Osteoporosis Update: Denosumab Transition, Teriparatide Label Change and Much More

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Intervention

- We have determined T-scores
- We know risk factors
- We have diagnosed and treated secondary causes of osteoporosis
- Our objective is to prevent fractures

Who Do You Treat with Low Bone Mass (Osteopenia)?

Postmenopausal women and men aged 50 years and older presenting with the following should be treated (after appropriate evaluation to exclude secondary causes):

Based on the US-adapted WHO algorithm of FRAX

Low bone mass (T-score between -1.0 and -2.5 at the femoral neck, total hip, or spine); *AND*

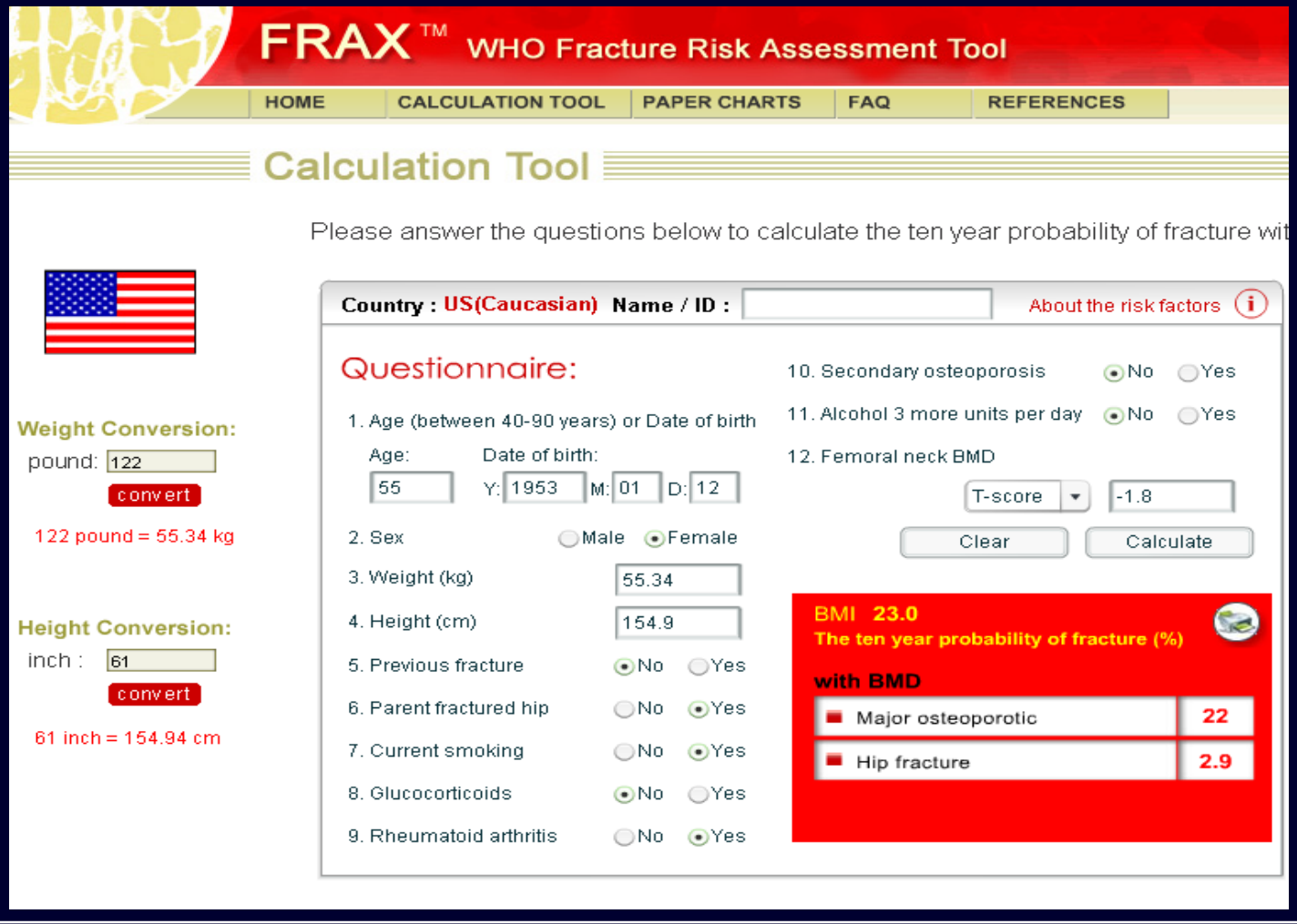
10-yr probability of fracture greater than or equal to	*For the following type of fracture*
3%	Hip fracture
20%	Any major osteoporosis-related fracture

Adapted from National Osteoporosis Foundation; www.nof.org.

Quantifying Fracture Risk

www.shef.ac.uk/FRAX

Age	55
Sex	F
Wt	122
Ht	61
Fracture	No
Parent Fracture	Yes
GCs	No
R.A.	Yes
2nd OP	No
Alcohol	No
FN	-1.8
L1-4	-2.4



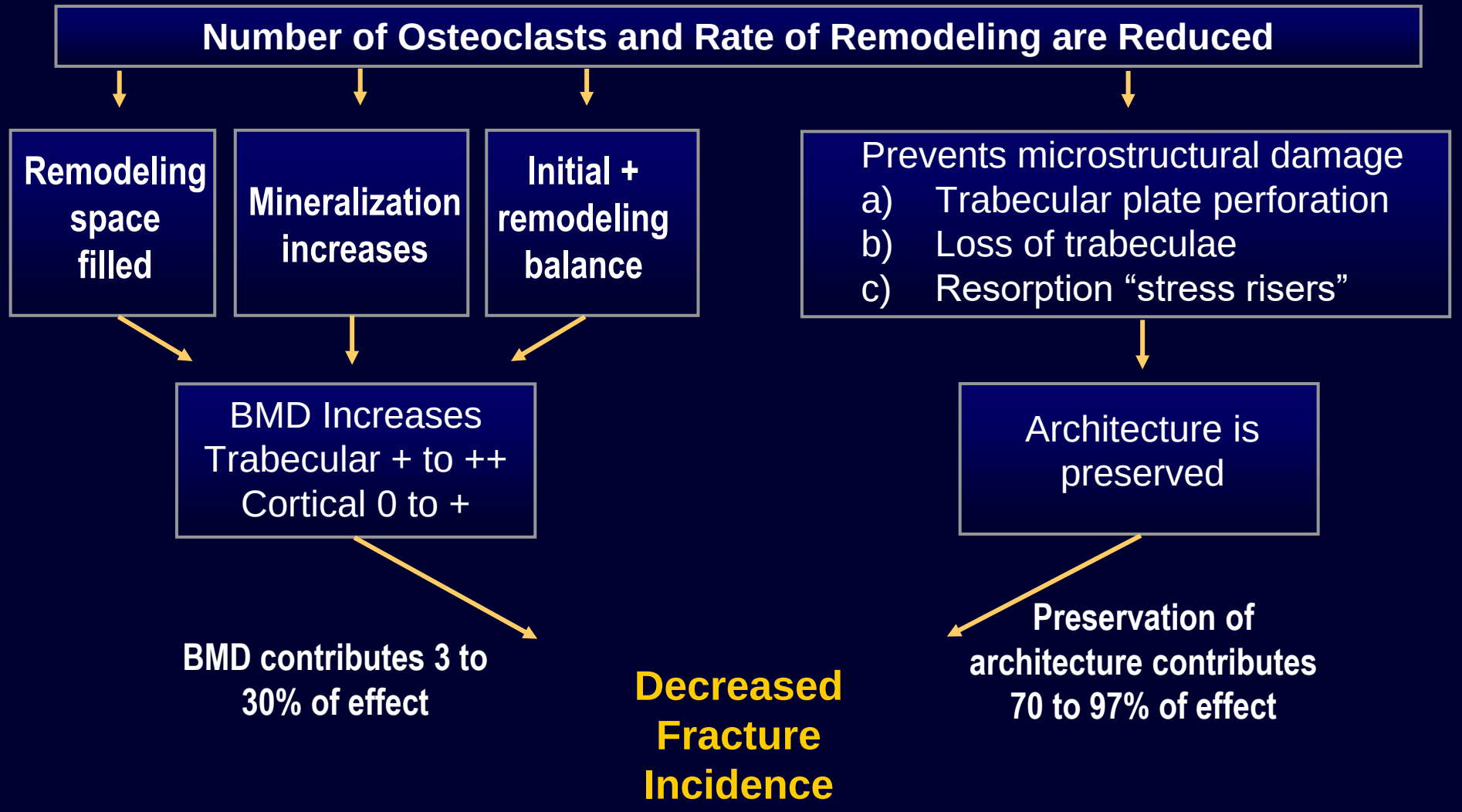
Osteoporosis: Treatment Goals

- Prevent fractures
- Stabilize or increase bone mass
- Relieve symptoms of fractures and skeletal deformity
- Affect patient’s perceived goals of improving physical function

