Current evidence:Osteoporosis DrugTherapies and Drug Holidays

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- **Speaker's Bureau for:**
  - Amgen, Eli Lilly

Objectives

1. Summarize the long-term efficacy data with different osteoporosis therapies;
2. Describe the long-term safety data with different osteoporosis therapies;
3. Identify who should have a drug holiday and for how long.

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women*

Type of Fracture	Antiresorptive therapy						Bone formation therapy
	Bisphosphonates			Denosumab	Raloxifene	Hormone therapy (Estrogen)**	Teriparatide
	Alendronate	Risedronate	Zoledronic acid				
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓	-	✓	-
Non-vertebral+	✓	✓	✓	✓	-	✓	✓

* For postmenopausal women, indicates first line therapies and Grade A recommendation.
For men requiring treatment, alendronate, risedronate, denosumab and zoledronic acid can be used as first line therapies for prevention of fractures [Grade D].
In clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.
** Hormone therapy (estrogen) can be used as first line therapy in women with menopausal symptoms.
Papaioannou A, et al. CMAJ 2010; **182**(17):1864-73.

Comparative Effectiveness of Osteoporosis Therapies to Prevent Fragility Fractures : A Systematic Review and Meta-Analysis

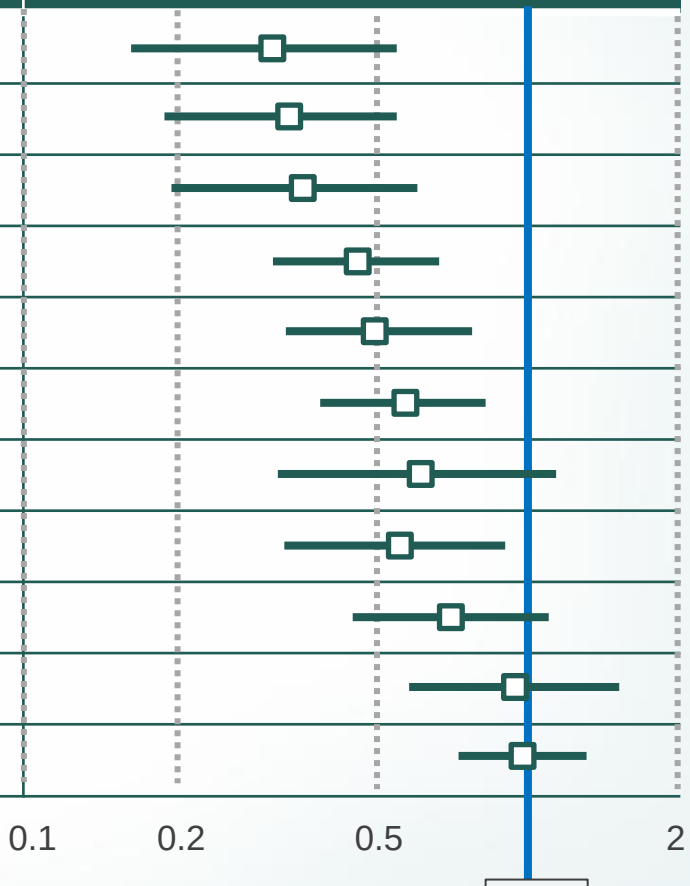
Background

- An Endocrine Society meta-analysis undertaken at the Mayo clinic
- Meta-analysis of randomized controlled trials evaluating the efficacy of bisphosphonates, denosumab, teriparatide, selective estrogen receptor modulators, or calcium and vitamin D
- It is a meta-analysis of 116 trials
  - n=139,647 patients, median age 64 years

Murad MH, et al *J Clin Endocrinol Metab* 2012; **97**: 1871–1880

Meta-analysis of Efficacy of Osteoporosis Therapies: Vertebral Fracture

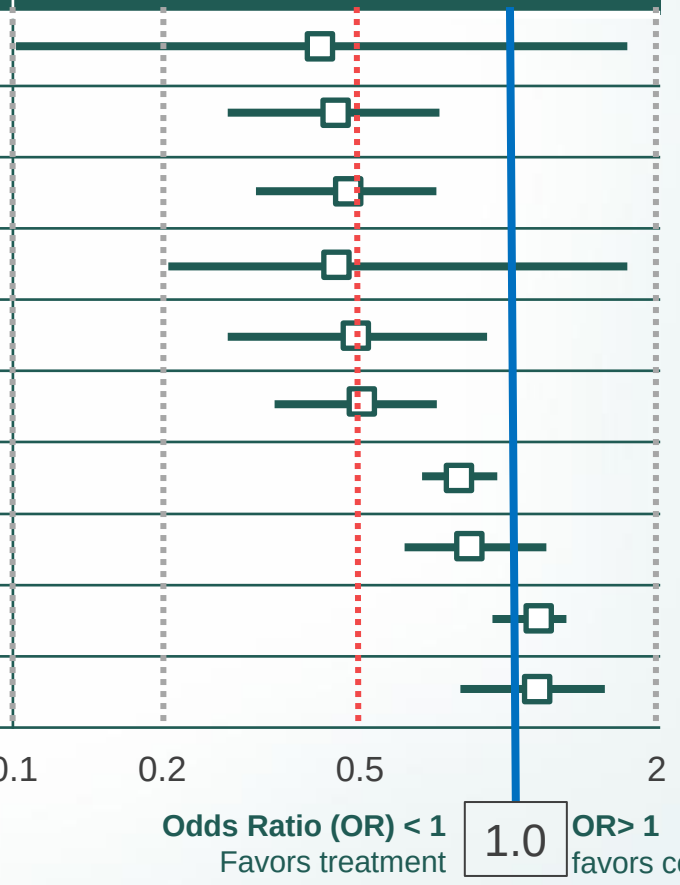
First Line	Odds ratio	CI		P-Value	Odds ratio and 95% CI
		Lower	Upper		
Teriparatide	0.30	0.16	0.55	0.00	
Denosumab	0.33	0.19	0.65	0.00	
Zoledronic acid	0.35	0.20	0.64	0.00	
Risedronate	0.46	0.31	0.68	0.00	
Alendronate	0.50	0.33	0.79	0.00	
Raloxifene	0.57	0.39	0.83	0.00	
Bazedoxifene	0.61	0.32	1.18	0.14	
Ibandronate	0.62	0.37	0.98	0.04	
Calcium	0.71	0.45	1.12	0.14	
Vitamin D	0.96	0.59	1.58	0.87	
VitD+Calcium	0.99	0.74	1.41	0.95	



Murad MH, *et al. J Clin Endocrinol Metab* 2012; **97**:1871-80.

Meta-analysis of Efficacy of Osteoporosis Therapies: Hip Fracture

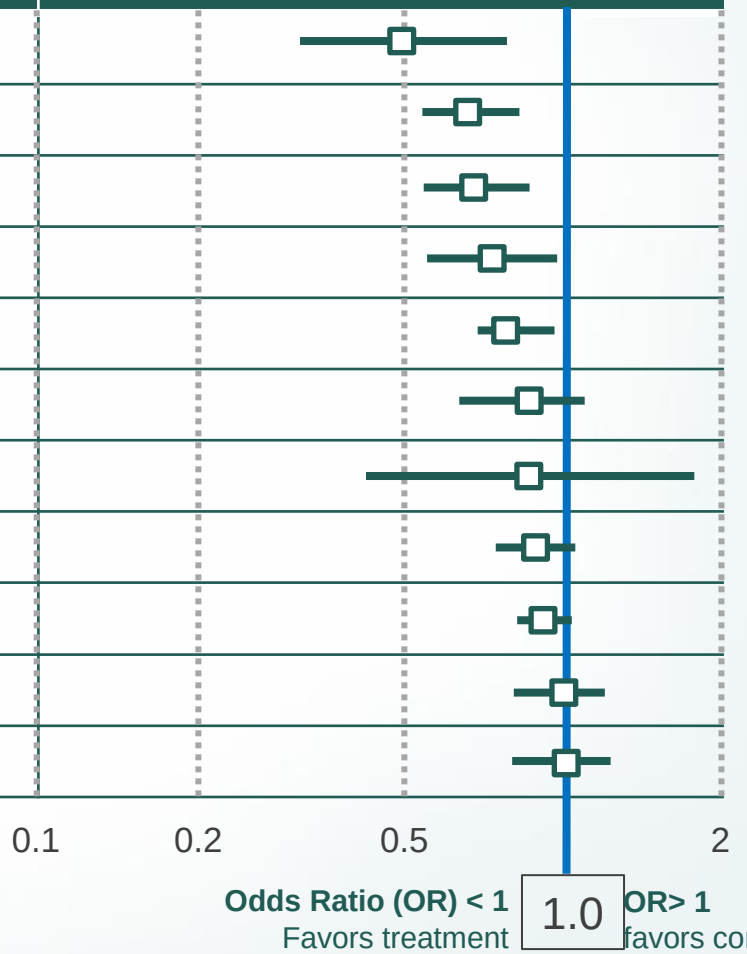
First Line	Odds ratio	CI Limits		P-Value
		Lower	Upper	
Teriparatide	0.42	0.10	1.82	0.24
Alendronate	0.45	0.27	0.68	0.00
Risedronate	0.48	0.31	0.66	0.00
Ibandronate	0.49	0.20	1.82	0.11
Denosumab	0.50	0.27	0.86	0.03
Zoledronic acid	0.50	0.34	0.73	0.00
Vit.D+Calcium	0.81	0.68	0.96	0.02
Raloxifene	0.87	0.63	1.22	0.41
Vitamin D	1.13	0.95	1.34	0.18
Calcium	1.14	0.82	1.59	0.44



Murad MH, *et al. J Clin Endocrinol Metab* 2012; **97**:1871-80.

