Osteoporosis treatment: Antiresorptive agents

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Disclosure

Declaração de conflitos de interesse

None

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**	Zoledronate
SOTI	14%	41%	100%	**11% / 9**	Strontium Ranelate
FREEDOM	10%	68%	23%	**4.8 / 21**	Denosumab

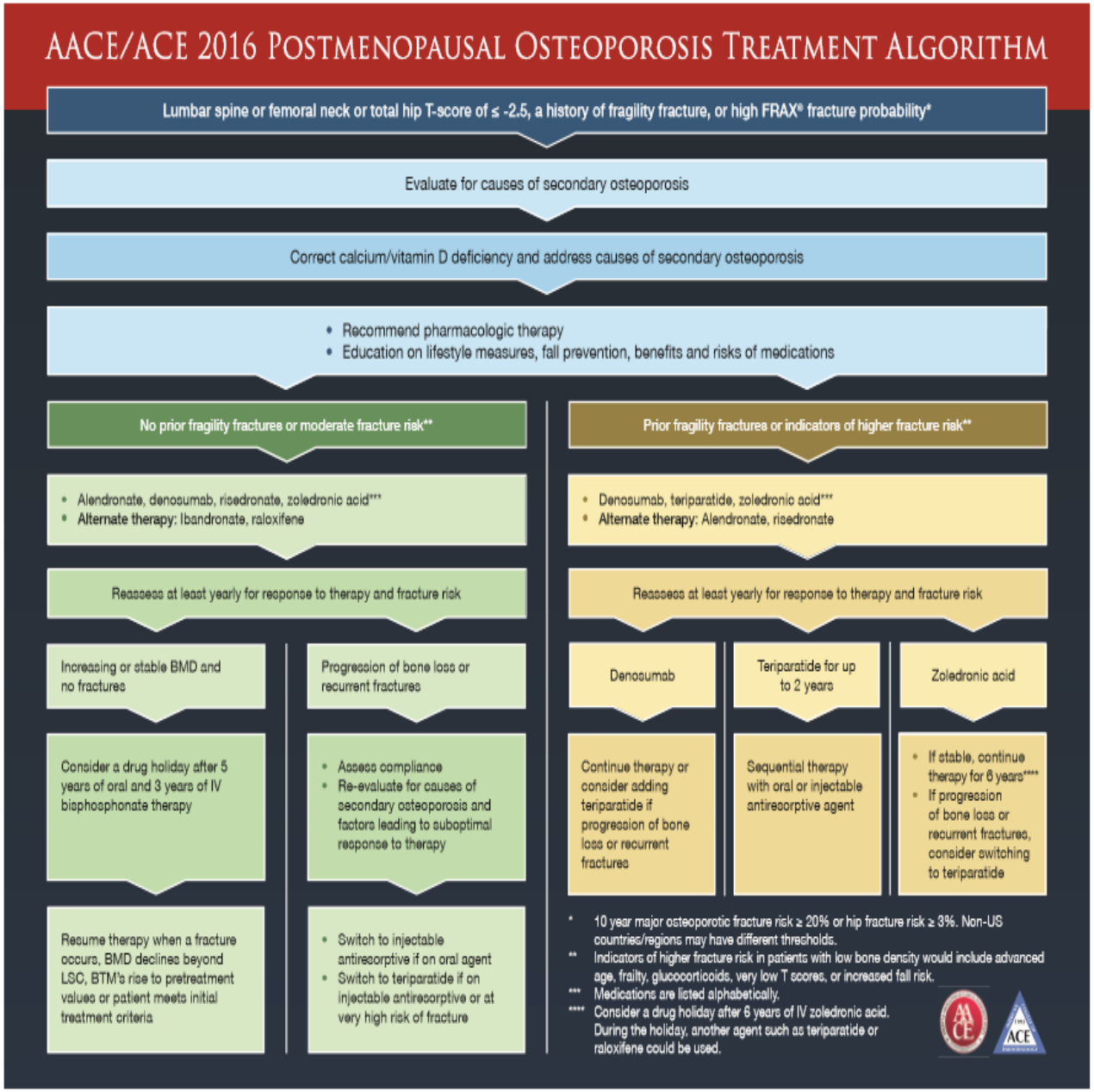
Bandeira F et al (Eds.) Endocrinology and Diabetes: A Problem-Oriented Approach; 2nd Ed. Springer, New York (in press)

Global Fracture 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

Bandeira F, 2018



Camacho PM, Petak SM, Binkley N, et al. Endocr Pract. 2016;22(Suppl 4):1-42.

ZOL in Osteopenia

Mean FRAX RS for Hip Fx 2.3%

Mean FNBMD T-score -1.6

Vitamin D: 50,000 IU/mo

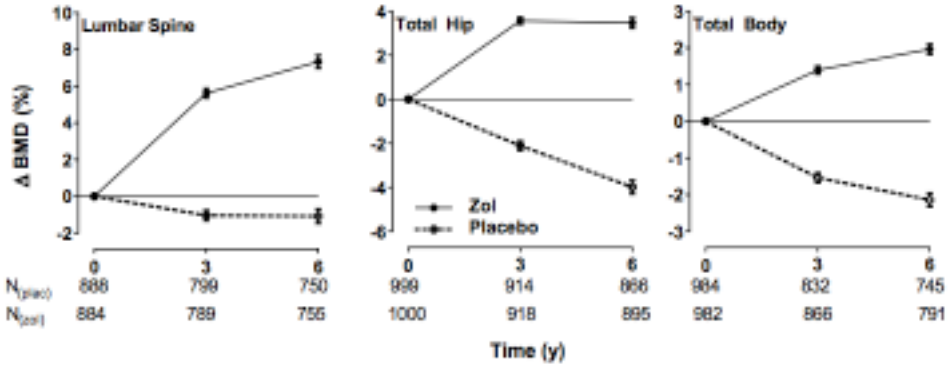
Zol 5 mg or placebo each 18 mo
6 yr duration

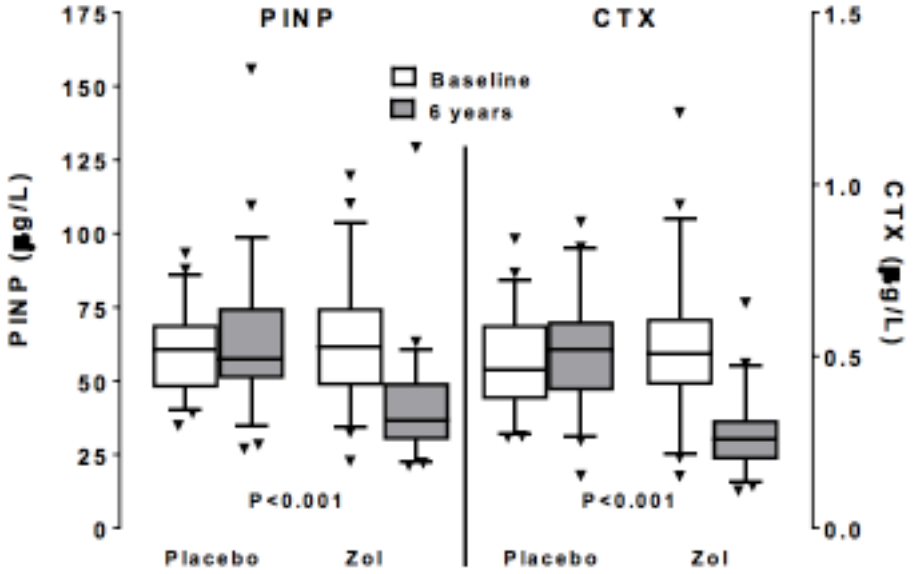
Table 1. Characteristics of the Trial Participants at Baseline.*

