Le Strategie Terapeutiche nella Gestione del Paziente Osteoporotico

La gestione del paziente osteoporotico: dai risultati dello studio AIFA-best alla pratica clinica

Firenze – 4 giugno 2012

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OSTEOPOROSIS
Treatment Options

1. **Optimize Mineralization**
   - Restore vitamin D status
2. **Reduce deep excavations by osteoclasts**
   - Prevent merging of clusters into composite osteons
   - Prevent fenestration of trabeculae
3. **Increase bending resistance**
   - Trabeculae: make them thicker and if possible more connected
   - Tubular bones: add bone on the *periosteal* surface

PRODUCTION, METABOLISM AND BIOLOGIC FUNCTIONS OF VITAMIN D

Inert Photoproducts

UVB

HEAT

Total body sun exposure easily provides 250 μg (10.000 IU) Vitamin D/d with circulating 25(OH)D levels ~140 nmol/l (56 ng/ml)

$ProD_3$ (7-DHC) → $PreD_3$ → Vitamin D_3

SKIN

chylomicrons

LIVER

25(OH)D

PROSTATE
BREAST
OVARY
COLON
OSTEOBLASTS

KIDNEY

Calciferol

Ergosterol

DIET

<2.5 μg (<100 IU)/d

PTH (+)

(+) Low PO_4^{2-}

CALCITROIC ACID

24-OHase

$1, 25(OH)_2D$

INTESTINE
↑ Calcium and Phosphorus Absorption

BONE
↑ Mineralization Mobilizes Calcium Stores

PARATHYROID GLANDS
↓ PTH

MUSCLE
↑ Muscle Strength

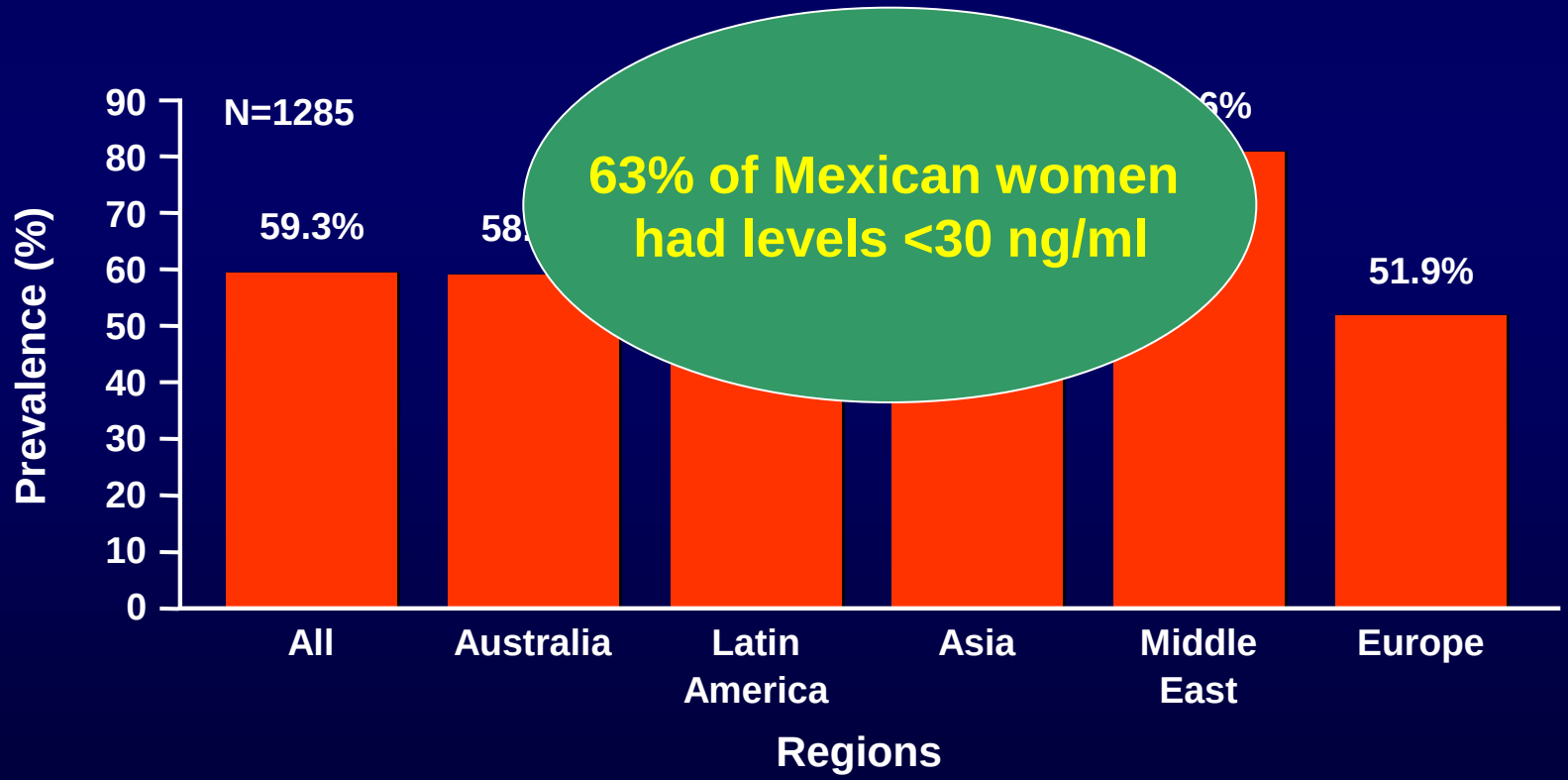
T and B LYMPHOCYTES
Immunomodulation (Prevention of Autoimmune Diseases)

HEART
Renin-Angiotensin (Prevention CVD)

CANCER
Regulation of Cell Growth (Cancer Prevention)

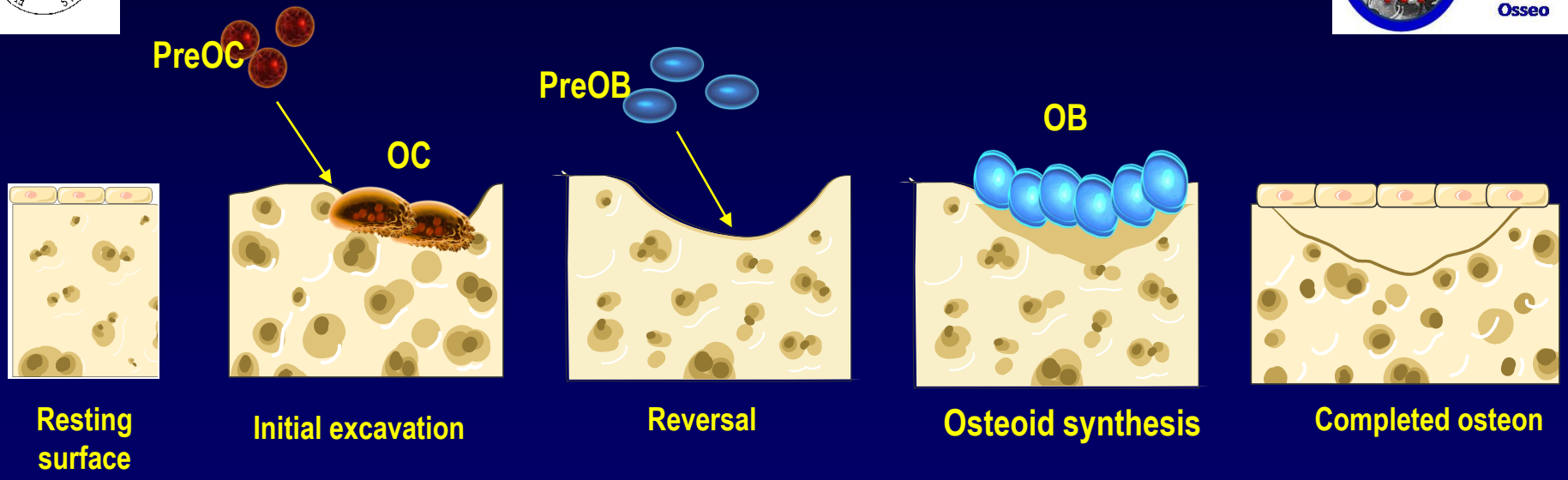
Prevalence of Vitamin D inadequacy (<30 ng/ml) by region in postmenopausal women with osteoporosis

A high prevalence of vitamin D inadequacy was seen across all geographic regions studied

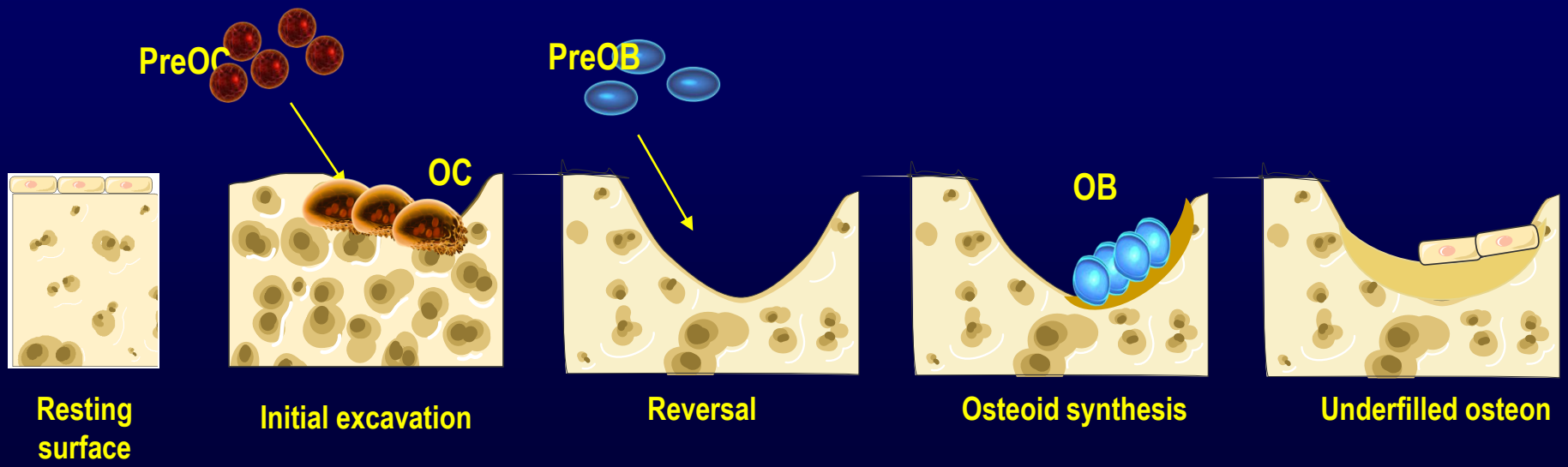


Adapted from Lim S-K et al. Poster presented at ISCD, February 16–19, New Orleans, LA.

