Endocrine Unit and Chair of
Endocrinology
Director Prof. Manuela Simoni

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Modena

Bari,
7-10 novembre 2013

Hot topics in osteoporosis

How long to treat

Dott. Bruno Madeo
bruno.madeo@unimore.it
www.endocrinologia.unimore.it/on-line/Home.html

Bari,
7-10 novembre 2013

- **Simposio "Hot topics in osteoporosis"**
  che si svolgerà dalle ore 15.30 alle ore 16.45 di venerdì 8 novembre con l'intervento "How long to treat"

12° Congresso Nazionale AME
Associazione Medici Endocrinologi

6th Joint Meeting with AACE
American Association of Clinical Endocrinologists

Bari, 7-10 novembre 2013

Udine, 29 luglio 2013

Caro Bruno,

abbiamo il piacere di annunciarti che il 12° Congresso Nazionale AME, si terrà a Bari presso lo Sheraton Nicolaus Hotel & Conference Center dal 7 al 10 novembre 2013.
Conoscendo la tua competenza, abbiamo il piacere di invitarti a partecipare al seguente evento:

Duration of the studies

Bari,
7-10 novembre 2013

Neer et al. N Engl J Med 2001 Fracture Prevention Trial

Black et al. Lancet 1996 FIT1

Cummings et al JAMA 1998 FIT2

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Reginster et al. Arthritis & Rheumatism 2008 TROPOS

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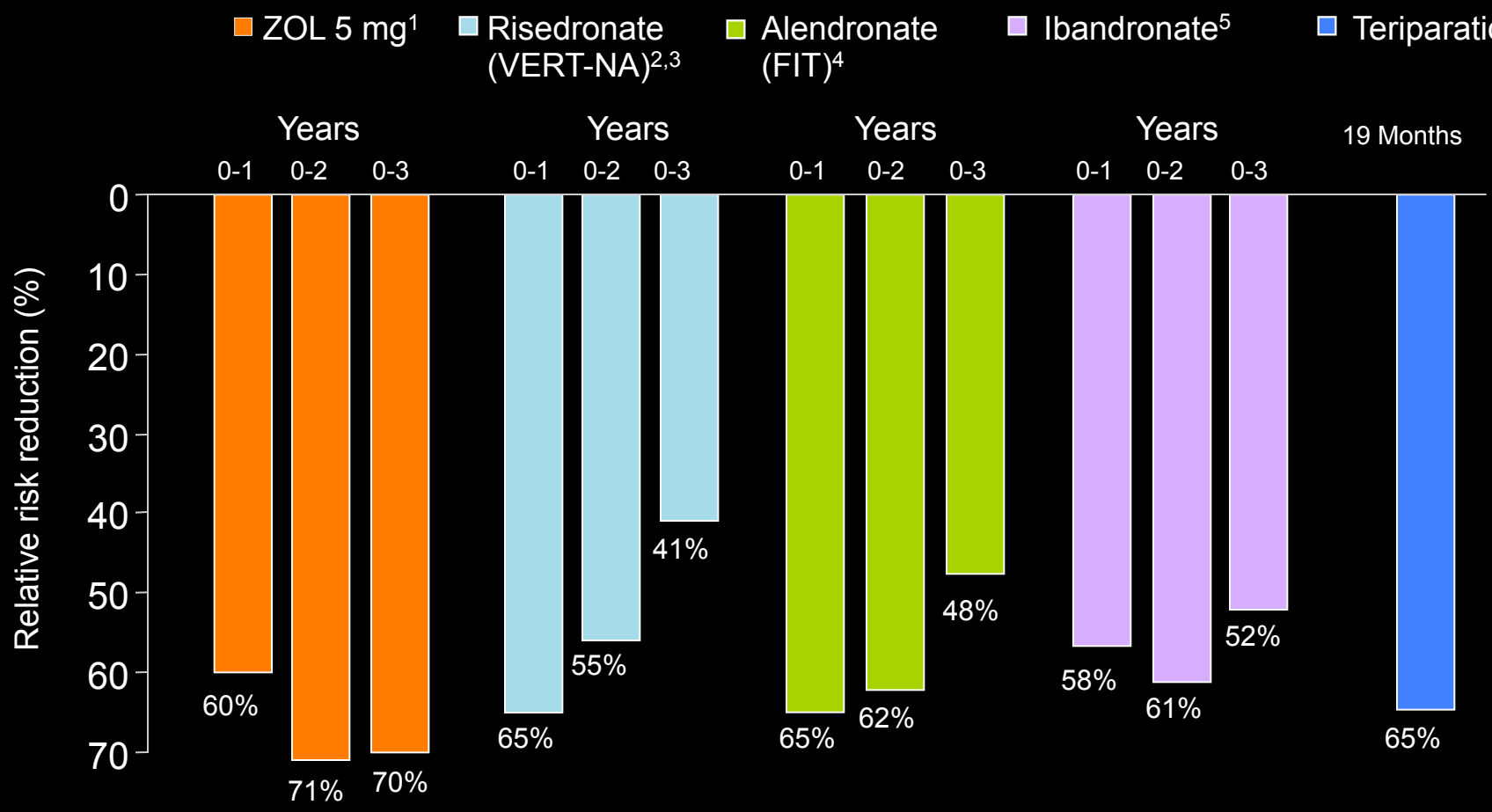
Bisphosphonates and Teriparatide
Vertebral Fractures

Bari,
7-10 novembre 2013



1. Black DM, et al. *N Engl J Med.* 2007;356:1809-1822. 2. Harris ST, et al. *JAMA.* 1999;282:1344.
3. Actonel foglietto illustrativo 4. Black D, et al. *J Clin Endocrinol Metab.* 2000;85:4118-4124.
5. Chesnut CH, et al. *J Bone Miner Res.* 2004;19:1241. 6. Neer RM, et al. *N Engl J Med.* 2001;344:1434.

