ASPETTI ENDOCRINO-METABOLICI NELL'ANZIANO

Bari,
7-10 novembre 2013

LA TERAPIA DELL'OSTEOPOROSI: RISCHIO O BENEFICIO?

Stefania Bonadonna
U.O. di Malattie Metaboliche Ossee
Istituto Auxologico Italiano, Milano

ISTITUTO AUXOLOGICO ITALIANO
Istituto di Ricovero e Cura a Carattere Scientifico

DEFINIZIONE OSTEOPOROSI

Bari,
7-10 novembre 2013

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

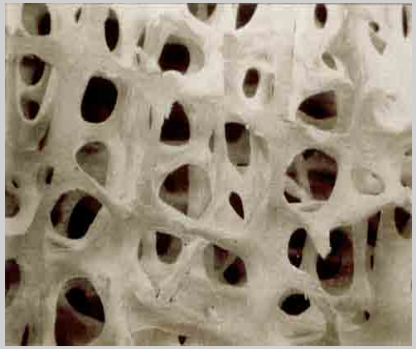
Definition of osteoporosis:

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

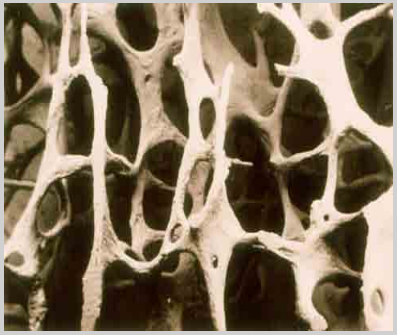
> "Osteoporosis is one of the most common and debilitating chronic diseases, and a global healthcare problem."
>
> International Osteoporosis Foundation

> "Osteoporosis has financial, physical, and psychosocial consequences, all of which significantly affect the individual, the family, and the community."
>
> NIH Consensus Statement

Normal



Osteoporosis



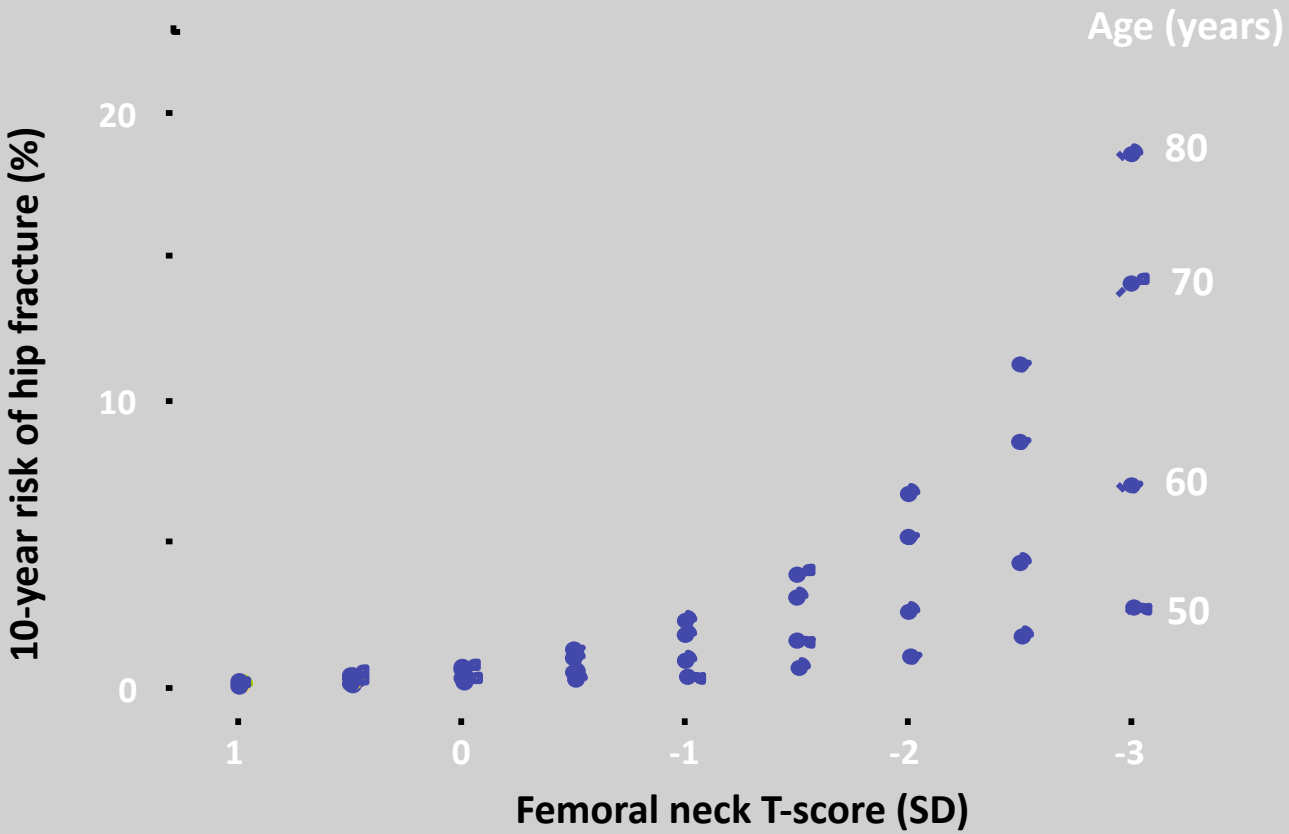
Boyle WJ, et al. *Nature* 2003;423: 337-342;
NIH Consensus Development Panel. *JAMA.* 2001;285: 785-795.

