Definition and Mechanism
Definition (Characteristics)

- Low bone mass
- Deterioration of bone tissue
- Disruption of bone architecture
- Compromised bone strength
- Increased Risk of fracture
- BMD \leq 2.5\ SD below young normal reference population
Normal Bone

Boyde A, London

Female, age 30 years
Transition from Normal Bone Structure to Osteoporosis

Loss of horizontal cross-ties greatly reduces strength of the remaining vertical trabeculae

Normal 30 year old on left. Loss of trabecular connectivity and perforation of trabecular plates in OP
Severe Osteoporosis

Male, age 89 years

Boyde A, London
Prevalence

• More than 10 million Americans have OP
  – 33.6 million Americans have low hip BMD
    » NHANES III

• One out of every two white women will experience an osteoporotic fracture
  – One in every five men

• OP less frequent in African Americans
  – Those with OP same elevated risk of fracture
FRACTURE IMPACT

- Hip Fxs 8.4-36% excess mortality @ 1 year
  - Higher mortality in men than women
- 1/3 of hip Fx patients will Fx the other hip
- ≤ 20% of hip Fx patients require long term care
  - 40% fully regain pre Fx degree of independence
- Following Vertebral Fx:
  - Increased mortality, back pain, height loss, kyphosis
    - Restrictive lung disease, abdominal symptoms

NOF Guideline 2013
Complications of Osteoporosis

- Pain
- Height loss
- Kyphosis
- Activity limitations
- Restrictive lung disease
- Altered abdominal condition
- Psychological symptoms
DISEASE IMPACT

• 50 YEAR OLD CAUCASIAN WOMAN
  FRACTURE RISK IN REMAINING LIFE
    – 16 % RISK OF HIP Fx
    – 32% RISK OF VERTEBRAL Fx

• WOMEN WITH VERTEBRAL Fx
    – 5 X HIGHER RISK OF VERTEBRAL Fx
    – 2 X HIGHER RISK OF HIP Fx

MORTALITY FOLLOWING CLINICAL FRACTURE

• 6459 🩸 in fracture intervention trail (FIT)
  – Age: 55-81 years  - F/U: Ave. 3.8 years
• 907 🩸 experienced a clinical Fx:
  – Older, Lower BMD, History of previous Fx
• 122 🩸 died during F/U period:
  – 23/122 (19%) occurred after clinical Fx

Cauley, JA et al. Osteoporosis Int. 2000;11:556-561
Relative Risk of Death Following Clinical Fractures Fracture Intervention Trial (FIT)*


*6459 postmenopausal women ages 55-81 years followed for an average of 3.8 years
PREVENTION AND TREATMENT OF
OSTEOPOROSIS

Guidelines Developed By The
National Osteoporosis
Foundation

NOF Guideline 2013
Physician Recommendations

• For all patients: counsel on the risk of OP and related low trauma fractures
• Advise adequate intake of fruits & vegetables:
  – \( \geq 1200 \) mg/day calcium for W \( >51 \) & M \( >71 \) yrs.
  – 800-1000 IU/day Vitamin D in those \( \geq 50 \) yrs.
• Recommend regular weight bearing and muscle strengthening exercise to reduce the risk of falls and fracture
Physician Recommendations

• Advise avoidance of tobacco smoking and excessive alcohol intake
• Measure height annually (stadiometer best)
• Recommend BMD testing:
  – Women ≥ 65 years of age
  – Men ≥ 70 years of age
  – Younger postmenopausal women (PMW) and men 50-69 years based on risk factor profile
  – All patients with low trauma fracture

NOF Guideline 2013
Appropriate Testing Interval?

- 4957 women ($\geq 67$ years old)
- No osteoporosis at baseline BMD assessment
- Follow up longitudinally up to 15 years
- Screening interval defined as time until 10% of subjects to transition to osteoporosis:
  - DXA T score $< -2.5$ SD
  - BEFORE any osteoporotic fracture occurs

Gourlay ML et al. 2012 NEJM 366:225-33
Appropriate Monitoring Interval?