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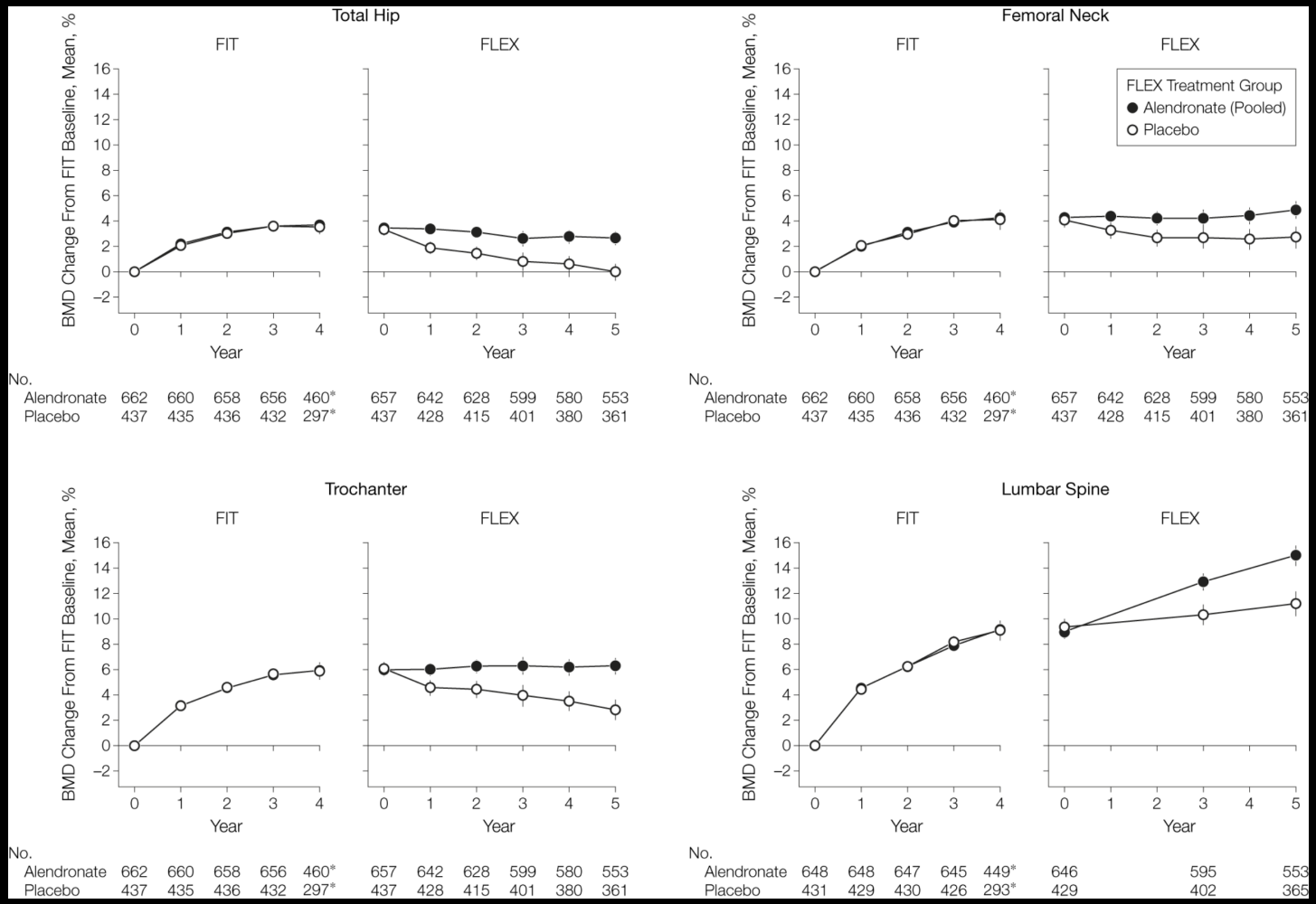
Black et al JAMA. 2006 FLEX

Effects of Continuing or Stopping Alendronate After 5 Years of Treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

Bari,
7-10 novembre 2013

Black et al JAMA. 2006;296(24):2927-2938. doi:10.1001/jama.296.24.2927

PRIMARY ENDPOINT: BMD



Effects of Continuing or Stopping Alendronate After 5 Years of Treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

Bari,
7-10 novembre 2013

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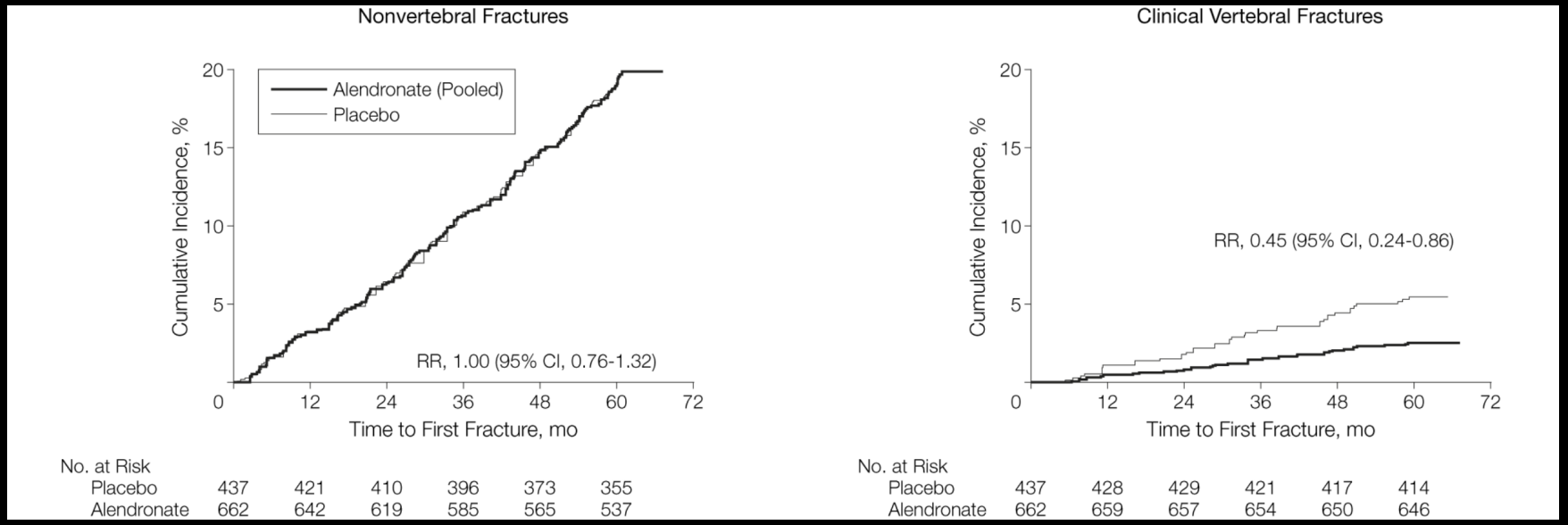


Table 3. Incidence of Fracture by Treatment Group

Fractures	Placebo, No. (%) (n = 437)	Pooled Alendronate, No. (%) (n = 662)	Relative Risk (95% Confidence Interval)*
Vertebral			
Clinical	23 (5.3)	16 (2.4)	0.45 (0.24-0.85)
Morphometric	46 (11.3)	60 (9.8)	0.86 (0.60-1.22)
Clinical			
Any	93 (21.3)	132 (19.9)	0.93 (0.71-1.21)
Nonspine	83 (19.0)	125 (18.9)	1.00 (0.76-1.32)
Hip	13 (3.0)	20 (3.0)	1.02 (0.51-2.10)
Forearm	19 (4.3)	31 (4.7)	1.09 (0.62-1.96)

*Adjusted for clinic and stratum.

ESPLORATORY ENDPOINT:

Fractures

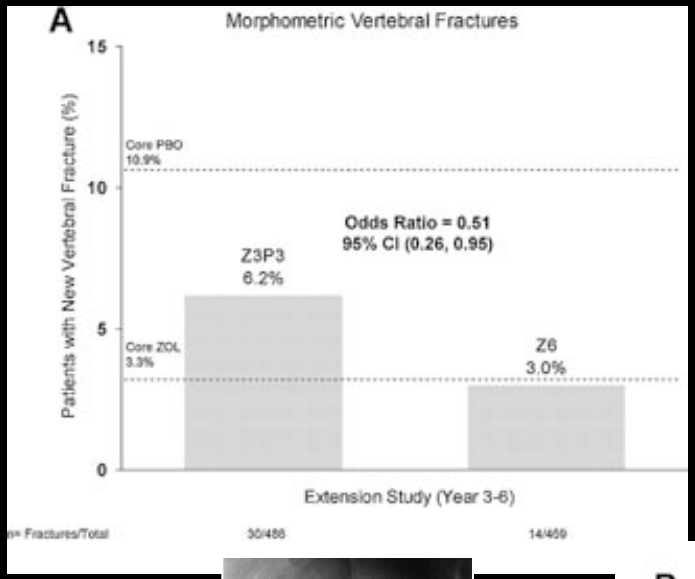
The effect of 3 versus 6 years of Zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT)

