Glucocorticoid-Induced Osteoporosis (GIOP)

2025 Update

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XXXII CONGRESO DE LA SOCIEDAD CHILENA DE OSTEOLOGÍA Y METABOLISMO MINERAL - SCHOMM

Disclosures

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  - **NIH: NIAMS, NCATS**
  - **PCORI**
  - **Industry: Amgen, Angitia, Radius**

- **Consultant: Amgen, Angitia, Kyowa, Radius**

GIOP Presentation Outline

- Epidemiology of GIOP
- Treatment and Prevention Studies (focus on new therapeutic opportunities and challenges)
- New Guidelines and GIOP treatment conundrums

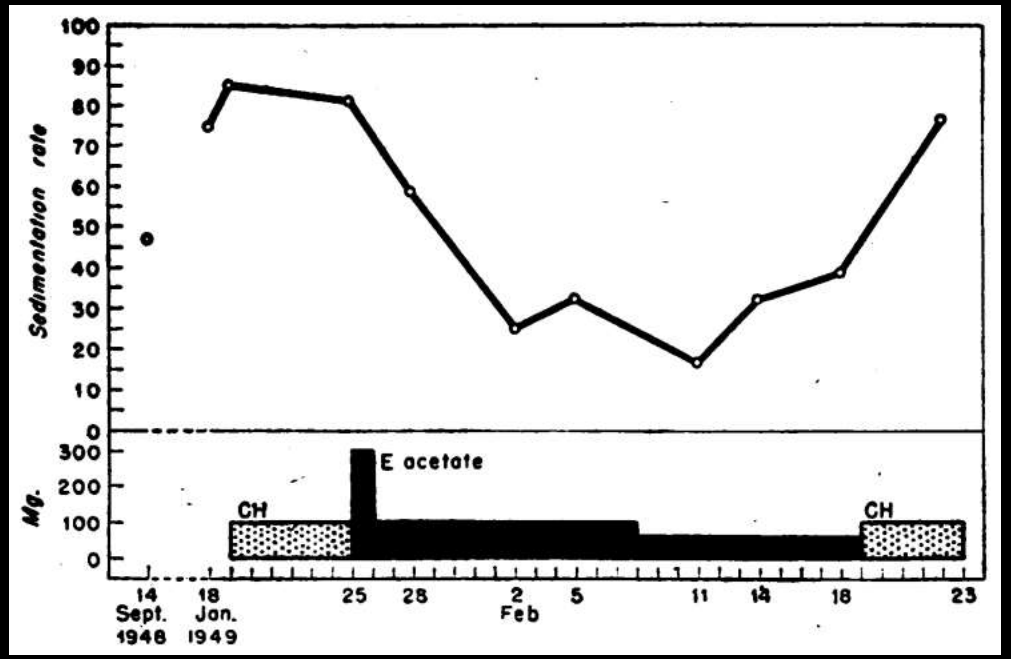
THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX (17-HYDROXY-11-DEHYDROCORTICOSTERONE: COMPOUND E) AND OF PITUITARY ADRENOCORTICOTROPHIC HORMONE ON RHEUMATOID ARTHRITIS*

PRELIMINARY REPORT

BY

PHILIP S. HENCH, EDWARD C. KENDALL, CHARLES H. SLOCUMB, and HOWARD F. POLLEY

From the Mayo Clinic, Rochester, Minnesota, U.S.A.



The Nobel Prize in Physiology or Medicine 1950

Philip S. Hench

Photo from the Nobel Foundation archive.

VERTEBRAL FRACTURES RESULTING FROM PROLONGED CORTISONE AND CORTICOTROPIN THERAPY

Paul H. Curtiss Jr., M.D., William S. Clark, M.D.
and
Charles H. Herndon, M.D., Cleveland

October 2, 1954

JAMA. 1954;156(5):467-469. doi:10.1001/jama.1954.02950050007002

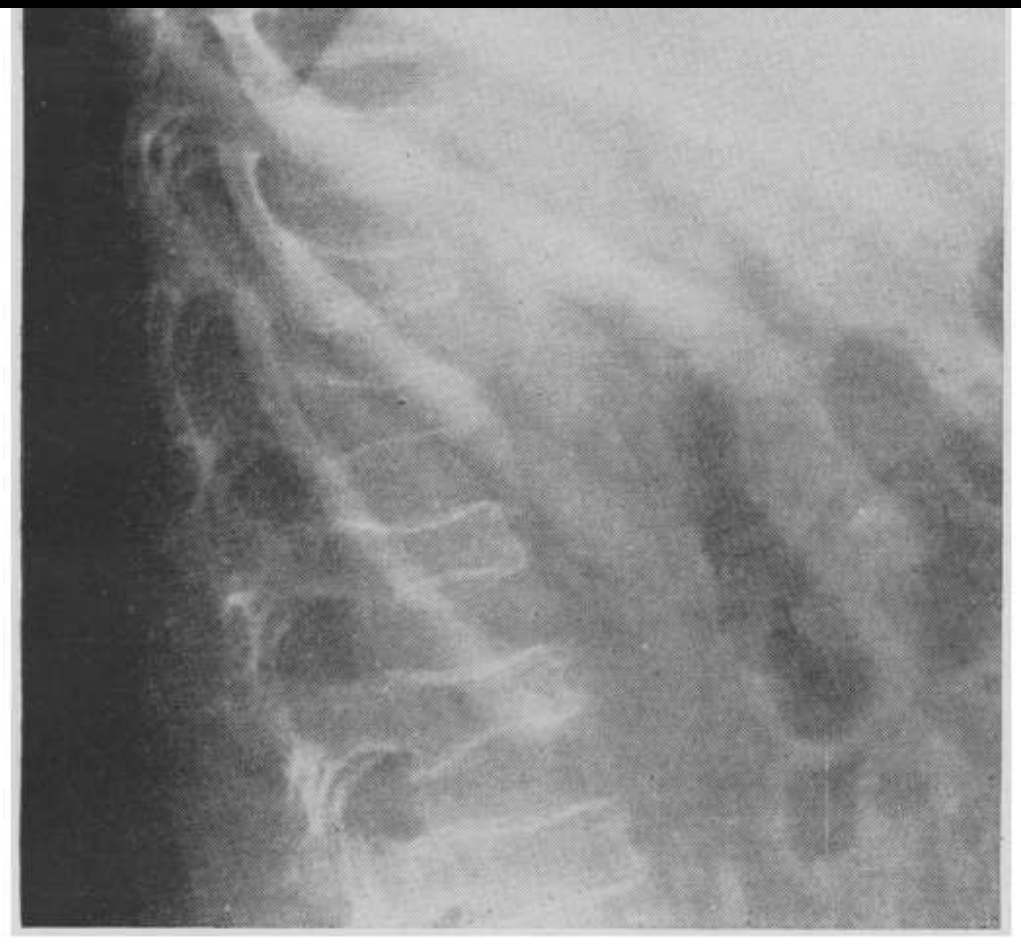


Fig. 3.—Roentgenogram showing lateral view of the dorsolumbar spine of the patient reported on in case 3. Multiple compression lesions of the vertebral bodies with marked osteoporosis are seen.

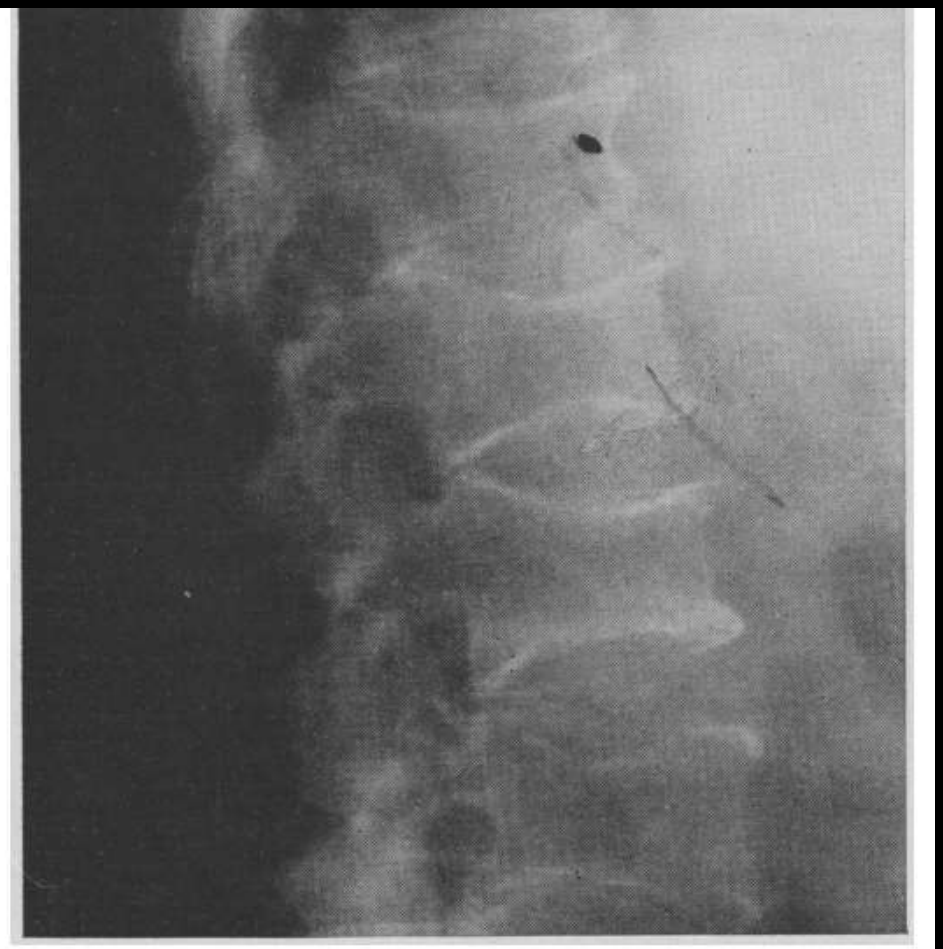


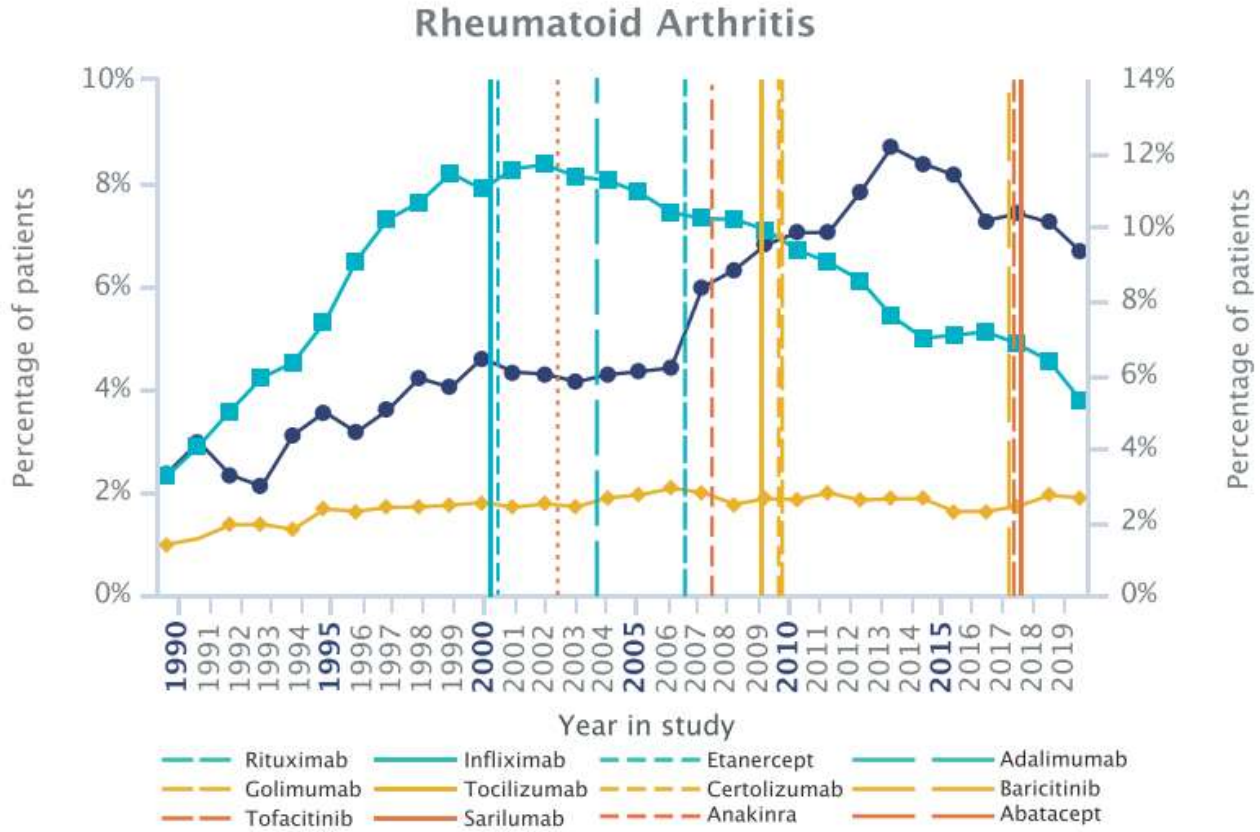
Fig. 1.—Roentgenogram showing lateral view of the patient reported on in case 1. Partial collapse of several vertebrae and marked generalized osteoporosis are seen.

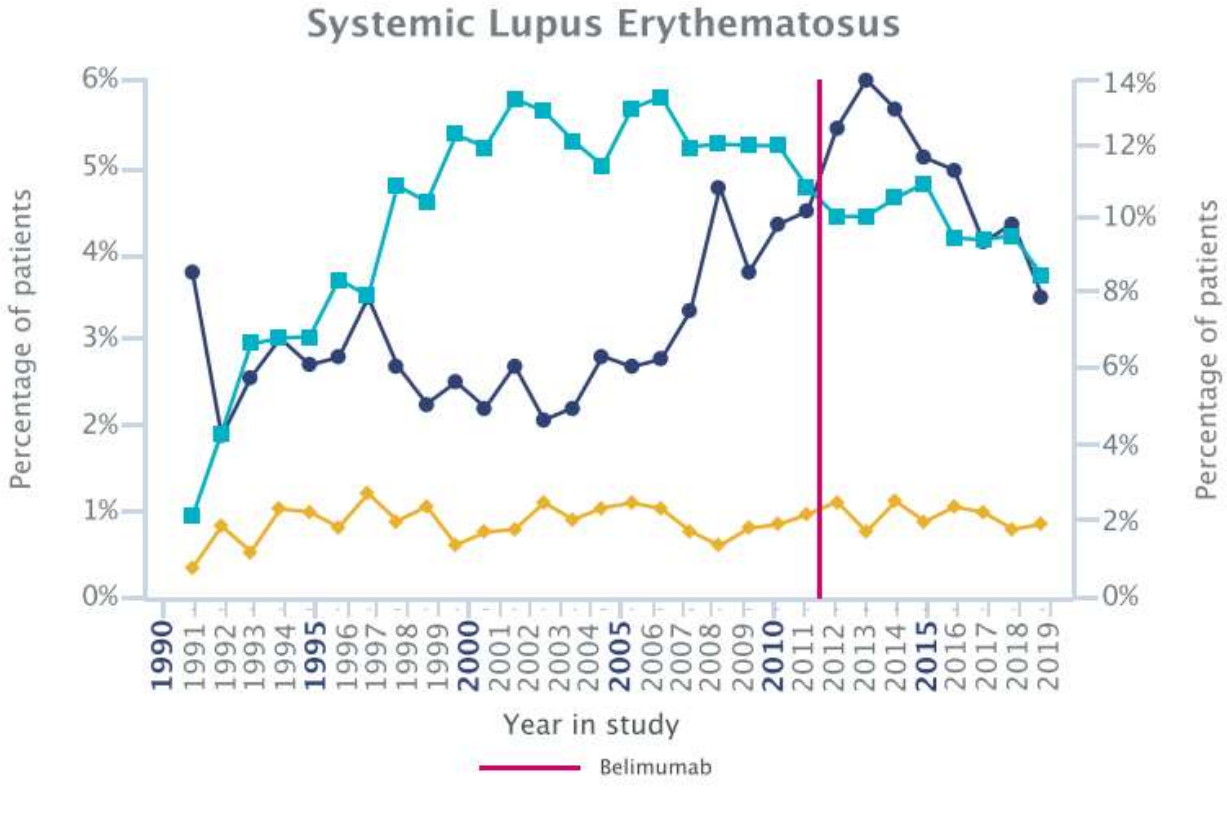
Glucocorticoid Use in the U.K. and U.S.

- Glucocorticoids used chronically by 0.5% of population[1]
- Aetna managed care members beginning long-term (≥3 mo.) steroid therapy (n = 6756)[2]
  - Rheumatoid arthritis (21%)
  - Emphysema (16%)
  - Asthma (15%)
  - Lupus (7%)
  - Inflammatory bowel disease (7%)
  - Polymyalgia rheumatica (5%)

1. Walsh LJ. *Brit Med J* 1996;314:344
2. Mudano A, *J Rheumatol*, 2001;28:1298

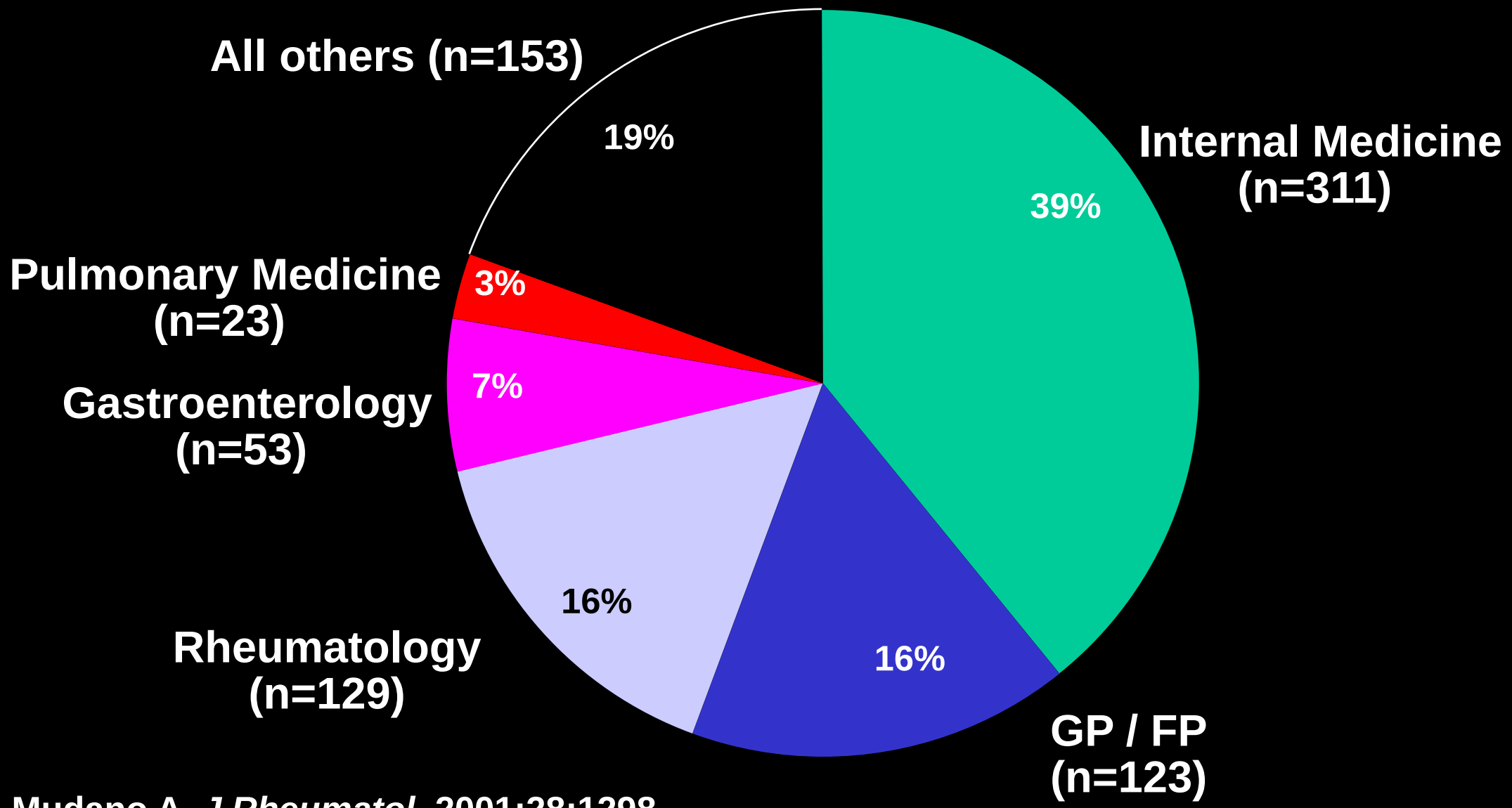
Trends in Systemic Glucocorticoid Utilization in the United Kingdom from 1990 to 2019





