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ZOLEDRONATO: APPROPRIATEZZA TERAPEUTICA ED ADERENZA AL TRATTAMENTO

BRUNO FREDIANI

Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED 1812 MAY 3, 2007 VOL. 356 NO. 18

Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

Dennis M. Black, Ph.D., Pierre D. Delmas, M.D., Ph.D., Richard Eastell, M.D., Ian R. Reid, M.D., Steven Boonen, M.D., Ph.D., Jane A. Cauley, Dr.P.H., Felicia Cosman, M.D., Péter Lakatos, M.D., Ph.D., Ping Chung Leung, M.D., Zulema Man, M.D., Carlos Mautalen, M.D., Peter Mesenbrink, Ph.D., Huilin Hu, Ph.D., John Caminis, M.D., Karen Tong, B.S., Theresa Rosario-Jansen, Ph.D., Joel Krasnow, M.D., Trisha F. Hue, M.P.H., Deborah Sellmeyer, M.D., Erik Fink Eriksen, M.D., D.M.Sc., and Steven R. Cummings, M.D., for the HORIZON Pivotal Fracture Trial

Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

HORIZON Pivotal Fracture Trial (PFT) Overview

- Objective: To evaluate the potential of once yearly ZOL 5 mg to decrease fracture risk in postmenopausal women with osteoporosis
- 3-year, randomized, double-blind, placebo-controlled clinical trial
  - 7736 women from 239 clinical centers in 27 countries
- Treatment
  - Annual infusion of either ZOL 5 mg or placebo
  - Calcium 1000–1500 mg/d; vitamin D 400–1200 IU/d
- Follow-up visits at 6, 12, 24 and 36 months
  - Telephone interviews every 3 months

ZOL = zoledronic acid

Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

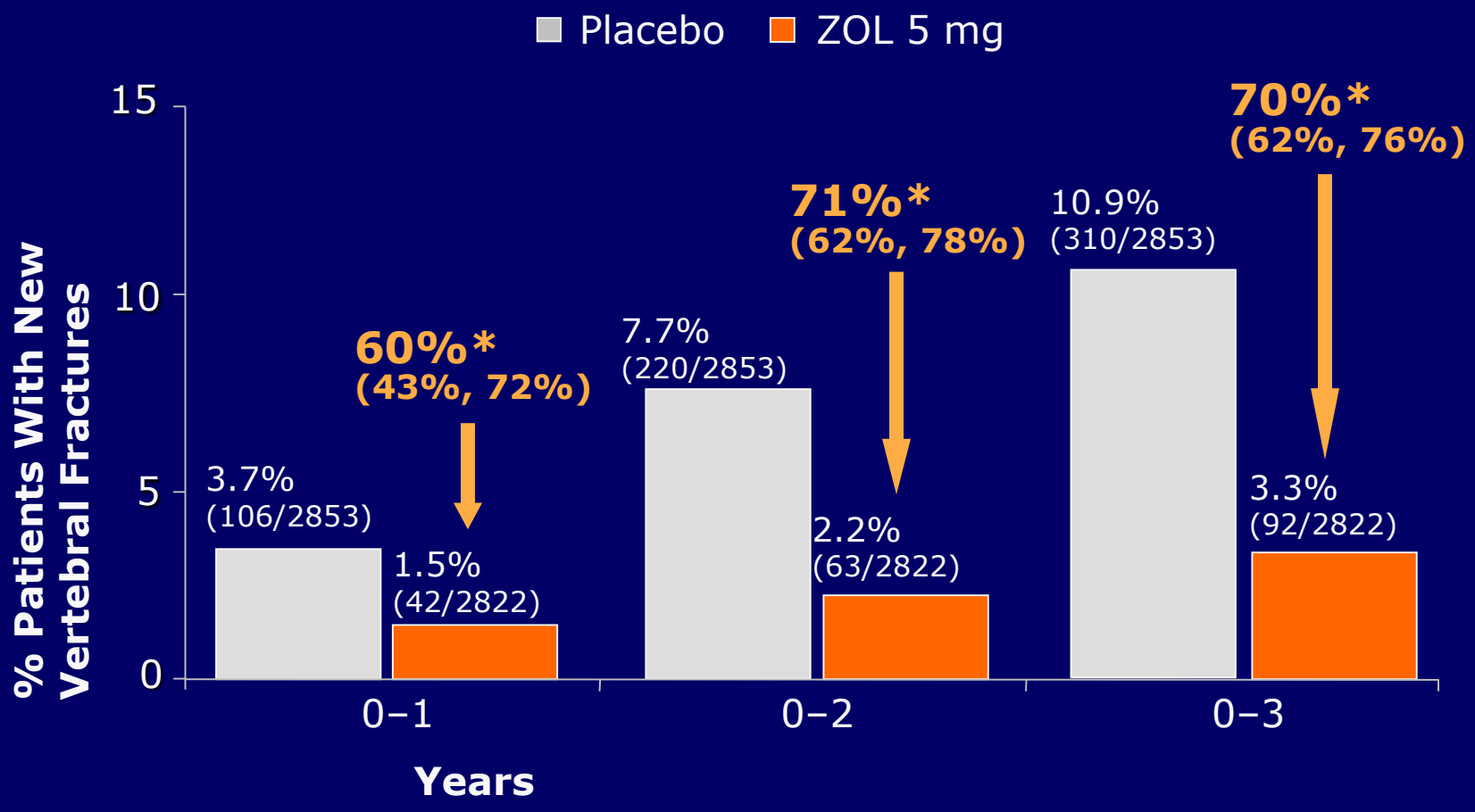
Study Population

- Inclusion
  - Women 65 to 89 years of age
  - Femoral neck T-score ≤–2.5 with or without fracture **or** ≤–1.5 with 2 mild or 1 moderate vertebral fracture
- Exclusion
  - Current use of PTH or strontium ranelate
  - Failure to meet specified washout periods for previous bisphosphonate (BP) use
- Two strata
  - Stratum I: no current osteoporosis therapy
  - Stratum II: SERMs, calcitonin, HT/ET, or tibolone at baseline

HT/ET = hormone or estrogen therapy; PTH = parathyroid hormone; SERMs = selective estrogen receptor modulators

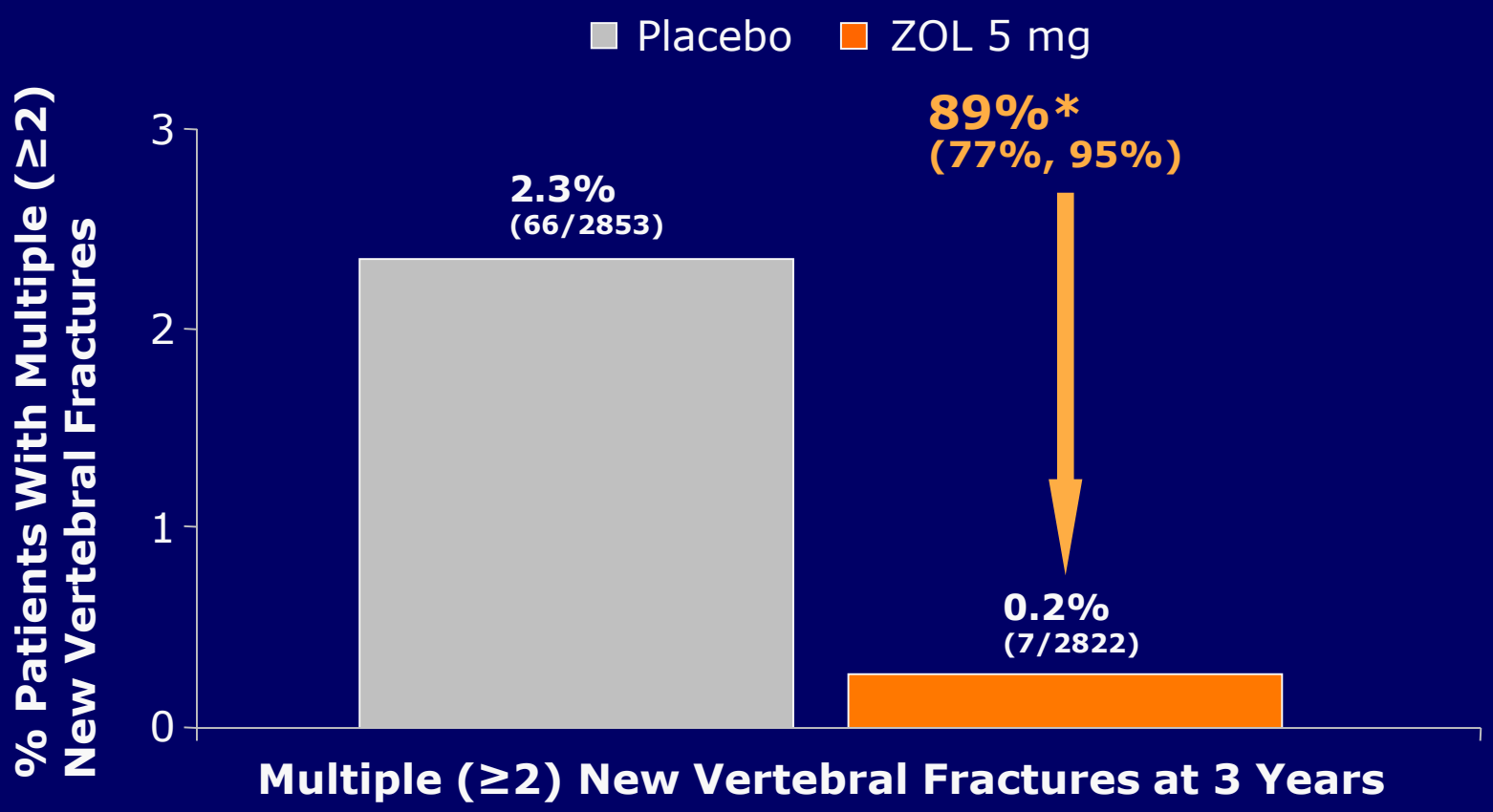
Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

Zoledronic Acid Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I) by 70%



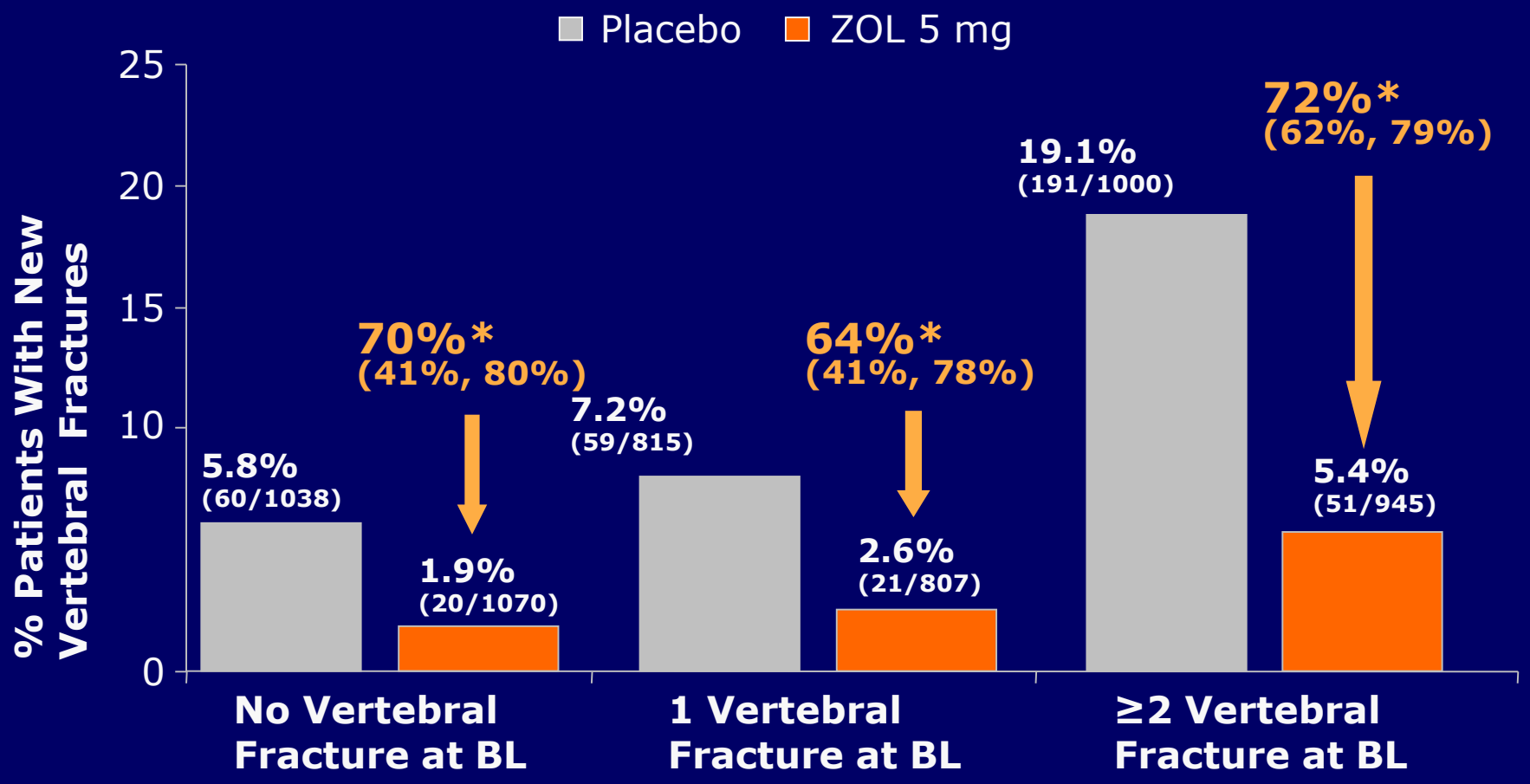
*P < .0001, relative risk reduction vs placebo (95% confidence interval)
Adapted from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

Zoledronic Acid Reduced 3-Year Risk of Multiple (≥2) New Morphometric Vertebral Fractures (Stratum I) by 89%



*P = .0001, relative risk reduction vs placebo (95% confidence interval)
Data from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

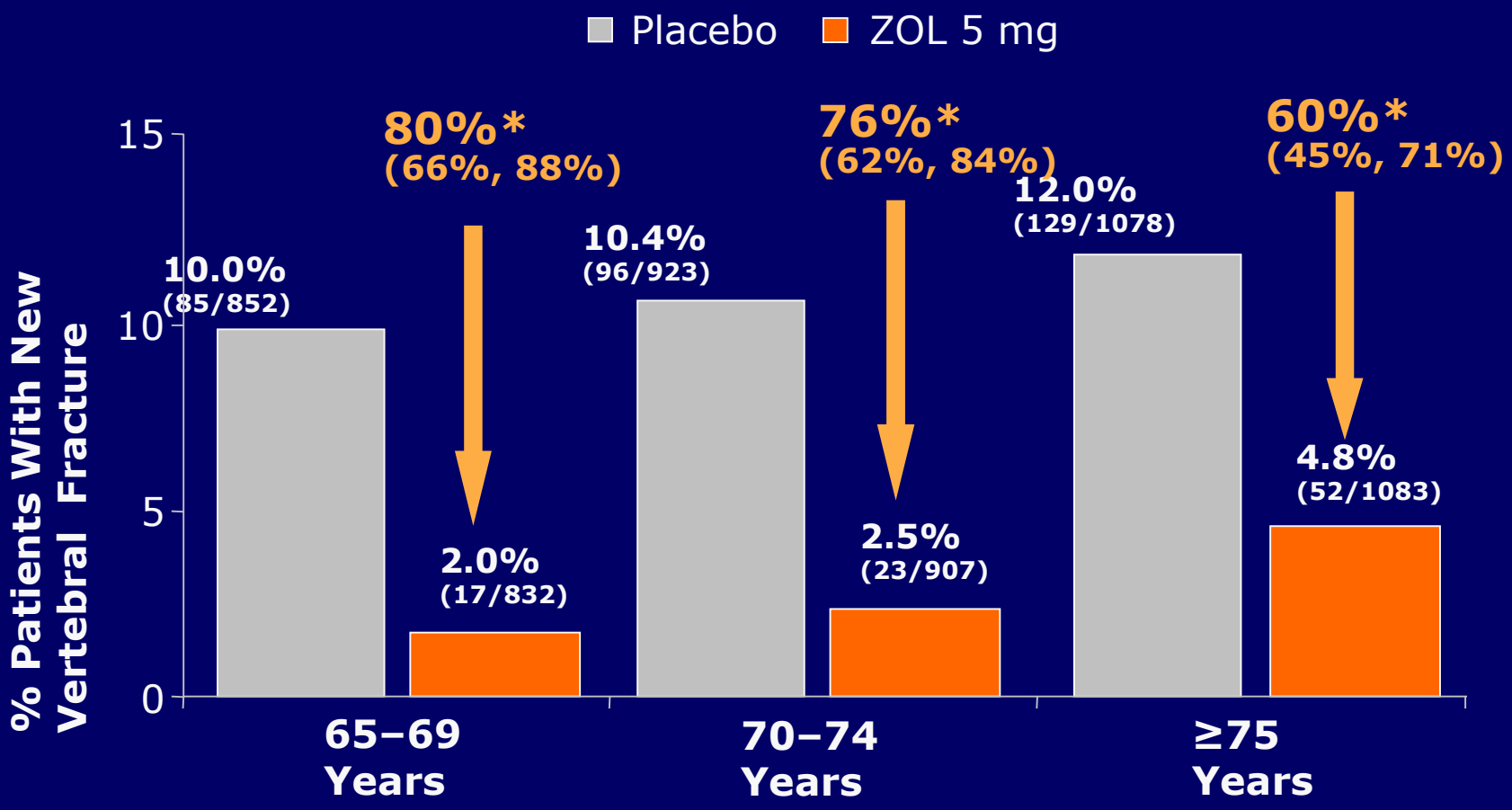
Zoledronic Acid Reduced 3-Year Risk of New Vertebral Fractures (by Baseline Prevalence)



*P < .0001, relative risk reduction vs placebo.

Cauley J, et al. *Osteoporos Int*. 2007;18(suppl 1):S26. Abstract OC53.

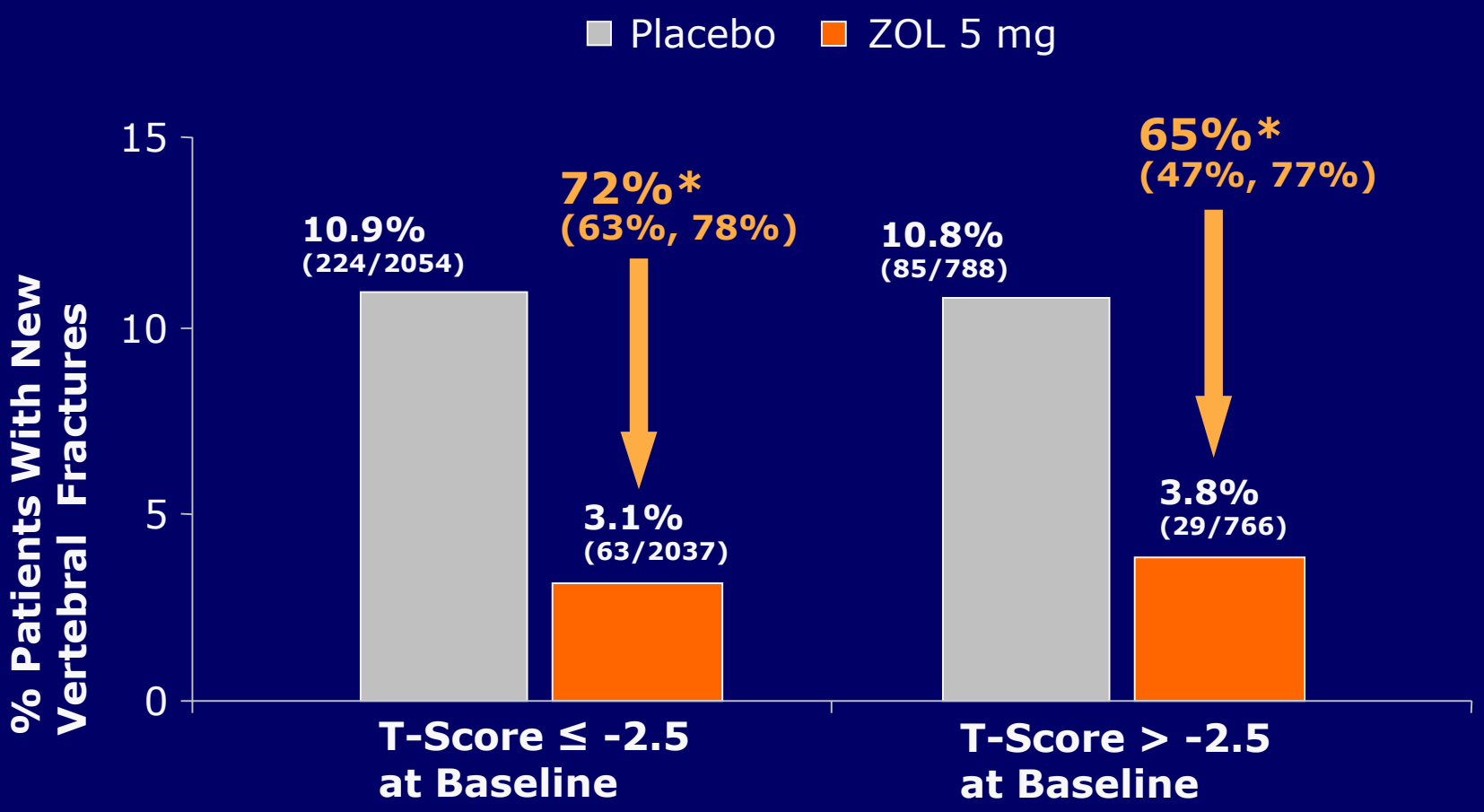
Zoledronic Acid Reduced 3-Year Risk of Vertebral Fractures (by Age)



*P < .0001, relative risk reduction vs placebo.