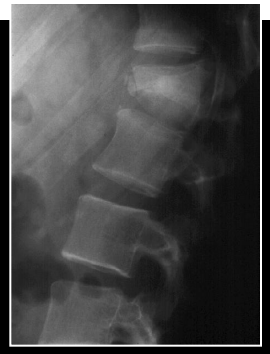
Bari,
7-10 novembre 2013

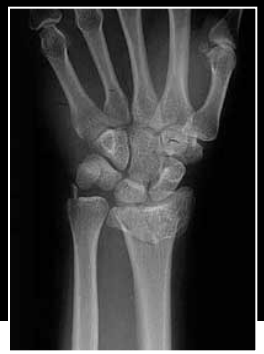
Black et al. JBMR 2012 27 (2): 243-254, DOI: 10.1002/jbmr.1494

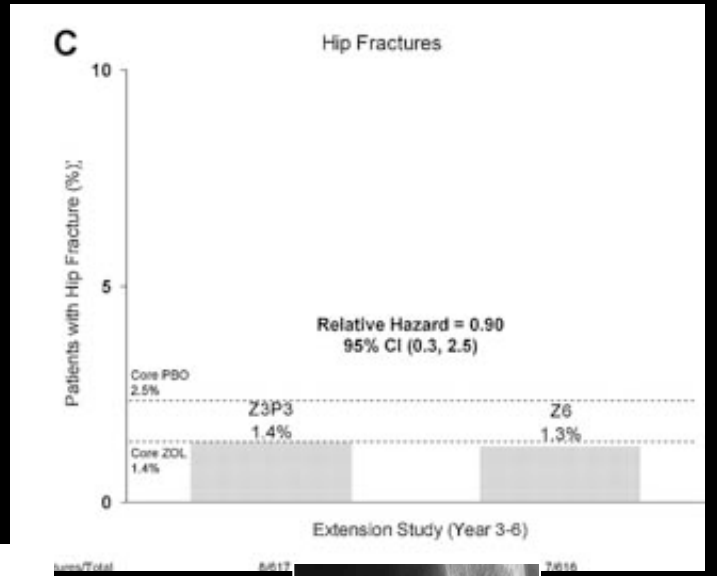
ESPLORATORY ENDPOINT:

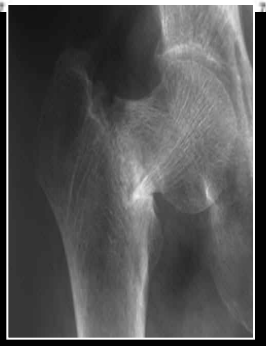
Fractures

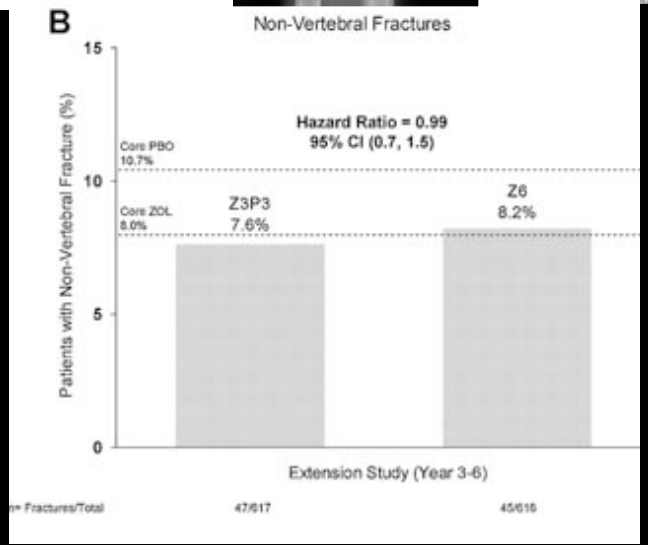












Duration of the studies

Bari,
7-10 novembre 2013

Alendronate 5/10 mg
FIT 1 e 2

Risedronate 2.5/5 mg
VERT

Ibandronate 2.5/20 mg
BONE

Zoledronate 5 mg
HORIZON

Raloxi

Stronti

Teriparatide 2
Fracture Preventior

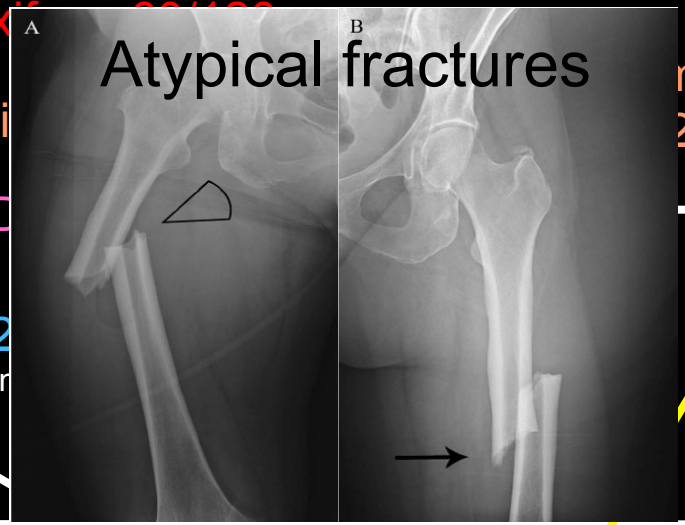
Zoledronate 5 mg
HORIZON

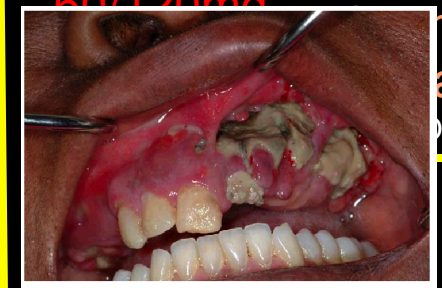
Risedronate
2.5/5 mg
VERT

Raloxifene

Alendronate
5/10 mg
FLEX

ntium
ate 2 g
POS




Osteonecrosis of the jaw

0 1 2 3 4 5 6 7 8 9 10 years

Neer et al. N Engl J Med 2001 Fracture Prevention Trial
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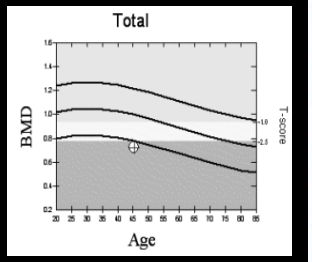
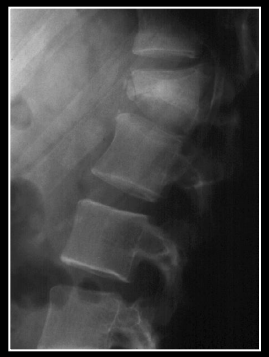
Reginster et al. Arthritis & Rheumatism 2008 TROPOS
Black et al JAMA. 2006 FLEX

Continuing Bisphosphonate Treatment for Osteoporosis - For Whom and for How Long?

Bari,
7-10 novembre 2013

Black D. et al NEJM 366(22):2051-2053, May 31, 2012.