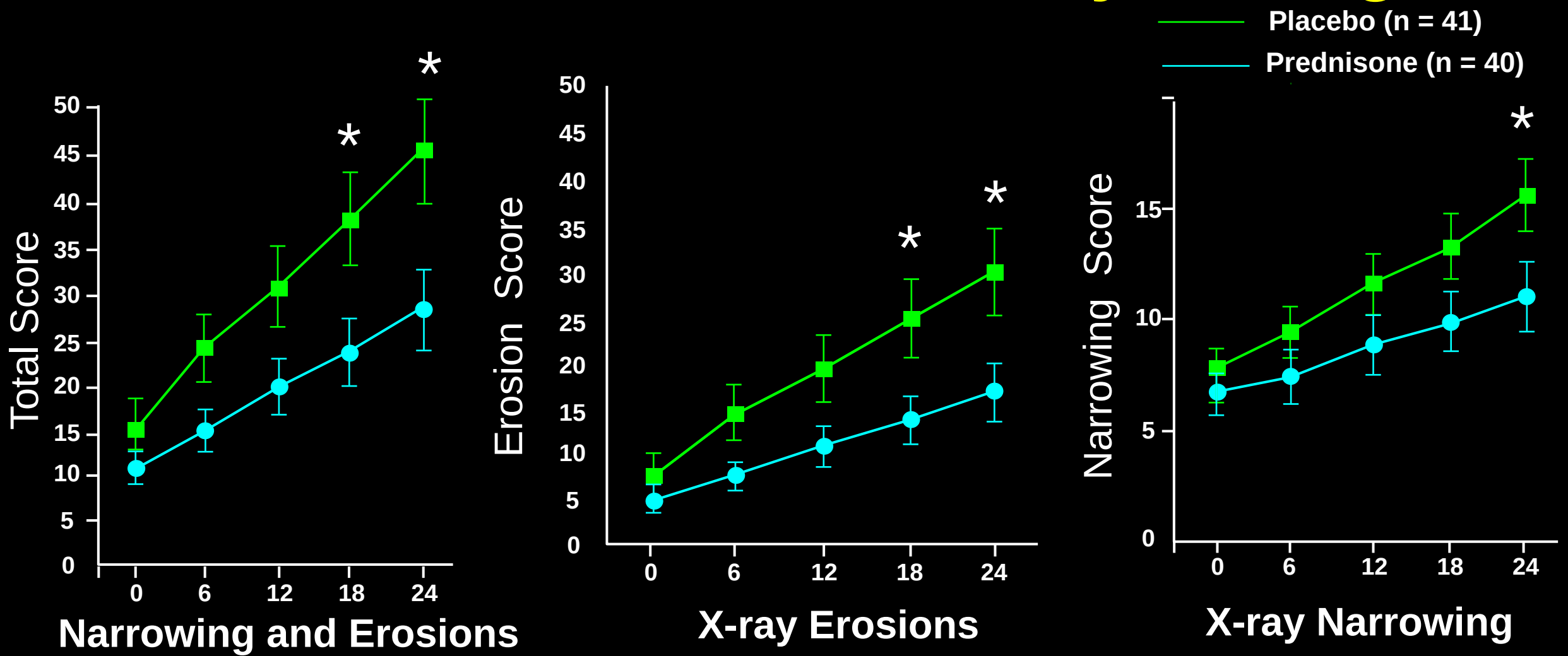
>0 to ≤500 mg (left axis) >500 to ≤1000 mg (right axis) >1000 mg (right axis)

Physicians Prescribing Glucocorticoids *(n=792)*



Mudano A. *J Rheumatol*, 2001;28:1298

Prednisone Monotherapy Attenuates Rheumatoid Arthritis X-ray Damage



van Everdingen *Ann Int Med* 2002;136:1

* P < 0.05


SIDE
EFFECTS

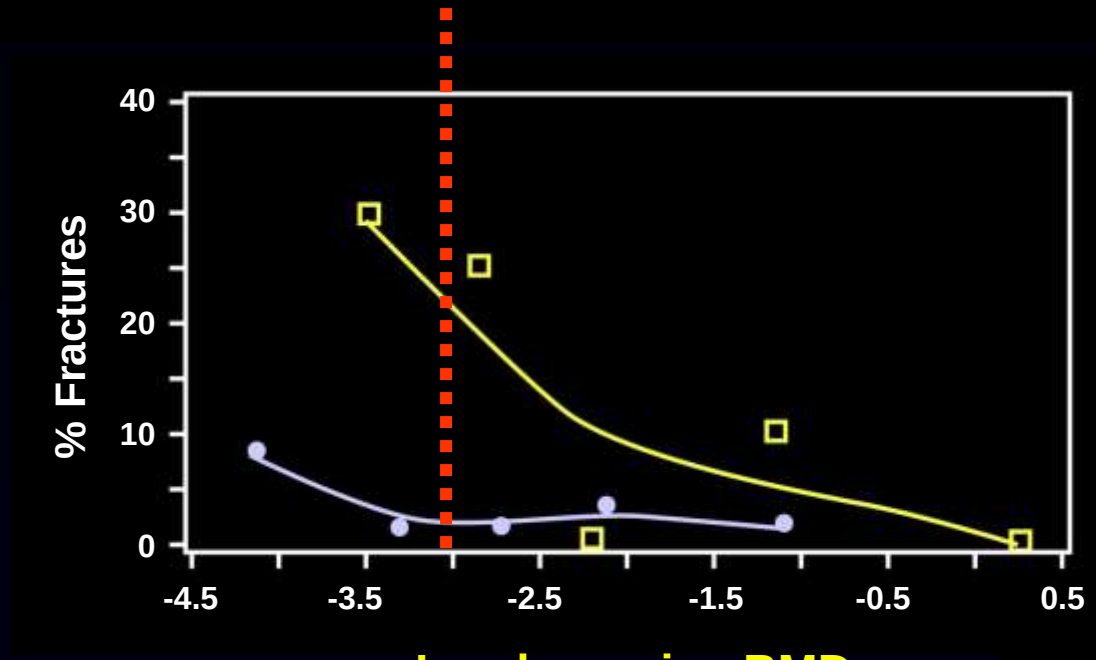
Annual Incidence of Fractures on Glucocorticoids

Meta-regression of Control Arms of GIOP Clinical Trials

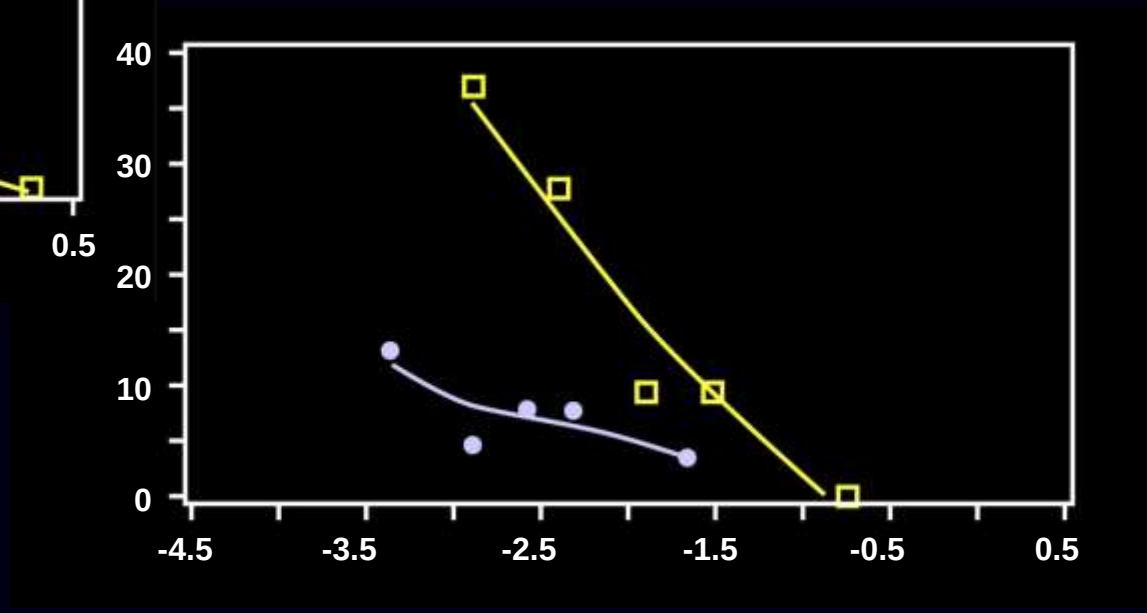
	Vertebral	Non-Vertebral
Glucocorticoid Initiating	5.1 % (95 % CrI = 2.8–8.2)	2.5 % (95 % CrI = 1.2-4.2)
Glucocorticoid Continuing	3.2 % (95 % CrI = 1.8–5.0)	3.0 % (95 % CrI = 0.8–5.9)

Amiche M. *Osteop Int* 2016;27:1709

Glucocorticoids Alter the BMD Fracture Threshold



Lumbar spine BMD

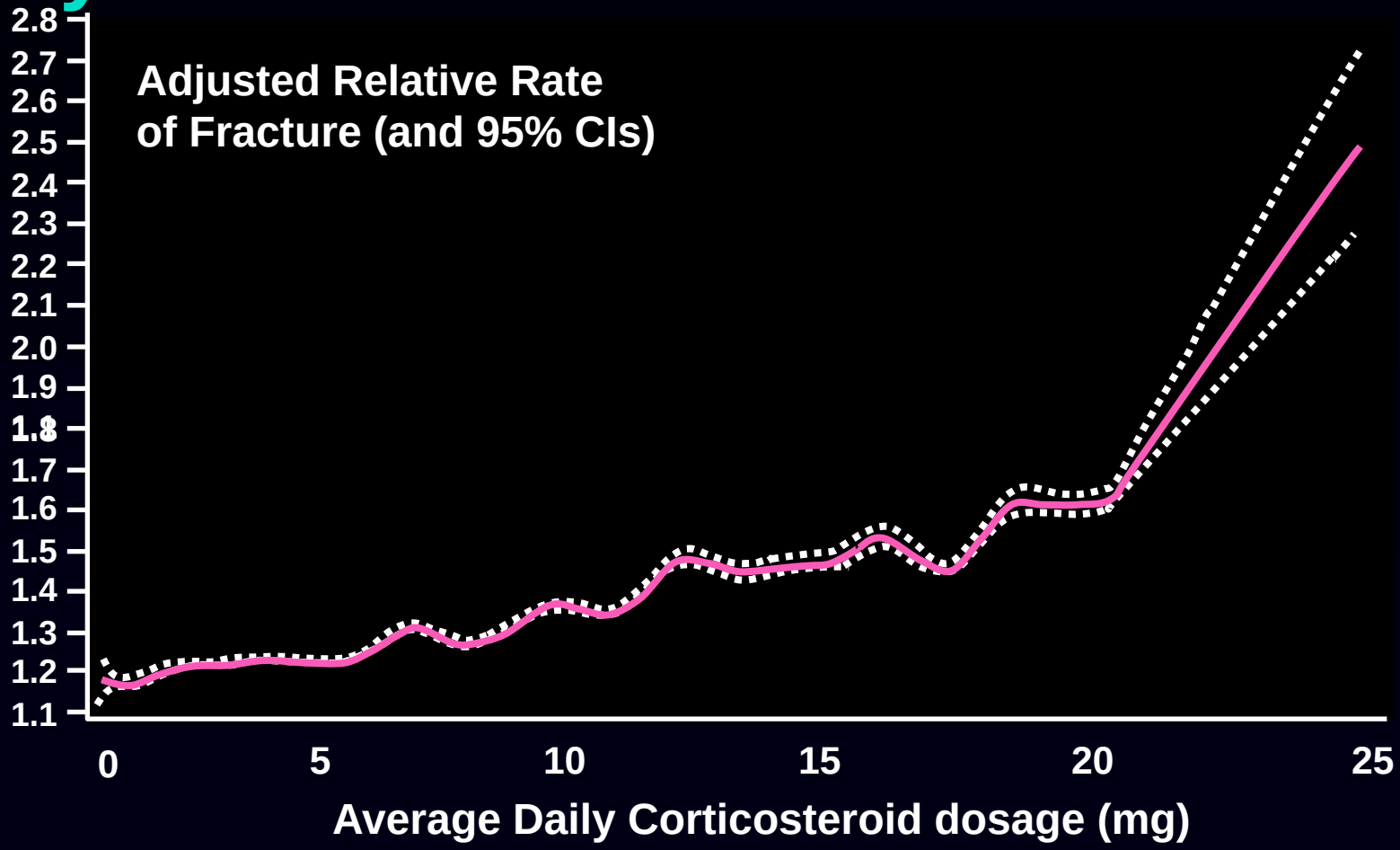


Femoral neck BMD

van Staa T. *Arth Rheum* 2003; 48: 3224

Effect of Daily Glucocorticoid Dose on Non-Vertebral Fractures

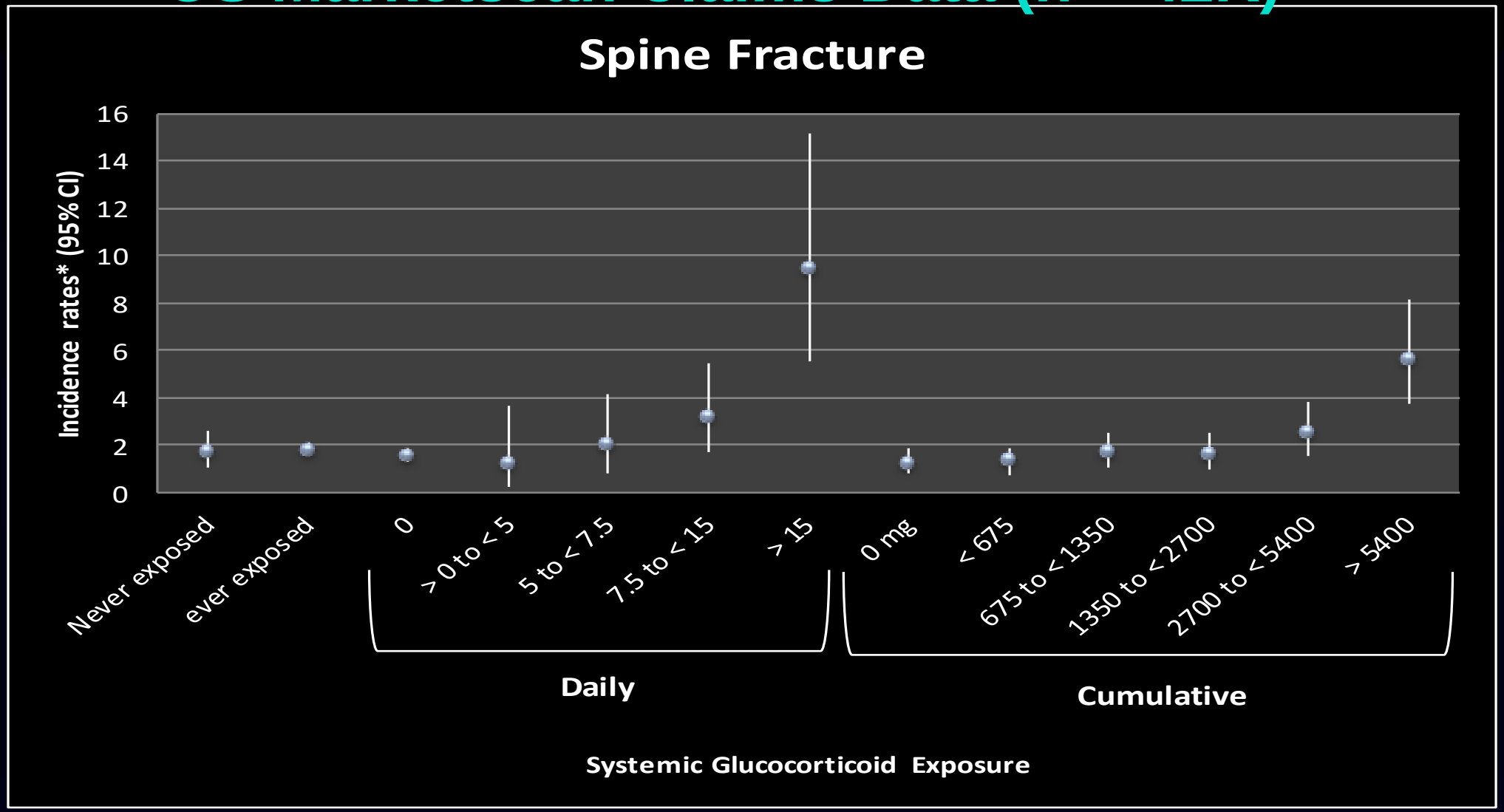
No Fully Safe Dose For Bone but > 20 mg worse!



van Staa T. *Rheumatology* 2000;39:1383

Dose-Response of Glucocorticoid Impact on Fracture Risk Observed among RA Patients

US Marketscan Claims Data (n = 42K)



* Incidence rates per 1000 person years

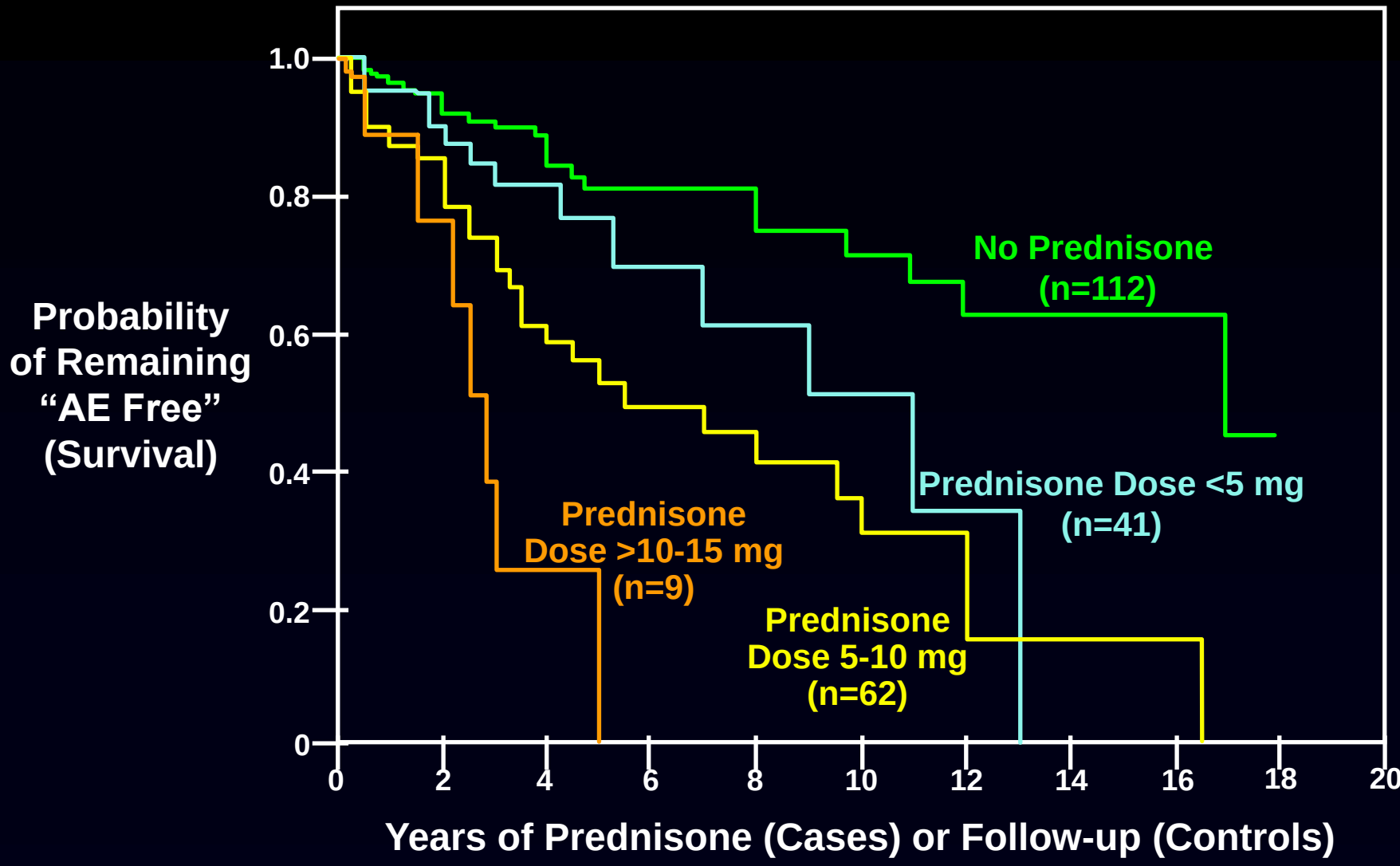
Balasubramanian A. *Osteop Int* 2016;27:3239

Fractures Are the Most Common Serious Glucocorticoid (GC) Adverse Event Among Rheumatoid Arthritis (RA) Patients

Adverse Events (AEs)	GC User (112)	GC Nonuser (112)
Fracture	21 (19%)	8 (7%)
Cataract	17	5
Serious Infection	14	4
GI Bleed or Ulcer	11	4
Diabetic Complication	8	3
Herpes Zoster	8	1
Myocardial Infarction	4	4
Stroke	6	1
Glaucoma	1	1
Death	2	0

Saag K. *Am J Med.* 1994;96:115

Time to the Development of the First Adverse Event (AE)