Two Types of Drug Therapy for Osteoporosis

- Antiresorptive
  - Lowers bone turnover
  - Maintains or improves bone mass
- Anabolic
  - Increases bone turnover with bone formation exceeding bone resorption, increases bone mass, and stimulates bone formation

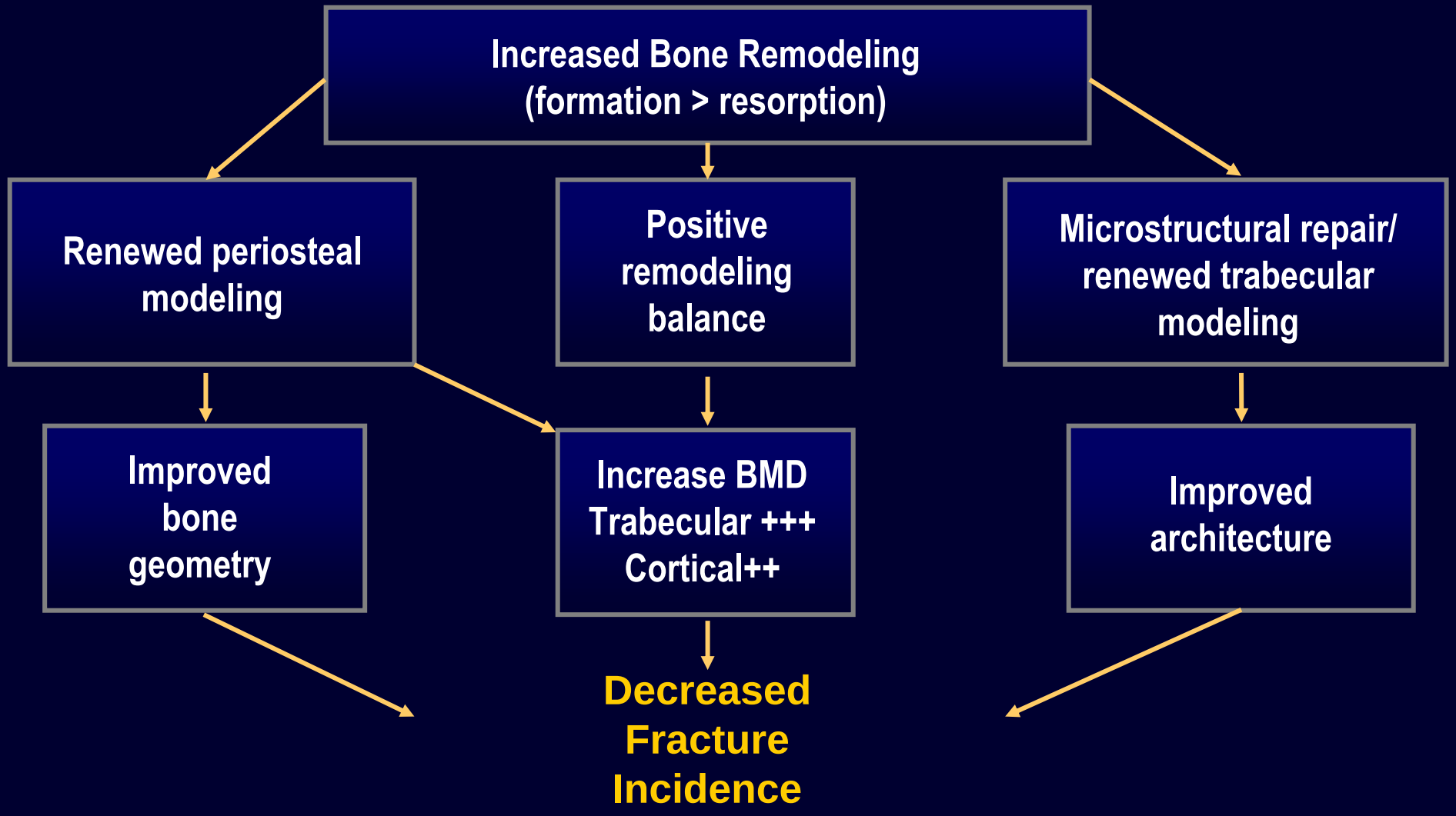
Antiresorptive Therapy
Mechanism of Increase in Bone Strength



Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. J Bone Miner Res 2005;20:177-184.

See also, **Seeman E, Delmas PD.** Bone Quality — The Material and Structural Basis of Bone Strength and Fragility. *N Eng J Med* 2006:354:2250-2261

Anabolic Therapy
Mechanism of Increase in Bone Strength



Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. J Bone Miner Res 2005;20(2):177-184.

Two Types of Drug Therapy for Osteoporosis

- Antiresorptive
  - Bisphosphonates
    - Alendronate - Fosamax®
    - Risedronate - Actonel®
    - Ibandronate - Boniva®
    - Zoledronate - Reclast®
  - Hormone therapy
    - Estrogen
    - Estrogen progestin therapy
  - Selective estrogen receptor modulator
    - Raloxifene - Evista®
  - RANKL inhibitor
    - Denosumab (Prolia)
  - Calcitonin
    - Miacalcin, Fortical>
- Anabolic
  - Teriparatide – Forteo
  - Abaloparatide-Tymlos
  - Romosozumab-aqqg-Evenity

1. Indicated for use in United States. Additional therapeutic options are approved in other countries.

Treating Low Bone Mass or Fracture
Decision-Making in 2021

Patient Variables

- Age
- Fracture history
- FRAX score
- T-Score
- Concomitant medications
- Propensity to fall
- Compliance
- Side effect concerns (fears)
- Patient history, including GI
- Comorbid conditions

Current Options

- Bisphosphonates
- SERMs
- Estrogen
- Calcitonin
- Parathyroid hormones

Denosumab

Romosozumab

The “Basics”

- Calcium
- Vitamin D

“Basic” Intervention

- *2021 Updated Recommendation:* Ensure adults age 50 and older have adequate calcium and Vitamin D intake, with supplementation only if necessary
  - Calcium: 1000-1200 mg per day
  - Vitamin D: 800 to 1000 IU per day (if 25-hydroxyl Vit D level normal)

- Other
  - Avoid tobacco and excessive alcohol
  - Physical therapy evaluation and instruction for cane or walker use
  - Regular exercise to increase muscle tone and improve balance
  - Occupational therapy to assess at-home fall risk
  - Decrease fall risk — review of medications, especially antihypertensive agents, sedative-hypnotics and environment

*National Osteoporosis Foundation’s Updated Recommendations for Calcium and Vitamin D, nof.org 2021
Campion JM, Maricic MJ. *Am Fam Phys*. 2003;67(7):1521-1525

Indications for Treatment: NOF Guidelines

- Prior hip or vertebral fracture
- DXA hip or spine T-score ≤2.5
- T-score between -1.0 and -2.5 with a 10-year risk of major osteoporotic fracture of ≥20% or a 10-year hip fracture of ≥3

