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Hot topics in osteoporosis

Is drug holiday a useful trick?

AME / AACE 2013

Francisco Bandeira,M.D.,PhD.,F.A.C.E.

Professor of Medicine and Chairman, Division of Endocrinology and Diabetes, Agamenon Magalhães Hospital, University of Pernambuco Medical School, Recife, Brazil

Disclosure

Consultant (Advisor):
Paget Foundation (USA), MSD, Servier

Research Grant:
MSD, GSK, BMS/AZ, Novo Nordisk, Amgen, Takeda, Amylin

Outline

- Effects of treatment on fracture risk
- The residual effect of bisphosphonates
- Long-term adverse effects of bisphosphonate use
- Alternatives to “drug holiday”

Vertebral Fracture reduction in Pivot Trials

study	Increase in BMD	Reduction in vertebral Fx (RRR)	Baseline Vertebral Fx	ARR / NNT (3yr)	Drug
FIT II	8.3%	44%	0%	**1.7% / 59**	alendronate
FIT I	7.9%	47%	100%	**7% / 15**	alendronate
VERT$_{MN}$	7.1%	39%	100%	**10% / 10**	risedronate
VERT$_{NA}$	5.4%	31%	100%	**5% / 20**	risedronate
MORE	2.6%	35%	37%	**6.5% / 16**	raloxifen
BONE	6.0%	52%	100%	**4.9% / 21**	ibandronate
FPT	14%	65%	100%	**9% / 12**	teriparatide
HORIZON	7.0%	70%	60%	**7.6% / 14**	Zoledronic acid
SOTI	14%	41%	100%	**11% / 9**	Strontium Ranelate
FREEDOM	10%	68%	23%	**4.8 / 21**	Denosumab

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Global Fracture Risk Reduction

	Vertebral Fracture	Non-vertebral Fracture	Hip Fracture
ZOL	+	+	+
RIS	+	+	+
ALN	+	+	+
Strontium	+	+	+ (*)
Estrogen	+	+	+
TPD	+	+	-
Calcitriol	+	-	-
IBN	+	+ (*)	+ (*)
RLX	+	-	-
PTH 1-84	+	-	-
Calcitonin	+	-	-
Denosumab	+	+	+

*post-hoc subgroup analysis

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Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis.

Network meta-analysis techniques (meta-analysis, adjusted indirect comparison, and mixed treatment comparison [MTC]) allow for treatment comparisons in the absence of head-to-head trials. In this study, conditional estimates of relative treatment efficacy derived through these techniques show important differences in the fracture risk reduction profiles of marketed pharmacologic therapies for postmenopausal osteoporosis.

Source articles were identified in MEDLINE; EMBASE; Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Interscience; and Cumulative Index to Nursing and Allied Health Literature (CINAHL) between April 28, 2009 and November 4, 2009. Two reviewers identified English-language articles reporting randomized controlled trials (RCTs) with on-label dosing of marketed osteoporosis agents and fracture endpoints.

RESULTS:

Using data from 34 studies, random effects meta-analysis showed:

All agents except etidronate significantly reduced the risk of new vertebral fractures compared with placebo.

Denosumab, risedronate, and zoledronic acid significantly reduced the risk for nonvertebral and hip fracture.

Alendronate, strontium ranelate, and teriparatide significantly reduced the risk for nonvertebral fractures.

MTC showed denosumab to be more effective than strontium ranelate, raloxifene, alendronate, and risedronate in preventing new vertebral fractures.

