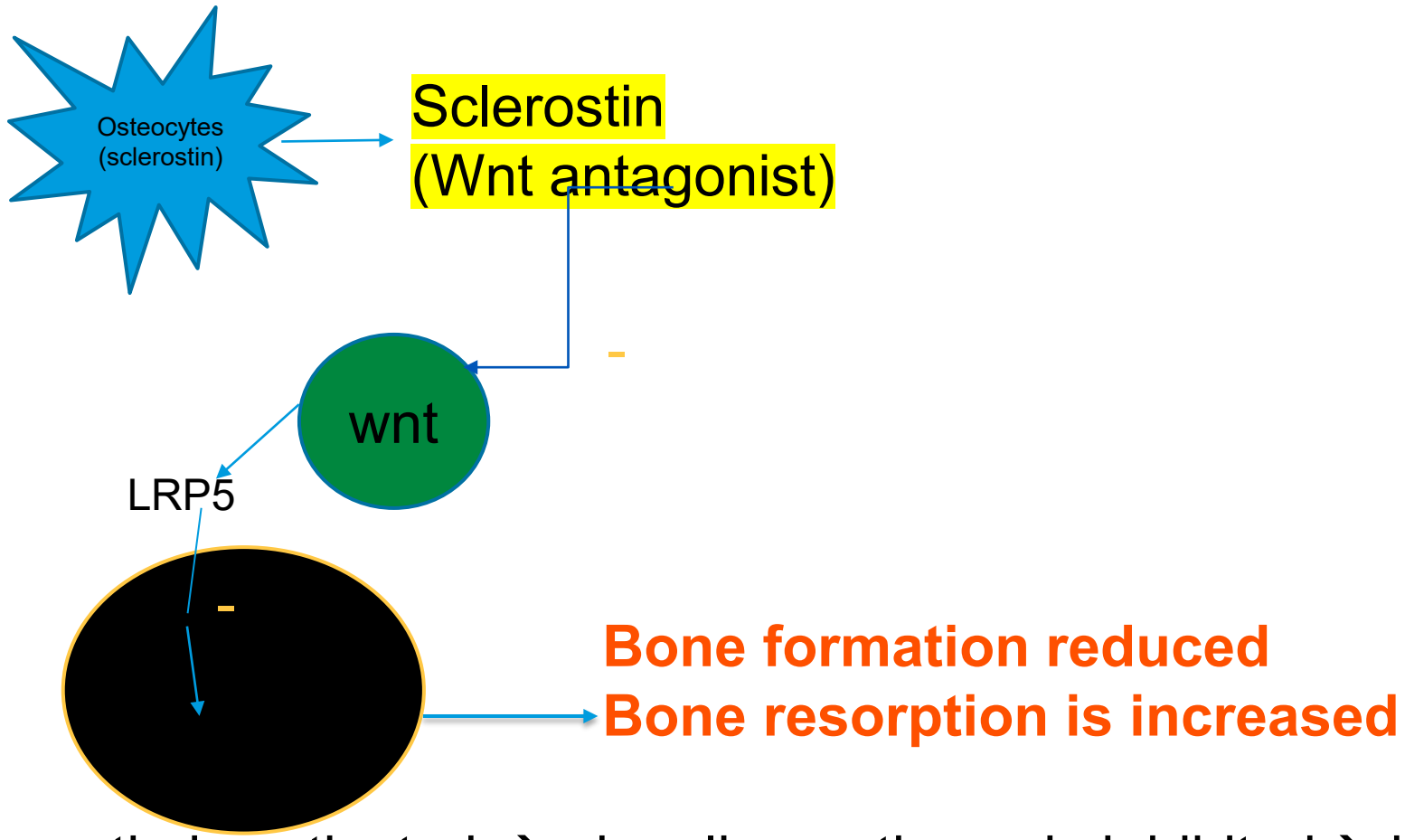
ROMOSOZUMAB AFFECT WNT SIGNALING PATHWAY TO ANTAGONIZE SCLEROSTIN (INHIBITOR OF BONE FORMATION)



So when sclerostin is activated → signaling pathway is inhibited→ increased bone resorption

