Post-Menopausal Osteoporosis:

"WHO" Do We Treat Now

Verona Italy – October27, 2006

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Texas Institute for Reproductive Medicine And Endocrinology, Houston, Texas
Past President, International Society of Clinical Densitometry (ISCD)
President, American Association of Clinical Endocrinologists (AACE)
Endocrine and Bone Densitometry Consultant – NASA: Johnson Space Center

Disclaimer

- *Speaker for*
  - *GSK/Roche*
  - *Proctor & Gamble/Aventis*
  - *Merck*
  - *Eli Lilly*
  - *Wyeth*

- *Consultant*
  - *Eli Lilly*
  - *GSK/Roche*
  - *Novartis*

Roadmap

1. **The Stone Age**
2. The Industrial Revolution
3. The Information Age

The Stone Age

Mammoth injury: vertebral fractures

Kyphosis
post-menopausal

Diagnosis based on obvious clinical findings.
Oral reports (before writing invented).

ISCD: International Society of Cave Dwellers

Cave painting found near Denver. Circa 60,000 BC

Osteoporosis testing: "*Take rock. Hit bone. It break!*"*

***Miller PD, Bilezikian J et al. J Paleolithic Medicine 60,000 BC 1(1):1-2**

Modern Stone Age Equivalent: Case 1

67 year old Caucasian woman with a history of a 2 recent minimal trauma grade 2 painful vertebral fractures at T10 and T11 by VFA.

- DXA results show a L1-L4 T-score of -1.9 with little variability between vertebral bodies and the lowest hip site at the left femoral neck at a T-score of -1.7. The technical quality of the study was good.

What is her diagnosis?

- A. Low bone density (osteopenia)
- B. Osteoporosis
- C. Severe Osteoporosis
- D. None of the above

Case 1

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What is her diagnosis?

- A. Low bone density (osteopenia)
- **B. Osteoporosis**
- C. Severe Osteoporosis
- D. None of the above

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Case 1: Lessons to be Learned…

We are still in the stone age as far as recognizing and treating the "low hanging fruit"

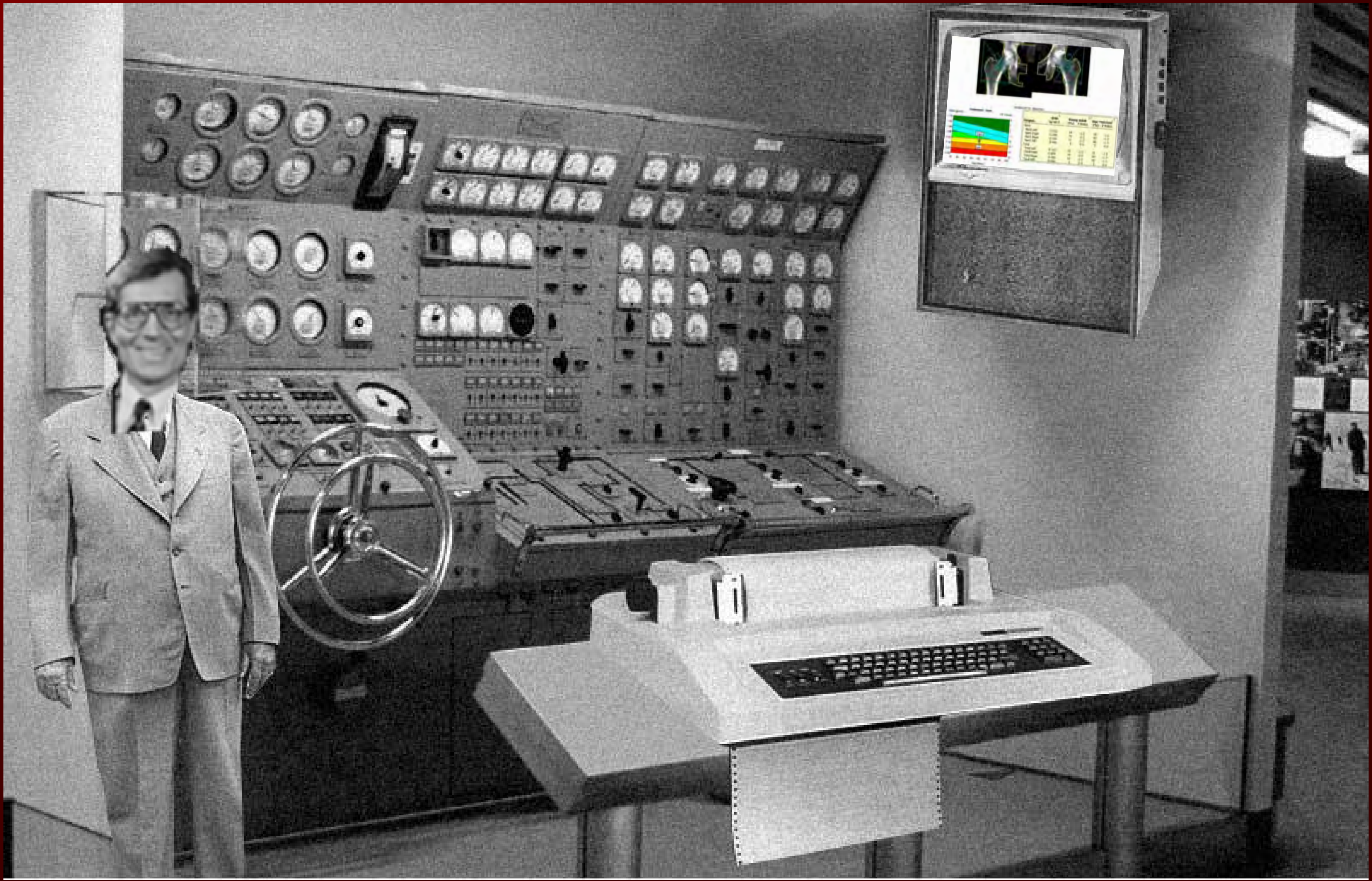
Fracture Patients!

For more information: see ISCD VFA Course: www.iscd.org

Roadmap

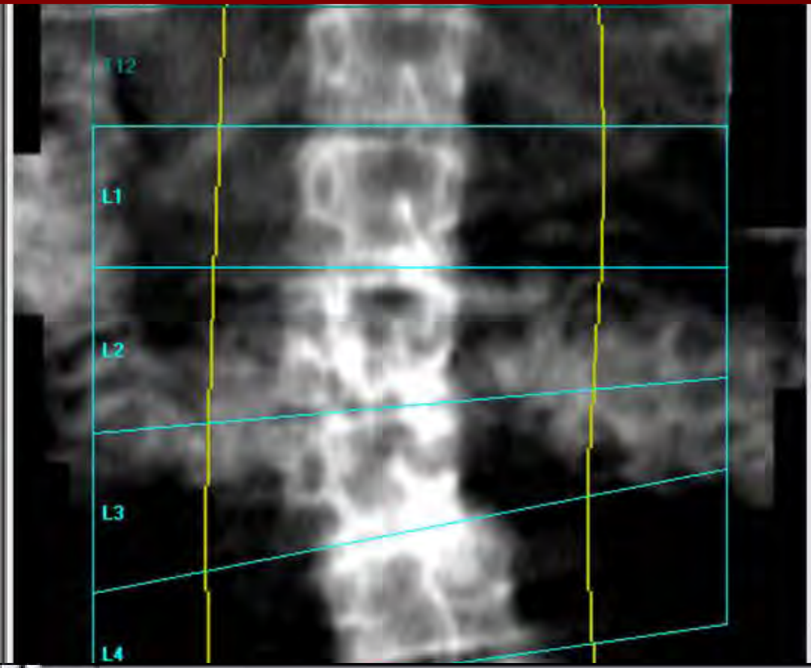
1. The Stone Age
2. **The Industrial Revolution**
3. The Information Age

