Osteoporosis in Men and Women: An Update on Diagnosis and Management for Fracture Prevention: Part 1

Nancy R. Berman MSN, ANP-BC, MSCP, FAANP
Adult Nurse Practitioner/Colposcopist
Certified Menopause Practitioner (NAMS)
Millennium Affiliated Physicians
Division of Michigan Healthcare Professionals
Farmington Hills, Michigan
Clinical Instructor
Department of Obstetrics and Gynecology
Wayne State University School of Medicine
Detroit, Michigan

1

Disclosures

Advisory Board:
Astellas
Speakers Bureau:
Astellas

2

Objectives

1. Discuss the diagnosis of osteoporosis, low bone mass and high risk for fracture
2. Discuss current pharmacologic options for fracture prevention including bisphosphonates, rank ligand inhibitors, anabolic agents and an anti-sclerostin agent .
3. Discuss appropriate clinical management with case studies

3

Historical Perspective

- > Approximately 1995: bone densitometry became available in limited locations
- > Over the next few years BMD testing became more widely available
- > Limited medication and minimally effective calcitonin nasal spray available (FDA approved 1986: injection, 1995: nasal spray)
- > Branded bisphosphonate oral therapy became widely available in 1995
- > Guidelines for practice: Recommended initiating pharmacotherapy with T-scores of -2.0

4

Historical Perspective

- > Over the next 15 years, multiple bisphosphonate medications became available
- > Raloxifene was approved in 1997
- > Guidelines and recommendations changed with medication recommended at T-scores of -2.5
- > 11/26/2002 An anabolic therapy option was FDA approved and the black box warning for osteosarcoma was a prominent concern for patients and clinicians
- > 4/28/17 A second anabolic therapy option was FDA approved

5

Historical Perspective

- > The FRAX calculation from the University of Sheffield was developed to identify patients at high fracture risk who are not yet osteoporotic and where preventative medication may be considered
- > Long term use concerns developed for using oral bisphosphonate therapy longer than 3 to 5 years or IV infusion more than 3 years
- > Concerns developed for rare cases of osteonecrosis of the jaw (ONJ)
- > The report of atypical subtrochanteric fractures with long term use of bisphosphonates added another concern to drug therapy
- > 2018 saw the report of increased risk of vertebral fractures with discontinuation of denosumab
- > Guidelines changed that levels of fracture risk by FRAX lead to a diagnosis of osteoporosis

6

Historical Perspective

> 2020 New Guidelines for Diagnosis and Treatment of Post Menopausal Osteoporosis: Emphasis on identifying post menopausal women with osteoporosis as high or very high risk for fracture
  – Very high risk: sequencing with bone building anabolic agents followed by maintenance with anti-resorptive therapy recommended
> November 2020: the US Food and Drug Administration (FDA) approved changes to the label for the parathyroid hormone (PTH) analogue teriparatide (PTH 1-34), by removing the 2-year lifetime treatment limitation and the boxed warning about the potential risk of osteosarcoma.
> December 2022:The FDA approved abaloparatide, a parathyroid hormone-related peptide analog, to increase bone mineral density among men with osteoporosis at high risk for fracture

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

7

Media sensationalism of risks of drug therapy began to greatly impact patient acceptance of pharmacologic therapy

8

Osteoporosis Overview

9

Osteoporosis: Definition

A disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk

Pentice A *Public Health Nutr* 2004;7:227-43; WHO Study Group In *Assessment of Facture Risk and Its Application to Screening for Postmenopausal Osteoporosis.* Geneva: WHO, 1994

10

A Gender Related Condition

> Osteoporosis is the most common bone disorder affecting humans
> The risk of hip fracture doubles for every 5- to 6-year increase in age from ages 65-85
> Of the 10 million Americans estimated to have osteoporosis, 8 million are women (80%)

LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022. Epub 2022/04/29. doi: 10.1007/s00198-021-05900-y. PubMed PMID: 35478046.

11

Vertebral Fractures

Significant consequences for patients
> Acute and chronic pain
> Kyphosis and height loss
> Impaired function
> Increased morbidity and mortality
> Increased fracture risk

Delmas PD, et al. J Bone Miner Res. 2005;20:557-563

12

Hip and Other Non-Vertebral Fractures Have Significant Consequences

> Hip fracture associated with
  – Loss of ambulatory status in 30% of patients
  – Increased morbidity and mortality
  – Increased fracture risk
  – Major reason for admission to chronic care facilities
> Non-vertebral fractures
  – Pain
  – Increased risk of future fractures

LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022. Epub 2022/04/29. doi: 10.1007/s00198-021-05900-y. PubMed PMID: 35478046.

