Closing Performance Gaps in the Diagnosis and Management of Osteoporosis

Andrea J. Singer, MD, FACP, CCD
Associate Professor of Medicine and Obstetrics and Gynecology
Director, Bone Densitometry
Medstar Georgetown University Hospital
Clinical Director, National Osteoporosis Foundation

Objectives

- Identify performance gaps in the diagnosis and treatment of osteoporosis in patients at risk for fracture
- Apply clinical tools and practice guidelines in the management of patients with osteoporosis
- Recognize the connection between fractures and osteoporosis, and ensure that patients who suffer a fracture receive appropriate diagnosis, treatment and support through a multidisciplinary approach
- Discuss compliance and persistence with therapy for osteoporosis
- Identify recent advances in the treatment of osteoporosis
Osteoporosis

- Reduced bone strength leading to increased risk of fractures
- 9 million Americans with osteoporosis and more than 48 million with low BMD

Consequences
- Over 2 million osteoporotic fractures per year
- 1 of every 2 women age 50+ will have a fracture before her death
- Fractures lead to disability and increased mortality
- Cost of $17 billion in 2005

Management
- Assessment of fracture risk
- Treatment decisions
- Follow-up for response, tolerance, adherence, safety

Performance Gaps

- Under-identification
  - Many patients who meet guidelines for bone density testing are not tested
  - Many patients with fractures are not diagnosed as having osteoporosis

- Under-treatment
  - Most patients with osteoporosis or fractures are not treated to reduce risk of future fractures

- Poor compliance and persistence with therapy
  - Estimated about 50% of new users of medication for osteoporosis continue therapy for a 7-12 month treatment period
  - Oral bisphosphonates are frequently taken incorrectly

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Case Study - TA

TA, a 61-year-old postmenopausal Caucasian woman, presents for annual wellness evaluation.

- PMH: Hypothyroidism on levothyroxine 50 mcg daily
- Does not smoke; drinks wine with dinner on weekends
- Accountant, sedentary job, no regular exercise program
- Diet: well-balanced, but "lactose intolerant," so no regular intake of dairy products; No vitamins or supplements
- No personal history of fracture
- Mother had hip fracture at age 82
- Height 5'2", Weight 110 pounds

Assessing Risk and Diagnosing Osteoporosis - 1

Assessment of clinical risk factors to identify an increased risk of low bone mass and fractures

<table>
<thead>
<tr>
<th>Lifestyle-Related Risk Factors</th>
<th>Other Significant Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (3 or more drinks per day)</td>
<td>Prior fracture without major trauma</td>
</tr>
<tr>
<td>Aluminum ingestion (antacids)</td>
<td>Clinical risk factors</td>
</tr>
<tr>
<td>Excessive vitamin A intake</td>
<td>Age ≥65</td>
</tr>
<tr>
<td>Falling</td>
<td>Family history of osteoporosis or fractures</td>
</tr>
<tr>
<td>High caffeine intake</td>
<td>Early menopause</td>
</tr>
<tr>
<td>High sodium (salt) intake</td>
<td>Secondary osteoporosis</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Height loss or kyphosis</td>
</tr>
<tr>
<td>Inadequate physical activity</td>
<td>Risk factors for falling</td>
</tr>
<tr>
<td>Low calcium intake</td>
<td>Patient’s reliability, understanding, and</td>
</tr>
<tr>
<td>Smoking</td>
<td>willingness to accept intervention</td>
</tr>
<tr>
<td>Thinness (body weight &lt;127 pounds)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td></td>
</tr>
</tbody>
</table>


Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Assessing Risk and Diagnosing Osteoporosis - 2

Bone mineral density testing if indicated from the risk factor assessment or criteria below

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-Based</td>
<td>65 years and older</td>
<td>70 years and older</td>
</tr>
<tr>
<td>Based on Risk Factors</td>
<td>Postmenopausal, &lt; 65</td>
<td>50-70 years with 1+ risk factor(s)</td>
</tr>
<tr>
<td></td>
<td>with 1+ risk factor(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perimenopausal with specific risk factor* associated with increased fracture risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postmenopausal, discontinuing estrogen</td>
<td></td>
</tr>
<tr>
<td>Regardless of Gender</td>
<td>Fragility fracture (adulthood/after age 50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbid high-risk condition or exposure to high-risk medication associated with low bone mass or bone loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anyone being considered for pharmacologic therapy</td>
<td></td>
</tr>
</tbody>
</table>

*Low body weight, prior low-trauma fracture or high risk medication


Bone Mineral Density Results and WHO Classification

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (L1-L4)</td>
<td>-2.1</td>
</tr>
<tr>
<td>Left total hip</td>
<td>-2.4</td>
</tr>
<tr>
<td>Left femoral neck</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO Diagnostic Category</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BMD</td>
<td>≥ -1.0</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>Between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T-score ≤ -2.5</td>
</tr>
</tbody>
</table>

T-score is the number of standard deviations the patient’s BMD is above or below mean BMD of young-adult reference population.