Gourlay ML et al. 2012 NEJM 366:225-33

Cumulative Incidence of Osteoporosis (%)

- Advanced osteopenia
  - T score, -2.00 to -2.49
  - (N=1351)

- Moderate osteopenia
  - T score, -1.50 to -1.99
  - (N=1478)

- Mild osteopenia
  - T score, -1.01 to -1.49
  - (N=1386)

- Normal BMD
  - T score, -1.00 or higher
  - (N=1255)

Years since Baseline Study Visit
### Table 3. Interval between Baseline Osteopenia and the Development of Osteoporosis in 10% of Study Participants, According to Age, BMI, and Estrogen-Use Status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild Osteopenia</th>
<th>Moderate Osteopenia</th>
<th>Advanced Osteopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of years (95% CI)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>67 yr</td>
<td>—</td>
<td>5.6 (4.9–6.4)</td>
<td>1.3 (1.1–1.6)</td>
</tr>
<tr>
<td>70 yr</td>
<td>—</td>
<td>5.1 (4.6–5.7)</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>75 yr</td>
<td>16.2 (13.0–20.2)</td>
<td>4.4 (3.9–4.9)</td>
<td>1.0 (0.9–1.2)</td>
</tr>
<tr>
<td>80 yr</td>
<td>13.8 (10.9–17.6)</td>
<td>3.7 (3.2–4.3)</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>85 yr</td>
<td>11.8 (9.0–15.5)</td>
<td>3.2 (2.6–3.9)</td>
<td><strong>0.8 (0.6–0.9)</strong></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5</td>
<td>—</td>
<td>4.4 (3.5–5.4)</td>
<td><strong>0.8 (0.6–0.9)</strong></td>
</tr>
<tr>
<td>25.0</td>
<td>18.7 (14.5–24.0)</td>
<td>4.6 (4.1–5.1)</td>
<td>1.0 (0.9–1.2)</td>
</tr>
<tr>
<td>30.0</td>
<td>14.6 (12.0–17.9)</td>
<td>4.8 (4.2–5.5)</td>
<td>1.3 (1.1–1.5)</td>
</tr>
<tr>
<td><strong>Estrogen use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>—</td>
<td>6.9 (5.7–8.4)</td>
<td>1.6 (1.3–2.0)</td>
</tr>
<tr>
<td>Past or none</td>
<td>16.1 (12.9–20.0)</td>
<td>4.3 (3.9–4.8)</td>
<td><strong>1.0 (0.9–1.2)</strong></td>
</tr>
</tbody>
</table>
• Vertebral imaging should be performed:
  – Women ≥ 70 and Men ≥ 80
  – Women 65-69, Men 75-79 AND BMD T ≤ -1.5
  – Postmenopausal Women 50-64, Men 50-69 years:
    • History low trauma fracture
    • History of height loss ≥ 1.5 inches (4 cm)
    • Prospective (measured) height loss ≥ 0.8 inches (2 cm)
    • Recent or ongoing longterm glucocorticoid therapy

• Check for causes of secondary osteoporosis
RISK FACTORS FOR OSTEOPOROTIC FRACTURE

• NONMODIFIABLE
  – PERSONAL history of FRACTURE as an adult
  – Hx of FRACTURE IN 1° RELATIVE
  – Caucasian Race
  – Advanced Age
  – Female Sex
  – Dementia, Poor Health/ Frailty
RISK FACTORS FOR OSTEOPOOROTIC FRACTURE

• POTENTIALLY MODIFIABLE
  – CURRENT cigarette SMOKING

  – LOW BODY WEIGHT (<127 lbs.)

  – Estrogen deficiency
    • Early menopause (< age 45) or bilateral ovariectomy
    • Prolonged premenopausal amenorrhea (> 1 year)
RISK FACTORS FOR OSTEOPOOROTIC FRACTURE

• Potentially modifiable (cont.)
  – Low calcium intake (lifelong)
  – Alcoholism
  – Inadequately corrected eyesight
  – Recurrent falls
  – Inadequate physical activity
  – Poor health/frailty
Physician Recommendations

• **Initiate treatment**
  - PMW and M ≥ 50 with vertebral and hip fractures

• **Initiate treatment in PMW/ M ≥ 50 if:**
  - DXA BMD T score ≤ -2.5 after appropriate W/U
    • Femoral neck, Total hip, L spine
  - BMD T score −1 to −2.5 if
    • 10 year hip fracture risk ≥ 3%
    • 10 year OP related Fx risk ≥ 20%
    • FRAX®; www.shef.ac.uk/FRAX

