Management of Osteoporosis:
Optimizing Outcomes for Patients

J R Minkoff MD, FACP
Endocrinology
Clinical Professor of Family and Community Medicine
University of California, San Francisco

Objectives - At the conclusion of this activity learners should be able to:
1. Better assess and evaluate bone strength using noninvasive technologies and thus further define or identify patients at high risk for fracture
2. Review and appraise current FDA-approved treatments in preventing fractures in patient with low bone mass
3. Discuss risk factors for osteoporosis and primary prevention with all patients presenting for preventive/wellness health visits
4. Address pharmacologic options for prevention and treatment of osteoporosis with appropriate patients at risk for or who currently have signs and symptoms of osteoporosis.

What is Osteoporosis?
Systemic skeletal disease characterized by:
- low bone mass (T-score < -2.5)
- biochemically normal bone
- microarchitectural deterioration of bone tissue

Hallmark-
Increased bone fragility and susceptibility to fracture
Effect of Age on Fracture Incidence in Women

Healthy Trabecular Bone vs Osteoporotic Bone: 3-D Micro CT

Prevalence of Low Femoral Neck BMD in U.S. Adults Ages 50+

Prevalence and Epidemiology of Postmenopausal Osteoporosis (PMO)

- Primarily affects Caucasians and Asians
- 40-50% of Caucasian women over age 50 are expected to fracture in their remaining lifetime
- Lower risk exists for Latina and African-American women
- Lower risk for men (20-30% will fracture)

Factors Leading to Increased Fracture Risk

![Fracture Risk Factors Diagram]

US Economic Burden of PMO

- Fractures associated with osteoporosis account for:
  - ~ $14-17 billion direct medical costs
  - ($140-170 million KPNC)
  - > 400,000 hospital admissions
  - ~ 2.5 million physician visits
  - > 180,000 nursing home admissions
- Costs of osteoporosis associated fractures by 2040:
  - ~ $50 billion
Burden of disease – hip fracture

4-6 million women in US fracture

13-17 million in US with low bone density are at ↑ risk for hip fracture

Men have about 1/3 - 1/2 this risk

Hip Fractures - Associated Morbidity and Mortality

Death within one year
Permanent disability
Unable to walk independently
Unable to carry out at least one independent activity of daily living

20%
30%
40%
80%

Yet of fracture patients over 50 years old:
< 10% receive osteoporosis therapy

Let's discuss the gaps in care which result in this lack of treatment with effective drugs.

Identify patients at risk
Evaluate secondary causes
Measure bone density and assess fracture risk
Treat and monitor
Prevention of Osteoporosis
(Improving Bone Mineral Density)

- Heredity predicts about 20%
- Attainment of peak bone density and avoiding bone loss thereafter = skeletal hygiene
  - Calcium intake: 1000 - 1200mg in children and adults, 1500mg after menopause
  - Weight-bearing exercise
  - Adequate gonadal steroids
  - Avoid smoking and excess EtOH
  - Adequate vitamin D – 400 IU in youth, then 800-1200 IU

Management of Osteoporosis:
Prevent first fragility fracture

- Primary prevention
  - Skeletal hygiene
  - Look for secondary causes of bone loss
  - Fall prevention
  - Medication

- Secondary prevention
  - Primary prevention +
    - Stabilize/increase bone mass
    - Medications
  - This is the HEDIS goal – to treat with effective meds to prevent further fracturing.

Pathophysiology of PMO: Overview

- Bone remodeling occurs throughout life to repair microfractures and supply Ca++
- In normal adults, the activity of osteoclasts (bone resorption) is balanced by that of osteoblasts (bone formation)
- With diminishing estrogen levels (mid-forties or fifties) excessive bone resorption is not fully compensated by an increase in bone formation
Bone Remodeling

Stable bone maintained by healthy osteocytes.

Activation of resorption
- Repair microfractures
- Supply calcium
- Remodel bone
- Inflammation

Multinucleated giant cells in acidic environment dig pits and recruit osteoblastic formation of osteoid.