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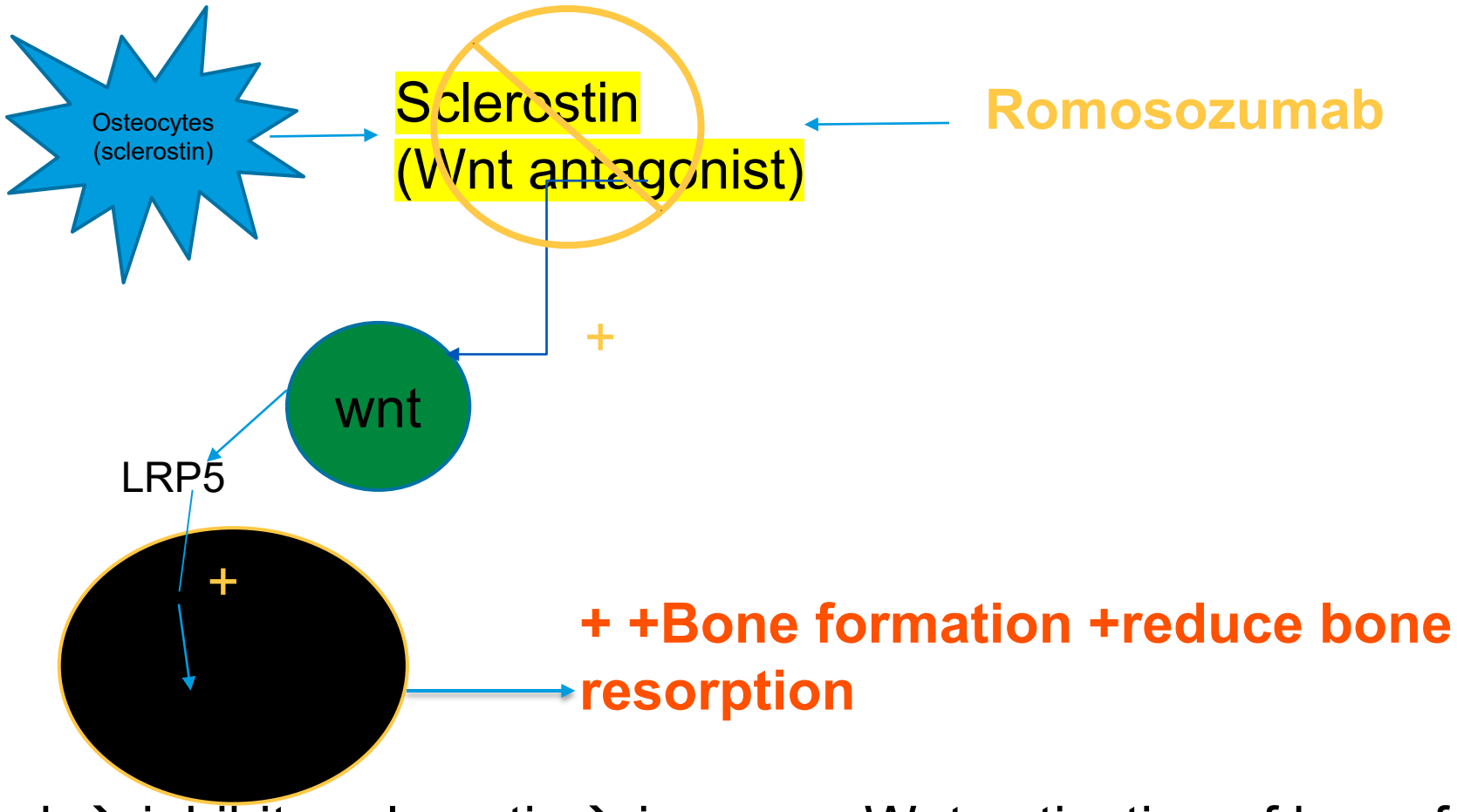
ROMOSOZUMAB AFFECT WNT SIGNALING PATHWAY TO ANTAGONIZE SCLEROSTIN (INHIBIT BONE FORMATION)



Romosozumab→ inhibits sclerostin→ increase Wnt activation of bone formation

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EFFICACY OF BISPHOSPHONATES

	Vert fracture eduction	Non vert fx reduction	Hip fracture	significant
Alendronate	43%	16%	39%	Yes
risedronate	39%	22%	27%	Yes
ibandronate	33%	Not significant	Not significant	No
Zoledronic acid	62%	21%	40%	Yes

Black et al. N Eng J Med May 3, 2007

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ORAL BISPHOSPHONATE

- Use with calcium +D
- Contraindication: GI intolerance, history of Barret's disease or dysplasia, uncontrolled GERD, gastric ulcers, unable to stay upright, memory problems, or CKD (cr clearance <32 for risedronate and ibandronate and <35 for alendronate).

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ZOLEDRONIC ACID 5 MG IV ANNUALLY

- HORIZON (The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) pivotal fracture trial:
- Total of 7765 women (ZA=3875 vs. Placebo N=3861)
  - Mean age, 73 years
  - FN T score= <-2.5 in 72.6%, osteopenia in 25.9% and >-1.5= 0.9%
  - 37.6% no prior vertebral fracture 34.1% had >2 vertebral fracture
  - 3-year follow-up
  - Primary end point: fracture reduction
  - Secondary end point: BMA
    - Black et al. N Eng J Med May 3, 2007

