Preventie en behandeling van door glucocorticoiden geïnduceerde osteoporose en fracturen

Prof. Dr. Stefan Goemaere

Alumni Avond Colloqium: 24 Februari 2021

Unit for Osteoporosis & Metabolic Bone Disease

Fracture Liaison Service Coordinator

Departments of Rheumatology & Endocrinology

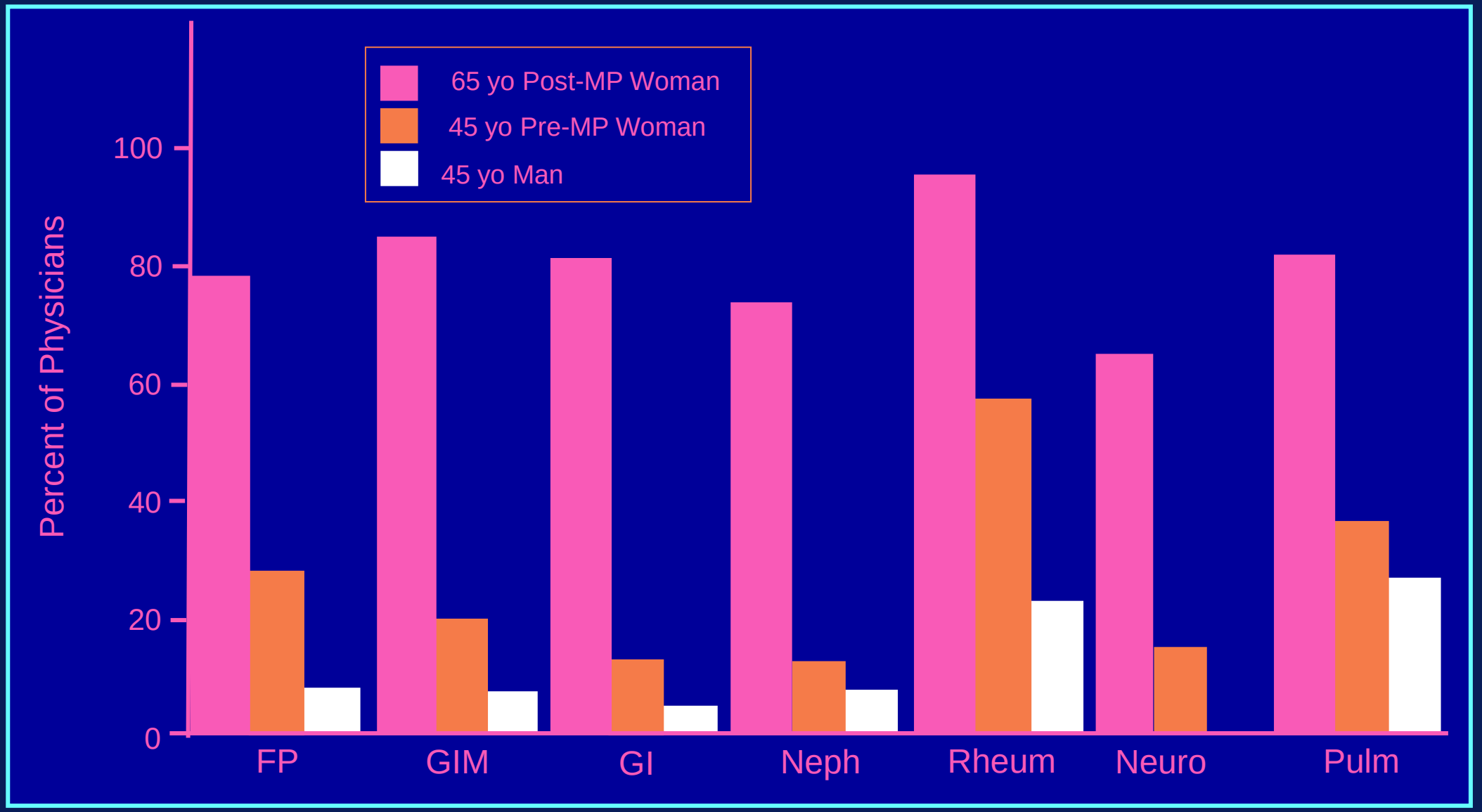
University Hospital Ghent, Belgium

Contents of the presentation

- Introduction and general remarks
- Epidemiology of use of GCs
- Pathogenesis of GC-induced bone loss
- Consequence of GCs: bone loss and fractures
- Literature review on GIOP prevention and treatment
- Guidelines for management of the individual patients treated with oral GCs

List of Side Effects of Chronic & Systemic Glucocorticoid Use

- Increased risk for **infections**
- Thinning of the skin (striae)
- Echymoses
- Decrease wound healing
- Fluid retention
- Weight gain (mainly abdominal trunk)
- Face swelling and buffalo neck
- Increase hear growth and acne
- Stomach ulcer
- Muscle weakness
- Onset or uncontrolled **diabetes**
- Osteoporosis
- Ocular cataract
- Amenorhoe
- Mood swings or psychoses
- Growth retardation in children



Percentage of physicians of different specialties rating osteoporosis as one of the 3 most significant side effects of one year of high dose corticosteroid treatment for 3 different types of patients

Buckley L. et al J Rheumatol 1998;25 (11):2195-202.

Introductory remarks

- Glucocorticoid induced Osteoporosis (GIOP) is a major complication of glucocorticoid therapy known from the beginning of its use in the 1950s.
- The available literature is difficult to interpret because the effects of GC are dependent on :
  - dose and duration GC
  - disease
  - patient population (which is often small and heterogenuous)

CORTICOSTEROÏDEN
Farmacologische eigenschappen

DRIE GROTE EIGENSCHAPPEN

ANTI-INFLAMMATOIRE

IMMUNO-SUPPRESSIEVE

ANTI-ALLERGISCHE

Uitsluitend symptomatische werking

CORTICOSTEROÏDEN
Omzettingsfactor

	equivalent prednisone (mg)	1/x
Prednisone	1	1,000
Prednisolone	1	1,000
Betamethasone	6,67	0,150
Cortisone	0,2	5,000
Dexamethasone	6,58	0,152
Methylprednisolone	1,25	0,800
Triamcinolone	1,25	0,800

Llorca - G Rev Prat 1996

Contents of the presentation

- Introduction and general remarks
- ***Epidemiology of use of GCs***
- Pathogenesis of GC-induced bone loss
- Consequence of GCs: bone loss and fractures
- Literature review on GIOP prevention and treatment clinical studies/trials
- Guidelines for management of the individual patients treated with oral GCs

The scope of the problem
Sex and age distribution of chronic GC use

- 0.5 % of the population
- 1.4 % of the population of > 55 y
- 1.7% of the female population of > 55y

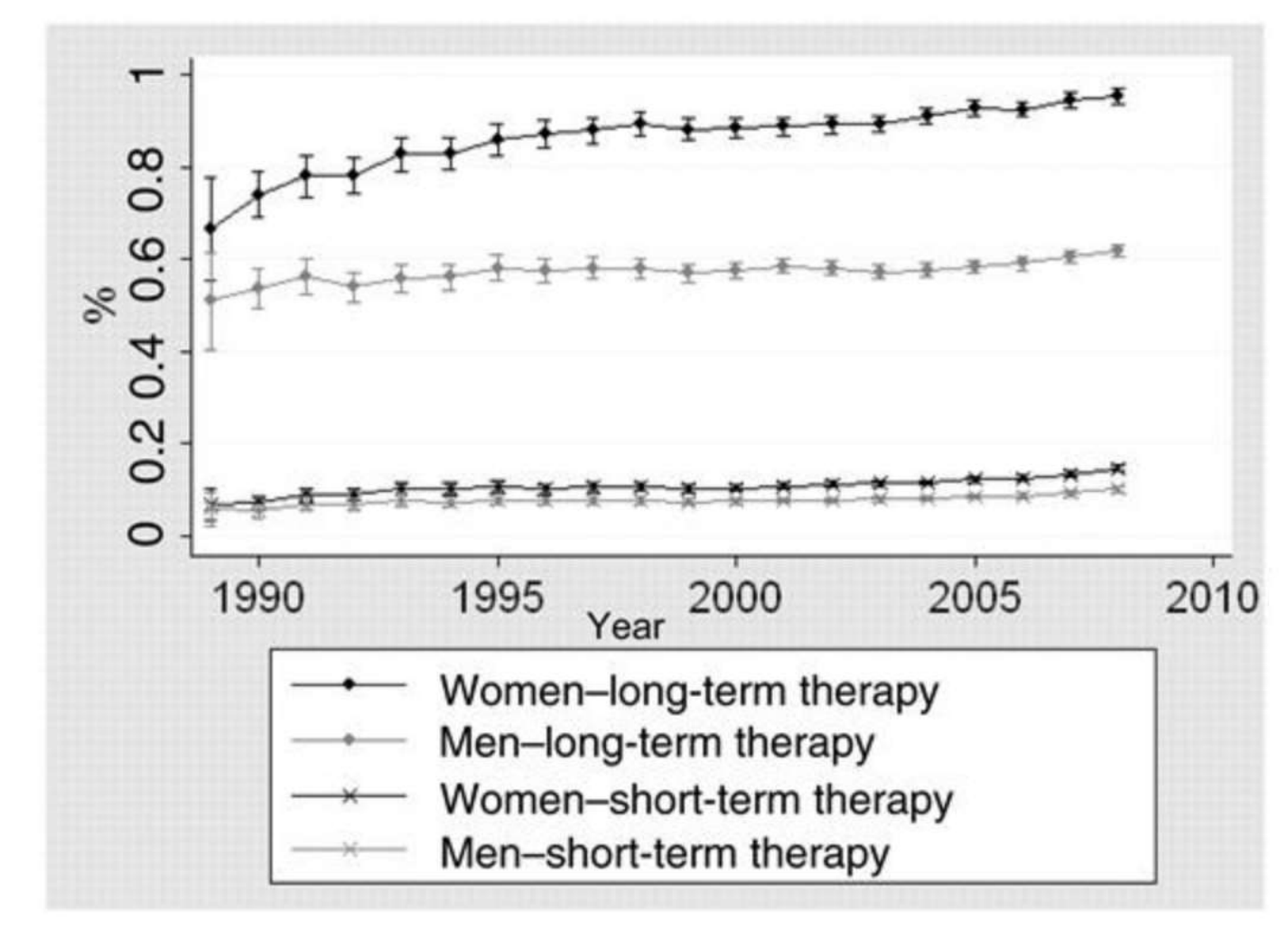
Corticosteroid requiring diseases in in a population based survey (303 cases)

Rheumatoid arthritis	70
Polymyalgia rheumatica	66
COPD	59
Arteritis temporalis	17
Colitis ulcerosa	10
Other*	79

*Transplants, SLE, Alveolitis,Myasthenia, Crohn, Chonic hepatitis, Pemphigus, Neoplastic, Glomerulonephitis, …

Walsh LJ et al, BMJ 1996; 313: 344-8

Prevalence of long-term oral glucocorticoids in UK over the 20 years

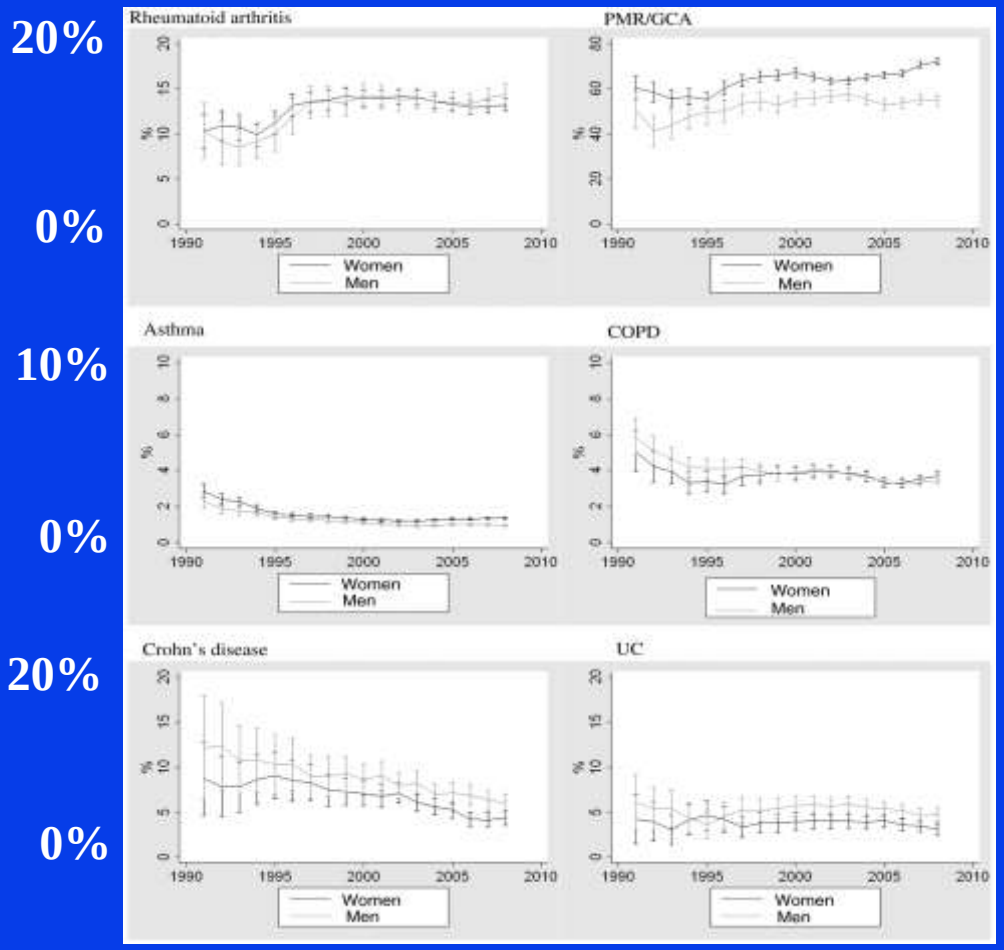


Over the 20 years long-term oral GC increased by **34%**.

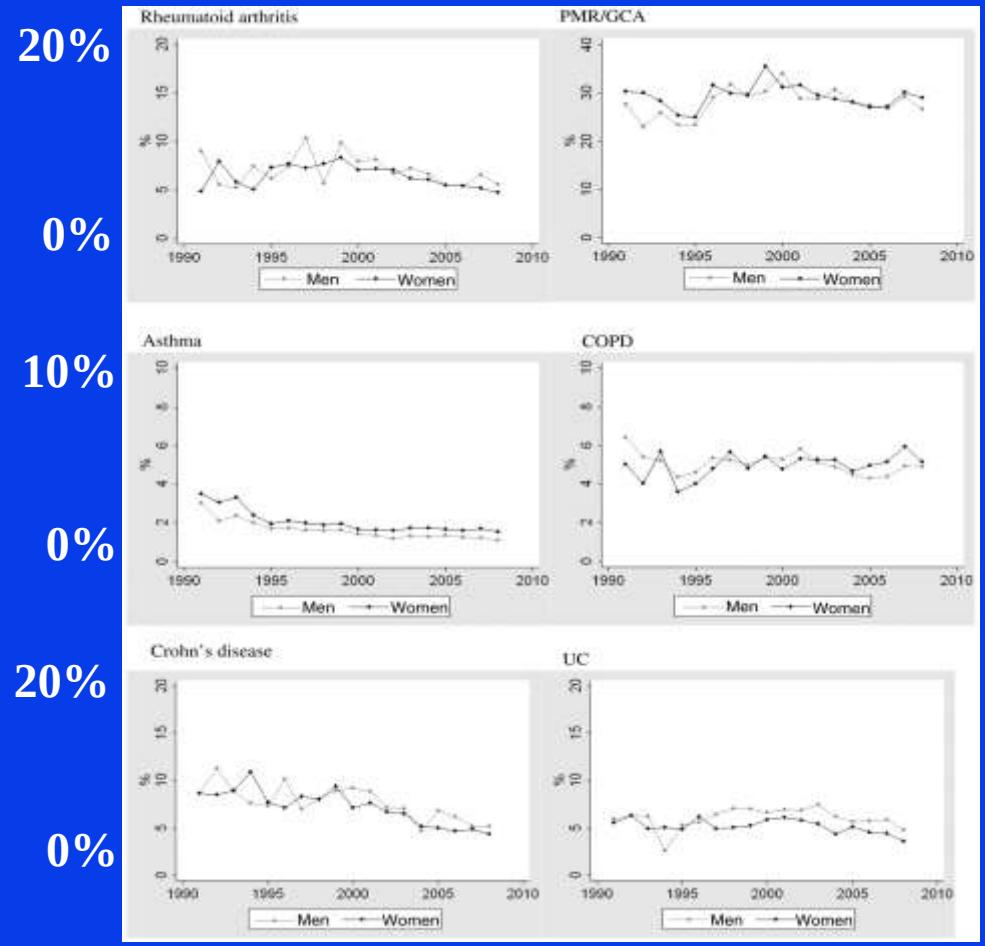
L. Fardet, I. Petersone, I. Nazareth

Rheumatology, 2011 (1): 1982–1990, https://doi.org/10.1093/rheumatology/ker017

Prevalence of long-term oral GC according to underlying disease/sex.



Percentage of patients starting long-term GC therapy by calendar year.



Rheumatology, 2011 (1): 1982–1990,
/doi.org/10.1093/rheumatology/ker017

Patients newly diagnosed with RA, Crohn's disease or UC less likely to receive long-term GC suggesting changes in physicians' practice.

Contents of the presentation

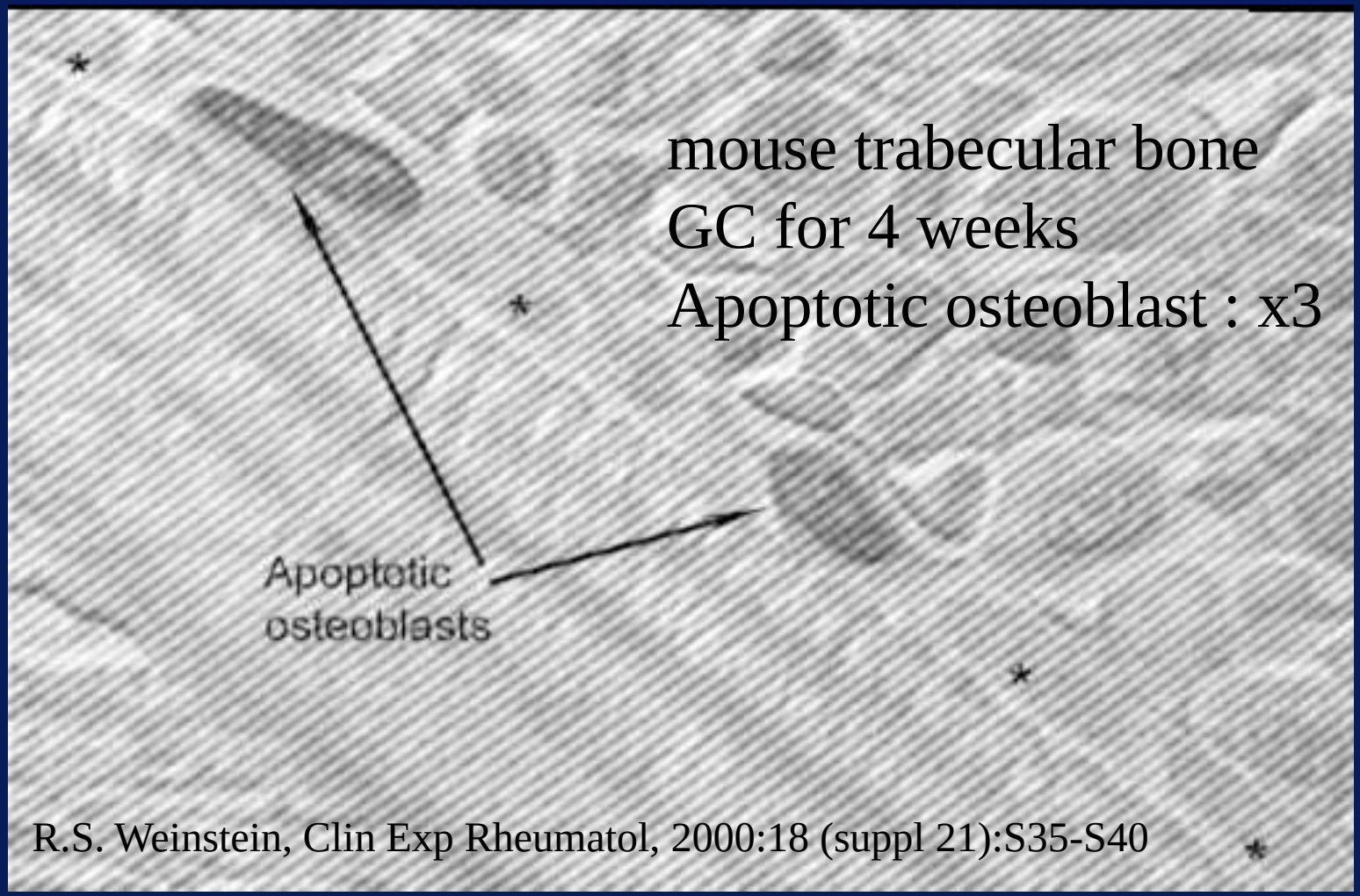
- Introduction and general remarks
- Epidemiology of use of GCs
- ***Pathogenesis of GC-induced bone loss***
- Consequence of GCs: bone loss and fractures
- Literature review on GIOP prevention and treatment clinical studies / trials
- Guidelines for management of the individual patients treated with oral GCs

Pathophysiology of GIOP

Cellular changes in glucocorticoid-induced osteoporosis

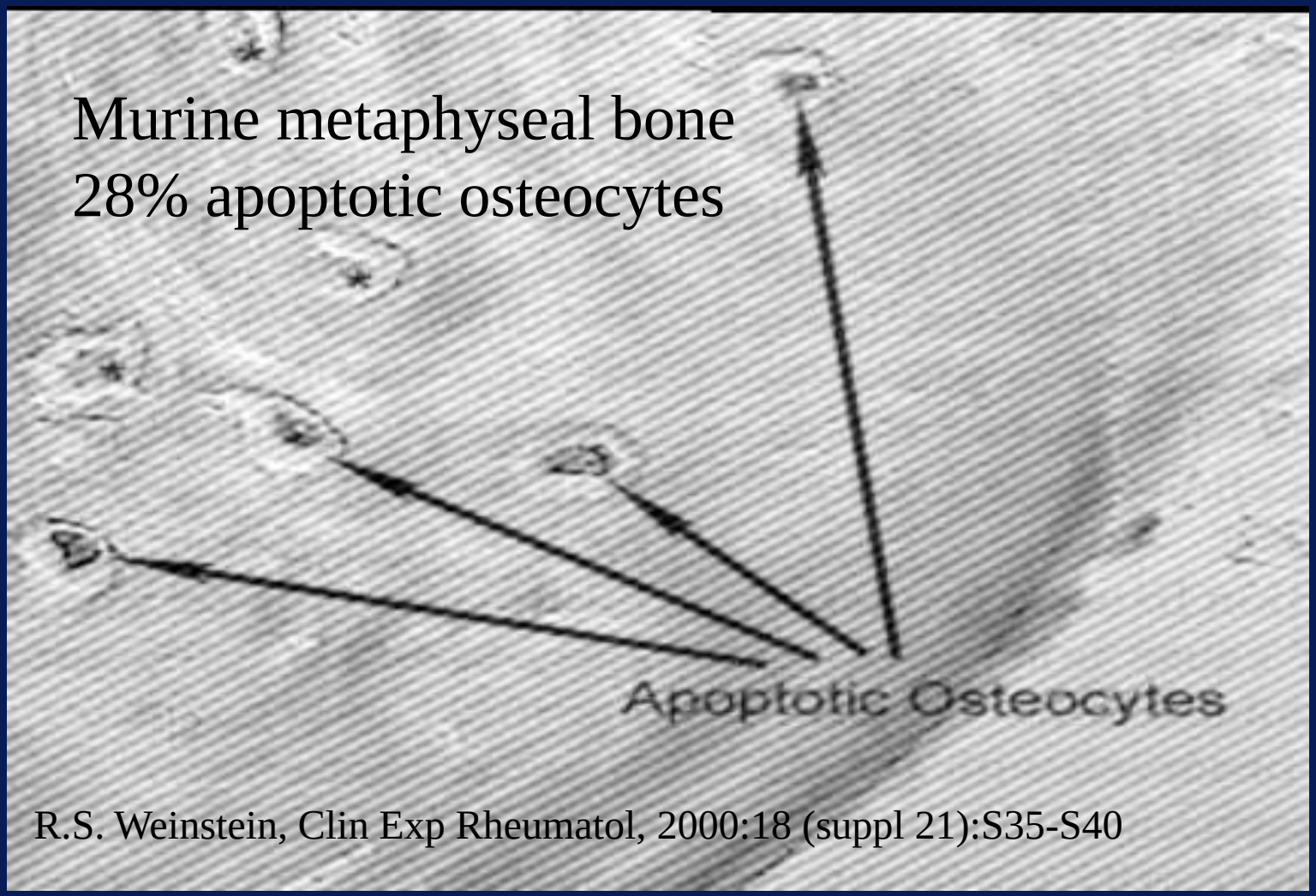
Cellular changes	Explanation
↓ Osteoblastogenesis	Decreased Cbf1, TGF-β Rec, BMP2, IGF1
Osteoclast numbers	
↑ Early	Transient increase RANK ligand/OPG
↓ Late	Decrease osteoblast osteoprogenitors
↓ Lifespan osteoblasts	
↓ Lifespan osteocytes	

Osteoblastic apoptosis after glucocorticoid treatment



Weinstein, R. S., Jilka, R. L., Parfitt, A. M. & Manolagas, S. C. ; J. Clin. Invest. 102, 274–282 (1998).
Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids.
Potential mechanisms of their deleterious effects on bone.

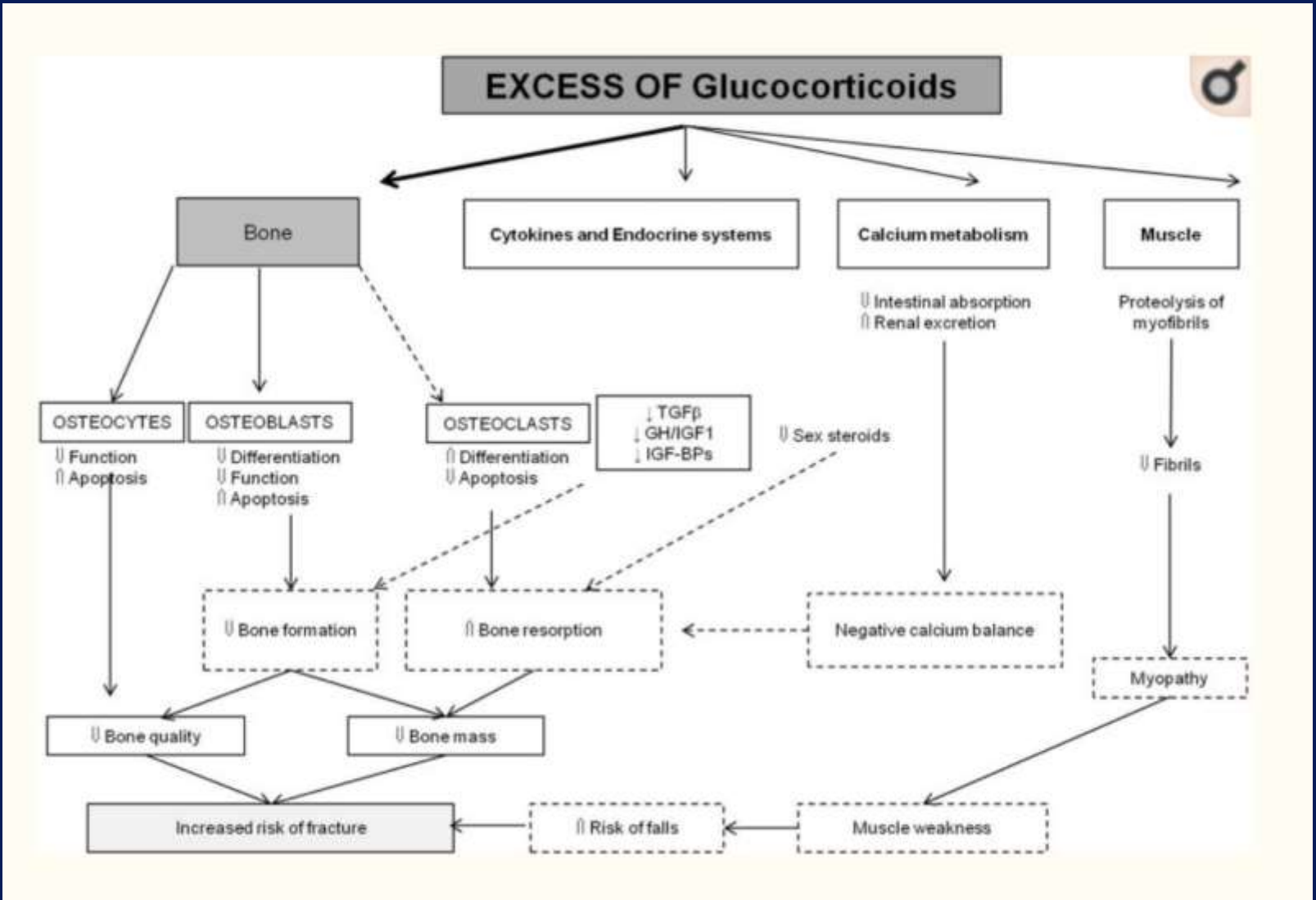
Osteocytic apoptosis after glucocorticoid treatment



R.S. Weinstein, Clin Exp Rheumatol, 2000:18 (suppl 21):S35-S40

Weinstein, R. S., Jilka, R. L., Parfitt, A. M. & Manolagas, S. C. ; J. Clin. Invest. 102, 274–282 (1998). Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone.