This is passively mineralized into new bone - hydroxyapatite matrix.

Osteocytes maintain bone metabolism.
Normal skeletal turnover takes about 2-4 years.

Microarchitectural Instability

Trabecular bone accounts for most bone turnover
- Only 25% of the skeletal mass
- >> 50% bone turnover
- Verterbrae, distal radius and femoral neck

The process is not 100% efficient and there is net loss of bone after the third decade

Anything which increases the activity or number of osteoclasts or decreases osteoblasts causes increased bone loss.

Pathophysiology of PMO: Overview
Fractures Increase with Age

The steep rise in fractures among men occurs about 10 years later than it does in women.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-44</td>
<td>500</td>
<td>2,000</td>
</tr>
<tr>
<td>45-49</td>
<td>1,000</td>
<td>1,500</td>
</tr>
<tr>
<td>50-54</td>
<td>2,000</td>
<td>1,000</td>
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<tr>
<td>55-59</td>
<td>2,500</td>
<td>500</td>
</tr>
<tr>
<td>60-64</td>
<td>1,500</td>
<td>0</td>
</tr>
<tr>
<td>65-69</td>
<td>1,000</td>
<td>0</td>
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<tr>
<td>70-74</td>
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<td>75-79</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>80-84</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

BMD and Fracture Risk Are Inversely Related

BMD and fracture risk are inversely related. A lower BMD is associated with an increased risk of fracture.

Bone Gain and Loss Over a Woman’s Lifetime

Bone mass decreases over time, with the greatest loss occurring during the postmenopausal years. Adapted from Wasnich, R.D. et al.: Osteoporosis: Critique and Practicum, Honolulu, Banyan Press, 1989. pp. 179-213.
Risk Factors for Hip Fracture in White Women from the Study of Osteoporotic Fractures

<table>
<thead>
<tr>
<th>Factor</th>
<th>Increase in Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcaneal BMD (per 1 SD)</td>
<td>60</td>
</tr>
<tr>
<td>Age (per 5 yrs)</td>
<td>40</td>
</tr>
<tr>
<td>Hx maternal hip Fracture</td>
<td>80</td>
</tr>
<tr>
<td>Any Fracture since age 50</td>
<td>50</td>
</tr>
<tr>
<td>On feet &lt; 4 hr/day</td>
<td>70</td>
</tr>
<tr>
<td>Inability to rise from chair</td>
<td>70</td>
</tr>
<tr>
<td>Reduced depth perception</td>
<td>40</td>
</tr>
<tr>
<td>Current benzodiazepine use</td>
<td>60</td>
</tr>
<tr>
<td>Walk for exercise</td>
<td>-30</td>
</tr>
</tbody>
</table>

Cummings et al. NEJM 1995

Indications for DXA Scan
- Women 65+
- Men 70+
- Adults >55 with Fractures or Risk Factors
- Other circumstances:
  - Primary hyperparathyroidism
  - Chronic glucocorticoid use
  - Male hypogonadism or androgen deprivation therapy
  - Premature menopause, aromatase inhibitors
  - Prolonged hyperthyroidism
  - DM1 55+ women, 65+ men
- Monitoring Treatment (Q 3-5 yrs)

Case
GR: 67 yr old post menopausal female
Off HRT for 6 years
Exercises regularly, BP okay on HCTZ
122#, 5’ 4”, quit smoking 15 yr ago, no h/o Fx
Takes calcium and a multivitamin occasionally
Mom had a “hump” but ↓ age 84 from CVA
BMD ?
YES! > 65
Bone Density Scans

Purpose:
1. Screening for disease
2. Fracture risk assessment
3. Monitor treatment

Account for only 60-80% of bone strength.

~50% of patients with osteoporotic fracture DO NOT have osteoporotic T scores.

