12° Congresso Nazionale AME
Associazione Medici Endocrinologi

Bari,
7-10 novembre 2013

La terapia con bisfosfonati nell'osteoporosi

Opzioni terapeutiche

Dr. Edda Vignali
UO Endocrinologia 2

Azienda Ospedaliero-Universitaria Pisana

Terapia medica dell'osteoporosi

Bari,
7-10 novembre 2013

FARMACI ANTI-CATABOLICI

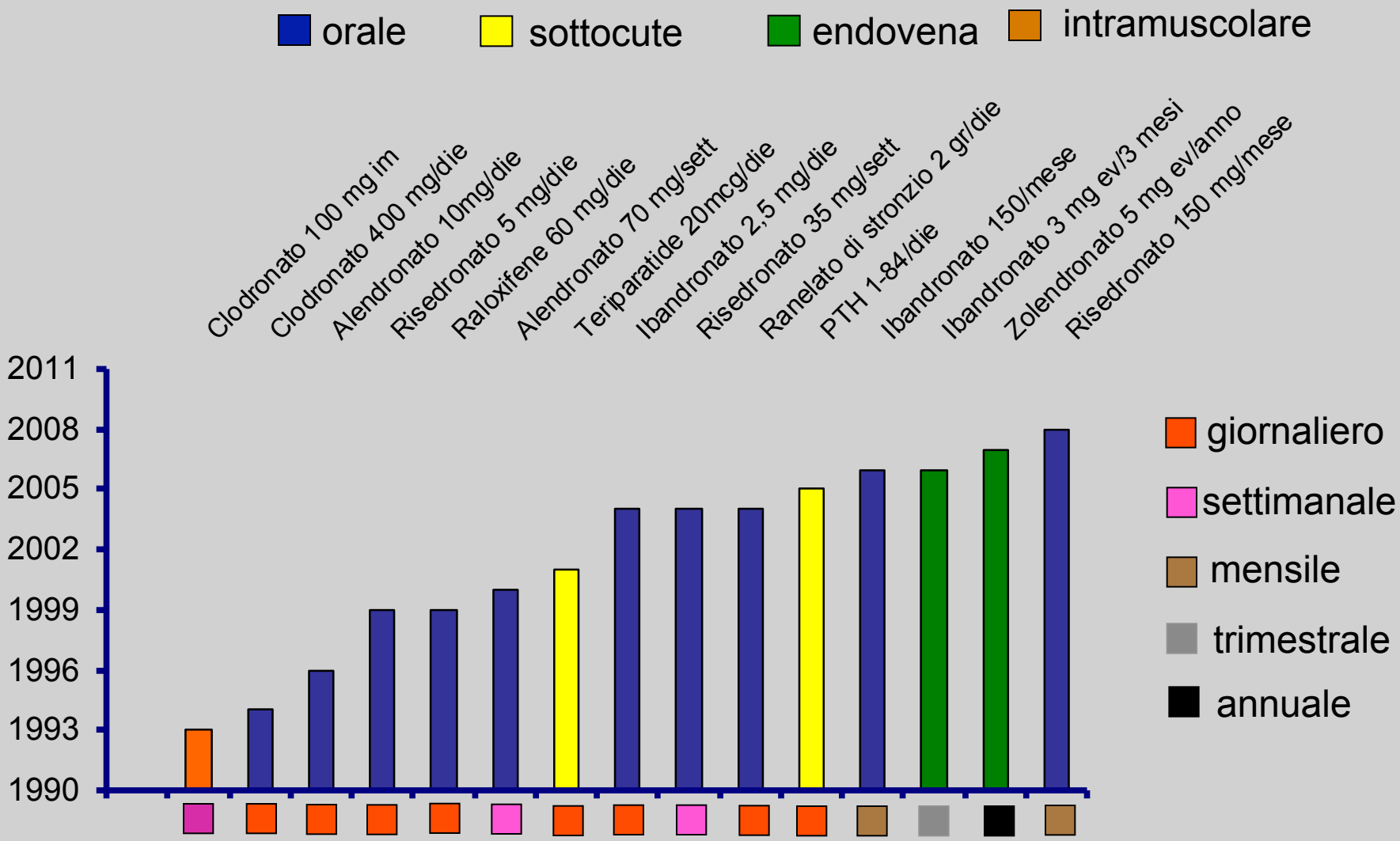
- BISFOSFONATI
- TP. ORMONALE SOSTITUTIVA
- SERM (RALOXIFENE, BAZEDOXIFENE)
- RANELATO DI STRONZIO
- DENOSUMAB
- INIBITORI DELLA CATEPSINA

FARMACI ANABOLICI

- PTH (1-84)
- PTH (1-34) TERIPARATIDE
- Anti-sclerostina e anti DKK1

Storia della terapia per l'osteoporosi

Bari,
7-10 novembre 2013



Clodronate Reduces Vertebral Fracture Risk in Women With Postmenopausal or Secondary Osteoporosis: Results of a Double-Blind, Placebo-Controlled 3-Year Study

Eugene McCloskey, Peter Selby, Mike Davies, John Robinson, Roger M Francis, Judith Adams, Karthik Kayan, Monique Beneton, Tarja Jalava, Liisa Pylkkänen, Juha Kenraali, Sakari Aropuu, and John A Kanis

483 donne in post-menopausa con Op e/o almeno un frattura vertebrale (stratum 1)

2 gruppi: clodronato 800 mg per os o placebo

Durata dello studio 3 anni

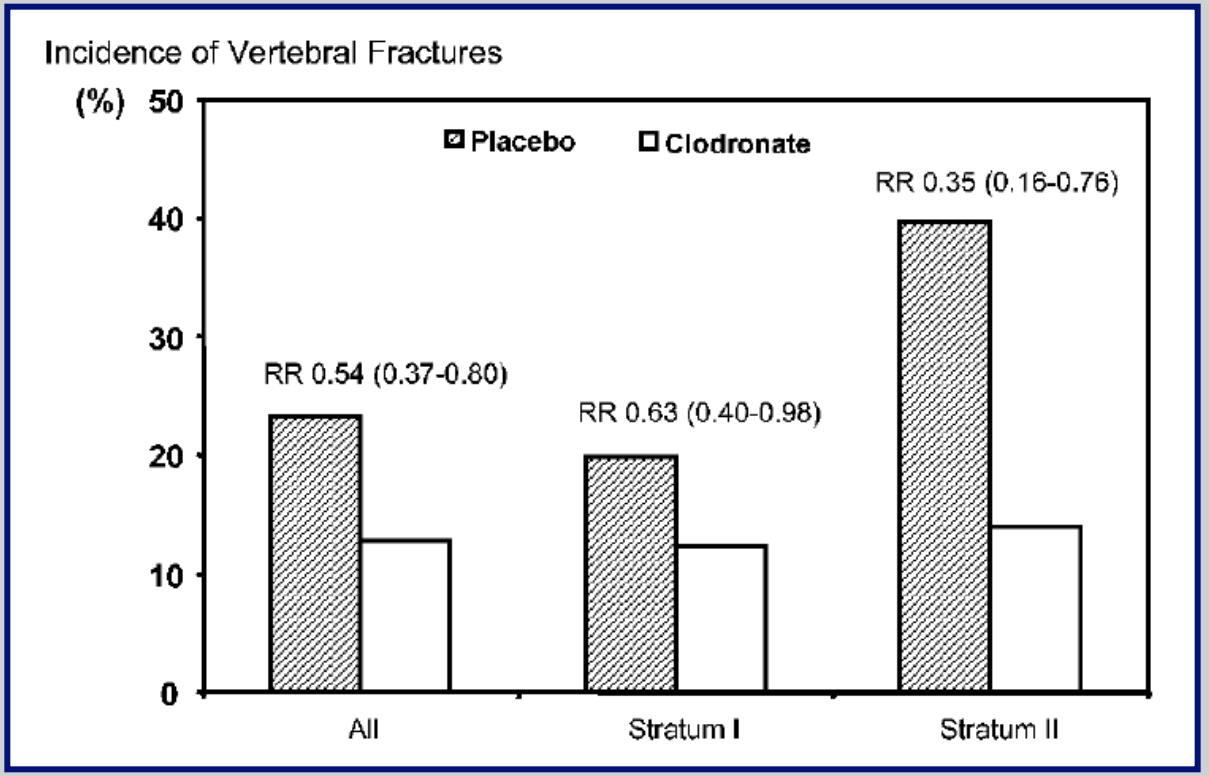


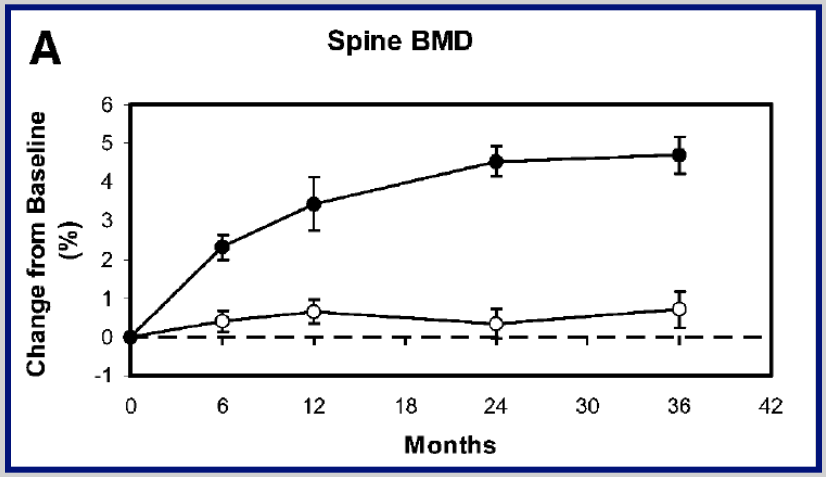
FIG. 2. Incidence of vertebral fractures over 3 years in osteoporotic women. Clodronate 800 mg daily significantly reduced the incidence in all women, with similar effects in women with uncomplicated post-menopausal osteoporosis and with secondary osteoporosis.

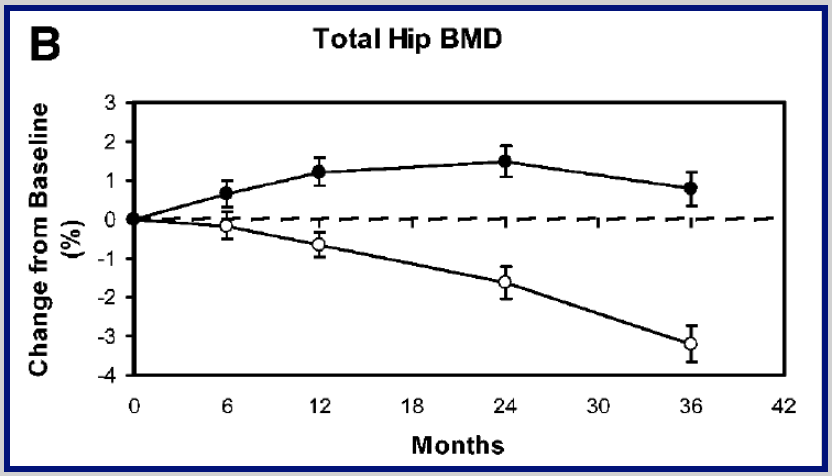
J Bone Miner Res 2004;19:728–736.

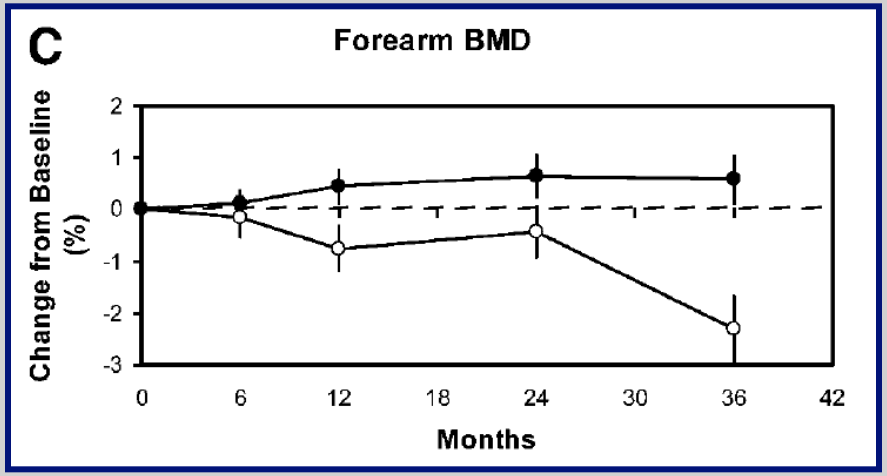
Bari,
7-10 novembre 2013

Clodronate Reduces Vertebral Fracture Risk in Women With Postmenopausal or Secondary Osteoporosis: Results of a Double-Blind, Placebo-Controlled 3-Year Study

Eugene McCloskey, Peter Selby, Mike Davies, John Robinson, Roger M Francis, Judith Adams, Karthik Kayan, Monique Beneton, Tarja Jalava, Liisa Pylkkänen, Juha Kenraali, Sakari Aropuu, and John A Kanis







J Bone Miner Res 2004;19:728–736.

Bari,
7-10 novembre 2013

Clodronate Reduces the Incidence of Fractures in Community-Dwelling Elderly Women Unselected for Osteoporosis: Results of a Double-Blind, Placebo-Controlled Randomized Study

Eugene V McCloskey,[1] Monique Beneton,[2] Diane Charlesworth,[1] Karthik Kayan,[1] Dominic deTakats,[1] Abhijit Dey,[1] Jane Orgee,[1] Robert Ashford,[1] Martin Forster,[1] Jennifer Cliffe,[1] Linda Kersh,[1] John Brazier,[3] Jon Nichol,[3] Sakari Aropuu,[4] Tarja Jalava,[4] and John A Kanis[2]

5592 donne di età≥75 anni

2 gruppi: clodronato 800 mg per os o placebo

Durata dello studio 3 anni

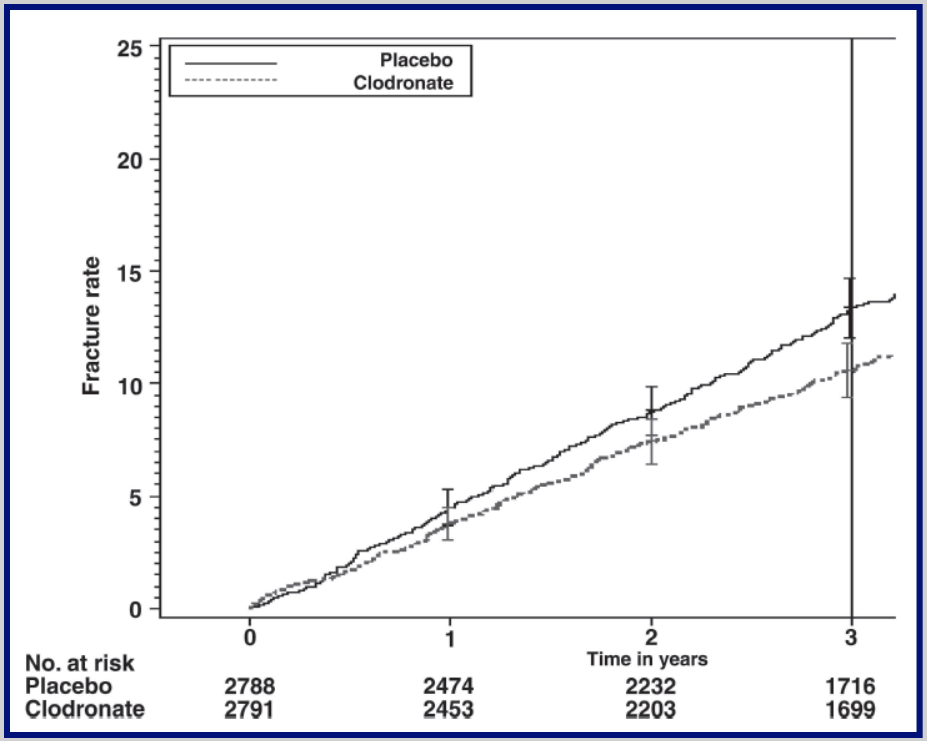


FIG. 3. Kaplan-Meier plot of incident clinical fractures over entire study duration.