NOF Guideline 2013
Physician Recommendations

• Current FDA-approved Pharmacologic Rx:
  – Bisphosphonates
    • Alendronate, Risedronate, Ibandronate, Zolendronate
Alendronate: ↓ Fractures (FIT I)

- ≥ 1 NEW VERT. Fx
  - ALEN. 78 (8.0%)
  - PLAC. 145 (15%)
  - REL. RISK ↓
    - 0.53 (0.41–0.68)
- CLINICAL VERT. Fx
  - ALEN. 23 (2.3%)
  - PLAC. 50 (5%)
  - REL. RISK ↓
    - 0.45 (0.27–0.72)

Black et al. 1996 Lancet;348:1535-41
Alendronate: ↓ Fx 2° Outcome

- **Risk hip fracture**
  - Alendronate 11 (1.1%)
  - Placebo 22 (2.2%)
  - Relative Risk ↓
    - 0.49 (0.23-0.99)

- **Risk wrist fracture**
  - Alendronate 22 (2.2%)
  - Placebo 41 (4.1%)
  - Relative Risk ↓
    - 0.52 (0.31-0.87)

Black et al. 1996 Lancet;348:1535-41
Hip Fracture Incidence in High Risk Patients: Patients with Prevalent Vertebral Fracture*

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT 1 (Alendronate)</td>
<td>2.2</td>
<td>0.047</td>
</tr>
<tr>
<td>HIP, LBD (Risedronate)</td>
<td>5.7</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>PROOF (Calcitonin)</td>
<td>3.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Data not comparable since extracted from independent studies.

Yearly Zolendronic Acid

• 7765 PMO randomized:
  – Annual 15 minute infusions over 3 years
    • 3889 5 mg Z-acid (mean age 73 yrs)
• Primary end points @ 3 years follow up:
  – Vertebral Fractures (morphometric) ARR
    • Reduced 70% (CI 0.24-0.38)
  – Hip Fractures ARR 2.5 vs. 1.4%
    • Reduced 41% (CI 0.42-0.83)

Black DM et al. 2007 NEJM 356:1809-22
Zolendronic Acid Vertebral Fx

Black DM et al. 2007 NEJM 356:1809-22
Z Acid: Hip and Non-vert Fx

B Hip Fracture

C Nonvertebral Fracture

- Hazard ratio, 0.59 (95% CI, 0.42–0.83)
P=0.002

- Hazard ratio, 0.75 (95% CI, 0.64–0.87)
P<0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>3875</td>
</tr>
<tr>
<td>Placebo</td>
<td>3861</td>
</tr>
<tr>
<td></td>
<td>3807</td>
</tr>
<tr>
<td></td>
<td>3674</td>
</tr>
<tr>
<td></td>
<td>3553</td>
</tr>
<tr>
<td></td>
<td>3494</td>
</tr>
<tr>
<td></td>
<td>3387</td>
</tr>
<tr>
<td></td>
<td>3161</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>3875</td>
</tr>
<tr>
<td>Placebo</td>
<td>3861</td>
</tr>
<tr>
<td></td>
<td>3806</td>
</tr>
<tr>
<td></td>
<td>3694</td>
</tr>
<tr>
<td></td>
<td>3577</td>
</tr>
<tr>
<td></td>
<td>3499</td>
</tr>
<tr>
<td></td>
<td>3397</td>
</tr>
<tr>
<td></td>
<td>3144</td>
</tr>
</tbody>
</table>

Black DM et al. 2007 NEJM 356:1809-22
Zolendronate after Hip Fracture

- 2127 hip fracture patients
  - 75% women, mean age 74.5, all Rx Ca/Vit D
- Intervention: 15 minute Z-acid infusion vs. P
  - Within 90 days after surgical Hip Fracture repair
- Evaluation: median follow up 1.9 years
  - Primary end-point new clinical fracture
  - Secondary end-point survival, AEs

Lyles KW et al. 2007 NEJM 357:1799-1809
Zolendronate after Hip Fracture

Lyles KW et al. 2007 NEJM 357:1799-1809

* p<0.05
### Table 3. Adverse Events in the Safety Population.