13

Who Should Be Screened?

National Osteoporosis Foundation (NOF) (10/21: Renamed Bone Health & Osteoporosis Foundation (BHOF)) recommends screening for:

  – Women aged ≥65 years and men aged ≥70 years, regardless of risk factors
  – Postmenopausal and menopausal transitioning women and men aged 50 to 69 years with clinical risk factors for fracture
  – Postmenopausal women and men aged >50 years who have had an adult-age fracture
  – Adults with a condition or taking a medication associated with low bone mass or bone loss

Dual-energy x-ray absorptiometry (DXA) is the current standard for measuring bone mineral density (BMD)

LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022. Epub 2022/04/29. doi: 10.1007/s00198-021-05900-y. PubMed PMID: 35478046.

14

Who Should Be Screened?

US Preventive Services Task Force (USPSTF):

> All women 65 and older
> Younger women whose fracture risk is equal to or greater than that of a 65- year- old white woman who has no additional risk factors

Nelson HD, Haney EM, et al. Screening for osteoporosis: an update for the U.S. Preventative Services Task Force. Ann Intern Med. 2010 153;153-99-11.

15

What Are the Risk Factors?

Most common risk factors:[1,2,3]

  – Postmenopausal
  – Female
  – Low body mass index (BMI)
  – Caucasian
  – Poor calcium intake
  – Lifestyle (eg, smoking, caffeine consumption >300 mg/d)

1. Watts N, et al. *Endo Pract.* 2010; 16(Suppl 3):1-37.
2. Li S, et al. *Nutr J.* 2015 Apr 18; 14:38.
3. Cosman F, et al. *Osteoporosis Int.* 2014; 25(10): 2359-2381.

16

Other Risk Factors

Chronic medical conditions may also increase risk:[1,2,3]

  – Chronic kidney disease
  – Oral glucocorticoids (≥5 mg/d of prednisone for >3 months)
  – Estrogen deficiency
  – Hyperparathyroidism
  – Systemic lupus erythematosus
  – Conditions associated with malabsorption (eg, celiac disease, inflammatory bowel disease)
  – Chronic obstructive pulmonary disorder

1. Watts N, et al. *Endo Pract.* 2010; 16(Suppl 3):1-37.
2. Li S, et al. *Nutr J.* 2015 Apr 18; 14:38.
3. Cosman F, et al. *Osteoporosis Int.* 2014; 25(10): 2359-2381.

17

Routine Screening prior to age 65 is not recommended

> USPSTF guidelines do not recommend routine screening in this age group
> A risk-based approach is recommended

Curry SJ, Krist AH, Owens DK, et al. Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement. Jama. 2018;319(24):2521-2531.

18

Screening in Post-Menopausal Women Age 50-64

United States Preventative Services Task Force (USPSTF) 2018 screening recommendations

> Postmenopausal women younger than 65 years:
  – BMD test if they are at increased risk of osteoporosis (smoking, parental hip fracture, excess alcohol intake, low body weight),
  – Or **use a clinical risk assessment tool**

Curry SJ, Krist AH, Owens DK, et al. Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement. *Jama*. 2018;319(24):2521-2531.

19

USPSTF Screening Women < 65 y/o

Does she have any risk factors:
> Excessive alcohol consumption
> Low body weight
> Parental history hip fracture
> Smoking

If the threshold for screening is met:
Order BMD

No: Encourage
> Weight-bearing and resistance exercise
> Sufficient calcium and vitamin D intake
> Avoid excessive alcohol, smoking

Yes: Risk Assessment Tool
> OST(osteoporosis self-assessment tool) - simplest
> FRAX
> ORAI
> OSIRIS

Curry SJ, Krist AH, Owens DK, et al. Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement. *Jama*. 2018;319(24):2521-2531.

20

Summary of Risk Tools Among Women Aged 50-64 years old

> Goal of osteoporosis screening: identify postmenopausal women with BMD T-score ≤-2.5 for pharmacologic therapy.
  – OST and SCORE work better than FRAX for that
  – OST is the simplest

  – Tools with more risk factors do not have better discrimination (AUC) to identify those women than tools with fewer risk factors

Viswanathan JAMA 2018 systematic review
Edwards BJ. Osteoporosis Risk Calculators. *J Clin Densitom*. 2017;20(3):379-388.

