

# Controversies in Present-Day Management of Osteoporosis

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## *I: Bisphosphonates:*

Are They the Same?

Long-term Safety and Efficacy?

How Long Should They Be Used?

Ashland Endocrine  
Conference

August 3, 2007



OREGON  
HEALTH & SCIENCE  
UNIVERSITY



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# Disclosure and Conflict of Interest

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

Amgen	Novartis	Roche
Lilly	Procter & Gamble	sanofi-aventis
Merck		Wyeth

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

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

Michael McClung, MD

August 2007



# Bisphosphonates

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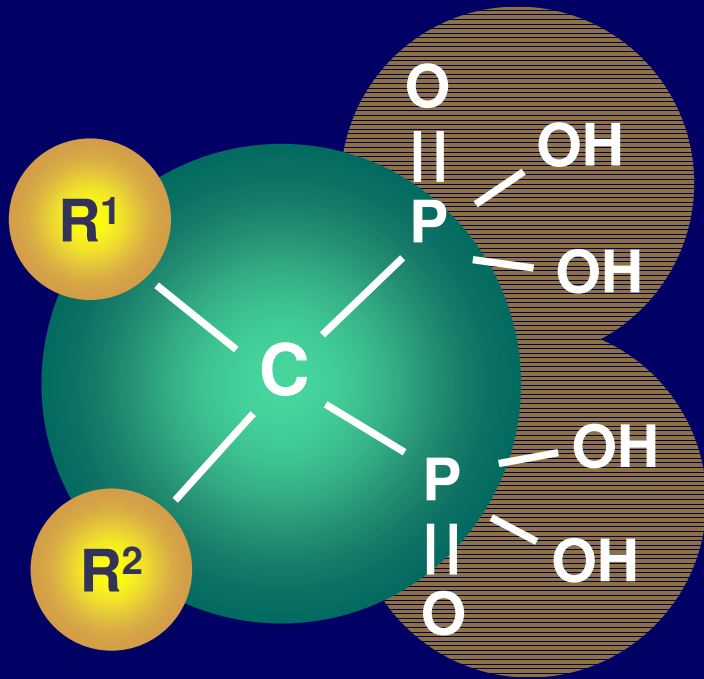
- **Inhibit osteoclast proliferation, activity and lifespan**
- **Reduce indices of bone turnover and increase bone density at important skeletal sites**
- **Reduce incidence of vertebral and other fractures in patients with osteoporosis**
- **Mainstay of osteoporosis therapy since 1995**

# Postmenopausal Osteoporosis: Approved Bisphosphonates 2007

<b>DRUG</b>	<b>APPROVED FOR</b>			<b>COMMENTS</b>
	<b>Treatment</b>		<b>Prevention</b>	
	<b>Vertebral</b>	<b>Non-vertebral</b>	<b>Hip</b>	
<b>Alendronate 10 mg</b>	<b>X</b>		<b>X</b>	<b>Weekly dosing</b>
<b>Ibandronate 2.5 mg</b>	<b>X</b>	<b>--</b>	<b>--</b>	<b>Monthly and IV dosing</b>
<b>Risedronate 5 mg</b>	<b>X</b>	<b>X</b>		<b>Weekly, monthly dosing</b>
<b>Zoledronic acid (pending)</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>? Annual intravenous dosing</b>



# Properties of Bisphosphonates

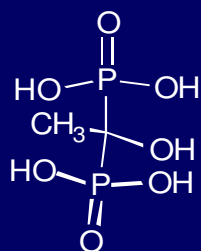


- Chemically very stable
- “Non”-metabolised, but some form ATP derivatives
- Strong chelation to Ca<sup>2+</sup>, Mg<sup>2+</sup> etc
- Binding to calcium phosphates and bone mineral
- Inhibit mineral growth and dissolution
- Do not enter cells readily, except by endocytosis, e.g. in macrophages, osteoclasts, etc.

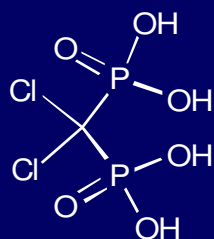
# A New Classification of Bisphosphonates Based on Mechanism of Action