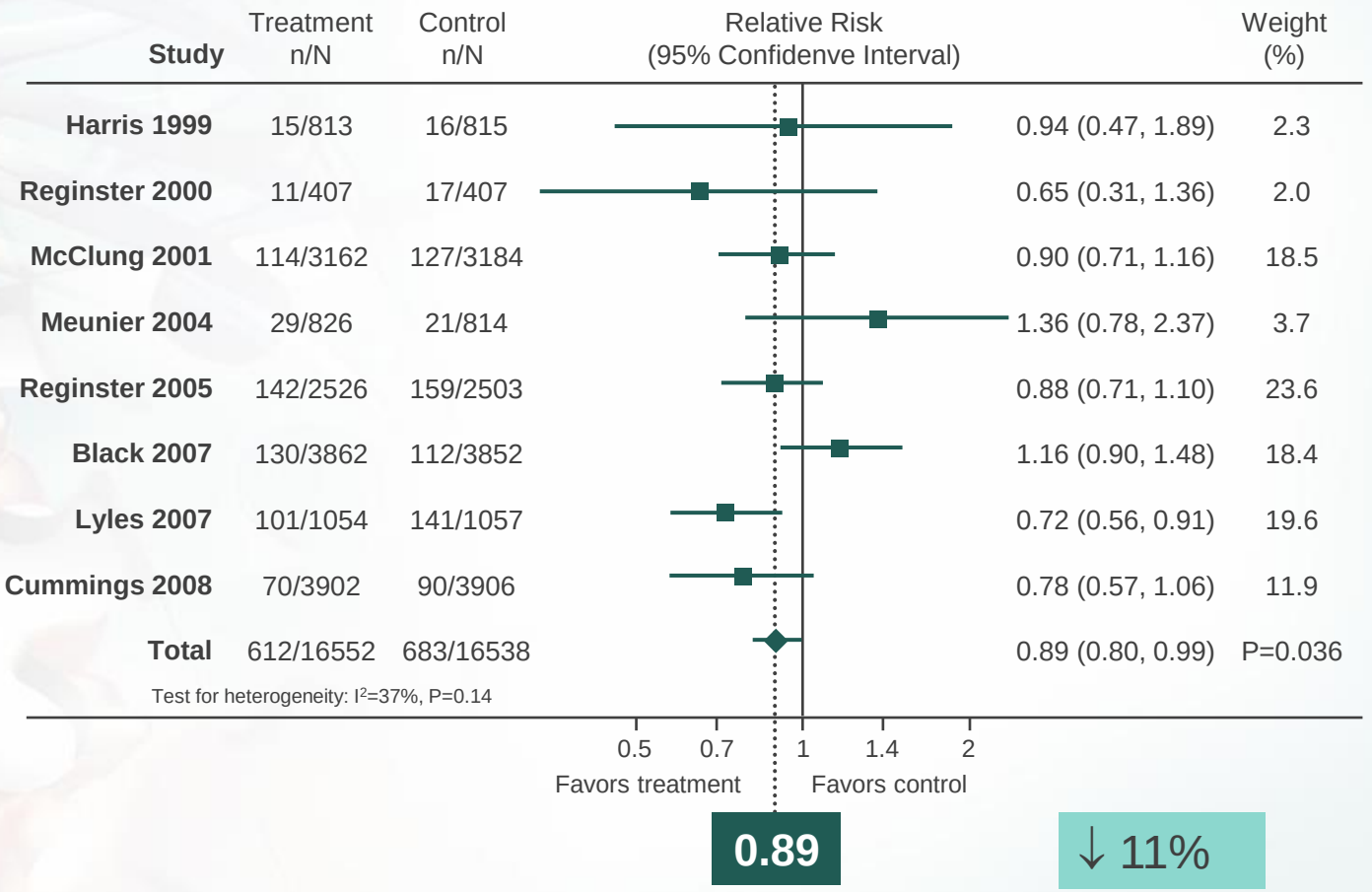
Meta-analysis of Efficacy of Osteoporosis Therapies: Non-vertebral Fracture

First Line	Odds ratio	CI		P-Value	Odds ratio and 95% CI
		Lower	Upper		
Teriparatide	0.50	0.32	0.78	0.00	
Risedronate	0.68	0.55	0.81	0.00	
Zoledronic acid	0.69	0.55	0.84	0.00	
Denosumab	0.74	0.56	0.94	0.03	
Alendronate	0.78	0.66	0.92	0.00	
Bazedoxifene	0.85	0.65	1.11	0.23	
Ibandronate	0.88	0.43	1.64	0.73	
Raloxifene	0.90	0.76	1.03	0.22	
VitD+Calcium	0.94	0.84	1.02	0.28	
Calcium	1.00	0.82	1.22	1.00	
Vitamin D	1.01	0.82	1.20	0.93	



Murad MH, *et al. J Clin EndocrinolMetab* 2012; **97**:1871-80.

Reduction in Mortality Risk with Osteoporosis Treatments: Meta-analysis



Bolland MJ, *et al. J Clin Endocrinol Metab* 2010; **95**(3):1174-81.

Rare Potential Harms Associated with Osteoporosis Medications

- **Osteonecrosis of the jaw (ONJ)**
  - Very rare (1/100,000 person-years) with bisphosphonates and denosumab in postmenopausal osteoporosis[1,2]
  - Average annual incidence with metastatic cancer doses of denosumab or bisphosphonate (12 to 15 times what is used in osteoporosis) 2 to 5%[2,3]
- **Atypical Femur Fracture (AFF)**
  - Very rare (2-78/100,000 person-years) with bisphosphonates and denosumab in postmenopausal osteoporosis[1,4,5]
- **Severe Hypocalcemia**
  - Rare occurrence with i.v. zoledronic acid [6] and denosumab,[7] usually in patients with calcium malabsorption, vitamin D insufficiency, secondary hyperparathyroidism, and/or renal insufficiency [7,8]

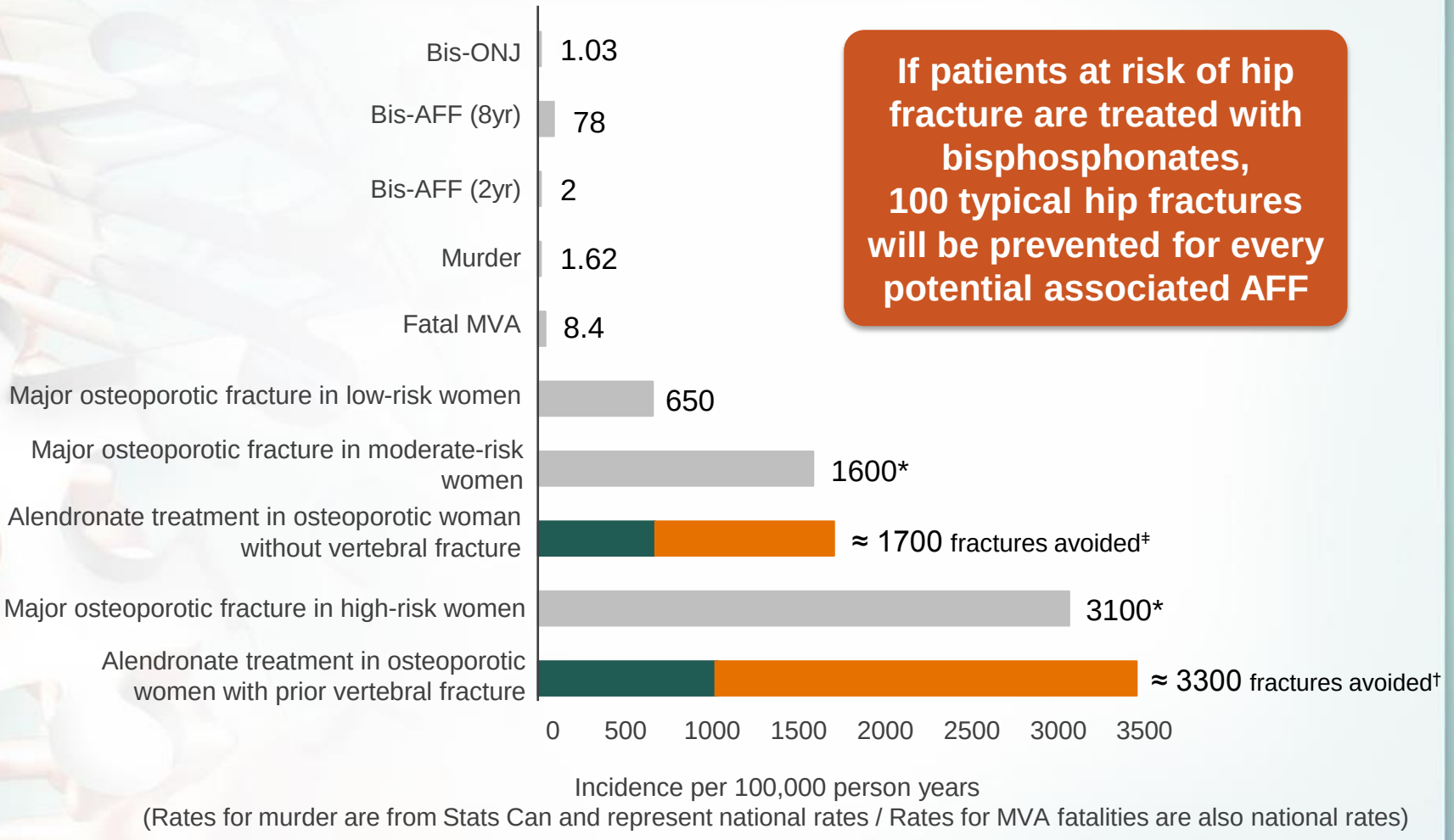
[1] Brown JP, et al. *Can Fam Physician* 2014;60:324-33, [2] Khan AA, et al. *J Rheumatol* 2011;38(7):1396-402., [3] Khan A, *et al*. International Task Force on Osteonecrosis of the Jaw , *JBMR* 2014 doi: [10.1002/jbmr.2405]; [4] Shane E, et al. ASBMR 2010 Task Force on AFF *JBMR* 2010;25(11):2267-2294., [5] Shane E, et al.ASBMR 2013 Task Force on AFF *JBMR* 2014;29(1):1-23., [6] Do WS , *J Bone Metab* 2012;19(2):139-145, [7] Ungpraset P, et al*. Am J Emerg Med*. 2013;31(4):756.e1-2., [8] Okada N, et al. *Biol Pharm Bull*. 2013;36(10):1622-6.