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 1057)</th>
<th>Zoledronic Acid (N = 1054)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>852 (80.6)</td>
<td>867 (82.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>436 (41.2)</td>
<td>404 (38.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Death‡</td>
<td>141 (13.3)</td>
<td>101 (9.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Discontinuation of follow-up owing to adverse event</td>
<td>18 (1.7)</td>
<td>21 (2.0)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Renal event — no./total no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in serum creatinine &gt;0.5 mg/dl</td>
<td>50/900 (5.6)</td>
<td>55/886 (6.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>Calculated creatinine clearance &lt;30 ml/min</td>
<td>65/891 (7.3)</td>
<td>72/882 (8.2)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Five typical symptoms ≤3 days after infusion — no. (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>9 (0.9)</td>
<td>33 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>3 (0.3)</td>
<td>6 (0.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (0.9)</td>
<td>16 (1.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23 (2.2)</td>
<td>33 (3.1)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Pyrexia‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>9 (0.9)</td>
<td>73 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After first infusion</td>
<td>7 (0.7)</td>
<td>72 (6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After second infusion</td>
<td>2 (0.3)</td>
<td>3 (0.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>After third infusion</td>
<td>0</td>
<td>3 (0.9)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Lyles KW et al. 2007 NEJM 357:1799-1809
# Zolendronate after Hip Fracture

<table>
<thead>
<tr>
<th>Cardiovascular or cerebrovascular event — no. (%)</th>
<th>Placebo</th>
<th>Z Acid</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>27 (2.6)</td>
<td>29 (2.8)</td>
<td>0.79</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>14 (1.3)</td>
<td>12 (1.1)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>38 (3.6)</td>
<td>46 (4.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Fatal event</td>
<td>6 (0.6)</td>
<td>9 (0.9)</td>
<td>0.45</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>17 (1.6)</td>
<td>13 (1.2)</td>
<td>0.58</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>52 (4.9)</td>
<td>36 (3.4)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Lyles KW et al. 2007 NEJM 357:1799-1809
ONJ and Bisphosphonates

- ONJ associated with aminobisphosphonates
- 94% of cases Rx with IV Z-acid or APD
  - 85% of affected have M-M or Breast CA
- Prevalence in CA patients 6-10%
- Prevalence in PMOP patients unknown
- 60%: dentoalveolar surgery, 40%: infection, denture trauma, other physical trauma

Woo S-B et al. 2006 AIM 144:753-761
Prevalence of ONJ

- ONJ NOT identified prospectiely in any of the clinical trials with > 60,000 patient years
- HORIZON trial 2 cases of ONJ (1 ZA, 1 P)
- No causal link of Bisphosphonates and ONJ
- Estimated that there have been 190 million Rxs for PO and 6 million Rxs for IV
- Oral ONJ incidence 1:10,000-600,000

Watts & Diab 2010 JCEM 95:1555-65
Practice Recommendations: ONJ

- Patients should maintain good oral hygiene
- Patients starting therapy:
  - Inform of minimal risks of ONJ
  - Dental exam and any procedures should be completed and healed prior to initiation
- During treatment:
  - Routine cleaning / restorative procedures OK
  - Invasive procedures consider drug holiday
    - Recognize that there is no data to indicate that this is effective

Watts & Diab 2010 JCEM 95:1555-65
Subtrochanteric and Diaphyseal Fractures and Bisphosphonates

- Recent case reports and small series have identified bisphosphonate use associated with atypical fractures of the femoral shaft.

- A population based registry study concluded that there was no evidence of an increased risk of these fractures with either short or long term bisphosphonate use

  - Abrahamson et al. JBMR 2009;24:1095-102
Prospective Placebo Controlled Evidence and Atypical Fxs

- 14,915 women in FIT, FLEX, HORIZON
- 284 suffered femoral fractures
- 12 fractures in 10 patients were atypical
  - 2.3 atypical fractures per 10,000 patient-years (rare event)

All RR = NS

Rarity of event Limits power

Black DM et al. 2010 JCEM 362:1761-1771
# Duration and Drug Holidays

<table>
<thead>
<tr>
<th>Risk</th>
<th>Therapy</th>
<th>Holiday Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Mild↑</td>
<td>≤ 5 yrs</td>
<td>→ sig. ↓ BMD or Fx</td>
</tr>
<tr>
<td>Mod↑</td>
<td>5-10 yrs</td>
<td>2-3 years or → sig. ↓ BMD or Fx</td>
</tr>
<tr>
<td>High↑</td>
<td>10 years</td>
<td>1-2 years or → sig. ↓ BMD or Fx Alt Rx (raloxifene or teriparatide)</td>
</tr>
</tbody>
</table>