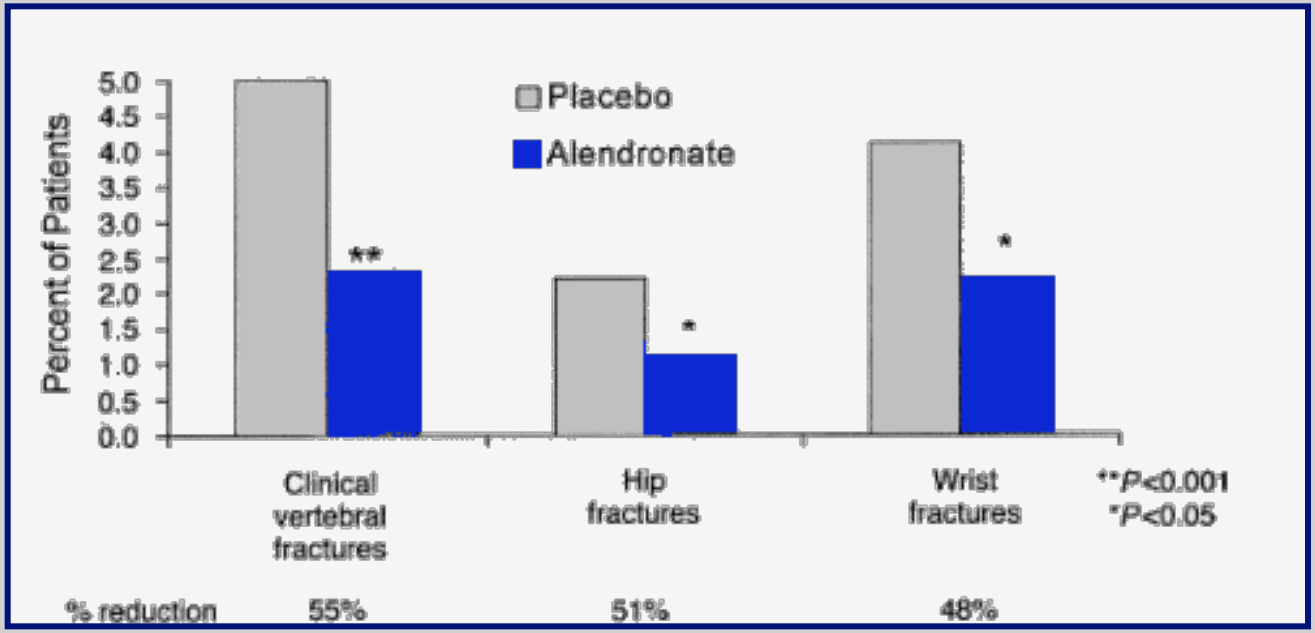
% riduzione: Fx cliniche 20 %, Fx di femore 29%

J Bone Miner Res 2007;21:135–141.

ALENDRONATO

Bari,
7-10 novembre 2013

Studio **FIT**



donne in post-menopausa di età tra 55 e 81 anni con Op con o senza una frattura vertebrale

2 gruppi: alendronato per os o placebo

Valutazione: Rx colonna, marcatori ossei, DXA

Durata dello studio 3 anni

EFFECTS OF RISEDRONATE TREATMENT ON VERTEBRAL AND NON VERTEBRAL FRACTIRE IN WOMEN WITH POSTMENOPAUSAL OSTEOPOROSIS

Bari,
7-10 novembre 2013

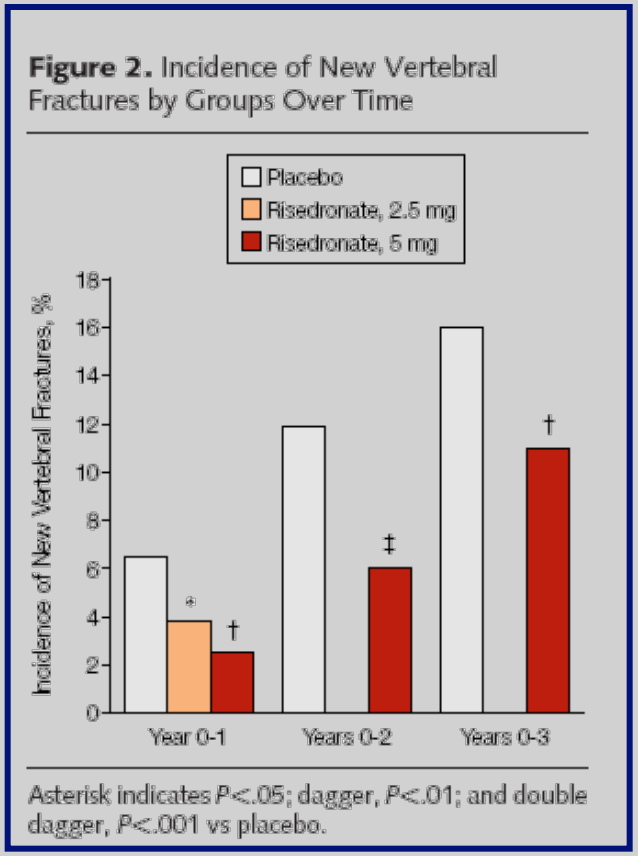
Studio VERT

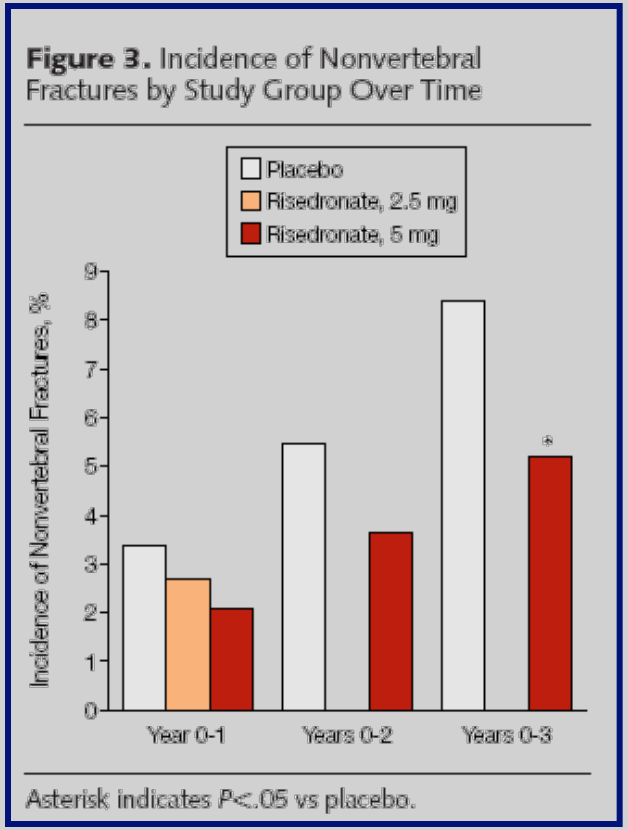
2458 donne in post-menopausa di età < 85 anni con almeno una frattura vertebrale

3 gruppi: risedronato 2.5 mg, risedronato 5 mg e placebo

Valutazione: Rx colonna, marcatori ossei, DXA

Durata dello studio 3 anni





% riduzione: Fx vertebrali 41%, Fx non vertebrali 39%

Modificato da: Harris ST *et al.* **JAMA** 1999

Effects of Oral Ibandronate Administered Daily or Intermittently on Fracture Risk in Postmenopausal Osteoporosis

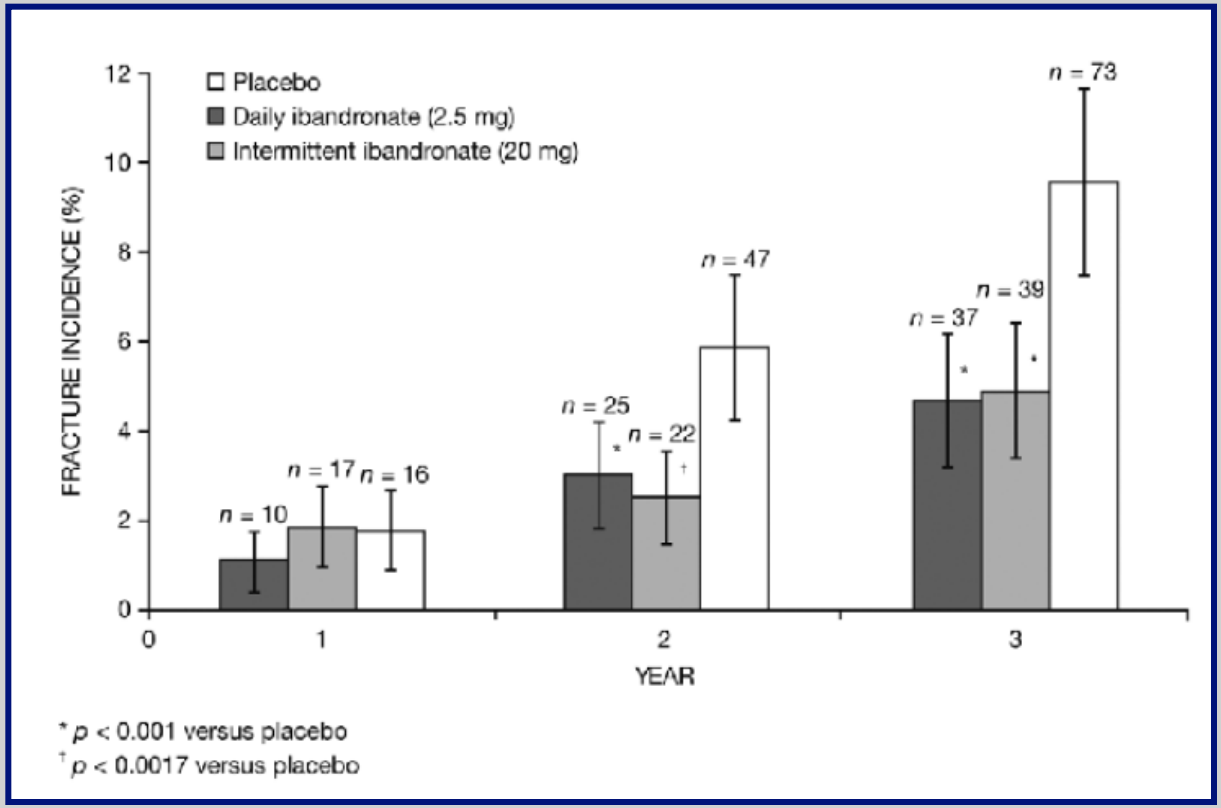
Charles H Chesnut III, et al

Studio BONE

2.946 donne in post-menopausa

3 gruppi: ibandronato 2.5 al giorno, ibandronato 20 mg ogni giorno per 12 dosi ogni 3 mesi, placebo

Durata dello studio 3 anni



% riduzione: Fx vertebrali 62 %

J Bone Miner Res 2004;19:1241–1249.

Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

Bari,
7-10 novembre 2013

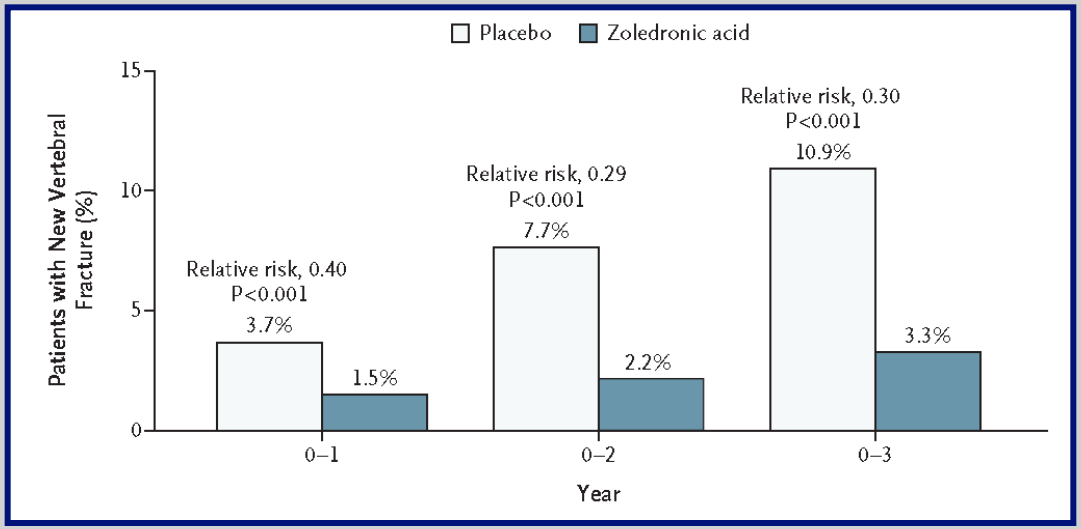
Dennis M. Black, et al

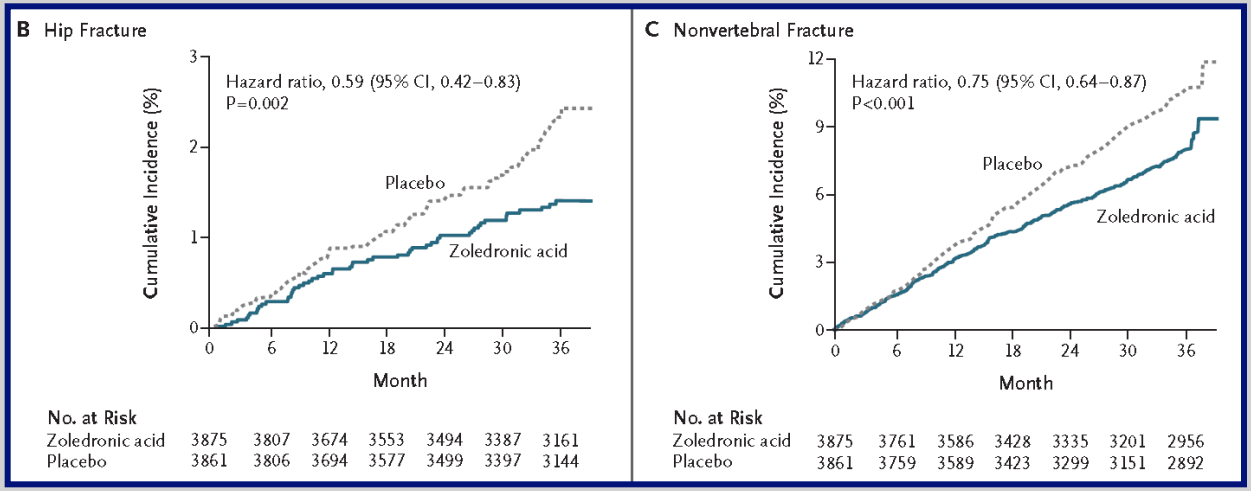
donne in post-menopausa di età tra 65 e 89 anni con Op con o senza una frattura vertebrale o con T-score femore <-1.5 e una frattura vertebrale moderata

