Pharmacological management of patients with fragility fractures

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Switzerland
What is the goal of osteoporosis therapy?

- Rapid reduction of fracture risk, particularly in patients at “imminent” risk
- Long-term restoration of bone mass and strength
10 yrs vs imminent fracture risk

1-Year Risk of Refracture in Patients With Incident Vertebral Fracture

<table>
<thead>
<tr>
<th>Body Part</th>
<th>1-Year Refracture Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip/Pelvis</td>
<td>3.6</td>
</tr>
<tr>
<td>Humerus/Leg</td>
<td>3.5</td>
</tr>
<tr>
<td>Spine</td>
<td>17.3</td>
</tr>
<tr>
<td>Wrist</td>
<td>1.5</td>
</tr>
<tr>
<td>Overall</td>
<td>26.0</td>
</tr>
</tbody>
</table>

Relative Risk of hip fracture after a hip fracture

Osteoporotic Fracture Risk (% per 10 Years) vs BMD T-Score

Age: 80, 70, 60, 50

BMD T-Score: -3, -2.5, -2, -1.5, -1, -0.5, 0, 0.5, 1
Fracture risk after hospitalization for vertebral fracture

Johnell et al., Osteoporos Int 2001
Refracture rates - Medicare
(Women and Men 65+, n=273’000, 1yr rate=4.3%, increases with age, comorbidities, and worst after hip =7.5%)

Bynum, OI 2016
Imminent fracture risk after a first MOF

Risk of 2nd MOF (/100,000)

Woman aged 75 years at first fracture

*MOF Major Osteoporotic Fracture

Johansson et al, Reykjavik Study
Numbers of fractures in the 10 years after an index fracture (in 5039 individuals)

Johansson et al, Reykjavik Study
Age and risk of subsequent MOF* following a first MOF.

*MOF Major Osteoporotic Fracture

Johansson et al, Reykjavik Study
1. Target selected patients at high risk for fracture

2. Treat with pharmacological therapy to prevent fracture

Identifying patients

Fracture liaison service

Primary prevention

Patients with hip fracture
Patients with prior fracture
Individuals at high fracture risk
Individuals at intermediate fracture risk
Individuals at low fracture risk

“The ultimate goal of any management strategy in osteoporosis is the prevention of fracture”*


IOF – Capture the Fracture Campaign and Slide Kit

www.capturethefracture.org/slide-kits-reports


Secondary prevention: Fracture liaison service

* Older patients, where appropriate, are identified and referred for falls assessment

Akesson, OI 2013
Prescriptions of ALN after hip fracture increase and subsequent fractures decrease suggesting clinical effectiveness of alendronate for secondary fracture prevention. This effect is preserved in very elderly patients.
CTF Map of Best Practice

298 FLS, 39 countries, 6 continents

- FLS in N. America = 39
- FLS in S. America = 29
- FLS in Europe = 168
- FLS in MENA region = 7
- FLS in APAC region = 55

September 11, 2018
Running an FLS? Join the Capture the Fracture® Programme

Why join?

• Showcase your achievements
• Learn from the BPF to improve your service
• Get international recognition with a Gold, Silver, or Bronze star
• Be part of a global initiative to prevent secondary fractures

Who can participate?

• Coordinator-based models of care
• All type of facilities
• At any stage in development
• Any size worldwide
The Process

Step 1
FLS submits online application

Step 2
FLS marked in green on the map while being reviewed

Step 3
BPF achievement level assigned

Step 4
FLS is scored and recognized on the map

https://youtu.be/gpAAvvukjQw  VIDEO!
Fracture risk reduction with anti-resorptives

RR of new vertebral fracture ± IC 95% - RCT (3-4 yrs)

- Raloxifene 60 $^a$
- Raloxifene 60 $^b$
- Bazedoxifene 20 $^a/b$
- Alendronate 5/10 $^a$
- Alendronate 5/10 $^b$
- Risedronate 5 $^a$
- Risedronate 5 $^a$
- Ibandronate 2.5 $^a/b$
- Ibandronate 20 inter $^a/b$
- Zoledronate 5 $^a/b$
- Denosumab 60 $^a/b$