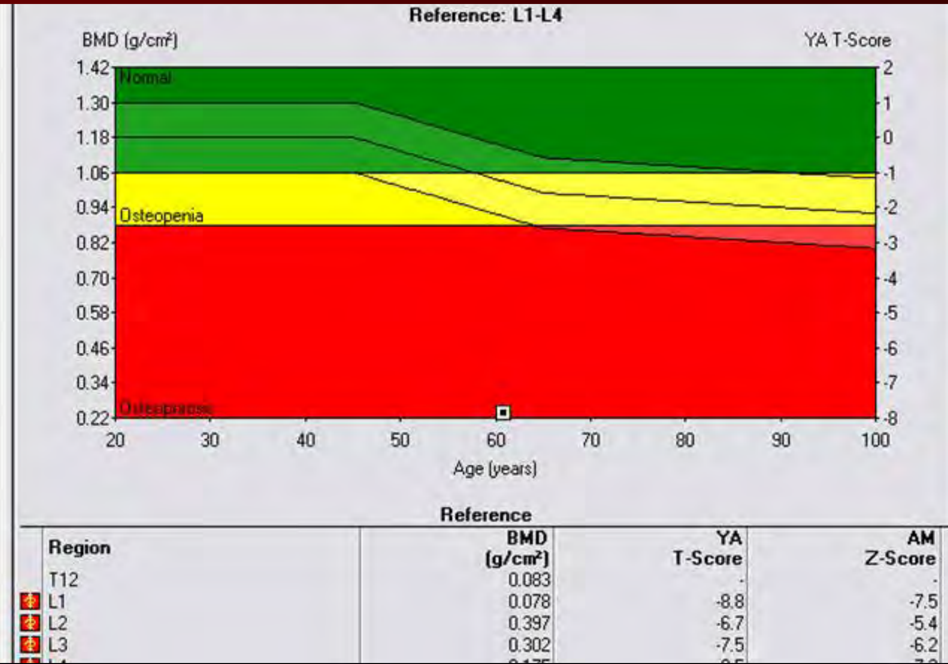
*Prototype Densitometer**



*not really…

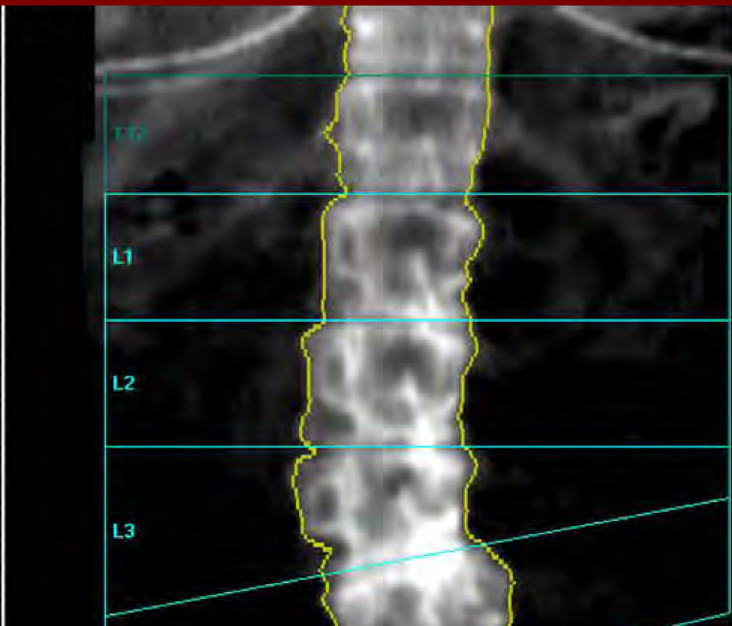
Case 2: How Does DXA Work? Baseline

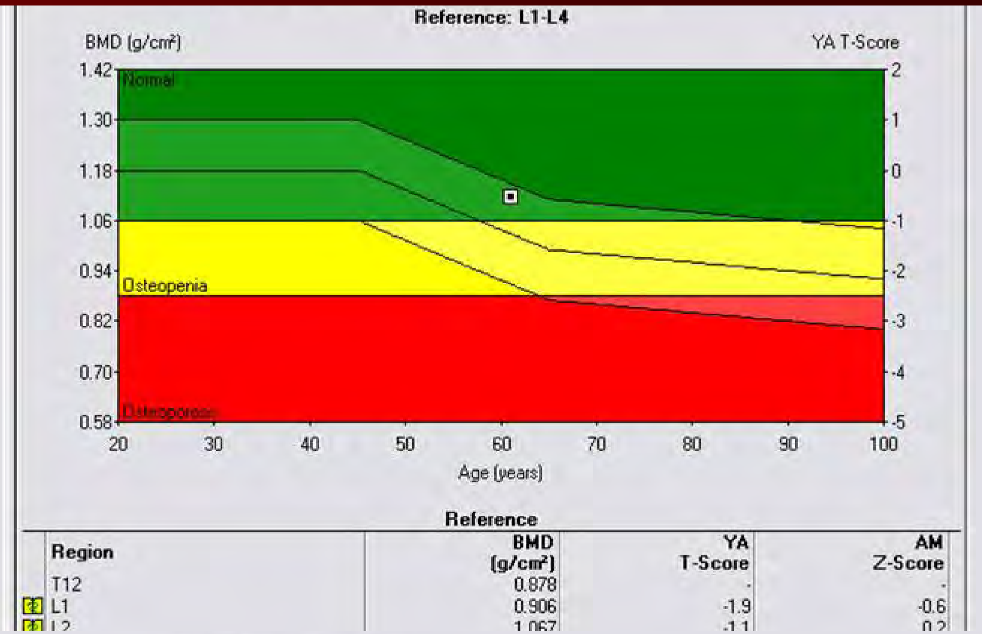




	Region	BMD (g/cm²)	YA T-Score
	T12	0.083	-
	L1	0.078	-8.8
	L2	0.397	-6.7
	L3	0.302	-7.5
	L4	0.175	-8.5
	L1-L2	0.235	-7.7
	L1-L3	0.256	-7.6
	L1-L4	0.236	-7.9

Case 2: How Does DXA Work? One week later





Reference

Region	BMD (g/cm²)	YA T-Score
T12	0.878	-
L1	0.906	-1.9
L2	1.067	-1.1
L3	1.235	0.3
L4	1.236	0.3
L1-L2	0.990	-1.5
L1-L3	1.071	-0.8
L1-L4	1.117	-0.5

Case 3

- 42 year old premenopausal woman with radiographic osteopenia
  - **Risk factors**: family history, low body weight

- Referred for significant decrease in bone density
- Two studies – 8 months apart. Studies done on same machine: Hologic Delphi

Case 3 – DXA of 12/6/2005

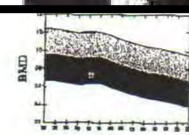
Name:
Patient ID
Age:

Sex: Female
Ethnicity: Black
Date of Birth: '1964

Height: 61.0 in
Weight: 113.0 lb

For Vertebral Deformity Evaluation Only
Scan Date: December 06, 2005
Scan ID
Scan Type: f SE R/L Lateral Image

For Vertebral Deformity Evaluation Only
Scan Date: December 06, 2005
Scan ID
Scan Type: f SE AP Image



Scan Type: x Right Hip

Sex: Female
Ethnicity: Black
Date of Birth: '1964
Height: 61.0 in
Weight: 113.0 lb

Scan Date: December 06, 2005

Results:

	BMD (g/cm^2)	T-Score	PR (%)	Z-Score	AM (%)
Left Hip (Neck)	0.727	-1.6	76	-1.4	79
Left Hip (Total)	0.879	-1.0	85	-0.9	86
Right Hip (Neck)	0.727	-1.6	76	-1.4	79
Right Hip (Total)	0.849	-1.2	82	-1.1	83
Spine (Total)	0.818	-3.0	71	-2.7	73

Total BMD CV 1%

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Spine (Total)	0.818	-3.0	71	-2.7	73

Total BMD CV 1%

A spine fracture indicates 5X risk for subsequent spine fracture and ... subsequent hip fracture.

World Health Organization criteria for BMD interpretation classify patients as Normal (T-score at or above -1.0), Osteopenic (T-score between -1.0 and -2.5), or Osteoporotic (T-score at or below -2.5).

HOLOGIC®

Spine T-score of -3.0

Case 3 - DXA of 4/29/2005

Name:
Patient ID:
DOB: 1964

Referring Physician:

Sex: Female
Ethnicity: White

Height: 61.0 in
Weight: 114.0 lb
Age: 40

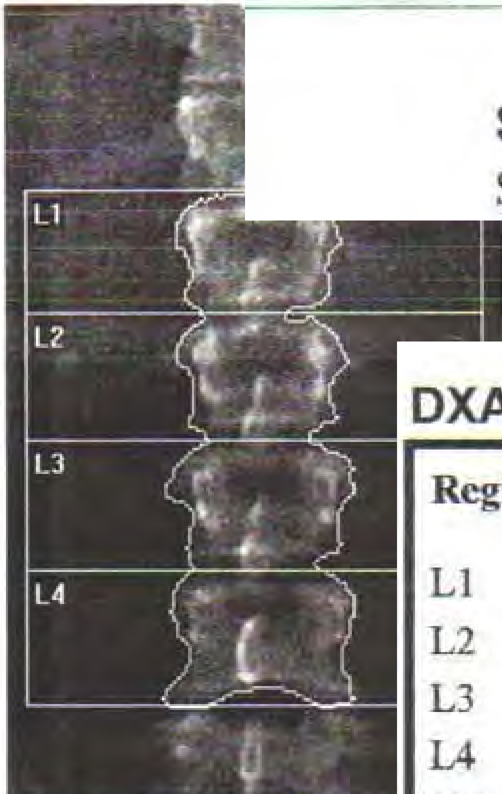

Image not for diagnostic use
k = 1.141, d0 = 45.7
116 x 131

Scan Information:

Scan Date: April 29, 2005
Model: Delphi C
Comment:

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - Score	Z - Score
L1	10.65	8.05	0.755	-1.5	-1.3
L2	11.48	9.24	0.805	-2.0	-1.8
L3	13.04	10.64	0.816	-2.4	-2.2
L4	14.16	11.97	0.845	-2.5	-2.2
Total	**49.33**	**39.90**	**0.809**	**-2.2**	**-1.9**

Spine T-score of -2.2

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Case 3 - Comparison

Sex: Female
Ethnicity: White

Height: 61.0 in
Weight: 114.0 lb
Age: 40

Scan Information:

Scan Date: April 29, 2005

L4	14.16	11.97	0.845	-2.5	-2.2
Total	**49.33**	**39.90**	**0.809**	**-2.2**	**-1.9**

Sex: Female
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Sex:	Female	Height:	61.0 in
Ethnicity:	Black	Weight:	113.0 lb
Date of Birth:	1964		

Scan Date: December 06, 2005

Spine (Total)	0.818	-3.0	71	-2.7	73

Case 3 - Lessons Learned

1. **Compare BMD values NOT T-scores**
2. **Manufacturers differ on comparing T-scores based on ethnicity. Hologic: ethnic T-scores and Z-scores; GE-Healthcare Lunar: ethnic specific Z-scores only.**
3. **ISCD recommends using the a standard ethnic reference population for T-scores and ethnic databases for Z-scores… for now**

Case 4

60 year old woman with DXA study showing a bone density of 0.806 g/cm^2 at the L1-L4 spine in 2004 and 0.795 g/cm^2 in 2006. The DXA lab did not do a precision study…

Her T-score in 2006 was -3.2.

Is this a significant change?

Case 4

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Her T-score in 2006 was -3.2.

Is this a significant change?