Bone remodeling in adulthood



Bone remodeling in postmenopausal osteoporosis



BONE REMODELING IN POSTMENOPAUSAL OSTEOPOROSIS

↑ rate remodeling

↑ resorption in BMU

↓ formation in BMU

↓ tissue mineral content

TREATMENT OBJECTIVES

↓ of resorption

↑ of formation

Therapeutic Strategies in Osteoporosis

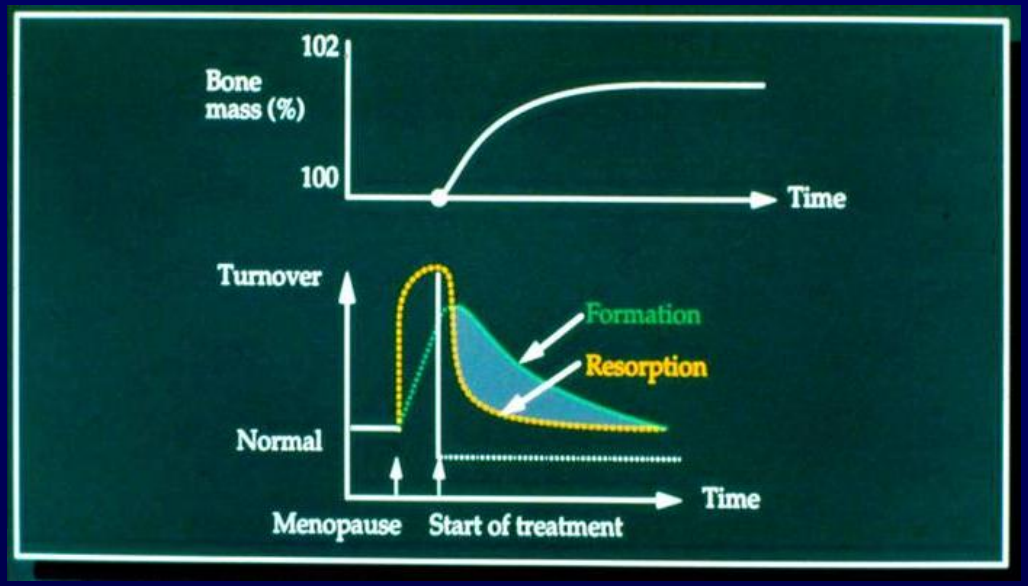
ANTIRIASSORBITIVI	OSTEOFORMATORI
BISFOSFONATI ▪ Alendronato ▪ Ibandronato ▪ Risedronato ▪ Zoledronato	**DUAL-ACTION** ▪ Stronzio ranelato
SERM ▪ Raloxifene ▪ Bazedoxifene	**PEPTIDI DEL PARATORMONE** ▪ Paratormone 1-84 ▪ Teriparatide
ANTICORPI MONOCLONALI ▪ Denosumab	

Osteoporosis Drugs: Mechanisms of Action on Bone Remodelling

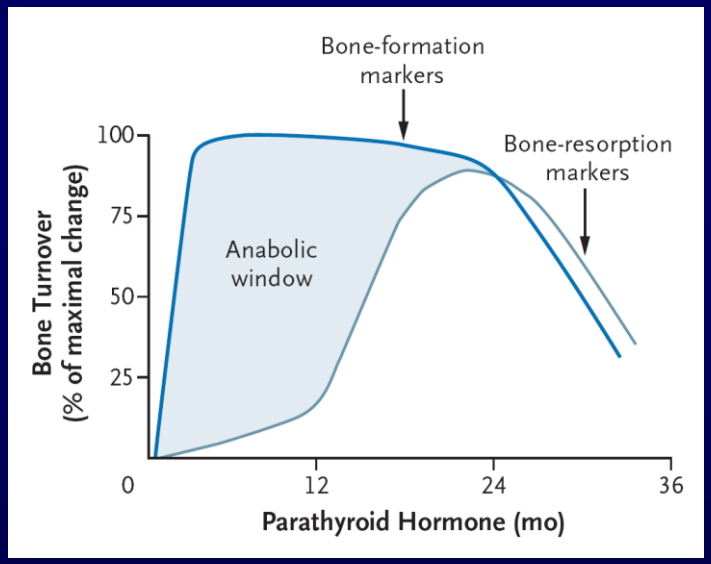
	Compounds	Resorption	Formation	Final result
ANTIRESORPTIVES	Bisphosphonates	↓↓	↓	Inhibited
	Denosumab	↓↓	↓	Inhibited
	SERMs	↓	↓	Inhibited
ANABOLICS	PTH peptides	↑	↑↑	Increased
	Strontium Ranelate	↓	↑↑	Unchanged

Therapeutical Windows

Antiresorptives



Anabolics



Antifracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomized controlled trials [updated from Kanis et al, 2008b]

	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	Osteoporosis	Established osteoporosis[a]	Osteoporosis	Established osteoporosis[a]
Alendronate	+	+	NA	+ (including hip)
Risedronate	+	+	NA	+ (including hip)
Ibandronate	NA	+	NA	+[b]
Zoledronic acid	+	+	NA (including hip)	+[c]
HRT	+	+	+	+
Raloxifene	+	+	NA	NA
Teriparatide and PTH	NA	+	NA	+[d]
Strontium ranelate	+	+	+ (including hip[b])	+ (including hip[b])
Denosumab	+	+[c]	+ (including hip)	+[c]

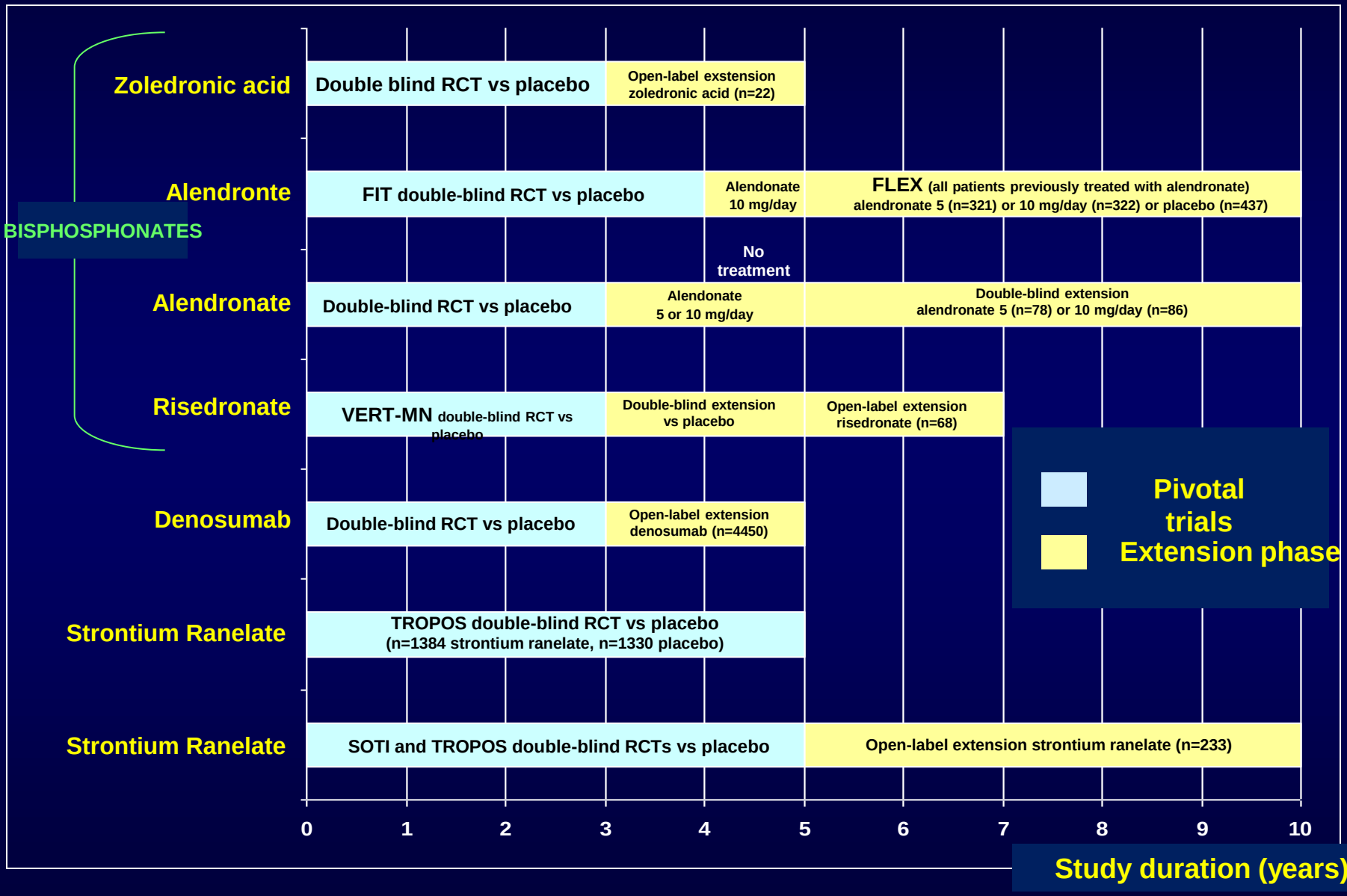
NA, no evidence available;
+ , effective drug ;
[a] women with a prior vertebral fracture;
[b] in subsets of patients only (post-hoc analysis);
[c] mixed group of patients with or without prevalent vertebral fractures
[d] shown for teriparatide only

OI, in press

FOR HOW LONG?