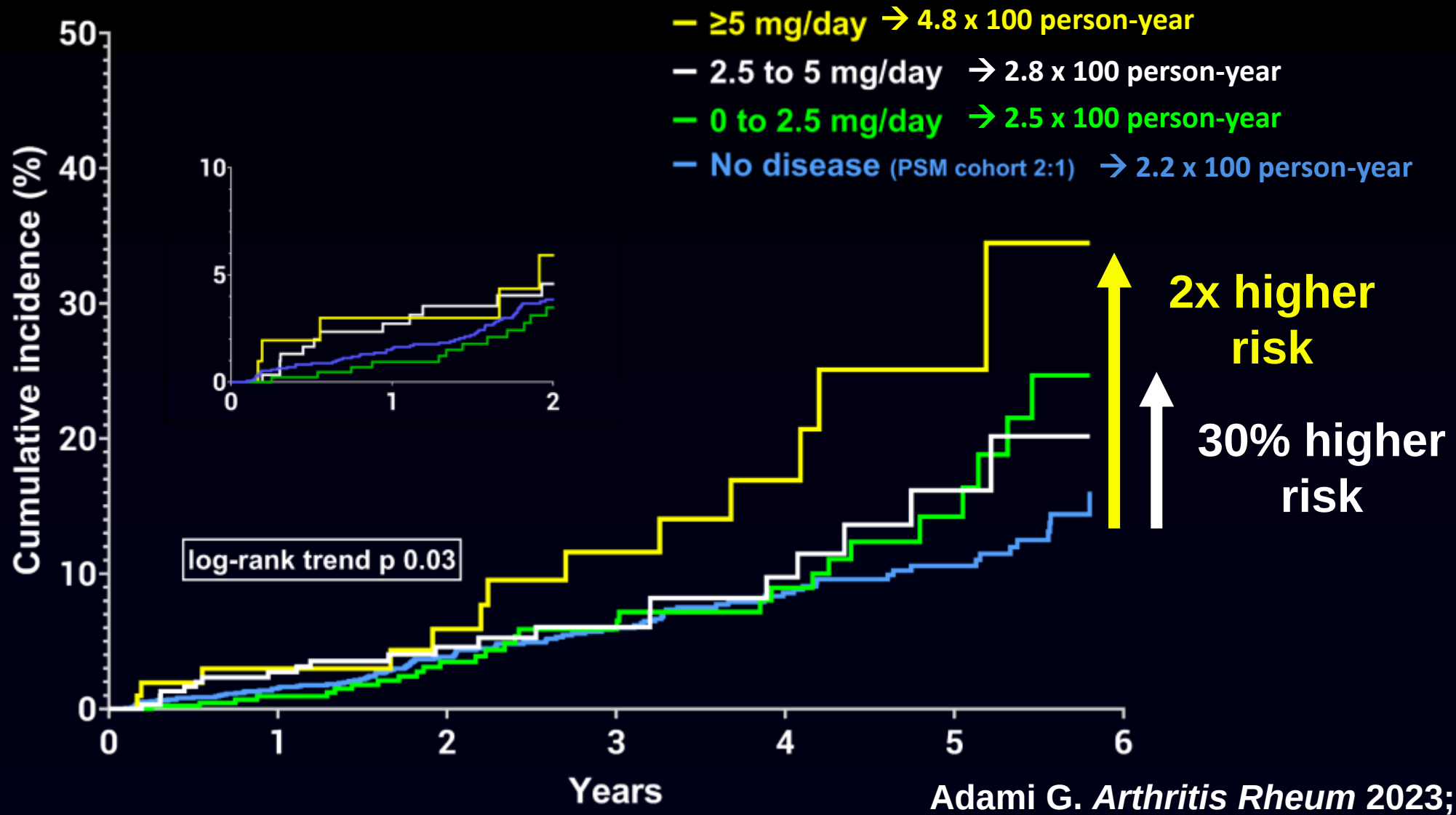


Saag K. *Am J Med* 1994;96:115

Risk Factors for the First AE Among RA Patients

Final Model Variables	Odds Ratio	95% CI	p-value
Average prednisone			
> 10-15 mg/d	32.3	4.6, 220	0.0004
5-10 mg/d	4.5	2.1, 9.6	0.0001
> 0- <5 mg/d	1.9	0.8, 4.7	0.15
Rheumatoid nodules	3.9	1.9, 8.0	0.0001
Bony erosions	2.4	1.2, 4.7	<0.02
Job: farmer/laborer	2.4	1.1, 5.6	<0.04
GI protective drugs	0.6	0.4, 0.9	<0.02

Even Low Dose Glucocorticoids Lead to Fractures (when not on anti-OP Rx)

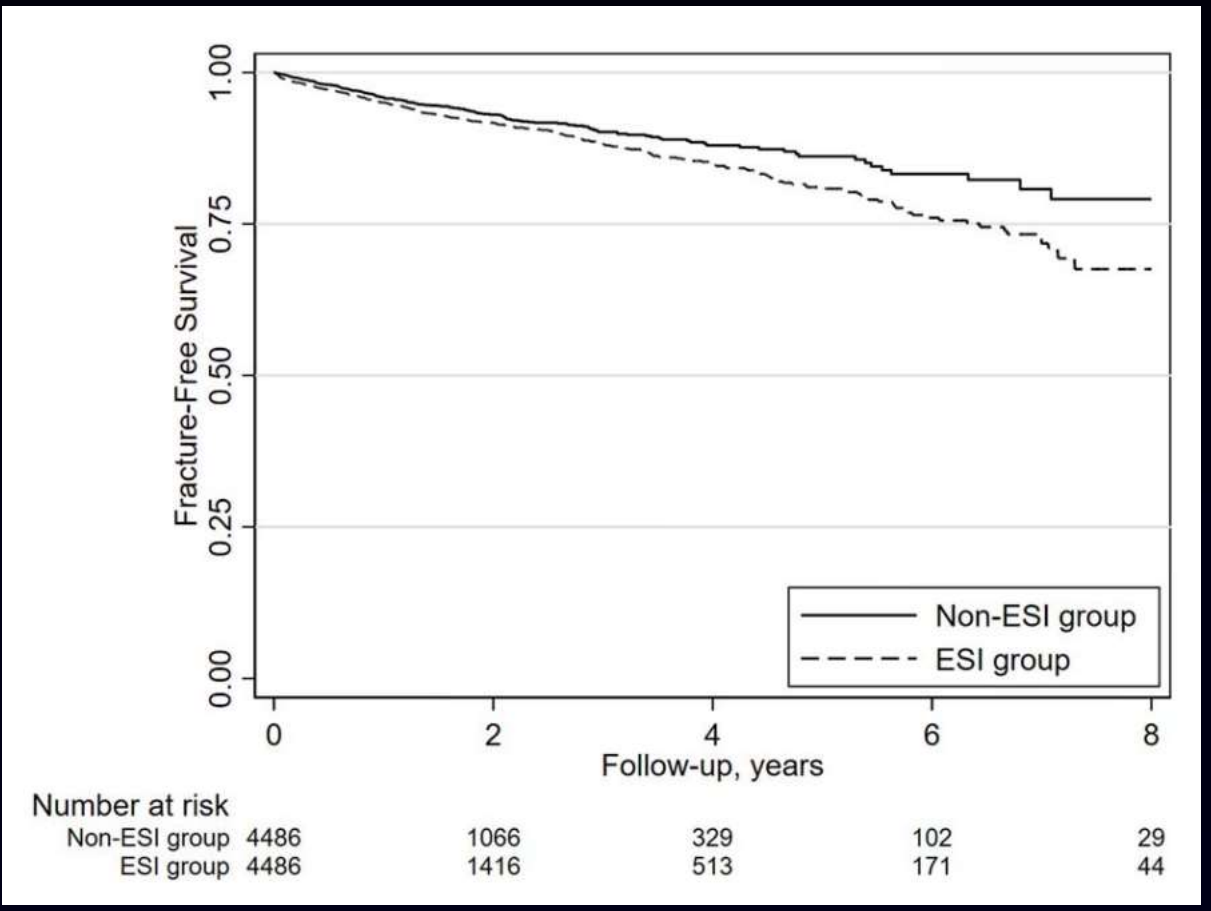


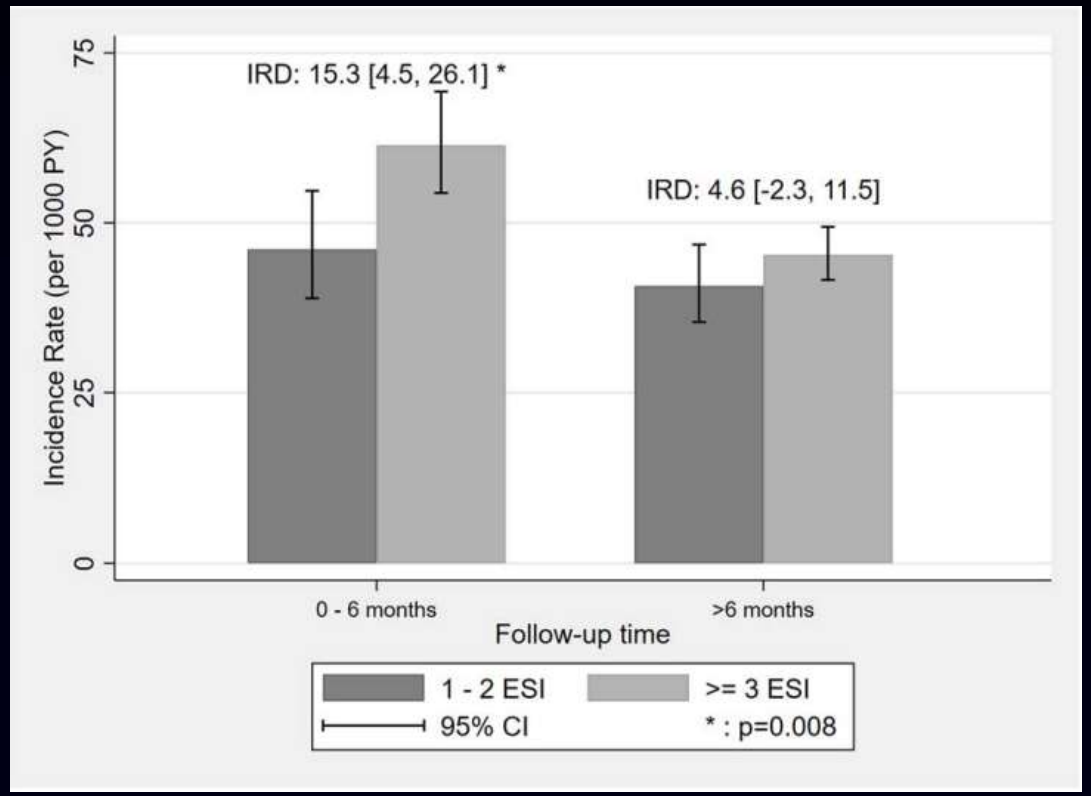
Adami G. *Arthritis Rheum* 2023;75:1762

Journal of Bone and Mineral Research, 2025, **40**, 176–183
https://doi.org/10.1093/jbmr/zjae162
Advance access publication: September 30, 2024
Research Article

Epidural steroid injections and fracture incidence among older individuals with radiculopathy

Huifeng Yun[1], Ye Liu[2], Jeffrey R. Curtis[2], Kenneth Saag[2], Giavanna D'Erasmo[3], Katherine Haseltine[3], Emily M. Stein[3,*]

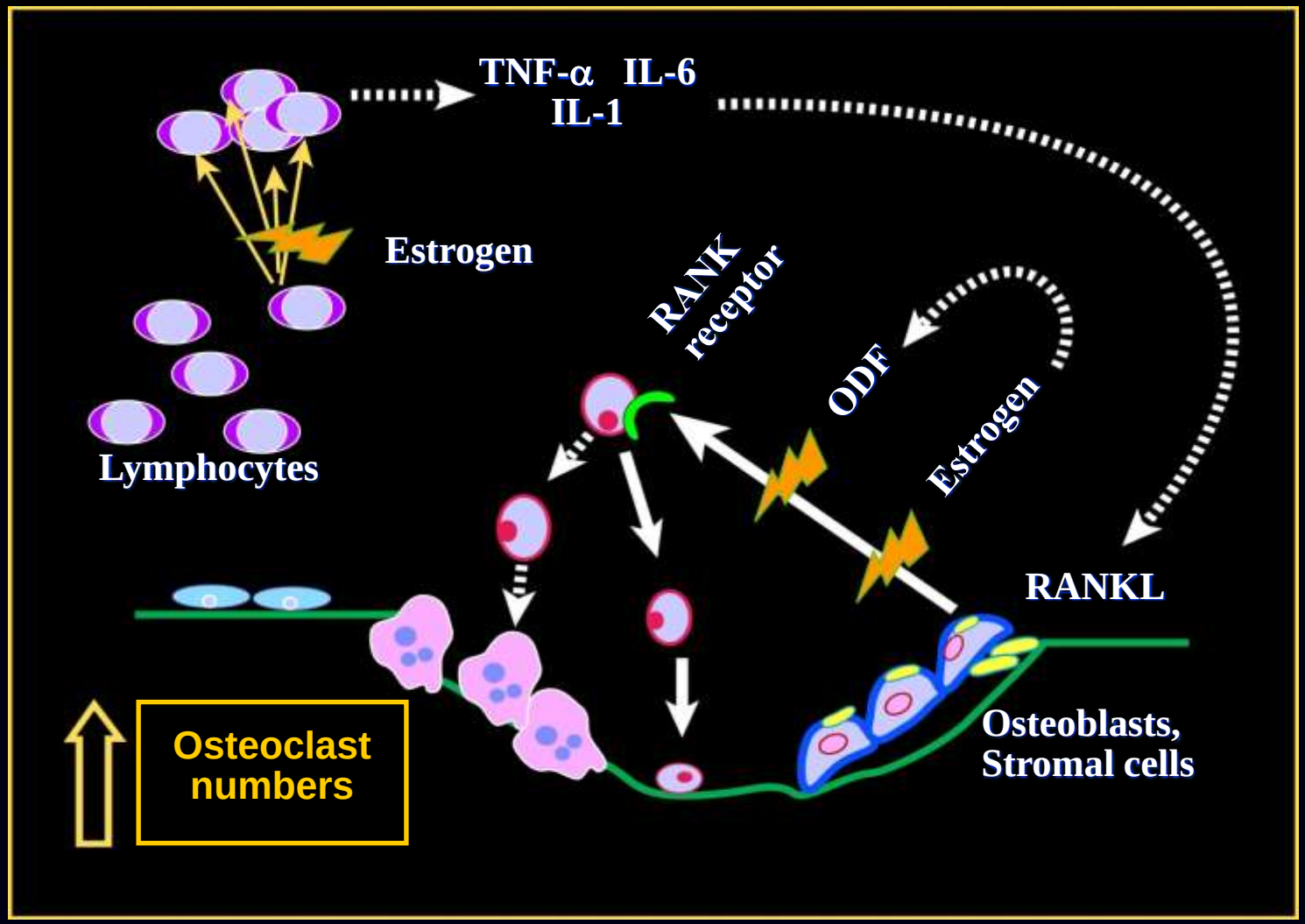




Osteoporosis and Rheumatoid Arthritis
Is it Steroids or RA ?

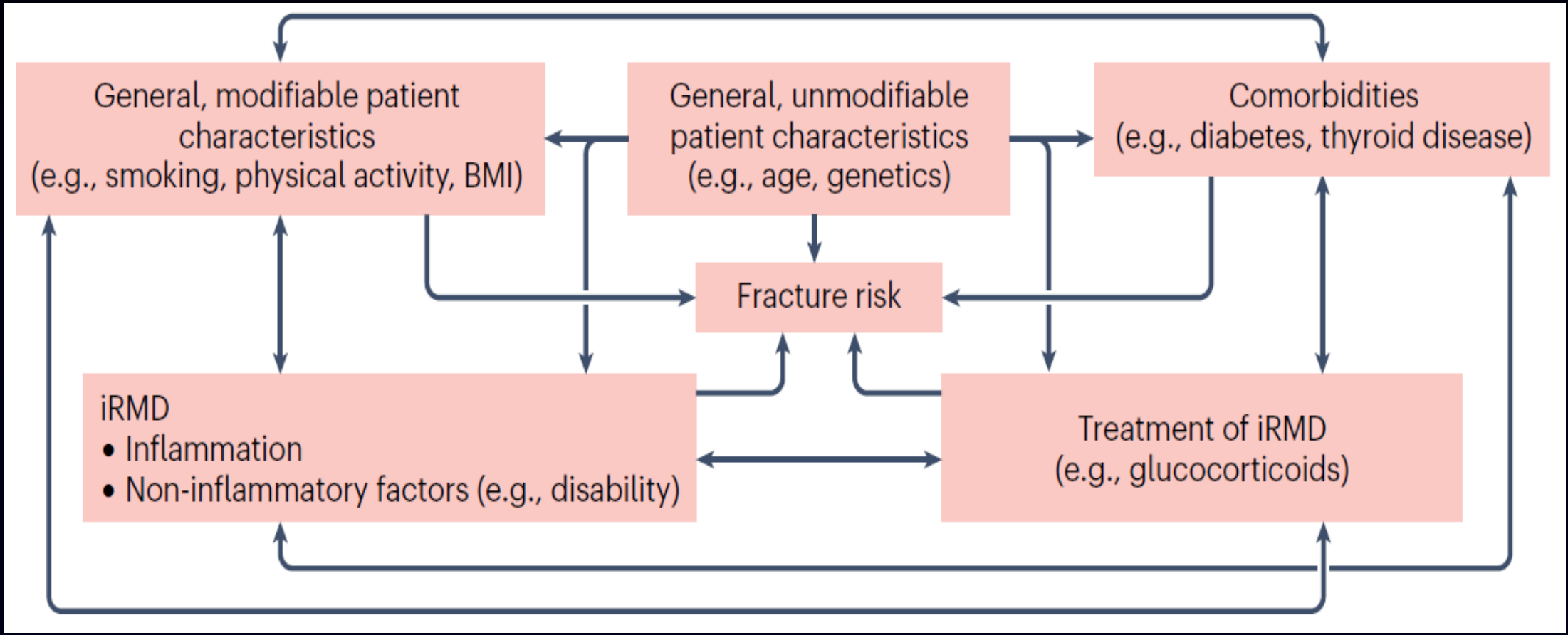
- **RA, NOT steroids, causes bone loss**

Verhoven A. *J Rheum* 1997;24:1495



Gravellese EM. *Arthritis Res* 2001;3:6
Madsen OR. *Ann Rheum Dis* 2002;61:325

Osteoporosis and Fracture Risk Multifactorial in Inflammatory Rheumatic Diseases



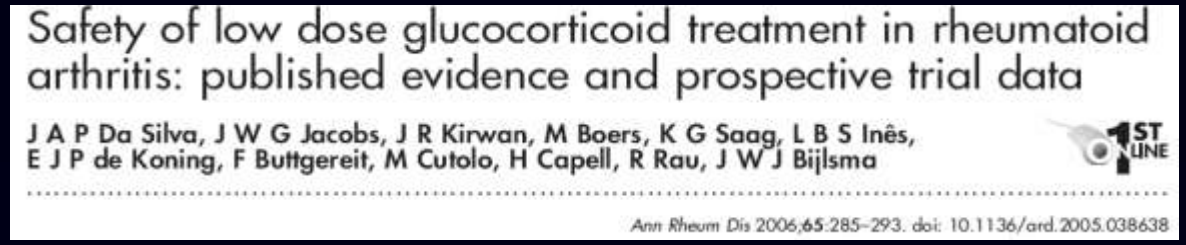
Buttgereit F. *Nat Rev Rheum* 2024;20:417

Safety of Low-Dose Glucocorticoids in Rheumatoid Arthritis

- Adverse effects widely reported, yet….

Problems with observational studies of steroids:

- Confounding by indication (susceptibility bias)
- Diagnostic detection bias
- Extrapolation across doses
- Effects of RA disease activity


Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data

J A P Da Silva, J W G Jacobs, J R Kirwan, M Boers, K G Saag, L B S Inês, E J P de Koning, F Buttgereit, M Cutolo, H Capell, R Rau, J W J Bijlsma

Ann Rheum Dis 2006;65:285–293. doi: 10.1136/ard.2005.038638

A Well Designed Randomized Trial Seems to be Needed!

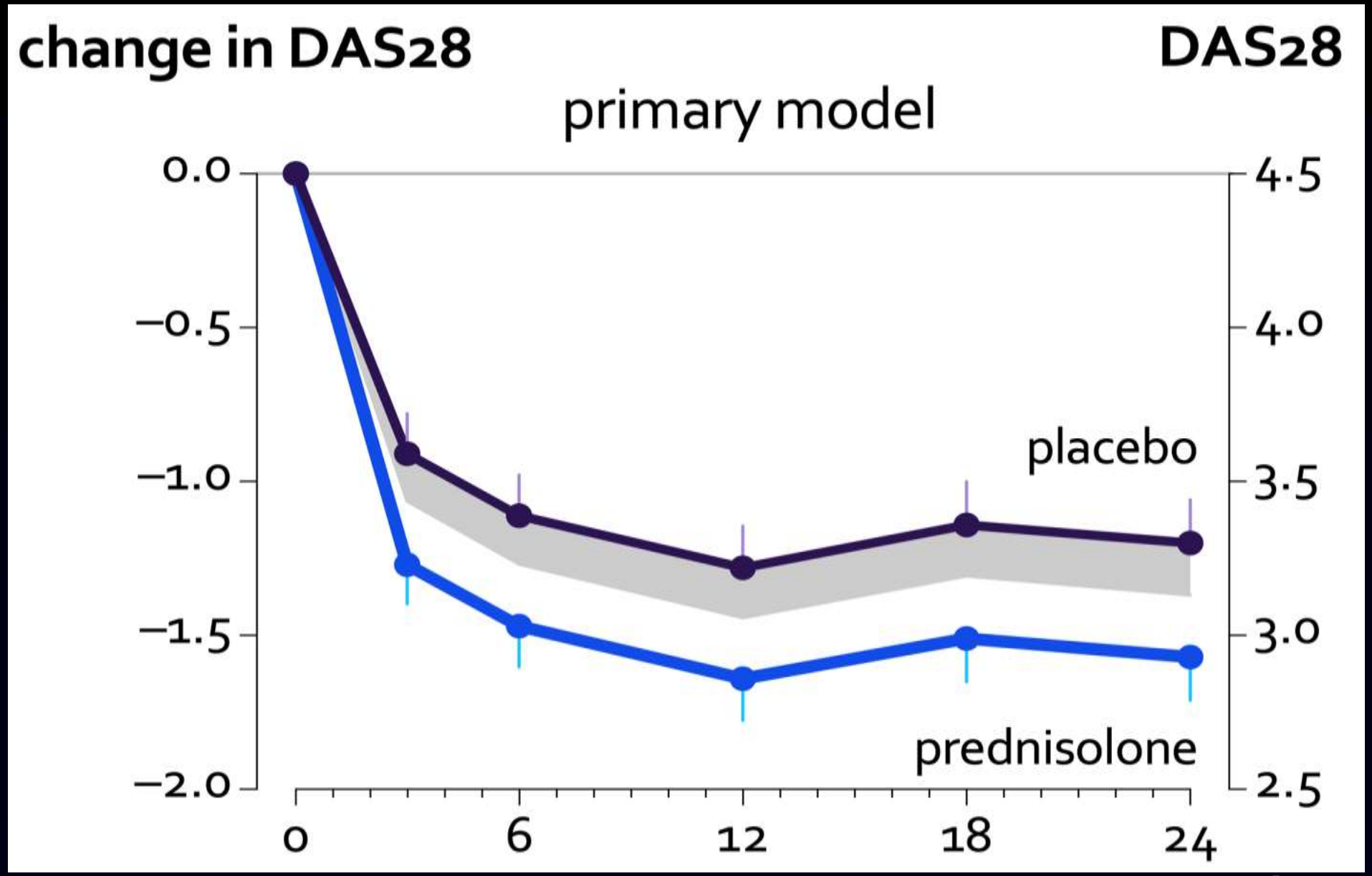
CLINICAL SCIENCE

Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial

Maarten Boers ,[1,2] Linda Hartman ,[1,2] Daniela Opris-Belinski,[3] Reinhard Bos,[4] Marc R Kok ,[5] Jose AP Da Silva ,[6] Eduard N Griep,[7] Ruth Klaasen,[8] Cornelia F Allaart,[9] Paul Baudoin,[10] Hennie G Raterman,[11] Zoltan Szekanecz ,[12] Frank Buttgereit ,[13] Pavol Masaryk,[14] L Thomas Klausch,[1] Sabrina Paolino,[15] Annemarie M Schilder,[4] Willem F Lems ,[2] Maurizio Cutolo ,[15] For the GLORIA Trial consortium