NOF. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2021

Behavioral/Lifestyle Measures to Prevent Osteoporosis

- Adequate intake of dietary calcium, vitamin D, and protein throughout life
- Regular physical activity; load-bearing exercise
- Minimize alcohol intake
- Stop smoking
- Take measures to prevent falls
- Use of hip protectors by patients prone to falling

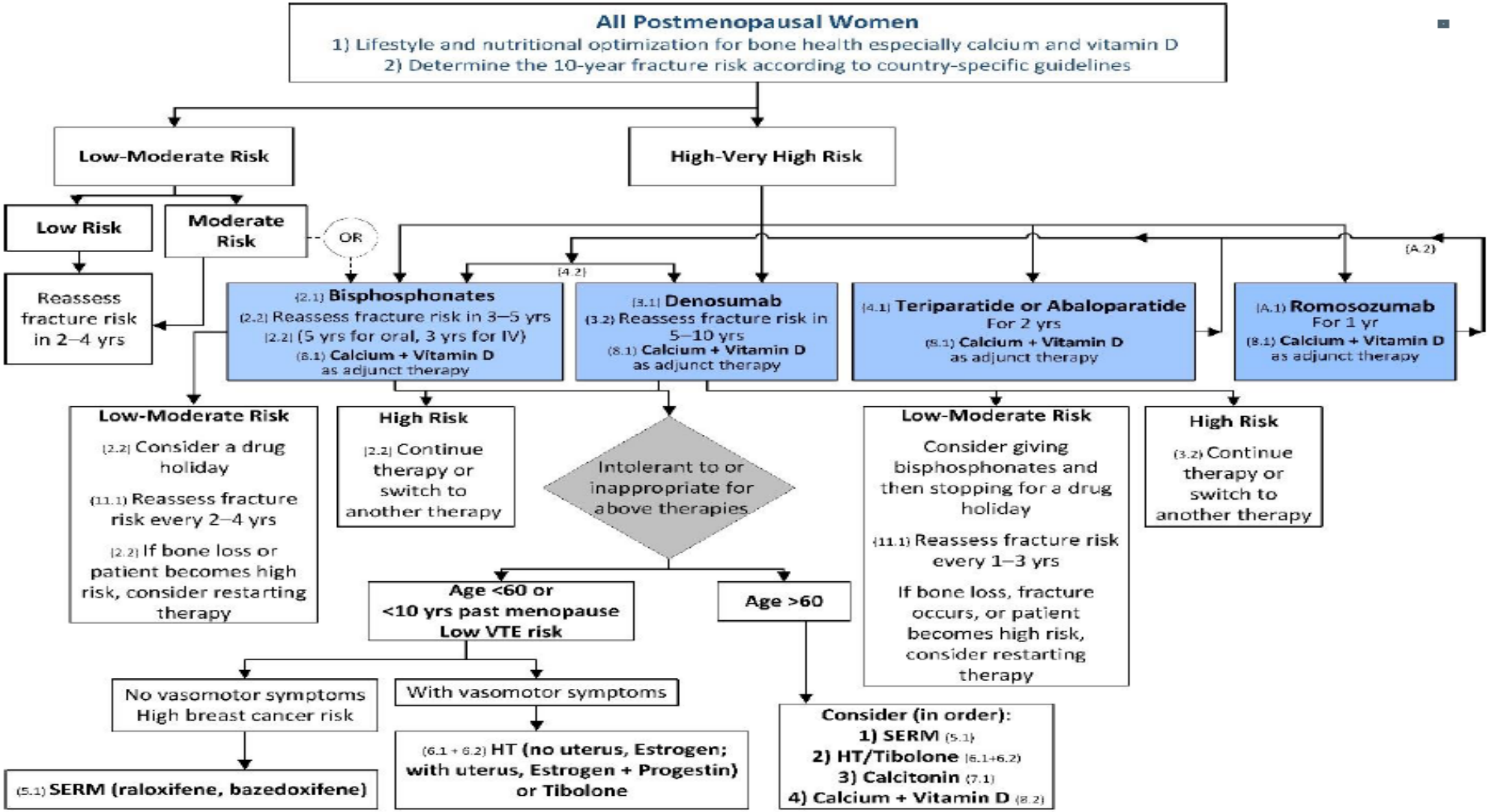
Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2021

Risk of Fracture

- Both the Endocrine Society and the North American Menopause Society recommend to treat patients based on their fracture risk and current BMD
- Moderate risk initiate therapy with raloxifene or a bisphosphonate
- High risk initiate therapy with a bisphosphonate or denosumab
- Very high risk initiate therapy with an anabolic therapy

Examples of Fracture risk

- Moderate fracture risk- 62 year old female with T-score of -2.6 in lumbar spine, -1.8 in femoral and no other risk factors
- High fracture risk- 68 year old female , mother with hip fracture, T-score in the femoral neck of -2.8 and personal history of wrist fracture at age 60
- Very high fracture risk- 72 year old, T-score of -3.0, humeral fracture at age 68 and two recent vertebral fractures
- Low fracture risk is not defined in these documents. My definition would be a 52 year old female with T-score of -2.5 in lumbar spine and -1.5 in the femoral neck with no other risk factors


All Postmenopausal Women
1) Lifestyle and nutritional optimization for bone health especially calcium and vitamin D
2) Determine the 10-year fracture risk according to country-specific guidelines
Low-Moderate Risk
High-Very High Risk
Low Risk
Moderate Risk
OR
Reassess fracture risk in 2–4 yrs
(2.1) Bisphosphonates
(2.2) Reassess fracture risk in 3–5 yrs
(2.2) (5 yrs for oral, 3 yrs for IV)
(8.1) Calcium + Vitamin D as adjunct therapy
(4.2)
(3.1) Denosumab
(3.2) Reassess fracture risk in 5–10 yrs
(8.1) Calcium + Vitamin D as adjunct therapy
(4.1) Teriparatide or Abaloparatide
For 2 yrs
(8.1) Calcium + Vitamin D as adjunct therapy
(A.2)
(A.1) Romosozumab
For 1 yr
(8.1) Calcium + Vitamin D as adjunct therapy
Low-Moderate Risk
(2.2) Consider a drug holiday
(11.1) Reassess fracture risk every 2–4 yrs
(2.2) If bone loss or patient becomes high risk, consider restarting therapy
High Risk
(2.2) Continue therapy or switch to another therapy
Intolerant to or inappropriate for above therapies
Low-Moderate Risk
Consider giving bisphosphonates and then stopping for a drug holiday
(11.1) Reassess fracture risk every 1–3 yrs
If bone loss, fracture occurs, or patient becomes high risk, consider restarting therapy
High Risk
(3.2) Continue therapy or switch to another therapy
Age <60 or <10 yrs past menopause Low VTE risk
Age >60
No vasomotor symptoms High breast cancer risk
With vasomotor symptoms
(5.1) SERM (raloxifene, bazedoxifene)
(6.1 + 6.2) HT (no uterus, Estrogen; with uterus, Estrogen + Progestin) or Tibolone
Consider (in order):
1) SERM (5.1)
2) HT/Tibolone (6.1+6.2)
3) Calcitonin (7.1)
4) Calcium + Vitamin D (8.2)

Essential Points of Endocrine Society Guidelines

- Essential points
  - Treat high risk individuals especially those with previous fracture
  - Consider BPs as the first line therapeutic choice for PMO women at high risk of fracture
  - Reassure fracture risk after patient has been on BPs for 3-5 yrs
  - Following assessment, prescribe a BP drug holiday for women on BPs who those who after treatment are at low-moderate risk of fracture
  - Consider anabolic therapy for women at very high risk of fractures, including those with multiple fractures

Case discussions to focus on (modified from Endo 2019):

1. Selecting Initial Treatment
2. Bisphosphonate Holidays
3. Denosumab: Why would you stop? What would you do?
4. Anabolic Agent for Initial Treatment
5. Combination Therapy
6. If you consider teriparatide for a denosumab user, would you add or switch?