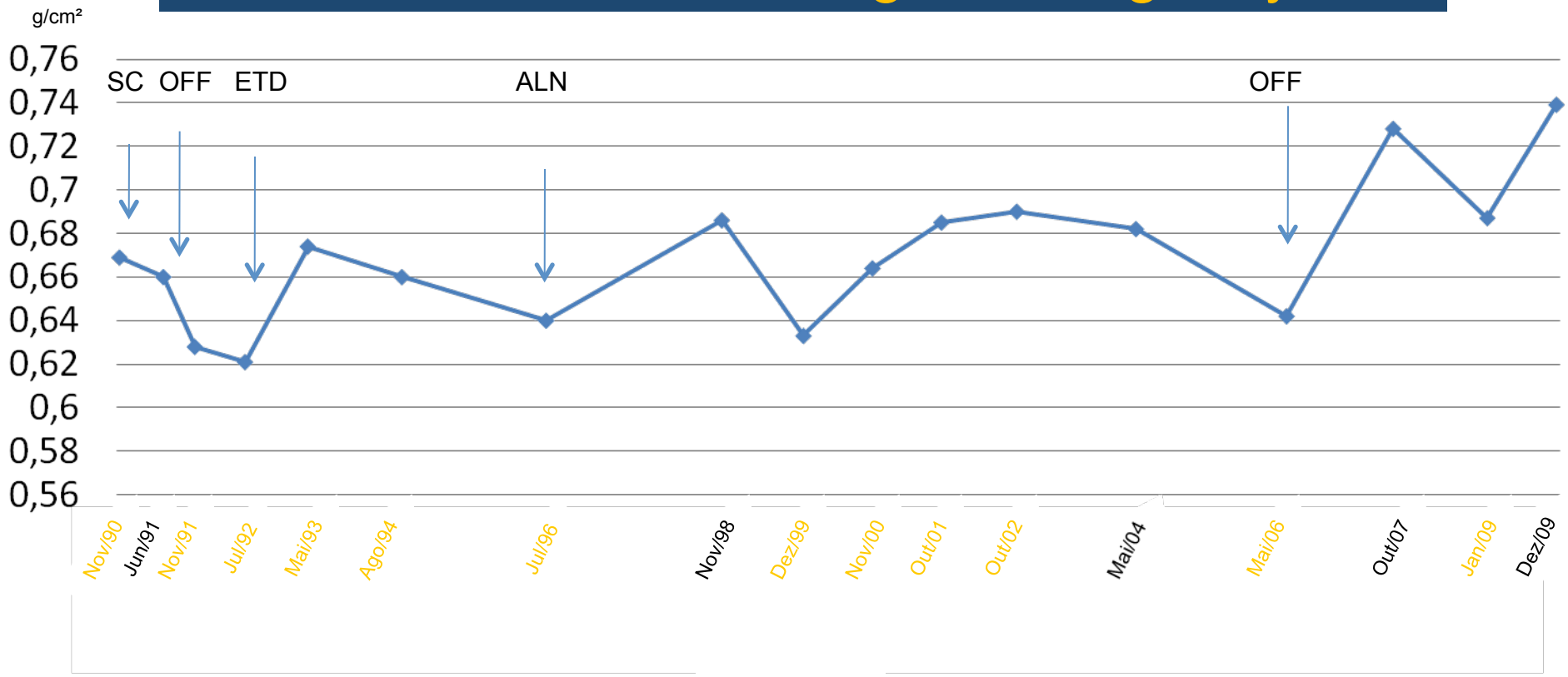
Freemantle N et al *Osteoporos Int 2012*

Nitrogen-containing bisphosphonates differ in the strength of binding to bone surface, so…

THE RESIDUAL EFFECT OF HIGHER-AFFINITY BISPHOSPHONATES MAY BE GOOD FOR THE PATIENT

62 yr, VF (T10, T12), LSBMD -3.2, FNBMD -3

Femoral Neck BMD changes during 20 years



CTX= 67 pg /ml
25OHD = 34 ng / ml

LSBMD +12.7%
FNBMD +17.6%

Diogenes L, Voss L & Bandeira F. *Arq Bras Endocrinol Metab*, 54(Suppl 4), S461, 2010

The goal of drug holiday is to allow suppressed bone turnover to partially recover without compromise anti-fracture efficacy,

WITH THE POTENTIAL TO REDUCE LONG-TERM ADVERSE EFFECTS SUCH AS ONJ AND AFF

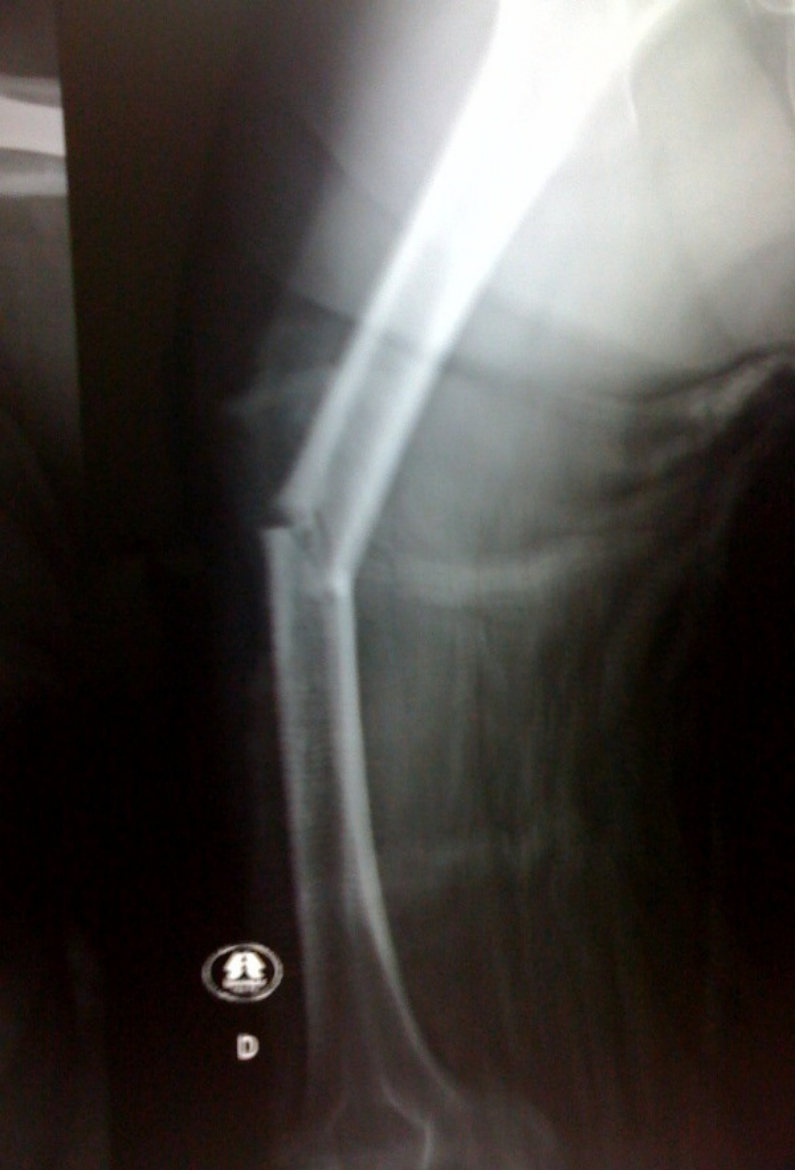
Adverse Effects of Bisphosphonate Therapy