Boers M. ***Ann Rheum Dis*** **2022;81:925**

GLORIA Trail- Benefit



-0.37 points

Boers M. *Ann Rheum Dis* 2022;81:925

GLORIA- Bone Health Outcomes

	Prednisolone		Placebo			
	baseline	change	baseline	change	diff	p
Bone mass, n	220	142	221	135		
T-score, lumbar spine	-0.48	-0.07	-0.71	0.19	0.27	<0.0001
T-score, total hip	-1.14	-0.04	-1.09	-0.01	-0.04	0.40
Fractures, n	211	120	220	124	RR	
Spine fx, n (%)	68 (32)	23 (19)	78 (36)	19 (15)	1.28	0.14
	SAE	AESI	SAE	AESI		
Symptomatic, total	2	11	4	6		
vertebral	0	4	2	2		
pelvis	2	1	0	0		
hip	0	0	1	0		
foot	0	4	0	1		
arm/hand	0	2	0	3		
multiple limb	0	0	1	0		

Boers M. *Ann Rheum Dis* 2022;81:925

GIOP Pathophysiology

Glucocorticoid Therapy

↑ PPARγ2
↑ Sclerostin
↓ Wnt signaling
↓ BMPs

Activation of pro-apoptotic molecules

Osteoblasts

Decreased osteoblastogenesis
Decreased osteoblast number

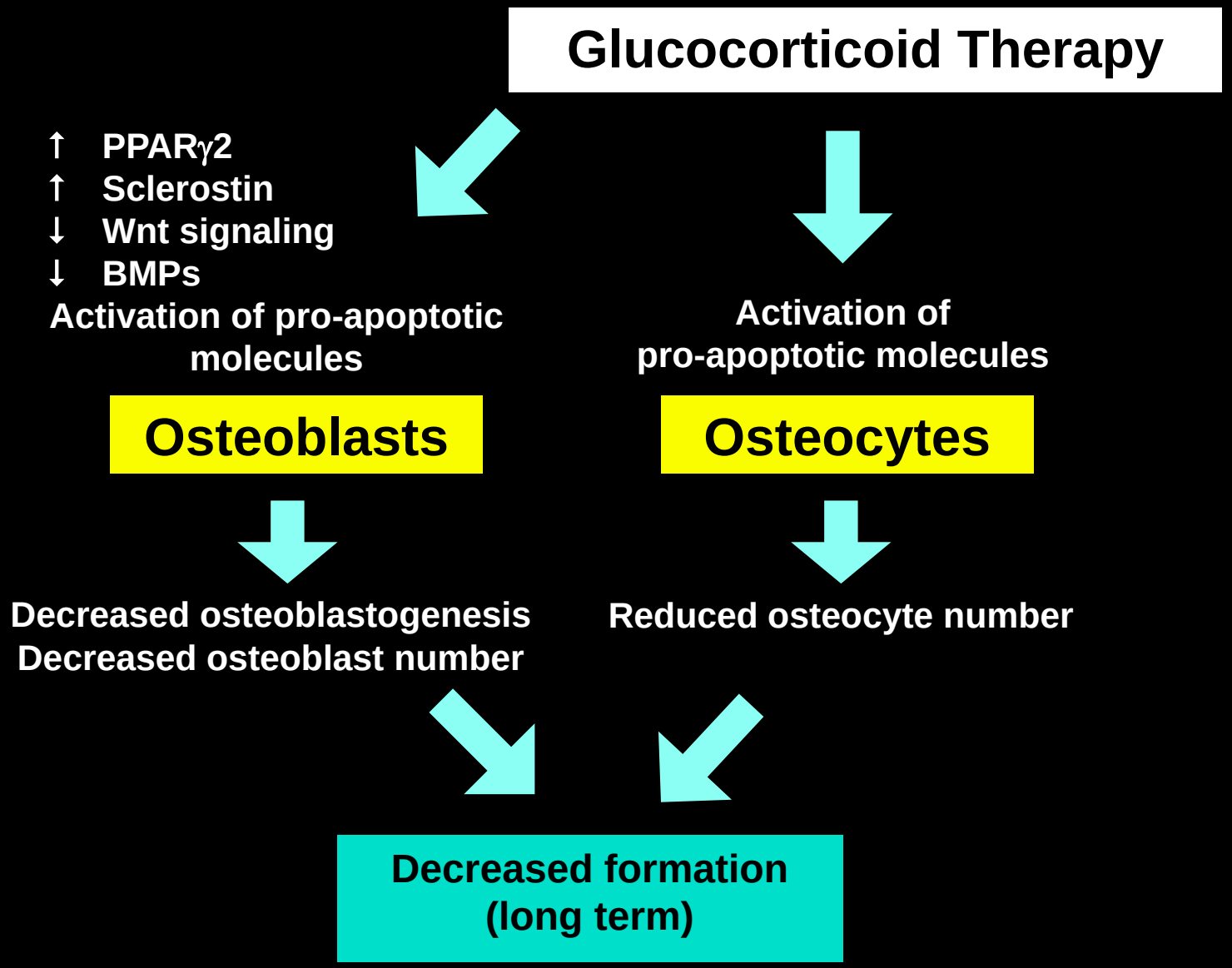
Activation of pro-apoptotic molecules

Osteocytes

Reduced osteocyte number

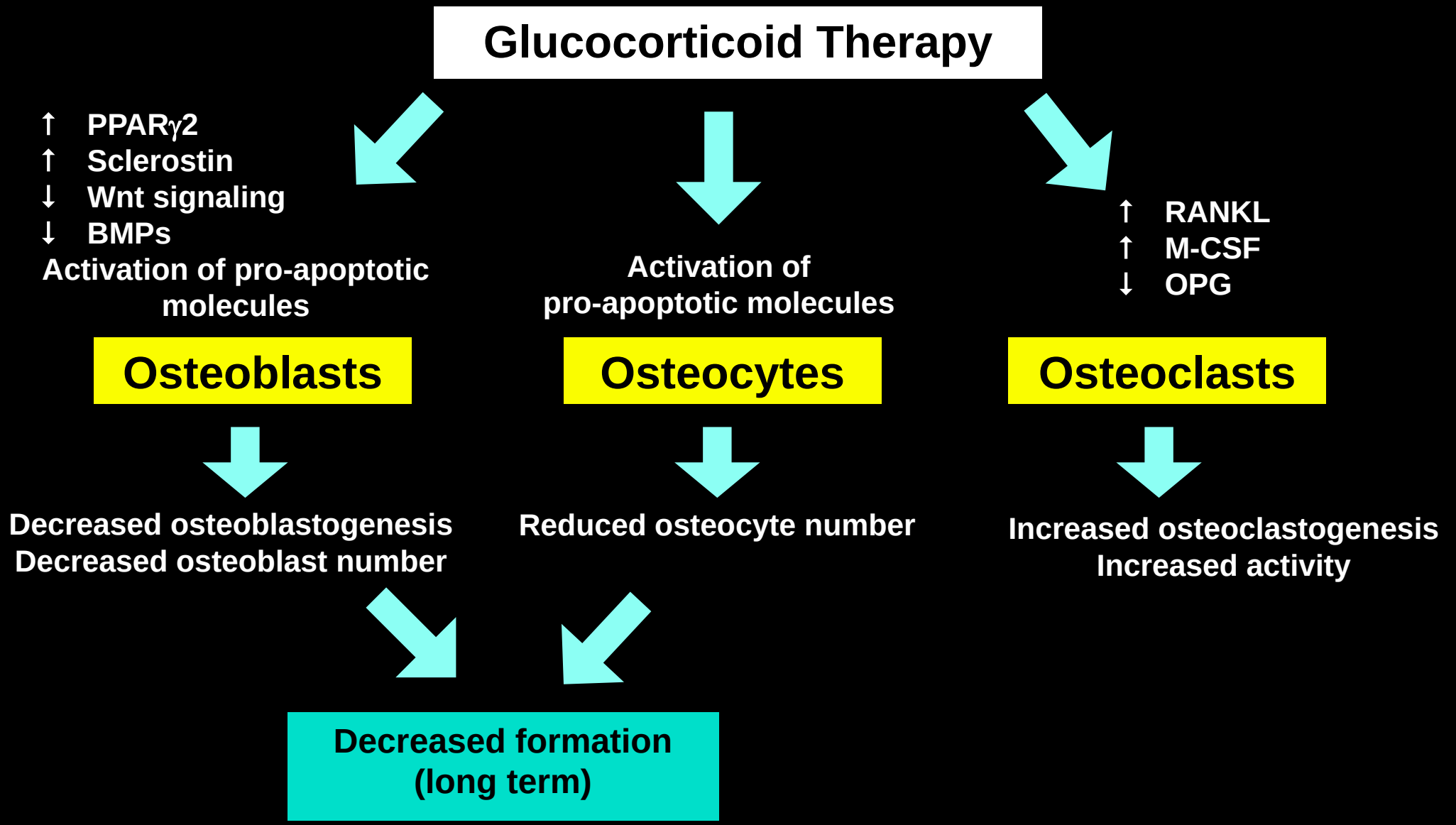
Compston J. *Endocrine* 2018;61:7

GIOP Pathophysiology



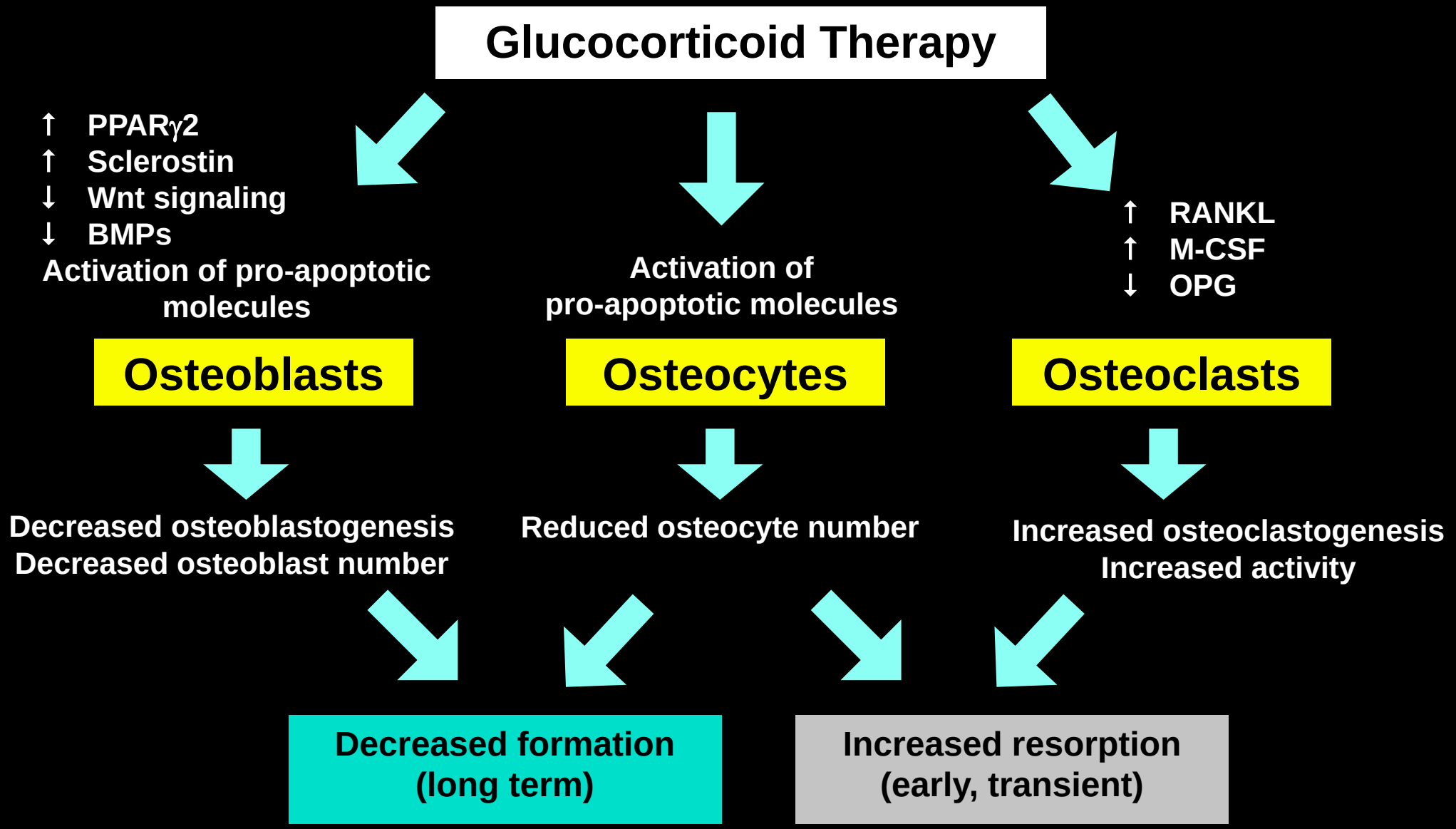
Compston J. *Endocrine* 2018;61:7

GIOP Pathophysiology



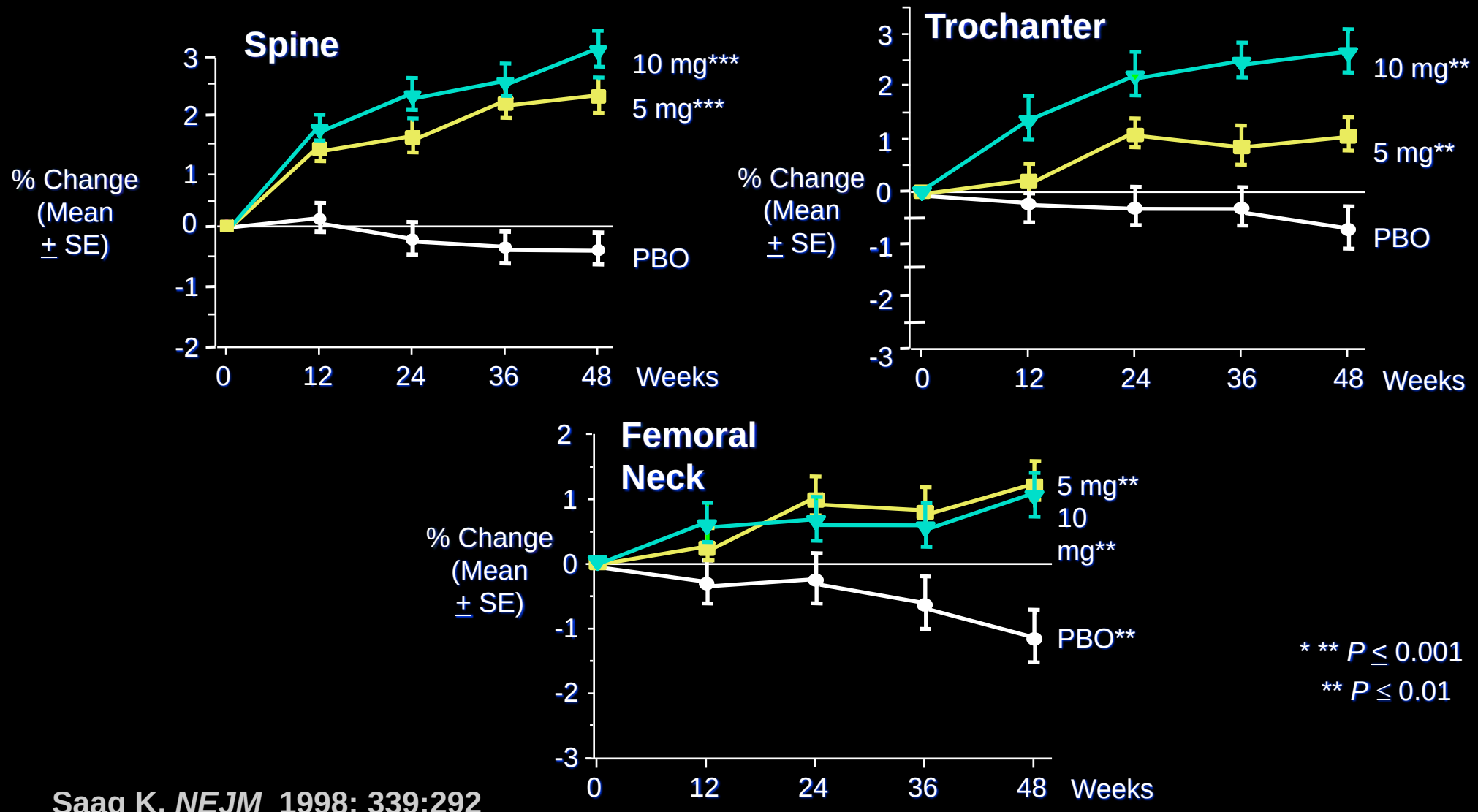
Compston J. *Endocrine* 2018;61:7

GIOP Pathophysiology



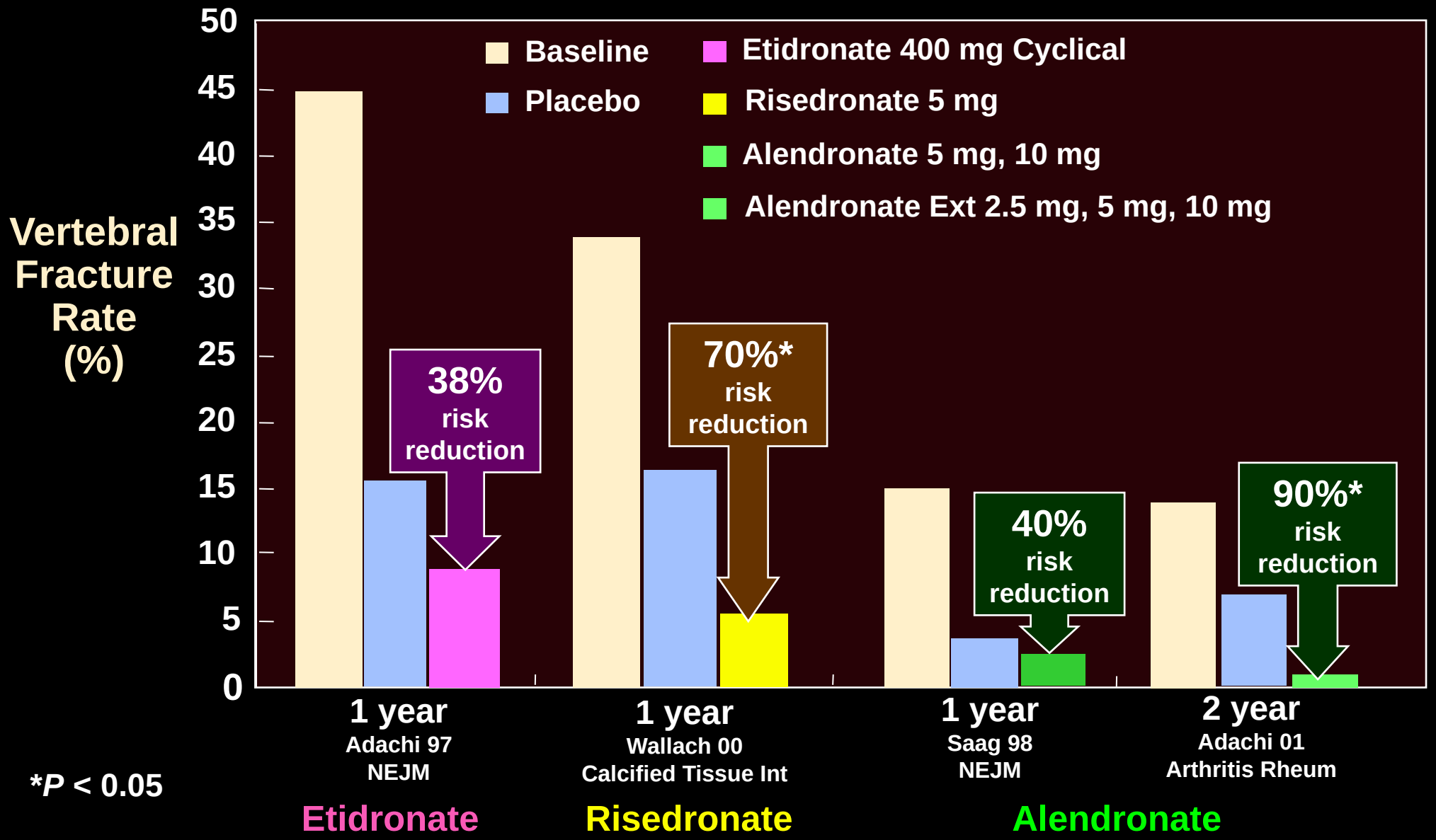
Compston J. *Endocrine* 2018;61:7

Alendronate GIOP Prevention and Treatment



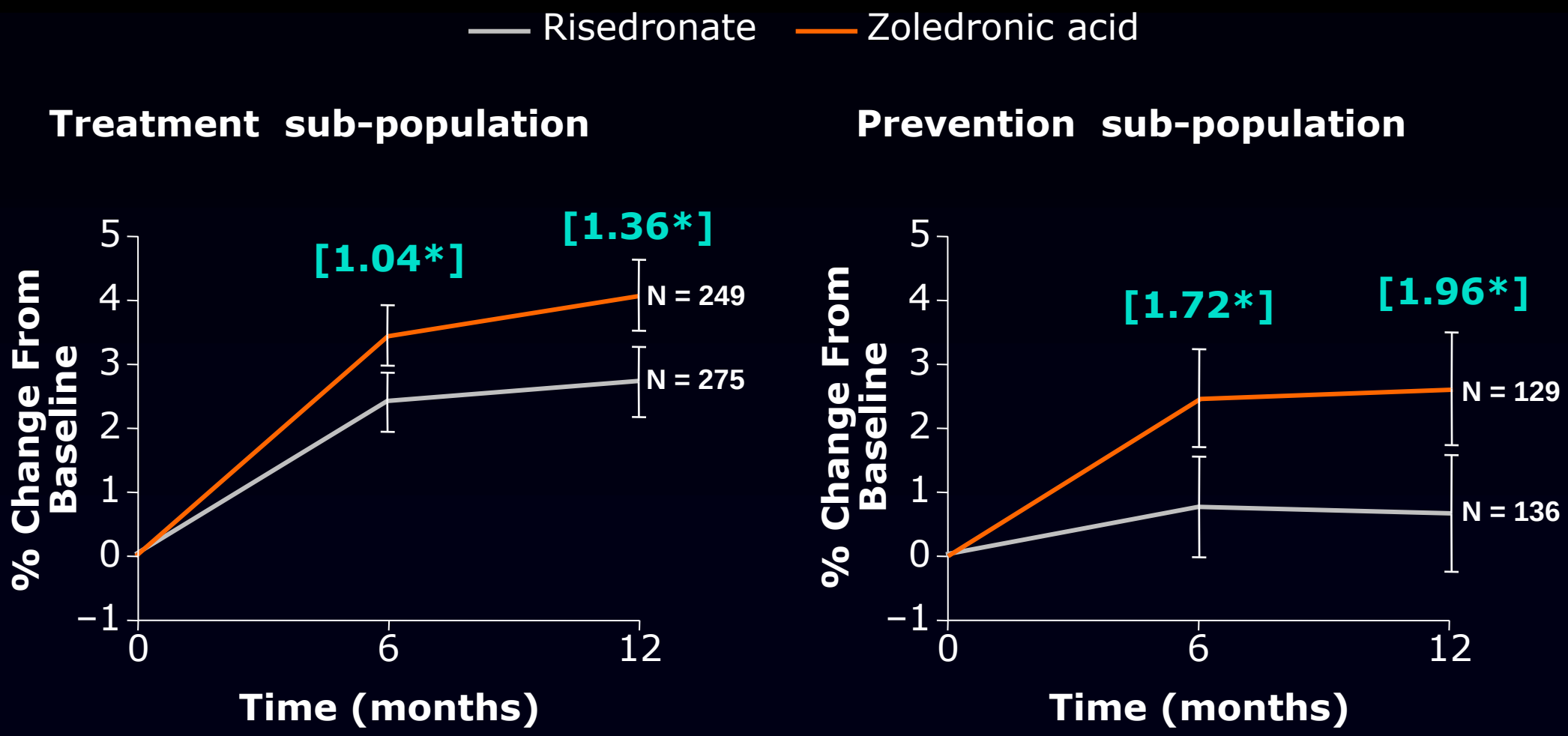
Saag K. *NEJM* 1998; 339:292

GIOP Bisphosphonate Trials: Fracture Rates



*$P < 0.05$

Zoledronic Acid vs. Risedronate in GIOP Lumbar Spine BMD

