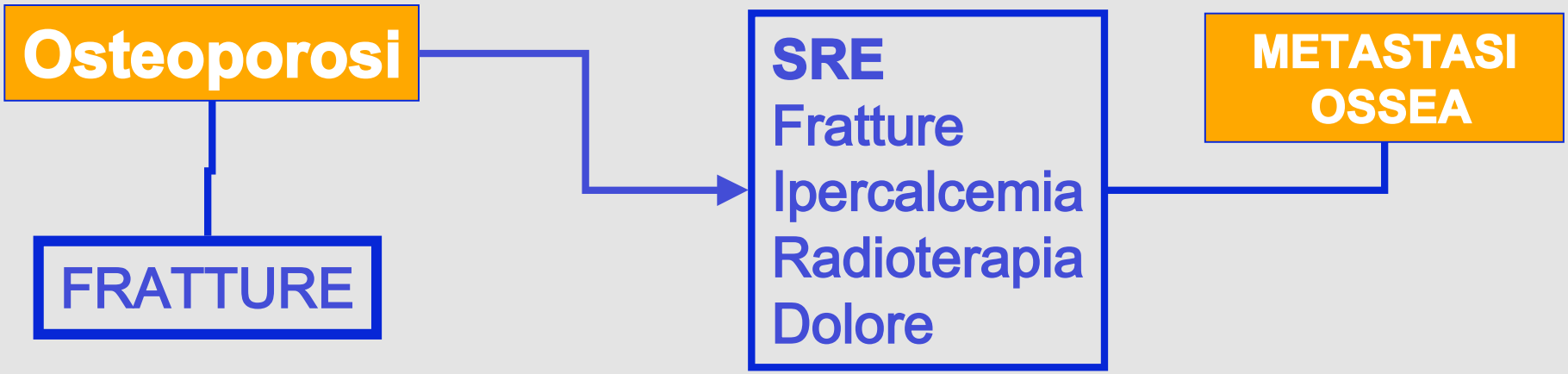
I Bisfosfonati nel Paziente Oncologico ed Ematologico

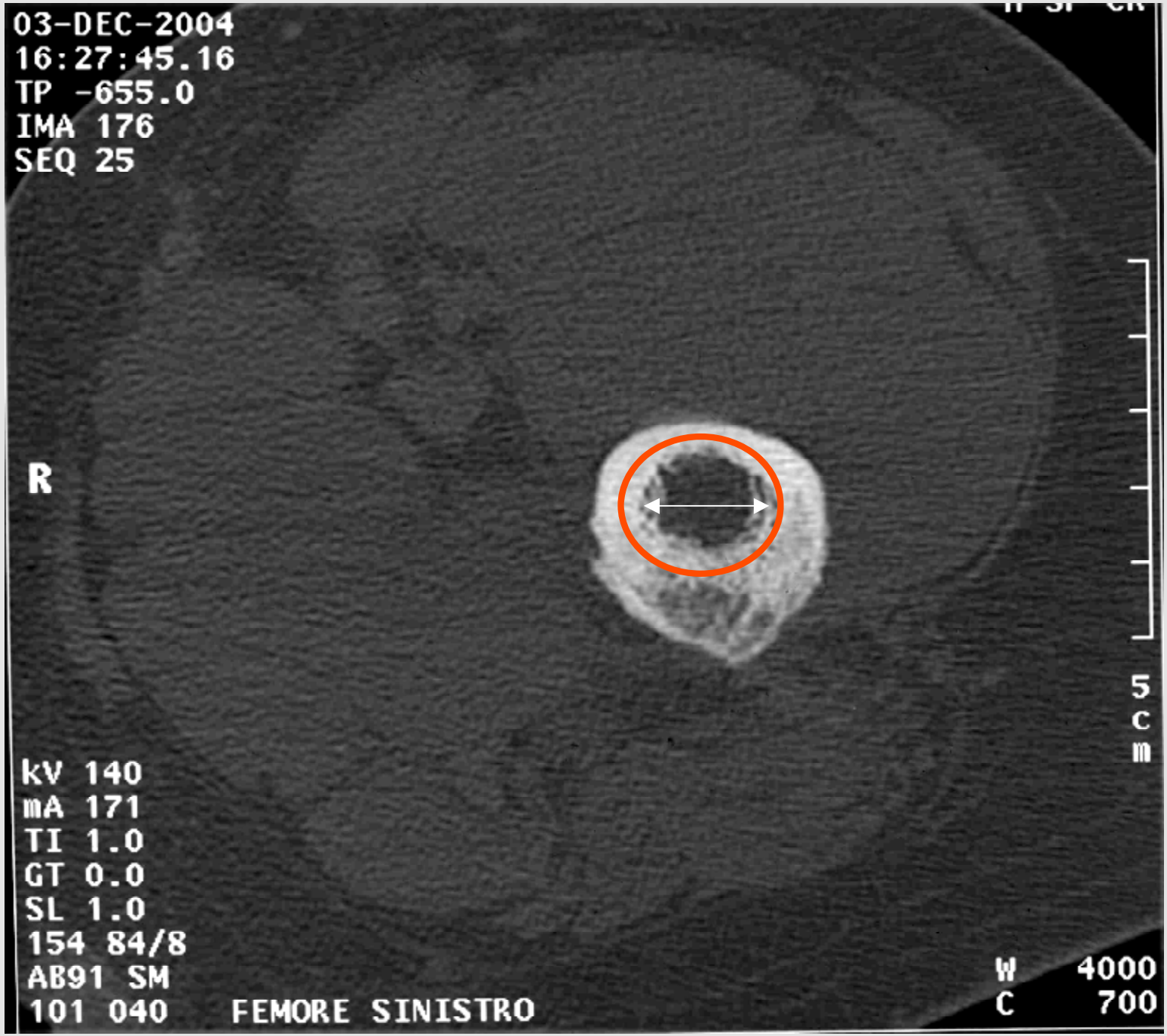
IL FUTURO DEI BISFOSFONATI

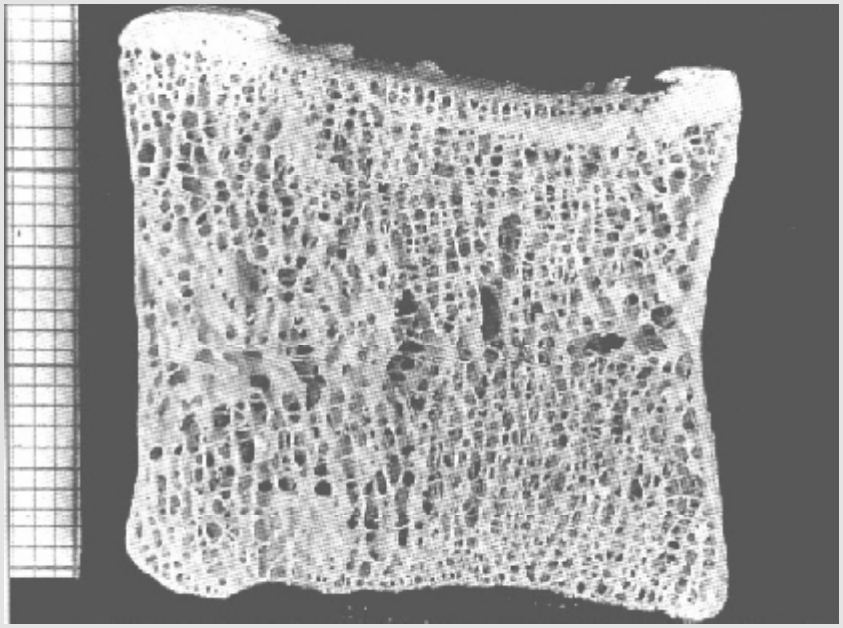
Cancer Treatment Induced Bone Loss

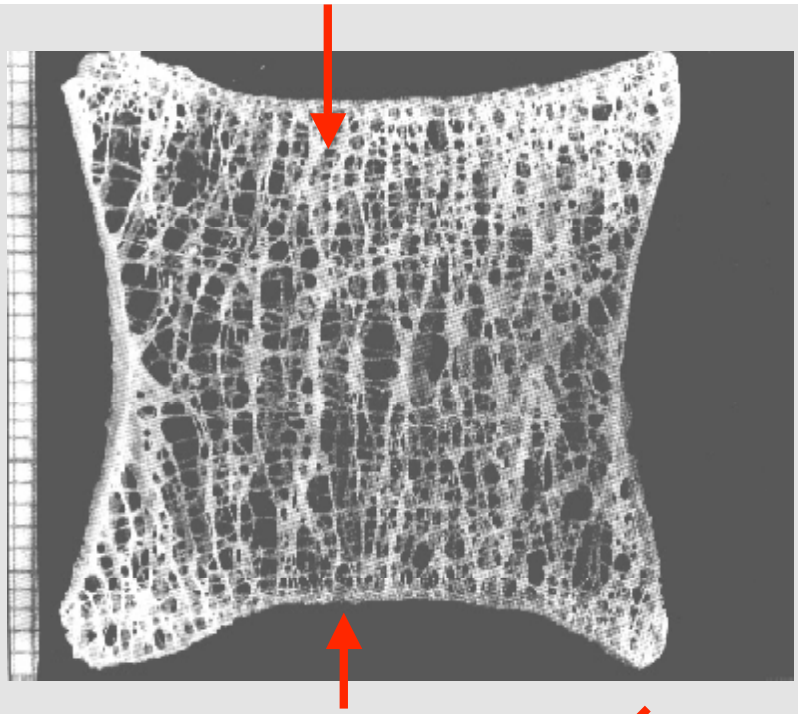
Francesco Bertoldo
Dipartimento di Scienze Biomediche e Chirurgiche
Università di Verona

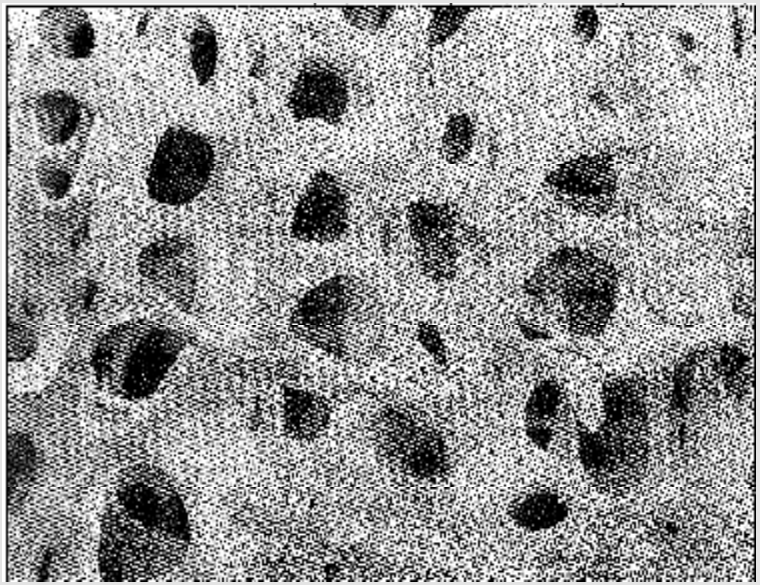
“Bone Health” nel Paziente Neoplastico

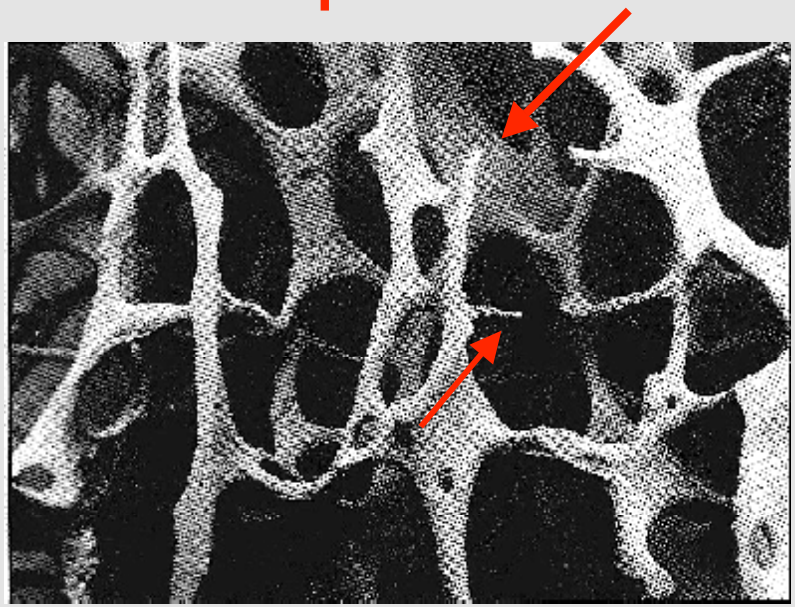



03-DEC-2004
16:27:45.16
TP -655.0
IMA 176
SEQ 25
R
5 cm
kV 140
mA 171
TI 1.0
GT 0.0
SL 1.0
154 84/8
AB91 SM
101 040
FEMORE SINISTRO
W 4000
C 700

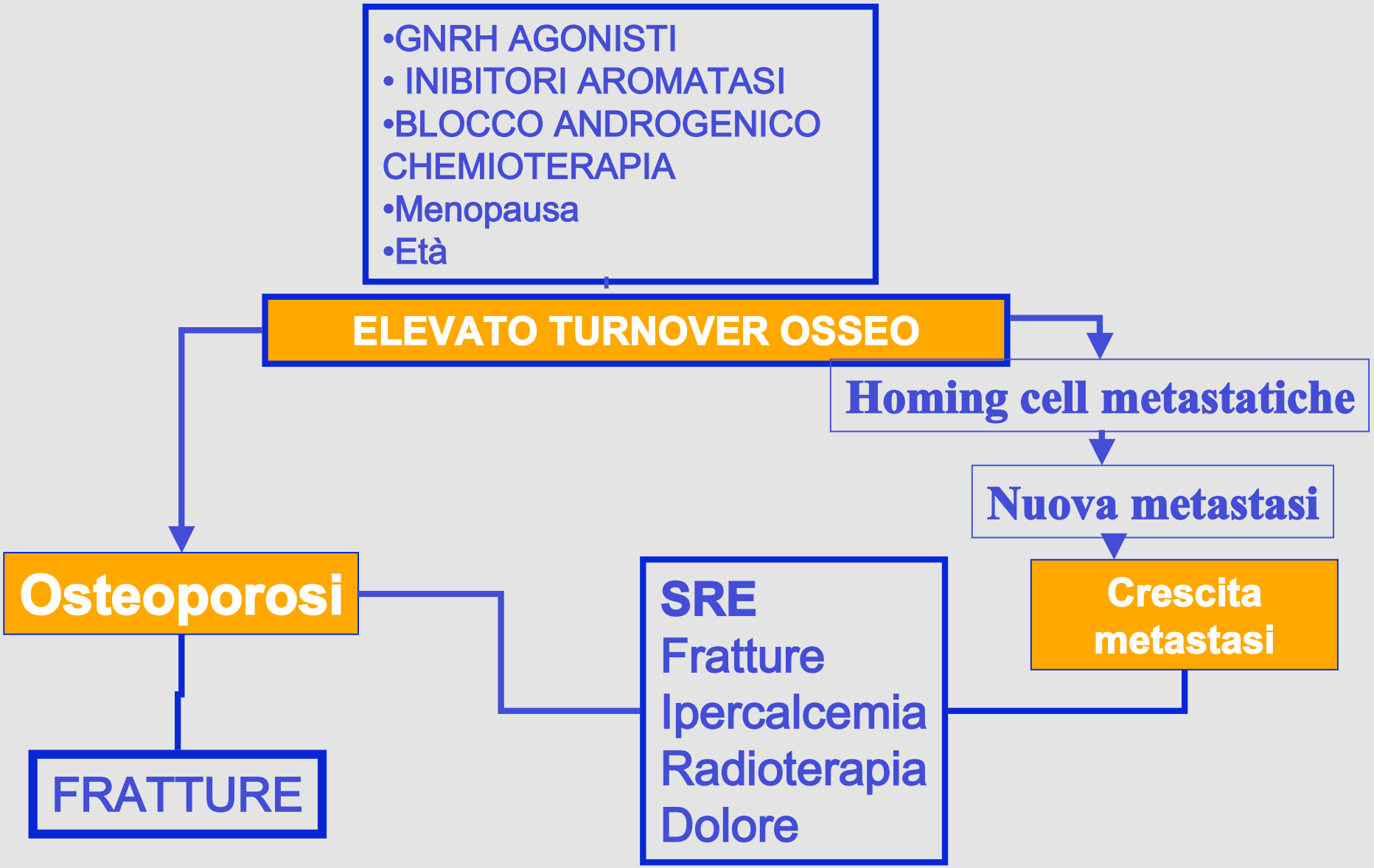




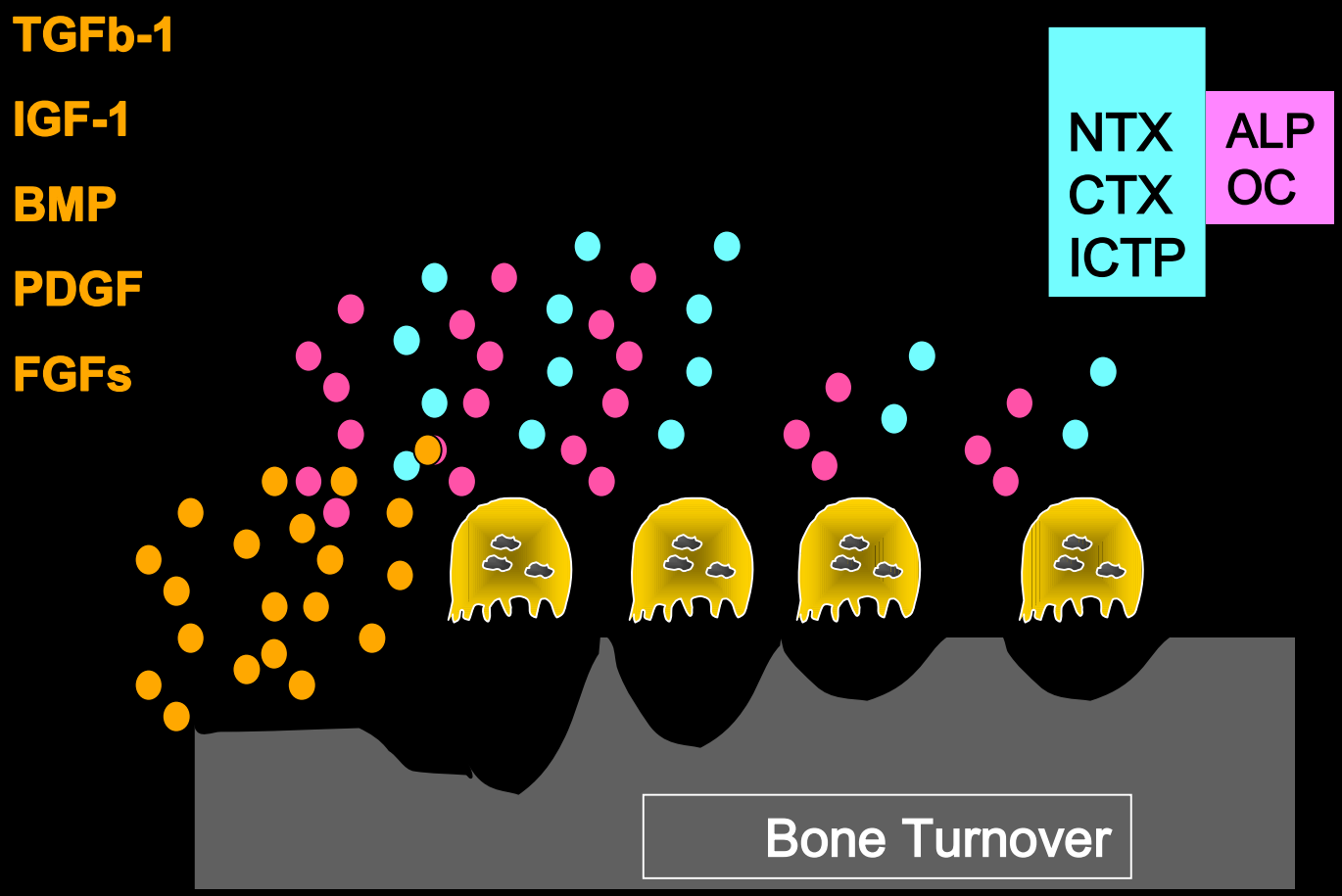




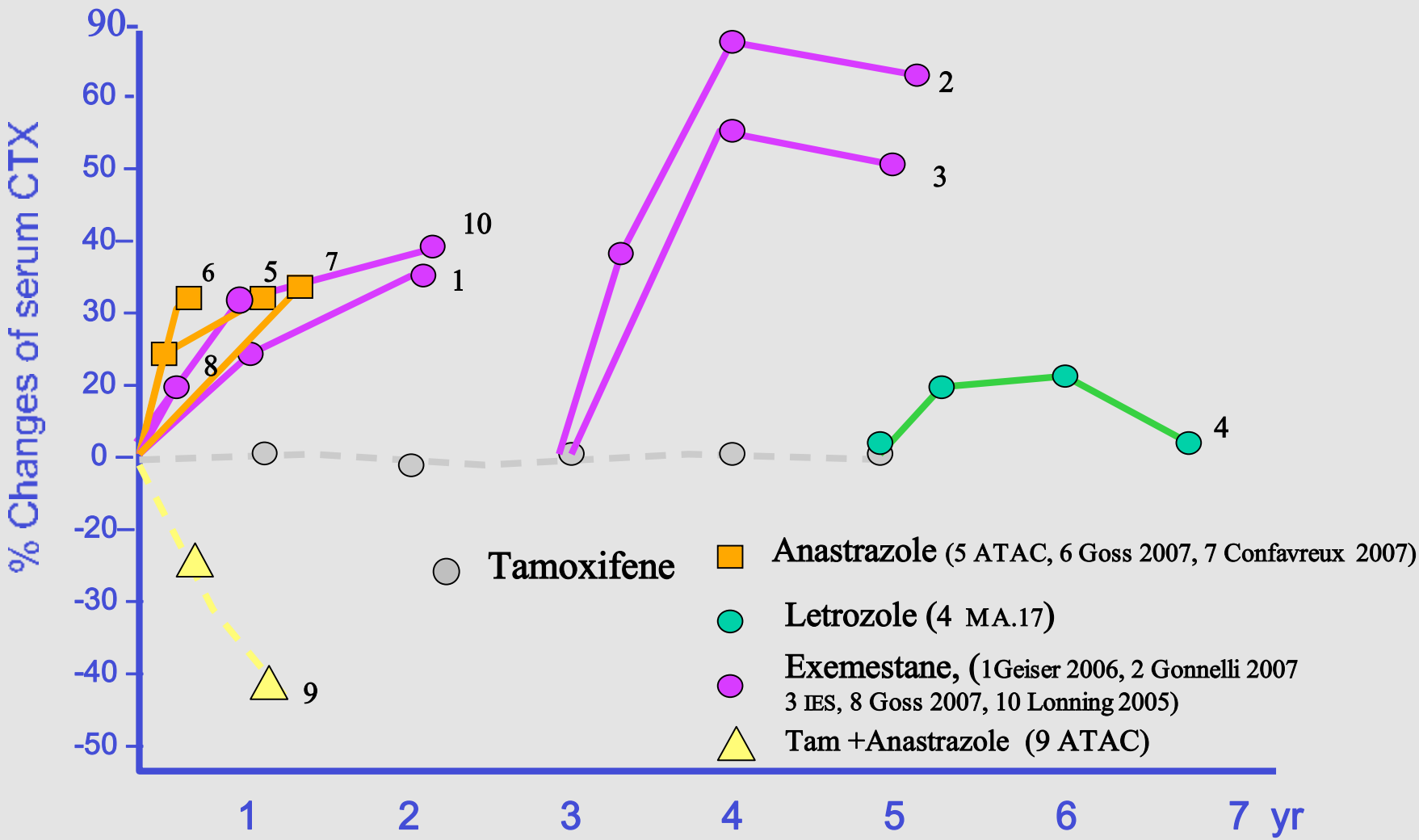
“Bone Health” nel Paziente Neoplastico



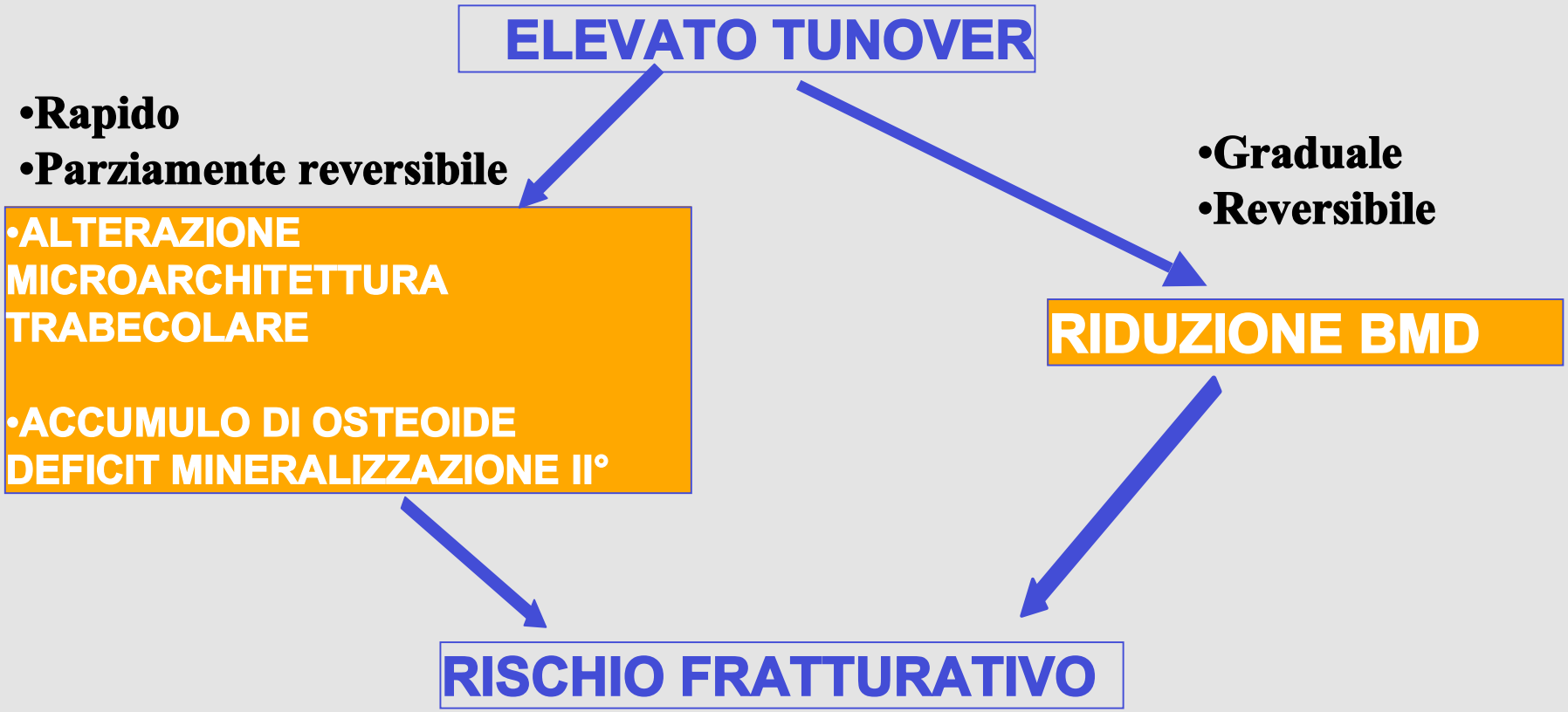
TURNOVER OSSEO



BONE TURNOVER: BONE RESORPTION DURING AIs TREATMENT

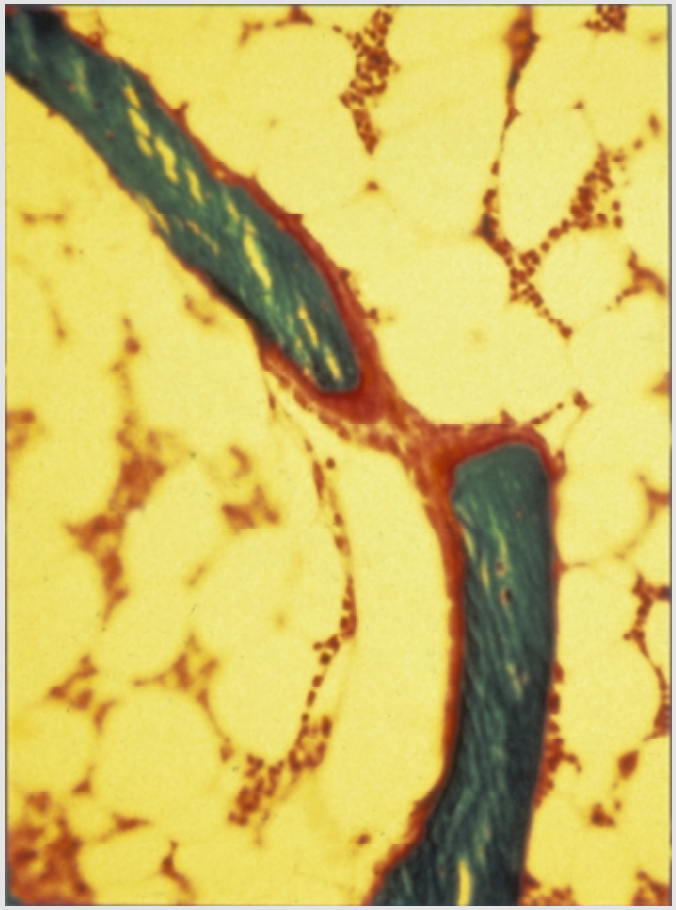


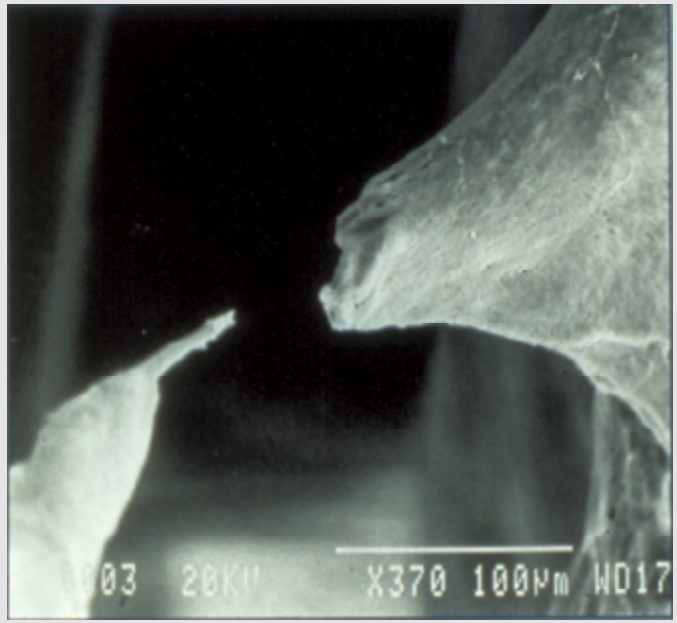
BMD, TURNOVER OSSEO E RISCHIO DI FRATTURA



Boivin G et al. *Connect Tissue Res.* 2002;43:535-537.