Characteristic	Placebo (N=1000)	Zoledronate (N=1000)
Age — yr	71±5.1	71±5.0
Ethnic group — no. (%)†		
European	940 (94.0)	954 (95.0)
Maori	14 (1.4)	17 (1.7)
Pacific Islander	15 (1.5)	7 (0.7)
East Asian	24 (2.4)	15 (1.5)
Indian	5 (0.5)	5 (0.5)
Other	2 (0.2)	2 (0.2)
Height — cm	160.4±5.8	160.7±5.8
Weight — kg	69.2±12.2	69.1±12.5
Body-mass index‡	26.9±4.7	26.8±4.6
Dietary calcium intake — mg per day	882±388	871±360
History of nonvertebral fracture after 45 yr of age — no. (%)§	238 (23.8)	237 (23.7)
Prevalent vertebral fracture — no. (%)¶	126 (12.6)	137 (13.7)
Median 10-year risk of osteoporotic fracture (IQR) — %	12 (9–15)	12 (9–16)
Median 10-year risk of hip fracture (IQR) — %	2.3 (1.5–3.8)	2.4 (1.5–3.9)
Bone mineral density — g/cm^2		
Lumbar spine	1.08±0.14	1.07±0.13
Total hip	0.85±0.08	0.85±0.08
Femoral neck	0.81±0.07	0.81±0.07
Total body	1.06±0.07	1.06±0.07
Bone density T score		
Lumbar spine	−0.87±1.16	−0.91±1.12
Total hip	−1.24±0.60	−1.27±0.59
Femoral neck	−1.63±0.47	−1.64±0.47
Total body	−0.80±0.90	−0.81±0.86
Current smoker — no. (%)	33 (3.3)	23 (2.3)

Reid I et al NEJM 2018

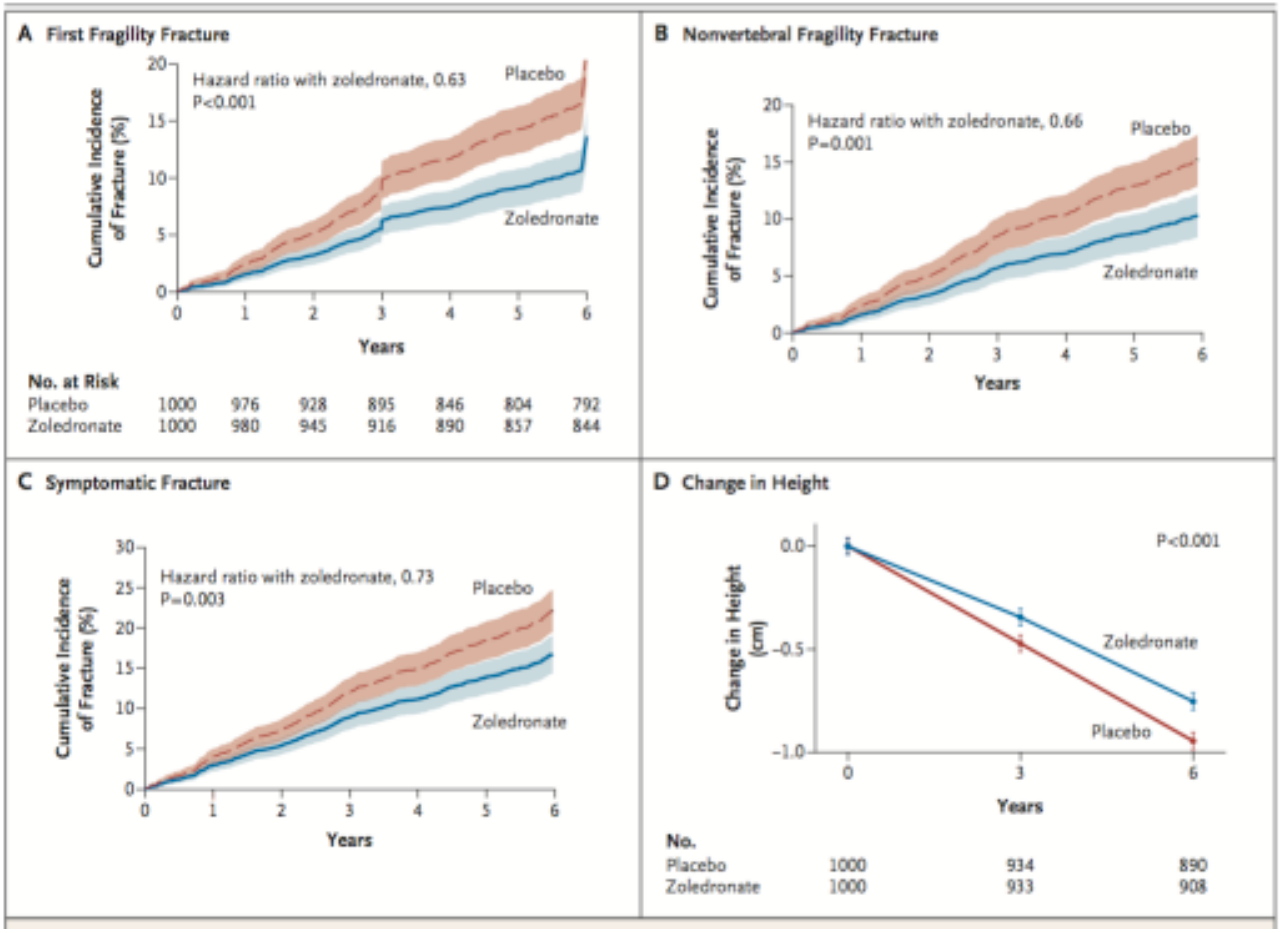
Changes in BMD and BTM





Reid I et al NEJM 2018

Cumulative Incidence of Fractures and Change in Height



Reid I et al NEJM 2018

Non-Skeletal Data

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)

* This category included any of the following events: sudden death, myocardial infarction, coronary-artery revascularization, or stroke.
† This category excluded nonmelanoma skin cancers.

