Effects of glucocorticoids in the management of reumatic diseases

Genoa, October 2016

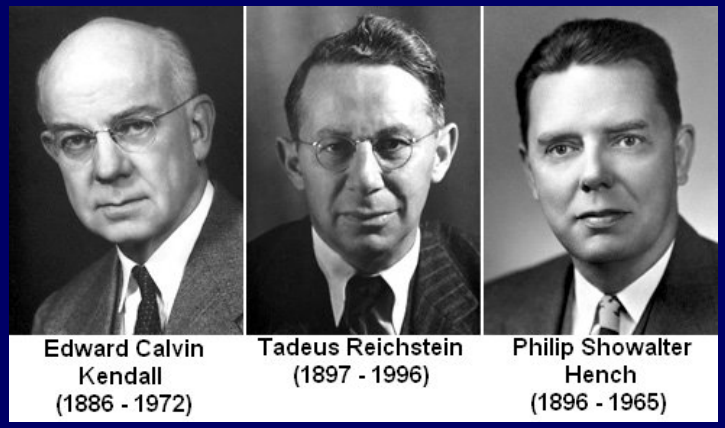
Prof Dr Willem F Lems
Department of Rheumatology
EULAR Centre of Excellence
VU University medical centre and Reade,
Amsterdam, the Netherlands

Disclosure:
Willem F. Lems, MD

	Company
Speaking Fees/ Advisory Boards	Amgen, Eli Lilly, Merck, Novartis, Servier, WarnerChilcott, Will Pharma, Abbott, Pfizer, Roche.

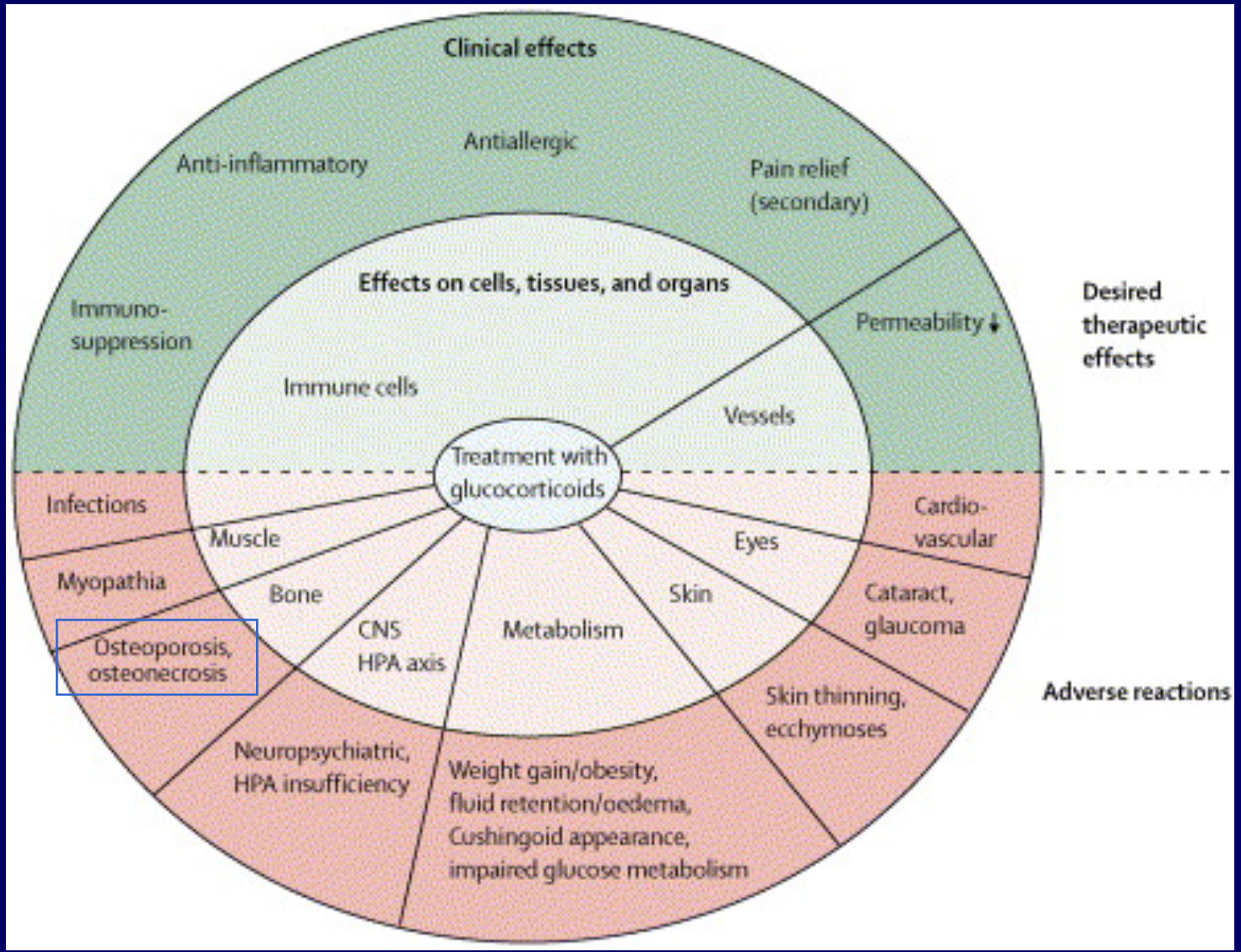
Introduction

- Glucocorticoids (GCs)
  - Steroid hormones produced by adrenal cortex
  - 1948: first administation of hydrocortisone to a patient with rheumatoid arthritis by rheumatologist Hench and associates
  - 1950: Nobel Prize in Medicine



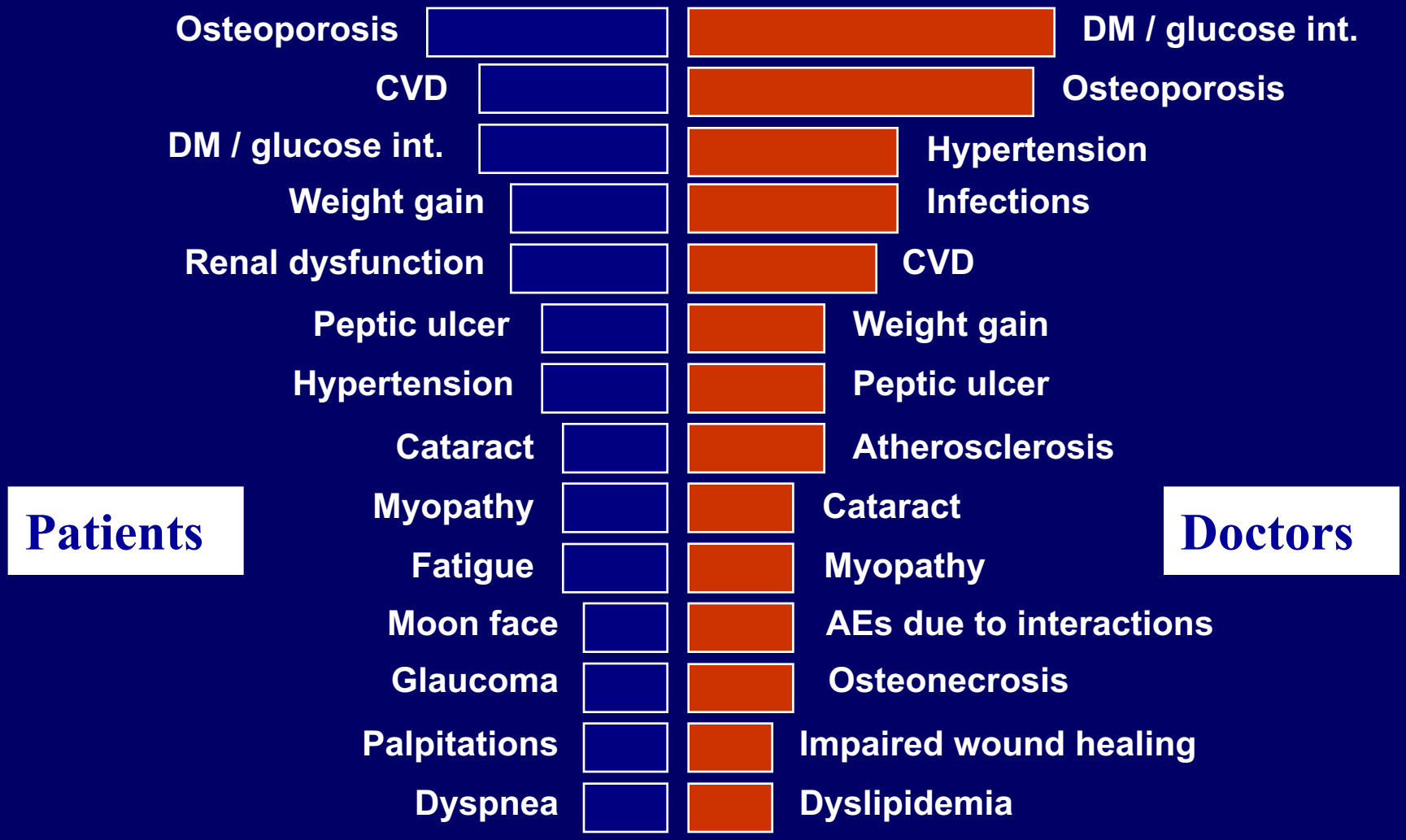
Optimised glucocorticoid therapy: the sharpening of an old spear