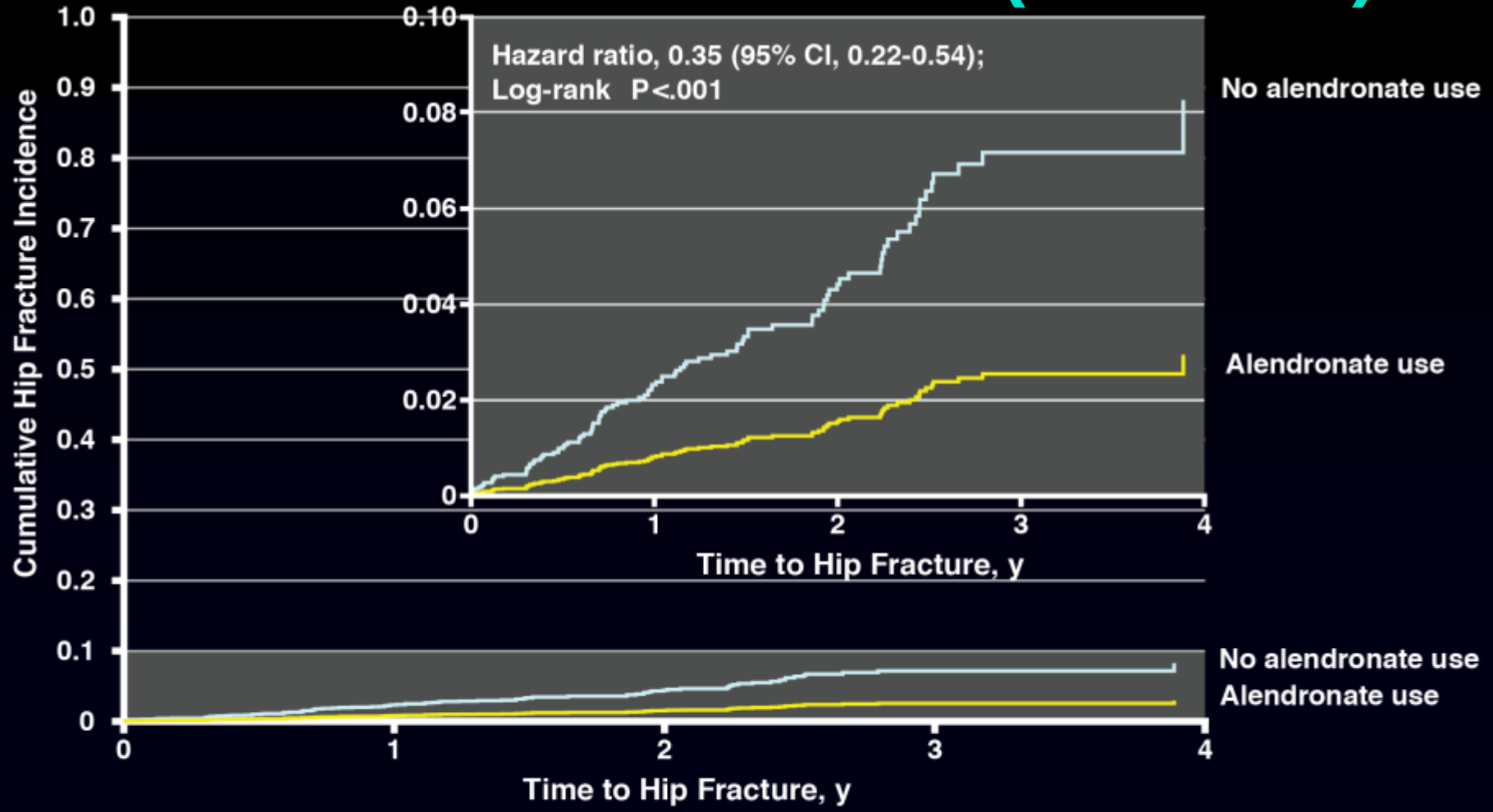


* p-value < 0.01

Reid D. *Lancet* 2009; 373: 1253

Alendronate Reduces Hip Fx in GIOP

Swedish National Data Base (n = 433K)



No. at risk

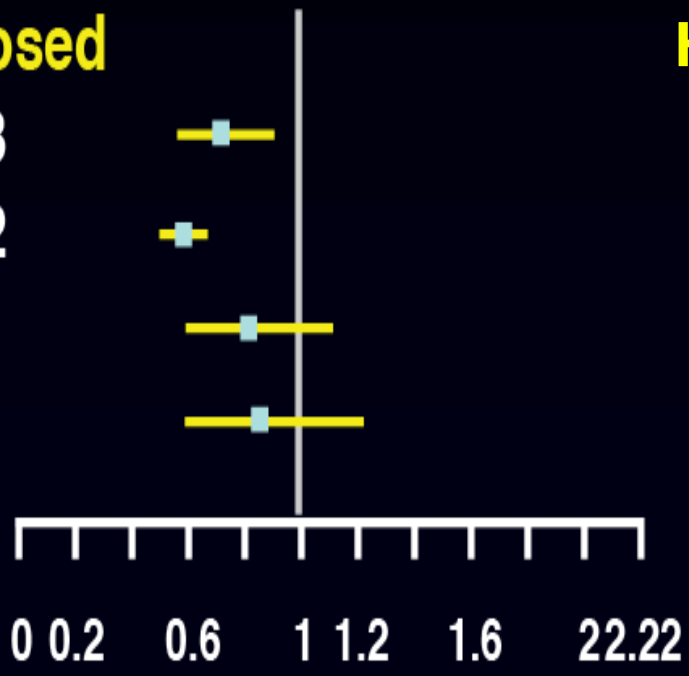
No alendronate use	1802	1044	556	226	42
Alendronate use	1802	1110	588	230	64

Axelsson KF. *JAMA*. 2017;318:146

Oral Bisphosphonates Reduce Fracture Risk Among Oral Glucocorticoid Users in Canada

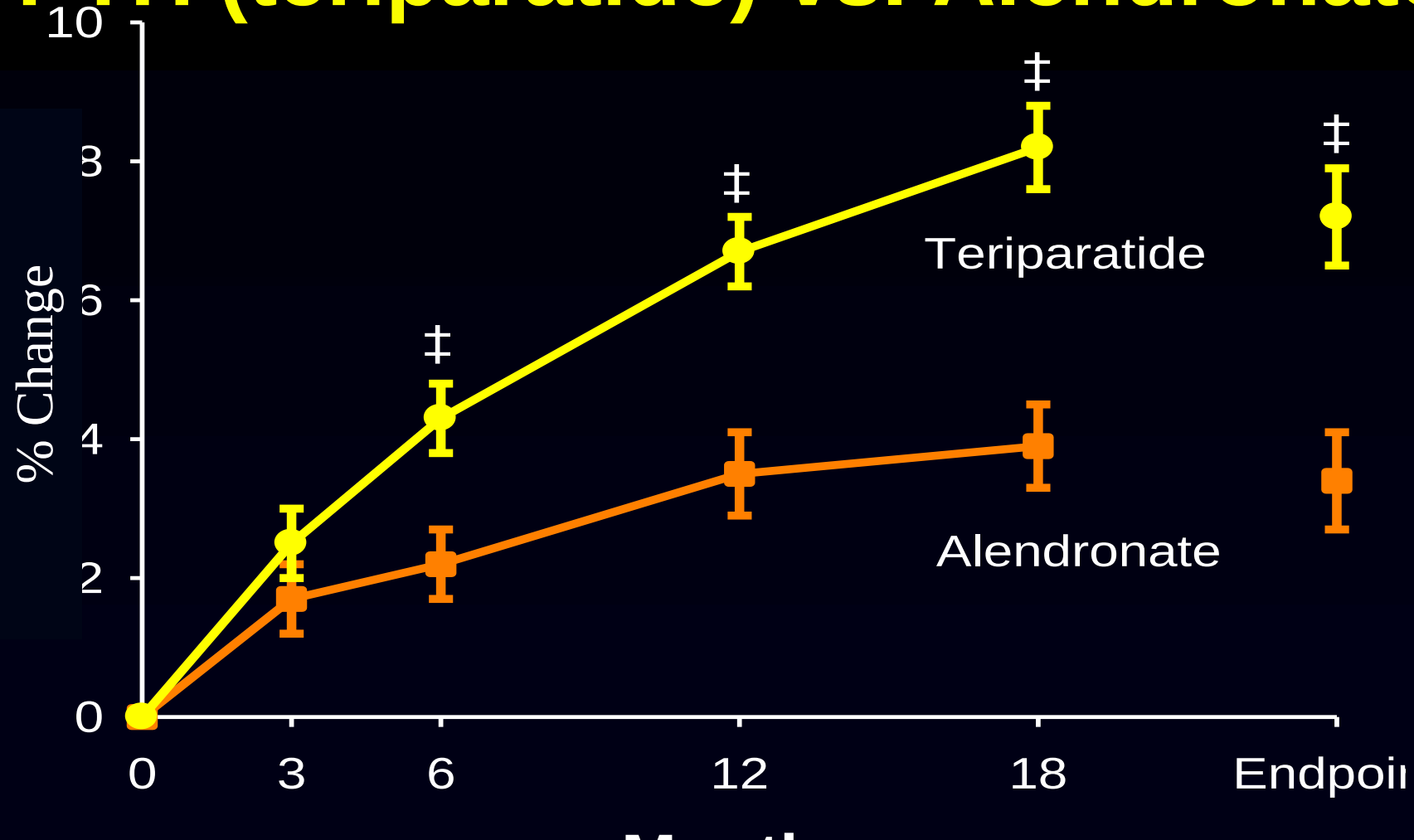
(3945 Alendronate, 5825 Risedronate, and 8464 Etidronate)

	Exposed	Unexposed	Hazard Ratios
Hip	131	183	0.71 (0.57 - 0.89)
Vertebral	323	552	0.58 (0.51 - 0.66)
Forearm	76	98	0.81 (0.60 - 1.11)
Humerus	46	56	0.85 (0.60 - 1.21)



Amiche M. *JBMR* 2018; 33:419

Lumbar Spine BMD in GIOP
PTH (teriparatide) vs. Alendronate



‡P<0.001

Alendronate N=	195	184	173	159	148	195
Teriparatide N=	198	183	178	170	156	198

Saag K. *NEJM* 2007;357:2028

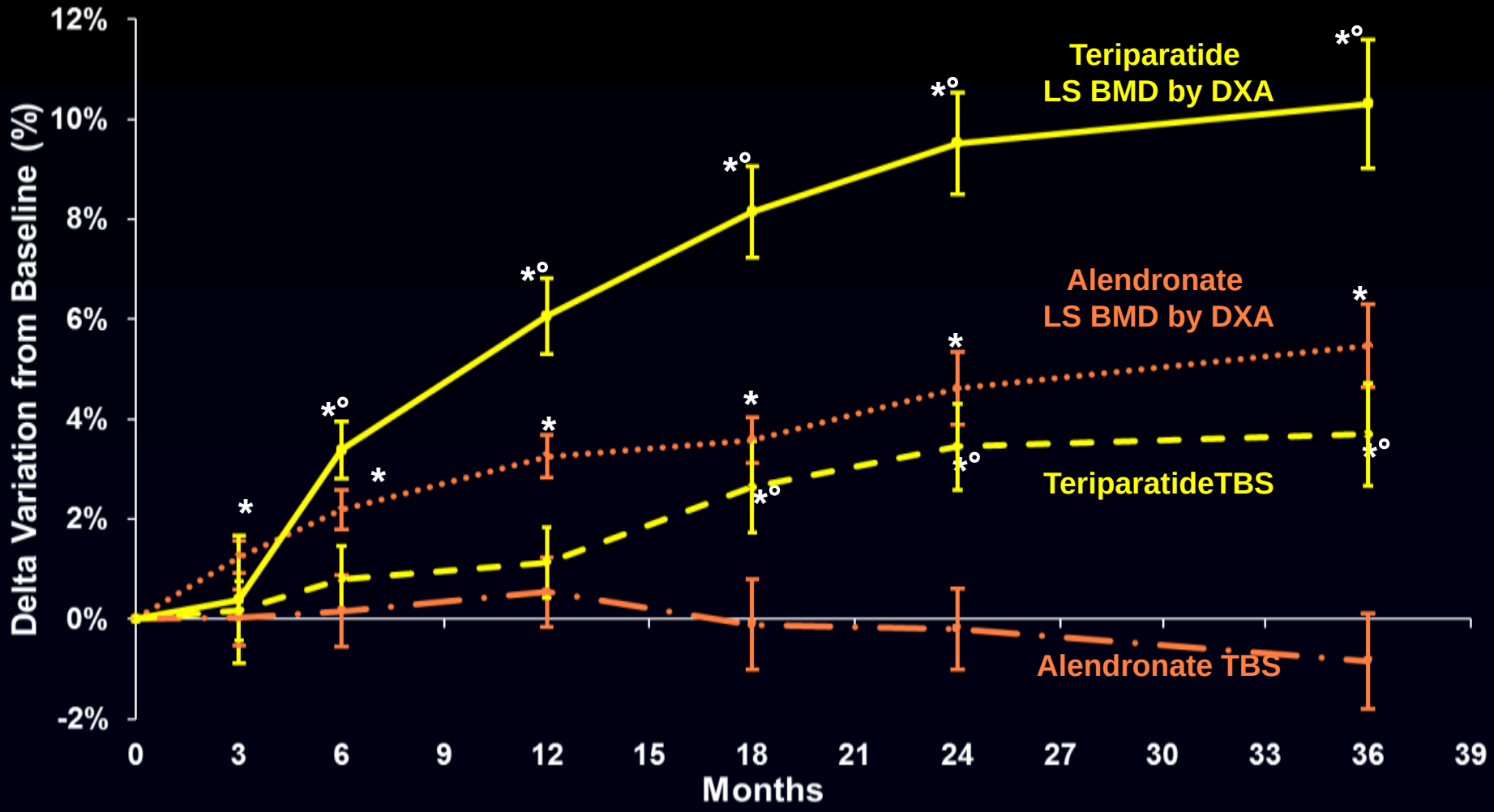
Teriparatide vs. Alendronate
New Vertebral Fractures

	Alendronate (n=169)*	Teriparatide (n=173)*	P-value
Vertebral radiographic	13 (7.7%)	3 (1.7%)	0.007
Clinical vertebral**	4 (2.4%)	0	0.037

*Number (%) of patients with paired baseline and postbaseline spinal radiographs
**Radiographically confirmed vertebral fracture(s) associated with symptoms such as back pain; vertebrae graded individually for compression deformity using semiquantitative criteria

Saag K. *NEJM* 2007;357:20

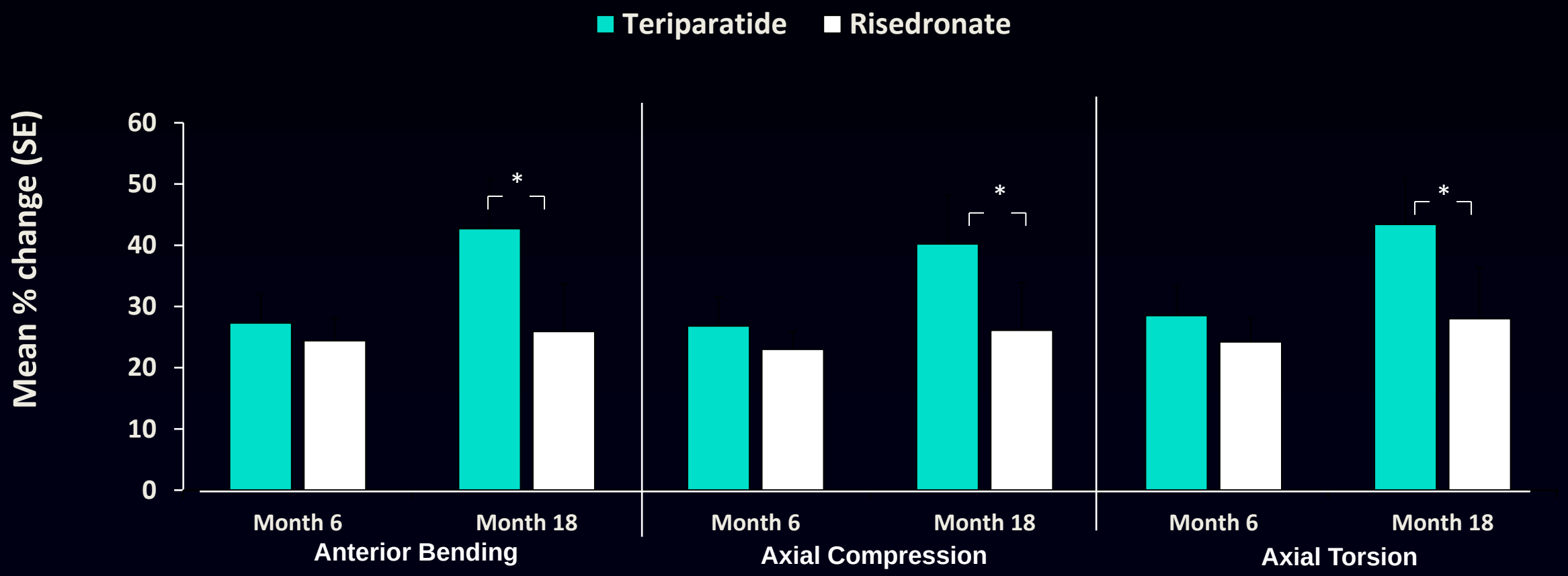
Trabecular Bone Score (TBS) and BMD by DXA in GIOP Trial