Risk of Clinical Vertebral Fracture and Number Needed to Treat for 5 Years to Prevent One Clinical Vertebral Fracture in the Fracture Intervention Trial Long-Term Extension (FLEX) Study.*

Femoral Neck BMD T Score at Start of Extension†	5-Yr Risk of Clinical Vertebral Fracture		Risk Difference (95% CI)	Number Needed to Treat
	Placebo Group	Alendronate Group‡		
	no./total no. (%)			
All women in study				
All BMD T scores	23/437 (5.5)	16/662 (2.5)	2.9 (0.3–5.4)	34
Less than or equal to –2.5	11/132 (9.3)	9/190 (4.5)	4.8 (0.8–9.2)	21
Greater than –2.5 and less than or equal to –2.0	9/126 (5.8)	3/185 (2.8)	3.0 (0.3–6.7)	33
Greater than –2.0	3/179 (2.3)	4/282 (1.1)	1.2 (0.2–2.8)	81
Women with no prevalent vertebral fracture at start of FLEX study				
Less than or equal to –2.5	6/75 (8.0)	4/109 (3.8)	4.2 (0.6–9.1)	24
Greater than –2.5 and less than or equal to –2.0	3/82 (3.0)	1/121 (1.4)	1.6 (0.2–5.0)	63
Greater than –2.0	2/130 (1.8)	2/203 (0.9)	1.0 (0.1–2.6)	102
Women with prevalent vertebral fracture at start of FLEX study				
Less than or equal to –2.5	5/57 (11.1)	5/81 (5.3)	5.8 (0.8–12.1)	17
Greater than –2.5 and less than or equal to –2.0	6/44 (11.1)	2/64 (5.3)	5.8 (0.8–13.6)	17
Greater than –2.0	1/49 (3.7)	2/79 (1.7)	2.0 (0.3–5.6)	51

* The risks, risk differences, and numbers needed to treat were estimated from proportional-hazards models for the effect of treatment — first unadjusted, then adjusted for bone-mineral-density (BMD) categories, and finally adjusted for BMD categories and baseline prevalent vertebral fracture together. The 5-year risks (percentages) were derived from the proportional-hazards model and account for censoring. Confidence intervals were calculated with the use of the bootstrap method with 1000 replications. CI denotes confidence interval.
† The extension period began after 5 years of initial treatment.
‡ Included are patients who received the drug at a dose of 5 mg per day and those who received the drug at a dose of 10 mg per day.

Bisphosphonates for Osteoporosis - Where Do We Go from Here?

Bari,
7-10 novembre 2013

Whitaker et al. NEJM 366(22):2048-2051, May 31, 2012.

Long-Term Efficacy against Fracture for Three Bisphosphonates in Core Registration and Extension Studies.*

Study Phase	Alendronate (Fosamax)		Risedronate (Actonel)		Zoledronic Acid (Reclast)	
	Yr	Patients with Osteoporotic Fracture	Yr	Patients with Osteoporotic Fracture	Yr	Patients with Osteoporotic Fracture
Core registration study†	0–4	Placebo, 21.0%; alendronate, 10.6%	0–3	Placebo, 32.1%; risedronate, 20.5%	0–3	Placebo, 20.0%; zoledronic acid, 9.8%
Extension study	5–10	Alendronate/alendronate, 17.7%; alendronate/placebo, 16.9%	4–5	Placebo, 32.1%; risedronate/risedronate, 19.3%;	4–6	Zoledronic acid/zoledronic acid, 8.6%; zoledronic acid/placebo, 12.0%
			6–7	Risedronate/ risedronate/ risedronate, 13.3%		

* Osteoporotic fracture was defined as a morphometric vertebral or a clinical vertebral or nonvertebral fracture, excluding fractures of the fingers, toes, hands, feet, and skull; traumatic fractures; or pathologic fractures. Data for the placebo groups in the core registration studies of alendronate and zoledronic acid are estimates. Alendronate data are from FLEX, involving 1099 patients with a maximum enrollment of 10 years. In the extension study, the patients received either continuous alendronate (alendronate/alendronate) or alendronate for 5 years followed by placebo for 5 years (alendronate/placebo). Risedronate data are from VERT-MN, involving 164 patients with a maximum enrollment of 7 years. In the extension study, the patients received either continuous risedronate for 5 or 7 years (risedronate/risedronate or risedronate/risedronate/risedronate) or continuous placebo for 5 years (placebo). Zoledronic acid data are from HORIZON-PFT, involving 1233 patients with a maximum enrollment of 6 years. In the extension study, the patients received either continuous zoledronic acid for 6 years (zoledronic acid/zoledronic acid) or zoledronic acid for 3 years followed by placebo for 3 years (zoledronic acid/placebo).

† For purposes of comparison, proportions of patients with fractures in the core registration study are based on enrollment in the extension studies.

Bisphosphonates for Osteoporosis - Where Do We Go from Here?

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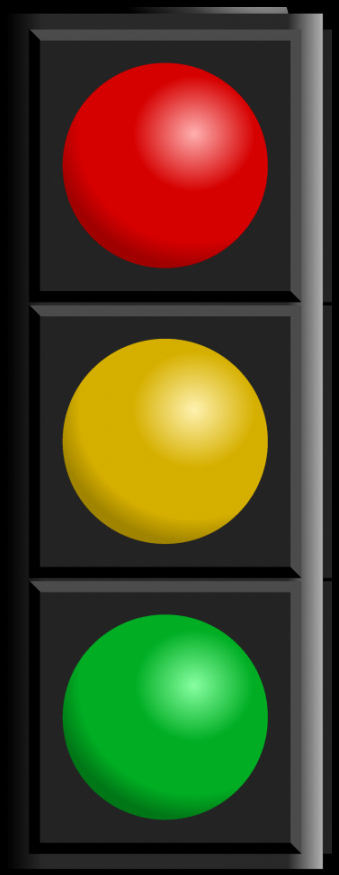
Whitaker et al. NEJM 366(22):2048-2051, May 31, 2012.



…patients at low risk for fracture (e.g., younger patients without a fracture history and with a bone mineral density approaching normal) may prove to be good candidates for discontinuation of bisphosphonate therapy after 3 to 5 years,

whereas patients at increased risk for fracture (e.g., older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy.

Duration of the studies

Bari,
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Neer et al. N Engl J Med 2001 Fracture Prevention Trial

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Cummings et al NEJM 2009 FREEDOM

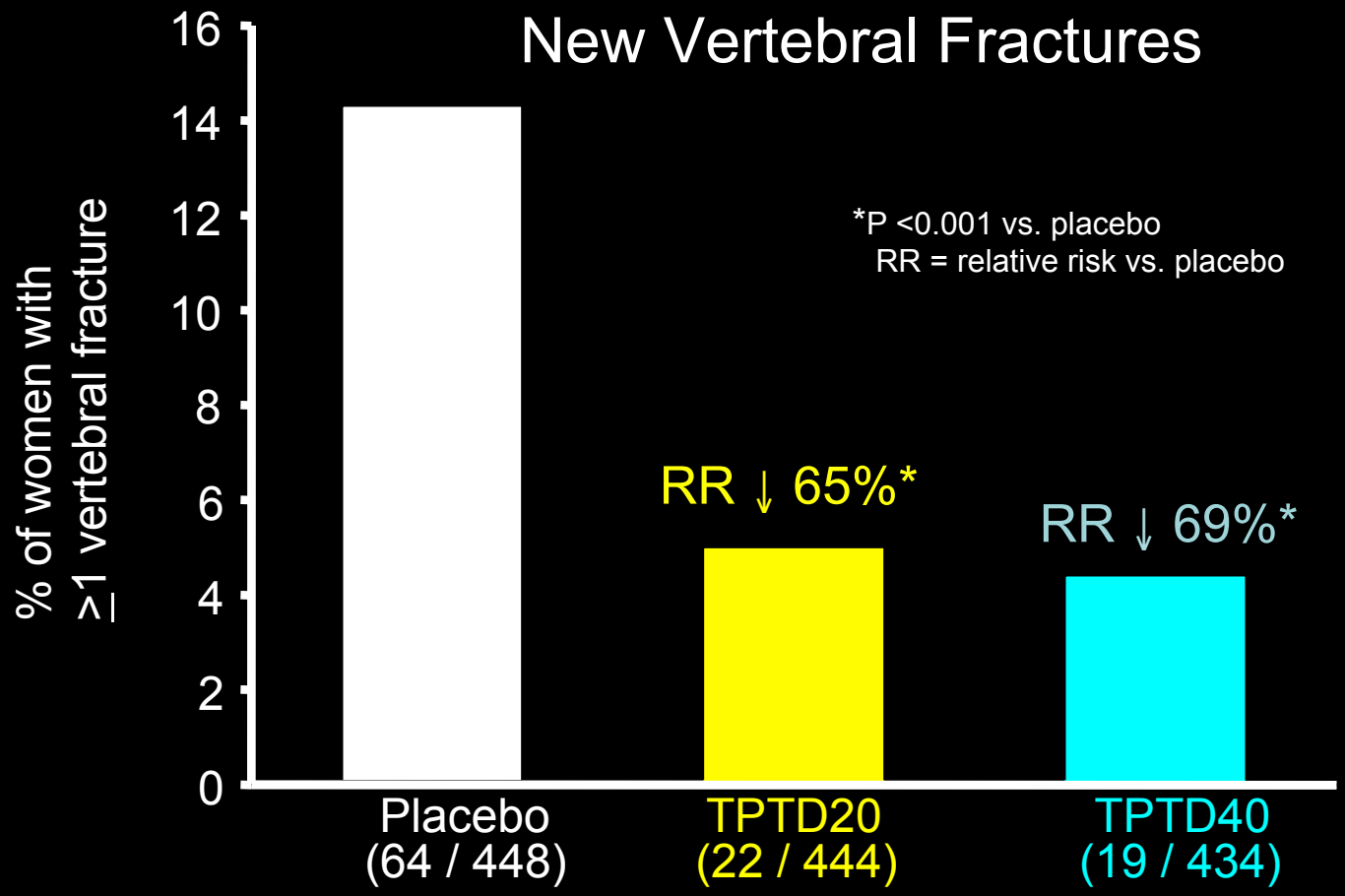
Reginster et al. Arthritis & Rheumatism 2008 TROPOS

