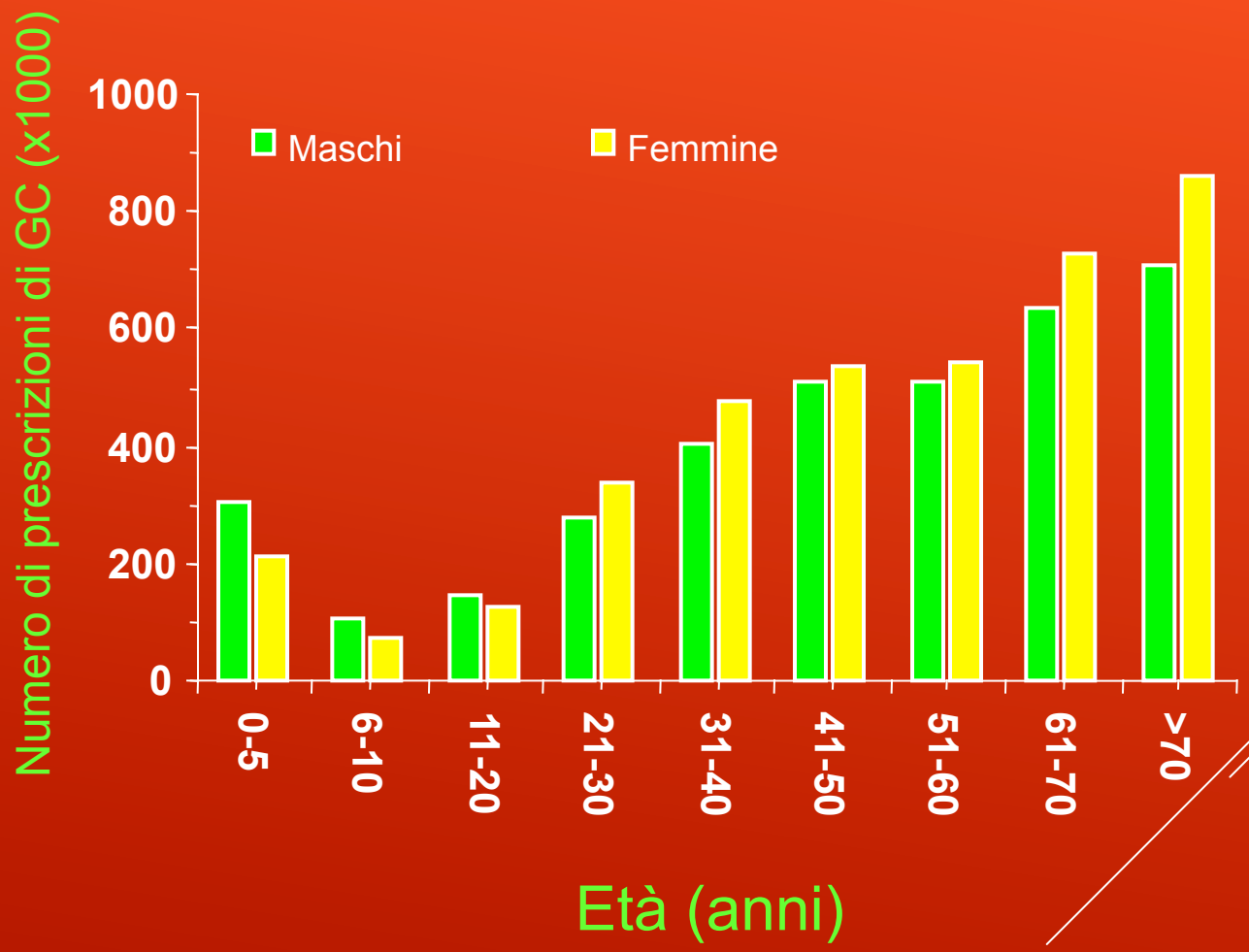
Osteoporosi da glucocorticoidi

Andrea Giustina

Chair of Endocrinology

Vita Salute San Raffaele University Milano

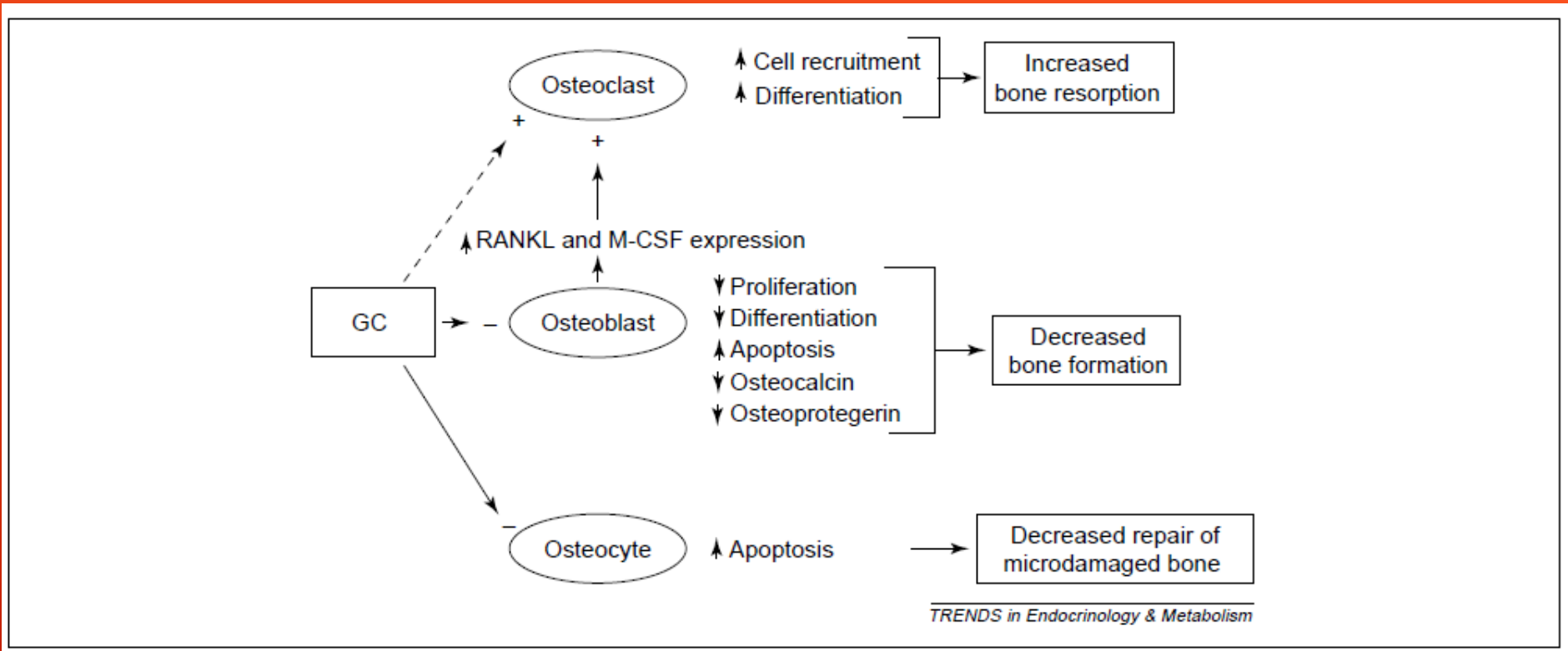
PRESCRIZIONE DI GLUCOCORTICOIDI SISTEMICI IN ITALIA



GLUCOCORTICOIDI ED OSSO/1

Aspetti fisiopatologici/1

Effetti diretti /1



Mazziotti et al., Trends Endocrinol Metab 2006

GLUCOCORTICOIDI ED OSSO/2

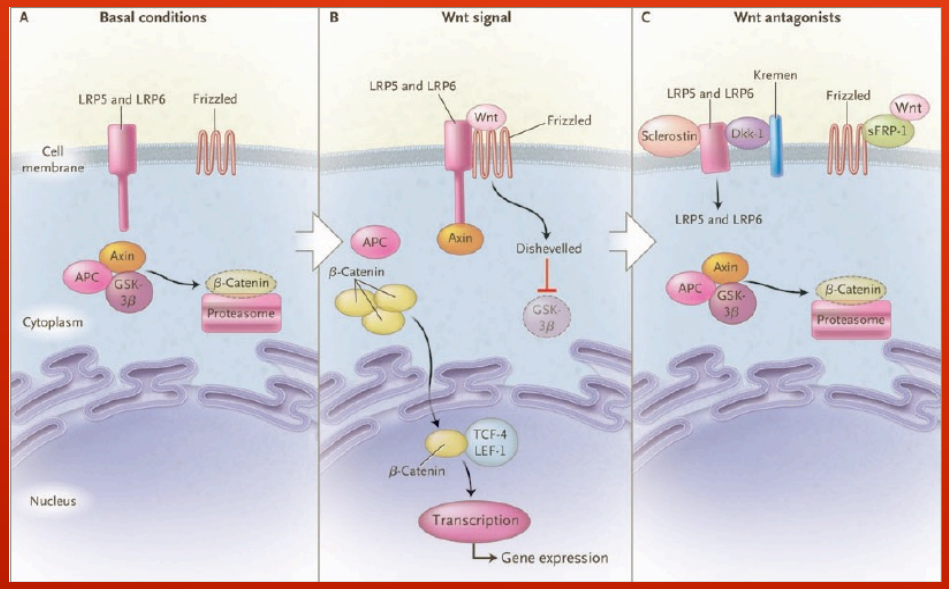
Aspetti fisiopatologici/2

Effetti diretti /2

MEDICAL PROGRESS

Mechanisms of Anabolic Therapies for Osteoporosis

Ernesto Canalis, M.D., Andrea Giustina, M.D., and John P. Bilezikian, M.D.



LRP5/LRP6 ↓

β-catenin ↓

GSK-3β ↑

Dickkopf-1 (Dkk1) ↑

sFRP-1 ↑

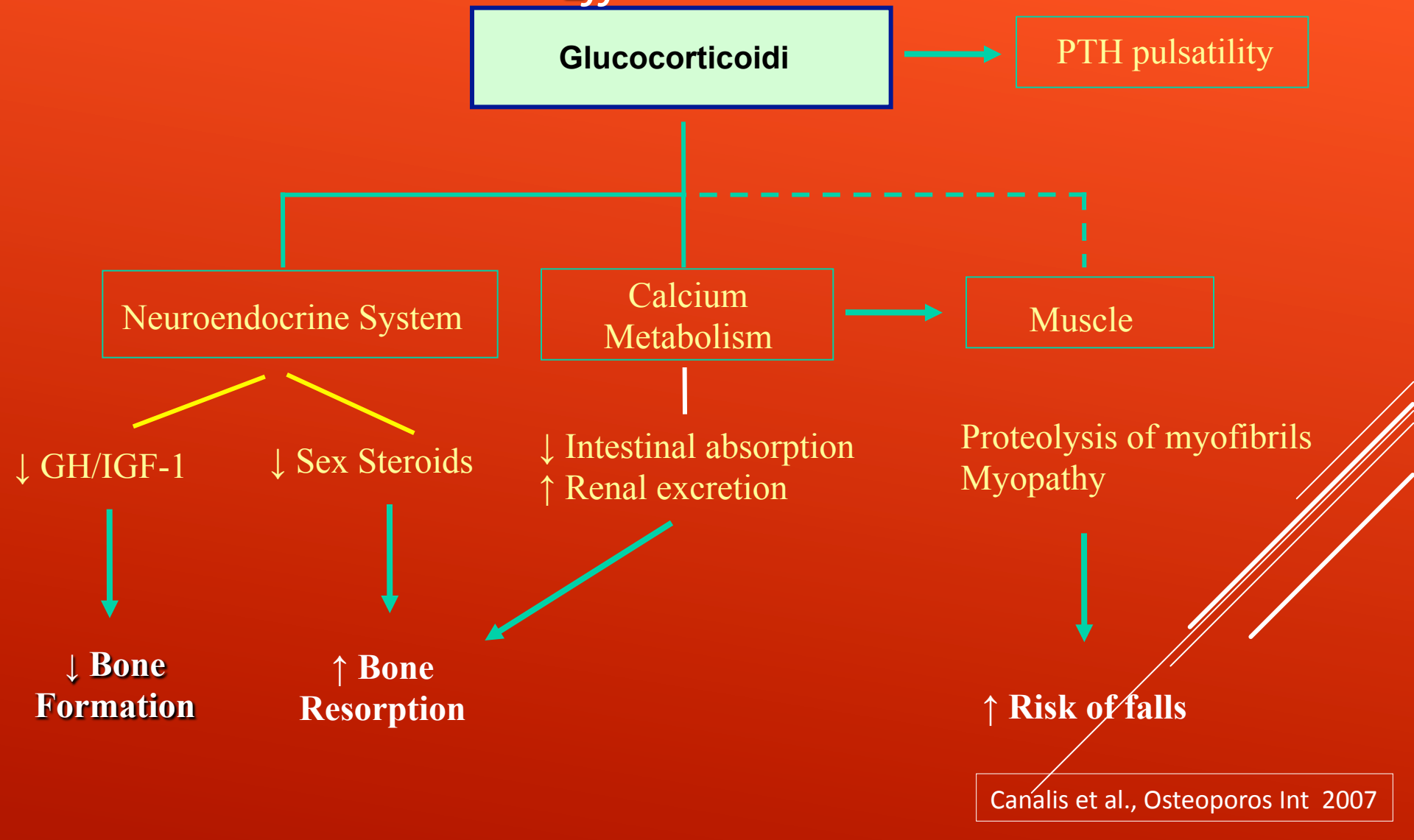
Sclerostin ?

N Engl J Med 2007;357:905-16.