Case 1: Selecting Initial Treatment

Presentation:

Helen is a 74-year old woman who has been well all her life. Her weight is 105 pounds (47.6 Kgs) and is 5’8” (1.7 m) tall. BMI is 16 kg/m^2. Menopause was age 53. Her mother had a hip fracture at age 82.

T- scores:

Spine -3.2; Femoral neck -2.7

Z-scores:

Spine -1.0; Femoral neck -0.9

Other Labs:

Calcium and creatinine - normal;
25-OH D -satisfactory

Question: What pharmacologic treatment would you recommend?

A. An oral bisphosphonate
B. An IV bisphosphonate
C. Raloxifene
D. Denosumab

Selecting Initial Treatment

Panel Discussion
Audience Questions

Guideline:

- Her T-score is below -2.5 so she needs pharmacologic therapy
- Thus, the guidelines would recommend bisphosphonate (oral or iv) or denosumab, taking into account patient preference.
- We would have recommended raloxifene (or menopausal hormone therapy) had the patient been intolerant of the above treatments.

Case 2: Bisphosphonate Holidays

Presentation:

Teresa is a 60-year old woman with a history of facial neuralgia and acid reflux. She is known to have osteoporosis and had fractures at spine (T6 in 2013 - fell down the stairs), clavicle, and humerus.

Treatment:

Received 3 annual infusions of zoledronic acid, last in March 2017. Now on vitamin D and calcium.

T- scores:

Spine -2.4 (-4.4% since 2016)
Total hip -1.0 (-3.5% since 2016)

Other Labs:

P1NP - 39 µg/L (previous 13 in 2015)

Question: What is the next best step?

A. Nothing; follow up
B. Give another 3 infusions of zoledronic acid
C. Give 1 infusion of zoledronic acid
D. Switch to another treatment
E. Discharge; she no longer has osteoporosis according to BMD criteria

Bisphosphonate Holidays

Panel Discussion
Audience Questions

➢ Guideline

- A bisphosphonate drug holiday is considered after 3 years of treatment with zoledronic acid if the BMD T-scores is above -2.5.
- Bisphosphonate (or other treatment) should be resumed within 5 years of stopping it or when there is evidence that the treatment is no longer working.
- Here, the PINP level has increased significantly (by more than 10 mcg/L) and the BMD decreased significantly so her drug holiday should be ended and therapy initiated.

Case 3: Denosumab

- Presentation:
- Denise is a 71-year old woman who has been receiving denosumab every 6 months without side effects, started 5 years ago.
- T- scores:
- Spine -3.2 → -1.1
- Total hip -2.7 → -0.9

Question: What is the next best step?

A. Stop treatment
B. Continue denosumab
C. Change to zoledronic acid
D. Change to an oral bisphosphonate

Denosumab

- Why would you stop? What would you do?

- Panel Discussion
  Audience Questions

Guideline:

- Denosumab should not be stopped without subsequent anti-resorptive therapy
- Follow-on treatment would hopefully mitigate the rebound in bone turnover, rapid bone loss and increased risk of vertebral fracture that occurs after stopping denosumab.
- This will be discussed extensively in upcoming slides

Case 4: Anabolic Agent for Initial Rx

Presentation:

Joan is 70 year-old woman, menopausal for 25 years, referred for osteoporosis management. No prior therapy. No prior radiation therapy. Recent painful T12 compression fracture. No CHD

T-scores:

Spine -3.5; Femoral neck -2.9

Z-scores:

Spine -1.3; Femoral neck -1.1

Other Labs:

Calcium, creatinine, PTH, ALP, SPEP, UPEP normal
25-OH D satisfactory

Question: What therapy would you initiate?

A. An oral bisphosphonate
B. An IV bisphosphonate
C. Denosumab
D. Teriparatide, abaloparatide or romosozumab

Anabolic Agent for Initial Rx

Panel Discussion
Audience Questions

➢ Guideline:

- She is at very high risk of fracture as she has a recent vertebral fracture as well as BMD T-score of -2.5 or less.
- She could be considered for an anabolic treatment (teriparatide, abaloparatide or romosozumab) or for an anti-resorptive treatment.
- If she receives an anabolic treatment this should be followed by an anti-resorptive treatment to maintain bone density gains.

Case 5: Combination Therapy

Presentation:

Rebecca is a 58-year old woman. Natural menopause was age 52. Wrist fracture age 57 (fell while fly fishing) – “worst the orthopedist had ever seen”. Calcium intake and exercise are OK. Father - hip fracture age 79. Mother - may have had osteoporosis (stroke age 62).

T- scores:

Spine -3.2 Femoral neck -3.0

Z-scores:

Spine -1.8 Femoral neck -1.9

Other Labs:

Calcium, creatinine, SPEP, kappa and lambda light chains, PTH, 24-h urine calcium normal.

25-OH D satisfactory.

She wants whatever will increase her bone density fastest and greatest.

Question: What do you tell her that would be?

A. Teriparatide
B. Abaloparatide
C. Denosumab
D. Combination teriparatide + denosumab
E. Romosozumab

Combination Therapy

Panel Discussion
Audience Questions

Guideline:

- She is at high risk of fracture as she has BMD T-score of -2.5 or less and has fractured.
- Recommend teriparatide, abaloparatide or romozosumab
- A combination of teriparatide and denosumab would increase the BMD rapidly as well but is not necessary in my opinion as she is young and fracture was not recent

Case 6: Teriparatide for Denosumab User - Add or Switch?

Presentation:

Jane is a 67-year old white woman. She had a vertebral fracture discovered one year ago. She has ; no history of radiation therapy or CHD. Treatment with denosumab was started (2 doses so far). She fell last week and sustained a fracture of her proximal humerus.

T-scores:

Spine -3.5; Femoral neck -2.7

Other Labs:

Calcium and creatinine are normal, 25-OH D is satisfactory.

- You are considering anabolic therapy.
- **Question: What would you do?**

A. Continue denosumab and not add anabolic therapy

B. Continue denosumab and add anabolic therapy

C. Stop denosumab. Change to anabolic therapy

Teriparatide For A Denosumab User - *Add Or Switch?*

Panel Discussion
Audience Questions

Guideline:

- In clinical practice, the occurrence of one fracture while on effective therapy and in a compliant patient will raise the consideration of changing therapy.
- The only anabolic therapy that has been shown as monotherapy to prevent rapid decline in BMD when stopping denosumab therapy is romozosumab
- Teriparatide could be added to denosumab. This will be discussed in future slides