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HORIZON TRIAL

- Once a year ZA:
  - Reduced morphometric vertebral fracture by 70% for 3 years period compared to placebo (3.3% in ZA vs 10.9% in placebo RR 0.30)
  - Reduced hip fracture by 41% (1.4% in ZA vs. 2.5% in placebo)
  - Secondary outcome: BMD
    - Increased lumbar spine 6.7%, Total hip 6.02%, femoral neck 5.06% vs. placebo ($p<0.001$)

Black et al. N Eng J Med May 3, 2007

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POTENTIAL SIDE EFFECT

- Flu like symptoms
  - Acute phase reactant
  - Can occur up to 25% of patients with first time use
  - Can last up to 3-5 days
  - Hydration with water prior and for 3 days helps
  - Can take Tylenol for symptoms (avoid NSAIDS)
- Nephrotoxicity
  - In elderly or unstable kidney function
    - Measure creatinine clearance or calculate cr clearance rather than eGFR
    - Cr clearance >35
    - Infuse over 30 minutes helps reduce nephrotoxicity

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CONTRAINDICATION

- Hypocalcemia
- Cr clearance <35
- Allergy to bisphosphonates (anaphylaxis, severe body pain, rash etc)

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DURATION OF BISPHOSPHONATE TREATMENT

- Low risk
  - No prior fracture
- Duration of treatment:
  - Oral bisphosphonates- 5 years
  - Iv bisphosphonate 3 years

- High risk
  - Prior history of fracture (prior to initiating therapy or during therapy)
  - T score <-3.0 w/o fracture
  - Therapy:
  - Oral: up to 10 years
  - IV: up to 6 years

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SAFETY OF LONG-TERM USE- FLEX TRIAL

- Fracture Intervention Trail Long term Extension (FLEX)
  - 1099 postmenopausal women who previously received alendronate for 5 years (FIT)
  - Assigned to either 5 more years of alendronate (5 or 10 mg daily) or placebo
    - Excluded high risk for fracture (baseline hip scores <-3.5)
    - Mean age 73
    - 35% had vertebral fracture

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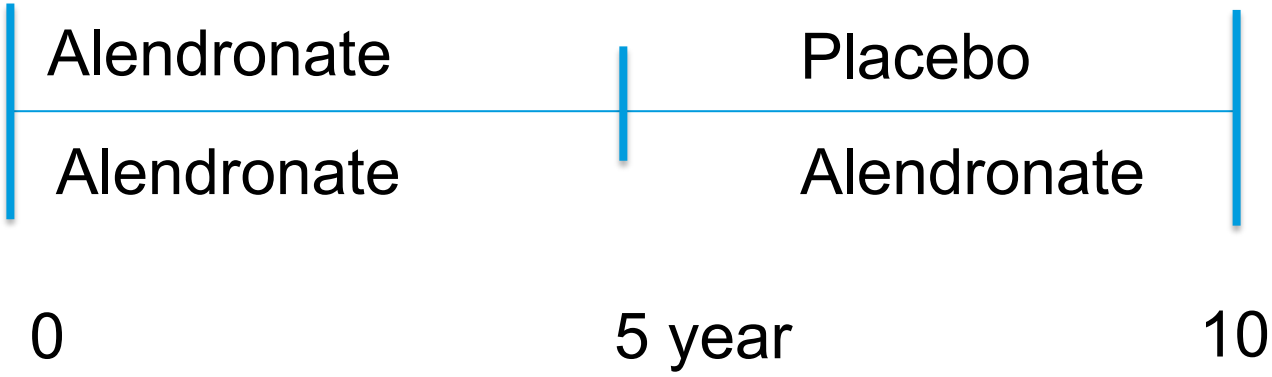
FLEX STUDY



	Hip BMD	spine BMD	BTM (CTX)	Non vert fx	Morphometric vertb fx	Clinical vert fx
Alendronate	Stable	stable	-	18.9	+9.8%	+2.4%
placebo	-2.4%	-3.7%	↑	19	+11.3%	+5.3%
	Significant	Significant		Not significant	Not significant	significant

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

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BISPHOSPHONATE THERAPY DURATION AND DRUG HOLIDAY

- Indication for discontinuation - 5-year course of bisphosphonate treatment and 3 years of IV bisphosphonates
  - BMD stable or improved
  - No fractures since starting treatment and
  - BMD above –2.5 at the main skeletal sites

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

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DRUG HOLIDAY

- Period of observation off bisphosphonate
- Applies only to bisphosphonate
- Bone density every two years
- Clinical evaluation (for fracture, possible risks such as starting GC etc)
- Calcium and vitamin D supplements
- Reinforce fall prevention and healthy lifestyle
- Because they bind to skeletal minerals, bisphosphonates will provide residual protection from fractures even after discontinuation of the medication for 3-5 years

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WHEN TO RESTART BISPHOSPHONATE

- Duration of drug holiday depends on the affinity of the medication to the bone

  -risedronate (least affinity) → , Ibandronate→ Alendronate → , Zoledronic acid (highest affinity so it may take several years)