GLUCOCORTICOIDI ED OSSO/3

Aspetti fisiopatologici/3

Effetti indiretti

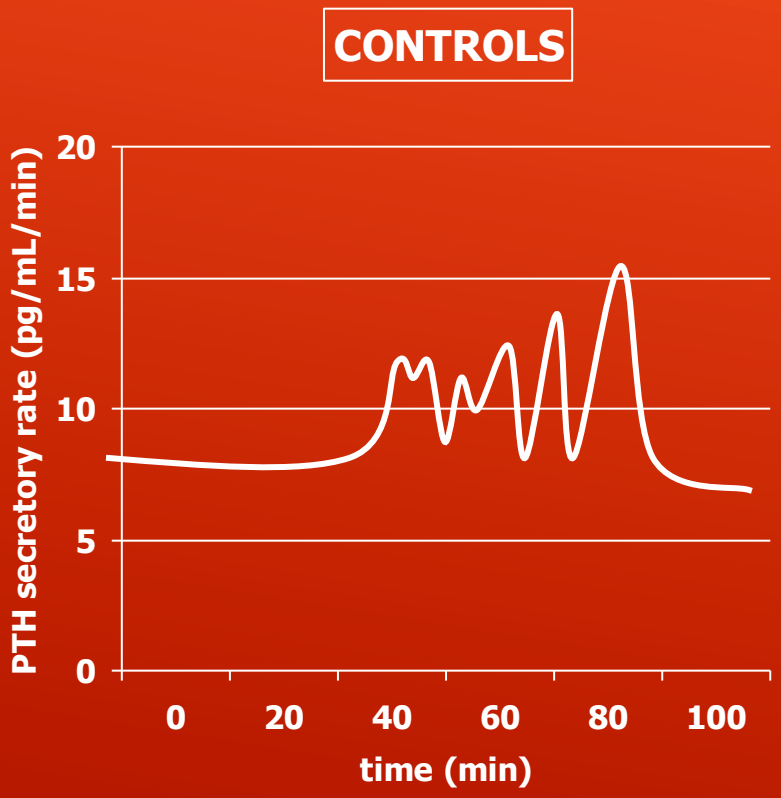


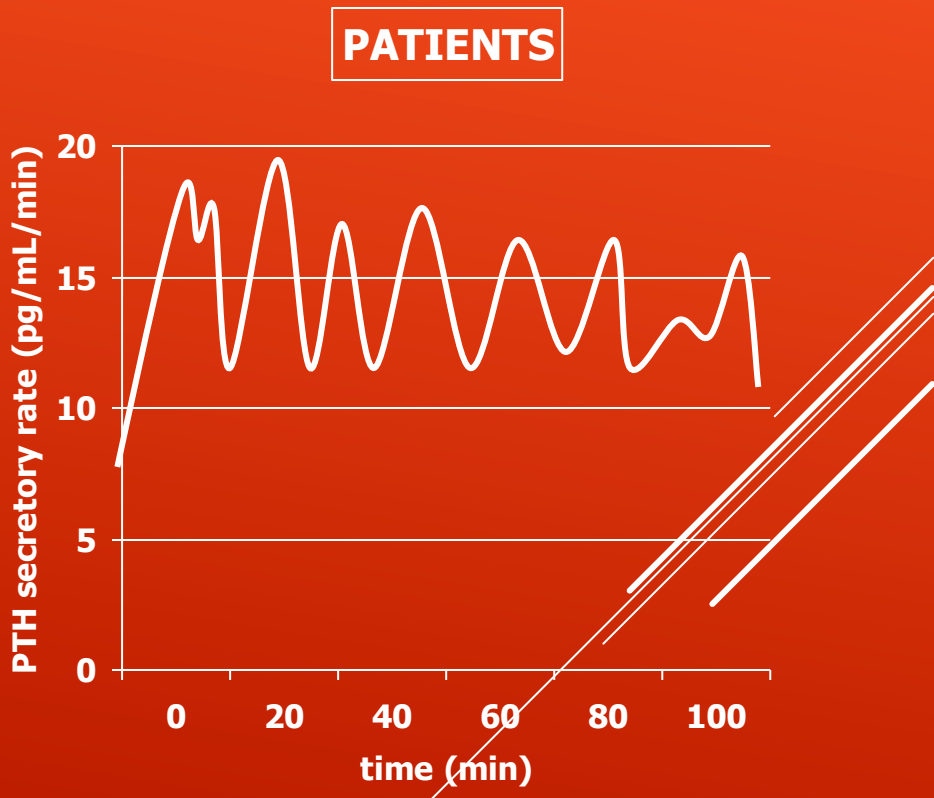
Canalis et al., Osteoporos Int 2007

GLUCOCORTICOIDI ED OSSO/4

Aspetti fisiopatologici/4

Effetti sulla secrezione pulsatile di PTH/1



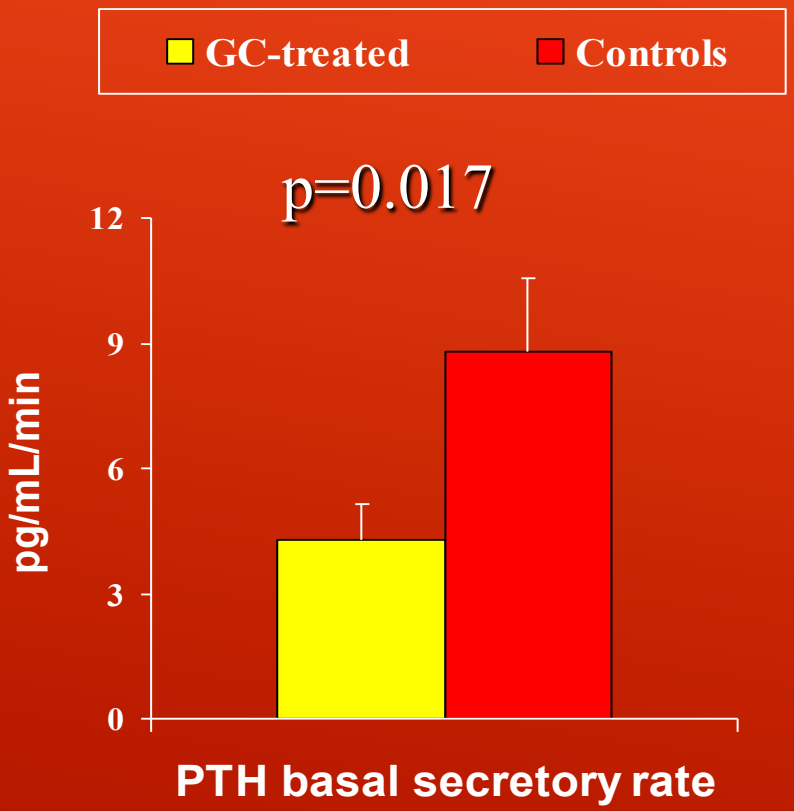


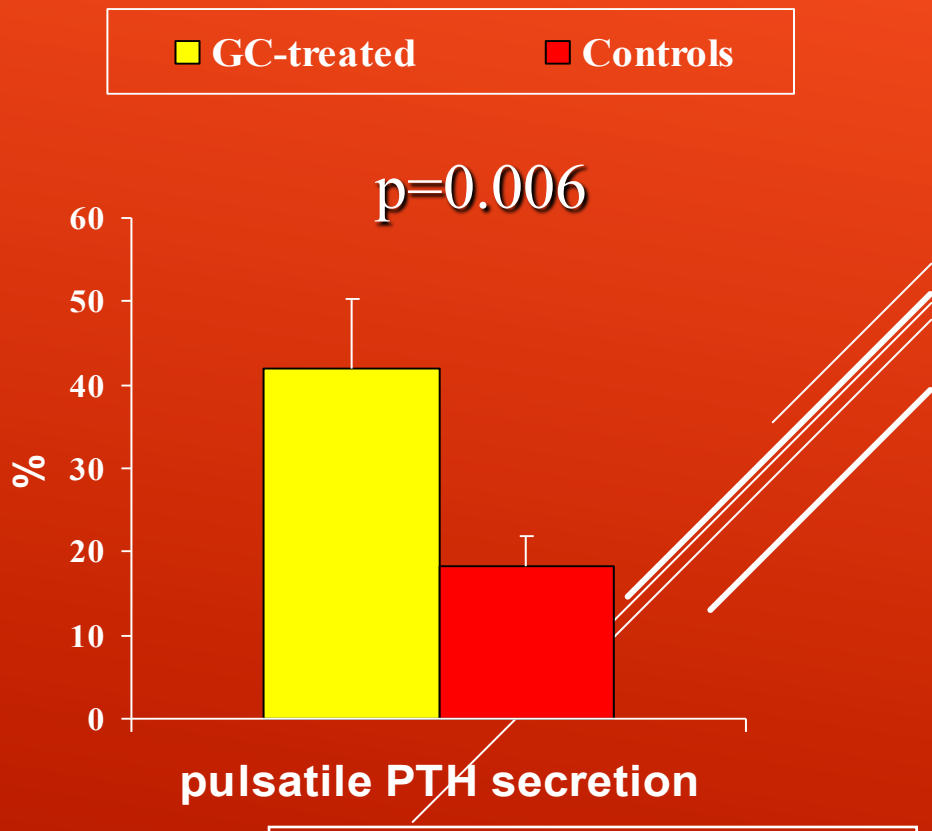
Bonadonna et al., Eur J Endocrinol 2004

GLUCOCORTICOIDI ED OSSO/5

Aspetti fisiopatologici/5

Effetti sulla secrezione pulsatile di PTH /2



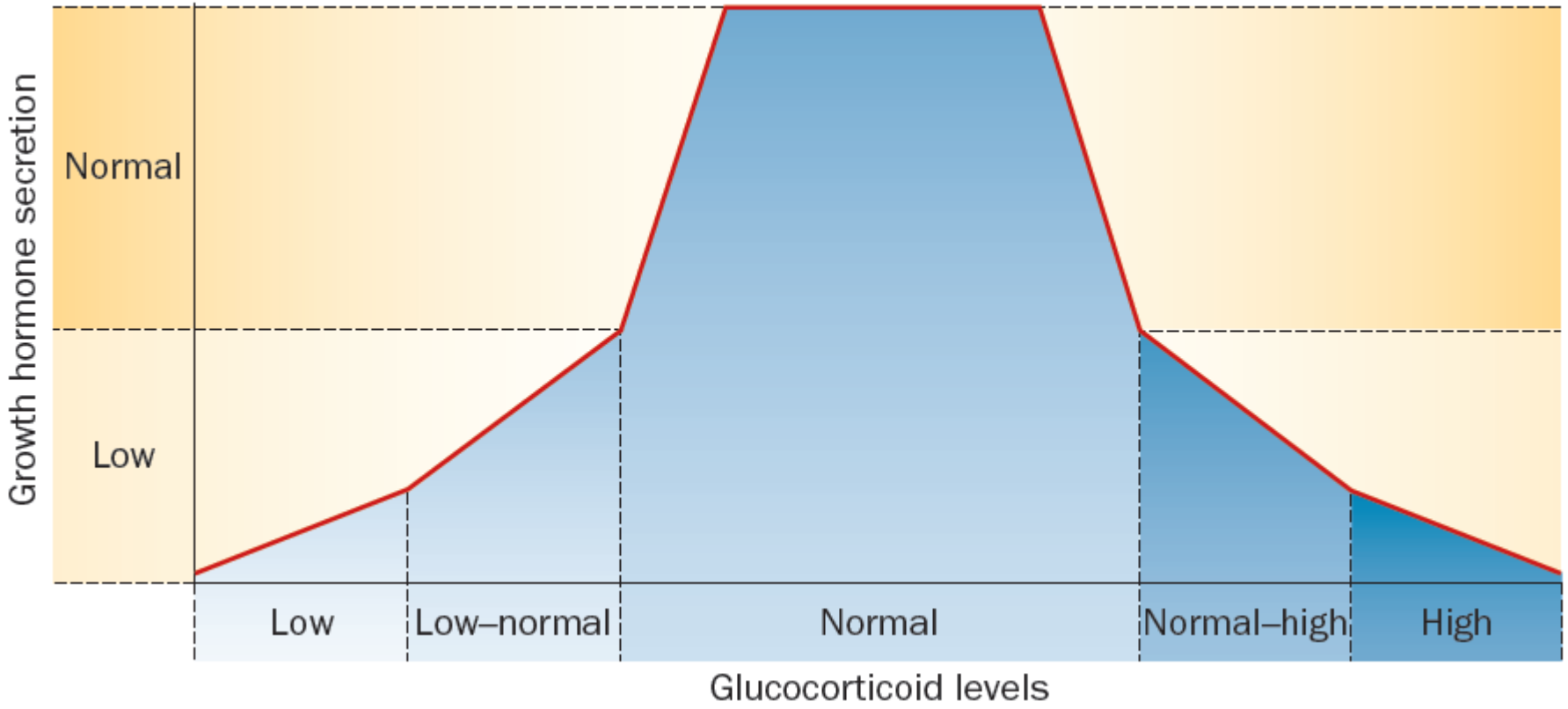


Bonadonna et al., Eur J Endocrinol 2004

GLUCOCORTICOIDI ED OSSO/6

Aspetti fisiopatologici/6

Effetti sull'asse GH-IGF-I

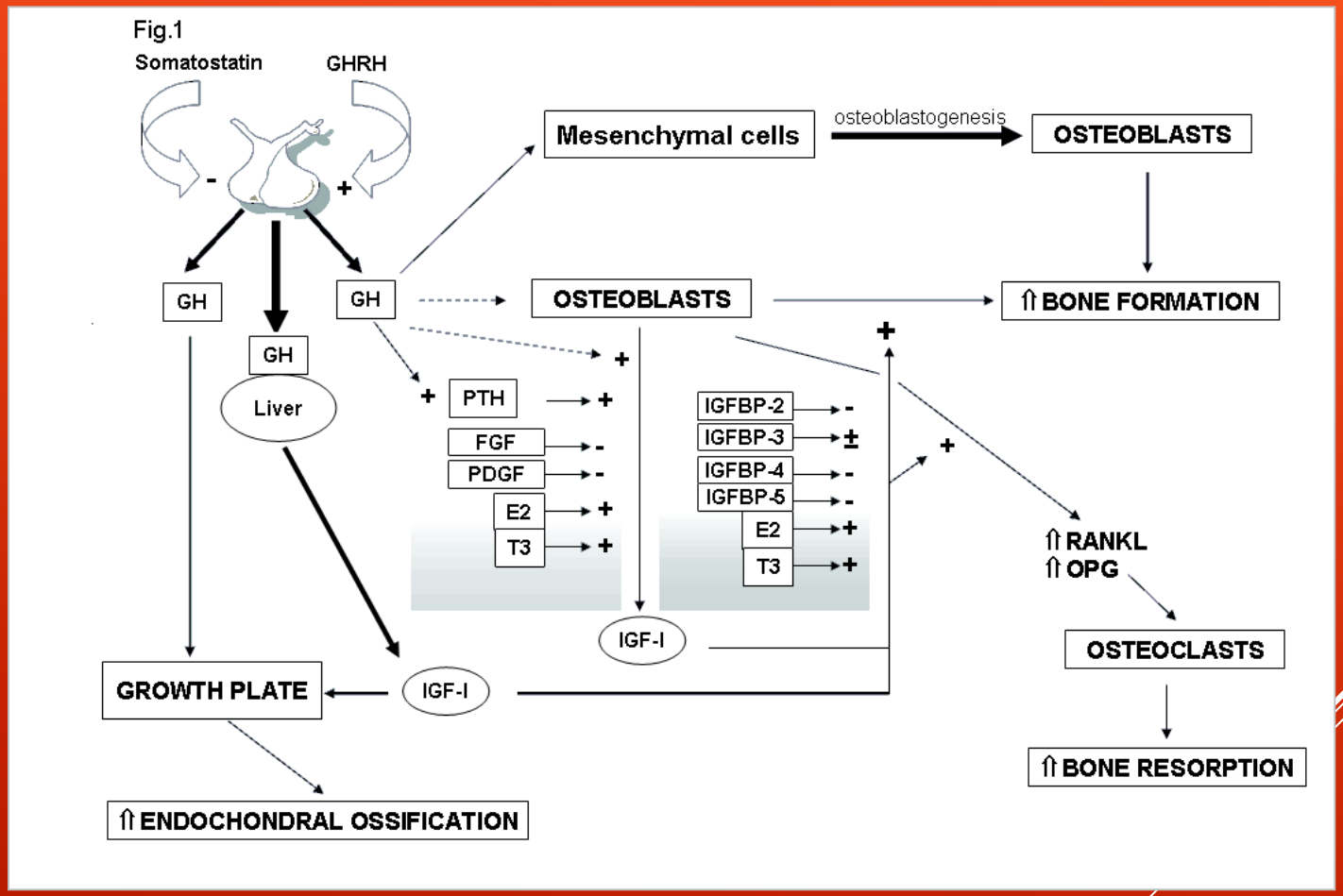


Mazziotti & Giustina, Nature Rev Endocrinol 2013

GLUCOCORTICOIDI ED OSSO/7

Aspetti fisiopatologici/7

GH-IGF-I e osteoporosi da glucocorticoidi (GIO)



Giustina et al. Endocr Rev 2008

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/1

Aspetti clinici/1

Aumentato rischio di fratture vertebrali

J Bone Miner Res 15:993-1000, 2000.

Use of oral corticosteroids and risk of fractures.