21

Osteoporosis Self Assessment Tool (OST)

OST = (weight (kg) – age in years) / 5

Truncate to integer
BMD test: If score < 2

FRAX Threshold score for screening BMD
≥ 8.4% 10-year risk of Major Osteoporotic Fracture

JAMA, 2018;319(24):2521-2531

22

Using an Osteoporosis Risk Calculator

55 yo: Mother had a hip fracture, history of adult fracture.
Weight: 5 ft 2, 130 pounds.
Osteoporosis Self Assessment Tool (OST)
59kg – 55 (age)/5 = 0.8 Value is < 2: order BMD

FRAX:
MOF > 8.4%
Order BMD

With permission: International Osteoporosis Foundation

Edwards BJ. Osteoporosis Risk Calculators. *J Clin Densitom*. 2017;20(3):379-388.

http://www.shef.ac.uk/FRAX/

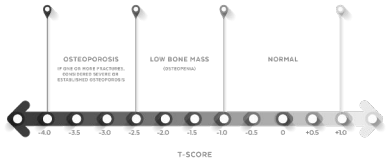
23

Interpreting Bone Densitometry Results

Bone Density
FRAX: 10-Year Fracture Risk Calculation

24

T-Score Classifications



Cosman F, et al. Osteoporos Int. 2014;25(10):2359-2381.

25

Using FRAX

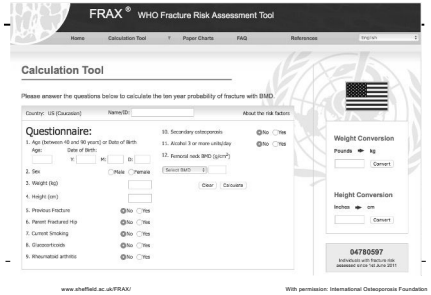
To find those individuals at high risk for fracture, who are not yet osteoporotic by T- Score!

If your patient has osteoporosis by T-score, you do not have to look at FRAX. BUT, you may look at FRAX!

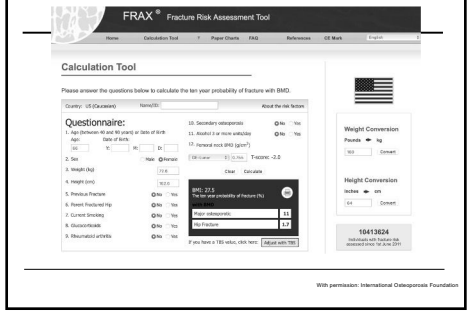
There are more fractures occuring in men and women with T-scores from -1.0 to -2.5!

26

FRAX: Gauging 10 Year Fracture Probability



27



28

Application of FRAX™ In the US

> Intended for post-menopausal women and men age 50 and older
> Has not been validated in patients currently or previously treated with pharmacotherapy for osteoporosis. In such patients, clinical judgment must be exercised in interpreting FRAX scores.
  – Patients who have been off osteoporosis medication for 1 to 2 years or more might be considered untreated.

http://www.shef.ac.uk/FRAX/

LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022. Epub 2022/04/29. doi: 10.1007/s00198-021-05900-y. PubMed PMID: 35478046.
National Osteoporosis Foundation 2013

29

Application of FRAX™ In the US

> Frax can be calculated with either femoral neck BMD or total hip BMD, but, when available, femoral neck BMD is preferred. Use of BMD from non hip sites is not recommended.
> T scores must be converted to a reference standard to be used. The FRAX patch is available at www.NOF.org to make the calculation
> FRAX may be calculated by going to the FRAX calculator at the University of Sheffield website

LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022. Epub 2022/04/29. doi: 10.1007/s00198-021-05900-y. PubMed PMID: 35478046.