Frank Buttgereit, Gerd-Rüdiger Burmester, Brian J Lipworth



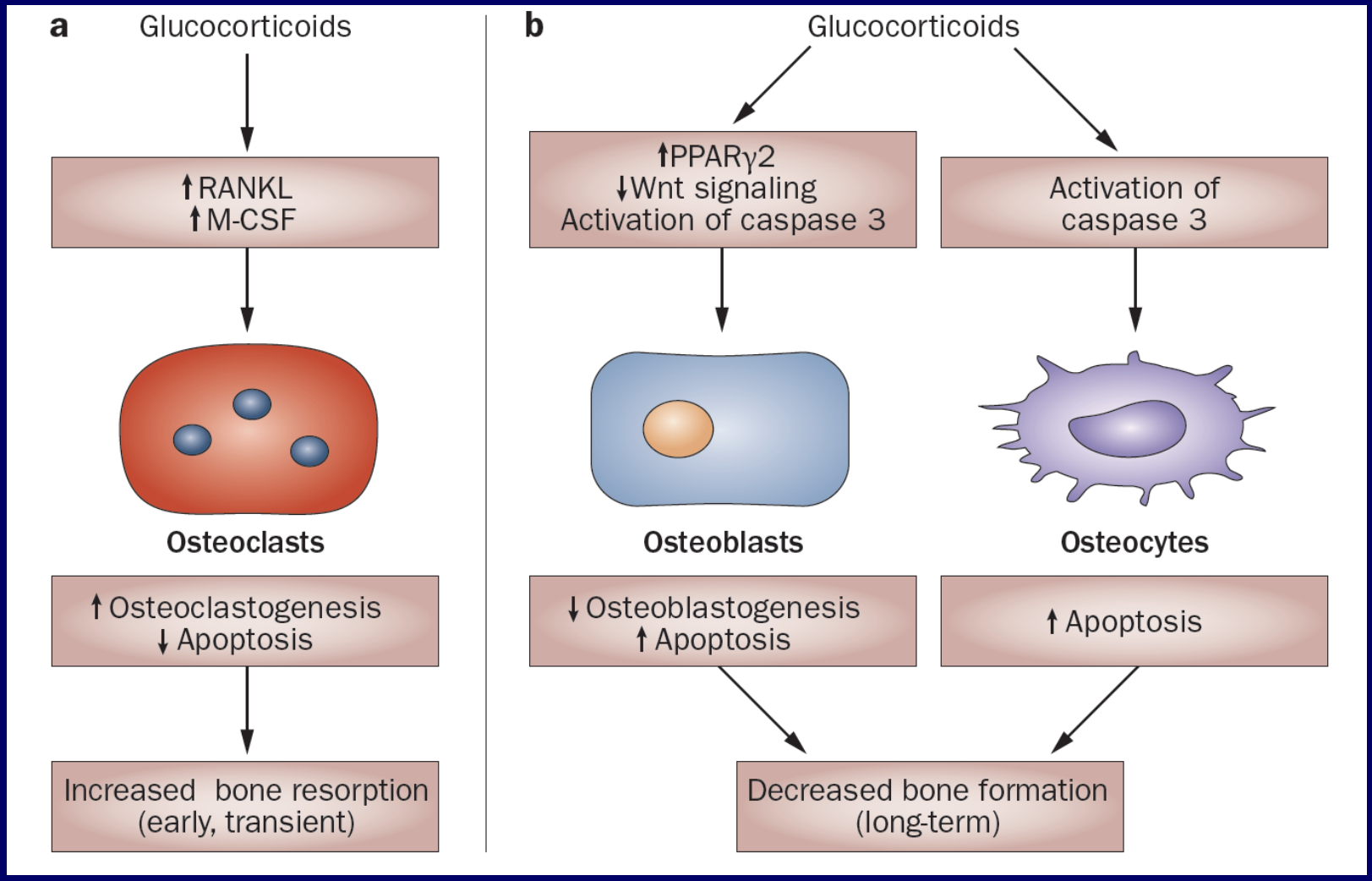
Lancet 2005; 365: 801–03

Ranking adverse events

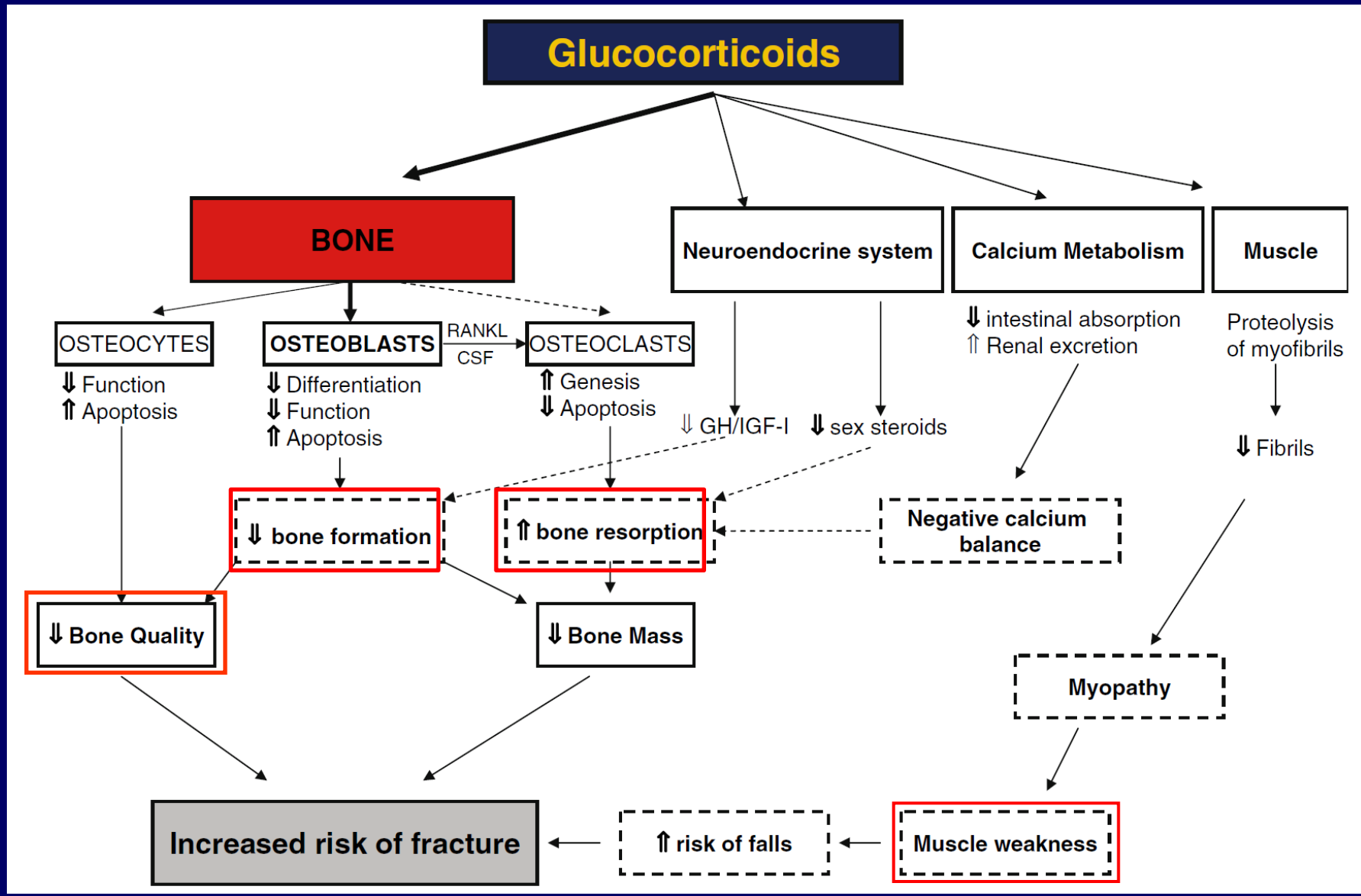


Van der Goes et al. Patients' and rheumatologists' perspectives on glucocorticoids. Ann Rheum Dis 2010

Pathogenesis of GIOP: Direct Effects on Bone

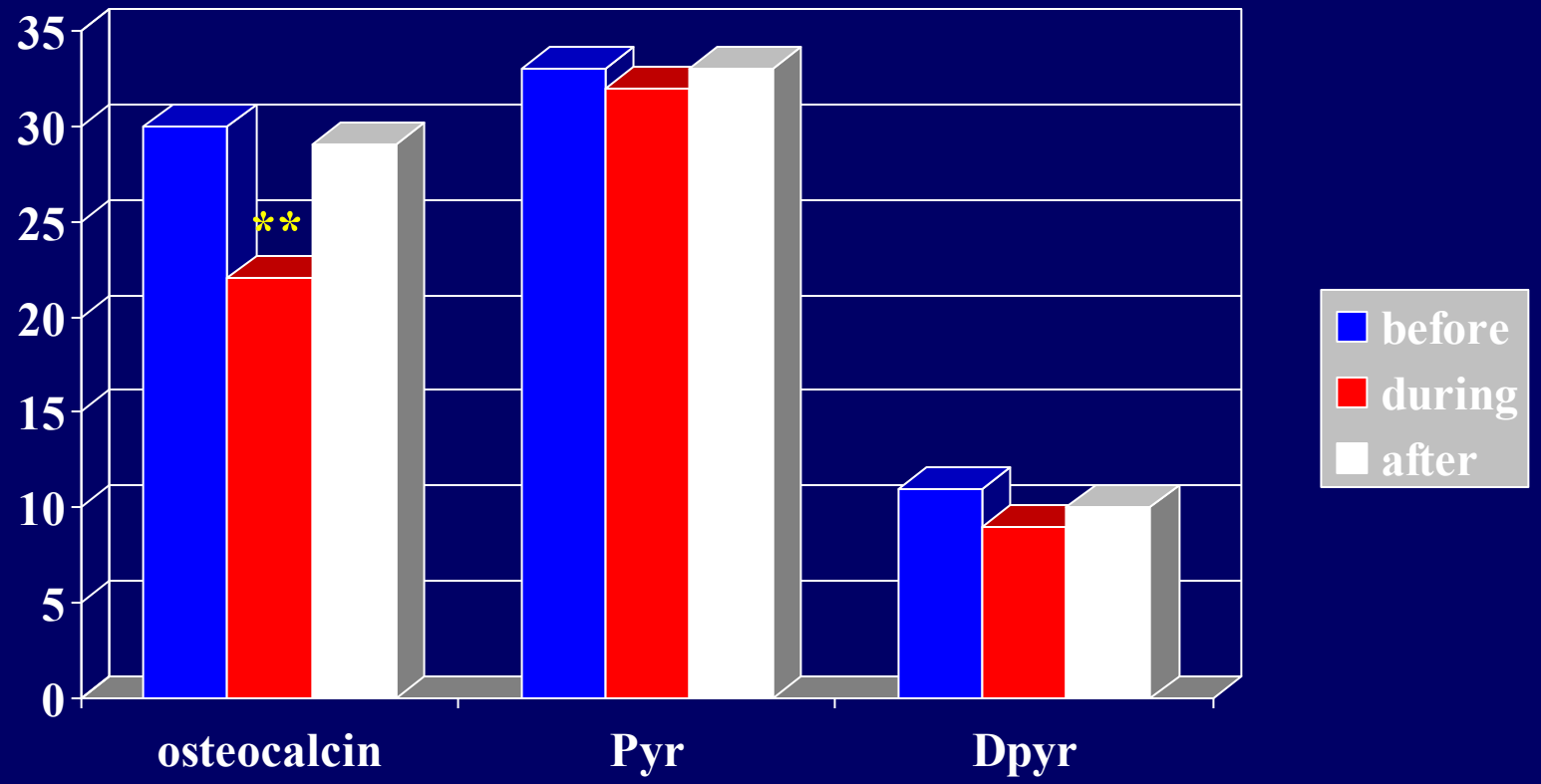


Compston, Clin Nat Rev, 2010



Canalis, OI, 2007, 1319

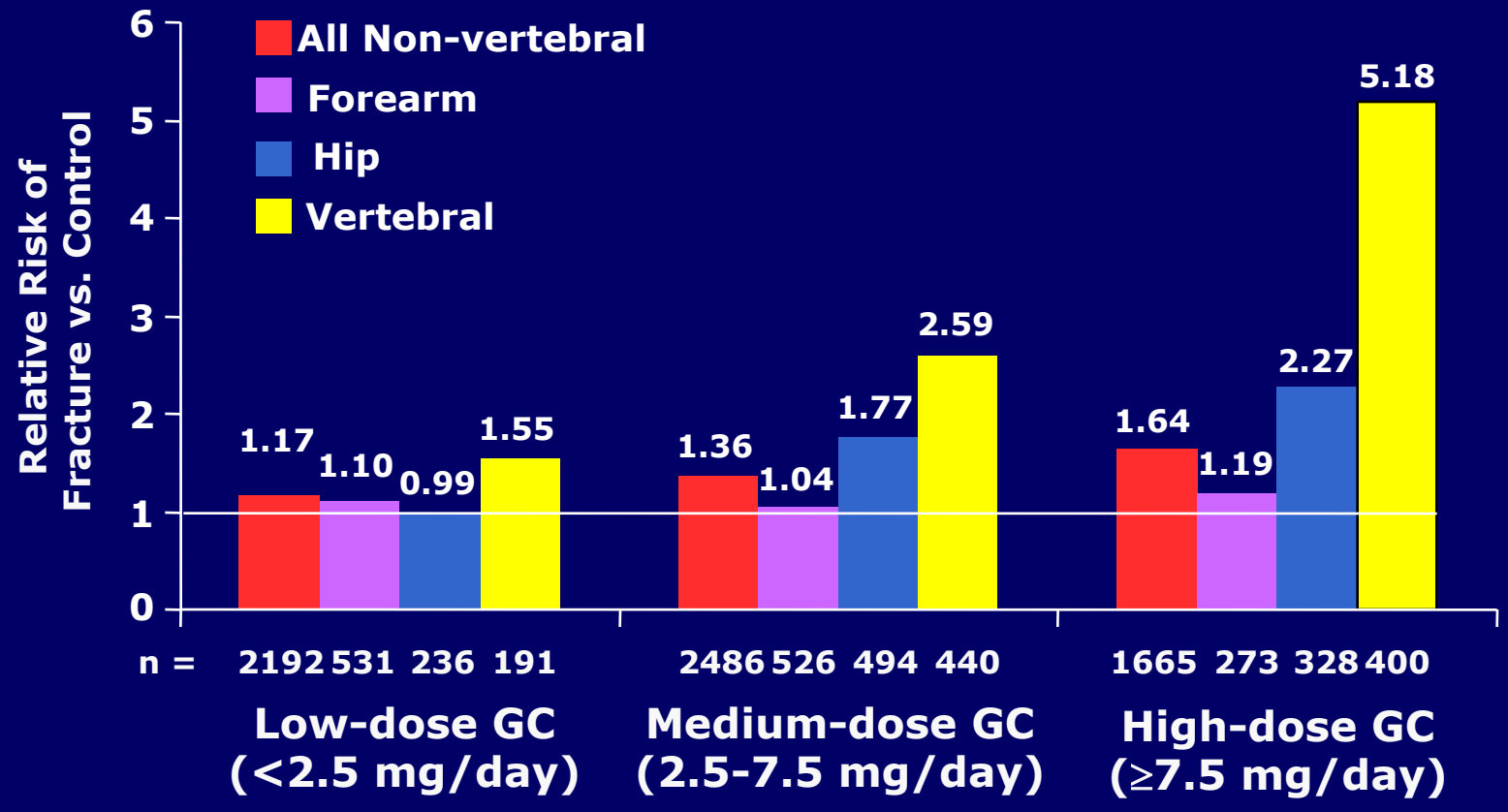
Effect of low dose prednisone (10 mg/day during 1 week) on markers of bone metabolism in healthy volunteers



**: p <0,05

WF Lems et al, Br J Rheum 1998; 37: 23-33.

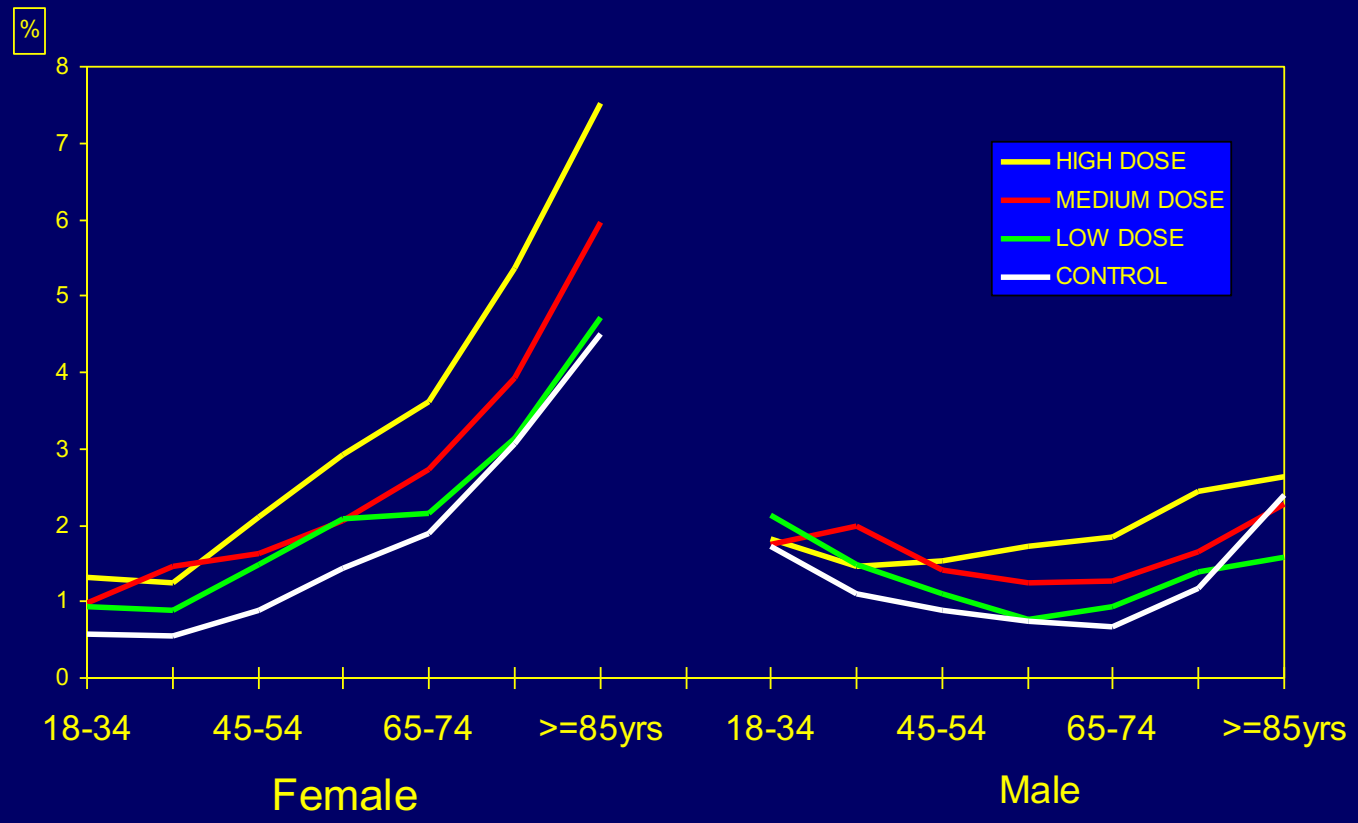
Glucocorticoid Use and Fracture Risk: Dose Related.