Teriparatide

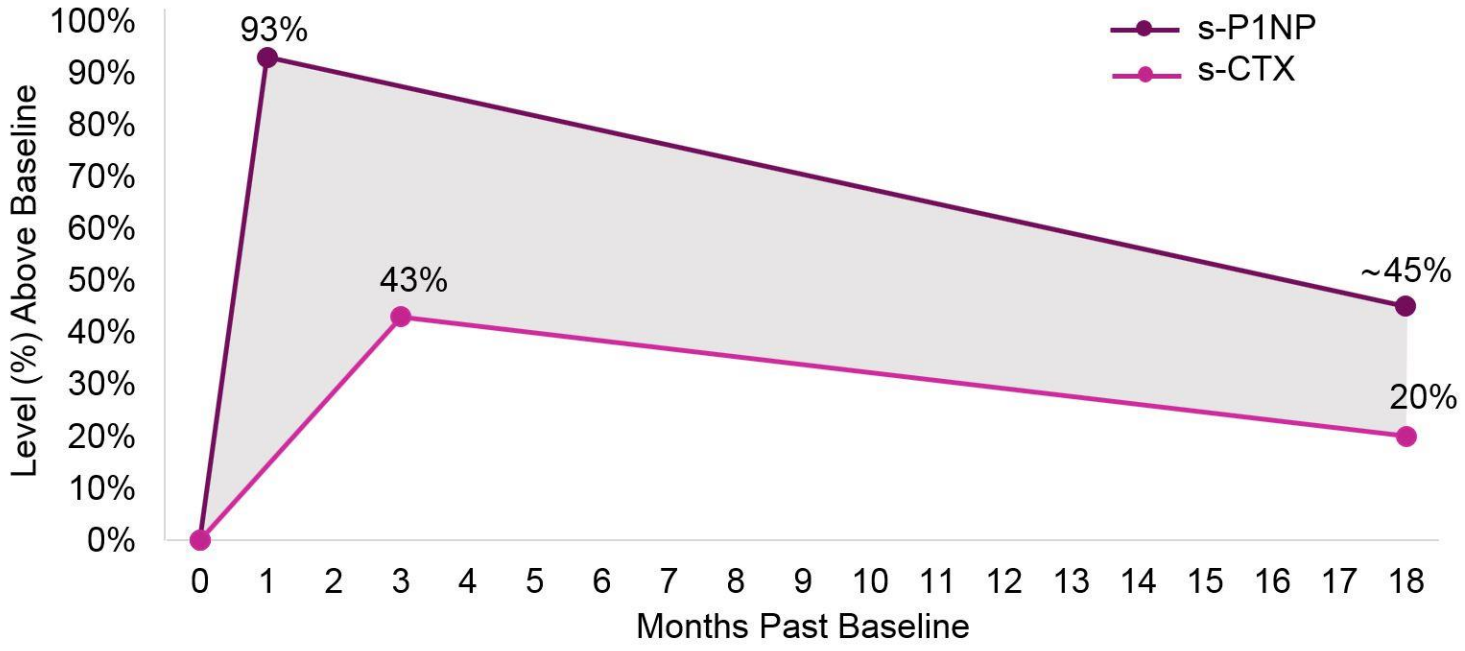
- Recommended Treatment Duration
  - Use of FORTEO for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture
  - The Bonsity (biosimilar for Forteo) package insert still states "the safety and efficacy of teriparatide have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patient's lifetime is not recommended".

Abaloparatide

- PTHrp given as a daily self-injection of 80mcg subcutaneously for 24 months using a pre-filled pen with 30 day supply of medication
- It is approved for the treatment of postmenopausal women with osteoporosis who are at high risk of fracture but is not approved for use in men or glucocorticoid osteoporosis presently
- Has same adverse reactions as teriparatide although hypercalcemia is more commonly reported with abaloparatide
- Has convenience factor that does not need to be refrigerated once the pen is in use
- Has been shown to reduce the incidence of vertebral and non-vertebral fractures

Abaloparatide (cont)

Effects on Markers of Bone Turnover



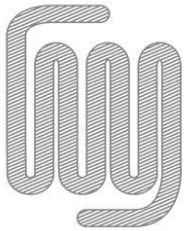
s-P1NP = serum procollagen type 1 N-terminal propeptide; s-CTX = serum carboxy-terminal cross-linking telopeptide of type 1 collagen.

TYMLOS [package insert]. Waltham, MA: Radius Health, Inc; 2017.

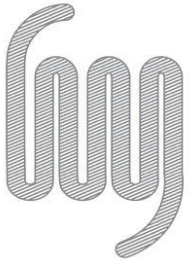
Abaloparatide (cont)

Abaloparatide Exhibits Higher Selectivity for the RG Conformation of the PTH1 Receptor vs the R^0 Conformation

PTH1 receptor R^0 conformation



PTH1 receptor RG conformation



Abaloparatide

1600X
more selective to RG than R^0

Data based on an *in vitro* study examining the binding of abaloparatide to RG and R^0 as well as the associated cAMP signaling and duration of response.

PTH = parathyroid hormone; cAMP = cyclic adenosine monophosphate.
Hattersley G, et al. *Endocrinology*. 2016;157(1):141–149.

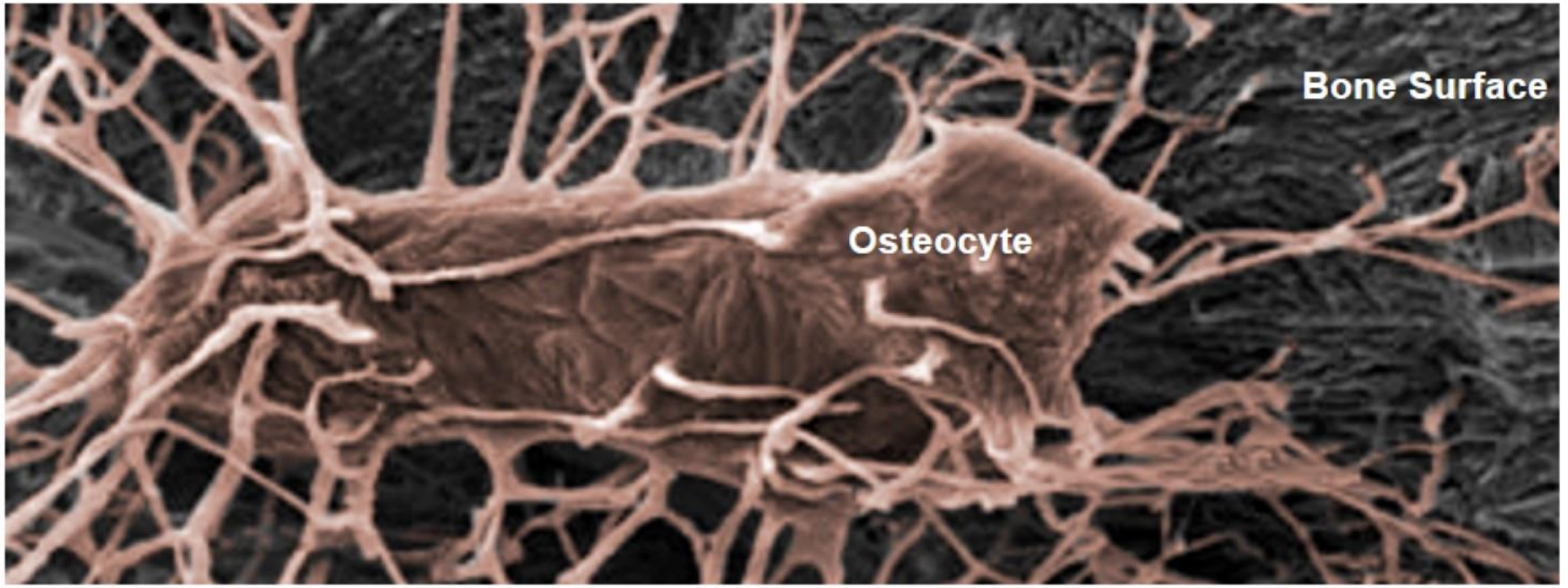
Romosozumab-aqqp

- Most recent anabolic agent approved
- Two monthly injections of 110mg each given subcutaneously by a health care professional for 12 months
- Has anabolic and anti-resorptive properties
- Is a monoclonal antibody directed against sclerostin which is an inhibitor of bone formation
- Is approved for the treatment of postmenopausal women with osteoporosis who are at high risk of fracture
- Has been shown to reduce the incidence of vertebral fractures
- Was not shown to reduce the incidence of non-vertebral fractures most likely due to an imbalance of subjects from South America

Romosozumab-aqqp (cont)

- Since it has both anabolic and anti-resorptive properties it does increase the risk of ONJ and AFF slightly
- There is no boxed warning with regards to increased risk of osteosarcoma, so post-menopausal women with osteoporosis who are at high risk of fracture and who have had radiation therapy to the skeleton, are candidates for this therapy unlike teriparatide or abaloparatide
- Like all anabolic therapy, follow up therapy must be given to prevent a subsequent decrease in BMD
- In the clinical trials, both denosumab and zoledronic acid were shown to continue to increase BMD after romosozumab therapy