30

Understanding FRAX

- FRAX underestimates future fracture risk
- Reports only hip fracture and major fractures
  - Half of all fragility fractures
- Underestimates risk in patients with:
  - Multiple osteoporotic fractures
  - Recent fractures
  - Lumbar spine BMD lower than femoral neck
  - Secondary osteoporosis
  - Those at increased risk of falls

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

31

Criteria for the Diagnosis of Osteoporosis

- Fragility fracture (lumbar spine or hip) *even with a normal bone density*
- T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, or 1/3 radius (33%)
  - The diagnosis *persists* even when a subsequent DXA measurement shows better than -2.5
- T score between -1.0 and -2.5 and fragility fracture of proximal humerus, pelvis, or distal forearm
- T-score between -1 and -2.5 with an increased fracture risk by *FRAX ≥ 20% for major osteoporotic fracture and ≥ 3% at the hip)*

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

32

Laboratory Evaluation in Osteoporosis

- CBC
- Comprehensive metabolic panel
- 25-hydroxyvitamin D (25/OH/D)
- Intact parathyroid hormone (PTH)
- Phosphate
- 24-hour urine collection for calcium, sodium, creatinine
- TSH and celiac antibodies can be considered
- Serum/urine protein electrophoresis could also be obtained

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

33

Vertebral Fracture Detection

Most common osteoporotic fracture and indicates a high risk for future fractures (even when the T-score does not meet the threshold for osteoporosis).

- Prevalent fractures may change the risk of future fractures and clinical management
  - Many remain undetected without imaging techniques
    - Spine x-ray
    - VFA used with DXA technology

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

34

Vertebral Fracture Detection

- Lateral spine imaging indicated by standard radiography or VFA when T-score is less than -1.0 and one or more of the following is present:
  - Women aged 70 or older and men 80 or older
  - Historical height loss >4cm (>1.5 inches)
  - Self-reported but undocumented prior vertebral fracture
  - Glucocorticoid therapy equivalent to ≥ 5mg of prednisone or equivalent per day for ≥ for 3 months
  - Kyphosis

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

35

Who Should Be Treated?

- Patients 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
- Patients with a T-score of –2.5 or lower in the spine, femoral neck, total hip, or 1/3 of radius
- Patients with a T-score between –1.0 and –2.5 if the FRAX 10-year risk for major osteoporotic fracture is ≥20% or if the 10-year risk of hip fracture is ≥3%

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

36

High and Very High Risk for Fracture in Men and Women With Osteoporosis

High risk for fracture:

BMD: -2.5 to -3.0

FRAX: Major Osteoporotic Fracture: 20% to 30%

Hip: 3% to 4.5%

Very high risk for fracture:

BMD: <-3.0%

FRAX Hip: >4.5%

Camacho PM, Petak SM, et al; American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020;26:5-6.

37

Clinical Case

A 79-year-old Caucasian female presents for an osteoporosis risk evaluation. She has no medical problems, no history of fracture, and no family history of fracture. Her history is negative for smoking, glucocorticoid use, and excessive alcohol consumption.

Exam: weight, 154 lb; height, 64 in

DXA results:

Femoral neck BMD (g/cm^2), 0.730

GE Lunar T-score: spine, –1.5; hip, –2.2

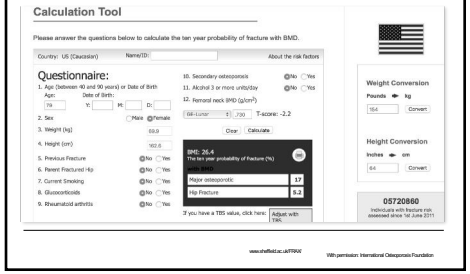
FRAX 10-year risk of fracture: Major osteoporotic, 17%; hip, 5.2%

Based on this information:

- Does she require treatment for to osteoporosis?
- Is she at risk for a major fracture in the next 10 years?
- Is she at high or very high risk for fracture?

38

Clinical Case #1 (Cont)



39

Treatment

When and How

Identifying patients and level of risk and choice of pharmacologic agent

40

Non-Pharmacologic Interventions

> Goal of non-pharmacologic intervention is to prevent future fractures through lifestyle change

> Counsel all patients on risk reduction, avoidance of smoking and excessive alcohol intake

> The role of Vitamin D in osteoporosis

- May be important as both adjuvant and treatment
- Might be important in the response to therapy
- The effect on muscle strength, balance and risk of falls is important

41

Non-Pharmacologic Interventions

> Exercise

- Include Strength/Resistance Training
- Balance Training
- Aerobic exercise

> Fall Prevention

- Gait and balance assessment and training
- Minimize/adjust dose of drugs with sedative effects
- Anchor rugs, minimize clutter, remove loose wires, etc.

