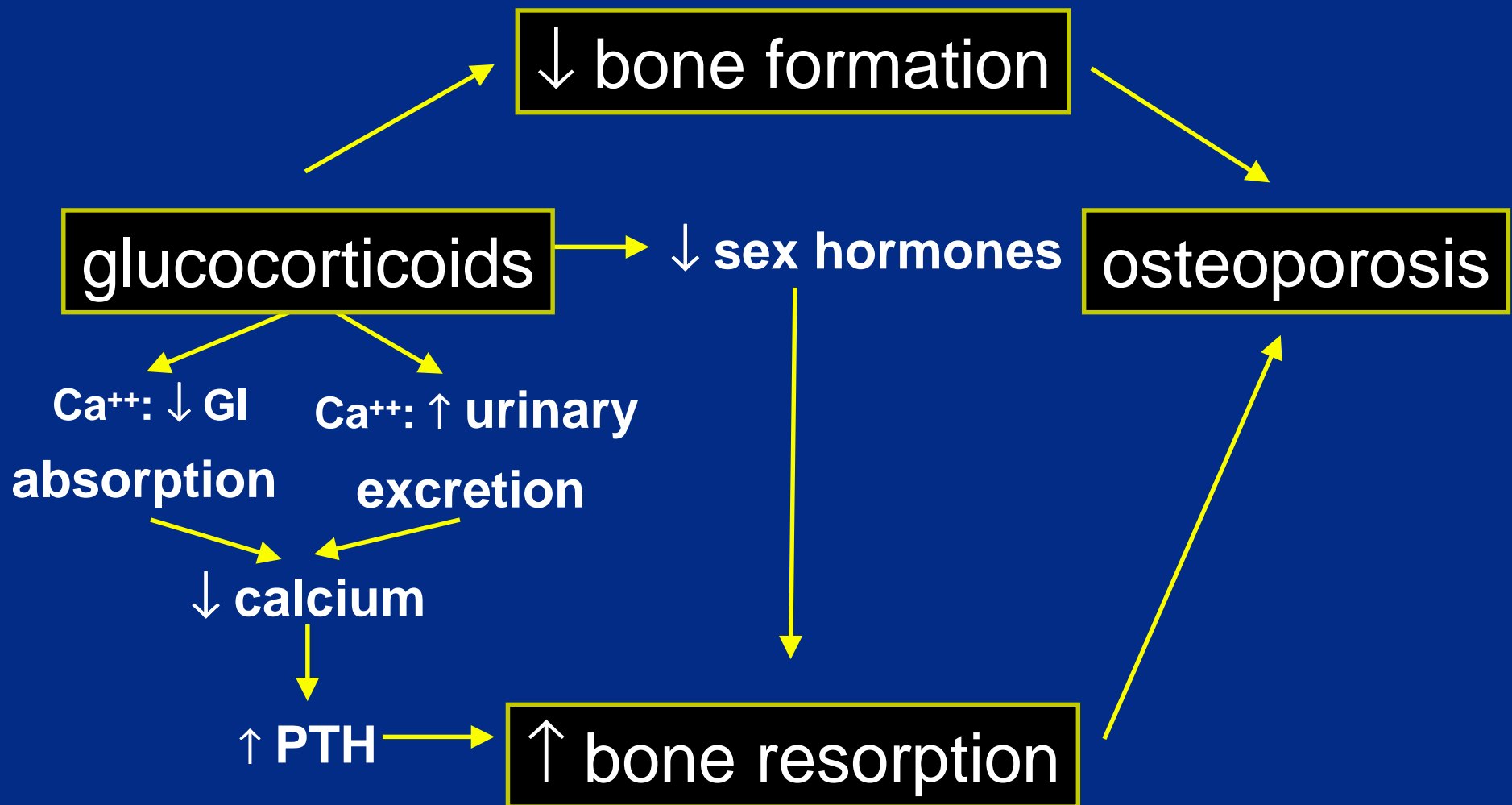

GIOP

**GLUCOCORTICOID-INDUCED
OSTEOPOROSIS**

Glucocorticoid-Induced Osteoporosis

Pathophysiology



Glucocorticoid-Induced Osteoporosis

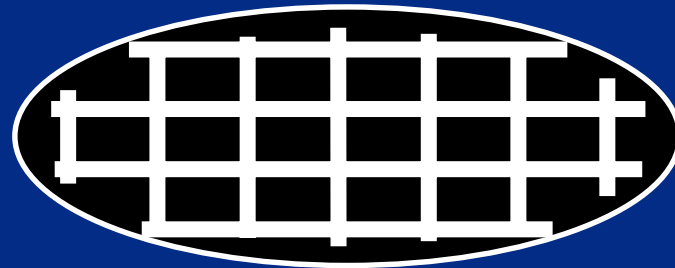
- **50%** of glucocorticoid users lose bone (genetic variability)
- **30 - 50%** of glucocorticoid users sustain vertebral fractures
- Rate of bone loss: up to **15%** per annum
- Bone loss most pronounced in the first **6 - 12** months of therapy

GIOP

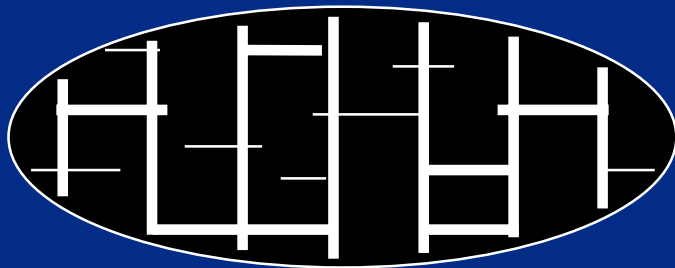
Dose and Duration Dependent

- Prednisone > 7.5 mg will double the fracture risk
- Cumulative dose affects the severity of bone loss
- Alternate day dosing does not work
- Inhaled steroids do result in bone loss
 - › 1000 $\mu\text{g}/\text{day}$ per year \downarrow BMD 0.1 SD
 - › Significant loss over 10 - 20 years

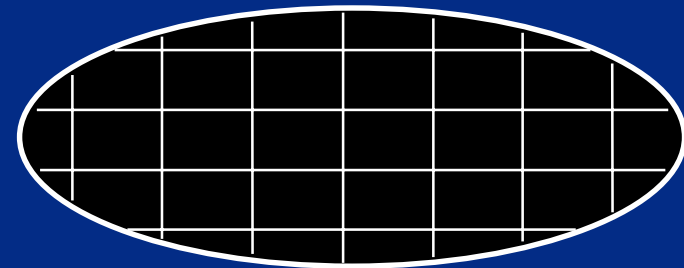
GIOP: *BMD Measurement May Underestimate Fracture Risk Compared to Postmenopausal Osteoporosis*



NORMAL VERTEBRAL BODY



**POSTMENOPAUSAL
OSTEOPOROSIS**



**GLUCOCORTICOID-INDUCED
OSTEOPOROSIS
(general trabecular narrowing)**

GIOP

- Trabecular bone is affected earlier and more severely than cortical bone
- Glucocorticoids often coexist with other risk factors
 - › Rheumatoid arthritis and glucocorticoids increase vertebral fracture risk by **4-5** fold compared to R.A. alone
 - › Rheumatoid arthritis and glucocorticoids **double hip** fracture risk compared to R.A. alone
- Men and women are equally susceptible to the effects of glucocorticoids