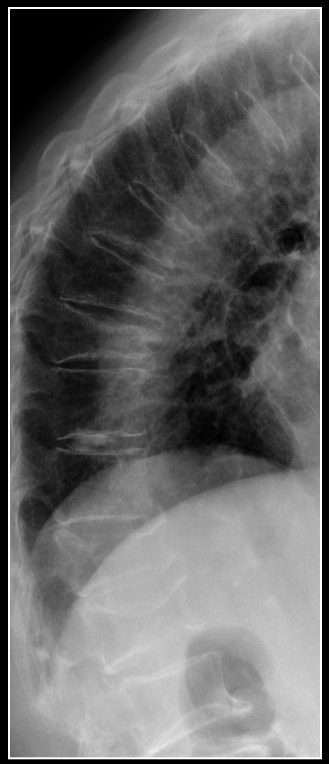
Black et al JAMA. 2006 FLEX

Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.

Bari,
7-10 novembre 2013

Adapted from Neer RM et al NEJM 2001 y 10;344(19):1434-41.

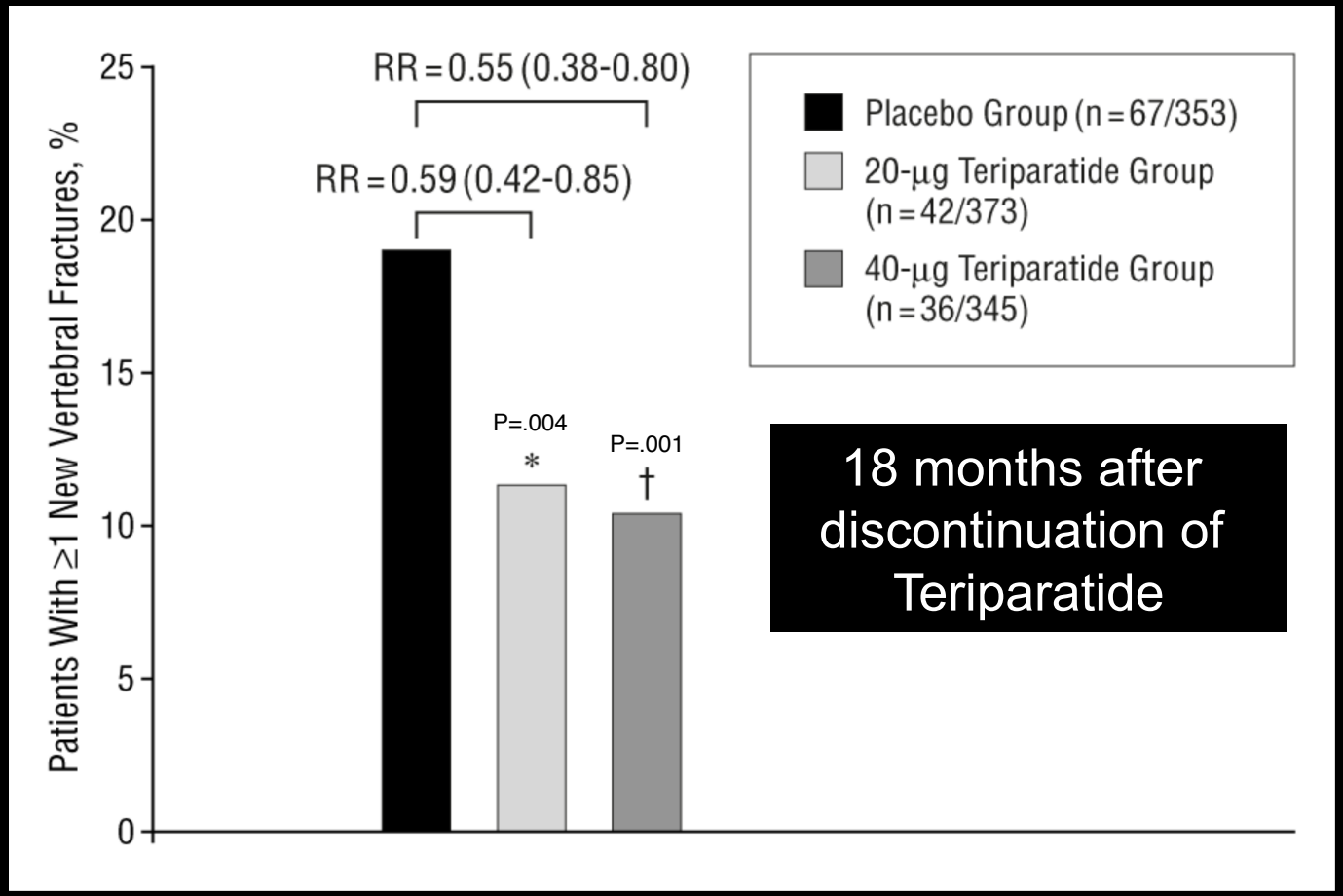


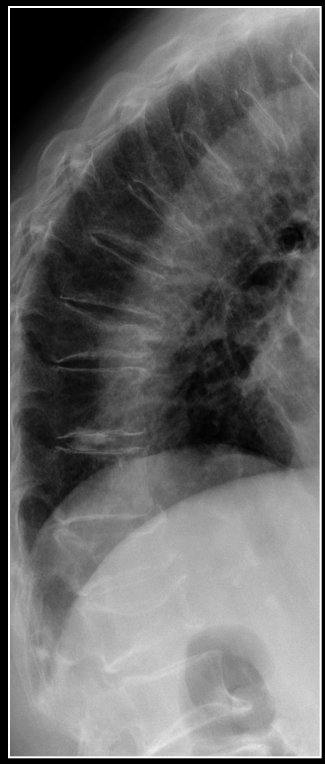


Sustained Vertebral Fracture Risk Reduction After Withdrawal of Teriparatide in Postmenopausal Women With Osteoporosis