Pathophysiology of GIOP



Canalis E, Mazziotti G, Giustina A et al. Osteoporos Int 2007;18:1319–28. 10.1007/s00198-007-0394-0
Glucocorticoid-induced osteoporosis: pathophysiology and therapy.

Contents of the presentation

- Introduction and general remarks
- Epidemiology of use of GCs
- Pathogenesis of GC-induced bone loss
- ***Consequence of GCs: bone loss and fractures***
- Literature review on GIOP prevention and treatment clinical studies / trials
- Guidelines for management of the individual patients treated with oral GCs

Pattern of GC-induced bone loss

- At both lumbar spine and hip (Trab. > Cort.)
- Dose related
- Most rapid in first months and year
- 10 to 15 % decrease (2x fracture rate)
- Continues at an increased rate (2 to 3x) on longterm GC-therapy
- Individual variability (genetic,pharmacokinetic,disease)

Risk factors for GC-induced bone loss

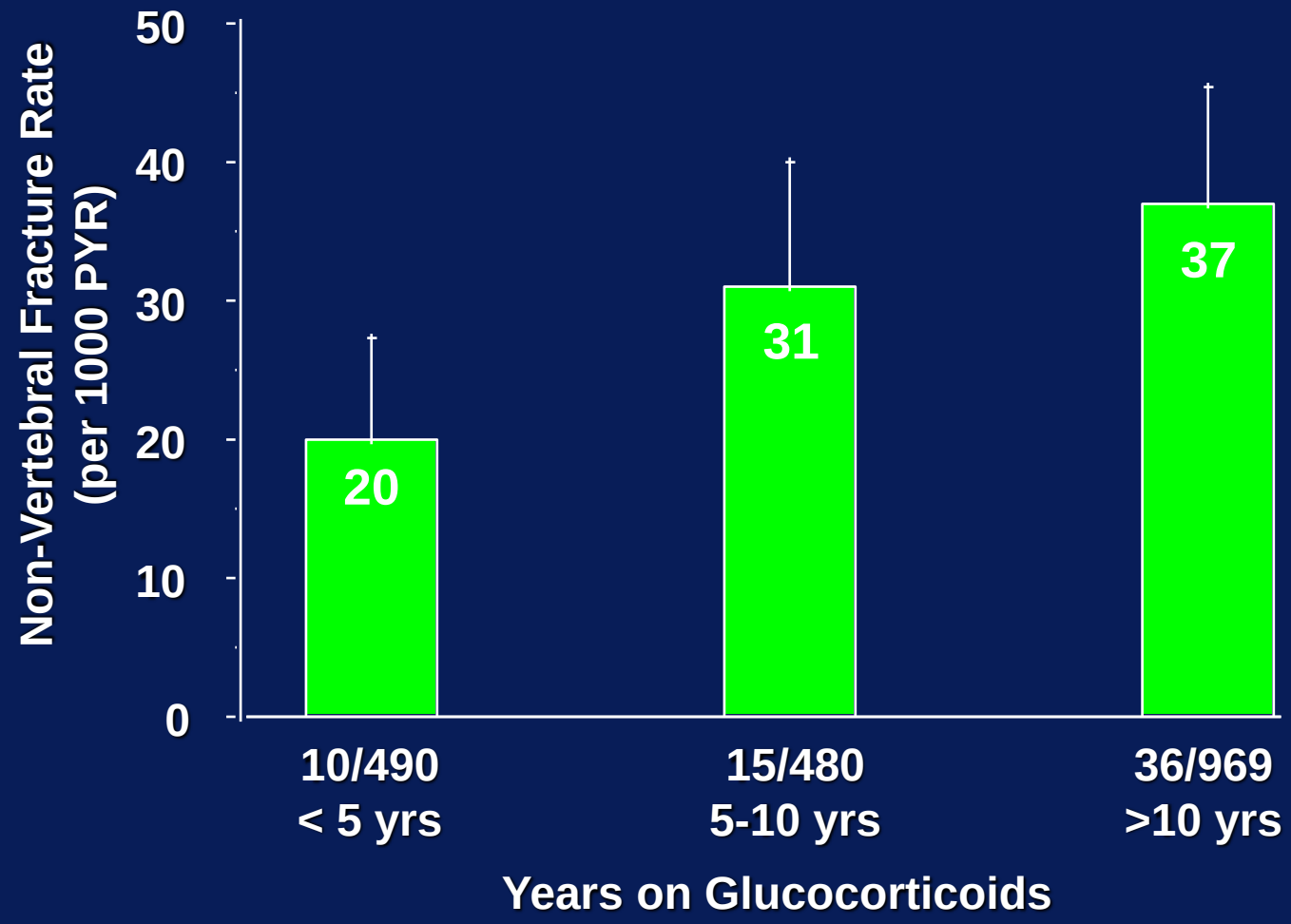
- Major
  - high total cumulative dose
  - age (< 15 y or > 50 y)
  - postmenopausal status
- Secondary
  - Long duration, disease severity (with increased IL-1), small body build, caucasion or asian race

Recovery of GC-induced bone loss after glucocorticoid treatment

- Incomplete recovery:
  - Pocock (‘87): treatment of cushing
  - Identical twin case with treated cushing
  - Longitudinal study of RA
  - Persistent increase of non-VF fracture rates
    - » < 2 year: RR= 1.8
    - » < 5 year: + 20%

Non-VF Rate by Time Spent on GC

Retrospective analysis of baseline data in GIOS trial



Goemaere et al, 2003 . J Clin Rheumatol 9:170-175

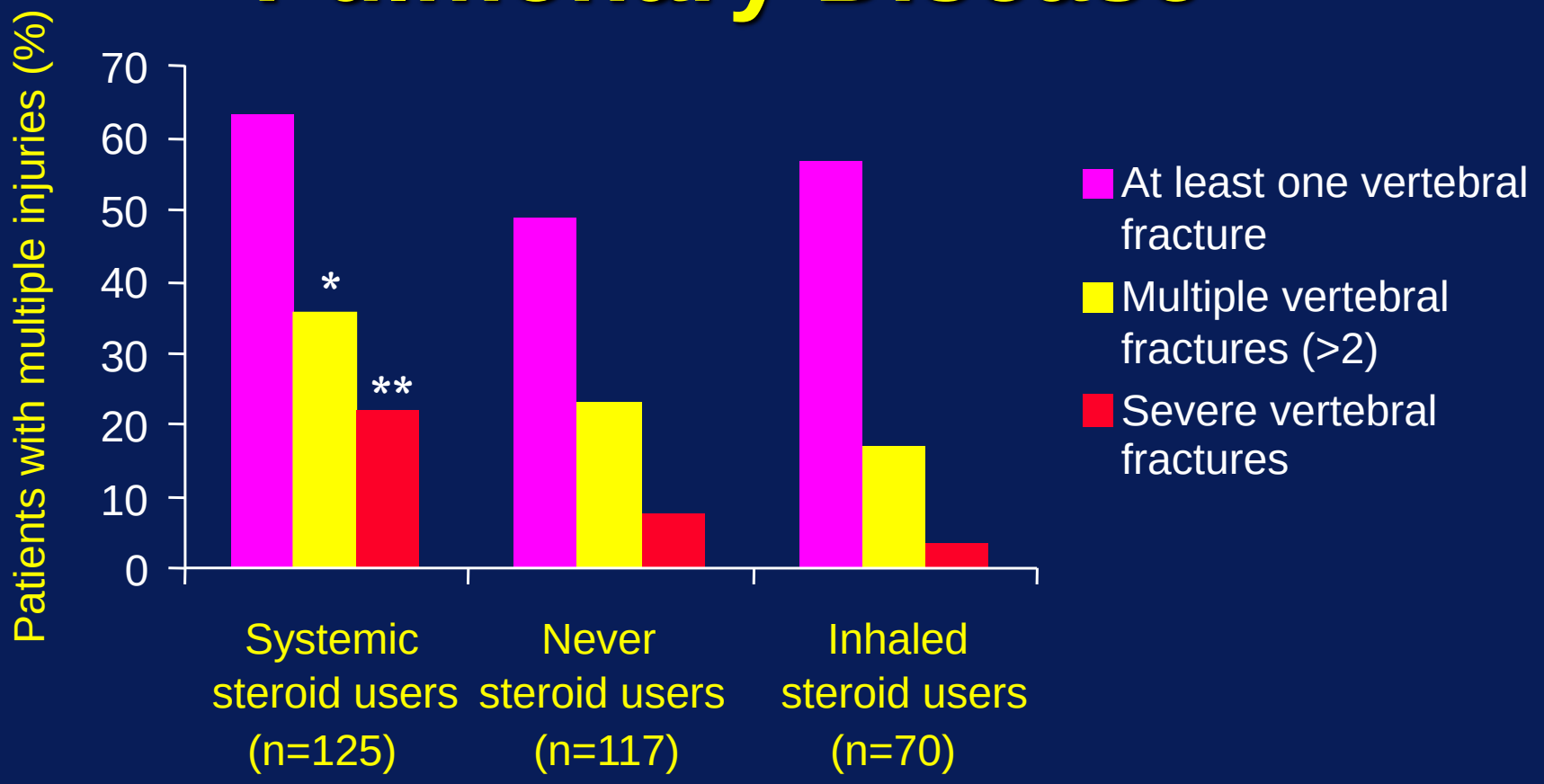
Incidence of nonvertebral fractures in relation to time on treatment and bone density in glucocorticoid-treated patients

Rheumatoid Arthritis, Corticosteroid Use, and Increased Risk of Hip Fracture

Risk factor	Odds ratio unadjusted	Odds ratio adjusted for other variables
Rheumatoid arthritis	2:1 (*P* =0.06)	BMI, smoking, alcohol: 1:9 BMI, smoking, alcohol, ADL: 1:3
Corticosteroid use	2:7 (*P* =0.01)	BMI, smoking, alcohol: 2:5 BMI, smoking, alcohol, ADL: 2:1

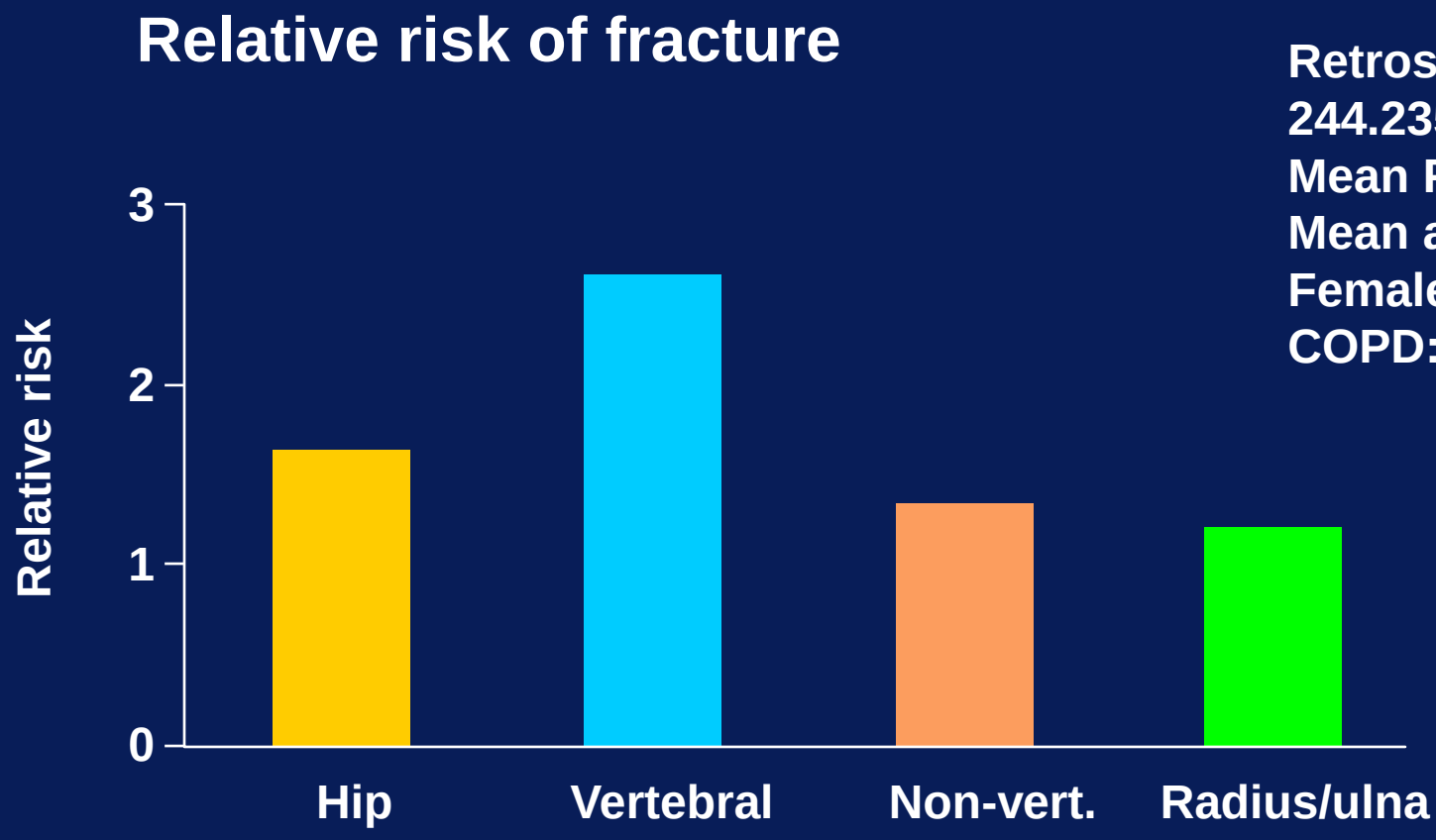
BMI=Body mass index; ADL=activities of daily living.
Cooper C, et al, 1995.

CIO and Chronic Obstructive Pulmonary Disease



*P<0.05 vs. ISU or NSU; **P<0.005 vs ISU.
McEvoy CE, et al, 1998.

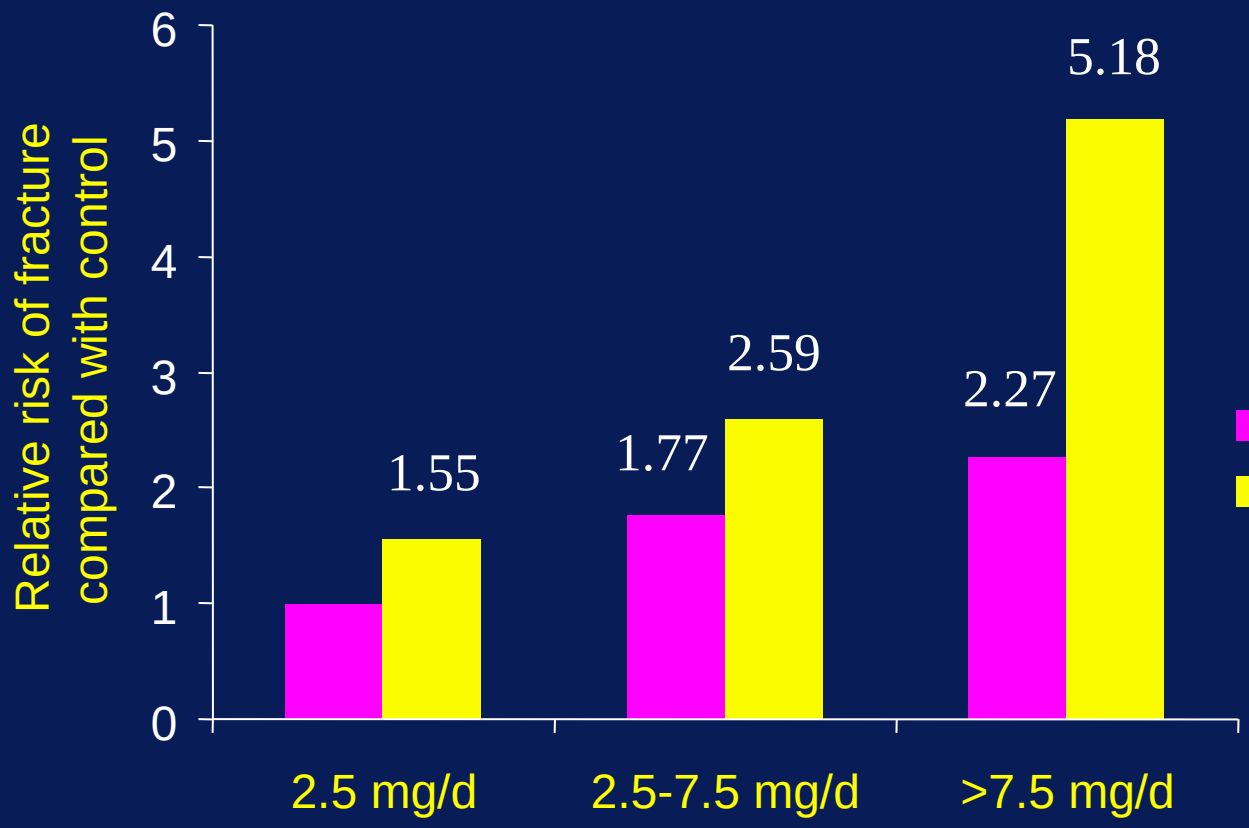
GPRD (General Practionners Research Database)
Effect of CS on Fracture Risk



Retrospective cohort
244.235 cases vs Ctrls
Mean FU: 1.3y
Mean age: 57y
Female: 58.6%
COPD: 40%

TP Van Staa *et al*, 1998

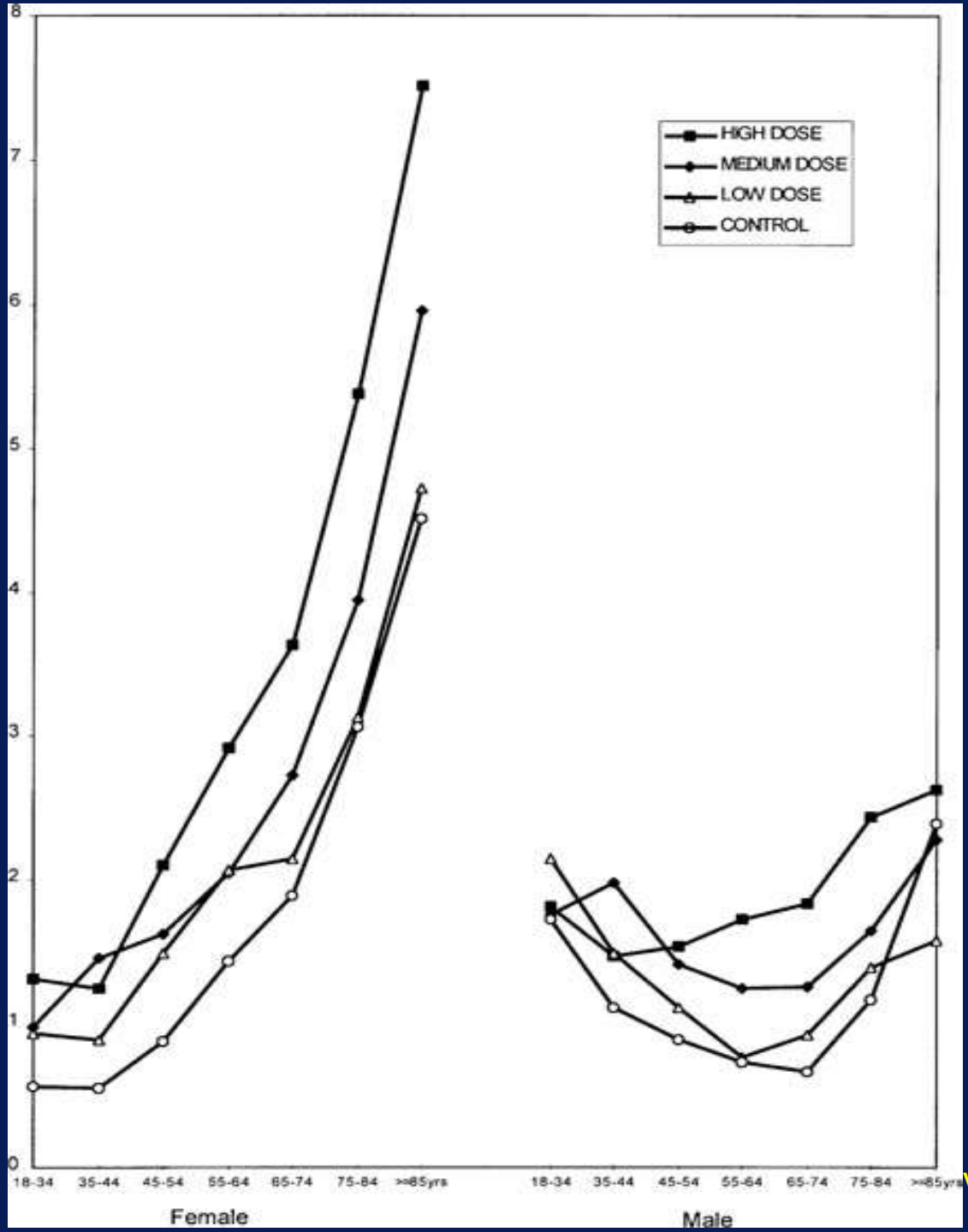
Fracture Risk & Dose of Corticosteroids



Retrospective cohort
244.235 cases vs Ctrls
Mean FU: 1.3y
Mean age: 57y
Female: 58.6%
COPD: 40%

Hip fracture
Vertebral fracture

Relative risk of fracture by dosages of prednisolone.
van Staa TP, et al, 1998.



Use of Oral Corticosteroids and Risk of non-VF

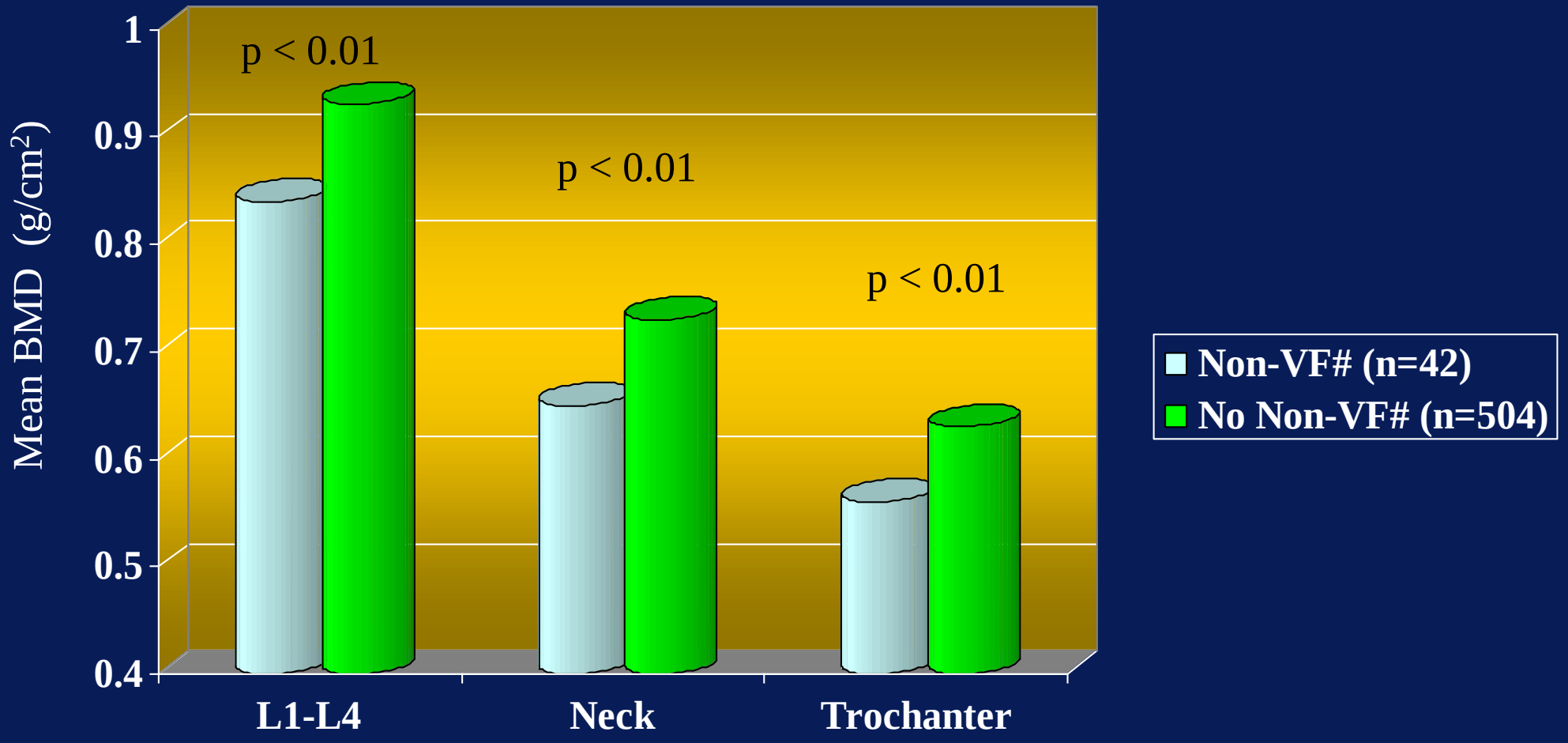
Dose relationship in non-VF

GPRD - retrospective
244.235 Case vs Crtls
Mean FU: 1.3y
Mean age: 57y
Female: 58.6%
COPD: 40%

Van Staa et al 2000; JBMR (6), 993-1000, DOI: (10.1359/jbmr.2000.15.6.993)

Non-VF# in relation to BMD

Retrospective analysis of the baseline data in the GIOS trial



Goemaere et al, 2003 . J Clin Rheumatol 9:170-175

Incidence of nonvertebral fractures in relation to time on treatment and bone density in glucocorticoid-treated patients

BMD - fracture relationship in GIOP

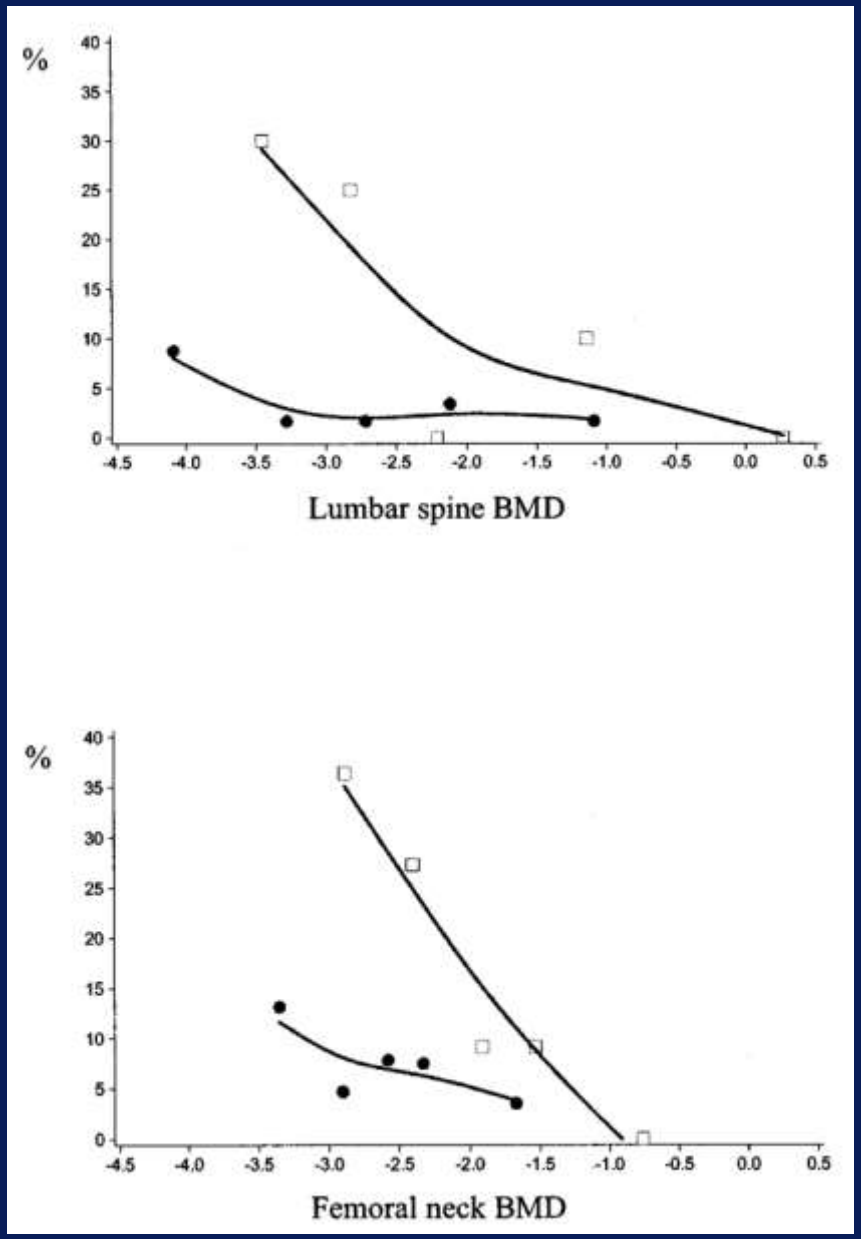
- Fracture threshold ?
  - Higher in astma/COPD
  - Pre-treatment BMD cutoff : T-score = -1 or -1.5