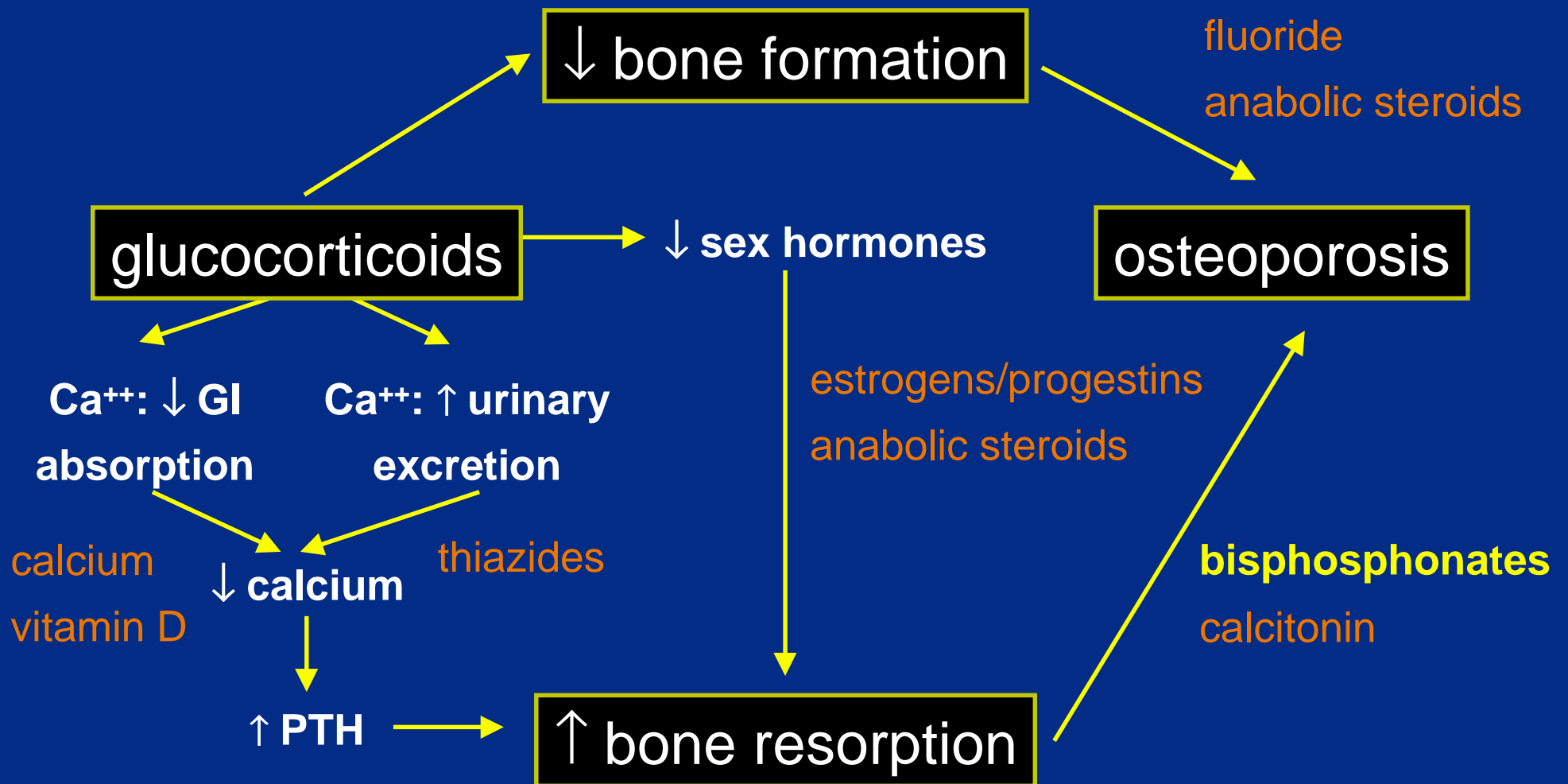
GIOP

Objective

To prevent patients treated with glucocorticoids from losing bone and increasing fracture risk.

Glucocorticoid-Induced Osteoporosis

Treatment Options



Rationale for Alendronate

Calcium and Vitamin D are often insufficient

- 50% lose bone
- 30 - 50% sustain vertebral fractures

Alendronate as shown in FIT and Pivotal Studies:

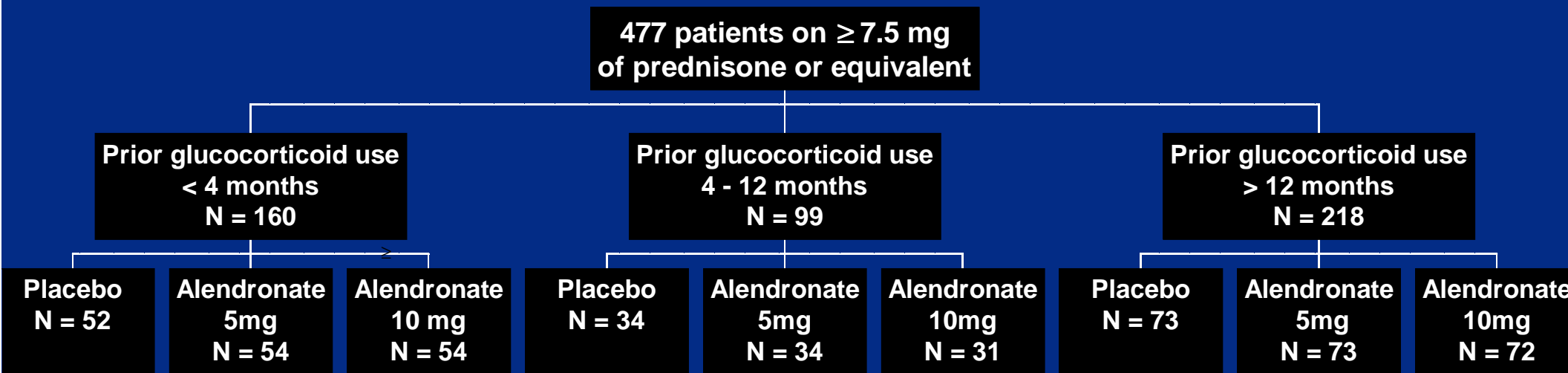
- Reduces the incidence of fractures at all sites
- Antifracture efficacy is independent of age, baseline BMD and baseline fracture status
- Maintaining or increasing BMD is predictive of reduced fracture risk

Alendronate for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Saag K, Brown J et al.

Alendronate for the management of glucocorticoid-induced osteoporosis: results of the combined multicenter study. Annual Meeting of the American College of Rheumatology, November, 1997 (Poster & Oral Presentation)

Study Design



All groups received:

Calcium 800 to 1000 mg/day and Vitamin D 250 to 500 IU/day¹

Endpoints

- Primary: Spine BMD
- Secondary:
 - › Femoral neck, trochanter, total body BMD
 - › Urine NTx, bone-specific alkaline phosphatase
 - › Histomorphometry
 - › Vertebral morphometry, fracture
 - › Stature
 - › Clinical and laboratory safety monitoring

Baseline Characteristics

	PBO	ALN 5	ALN 10
Mean age (yr)	54	56	55
Mean <i>dietary</i> calcium intake (mg/day)	698	732	731
Mean daily glucocorticoid dose	19.0	18.8	17.3
Median daily glucocorticoid dose	11.1	10.0	10.0
Spine BMD (T-score) (All patients)	-1.13	-1.34	-1.15
Men (n=137)	-1.09	-1.47	-1.18
Premenopausal women (n=102)	-0.63	-0.64	-0.28
Postmenopausal women (n=222)	-1.48	-1.54	-1.45

No significant difference between treatment groups

Glucocorticoid Dosing

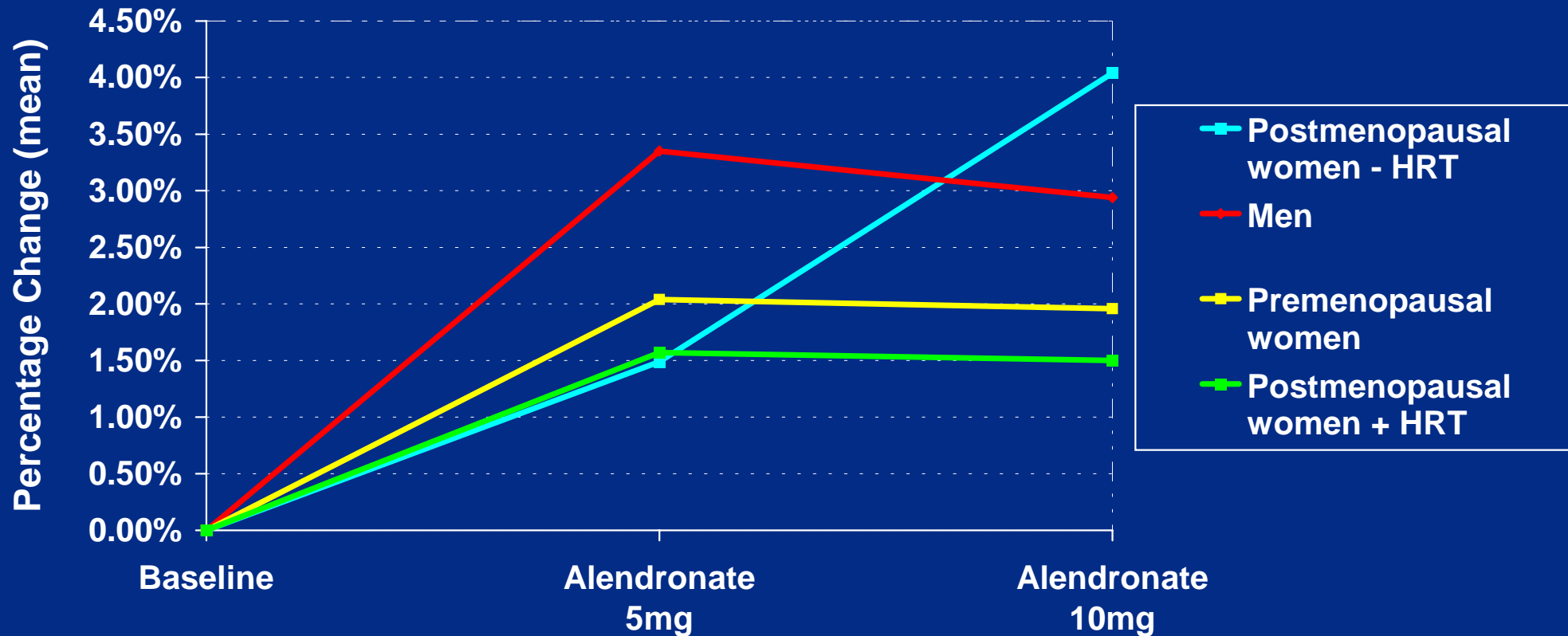
- **Estimated Average Daily Study Dose**
 - › **Baseline**
 - Mean approximately 18 mg/day
 - Median approximately 10 mg/day
 - › **End of Study**
 - Mean approximately 9.1 mg/day
 - Median approximately 7.8 mg/day

Predefined Subgroup Analyses

- Gender
- Menopausal status
- Baseline BMD
- Duration corticosteroid use
- Dose of corticosteroids
- Disease
- Age
- Height/weight
- Concomitant drugs (methotrexate)

