Current Osteoporosis Therapies and Their Long-term Use

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Quiescent bone surface covered by lining cells

Osteoclasts on the bone surface resorbing old bone

Osteoid becoming mineralized

Osteoblasts appearing at the resorption site

Osteoblasts filling the resorption cavity with osteoid
Treatment Approach

Assess fracture risk

Correct reversible risk factors

Treat if risk justifies

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

Country: UK
Name / ID:

**Questionnaire:**

1. **Age (between 40-90 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 more units per day**
    - No
    - Yes

12. **Femoral neck BMD**
    - Select
    - [ ]

**Risk factors**
Major osteoporotic fracture is hip fracture, clinically evident vertebral fracture, proximal humerus fracture and distal forearm fracture. This is about half of total fractures (SOF, Stone JBMR 18:1947, 2003).
FRACTURE RISK CALCULATOR

Fill out the following to estimate your fracture risk

- Full Name (optional): Test
- Sex? (Circle one):
  - Male
  - Female
- Age: 70
- Fractures since the age of 50 (excluding major trauma, e.g., car accidents): 0
- Falls over last 12 months: 0
- Do you have a Bone Mineral Density (BMD) measurement?
  - Yes
  - No
- Score: -2.5 -3
Efficacy of Osteoporosis Treatments

Murad, Endo Soc
Reid, Nature Rev Endo 2015
Patient 1

- 58 year-old woman
- 2 forearm fractures
- 2 falls in the last year
- No osteoporosis treatment to-date
- Femoral neck T-score –1.8
- FRAX: hip 1.9%
  major osteoporotic 11%

- What do you recommend?
Patient 1

- 58 year-old woman
- 2 forearm fractures
- 2 falls in the last year
- No osteoporosis treatment to-date
- Femoral neck T-score –1.8
- FRAX: hip 1.9%
  - major osteoporotic 11%
- Garvan: hip 17%
  - osteoporotic 43%
- What do you recommend?
Patient 2

- 68 year-old woman
- Previous forearm fracture, 6 years ago
- On alendronate 70 mg/week for 5 years
- T-score 5 years ago -3.6
- Current T-score -2.9

What do you recommend?

1. Stop alendronate
2. Continue alendronate 70 mg/week
3. Change to alendronate 70 mg/2 weeks
4. Change to parenteral therapy
5. Carry out investigations
Patient 3

• 68 year-old woman
• Previous forearm fracture, 6 years ago
• On alendronate 70 mg/week for 5 years
• T-score 5 years ago -3.6
• Current T-score -2.3

What do you recommend?

1. Stop alendronate
2. Continue alendronate 70 mg/week
3. Change to alendronate 70 mg/2 weeks
4. Change to parenteral therapy
5. Carry out investigations
Patient 4

- 68 year-old woman
- Previous forearm fracture, 6 years ago
- On alendronate 70 mg/week for 5 years
- T-score 5 years ago -3.6
- Current T-score -3.7

What do you recommend?
1. Stop alendronate
2. Continue alendronate 70 mg/week
3. Change to alendronate 70 mg/2 weeks
4. Change to parenteral therapy
5. Carry out investigations
Patients 2 - 4: Questions to Consider

- Has patient responded appropriately to therapy?
- If not, what tests might be helpful?
- Is continued therapy needed?
- If so, what?
Patient 2

• 68 year-old woman
• Previous forearm fracture, 6 years ago
• On alendronate 70 mg/week for 5 years
• T-score 5 years ago -3.6
• Current T-score -2.9

Has patient responded appropriately to therapy?
Long-Term Effects of Anti-Resorptives on Total Hip BMD

Patient 2

- 68 year-old woman
- Previous forearm fracture, 6 years ago
- On alendronate 70 mg/week for 5 years
- T-score 5 years ago -3.6
- Current T-score -2.9

Is continued therapy needed?
FLEX

Clinical Vertebral Fractures

RR, 0.45 (95% CI, 0.24-0.86)
FLEX

Nonvertebral Fractures

Cumulative Incidence, %

- Alendronate (Pooled)
- Placebo

RR, 1.00 (95% CI, 0.76-1.32)

Time to First Fracture, mo

Black JAMA 296:2927, 2006
Nonvertebral Fracture by FLEX Baseline T-Score

Schwartz, JBMR 25:976, 2010
Patient 2

- 68 year-old woman
- Previous forearm fracture, 6 years ago
- On alendronate 70 mg/week for 5 years
- T-score 5 years ago -3.6
- Current T-score -2.9

Is continued therapy needed?