*Low potency, act via  
ATP-BP metabolites*

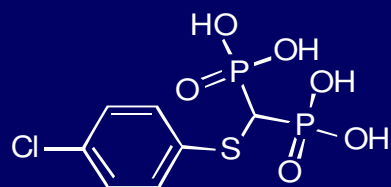
**'Simple' non-N BPs**



**Etidronate**



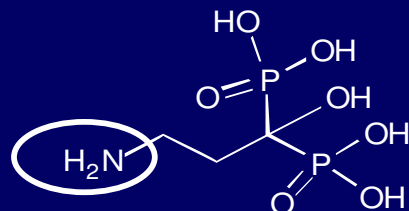
**Clodronate**



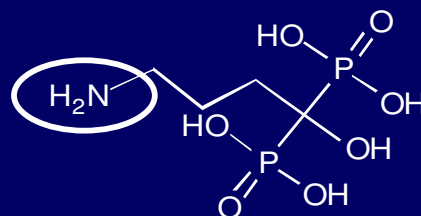
 **Tiludronate**

*Intermediate potency,  
act via FPPS*

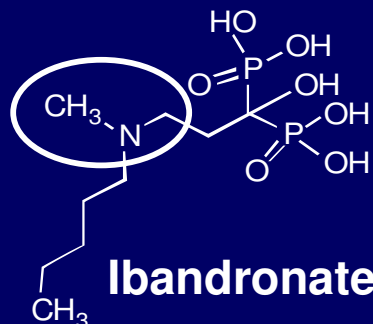
**Alkyl-amino BPs**



**Pamidronate**



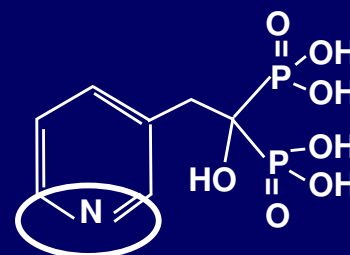
**Alendronate**



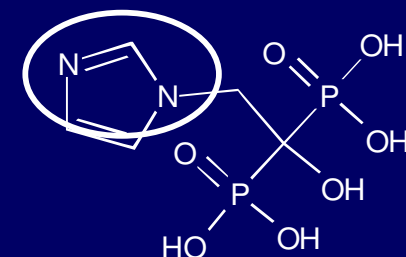
**Ibandronate**

*High potency, act via almost  
irreversible inhibition of FPPS*

**Heterocyclic N BPs**



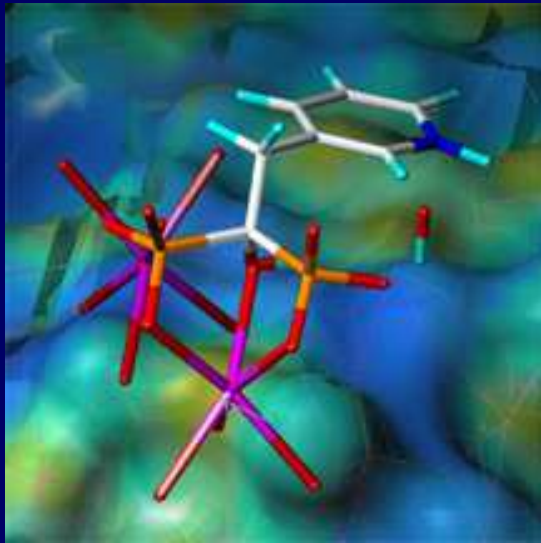
**Risedronate**



**Zoledronic acid**

# Fundamental Components of N-Bisphosphonate Anti-resorptive Activity

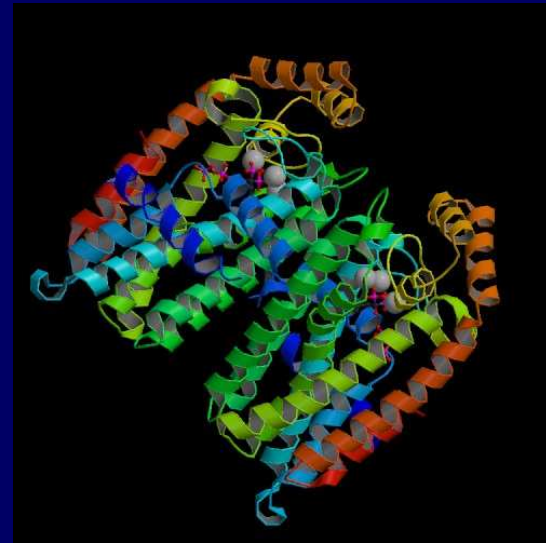
## Bone Mineral Affinity



## Bone Uptake and Release

Availability  
Distribution  
Offset of Action

## FPPS Enzyme Inhibition



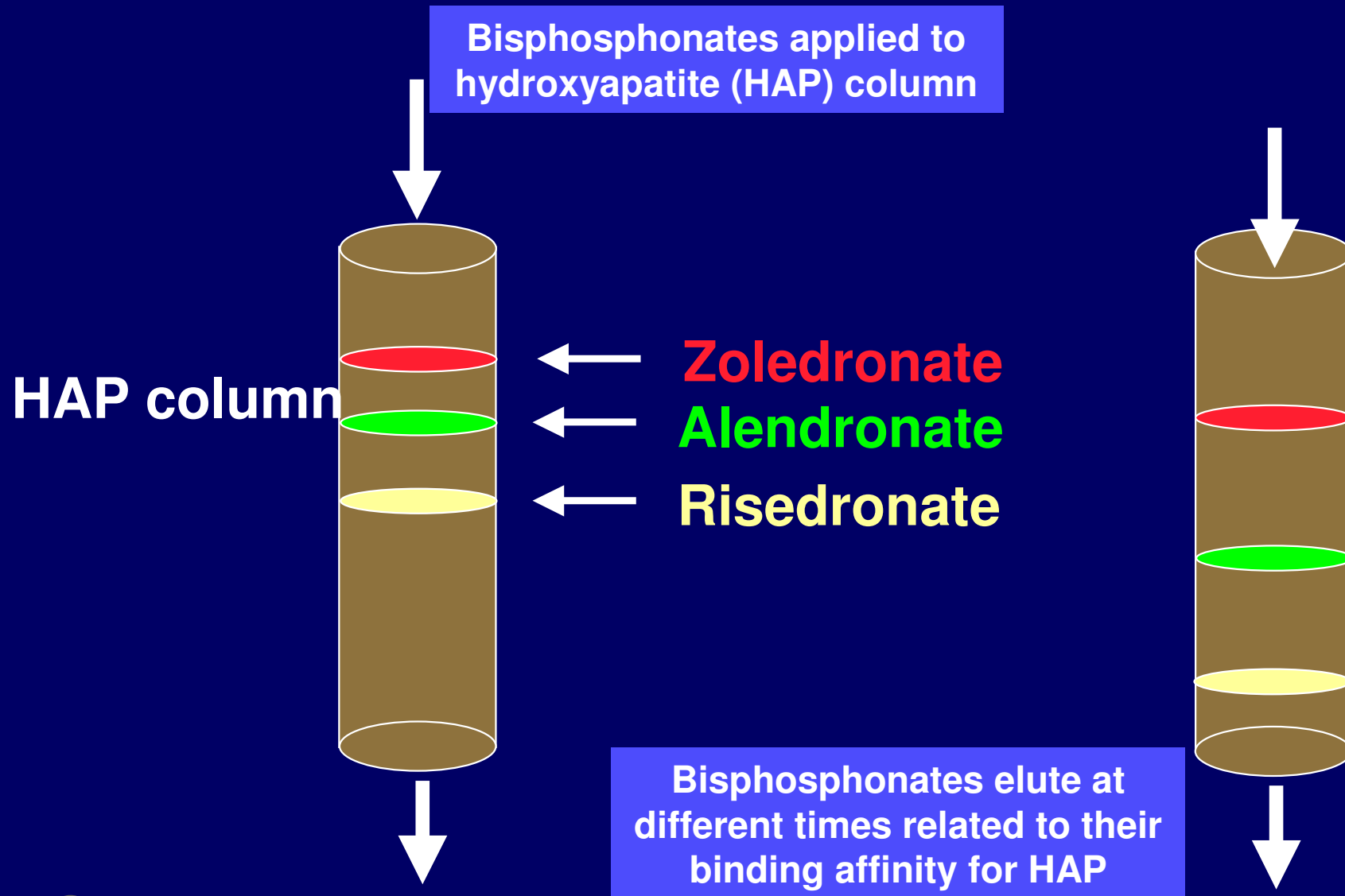
## Osteoclast Function

Potency

FPPS = Farnesyl pyrophosphate synthase

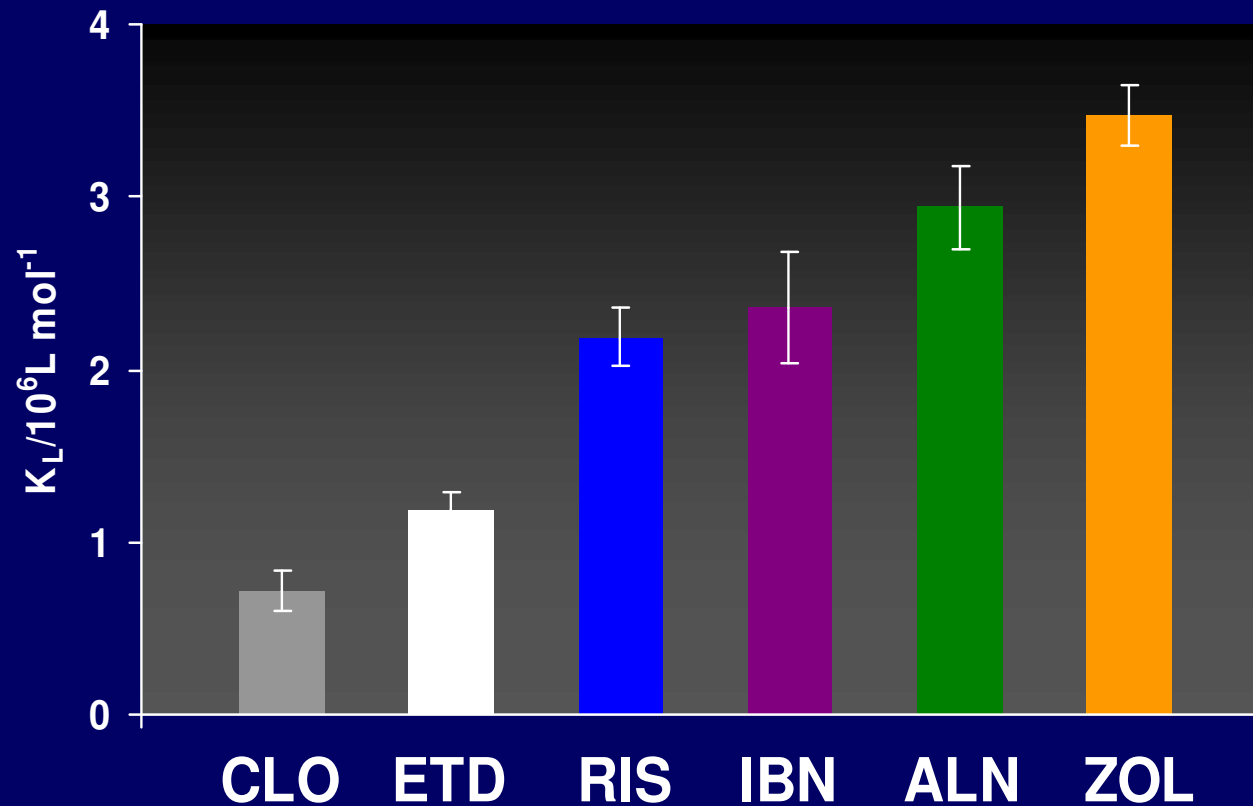


# Differential Binding of BPs to Hydroxyapatite (HAP) Revealed by Affinity Chromatography

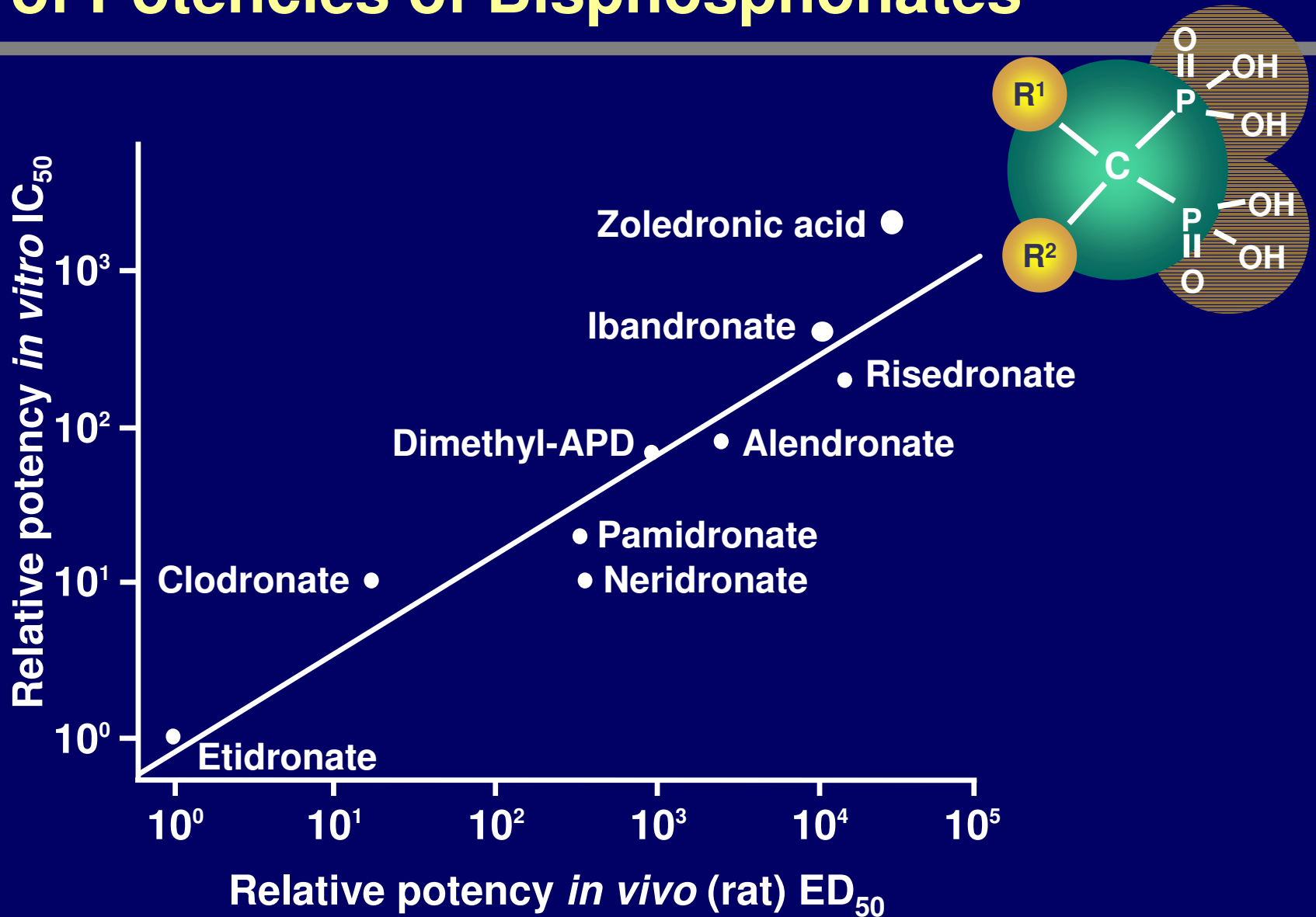


# Differential Binding Affinity of Bisphosphonates to Bone Mineral

## HAP Adsorption Affinity Constants at pH 7.4



# Range of Potencies of Bisphosphonates



# Bisphosphonates: Key Pharmacological Characteristics

## Binding affinity for bone in vitro

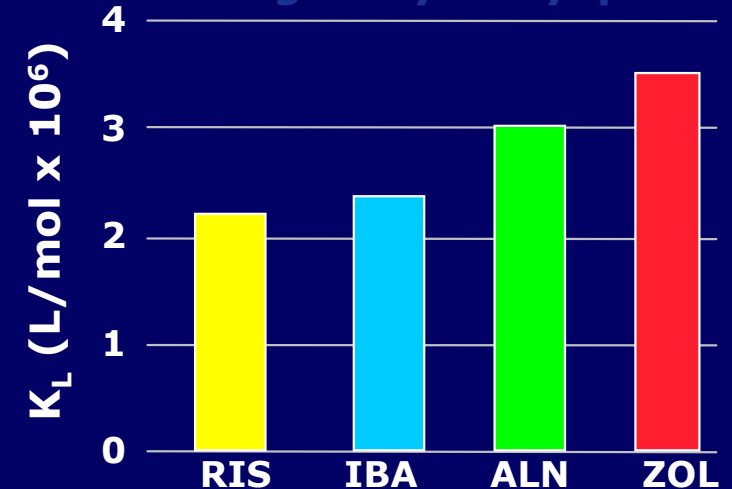
Determines attachment to bone  
and duration of effect

## FPP synthase inhibition in vitro

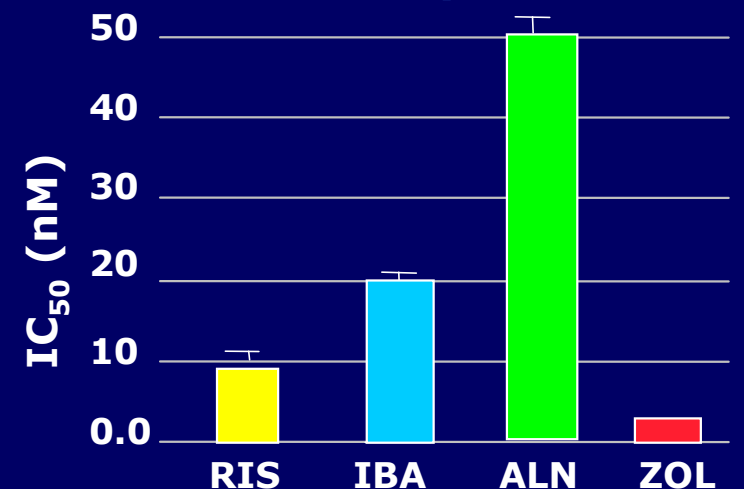
Determines antiresorptive  
potency

*Low values reflect higher potency*

Binding to Hydroxyapatite<sup>1</sup>



rhFPP synthase<sup>2</sup>



1. Nancollas GH, et al. *Bone*. 2006;38: 617-627.

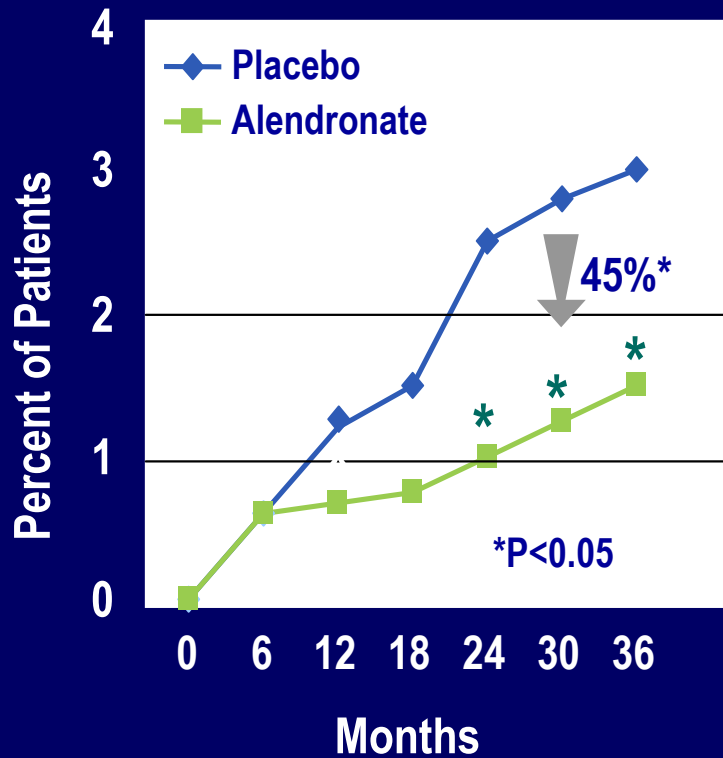
2. Dunford JE, et al. *J Pharmacol Exp Ther*. 2001;296:235-242.



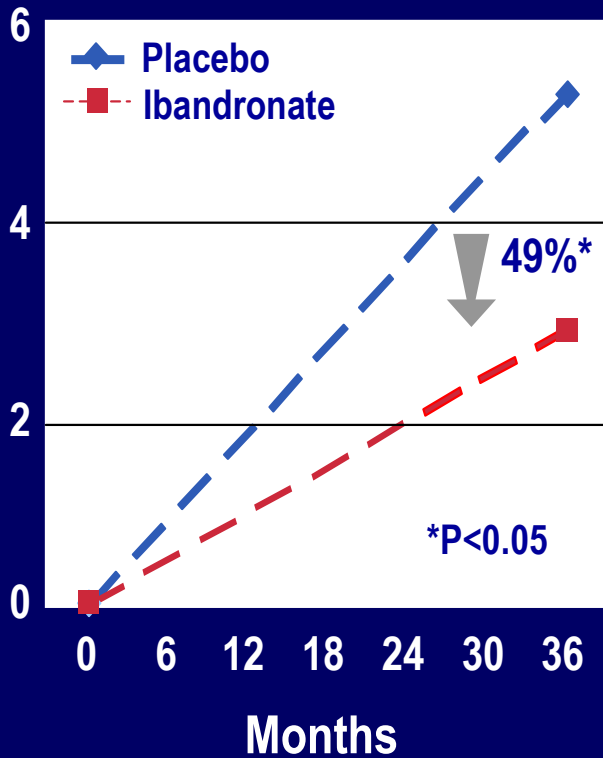
# Time Course: Clinical Vertebral Fractures

*Not head-to-head: studies cannot be directly compared*

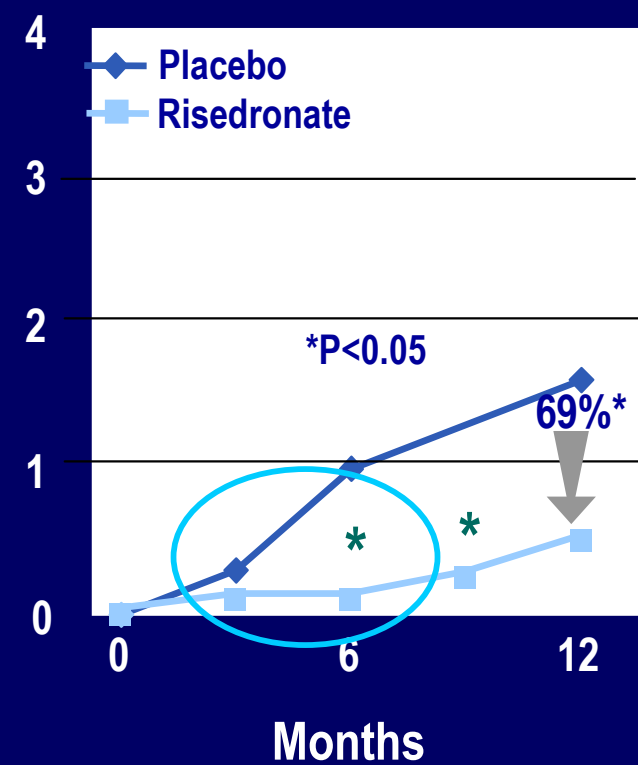
## Alendronate<sup>1</sup>



## Ibandronate<sup>2</sup>



## Risedronate<sup>3</sup>

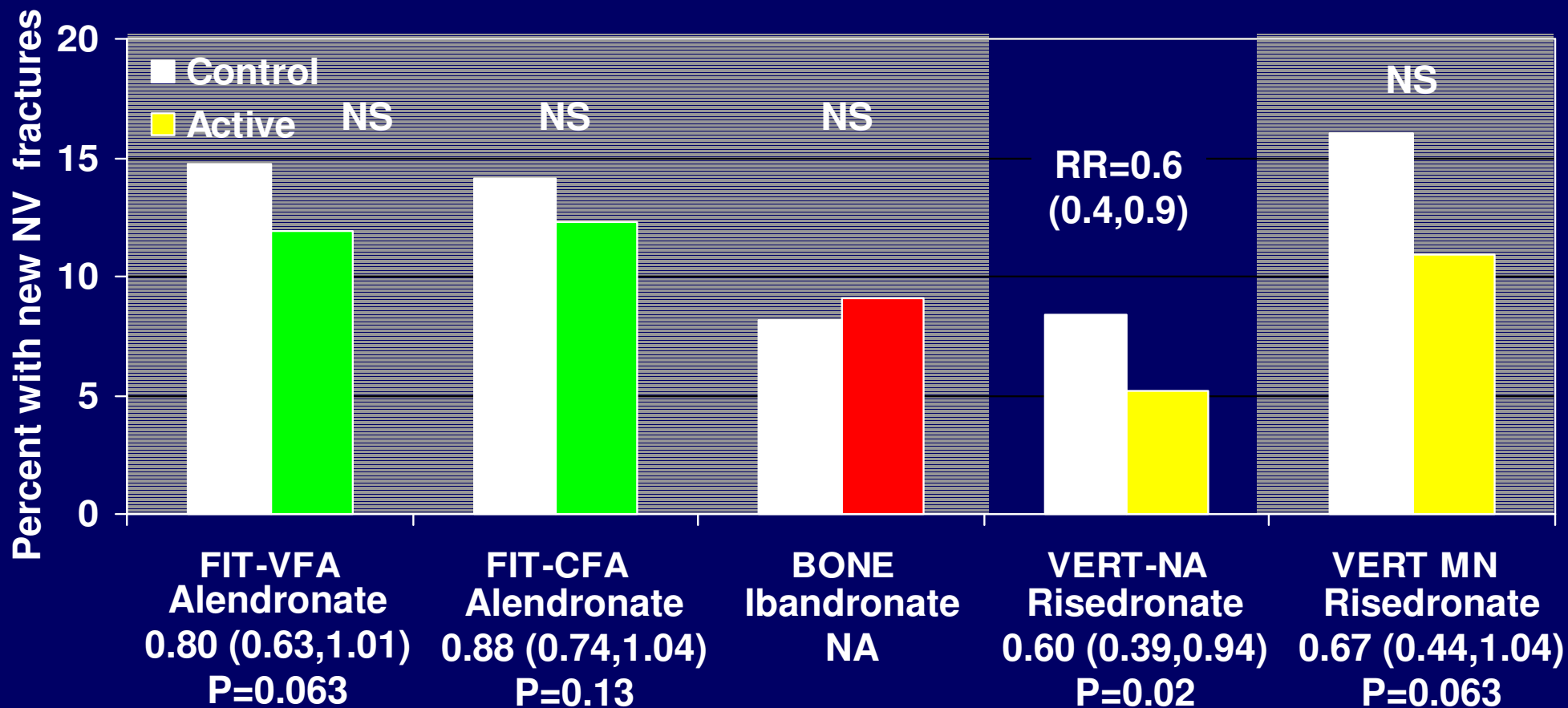


1. Black DM, et al. *J Clin Endocrinol Metabol.* 2000;85:4118-4124.
2. Chesnut CH, et al. *J Bone Miner Res.* 2004;19:1241-1249.
3. Roux C, et al. *Curr Med Res Opin.* 2004;4:433-439.