Short-term:

- Erosive pharingitis
- Upper GI Adverse Effects
- Acute Phase Reaction
- Severe Musculoskeletal Pain
- Hypocalcemia
- Ocular Inflammation
- Atrial Fibrilation
- Seizures

Long-Term

- Esophageal Cancer with oral BPs??
- Atypical femoral fractures
- Osteonecrosis of jaw
- Zebra lines at diaphysis



A 63-year-old white woman, menopausal for 13 years, was referred because of recurrent femoral subtrochanteric fractures.

The first one was at the left femur, which she had had for one year and which had not healed, as well as a recent fracture located at the right femur.

She reported pain at the fracture sites, but no history of trauma.

She has been taking alendronate for approximately five years and risedronate 35 mg/week during the previous 12 months

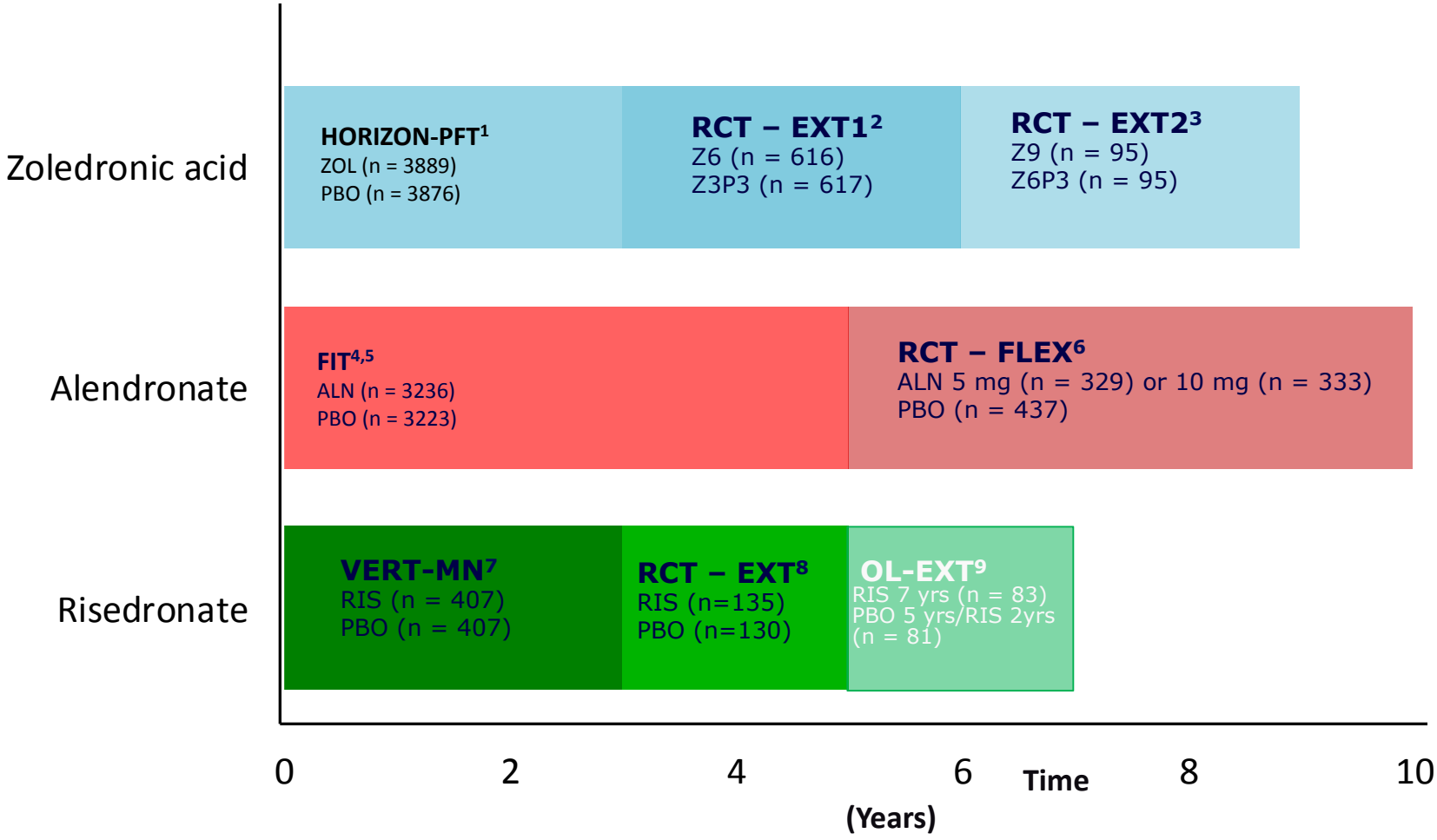
4 cases out of 790 pmw on long-term BPs (0.5%)