If so, what?
Patient 3

- 68 year-old woman
- Previous forearm fracture, 6 years ago
- On alendronate 70 mg/week for 5 years
- T-score 5 years ago -3.6
- Current T-score -2.3
  - Has patient responded appropriately to therapy?
  - Is continued therapy needed?
How long is a drug holiday?

Alendronate – 1-5 years
Risedronate – 6-12 months
Long-Term Zoledronate

• Dose every 18 months initially

• With satisfactory BMD response at 3-5 years, extend inter-dose interval to 24-36 months
Why minimise the duration of anti-resorptive treatment?
Atypical Sub-Trochanteric Fractures

AFF Rates by Duration of Use

Incidence (10,000 person yrs)

0-1 yr: 0.2
1-3 yr: 0.8
3-5 yr: 2.5
5-8 yr: 6
> 8 yr: 12.9

Geiger et al, ASBMR 2018
AFF Rates by Time Since Discontinuation

Geiger et al, ASBMR 2018
Patient 4

- 68 year-old woman
- Previous forearm fracture, 6 years ago
- On alendronate 70 mg/week for 5 years
- T-score 5 years ago -3.6
- Current T-score -3.7
  - Has patient responded appropriately to therapy?
  - If not, what tests might be helpful?
  - Is continued therapy needed?
  - If so, what?
Exclude Secondary Osteoporosis (e.g. if Z < -2)

- Clinical history and examination
- Serum calcium
- Serum phosphate
- Alkaline phosphatase
- Cortisol
- TSH
- Coeliac screen
- Liver function tests
- Creatinine
- Protein electrophoresis
- Full blood count
- C-reactive protein
- Testosterone
- 25(OH)D
PINP Off and On Bisphosphonates

Ugur et al, ASBMR 2018
BMD Change in PINP Responders

Ugur et al, ASBMR 2018
Teriparatide

- Have a plan for post-teriparatide treatment before starting teriparatide
Ca+D Effects on Non-Hip Non-Vert Fractures

Women’s Health Initiative

Total fractures

HR: 0.96 (0.91–1.02)
N = 36,282

Jackson NEJM 354:669, 2006

Chapuy, NEJM 1992
Meta-Analysis of Vit D on Total Hip BMD

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted mean difference in total hip/trochanter BMD (%) [95% CI]</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ooms, 1995</td>
<td>-0.2 [-1.9, 1.5]</td>
<td>2</td>
</tr>
<tr>
<td>Hunter, 2000</td>
<td>0.7 [-0.5, 1.9]</td>
<td>4</td>
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<tr>
<td>Patel, 2001</td>
<td>-0.1 [-0.8, 0.6]</td>
<td>8</td>
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<tr>
<td>Cooper, 2003</td>
<td>0.3 [-1.0, 1.6]</td>
<td>3</td>
</tr>
<tr>
<td>Harwood, 2004</td>
<td>2.0 [0.5, 3.5]</td>
<td>3</td>
</tr>
<tr>
<td>Aloia, 2005</td>
<td>0.0 [-0.4, 0.4]</td>
<td>14</td>
</tr>
<tr>
<td>Zhu, 2008a</td>
<td>1.1 [-0.9, 3.2]</td>
<td>2</td>
</tr>
<tr>
<td>Zhu, 2008b</td>
<td>0.3 [-0.4, 1.0]</td>
<td>9</td>
</tr>
<tr>
<td>Islam, 2010</td>
<td>3.0 [1.2, 4.8]</td>
<td>2</td>
</tr>
<tr>
<td>Jorde 2010</td>
<td>0.1 [-0.3, 0.4]</td>
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<tr>
<td>Grimnes, 2011</td>
<td>-0.3 [-0.6, 0.1]</td>
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<tr>
<td>Rastelli, 2011</td>
<td>0.0 [-1.9, 1.8]</td>
<td>2</td>
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<tr>
<td>Steffensen, 2011</td>
<td>0.7 [-0.6, 2.0]</td>
<td>3</td>
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<tr>
<td>Verschueren 2011</td>
<td>-0.1 [-0.9, 0.8]</td>
<td>7</td>
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<tr>
<td>Nieves, 2012</td>
<td>0.2 [-0.4, 0.7]</td>
<td>11</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>0.2 [-0.1, 0.4]</strong></td>
<td><strong>P = 0.17</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 39\%, P = 0.06$