RISCHIO FRATTURATIVO

Bari,
7-10 novembre 2013

BMD and Age Are Independent Risk Factors for Fracture

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



Kanis JA, et al. *Osteoporos Int* 2001;12:989-995. Kanis JA, et al. *Osteoporos Int* 2001;12:417-427.
Kanis JA, et al. *Osteoporos Int* 2005;16:581-589.

INCIDENZA DI FRATTURE OSTEOPOROTICHE

Bari,
7-10 novembre 2013

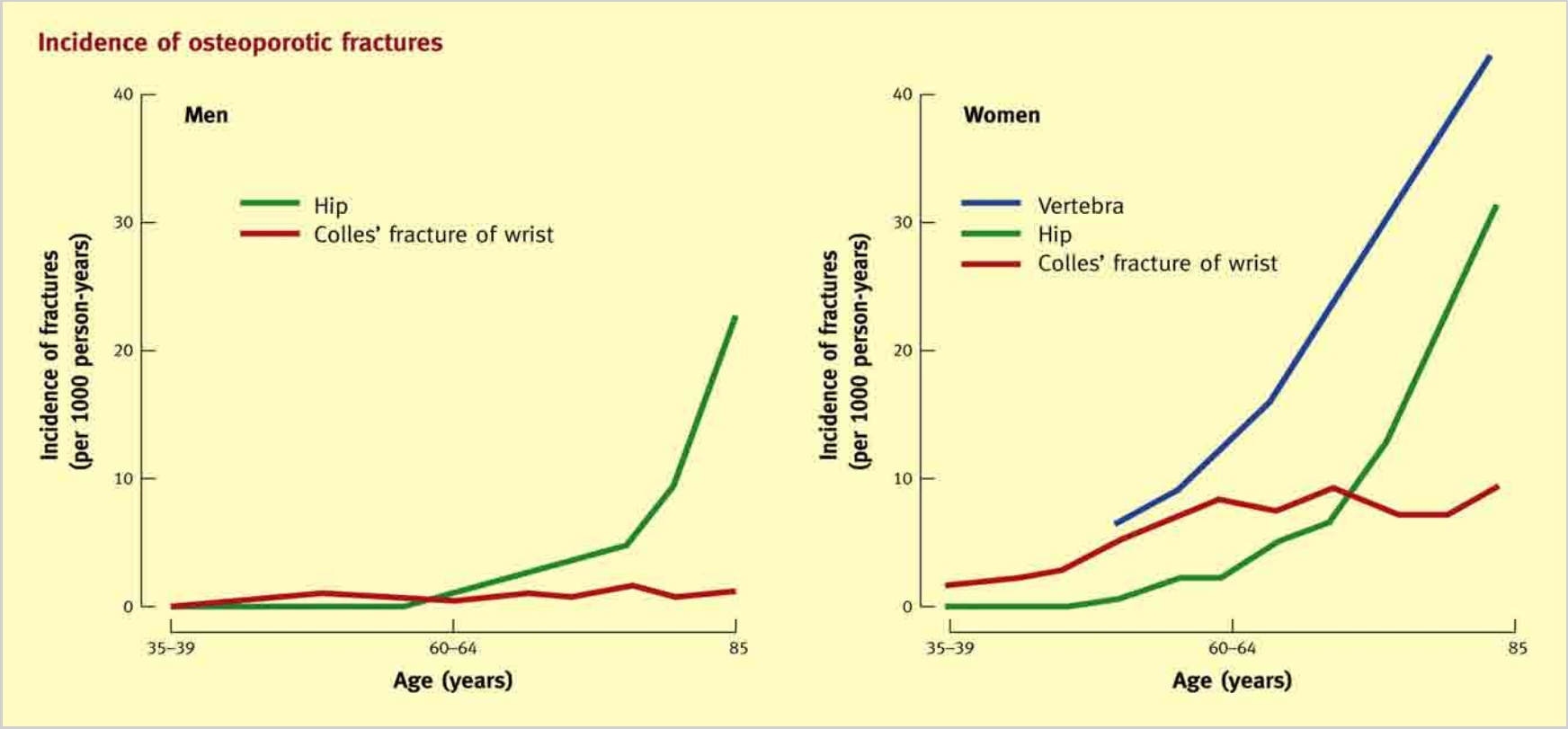
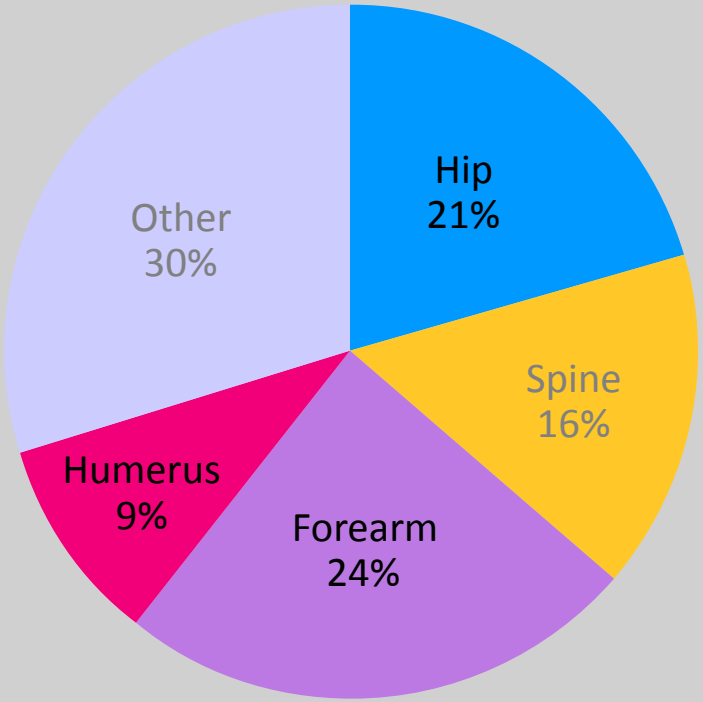


Figure 2 Incidence of osteoporotic fractures.

