Pharmacological treatment of osteoporosis

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Principles of the Care for a Patient with Osteoporosis

**General principles**
- elimination of known risk factors of osteoporosis
- reduction of risk of fall (various barriers, bad sight, drugs ...)
- modification of eating habits and physical activity

**Supporting therapy**
- physical therapy, physiotherapy, analgetics, myorelaxants

**Specific therapy**
Antiresorptive Agents

Antiresorptive Agents Should Prevent Fractures Through Effects on Bone Strength

Reduce biochemical markers of bone turnover to premenopausal levels

Increase both cortical and trabecular bone mass (bone mineral density) and improve bone quality

Decrease fracture risk
Short-time treatment of osteoporosis and bone density
Long-time treatment of osteoporosis and bone density
Guidelines for identification of patients with fracture risk and osteoporosis treatment

International Osteoporosis Foundation (IOF)

Risk factors
Fracture

Yes
No

BMD

T-score -2.5 or less then -2.5

Treatment

USA National Osteoporosis Foundation (NOF)

Age > 65 years

Yes
No

Risk factors

Yes
No

BMD

T-score -2.5 or less then -2.5

Treatment

McClung MR, Bone, 2006, 38, S13 – S17
The Fracture Risk Assessment Tool (FRAX®) has been developed for use in primary care settings to support the identification of those at risk for fracture and the selection of appropriate treatment.”
Who should be tested and treated

- Preventive measures for everyone: calcium, vitamin D, exercise, clean living
- Hip BMD: women > 65 y, men > 70 y., and after fracture
- Treatment thresholds:
  - Anyone with hip or spine fracture
  - T-score < -2.5
  - „Osteopenia“ and 10 year hip fracture risk > 3% or OP-related fracture risk > 20%
# Mode of Action

<table>
<thead>
<tr>
<th></th>
<th>Bone resorption</th>
<th>Bone formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium &amp; Vitamine D</td>
<td>⇩</td>
<td>⇩</td>
</tr>
<tr>
<td>HRST</td>
<td>⇩</td>
<td>⇩</td>
</tr>
<tr>
<td>Tibolone</td>
<td>⇩</td>
<td>⇩</td>
</tr>
<tr>
<td>SERMs</td>
<td>⇩</td>
<td>⇩</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>⇩</td>
<td>⇩</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>⇩</td>
<td>⇩</td>
</tr>
<tr>
<td>rhPTH (TPTD)</td>
<td>⇩</td>
<td>⇩</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>⇩</td>
<td>⇩</td>
</tr>
</tbody>
</table>
Bisphosphonates

- **Alendronate**
  - Alendronate 10 mg daily
  - Alendronate 70 mg 1x a week

- **Risedronate**
  - Risedronate 5 mg once a day
  - Risedronate 35 mg once a week
  - Risedronate 75 mg 2x monthly

- **Ibandronate**
  - Ibandronate tbl. 150 mg p.o. 1x a month
  - Ibandronate inj. 3 mg i.v. 1x in 3 months

- **Zolendronate**
  - Zolendronate inj. 5 mg i.v. 1x a year
**Bisphosphonate structures**

**A**

Inorganic pyrophosphate

\[
\begin{array}{c}
\text{O} \\
\text{P} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

Bisphosphonate

\[
\begin{array}{c}
\text{O} \\
\text{P} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

**B**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative potency</th>
</tr>
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<tbody>
<tr>
<td>Etidronate</td>
<td>1</td>
</tr>
<tr>
<td>Clodronate</td>
<td>10</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>10</td>
</tr>
</tbody>
</table>

**C**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>500</td>
</tr>
<tr>
<td>Risedronate</td>
<td>2000</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>1000</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>100</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>10,000</td>
</tr>
</tbody>
</table>

Molecular Mechanisms of Action of Nitrogen-Containing Bisphosphononates

HMG-CoA

Mevalonate

Geranylpyrophosphate + IPP

Farnesyl diphosphate (FPP)

Geranylgeranyl diphosphate (GGPP)

FPP synthase

NBPs inhibits FPP synthase, thus blocking the prenylation of small signaling proteins required for cell function and survival