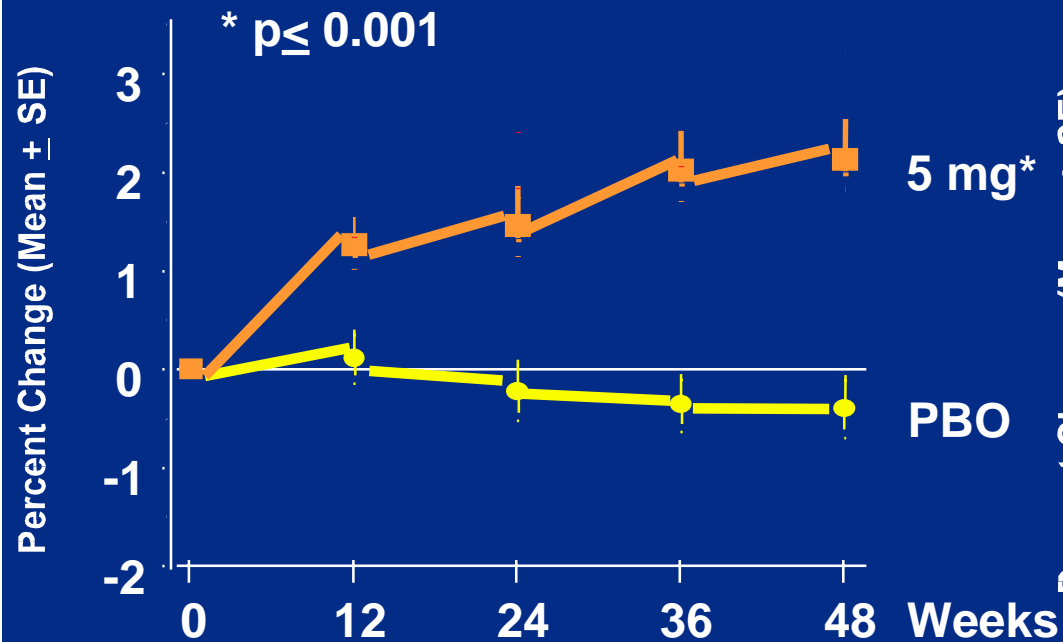
Effect of Gender and Menopausal Status on Spine BMD (12 months)

What Is the Minimal Dose of Alendronate Which Conteracts the Effect of Glucocorticoids?

