Learning Objectives:

- Describe the pathophysiology of osteoporosis and recognize its risk factors and methods for diagnosis
- Understand the implications of patient compliance with current osteoporosis treatment options
- Understand the novel mechanism of action of denosumab (Prolia™) and review the clinical evidence to support its use in the treatment of osteoporosis
- Review available literature on the risks associated with long-term antiresorptive therapy
Osteoporosis

- A skeletal disorder characterized by compromised bone strength which predisposes an individual to an increased risk of fracture\(^1,2\)
  - Bone strength is a combination of both bone density and bone quality
  - Bone density is determined by peak bone mass and subsequent of bone loss
  - Bone quality refers to bone architecture, turnover, mineralization, and accumulation of damage
- There is currently no accurate measure of overall bone strength\(^2\)
- The World Health Organization (WHO) defines osteoporosis as a bone mineral density value more than 2.5 standard deviations below the mean for young, healthy, white women\(^2,3\)

Epidemiology\(^1-3\)

- 10 million individuals in the US with osteoporosis
- An estimated 34 million individuals have osteopenia or low bone mass
- Affects both men and women across all ethnic groups, although not to the same degree

![Figure 1. Projected Prevalence of Osteoporosis and/or Low Bone Mass of the Hip in Women, Men, and Both Sexes, 50 Years of Age or Older\(^3\)](image)

![Figure 2. Mean Bone Mineral Density of the Femoral Neck by Age for U.S. Men and Women of Different Racial/Ethnic Groups (1998)\(^3\)](image)
Fractures: Incidence, Morbidity and Mortality

- An estimated 1.5 million osteoporotic fractures occur annually, leading to more than 500,000 hospitalizations, over 800,000 emergency department visits, over 2.6 million physician visits, and the placement of approximately 180,000 individuals into nursing homes for either short-term rehabilitation or long-term stay.
- Estimates suggest 1 in 2 women and up to 1 in 4 men over the age of 50 will suffer a fracture in his or her remaining lifetime.

Table 1. Fracture Characteristics

<table>
<thead>
<tr>
<th>Hip Fractures</th>
<th>Vertebral Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have the most devastating consequences resulting in higher costs, disability, and mortality than other fracture types combined</td>
<td>Epidemiology less well established due to varying definitions and under diagnosis of a substantial portion of vertebral fractures</td>
</tr>
<tr>
<td>80% occur in women with average age of occurrence being in the 80s</td>
<td>Approximately 1/3 are diagnosed and less than 10% result in hospitalization</td>
</tr>
<tr>
<td>The rate of hip fractures is 2 to 3 times higher in women than in men; however, the 1-year mortality following a hip fracture is almost twice as high for men as for women</td>
<td>Existing vertebral fractures increase the risk of subsequent vertebral fractures ten-fold</td>
</tr>
<tr>
<td>1/3 require nursing home placement due to inability to regain their pre-fracture level of functioning</td>
<td>25% occur as a result of a fall, with the majority occurring after routine everyday activities</td>
</tr>
<tr>
<td>Most hip fractures take place after a fall</td>
<td>Prevalence similar between women and men</td>
</tr>
</tbody>
</table>

Types of Osteoporosis

- Primary - Typically occurs with aging and is the result of loss and deterioration of bone structure
  - Influenced by peak bone mass and rate of bone loss
    - Type I – Postmenopausal osteoporosis
    - Type II – Senile osteoporosis
- Secondary - Typically the result of another condition or medications
  - Approximately 50% of cases in perimenopausal women
  - Approximately 30% to 60% of cases in men

Table 2. Secondary Causes of Osteoporosis

<table>
<thead>
<tr>
<th>Diseases That Cause or Contribute to Secondary Osteoporosis</th>
<th>Anorexia Nervosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>Osteogenesis Imperfecta</td>
</tr>
<tr>
<td>Lupus</td>
<td>Adrenal Insufficiency</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Cushing’s Syndrome</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Gastrectomy</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Celiac Disease</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>End Stage Renal Disease</td>
</tr>
<tr>
<td>Post-Transplant Bone Disease</td>
<td>Breast, Prostate, and Lung Cancers</td>
</tr>
</tbody>
</table>

Medications Associated with Secondary Osteoporosis

| Glucocorticoids (≥ 5mg/day of prednisone or equivalent for ≥ 3 months) | Heparin (long-term) |
| Cytochrome A and Tacrolimus                                     | Lithium |
| Methotrexate                                                   | Thyroxine |
| Methotrexate                                                   | Gonadotropin-Releasing Hormone Agonists |
| Anticonvulsants                                                | Depo-Medroxyprogesterone |
| Aromatase Inhibitors                                           | Aromatase Inhibitors |

Pathophysiology

- Types of Bone
  - Trabecular Bone – comprises approximately 25% of the skeleton
    - Higher metabolic turnover rate than cortical bone
    - Fills the ends of the limb bones and vertebral bodies in the spine
  - Cortical Bone - comprises approximately 75% of the skeleton
    - Hard outer shell of the skeleton
    - Compact and dense

Figure 3. Types of Bone
- **Bone Modeling**
  - Occurs during growth (childhood and adolescence)
  - Osteoblast and osteoclast action are not coupled
  - Formation of new bone at one site and removal of old bone from a different site

- **Bone Remodeling**
  - Occurs throughout lifetime
  - Osteoblast action is coupled to osteoclast action
  - Repairs skeletal damage and microfractures and prevents the accumulation of too much old bone

![Figure 4. Bone Remodeling Process](image)