No

See: www.iscd.org

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Understanding the Guidelines for Fracture Prevention

- Background
- Risk Factor Assessment
- Screening

Case 5

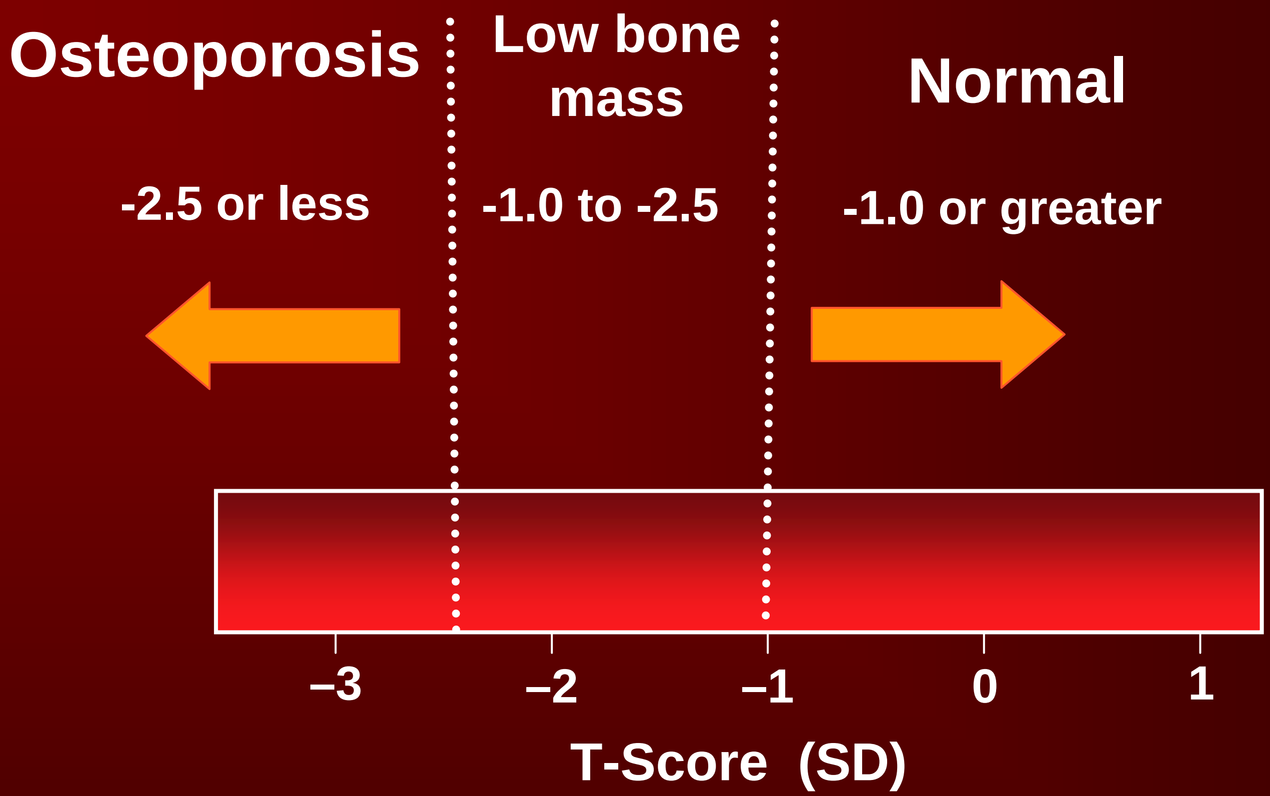
- 50 year old African American woman with menopause 6 months ago with a T-score of -2.5 at the spine and -2.5 at the hip
  - No other risk factors
- 80 year old Caucasian woman with a T-score of -2.4 at the spine and -2.4 at the hip
  - Prior spine fragility fracture, positive family history, smoker, body weight 120 pounds

- Same diagnosis?
- Same fracture risk?

WHO Report: 1994

"If all you have is a hammer, then everything starts to look like a nail"

Fracture Prediction by BMD



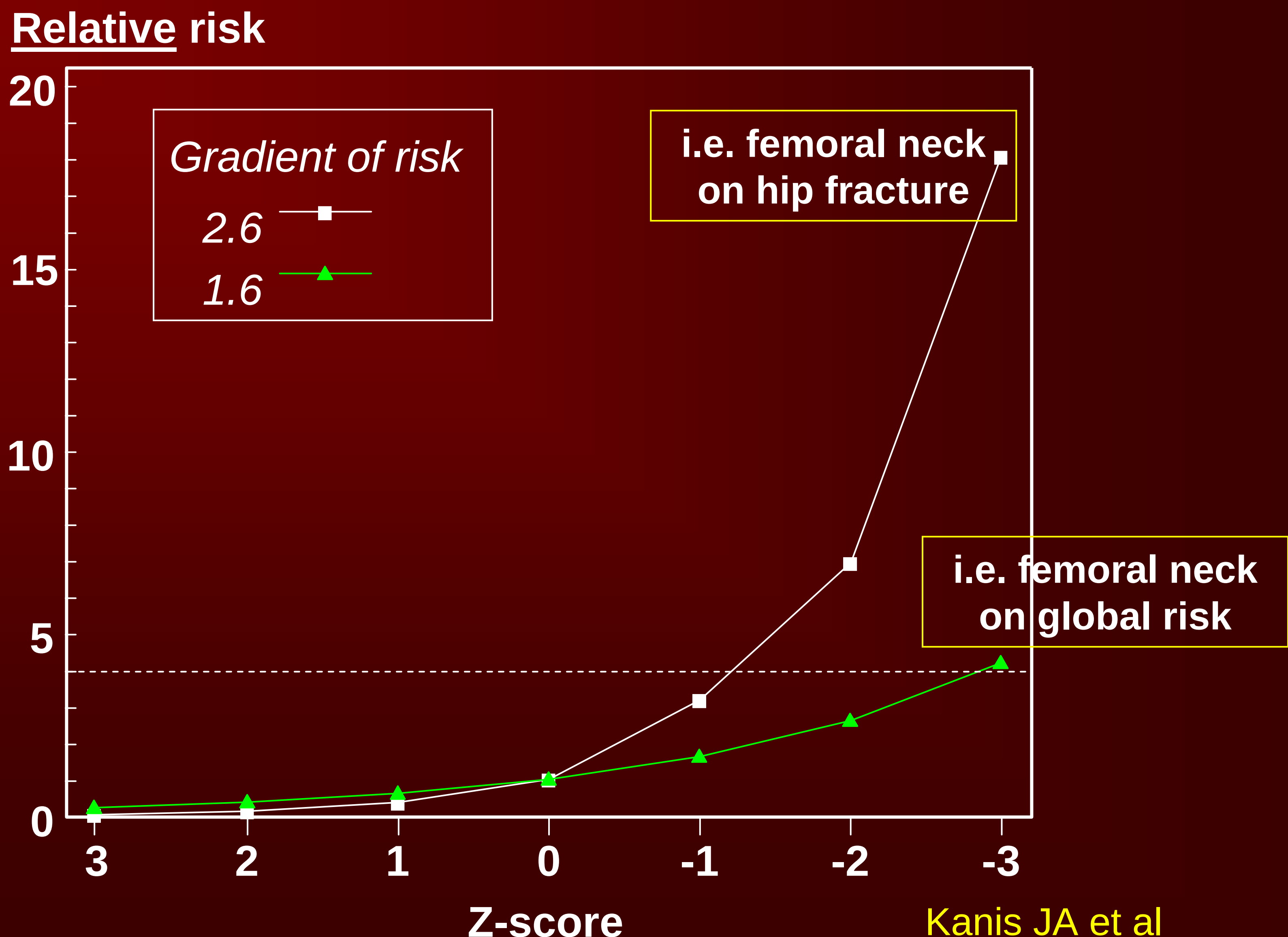
Kanis JA, et al. *Osteoporos Int*. 2004;15:20-26.

Prediction of fracture from BMD

Site of measurement	Forearm fracture	Hip fracture	Vertebral fracture	All fractures
Distal radius	**1.7**	1.8	1.7	1.4
Hip	1.4	**2.6**	1.8	1.6
Lumbar spine	1.5	1.6	**2.3**	1.5