Richard Eastell
Identification and management of osteoporosis in older adults
Medicine Volume 41, Issue 1 2013 47 - 52

Osteoporotic Fracture Incidence in Europe

Bari,
7-10 novembre 2013



Fractures by sites in women (EU 2000)[1]

1. Johnell O and Kanis JA. *Osteoporos Int* 2006;17:1726-1733.
2. European Commission. Report on osteoporosis in the European Community-action for prevention, 1998.

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**

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

Proiezione ISTAT: prima frattura di femore associata ad osteoporosi

2012 = 45.056 casi → **2017 = 48.115 casi**

+ 6.8%

COSTI TOTALI FRATTURE FEMORE IN ITALIA

Bari,
7-10 novembre 2013

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.)

Numero di ricoveri per frattura femorale	80.800
Costi diretti relativi ai ricoveri (euro)	394.000.000
Costi di 1 mese di riabilitazione postoperatoria (escluso 5% di mortalità acuta) (euro)	412.000.000
Costi sociali (pensioni d'invalidità ed accompagnamento per gli stimati 18000 pazienti disabili all'anno) (euro)	108.000.000
Costi indiretti (20% dei costi diretti totali) (euro)	183.000.000
Stima dei costi totali delle fratture femorali (euro)	1.097.000.000

Costo singola frattura : 13.576 Euro

MORTALITA' e DISABILITA'

Bari,
7-10 novembre 2013

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

Bari,
7-10 novembre 2013

DETERMINANTI DEL RISCHIO DI FRATTURA

- Funzione neuromuscolare
- Fattori di rischio ambientali
- Tempo di esposizione ai fattori di rischio ambientali

→ RISCHIO DI CADUTA

- Tipo di caduta
- Risposte protettive
- Assorbimento dell'energia

→ FORZA DI IMPATTO

- Massa ossea
- Geometria dell'osso
- Qualità della vita

→ RESISTENZA OSSEA

PREVENZIONE DELLE FRATTURE

Bari,
7-10 novembre 2013

TERAPIA NON FARMACOLOGICA

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

TERAPIA FARMACOLOGICA

- Calcio e vitamina D
- Bisfosfonati
- Ranelato di Stronzio
- 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

Bari,
7-10 novembre 2013

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

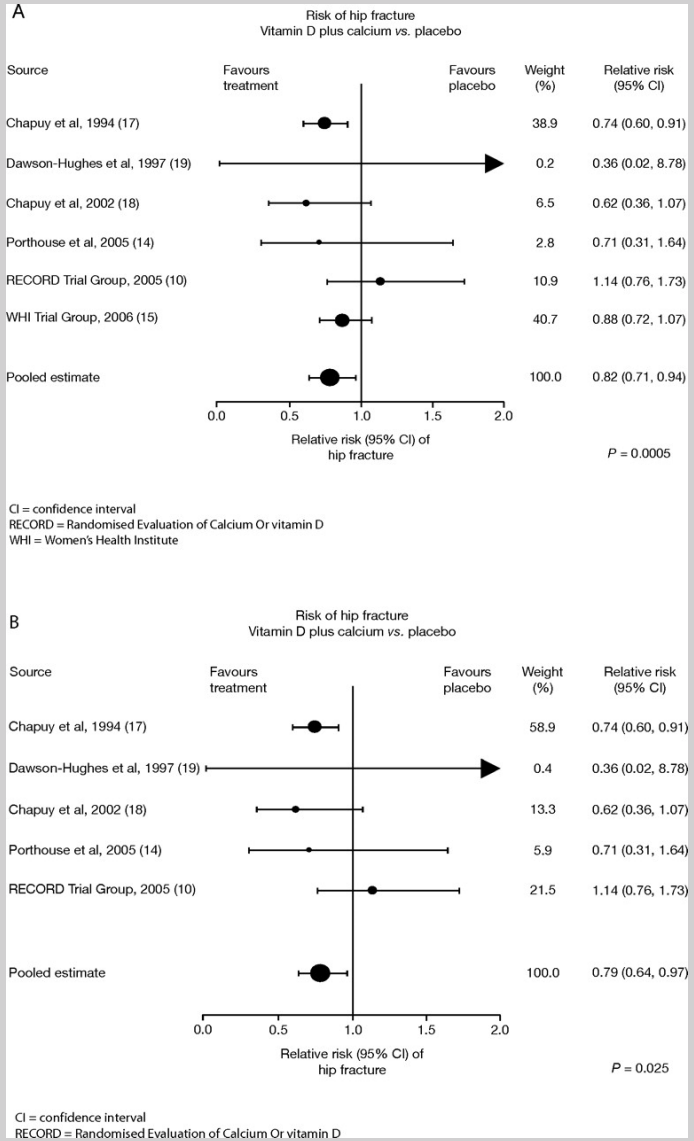
	Recommended Use for Osteoporosis			Effect on Fracture Risk			
	Prevention	Treatment in Women	Treatment in Men	Vertebral	Nonvertebral	Hip	Dosing
Antiresorptive Agents							
Bisphosponates							
Alendronate (Fosamax)[73,74]	√	√	√	√	√	√	70 mg oral weekly
Ibandronate (Boniva)[75,76]	√	√	—	√	—	—	150 mg oral monthly 3 mg IV every 3 mo
Risedronate (Actonel, Atelvia)[77,78]	√	√	√	√	√	√	35 mg oral weekly (Actonel, Atelvia) 75 mg oral 2 consecutive days each month (Actonel only) 150 mg oral monthly (Actonel only)
Zolendronic acid (Reclast)[64,79]	√	√	√	√	√	√	5 mg IV yearly
Denosumab (Prolia)[80,81]	—	√	√	√	√	√	60 mg SQ every 6 mo
Calcitonin (Miacalcin, Fortical)[82,83]	—	√	—	√	—	—	200 IU intranasally daily
Raloxifene (Evista)[84,85]	√	√	—	√	—	—	60 mg oral daily
Anabolic Agent							
Teriparatide (Forteo)[86,87]	—	√	√	√	√	—	20 μg SQ daily