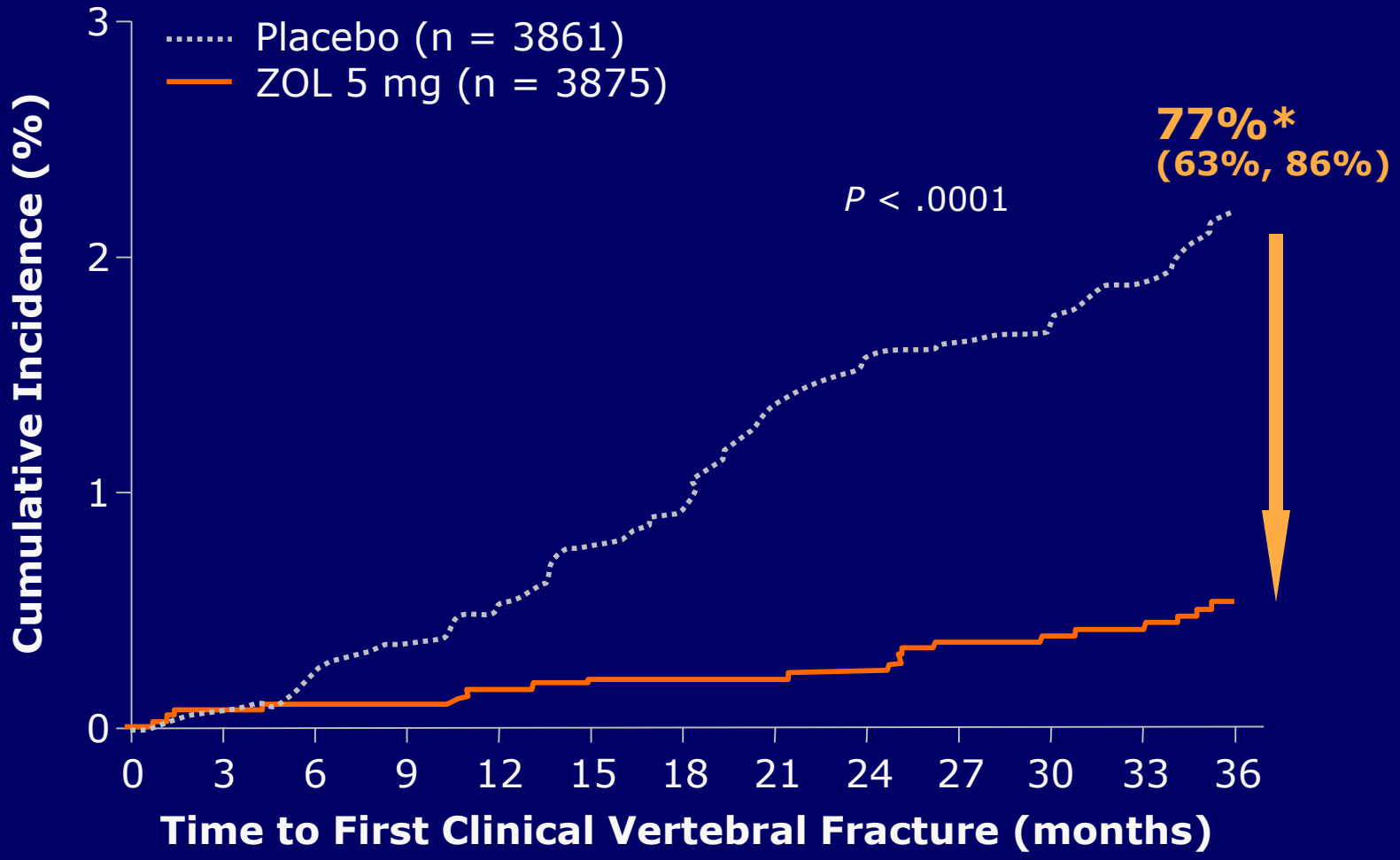
Cauley J, et al. *Osteoporos Int*. 2007;18(suppl 1):S26. Abstract OC53.

Zoledronic Acid 5 mg Reduced 3-Year Risk of Vertebral Fractures (by Baseline BMD T-Score)



*P < .0001, relative risk reduction vs placebo (95% confidence interval)
Data on file, Novartis

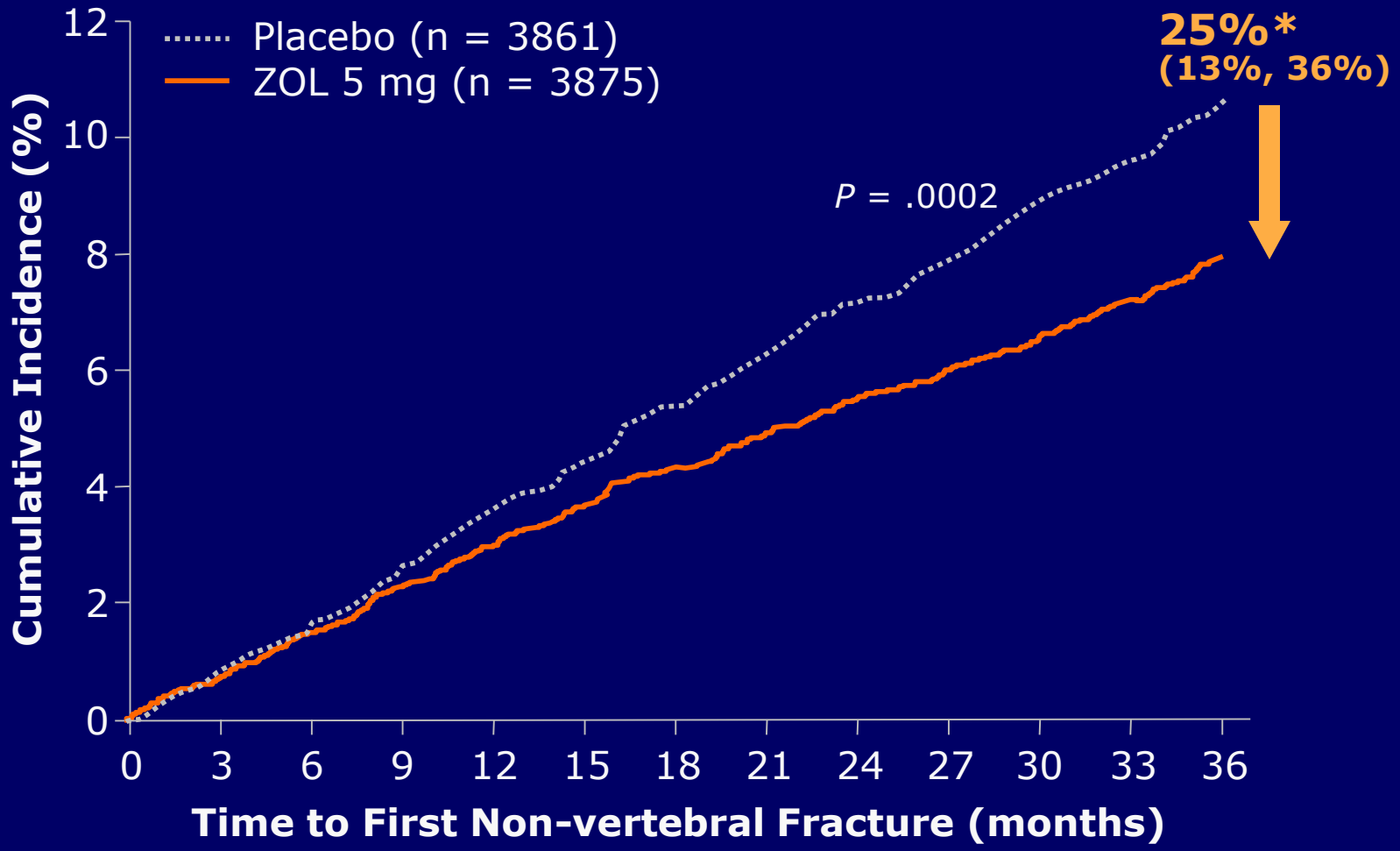
Zoledronic Acid Reduced Cumulative 3-Year Risk of Clinical Vertebral Fractures (Strata I + II) by 77%



*Relative risk reduction vs placebo (95% confidence interval)

Adapted from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

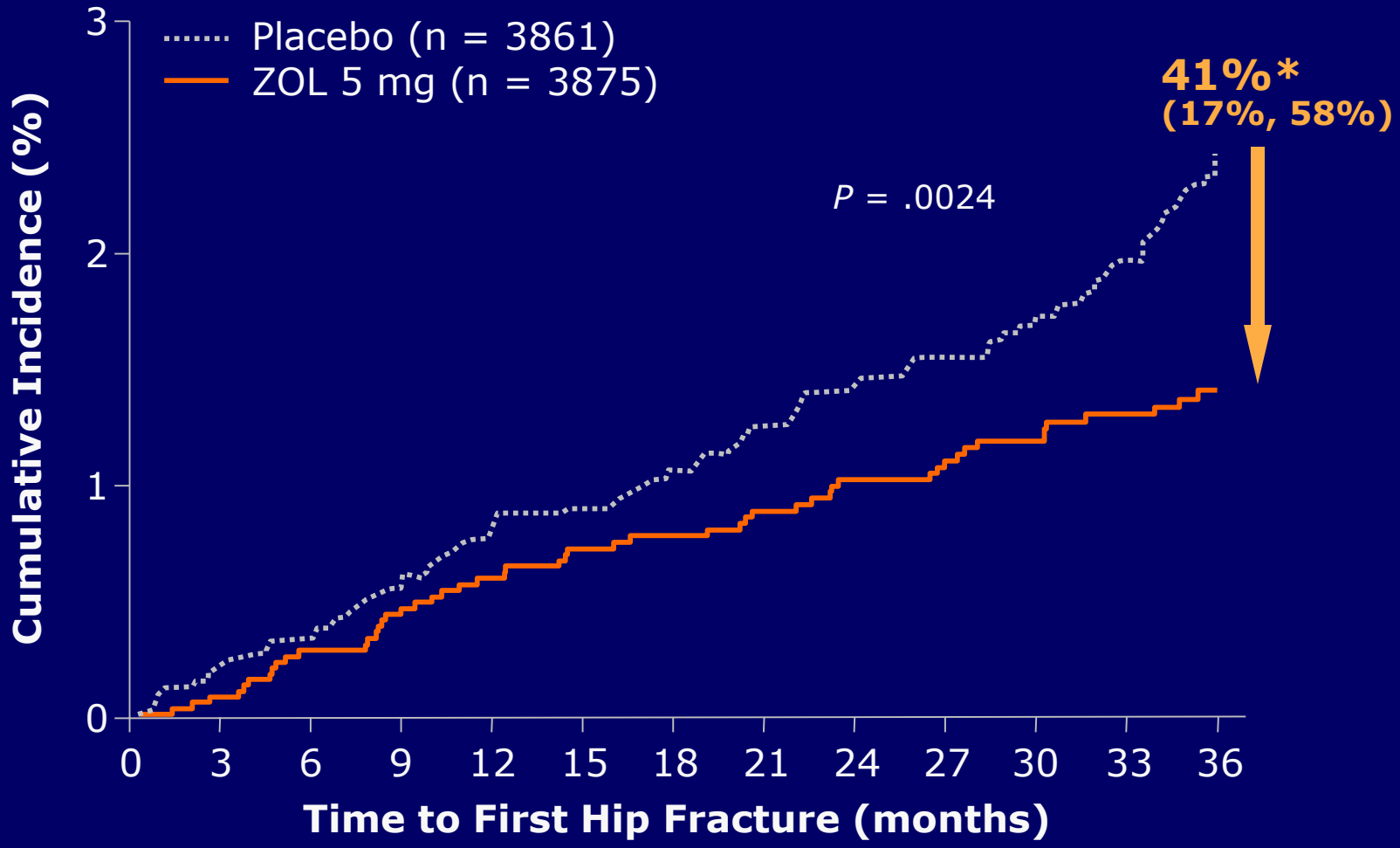
Zoledronic Acid Reduced Cumulative 3-Year Risk of Non-vertebral Fractures (Strata I + II) by 25%



*Relative risk reduction vs placebo (95% confidence interval)

Adapted from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

Zoledronic Acid Reduced Cumulative 3-Year Risk of Hip Fractures (Strata I + II) by 41%

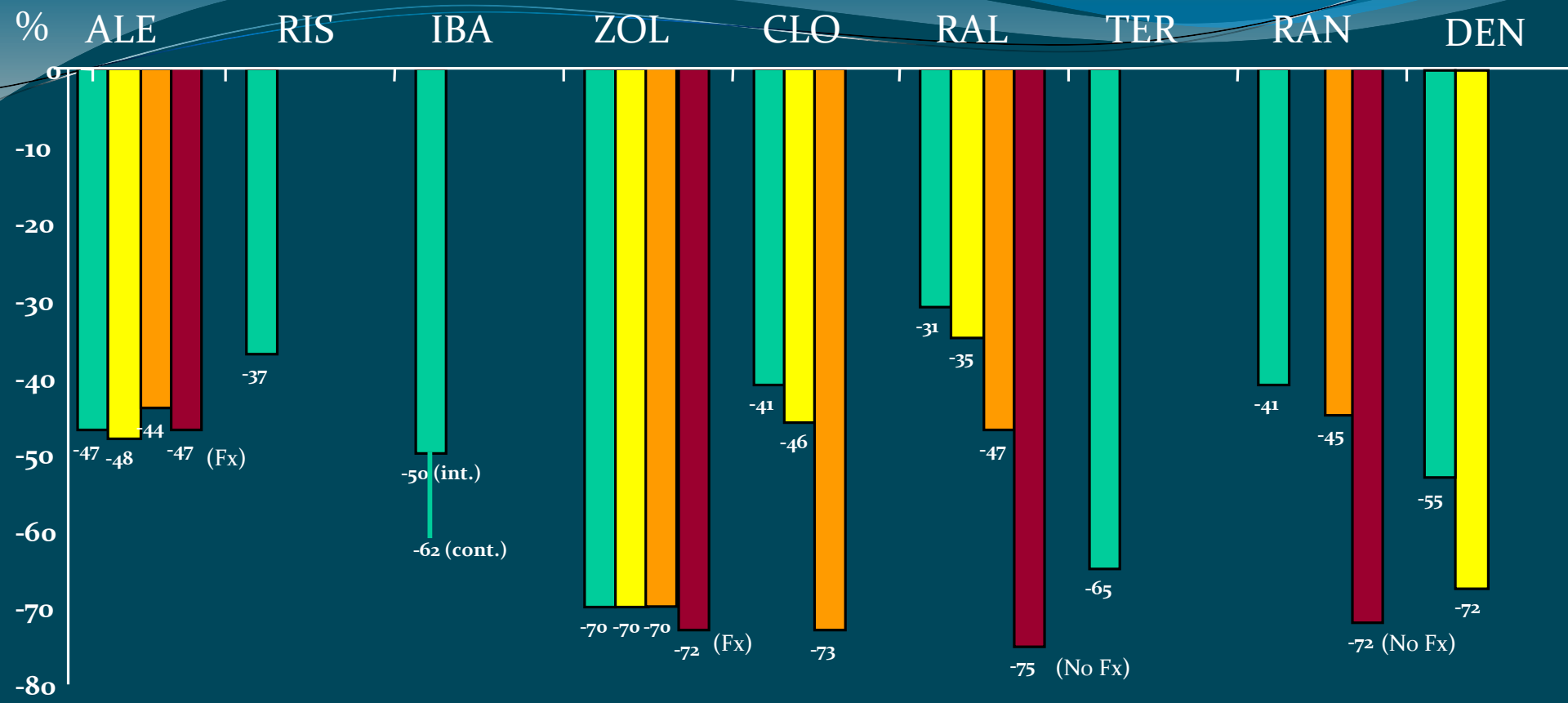


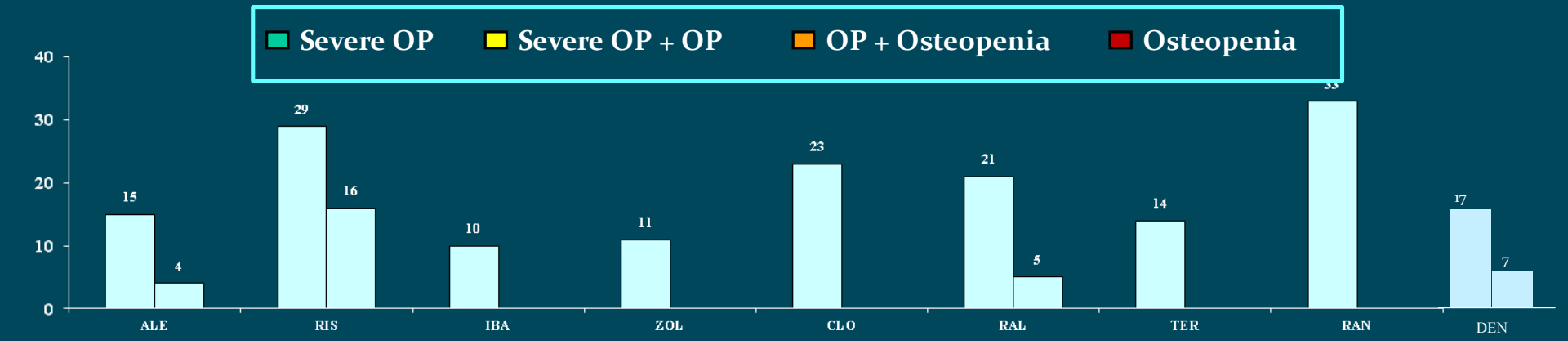
*Relative risk reduction vs placebo (95% confidence interval)

Adapted from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

efficacia

Vertebral Fracture risk reduction PMO





Fracture Risk in control Group

DMAB vs BP

ournal of Orthopaedic Surgery and Research (2018) 13:194
.org/10.1186/s13018-018-0865-3

Journal of Orthopaedic Surgery and Research

RESEARCH ARTICLE Open Access

Denosumab compared to bisphosphonates to treat postmenopausal osteoporosis: a meta-analysis

Jiaqi Wu, Qingsheng Zhang, Guanghui Yan and Xianhui Jin*

Fig. 4 Forest plots of the included studies comparing the risk of fracture

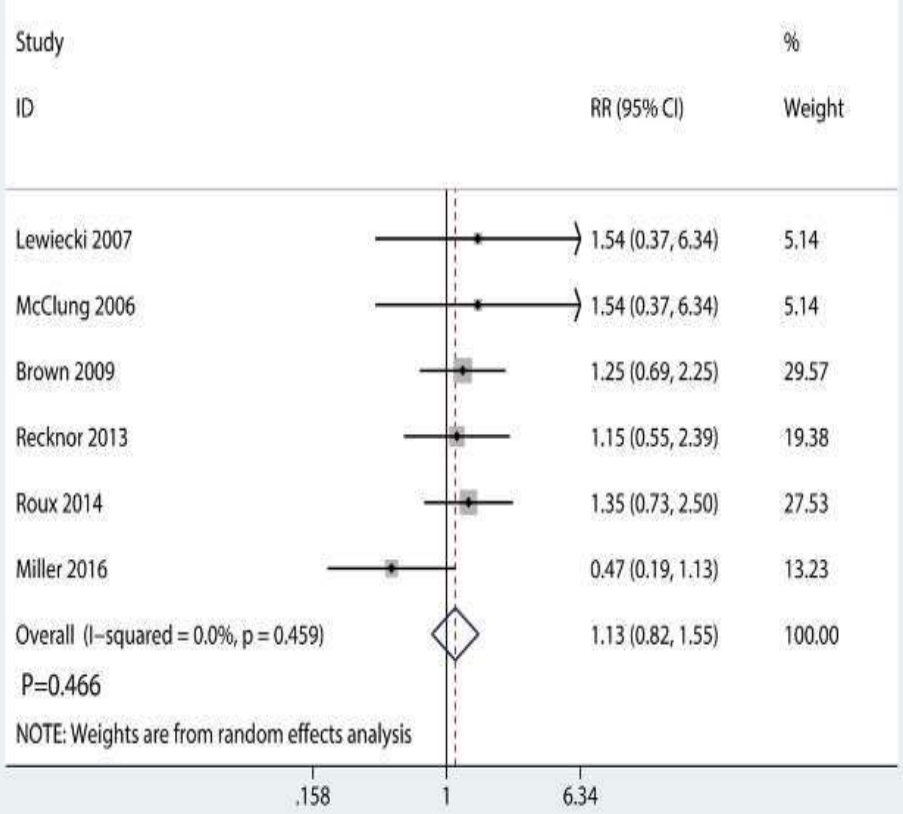


Table 2 Subgroup analysis of the risk of fracture

Subgroup	No. of included studies	RR (95% CI)	I^2 (%)
Comparator treatment			
Alendronate	3	1.10 (0.95, 1.23)	12.3
Ibandronate	1	1.08 (0.89, 1.16)	–
Risedronate	1	1.23 (0.75, 1.08)	–
Zoledronic acid	1	0.86 (0.74, 0.99)	–
Population who had been prescribed a treatment for osteoporosis			
No (< 100% of participants)	4	1.15 (0.67, 1.22)	0.0
No (> 100% of participants)	3	1.12 (0.85, 1.08)	0.0
High or unclear risk of bias			
No	2	1.09 (0.74, 1.26)	0.0
Yes	5	1.31 (0.89, 1.14)	0.0

Prevenzione secondaria in soggetti con pregresse fratture osteoporotiche

- **vertebrali o di femore**

Condizione	Trattamento I scelta [a]	II scelta	III scelta
1-2 fratture [b]	Alendronato (± vit.D), Risedronato, Zoledronato [d],	Denosumab [e], Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato [f]
≥ 3 fratture	Teriparatide [g]	Denosumab [e], Zoledronato [d]	Alendronato (± vit.D), Risedronato, Ibandronato Stronzio ranelato [f]
≥ 1 frattura + T-score colonna o femore [c] ≤ -4			
≥ 1 frattura + trattamento > 12 mesi con prednisone o equivalenti ≥ 5 mg/die			
Nuova frattura vertebrale o femorale nonostante trattamento in nota 79 da almeno 1 anno			

- **non vertebrali e non femorali**

+ T-score colonna o femore ≤ -3	Alendronato (± vit.D), Risedronato, Zoledronato [d],	Denosumab [e], Ibandronato, Raloxifene, Bazedoxifene	Stronzio ranelato [f]

AGENZIA ITALIANA DEL FARMACO

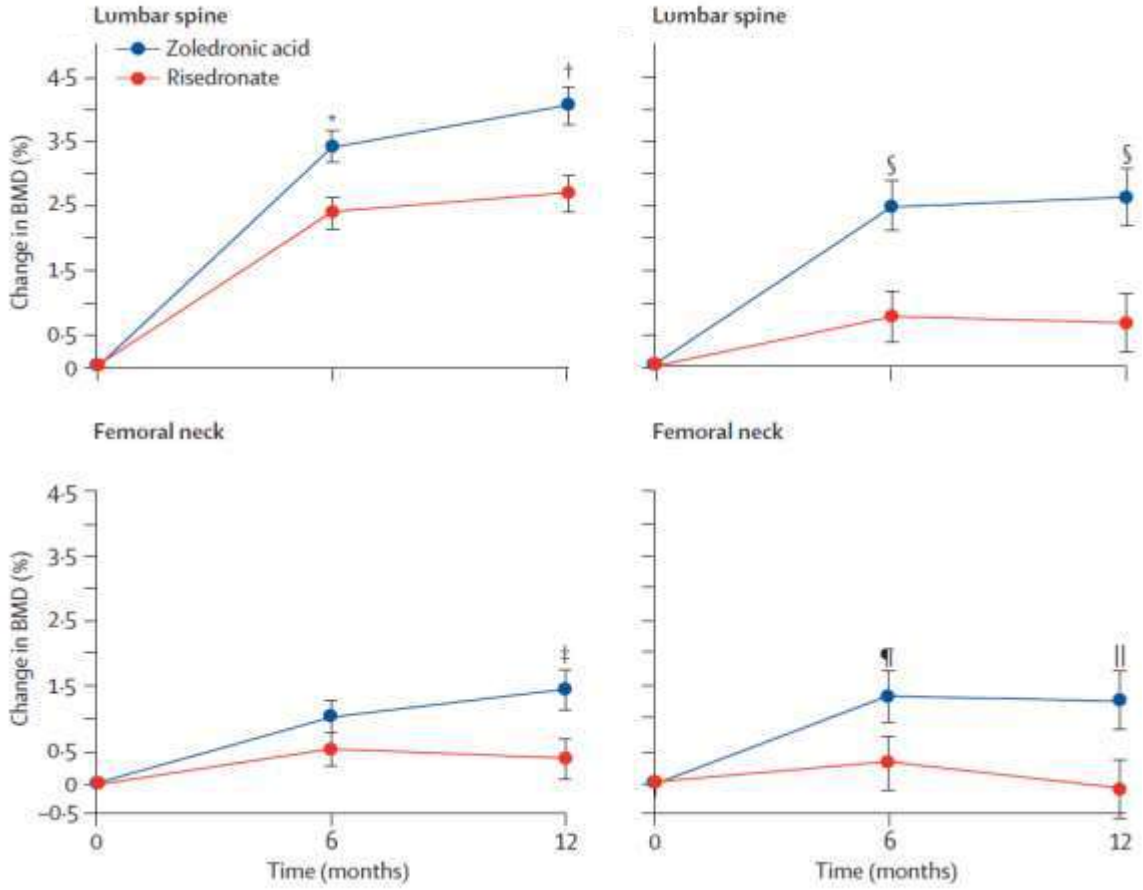
Prevenzione primaria in donne in menopausa o uomini di età ≥ 50 anni a rischio elevato di frattura a causa di almeno una delle condizioni sottoelencate:

Condizione	I scelta [a]	II scelta	III scelta
Trattamento in atto o previsto per > 3 mesi con prednisone equivalente ≥ 5 mg/die	Alendronato (± vitD), Risedronato, Zoledronato [d],	denosumab	----------
Trattamento in corso di blocco ormonale adiuvante in donne con carcinoma mammario o uomini con carcinoma prostatico	Alendronato (± vitD), Risedronato, Zoledronato [d], Denosumab [e]	----------	----------
T-score colonna o femore [c] ≤ -4	Alendronato (± vit.D), Risedronato,	Denosumab [e], Zoledronato [d], Ibandronato Raloxifene, Bazedoxifene	Stronzio ranelato [f]
T-score colonna o femore [c] ≤ -3 + almeno una delle seguenti condizioni: 1) Familiarità per fratture di vertebre o femore 2) Comorbilità a rischio di frattura (artrite reumatoide o altre connettiviti, diabete, broncopneumopatia cronica ostruttiva, malattia infiammatoria cronica intestinale, AIDS, parkinson,			

Lancet 2009

Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial

David M Reid, Jean-Pierre Devogelaer, Kenneth Saag, Christian Roux, Chak-Sing Lau, Jean-Yves Reginster, Philemon Papanastasiou, Alberto Ferreira, Florian Hartl, Taiwo Fashola, Peter Mesenbrink, Philip N Sambrook, for the HORIZON investigators



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EFFICACIA BLOCCO ORMONALE

Osteoporosis and Sarcopenia 5 (2019) 128–131

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

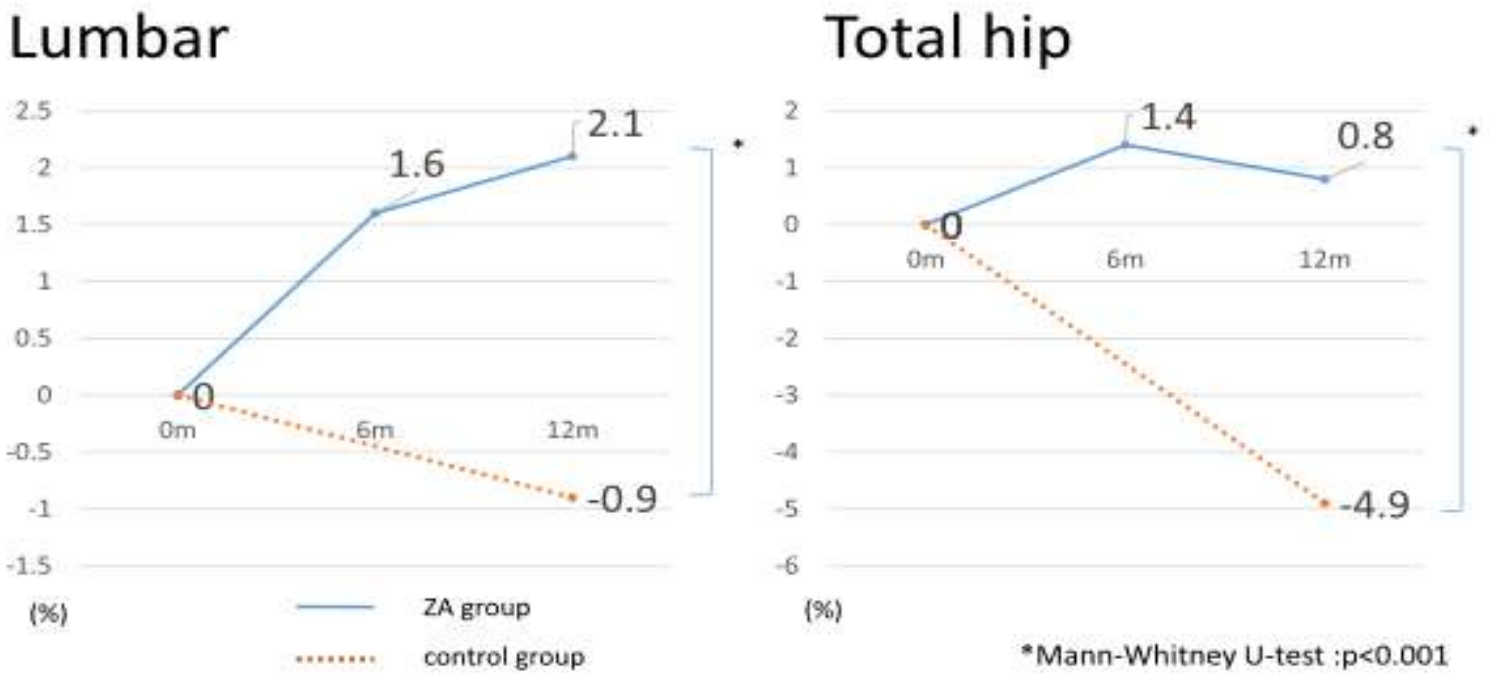
journal homepage: http://www.elsevier.com/locate/afos

Original article

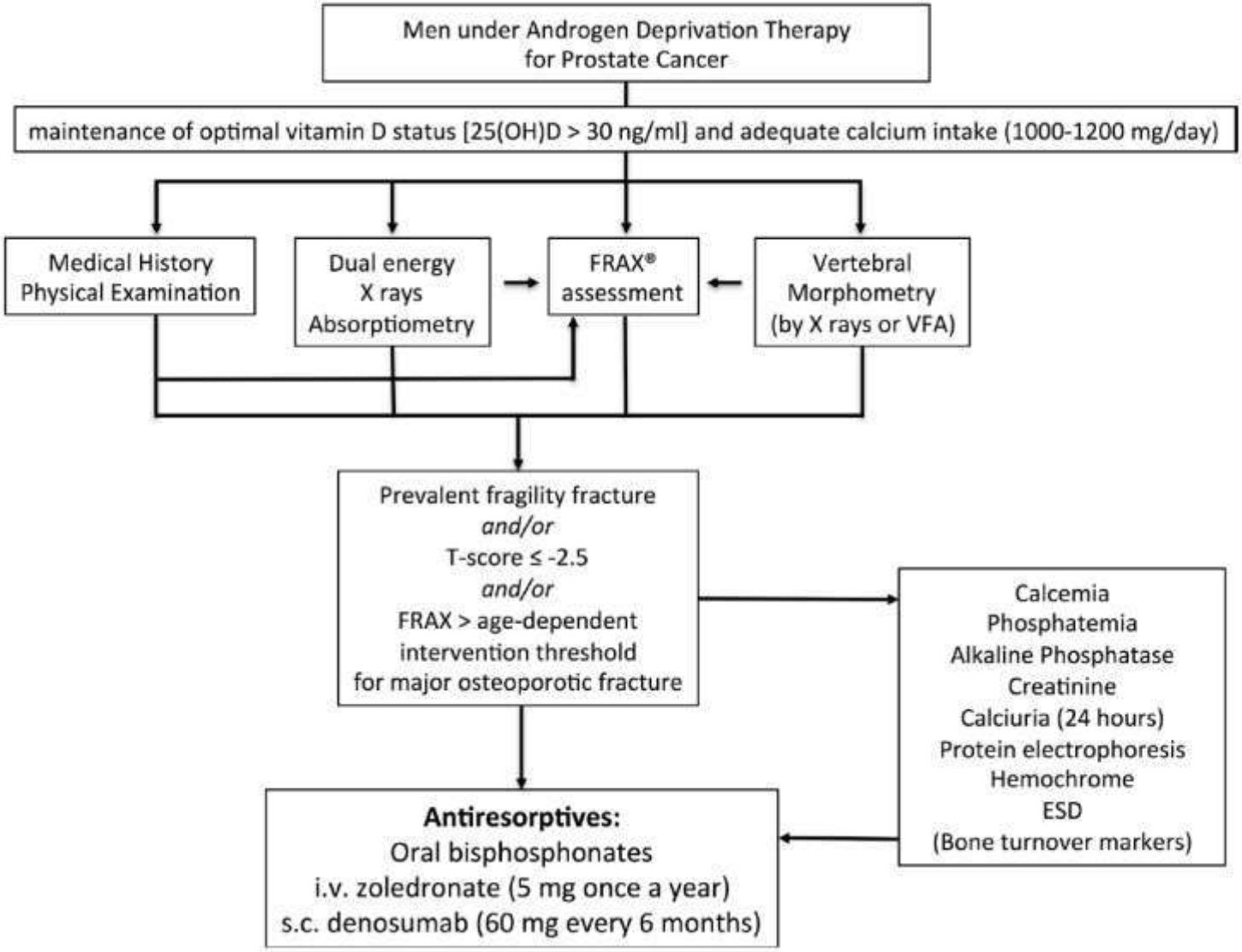
Efficacy of zoledronic acid in older prostate cancer patients undergoing androgen deprivation therapy

Ippei Kojima*, Yushi Naito, Akiyuki Yamamoto, Yasuhiro Terashima, Norie Sho, Jun Nagayama, Yurika Okada, Tatsuya Nagai

Department of Urology, Toyohashi Municipal Hospital, 50 Aza Hachiken Nishi, Aotake-Cho, Toyohashi, Aichi, 441-8570, Japan

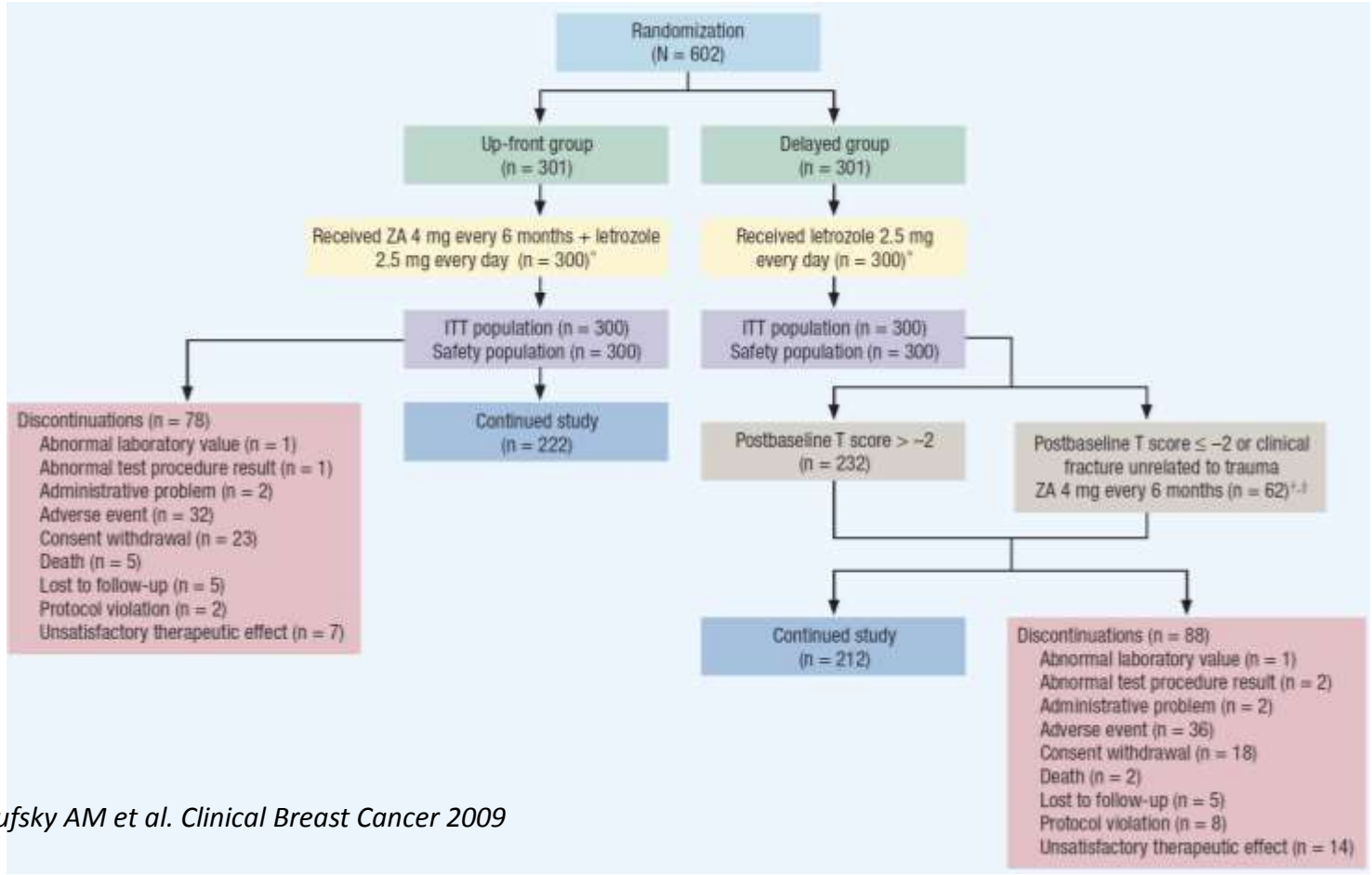


IOF's algorithm for the management of non-metastatic bone disease in prostate cancer patients receiving ADT



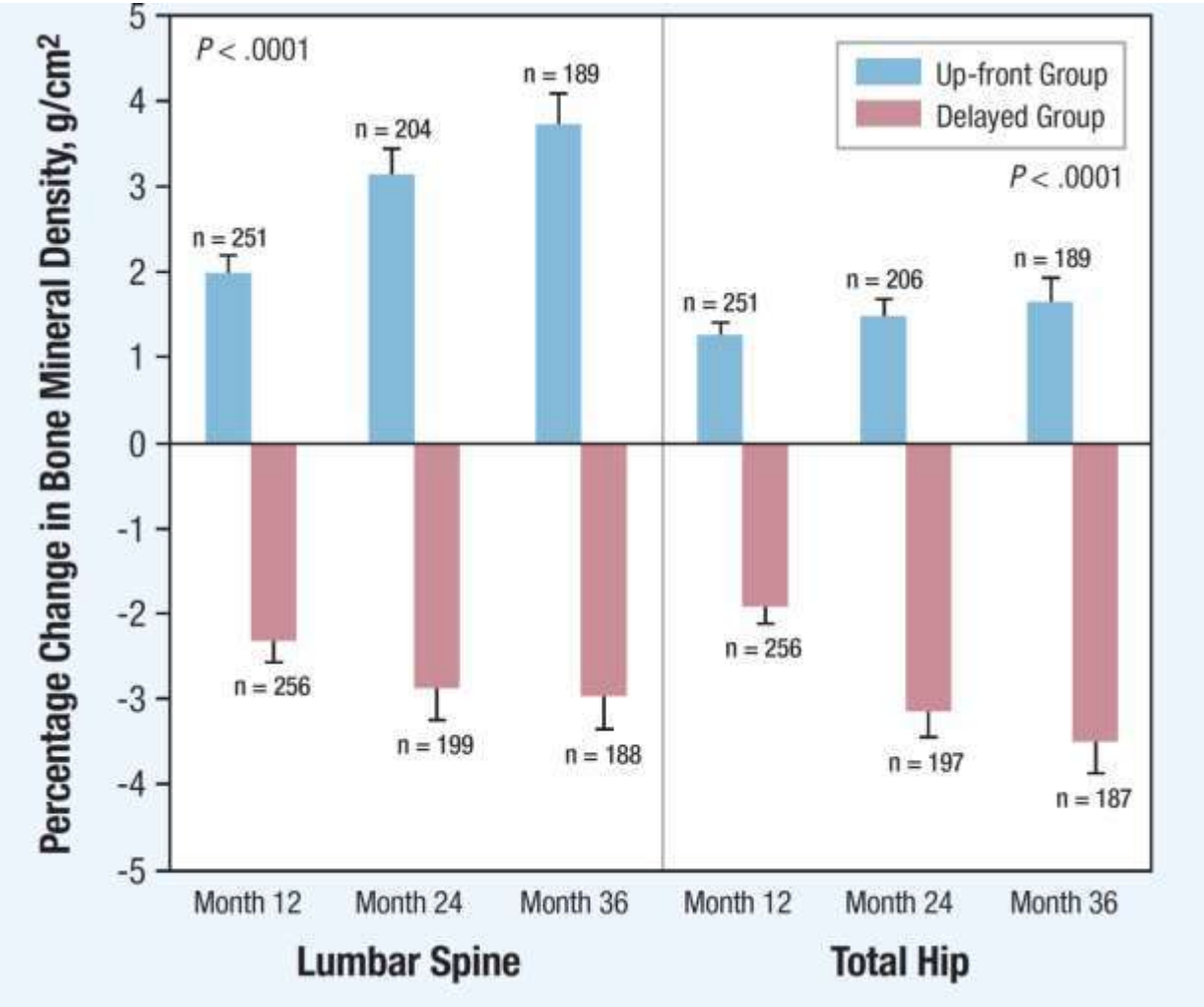
EFFICACIA BLOCCO ORMONALE

Zoledronic Acid Effectively Prevents Aromatase Inhibitor–Associated Bone Loss in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole: Z-FAST Study 36-Month Follow-up Results



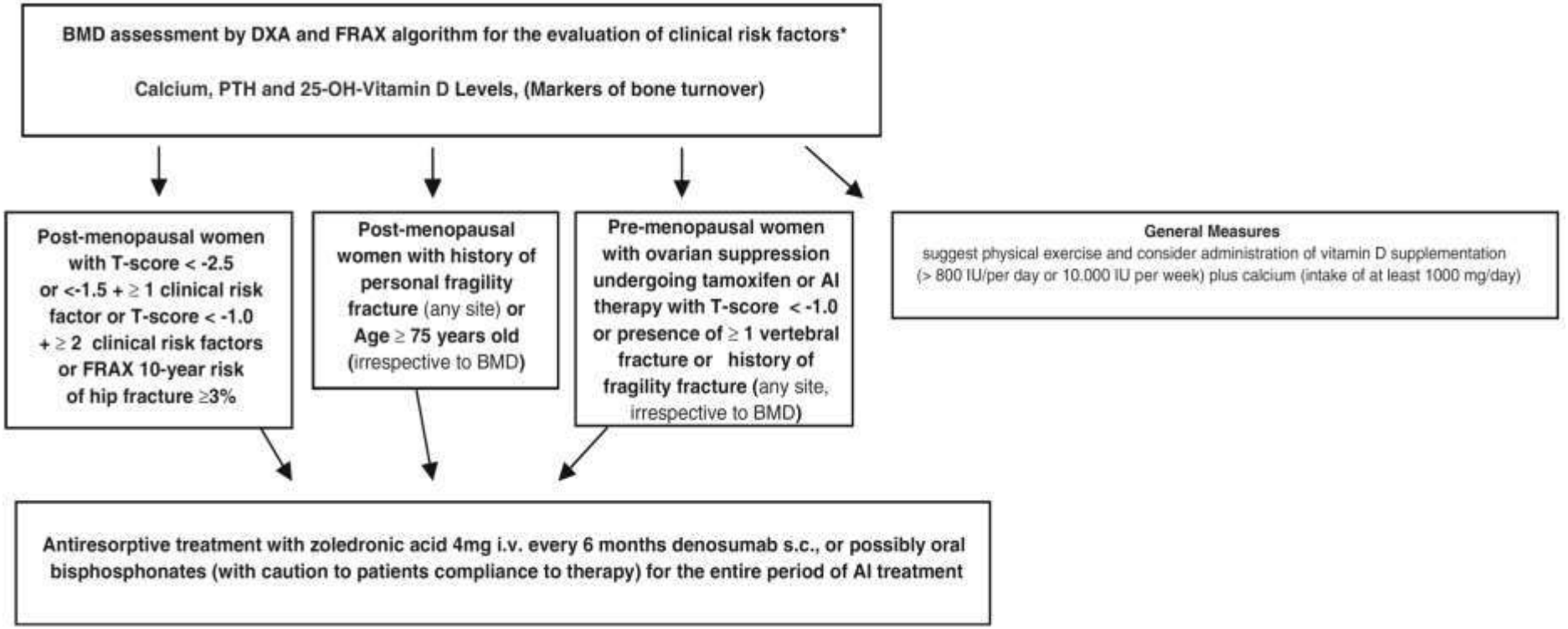
Brufsky AM et al. Clinical Breast Cancer 2009

Change in BMD



Brufsky AM et al. Clinical Breast Cancer 2009

Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper



Rizzoli R e al. Osteoporos Int 2012

AGENZIA ITALIANA DEL FARMACO

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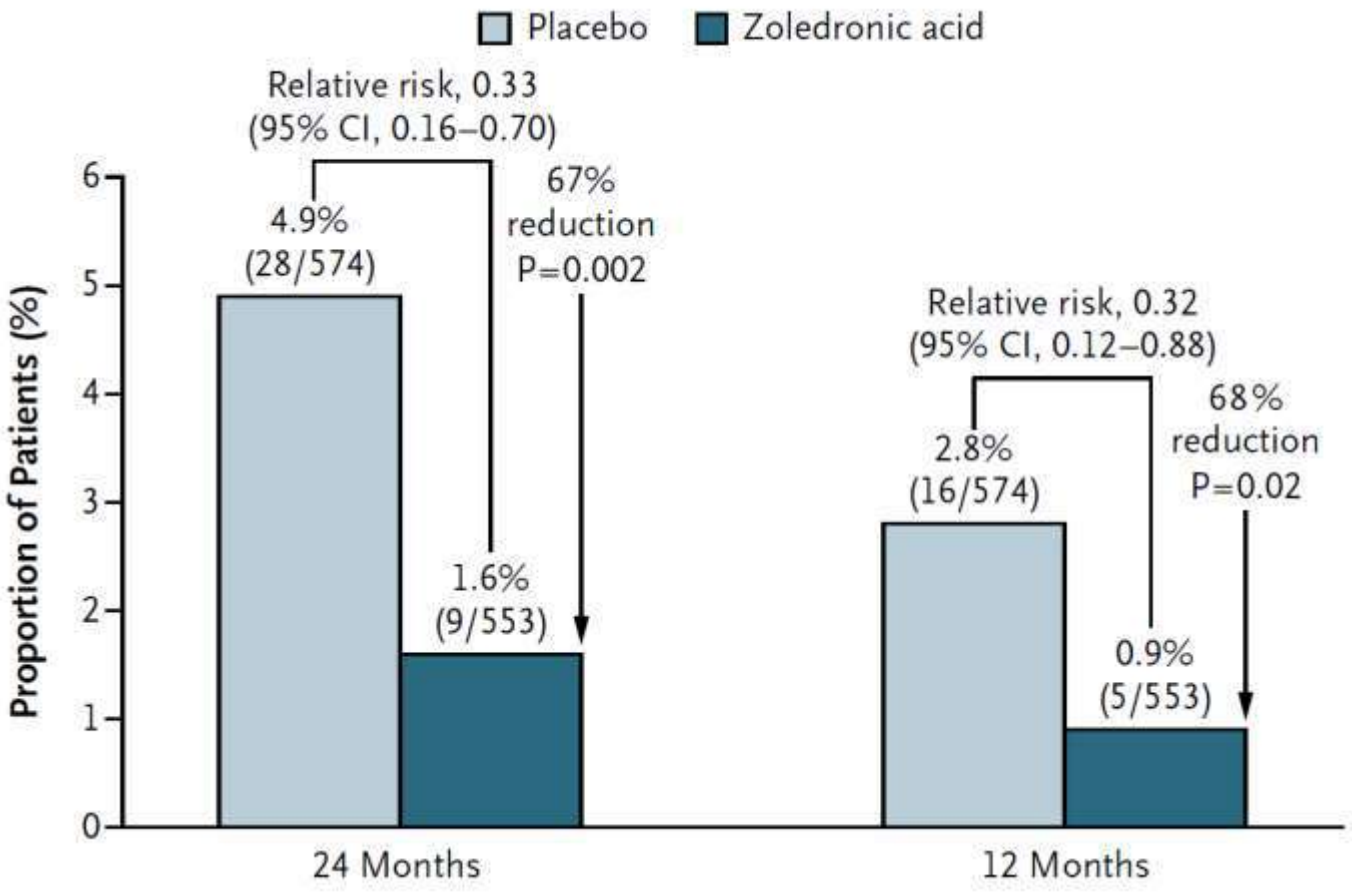
EFFICACIA MASCHIO

Zoledronic Acid Therapy in Men with Osteoporosis

2-Year study including 1199 men with primary or hypogonadism associated OP

Relative risk of new vertebral fracture



Boonen S et al. N Engl J Med 2012

TERAPIE SEQUENZIALI E DI COMBINAZIONE CON BISFOSFONATI

Bisfosfonati ⟶ Teriparatide (Zol + TPT) (Aln + TPT ?)

