Osteoporosis Update

Kristine E. Ensrud, MD, MPH
Professor, Department of Medicine and Division of Epidemiology
University of Minnesota
Staff Physician, General Internal Medicine
Core Investigator, Center for Chronic Disease Outcomes Research
Minneapolis VA Health Care System
Disclosure Information

• I have the following financial relationships to disclose:
  – Consultant on a Data Monitoring Committee for Merck Sharpe & Dohme

• I will not discuss off label use and/or investigational drug use in my presentation
Controversies & FAQ in Osteoporosis

• Who to screen among younger postmenopausal women?
• How to define osteoporosis in men?
• Who to screen among older men?
• How often to screen and when to stop screening?
• Should patients with osteopenia receive drug treatment?
• How long to treat with bisphosphonates?
Who to Screen: Women Age 50-64

• No data available on benefit of drug treatment beginning at age 50-64 and continuing over 3-4 decades

• Despite rapid rates of bone loss during menopausal transition, fracture risk for any given BMD much lower in younger vs. older women
5-Yr Probability of Fracture in Postmenopausal Women According to Baseline Age

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Clinical Vertebral Fracture, %</th>
<th>Hip Fracture, %</th>
<th>Other Fractures, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-54</td>
<td>0.3</td>
<td>0.0</td>
<td>1.7</td>
</tr>
<tr>
<td>55-59</td>
<td>0.5</td>
<td>0.2</td>
<td>2.1</td>
</tr>
<tr>
<td>60-64</td>
<td>1.0</td>
<td>0.2</td>
<td>3.1</td>
</tr>
<tr>
<td>65-69</td>
<td>1.6</td>
<td>0.8</td>
<td>4.3</td>
</tr>
<tr>
<td>70-74</td>
<td>2.5</td>
<td>1.6</td>
<td>6.3</td>
</tr>
<tr>
<td>75-79</td>
<td>3.8</td>
<td>4.0</td>
<td>7.6</td>
</tr>
<tr>
<td>80-84</td>
<td>3.8</td>
<td>6.9</td>
<td>10.9</td>
</tr>
<tr>
<td>85-89</td>
<td>3.8</td>
<td>16.7</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Doherty DA et al. Osteoporos Int 2001; 12:16-23
Who to Screen: Women Age 50-64

- Early drug treatment leads to prolonged duration of use-increased risk of net harms
- Overtreating younger women when fracture risk low leaves them with fewer options in their 70s, when hip fracture risk increases exponentially
Who to Screen: Women Age 50-64

- Risk assessment to select younger postmenopausal women for screening uncertain
- Current clinical guidelines encourage BMD testing in younger women with risk factors for fracture, but no agreement regarding which factors to choose
- Other approaches include use of weight alone (e.g. <70 kg), use of age and weight (e.g. OST) and use of fracture risk assessment tool (e.g. FRAX)
- USPSTF (2011) recommended screening women age 50-64 at increased fracture risk as defined by FRAX cutpoint
Osteoporosis Self-Assessment Tool (OST)

• Simple risk calculator designed to identify individuals more likely to have low BMD

• OST score = [wt (kg)-age (yrs)] X 0.2

• OST score <2 proposed as cutoff to select younger postmenopausal women for BMD testing

USPSTF Approach to Select Women 50-64 for BMD Testing

• Select women aged 50-64 yrs for BMD testing who have $\geq 9.3\%$ 10-yr probability of major osteoporotic fracture as calculated by FRAX tool

• Rationale for threshold: 65 year old white woman, average height and weight (5 ft 5 in; 150 lbs), no additional risk factors

## Comparison of OST vs. USPSTF Approach in Women Age 50-64

- 36% (OST<2) vs. 15% (USPSTF approach, FRAX >9.3%) of women selected for BMD testing

### Table: Identification of Osteoporosis (Femoral Neck BMD T-score ≤ −2.5)

<table>
<thead>
<tr>
<th>Untreated Participants (n=2163)</th>
<th>Identification of Osteoporosis (Femoral Neck BMD T-score ≤ −2.5)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>OST &lt;2 (tool based on age &amp; weight)</td>
<td>79</td>
<td>70</td>
</tr>
<tr>
<td>USPSTF (FRAX ≤9.3)</td>
<td>33</td>
<td>86</td>
</tr>
</tbody>
</table>

Who to Screen: Women Aged 50-64

• Complex risk assessment tools do not perform any better than simple tools in selecting younger postmenopausal women for BMD testing

• Despite accelerated bone loss associated with menopause, rates of major fracture events are LOW

• “Need a baseline” is not strong rationale for ordering BMD test

• IF drug treatment will be initiated for T-score ≤ −2.5, consider use of OST to determine if BMD testing is warranted
How to Define Osteoporosis in Men

• BMD cutoff value in men to identify osteoporosis has been controversial (male specific vs. female specific cutoff value?)