RR of new non-vertebral fracture ± IC 95% - RCT (3-4 yrs)

- RLX 60/120 $^a/b$
- BZX 20/40 $^a/b$
- ALN 5/10 $^a$
- ALN 5/10 $^b$
- RIS 5 $^a$
- RIS 5 $^a$
- RIS 2.5/5 $^a/b$
- IBN 2.5/20int $^a/b$
- ZOL 5 $^a/b$
- DMAB 60$^a/b$

$^a$ with prevalent vert fx  $^b$ without prevalent vert fx  $^{a/b}$ with or without prevalent vert fx
Hip fracture risk reduction (RR ± 95% CI)

**Significant hip fracture risk reduction: 4 studies**

Only studies with preplanned analysis:
- RIS 2.5/5 (Hip Study)
- ZOL 5 mg (Horizon Study)
- Denosumab (Freedom Study)

- RLX 60, 120 (MORE)***
- CT 200 (PROOF)*
- ALN 5/10 (FIT1)*
- ALN 5/10 (FIT2)**
- RIS 5 (VERT-NA)*
- RIS 5 (VERT-MN)*
- RIS 2.5/5 (Hip Study)***
- IBAN
- ZOL
- Denosumab ***
- Teriparatide 20µg*

* with prev vert  
*** with or without prev vert fractures
Zoledronic Acid 5 mg Reduced Subsequent Fracture Risk in post-hip fracture patients

*P = .0012; †P = .0338; ‡P = .0210, relative risk reduction vs placebo; NS = not significant.
Values above bars are cumulative event rates based on Kaplan-Meier estimates at Month 24.
Zoledronic Acid 5 mg Reduced Risk of All-Cause Mortality by 28% Over Time in patients with a recent hip fracture

Hazard Ratio, 0.72 (95% CI, 0.56–0.93)

$P = .0117$

Absolute Risk Reduction, 3.7%

EFFECTS OF 24 MONTHS TREATMENT OF TERIPARATIDE COMPARED WITH RISEDRONATE ON NEW FRACTURES IN POSTMENOPAUSAL WOMEN

• Compare the anti-fracture efficacy of teriparatide (TPTD) with risedronate (RIS) in postmenopausal women with severe osteoporosis (VERO study)

2 year randomized (1:1), double blind, double-dummy trial

1,360 women mean age 72.1 years *
at least 2 moderate or 1 severe vertebral fractures
low bone mass

TPTD 20 µg sc daily

RIS 35 mg oral weekly

* 36% with recent clinical VFx; 72% previously on AR (mean 4.5 yrs); 10% on GC

Kendler et al, Lancet 2017
EFFECTS OF 24 MONTHS TREATMENT OF TERIPARATIDE COMPARED WITH RISEDRONATE ON NEW FRACTURES IN POSTMENOPAUSAL WOMEN

KENDLER ET AL., UNIVERSITY OF BRITISH COLUMBIA, CA

<table>
<thead>
<tr>
<th></th>
<th>TPTD (n=680)</th>
<th>RIS (n=680)</th>
<th>Relative Risk or Hazard Ratio (95% CI) vs RIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral fracture (≥1)</td>
<td>28 (5.4)</td>
<td>64 (12.0)</td>
<td>0.44 (0.29; 0.68)</td>
</tr>
<tr>
<td>Moderate/severe vertebral fractures (≥1)</td>
<td>26 (5.0)</td>
<td>63 (11.8)</td>
<td>0.42 (0.27; 0.65)</td>
</tr>
<tr>
<td>Multiple vertebral fractures (≥2)</td>
<td>2 (0.4)</td>
<td>12 (2.3)</td>
<td>0.16 (0.04; 0.74)</td>
</tr>
<tr>
<td>Clinical fractures</td>
<td>30 (4.8)</td>
<td>61 (9.8)</td>
<td>0.48 (0.32; 0.74)</td>
</tr>
<tr>
<td>Non vertebral fragility fractures</td>
<td>24 (4.0)</td>
<td>38 (6.1)</td>
<td>0.66 (0.39; 1.10)</td>
</tr>
</tbody>
</table>