Osteocytes Produce Multiple Factors Including Sclerostin That Regulate Osteoblasts and Osteoclasts

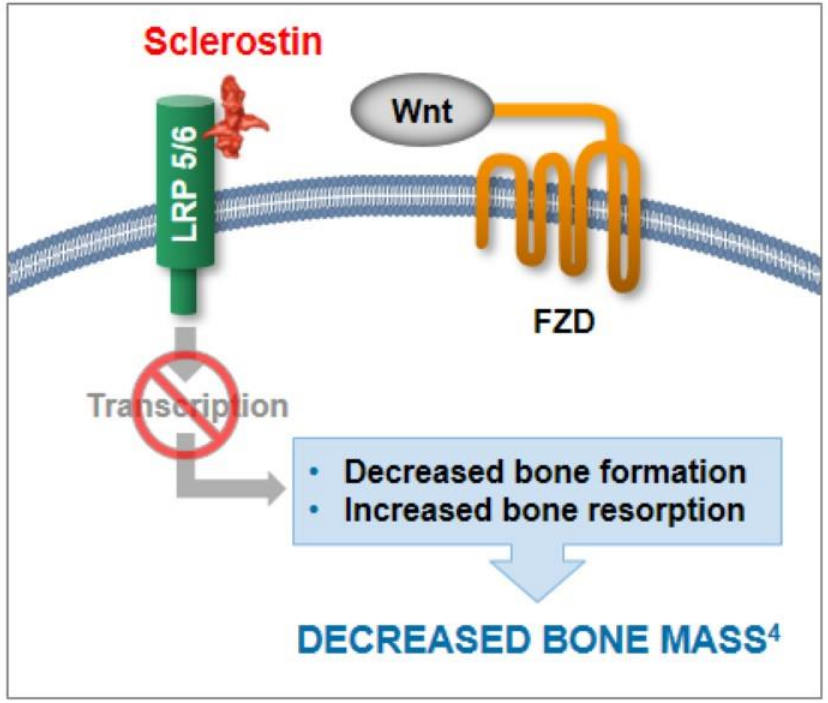


- Osteocytes reside within bone matrix where they detect various biochemical and biomechanical signals[1]
- Osteocytes respond by secreting several factors including sclerostin that regulate osteoblasts and osteoclasts[1]
- The main role of sclerostin is to inhibit osteoblasts and limit the accrual of bone mass[1,2]
- Sclerostin expression increases with estrogen deficiency, reduced weight-bearing, and other conditions associated with lower bone mass[4-6]

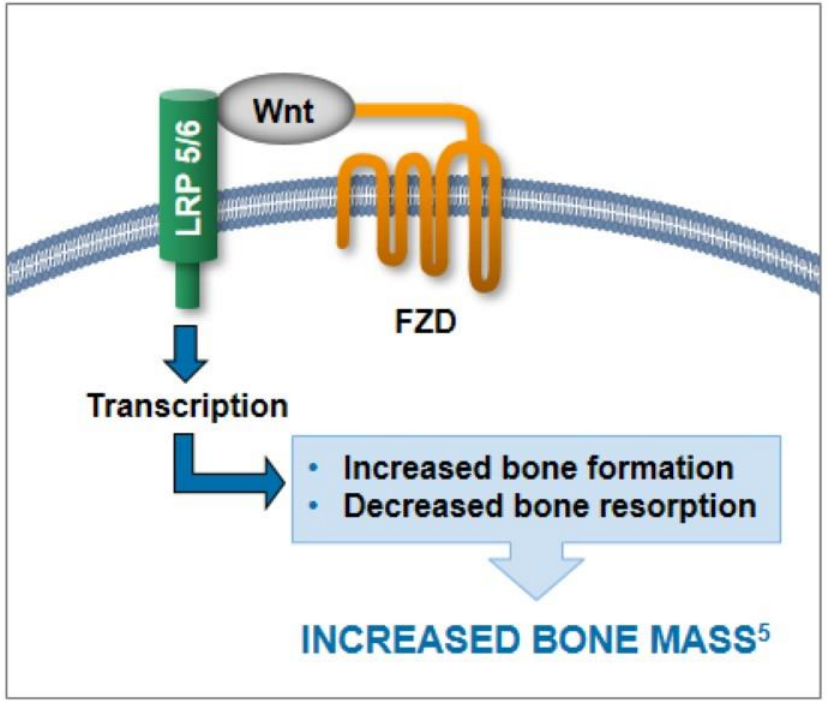
1. Bonewald LF. *J Bone Miner Res*. 2011;26:229-238. **2.** Brunkow ME, et al. *Am J Hum Genet*. 2001;68:577-589.
3. Bonewald LF. In: Marcus R, et al, eds. *Osteoporosis*. 4th ed. Cambridge, MA: Academic Press; 2013:Chapter 10:209-234.
4. Matsui S, et al. *Maturitas*. 2016;83:72-77. **5.** Robling AG, et al. *J Biol Chem*. 2008;283:5866-5875.
6. Ke HZ, et al. *Endocr Rev*. 2012;33:747-783.
Image adapted with permission Bonewald LF. In: Marcus R, et al, eds. Osteoporosis. *4th ed*. Cambridge, MA: Academic Press; 2013. © Elsevier, Inc.

Sclerostin Decreases Bone Formation and Increases Bone Resorption by Inhibiting Wnt Signaling in the Osteoblast Lineage

Sclerostin inhibits Wnt signaling by preventing the assembly of LRP5/6 and FZD, leading to decreased bone formation and increased bone resorption[1-3]



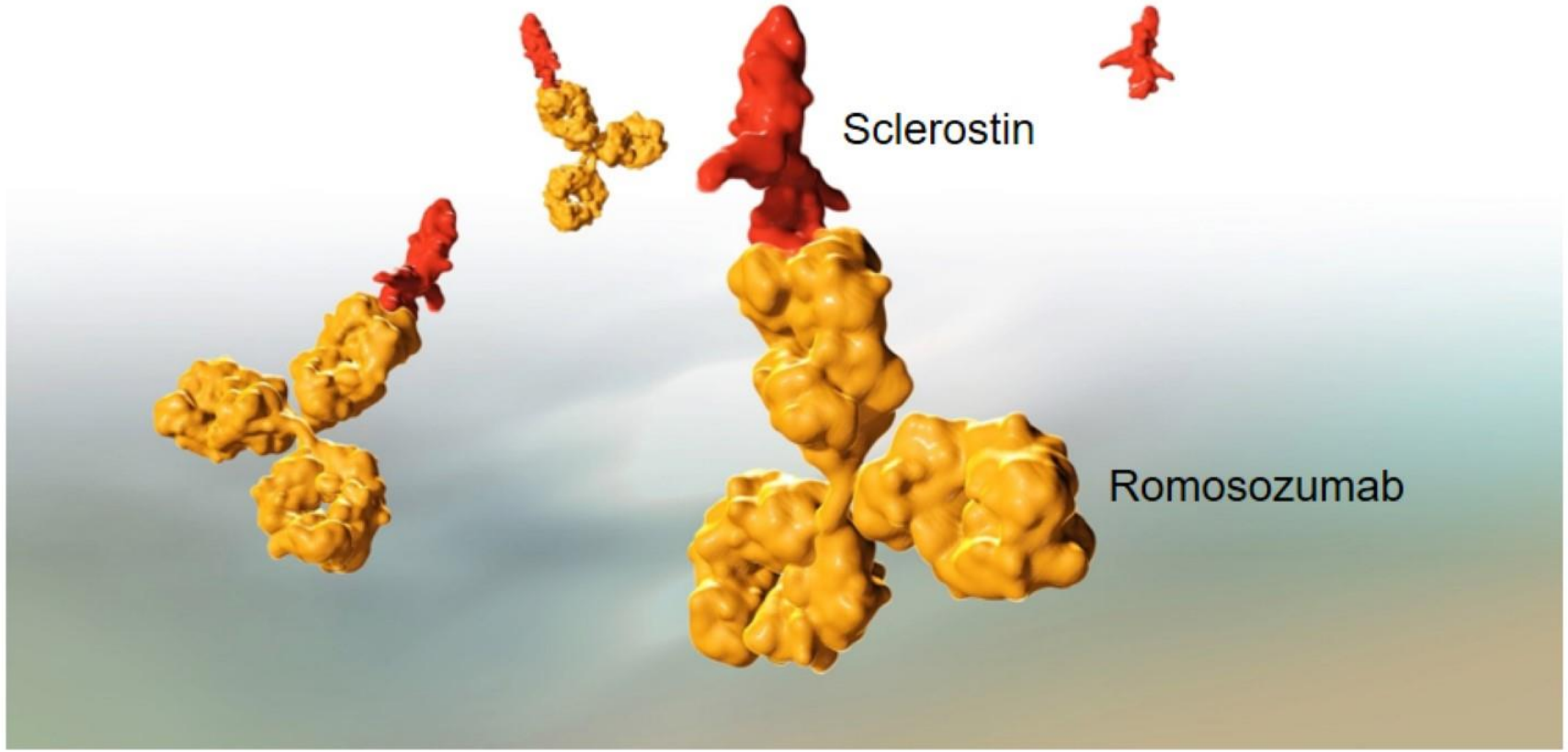
When sclerostin is absent, Wnts can activate signals that increase bone formation and decrease bone resorption[5]