Alendronate 10 mg daily
Alendronate 70 mg 1x a week
Alendronate in Osteoporosis Therapy

- in clinical practice since 1993
- 11 years of clinical trials with more than 20,000 patients,
- 10 years lasting monitoring
- more than 12 million treated patients
- "Evidence based medicine" trials:
  - prevention of postmenopausal osteoporosis
  - therapy of postmenopausal osteoporosis
  - therapy of osteoporosis induced by glucocorticoids
  - therapy of male osteoporosis
  - therapy of Paget’s disease
Alendronate and treatment of postmenopausal osteoporosis

Relative risk of vertebral fractures:
- RR - 0.52 (95% CI 0.43 - 0.65) – together
- RR - 0.45 (95% CI 0.06 - 3.15) – prevention
- RR - 0.53 (95% CI 0.43 - 0.65) – treatment
- Consistent reduction in all clinical trials

Relative risk of non-vertebral fractures:
- RR 0.45 - 0.57 for all categories of fractures
- RR 0.63 (0.43 - 0.92) for hip-fractures
  (markedly better effect for dose 10 mg and more)

Cranney, A. et al, End.Rev.23, 2002
Risedronate  5 mg once a day
Risedronate  35 mg once a week
(Risedronate  75 mg twice monthly)
VERT trial
The Vertebral Efficacy with Risedronate Therapy

- randomized, double-blind 3-year study conducted at multiple centres in North America, Europe, and Australia
- 2 arms
  - The multinational arm (MN) ... 80 centres ... 1226 patients
  - The North American arm ....... 110 centres ... 2458 patients
- women who were at least 5 years postmenopausal with two or more radiographically identified vertebral fractures or one vertebral fracture and low lumbar BMD, defined as a T-score of less than or equal to 2.5.
- treatment:
  - risedronate sodium, 2.5 mg/d; risedronate sodium, 5 mg/d; or placebo

Reginster, J.Y., Ost.Int., 2000
Harris, S a spol., JAMA, 1999
risedronate reduced the incidence of vertebral fracture after 1 year of treatment by 61% / 65%

risedronate reduced the incidence of vertebral fracture after 3 years of treatment by 49% / 41%

NNT per year = 14 / 25
Rapid Reduction of Fracture Risk with Risedronate

- Pooled from trials
  - VERT-MN,
  - VERT-NA,
  - BMD-MN,
  - BMD-NA

significantly reduced the incidence of fractures within 6 months

Harrington, JT a spol, Calcif Tissue Int, 74, 2004, 129-135
Risedronate
Rapidly Reduction of the Risk for Nonvertebral Fractures

- Risedronate 5 mg significantly reduced the incidence of nonvertebral fractures within 6 months compared with control.

  - after 6 months of treatment 66%
  - after 12 months of treatment 74%
  - after 3 years of treatment 59%

Harrington, JT a spol, Calcif Tissue Int, 74, 2004, 129-135
Long-term Effect of Risedronate on New Vertebral Fractures Risk – 7 Year Results

Annual incidence of new vertebral fractures in years 0-3, 4-5, and 6-7

VERT-MN: vertebral fracture on rtg

In the end of year 5 switch to risiedronate 5mg

*significant reduction of fractures in years 6/7 with Ris vs years 4/5 with Plc, p=0.007, McNemar Test

Sorensen, et al, ISCD abstract, 2/03 annual meeting.
HIP study
Risedronate in the therapy of postmenopausal osteoporosis

- 3-year randomised, double-blind, placebo-controlled study
- 9331 postmenopausal women

- 2 arms:
  - 5445 women (aged 70-79) with low BMD in the area of proximal femur (T score < -3) and at least 1 fracture risk factor
  - 3886 women (over 80) with at least 1 fracture risk factor regardless of BMD

**HIP – results**

- ↓ of relative risk of femur neck fracture in 30%
- ↓ of relative risk of femur neck fracture in the first group in 40%, and in case of former vertebral fractures, in 60%
- Risedronate reduces the risk of clinical vertebral fractures already after 6 months of the therapy

![Graph showing the reduction of patients (%) over time for control group and Risedronate treatment](image)

Roux, CH et al, Curr Med Res Opin, 20, 2004
Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women - Meta-analysis