Warriner and Saag, Orthop Clin N Am 44 (2013) 125-135

VITAMINA D E CALCIO

Bari,
7-10 novembre 2013

Forest plot comparing the risk of hip fracture between vitamin D and calcium and placebo/no-treatment groups.



Boonen S et al. JCEM 2007;92:1415-1423

BOLI AD ALTE DOSI DI VITAMINA D

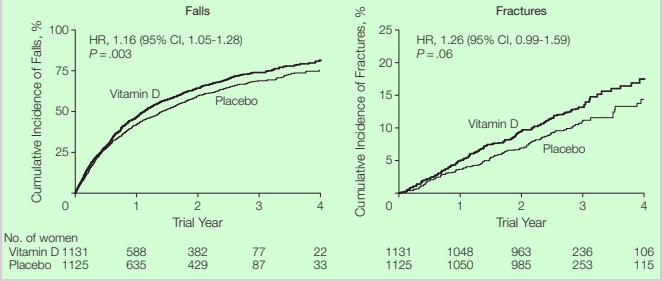
Bari,
7-10 novembre 2013

Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women

A Randomized Controlled Trial

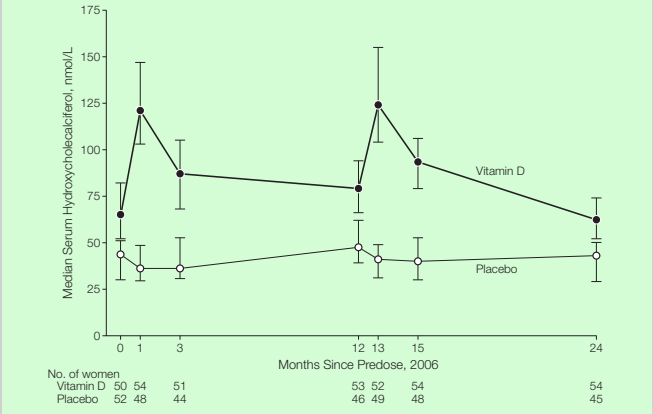
Kerrie M. Sanders, PhD
Amanda L. Stuart, BappSc
Elizabeth J. Williamson, MA, PhD
Julie A. Simpson, PhD
Mark A. Kotowicz, MBBS, FRACP
Doris Young, MD, MBBS, FRACGP
Geoffrey C. Nicholson, PhD, FRACP

Figure 2. Kaplan-Meier Plots of Cumulative Incidence of Time to First Fracture and First Fall



2256 donne, >70 aa, 500 000UI of colecalciferol or placebo

Figure 4. Serum 25-Hydroxycholecalciferol Levels Before Dose, and at 1, 3, and 12 Months After Dose



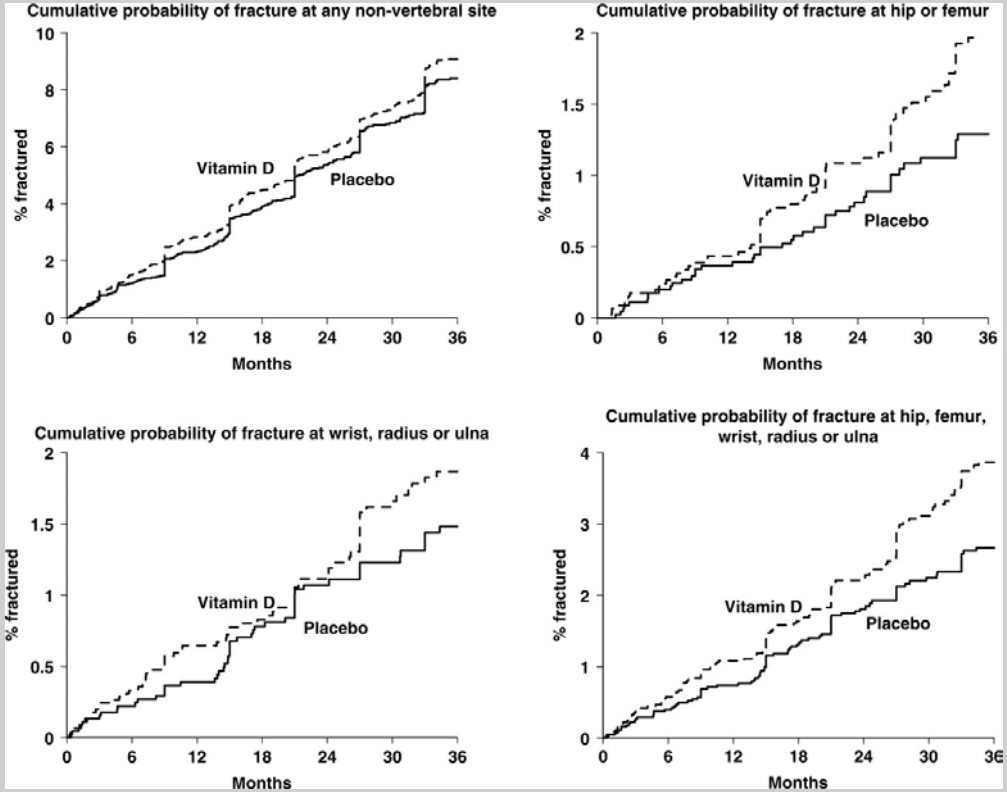
JAMA. 2010;303(18):1815-1822 www.jama.com

