LA TERAPIA DELL’OSTEOPOROSI:
RISCHIO O BENEFICIO?

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Osteoporosis Is a Common Disease with Increased Fracture Risk Across the Entire Skeleton

Definition of osteoporosis:

- Compromised bone strength predispose persons to increased risk of fracture
- Bone strength reflects the integration of bone density and bone quality

“Osteoporosis is one of the most common and debilitating chronic diseases, and a global healthcare problem.”

International Osteoporosis Foundation

“Osteoporosis has financial, physical, and psychosocial consequences, all of which significantly affect the individual, the family, and the community.”

NIH Consensus Statement

BMD and Age Are Independent Risk Factors for Fracture

Ten-year risk of hip fracture by BMD and age in women

Figure 2  Incidence of osteoporotic fractures.

Richard Eastell

Identification and management of osteoporosis in older adults
Medicine Volume 41, Issue 1 2013 47 - 52
Osteoporotic Fracture Incidence in Europe

Fractures by sites in women (EU 2000)

- Hip: 21%
- Spine: 16%
- Forearm: 24%
- Humerus: 9%
- Other: 30%

Mediterranean Osteoporosis Study (MEDOS):
Italia 80.800 ricoveri/anno (2002) per frattura di femore in soggetti > 65 aa

- 1 frattura ogni 30 secondi in Europa
- 500.000 nuovi casi/anno in Europa
- Circa 40.000 nuovi casi/anno in Italia

Proiezione ISTAT: prima frattura di femore associata ad osteoporosi
2012 = 45.056 casi  
2017 = 48.115 casi 
+ 6.8%

References:

Handoll H. Clinical Evidence, 2004
Cummings SR, Melton LJI. Epidemiology and Outcome of Osteoporotic 2002
Costi Diretti = Ospedalizzazione

568 milioni di euro/anno = costo giornaliero di ospedalizzazione, spese presidi e diagnostici, costo del personale, costo sala operatoria, materiali ecc.

Costi Indiretti (difficilmente quantificabili):
comparsa di patologie associate permanenti, modificazione stabile dello stato funzionale del paziente, eventuale istituzionalizzazione.

sanitari e sociali: raddoppiano nell’anno successivo all’intervento (fisioterapia, visite specialistiche, terapie mediche, invalidità ecc.)

Costo singola frattura: 13.576 Euro
MORTALITA’ e DISABILITA’

MORTALITA’
- 5% in acuto
- 25% ad un anno (sovrapponibile al Ca mammario)

DISABILITA’
- 20% perde l’ autonomia nelle ADL
- 50% perde l’ autonomia nel cammino
- Nei casi di invalidità permanente circa il 20-25% dei pazienti viene istituzionalizzato

Rosell PAE. Functional Outcome after Hip Fracture Injury, 2003
DETERMINANTI DEL RISCHIO DI FRATTURA

- Funzione neuromuscolare
- Fattori di rischio ambientali
- Tempo di esposizione ai fattori di rischio ambientali
- Tipo di caduta
- Risposte protettive
- Assorbimento dell’energia
- Massa ossea
- Geometria dell’osso
- Qualità della vita

RISCHIO DI CADUTA

FORZA DI IMPATTO

RESISTENZA OSSEA
PREVENZIONE DELLE FRATTURE

TERAPIA NON FARMACOLOGICA
- Valutazione del rischio di caduta e prevenzione
- Attività fisica
- Protettori di femore

TERAPIA FARMACOLOGICA
- Calcio e vitamina D
- Bisfosfonati
- Ranelato di Stronzo
- Teriparatide
- Raloxifene
- Denosumab

CAUSE DI CADUTA NELL’ANZIANO
- Accidentali/correlate all’ambiente
- Turbe di equilibrio/andatura o debolezza muscolare
- Vertigine
- Drop attack
- Stato confusionale
- Ipotensione posturale
- Deficit visivi
- Sincope
- Farmaci
Ruolo delle terapie

Table 3
Prescription osteoporosis prevention and treatment options approved by the Food and Drug Administration, and estimates of associated reduction in fracture risk

<table>
<thead>
<tr>
<th>Antiresorptive Agents</th>
<th>Recommended Use for Osteoporosis</th>
<th>Effect on Fracture Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevention</td>
<td>Treatment in Women</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Ibandronate (Boniva)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel, Atelvia)</td>
<td>√</td>
<td>√</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Zolendronic acid (Reclast)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Calcitonin (Miacalcin, Fortical)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Anabolic Agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide (Forteo)</td>
<td>—</td>
<td>√</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; SQ, subcutaneous.
Boonen S et al. JCEM 2007;92:1415-1423

Forest plot comparing the risk of hip fracture between vitamin D and calcium and placebo/no-treatment groups.
Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women
A Randomized Controlled Trial

Kerrie M. Sanders, PhD
Amanda L. Stuart, BAppSc
Elizabeth J. Williamson, MA, PhD
Julie A. Simpson, PhD
Mark A. Kotowicz, MBBS, FRACP
Doris Young, MD, MBBS, FRACGP
Geoffrey C. Nicholson, PhD, FRACP

Cumulative probability of fracture at various skeletal sites, according to treatment with vitamin D or placebo.