- **Bone Remodeling Steps**
  1. **Activation** – Mechanical forces, injury, growth factors and cytokines trigger bone lining cells or osteocytes leading to activation and maturation of osteoclasts
  2. **Resorption** – Osteoclasts bind to bone surface and secrete cathepsin K which degrades protein matrix and vacuolar hydrogen adenosine triphosphate which produces acid → demineralizes hydroxyapatite crystals → forming cavities
  3. **Reversal** – Bone surface is prepared for bone formation phase → release of growth factors → stimulate differentiation, maturation, and activation of osteoblasts
  4. **Formation** – Mature osteoblasts fill bone cavities in two step process involving protein matrix deposition and mineralization with calcium and phosphorus

- **Peak bone mass** – typically achieved by the third decade of life
  - Highly dependent on genetic factors, hormones, and modifiable factors, such as adequate nutrition and physical activity
  - An important determinant of lifelong skeletal health
  - Gives the greatest protective advantage when bone density declines with aging or from secondary causes

- **Bone loss** – occurs when there is an imbalance between the activity of osteoclasts (bone resorption) and osteoblasts (bone formation)
Risk Factors

- Risk factors for osteoporosis and for fractures overlap but are not identical\(^2\)
- The single most important predictor of fracture risk is bone mineral density (BMD)\(^{17,18,19}\)
- Osteoporosis or low BMD is only ONE risk factor for fracture\(^3\)
- Combining BMD measurements with other independent risk factors for fracture (e.g., age, prior fracture history, and risk for falling) provides a more accurate assessment of a patient’s fracture risk than BMD alone\(^9,21\)

### Table 3. Risk Factors for Osteoporosis and Fractures\(^3,5,11,12\)

<table>
<thead>
<tr>
<th>Osteoporosis</th>
<th>Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Age</td>
<td>Advanced Age</td>
</tr>
<tr>
<td>Female Sex</td>
<td>Female Sex</td>
</tr>
<tr>
<td>Genetics</td>
<td>Parental History of Fracture</td>
</tr>
<tr>
<td>Lifestyle Factors</td>
<td>Lifestyle Factors (e.g., smoking, alcohol intake of ≥ 3 drinks/day, etc.)</td>
</tr>
<tr>
<td>(e.g., low calcium and vitamin D intake, smoking, etc.)</td>
<td></td>
</tr>
<tr>
<td>Thinness</td>
<td>Low Body Mass Index</td>
</tr>
<tr>
<td>Estrogen Deficiency</td>
<td>Prior Fragility Fracture</td>
</tr>
<tr>
<td></td>
<td>Long-Term Use of Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td></td>
<td>Propensity to Fall</td>
</tr>
</tbody>
</table>

### Evaluation\(^2,11-13\)

- History and physical exam
  - Loss of height and change in posture (e.g., kyphosis)
  - Laboratory evaluation for possible secondary causes of bone loss
  - Medication history
- BMD and other diagnostic tests
  - BMD testing at hip, femoral neck, lumbar spine with central dual-energy x-ray absorptiometry (DXA) – gold standard test for diagnosis
  - Peripheral dual-energy x-ray absorptiometry (pDXA) of the forearm, finger, or heel
  - CT-based absorptiometry – Quantitative computed tomography (QCT) and peripheral QCT
  - Quantitative ultrasound densitometry (QUS)

### Diagnosis\(^11-13\)

- BMD testing at the femoral neck or lumbar spine

### Table 4. World Health Organization (WHO) Diagnostic Criteria

<table>
<thead>
<tr>
<th>Classification</th>
<th>T-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≥ -1.0</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>-1.0 to -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>≤ -2.5 with fractures</td>
</tr>
</tbody>
</table>

- Presence of fragility fracture constitutes clinical diagnosis of osteoporosis

### Indications for BMD testing\(^11,12\) (for complete list of indications, see Appendix I)

- Women 65 years of age or older\(^11,12\)
  - Younger post-menopausal women with clinical risk factors for fracture
- Men 70 years of age or older\(^11\)
  - Younger men 50 to 69 years of age with clinical risk factors for fracture
- Patients who have had a fracture after the age of 50, to determine degree of disease severity
- Patients with a condition or taking a medication associated with bone loss or low bone mass
WHO Fracture Risk Assessment Tool (FRAX®)\textsuperscript{15} (see Appendix II)
- Risk-based assessment tool that calculates the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture (defined as clinical vertebral, hip, wrist or shoulder) taking into account femoral neck BMD and clinical risk factors
- Intended for use in postmenopausal women and men age 50 and older
- FRAX® algorithm available at www.nof.org and www.shef.ac.uk/FRAX and on newer DXA scanners

Strengths and Limitations of FRAX®\textsuperscript{16}
- **Strengths**
  - Based on extensive global population-based cohorts involving over 60,000 patients and over 5,000 fractures to identify risk factors independent of BMD
  - Tool can help identify patients who would benefit most from pharmacologic therapy and in whom it is likely to be cost-effective to initiate treatment to reduce fracture risk
- **Limitations**
  - Key variables that contribute to fracture incidence were excluded such as fall history or propensity to fall and vitamin D deficiency
  - FRAX® does not take into account dose-response relationships
    - FRAX does not show a change in fracture risk between single versus multiple fractures, varying exposures to glucocorticoids, or smoking duration
  - FRAX® can only be used in treatment naïve patients
  - BMD input is only allowed for femoral neck, so does not account for patients with a normal femoral neck but low lumbar BMD
  - Algorithm is based on the assumption that additional fracture risk from secondary osteoporosis is mediated largely through BMD
    - If a BMD value is entered in the tool, secondary osteoporosis does not change the fracture risk

Available Treatment Modalities

**Goal of osteoporosis management is to reduce fracture risk**\textsuperscript{11,12}
This can be done by slowing or stopping bone loss, increasing bone mass or improving bone architecture, maintaining or increasing bone strength, and minimizing factors that contribute to falls