Use the lowest T-score of the femoral neck, total hip, lumbar spine, or 33% radius (if measured) for diagnostic classification.

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
**Case Study - TA**

Does TA meet current guidelines for treatment with a pharmacological agent to reduce fracture risk?

1. Yes, because she has a T-score <-2.0
2. Yes, because she has low bone mass (osteopenia) and a clinical risk factor for fracture
3. No, because she does not meet criteria for osteoporosis
4. Not sure, I need more information regarding assessment of fracture risk

---

**FRAX – Fracture Risk Assessment Tool**

- Available online at [http://www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)
- Included in some DXA printouts
- FRAX provides a quantitative risk estimate based on BMD and an assessment of other key factors in **treatment-naïve patients** between 40 and 90 years
- General parameters for use of FRAX: patients with low bone mass (osteopenia)
- Provides estimate of 10-year probability of major osteoporotic fracture (hip, spine, proximal humerus, distal forearm) and 10-year probability of hip fracture
- Fracture probability can be used with treatment guidelines to determine when treatment should be recommended

---

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Assessing Fracture Risk: FRAX®

FRAX Risk Factors
- Age, Sex, Height, Weight
- FN BMD (optional)
- Previous fracture
- Parent hip fracture
- Current smoking
- Glucocorticoids (ever)
- Rheumatoid arthritis
- Secondary osteoporosis
- Alcohol

FRAX Benefits and Limitations

Benefits
- Validated in large cohort of ~60,000 patients
- Combined use of BMD and clinical risk factors improves case finding
- Quantitative estimation of fracture risk – more comprehensible to patients
- Applicability to men and women worldwide
- Can be used with economic modeling to determine cost-effective intervention thresholds

Limitations
- Limited to 4 ethnicities in US (Caucasian, Black, Hispanic, Asian)
- Dichotomous input for continuous variables
- Discordantly low spine BMD cannot be used
- Not all risk factors can be incorporated
- No provision for nonskeletal risk factors (falling)
- May underestimate or overestimate fracture risk

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
NOF Treatment Recommendations

Consider pharmacological treatment in postmenopausal women and men ≥ 50 years of age with:

- Hip or vertebral fracture
- T-score < -2.5 at femoral neck or lumbar spine
- T-score between -1.0 and -2.5 and
  - 10-year probability of hip fracture ≥ 3%, or
  - 10-year probability of major osteoporotic fracture ≥ 20%

Clinician’s judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

Universal Prevention and Treatment Strategies

- Counsel all patients on fracture risk reduction
- Adequate calcium and vitamin D
- Weight-bearing exercise and muscular strengthening exercises
  - Consider avoidance of high-impact activities and activities that increase the risk of falling
  - Avoid forward or sideward trunk flexion because of increased load on spine
- Avoidance of smoking and excessive alcohol intake
- Fall prevention
  - Gait and balance training
  - Minimize/adjust dosages of drugs with sedative effects
  - Anchor rugs, minimize clutter, remove loose wires, etc.

IOM Recommendations and Response

<table>
<thead>
<tr>
<th>Organization</th>
<th>Calcium</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women age 51-70: 1200 mg/day</td>
<td>Women age 51-70: 600 IU/day</td>
<td></td>
</tr>
<tr>
<td>Men age 51-70: 1000 mg/day</td>
<td>Men age 51-70: 600 IU/day</td>
<td></td>
</tr>
<tr>
<td>Age &gt;70: 1200 mg/day</td>
<td>Age &gt;70: 800 IU/day</td>
<td></td>
</tr>
<tr>
<td>Upper limit of 4000 IU/day</td>
<td>Upper limit of 4000 IU/day</td>
<td></td>
</tr>
<tr>
<td>25(OH)D level of 20 ng/mL sufficient for ≥97.5% of healthy population</td>
<td>25(OH)D level of 20 ng/mL sufficient for ≥97.5% of healthy population</td>
<td></td>
</tr>
</tbody>
</table>

“The focus of all recommendations from the Food and Nutrition Board is for “normal healthy persons.” Those recommendations have no applicability for patients with disease or for physicians attempting to prevent disease in at-risk populations. That distinction is something clinicians need to know.”