2 gruppi: zolendronato iv o placebo

Valutazione: Rx colonna, marcatori ossei, DXA

Durata dello studio 3 anni





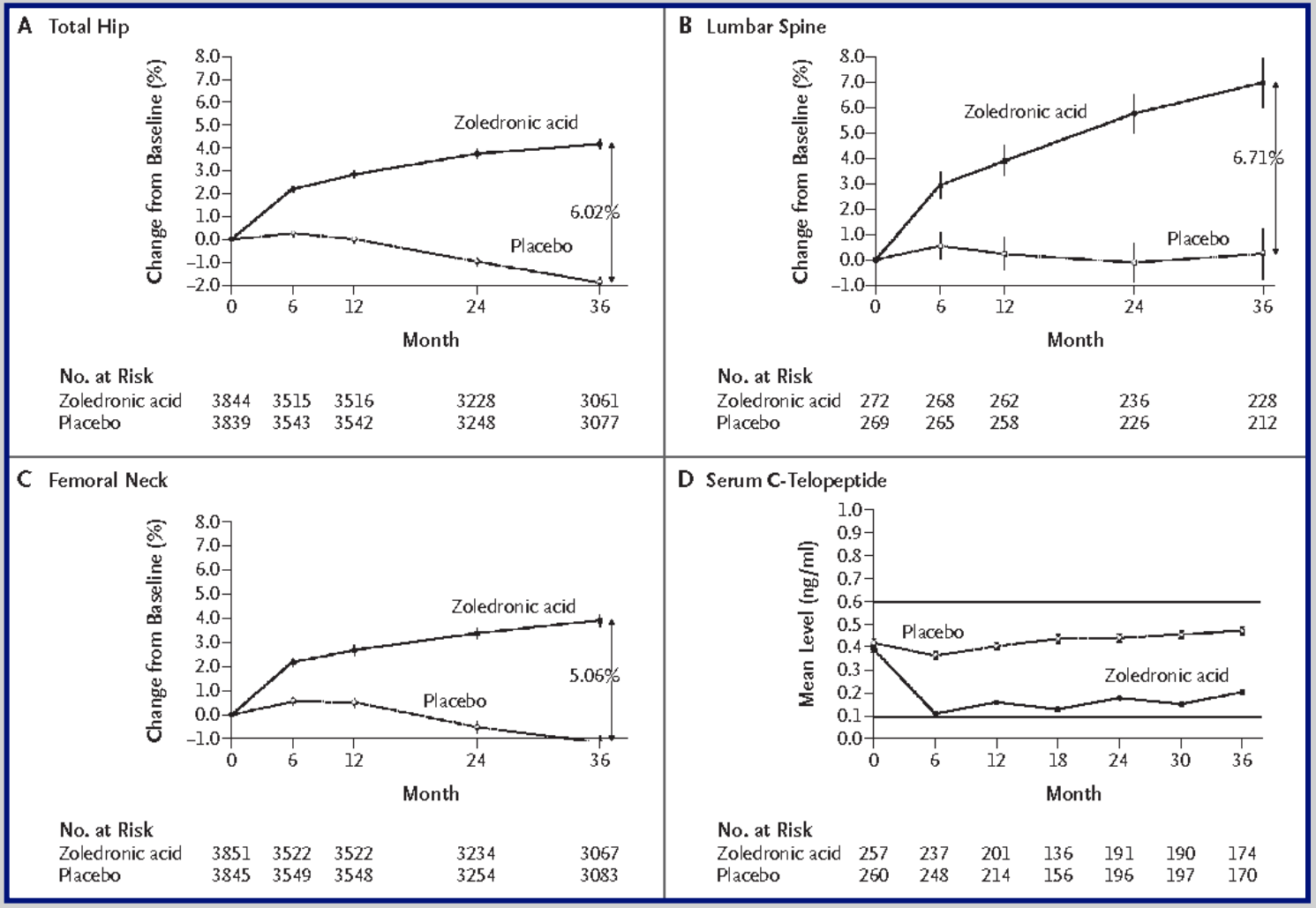
% riduzione: Fx vertebrali 70 %, Fx di femore 41%

N Engl J Med 2007;356:1809-22.

Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

Bari,
7-10 novembre 2013

Dennis M. Black, et al



N Engl J Med 2007;356:1809-22.

Bari,
7-10 novembre 2013

BISFOSFONATI REGISTRATI CON INDICAZIONE PER L'OSTEOPOROSI

Principio attivo	Dosaggio	Posologia
Ac. alendronico	10 mg 70 mg	1 cp/die 1 cp/settimana
Ac. alendronico + Vitamina D	70 mg	1 cp/settimana
Ac. risedronico	5 mg 35 mg 75 mg	1 cp/die 1 cp/settimana 2 cp/mese
Ac. ibandronico	150 mg 3 mg	1 cp/mese 1 f. e.v./3 mesi
Ac. zoledronico	5 mg	1 f. e.v./anno
Ac. clodronico	100 mg 200 mg 400 mg	1 f. i.m./7-14 giorni 1 f. i.m./3-4 settimane 1 cp/die

EFFICACIA ANTIFRATTURATIVA DEI FARMACI ANTIOSTEOPOROTICI

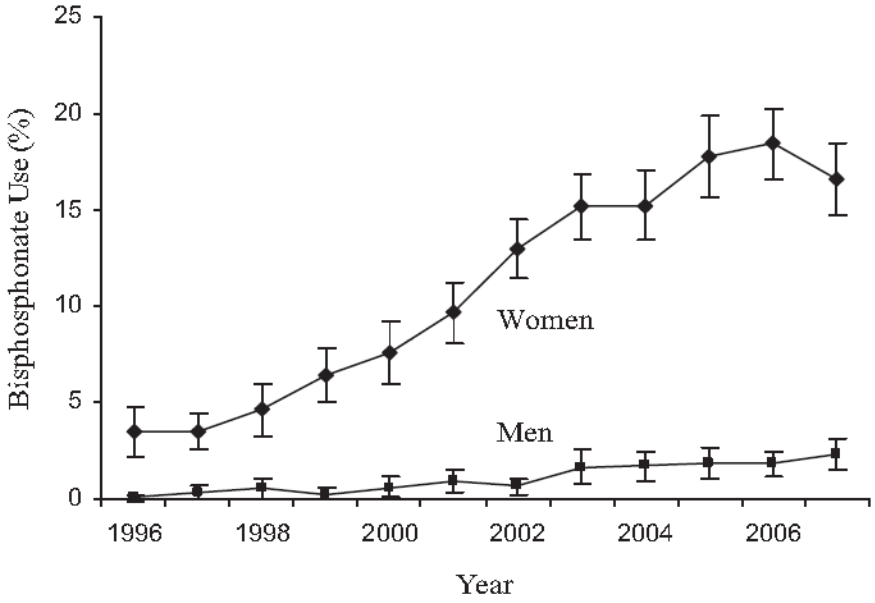
Bari,
7-10 novembre 2013

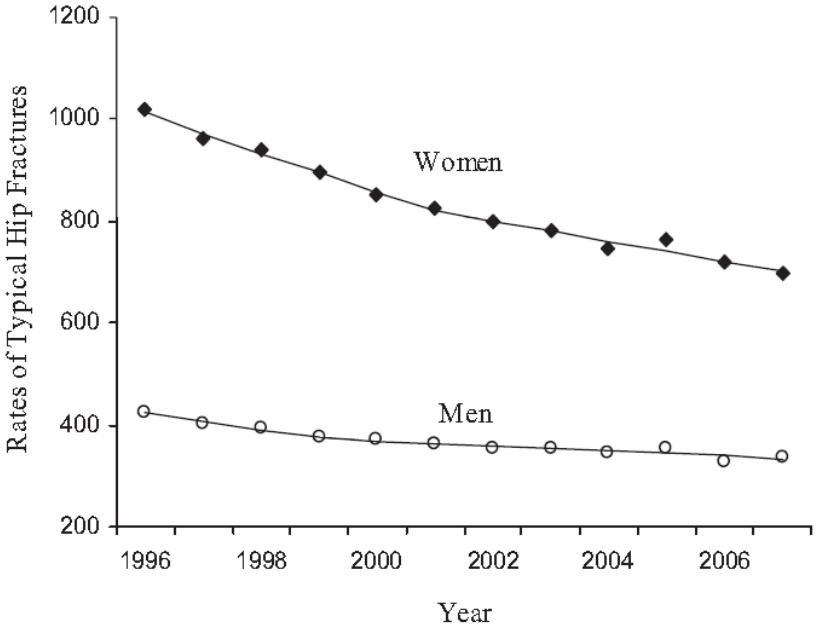
	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	Osteoporosis	Established osteoporosis[a]	Osteoporosis	Established osteoporosis[a]
Alendronate	+	+	NA	+ (Including hip)
Risedronate	+	+	NA	+ (Including hip)
Ibandronate	NA	+	NA	+[b]
Zoledronic acid	+	+	NA	+[c]
HRT	+	+	+	+ (Including hip)
Raloxifene	+	+	NA	NA
Teriparatide and PTH	NA	+	NA	+[d]
Strontium ranelate	+	+	+ (Including hip[b])	+ (Including hip[b])
Denosumab	+	+[c]	+ (Including hip)	+[c]
Clodronate	+	+		

FRATTURE DI FEMORE E BISFOSFONATI

Bari,
7-10 novembre 2013

Zhong Wang and Timothy Bhattacharyya





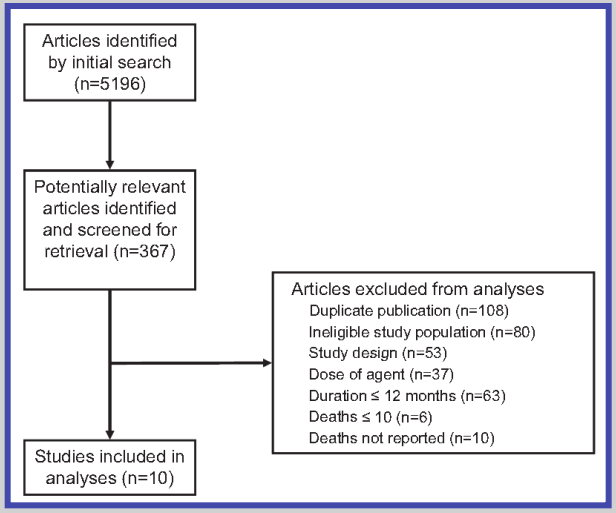
Riduzione fratture tipiche di femore:
Donne 31.7%
Uomini 20.4%

Journal of Bone and Mineral Research, Vol. 26, No. 3, March 2011

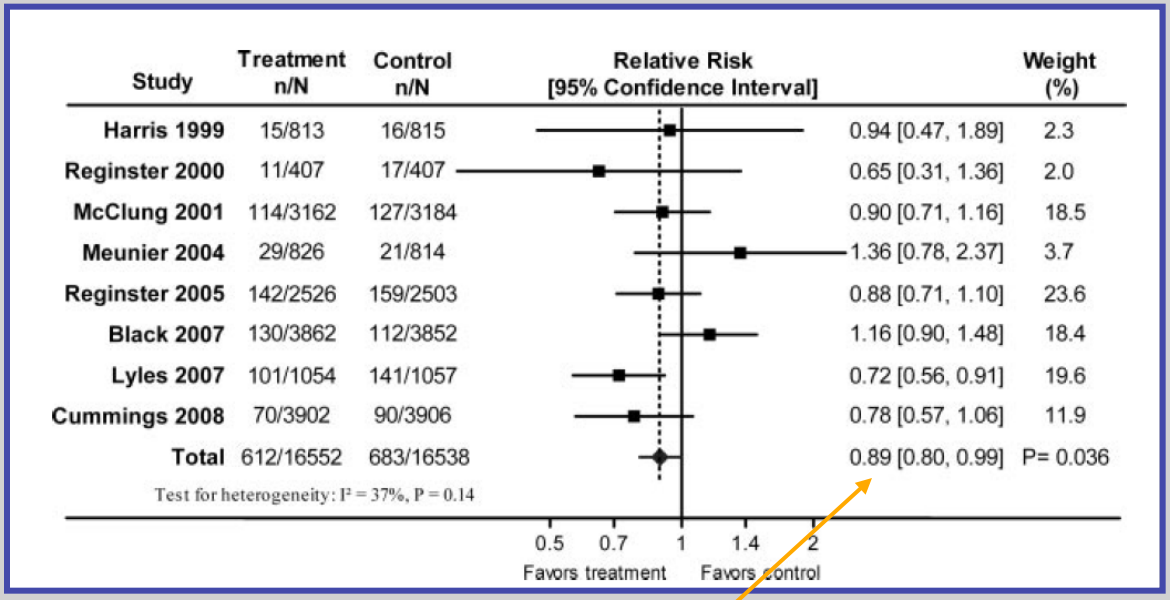
Effect of Osteoporosis Treatment on Mortality: A Meta-Analysis

Mark J. Bolland, Andrew B. Grey, Greg D. Gamble, and Ian R. Reid

Bari,
7-10 novembre 2013



Study flow diagram

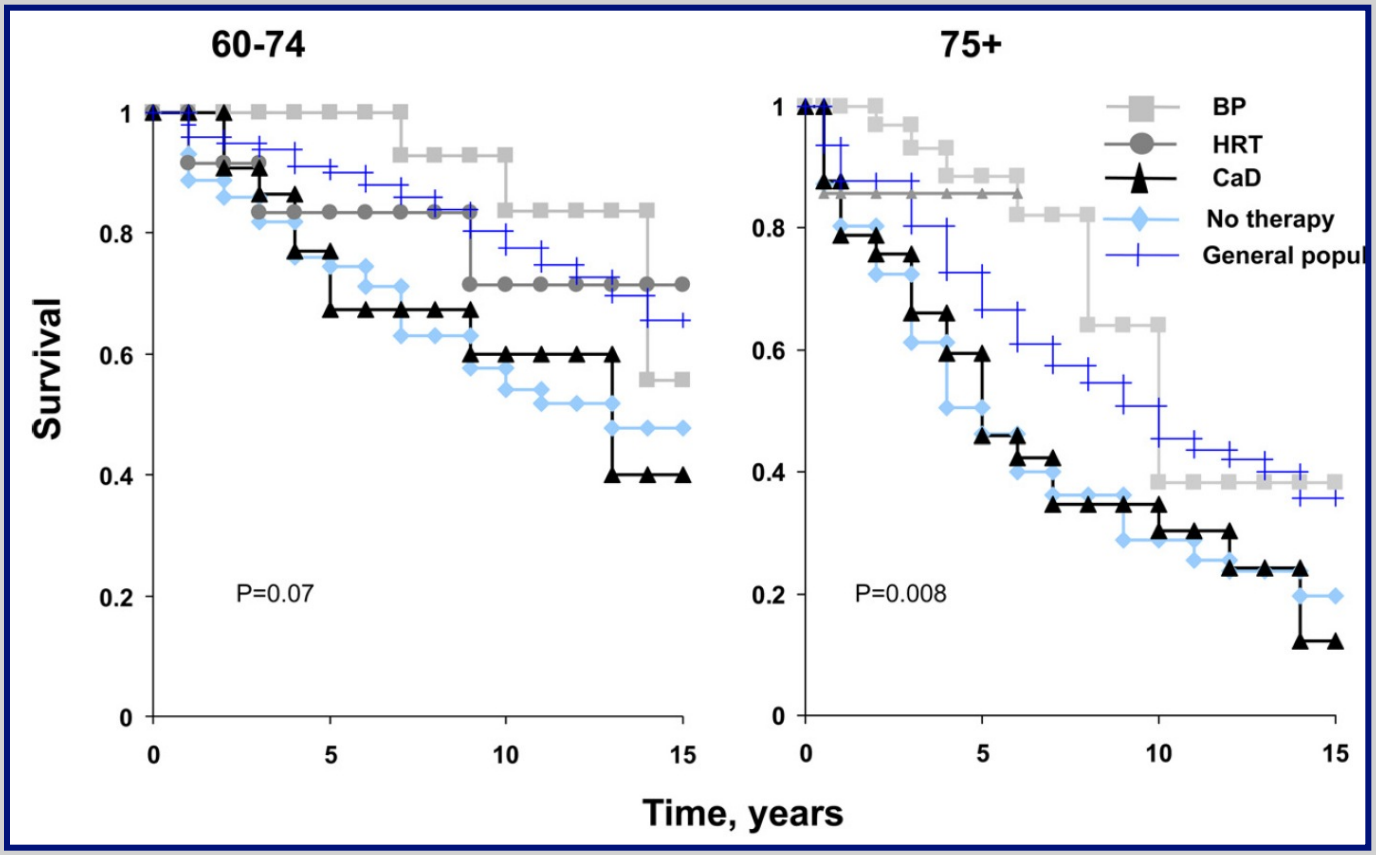


J Clin Endocrinol Metab 95: 1174–1181, 2010

Osteoporosis Medication and Reduced Mortality Risk in Elderly Women and Men

Jacqueline R. Center, Dana Bliuc, Nguyen D. Nguyen, Tuan V. Nguyen, and John A. Eisman

Bari,
7-10 novembre 2013



1223 donne di età ≥ di 60 anni

Durata dello studio 15 anni

FIG. 2. Kaplan-Meier survival curves according to osteoporosis medication for women with osteoporotic fractures aged 60–74 yr (A), aged 75+ yr (B). The *P* value refers to differences between treatment groups.