    (Luengo et al, Thorax 1991;46:803-6)

- Relationship BMD - fracture underestimated ?
  - RR / SD is higher : x5 in RA

    (Peel et al, Ann Rheum Dis 1995;54:801-6)

Incidence of vertebral fracture in PM women receiving GCs compared with nonusers

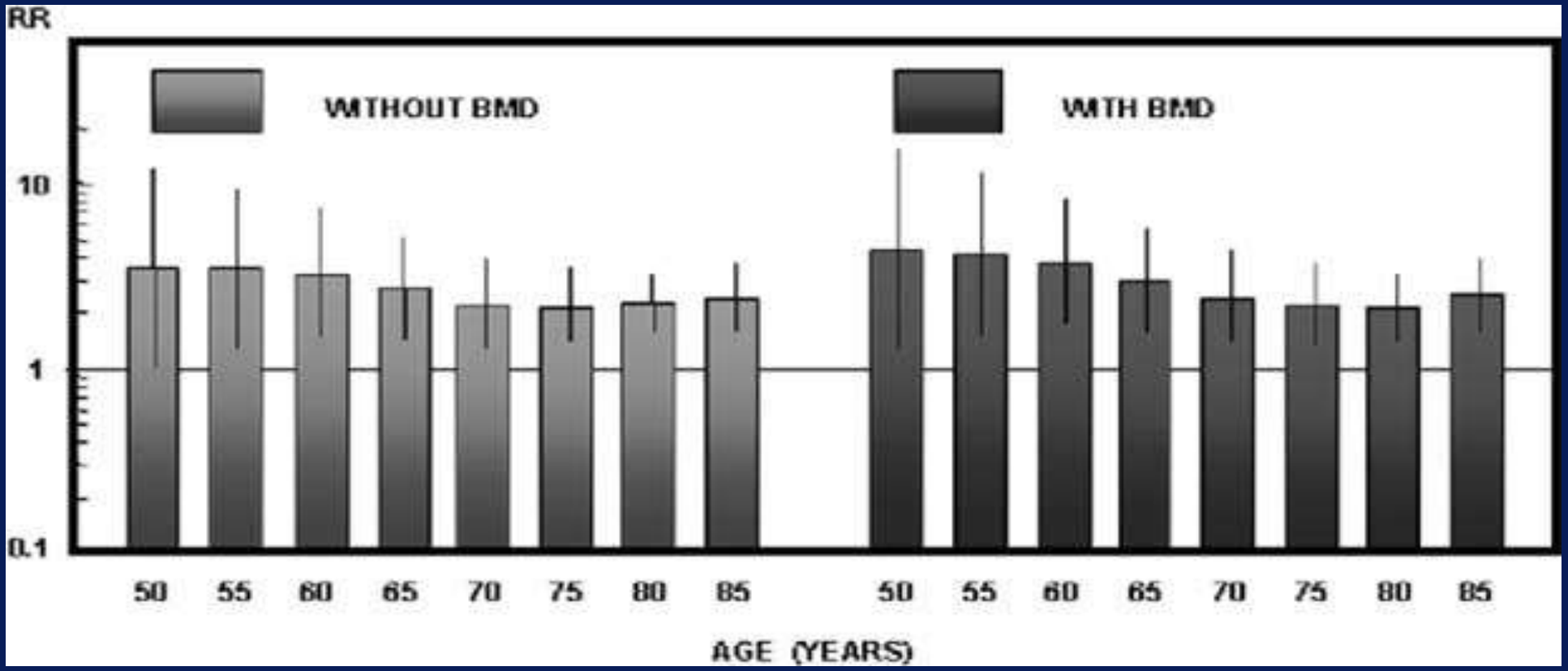


1 year prospective data from placebo controlled clinical trials with risedronate in PMO and GIOP

- The individual data points correspond to the incidence in subgroups of the GC user and nonuser populations, as based on quintiles of baseline BMD.
- The solid line is a curve representing smoothing of these individual estimates.

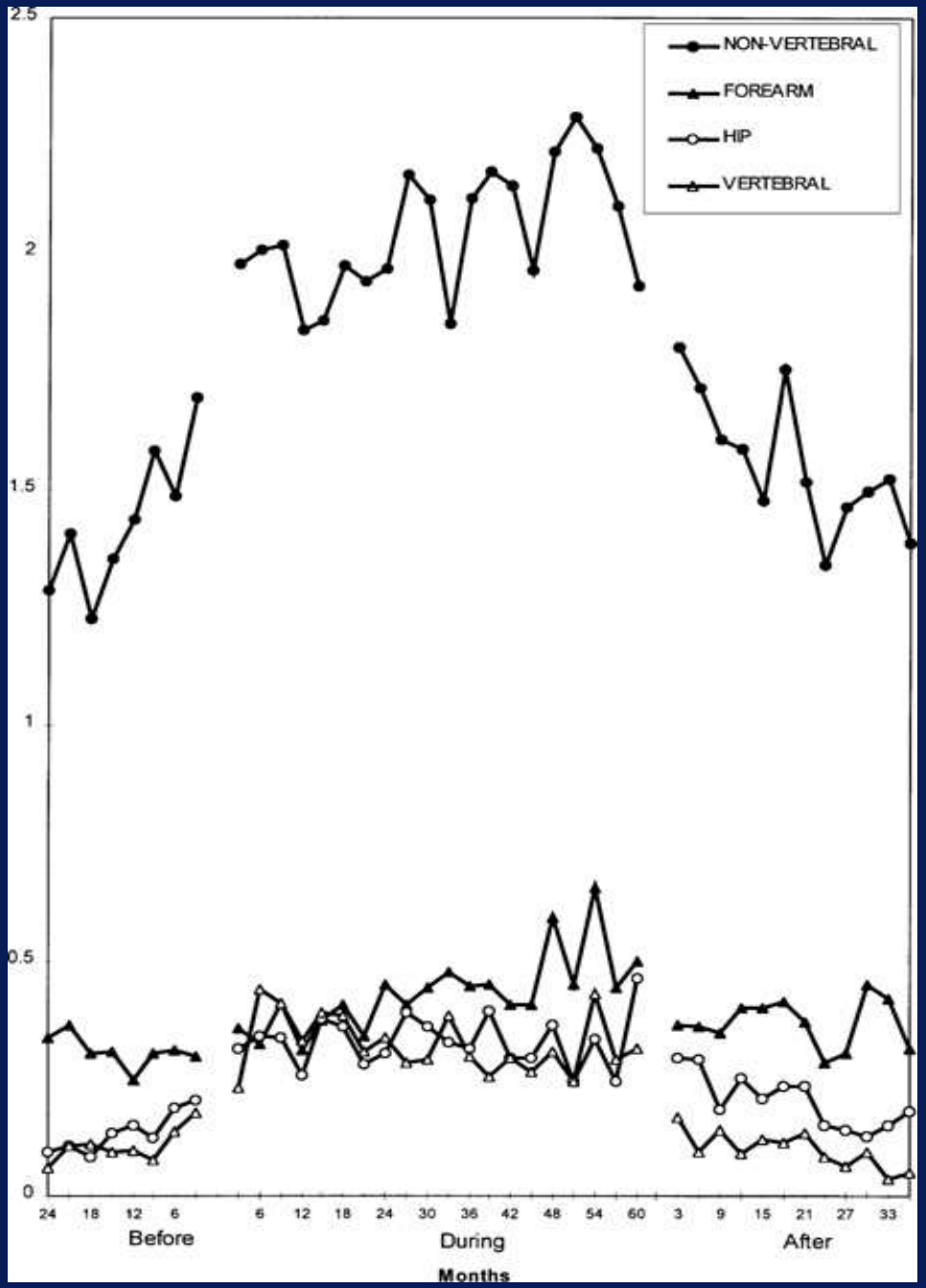
Van Staa et al, 2003
Arthirits & Rheumatism (48): 3224–3229
DOI 10.1002/art.11283

A Meta-Analysis of Prior Corticosteroid Use and Hip Fracture Risk
Prospective Cohort Studies



Kanis J et al, JBMR 2004 (19): 893-899, DOI: (10.1359/JBMR.040134)

Onset / Offset of fracture risk in oral glucocorticotherapy



GPRD - retrospective
244.235 Case vs Ctrls
Mean FU: 1.3y
Mean age: 57y
Female: 58.6%
COPD: 40%

← **Non-vertebral (RR = 1.33)**

← **Forearm (RR = 1.09)**

← **Hip (RR = 1.61)**

← **Vertebral (RR = 2.60)**

Van Staa et al 2000; JBMR (6), 993-1000, DOI: (10.1359/jbmr.2000.15.6.993)

GC and fracture incidence: conclusion

- Increased VF# (x2-5) and non-VF# (eg hip x2)
- Dose related increase # risk : no save dose !
- Early onset / offset of increase of fractures rates
- Type of fracture dependent on disease
- BMD - fracture relationship is different from PMO

Contents of the presentation

- Introduction and general remarks
- Epidemiology of use of GCs
- Pathogenesis of GC-induced bone loss
- Consequence of GCs: bone loss and fractures
- ***Literature review on GIOP prevention and treatment clinical studies/trials***
- Guidelines for management of the individual patients treated with oral GCs

Prevention and Treatment of GC-induced bone loss

- Observational data
- Randomized, controlled clinical trials
- Systematic Review and Meta-analysis (for guideline development)

Strategies of preventing bone loss/fractures

If dose > 5-7.5 mg/d for more than 3-6 months :

1. General measures (in all GC patients)
2. Bone specific intervention
   - a/ Bone resorption : Ca/D, Hormonal replacement, bisphosphonate, denosumab
   - b/ Bone formation : rhPTH (teriparatide)

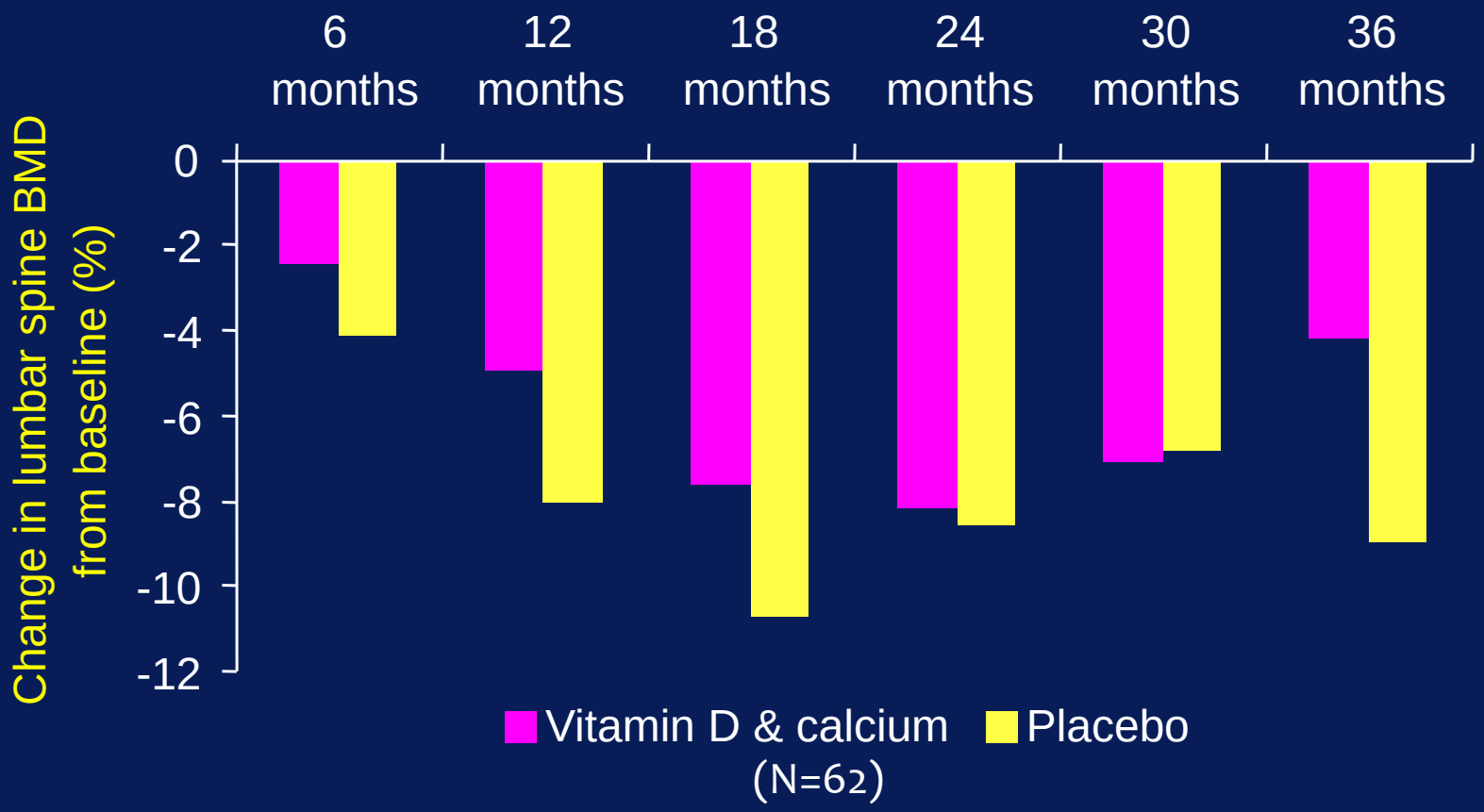
Strategies of preventing bone loss/fractures

- Primary prevention
  - at onset of GC therapy (< 3-6 months)
- Secondary prevention or treatment
  - after longterm GC therapy (> 6 months)
  - after low bone mass with or without fracture

General measures for preventing bone loss

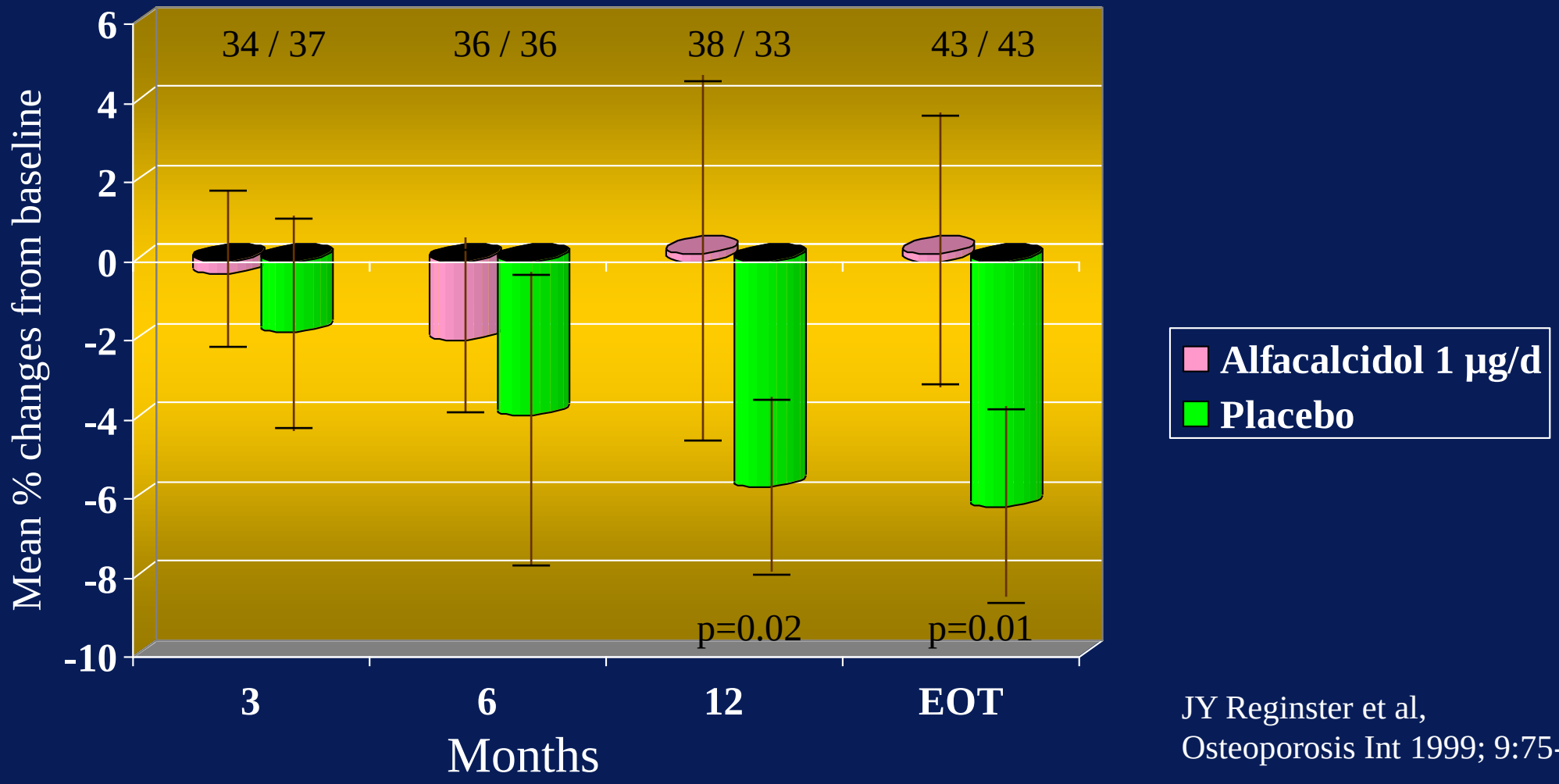
- Reduction of GC dose to minimum for disease control
- Nutritional measures:
  - calcium, vitamin D, protein
- Modification of lifestyle factors
  - smoking, alcohol, mobilisation & extension exercise of back
- Alternative route (oral vs inhaled)
- Alternative GC (budesonide)
- Alternate day (no proven preventive effect)

Vitamin D and Calcium in prevention of GIOP: a longitudinal study of 3 years



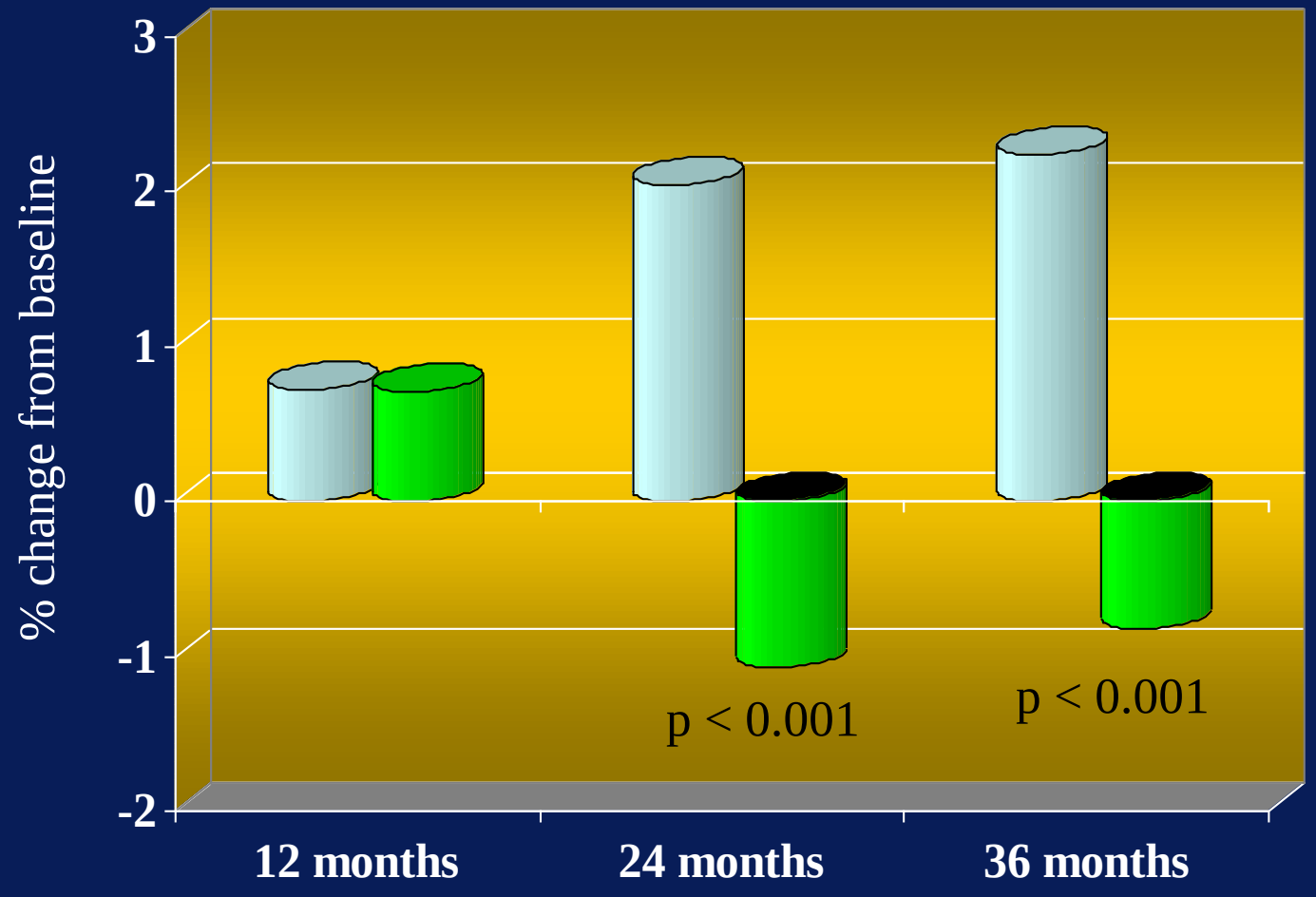
Adachi JD, Bensen WG, Bianchi F et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year follow-up. J Rheumatol, 1996; 23:995-1000.

Alfacalcidol in prevention of glucocorticoid-induced bone loss



JY Reginster et al,
Osteoporosis Int 1999; 9:75-81.

Plain vit D vs active metabolites in treatment of GIOP



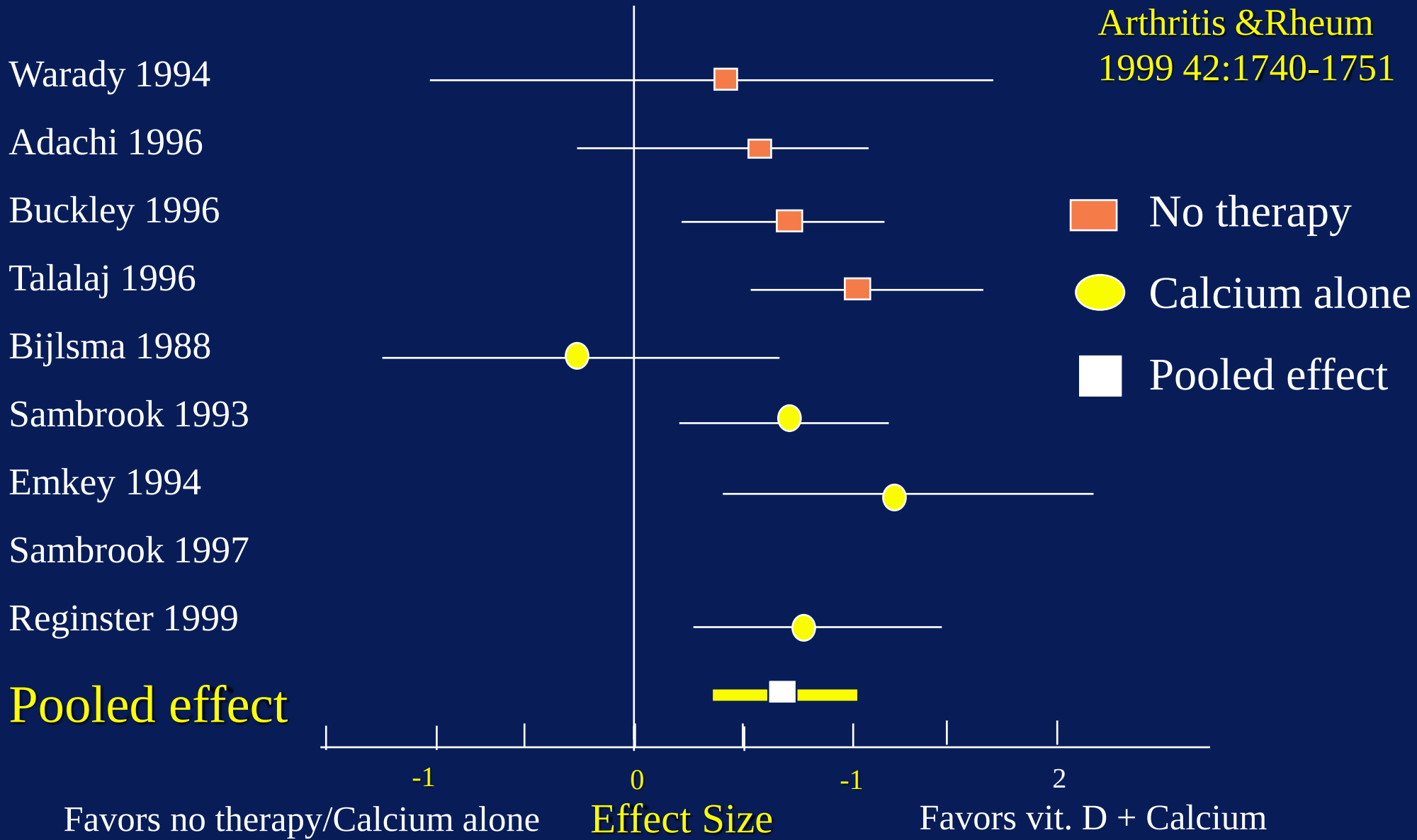
Spine fracture reduction
12/63 vs 22/61

Alfacalcidol 1µg/d
Vitamin D 1000 IU/d

+ 500 mg Calcium/d

JD Ringe et al, Calcif Tissue Int 1999;63:337-40

Meta-analysis of effects on spine BMD in GC-treated patients



Homik J, Suarez-Almazor ME, Shea B, et al.: Calcium and vitamin D for corticosteroid-induced osteoporosis. Cochrane Database Syst Rev 2002, (2):CD000952.