Very Rare Potential Harms Associated with Osteoporosis Medications

- **Atrial fibrillation with bisphosphonate**
  - No association with oral bisphosphonates; FDA warning of persistent increased risk of AF with longer use of annual i.v. zoledronic acid
- **Esophageal cancer with oral bisphosphonate**
  - No increased risk
- **Osteosarcoma with teriparatide**
  - Seen in rat after lifelong therapy with high dose teriparatide
  - No excess incidence of osteosarcoma noted with over 1 million treated patients[3]
  - The Osteosarcoma Surveillance Study (OSS) reported 7-year interim analysis which did not detect an association of teriparatide or recombinant human PTH use and incidence of osteosarcoma[4]

1. Brown JP, *et al. Can Fam Physician* 2014;**60**:324-33;
2. US Food and Drug Administration. *FDA Drug Safety Communication*: 2010, Available from: www.fda.gov/Drugs/DrugSafety/ucm229009.htm. Accessed Oct.23, 2014;
3. Capriani C et al. J Bone Miner Res 2012;**27**(12):2419-28;
4. Andrews EB, et al. J Bone Miner Res 2012; **27**(12):2429-37.

Osteoporosis Therapies: Proven Benefits Outweigh Rare Risks



If patients at risk of hip fracture are treated with bisphosphonates, 100 typical hip fractures will be prevented for every potential associated AFF

Bis-ONJ=bisphosphonate-associated osteonecrosis of the jaw; Bis-AFF=bisphosphonate-associated atypical subtrochanteric and diaphyseal femur fracture; MVA= motor vehicle accident; *10-year risk of major osteoporotic fracture by Canadian FRAX.
‡ About 700 nonvert (blue bar) and 1000 clinical vertebral fractures (red bar) would be avoided. Liberman UA et al. NEJM 1995;333:1437-1443.
† About 1000 nonvert (blue bar) and 2300 clinical vertebral fractures (red bar) would be avoided. Black DM et al. Lancet 1996;348:1535-1541.
Adapted from: Brown JP et al. *Canadian Family Physician* 2014;**60**:324-33.

Issues in Evaluating Long-term Efficacy and Safety in Osteoporosis Fracture Trials

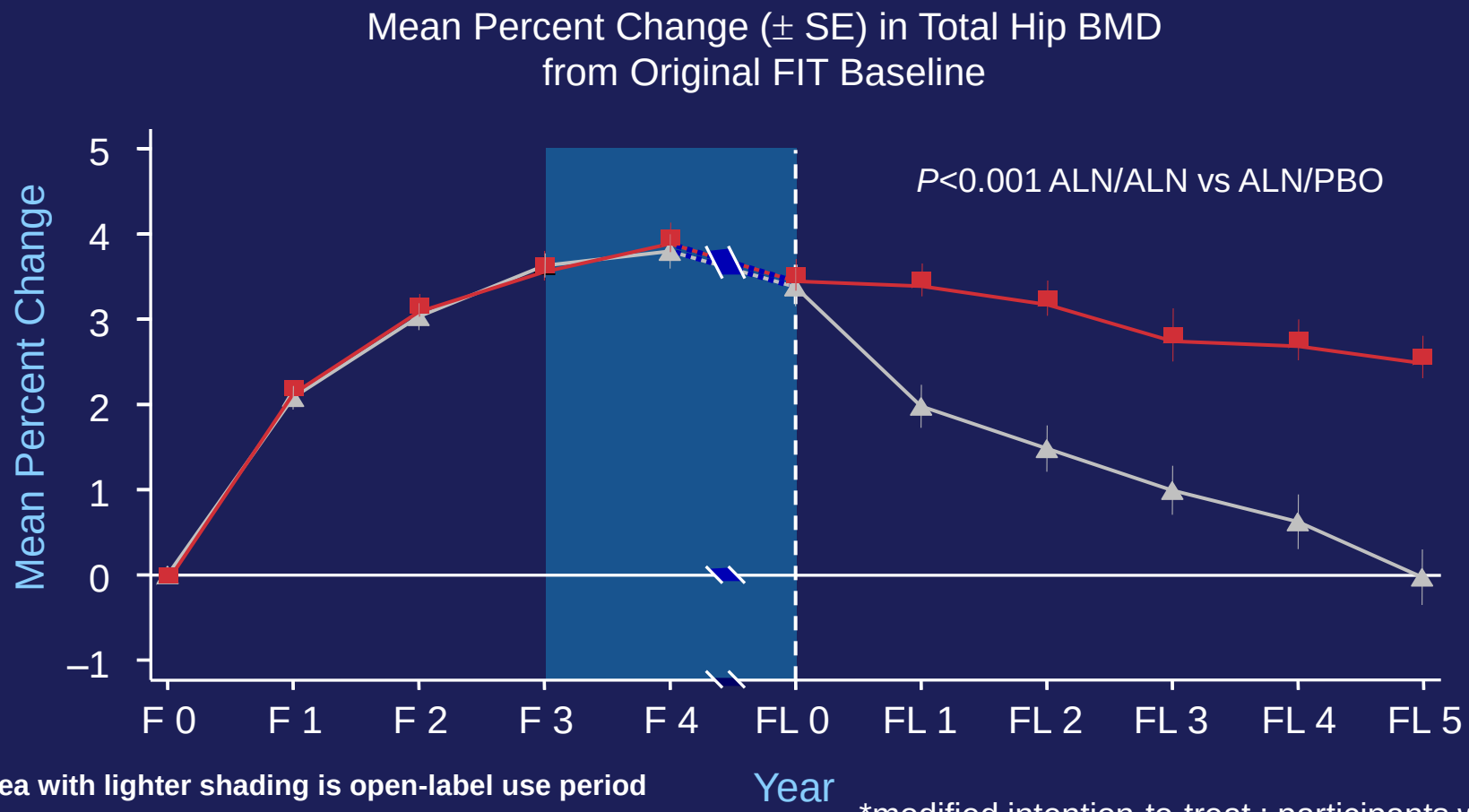
Limiting factors:

- Placebo-controlled RCTs are only 3 years long
- Elderly population with increasing risk of fracture
- Sample size calculated for 3 years not longer

Open-label extension studies (6 to 10 years):

- Main objective: Safety
- Surrogates for efficacy: BMD, BTMs
  Rates of fracture

Total Hip BMD Changes from FIT Baseline (mITT*)