J Clin Endocrinol Metab 96: 1006–1014, 2011

RISCHI ASSOCIATI ALLA TERAPIA CON BISFOSFONATI

- Osteonecrosi della mandibola
- Fratture atipiche del femore
- Fibrillazione atriale
- Cancro dell' esofago

- Disturbi gastro-intestinali
- Alterazione della funzione renale
- Sindrome influenzale
- Ipocalcemia
- Alterazioni infiammatorie degli occhi

Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite

Bari,
7-10 novembre 2013

G.H. Nancollas [a], R. Tang [a], R.J. Phipps [b], Z. Henneman [a], S. Gulde [a], W. Wu [a], A. Mangood [a], R.G.G. Russell [c], F.H. Ebetino [b,*]

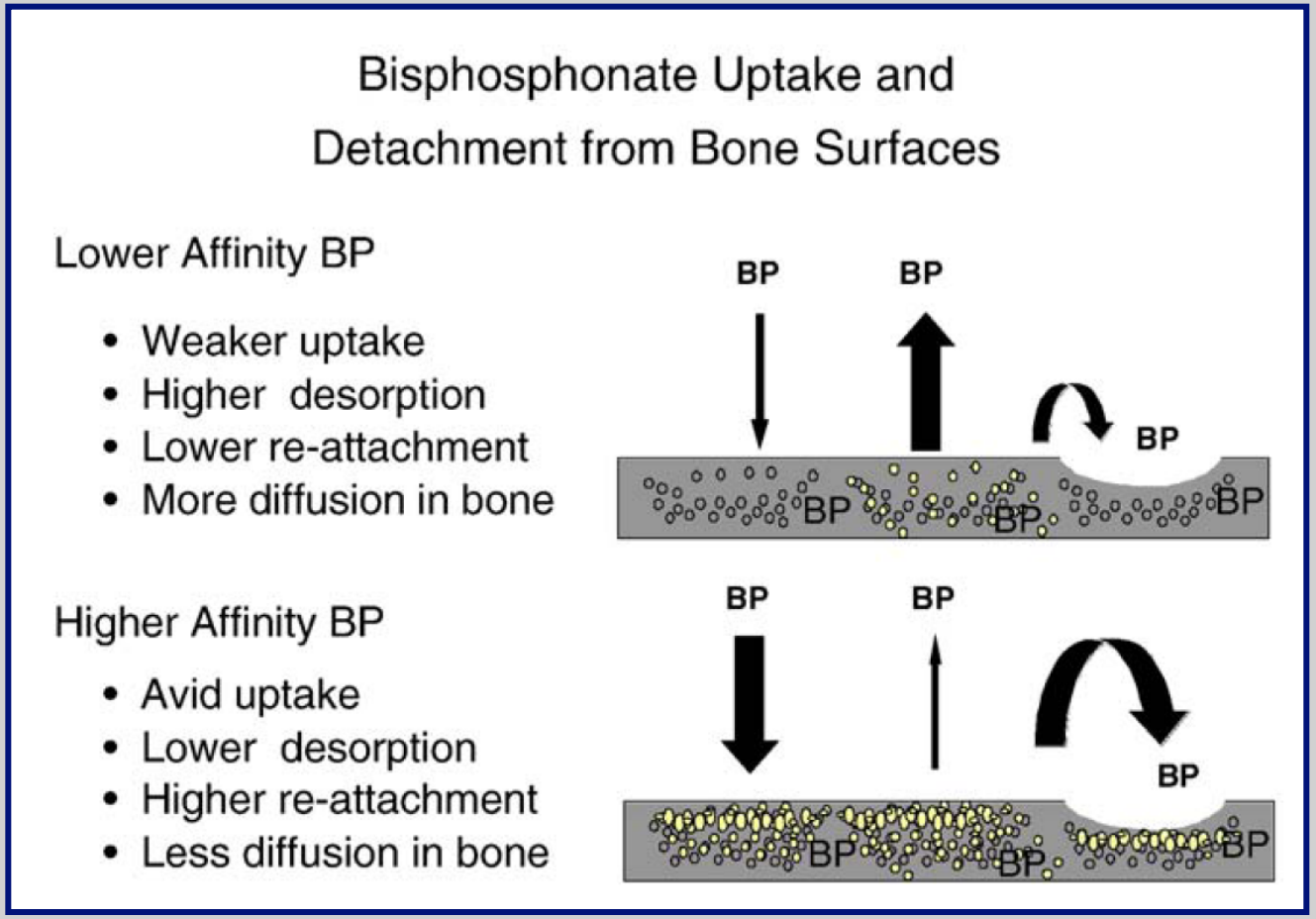


Fig. 7. Bisphosphonate interaction with bone.

Bone 38 (2006) 617–627

Bari,
7-10 novembre 2013

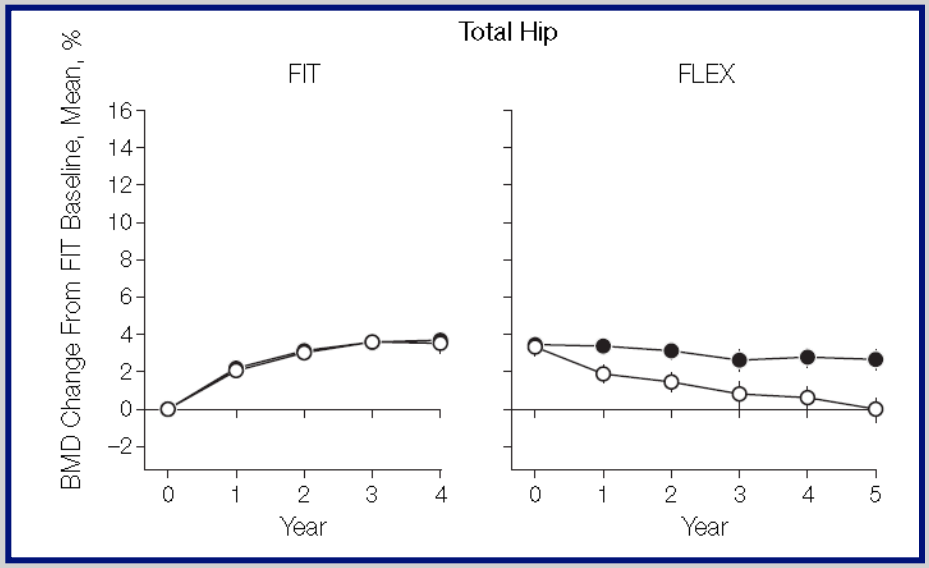
VACANZA TERAPEUTICA

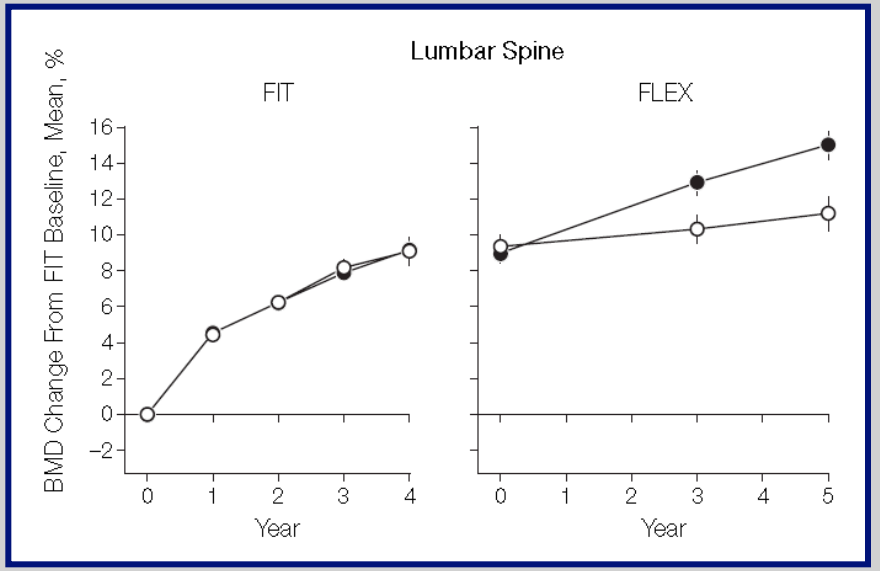
Effects of Continuing or Stopping Alendronate After 5 Years of Treatment

The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

Bari,
7-10 novembre 2013

Dennis M Black, et al





1099 donne che avevavo eseguito per 5 anni alendronato nello studio FIT

3 guppi: placebo e alendronato 5 mg e 10 mg.

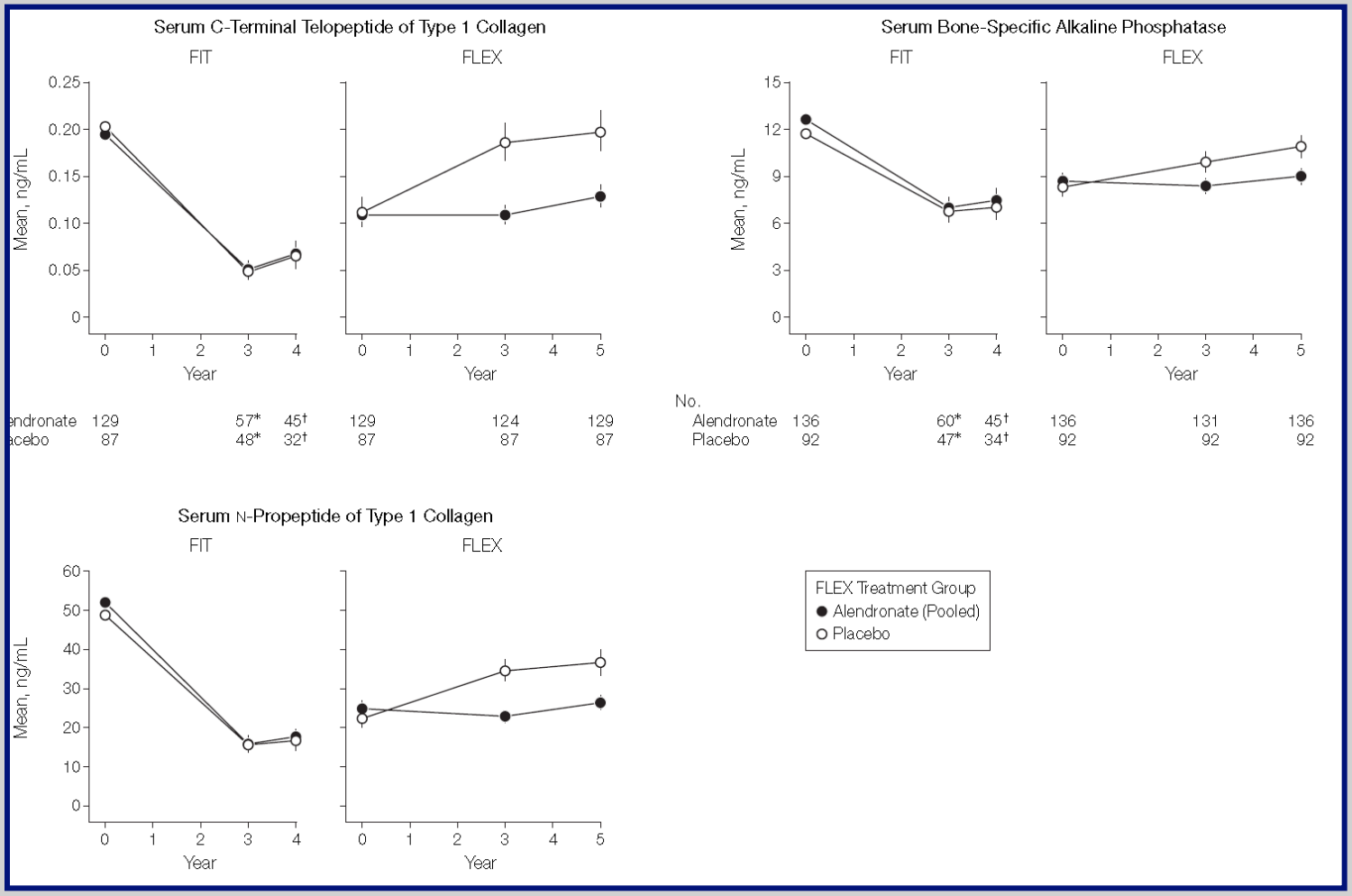
Durata dello studio 5 anni

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

Dennis M Black, et al



Effects of Continuing or Stopping Alendronate After 5 Years of Treatment

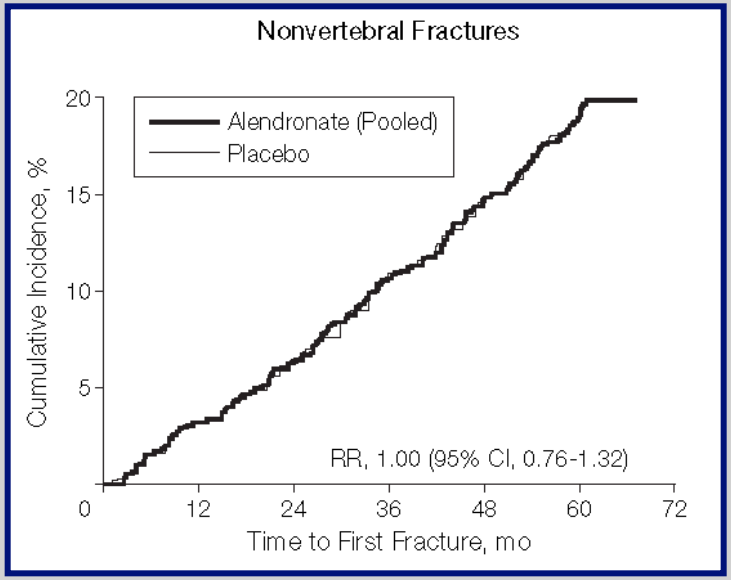
The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

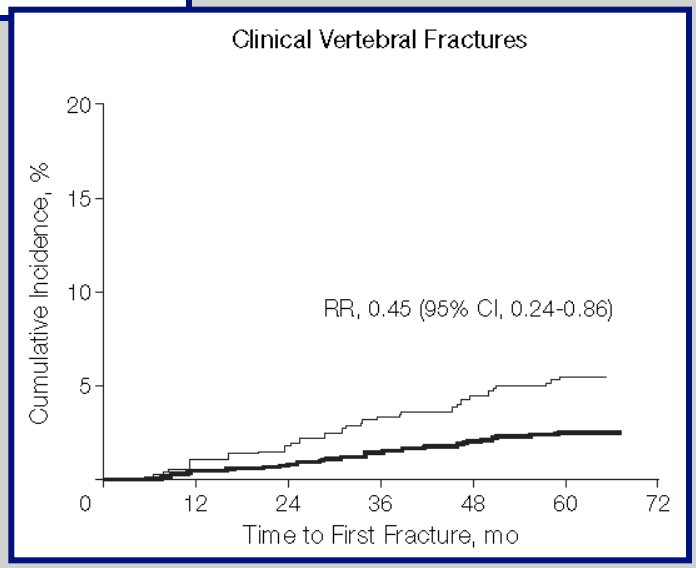
Dennis M Black, et al

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.