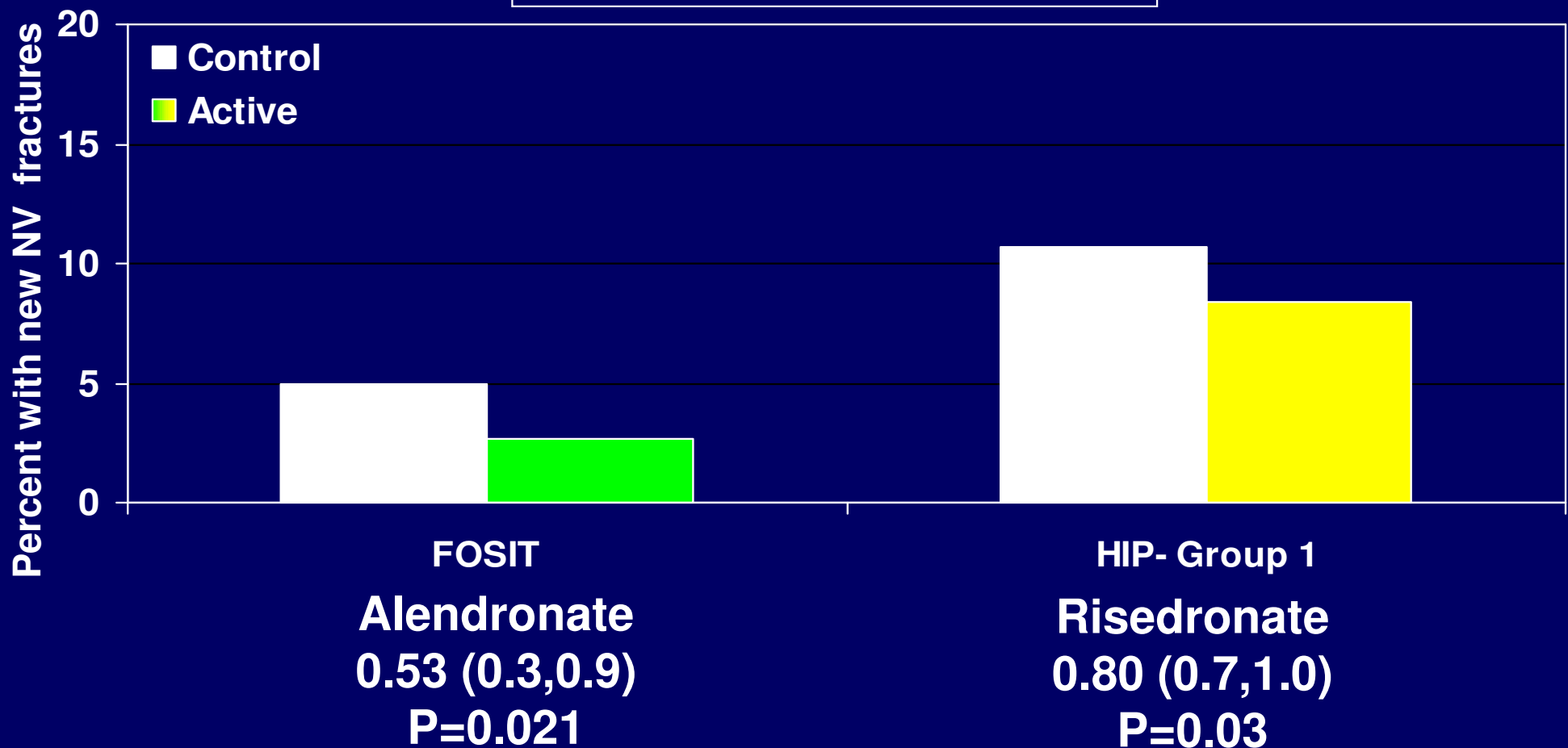
# Non-Vert Fracture Reduction: Data From Pivotal Trials

*NOTE: Not head-to-head trials*



# Non-Vert Fracture Reduction: Data From Other Trials

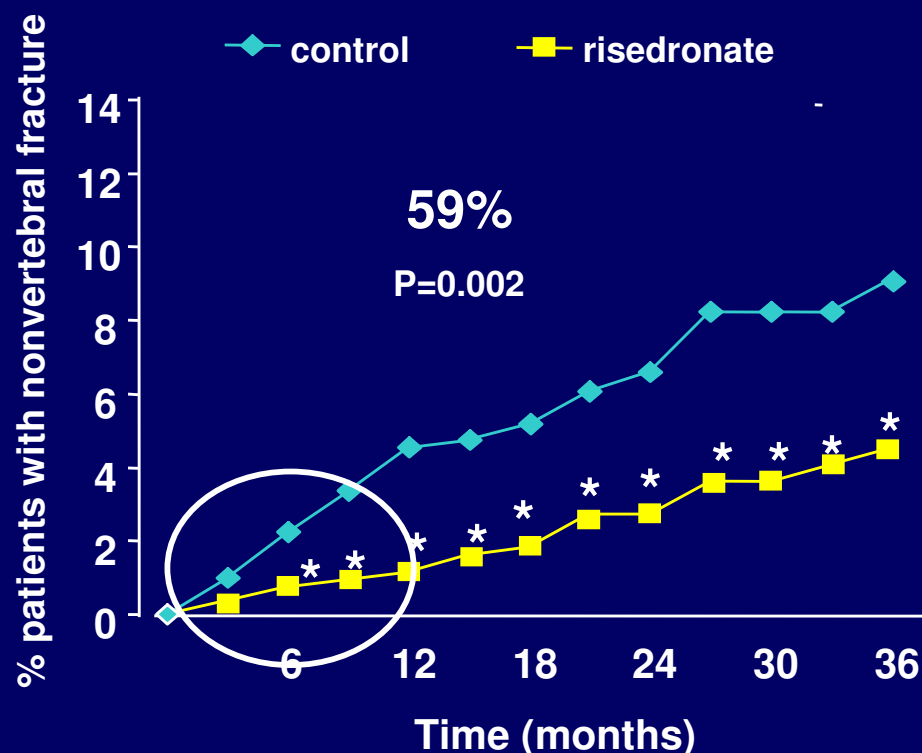
*NOTE: Not head-to-head trials*



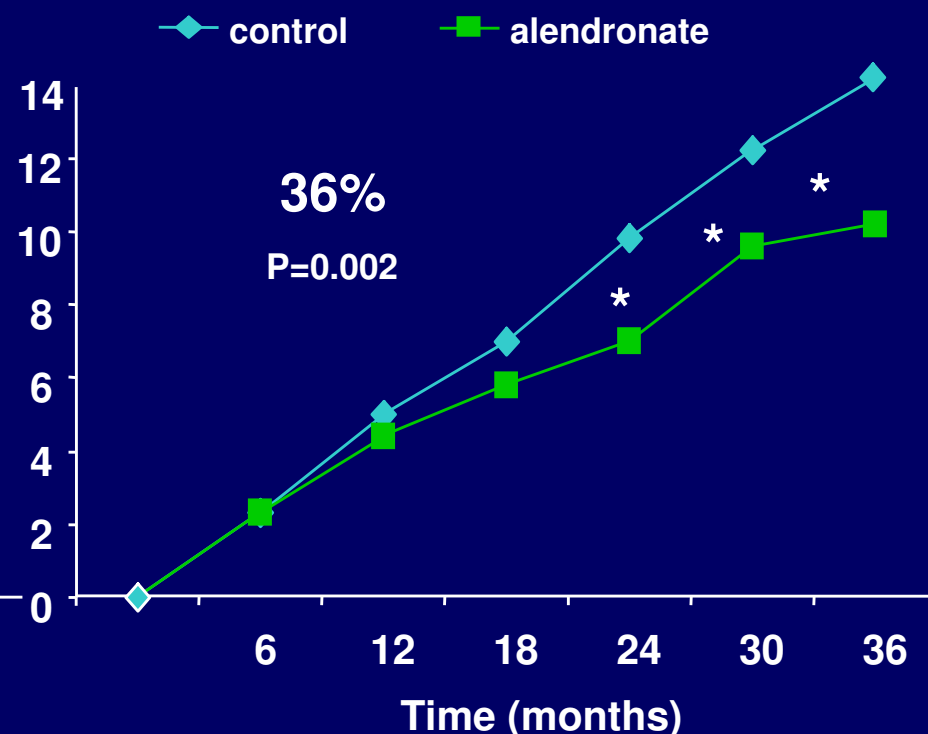
# Bisphosphonate Therapy and Nonvertebral Fracture

## Post-hoc Analyses of Pooled Clinical Trial Data

*Not from a head to head study*



n=1172; Patients with lumbar spine BMD T-score <-2.5. Nonvertebral fractures based on a composite endpoint of the following: clavicle, hip, humerus, leg, pelvis and wrist.



n= 3658; Patients with a baseline vertebral fracture or femoral neck T score of -2.5 or less. Nonvertebral osteoporotic fractures measured as a composite endpoint (sites are not defined).

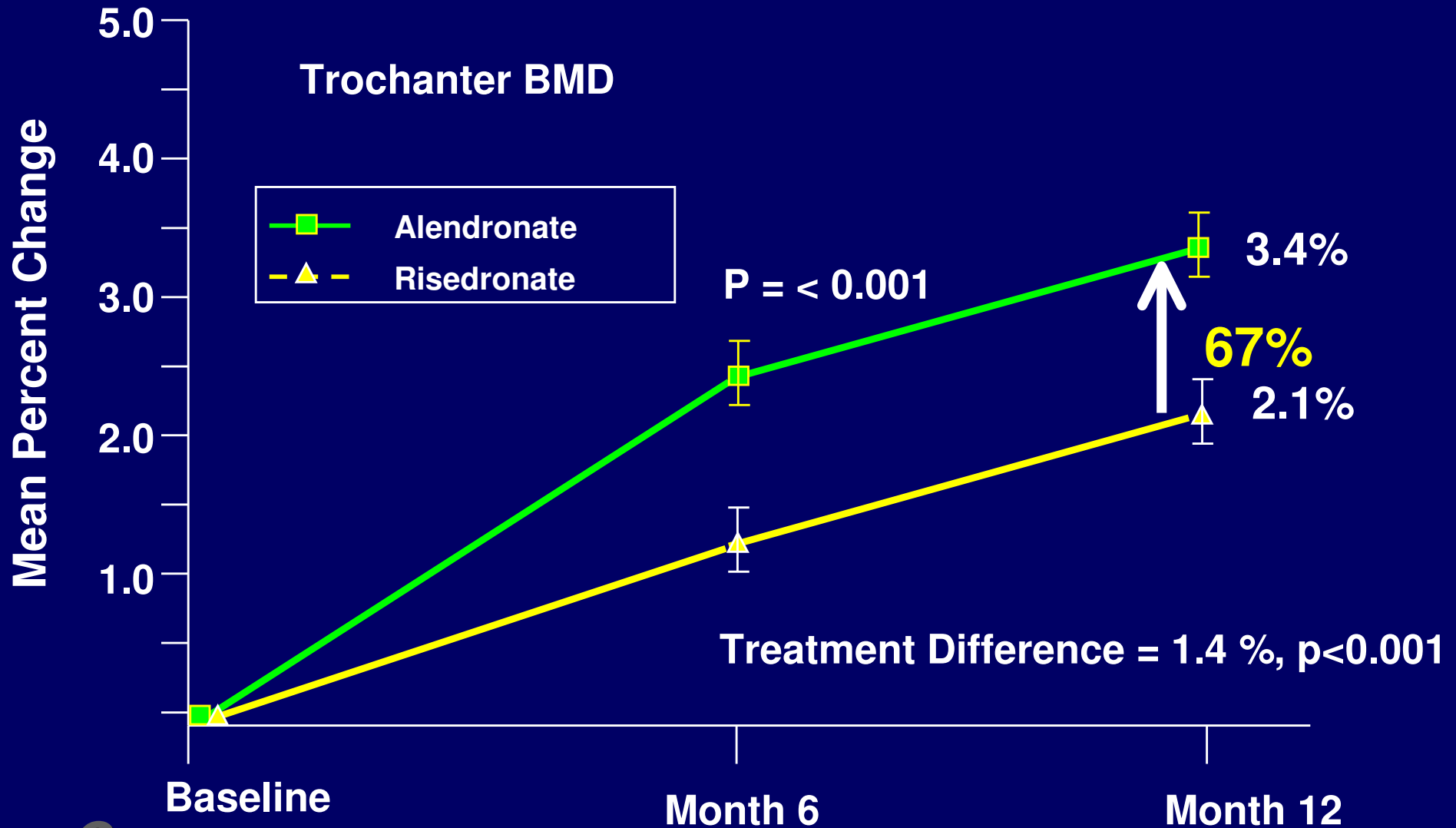


# Head-to-Head Studies

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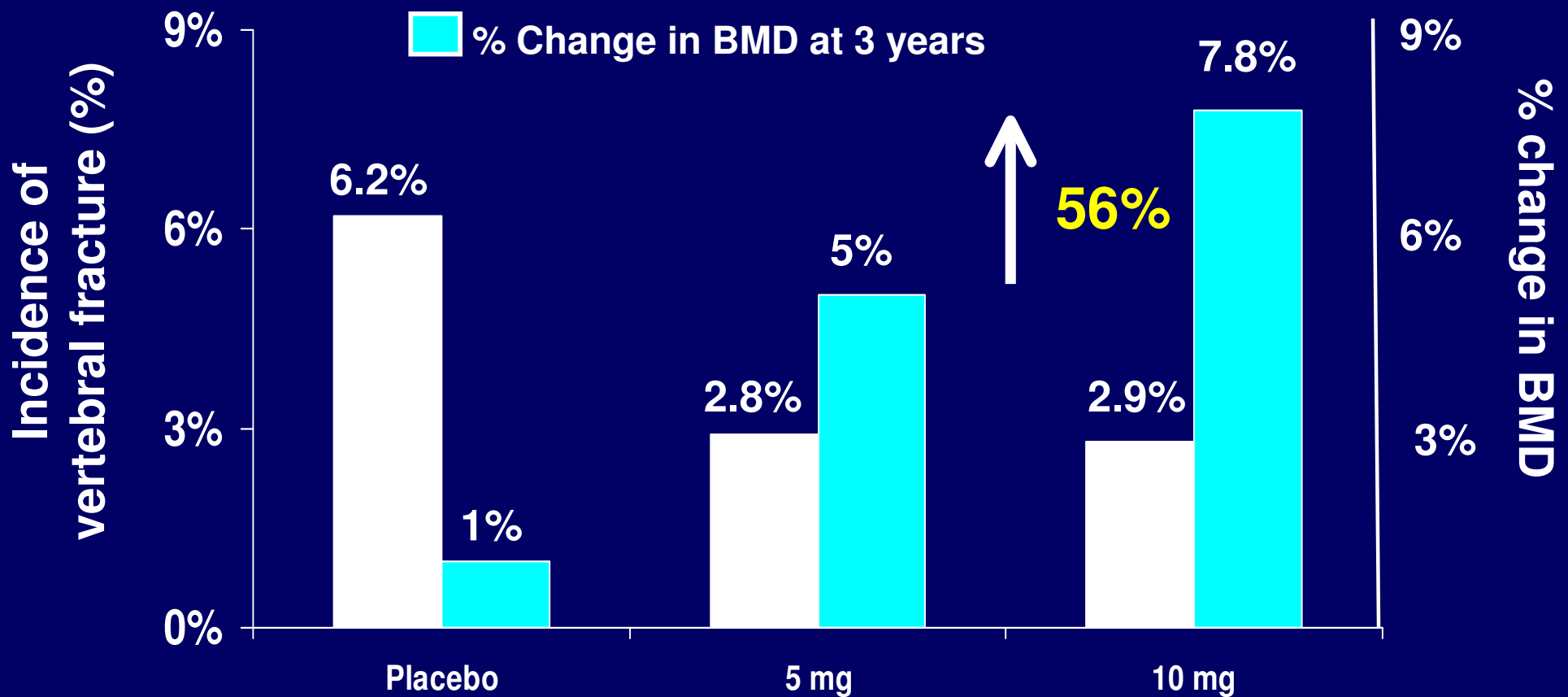
# FACT (2) Trial



# Relationship of BMD Change and Fracture Risk with Alendronate

## Pivotal Phase 3 study

- Incidence of vertebral fracture at 3 years
- % Change in BMD at 3 years



# Head-to-Head Trials

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**There is minimal correlation between changes in BMD in response to treatment and fracture protection.**

**Showing differences in BMD response does not prove difference in effectiveness.**

# Are Bisphosphonates Different?

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## *YES and MAYBE*

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



# Choosing Among Bisphosphonates

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**Do not be persuaded by studies with surrogate endpoints that do not correlate with fracture risk**

**Choose a bisphosphonate with which you have confidence in**

- **Effectiveness**
  - **Reduction in risk of all fractures**
  - **Consistency across several studies**
- **Tolerability**
- **Long-term safety**
- **Experience**

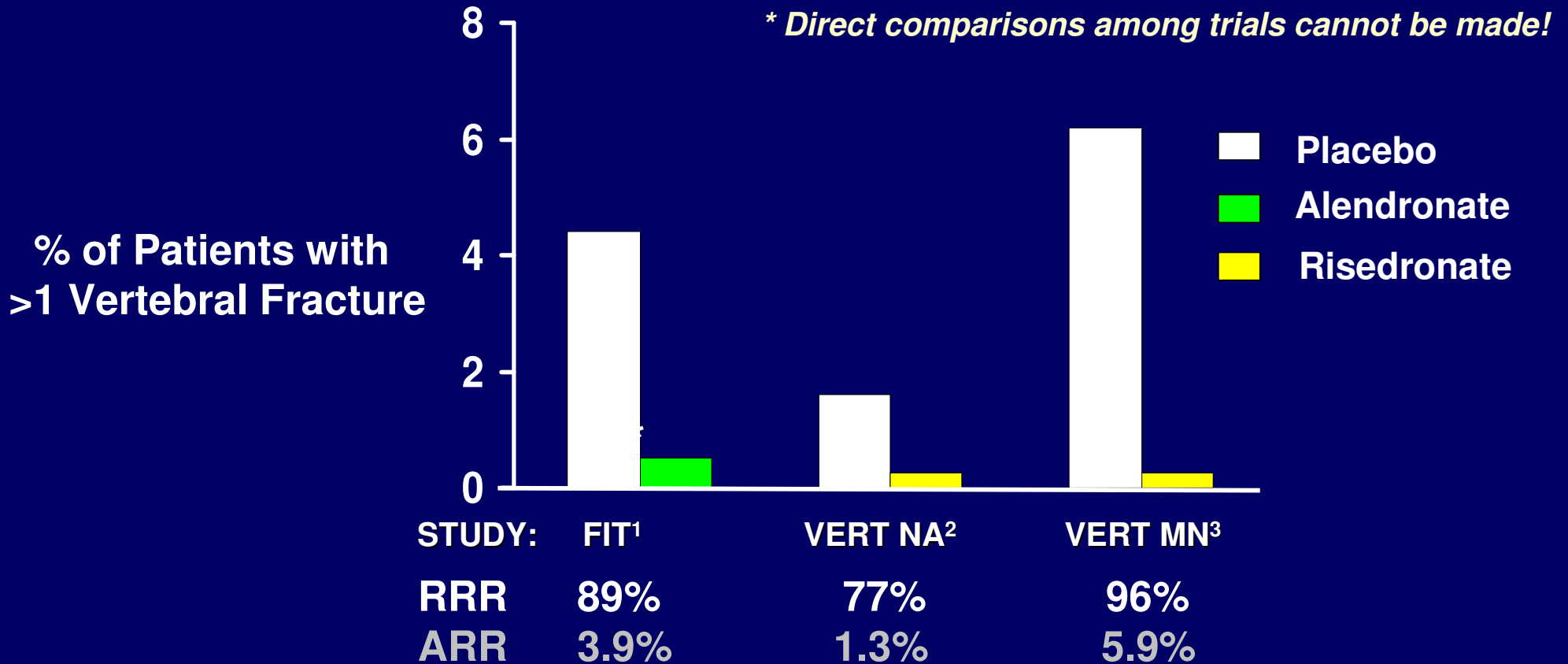
# Bisphosphonates: How Long to Treat?

