Osteoporosis: A Practical Approach for 2017

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• I have no financial disclosures

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  - NIDDK
  - Doris Duke Charitable Foundation
  - Seres Therapeutics™
Objectives

- **Who & When?**
  - Review bone density screening guidelines
  - Discuss use and limitations of fracture risk calculators

- **How to treat?**
  - Review risks and benefits of osteoporosis treatment options
  - Discuss controversies surrounding duration of treatment
  - New osteoporosis therapy
A Public Health Problem

• ½ of women and ¼ of men over 50 will have a low-trauma fracture during their lifetime
  » 2 million fractures/year in the U.S.
  » Associated medical costs $20 billion/year

• World population of adults ≥65 yrs will double between 2010 and 2040

• Osteoporotic fractures have dramatic impact on individuals
  » Spine fractures are associated with 2-5 times higher risk of future spine and hip fractures
  » Half of hip fracture victims never return to independent life
  » Hip fractures are associated with 25% increase in mortality risk

Burge et al, JBMR 2007
Forsen et al. Osteoporosis Int 1999;10:73-78
<table>
<thead>
<tr>
<th>U.S. Preventative Services Task Force</th>
<th>National Osteoporosis Foundation</th>
<th>American Association for Clinical Endocrinology</th>
<th>North American Menopause Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal women ≥65 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adults ≥50 years with risk factors</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Osteoporosis Risk Factors

- Previous fractures
- Low BMI
- Family history
- Lifestyle
  - Low calcium intake
  - Alcohol (>3 drinks/day)
  - Active smoking
  - Physical activity / Fall risk
- Medications
  - Glucocorticoids (≥5 mg prednisone/day)
  - GnRH agonists
  - Aromatase inhibitors
  - Anti-convulsants
- Co-morbidities
  - Rheumatoid arthritis
  - Vitamin D deficiency
  - Hyperthyroidism
  - Hyperparathyroidism
  - Early menopause
  - Hypothalamic amenorrhea/hypogonadism
  - Eating disorders
  - Inflammatory bowel disease
  - Celiac disease
  - Type 1 diabetes
  - Gastric bypass
  - Post-transplant bone disease
  - Mastocytosis
Underdiagnosed and Undertreated

- Among women recommended for bone density screening, ~50% did not receive a DXA test over a 7 year period.
  - King and Fiorentino, Health Affairs 2011

- Only 45% of vertebral fractures were mentioned in the radiologist’s report at a major tertiary-care teaching hospital.
  - Kim et al, Am J Roentgenol 2004;182:297

- < 30% of women who have sustained fragility fracture get evaluation or osteoporosis treatment.
  - NCQA, The State of Health Care Quality 2013
Declining use of osteoporosis medication

**Fig. 2.** Annual unadjusted probability of osteoporosis medication use within 12 months after discharge (Kaplan-Meier method).
Dual-energy X-ray Absorptiometry (DXA)
Bone Mineral Density (BMD)

Lumbar spine

Proximal femur
Bone mineral density (BMD) predicts fracture better than cholesterol predicts heart disease.
### Relationship between BMD and Fracture Risk

<table>
<thead>
<tr>
<th>BMD site</th>
<th>Hip Fx</th>
<th>Spine Fx</th>
<th>Wrist Fx</th>
<th>All Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>2.6</td>
<td>1.8</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>PA spine</td>
<td>1.6</td>
<td>2.3</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Distal radius</td>
<td>1.8</td>
<td>1.7</td>
<td>1.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

T-score threshold

- WHO working group

<table>
<thead>
<tr>
<th>Bone mineral density (BMD) T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Osteopenia</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>

- Doesn’t apply to:
  » Premenopausal women
  » Men under 65
  » Children

Kanis JBMR 1994
WHO Technical Report Series No 843, 1994
Bone density and fracture risk as a continuum

Remaining lifetime risk of hip fracture in women at age 50 years based on BMD at the femoral neck

**Lifetime risk (%)**

- Osteoporosis
- Osteopenia
- Normal

**Femoral neck BMD (g/cm²)**

**SD units**

-3  -2  -1  0  1  1.1  1.2

WHO Technical Report Series No 843, 1994
Most fractures occur in women without osteoporosis

Bone mineral density (BMD), osteoporotic fracture rate, and number of women with fractures.
Most fractures occur in women without osteoporosis

Bone mineral density (BMD), osteoporotic fracture rate, and number of women with fractures.