- Clinical fracture occurrence or
- BMD loss in the spine around 3-4% and 4-6% in the hip and femoral neck

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HOW TO RESTART THERAPY

- Usually, Risedronate→ Drug holiday duration 2-3 years
- Alendronate, ibandronate→ 3-5 years
- Restart bisphosphonate for another 3-5 years
- If a fracture occurs- intensify therapy; anabolic therapy is preferred
- Recalculate risk again and stratify to low risk, moderate and high risk

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WHEN TO SWITCH BISPHOSPHONATE THERAPY

- If GI side effect to oral bisphosphonate→ switch to IV bisphosphonate (Reclast)
- If BMD declines or therapy
  - Verify taking medication (compliance rate 20-30%)
  - If compliance is a question, switch to IV bisphosphonate
  - Evaluate for change in medical history (addition of Aromatase inhibitor, Glucocorticoid therapy, sarcopenia)
  - Check vitamin D, calcium intake
  - Check for change in lifestyle (stopped exercising, alcohol intake increase…)
  - Intervention: Switch to IV bisphosphonate, calcium intake of 1200 mg daily, ensure that total 25 OHD is 40-60, exercise with weights and walking.
  - Recheck bone density in 1 year

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HIGH RISK

- Those with recent fractures (within two years)
  - Risk of another fracture is about 20% within the first year of the fracture
- Patients with a history of multiple fractures
- individuals with T score <-3.0 with fracture

Management

- #1 Anabolic therapy (teriparatide, abaloparatide, romosozumab)
- #2 Denosumab
- #3 Bisphosphonate (IV zoledronic acid preferably) oral okay if compliant

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ANABOLIC THERAPY OPTIONS- MORE EFFECTIVE IN STIMULATION OF BOTH GROWTH AND REDUCE RISK OF FRACTURE IN 12 MONTHS-21 MONTHS

	Participants Characteristics	Vert frac reduction	Non vert reduction
Teriparatide 21 months	1637 women	65%	53%
Abaloparatide 18 months	2463 women >50% fracture	86%	43%
Romosozumab 12 months	7110 post meno Hip T score <-2.5	73%	42%

Neer RM. N Engl J Med. 2001;344(19):1434; Miller PD et al. JAMA. 2016 Aug 16;316(7):722-33; Cosman F et al. N Engl J Med. 2016;375(16):1532

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ANABOLIC AGENTS (TERIPARATIDE, ABALOPARATIDE)- STIMULATE BONE FORMATION

- PTH analog (Teriparatide) or PTH related protein analog (Abaloparatide)
- Build bone, slightly increase bone resorption in the beginning
- Indications: Treatment of women high risk for fracture
  - Increase bone mass in men with primary or hypogonadal osteoporosis high risk for fracture (Teriparatide only)
  - Patients who failed or intolerant to other available osteoporosis therapy
  - Treatment of men and women with Glucocorticoid induced osteoporosis
  - Adverse effect: nausea, hypercalcemia, worsening kidney stones, arthralgias
- Contraindication: risk of osteosarcoma (h/o bone radiation, personal or family h/o osteosarcoma or Paget's)

Duration of treatment: Treatment is for 18-24 months but must be followed by bisphosphonate or denosumab.

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THERAPY COMPARISON: TERIPARATIDE VS. ALENDRONATE IN HIGH-RISK FRACTURE

- VERtebral fracture treatment comparisons in osteoporotic women (VERO trial)
- 680 Postmenopausal women >45 years old in each group
- BMD T score -1.5 or less in the femoral neck, total hip or lumbar spine

And one or more vertebral fractures

Incidence of new vertebral fracture in Teriparatide 18/574 and risedronate 35/585 at 12 months and 28/516(5.4%) in teriparatide and 64/533 (12.0%) in risedronate group at 24 months with absolute risk reduction 6.6%

Kendler et al. Lancet 2018;230-40

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ROMOSOZUMAB (EVENITY)

- Sclerosteosis, rare genetic condition causing sclerostin deficiency characterized by high bone mass and resistance to fracture
- Sclerostin antibody that is anabolic
- Approved for postmenopausal women, high risk for fracture (history of osteoporotic fracture, multiple risk factor for fracture or patients who have failed or intolerant to other osteoporosis medications)
- 210 mg SQ monthly for 12 months (given in health care, hospital setting)
- Injected arm, abdomen or thighs
- Great choice for those who want to build bone but not candidate for teriparatide
- Must be followed by antiresorptive such as denosumab or bisphosphonate

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ROMOSOZUMAB 3 CLINICAL TRIALS

- Study 1: Romosozumab vs. placebo
  - 7180 postmenopausal women, 55-85, hip or FN BMD -2.0 to -3.5), no fracture
  - Exclusion: prior fracture, bisphosphonate previous 24 months, oral bisphosphonate, PTH, strontium within previous 12 months, calcitonin, SERM, estrogen previous 3 months or glucocorticoid within the previous 3 months
  - Vertebral fx reduction
- Study 2: Romosozumab vs. Alendronate in very high risk group