Bisfosfonati ⟶ Denosumab
(Aln)

Denosumab ⟶ Bisfosfonati ⇢ Teriparatide
(Zol)

Teriparatide ⟶ Denosumab (TPT + DMAB)

Terapie sequenziali

Journal of Bone and Mineral Metabolism
https://doi.org/10.1007/s00774-020-01126-w

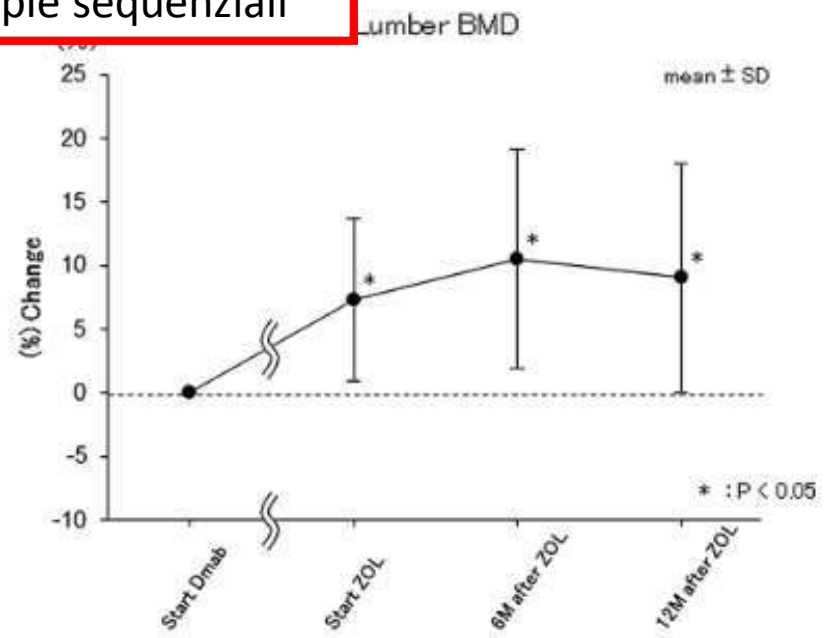
ORIGINAL ARTICLE

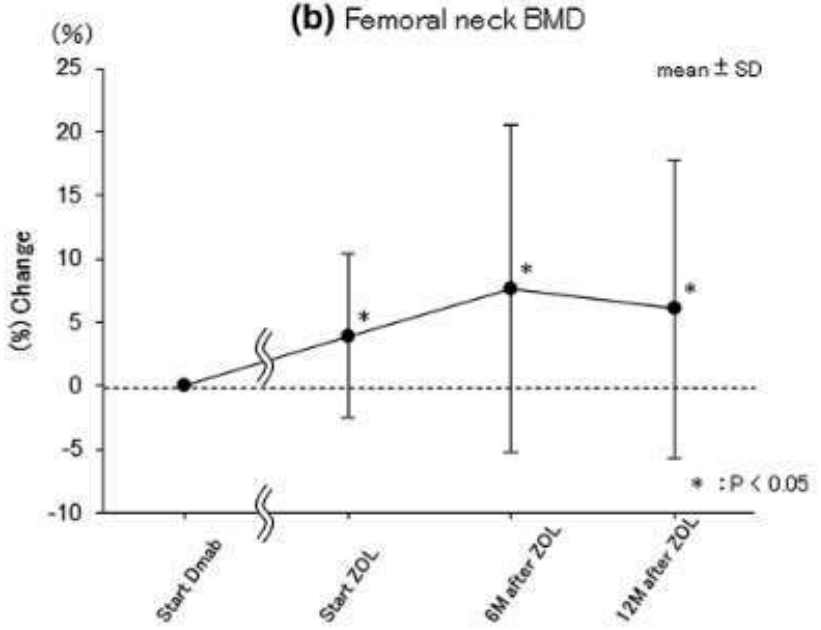
Zoledronic acid sequential therapy could avoid disadvantages due to the discontinuation of less than 3-year denosumab treatment

Hideomi Kondo[1] · Nobukazu Okimoto[2] · Toru Yoshioka[3] · Shojiro Akahoshi[1] · Yoshifumi Fuse[4] · Takayuki Ogawa[5] · Yuichi Okazaki[6] · Yuji Katae[7] · Manabu Tsukamoto[8] · Yoshiaki Yamanaka[8] · Makoto Kawasaki[8] · Akinori Sakai[8]

Received: 27 April 2020 / Accepted: 30 June 2020

Terapie sequenziali





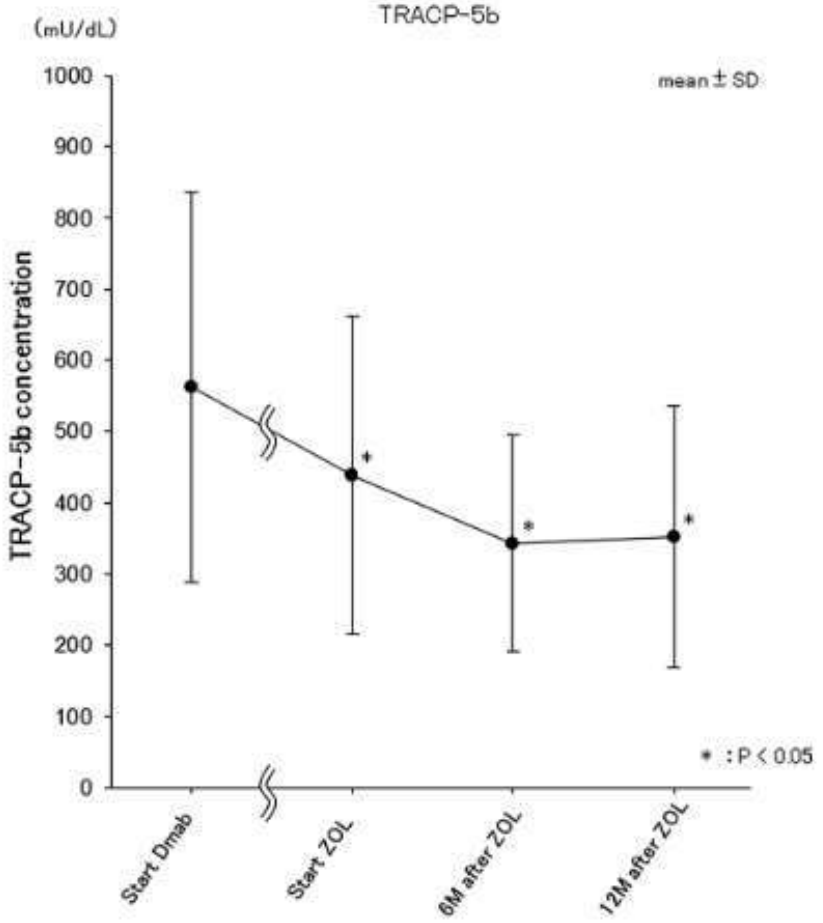
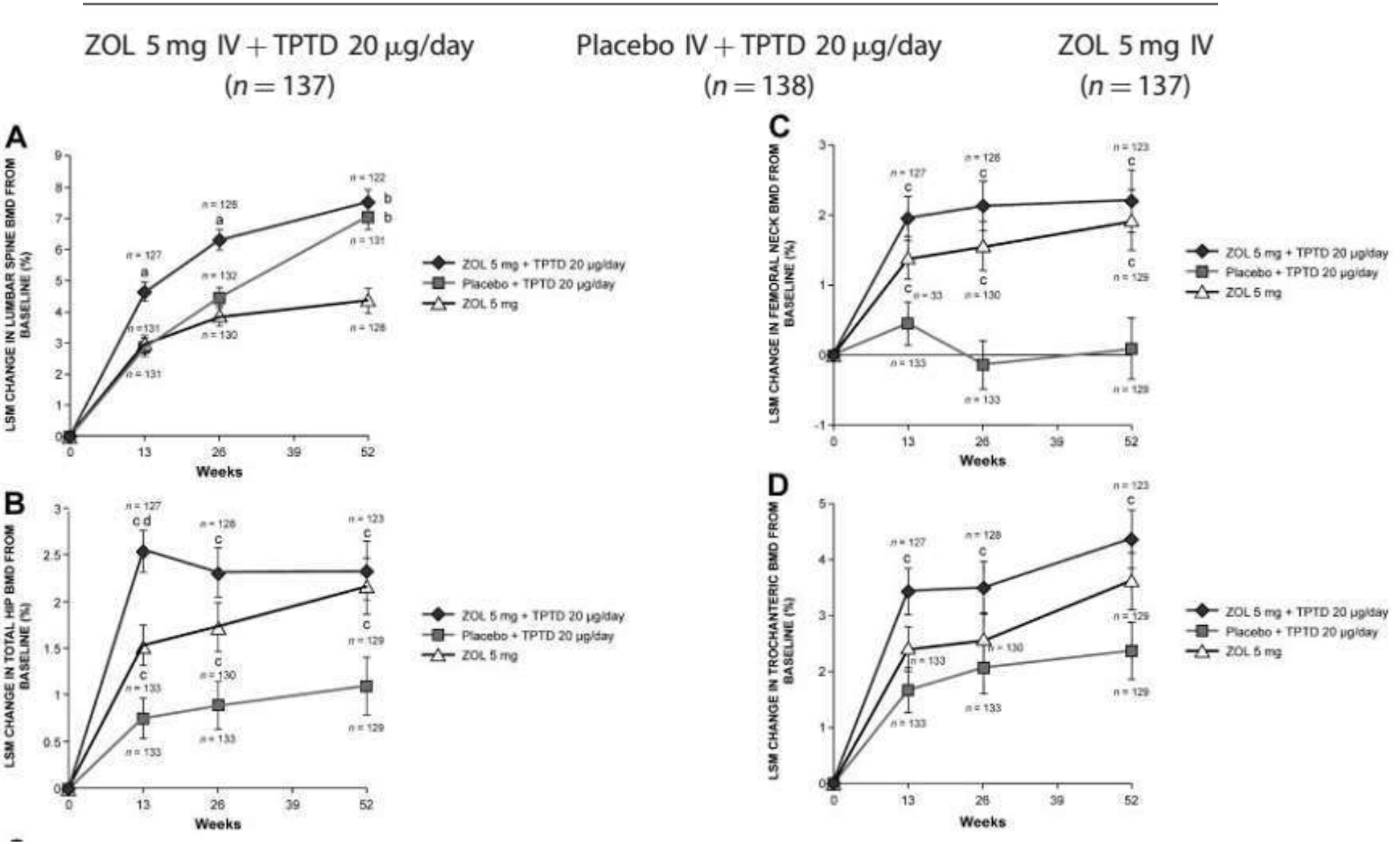


Fig. 4 The sequential changes in serum TRACP-5b. Value changes of serum TRACP-5b at 4 time points. *Start Dmab* at the start of Dmab administration, *Start ZOL* at the start of ZOL administration, *6 M after ZOL* at 6 months after ZOL administration, *12 M after ZOL* at 12 months after ZOL administration. Data are the mean ± SD. $^{*}p < 0.05$ vs. Start Dmab

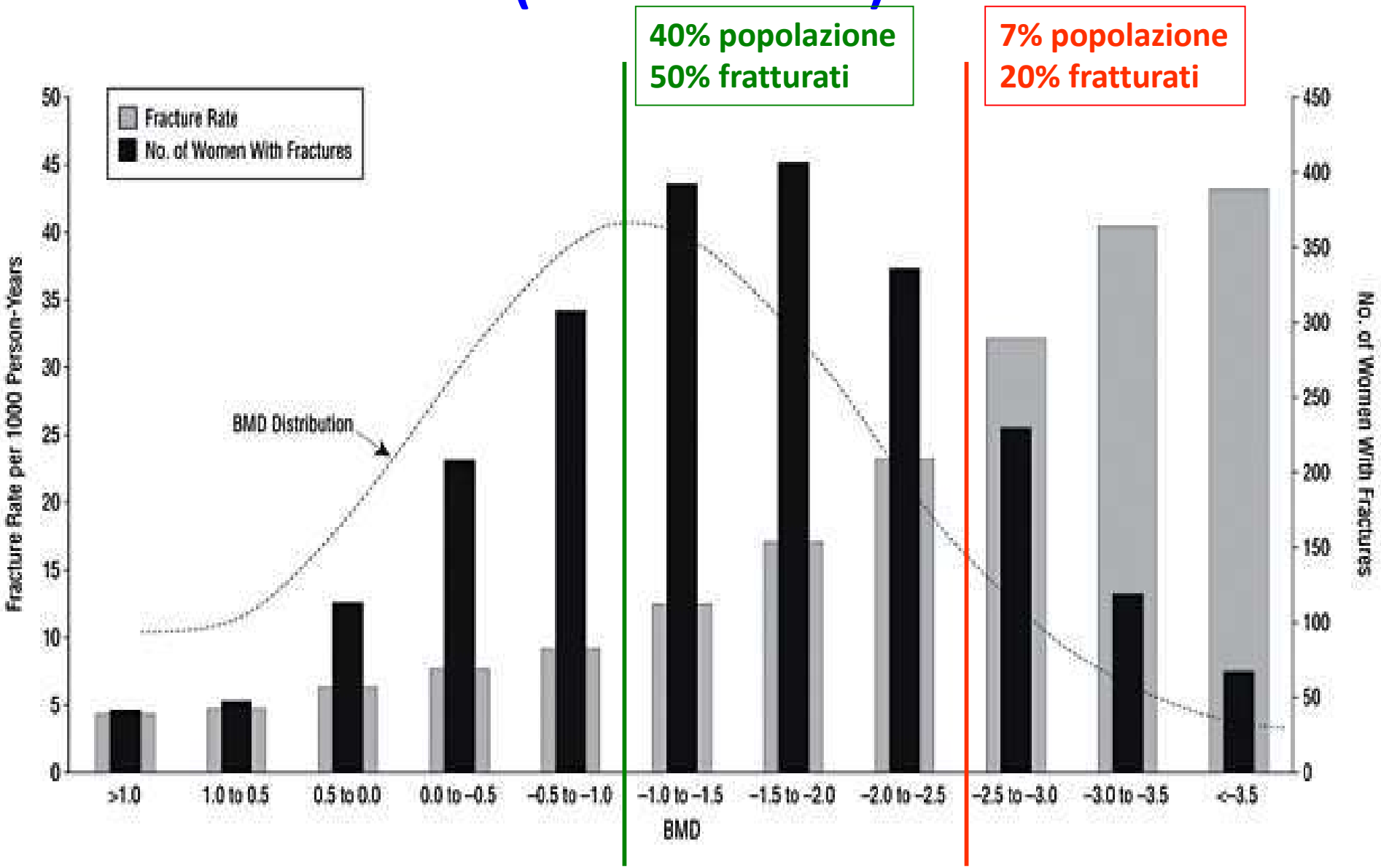
of ZOL on the adverse events after Dmab discontinuation. In our study, we retrospectively investigated new fragility fracture incidence, safety, and changes of BMD and BTM

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

(Felicia Cosman, Erik Fink Eriksen et al)



La maggior parte dei fratturati non è osteoporotica (Studio NORA)



Siris ES, Arch Intern Med, 2004

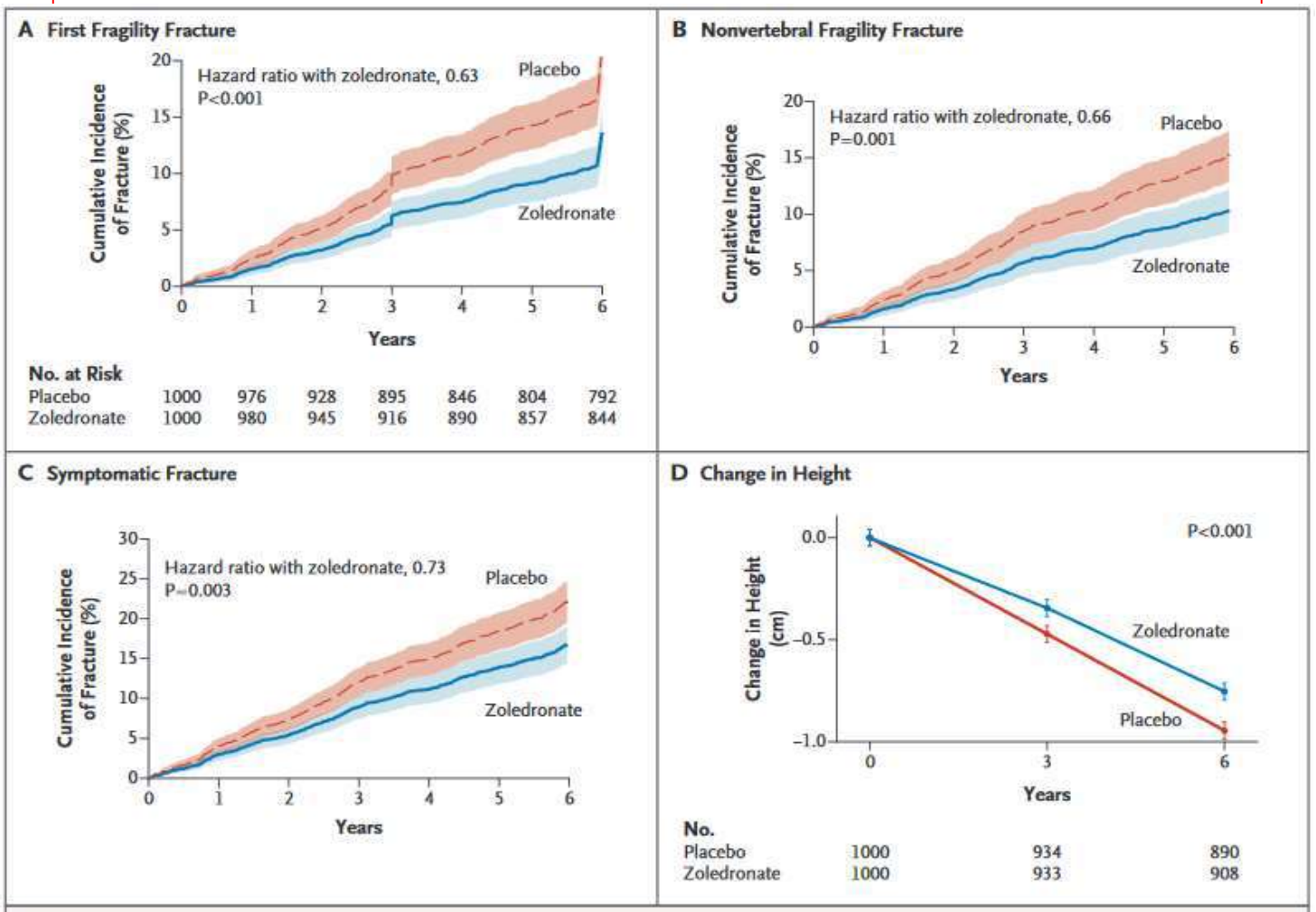
Efficacia OSTEOPENIA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fracture Prevention with Zoledronate in Older Women with Osteopenia

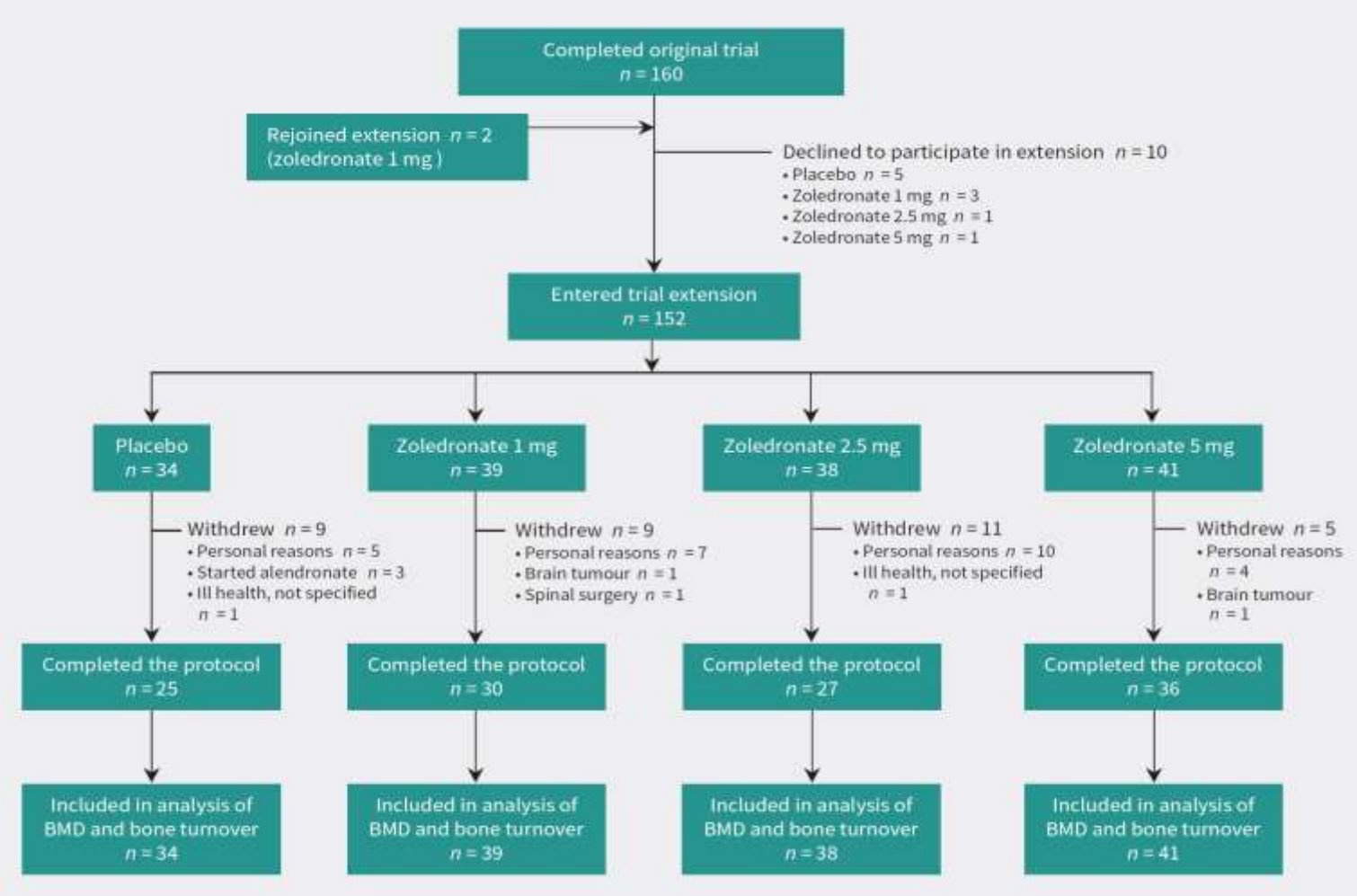
Ian R. Reid, M.D., Anne M. Horne, M.B., Ch.B., Borislav Mihov, B.Phty., Angela Stewart, R.N., Elizabeth Garratt, B.Nurs., Sumwai Wong, B.Sc., Katy R. Wiessing, B.Sc., Mark J. Bolland, Ph.D., Sonja Bastin, M.B., Ch.B., and Gregory D. Gamble, M.Sc.



