Conflict of Interest

Jonathan D. Adachi

Consultant/Speaker

- Actavis
- Amgen
- Eli Lilly
- Merck

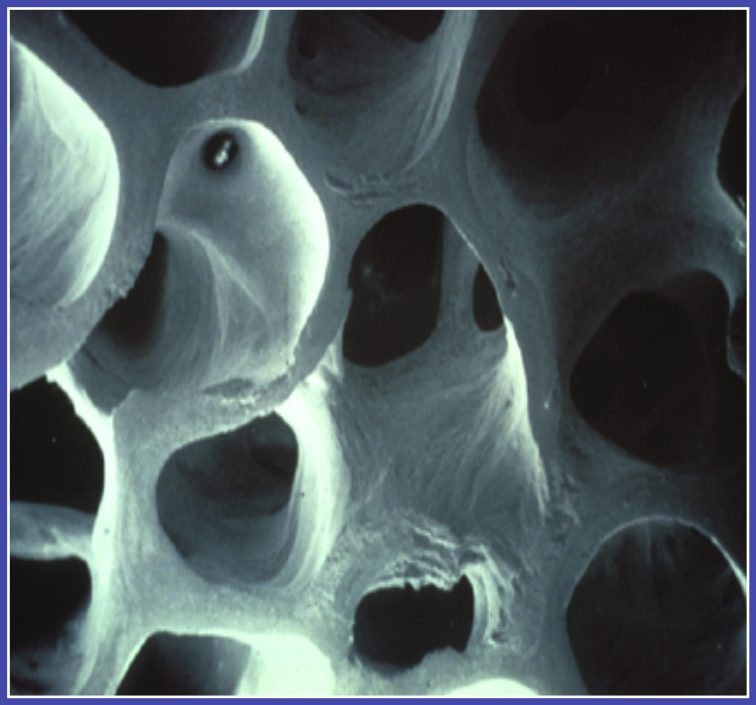
Clinical Trials

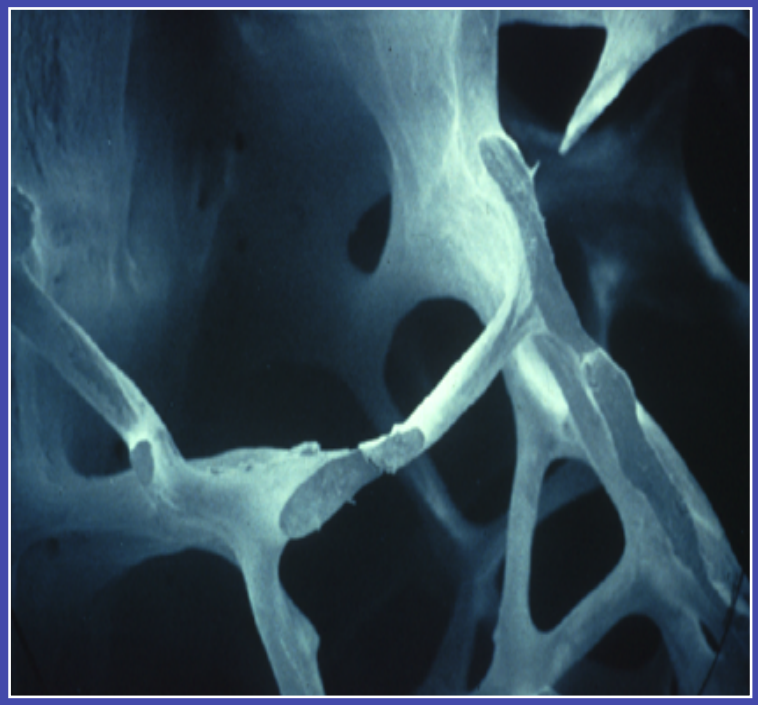
- Amgen
- Eli Lilly
- Merck
- Novartis

Stock

- None to declare

Current Controversies In Osteoporosis





Provided by D. Dempster, Ph.D., Helen Hayes Hospital, NY

Jonathan D. Adachi MD, FRCP(C)

Alliance for Better Bone Health Chair in Rheumatology

Professor, Department of Medicine

Michael G. DeGroote School of Medicine

St. Joseph's Healthcare – McMaster University

Objectives

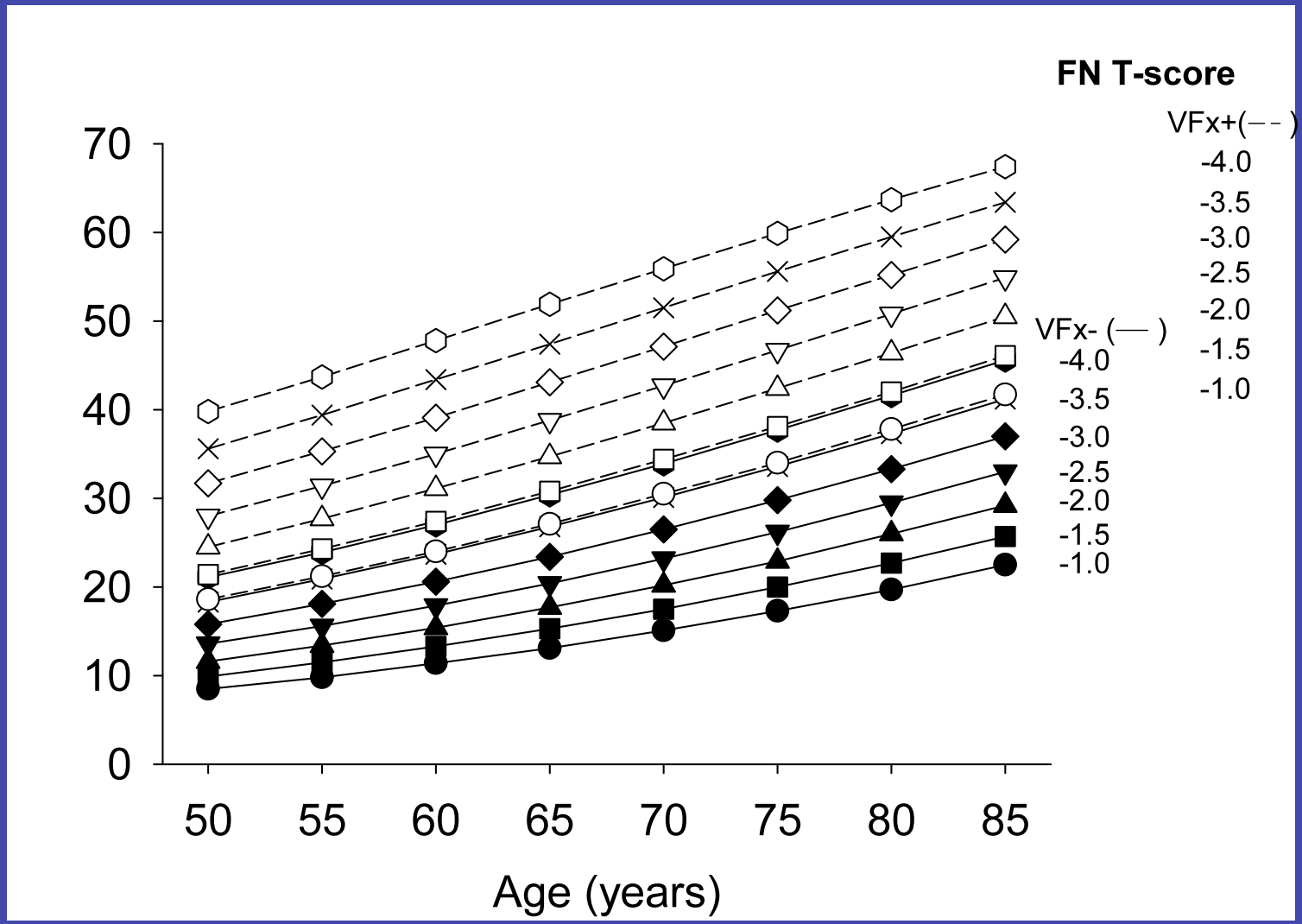
- Understand the benefits and risks of OP therapy
- Determine who should be given a drug holiday or treatment interruption
- Define “Treat to target” versus standard goal therapy

How do you identify patients at high risk of fracturing?

Who is at high fracture risk?

- Those with a fracture
  - Incident
  - Prevalent
- Those with a low t-score
  - -3.0 lumbar spine
  - -2.5 femoral neck

Fracture Risk Prediction: Importance of age, BMD and Spine Fracture

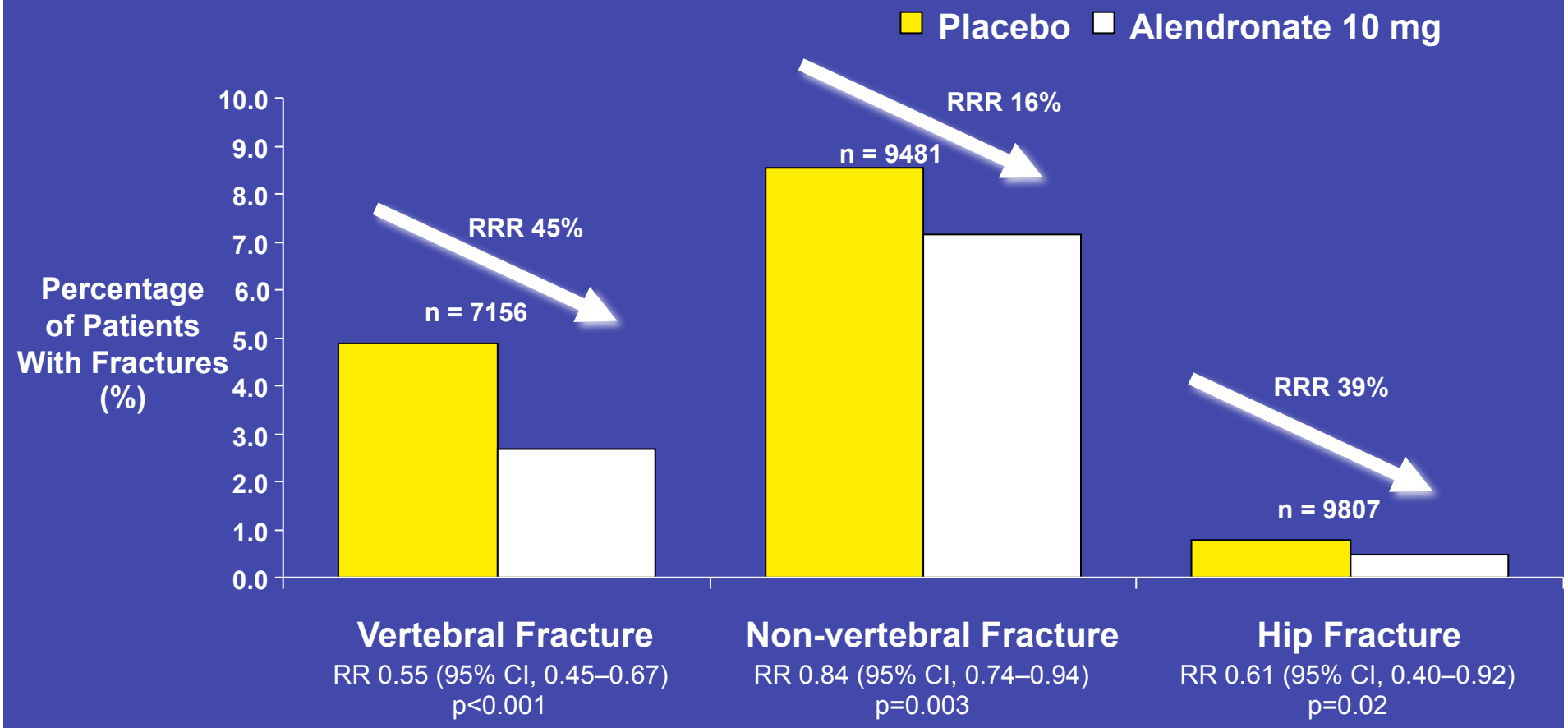


Krege JH et al Bonekey 2013

What is the data regarding treatment efficacy?

Alendronate reduces vertebral, Non-vertebral, and Hip Fractures

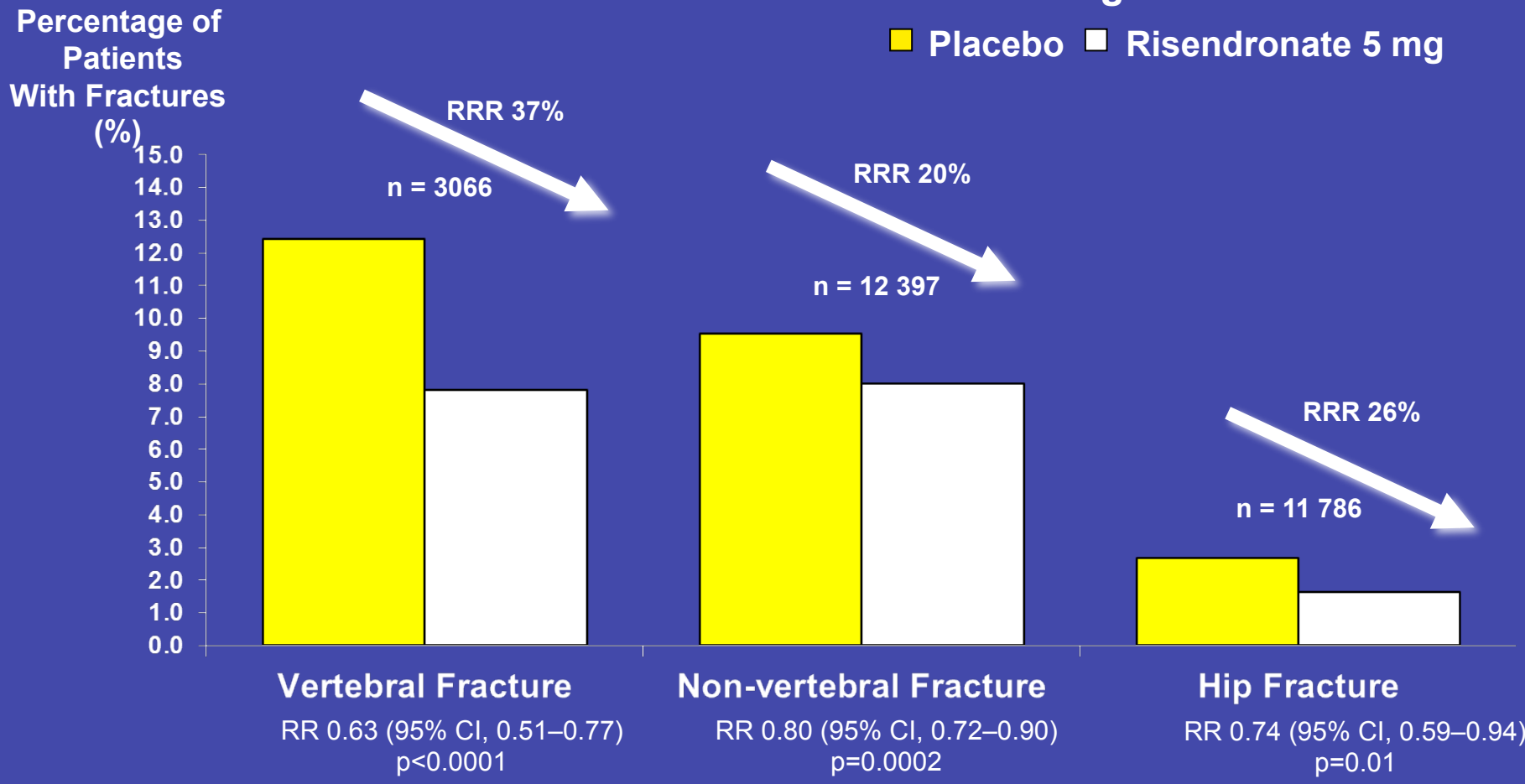
Cochrane meta-analysis: Patient incidence of fracture and weighted relative risk for fractures after treatment with 10 mg alendronate



Wells GA, *et al. Cochrane Database Syst Rev.* 2008 , Issue 1, CD001155

Risedronate Reduces Vertebral, Non-vertebral, and Hip Fractures

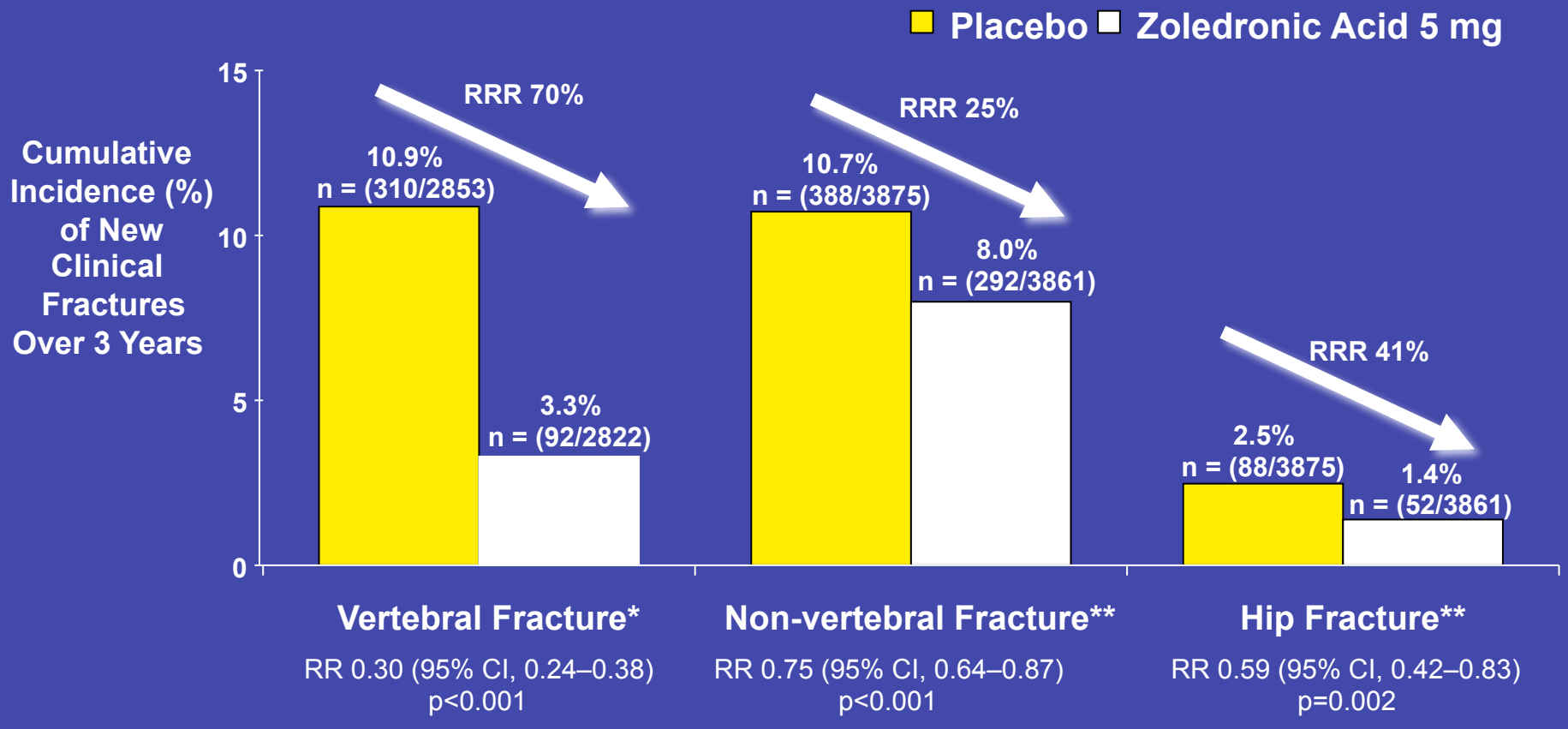
Cochrane meta-analysis: Patients' incidence of fracture and weighted relative risk for fractures after treatment with 5 mg risedronate



Wells GA, *et al. Cochrane Database Syst Rev.* 2008 Jan 23;(1):CD004523

Zoledronic Acid Reduces Vertebral, Non-vertebral, and Hip Fractures

RCT: HORIZON 3 year Pivotal Fracture Trial in PMO women

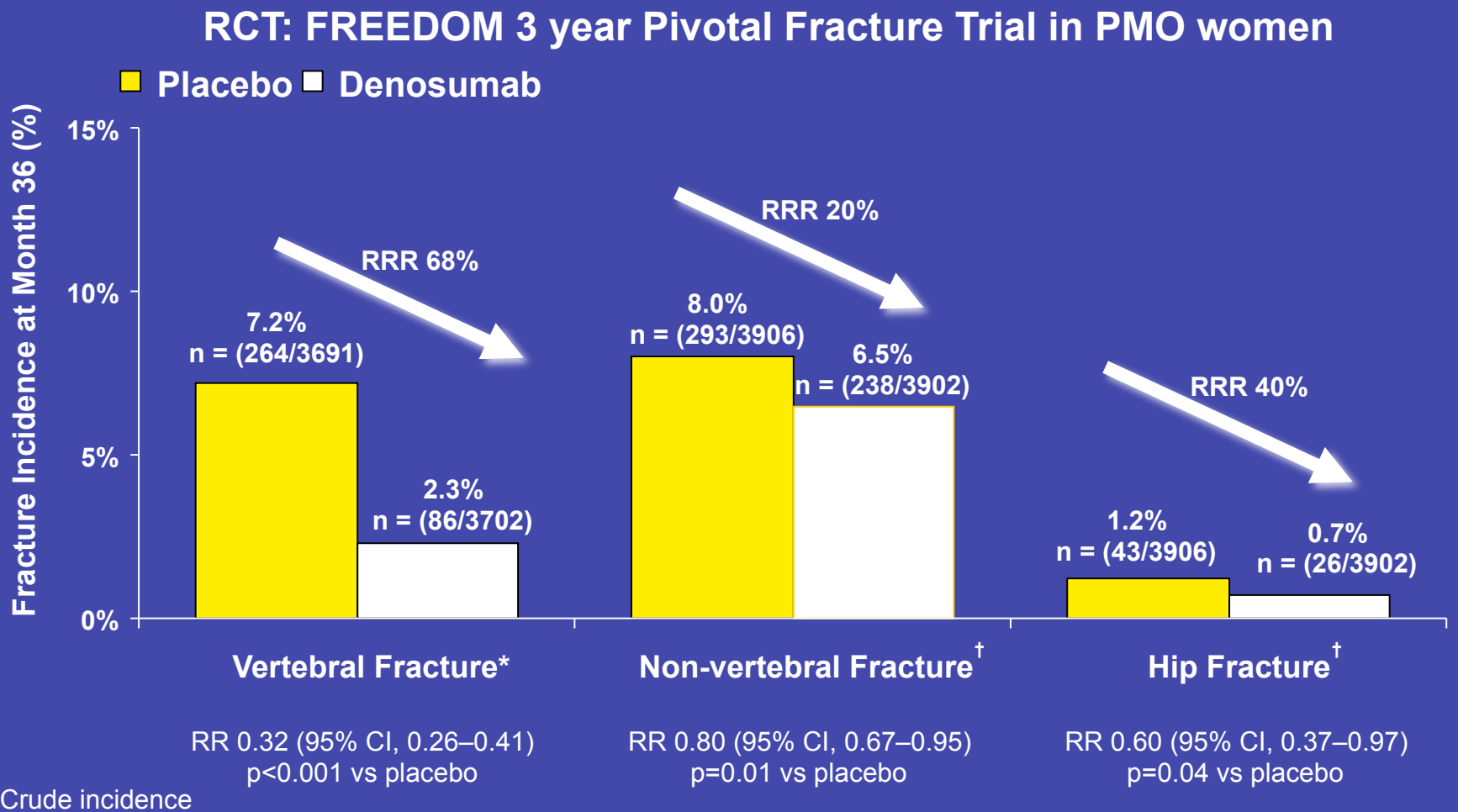


* Incidence rate

** 3-year cumulative event rates based on Kaplan-Meier estimates.

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

Denosumab Reduces Vertebral, Non-vertebral, and Hip Fractures in Women With PMO

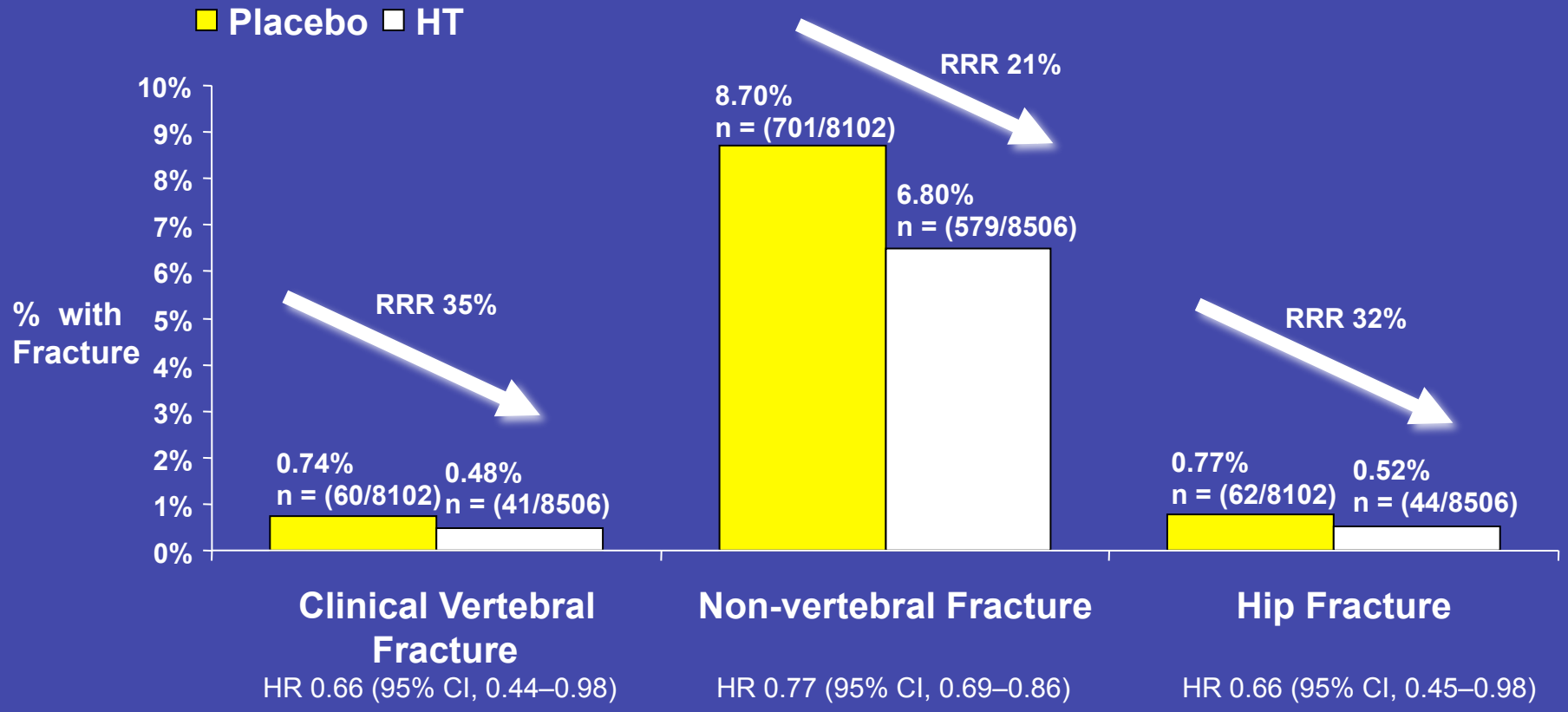


*Crude incidence
†Kaplan-Meier estimate of incidence

Cummings SR, *et al. N Eng J Med.* 2009;361:756

Hormone Therapy Prevents Vertebral, Non-vertebral, and Hip Fractures in Postmenopausal Women