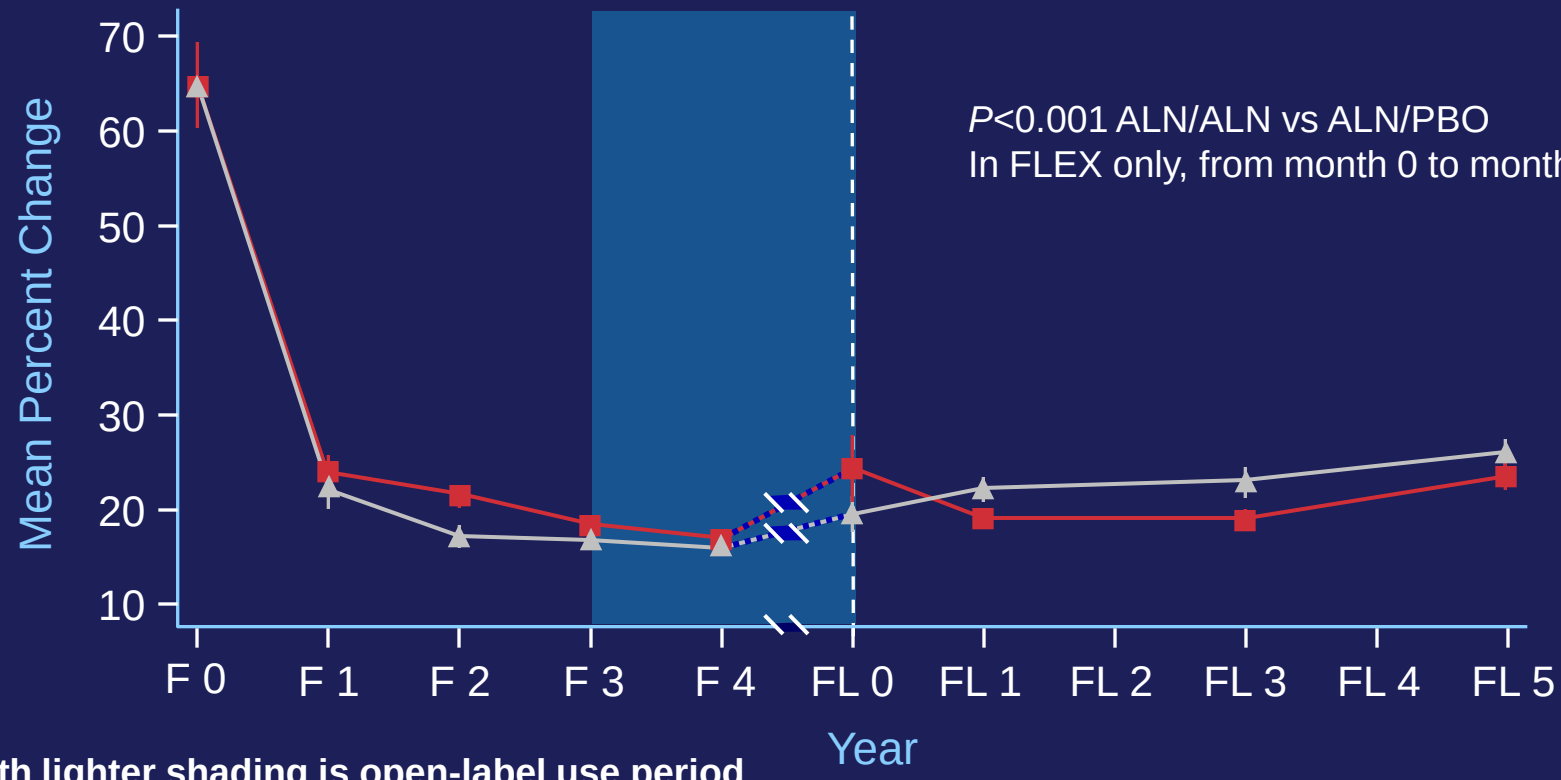


*modified intention-to-treat : participants with at least one follow-up point after FLEX baseline

Black DM, *et coll*. *JAMA*. 2006;**296**:2927–2938.

Urinary NTx Changes from FIT Baseline (PP*)

Mean Percent Change (± SE) of Urinary NTx
from Original FIT Baseline



P<0.001 ALN/ALN vs ALN/PBO
In FLEX only, from month 0 to month 120

Area with lighter shading is open-label use period

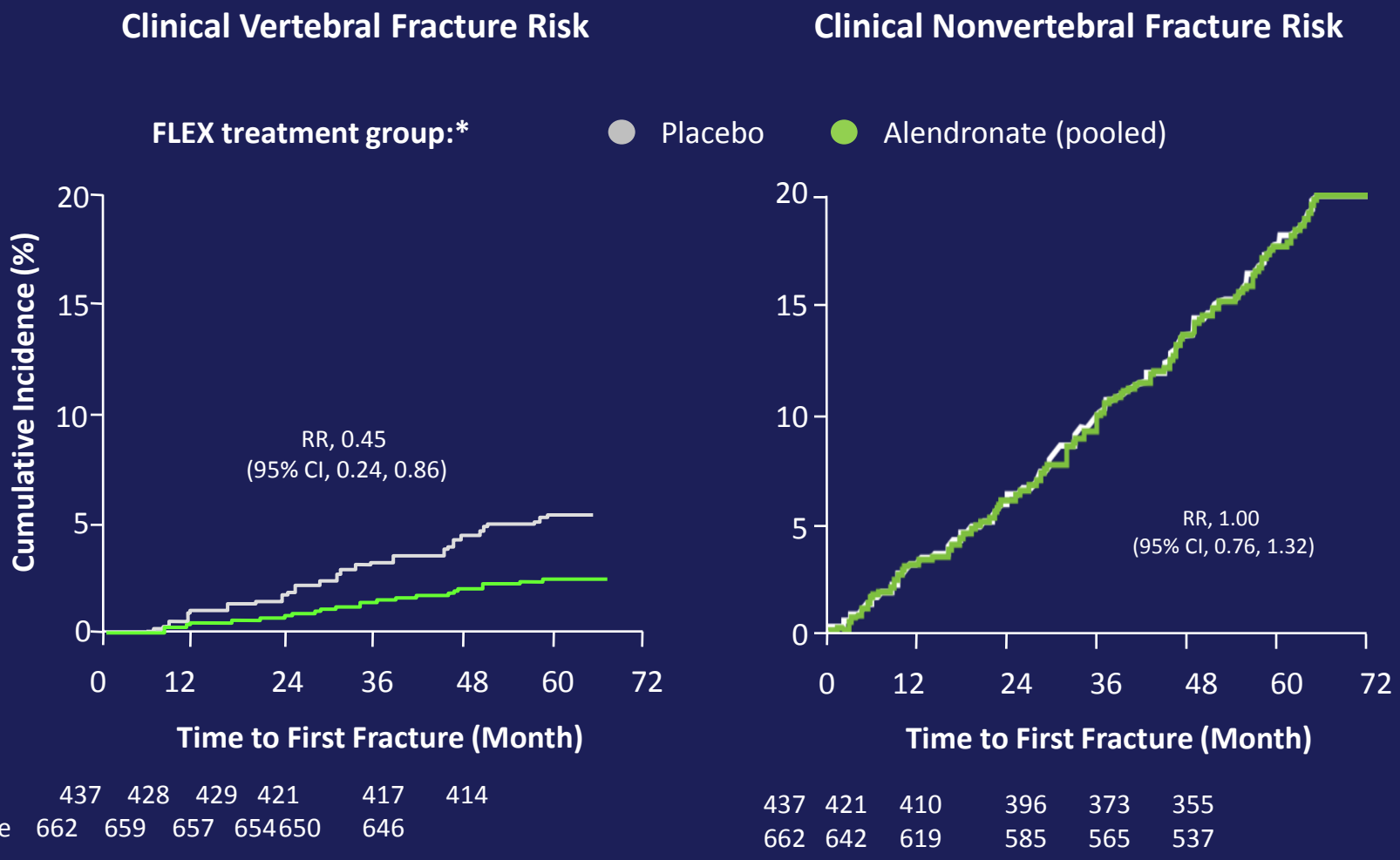
▲ = ALN/Placebo

■ = ALN/ALN (Pooled 5 mg and 10 mg groups)

*per-protocol: participants adherent to treatment

Black DM, *et coll*. *JAMA.* 2006;**296**:2927–2938.

Effect of Long-term Alendronate Treatment on Clinical Fracture Risk



RR = relative risk; *All patients included in FLEX received alendronate in FIT, and results from the alendronate group was pooled from the alendronate 5 mg/day and 10 mg/day groups.

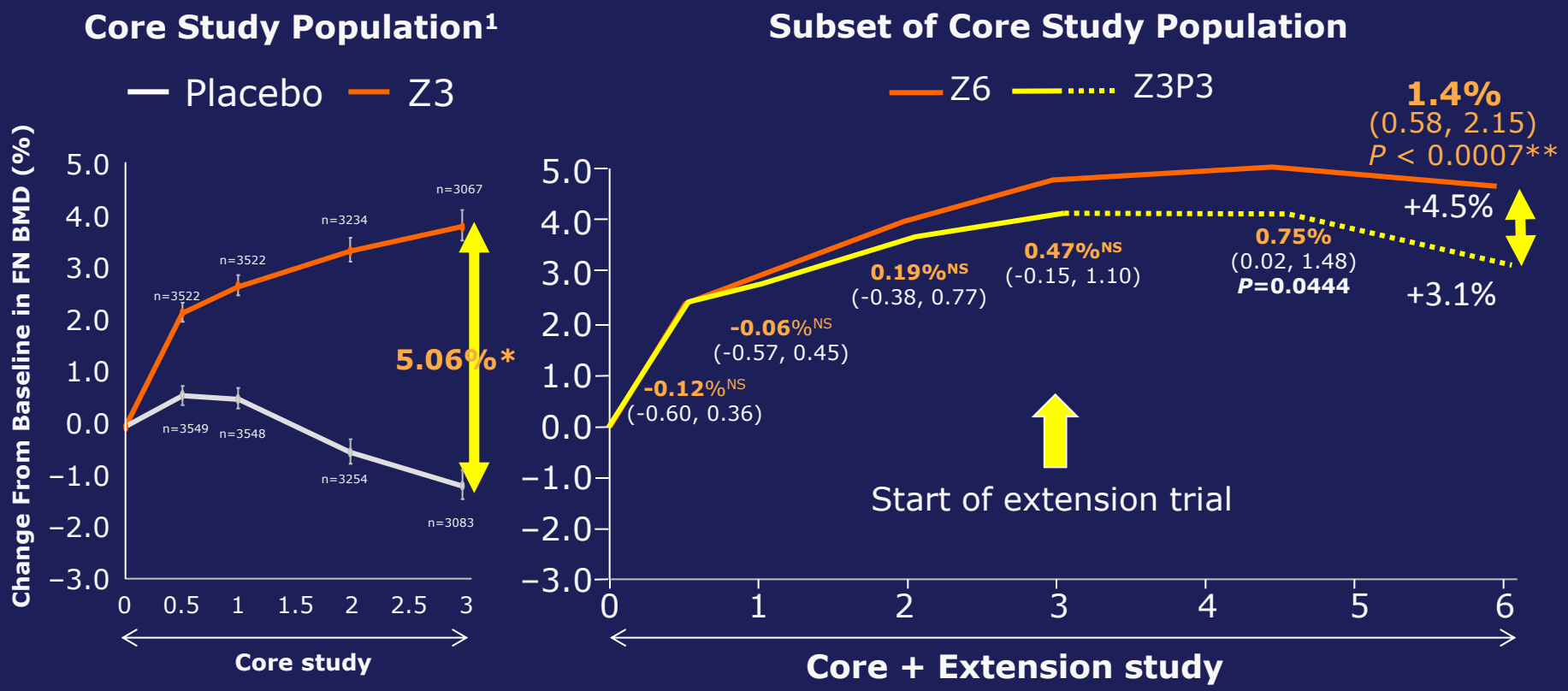
Black DM, et al. *JAMA.* 2006;**296**:2927–2938.