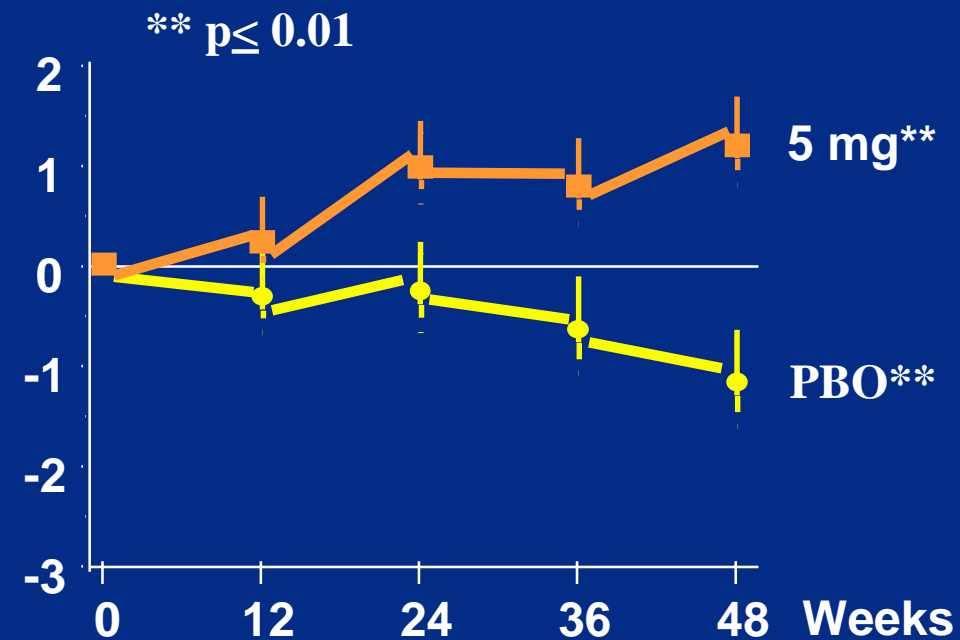


Effect of Alendronate on BMD

Lumbar Spine

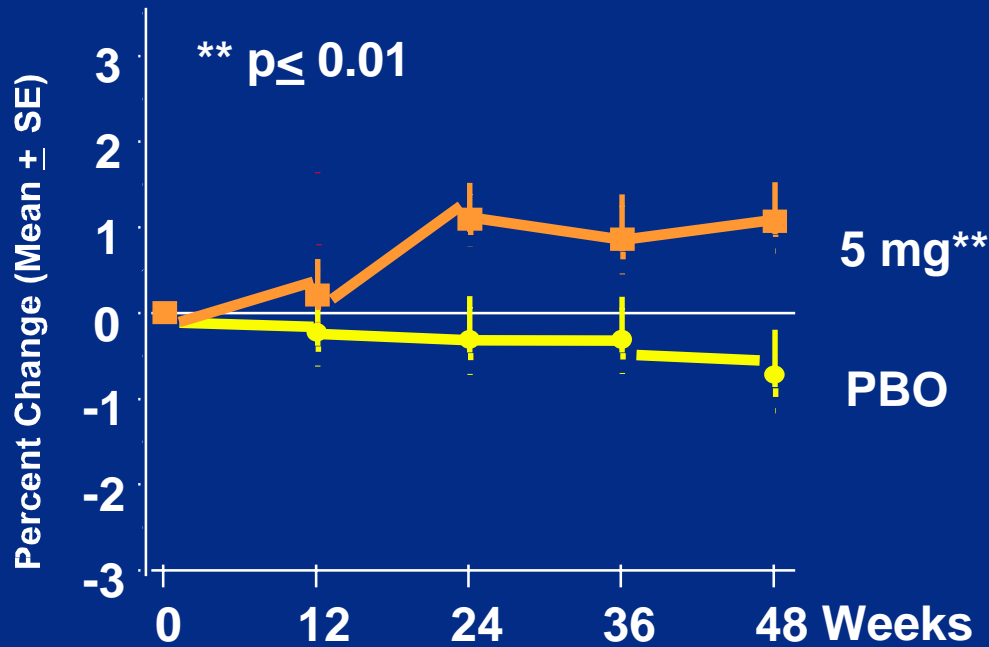


Femoral Neck

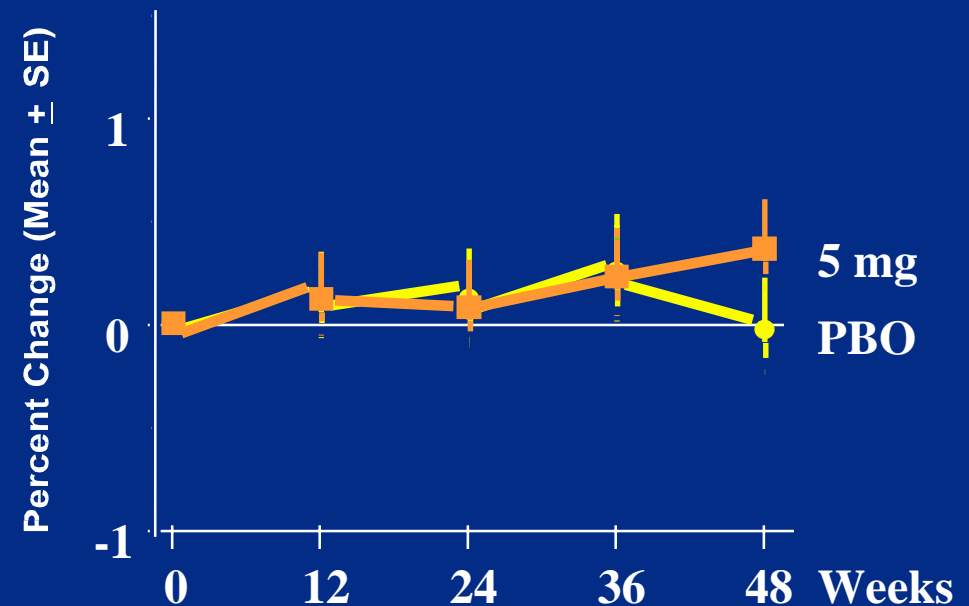


Effect on Alendronate on BMD

Trochanter

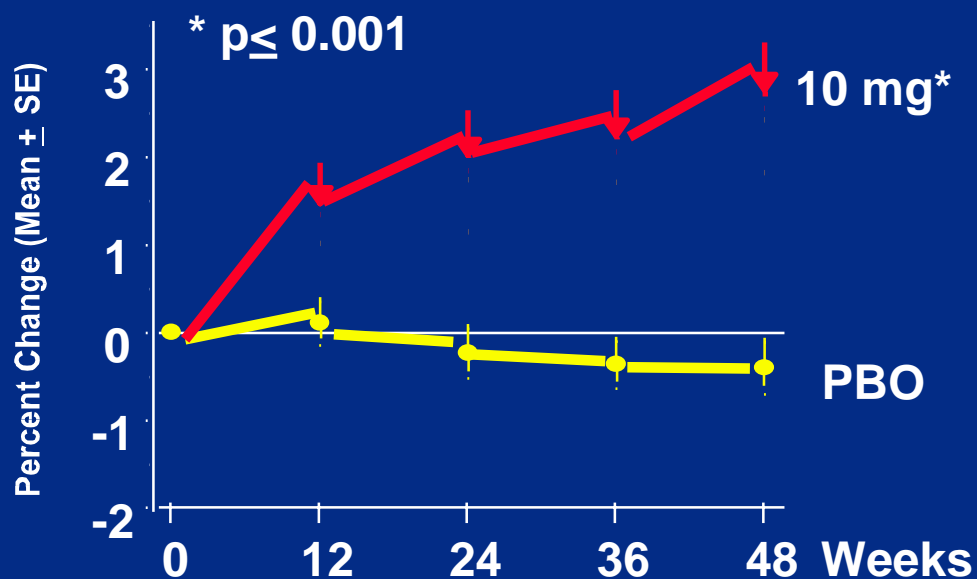


Total Body

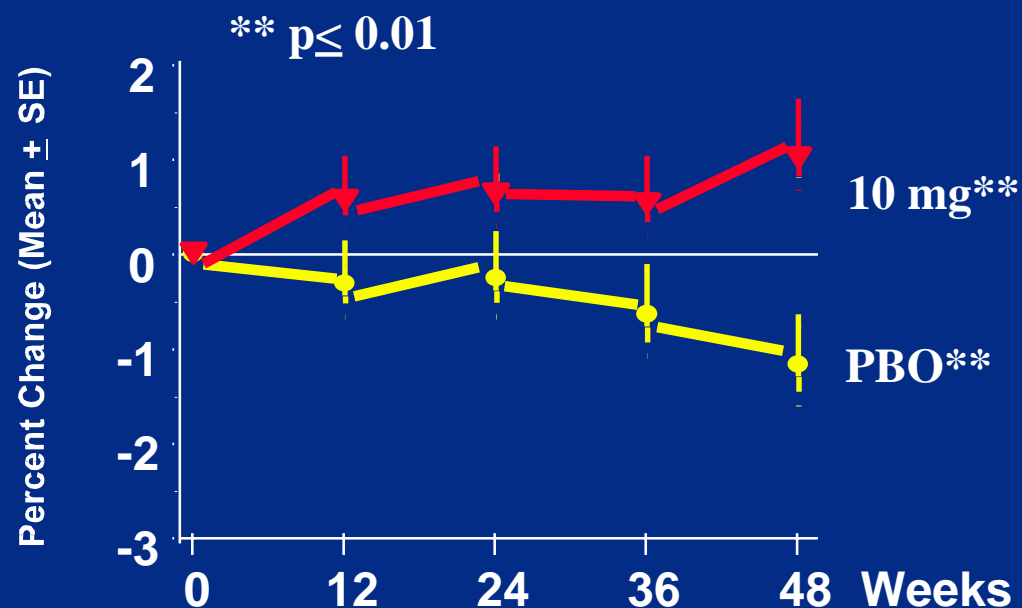


Effect of Alendronate on BMD

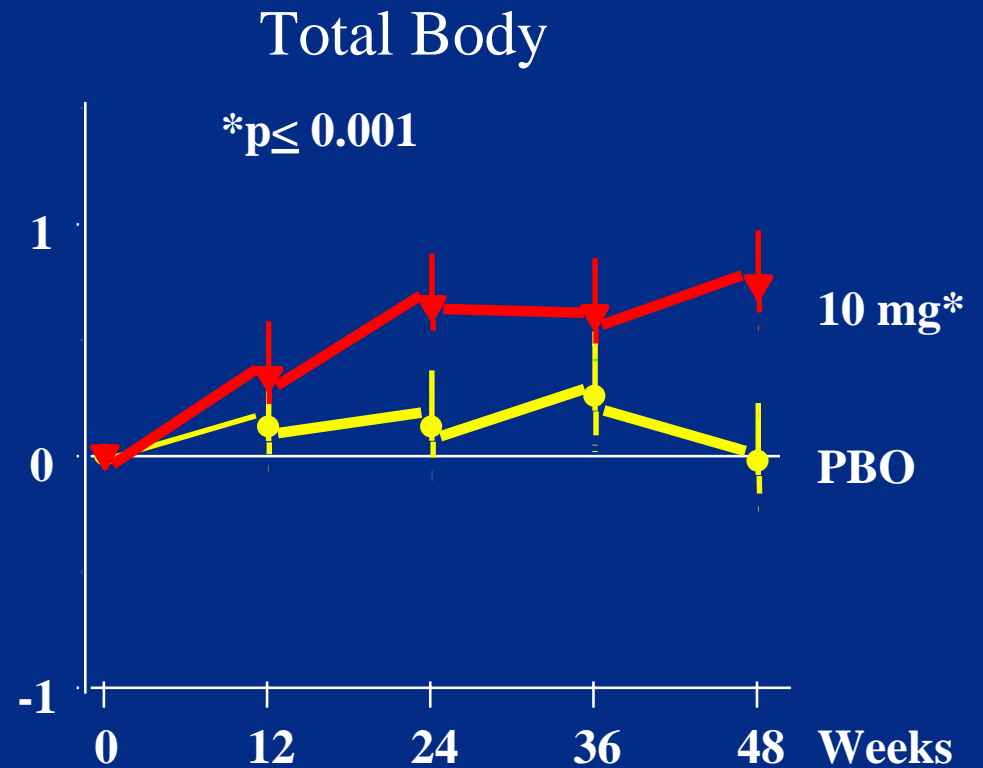
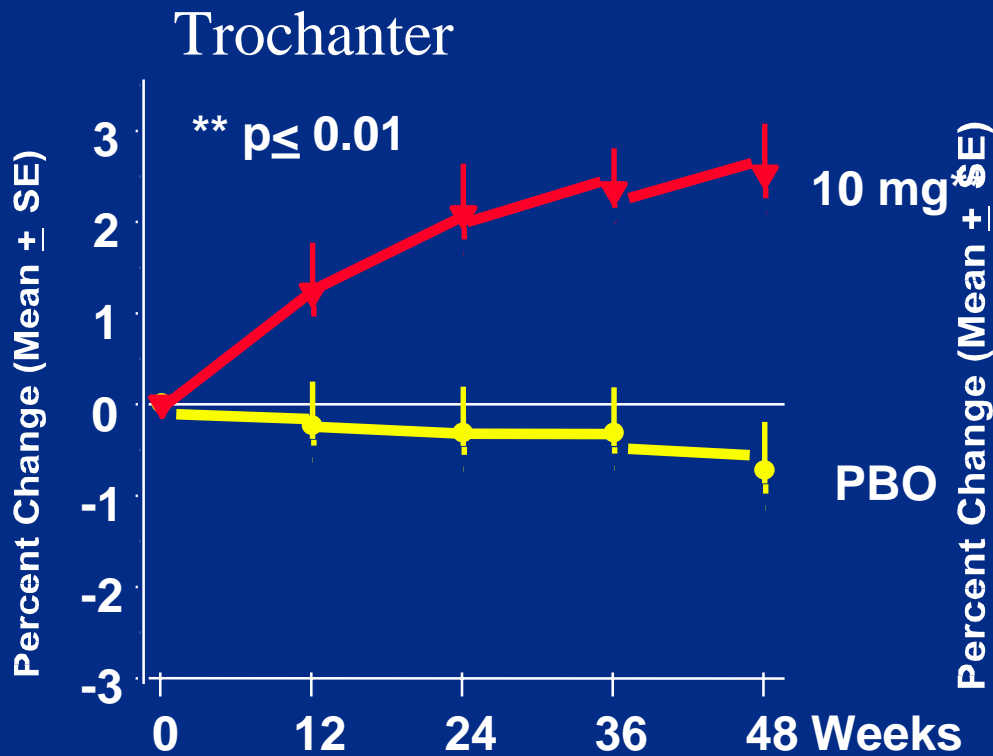
Lumbar Spine



Femoral Neck



Effect of Alendronate on BMD

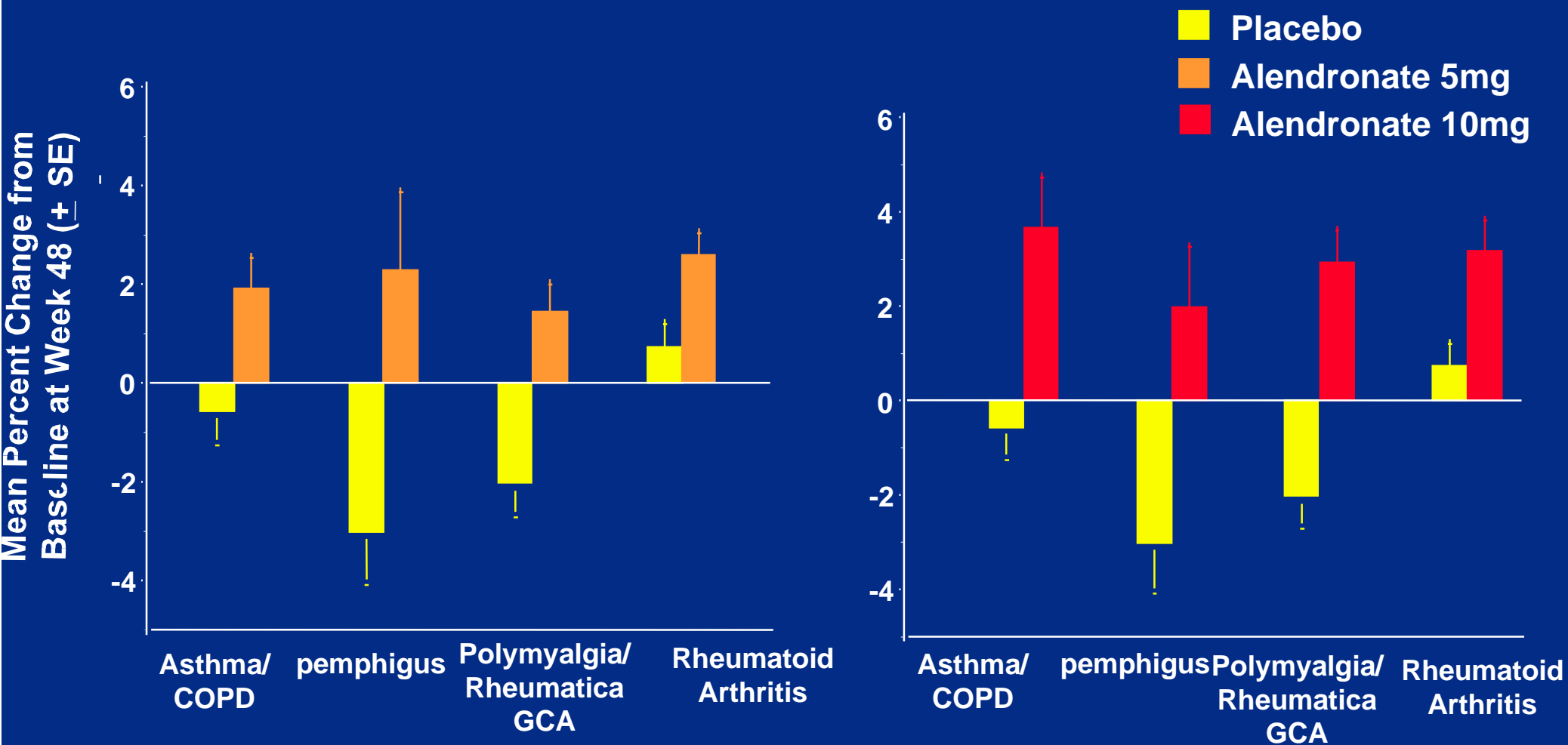


Baseline Risks Which May Affect the Minimal Dosage of Alendronate to Compensate the Effect of Glucocorticoids:

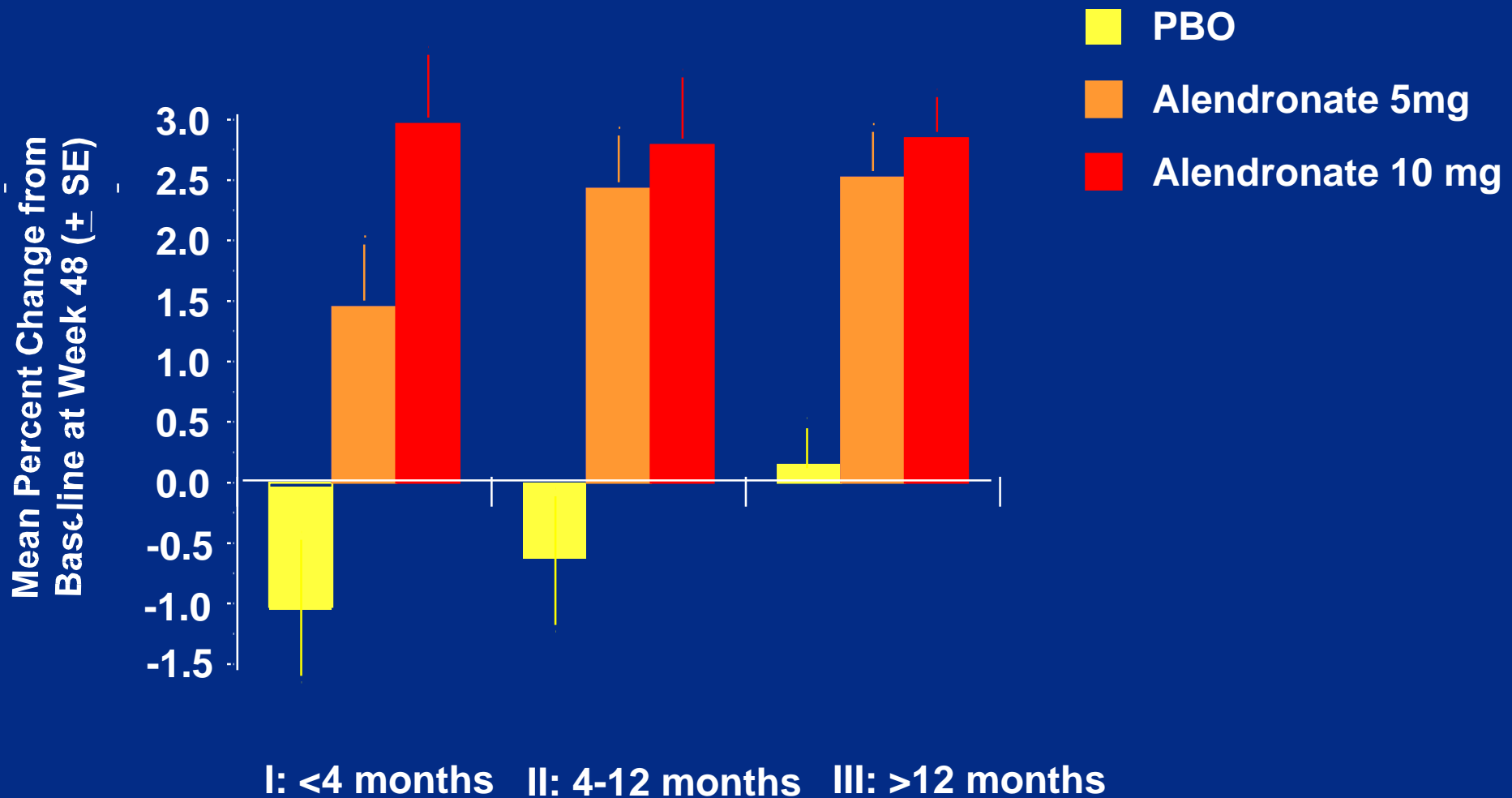
Results of Subgroup Analyses

- Hormonal status (YES)
- Gender (NO)
- Baseline BMD (NO)
- Duration of glucocorticoid use (NO)
- Dose of glucocorticoids (NO)
- Disease (NO)
- Age (NO)
- Height / Weight (NO)
- Concomitant drugs (NO)
(methotrexate)