GC, glucocorticoid

Van Staa TP, et al. *J Bone Miner Res* 2000;15:993-1000

INCIDENCE OF NON-VERTEBRAL FRACTURES STRATIFIED BY DAILY CORTICOSTEROID DOSE, AGE AND GENDER



Incidence: per 100 patient years

VAN STAA ET AL
JBMR 2000; 15: 993-1000

Generalised bone loss in patients with early rheumatoid arthritis

Andrew K S Gough, John Lilley, Sheila Eyre, Roger L Holder, Paul Emery

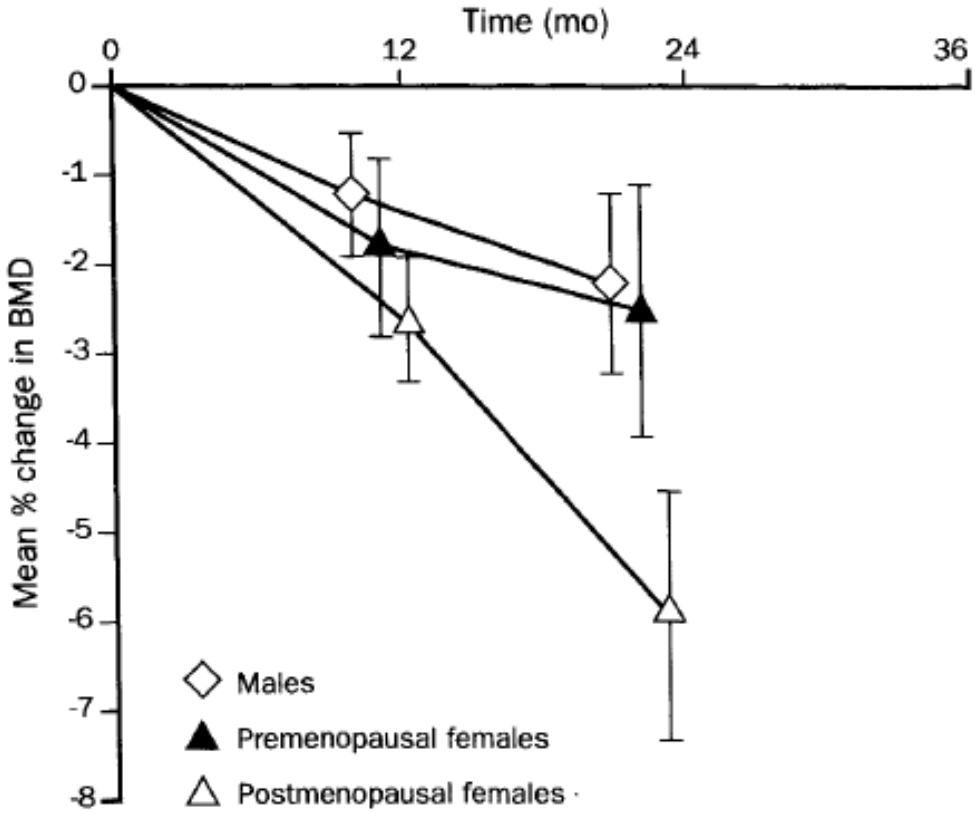
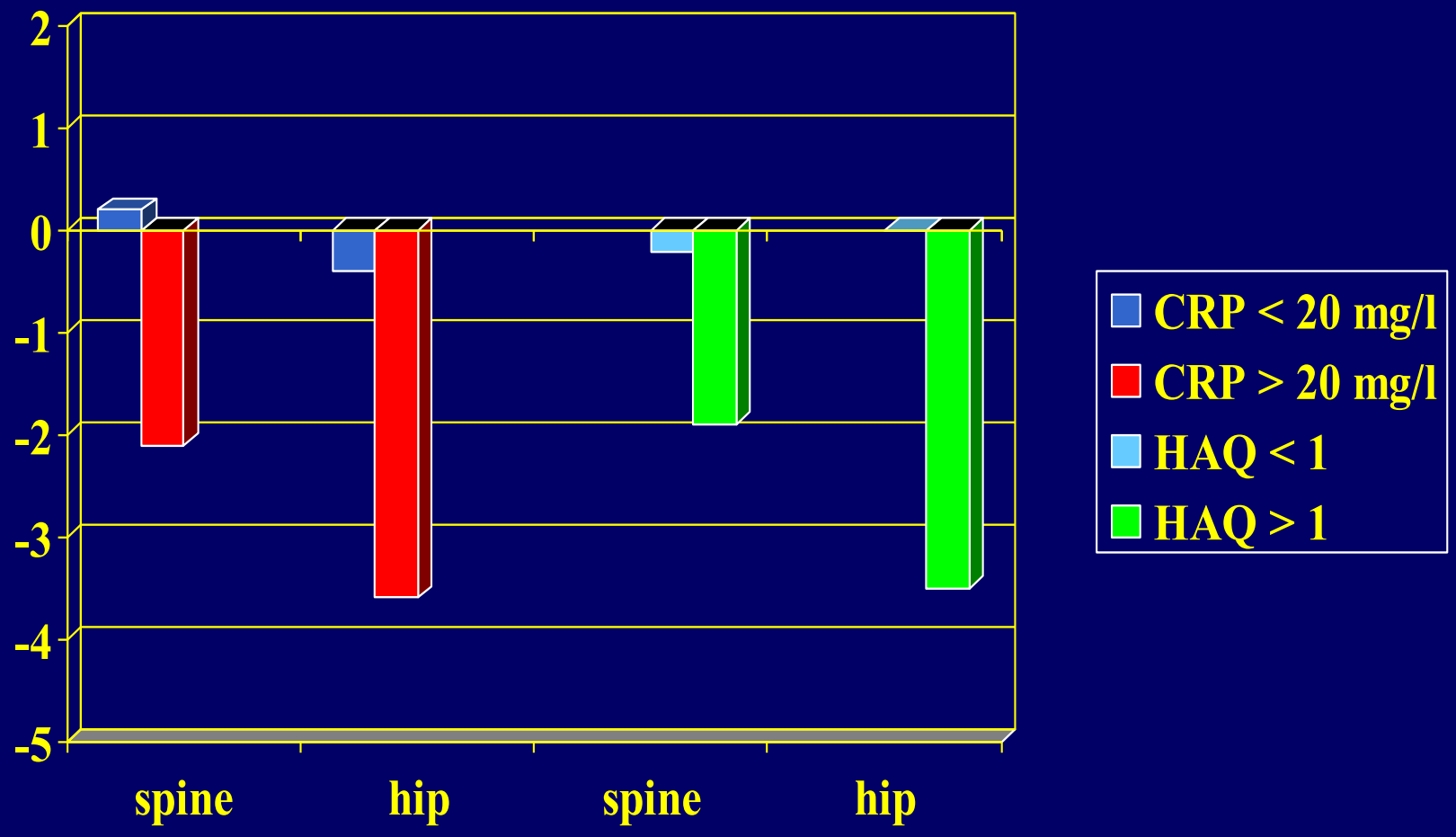


Figure 1: **Change in bone mineral density at femoral neck over 2 years in male, premenopausal, and postmenopausal patients with RA (n = 148)**

Lancet 1994; **344:** 23–27

Generalised bone loss in patients with early rheumatoid arthritis

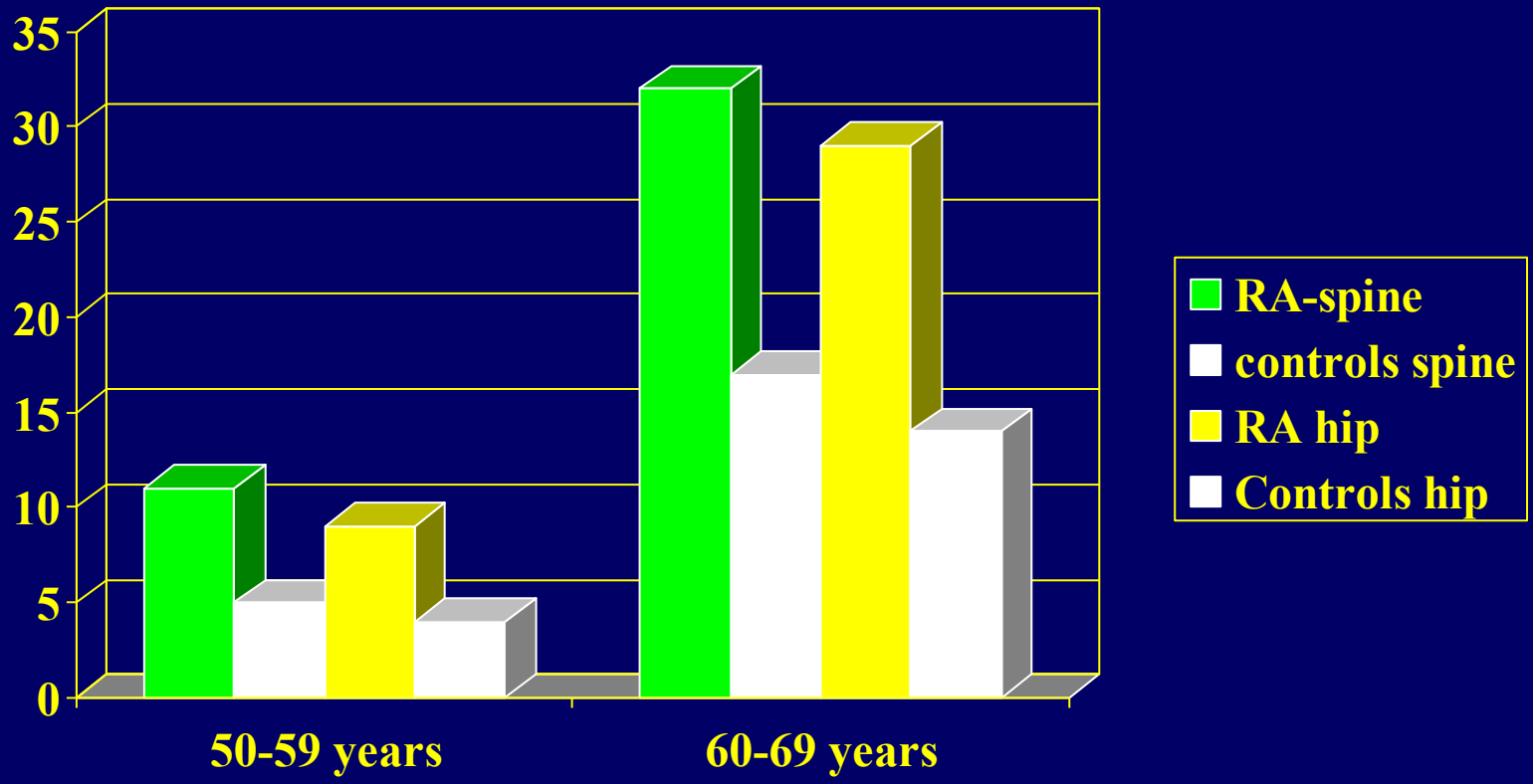
Andrew K S Gough, John Lilley, Sheila Eyre, Roger L Holder, Paul Emery



Lancet 1994; **344:** 23–27

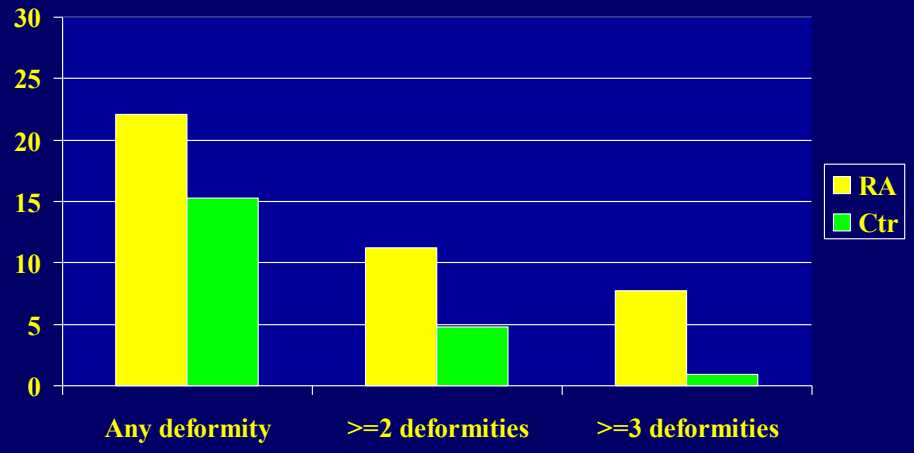
WIN WITH EULAR

2-Fold Increase in osteoporosis (T-score < -2,5) in 394 postmenopausal women with RA