Summary of literature search for risedronate

Wells GA et al. Cochrane Database of Systematic Reviews, Issue 1, 2009
Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women - Meta-analysis

### Summary of Findings for Secondary Prevention

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without risedronate</td>
<td>With risedronate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vertebral fractures</strong></td>
<td>Moderate-risk population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53 per 1000</td>
<td>32 per 1000 (27 to 40)</td>
<td>RR 0.61 (0.5 to 0.76)</td>
<td>2812 (3 studies)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>High-risk population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>112 per 1000</td>
<td>69 per 1000 (56 to 85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hip fractures</strong></td>
<td>moderate risk population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 per 1000</td>
<td>149 per 1000 (11 to 18)</td>
<td>RR 0.74 (0.59 to 0.94)</td>
<td>11786 (3 studies)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>High risk population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87 per 1000</td>
<td>64 per 1000 (51 to 82)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Withdrawals due to side effects</strong></td>
<td>176 per 1000</td>
<td>169 per 1000 (154 to 185) Not statistically significant</td>
<td>RR 0.96 (0.88 to 1.05)</td>
<td>8204 (5 studies)</td>
<td>Low</td>
</tr>
</tbody>
</table>
# Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women - Meta-analysis

<table>
<thead>
<tr>
<th>Fracture Sites</th>
<th>Primary / Secondary Prevention</th>
<th># of Trials</th>
<th># Participants (treatment / control)</th>
<th>RR (95% CI)</th>
<th>Association p-value</th>
<th>Heterogeneity p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>Overall</td>
<td>4</td>
<td>1534 / 1532</td>
<td>0.63 (0.51; 0.77)</td>
<td>&lt; 0.0001</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>2</td>
<td>166 / 161</td>
<td>0.97 (0.42; 2.25)</td>
<td>0.94</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>3</td>
<td>1405 / 1407</td>
<td>0.61 (0.50; 0.76)</td>
<td>&lt; 0.0001</td>
<td>0.75</td>
</tr>
<tr>
<td>Non-Vertebral</td>
<td>Overall</td>
<td>5</td>
<td>7731 / 4666</td>
<td>0.80 (0.72; 0.90)</td>
<td>0.0002</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>1</td>
<td>129/125</td>
<td>0.81 (0.25, 2.58)</td>
<td>0.72</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>4</td>
<td>7602 / 4541</td>
<td>0.80 (0.72; 0.90)</td>
<td>0.0002</td>
<td>0.43</td>
</tr>
<tr>
<td>Hip</td>
<td>Overall</td>
<td>3</td>
<td>7425 / 4361</td>
<td>0.74 (0.59; 0.94)</td>
<td>0.01</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>1</td>
<td>37 / 36</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>3</td>
<td>7425 / 4361</td>
<td>0.74 (0.59; 0.94)</td>
<td>0.01</td>
<td>0.95</td>
</tr>
<tr>
<td>Wrist</td>
<td>Overall</td>
<td>2</td>
<td>1265 / 1263</td>
<td>0.67 (0.42; 1.07)</td>
<td>0.10</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>1</td>
<td>37 / 36</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>2</td>
<td>1228 / 1227</td>
<td>0.67 (0.42; 1.07)</td>
<td>0.10</td>
<td>0.81</td>
</tr>
</tbody>
</table>

RR=Relative Risk; CI=Confidence Interval; NE=Not Estimable; N/A=Not Applicable
## Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women - Meta-analysis