From 52,595 pmw with at least 5 yr of BPs:
0.13% after 1yr
0.22% after 2yr

Carvalho NNC, Voss LA, Almeida MOP, Salgado CL & Bandeira F. *J Clin Endocrinol Metab* 2011

Park-Wyllie LY *et al JAMA* 2011

Osteoporosis Treatment Extension Studies



ALN = alendronate; DB = double-blind; EXT 1= extension 1; EXT 2= extension 2; FIT = Fracture Intervention Trial; FLEX = FIT Long-term EXtension; HORIZON-PFT = Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly Pivotal Fracture Trial; OL, Open-label; PBO = placebo; RCT = randomized controlled trial; RIS = risedronate; VERT-MN = Vertebral Efficacy with Risedronate Therapy MultiNational; Z3P3 = zoledronic acid treatment for 3 years followed by placebo for 3 years; Z6 = zoledronic acid treatment for 6 years; ZOL = zoledronic acid.

1. Black DM, et al. *N Engl J Med*. 2007;356:1809-1822. 2. Black DM, et al. *J Bone Miner Res*. 2012; 27:243-254. 3. ASBMR 2013 (abstract). 4. Black DM, et al. *Lancet*. 1996;348:1535-1541. 5. Cummings SR, et al. *JAMA*. 1998;280:1077–2082. 6. Black DM, et al. *JAMA*. 2006;296:2927-2938. 7. Reginster J-Y, et al. *Osteoporos Int*. 2000;11:83–91. 8. Sorensen OH, et al. *Bone*. 2003;32:120-126. 9. Mellström DD, et al. *Calif Tissue Int*. 2004;75:462-468.

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%		

Whitaker M *et al NEJM* 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

5 mg/day had the same result as 10 mg/day

Black D *et al NEJM* 2012

Extension of the HORIZON-FPT

- 67% reduction in new morphometric VFx at 3 yr (FPT)
- Z6 : 67% reduction in new VFx
- Z3P3: 37% reduction in new VFx

- RR=0.48 between the groups; p=0.04
- Benefit of 6 yr treatmen:

FNBMD at 3yr < 2.5 or a fracture during the 1st 3yr

Z6P3 vs Z9: NS

Black D *et al ASBMR* 2013

ALTERNATIVES TO “DRUG (bisphosphonate) HOLIDAY”

Other interventions during “drug holiday”

Interventions that Reduce Fall Risk in Older Adults

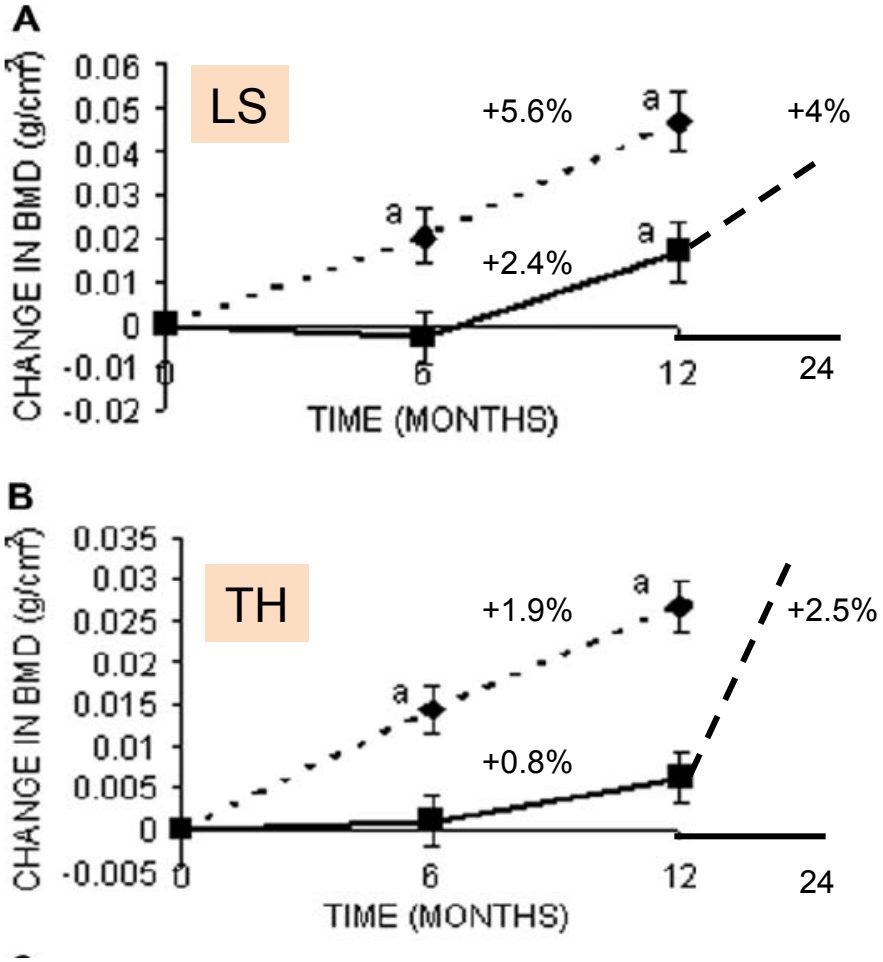
Intervention	Relative Risk Reduction
Multiple risk factor reduction	25%
Exercise interventions, Tai Chi	17-34%
Withdrawal of psychoactive medications	66%
Cataract surgery	34%
Home safety evaluation for high risk or visually impaired	22%
Vitamin D supplements (NH residents and insufficient community-dwellers)	25%