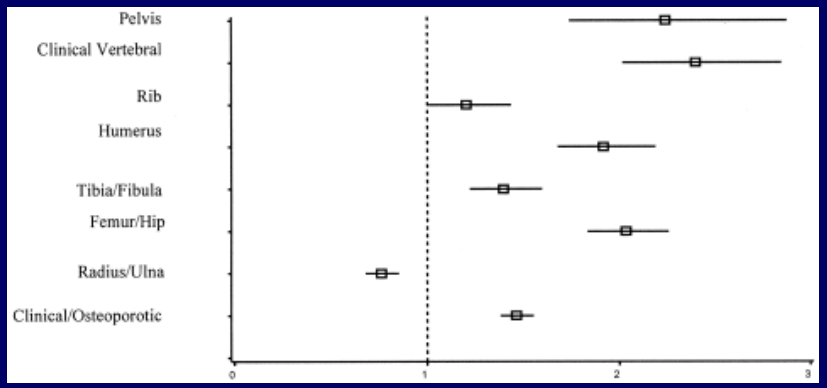


Haugeberg et al; Artritis Rheum 2000; 522-530

Elevated risk of vertebral- and nonvertebral fractures in RA



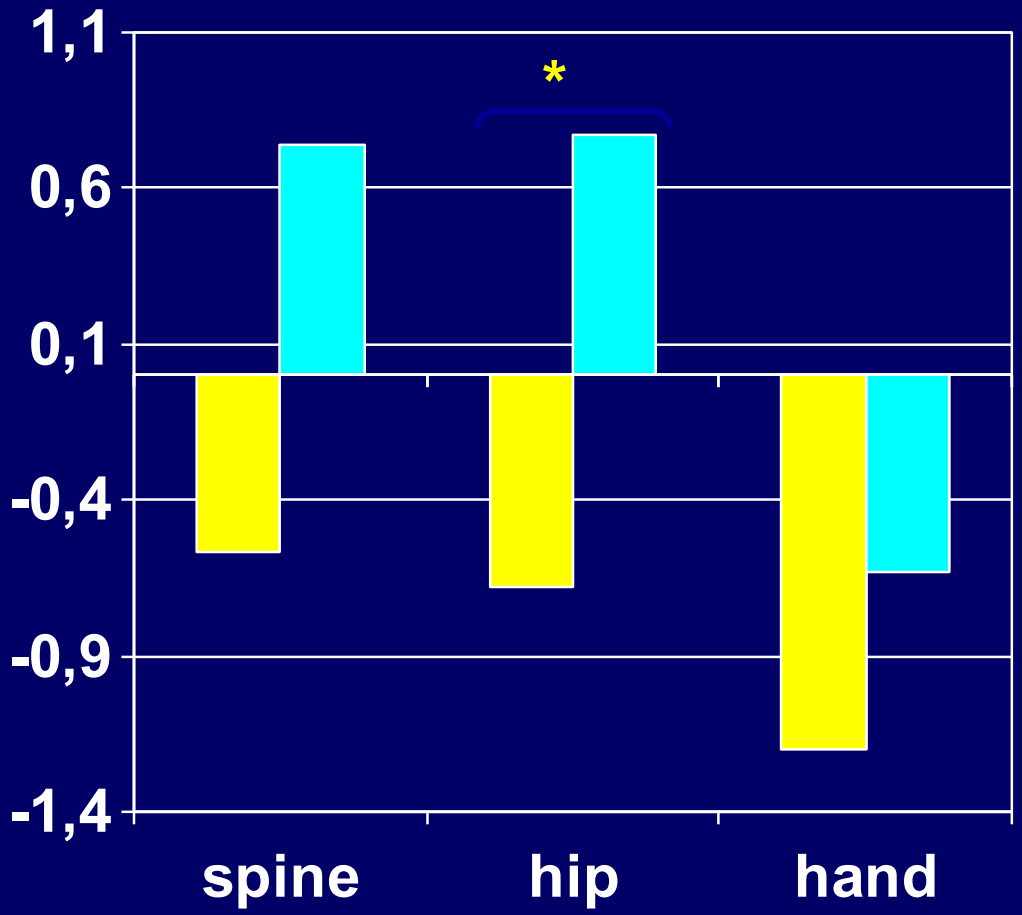
Orstavik, Arch Int Med 2004



Van Staa et al, Arthritis Rheum 2006

WIN WITH EULAR

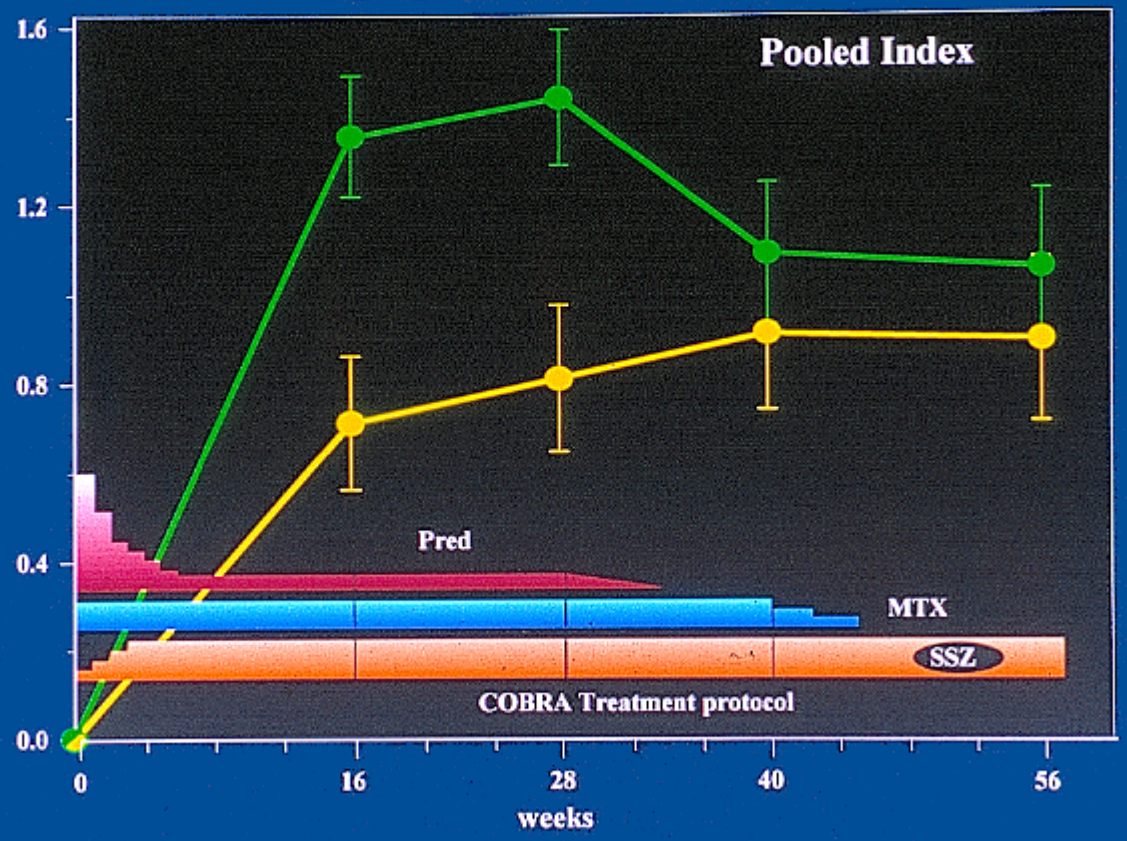
% Changes in BMD after 1 year treatment with infliximab



* p<0.05

Vis et al, Annals Rheum Dis 2006

COBRA trial



Boers et al., Lancet, 1997

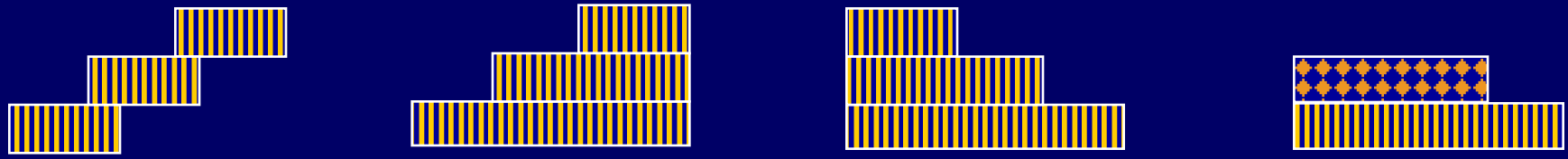
BeSt

Treatment Strategies
in Rheumatoid Arthritis

Glucocorticoid use and bone loss

in recent-onset active rheumatoid arthritis

BeSt treatment strategies



Sequential monotherapy starting with MTX

Step-up combination therapy starting with MTX

Initial combination therapy with MTX, SSA & prednisone

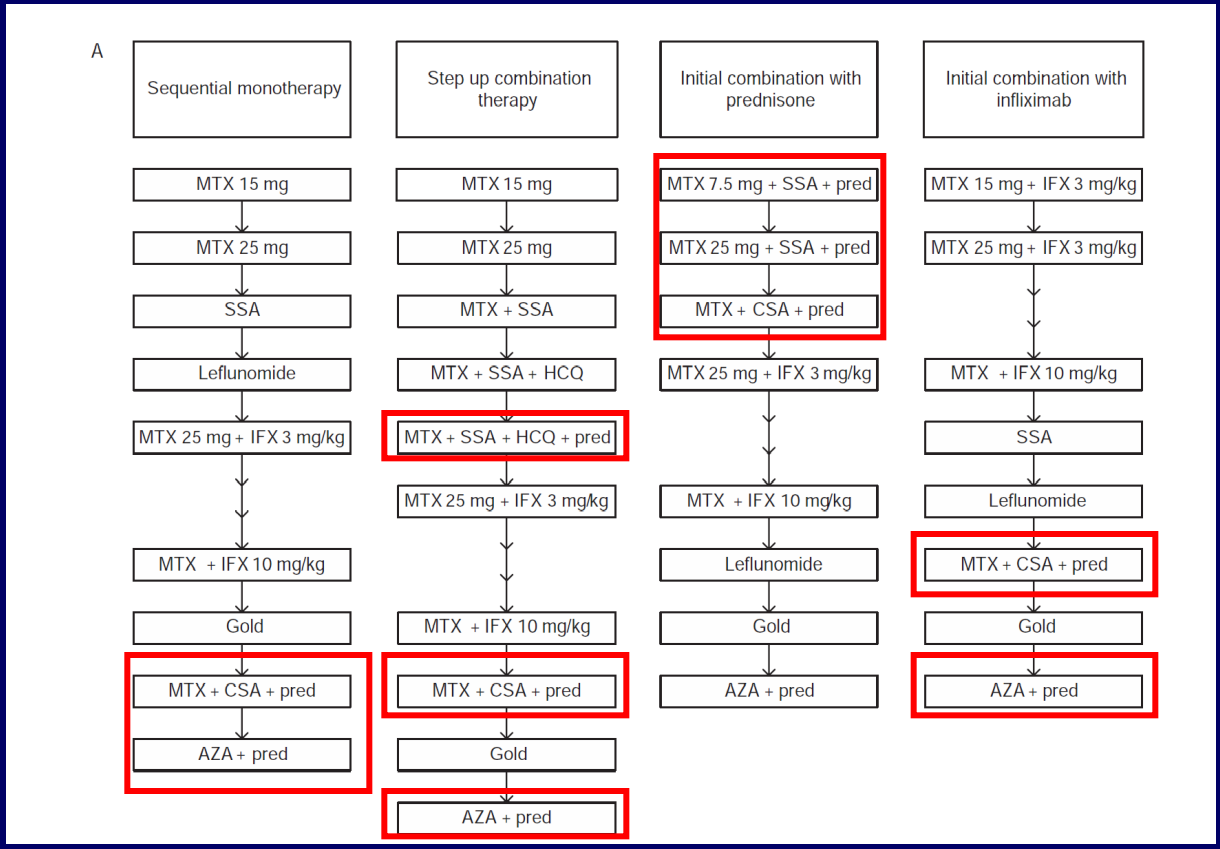
Initial combination therapy with MTX & infliximab

Every 3 months DAS_{44} by research nurse

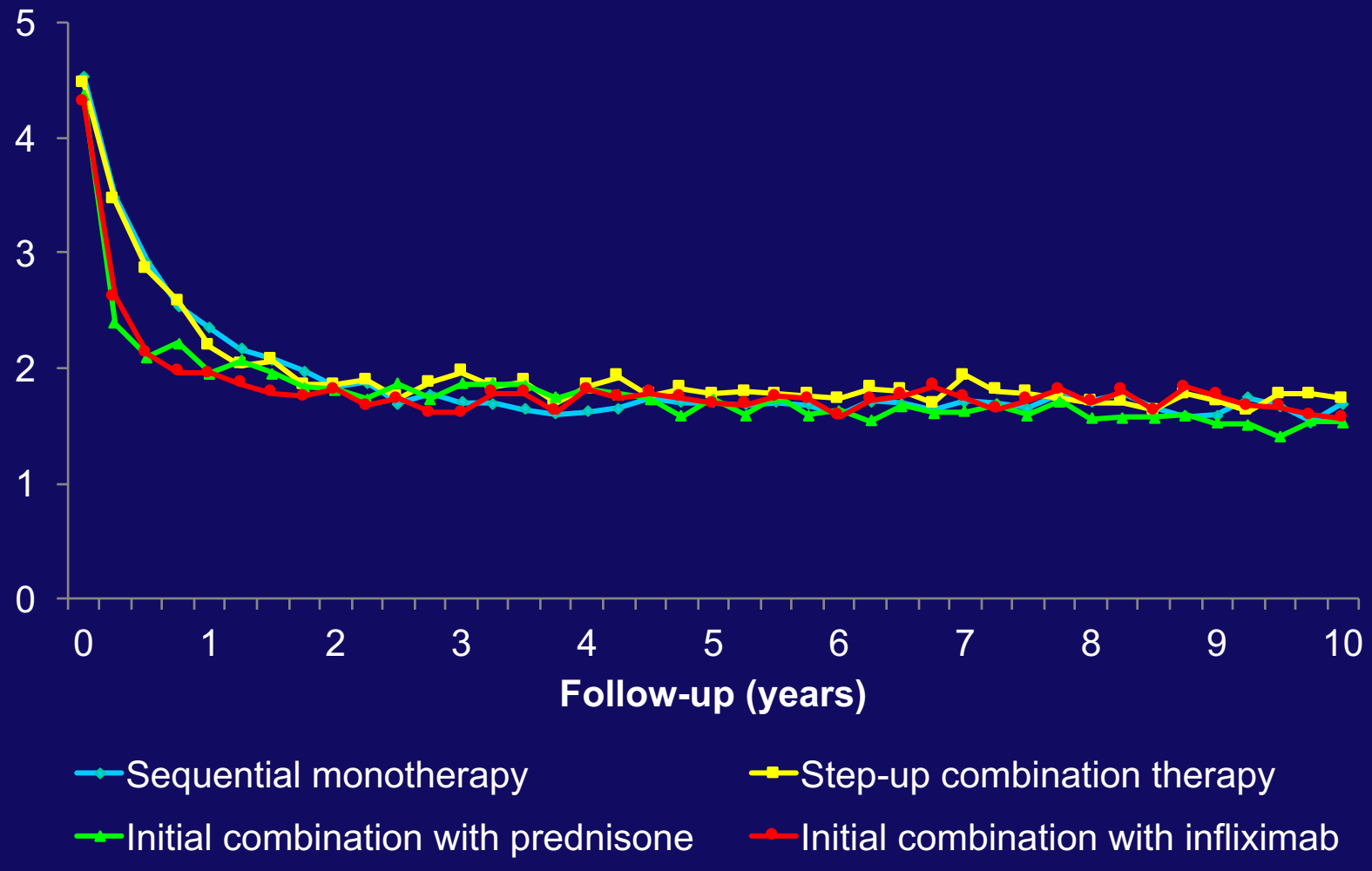
> 2.4: adjust treatment to next step

≤ 2.4: continue or (after 6 months) taper according to protocol per treatment group

BeSt study comparing treatment strategies, no treatments (GC versus placebo)