- **Bone Healthy Lifestyle**\textsuperscript{3,11,12}
  - Adequate calcium and vitamin D intake
    - Calcium:
      - 1,000 mg for adults
      - 1,200-1,500 mg if 50 years of age or older\textsuperscript{2,13}
      - Only about 50% to 60% meet this recommendation\textsuperscript{2}
    - Vitamin D:
      - 400-800 units daily for adults
      - 800-1,000 units daily if over 50 years of age\textsuperscript{11,12}
      - Maintain 25 (OH) vitamin D levels of at least 30 ng/mL\textsuperscript{11}
  - Weight-bearing exercise and muscle strengthening exercises
  - Smoking cessation
  - Fall prevention
  - Limit alcohol consumption to ≤ 2 drinks/day

- **Recommendations for Initiation of Pharmacologic Therapy**\textsuperscript{11,12}
  - Previous hip or vertebral fracture
  - BMD T-score ≤ -2.5 at the femoral neck or spine by DXA
  - Postmenopausal women and men age 50 and older with osteopenia at the femoral neck or spine and a 10-year hip fracture probability of ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the US WHO fracture risk model (FRAX®)
Pharmacologic Therapy\textsuperscript{11,12,22-23} (see Appendix III)

<table>
<thead>
<tr>
<th>Antiresorptive Agents (Bone Maintaining)</th>
<th>Anabolic Agents (Bone Building)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates – 1st line therapy</strong></td>
<td>Teriparatide</td>
</tr>
<tr>
<td>Hormone replacement therapy (HRT)</td>
<td></td>
</tr>
<tr>
<td>Selective estrogen receptor modifiers (SERMs)</td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td></td>
</tr>
</tbody>
</table>

Some Limitations of Standard Treatment Options

- **Bisphosphonates**
  - Oral formulations have poor absorption, consist of complicated protocols for ingestion, and may cause gastrointestinal side effects
  - Contraindicated in severe renal impairment
  - Black Box warning for osteonecrosis of the jaw (ONJ)

- **HRT**
  - Increased risk for thromboembolic events
  - Only recommended for use in women with menopausal symptoms

- **SERMs**
  - Adverse effects (e.g., increased risk for thromboembolic events, vasomotor side effects)
  - Black Box warning for fatal stroke

- **Calcitonin**
  - Efficacy less robust than other antiresorptive agents
  - Only indicated for treatment, not prevention

- **Teriparatide**
  - Requires daily subcutaneous injections
  - Little efficacy and safety data beyond 2 years
  - Black Box warning for osteosarcoma

Patient Adherence to Osteoporosis Therapy

**Patient Adherence** (Combination of persistence with therapy and medication compliance)\textsuperscript{27}

- Adherence to oral osteoporosis medications, particularly with bisphosphonates, is poor\textsuperscript{24-29}
- Many patients discontinue oral osteoporosis medications soon after treatment initiation\textsuperscript{25}
- Reasons for nonadherence\textsuperscript{24,26}
  - Experiencing adverse effects (e.g., stomach upset) from oral bisphosphonates
  - Disbelief that they have osteoporosis and are at risk of fracture
  - Cost
  - Complex dosing schedules
  - Forgetfulness

Effects of patient compliance and adherence on fracture incidence

- Solomon et al. studied compliance levels and determinants of compliance with osteoporosis medications from pharmacy claims data from US Medicare and from a state pharmaceutical benefits program\textsuperscript{25}
  - The outcome of interest was suboptimal medication compliance, defined as equal to or less than 66% of days with medication during a 60-day period.
  - One year after initiating osteoporosis treatment, 45.2% of patients were not continuing to fill prescriptions
- Sirus et al. examined the relationship of persistence and medication possession ratio to fracture rate of vertebral and nonvertebral fractures\textsuperscript{29}
  - At least 50% of patients stop bisphosphonates within 1 year of initiating therapy
  - Total, vertebral, nonvertebral, and hip fractures were significantly lower in refill-compliant and persistent patients, with relative risk reductions of 20% to 45%
**Denosumab (Prolia™)**

**Description**
- Denosumab is a fully human monoclonal IgG antibody with high affinity and specificity for human receptor activator of nuclear factor kappa-B ligand (RANKL)\(^{30-33}\)

**Mechanism of Action\(^{30-33}\)**
- Denosumab binds to RANKL, a transmembrane protein expressed by osteoblasts and their precursors, which is essential for the formation, function, and survival of osteoclasts
- Prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors thereby inhibiting osteoclast formation, function, and survival, resulting in decreasing bone resorption and bone loss
- Functions like osteoprotegerin (OPG), an endogenous decoy receptor produced and secreted by osteoblasts and their precursors that inhibits the effect of RANKL/RANK binding on osteoclastogenesis

![Figure 5. Mechanism of Action of Denosumab\(^{34}\)](image)

**Indication\(^{32}\)**
- The United States Food and Drug Administration (FDA) has approved denosumab for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy

**Dosing / Administration\(^{32}\)**
- Supplied in a prefilled syringe as a single 60 mg/mL fixed dose
- Administered as a single subcutaneous injection once every 6 months in upper arm, upper thigh, or abdomen
- Patients should also receive calcium 1000 mg and at least 400 IU vitamin D daily
- No food restrictions
- Requires refrigeration
- No dosage adjustment necessary in patients with renal impairment
Contraindications

- Hypocalcemia – Preexisting hypocalcemia must be corrected prior to initiating denosumab
  - Hypocalcemia may worsen in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault)

Pharmacokinetics

- Absorption
  - Time to peak plasma concentration: ~10 days (range: 3 to 21 days)
- Metabolism
  - No drug-drug interaction studies have been conducted
  - No clinical studies on the effects of hepatic impairment have been conducted
- Excretion
  - Elimination half-life: ~25.4 days

Pharmacodynamics

- Reduction of bone resorption marker, serum type I C-telopeptide (CTX), approximately 86% by 3 days with maximal reductions occurring by 1 month
- At end of dosing interval, CTX reductions ranged from 45% to 80% as serum denosumab levels diminished, reflecting the reversibility of its effects on bone remodeling