Confirmation of the efficacy of Ca/D supplementation
Compared to placebo or Calcium alone

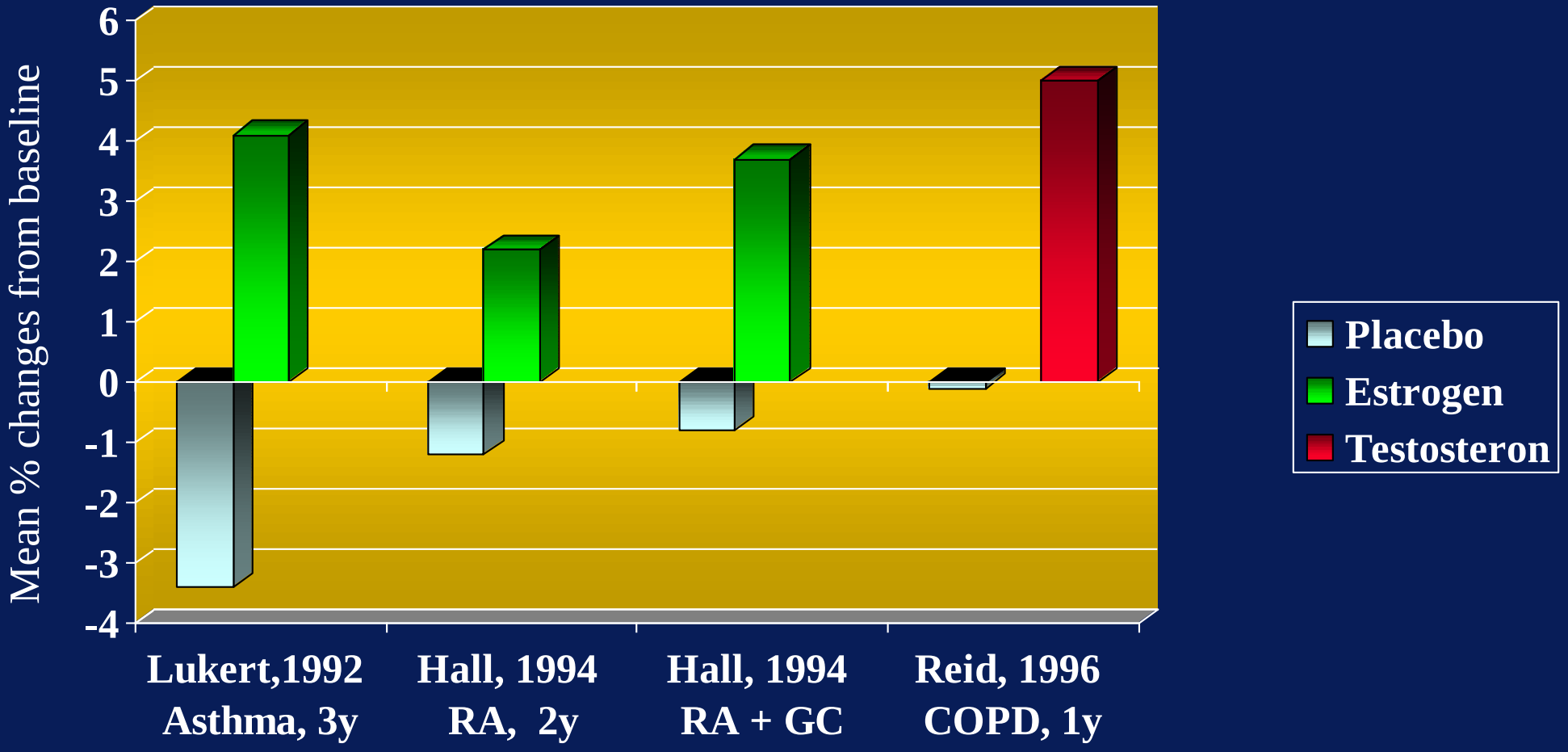
Role of calcium, vitamin D and metabolites in the management of GIOP: conclusions

- Calcium supplementation (500 - 1000 mg/) is not sufficient to stop bone loss (- 2 to 3% /year)

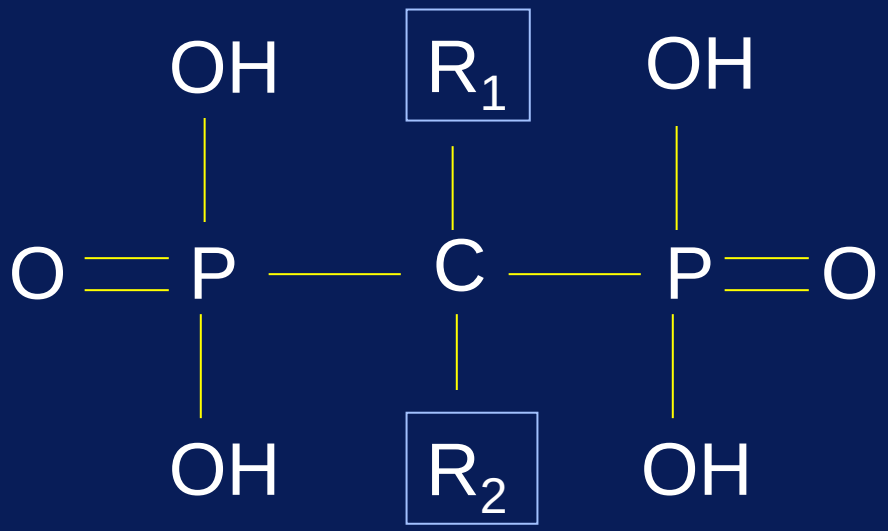
- Vitamin D plus calcium may moderately reduce bone loss (>> in first year and in Vit D depleted patients)

- Active metabolites calcitriol (0.5 µg/d) and alfacalcidol (1 µg/d) are effective in prevention & treatment of GIOP

Treatment of GC-induced spinal bone loss by Hormonal Replacement Treatment (HRT)



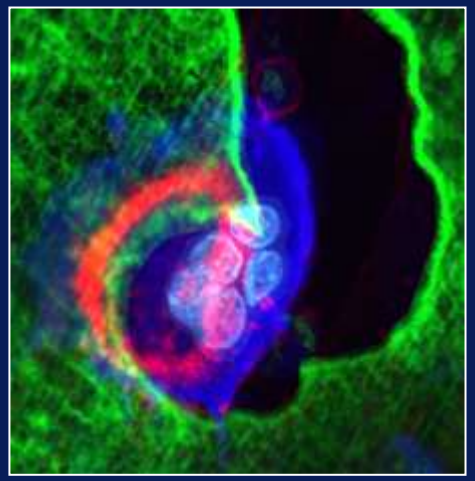
Bisphosphonates in GIOP



(Etidronate)
Pamidronate
Alendronate
Risedronate
Ibandronate
Zoledronate

Bisphosphonates Mode of Action

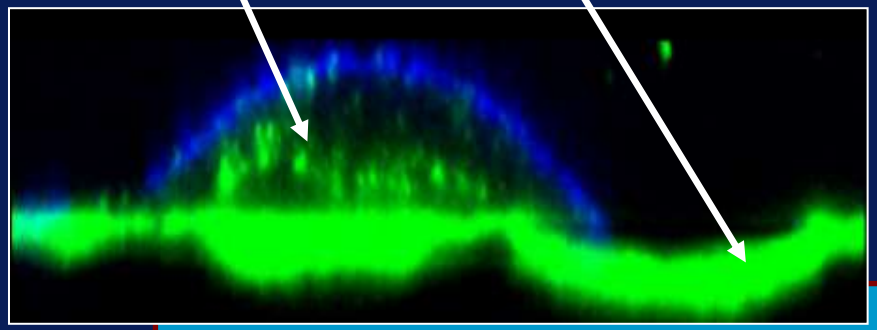
BP binding to the bone surfaces

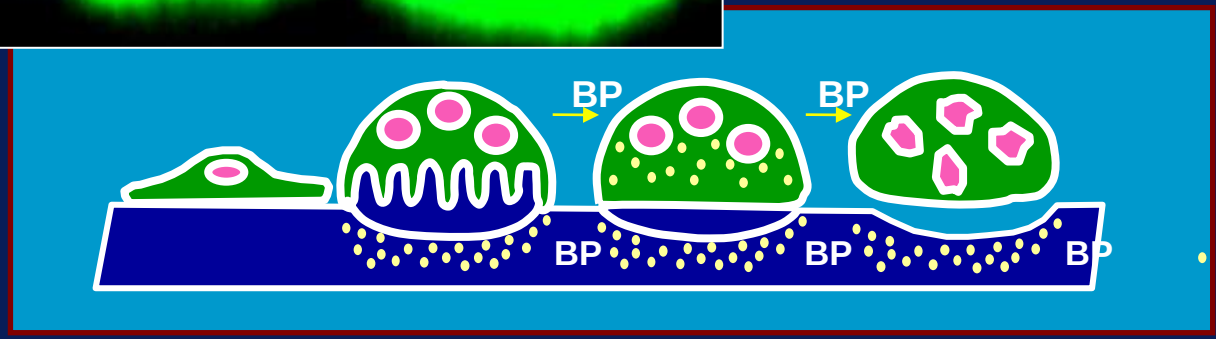


- Bisphosphonate (bone surface
- Osteoclast membrane/nucleus
- Cytoskeleton

Courtesy of Dr Fraser Coxon, University of Aberdeen

BP are internalized in the osteoclasts during the bone resorption





Mode of action of aminobisphosphonates

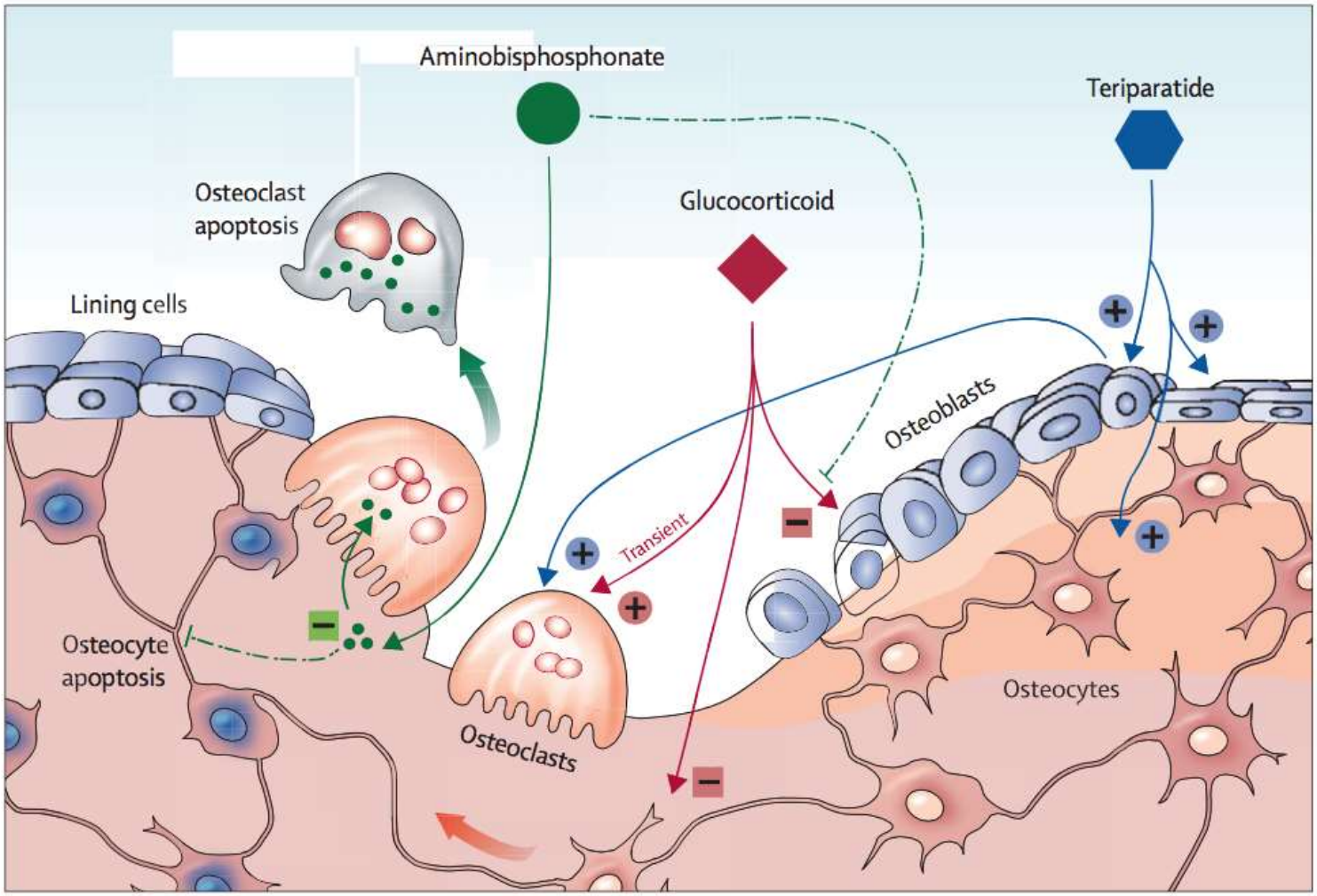
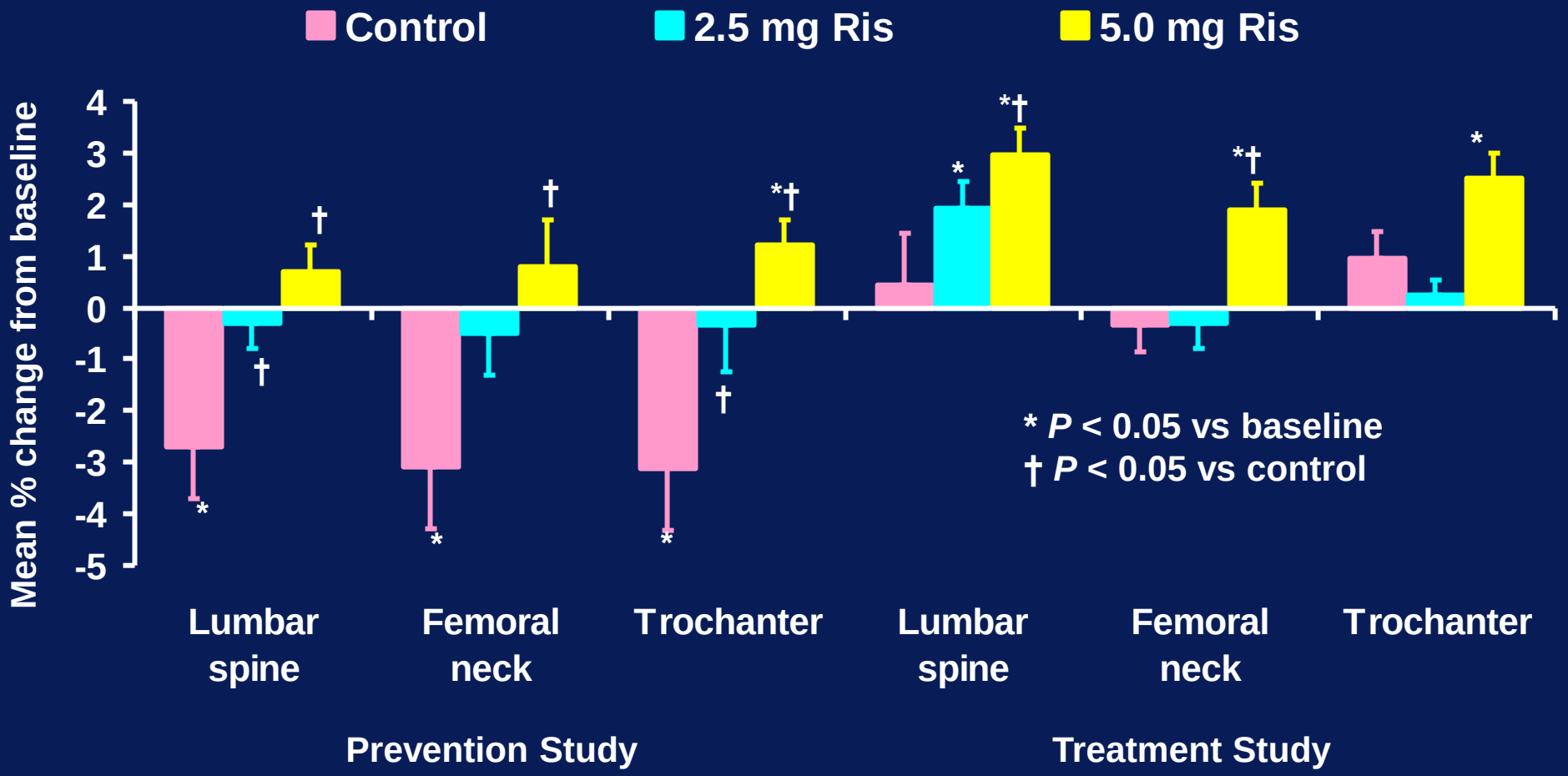


Figure: **Effects of glucocorticoids, bisphosphonates, and teriparatide on bone cells**
Dotted lines indicate potential effects of bisphosphonates.

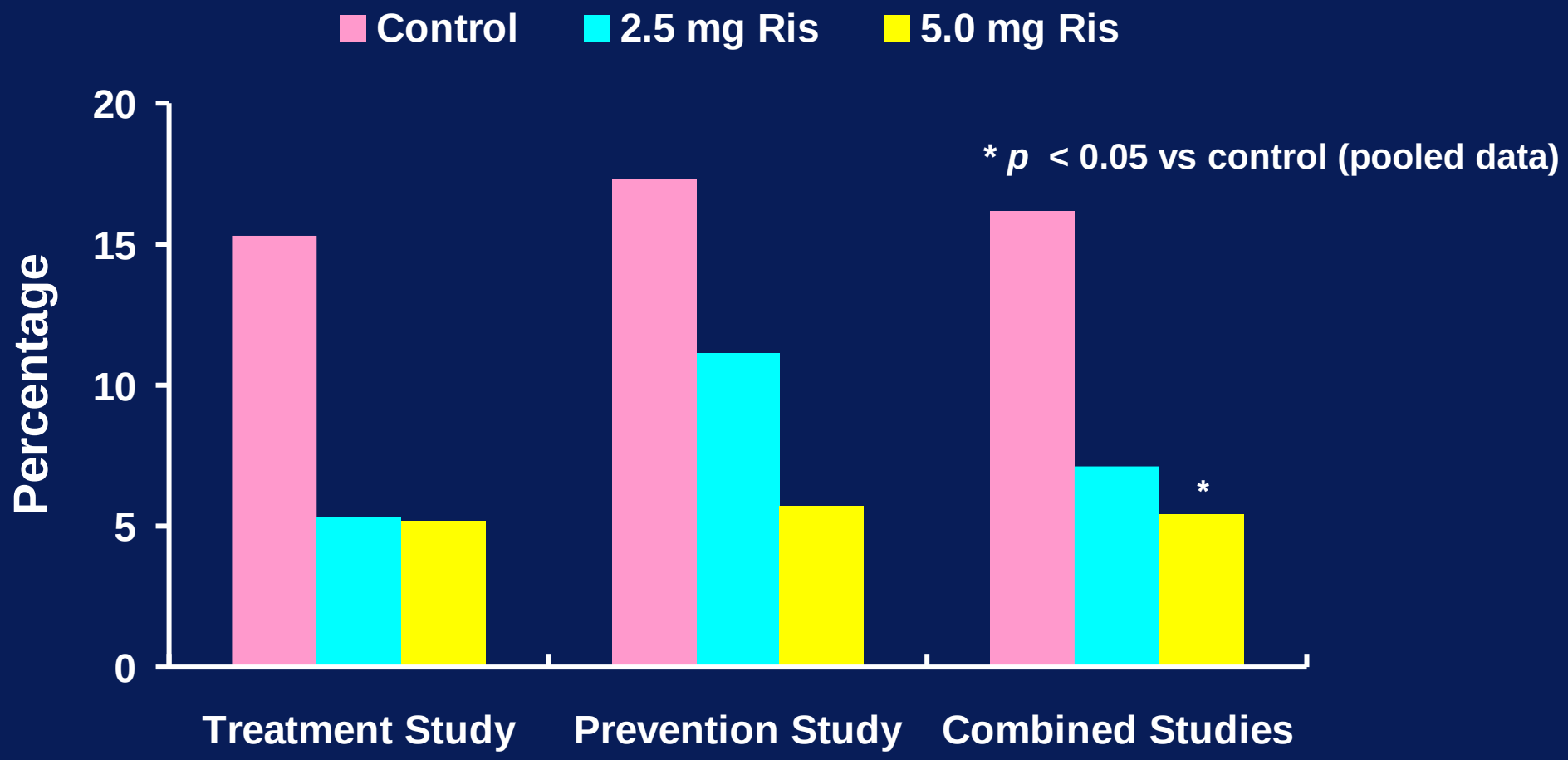
Luigi Gennari
John P Bilezikian
Lancet (373); 2009
p: 1225-6

Risedronate prevention/treatment in GIOP: BMD Change from Baseline at Month 12



Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, et al. Arthritis Rheum 1999; 42:2309–18.
Risedronate therapy prevents corticosteroid-induced bone loss – a twelve-month placebo-controlled trial

Risedronate in treatment of GIOP: Vertebral Fractures at Month 12



Wallach S, Cohen S, Reid DM, Hughes, RA, Hosking DJ, Laan RF, et al. y. Calcif Tissue Int 2000;67:277–85.
Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy

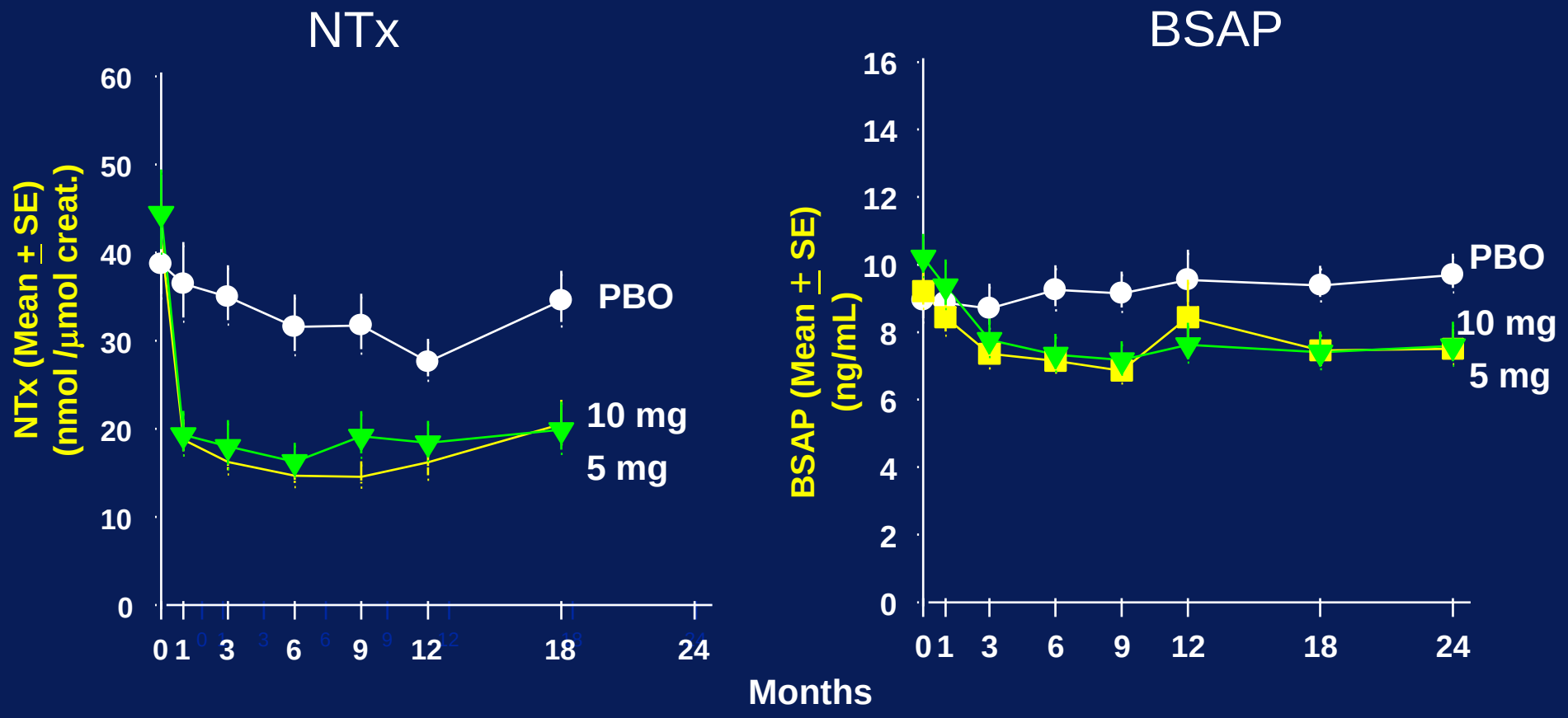
Reid D, Cohen S, Pack S, Chines A, Ethgen D. Arthritis Rheum 1998;41(9) Suppl:S136.
Risedronate reduces the incidence of vertebral fractures in patients on chronic corticosteroid therapy.

GIOS-Alendronate study: Treatment Groups

Year 1 (N=560)		Year 2 (N=208)	
PBO	(N=159)	PBO	(N=61)
ALN 5 mg	(N=161)	ALN 5 mg	(N=63)
ALN 10 mg	(N=157)	ALN 10 mg	(N=55)
ALN 2.5 mg	(N=83)	ALN 10 mg	(N=29)

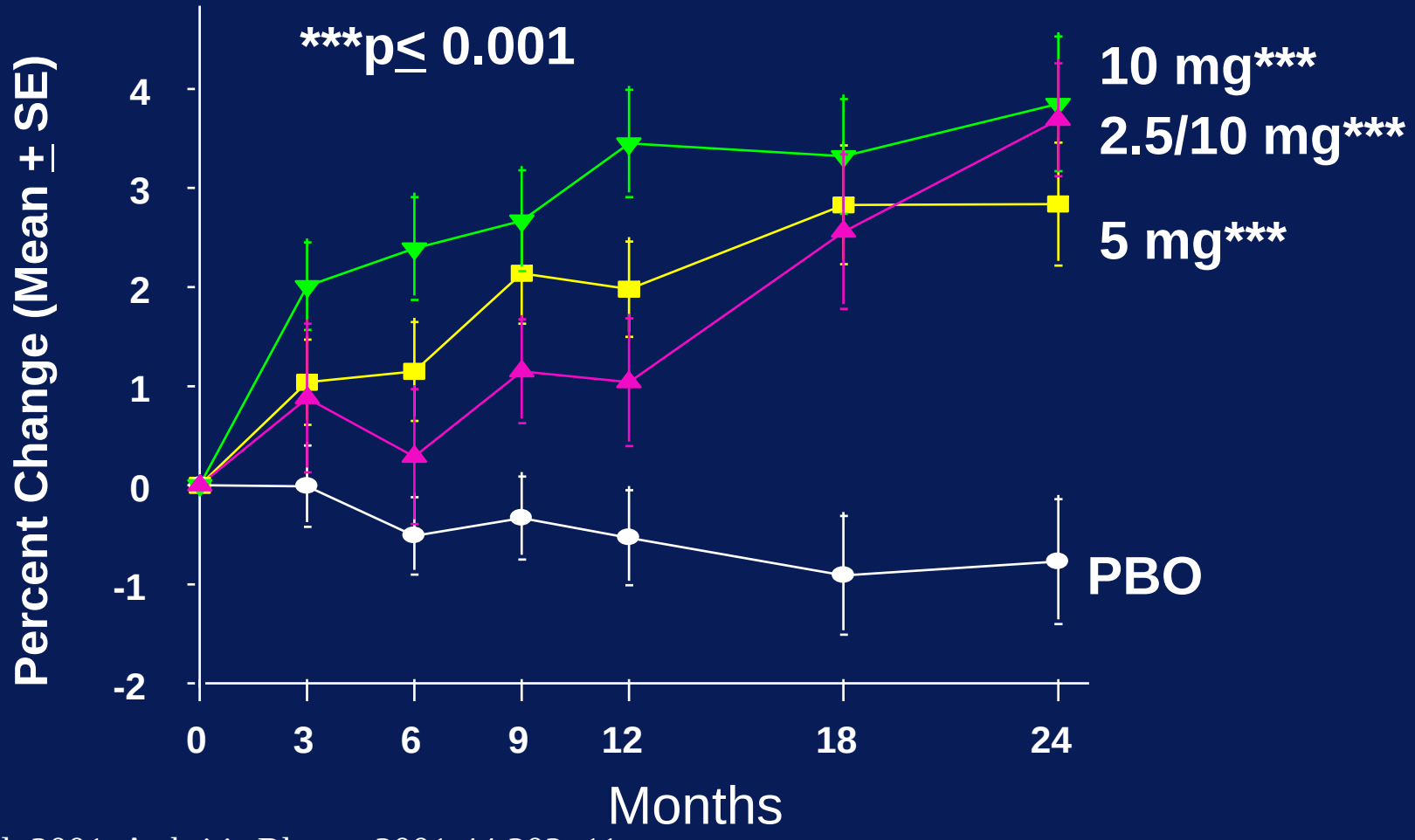
All patients continued on calcium and vitamin D

Alendronate effects on bone turnover in GIOP



Adachi JD et al, 2001. Arthritis Rheum 2001;44:202–11.
Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids..