<table>
<thead>
<tr>
<th>Fracture Site Prevention RR (95% CI)</th>
<th>Fracture</th>
<th>Risk Measure</th>
<th>Age Group (years)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>50-54</td>
<td>55-59</td>
<td>60-64</td>
<td>65-69</td>
<td>70-74</td>
<td>75-79</td>
<td>80-84</td>
<td>85-89</td>
</tr>
<tr>
<td>Vertebral Secondary 0.61 (0.50; 0.76)</td>
<td>First</td>
<td>ARR</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.4</td>
<td>0.6%</td>
<td>0.7%</td>
<td>1.3%</td>
<td>0.9%</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNT</td>
<td>1282</td>
<td>641</td>
<td>256</td>
<td>171</td>
<td>142</td>
<td>78</td>
<td>111</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Subsequent</td>
<td>ARR</td>
<td>0.2%</td>
<td>1.6%</td>
<td>3.8%</td>
<td>5.6%</td>
<td>6.7%</td>
<td>9.4%</td>
<td>7.4%</td>
<td>8.2%</td>
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<tr>
<td></td>
<td></td>
<td>NNT</td>
<td>513</td>
<td>64</td>
<td>26</td>
<td>18</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Non-Vertebral Secondary 0.80 (0.72; 0.90)</td>
<td>First</td>
<td>ARR</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.6%</td>
<td>0.8%</td>
<td>1.3%</td>
<td>1.5%</td>
<td>2.1%</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNT</td>
<td>313</td>
<td>238</td>
<td>161</td>
<td>119</td>
<td>77</td>
<td>68</td>
<td>49</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Subsequent</td>
<td>ARR</td>
<td>0.5%</td>
<td>0.7%</td>
<td>1.2%</td>
<td>1.7%</td>
<td>2.2%</td>
<td>2.4%</td>
<td>3.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNT</td>
<td>192</td>
<td>147</td>
<td>81</td>
<td>60</td>
<td>45</td>
<td>42</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Hip Secondary 0.74 (0.59; 0.94)</td>
<td>First</td>
<td>ARR</td>
<td>0.0%</td>
<td>0.05%</td>
<td>0.05%</td>
<td>0.2%</td>
<td>0.4%</td>
<td>1.0%</td>
<td>1.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNT</td>
<td>NE</td>
<td>1923</td>
<td>1923</td>
<td>481</td>
<td>240</td>
<td>101</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Subsequent</td>
<td>ARR</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0.05%</td>
<td>0.2%</td>
<td>0.6%</td>
<td>1.4%</td>
<td>2.4%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNT</td>
<td>NE</td>
<td>962</td>
<td>1923</td>
<td>427</td>
<td>175</td>
<td>74</td>
<td>42</td>
<td>19</td>
</tr>
</tbody>
</table>

RR=Relative Risk; CI=Confidence Interval; ARR=Absolute Risk Reduction; NNT=Number Needed to Treat; NE=Not

Five year age-specific risk of first and subsequent fracture after risedronate (5 mg)

Wells GA et al. Cochrane Database of Systematic Reviews, Issue 1, 2009
## Summary of adverse drug events reported in randomized placebo-controlled trials of risedronate

Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women - Meta-analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Risedronate 2.5 mg N(%)</th>
<th>Risedronate 5 mg N(%)</th>
<th>Control N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>118 (93%)</td>
<td>122 (95%)</td>
<td>115 (92%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>13 (10%)</td>
<td>12 (9%)</td>
<td>22 (18%)</td>
</tr>
<tr>
<td>Discontinuation fo AE</td>
<td>12 (9%)</td>
<td>7 (5%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Any upper GI AE</td>
<td>26 (21%)</td>
<td>25 (19%)</td>
<td>20 (16%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13 (10.2%)</td>
<td>8 (6.2%)</td>
<td>12 (9.6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (7.1%)</td>
<td>9 (7.0%)</td>
<td>6 (4.8%)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>1 (0.8%)</td>
<td>4 (3.1%)</td>
<td>4 (3.2%)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>3 (2.4%)</td>
<td>4 (3.1%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>3 (2.4%)</td>
<td>2 (1.6%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Esophageal ulcer</td>
<td>0</td>
<td>1 (0.8%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Stomach ulcer</td>
<td>1 (0.8%)</td>
<td>0</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Number of patients N = 383 (127/129/125)

Hooper 2005
Efficiency of bisphosphonates on nonvertebral and lumbal fractures in the first year of the therapy: cohort study with risedronate and alendronate