Marshall et al, 1996

Prediction of fracture: Relative Risk



Kanis JA et al

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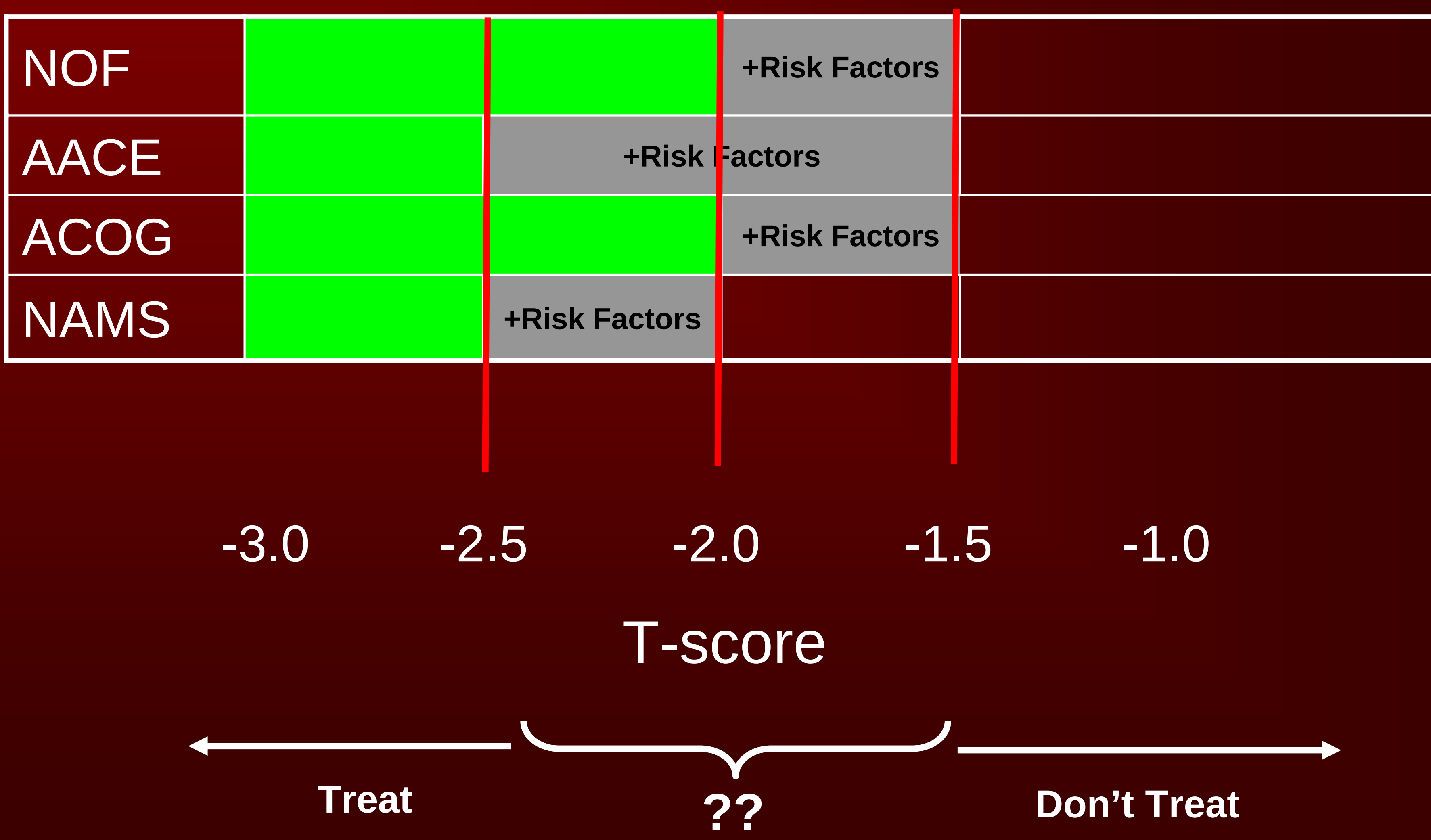
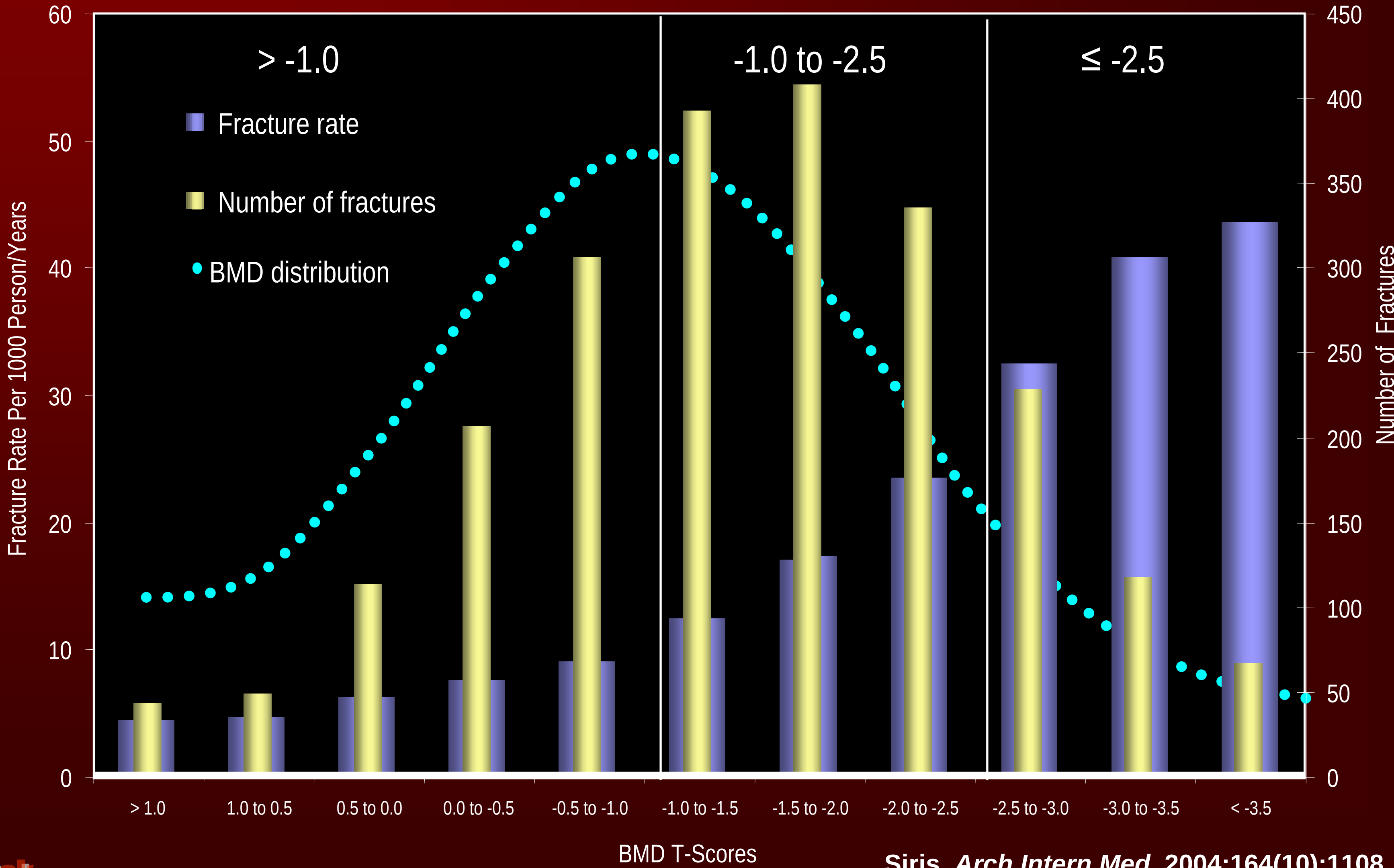
Some Treatment Guidelines Used in the United States