Adverse Effects

- Most Frequent
  - Back pain, pain in extremity, myalgia, hypercholesterolemia, cystitis
- Less Frequent
  - Anemia, bone pain, flatulence, hypocalcemia, pharyngitis, dermatologic reactions (e.g., dermatitis and eczema)
- Rare
  - Angina, ONJ, cellulitis, endocarditis, malignancy, severe infection

Table 6. Adverse Effects of Denosumab

<table>
<thead>
<tr>
<th>Event</th>
<th>Denosumab (N= 3886)</th>
<th>Placebo (N= 3876)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>3605 (92.8)</td>
<td>3607 (93.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Fatal</td>
<td>1004 (25.8)</td>
<td>972 (25.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Infection</td>
<td>70 (1.8)</td>
<td>90 (2.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2055 (52.9)</td>
<td>2108 (54.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Cancer</td>
<td>187 (4.8)</td>
<td>166 (4.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0</td>
<td>3 (0.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>144 (3.7)</td>
<td>125 (3.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Infection</td>
<td>159 (4.1)</td>
<td>133 (3.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiovascular Event</td>
<td>186 (4.8)</td>
<td>178 (4.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Adverse Events Occurring in at least 2% of Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>118 (3.0)</td>
<td>65 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flatulence</td>
<td>84 (2.2)</td>
<td>53 (1.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Serious Adverse Events Occurring in at least 0.1% of Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis (including erysipelas)</td>
<td>12 (0.3)</td>
<td>1 (&lt;0.1)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
### Microarchitectural Deterioration of Cortical and Trabecular Bone: Differing Effects of Denosumab and Alendronate

**Seeman, E, Delmas, P, Hanley, D, et al. J Bone Min Res 2010;25:1886-1894.**

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>1-year, pilot, phase 2, international, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Subjects randomized 1:1:1 to subcutaneous injection of denosumab 60 mg every 6 months, oral alendronate 70 mg weekly, or placebo. All patients received daily calcium (≥ 500 mg/day) and vitamin D (dose based on baseline serum concentrations of 25-hydroxyvitamin D)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td><strong>Inclusion Criteria</strong>&lt;br&gt;• Healthy ambulatory postmenopausal women between 50 and 70 years of age&lt;br&gt;• Lumbar spine or total hip BMD T-scores between -2.0 and -3.0 by DXA scan&lt;br&gt;• Subjects were included provided that high resolution peripheral quantitative computed tomography (HR-pQCT) could be performed in at least one wrist&lt;br&gt;&lt;br&gt;<strong>Exclusion Criteria</strong>&lt;br&gt;• Fragility fracture after age 50&lt;br&gt;• Moderate to severe vertebral deformity using semi-quantitative criteria&lt;br&gt;• Vitamin D deficiency (serum 25-hydroxyvitamin D &lt; 12 ng/mL)&lt;br&gt;• Subjects with conditions affecting bone metabolism; contraindications to alendronate; history of intravenous bisphosphonate, fluoride (except for dental use), or strontium ranelate use; cumulative oral bisphosphonate use for 3 months or more, bisphosphonate use for 1 month or more within the past year, or any use within 3 months of randomization; parathyroid hormone (PTH) or PTH derivative administration within past year; or drugs known to affect bone remodeling or density within 3 months of randomization</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td><strong>Endpoints</strong>: Percent change from baseline in cortical thickness; percentage changes in total, cortical, and trabecular volumetric BMD (vBMD); trabecular number, thickness, and separation as measured by HR-pQCT at distal radius and tibia; percentage change in QCT parameters, total vBMD and polar moment of inertia (PMI), at the distal radius site; changes in bone turnover markers serum C-telopeptide of type I collagen cross-links (CTX) and procollagen type 1 N-terminal propeptide (P1NP); safety was evaluated by adverse event reporting and monitoring changes in laboratory values and vital signs</td>
</tr>
<tr>
<td><strong>Statistics</strong></td>
<td>There was no information regarding magnitude of expected changes in HR-pQCT parameters with placebo or therapy, therefore formal statistical hypothesis testing was not preplanned for study&lt;br&gt;• $P$ values for the differences between treatments were calculated post hoc&lt;br&gt;• Treatment difference in the percent changes in volumetric and geometric bone parameters derived from HR-pQCT and QCT were evaluated using analysis of covariance model (ANCOVA), adjusting for age group and baseline values in addition to treatment effect&lt;br&gt;• Changes in biochemical markers of bone turnover had non-normal distribution, therefore were summarized using medians and interquartile ranges</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><strong>Baseline Characteristics</strong>&lt;br&gt;• Baseline demographics were similar among groups&lt;br&gt;• Most women (96%) were Caucasian&lt;br&gt;• 247 subjects were randomized to treatment and 217 (88%) completed 12 months of follow-up (Denosumab n = 83, Alendronate n=82, Placebo n = 82)&lt;br&gt;• Mean BMD T-score for hip was -1.1 for placebo group and -1.4 for alendronate and denosumab groups; Mean BMD T-score for lumbar spine was -2.4 for placebo group, -2.5 for alendronate group, and -2.4 for denosumab group</td>
</tr>
</tbody>
</table>
**Study Endpoints**

- At 12 months at the distal radius, *denosumab* resulted in significantly greater increases in both total and cortical vBMD compared with alendronate therapy and placebo.
- At 12 months at the distal tibia, *denosumab* resulted in significantly greater increases in total and cortical vBMD, and cortical thickness at 6 months compared with alendronate therapy and placebo.
- The reduction in bone turnover marker CTX occurred more rapidly and was greater with denosumab than with alendronate.
- Serum CTX decreased within the first week following each denosumab dose and the level increased to near baseline levels by the end of the dosing interval demonstrating reversibility.
- Incidence of adverse events was similar between treatment groups.