Adapted from Gillespie et. al., Cochrane Database of Systematic Reviews November, 2012
DOI: 10.1002/14651858.CD007146.pub3

For the high risk patient one alternative would be switch to another class of osteoporosis medication -

STRONTIUM RANELATE

Changes in BMD and BTM of postmenopausal women on SR with and without previous treatment with BP



- BPs naive: No significant changes in BTM

- Prior BPs:
- Serum CTX +61%
- Serum P1NP +55%
- Serum BSAP +46%

Middleton *et al JBMR* 2010
Middleton *et al Osteoporos Int* 2012

Changes in serum CTx and osteocalcin after starting SR in postmenopausal women previously treated with BPs

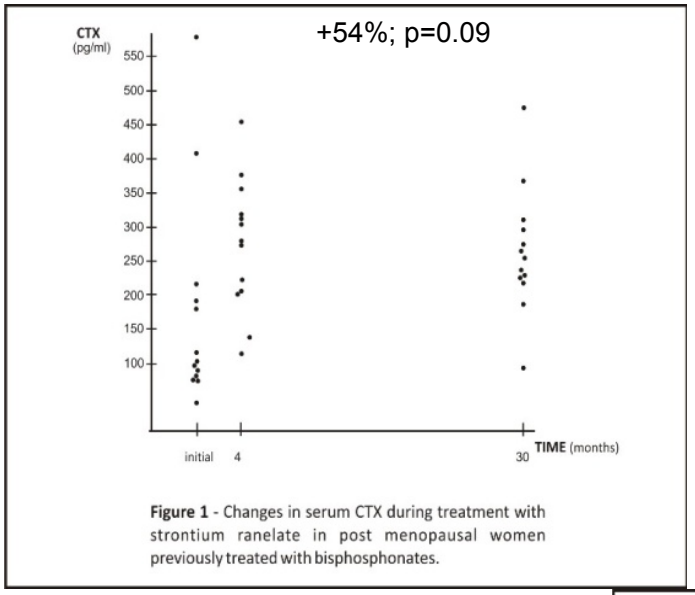


Figure 1 - Changes in serum CTX during treatment with strontium ranelate in post menopausal women previously treated with bisphosphonates.

CTX

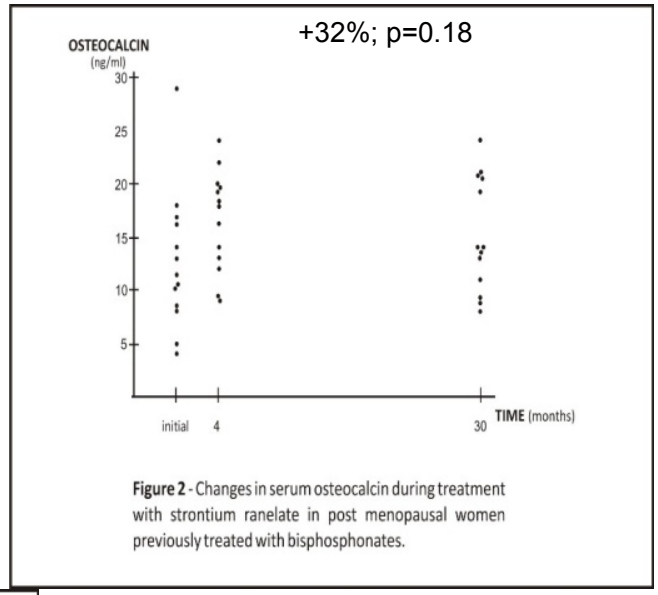


Figure 2 - Changes in serum osteocalcin during treatment with strontium ranelate in post menopausal women previously treated with bisphosphonates.

Osteocalcin

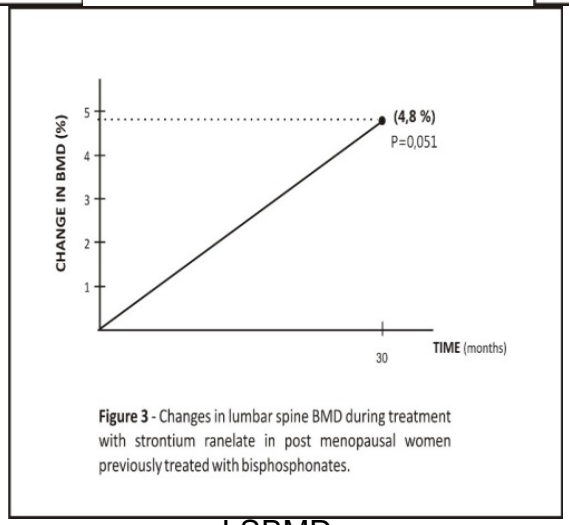


Figure 3 - Changes in lumbar spine BMD during treatment with strontium ranelate in post menopausal women previously treated with bisphosphonates.