9440 soggetti (4354 uomini – 5086 donne >70 aa, 300 000 UI of colecalciferol or placebo

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Corresponding Author: Kerrie Sanders, PhD, Department of Clinical and Biomedical Sciences, Barwon Health, PO Box 281, Geelong, Victoria, Australia 3220 (kerrie@barwonhealth.org.au).
Safety and Efficacy of Risedronate in Reducing Fracture Risk in Osteoporotic Women Aged 80 and Older: Implications for the Use of Antiresorptive Agents in the Old and Oldest Old

Steven Boonen, MD, PhD,* Michael R. McClung, MD,† Richard Eastell, MD,‡ Ghada El-Hajj Fuleihan, MD, MPH,§ Ian P. Barton, BSc,‖ and Pierre Delmas, MD, PhD¶

Figure 1. Risk of new vertebral fracture during 1 year of treatment with risedronate 5 mg relative to the risk during treatment with placebo in patients with osteoporosis (aged ≥80) in the overall analysis population and in the Vertebral Efficacy with Risedronate Therapy (VERT) and Hip Intervention Program (HIP) trials. Bars represent 95% confidence intervals.

Figure 2. Incidence of any upper gastrointestinal (UGI) adverse events and serious UGI adverse events associated with placebo (black bars) or risedronate 5 mg (white bars) treatment in all patients aged 80 and older (overall) and in subgroups of patients aged 80 and older who had active gastrointestinal (GI) disease, who were using aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), or who were using histamine₂-receptor antagonists (H₂-RAs) or proton pump inhibitors (PPIs).
Efficacy and Safety of a Once-Yearly Intravenous Zoledronic Acid 5 mg for Fracture Prevention in Elderly Postmenopausal Women with Osteoporosis Aged 75 and Older

Steven Boonen, MD, PhD∗, Dennis M. Black, PhD†, Cathleen S. Colón-Emeric, MD, MHSc‡,§, Richard Eastell, MD||, Jay S. Magaziner, PhD††, Erik Fink Eriksen, MD, DMSc†‡, Peter Mesenbrink, PhD†‡, Patrick Haentjens, MD, PhD†††, and Kenneth W. Lyles, MD‡,§,§§


Figure 1.
Event rate of new fractures in patients receiving zoledronic acid (ZOL) 5 mg once yearly and those receiving placebo at 1 and 3 years. †Hazard ratio (HR) (95% confidence interval) of ZOL versus placebo computed from the Cox proportional hazards regression model stratified according to study with treatment as a factor within the subgroup. ‡Event rate calculated from Kaplan-Meier estimates.
Safety and Efficacy of Teriparatide in Elderly Women with Established Osteoporosis: Bone Anabolic Therapy from a Geriatric Perspective

Steven Boonen, MD, PhD,* Fernando Marin, MD, PhD,† Dan Mellstrom, MD, PhD,‡ Li Xie, MS,† Durisala Desai, PhD,‡ John H. Krege, MD,† and Clifford J. Rosen, MD§

JAGS 54:782–789, 2006

Figure 3. The relative risk (95% confidence interval (CI)) teriparatide versus placebo of new vertebral (VFx) and nonvertebral fragility fractures (nonvert F Fx) by age.
Five years treatment with strontium ranelate reduces vertebral and nonvertebral fractures and increases the number and quality of remaining life-years in women over 80 years of age

Ego Seeman a,*, Steven Boonen b, Frederik Borgström c, Bruno Vellas d, Jean-Pierre Aquino e, Jutta Semler f, Claude-Laurent Benhamou g, Jean-Marc Kaufman h, Jean-Yves Reginster i

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d CHU Purpan, Toulouse, France  
e Clinique Médicale de la Porte Verte, Versailles, France  
f Immanuel Krankenhaus Rheumaklinik, Berlin, Germany  
g Hôpital de la Madeleine, Orléans, France  
h U.Z. Gent Department of Internal Medicine, Gent, Belgium  
i University of Liège, Liège, Belgium

Frequency of adverse events (N = number of exposed patients, % of patients with at least one emergent AE, E(SE) = estimate (standard error) of the difference between group percentages, 95% CI of the estimate), *statistically significant difference between treatment groups.

