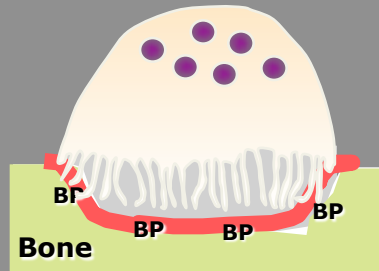
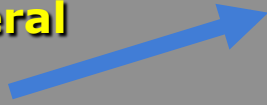
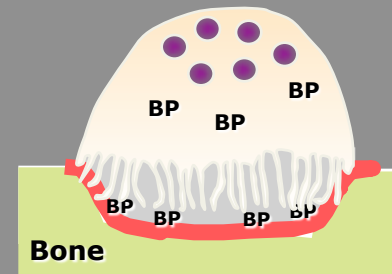
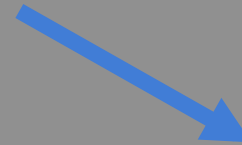


# Action of Bisphosphonates Depends on Mineral Binding and Effects on Osteoclasts

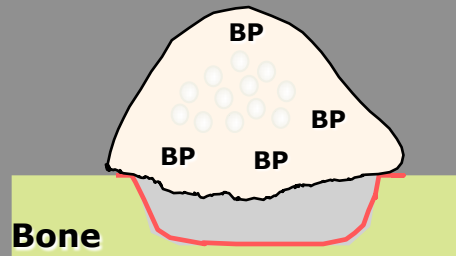
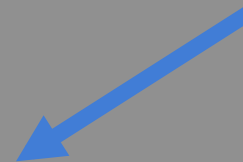
**Bind to bone mineral**