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- **Pivotal trials demonstrate fracture risk reduction over 3 years with bisphosphonate therapy**
- **Spine fracture:**
  - **60-65% at 1 year**
  - **40-50% at 3 years**
- **Hip fracture**
  - **40-59% at 3 years**
- **Non-vertebral fracture**
  - **30-40% at 3 years**

# Therapy Interrupts Cycle of Multiple Vertebral Fractures

Patients: Low BMD and prevalent vertebral fracture



<sup>1</sup>Black DM, et al. *Lancet*. 1996;348:1535

<sup>2</sup>Harris ST, et al. *JAMA*. 1999;282:1344

<sup>3</sup>Reginster J, et al. *Osteoporos Int*. 2000;11:83-91.



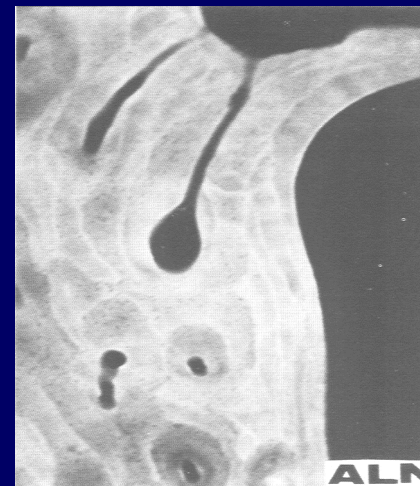
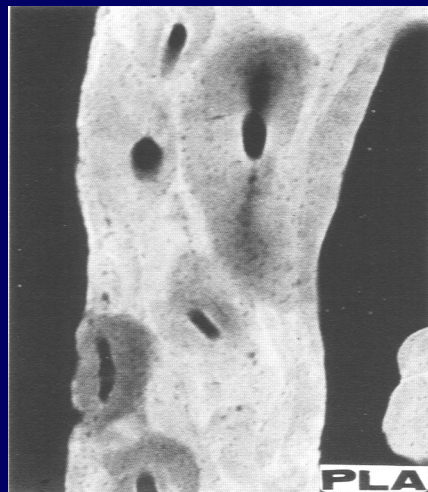
# Bisphosphonates: Reasons to Stop Therapy

## - Concern About Long-term Safety

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- **Accumulate in the skeleton; theoretical concern about long-term therapy**
  - **Increase number of "micro-cracks"**
  - **Increase in tissue mineralization Boivin 2000**

**MICRORADIOGRAPHS OF CORTICAL BONE**



# **Bisphosphonates: Reasons to Stop Therapy - Concern About Long-term Safety**

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- **Accumulate in the skeleton; theoretical concern about long-term therapy**
  - **Increase number of "micro-cracks"**
  - **Increase in tissue mineralization** Boivin 2000
- **Anecdotal concerns about long-term safety in patients**
  - **Non-healing unusual fractures** Odvina 2005
  - **Sub-trochanteric fractures (5/9 were on alendronate)** Goh 2007

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

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- 9 patients reported slow healing nonvertebral insufficiency fractures
  - Alendronate therapy for 3-8 years in standard doses
  - Fractures of sacrum, rib, pelvis, femoral shaft
  - Re-fracture of femur in patients on GC
  - 3 took ERT
  - 2 took glucocorticoids
  - Bone biopsy: low osteoclastic activity and absent osteoblastic activity
  - NTX-u: 8-54 units (reference 5-65)



# **Bisphosphonates: Reasons to Stop Therapy - Persistent Benefit After Stopping**

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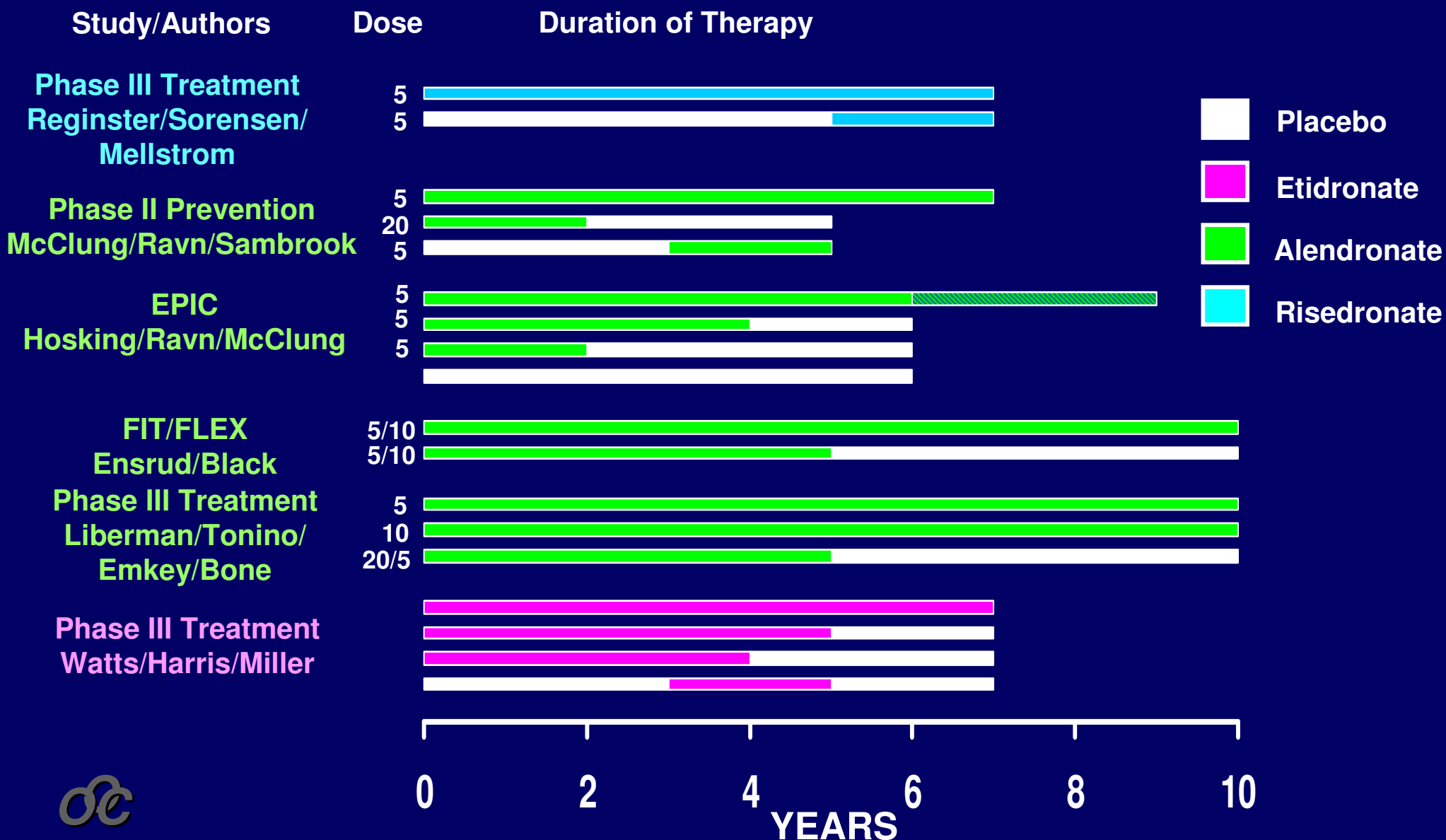
- **BMD remains stable or decreases slowly when therapy is stopped**
- **Markers remain suppressed (compared to untreated subjects) when alendronate is stopped**

# Bisphosphonates: When or Whether to Stop?

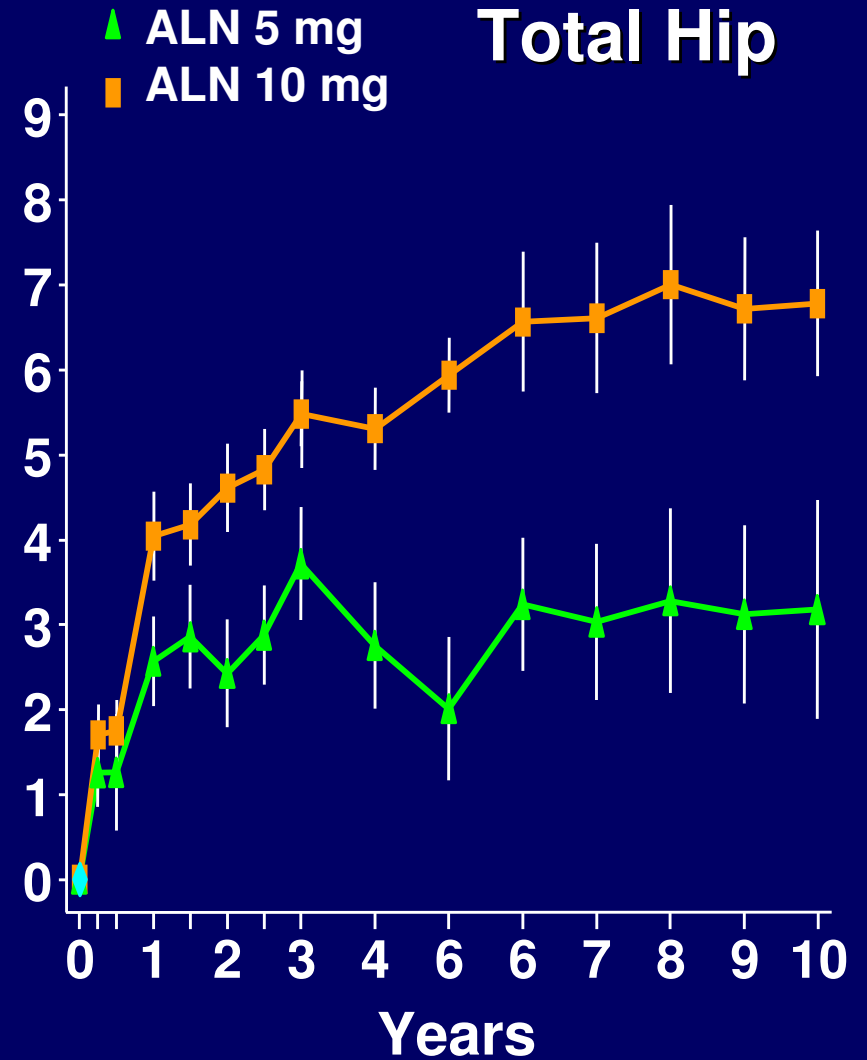
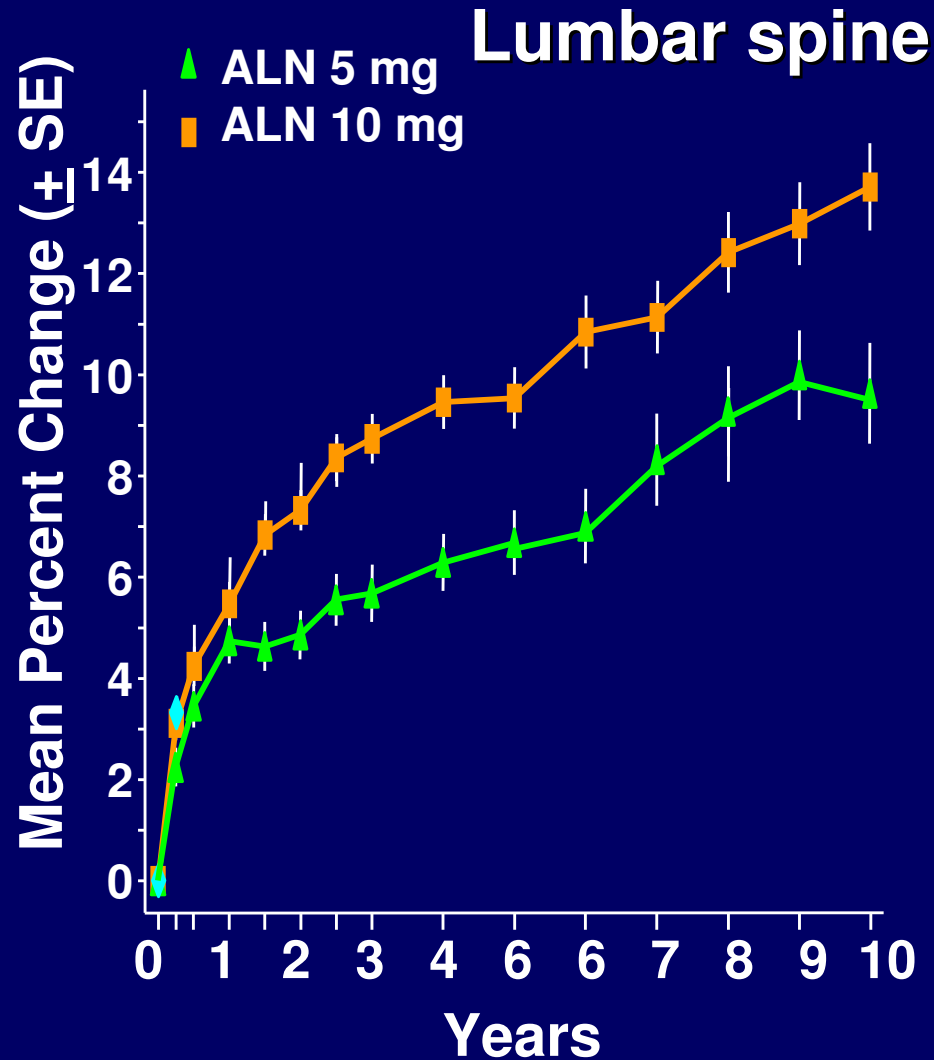
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- To address these issues we need to know
  - What happens with long-term administration?
    - efficacy
    - safety
  - What happens when treatment is stopped?
    - fracture rates