Saag KG et al. Arth Rheum 2016

*p<0.05 from baseline; ° **p**<0.05 between groups

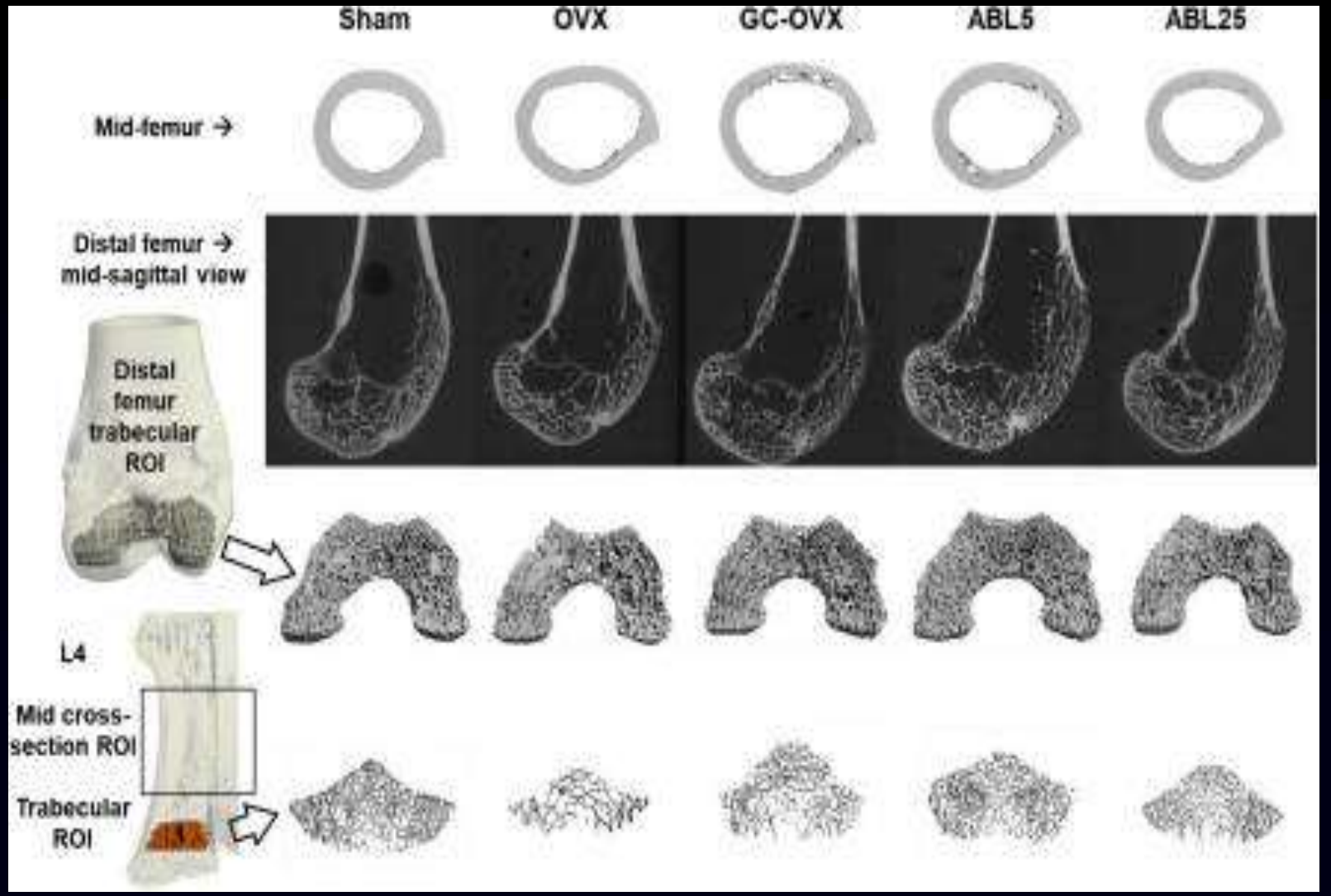
Teriparatide vs. Risedronate Finite Element Analysis - Strength



* P ≤ 0.015 for the between-treatment comparison (MMRM model)

Glüer C. *J Bone Miner Res* 2013;28:1355

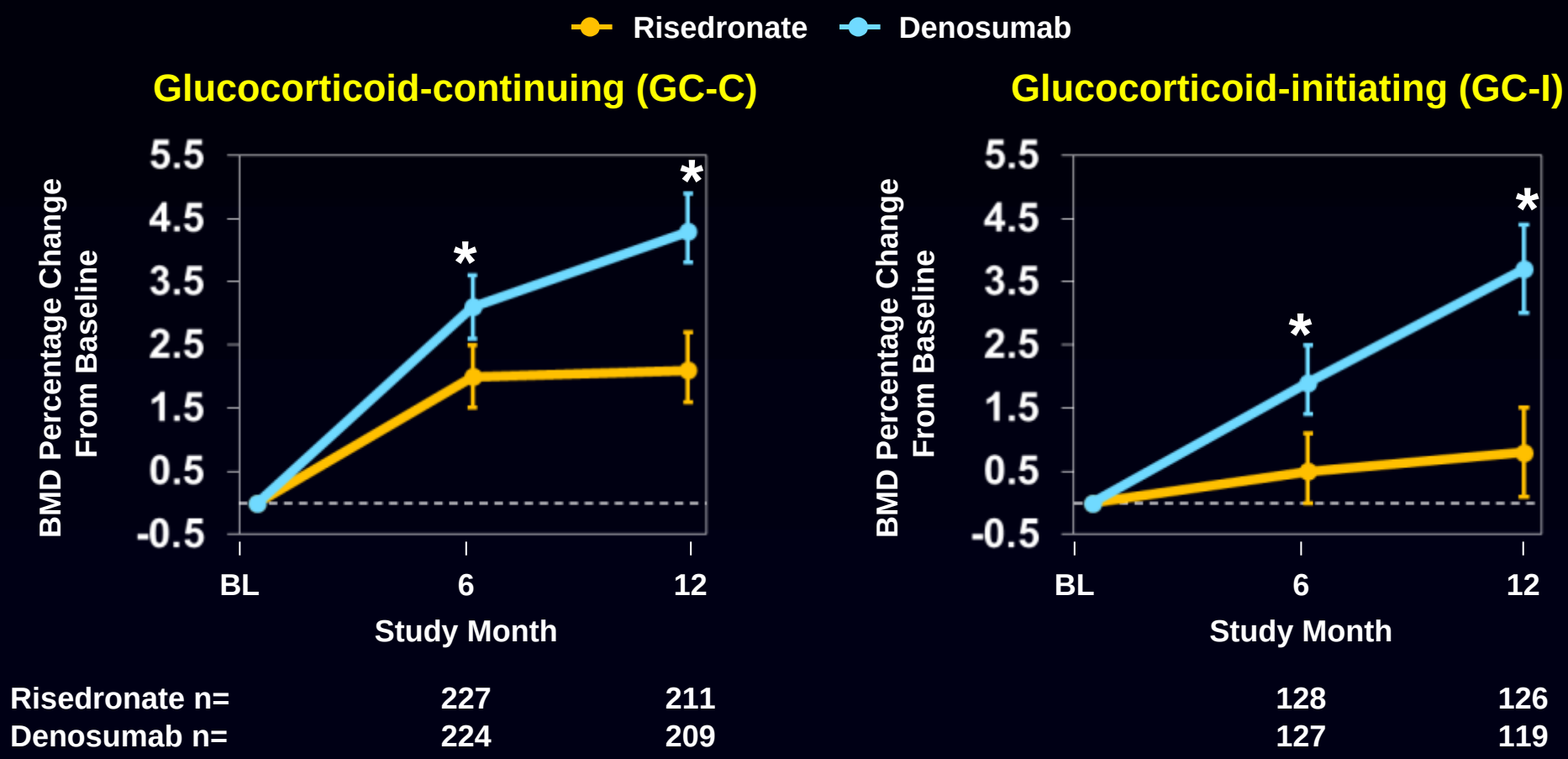
Abaloparatide in OVX Rabbits with GIOP



Chandler H. *Osteoporos Int* 2019;30:1607

Densosumab in GIOP

Lumbar Spine BMD Percentage Change From Baseline Months 6 and 12



n = Number of subjects with observed values at baseline and the time point of interest; *p ≤ 0.002

Saag KG. *Lancet Diab Endo*,2018;6:445

Serious Infections by High Risk Subgroups In Denosumab Glucocorticoid-Induced OP Study

With Concomitant Biologics Medication, n (%)

Risedronate N = 27	Denosumab N = 17
2 (7.4)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of IP with or without concomitant biologics medication

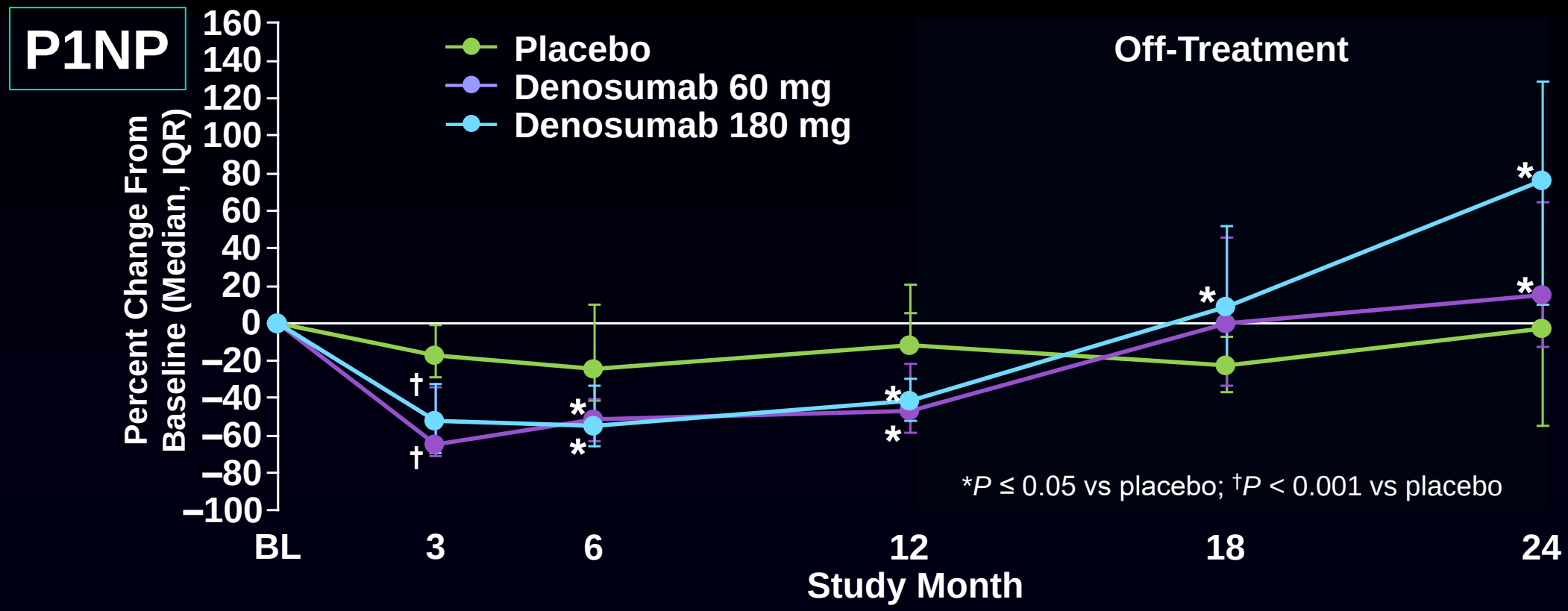
With Concomitant Biologics Medication or Immunosuppressants, n (%)

Risedronate N = 227	Denosumab N = 208
9 (4.0)	6 (2.9)

N = Number of subjects who received ≥ 1 dose of IP with or without concomitant biologics medication or immunosuppressants

Saag KG. *Lancet Diab Endo*,2018;6:445

Results: Change in P1NP From Baseline Upon Denosumab Discontinuation in Subjects With Rheumatoid Arthritis

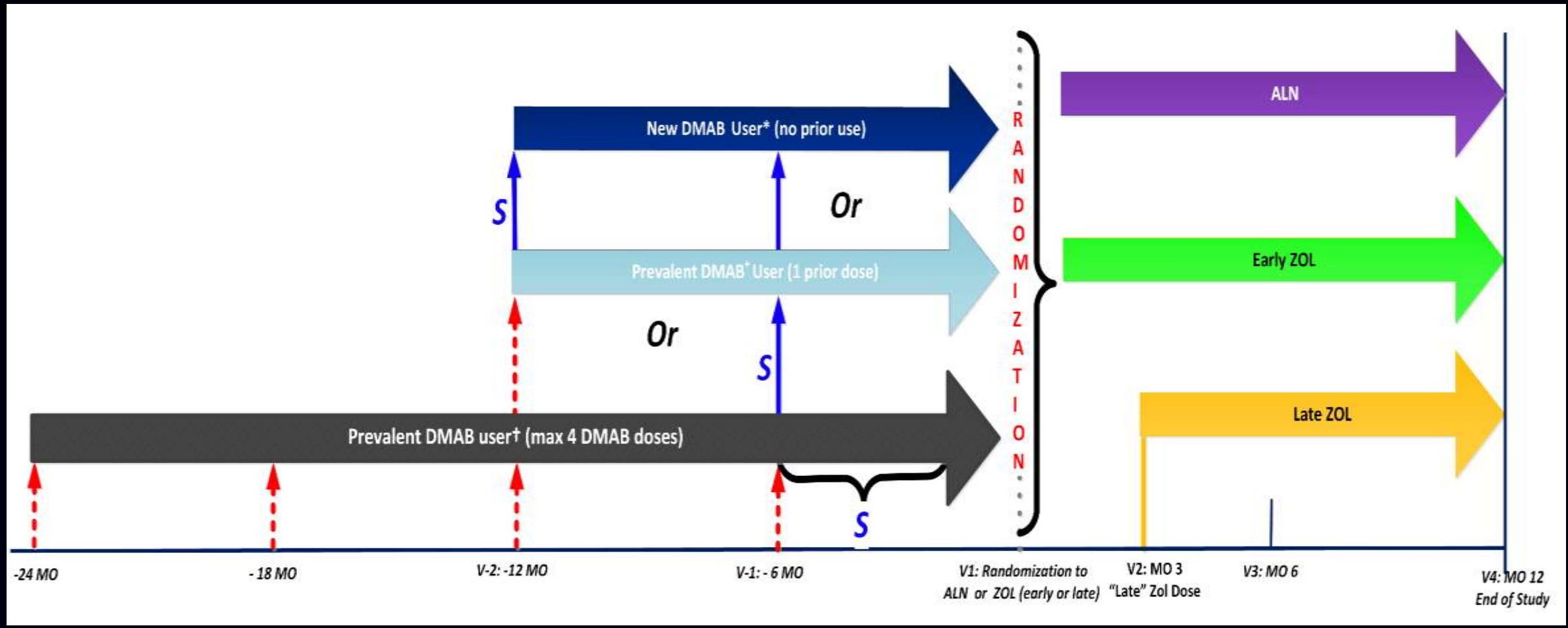


	BL	3	6	12	18	24
Placebo n =	26	25	9	14	15	
Denosumab 60 mg n =	27	27	17	19	14	
Denosumab 180 mg n =	29	26	16	20	16	

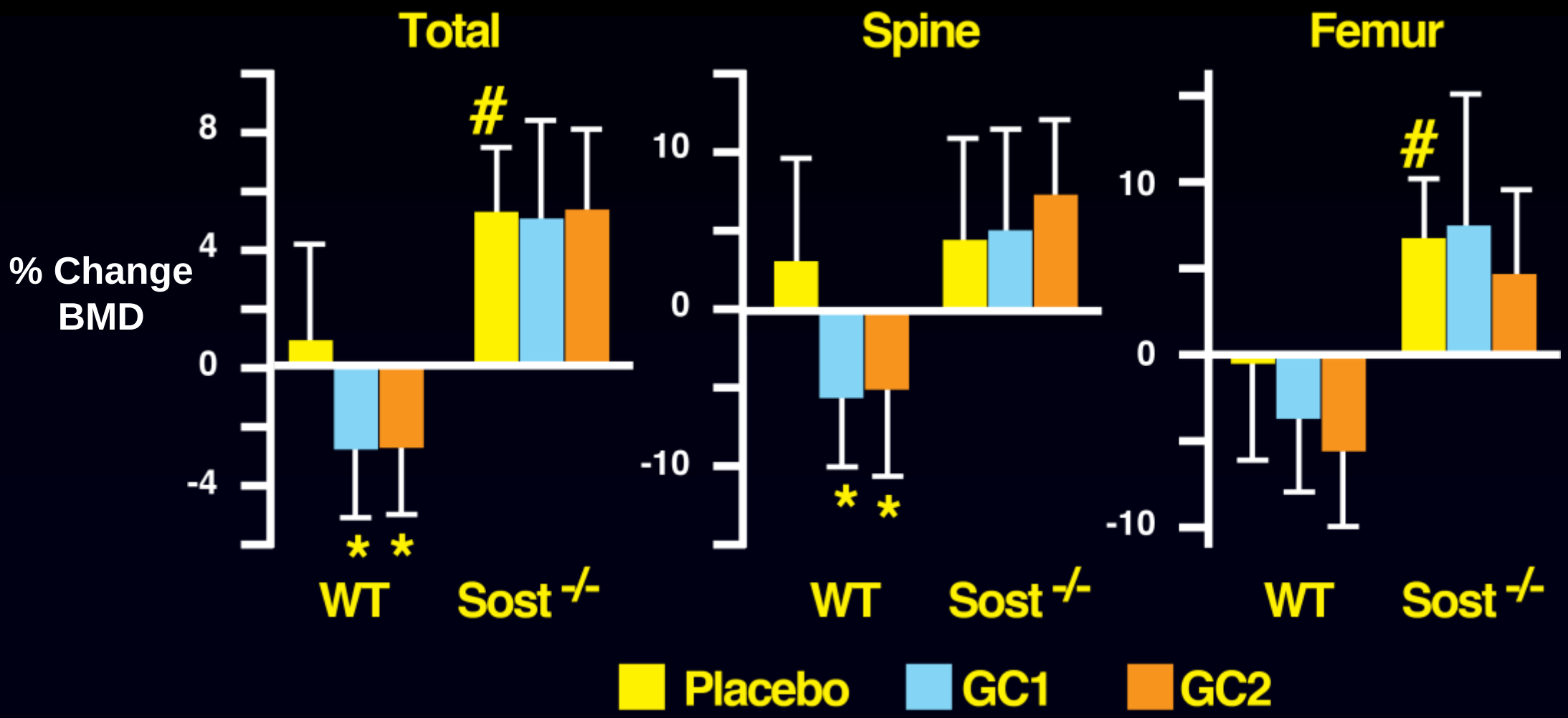
BL=baseline; IQR=interquartile range (Q1, Q3); P1NP=serum procollagen type I N-terminal propeptide
Includes subjects enrolled in the off-treatment phase with observed values at baseline and time point of interest

Saag K. *Arth Rheum,* 2022;74:604

Denosumab GIOP Switching Trial

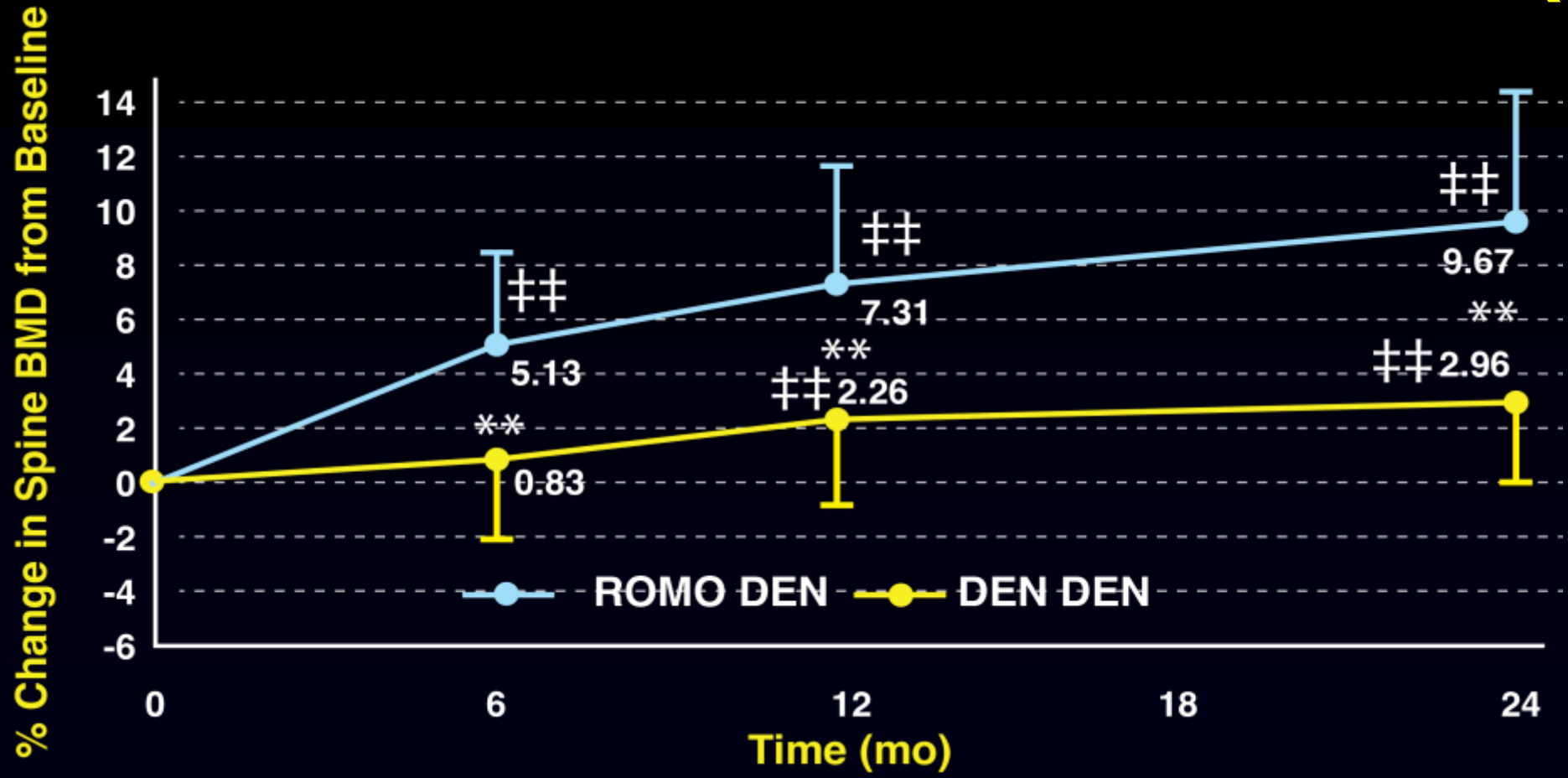


Protection From GIOP
in the Absence of Sost/Sclerostin



Sato AY. *JBMR* 2016; 31:1791

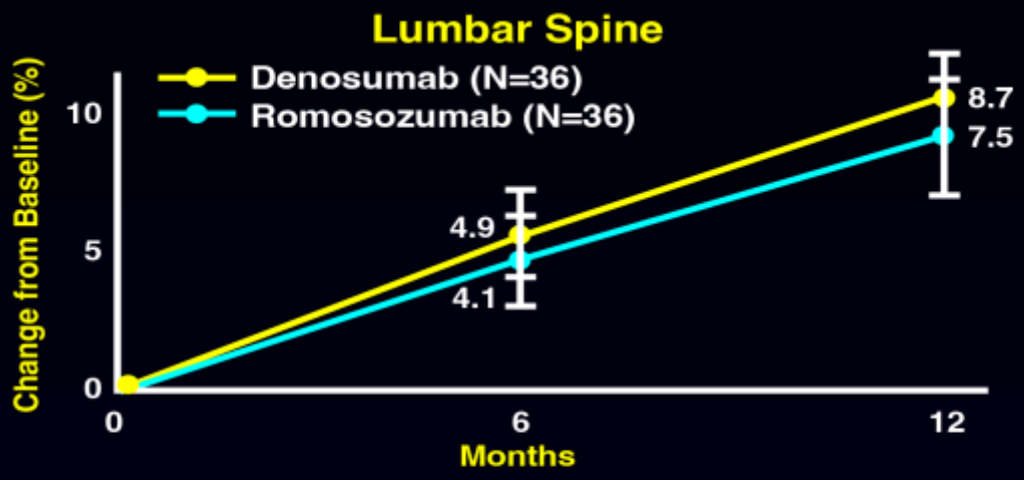
Romo vs Dmab in GIOP – 12 mo data (n= 70)