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Conclusions

- In postmenopausal women with severe osteoporosis, the risk for new vertebral and clinical fractures was significantly reduced in patients randomized to TPTD compared to RIS.
- There was a trend to fewer NVF in patients on TPTD compared to RIS.
- These results support TPTD as 1st line treatment for women with severe osteoporosis, superior to RIS antiresorptive therapy.

Kendler et al, Lancet 2017
Ferrari, Lancet (editorial) 2017
Risk Ratios for New Vertebral Fractures: stratification by risk subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Teriparatide n/N (%)</th>
<th>Risedronate n/N (%)</th>
<th>Interaction p value</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalent VFx (number)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>7/180 (3.9)</td>
<td>16/191 (8.4)</td>
<td>0.81</td>
<td>0.42 [0.27, 0.66]</td>
</tr>
<tr>
<td>1</td>
<td>4/132 (3.0)</td>
<td>14/135 (10.4)</td>
<td></td>
<td>0.46 [0.19, 1.08]</td>
</tr>
<tr>
<td>3</td>
<td>5/86 (5.8)</td>
<td>10/82 (12.2)</td>
<td></td>
<td>0.28 [0.09, 0.81]</td>
</tr>
<tr>
<td>&gt;3</td>
<td>12/118 (10.2)</td>
<td>24/125 (19.2)</td>
<td></td>
<td>0.50 [0.18, 1.38]</td>
</tr>
<tr>
<td><strong>Prevalent VFx (severity)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1/59 (1.7)</td>
<td>7/57 (12.3)</td>
<td>0.18</td>
<td>0.26 [0.09, 0.73]</td>
</tr>
<tr>
<td>SQ2</td>
<td>27/457 (5.9)</td>
<td>57/476 (12.0)</td>
<td></td>
<td>0.14 [0.02, 1.07]</td>
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<tr>
<td>SQ3</td>
<td></td>
<td></td>
<td></td>
<td>0.48 [0.31, 0.74]</td>
</tr>
<tr>
<td><strong>Prior nonvertebral fracture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>20/355 (5.6)</td>
<td>38/385 (9.9)</td>
<td>0.13</td>
<td>0.39 [0.25, 0.61]</td>
</tr>
<tr>
<td>no</td>
<td>8/161 (5.0)</td>
<td>26/148 (17.6)</td>
<td></td>
<td>0.55 [0.33, 0.92]</td>
</tr>
<tr>
<td>yes</td>
<td>25/466 (5.4)</td>
<td>57/491 (11.6)</td>
<td></td>
<td>0.27 [0.13, 0.58]</td>
</tr>
<tr>
<td><strong>Glucocorticoid use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>14/280 (5.0)</td>
<td>34/281 (12.1)</td>
<td>0.76</td>
<td>0.40 [0.20, 0.79]</td>
</tr>
<tr>
<td>no</td>
<td>1/23 (4.3)</td>
<td>3/25 (12.0)</td>
<td></td>
<td>0.45 [0.29, 0.70]</td>
</tr>
<tr>