Silverman SL, Watts NB, Delmas PD, Lange JL, Lindsay R

OP Int 2007 18: 25-34

## Input Characteristics

**Input factors affecting the risk of fractures**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Risedronate</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group size (n)</td>
<td>12.215</td>
<td>21.615</td>
</tr>
<tr>
<td>Age (years) at the start of the study (average)*</td>
<td>74.8</td>
<td>74.6</td>
</tr>
<tr>
<td>Medication – 6 month anamnesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current number of drugs (average)*</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Gastrointestinal drugs (%)*</td>
<td>26.2</td>
<td>20.1</td>
</tr>
<tr>
<td>Estrogens (%)</td>
<td>17.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Glucocorticosteroids (%)*</td>
<td>10.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Personal – 6 months anamnesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Check-ups (average)*</td>
<td>5.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Diagnosis of rheumatoid arthritis (%)*</td>
<td>2.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

* p<0.05 among the groups
Cumulative incidence of nonvertebral fractures (lumbus, wrist, arm, clavicula, pelvis, leg)

- Alendronate
  - ↓18%* in 12th month
- Risedronate

*Adjusted Relative Rate Reduction, p = 0.03, 95% CI: 9% - 32%

Cumulative incidence of hip fractures

- alendronate
- risedronate

↓43% *
In 12th month

% of patients with lumbar fracture

*Adjusted Relative Rate Reduction, p = 0.01, 95% CI: 13% - 63%

Risedronate summary

- Risedronate is the drug that **significantly reduces** incidence vertebral and nonvertebral osteoporotic fractures.
- Risedronate maintains normal bone formation and mineralization and induces reduction of bone turnover in accordance with its known antiresorption effect.
- This effect on bone turnover causes prompt and long-lasting effect against fractures.
**IBANDRONATE**

- **Ibandronate tbl.**
  150 mg p.o. 1x a month

- **Ibandronate inj.**
  3 mg i.v. 1x in 3 months
Reduction of Vertebral Fracture Risk

ITT population after 3 years

NS = non-significant (p=0.2785 between the groups for incidence of fractures)

Reduction in Risk of Non-Vertebral Fractures in Subgroups with Higher Risk

**Placebo**
- Incidence of non-vertebral fractures (%): 20
- Reduction in risk of fractures: 69%

**Ibandronate**
- Incidence of non-vertebral fractures (%): 6%
- Reduction in risk of fractures: 60%


*Patients with baseline BMD T-score of femur neck <-3.0; ‡p=0.012

2Bauss F, Schimmer R. Ther Clin Risk Manage 2006;2:3–18

†BMD lumbar spine (T-score <-2.5) and anamnèsis of clinical fracture in the last 5 years; §p=0.037
BISPHOSPHONATES

Zolendronate inj.
5 mg i.v. 1x a year
Values above columns are 3-year cumulative numbers of attacks based on Kaplan-Meier assumptions.

* $P = .0024$; † $P < .0001$; ‡ $P = .0002$; reduction of relative risk as compared to placebo

§ Fracture of hip joint was not excluded from analysis of other fractures than vertebral fractures.

HORIZON Pivotal Fracture Trial (PFT)
Safety and tolerance

Prevalence (%) | Pyrexia | Myalg | Flu-like syndrome | Headache | Arthralgy

15% | 8% | 7% | 6% | 5%

Infusion once a year

SELECTIVE ESTROGEN RECEPTOR MODULATOR

Raloxifene HCl 60 mg/day orally
Selective Estrogen Receptor Modulator

- Not an estrogen, progestin or other hormone
- Binds to estrogen receptors
- Has estrogen-like effects in some tissues
- Blocks estrogen effects in some tissues
Selective Estrogen Receptor Modulators II. generation

Raloxifene

Agonist

Antagonist
Effect on serious vertebral fractures

- Placebo: 61% of women with new fracture
- RLX 60g: 37% of women with new fracture

RR 0.39 (95% CI = 0.17, 0.69)
RR 0.63 (95% CI = 0.49, 0.83)

Reductions in Invasive Breast Cancer

- Placebo: 71%
- Raloxifene: 56%
- Reductions in Invasive Breast Cancer
CALCITONIN

Daily – nasal spray 200 I.U

© 2000 David W. Dempster, PhD.
**Calcitonin**

- Calcitonin is a polypeptide (with 32 aminoacids) hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobrachial glands of birds and fish.

  - **Skeletal effects of calcitonin**
    - decreases the rate of bone resorption
    - binds to specific receptors on osteoblasts and decreases the activity of those cells
    - bone formation may be augmented by calcitonin through increased osteoblastic activity

- Calcitonin – nasal spray is used:
  - In Europe since 1987
  - In USA since 1995
New vertebral fractures

* P < .05 vs placebo.