**Recommended Calcium and Vitamin D Intake**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Calcium</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOF</td>
<td>• 1200 mg/day</td>
<td>• 800-1000 IU/day</td>
</tr>
<tr>
<td></td>
<td>• Caution against intake &gt;1500 mg/day</td>
<td>• Upper limit of 4000 IU/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Target 25(OH)D level is 30 ng/mL</td>
</tr>
<tr>
<td>AACE</td>
<td>• 1200 mg/day</td>
<td>• 1000-2000 IU/day</td>
</tr>
<tr>
<td></td>
<td>• Upper limit of 2000 IU/day</td>
<td>• Maintain 25(OH)D level of 30-50 ng/mL</td>
</tr>
</tbody>
</table>

Calcium intake includes dietary sources plus supplements; Encourage patients to obtain the bulk of their intake from dietary sources.

AACE – American Association of Clinical Endocrinologists; IOM – Institute of Medicine

---

**IOF Position Statement**

**Vitamin D Recommendations for Older Adults**

- Stratify into average risk and high risk groups
- High risk groups
  - Osteoporosis
  - Obese
  - Little effective sun
    - Little exposure
    - Dark skin
    - Northern latitude
    - Sunscreen use
  - Malabsorption
  - Anti-epileptics (increase metabolism)

International Osteoporosis Foundation Position Statement; Osteoporosis Int 2010;21:1151-4

---

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
IOF Position Statement
Vitamin D Recommendations for Older Adults

- Average risk adults (with little regular sun exposure)
  - No need to measure vitamin D
  - 800-1000 IU/day
  - This should bring their mean serum 25-OH vitamin D to the desired level of 30 ng/mL (75 nmol/L)

- High risk adults
  - Measure 25-OH vitamin D
  - Supplement to reach 30 ng/mL (75nmol/L)
  - Re-measure 25-OH vitamin D 3 months later to confirm repletion

- Vitamin D deficiency
  - Replete with higher dose daily or weekly vitamin D and recheck level after 12 weeks
  - Maintain with 50,000 IU every 2-4 weeks or 1000-2000 IU daily


Case Study TA

- You discuss prevention strategies with TA
- As an aside, TA mentions that she thinks she is about an inch shorter than she was several years ago.
- You review the chart and serial height measurements and find that she has lost 1” over the past 4 years.
- Physical examination is significant for mild kyphosis in her upper back.

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Case Study TA

- Which of the following would be **most helpful** for further assessment of skeletal health at this point?
  1. No additional testing needed
  2. Serum vitamin D level
  3. Spine imaging
  4. Refer to osteoporosis specialist

Vertebral Fractures

- Vertebral fracture is the most common osteoporotic fracture and indicates a high risk for future fractures.
- 26% of women with a vertebral fracture will fracture again within 1 year
- Only 1/3 of vertebral fractures are symptomatic and diagnosed at the time they occur; 2/3 are “silent”
- Red flags for vertebral fractures:
  - Height loss
  - Postural changes (kyphosis)
  - Worsening back pain
- Consider evaluation with lateral spine x-rays or vertebral fracture assessment (VFA)

Indications for Vertebral Imaging

- Women age 65 and older and men age 70 and older, if T-score is -1.5 or below.
- Women age 70 and men age 80 and older regardless of T-score.
- Postmenopausal women and men age 50 and older with a low trauma fracture.
- Postmenopausal women and men age 50-69, if there is historical height loss of 1½ inches or more, prospective height loss of 0.8 inches or more or recent or ongoing long-term glucocorticoid treatment.


Case Study TA - VFA

- Vertebral Fracture- This finding changes the diagnosis, assessment of fracture risk, and treatment decisions
- Clinical diagnosis of osteoporosis
- Meets NOF guidelines for pharmacologic therapy regardless of T-score

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Factors That Contribute to or Cause Osteoporosis

- In patients who are candidates for pharmacologic therapy, laboratory evaluation to identify coexisting conditions that may contribute to bone loss or interfere with therapy (or both) is warranted.
- Approximately 20%-30% women and 50% of men with osteoporosis have secondary factors.
- In one study of 173 “healthy,” osteoporotic women aged 46-87 evaluated for secondary osteoporosis, 44% were found to have underlying disease:
  - Vitamin D deficiency: 20%
  - Hypercalciuria: 10%
  - Malabsorption (incl celiac): 7%
  - Hyperparathyroidism: 3%