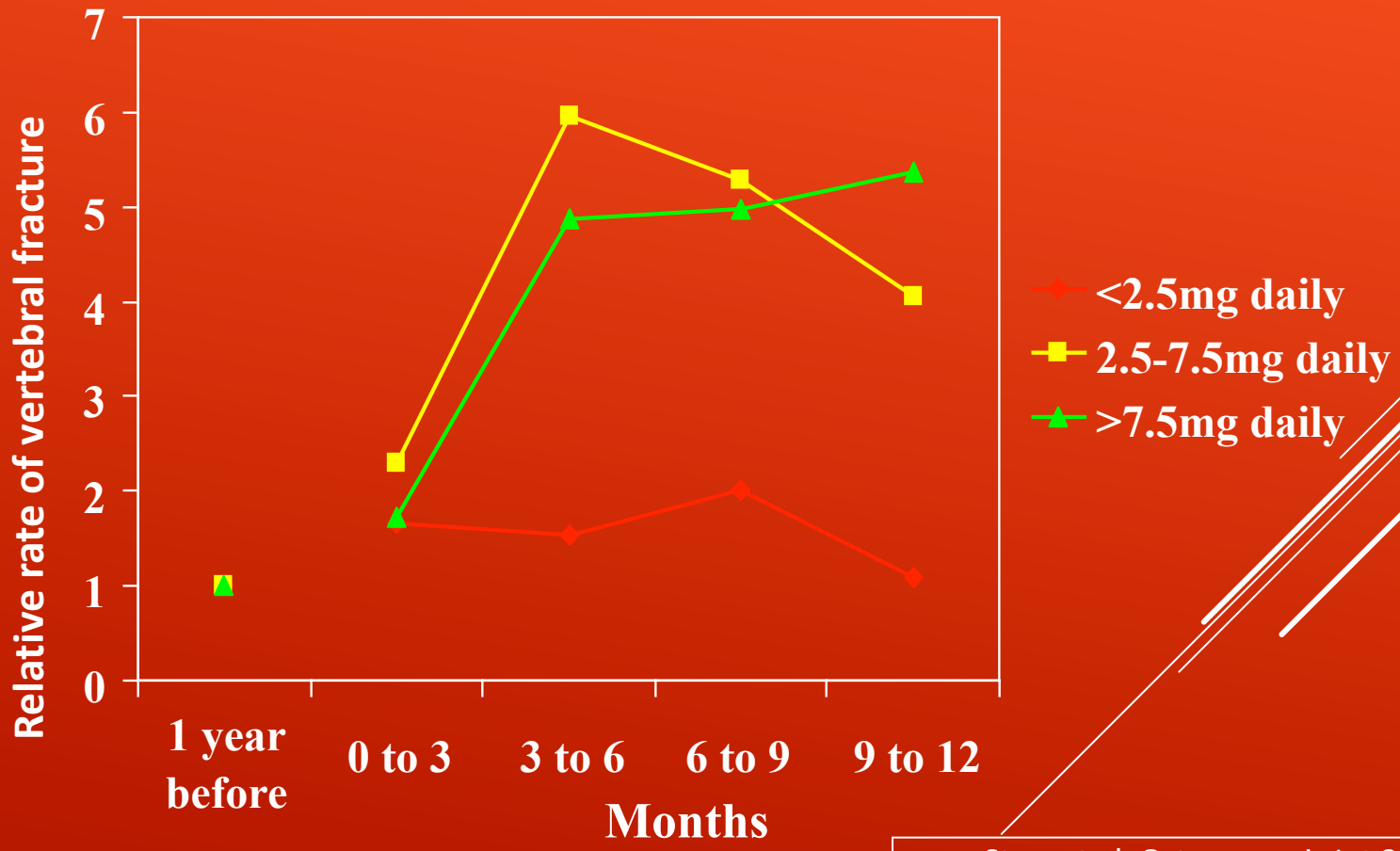
Van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C.

- **Spine > hip**
- **Dose dependent**
- **Early**
- **Reversible**

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/2

Aspetti clinici/2

Rischio precoce di fratture vertebrali correlato alla dose

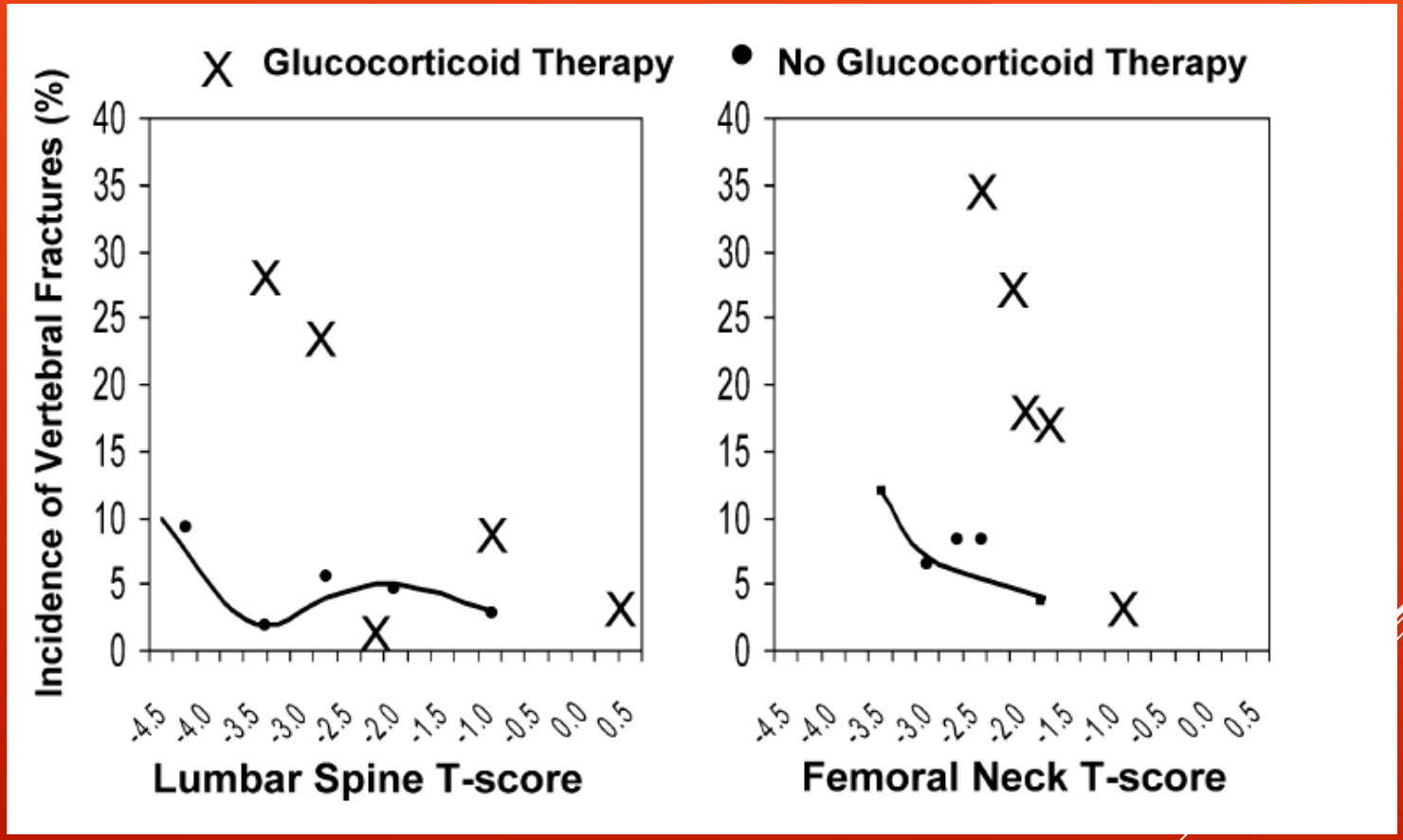


van Staa et al, Osteoporosis Int 2002

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/3

Aspetti clinici/3

Rischio di fratture aumenta anche nei pazienti con BMD normale

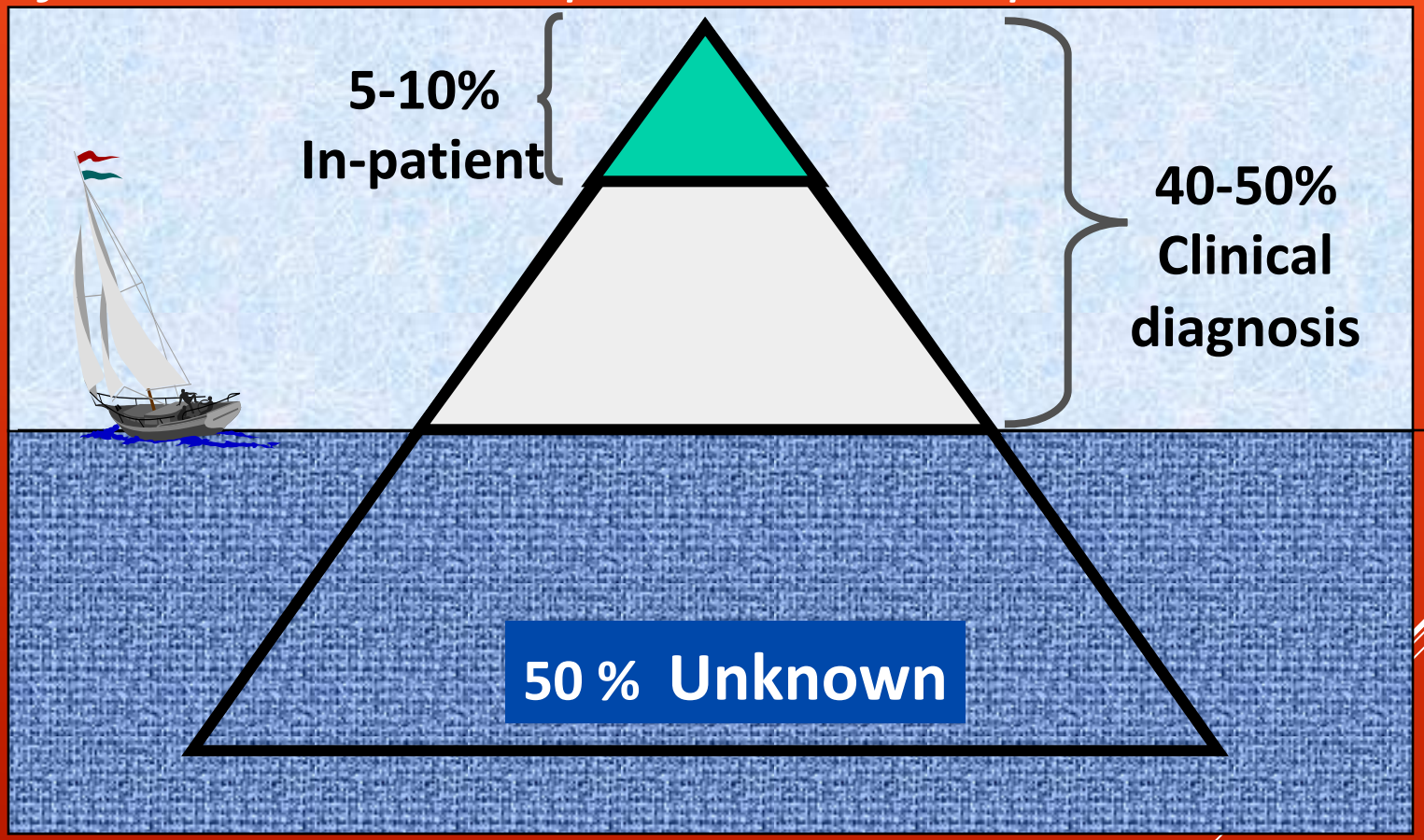


Van Staa et al., Arthritis Rheum 2003

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/4

Aspetti clinici/4

Le fratture vertebrali possono essere pauci-sintomatiche



Importanza della morfometria vertebrale

Studio GIOVE/1

ELSEVIER

Bone 39 (2006) 253–259

BONE

www.elsevier.com/locate/bone

High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: A cross-sectional outpatient study

Alberto Angeli [a,*], Giuseppe Guglielmi [b], Andrea Dovio [a], Giovanni Capelli [c], Daniela de Feo [d], Sandro Giannini [e], Ruben Giorgino [d], Luigi Moro [f], Andrea Giustina [g]

[a] *Internal Medicine, University of Turin, Italy*
[b] *Department of Radiology, Scientific Institute Hospital "Casa Sollievo della Sofferenza", S. Giovanni Rotondo, Foggia, Italy*
[c] *Public Health, University of Cassino, Frosinone, Italy*
[d] *Procter and Gamble Italy*
[e] *Internal Medicine, University of Padova, Italy*
[f] *Department of Biochemistry, Biophysics and Macromolecules Chemistry, University of Trieste, Italy*
[g] *Internal Medicine, University of Brescia, Italy*

Received 3 November 2005; revised 1 February 2006; accepted 4 February 2006
Available online 30 March 2006

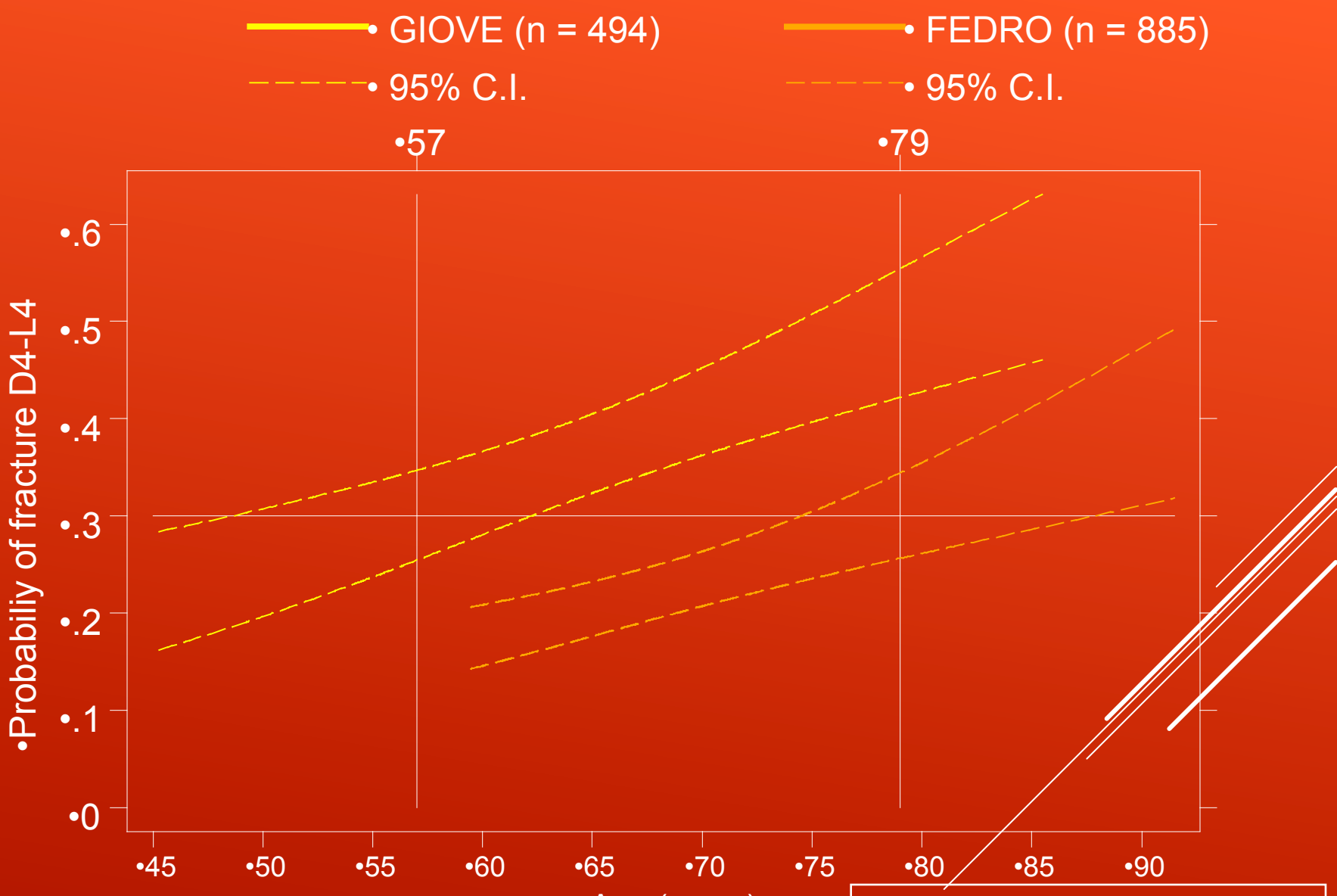
Studio GIOVE/2

- Inclusione: donne in post-menopausa e terapia cortisonica da > 6 mesi (n= 563)
- Obiettivo primario: prevalenza di deformità vertebrali radiologiche (morfometria)