42

Treatment Recommendations

> No pharmacologic therapy should be considered indefinite in duration
> After the initial three to five year treatment period, a comprehensive risk assessment should be performed
> There is no uniform recommendation that applies to all patients and duration decisions need to be individualized

Camacho PM, Petak SM, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020;26:5-6.

43

Current Pharmacologic Agents Approved for the Treatment of Osteoporosis

> Anti-resorptive agents
  – Bisphosphonates
    • Weekly oral alendronate (Fosamax)
    • Weekly or monthly risedronate (Actonel)
    • Monthly oral or quarterly IV ibandronate (Boniva)
    • Once yearly infusion Zoledronic Acid (Reclast)
  – Rank Ligand Inhibitor
    • Denosumab (Prolia)

Camacho PM, Petak SM, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020;26:5-6.

44

Current Pharmacologic Agents Approved for the Treatment of Osteoporosis

  – Calcitonin
  – Selective estrogen receptor modulators (SERMS)
    • Raloxifene (Evista)
> Anabolic agents
  – Parathyroid hormone (Forteo)
  – Abaloparatide (Tymlos)
> Sclerostin Binding
  – Romosuzomab (Evenity)

45

Anti-resorptive Therapy

Bisphosphonates
Rank Ligand Inhibitors
SERMS
Calcitonin

46

Osteoporosis Treatment

Bisphosphonates

47

Effects of Bisphosphonates

> Decreased bone turnover
> Increased BMD at spine and hip
> Decreased risk of vertebral and hip fractures
> Sustained effects with continued treatment
> Best studied class of agents used in treating osteoporosis
> Long term safety record

Black DM, et al. *Lancet*. 1996;348:1535-1541, Body J, et al. J Clin *Endocrinol Metab*. 2002;87:4528-4535

48

Bisphosphonates

Drug	Mechanism of action	Prevention dose	Treatment dose	Fracture risk reduction
Alendronate	Antiresorptive agents that inhibit osteoclast function	5 mg/d[a] or 35 mg/wk[a]	10 mg/d[a] or 70 mg/wk[a]	Spine, hip, nonvertebral
Ibandronate		2.5 mg/d[a] or 150 mg/mo[a]	2.5 mg/d[a], 150 mg/mo[a], or 3 mg[b] every 3 mo	Vertebral
Risedronate		5 mg/d[a], 35 mg/wk[a], or 150 mg/mo[a]	5 mg/d[a], 35 mg/wk[a], or 150 mg/mo[a]	Spine, hip, nonvertebral
Zoledronic acid		5 mg[b] every second year	5 mg/y[b]	Spine, hip, nonvertebral

[a]By mouth.
[b]Intravenously.

Camacho PM, et al. *Endo Prac.* 2016;22(suppl 4):1-42.
McClung M, et al. *Am J Med.* 2013;126(1):13-20.

49

ORAL BISPHOSPHONATES

> Pros
- Osteoporosis prevention and treatment
- Reduction in risk of vertebral fractures (w/ and w/o pre-existing fx)

> Cons
- Require lifestyle change
  - empty stomach
  - water only
  - may lead to non-compliance
- GI adverse effects
- Marginal efficacy in non-vertebral fractures (e.g. hip)
- Long-term safety is unconfirmed

50

Additional Oral Bisphosphonate Therapy Indications

> Treatment of Glucocorticoid-Induced Osteoporosis
- Glucocorticoid-induced osteoporosis in patients receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density

> Treatment of Paget's Disease Of Bone
- When alkaline phosphatase is at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020;26:5-6.

51

Absorption and Tolerability of Oral Bisphosphonates Are Affected When Dosing Instructions are not Followed

> Coffee or juice can reduce absorption by as much as 60%
> Calcium supplements can interfere with absorption and should not be taken at the same time as oral bisphosphonate therapy
> GI side effects are more likely when dosing instructions are not followed
> Even when complete instructions are given, between 25% and 50% of patients disregard at least one requirement

Gert FJ, et al. *Clin Pharmacol Ther.* 1995;58d:288-298d, Seeman E, et al. *Osteoporos Int.* 2007;a8:711-719

52

IV Bisphosphonate

53

Zoledronic Acid

HORIZON Fracture Trials: Efficacy Conclusions
> Reduces incidence of vertebral fractures by 70% (with significant reduction at 1 year)
> Reduces hip fractures by 41%
> Reduces nonvertebral fractures by 25%, over 3 years in patients with osteoporosis, defined by prevalent vertebral fractures and osteoporosis by BMD of the hip