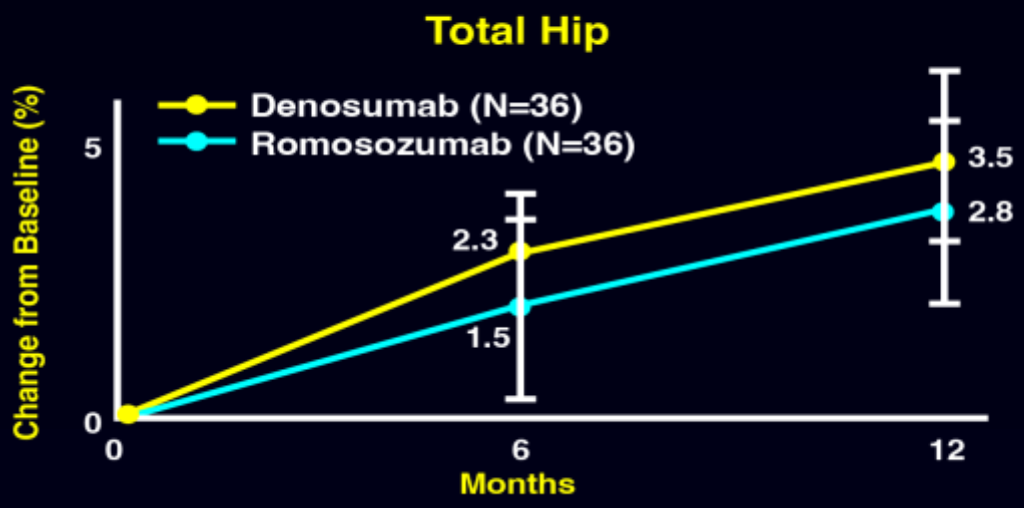


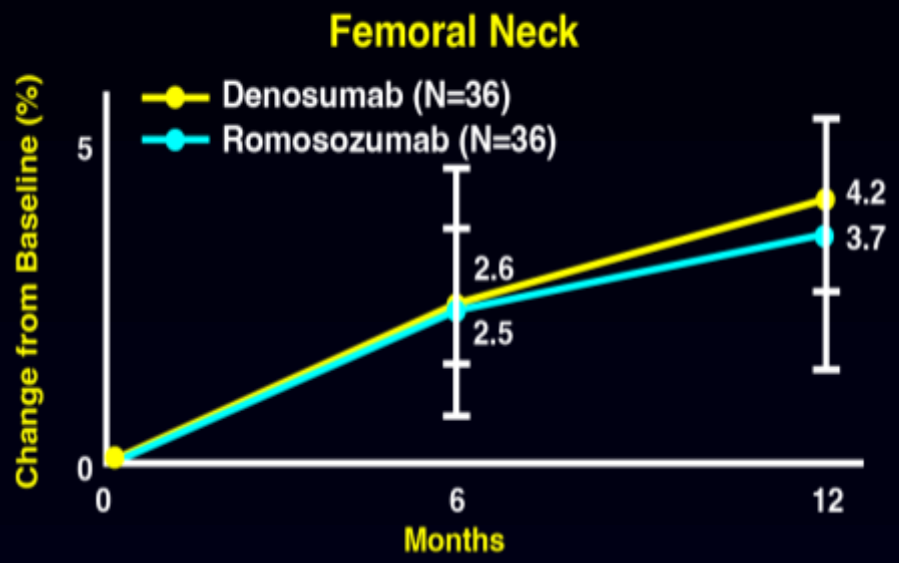
- Romosozumab superior to denosumab in increasing spine BMD at month 12 in chronic GC users with high fracture risk
- Both drugs well-tolerated

Mok CC. *J Int Med* 2024;0:1

Denosumab vs Romosozumab in RA Patients on Glucocorticoids (n = 36)

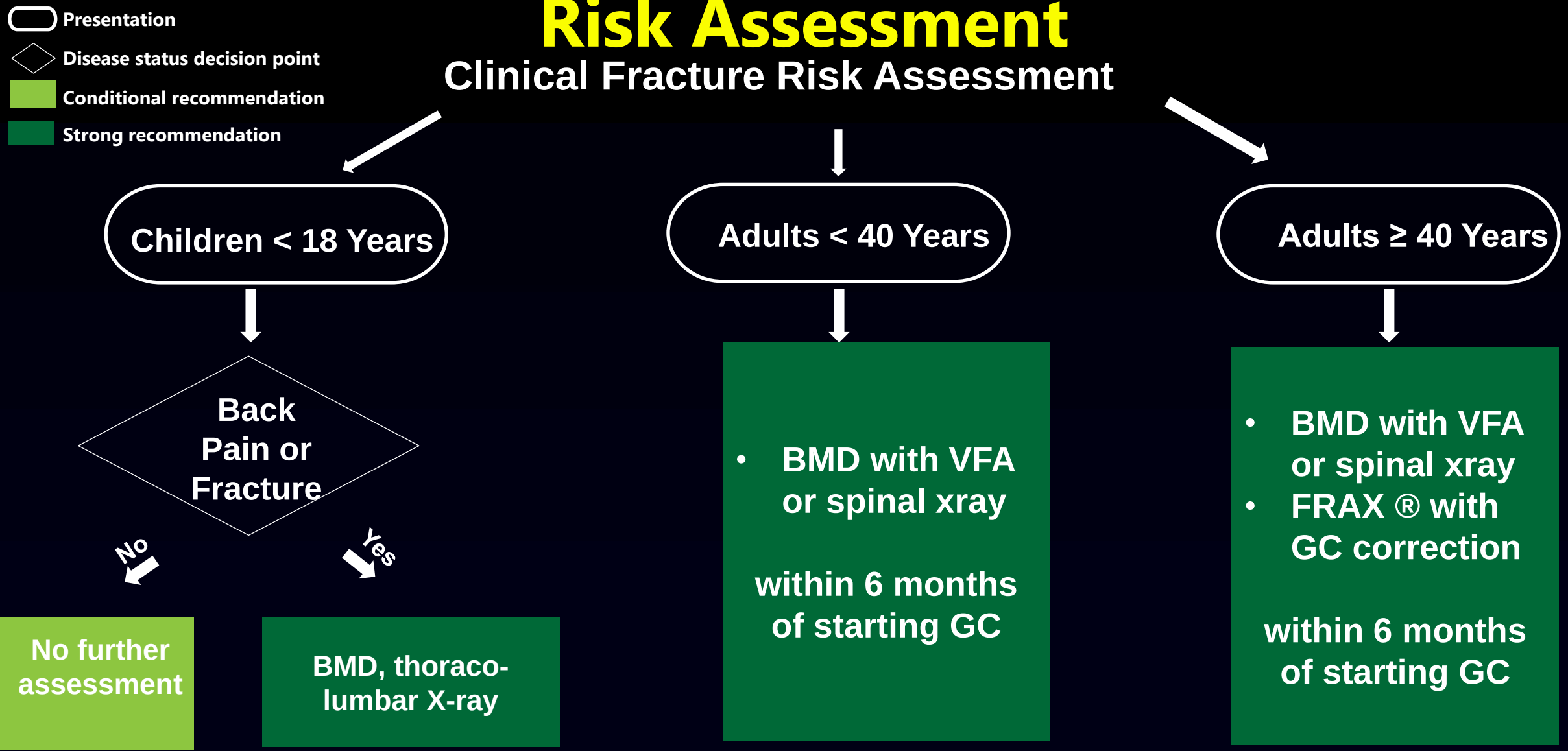




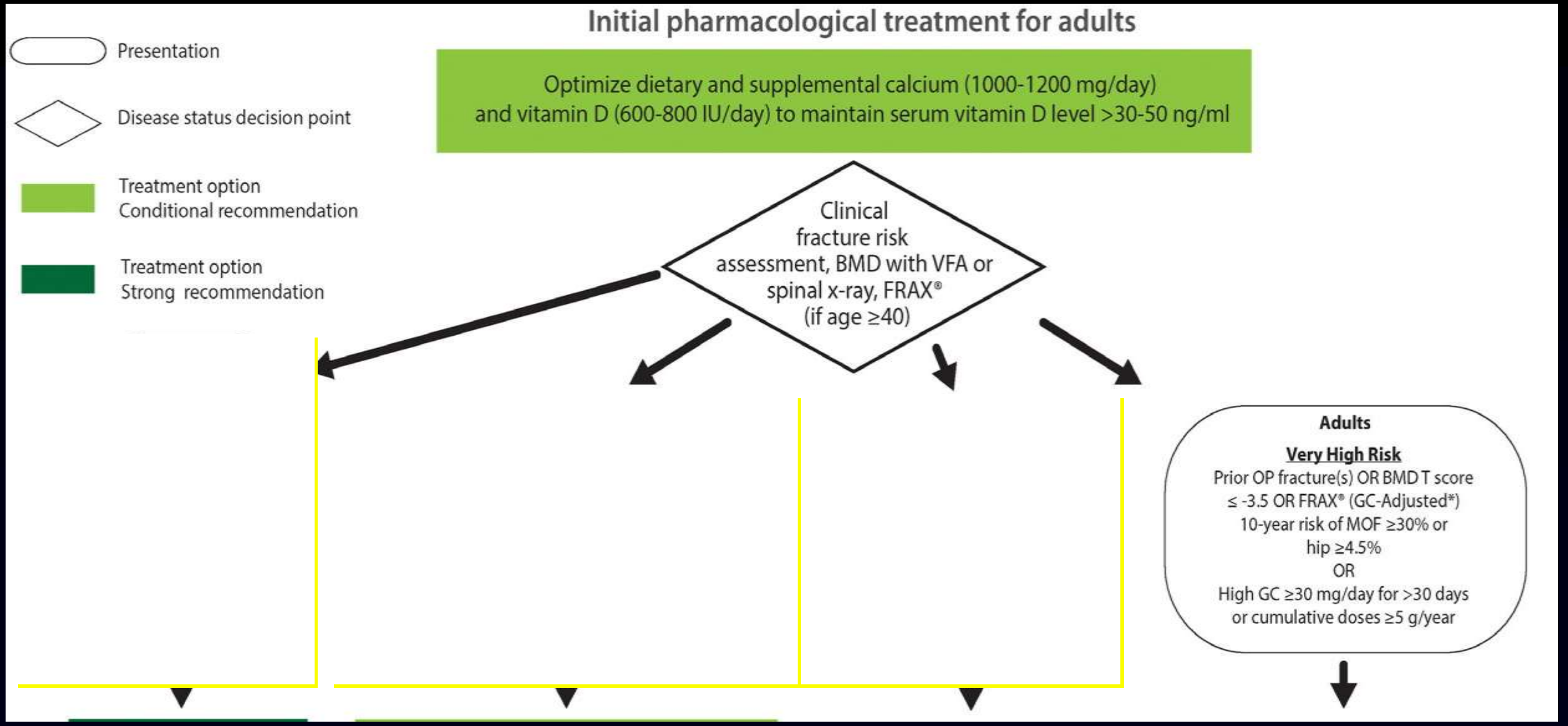


Kobayakawa T. *Modern Rheum* 2023;33:26

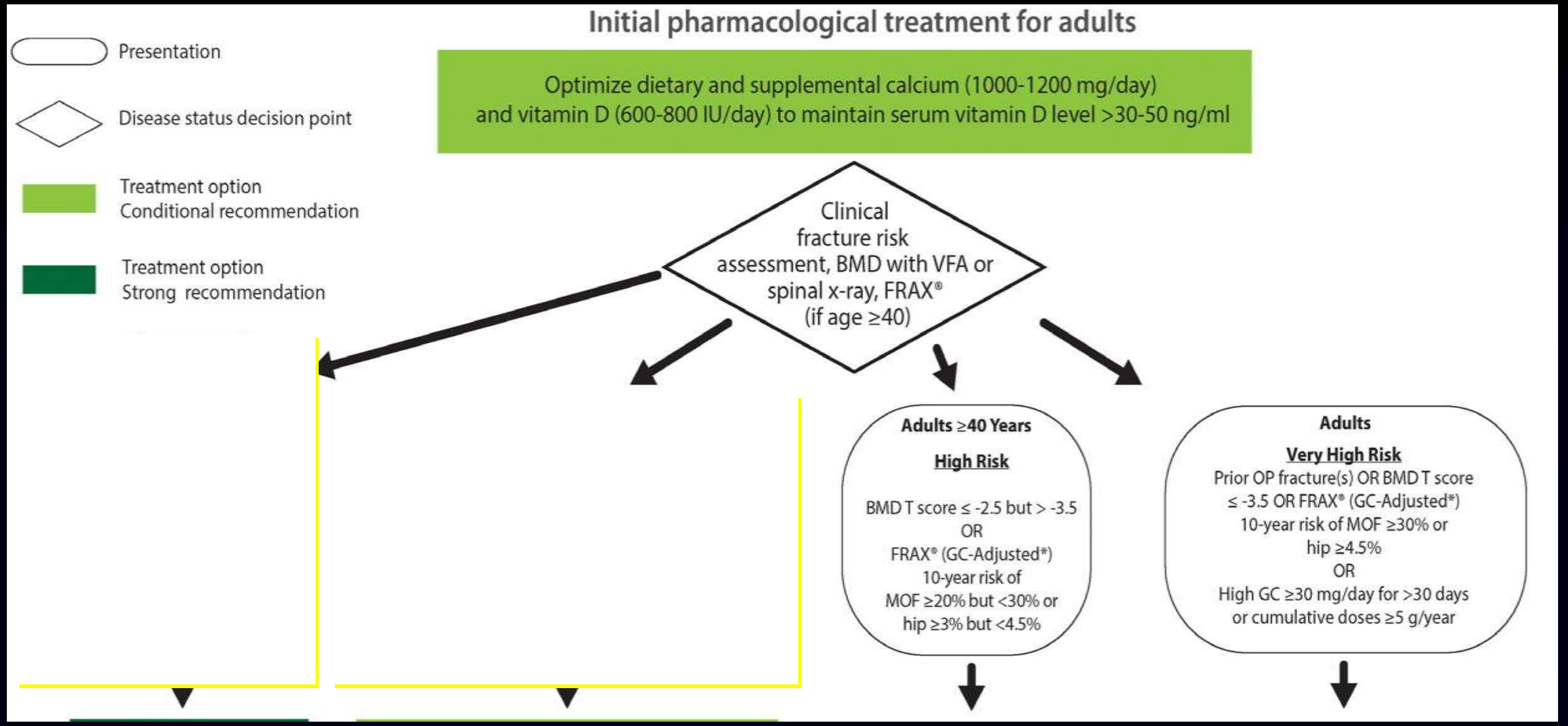
ACR GIOP 2022- Initial Fracture Risk Assessment