	Soglia di deformità considerata	
	15% riduzione	20% riduzione
% 1+ Fratture	67,2	37,6
% 2+ Fratture	36,3	13,9
% 1+ Fratture dorsali	56,5	31,1
% 1+ Fratture lombari	22,7	9,5

Studio Giove: Angeli et al., Bone 2006

Studio GIOVE/3



Studio Giove: Angeli et al., Bone 2006

GIO AWARENESS /1

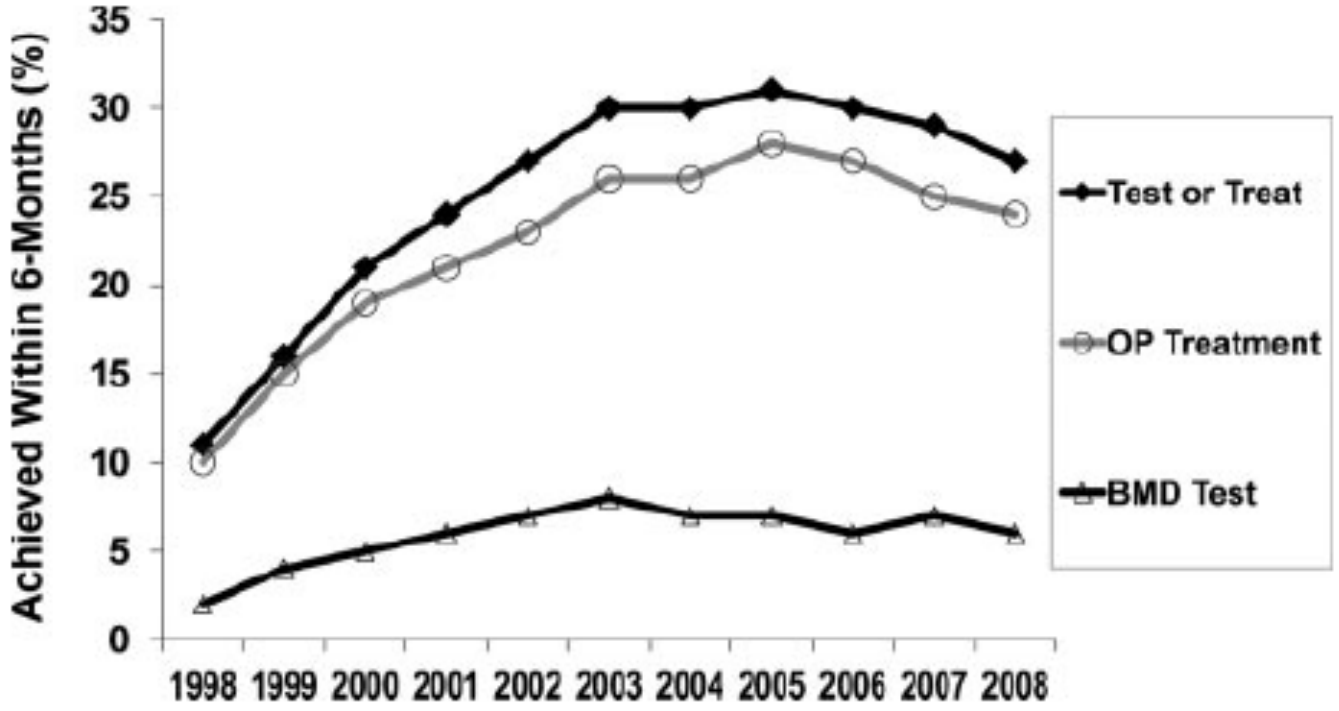


FIG. 1. Temporal trends in osteoporosis (OP) management among new initiations of long-term systemic glucocorticoids (1998–2008).

Majundar et al., JCE&M 2012

GIO AWARENESS/2

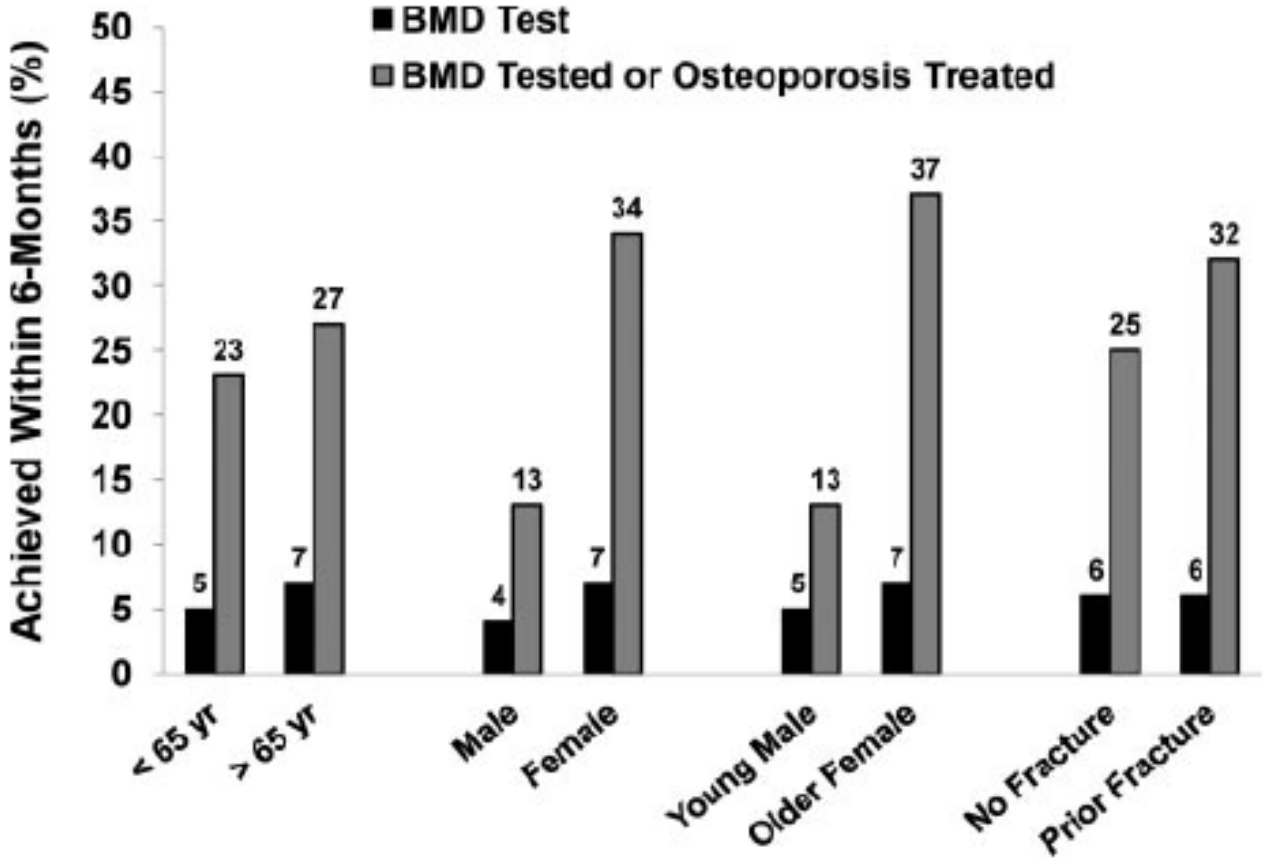


FIG. 2. Associations between quality of glucocorticoid preventive care and age, sex, and previous fracture history: exploratory analyses.

Majundar et al., JCE&M 2012

GIO AWARENESS/3

SPECIALITA'	CALCIO	VIT. D	ESERCIZIO	BMD	TERAPIA
Reumatologia (n=69)	44 (64)	44 (64)	16 (23)	39 (57)	27 (39)
Medicina Interna (n=60)	16 (27)	11 (18)	8 (13)	6 (10)	11 (18)
Pneumologia (n=47)	17 (36)	16 (34)	5 (11)	13 (35)	11 (23)
Altre (n=48)	11 (23)	12 (25)	5 (10)	15 (31)	6 (13)

Yood et al., Am Med Ass 2001

GIO

GIO AWARENESS/4

UTILITÀ DELLA DEXA

Ann Rheum Dis 2004, 63: 183-186

Access to bone densitometry increases general practitioners' prescribing treatment for osteoporosis

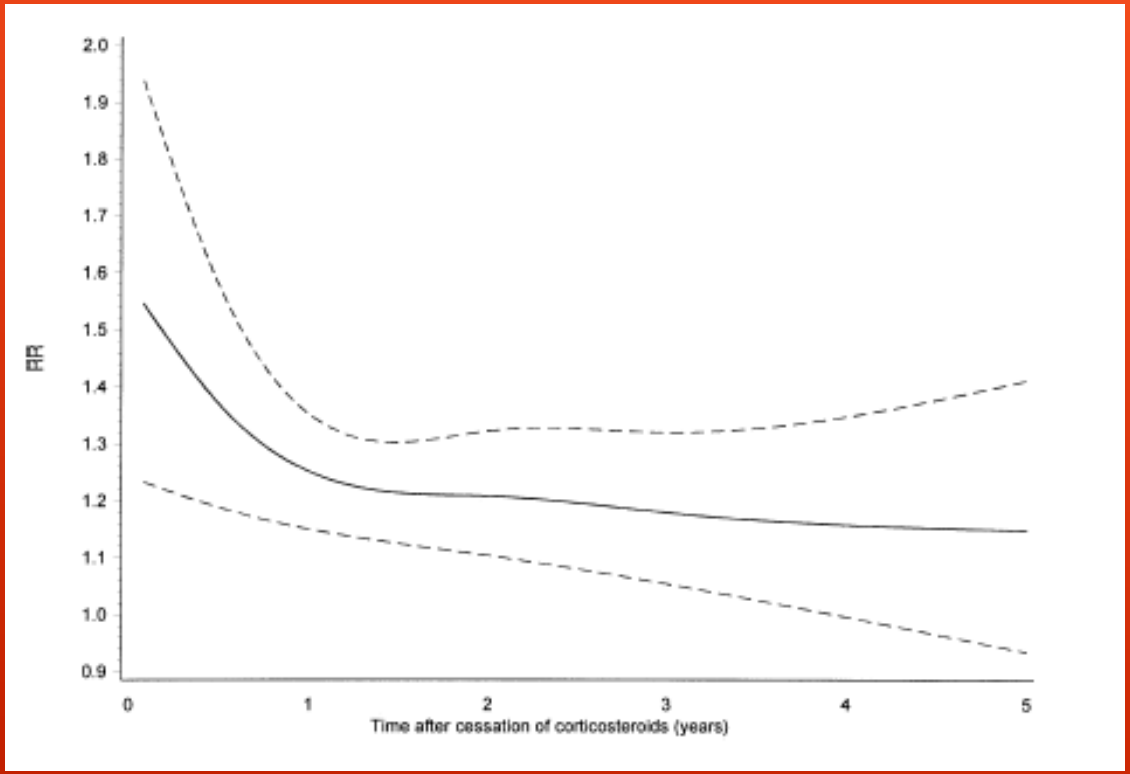
Dolan AL *et al*.

	Nessuna terapia	Ca+vit.D	Bifosfonati
DEXA			
Normale (27 casi)	22 (81.5%)	4 (14.8%)	1 (3.7%)
Patologica (21 casi)	8 (38.1%)	3 (14.3%)	10 (47.6%)
No DEXA (44 casi)	31 (70.5%)	6 (13.6%)	7 (15.9%)

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/5

Aspetti terapeutici/1

Rischio fratturativo dopo sospensione



Gli effetti della sospensione sono variabili in funzione della durata di terapia

Van Staa et al, JBMR 2000

Vestergaard et al, Calcif Tissue Int 2008

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/6

Aspetti terapeutici/2

Calcio e vitamina D/1

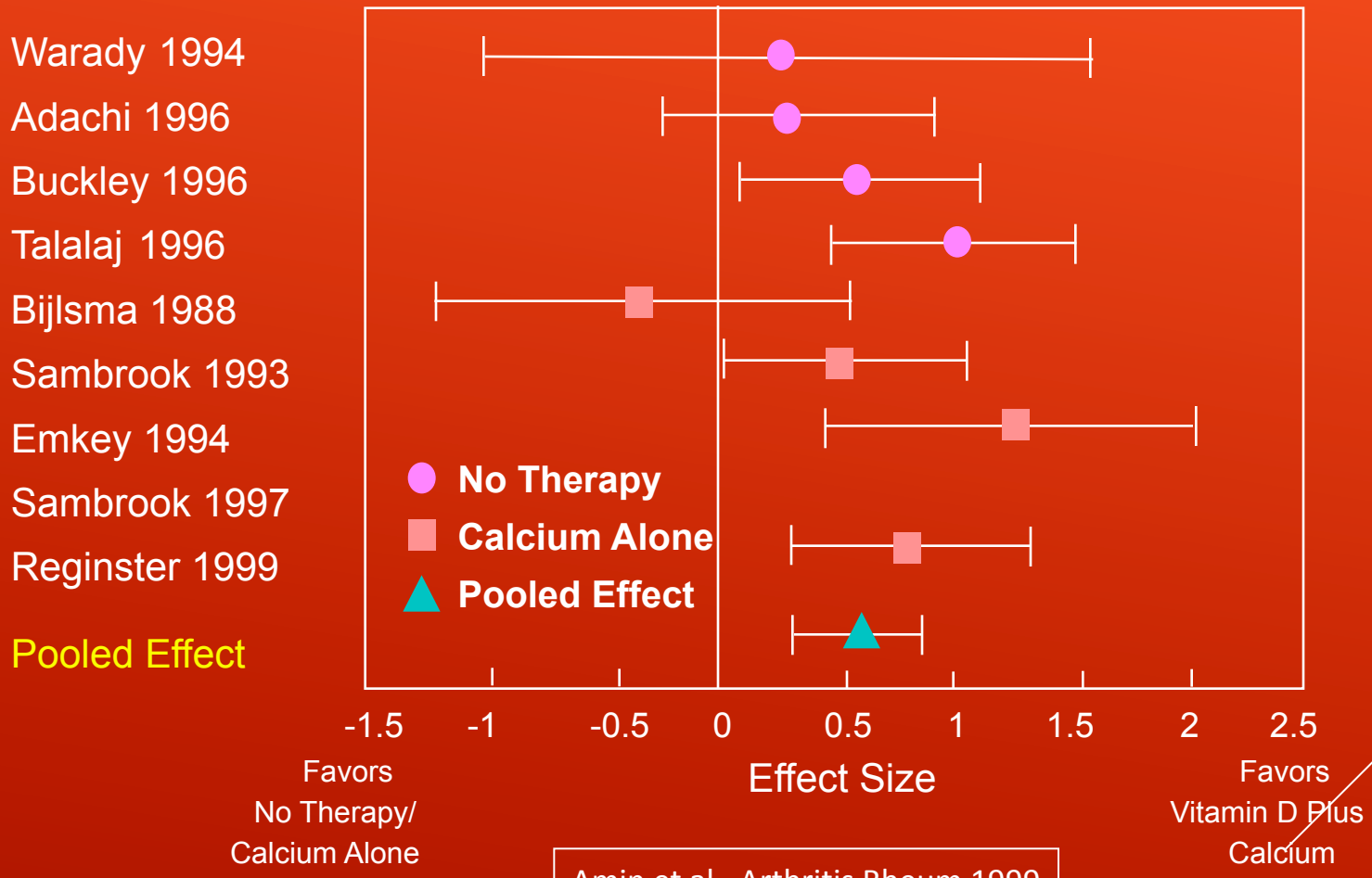
Recommendation	Level of evidence
Weight-bearing activities	C
Smoking cessation	C
Avoidance of excessive alcohol intake (2 drinks per day)	C
Nutritional counseling on calcium and vitamin D intake	C
Fall risk assessment	C
Baseline dual x-ray absorptiometry	C
Serum 25-hydroxyvitamin D level	C
Baseline height	C
Assessment of prevalent fragility fractures	C
Consider radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone 5 mg/day or its equivalent	C
Calcium intake (supplement plus oral intake) 1,200–1,500 mg/day*	**A**
Vitamin D supplementation*	**A**

Grossman et al., Arthritis Care Res 2012

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/7

Aspetti terapeutici/3

Calcio e vitamina D/2



Amin et al., Arthritis Rheum 1999

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/8

Aspetti terapeutici/4

Vitamina D/3

- Resistenza alla vitamina D
- Dose giornaliera richiesta > 2000 IU al giorno
- Target biochimico: 25OH vitamina D > 40 ng/ml

Canalis et al., Osteoporos Int 2007
Heaney RP. J Steroid Biochem Mol Biol 2005

Management "osteometabolico" del paziente in terapia cronica con glucocorticoidi/9

Aspetti terapeutici/5

Farmaci anti-osteoporotici/1

Table 1. Approved pharmacological interventions for the management of GIOP

Intervention	Dosing regimen	Formulation	Population
Alendronate	5 or 10 mg once daily 70 mg once weekly*	Oral	Not specified
Etidronate	400 mg daily for 2 weeks every 3 months	Oral	Not specified
Risedronate	5 mg once daily 35 mg once weekly*	Oral	Postmenopausal women
Zoledronate	5 mg once yearly	Intravenous infusion	Men and postmenopausal women
Teriparatide	20 μg once daily	Subcutaneous injection	Men and postmenopausal women

*Only the once daily regimens are approved for glucocorticoid-induced osteoporosis.