Factors That Contribute to or Cause Osteoporosis

<table>
<thead>
<tr>
<th>Endocrine Disorders</th>
<th>Hematologic &amp; Rheumatologic Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing syndrome</td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Rheumatic diseases (RA)</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Leukemia, lymphoma</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>SLE</td>
</tr>
<tr>
<td>Surgery (gastric bypass)</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>IBD</td>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Genetic Disorders</td>
<td>Medications</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Idiopathic hypercalciuria</td>
<td>Lithium</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td></td>
<td>PPIs</td>
</tr>
<tr>
<td></td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
</tr>
<tr>
<td></td>
<td>DMPA</td>
</tr>
<tr>
<td></td>
<td>Steroid therapy</td>
</tr>
<tr>
<td></td>
<td>GnRH agonists</td>
</tr>
<tr>
<td></td>
<td>TZDs</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
<td>Alcoholism</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Transplantation</td>
</tr>
<tr>
<td></td>
<td>Emphysema</td>
</tr>
</tbody>
</table>

Evaluation for Secondary Osteoporosis

- Complete blood cell count (CBC)
- Comprehensive metabolic panel (CMP), including phosphorus
- 24 hour urine calcium (identifies both malabsorption and hypercalciuria)
- 25-OH vitamin D
- Testosterone (in men)

Consider further testing when
- Medical history or physical findings suggest underlying causes or screening labs reveal abnormalities
- Osteoporosis is unexpected or unexpectedly severe
- A compliant patient has bone loss on therapy
- The patient who just doesn’t fit

Case Study TA

- TA had the following laboratory tests which were normal:
  - CBC
  - CMP
  - 25-OH vitamin D
  - 24-hour urine calcium
  - TSH and free T4

Which pharmacologic agent would you choose?
FDA Approved Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Indication</th>
<th>Dose and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>PMO prevention</td>
<td>Multiple formulations and regimens; oral, topical, cyclic, continuous</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>PMO prevention and treatment</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>PMO treatment in women ≥5 years postmenopause</td>
<td>200 IU intranasally once daily (alternate nostrils) 100 IU SQ every other day</td>
</tr>
<tr>
<td>Alendronate</td>
<td>PMO prevention</td>
<td>Prevention: 5 mg PO daily or 35 mg PO weekly</td>
</tr>
<tr>
<td></td>
<td>PMO, male, GIOP treatment</td>
<td>Treatment 10 mg PO daily or 70 mg PO weekly</td>
</tr>
<tr>
<td>Risedronate</td>
<td>PMO, GIOP prevention</td>
<td>5 mg PO daily; 35 mg PO weekly; 150 mg PO monthly Delayed release/Enteric Coated form – 35 mg PO weekly after breakfast</td>
</tr>
<tr>
<td></td>
<td>PMO, male, GIOP treatment</td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td>PMO prevention and treatment</td>
<td>150 mg PO monthly 3 mg IV every 3 months</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>PMO, GIOP prevention</td>
<td>Prevention: 5 mg IV every 2nd year Treatment: 5 mg IV once yearly</td>
</tr>
<tr>
<td></td>
<td>PMO, male, GIOP treatment</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>PMO treatment</td>
<td>60 mg SQ every 6 months</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>PMO, male, GIOP treatment</td>
<td>20 mcg SQ daily (for maximum 2 years lifetime)</td>
</tr>
</tbody>
</table>

PMO = Post menopausal; GIOP – Glucocorticoid-induced osteoporosis
Data from prescribing information for individual medications

Fracture Risk Reduction in RCTs in Women with Postmenopausal Osteoporosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vertebral Fracture</th>
<th>Hip Fx</th>
<th>Nonvertebral Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin (Miacalcin®, Calcimar®)</td>
<td>✓</td>
<td></td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Raloxifene (Evista®)</td>
<td>✓</td>
<td></td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate (Boniva®)</td>
<td>✓</td>
<td></td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Risedronate (Actonel®, Atelvia®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronic acid (Reclast®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Denosumab (Prolia®)</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>✓</td>
<td></td>
<td>No effect demonstrated</td>
</tr>
</tbody>
</table>