Watts & Diab 2010 JCEM 95:1555-65
What to do After 3-5 years Rx

- Patients with Femoral Neck T ≤ -2.5
  - Highest risk of vertebral Fx
  - Continue the bisphosphonate
- Patients with Vert Fx and FNeck T ≤ -2.0
  - May also benefit from continued Rx
- Patients with Fneck T > -2.0
  - Low risk of Vert Fx, unlikely benefit of Rx

Physician Recommendations

• Current FDA-approved Pharmacologic Rx:
  – Bisphosphonates
    • Alendronate, Risedronate, Ibandronate, Zolendronate
  – Calcitonin

NOF Guideline 2013
Prospective Vertebral Fracture Studies in Postmenopausal Women With Prevalent Fractures*

Raloxifene¹ (60 mg/d)  
RR = 0.70  
P < .001

Alendronate² (5/10 mg/d)  
RR = 0.53  
P < .001

Risedronate³ (5 mg/d)  
RR = 0.59  
P < .003

Calcitonin⁴ (200 IU/d)  
RR = 0.63  
P = .04

% Women With ≥ 1 Vertebral Fracture

(N=169) (N=121) (N=145) (N=78) (N=50) (N=33)

% Δ LS BMD†  2.2  6.2  4.3  0.2

Not head-to-head comparison, † Vs. placebo
Physician Recommendations

- Current FDA-approved Pharmacologic Rx:
  - Bisphosphonates
    - Alendronate, Risedronate, Ibandronate, Zolendronate
  - Calcitonin
  - Estrogens
WHI HAZARD RATIOS

N=8102

N=8506

* = CI ≠ 1

JAMA 2002;288:321-333
Physician Recommendations

• Current FDA-approved Pharmacologic Rx:
  – Bisphosphonates
    • Alendronate, Risedronate, Ibandronate, Zolendronate
  – Calcitonin
  – Estrogens
  – SERM: Raloxifene

NOF Guideline 2013

**Effect of Raloxifene Treatment in Women With or Without Existing Fractures**

- MORE Trial 36 Months -

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients With Incident Fracture, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Existing Fx</td>
<td>RR 0.45* (95% CI 0.29, 0.71)</td>
</tr>
<tr>
<td>Existing Fx</td>
<td>RR 0.70* (95% CI 0.56, 0.86)</td>
</tr>
</tbody>
</table>

* rounded off in paper

1 year clin Fxs
Effects of Antiresorptive Therapy on the Incidence of Hip Fractures in Postmenopausal Women With Osteoporosis

% of Women With ≥1 New Hip Fracture

- Raloxifene MORE\textsuperscript{1}
- Alendronate FIT\textsuperscript{12}
- Alendronate FIT\textsuperscript{2 3}
- Risedronate VERT-NA\textsuperscript{4}
- Risedronate VERT-MN\textsuperscript{5}
- Risedronate HIP\textsuperscript{6}


Placebo compared to active therapy for each study
Not head-to-head comparisons
Relative Effectiveness for Non-Vertebral Fracture Prevention

- 43,135 recipients of statewide Rx benefits
  - oral bisphosphonates, nasal calcitonin, raloxifene
  - Mean age 79 years, 96% women, Rx 2000-2005

- Primary outcome:
  - Non vertebral Fracture ≤ 12 months of Rx start

- Results: 1051 NVFx observed ≤ 12 months of Rx start
  - 2.62 fractures per 100 person-years

Cumulative incidence of NVFx < 12 months of treatment initiation, by drug

Physician Recommendations

• Current FDA-approved Pharmacologic Rx:
  – Bisphosphonates
    • Alendronate, Risedronate, Ibandronate, Zolendronate
  – Calcitonin
  – Estrogens
  – SERM: Raloxifene
  – Parathyroid hormone
    • Teriparitide (PTH 1-34)

NOF Guideline 2013
PTH - Mechanism of Action

PTH binds to cell surface G protein-coupled receptor

- Decreased apoptosis of osteoblasts
- Stimulate differentiation: preosteoblasts to osteoblasts