Compston, Clin Endocrinol 2011

Management "osteometabolico" del paziente in terapia cronica con glucocorticoidi/10

Aspetti terapeutici/6

Bisfosfonati/1

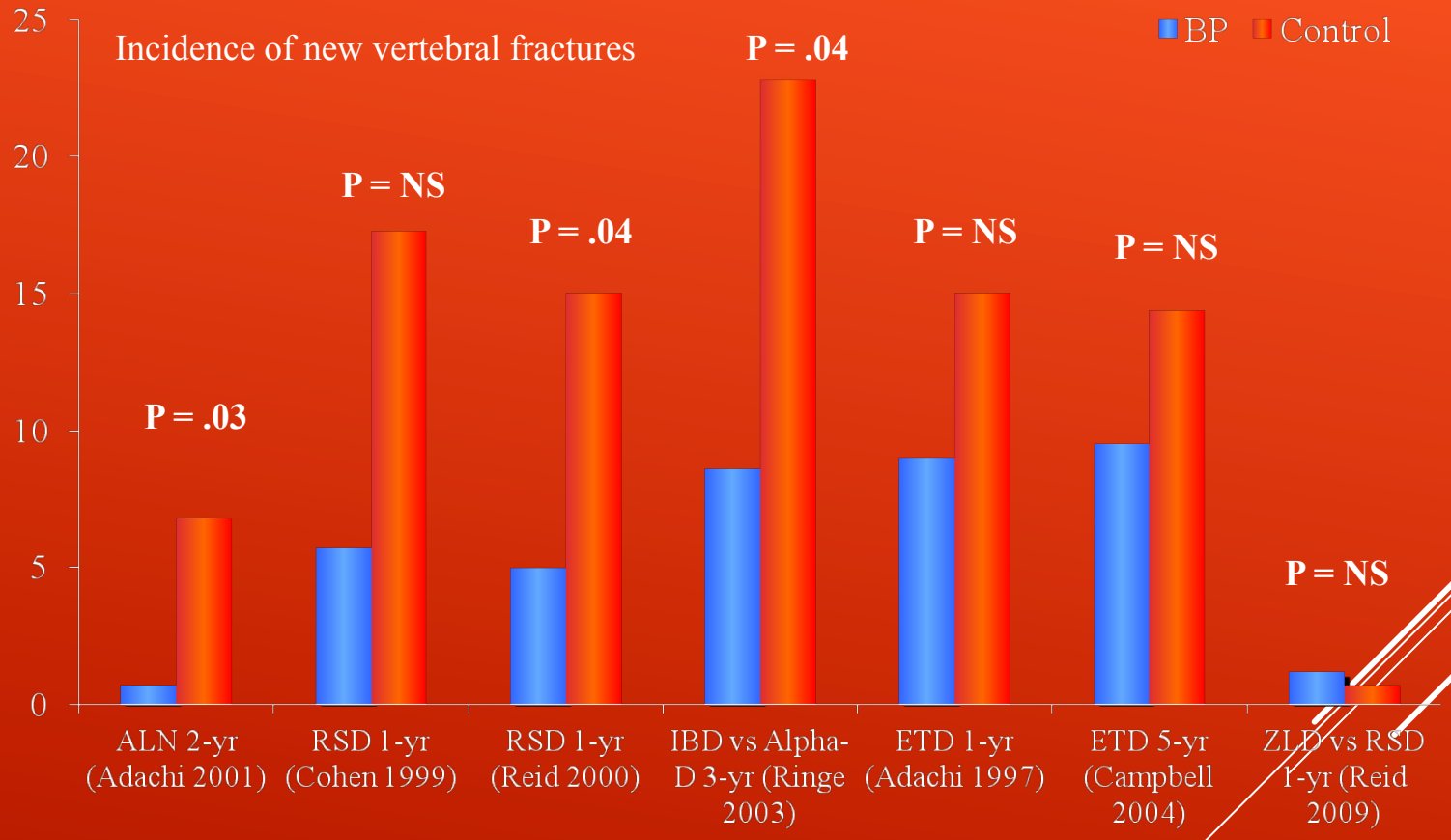
Trials	Drugs	Pts	Duration of treatment	Effect on lumbar spine (change)	Effect on incident vertebral deformities (rate)
Saag et al. 1998 [ref. 26]	Alendronate vs. placebo*	477	12 months	↑ (+2.9% vs. -0.4%)	↔ (2.3% vs. 3.7%)
Cohen et al. 1999 [ref. 27]	Risedronate vs. placebo*	224	12 months	↑ ↔ (+0.6% vs. -2.8%)	↓ ↔ (5.7% vs. 17.3%)
Reid et al. 2000 [ref. 29]	Risedronate vs. placebo*	290	12 months	↑ (+2.9% vs. +0.9%)	↓ (5% vs. 15%)
Adachi et al. 2001 [ref. 30]	Alendronate vs. placebo*	142	24 months	↑ (+3.9% vs. -0.8%)	↓ (0.7% vs. 6.8%)
Sambrook et al. 2003 [ref. 31]	Alendronate vs. Vitamin D	195	24 months	↑ (+5.9% vs. -0.7%)	↓ (0% vs. 5.3%)
Campbell et al. 2004 [ref. 32]	Etidronate vs placebo/ calcium	349	60 months	↑ (+5.0% vs. -1.5%)	↓ ↔ (9.5% vs. 14.4%)
Shane et al. 2004 [ref. 33]	Alendronate vs. Vitamin D	149	12 months	↔ (-0.7% vs. -1.7%)	↔ (6.8% vs. 3.6%)
De Nijs et al. 2006 [ref. 34]	Alendronate vs. Vitamin D	201	18 months	↑ (+2.1% vs. -1.9%)	↓ ↔ (3.0% vs. 8.0%)
Saag et al. 2007 [ref. 45]	Alendronate vs.Teriparatide	428	18 months	↑ (+3.4 vs. +7.2%)	↑ (6.1% vs. 0.6%)

Doga et al, JEI 2008

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/11

Aspetti terapeutici/7

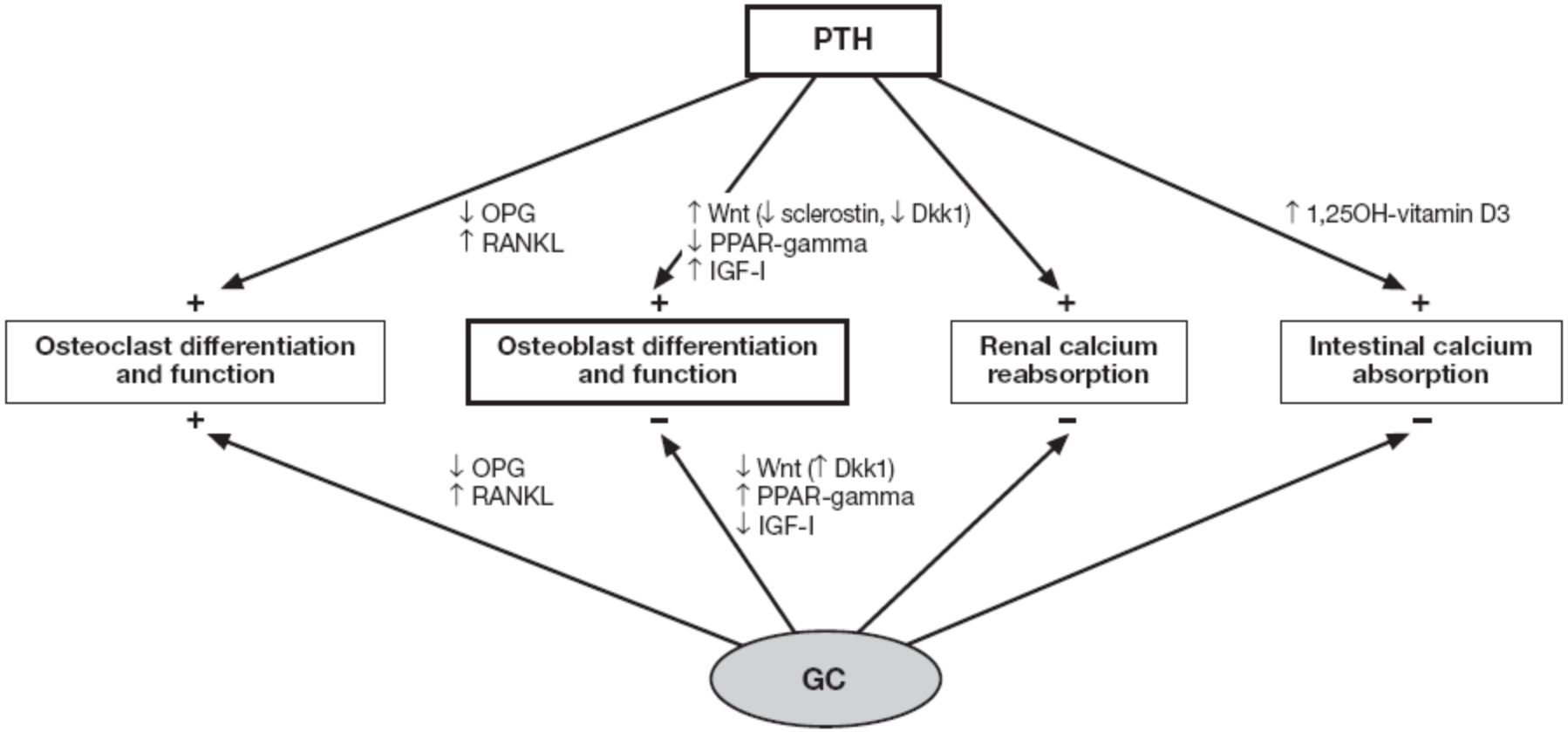
Bisfosfonati/2



Management "osteometabolico" del paziente in terapia cronica con glucocorticoidi/12

Aspetti terapeutici/8

Teriparatide/1



Carpinteri et al, J Endocrinol Invest 2011

Management "osteometabolico" del paziente in terapia cronica con glucocorticoidi/13

Aspetti terapeutici/9

Teriparatide/2

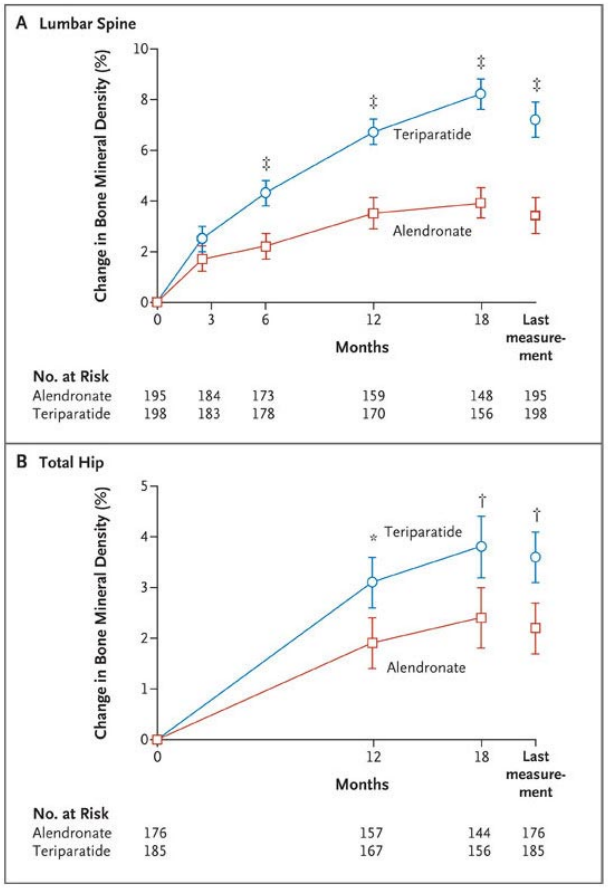


Table 2. Summary of New Fractures and Clinically Relevant Adverse Events.