![Graphs showing percent changes in vBMD and cortical thickness](image)

**Authors’ Conclusions**

- Denosumab demonstrated greater potency in suppressing bone remodeling and a greater effect on vBMD than alendronate, particularly at predominantly cortical sites such as the 1/3rd distal radius and tibia.
- Benefits observed with denosumab over alendronate in total and cortical vBMD may be the result of differences in the mechanism of action of these drugs and how they affect osteoclast function.

**Critique**

**Strengths**
- Randomized, double-blind design
- Allowed head-to-head comparison between denosumab and alendronate with regards to changes in cortical and trabecular density and microarchitecture.

**Limitations**
- *P* values for the differences between treatments were calculated post hoc.
- Monitoring CTX levels and performing QCT scans do not reflect current practices.
- Conflict of interest (study supported by Amgen).
### Effects of Denosumab on Bone Mineral Density and Bone Turnover in Postmenopausal Women Transitioning from Alendronate Therapy (STAND Trial)


#### Design
- 1-year, multicenter, international, randomized, double-blind, double-dummy, parallel-group, phase 3 trial

#### Intervention
- Open-label branded alendronate 70 mg once weekly for 1 month for all patients
- Patients randomized to either continue weekly alendronate therapy or receive subcutaneous denosumab 60 mg every 6 months

#### Population

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory postmenopausal women at least 55 years of age</td>
<td>Women with current hyper- or hypothyroidism, current hyper- or hypoparathyroidism, elevated transaminases, significantly impaired renal function (CrCl ≤ 35 mL/min by Cockcroft and Gault method), hyper- or hypocalcemia, serum 25-hydroxyvitamin D levels &lt; 20 ng/mL or any other condition that could result in impaired calcium metabolism, or any metabolic bone disease that could interfere with interpretation of the findings</td>
</tr>
<tr>
<td>T-score between -2.0 and - 4.0 at the lumbar spine or total hip</td>
<td>Women intolerant of alendronate therapy or for whom it was contraindicated or if taken any bisphosphonate other than alendronate within 1 year of screening</td>
</tr>
<tr>
<td>Receiving alendronate treatment equivalent to 70 mg/week for at least 6 months</td>
<td>If ever received intravenous bisphosphonates, fluoride, or strontium ranelate</td>
</tr>
</tbody>
</table>

#### Endpoints
- **Primary Endpoints**: Percent change in total hip BMD from baseline to month 12
- **Secondary Endpoints**: Percent change from baseline in serum type 1 C-telopeptide (CTX-1) at month 3 and percent change from baseline in lumbar spine BMD at month 12
- **Other Endpoints**: Percent change from baseline in BMD at femoral neck and 1/3rd radius at month 12

#### Statistics
- Repeated-measure model used as primary analysis method for the percent change in BMD
- Wilcoxon rank-sum test adjusting for time-on-prior-alendronate stratum used to assess significance of treatment difference at each time point for bone turnover markers
- Noninferiority design

#### Results

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and clinical characteristics similar between treatment groups</td>
</tr>
<tr>
<td>(Alendronate n = 238, Denosumab n = 243)</td>
</tr>
<tr>
<td>Treatment with bisphosphonate therapy for a median of 36 months (range 6 to 192 months)</td>
</tr>
<tr>
<td>in period immediately before screening</td>
</tr>
<tr>
<td>Average BMD T-scores at total hip and lumbar spine were -1.80 and -2.63, respectively, and 50% had previous osteoporosis-related fracture</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
</tr>
<tr>
<td>o 94% of subjects in each group received both injections (denosumab or matching placebo)</td>
</tr>
<tr>
<td>and at least 80% of the tablets (alendronate or matching placebo) through month 12</td>
</tr>
</tbody>
</table>
Primary Endpoint

Figure 7. Percent Change from Baseline in vBMD of the total hip

Secondary/Other Endpoints

Figure 8. Percent Change from Baseline in BMD of the Lumbar Spine

Figure 9. Percent Change from Baseline in BMD of the 1/3rd Radius

- Denosumab increased BMD at the lumbar spine by 3.03% (95% CI 2.63-3.44) at 12 months ($p<.0001$) and BMD at the femoral neck and one-third radius ($p≤.0121$)

Authors’ Conclusions

- Postmenopausal women with low BMD who were previously taking alendronate, experienced a greater increase in BMD and a greater reduction in bone turnover markers when transitioned to denosumab than if alendronate therapy was continued

- Denosumab treatment resulted in significantly greater BMD gains than continued alendronate therapy at all skeletal sites measured (hip, lumbar spine, femoral neck, and 1/3rd radius) at study month 12

Critique

Strengths

- Randomized, double-blind, double-dummy design
- Noninferiority margin based on comparison of data from 2 studies with patients previously on alendronate
- Study design attempts to reflect what would typically be seen in patients eligible for denosumab therapy
- Head-to-head design allowed direct comparison of alendronate with denosumab on BMD and bone turnover markers

Limitations

- Fracture reduction efficacy not studied
- Average BMD T-score at total hip for study patients was -1.8, which is above the threshold for osteoporosis, so results may not extrapolate to women with BMD ≤ -2.5 at that site
- Percentage of patients having received previous antiresorptive or anabolic therapy was not reported
- Conflict of interest (several researchers employed by and having an equity interest in Amgen)
Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis
(FREEDOM Trial)

**Design**
3-year, multicenter, international, randomized, double-blind, placebo-controlled, phase III trial

**Intervention**
- Denosumab 60 mg or placebo subcutaneous injection every 6 months
- All patients received daily supplements of at least 1,000 mg calcium along with 400 to 800 IU vitamin D (depending on 25-OH vitamin D levels at baseline)