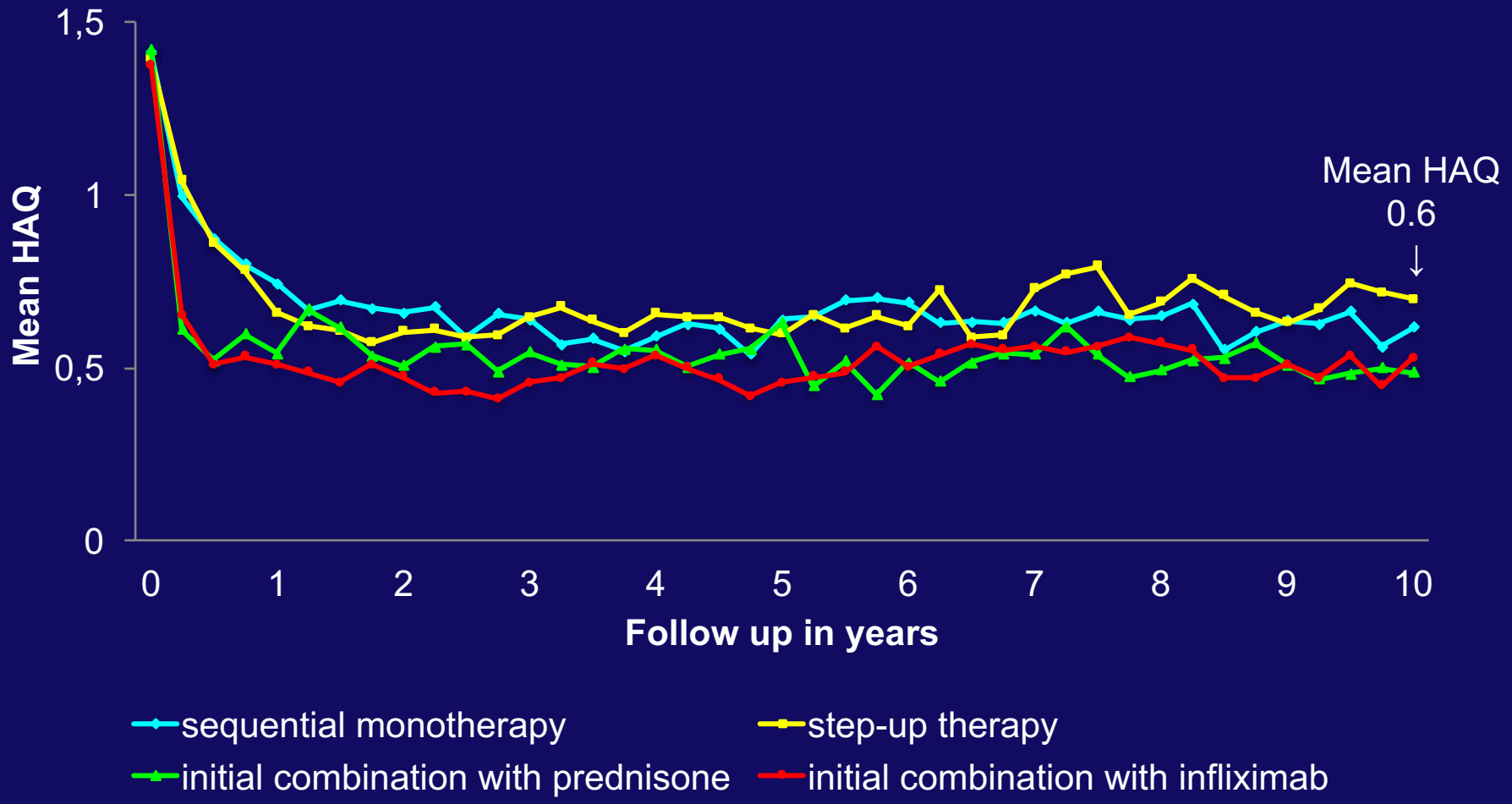


Disease activity score



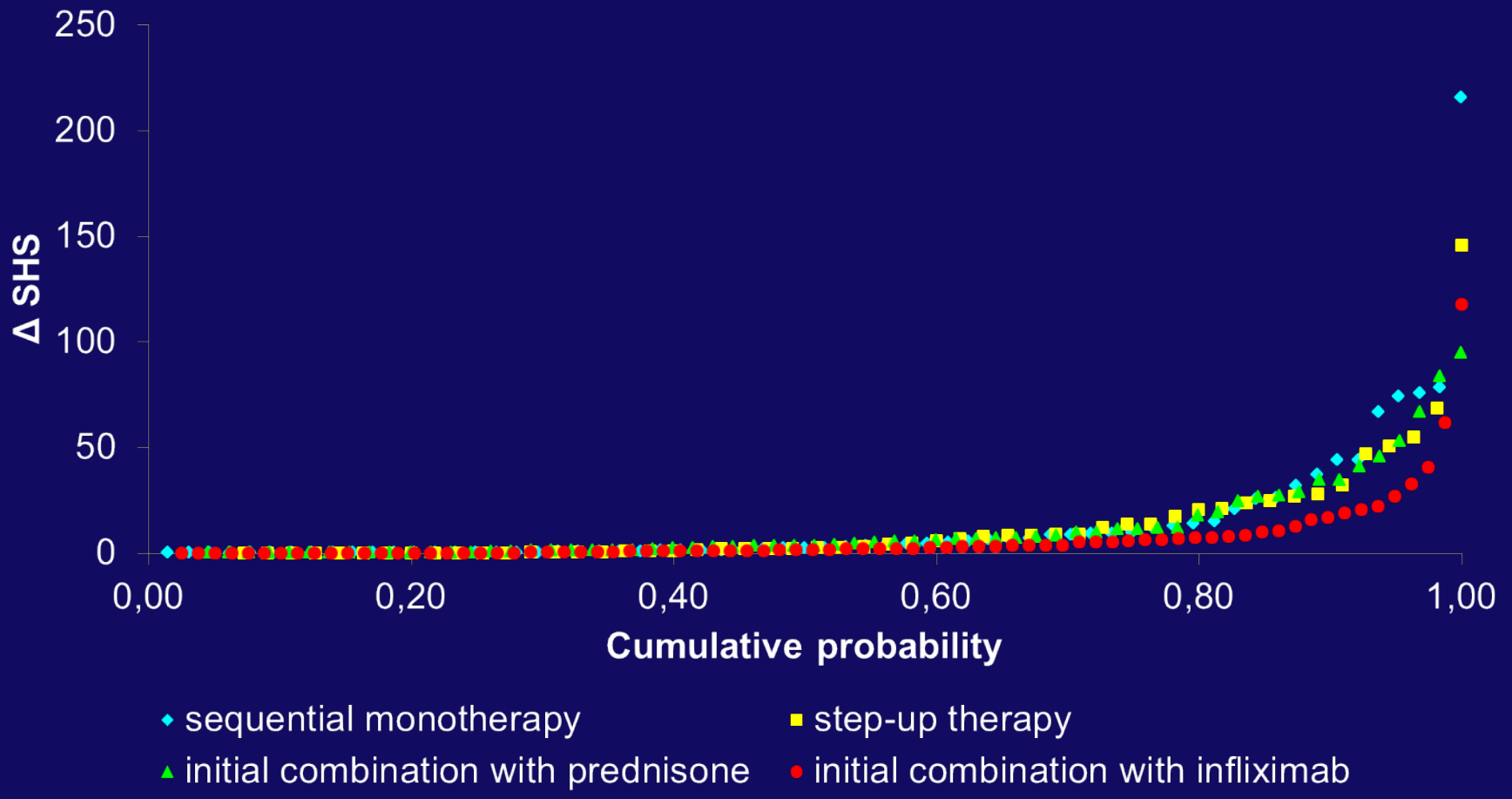
Ann int med 2016

Functional ability

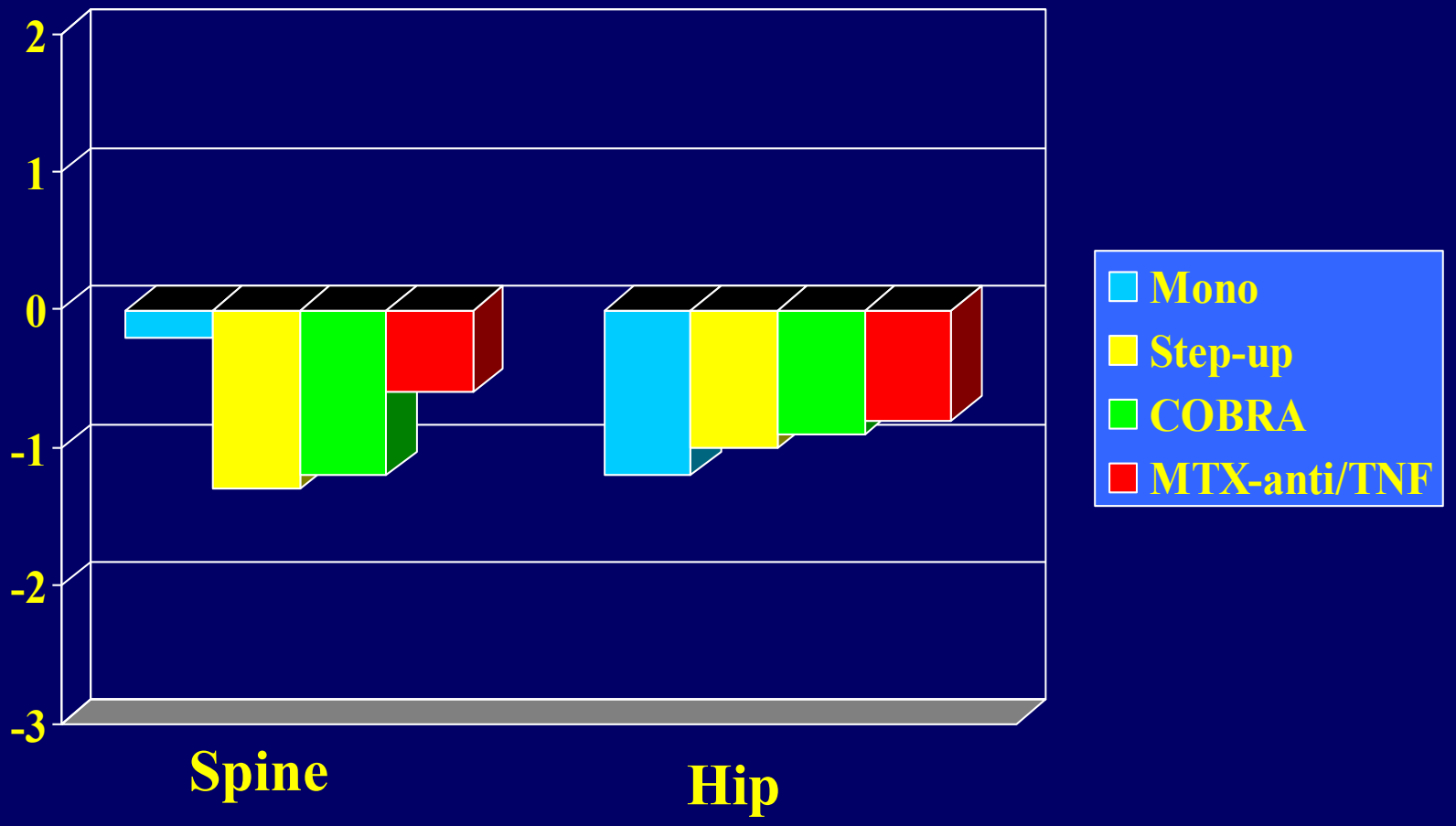


Over time: group 2 vs 4 $p<0.05$, with a mean difference of 0.14
Other comparisons non-significant.

Radiographic progression



% change in BMD of lumbar spine and hips during 2 years observation in early RA (BEST-study)



Guler-Yuksel, Ann Rheum Dis 2007

Median BMD loss after 1 year (% of baseline) in the 4 treatment groups

	Sequential mono	Step-up combi	Initial combi prednisone	Initial combi infliximab
Δ BMD in hands	-2.6 *	-1.7 *	-0.6 *	-0.9 *
Δ BMD in hip	-1.6	-0.4	-1.0	-0.6
Δ BMD in spine	-0.2	-1.1	-1.0	-0.1

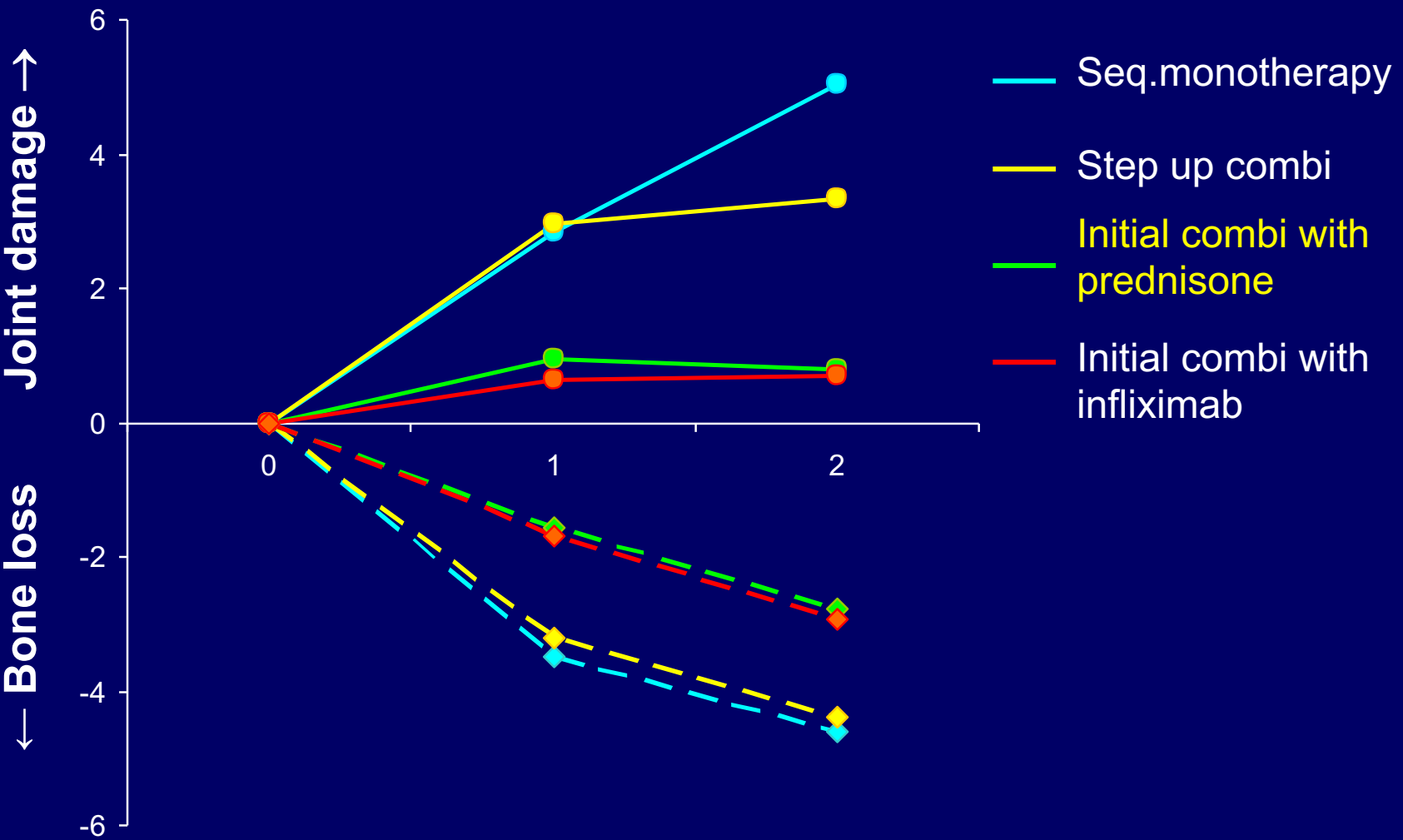
***: p<0.05 in group 3 and 4 versus group 1 and 2**

Median BMD loss after 2 year (% of baseline) in the 4 treatment groups

	Sequential mono	Step-up combi	Initial combi prednisone	Initial combi infliximab
Δ BMD in hands	-3.6 *	-3.3 *	-1.4 *	-1.6 *
Δ BMD in hip	-1.1	-0.2	-0.2	-0.6
Δ BMD in spine	-0.4	-1.6	-0.5	-1.0