Reid I et al NEJM 2018

ASBMR task-force for prolonged treatment

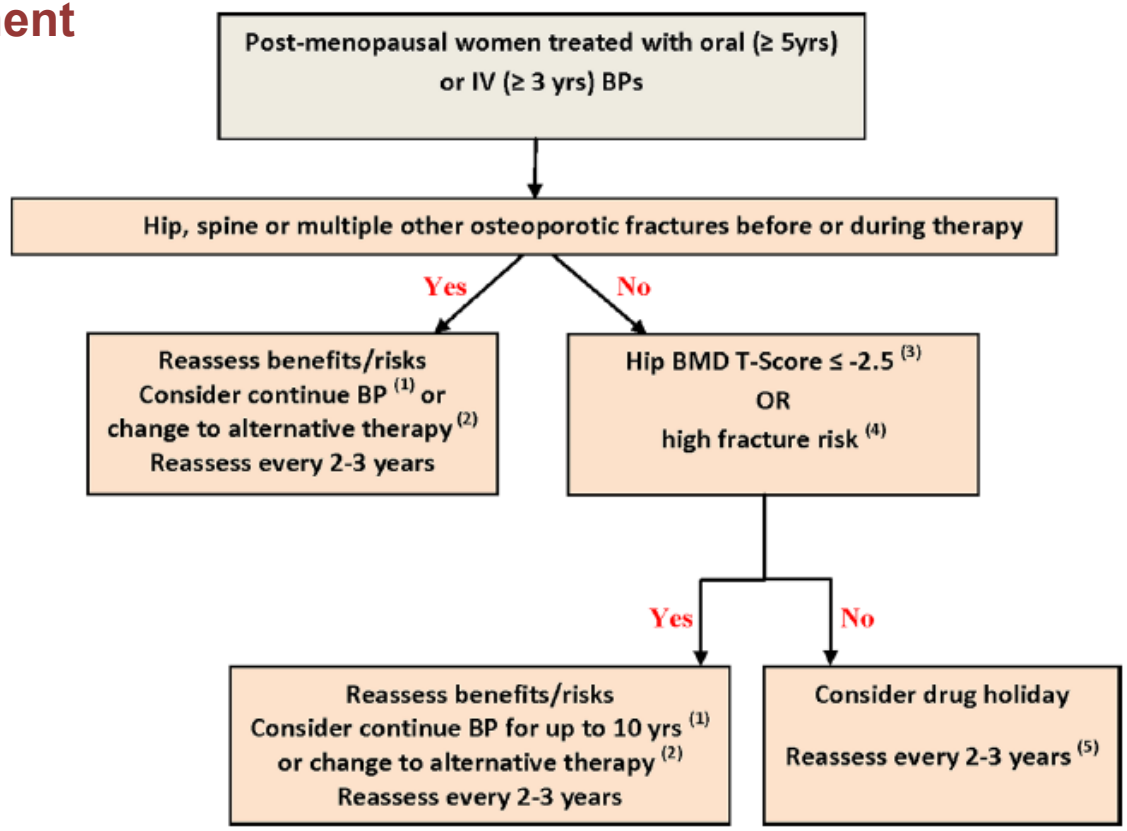


Fig. 2. Approach to the management of postmenopausal women on long-term bisphosphonate therapy. (1) From the registration trials, the benefits of 5 years of therapy clearly outweigh the risks. For treatment up to 10 years with oral bisphosphonates (FLEX extension) and 6 years with intravenous bisphosphonates (HORIZON extension), estimates of benefits and risks are based on much weaker data. For patients who fracture on therapy, assess adherence and rule out secondary causes of osteoporosis. Management of high risk patients is discussed in the text. (2) The benefits of switching to an alternative anti-fracture therapy after prolonged bisphosphonate treatment have not been adequately studied. (3) Based on FLEX and Horizon extension study (Caucasian women), may not apply to other populations. (4) High fracture risk: defined by older age (70–75 years), other strong risk factors for fracture, or FRAX fracture risk score that is above country specific thresholds. The use of FRAX in patients on therapy was only assessed in the Manitoba observational cohort.[66] (5) Reassessment includes clinical evaluation, risk assessment including risk factors, and may include bone density measurement by DXA. The monitoring interval with DXA should be based upon changes that are detectable and clinically significant. Reassessment may be necessary at less than 2 years in patients with a new fracture, or in light of anticipated accelerated bone loss (e.g. institution of aromatase inhibitor or glucocorticoid therapy).

Adler R et al J Bone Miner Res 2016

J Endocrinol Invest
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CONSENSUS STATEMENT

Italian association of clinical endocrinologists (AME) position statement: drug therapy of osteoporosis

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Recommendations

We recommend continuing therapy in patients with no prevalent vertebral fracture, after 5 years on oral alendronate or risedronate and a T-score BMD≤−2.5

We recommend continuing therapy in patients with a prevalent vertebral fracture, after 5 years on oral alendronate or risedronate and a T-score BMD ≤−2.0

We suggest considering the possible use of oral alendronate doses lower than 70 mg per week for treatment beyond 5 years

We recommend continuing annual infusions of zoledronate for up to 6 years in patients with a prevalent vertebral fracture, or in patients without prevalent fractures but with a FN T-score at 3 years ≤−2.5

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

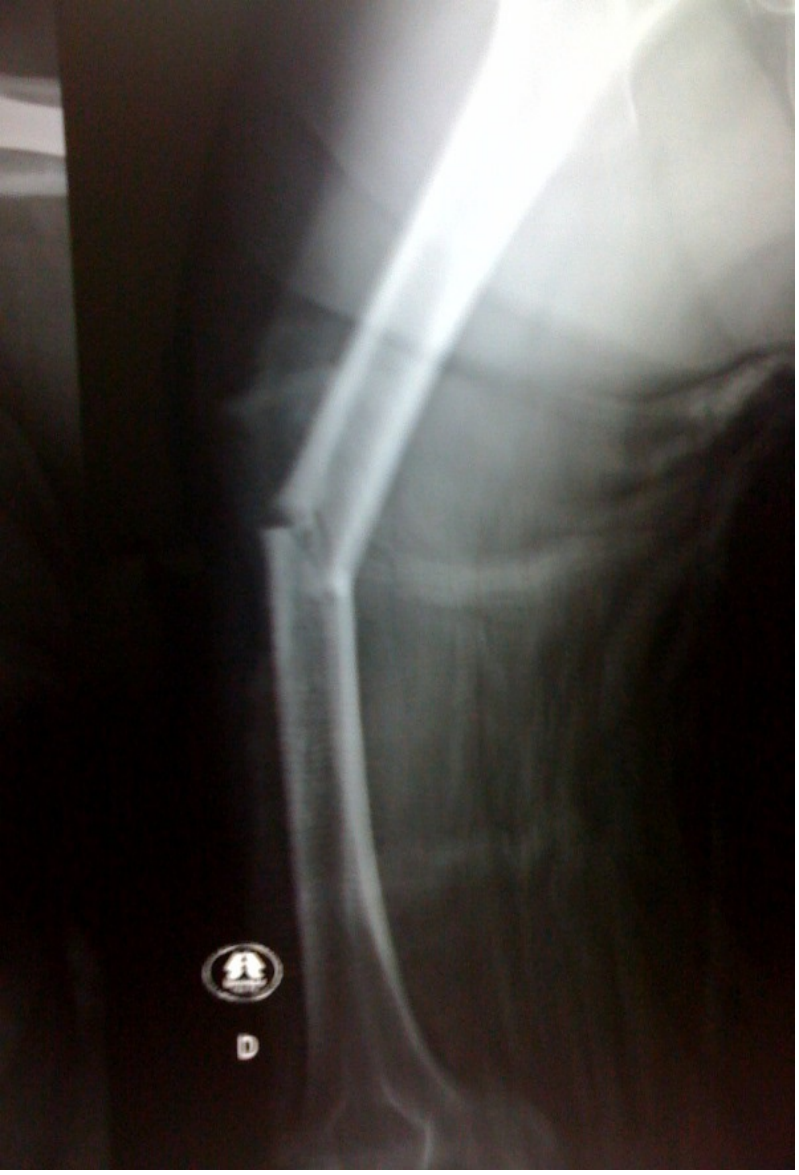
Extension of the HORIZON-FPT

- 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

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

Black D et al JBMR 2012



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

9 cases out of 1320 pmw on long-term BPs (0.68%)

Southern California Osteoporosis Cohort Study (SOCS)
The cohort included 152,934 women meeting inclusion criteria with 185 AFF (incidence rate 1.70 per 10,000 person-years). After adjustment for all confounders, there was a 44% reduction in the risk of AFF in the first year after discontinuation compared to women who continued to use BP (HR 0.56, CI 0.38-0.82). In years 1 to 4 after discontinuation, AFF risk was decreased by 80% (HR 0.20, CI 0.10-0.37) and after >4 years, AFF risk was reduced by 78% (HR 0.22, CI 0.08-0.59) compared to current users.

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

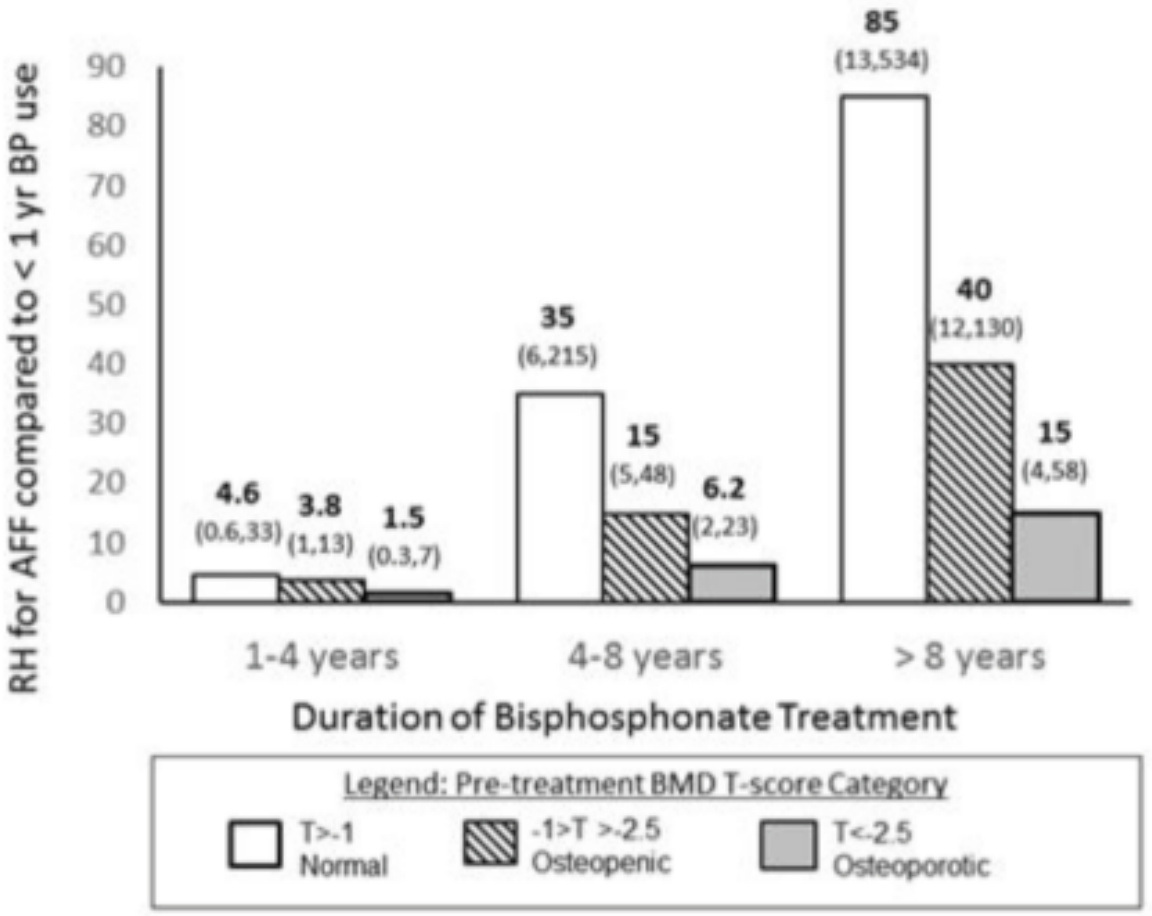
Carvalho NNC, Voss LA, Almeida MOP, Salgado CL & Bandeira F. *J Clin Endocrinol Metab* 2011