• At femoral neck:
  – 0.592 g/cm$^2$ is male specific T score of $-2.5$
  – 0.558 g/cm$^2$ is female specific T score of $-2.5$
Proportion of Older Men Identified with Osteoporosis

Ensrud KE et al. BMJ 2014; 349:g4120
How to Define Osteoporosis in Men

• Similar relative risk of fracture per unit ↓ in hip BMD in men and women.

• For any given absolute value of hip BMD, age-adjusted hip fracture rates similar in men and women.

• Diagnosis of osteoporosis in men should be based on same BMD cutoff value used in women, female specific T score −2.5 or below.
Who to Screen: Older Men

- No RCT in men has demonstrated benefit of drug treatment in reducing clinical fractures
- BMD testing proposed in older men to prevent fractures largely because it is accepted strategy in older women
Who to Screen: Older Men

- Some guidelines recommend BMD testing in all men \( \geq 70 \) yrs and in men 50-69 yrs with clinical risk factors.
- ACP (2007): BMD testing in men at increased risk of osteoporosis who are candidates for drug treatment.
- USPSTF (2011): No recommendation, but men most likely to benefit from screening have 10-year probability of major osteoporotic fracture \( \geq 9.3\% \).
- Other potential approaches include use of wt alone (BMI <20 to 25), age and wt (OST).

Comparison of OST vs. USPSTF Approach in Men Aged ≥70

- 65% (OST) vs. 45% (USPSTF) selected for BMD testing

<table>
<thead>
<tr>
<th>Untreated Participants (n=4053)</th>
<th>Identification of Osteoporosis (T-score ≤ −2.5 at Hip or Spine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
</tr>
<tr>
<td>OST (&lt;2) (tool based on age &amp; weight)</td>
<td>83 (77-87)</td>
</tr>
<tr>
<td>USPSTF (FRAX ≤9.3)</td>
<td>59 (52-66)</td>
</tr>
</tbody>
</table>

- AUC over full range of tool: 0.68 for OST vs. 0.62 for FRAX

Who to Screen: Older Men

- Recommendations for universal screening of all men age ≥70 may be premature
- OST performs better than more complex FRAX-based strategy to select older men for BMD testing
- Additional research on development and validation of risk assessment tools is warranted
How Often to Screen Older Adults

- Bone loss accelerates with advancing age in both sexes
- Paucity of data to guide decisions about the interval between BMD tests
How Often Should Older Women Be Screened?

Unadjusted Cumulative Incidence of Osteoporosis According to Baseline T-Score Range

How Often Should Older Men Be Screened?

Time for 10% of Men without Osteoporosis to Transition to Osteoporosis

<table>
<thead>
<tr>
<th>Baseline T-score range</th>
<th>Osteoporosis events, n (%)</th>
<th>Time interval for 10% of ppts to develop osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted years (95% CI)</td>
</tr>
<tr>
<td>&gt; −1.50 (normal BMD or mild osteopenia)</td>
<td>9/4203 (0.21)</td>
<td>−</td>
</tr>
<tr>
<td>− 1.50 to − 1.99 (moderate osteopenia)</td>
<td>35/680 (5.15)</td>
<td>8.57 (6.67, 10.99)</td>
</tr>
<tr>
<td>− 2.00 to − 2.49 (advanced osteopenia)</td>
<td>73/352 (20.74)</td>
<td>2.59 (2.03, 3.30)</td>
</tr>
</tbody>
</table>

How Often to Screen Older Adults

- Baseline BMD is MAJOR determinant of BMD testing interval in older adults without osteoporosis at initial assessment
- Lower the BMD at initial assessment, shorter the rescreening interval
When to Stop Screening?

• Age to stop or decrease use of BMD testing has not been examined
• Women with high BMD T-scores (e.g. > −1.5) have very low risk of fracture before estimated time to death and benefit less from rescreening
• Women with low BMD T-scores (e.g. between −2.0 and −2.5) have high risk of fracture before estimated time to death and benefit more from rescreening
• Age to stop may be lower in men vs. women due to higher competing risk of mortality
Who to Treat: RCT Evidence for Drug Treatment to Prevent Fracture (Fx)

- In postmenopausal women with BMD T-score ≤ −2.5 or existing radiographic vertebral fx:
  - Some drug treatments (bisphosphonates and denosumab) lower risk of clinical fx incl hip fx
  - Several drug treatments lower risk of new radiographic vertebral fx

- IV zoledronic acid lowers risk of clinical fx among patients with recent hip fx
Expanding Indications for Drug Treatment to Prevent Fracture

• Some US guidelines (NOF, Endocrine Society) endorse use of FRAX thresholds to aid in decision whether or not to initiate drug treatment in adults aged ≥50 yrs with osteopenia (T-score between −1.0 and −2.5)
  – 10 yr hip fx probability ≥3%
  – 10 yr major osteoporotic fx (MOF) probability ≥20%