Efficacia OSTEOPENIA

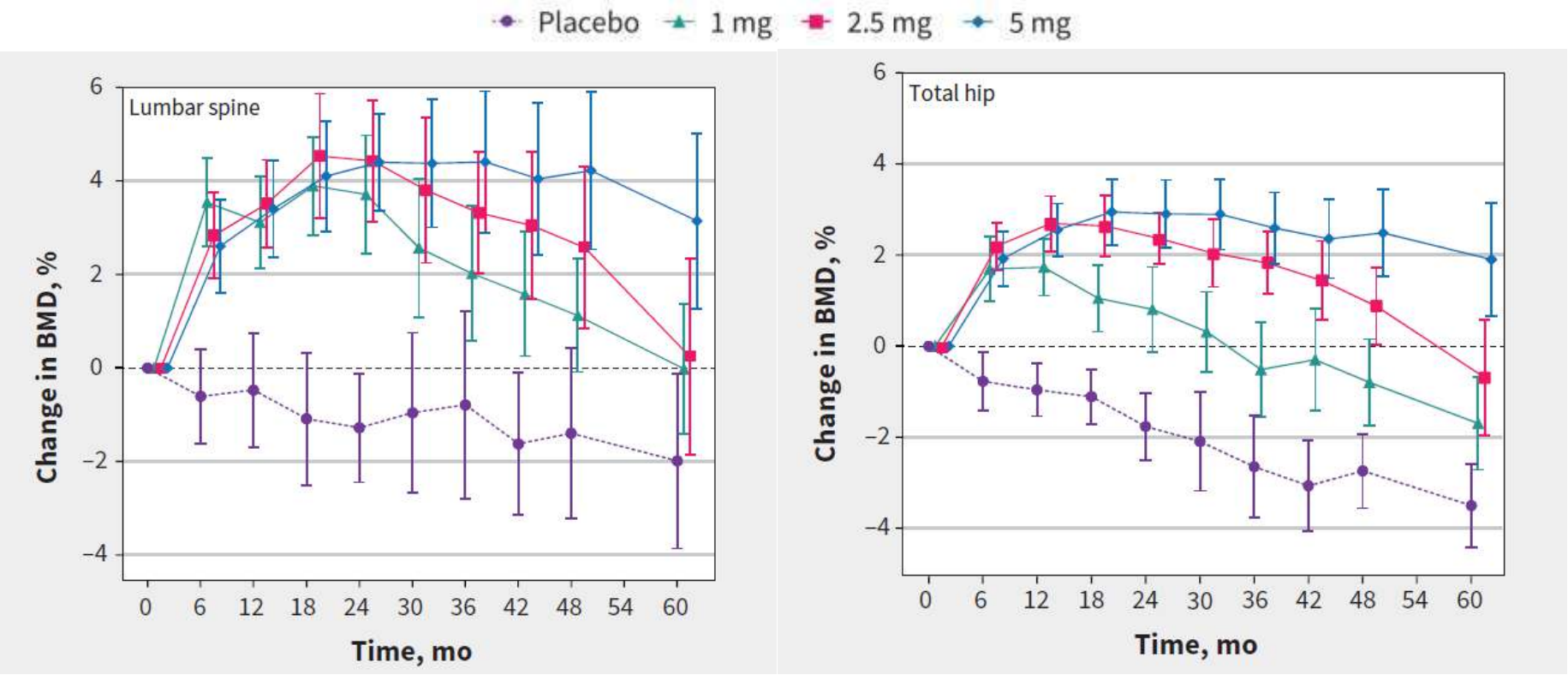
n of antiresorptive activity of zoledronate in postmenopausal women with osteopenia: a randomized, controlled multidose trial

Andrew Grey MD, Mark J. Bolland PhD, Anne Horne MBChB, Borislav Mihov BPhty, Greg Gamble MSc, Ian R. Reid MD



Efficacia OSTEOPENIA

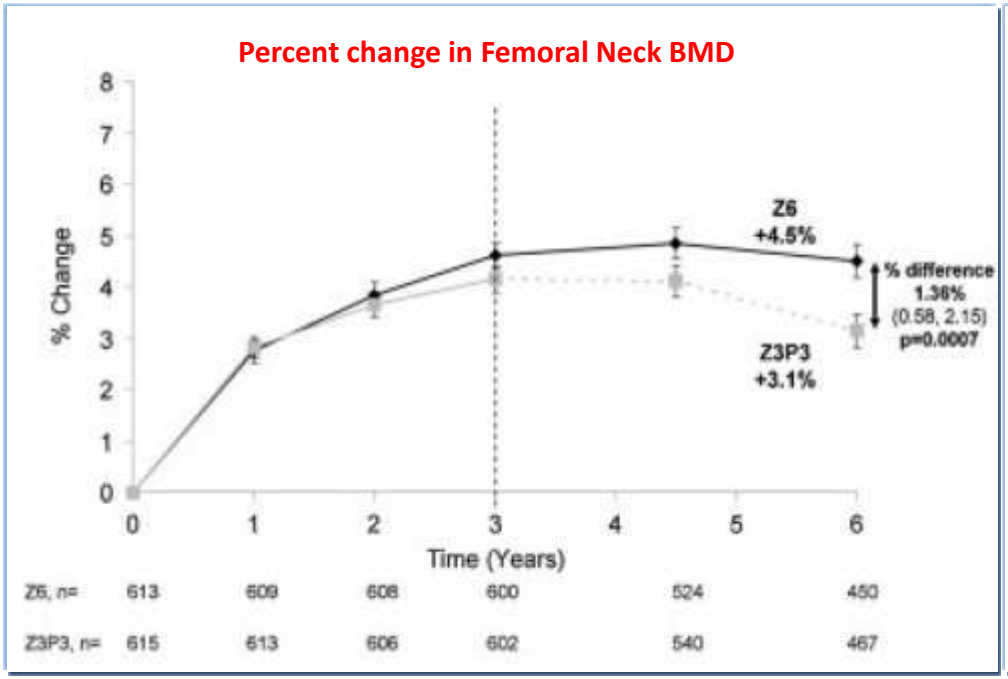
Effects of study treatments on BMD of the lumbar spine and total hip

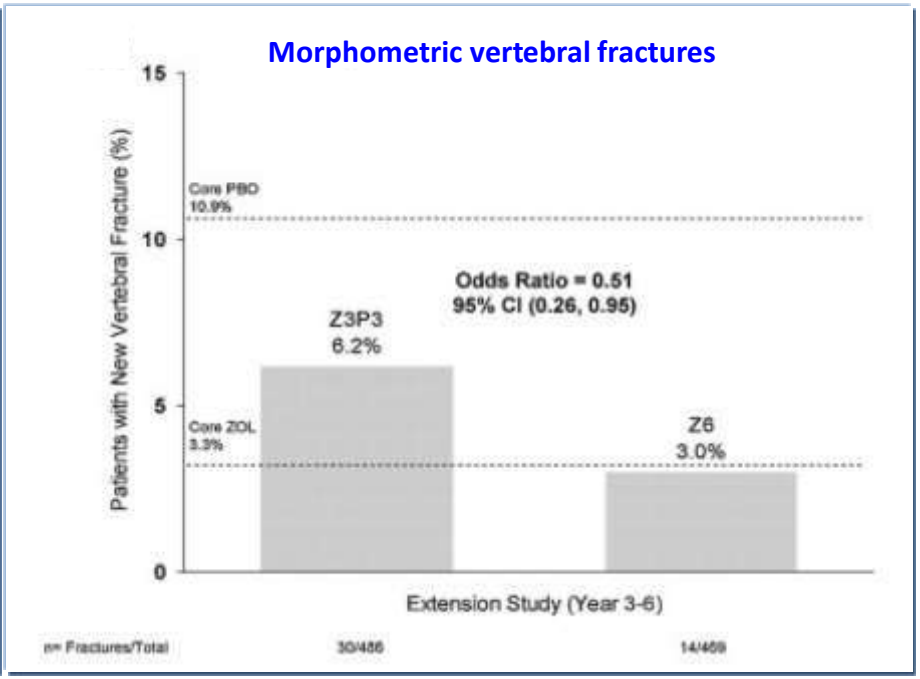


Gray A et al. CMAJ 2017

Efficacia LONG-TERM

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





Black DM et al. J Bone Miner Res 2012

MORTALITA’

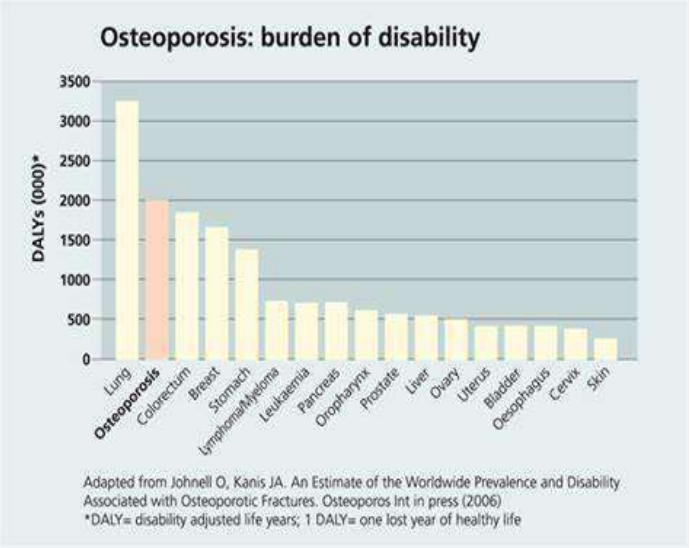
BISFOSFONATI E MORTALITA’ DA OSTEOPOROSI

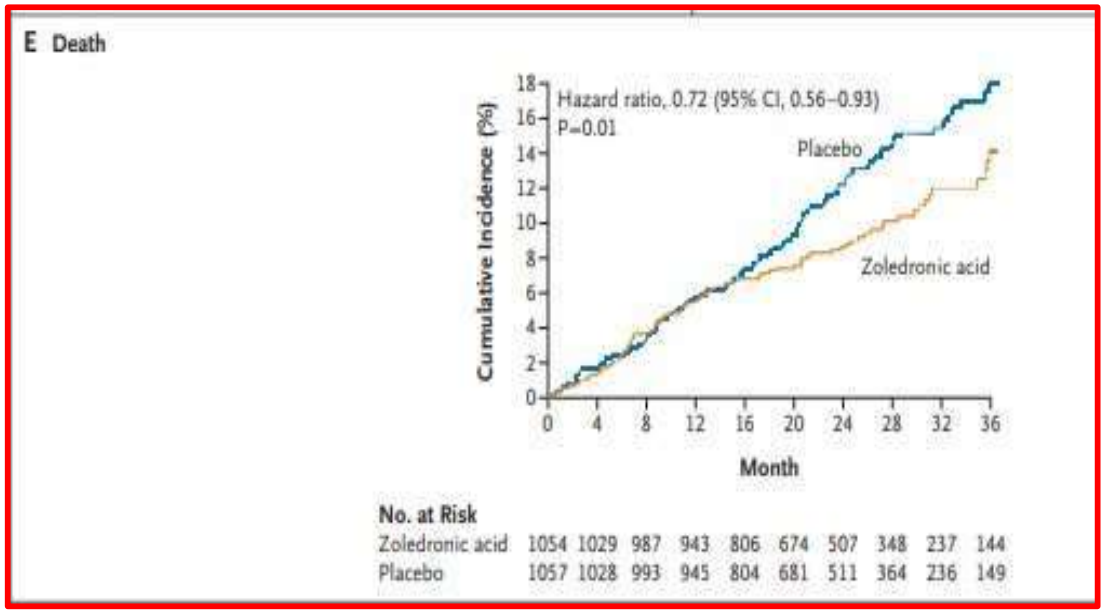
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 1, 2007 VOL. 357 NO. 18

Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

Kenneth W. Lyles, M.D., Cathleen S. Colón-Emeric, M.D., M.H.Sc., Jay S. Magaziner, Ph.D., Jonathan D. Adachi, M.D., Carl F. Pieper, D.P.H., Carlos Mautalen, M.D., Lars Hyldstrup, M.D., D.M.Sc., Chris Recknor, M.D., Lars Nordsletten, M.D., Ph.D., Kathy A. Moore, R.N., Catherine Lavecchia, M.S., Jie Zhang, Ph.D., Peter Mesenbrink, Ph.D., Patricia K. Hodgson, B.A., Ken Abrams, M.D., John J. Orloff, M.D., Zebulun Horowitz, M.D., Erik Fink Eriksen, M.D., D.M.Sc., and Steven Boonen, M.D., Ph.D., for the HORIZON Recurrent Fracture Trial*





Large randomized controlled trial comparing zoledronate to placebo in hip fracture patients. A **28% reduction in mortality** was observed in the zoledronate group.

MORTALITA’

BISFOSFONATI E MORTALITA’: OLTRE L’OSTEOPOROSI

CLINICAL TRIALS

JBMR

Potential Mediators of the Mortality Reduction With Zoledronic Acid After Hip Fracture

Cathleen S Colón-Emeric,[1] Peter Mesenbrink,[2] Kenneth W Lyles,[1] Carl F Pieper,[1] Steven Boonen,[3] Pierre Delmas,[4] Erik F Eriksen,[5] and Jay Magaziner[6]

[1]Duke University Medical Center and the Durham VA Geriatrics Research Education and Clinical Center, Durham, NC, USA
[2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
[3]Katholieke Universiteit Leuven, Leuven, Belgium
[4]Claude Bernard University, Lyon, France
[5]Novartis Pharma AG, Basel, Switzerland
[6]School of Medicine, University of Maryland, Baltimore, MD, USA

Analisi post-hoc del precedente, pubblicato nel 2010, che evidenzia come **l’effetto anti-fratturativo** dello Zoledronato spieghi soltanto **l’8% dell’effetto di riduzione della mortalità** osservato nel trial citato.

Quali sono gli altri meccanismi di azione dei bisfosfonati nel ridurre la mortalità?

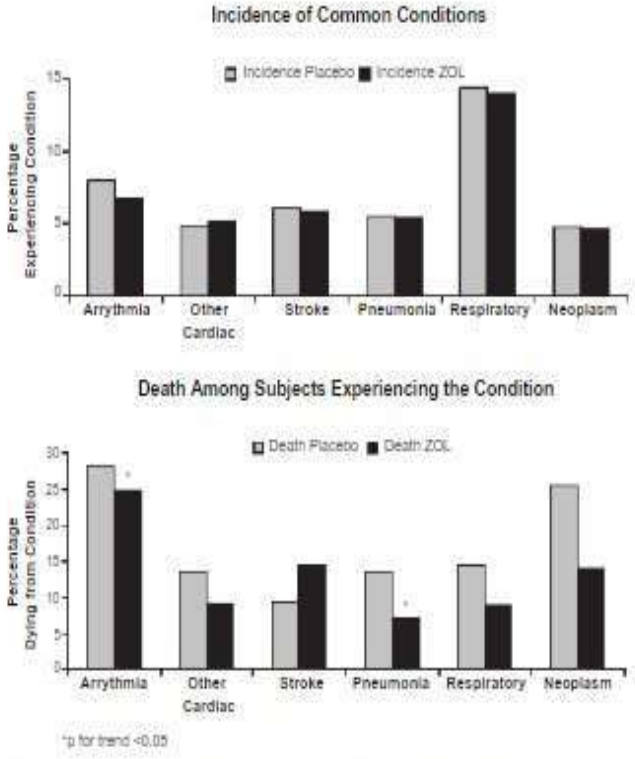


Fig. 2. Incidence of common conditions in the zoledronic acid (ZOL) and placebo groups (*top panel*) and the risk of dying from a given condition among subjects who experienced that condition (*bottom panel*).

MORTALITA'

Prespecified Adverse Events of Interest

Adverse Event	Placebo (N=1000)			Zoledronate (N=1000)			Odds Ratio with Zoledronate (95% CI)
	Events	Events per 1000 Woman-Yr (95% CI)	Women with at Least One Event	Events	Events per 1000 Woman-Yr (95% CI)	Women with at Least One Event	
	no.		*no.*	*no.*		*no.*	
Death	41	7.0 (5.4–9.4)	41	27	4.5 (3.0–6.6)	27	0.65 (0.40–1.05)
Sudden death	1	0.2 (0.002–0.9)	1	3	0.5 (0.1–14.8)	3	3.01 (0.3–28.9)
Myocardial infarction	43	7.3 (5.3–9.8)	39	25	4.2 (2.7–6.2)	24	0.61 (0.36–1.02)
Coronary-artery revascularization	32	5.4 (3.7–7.7)	30	23	3.9 (2.5–5.8)	21	0.72 (0.41–1.27)
Stroke	22	3.7 (2.3–5.7)	20	20	3.4 (2.1–5.2)	17	0.85 (0.44–1.63)
Composite of vascular events*	98	16.6 (13.5–20.3)	69	71	12.0 (9.3–15.1)	53	0.76 (0.52–1.09)
Transient ischemic attack	15	2.5 (1.4–4.2)	14	24	4.0 (2.6–6.0)	23	1.66 (0.85–3.24)
Cancer†	127	21.5 (18.0–18.1)	121	87	14.7 (11.7–18.1)	84	0.67 (0.50–0.89)
Osteonecrosis of the jaw	0	0	0	0	0	0	Not applicable
Atrial fibrillation	92	15.6 (12.6–19.1)	55	88	14.8 (11.9–18.3)	54	0.98 (0.67–1.44)

Reid IR et al. N Engl J Med 2018

MORTALITA'

ORIGINAL ARTICLE

JBMR®

Effects of Zoledronate on Cancer, Cardiac Events, and Mortality in Osteopenic Older Women

Ian R Reid,[1,2] Anne M Horne,[1] Borislav Mihov,[1] Angela Stewart,[1] Elizabeth Garratt,[1] Sonja Bastin,[2] and Gregory D Gamble[1]

[1]Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
[2]Auckland District Health Board, Auckland, New Zealand

RCT del 2020 eseguito su 2000 donne post-menopausali (età media 71 anni) con bassa BMD e randomizzate a ricevere Zoledronato o placebo per 6 anni.

Lo studio ha evidenziato **meno decessi** nel gruppo trattato (HR 0.65, 95% CI 0.40–1.06), e tale differenza si è mantenuta **anche quando l'analisi è stata ristretta alle 1688 donne che non sono incorse in fratture da fragilità** (HR 0.51, 95% CI 0.30–0.87); la riduzione del rischio sembra pertanto mediate dalla riduzione delle morti correlate a **neoplasie e ictus cerebri.**

QUALITA' DI VITA

Bone 48 (2011) 1298–1304

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Health-related quality of life and treatment of postmenopausal osteoporosis: Results from the HORIZON-PFT

Philip N. Sambrook [a,*], Stuart L. Silverman [b], Jane A. Cauley [c], Chris Recknor [d], Melvin Olson [e], Guoqin Su [f], Steven Boonen [g], Dennis Black [h], Jonathan D. Adachi [i]
and for the HORIZON Pivotal Fracture Trial

QUALITA’ DI VITA

Journal of Research in Medical Sciences

IUMS

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J Res Med Sci. 2016; 21: 112.
Published online 2016 Nov 7. doi: 10.4103/1735-1995.193503

PMCID: PMC5331768
PMID: 28255320

The effects of zoledronic acid treatment on depression and quality of life in women with postmenopausal osteoporosis: A clinical trial study

Feyzi Gokosmanoglu, Ceyhun Varim,[1] Aysegul Atmaca,[2] Mehmet Hulusi Atmaca,[2] and Ramis Colak[2]

QUALITA' DI VITA

diagnostics

MDPI

Article

The Effect of Zoledronic Acid on Serum Biomarkers among Patients with Chronic Low Back Pain and Modic Changes in Lumbar Magnetic Resonance Imaging

Katri Koivisto [1,*], Jaro Karppinen [1,2,3], Marianne Haapea [1,2,4], Jyri Järvinen [1,4], Eero Kyllönen [1], Osmo Tervonen [4], Jaakko Niinimäki [4], Mauro Alini [5], Jeffrey Lotz [6], Stefan Dudli [7], Dino Samartzis [8], Juha Risteli [9], Marja-Leena Majuri [1], Harri Alenius [10] and Sibylle Grad [5]

($p < 0.001$ for both). Change in iPINP correlated with change in the volume of all MC and M1 lesions. ZA downregulated bone turnover markers as expected and, surprisingly, increased the chemokine IP-10 relative to placebo treatment. This adds to our knowledge of the effects of ZA on MC and the biomarkers that signal this process.