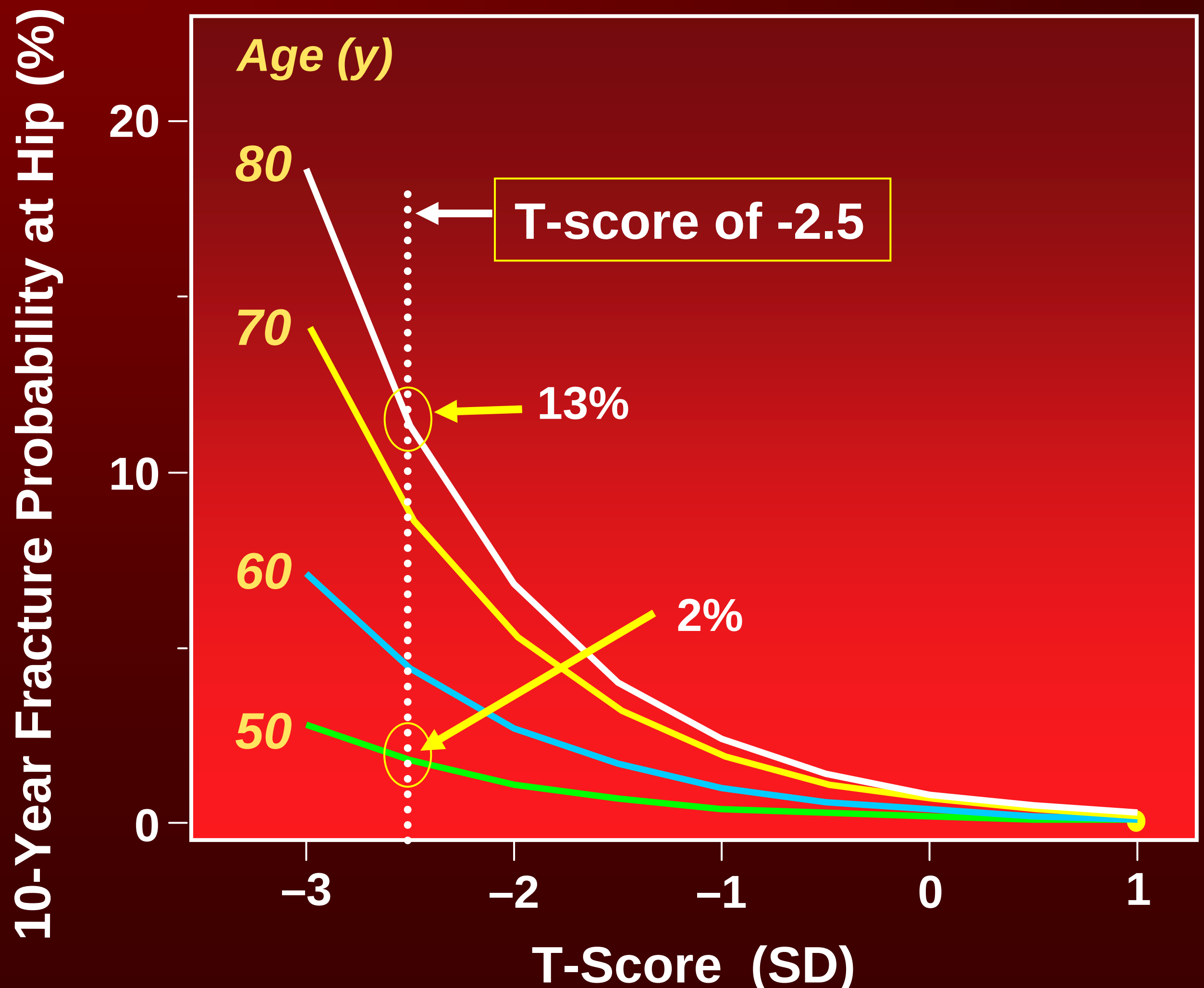
Problems…

Fracture Rates, Population T-Score Distribution, and Number of Fractures in NORA



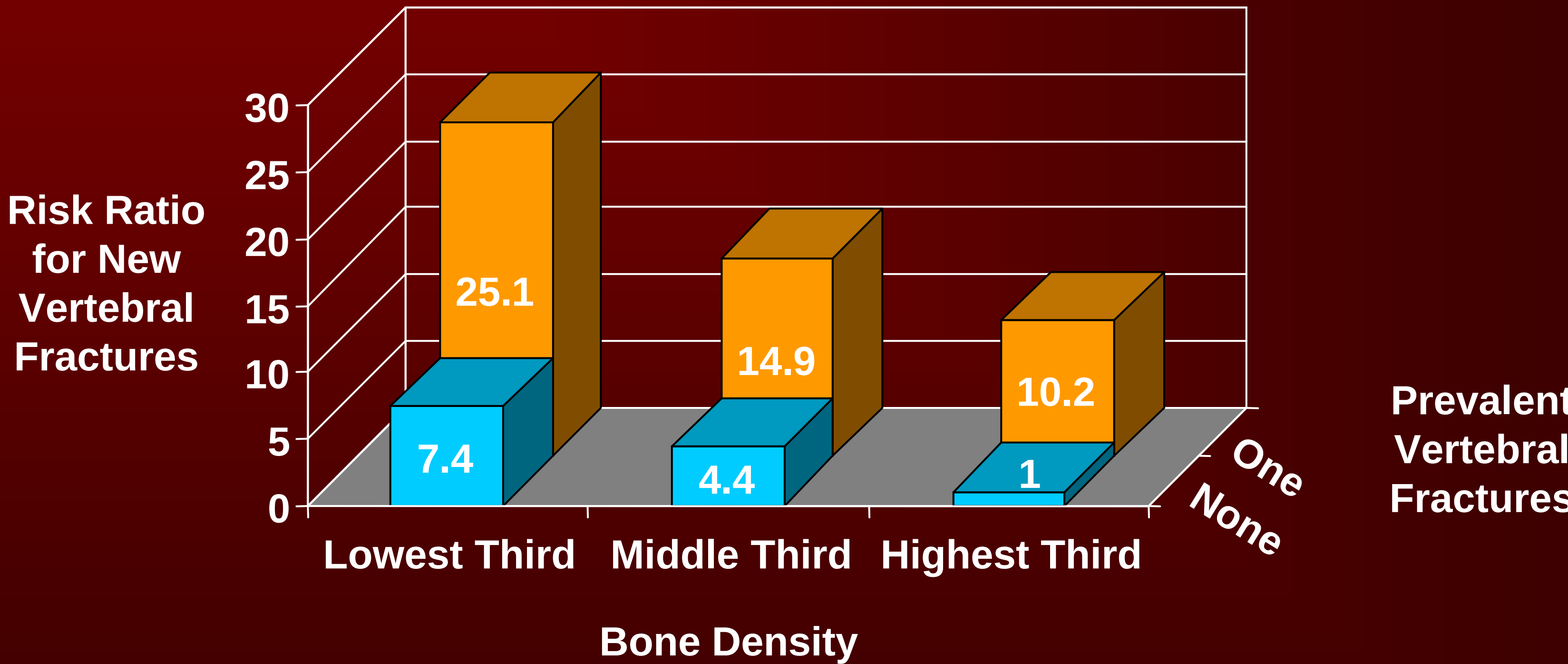
Siris. *Arch Intern Med*. 2004;164(10):1108.

Fracture Probability at Hip by Age and BMD



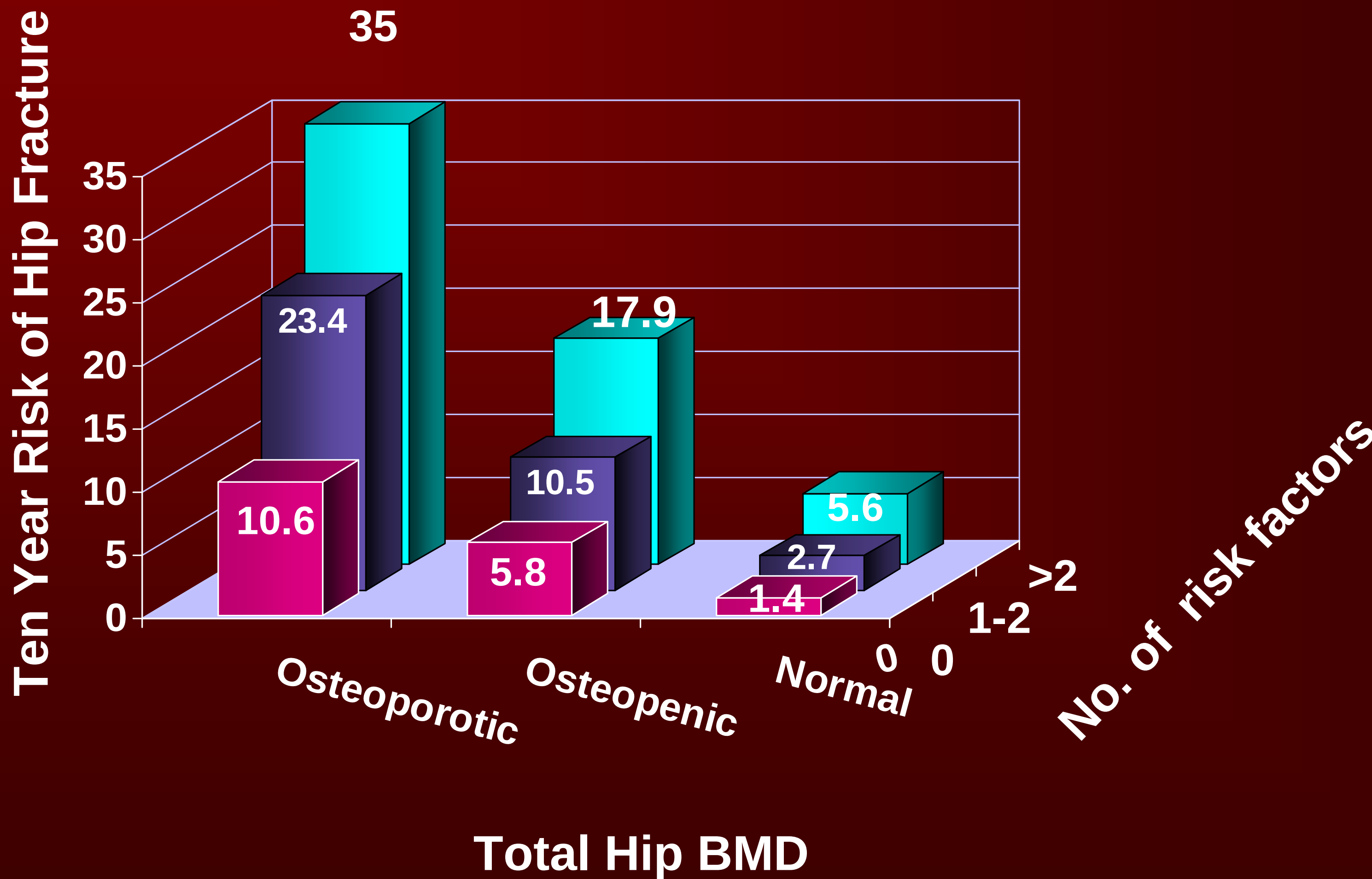
Kanis JA, et al. *Osteoporos Int*. 2004;15:20-26.

Combined Effect of Bone Density and Prevalent Fractures



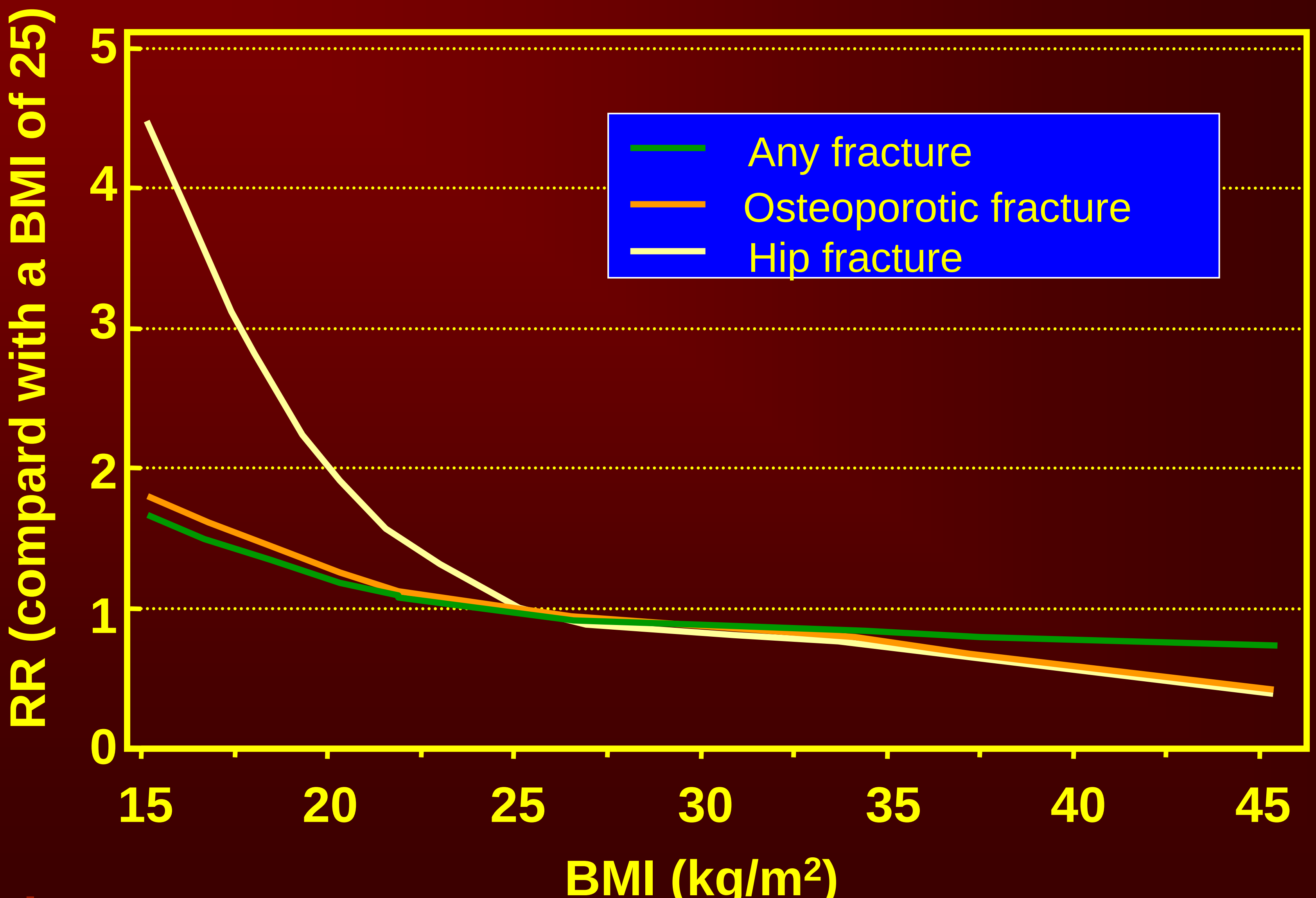
Ross PD et al. *Ann Intern Med.* 1991;114:919-923.