Cosman F et al. Osteoporos Int 2014; 25:2359-2381
Movement to Broaden Criteria by Which Osteoporosis is Diagnosed

- National Bone Alliance 2014 Position Paper
  - “Postmenopausal women and men ≥50 yrs should be diagnosed with osteoporosis if they have elevated risk for future fractures”
  - Increased fracture risk defined as 10 yr hip fx probability ≥3% or 10 yr MOF probability ≥10%

Siris ES et al. Osteoporos Int 2014; 25:1439-1443
Proportion of Older Adults Identified as Candidates for Drug Treatment to Prevent Fracture

Proportion of Women Identified as Candidates for Drug Treatment to Prevent Fracture

Proportion of Men Identified as Candidates for Drug Treatment to Prevent Fracture

## Effect of Alendronate Treatment on Risk of Clinical Fractures According to BMD T-score

<table>
<thead>
<tr>
<th>BMD T-score</th>
<th>Placebo, n/N (%)</th>
<th>Alendronate, n/N (%)</th>
<th>RH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; −2.5</td>
<td>159/812 (19.6)</td>
<td>107/819 (13.1)</td>
<td>0.64 (0.50-0.82)</td>
</tr>
<tr>
<td>−2.5 to −2.0</td>
<td>87/710 (12.3)</td>
<td>92/726 (12.7)</td>
<td>1.03 (0.77-1.39)</td>
</tr>
<tr>
<td>−2.0 to −1.6</td>
<td>66/696 (9.5)</td>
<td>73/669 (10.9)</td>
<td>1.14 (0.82-1.60)</td>
</tr>
</tbody>
</table>

Cummings SR et al. JAMA 1998; 280:2077-2082
Relative Hazard of Clinical Fracture According to Treatment and BMD

![Graph showing relative hazard of clinical fracture against treatment and BMD.]

Relative Hazard

- Favors Treatment
- Favors Placebo

Alendronate (FOSIT)
Ibandronate
Risedronate
Estrogen
Bazedoxifene
Raloxifene
PTH (1-84)
Denosumab

Used with permission, Black DM
American Society for Bone and Mineral Research 2012 Annual Meeting
What about Patients with BMD T-score > −2.5?

• Effectiveness of drug treatment in reducing clinical fxs among middle-aged and older adults without prevalent vertebral fxs and T-score > −2.5 unproven

• Adoption of NOF FRAX treatment thresholds labels a substantial proportion of older adults with a problem that might not benefit from drug treatment

• RCT are warranted to determine if drug treatment is efficacious among patients with T scores > −2.5 selected on the basis of high fracture risk
How Long to Treat with Bisphosphonates?

• Potential long-term safety issues:
  – ONJ, atypical femoral fractures (AFF)

• ONJ incidence very low (<1 case per 10,000 patient treatment years)

• AFF are rare events in the general population (3 AFF vs. 103 hip fxs per 10,000 person-yrs)

• Concerns of many women regarding these adverse effects have become a barrier to treatment initiation and adherence
Association of Bisphosphonate Use with AFF

Effect of Stopping vs. Continuing Alendronate Treatment on Fracture Risk

- Among older women who used alendronate for 5 yrs, those randomized to placebo vs. those randomized to alendronate for additional 5 yrs had
  - Similar rate of nonvertebral fx and new radiographic vertebral fx
  - Higher rate of clinical vertebral fx

Effect of Stopping vs. Continuing Zoledronic Acid Treatment on Fracture Risk

• Among older women who received zoledronic acid annually for 3 yrs, those randomized to placebo vs. those randomized to zoledronic acid for additional 3 yrs had
  – Similar rate of nonvertebral fx and clinical vertebral fx
  – Higher rate of new radiographic vertebral fx

Fracture Risk Prediction After Bisphosphonate Discontinuation

• Older age and lower hip BMD (BMD T score \(\leq -2.3\)) at time of discontinuation of alendronate were associated with higher risk of clinical fractures after discontinuation

• Follow-up BMD measurements 1 yr after alendronate discontinuation and bone turnover markers 1-2 yrs after discontinuation were not associated with fracture risk after discontinuation

Bauer DC et al. JAMA Intern Med 2014; 174:1126-1134
How Long to Treat with Bisphosphonates?

• Drug holiday should be considered in women after 3-5 yrs of oral bisphosphonates or 2-3 yrs of IV bisphosphonates

• Women with low BMD (e.g. T-scores ≤ −2.5) at this time point or those who experienced major osteoporotic fracture on treatment should consider continuing treatment

• No data to support periodic monitoring of BMD or bone turnover markers during holiday
How Long to Treat with Bisphosphonates?

• Among women on drug holiday, reassess BMD and fracture risk 3-5 yrs after discontinuation
• Further research warranted to quantify fracture risk after discontinuation and to determine best practice strategy for patients who remain at high fracture risk after discontinuation
"I think we can rule out osteoporosis."