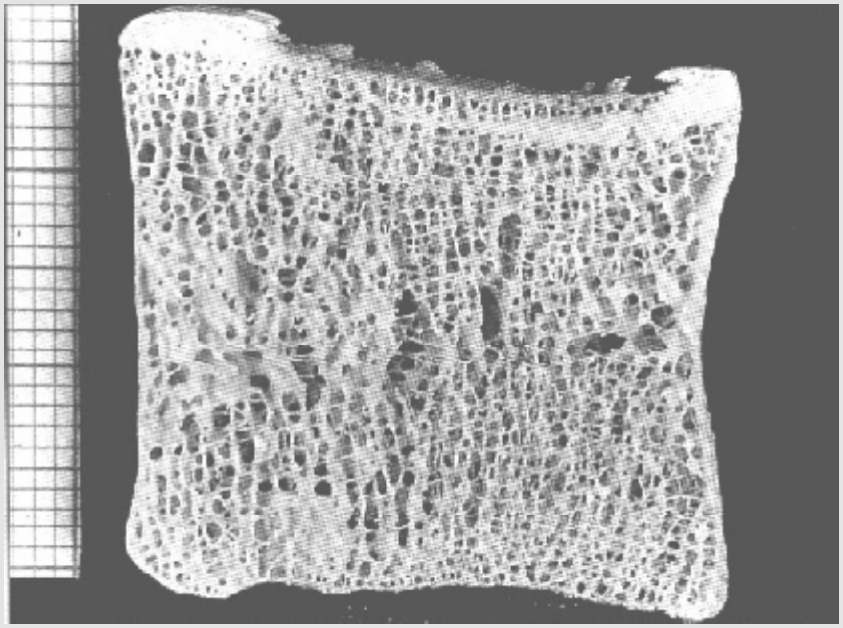
Perforazioni trabecolari

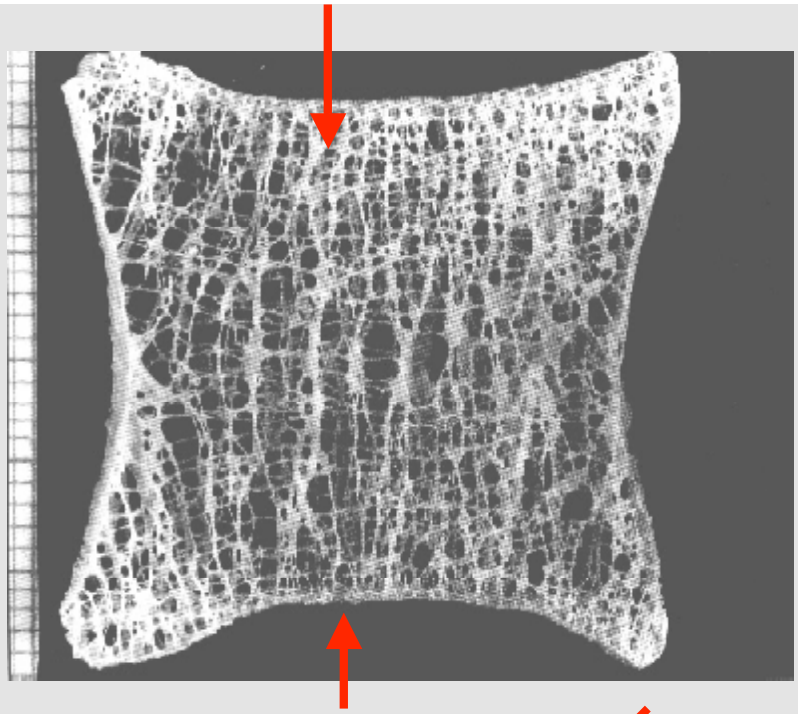


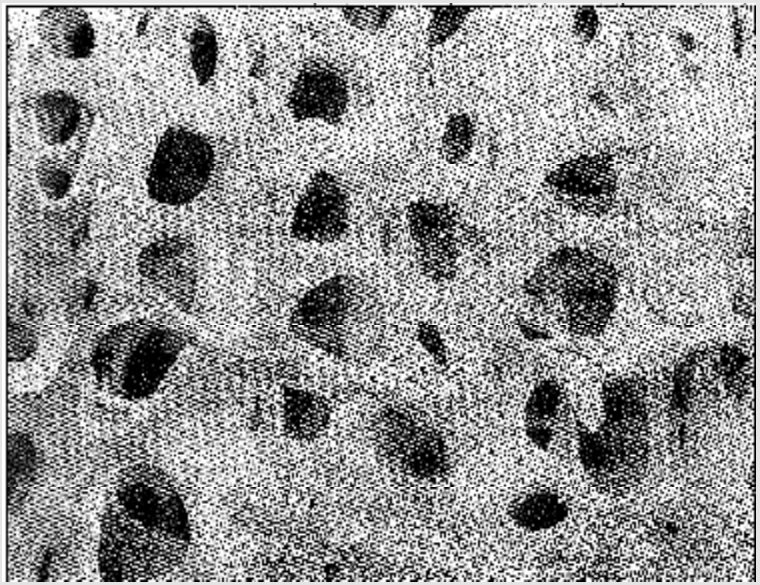


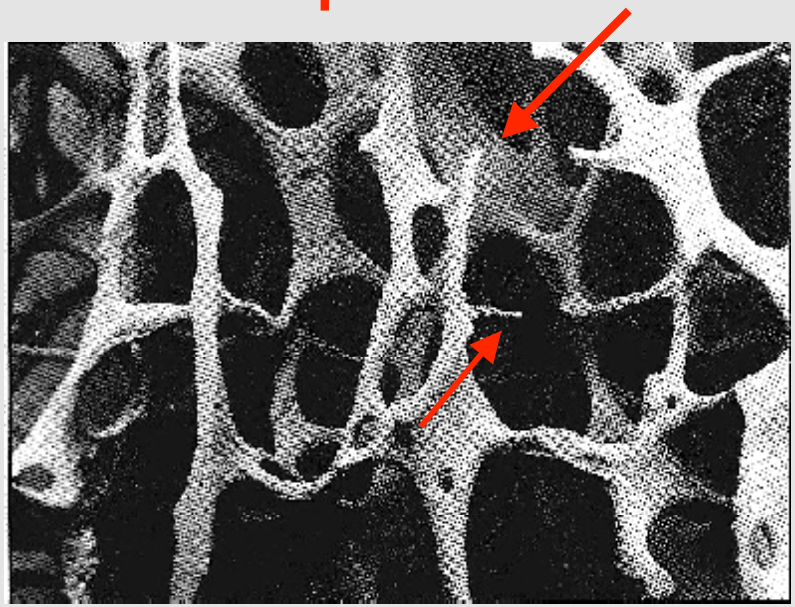
Mosekilde L. *Bone Miner* 10: 13-35, 1990

Seeman *Lancet* 359, 1841-1850, 2002.



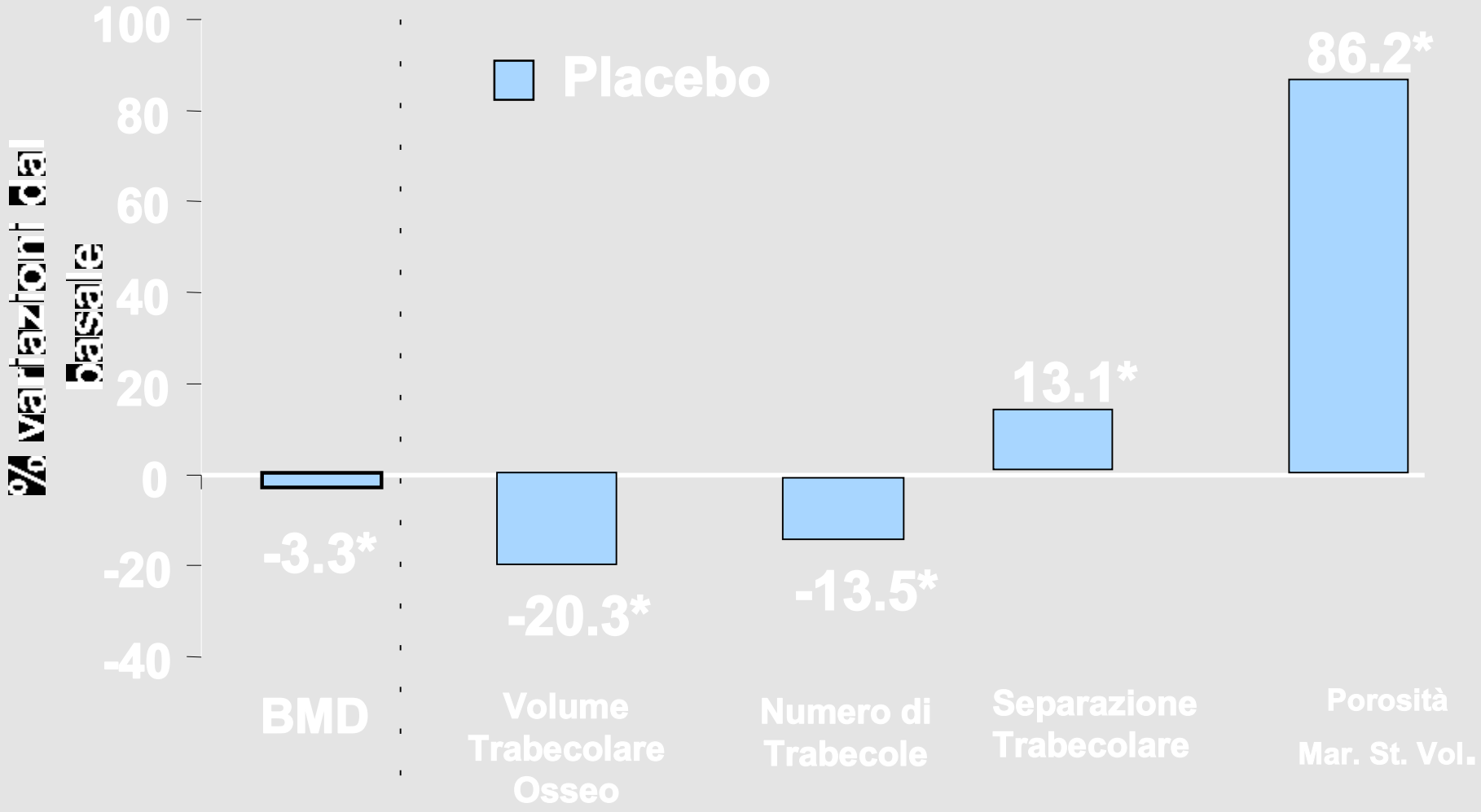






Rapido deterioramento della micro-architettura

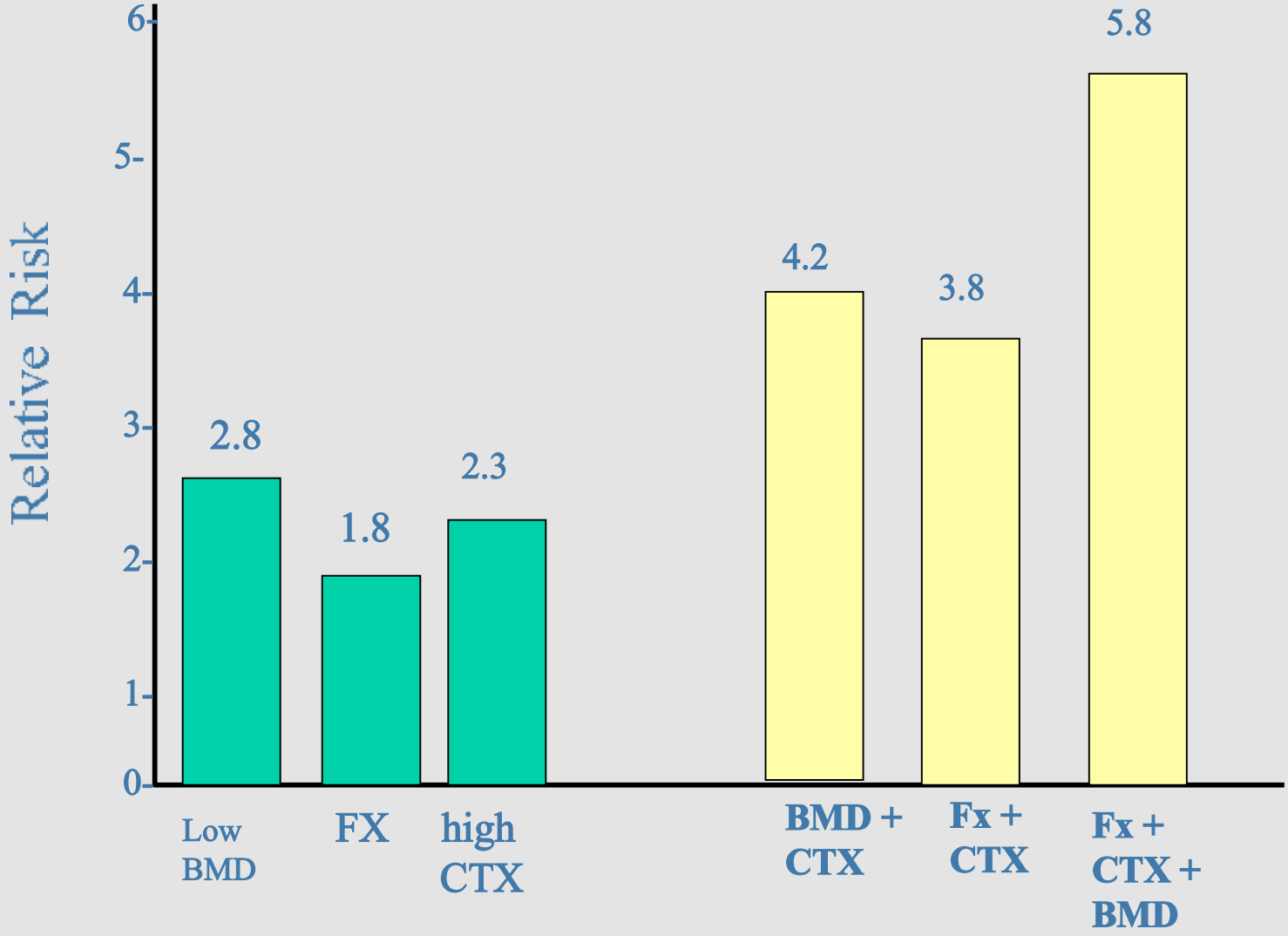
ad 1 Anno



*p<0.05 vs basale

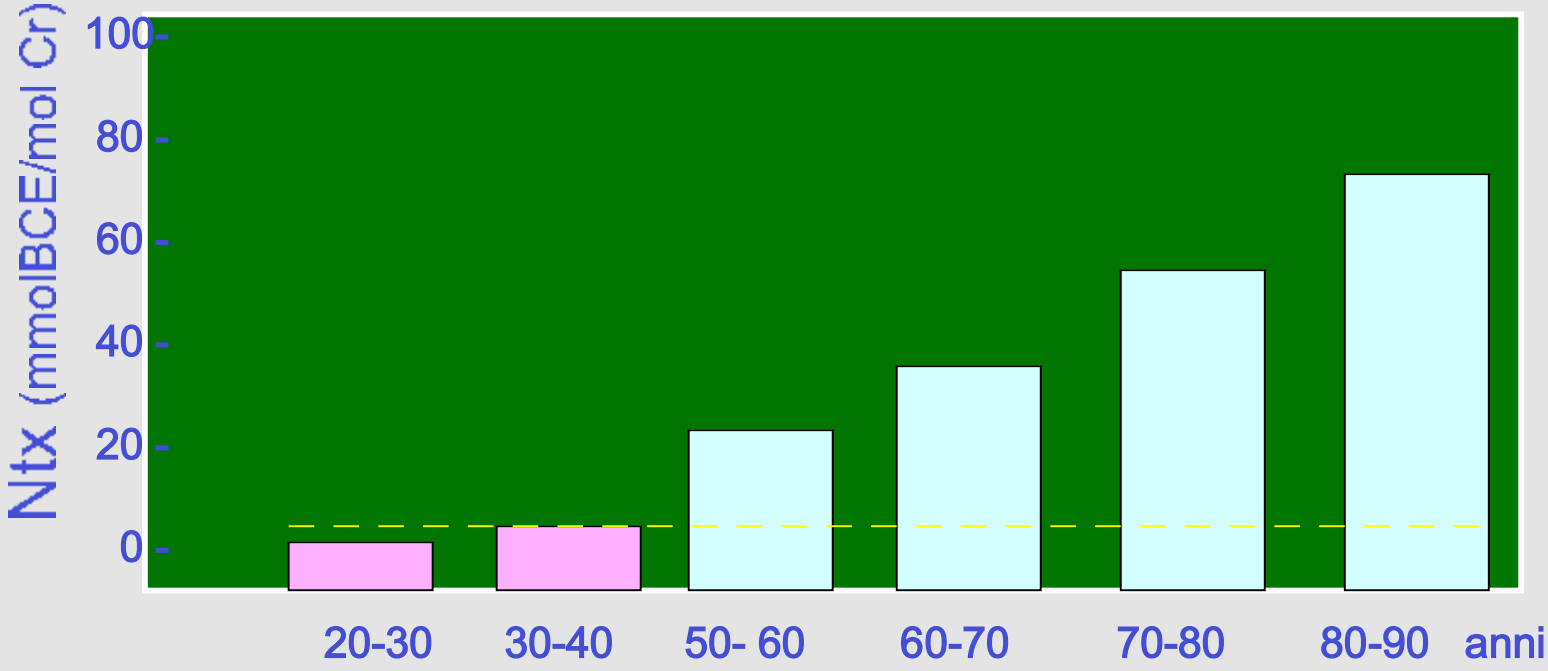
Dufresne TE, et al. Calcif Tis Int 2003

La Combinazione di più Fattori di Rischio Indipendenti nella Predizione del Rischio di Frattura



Garnero P, J Bone Min Res 2000

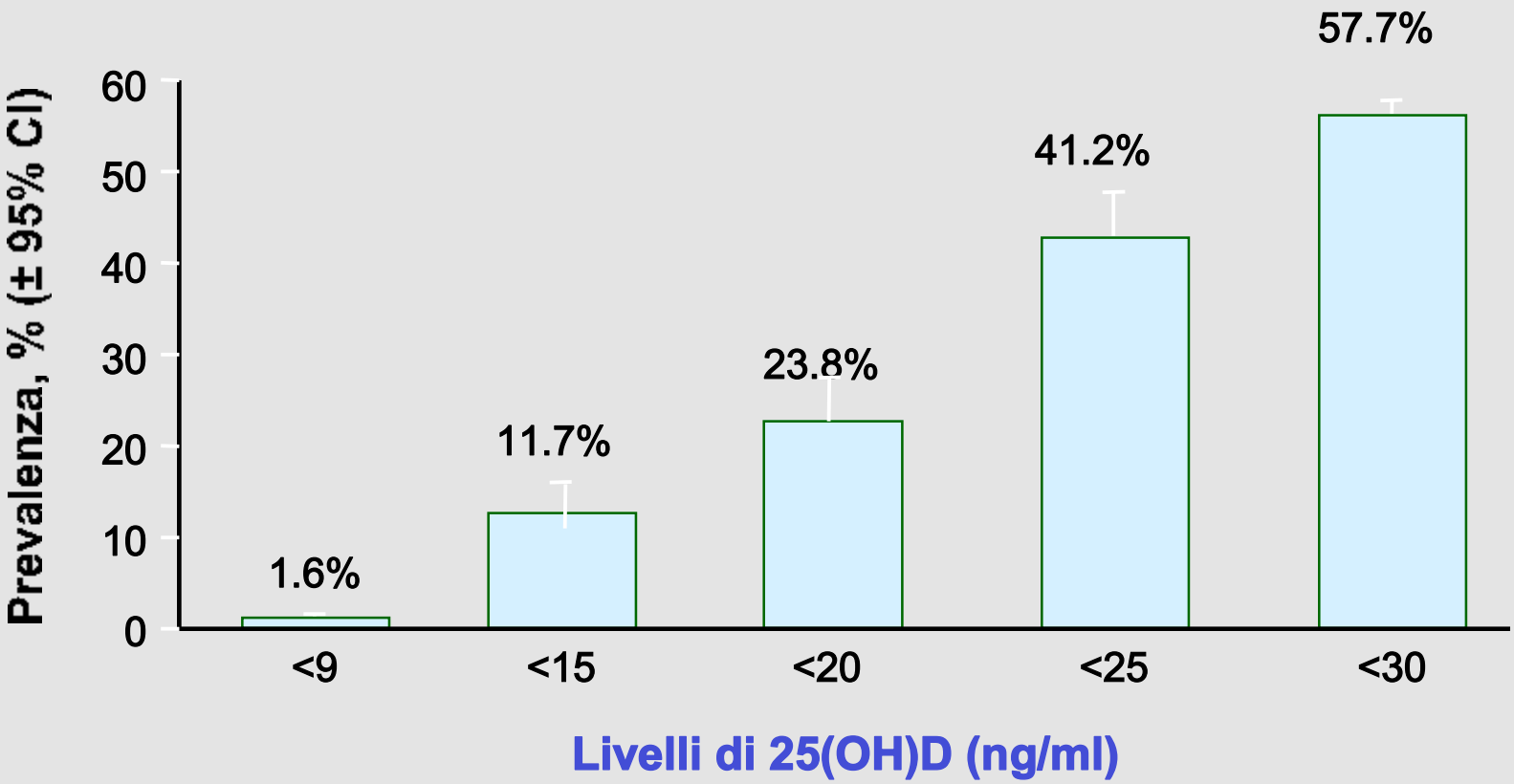
Turnover Osseo ed Età



Garnero JBMR 1996; Bauer JBMR 1999

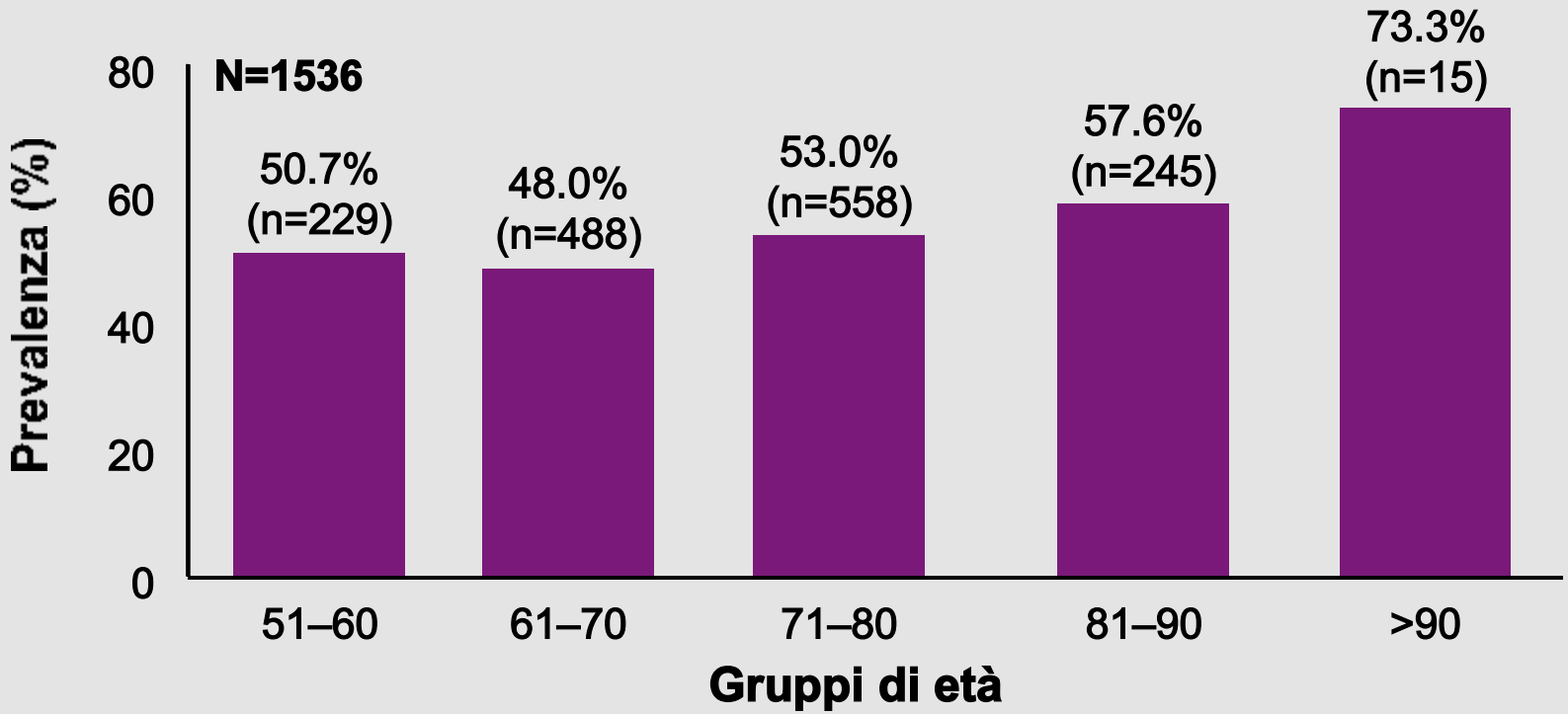
The Prevalence of Vit D Inadequancy Among Women

(Europe 10200 women >50 yo)



Lips P *J Int Med 2006*

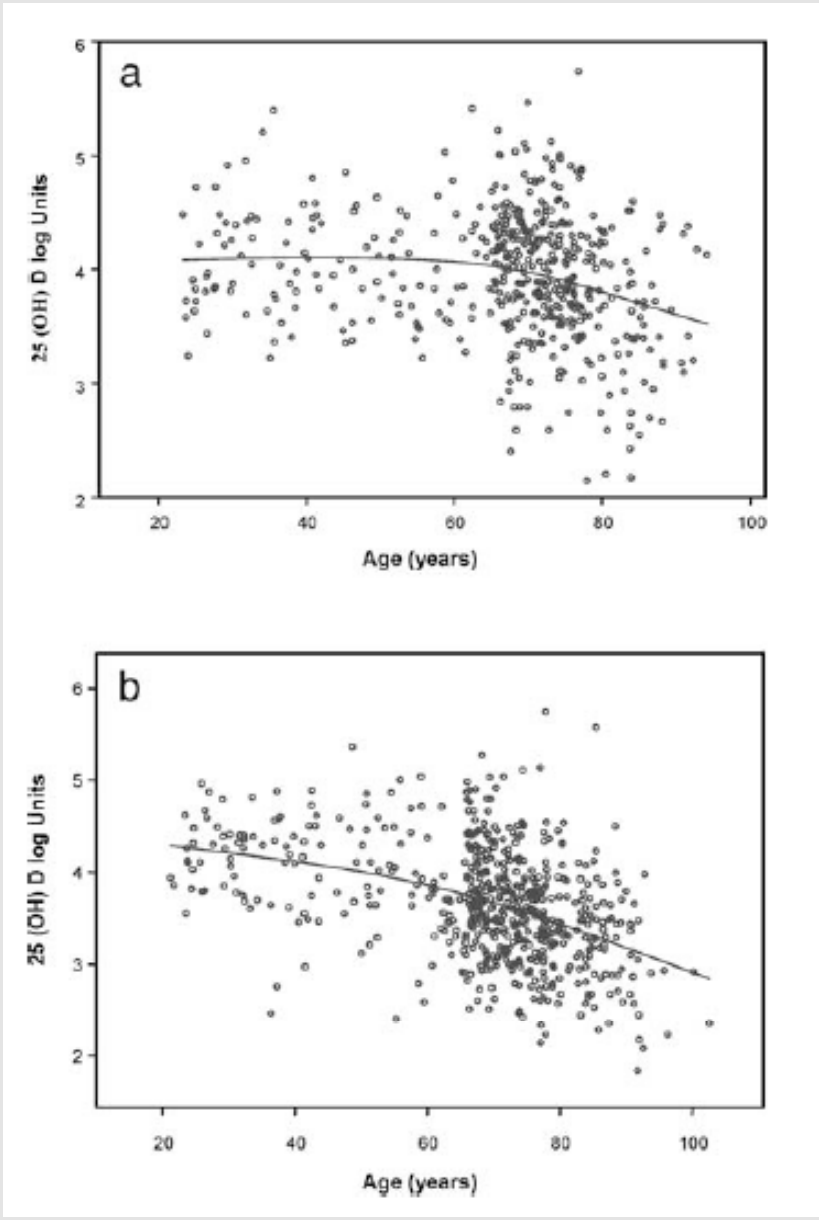
Prevalenza di Livelli Inadeguati di Vitamina D (<30ng/ml), per Gruppi di Età, nelle Donne in Postmenopausa



p=0.015 per test di tendenza

Tratto da Holick MF et al. Poster presented at ASBMR, October 1–5, 2004, Seattle, WA, USA.