Favours decreased BMD with vitamin D  Favours increased BMD with vitamin D

Reid et al, Lancet 2014
Vit D Effects on BMD Over 2 Years

Baseline 25(OH)D ≤ 30 nmol/L

- Spine: Placebo P=0.035
- Femoral Neck: Placebo P=0.047
- Total Hip: Placebo P=0.35
- Total Body: Placebo P=0.93

Baseline 25(OH)D > 30 nmol/L

- Spine: Vitamin D P=0.19
- Femoral Neck: Vitamin D P=0.079
- Total Hip: Vitamin D P=0.0088
- Total Body: Vitamin D P=0.94

Reid, J Int Med 2017
Response to Daily Vitamin D Supplementation in Postmenopausal Women

Baseline 25(OH)D ≤ 30 nmol/L

- Placebo (n=44)
- 400 IU (n=39)
- 1000 IU (n=42)

Baseline 25(OH)D > 30 nmol/L

- Placebo (n=44)
- 400 IU (n=45)
- 1000 IU (n=42)

% Change BMD

Spine
- P1 = 0.027
- P2 = 0.019

Total Hip
- P1 = 0.082
- P2 = 0.045

Spine
- P1 = 0.34
- P2 = 0.94

Total Hip
- P1 = 0.20
- P2 = 0.23

Macdonald et al, JBMR 2018
### Effect of Calcium on Total Fracture, by Risk of Bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Calcium (n/N)</th>
<th>Control (n/N)</th>
<th>Relative risk of total fracture [95% CI]</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All studies</strong></td>
<td>3246/29115</td>
<td>3479/29458</td>
<td>0.89 [0.81-0.96]</td>
<td>0.004</td>
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<td></td>
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<td>Test for heterogeneity: I² = 27%, P = 0.17</td>
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<tr>
<td>Grant 2005</td>
<td>364/2617</td>
<td>400/2675</td>
<td>1.0</td>
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<tr>
<td>Jackson 2006</td>
<td>2102/18176</td>
<td>2158/18106</td>
<td>0.96 [0.91-1.01]</td>
<td>76</td>
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<td>Prince 2006</td>
<td>110/730</td>
<td>126/730</td>
<td>0.96 [0.91-1.01]</td>
<td>4</td>
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<tr>
<td>Reid 2006</td>
<td>134/732</td>
<td>147/739</td>
<td>0.96 [0.91-1.01]</td>
<td>5</td>
</tr>
<tr>
<td><strong>Low risk of bias</strong></td>
<td>2710/22255</td>
<td>2831/2250</td>
<td>0.96 [0.91-1.01]</td>
<td>77</td>
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<tr>
<td>Reid 1993</td>
<td>8/68</td>
<td>10/67</td>
<td>1.6</td>
<td>61</td>
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<tr>
<td>Chapuy 1994</td>
<td>240/1537</td>
<td>290/1539</td>
<td>0.4</td>
<td>0.4</td>
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<td>Chevalley 1994</td>
<td>2/62</td>
<td>2/31</td>
<td>2.4</td>
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<td>Riggs 1998</td>
<td>11/119</td>
<td>12/117</td>
<td>1.2</td>
<td>1.2</td>
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<td>Baron 1999</td>
<td>4/464</td>
<td>14/466</td>
<td>1.4</td>
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<td>Porthouse 2005</td>
<td>58/1321</td>
<td>91/1993</td>
<td>1.7</td>
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<td>Reid 2008</td>
<td>9/216</td>
<td>8/107</td>
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<td>Salovaara 2010</td>
<td>78/1718</td>
<td>94/1714</td>
<td>1.6</td>
<td>1.6</td>
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<tr>
<td><strong>Moderate risk of bias</strong></td>
<td>408/5505</td>
<td>521/6034</td>
<td>0.83 [0.73-0.93]</td>
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<tr>
<td>Dawson-Hughes 1997</td>
<td>11/187</td>
<td>26/202</td>
<td>1.5</td>
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<tr>
<td>Peacock 2000</td>
<td>11/126</td>
<td>10/135</td>
<td>1.2</td>
<td>12</td>
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<td>Chapuy 2002</td>
<td>69/389</td>
<td>34/194</td>
<td>2.4</td>
<td>24</td>
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<td>Avenell 2004</td>
<td>9/64</td>
<td>8/70</td>
<td>1.1</td>
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<td>Harwood 2004</td>
<td>6/75</td>
<td>5/75</td>
<td>1.1</td>
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<td>Bolton-Smith 2007</td>
<td>2/62</td>
<td>2/61</td>
<td>1.3</td>
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<td>Bonnick 2007</td>
<td>9/282</td>
<td>28/281</td>
<td>1.3</td>
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<td>Sambrook 2012</td>
<td>11/170</td>
<td>14/156</td>
<td>0.77 [0.53-1.11]</td>
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<td>Test for heterogeneity: I² = 44%, P = 0.08</td>
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<td>Test for heterogeneity between subgroups: P = 0.05</td>
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</table>