FZD = frizzled coreceptor; LRP5/6 = low-density lipoprotein receptor-related proteins 5 or 6

1. Li X, et al. *J Biol Chem*. 2005;280:19883-19887. **2.** Semënov M, et al. *J Biol Chem*. 2005; 280:26770-26775.
3. Wijenayaka AR, et al. *PLoS One*. 2011;6:e25900. **4.** Winkler DG, et al. *EMBO J*. 2003;22:6267-6276. **5.** Taylor S, et al. *Bone*. 2016;84:148-159.

Romosozumab Is a Humanized Monoclonal Antibody That Binds and Inhibits Sclerostin

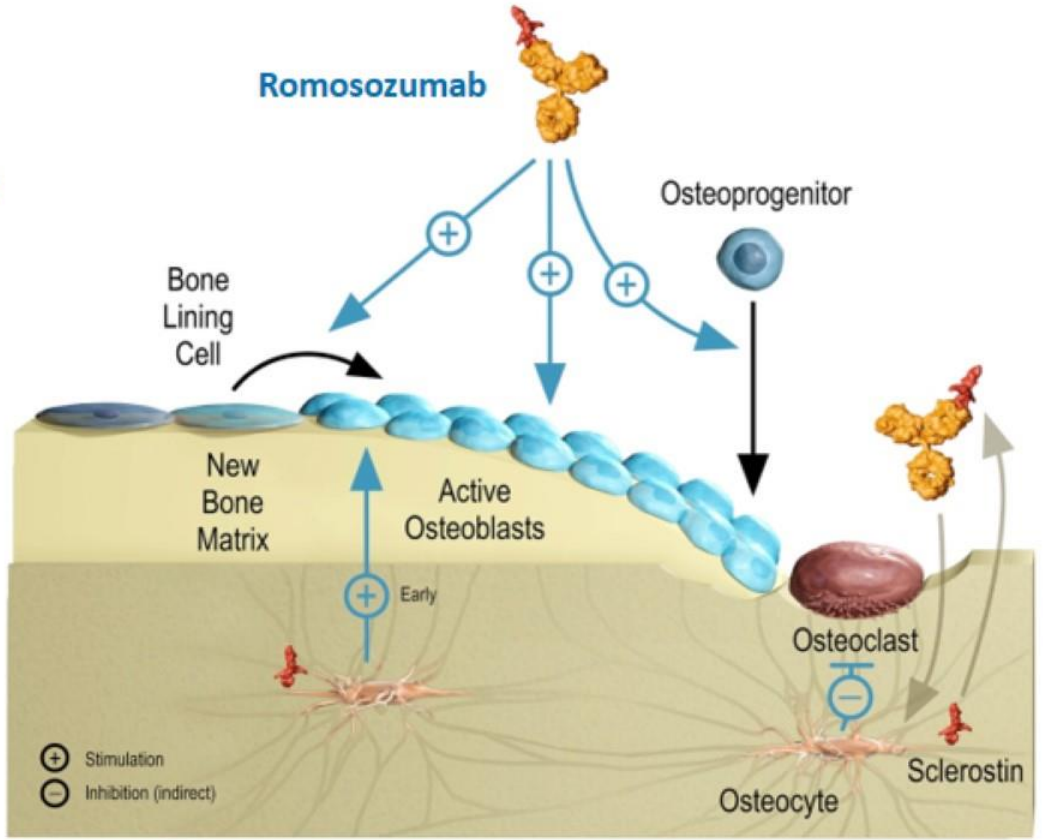


Paszty C, et al, inventors; UCB SA, Amgen Inc., assignees. US patent 7592429 B2. September 22, 2009.

Romosozumab Exerts a Dual Effect on Bone, Increasing Bone Formation and Decreasing Bone Resorption

Romosozumab Increases Bone Formation

- Activates bone lining cells
- Increases bone matrix production by osteoblasts
- Recruits osteoprogenitor cells