Variable	Alendronate (N=214)	Teriparatide (N=214)	P Value
Fractures			
Vertebral — no./total no. (%)*			
Radiographic evidence	10/165 (6.1)	1/171 (0.6)	0.004
Clinical evidence†	3/165 (1.8)	0	0.07
Nonvertebral — no. (%)‡			
Any	8 (3.7)	12 (5.6)	0.36
Nonvertebral fragility	3 (1.4)	5 (2.3)	0.46

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

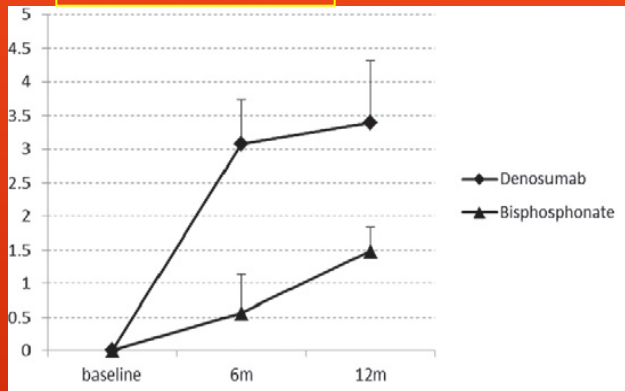
Saag et al, N Eng J Med 2007
Saag et al, Arthritis Rheum 2009

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/14

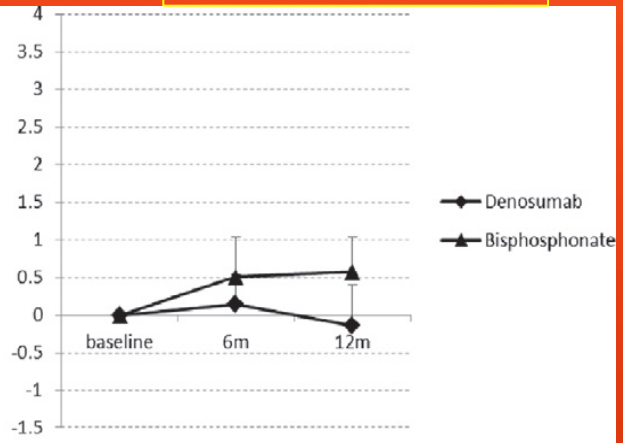
Aspetti terapeutici/10

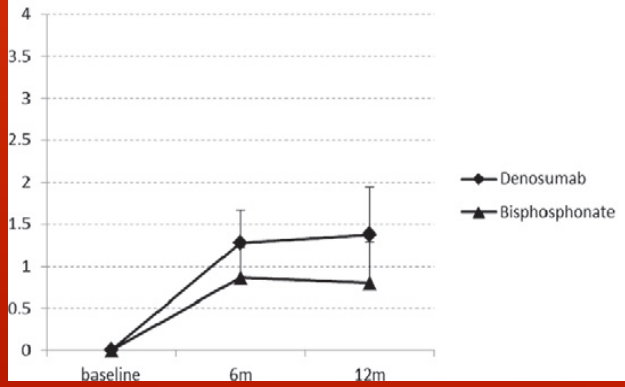
Denosumab/1

BMD lombare



BMD femore in toto





BMD collo femore

In patients receiving long-term glucocorticoids, switching from oral bisphosphonates to denosumab
resulted in greater gain of spinal BMD

Mok et al., Bone 2015

MANAGEMENT "OSTEOMETABOLICO" DEL PAZIENTE IN TERAPIA CRONICA CON GLUCOCORTICOIDI/15

ASPETTI TERAPEUTICI/11

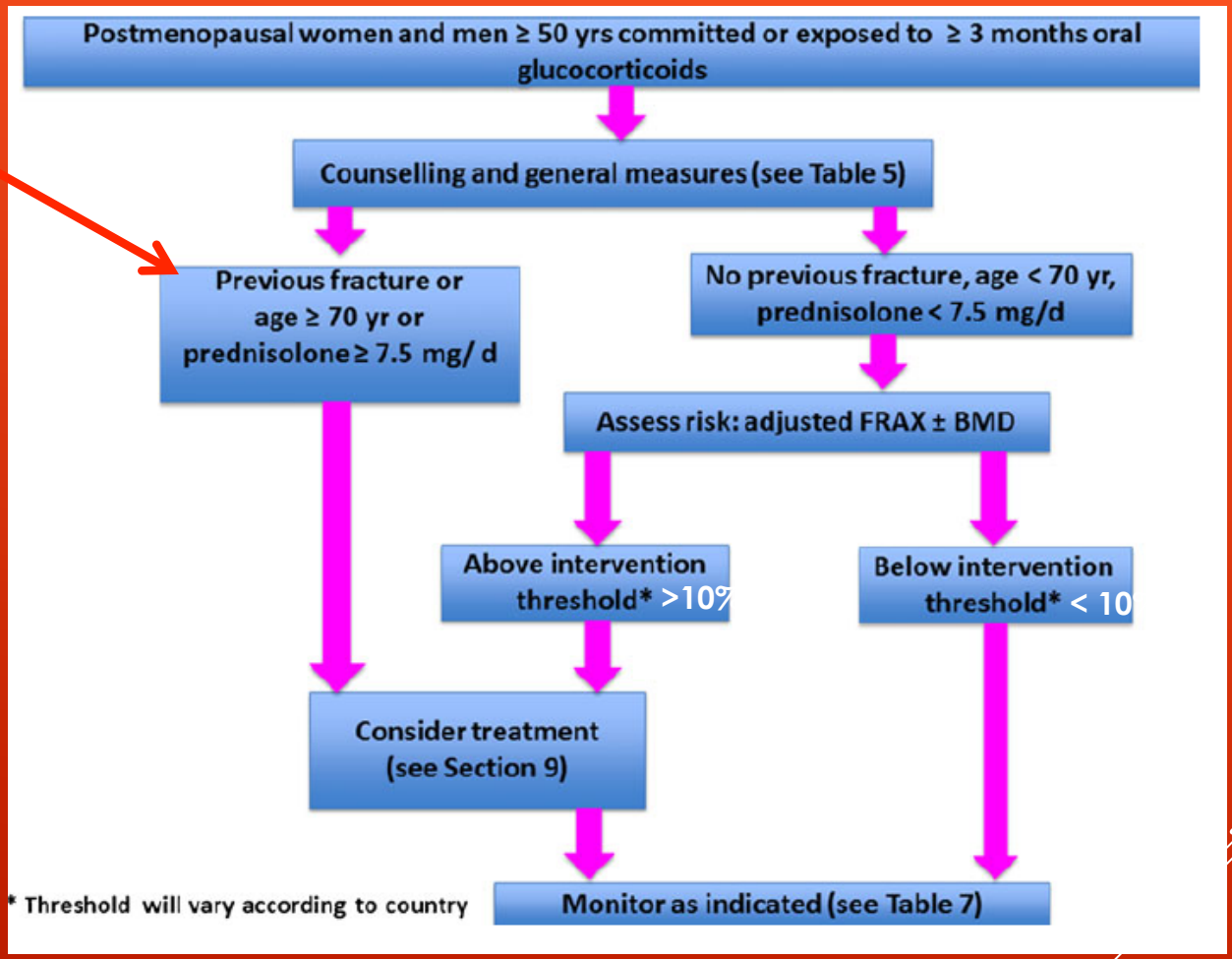
DENOSUMAB/2

1. Saag et al (LDE 2018): Trial di 24 mesi Denosumab superiore a Risedronato su LS BMD sia nei pazienti in terapia cronica (4.4% vs 2.3%) che in coloro che umiziavano la terapia steroidea (3.8 vs 0.8%). Sulla base di questi dati approvazione indicazione GIO EMA e FDA (giugno 2018) e aggiornamento RCP AIFA (luglio 2018);
2. Saag et al. (LDE 2018): Non differenza significativa sia per insorgenza di effetti collaterali rispetto a risedronato (comprese le infezioni) che per fratture;
3. *Iwamoto et al (JBMM 2018): Denosumab aumenta LS BMD a 6 e 12 mesi (4%) indipendentemente dal trattamento precedente (BPs o Teriparatide)*

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/16

Linee Guida/1

Cliniche/
Morfometriche



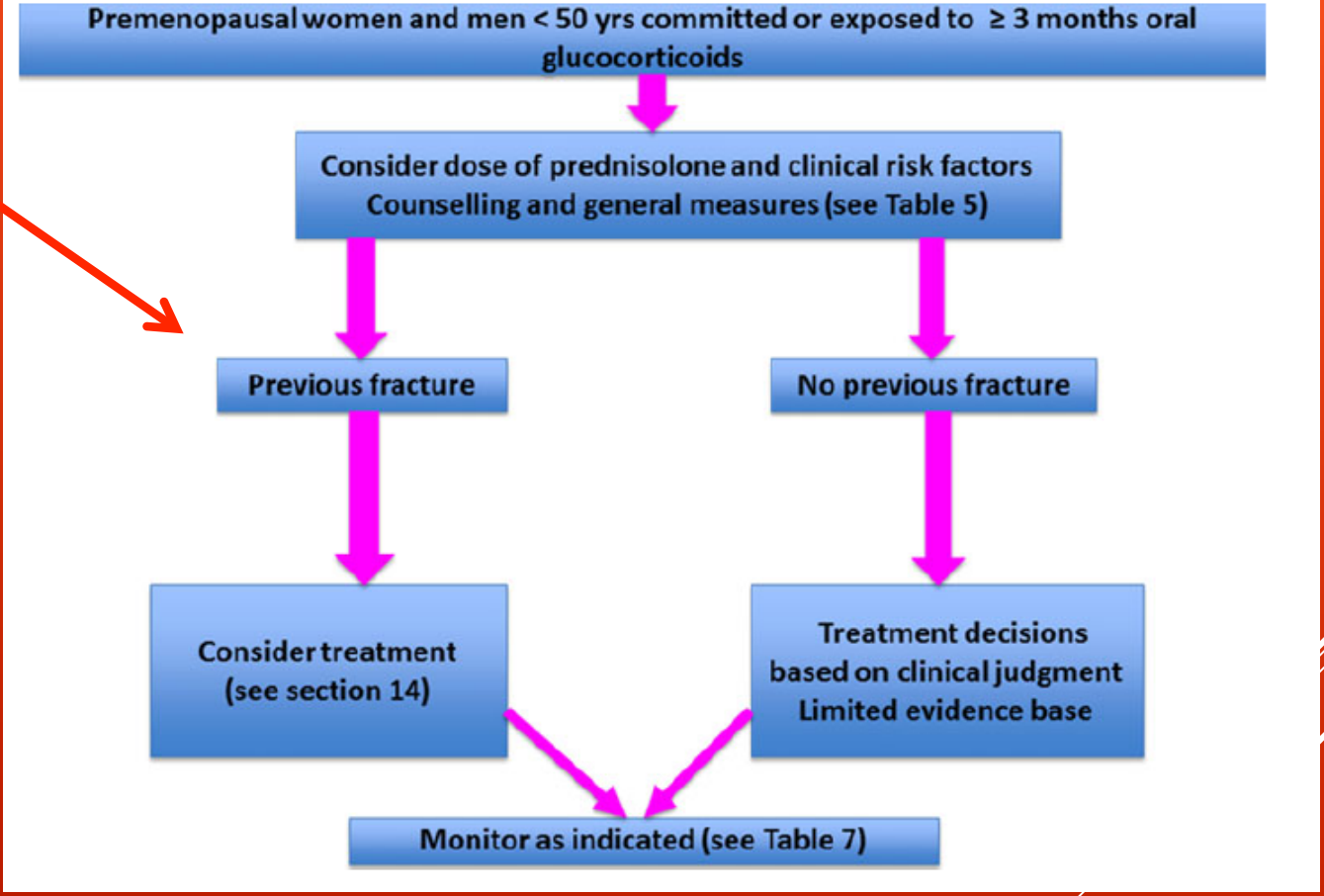
L’algoritmo FRAX prende in considerazione: età, sesso, familiarità per fratture, assunzione di alcool, fumo, pregresse fratture

Lekamwasam et al., Osteoporos Int 2012

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/17

Linee Guida/2

Cliniche/
Morfometriche



Lekamwasam et al., Osteoporos Int 2012

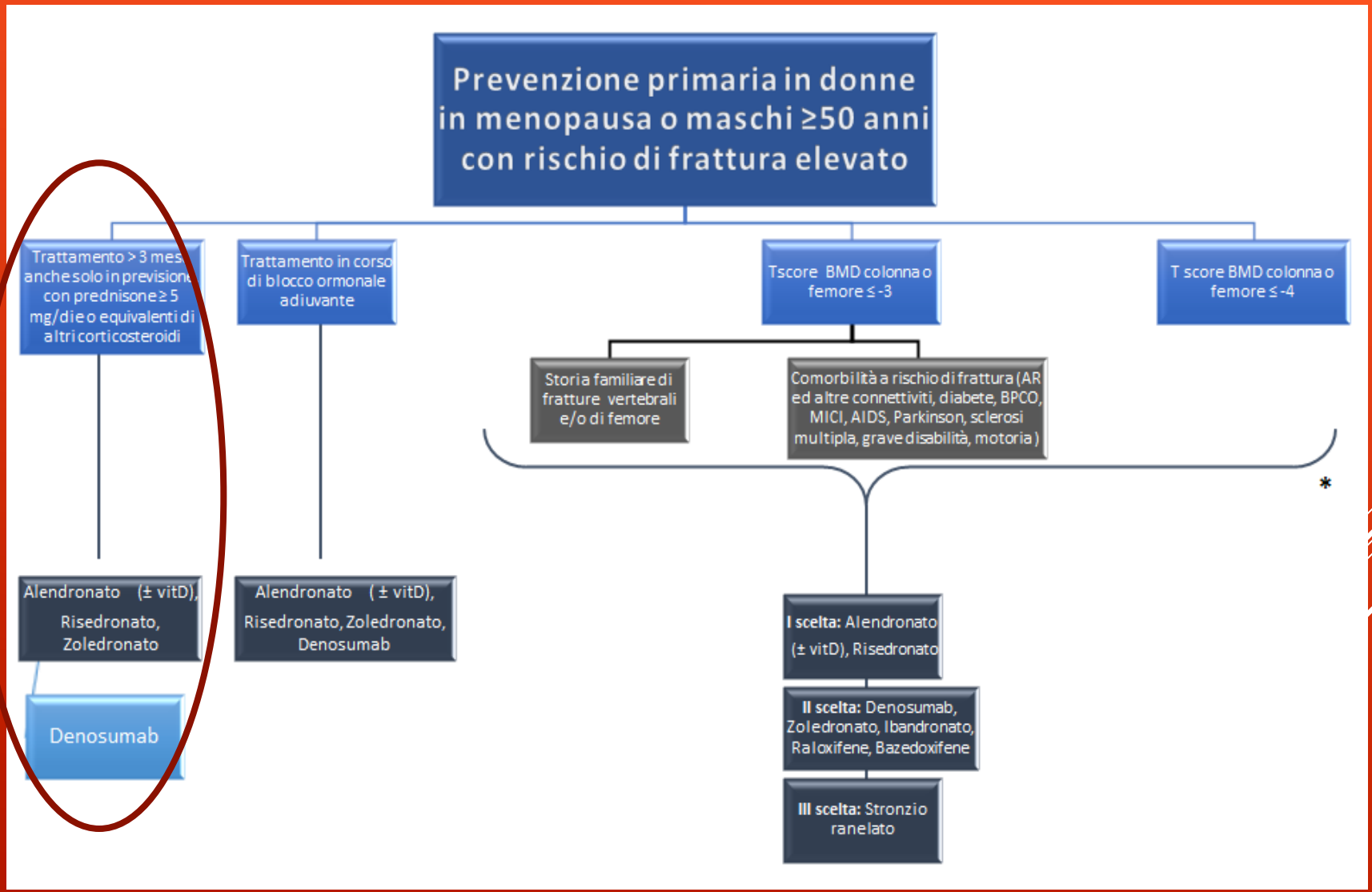
MANAGEMENT "OSTEOMETABOLICO" DELLA TERAPIA CRONICA CON GLUCOCORTICOIDI/18

LINEE GUIDA/3

1. Buckley et al (Arthritis Rheumatol 2017): Nuove linee guida GIO ACR: Per la prevenzione nei pazienti ad alto rischio di frattura che iniziano terapia cortisonica BP orali da preferire vs IV BP (peggiore profilo di rischio vs Teriparatide (costi e burden della terapia) vs Denosumab (non dati su pazienti con terapie immunosoppressive precedenti) vs Raloxifene (solo donne in PM, mancanza di evidenze di rapporto costo beneficio favorevole);
2. Pazienti non responder ai BP orali (nuova frattura o riduzione BMD) switch a Teriparatide o Denosumab (BP IV solo se problema di compliance);
3. *Pazienti che continuano (ma anche che sospendono) terapia cortisonica e ad alto rischio di frattura anche se hanno raggiunto i 5 anni di terapia con BP orali consigliato prolungare terapia con BP orali (7-10 anni);*