25(OH)D serum levels decline with age earlier in women and in men



men

women

Maggio D et al, J Geront, 2005

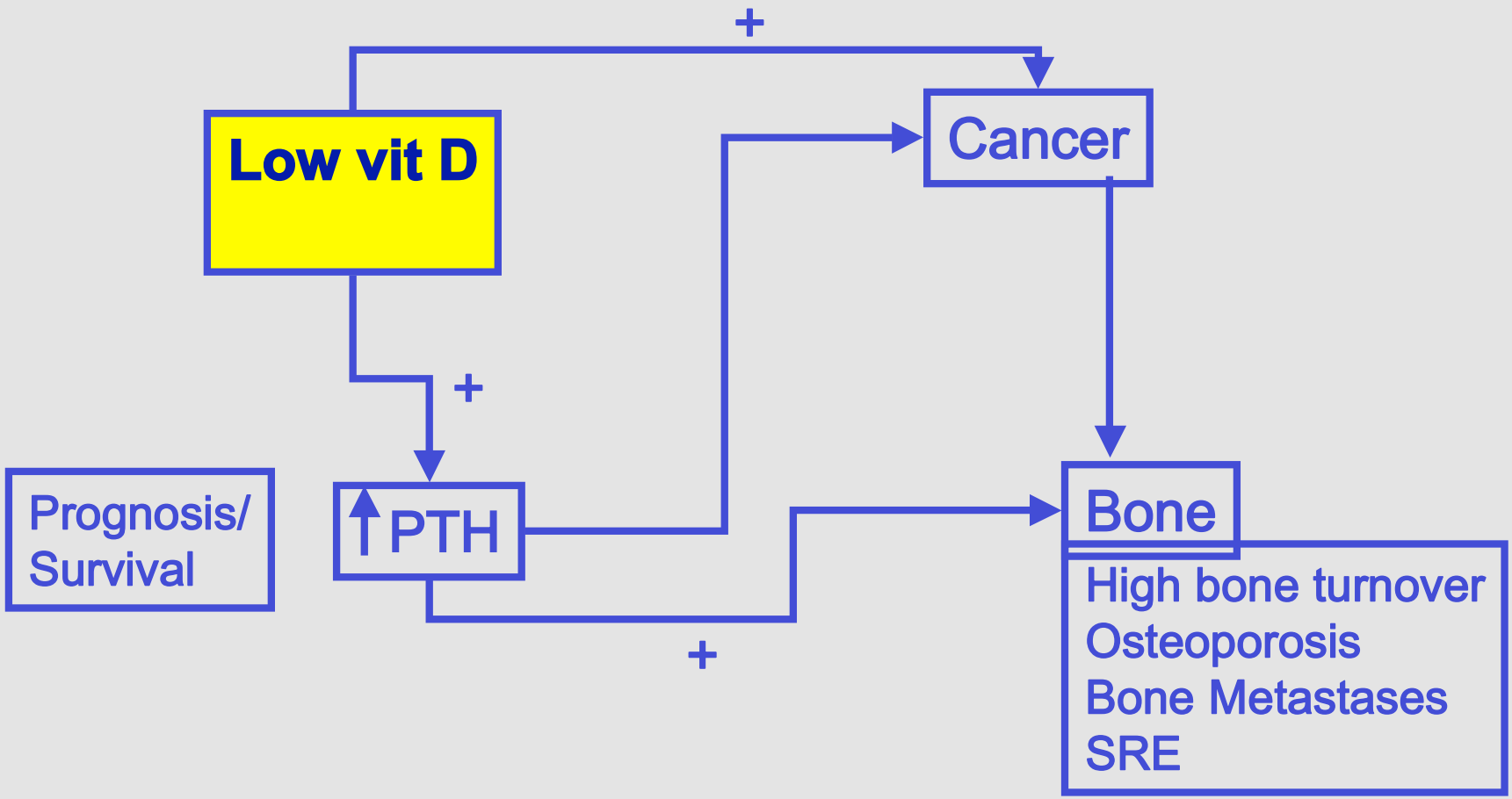
Prevalence of Vitamin D Deficency in Prostate Cancer Men

Study	Reference	Study Population		Vitamin D Level in Control Participants		
		Country	Patient/Control Participant	25(OH)D		$1,25(OH)_2D$
				Median (ng/ml)	Deficiency[a] (%)	Median (pg/ml)
Corder et al. (1993)	[15]	US	181/181	~22	~50	~33
Braun et al. (1995)[b]	[16]	US	61/122	33[c]	13	40[c]
Gann et al. (1996)	[17]	US	232/414	29	19	34
Nomura et al. (1998)	[18]	US (Hawaii)	136/136	42	0	40
Ahonen et al. (2000)	[19]	Finland	149/566	16	>60	NA
Tuohimaa et al. (2004)	[20]	Norway, Finland, Sweden	622/1,451	20	~50	NA
Jacobs et al. (2004)[b]	[21]	US	83/166	~29	~20	~31
Platz et al. (2004)	[22]	US	460/460	24[c]	20–25	34[c]
Current study	NA	US	492/664	29	19	33

[a]Vitamin D deficiency was defined as level of 25(OH)D <20 ng/ml.
[b]Season of blood collection was not adjusted in models.
[c]Mean level.
doi:10.1371/journal.pmed.0040103.t005

Haojie Li *PLoS Med 2007*

THE ROLE OF VITAMIN D ON BONE HEALTH
In CANCER PATIENT



PRINCIPALI CONSEGUENZE DELLA TERAPIA ORMONALE NEL PAZIENTE NEOPLASTICO

- **Perdita BMD**

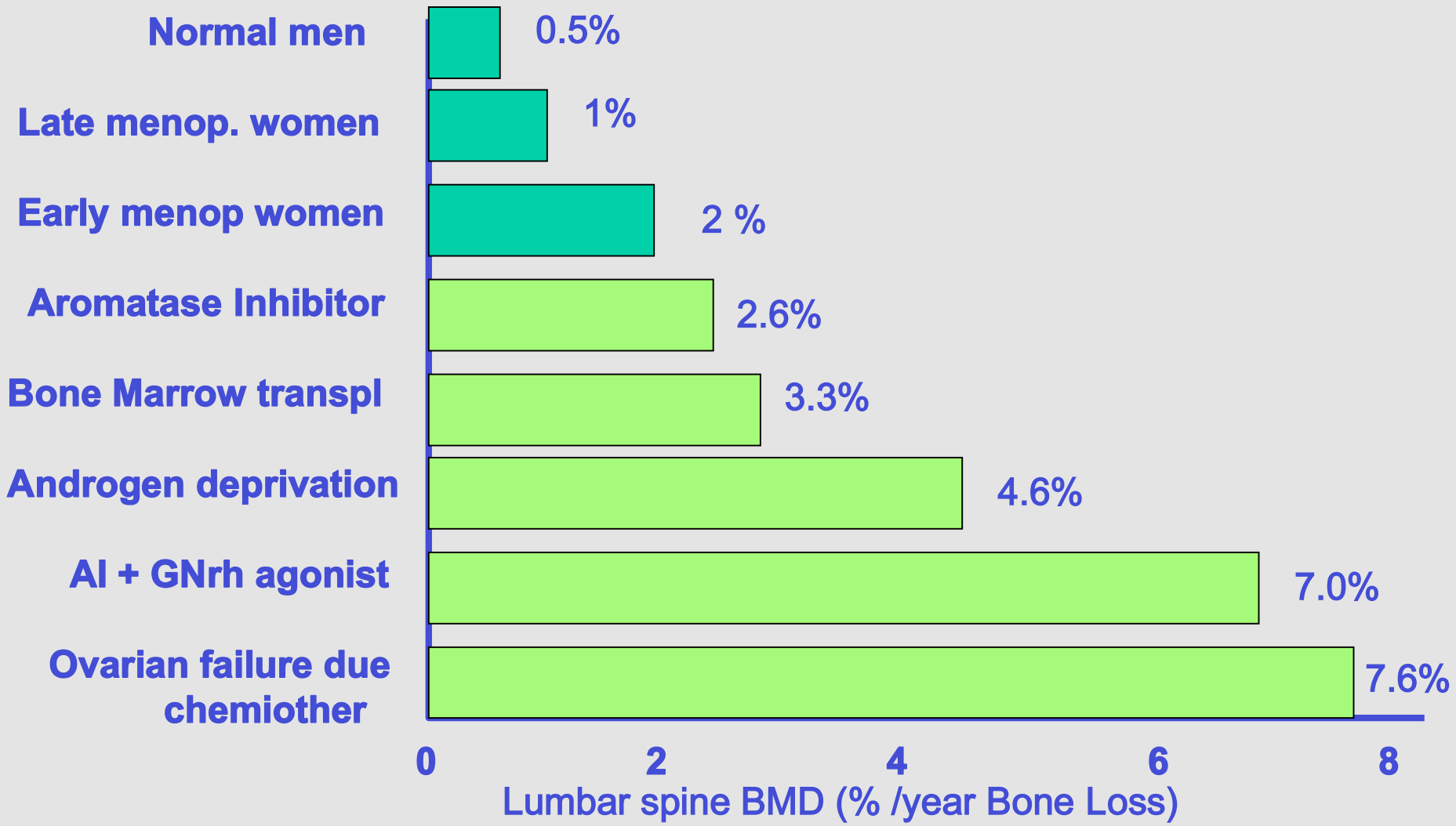
- **Rischio fratturativo**

PRINCIPALI CONSEGUENZE DELLA TERAPIA ORMONALE NEL PAZIENTE NEOPLASTICO

- **Perdita BMD**

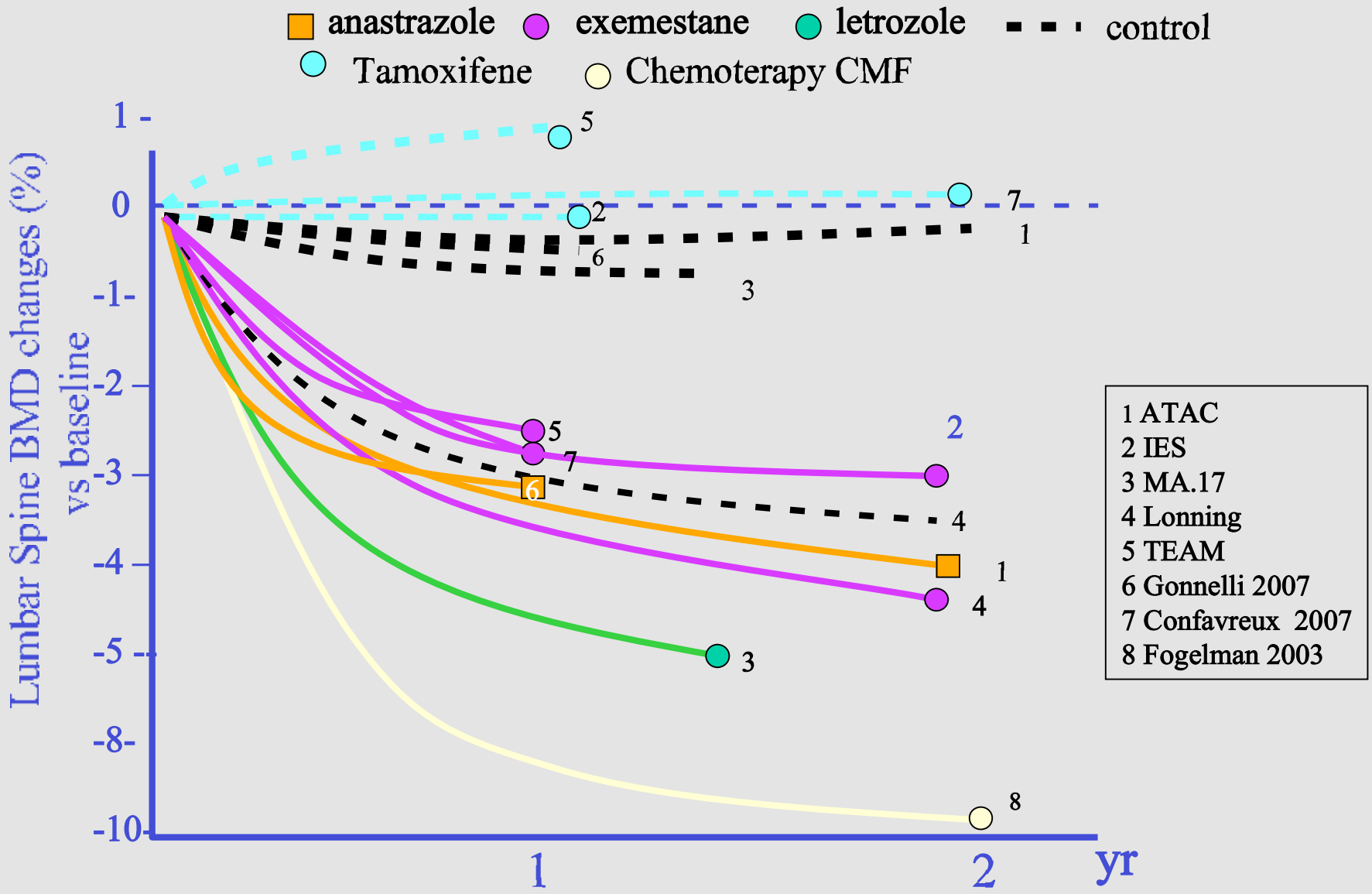
- **Rischio fratturativo**

CANCER TREATMENT INDUCED BONE LOSS

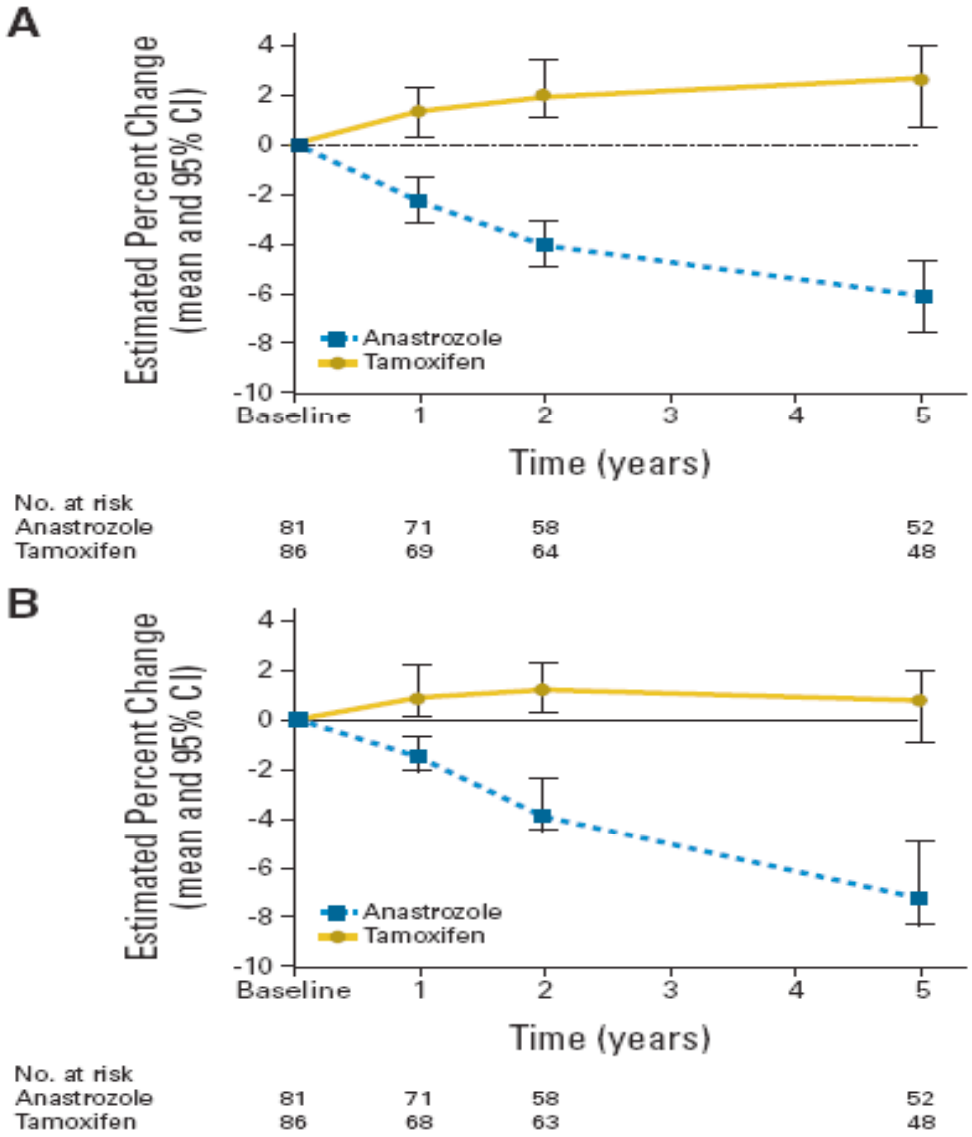


Hirbe A *Clin Cancer Res 2006*

RATE OF BONE LOSS IN AI TREATMENT



Effect of Anastrozole on BMD: 5-year Results



Eastell R J Clin Oncol 2008

Androgen Deprivation Therapy Decreases Bone Mineral Density

Study	N	Treatment	Change from Baseline BMD
Eriksson et al[1]	11	Orchiectomy	Hip: -9.6% Radius: -4.5%
Maillefert et al[2]	12	GnRH agonist	Hip: -3.9% spine: -4.6%
Daniell et al[3]	26	Orchiectomy or GnRH agonist	Hip: -2.4%
Berrutti et al[4]	35	GnRH agonist	Hip: -9.6%

L

1. Eriksson S, et al. *Calcif Tissue Int*. 1995;57:97-99.
2. Maillefert JF, et al. *J Urol*. 1999;161:1219-1222.
3. Daniell HW, et al. *J Urol*. 2000;163:181-186.
4. Berruti A, et al. *J Urol*. 2002;167:2361-2367.

Osteoporosis in Men with Prostate Carcinoma Receiving Androgen-Deprivation Therapy

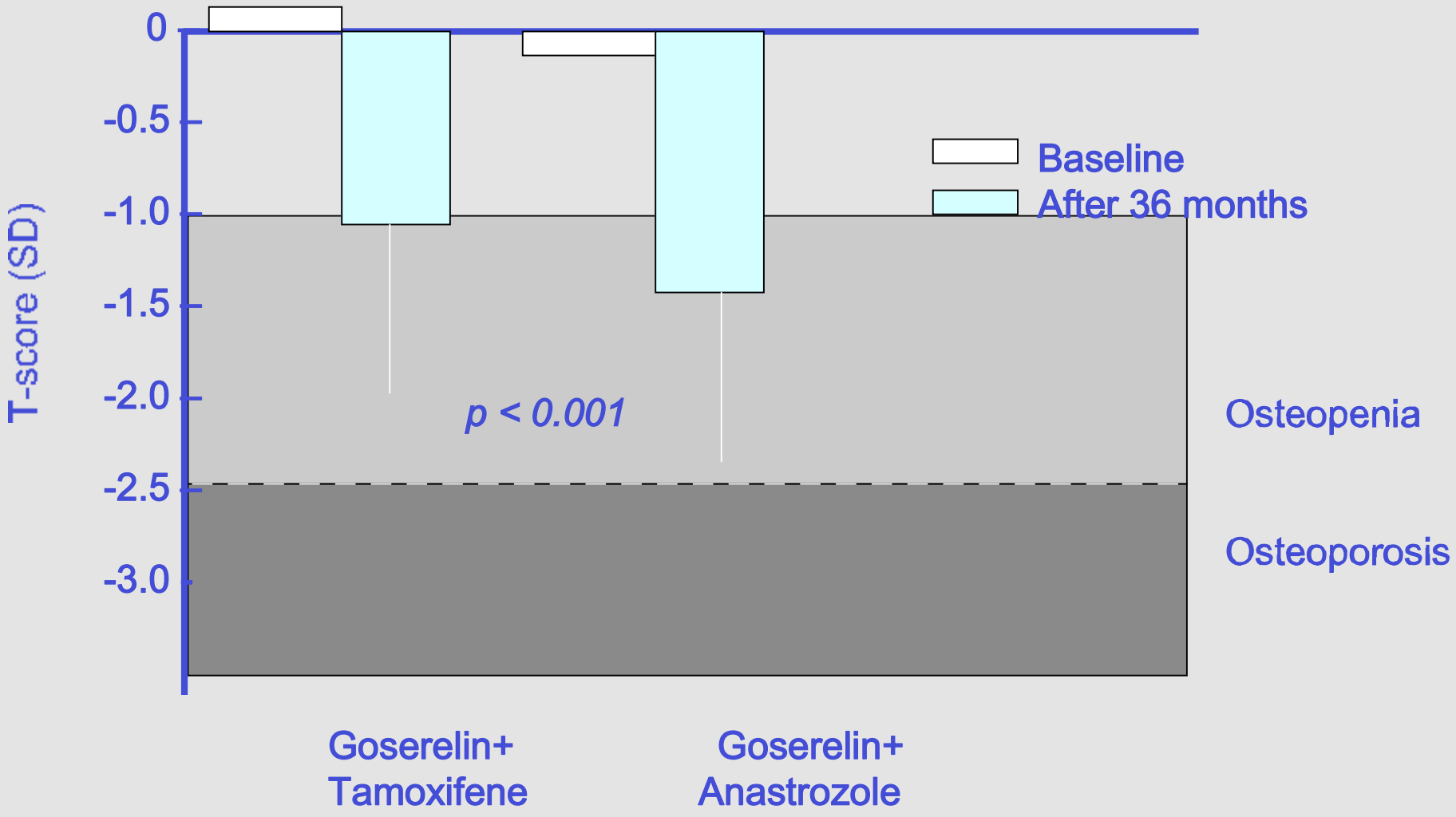
TABLE 1
Percent Change in Lumbar Spine and Hip Bone Mineral Density in Men with Prostate Carcinoma Receiving Androgen-Deprivation Therapy

Study	No. of patients	Treatment	Percent change in BMD per year		
			LS DXA	LS QCT	Hip DXA[a]
Maillefert et al.,[6] 1999	12	LHRH agonist	−4.6	—	−3.9
Daniell et al.,[9] 2000	16	Orchiectomy/LHRH agonist	—	—	−3.4
Higano et al.,[7] 1999	18	CAB	−4.5	—	−2.5
Diamond et al.,[4] 1998	12	CAB	—	−6.6	−6.5
Smith et al.,[12] 2001	21	CAB	−3.3	−8.5	−1.8
Diamond et al.,[11] 2001	21	CAB	—	−5.7	−2.3
Smith et al.,[13] 2003	51	LHRH agonist/CAB	−2.2	—	−2.8
Mittan et al.,[15] 2002	15	CAB	−2.8	—	−3.3
Berruti et al.,[14] 2002	42	LHRH agonist	−2.3	—	−0.5

BMD: bone mineral density; LS: lumbar spine; DXA: dual-energy X-ray absorptiometry; QCT: quantitative computed tomography; LHRH: luteinizing hormone–releasing hormone; CAB: combined androgen blockade.
[a] Hip bone BMD measured by DXA.

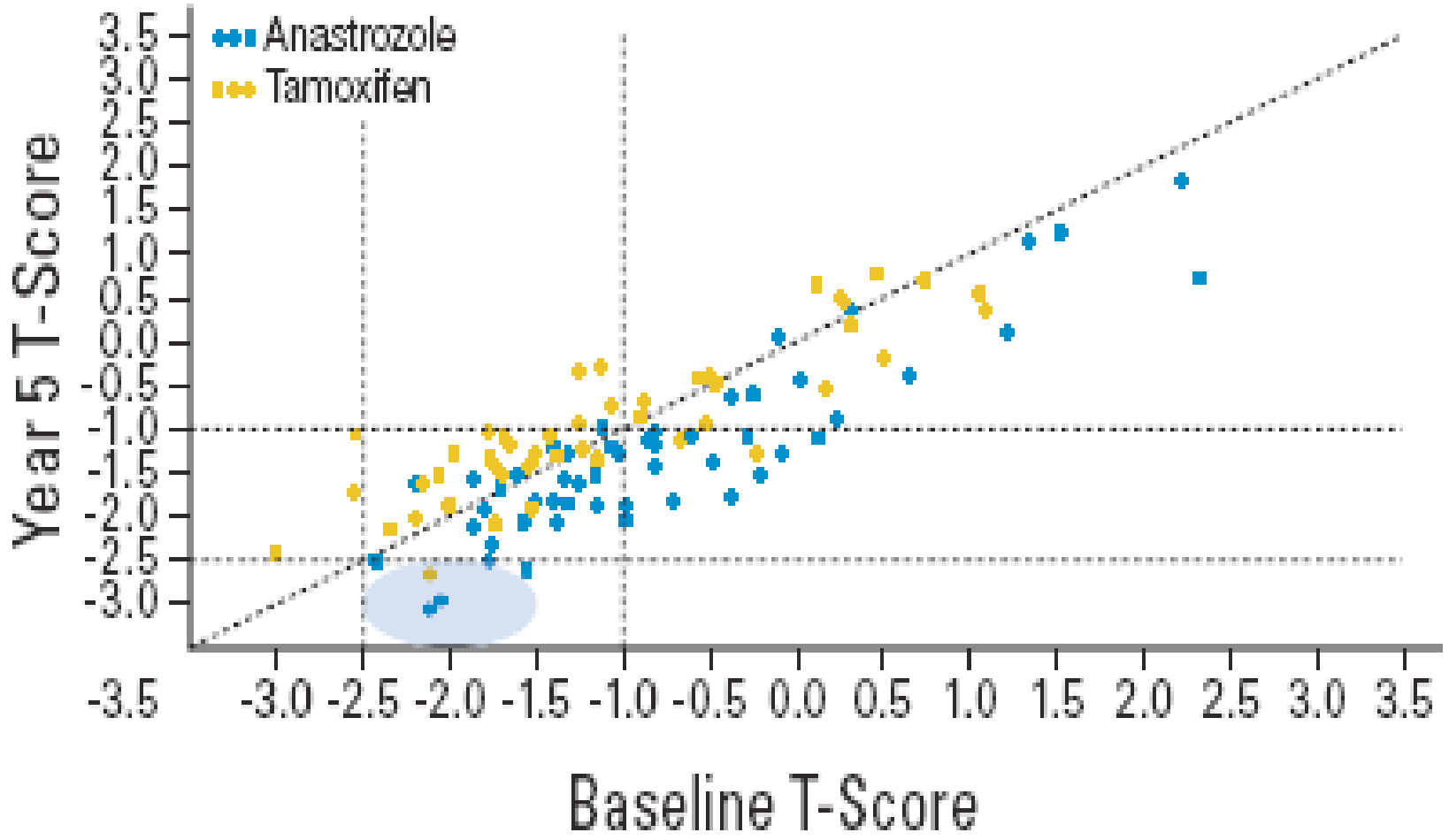
Diamond TH, Cancer 2004

BMD changes in Early Breast Cancer in Pre-menopasual Women (ABCSG-012 trial)