QUALITA' DI VITA

ORIGINAL ARTICLE

JBMR®

Effect of Zoledronic Acid and Denosumab in Patients With Low Back Pain and Modic Change: A Proof-of-Principle Trial

Guoqi Cai,[1*] Laura L Laslett,[1*] Dawn Aitken,[1] Andrew Halliday,[2] Feng Pan,[1] Petr Otahal,[1] Deborah Speden,[3] Tania M Winzenberg,[1] and Graeme Jones[1]

[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia
[2]Department of Radiology, Royal Hobart Hospital, Hobart, TAS, Australia
[3]Department of Rheumatology, Royal Hobart Hospital, Hobart, TAS, Australia

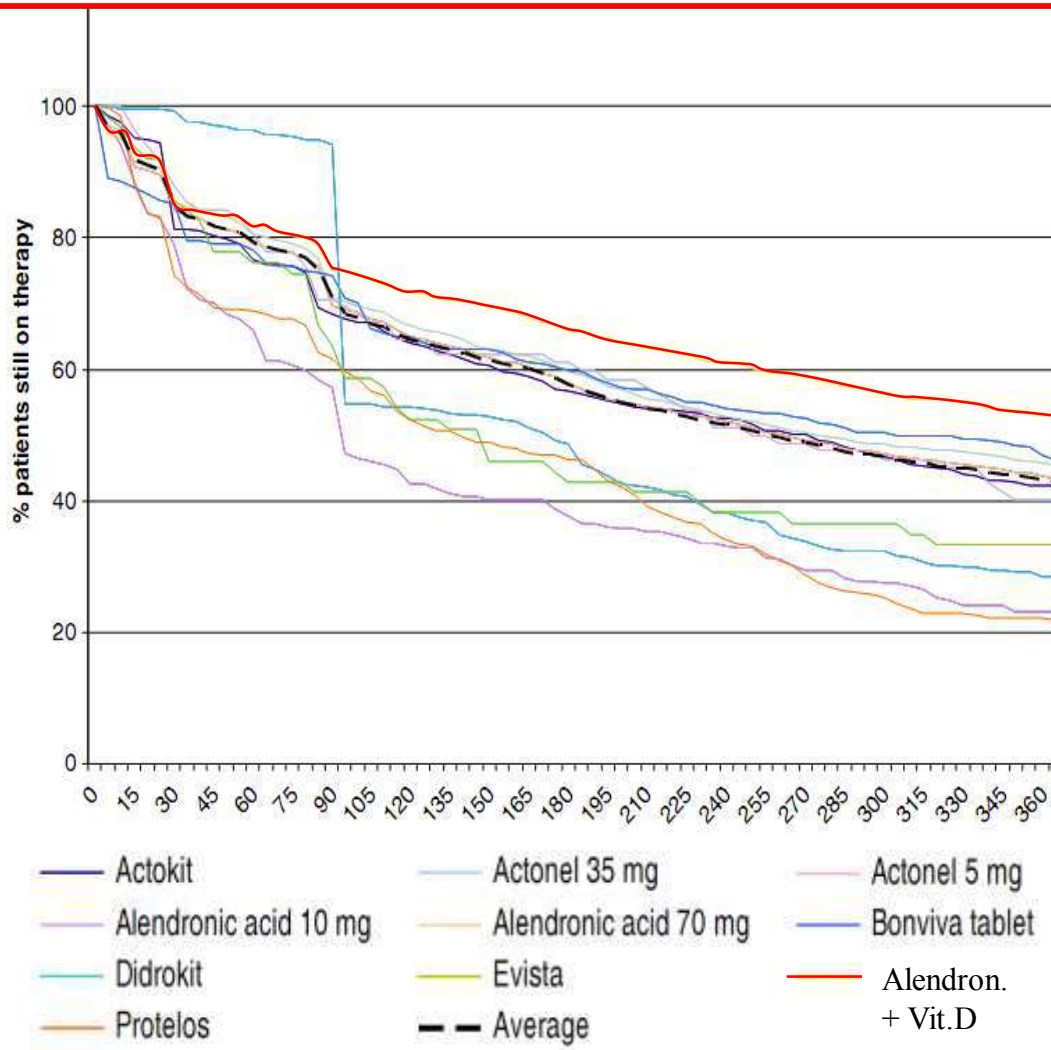
lerenza

erence and profile of non-persistence in patients treated for osteoporosis—a large-scale, long-term retrospective study in The Netherlands

J. C. Netelenbos · P. P. Geusens · G. Ypma · S. J. E. Buijs

Osteoporos Int (2011) 22:1537–1546

- Twelve-month persistence was measured in all 8626 patients.
- MPR of ≥80% was found in 91% of patients.
- Persistence was 43% (range, 29-52%).
- Of nonpersistent patients, 22% restarted within 18 months with oral osteoporosis drugs.
- One-year compliance for all available oral osteoporosis medications was high, but 1-year persistence was low. Most stoppers did not restart or switch during an additional 18-month follow-up.



ADERENZA

Review

Adherence and preference of intravenous zoledronic acid for osteoporosis versus other bisphosphonates

Maria José Fobelo Lozano,[1] Susana Sánchez-Fidalgo[1,2]

Review

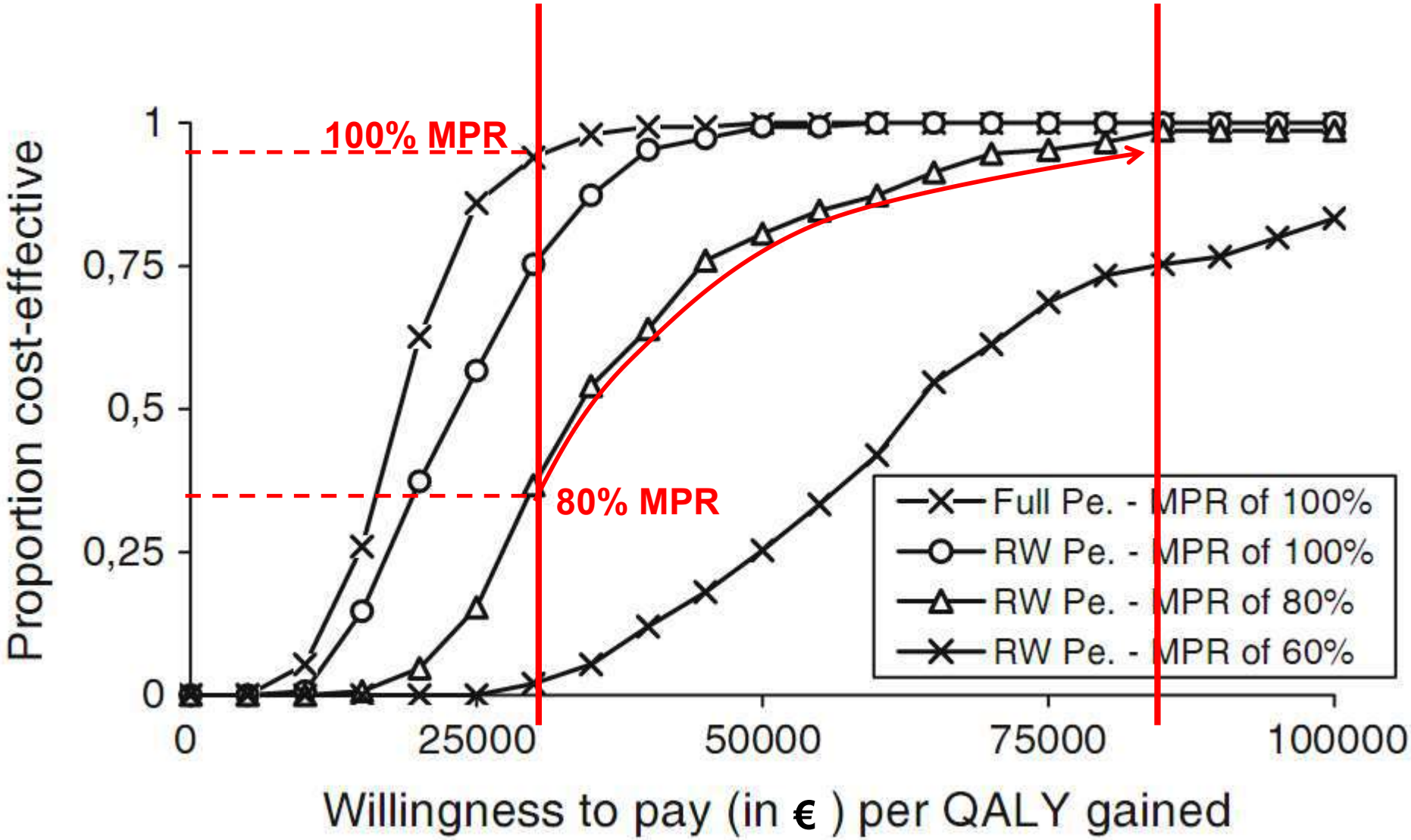
Table 1 Adherence data among once-yearly intravenous zoledronate and shorter interval bisphosphonates

Reference	Study design	Duration	Population	Osteoporosis treatment	Methodology	Results
Eliasaf *et al*[24]	Observational prospective study	6-month period	Postmenopausal women (n=86)	Oral BPS (n=39) Intravenous ZOL annually (n=12) Other therapies (n=35)	Compliance: MPR, number of doses dispensed in relation to those prescribed over a period and reported as a percentage	100%±0 (ZOL) p<0.0001 83.5%±28.3 (BPS)
					Persistence, continuation of treatment without a >30-day gap in prescription refills	77% (BPS) No data (ZOL)
Chávez-Valencia *et al*[23]	Observational prospective study	12-month period	Postmenopausal women (n=104)	Oral ALE weekly (n=52) Intravenous ZOL annually (n=52) +calcium and vit D	Compliance: MPR, defined by the ratio of supplied-to-required pills in 1 year. (Pill counts and exchange of empty boxes)	Group ALE: 66% for both medications Group ZOL: 100% for ZOL 86% calcium and vit D
Ziller *et al*[25]	Observational retrospective cohort study	24-month period	Patients with at least one prescription of BP (n=261 289)	Oral: IBA monthly (n=14 426) ALE daily/weekly (n=173 662) ETD daily (n=1002) RIS (daily/weekly) (n=46 542) Intravenous: ZOL annually (n=13 132) IBA quarterly (n=12 525)	Compliance: MPR, total number of treatment days covered within the 1 year period after index prescription date	100% (ZOL) p<0.0001 70% (IBA quarterly), 62% (IBA monthly), 57% (ALE weekly), 59% (ETD daily), 58% (RIS daily), 53% (ALE daily), 53% (RIS weekly), 47% (RIS daily), 33% (ALE daily)
					Persistence, the proportion of patients who remained on their initially prescribed therapy at 1 year	65.6% (ZOL) p<0.0001 56.6% (IBA, quarterly), 51% (IBA monthly), 44.8% (ALE weekly), 43.4% (ETD daily), 42.3% (RIS daily), 37.8% (ALE daily), 35.2% (RIS weekly), 30.6% (RIS daily), 17.3% (ALE daily)
Curtis *et al*[22]	Observational prospective study	18-month period	Individuals receiving IBA or ZOL for osteoporosis	Intravenous ZOL annually (n=775) Intravenous IBA quarterly (n=846)	Adherence: quantified by the PDC, measured continuously and dichotomously (>=80%)	Group ZOL: 82%, p<0.0001 Group IBA: 58%–62%, depending on time period

ALE, alendronate; BPS, bisphosphonates; ETD, etidronate; IBA, ibandronate; MPR, medication possession ratio; PDC, proportion of days covered. It is expressed as a proportion, computed by summing the number of days the patient is exposed to the medication, beginning with the first infusion and extending to the end of follow-up and dividing by the amount of follow-up time; RIS, risedronate; ZOL, zoledronate.

ADERENZA

L CLINICAL AND ECONOMIC IMPACT OF NONADHERENCE WITH OSTEOPOROSIS MEDICATIONS



Hiligsmann M, Calcif Tissue Int, 2010

COSTO/BENEFICIO

99:131–141
-0132-8

CrossMark

ORIGINAL RESEARCH

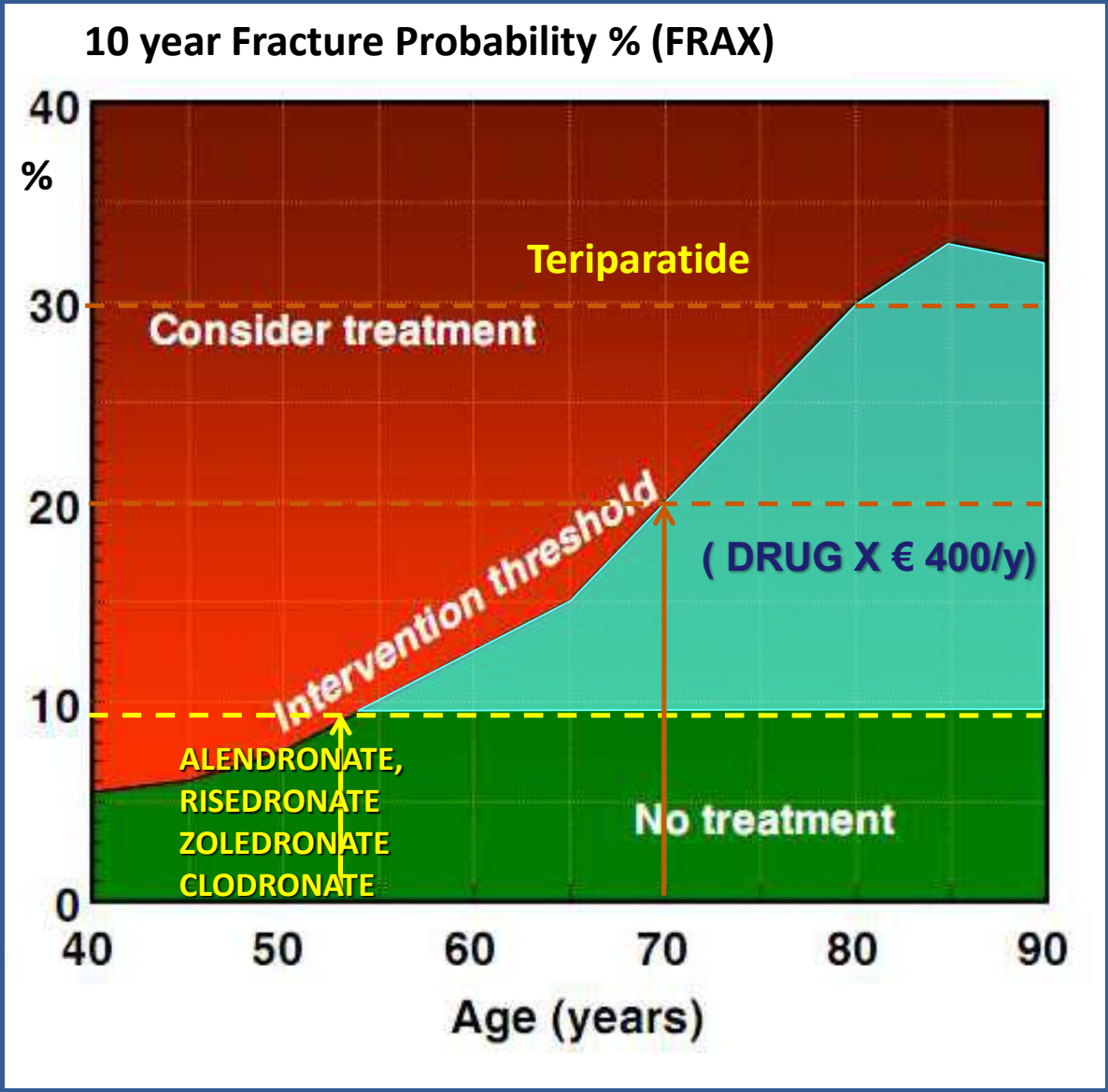
Cost-Effectiveness of Intervention Thresholds for the Treatment of Osteoporosis Based on FRAX®

Andréa Marques[1,2] · Óscar Lourenço[3] · Gustaf Ortsäter[4] · Fredrik Borgström[4] · John A. Kanis[5] · José António P. da Silva[1,6]

Table 4 Cost-effective intervention thresholds expressed as the 10-year probability of major or hip fracture (%) for the different interventions, versus no treatment, according to age, at WTPs of €20,000 and €32,000

Age	10-year probability of a major fracture				10-year probability of a hip fracture			
	Generic alendronate versus no treatment (%)	Zoledronic acid versus no treatment (%)	Denosumab versus no treatment (%)	Teriparatide versus no treatment (%)	Generic alendronate versus no treatment (%)	Zoledronic acid versus no treatment (%)	Denosumab versus no treatment (%)	Teriparatide versus no treatment (%)
WTP = €32,000								
50	8.6	16.7	22.5	37.1	2.6	9.5	15.5	35.6
55	8.7	17.8	24.7	30.9	2.4	8.6	14.5	21.2
60	10.4	23.2	33.7	63.8	3.0	11.9	20.7	47.8
65	9.2	20.5	31.2	60.8	2.3	8.8	16.4	39.8
70	8.6	21.0	33.0	60.0	2.3	10.5	20.9	47.1
75	8.1	22.9	38.7	76.3	2.1	12.3	27.1	63.3
80	7.1	21.8	39.6	84.3	1.7	11.4	27.9	69.7
85	5.9	18.6	36.9	71.3	1.3	9.0	25.9	60.6
All ages	8.8	20.4	34.9	77.8	2.5	10.1	22.6	62.6

LA SOGLIA DI INTERVENTO PUO' VARIARE IN BASE AL COSTO ED ALLA EFFICACIA DEL FARMACO ED A QUANTO UNA COMUNITA' PUO' SPENDERE (ad es. WTP € 30.000/QALY)



Kanis JA, Osteoporos Int 2009 (modif.)

SOGLIA DI INTERVENTO (Cost/Effective) NELL' O.P. IN BASE AL NUMERO DEI FATTORI DI RISCHIO

Patologia Osteopenizzante	1
BMI < 19	1
Familiarità per fratture	1
BMD -1, -2.5	1
BMD ≤ -2.5	2
Frattura	1
2 o più Fratture	2
Frattura Vert. ≥ 40%	2
Dose Prednisone ≤ 5 mg	1
Dose Prednisone >5 mg – 15 mg	2
Dose Prednisone > 15 mg	3
Cadute Pregresse nell'ultimo anno	1
Età ≥ 65 aa e < 80 aa	1
Età ≥ 80 aa	2
Fumo	1
Alcol (≥ 3 unità)	1
TOTALE	**X**

TOTALE:

2 : Farmaci +
(> Aderenza (30-40%)
(> vit D, < Costo)

≥3 : Alendronato
Zoledronato
Risedronato
Clodronato
Denosumab

≥4 : Stronzio Ranelato

≥6 : Teriparatide
(cortisonati)

COSTO/BENEFICIO

Journal of Medical Economics ›
Volume 14. 2011 - Issue 1

Original Article

The cost effectiveness of zoledronic acid 5 mg for the management of postmenopausal osteoporosis in women with prior fractures: evidence from Finland, Norway and the Netherlands

R. Akehurst, N. Brereton, R. Ariely, T. Lusa, M. Groot, P. Foss & ...show all

Pages 53-64 | Accepted 03 Dec 2010, Published online: 11 Jan 2011

Download citation https://doi.org/10.3111/13696998.2010.545563

Conclusions:

Using local or commonly used thresholds, this analysis suggests that zoledronic acid would be a cost-effective first-line option compared with other branded bisphosphonates and, in some scenarios, compared with generic alendronate, for the secondary prevention of fractures in women with postmenopausal osteoporosis in Finland, Norway and the Netherlands.

EFFICACIA EDEMA

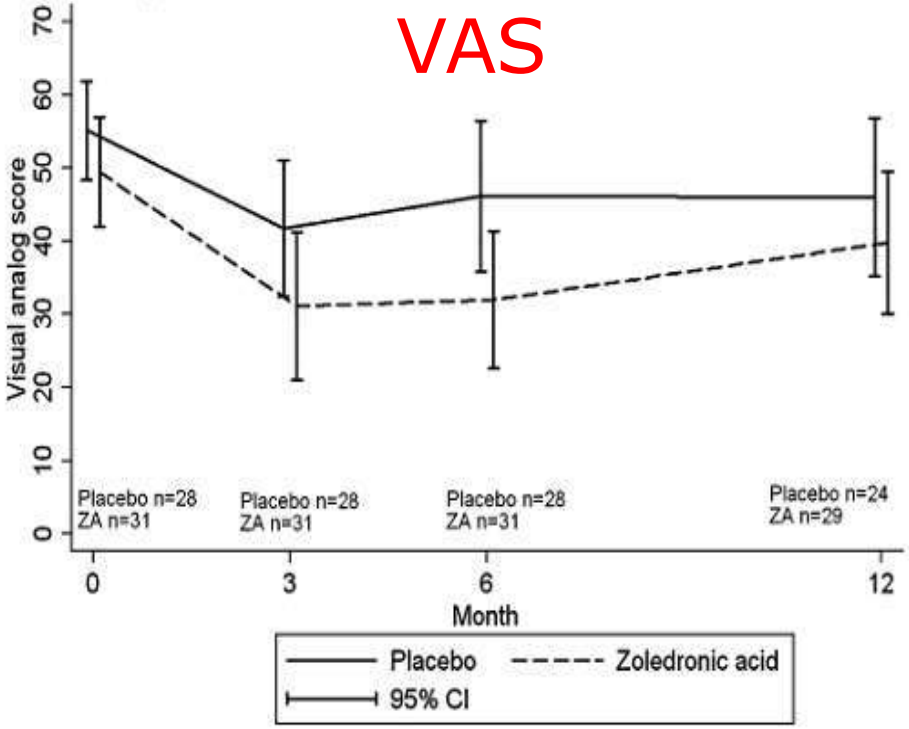
Ann Rheum Dis 2012;**71**:1322–1328.

EXTENDED REPORT

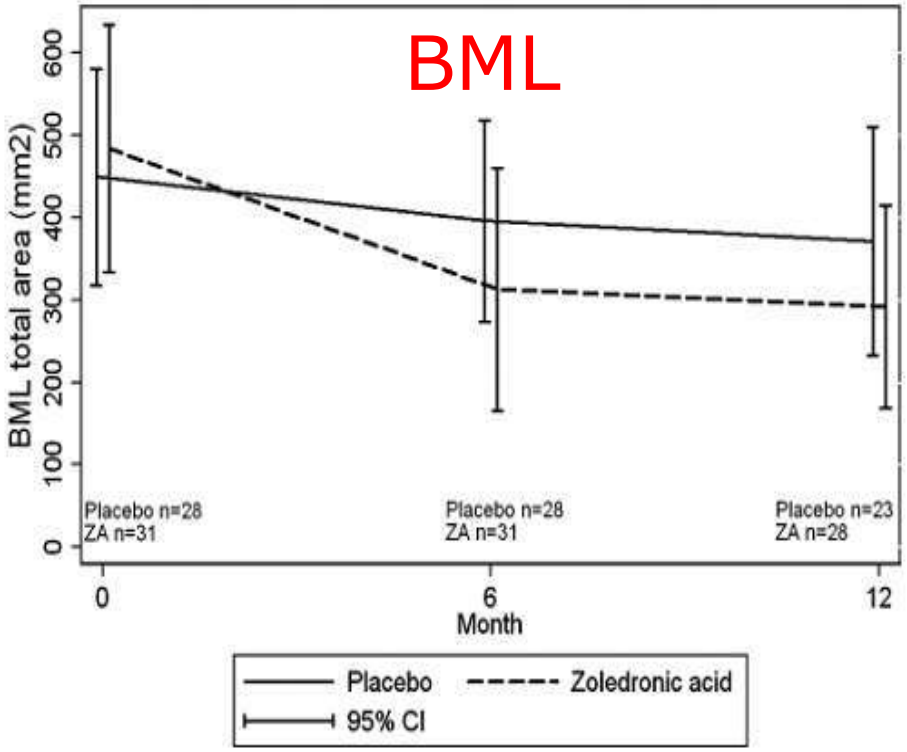
Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial

Laura Louise Laslett,[1] Dawn A Doré,[1] Stephen J Quinn,[2] Philippa Boon,[1] Emma Ryan,[1] Tania Maree Winzenberg,[1] Graeme Jones[1]

VAS



BML



EFFICACIA EDEMA

Aitken et al. BMC Musculoskeletal Disorders (2018) 19:217
https://doi.org/10.1186/s12891-018-2143-2

BMC Musculoskeletal Disorders

STUDY PROTOCOL Open Access

A protocol for a multicentre, randomised, double-blind, placebo-controlled trial to compare the effect of annual infusions of zoledronic acid to placebo on knee structural change and knee pain over 24 months in knee osteoarthritis patients – ZAP2

Dawn Aitken[1*†], Laura L. Laslett[1†], Guoqi Cai[1], Catherine Hill[2,3], Lyn March[4], Anita E. Wluka[5], Yuanyuan Wang[5], Leigh Blizzard[1], Flavia Cicuttini[5] and Graeme Jones[1]

EFFICACIA OP PERIPR.