  ARCH trial (Active-controlled fracture study in postmenopausal women with osteoporosis at high risk

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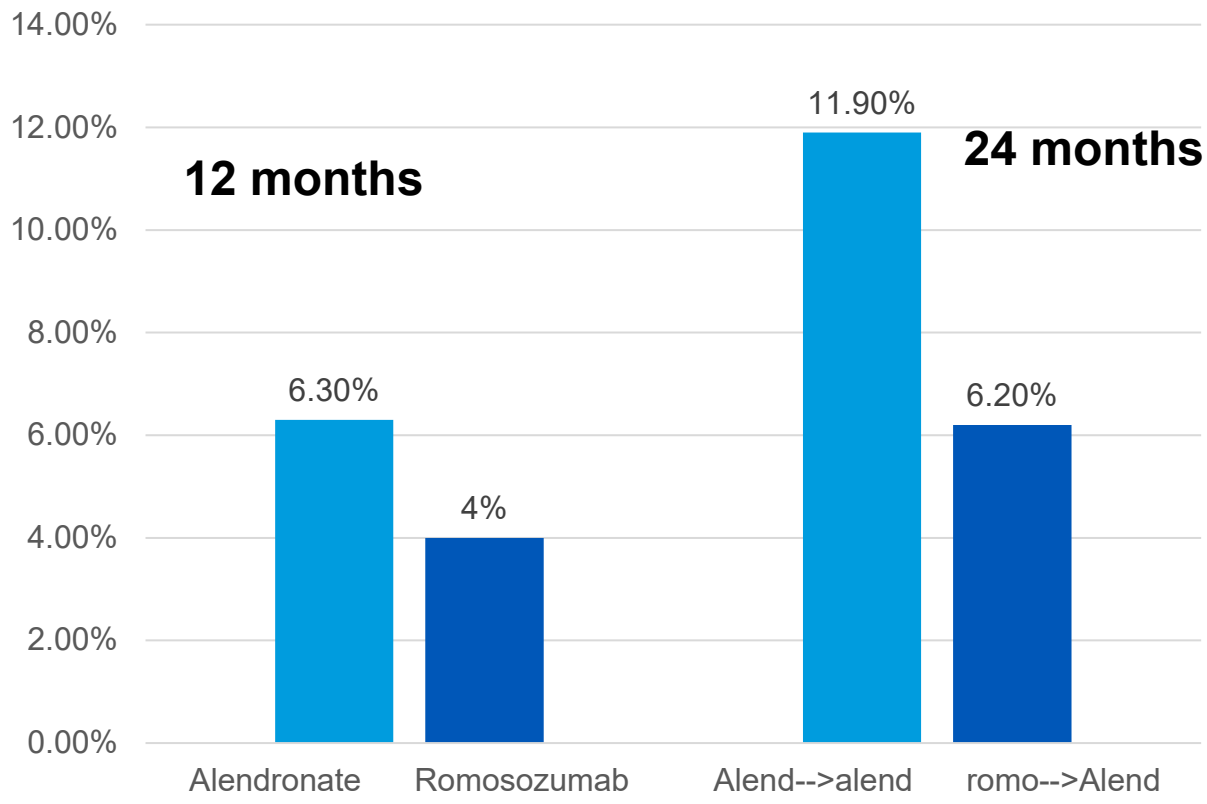
Saag KG et al. N Engl J Med 2017:377:1417-1427

INCIDENCE OF NEW VERTEBRAL FRACTURES



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There was a higher rate of major adverse event (MACE), a composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke in patients with Evenity compared to those treated with Alendronate

Study 1 (excluded those with prior fracture)			**Study 2 : Open label 24 months romo→alend vs. alend→alend (prior fracture w/in 3-24m)**	
	Romosozumab (n=3581)	Placebo (3576)	Romosozumab- (N=2040)	Alendronate (N=2014)
Myocardial infarction	9 (0.3%)	8 (0.2%)	16 (0.8%)	5 (0.2%)
stroke	8(0.2%)	10 (0.3%)	16 (0.8%)	7 (0.3%)
CV death	17 (0.5%)	15 (0.4%)	17 (0.8%)	12 (1.1%)
OJN	0	0	1 (<0.1%)	1 (<0.1%)
Atypical femur fx	0	0	2 (<0.1%)	4(0.2%)

Event occurred in patients with and without history of MI or stroke

Saag KG et al. N Engl J Med 2017;377:1417-142

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ROMOSOZUMAB CANDIDATES

- Women High risk for fracture (prior h/o fracture, multiple risk factor for fracture, and/or BMD <-3.0
- Contraindication to teriparatide or abaloparatide
- No history of myocardial infarction or stroke in the past year
- ASCVD risk is not high (if high, benefit vs. risk must be weighted) and if CV or CVA complication during therapy, stop Romosozumab
- No approved for men yet
- Can be used in renal impairment