Bolland, BMJ, 2015
Zoledronate Effect on Fractures in Osteopenic Women – No Calcium Supplements

Non-Vertebral Fragility Fracture

HR 0.66, P = 0.0014

Vertebral Fractures:
OR = 0.47
P = 0.0018

N = 2000

Reid, NEJM 2018
## Pro’s and Cons of Agents for Managing Osteoporosis - 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pro’s</th>
<th>Con’s</th>
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</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Cheap</td>
<td>Low efficacy, ↑ GI, calculi, CVD</td>
</tr>
<tr>
<td>HRT</td>
<td>↓ all #s</td>
<td>↑ breast ca, ↑ DVT, ↑ CVD</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>↓ vert #s, ↓ breast ca</td>
<td>↑ DVT</td>
</tr>
<tr>
<td>Sr</td>
<td>↓ vert &amp; nonvert #s</td>
<td>? Mechanism, skin AEs, ↑ CVD</td>
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</table>
### Pro’s and Cons of Agents for Managing Osteoporosis - 2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pro’s</th>
<th>Con’s</th>
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<tr>
<td>BPs</td>
<td>↓ vert/nonvert/hip #s</td>
<td>GI, APR</td>
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<tr>
<td></td>
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<td>Atypical #, ?ONJ</td>
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<td>IV BPs are nephrotoxic</td>
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<tr>
<td>D’mab</td>
<td>↓ vert/nonvert/hip #s</td>
<td>Very low turnover, atypical #, ?ONJ</td>
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<tr>
<td></td>
<td></td>
<td>Rapid offset – multiple vert #s</td>
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<tr>
<td>PTH</td>
<td>↓ vert &amp; nonvert #s</td>
<td>Expensive, daily injections</td>
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<tr>
<td></td>
<td></td>
<td>Cortical bone loss</td>
</tr>
<tr>
<td></td>
<td>Maintain 25OHD &gt; 40 nmol/L Year round</td>
<td>Efficacy against hip fracture?</td>
</tr>
</tbody>
</table>
Conclusions - Osteoporosis

- Screen with BMD measurements
- Calcium from diet
- Vitamin D supplementation in frail elderly
- Potent bisphosphonates are the mainstay of treatment
- PTH analogues in severe disease
- Denosumab well tolerated but rapid offset
- Anti-sclerostin drugs are coming?