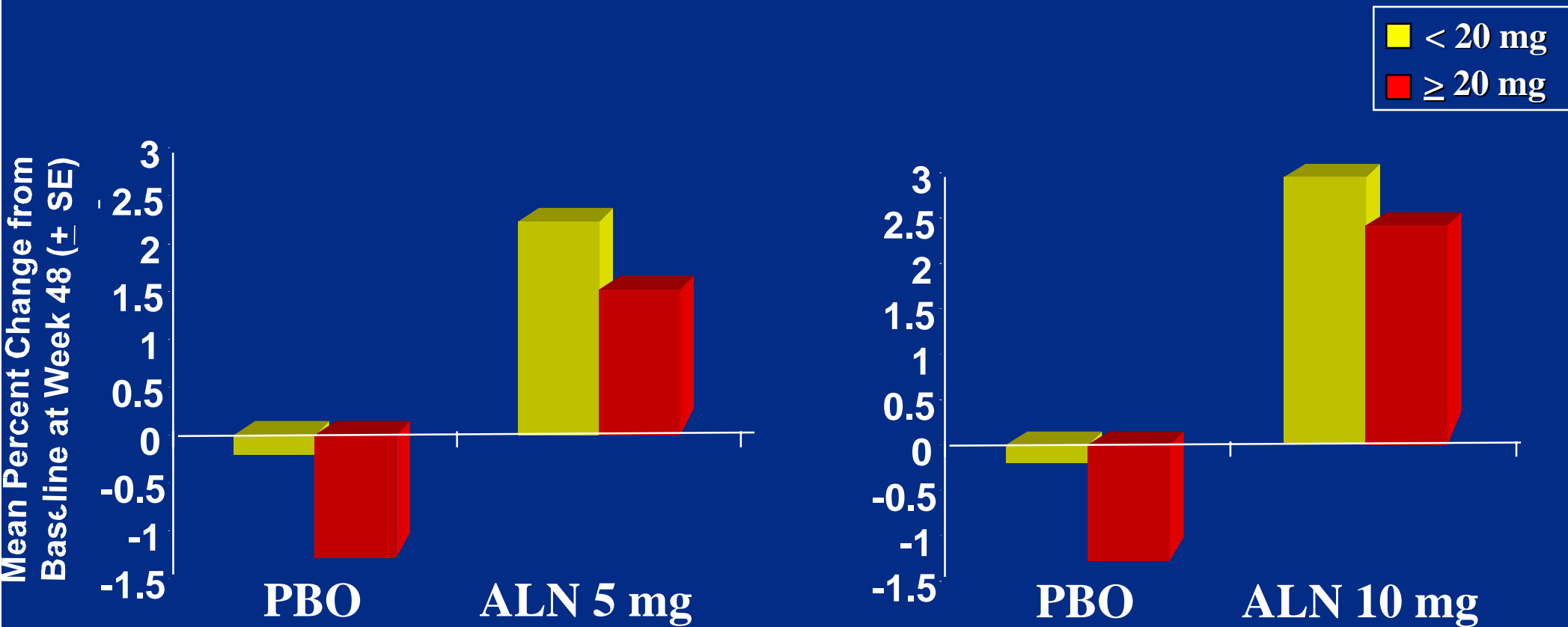
Effect of Disease on Spine BMD



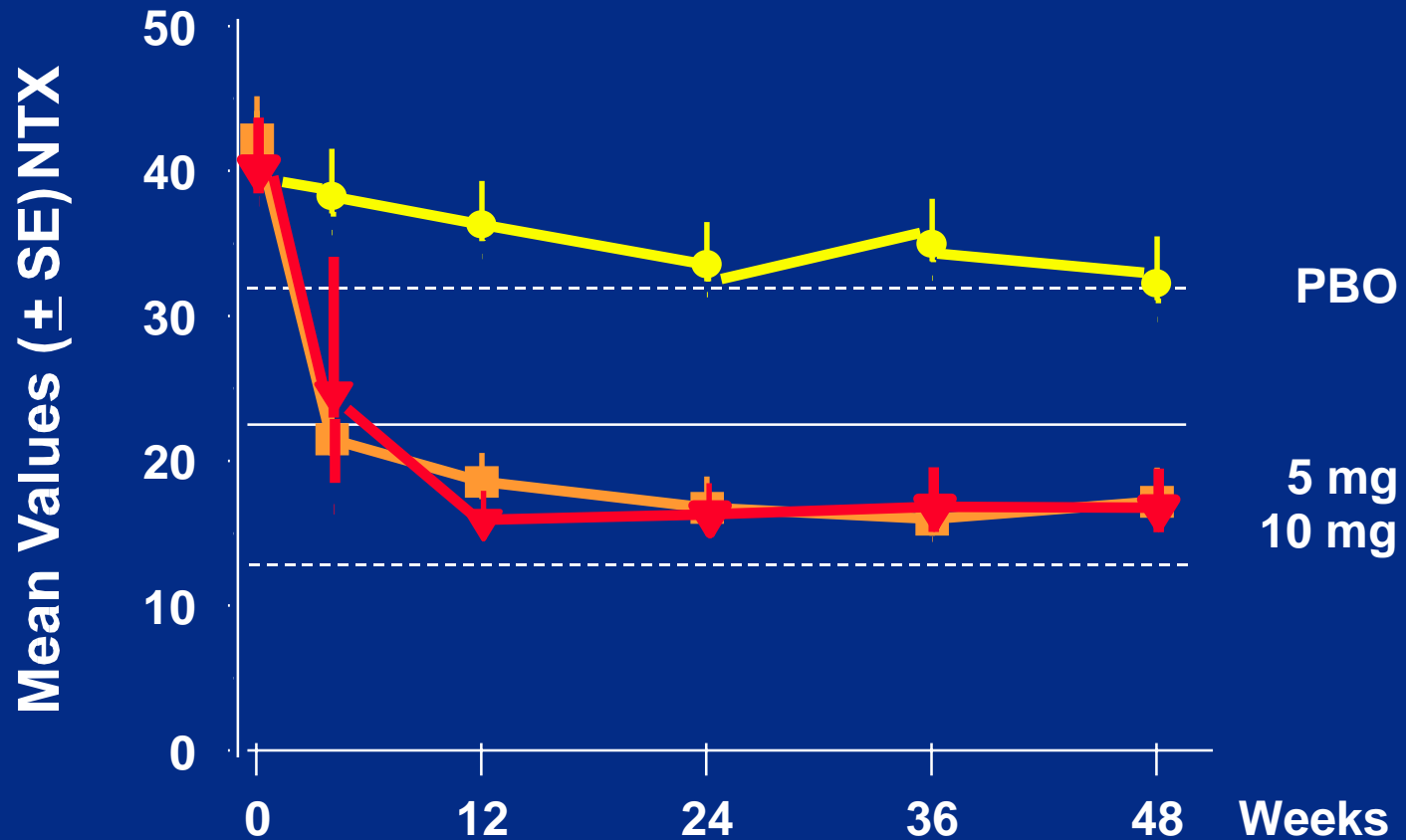
Effect of Duration of Prior Glucocorticoid Use on Spine BMD



Effect of Glucocorticoid Dose on Spine BMD



Effect on N-Telopeptide Crosslinks



* Premenopausal Reference Range Garnero; *Bone*, 1995

Vertebral Fracture

(Semiquantitative/Binary)

Population	No. of pts. with fractures/ No. of pts. with evaluable x-rays (%)			
	PBO		ALN 5 & 10	
All	8/135	(5.9)	8/268	(3.0)*
Premenopausal	0		0	
Postmenopausal	7/54	(13.0)	6/135	(4.4)**
Male	1/48	(2.1)	2/75	(2.6)

* p=0.180

**p=0.053

Proven Reduction in Vertebral Fractures with Alendronate in Major Studies

Study	Patients (N)	↓ VFx
Phase III	994	48%
FIT <ul style="list-style-type: none">• with existing vertebral fractures• without existing vertebral fractures	2027 4432	47% 44%
GIOP	560	49%

Adverse Experience Summary

Number (%) of patients	<u>PBO</u>	<u>ALN 5 mg</u>	<u>ALN 10 mg</u>
	(N=159)	(N=161)	(N=157)
With any serious AE	34 (21.4)	25 (15.5)	30 (19.1)
Withdrawn due to an AE	8 (5.0)	8 (5.0)	6 (3.8)
With any upper GI AE	26 (16.4)	30 (18.6)	40 (25.5)
Abdominal pain	8 (5.0)	9 (5.6)	15 (9.6)
Gastric, peptic, duodenal ulcer	3 (1.9)	1 (0.6)	2 (1.2)
Esophageal irritation *	4 (2.5)	5 (3.1)	3 (1.9)
Any serious upper GI AE	2 (1.3)	0	2 (1.3)
Discontinued due to upper GI AE	0	1 (0.6)	2 (1.3)





*Includes dysphagia, esophagitis, reflux esophagitis, and ulcer

Summary

- Alendronate:
 - › Is highly effective in preventing and treating GIOP in both men and women
 - › Significantly increases BMD at the important sites (spine, hip)
 - › Is effective in patients taking glucocorticoids for a variety of conditions, including rheumatoid arthritis, polymyalgia rheumatica and asthma
 - › Is safe and well tolerated in patients receiving glucocorticoid therapy

Conclusion

Alendronate can be prescribed to compensate the effects of glucocorticoids.

Medication		Pre-menopausal	Post-menopausal	Post-menopausal
			 on HRT	 not on HRT
Alendronate 5 mg	X	X	X	
Alendronate 10 mg				X

Back-up

Patients at Risk

Other Factors

- Past history of low trauma fractures
- Low body weight
- Sedentary life-style / immobilization
- Diet low in calcium
- Family history of osteoporosis
- Estrogen / testosterone deficiency
- Heavy smoking
- Underlying disease: independent risk factors

GIOP

Clinical Trials - Observations

- **ISSUES:**
 - › Few randomized controlled prospective studies
 - › Small sample size
 - › Unevenly matched study groups

- **NEEDS:**
 - › Larger size studies
 - › Longer follow-up periods
 - › Fracture assessment

GIOP — Studies

AUTHORS	N	PRODUCTS	DESIGN	RESULTS
Saag et al, 1998 in press	560	alendronate 5 and 10 mg All patients given both Ca ⁺⁺ 800 to 1000 mg/d and Vit D 250 to 500 IU/ d	DB, RCT , 1 yr	LS: ALN 5 ↑ 2.13% from baseline; 2.53% diff. from Pbo LS: ALN 10 ↑ 2.88% from baseline; 3.28% diff. from Pbo FN: ALN 5 ↑ 1.18% from baseline; 2.35% diff. from Pbo FN: ALN 10 ↑ 1.01% from baseline; 2.18% diff. from Pbo TR: ALN 5 ↑ 1.06% from baseline; 1.79% diff. from Pbo TR: ALN 10 ↑ 2.65% from baseline; 2.18% diff. from Pbo ALN 5 & 10 ↑ significantly LS, FN and TR BMD compared to baseline and Pbo.
Gonnelli et al, 1997	43	alendronate 5 mg	DB, RCT , 1 yr, only sarcoidosis (DPA only)	ALN prevents bone loss. Ultradistal radius: Pbo ↓ BMD by 4.5% ALN ↑ BMD by 0.8% Diff. from Pbo: 5.3% (P <0.01)
Roux et al, 1998	117	etidronate; All patients given Ca ⁺⁺ 500 mg/d	DB, RCT, 1 yr	LS: ↑ 0.30% from baseline; 3.0% diff. from Pbo FN: ↓ 1.28% from baseline; 1.30% diff. from Pbo TR: ↓ 1.35% from baseline; 0.4% diff. from Pbo Only LS diff. from Pbo was significant
Adachi et al, 1997	141	etidronate; All patients given Ca ⁺⁺ 500 mg/d	DB, RCT, 1 yr;	LS: ↑ 0.61% from baseline; 3.72% diff. from Pbo FN: ↑ 0.19% from baseline; 1.88% diff. from Pbo TR: ↑ 1.46% from baseline; 4.14% diff. from Pbo Only LS and TR diff. from Pbo was significant

GIOP — Studies

AUTHORS	N	PRODUCTS	DESIGN	RESULTS
Sebaldt et al, 1996	88	etidronate compared to no Tx	cohort study, 2 yrs	↑ 3.9% LS at yr 1, ↑ 5.6% LS at yr 2
Struys et al, 1995	39	etidronate or 500 mg of Ca ⁺⁺	open-label, prosp. 1 yr	↑ 5.7% LS, ↑ 6.8% T. hip, Pbo: ↓ 3.4% LS and ↓ 4.1% T. hip. Ca ⁺⁺ : no benefit
Adachi et al, 1994	68	etidronate compared to no Tx	1 yr., prosp., cohort study	↑ 4% LS BMD ↓ 2% Pbo, not at the hip
Mulder & Struys, 1994	20	etidronate compared to no Tx	prosp., random., 1 yr	Prevented bone loss (↑ 1.4% LS, ↓ 5% Pbo)
Worth et al, 1994	33	1000 IU Vit D/d, 1 g Ca ⁺⁺ etidronate	RCT, 6 mths	↑ 5% LS ↓ 4.3% Pbo-LS

GIOP — Studies

AUTHORS	N	PRODUCTS	DESIGN	RESULTS
Diamond et al, 1993	26	etidronate, ergocalciferol 0.5 µg/wk, 1 g Ca ⁺⁺ compared to 1 g Ca ⁺⁺	prosp., open-study, 2 yrs	↑ LS (7%) - hip BMD (2.5%) at 1 yr, sustained at 2 yrs
Adachi et al, 1996	62	Vit D 50,000 IU/wk and Ca ⁺⁺ 1g/d or double placebo	DB, RCT, 3 yrs	N.S. at LS at 36 mths
Bernstein et al, 1996		1g Ca ⁺⁺ , Vit D 250 IU	RCT, DB, 1 yr	no benefit
Buckley et al, 1996	96	Ca ⁺⁺ 1g/d., Vit D ₃ 500 IU/d. or Pbo	RCT, DB, 2 yrs	LS BMD ↑ 2%/ yr, TR. BMD ↑ 0.9%/ yr, Pbo: LS BMD ↓ 0.72%/ yr, Pbo: TR. BMD ↓ 0.85%/yr No benefit at FN