Bari,
7-10 novembre 2013

Lindsay et al Arch Intern Med. 2004;164(18):2024-2030. doi:10.1001/archinte.164.18.2024

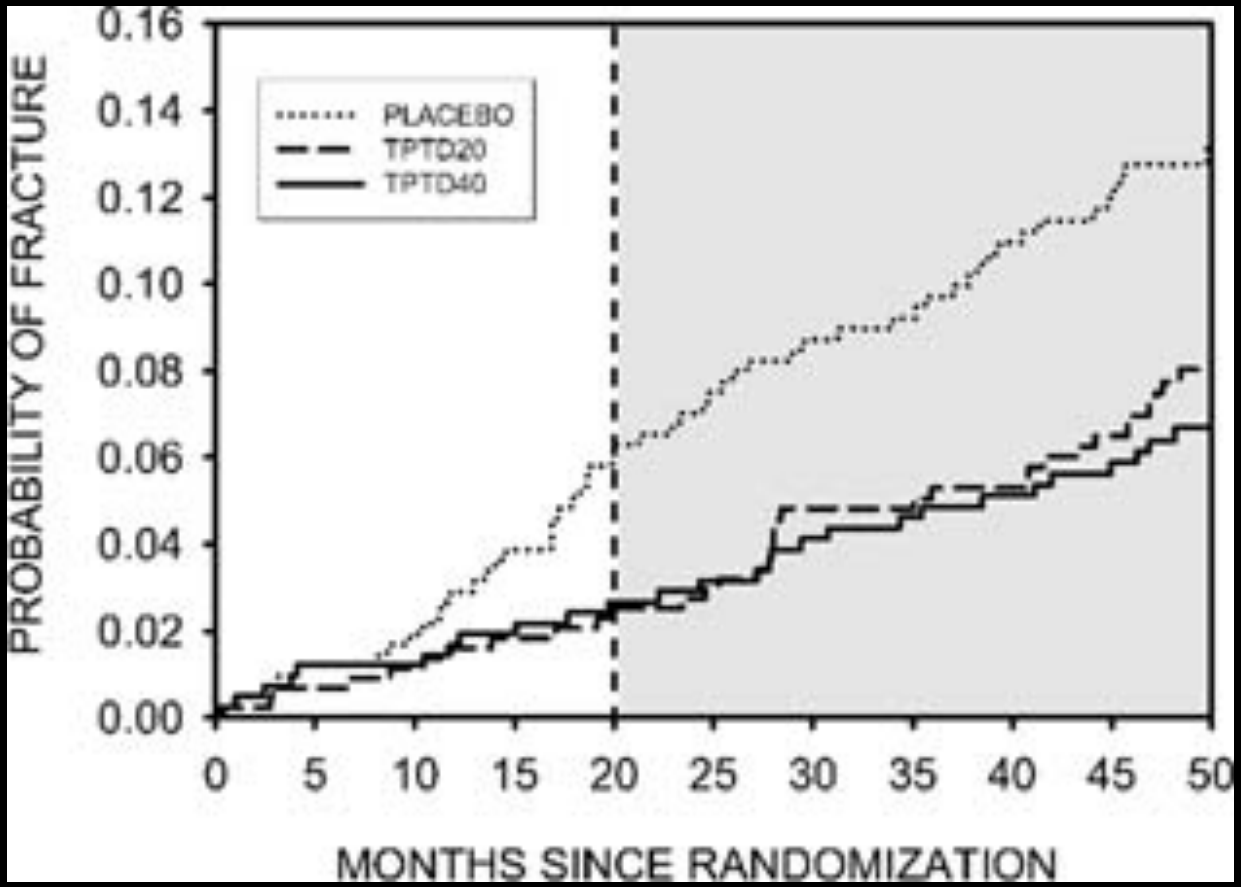


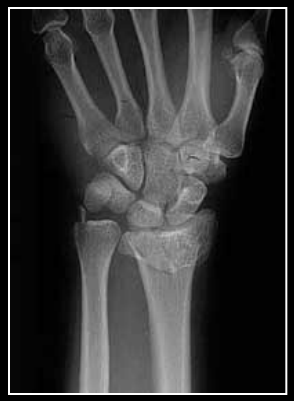


Sustained Nonvertebral Fragility Fracture Risk Reduction After Discontinuation of Teriparatide Treatment

Bari,
7-10 novembre 2013

Prince et al JBMR 2005 20 (9): 1507-1513, DOI: 10.1359/JBMR.050501





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Reginster et al. Arthritis & Rheumatism 2008 TROPOS

Black et al JAMA. 2006 FLEX

Strontium ranelate for preventing and treating postmenopausal osteoporosis

Bari,
7-10 novembre 2013

O'Donnell S et al Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005326

Analysis 1.1. Comparison 1 Fractures, Outcome 1 Verterbral fractures.

Review: Strontium ranelate for preventing and treating postmenopausal osteoporosis

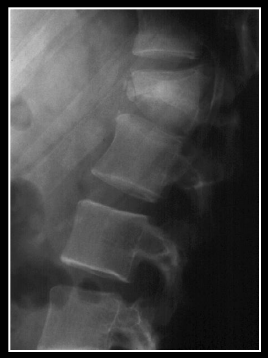
Comparison: 1 Fractures

Outcome: 1 Verterbral fractures

Study or subgroup	Strontium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 2 g/day - 1 Year					
Meunier 2002	22/85	28/87		20.8 %	0.80 [0.50, 1.29]
Meunier 2004-1	44/719	85/723		38.0 %	0.52 [0.37, 0.74]
Reginster 2005	51/1817	93/1823		41.2 %	0.55 [0.39, 0.77]
Subtotal (95% CI)	**2621**	**2633**		**100.0 %**	**0.59 [0.46, 0.74]**
Total events: 117 (Strontium), 206 (Placebo)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.34$, df = 2 (P = 0.31); $I^2 = 14\%$					
Test for overall effect: Z = 4.47 (P < 0.00001)					
2 2 g/day - 3 Years					
Meunier 2004-1	139/719	222/723		43.8 %	0.63 [0.52, 0.76]
Reginster 2005	202/1817	321/1823		56.2 %	0.63 [0.54, 0.74]
Subtotal (95% CI)	**2536**	**2546**		**100.0 %**	**0.63 [0.56, 0.71]**
Total events: 341 (Strontium), 543 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 7.37 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours strontium Favours placebo



THE COCHRANE COLLABORATION®

Strontium ranelate for preventing and treating postmenopausal osteoporosis

Bari,
7-10 novembre 2013

O'Donnell S et al Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005326

Analysis 1.2. Comparison 1 Fractures, Outcome 2 Non-vertebral fractures.