<td>yes</td>
<td>17/270 (6.3)</td>
<td>22/236 (9.3)</td>
<td></td>
<td>0.36 [0.10, 1.30]</td>
</tr>
<tr>
<td><strong>Prior osteoporosis drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10/184 (5.4)</td>
<td>28/202 (13.9)</td>
<td>0.97</td>
<td>0.42 [0.19, 0.92]</td>
</tr>
<tr>
<td>BP</td>
<td>8/180 (4.4)</td>
<td>18/139 (12.9)</td>
<td></td>
<td>0.42 [0.23, 0.76]</td>
</tr>
<tr>
<td>non-BP</td>
<td>12/207 (5.8)</td>
<td>25/209 (12.0)</td>
<td></td>
<td>0.46 [0.25, 0.87]</td>
</tr>
<tr>
<td>treatment-naive</td>
<td>10/184 (5.4)</td>
<td>28/202 (13.9)</td>
<td></td>
<td>0.44 [0.29, 0.67]</td>
</tr>
<tr>
<td><strong>Lowest BMD T-score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>17/270 (6.3)</td>
<td>42/297 (14.1)</td>
<td>0.86</td>
<td>0.45 [0.29, 0.69]</td>
</tr>
<tr>
<td>&lt; -2.5</td>
<td>11/246 (4.5)</td>
<td>22/236 (9.3)</td>
<td></td>
<td>0.43 [0.25, 0.73]</td>
</tr>
<tr>
<td>≥ -2.5</td>
<td>10/152 (6.6)</td>
<td>18/192 (9.4)</td>
<td></td>
<td>0.47 [0.23, 0.94]</td>
</tr>
<tr>
<td><strong>Age (tertiles), years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10/184 (5.4)</td>
<td>28/202 (13.9)</td>
<td>0.44</td>
<td>0.44 [0.29, 0.67]</td>
</tr>
<tr>
<td>&lt;68.7</td>
<td>12/207 (5.8)</td>
<td>25/209 (12.0)</td>
<td></td>
<td>0.42 [0.24, 0.74]</td>
</tr>
<tr>
<td>≥ 68.7 and &lt; 76.8</td>
<td>10/152 (6.6)</td>
<td>18/192 (9.4)</td>
<td></td>
<td>0.46 [0.24, 0.88]</td>
</tr>
<tr>
<td>≥ 76.8</td>
<td>8/180 (4.4)</td>
<td>18/139 (12.9)</td>
<td></td>
<td>0.33 [0.15, 0.73]</td>
</tr>
<tr>
<td><strong>Recent bisphosphonate use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>16/309 (5.2)</td>
<td>39/324 (12.0)</td>
<td>0.85</td>
<td>0.44 [0.29, 0.68]</td>
</tr>
<tr>
<td>no</td>
<td>14/197 (7.1)</td>
<td>39/192 (20.3)</td>
<td></td>
<td>0.42 [0.24, 0.74]</td>
</tr>
<tr>
<td>yes</td>
<td>14/319 (4.4)</td>
<td>25/341 (7.3)</td>
<td></td>
<td>0.46 [0.24, 0.88]</td>
</tr>
<tr>
<td><strong>Recent clinical VFx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>14/319 (4.4)</td>
<td>25/341 (7.3)</td>
<td>0.22</td>
<td>0.46 [0.30, 0.70]</td>
</tr>
<tr>
<td>no</td>
<td>14/197 (7.1)</td>
<td>39/192 (20.3)</td>
<td></td>
<td>0.60 [0.32, 1.13]</td>
</tr>
<tr>
<td>yes</td>
<td>28/516 (5.4)</td>
<td>64/533 (12.0)</td>
<td>0.44 [0.29, 0.68]</td>
<td></td>
</tr>
</tbody>
</table>