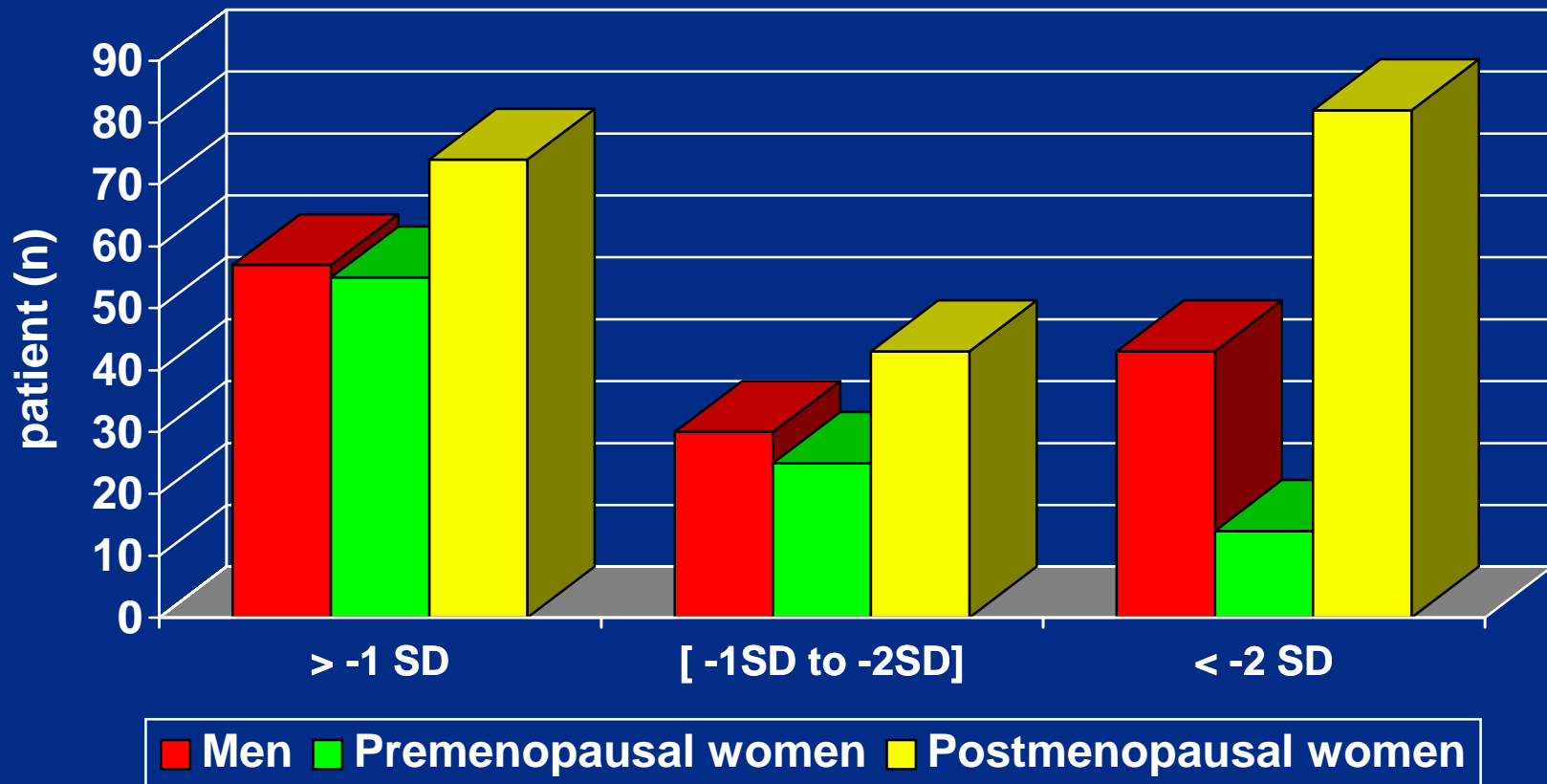
GIOP — Studies

AUTHORS	N	PRODUCTS	DESIGN	RESULTS
Sambrooke et al, 1993	103	Ca ⁺⁺ 1g/d, calcitriol 0.5-1 μ g/d and calcitonin intranasal 400 IU/d. compared to Ca ⁺⁺ - calcitriol - placebo and Ca ⁺⁺ - placebo placebo	DB,RCT, 2 yrs (1 yr on Tx and 1 yr no Tx)	calcitriol prevented bone loss at the LS (with or without calcitonin), not at the hip (1 yr. data) ↓ 4.3% Calcium ↓ 0.2% Calcitriol - Calcitonin. (LS loss did not occur during yr 2) ↓ 1.3% Calcitriol
Adachi et al, 1997	31	nasal salmon calcitonin 200 IU/d		prevent bone loss
Healy et al, 1996	48	salmon calcitonin sc 100 IU or Pbo: with 1.5g Ca ⁺⁺ and Vit. D 400 IU	RCT, DB, 2 yrs	LS BMD remained stable, no ↑ (no benefit)
Luengo et al, 1994	44	nasal salmon calcitonin 200 IU (every other day), 1 g Ca ⁺⁺	prosp., 2 yrs	calcitonin ↑ BMD (no Fx data)
Montemurro et al, 1991	64	calcitonin sc or nasal	2 yrs not RCT	calcitonin prevented LS bone loss (QCT)

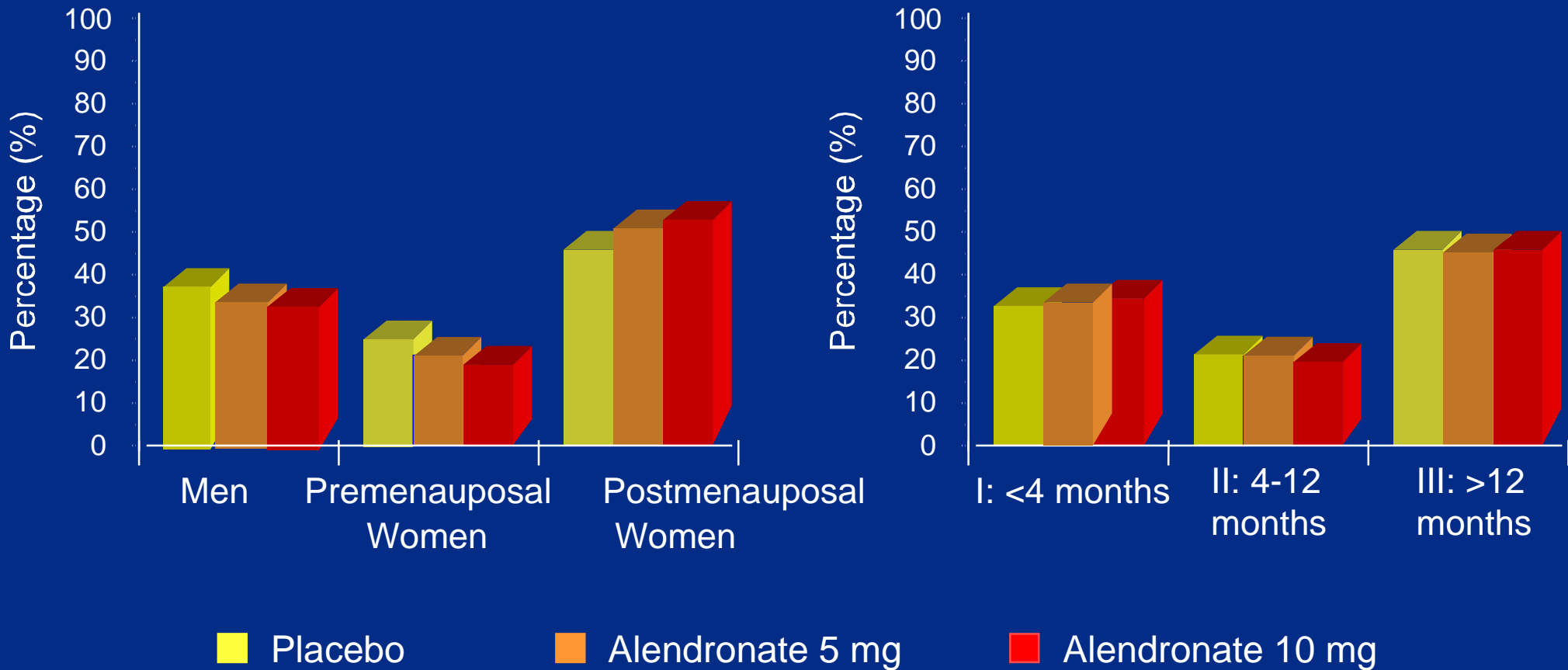
GIOP — Studies

AUTHORS	N	PRODUCTS	DESIGN	RESULTS
Reid et al, 1996	15	testosterone / month compared to control	random., 1 yr	↑ LS BMD (5%), not at hip
Hall et al, 1994	21	HRT (50 μ g/d transdermal estradiol) or Ca ⁺⁺ 400 mg/d.	random., 2 yrs	↑ 3.75 LS BMD, ↓ 0.9 Pbo, not at hip, preserve BMD
Adami & Rossini, 1993	35	nandrolone decanoate 50 mg i.m./3 wks.	controlled, 18 mths	↑ forearm BMD at 6 mths and sustained thereafter
Lukert et al, 1992	15	HRT (premarin and provera)	1 yr	↑ LS BMD, not at hip
Greenwald et al, 1992	10	slow-release enteric coated fluoride 20-30 mg/d		↑ 18.7%/ yr at LS, not at hip