**Population**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Postmenopausal women between 60 and 91 years of age</td>
<td>- Patients with conditions that influenced bone metabolism or had taken oral bisphosphonates for &gt; 3 years</td>
</tr>
<tr>
<td>- T-score between -2.5 and -4.0 at the lumbar spine or total hip</td>
<td>- If used intravenous bisphosphonates, fluoride, or strontium for osteoporosis within past 5 years</td>
</tr>
<tr>
<td></td>
<td>- If taken parathyroid hormone or its derivatives, corticosteroids, systemic hormone-replacement therapy, selective estrogen-receptor modulators, or tibolone, calcitonin, or calcitriol within 6 weeks prior to study</td>
</tr>
<tr>
<td></td>
<td>- T-score less than -4.0 at the lumbar spine or total hip or any severe (or more than 2 moderate) prevalent vertebral fractures</td>
</tr>
<tr>
<td></td>
<td>- Serum 25-OH vitamin D level of less than 12 ng/mL</td>
</tr>
</tbody>
</table>

**Endpoints**

- **Primary Endpoints**: Incidence of new vertebral fractures at 3 years
- **Secondary Endpoints**: Time to first nonvertebral and hip fracture

**Statistics**
- Intention-to-treat principle
- Logistic-regression model with adjustment for age strata
- Age-stratified Cox proportional-hazards model was used to compare the groups for the secondary endpoints
- Radiographically defined vertebral fractures were analyzed by cumulative incidence
- Secondary endpoints analyzed by time-to-event analysis via Kaplan Meier methods

**Results**
- Similar between study groups (Denosumab n = 3902, Placebo n = 3906)
- Overall mean BMD T-scores were -2.8 at the lumbar spine, -1.9 at the total hip, and -2.2 at the femoral neck
- Approximately 24% of subjects had a vertebral fracture at baseline

**All Endpoints**

**Table 7. Effect of Denosumab on the Risk of Fracture at 36 Months**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Denosumab no. (%)</th>
<th>Placebo no. (%)</th>
<th>Difference in Rates (95% CI)</th>
<th>Relative Risk or Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New vertebral fracture</td>
<td>86 (2.3)</td>
<td>264 (7.2)</td>
<td>4.8 (3.9 to 5.8)</td>
<td>0.32 (0.26 to 0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvertebral fractures:</td>
<td>238 (6.5)</td>
<td>293 (8.0)</td>
<td>1.5 (0.3 to 2.7)</td>
<td>0.80 (0.67 to 0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>26 (0.7)</td>
<td>43 (1.2)</td>
<td>0.3 (-0.1 to 0.7)</td>
<td>0.60 (0.37 to 0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Other fracture end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New clinical vertebral fracture</td>
<td>29 (0.8)</td>
<td>92 (2.6)</td>
<td>1.7 (1.1 to 2.3)</td>
<td>0.31 (0.20 to 0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple (≥2) new vertebral fractures</td>
<td>23 (0.6)</td>
<td>59 (1.6)</td>
<td>1.0 (0.5 to 1.5)</td>
<td>0.39 (0.24 to 0.63)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Denosumab (Prolia™): Strong Evidence in the Case Against Osteoporosis
Page 14
Primary Endpoint

- Denosumab significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$)
- The absolute risk reduction was 4.9% and relative risk reduction was 68% at year 3

![Figure 10. New Vertebral Fractures](image)

Secondary Endpoints

- The absolute risk reduction of hip fractures was 0.5% with a relative risk reduction of 40% at 3 years ($p = 0.04$)
- The absolute risk reduction of nonvertebral fractures was 1.5% with a relative risk reduction of 20% at 3 years ($p = 0.04$)
- Relative increase in BMD by 9.2% (95% CI, 8.2-10.1) at the lumbar spine and 6.0% (95% CI, 5.2-6.7) at the total hip, as compared with placebo

![Figure 11. Time to First Nonvertebral Fracture](image)  ![Figure 12. Time to First Hip Fracture](image)

Authors’ Conclusions

- Denosumab was associated with a significant reduction in the risk of vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis
- Denosumab offers an alternative treatment approach for osteoporosis by decreasing bone resorption through the inhibition of RANKL

Critique

Strengths

- Randomized, double-blind design
- Multicenter, international study
- Used fracture incidence as outcome measure as opposed to a proxy measure of bone strength such as BMD
- Adequately powered
- Long trial duration

Limitations

- Average BMD T-score at total hip for study patients was -1.90 and femoral neck was -2.2, which are above the threshold for osteoporosis, so results may not extrapolate to women with BMD ≤ -2.5 at those sites
- Percentage of patients having received previous antiresorptive or anabolic therapy was not reported
- Conflict of interest (several researchers employed by and having an equity interest in Amgen)
Consequences of Long-Term Antiresorptive Therapy

Atypical Fractures\textsuperscript{38-43}

- Associated with no trauma or minimal trauma
- Occurring at atypical sites such as the femoral shaft, pubic bone, and ischium
- Characteristic radiographic findings include cortical hypertrophy, a transverse pattern, and medial cortical spiking
- Often occurs with prodromal pain in the region of the fracture weeks to months prior to fracture
- Numerous case reports and case series suggest a link between bisphosphonate use and the occurrence of atypical fractures\textsuperscript{38,39}
  - Reports of spontaneous, nontraumatic atypical fractures after alendronate use (3 to 8 years treatment duration)
  - Bone biopsies showed a marked decrease in bone formation
  - 6 patients continued to take alendronate following fracture and all showed incomplete healing
- Other studies dispute an association between bisphosphonate use and atypical fractures
  - Black et al conducted a population-based study which did not support the association and concluded that atypical fractures are rare even in women treated with bisphosphonates for as long as 10 years\textsuperscript{41}
    - Black et al. estimated a hypothetical risk that bisphosphonate treatment would result in an annual rate of 2.3 atypical fractures per 10,000 patient-years in untreated women with osteoporosis
  - Abrahamsen et al. conducted 2 national register-based studies to address association and concluded that patients with these atypical femur fractures were no more likely to be on alendronate treatment than patients with hip fractures, but oral glucocorticoid use was more prevalent\textsuperscript{42}
- American Society for Bone and Mineral Research (ASBMR) Task Force assembled to address key questions related to the proposed link between bisphosphonates and atypical fractures\textsuperscript{43}
- Denosumab’s reversible effects on bone resorption and relatively short duration of action compared with bisphosphonates could potentially reduce the concerns associated with long-term antiresorptive therapy.