*Hip, radius, humerus, ribs, pelvis, and femur
**Prior BP users, non-BP users, treatment naive

The Effect of Denosumab on New Hip Fractures in Higher Risk Populations

Phase 3: The FREEDOM Trial – Higher Risk Sub-analysis

**Placebo**

**Denosumab**

<table>
<thead>
<tr>
<th>Risk of Hip Fracture</th>
<th>Prespecified Analysis* (45% of trial population)</th>
<th>Post-Hoc Analysis† FN T-score ≤ −2.5 (36% of trial population)</th>
<th>Post-Hoc Analysis‡ Age ≥ 75 years (32% of trial population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR = 48%</td>
<td>RR = 47%</td>
<td>RR = 62%</td>
</tr>
<tr>
<td></td>
<td>P = 0.0208</td>
<td>P = 0.0227</td>
<td>P = 0.0065</td>
</tr>
</tbody>
</table>

*In a subset of higher risk patients with ≥ 2 of the following: (a) age > 70 years, (b) baseline BMD T-score ≤ −3.0 at lumbar spine, total hip, or femoral neck, (c) prevalent vertebral fracture at baseline

†In a subset of higher risk patients with femoral neck BMD T-score ≤ −2.5; ‡In a subset of higher risk patients age ≥ 75 years

FN = femoral neck

Boonen S, et al. *JCEM 2011* ; McClung et al., *JBMR 2011*
Risk factors for oral BP failure in Spain (frac. on Tx, > 80% compliance)

- Age 60 to <80y: HR 2.18 [1.70-2.80]
- Age ≥ 80y: HR 2.50 [1.82-3.43]
- Underweight: HR 2.11 [1.14-3.92]
- Overweight: HR 0.85 [0.69-1.05]
- G1 Obesity: HR 0.80 [0.63-1.02]
- G2 Obesity: HR 0.86 [0.63-1.19]
- Old fracture: HR 1.75 [1.39-2.20]
- Recent fracture: HR 2.49 [1.98-3.13]
- Vitamin D deficiency: HR 2.69 [1.27-5.72]
- Inflammatory arthritis: HR 1.46 [1.02-2.10]
- PPI use: HR 1.22 [1.02-1.46]
- Osteoporosis:
  HR 0.67 [0.55-0.81]

Prieto, JBMR 2013
Real world effectiveness of OP therapies

Eligibility Criteria:
- Women age ≥ 65 years receiving treatment with:
  - Denosumab
  - Oral bisphosphonates (alendronate, risedronate, ibandronate)
  - IV bisphosphonates (IV ibandronate, zoledronic acid)
  - Teriparatide
  - Raloxifene
- Period 01/01/2009 to 06/30/2012
- Available data for at least 12 months prior to index prescription date and at least 4 months after
- Excluded patients with baseline diagnoses of Paget’s disease or malignancy
- Excluded patients who switched study medications or received calcitonin within 3 months following treatment index date

1.3 mio women, Mean age 78 years

Yusuf, Archives Osteop 2018
Within-patient analytic approach used to evaluate fracture risk reduction with denosumab and other OP pharmacotherapies

For each patient, fracture risk during early period is compared to the risk during on-treatment period.
Incidence of all fracture endpoint during early and late periods, by treatment cohort

Yusuf, Archives Osteop 2018
What is the goal of osteoporosis therapy?

- Rapid reduction of fracture risk, particularly in patients at "imminent" risk
- Long-term restoration of bone mass and strength
Femoral strength and BMD threshold for hip fractures

Case-control study, 5 yrs follow-up, from the AGES-Reykjavik cohort

BMD = bone mineral density.

Greater Hip BMD gains = Greater Reduction in Hip Fracture Risk in Osteoporosis Trials: A Meta-Regression

DENNIS BLACK, ERIC VITTINGHOFF, RICHARD EASTELL, MARY BOUXSEIN, ET AL.
Relationship Between Total Hip T-score and Nonvertebral Fracture in the FREEDOM & Extension (denosumab) trial

Expected 1-Year Nonvertebral Fracture Incidence (%)

- 3.0
- 2.5
- 2.0
- 1.5
- 1.0

Total Hip T-score

Ferrari et al. (in revision)
FLEX Trial: Non-vertebral fracture risk by T-score after ALN is stopped (> 5yrs)

Bauer JAMA 2014
Conclusions

- Patients with recent fractures are at imminent risk of refracturing (5-20% in one year)
- Identification and immediate treatment of osteoporosis is mandatory in these patients
  - FLS
- There is good evidence that OP drugs reduce fracture risk, including in these high risk / imminent risk patients, particularly with ZOL, Dmab and TPT
- Treatment should be pursued at least until bone mass is restored to near optimal bone strength levels (T-scores $\geq-2$)