Wainwright et al, JBMR 2001
Siris et al, Arch Int Med 2004
Schuit et al Bone 2004
Most fractures occur in women without osteoporosis

### Fracture Rate

<table>
<thead>
<tr>
<th>BMD Distribution</th>
<th>Fracture Rate</th>
<th>No. of Women with Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.0</td>
<td>0.5 to 0.0</td>
<td>0.0 to -0.5</td>
</tr>
<tr>
<td>1.0 to 0.5</td>
<td>-0.5 to -1.0</td>
<td>-1.0 to -1.5</td>
</tr>
<tr>
<td>0.5 to 0.0</td>
<td>-1.5 to -2.0</td>
<td>-2.0 to -2.5</td>
</tr>
<tr>
<td>0.0 to -0.5</td>
<td>-2.5 to -3.0</td>
<td>-3.0 to -3.5</td>
</tr>
<tr>
<td>-0.5 to -1.0</td>
<td>-3.5</td>
<td></td>
</tr>
</tbody>
</table>

Bone mineral density (BMD), osteoporotic fracture rate, and number of women with fractures.

55-80% of women who fracture have non-osteoporotic T-scores

Wainwright et al, JBMR 2001
Siris et al, Arch Int Med 2004
Schuit et al Bone 2004
Fundamental problem

Fractures

Osteoporosis
$T \leq -2.5$

Risk stratification on the basis of T-score alone is insufficient
Age increases fracture risk independent of bone density.

Hui et al, JCI 1998
Other clinical factors increase fracture risk independent of bone density

Kanis et al, Bone 2009
FRAX: Fracture Risk Assessment Tool

- Online tool developed by WHO
- Country-specific and ethnic-specific calculations
- Goal: to risk-stratify treatment-naïve osteopenic patients

http://www.shef.ac.uk/FRAX/
Notes on FRAX

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian)  Name/ID:  

Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
   - Age: Y: [ ], M: [ ], D: [ ]
2. Sex
   - Male  Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture
   - No  Yes
6. Parent Fractured Hip
   - No  Yes
7. Current Smoking
   - No  Yes
8. Glucocorticoids
   - No  Yes
9. Rheumatoid arthritis
   - No  Yes
10. Secondary osteoporosis
    - No  Yes
11. Alcohol 3 or more units/day
    - No  Yes
12. Femoral neck BMD (g/cm²)

Select BMD
- CE-Lunar
- Hologic
- Norland
- T-Score
- DMS/Medlink
- Mindways QCT

Weight Conversion
Pounds  kg

Height Conversion
Inches  cm

03531556
Individuals with fracture risk assessed since 1st June 2011

Print tool and information
FRAX underestimates fracture risk in T2DM

Giangregorio et al, JBMR 2012
FRAX adjustment for DM2

Use as proxy for DM2?
Limitations of FRAX

• May **underestimate** risk of fracture in patients with:
  » Diabetes
  » Discordance between spine vs. femoral neck T-score
  » Frequent falls

• Cannot take into account **dose-response** relationships:
  » Smoking
  » Glucocorticoids
  » Number and severity of previous fracture history

• Should not be used in patients who have received pharmacologic osteoporosis therapy
Lab testing

- Standard testing:
  » Ca, Pi, Cr, Alk Phos, 25OHD, PTH

- Further w/u indicated when severity of osteoporosis exceeds expectations
  » Z-score < -2.0 (*not validated*)

- Based on clinical history, consider:
  » TSH
  » SPEP/UPEP
  » Testosterone
  » 24 hr urine Ca + Cr
  » iCa + 1,25(OH₂)D
  » Celiac panel
  » 24 hour urine free cortisol

Data from WHO 2004
Postmenopausal Osteoporosis Treatment (NOF)

- Treat with osteoporosis medications if **any** of the following:
  - History of fragility fractures
  - T-score ≤ -2.5 at PA spine, total hip, or femoral neck
  - Absolute 10-year fracture risk (FRAX score)
    - ≥ 3% for hip or
    - ≥ 20% for major osteoporotic fracture

- Supported by AACE, ISCD, IOF, NAMS, ACOG, ACR, ASBMR, Endocrine Society, and others
Lifestyle improvements

- Calcium ~1200mg/day
  - Milk = 300 mg/cup
  - Cheese = 150-300 mg/oz
  - Yogurt = 300-450 mg/8 oz
  - Calcium supplements: calcium carbonate, calcium citrate