Risk Factors For Osteoporosis

- Age
- History of Fracture
- Ethnicity
  - Highest risk = Caucasian women
- Family History
- Low BMI
- Hypogonadism
  - Low estrogen in women, low testosterone in men
- Glucocorticoid use
  - ≥ 7.5mg prednisone daily for > 3 mo
- Inadequate calcium and vitamin D intake
- Immobilization
- Smoking
- Heavy alcohol use
  - ≥ 3 or more drinks/day
Causes of Secondary Osteoporosis

- **Medications**
  - Glucocorticoids
  - Antiepileptics
  - Lithium
  - Methotrexate
  - PPI’s
  - SSRIs (?)
  - Thiazolidinediones

- **Connective tissue dz**
  - Rheumatoid arthritis
  - Ankylosing spondylitis
  - Lupus

- **Nutritional factors**
  - Anorexia nervosa
  - ↓ Ca++ intake
  - ↓ Vitamin D intake
  - Excess caffeine or alcohol
  - Excess Sodium

- **Lifestyle**
  - Smoking
  - Immobilization
  - Excessive exercise
  - Sedentary lifestyle

Causes of Secondary Osteoporosis

- **Endocrine causes**
  - Hypogonadism
  - Hyperthyroidism
  - Hyperparathyroidism
  - Glucocorticoids
  - Type 1 Diabetes
  - Type 2 Diabetes

- **Hemochromatosis**

- **COPD**

- **Depression**

- **Chronic Renal Failure**

- **Pregnancy**

- **Malignancy**
  - Multiple myeloma
  - Systemic mastocytosis
  - Leukemia

- **GI diseases**
  - Liver failure
  - Biliary cirrhosis
  - Inflammatory bowel disease
  - Post gastrectomy, Roux-en-Y or **duodenal** switch
  - Gluten-sensitive enteropathy (sprue)

Most Important Risk Factors for Osteoporotic Fracture

1. Age

2. History of Fracture

3. Everything else…. 
Effect of Age on Fracture Incidence in Women

Fracture History = ↑ Fracture Risk

20% of patients with vertebral fractures will have another within a year.

Lindsay R, et al., JAMA 2001;285:320

Table 3. Incidence of New Vertebral Fracture in Year Following Vertebral Fracture During Study

<table>
<thead>
<tr>
<th>Subjects With New Vertebral Fracture in Year Following Incident Vertebral Fracture, No. (%)</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population (n = 581)</td>
<td>58 (10)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Vertebral Fractures at baseline, No. (%)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>0 (n = 581)</td>
<td>1 (0.4)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>1 y (n = 569)</td>
<td>3 (11.5)</td>
<td>4.1 (2.4-6.8)</td>
<td>.22</td>
</tr>
<tr>
<td>2 y (n = 552)</td>
<td>21 (11.8)</td>
<td>9.0 (1.3-60.1)</td>
<td>.09</td>
</tr>
</tbody>
</table>

* Kaplan-Meier estimate of the survival function.

Calculation Tool

Weight Conversion

Height Conversion

Please answer the questions below to calculate the 1-year probability of fracture with OSE:

- Gender: Male
- Height: 5 ft 6 in
- Weight: 150 lbs
- Menses: Yes
- Bone density: Not osteoporotic
- Ever been pregnant: Yes
- Family history: Yes
- Personal history: Yes
- Recent history: No
- Bone loss: Yes
- Bone density: No
- Bone density: Yes
- Bone density: No
- Bone density: Yes
- Bone density: Yes
- Bone density: Yes
Most Important Risk Factors for Osteoporotic Fracture

1. Age
2. History of Fracture
3. Everything else….

Using FRAX

What if she had a fracture?