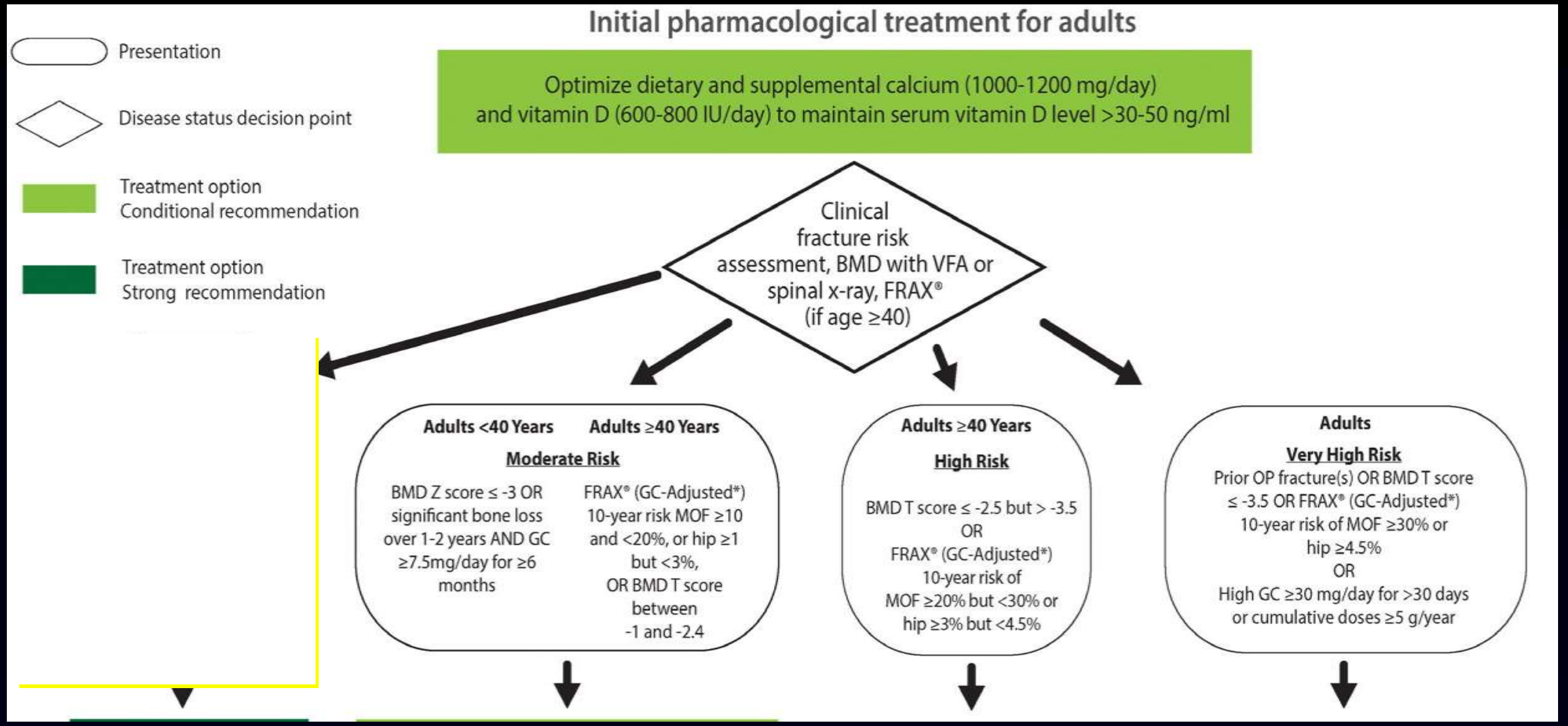
ACR GIOP 2023



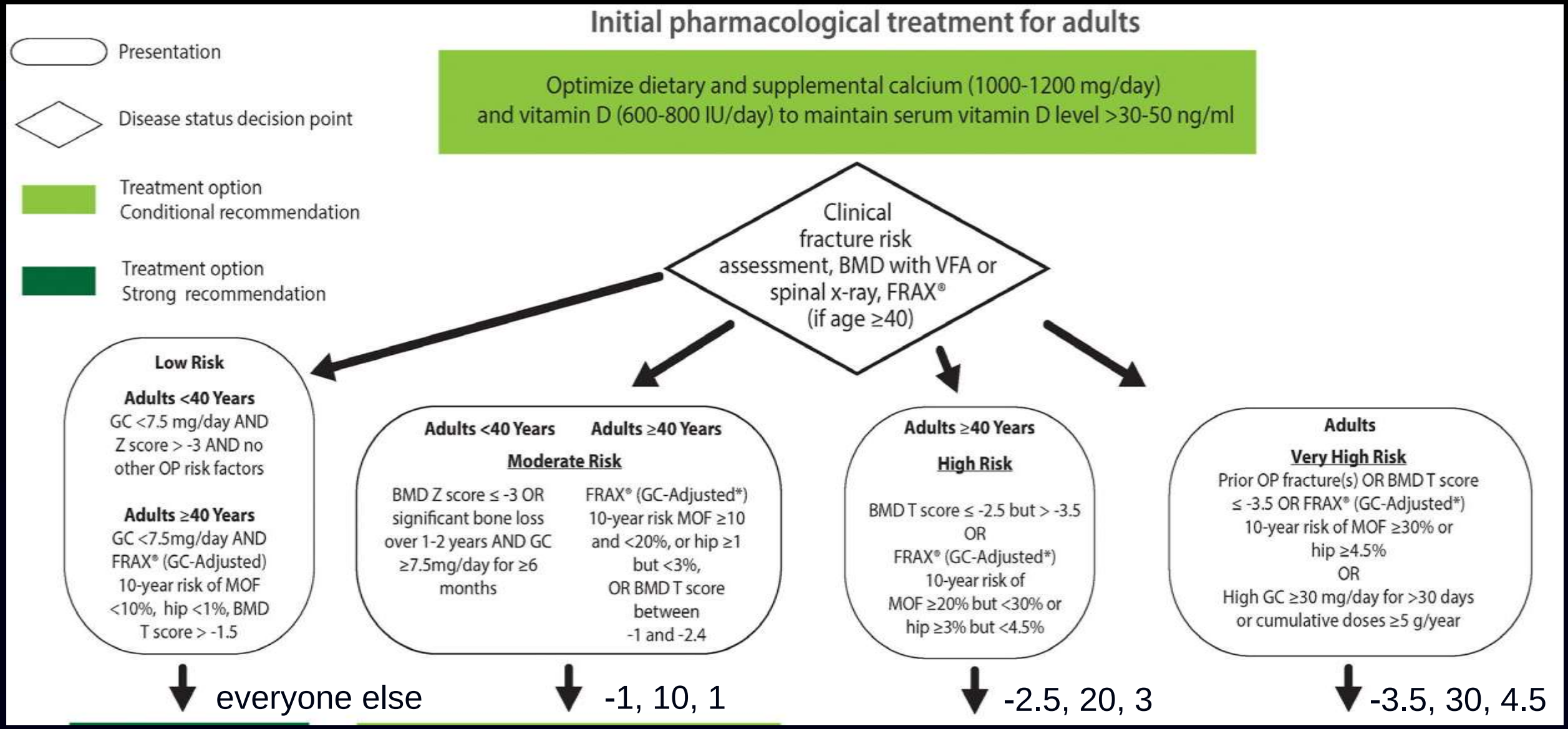
ACR GIOP 2023



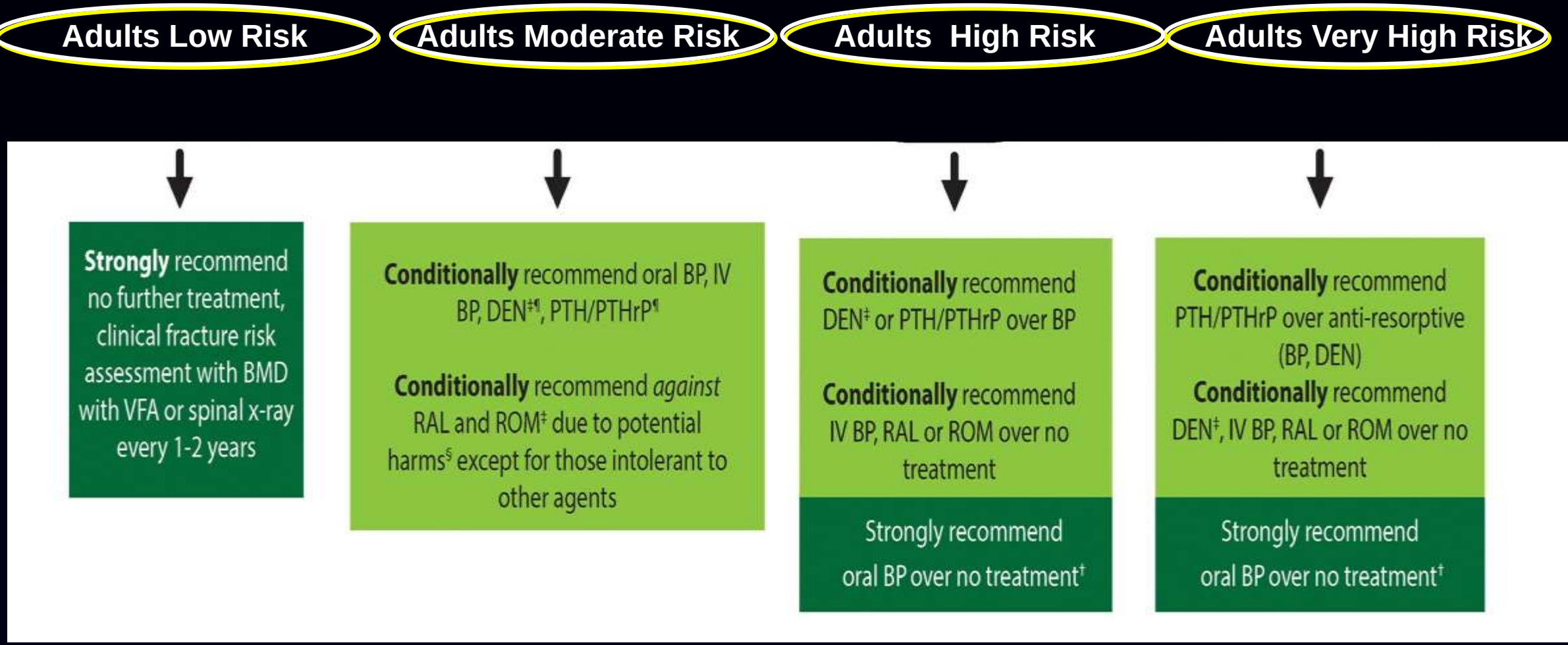
ACR GIOP 2023



ACR GIOP 2023



ACR GIOP


Adults Low Risk
Adults Moderate Risk
Adults High Risk
Adults Very High Risk
Strongly recommend no further treatment, clinical fracture risk assessment with BMD with VFA or spinal x-ray every 1-2 years
Conditionally recommend oral BP, IV BP, DEN‡¶, PTH/PTHrP¶
Conditionally recommend against RAL and ROM‡ due to potential harms§ except for those intolerant to other agents
Conditionally recommend DEN‡ or PTH/PTHrP over BP
Conditionally recommend IV BP, RAL or ROM over no treatment
Strongly recommend oral BP over no treatment†
Conditionally recommend PTH/PTHrP over anti-resorptive (BP, DEN)
Conditionally recommend DEN‡, IV BP, RAL or ROM over no treatment
Strongly recommend oral BP over no treatment†

Aging Clinical and Experimental Research (2022) 34:2591–2602
https://doi.org/10.1007/s40520-022-02261-2

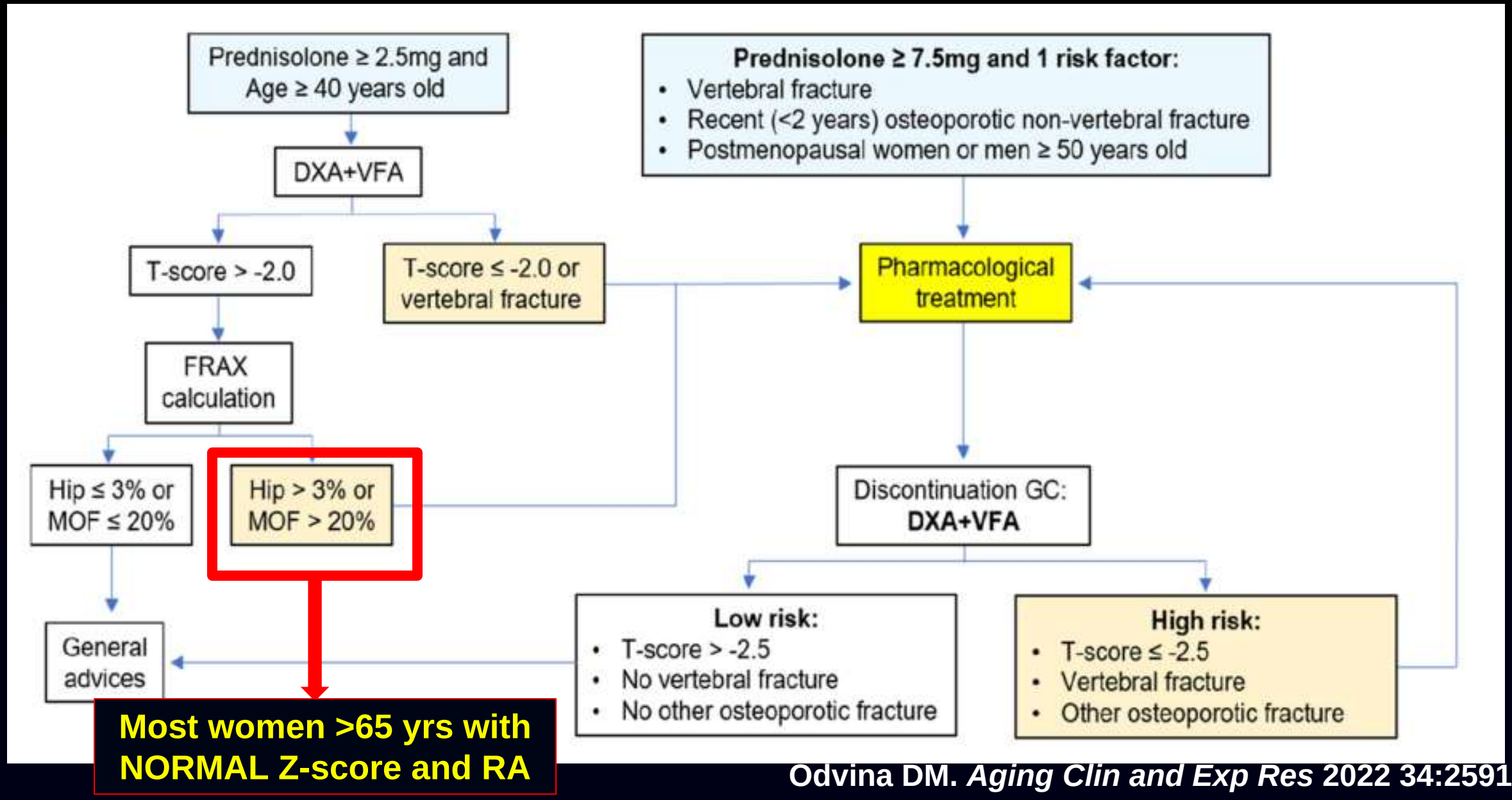
CONSENSUS DOCUMENT

Evidence based Latin American Guidelines of clinical practice on prevention, diagnosis, management and treatment of glucocorticoid induced osteoporosis. A 2022 update

This manuscript has been produced under the auspices of the Committee of National Societies (CNS) and the Committee of Scientific Advisors (CSA) of the International Osteoporosis Foundation (IOF)

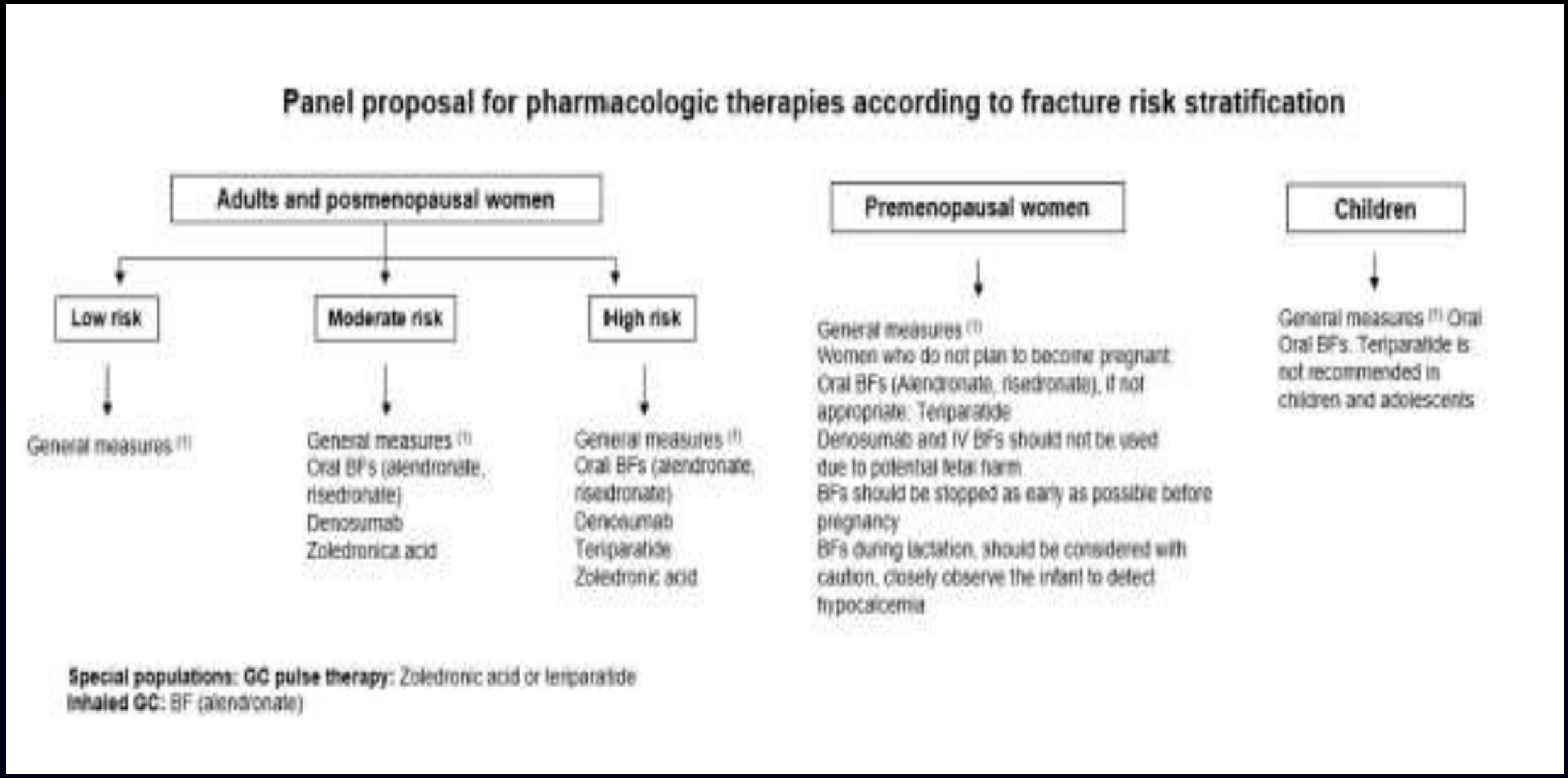
Osvaldo Daniel Messina[1,2] · Maritza Vidal[3] · Jorge A Morales Torres[4] · Luis Fernando Vidal[3,5] · Constanza Arguissain[1] · Rosa María Pereira[6,7] · Patricia Clark[2,8] · Sonia Cerdas Perez[9,10] · Claudia Campusano[2,11] · Marise Lazaretti-Castro[12] · Cristiano Zerbini[13] · Juan J. Scali[14,15] · Lucia Mendez Sanchez[8] · Maria L. Peralta-Pedrero[16] · Andrea Cavallo[1] · Francisco J. Valdivia Ibarra[17] · Talina Hernandez Pérez[17]

Odvina DM. *Aging Clin and Exp Res* 2022 34:2591



Odvina DM. *Aging Clin and Exp Res* 2022 34:2591

2022 LATAM GIOP Guidance



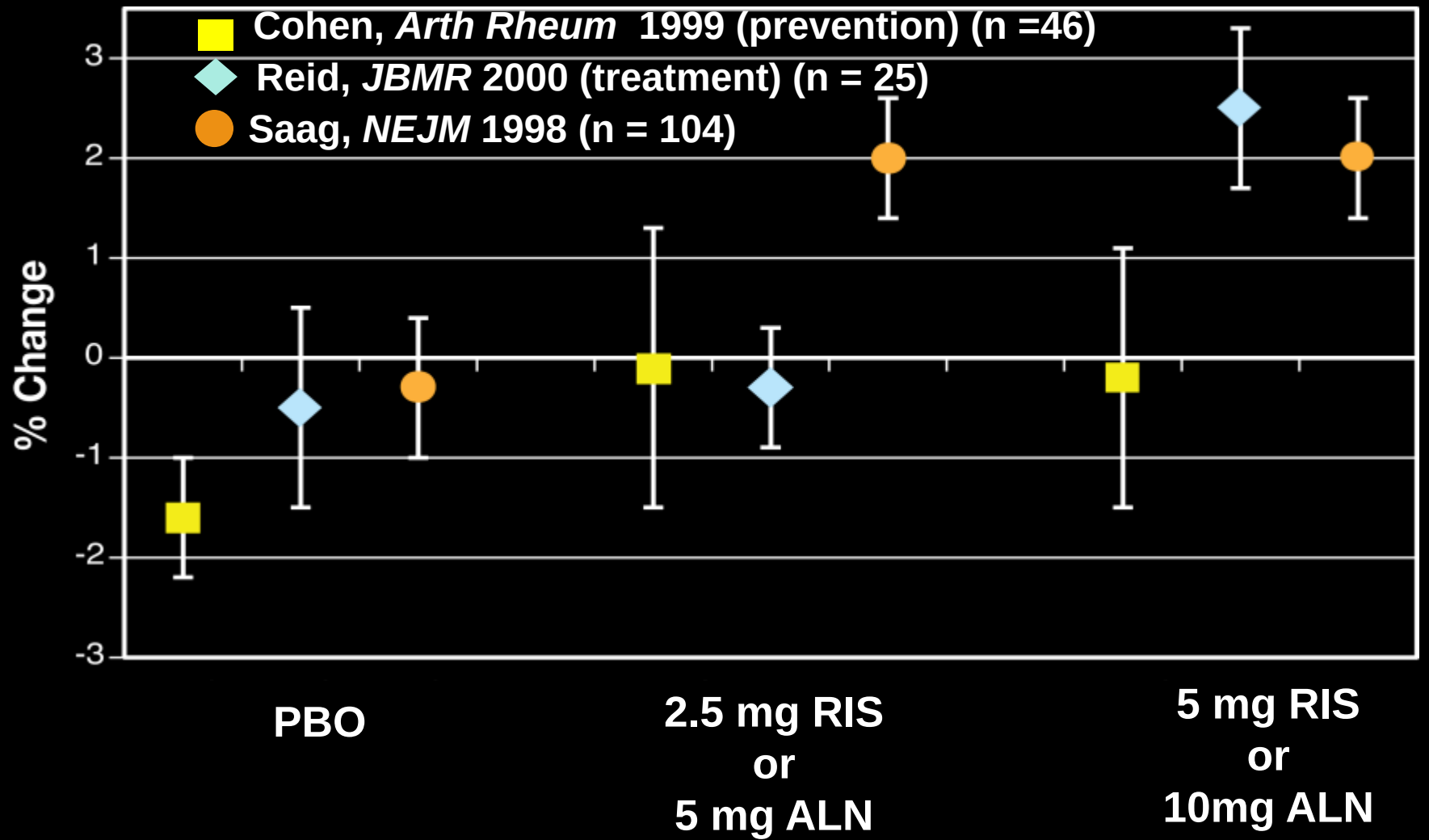
Odvina DM. *Aging Clin and Exp Res* 2022 34:2591

GIOP Controversies and Challenges Requiring A Personalized Approach

"The Data Free Zone"

- Indications for Osteoporosis Therapy
  - Premenopausal women (particularly of child bearing potential)?
- Duration of Osteoporosis Therapy
  - "Drug Holidays" ?
  - Rx after first teriparatide ?
- Bone Rx with CKD

Bisphosphonates in Premenopausal Women on Glucocorticoids Effects on Lumbar Spine BMD



ARTHRITIS & RHEUMATISM
Vol. 63, No. 2, February 2011, pp 325–328
DOI 10.1002/art.30135

COMMENTARY

Should Bisphosphonates Be Used for Long-Term Treatment of Glucocorticoid-Induced Osteoporosis?

Steven L. Teitelbaum,[1] Margaret P. Seton,[2] and Kenneth G. Saag[3]

Atypical Femoral Fractures (AFF) Associated with Longer Use of Glucocorticoids

Any Dispensing of Glucocorticoids in past 12 Months, n (%) (in blue)

Femoral neck (n = 207)	Intertrochanteric (n = 329)	Femoral Shaft NOT atypical (n = 122)	Femoral Shaft Atypical (n = 75)
28 (14.5)	46 (15.2)	19 (16.7)	9 (12.9)

Cumulative steroid use, yrs mean ± SD

Femoral Shaft NOT atypical (n = 122)	Femoral Shaft Atypical Major criteria ONLY (n = 53)	Femoral Shaft Atypical Major AND "Minor"* Criteria (n = 22)
2.7 ± 2.9 (n = 43)	2.6 ± 2.6 (n = 17)	4.8 ± 4.1 (n= 8)

*Minor criteria of lateral stress fx at time of study is NOW major AFF criteria

Feldstein AC. *JBMR* 2012;27:977

What Happens to BMD When Alendronate is Withdrawn and Glucocorticoid Use (> 6 mg per day) Continues?

	Lumbar Spine		Femoral Neck		Total Hip	
	No.	Mean ± SEM	No.	Mean ± SEM	No.	Mean ± SEM
Alendronate continued for < 90 days	11	-5.1 ± 2.7	11	-9.2 ± 2.9	9	-6.6 ± 3.2
Alendronate continued for > 300 days	31	0.1 ± 1.1	30	-0.9 ± 1.1	20	1.8 ± 1.1

Emkey R. *Arth Rheum* 2003;48:1102

Caveats on Treating Low Bone Mass Among Glucocorticoid Users with CKD

- Is it osteoporosis or is it CKD MBD (or both)
- Adynamic bone disease is common (look for lowish PTH and low alk phos) and anti-resorptives are contraindicated
- IV and po bisphosphonates (with some exceptions) are contra-indicated with GFR < 30
- Denosumab associated with prolonged, severe hypocalcemia in CKD setting
- Limited evidence around PTH analogs with adynamic disease; limited effectiveness if PTH level is high
- Romosozumab use in mild CKD possible; advanced CKD anecdotal

Cejka D. *Kid Blod Press Res* 2010;33:221
Miller PD. *JBMR* 2022:37:1437

What Are Newer Strategies to Make Glucocorticoids Less Toxic?

- 11 Beta-Hydroxysteroid dehydrogenase type 1 (HSD1) Inhibitors
  - Retard conversion of prednisone to prednisolone at cellular level
  - Preliminary reports suggest reduced adverse effects on bone turnover, lipids and blood pressure
- SElective Glucocorticoid Receptor Agonists (SEGRAs)
  - Many tries and many misses to find the " Holy Grail" of a safe, effective glucocorticoid mimetic compound

Pofi R. *Endo Revs* 2023; 44:975
Othonos N. *Nat Com* 2023;13:1025

GIOP Update 2025

- Increasing evidence on glucocorticoid dose and duration effects on fracture risk, risk likely varies by fx site and across disease- 75 yrs later !
- RCT data for BMD benefit with bisphosphonates, denosumab, teriparatide and perhaps romozosumab (no regulatory indication yet) in GIOP
- Observational studies of bisphosphonates show reduced fractures
- GIOP guidelines from ACR and LATAM are very helpful but not proscriptive
- Quality of GIOP (and post-fracture) care remains suboptimal and difficult to fix in many international health systems

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