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CAUTION

- Romosozumab may increase the risk of myocardial infarction, stroke and cardiovascular death
- Romosozumab should not be initiated in patient who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefit outweighs the risk in patients with other cardiovascular risk factors
- If a patient experiences a myocardial infarction or stroke during therapy, Romosozumab should be discontinued

- Romosozumab prescribing information. April 23, 2022

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DENOSUMAB

- 60 mg SQ twice per year approved for osteoporosis
  - (note similar medication dosage that denosumab 120 mg used every 1-3 months for metastatic cancer)
- Along with calcium 1000 mg and at least vitamin D 400 iu daily
- Indication:
  - Treatment of postmenopausal women and men with osteoporosis at high risk for fracture (h/o osteoporotic fracture or multiple risk factor for fracture or patients who have failed or are intolerant to other available osteoporosis therapy)Men at high risk for fracture receiving androgen deprivation therapy
  - For women high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
  - Safe for renal patients including dialysis

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DENOSUMAB POTENTIAL SIDE EFFECTS TO

- Hypocalcemia (especially in patients with malabsorption and renal impairment) consider checking serum calcium 7-10 days after injection
- Serious infections- skin infection cellulitis, urinary tract infections
- Dermatitis, eczema, rashes
- Osteonecrosis of the jaw (ONJ)
- Atypical femur fractures (evaluate patients with thigh or groin pain for femoral fracture)
- Severe bone, joint, muscle pain. Discontinue if severe
- Elevated cholesterol

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DENOSUMAB

- Risk of ONJ 0.85% with invasive oral procedures
- Do not delay for dental treatment
- >1 extraction should be staged
- If ONJ develops and not healing, do not stop denosumab but some benefit to adding anabolic therapy to Prolia has been reported.

- Watts NB et al. JCEM 2019.

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CONTRAINDICATION

- Hypocalcemia
- Pregnancy
- Known sensitivity to denosumab
- If patient can not be reliable to followup on time
- Future potential need for dental work that may require interruption of denosumab
- Patients who do not want long term therapy

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Cummings SR. Bone Miner Res. 2018;33(2):190.

- In a post hoc analysis of 1000 women who stopped denosumab followed for 9-12 months since last injection
- Risk of vertebral fracture 7.8% in denosumab groups vs. 7.1% in placebo
- However, patients who discontinued denosumab had a higher rate of multiple vertebral fractures than the placebo group (60.7 versus 38.7 %)
- Patients with a prior vertebral fracture were at greatest risk for multiple fractures upon discontinuation.

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DENOSUMAB DISCUSSION PRIOR TO INITIATION AND AT EACH VISIT

- Long term 10+ year medication given every 6 months – freedom extension trial
- If stopped abruptly, there is a rebound bone turnover where bone resorption is increased within 30 days to 1 year leading to large bone loss
- There is increased risk of vertebral fracture (multiple) as early as 30 day relapse
    - High risk individuals are those with prior h/o vertebral fracture

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LONG TERM DENOSUMAB 10-YEAR DATA

- BMD continues to increase up to 10 years
  - 21·7% at the lumbar spine, 9·2% at the total hip, 9·0% at the femoral neck, and 2·7% at the one-third radius.
  - Reduces fracture risk up to 10 years
- No increased risk of atypical femur fracture or osteonecrosis of the jaw
- If denosumab is discontinued abruptly, BMD declines to baseline
  - Increased risk of multiple vertebral fractures
    - Risk is higher in those with prior history of vertebral fractures (2-fold increase in risk of multiple vertebral fractures)

Bone et al. Lancet 2017; 5:7, JULY 01, 2017

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DENOSUMAB TAKE HOME POINTS

- Duration of treatment is unknown
- Can not be discontinued abruptly without transition to antiresorptive
- When stopped abruptly, BMD and fracture risk returns to baseline within 9-12 months
- Increased risk of multiple vertebral fractures in those with prior h/o vertebral fractures
- Current data shows safety up to 10 years
- Most experts advocate consider stopping Prolia if BMD target (hip BMD T-score of -1.5 or -1) then consider changing treatment or discontinuing therapy (see transition plan)

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CURRENT DENOSUMAB RECOMMENDATION

- Young patients and those with low risk→ do not start denosumab
- Denosumab treatment <2.5 yrs. → oral bisphosphate 2-3 years or ZA x 1-2 years (depending on BMD and BTM)
- Denosumab use >2.5 yrs. or high-risk patient→ continue denosumab for 10 years and beyond
  - Give ZA at 6 and 12 months after the last denosumab injection (next preference)
  - Oral bisphosphonate for 12-24 months (consider checking bone turnover markers every 3 months) (last option)