Author Affiliations: Department of Clinical and Biomedical Sciences, Barwon Health, University of Melbourne, Geelong (Drs Sanders, Kotowicz, and Nicholson and Ms Stuart); Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, University of Melbourne, Carlton (Drs Williamson and Simpson); Murdoch Children's Research Institute, and Royal Children's Hospital (Dr Williamson); and Department of General Practice, University of Melbourne, Parkville, Victoria (Dr Young), Australia.
Corresponding Author: Kerrie Sanders, PhD, Department of Clinical and Biomedical Sciences, Barwon Health, PO Box 281, Geelong, Victoria, Australia 3220 (kerrie@barwonhealth.org.au).

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

Smith H et al. Rheumatology 2007;46:1852-1857

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



BISFOSFONATI ORALI

Bari,
7-10 novembre 2013

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¶*

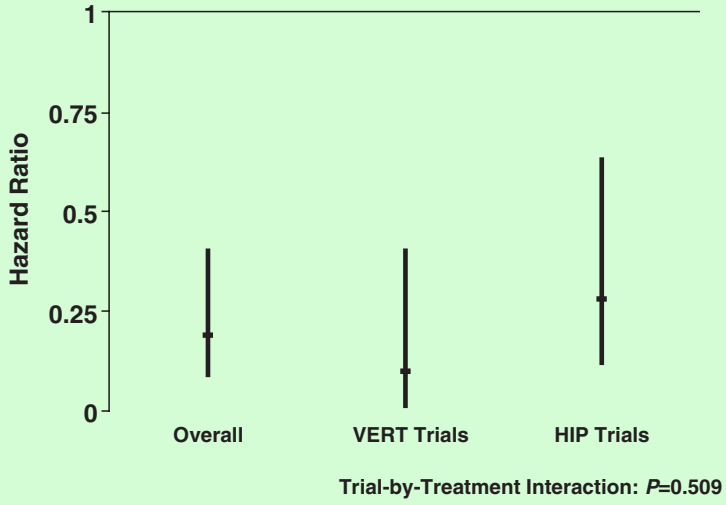


Figure 1. Risk of new vertebral fracture during 1 year of treatment with risedronate 5 mg relative to the risk during treatment with placebo in patients with osteoporosis (aged ≥80) in the overall analysis population and in the Vertebral Efficacy with Risedronate Therapy (VERT) and Hip Intervention Program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

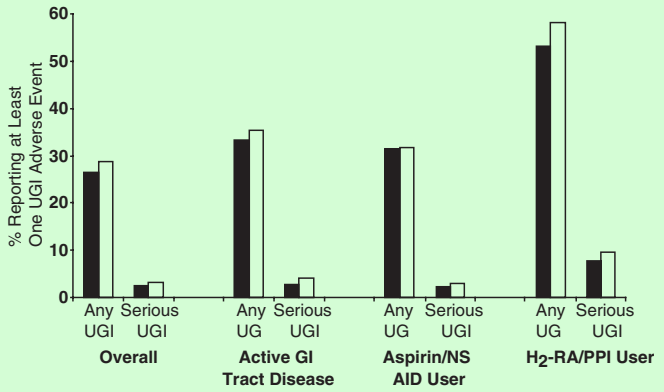


Figure 2. Incidence of any upper gastrointestinal (UGI) adverse events and serious UGI adverse events associated with placebo (black bars) or risedronate 5 mg (white bars) treatment in all patients aged 80 and older (overall) and in subgroups of patients aged 80 and older who had active gastrointestinal (GI) disease, who were using aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), or who were using histamine$_2$-receptor antagonists (H_2-RAs) or proton pump inhibitors (PPIs).

JAGS 52:1832–1839, 2004

ZOLEDRONATO

Bari,
7-10 novembre 2013

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[‡,§,§§]

J Am Geriatr Soc. 2010 February ; 58(2): 292–299.