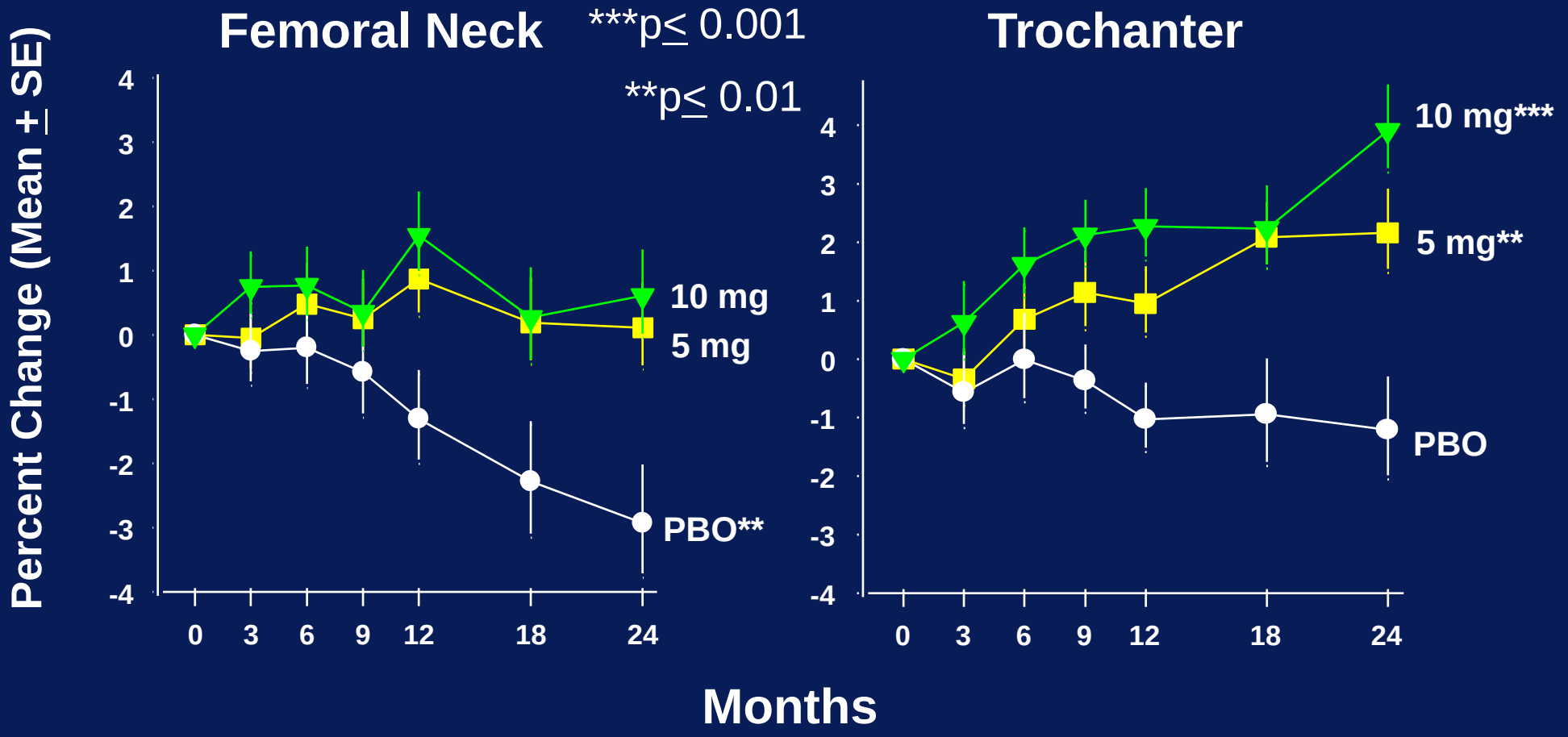
Lumbar Spine BMD in GIOP Extension Cohort



Adachi JD et al, 2001. Arthritis Rheum 2001;44:202–11.

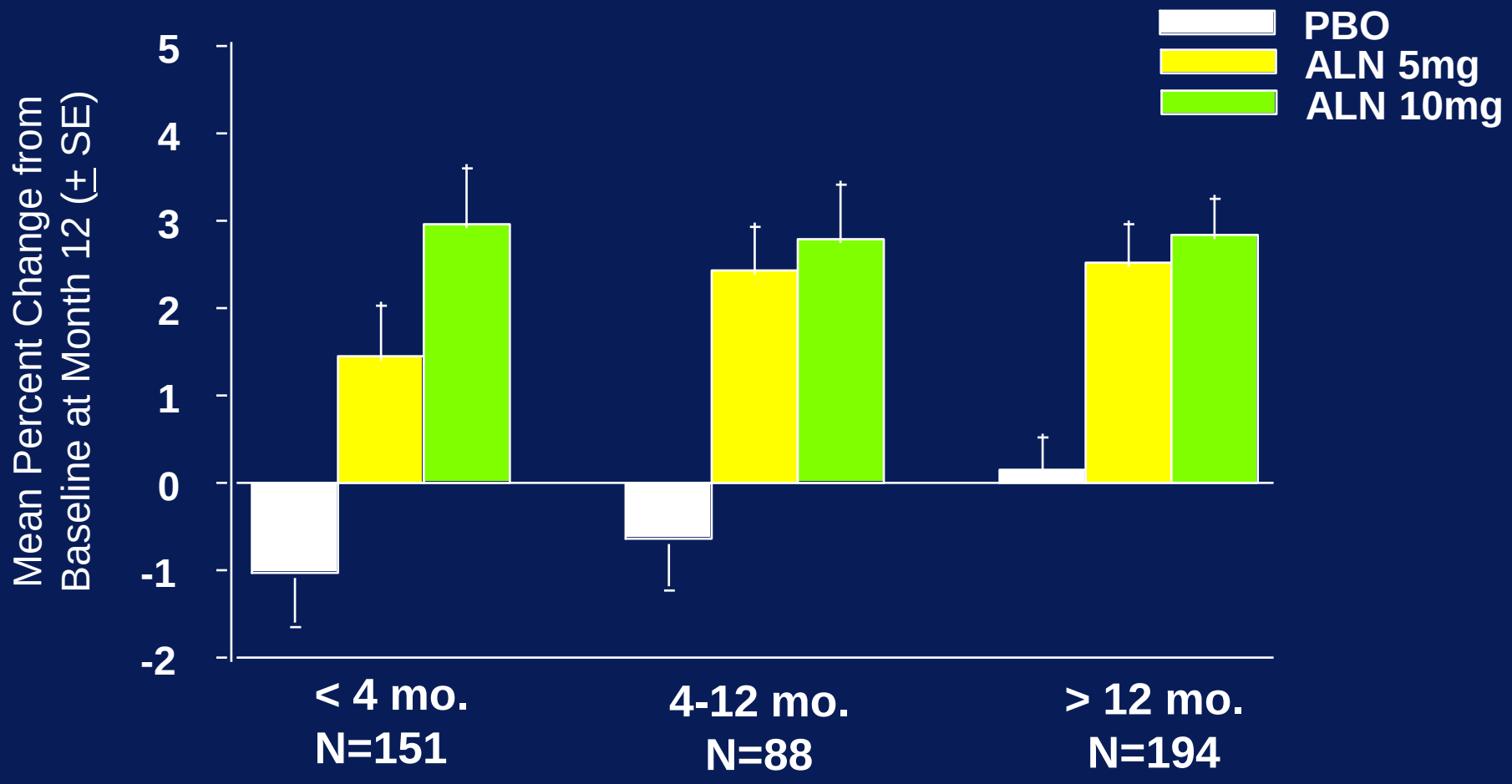
Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids..

Alendronate effects on Hip BMD in GIOP Extension Cohort



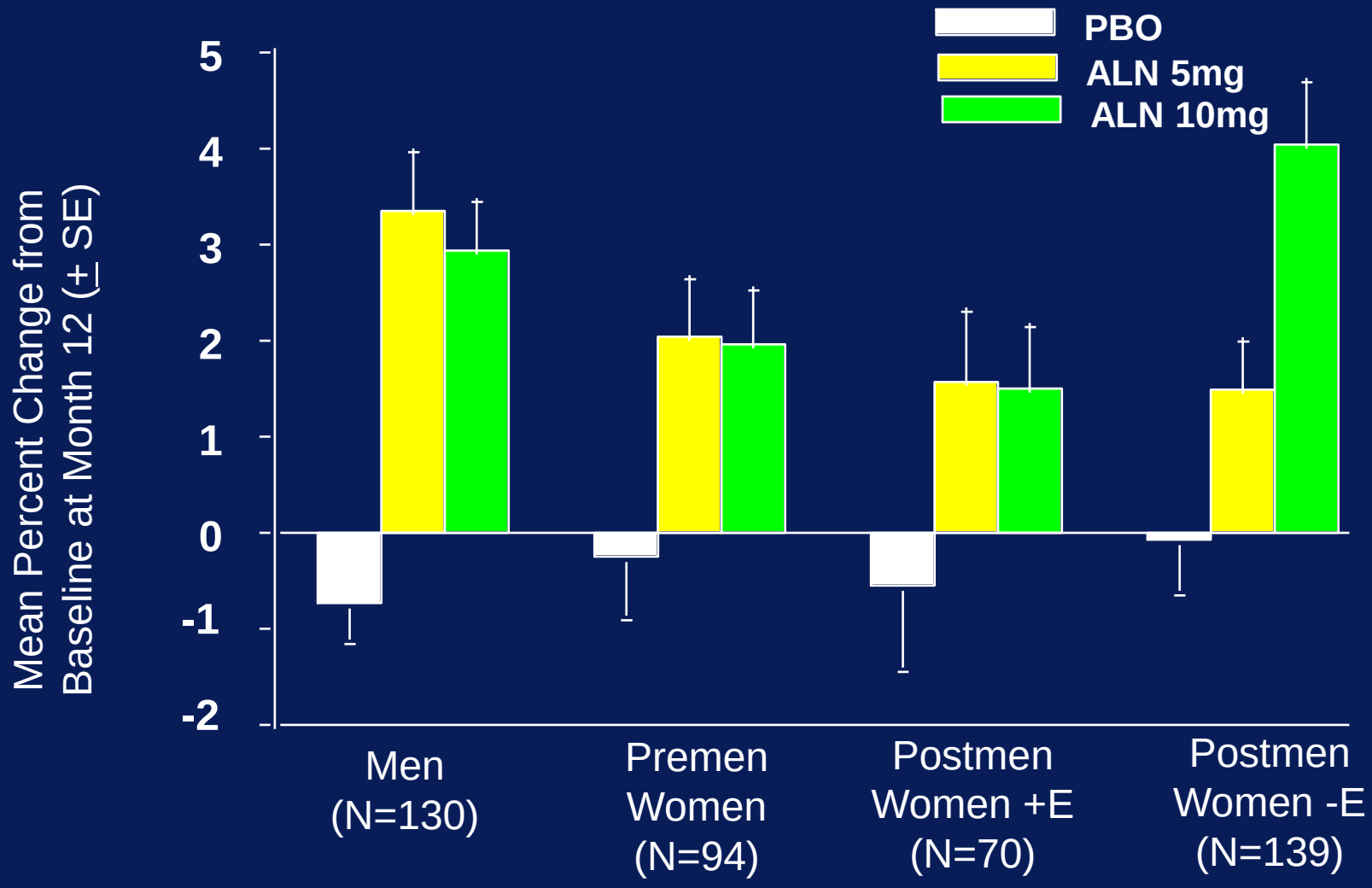
Adachi JD et al, 2001. Arthritis Rheum 2001;44:202–11.
Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids..

Effect of Duration of Prior Glucocorticoid Use on Lumbar Spine BMD



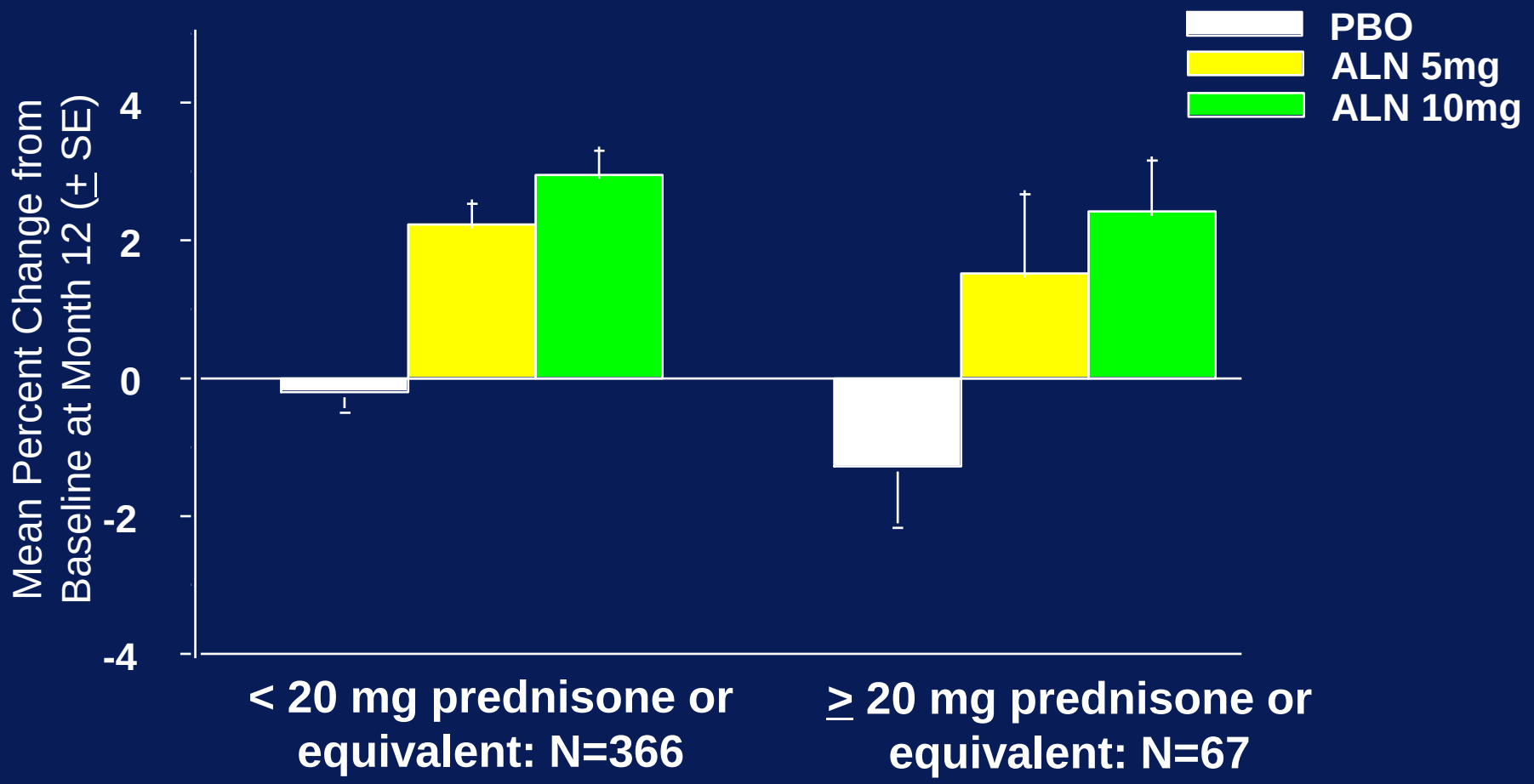
Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. N Engl J Med 1998;339:292–9. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis.

Effect of Alendronate on Lumbar Spine BMD by Gender/Menopause/ Estrogen Use



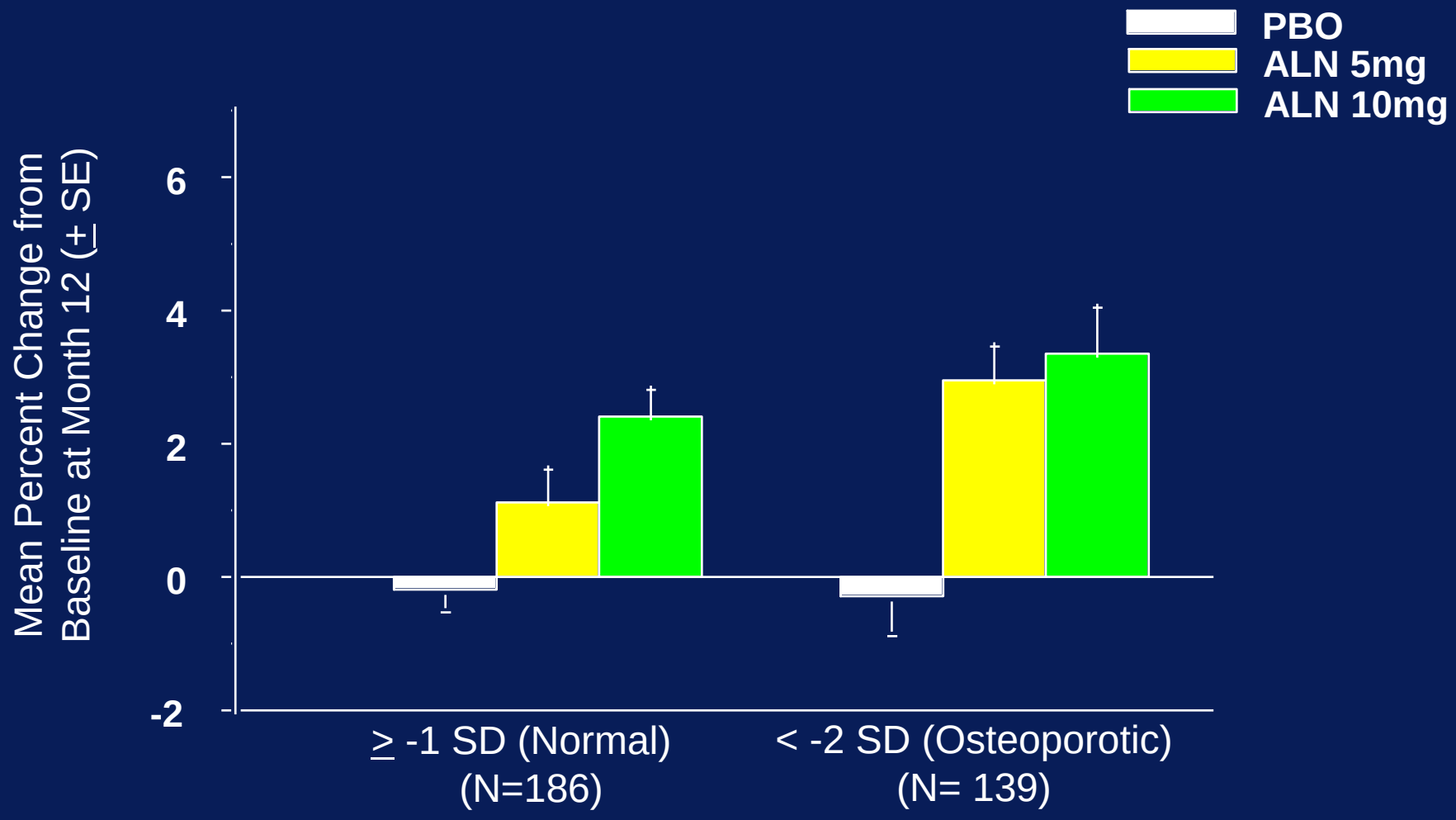
Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. N Engl J Med 1998;339:292–9. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis.

Effect of Alendronate on Spine BMD by Glucocorticoid Dose at 12 Months



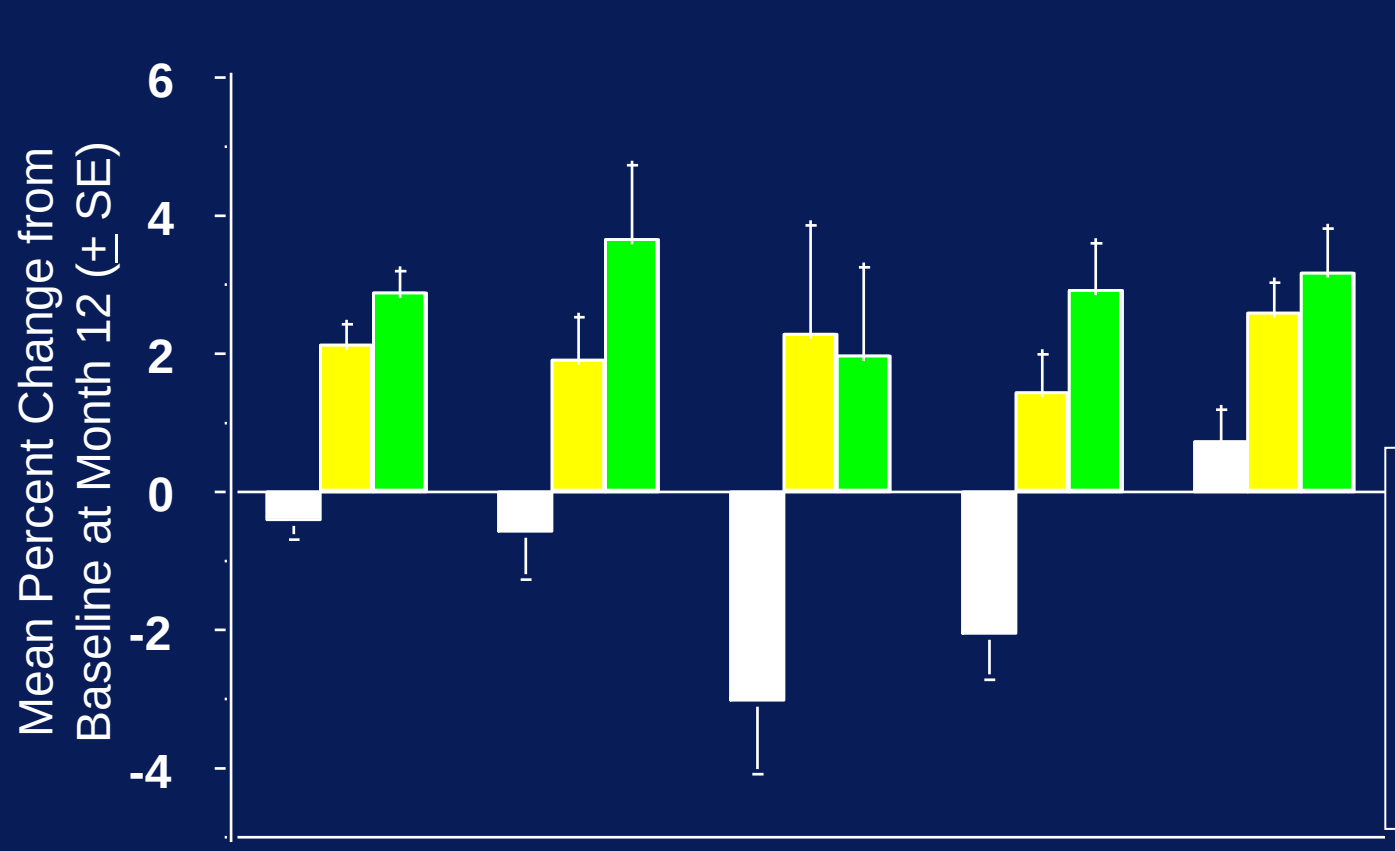
Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. N Engl J Med 1998;339:292–9. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis.

Spine BMD by Baseline BMD



Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. N Engl J Med 1998;339:292–9. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis.

Effect of Alendronate on Lumbar Spine BMD by Disease



Other	N (%)
SLE	48 (10.1)
Myositis	25 (5.2)
IBD	24 (5.0)
Sarcoidosis	15 (3.1)
Myasthenia gravis	15 (3.1)
Nephrotic syndrome	13 (2.7)

Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. N Engl J Med 1998;339:292–9. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis.

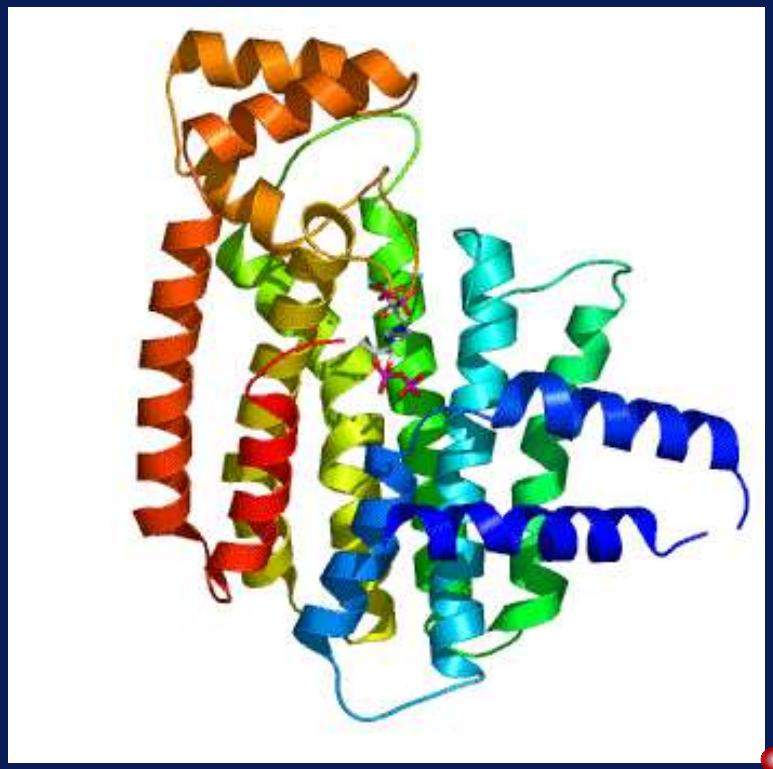
Pooled analysis on oral BP: new vertebral fracture in GIOP

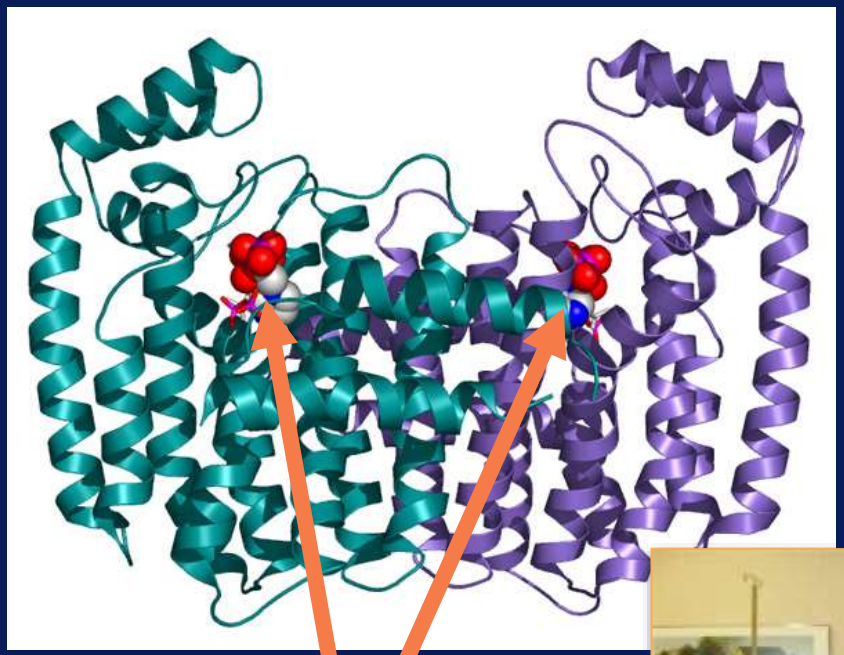
	Placebo n of VF/n of RX	Active R/ n of VF/n of RX	Statistics
Et*	15/131 11.4%	7/122 5.7%	RR= 0.50 (CI: 0.21-1.19)
Aln* 1y	8/135 5.9%	8/268 3.0%	RR=0.51 p=0.180
Aln** 2y	4/59 6.8%	1/143 0.7%	RR=0.10 p=0.026
Ris*	18/170 10.5%	6/174 3.4%	RR=0.32 p=0.016

* Semi-quantitative analysis ** Morphometric analysis

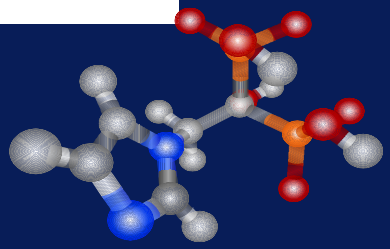
Zoledronate : Mode of Action

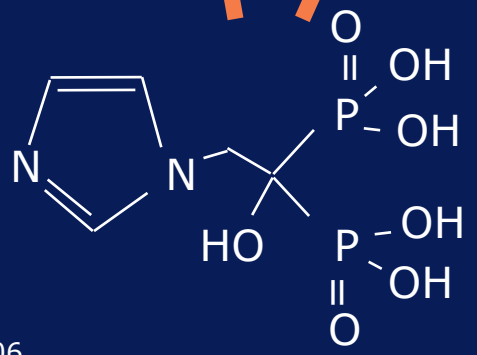
Crystal Structure of Human Farnesyl Pyrophosphate Synthase:
Site of Action of Nitrogen-containing Bisphosphonate