36%
STRONTIUM RANELATE

2g pulvis daily p.o.
Strontium Ranelate and Osteoporosis

↑ Bone formation

Preosteoblast

CaSR +?

↑ Replication

Osteoblasts

↑ Differentiation

↑ Synthesis of bone matrix

↓ Bone resorption

Preosteoclast

↓ Differentiation

Osteoclast

↓ Activity

CaSR

↑ Apoptosis

OPG

↓ RANKL

RANK
Strontium Ranelate reduces the risk of vertebral fracture (SOTI)

- 47%*

NNT = 9

- 49%*

RR=0.51, 95%CI [0.36:0.74] * p<0.001
RR=0.59, 95%CI [0.48:0.73] * p<0.001

Strontium Ranelate reduces non-vertebral fracture risk (TROPOS)

PARATHORMONE AND TERIPARATIDE

PTH 1.61 ug 1x daily subcutaneous
TPTD 20 ug 1x daily subcutaneous
**PTH**

### Once-daily
- ↓ osteoblast apoptosis
- ↓ osteoblast number/function
- ↓ bone mass/strength
- ↓ RANKL
- ↑ cbfa1
- ↑ BMP
- ↑ PPARγ
- ↑ Wnt
- ↑ IGF 1,2
- ↑ amphiregulin

### Continuous
- ↑ RANKL
- ↓ OPG
- ↑ osteoclast
- ↑ bone resorption
- ↑ serum Ca++
Teriparatide and risk of vertebral fractures

Risk of new fractures (primary endpoint)

RR ↓ 65%*   RR ↓ 69%*

% of women with ≥ 1 vertebral fracture

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>TPTD20</th>
<th>TPTD40</th>
</tr>
</thead>
<tbody>
<tr>
<td>(64 / 448)</td>
<td>(22 / 444)</td>
<td>(19 / 434)</td>
<td></td>
</tr>
</tbody>
</table>

Risk of multiple vertebral fractures

RR ↓ 77%*   RR ↓ 86%*

% of women with > 1 vertebral fracture

<table>
<thead>
<tr>
<th>Group</th>
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<th>TPTD20</th>
<th>TPTD40</th>
</tr>
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<tbody>
<tr>
<td>(22 / 448)</td>
<td>(5 / 444)</td>
<td>(3 / 434)</td>
<td></td>
</tr>
</tbody>
</table>

*P <0.001 vs. placebo
RR = relative risk vs. placebo

Fracture Prevention Trial
Risk of nonvertebral osteoporotic fractures

* P = 0.02 vs. placebo
† P = 0.01 vs. placebo
RR = relative risk vs. placebo

Correlation between increase of BMD and efficiency of antiosteoporotic treatment

0% 10% 20% 30% 40% 50% 60% 70% 80%
raloxifene alendronate risedronate PTH Strontium ranelate

Bruyère P et all. J Clin Endocrinol Metab. 2007; 92(8): 3076-3081
Sarkar S et al. JBMR 2002; 17:1-10
### Antifracture efficacy

**IOF Clinician's Guidelines to Prevention and Treatment of Osteoporosis**

<table>
<thead>
<tr>
<th></th>
<th>Effect on vertebral fracture risk</th>
<th>Effect on nonvertebral fracture risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Established osteoporosis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Alendronate</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Risedronate</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Ibandronate</strong></td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td><strong>Zolendronic acid</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>HRT</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Raloxifene</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Teriparatide and PTH</strong></td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td><strong>Strontium ranelate</strong></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

NA: no evidence available
+ : effective drug
<sup>a</sup> women with a prior vertebral fracture
<sup>b</sup> In subset of patients only (post-hoc analysis)
<sup>c</sup> Mixed group of patients with or without prevalent vertebral fractures

Delmas P.D. Lindsay R. *Osteoporosis Int* (2008) 19: 399-428
Main aspects for treatment

- Individual profil of the patient
- EBM datas
- Aditive benefits
- Safety and tolerance
- Price

Fracture reduction

Better life expectancy of patients with OP
Thank you for your attention!