Fracture Risk After Alendronate Discontinuation: FLEX Study

- After discontinuation of alendronate: 22% of women experienced fracture during the subsequent 5 years[1]
- Older age, prevalent fragility fracture, hip BMD < -2.5 strongly predict fracture risk after 5 years of alendronate therapy[1]
- Neither 1-year change in hip BMD nor 1- or 3-year change in bone turnover markers (NTX/ BSAP) predict the risk of fracture after discontinuation[2]

1. Black DM, et al. *JAMA.* 2006;**296**:2927–2938.
2. Bauer D *et al. JAMA Intern Med* 2014; **174**(7):1126-34

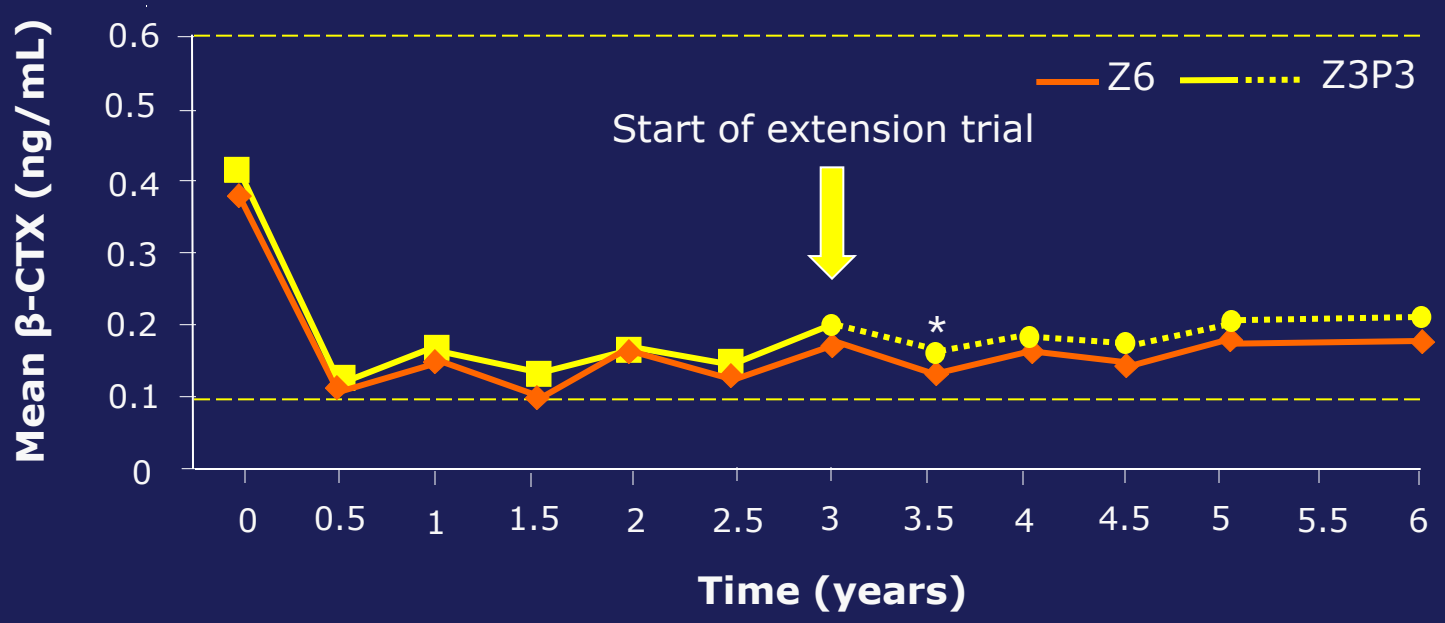
6 Years of ZOL Treatment Maintains Increases in FN BMD



Z3 n= 3851	Z6 n=	589	609	608	600	524	450
PBO n= 3845	Z3P3 n=	599	613	606	602	540	467

*P < 0.0001, P value computed from 3-way ANOVA with treatment, stratum and region as explanatory variables
**P value computed from 2-way ANOVA with treatment and region as explanatory variables.
MITT = modified intention to treat
1. Black DM, et al. *N Engl J Med*. 2007;356:1809–1822.

6 Years of ZOL Treatment Maintains Reduction in β-CTX (ITT)

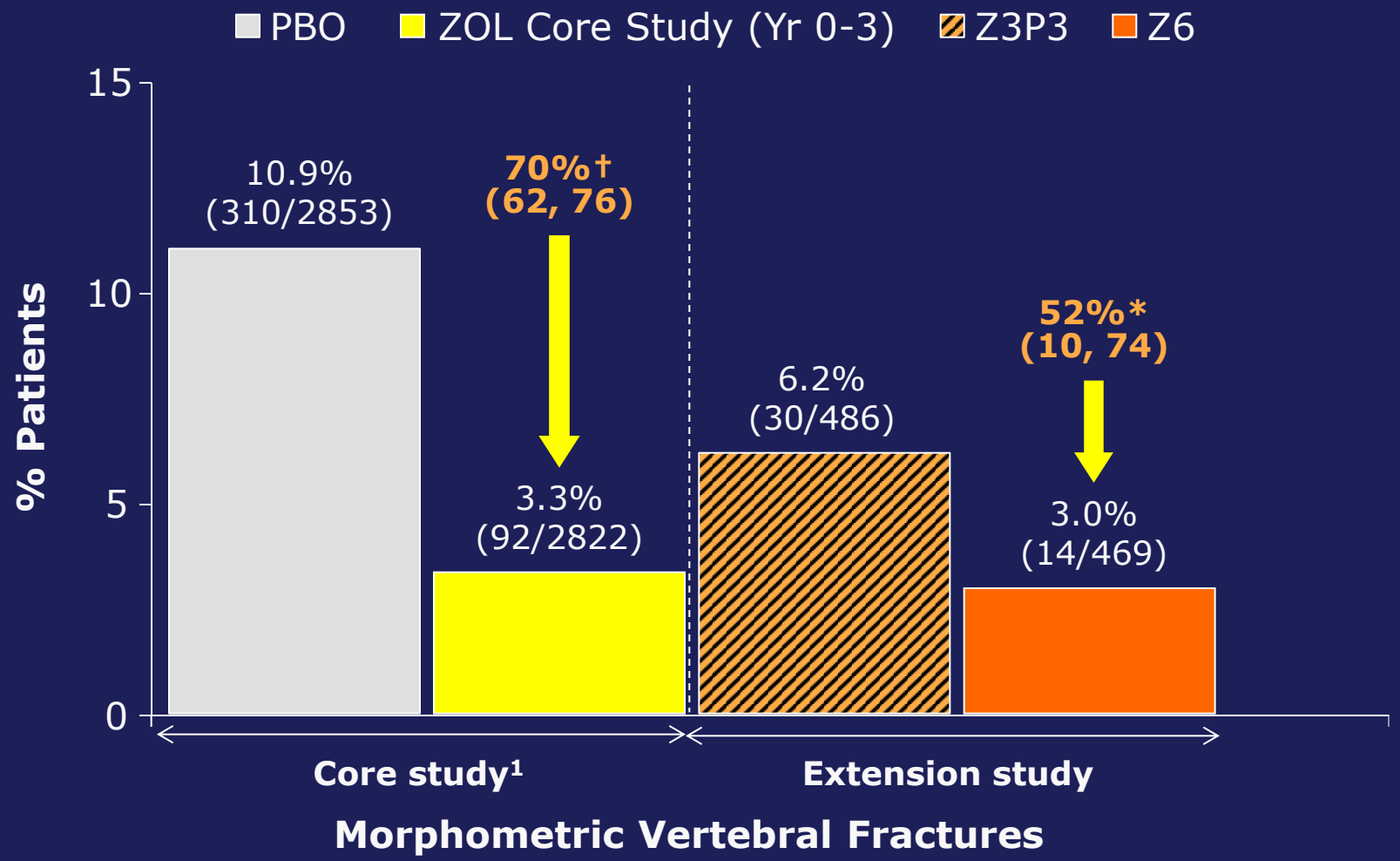


Z6 n=	44	40	39	31	41	40	44	20	21	18	19	27
PBO/Z3P3 n=	46	44	37	32	38	42	46	19	25	17	22	28