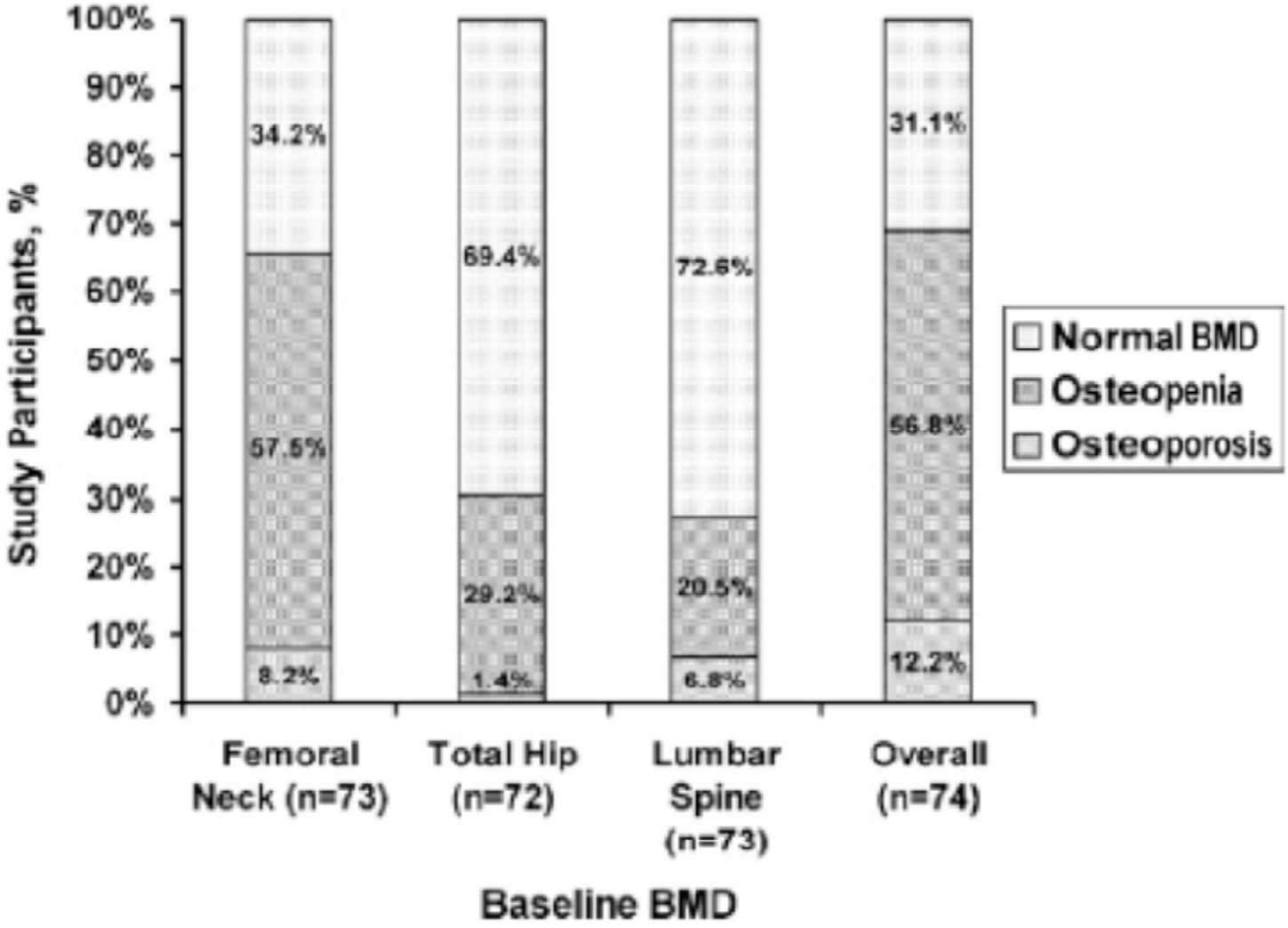
Gnant MF *J Clin Oncol 2007*

Shift of T-score from Baseline to Years 5



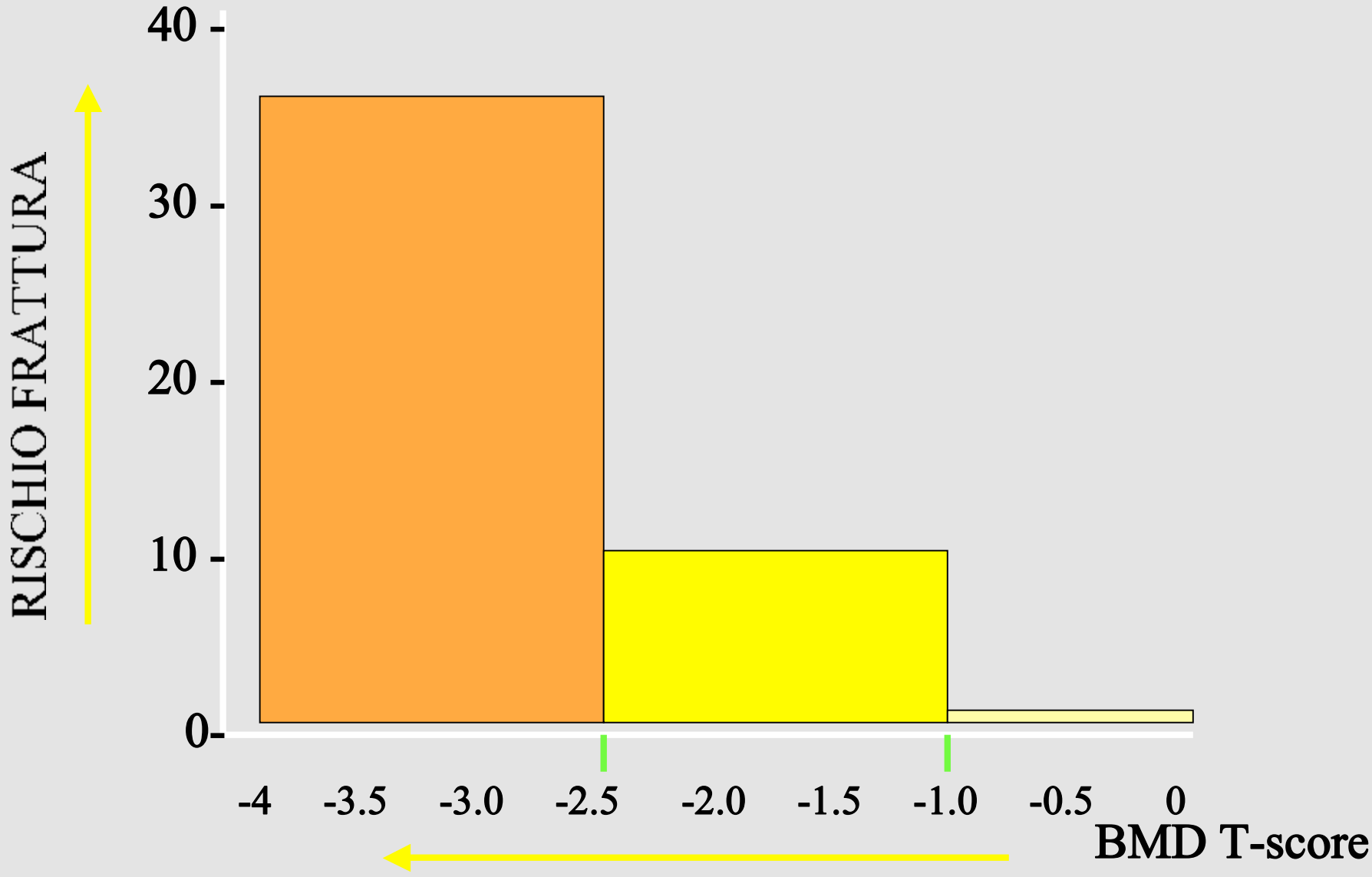
Eastell R J Clin Oncol 2008

PREVALENCE OF OSTEOPOROSIS AT BASELINE OF ADT IN PROSTATE CANCER PATIENTS



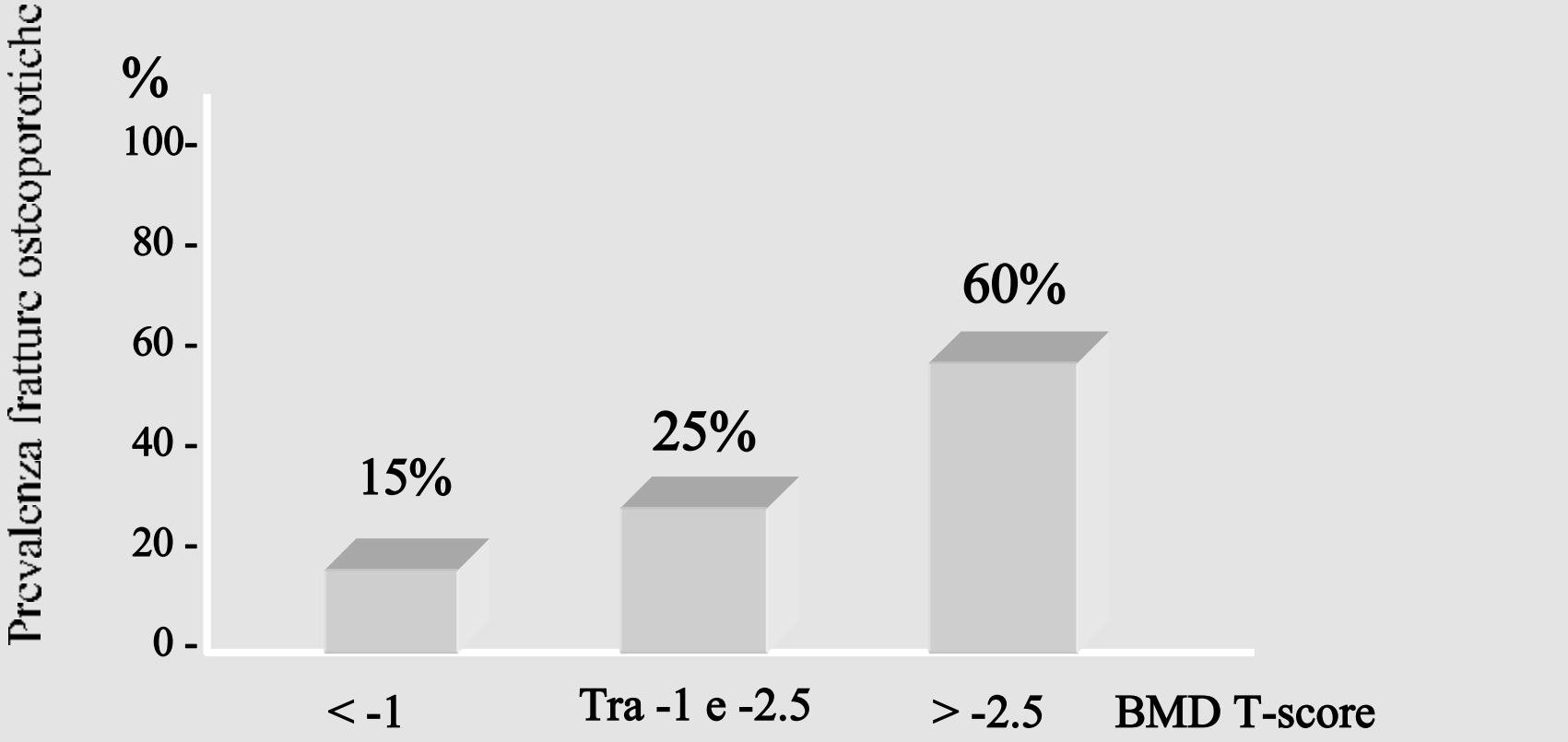
Ryan CV Urology 2007

RELAZIONE TRA BMD E RISCHIO DI FRATTURA



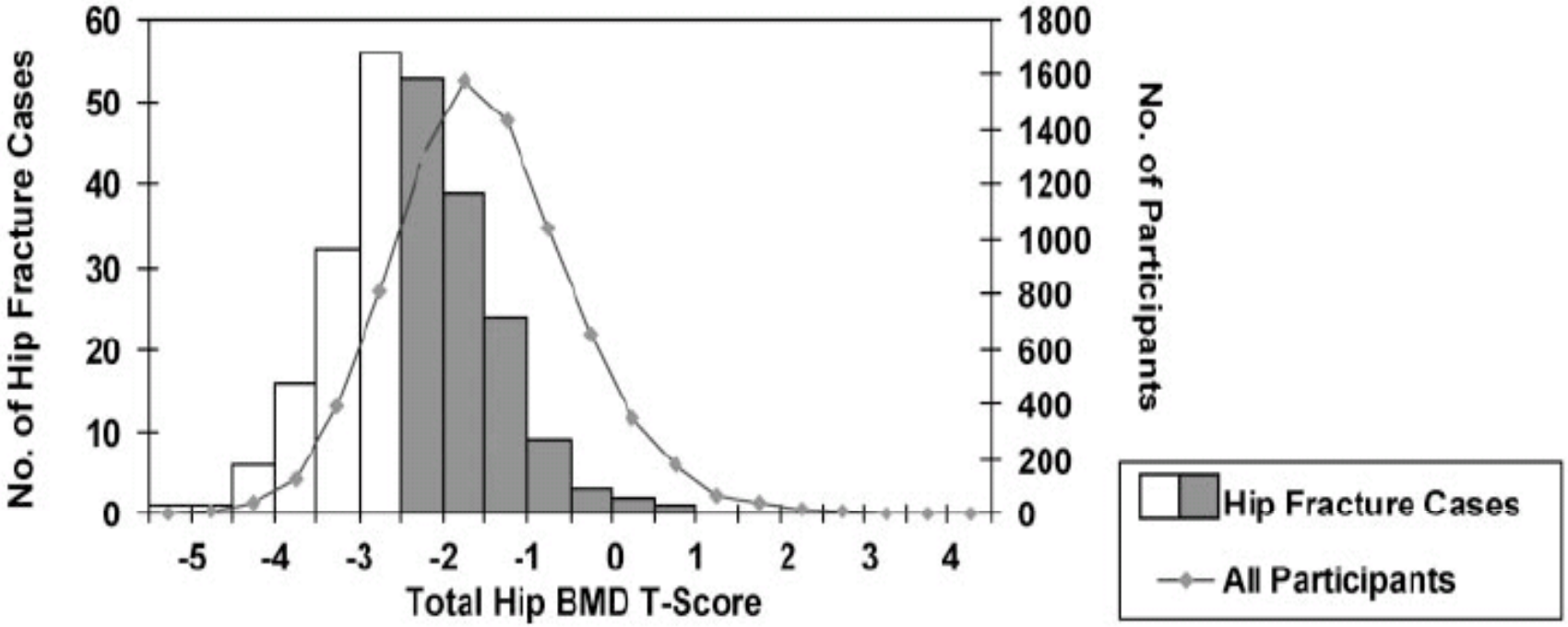
PERCHE' LA BMD NON PUO' ESSERE UTILIZZATA COME UNICO CRITERIO PER SCEGLIERE CHI TRATTARE

La BMD riconosce solo il 55-60% dei soggetti con fratture VERTEBRALI.



Robbins JA, *Osteop. Int 2005*

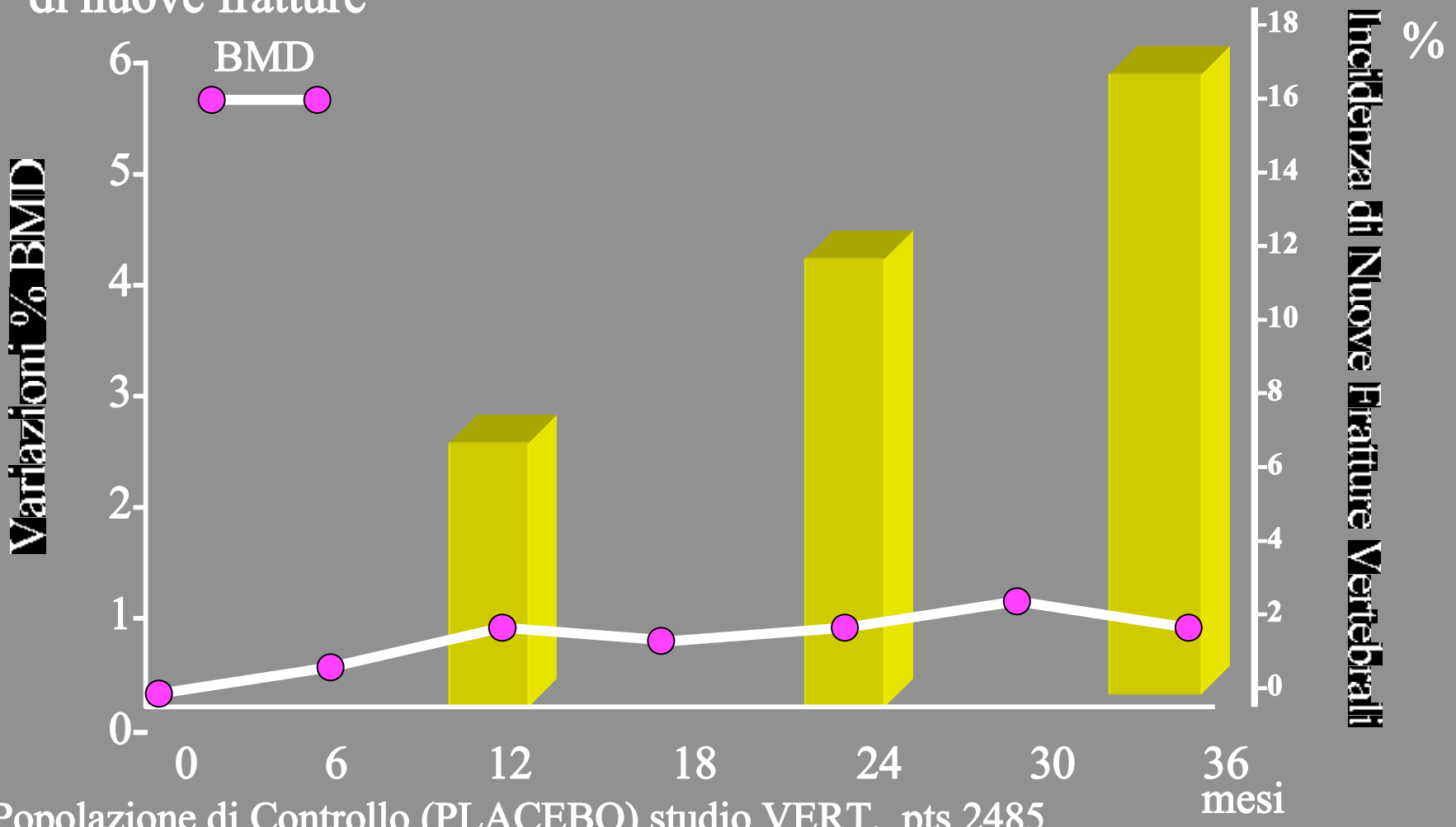
HIP FRACTURE IN WOMEN WITHOUT OSTEOPOROSIS



Wainwright SA *JCEM 2005*

LA BMD E' L'OBIETTIVO TERAPEUTICO NELLA TERAPIA DELL OP?

Le variazioni di BMD non predicono correttamente l'incidenza di nuove fratture



Popolazione di Controllo (PLACEBO) studio VERT, pts 2485

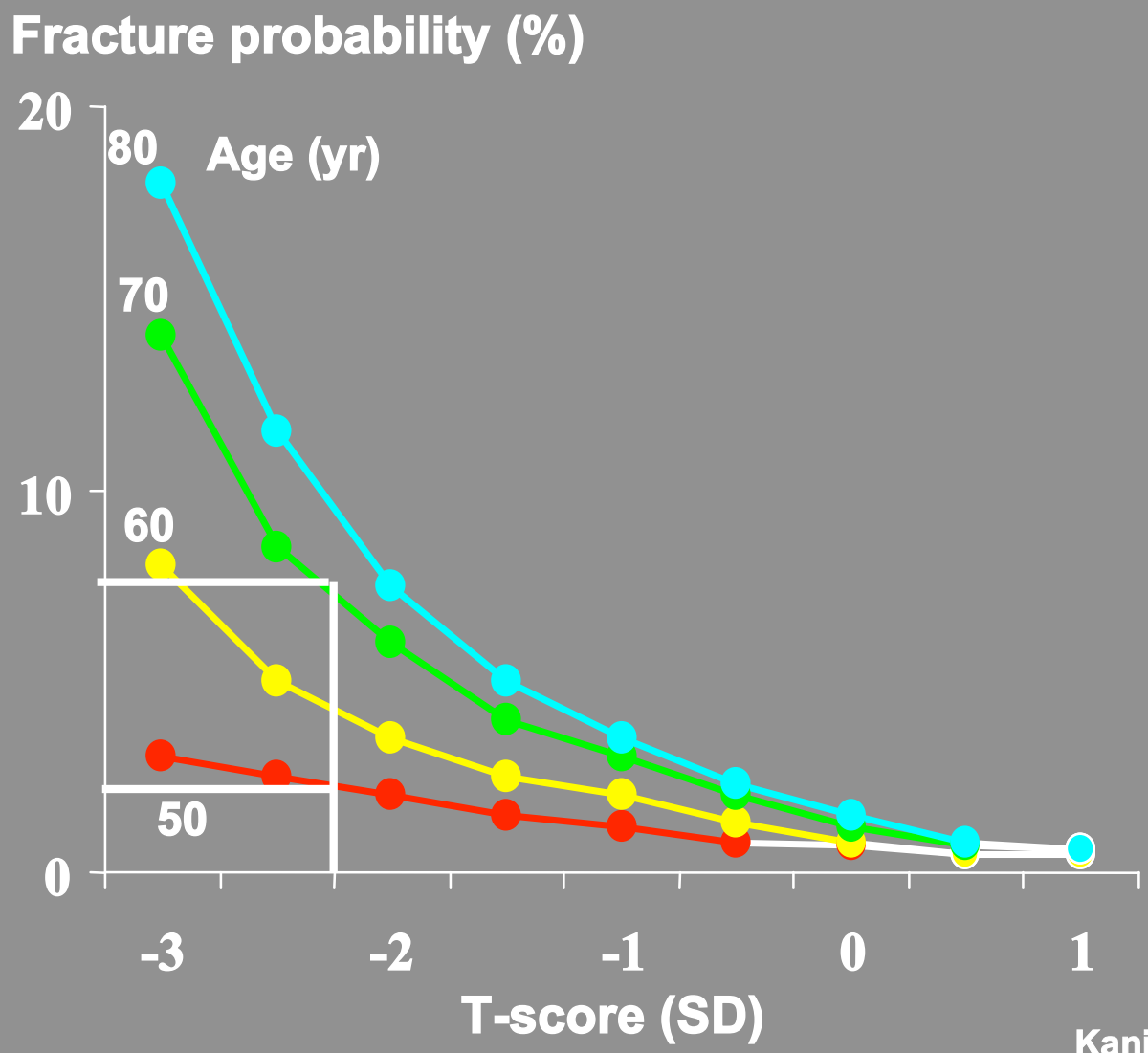
Harris ST *et al JAMA 1999*

TABELLA DI RISCHIO FRATTURATIVO DI FEMORE A 10 ANNI (%) CALCOLATO SU ETA' E BMD

Età (anni)	T score (collo femore)									
	1	0.5	0	-0.5	-1	-1.5	-2	-2.5	-3	-4
	Rischio a 10 anni di ogni tipo di frattura osteoporotica (%)									
45	1.8	2.3	2.8	3.5	4.3	5.4	6.6	8.1	10	15
50	2.4	3	3.8	4.7	5.9	7.4	9.2	11.3	14.1	21.3
55	2.6	3.3	4.1	5.3	6.7	8.5	10.7	13.4	16.8	26
60	3.2	4.1	5.1	6.5	8.2	10.4	13	16.2	20.2	30.6
65	4	5	6.3	8	10	12.6	15.6	19.3	23.9	35.5
70	4.3	5.5	7.1	9	11.5	14.6	18.3	22.8	28.4	42.3
75	4.2	5.4	7	9.1	11.8	15.2	19.4	24.5	30.8	46.2
80	4.6	6	7.7	9.9	12.7	16.2	20.5	25.6	31.8	46.4
85	4.5	5.8	7.4	9.4	12	15.3	19.1	23.8	29.4	42.7

Kanis J Osteop Int 2002

Ten-year probability of hip fracture according to age and femoral neck T-score



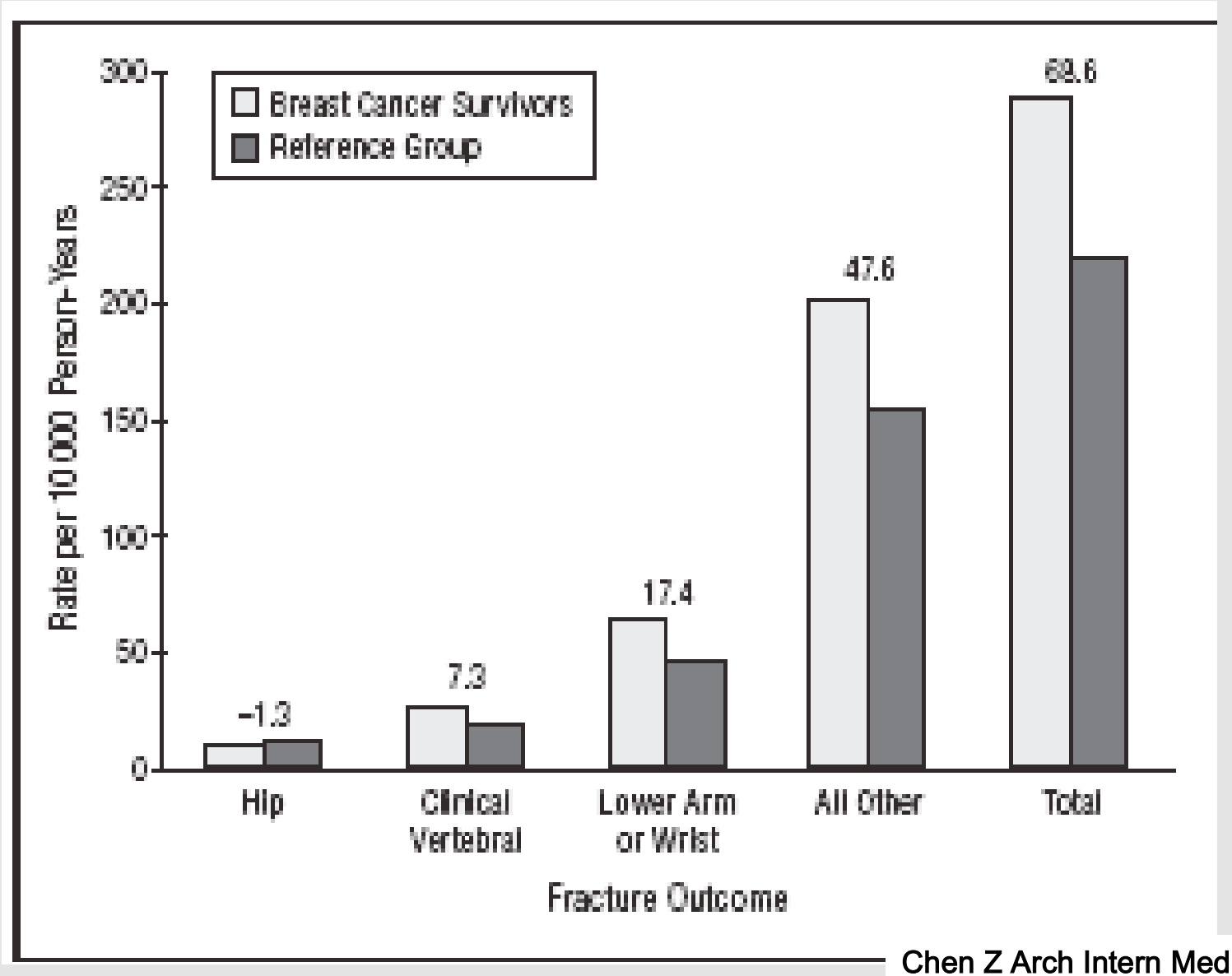
Kanis JA et al, Bone 2000

PRINCIPALI CONSEGUENZE DELLA TERAPIA ORMONALE NEL PAZIENTE NEOPLASTICO

- Perdita BMD

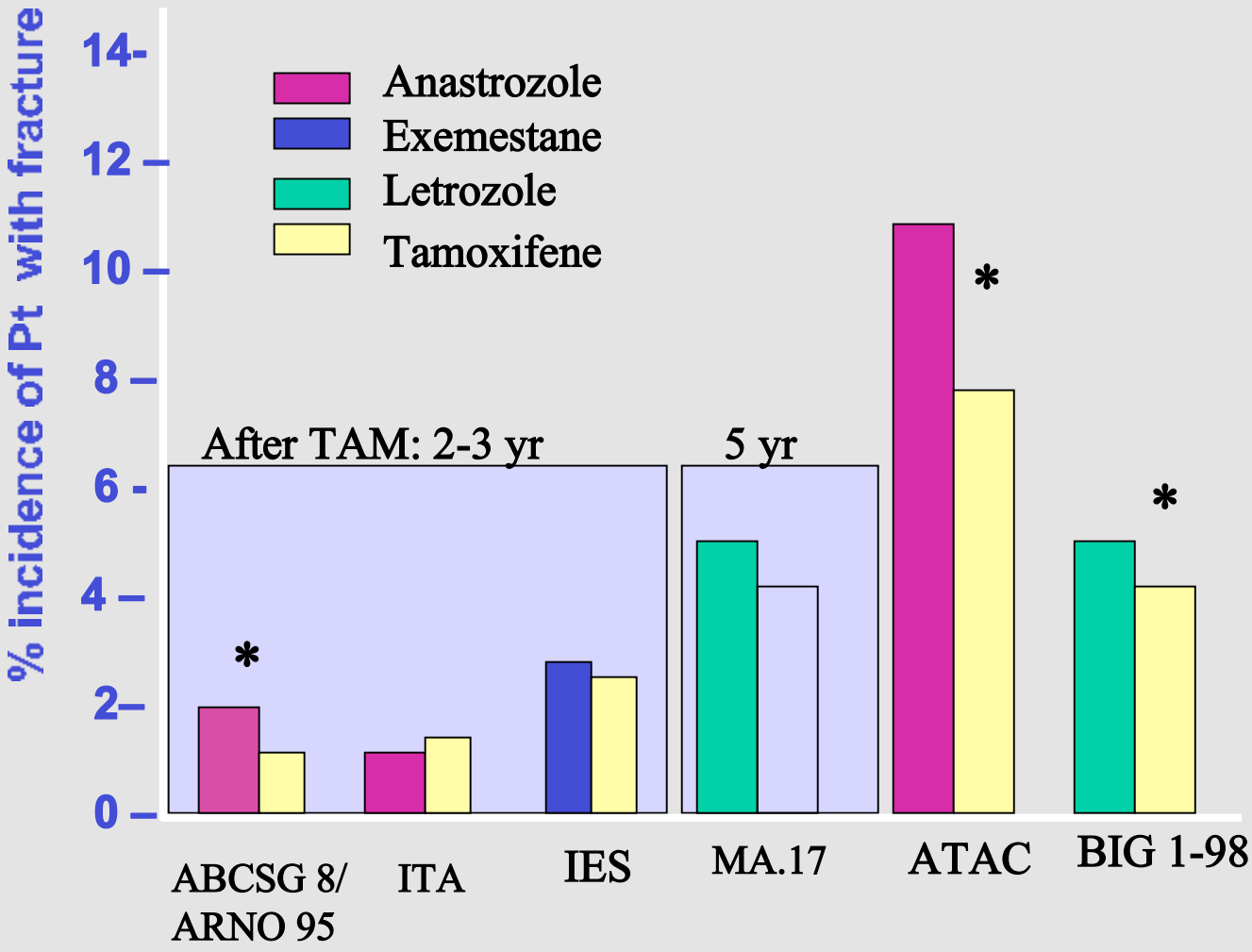
- **Rischio fratturativo**

FRACTURE RISK AMONG BREAST CANCER SURVIVORS (WHI study)



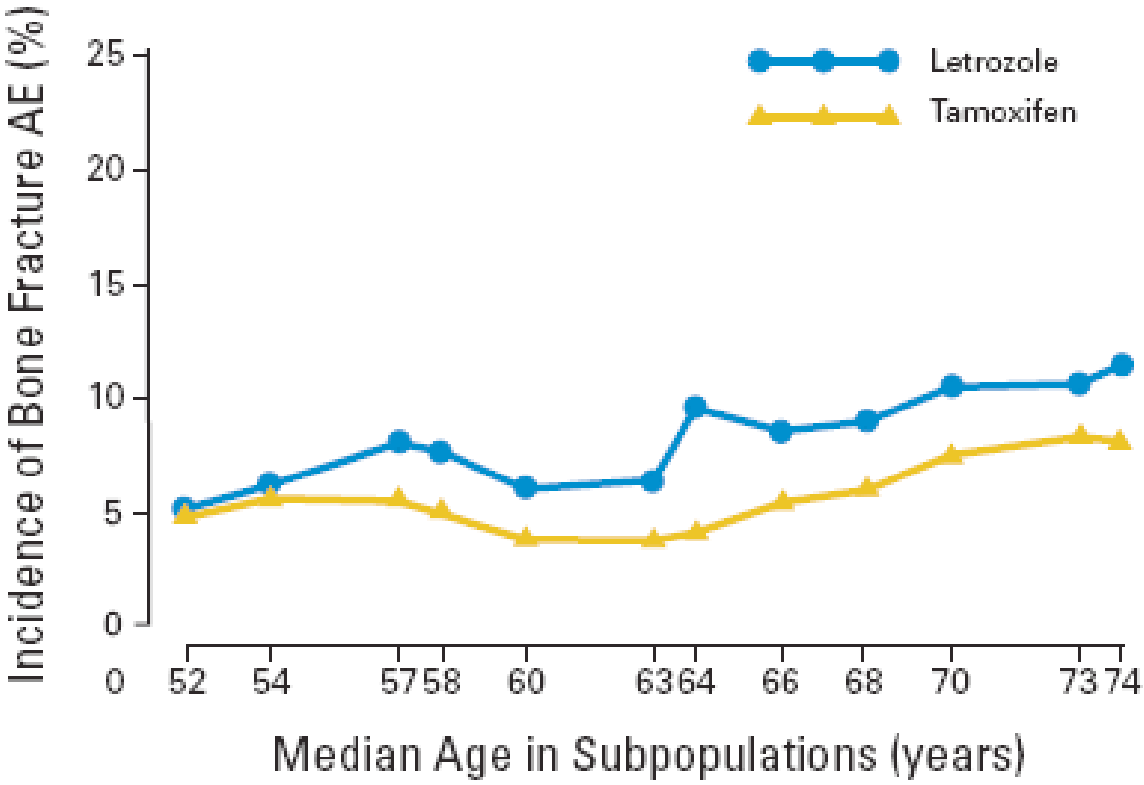
Chen Z Arch Intern Med 2005

CLINICAL FRACTURE IN BREAST CANCER PATIENTS TREATED WITH AI



Chien AJ, Goss PE J Clin Oncol 2006

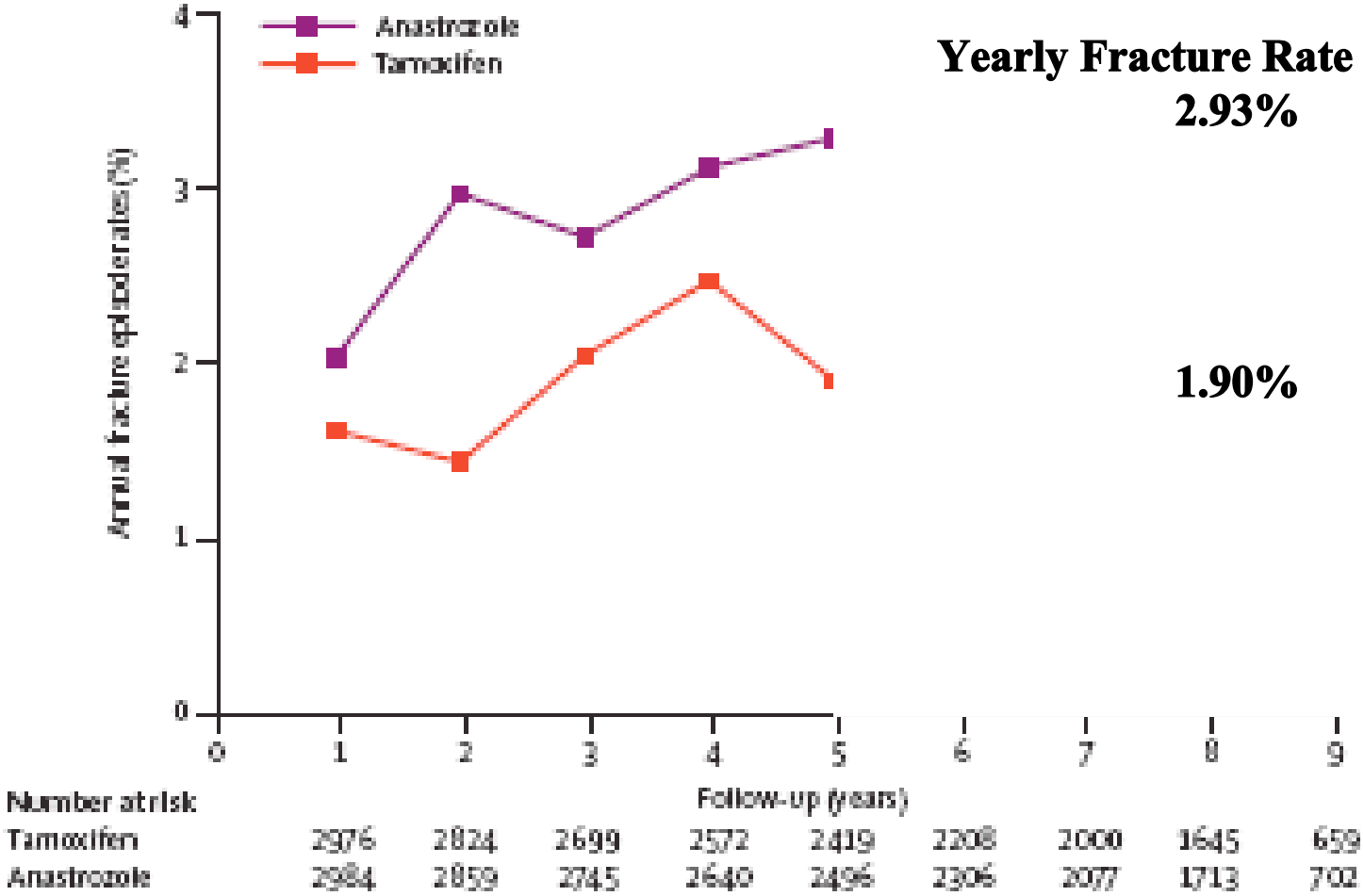
Letrozole Compared With Tamoxifen for Elderly Patients With Endocrine-Responsive Early Breast Cancer: The BIG 1-98 Trial



Fracture incidence
8.0%
vs
5.4%

Crivellari D JCO 2008

100-Month Analysis of the ATAC Trial



Yearly Fracture Rate

2.93%

1.90%

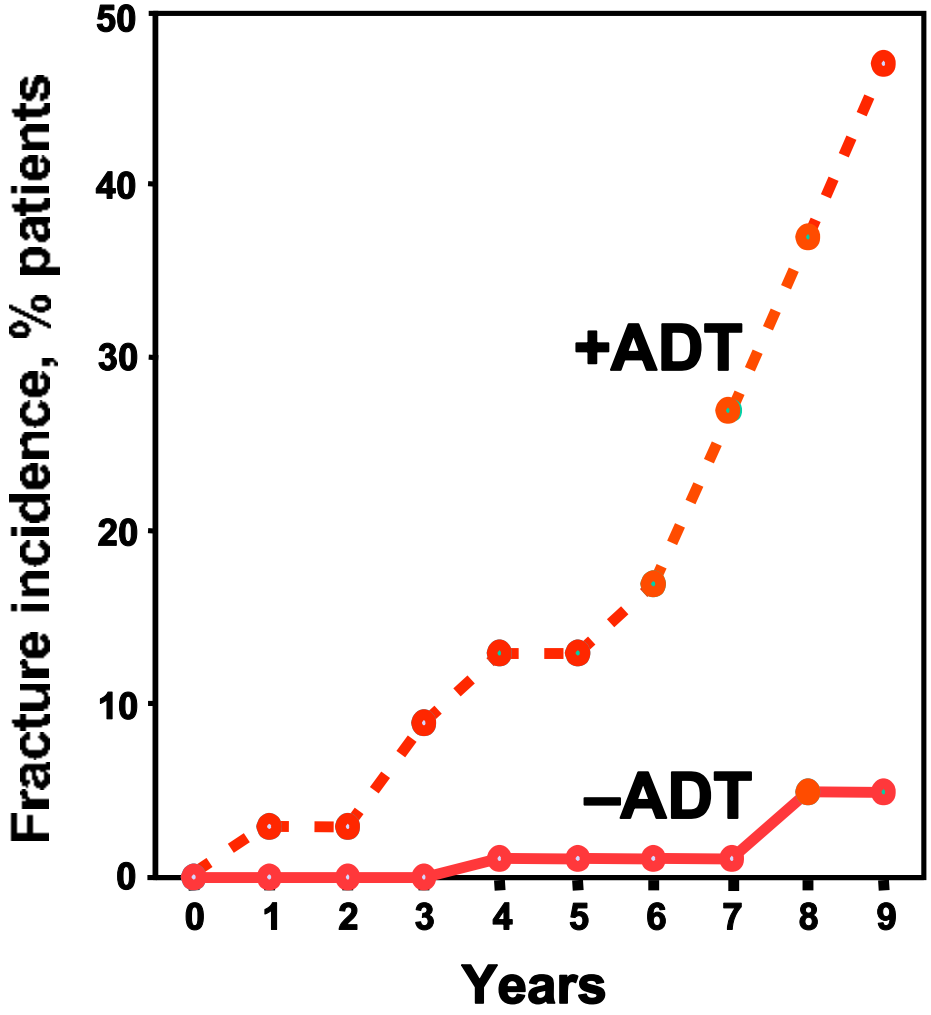
Lancet Oncol 2008

Retrospective Studies of Fracture in Men Treated With ADT

Study	N	Duration of ADT	Fracture Prevalence
Townsend et al[1]	224	22 months	9%
Hatano et al[2]	218	28 months	6%
Oefelein et al[3]	181	47 months	13%

1. Townsend MF et al. *Cancer*. 1997;79:545-550.
2. Hatano T et al. *BJU Int*. 2000;86:449-452.
3. Oefelein MG et al. *J Urol*. 2001;166:1724-1728.