RCT = randomized placebo-controlled clinical trial

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
## Medication Considerations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Contraindications/Warnings</th>
<th>Other Considerations</th>
</tr>
</thead>
</table>
| Raloxifene | • Increased risk of venous thromboembolism and death from stroke  
             • Contraindicated in patients with VTE                                            | Reduction of invasive breast cancer risk in postmenopausal women with osteoporosis and women at high risk for breast cancer |
| Calcitonin | Rhinitis, nasal irritation, back pain                                                       | May provide an analgesic effect in patients with painful vertebral fractures           |
| Alendronate| • Uncorrected hypocalcemia  
             • Inability to stand or sit upright for at least 30 minutes  
             • May cause GI disorders                                                   | Avoid in patients with creatinine clearance < 35 mL/min                                 |
| Risedronate| • Uncorrected hypocalcemia  
             • Inability to stand or sit upright for at least 30 minutes  
             • May cause GI disorders                                                   | Avoid in patients with creatinine clearance < 30 mL/min                                 |
| Ibandronate| • Uncorrected hypocalcemia  
             • Inability to stand or sit upright for at least 60 minutes  
             • May cause GI disorders (oral route)                                       | Avoid in patients with creatinine clearance < 30 mL/min                                 |
| Zoledronic acid | • Contraindicated in hypocalcemia, creatinine clearance < 35 mL/min  
                • Acute phase reaction                                                      | • Acute renal impairment has occurred                                              |
| Denosumab  | • Uncorrected hypocalcemia  
             • May cause serious skin infections and dermatologic reactions (dermatitis, rash, eczema) | • Treatment of postmenopausal women at high risk of fracture defined as having a history of osteoporotic fracture, having multiple risk factors for fracture, or having failed or been intolerant of other osteoporosis therapies  
             • 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  
             • No dose adjustment necessary in renal impairment (monitor Ca++, Mg++, Phos) |
| Teriparatide| • Black-box warning: Increased incidence of osteosarcoma in rats  
             • Contraindicated in patients with increased baseline risk of osteosarcoma (Paget’s disease, prior radiation to the skeleton, history of skeletal malignancy, young adults with open epiphyses), hypercalcemia | • Treatment of patients at high risk for fracture  
             • Limited to 2 years total lifetime exposure                                       |

Data from prescribing information for individual medications; 2. Lyles KW et al. N Engl J Med 2007;357:1799-1809

**Closing Performance Gaps in the Diagnosis and Management of Osteoporosis**
Choosing an Osteoporosis Therapy

AACE recommends the following:

- Use alendronate, risedronate, zoledronic acid or denosumab as the first line of therapy
- Use ibandronate as a second-line agent
- Use raloxifene as a second- or third-line agent
- Use calcitonin as the last line of therapy
- Use teriparatide for patients with very high fracture risk or patients in whom bisphosphonate therapy has failed
- Advise against the use of combination therapy

Watts, NB et al. AACE Postmenopausal Osteoporosis Guidelines; Endocr Pract. 2010;16(Suppl 3)

Individualizing Osteoporosis Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Potential Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>• Older patients</td>
</tr>
<tr>
<td></td>
<td>• Patients at high risk for fracture/hip fracture</td>
</tr>
<tr>
<td></td>
<td>• IV for those who cannot tolerate oral agents</td>
</tr>
<tr>
<td></td>
<td>• IV for easier dosing regimen or those with compliance issues, nursing home patients (but consider/evaluate renal function)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>• Patients at high risk for fracture/hip fracture</td>
</tr>
<tr>
<td></td>
<td>• Patients who cannot tolerate oral bisphosphonates</td>
</tr>
<tr>
<td></td>
<td>• Patients with decreased kidney function</td>
</tr>
<tr>
<td></td>
<td>• Nursing home patients</td>
</tr>
<tr>
<td></td>
<td>• Desire for easier dosing regimen or those with compliance issues</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>• Younger woman at low risk for hip and nonvertebral fractures</td>
</tr>
<tr>
<td></td>
<td>• Postmenopausal woman who cannot tolerate other therapies</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>• Patients at high risk for fracture</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>• Unable or unwilling to take other agents</td>
</tr>
</tbody>
</table>


Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
## Monitoring Response to Therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>BMD</th>
<th>BTMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSC with 95% CI</td>
<td>~3%-4%</td>
<td>~30%-60%</td>
</tr>
<tr>
<td>Time to reach LSC change</td>
<td>1-2 years</td>
<td>Days to ~ 3 months (depends on drug)</td>
</tr>
<tr>
<td><strong>Therapeutic goal</strong></td>
<td><strong>Stability or increase</strong></td>
<td><strong>Significant decrease with antiresorptive agent and increase with anabolic agent</strong></td>
</tr>
</tbody>
</table>

- **LSC** = least significant change: the magnitude of change required to be confident that the measured change reflects a true biologic change rather than technical variability in measurement.
- **LSC** = precision error x 2.77 for a 95% confidence interval.
- **BMD**= bone mineral density; **BTMs**= bone turnover markers; **CI** = confidence interval.