Open Access

CLINICAL ARTICLE

Efficiency of Zoledronic Acid in Inhibiting Accelerated Periprosthetic Bone Loss After Cementless Total Hip Arthroplasty in Osteoporotic Patients: A Prospective, Cohort Study

Guang-tao Fu, PhD[1,2,†], Li-jun Lin, PhD[3,†], Pu-yi Sheng, PhD[4,†], Chang-chuan Li, PhD[1], Jin-xin Zhang, PhD[5], Jun Shen, PhD[6], Sheng Liu, MD[7], Yun-lian Xue, PhD[8], Si-peng Lin, PhD[1], Kun Wang, PhD[9], Qiu-jian Zheng, MD[2], Yue Ding, PhD[1,10]

Department of [1]Orthopaedics, Sun Yat-sen Memorial Hospital, [4]Orthopaedics, the First affiliated Hospital, [5]Public Health College, [6]Radiology, Sun Yat-sen Memorial Hospital and [9]Orthopaedics, The Third affiliated Hospital, Sun Yat-sen University, Division of [2]Orthopaedics, Guangdong Provincial People's Hospital and [8]Statistics, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, [3]Department of Orthopaedics, Zhujiang Hospital of Southern Medical University and [10]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, Guangdong Province and [7]Department of Nuclear Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

comorbilità

ARTHRITIS & RHEUMATISM
Vol. 54, No. 5, May 2006, pp 1410–1414
DOI 10.1002/art.21824

Preliminary Evidence for a Structural Benefit of the New Bisphosphonate Zoledronic Acid in Early Rheumatoid Arthritis

Stephen J. Jarrett,[1] Philip G. Conaghan,[1] Victor S. Sloan,[2] Philemon Papanastasiou,[3] Christine-Elke Ortmann,[3] Philip J. O'Connor,[1] Andrew J. Grainger,[1] and Paul Emery[1]

The results of this study suggest a structural benefit associated with zoledronic acid therapy in patients with RA, as demonstrated by consistent results in structural end points in favor of zoledronic acid plus MTX compared with MTX alone.

safety

Antiresorptives: Safety Concerns—Clinical Perspective

Toxicologic Pathology
2017, Vol. 45(7) 859-863
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DOI: 10.1177/0192623317737066
journals.sagepub.com/home/tpx
SAGE

Jacques P. Brown[1]

In the osteoporosis patient population, who receive much lower doses of bisphosphonate (BP) or Dmab, the incidence of **ONJ** is estimated at **0.001% to 0.01%,** which is only slightly higher than that seen in the general population.
Incidence rates of **AFF** range from **1.8/100,000** per year with a 2-year BP exposure to **113/100,000** per year with BP exposure from 8 to 9.9 years

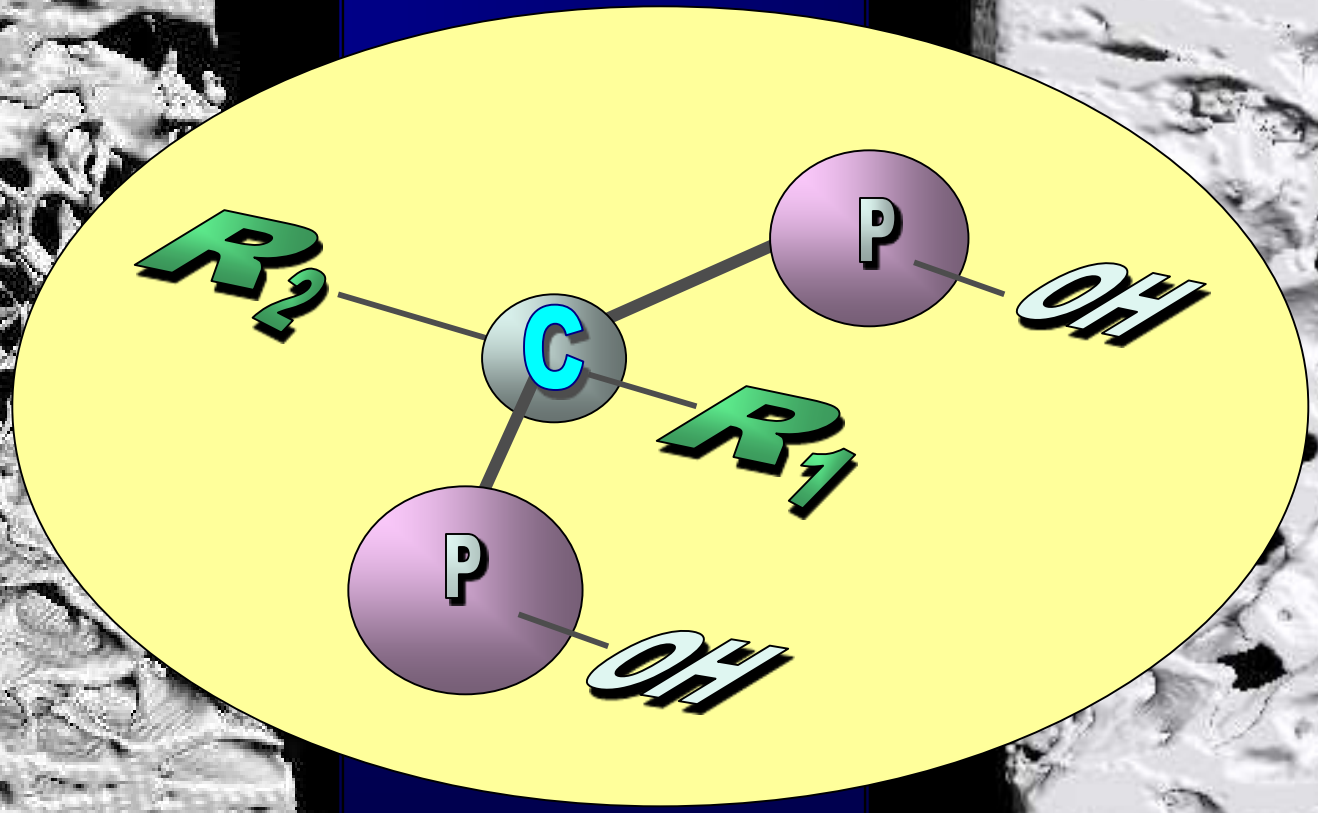
Factors associated with the development of ONJ include poor oral hygiene, glucocorticoid use, and invasive dental pro-cedures such as dental extraction (Khan et al. 2015). Therefore, **patients should complete any invasive dental procedures before initiating an antiresorptive (BPs orDmab)** to minimize the already small risk; however, **those on treatment should not delay emergency dental procedures** nor discount dental implants (Khan et al. 2015).

the prolonged reduction in bone remodeling, observed in all patients receiving BPs or Dmab, alone cannot explain the pathogenesis of AFF. **Bone material properties,proximal femoral geometry, and genetic predispositions might be involved individually or in combination**

ZOLEDRONATO

- Potenza antifratturativa in tutte le sedi scheletriche
- Efficacia Indipendente dalla BMD
- Efficacia indipendente dall' età
- Efficacia in prevenzione primaria e secondaria
- Efficacia nell'OP secondaria (Steroidi, antiormoni)
- Efficacia a lungo termine
- Efficacia in terapia sequenziale e di associazione
- Impatto sulla qualità di vita
- Impatto sulla mortalità

Grazie dell'Attenzione!

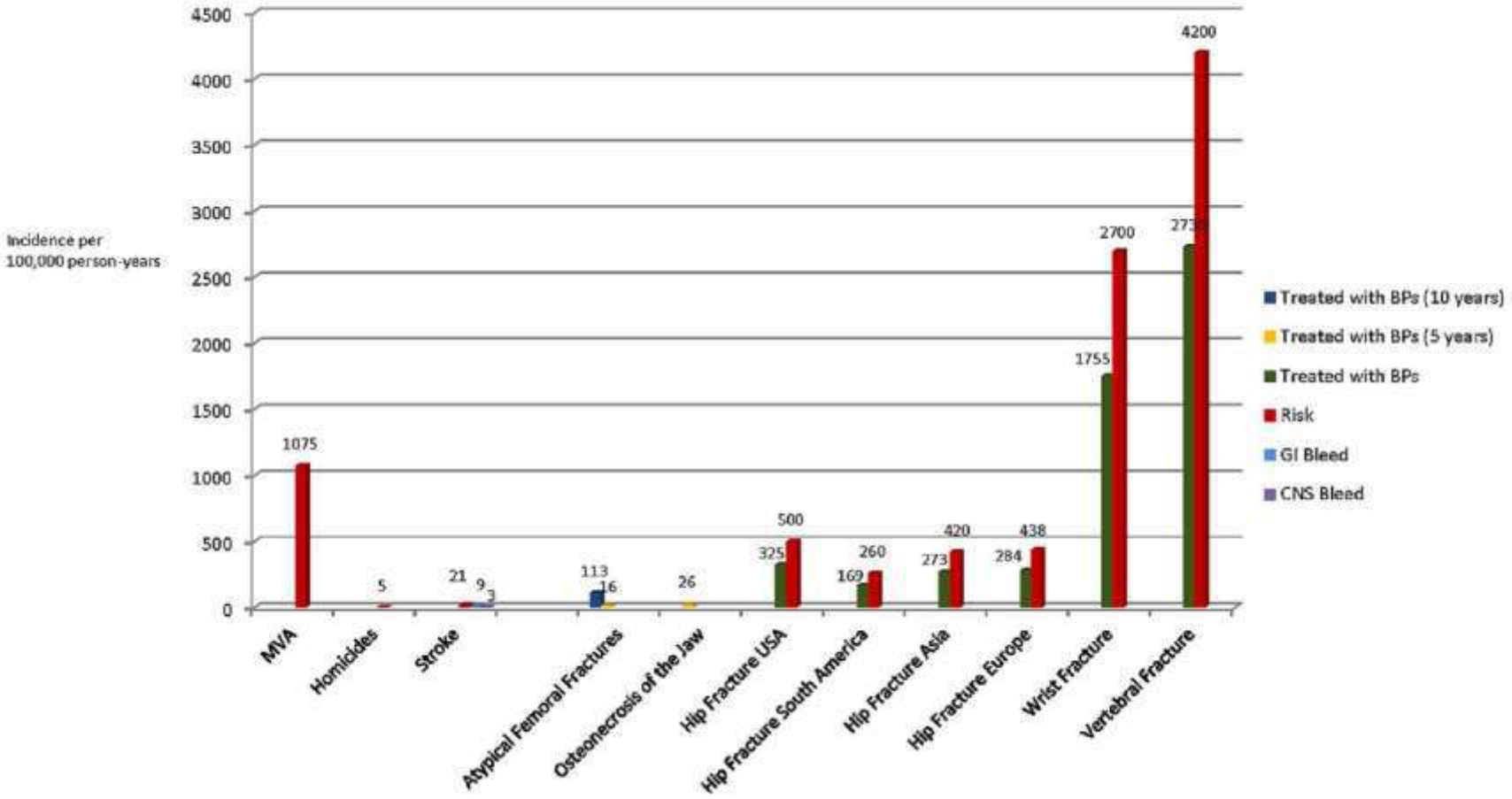


% pazienti in terapia con Zoledronato 5 mg per regione

AREA	% PAZIENTI
NORD	61%
CENTRO	36%
SUD	3%

Source: IMS data 07/2009

Risks associated with bisphosphonate use and other health outcomes



Adler AR et al. J Bone Miner Res 2016

Zoledronato: altre possibilità d'impiego?

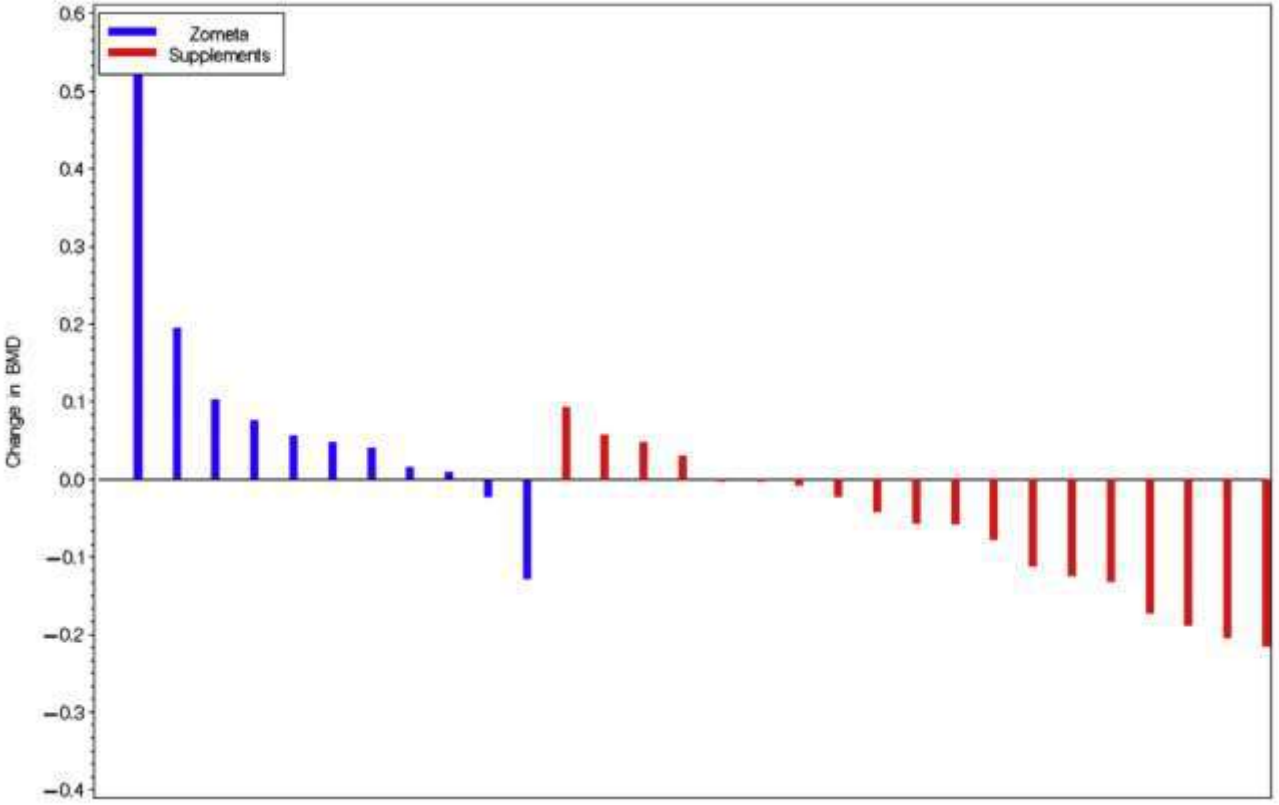
Intermittent Zoledronic Acid Prevents Bone Loss in Adults after Allogeneic Hematopoietic Cell Transplantation

Parameswaran Hari [1,*], Todd E. DeFor [2], David H. Vesole [3], Christopher N. Bredeson [4], Linda J. Burns [5]

ASBMT American Society for Blood and Marrow Transplantation

Biol Blood Marrow Transplant 2013

Change in Lumbar Spine BMD by treatment



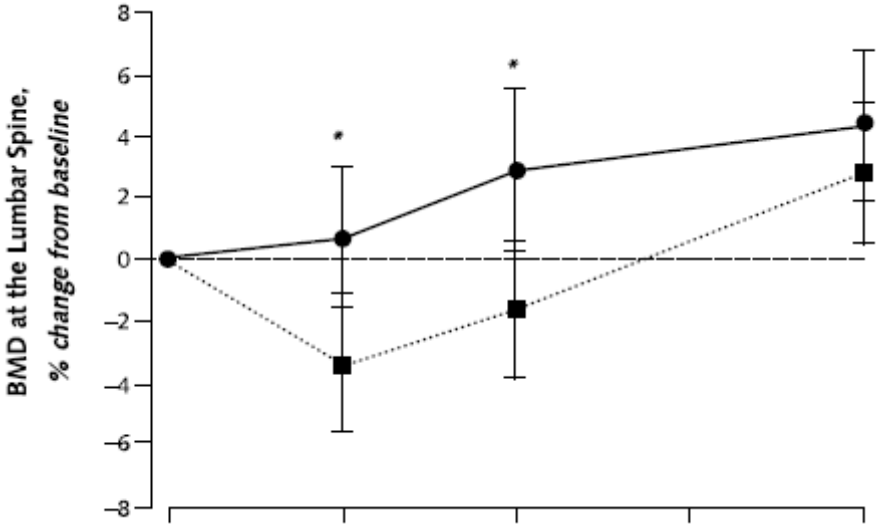
Annals of Internal Medicine 2006

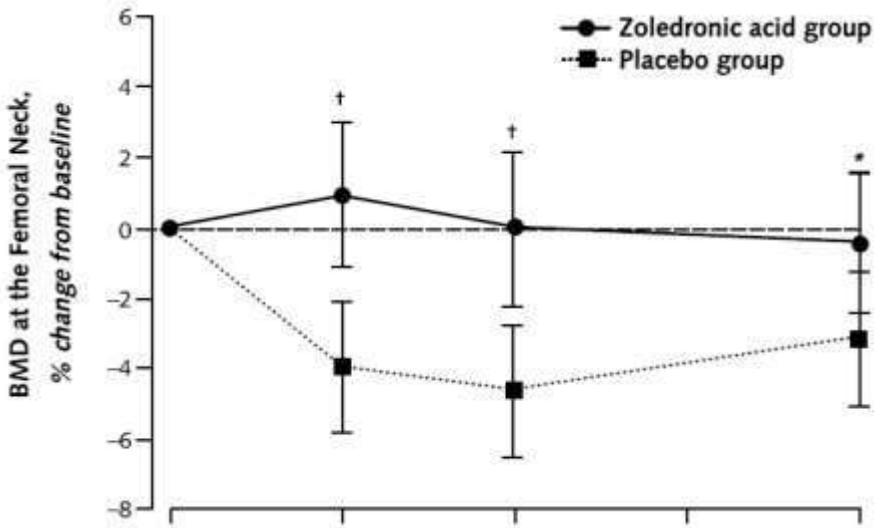
ARTICLE

Zoledronic Acid Prevents Bone Loss after Liver Transplantation

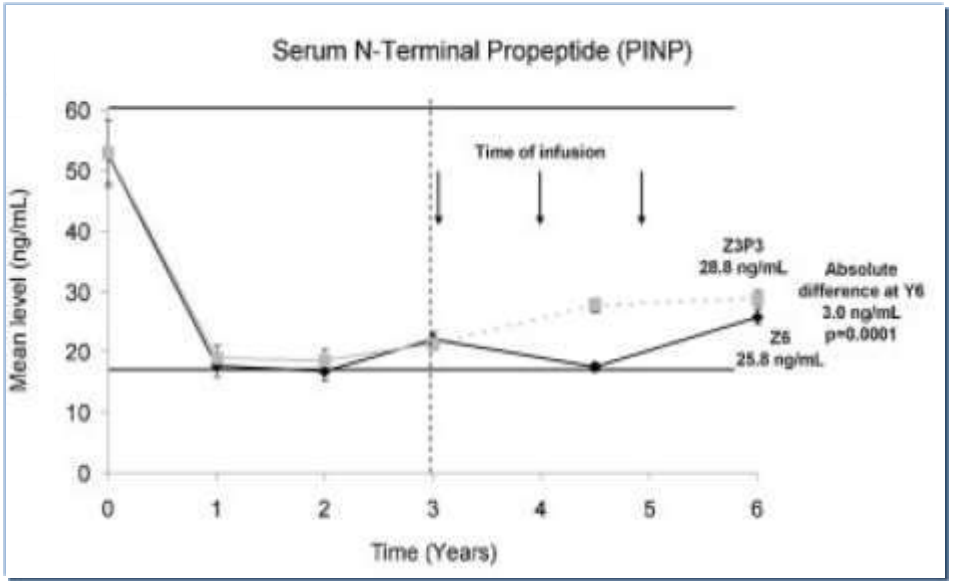
A Randomized, Double-Blind, Placebo-Controlled Trial

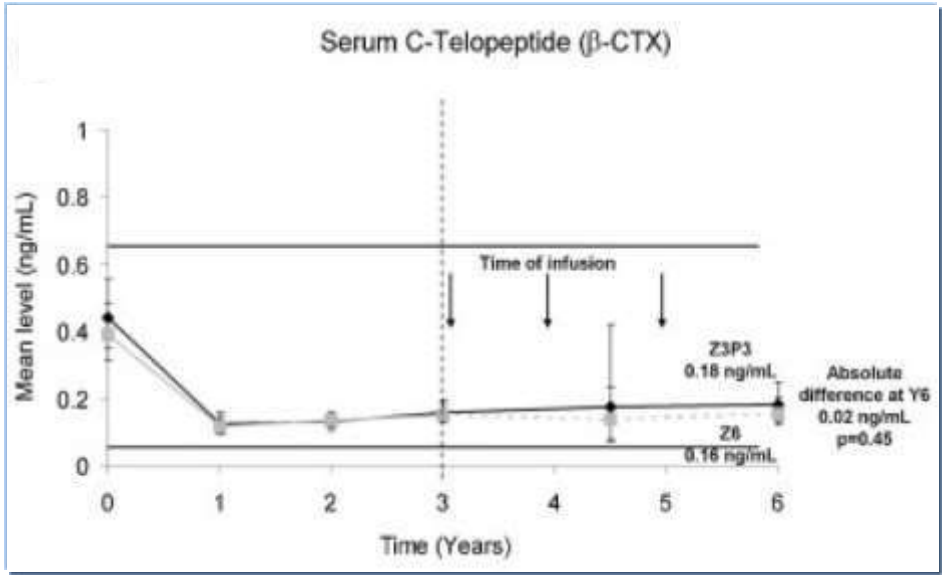
Bronwyn A.L. Crawford, MBBS, PhD; Cherie Kam, MPH, GDipScMed; Julie Pavlovic, RN; Karen Byth, PhD, DIC, CStat RSS; David J. Handelsman, MBBS, PhD; Peter W. Angus, MBBS, MD; and Geoffrey W. McCaughan, MBBS, PhD





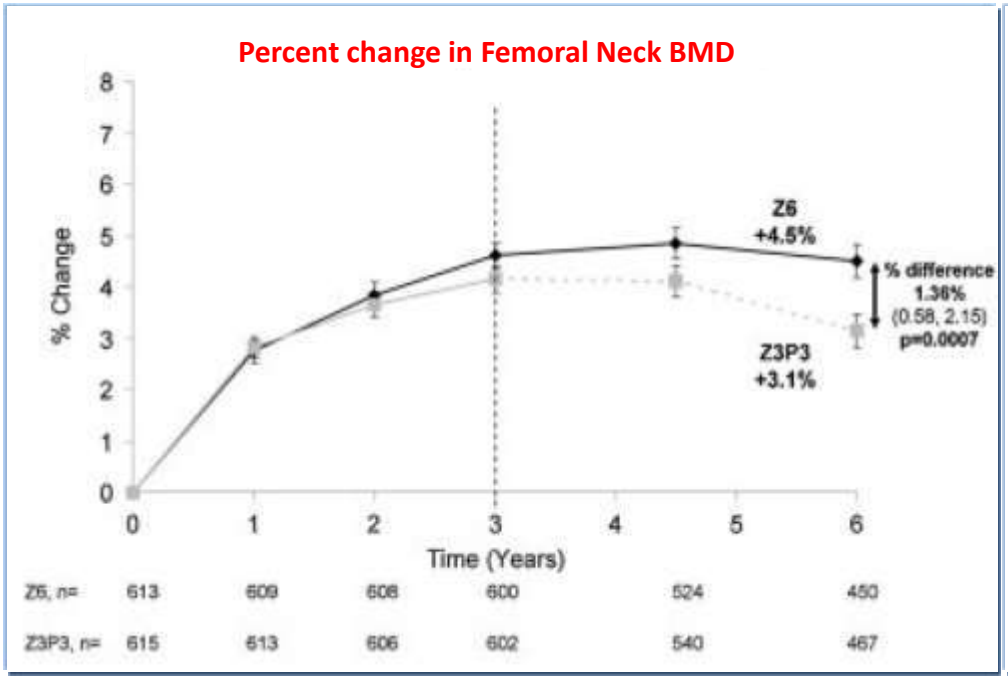
Mean changes in bone turnover markers over 6 years of treatment of zoledronate