# Clinical Trials of 5 Years or Longer: Study Arms

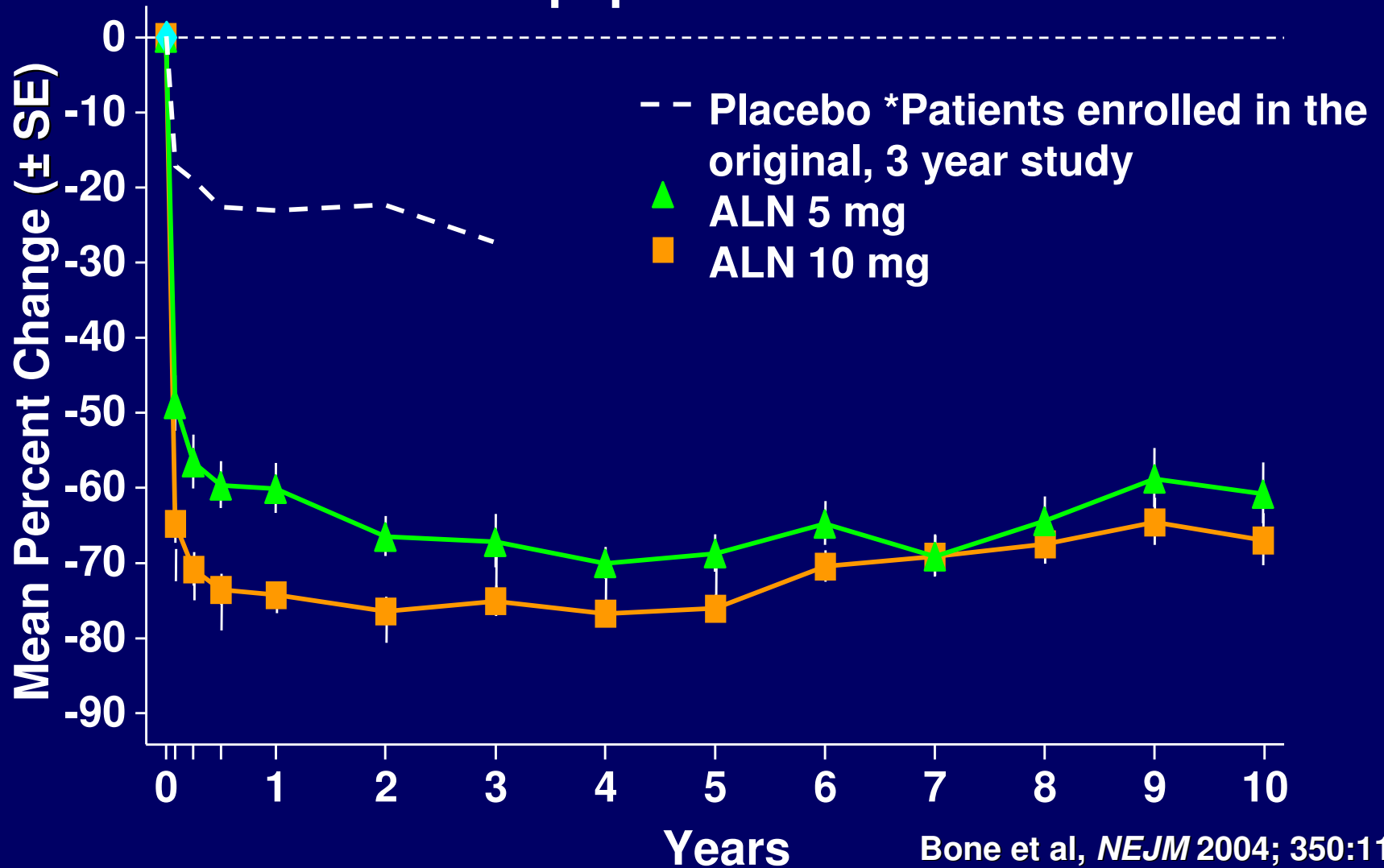


# Long-term Alendronate Therapy



# Long-term Alendronate Therapy

## Urine N-telopeptide



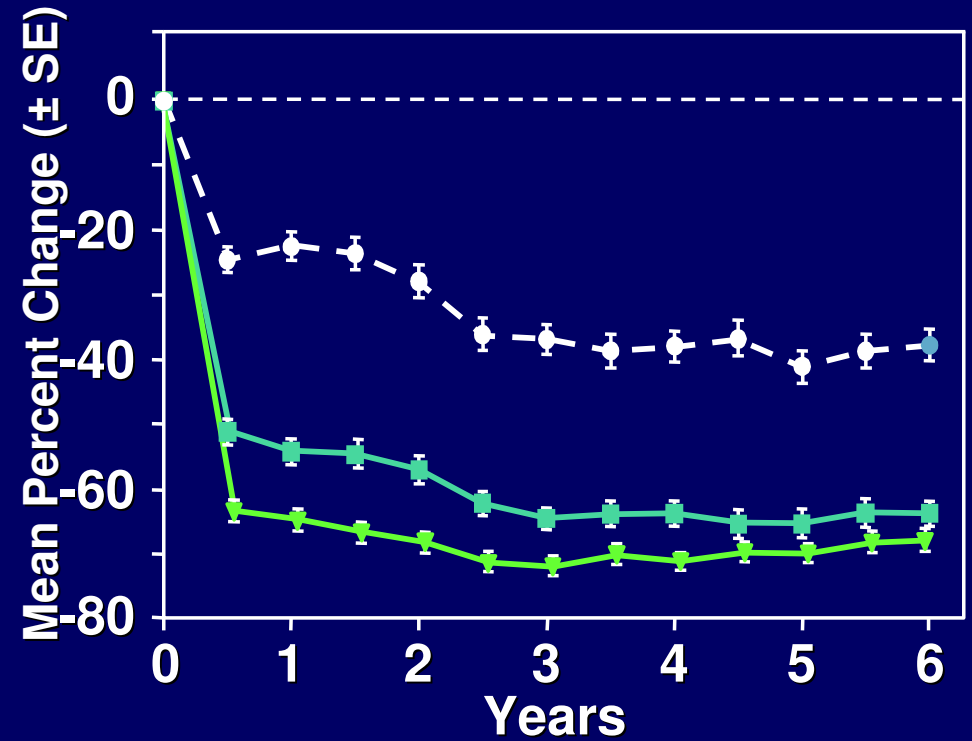
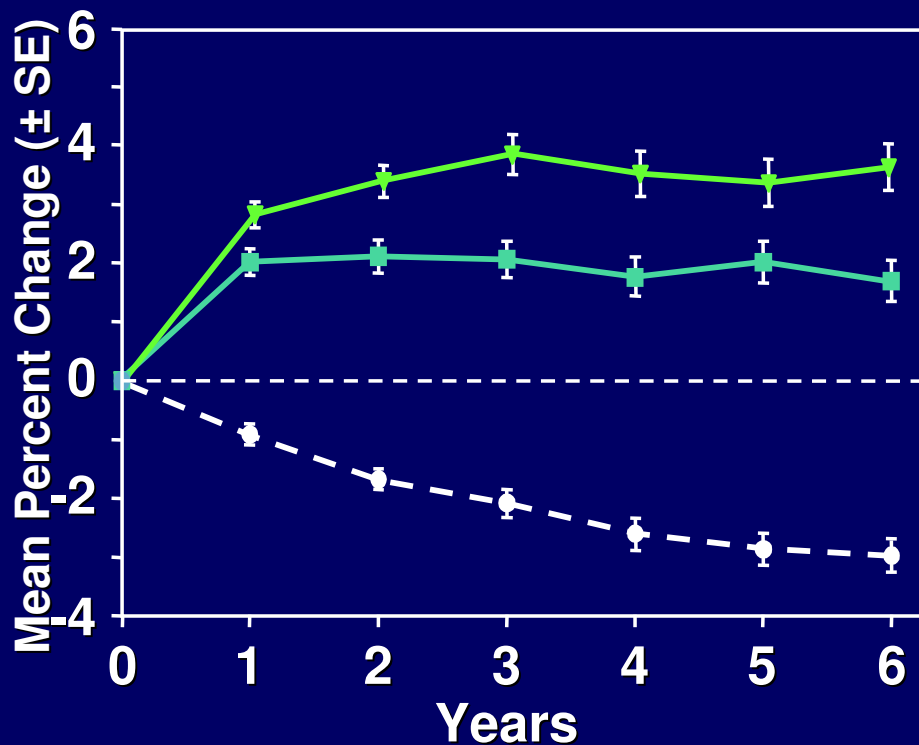
# EPIC: 6 Years

1609 women ages 45-59

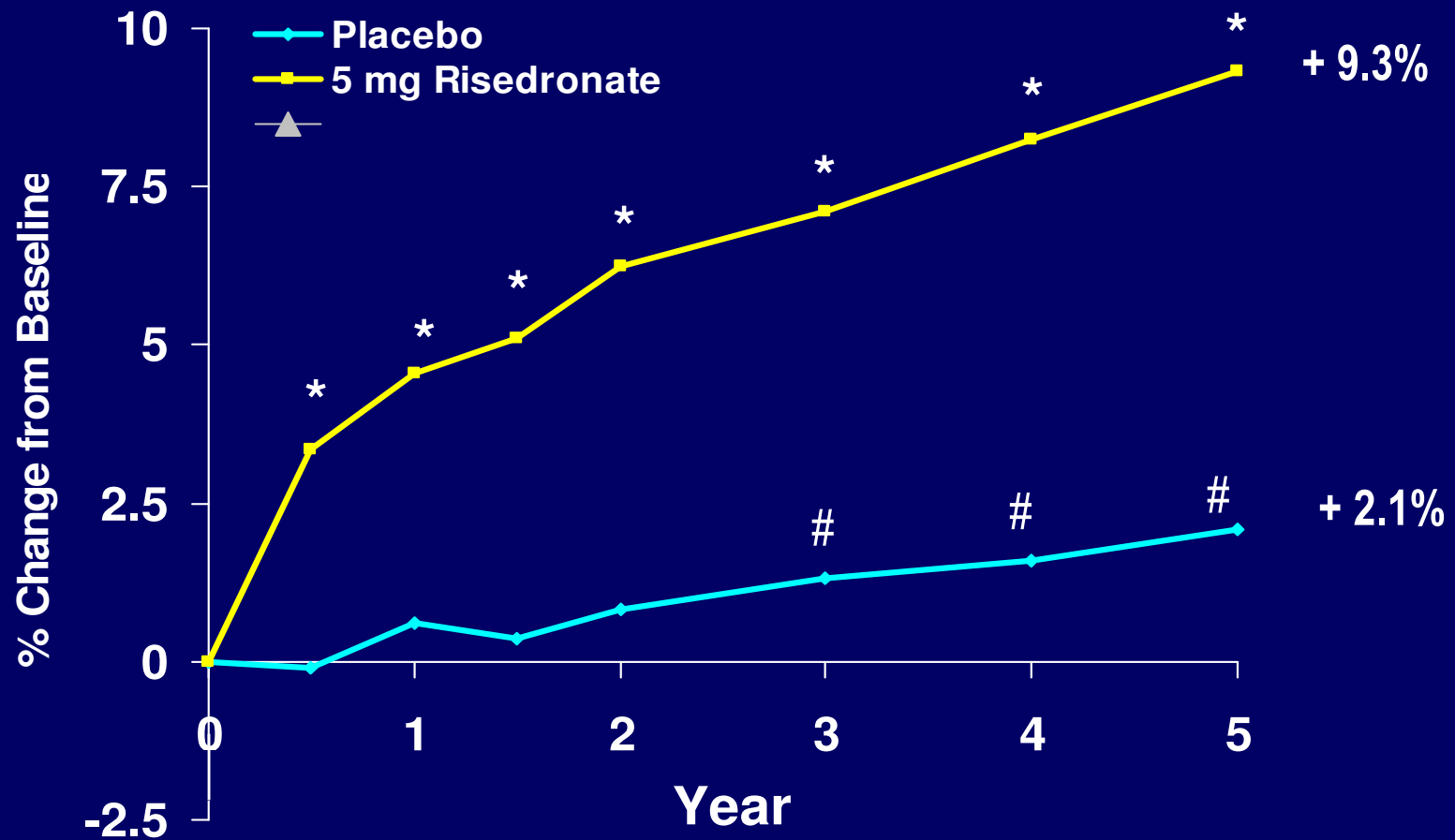
## Lumbar Spine BMD

## Urine N-TX/Cr

● PBO   ■ ALN 2.5 mg   ▼ ALN 5 mg



# Risedronate: Lumbar Spine BMD



\* p < 0.05 vs baseline and placebo.

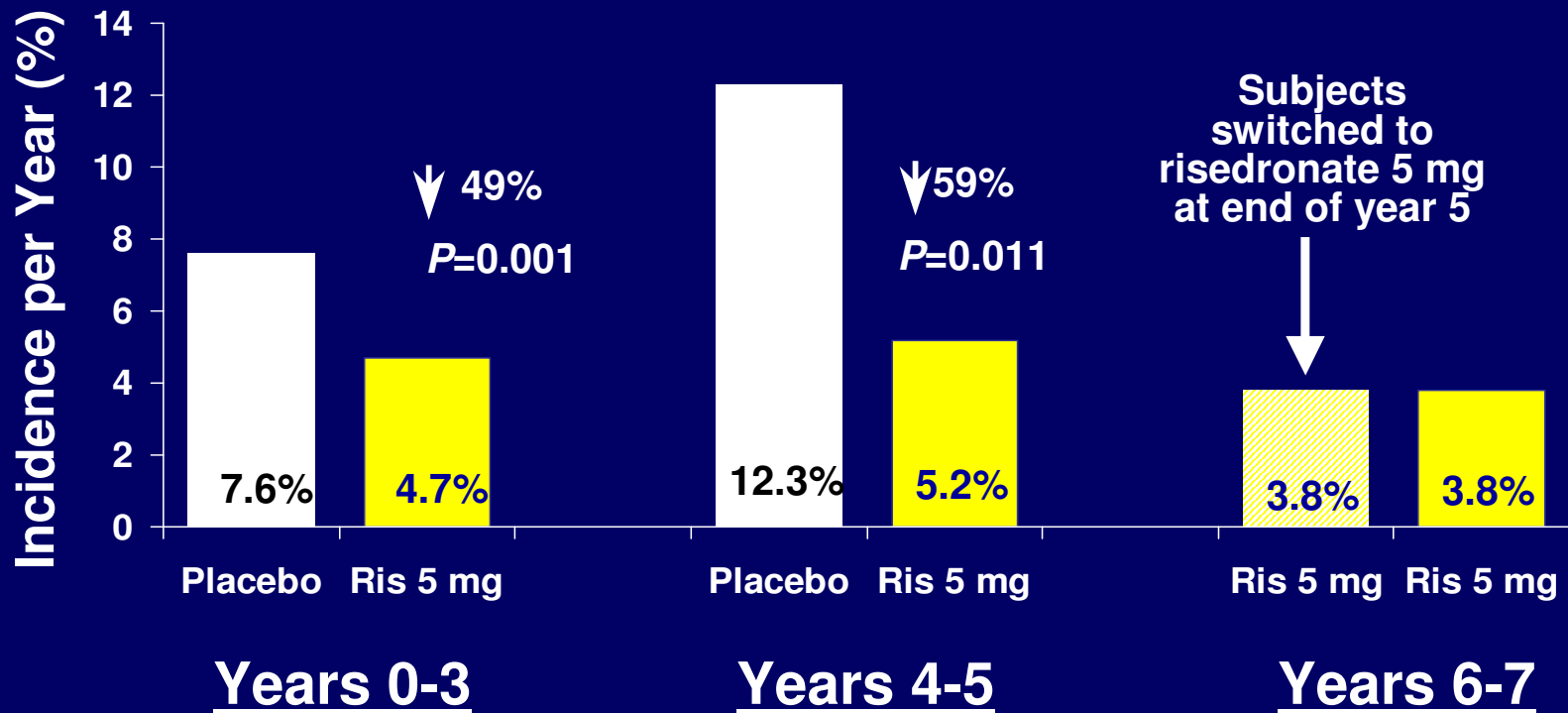
# p < 0.05 vs baseline.

Sorensen et al, *Bone* 2003



# Vertebral Fracture Risk on 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.



# Zoledronic Acid: Intravenous Dosing

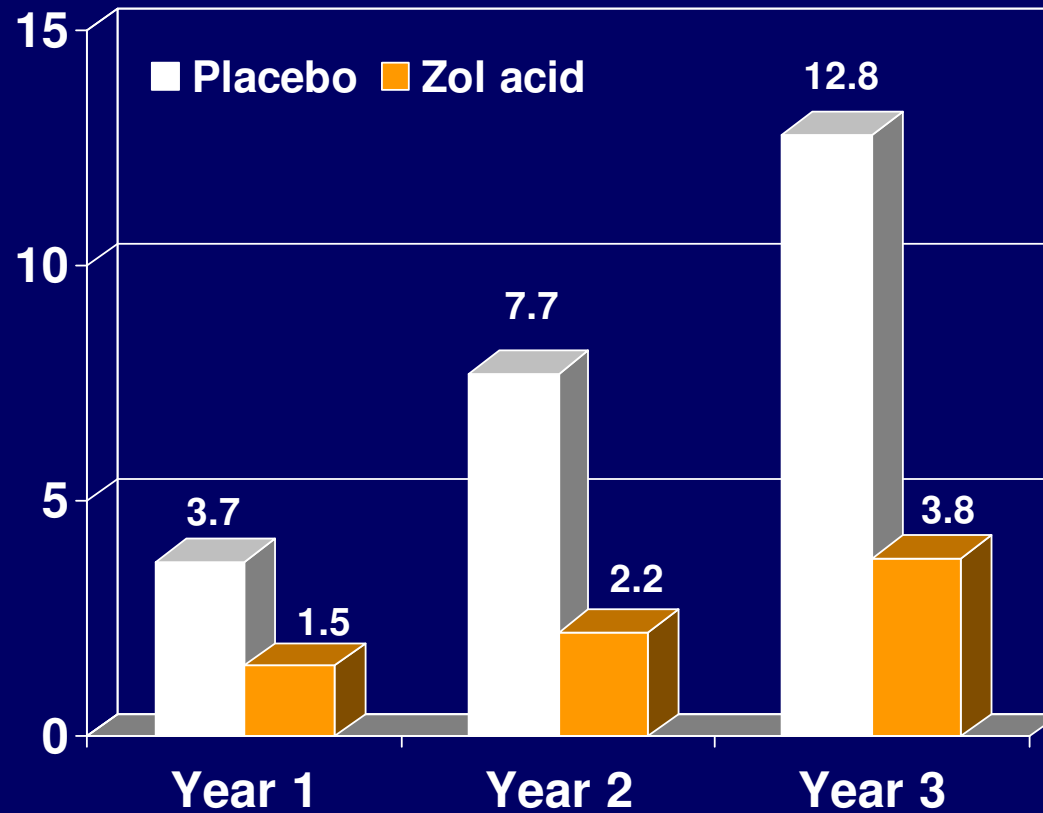
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- 7736 postmenopausal women age 65-89 (mean 73.1)
- T-score -  $\leq -2.5$  at lumbar spine (73%) or  
-1.5 to -2.5 with no more than one moderate or 2 mild vertebral deformities (fractures in 63%)
- No bisphosphonates x 2 years (15% prior use)
- Could take estrogen, SERMs or calcitonin (21%)
- All received 1000 mg calcium + vitamin D
- Randomly assigned to receive
  - Placebo
  - Zoledronic acid 5 mg IV once yearly for 3