Efficacy of Continued Alendronate for Fractures in Women With and Without Prevalent Vertebral Fracture: The FLEX Trial

Ann V Schwartz, et al

Bari,
7-10 novembre 2013

Table 2. Continuing or Discontinuing ALN Treatment and Risk of Fracture Stratified by Baseline Presence of Vertebral Fracture and Femoral Neck *T*-Score

		Nonvertebral			Morphometric vertebral		
Femoral neck *T*-score at FLEX baseline	No.	Pbo, No. (%)[a]	Aln, No. (%)[b]	Relative risk[c] (95% CI)	Pbo, No. (%)[a]	Aln, No. (%)[b]	Relative risk[d] (95% CI)
NVF at FLEX baseline							
$-2 <$ FLEX FN *T*- score	333	14 (10.8)	30 (14.8)	1.41 (0.75–2.66)	7 (5.7)	9 (4.8)	0.84 (0.30–2.31)
$-2.5 <$ FLEX FN *T*-score ≤ -2	203	13 (15.9)	15 (12.4)	0.79 (0.37–1.66)	6 (7.6)	6 (5.4)	0.69 (0.21–2.22)
FLEX FN *T*-score ≤ -2.5	184	21 (28.0)	16 (14.7)	**0.50 (0.26–0.96)**	8 (11.0)	8 (7.7)	0.68 (0.24–1.90)
p Value for interaction[e]				**.019**			.92
Vertebral fracture at FLEX baseline:							
$-2 <$ FLEX FN *T*- score	128	4 (8.2)	12 (15.2)	1.68 (0.54–5.21)	2 (4.7)	9 (11.5)	2.67 (0.55–12.98)
$-2.5 <$ FLEX FN *T*-score ≤ -2	108	13 (29.5)	23 (35.9)	1.32 (0.67–2.61)	9 (23.1)	11 (17.7)	0.72 (0.27–1.93)
FLEX FN *T*-score ≤ -2.5	138	18 (31.6)	27 (33.3)	1.11 (0.61–2.02)	14 (27.5)	17 (25.4)	0.90 (0.39–2.05)
p Value for interaction[e]				.60			.96

[a]Number of participants with at least one fracture in the FLEX placebo group.
[b]Number of participants with at least one fracture in the FLEX ALN group (5 and 10 mg/day combined).
[c]Relative hazard estimated with Cox proportional hazard models for time to first fracture.
[d]Odds ratio estimated with logistic regression models.
[e]*p* Values for tests of interaction. Relative risks were tested for multiplicative interaction with FN *T*-score as a continuous variable.

Journal of Bone and Mineral Research, Vol. 25, No. 5, May 2010, pp 976–982

Efficacy of Continued Alendronate for Fractures in Women With and Without Prevalent Vertebral Fracture: The FLEX Trial

Ann V Schwartz, et al

Bari,
7-10 novembre 2013

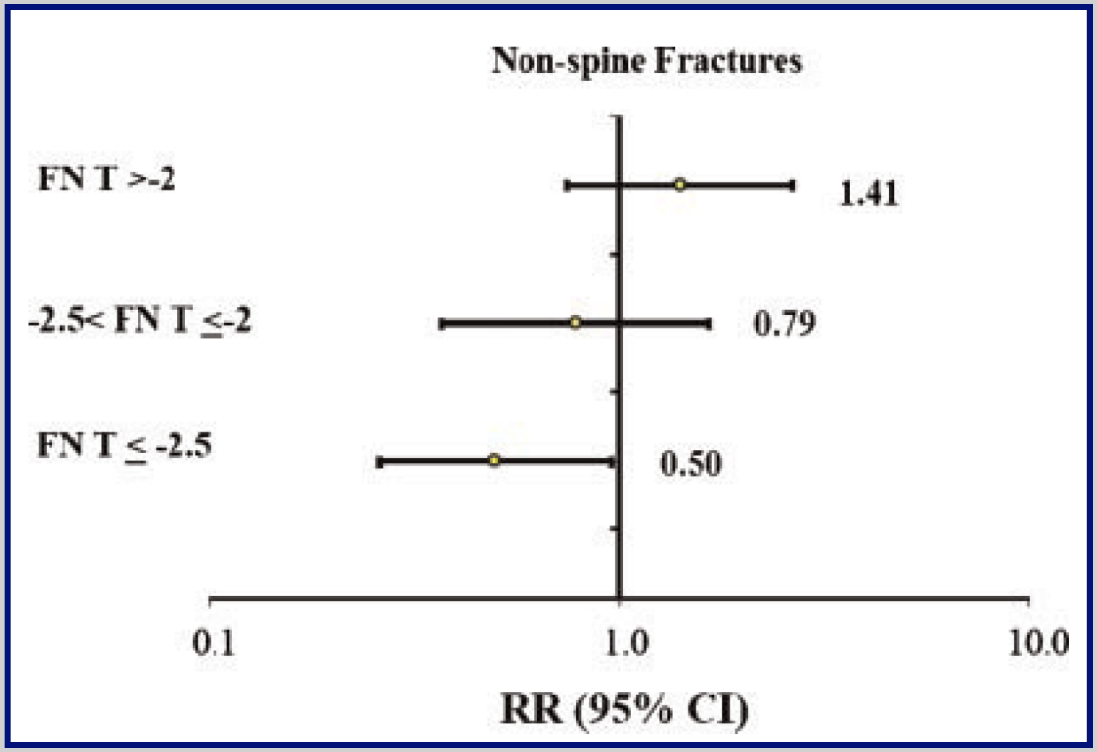


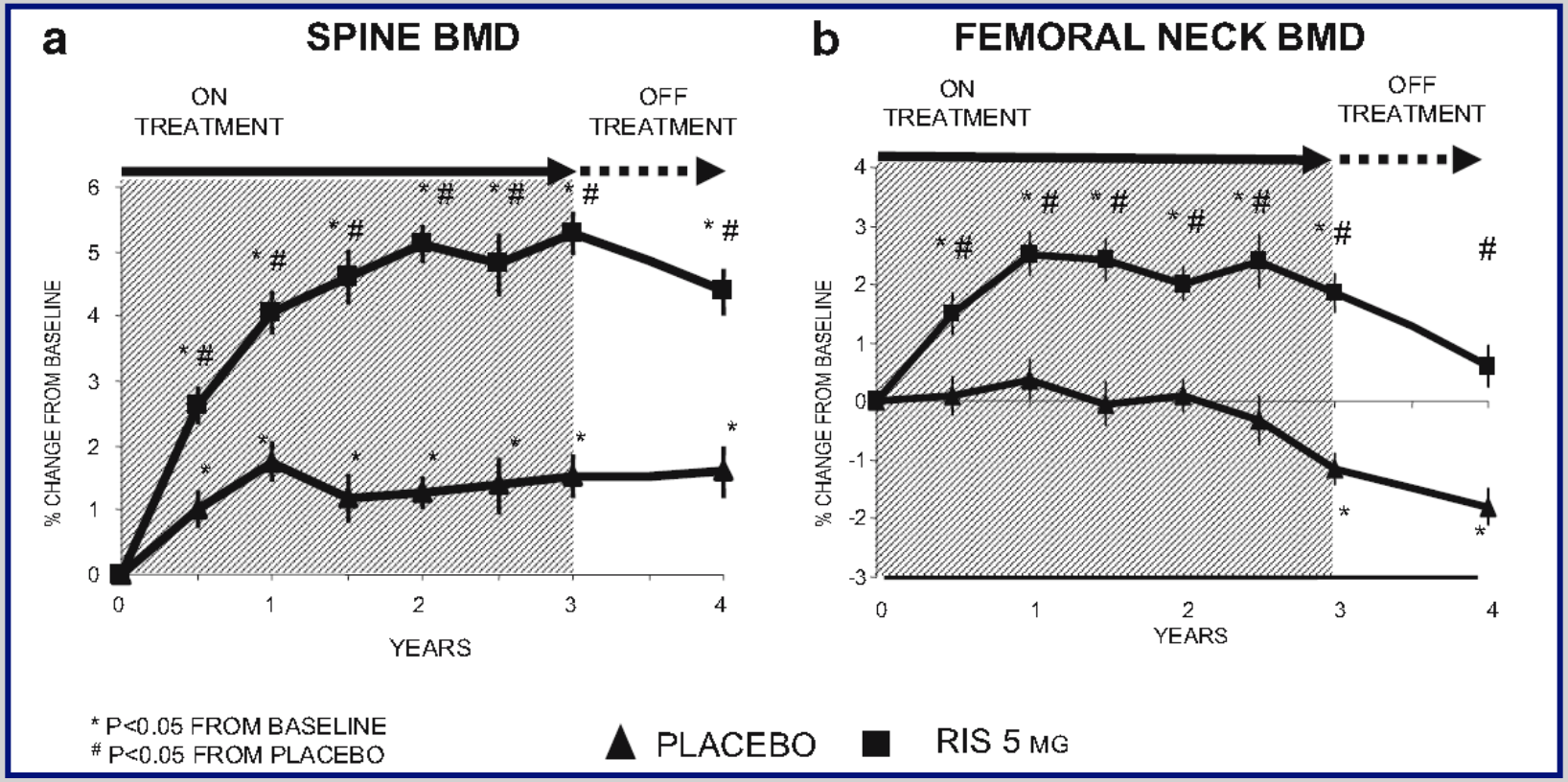
Fig. 1. Relative risk (95% confidence interval) of nonvertebral fracture for women without a prevalent vertebral fracture who were randomized to continue or discontinue ALN treatment after an average of 5 years of prior use in the FIT stratified by femoral neck (FN) *T*-score at FLEX baseline.

Journal of Bone and Mineral Research, Vol. 25, No. 5, May 2010, pp 976–982

Fracture risk remains reduced one year after discontinuation of risedronate

N. B. Watts · A. Chines · W. P. Olszynski · C. D. McKeever · M. R. McClung · X. Zhou · A. Grauer

Bari,
7-10 novembre 2013



Donne che avevavo eseguito per 3 anni risedronato o placebo nello studio VERT-NA

Sono state seguite per 1 anno solo con calcio e vitamina D

Osteoporos Int (2008) 19:365–372

Fracture risk remains reduced one year after discontinuation of risedronate

N. B. Watts · A. Chines · W. P. Olszynski · C. D. McKeever · M. R. McClung · X. Zhou · A. Grauer

Bari,
7-10 novembre 2013

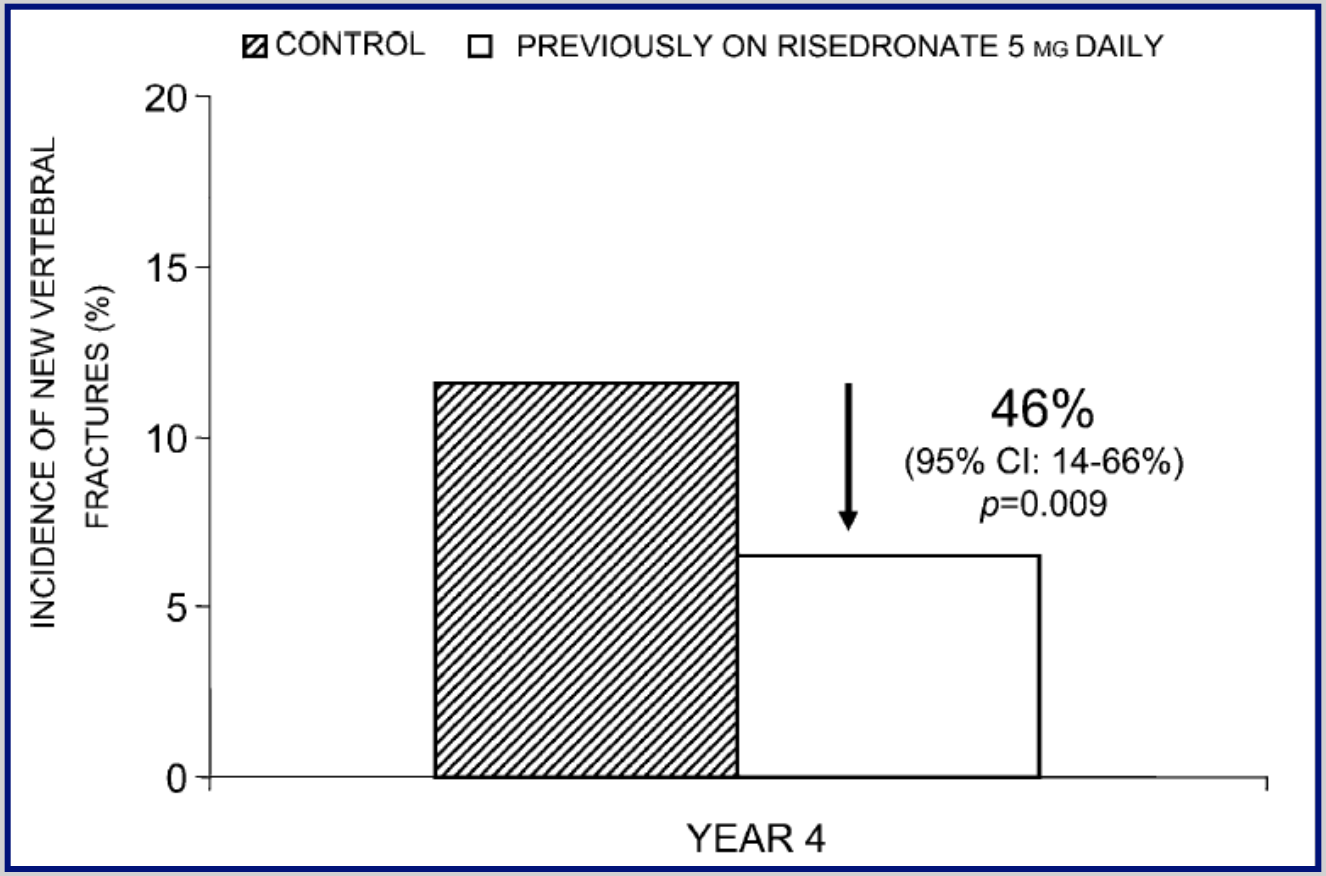


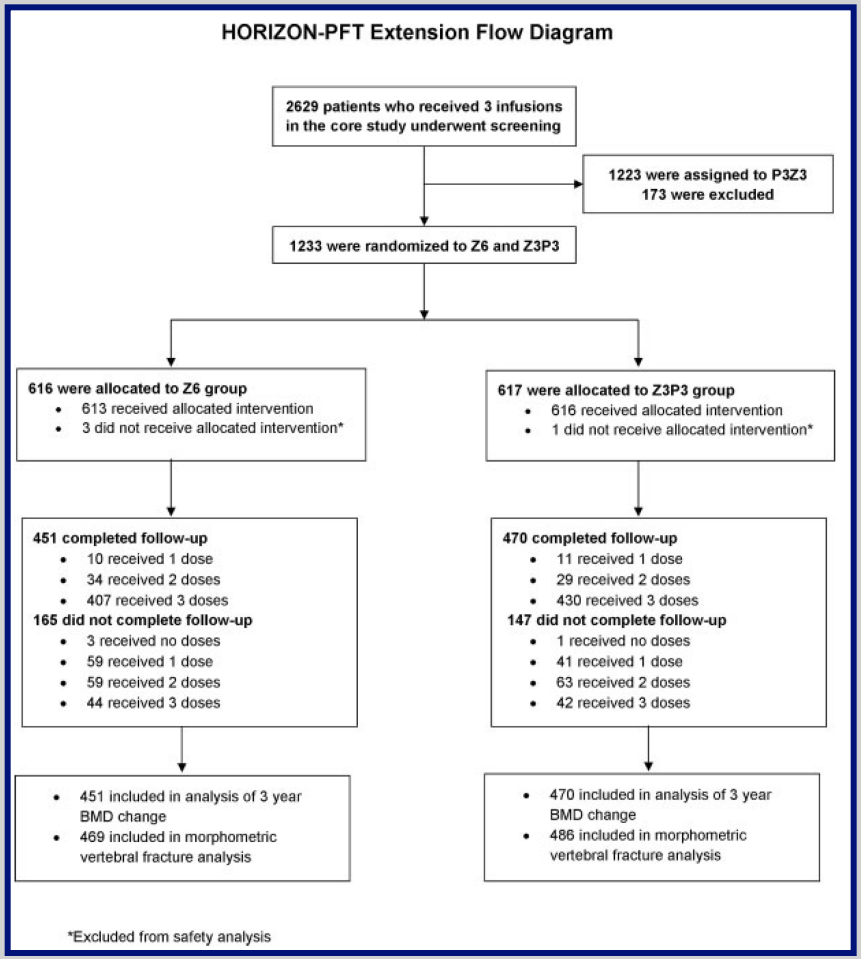
Fig. 4 New vertebral fractures in the subjects previously treated with risedronate and those in the control group in the year after discontinuation of risedronate 5 mg daily