Effects of Combining BMD and Number of Risk Factors



Taylor BC, et al Journal of the American Geriatrics Society 52: 1479, 2004

BMI and Risk of Fracture



Roadmap

1. The Stone Age
2. The Industrial Revolution
3. **The Information Age**

The “Manhattan” Project of Osteoporosis

WHO Report on Fracture Risk Reporting

Scientific Meeting: Brussels, Belgium, May 5-7, 2004

Represented Organizations: ASBMR, IOF, ISCD, NOF

•John Kanis, UK - Chair

- Phillipe Bonjour, Switzerland
- Patricia Clarke, Mexico
- Juliet Compston, UK
- Cyrus Cooper, UK
- Bess Dawson-Hughes, USA
- Chris de Laet, Netherlands
- Pierre Delmas, France
- Claus Glüer, Germany
- Helena Johansson, Sweden
- Olaf Johnell, Sweden
- Mike Lewiecki, USA
- Paul Lips, Netherlands
- Joe Melton, USA
- Mike McClung, USA
- Paul Miller, USA
- Anders Oden, Sweden
- Socrates Papapoulos, Netherlands
- Stuart Silverman, USA

Cohorts Studied

EVOS/EPOS	**Hiroshima**	**CaMoS**
Rochester	**Sheffield**	**Rotterdam**
Kuopio	**Gothenburg I**	**Gothenberg II**
EPIDOS	**Dubbo**	**OFELY**

N = 59,232 **Person-years = 249,898** **% Female = 74**

Any fracture = 5444

Osteoporotic fractures = 3495

Hip fractures = 957

Proposed Risk Factors for WHO Model

- Femoral neck T-score by DXA
  - Using female Caucasian NHANES III
  - Future: other skeletal sites, other technologies
- Age
- BMI
- Previous low trauma fracture
- Current cigarette smoking
- Rheumatoid arthritis
- High alcohol intake (> 2 units/day)*
- Parental history of hip fracture
- Prior or current glucocorticoid use

*1 unit = 8 gm alcohol ~ ½ pt. beer ~ glass wine

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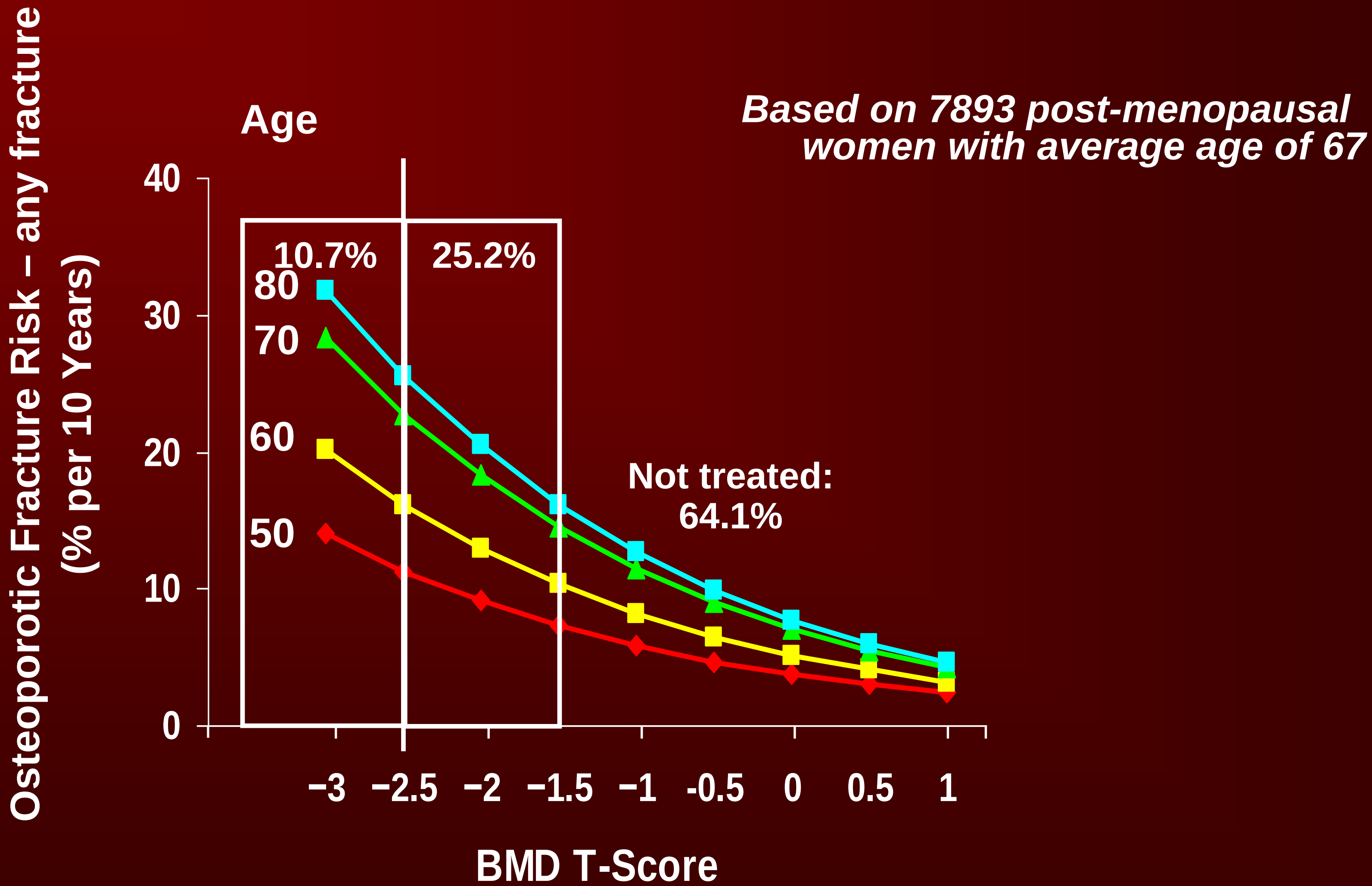
Current Treatment Model



Kanis JA, et al. *Osteoporos Int.* 2001;12:989–995.

McClung MR. *Current Osteoporos Reports* 2005;3:57-63.

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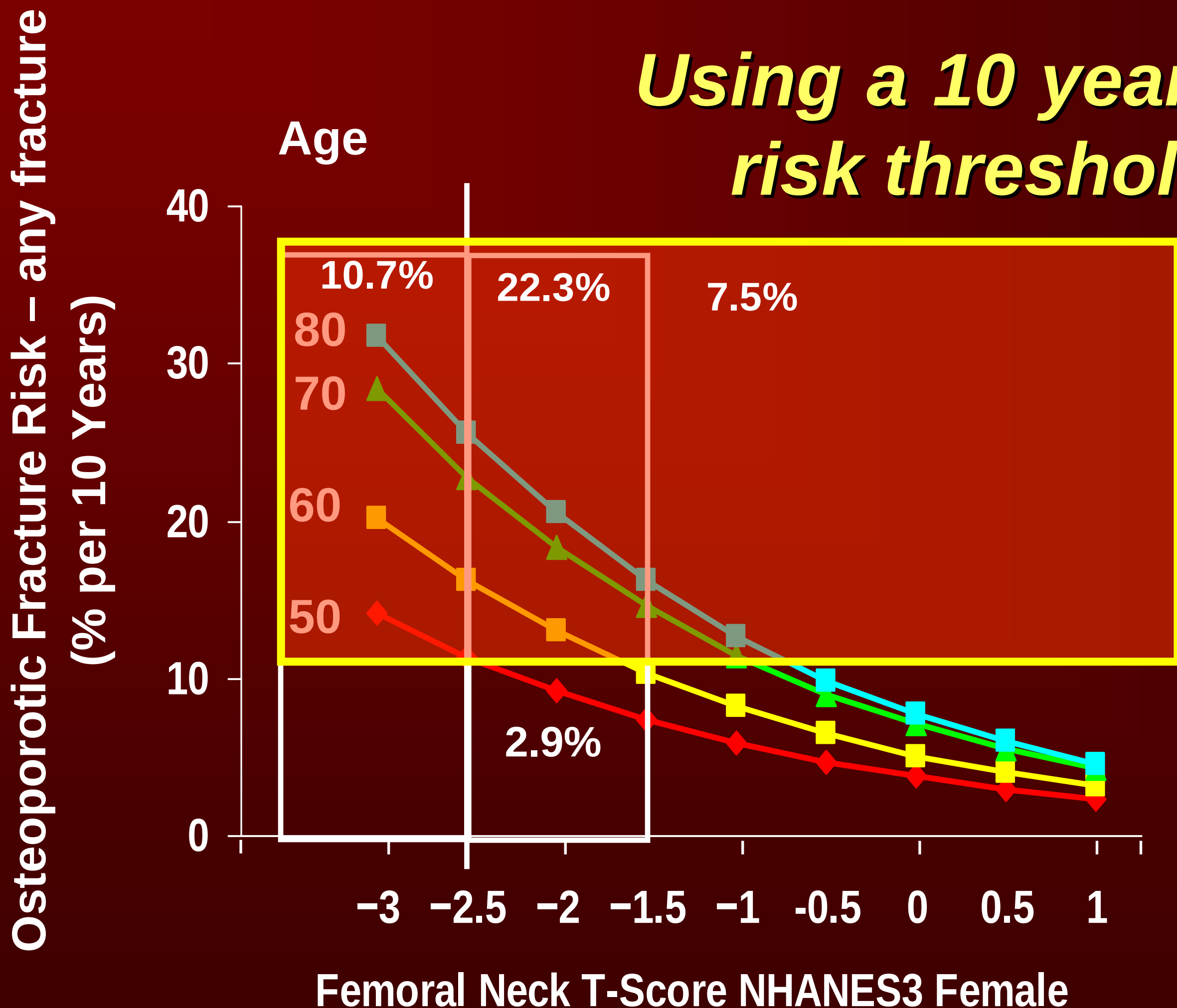
A Possible Future Treatment Model

Using a 10 year any fracture risk threshold of 12%



Kanis JA, et al. *Osteoporos Int.* 2001;12:989–995.