RCT: WHI study with postmenopausal women treated with hormone therapy for 5.2 years

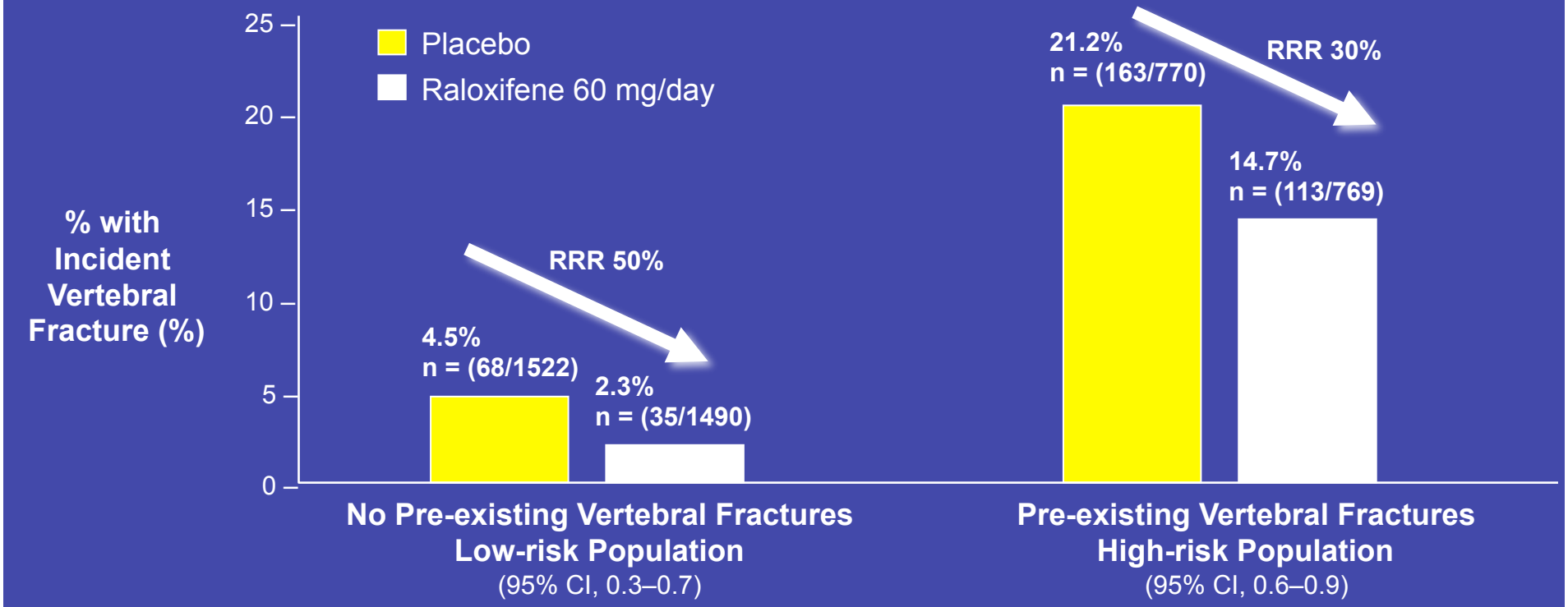


CI = confidence interval, HR = hazard ratio, RRR = relative risk reduction HT = daily combined estrogen and progestin

Rossouw JE, *et al. JAMA*. 2002;288:321

Raloxifene Reduces Vertebral Fractures

RCT: MORE Study in postmenopausal women for 3 years[1]



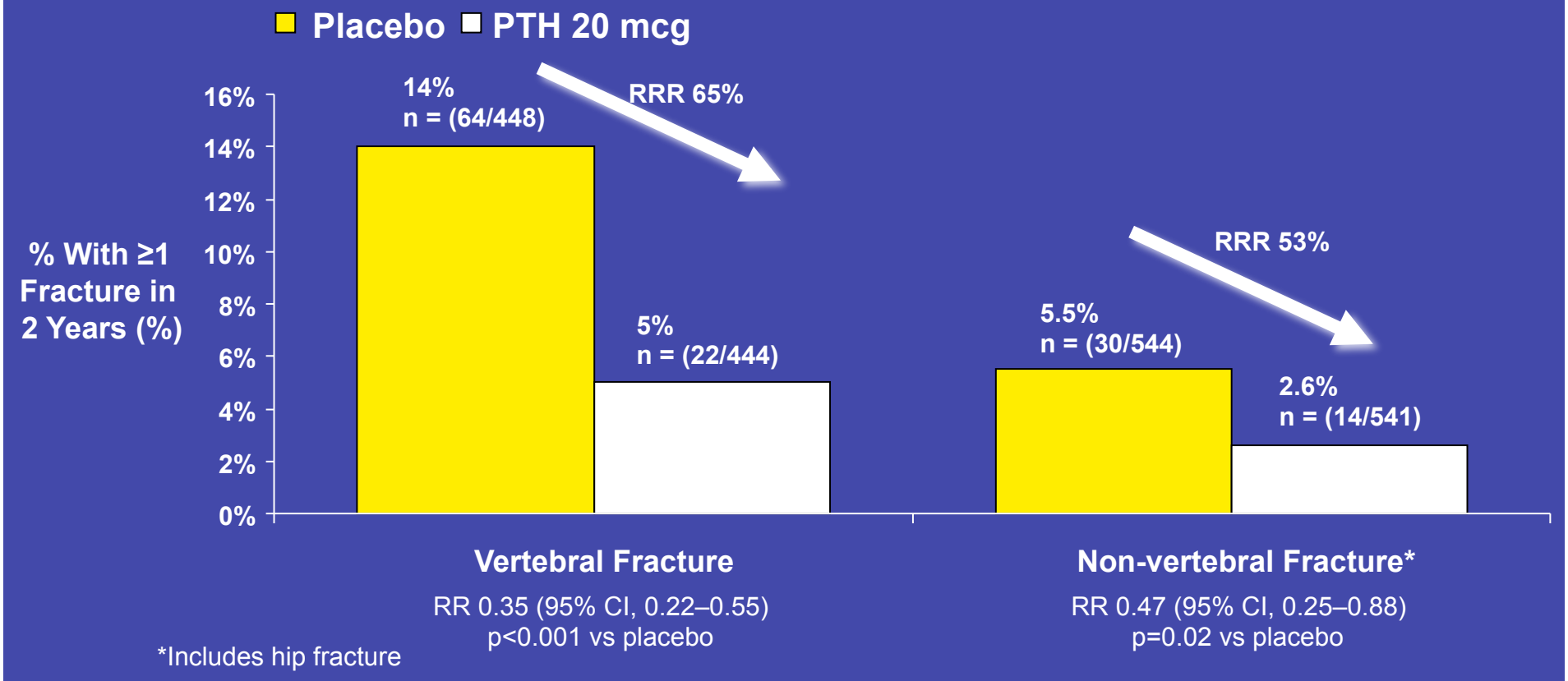
Relative risk of non-vertebral, including hip, fractures was not significant (RR 0.9, 95% CI, 0.8–1.1)[1]

Meta-analysis of 7 Raloxifene clinical trials reported fracture reductions results consistent with results from the MORE study; overall odds ratio of 0.60[2]

1. Ettinger B, *et al*. *JAMA.* 1999;282:637
2. Seeman E, *et al*. *Osteoporos Int.* 2006;17:313

Teriparatide Reduces Risk of Vertebral and Non-vertebral Fractures in Women With PMO

RCT: Effect of daily PTH for 18 months on vertebral and non-vertebral fractures



*Includes hip fracture

Neer RM, *et al. N Engl J Med*. 2001;344:1434

First Line Therapies with Evidence for Fracture Prevention in Postmenopausal Women[1]

Based on GRADE A evidence as assessed in the Osteoporosis Canada 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada[1]*

Type of Fracture	Antiresorptive Therapy						Bone Formation Therapy
	Bisphosphonates			Denosumab	Raloxifene	Estrogen ** (Hormone Therapy)	Teriparatide
	Alendronate	Risedronate	Zoledronic Acid				
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓		✓	
Non-Vertebral	✓	✓	✓	✓		✓	✓

*For postmenopausal women, indicates first line therapies and Grade A recommendation.
**Hormone therapy (estrogen) can be used as first-line therapy in women with menopausal symptoms.
In Clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

Papaioannou A, Morin S. *CMAJ*. 2010.DOI:10.1503/cmaj.100771

Keypoint

- Numerous therapies with fracture efficacy
- Parenteral therapies seem to have greater efficacy
  - Teriparatide
  - Denosumab
  - Zoledronic acid

Treatment Failure?

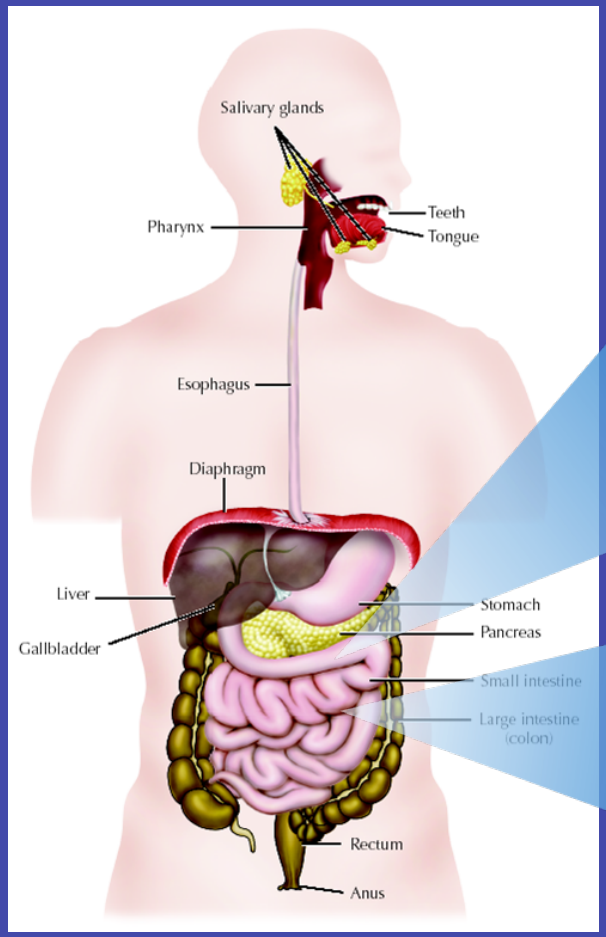
Treatment Failure

- 60 yr old women with FN-BMD of -3.5
- Treated with Actonel with a loss in BMD after 2 years of treatment
- How do you explain the bone loss?

Adherence

- On further questioning she admits to sometimes forgetting to take her medication on an empty stomach
- Stomach upset that she had resolved with taking it with a meal

Actonel DR Formulation



pH-sensitive enteric coating

EC

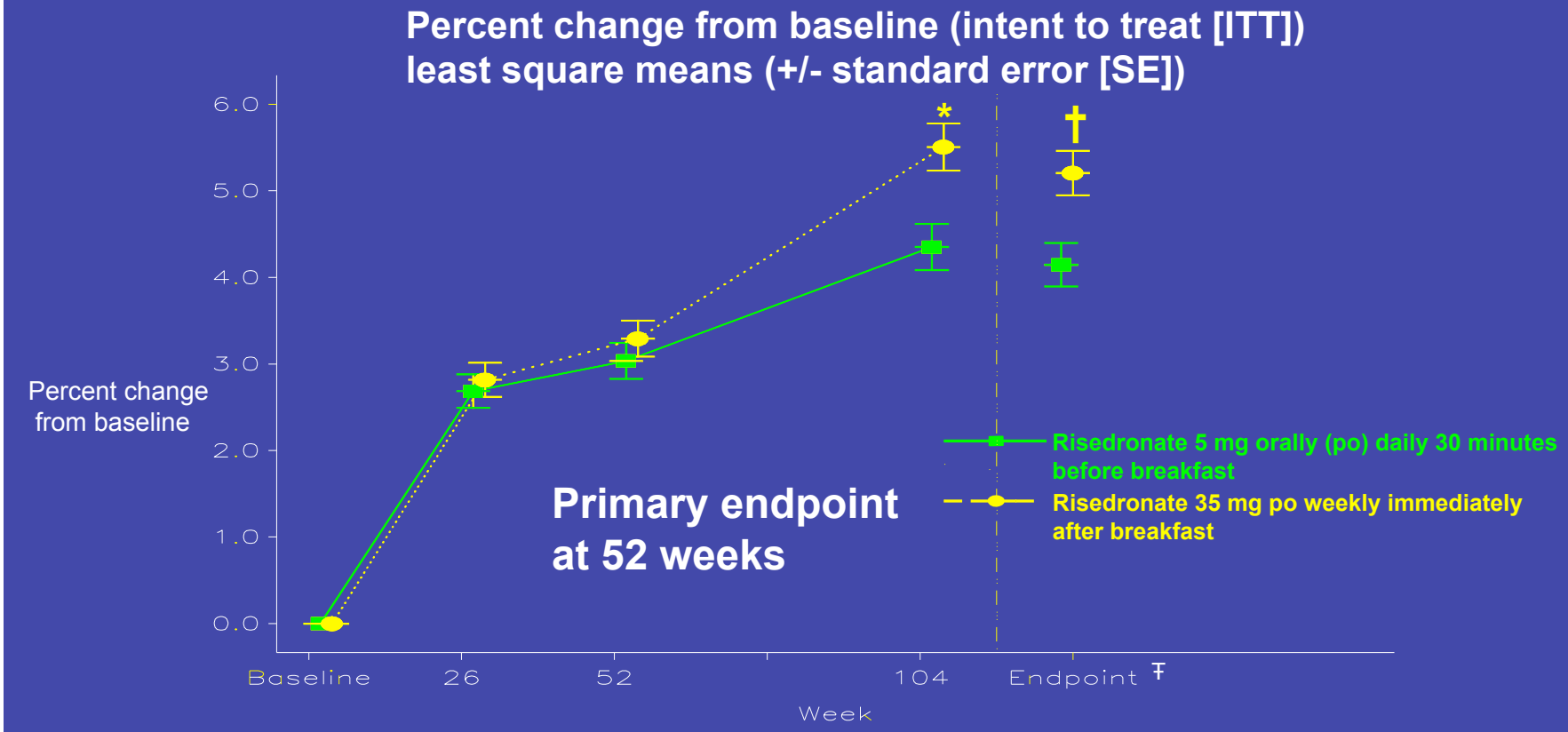
Bypasses esophagus and stomach and delays release until the small intestine, where the pH >5.5

Chelating agent (EDTA)

Intended to reduce the binding of risedronate with dietary calcium

Actonel® and Actonel® DR Product Monograph: Warner Chilcott Canada Co.; 2011.
McClung MR, Miller PD, Brown JP, Zanchetta J, Bolognese MA, Benhamou CL, *et al. Osteoporos Int* 2011, In Press.

Mean Percent Change from Baseline in Lumbar Spine BMD



At all time points, increases in BMD were statistically significant vs. baseline

* In the per protocol analysis at Week 104, 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.811; -0.220

† At endpoint (end of study), 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.762; -0.355

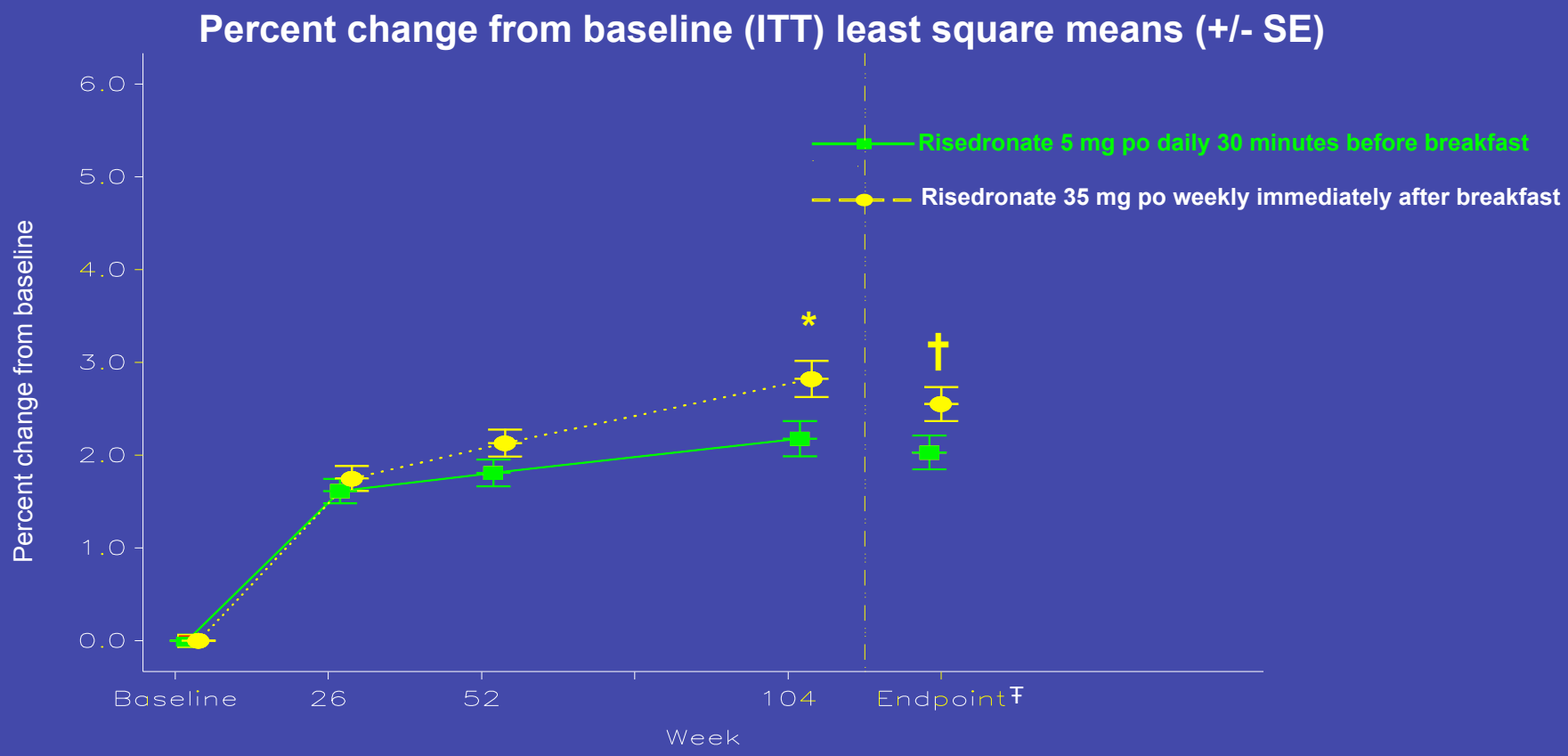
∓ including Last Observation Carried Forward (LOCF) patients

35 mg DR before breakfast is not shown

McClung MR, Miller PD, Brown JP, Zanchetta J, Bolognese MA, Benhamou CL, *et al. Osteoporos Int.* 2011, In Press.

Data on file. Rockaway, NJ: Warner Chilcott (US), LLC.

Mean Percent Change from Baseline in Total Proximal Femur BMD



At all time points, increases in BMD were statistically significant compared to baseline

* At Week 104, 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.179; -0.110

† At endpoint (end of study), 35 mg DR was associated with statistically greater increase than Actonel® 5 mg daily; 95% CI = -1.030; -0.014

Ŧ including Last Observation Carried Forward (LOCF) patients

35 mg DR before breakfast is not shown

McClung MR, Miller PD, Brown JP, Zanchetta J, Bolognese MA, Benhamou CL, *et al. Osteoporos Int.* 2011, In Press.

Keypoint

- Adherence remains our greatest challenge with only between 20-40 % adherent to therapy at 1 year
- Oral bisphosphonates need to be taken on an empty stomach, half an hour prior to food

Generic bisphosphonates?

Case Report - NY

- 62 year female with OP, LS T-score -3.0, commenced on Fosamax 70 mg weekly in May 2002.
- Followed on annual basis, tolerated her medication well. LS T-score of -2.61 in Sept 2004.
- Aug 2005, switched from Fosamax to apo-ALN, told this was Fosamax.
- Jan 2006, gave a history of severe stomach upset,10-15 pounds of weight loss.

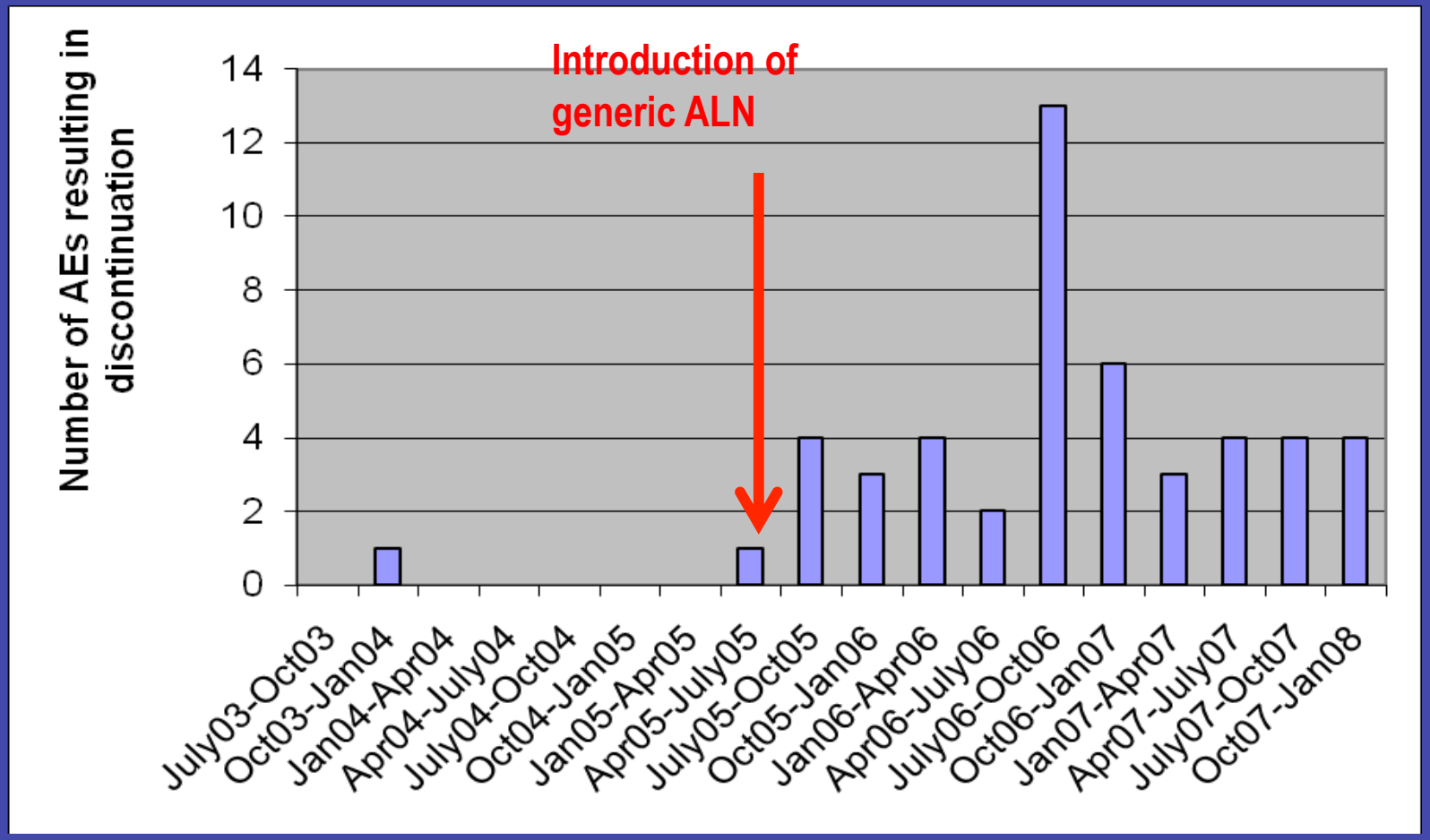
Grima D et al. BMC Musculoskeletal Disorders 2010, 11:68

Case Report - NY

- Had normal upper GI endoscopy, colonoscopy and small bowel follow through MRI and CT abdomen negative.
- Didn't link her GI problems to apo-ALN as she was told this was Fosamax and had never had any problems.
- D/C'd apo-ALN, problems resolved. Rechallenged recurred.
- Started on novo-ALN.
- With novo-ALN had problems with stomach pain, that persisted even with a PPI.
- Switched to Actonel 35 mg without difficulty.

Grima D et al. BMC Musculoskeletal Disorders 2010, 11:68

Generic ALN, AE's and Efficacy



Grima D et al. BMC Musculoskeletal Disorders 2010, 11:68

Results

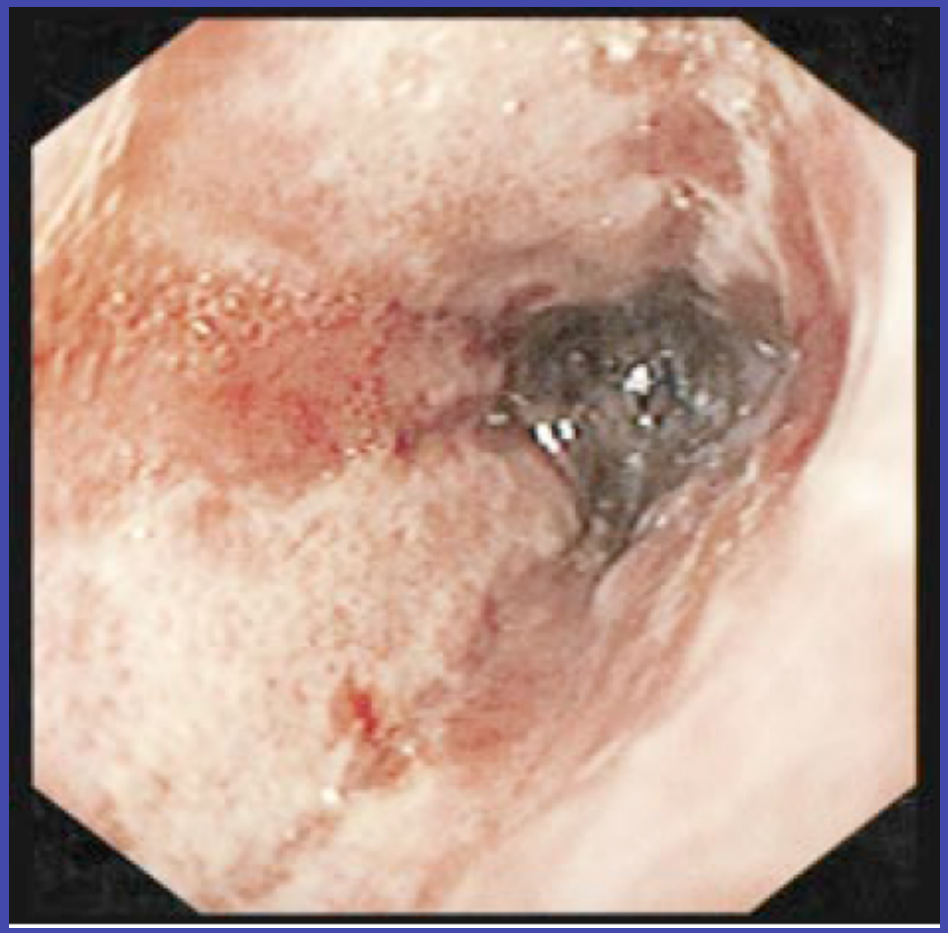
Tablet and dose	Lot number	Average disintegration time in seconds (SD)	Number of tablets tested
Novo-Alendronate 70mg	A34021	12.7 (1.09)	18
Apo-Alendronate 70mg	(L) JD 7416	25.7 (5.59)	20
Actonel 35mg	425314	101.2 (20.56)	20
Fosavance 70mg	Y 1382	378.0 (60.5)	20
Fosamax 70mg	Y1277 & Y1498	147.4 (50.47)	20

Olszynski WP et al. J Bone Miner Res 2010;25;S125

Esophagitis due to bisphosphonates.

ESOPHAGITIS ASSOCIATED WITH THE USE OF ALENDRONATE

PIET C. DE GROEN, M.D., DIETER F. LUBBE, M.B., CH.B., LAURENCE J. HIRSCH, M.D., ANASTASIA DAIFOTIS, M.D., WENDY STEPHENSON, M.D., M.P.H., DEBRA FREEDHOLM, B.S.N., SUZANNE PRYOR-TILLOTSON, M.S., MITCHEL J. SELEZNICK, M.D., HAIM PINKAS, M.D., AND KENNETH K. WANG, M.D.

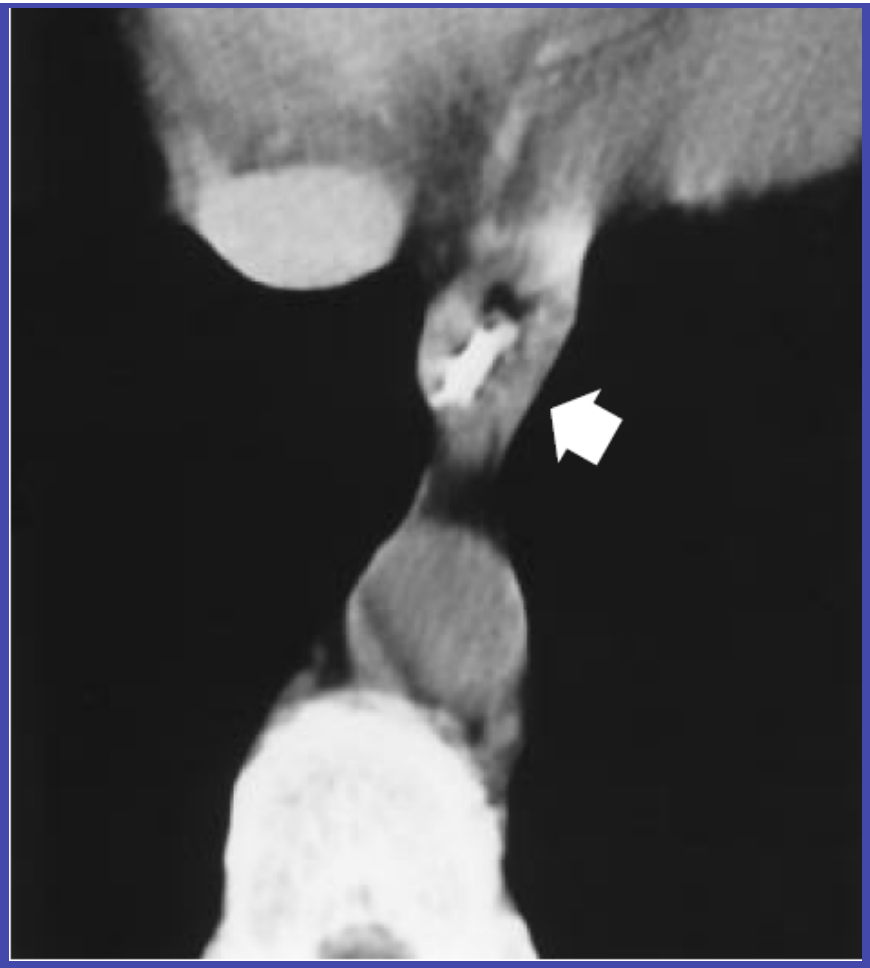


Severe, extensive hemorrhagic ulcerations and inflammatory exudates, which were still present in the distal esophagus on the ninth day of hospitalization.

N Engl J Med 1996;335:1016-21

ESOPHAGITIS ASSOCIATED WITH THE USE OF ALENDRONATE

PIET C. DE GROEN, M.D., DIETER F. LUBBE, M.B., CH.B., LAURENCE J. HIRSCH, M.D., ANASTASIA DAIFOTIS, M.D., WENDY STEPHENSON, M.D., M.P.H., DEBRA FREEDHOLM, B.S.N., SUZANNE PRYOR-TILLOTSON, M.S., MITCHEL J. SELEZNICK, M.D., HAIM PINKAS, M.D., AND KENNETH K. WANG, M.D.

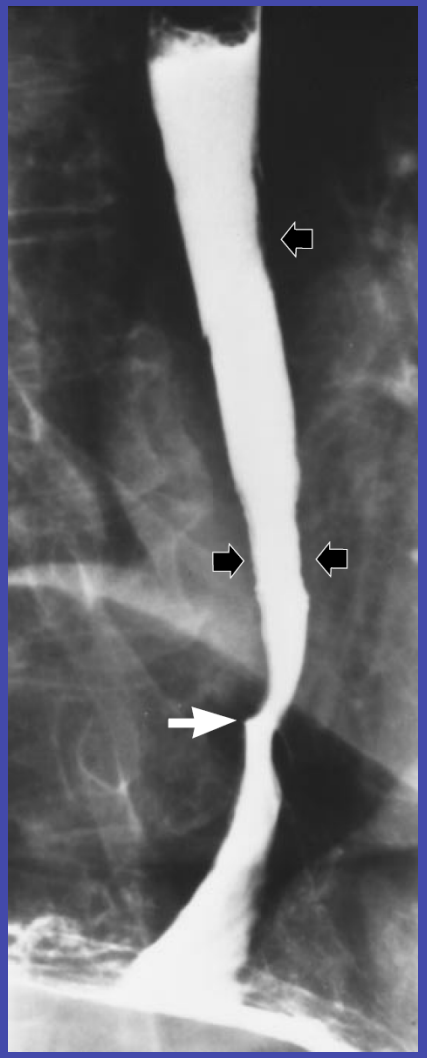


- Panel B shows concentric esophageal-wall thickening (arrow) suggestive of transmural inflammation.

N Engl J Med 1996;335:1016-21

ESOPHAGITIS ASSOCIATED WITH THE USE OF ALENDRONATE

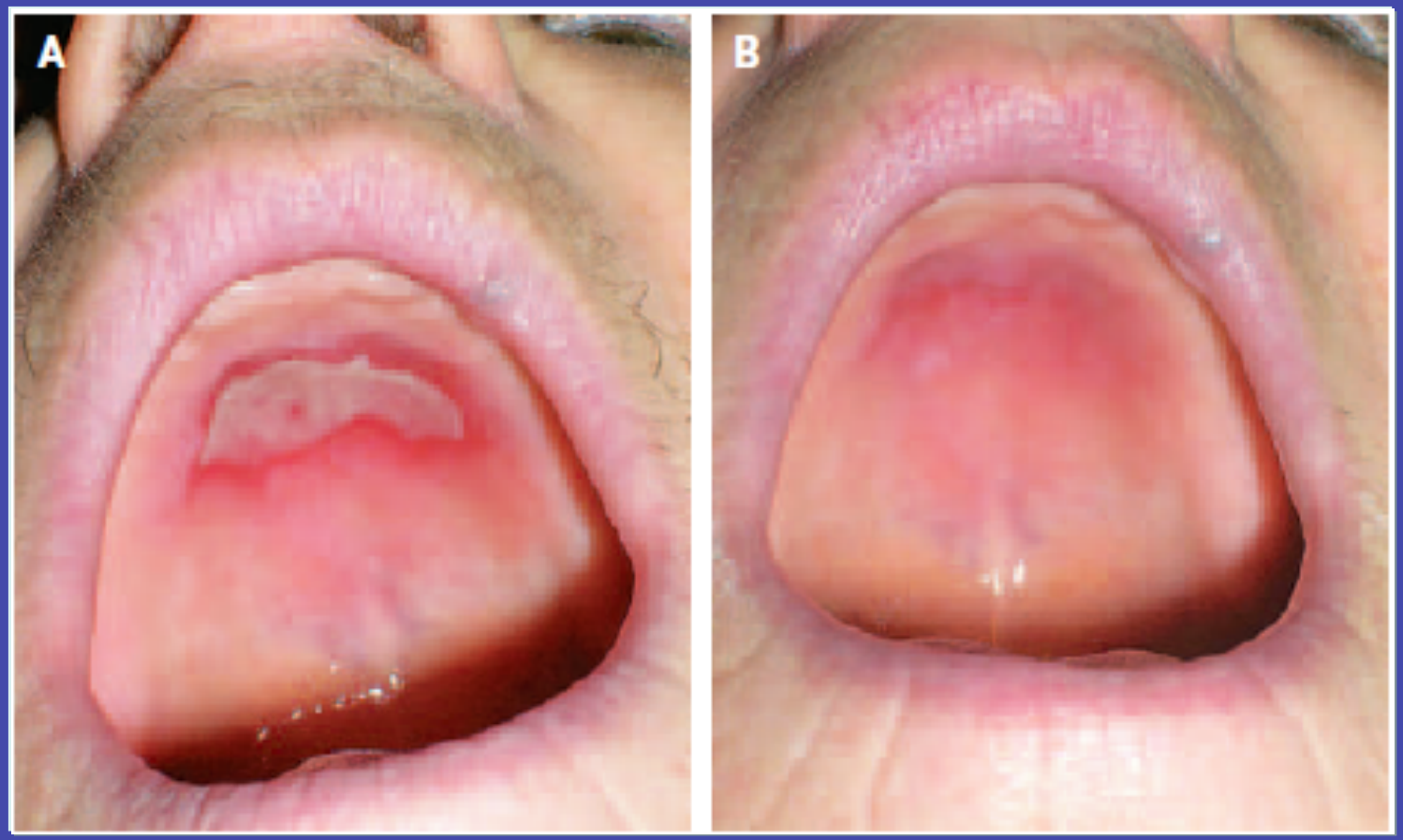
PIET C. DE GROEN, M.D., DIETER F. LUBBE, M.B., CH.B., LAURENCE J. HIRSCH, M.D., ANASTASIA DAIFOTIS, M.D., WENDY STEPHENSON, M.D., M.P.H., DEBRA FREEDHOLM, B.S.N., SUZANNE PRYOR-TILLOTSON, M.S., MITCHEL J. SELEZNICK, M.D., HAIM PINKAS, M.D., AND KENNETH K. WANG, M.D.



- The irregularity of the mucosa is consistent with esophagitis
- (black arrows). The distal esophagus is strictured (white arrow).

N Engl J Med 1996;335:1016-21

Bisphosphonate Associated Contact Stomatitis



Rubegni NEJM 2006;355:22 e25

Keypoint

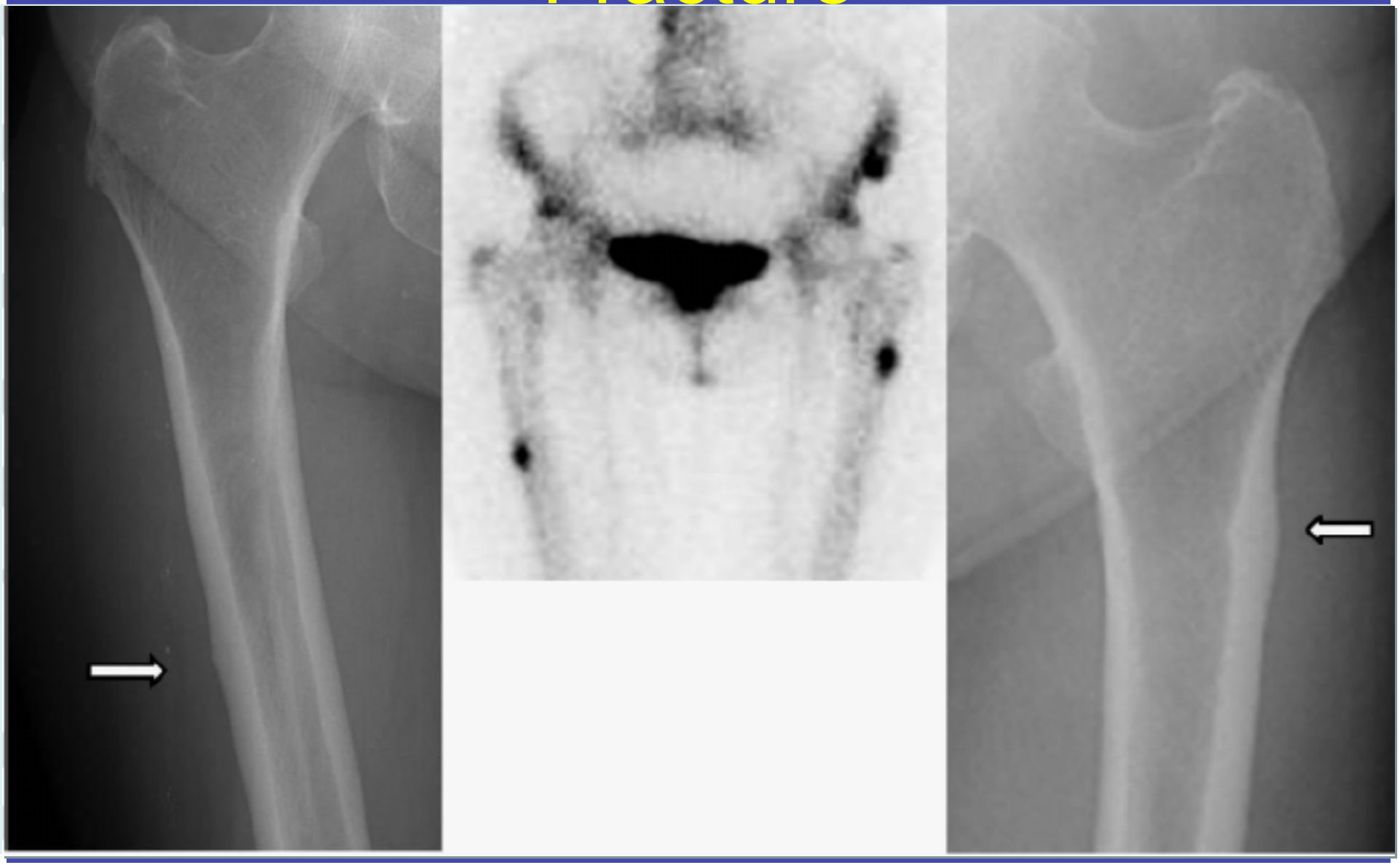
- Generic bisphosphonates may lead to increased GI side effects
- This may be related to rapid disintegration of the generics

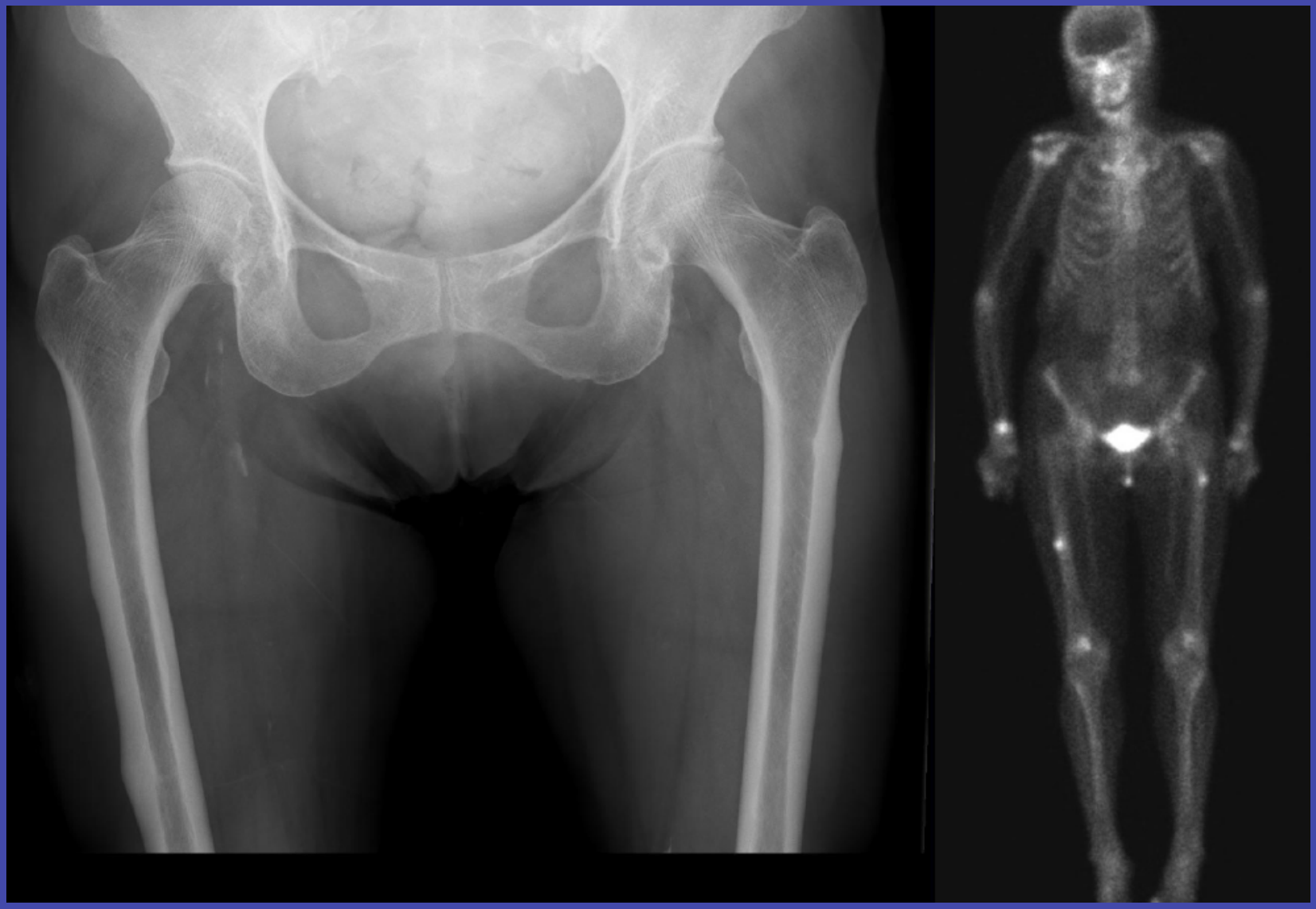
Atypical Femoral Fracture

- 65 yr old female, 8 yrs of BP therapy
- Complaining of bilateral thigh pain
- Constant dull ache

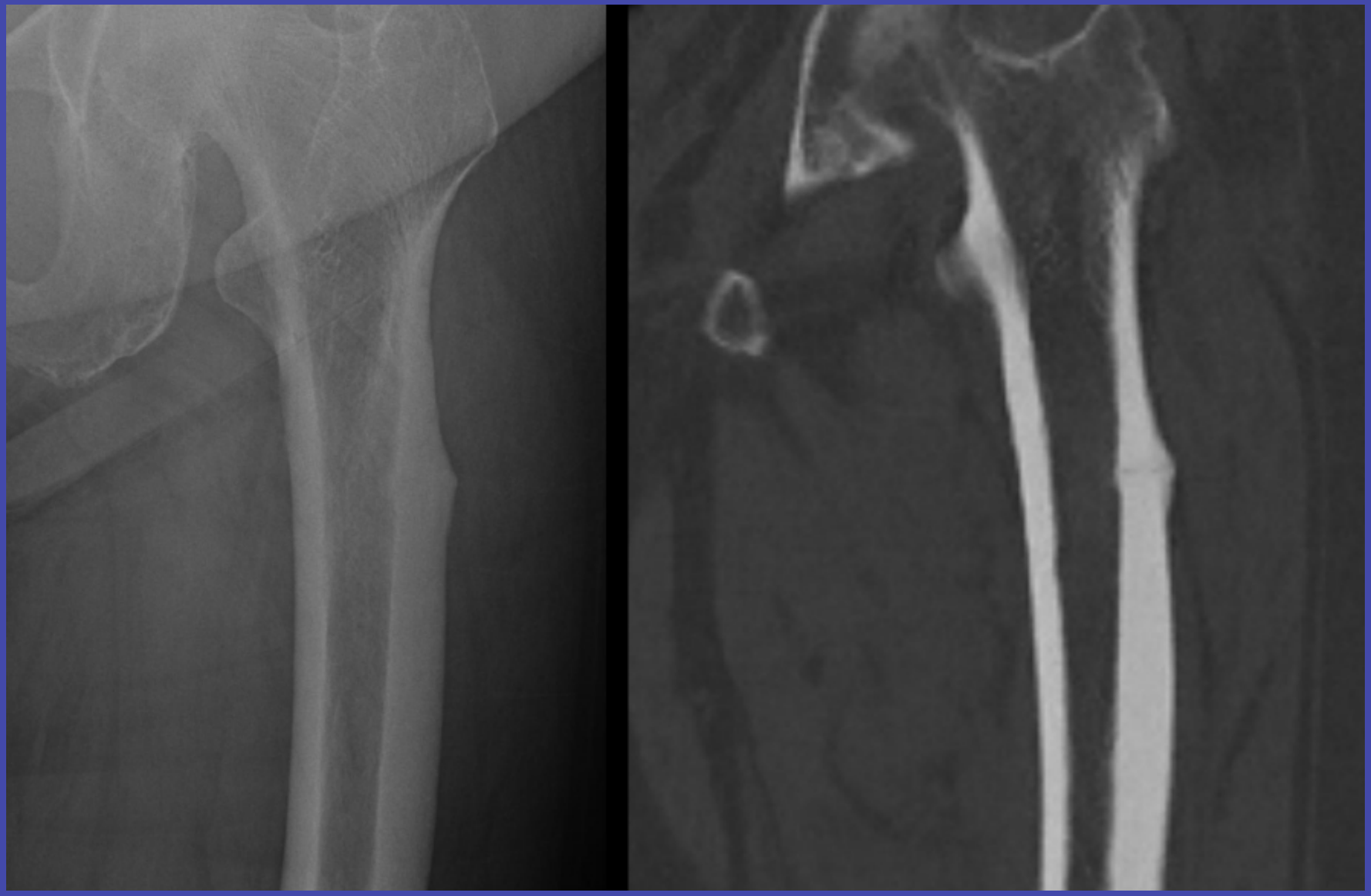
What would you do next?

Incomplete Atypical Femoral Fracture

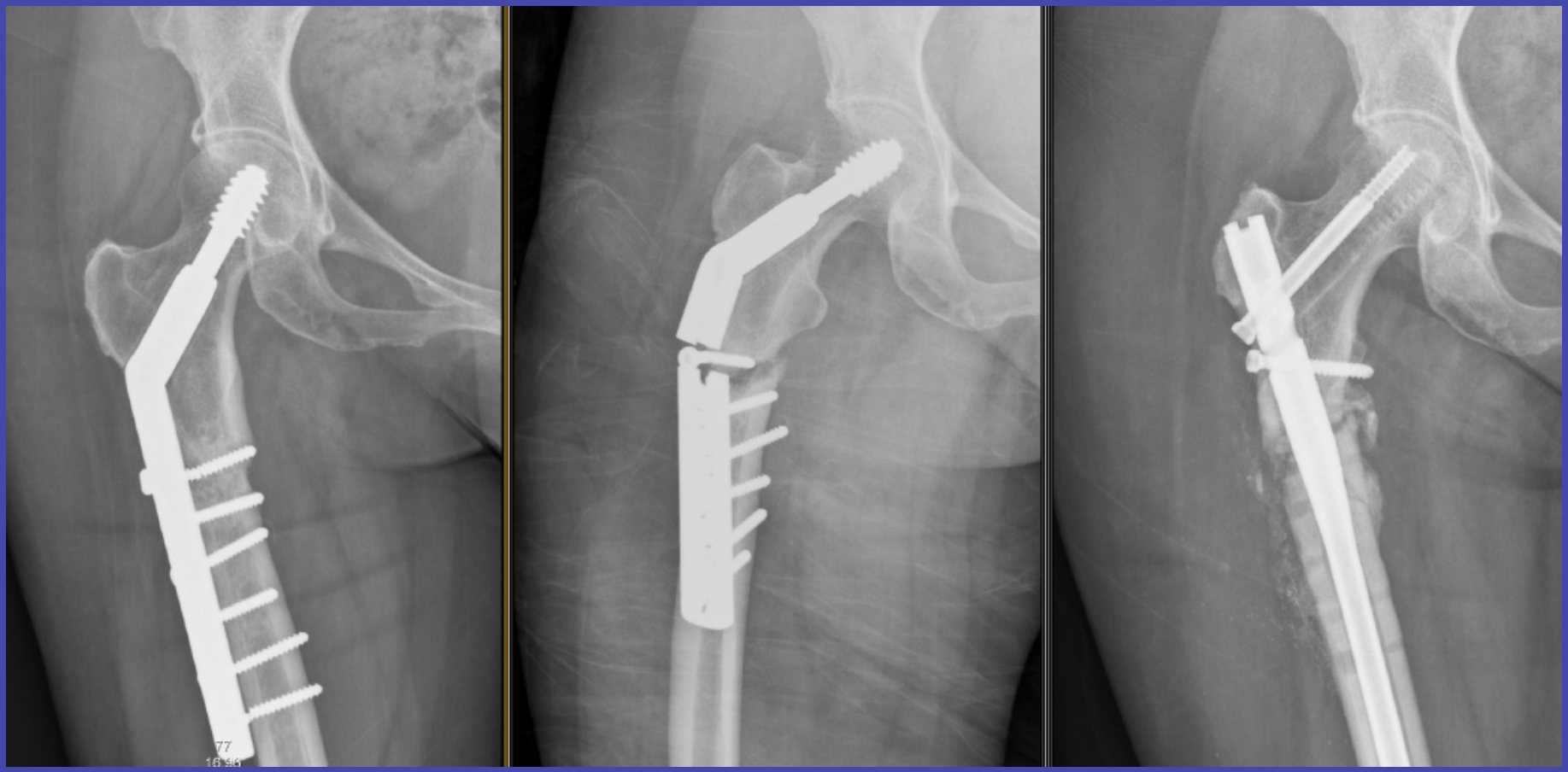




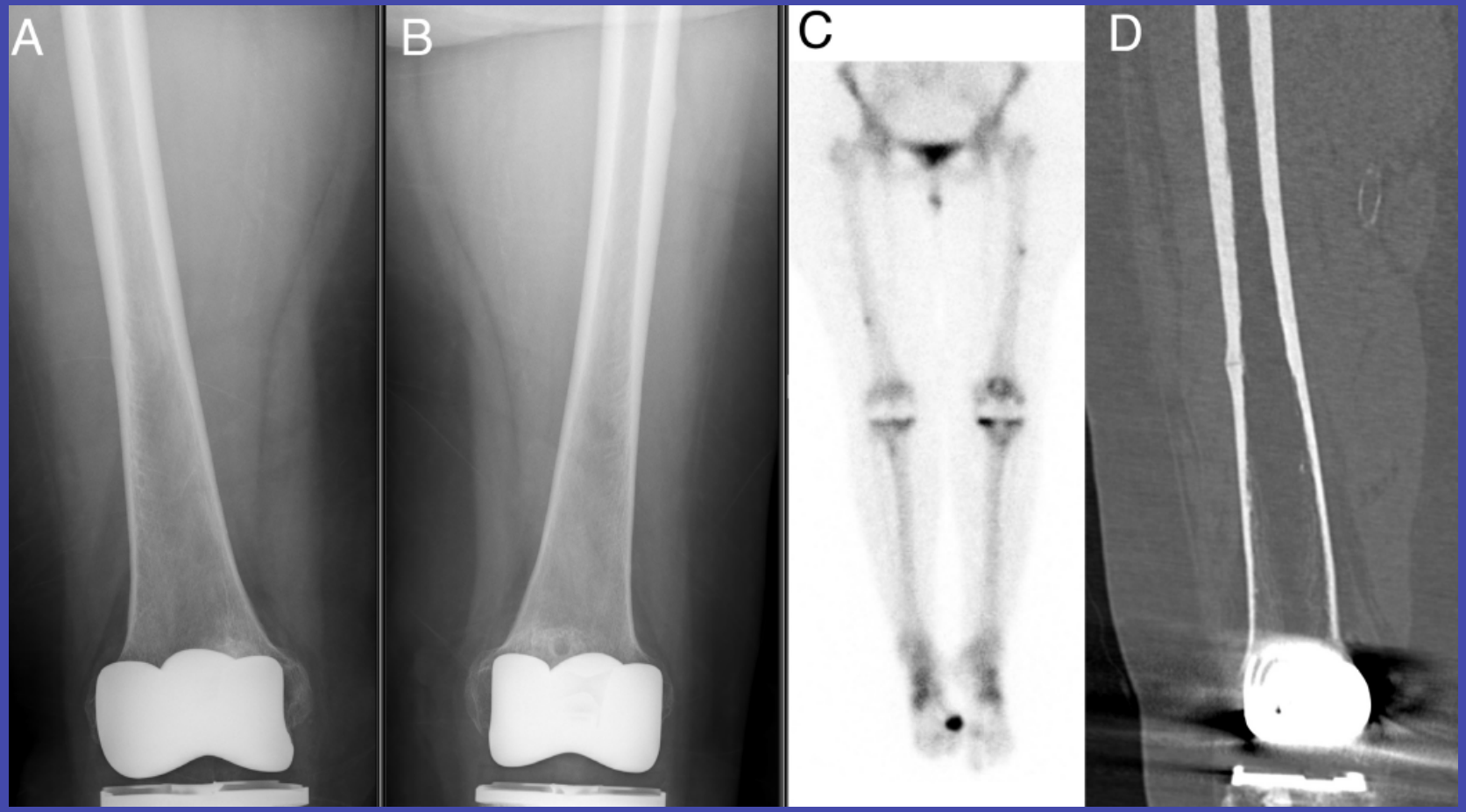
Bilateral incomplete AFFs on plain film and bone scan



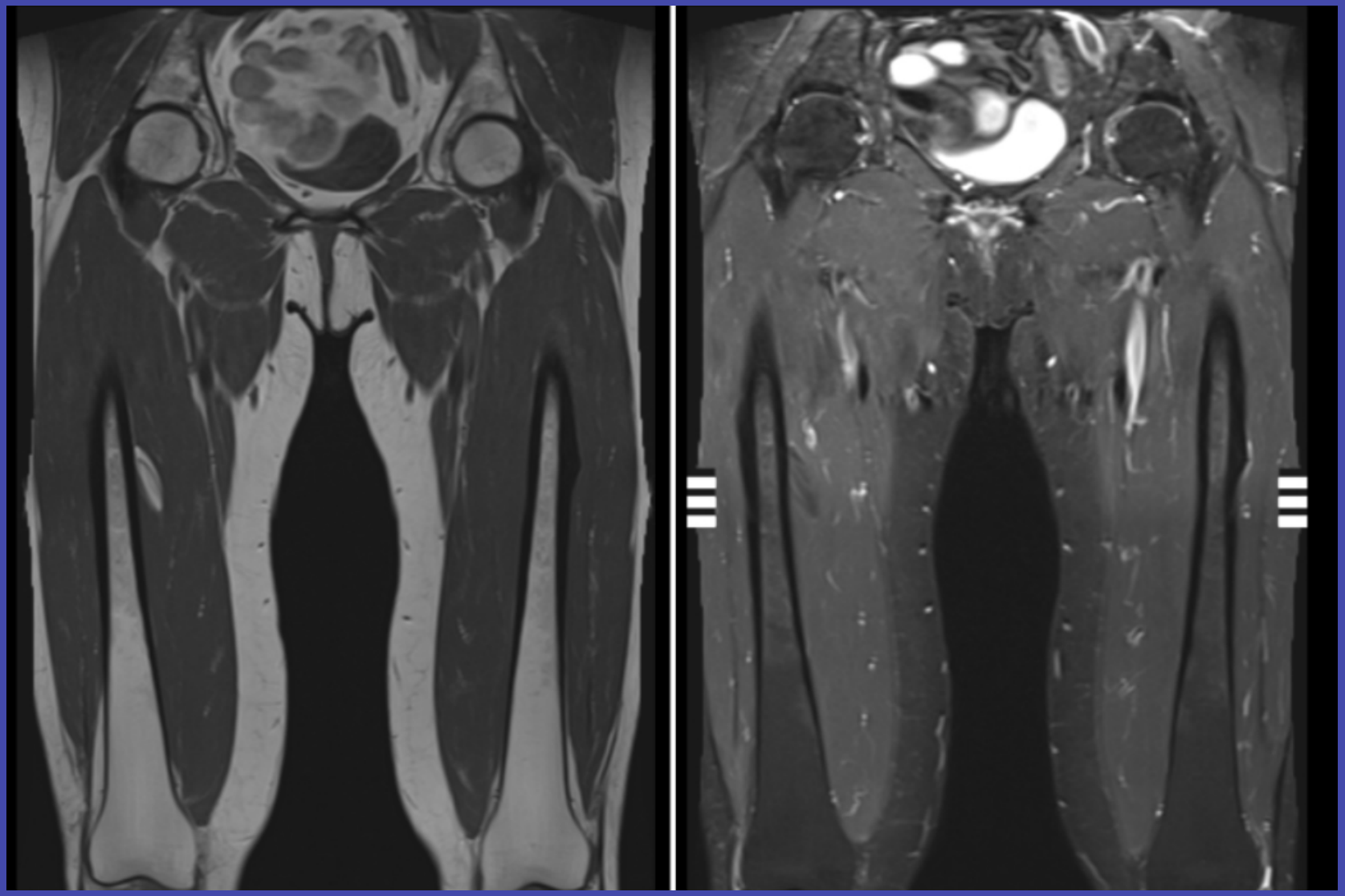
Incomplete AFF with focal lateral cortical thockening on plain film CT demonstrates a focal lucent cleft / fracture line



Complete AFF treated with lateral compression plate with subsequent failure and ultimate Gamma nail

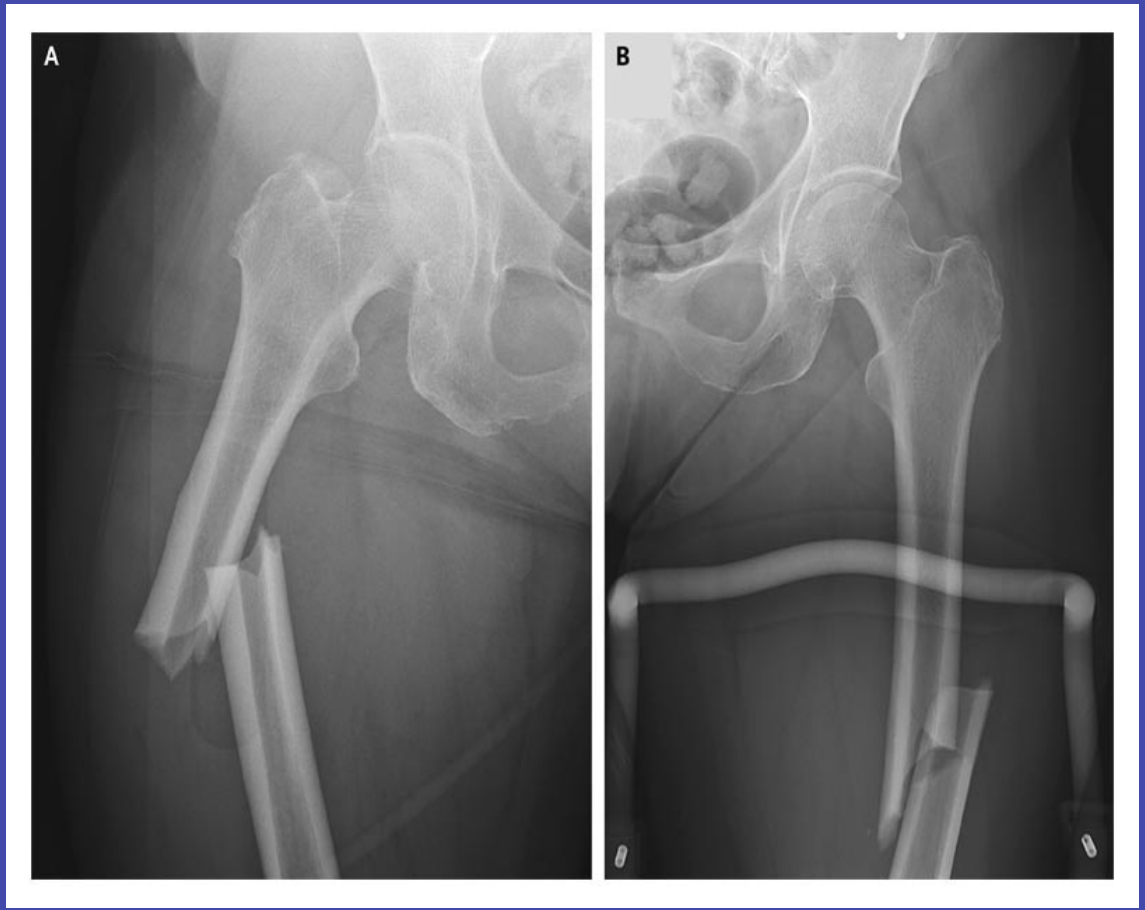


Subtle incomplete AFF's on plain film (A and B) areas of increased uptake on bone scan (C) and focal lucent cleft identified with CT (D)



Bilateral incomplete AFFs on MRI showing focal cortical thickening and periosteal/surface edema

Atypical Fractures of the Femoral Diaphysis in Postmenopausal Women Taking Alendronate



Lenart et al. N Engl J Med 2008;358:12

For every 100 or so reduction in typical hip fractures, there was an increase of one subtrochanteric fragility fracture

Wang et al. JBMR 2011;26:553-560

Effect of Teriparatide on Fracture Healing in Patients with Non-Displaced Incomplete Atypical Femur Fractures

Angela Cheung, UHN

TPTD and Fracture Healing in Patients with AFF

- 13 pts with incomplete AFF treated with TPTD.
- All PMP women, mean age 68.6 (57.5- 81.0) yrs
  - 9 Caucasians,
  - 2 Southeast Asians,
  - 2 South Asian
- 8/13 had previous complete AFF.
- Average duration of BP 12.6 yrs (3.0-28.0).
- Mean BMD T-scores at diagnosis of AFF were:
  - LS -1.87
  - TH -1.14
  - FN -1.85

TPTD and Fracture Healing in Patients with AFF

- TPTD therapy mean 13.4 months (1.4 to 20.2).
- 3 pts prophylactic surgical repair (2 for progression of fracture and 1 for preference).
- 10 patients:
  - 5 radiographic improvement,
  - 4 had no change and
  - 1 progressed despite TPTD.
- Unclear whether TPTD improves fracture healing in patients with incomplete non-displaced AFFs.

"Importantly, the results of our study should not deter clinicians and patients from using bisphosphonates in appropriate patients."

Park-Wyllie et al. JAMA. 2011;305(8):783-789

Keypoint

- Atypical femoral fractures while devastating, are rare
- Often present bilaterally
- Tend to occur in Asians, with longer duration of use and relatively good BMD's
- Teriparatide might be of benefit

Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates

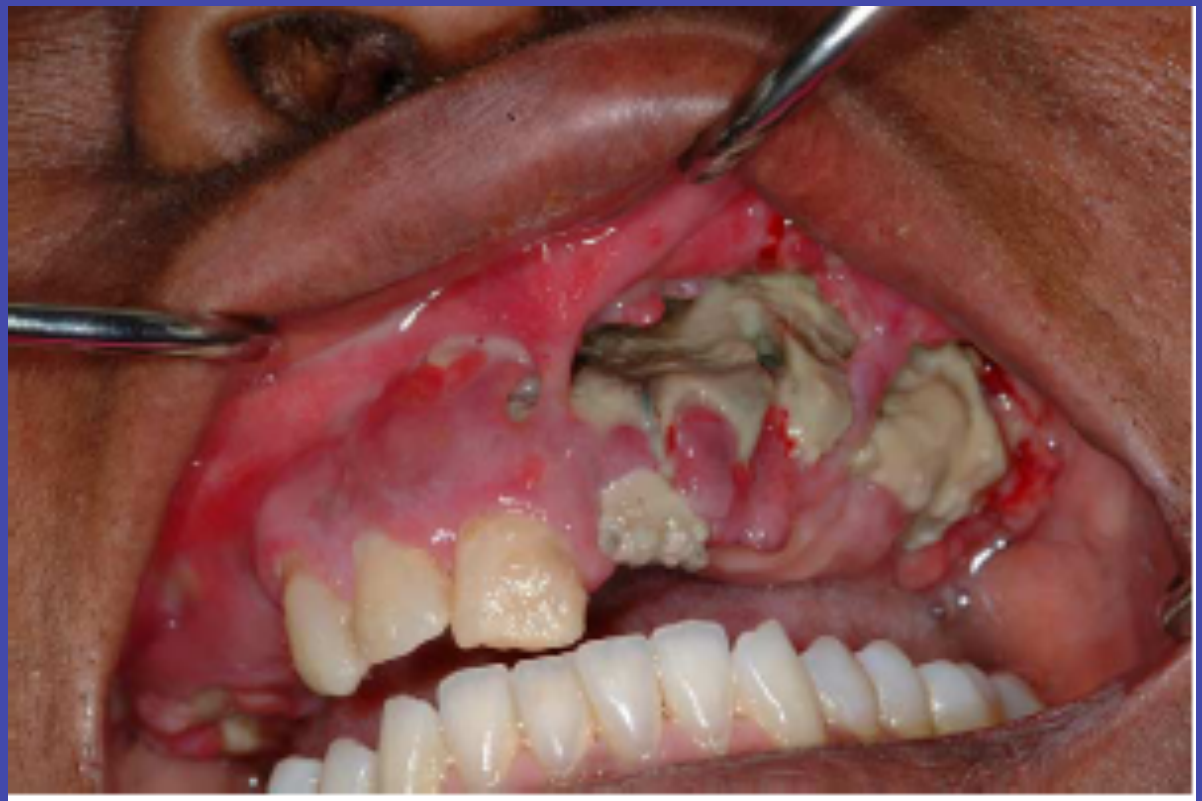


FIGURE 1. Exposed necrotic maxillary bone in a patient receiving zolendronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr Jay Neugarten, New Hyde Park, NY.)

Are there any dental benefits to bisphosphonate therapy?

Early Dental Implant Stability Correlates With Bone Turnover in BP Exposed Patients

Objective:

To assess the relationship between dental implant stability and bone turnover in patients with or without BP exposure

Early Dental Implant Stability Correlates With Bone Turnover in BP Exposed Patients

Study Design & Methods

Descriptive “best practice” prospective cohort study

Participants were asked to discontinue BPs around dental implant placement

Investigations

- Implant stability was assessed at surgery and 8 weeks later by resonance frequency analysis (RFA ISQ value), with values > 50 considered adequate
- sCTX measurement before treatment and at 1 and 8 weeks post-implant surgery

Early Dental Implant Stability Correlates With Bone Turnover in BP Exposed Patients

Results

- RFA ISQ demonstrated association between lower bone turnover and short-term implant stability in the “past/current” BP user group
- Studies with a larger population and longer follow-up are required to determine improvement in implant stability with antiresorptive medicines

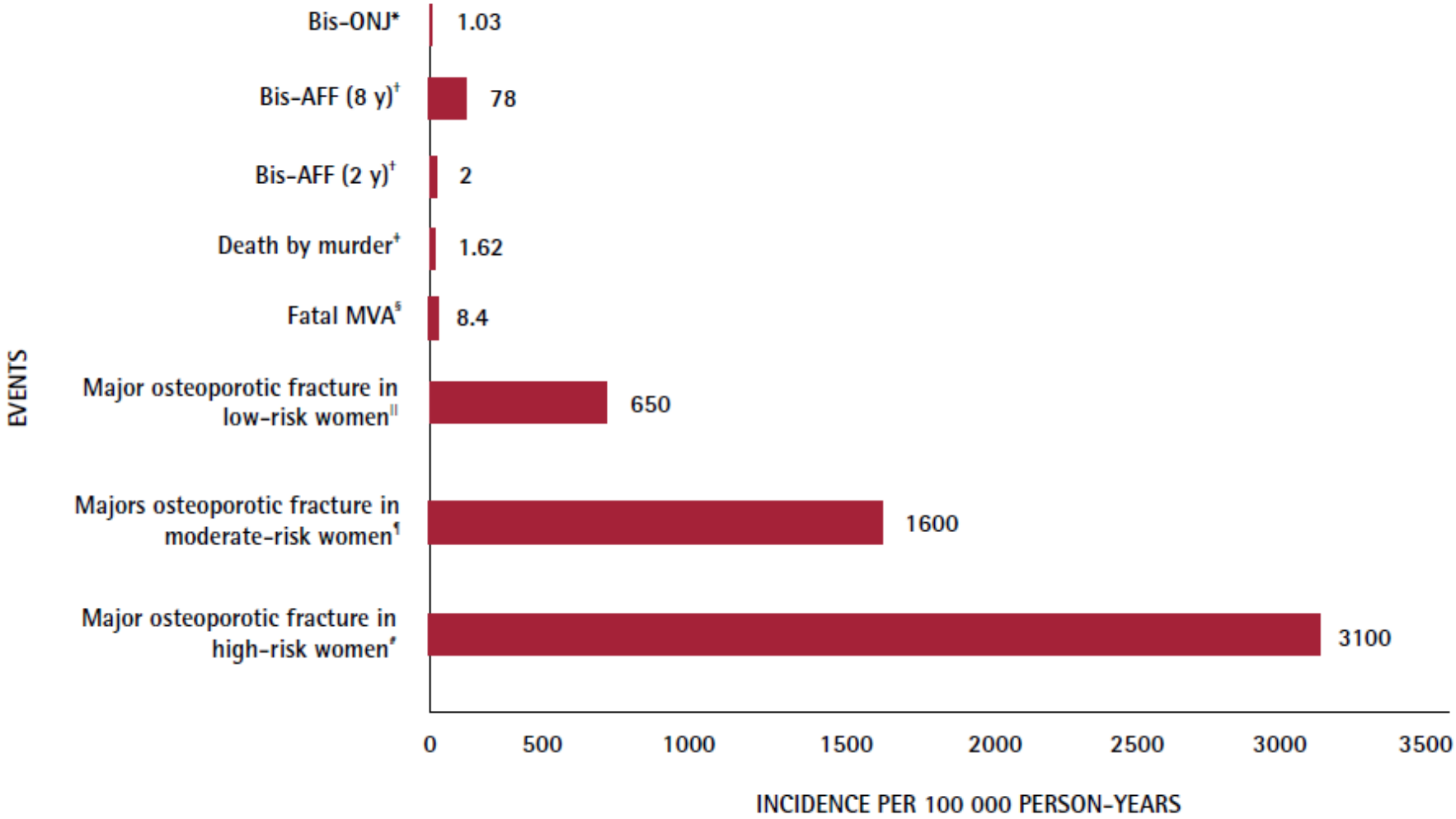
Early Dental Implant Stability Correlates With Bone Turnover in BP Exposed Patients

Clinical implications

- In the era of ONJ, warnings have been raised in practicing dental procedures in subjects receiving BP's
- Current or previous use of BP's is not detrimental for the stability of dental implant procedures
- The greater the suppression bone resorption with BP's, greater the short-term implant stability
- BP treatment may became a therapeutic strategy to improve dental implant stability in patients at risk of poor surgical outcomes if confirmed in long-term studies

BP: bisphosphonate, RFA ISQ: reference frequency analysis implant stability quotient.

Risks of major osteoporotic fracture and other rare events



Brown et al Can Fam Phys 2014;60:324-333

Keypoint

- Benefits of therapy even in relatively low risk individuals outweigh the risks of rare events like ONJ and atypical fractures

Should we suggest a drug holiday after several years treatment?

Drug Holiday

- Who should be considered for a drug holiday?
- Who should not be considered for a drug holiday?
- How long should the drug holiday last?

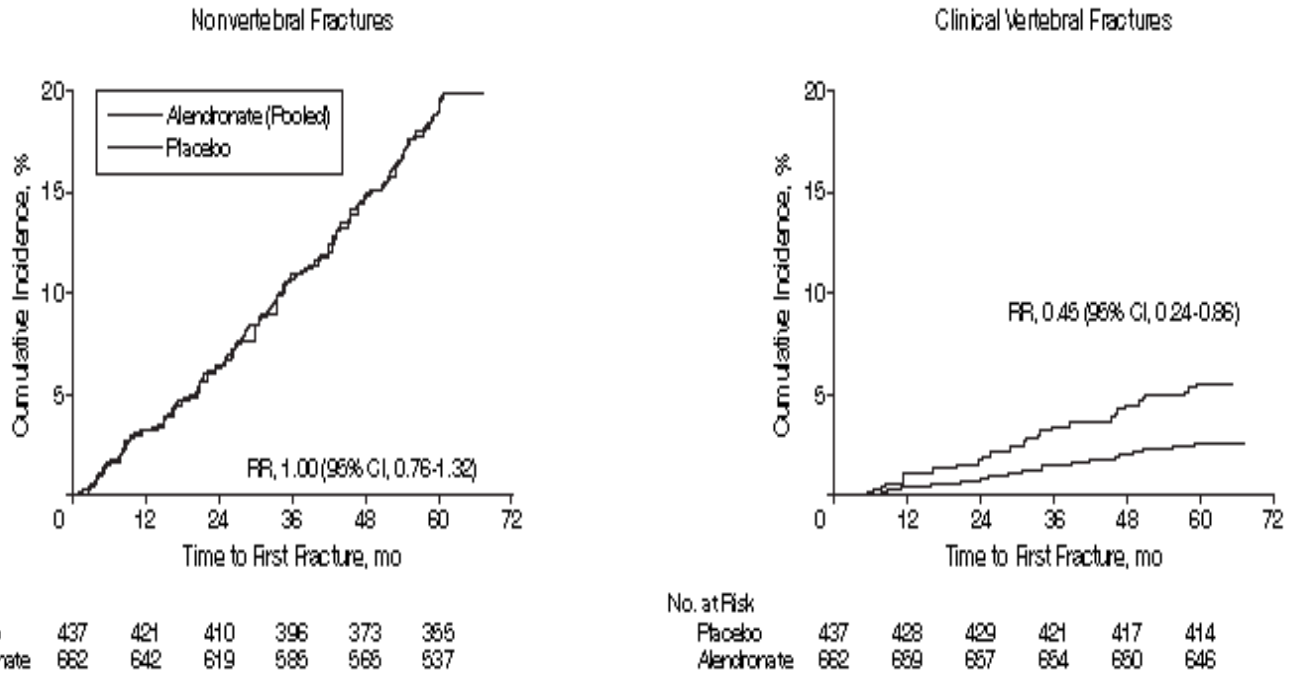
Effects of Continuing or Stopping Alendronate After 5 Years of Treatment The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR

JAMA. 2006;296:2927-2938

Effects of Continuing or Stopping Alendronate After 5 Years of Treatment The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

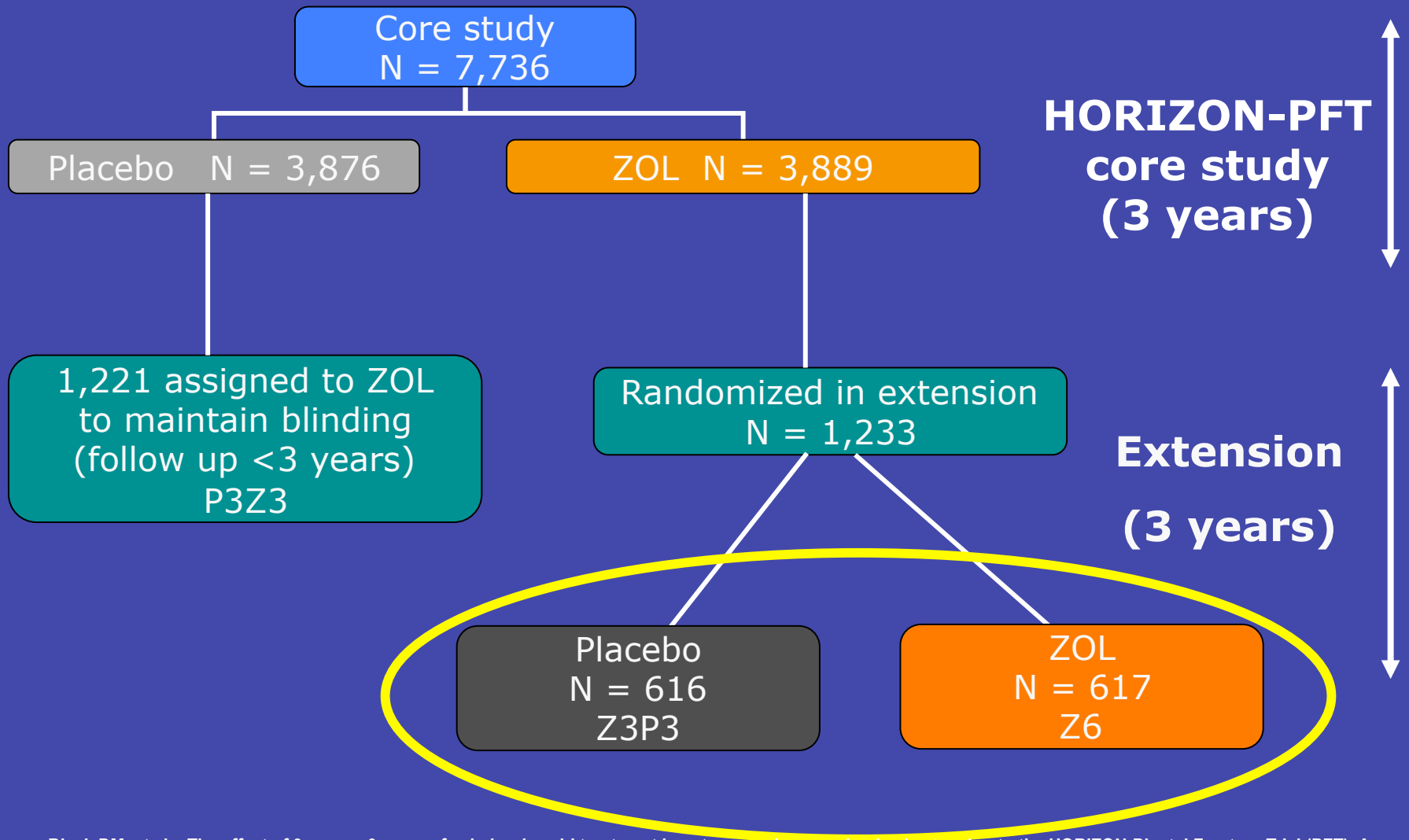
Figure 4. Survival Curve for Time to First Nonvertebral Fracture and Time to First Clinical Vertebral Fracture



CI indicates confidence interval; RR, relative risk.

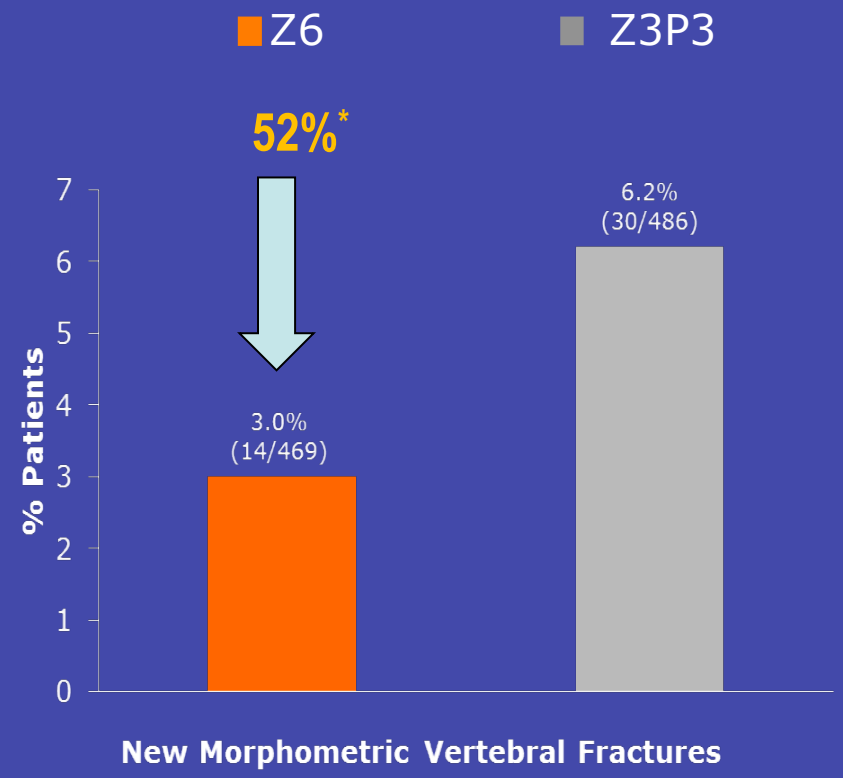
JAMA. 2006;296:2927-2938

Patient Flow From Core Study to Extension



Black DM, et al. . The effect of 3 versus 6 years of zoledronic acid treatment in osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). Annual Meeting of the American Society of Bone and Mineral Research; October 15-19, 2010; Toronto, Canada. Abstract., 1070.

Between-treatment Comparison of the Proportion of Patients with Morphometric Vertebral Fractures Between Year 3 and Year 6 (ITT)



*P = .03, **P = .03, 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

Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday

J. R. Curtis, A. O. Westfall, H. Cheng, E. Delzell, and K. G. Saag

Curtis et al. Osteoporos Int 2008;19:1613-1620

Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday

Results

- 9,063 women
- Hip fracture incidence
  - discontinued 8.43 versus
  - continued 4.67 per 1000 person years (p=0.016).

Curtis et al. Osteoporos Int 2008;19:1613-1620

Who should ***not*** be considered for a BP drug holiday

- osteoporotic femoral neck BMD at discontinuation (ie, T-score ≤ -2.5),
- a history of fragility fracture, or prevalent vertebral fracture associated with increased risk of fracture
- high-risk patients with osteoporotic BMD or history of fragility fracture (including prevalent vertebral fracture) *should not* be candidates for BP drug holiday

Brown et al Can Fam Phys 2014;60:324-333

When and for whom should BP holidays be considered?

FRACTURE RISK	CLINICAL PROFILE AND TESTS	IS A BISPHOSPHONATE HOLIDAY APPROPRIATE?
Low (< 10% 10-y risk)	• No important clinical risk factors for fracture	• Yes • At low future fracture risk, should be withdrawn from therapy • Monitor at extended intervals (3-5 y)
Moderate (10%-20% 10-y risk)	• Assess clinical risk factors for fracture • Assess femoral neck BMD • Request lateral spine x-ray scan to investigate for any subclinical vertebral fractures	• Maybe • If vertebral fractures are found, stratify patient as high risk and continue bisphosphonate therapy • If there is no previous history of fragility fracture, a drug holiday can be considered if femoral neck BMD T-score is > -2.5 and there are no other important clinical risk factors

Brown et al Can Fam Phys 2014;60:324-333

Keypoint

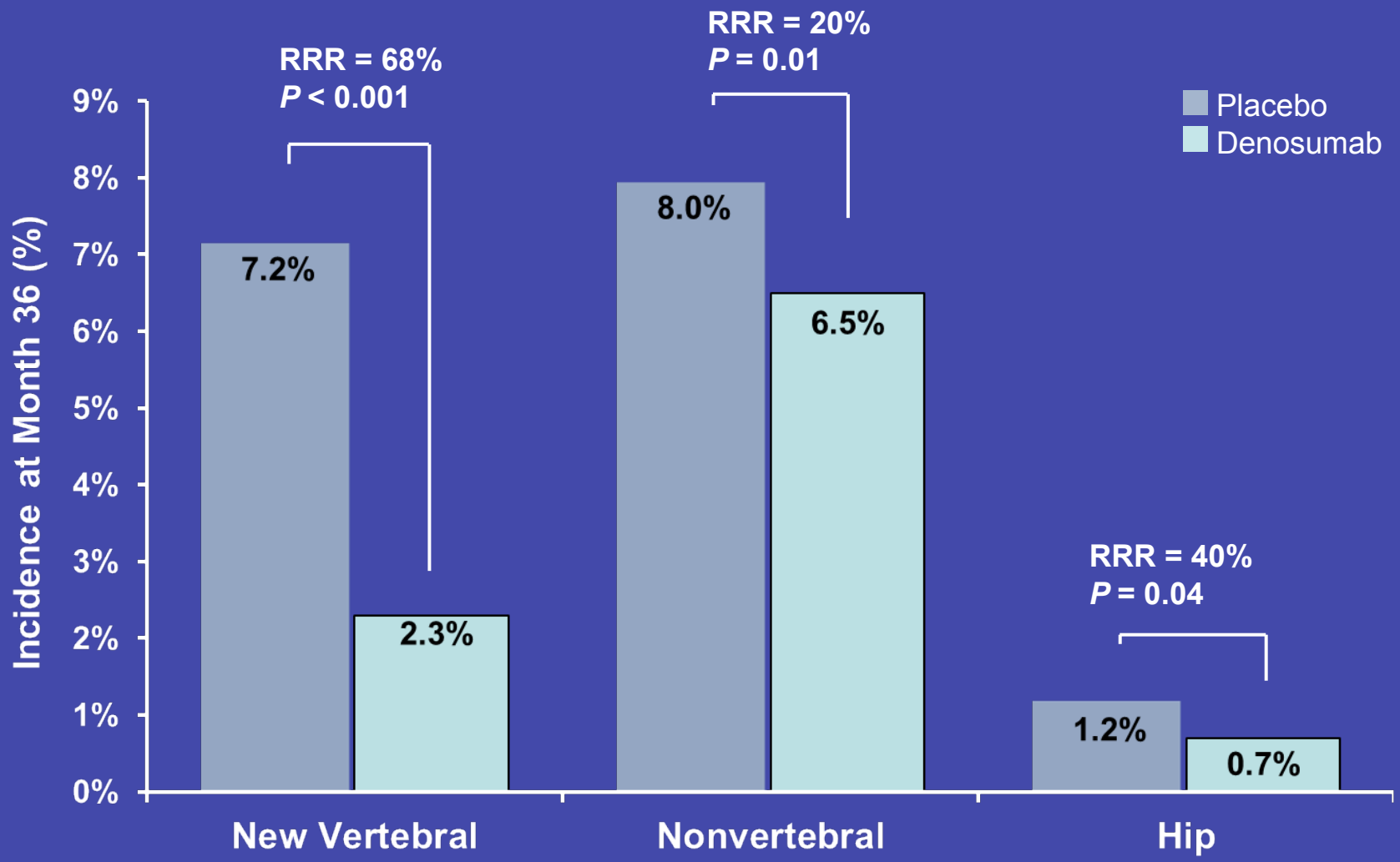
- High risk individuals should not be given a drug holiday
- Low risk individuals or those should probably be given a drug holiday

Long-term Effects of Prolia

Long-term effects of Prolia

- 70 yr old women with osteoporosis and prior vertebral fractures
- Treated ALN for 3 yrs, switched to Prolia 3 years ago due to further fractures
- Excellent response to Prolia with ↑ in BMD
- She has heard about side effects, wants to know about the long-term effects of Prolia
- What go you tell her?

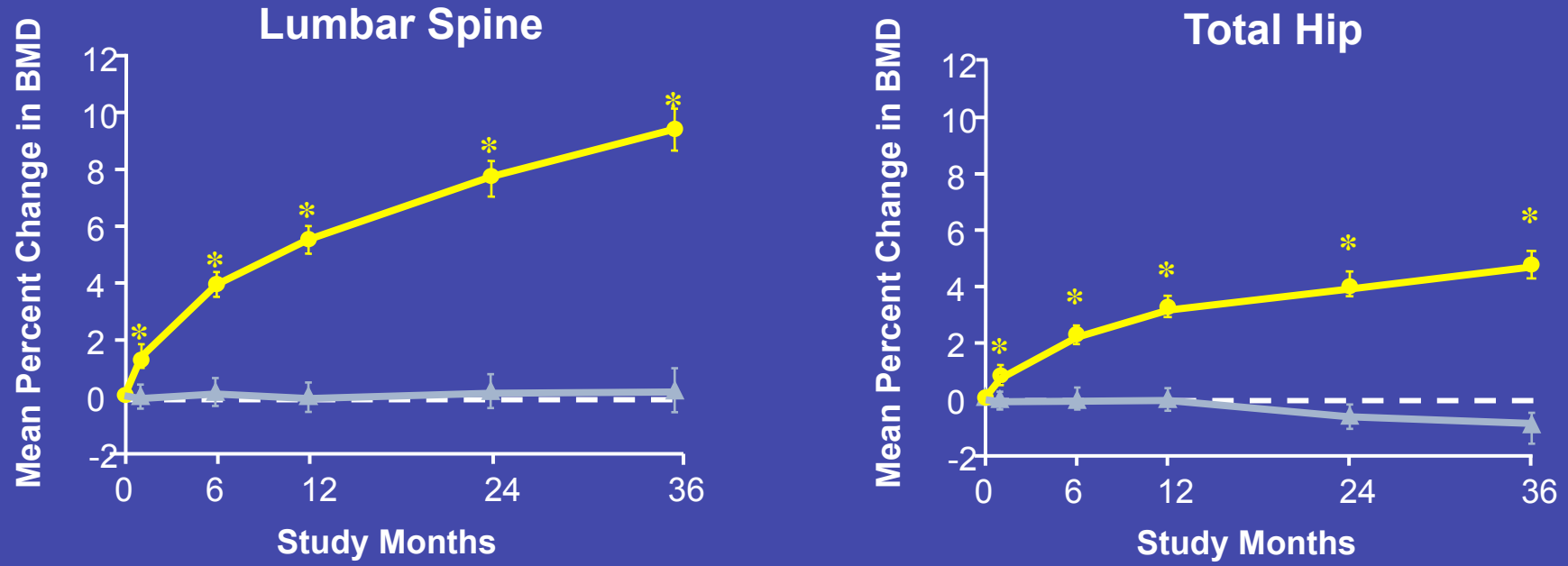
The Effect of Denosumab on Fracture Risks at 36 Months



Cummings SR, et al. *N Engl J Med*. 2009;361:756-765

The Percent Change in Bone Mineral Density Over 36 Months With Denosumab

Bone Mineral Density Substudy n = 441

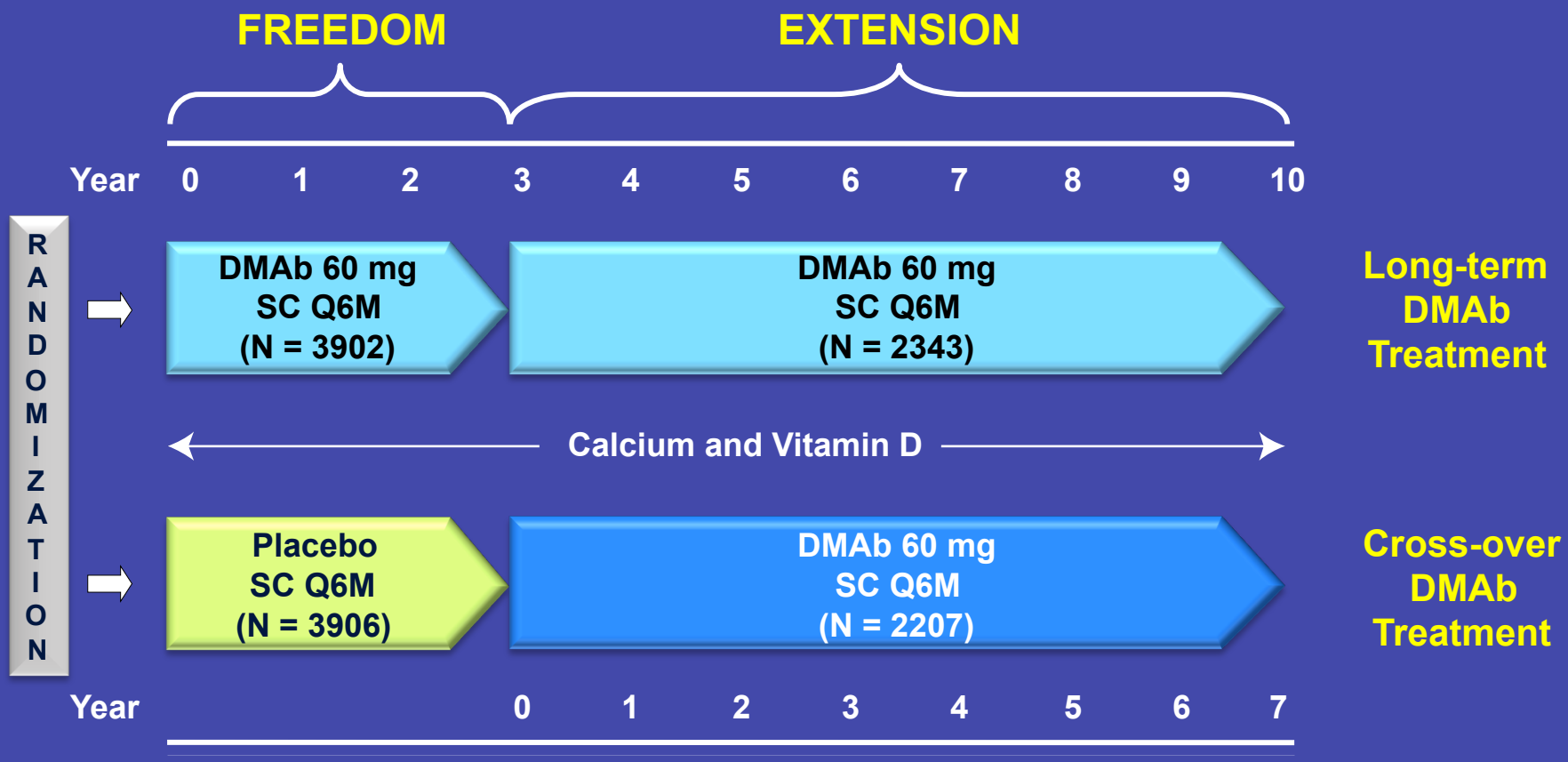


Intent-to-treat, last observation carried forward analysis
***P* < 0.001 for denosumab vs.. Placebo**

Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.

FREEDOM Extension Study Design

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

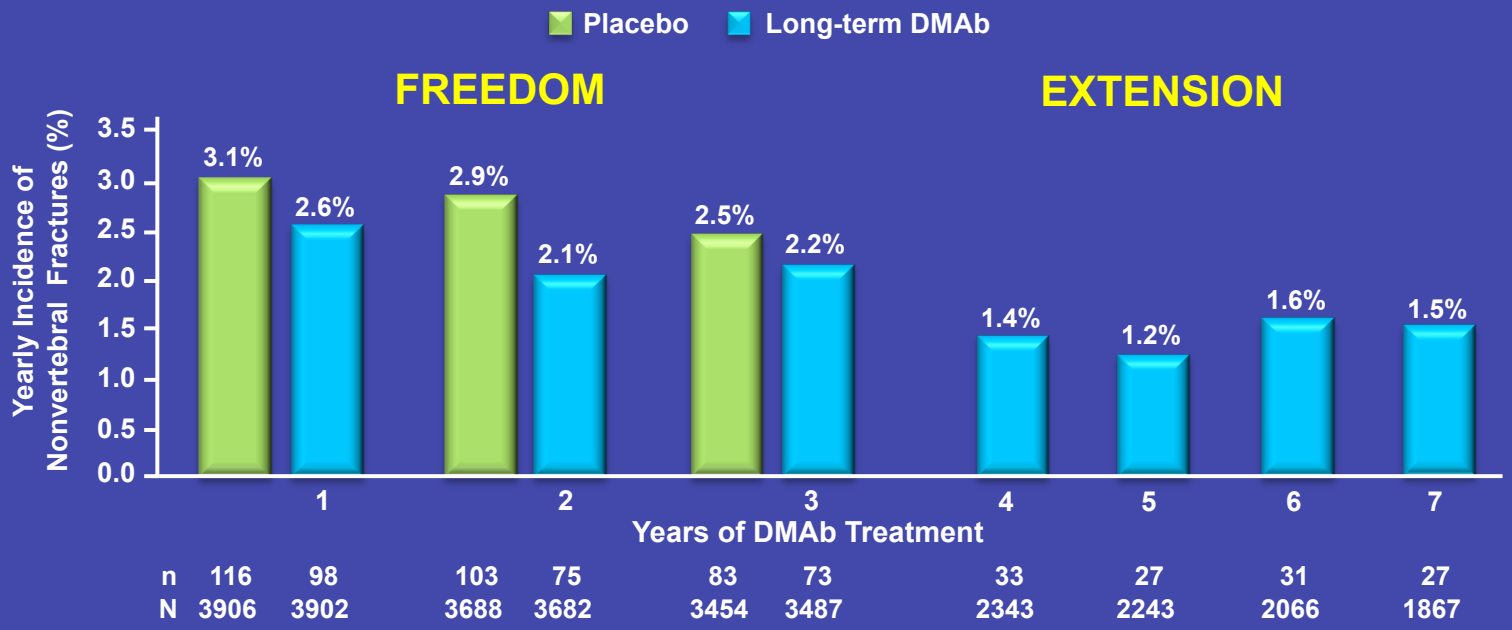


Key Inclusion Criteria for the Extension:

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

Continued DMAb Treatment in the FREEDOM Extension for Up to 7 Years

- Maintained reduction in bone turnover
- Was associated with a low incidence of nonvertebral and clinical vertebral fractures
- Remained well tolerated



n = number of subjects with ≥ 1 fracture. N = number of randomized subjects who remained on study at the beginning of each period.
Percentages for nonvertebral fractures are Kaplan-Meier estimates.

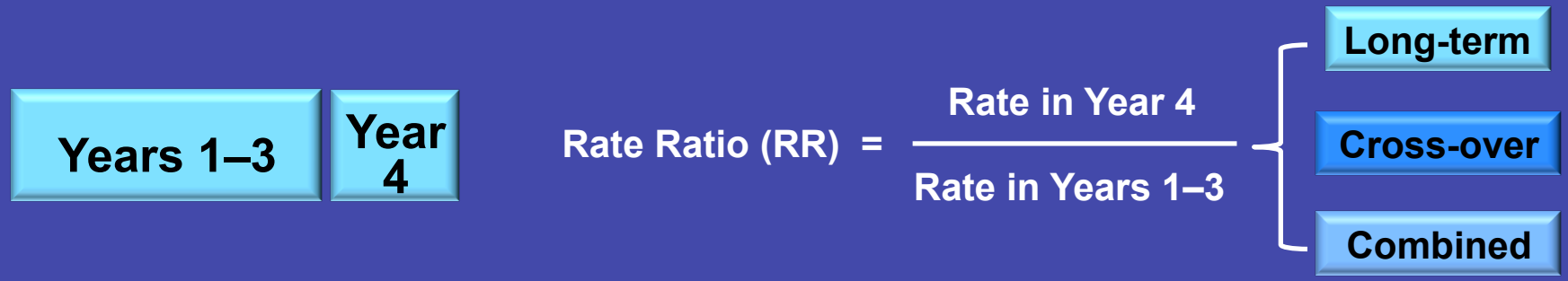
Lippuner K et al. *Osteoporos Int.* 2013;24(suppl 1):S39-40.

Objective

- To evaluate if continued DMAb treatment in year 4 and beyond is associated with a further reduction in nonvertebral fracture incidence compared with the first 3 years of treatment.

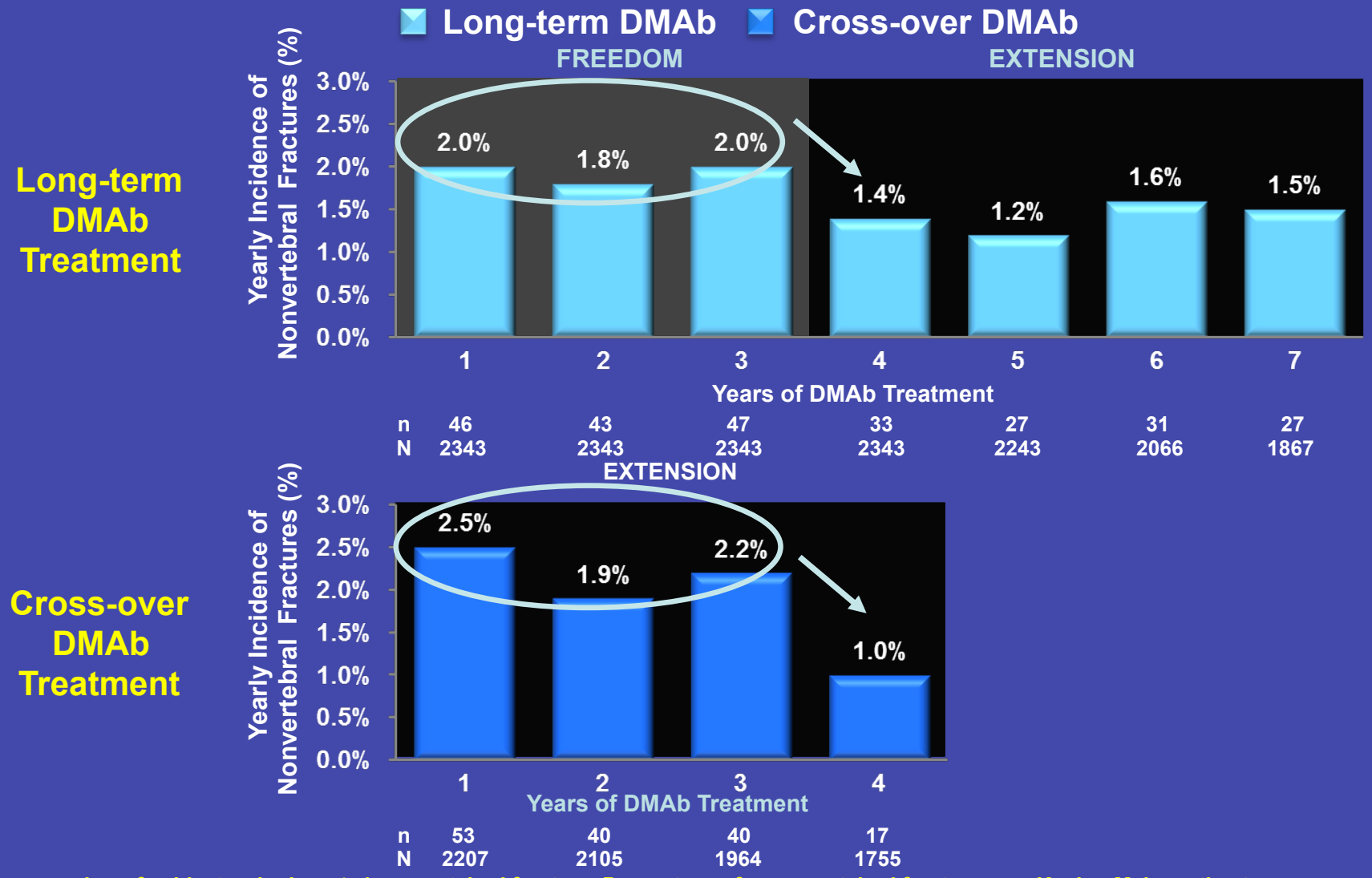
Methods

Nonvertebral fracture rates and rate ratios were calculated in subjects who enrolled into the FREEDOM extension



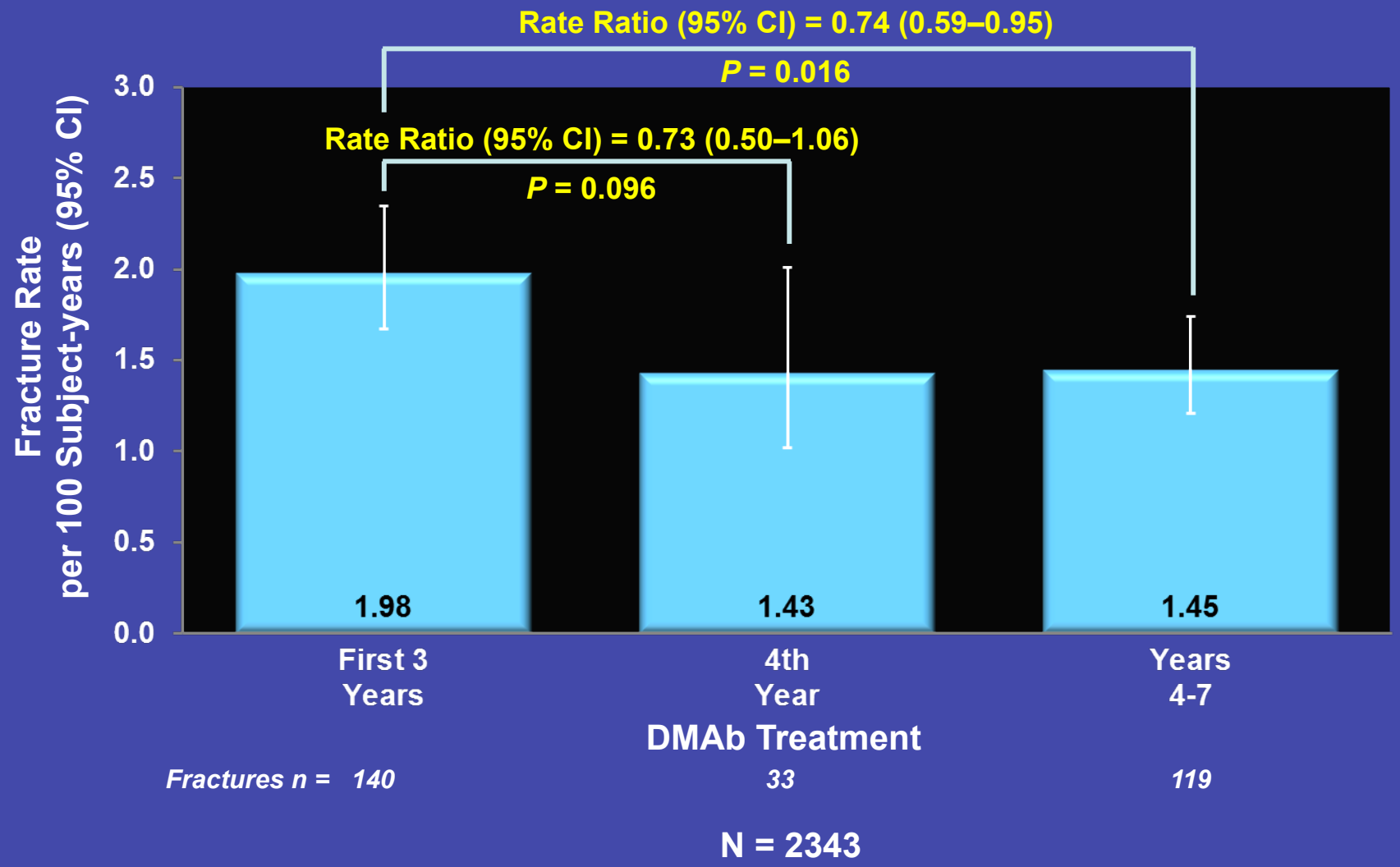
Rates per 100 subject-years and rate ratios using GEE Poisson regression were adjusted for age, total hip BMD T-score, weight, and history of nonvertebral fracture at the beginning of DMAb treatment. Treatment group was included in the model for the combined (long-term + cross-over groups) analysis only.

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



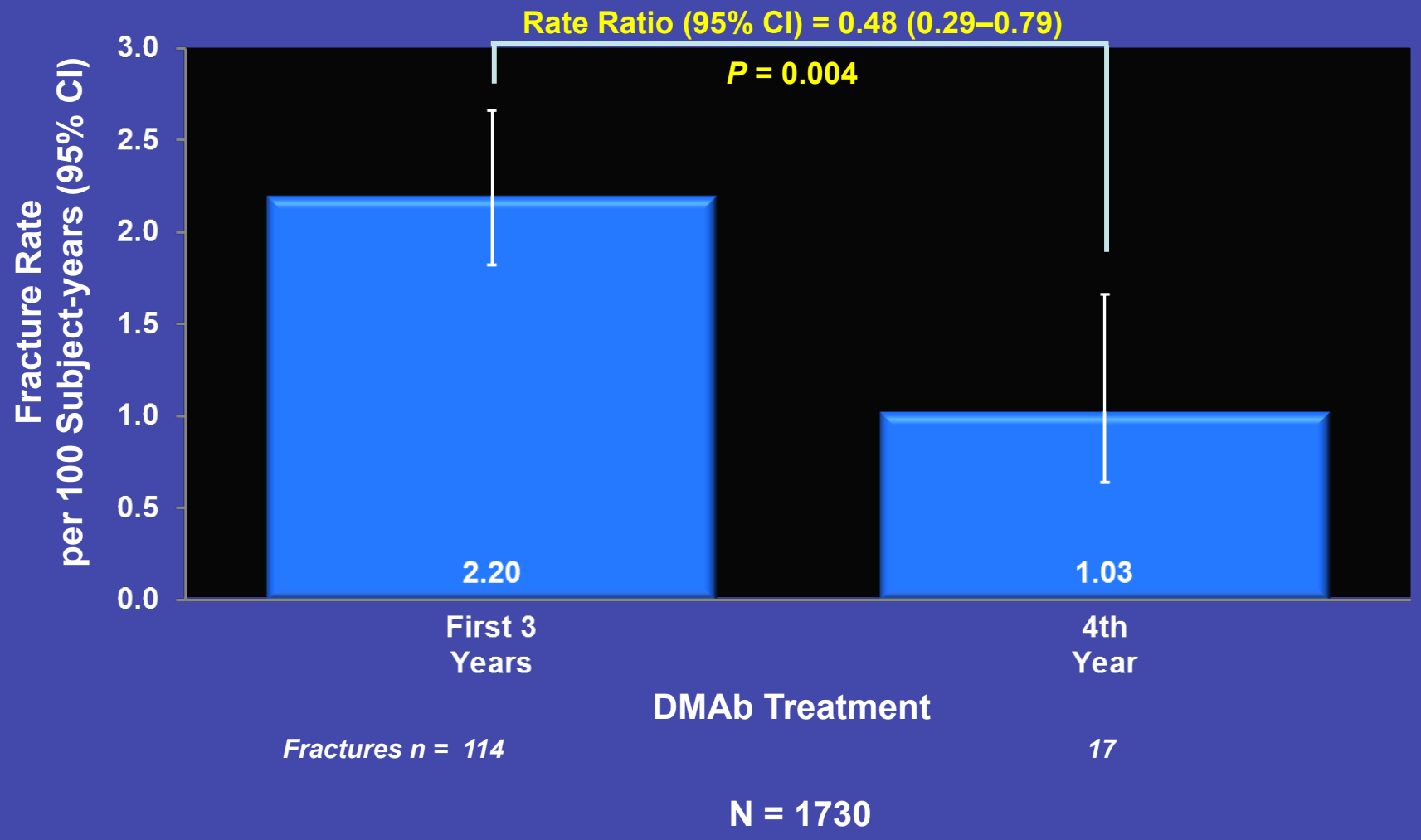
n = number of subjects who have ≥ 1 nonvertebral fracture. Percentages for nonvertebral fractures are Kaplan-Meier estimates.

Nonvertebral Fracture Rate Ratios: Long-term DMAb Subjects



N = number of subjects who did not miss >1 dose of DMAb during FREEDOM and enrolled into the extension.

Nonvertebral Fracture Rate Ratios: Cross-over DMAb Subjects



N = number of subjects who did not miss >1 dose of DMAb during the first 3 years in the extension.

Summary

- When DMAb was continued beyond 3 years of therapy, the nonvertebral fracture rate during year 4 was significantly further decreased compared with the first 3 years of treatment.
- When DMAb was continued for up to 7 years, the nonvertebral fracture rate remained significantly decreased compared with the first 3 years of treatment.

What is the safety data available for patients on 6 years of denosumab therapy? Exposure-adjusted Subject Incidence of AEs

	FREEDOM Study		EXTENSION
	Placebo Years 1-3 N = 3883	Prolia® (denosumab) Years 1-3 N = 3879	Denosumab Years 4-6 N = 2343
	Rates per 100 Subject-years (n)		
All AEs	156.1 (3614)	154.3 (3598)	106.2 (2067)
Infections	30.7 (2113)	29.3 (2052)	23.4 (1070)
Malignancies	1.6 (167)	1.8 (187)	1.9 (120)
Eczema	0.6 (67)	1.1 (119)	1.0 (65)
Hypocalcemia	< 0.1 (3)	0.0	< 0.1 (1)
Serious AEs	10.4 (974)	10.6 (1002)	10.6 (597)
Infections	1.3 (134)	1.5 (160)	1.3 (82)
Cellulitis or erysipelas	< 0.1 (1)	0.1 (12)	< 0.1 (5)

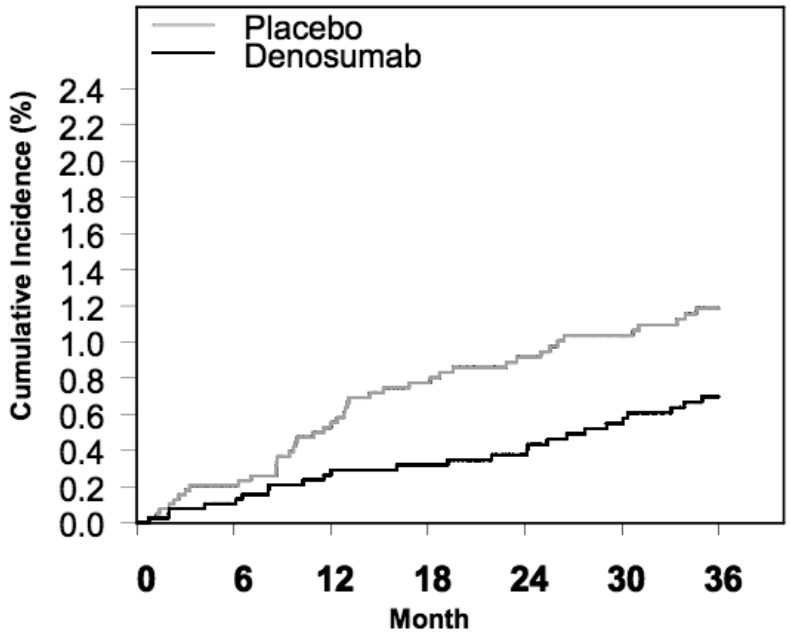
Osteonecrosis of the jaw (ONJ) and atypical femoral fracture have been reported.[1,2]

N = number of subjects who received ≥ 1 dose of investigational product. Treatment groups are based on the original randomized treatments received in the Pivotal Phase 3 Fracture Study. Rate = exposure-adjusted subject incidence per 100 subject-years. n = total number of subjects with an AE. AEs coded using MedDRA v13.0. AE = adverse events.

1. Adapted from Brown JP, et al. Presented at: ACR; November 5-9, 2011; Chicago, Ill.
2. Data on file, Amgen.

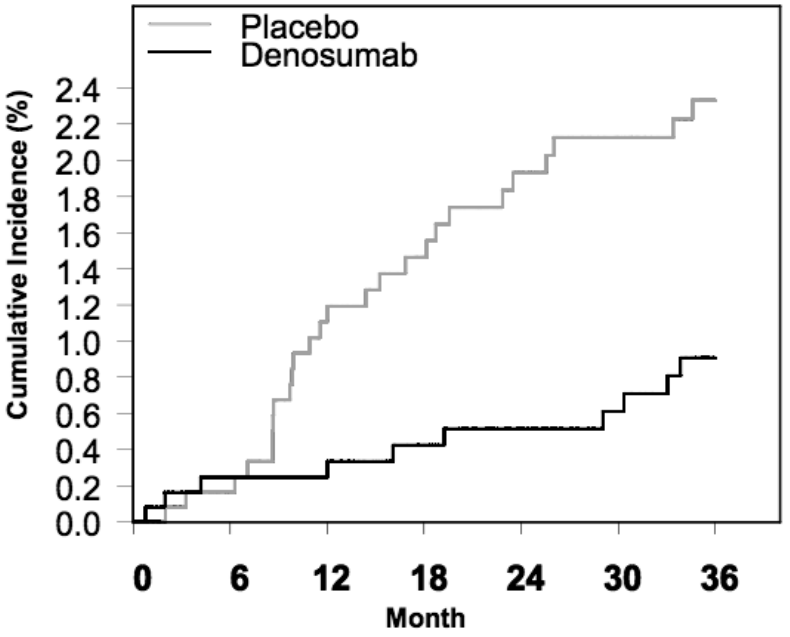
Hip Fracture

All FREEDOM study participants



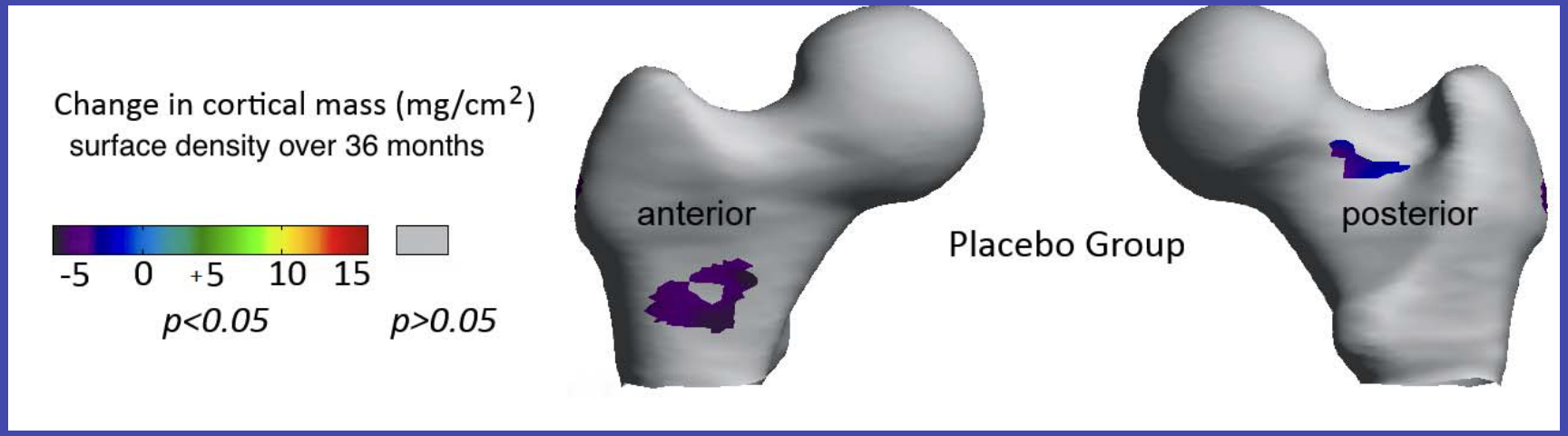
No. at Risk							
Placebo	3906	3799	3672	3538	3430	3311	3221
Denosumab	3902	3796	3676	3566	3477	3397	3311

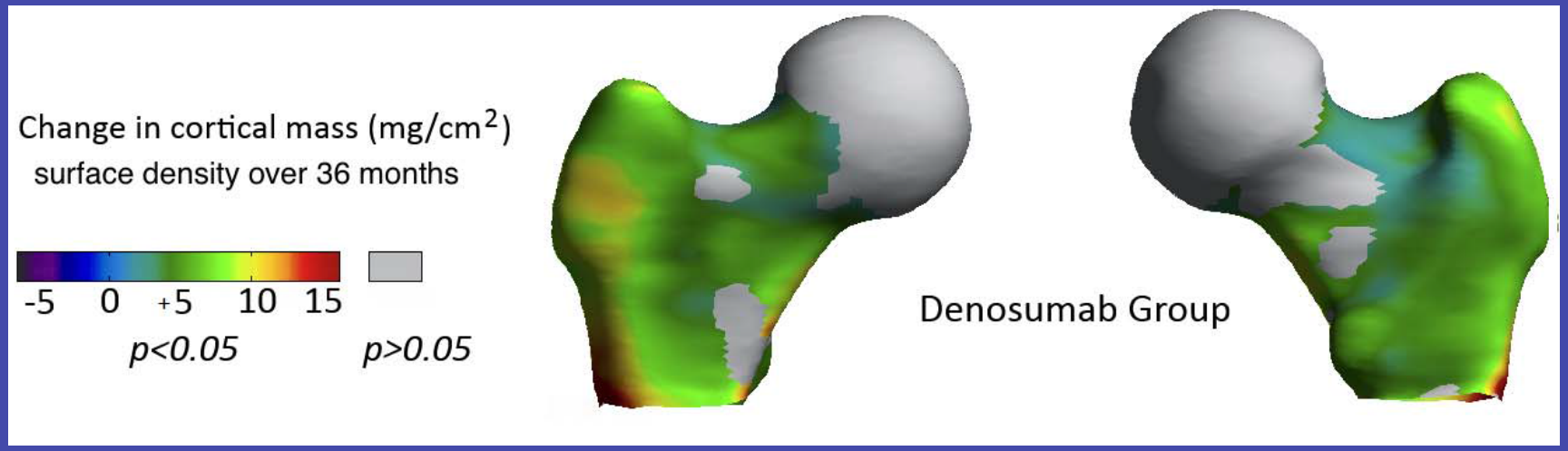
FREEDOM study participants aged 75 and older



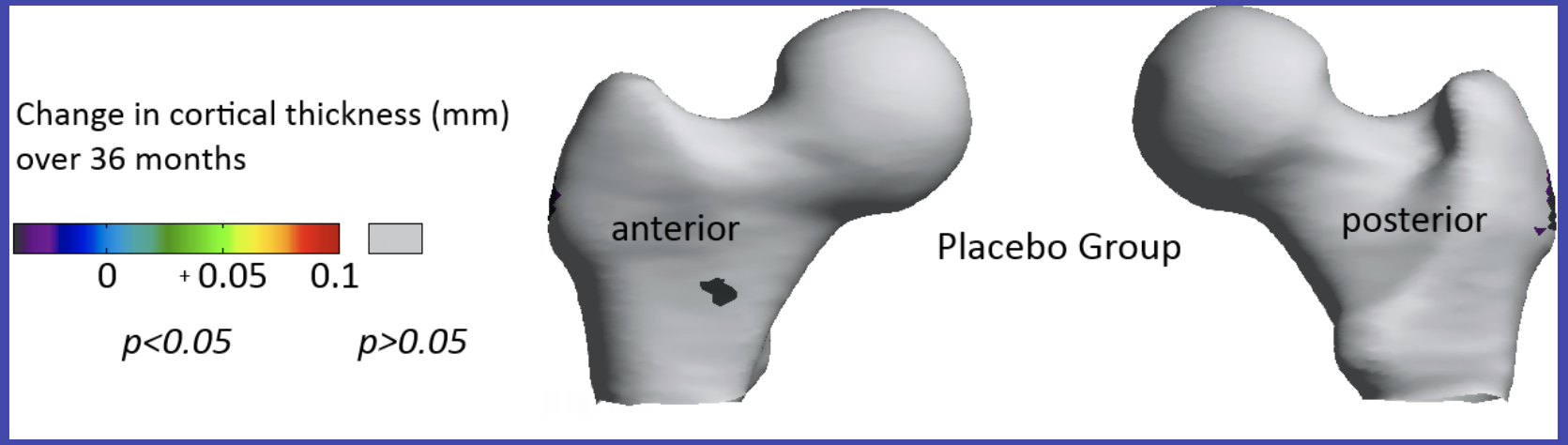
No. at Risk							
Placebo	1236	1196	1133	1082	1024	975	942
Denosumab	1235	1192	1147	1099	1054	1027	987

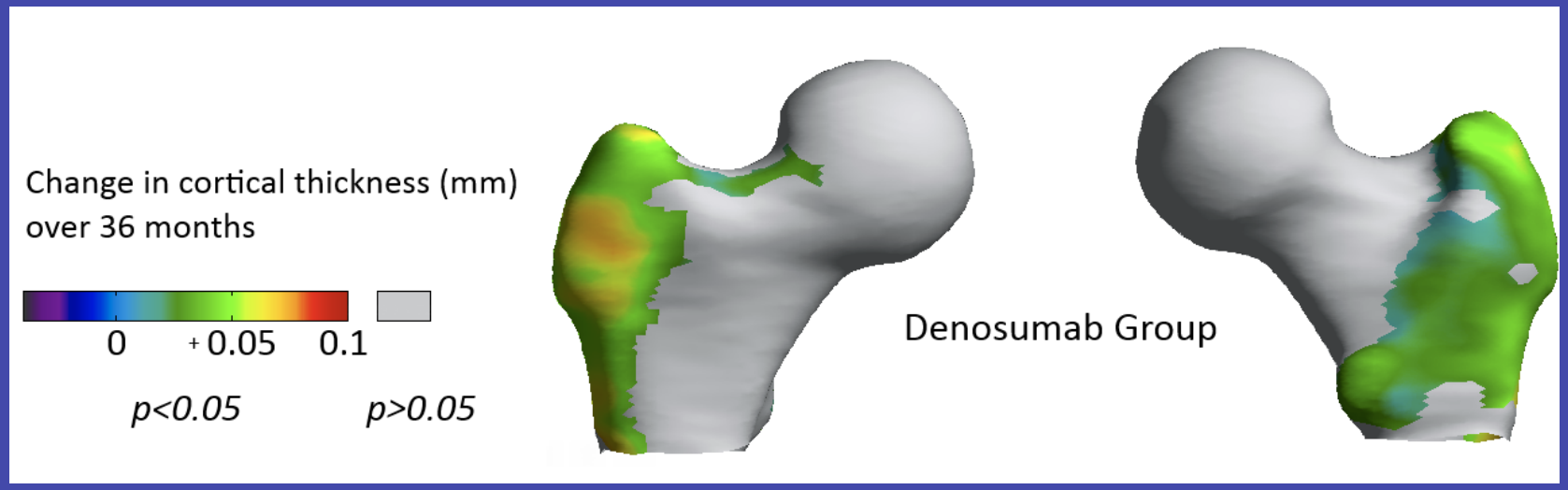
Change in Cortical Mass Surface Density (mg/cm2)





Change in Cortical Thickness (mm) over 36 months





Keypoint

- Ongoing therapy with denosumab results in ongoing treatment benefit.

What about combination therapy?

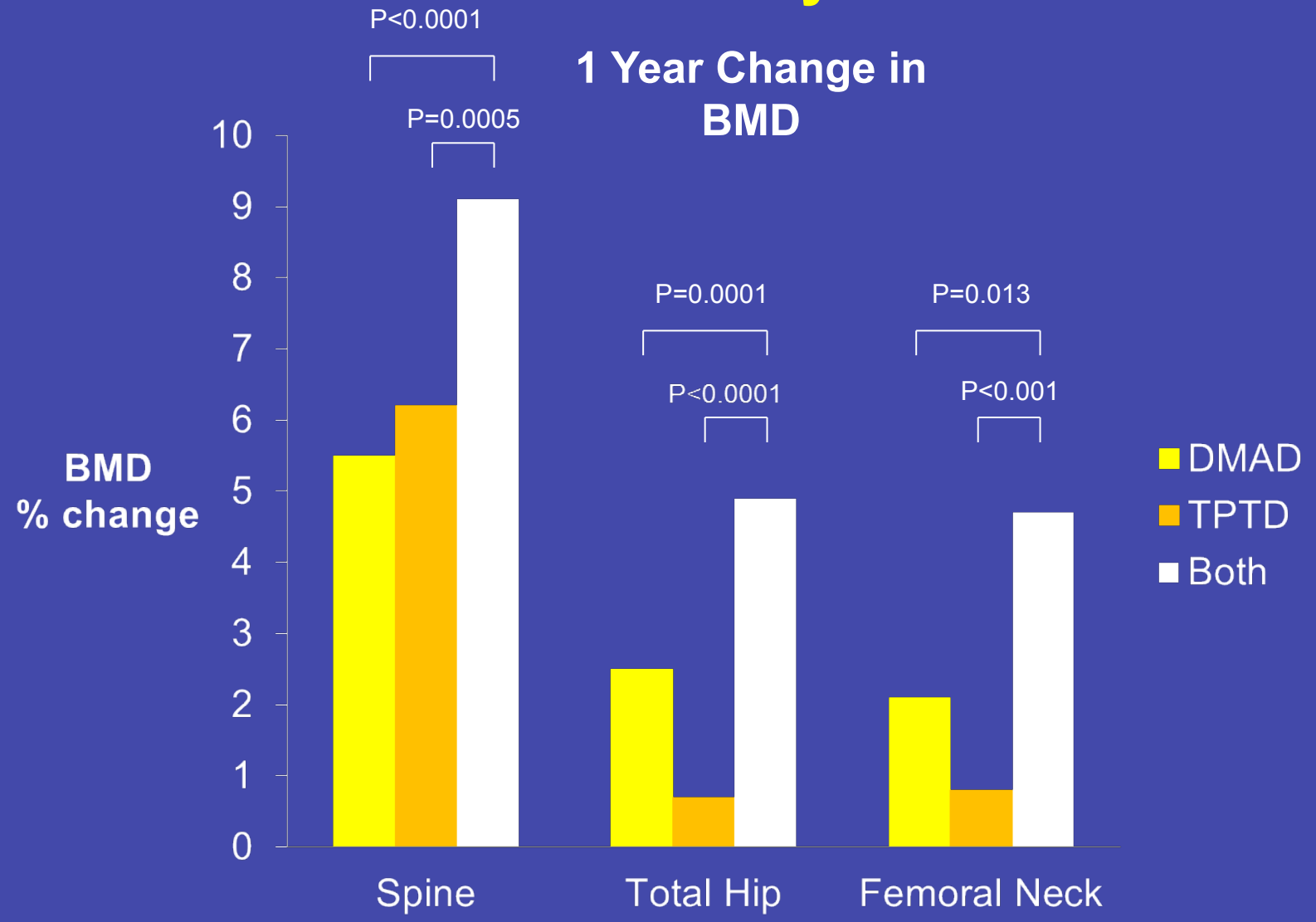
Combination Therapy

- 75 yr old female:
  - on ALN for 3 years
  - multiple vertebral fractures
  - FN-BMD <-4.0
  - presents with history of recent hip fracture
- Pt. has heard about combination therapy
- What do you recommend?

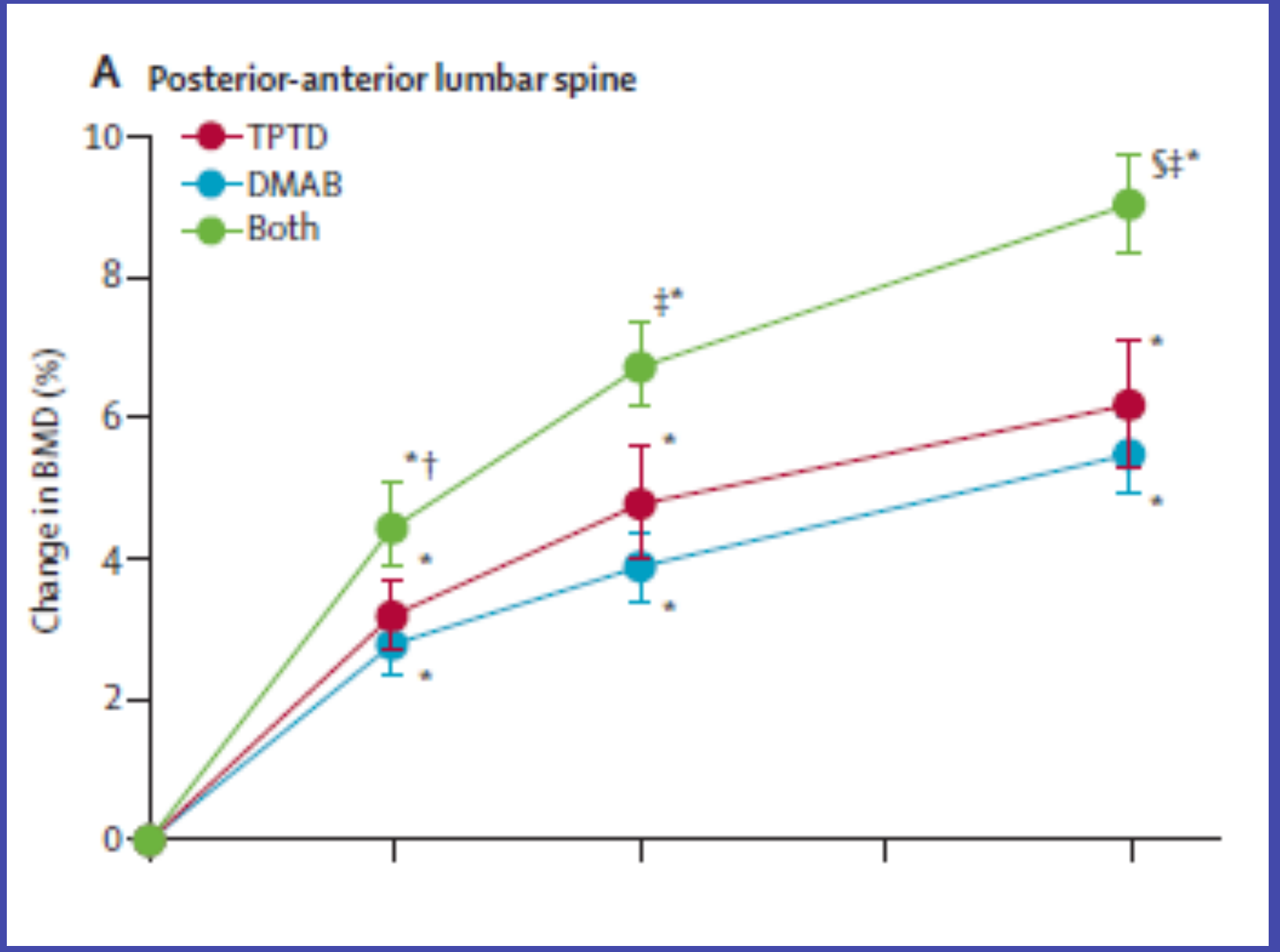
Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial

Joy N Tsai*, Alexander V Uihlein*, Hang Lee, Ruchit Kumbhani, Erica Siwila-Sackman, Elizabeth A McKay, Sherri-Ann M Burnett-Bowie, Robert M Neer, Benjamin Z Leder

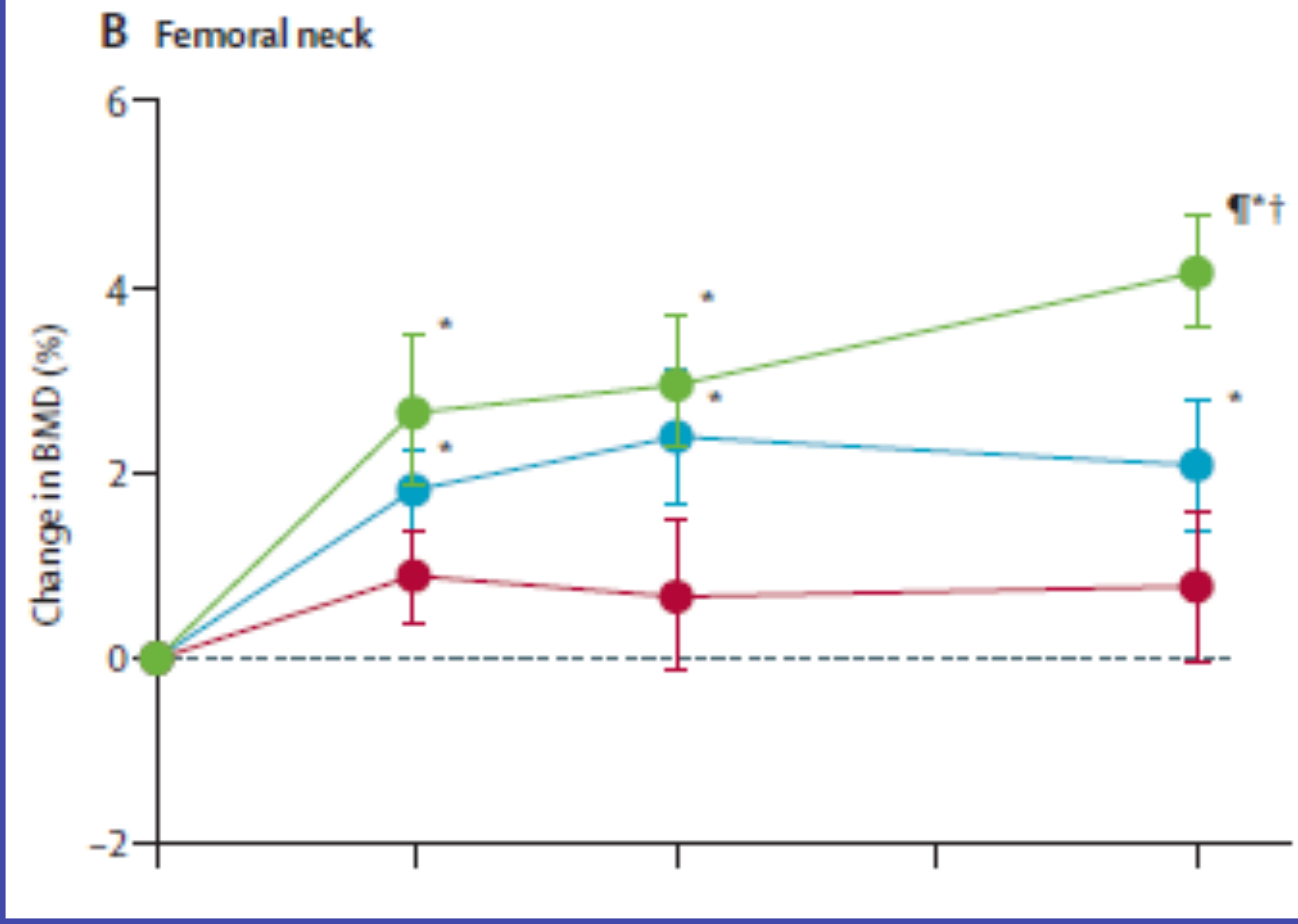
ASBMR 2012 Update
DATA Study



Tsai et al. Lancet 2013



Tsai et al. Lancet 2013



Tsai et al. Lancet 2013

Combined Dmab and TPTD in PMO: The DATA Study

- Unlike concomitant TPTD and BPs, TPTD and DMAB increased BMD at the hip and spine more than either drug alone.
- DMAB-TPTD co-administration may be an important treatment option in patients at high risk of fracture.

Tsai et al. Lancet 2013

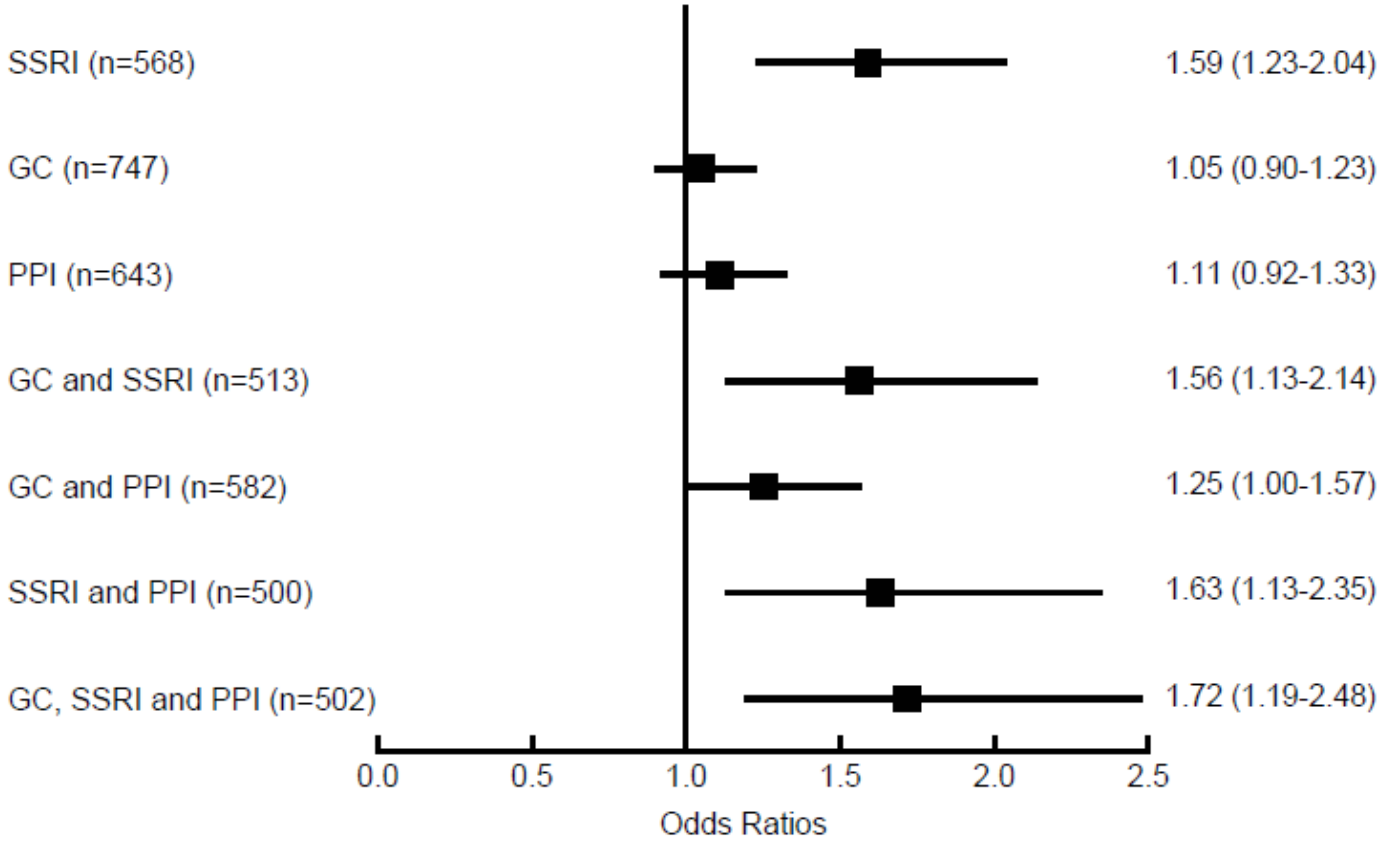
Introduction

- Selective serotonin receptor inhibitors (SSRIs), proton pump inhibitors (PPIs) and glucocorticoids (GCs) are associated with increased fracture risk
- The complications of GCs are well known, with more recent attention being paid to the commonly used medications, SSRIs and PPIs

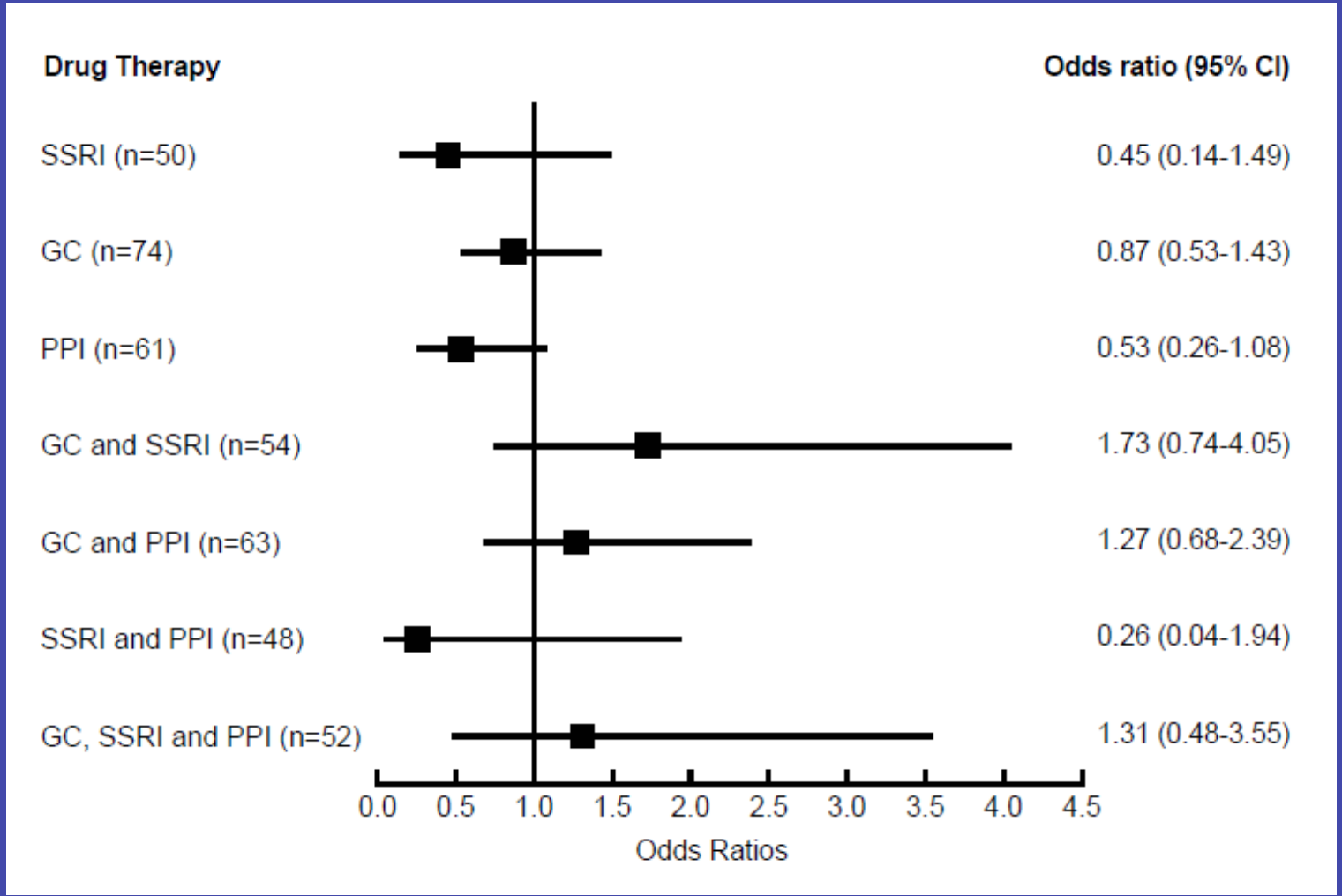
Which therapy or combination of therapies has the greatest risk for fracture?

a) SSRI
b) PPI
c) Glucocorticoids
d) SSRI and glucocortiocids
e) PPI and glucocorticoids

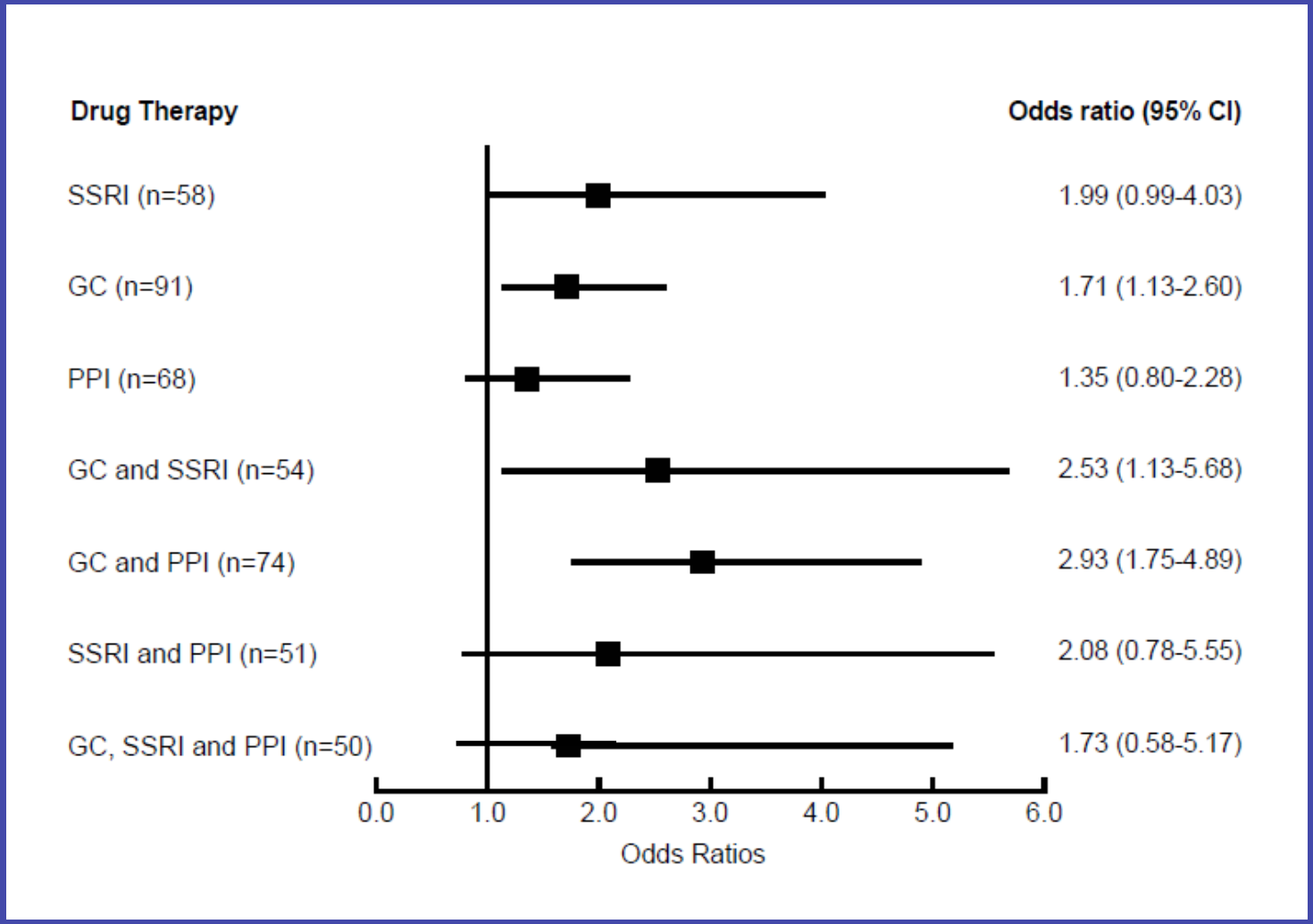
Adjusted Odds Ratios and 95% CIs for Any Fracture in Year 3 or 5, by Drug Therapy



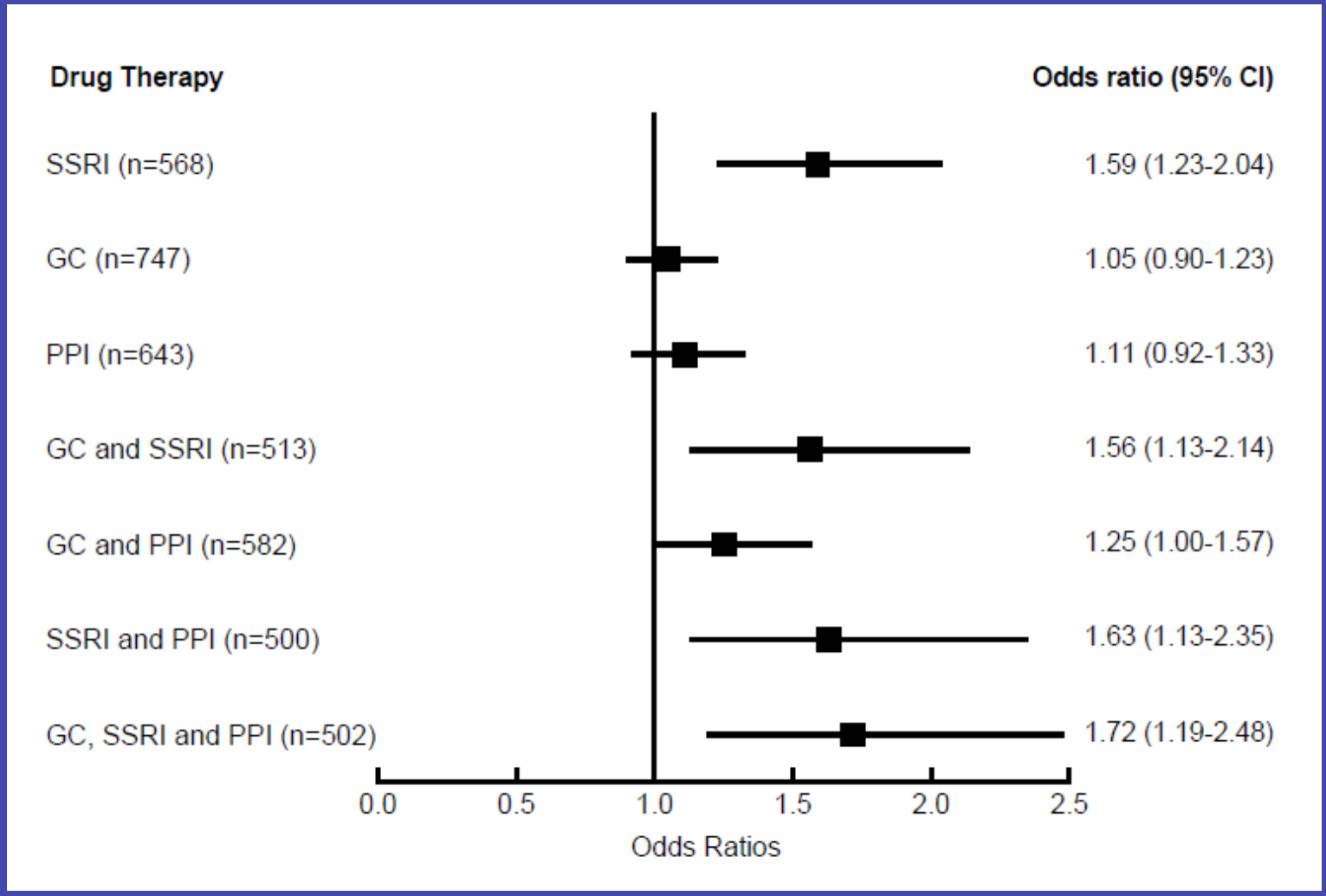
Adjusted Odds Ratios and 95% CIs for Hip Fracture in Year 3 or 5, by Drug Therapy



Adjusted Odds Ratios and 95% CIs for Spine Fracture in Year 3 or 5, by Drug Therapy



Adjusted Odds Ratios and 95% CIs for Non-Hip, Non-Spine Fracture in Year 3 or 5, by Drug Therapy



Results
Single medication use

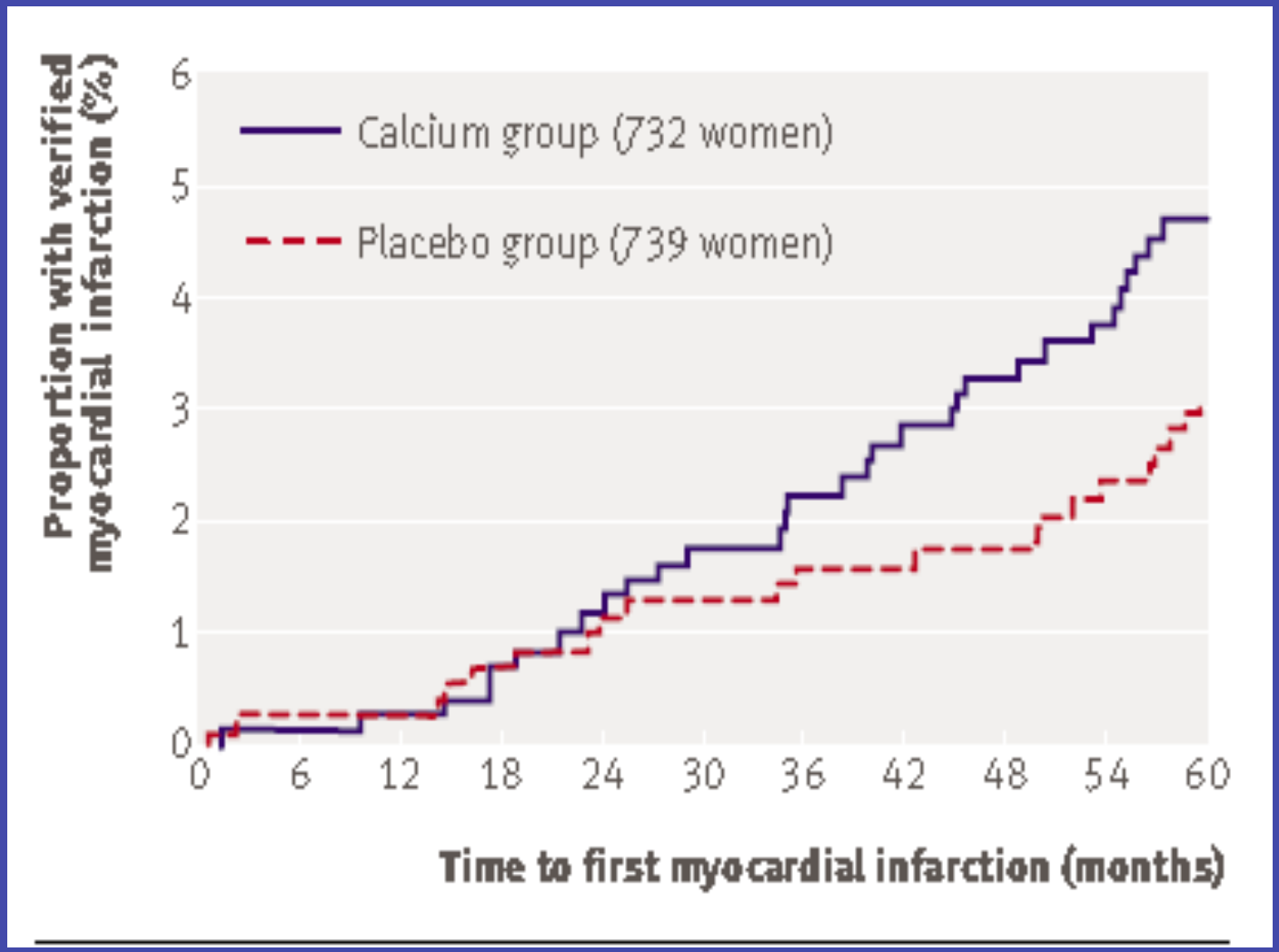
- SSRI use was the only therapy associated with a statistically significant increase in overall and non-hip, non-vertebral fractures and while not statistically significant with spine fractures
- GCs were significantly associated with spine fractures
- PPIs, were not statistically significantly associated with fractures

Results
Combination Medication Use

- Significant increases in spine fractures seen with:
  - SSRIs and GCs
  - GCs and PPIs
  - GCs, PPIs and SSRIs
- Significant non-hip, non-spine fractures seen with:
  - SSRI's and GCs
  - SSRIs and PPIs
  - PPIs and GCs
  - SSRIs, GCs and PPIs

The calcium controversy

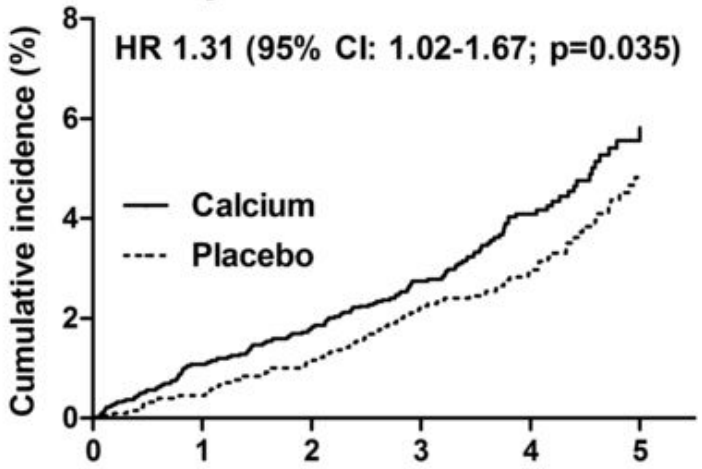
Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial



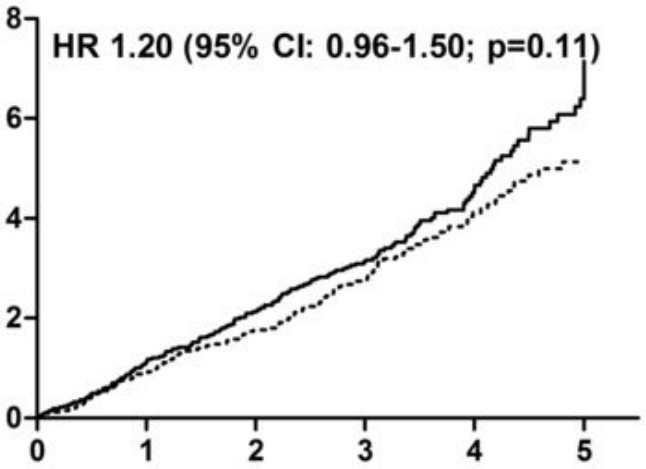
Subgroup analysis for the risk of cardiovascular disease with calcium supplements

Loretta T Radford, Mark J Bolland,
Greg D Gamble, Andrew Grey,
Ian R Reid

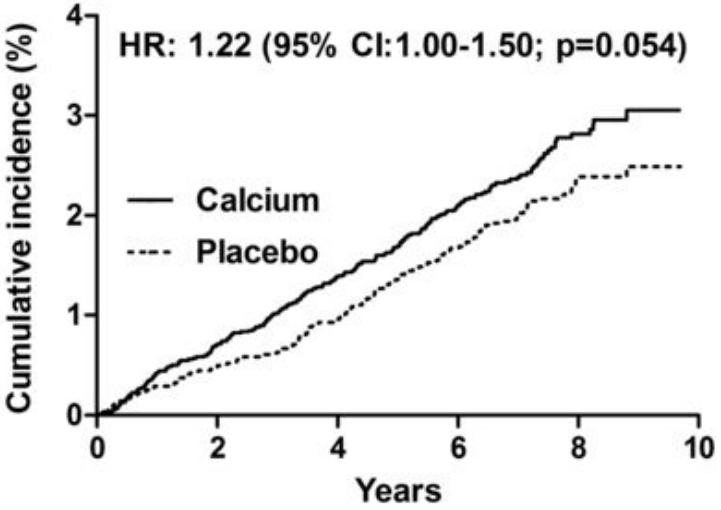
Calcium Meta-analysis
Myocardial Infarction



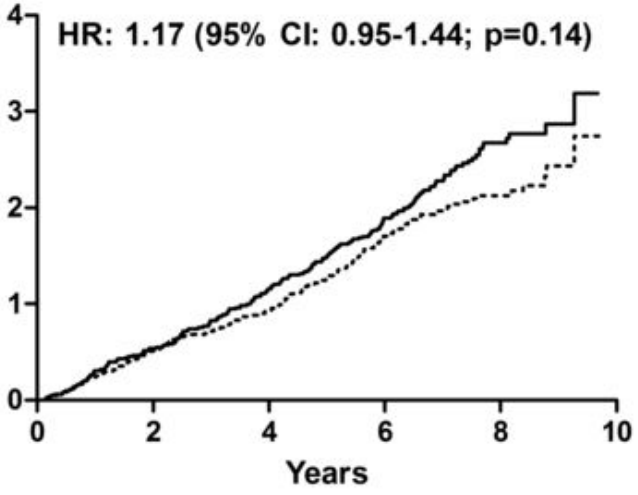
Calcium Meta-analysis
Stroke



WHI
Myocardial Infarction



WHI
Stroke



The Women's Health Initiative (WHI) Calcium plus Vitamin D Supplementation Trial: Health Outcomes 5 years after Trial Completion

Jane Cauley, University of Pittsburgh Graduate School of Public Health

WHI Calcium/Vit D Supp'n: 5 yrs after Trial

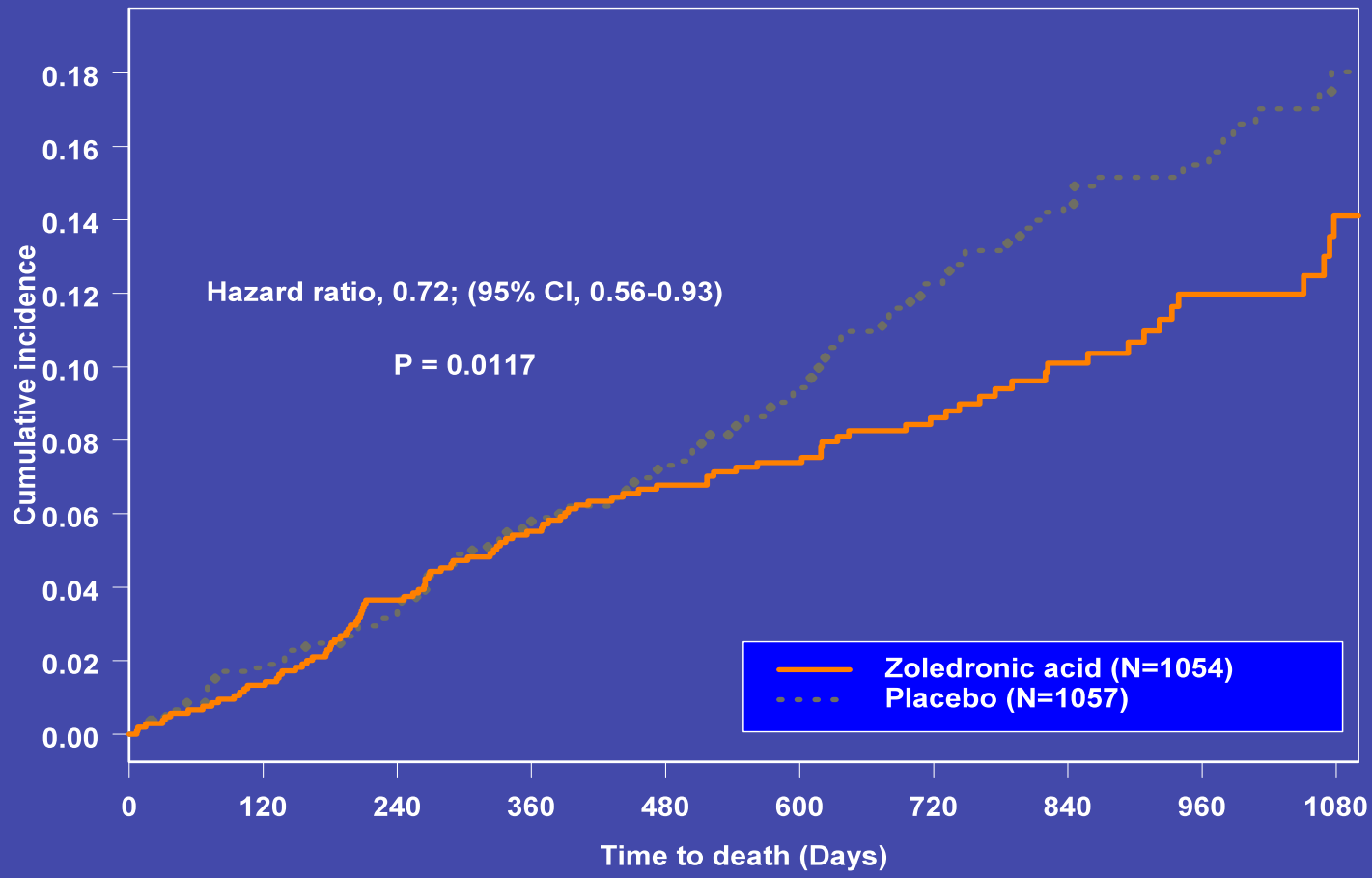
- No difference in CVD or disease mortality in the post-intervention period.
- Vertebral fractures 13% lower with CaD vs PBO, HR=0.87; 95% CI (0.76, 0.98).
- Among postmenopausal women followed for up to 12 yrs, CaD was associated with a decreased risk of vertebral fractures
  - Little effect on other skeletal and non-skeletal outcomes.

Keypoint

- Calcium supplementation may be of fracture benefit
- Calcium supplementation may be associated with CVS events
- Daily calcium requirements should be met through diet if possible
- For those at high risk for fracture, calcium alone is not enough
-

Does treatment reduce mortality?

Zoledronic Acid Reduced Risk of All-cause mortality by 28% Over Time



Lyles, K et al. N Engl J Med 2007;357:1799-809.

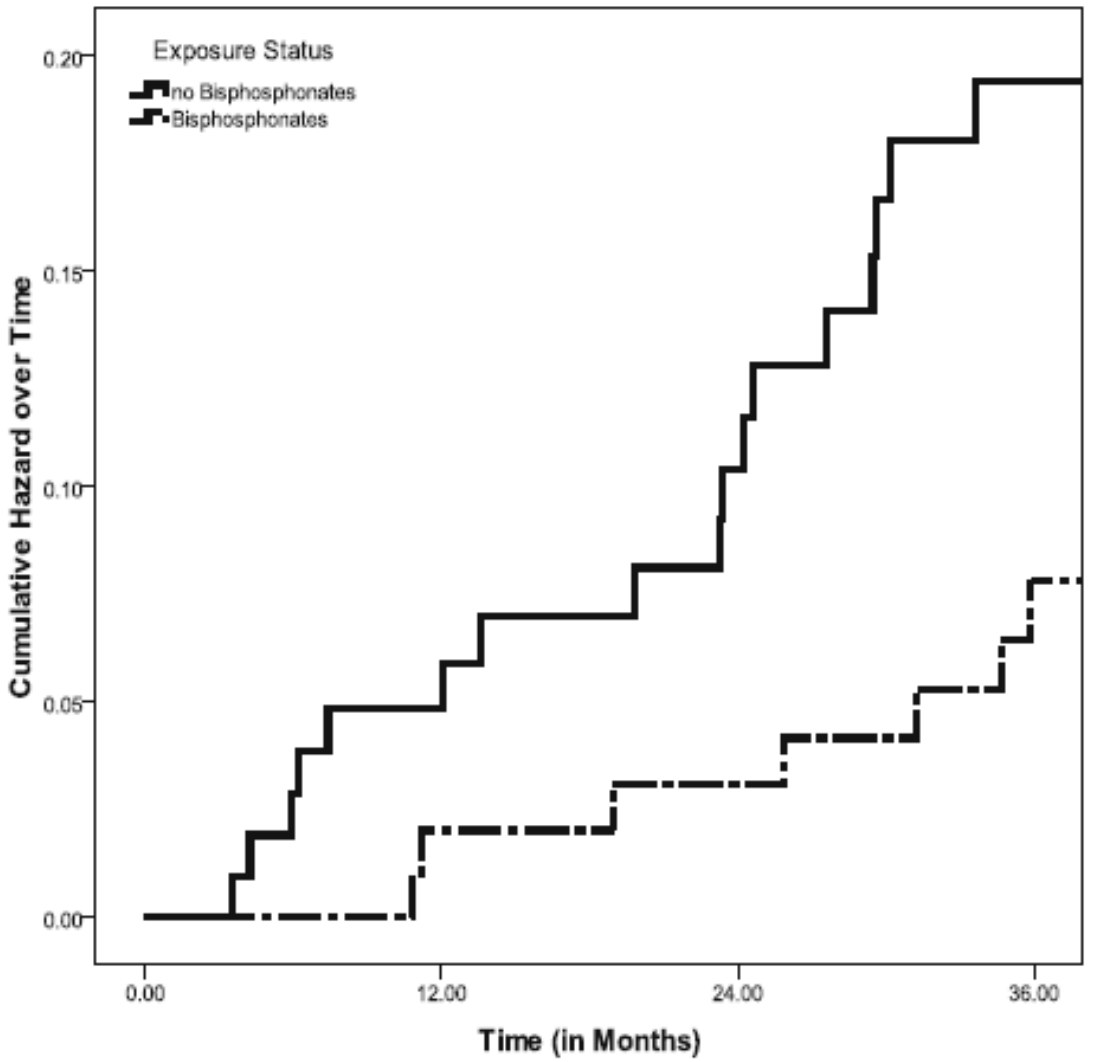
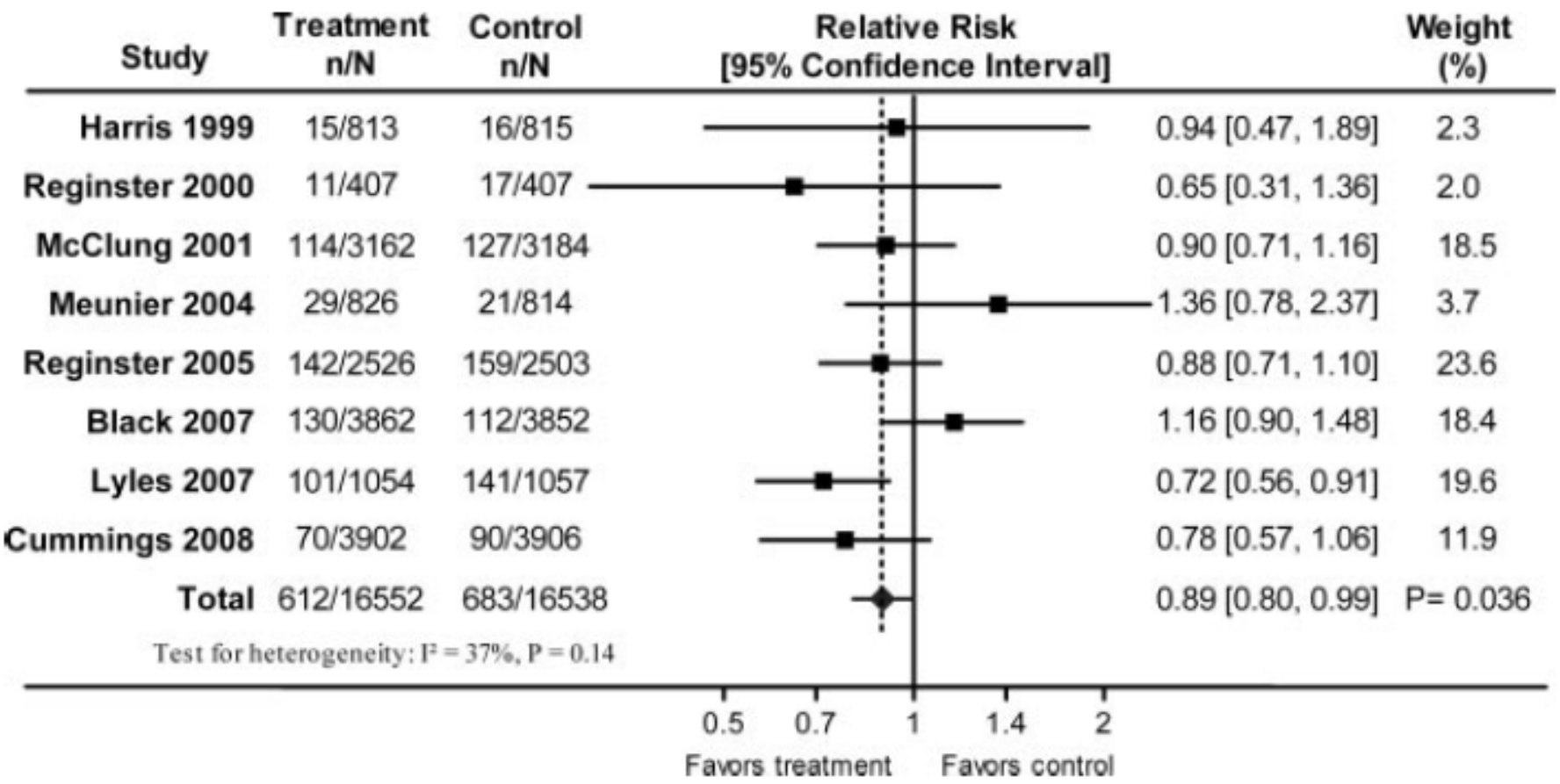
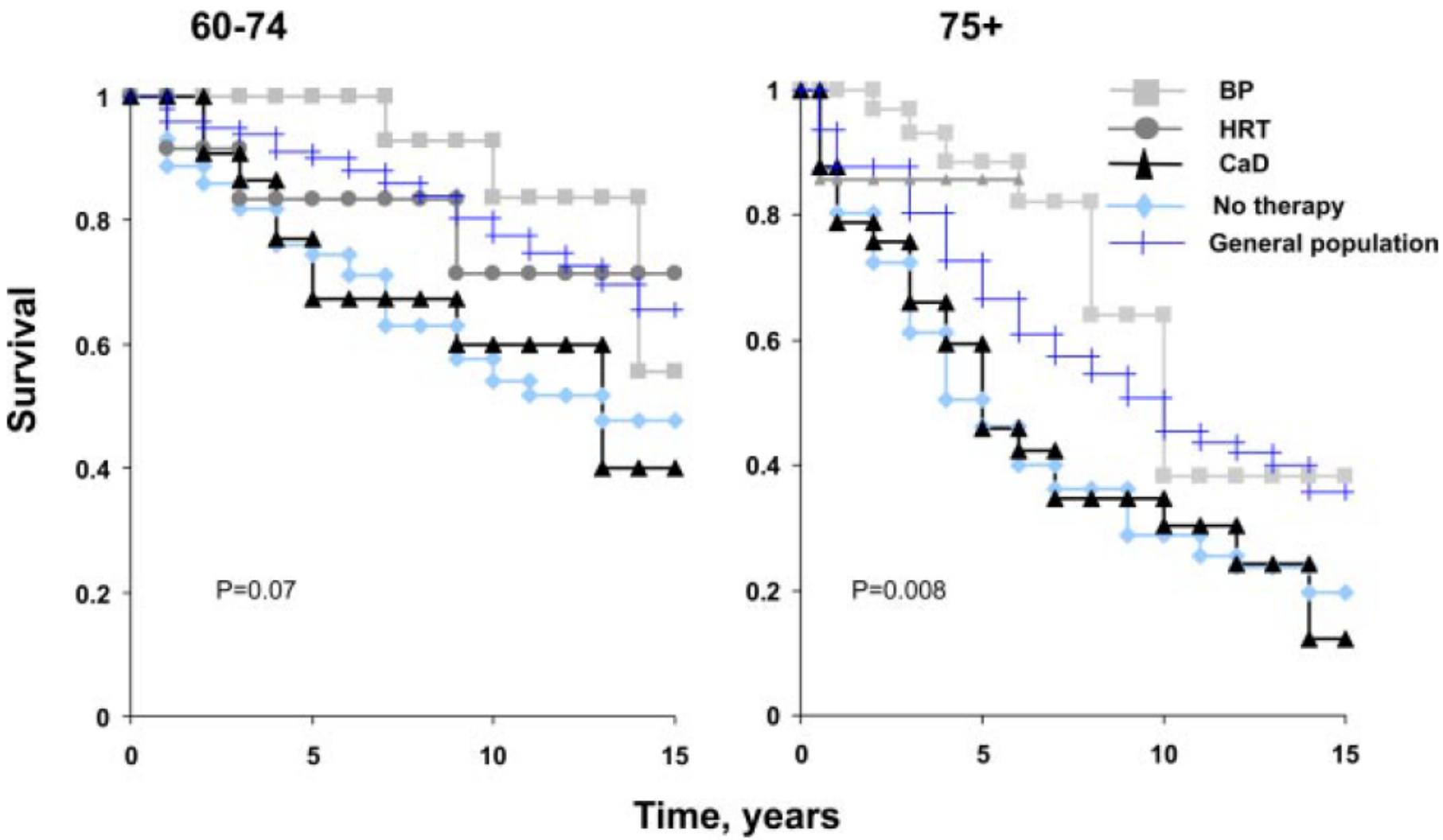


Fig. 2 Mortality for survivors of hip fracture according to bisphosphonate treatment (Kaplan–Meier analyses)

Beaupre et al. Osteoporos Int (2011) 22:983–991



Bolland J Clin Endocrinol Metab 95: 1174–1181, 2010



Centre (*J Clin Endocrinol Metab* 96: 0000– 0000, 2011)

Keypoint

- Treatment not only reduces fractures and fracture related morbidity, but it reduces mortality

Summary

- While there are controversies around treatment, there is no doubt that the benefits of therapy out weigh the risks, so treatment should be considered for all high risk individuals