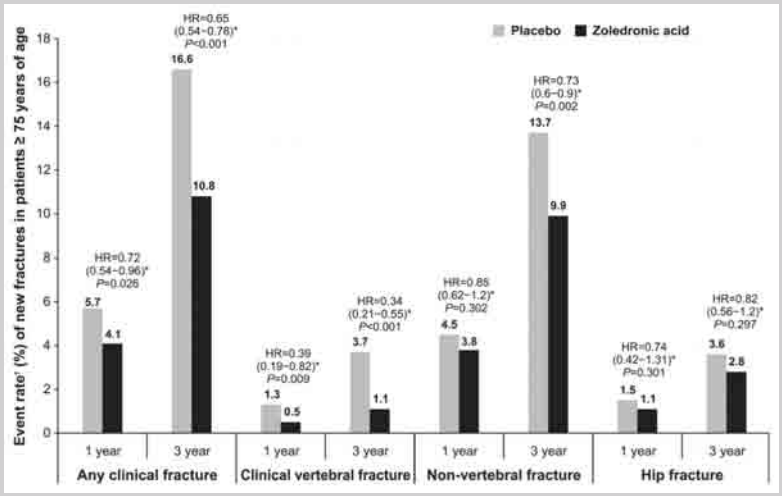


Figure 1.
Event rate of new fractures in patients receiving zoledronic acid (ZOL) 5 mg once yearly and those receiving placebo at 1 and 3 years. *Hazard ratio (HR) (95% confidence interval) of ZOL versus placebo computed from the Cox proportional hazards regression model stratified according to study with treatment as a factor within the subgroup. †Event rate calculated from Kaplan-Meier estimates.

EVENTI AVVERSI

Flue-like syndrome
ONJ
Atipical fracture

TERIPARATIDE

Bari,
7-10 novembre 2013

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 Desaiah, PhD,† John H. Krege, MD,† and Clifford J. Rosen, MD§*

JAGS 54:782–789, 2006

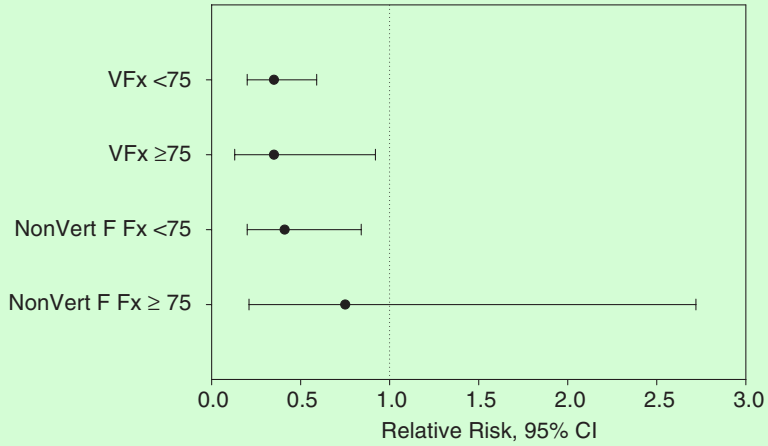


Figure 3. The relative risk (95% confidence interval (CI)) teriparatide versus placebo of new vertebral (VFx) and nonvertebral fragility fractures (nonvert F Fx) by age.

	Aged ≥75		
	Placebo (N = 118)	Teriparatide (N = 126)	
Adverse Event	n (%)		Interaction *P*-values
Patients with ≥1 adverse event	107 (91)	104 (83)	.27
Asthenia	10 (8)	13 (10)	.98
Arrhythmia	5 (4)	1 (1)	.09
Hypertension	13 (11)	11 (9)	.62
Syncope	1 (1)	3 (2)	.71
Abdominal pain	15 (13)	8 (6)	.07
Constipation	12 (10)	9 (7)	.10
Diarrhea	4 (3)	12 (10)	.04
Dyspepsia	6 (5)	5 (4)	.34
Nausea	11 (9)	10 (8)	.30
Vomiting	4 (3)	4 (3)	.62
Ecchymosis	6 (5)	8 (6)	.33
Peripheral edema	10 (8)	4 (3)	.08
Arthralgia	12 (10)	10 (8)	.28
Back pain	30 (25)	19 (15)*	.32
Leg cramps	2 (2)	3 (2)	.39
Headache	6 (5)	7 (6)	.84
Dizziness	9 (8)	11 (9)	.46
Vertigo	5 (4)	6 (5)	.74
Cataract	12 (10)	3 (2)*	.003
Deafness	4 (3)	1 (1)	.006
Pruritus	6 (5)	0 (0)*	.02
Rash	5 (4)	8 (6)	.50
Cyst	0 (0)	5 (4)	.09
Fever	7 (6)	1 (1)	.08
Weight loss	6 (5)	2 (2)	.03
Cancer	3 (3)	0 (0)	.53
Vaginitis	4 (3)	0 (0)	.10

RANELATO DI STRONZIO

Bari,
7-10 novembre 2013

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]

[a] *Austin Health, University of Melbourne, Melbourne, Australia*
[b] *Leuven University Center for Metabolic Bone Diseases and Division of Geriatric Medicine, Leuven, Belgium*
[c] *i3 Innovus, Stockholm, Sweden*
[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*

Bone 46 (2010) 1038–1042

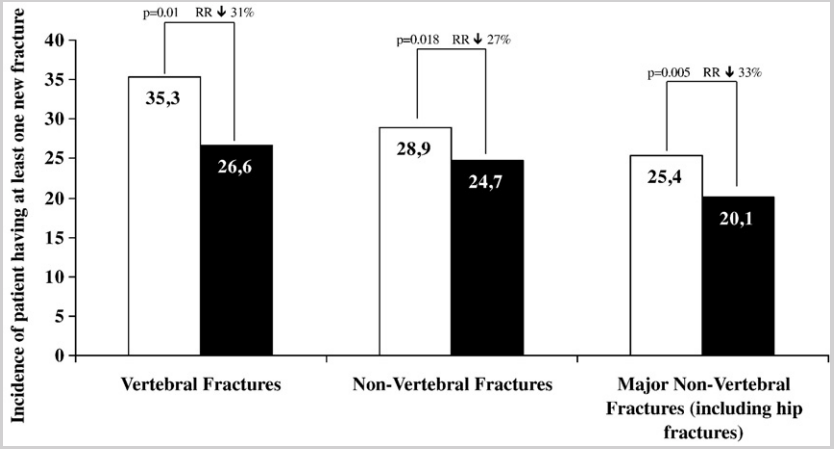


Fig. 1. Relative reduction of fracture risk with strontium ranelate over 5 years in the ITT pooled population (□ placebo; ■ strontium ranelate 2 g/d).