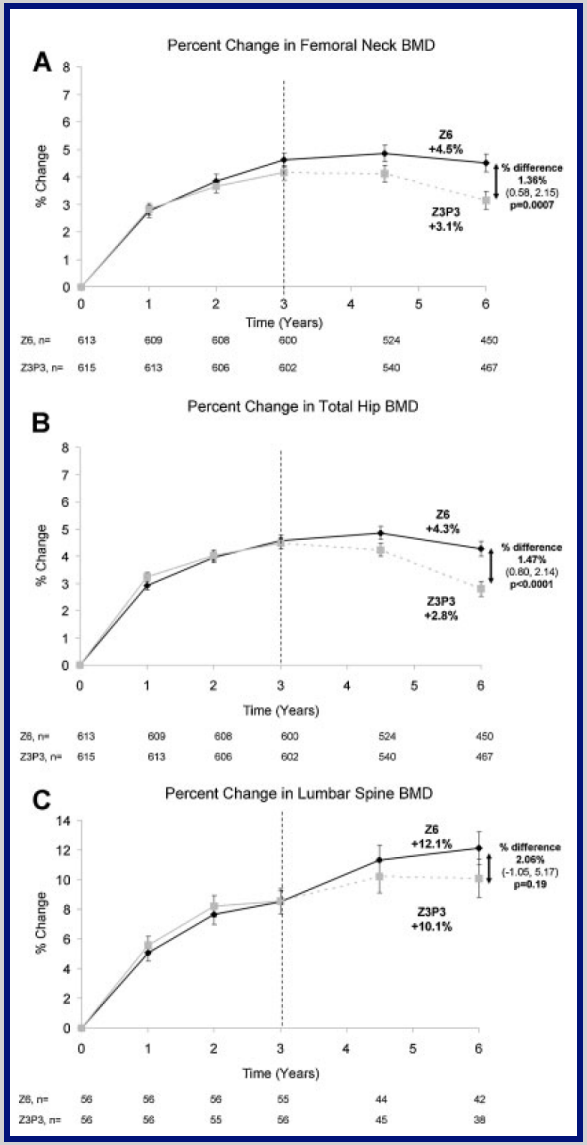
Osteoporos Int (2008) 19:365–372

The Effect of 3 Versus 6 Years of Zoledronic Acid Treatment of Osteoporosis: A Randomized Extension to the HORIZON-Pivotal Fracture Trial (PFT)

Bari,
mbre 2013

Dennis M Black, et al

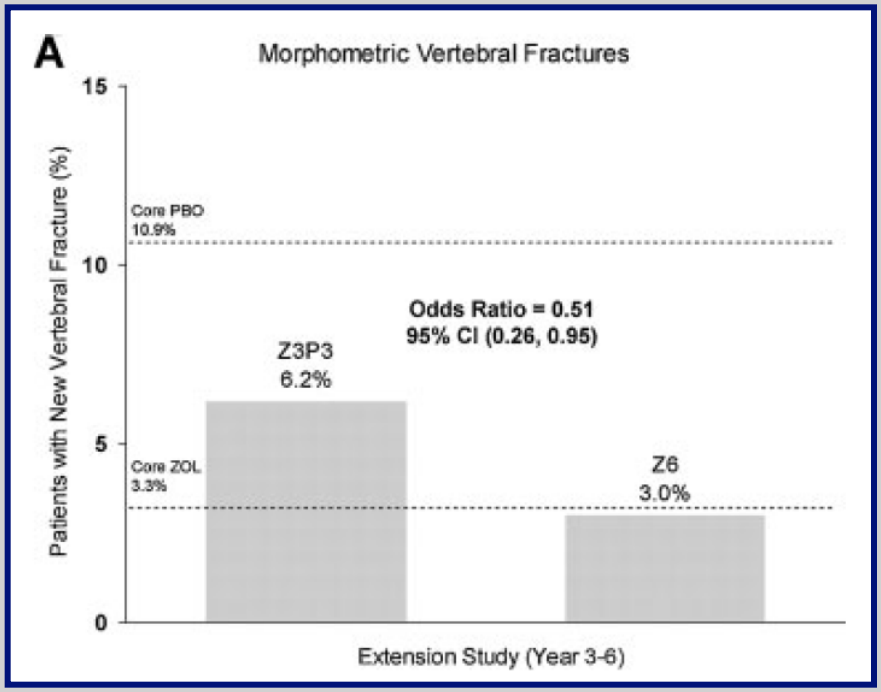


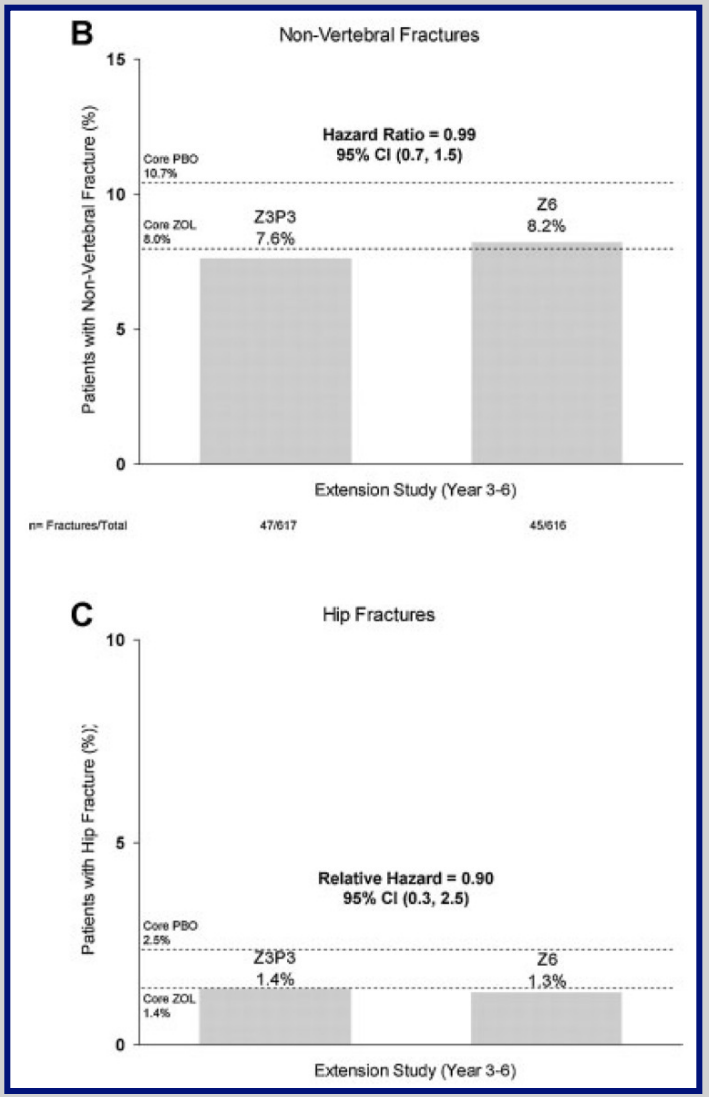


Journal of Bone and Mineral Research, Vol. 27, No. 2, February 2012

The Effect of 3 Versus 6 Years of Zoledronic Acid Treatment of Osteoporosis: A Randomized Extension to the HORIZON-Pivotal Fracture Trial (PFT)

Dennis M Black, et al





Journal of Bone and Mineral Research, Vol. 27, No. 2, February 2012

Medication (Clinical Trial)	Y	Number Needed to Treat to Prevent One Fracture: Vert fx	Non-vert fx	Hip fx
Alendronate (FIT I)[4]	3	14	36	90
Alendronate (FIT II)[5]	3	60	68	447
Risedronate (VERT NA)[6]†	3	20	31	276
Risedronate (VERT MN)[7]†	3	9	20	203
Risedronate (HIP)[8]	3	NA	56	91
Zoledronic acid (HORIZON PFT)[9]	3	13	37	91
Zoledronic acid (HORIZON RFT)[10]	3	NA	32	67
Ibandronate (BONE)[15]†	3	20	NA	NA
Alendronate (Men)[17]	2	9	NA	NA
Risedronate (GIO)[18]	1	9	NA	NA

ONJ: 1:10.00-1:100.000
Fratture atipiche: 8:10.000 pazienti/anno

Bisphosphonate Therapy for Osteoporosis: Benefits, Risks, and Drug Holiday

Michael McClung,et al

Bari,
7-10 novembre 2013

Table 2 Recommendations for Drug Holiday from Bisphosphonates

Patient Category	Recommendation	Comment
High-risk: T-score still ≤ -2.5 at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.	Drug holiday not justified.	Re-assess the need for therapy at regular intervals.
Moderate risk: Hip bone mineral density value is now > -2.5 (T-score), and no prior hip or spine fracture.	Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy. No information about ibandronate and drug holidays.	These patients should not be forced to take a drug holiday—decision should be an individual, informed choice with discussion of the potential benefits and risks.
Low risk: Did not meet current treatment criteria at the time of treatment initiation.	Discontinue therapy	Re-start when indications for therapy are met.

The American Journal of Medicine (2013) 126, 13-20

MONITORAGGIO DELLA VACANZA TERAPEUTICA

Bari,
7-10 novembre 2013

- Significativa diminuzione della densità ossea
- Aumento significativo dei marcatori ossei
- Rivalutazione dei pazienti dopo 2-3 anni dall'interruzione della terapia con la valutazione del rischio di frattura con le carte del rischio
- Comparsa di una nuova frattura da fragilità

NUOVI SCHEMI TERAPEUTICI

Bari,
7-10 novembre 2013

- Terapia sequenziale
  - Bisfosfonato → bisfosfonato
  - Bisfosfonato → altro farmaco antiriassorbitivo
  - Bisfosfonato → farmaco anabolico
  - Farmaco anabolico → bisfosfonato
- Terapia combinata
  - Farmaco anabolico + farmaco antiriassorbitivo
  - farmaco antiriassorbitivo + farmaco antiriassorbitivo

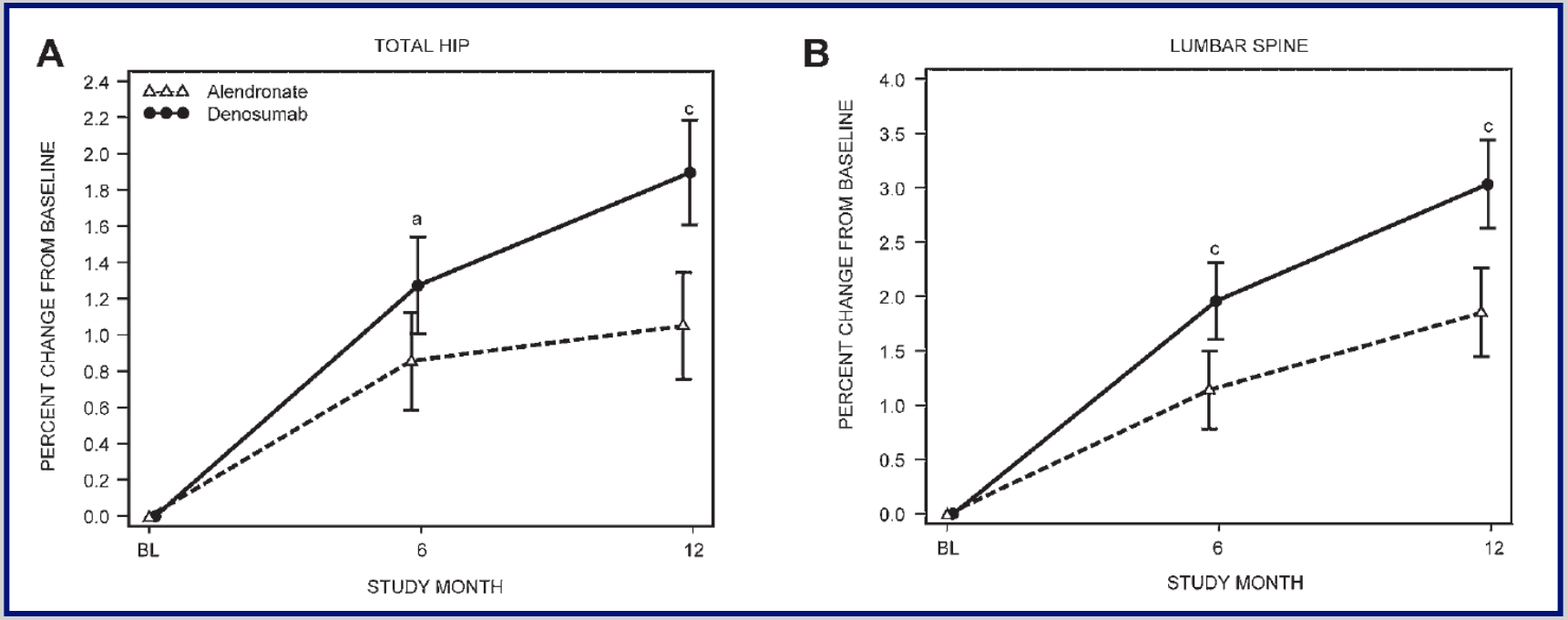
BSF orale

- BSF im o iv
  - Clodronato
  - zoledronato
- Denosumab sc

Bari,
7-10 novembre 2013

Effects of Denosumab on Bone Mineral Density and Bone Turnover in Postmenopausal Women Transitioning From Alendronate Therapy

David L Kendler, et al



504 donne in post-menopausa di età ≥ 55 anni con T-score femorale ≤ -2 che avevano eseguito terapia con alendronato per almeno 6 mesi

2 guppi: alendronato 70 mg e denosumab

Durata dello studio 1 anno

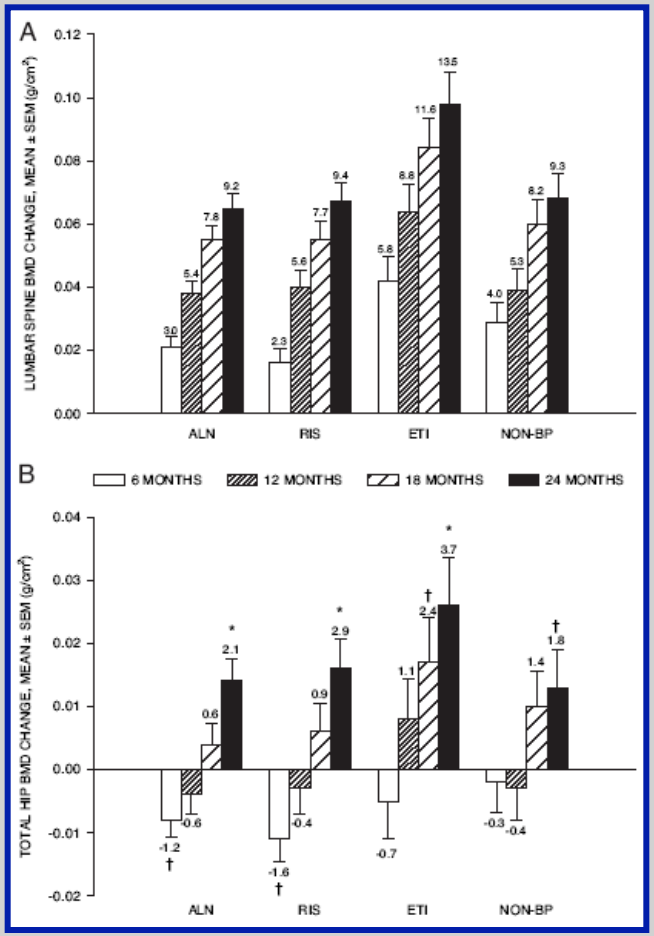
Journal of Bone and Mineral Research, Vol. 25, No. 1, January 2010, pp 72–81

Bari,
7-10 novembre 2013

Effects of Previous Antiresorptive Therapy on the Bone Mineral Density Response to Two Years of Teriparatide Treatment in Postmenopausal Women with Osteoporosis

Steven Boonen, Fernando Marin, Barbara Obermayer-Pietsch, Maria E. Simões, Clare Barker, Emmett V. Glass, Peyman Hadji, George Lyritis, Heide Oertel, Thomas Nickelsen, and Eugene V. McCloskey, for the EUROFORS Investigators

EUROFORS è uno studio prospettico aperto in donne con osteoporosi trattate per 2 anni con TPTD
95 centri in 10 stati europei
Analisi eseguita su 245 che donne hanno concluso lo studio
Stratificazione delle pazienti secondo la terapia precedentemente eseguita: alendronato, risedrotnato, etidronato e nessuna terapia.