FRAX 10 year fracture risk:
   Treatment advised
With major fracture risk over 20-30%
   or
   hip fracture risk over 3-4%

Previous Vertebral Fx Predicts Risk of Future Hip Fx

Case

GR: 67 yr old post menopausal female
Off HRT for 6 years
Exercises regularly, BP okay on HCTZ
122#, 5’ 4”, quit smoking 15 yr ago, no h/o Fx
Takes calcium and a multivitamin occasionally
Mom had a “hump” but ↓ age 84 from CVA

Fell and broke her wrist.
Treat?
84 y/o with Osteopenia

Treatment of Osteoporosis = Prevention of Fracture

- Calcium and Vitamin D
- Exercise
  - Osteoblast Stimulation
  - Fall Prevention
- Fall Risk Reduction
- Minimize Other Risk Factors
  - Tobacco and alcohol
  - Glucocorticoids
  - Hypogonadism
- Pharmacologic
  - Bisphosphonates
    - PO or IV
  - Estrogen
  - SERMs (Evista)
  - Teriparatide (Forteo)
  - Denosumab (Prolia)
Other Factors

- Calcium
- Vitamin D
- Ethnic factors
- Exercise – just do it!

Daily Calcium Intake

All calcium salts are not created equal

Elemental Calcium in common products

- 40 percent of calcium carbonate
  - take after meals; need low pH to dissociate
- 21 percent of calcium citrate
  - take any time
- 13 percent of calcium lactate
- 9 percent of calcium gluconate

Aim for 1200-1500 mg TOTAL DAILY ELEMENTAL CALCIUM intake
Is calcium either necessary or sufficient?

- Many studies suggest benefit of adequate calcium intake in post-menopausal women
- Many studies show improved BP and CV outcomes in calcium sufficient populations
- The safety of calcium supplements (without vitamin D supplements) has been questioned
- All medication studied include calcium and vitamin D in both placebo and intervention groups

Current knowledge:
- Dietary calcium may be better
- Supplement deficient patients
- Supplement patient you are treating for osteoporosis

Vitamin D Levels – Lower in Higher Latitudes

1. Calcium Flow

- ↑ Osteoclastic resorption of bone
- ↑ Serum Ca **
- ↑ absorption in gut
- ↑ Renal calcium reabsorption
-↑ PTH
- ↑ 1,25 diOH vitamin D
- 25 OH vitamin D
- 7-deoxycolesterol
Vitamin D for Muscle and Bone Health

- Metabolism and signaling decrease with age.
- Prevents falls and fractures
  - Multiple studies show fracture prevention with calcium and vitamin D.
  - Negative studies had poor compliance (<60%), inadequate doses (< 800 IU) or 25OH D levels < 30 ng/ml

Vitamin D and PTH

290 consecutive pts. on a general medical ward – MGH

Thomas 1998. NEJM

Measuring Vitamin D

- 1 ng/mL = 2.5 nmol/L
- 40 ng/mL = 100 nmol/l

One caveat:
Most clinical assays are inaccurate
CV up to 20%
  e.g. 24 ng/mL could be <20 or over 30
Vitamin D and Ca absorption

Optimal Vitamin D
Desirable level begins at 30 -32ng/mL
(75-80 nmol/L)

Do my patients need vitamin D?

Evidence on fractures tells the story

Calcium and vitamin D supplementation in ambulatory elder population - hip fracture

Chapuy MC et al. NEJM 327:537, 1992
How much Vitamin D?

New Guidelines recommend:
- **800 IU vitamin D** and **1000mg calcium** daily for pre-menopausal women
- **800 IU vitamin D** and **1500mg Calcium** daily for post-menopausal women and men over 50.

Pharmacologic Treatment of PMO: Overview

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Action</th>
<th>Pathophysiology of Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone therapy (HT) or ET</td>
<td>Inhibit bone resorption</td>
<td>Bone Remodeling</td>
</tr>
<tr>
<td>Selective estrogen receptor modulators (SERMs): raloxifene</td>
<td>Maintain or increase bone mass</td>
<td>Activation Restoration</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Reduce fracture risk</td>
<td>Bone</td>
</tr>
<tr>
<td>Bisphosphonates*</td>
<td></td>
<td>Removal Formation</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td></td>
<td>Bone</td>
</tr>
<tr>
<td>rPTH (Forteo)</td>
<td>Increases bone formation</td>
<td>Bone</td>
</tr>
<tr>
<td></td>
<td>increases bone mass</td>
<td>Bone</td>
</tr>
<tr>
<td></td>
<td>* decrease hip fractures</td>
<td>Bone</td>
</tr>
</tbody>
</table>