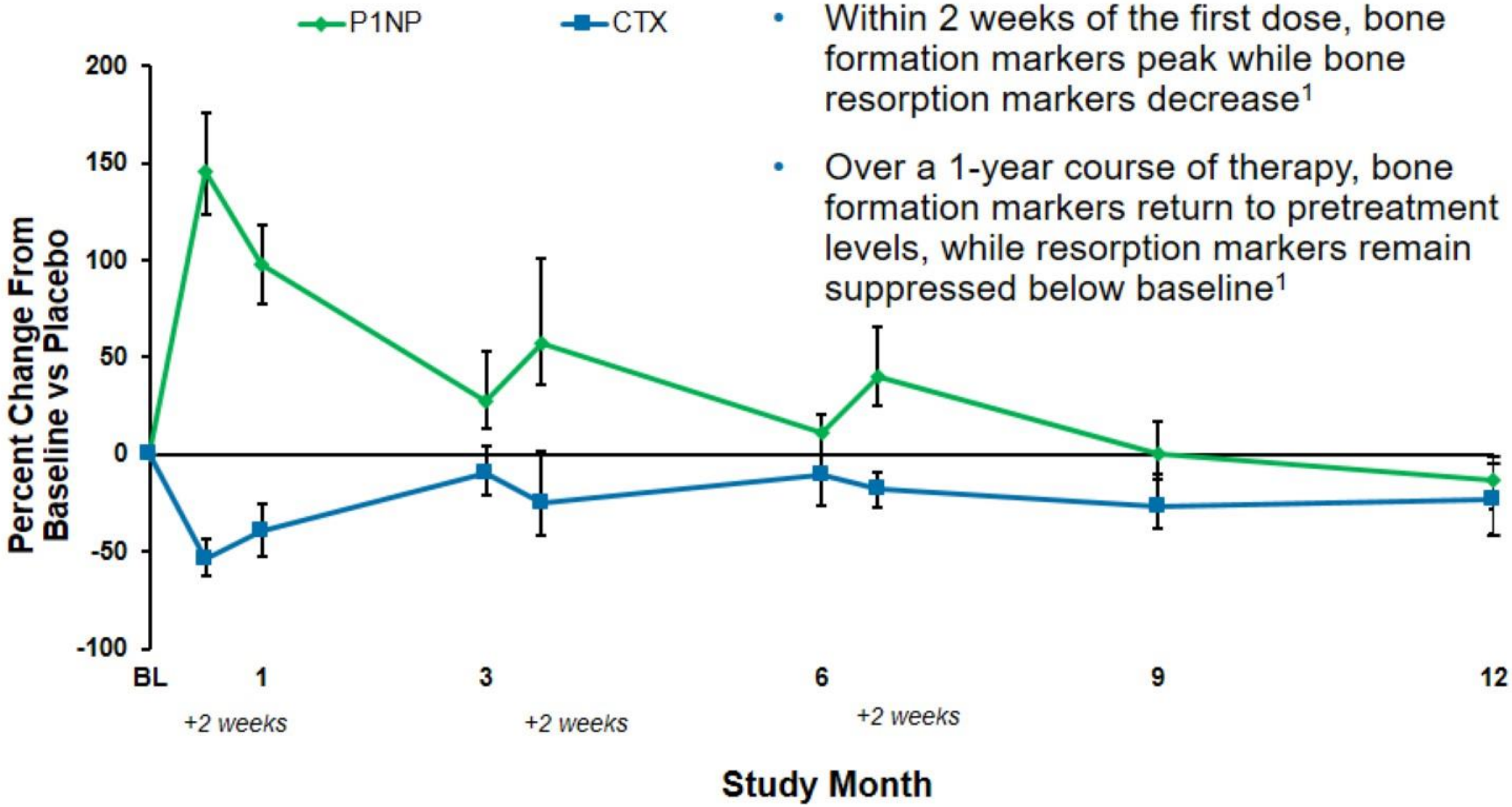
Romosozumab Decreases Bone Resorption

- Changes in osteocytic expression of osteoclast mediators (OPG, RANKL, CSF-1, and WISP1)

OPG = osteoprotegrin; RANKL = RANK ligand; Scl-Ab = sclerostin antibody; WISP = WNT1 inducible signaling pathway protein

Ominsky MS, et al. *Bone*. 2016; doi:10.1016/j.bone.2016.10.019.

Clinical Evidence of Dual Effect



- Within 2 weeks of the first dose, bone formation markers peak while bone resorption markers decrease[1]
- Over a 1-year course of therapy, bone formation markers return to pretreatment levels, while resorption markers remain suppressed below baseline[1]

P1NP, romosozumab n=62, placebo n=62; CTX, romosozumab n=61, placebo n=62. Data presented as bootstrapped median treatment difference and 95% CI. CI = confidence interval; CTX = C-terminal telopeptide; P1NP = procollagen type 1 N-terminal propeptide

1. Cosman F, et al. *N Engl J Med*. 2016;375:1532-1543.

Denosumab

- Indications:
  - Treatment of osteoporosis in postmenopausal women at high risk for fractures and to increase bone mass in men with osteoporosis at high risk of fracture
  - Increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
  - Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
- Increases BMD[1]
- Reduces risk of fracture versus placebo[2]
  - 20% nonvertebral
  - 40% hip
  - 68% new vertebral
- Available as twice yearly injection
- Human monoclonal antibody against RANKL

1. Bone HG, et al. *J Clin Endocrinol Metab*. 2008;93:2149-2157; 2. Cummings SR, et al. *N Engl J Med.* 2009;361:756-765; National Osteoporosis Foundation Available at: http://www.nof/org/articles/22

Denosumab (cont)

- Unlike bisphosphonates that have a long half-life in bone, the effects of denosumab on bone stop after six months
- Therefore, a patient cannot take a “drug holiday” from denosumab as is recommended after 3-5 years of bisphosphonate therapy
- If a patient is more than one month late for their denosumab injection, there can be a rapid decrease in BMD and a sudden increase in multiple vertebral fractures
- This occurs as during denosumab therapy, no osteoclastogenesis occurs
- Once denosumab is discontinued, there is a rebound in osteoclast activity with resultant decrease in BMD
- Within 18-24 months of denosumab discontinuation, BMD has returned to baseline

Fracture Risk and Management of Discontinuation of Denosumab Therapy

- What are the risk factors for fracture after stopping denosumab after at least two injections
  - Prevalent vertebral fractures
  - Longer duration of therapy
  - Greater gain in hip BMD on therapy
  - Younger age of denosumab initiation
  - Initially pre-treatment with BPs was felt to provide some protection but subsequently was not found to be the case

Treatment after denosumab discontinuation

- Zoledronic acid (ZOL) seems to provide some protection from rapid bone loss if the period of denosumab (D-Mab) treatment is < 2.5 years and the ZOL is started 6 months after the most recent denosumab injection
- Solling et al. presented their data from an ongoing RCT of subsequent ZOL treatment after D-Mab discontinuation
  - 60 post-menopausal women and elderly men who had been treated with D-Mab for a mean duration of 4.6 years were randomly assigned to receive a dose of ZOL either at 6 months, 9 months or when bone turnover markers increased

Treatment after D-Mab discontinuation (cont)

- Twelve months after the ZOL infusion, BMD decreased at LS, TH and FN in all 3 groups without differences between groups
- The decline in BMD was more rapid in the 9 month and the observation group
- Two women both in the 9 month group experienced a VFx
- Ten patients from the 6 month group needed retreatment with ZOL at 6 or 12 months based on following markers of bone turnover
- The authors of this study concluded that treatment with ZOL irrespective of the timing did not fully prevent BMD loss in patients with osteopenia who had been treated with 4.6 years of D-Mab

Other Therapies after D-Mab Discontinuation

- Raloxifene was not found to prevent the BMD loss or subsequent vertebral fractures
- An observational study of 18 post-menopausal women who were treated with weekly risedronate for 3 months after 3 years of D-Mab therapy showed that short term risedronate therapy was unable to prevent bone loss
- A retrospective review of 35 patients who received oral bisphosphonates an average of 182 days (about 6 months) after the last D-Mab injection did not prevent BMD loss
- Data from the phase 2 trial of romosozumab following D-Mab discontinuation demonstrated increases in BMD
- Teriparatide after D-Mab discontinuation did not prevent BMD loss

Recommendation of ECTS (European Calcified Tissue Society)

- Recommendations are based on the fact that there is no long term data after 10 years for denosumab
- In young patients with low risk of fracture, D-Mab is not recommended
- If denosumab treatment is limited to 2.5 years switch to oral BPs for 12-24 months or ZOL for 1-2 years (depending on re-evaluation of BTMs and BMD)
- In patients with high fracture risk continue D-Mab for up to 10 yrs
- In patients with high fracture risk could also switch to ZOL beginning 6 months after last D-Mab injection and measure BTMs 3-6 months later. Consider repeat ZOL infusion in case of persistently increased BTMs

ECTS Recommendations (cont)

- Taking into consideration that longer treatment duration can involve a risk of unplanned discontinuation, a very careful assessment of the indications to start D-Mab initially should be performed especially in younger patients who may be at a higher risk of fracture or BMD loss after discontinuation
- If vertebral fractures occur after D-Mab discontinuation do not perform vertebral augmentation as this increases the risk of adjacent vertebral fractures
- Bone loss after D-Mab discontinuation also occurs in the hip which can be associated with an increased risk of hip fractures
- BMD decrease also occurs in males after D-Mab discontinuation and in patients on AI when D-Mab and AI therapy are stopped simultaneously

Long-term Management

Monitoring Patient

To ensure that:

- Medication is taken regularly and correctly
- Calcium and vitamin D intake are sufficient
- The patient has no adverse effects or fear of adverse effects that must be addressed
- There are no comorbidities or other medications that might alter the expected treatment effect

Assessing “Treatment Failure”

- If the BMD declines beyond least significant change which is usually 3%:
  - Rule out undiagnosed secondary problems
  - Evaluate compliance and absorption issues

Treatment Across the Lifespan

- Different agents might have different benefits/risks at different ages
- Osteoporosis treatment should be reviewed annually and length of treatment should be individualized
  - Medical and fracture history
  - Initial and recent bone mineral density test results
  - The EMAS suggests changing OP therapy based on age, type of fracture risk (VFx vs non-VFx) and risk of fracture (moderate to high risk)
- Drug holidays may be considered in certain patients but not for those on denosumab
- Keep patients involved in their care and aware of evolving concepts in osteoporosis