Review: Strontium ranelate for preventing and treating postmenopausal osteoporosis

Comparison: 1 Fractures

Outcome: 2 Non-vertebral fractures

Study or subgroup	Strontium ranelate n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 2 g/day - 3 Years					
Meunier 2004-1	112/826	122/814		32.6 %	0.90 [0.71, 1.15]
Reginster 2005	233/2479	276/2453		67.4 %	0.84 [0.71, 0.99]
Subtotal (95% CI)	**3305**	**3267**		**100.0 %**	**0.86 [0.75, 0.98]**

Total events: 345 (Strontium ranelate), 398 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.29$, df = 1 ($P = 0.59$); $I^2 = 0.0\%$

Test for overall effect: $Z = 2.22$ ($P = 0.026$)

0.1 0.2 0.5 1 2 5 10

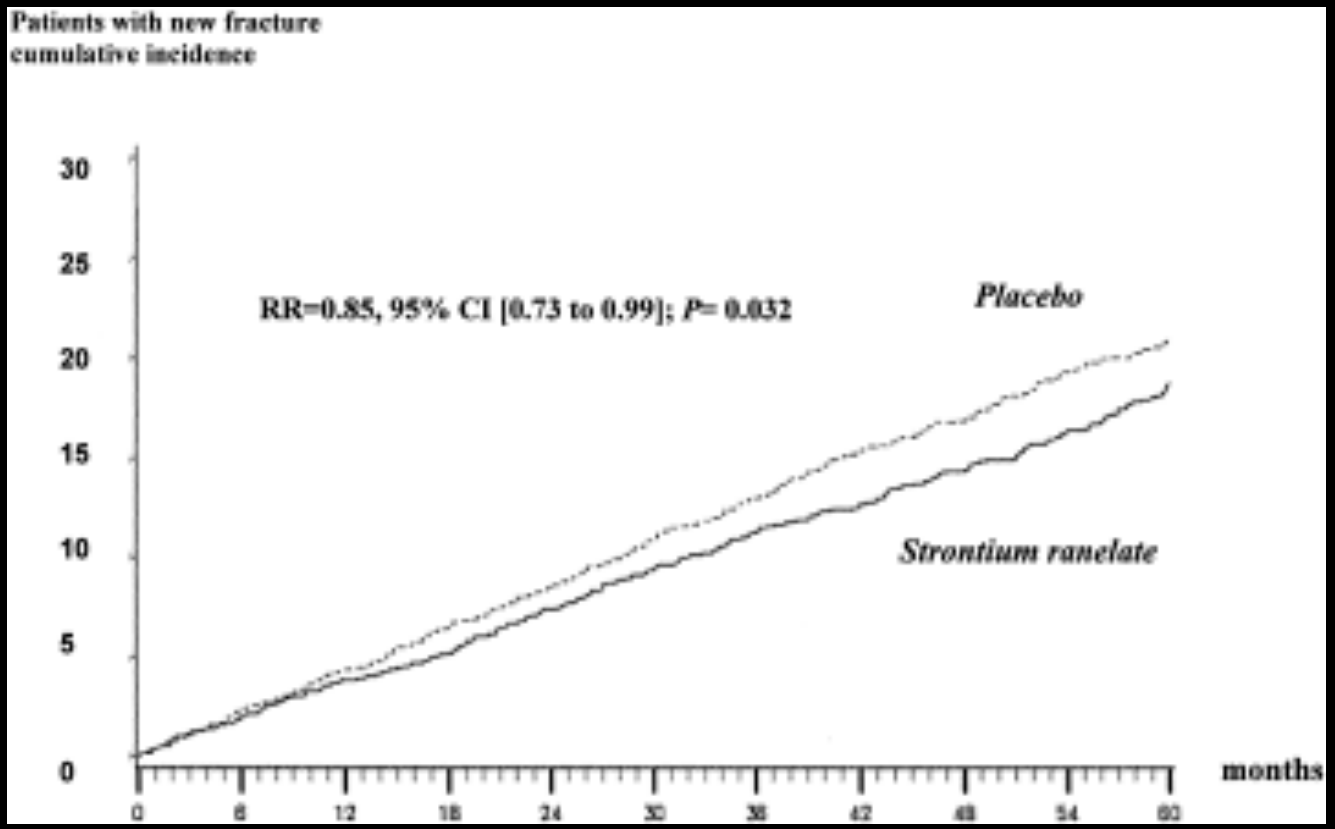
Favours strontium Favours placebo

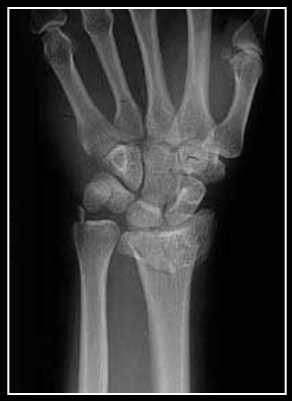
THE COCHRANE COLLABORATION®

Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial

Bari,
7-10 novembre 2013

Reginster JY et al Arthritis & Rheumatism 2008 58 (6) 1687-1695, 31 DOI: 10.1002/art.23461





Strontium ranelate
Side effects

Bari,
7-10 novembre 2013

SOTI & TROPOS

Symptoms *(N° patients)*	Strontium ranelate N=3352	placebo N=3317	
Nausea	+17	+9	NS
Diarrhea	+15	+13	NS
Headache	+11	+10	NS
Dermatitis	+7	+11	NS
Eczema	+9	+7	NS
Venous thromboembolism	+13	+12	NS

Strontium ranelate

Bari,
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2013
EMA/258269/2013

Recommendation to restrict the use of Protelos/Osseor (strontium ranelate)

CHMP confirms recommendation from the PRAC

Healthcare professionals in the EU Member States will receive a letter informing them of the updated recommendations on the use of Protelos/Osseor. The letter will advise them of the following:

- Protelos/Osseor should only be used for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture and severe osteoporosis in men at increased risk of fracture.
- Protelos/Osseor is contraindicated in patients with a current or past history of ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease, or in patients with uncontrolled hypertension.
- Treatment with Protelos/Osseor should only be started by a physician experienced in the treatment of osteoporosis.
- The physician should base their decision to prescribe Protelos/Osseor on an assessment of the individual patient's risks. The patient's risk of developing cardiovascular disease should be evaluated before and at regular intervals during treatment
- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease or cerebrovascular disease or if hypertension becomes uncontrolled.

Strontium ranelate

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Agenzia Italiana del Farmaco
AIFA

PIANO TERAPEUTICO AIFA
PER LA PRESCRIZIONE DI RANELATO DI STRONZIO
(da rinnovare ogni 6 mesi)

Centro prescrittore _____

Nome e cognome del Clinico prescrittore _____

Recapito telefonico _____

Paziente (nome, cognome) _____ Età _____
Sesso M ☐ F ☐ Peso (kg) _____ Altezza (cm) _____
Codice fiscale (CF) _____
Indirizzo_____ _____Tel._____
ASL di residenza _____Medico curante (MMG)_____

Il ranelato di stronzio è indicato nelle donne postmenopausali o nei maschi con osteoporosi severa a elevato rischio di frattura. Può essere prescritto solo da centri specializzati esperti di osteoporosi, Universitari o delle Aziende Sanitarie, individuati dalle Regioni e dalle Province autonome di Trento e Bolzano, per una delle seguenti condizioni:

- ☐ soggetti con pregresse fratture osteoporotiche vertebrali o di femore;
- ☐ soggetti di età superiore a 50 anni con valori di T-score della BMD femorale o ultrasonografica del calcagno < - 4 (o < -5 per ultrasuoni falangi);
- ☐ soggetti di età superiore a 50 anni con valori di T-score della BMD femorale o ultrasonografica del calcagno < -3 (o < - 4 per ultrasuoni falangi) e con almeno uno dei seguenti fattori di rischio aggiuntivi:
  - Storia familiare di fratture vertebrali e/o di femore;
  - Artrite reumatoide e altre connettiviti;
  - Pregressa frattura osteoporotica al polso;
  - Menopausa prima 45 anni di età;
  - Terapia cortisonica cronica.