<table>
<thead>
<tr>
<th>Condition</th>
<th>N safety set</th>
<th>Placebo N</th>
<th>E (SE)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>3.3</td>
<td>1.7</td>
<td>1.6 (0.8)</td>
<td>[0.1; 3.3]*</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7.1</td>
<td>4.8</td>
<td>2.4 (1.4)</td>
<td>[−0.4; 5.2]</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.1</td>
<td>6.2</td>
<td>1.9 (1.3)</td>
<td>[−0.8; 4.5]</td>
</tr>
<tr>
<td>Dermatitis and eczema</td>
<td>4.8</td>
<td>5.1</td>
<td>−0.3 (1.1)</td>
<td>[−2.5; 1.9]</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0.5</td>
<td>0.4</td>
<td>0.1 (0.4)</td>
<td>[−0.7; 1.0]</td>
</tr>
<tr>
<td>Deep venous</td>
<td>4.5</td>
<td>2.5</td>
<td>2.0 (0.9)</td>
<td>[0.2; 4.0]*</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disturbance in consciousness</td>
<td>4.1</td>
<td>3.8</td>
<td>0.3 (1.0)</td>
<td>[−1.7; 2.4]</td>
</tr>
<tr>
<td>Memory loss</td>
<td>4.4</td>
<td>2.9</td>
<td>1.5 (1.0)</td>
<td>[−0.4; 3.5]</td>
</tr>
<tr>
<td>Seizures and seizure disorders</td>
<td>0.7</td>
<td>0.0</td>
<td>0.7 (0.3)</td>
<td>[0.04; 1.54]*</td>
</tr>
</tbody>
</table>

**Fig. 1.** Relative reduction of fracture risk with strontium ranelate over 5 years in the ITT pooled population (□ placebo; ■ strontium ranelate 2 g/d).
Denosumab 60 mg SC Q6M (N = 3902)

Placebo SC Q6M (N = 3906)

Denosumab 60 mg SC Q6M (N = 2343)

Denosumab 60 mg SC Q6M (N = 2207)

Long-term Denosumab

Cross-over Denosumab

Calcium and Vitamin D

Red box defines the scope of the current analysis including the first 3 years of the extension (6 years overall) for the long-term denosumab group only.
Subject Incidence of Fractures in the FREEDOM and Extension Studies

A. New Vertebral Fractures

<table>
<thead>
<tr>
<th></th>
<th>Overall Long-term Group</th>
<th>&lt; 75 Years Group</th>
<th>≥ 75 Years Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture Incidence (%)</td>
<td>FREEDOM</td>
<td>Extension</td>
<td>FREEDOM</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.2%</td>
<td>2.3%</td>
<td>6.5%</td>
</tr>
<tr>
<td>DMAb</td>
<td>5.5%</td>
<td>3.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Long-term DMAb</td>
<td>N = 2114</td>
<td>Years 1-3</td>
<td>N = 1555</td>
</tr>
</tbody>
</table>

B. Nonvertebral Fractures

<table>
<thead>
<tr>
<th></th>
<th>Overall Long-term Group</th>
<th>&lt; 75 Years Group</th>
<th>≥ 75 Years Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture Incidence (%)</td>
<td>FREEDOM</td>
<td>Extension</td>
<td>FREEDOM</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.0%</td>
<td>6.5%</td>
<td>7.6%</td>
</tr>
<tr>
<td>DMAb</td>
<td>6.5%</td>
<td>3.8%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Long-term DMAb</td>
<td>N = 2343</td>
<td>Years 1-3</td>
<td>N = 1681</td>
</tr>
</tbody>
</table>

Fracture incidence is based on crude incidence rate for panel A and Kaplan-Meier estimate for panels B and C.
N = number of subjects in the respective primary efficacy analysis set.
DMAb = denosumab.
CONCLUSIONS

• Denosumab treatment for 6 years (overall long-term group) and regardless of age (< 75 years and ≥ 75 years groups):
  – Was associated with low incidences of new vertebral, nonvertebral, and hip fractures
  – Continued to significantly increase BMD year to year
  – Remained well tolerated

• These results underscore the consistent anti-fracture efficacy and safety profile of continued denosumab treatment over 6 years.

• Denosumab is a therapeutic option for women at higher risk for fracture, notably those ≥ 75 years, in whom hip fractures increase exponentially due to trabecular and cortical bone decay.
CONCLUSIONI

ANALISI COMPARATIVA DI EFFICACIA

<table>
<thead>
<tr>
<th>Terapia</th>
<th>Evento pericolo</th>
<th>Efficacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-ipertensiva</td>
<td>Ictus cerebri</td>
<td>~ 40 %</td>
</tr>
<tr>
<td>ipolipemizzante</td>
<td>Infarto miocardico</td>
<td>~ 30 %</td>
</tr>
<tr>
<td>osteoporosi</td>
<td>Frattura</td>
<td>~ 60 %</td>
</tr>
</tbody>
</table>

![Diagrama di rischio per osteoporosi per sesso](image.png)
CONCLUSIONI

NATIONAL OSTEOPOROSIS FOUNDATION

Box 1
Indications for osteoporosis prescription therapy

Hip or vertebral fracture
Osteoporosis based on BMD (T-score ≤ −2.5) after appropriate evaluation for secondary causes
Low bone density by BMD (T-score of −1.0 to −2.5) and risk based on the FRAX algorithm (10-year probability of a major osteoporosis-related fracture of ≥20% or 10-year probability of a hip fracture of ≥3%)
Clinical judgment based on overall fracture risk