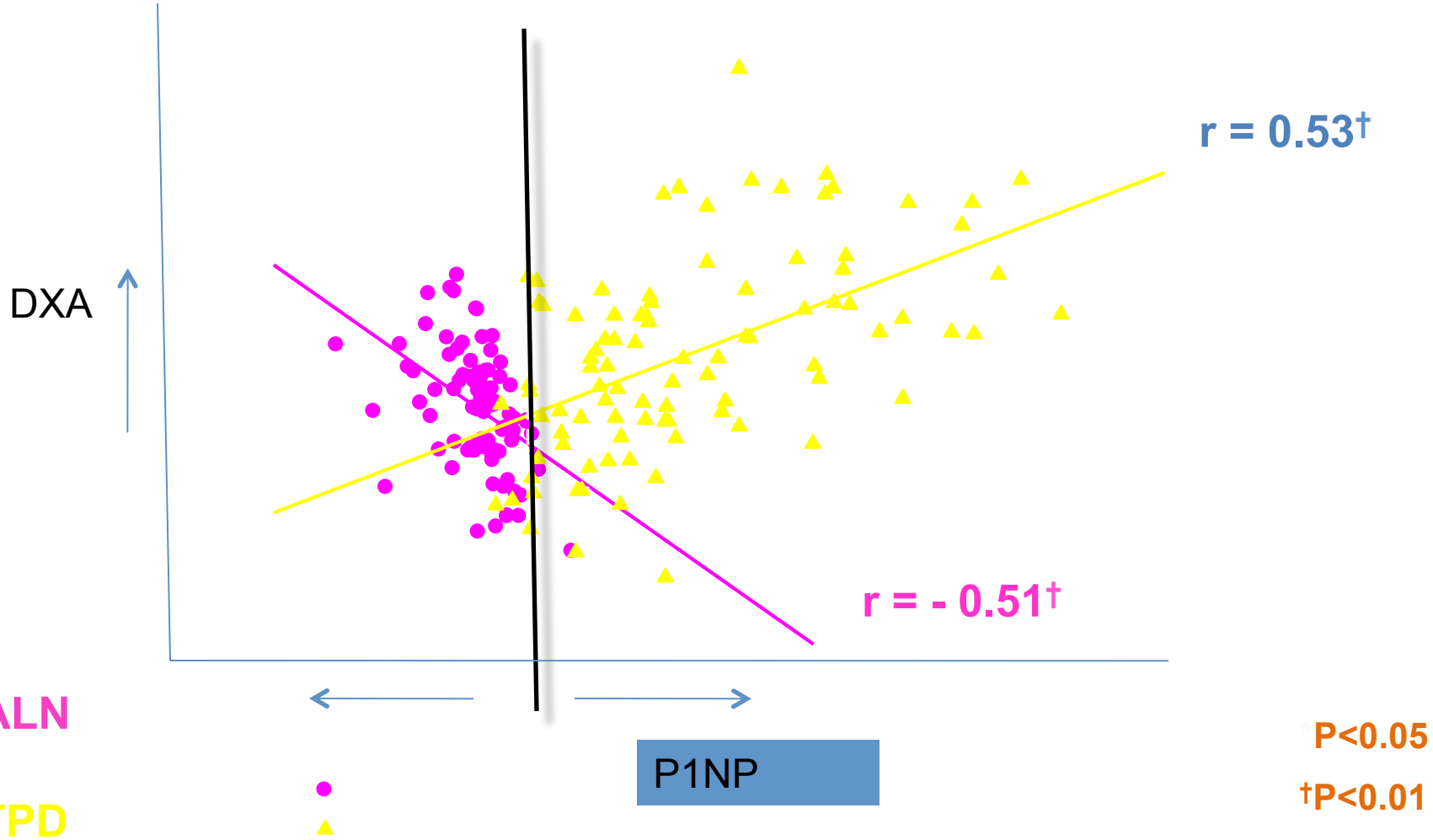
LSBMD

Souza IO, Diniz ET, Marques TF, Griz LH, Countinho M & Bandeira F. *Arq Bras Endocrinol Metab* 2010