Zoledronate

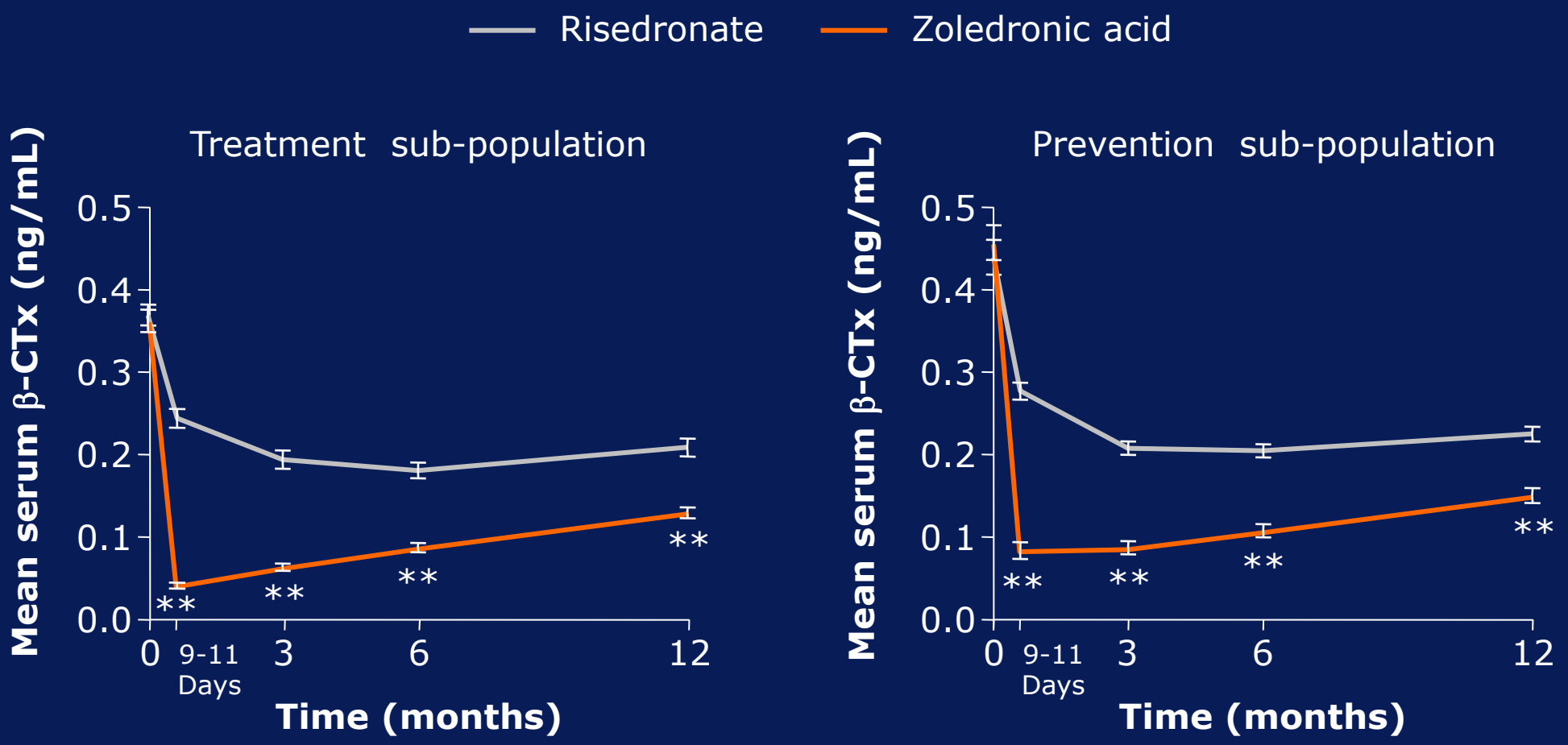




Aclasta 5mg IV 1x/jr

Kavanagh KL, et al. J Bone Miner Res. 2005;20(suppl):S95: Proc Nat Acad Sci 2006

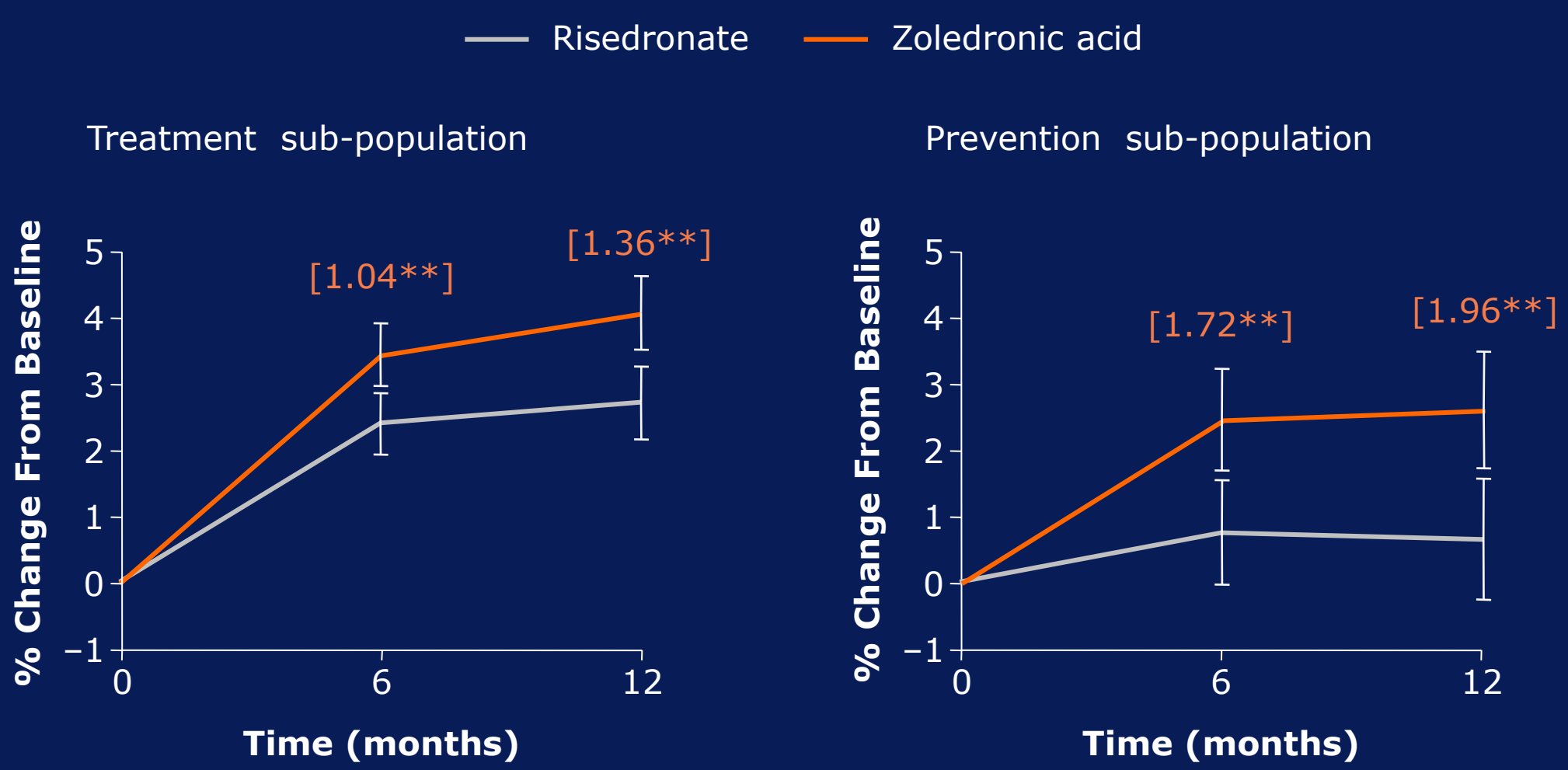
Mean Serum β-CTx Over Time
Treatment & Prevention Sub-population



Graphs present unadjusted mean ± SEM; ** p-value<0.01

Reid D et al, Lancet 2009 Apr 11;373(9671):1253-63. doi: 10.1016/S0140-6736(09)60250-6.

Mean % Change in BMD at Lumbar Spine Relative to Baseline
Treatment & Prevention Sub-populations

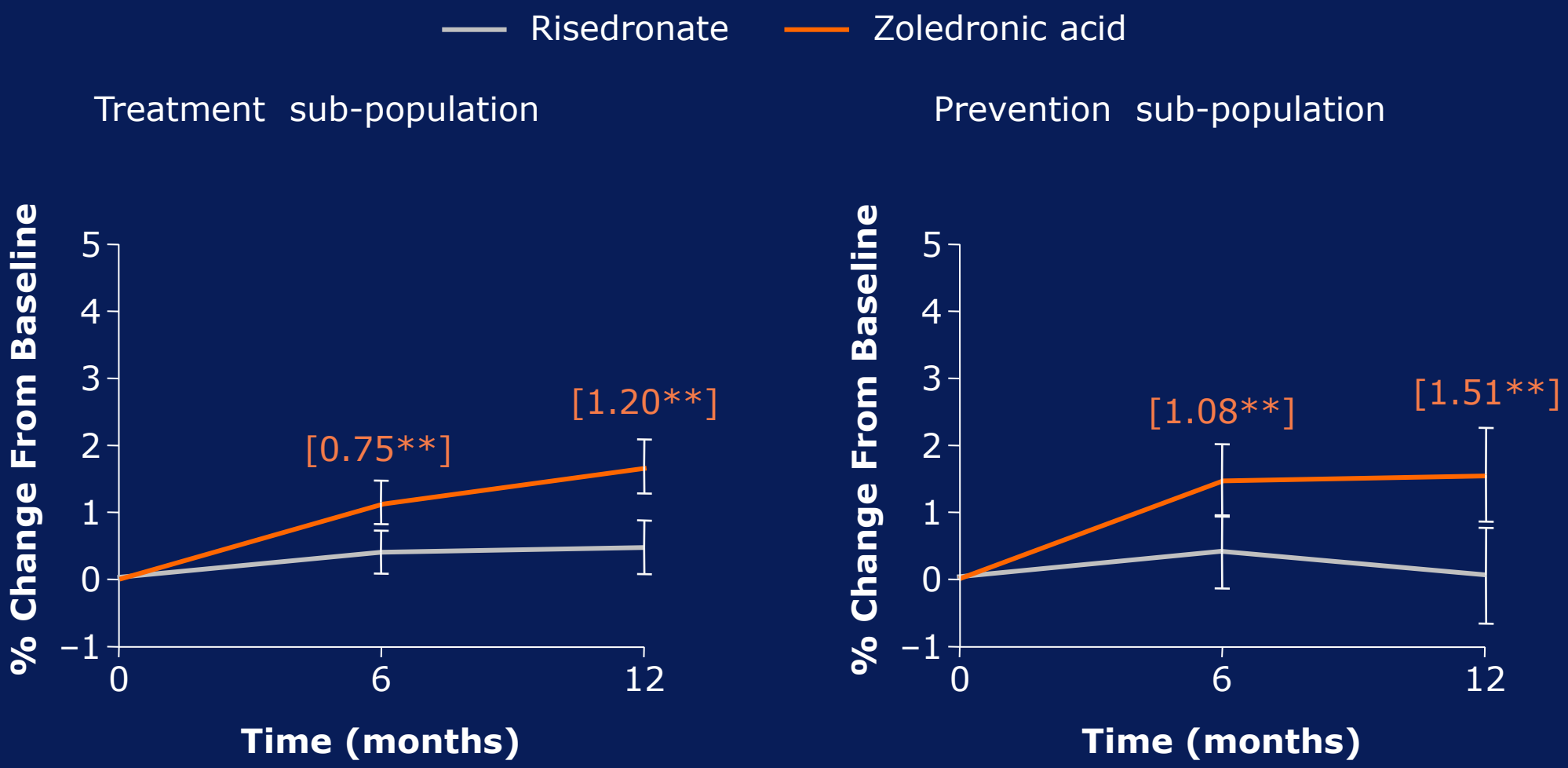


Graphs present LS means and 95% confidence intervals; ** p-value<0.01

Reid D et al, Lancet 2009 Apr 11;373(9671):1253-63. doi: 10.1016/S0140-6736(09)60250-6.

Mean % Change in BMD at Total Hip Relative to Baseline

Treatment & Prevention Sub-population



Graphs present LS means and 95% confidence intervals; ** p-value<0.01

Reid D et al, Lancet 2009 Apr 11;373(9671):1253-63. doi: 10.1016/S0140-6736(09)60250-6.

Fracture Incidence
Treatment & Prevention Sub-population

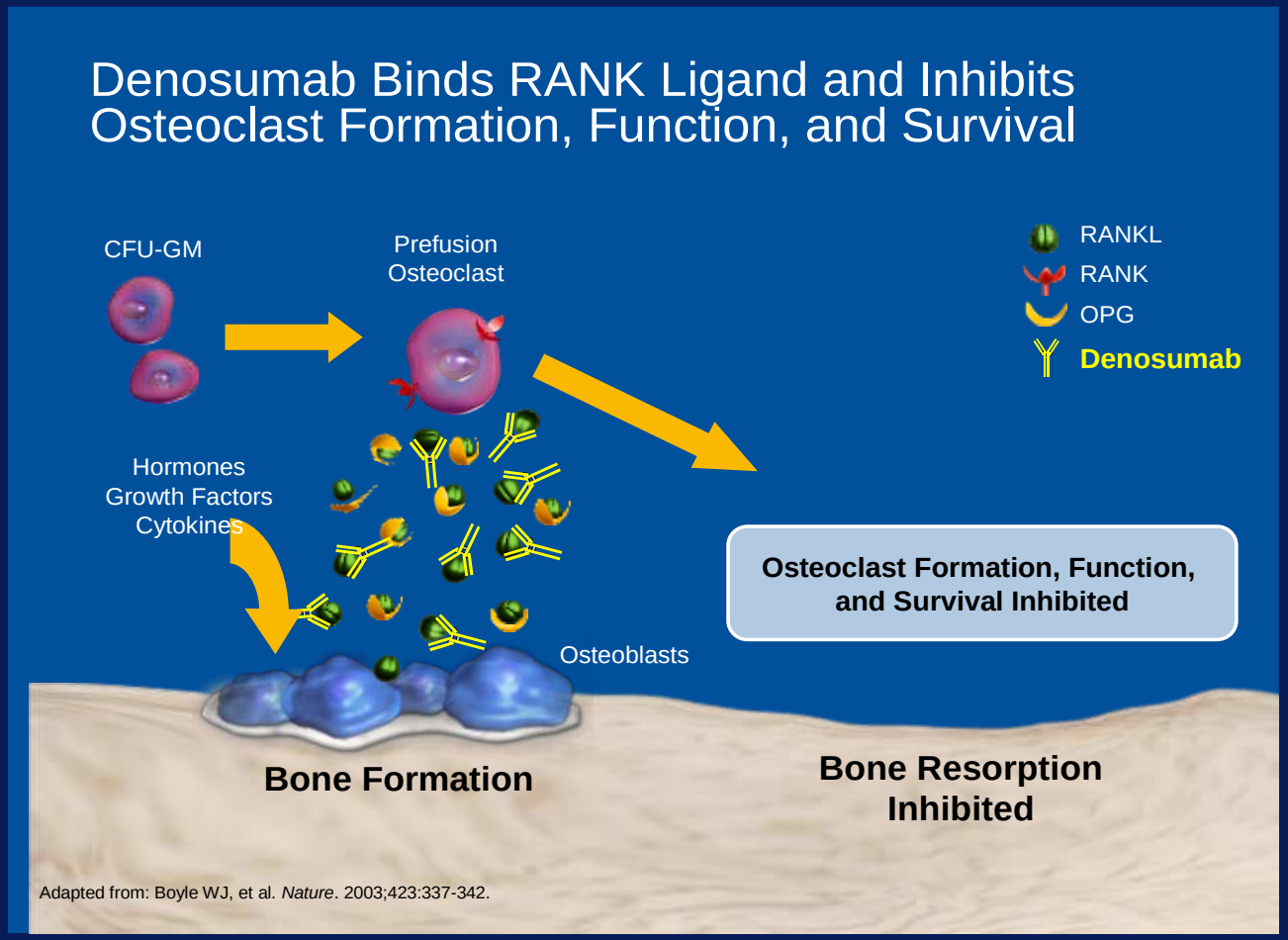
- New Morphometric Vertebral fractures
  - 5/379 in Zoledronic acid group
  - 3/381 in Risedronate group
- New Clinical fractures
  - 8/416 in Zoledronic acid group
  - 7/417 in Risedronate group
- The number of fractures observed was too small to draw any meaningful conclusions

Reid D et al, Lancet 2009 Apr 11;373(9671):1253-63. doi: 10.1016/S0140-6736(09)60250-6.

Bisphosphonate treatment in GIOP: Conclusions

- Consistantly maintains or increases BMD at spine and hip
- Significant effects in almost all subgroups
- Trend & significant vertebral fracture reduction vs placebo
  - (in postmenopausal women)
- Too small studies for non-vertebral fractures evaluation
- Generally well tolerated

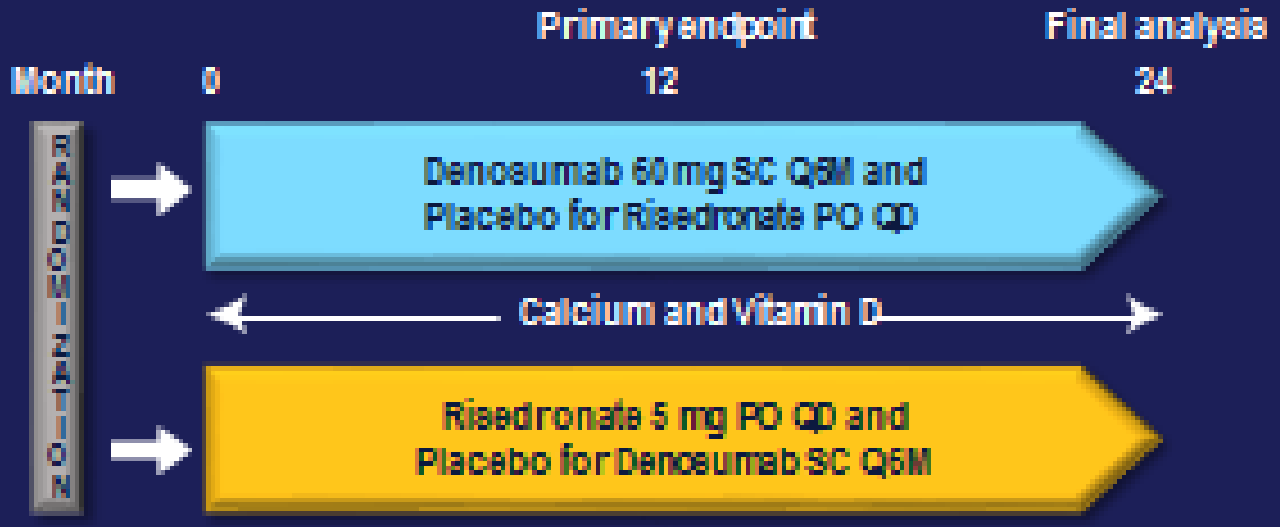
Denosumab : Mode of Action



Prolia 60 mg SC
1x 6 maand

Denosumab vs Risedronate in GIOP Study Design

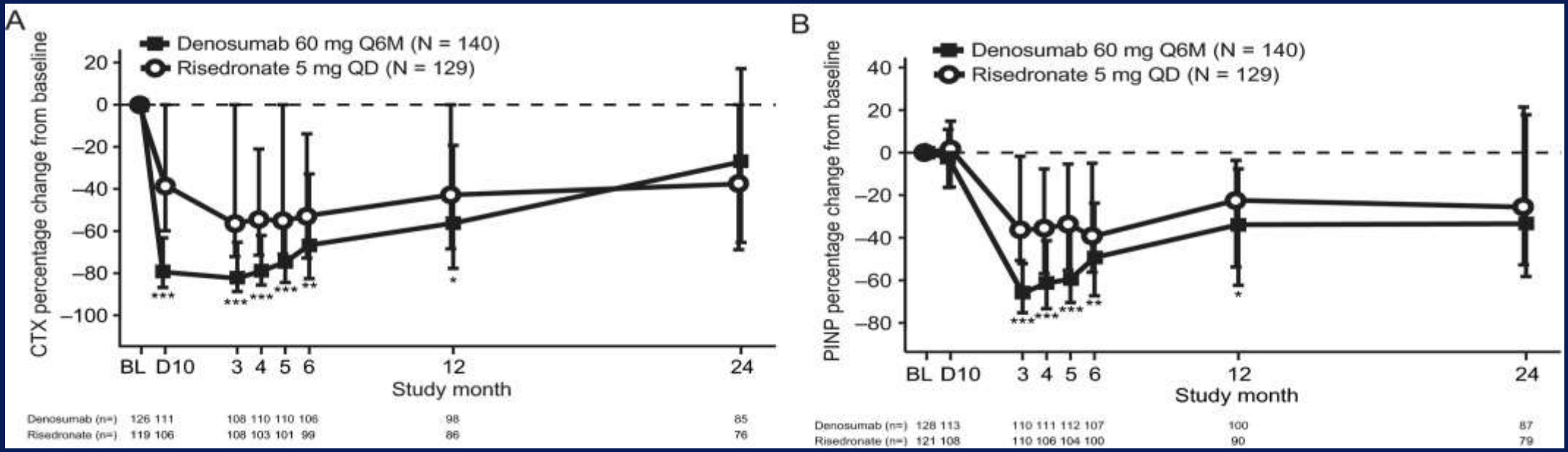
- Randomized, double-blind, double-dummy, active-controlled Study (NCT01575873)[1,2]
- Women and men aged ≥ 18, receiving ≥ 7.5 mg prednisone or its equivalent daily prior to screening; stratified for:
  - < 3 months (GC-Initiating [GC-I])
  - ≥ 3 months (GC-continuing [GC-C])
- All subjects aged < 50 years required to have a history of OP-related fracture
- GC-C subjects aged ≥ 50 years required to have
  - lumbar spine (LS), total hip (TH), or femoral neck (FN) BMD T-score ≤ –2.0; or
  - T-score ≤ –1.0 with history of osteoporosis-related fracture



References: 1. Saag, Lancet Diabetes Endocrinol, 2018; 2. Saag, Arthritis Rheumatol, 2018.

Denosumab Versus Risedronate in GIOP Results of a 24 Month Randomized, Double-Blind, Double-Dummy Trial

Effects on bone turnover



Saag K et al, 2019 Arthritis & Rheumatology, 71 (7) : 1174-1184,
DOI: (10.1002/art.40874)

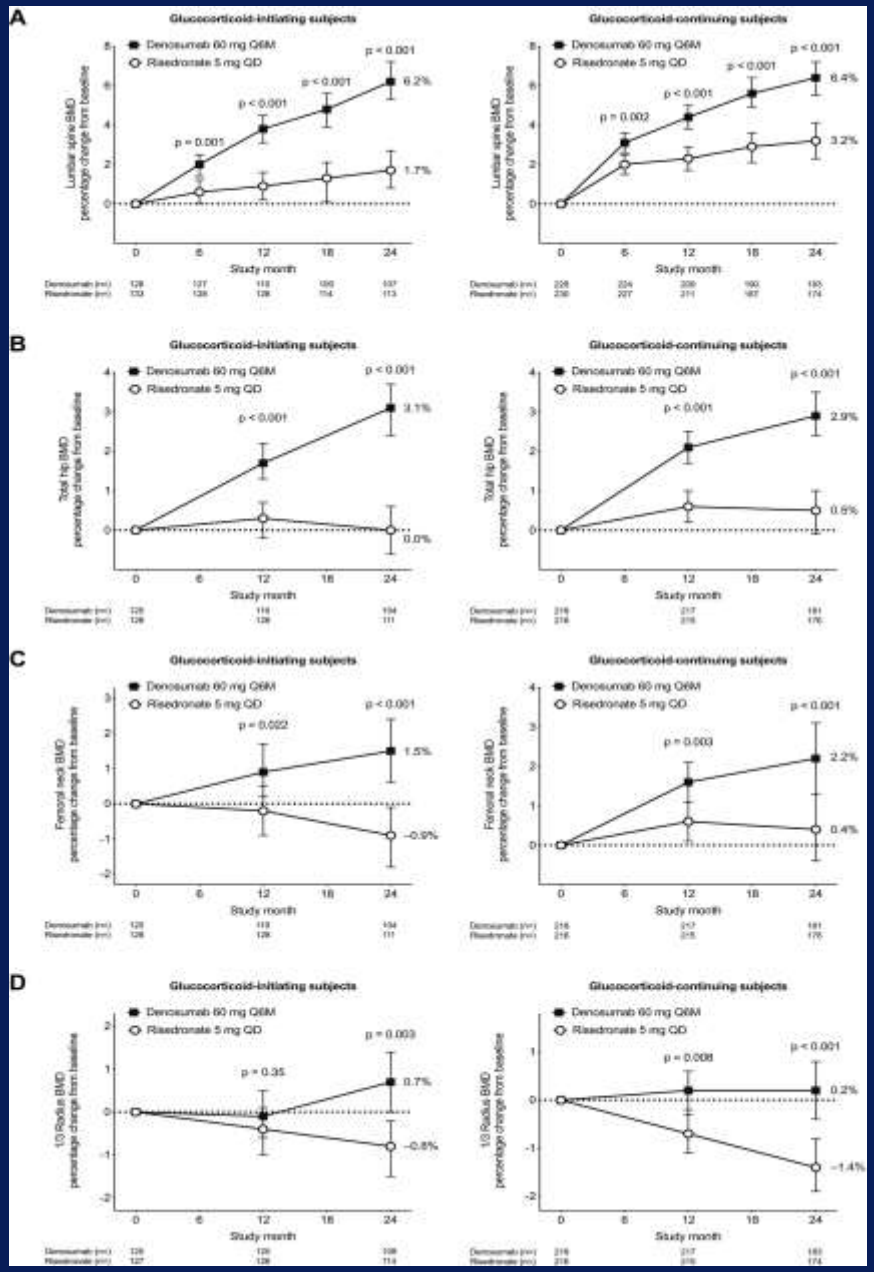
Prevention Study Treatment Study

Spine

Total Hip

Femoral Neck

Radius 1/3



Dmab Vs Ris in GIOP Results of a 24 Month Randomized, Double-Blind, Double-Dummy Trial

% change in BMD

Saag K et al, 2019
Arthritis & Rheumatol (7) : 1174-84,
DOI: (10.1002/art.40874)

Bone forming agents in GIOP

- Teriparatide (rhPTH1-34 : Forsteo)

Remark :

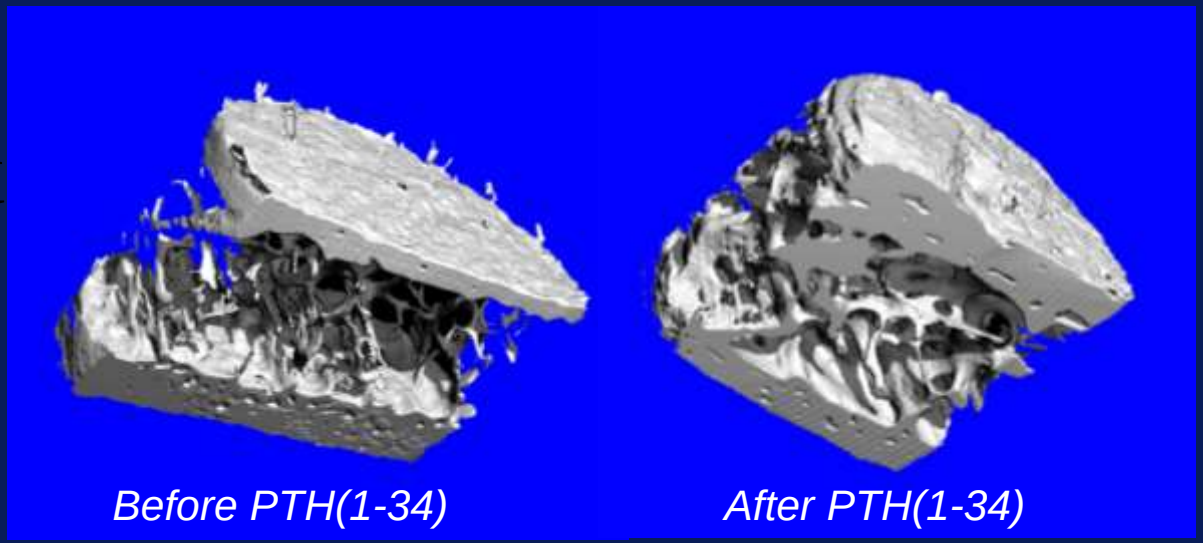
Strontium ranelate : not available anymore and not investigated in GIOP