**Concentrate at sites of bone resorption**

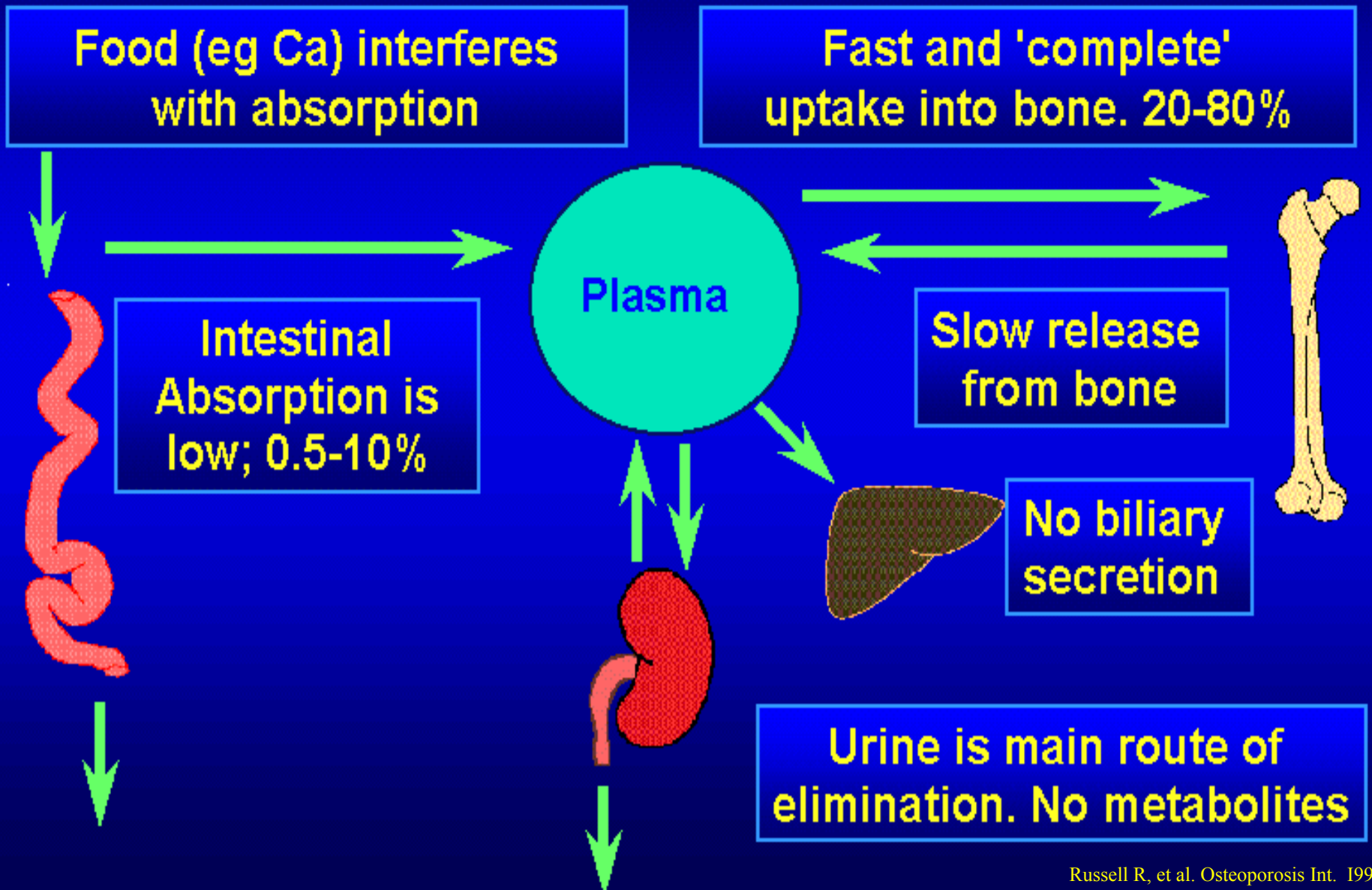


**Release and intracellular uptake during resorption**



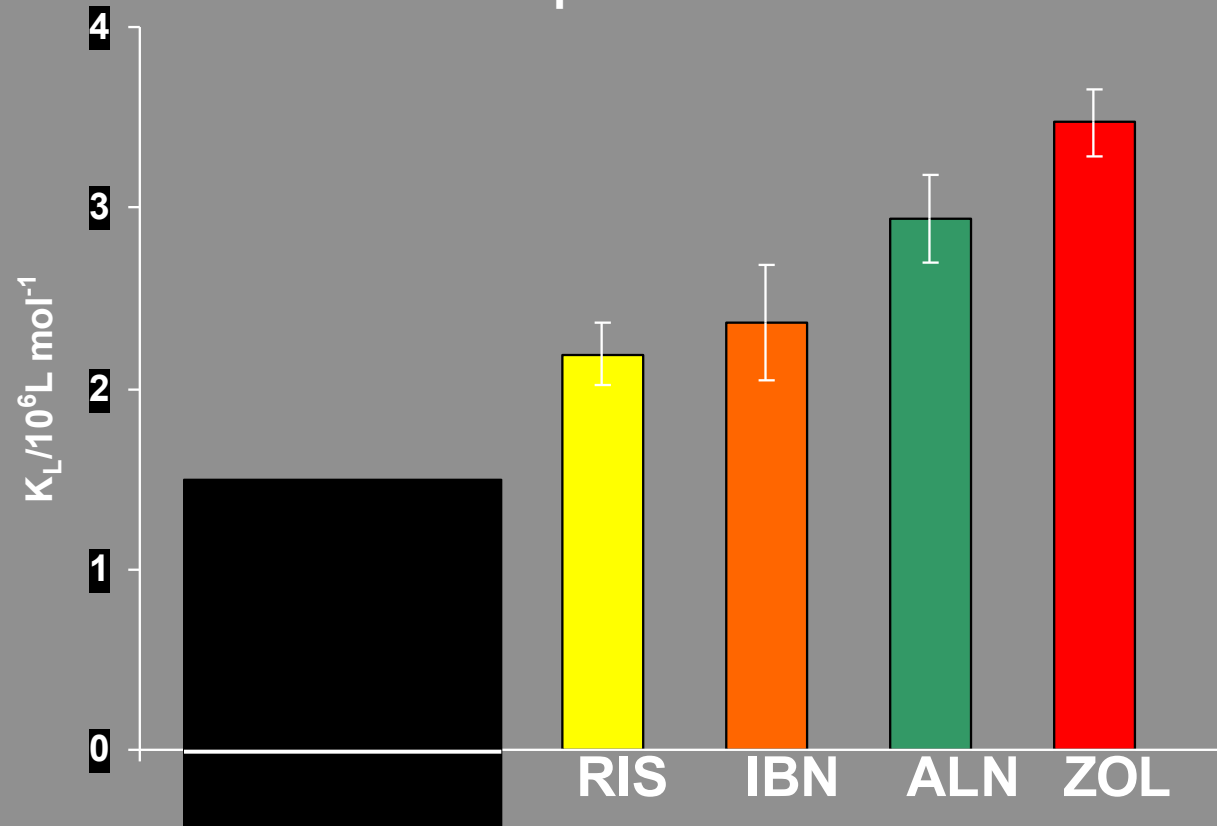
**Loss of resorptive function**

# Bisphosphonates Pharmacokinetics

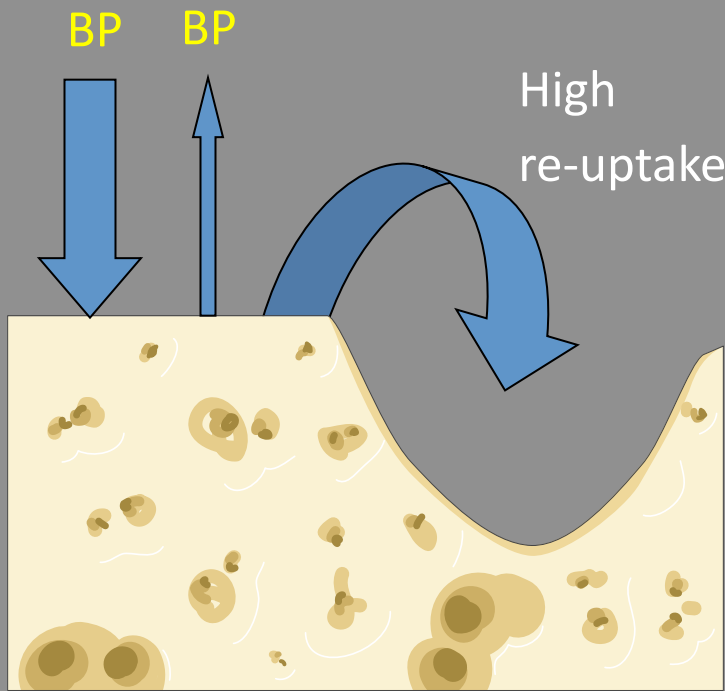


# Affinità di legame alla componente minerale dell' osso

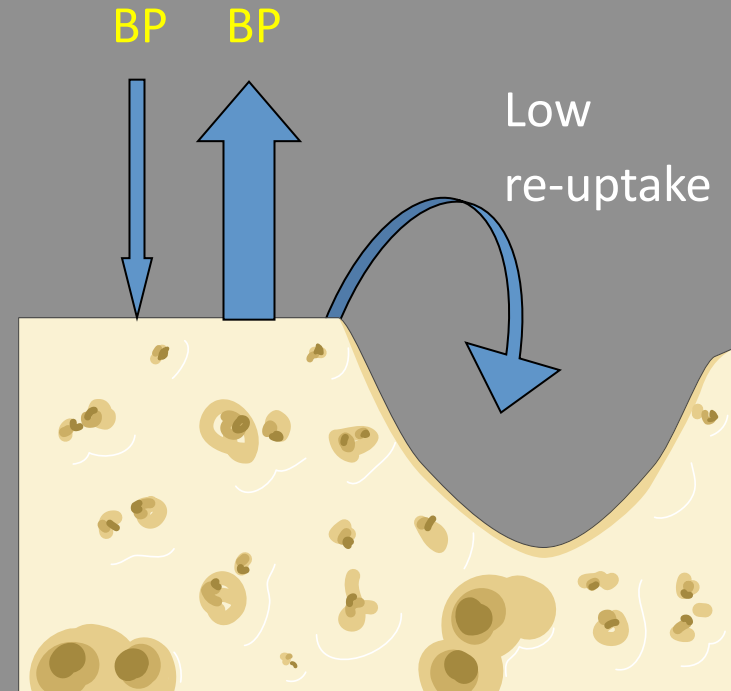
Costanti di affinità dell'assorbimento HAP a pH 7.4