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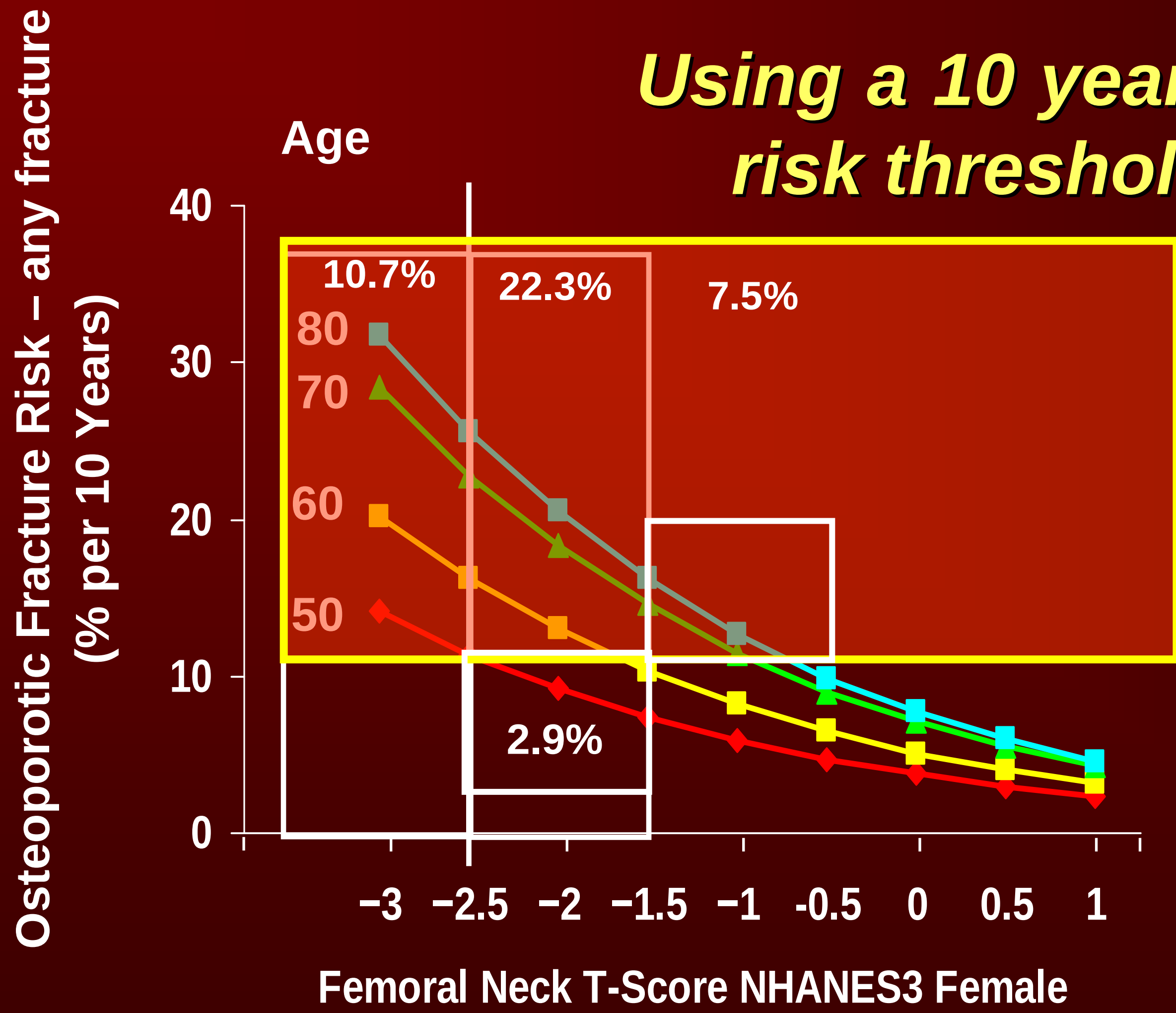

Kanis JA, et al. *Osteoporos Int.* 2001;12:989–995.

McClung MR. *Current Osteoporos Reports* 2005;3:57-63.

Next Steps…
Implementation at Country/Region Level

- Use of disutility calculations to get hip fracture equivalents
- Analysis of economic resources using a 50% fracture reduction from pharmacologic therapy as a basis
- Implementation in USA in progress by NOF and AACE
- Awaiting final WHO materials before new AACE guidelines finalized

AACE Osteoporosis Guidelines Taskforce 2006

- Dr. Nelson Watts, Chair
- Dr. John Bilezikian
- Dr. Pauline Camacho
- Dr. Susan Greenspan
- Dr. Steven Harris
- Dr. Stephen Hodgson
- Dr. Michael Kleerekoper
- Dr. Marjorie Luckey
- Dr. Michael McClung
- Dr. Steven Petak

Implications of WHO 2007 (?) Model

- **ISCD PDC 2005: Diagnostic classification of osteoporosis will not change**
- **Distinguishes between diagnostic threshold and intervention threshold**
- **"Osteopenia" will no longer be relevant**
- **Fewer younger patients at low risk will be treated and more older patients at higher risk will be treated**

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Limitations

- Limited as to reference site for BMD
- Does not apply to secondary osteoporosis
- Does not determine which interventions will be effective at lowering the fracture risk
  - Medications
  - Non-pharmacologic interventions
  - Nothing?

Thank you Prof. Coculescu, Prof. Ionescu

and the RSE for the kind invitation

www.associazionemediciendocrinologi.it

www.aace.com

3rd Joint Meeting AME-AACE - Verona 27-29 October 2006

Friday October 27, 2006 *9.00 a.m.- 12.45 a.m.*

Pre-congress symposium: **Osteoporosis**

Therapy of osteoporosis: *the present*

Michele Zini

Servizio di Endocrinologia, Arcispedale “S. Maria Nuova” – Reggio Emilia

Roma, November 5-7, 2004

4th AME Italian Meeting
Associazione Medici Endocrinologi- Italian Association of Clinical Endocrinologists
2nd Joint Meeting with AACE
American Association of Clinical Endocrinologists

Update in Clinical Endocrinology

Rome, November 5-7, 2004

Clinical Symposium

An EBM-guided treatment of osteoporosis
Choices and Outcomes of treatment

Chairs:	D. Bergman – M.L. Brandi
EBM expert:	M. Zini
Discussants:	S.M. Petak – A. Piovesan

The evidence-based treatment of osteoporosis

Michele Zini
Servizio di Endocrinologia, Arcispedale "S. Maria Nuova" – Reggio emilia
michele.zini@asmn.re.it

Michele Zini

Roma, November 5-7, 2004

Pharmacological treatment

calcium
vitamin D
estrogen & SERM
bisphosphonates
calcitonin
fluoride
teriparatide
strontium ranelate
other

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ALENDRONATE – Phase III study

Liberman UA et al., N Engl J Med 333:1437-43, 1995

Table 2. Women with New Vertebral Fractures during the Three-Year Study Period.*

Group of Women	Placebo Group	Alendronate Group
	% of women with fractures (no./total no.)	
All	6.2 (22/355)	3.2 (17/526)†

†P = 0.03, relative risk = 0.52 (95 percent confidence interval, 0.28 to 0.95).