- Mean values remained within the premenopausal reference range throughout

*$P < 0.05$. No significant difference at any other time point in the extension study. Horizontal dashed lines represent premenopausal reference range (Adapted from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822). ITT = intention to treat, Z3P3 = ZOL for 3 years and placebo for 3 years, Z6 = ZOL for 6 years

Significantly Fewer New Morphometric Vertebral Fractures in Years 3-6 (Z6 vs Z3P3)



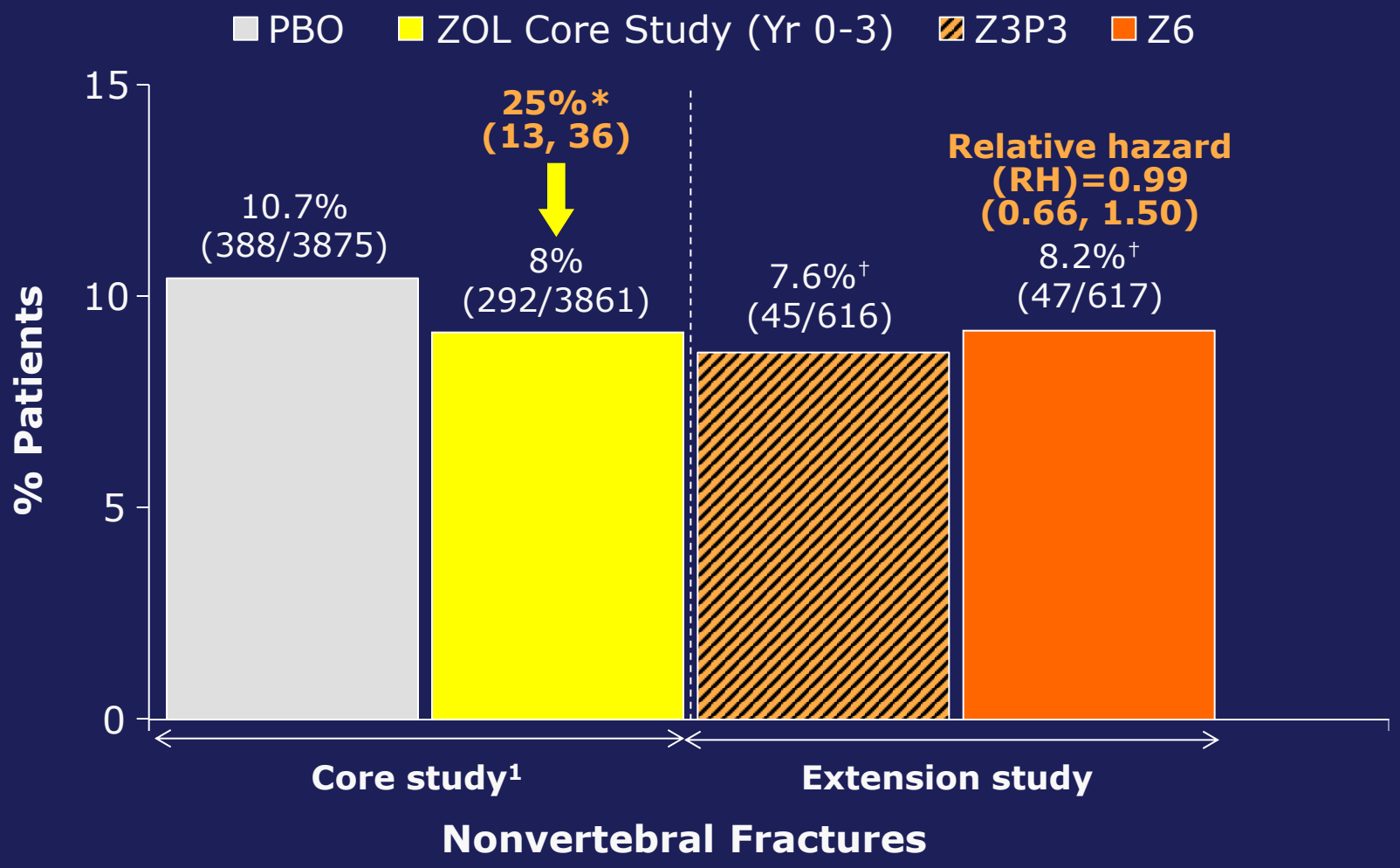
Core study: †$P < 0.001$ relative risk reduction vs placebo (PBO)

*$P = 0.0348$, relative risk reduction vs Z3P3; n = the number of patients in the analysis population with X-rays at Year 3 and Year 6

ITT = intention to treat , Z3P3 = ZOL for 3 years and placebo for 3 years, Z6 = ZOL for 6 years

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

Similar Risk of Nonvertebral Fracture in Years 3–6 (Z6 vs Z3P3)

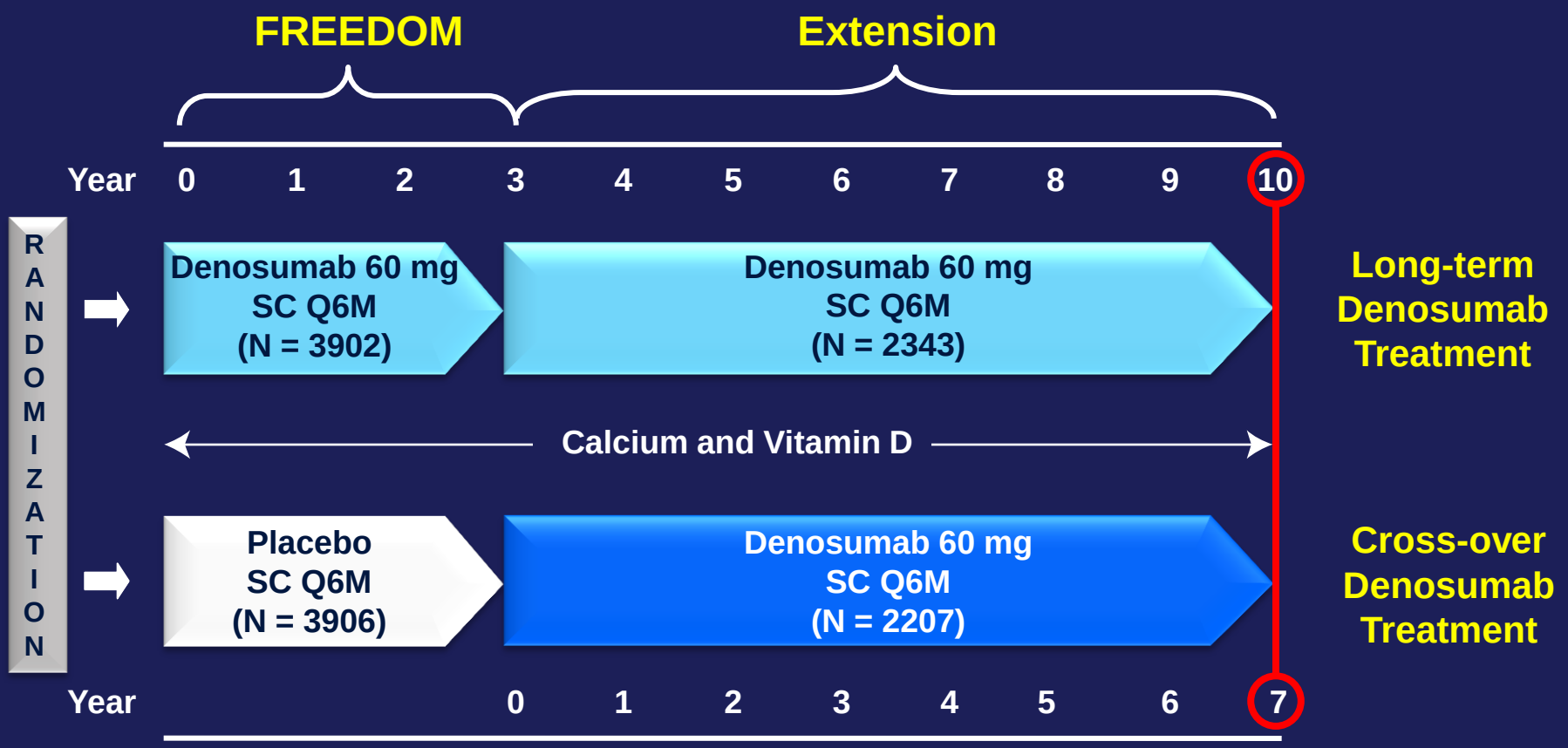


*$P < 0.001$; †The event rate is from Kaplan-Meier estimate at Month 36 in the extension study

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

FREEDOM Extension Study Design

International, multicenter, open-label, single-arm study



Key Inclusion Criteria for the Extension:

- Completed the FREEDOM study (completed the 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
- Not receiving any other osteoporosis medications