Summary of published STUDY DESIGN FOR THE LONG TERM TRIALS

with osteoporosis treatments with fracture related end-points

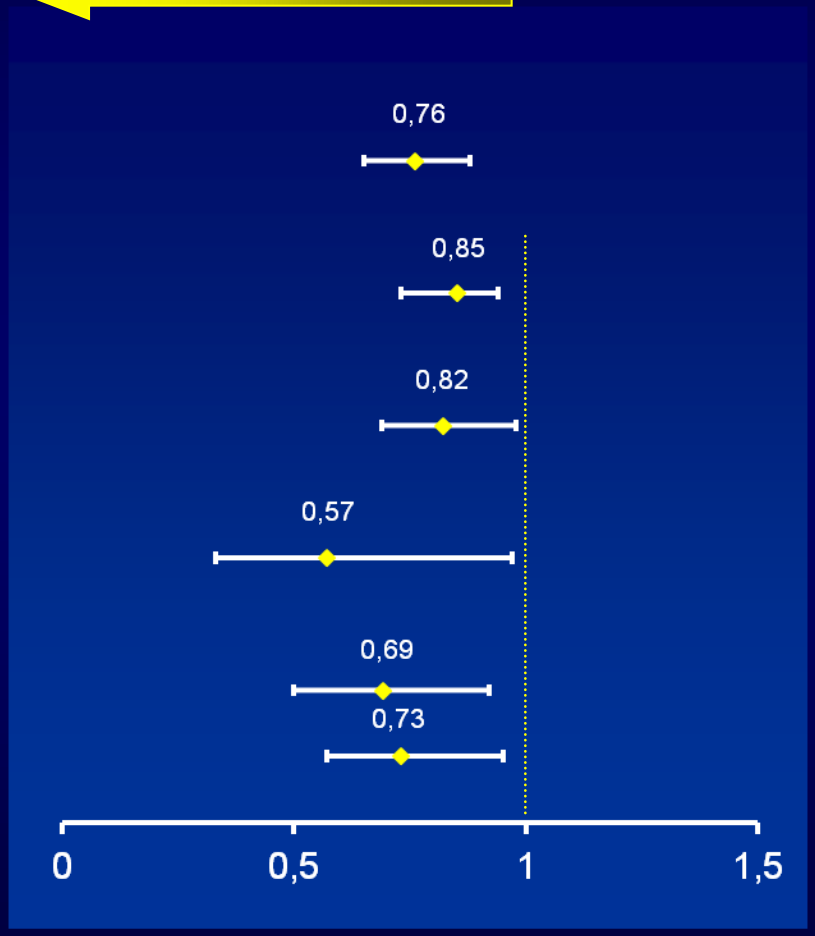


Cooper C, et al. Current Medical Research & Opinion Vol. 28, No. 3, 2012, 1–17

ANTIFRACTURE EFFICACY in the long term (RCTs)

FAVORS STRONTIUM RANELATE

Over 5 years	↓ RR	
Vertebral F	- 24%	P<0.001
Non-Vertebral F	- 15%	P=0.032
Major Non-Vertebral F	- 18%	P=0.025
Hip F*	- 43%	P=0.036
Vertebral F, ≥ 80 years	- 31%	P<0.01
Non-Vertebral F, ≥ 80 years	- 27%	P=0.018



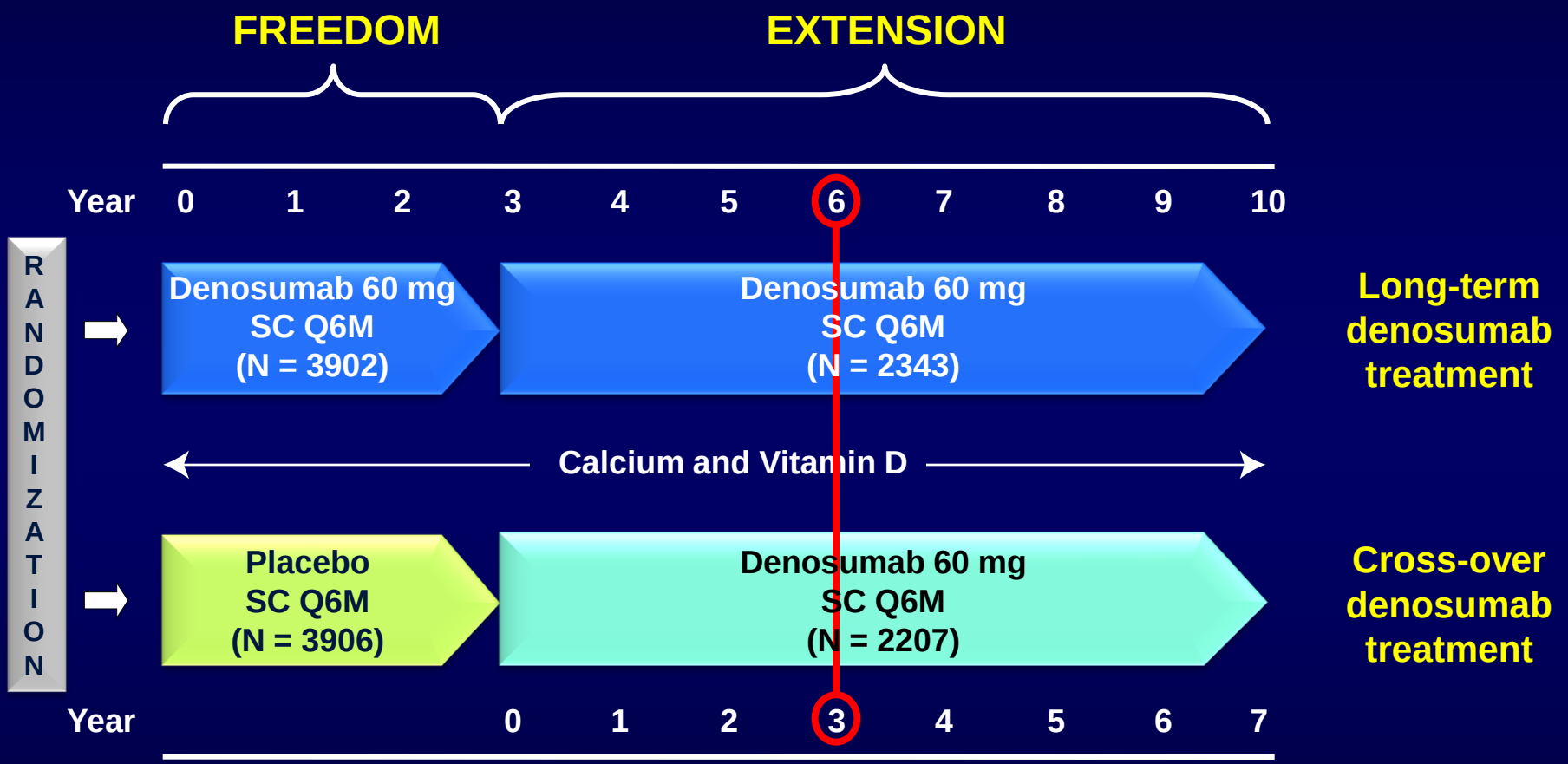
Relative Risk and 95% CI

Reginster JY, et al. *Arthritis Rheum*. 2008;58(6):1687-1695

* Women ≥ 74 years and FN and LS T-score ≤ -2.4

FREEDOM Extension study design

International, multicentre, open-label, single-arm study



Key Inclusion Criteria:

- Completed the FREEDOM study (completed their 3-year visit, did not discontinue investigational product, and did not miss more than 1 dose).
- Not receiving any other osteoporosis medications.