Park-Wyllie LY *et al JAMA* 2011

Adams AI et al ASBMR 2018 #1005

Bisphosphonate Use and Risk of AFF Varies by Pre-treatment BMD values

Southern California Osteoporosis Cohort Study (SOCS)



Black D et al ASBMR 2018 #1007

Hip Fracture Rate during Drug Holiday

A population-based cohort study of women on long term BP therapy to evaluate the rate of hip fracture following a drug holiday (temporary or permanent BP discontinuation).
Medicare data (2006-2015) were used to identify all women with medical and pharmacy coverage who initiated a BP and were at least 80% adherent for at least 3 years ('baseline'), at which time follow-up began.

Table: Hip fracture Rate for BP Drug Holiday >2 years

Cohort	Women, n	Number of hip fractures, n	Crude Incidence Rate per 1000 person-years	Adjusted* Hazard Ratio (95% CI)
Any BP	160,369	4,823	14.0	1.22 (1.11 – 1.34)
Alendronate users	81,287	2,245	13.1	1.28 (1.12 – 1.46)
Risedronate users	9,823	269	13.8	1.45 (1.00 - 2.11)
Zoledronate users	13,885	367	18.0	1.31 (0.94 - 1.82)
Prior fragility fracture	6,914	430	37.4	1.38 (1.01 – 1.89)

*Hazard ratio for women with a drug holiday of >2 years compared to persistent users, adjusted for age, region, race, rural or urban, median income, calendar year of study entry, comorbidity (fragility fracture, Charlson comorbidity index), DXA, office visits, office visits with bone specialists, long term care residence, vitamin D deficiency, glucocorticoids, and other factors, assessed...

Curtis J et al ASBMR 2018; #1006

CLINICAL INVESTIGATION

Long-Term Oral Bisphosphonate Therapy and Fractures in Older Women: The Women's Health Initiative

In multivariate-adjusted analysis, 10 to 13 years of bisphosphonate use was associated with higher risk of any clinical fracture than 2 years of use (hazard ratio (HR) = 1.29, 95% confidence interval (CI) = 1.07– 1.57).

Drieling R et al J Am Geriatr Soc 2017

Fracture Incidence in 5,120 Postmenopausal Women with a 5-Year Risk of Hip Fracture of 1.5% or Greater and Risk of Fracture According to Duration of Bisphosphonate Use at 2008–09 Medication Inventory

Duration of Bisphosphonate Use, Years	Subjects, n	Fractures		Adjusted Hazard Ratio (95% Confidence Interval)
		N[a]	Incidence per 1,000 Person-Years	
	Hip fracture			
2	607	11	6.5	1.00
3–5	1,607	38	8.0	1.12 (0.53–2.34)
6–9	987	20	7.0	1.26 (0.56–2.81)
10–13	1,648	58	12.2	1.66 (0.81–3.40)
	Wrist or forearm fracture			
2	502	20	14.5	1.00
3–5	1,374	53	13.9	0.96 (0.55–1.66)
6–9	787	29	12.8	0.96 (0.53–1.75)
10–13	1,280	57	15.6	1.16 (0.67–2.00)
	Clinical vertebral fracture			
2	590	21	12.8	1.00
3–5	1,621	77	17.0	1.23 (0.73–2.06)
6–9	977	53	18.8	1.37 (0.80–2.37)
10–13	1,571	84	18.7	1.65 (0.99–2.76)
	Any clinical fracture			
2	642	141	86.1	1.00
3–5	1,746	419	92.1	1.04 (0.85–1.26)
6–9	1,031	254	92.2	1.04 (0.84–1.29)
10–13	1,701	499	112.2	1.29 (1.07–1.57)

Drieling R et al J Am Geriatr Soc 2017

DENOSUMAB

10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension

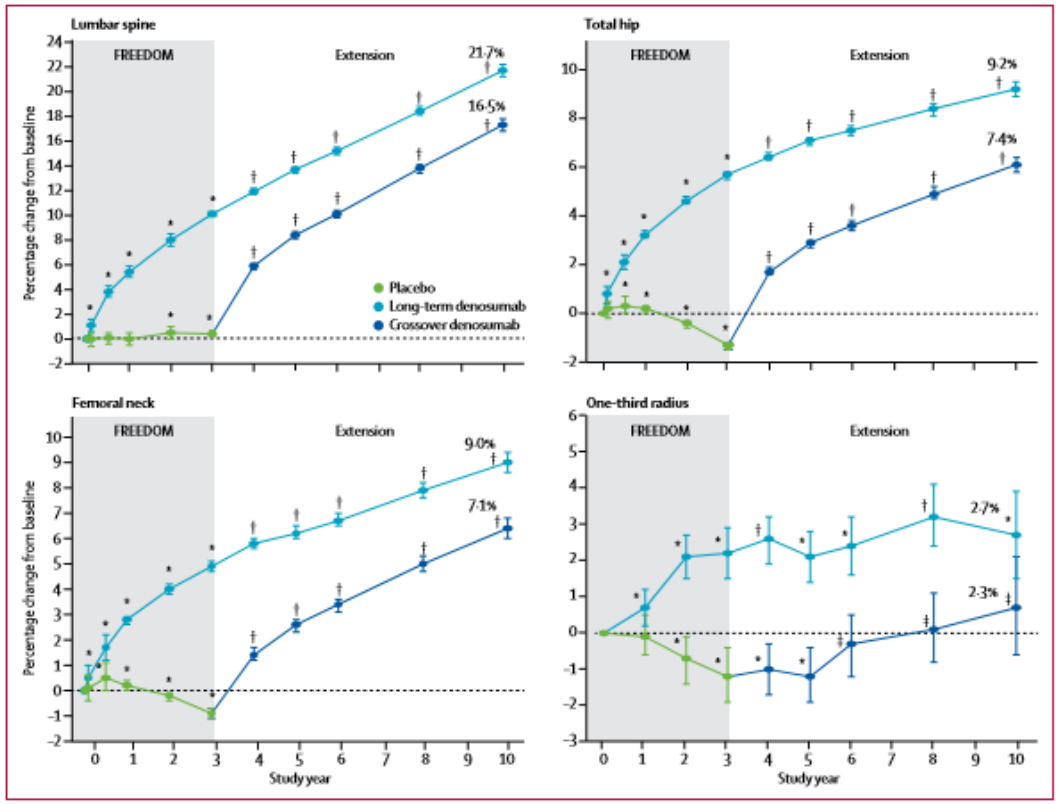


Figure 4: BMD during FREEDOM and the FREEDOM extension
Percentage changes from FREEDOM baseline in BMD are shown for the lumbar spine, total hip, femoral neck, and one-third radius. Final number listed at year 10 represents BMD percentage change while on denosumab treatment (from FREEDOM baseline for the long-term group and from extension baseline for the crossover group). Data are least-squares means (95% CI). BMD=bone mineral density. *p<0·05 compared with FREEDOM baseline. †p<0·05 compared with FREEDOM and extension baselines. ‡p<0·05 compared with extension baseline.