- Vitamin D ~800 IU/day
  - IOM suggests >20 ng/dL
  - Osteoporosis experts suggest >30 ng/dL

- Weight-bearing exercise
  - Work with a physical therapist
  - Discuss fall prevention and home safety

- Calcium and vitamin D modestly reduce fracture risk Chung et al Ann Intern Med. 2011;155(12):827-838
800 mg elemental calcium / serving
400 mg elemental calcium / tablet
Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology

Stephen L. Kopecky, MD; Douglas C. Bauer, MD; Martha Gulati, MD; Jeri W. Nieves, PhD; Andrea J. Singer, MD; Peter P. Toth, MD, PhD; James A. Underberg, MD; Taylor C. Wallace, PhD; and Connie M. Weaver, PhD

**Description:** Calcium is the dominant mineral present in bone and a shortfall nutrient in the American diet. Supplements have been recommended for persons who do not consume adequate calcium from their diet as a standard strategy for the prevention of osteoporosis and related fractures. Whether calcium with or without vitamin D supplementation is beneficial or detrimental to vascular health is not known.

**Recommendation:** The National Osteoporosis Foundation and American Society for Preventive Cardiology adopt the position that there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time. In light of the evidence


For author affiliations, see end of text.

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Mechanism of Action</th>
<th>Mode of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen*</td>
<td>Hormone replacement therapy</td>
<td>Anti-resorptive</td>
<td>PO daily</td>
</tr>
<tr>
<td>Calcitonin (Miacalcin®, Fortical®)</td>
<td>Anti-resorptive</td>
<td>Anti-resorptive</td>
<td>Nasal spray daily</td>
</tr>
<tr>
<td>Raloxifene (Evista®)*</td>
<td>Selective estrogen receptor modulator</td>
<td>Anti-resorptive</td>
<td>PO daily</td>
</tr>
<tr>
<td>Alendronate (Fosamax®)*</td>
<td>Bisphosphonate</td>
<td>Anti-resorptive</td>
<td>PO weekly</td>
</tr>
<tr>
<td>Risedronate (Actonel®)*</td>
<td>Bisphosphonate</td>
<td>Anti-resorptive</td>
<td>PO weekly</td>
</tr>
<tr>
<td>Ibandronate (Boniva®)*</td>
<td>Bisphosphonate</td>
<td>Anti-resorptive</td>
<td>PO monthly or IV q3 months</td>
</tr>
<tr>
<td>Zoledronate (Reclast®)*</td>
<td>Bisphosphonate</td>
<td>Anti-resorptive</td>
<td>IV yearly</td>
</tr>
<tr>
<td>Denosumab (Prolia™)</td>
<td>Monoclonal RANKL antibody</td>
<td>Anti-resorptive</td>
<td>SC q6 months</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>Recombinant PTH(1-34)</td>
<td>Anabolic</td>
<td>SC daily</td>
</tr>
</tbody>
</table>

*generic available in U.S.

Calcitonin is not recommended → lack of efficacy, cancer risk
Strontium is not recommended or FDA-approved → lack of efficacy, CVD risk
<table>
<thead>
<tr>
<th>Drug</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen*</td>
<td>↓ Spine and hip fx</td>
</tr>
<tr>
<td>Raloxifene (Evista®)*</td>
<td>↓ Spine fx</td>
</tr>
<tr>
<td></td>
<td>Reduces risk of breast and uterine cancer</td>
</tr>
<tr>
<td>Alendronate (Fosamax®)*</td>
<td>↓ Spine and hip fx</td>
</tr>
<tr>
<td></td>
<td>Continues working after medication is stopped</td>
</tr>
<tr>
<td>Risedronate (Actonel®)*</td>
<td>↓ Spine and hip fx</td>
</tr>
<tr>
<td>Ibandronate (Boniva®)*</td>
<td>↓ Spine fx</td>
</tr>
<tr>
<td>Zoledronate (Reclast®)*</td>
<td>↓ Spine and hip fx</td>
</tr>
<tr>
<td></td>
<td>Continues working after medication is stopped</td>
</tr>
<tr>
<td>Denosumab (Prolia™)</td>
<td>↓ Spine and hip fx</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>↓ Spine and nonvertebral fx</td>
</tr>
</tbody>
</table>