***: p<0.05 in group 3 and 4 versus group 1 and 2**

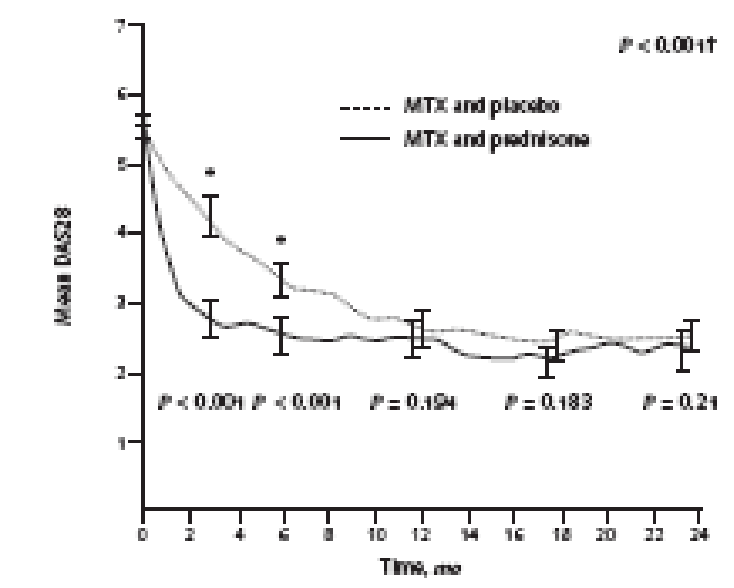
Hand BMD loss & erosion progression



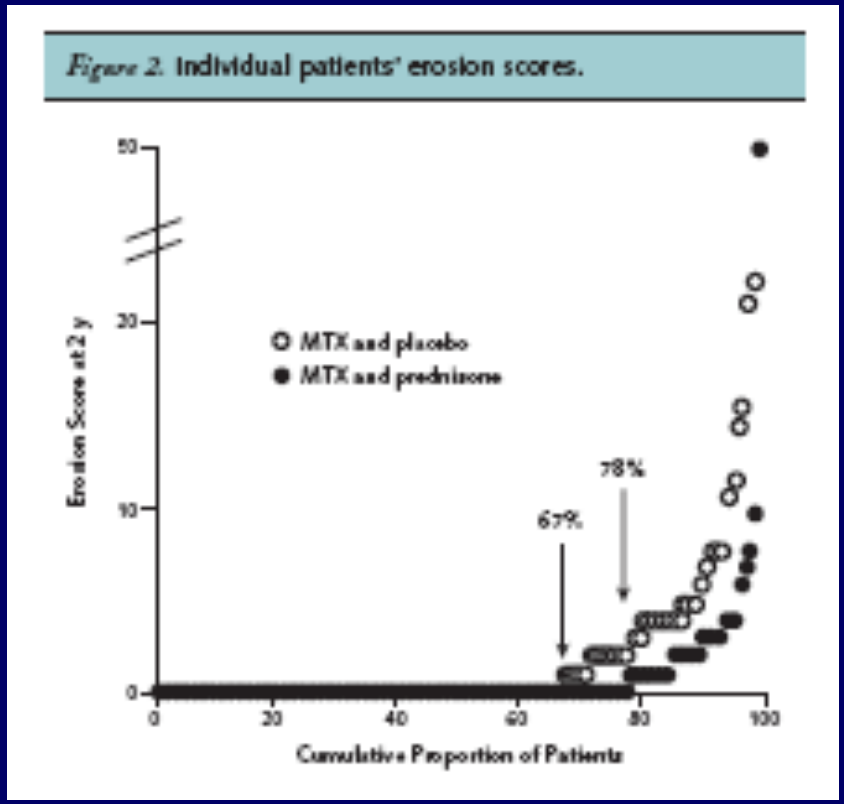
Annals of Internal Medicine | ORIGINAL RESEARCH

Low-Dose Prednisone Inclusion in a Methotrexate-Based, Tight Control Strategy for Early Rheumatoid Arthritis

A Randomized Trial

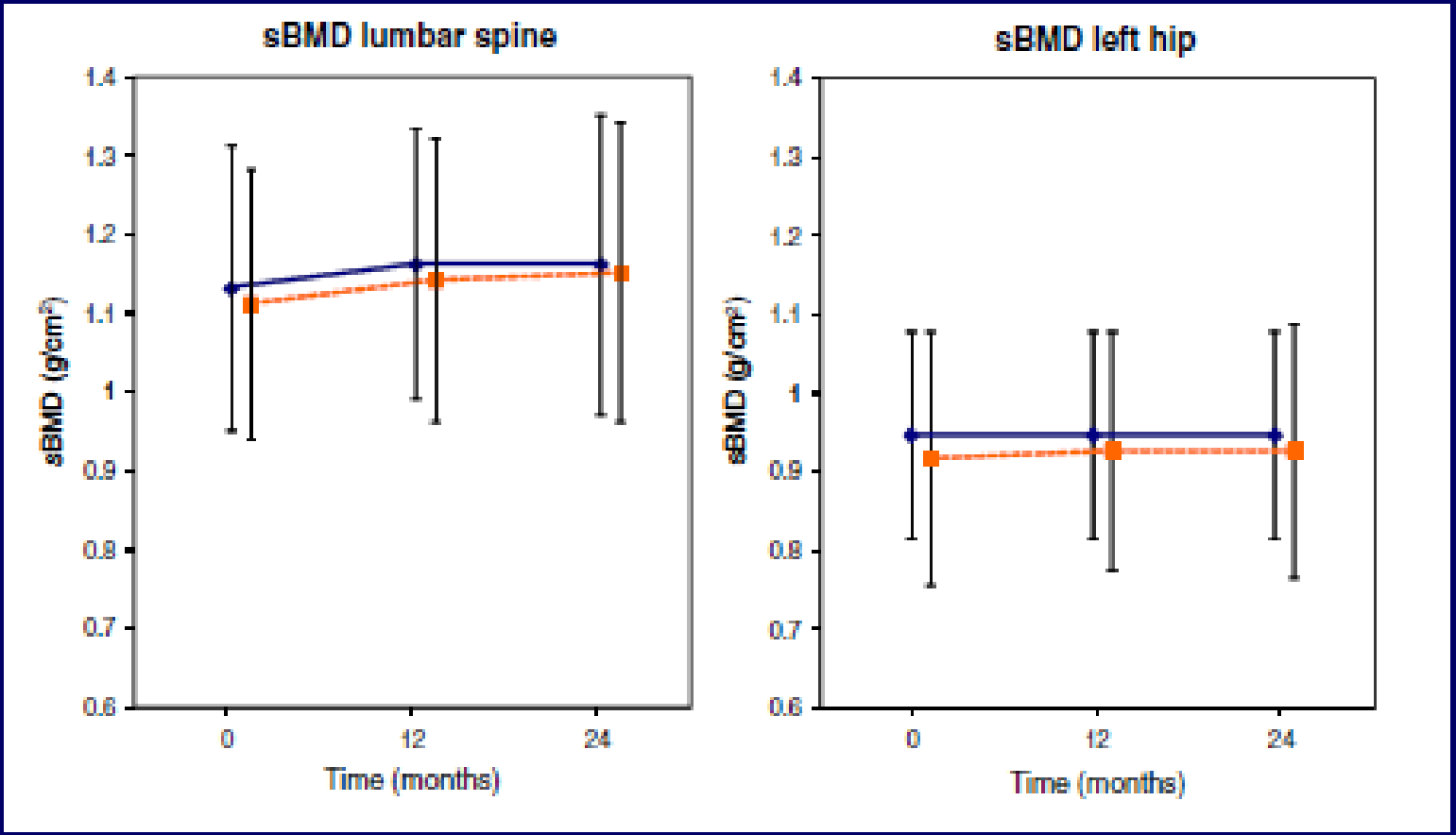


Ann Int Med 2012



Are changes in bone mineral density different between groups of early rheumatoid arthritis patients treated according to a tight control strategy with or without prednisone if osteoporosis prophylaxis is applied?

M. C. van der Goes · J. W. G. Jacobs · M. S. Jurgens · M. F. Bakker · M. J. van der Veen · J. H. van der Werf · P. M. J. Welsing · J. W. J. Bijlsma



Ost Int 2012

"Some data suggest that low dose GCs may even benefit the bones of patients with RA"

- *"A little GC, like a glass of wine, may benefit many people, whereas a high dose of GC, like a bottle of wine, is harmful to all".*

Glucocorticoids in the treatment of early and late RA

J W J Bijlsma, M Boers, K G Saag, D E Furst

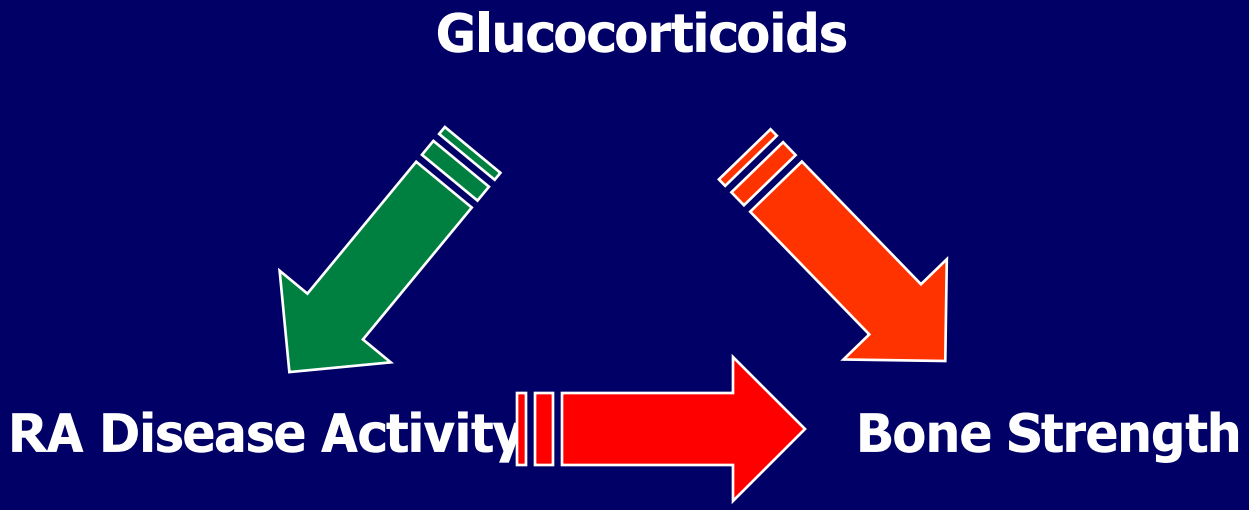
Ann Rheum Dis 2003;62:1033–1037

"Some data suggest that GCs may even benefit the bones of patients with RA"

- disease activity ↓
- weightbearing activity ↑
- pro-inflammatory cytokines deleterious to bone ↓

Bijlsma: Annals Rheum Dis 2003 1033-37

"Not only Glucocorticoids, but also the underlying disease might have a negative effect on bone strength! (drug/disease confounding)



Secondary Osteoporosis: RA, SLE, Vasculitis, COPD, Inflammatory Bowel Disease, etc

One-Year Effects of Glucocorticoids on Bone Density

Meta-Analysis in Cohorts on High and Low Dose Therapy

Merel Baak, Willem Lems, Mariëtte Lodder*,
Lilian van Tuyl, Ben Dijkmans, Maarten Boers

Departments of Rheumatology;
Epidemiology and Biostatistics
VU University Medical Center Amsterdam
**Spaarne Hospital Haarlem*
Netherlands

VU medisch centrum

patient characteristics

	chronic inflammatory disease	transplantation
cohorts (RCT arms)	51 34	18 11
patients	1846: 1565 w FU data	705: 635 w FU data
diagnoses	RA 359 SLE 200 PMR 91 mixed 915	kidney 530 heart 48 lung±heart 32 liver 25
women (%)	73	36
mean age	56	46
% starters	41% cohorts; 34% pts	83% cohorts; 92% pts
% Ca/D suppl	59% cohorts; 85% pts	61% cohorts; 88% pts
GC dose (mean, range)	8,7 mg/d (1,2-16,4)	18,9 mg/d (6,0-52,7)

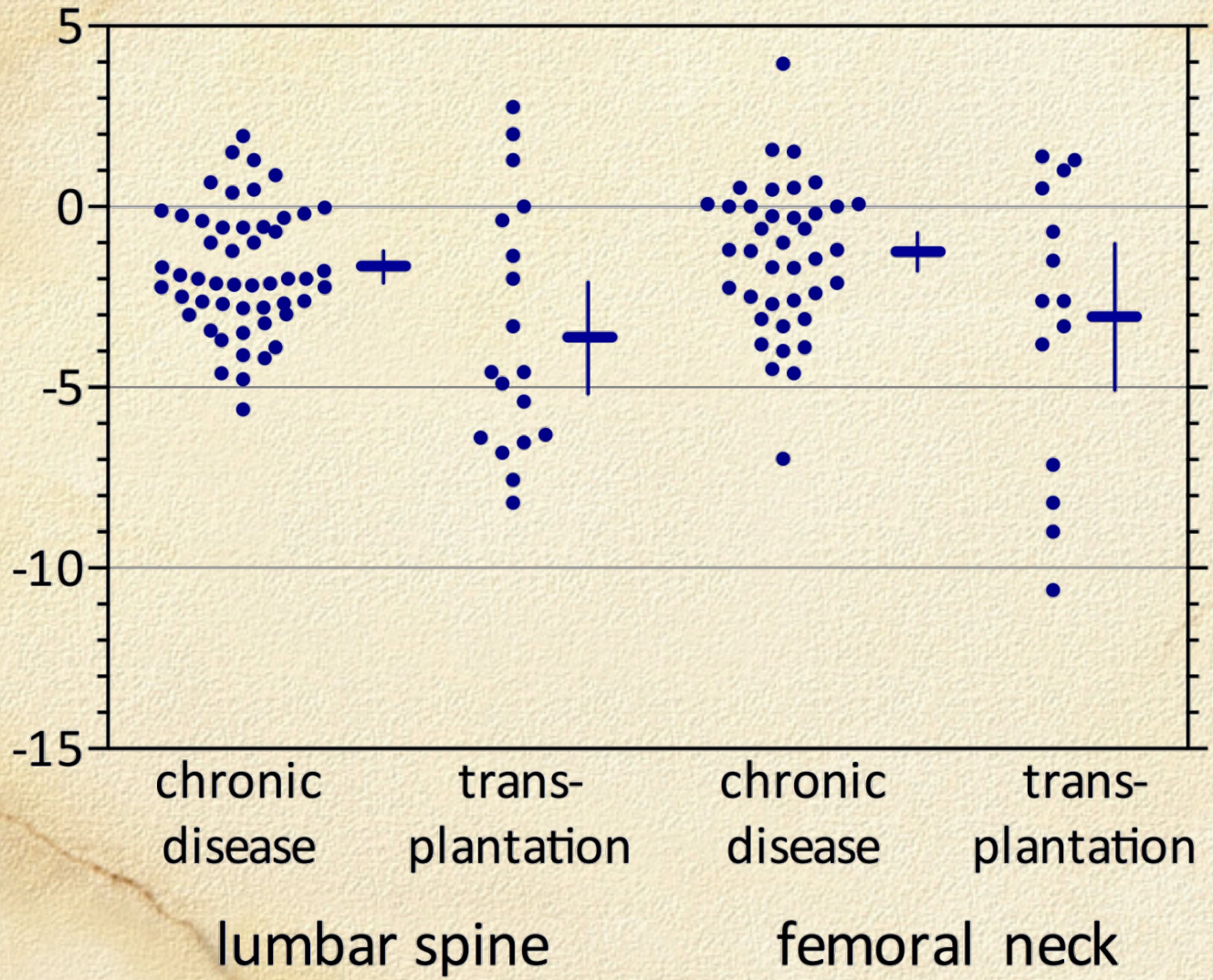
Results: bone loss
% of baseline BMD (95% CI)

	chronic inflammatory disease	transplantation	difference
lumbar spine	**–1,7** (–2,2;–1,3) n= 1565	**–3,6** (–5,1;–2,0) n= 679	**–1,9** (–2,2;–1,3)
femoral neck	**–1,3** (–1,9;–0,9) n= 1255	**–3,1** (–5,1;–1,1) n= 551	**–1,8** (–3,1;–0,1)

random effects model due to high heterogeneity

bone loss

% of baseline BMD (mean$_w$, 95% CI)



VS

REGULAR OR (COBRA) LIGHT

Interventions; COBRA (conventional) versus COBRA-light (Amsterdam)

- COBRA

Week 1:	Pred 60	MTX 7.5	SSZ 500
Week 2:	Pred 40	MTX 7.5	SSZ 1000
Week 3:	Pred 30	MTX 7.5	SSZ 1500
Week 4:	Pred 20	MTX 7.5	SSZ 2000
Week 5:	Pred 15	MTX 7.5	SSZ 2000
Week 6:	Pred 10	MTX 7.5	SSZ 2000
Va wk 7:	Pred 7,5	MTX 7.5	SSZ 2000

- Decision week 26, 39
- DAS (44) >1,6: active disease, start anti TNF.