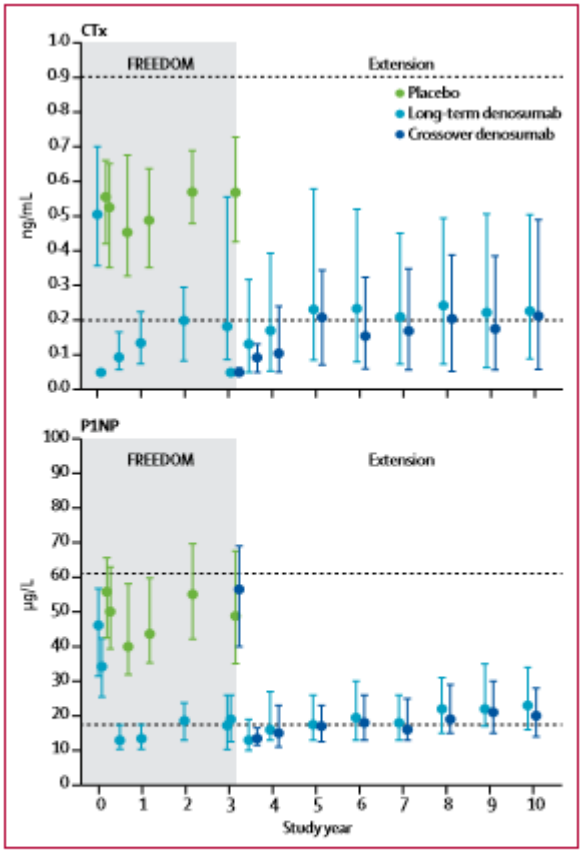


Figure 3: Serum bone turnover markers during FREEDOM and the FREEDOM extension
Serum concentrations of predose C-telopeptide of type I collagen (CTx) and procollagen type 1 N-terminal propeptide (P1NP) are shown. Dashed lines represent the premenopausal reference ranges: 0·20–0·90 ng/mL for CTx and 17·4–61·6 µg/L for P1NP. Data are median (IQR).

Bone H et al Lancet Diabetes Endocrinol 2017

10 years of denosumab

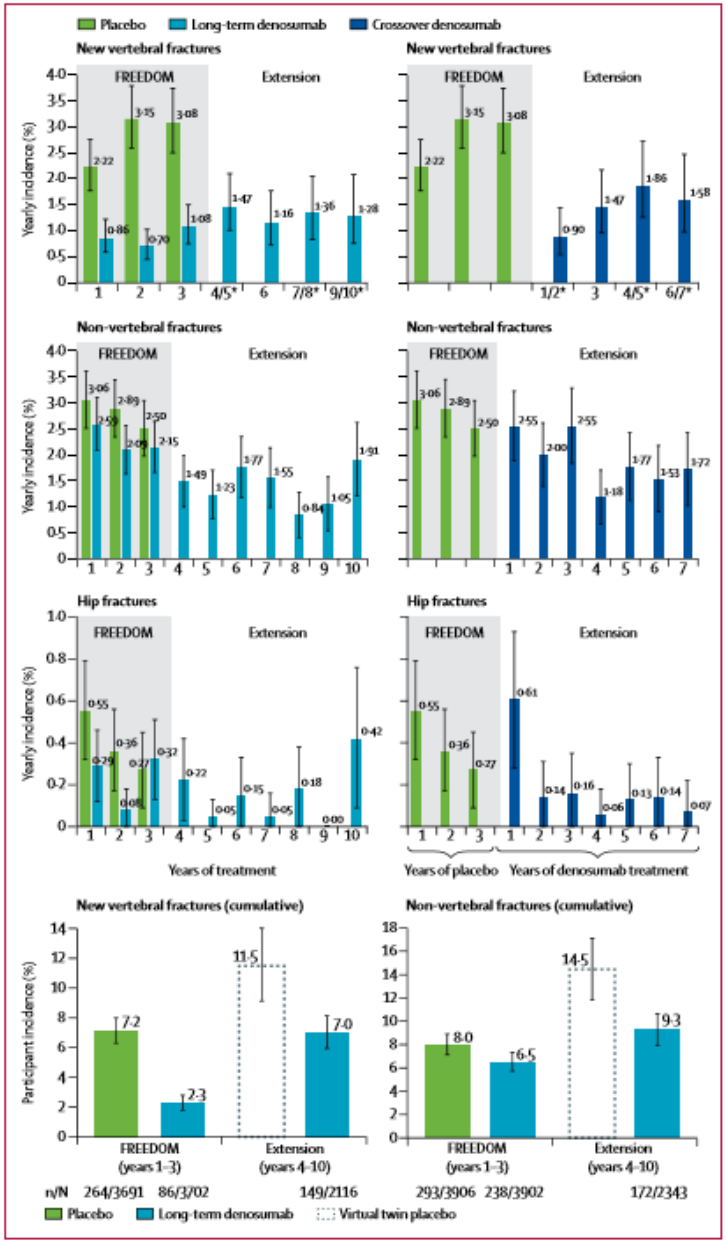


Figure 2: Yearly incidence of new vertebral, non-vertebral, and hip fractures and cumulative incidence of new vertebral and non-vertebral fractures during FREEDOM and the FREEDOM extension
For new vertebral fractures, percentages are crude incidence (95% CI); lateral radiographs (lumbar and thoracic) were not obtained at extension years 1, 4, and 6 (long-term denosumab treatment years 4, 7, and 9). For non-vertebral and hip fractures, percentages are Kaplan-Meier estimates (95% CI). For incidence of cumulative new vertebral fractures and non-vertebral fractures, solid bars represent actual data collected and dashed bars represent virtual placebo data. Percentages for new vertebral fractures are crude incidence (95% CI) and percentages for non-vertebral fractures are Kaplan-Meier estimates (95% CI). *Annualised incidence (2-year incidence/2).

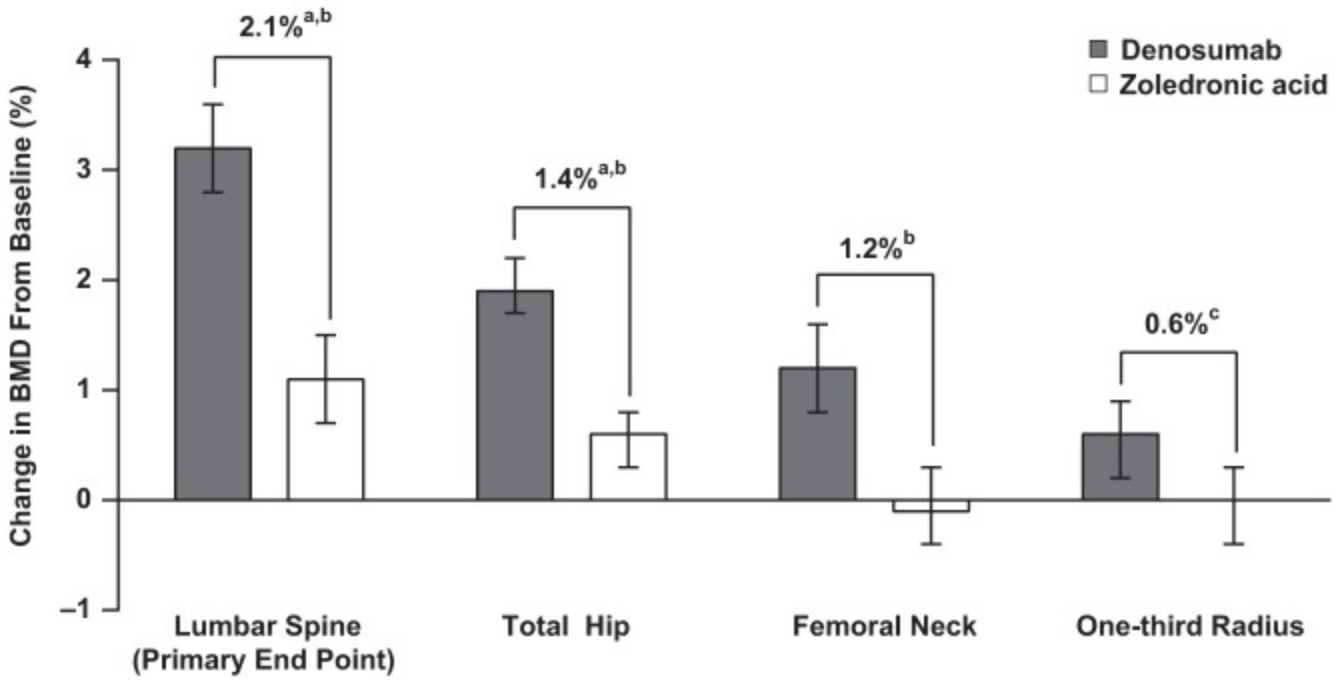
Bone H et al Lancet Diabetes Endocrinol 2017