---

## Markers of Bone Turnover

<table>
<thead>
<tr>
<th>Bone Marker</th>
<th>Origin</th>
<th>Measured in:</th>
<th>Circadian Rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone Resorption Markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-telopeptide (NTX)</td>
<td>Degradation of type I collagen</td>
<td>Urine or serum</td>
<td>yes</td>
</tr>
<tr>
<td>C-telopeptide (CTX)</td>
<td>Degradation of type I collagen</td>
<td>Urine or serum</td>
<td>yes</td>
</tr>
<tr>
<td>Deoxypyridinoline (DPD)</td>
<td>Degradation of type I collagen</td>
<td>Urine, as total or free</td>
<td>yes</td>
</tr>
<tr>
<td>Pyridinoline (PYD)</td>
<td>Degradation of type I collagen</td>
<td>Urine, as total or free</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Bone Formation Markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteocalcin (OC)</td>
<td>Osteoblasts</td>
<td>Urine or serum</td>
<td>yes</td>
</tr>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>Enzyme in many tissues, including bone</td>
<td>Serum; ~50% of bone origin</td>
<td>very small</td>
</tr>
<tr>
<td>Bone Specific Alk Phos (BAP)</td>
<td>Enzyme on outer surface of osteoblasts</td>
<td>Serum; ~20% cross reactivity with liver form</td>
<td>very small</td>
</tr>
<tr>
<td>Procollagen of type 1 N-propeptide (P1NP)</td>
<td>Type I collagen produced by osteoblasts</td>
<td>Serum; mostly specific to bone</td>
<td>small</td>
</tr>
</tbody>
</table>

---

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
# US Clinical Practice Guidelines for BTMs

<table>
<thead>
<tr>
<th>Source</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Osteoporosis Foundation 2008, updated 2013</td>
<td><strong>Fracture prediction:</strong> BTMs may be measured to assess fracture risk in untreated patients.  <strong>Bone loss:</strong> BTMs may predict bone loss.  <strong>Monitoring therapy:</strong> Suppression of BTMs 3-6 months after starting antiresorptive osteoporosis therapy and increases in BTMs 1-3 months after starting osteoanabolic therapy have been predictive of greater BMD responses in large clinical trials.</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists 2010</td>
<td><strong>Fracture prediction:</strong> BTMs may be useful for assessing fracture risk when the finding of elevated levels would influence the decision to begin therapy.  <strong>Bone loss:</strong> High levels of BTMs have been shown to predict rapid rates of bone loss  <strong>Monitoring therapy:</strong> BTMs can be used as early indicators of response to antiresorptive or osteoanabolic therapy.</td>
</tr>
<tr>
<td>North American Menopause Society 2010</td>
<td><strong>Fracture prediction:</strong> BTMs have varying ability to predict fracture risk in clinical trials  <strong>Monitoring therapy:</strong> BTMs have varying value in predicting response to therapy in individual patients, but may show a response to therapy earlier (2-3 months) than BMD (1-3 years).</td>
</tr>
</tbody>
</table>

## Factors Affecting BTMs

- **Biological variability**
  - Non-modifiable factors
    - Age, gender, menopausal status, fractures, coexisting diseases (DM, renal, liver and thyroid disease), drugs, immobility
  - Modifiable factors
    - Dietary and calcium intake, time of day (circadian variability), exercise
  - Timing of sample to reduce variability
    - Serum: morning (before 9 am) after an overnight fast
    - Urine: first or second morning void, after an overnight fast
- **Analytical variability**
  - Specimen processing, assay characteristics, between laboratory variability - absence of uniform standardization
- **Looking ahead and expanding use**
  - Adoption of international reference standards; improved precision
  - Research to establish cut points to distinguish “suboptimal” from “adequate” responders
  - Greater clinical experience and data

---

### Monitoring Response to Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Test</th>
<th>Monitoring Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMD</strong></td>
<td></td>
</tr>
<tr>
<td>Normal baseline BMD, T-score ≥ -1.0</td>
<td>Every 3-5 years</td>
</tr>
<tr>
<td><strong>Every 3-5 years</strong></td>
<td>If well above normal, no further testing may be needed</td>
</tr>
</tbody>
</table>

| Patients in an osteoporosis prevention program/ low bone mass | Every 1-2 years until BMD stability is attained |
|                                                              | After BMD stabilization, every 2-3 years      |

| Patients receiving osteoporosis treatment                   | Every 1-2 years until BMD is stable                                      |
|                                                              | Once stable, every 2 years                                                    |
|                                                              | May be reduced further with persistent BMD stability                         |

| **BTMs**                                                  | 3-6 months after initiating treatment for osteoporosis                        |


### Case Study TA

TA was started on an antiresorptive agent as well as supplemental calcium 500 mg twice daily and vitamin D 1000 IU daily

- Follow-up DXA at 2 years: Report of BMD loss despite treatment with an antiresorptive
- Patient is told she is a treatment failure
- How do you evaluate and counsel TA?