Black DM, etal. N Engl J Med. 2007;356:1809-1822

54

Bioavailability and High Binding Affinity Allow Zoledronic Acid to be Dosed Once Yearly

> Zoledronic acid bypasses the GI tract, eliminating absorption limitations
> Year long efficacy of zoledronic acid is attributable to the high binding affinity of zoledronic acid to bone
> Bioavailability:
  – approximately 61% directly to bone
  – Approximately 39% eliminated from circulation within 24 hours

Zoledronic acid (prescribing information) East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2008

55

Rank Ligand Inhibitor

56

Denosumab

RANK Ligand Inhibitor

> Fully human monoclonal antibody
> Specifically targets a ligand called RANKL (that binds to a receptor called RANK) which is a key mediator of:
  – Osteoclast formation
  – Function
  – Survival
> Improves cortical and trabecular bone density, volume and strength
> Currently being studied across a range of conditions including osteoporosis, treatment induced bone loss, bone metastases, multiple myeloma and rheumatoid arthritis

57

Expanded Indications For Denosumab

> Treatment of postmenopausal women with osteoporosis at high risk for fracture
> Treatment to increase bone mass in men with osteoporosis at high risk for fracture
> **Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture**
> **Treatment to increase bone mass in men at high risk for 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**

58

Aromatase Inhibitor Therapy (AI)

> All patients initiating AI treatment:
  – Fracture risk should be assessed
  – Recommendation with regard to exercise and calcium/vitamin D supplementation given.
> Bone-directed therapy should be given to all patients with:
  – T-score<−2.0 or with a T-score of <–1.5 SD with one additional RF, or with ≥2 risk factors (without BMD) for the duration of AI treatment.

Peyman H, Aapro M, Body J, Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO, IMS, and SIOG. J Bone Oncol. 2017 Jun; 7: 1–12

59

Aromatase Inhibitor Therapy (AI)

> Patients with T-score>−1.5 SD and no risk factors should be managed based on BMD loss during the first year and the local guidelines for postmenopausal osteoporosis.
> Risk Factors:
  – Age >65 years, low BMI (<20 kg/m2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use of >6 months, and current or history of smoking.
> Compliance should be regularly assessed as well as BMD on treatment after 12 - 24 months.

Peyman H, Aapro M, Body J, Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO, IMS, and SIOG. J Bone Oncol. 2017 Jun; 7: 1–12

60

Discontinuation of Denosumab Therapy

> Denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.
> Re-evaluation should be performed after 5 years of denosumab treatment.
> Patients considered at high fracture risk should either:
  – Continue denosumab therapy for up to 10 years
  – Or be switched to an alternative treatment.

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS.
Tsourdi E[1], Langdahl B[2], Bone. 2017 Dec;105:11-17. doi: 10.1016/j.bone.2017.08.003. Epub 2017 Aug 5.

61

Discontinuation of Denosumab Therapy

> For patients at low risk, a decision to discontinue denosumab could be made after 5 years,
  – Bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover.
> Continuation of denosumab can also be considered until results from ongoing trials become available.
> Denosumab should not be stopped without considering alternative treatment
  – To prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS.
Tsourdi E[1], Langdahl B[2], Bone. 2017 Dec;105:11-17. doi: 10.1016/j.bone.2017.08.003. Epub 2017 Aug 5.

62

Effects of SERMS (Estrogen agonist/antagonists)

> SERMS exert estrogen like effects on the skeleton
> Decrease bone turnover
> Increase bone density, but to a lesser degree than with bisphosphonates
> Decrease risk of vertebral fracture
> No hip or non-vertebral fracture

Ettinger B, et al.,JAMA.1999; 282:637-85

63

Raloxifene

> Pros
– Osteoporosis prevention
– No endometrial or breast stimulation
– LDL reduction

> Cons
– No current non-vertebral fracture data (e.g. hip)
– No effect on vasomotor symptoms
– Thrombosis
– Effects on cholesterol are modest
– Leg cramps

Fuleihan. *N Engl J Med*. 1997;337:1685-1686. Editorial.