Osteonecrosis of the Jaw (ONJ)\textsuperscript{38, 40,44,45}

- Defined as the presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and with no history of craniofacial radiation\textsuperscript{44}
- Appears as areas of exposed yellow or white hard bone
- Often follows a dental extraction or other invasive dental procedure or occurs in patients with ill-fitting dentures
- Signs and symptoms include pain, swelling, paresthesias, soft tissue ulceration, and loosening of teeth
- Lesions often do not heal, or heal very slowly
- First report linking ONJ with bisphosphonate use appeared in 2003\textsuperscript{38}
  - All 36 patients were being treated with high doses of IV bisphosphonates (~10 times higher than doses used for osteoporosis treatment) for skeletal complications from malignancy
  - Subsequent cases involved patients on lower doses of bisphosphonates for osteoporosis treatment, but over 90% were cancer patients
- Risk of developing ONJ with routine oral bisphosphonate therapy for osteoporosis or Paget’s disease is estimated to be less than 1 in 100,000 patient-years of exposure, with the risk being higher in patients receiving high doses of IV bisphosphonates
- There have been case reports of ONJ occurring in patients with metastatic cancer receiving denosumab, but no reports exist in patients being treated for osteoporosis
  - Appears to be a dose-related effect, given that occurrence of ONJ was in patients being treated with denosumab for bone metastases at a dose of 120 mg monthly
Risk versus benefit?
- Low reported incidence of both atypical fracture and ONJ
- The occurrence of atypical fractures and ONJ in patients exposed to long-term bisphosphonate use does not prove causality
- ONJ was never identified prospectively in any of the clinical trials that included more than 60,000 patient-years in studies for osteoporosis or Paget's
- Benefits of long-term osteoporosis therapy in high fracture risk patients likely outweighs the risks

Unanswered Questions
1. Is there such a thing as over suppression of bone turnover?
2. What is the optimal treatment duration for osteoporosis?
3. What are the long-term consequences of denosumab on malignancy, and immune function?

Summary and Conclusions
- There is significant morbidity and mortality associated with osteoporotic fractures. Awareness should be raised to improve the recognition of vertebral fractures which are underdiagnosed and underreported.
- Bisphosphonates will likely remain the mainstay of osteoporosis therapy, but patient adherence is often poor with oral osteoporosis medications. Treatment decisions should be based on the risks and benefits of the drug therapy in addition to patient preferences and lifestyle considerations.
- Denosumab offers a novel approach to the treatment of postmenopausal osteoporosis in women at high risk for fracture. With its unique mechanism of action, treatment with denosumab has been shown to significantly reduce the risk of vertebral, hip, and nonvertebral fractures.
- Head-to-head studies have not been conducted comparing denosumab to standard treatment options with respect to fracture risk.
- The question still remains as to the optimal degree of suppression of bone turnover and the long-term consequences of antiresorptive therapy. Additional research is needed to determine the safest duration of therapy to treat osteoporosis.
Appendix I

National Osteoporosis Foundation (NOF) and North American Menopause Society (NAMS) Recommendations for BMD testing\textsuperscript{11,12}

<table>
<thead>
<tr>
<th>NOF Recommendations for BMD Testing</th>
<th>NAMS Recommendations for BMD Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women age 65 and older and men age 70 and older regardless of clinical risk factor</td>
<td>All women 65 and over, regardless of clinical risk factors</td>
</tr>
<tr>
<td>Younger postmenopausal women and men age 50 to 69 about whom you have concern based on their clinical risk factor profile</td>
<td>Postmenopausal women with medical causes of bone loss (e.g., steroid use, hyperparathyroidism), regardless of age</td>
</tr>
<tr>
<td>Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk such as low body weight, prior low-trauma fracture or high risk medication</td>
<td>Postmenopausal women age 50 and over with additional risk factors (see below)</td>
</tr>
<tr>
<td>Adults who have a fracture after age 50</td>
<td>Postmenopausal women with fragility fracture (e.g., fracture from a fall from standing height)</td>
</tr>
<tr>
<td>Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months) associated with low bone mass or bone loss</td>
<td>Testing should be considered for postmenopausal women age 50 and over when one or more of the following risk factors for fracture have been identified:</td>
</tr>
<tr>
<td>Anyone being considered for pharmacologic therapy for osteoporosis</td>
<td>Fracture (other than skull, facial bone, ankle, finger, and toe) after menopause</td>
</tr>
<tr>
<td>Anyone being treated for osteoporosis, to monitor treatment effect</td>
<td>Thinness (body weight &lt; 127 lb [57.7 kg] or BMI &lt; 21 kg/m\textsuperscript{2})</td>
</tr>
<tr>
<td>Anyone not receiving therapy in whom evidence of bone loss would lead to treatment</td>
<td>History of hip fracture in a patient</td>
</tr>
<tr>
<td>Postmenopausal women discontinuing estrogen should be considered for bone mineral density testing</td>
<td>Current smoker</td>
</tr>
<tr>
<td>Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months) associated with low bone mass or bone loss</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Alcohol intake of more than 2 units per day (one unit is 12 oz of beer, 4 oz of wine, or 1 oz of liquor)</td>
<td></td>
</tr>
</tbody>
</table>

Appendix II

World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX®)\textsuperscript{16}

![FRAX® Fracture Risk Assessment Tool](image)

The model accepts ages between 40 and 90 years.