Denosumab or zoledronic acid in postmenopausal women previously treated with bisphosphonates

	Denosumab (n = 321)	Zoledronic Acid (n = 322)
Age, y, mean (SD)	68.5 (7.1)	69.5 (7.7)
Race/ethnic group, n, %		
White or Caucasian	309 (96.3)	314 (97.5)
Asian	5 (1.6)	4 (1.2)
Black or African American	1 (0.3)	0
Other[a]	6 (1.8)	4 (1.2)
BMI, kg/m^2, mean (SD)	24.3 (4.0)	24.3 (4.2)
Years since menopause, mean (SD)	19.9 (8.2)	20.8 (8.9)
History of fracture, n, %		
Any	169 (52.6)	159 (49.4)
Osteoporotic	120 (37.4)	121 (37.6)
Nonvertebral	109 (34.0)	106 (32.9)
Vertebral	24 (7.5)	28 (8.7)
Lumbar spine BMD T-score		
Mean (SD)	−2.74 (0.83)	−2.64 (0.86)
≤−2.5, n, %	230 (71.7)	229 (71.1)
>−2.5, n, %	91 (28.3)	91 (28.3)
Total hip BMD T-score		
Mean (SD)	−1.93 (0.74)	−1.93 (0.80)
≤−2.5, n, %	74 (23.1)	75 (23.3)
>−2.5, n, %	246 (76.6)	243 (75.5)
Prior oral bisphosphonate treatment duration, y, mean (SD)	6.2 (3.8)	6.4 (3.7)
Serum CTX, pg/mL, median (Q1, Q3)	209 (146, 303)	212 (151, 297)
Serum CTX,[b] pg/mL, median (Q1, Q3)	211 (134, 303)	194 (133, 292)
Serum P1NP,[b] ng/mL, median (Q1, Q3)	26 (16, 34)	23 (19, 32)
Serum iPTH,[b] ng/mL, median (Q1, Q3)	39 (29, 49)	36 (29, 51)

Miller P et al JCEM 2016

Dmab or Zol after Bps



Miller P et al JCEM 2016

Dmab or Zol after BPs

Adverse Events

	Denosumab (N = 320) n, %	Zoledronic Acid (N = 320) n, %
Any AE	199 (62.2)	199 (62.2)
Serious AEs	25 (7.8)	29 (9.1)
AEs leading to discontinuation of study drug	4 (1.3)	9 (2.8)
Fatal AEs	0 (0.0)	1 (0.3)
Selected AEs of interest		
Atypical femoral fracture	2 (0.6)	1 (0.3)
AEs potentially related to hypersensitivity	12 (3.8)	6 (1.9)
Serious infection	5 (1.6)	6 (1.9)
Malignancy	5 (1.6)	8 (2.5)
Cardiac disorders	11 (3.4)	4 (1.3)
Vascular disorders	13 (4.1)	16 (5.0)
Eczema[a]	5 (1.6)	1 (0.3)
Musculoskeletal pain	43 (13.4)	63 (19.7)

Abbreviations: N, number of subjects who received one or more doses of study drug; n, number of subjects reporting one or more events.

[a]Events included eczema, dermatitis, and allergic dermatitis.

MIller P et al JCEM 2016

Evaluation of Invasive Oral Procedures and Events in Women With Post- menopausal Osteoporosis Treated for up to 10 Years With Denosumab: Results From the Phase 3 FREEDOM Open-label Extension

- There were 12 confirmed cases of ONJ among women who participated in the survey (11 had OPE and one did not) and one additional case in a woman who did not complete the survey.
- ONJ incidence was 0.7% (11/1621 patients) in women reporting invasive OPEs and 0.05% (1/1970 patients) in women reporting no invasive OPEs.

- Ten cases resolved with treatment.

Watts N et al. ASBMR 2017

Evaluation of Invasive Oral Procedures and Events in Women With Post- menopausal Osteoporosis Treated for up to 10 Years With Denosumab: Results From the Phase 3 FREEDOM Open-label Extension

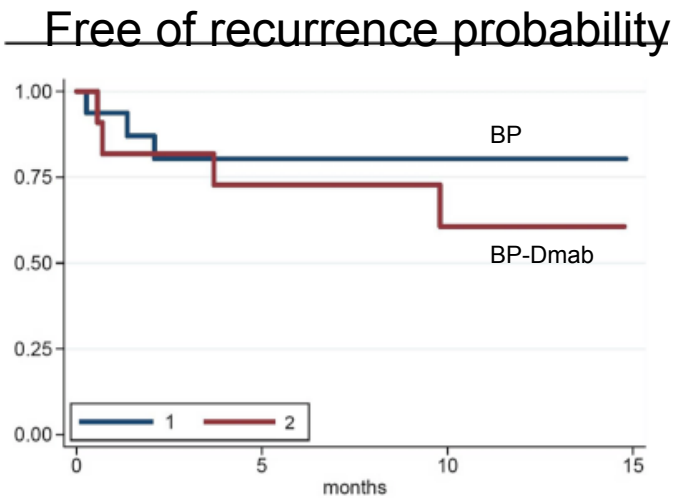
	7-year FREEDOM Extension		
	Cross-over (N = 1731)	Long-term (N = 1860)	All (N = 3591)
Age at EXT baseline in years, mean (SD)	74.3 (4.9)	74.4 (4.8)	74.3 (4.8)
Any invasive oral procedure or event, n (%)	795 (45.9)	826 (44.4)	1621 (45.1)
Scaling or root planing	503 (29.1)	531 (28.5)	1034 (28.8)
Tooth extraction	434 (25.1)	458 (24.6)	892 (24.8)
Dental implant	100 (5.8)	112 (6.0)	212 (5.9)
Natural tooth loss	72 (4.2)	75 (4.0)	147 (4.1)
Jaw surgery*	16 (0.9)	17 (0.9)	33 (0.9)

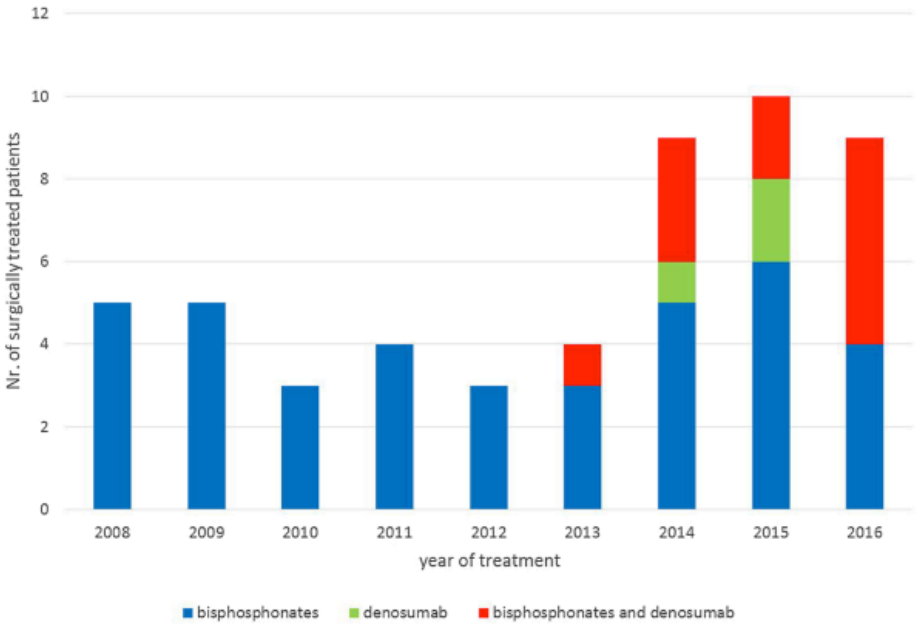
N = Number of patients who received ≥1 dose of investigational product in the EXT and responded to ≥1 oral event questionnaire related to the EXT
n = Number of patients with an OPE
*Collected in the oral event questionnaire every 6 months; therefore, jaw surgery in the first 2.5 years of the EXT was not captured