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
What is Treatment Failure?
Defining Suboptimal Response

- Suboptimal response is defined as
  - Fracture
  - Decrease in BMD more than the least significant change
  - BTMs that do not decrease at least 50% from baseline levels during antiresorptive therapy or to premenopausal levels
- Having a fracture, however, does not prove drug failure
  - Fracture prevention medications reduce, but do not eliminate the risk of fractures
  - Treatment reduces the risk of multiple fractures to a greater magnitude than the risk of the first incident fracture in clinical trials


Report of BMD Loss on DXA

- Validate that the DXA has been acquired, analyzed, and interpreted correctly – look at the images
  - Technical errors can be caused by:
    - Changes in patient positioning
    - Measuring a different area of bone (region of interest)
    - New artifacts on the scan
    - Using a different densitometer
- Consider checking BTM to see if patient is truly getting an effect from medication
- Assess adequacy of calcium and vitamin D intake
- Investigate secondary causes, new illnesses
- Assess compliance, persistence, and absorption
  - Compliance – the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen
  - Persistence – the duration of time from initiation to discontinuation of therapy


Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Report of BMD Loss on DXA

- Validate that the DXA has been acquired, analyzed, and interpreted correctly – look at the images
- Consider checking BTM to see if patient is truly getting an effect from medication
- Assess adequacy of calcium and vitamin D intake
- Investigate secondary causes, new illnesses
- Assess compliance, persistence, and absorption
  - Compliance – the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen
  - Persistence – the duration of time from initiation to discontinuation of therapy
- If all are noncontributory, consider changing or adding agent


Clinical Consequences of Poor Compliance and Persistence

Probability of Fracture in Bisphosphonate-Treated Patients After 24 Months

Virtually no treatment benefit was obtained when the MPR was <50%

100% compliance is associated with a fracture rate of ~8%

21% reduction in overall fracture risk in refill-compliant patients (P<0.001)

Data on 36,537 patients from 2 claims databases.

Medication Possession Ratio (MPR) is a measure of refill compliance using the percentage of time a medication was available to the patient.


Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Strategies for Improving Compliance and Persistence

- Provide targeted patient education
  - Fracture risk, consequences of fracture, benefits and risks of treatment
  - Supplement with written information, handouts
  - Review FRAX assessment

- Shared decision making
  - Consider all available clinical information
  - Negotiate a treatment plan that is medically reasonable and acceptable to the patient
  - Ensure that patient understands treatment instructions – specific metrics and directions for exercise, vitamin use, and medications

- Follow-up
  - Regular contact with HCP and staff – visits, emails, phone calls
  - Assess tolerance, compliance, persistence – uncover causes you can help patients overcome
  - Monitor for therapeutic effect – BMD, BTMs

Addressing Gaps in Osteoporosis Care

- Acknowledging the gap
  - Numerous studies show a failure to diagnose and treat osteoporosis, even in patients who have sustained a fracture
  - The gap between what is known about bone health and the application of that knowledge to patient care remains large
  - 2003 NCQA/HEDIS data:
    - Myocardial infarction: 93% receive beta-blockers
    - Breast cancer screening: 74% of eligible patients
    - Colorectal cancer screening: 49.5% of eligible patients
    - Osteoporotic fracture: 18% receive osteoporosis management

Addressing Gaps in Osteoporosis Care

- Critical issues
  - Change health care provider, patient, and health systems behavior
  - Identify, evaluate, and initiate evidence-based care for osteoporosis and low bone density after a fragility fracture
  - Primary fracture prevention


Multidisciplinary Approach to Care: Improving Collaboration

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Fracture Liaison Service (FLS) Model of Care

A coordinated preventive care model which operates under the supervision of bone health specialists and collaborates with the patient’s primary care physician

- FLS programs coordinate post-fracture care through an FLS coordinator (generally a nurse or other allied health professional)
- Patients with recent fractures are tracked via a population registry
- Processes and timelines established for patient assessment and follow-up
- FLS programs
  - recognize that patients who have fractured are at highest risk of future fractures.
  - have greatly reduced the number of fractures and have achieved cost savings by identifying and appropriately treating post-fracture patients

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Controversies in Osteoporosis Care

- **Optimal duration of therapy**
  - Drug holiday is a concept that applies only to bisphosphonates
    - Unique pharmacokinetics
    - Long retention time in bone
  - "Holiday" suggests that treatment is restarted at some point
  - Benefits and risks of both continuation and discontinuation must be considered

- **High profile possible adverse effects**
  - Osteonecrosis of the jaw
  - Atypical femur fractures

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Effects of Longer-term Treatment and Discontinuation