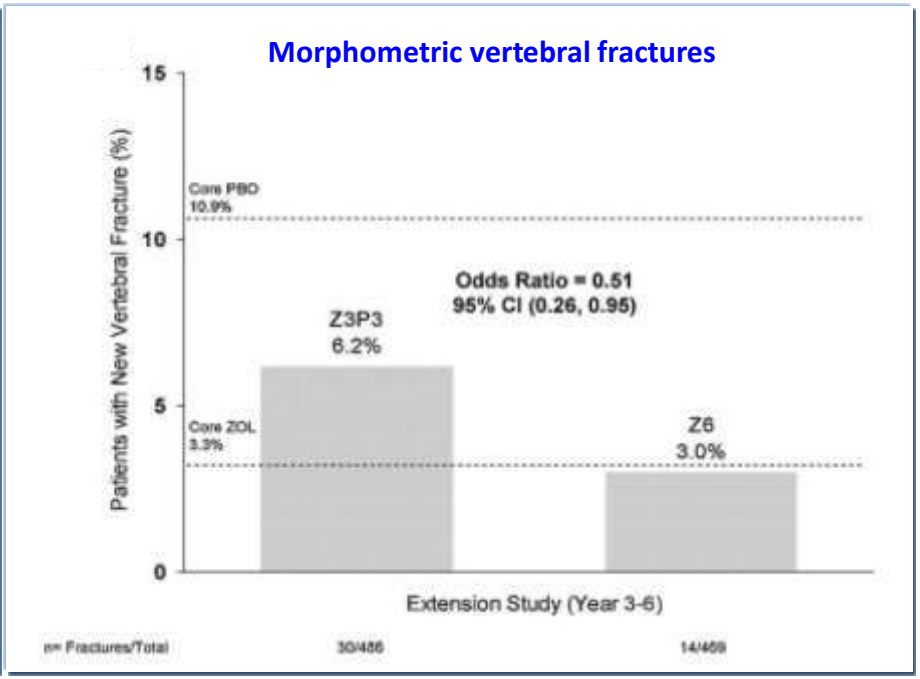




Black DM al. J Bone Min Res 2012

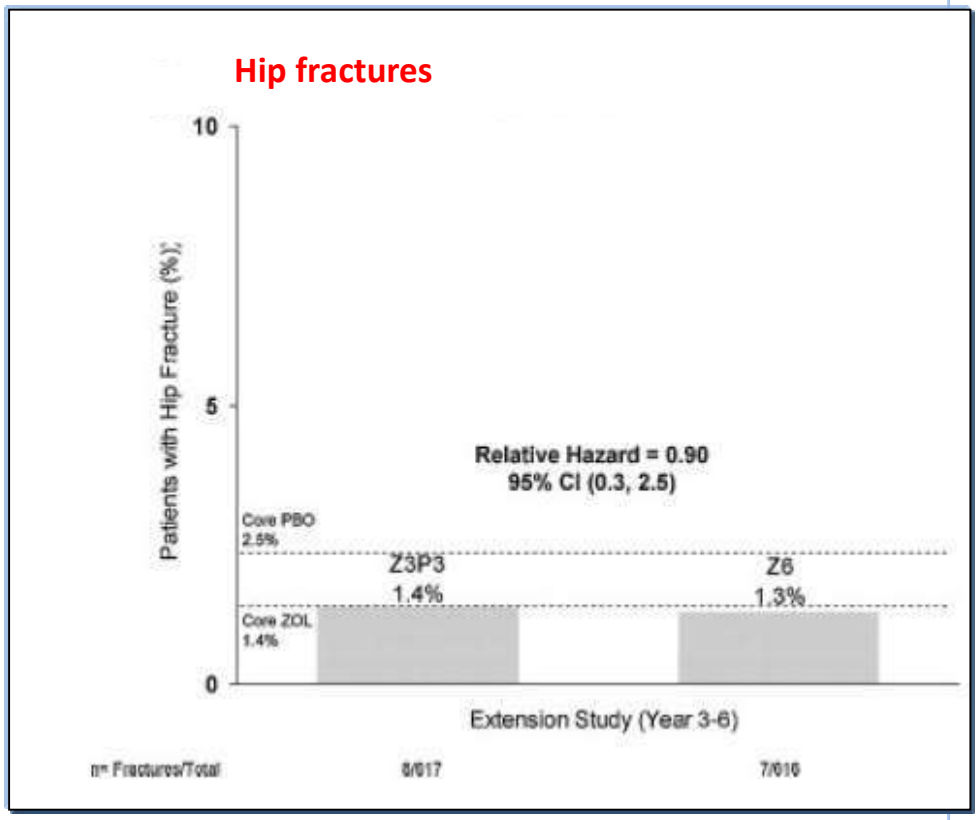
The Effect of 3 Versus 6 Years of Zoledronic Acid Treatment of Osteoporosis: A Randomized Extension to the HORIZON-Pivotal Fracture Trial (PFT)

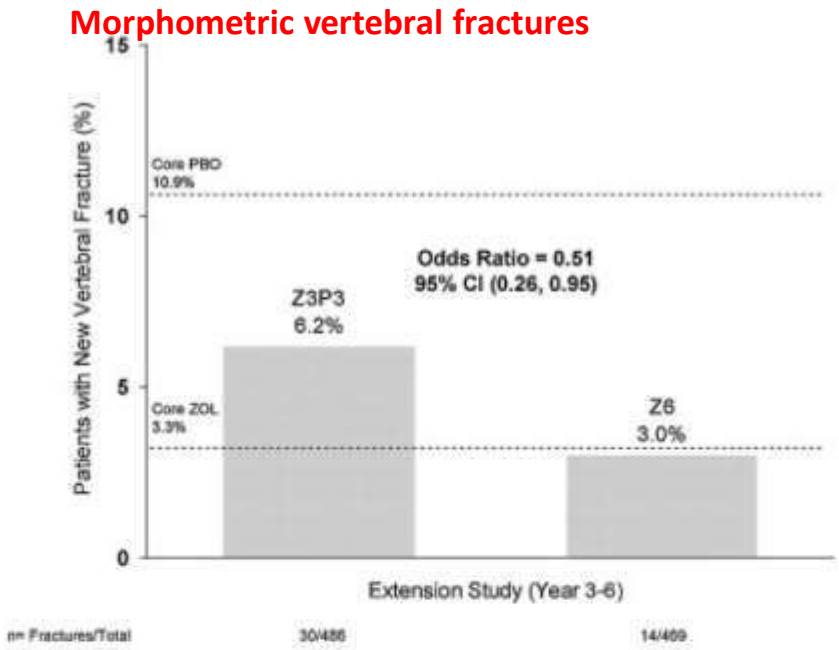


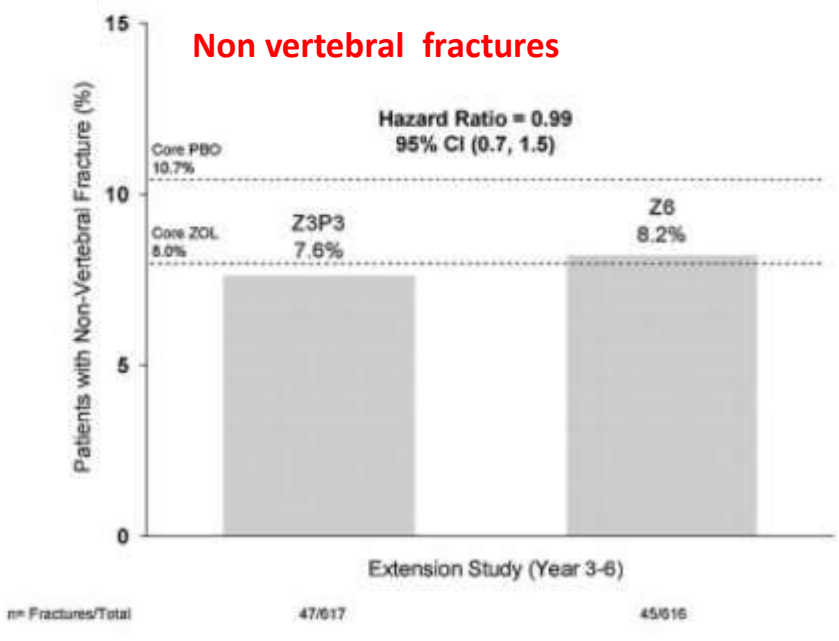


Black DM et al. J Bone Miner Res 2012

Incidence of fractures by treatment in the extension

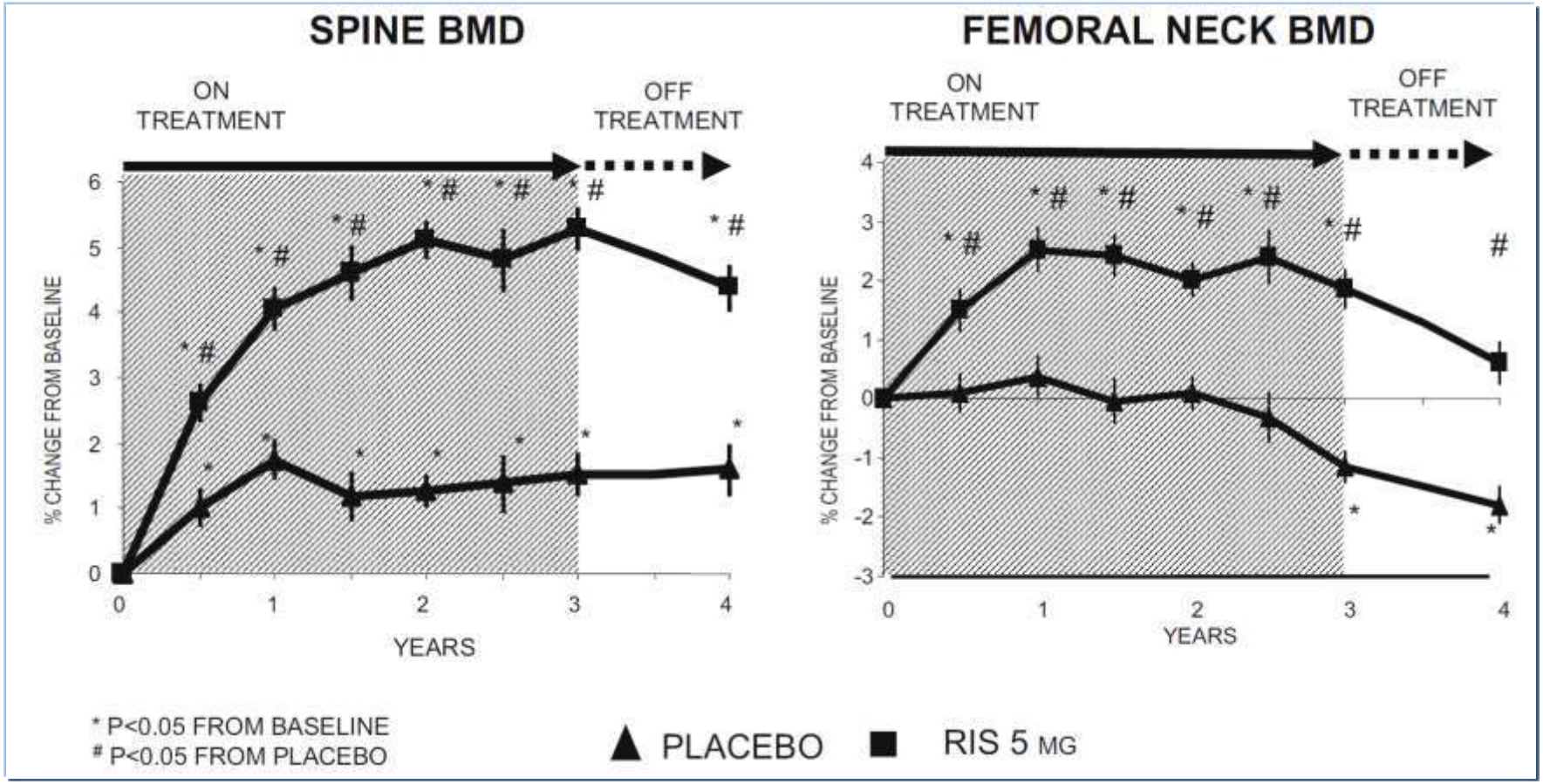






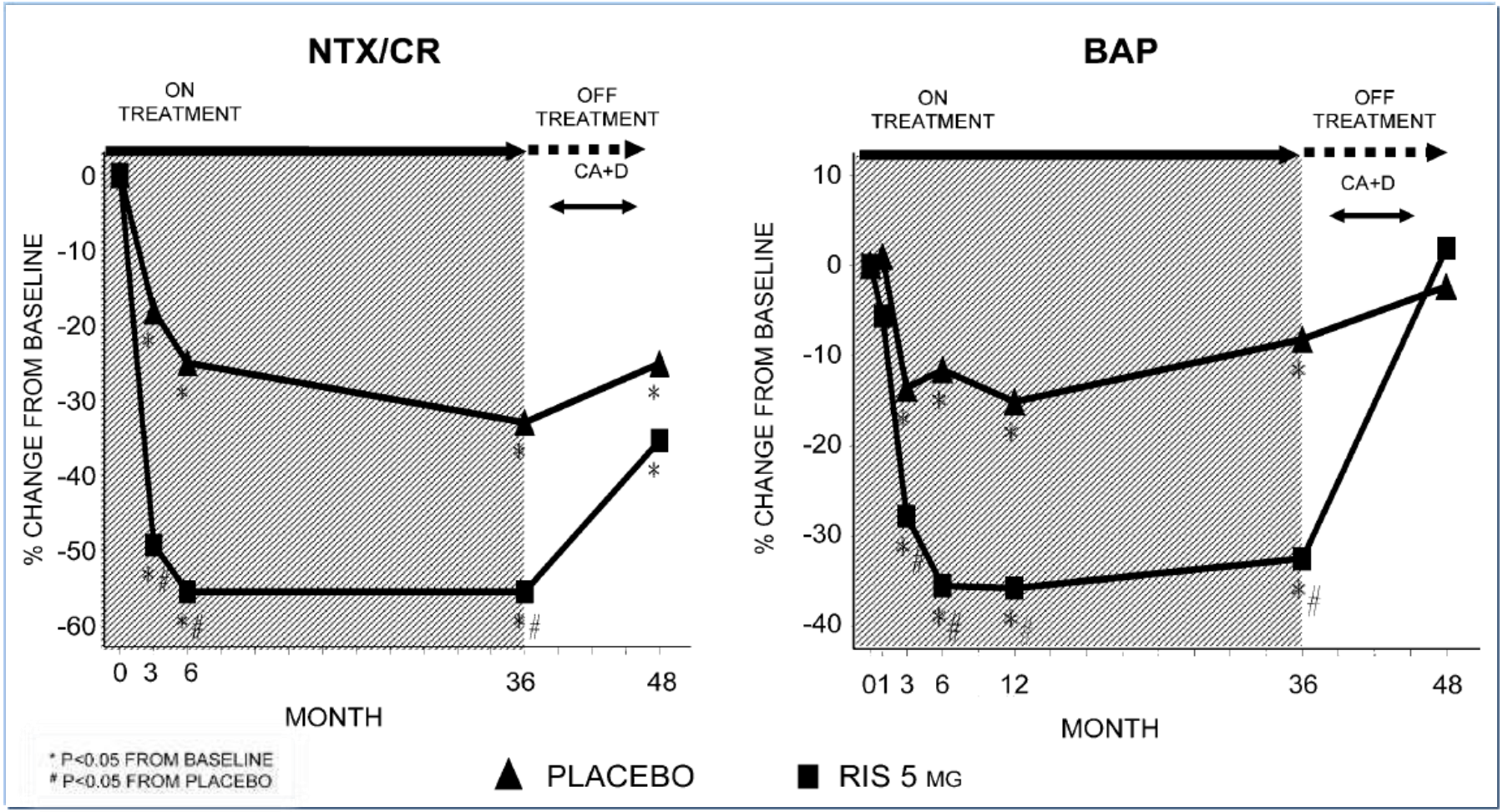
Black DM al. J Bone Min Res 2012

Change in BMD during 3 yrs of blinded treatment with placebo or risedronate 5 mg daily, followed by 1 year of open label treatment



Watts NB al. Osteoporos Int 2008

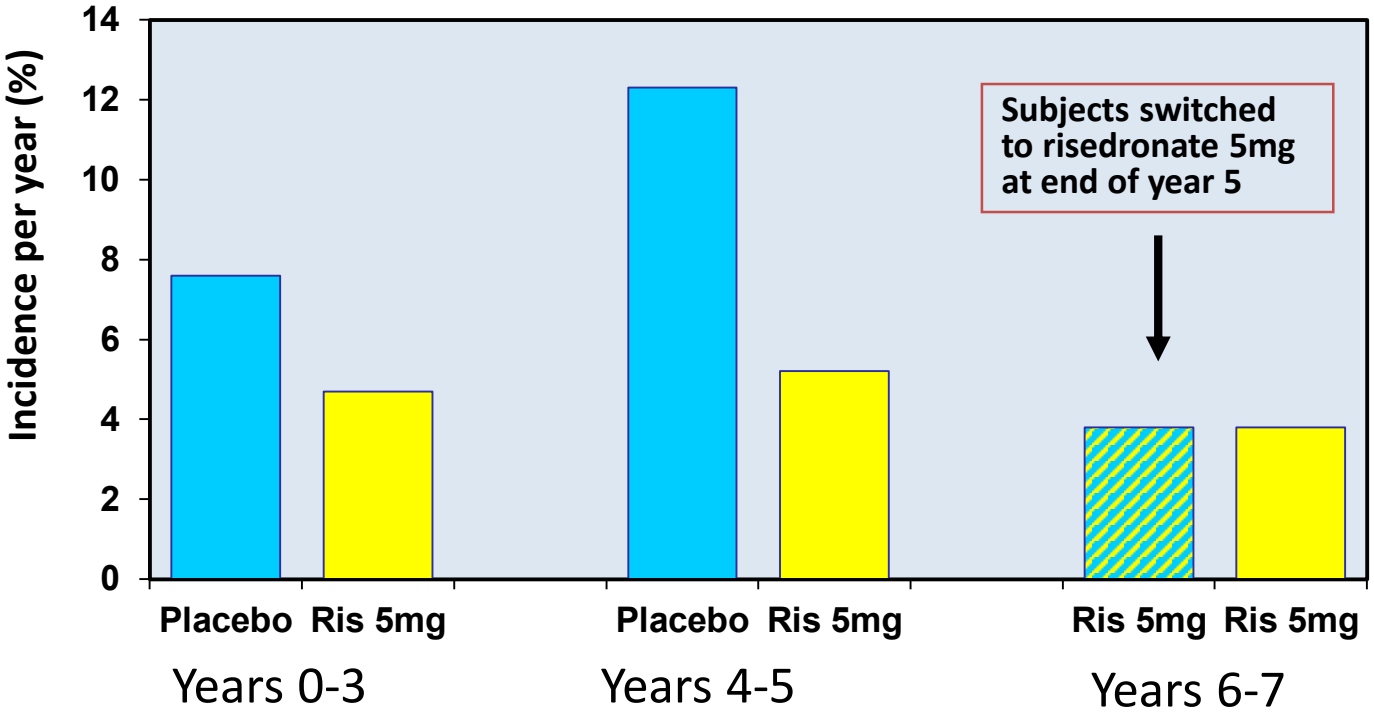
Percent change in bone markers during 3 years of blinded treatment with placebo or risedronate 5 mg daily, followed by 1 year of open label treatment with calcium



Watts NB al. Osteoporos Int 2008

Annualised Incidence of Patients with New Vertebral Fracture During Years 0-3, 4-5 or 6-7

VERT-MN: Radiographic Vertebral Fracture



Mellström DD et al. Calcif Tissue Int 2004

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.

McClang M et al. Am J Med 2013

frontiers in Pharmacology

ORIGINAL RESEARCH
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Cost-Effectiveness of Zoledronic Acid Versus Oral Alendronate for Postmenopausal Osteoporotic Women in China

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Conclusions: Among postmenopausal osteoporotic women in China, zoledronic acid therapy is cost-effective at all ages examined from health care payer perspective, compared with weekly oral alendronate. In addition, alendronate treatment is shown to be dominant for patients at ages 65 and 70 with full persistence. This study will help

Drug holiday studies

STUDY	COMPARATOR GROUPS	LENGTH OF TREATMENT, Y	DRUG HOLIDAY, Y	FRACTURE CHANGES DURING DRUG HOLIDAY PERIOD	SURROGATE MEASURE CHANGES DURING DRUG HOLIDAY PERIOD
Black et al,[56] 2012	ZOL (6 y) vs ZOL (3 y) then PBO (3 y)	3 or 6	3	• No significant differences between groups for all clinical fractures (HR = 1.04, 95% CI 0.71 to 1.54) • No significant difference between groups for nonvertebral fractures (8.2% with ZOL, 7.6% with PBO; HR = 0.99, 95% CI 0.26 to 0.95) • Significant difference between groups for morphometric vertebral fractures (3.0% with ZOL, 6.2% with PBO; OR = 0.51, 95% CI 0.26 to 0.95) • No significant difference between groups for clinical vertebral fractures (HR = 1.81, 95% CI 0.53 to 6.2, NS)	• ZOL mean FN BMD change of 0.24% vs -0.80% in PBO (mean difference 1.04%, $P < .001$) • ZOL mean LS BMD increased by 3.20% vs 1.18% for PBO (mean difference 2.03%, $P < .01$) • At all sites, BMD after 6 y of ZOL therapy was significantly ($P < .05$) greater than for those given ZOL for 3 y and then PBO for 3 y (except distal radius) • Serum N-terminal propeptide of type I collagen rose slightly in both the ZOL (19%) and PBO (33%) groups ($P < .001$), but remained substantially below pretreatment levels • Adverse events were similar between groups, but there was a significantly larger incidence of elevated serum creatinine > 0.5 mg/dL from baseline in the ZOL group (n = 18) compared with the PBO (n = 4) group ($P < .01$). All cases were transient and resolved without affecting renal function
Watts et al,[91] 2008	RIS vs PBO	3	1	• Previous RIS group (1-y holiday) had 46% lower risk of morphometric vertebral fracture (RR = 0.54, 95% CI 0.34 to 0.86) compared with previous PBO • Nonvertebral fractures were 5.0% in previous PBO group and 4.8% in previous RIS group (NS)	• In the previous RIS group, BMD significantly decreased at the LS (-0.83%, 95% CI -1.30 to -0.35) and FN (-1.23%, 95% CI -1.87 to -2.19), but remained above baseline • BTM after 1 y returned to baseline levels

Brown JP, 2014