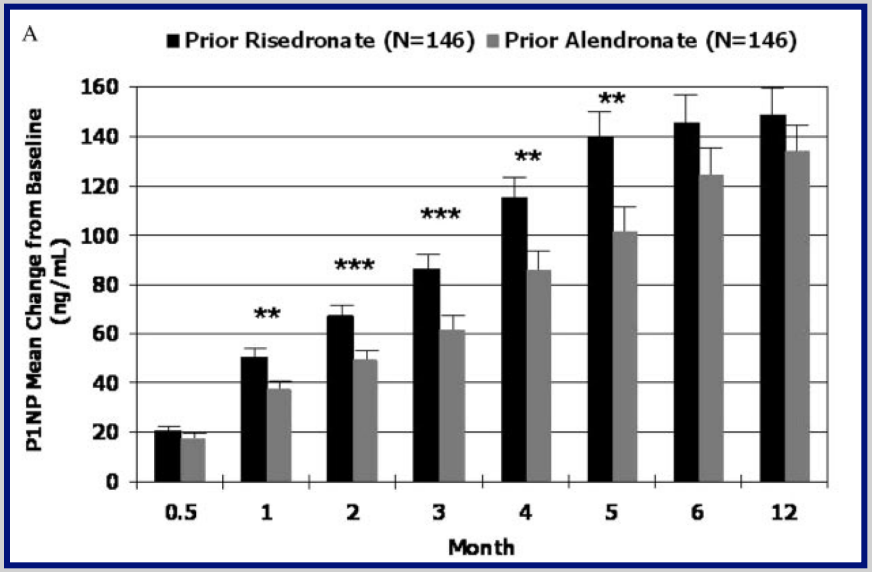


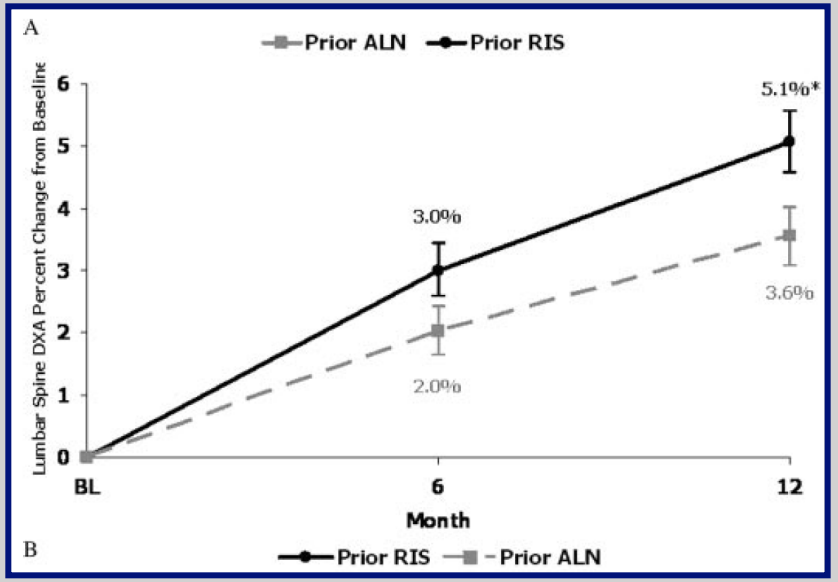
J Clin Endocrinol Metab, March 2008,

Early Responsiveness of Women with Osteoporosis to Teriparatide After Therapy with Alendronate or Risedronate

Bari,
7-10 novembre 2013

Paul D. Miller et al





Studio non randomizzato, prospettico, aperto
146 donne che avevano eseguito terapia con risedronato e 146 donne che avevano eseguito terapia con alendronato per 24 mesi.
Successiva terapia con teriparatide per 12 mesi.

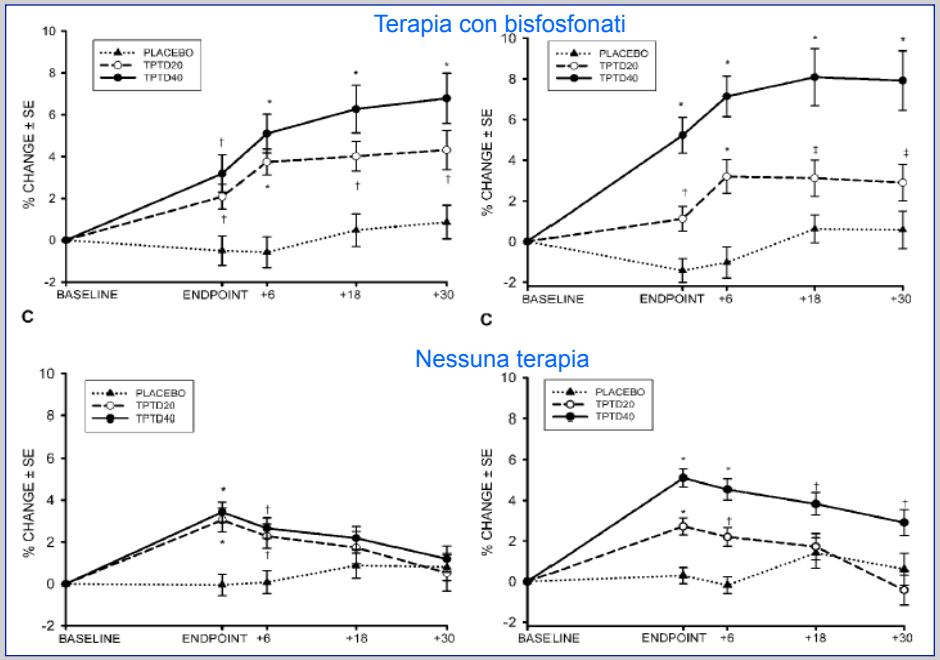
J Clin Endocrinol Metab, October 2008, 93(10):3785–3793

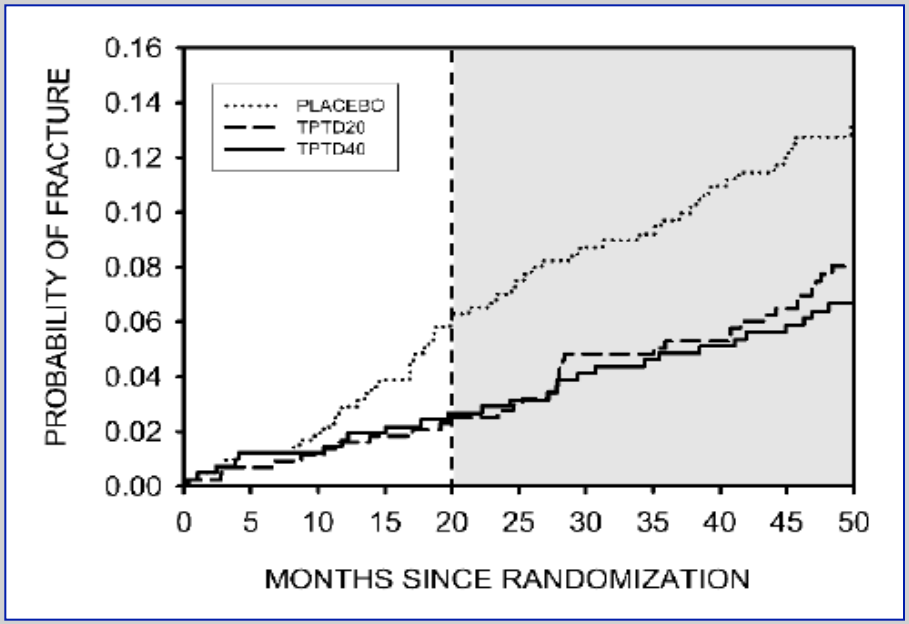
Bari,
7-10 novembre 2013

Sustained Nonvertebral Fragility Fracture Risk Reduction After Discontinuation of Teriparatide Treatment*

Richard Prince,[1] Adrien Sipos,[2] Anwar Hossain,[2] Unni Syversen,[3] Sophia Ish-Shalom,[4] Ewa Marcinowska,[5] Johan Halse,[6] Robert Lindsay,[7] Gail P Dalsky,[2] and Bruce H Mitlak[2]

Total hip **Femoral neck**





J Bone Miner Res 2005;20:1507–1513

One Year of Alendronate after One Year of Parathyroid Hormone (1–84) for Osteoporosis

Bari,
7-10 novembre 2013

238 PM women with OP randomly assigned to PTH (1-84) or alendronate (10 mg) or both treatments for one yr

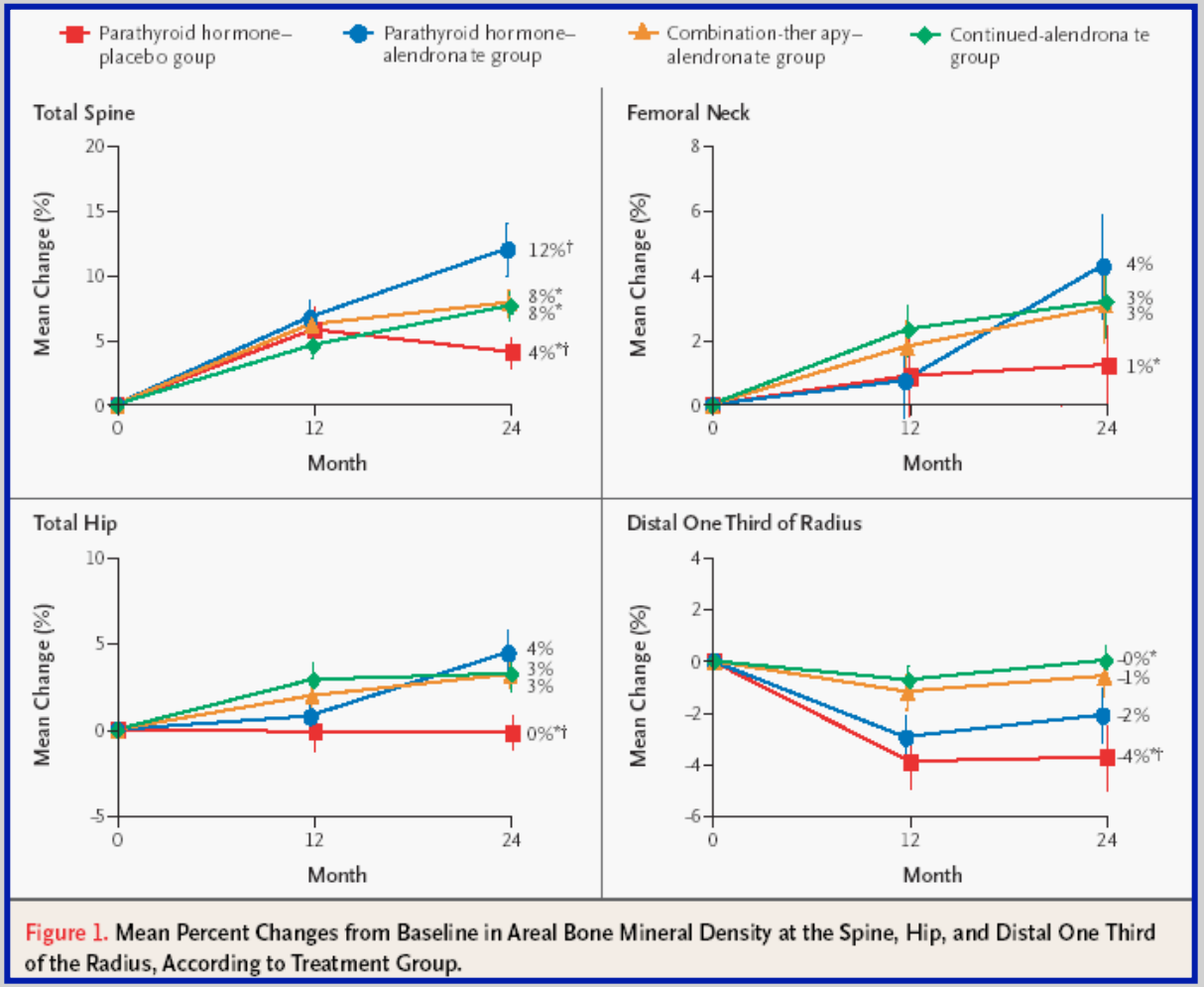
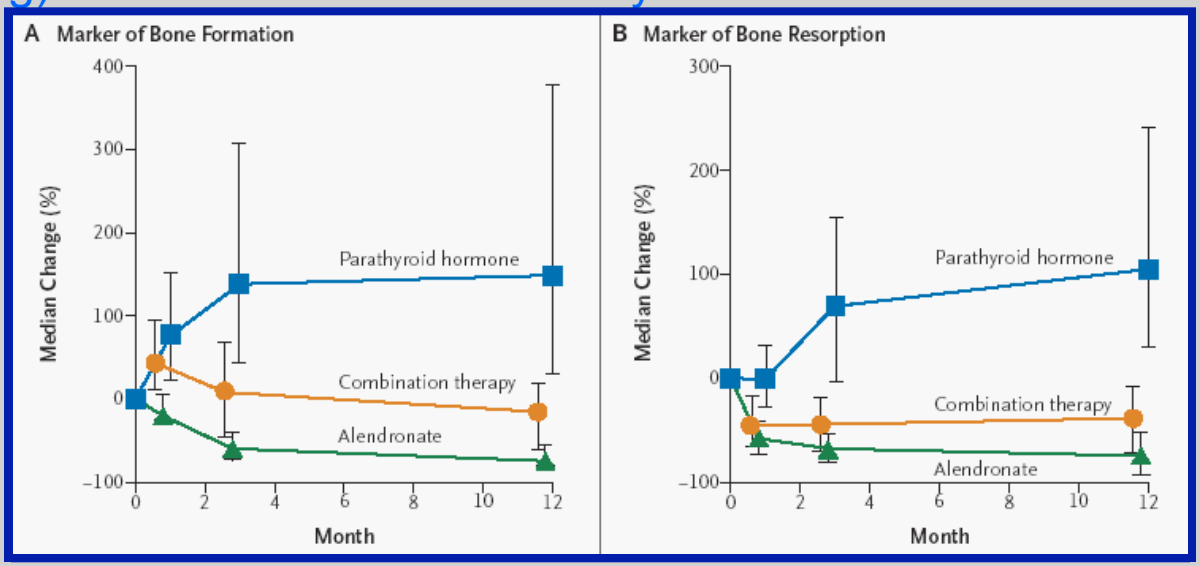


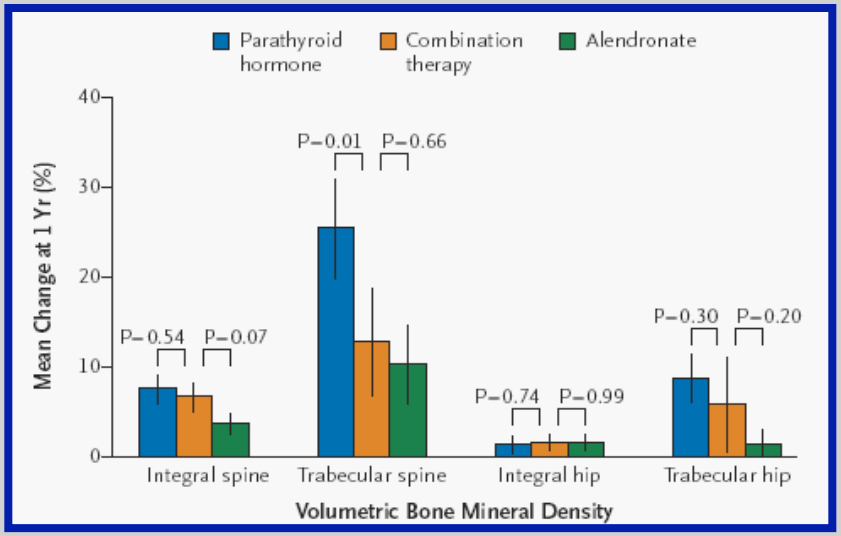
Figure 1. Mean Percent Changes from Baseline in Areal Bone Mineral Density at the Spine, Hip, and Distal One Third of the Radius, According to Treatment Group.