Net increase in number and action of bone forming osteoblasts
Effect of rhPTH(1-34) on the Risk of New Vertebral Fractures

<table>
<thead>
<tr>
<th>Risk Reduction (RR)</th>
<th>Placebo (n=448)</th>
<th>rhPTH 20 (n=444)</th>
<th>rhPTH 40 (n=434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 0.31 (95% CI, 0.19 to 0.50)*</td>
<td>64%</td>
<td>65%</td>
<td>69%</td>
</tr>
<tr>
<td>RR 0.35 (95% CI, 0.22 to 0.55)*</td>
<td>22%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

No. of women who had ≥ 1 fracture

Neer et al. NEJM 2001; 334:1434-41

*p <0.001 vs. Placebo
rhPTH(1-34): Risk of Nonvertebral Fragility Fractures

* Percent of women who had one or more nonvertebral fragility fractures during the study

*p <0.05 vs. Placebo

(time to first fracture)

* Percent of women who had one or more nonvertebral fragility fractures during the study

Neer et al. NEJM 2001; 334:1434-41
Physician Recommendations

• Current FDA-approved Pharmacologic Rx:
  – Bisphosphonates
    • Alendronate, Risedronate, Ibandronate, Zolendronate
  – Calcitonin
  – Estrogens
  – SERM: Raloxifene
  – Parathyroid hormone
    • Teriparitide (PTH 1-34)
  – RANKL inhibitor: Denosumab

NOF Guideline 2013
Denosumab

• Receptor Activator of Nuclear Factor Kappa ligand (RANKL) results in:
  – Osteoclast differentiation, activation, survival

• Denosumab:
  – Fully human monoclonal antibody binds RANKL and inhibits RANKL activity
    • Results in osteoclast inhibition
    • Decreases bone resorption and increases bone density
Denosumab in PM Osteoporosis

- 7868 women 60-90 years old
  - BMD T score < - 2.5 but > - 4.0 (LS or T-Hip)
- Randomized to denosumab 60 mg or Placebo
  - S.C. injections Q 6 months for 36 months
- Efficacy end points
  - Primary: New vertebral fractures
  - Secondary: Non-vertebral and Hip fractures

Denosumab Fracture Outcomes


All RR reductions P < 0.05 vs. P
Denosumab Tolerability


* p<0.05 vs. P
Denosumab: FDA approval

• 06/01/10: Prolia® approved PMO therapy
• Indication: Women at high risk of fracture
  – Previous fracture
  – Multiple risk factors for fracture
  – Failure or intolerance of other PMO therapies
• Dosing 60 mg s.c. Q 6 months ($825.00/ injection)
• PI side effects: Back pain, extremity pain, high cholesterol levels, UTI (bladder), hypocalcemia, serious infections, dermatitis, rash and eczema
Physician Recommendations

• Current FDA-approved Pharmacologic Rx:
  – Bisphosphonates
    • Alendronate, Risedronate, Ibandronate, Zolendronate
  – Calcitonin
  – Estrogens
  – SERM: Raloxifene
  – Parathyroid hormone
    • Teriparatide (PTH 1-34)
  – RANKL inhibitor: Denosumab

• No Rx is indefinite, after 3-5 years re-assess
Future Treatment

New mechanisms for intervention
Osteocyte (SOST gene)

Sclerostin

Wnt Signaling pathway

Anti-sclerostin antibody??

Bone morphogenic protein Signaling pathway

Osteoblast
  Proliferation Function

Genetic Sclerostin deficiency
  → High bone mass
  → Increased bone strength
  → Resistance to fractures

Decreased Bone Formation
**Romosozumab**

- Humanized monoclonal anti-sclerostin ab
- Phase 2, MC, RPC, 8 group study
  - 5 doses of Romosozumab
  - Placebo, Alendronate and Teriperitide
- 367 postmenopausal women 55-85 years
  - DXA T ≤ -2.0 and ≥ 3.5
  - Excluded those with Fx, medications, illnesses

McClung MR et al. 2014 NEJM  epub ahead of print
Bone Density Results

McClung MR et al. 2014 NEJM  epub ahead of print
Bone Turnover Markers

McClung MR et al. 2014 NEJM  epub ahead of print
Androgen Deprivation Rx

• 112 men with non-metastatic Prostate CA
  – Receiving ADT for mean of 14 months @ baseline

• Alendronate 70 mg/week or placebo
  – All received Calcium and Vitamin D

• Primary outcomes:
  – DXA Spine and Hip; Bone turnover markers

• Results:
  – Baseline 39% OP, 52% Low bone mass
  – 12 months: NS difference in side effects

Figure 2. Mean (±SE) observed percentage change in bone mineral density from baseline to 6 and 12 months.