Aboloparatide (SC hrPTHrp); not investigated in GIOP

Romosozumab (SC aSclerostine Ab): not investigated in GIOP

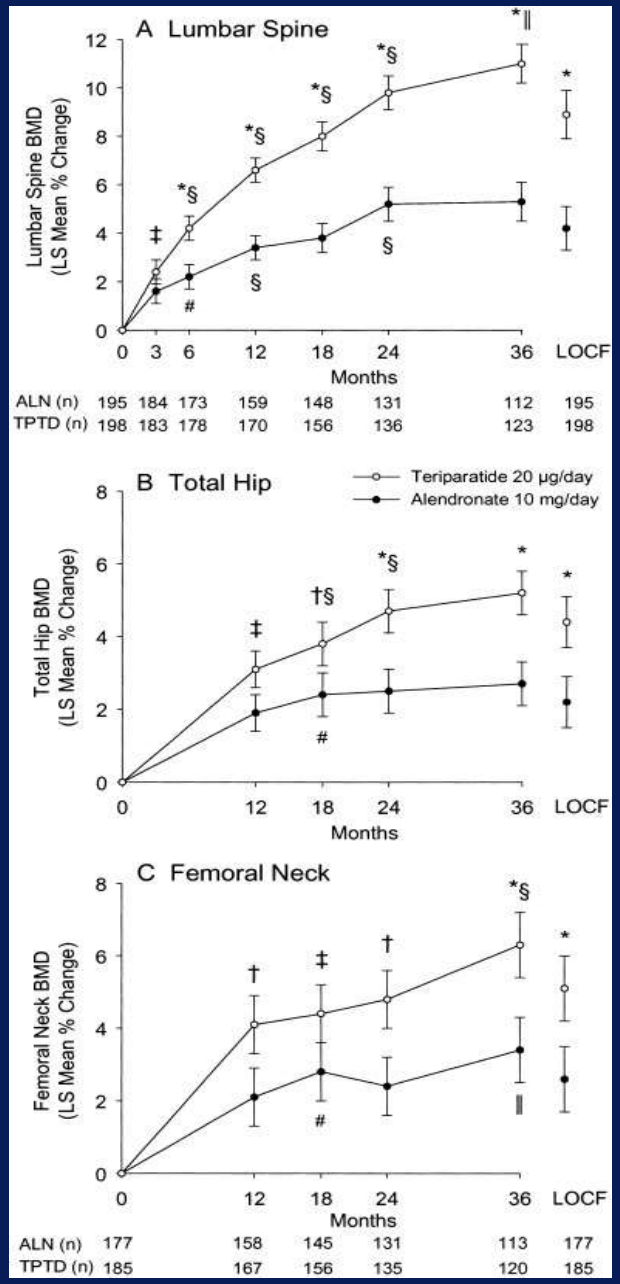
Daily SC Teriparatide injection

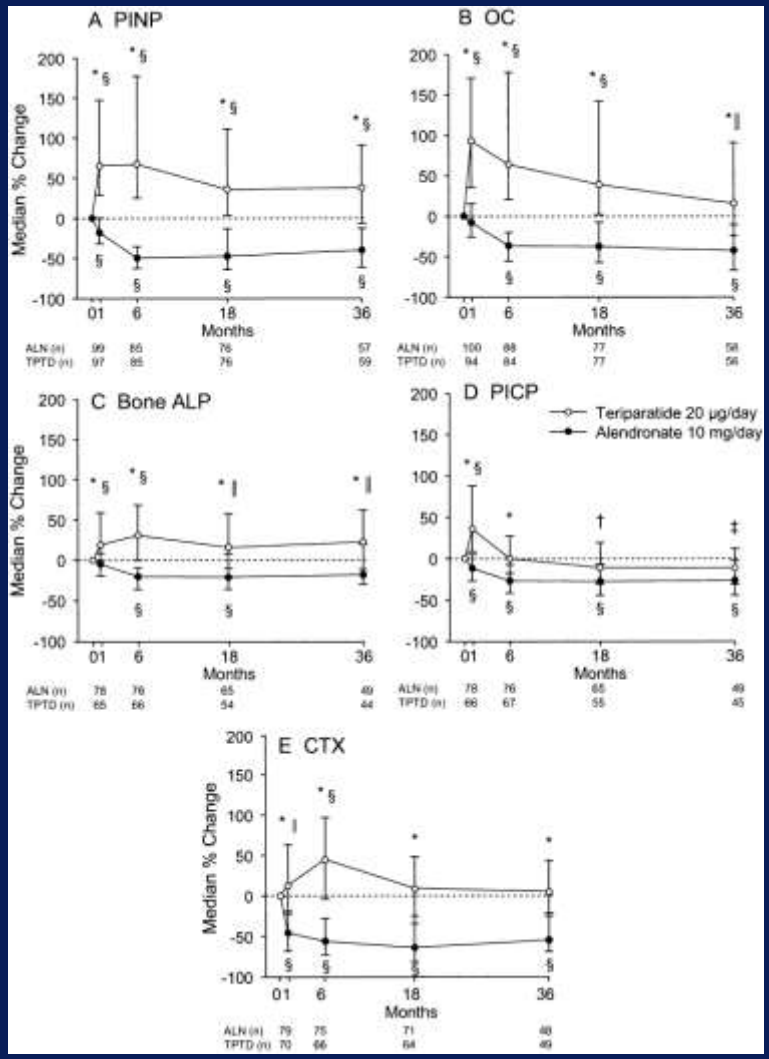
rhPTH(1-34)



JBMR 2001; 16: 1846-1853 – JBMR 2003; 18: 1932-1941

Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: Thirty-six–month results of a randomized, double-blind, controlled trial





Saag K et al, 2009
Arthritis & Rheum 11: 3346–3355
DOI 10.1002/art.24879

Effects of teriparatide vs alendronate for treating glucocorticoid-induced osteoporosis: Thirty-six–month results of a randomized, double-blind, controlled trial

Table 2. Incident vertebral and nonvertebral fractures in subjects with glucocorticoid-induced osteoporosis *

Fracture type	Subjects taking alendronate (n = 214)	Subjects taking teriparatide (n = 214)	*P*
≥1 radiographic vertebral †	13 (7.7)	3 (1.7)	0.007
≥1 clinical vertebral ‡	4 (2.4)	0	0.037
≥1 nonvertebral	15 (7.0)	16 (7.5)	0.843
≥1 nonvertebral fragility	5 (2.3)	9 (4.2)	0.256

* Values are the number (%).

Saag K et al, 2009; Arthritis & Rheum 11: 3346–3355
DOI 10.1002/art.24879

Contents of the presentation

- Introduction and general remarks
- Epidemiology of use of GCs
- Pathogenesis of GC-induced bone loss
- Consequence of GCs: bone loss and fractures
- Literature review on GIOP prevention and treatment clinical studies/trials
- ***Guidelines for management of the individual patients treated with oral GCs***

1996 American College of Rheumatology guidelines for GIOP

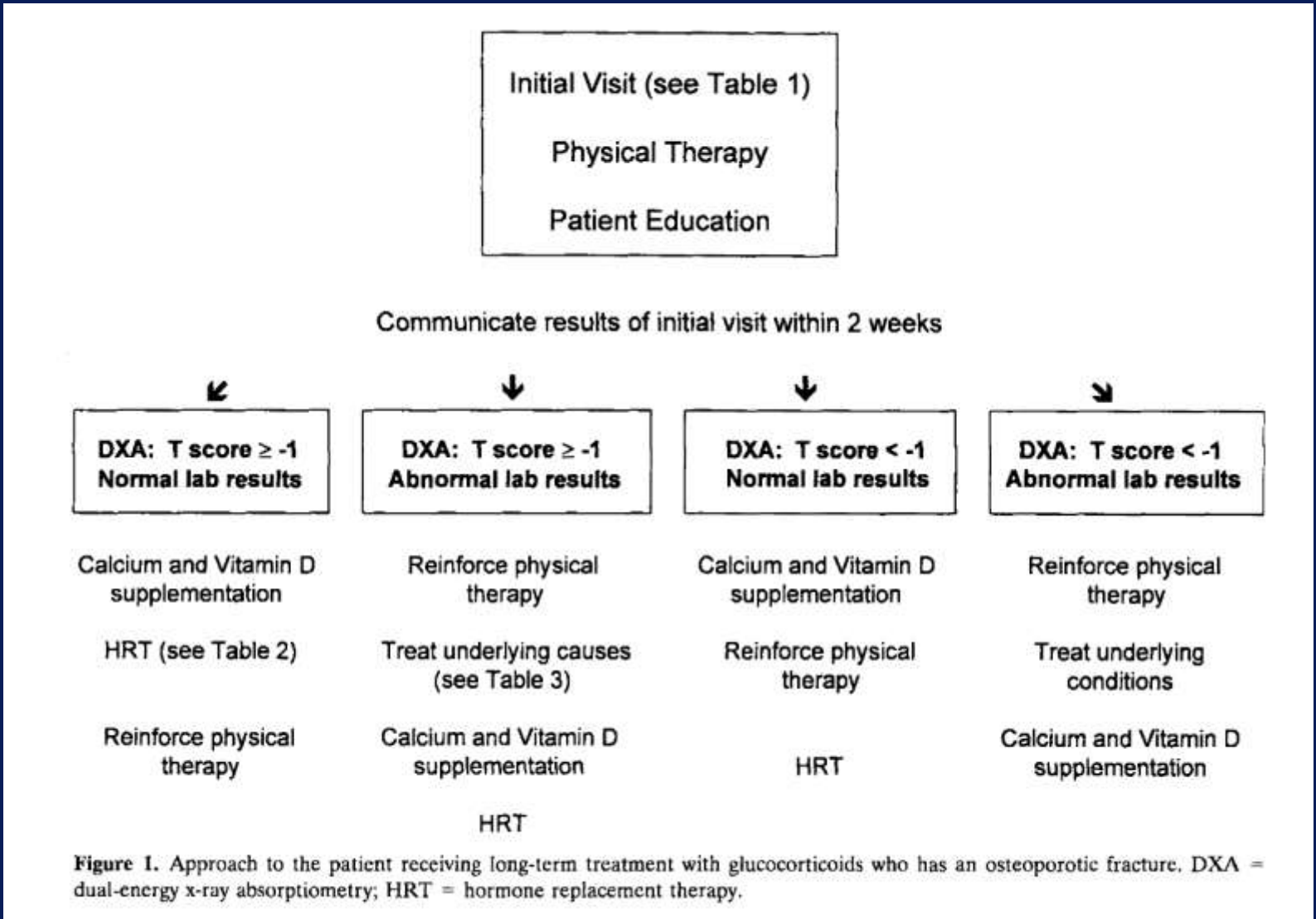


Figure 1. Approach to the patient receiving long-term treatment with glucocorticoids who has an osteoporotic fracture. DXA = dual-energy x-ray absorptiometry; HRT = hormone replacement therapy.

ARTHRITIS & RHEUMATISM 1996 (39) 1791-1801 0 1996,
American College of Rheumatology

Eastell R, Reid DM, Compston J, Cooper C, Fogelman I, Francis RM, Hosking DJ, Purdie DW, Ralston SH, Reeve J, Russell RG, Stevenson JC, Torgerson DJ (1998) A UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update. J Intern Med 244:271–292

Bone and Tooth Society of Great Britain, National Osteoporosis Society and Royal College of Physicians (1999) Glucocorticoid-induced osteoporosis. Guidelines on prevention and treatment. Royal College of Physicians, London. www.rcplondon.ac.uk

Guidelines for management of the individual patients with GC-use

	ACR 1996	UK 1998
Work up	Lab BMD	Lab ± BMD - Risk factors
BMD Cutoff	T-score -1	T-score –1.5
Categorie	Fract/Sec/Prim	Prim = Sec
Menopause	HRT	HRT

Guidelines for management of the individual patients with GC-use

	ACR 1996	UK 1998
Additional R/	Bisphosph or Calcitonin	1/ Bisphosph 2/ Calcitriol 3/ Fluor/Calcitonin
Follow up 1month	Ca/Vit D adj ± thiazide	-
6-12 months	BMD : - 5%	BMD-L : -4% BMD-H : -7%

Table 2. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis

Patient begining therapy with glucocorticoid (prednisone equivalent of ≥5 mg/day) with plans for treatment duration of ≥3 months:
- Modify lifestyle risk factors for osteoporosis.
  - Smoking cessation or avoidance
  - Reduction of alcohol consumption if excessive
- Instruct in weight-bearing physical exercise.
- Initiate calcium supplementation.
- Initiate supplementation with vitamin D (plain or activated form).
- Prescribe bisphosphonate (use with caution in premenopausal women).

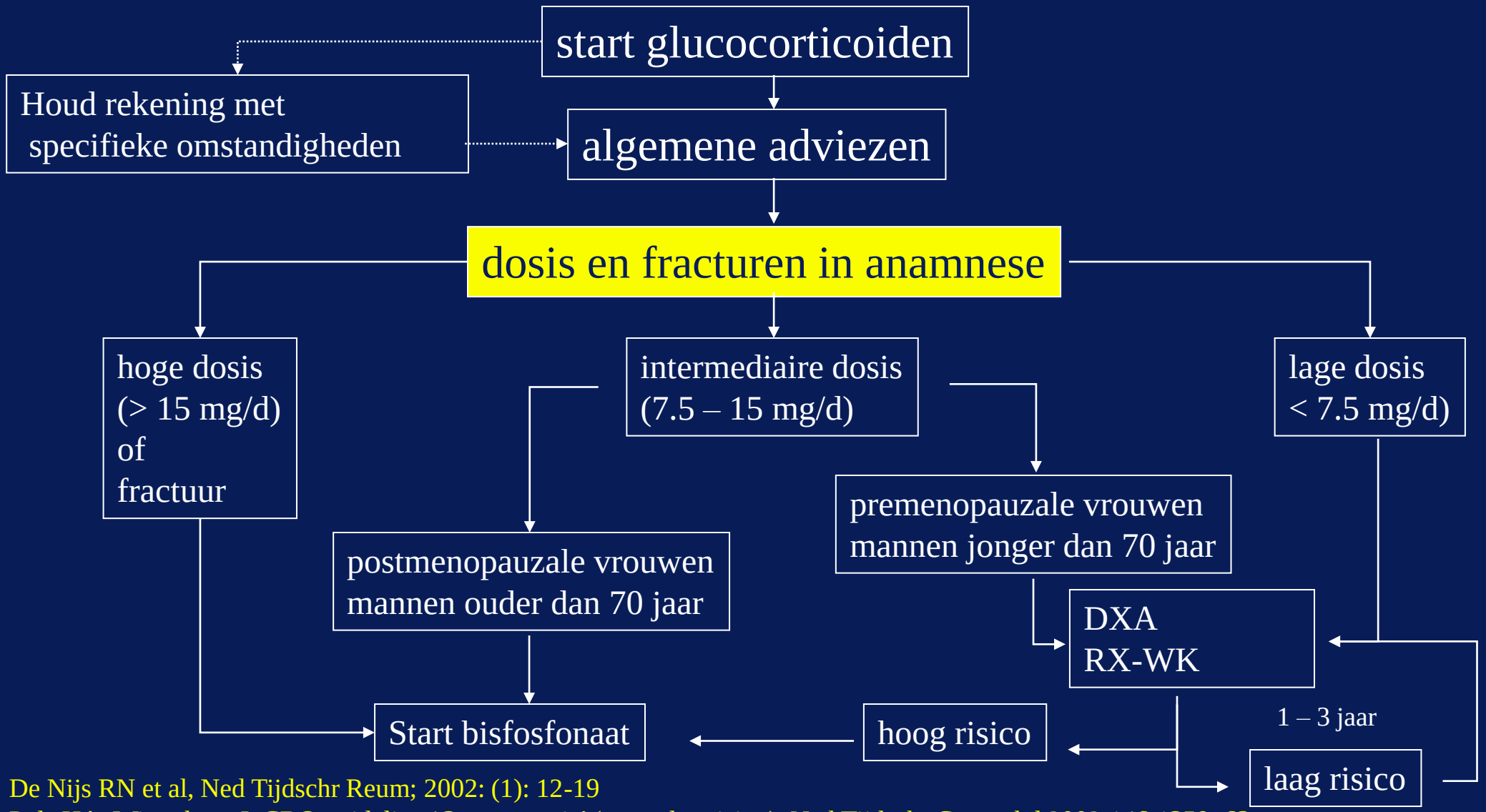
Patient receiving long-term glucocorticoid therapy (prednisone equivalent of ≥5 mg/day):
- Modify lifestyle risk factors for osteoporosis.
  - Smoking cessation or avoidance
  - Reduction of alcohol consumption if excessive
- Instruct in weight-bearing physical exercise.
- Initiate calcium supplementation.
- Initiate supplementation with vitamin D (plain or activated form).
- Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated.
- Measure bone mineral density (BMD) at lumbar spine and/or hip.
- If BMD is not normal (i.e., T-score below −1), then
  - Prescribe bisphosphonate (use with caution in premenopausal women).
  - Consider calcitonin as second-line agent if patient has contraindication to or does not tolerate bisphosphonate therapy.
- If BMD is normal, follow up and repeat BMD measurement either annually or biannually.

2001 ACR Guideline Prev/Treatment of GIOP Update

Introduction of BP if BMD T-score < -1

ARTHRITIS & RHEUMATISM 2001 (44): 1496–1503

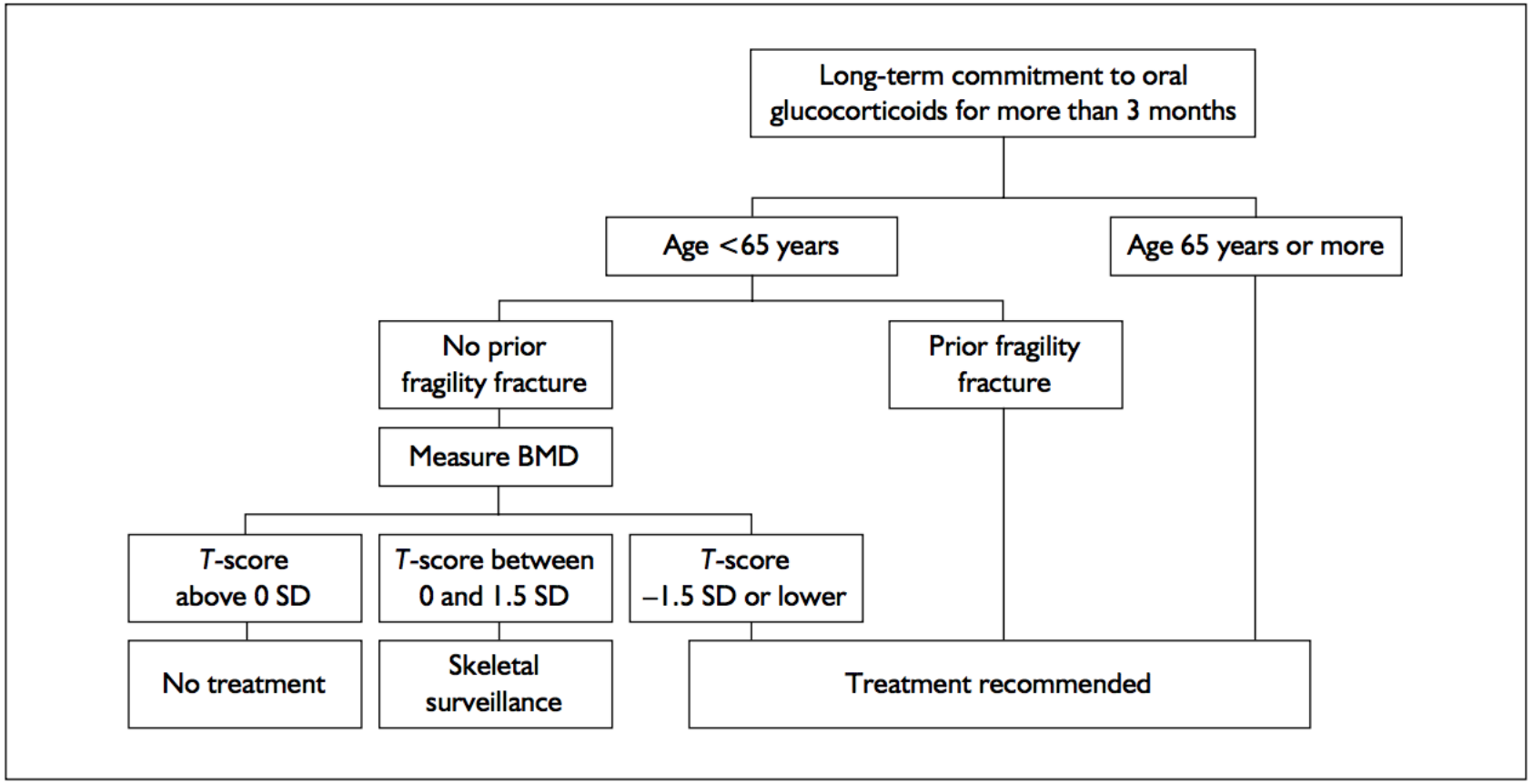
CBO GIOP Experts – Ronde tafel bijeenkomst 2002



De Nijs RN et al, Ned Tijdschr Reum; 2002: (1): 12-19

Pols HA, Wittenberg J. CBO guideline 'Osteoporosis' (second revision). Ned Tijdschr Geneeskd 2002;146:1359–63.

2002 UK Management algorithm for longterm GC treatment



Bone and Tooth Society, National Osteoporosis Society and Royal College of Physicians. Glucocorticoid-induced osteoporosis. A concise guide to prevention and treatment. London: Royal College of Physicians; 2002.

Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus of the Belgian Bone Club (2006)

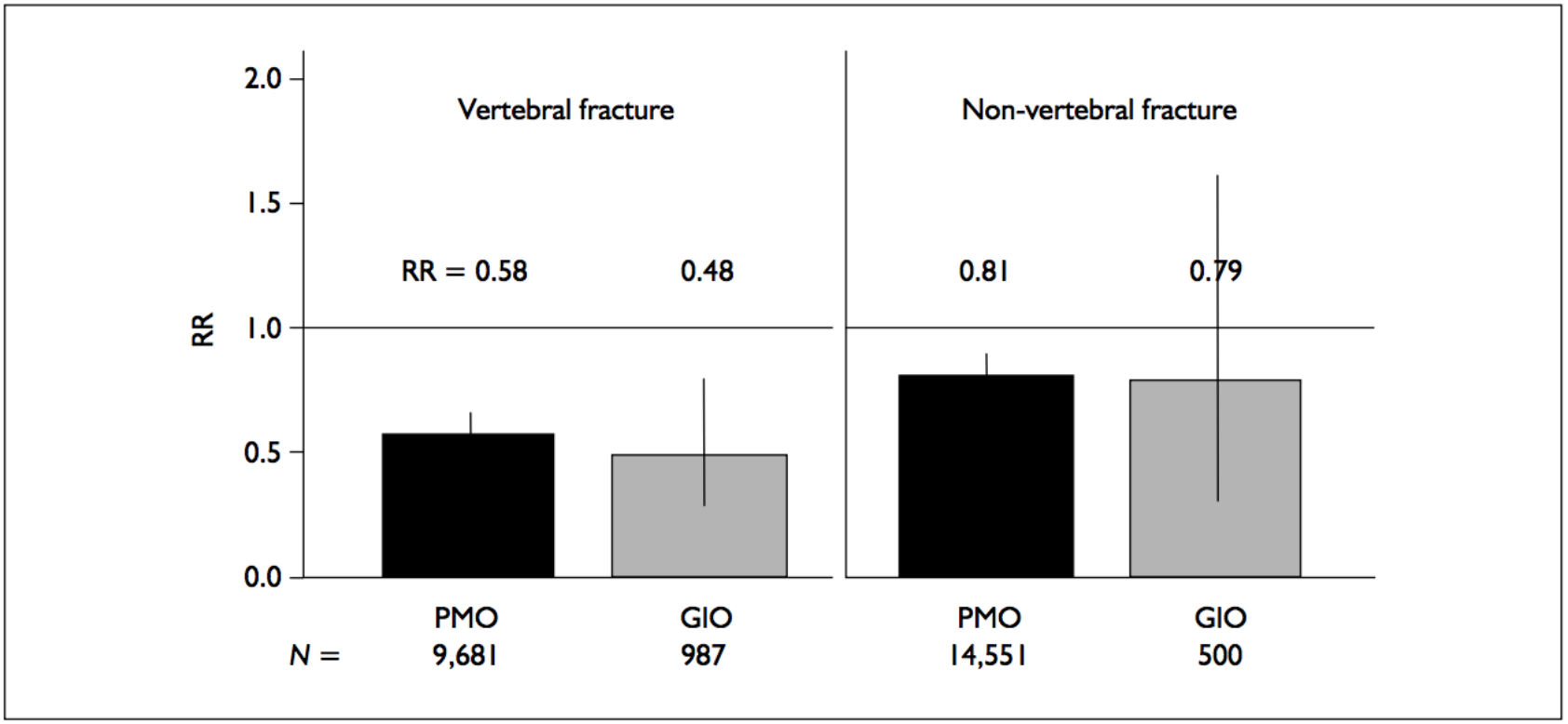
- Prevention and treatment of GC-OP should be considered in post-menopausal females and in osteopenic premenopausal females and males put on a daily dose of at least **7.5 mg** equivalent predniso(lo)ne, expected to be maintained at least 3 months.

