Osteoporosis Update

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Osteoporosis Facts

- 2 million bone breaks a year (“2 million 2 many”)\(^1\)
- Only 2 in 10 patients with osteoporosis get a follow-up test or treatment for osteoporosis\(^1\)
- Fractures may have serious consequences\(^2\)
  - Hip fracture
    - 10%-20% additional mortality per year
    - 20% of hip fracture patients require long-term nursing home care
    - Only 40% fully regain their pre-fracture level of independence\(^1\)

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\(^1\) National Bone Health Alliance. 2 Million 2 Many. Available at: http://www.2million2many.org/. Accessed September 13, 2013.

Often asymptomatic . . .

- Until fracture occurs

- Even after some fractures (e.g., 2/3 of vertebral fractures are asymptomatic)

The challenge to clinicians:

- Identify patients at high risk for fracture

- Prevent first fracture

Assessment: FRAX tool

- Web-based tool which helps determine fracture risk, taking into account many factors
- Must be matched to specific population
- Pharmacologic treatment (in addition to Ca/vitamin D) recommended for persons with:
  - 10-year risk of hip fracture 3% or greater
  - 10-year risk of major osteoporotic fracture 20% or greater
- FRAX is only relevant to treatment-naïve patients, not those who have ever been treated
Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: **US (Caucasian)**

### Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   - Age: 57
   - Date of Birth: Y: __, M: __, D: __

2. Sex
   - Male
   - Female

3. Weight (kg)
   - 75

4. Height (cm)
   - 165

5. Previous Fracture
   - No
   - Yes

6. Parent Fractured Hip
   - No
   - Yes

7. Current Smoking
   - No
   - Yes

8. Glucocorticoids
   - No
   - Yes

9. Rheumatoid arthritis
   - No
   - Yes

10. Secondary osteoporosis
    - No
    - Yes

11. Alcohol 3 or more units/day
    - No
    - Yes

12. Femoral neck BMD (g/cm²)
    - Select BMD
    - 0.65

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**BMI: 27.5**

The ten year probability of fracture (%)

- **without BMD**
  - Major osteoporotic: 23
  - Hip Fracture: 1.7

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[Print tool and information](#)
Majority of Fractures Occur in Patients With Osteopenia, Not Osteoporosis

- Osteopenic patients outnumber those with osteoporosis 3:1
- Fracture risk—determined by more than just BMD
- Clinical factors such as age, lifestyle, and family and personal medical history also play a role
- Appropriate treatment depends on being able to accurately determine the risk of future fractures

After exclusion of secondary causes, treat postmenopausal women and men age 50 and older who have...

**Osteoporosis**

**Clinical diagnosis:** Hip or spine fracture

**DXA diagnosis:** T-score -2.5 or below in the spine or hip

**T-scores between** -1.0 and -2.5 and

**10-year risk of fracture:**

≥ 3% for hip fracture or

≥ 20% for a major osteoporotic fracture

National Osteoporosis Foundation (NOF) Guidelines 2010: Who Should be Treated?

Antiresorptive and Anabolic Therapies

- **Antiresorptive**
  - Decrease bone resorption
  - Most treatment agents
  - Bisphosphonates, SERMs, calcitonin, estrogen, denosumab

- **Anabolic**
  - Stimulate bone formation
  - Teriparatide is only drug which has this effect
Estrogen Treatment (ET)

- Several approved oral and transdermal preparations
- Treats symptoms of estrogen deficiency
- Skeletal effects:
  - Decrease in biochemical markers of 50% to 60%
  - 2-year BMD increase of 4% to 6% at hip and spine
  - Decreased incidence of vertebral and hip fractures (34%) after 5 years in the Women’s Health Initiative (WHI)
  - Effects in women with osteoporosis have not been evaluated in randomized controlled trials
- Concern about adverse effects
- Long-term use not recommended

• Raloxifene (60 mg daily)
• Skeletal effects:
  – Decrease in biochemical markers of 30%
  – 3-year BMD increases of 2% to 3% at hip and spine
  – Decreased incidence of vertebral fractures (30% to 50%) in women with pre-existing vertebral fractures or low bone density
  – No effect on nonvertebral or hip fractures has been observed
• Extra-skeletal effects: reduction in invasive breast cancer

Adverse effects

- Hot flashes
- 2- to 3-fold increased risk of venous thromboembolic events
- No increased risk of stroke, but *Black Box Warning* for increased risk of death following stroke
- Leg cramps

Calcitonin (200 units daily by nasal spray)

Skeletal effects:
- Decrease in biochemical markers by 20%
- Small effect (1% to 2%) on bone density in spine
- Reduced incidence of vertebral fractures (36%) in women with pre-existing vertebral fractures
- No effect on nonvertebral or hip fractures has been observed

Adverse effects
- Nasal stuffiness
- Possible increased cancer risk


European Medicines Agency. Press release. July 20, 2012. Available at:
Bisphosphonates: indications

- Treatment and prevention of postmenopausal osteoporosis
  - Alendronate, risedronate, ibandronate, zoledronic acid

- Prevention and/or treatment of glucocorticoid-induced osteoporosis
  - Risedronate, zoledronic acid, alendronate

- Treatment of men with low bone density
  - Alendronate, risedronate, zoledronic acid
Bisphosphonates:
Alendronate, Risedronate, Ibandronate, Zoledronic Acid

- Alendronate: 10 mg daily (tablet) or 70 mg weekly (tablet or liquid) for treatment, 5 mg daily or 35 mg weekly for prevention

- Risedronate: 5 mg daily or 35 mg weekly (tablet); 150 mg monthly (tablet)

- Ibandronate: 150 mg monthly by tablet; 3 mg intravenously over 15 to 30 seconds every 3 months