# Zoledronic Acid: Effect on Vertebral Fractures

Incidence (%) of  
new vertebral  
fractures



Rel risk reduction : 60%

71%

70%

Conf interval: 43-72%

61-78%

62-76%



# Zoledronic Acid: Fracture Reduction

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<u>FRACTURE</u>	<u>Placebo</u>	<u>Zol acid</u>	<u>RRR</u>	<u>CI</u>	<u>p value</u>
Hip	2.5%	1.5%	40%	15,57	0.0032
Non-vertebral	10.8%	7.6%	25%	13,36	0.0002
Clinical vertebral	2.5%	0.6%	75%	60,85	<0.0001

No difference by BMD, prior fracture or use of other drugs



# Zoledronic Acid: Intravenous Dosing

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- **Decrease NTX by 70-80% with return to 60-70% below baseline at 12 months**
- **Pattern of reduction in turnover markers the same with subsequent doses**

## ***SAFETY:***

- **Acute phase reaction symptoms in about 10%**
- **No renal toxicity noted**
- **ONJ: 1 subjects receiving placebo and in 1 on zol acid**

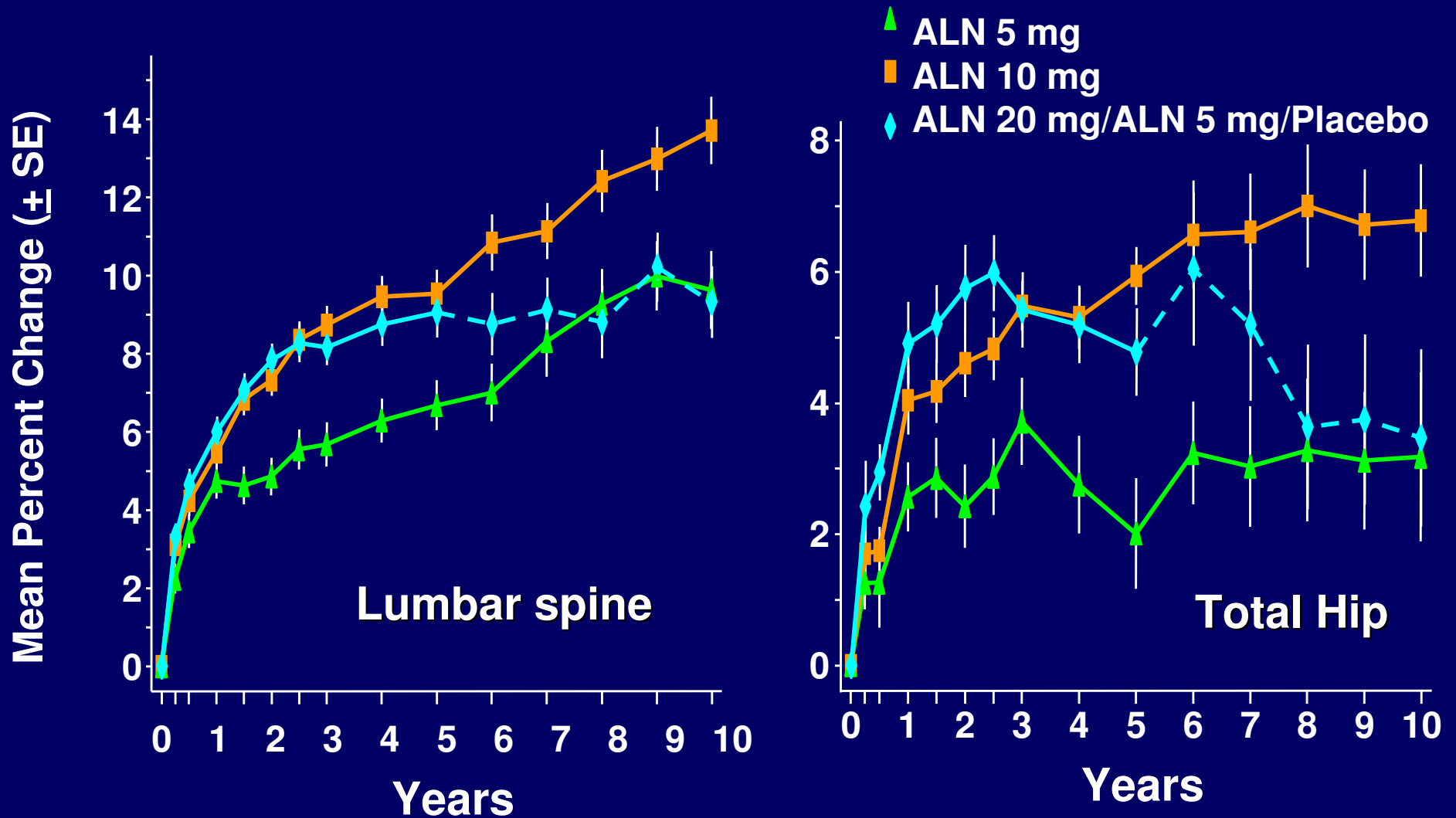


# Bisphosphonates: Long-term Therapy

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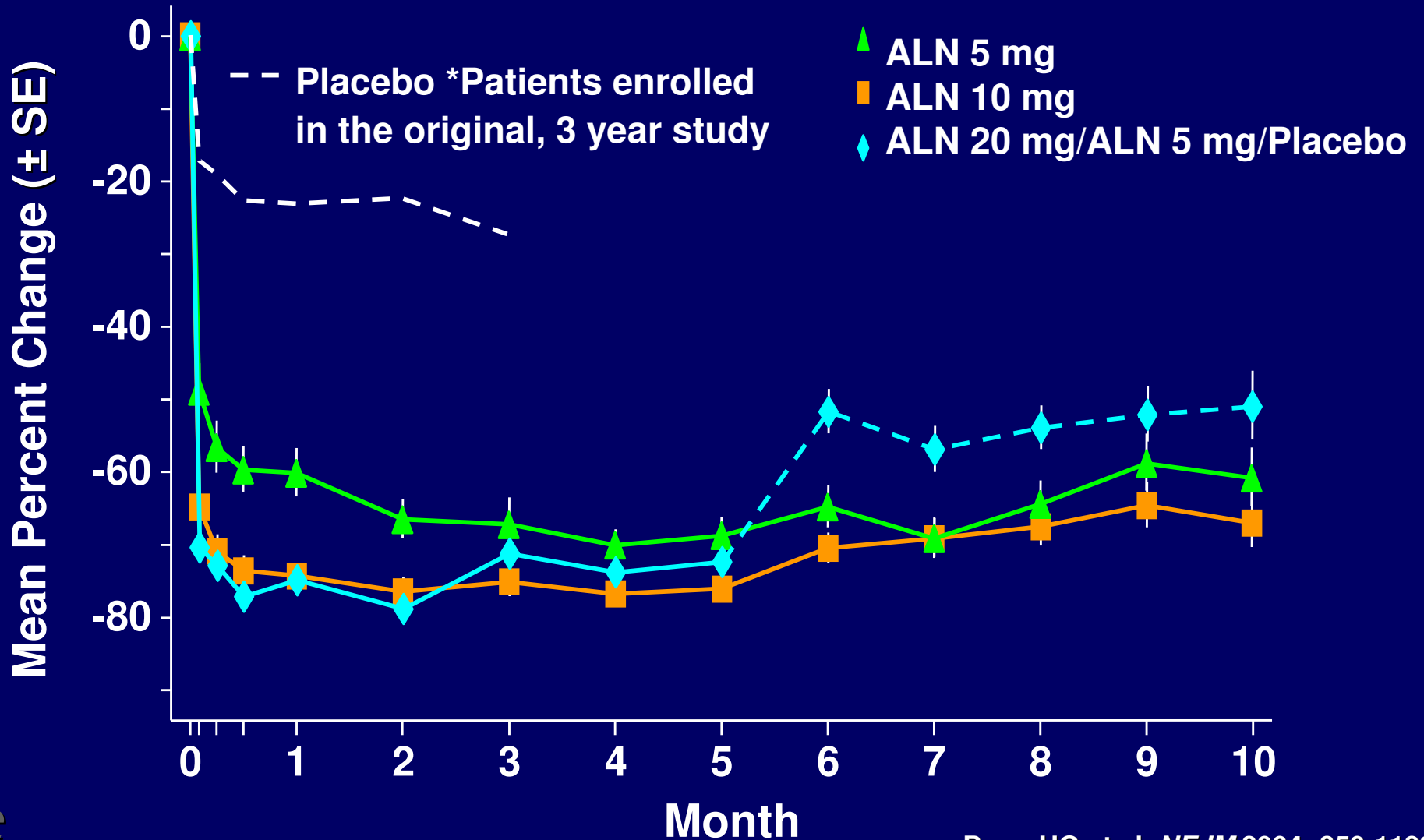
- **Persistent but not progressive inhibition of bone turnover (markers and bone biopsy)**
- **BMD increase is maintained (hip) or progressive (spine)**
- **No evidence of waning of effects**
- **Fracture risk reduction seems to persist**
- **No new side effects with long-term therapy**
- **No suggestion of adverse skeletal effect**