Duration of the studies

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7-10 novembre 2013

Neer et al. N Engl J Med 2001 Fracture Prevention Trial

Black et al. Lancet 1996 FIT1

Cummings et al JAMA 1998 FIT2

Harris et al JAMA 1999 VERT

Chesnut CH, et al. J BMR 2004 BONE

Black et al. N EJ M 2007 HORIZON

Delmas et al. JCEM 2002 MORE

Meunier et al. NEJM 2004 SOTI

Cummings et al NEJM 2009 FREEDOM

Reginster et al. Arthritis & Rheumatism 2008 TROPOS

Black et al JAMA. 2006 FLEX

Yearly Incidence of New Vertebral Fractures Through 6 Years

The Pivotal Phase 3 Study – Extension

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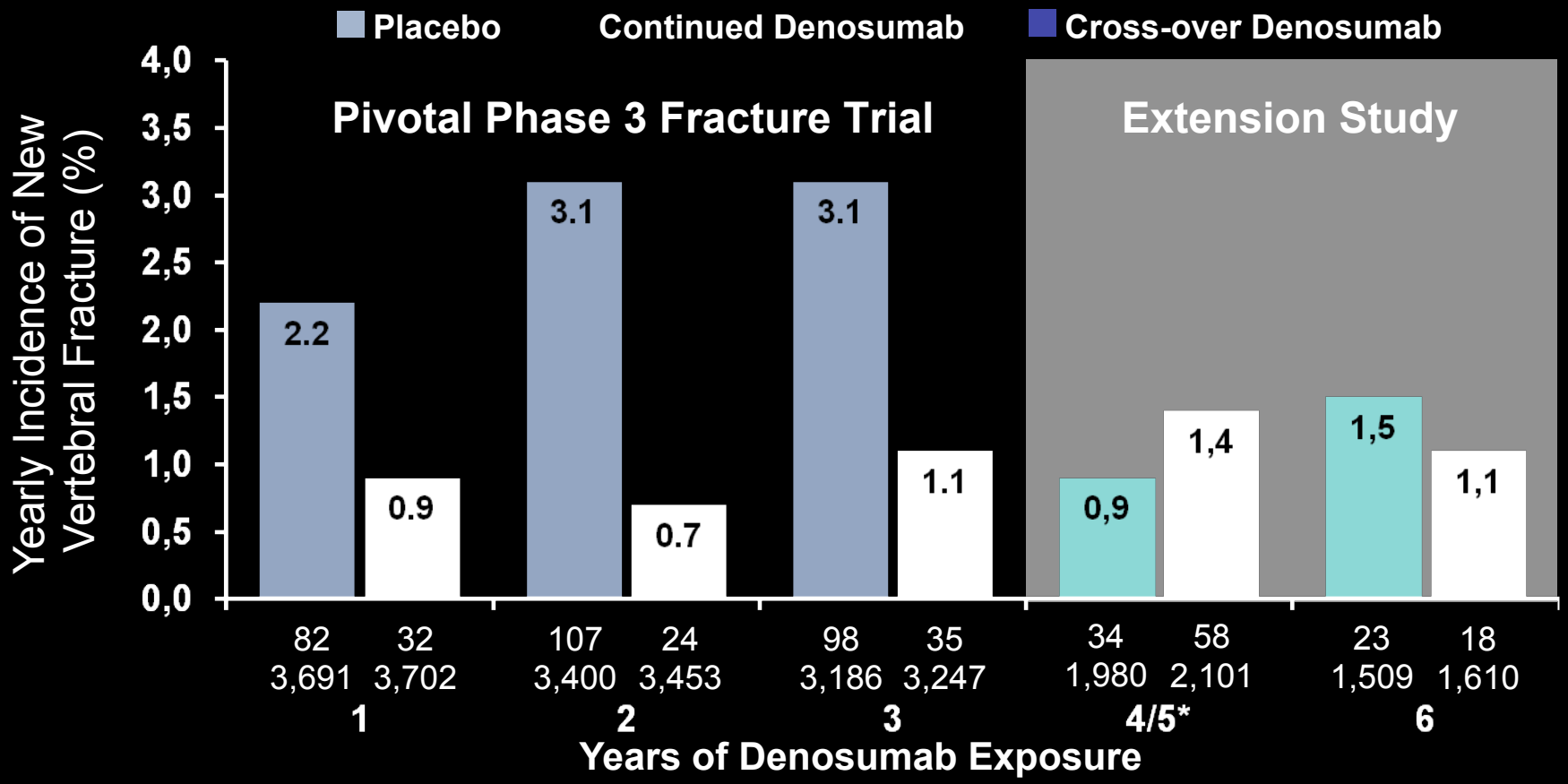
7-10 novembre 2013

Adapted from **Bone H G et al. JCEM 2013;98:4483-4492**



n = number of patients with ≥1 fracture. N = number of randomized patients who remained on study at the beginning of each period and had available spine x-rays during the period of interest. *Annualized rate: (2-year rate)/2. Lateral radiographs (lumbar and thoracic) were not obtained at year 4 (year 1 of the Extension).

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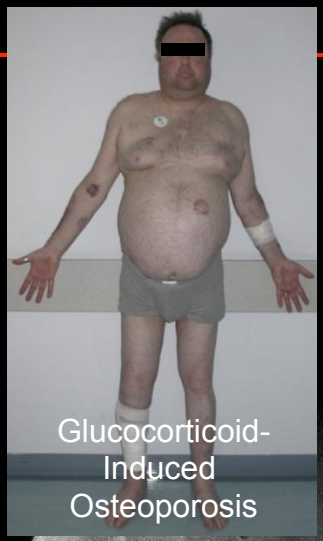
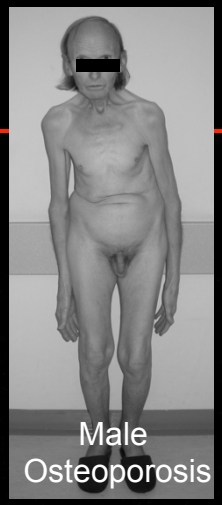


Glucocorticoid-Induced Osteoporosis



Male Osteoporosis

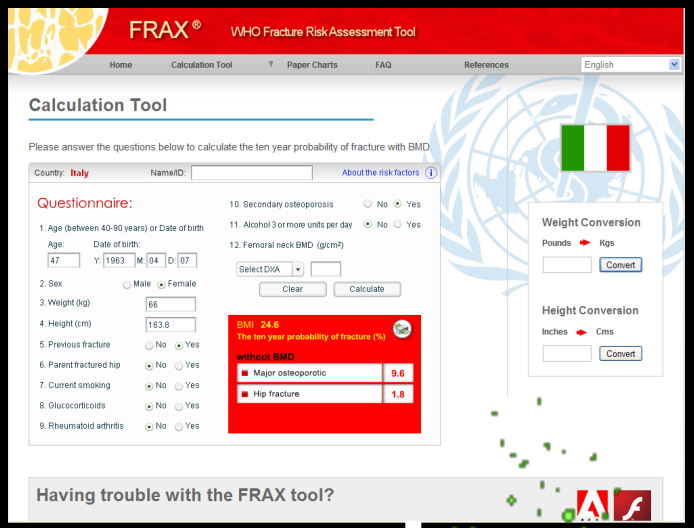
Osteogenesis Imperfecta

Post-menopausal Osteoporosis

Osteoporosis in young adult

CONCLUSIONS

Bari,
7-10 novembre 2013



Low risk patient

Discontinue treatment

High risk patient

Continue treatment

Treatment failure

Change treatment

Treatment

Treatment

0 1 2 3 4 5 6 7 8 9 10 years

ADVICE

Bari,
7-10 novembre 2013

Tribute the due time to the patients:

more the clinical approach accuracy, better treatment accuracy

Bari,
7-10 novembre 2013

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e Cattedra di
ENDOCRINOLOGIA
Modena

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