- Zoledronic acid: 5 mg by intravenous infusion over a minimum of 15 minutes once every year for treatment, and every other year for prevention

Osteoporosis Foundation; 2013. Available at: http://www.nof.org/hcp/clinicians-guide
Bisphosphonates: Effects
Alendronate, Risedronate, Ibandronate, Zoledronic Acid

- Increased bone density in the spine by 5% to 8% and at the hip by 3% to 6% after 3 years
- Reduced incidence of vertebral fractures by 40% to 70%
- Alendronate, risedronate and zoledronic acid reduced non-vertebral fractures (25% to 40%), including hip fractures (40% to 60%), in women with osteoporosis
- Ibandronate: Overall, no effect observed on non-vertebral or hip fractures. In a post-hoc analysis, non-vertebral fracture reduction was seen in a high-risk subgroup with a baseline femoral neck T-score less than -3.0
Contraindications/Warnings/Precautions

- Hypocalcemia
- Creatinine clearance <30 cc/min (<35 cc/min for zoledronic acid)
- For oral dosing: Esophageal stricture or impaired esophageal motility (alendronate); inability to stand or sit for at least 30 minutes (alendronate/risedronate) or 60 minutes (ibandronate)

Notes: UGI symptoms per se are not a contraindication to oral dosing

Bisphosphonates: other considerations

Oral dosing requirements

- Tablets (exception: delayed release risedronate) taken on empty stomach after overnight fast with 6-8 oz of plain water while in upright position
- Patients should not eat or lie down for at least 30 minutes (alendronate and risedronate) or 60 minutes (ibandronate)
- Calcium and vitamin D supplements, if needed, should be taken at a different time of day than the oral bisphosphonate

Osteonecrosis of the Jaw (ONJ)

- Area of exposed alveolar or palatal bone that typically shows poor healing over several months
  - 95% of cases have been reported with high-dose, chronic IV bisphosphonate treatment of myeloma and cancer metastatic to bone
  - May also occur with denosumab
  - Pain in 2/3 cases: infection may or may not be present
  - Known risk factors: invasive dental procedures, oral trauma, periodontitis, poor oral hygiene, radiotherapy to the jaw, chemotherapy, corticosteroids, infection
  - Pathogenesis is not known

Atypical Femoral Fractures in Patients Taking Long-Term Anti-Resorptive Agents

- May begin with stress reaction or stress fracture of lateral femoral cortex (A)
- Transverse fractures of femoral diaphysis or in subtrochanteric region (B)
- Often bilateral
- Prodromal pain in thigh or groin in 70%
- Occurs in untreated patients, but increased incidence with long-term antiresorptive therapy, particularly bisphosphonates and denosumab

FDA Safety Update

- Recognize the possibility of atypical fractures in patients taking bisphosphonates
- Evaluate any patient who presents with new groin or thigh pain to rule out femoral fracture
- Discontinue potent antiresorptive medication in patients with atypical fractures
- Periodic reevaluation of need to continue bisphosphonate therapy, particularly in patients treated > 5 years

Bisphosphonate Therapy: Long-Term Treatment

- Stopping treatment in high-risk patients
  - After 5 years of alendronate-decline in BMD, rise in biochemical markers, no increased fracture risk except clinical vertebral fractures\(^1\)
  - After 3 years of risedronate, spine BMD rose, vertebral fracture risk was still reduced compared with control patients\(^2\)
  - After 3 years of zoledronic acid, slight increase in morphometric fractures vs clinical vertebral fractures\(^3\)

Bisphosphonate holidays

- In patients at high risk for fractures, continued treatment seems reasonable.
- Consider a drug holiday of 1 to 2 years after 10 years of treatment.
- For lower risk patients, consider “drug holiday” after 4 to 5 years of stability.
- Follow BMD and bone turnover markers during a drug holiday period, and reinitiate therapy if bone density declines or markers increase.

Monoclonal antibody to RANKL

60 mg subcutaneous injection every 6 months

9% increase in spinal BMD after 3 years in the pivotal FREEDOM trial; 4% to 5% increase in hip BMD

Reduction in fracture risk after 3 years:
- 68% decrease in new vertebral fractures
- 40% decrease in hip fractures
- 20% decrease in nonvertebral fractures

8-year data: continued increase BMD, reduced bone turnover, good safety

Dénosumab: adverse events

Adverse events that occurred more commonly in denosumab group:

- Serious infections leading to hospitalization
- Dermatitis, eczema, rashes
- Back pain, pain in the extremity, musculoskeletal pain, hypercholesterolemia, cystitis
- Pancreatitis
- Osteonecrosis of the jaw
- Significant suppression of bone remodeling

Teriparatide: rhPTH [1-34]

- Only treatment agent that is anabolic: stimulates bone formation rather than inhibiting bone resorption
- 20 μg daily (subcutaneously) for no more than 2 years
- Indication: treatment of men and postmenopausal women with osteoporosis who are at high risk for fracture

Forteo (prescribing information). Indianapolis, IN: Eli Lilly and Company; March 21, 2012.
Teriparatide: rhPTH [1-34]

• Effects:
  – Increased BMD density in spine by 9% and hip by 3% vs placebo over 18 months
  – Reduced incidence of vertebral fractures (65%) and nonvertebral fragility fractures (53%) in women with pre-existing vertebral fractures
  – Studies too small to evaluate effect on hip fractures

• Adverse reactions: arthralgia, pain, nausea; warning about osteosarcoma risk in rats

• Prior radiation therapy a contraindication


Forteo (prescribing information). Indianapolis, IN: Eli Lilly and Company; March 21, 2012.
Thank you!

Questions?