Lima H & Bandeira F. *Arq Bras Endocrinol Metab* 2013

TERIPARATIDE

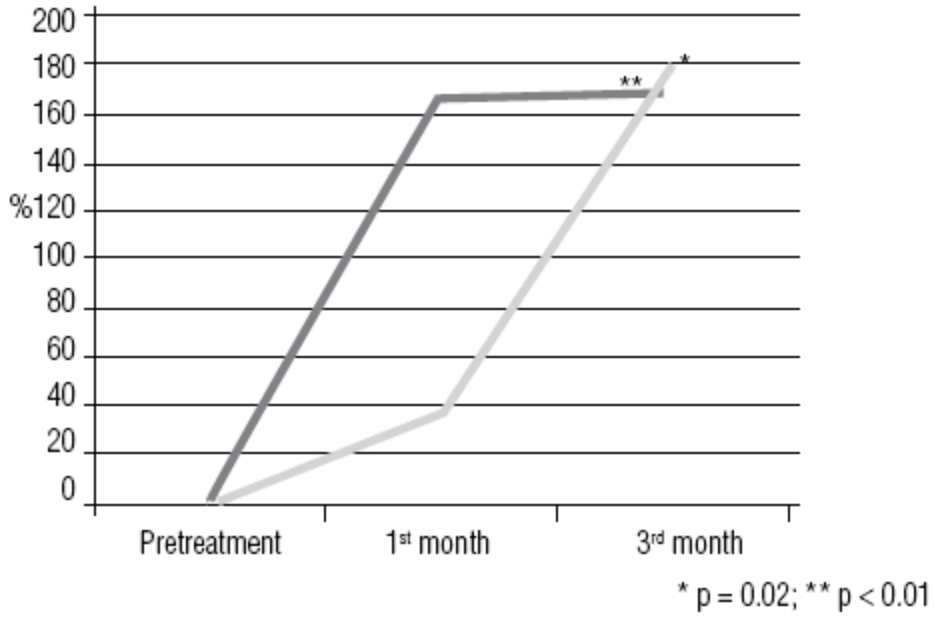
Alendronate *vs* Teriparatide: BMD and P1NP



McClung M, San Martin J, Miller P, Bandeira F. *Arch Intern Med* 2005

Teriparatide in pmw after long-term BPs

Short-term changes in BTM



- ** OC
- * CTx

Figure 2. Percent changes in serum β-CTX and osteocalcin after 1 and 3 months of therapy with teriparatide in patients with osteoporosis previously treated with bisphosphonates.

Souza IO, Diniz ET, Marques TF, Griz LH, Countinho M & Bandeira F.
Arq Bras Endocrinol Metab 2010

Baseline characteristics of postmenopausal women on TPD with and without previous treatment with BPs

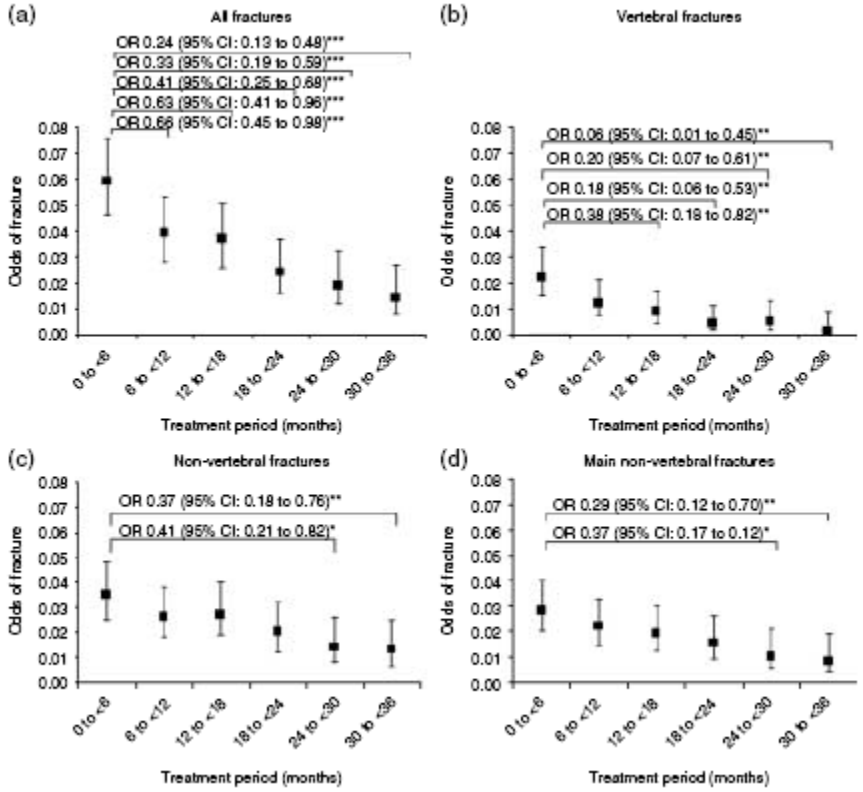
European Forsteo Observation Study - EFOS