# Stopping Alendronate Therapy



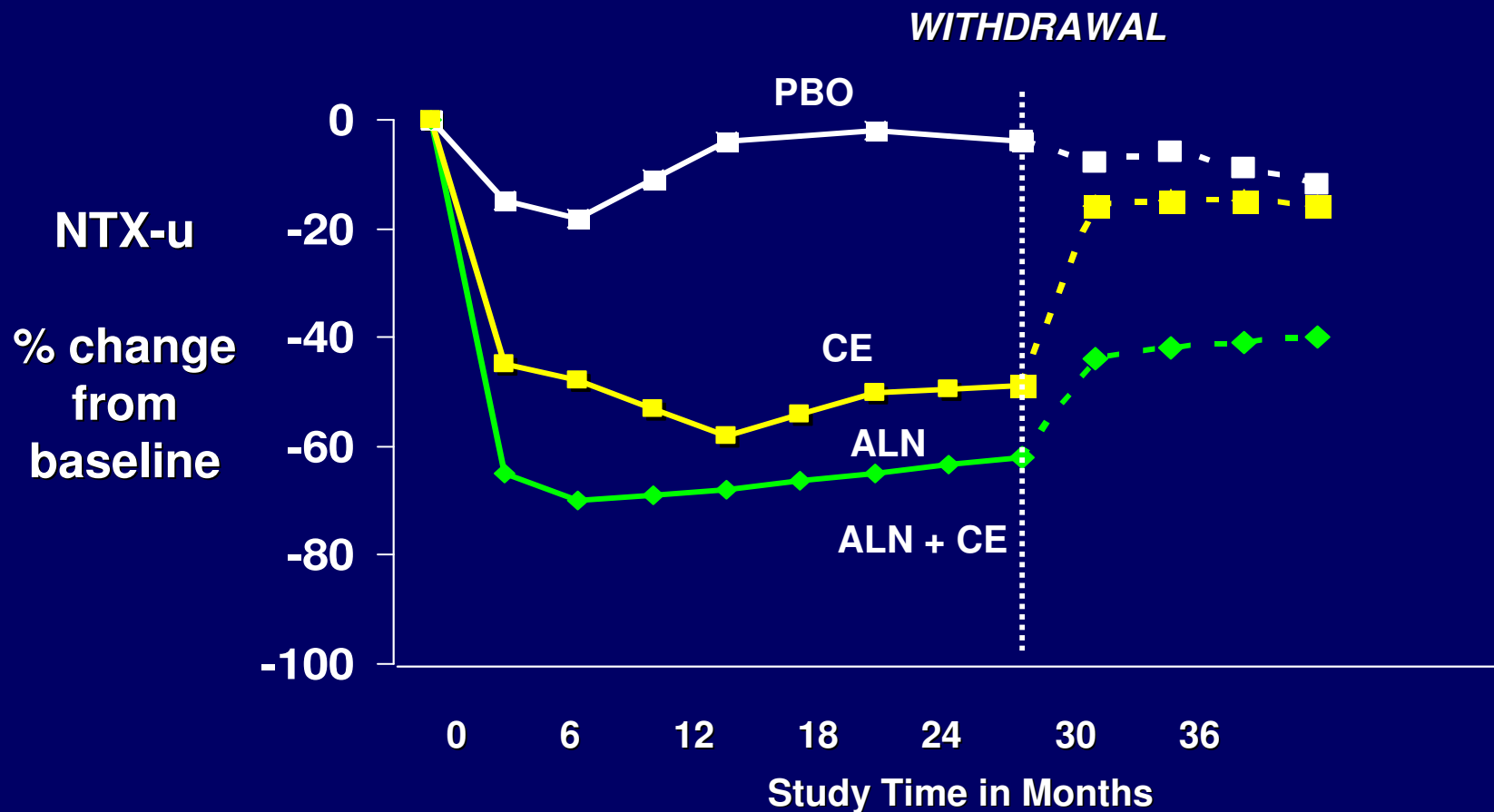
# Stopping Alendronate Therapy

## Urinary N-telopeptide



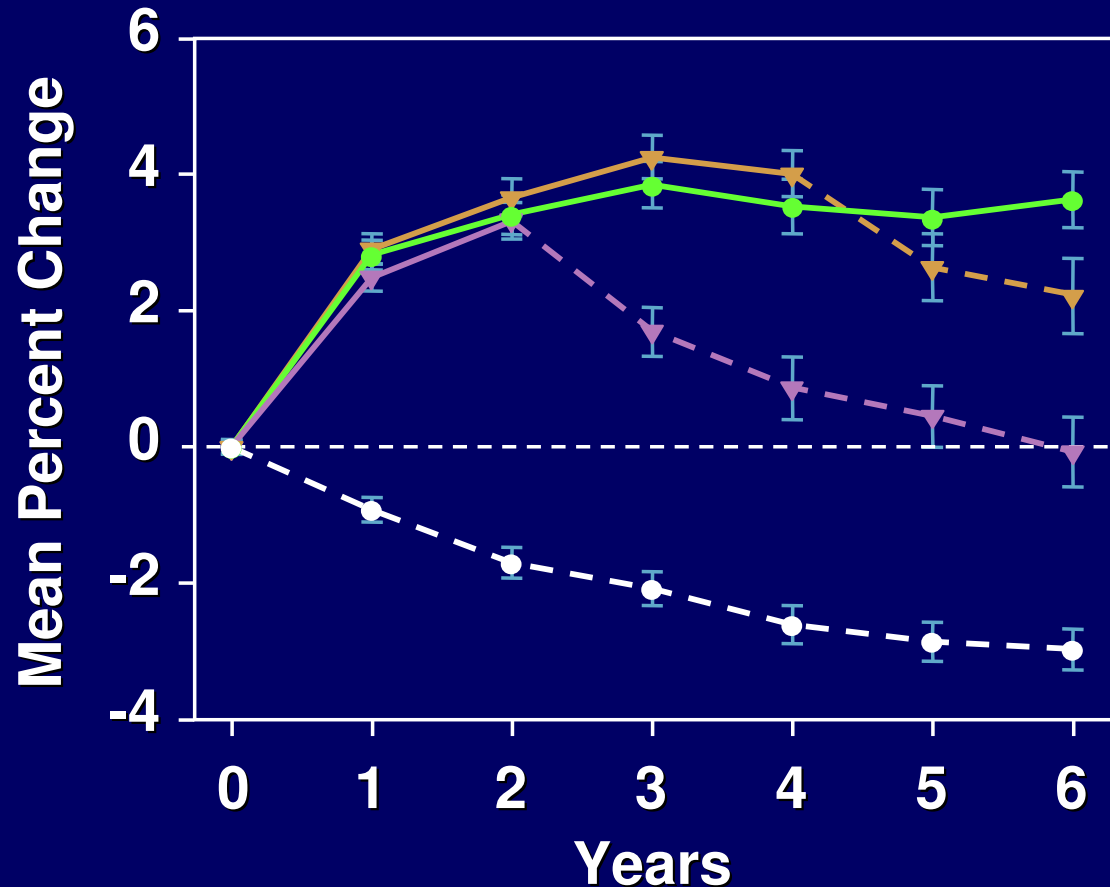
# NTX-u: Stopping Alendronate Therapy

Postmenopausal women with low BMD



# Effect of Withdrawing Alendronate: Lumbar Spine BMD: Mean Percent Change ( $\pm$ SE)

Women between ages 45-59



—●— PBO for 6 yr

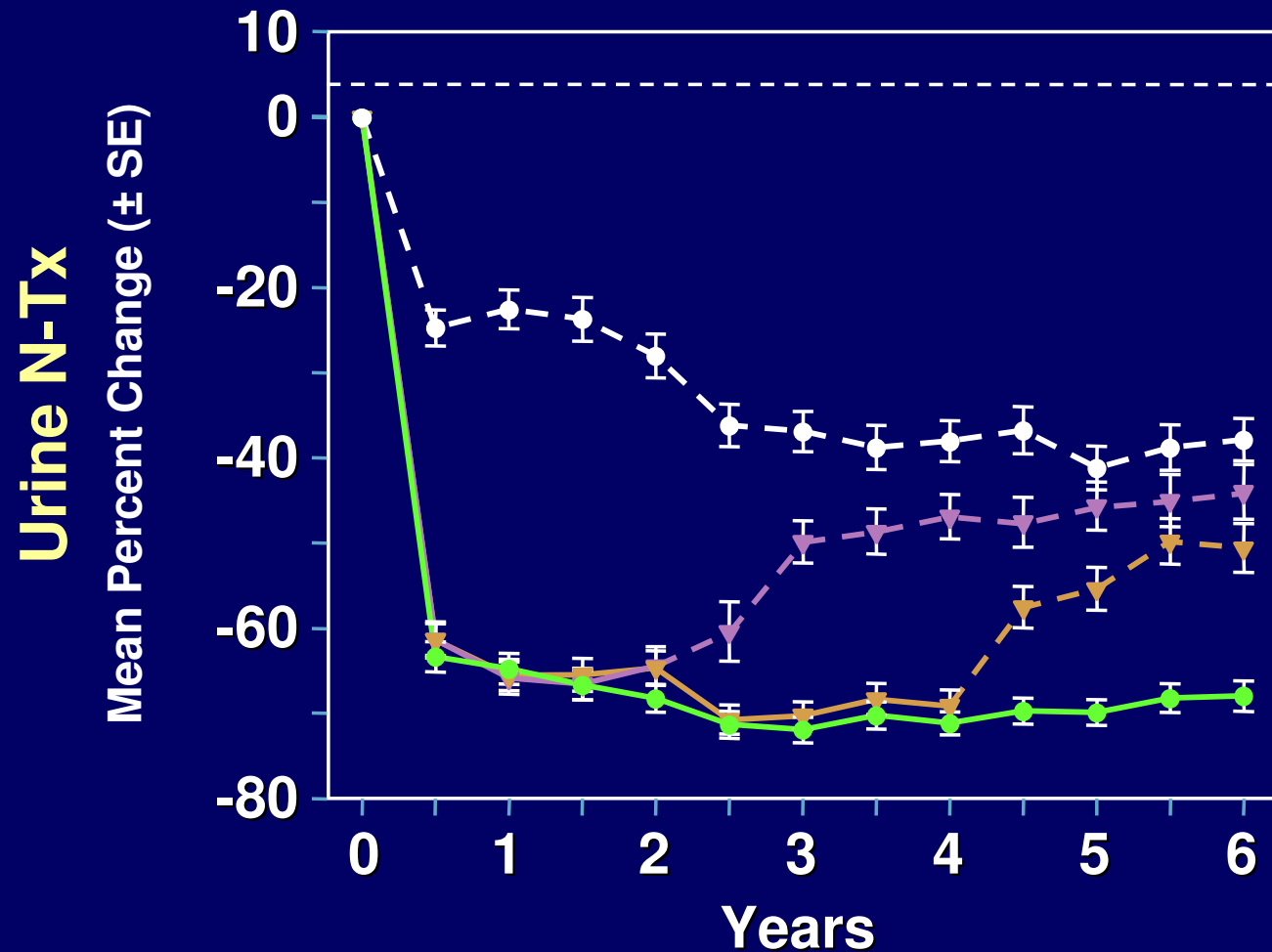
—●— ALN 5 mg for 6 yr

—▲— ALN 5 mg for 4 yr followed by PBO for 2 yr

—▲— ALN 5 mg for 2 yr followed by PBO for 4 yr



# Effect of Withdrawing Alendronate:



—●— PBO for 6 yr

—●— ALN 5 mg for 6 yr

—▲— ALN 5 mg for 4 yr followed by PBO for 2 yr

—▼— ALN 5 mg for 2 yr followed by PBO for 4 yr



# Alendronate: Withdrawal of Treatment

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- **Markers of bone turnover increase toward but not to baseline**
- **BMD decreases in hip; decreases or remains stable in spine**
- **No “catch-up” loss**
- **Little information about fracture risk, but a suggestion that fracture risk reduction persists upon withdrawal of treatment**

# Bisphosphonates: When or Whether to Stop?

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- To address these issues we need to know
  - What happens with long-term administration?
    - efficacy
    - safety
  - What happens when treatment is stopped?
    - fracture rates

# Fractures after Bisphosphonate Withdrawal

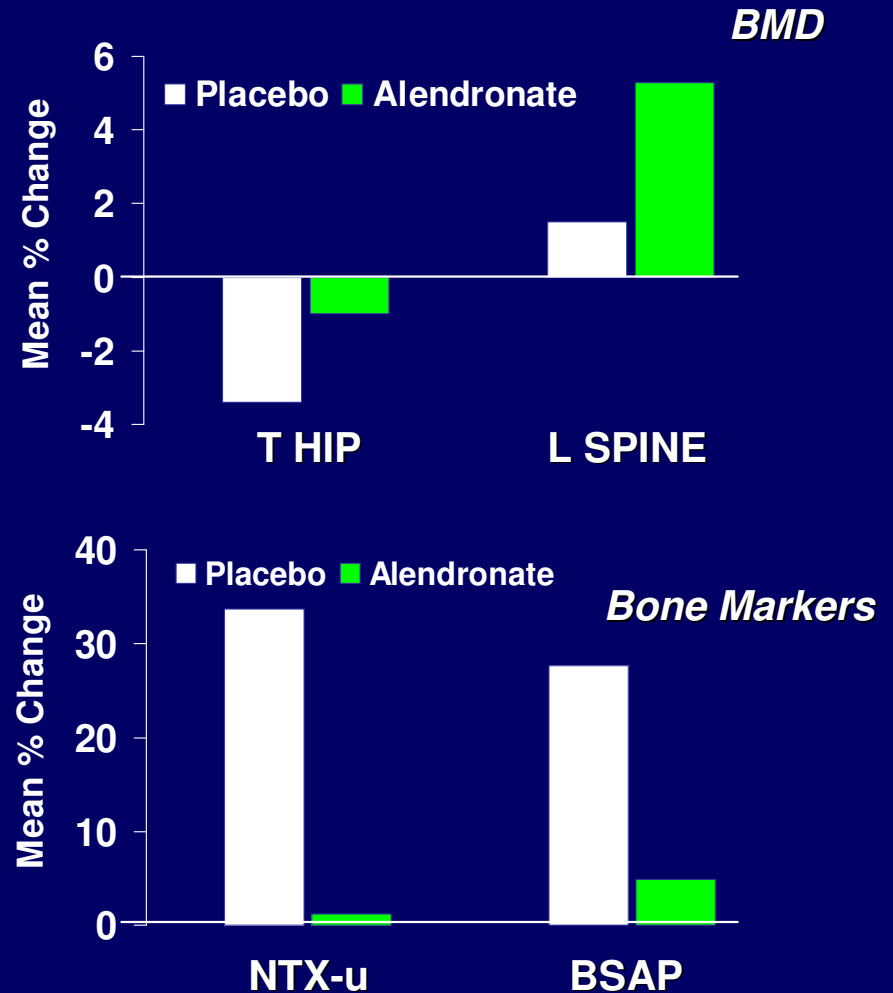
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- **FLEX: 5 year extension of FIT**
- **Treatment for 3-6 years (avg 5); then randomized to alendronate 10 mg daily or placebo for next 5 years**



# FLEX: Alendronate 5 Years Followed by Withdrawal or Continued Treatment

1099 women who completed FIT on alendronate for 3-6 years (mean 5) with T-scores >-3.5 randomly assigned to receive placebo or alendronate 5 or 10 mg daily for 5 additional years



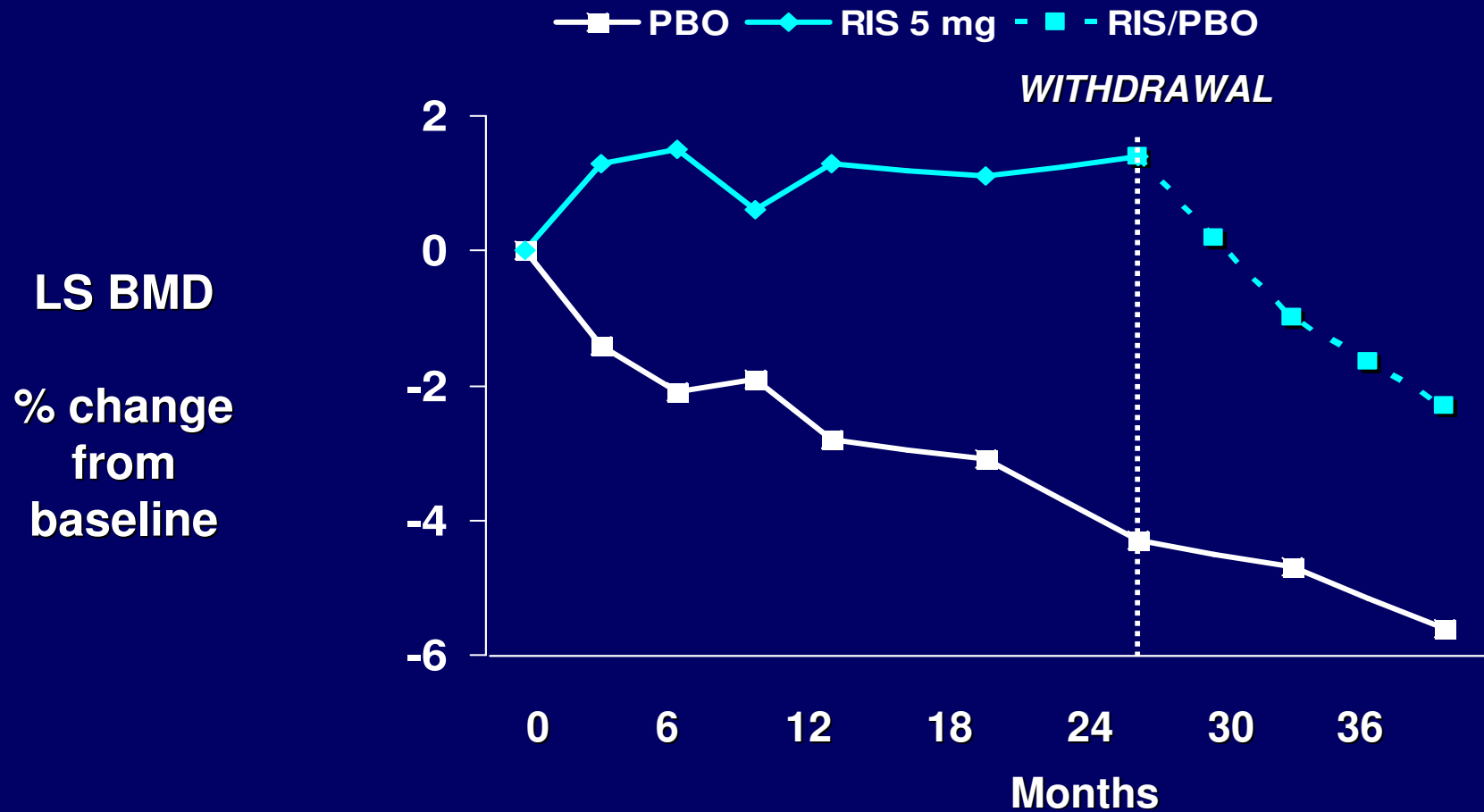
# FLEX: Fractures

## Fracture Risk in FLEX

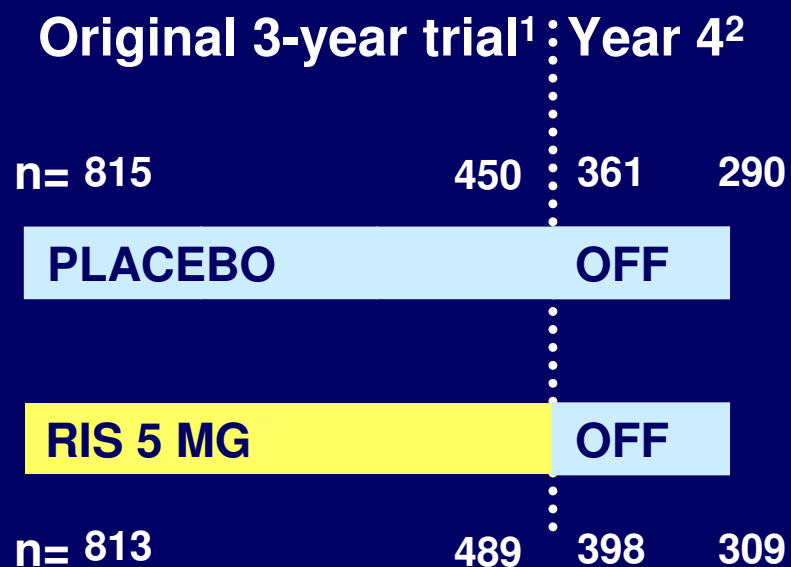


# Withdrawal Of Risedronate

Women between 6-60 months since menopause



# Risedronate: VERT-NA Extension



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

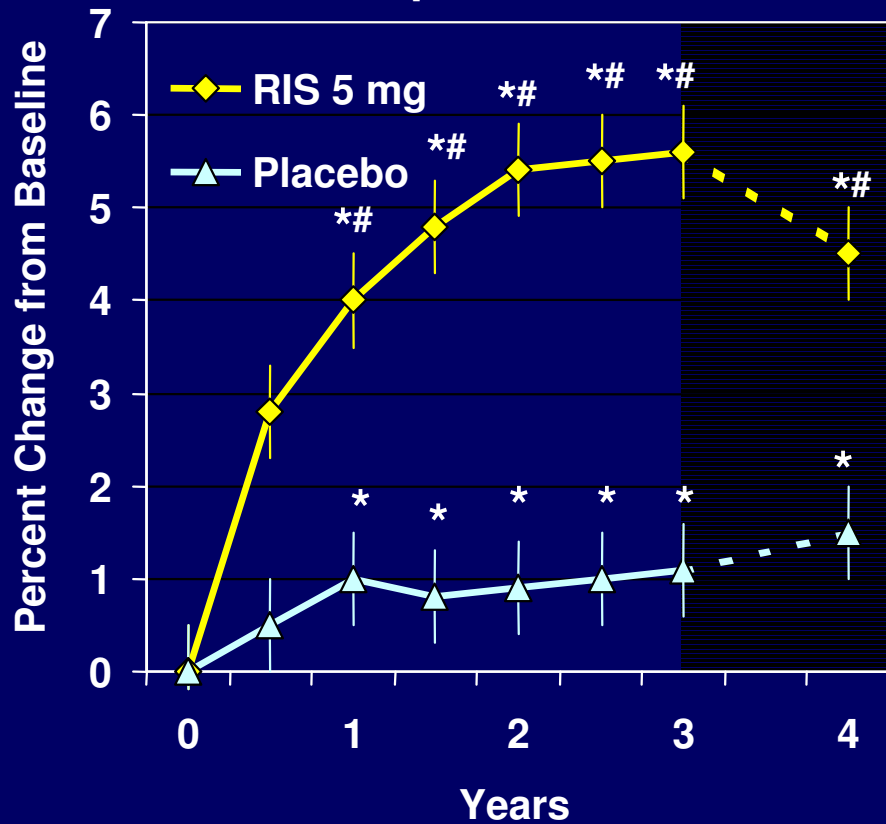
2. Watts NB et al, *Osteoporos Int* 2005;16 (suppl 3):S7