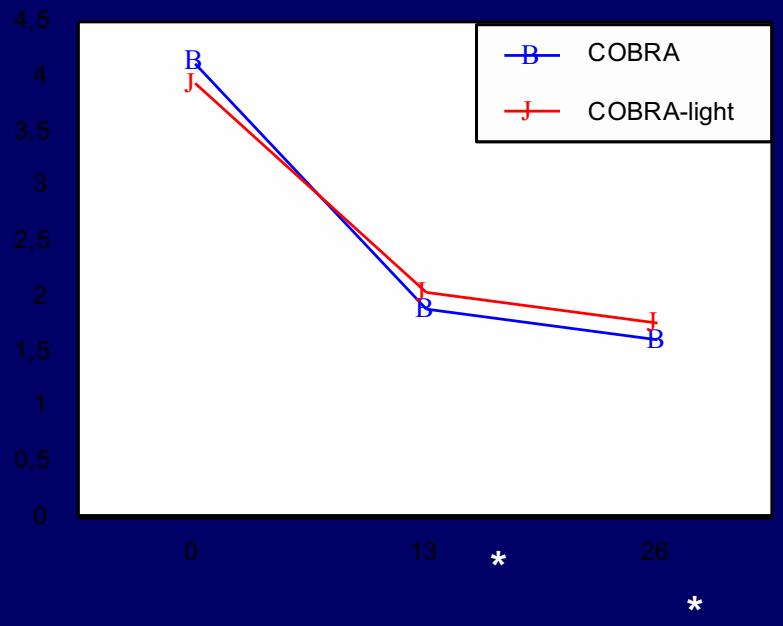
- COBRA-light

Week 1:	Pred 30	MTX 10
Week 2:	Pred 20	MTX 10
Week 3:	Pred 15	MTX 10
Week 4:	Pred 10	MTX 10
Week 5:	Pred 10	MTX 17,5
Week 6:	Pred 10	MTX 17,5
Week 7:	Pred 10	MTX 17,5
Week 8:	Pred 10	MTX 17,5
Va wk 9:	Pred 7,5	MTX 25

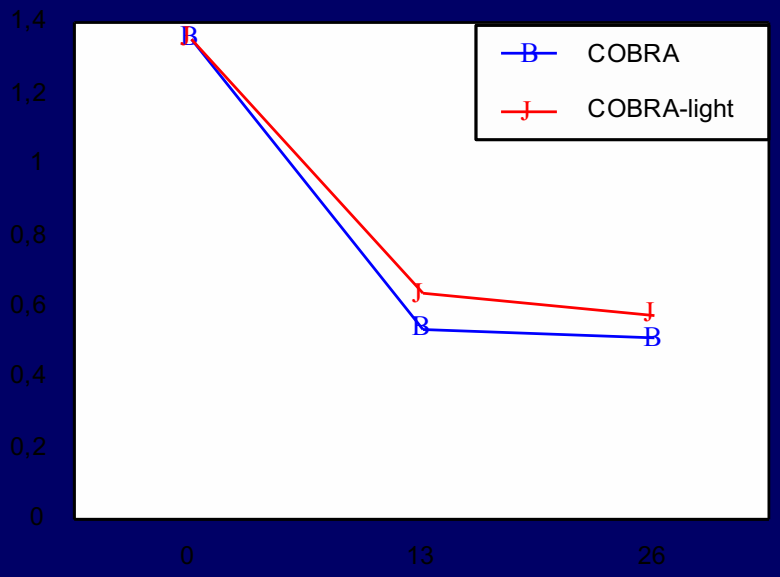
- Decision week 26, 39
- DAS 44 > 1.6: active disease, start anti TNF

Results COBRA-light study

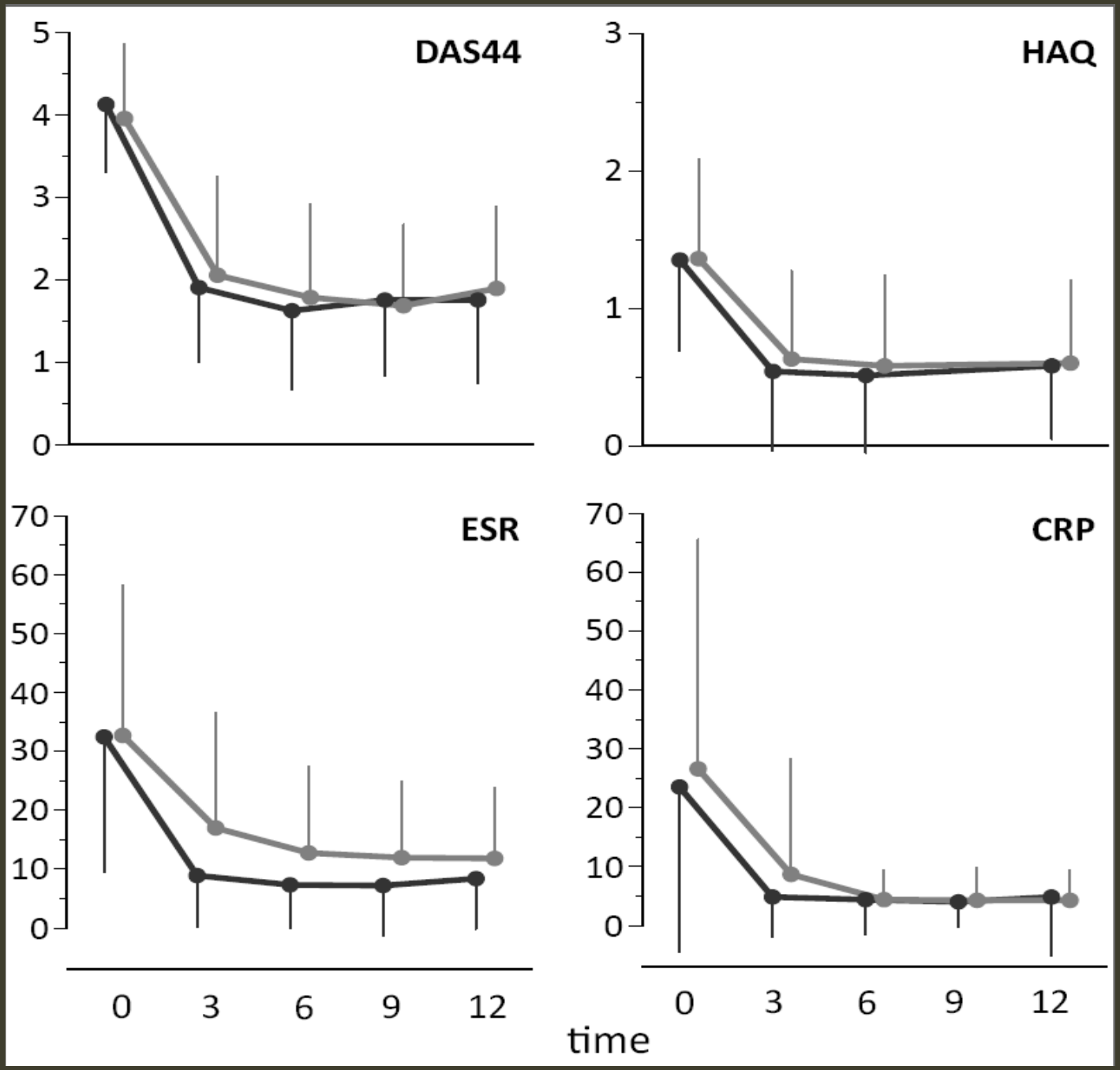
DAS44



HAQ



D Den Uyl et al, Ann Rheum Dis 2012

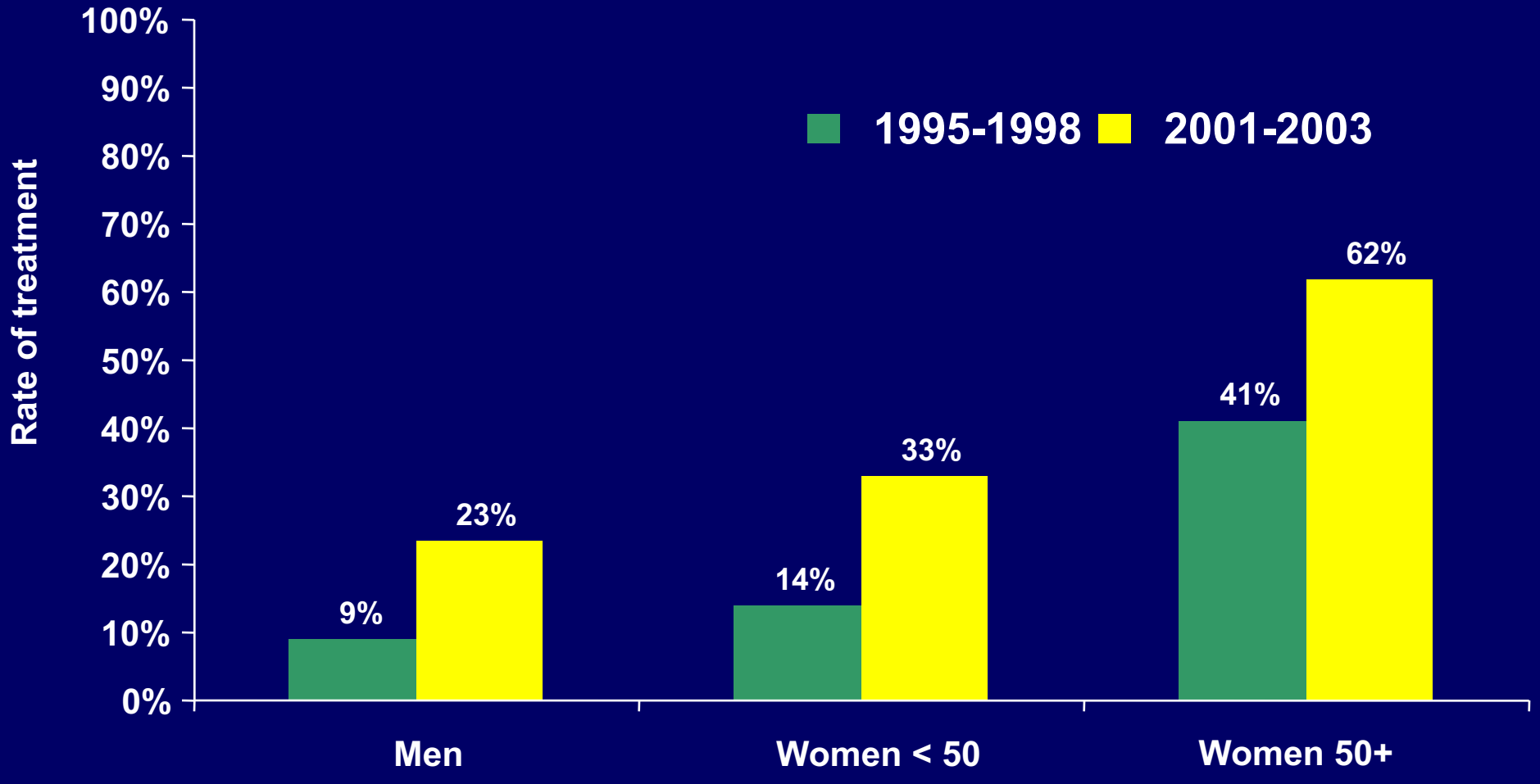


COBRA

COBRA-light

Ter Wee et al, Ann Rheum Dis, 2014

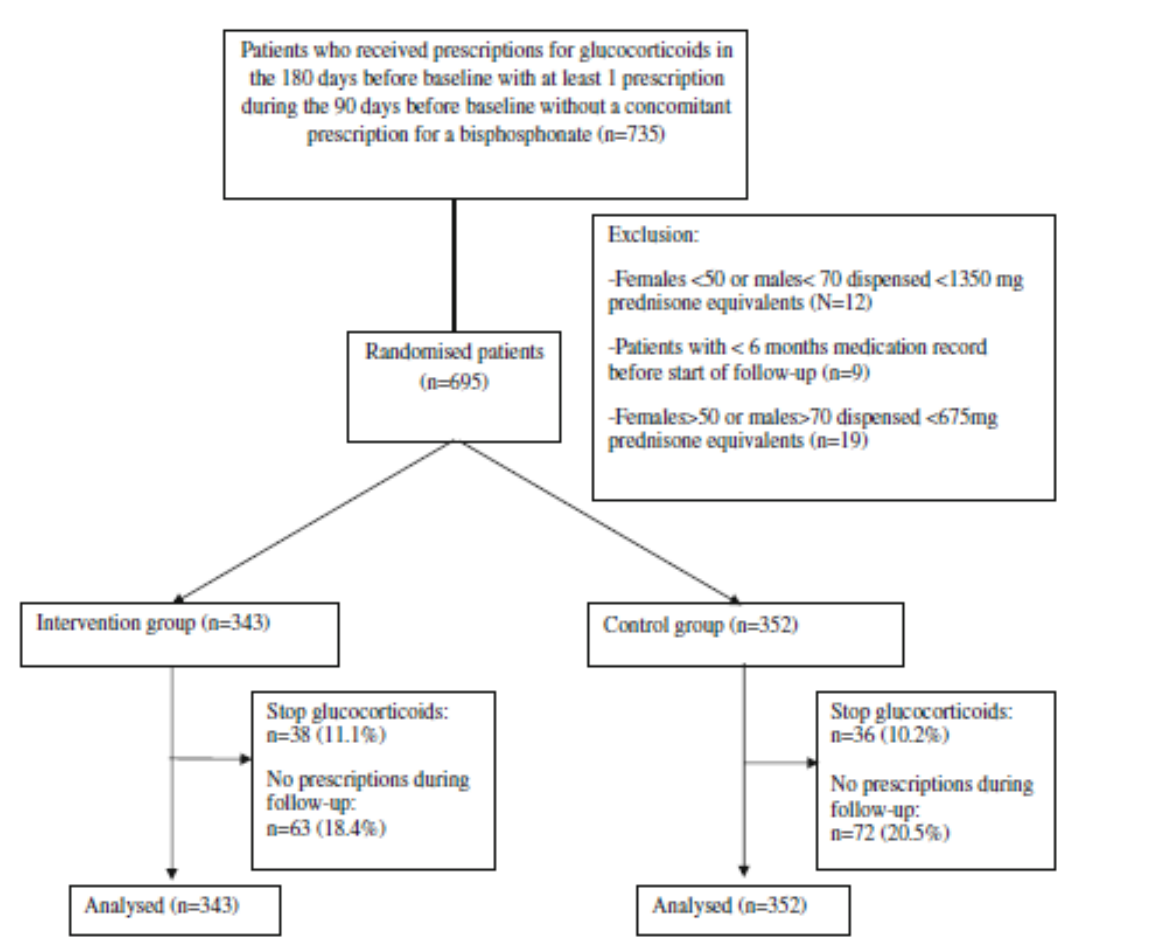
Changing Patterns of anti-osteoporotic treatment in New Glucocorticoid Users (n = 5,471)