*generic available in U.S.
## FDA-approved Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Benefits</th>
<th>Side effects</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen*</td>
<td>↓ Spine and hip fx</td>
<td>VTE, CVD, breast cancer</td>
<td>$$</td>
</tr>
<tr>
<td>Raloxifene (Evista®)*</td>
<td>↓ Spine fx</td>
<td>Hot flashes, VTE</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>Reduces risk of breast and uterine cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax®)*</td>
<td>↓ Spine and hip fx</td>
<td>GI intolerance, ONJ, AFF</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Continues working after medication is stopped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel®)*</td>
<td>↓ Spine and hip fx</td>
<td>GI intolerance, ONJ, AFF</td>
<td>$$</td>
</tr>
<tr>
<td>Ibandronate (Boniva®)*</td>
<td>↓ Spine fx</td>
<td>GI intolerance, ONJ, AFF</td>
<td>$$</td>
</tr>
<tr>
<td>Zoledronate (Reclast®)*</td>
<td>↓ Spine and hip fx</td>
<td>Inflammatory reaction, hypocalcemia, ONJ, AFF</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>Continues working after medication is stopped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab (Prolia™)</td>
<td>↓ Spine and hip fx</td>
<td>Hypocalcemia, ONJ, AFF, rapid bone loss after therapy stopped</td>
<td>$$$</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>↓ Spine and nonvertebral fx</td>
<td>Theoretical risk of osteosarcoma, rapid bone loss after therapy stopped</td>
<td>$$$$</td>
</tr>
</tbody>
</table>

*generic available in U.S.

VTE = venous thromboembolism
CVD = cardiovascular disease
ONJ = osteonecrosis of the jaw
AFF = atypical femoral fracture
Clinical Benefit of Bisphosphonates

- Relative risk reduction for fractures
- Postmenopausal women with osteoporosis
- 3 years bisphosphonate treatment

Which medication to choose?

- First-line therapy in most women → alendronate

- Considerations in other situations
  - Younger women with perimenopausal symptoms → hormone replacement therapy
  - Younger postmenopausal women → raloxifene
  - Recent hip fracture → zoledronate
  - GERD, gastric bypass → zoledronate
  - Poor compliance → zoledronate
  - Renal failure → denosumab
  - Severe osteoporosis (particularly at the spine), and/or “failure” on standard Rx → teriparatide
How long to treat for?

- Bisphosphonates have a long half-life (~years) within the skeleton
  - May convey long-term fracture benefit even after stopping medication
  - Concern about long-term suppression of bone remodeling
- Long-term treatment (beyond 3-5 years) may have fracture benefit in high-risk patients
Long-Term Efficacy Data: ALN

- **FLEX Study**
  - 1099 osteoporotic women assigned to alendronate group in FIT (4 years ALN 5 or ALN 10 QD)
  - Re-randomized to ALN 5, ALN 10 or placebo for an additional 5 years

Black et al, JAMA 2006
Long-Term Efficacy Data: ALN

Fractures: Fewer clinical spine fractures in continuous ALN group

Black et al, JAMA 2006
Long-Term Efficacy Data

All non-spine fractures

Favors ALN  Favors PBO

FN T>-2.0

-2.5<FN T<-2.0

FN T<-2.5

RR (95% CI)

0.1  1  10

0.50  0.79  1.41

Schwartz et al, JBMR 2010
HORIZON-PFT Extension study  
N=1233 osteoporotic women

Long-term treatment with alendronate (up to 10 years) and zoledronate (up to 6 years) may reduce risk of vertebral fractures, particularly among patients who continue to have osteoporotic bone density.

Black et al, JBMR 2012
Fearing Drugs’ Rare Side Effects, Millions Take Their Chances With Osteoporosis

By GINA KOLATA  JUNE 1, 2016

CT scans show the progression of one patient's vertebra over a six- to eight-year period, from normal bone density to moderate osteoporosis and severe osteoporosis. A. Boyle and F.D. Miller
Osteonecrosis of the jaw

- Necrosis of jaw bone due to obstruction of its blood supply
  - Chronic condition >8 weeks
  - Often accompanied by osteomyelitis

- Prevalence in bisphosphonate-treated population 0.01-0.1%

- Risk factors:
  - major dental surgery, poor underlying dentition, chronic glucocorticoids, radiation therapy, high-dose bisphosphonate therapy
Osteonecrosis of the jaw

• American Dental Association does not require stopping bisphosphonate prior to procedure
  » If elective dental procedure, then consider delaying initiation or stopping bisphosphonate for ~3 months prior to procedure and during healing
  » If urgent dental procedure, proceed without delay