Watts N et al. ASBMR 2017

Osteonecrosis of the jaw in patients transitioning from bisphosphonates to denosumab treatment for osteoporosis

52 pts treated with ARONJ
38 BPs
11 BPs to Dmab
3 Dmab

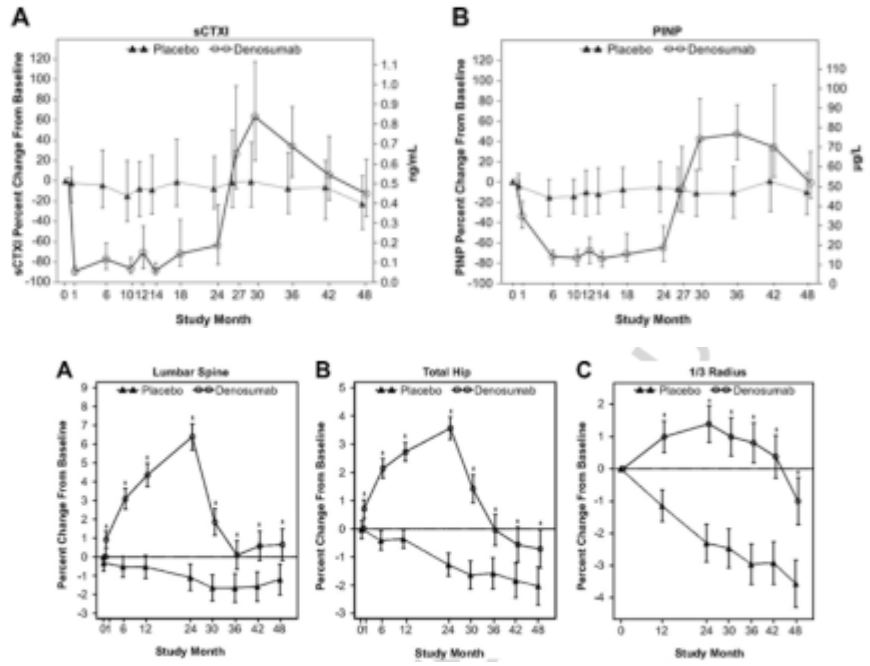




Recurrences in 17.6% of the patients with BP monotherapy and in 45.5% of the patients with transitioning therapy from BPs to denosumab. Transitioning antiresorptive therapy from BPs to denosumab may be an additional risk factor for developing ARONJ.

Voss PJ et al Odontol 2018

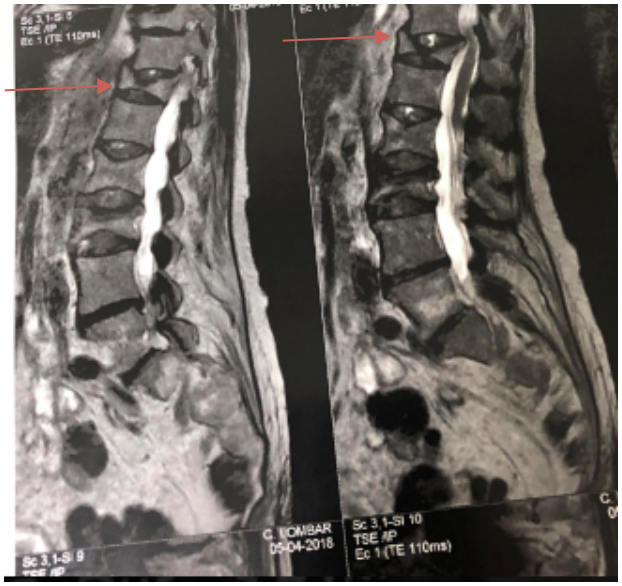
BTM and BMD responses after Dmab discontinuation



Bone H et al JCEM 2011

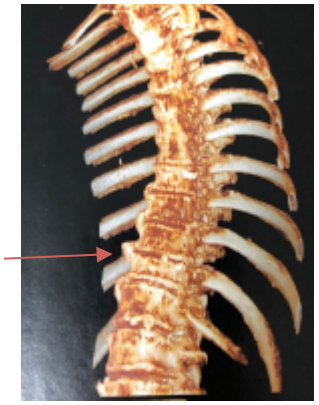
DMAB REBOUND

82 yr-old pmw; Dmab for 4 yr
30 days after a missing dose
New VFx (D12)
CTX: 560 pg/mL

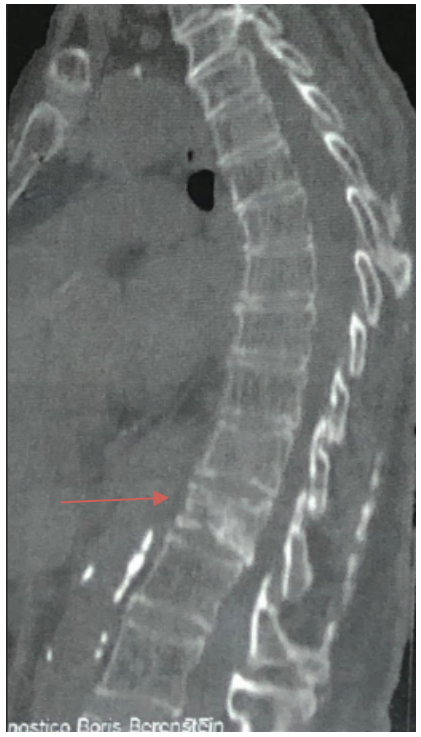


LSBMD -4.2 (8% loss in1 yr)
FNBMD -2.1 (7% gain in 1 yr)

85 yr-old pmw,
Dmab for 3 yr
3 months after a missing dose
New VFx (D11)
CTX: 925 pg/mL



LSBMD -2.7 (7% loss in1 yr)
FNBMD -2.2 (stable)



Bandeira F et al (Submitted) 2018

Dmab Rebound

- In the FREEDOM Extension trial, Bone et al reported that the incidence of new vertebral fractures remained lower in patients on denosumab during the 10-yr follow-up, as was during the 3-yr period, including the comparison with an estimated virtual placebo.
- However, a new analysis of the same study showed that among patients with one or more off-treatment vertebral fracture, the proportion with multiple (>1) was greater among those who discontinued denosumab (60.7%) than placebo (38.7%), corresponding to a 3.4% and 2.2% risk of multiple vertebral fractures, respectively.