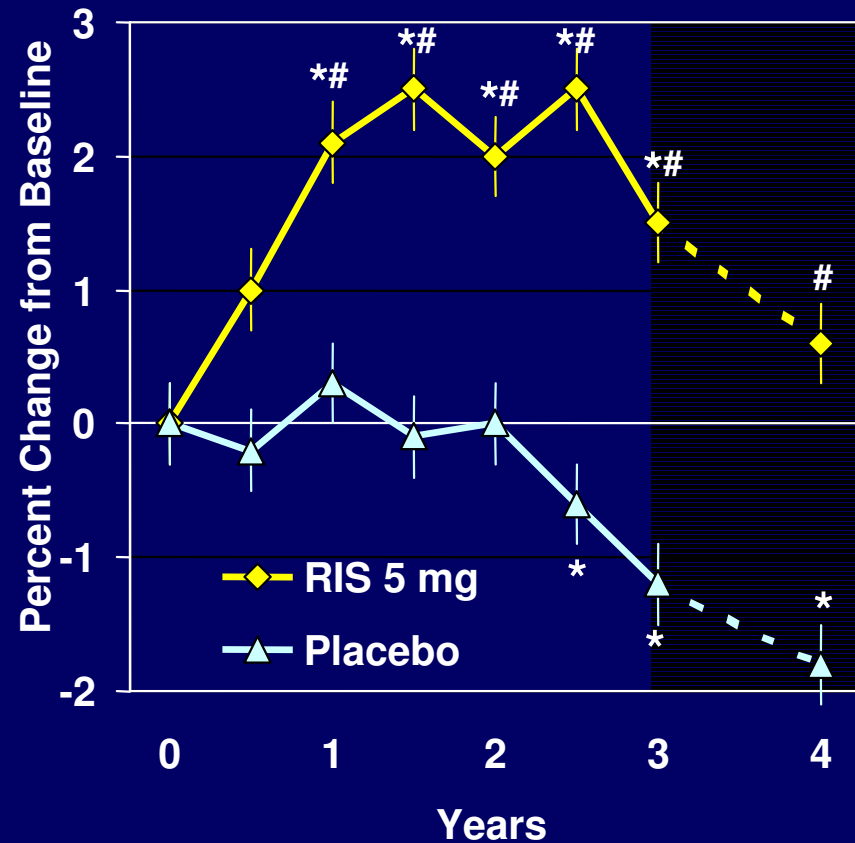
# Withdrawal of Risedronate

## VERT-NA Extension

### Spine BMD



### Femoral Neck BMD



\*p<0.05 vs baseline

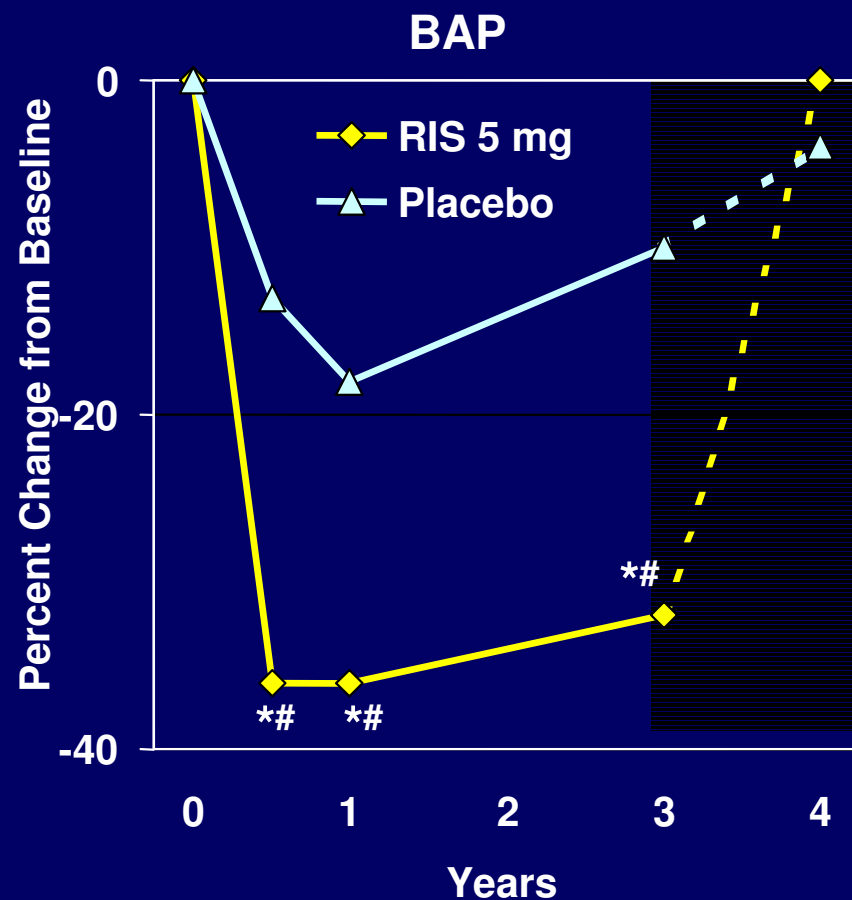
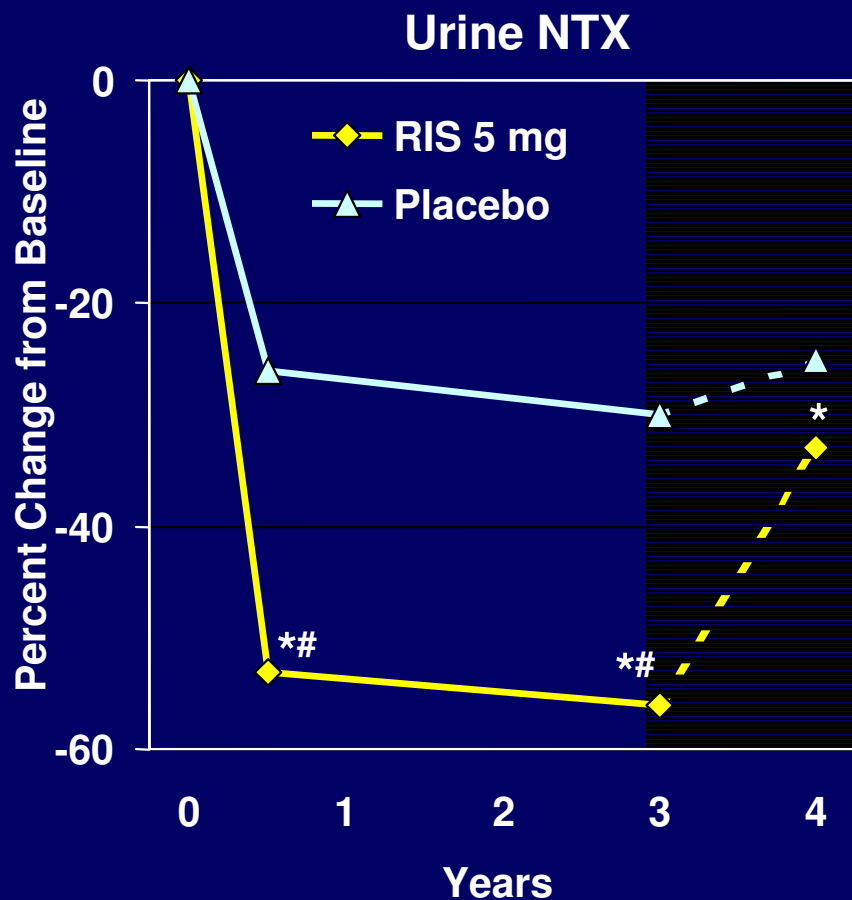
#p<0.05 vs placebo

Watts NB, McClung MR et al. *ISCD Annual Meeting 2004*



# Long-term Experience with Risedronate

## VERT-NA Extension



\*p<0.05 vs baseline

#p<0.05 vs placebo

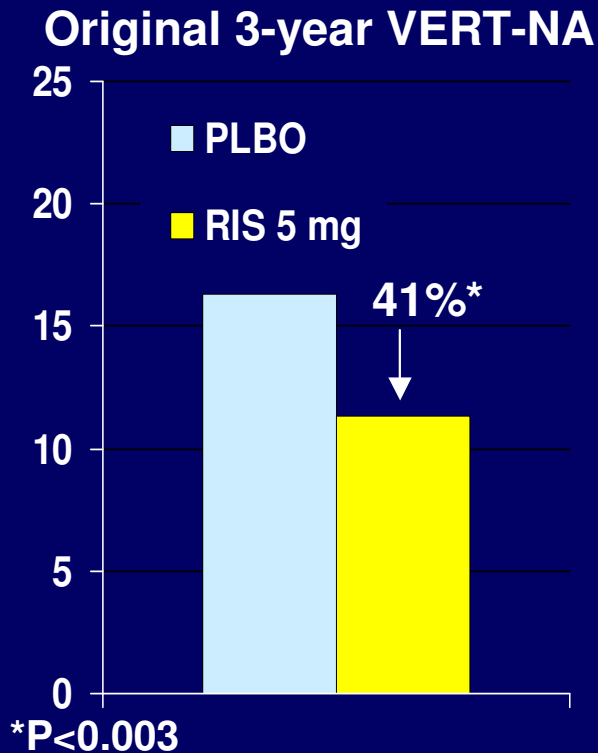
Watts NB, McClung MR et al. *ISCD Annual Meeting 2004*



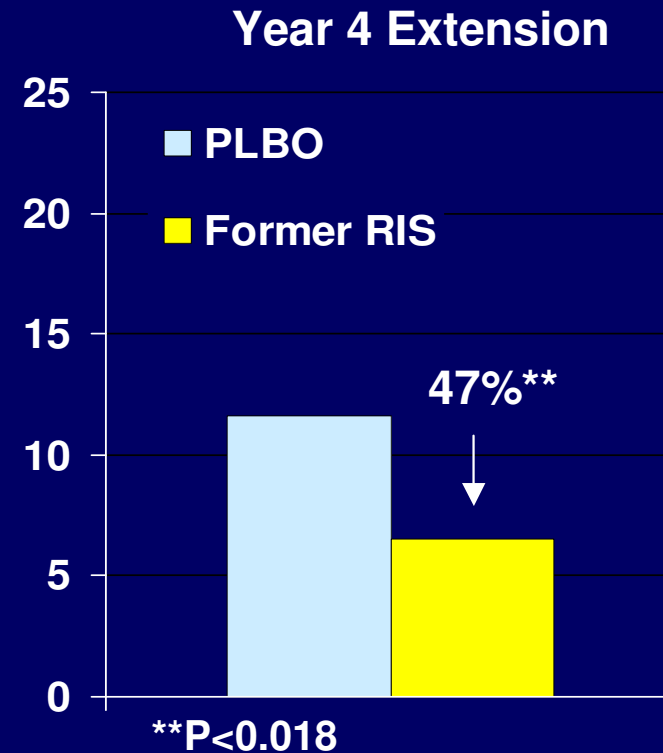
# Vertebral Fractures with Risedronate

## EFFECT ON NEW RADIOGRAPHIC VERTEBRAL FRACTURES

Percent of subjects with new fractures



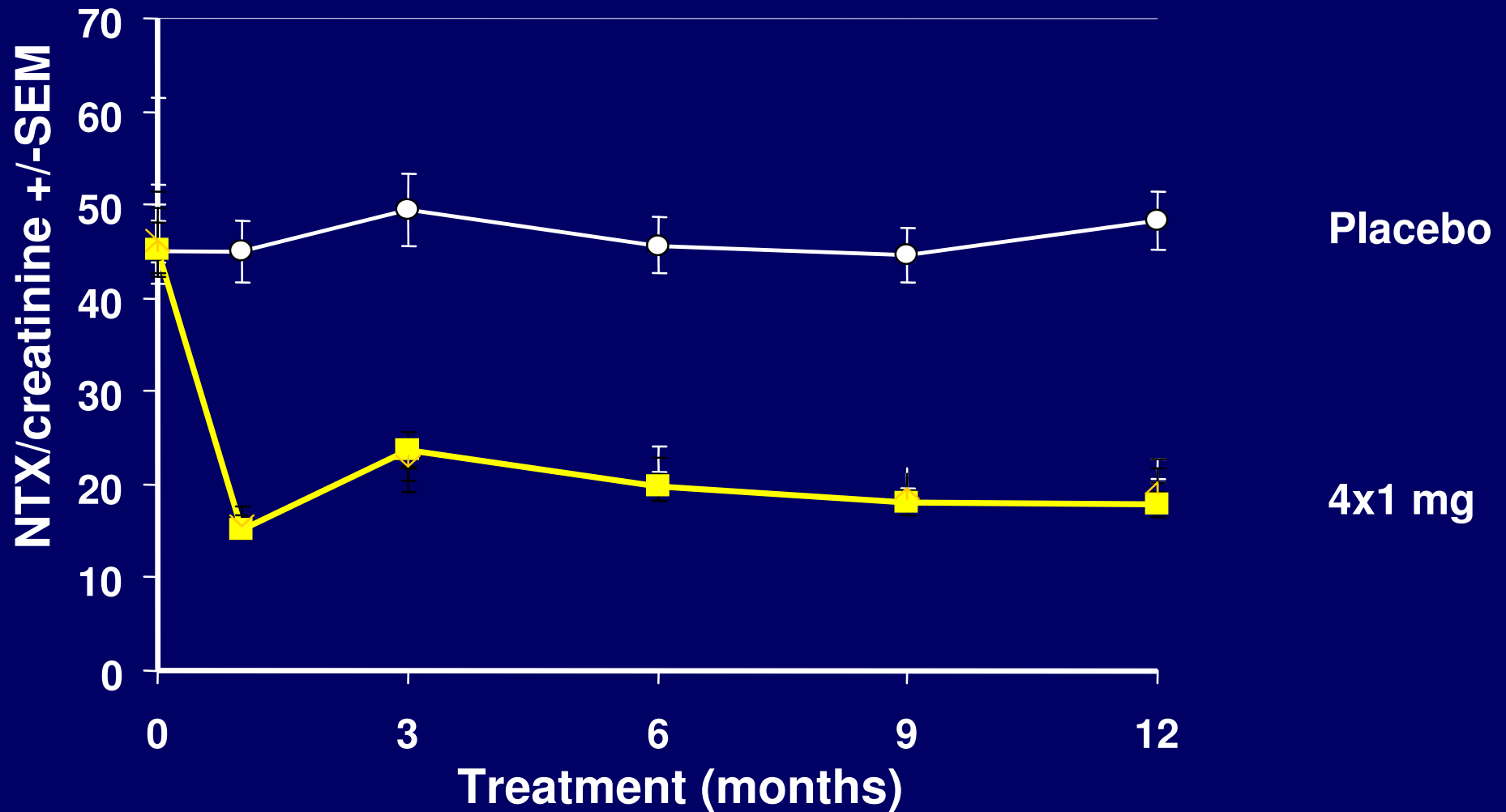
Harris ST et al, *JAMA*  
1999;282:1344-1353



Watts NB et al, *Osteoporos Int*  
2005;16 (suppl 3):S7



# Zoledronic Acid: Single Dose Persists for At Least 1 year



# Case 1

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- 73 year-old woman diagnosed with osteoporosis and 1 vertebral fracture in 1998.
- Alendronate therapy was begun which has taken without difficulty.
- She has had no new fractures

	<u>1998</u>	<u>2001</u>	<u>2004</u>	<u>2007</u>
BMD T-score: LSpine	-3.1	-2.5	-2.3	-2.3
THip	-2.5	-2.4	-2.4	-2.4

# Case 1: Options

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- **Continue alendronate 70 mg Q week**
- **Switch to**
  - **Another bisphosphonate**
  - **SERM (raloxifene)**
  - **Calcitonin**
  - **Teriparatide**
- **Discontinue treatment (drug holiday)**
- **Reduce dose of alendronate**



# Case 1: Options

---

- Continue alendronate 70 mg Q week
- Switch to
  - Another bisphosphonate
  - SERM (raloxifene)
  - Calcitonin
  - Teriparatide
- Discontinue treatment (drug holiday)
- Reduce dose of alendronate



## Case 2

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- 53 year-old woman, 2 years postmenopausal, diagnosed with low BMD. No other risk factors.
- Calcium and vitamin D intake are adequate.
- Alendronate therapy was begun which has taken without difficulty.
- She has had no fractures

	<u>2004</u>	<u>2007</u>
BMD T-score: LSpine	-2.1	-1.5
THip	-1.7	-1.5



## Case 2: Options

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- **Continue alendronate 70 mg Q week**
- **Switch to**
  - **Another bisphosphonate**
  - **SERM (raloxifene)**
  - **Calcitonin**
  - **Teriparatide**
- **Discontinue treatment (drug holiday)**
- **Reduce dose of alendronate**



## Case 2: Options

---

- Continue alendronate 70 mg Q week
- Switch to
  - Another bisphosphonate
  - SERM (raloxifene)
  - Calcitonin
  - Teriparatide
- Discontinue treatment (drug holiday)
- Reduce dose of alendronate



# How Long Should Bisphosphonates Be Used?

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- **No justification for stopping treatment in high risk patients**
- **Discontinuation of alendronate therapy after 5 years seems appropriate in patients not at high risk**
- **Uncertain whether this applies to other bisphosphonates**

# What to Do When Treatment is Stopped?

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- **When to re-start treatment?**
  - **After fixed interval?**
  - **With evidence of “relapse”**
- **How to monitor?**
  - **Not BMD**
  - **Markers**
    - **Most rational and physiologic, but little clinical evidence to date**

# Thank You

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