Population Stratification According to Baseline BMD



Baseline Characteristics of Study Patients



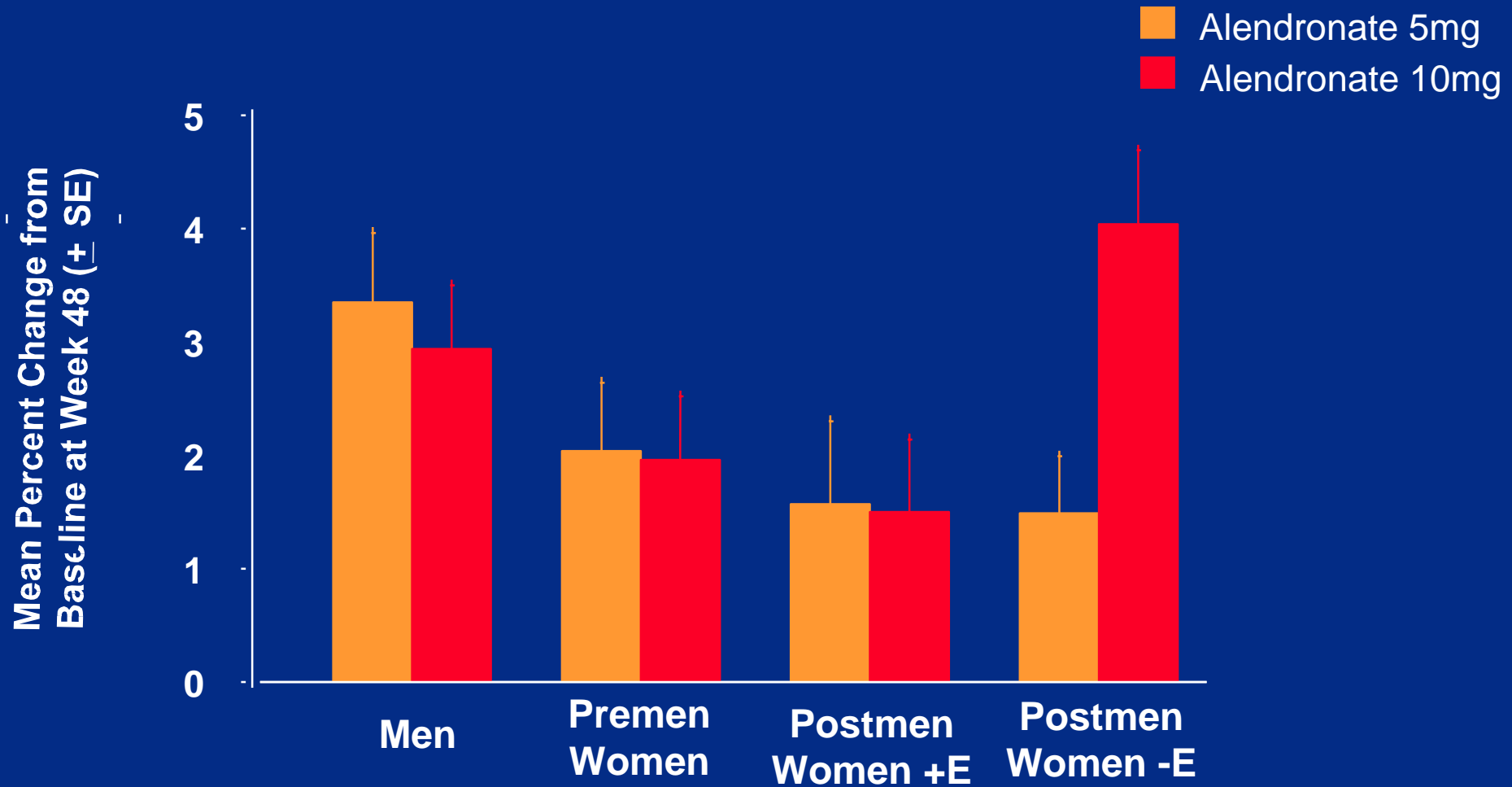
Baseline Characteristics

Glucocorticoid Requiring Illnesses ($\geq 5\%$)

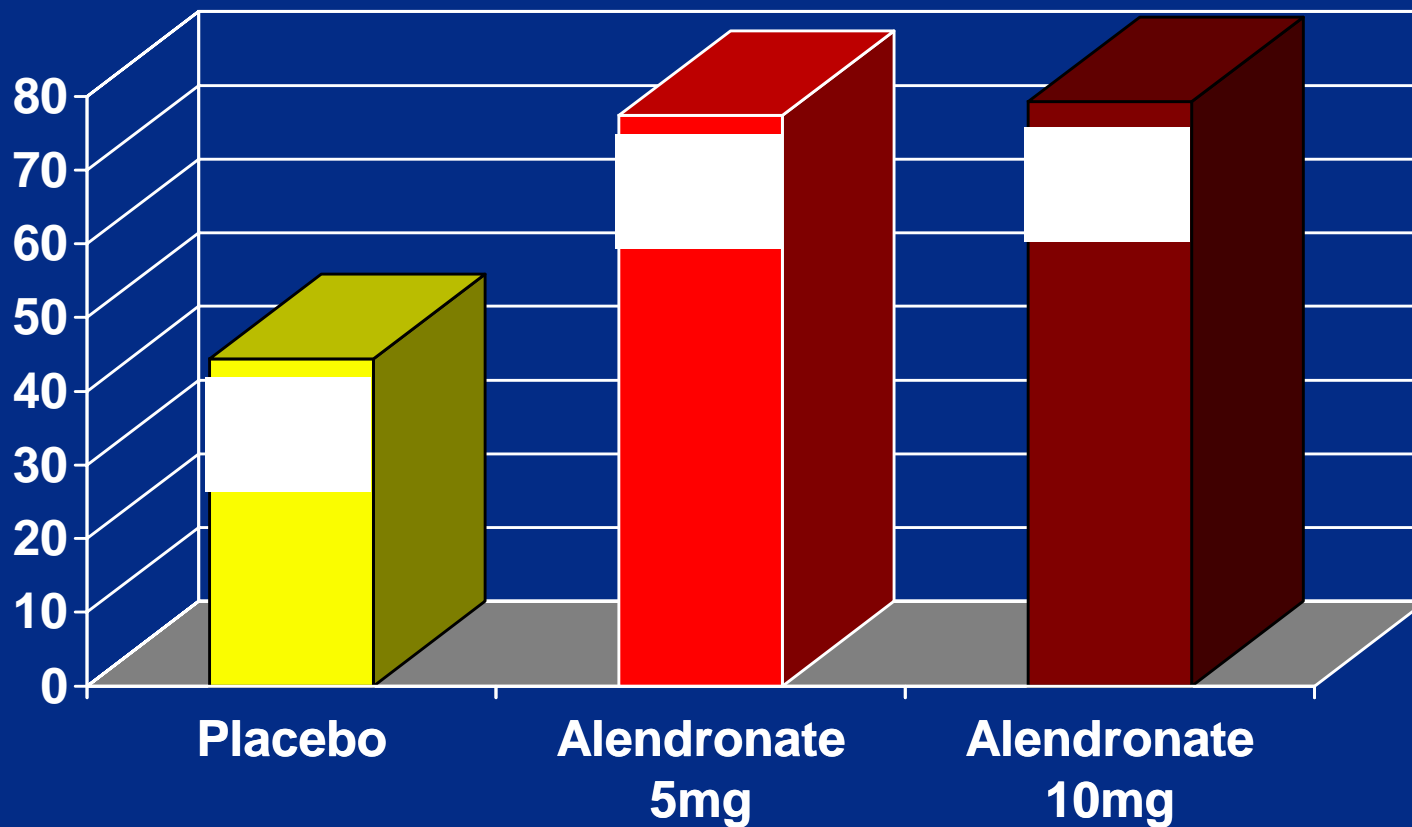
Disorder	No. (%) of Patients	
	Placebo	Alendronate 5 and 10 mg
Rheumatoid arthritis	43 (27.0)	100 (31.4)
Polymyalgia rheumatica	24 (15.1)	67 (21.1)
Systemic lupus erythmatosus	19 (11.9)	29 (9.1)
Pemphigus	12 (7.5)	25 (7.9)
Asthma	15 (9.4)	21 (6.6)
Inflammatory myopathy	10 (6.2)	15 (4.7)
Inflammatory bowel disease	8 (5.0)	16 (5.0)

Other diseases: giant cell arteritis, sarcoidosis, myasthenia gravis, chronic obstructive pulmonary disease, nephrotic syndrome

Effect of Gender and Menopausal Status on Spine BMD



Spine BMD Responders (BMD Changes > 0%)



Vertebral Fracture *(morphometric)*

Population	No. of pts. with fractures/ No. of pts. with evaluable x-rays (%)			
	PBO		ALN 5 & 10	
All	5/134	(3.7)	6/266	(2.3)
Premenopausal	0		0	
Postmenopausal	4/53	(7.6)	5/134	(3.7)
Male	1/48	(2.1)	1/74	(1.4)

Summary

- In men and women on glucocorticoids
 - › Alendronate 5 and 10 mg increase spine and hip BMD relative to placebo and baseline
 - › In postmenopausal women not on HRT, alendronate 10 mg increased lumbar spine BMD more than 5 mg
 - › Alendronate was effective irrespective of baseline characteristics

Summary (Continued)

- › Reduction in vertebral fracture incidence is consistent with reduction in studies of women with postmenopausal osteoporosis
- › Alendronate 5 and 10 mg was generally well tolerated
- › Alendronate 10 but not 5 mg was associated with a small increase in nonserious upper GI adverse experiences

Conclusion

- Alendronate is an effective and generally well tolerated therapy for the prevention and treatment of glucocorticosteroid-induced osteoporosis in men and women

Effect of Baseline BMD on Spine BMD