- **FLEX Trial**
  - Compared the effects of discontinuing alendronate treatment after 5 years vs. continuing for 10 years
  - Switching to placebo for 5 years resulted in declines in BMD and increases in BTMs, but not to pretreatment levels
  - Incidence of all clinical fractures and nonvertebral fractures similar in both groups, but lower risk of clinical vertebral fractures in those who continued therapy
  - Post hoc analyses suggested that continuation was associated with lower risk of nonvertebral fractures in women with femoral neck T-score ≤ -2.5

- **VERT-NA Extension Study**
  - After treatment with risedronate for 3 years and discontinuation for 1 year:
    - Spine and hip BMD decreased significantly and BTMs increased to placebo levels
    - The risk of new vertebral fractures was reduced by 46% in the former risedronate users compared with the former placebo patients in the year off treatment

Effects of Longer-term Treatment and Discontinuation

- **HORIZON Pivotal Fracture Trial Extension Study**
  - Compared the effects of discontinuing zoledronic acid treatment after 3 years vs. continuing for an additional 3 years
  - Femoral neck BMD remained constant in the continuation group and showed a small decrease in the discontinuation group
  - Significantly fewer morphometric vertebral fractures occurred in the continuation group than in the discontinuation group; no difference in nonvertebral, clinical vertebral, or hip fractures.

Black, DM et al. J Bone Miner Res. 2012;27(2)
Bisphosphonate Drug Holidays

- Duration of treatment should be based on:
  - Patient’s risk of fracture
  - Patient’s response to therapy
  - Pharmacokinetics of the agent used
  - Patient preferences (shared decision making)
- At the 5 year treatment point, reassess need for continuing treatment based on fracture history, BMD, clinical risk factors
  - For those at low or moderate risk, stopping therapy is a possibility
  - For those at higher risk, opinion varies
    - Consider continuing therapy
    - Consider drug holiday
    - Consider alternative medication during bisphosphonate holiday
- Ending drug holiday
  - Consider fractures, BMD, BTMs, FRAX


Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
High Profile Adverse Events

- Osteonecrosis of the jaw (ONJ)
  - Risk factors:
    - Cancer and anti-cancer therapy
    - Poor oral hygiene
  - Prevalence of 1/10,000 to ≤ 1/100,000 patient-years in patients treated for osteoporosis

- Atypical femur fractures
  - Associated with bisphosphonates- low absolute risk
  - Causality not established
  - Pathophysiology unknown- low bone turnover leading to impaired remodeling and accumulation of microdamage?

**Risk-benefit ratio for use of bisphosphonates for fracture reduction in osteoporotic patients is favorable**


ASBMR Task Force Report on Atypical Femoral Fractures

- 310 reported cases
- Age range 36-92
- Mostly women
- Duration of bisphosphonate treatment 1.3-17 years, median duration 7 years

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
## ASBMR Case Definition

### Major Features
- Located anywhere from just distal to the lesser trochanter to just proximal to the diaphyseal flare
- Minimal or no trauma
- Transverse or short oblique orientation
- Non-comminuted
- May be complete or incomplete
  - Completed fractures extend through both cortices and may be associated with a medial break
  - Incomplete fractures involve only the lateral cortex

### Minor Features
- Generalized increase in cortical thickness of the diaphysis
- Localized periosteal reaction to the lateral cortex — “beaking” or “flaring”
- Prodrome of dull or aching pain in the groin or thigh (70%)
- Bilateral symptoms or fractures (28%)
- Delayed healing (26%)
- Comorbid conditions (vitamin D deficiency, RA)
- Concomitant drugs (bisphosphonates, glucocorticoids, estrogen, SERMS, PPIs)

---

## Benefit-Risk Estimates

- If you treat 1000 women with BPs for 5 years
  - Fracture risk similar to Fracture Intervention Trial (FIT)
  - Femoral neck T-score ≤-1.5 +/- prevalent vertebral fracture
- You would prevent 35-50 non-vertebral fractures
- You would prevent 50-115 vertebral fractures
- You might cause 5 atypical femur fractures (AFF)
- The risk of an AFF is low compared to the risk of common osteoporotic fractures

---

Closing Performance Gaps in the Diagnosis and Management of Osteoporosis
Summary

- Osteoporosis is a common disease with serious clinical consequences due to fractures
- Clinical tools to diagnosis osteoporosis, assess fracture risk, and identify patients for pharmacological therapy are easily available
- Osteoporosis can be prevented and treated
- All patients should have an adequate intake of calcium and vitamin D, with regular weight-bearing exercise
- Pharmacological agents can reduce fracture risk
- Treatment decisions for each patient should be individualized considering the balance of expected benefit and potential risks