Black et al, NEJM 2005

The Effects of Parathyroid Hormone and Alendronate Alone or in Combination in Postmenopausal Osteoporosis

238 PM women with OP randomly assigned to PTH (1-84) or alendronate (10 mg) or both treatments for one yr





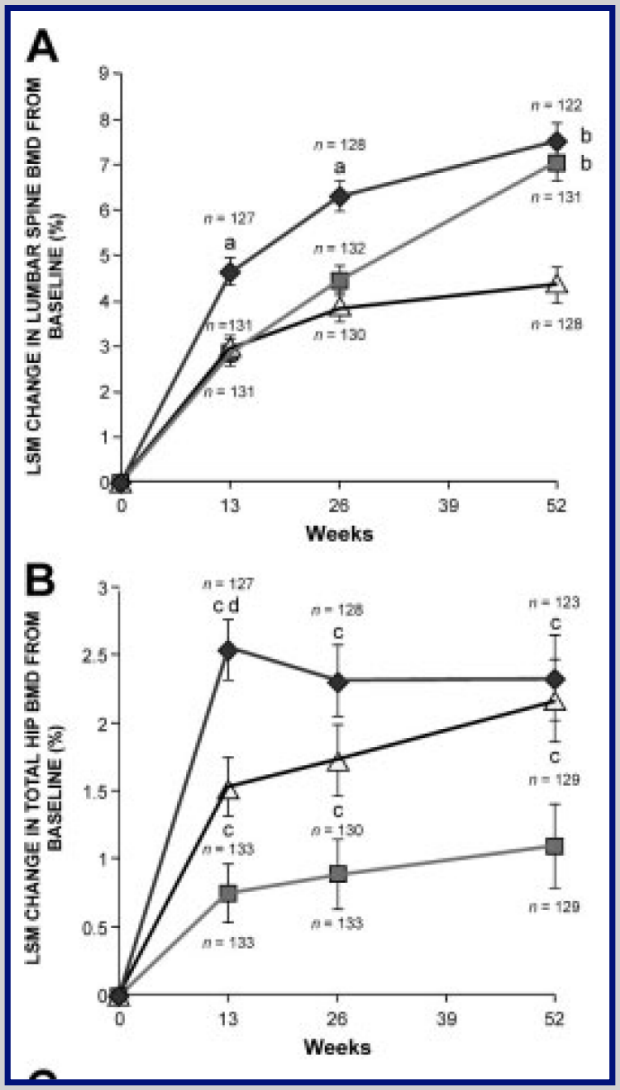
Dominant effect of antiresorptive therapy on bone dinamics

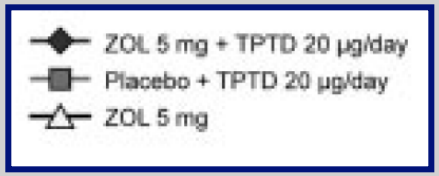
Black et al, NEJM 2003

Effects of Intravenous Zoledronic Acid Plus Subcutaneous Teriparatide [rhPTH(1–34)] in Postmenopausal Osteoporosis

Felicia Cosman, et al

Bari, [illegible]mbre 2013

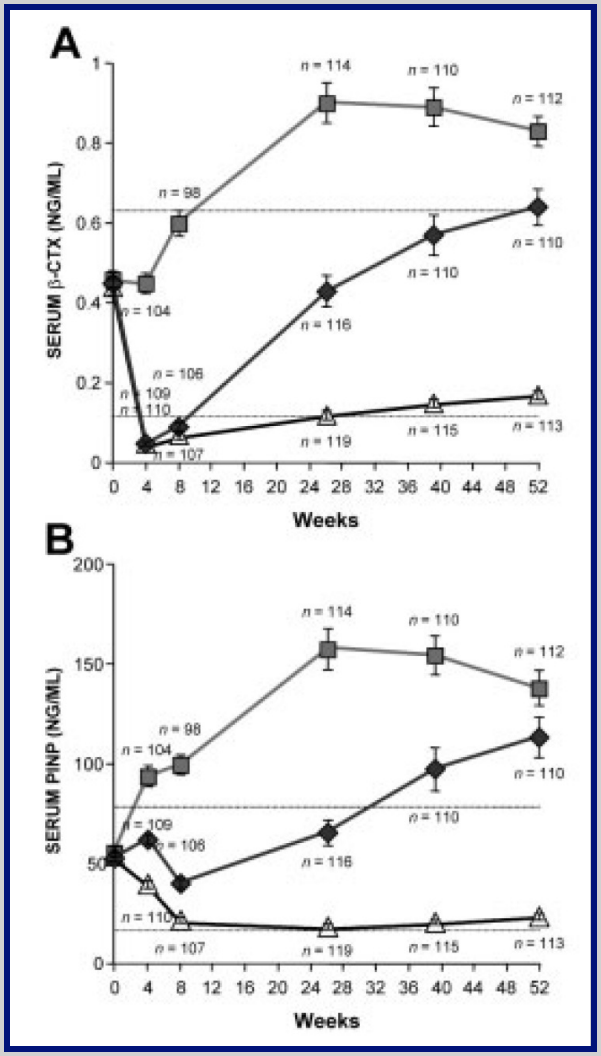




412 donne in postmenopausa con osteoporosi

3 guppi: Acido Zoledronico 5 mg più teriparatide giornaliero, acido zoledronico da solo o teriparatide da solo

Durata dello studio 52 settimane

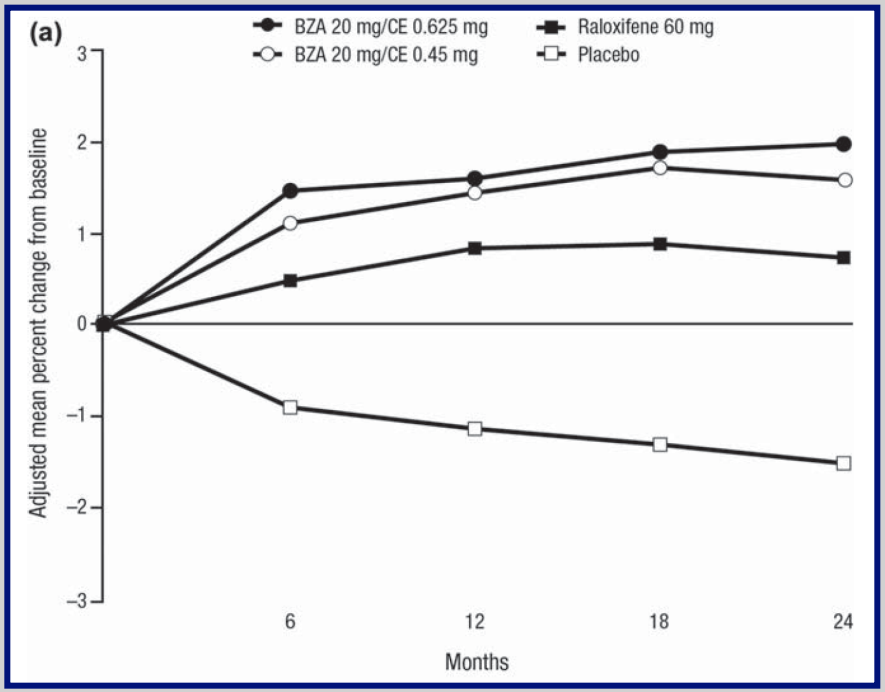


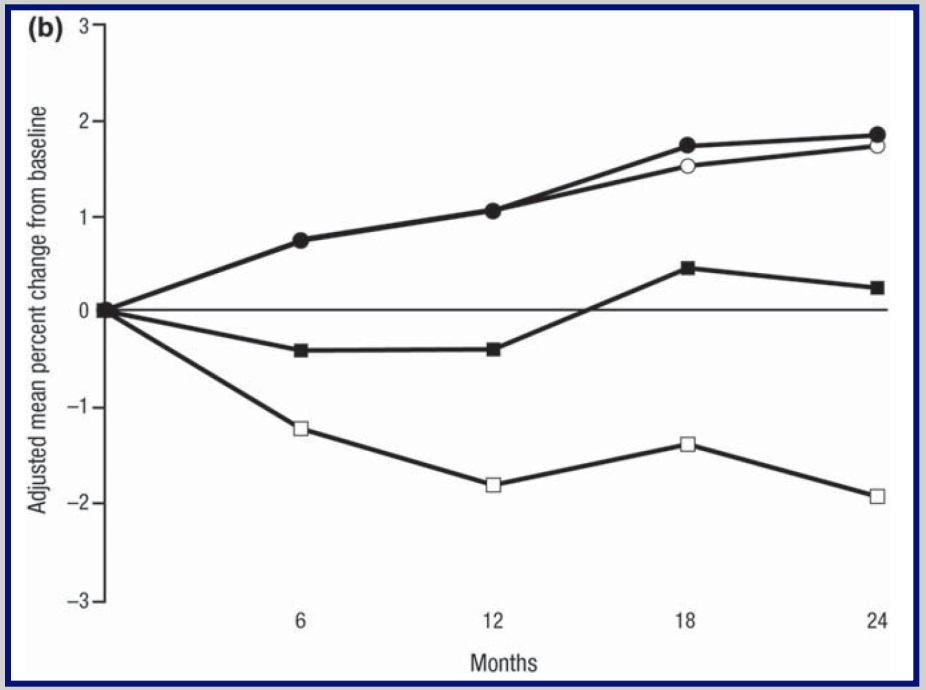
Journal of Bone and Mineral Research, Vol. 26, No. 3, March 2011

Bazedoxifene/conjugated estrogens for menopausal symptom treatment and osteoporosis prevention

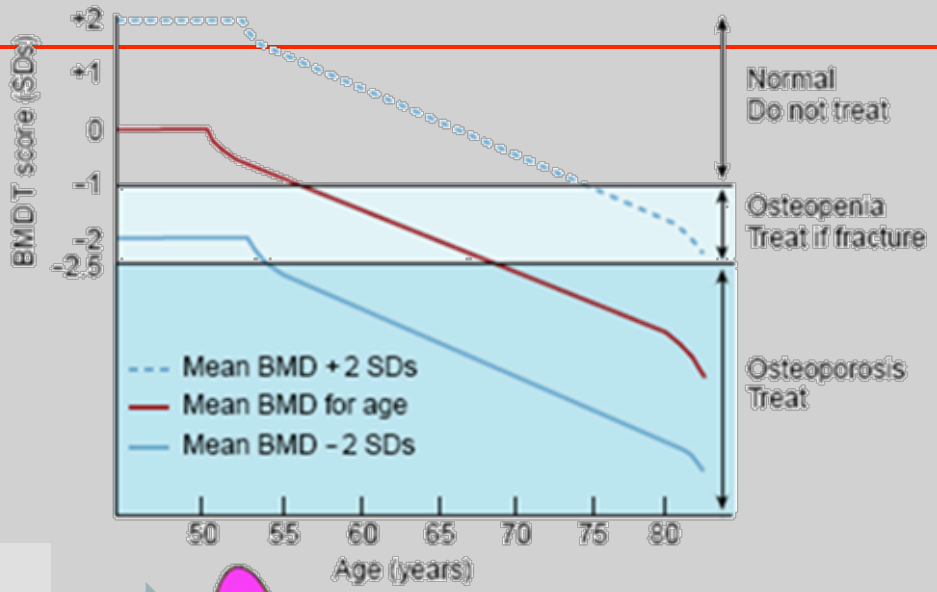
Bari,
7-10 novembre 2013

J. V. Pinkerton, J. H. Pickar, J. Racketa† and S. Mirkin†*





CLIMACTERIC 2012;15:411–418



solo se concomitano sintomi climaterici

TSEC

- HRT
- raloxifene
- Bisfosfonati
- ranelato di Stronzio
- PTH
- Denosumab

Vacanza terapeutica

max 2 anni

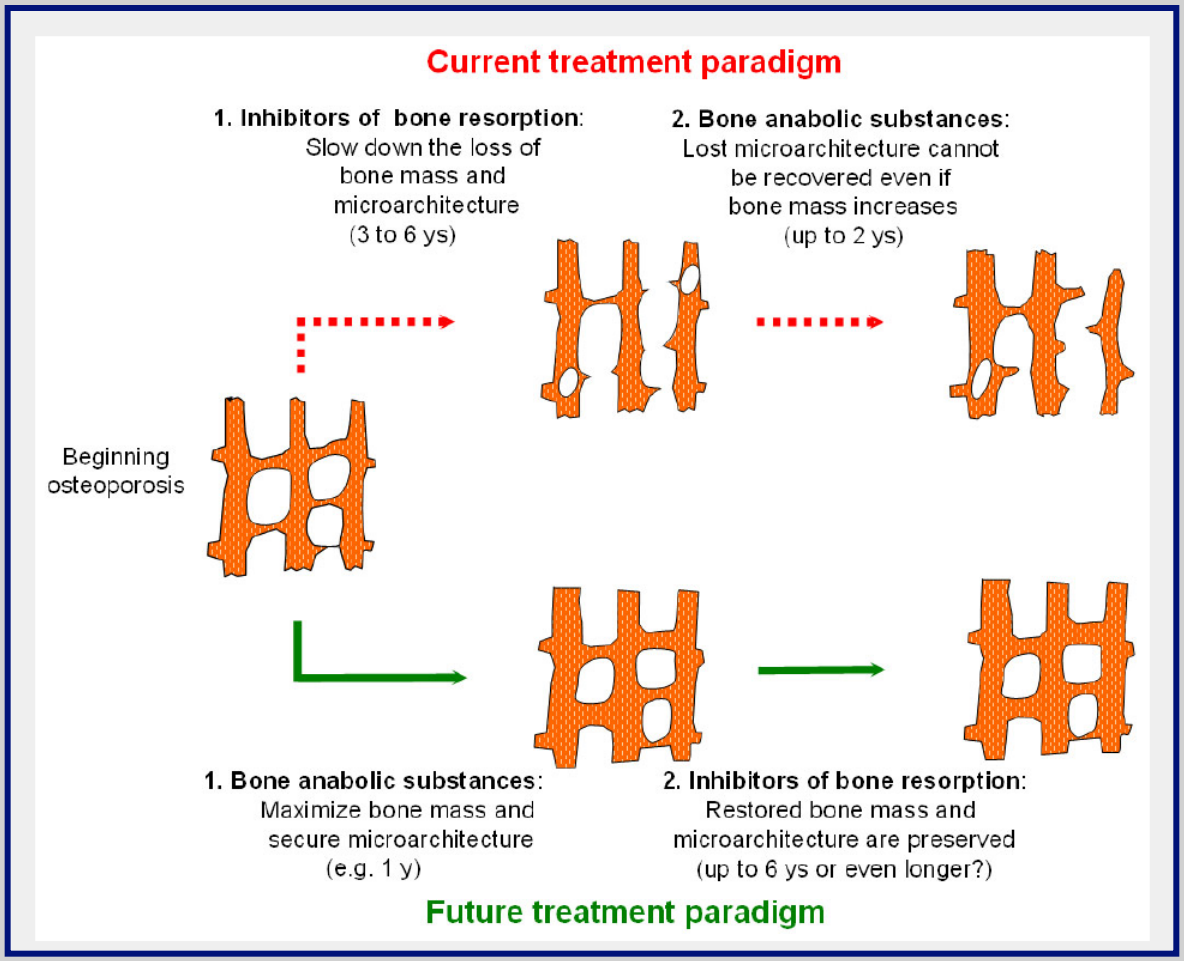
- supplem di calcio (se carente)
- supplem di vitD (se carente)
- corretto stile di vita

Modificato da: Seeman E *et al.* **Med J Aust** 2004

The future of osteoporosis treatment – a research update

Kurt Lippuner

Bari,
7-10 novembre 2013



Swiss Med Wkly. 2012;142:w13624