Clinical Question:
3 Ways to Use Anabolics with Antiresorptives

1. **Antiresorptives + Anabolics**
2. **Anabolics** → **Antiresorptives**
3. **Antiresorptives** → **Anabolics**

Combination Regimen #1

- Simultaneous start of anabolics and antiresorptives

Anabolics + Antiresorptives

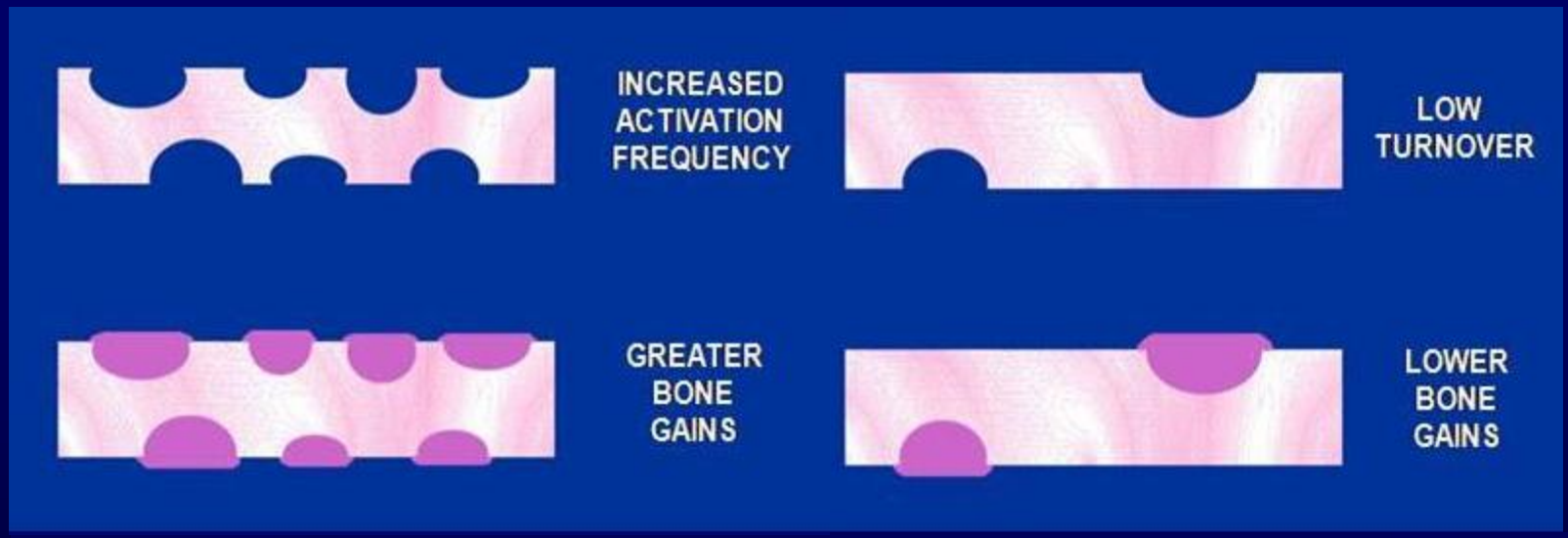
Summary: Concurrent Start of Anabolics with Antiresorptives?

- Daily use of alendronate greatly decreases anabolic action of PTH 1-84
- Studies of a less frequent bisphosphonate not much better on the anabolic action of PTH 1-84
- More mild antiresorptive, like raloxifene, may enhance the bone forming effect of teriparatide
- Bottom Line:
  - We know that anabolics alone work really well. Perhaps best to start anabolics alone until we are certain that combination is superior

Combination Regimen #2

Anabolics → **Antiresorptives**

- Use of antiresorptives following anabolics



Anabolic effect at the level of the individual bone remodelling unit causes an increase in the thickness of complete packets

Summary : Antiresorptives after Anabolics:

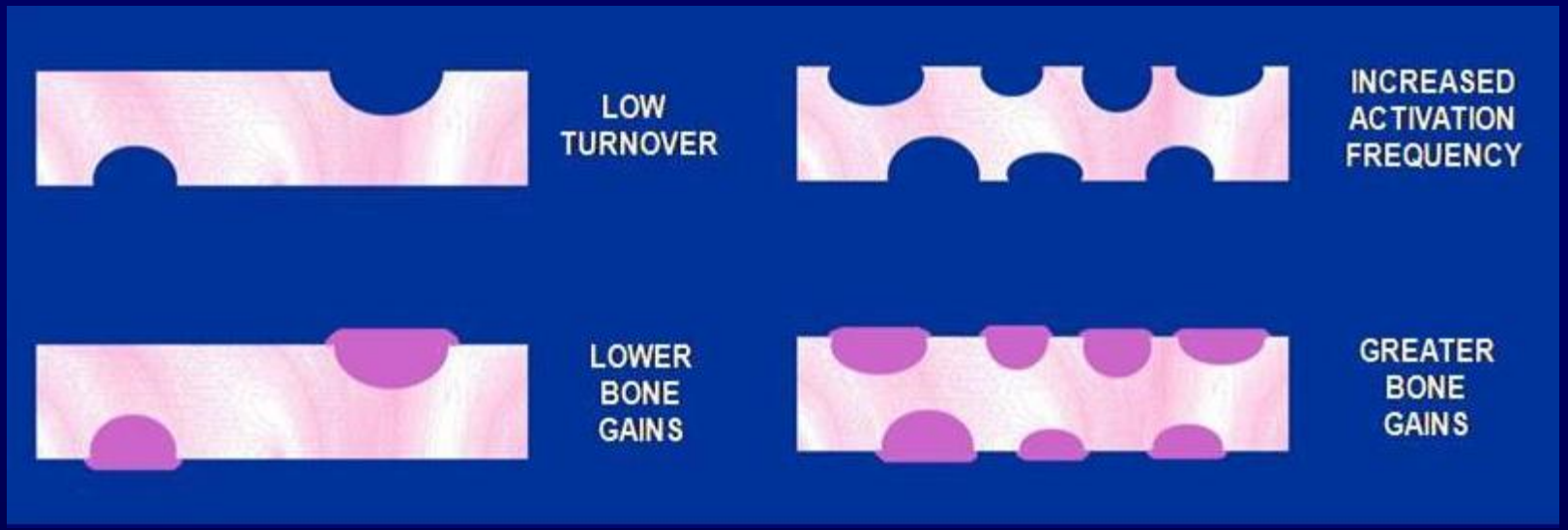
- Data are **consistent across** several studies:
  - Large loss of BMD after stopping PTH (if nothing is used)
  - Use of antiresorptives after PTH will retain BMD (and probably bone strength) gains

- **Suggests that in clinical practice PTH should be followed by antiresorptive therapy**

Combination Regimen #3

- Pre-treatment with antiresorptives followed by anabolics

Antiresorptives → **PTH**



Anabolic effect at the level of the individual bone remodelling unit causes an increase in the thickness of complete packets

Summary: Anabolics Following Antiresorptives

- Several studies in the last few years
- A strong anabolic effect with anabolics following antiresorptives
  - Small delay and blunting in the anabolic effect

- **Clinical recommendation:**
  - Bone forming will have a strong anabolic effect on patients on antiresorptives
  - Consider anabolics in high risk patients currently on antiresorptives (continuing to fracture or very low BMD)

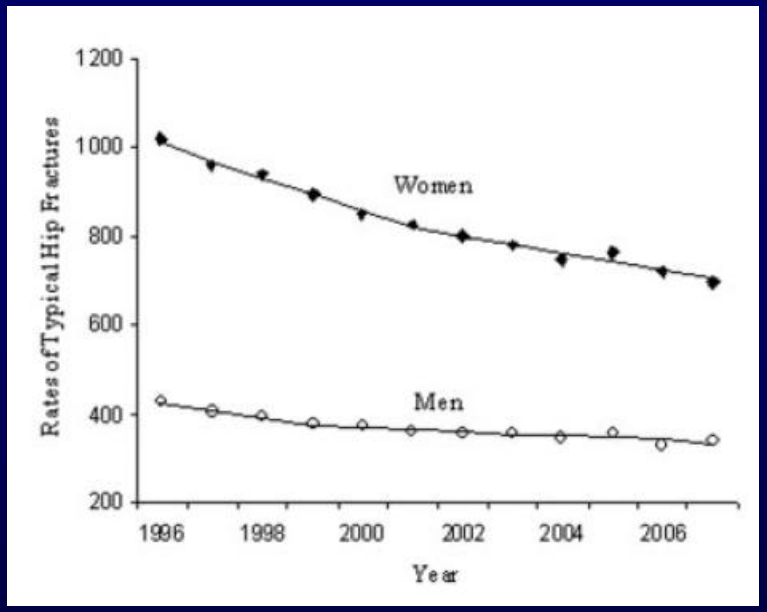
Source of evidence for adverse reactions to treatments in osteoporosis