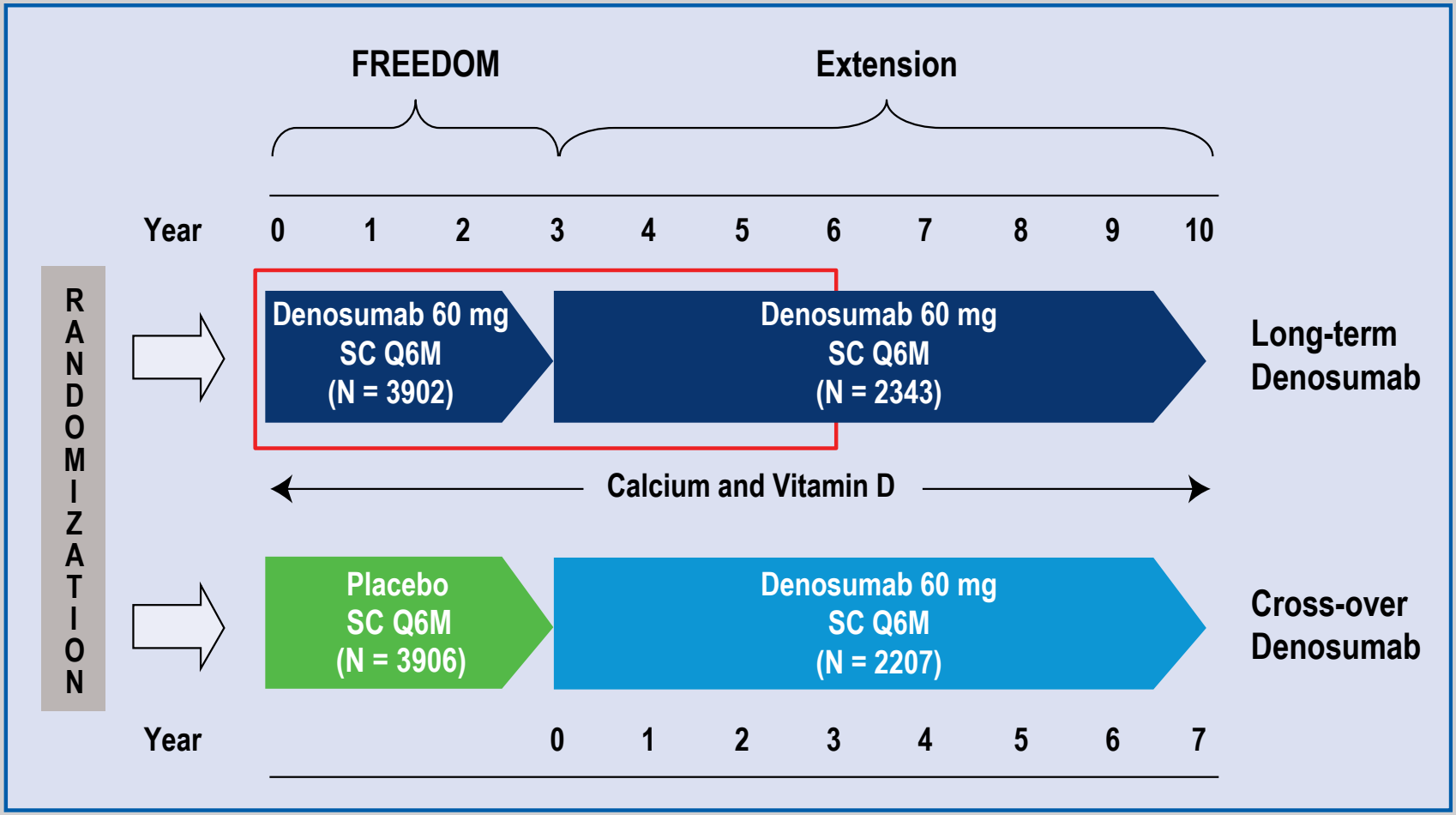
Frequency of adverse events (N = number of exposed patients, % of patients with at least one emergent AE, E(SE) = estimate (standard error) of the difference between group percentages, 95% CI of the estimate), *statistically significant difference between treatment groups.

$N_{safety\ set}$ = 1528	Strontium ranelate N = 756	Placebo N = 772	E (SE)	95% CI
	%	%		
Headaches	3.3	1.7	1.6 (0.8)	[0.1;3.3]*
Nausea and vomiting	7.1	4.8	2.4 (1.4)	[−0.4;5.2]
Diarrhea	8.1	6.2	1.9 (1.3)	[−0.8:4.5]
Dermatitis and eczema	4.8	5.1	−0.3 (1.1)	[−2.5;1.9]
Alopecia	0.5	0.4	0.1 (0.4)	[−0.7;1.0]
Deep venous thromboembolic events	4.5	2.5	2.0 (0.9)	[0.2;4.0]*
Disturbance in consciousness	4.1	3.8	0.3 (1.0)	[−1.7;2.4]
Memory loss	4.4	2.9	1.5 (1.0)	[−0.4;3.5]
Seizures and seizure disorders	0.7	0	0.7 (0.3)	[0.04;1.54]*