Slowing down the osteoclasts allow bone remodeling ‘space’ to be refilled.
Hundreds of bone remodeling units effected over years

Usually entire skeleton remolds over 3 years

Bone Turnover


Effect of Unopposed Estrogen and HRT on Spine and Hip BMD in Postmenopausal Women: The PEPI Trial

Effect of Raloxifene on BMD in Postmenopausal Women Without Osteoporosis

<table>
<thead>
<tr>
<th>Months</th>
<th>% change from baseline</th>
<th>Placebo</th>
<th>30 mg raloxifene</th>
<th>60 mg raloxifene</th>
<th>90 mg raloxifene</th>
</tr>
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<tbody>
<tr>
<td>–2</td>
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<tr>
<td>–1</td>
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<td>3</td>
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<td>6</td>
<td>0</td>
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<td>12</td>
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<td>18</td>
<td>0</td>
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<tr>
<td>24</td>
<td>0</td>
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</tbody>
</table>

*P < 0.05 vs. placebo for all treatment groups at 24 months.


Placebo (n=150)
30 mg raloxifene (n=152)
60 mg raloxifene (n=152)
150 mg raloxifene (n=147)

Cost Effectiveness of Osteoporotic Treatment

- NOF guidelines to improve 10 year fracture risk
  - > 20% major osteoporotic fracture
  - or > 3% hip fracture
- Bisphosphonates:
  - Women over 67 with fractures
- Vitamin D and calcium
  - Elderly patients

<table>
<thead>
<tr>
<th>Bisphosphonates approved for Postmenopausal Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Alendronate</td>
</tr>
<tr>
<td>Alendronate (cholecalciferol) (Fosamax Plus D)</td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
</tr>
<tr>
<td>Bisphosphonate (Boniva)</td>
</tr>
<tr>
<td>Bisphosphonate (Boniva) inj</td>
</tr>
<tr>
<td>Zoledronic Acid (Reclast)</td>
</tr>
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</table>

*Zoledronic Acid approved for Postmenopausal Osteoporosis
When prescribing bisphosphonates…work the patient up

- Ensure adequate Ca and vitamin D intake
- Discuss:
  - cost
  - projected duration of Rx
  - potential side effects: mostly GI.
  - use telephone follow-up
- NEVER cut pills
- IV meds may cause flu-like symptoms, rarely renal compromise – may vary dose for patients with CKD stage II and III

Unknown knowns

unproven side effects:
- a fib and esophageal cancer

Possible issues
- Osteonecrosis of the jaw (<1/1000 over 5 years)
- Possible risk of diaphyseal fractures with long-term Rx (<1/1000 over 5 years)
Is there magic in the dosing interval?

No

Several studies show prolonged effect on Bone turnover markers and maintenance of Bone Density for months to YEARS after stopping bisphosphonates


Monitor calcium, vitamin D and consider drug holidays

Newer Drugs

- Denosumab - humanized mouse monoclonal antibody to RANKL (a ligand that activates the osteoclasts) - blocks osteoclast differentiation, proliferation, and function.

And decreases fractures:
  sub-cutaneous injection twice a year
  $1650 per year
Change in bone density and decrease in bone turnover markers

Recombinant PTH - Forteo

Daily SQ injection 20 mcg for up to 2 years (limit due to osteosarcoma in rats)

Very expensive but unique mode of action – increases osteoblast function.

May cause hypercalcemia.

Contraindicated in: active malignancy
renal insufficiency
renal stone disease
**Effect of Teriparatide (20µg) on Skeletal Architecture**

**Baseline**

**Follow-up**

**Patient 1124**

---

**rPTH**

Daily 20 µg SQ injection

- Stimulates osteoblasts
- Increases bone mass
- Decreases fracture rate

Time limited

> $10,000 per year

Must be followed by antiresorptive or BMD is lost again.