Curtis JR. *Arth Rheum* 2005;52:2485

Increase in prophylaxis of glucocorticoid-induced osteoporosis by pharmacist feedback: a randomised controlled trial

C. Klop · F. de Vries · T. Vinks · M. J. Kooij · T. P. van Staa · J. W. J. Bijlsma · A. C. G. Egberts · M. L. Bouvy

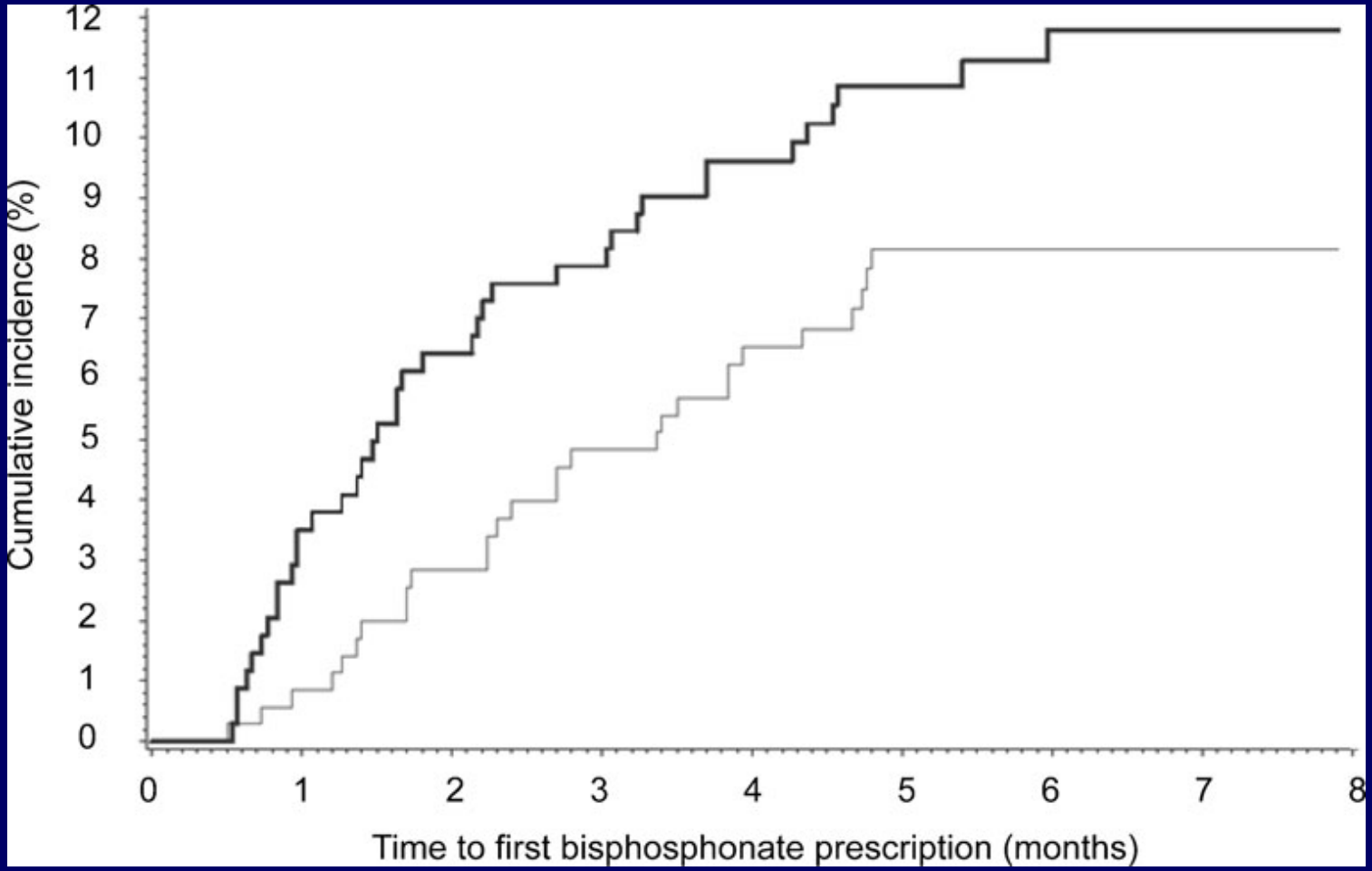


Osteoporos Int

Received: 27 June 2013 / Accepted: 16 October 2013

Increase in prophylaxis of glucocorticoid-induced osteoporosis by pharmacist feedback: a randomised controlled trial

C. Klop · F. de Vries · T. Vinks · M. J. Kooij · T. P. van Staa · J. W. J. Bijlsma · A. C. G. Egberts · M. L. Bouvy



Osteoporos Int

Received: 27 June 2013 / Accepted: 16 October 2013

Guidelines for Management of Glucocorticoid-Induced Osteoporosis.

Table 3. Guidelines for Management of Glucocorticoid-Induced Osteoporosis.*

Variable	American College of Rheumatology[24]	National Osteoporosis Foundation[25]	Royal College of Physicians of London[26]	Belgian Bone Club[27]
Dose and duration of glucocorticoid treatment warranting pharmacologic intervention†	≥7.5 mg/day for at least 3 months, but patients at increased risk require treatment with any dose or duration	≥5 mg/day for at least 3 months	Any oral dose for at least 3 months in patients ≥65 years of age and those with a prior fragility fracture	≥9.3 mg/day for at least 3 months
BMD threshold for treatment if dose and duration qualify	Threshold to be based on the FRAX algorithm in addition to "higher daily and cumulative dose, intravenous usage, and declining BMD"	T score, −2.5, unless patient is at high risk on the basis of a modified FRAX model	T score, −1.5	T score, −1.0 to −1.5
Yearly BMD testing recommended	Yes	Yes	Yes	Yes
Prevalent vertebral fractures as justification for pharmacologic intervention	Yes	Yes	Yes	Yes
Calcium and vitamin D supplementation	1200–1500 mg of calcium per day and 800–1000 units of vitamin D per day for all patients‡	1200 mg of calcium per day and 2000 units of vitamin D per day for all patients‡	Only for patients with low calcium intake (<1 g/day) or vitamin D deficiency (not defined)‡	For all patients
Pharmacologic intervention	Bisphosphonates; teriparatide reserved for patients at highest risk	Bisphosphonates; teriparatide only for patients at high risk	Bisphosphonates as first-line options, followed by teriparatide	Bisphosphonates

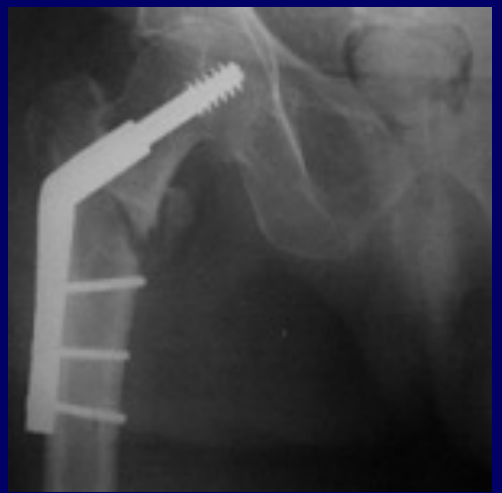
* BMD denotes bone mineral density, and FRAX fracture prevention algorithm.
† Glucocorticoid doses are given in prednisone equivalents.
‡ The recommended calcium intake refers to the total daily intake (diet and supplements).

Weinstein RS. N Engl J Med 2011;365:62-70

The NEW ENGLAND JOURNAL of MEDICINE

Discussion/Limitations (1)

- Data focus on bone mineral density;
- No data on bone quality or fracture incidence;
- BeSt study comparing treatment strategies, no treatments (GC versus placebo)



Discussion/Limitations (2)

- Substantial part of patients protected by calcium, vitamin D and bisphosphonates.
- Different guidelines for prevention of Glucocorticoid Induced Osteoporosis;
- Implementation of VFA for new GIOP-guidelines?

Conclusions

Combination therapy including Glucocorticoids is very effective in RA (and in some other reumatic diseases, such as SLE and vasculitis);

High dose GC can be associated with side effects;

High dose GC are usually prescribed in patients with high disease activity.

Conclusions

Low dose GC are usually well tolerated;

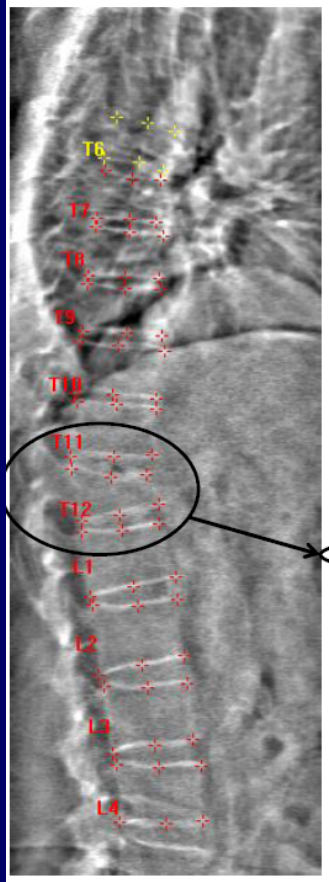
Low dose or shortterm GC use can be very effective in RA.

GC are inexpensive, which is nowadays very important;

MTX and GC first line drugs for early RA, according to EULAR-Guidelines

- Thank you for your attention!

Vertebral Fractures can easily be detected by Lateral Vertebral Assessment (LVA)



Vertebral Assessment

Label	Height (mm) Post	Mid	Ant	Deformity (Grade)	Percent Deformation Wedge	Biconcave	Crush
T6	19.5	19.0	19.1		1.6%	2.2%	0.0%
T7	22.6	18.7	19.8		12.5%	17.3%	0.0%
T8	23.1	20.7	19.4		16.0%	10.5%	0.0%
T9	22.4	20.9	21.9		1.9%	6.5%	0.0%
T10	24.3	22.7	22.9		5.7%	6.7%	0.0%
T11	25.7	23.9	21.7		15.7%	7.2%	0.0%
T12	25.0	18.1	15.1		39.4%	27.3%	0.0%
L1	30.6	26.6	26.3		14.2%	13.2%	0.0%
L2	32.8	27.5	26.0		20.8%	16.2%	0.0%
L3	31.6	27.0	26.3		16.7%	14.6%	0.0%
L4	26.6	26.4	25.9		2.6%	0.6%	0.0%

Objectives in BeSt study (section osteoporosis)

Is high BMD loss in hands, hip and spine in recent-onset RA associated with inflammation?

Is BMD loss suppressed by antirheumatic treatments in recent-onset RA?

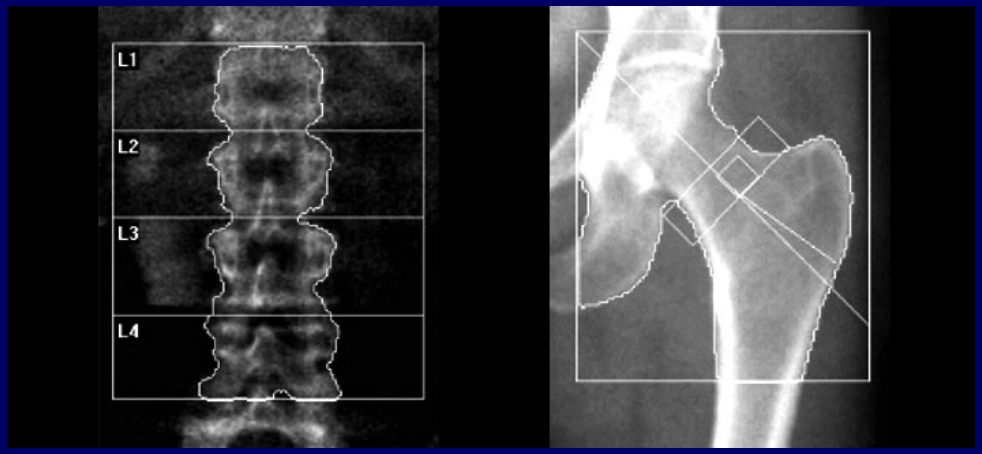
What is the effect of glucocorticoids (GC) on BMD loss?

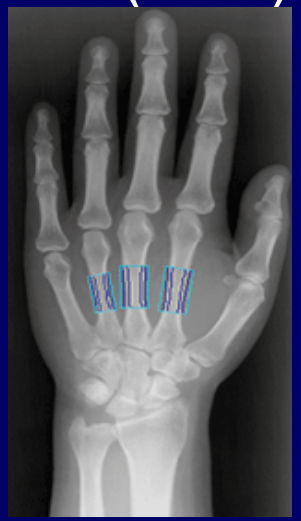
BMD measurements

Dual energy X-ray absorptiometry (DEXA) in total left hip and spine L2-4

Digital X-ray radiogrammetry (DXR) in metacarpals 2-4 in both hands

∆ BMD after 2 years from baseline BMD (in %)





Baseline characteristics (n=218)

Female, %	71
Postmenopausal, %	65
Age, years	54
Symptom duration, weeks	23
DAS (44 joint count)	4.4
Rheumatoid factor pos., %	64
Erosive disease, %	69

Independent riskfactors of high BMD loss in hands, hip and spine: multivariate analyses

	BMD loss in hands		BMD loss in hip		BMD loss in spine	
	β-coëff	p-value	β-coëff	p-value	β-coëff	p-value
Postmenop. status	-3.17	0.000	-	-	-	-
HAQ, t=0	-1.12	0.02	-	-	-	-
CRP, t=0	-0.025	0.000	-	-	-	-
Δ Erosions 0-1	-0.15	0.01	-0.19	0.004	-	-
Bisphosphonates	-	-	2.50	0.01	4.02	0.000

But..

GC use is not a risk factor
for high BMD loss!