DENOSUMAB

Bari,
7-10 novembre 2013

DISEGNO DELLO STUDIO

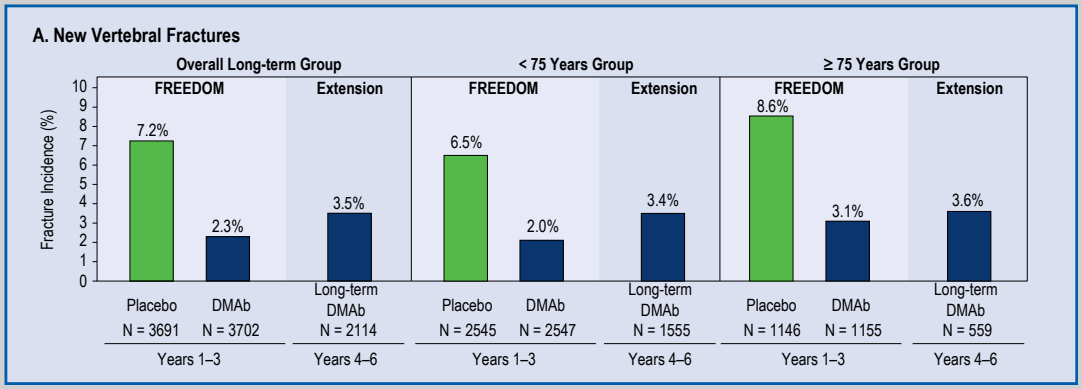


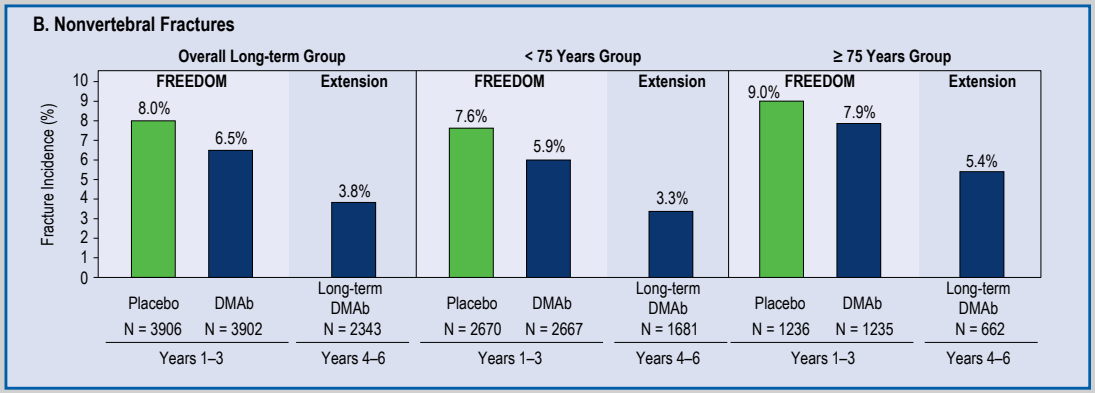
Red box defines the scope of the current analysis including the first 3 years of the extension (6 years overall) for the long-term denosumab group only.

denosumab

Bari,
7-10 novembre 2013

Subject Incidence of Fractures in the FREEDOM and Extension Studies





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.

Bari,
7-10 novembre 2013

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.

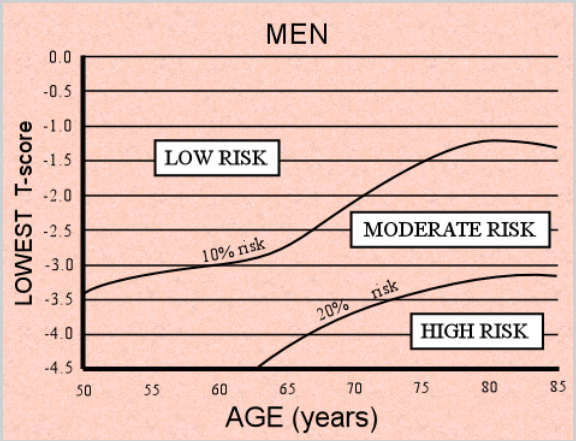
CONCLUSIONI

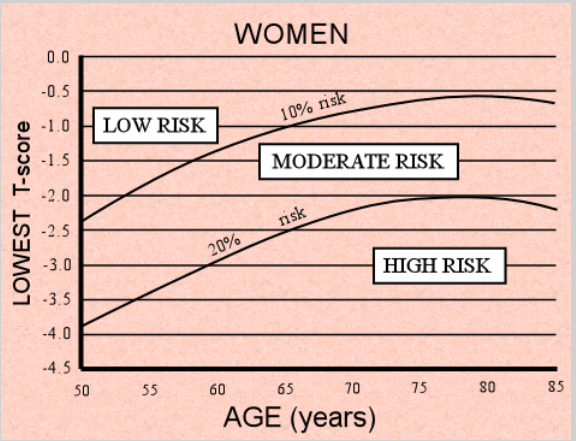
Bari,
7-10 novembre 2013

ANALISI COMPARATIVA DI EFFICACIA

Terapia anti-ipertensiva	**Ictus cerebri**	**~ 40 %**
Terapia ipolipemizzante	**Infarto miocardico**	**~ 30 %**
Terapia osteoporosi	**Frattura**	**~ 60 %**

!





CONCLUSIONI

Bari,
7-10 novembre 2013

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 $\geq 20\%$ **or** 10-year probability of a hip fracture of $\geq 3\%$)

Clinical judgment based on overall fracture risk