Bone HG et al Lancet Diabetes Endocrinol 2017
Cummings S et al J Bone Miner Res 2018
Leder B. J Bone Miner Res 2018
Bandeira F et al (Submitted)

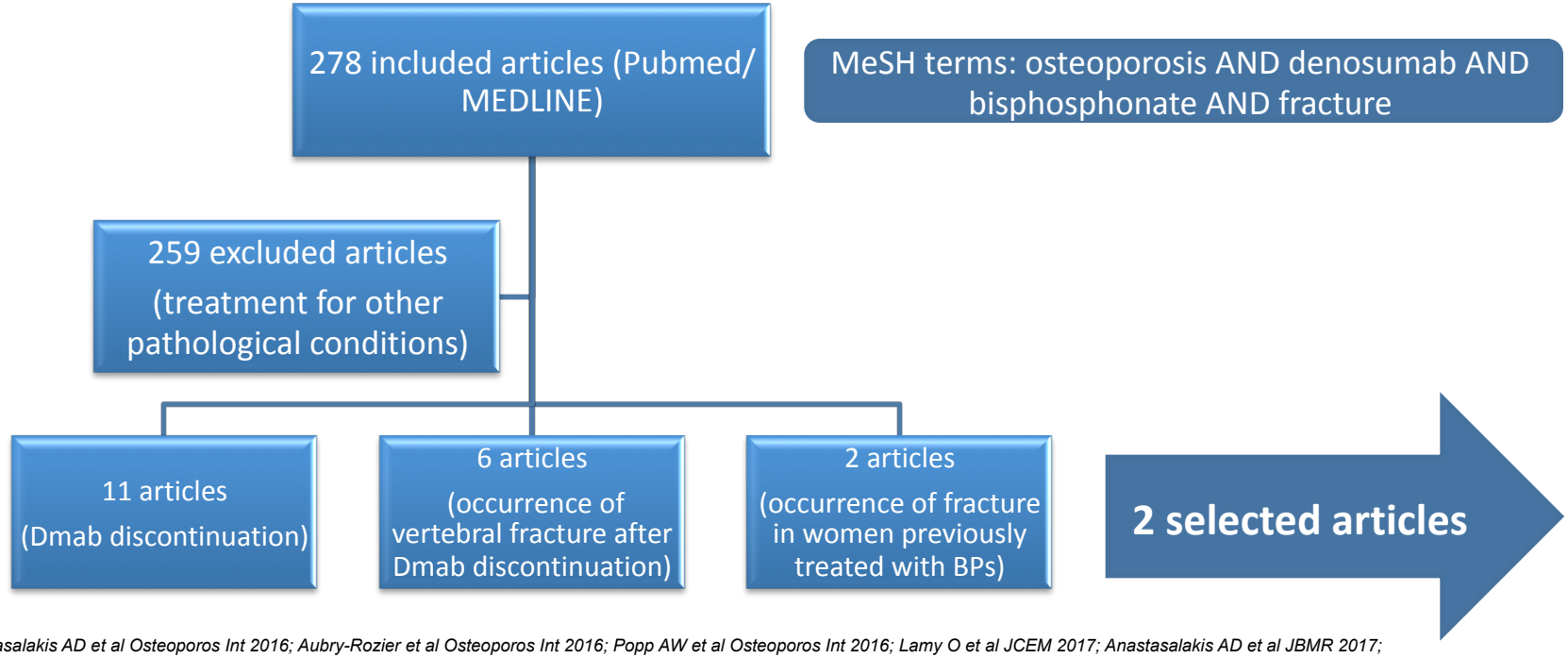
Dmab rebound

- There were six postmenopausal women (mean age, 75.7 ± 7.1 years) with osteoporosis who were previously exposed to long-term treatment (mean duration, 6.75 ± 3.5 years) with BPs before initiation of Dmab.

- After inadvertent discontinuation of Dmab, patients were reevaluated after an average of 2.3 years, and no significant elevations in bone turnover markers (CTx 131 ± 83.75 pg/mL), decreases in LSBMD (mean T-score -2.2) or clinical fractures were observed.

Bandeira F, Araujo V, Victor F et al (Submitted)
Bandeira F , Araujo V, Victor F et al. Presented at 8º. BRADOO, São Paulo 2018

Dmab rebound: Systematic Review



Anastasalakis AD et al Osteoporos Int 2016; Aubry-Rozier et al Osteoporos Int 2016; Popp AW et al Osteoporos Int 2016; Lamy O et al JCEM 2017; Anastasalakis AD et al JBMR 2017; Tripto-Shkolnik L et al Calcif Tissue Int 2018

Bandeira F, Araujo V, Victor F et al (Submitted)
Bandeira F , Araujo V, Victor F et al. Presented at 8º. BRADOO, São Paulo 2018

Dmab rebound

- Twenty of the 24 patients (83%) were treatment naive.
- The remaining 4 had received previous treatment for osteoporosis:
  - strontium ranelate and raloxifene (n=1), teriparatide (n=1),
  - and **bisphosphonates (n=2) ***.
- Eight patients (33%) had prevalent vertebral fractures, while 1 of them had also a non-vertebral fracture.
- Only 1 patient had received glucocorticoids.
- Five patients (21%) were receiving AI for breast cancer.
- Seventy-five percent of the patients had a lumbar spine T-score –2.5
- at the time of denosumab discontinuation.

* Larger series of 35 pts presented at ASBMR;
8 previously treated with BPs

Anastasalakis AD et al JBMR 2017
Gonzalez-Rodriguez E et al ASBMR 2018 #1008

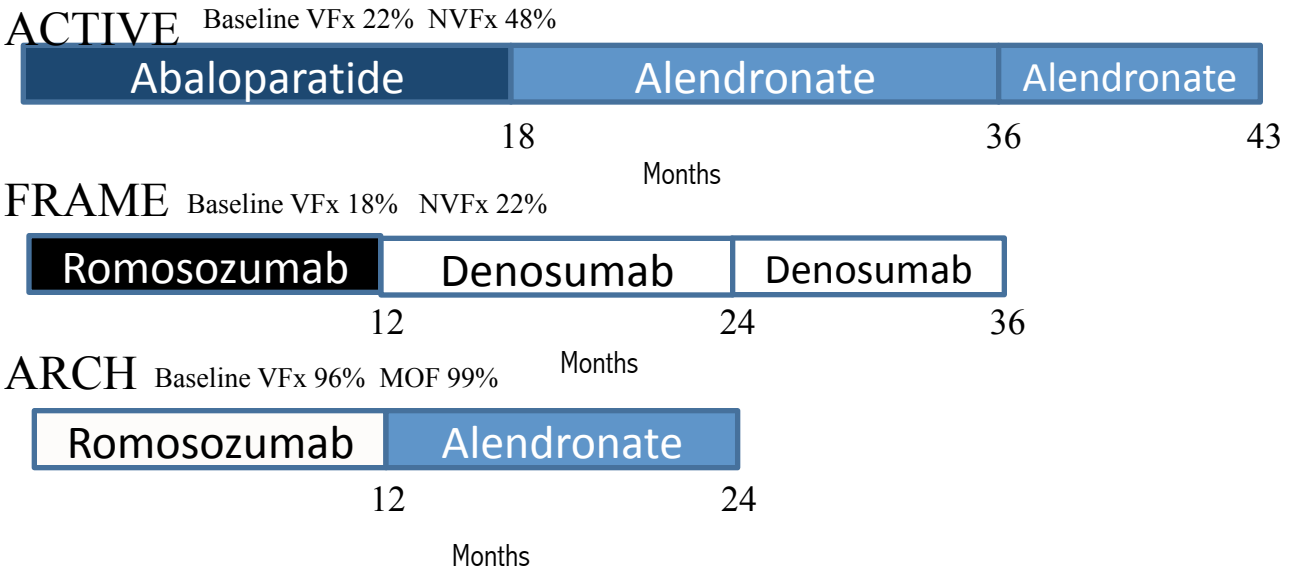
Dmab rebound

A more recent retrospective phone survey of physicians from nine hospitals in Israel identified nine elderly women, previously treated with bisphosphonate for a mean of 7.4 years, who developed multiple vertebral fractures following Dmab discontinuation.

Thirty-six vertebral fractures occurred in eight patients, and most were spontaneous.

Tripto-Shkolnik L et al Calcif Tissue Int 2018

Phase 3 Trial with PTHrp Analogue and Anti-Sclerostin Antibody



Miller PD et al JAMA 2016
Cosman F et al Mayo Clin Proc 2017
Cosman F et al N Engl J Med 2016
Saag K et al N Engl J Med 2017
Lewiecki M et al ASBMR 2017
Bone H et al ASBMR 2017

Conclusions

- The 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.

- In low-risk patients *drug holiday* may decrease the risk of AFF without compromising its therapeutic efficacy.

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

- Switch to denosumab may be effective but some data suggest an increased risk for AFF and ONJ.

3rd Annual Meeting of The AACE Brazilian Chapter

November 16-17, 2018

Mar Hotel and Convention, Recife , Brazil

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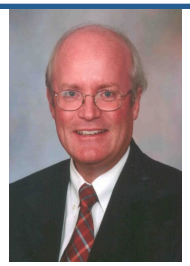

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