---

**Other medications for osteoporosis**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose / Interval</th>
<th>Cost</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolia (Denosumab)</td>
<td>60 mg SQ q 6 mo in office</td>
<td>$800 - 1000 per dose q 6 months</td>
<td>Preferred in CKD up to stage 4</td>
</tr>
<tr>
<td>Forteo (Teriparatide)</td>
<td>20mcg daily – self injection</td>
<td>$8000 - 10,000 per year</td>
<td>Restricted to 2 years – must be followed by anti-resorptive agent</td>
</tr>
</tbody>
</table>
Primary vs Secondary Prevention

Women on estrogen do not need an additional medication, although HT is no longer considered osteoporosis treatment. (Hypogonadal men similar)

Fracture patients over age 50 deserve FRAX assessment and treatment if risk is high enough

Alendronate Reduces Fracture Risk in Women with Osteopenia (T = -1.6 to –2.5)

Using Fracture Intervention Trial data
n = 3737
Average age 69
- In Women With Low BMD but No Prior Vertebral Fracture  
  NNT = 175
- In Women With Low BMD and Prior Vertebral Fracture  
  NNT = 26


Subtrochanteric fractures

- Most hip fractures occur at the neck
- Diaphyseal fractures
- Concern in younger patients who do not benefit from therapy

Not cumulative dose

No more frequent in Bisphosphonate Treatment compared to Calcitonin or Raloxifene

Total of 12 Fractures in 14,195 trial participants (FIT, FLEX, HORIZON) no more common in treated v placebo (Black CM NLM
20102621794)
I'm just sayin'

Case Control Study
NNT for 5 years to prevent hip fracture = 3-5
but increased risk (1/750 after 6 years of bisphosphonate, 1/450 after 7
years) of atypical fractures
NNT harm = thousands
Park-Wyllie LY. JAMA. 2011;305:783

Use medications for high risk patients and work up before treating:
FRAX 10 year risk score
> 20-30% major osteoporotic
or
> 3-4 % hip
Consider drug Holiday

Atypical Femoral Fractures

Desai PA 2013 Current Osteop Rep 11: 179

Appearance:
Lateral cortical stress fx with ‘beaking’
*natural prevalence: 1-2/100000 patients
78/100000 patients on bisphosphonates for 8 years

So,
ONLY TREAT HIGH RISK PATIENTS

Osteonecrosis of the Jaw

- PROBE study (KPNC DOR study)
- 13,946 KP members surveyed
  (8,572 responded, 71±9 years)
  – 2,159 reported dental symptoms (25%)
  – 1005 examined (536 provided dental
    records)
  – 9 had ONJ (1 in 952)

Major problem: what is the natural incidence of ONJ?
Drug Holidays

Inhibiting osteoclasts may inhibit bone healing of microfractures
Allowing normal re-modeling may be beneficial
Assuming patient is still high risk, bone turnover markers may be appropriate
Effect of bisphosphonates very long-lasting
Stop med and repeat markers 1-2 years.
Re-assess fracture risk and bone turnover
No evidence that this prevents ONJ or atypical fractures

When/Why Should I Consider a Drug Holiday?
And for How Long?

Drug Holidays: FLEX Trial

Effects of Continuing or Stopping Alendronate After 5 Years of Treatment
The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

After 5 years of oral alendronate (FIT)
1099 post menopausal women randomized to 5 more years of alendronate or placebo (FLEX).
Drug Holidays and FLEX: Fractures

FIG. 3. Mean (± SE) percentage changes in markers of bone turnover from FLEX baseline to FLEX month 36 (mean, 2.9 years) in women receiving alendronate or placebo during FLEX.

Drug Holidays and FLEX: Fractures

FIG. 4. Cumulative incidence of nonvertebral fracture and hip fracture in FLEX: Relationship to prior treatment status.