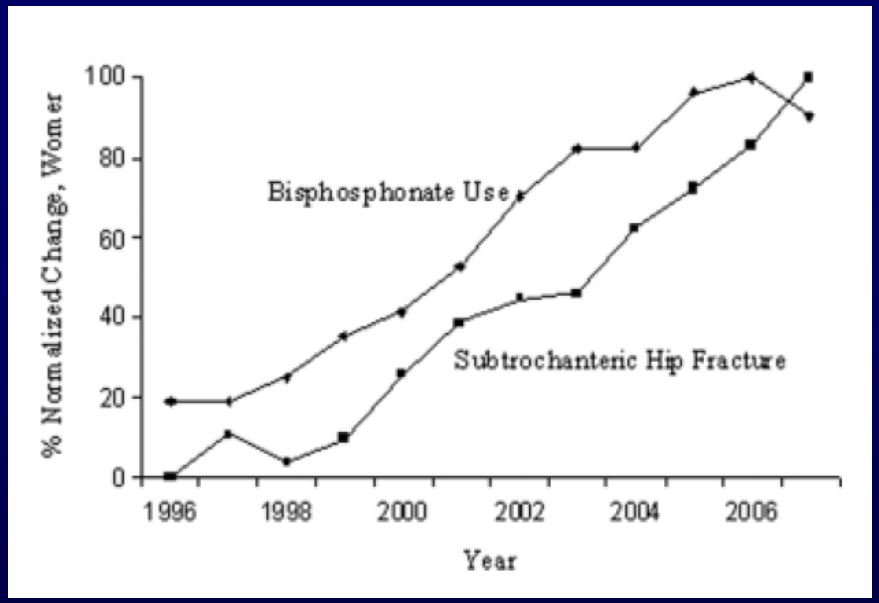
	Source of evidence			Duration of postapproval experience in 2010
	RCT	Pharmacovigilance	Case series	
Bisphosphonates				Alendronate, 15 years
GI effects	✔	✔		Risedronate, 10 years
Musculoskeletal pain		✔		Ibandronate (oral), 5 years
Acute-phase reactions	✔	✔		Ibandronate (IV), 4 years
Atrial fibrillation	✔	✔		Zoledronic acid, 3 years
Atypical fracture/delayed fracture healing		✔	✔	
Osteonecrosis of the jaw		✔	✔	
Hypersensitivity reactions		✔	✔	
Renal impairment		✔		
Denosumab				New agent
Severe infection	✔			
Osteonecrosis of the jaw		✔	✔	
Cancer	✔			
SERMs				Raloxifene, 13 years
Hot flushes	✔	✔		Bazedoxifene, new agent
Leg cramps	✔	✔		Lasofoxifene, new agent
Venous thromboembolism	✔	✔		
Stroke	✔			
Endometrial effects	✔			
Strontium ranelate				8 years
Venous thromboembolism	✔			
Hypersensitivity reactions		✔	✔	
Teriparatide or PTH(1–84)				8 years
Headache, nausea, dizziness, and limb pain	✔	✔		
Osteosarcoma		✔	✔	

From: Calcif Tissue Int, 2011

Subtrochanteric fractures with bisphosphonates

- 12-year study (from 1996 to 2007) in the USA
- Patients aged 65 and older (over 90 million hospital discharge records)
- Analysis: incidence of subtrochanteric fractures and hip fractures in relation with bisphosphonate use





Wang Z, Bhattacharyya T. *J Bone Miner Res*. 2010, on line.

The NEW ENGLAND JOURNAL *of* MEDICINE

Jörg Schilcher, M.D., Karl Michaëlsson, M.D., Ph.D.,and Per Aspenberg, M.D., Ph.D.

Table 4. Odds Ratios for Atypical Femoral Fractures Associated with Bisphosphonate Use.*

Variable	Case Patients (N=59)	Controls (N=263)	Odds Ratio (95% CI)	
			Age-Adjusted	Multivariable-Adjusted†
Bisphosphonate use				
Never	13	237	1.0 (reference)	1.0 (reference)
Ever	46	26	27.2 (12.8–58.1)	33.3 (14.3–77.8)
Type of bisphosphonate				
Alendronate	38	18	34.1 (15.2–76.6)	38.8 (15.9–94.6)
Risedronate	6	4	19.7 (4.7–83.0)	41.2 (6.9–247.7)
Etidronate	0	5	NA	NA
Ibandronate	2	0	NA	NA
Risk of fracture per 100 defined daily doses	NA	NA	1.4 (1.2–1.6)	1.3 (1.1–1.6)
Duration of use				
<1.0 yr	3	7	6.8 (1.5–31.4)	9.8 (1.9–49.9)
1.0–1.9 yr	4	6	7.1 (1.6–30.7)	9.5 (2.1–43.3)
≥2.0 yr	39	13	49.3 (20.6–118.0)	51.1 (20.3–128.2)

- **The risk of an atypical fracture was higher with an increasing duration of bisphosphonate use**

Schilcher J et al New Engl J Med 2011; 364: 1728-37

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≥2.0 yr	39	13	49.3 (20.6–118.0)	51.1 (20.3–128.2)
Time since last use				
<1.0 yr	42	16	44.0 (19.0–102.0)	47.5 (19.2–117.6)
1.0–1.9 yr	1	4	2.4 (0.2–24.7)	3.7 (0.3–41.6)
≥2.0 yr	3	6	6.4 (1.3–31.9)	9.0 (1.8–45.8)
Risk of fracture per yr since last use	NA	NA	0.29 (0.22–0.38)	0.28 (0.21–0.38)

- **There was a 70% reduction in risk for every year since the last use.**

Schilcher J et al New Engl J Med 2011; 364: 1728-

Bisphosphonates for Osteoporosis — Where Do We Go from Here?

Marcea Whitaker, M.D., Jia Guo, Ph.D., Theresa Kehoe, M.D., and George Benson, M.D.

Continuing Bisphosphonate Treatment for Osteoporosis — For Whom and for How Long?

Dennis M. Black, Ph.D., Douglas C. Bauer, M.D., Ann V. Schwartz, Ph.D., M.P.H., Steven R. Cummings, M.D., and Clifford J. Rosen, M.D.

From: NEJM 366:22, 2012

Terapia antifratturativa: Rimborso

Prevenzione PRIMARIA

Prevenzione SECONDARIA

ETA' > 50 ANNI

FRATTURA DI VERTEBRA o FEMORE

BMD femorale < -4
oppure
US calcagno < -4
oppure
US falangi < -5

BMD femorale < -3
Oppure **US calcagno < -3**
Oppure **US falangi < -4**
+ 1 fattore di rischio:

- familiarità per fratture vertebrali e/o di femore
- artrite reumatoide/altre connettività
- **pregresse fratture OP di polso**
- menopausa prima dei 45 anni
- terapia cortisonica cronica

RIMBORSO (nota 79)

stronzio ranelato, alendronato, alendronato + Vit.D3, risedronato, ibandronato, raloxifene, bazedoxifene,

Nota 79. Supplemento ordinario alla GAZZETTA UFFICIALE. Serie Generale N.137 del 15/06/2011; 49-53.

Terapia antifratturativa: Rimborso

Osteoporosi SEVERA

- Nuova frattura vertebrale da moderata a severa o frattura di femore in corso di trattamento con uno degli altri farmaci della Nota 79 da almeno 1 anno per pregressa frattura vertebrale (da moderata a severa) o di femore
- 3 o più pregresse fratture vertebrali o severe, o frattura di femore anche se mai trattati
- 2 fratture vertebrali severe + 1 frattura femorale prossimale anche se mai trattati

RIMBORSO (nota 79)

con piano terapeutico della durata di 6 mesi
(rinnovabile per altre 3 volte, per un totale di 24 mesi)

Paratormone, teriparatide

Nota 79. Supplemento ordinario alla GAZZETTA UFFICIALE. Serie Generale N.137 del 15/06/2011; 49-53.

Terapia antifratturativa: Rimborso

Osteoporosi 2ª all'uso di glucocorticoidi

Prevenzione PRIMARIA

- Previsto trattamento > di 3 mesi con dosi > 5mg/die di prednisone o dosi equivalenti di altri

RIMBORSO (nota 79)

alendronato, alendronato + Vit.D3, risedronato

Prevenzione SECONDARIA

- Età > 50aa, in trattamento da > 12 mesi con dosi > 5mg/die di prednisone o dosi equivalenti di altri corticosteroidi
- + frattura vertebrale severa o 2 fratture vertebrali moderate

RIMBORSO (nota 79)

con piano terapeutico della durata di 6 mesi (rinnovabile per altre 3 volte, per un totale di 24 mesi)

teriparatide

Nota 79. Supplemento ordinario alla GAZZETTA UFFICIALE. Serie Generale N.137 del 15/06/2011; 49-53.

Terapia antifratturativa: Rimborso

Denosumab

PRESCRIZIONE:

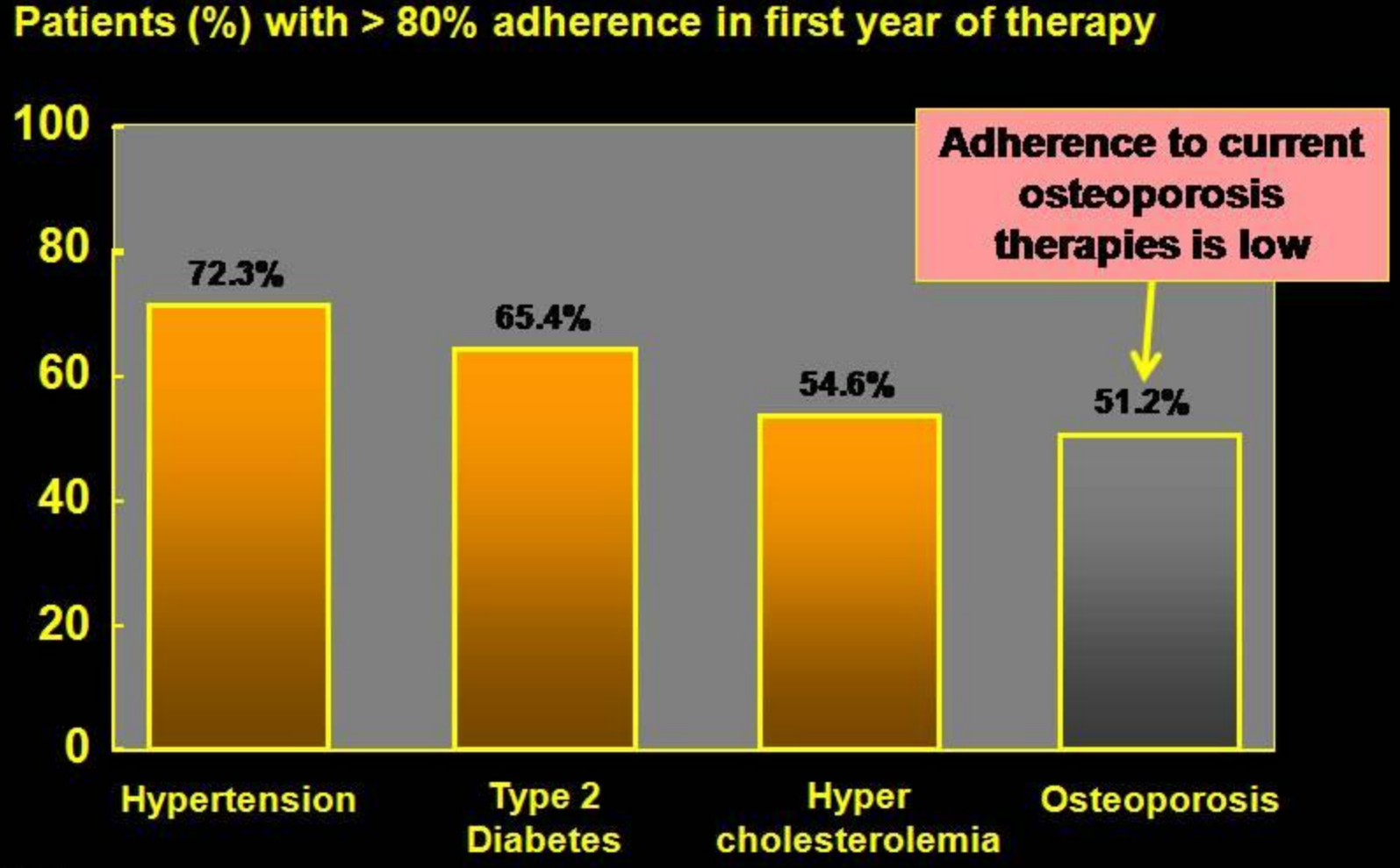
- **Centri ospedalieri o di specialisti**
  (internista, ortopedico, reumatologo, fisiatra, geriatra, endocrinologo)
- **<u>Piano Terapeutico on-line</u>, secondo le seguenti condizioni di rischio:**

- **Paziente donna con età > 70 anni**
- **Pregresse fratture vertebrali o frattura di femore**
- **valori di T-score BMD femorale o US del calcagno < -4 (< -5 per US falangi)**
  oppure
  valori di T-score BMD femorale o US del calcagno < -3 (< -4 per US falangi) e + almeno 1 fattore di rischio della Nota 79:
  - **familiarità per fratture vertebrali e/o di femore**
  - **artrite reumatoide/altre connettività**
  - **pregresse fratture OP di polso**
  - **menopausa prima dei 45 anni**
  - **terapia cortisonica cronica**

Effective Treatment Is Based on Efficacy, Safety/Tolerability and Adherence

Payer J, et al. *Biomed Pharmacother* 2007;61:191-193.

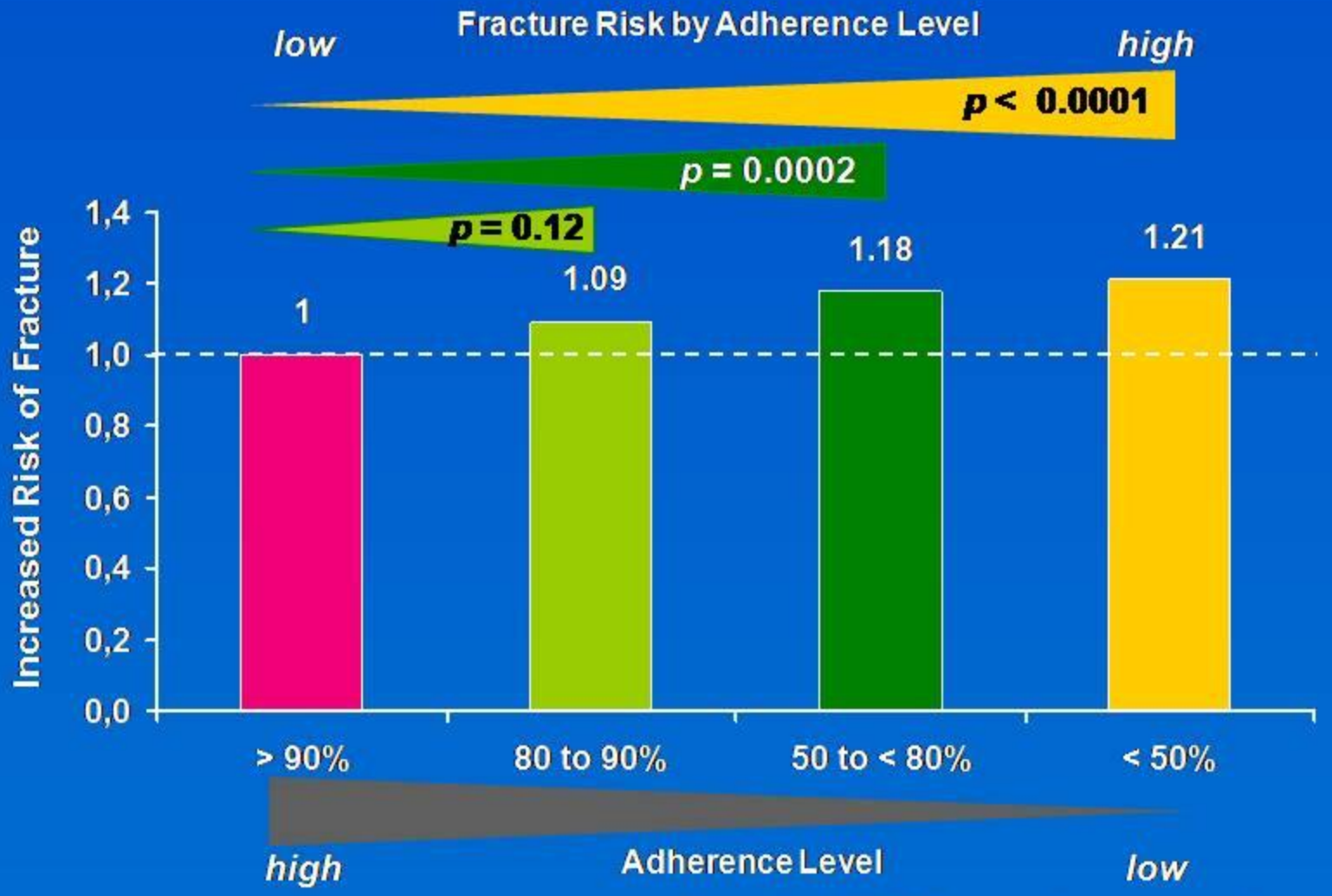
Why consider adherence



International Osteoporosis Foundation

Lekkerkerker et al, Osteoporos Int 2007;8(10):1311–7
Briesacher at al. Pharmacotherapy 2008;28(4):437–443

Poor Adherence is Associated with Increased Fracture Risk

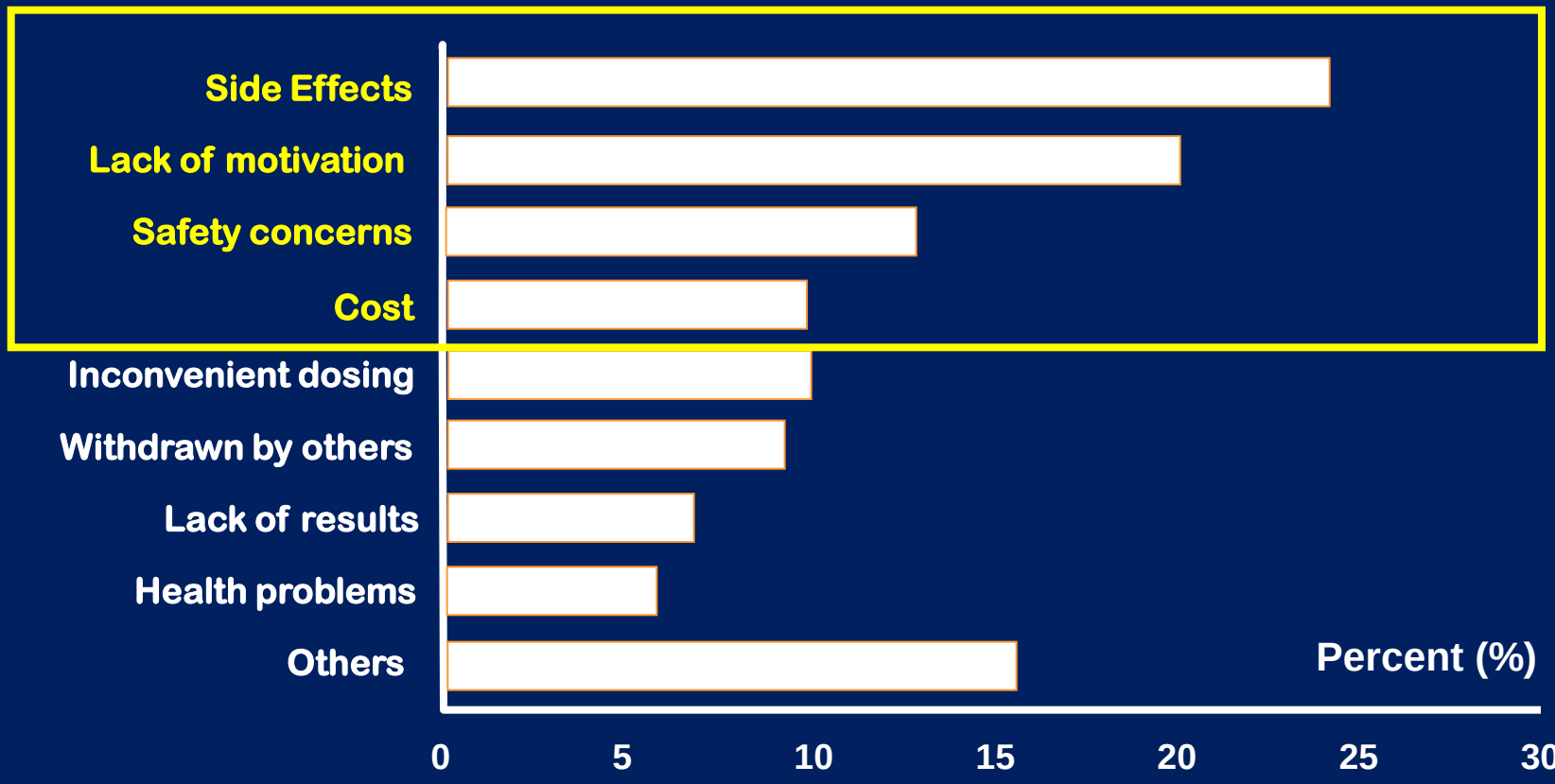


Huybrechts KF, et al. *Bone*. 2006;38:922-928.