Bone H *et al*. ASBMR 2015

Effects of Denosumab Treatment on Bone Turnover Markers Through 10 Years

Unpublished data

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years

Unpublished data

Effects of Denosumab Treatment on Total Hip BMD and Nonvertebral Fractures Through 10 Years

Unpublished data

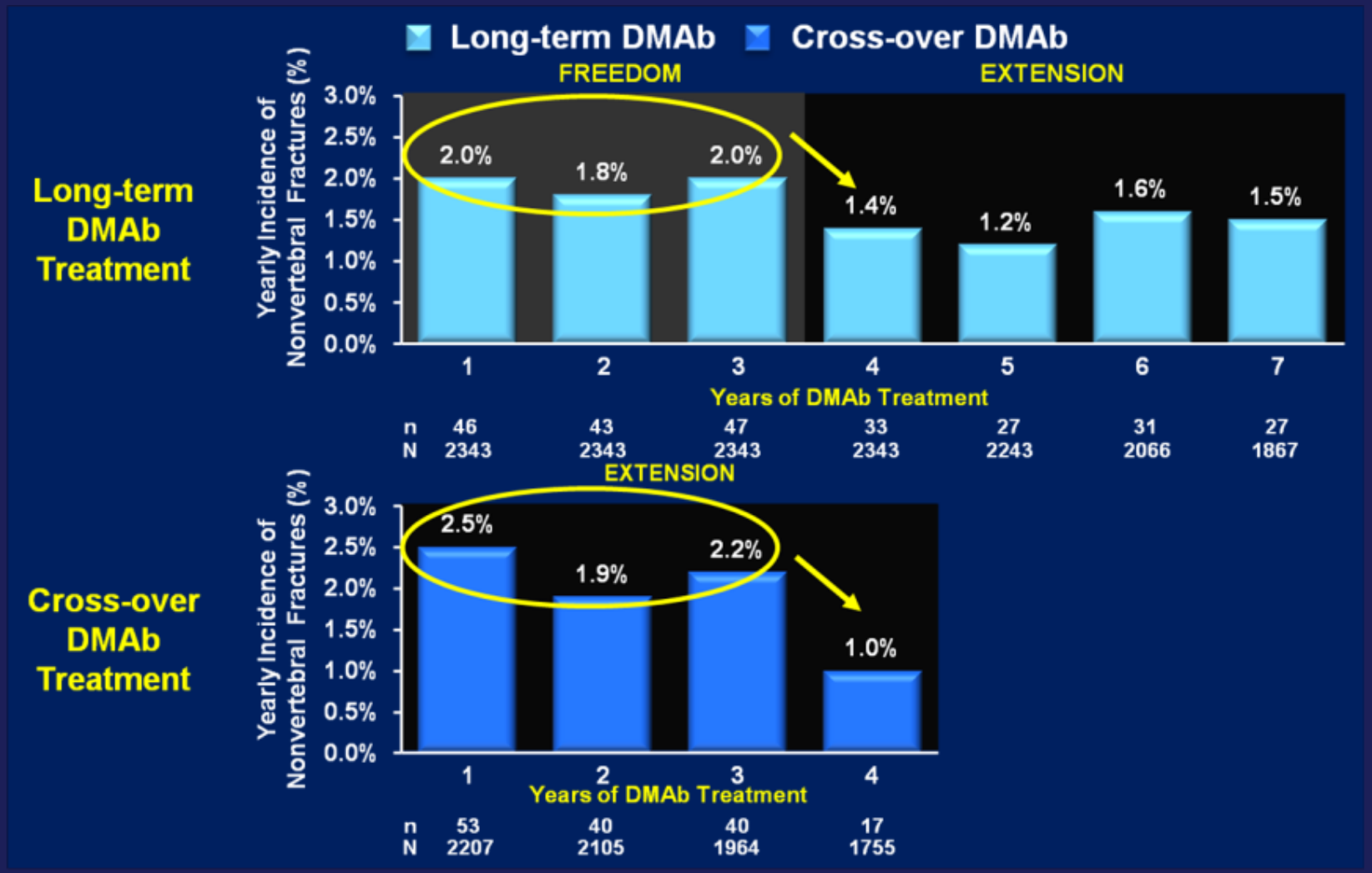
Exposure-adjusted Subject Incidence of Adverse Events (Rates per 100 Subject-years)

Unpublished data

Summary

- Denosumab treatment for up to 10 years was associated with:
  - persistent reduction of bone turnover
  - continued increases in BMD without therapeutic plateau
  - low incidence of new vertebral and nonvertebral (including hip) fracture
- The benefit/risk profile for denosumab in an aging population of postmenopausal women remains favorable

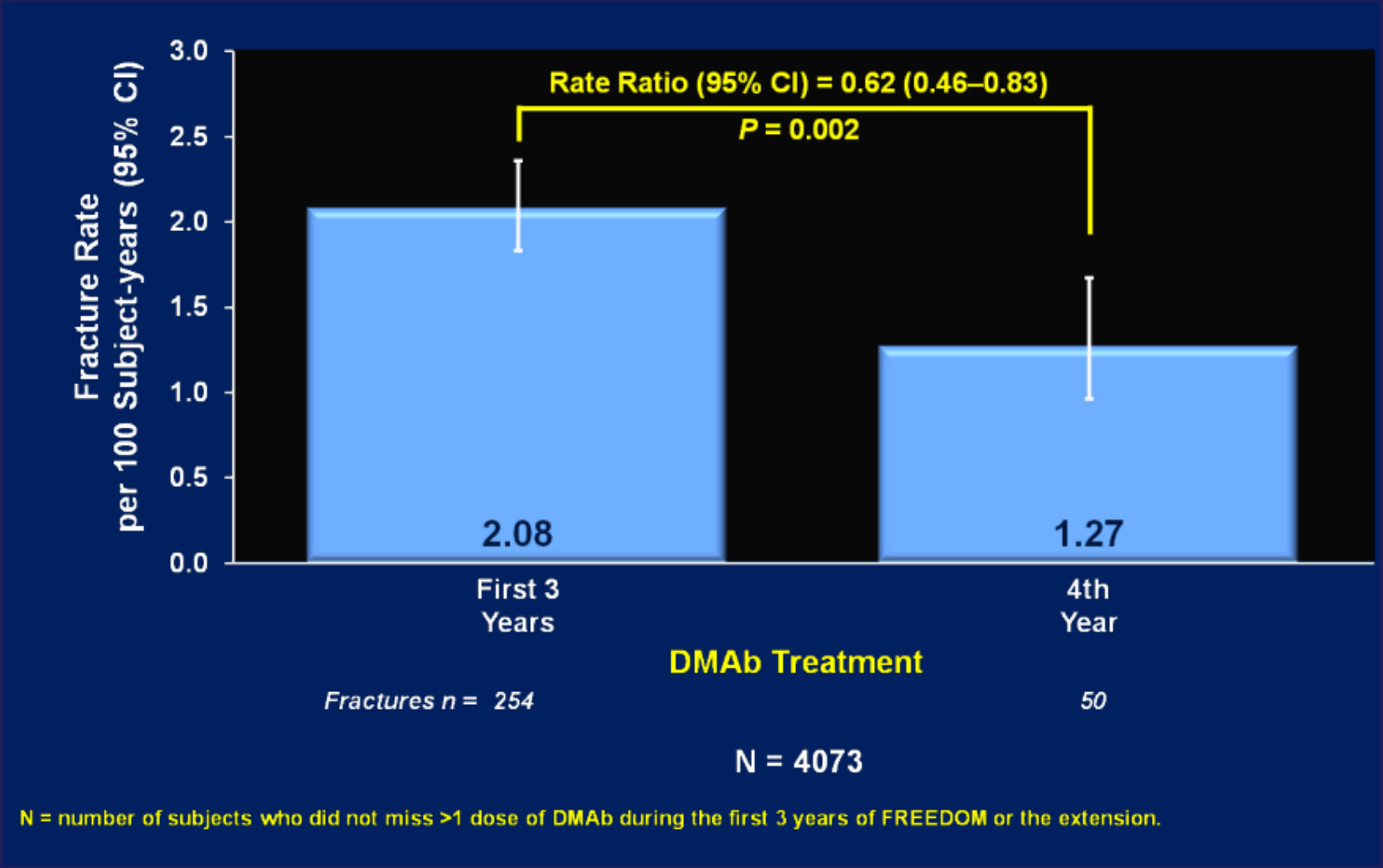
Yearly Nonvertebral Fracture Incidence With Denosumab Treatment for Up to 7 Years



n = number of subjects who have ≥ 1 nonvertebral fracture. Percentages for nonvertebral fractures are Kaplan-Meier estimates.

Ferrari et al. Osteoporos Int. 2015 Dec;26(12):2763-71.