• In cases of ONJ, wide range of treatments
  » Mouth rinses, antibiotics
  » Teriparatide
  » Surgical debridement

Atypical femoral fractures (AFF)

- Subtrochanteric or diaphyseal
- Prodromal pain
- Minimal trauma
- Frequently bilateral
- Key radiologic features: cortical thickening, originates in lateral cortex, periosteal “beaking”
- Delayed healing

Very few subtrochanteric fractures are AFFs

ASBMR Task Force Report, JBMR 2013
Radiographic Features of AFFs

Transverse orientation
Cortical thickening
Transverse fracture
Medial spike
Lateral periosteal beaking
Cortical thickening
Lateral periosteal beaking
Atypical femoral fractures

- AFFs are rare
  - ~0.5% of all hip fractures
  - ~0.05% of all patients treated with bisphosphonates

- Associated with bisphosphonate and denosumab use
  - Risk increases with longer duration of use
  - Risk decreases after stopping bisphosphonates: 70% decline in risk each year off bisphosphonate

- Also occur among adults who have never taken antiresorptive medications

- Other possible risk factors
  - Glucocorticoid use, Asian ethnicity, active RA, severe vitamin D deficiency, PPI

ASBMR Task Force Report, JBMR 2013
Schilcher et al, NEJM 2011
## Table 3. Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture versus the Hypothetical Number Associated with an Increase of One Atypical Femur Fracture.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Needed to Treat (3 yr)</th>
<th>No. of Events Prevented per 1000 Patients Treated (3 yr)</th>
<th>No. Needed to Harm (3 yr)</th>
<th>No. of Atypical Femur Fractures Associated with Treating 1000 Women for 3 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any nonvertebral, including hip</td>
<td>35</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>90</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral fracture (morphometric)</td>
<td>14</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fracture</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Assumption #1: Treating patients of equivalent risk to these seminal osteoporosis trials

### Assumption #2: Treatment duration of 3 years; less data to calculate NNT and NNH for longer treatment times
Atypical Fractures: Conclusions

• Collective evidence does indicate an association between bisphosphonates and atypical fractures of the femur.

• The absolute risk of these fractures appears to be extremely low.

• In patients with osteoporosis treated for 3 years, the number of fractures prevented far exceeds the number caused (100:1).
Consider discontinuing therapy after 3-5 years if the patient’s BMD and other risk factors no longer meet the criteria for initial treatment.

- Monitor BMD and consider resuming treatment if rapid bone loss ensues
- Consider “off-effect” of non-bisphosphonate treatments

Continue therapy for up to 10 years and/or switch to teriparatide if the risk of fracture remains high.

If a patient experiences a serious adverse effect and is still at high risk of fracture, consider changing to teriparatide.

- Very preliminary evidence that teriparatide may be beneficial after atypical fracture, ONJ
Abaloparatide: osteoanabolic

- FDA approved in April 2017
- Daily SC self-injection
- Increases bone formation and bone resorption, with net anabolic effect
- Potential concerns: hypercalcemia, osteosarcoma

**PTHrP analogue:**
Binds to same PTH1R as teriparatide

![Image of Abaloparatide pen and diagram of PTHrP analogue]
Abaloparatide: bone density

- ACTIVE trial, n=2463 women, 18 months
  - ABL 80 mcg
  - TPT 20 mcg
  - Placebo

Miller et al, JAMA 2016
Abaloparatide: fracture efficacy

- ACTIVE trial, n=2463 women, 18 months
  - ABL 80 mcg
  - TPT 20 mcg
  - Placebo

- ABL vs. Placebo
  - -86% vertebral fx
  - -43% nonvertebral fractures

- Hypercalcemia: 3.4% for ABL vs. 6.4% for TPT
Take-Home Points: Diagnosis

• Osteoporosis is underdiagnosed and undertreated

• Universal screening of postmenopausal women ≥ 65 is recommended

• Although osteoporotic BMD greatly increases fracture risk, most fractures occur in osteopenic patients

• Clinical risk factors should be incorporated along with T-scores to guide treatment decisions
  » FRAX is useful to risk stratify osteopenic patients, with understanding of potential limitations
Take-Home Points: Treatment

- Osteoporosis medications reduce risk of fractures by ~40-60%
- Atypical femoral fractures are associated with long-term anti-resorptive therapy but absolute risk is extremely low
- After 3-5 years of treatment, consider drug holiday in lower-risk patients
- For high-risk patients, fracture reduction benefits of long-term treatment outweigh potential risks