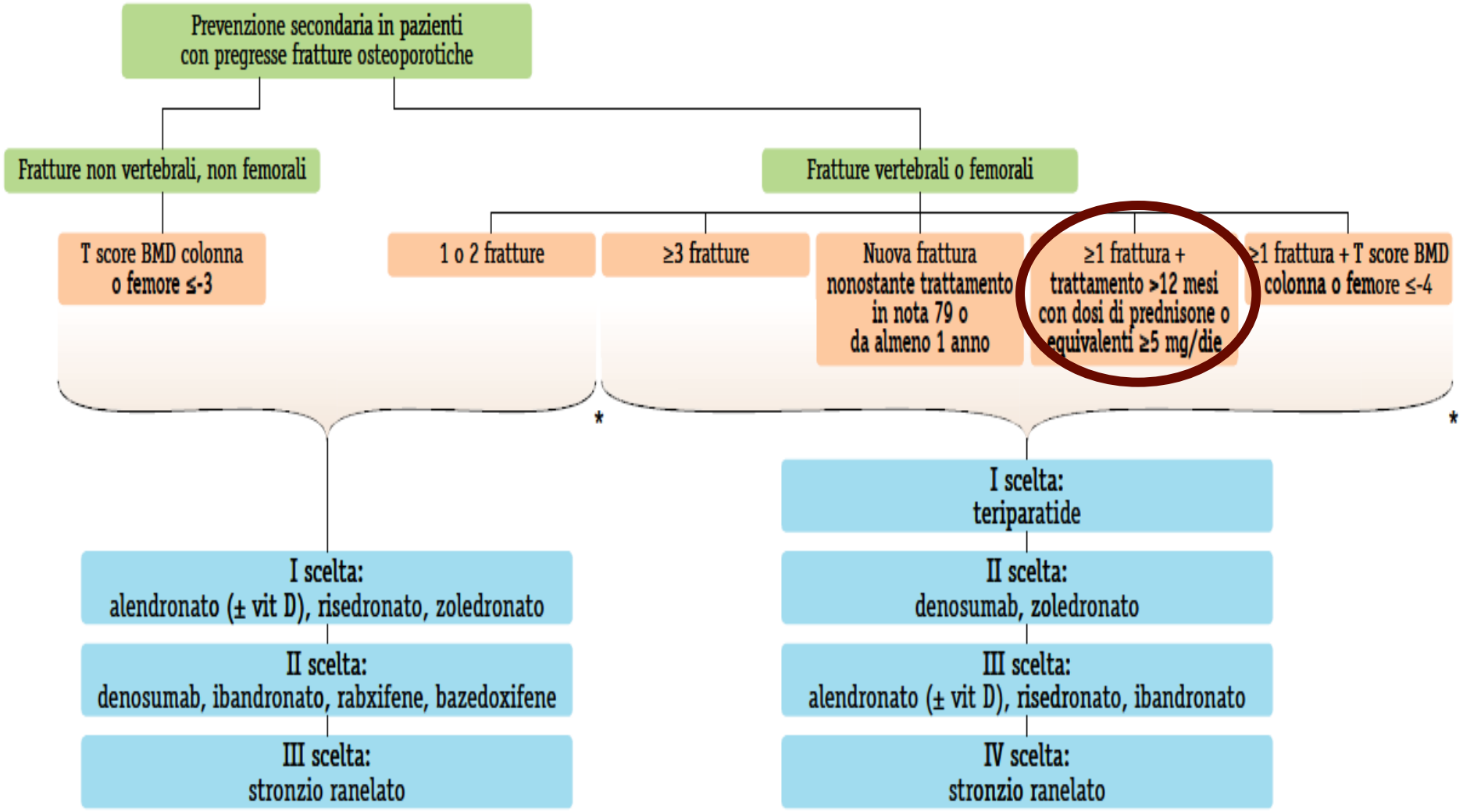
MANAGEMENT "OSTEOMETABOLICO" DEL PAZIENTE IN TERAPIA CRONICA CON GLUCOCORTICOIDI/19

RIMBORSABILITA' SECONDO LA NUOVA NOTA 79/1



MANAGEMENT "OSTEOMETABOLICO" DEL PAZIENTE IN TERAPIA CRONICA CON GLUCOCORTICOIDI/2'

RIMBORSABILITA' SECONDO LA NUOVA NOTA 79/2



Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi/21

Aspetti dibattuti

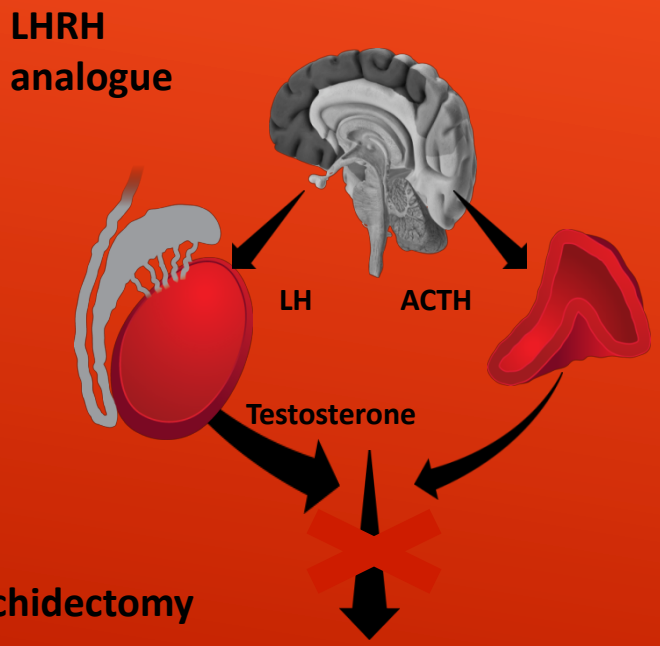
- Ruolo della morfometria vertebrale nella definizione del rischio fratturativo e della diagnosi di GIO.
- Durata del trattamento anti-osteoporotico (clinical trials < 3 anni).
  - Cosa fare alla sospensione del cortisonico
  - Safety dei trattamenti anti-osteoporotici cronici
- Prevenzione delle fratture non-vertebrali (fratture di femore).
- Quando usare il teriparatide (solo nei pazienti “ad alto rischio”?)
- Efficacia delle terapie di associazione (zol + 1-34PTH)
- Trattamento delle donne in pre-menopausa (morfometria!)

Hansen et al., J Bone Miner Res 2011

ABIRATERONE NEL TRATTAMENTO DEL CARCINOMA PROSTATICO

RAZIONALE

ADT reduces circulating testosterone by 90–95%[2,3]

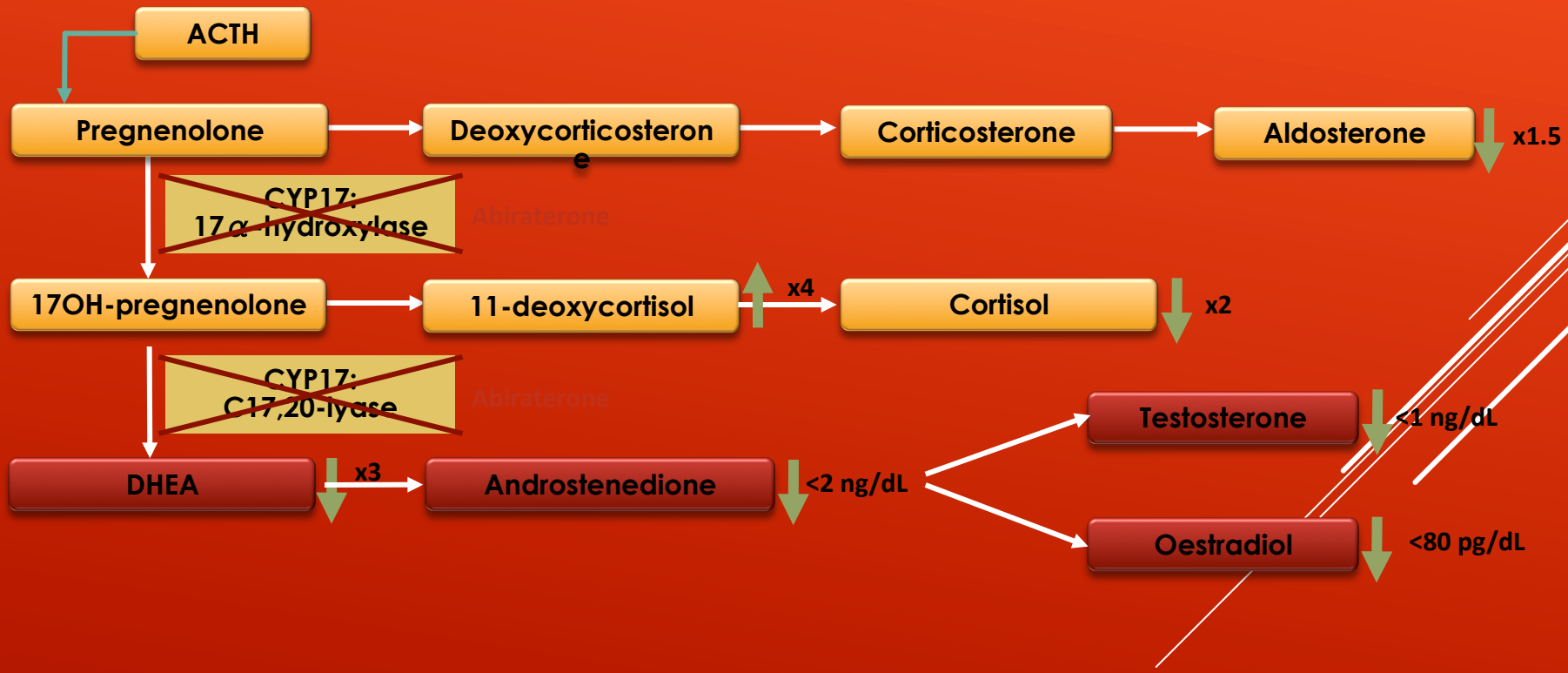


TUMOUR PROGRESSION

Androgen production by the adrenal gland remains unaffected

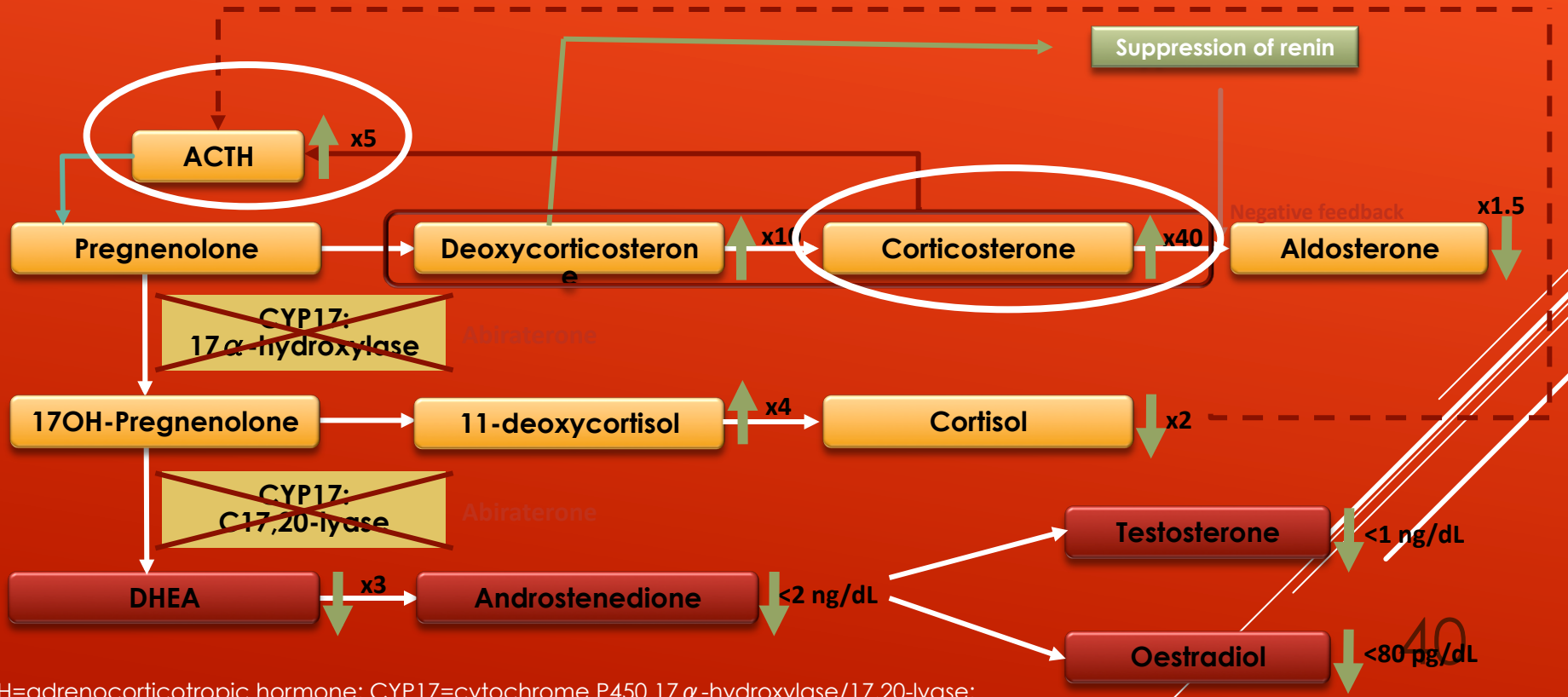
TERAPIA CON ABIRATERONE: MODELLO CLINICO DI DEFICIT ACQUISITO DELLA 17-IDROSSILASI/1

- Abiraterone is a selective and irreversible inhibitor of CYP17 – a key enzyme required for androgen biosynthesis



TERAPIA CON ABIRATERONE: MODELLO CLINICO DI DEFICIT ACQUISITO DELLA 17-IDROSSILASI/2

Eccesso di mineralcorticoidi dipendente dall'aumento di ACTH secondario al deficit di cortisolo (ipertensione arteriosa, edemi, ipopotassiemia)

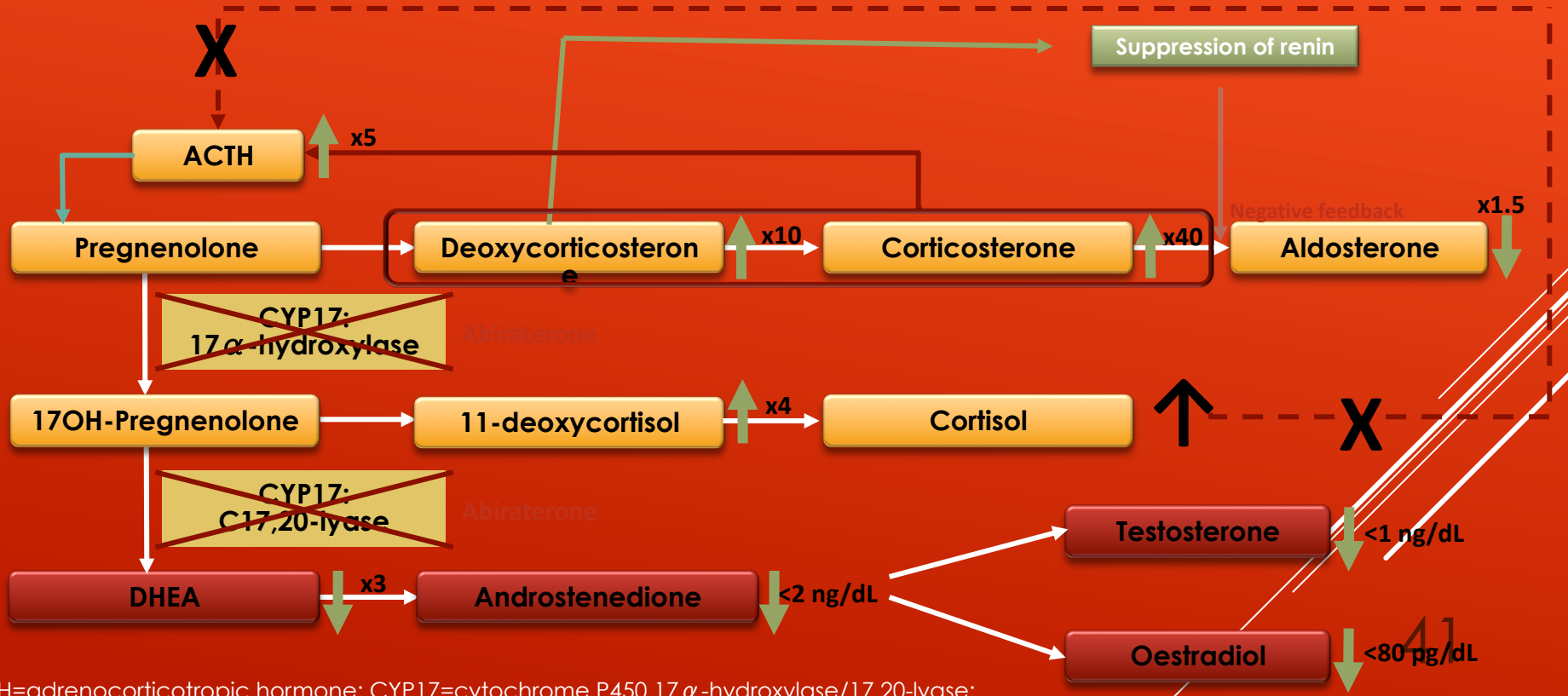


ACTH=adrenocorticotropic hormone; CYP17=cytochrome P450 17α-hydroxylase/17,20-lyase; DHEA=dehydroepiandrostenedione.