Tibolone

- Synthetic steroid

- Commonly used to treat:
  - Menopausal symptoms
  - Prevent bone loss

- Metabolites bind to steroid receptors
  - $\Delta^4$-tibolone binds:
    - Progesterone & androgen Receptors
  - $3\alpha$ & $\beta$-OH tibolone bind to estrogen Receptors
Strontium Ranelate in PMOP

• Patients: 1649 PM women
  – ≥ 1 vertebral Fx, LS BMD < 0.840 g/cm²
• Treatment:
  – Supplemented to 1500 mg Ca/day
  – 400-800 IU Vit. D/d (dep. on base 25-OH D)
• Randomized:
  – 2 grams Strontium Ranelate daily for 3 years
  – Placebo

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=723)</th>
<th>Strontium (n=719)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr ± SD)</td>
<td>69.2 ± 7.3</td>
<td>69.4 ± 7.2</td>
</tr>
<tr>
<td>Years P M</td>
<td>21.6 ± 8.7</td>
<td>22.1 ± 8.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 4.1</td>
<td>26.2 ± 4.1</td>
</tr>
<tr>
<td># prev. V. Fxs</td>
<td>2.2 ± 2.2</td>
<td>2.2 ± 2.0</td>
</tr>
<tr>
<td>LS BMD (g/cm²)</td>
<td>0.720 ± .12</td>
<td>0.731 ± .13</td>
</tr>
<tr>
<td>LS T score</td>
<td>-3.6 ± 1.2</td>
<td>-3.5 ± 1.3</td>
</tr>
</tbody>
</table>

Vertebral Fx Risk Reduction

* = p < 0.001

(0.36-0.74)

(0.48-0.73)

NNT = 9 X 3 yrs

Clinical Vertebral Fx Risk

* = p<0.003

(0.29-0.80)

(0.47-0.83)

Strontium Ranelate: BMD

Mean (+) ∆ adjusted BMD

Strontium Ranelate: BTM

Strontium Ranelate: BTM

Strontium Ranelate: Safety

- Bone Biopsies @ 36 months: Nl Bone!
  - No osteomalacia, No mineralization defects
- Metabolic effects:
  - Minor ↓ Ca, P04, PTH (no Sx), No Δ 25 or 1-25 Vit D
  - ↑ CPK (≥ 2 X ULN) 3.4% S-R, 1.8% P (no Sx)
    - > 88% returned to normal with further Rx
- Adverse effects:
  - Diarrhea, 6.1% S-R, 3.6% Placebo (p=0.02)
    - effect disappeared after 3 months

CLINICAL VERTEBRAL Fxs @ 1 YEAR

Women with Fx %

<table>
<thead>
<tr>
<th>Group</th>
<th>TOTAL POP</th>
<th>PREV Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLACEBO</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>RALOX 60</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>

RR = 0.32 (.13-.79)  RR = 0.32 (.11-.77)

N = 2292  N = 2259

* CI ≠ 1

CLINICAL VERTEBRAL Fxs @ 1 YEAR

* = p< 0.05

Risedronate: L Spine BMD Change versus Vertebral Fracture Incidence

*Please see Actone® package insert for full prescribing information.*
Changes in Microarchitecture in 1 Year: Effect of Risedronate

-3.3

-20.3

-15.2

-13.5

-7.2

BMD
Trabecular Bone Volume
Trabecular Number
Trabecular Separation

p < 0.0001*
p = 0.011*
p = 0.01*
p = 0.01*

* p values significant vs placebo.

Please see Actonel® package insert for full prescribing information.
Bone Turnover vs. Fx Reduction

- There is a range of change in bone resorption markers (NTx) that correlates well with fracture risk reduction.

![Graph showing the relationship between NTx (% change) and incidence of new vertebral fractures.](image)


Please see Actonel® package insert for full prescribing information.