# Persistenza dell'effetto alla sospensione

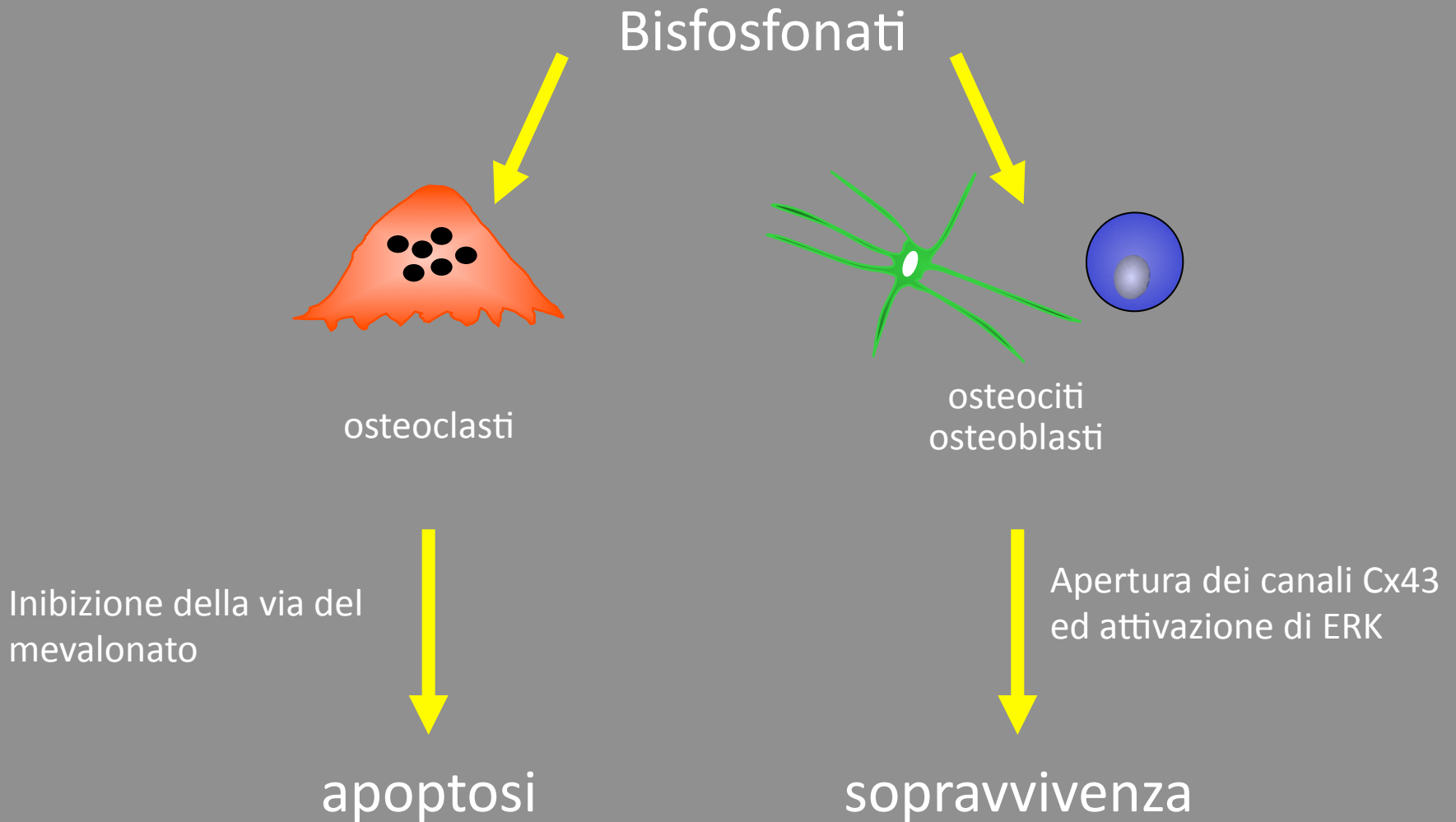


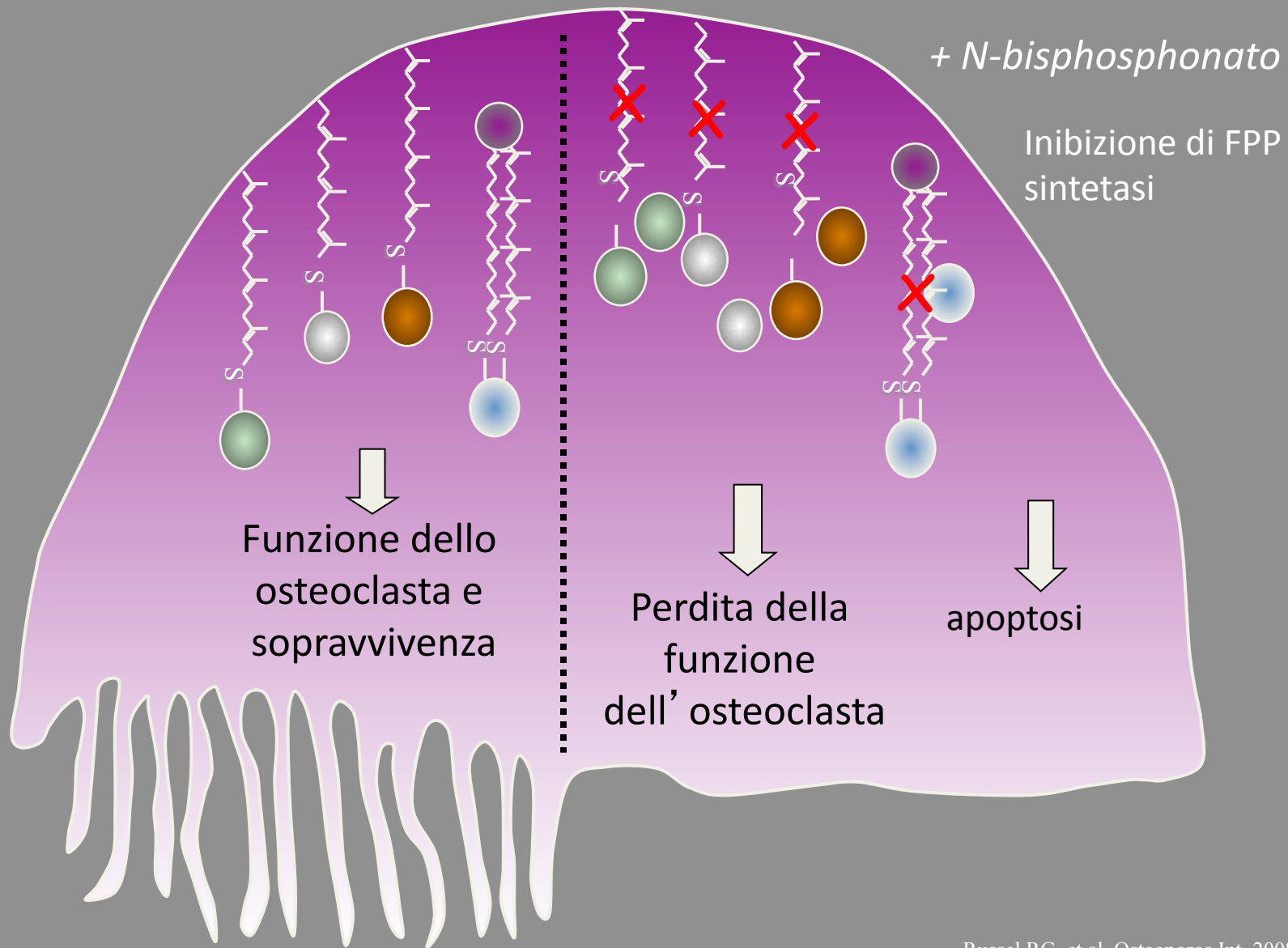
HIGH AFFINITY FOR HAP



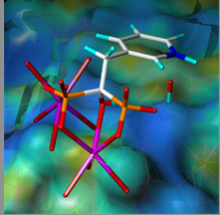
LOW AFFINITY FOR HAP

# Modello proposto per l'effetto dei BPs su Osteoclasti e Osteociti





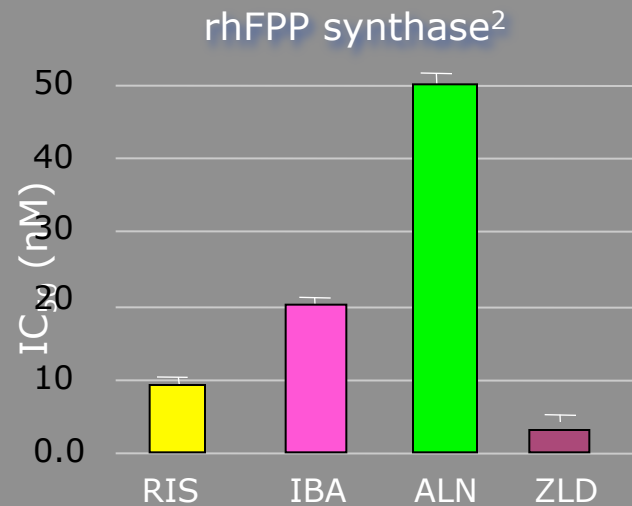
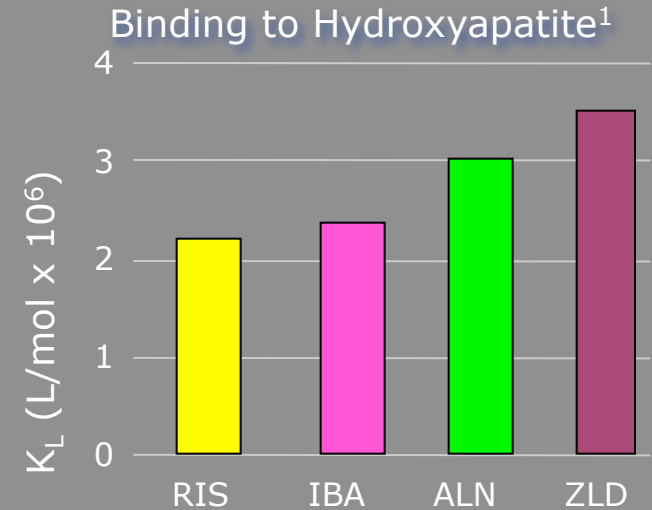
# Bisphosphonates: Key Pharmacological Characteristics



- Binding affinity for bone *in vitro*
  - Determines *in vivo* attachment to bone, potency and duration of effect



- FPP synthase inhibition *in vitro*
  - Determines antiresorptive potential

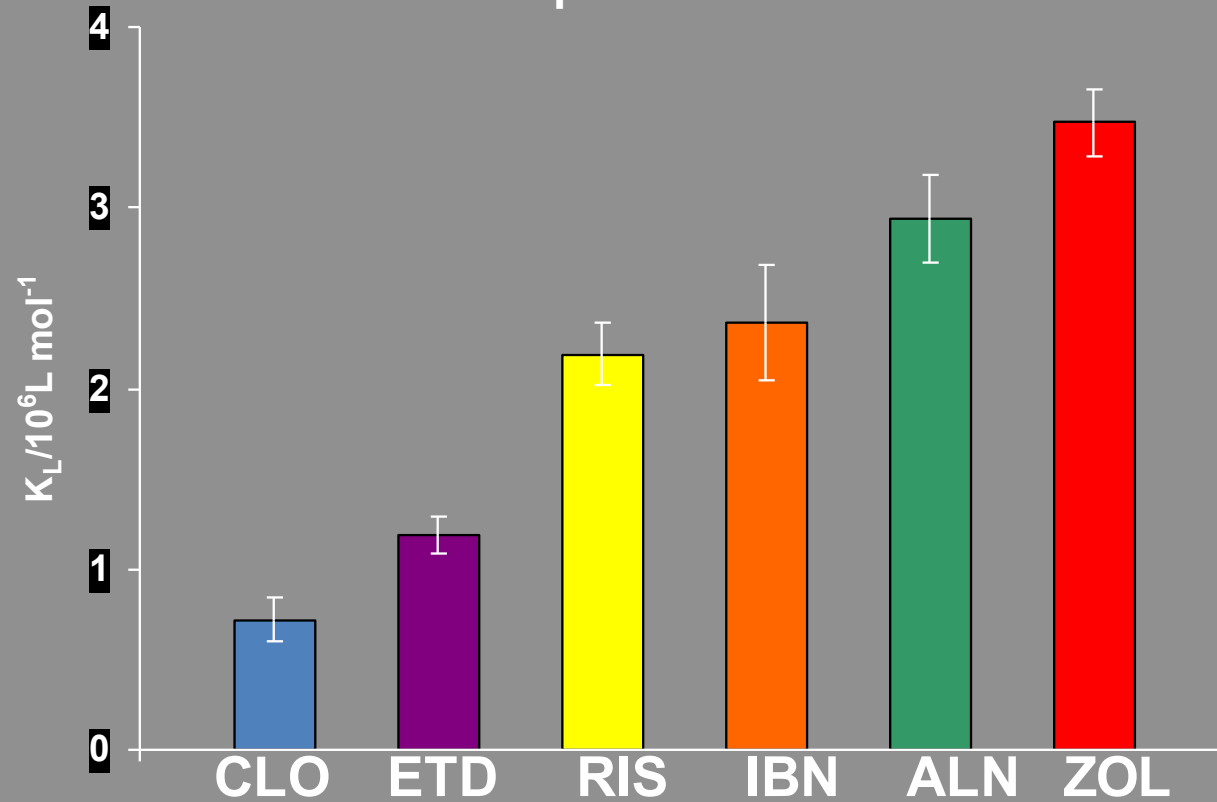


1. Nancollas GH, et al. Bone. 2006;38: 617-627.

2. Dunford JE, et al. J Pharmacol Exp Ther. 2001;296:235-242.

# Affinità di legame alla componente minerale dell' osso

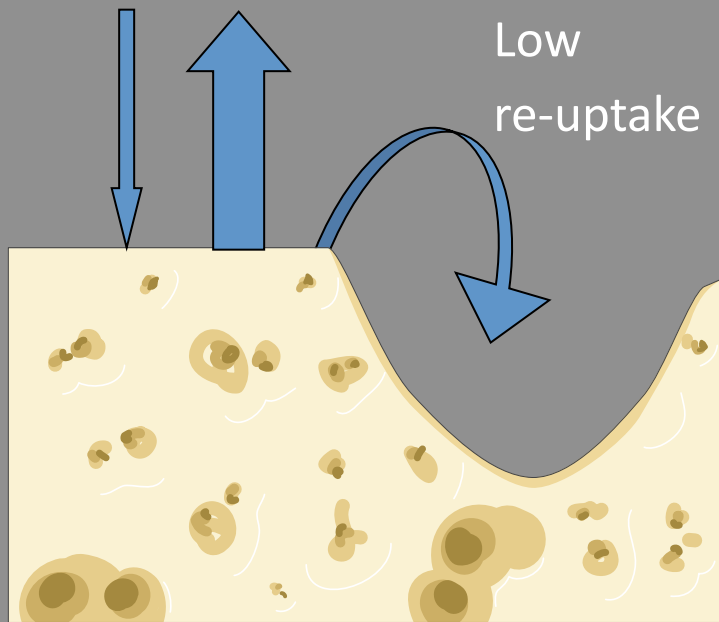
Costanti di affinità dell'assorbimento HAP a pH 7.4



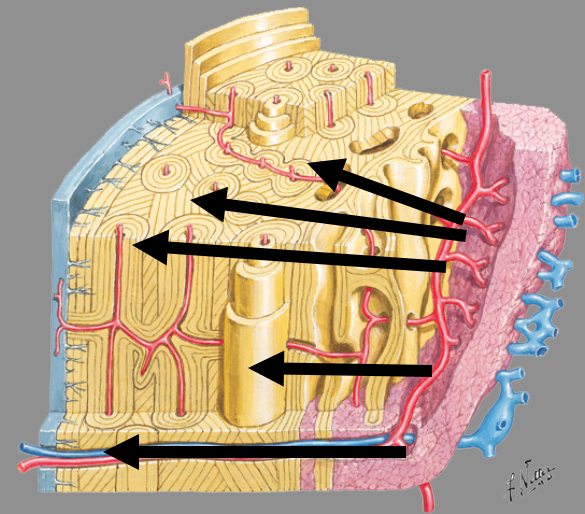


# Effetto alla sospensione

CLODRONATO



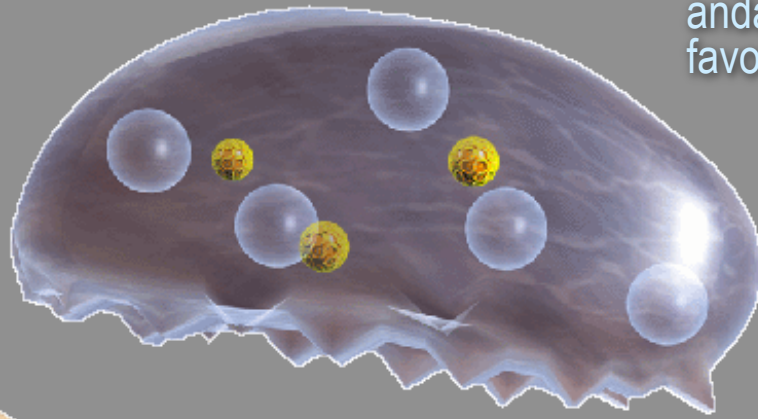
LOW AFFINITY FOR HAP



HIGHER DIFFUSION AT DIFFERENT BONE SITES

# Meccanismo d'azione dei bisfosfonati

3° Vengono internalizzati nell'osteoclasta, andandone ad alterare la funzionalità e favorendone l'apoptosi

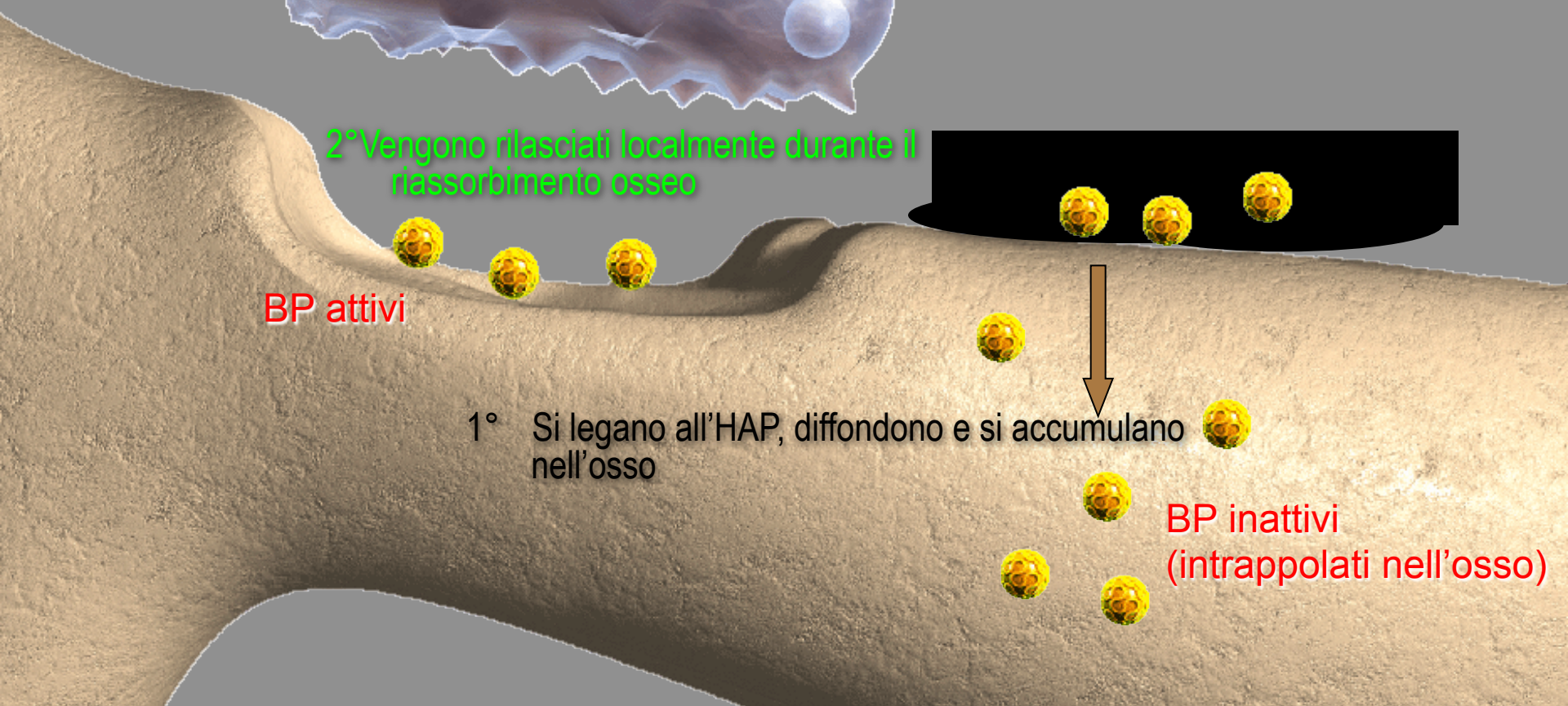


2° Vengono rilasciati localmente durante il riassorbimento osseo

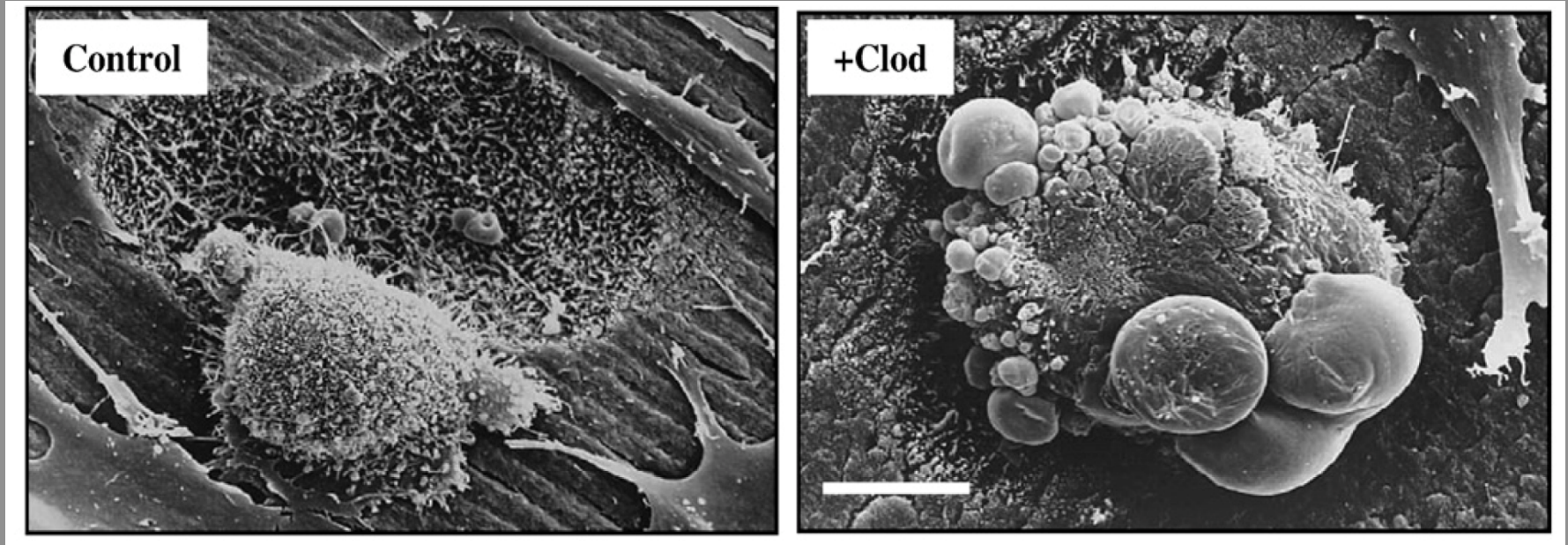
BP attivi

1° Si legano all'HAP, diffondono e si accumulano nell'osso

BP inattivi  
(intrappolati nell'osso)



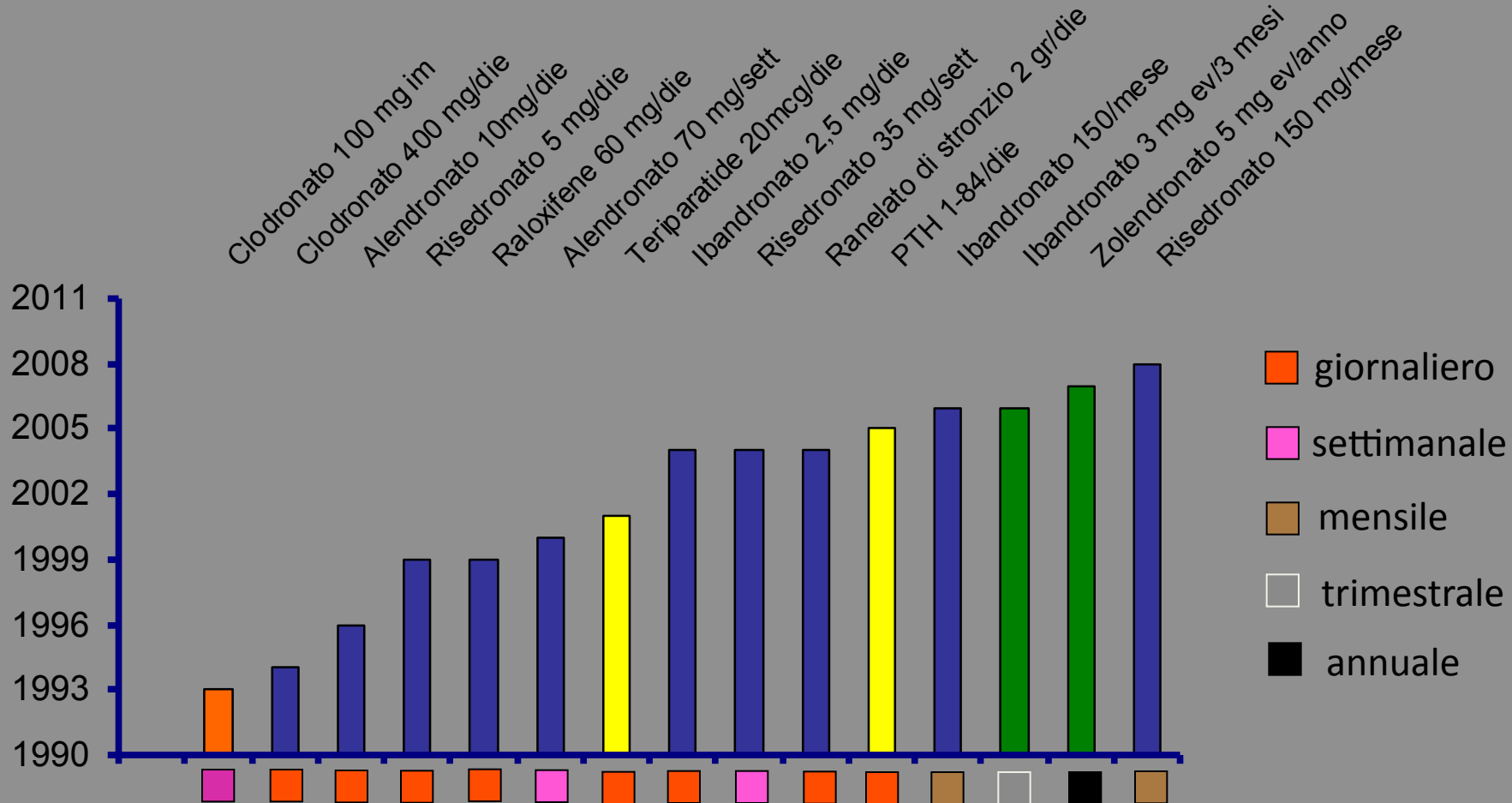
# Effetti del clodronato sulla struttura degli osteoclasti



- ❑ Distruzione del "ruffled border" (adesione tra osteoclasta e matrice ossea)
- ❑ Distruzione dello scheletro endocellulare di actina
- ❑ Apoptosi

# Storia della terapia per l'osteoporosi

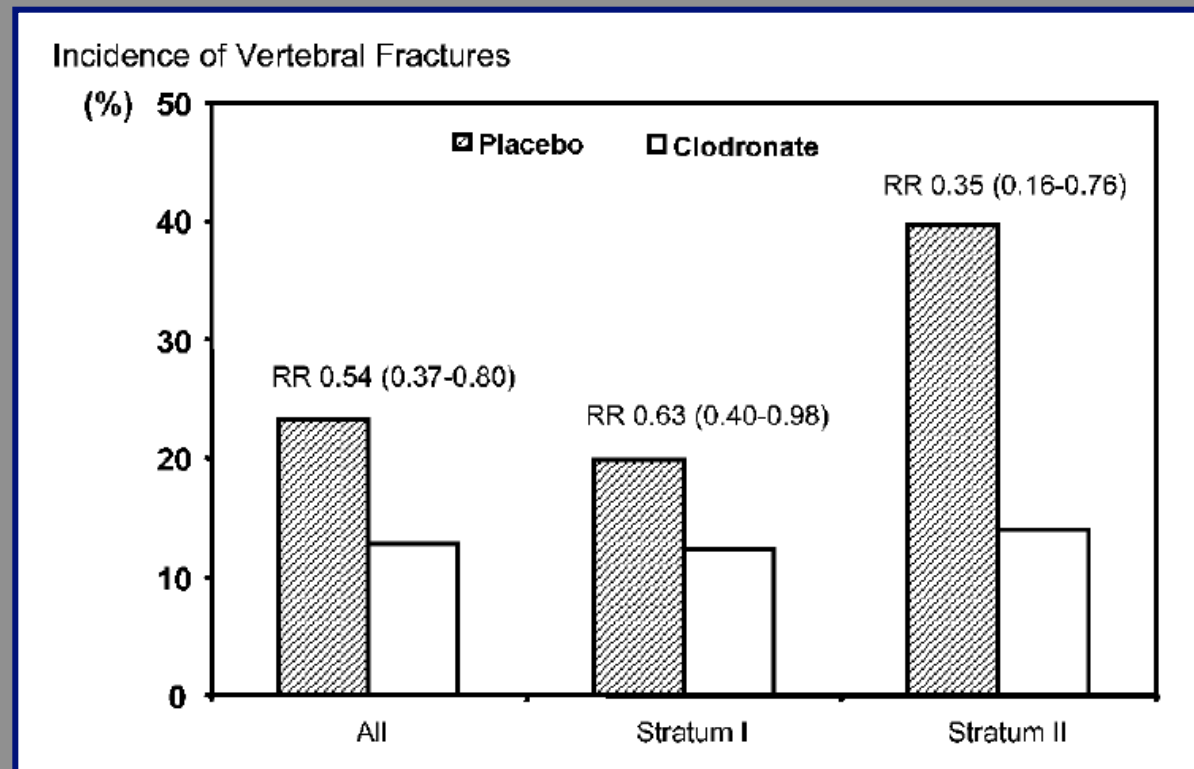
■ orale    
 ■ sottocute    
 ■ endovena    
 ■ intramuscolare



# Clodronate Reduces Vertebral Fracture Risk in Women With Postmenopausal or Secondary Osteoporosis: Results of a Double-Blind, Placebo-Controlled 3-Year Study

Eugene McCloskey, Peter Selby, Mike Davies, John Robinson, Roger M Francis, Judith Adams, Karthik Kayan, Monique Beneton, Tarja Jalava, Liisa Pylkkänen, Juha Kenraali, Sakari Aropuu, and John A Kanis

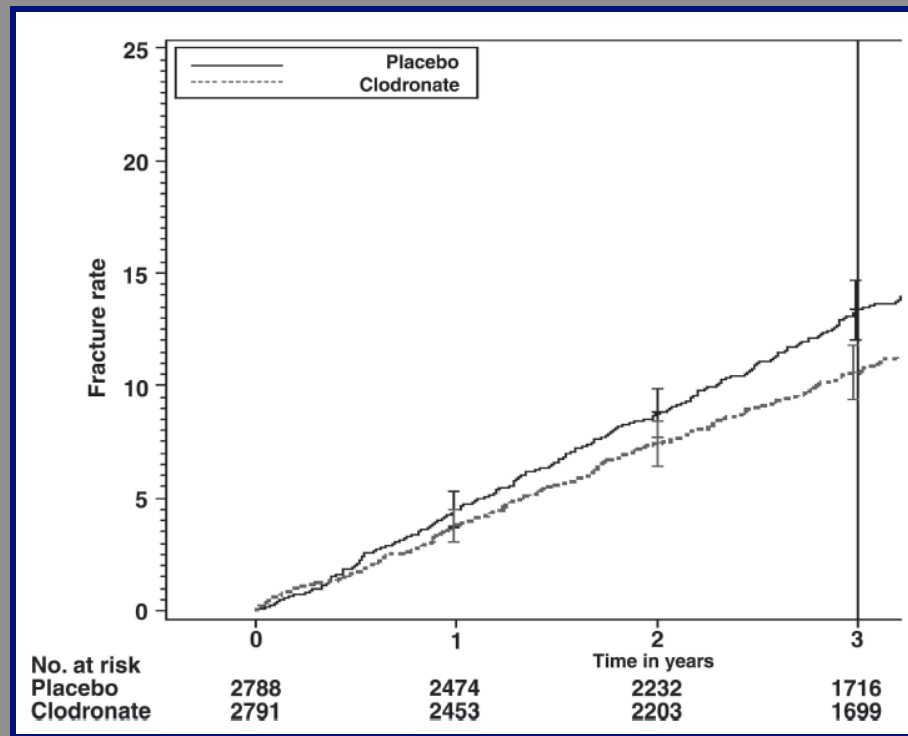
483 donne in postmenopausa con Op e/o almeno un frattura vertebrale (stratum 1)  
2 gruppi: clodronato 800 mg per os o placebo  
Durata dello studio 3 anni



**FIG. 2.** Incidence of vertebral fractures over 3 years in osteoporotic women. Clodronate 800 mg daily significantly reduced the incidence in all women, with similar effects in women with uncomplicated postmenopausal osteoporosis and with secondary osteoporosis.

# Clodronate Reduces the Incidence of Fractures in Community-Dwelling Elderly Women Unselected for Osteoporosis: Results of a Double-Blind, Placebo-Controlled Randomized Study

Eugene V McCloskey,<sup>1</sup> Monique Beneton,<sup>2</sup> Diane Charlesworth,<sup>1</sup> Karthik Kayan,<sup>1</sup> Dominic deTakats,<sup>1</sup> Abhijit Dey,<sup>1</sup> Jane Orgee,<sup>1</sup> Robert Ashford,<sup>1</sup> Martin Forster,<sup>1</sup> Jennifer Cliffe,<sup>1</sup> Linda Kersh,<sup>1</sup> John Brazier,<sup>3</sup> Jon Nichol,<sup>3</sup> Sakari Aropuu,<sup>4</sup> Tarja Jalava,<sup>4</sup> and John A Kanis<sup>2</sup>



**FIG. 3.** Kaplan-Meier plot of incident clinical fractures over entire study duration.

% riduzione: Fx cliniche 20 %, Fx di femore 29%

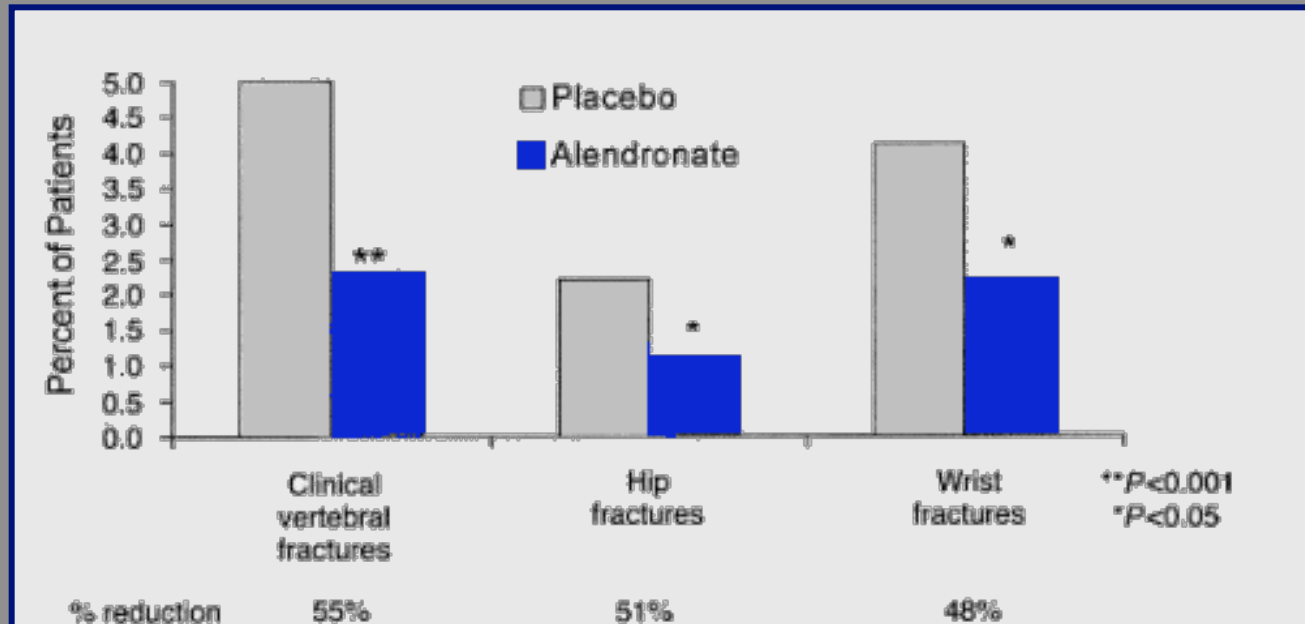
5592 donne di età ≥ 75 anni

2 gruppi: clodronato 800 mg per os o placebo

Durata dello studio 3 anni

# ALENDRONATO

Studio **FIT**



donne in post-menopausa di età tra 55 e 81 anni con Op con o senza una frattura vertebrale

2 gruppi: alendronato per os o placebo

Valutazione: Rx colonna, marcatori ossei, DXA

Durata dello studio 3 anni

# Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

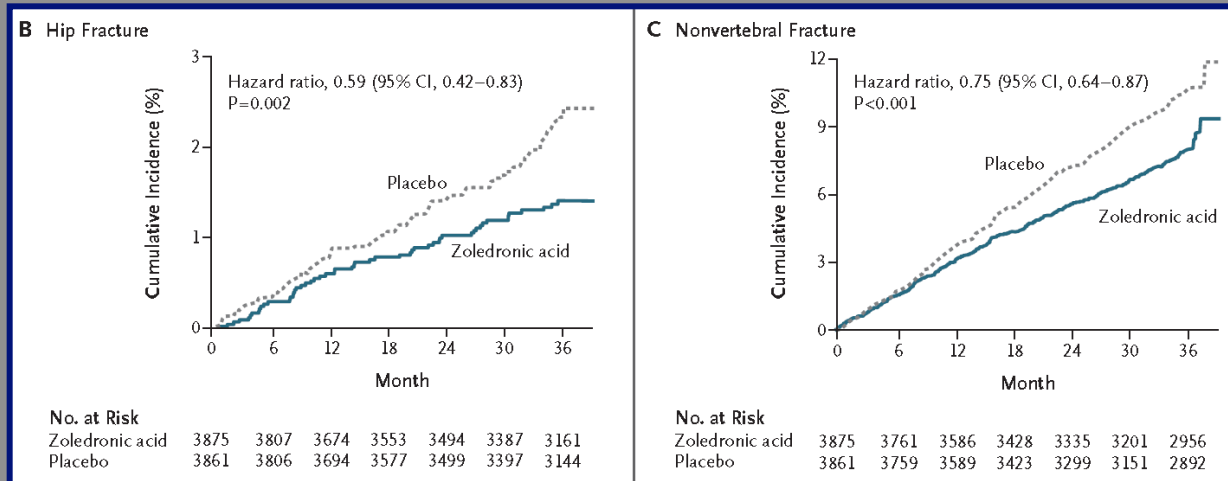
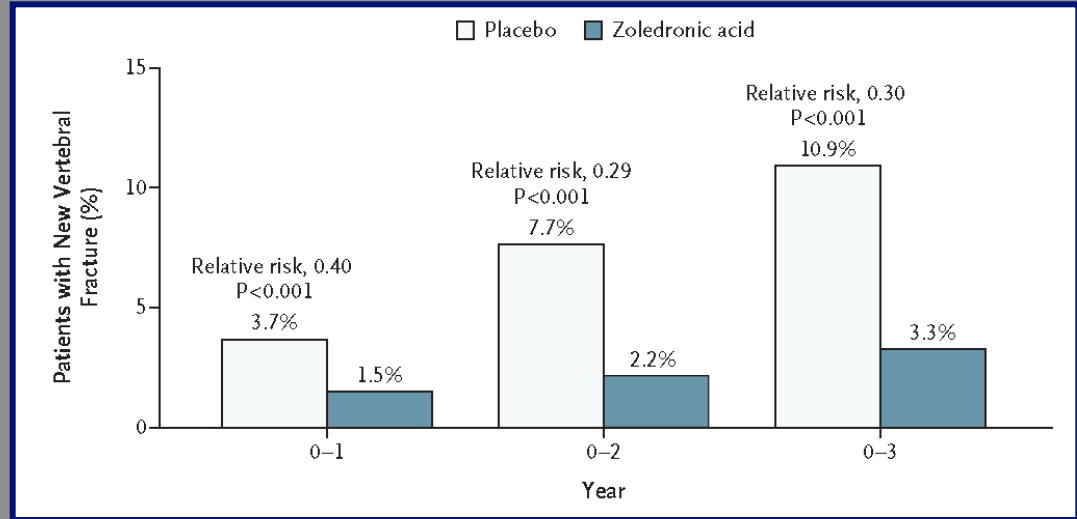
Dennis M. Black, et al

donne in post-menopausa di età tra 65 e 89 anni con Op con o senza una frattura vertebrale o con T-score femore <-1.5 e una frattura vertebrale moderata

2 gruppi: zolendronato iv o placebo

Valutazione: Rx colonna, marcatori ossei, DXA

Durata dello studio 3 anni



% riduzione: Fx vertebrali 70 %, Fx di femore 41%

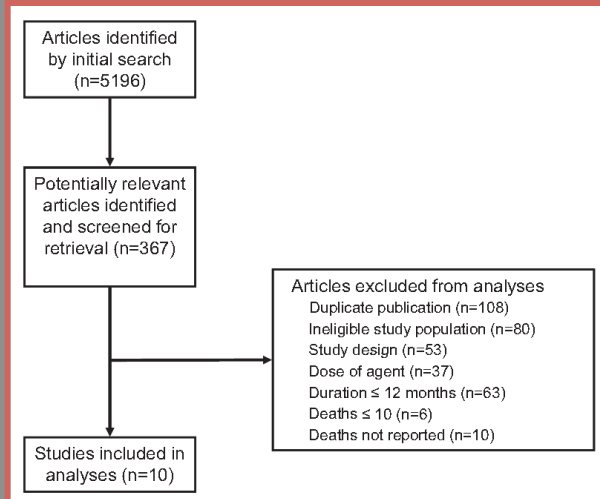


# EFFICACIA ANTIFRATTURATIVA DEI FARMACI ANTIOSTEOPOROTICI

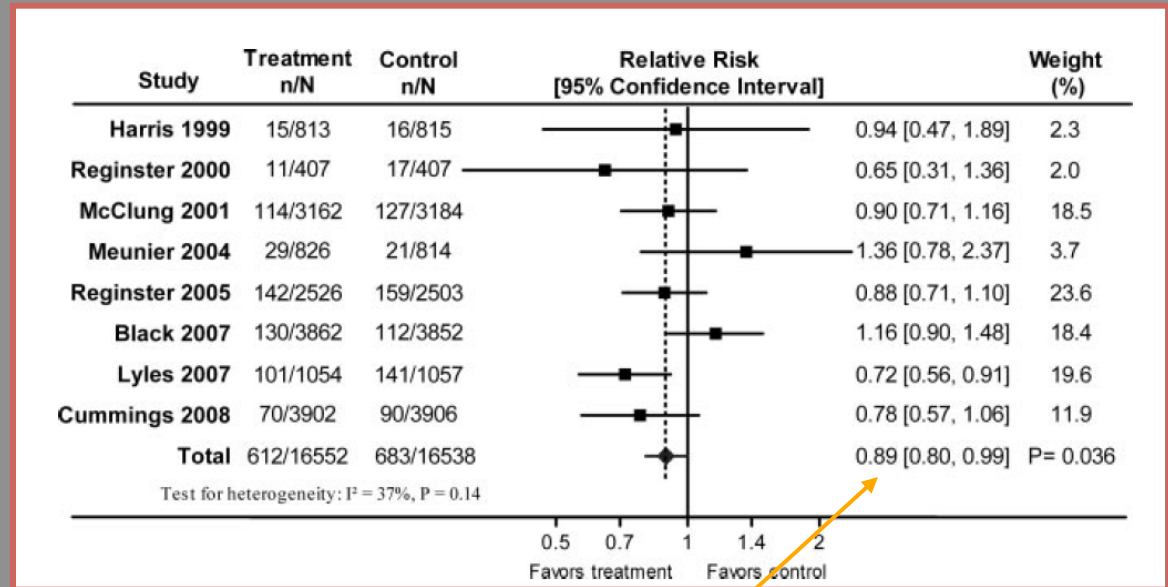
	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	Osteoporosis	Established osteoporosis <sup>a</sup>	Osteoporosis	Established osteoporosis <sup>a</sup>
Alendronate	+	+	NA	+ (Including hip)
Risedronate	+	+	NA	+ (Including hip)
Ibandronate	NA	+	NA	+ <sup>b</sup>
Zoledronic acid	+	+	NA	+ <sup>c</sup>
HRT	+	+	+	+ (Including hip)
Raloxifene	+	+	NA	NA
Teriparatide and PTH	NA	+	NA	+ <sup>d</sup>
Strontium ranelate	+	+	+ (Including hip <sup>b</sup> )	+ (Including hip <sup>b</sup> )
Denosumab	+	+ <sup>c</sup>	+ (Including hip)	+ <sup>c</sup>
Clodronate	+	+		

# Effect of Osteoporosis Treatment on Mortality: A Meta-Analysis

Mark J. Bolland, Andrew B. Grey, Greg D. Gamble, and Ian R. Reid

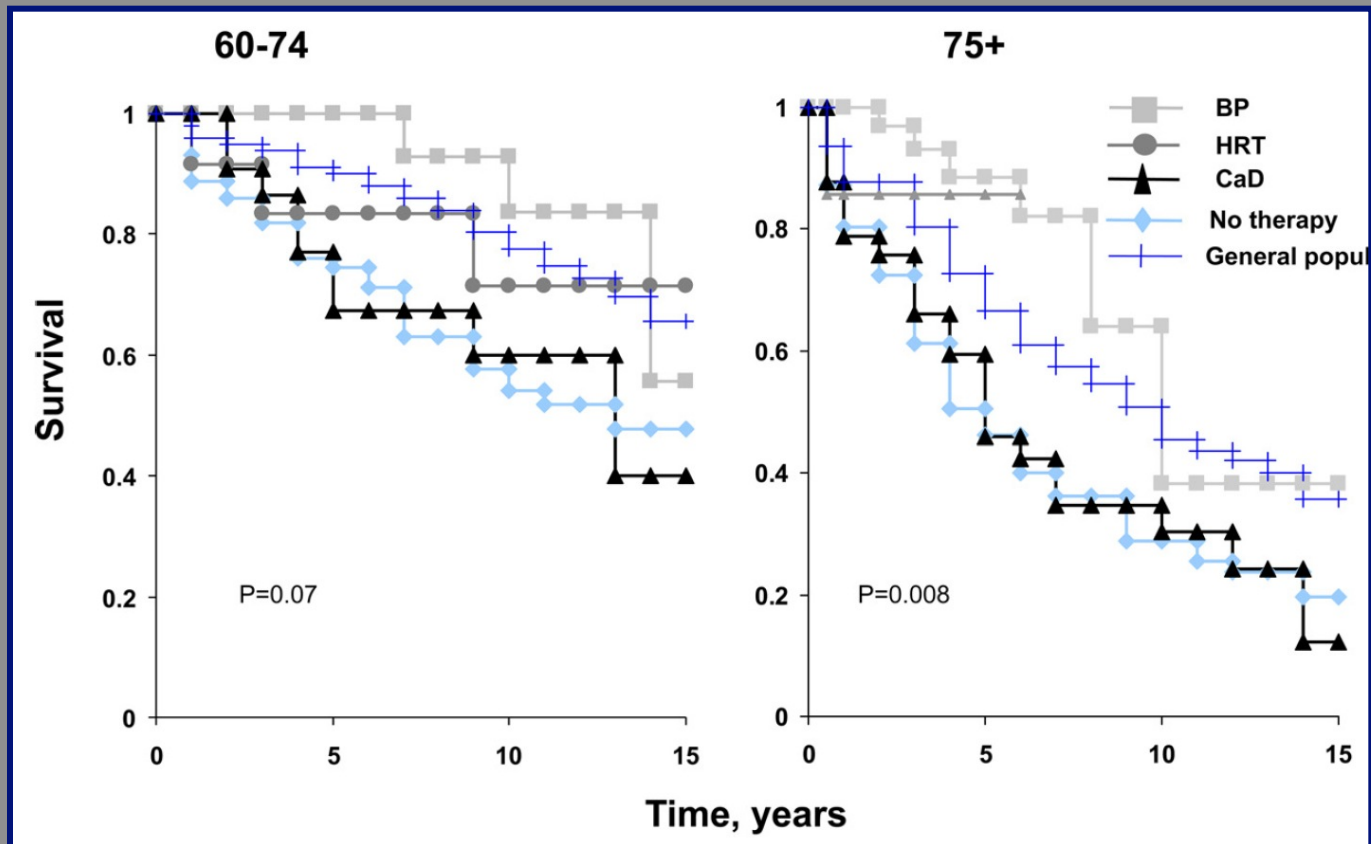


Study flow diagram



# Osteoporosis Medication and Reduced Mortality Risk in Elderly Women and Men

Jacqueline R. Center, Dana Bliuc, Nguyen D. Nguyen, Tuan V. Nguyen, and John A. Eisman



1223 donne di età ≥ di 60 anni  
Durata dello studio 15 anni

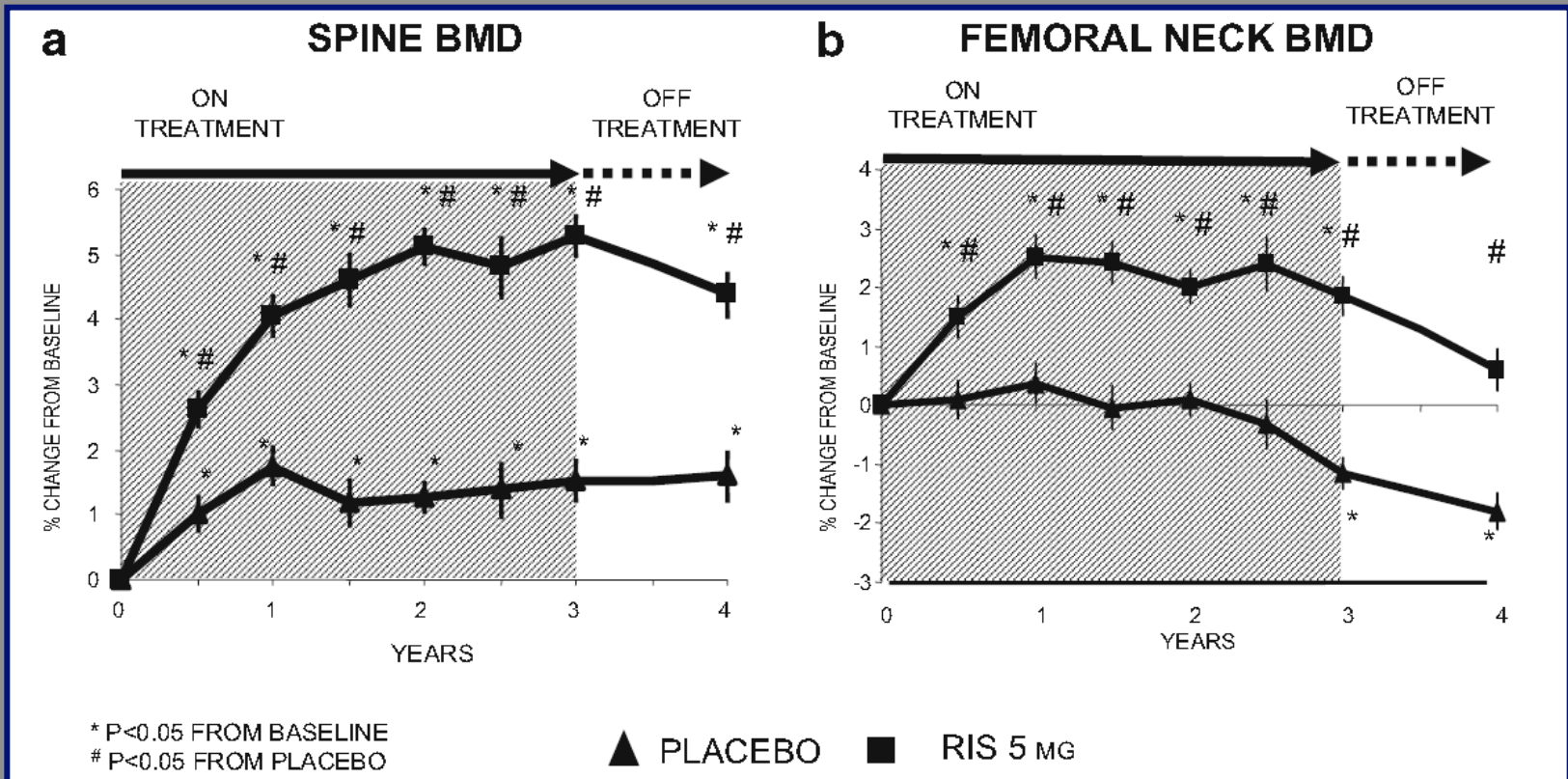
**FIG. 2.** Kaplan-Meier survival curves according to osteoporosis medication for women with osteoporotic fractures aged 60–74 yr (A), aged 75+ yr (B). The *P* value refers to differences between treatment groups.

## RISCHI ASSOCIATI ALLA TERAPIA CON BISFOSFONATI

- Osteonecrosi della mandibola
- Fratture atipiche del femore
- Fibrillazione atriale
- Cancro dell'esofago
- Disturbi gastro-intestinali
- Alterazione della funzione renale
- Sindrome influenzale
- Ipocalcemia
- Alterazioni infiammatorie degli occhi

# Fracture risk remains reduced one year after discontinuation of risedronate

N. B. Watts · A. Chines · W. P. Olszynski ·  
C. D. McKeever · M. R. McClung · X. Zhou · A. Grauer



Donne che avevano eseguito per 3 anni risedronato o placebo nello studio VERT-NA

Sono state seguite per 1 anno solo con calcio e vitamina D

Medication (Clinical Trial)	Y	Number Needed to Treat to Prevent One Fracture		
		Vert fx	Non-vert fx	Hip fx
Alendronate (FIT I) <sup>4</sup>	3	14	36	90
Alendronate (FIT II) <sup>5</sup>	3	60	68	447
Risedronate (VERT NA) <sup>6</sup> †	3	20	31	276
Risedronate (VERT MN) <sup>7</sup> †	3	9	20	203
Risedronate (HIP) <sup>8</sup>	3	NA	56	91
Zoledronic acid (HORIZON PFT) <sup>9</sup>	3	13	37	91
Zoledronic acid (HORIZON RFT) <sup>10</sup>	3	NA	32	67
Ibandronate (BONE) <sup>15</sup> †	3	20	NA	NA
Alendronate (Men) <sup>17</sup>	2	9	NA	NA
Risedronate (GIO) <sup>18</sup>	1	9	NA	NA

ONJ: 1:10.00-1:100.000

Fratture atipiche: 8:10.000 pazienti/anno

# Bisphosphonate Therapy for Osteoporosis: Benefits, Risks, and Drug Holiday

Michael McClung, et al

**Table 2** Recommendations for Drug Holiday from Bisphosphonates

Patient Category	Recommendation	Comment
High-risk: T-score still $\leq -2.5$ at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.	Drug holiday not justified.	Re-assess the need for therapy at regular intervals.
Moderate risk: Hip bone mineral density value is now $> -2.5$ (T-score), and no prior hip or spine fracture.	Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy. No information about ibandronate and drug holidays.	These patients should not be forced to take a drug holiday—decision should be an individual, informed choice with discussion of the potential benefits and risks.
Low risk: Did not meet current treatment criteria at the time of treatment initiation.	Discontinue therapy	Re-start when indications for therapy are met.

## MONITORAGGIO DELLA VACANZA TERAPEUTICA

- Significativa diminuzione della densità ossea
- Aumento significativo dei marcatori ossei
- Rivalutazione dei pazienti dopo 2-3 anni dall'interruzione della terapia con la valutazione del rischio di frattura con le carte del rischio
- Comparsa di una nuova frattura da fragilità



# NUOVI SCHEMI TERAPEUTICI

- Terapia sequenziale

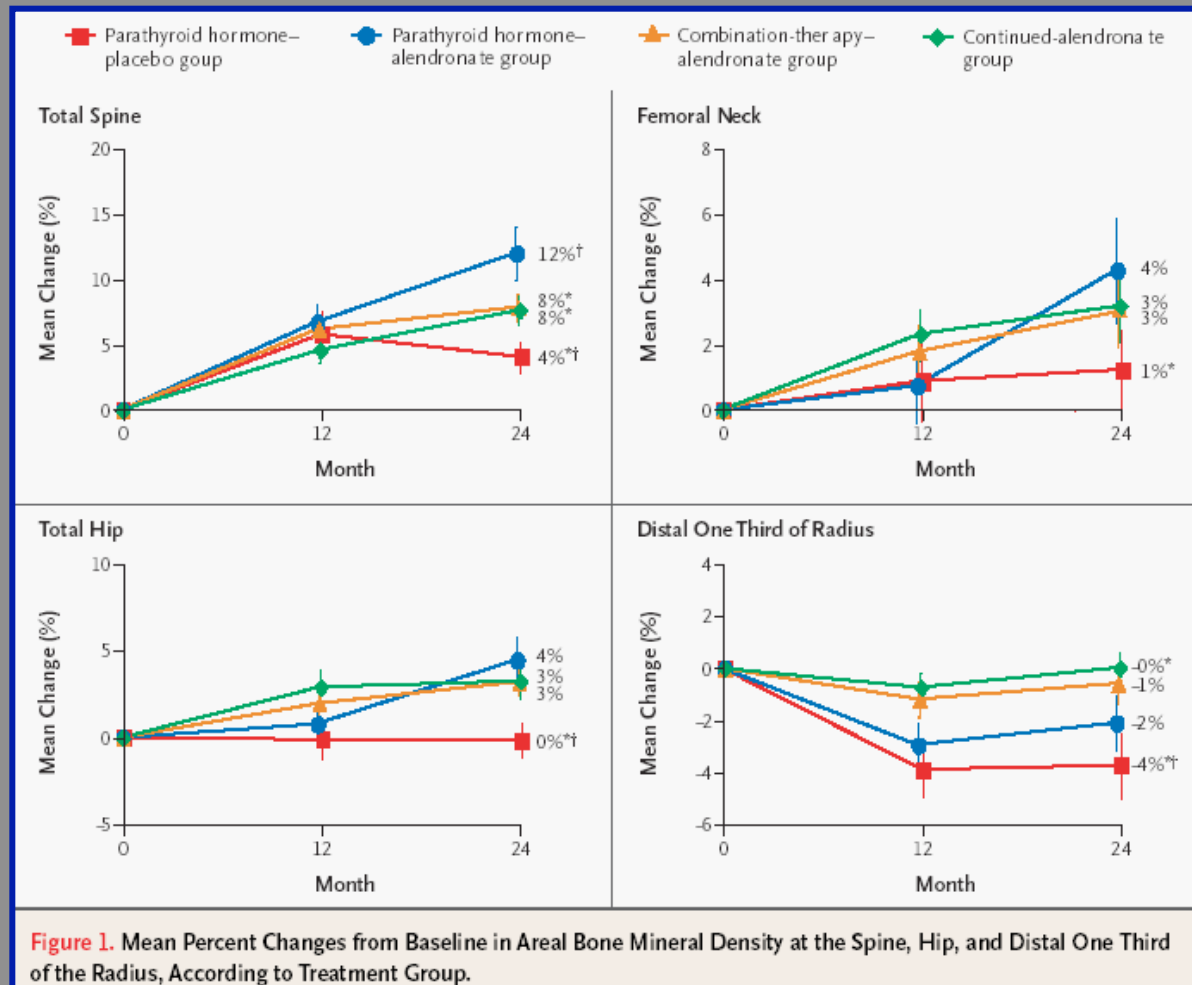
- Bisfosfonato  bisfosfonato
- Bisfosfonato  altro farmaco antiriassorbitivo
- Bisfosfonato  farmaco anabolico
- Farmaco anabolico  bisfosfonato

- Terapia combinata

- Farmaco anabolico + farmaco antiriassorbitivo
- farmaco antiriassorbitivo + farmaco antiriassorbitivo

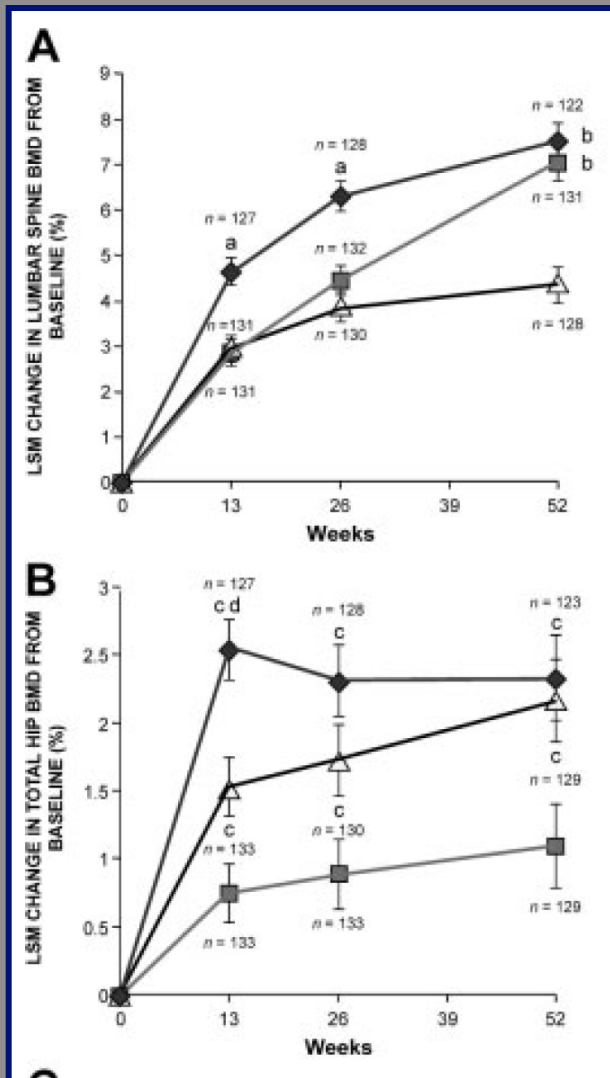
# One Year of Alendronate after One Year of Parathyroid Hormone (1–84) for Osteoporosis

238 PM women with OP randomly assigned to PTH (1-84) or alendronate (10 mg) or both treatments for one yr



# Effects of Intravenous Zoledronic Acid Plus Subcutaneous Teriparatide [rhPTH(1-34)] in Postmenopausal Osteoporosis

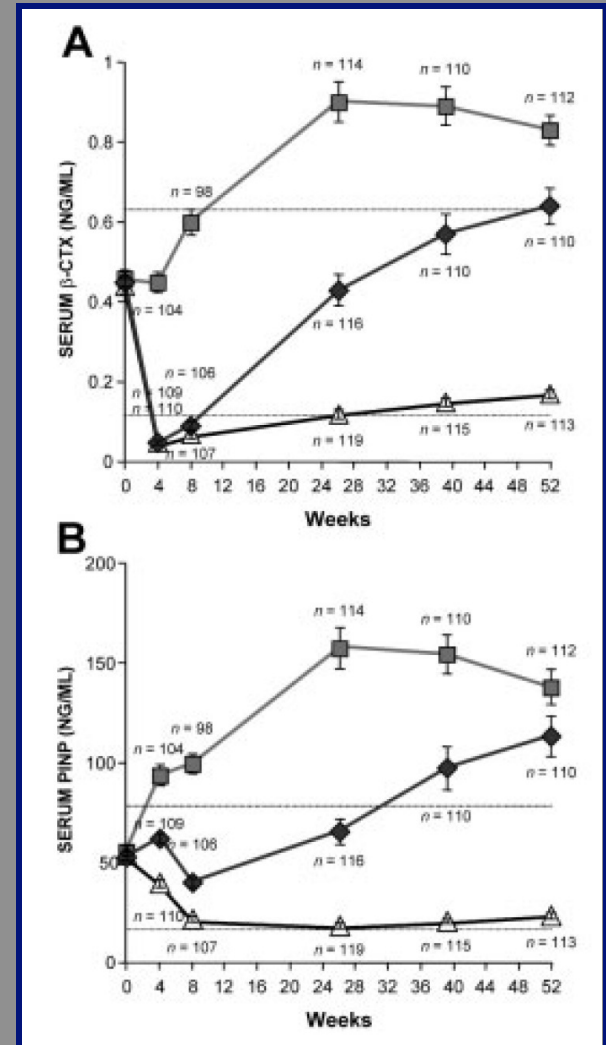
Felicia Cosman, et al

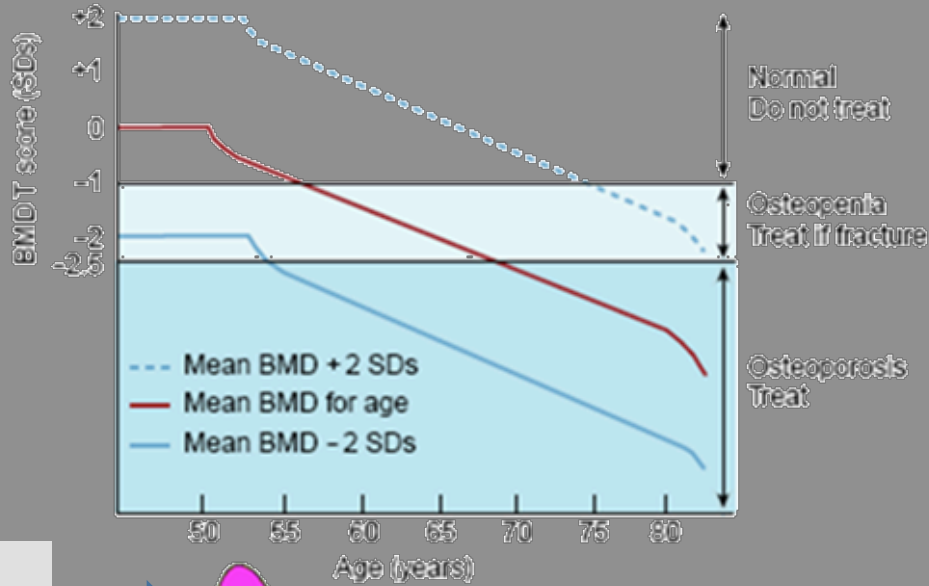


412 donne in postmenopausa con osteoporosi

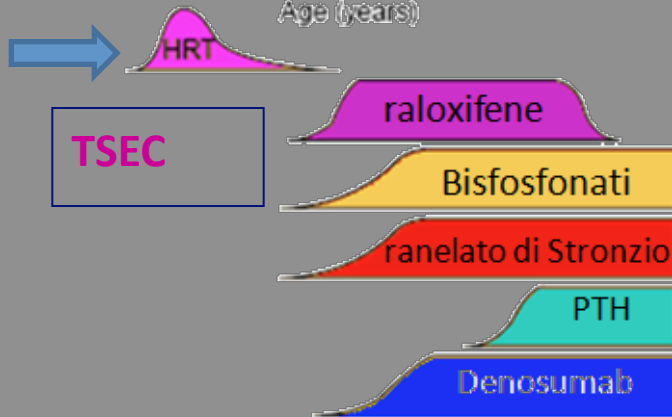
3 gruppi: Acido Zoledronico 5 mg più teriparatide giornaliero, acido zoledronico da solo o teriparatide da solo

Durata dello studio 52 settimane





solo se  
concomitano  
sintomi climaterici



Vacanza terapeutica

max 2 anni

- supplem di calcio (se carente)
- supplem di vitD (se carente)
- corretto stile di vita

# The future of osteoporosis treatment – a research update

*Kurt Lippuner*