64

Anabolic Agents

> Unique from other treatments because they are bone building through increased osteoblast activity
> Effects diminish quickly after discontinuing therapy
> Teriparatide
  ▪ Increases BMD up to 13% at spine and to a lesser degree at hip[1,2]
  ▪ Correlates to 72% relative risk reduction of new vertebral fractures[3]
> Abaloparatide
  ▪ Increases BMD at all sites
  ▪ Relative risk reduction of 86% for new vertebral fractures and 43% for nonvertebral fractures[4]

1. Neer RM, et al. *N Engl J Med*. 2001;344(19):1434-1441.
2. Marcus R, et al. *J Bone Miner Res*. 2003;18(1):18-23.
3. Bouxsein ML, et al. *J Bone Joint Surg Am*. 2009;91(6):1329-1338.
4. Miller PD, et al. *JAMA*. 2016;316(7):722-733.

65

Effects of Parathyroid Hormone

> Stimulates osteoblast activity preferentially
> Increases bone turnover and creates a positive bone balance
> Improves trabecular microarchitecture and increases cortical thickness
> Increases bone mass
> Decreases risk of vertebral and nonvertebral fractures
> Requires daily injections

Neer RM, et al. N Engl J Med. 2001:344:1434-1441,

66

Parathyroid Hormone

> Pros
- Osteoporosis treatment
- Reduction in risk of vertebral and nonvertebral fractures
- May be used in conjunction with other OP therapies (e.g. anti-resorptive)

> Cons
- Osteosarcoma risk?
- Long-term use not established
- Long-term safety not established
- Hip fracture prevention?
- Daily sq injections
- Nausea, headache, etc.

67

Teraparatide

> FDA approved 2002
> Recombinant human parathyroid hormone analog (1-34), [rhPTH(1-34)] indicated for:
- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

> Self administered subcutaneous infection for 2 years followed by bisphosphonate therapy
> Carried a label warning regarding osteosarcoma

68

Abaloparatide

FDA approved 4/28/17
> Indicated for:
- Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as:
  - A history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

> Lab-made copy of part of the human parathyroid hormone-related protein (PTHrP)
> Daily subcutaneous injection
> Recommended for two years and followed with bisphosphonates for several years
> Carried a label warning regarding osteosarcoma
> Side effects include nausea, dizziness, and vomiting

69

Abaloparatide

> Abaloparatide injection:
- Approved by the U.S. Food and Drug Administration in April 2017 for the treatment of postmenopausal women with osteoporosis at high risk for fracture
- In **December 2022** for the treatment of men with osteoporosis at high risk for fracture.

70

New Agent: Romosozumab

FDA approved April 2019:
> Monoclonal antibody that binds sclerostin
- **Increases bone formation**
- **Decreases bone resorption**
- Rapid onset of fracture reduction, in the first 6 months

> Adverse events were balanced in the 12 and 24 month studies between placebo and treatment groups
> One atypical fracture and 2 cases of osteonecrosis of the jaw in the treatment group

Felicia Cosman, M.D., Darla B. Crittenden, M.D., Jonathan D. Adachi, M.D., et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med 2016; 375:1532-1543

71

Romosozumab

> Currently an option for patients at very high fracture risk
> Option for patients previously treated with teriparatide or abaloparatide
- Future retreatment with romosozumab may be possible

> In the smaller of the phase 3 trials (n = 4,093), serious cardiovascular events were significantly more common with romosozumb compared to alendronate
- The increased risk did not persist and was small
- This led to a black box warning: should not be used in patients at high risk for cardiovascular events or who have had n MI or stroke in the last year

72

Risk Stratification and Treatment Decisions

> **Low risk**
  – No prior fracture, and T-score ≥ -1 and FRAX < 20% MOF, <3% Hip
  – Non-pharmacologic treatment. No pharmacologic treatment needed
> **Moderate risk**
  – No prior fracture and T-score between -1 and -2.5 and FRAX probabilities <20%MOF, <3% Hip
  – Some may benefit from sequential antiresorptive monotherapy especially those with BMD close to -2.5
    • Estrogen in early menopause
    • Raloxifene in 50's to 60's
    • Bisphosphonates mid/late 60's

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

73

Osteoporotic Patients: Level of Risk and Choice of Pharmacologic Agent

High Risk (not meeting previous criteria but diagnosed with osteoporosis):
>Postmenopausal women or men over age 50 with a prior hip or spine fracture
>Postmenopausal women or men over 50 with a BMD T-score of -2.5 or lower at the hip or spine
>Postmenopausal women or men over 50 with T-score between -1 and -2.5 at the femoral neck, total hip, or spine if:
  – 10 year probability (from FRAX) of hip fracture is ≥ 3%
  – 10 year probability of a major osteoporosis-related fracture is ≥ 20%