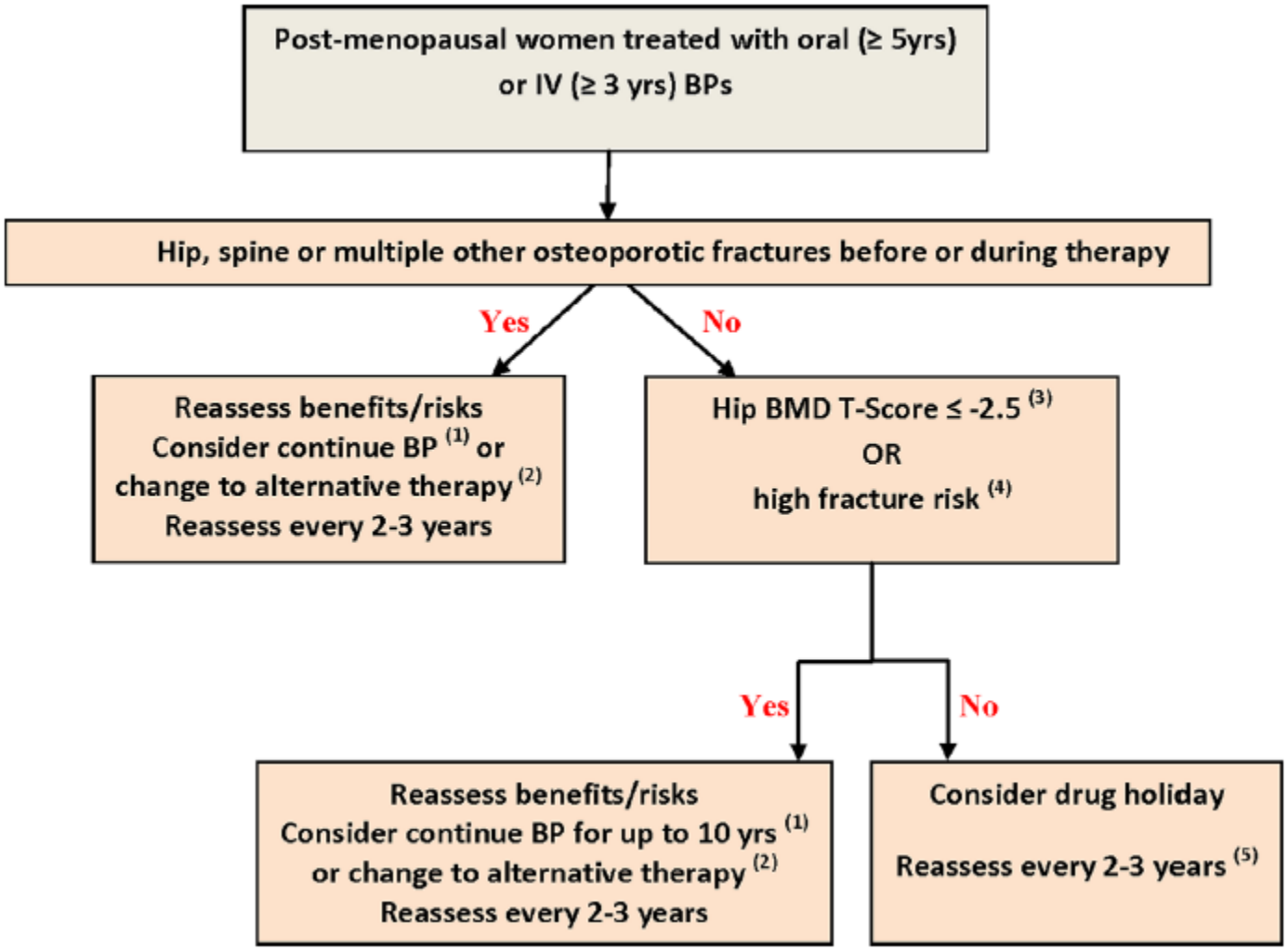
Nonvertebral Fracture Rate Ratios: All Denosumab-treated Subjects



Ferrari S. *et al. Osteoporos Int.* 2015;**26**(12):2763-71.

Duration of Therapy/ Drug Holiday

Approach to the Management of Postmenopausal Women on Long-term Bisphosphonate Therapy



Adler RA *et al. J Bone Miner Res* 2016;**31**(1):16–35

Drug Holiday (Bisphosphonate therapy interruption)

1. **Drug holiday** (not retirement) is feasible with ALN, RIS and ZOL after 3-5 years **<u>if patient at moderate risk</u>**
   - If bisphosphonate interrupted, reassess risk (BMD) after
     - 1 yr for risedronate
     - 2 yrs for alendronate
     - 3 yrs for zoledronic acid
2. Long term adverse effects of osteoporosis therapies are offset in high risk patients by the benefits of long-term reduction in fractures

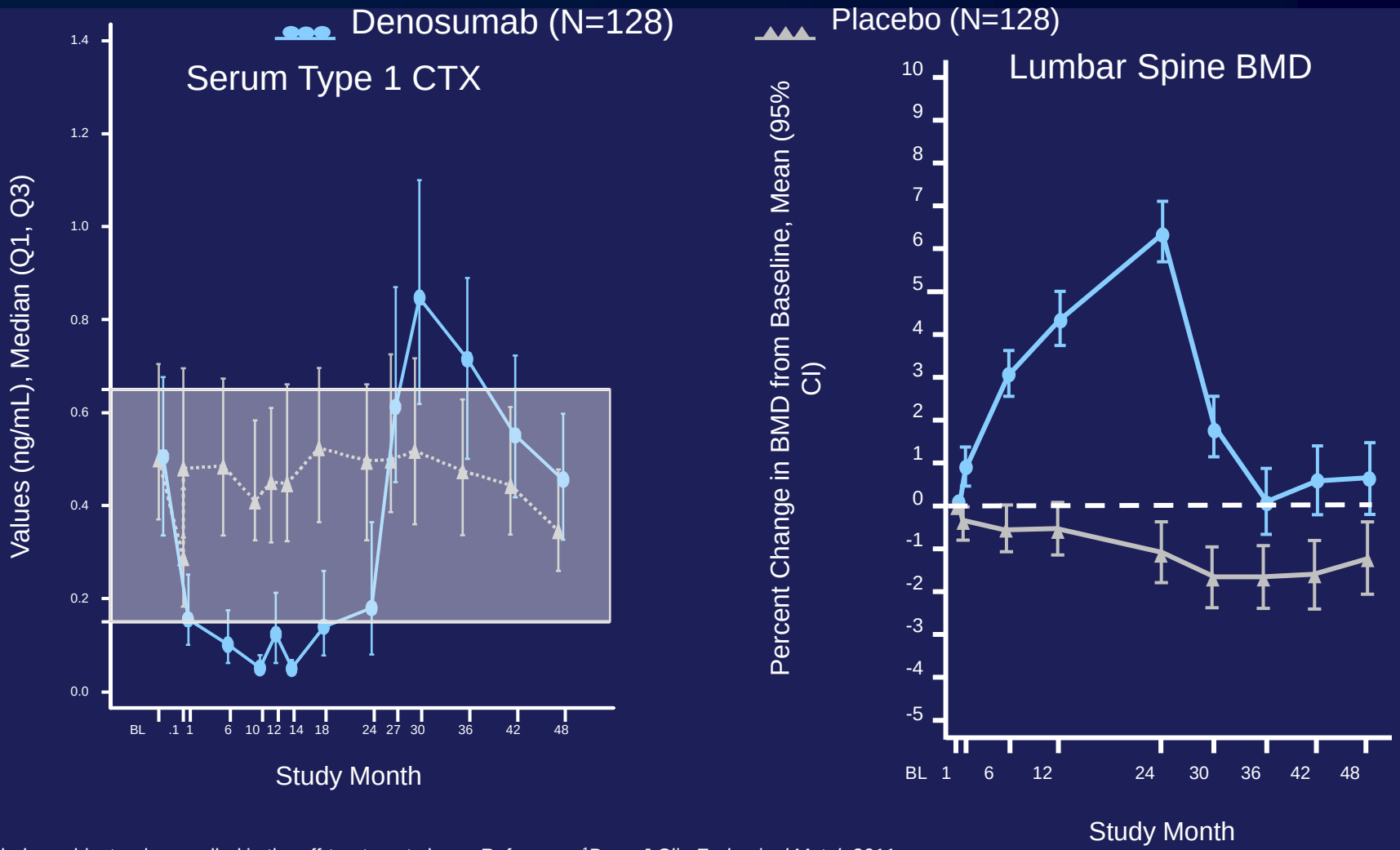
Brown JP *et al*. *Can Fam Physician* 2014;**60**:324-33.

No Drug Holiday For Reversible Drugs

- Hormone therapy (HT)
- Selective estrogen receptor Modulators (SERM)
- Denosumab
- Teriparatide

Brown JP *et al. Can Fam Physician* 2014;**60**:324-33.

Reversibility of Denosumab Action on Bone Turnover and Bone Mineral Density[1]



Includes subjects who enrolled in the off-treatment phase; Reference: [1]Bone *J Clin Endocrinol Metab* 2011
BMD: bone mineral density; CI: confidence interval; CTX: carboxy-terminal collagen crosslinks; P1NP: amino-terminal propeptide of type I collagen; Q1, Q3: first, third quartile

Summary and Conclusion

- Osteoporosis is a chronic disease requiring prolonged treatment.
- Long-term efficacy and safety data for osteoporosis therapies are reassuring
- High risk patients : hip, spine or multiple fragility fractures

  before or during treatment

  should continue on BPs up to 10 yrs **or**

  consider alternative therapy
- Drug holiday is feasible with ALN, RIS and ZOL after 3-5 years if patient at moderate risk
- No drug holiday for reversible drugs: HT, SERMs, DMAb, TPTD