A previous fracture as an adult occurring spontaneously or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture.

Current smoking status.

Enter ‘Yes’ if patient exposed to oral glucocorticoids or has been exposed for more than 3 months at a dose of prednisolone 5 mg daily or more (or the equivalent).

Enter ‘Yes’ if patient has a disorder strongly associated with osteoporosis including: Type 1 diabetes, osteogenesis imperfect, untreated long-standing hypothyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition, or malabsorption and chronic liver disease.

Select the make of DXA scanning machine used and enter the actual femoral neck BMD (in g/cm\textsuperscript{2}). In patients without a BMD test, leave field blank.

Questionnaire:

1. Age (between 40-90 years) or Date of birth
2. Sex
3. Weight (kg)
4. Height (cm)
5. Previous fracture
6. Parent fractured hip
7. Current smoking
8. Glucocorticoids
9. Rheumatoid arthritis
10. Secondary osteoporosis
11. Alcohol 3 or more units per day
12. Femoral neck BMD (g/cm\textsuperscript{2})

Select ‘No’ or ‘Yes’. Calculate the fracture risk.
### Current Pharmacologic FDA-Approved Treatment Options for Osteoporosis[^1][^2][^3][^4]

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>FDA-Approval</th>
<th>Vertebal Fracture Risk</th>
<th>Nonvertebral Fracture Risk</th>
<th>Hip Fracture Risk</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Alendronate (Fosamax®)</td>
<td>Prevention and treatment of postmenopausal osteoporosis; Treatment of GIO in women</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Oral formulations: Upper GI side effects including difficulty swallowing, inflammation of the esophagus, and gastric ulcer, muscle, bone, and joint pain; rare reports of osteonecrosis of the jaw (ONJ) and visual disturbances</td>
<td>Oral formulations: Dosing regimen requires patients to fast and remain upright for at least 30 to 60 minutes IV ibandronate: Injected over 15 to 30 seconds, once every 3 months IV Zoledronic acid: Given once yearly or every 2 years by IV infusion over at least 15 minutes Serum calcium and creatinine should be measured prior to initiation of therapy and low calcium corrected</td>
</tr>
<tr>
<td></td>
<td>Risedronate (Actonel®)</td>
<td>Prevention and treatment of postmenopausal osteoporosis; treatment of male osteoporosis; prevention and treatment of GIO in men and women</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Poorly absorbed (0.5% of oral dose)</td>
</tr>
<tr>
<td></td>
<td>Ibandronate (Boniva®)</td>
<td>Prevention and treatment of postmenopausal osteoporosis</td>
<td>↓</td>
<td>←—</td>
<td>←—</td>
<td>Women’s Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis</td>
<td>Indicated in women experiencing moderate to severe menopause symptoms (i.e. vasomotor symptoms, vaginal atrophy)</td>
</tr>
<tr>
<td></td>
<td>Zoledronic Acid (Reclast®)</td>
<td>Prevention and treatment of postmenopausal osteoporosis; prevention and treatment of GIO in men and women</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone Replacement Therapy (HRT)</td>
<td>Estrogen/ Hormone Therapy (various brand names)</td>
<td>Prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Indicated in women experiencing moderate to severe menopause symptoms (i.e. vasomotor symptoms, vaginal atrophy)</td>
</tr>
<tr>
<td>Selective Estrogen Receptor Modifiers (SERMs)</td>
<td>Raloxifene (Evista®)</td>
<td>Prevention and treatment of postmenopausal osteoporosis</td>
<td>↓</td>
<td>←—</td>
<td>←—</td>
<td>Increases risk of deep vein thrombosis; Is associated with an increase in vasomotor symptoms and leg cramps; Black Box warning for fatal stroke</td>
<td>Indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis; Consider baseline cardiovascular risk prior to initiating therapy</td>
</tr>
<tr>
<td>Non-Sex Steroid Hormone</td>
<td>Calcitlonin (Miacalcin® or Fortical®)</td>
<td>Treatment of osteoporosis in women who are at least 5 years postmenopausal</td>
<td>↓/←—</td>
<td>←—</td>
<td>←—</td>
<td>Intransal formulation: Rhinitis, and rarely, epistaxis</td>
<td>Less effective than other antiresorptive agents</td>
</tr>
<tr>
<td>Anabolic Therapy 1-34 recombinant human parathyroid hormone</td>
<td>Teriparatide (Forteo®)</td>
<td>Treatment of postmenopausal osteoporosis women and men at high risk for fracture; treatment of men and women at high fracture risk with osteoporosis associated with sustained systemic glucocorticoid therapy; to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture</td>
<td>↓</td>
<td>↓</td>
<td>←—</td>
<td>Leg cramps, dizziness, nausea, and hypercalcemia; Can increase risk of osteosarcoma, so avoid in patients with increased risk of osteosarcoma (Paget's disease, prior radiation of skeleton, bone metastases, hypercalcemia, or skeletal malignancy)</td>
<td>Administered by daily SC injections; Safety and efficacy has not been studied beyond 2 years; After discontinuation of PTH, an antiresorptive agent is needed to retain the gains in BMD; Commonly followed with antiresorptive treatment to maintain BMD gains</td>
</tr>
<tr>
<td>Human Monoclonal Antibody</td>
<td>Denosumab (Prolia™)</td>
<td>Treatment of postmenopausal women at high risk for fracture</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Arthralgias, nasopharyngitis, back pain, headache, bone pain, risk of infections, hypocalcemia, dermatologic reactions and infections</td>
<td>Administered by SC injection once every 6 months in addition to calcium 1000 mg daily and at least 400 IU vitamin D</td>
</tr>
</tbody>
</table>

[^1]: Glucocorticoid-Induced Osteoporosis (GIOP)

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Denosumab (Prolia™): Strong Evidence in the Case Against Osteoporosis
References:


