

Update in Osteoporosis:

New Treatments and Controversies Surrounding the Bisphosphonates

Oregon Geriatric Society

October 12, 2008

Copies of slides available Monday at
http://www.orost.com/mm_pres.htm



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Disclosure and Conflicts of Interest

I receive research grants and consulting fees from the following companies:

Amgen

Merck

Roche

GSK

Novartis

sanofi-aventis

Lilly

Procter & Gamble

Takeda

Wyeth

I am a member of the Speaker's Bureau for these companies:

Lilly, Merck, Novartis, Procter&Gamble, sanofi-aventis



Michael McClung, MD

October 2008

Topics (Selected)

1. Calcium and vitamin D
2. Bisphosphonates
 - a. Effectiveness - in elderly patients
 - b. Are all bisphosphonates the same?
 - c. Safety vs Benefits of bisphosphonate therapy?
 - atrial fibrillation
 - over-suppression of bone turnover
 - ONJ and unusual fractures
 - d. How long to treat (drug holiday)?
3. New treatments



Calcium Intake

Belief:

Daily calcium intake of 1500 mg is required for bone health.

**Often interpreted as meaning that patients are given
1500 mg calcium supplement daily**



Calcium Intake

Belief:

Daily calcium intake of 1500 mg is required for bone health.

Some Facts:

1. Calcium intake not correlated with bone loss in elderly men and women. [Hannan *J Bone Miner Res* 2000;15:710-20]
2. In vitamin D-replete adults, no further suppression of PTH beyond calcium intakes of 800 mg/d [Steingrimsdottir *JAMA*. 2005;294:2336-41]
3. Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones. [Jackson *NEJM* 2006;354:669-83]



Calcium Intake

Belief:

Daily calcium intake of 1500 mg is required for bone health.

More facts:

- 4. Pooled results from prospective cohort studies suggest that calcium intake is not significantly associated with hip fracture risk in women or men.**
- 5. Pooled results from randomized controlled trials show no reduction in hip fracture risk with calcium supplementation, and an increased risk is possible. For any nonvertebral fractures, there was a neutral effect in the randomized trials. [Bischoff-Ferrari *Am J Clin Nutr* 2007;86:1570-80]**



Calcium Intake

Belief:

Daily calcium intake of 1500 mg is required for bone health.

Another fact:

- 6. Calcium supplementation in healthy postmenopausal women is associated with upward trends in cardiovascular event rates. This potentially detrimental effect should be balanced against the likely benefits of calcium on bone. The composite end point of myocardial infarction, stroke, or sudden death was also more common in the calcium group (101 events in 69 women v 54 events in 42 women, $P=0.008$) [Bolland *BMJ* 2008;336:262-6]**



Calcium Intake

Belief:

Daily calcium intake of 1500 mg is required for bone health.
Often interpreted as meaning that patients are given
1500 mg calcium supplement daily

Fact:

No benefit in total (diet + supplement) of more than 800-
1000 mg daily if patient is vitamin D replete

Almost no one needs to take a supplement of more than 600
mg calcium daily (one tablet) if vitamin D intake is adequate



Vitamin D

Belief:

Daily vitamin D intake of 400-600 IU is adequate for bone health.

This is the amount in once-daily multivitamin tablets



Vitamin D

Belief:

Daily vitamin D intake of 400-600 IU is adequate for bone health.

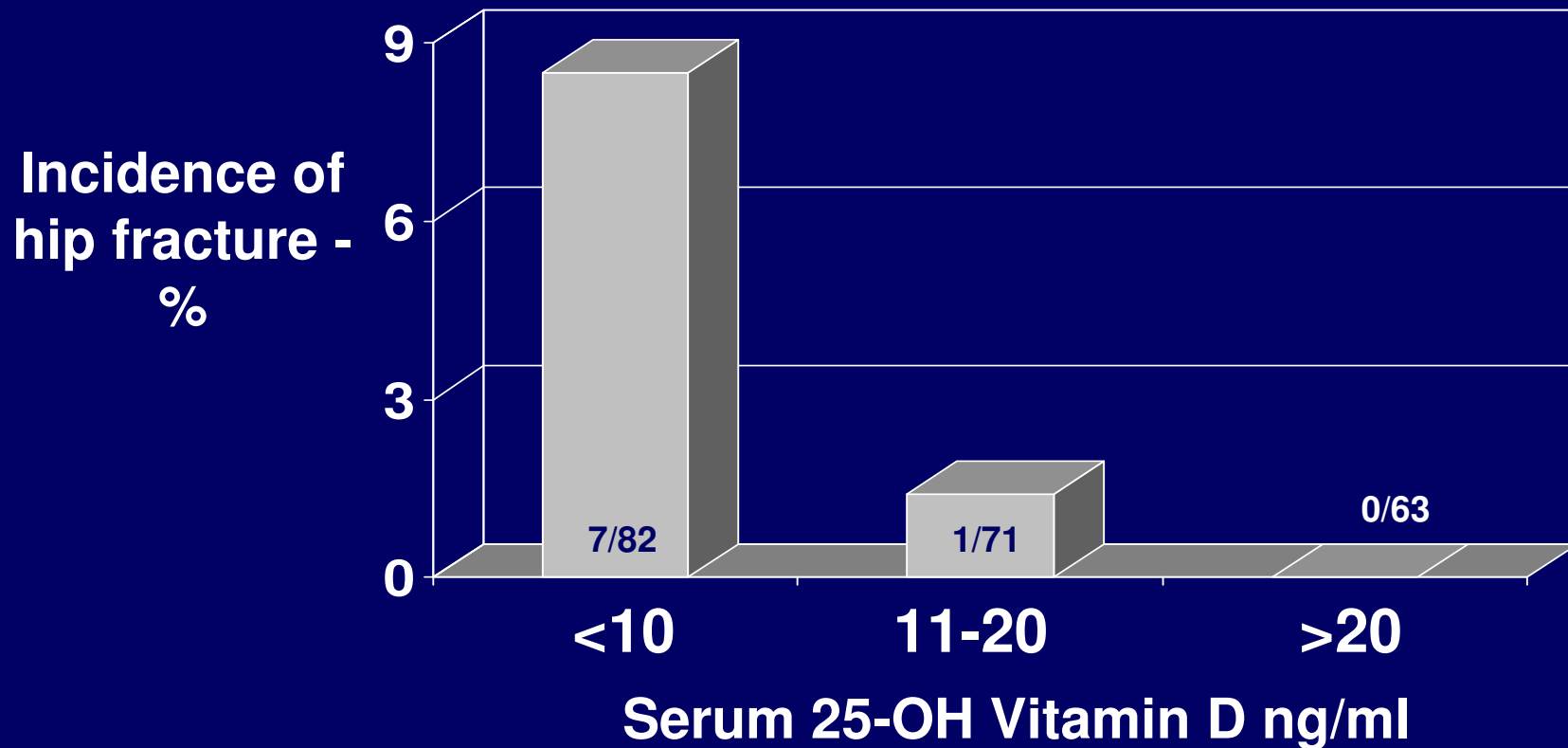
Some facts

1. Serum level of 25-OH vitamin D of at least 30 ng/ml now thought to be “optimal”
2. Daily intake of at least 2000 IU D3 daily required to achieve that serum level
3. Only studies using at least 800 IU D3 daily have shown reduction in fall and fracture risk.
4. In absence of hypercalcemia or granulomatous disease, intakes of several thousand units per day is safe



Vitamin D Status and Hip Fracture

- 216 patients 65 and older with previous stroke
- Followed for 2 years

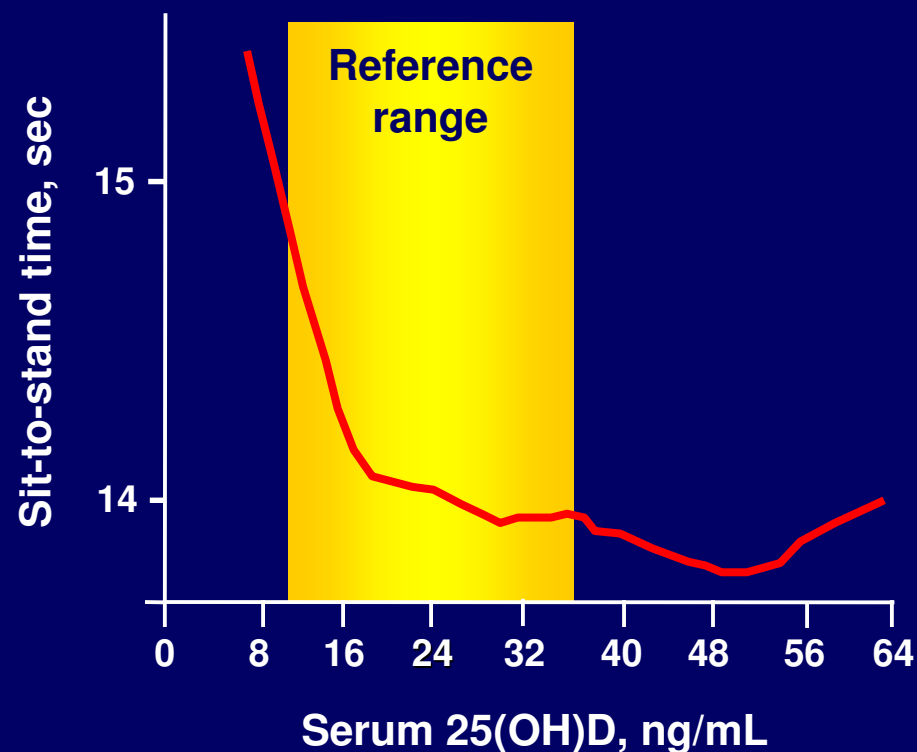


Higher 25(OH)D Levels Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥ 90 years
- Functional measurements used to assess lower extremity function:
 - 8-ft walking speed test
 - Timed sit-to-stand test

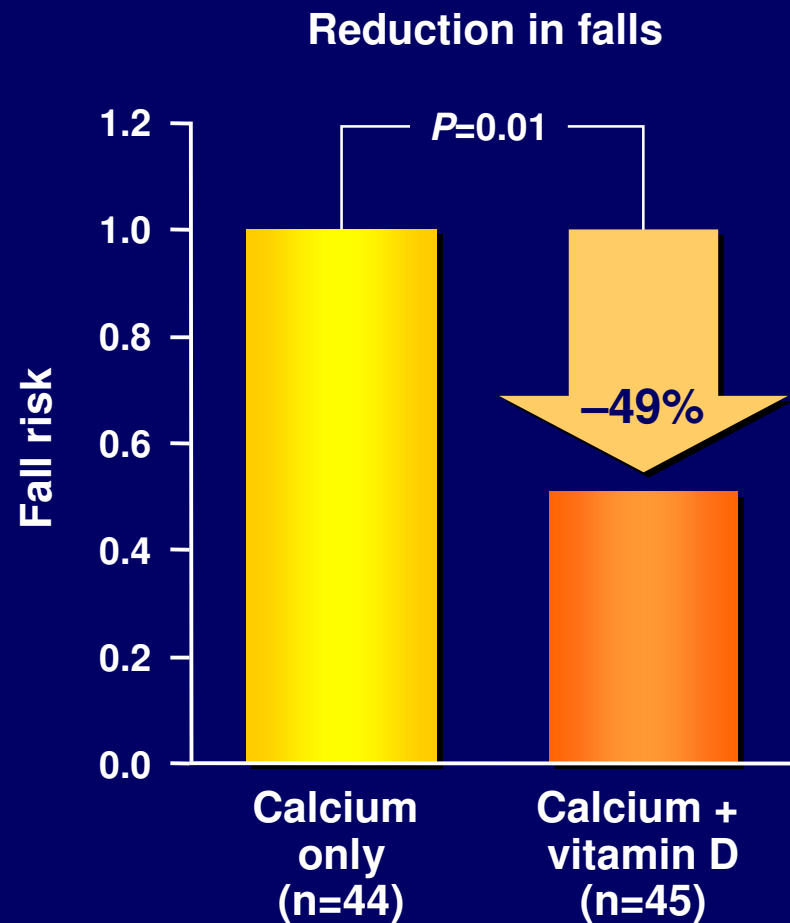
Timed Sit-to-Stand Test

LOWESS regression plot of lower extremity function vs vitamin D levels



Vitamin D Reduces Risk of Falling

- N =122
- Ages: 63–99
- Randomized, double-blind, controlled trial
 - Calcium 1200 mg/d
 - Calcium 1200 mg/d + vitamin D 800 IU/d
- 12-week duration
- Mean serum 25(OH)D 12 ng/mL at baseline
- Women living in long-term care units

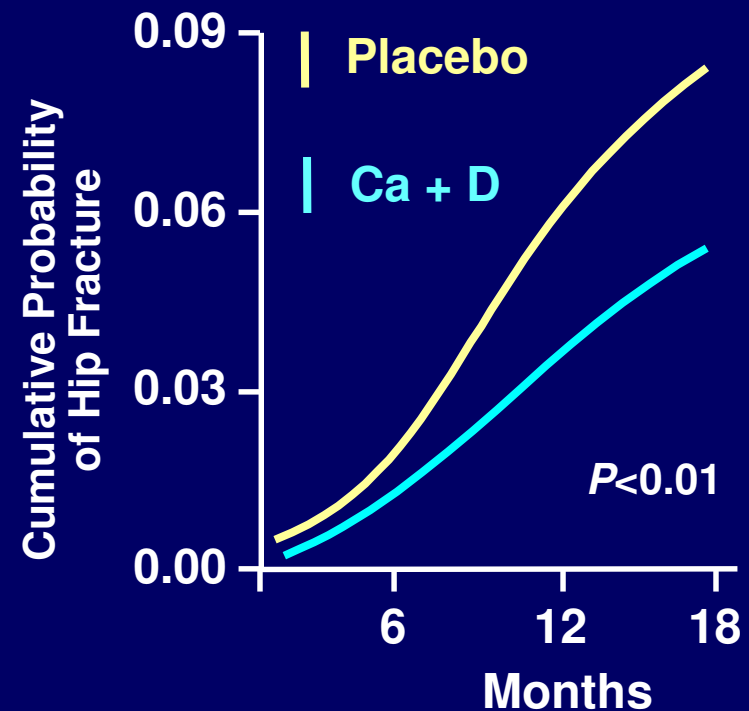


Calcium and Vitamin D Reduce Hip Fractures

Subjects: elderly women in French nursing home (n=3270)

Therapy: Calcium 1200 mg and vitamin D 800 IU daily

Outcome: 30% decrease in hip fracture risk over 18 months



Vitamin D: Clinical Fracture Risk

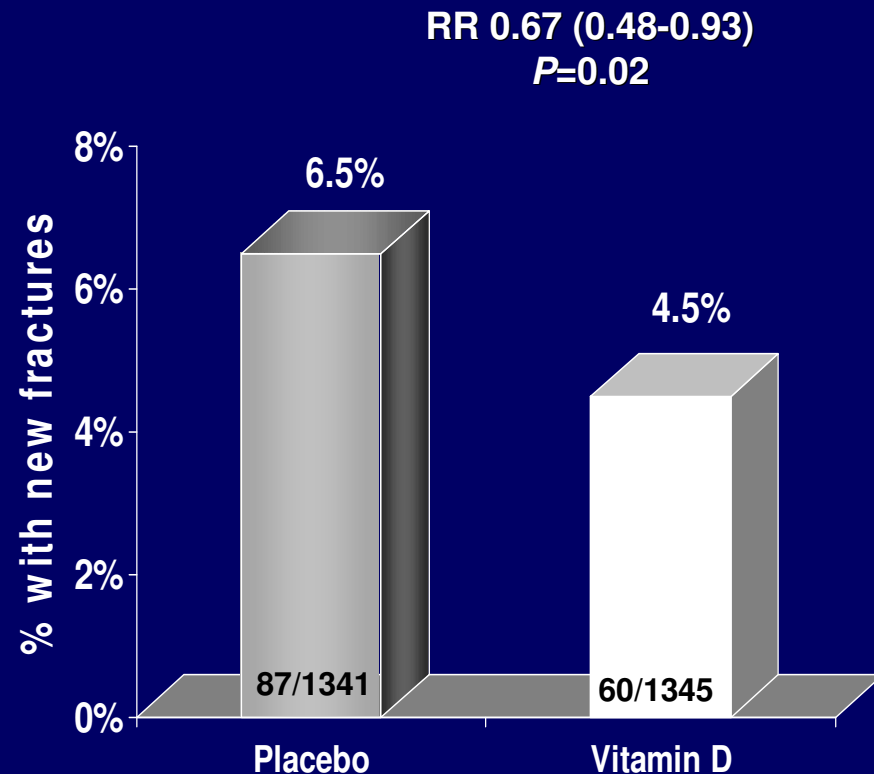
N=2686: Men and women 65-85

Mean age: 74.7

Placebo or vitamin D₃ 100,000 IU
PO every 4 months

Fractures: Hip, wrist, spine and
forearm

Treatment interval: 5 years



Vitamin D

Belief:

Daily calcium intake of 1500 mg is required for bone health.
Often interpreted as meaning that patients are given
1500 mg calcium supplement daily

Fact:

Intake of at least 2000 IU D3 daily (or 50,000 IU D2 per week)
is both important and safe



Osteoporosis: Approved Bisphosphonates 2008

- **Alendronate 10 mg**
- **Ibandronate 2.5 mg**
- **Risedronate 5 mg**
- **Zoledronic acid 5 mg**



Are There Differences Among Bisphosphonates?



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FOR BONE HEALTHSM

"I take BONIVA to help me manage my osteoporosis and strengthen my bones."

Like Sally Field, you, too, can help protect your bones with once-monthly BONIVA.

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FREE
information
about Reclast
▶ [Sign Up Now](#)

Only drug that prevents fractures at all sites



My doctor says that only Fosamax protects both my hip and spine. Boniva does not.
Ask your doctor.



Osteoporosis: Approved Bisphosphonates 2008

DRUG	APPROVED FOR						NON-DAILY DOSING
	Treatment			Prevention	Men	GIO	
	Vertebral	Non-vertebral	Hip				
Alendronate 10 mg	X		X	X	X	X	Weekly po
Ibandronate 2.5 mg	X	--	--	X	--	--	Monthly po IV Q 3 Mo
Risedronate 5 mg	X	X		X	X	X	Weekly po Monthly po
Zoledronic acid 5 mg once yearly	X	X	X	--	--	--	IV annual



Are There Differences Among Bisphosphonates?

Issue:

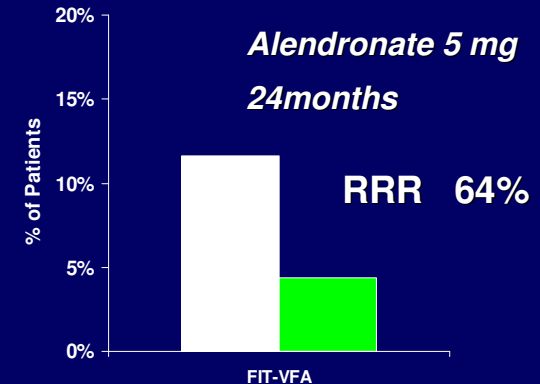
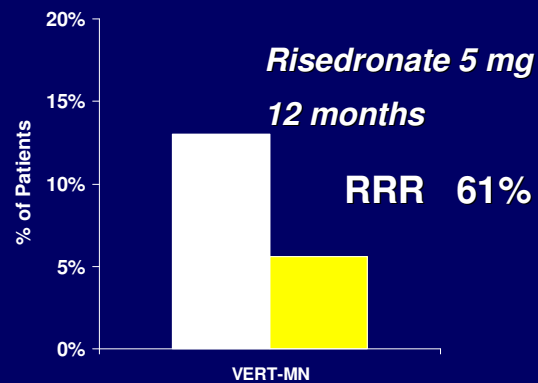
Are there clinically meaningful differences among bisphosphonates?



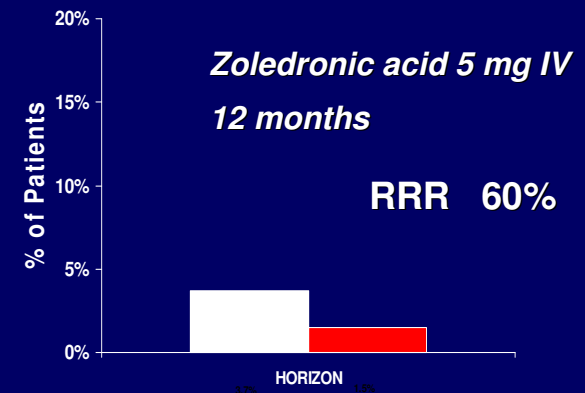
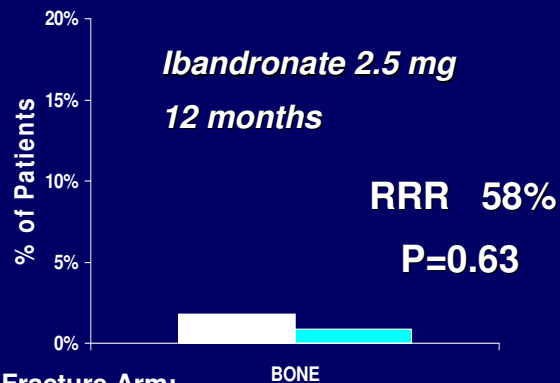
Bisphosphonates: Vertebral Fracture Risk

** Direct comparisons among trials cannot be made!*

Subjects:
Postmenopausal women
with previous vertebral
fractures



Subjects:
Postmenopausal women
with low BMD



FIT-VFA, Fracture Intervention Trial Vertebral Fracture Arm;
RRR, relative risk reduction; VERT-MN, Vertebral Efficacy
With Risedronate Therapy-Multinational

¹Reginster J, et al. *Osteoporos Int.* 2000;11:83

²Neer RM, et al. *N Engl J Med.* 2001;344:1434

³Black DM, et al. *Lancet.* 1996;348:1535



Bisphosphonate Therapy: Hip Fracture Incidence

Not head-to-head: Studies cannot be directly compared



•McClung MR, et al. *N Engl J Med.* 2001;344:333

Black DM, et al. *Lancet.* 1996;348:1535

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



No effect observed with ibandronate

Are There Differences Among Bisphosphonates?

YES and MAYBE

My conclusions:

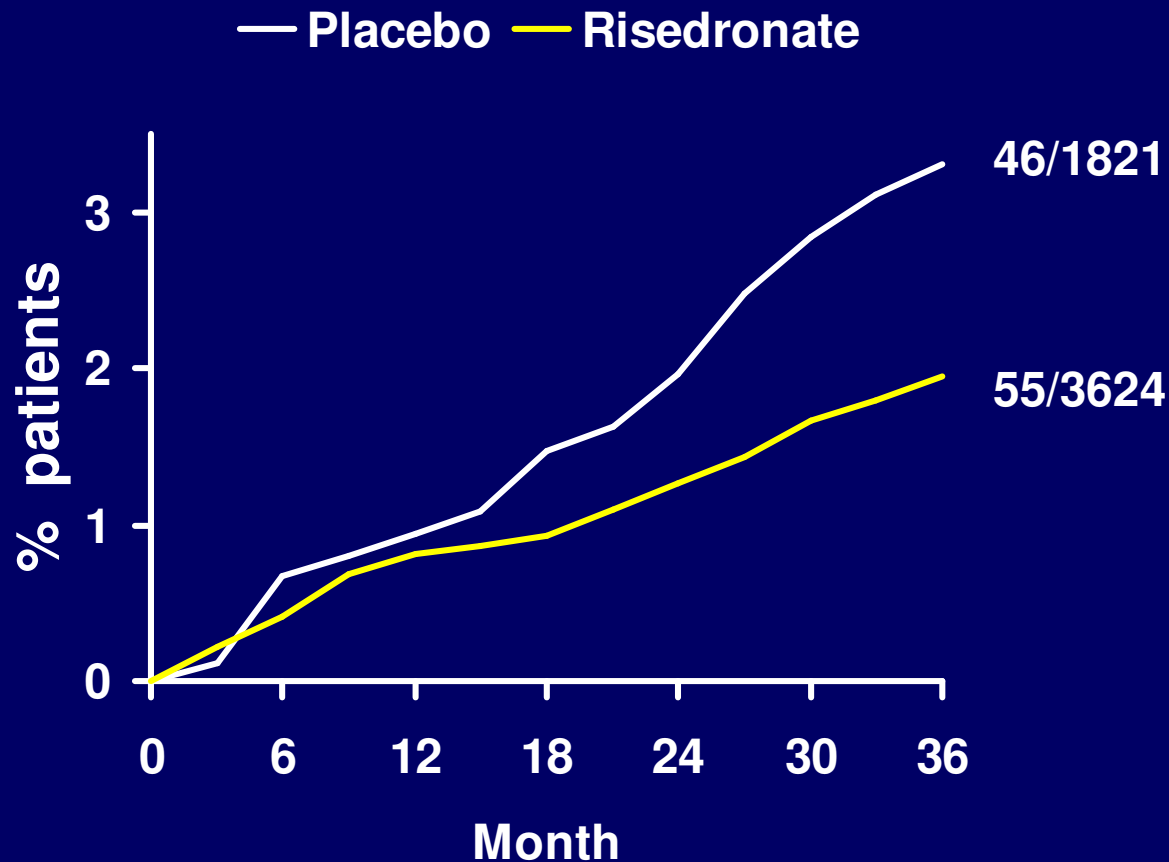
- 1. Bisphosphonates differ in structure and properties in the lab.**
- 2. Approved doses of drugs produce different responses of BMD and biomarkers.**
- 3. However, it is uncertain whether differences in effects on fracture risk exist among drugs.**



Risedronate Reduces Hip Fracture Incidence

Group 1 – 70-79 years, Low BMD

N = 5445



PBO 3.2%

RIS 1.9%

Risk Reduction
40%

CI=(10, 60)
p=0.009

NNT=72



Risedronate and Hip Fracture Risk

Reduction = 60%
C.I. 20%, 80%
p = 0.003

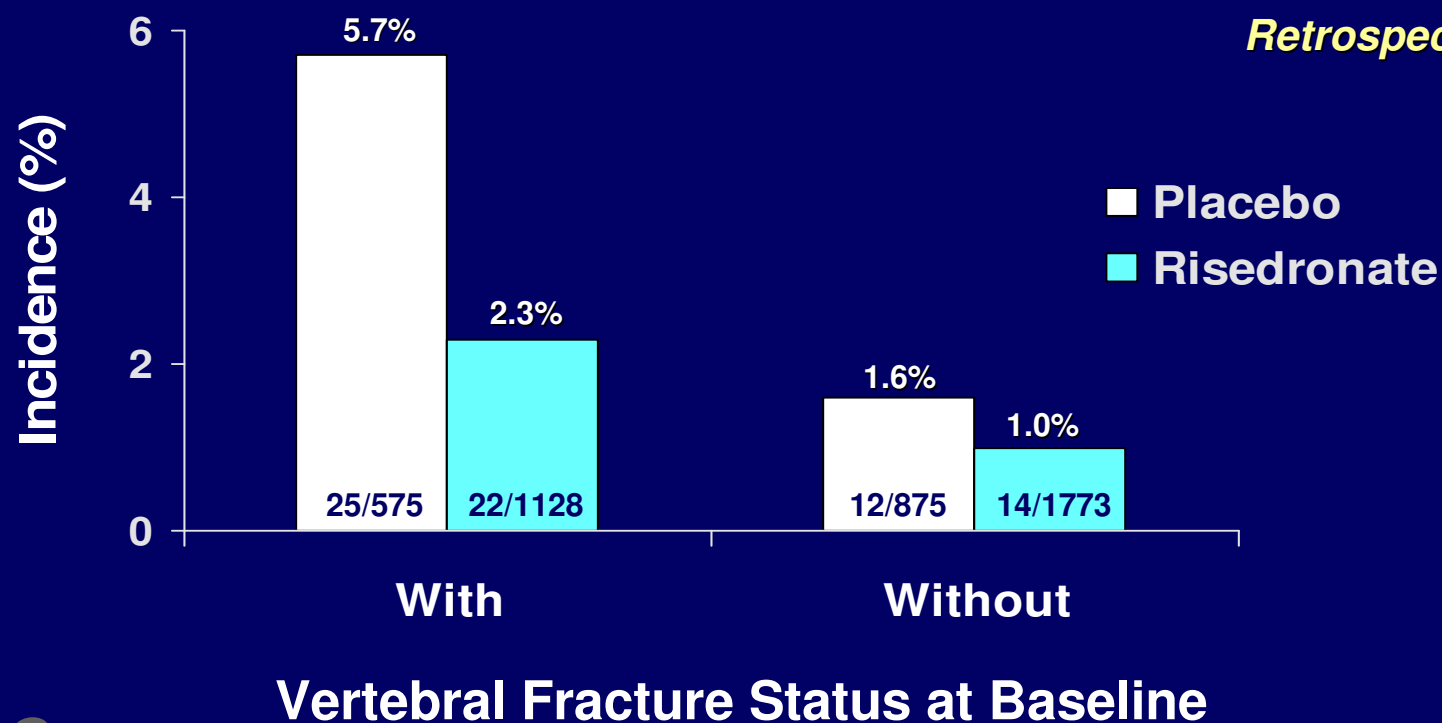
NNT = 29

Reduction = 40%
C.I. 70%, -20%
p = 0.14

NNT = 167

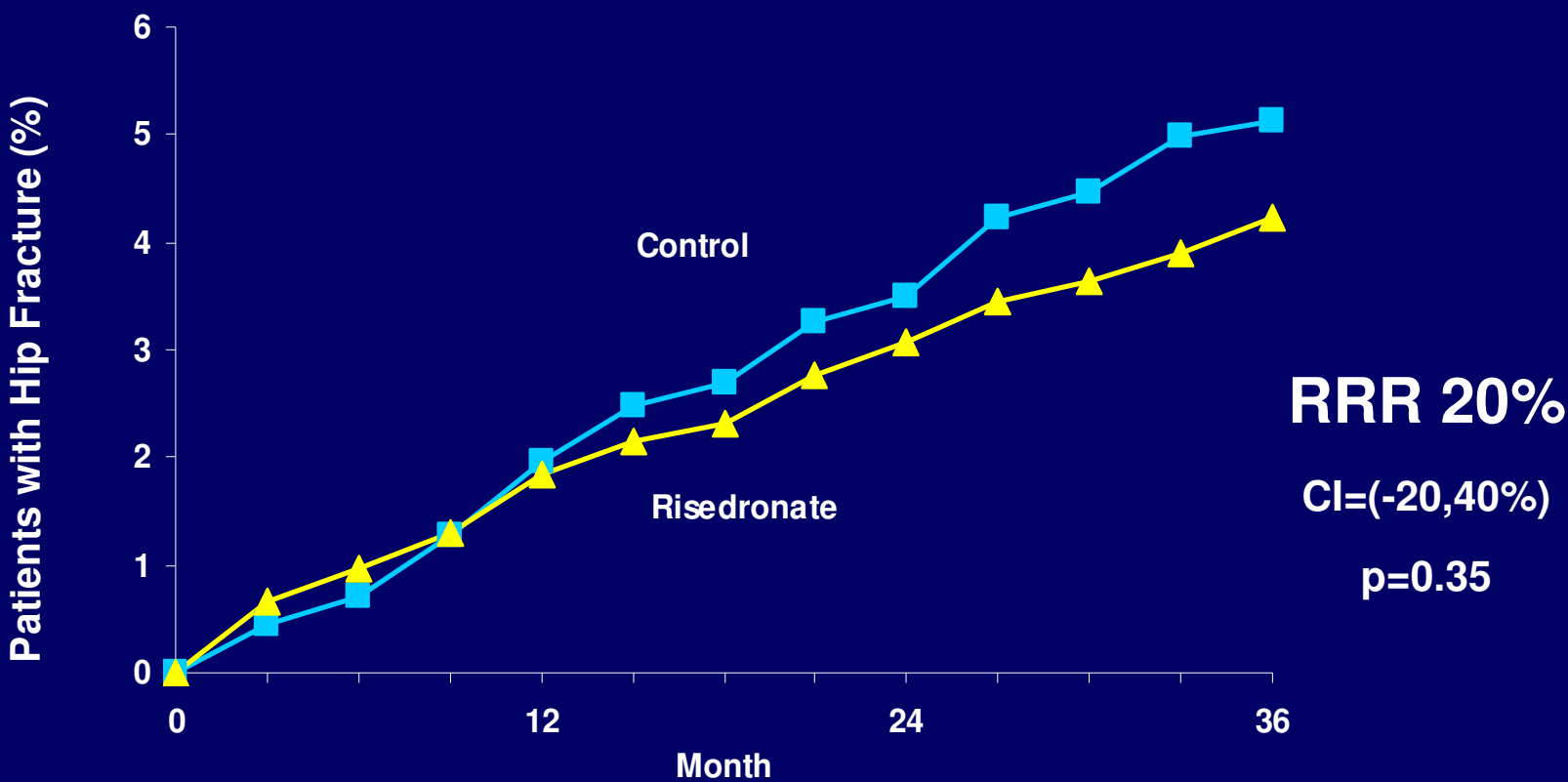
*Women ages 70-79
with low FN BMD*

Retrospective analysis



Risedronate Effect on Hip Fracture in Clinical Risk Factors Group

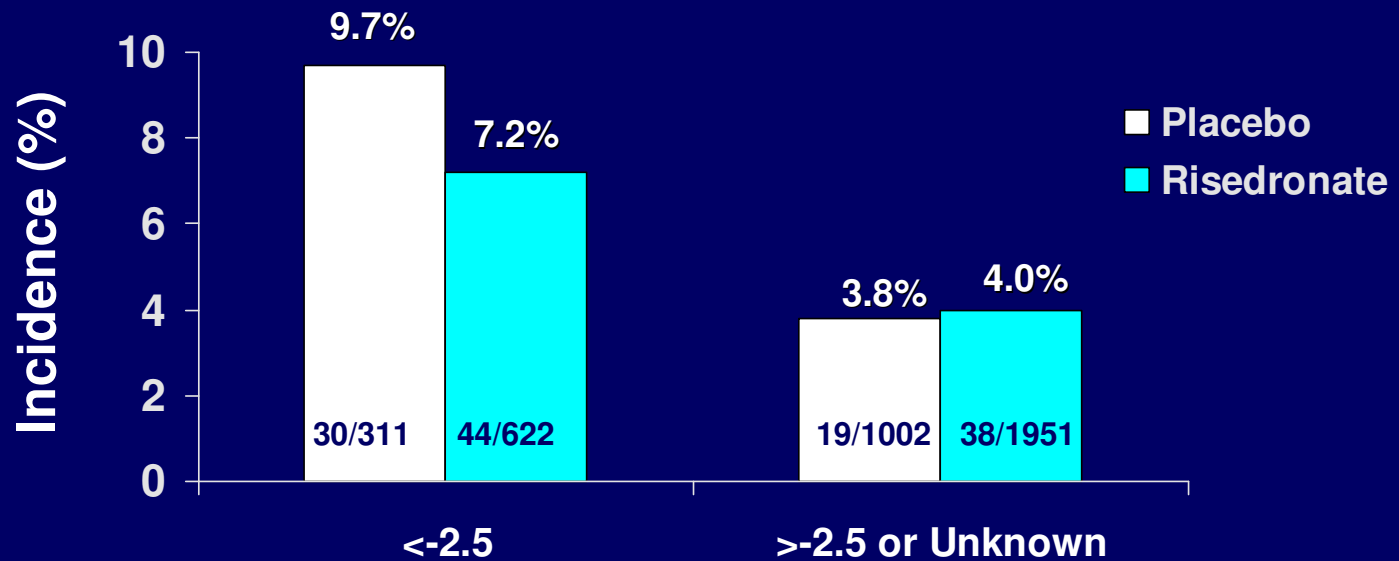
Number patients 3886
Patients ≥ 80 with Risk Factors for Hip Fracture



Risedronate: Group 2 Subgroups

*Women ages ≥ 80 with
 ≥ 1 RF for hip fracture*

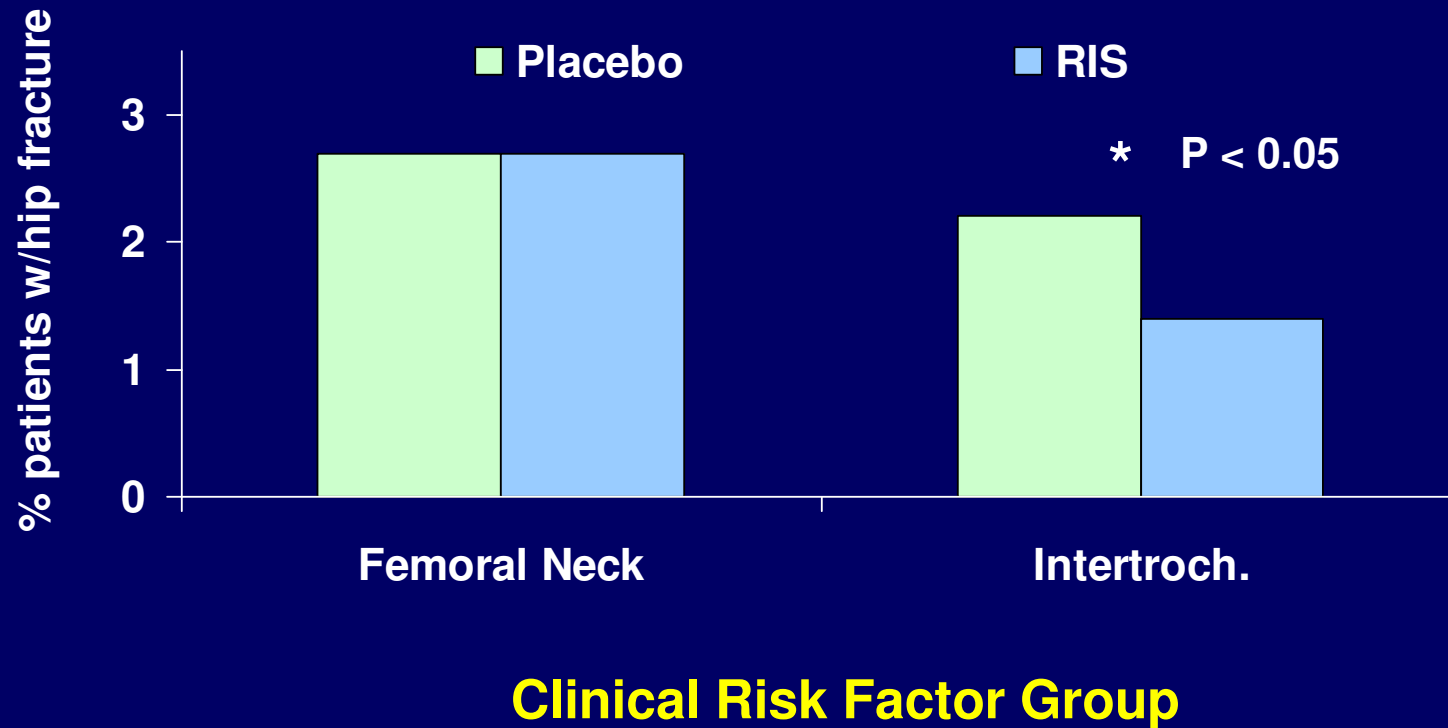
Relative Risk Reduction:	26%	-8%
p value	0.37	NA
NNT	40	-



BMD at Baseline

McClung et al. NEJM 2001

Effect of Risedronate on Hip Fractures at Different Sites



Effect of Risedronate on Vertebral Fractures in the Elderly

- Pooled analyses of the 3 large Phase III studies with risedronate vs placebo
- In subjects with osteoporosis aged 80 and older, vertebral fracture risk was reduced from 10.9% after 1 year to 2.5%
 - Absolute risk reduction 8.4%; NNT = 12
 - Relative risk reduction = 81% (CI 60-91%), P= <0.001



Zoledronic Acid After Hip Fracture

- 2127 men and women within 3 months of hip fracture
- Median age 76 years (14% >85 years)
- Received large dose of vitamin D
- Randomly assigned to receive placebo or IV zoledronic acid 5 mg Q12Mo
- Event-driven trial – average duration of treatment 1.9 years



Zoledronic Acid After Hip Fracture

Table 2. Rates of Fracture and Death in the Study Groups.*

Variable	Placebo	Zoledronic Acid	Hazard Ratio (95% CI)	P Value
Fracture — no. (cumulative %)				
Any	139 (13.9)	92 (8.6)	0.65 (0.50–0.84)	0.001
Nonvertebral	107 (10.7)	79 (7.6)	0.73 (0.55–0.98)	0.03
Hip	33 (3.5)	23 (2.0)	0.70 (0.41–1.19)	0.18
Vertebral	39 (3.8)	21 (1.7)	0.54 (0.32–0.92)	0.02
Death — no. (%)	141 (13.3)	101 (9.6)	0.72 (0.56–0.93)	0.01

* Rates of clinical fracture were calculated by Kaplan–Meier methods at 24 months and therefore are not simple percentages. There were 1062 patients in the placebo group, and 1065 in the zoledronic acid group. Because of variable follow-up, the number and percentage of patients who died are provided on the basis of 1057 patients in the placebo group and 1054 patients in the zoledronic acid group in the safety population.



Bisphosphonates and Atrial Fibrillation

- In the HORIZON Fracture Prevention Trial, incidence of “serious adverse events” related to atrial fib was 1.2% with zoledronic acid vs 0.4% with placebo ¹
 - Overall incidence of atrial fibrillation was same between the two groups
 - No difference in stroke, mortality
 - RR of atrial fibrillation serious AE in other large HORIZON was 0.8 with treatment ²



¹ Black DM, et al. *N Engl J Med.* 2007;356:1809-22.

² Lyles KW, et al. *N Engl J Med.* 2007;357:1799-1809.

Bisphosphonates and Atrial Fibrillation

- In alendronate FIT study, there was an insignificant “trend” toward increased frequency of serious AE with a fib

Cummings SR et al. [letter] *N Engl J Med* 207;356:1895

- Review of entire risedronate clinical development program revealed no signal of atrial fib, other arrhythmias, heart disease or related problems

Karam R, Camm J, McClung M. [letter]. *N Engl J Med*. . 2007;35:712-713



FDA: Bisphosphonates and Atrial Fibrillation

- The FDA reviewed spontaneous post-marketing reports of atrial fibrillation reported in association with oral and intravenous bisphosphonates and did not identify a population of bisphosphonate users at increased risk of a group of relation.
- Upon initial review, it is unclear how these data on serious atrial fibrillation should be interpreted.
- Therefore, FDA does not believe that health care providers or patients should change either their prescribing practice or their use of bisphosphonates at this time.



Bisphosphonates and Atrial Fibrillation

- **April 28, 2008: Case control study from Seattle**
 - **719 women with atrial fib – 6.5% (N=41) on alendronate**
 - **966 matched controls – 4.0% (N=40) on alendronate**
 - **P = 0.03**
 - **BUT, treated group was**
 - **older by 4 years**
 - **more likely to have osteoporosis (osteoporosis correlated with heart disease)**
 - **may have been taking more calcium (high calcium intake may be associated with heart disease)**



Bisphosphonates and Atrial Fibrillation

- **Case control study in Denmark:**
 - **13,586 patients with atrial fibrillation and flutter and 68,054 population controls. No evidence was found that use of bisphosphonates increases the risk of atrial fibrillation and flutter.**
- **Adjusted relative risk:**
 - **for users vs non-users 0.95 (95% CI 0.84,1.07)**
 - **new users vs non-users 0.75 (95% CI 0.49,1.16)**
 - **continuing users vs non-users 0.96, (95% CI 0.85,1.09)**

Sørensen HT et al. *BMJ*. 2008;336:813-6.



Safety vs Benefits of Bisphosphonate Therapy

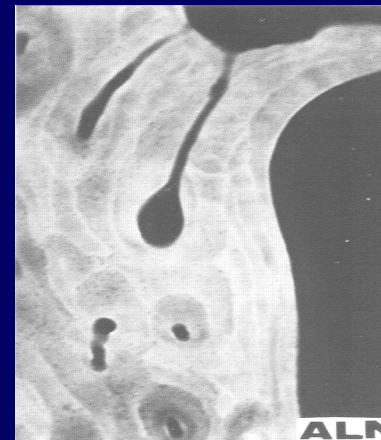
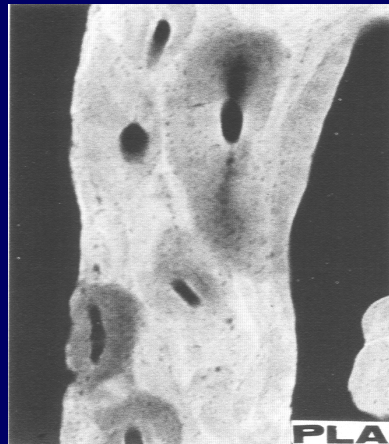
- **A concern since beginning of studies with alendronate**
 - Elderly Study – Bone HG, McClung MR et al. *J Clin Endocrinol Metab* 1997;82:265-274.
- **Impaired bone quality**
 - Increased mineral density
 - Micro-cracks with bisphosphonate therapy
- **Clinical consequences**
 - Osteonecrosis of jaw
 - Unusual, non-healing fractures



Bisphosphonates and Bone Quality

- Robust pre-clinical data demonstrating increases in bone strength that are at least as much as predicted by BMD
- Increased mineral density

Boivin GY et al. *Bone*. 2000;27:687-94. 2000



- but no evidence that bone is hypermineralized
- Not observed with zoledronic acid Recker et al., *JBMR*. 2007: E-pub Sept 10

Bisphosphonates and Micro-cracks

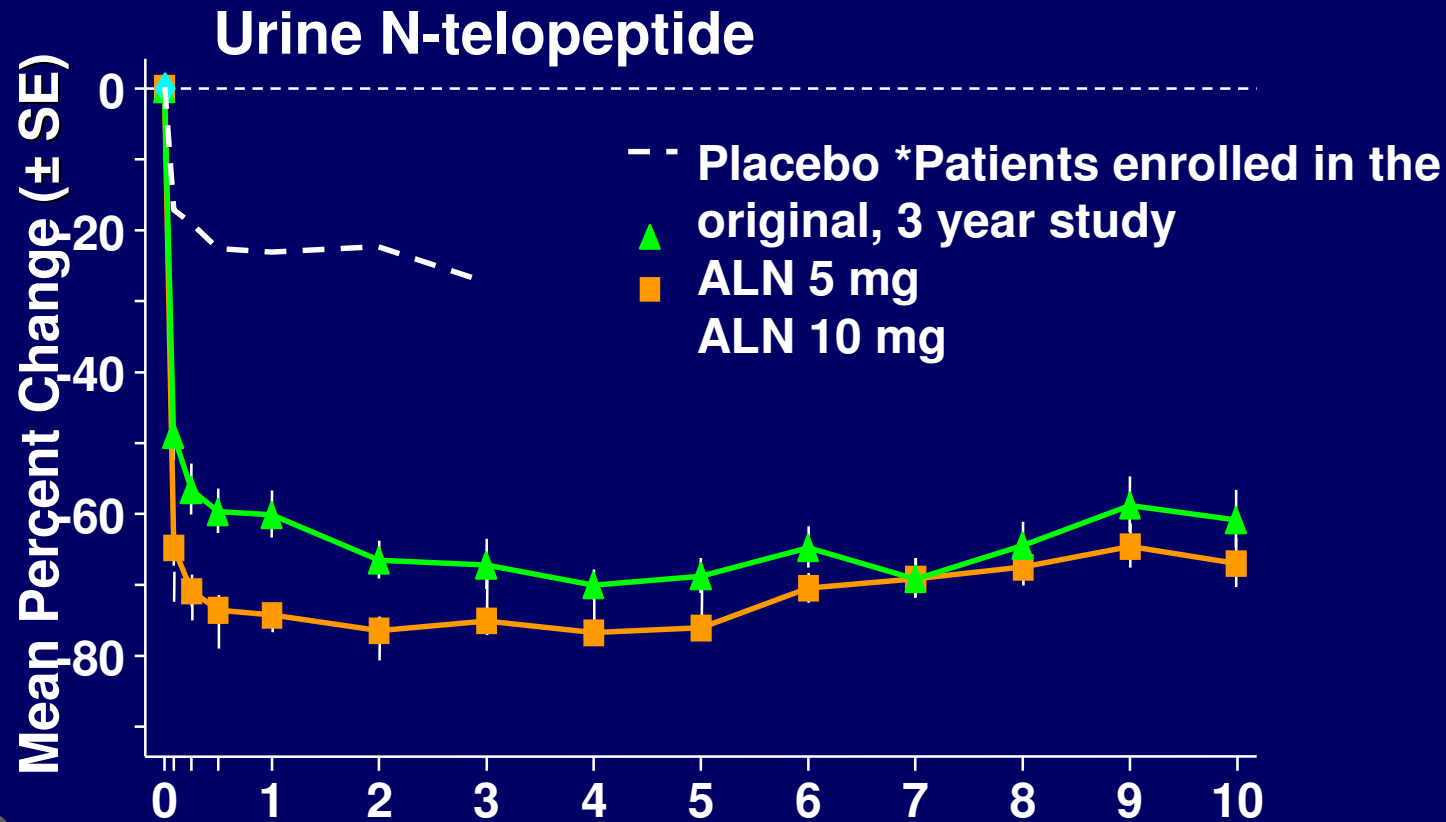
- Increased micro-cracks identified in bone from patients with osteoporosis
- Micro-cracks identified in dogs receiving high dose-alendronate
 - But mechanical properties of bone minimally effected
- No difference in micro-crack density between treated and untreated patients with osteoporosis ¹



¹ Chapurlat RD, *J Bone Miner Res.* 2007;22:1502-9

Bisphosphonates: Concern About Long-term Safety

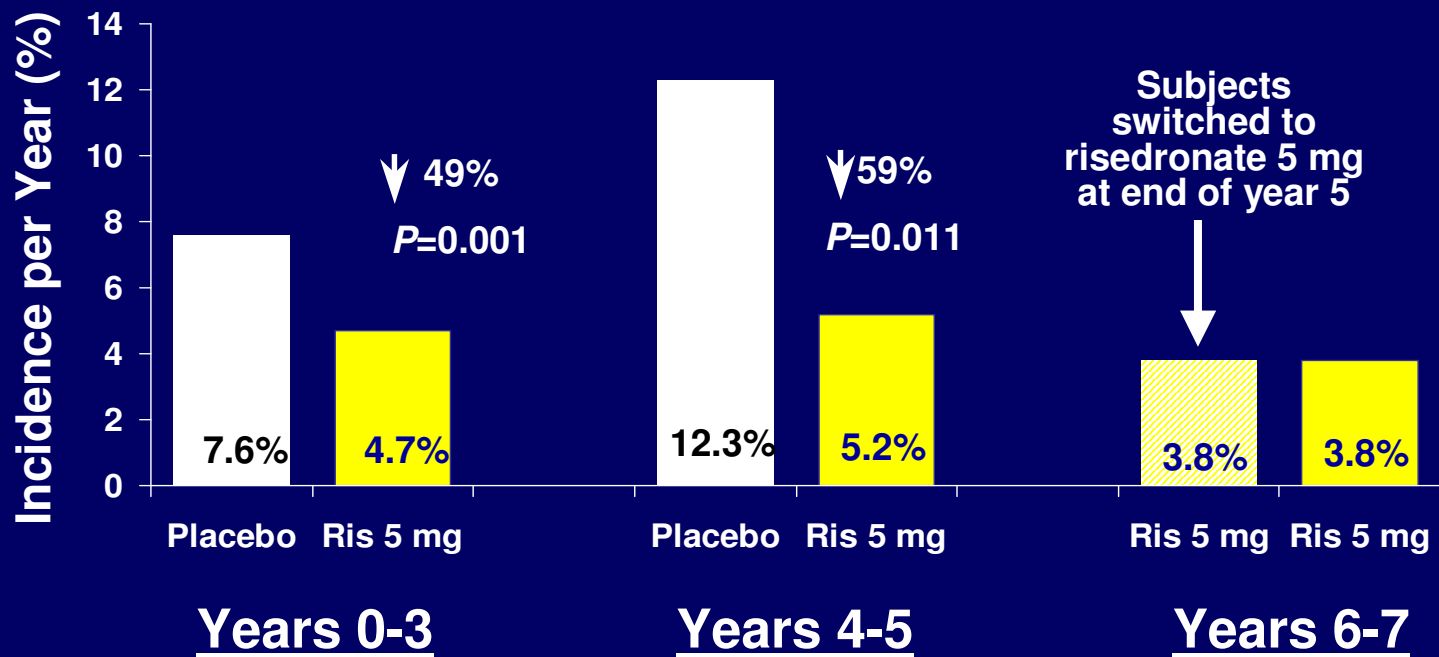
- Marked, progressive suppression of bone turnover



Bone et al, *NEJM* 2004; 350:1189

Vertebral Fracture Risk on Long-term Risedronate Therapy

VERT-MN: Radiographic Vertebral Fracture*



*Annualized fracture incidence represents the percentage of subjects experiencing any new vertebral fracture divided by the number of years in the observed interval.



Mellstrom DD et al. *Calcif Tissue Int.* 2004;75:462-8.

Bisphosphonates: Concern About Long-term Safety

- **Anecdotal reports of fractures and impaired healing**

- **Non-healing unusual fractures**

Odvina C et al. *J Clin Endo Metab.* 2005;90:1294-1301

- **Sub-trochanteric fractures**

(5/9 were on alendronate) Goh 2007



Bisphosphonates and Non-healing Fractures - “Frozen Bone”?

- Several small series of cases experiencing unusual lower extremity fractures
 - Not always old
 - Time on therapy variable
 - Often on other drugs, esp. steroids
- Bone turnover: low normal resorption but very low or absent formation
- Slow or absent healing
- ?? a small cohort of patients predisposed because of osteoclast dysfunction??



Goh S-K, et al. *J Bone Joint Surgery*, 2007;89-B:349-353.
Kazuhiro I, et al. *J Bone Mineral Metab* 2007. 25: 333-336.
Lenart BA, Lorich DG, Lane JM. *N Engl J Med*. 2008;358:1304-6.
Nevaser AS, et al. *J Orthop Trauma*. 2008;22:346-50.



Bisphosphonates and Osteonecrosis of Jaw

- Exposed bone for at least 6-8 weeks
- Most often in patients receiving high-dose bisphosphonate therapy for cancer-related bone diseases.
- After invasive dental procedures
- Risk factors: poor oral hygiene, other diseases

- Observed in patients receiving bisphosphonates for osteoporosis

Ruggiero SL et al. *J Oral Maxillofac Surg.* 2004;62:527-34



Bisphosphonates, ONJ and Osteoporosis

- Incidence not known
 - (estimates 1/10,000-1/100,000 patient years)
- Pathogenesis uncertain
 - ONJ and estrogen?
- Link to bisphosphonate therapy not proven to be causal
- No spontaneously reported ONJ in clinical trials
- No evidence that discontinuing bisphosphonate therapy before dental procedures reduces risk of ONJ



Bisphosphonates and Bone Safety

- **Persistent but not progressive inhibition of bone turnover (markers and bone biopsy)**
- **No evidence of loss of fracture protection with 7 years of risedronate therapy**
- **Bone turnover is not maximally suppressed in patients on long-term bisphosphonate therapy**
- **No evidence of skeletal harm in clinical trials**
- **Overall, minimal reason for concern about long-term skeletal safety of oral bisphosphonates for osteoporosis**
- **Are there specific individuals at risk for complications?**

McClung MR 2008. Personal opinion



Is a Drug “Holiday” Justified or Necessary?

Issue:

Should bisphosphonate therapy be interrupted after several years?

Rationale

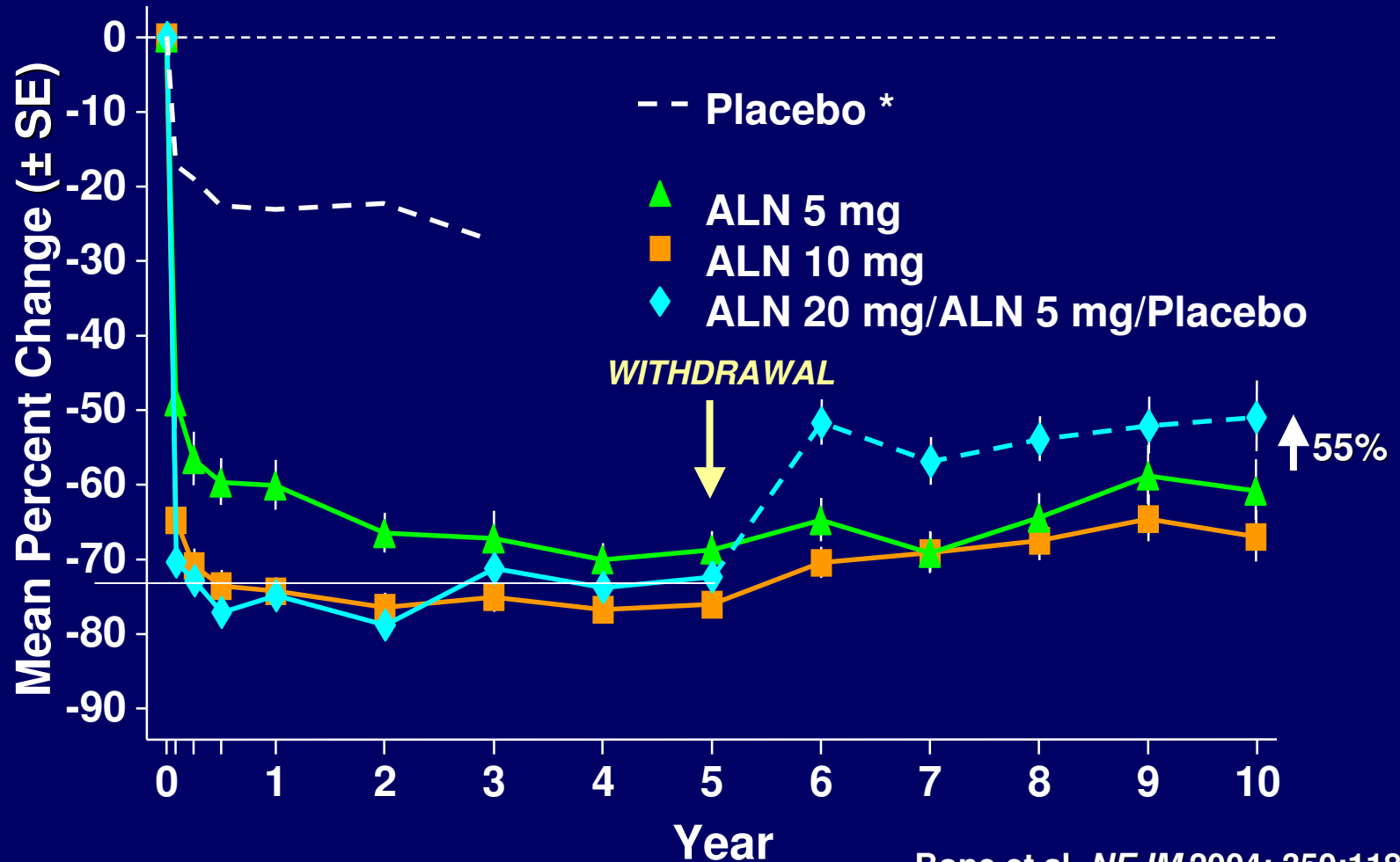
1. Long-term safety concerns
2. Inhibition of bone remodeling persists after stopping alendronate therapy



Persistence of Treatment Effect

Urine N-telopeptide

*Patients enrolled in the original, 3 year study



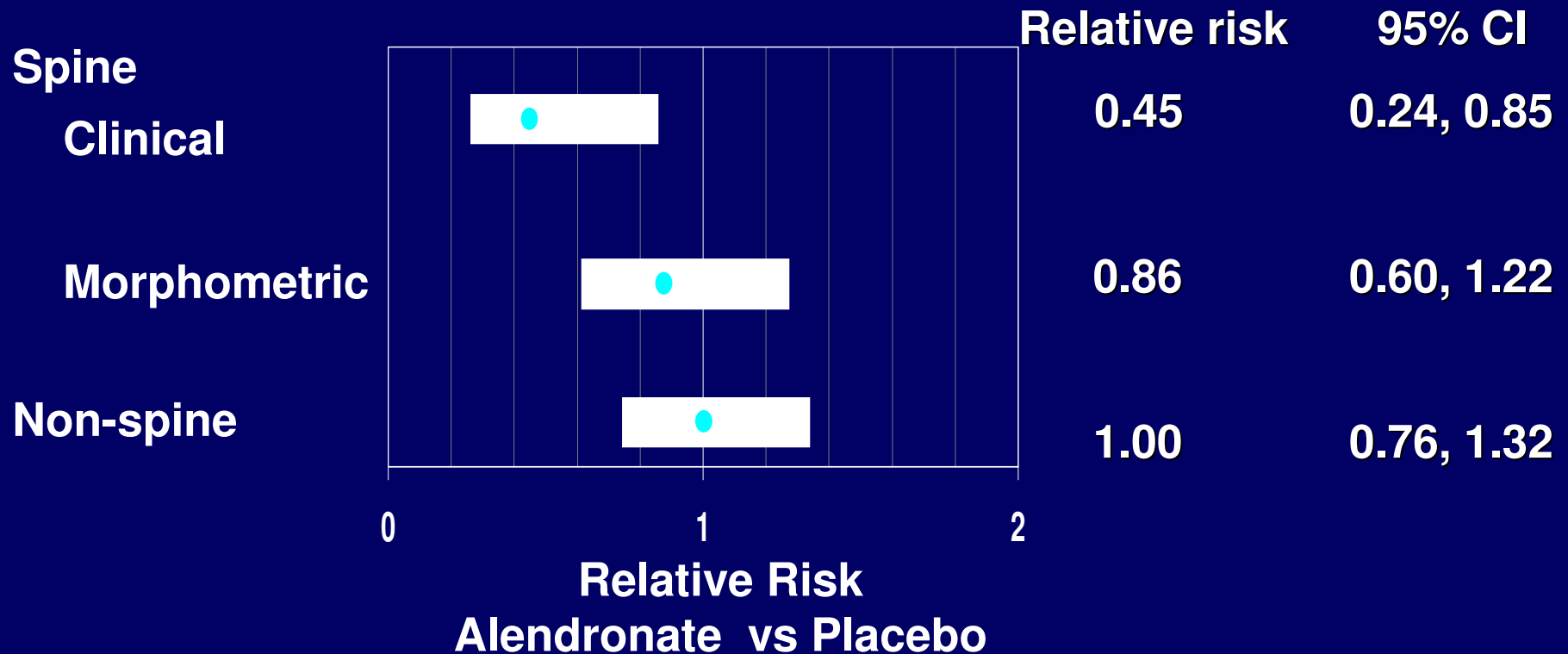
Fractures after Alendronate Withdrawal

- **FLEX: 5 year extension of FIT**
- **Treatment for 3-6 years (avg 5); then randomized to alendronate 10 mg daily or placebo for next 5 years**



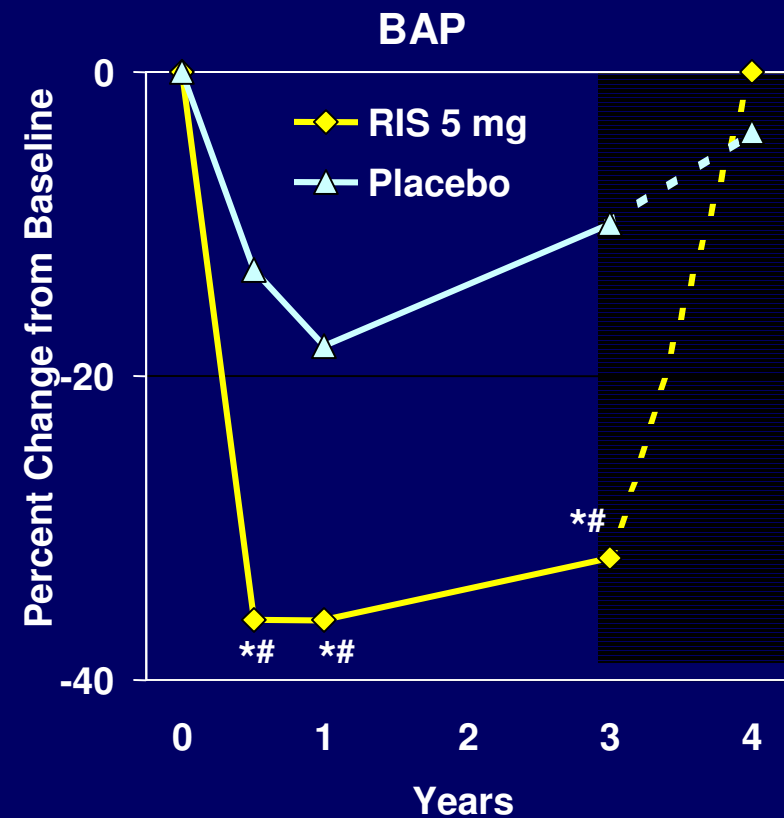
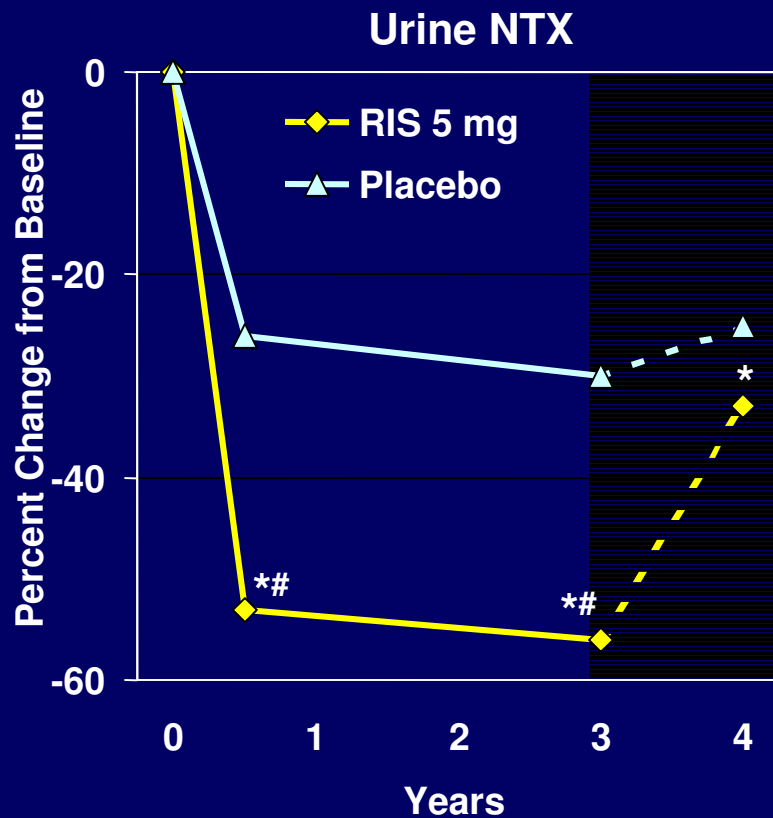
Withdrawing Alendronate Therapy

Fracture Risk in FLEX



Withdrawal of Risedronate

VERT-NA Extension



*p<0.05 vs baseline

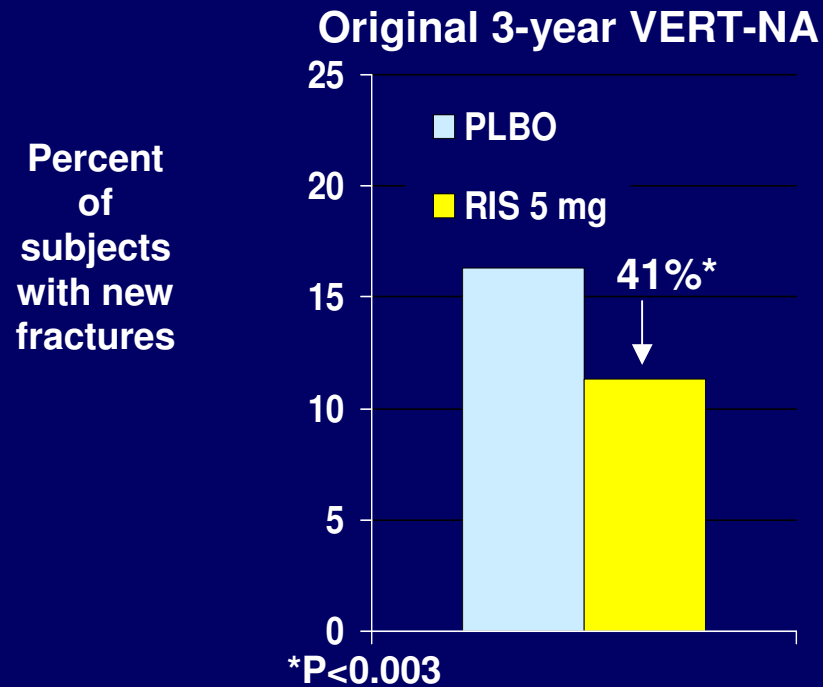
#p<0.05 vs placebo



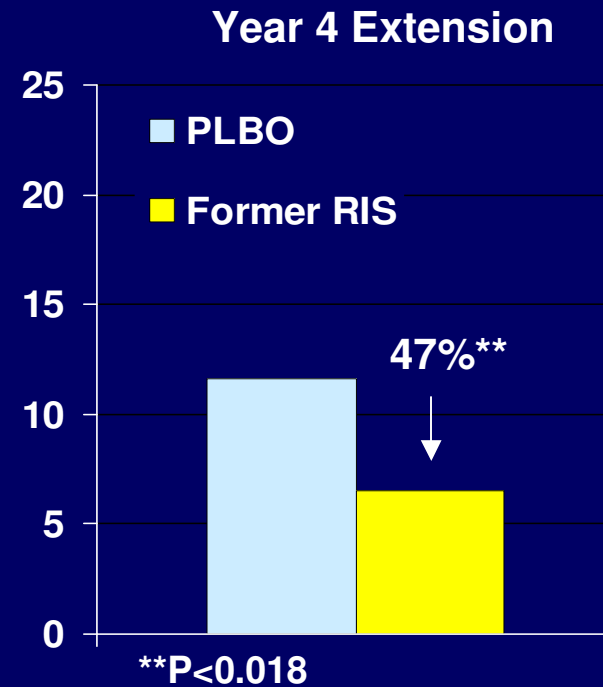
Watts NB, McClung MR et al. *Osteoporos Int.* 2007 Oct 16; [Epub ahead of print]

Withdrawal of Risedronate

EFFECT ON NEW RADIOGRAPHIC VERTEBRAL FRACTURES



Harris ST et al, *JAMA*
1999;282:1344-1353



Watts NB, McClung MR et al. *Osteoporos Int.* 2007 Oct
16; [Epub ahead of print]



Is a Drug “Holiday” Justified or Necessary?

Issue:

Should bisphosphonate therapy be interrupted after several years?

My conclusions:

1. Patients at high fracture risk – no clear justification to stop treatment
2. Patients at moderate risk – drug holiday from alendronate seems reasonable
3. Uncertain what to do with other bisphosphonates



Treating Osteoporosis

- **Calcium and especially vitamin D are important for all adults**
- **Current treatments are effective in reducing fracture risk in patients at high risk from fracture.**
- **New treatments, including some with novel mechanisms of action, will be available soon.**
- **Beneficiaries of these advances and our work will be our patients.**



Thank You



Michael R. McClung, MD, FACP
Founding Director
Oregon Osteoporosis Center
Portland, Oregon, USA

Copies of slides available Monday at
http://www.orost.com/mm_pres.htm