J.-P. Devogelaer et al, Osteoporos Int (2006) 17:8–19

Pharmaco-economy of OP treatments

Glucocorticoid-induced osteoporosis: systematic review & cost-utility analysis

Effects on fracture risk



Kanis J et al, Health Technol Assess 2007;11(7); doi.org/10.3310/hta11070

Glucocorticoid-induced osteoporosis: systematic review & cost-utility analysis

Cost-effectiveness (ICER < 30.000 pound) scenarios of oral BP in GIOP

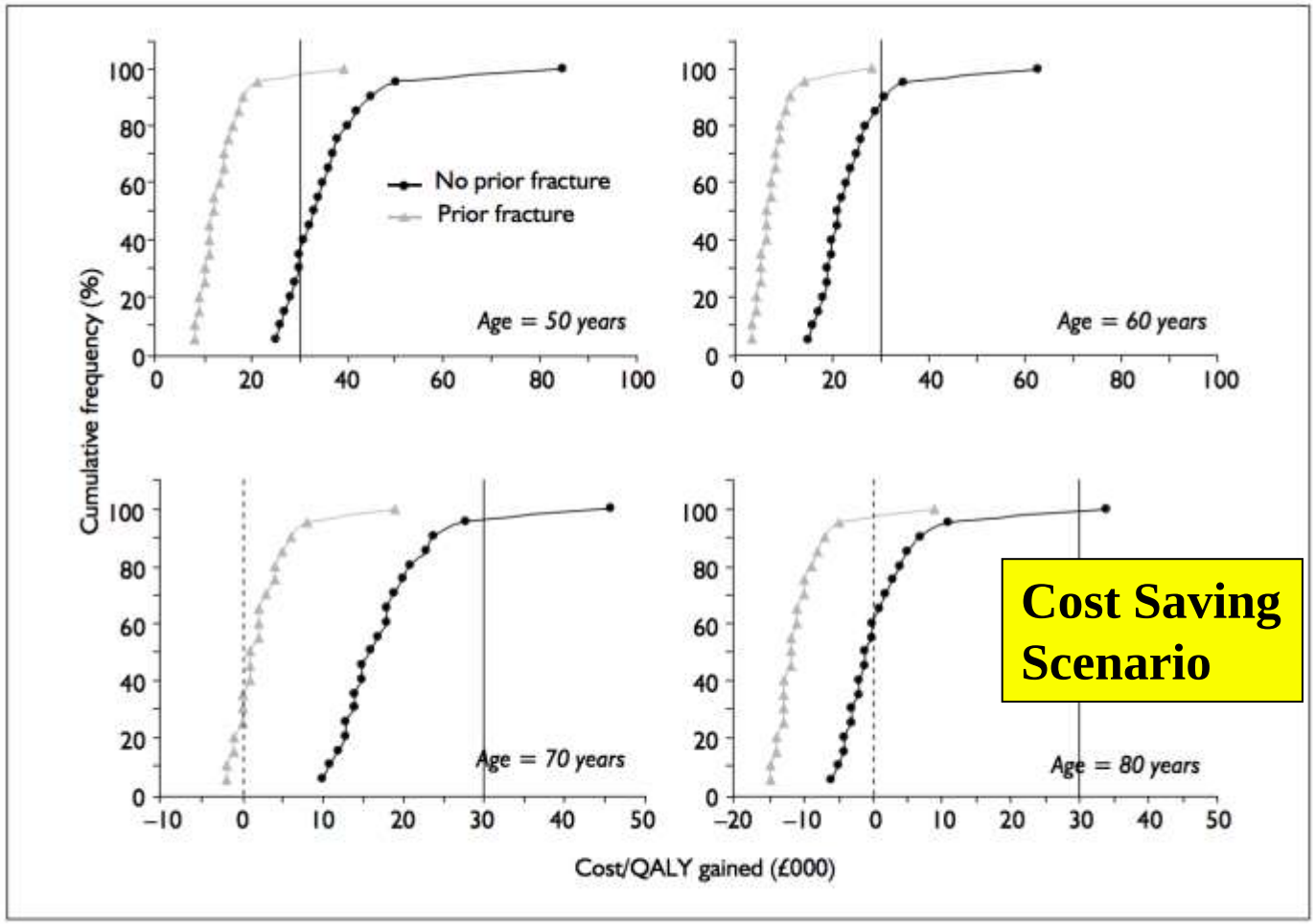


FIGURE 8 *Distribution of cost-effectiveness of treatment with bisphosphonate in patients at the ages shown with a T-score of –2.5 SD with and without a prior fragility fracture*

Kanis J et al, Health Technol Assess 2007;11(7); doi.org/10.3310/hta11070

Glucocorticoid-induced osteoporosis: systematic review & cost-utility analysis

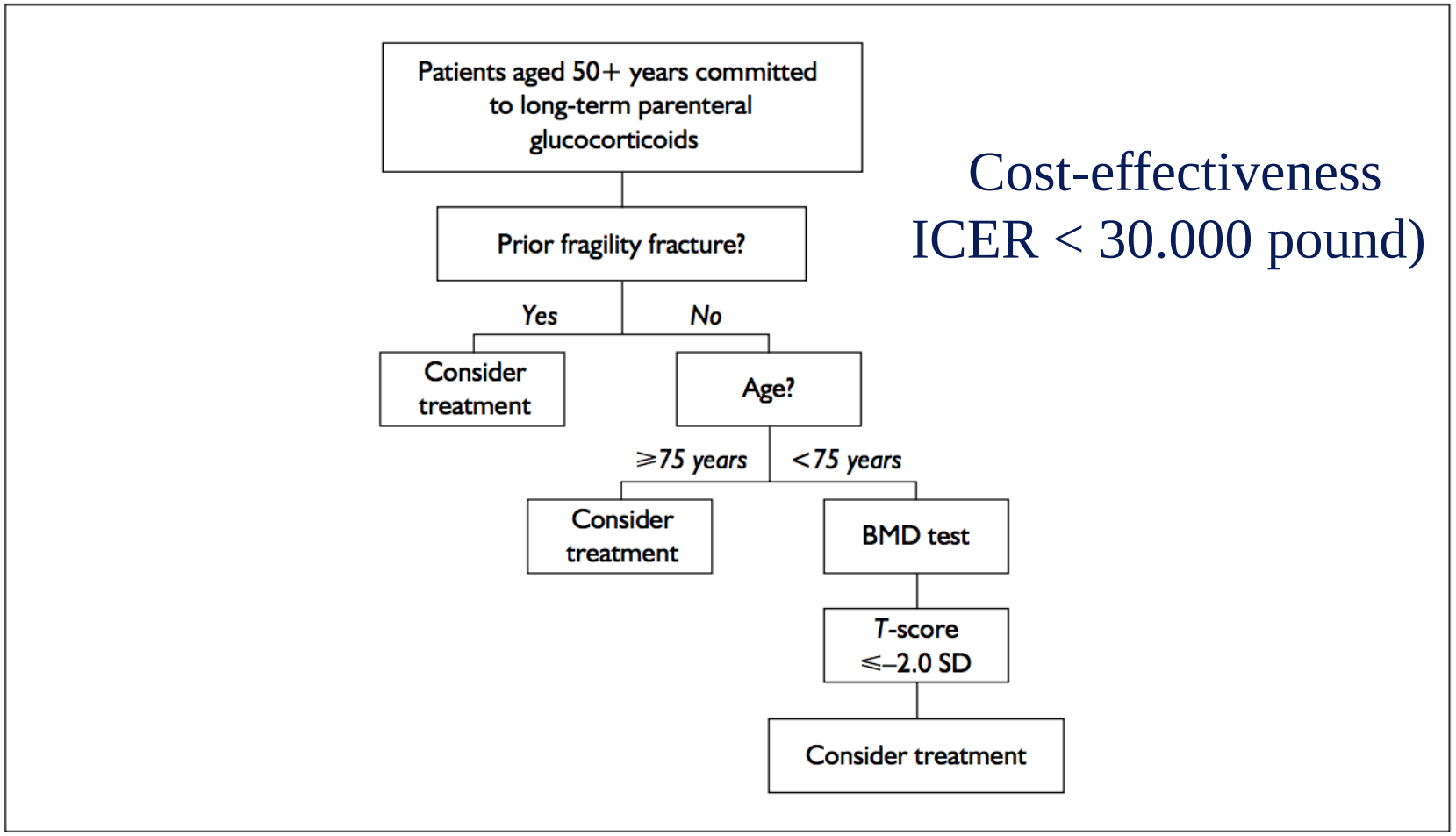
Cost-effectiveness (ICER < 30.000 pound) of BP in GIOP

- Cost-effectiveness was shown in patients with a prior fracture.
- In patients with no prior fracture, cost-effectiveness was observed in individuals aged 75 years or more.
- In younger patients without a prior fracture, costeffective scenarios were found upon a T-score for BMD that was ≤2.0 SD.

The proposed assessment algorithm derived from these analyses is shown in the next Figure.

Kanis J et al, Health Technol Assess 2007;11(7); doi.org/10.3310/hta11070

2007 Proposed Algorithm based on Cost-effectiveness of oral BP in GIOP



Cost-effectiveness
ICER < 30.000 pound)

FIGURE 10 *Assessment algorithm for patients committed to long-term treatment with oral glucocorticoids*

Kanis J et al, Health Technol Assess 2007;11(7); doi.org/10.3310/hta11070

Emerging Consensus on Prevention and Treatment of Glucocorticoid-induced Osteoporosis

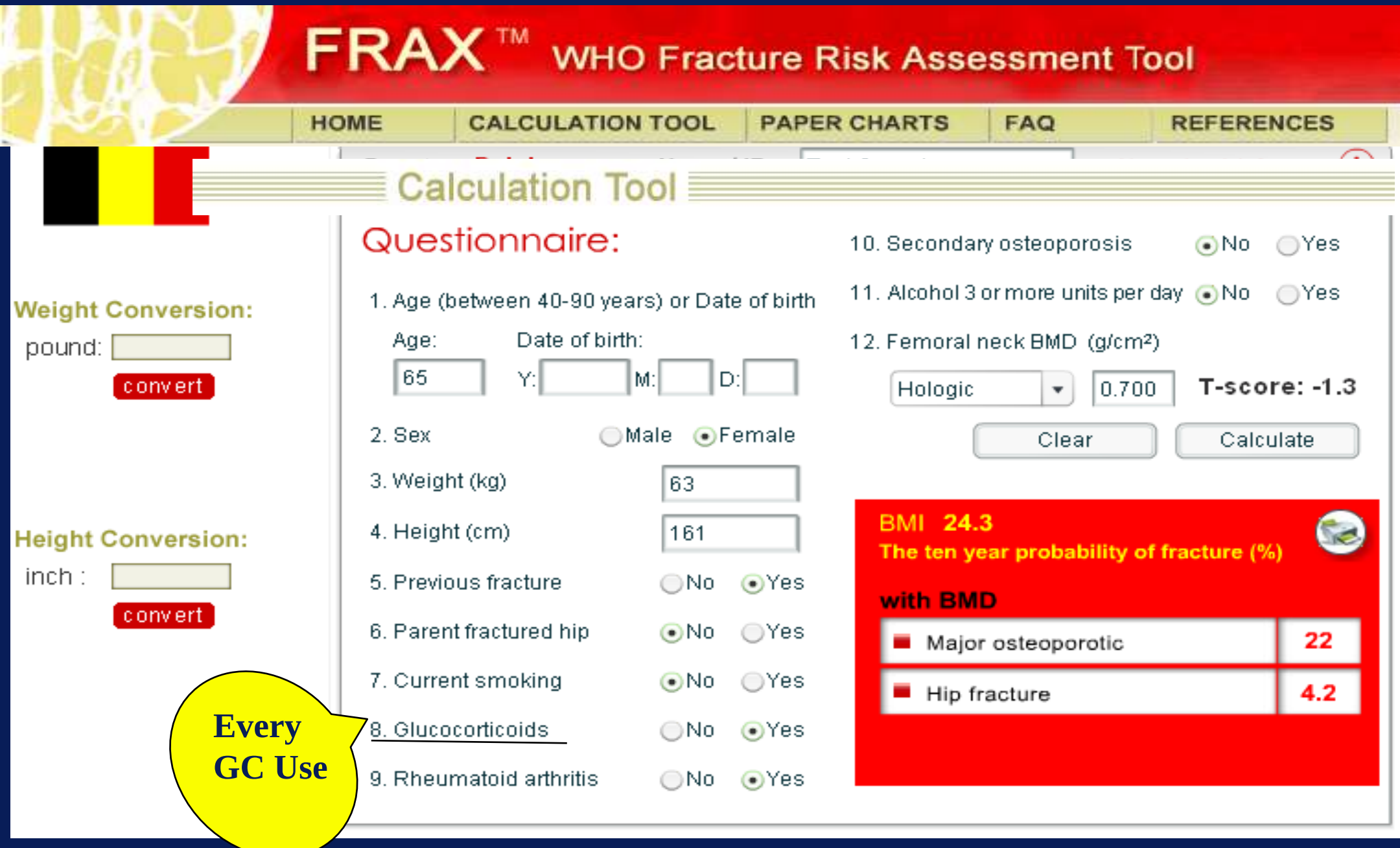
Table 2. Comparison of ACR and RCP guidelines for the management of glucocorticoid-induced osteoporosis

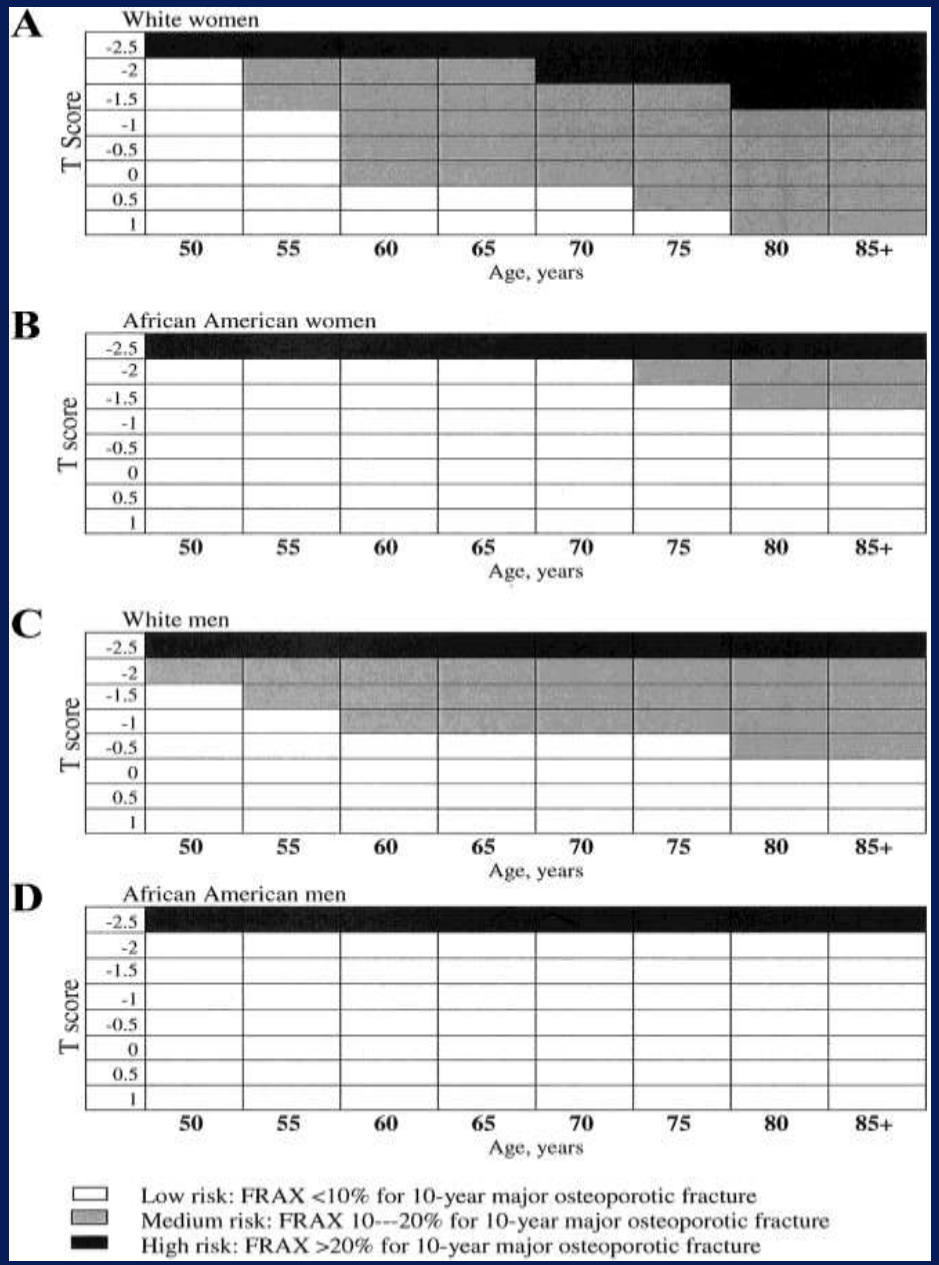
	ACR	RCP
Minimum dose/duration	5 mg/d for ≥ 6 months	Any dose for ≥ 3 months
Calcium and vitamin D	All patients	As adjunct to bisphosphonates and in individuals with evidence of deficiency
Primary prevention	All patients	Men and women ≥ 65 years old or older; previous fragility fracture
BMD measurement	All patients	Those not offered primary prevention
T-score threshold for intervention	-1	-1.5

ACR—American College of Rheumatology; RCP—Royal College of Physicians of London.

Juliet E. Compston, MD. Current Rheumatology Reports 2007, 9:78–84

www.shef.ac.uk/FRAX





2010 ACR recommendationsfor the prevention and treatment of GIOP

Risk stratification : Expert Panel recommended :

A/ Use of either the actual FRAX tool

1.Low risk : 10-yr risk of MOF10% or less

2.Medium risk : 10-yr risk of MOF 10–20%

3.High risk

- 10-yr risk of MOF greater than 20%
- or T score of less than or equal to −2.5
- or a history of a fragility fracture

B/ Reliance by clinicians upon examples of patients (as shown in the Figure + Table 1):

Typical examples of postmenopausal women and men age ≥50 years with a history of glucocorticoid use at high, medium, and low risk of fracture in the absence of other risk factors.

Grossman JM et al, Arthritis Care & Research 2010; (62): 1515-1526, DOI: (10.1002/acr.20295)

2010 ACR recommendations for the prevention and treatment of GIOP

Risk stratification by the Expert Panel

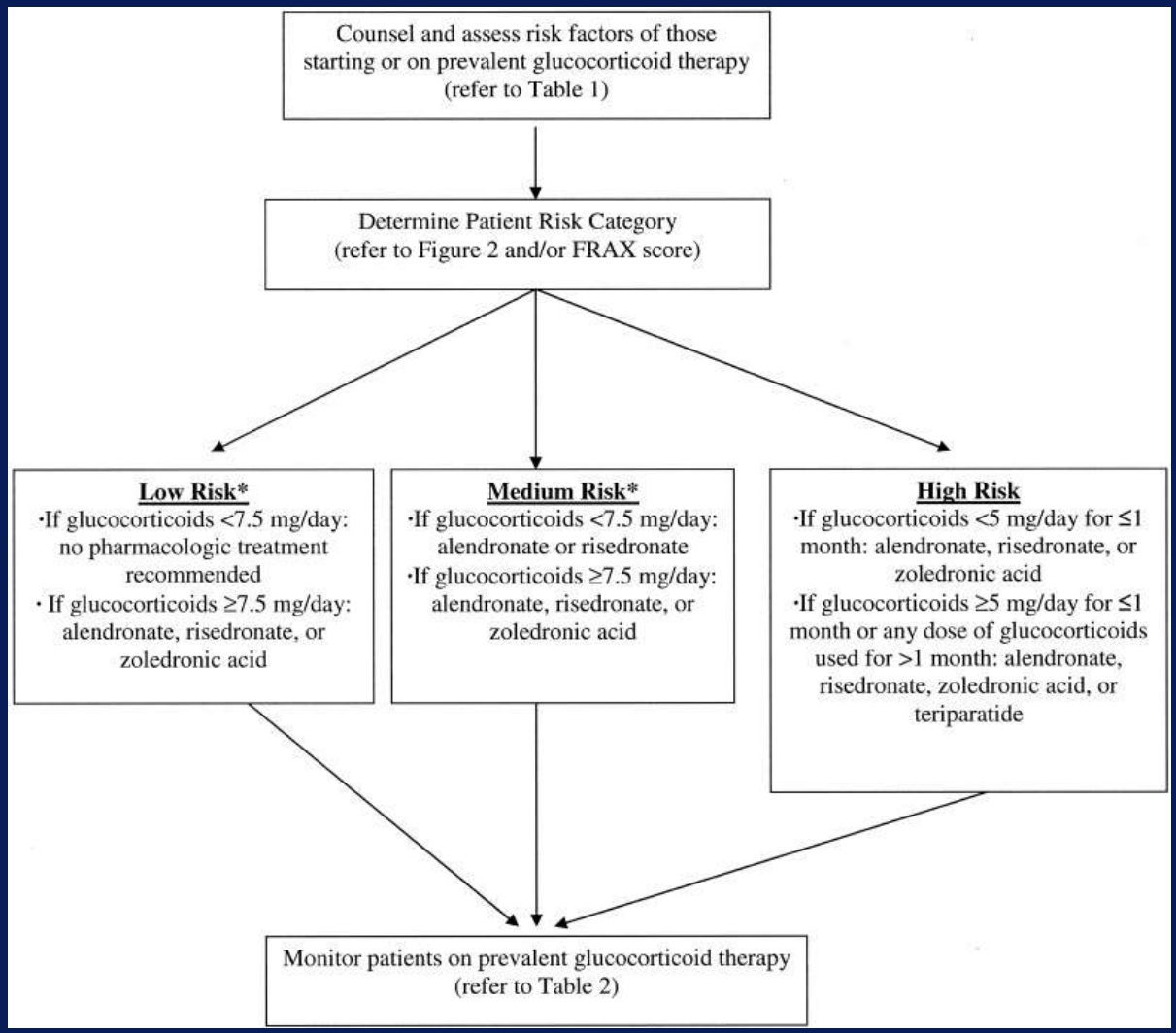
Table 1. Clinical factors that may shift an individual to a greater risk category for glucocortcoid-induced osteoporosis

Low body mass index
Parental history of hip fracture
Current smoking
≥3 alcoholic drinks per day
Higher daily glucocorticoid dose
Higher cumulative glucocorticoid dose
Intravenous pulse glucocorticoid usage
Declining central bone mineral density measurement that exceeds the least significant change

Grossman JM et al, Arthritis Care & Research 2010; (62): 1515-1526, DOI: (10.1002/acr.20295)

2010 American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis

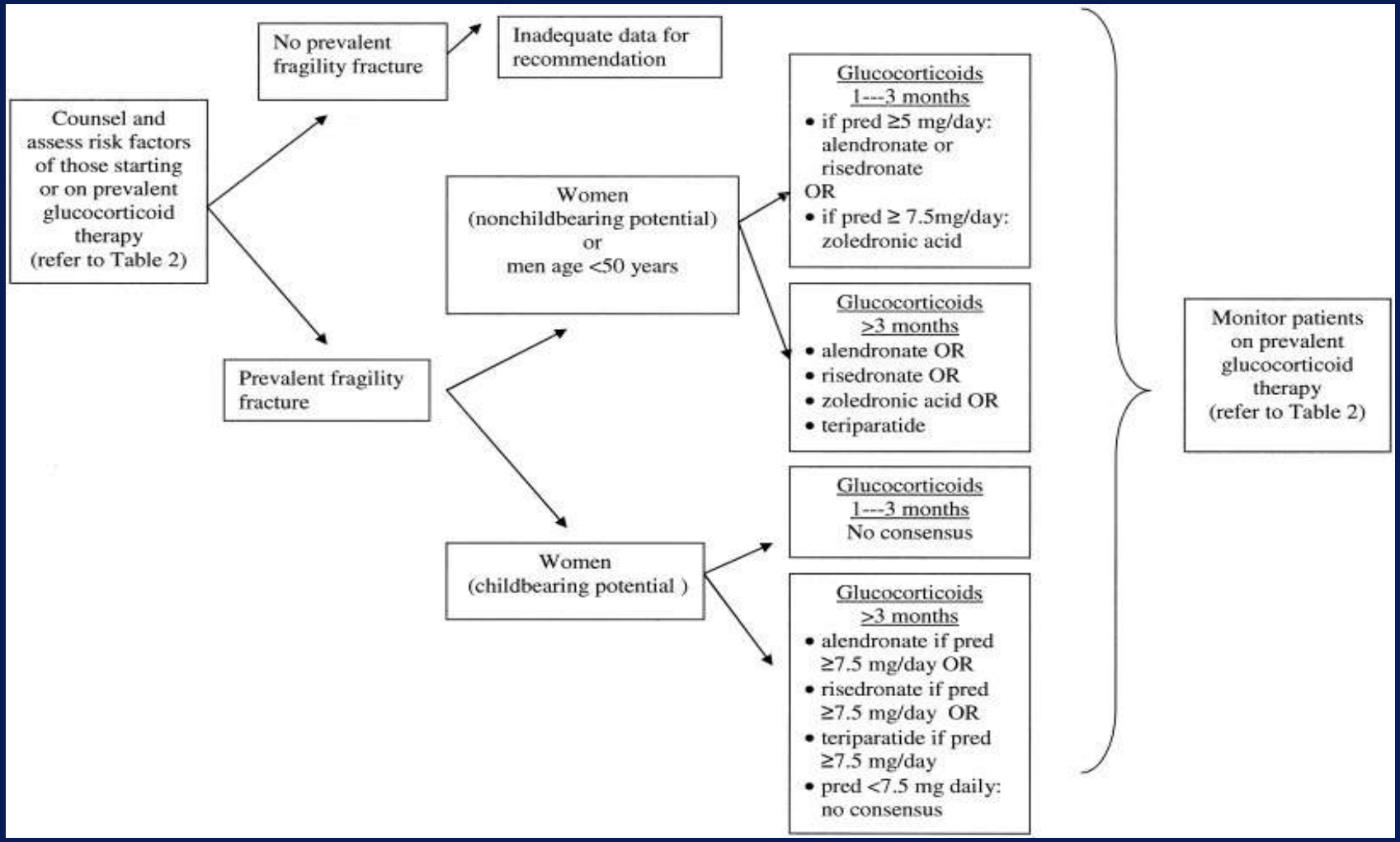
Approach to postmenopausal women and men age >50 years initiating or receiving GC



Grossman JM et al, Arthritis Care & Research 2010; (62): 1515-1526, DOI: (10.1002/acr.20295)

2010 American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis

Approach to premenopausal women and men age <50 years initiating or receiving GC



Grossman JM et al, Arthritis Care & Research 2010; (62): 1515-1526, DOI: (10.1002/acr.20295)

Guidance for the adjustment of FRAX according to the dose of glucocorticoids.

10yr fracture probability by FRAX for MOF & Hip fracture

- For low-dose GCs (< 2.5 mg/d prednisolone) :
  decreased by about 20% depending on age.

- For medium doses GCs (2.5-7.5 mg daily)
  unadjusted FRAX value can be used.

- For high doses (> 7.5 mg daily)
  upward revised by about 15% for MOF and 20% for Hip.

Kanis et al, Osteoporos Int. 2011 (22):809-16. doi: 10.1007/s00198-010-1524-7

2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Arthritis Care & Research, Volume: 69, Issue: 8, Pages: 1095-1110, First published: 06 June 2017, DOI: (10.1002/acr.23279)

Table 1. Fracture risk categories in GC-treated patients

	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤−2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥20% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z score <−3 **or** rapid bone loss (≥10% at the hip or spine over 1 year) **and** Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ <10% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment

* https//www.shef.ac.uk/FRAX/tool.jsp.
† Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is >7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
‡ Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus.

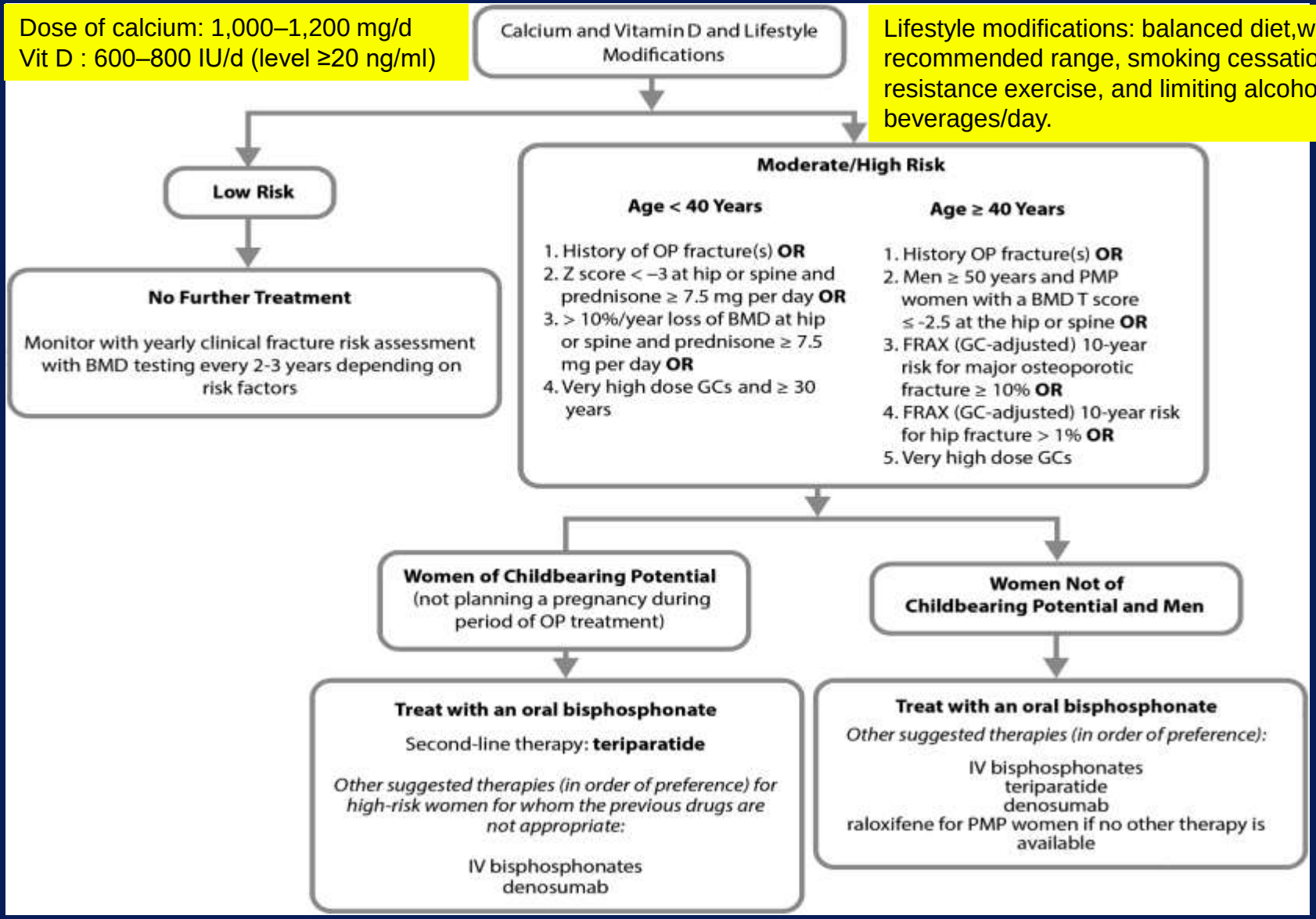
2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Arthritis Care & Research, Volume: 69, Issue: 8, Pages: 1095-1110, First published: 06 June 2017, DOI: (10.1002/acr.23279)

Initial pharmacologic treatment for adults

Dose of calcium: 1,000–1,200 mg/d
Vit D : 600–800 IU/d (level ≥20 ng/ml)

Lifestyle modifications: balanced diet,weight in the recommended range, smoking cessation, weight-bearing and resistance exercise, and limiting alcohol intake to 1–2 alcoholic beverages/day.




That's all Folks!