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

74

Risk Stratification and Treatment Decisions

High risk
> Older single prior fracture (> 2 years earlier) or T-score -2.5 or T-score -1 to -2.5 with FRAX ≥20% MOF or ≥3% Hip

Goal: Improve BMD to T-score >-2.5 and reduce fracture risk
  – Younger women may benefit from estrogen/raloxifene especially if spine T-score is low and hip is > -2.5
  – Usually bisphosphonates or denosumab
  – Anabolic agents are appropriate for some

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

75

Osteoporotic Patients: Level of Risk and Choice of Pharmacologic Agent

Very High Risk:
> Recent fracture (within the last 12 months)
> Fractures while on approved drug therapy, multiple fractures, fractures while on drugs causing skeletal harm (i.e. glucocorticoids)
> Very low T-score (e.g. less than -3.0)
> High risk for falls or history of injurious falls
> Very high fracture probability by FRAX
  – Major osteoporotic fracture >30%
  – Hip fracture >4.5%

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

76

Choosing a Pharmacologic Agent

Approved agents with efficacy to reduce hip, nonvertebral and spine fractures as initial therapy:
> High fracture risk:
  – Alendronate, risedronate, zolendronate, denosumab appropriate
> Very high fracture risk:
  – Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronic acid
    • And consider for patients who are unable to tolerate oral therapy

Camacho PM, Petak SM, et al, American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines For The Diagnosis and Treatment of Post Menopausal Osteoporosis- 2020 Update, endocrine Practice, 2020:26:5-6.

77

Cases: **High** Risk for Fracture

BMD
FRAX

The Art of Managing Osteoporosis and Fracture Prevention!

78

Case #1

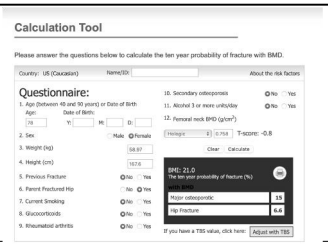
> 72 year old Caucasian woman
> Non-smoker
> F.H. Osteoporosis in Mother
> Mother had a hip fracture
> Negative for secondary causes of osteoporosis

BMD:
LS Total: -1.3
Hip: Neck - 0.8
Total -0.4

79

80

Let's Make Her Older:



81

Case #2

> 64 year old Caucasian
> Non-smoker
> Negative for secondary causes of Osteoporosis

BMD
LS Total: -1.5
Hip: Neck -2.2
Total -2.1

82

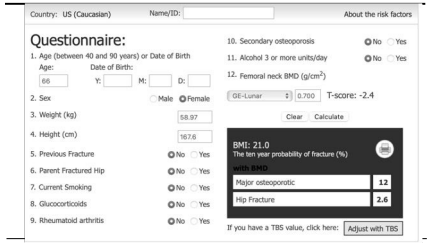
83

Case #3

> 66 yo woman has a family history of breast cancer in her Mother.
> Bone density test
  – LS: T-score -2.4
  – Hip: -1.6 at femoral neck
> Does she have osteoporosis?
> Is it important to look at her FRAX score?
> What are her options for therapy?

84

Is She Osteoporotic by FRAX?



85

Case #3

> Pt prefers to take Raloxifene and starts the medication
> What risk factors are important to identify for this patient?
> The patient has her bone density repeated in 2 years and stays on her Raloxifene
> 2 years later her BMD shows a T score of -2.5 in the femoral neck
> What will you do about her treatment plan?
> Will she stay on Raloxifene?

86

Case #4

73 yo woman recently diagnosed with osteoporosis

> Bone Density Test
  – Hip -2.5, LS -0.4
> H/O Gerd/esophagitis
> Normal kidney function
> Pt states that she is planning to have a tooth implant once she is able to use dental insurance sometime in the future

What will your management plan be?

87

Case #5

79 yr old patient who has been on oral bisphosphonate for 3 years. She states that she has had trouble remembering to take her pill once a week.

BMD:

LS: +1.5

Hip: left femoral neck: -2.9

Loss from 2 year previous BMD: 4.5% at total hip

88

Case #5

> Is the patient compliant to her treatment regimen?
> What are your options for managing her osteoporosis?
> What do you need to know about her medical history and kidney function?
> What will you do?

89