    - Tsourdi, E et al. *The Journal of Clinical Endocrinology & Metabolism*, 2021, Vol. 106, No. 1, 264–281

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- Current expert recommendation:
  - Do not start denosumab in patients who are noncompliant
  - Denosumab should be reserved for high to very high risk patients who will need lifelong treatment
  - Patient should understand that it may not discontinued
  - Be carful in those with prior vertebral fractures

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OSTEOPOROSIS TREATMENT FAILURE

- Compliance
- Recurrent falls
- Low BMI (nutrition)
- Missed secondary cause of osteoporosis
- Very low BMD before initiation of treatment
- Missed/delayed treatment

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SEQUENTIAL THERAPY

- Drug holiday
- Bisphosphonates
  - Oral
  - IV

- Drug holiday Does not apply
- Teriparatide
- Abaloparatide
- Denosumab
- Romosozumab

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CURRENT PRACTICE FOR SEQUENTIAL THERAPY

- Denosumab→ Bisphosphonate (IV, Oral), raloxifene is not recommended, anabolic therapy is not recommended
- Teriparatide x 24 months → Denosumab or Bisphosphonate
  - Some data to switching to Raloxifene
- Abaloparatide x 18 months → bisphosphonate 3-5 years
- Romosozumab x 12 months → Denosumab or Bisphosphonate

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WHEN TO CHANGE OSTEOPOROSIS THERAPY

- International osteoporosis foundation guidelines for treatment failure in osteoporosis:
  - Two or more fragility fractures
  - One fragility fracture and no reduction in turnover markers and/or significant decrease in BMD
  - Fractures of the hand, skull, feet, and ankle are not considered fragility fractures

Diez-Perez A et al. osteop int 2012

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ATYPICAL FEMUR FRACTURE

- Risk factors
  - Longer duration of bisphosphonate use
  - Asians
  - Height and weight loss
  - Glucocorticoid use >1 year

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SECONDARY FRACTURE PREVENTION

- Risk: high risk for future fracture
  - The relative risk of having a hip or a vertebral fracture is 2 folds higher for prior fractures of major osteoporotic fracture (hip, forearm, spine or humerus)
  - The risk is the highest closest to the fracture
  - Increased mortality 12-37% in the first year post hip fracture
  - Studies show that only 20% of patients receive treatment after a hip fracture

Black et al. N Eng J Med May 3, 2007

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INITIATING IV BISPHOSPHONATE AFTER HIP FRACTURE AND SECONDARY PREVENTION

- 1065 pts given ZA and 1062 pt in placebo (HORIZON)
- Given ZA within 90 days after surgical repair of the hip fracture
- Average age 74.5 (about 13% were >85 y/o), f/u 1.9 years
- New clinical fracture 8.6% in ZA and 13.9% in placebo (35 % reduction)P=0.001
- New clinical vertebral fx 1.7% in ZA vs. 3.08 in placebo (P=0.02)
- New nonvert fx fx 7.6% vs. 10.7% p=0.03

Lyles K et al. NEJM 2007

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GIVING BISPHOSPHONATE AFTER FRACTURE DOES NOT DELAY HEALING

- Incidence of delayed healing in ZA vs. placebo 3.2 vs 2.7% (p= 0.61)
- No difference in nonunion rate between zoledronic acid and placebo when ZA given within 2 weeks, 2-4 weeks, 4-6 weeks, and >6 weeks post hip fracture
- Mortality reduction of 28% from any causes with ZA when given within 90 days post hip fracture (p=0.01)

- Lyles K et al. NEJM 2007 ;Colon-Emeric C et al. Osteoporos Int (2011) 22:2329–2336

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SPECIAL GROUPS TO CONSIDER

- Type 2 Diabetes- high risk for poor bone quality (due to high glycated byproducts) so high risk for fracture with normal BMD or osteopenia
  - Check BMD. if osteoporosis→ treat
  - If BMD is normal or Osteopenia range
    - + fracture→ osteoporosis start treatment + control diabetes
    - No fracture→ control diabetes
- Transplant patients→ pretransplant
  - BMD osteopenia or normal→ get spine x-ray and if fx treat (IV or oral bisphosphonate preferred)
  - BMD osteoporosis→ treat prior to transplant if possible
    - Abate et al. Endocrine practice 2021

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SUMMARY

- Osteoporosis related fracture are preventable
- Fall prevention, weight-bearing exercise, and adequate intake of calcium and vitamin D are cornerstones of fracture prevention.
- However, medical therapy is often required to treat osteoporosis. Patients who have already sustained a fragility fracture of the hip or spine should be considered for medical therapy to prevent additional fractures, even without bone mineral density (BMD) testing.