FLEX trial

FIG. 3. Mean (± SE) percentage changes in markers of bone turnover from FLEX baseline to FLEX month 36 (mean, 2.9 years) in women receiving alendronate or placebo during FLEX.
Conclusions from FLEX: 5 vs. 10 yrs of alendronate

- Compared to 5 years, 10 years of alendronate offers:
  - Stabilization of BMD
  - Reduction in the risk of vertebral fractures
  - No impact on the rate of non vertebral fractures

Bottom Line: consider 10 yrs instead of 5 for those at highest risk of vertebral fracture:
- Prior hx of vertebral fracture
- Very low T scores or highest FRAX scores

FLEX Results: Highest Risk Women

For women at highest risk, defined as femoral neck T score <-2.5, five additional years of bisphosphonate did result in fewer non vertebral fractures.

HORIZON Extension Trial

- HORIZON:
  - Zoledronic acid 5mg IV or placebo annually for 3 years

- HORIZON EXTENSION:
  - Those who received ZOL randomized to more ZOL (Z6) or placebo for more three years (Z3P3)
HORIZON Extension: Results

- BMD: declined slightly in the Z3P3 group vs. Z6
  - True for all sites (spine and hip)
  - Z3P3 BMD still above Z0 baseline

- Vertebral fractures: lower in Z6 group
  - 3.0% vs. 6.2% - NNT 32

- Non vertebral fractures: no difference
  - 8.2 vs. 7.6%

- Hip fractures: no difference
  - 1.3 vs. 1.4%

Discussing side effects and follow-up

- Chronic disease
  - Fracture patients may require long-term treatment (>5 years)
  - Preventive (prophylactic) therapy. Consider ‘drug holiday’ and reassess risk

- Very high risk
  - Consider combination or sequential therapy
  - Consultation with osteoporosis expert

FLEX trial follow-up

Initial bone density and age predicted future fracture
Bone turnover markers did not predict fracture at baseline or at 1 year post ALN.
This does not help us with prevention of ONJ nor Atypical fractures
Bauer et al.JAMA Internal Medicine 2014, 174(7):1126
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For how long is Denosumab safe?

10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Bone HG et al 2017
Lancet Diab & Metab. doi.org/10.1016/S2213-8587(17)30148-9

BMD continued to improve and fracture prevention persisted in initial FREEDOM treatment group.
BMD markedly increased and fracture prevention was noted in crossover group.
Side effects seemed fewer in extension group and adverse events were similar.

So what is the best strategy for our patients?

Use the same principles

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Bone turnover markers did not predict baseline fracture or 1 year post ALN.
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My approach

Screen men and women at high risk:
- Previous fragility fractures over age 45-50
- Glucocorticoids
- DM

Assess FRAX fracture risk

Look for secondary causes

Routine labs:
- Calcium, PTH, 25 OH vitamin D, Cr, CBC, Testosterone in men.

Discuss long term and short term plans for follow-up

My approach

Lower risk (osteopenia, FRAX > 3% hip or > 20% major):
  - Initial anti-resorptive agent
  - Consider side effect profile, other risks and cost.
  - Stop anti-resorptive agent after 3-5 years.
  - Repeat DEXA at 1-2 years and reassess risk.

Moderate risk (osteoporosis + fragility fracture or high FRAX):
  - After 5 years of treatment (improved bone density) – "drug holiday"
  - Use bone turnover markers to determine when to restart anti-resorptive agent

High risk
  - After 5 years consider drug holiday, offer a course of rPTH.
  - ALWAYS give anti-resorptive agent after (if not during) rPTH treatment.

Conclusions

- Risk of fracture should be high before initiating treatment with antiresorptive agents
- Reassessing risk and discontinuing medications is an option
- Communication between providers may improve patient outcomes
- No known protection from ONJ
Fractures will happen
Screen patients at risk
Preventive measures
Treat high risk patients
A fracture in a susceptible patient requires work-up and treatment
Have a treatment goal and re-visit the issue annually.

THANK YOU!
Comments, Questions?