Androgen Deprivation Therapy Increases Fracture Risk



Daniell HW, et al. *J Urol.* 1997;157:439-444.

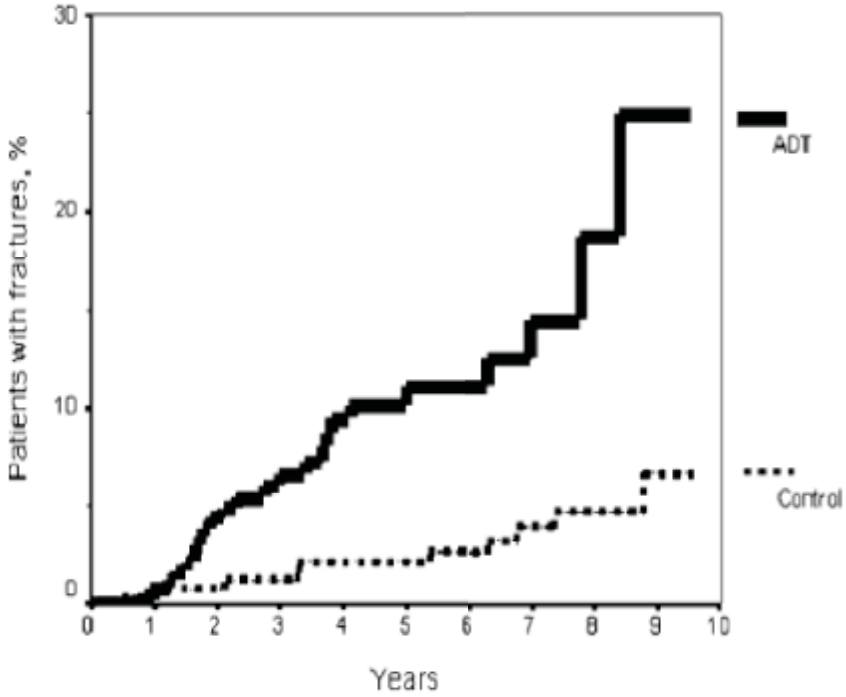
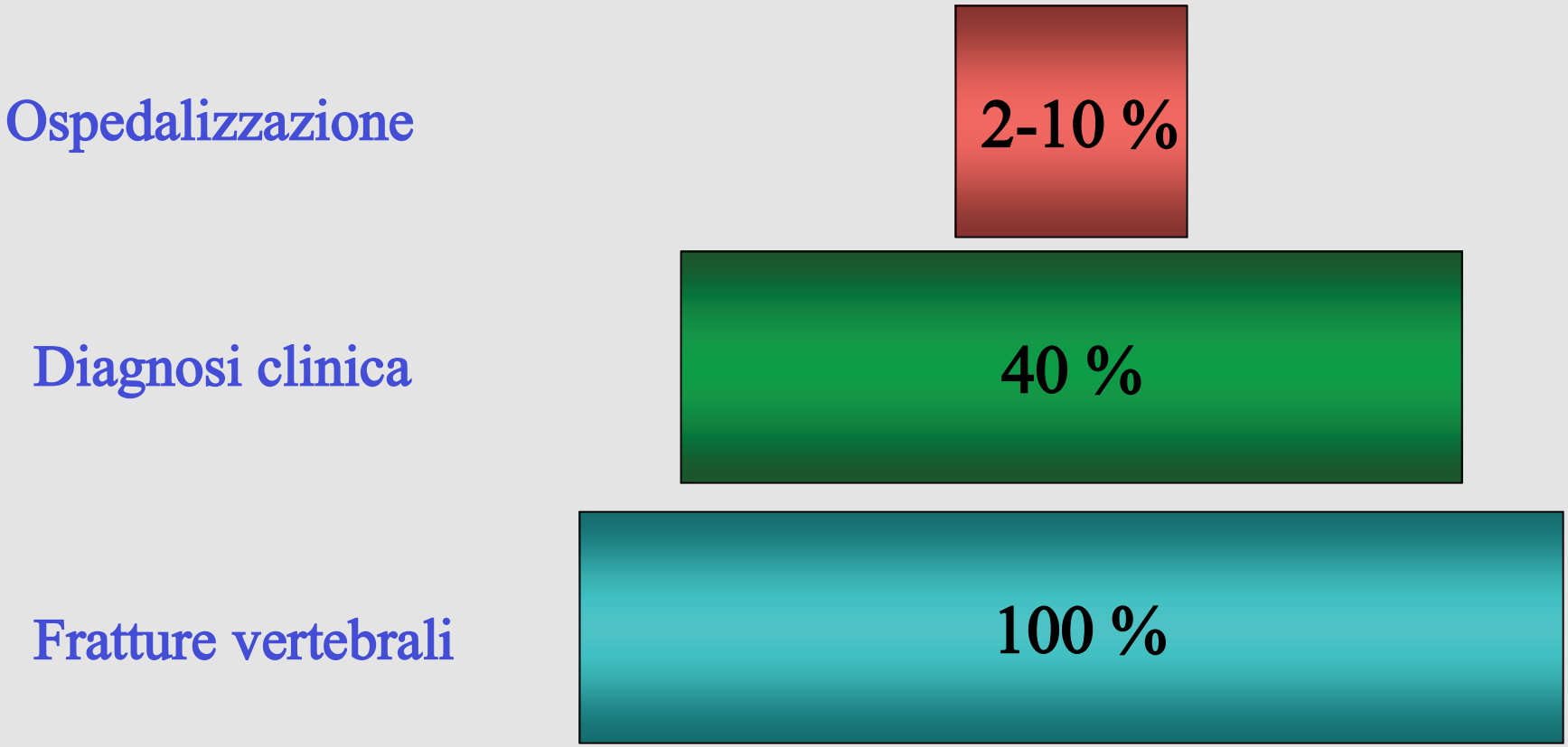


Fig. 1 Kaplan–Meier plots of patients with fractures after ADT (patient group) or diagnosis (control group)

Fracture risk in patients with prostate cancer on androgen deprivation therapy

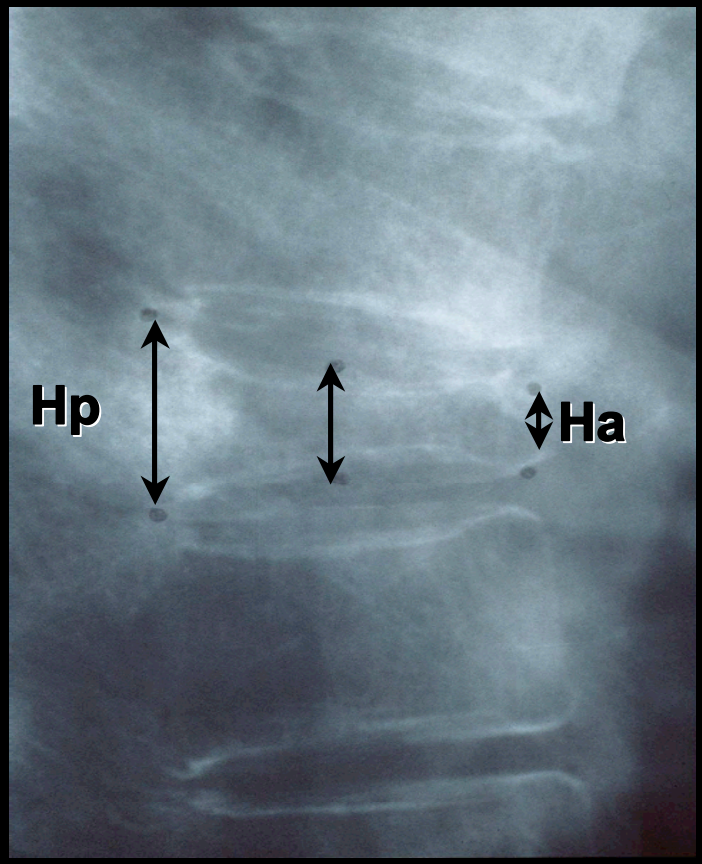
Ana M. López · María A. Pena · Rafael Hernández
Fernando Val · Bernardo Martín · José A. Riancho

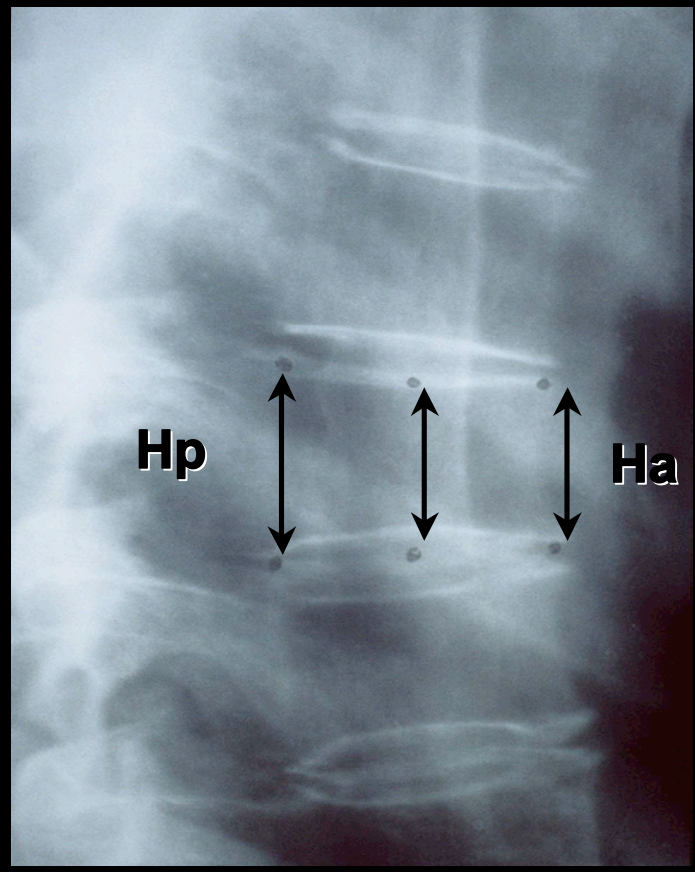
Le fratture vertebrali: clinica



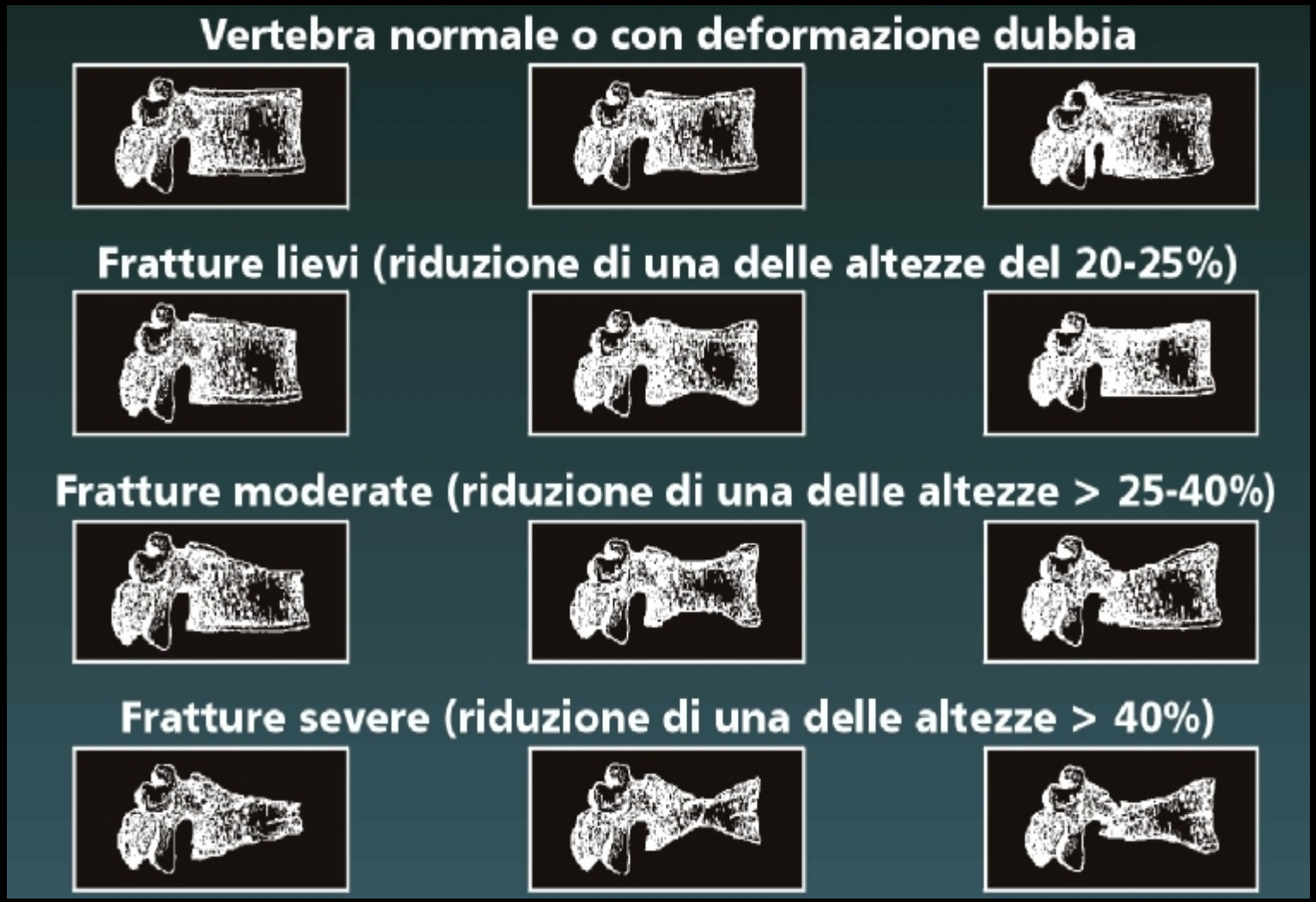
Cooper C, 1993

La frattura Morfometrica all'esame radiografico, non sempre di facile individuazione





Valutazione Semiquantitativa delle fratture vertebrali



GRADO

1

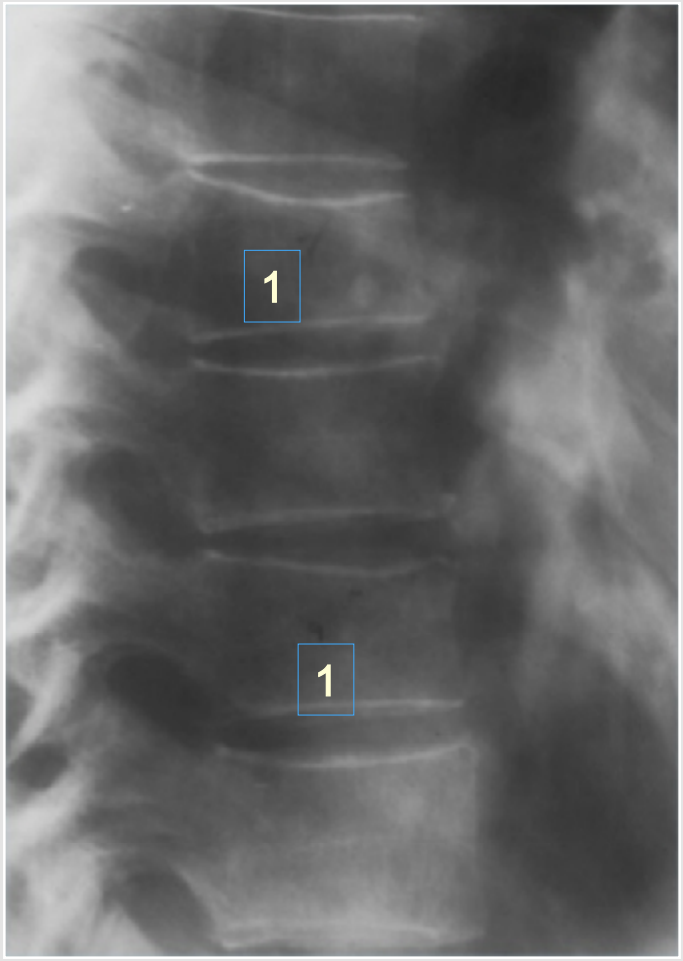
2

3

Genant HK et al, J Bone Miner Res, 1996

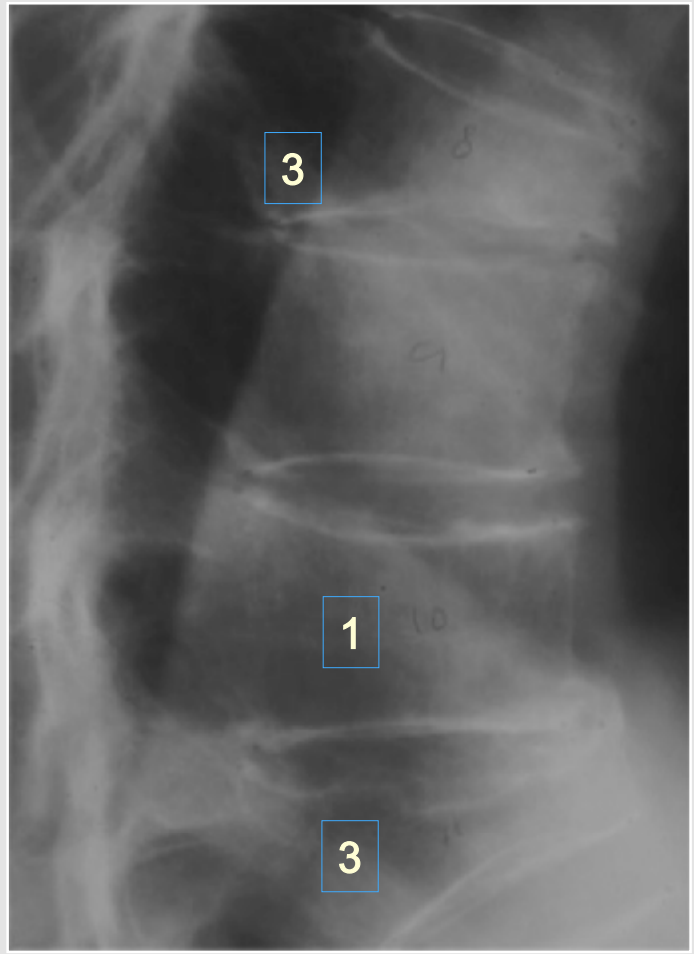
Valutazione Morfometrica delle fratture vertebrali: Spine Deformity Index

2 Fratture (grado 1)



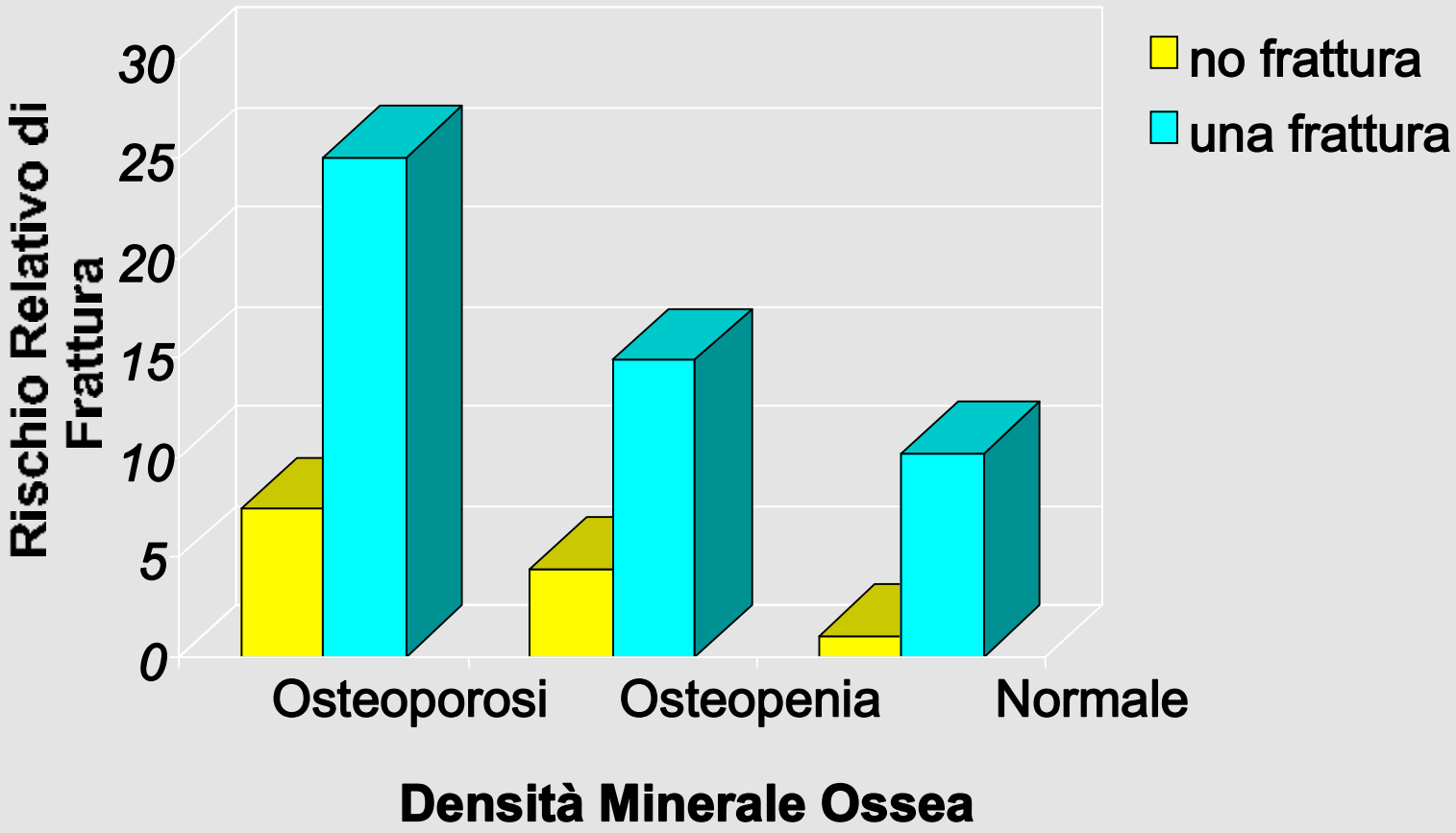
SDI 2

2 Fratture (grado 3)+
1 Frattura (grado 1)



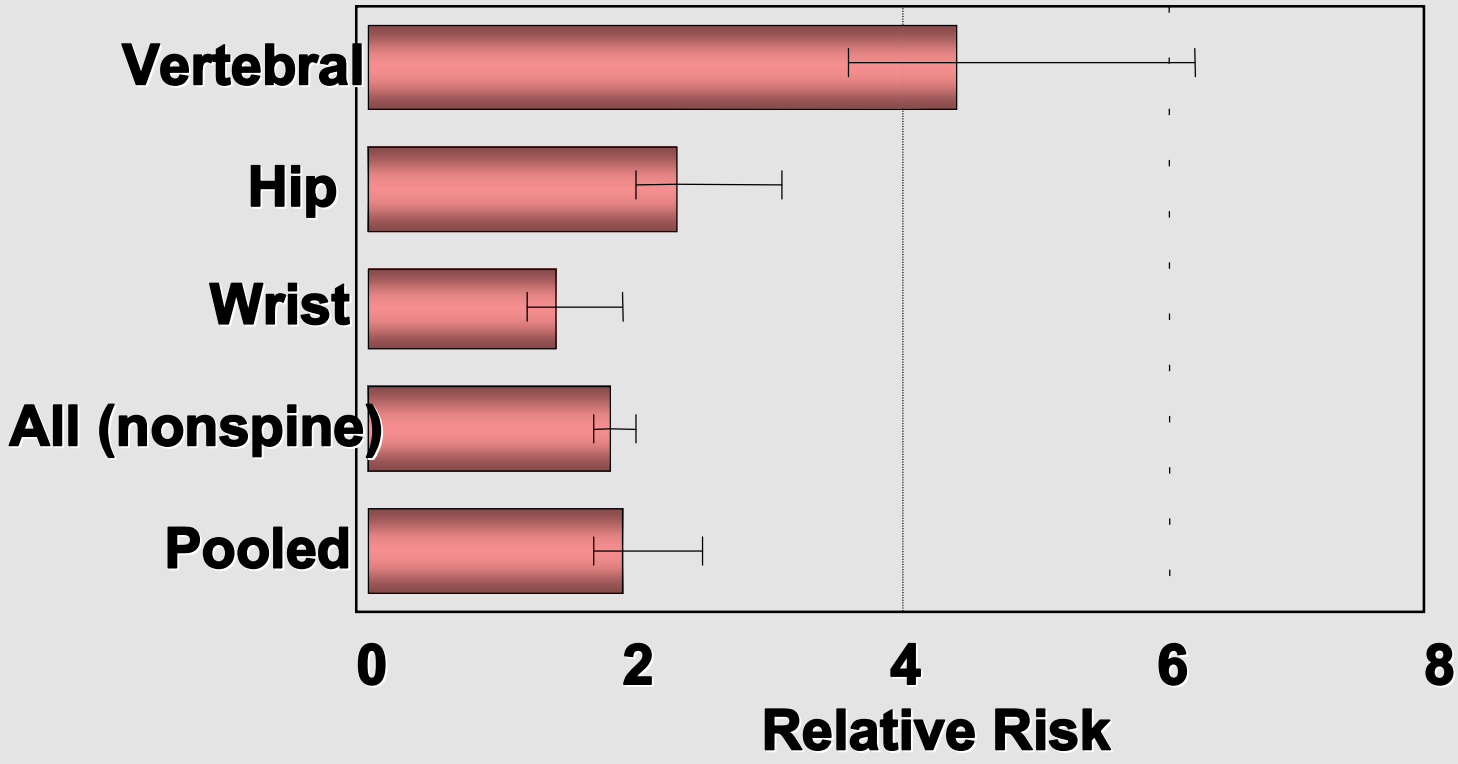
7

BMD, PREGRESSA FRATTURA VERTEBRALE E RISCHIO DI UNA NUOVA FRATTURA



Ross et al, Ann Intern Med, 1991

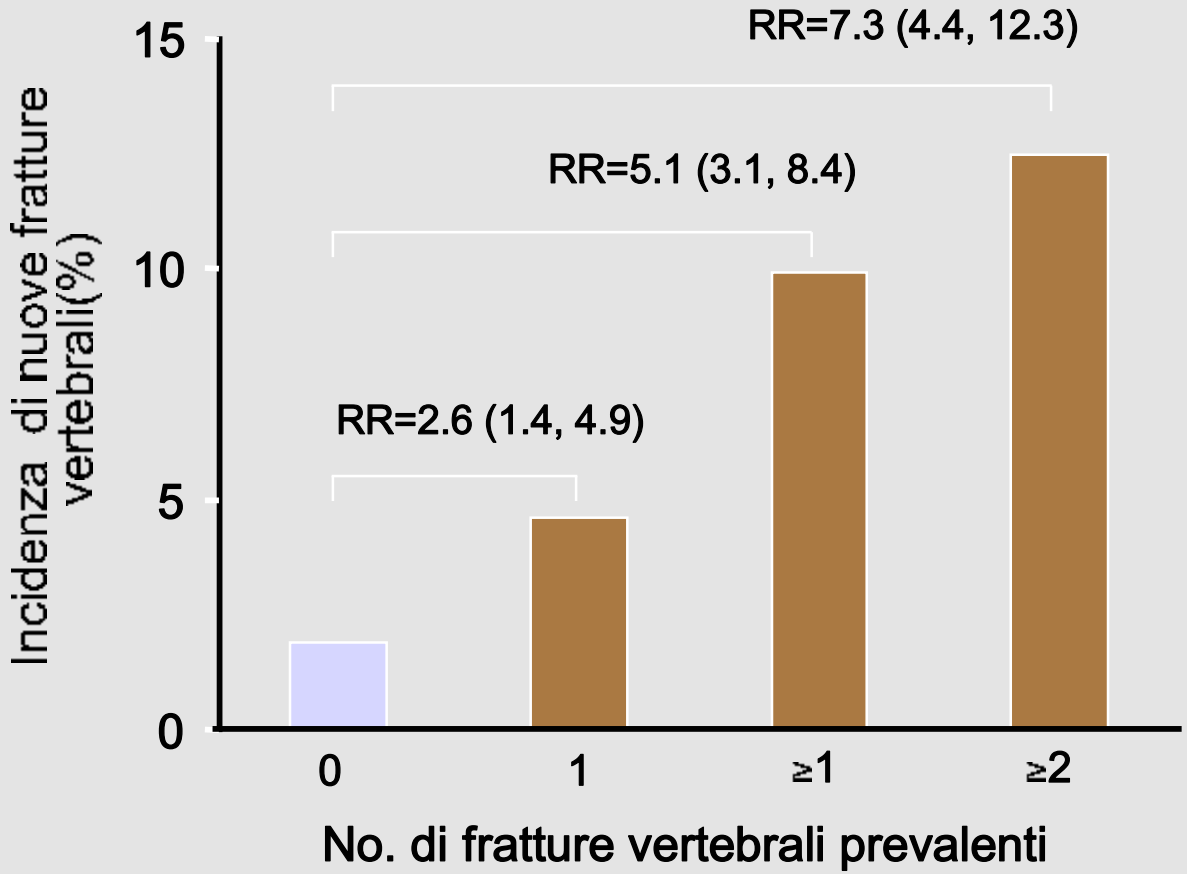
Risk of subsequent fractures in peri/postmenopausal women with prevalent vertebral fractures



Klotzbuecher et al., J Bone Min Res, 200

Effetto del NUMERO di fratture vertebrali prevalenti sul rischio di successive fratture vertebrali

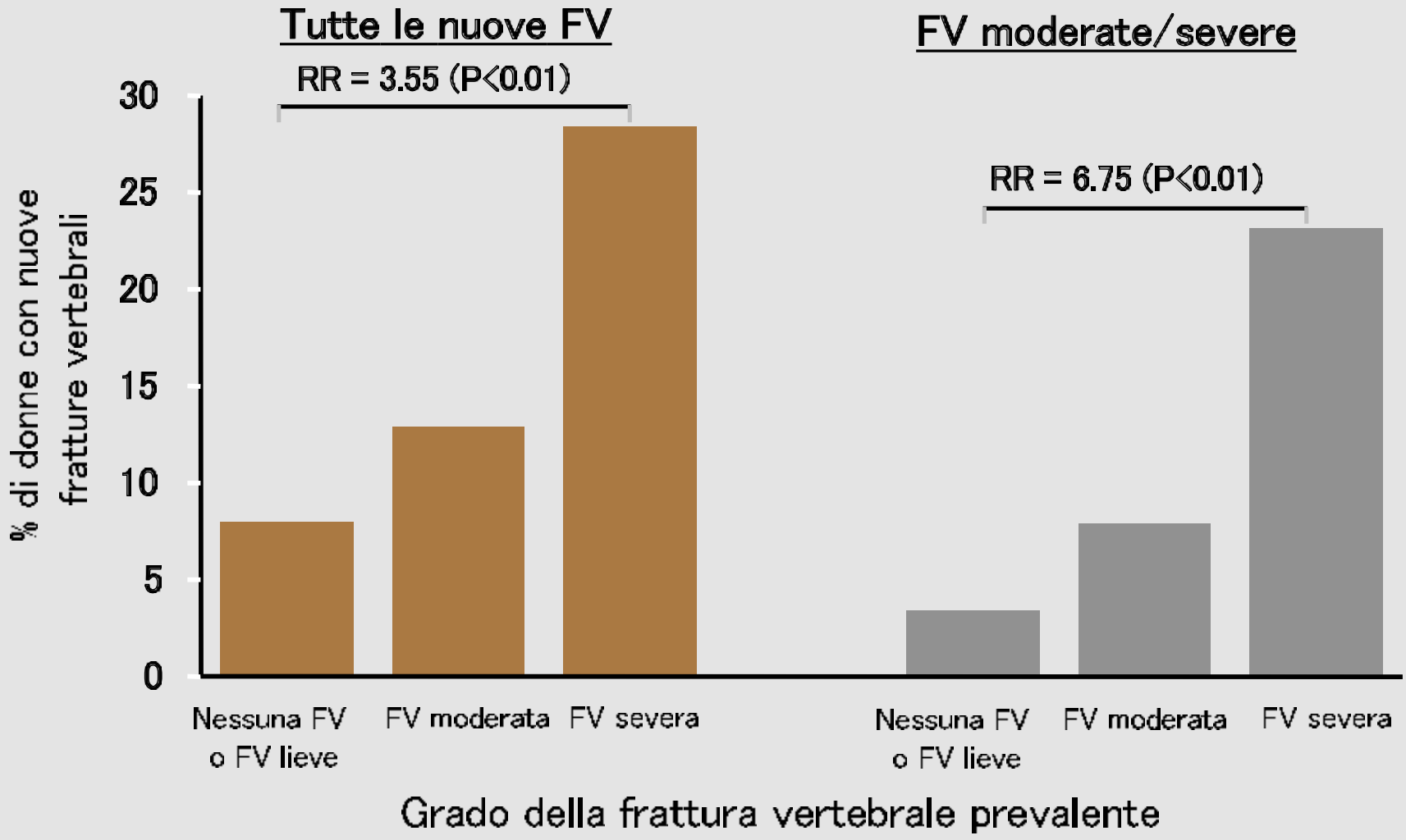
Primo anno di studio



Adapted from Lindsay R et al. *JAMA* 285:320-23, 2001

» 2725 donne in postmenopausa randomizzate a placebo

La severità delle fratture vertebrali prevalenti predice l'incidenza di nuove fratture vertebrali



Gallagher et al. Calcif Tissue Int. 2003

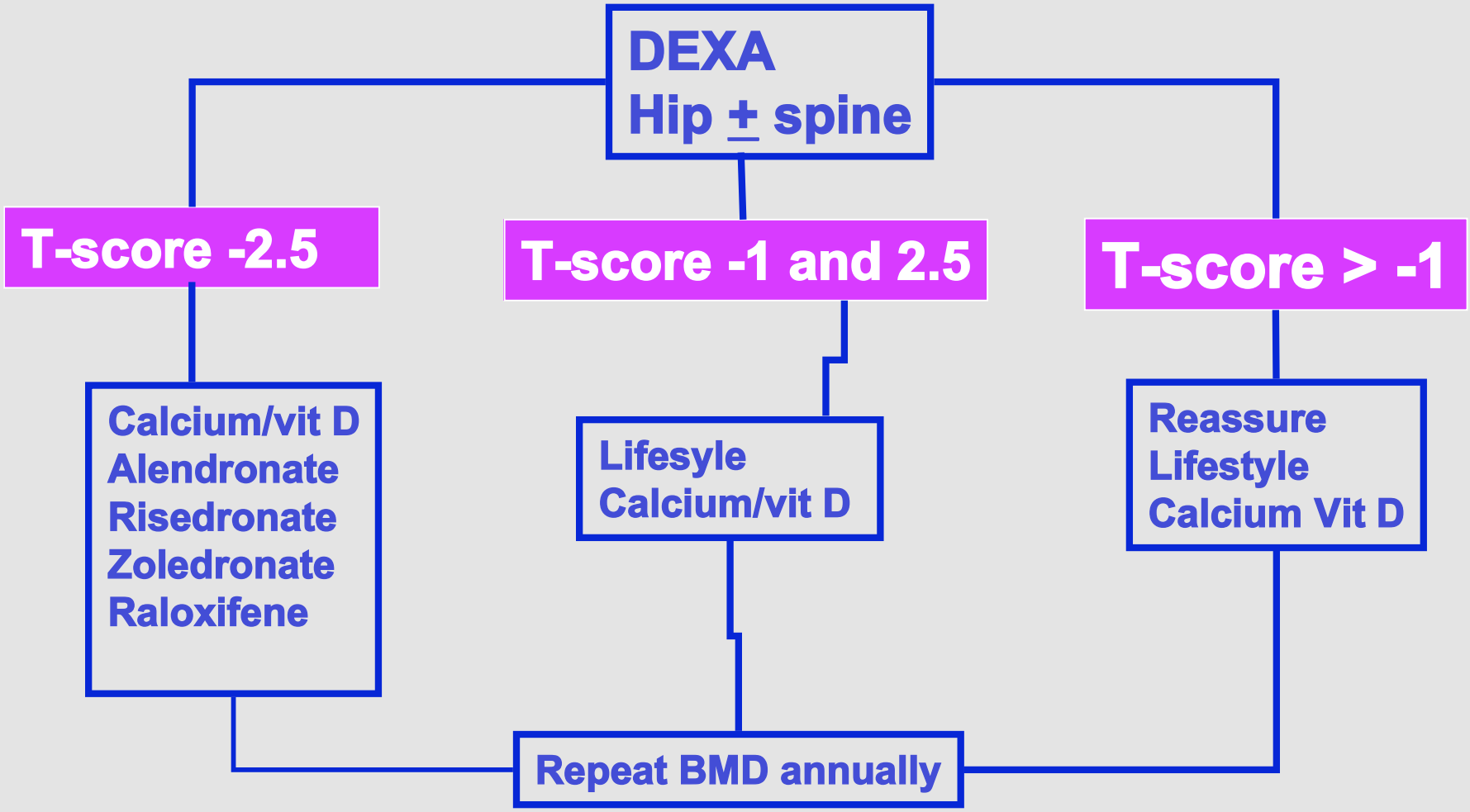
RR= rischio relativo

RISCHIO DI NUOVA FRATTURA IN SOGGETTI CON FRATTURA DI COLLE'S

	RR
Radio	2.78
Omero pross.	1.97
Vertebre	5.72
Bacino	2.34
Collo femore	1.58

Eastell et al *QJM 2001*

ASCO GUIDELINES (2003)



RECOMMENDATIONS FOR THE MANAGEMENT OF CTIBIL

Consensus Statement Belgian Bone Club

In all patients:

- Measurement of BMD by DXA *(baseline and every 18 mo)*
- Evaluation of specific risk factors for fractures

Consideration for therapy (BPs):

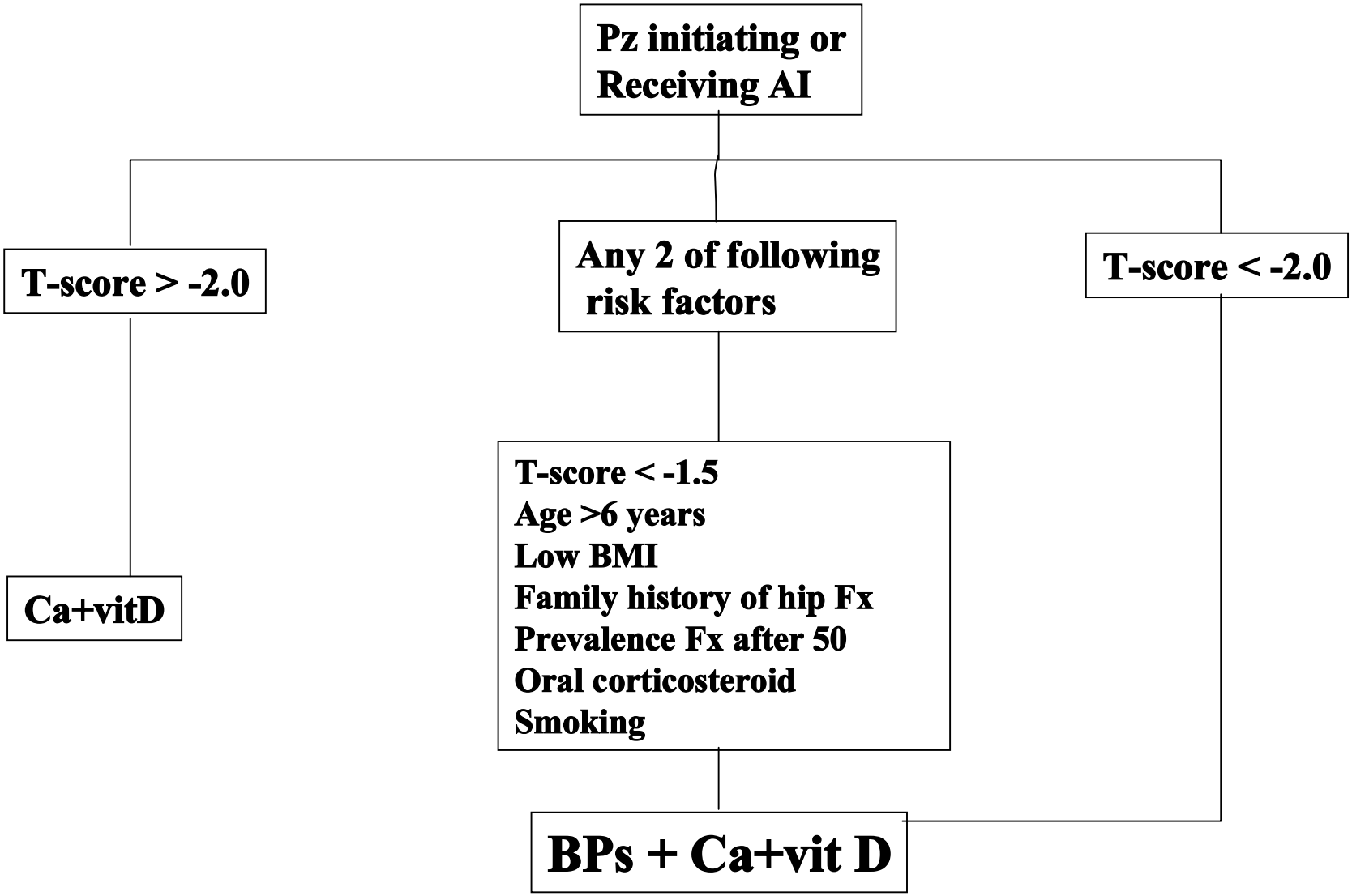
- Fragility fractures (clinical and morphometric spine,hip, wrist,homerus)
- T-score <-2.5
- T-score between -1.0 and -2.5 (osteopenia) considering the presence of other risk factors

Regular measurement of BMD in untreated patients (18 months)

- Initiation therapy if significant bone loss is detected (more than 2% at the spine and 4% at the hip)

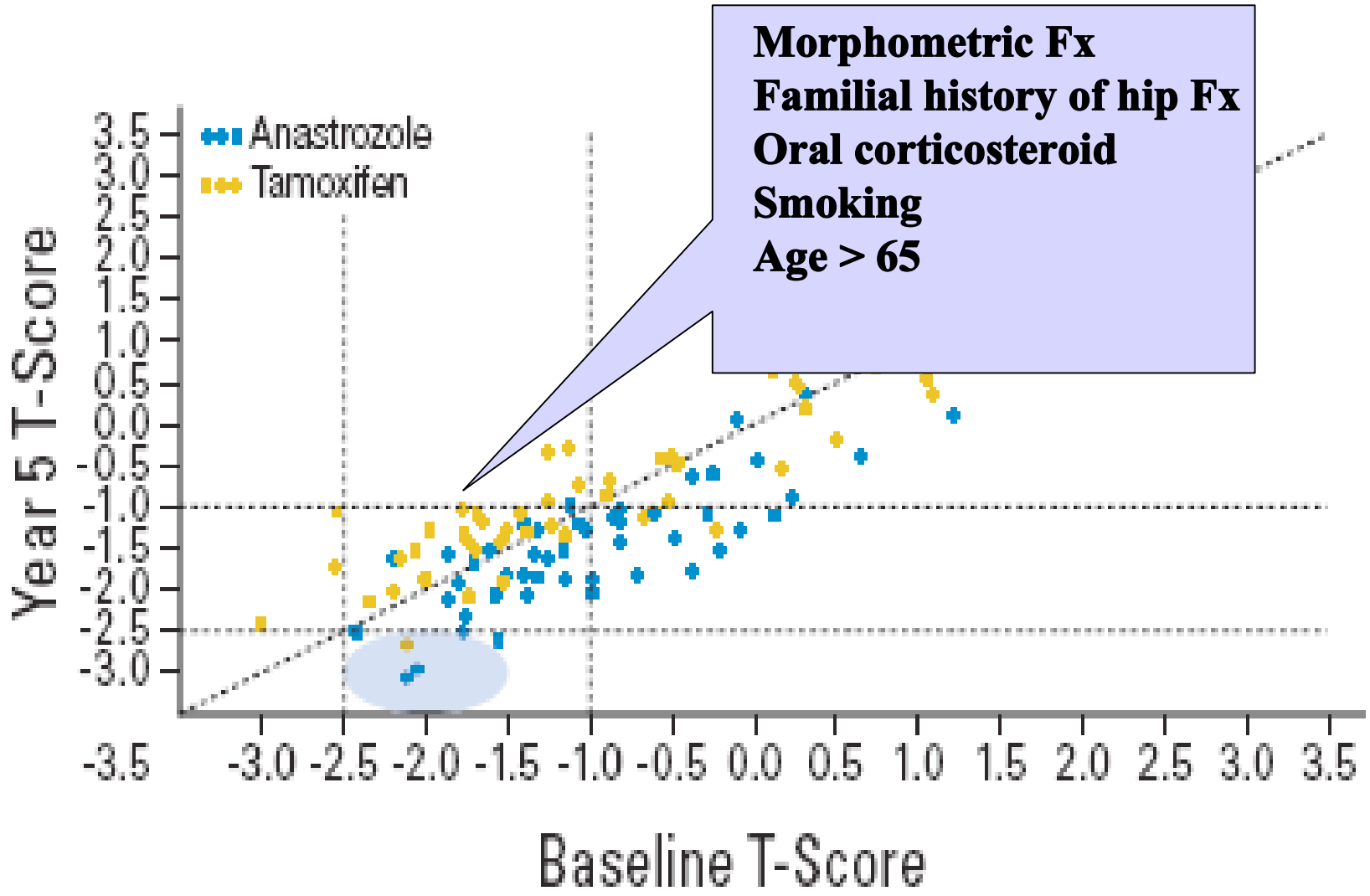
Body JJ Osteoporos Int 2007

Practical Guidance for the Management of AI Associated Bone Loss



Hadji P Ann Oncol 2008

Shift of T-score from Baseline to Years 5



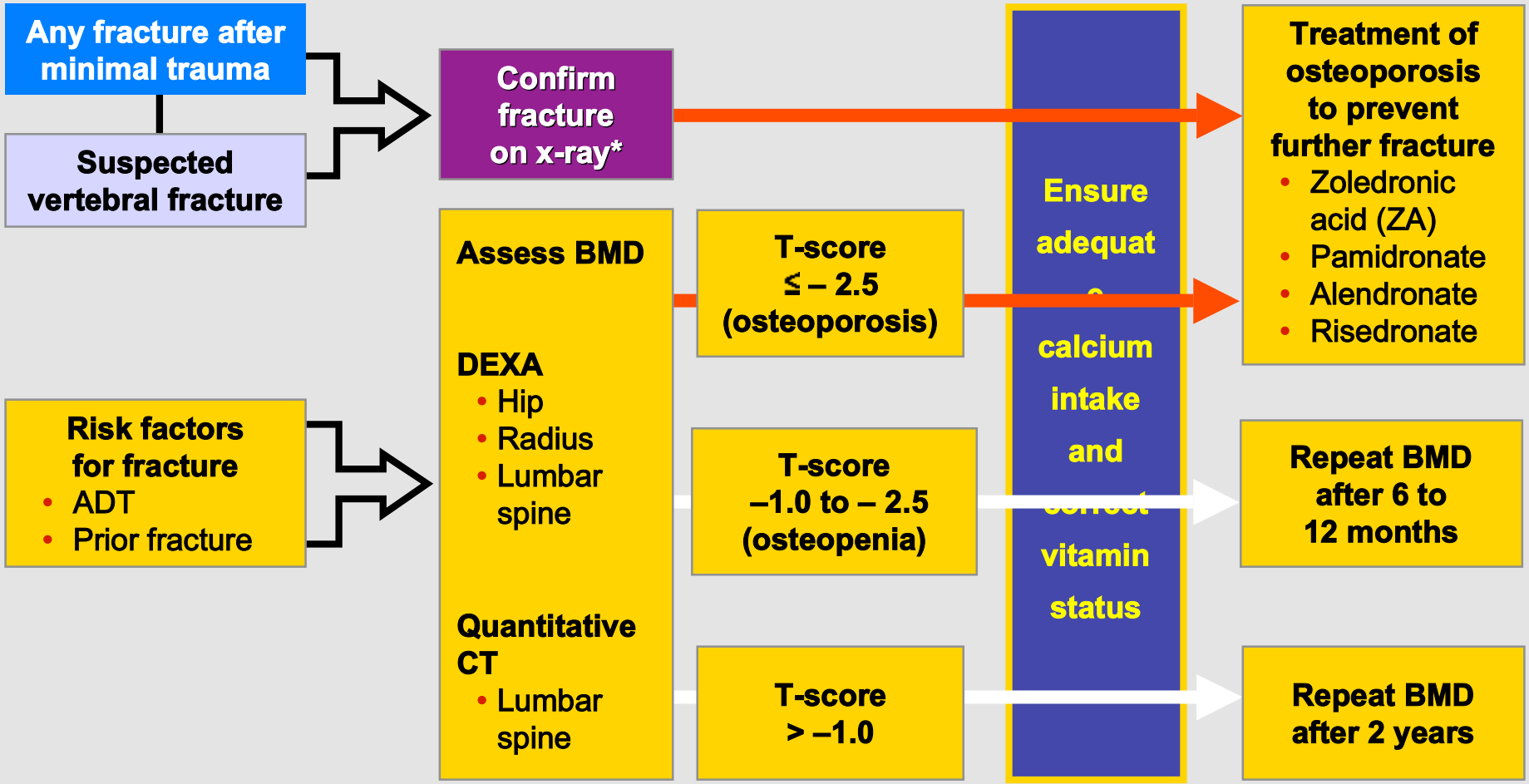
Eastell R J Clin Oncol 2008

TABELLA DI RISCHIO FRATTURATIVO DI FEMORE A 10 ANNI (%) CALCOLATO SU ETA' E BMD

Età (anni)	T score (collo femore)									
	1	0.5	0	-0.5	-1	-1.5	-2	-2.5	-3	-4
	Rischio a 10 anni di ogni tipo di frattura osteoporotica (%)									
45	1.8	2.3	2.8	3.5	4.3	5.4	6.6	8.1	10	15
50	2.4	3	3.8	4.7	5.9	7.4	9.2	11.3	14.1	21.3
55	2.6	3.3	4.1	5.3	6.7	8.5	10.7	13.4	16.8	26
60	3.2	4.1	5.1	6.5	8.2	10.4	13	16.2	20.2	30.6
65	4	5	6.3	8	10	12.6	15.6	19.3	23.9	35.5
70	4.3	5.5	7.1	9	11.5	14.6	18.3	22.8	28.4	42.3
75	4.2	5.4	7	9.1	11.8	15.2	19.4	24.5	30.8	46.2
80	4.6	6	7.7	9.9	12.7	16.2	20.5	25.6	31.8	46.4
85	4.5	5.8	7.4	9.4	12	15.3	19.1	23.8	29.4	42.7

Kanis J Osteop Int 2002

Recommendations for Prostate Cancer Patients



*Rule out pathologic fracture from bone metastases.
Adapted from Diamond TH, et al. *Cancer*. 2004;100:892-899.

NOTA 79 2007 PER LA RIMBORSABILITA'
FARMACI PER OSTEOPOROSI

Soggetti sopra i 50 anni o donne in menopausa

-Frattura vertebrale (morfometrica) o femorale
-Terapia corticosteroidea (> 5 mg/Pn per almeno 3 mesi)
-T-score <- 3 femore + 1 fattore rischio
-T-score <- 4 femore

PRINCIPALI CONSEGUENZE E OBIETTIVI DELLA TERAPIA NELLA CTIBL

	End point
- Perdita BMD	Obbiettivo Surrogato
- Elevazione del turnover osseo	Obbiettivo Surrogato
-Rischio fratturativo	Obbiettivo Principale

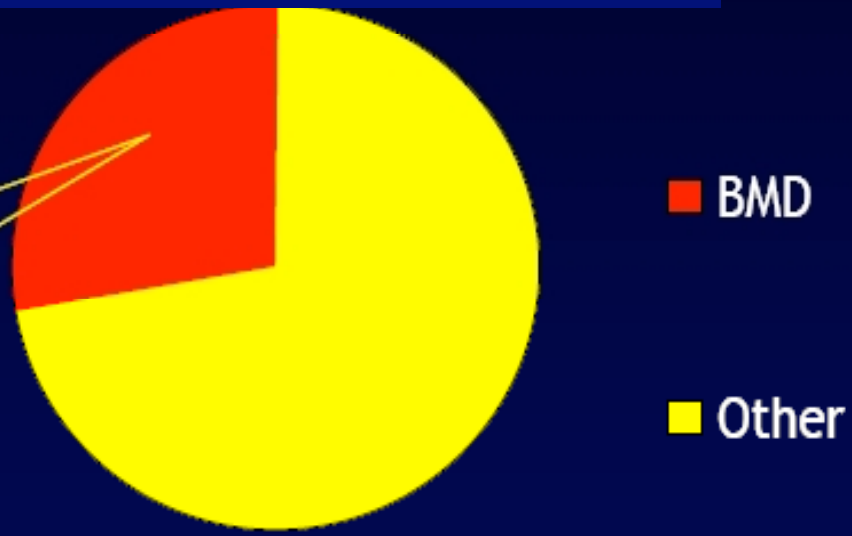
Contribution of BMD increase on vertebral fracture risk reduction

Baseline BMD is a stronger predictor of Fracture Risk than changes of BMD under therapy

Risedronate 7%-28%[1]

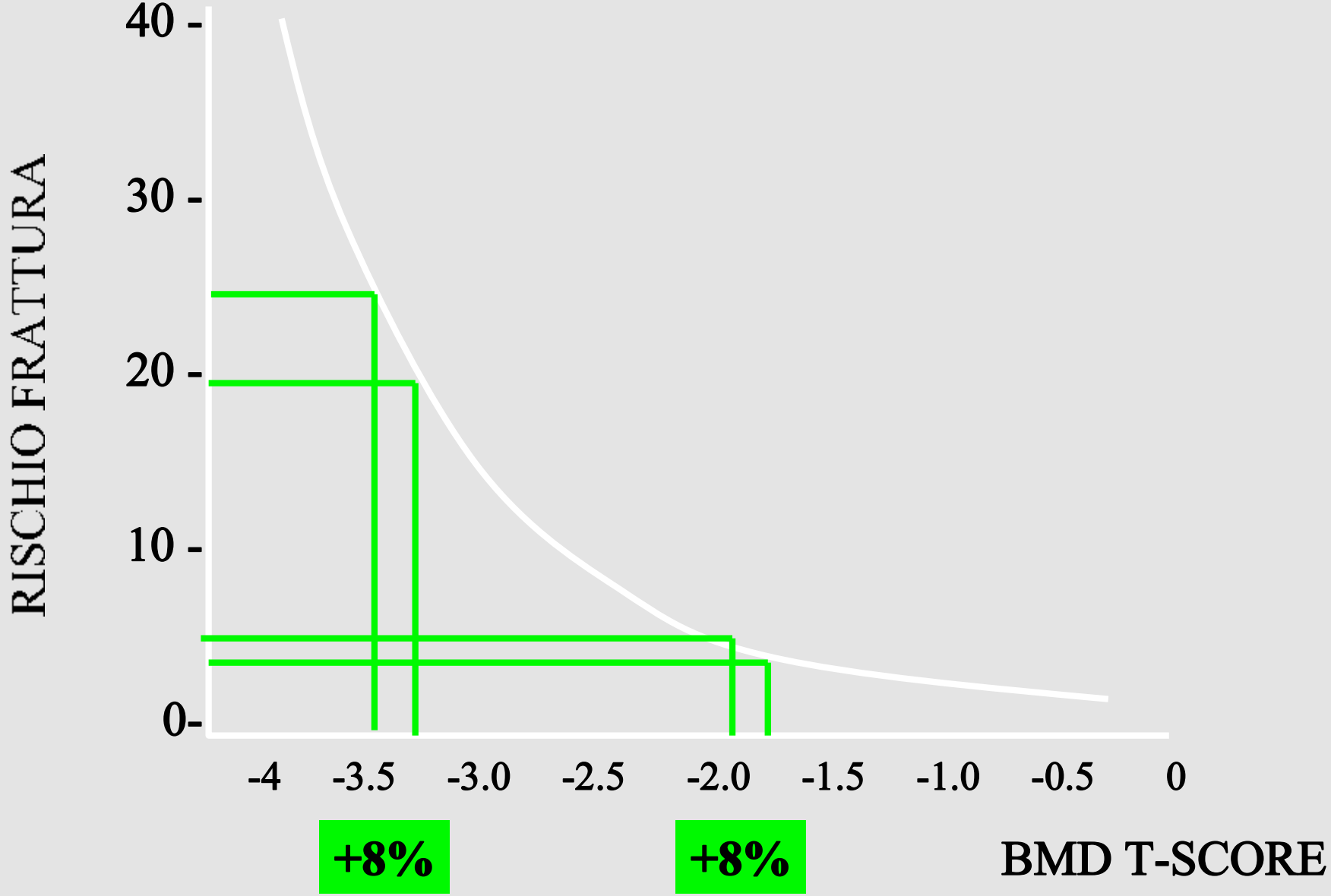
Alendronate 17%[2]

Raloxifene 4%[3]



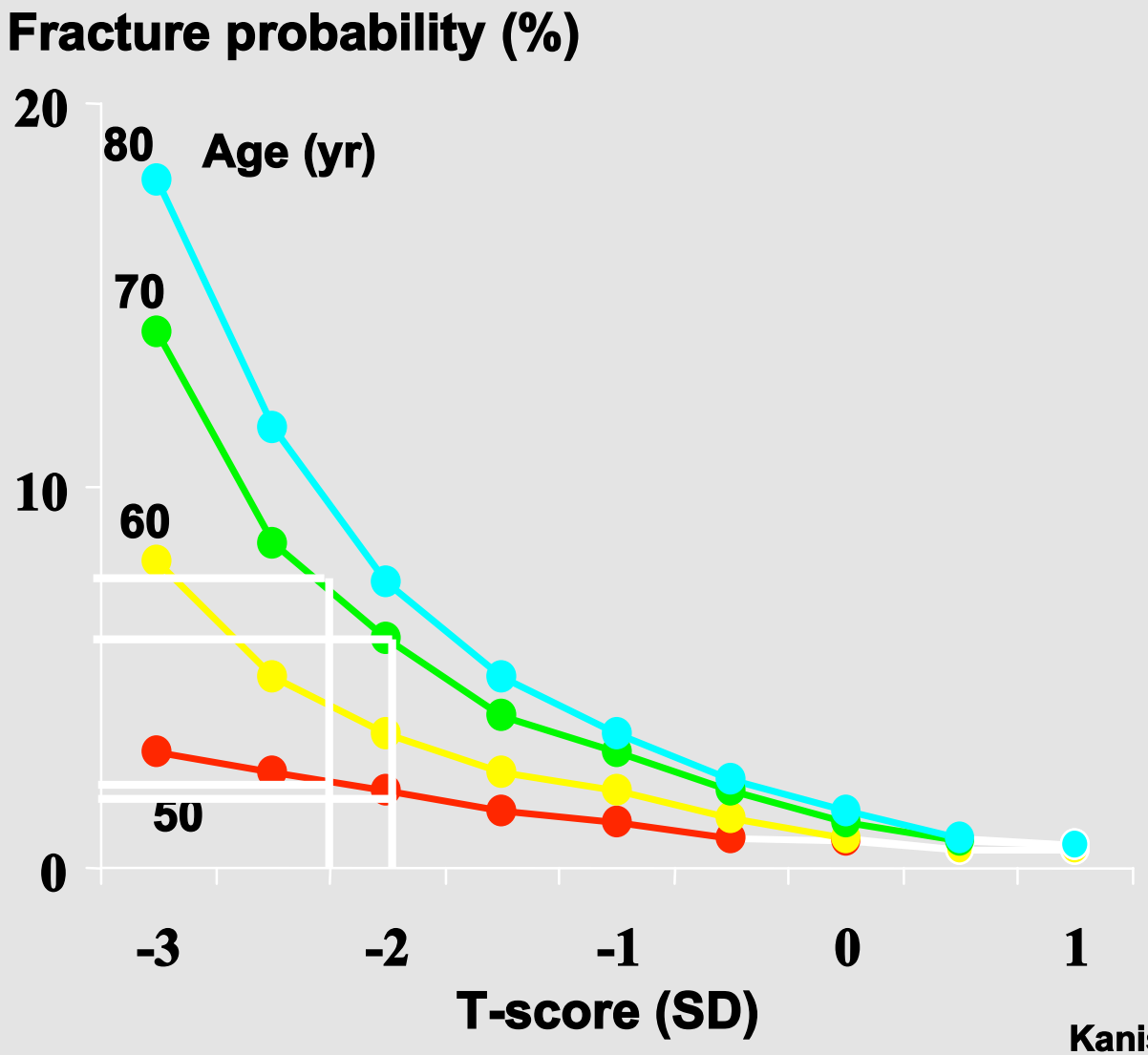
1 Li et al, 2001
2 Cummings et al, 1999
3 Sarkar et al, 2002

RELAZIONE TRA BMD E RISCHIO DI FRATTURA



Watts, ASBMR 2001

Ten-year probability of hip fracture according to age and femoral neck T-score



Kanis JA et al, Bone 2000

QUALE TERAPIA DELLA CTBIL?

LA CTBL è paragonabile all'Osteoporosi postmenopausale?

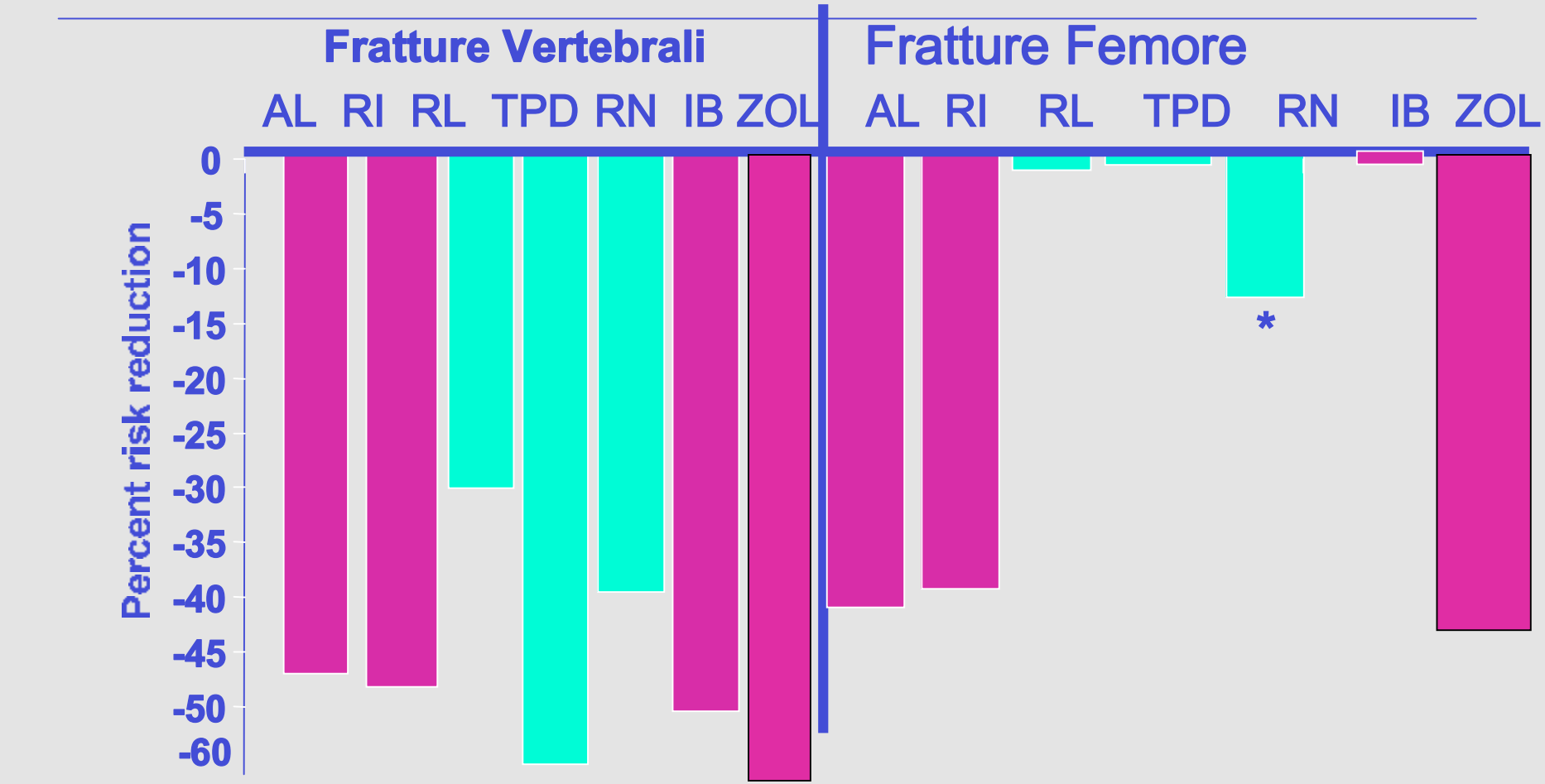
- Sono sufficienti i dati su parametri surrogati (BMD/turnover)?
- Possiamo estrapolare i dati di efficacia ottenuti nella PMO?
- Si deve usare una posologia diversa rispetto alla PMO?
- Per quanto va protratta la terapia?
- Cosa succede quando si sospende il blocco ormonale?

QUALI BISFOSFONATI ?

(evidenza antifratturativa)

	OP Postmenop		OP Maschio	OP Cortis
	VFx	Hip Fx		
OS				
Alendronato 70mg/sett	*	*	*	*
Risedronato 35 mg/sett	*	*	*	*
Ibandronato 150 mg/mese	*			
EV				
Zoledronato 5 mg/anno	*	*		
Ibandronato 3 mg/ 3 mesi	*			
Neridronato 25 mg/mese				

Efficacia Antifratturativa nell'Osteoporosi Postmenopausale



AL **Alendronate** *RL* **Raloxifene** *RN* Ranelato

RI **Risedronate** *TPD* Teriparatide *IB* Ibandronato

ZOL zoledronate

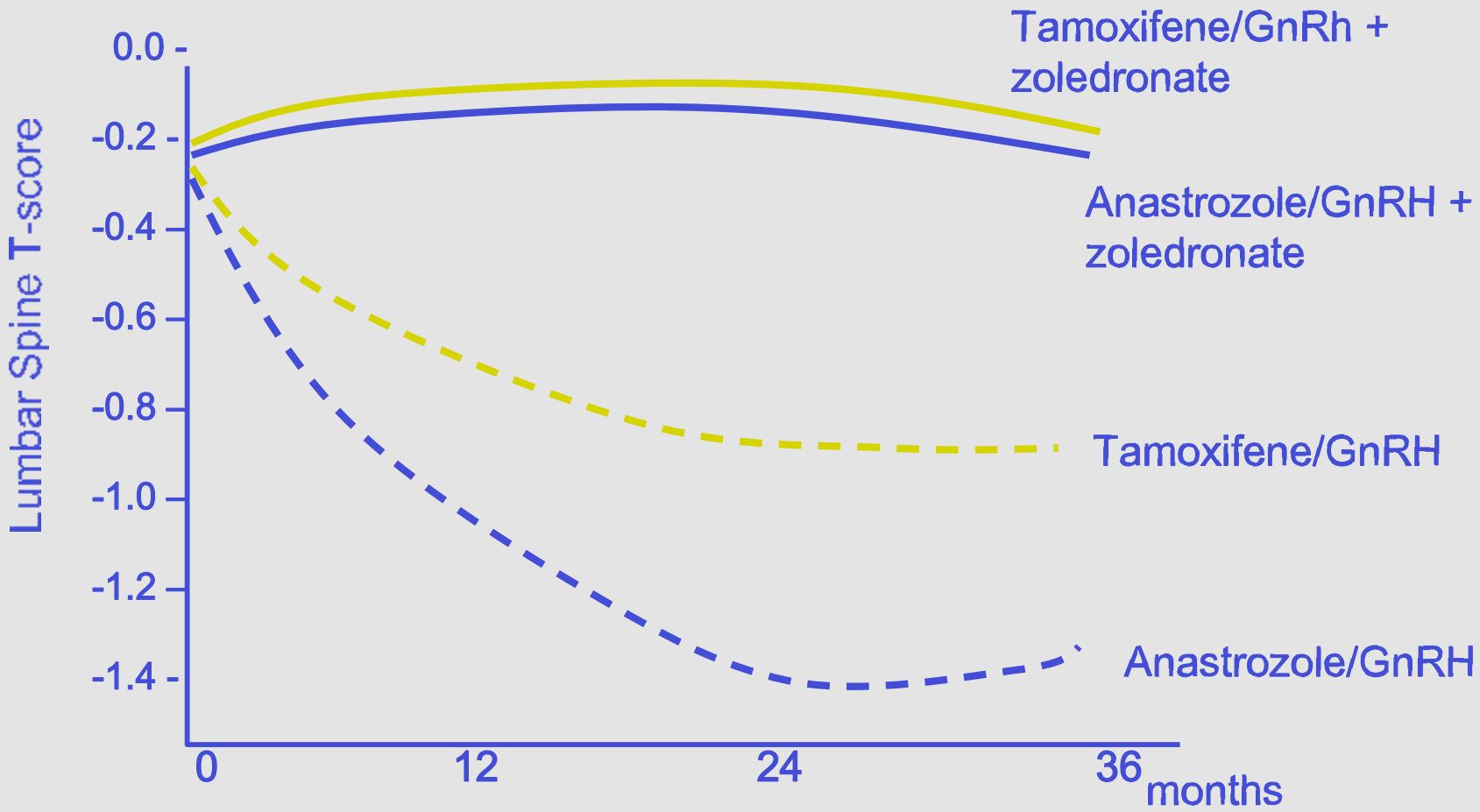
Guyatt et al ***Endocrine Review 2002***

QUALI BPs NELLA CTIBIL?

- Dati esclusivamente su BMD e Turnover
- Dati prevalentemente in prevenzione

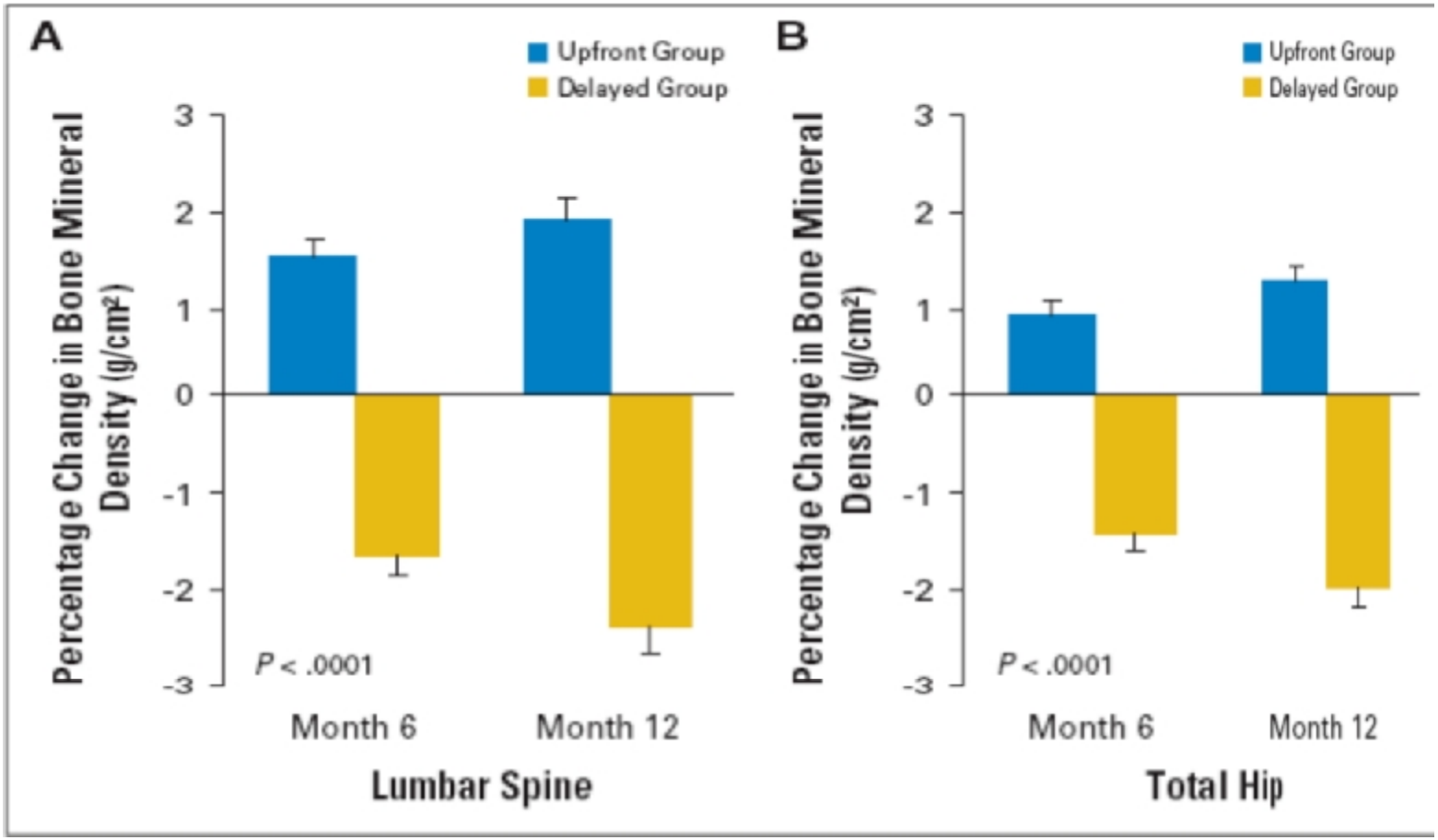
- Zoledronato 4 mg /anastrazolo 1 fl/ 6 mesi (Gnant ABCSG 2007)
- Zoledronato 4 mg /letrozolo 1 fl/6 mesi (Brufsky 2007; Bundred 2008)
- Risedronato 35 mg /exemestane 1 cp/sett (Confavreux CB , Bone 2007)
- Risedronato 35 mg/ tamoxifene/AI 1cp/sett (Greenspan JCO 2008)

Effect of Zoledronate (4mg/6 month) on BMD
ABCSG 12 Trial



Gnant et al *J Clin Onc 2007*

Zoledronic Acid Inhibits Adjuvant Letrozole-Induced Bone Loss In Postmenopausal Women (Z-FAST Study)

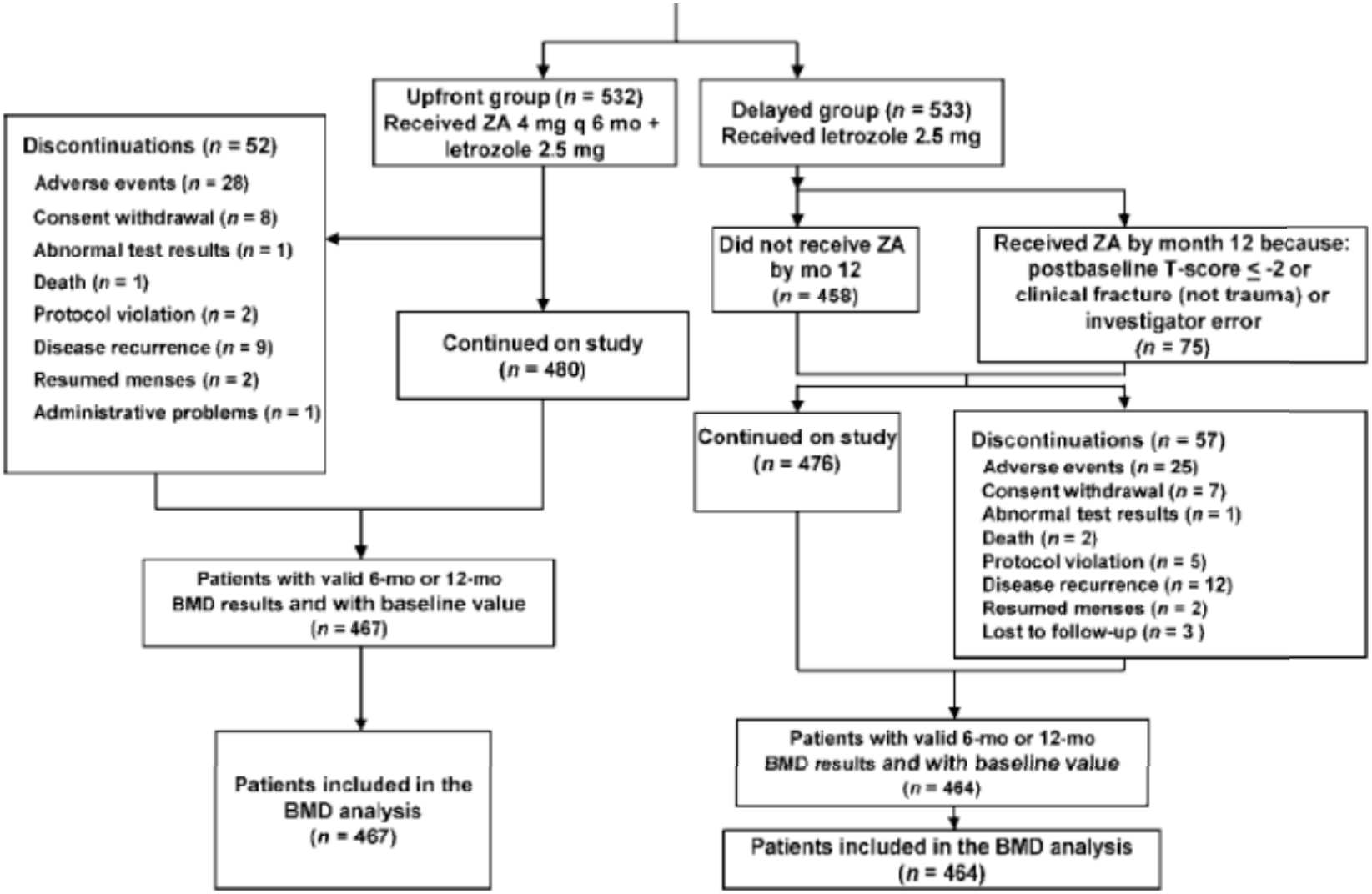


Delayed : when T-score > -2 or clinical fracture (8.3%)

Brufsky A J Clin Oncol

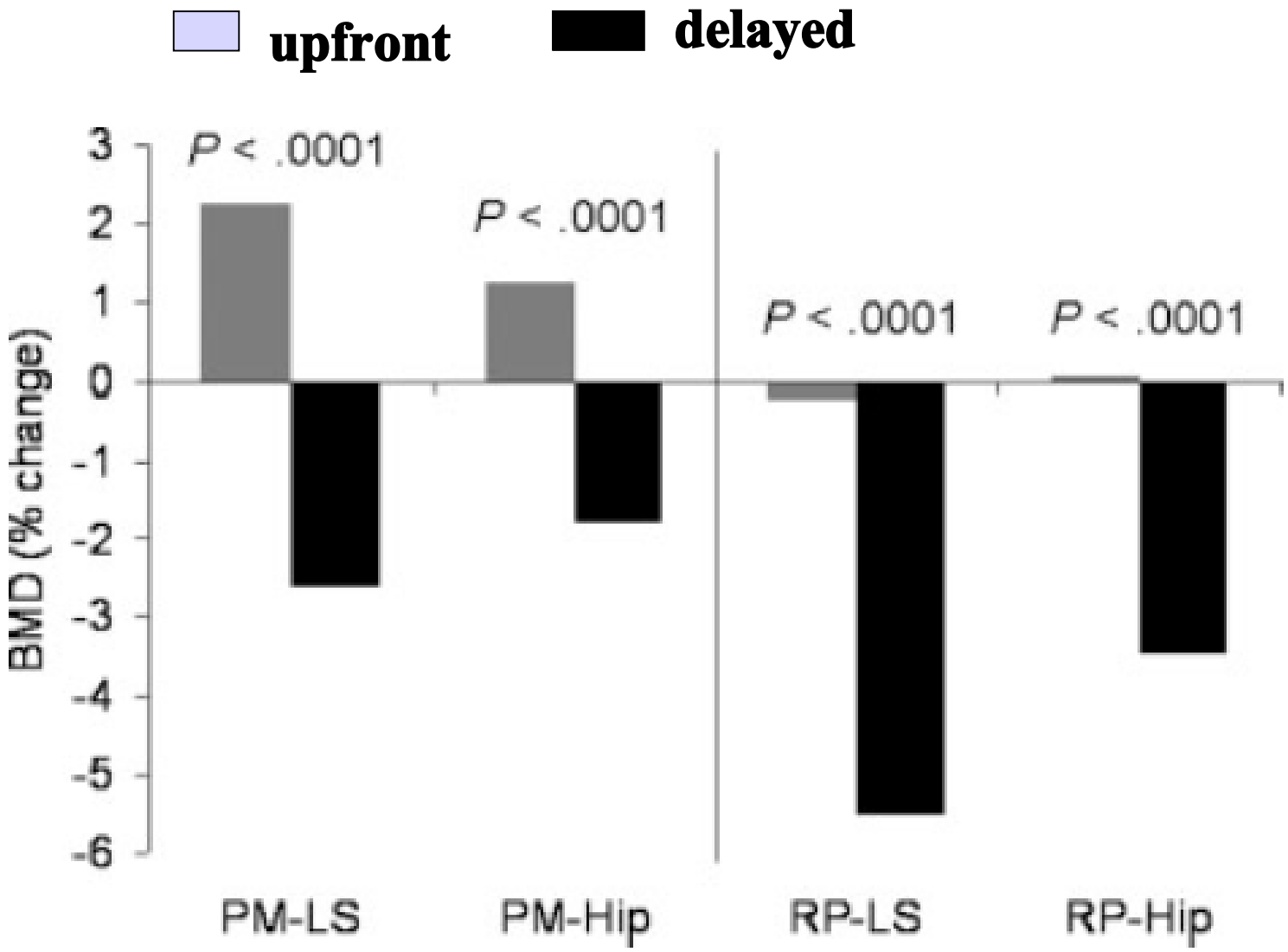
Effective Inhibition of Aromatase Inhibitor-associated Bone Loss by Zoledronic Acid in Postmenopausal Women With Early Breast Cancer Receiving Adjuvant Letrozole

ZO-FAST Study Results



Bundred Ni Cancer 2008

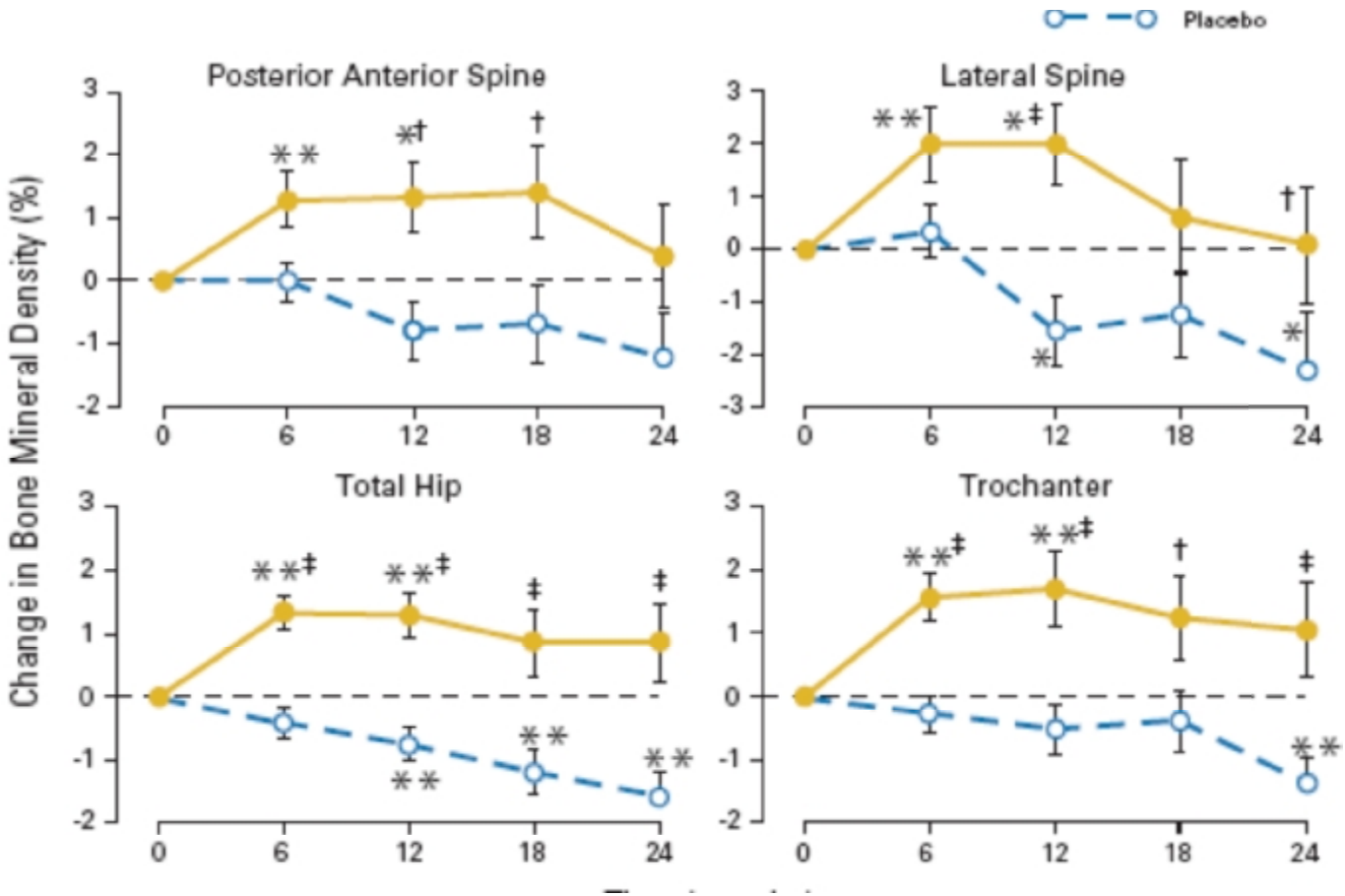
Zo-FAST Study (zoledronate 4mg/6 mo)



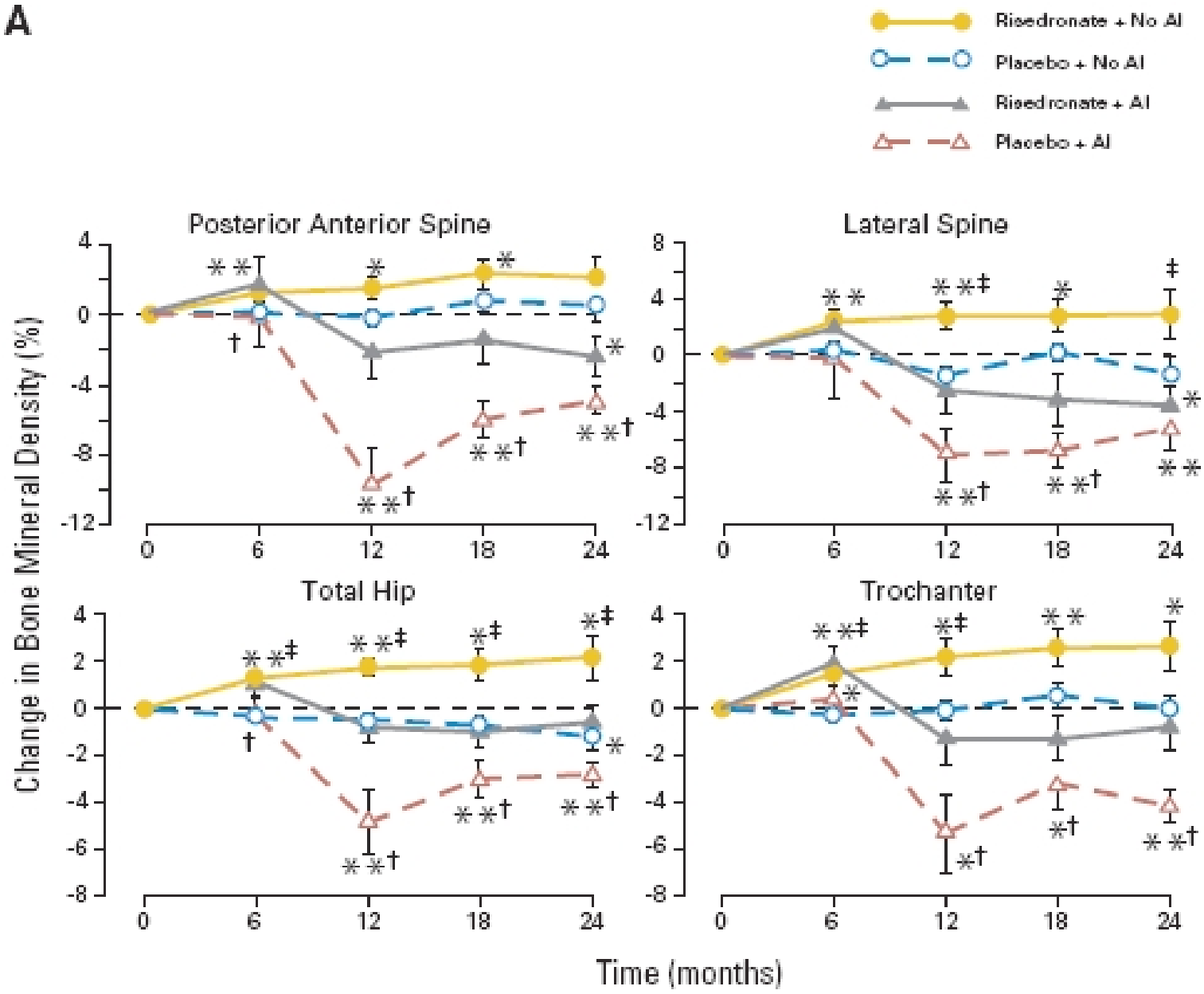
Bundred Ni Cancer 2008

Risedronate Prevents Bone Loss in Breast Cancer Survivors: A 2-Year, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Susan L. Greenspan, Adam Brufsky, Barry C. Lembersky, Rajib Bhattacharya, Karen T. Vujevich, Subashan Perera, Susan M. Sereika, and Victor G. Vogel



J Clin Oncol 2008

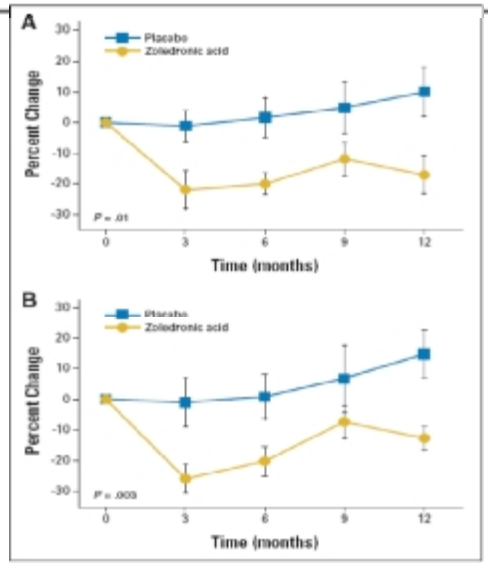


J Clin Oncol 2008

Randomized Controlled Trial of Annual Zoledronic Acid to Prevent Gonadotropin-Releasing Hormone Agonist–Induced Bone Loss in Men With Prostate Cancer

Table 2. Percent Changes in Bone Mineral Density From Baseline to 12 Months

Measure	% Change in Placebo Group		% Change in Zoledronic Acid Group		Between-Group Difference		
	Mean	SE	Mean	SE	%	95% CI	*P*
Posteroanterior lumbar spine	−3.1	1.0	4.0	1.0	7.1	4.2 to 10.0	< .001
Total hip	−1.9	0.7	0.7	0.5	2.6%	0.9 to 4.3	.004
Femoral neck	−0.1	1.0	2.0	0.6	2.1%	−0.1 to 4.4	.06
Trochanter	−1.4	0.7	1.7	0.8	3.1%	0.9 to 5.3	.008



U-NTX

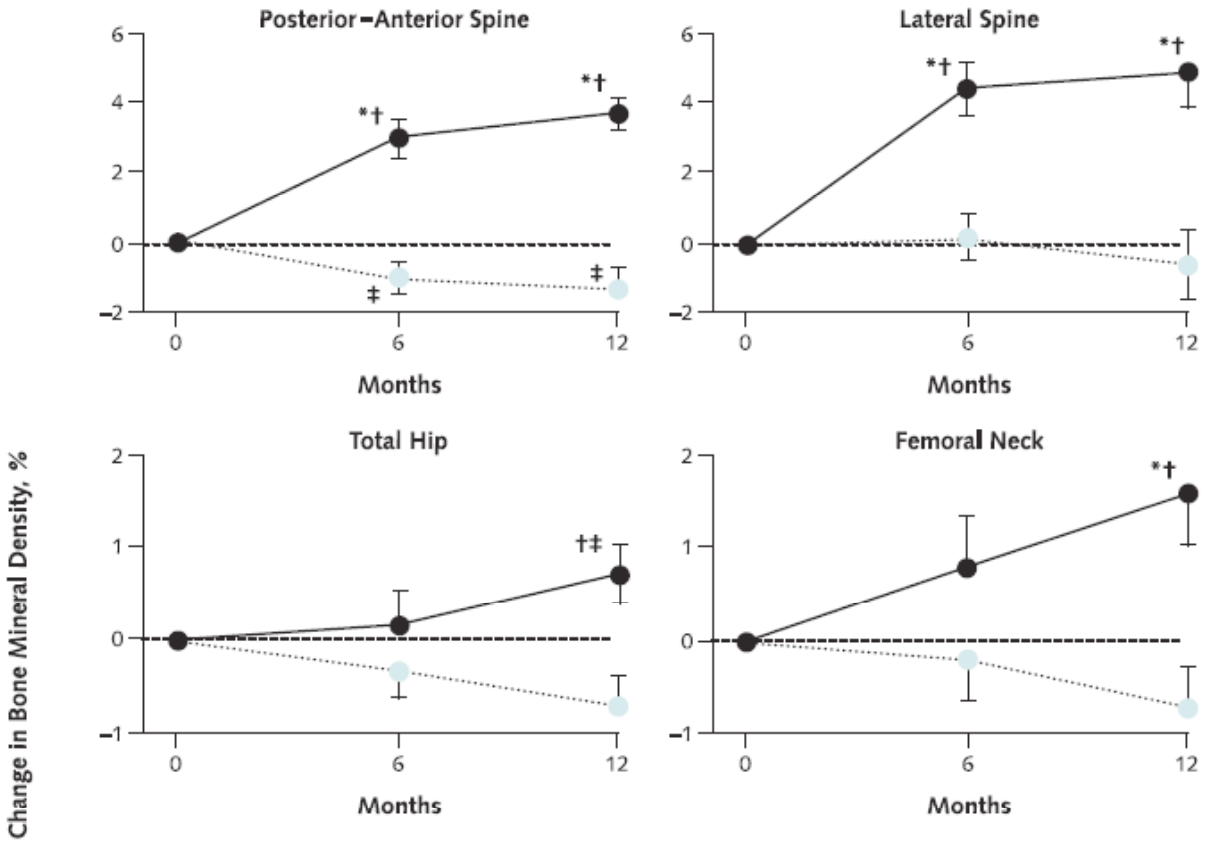
B-ALP

Michaelson Md J Clin Oncol 2007

Effect of Once-Weekly Oral Alendronate on Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

A Randomized Trial

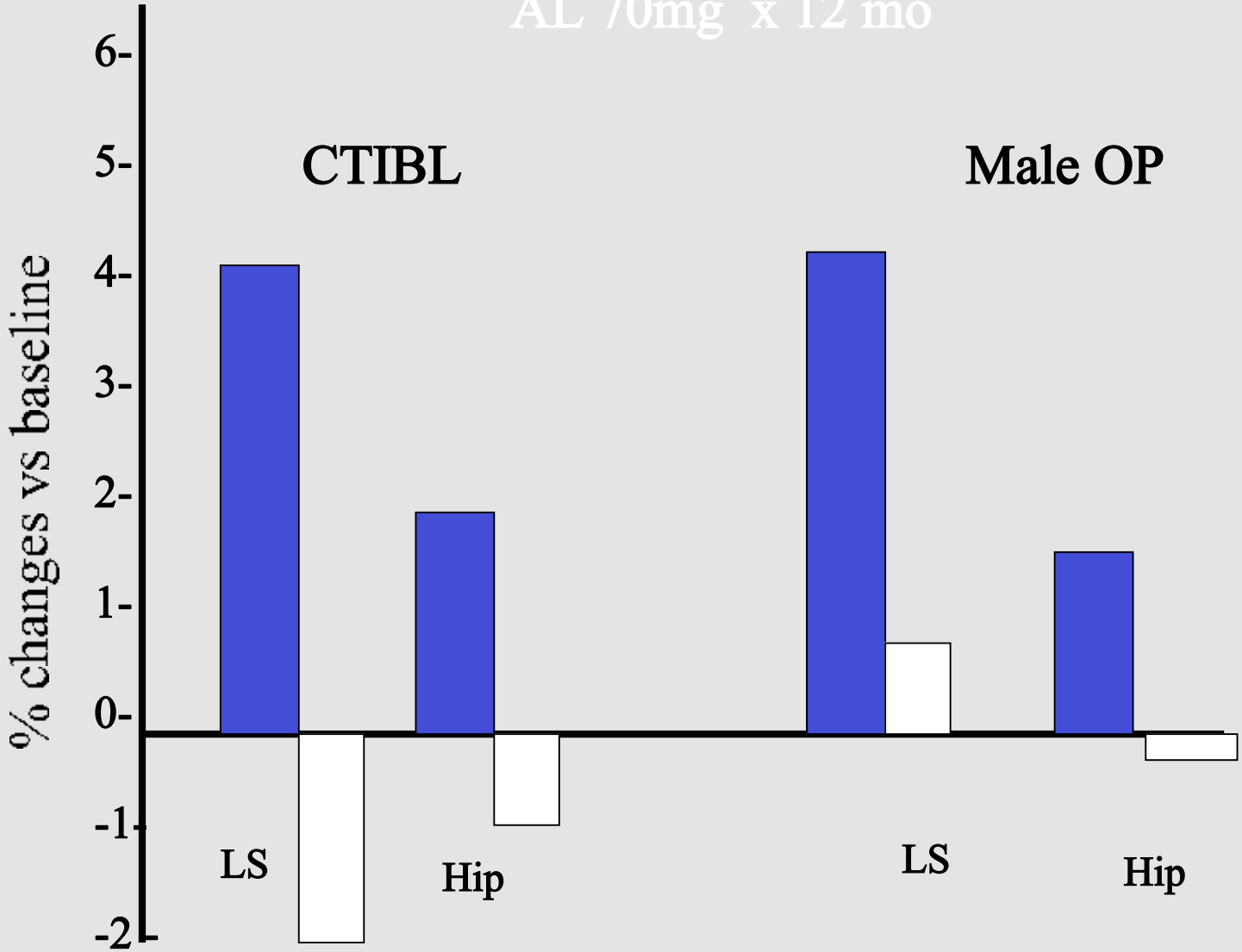
Susan L. Greenspan, MD; Joel B. Nelson, MD; Donald L. Trump, MD; and Neil M. Resnick, MD



Ann Int Med 2007

BMD CHANGES WITH ALENDRONATE THERAPY

AL 70mg x 12 mo



Greenspan L Ann Int Med 2007

Miller P et al. ASBMR 2002

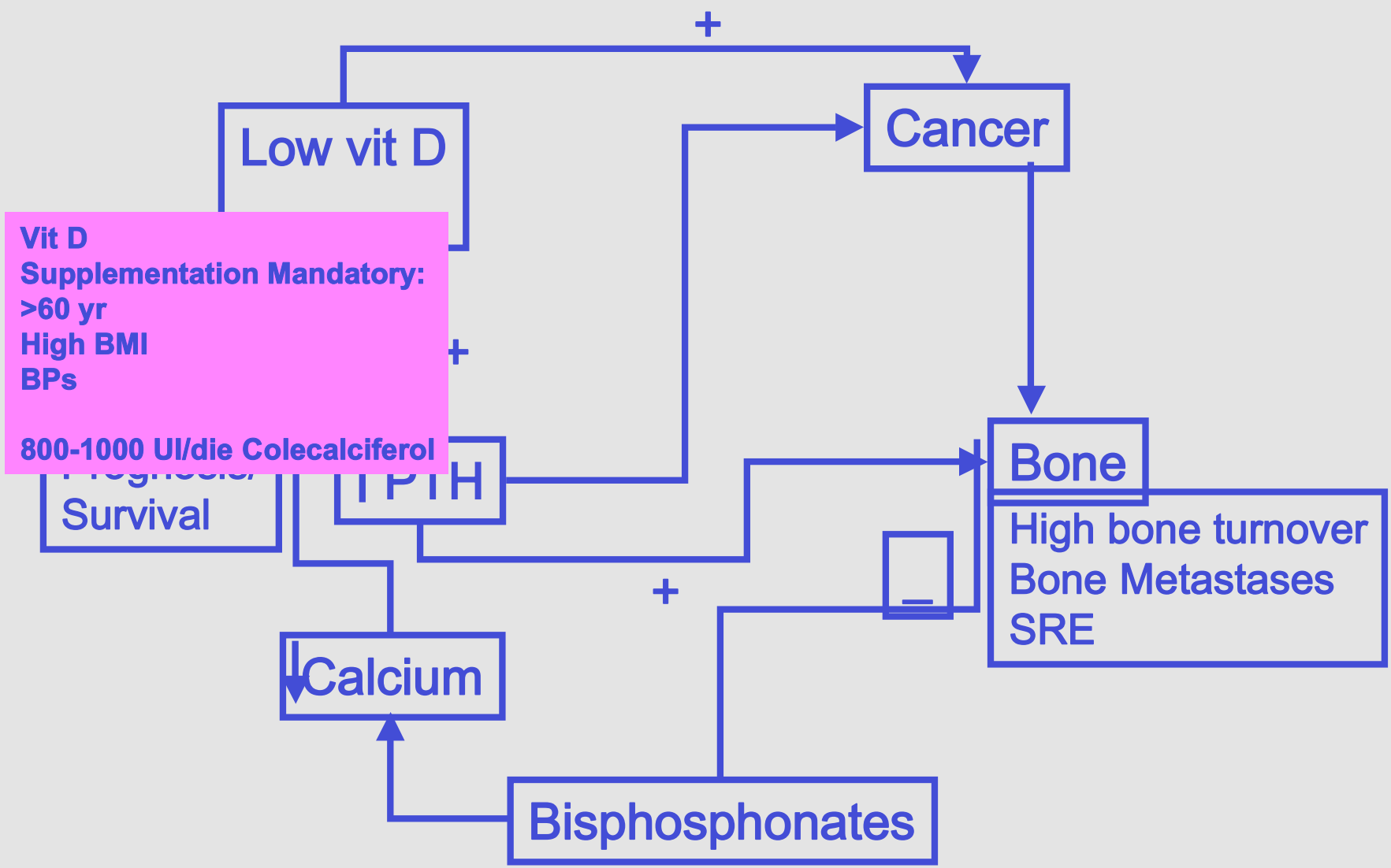
Quale Terapia nell'osteoporosi maschile e (CTBIL?)

- **Alendronato 10 mg die o 70 mg/settimana(nota 79)**

- **Zoledronato 5 mg 1 fl anno**

dati solo su parametri surrogati (BMD e turnover) Non ancora registrato

THE ROLE OF VITAMIN D IN BONE HEALTH
In CANCER PATIENT



RECOMMENDED DOSES OF VITAMIN D INTAKE (30-40 ng/ml 25OH vit D)

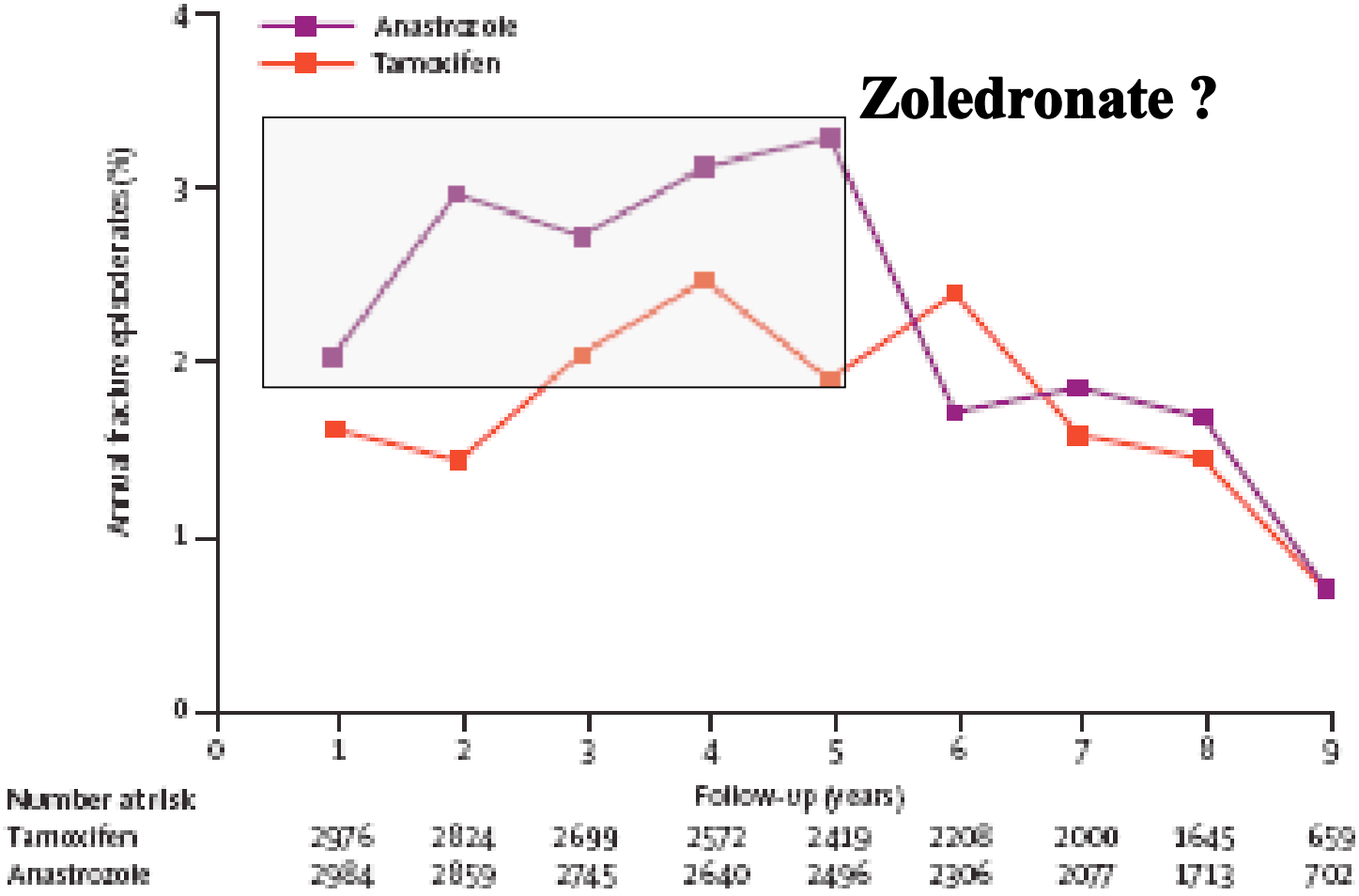
National .Accademy of Sciences. 2007

2005	0-50	200 UI /day	Europe
	50-70	400 UI/day	
	> 70	600-800 I/day	
2007	1000 UI/day vit D3 (colecalciferol)		USA

Mandatory: Age > 55-60,
high BMI,
Bisphosphonate therapy

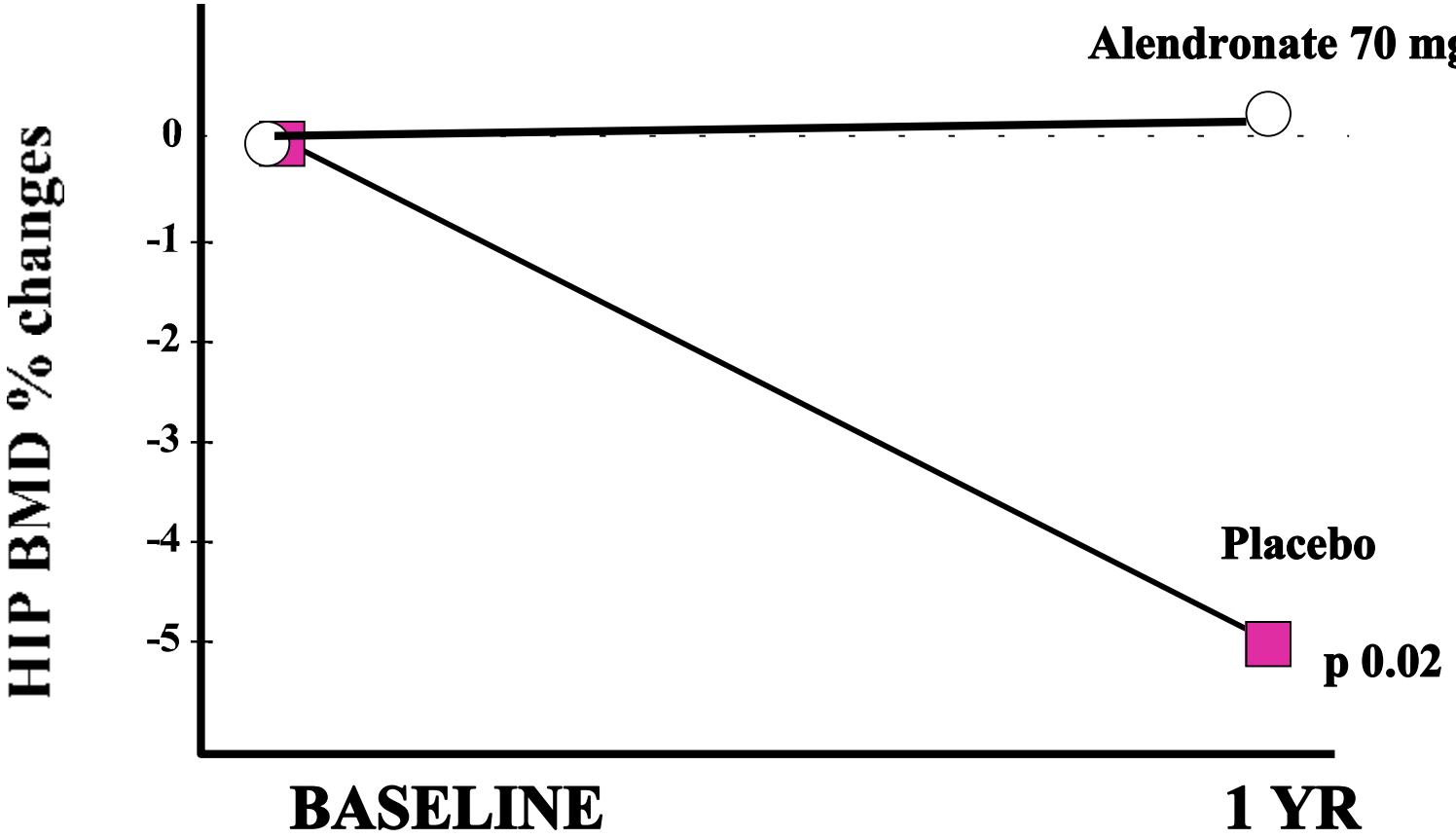
Dibase 30-40gtt/week
Dibase 100.000 UI/mo.

100-Month Analysis of the ATAC Trial



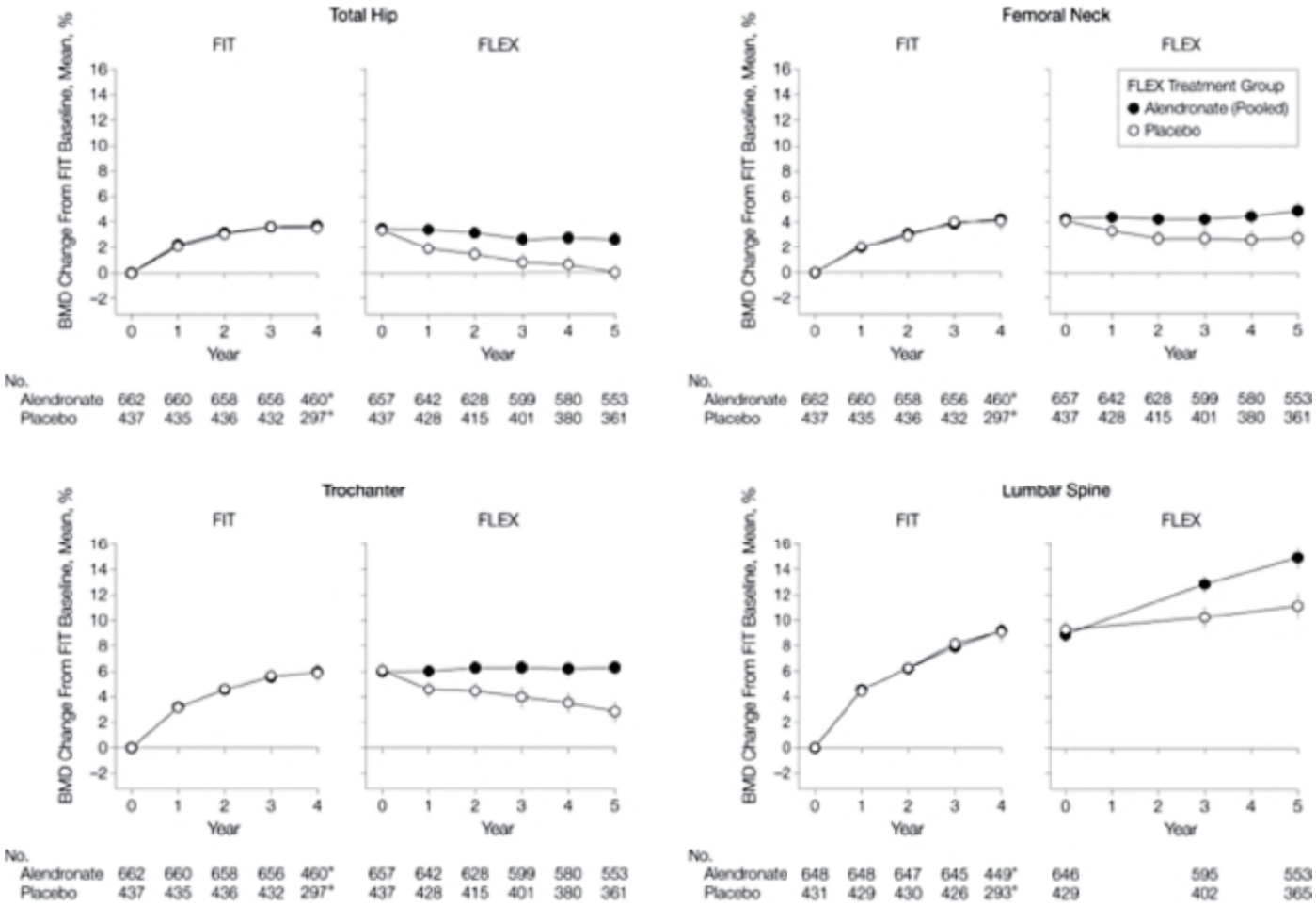
Lancet Oncol 2008

Prevention of Bone Loss after withdrawal Tamoxifene

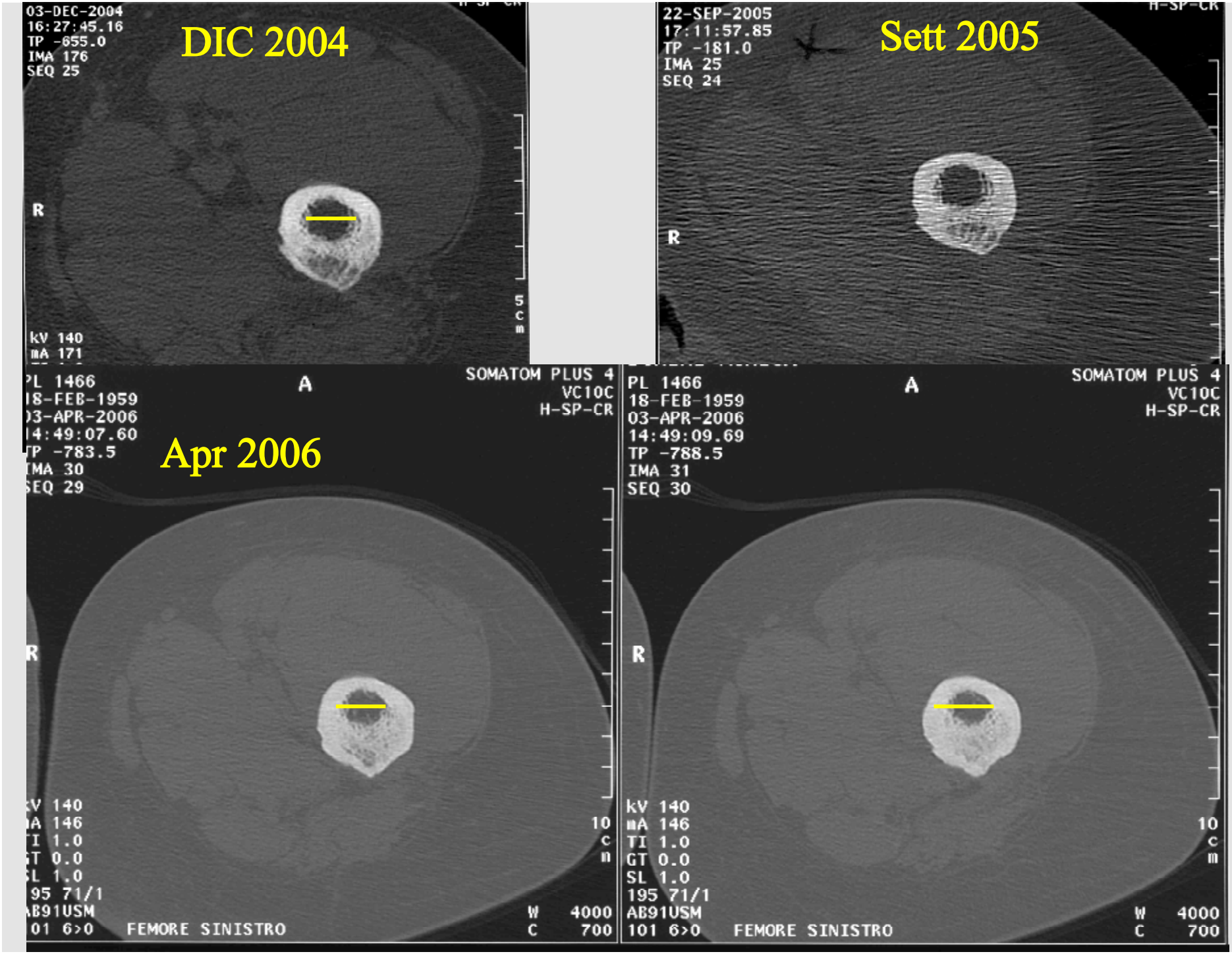


Cohen A Endocr Pract 2008

BMD Change in FLEX Participants (5 y after AL withdrawal)



Black, D. M. et al. JAMA 2006;296:2927-2938.


DIC 2004
03-DEC-2004
16:27:45.16
TP -655.0
IMA 176
SEQ 25
R
kV 140
mA 171
Sett 2005
22-SEP-2005
17:11:57.85
TP -181.0
IMA 25
SEQ 24
R
Apr 2006
A
SOMATOM PLUS 4
VC10C
H-SP-CR
PL 1466
18-FEB-1959
03-APR-2006
14:49:07.60
TP -783.5
IMA 30
SEQ 29
R
kV 140
mA 146
TI 1.0
GT 0.0
SL 1.0
195 71/1
AB91USM
101 6>0
FEMORE SINISTRO
W 4000
C 700
A
SOMATOM PLUS 4
VC10C
H-SP-CR
PL 1466
18-FEB-1959
03-APR-2006
14:49:09.69
TP -788.5
IMA 31
SEQ 30
R
kV 140
mA 146
TI 1.0
GT 0.0
SL 1.0
195 71/1
AB91USM
101 6>0
FEMORE SINISTRO
W 4000
C 700