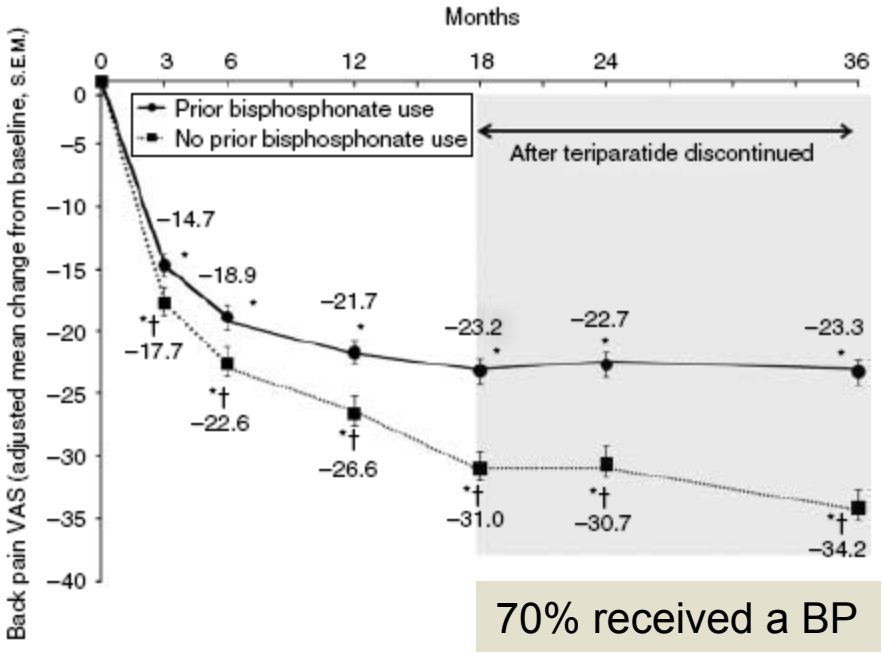
Characteristic	Prior BP use (n=1161)	No prior BP use[a] (n=420)	P value[b]
Demographics			
Age (years)	71.2 (8.1)	70.2 (9.0)	0.038
Caucasian (%)	99.1	99.5	0.738
BMI (kg/m^2)	25.0 (4.3)	25.5 (4.3)	0.035
Menopausal status			
Early menopause, <40 years of age (%)	8.4	10.4	0.253
Surgical menopause (%)	20.4	13.9	0.005
Risk factors			
Nulliparous (%)	13.5	11.9	0.401
Current smoker (%)	13.2	12.4	0.675
Osteoporotic hip fracture in mother (%)	20.3	22.4	0.445
Lumbar spine BMD *T*-score	−3.22 (1.22)	−3.41 (0.96)	0.018
Total hip BMD *T*-score	−2.59 (1.06)	−2.71 (0.99)	0.087
Uses arms when standing up from chair (%)	60.8	70.2	0.001
Sight problems (%)	47.8	37.4	<0.001
>1 fall in the last year (%)	22.7	23.9	0.821
Concomitant medications	747 (65.0)	253 (60.5)	0.102
Antihypertensives (%)	36.6	39.0	0.377
Glucocorticoids (%)[c]	16.1	11.2	0.017
Thyroid hormones (%)	13.3	13.4	0.967
Benzodiazepines (%)	13.2	8.6	0.013
Antidepressants (%)	10.9	8.4	0.147
Anticonvulsants (%)	2.3	0	<0.001
Comorbidities			
Rheumatoid arthritis (%)	12.4	10.5	0.296
Chronic obstructive pulmonary disease (%)	9.2	7.4	0.254
Diabetes mellitus (%)	4.7	7.9	0.014
Parkinson disease and other movement disorders (%)	1.2	2.9	0.023
Prior fractures			
Patients with prior fractures (%)	91.6	78.3	<0.001
Time since most recent fracture (years)[d]	0.9 (0.2:2.6)	0.4 (0.1:1.7)	<0.001
Number of previous fractures after age 40	3.2 (2.0)	2.1 (1.7)	<0.001
At least one fracture in 12 months before study entry (%)	47.2	51.7	0.117
Baseline back pain and HRQoL			
Back pain VAS	57.1 (26.4)	59.4 (27.3)	0.135
EQ-VAS	52.2 (20.8)	51.6 (25.1)	0.653

[a]Of these 420 patients, 292 (69.5%) reported having prior osteoporosis medication use, mostly antiresorptives (n=217, 51.7%); 121 (28.8%) reported being treatment naive; data on other osteoporosis medication was missing/unknown for seven patients.

Jakob *et al EJE* 2012

EFOS - results





70% received a BP

Jakob *et al EJE* 2012

Conclusions

- Bisphosphonates continue to be the first-line agents for the treatment of postmenopausal osteoporosis and the residual effect of some BPs may allow "drug holiday“ to be implemented.

  Although AFF is a rare event, it may cause considerable limitation for the patient, require surgical treatment and may follow with delayed healing.

  "Drug holiday" may decrease the risk of adverse events without compromise the anti-fracture efficacy.

  Follow up with BTM and BMD will allow the recognition of the appropriate time to re-started treatment.

  Switch to strontium ranelate or teriparatide, or reduce the BP dose, beyond 5 years for ALN and 3 years for ZOL may be alternatives for the high risk patient.

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Bandeira
Gharib
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Faria
Editors
Endocrinology and Diabetes
A Problem-Oriented Approach

Internal Medicine

ISBN 978-1-4614-8683-1

9 781461 486831

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PRO HUMANITAS
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Metabolic Group

Francisco Bandeira, MD,PhD
Luiz Griz, MD,PhD
Elba Bandeira, MD, MSc
Jessica Garcia, MD, MSc
Cynthia Salgado, MD, MSc
Fernando Gondim, MD, MSc
Erik Diniz,MD, MSc
Patricia Mesquita, MD
Juliana Maia, MD
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