Data from 38,000 women in a managed care database

Terapie per l'osteoporosi: ADERENZA

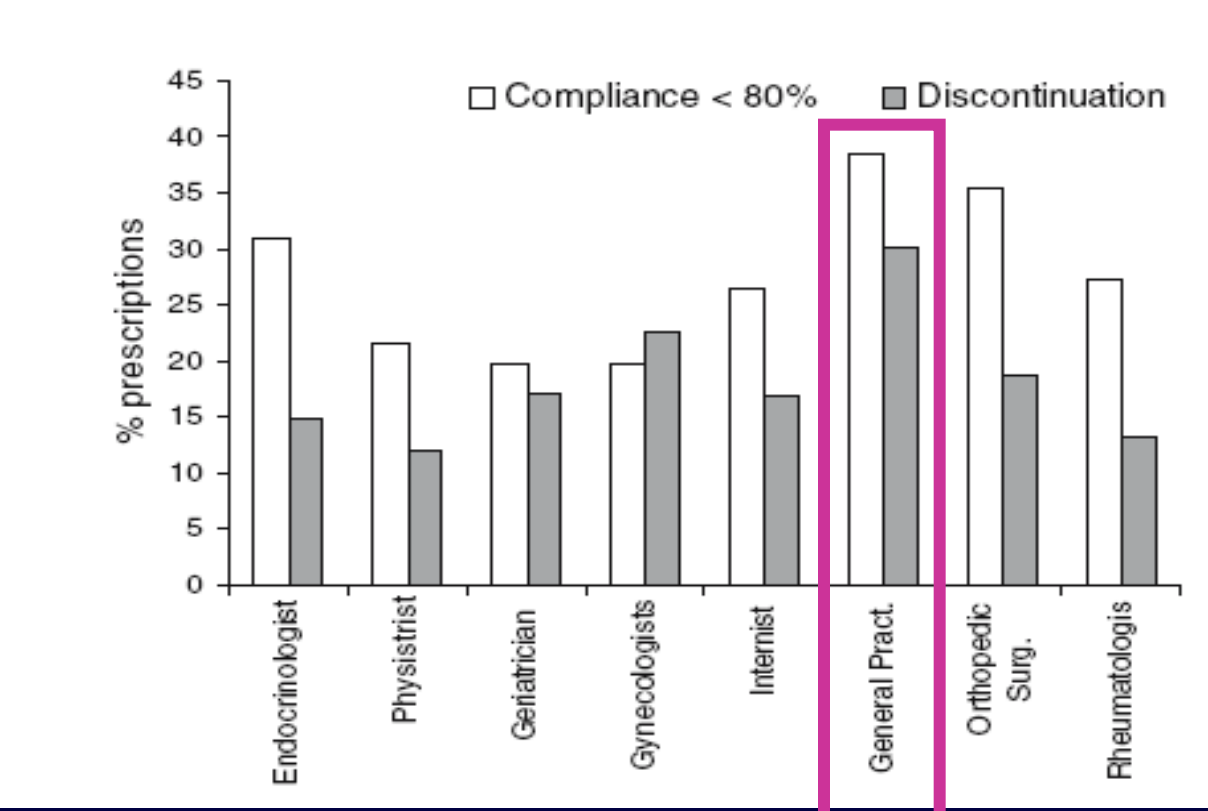
REASONS FOR DISCONTINUATION



Rossini et al Osteoporos Int (2006) 17: 914–921

Terapie per l'osteoporosi: ADERENZA

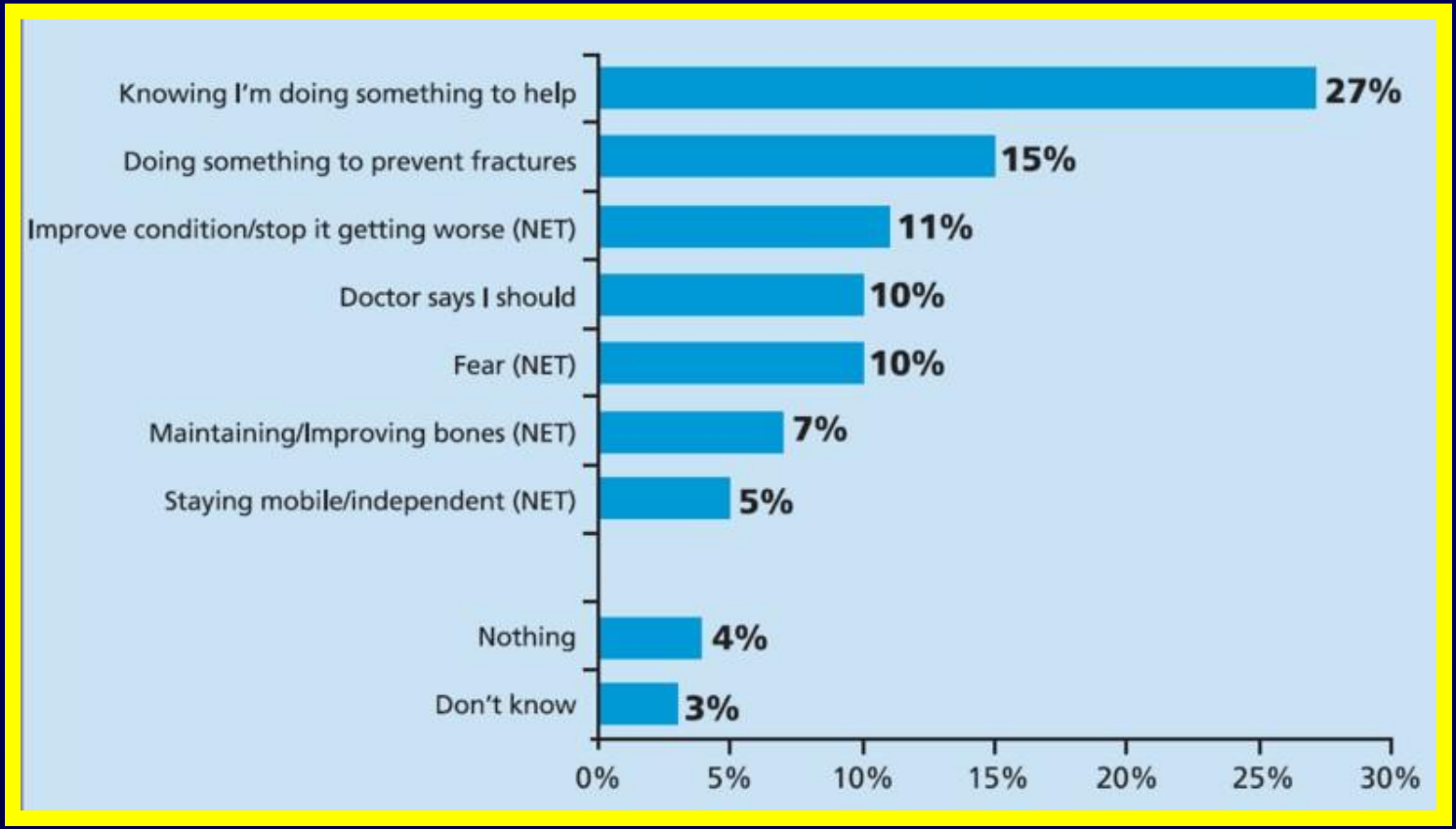
Proportion of patients who discontinued therapy and with low compliance (<80%) - according to prescriber



Rossini et al Osteoporos Int (2006) 17: 914–921

Terapie per l'osteoporosi: ADERENZA

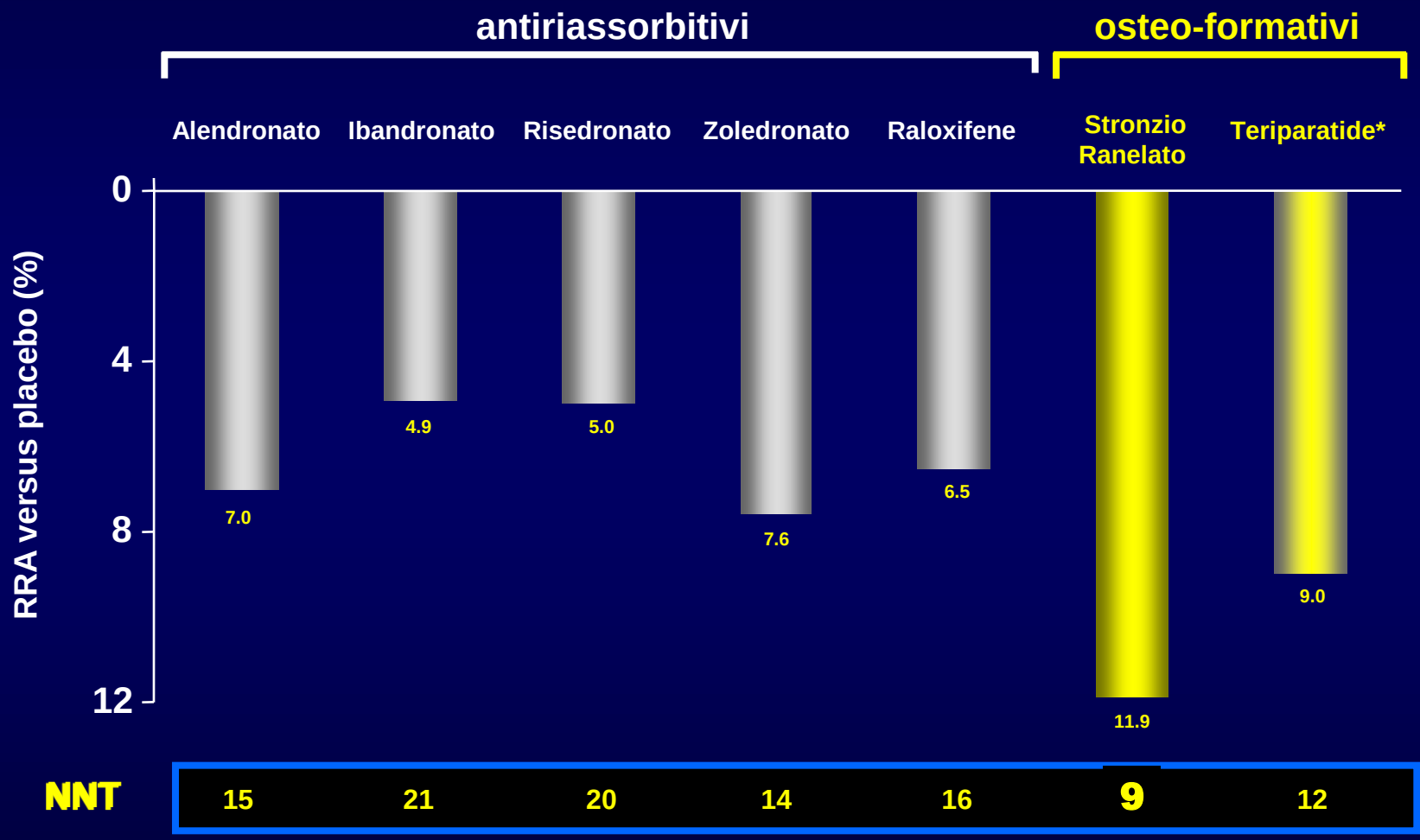
Factors Motivating Women to Stay on Their Osteoporosis Treatment



International Osteoporosis Foundation http://www.osteofound.org

COSTS

Terapie per l'osteoporosi: confronto dell'efficacia antifrattura VERTEBRALE



* *Valutazione a 18-21 mesi*

Adattato da Ringe JD et al., *Rheumatol Int* 2009; DOI 10.1007/s00296-009-1311-y

Terapie per l'osteoporosi: confronto dell'efficacia antifrattura FEMORALE

I dati sulle fratture di femore non sono disponibili per ibandronato, raloxifene, teriparatide

* *Valutazione a 18-21 mesi*

Adattato da Ringe JD et al., *Rheumatol Int* 2009; DOI 10.1007/s00296-009-1311-y

Comparison of the cost-effectiveness of alendronate with other interventions in women aged 70 years from the UK [data for treatments other than alendronate from [121], with permission from Elsevier]

Intervention	T-score = -2.5 SD		no BMD
	No prior fracture	Prior fracture	Prior fracture
Alendronate	6 225	4 727	6 294
Etidronate	12 869	10 098	9 093
Ibandronate daily	20 956	14 617	14 694
Ibandronate intermittent	31 154	21 587	21 745
Raloxifene	11 184	10 379	10 808
Raloxifene without breast cancer	34 011	23 544	23 755
Risedronate	18 271	12 659	13 853
Strontium ranelate	25 677	18 332	19 221
Strontium ranelate, post hoc analysis	18 628	13 077	13 673

OI, in press

A Reappraisal of Generic Bisphosphonates in Osteoporosis

- The competitive price of generic bisphosphonates has had a marked effect on practice guidelines, but an increasing body of evidence suggests that they have more limited effectiveness than generally assumed
- A substantial body of evidence indicates that many generic formulations of alendronate are more poorly tolerated than the proprietary preparations which results in significantly poorer adherence and thus effectiveness
- Unfortunately, market authorisation, based on the bioequivalence of generics with a proprietary formulation, does not take into account the potential concerns about safety
- The poor adherence of many generic products has implications for guideline development, cost-effectiveness and impact of treatment on the burden of disease
- The impact of generic bisphosphonates requires formal testing to re-evaluate their role in the management of osteoporosis

From: Osteoporos Int 23:213, 2012

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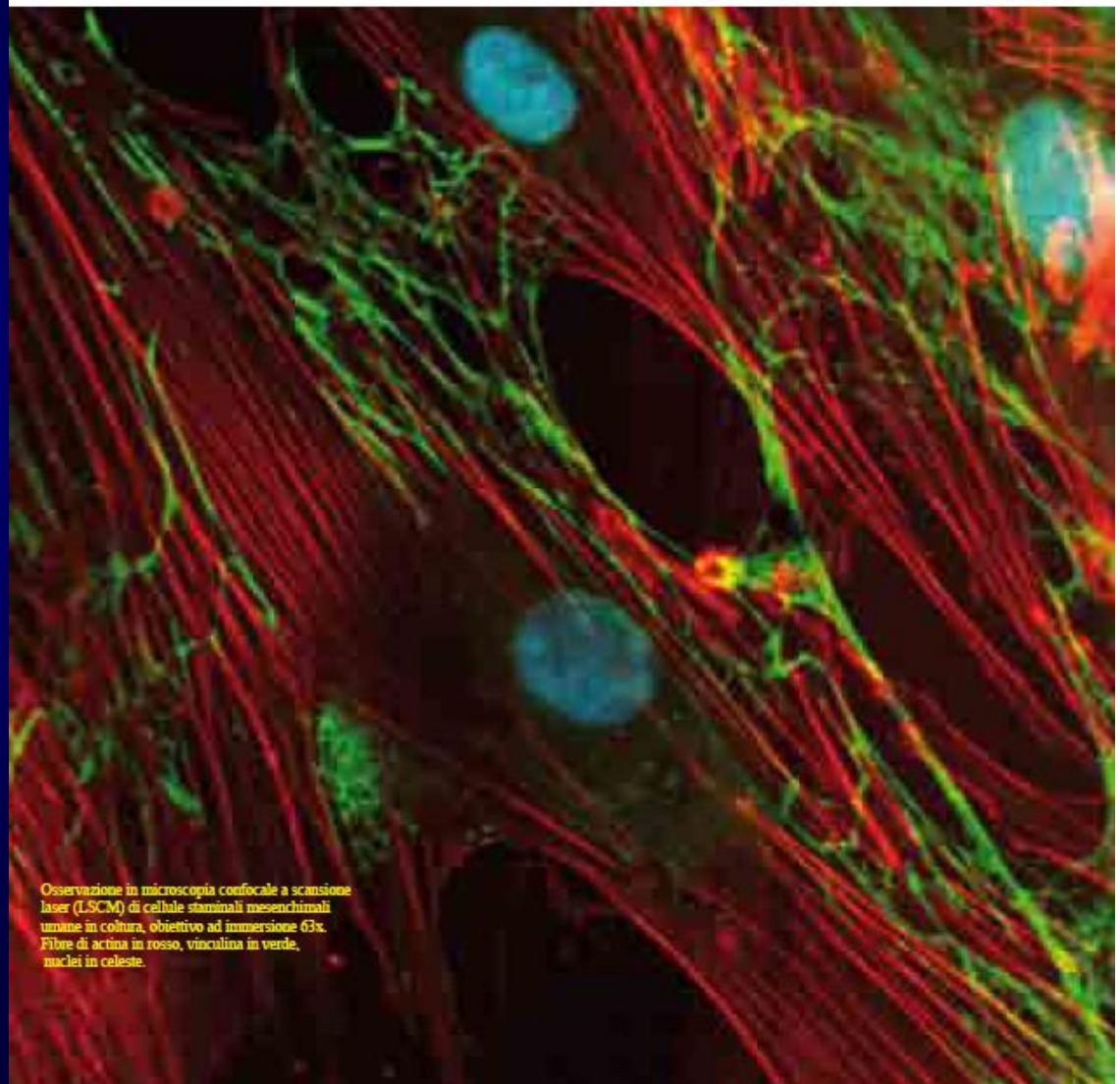

Osservazione in microscopia confocale a scansione laser (LSCM) di cellule staminali mesenchimali umane in coltura, obiettivo ad immersione 63x. Fibre di actina in rosso, vinculina in verde, nuclei in celeste.