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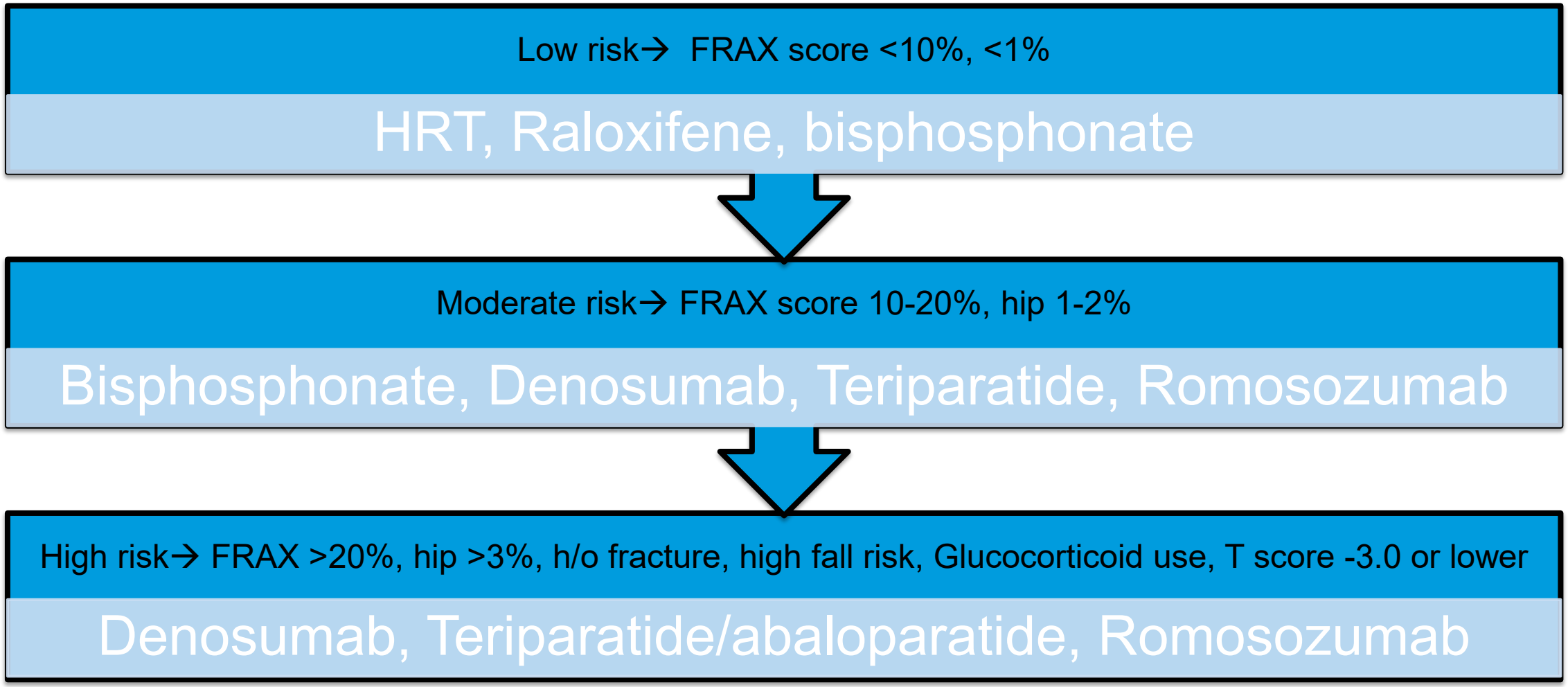
RISK ANALYSIS, COMORBIDITIES AND PATIENT PREFERENCE



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REFERENCE

- Abate et al. Evaluation of Factors Associated With Fracture and Loss of Bone Mineral Density Within 1 Year After Liver Transplantation. Endocrine practice. (2021) 27: 426-432
- Abate, E and Bernet, V. How to interpret Dual Energy Absorptiometry (DXA) for Clinicians. Video in Endocrinology. September 8, 2020
- Black DM, Cummings SR, Karpf DB. et al. Fracture Intervention Trial Research Group. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535-15418950879
- Cummings SR, Black DM, Thompson DE. et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*. 1998;280:2077-20829875874 vertebral fractures. *Lancet*. 1996;348:1535-1541
- Ensrud KE, Barrett-Connor EL, Schwartz A, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention TrialLong-Term Extension. *J Bone Miner Res*. 2004;19:1259-1269.

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- Black DM et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809
- Black et al. Effects of continuing or stopping alendronate after 5 years of treatment. The Fracture intervention Trial Long-term extension (FLEX): A randomized trial. *JAMA. 2006;296:2927-2938*
- Schilcher et al. Bisphosphonate Use and Atypical Fractures of the Femoral Shaft. N engl j med 364;18: 1728- 1737
- McClung et al. Romosozumab in Postmenopausal Women with Low Bone Mineral Density. N Engl J Med 2014; 370:412-420
- Miller PD et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial JAMA. 2016 Aug 16;316(7):722-33

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QUESTIONS & ANSWERS

#transformWH

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