1.Attard G, *et al. J Clin Oncol* 2008;26:4563–71.
2.Ang JE, *et al. Br J Cancer* 2009;100:671–5.

TERAPIA CON ABIRATERONE: MODELLO CLINICO DI DEFICIT ACQUISITO DELLA 17-IDROSSILASI/3

Effetto potenzialmente reversibile con la somministrazione di corticosteroidi (dose raccomandata 10 mg/die)



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1.Attard G, *et al. J Clin Oncol* 2008;26:4563–71.
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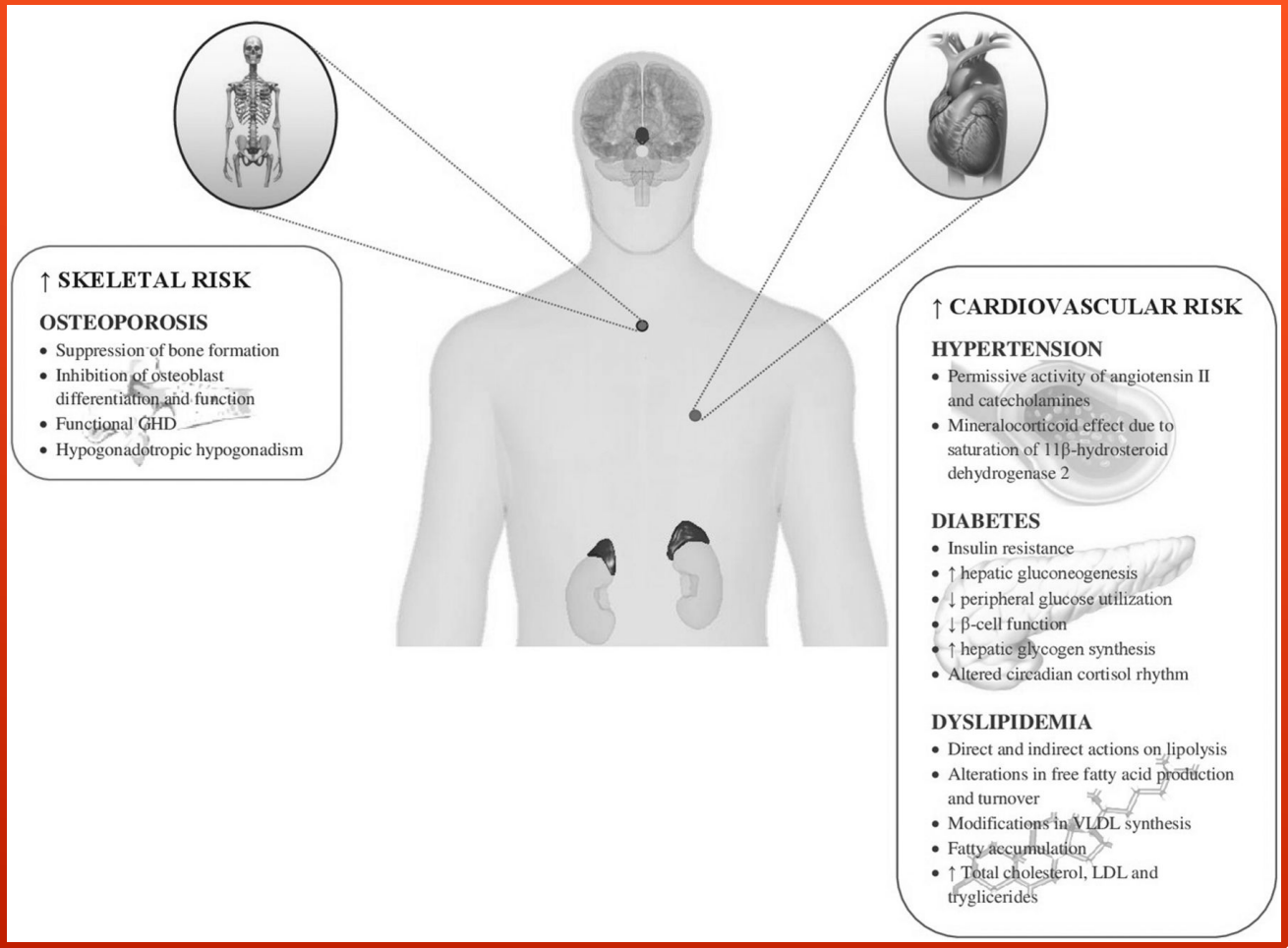
TERAPIA DELL'IPERPLASIA SURRENALICA IN ETÀ ADULTA

LINEE GUIDA

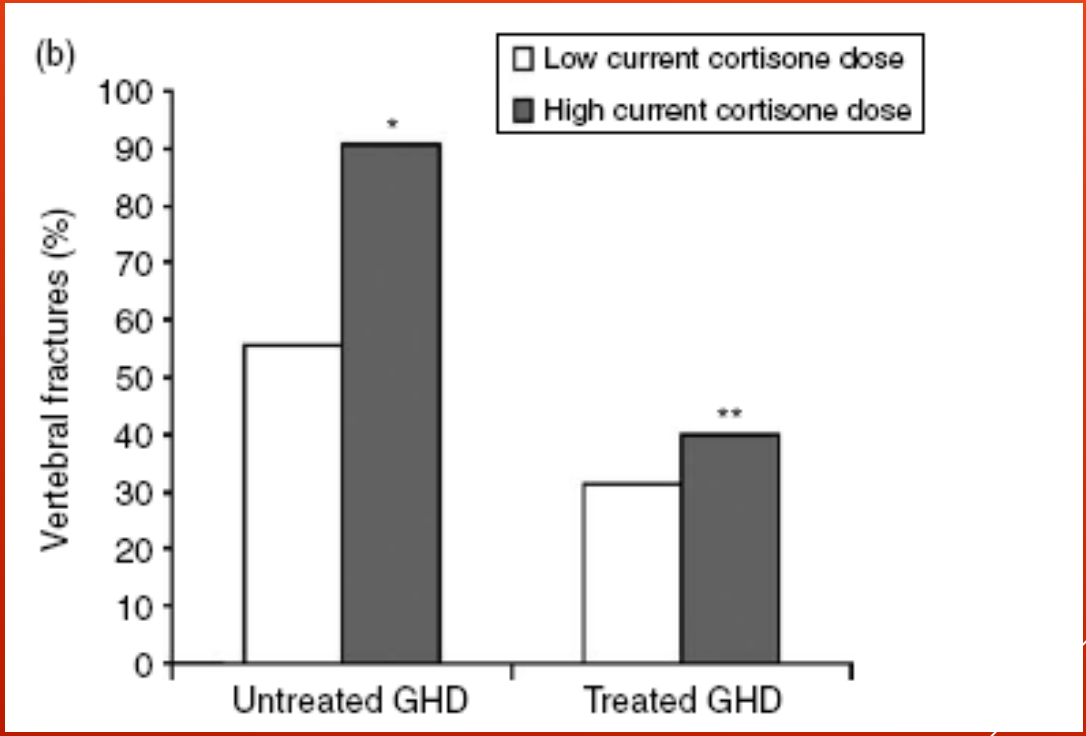
Type of long-acting GC	Suggested dose (mg/d)	Daily doses
HC	15–25	2–3
Prednisone	5–7.5	2
Prednisolone[a]	4–6	2
Dexamethasone[a]	0.25–0.5	1

Speiser et al., JCE&M 2010


↑ SKELETAL RISK
OSTEOPOROSIS
• Suppression of bone formation
• Inhibition of osteoblast differentiation and function
• Functional GHD
• Hypogonadotropic hypogonadism
↑ CARDIOVASCULAR RISK
HYPERTENSION
• Permissive activity of angiotensin II and catecholamines
• Mineralocorticoid effect due to saturation of 11β-hydrosteroid dehydrogenase 2
DIABETES
• Insulin resistance
• ↑ hepatic gluconeogenesis
• ↓ peripheral glucose utilization
• ↓ β-cell function
• ↑ hepatic glycogen synthesis
• Altered circadian cortisol rhythm
DYSLIPIDEMIA
• Direct and indirect actions on lipolysis
• Alterations in free fatty acid production and turnover
• Modifications in VLDL synthesis
• Fatty accumulation
• ↑ Total cholesterol, LDL and tryglicerides

ECCESSO DI GLUCOCORTICOIDI E FRAGILITÀ SCHELETRICA

L'aumento del rischio si osserva anche nei pazienti con iposurrenalismo in trattamento sostitutivo (se ad alto dosaggio ed in presenza di GHD)



Mazziotti et al., Eur J Endocrinol 2010

Author, year	Pts.	PAI/SAI/CAH	Study design	Main results
Zelissen, 1994 (90)	91	91/0/0	Cross-sectional	↓ LS BMD (in relationship with HC dose in men)
Peacey, 1999 (97)	12	6/6/0	Prospective	↓ or ↑ LS BMD after decreasing HC dose
Jodar, 2003 (91)	25	25/0/0	Cross-sectional	↑ Osteoporosis (PDN vs HC)
Løvås, 2009 (92)	292	292/0/0	Cross-sectional	↓ FN and LS BMD (PAI vs reference population, in relationship with HC dose); ↔ VFs
Mazziotti, 2010 (93)	41	0/41/0	Cross-sectional	↑ VFs (untreated GHD and over-treated SAI vs treated GHD)
Koetz, 2012 (94)	122	81/0/41	Cross-sectional	↓ Bone turnover markers, LS and FN BMD (PDN vs HC)
Falhammar, 2013 (95)	32	0/0/32	Cross-sectional	↑ Osteoporosis (PDN vs HC)
Ceccato, 2016 (96)	38	0/0/38	Cross-sectional	↓ FN BMD (CAH vs controls); no correlation with GC dose
Schulz, 2016 (98)	90	57/0/33	Prospective	↑ TH and LS BMD after decreasing HC dose; ↓ FN BMD after increasing HC dose

BMD, bone mineral density; CAH, congenital adrenal hyperplasia; FN, femoral neck; GC, glucocorticoid; GHD, growth hormone deficiency; HC, hydrocortisone; LS, lumbar spine; PAI, primary adrenal insufficiency; PDN, prednisolone; Pts., patients; SAI, secondary adrenal insufficiency; TH, total hip; VFs, vertebral fractures.

Management “osteometabolico” del paziente in terapia cronica con glucocorticoidi

Conclusioni

1. La GIO è una delle più frequenti e severe forme di osteoporosi e si annida anche in situazioni cliniche «parafisiologiche».
2. La GIO è “democratica” (colpisce sia femmine che maschi) ed è ampiamente sottodiagnosticata e sottotrattata.
3. La valutazione delle fratture vertebrali morfometriche prevalenti ed incidenti è fondamentale nel *management* della GIO.
4. Oggi esistono strumenti terapeutici particolarmente efficaci e “patogenetici”. Non prevenire, trattare o causare la GIO è cattiva pratica clinica.

EUROPEAN SOCIETY OF ENDOCRINOLOGY

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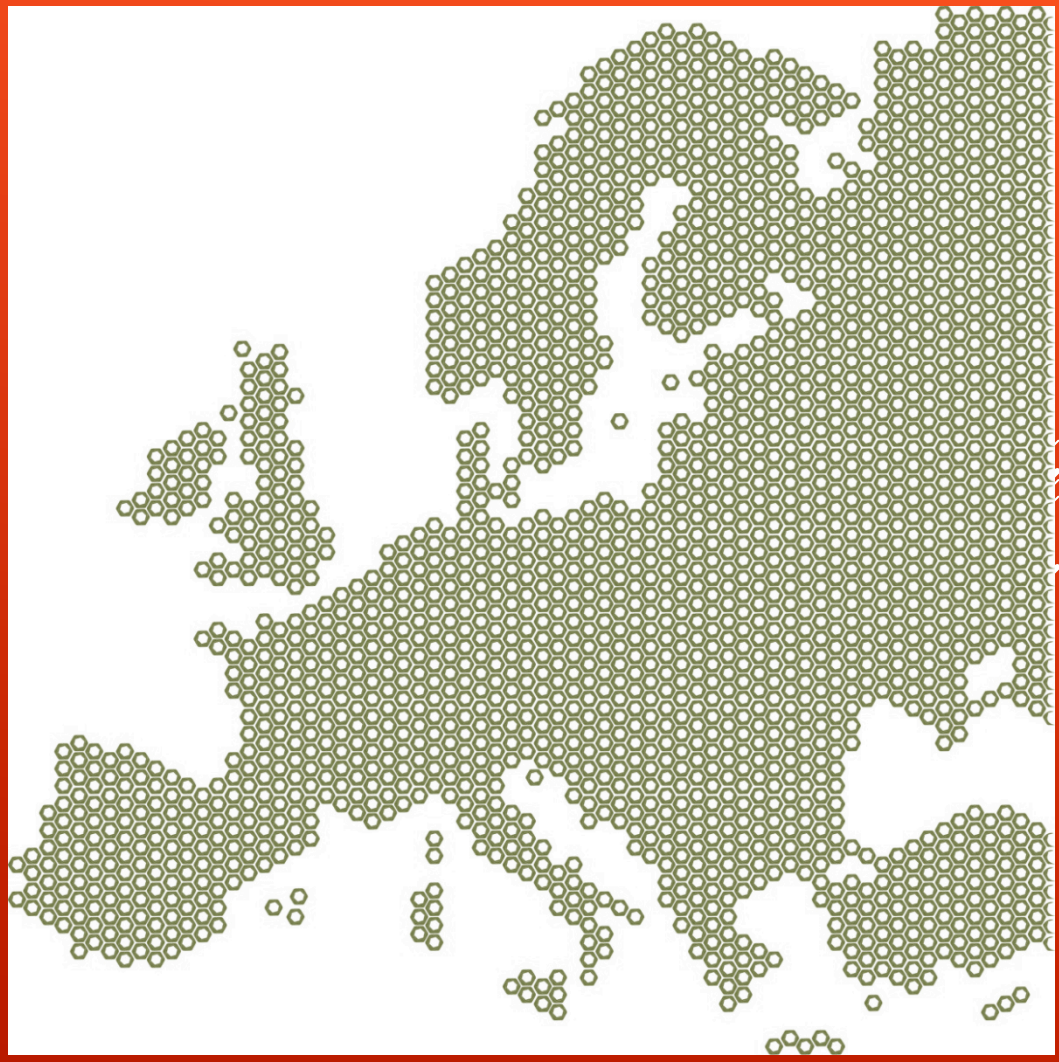
- Representing **51 National Affiliated Societies** across Europe
- Collaborating with **12 Specialty Affiliated Societies**
- **ECE 2022 will be in Milano!!**



- **GRAZIE**