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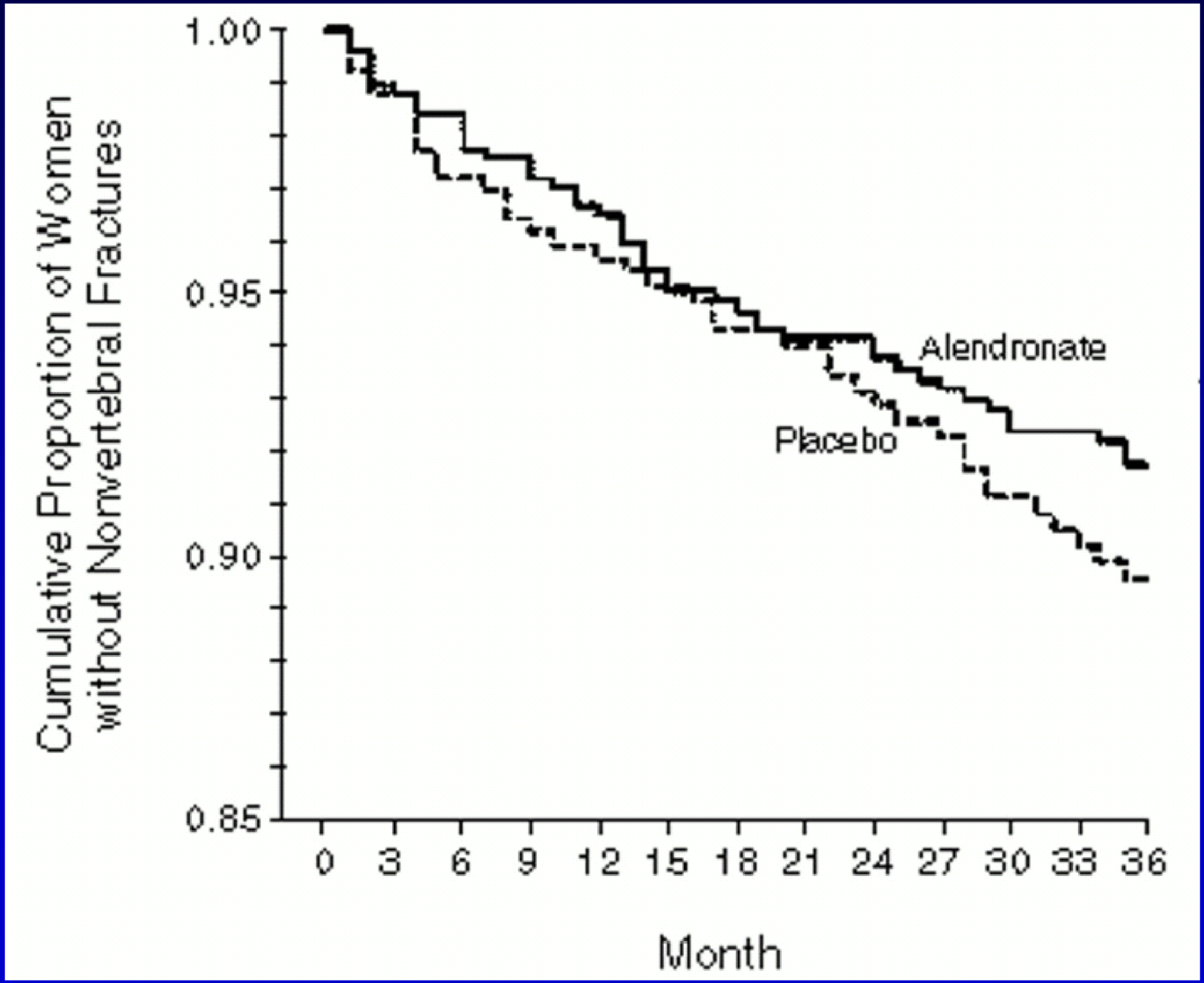
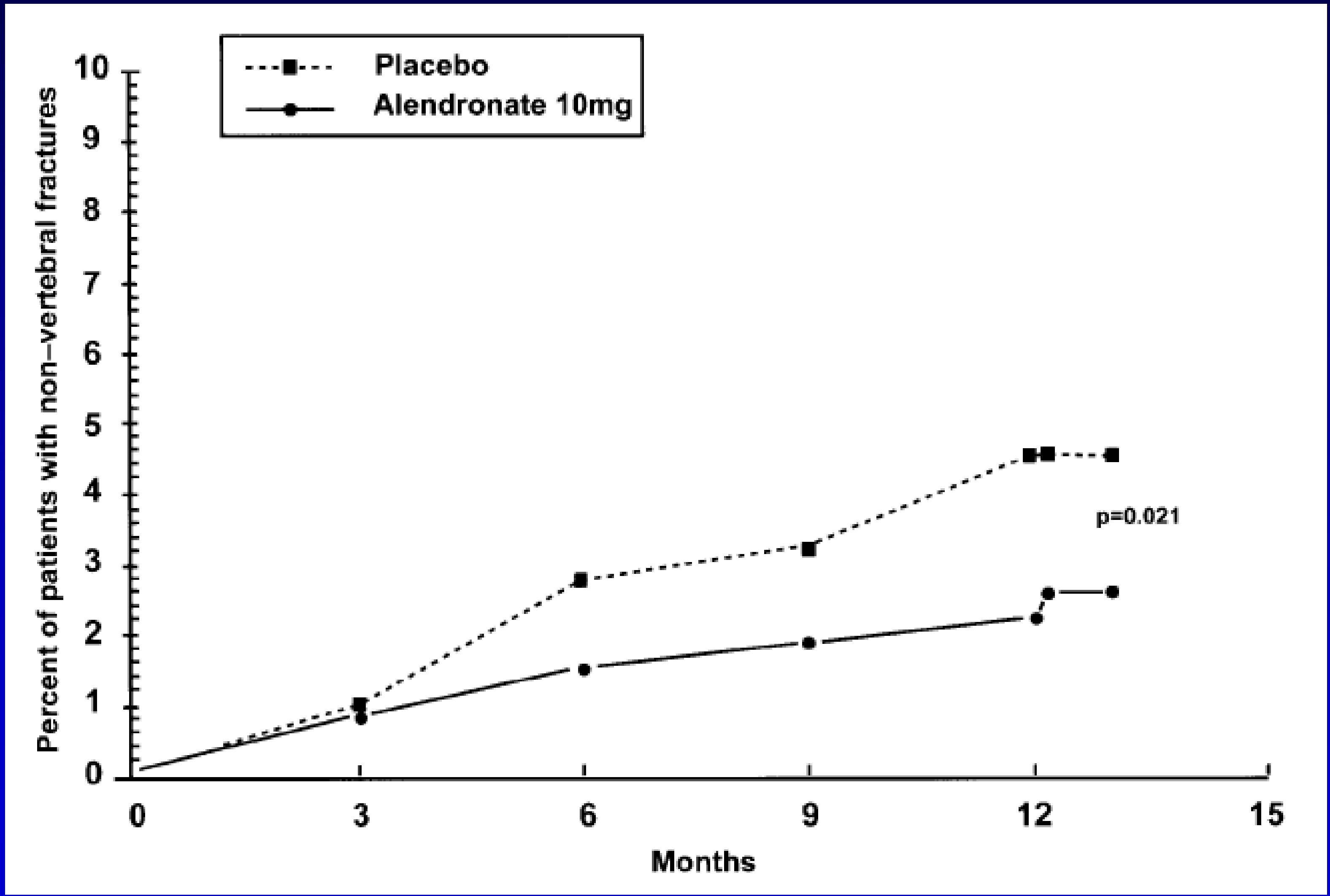
ALENDRONATE – Phase III study

Liberman UA et al., N Engl J Med 333:1437-43, 1995



ALENDRONATE - FOSIT study

Pols HAP et al., Osteoporos Int (1999) 9:461–468



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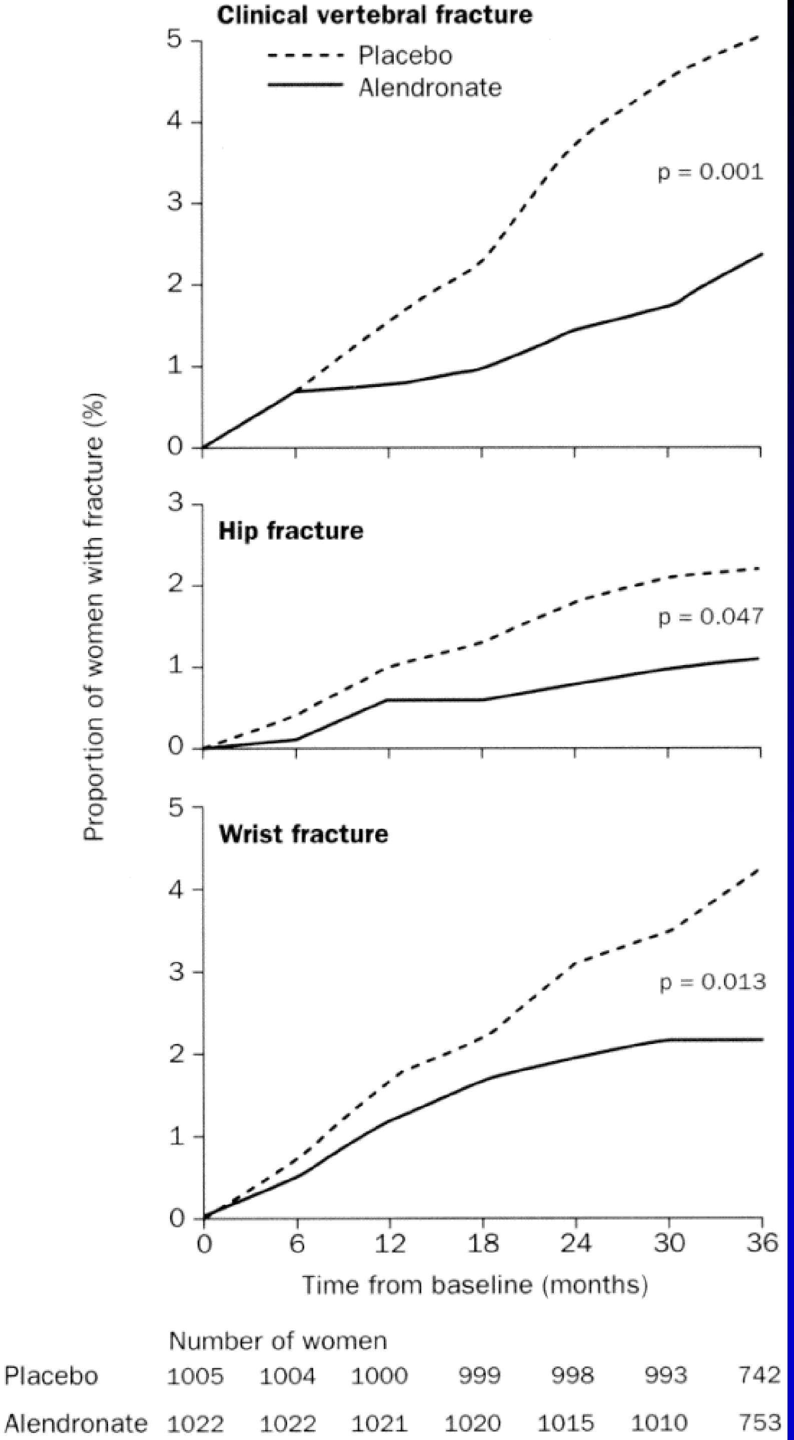
ALENDRONATE
FIT study

Black DM et al., Lancet 1996; 348: 1535-41

“clinical fracture” arm



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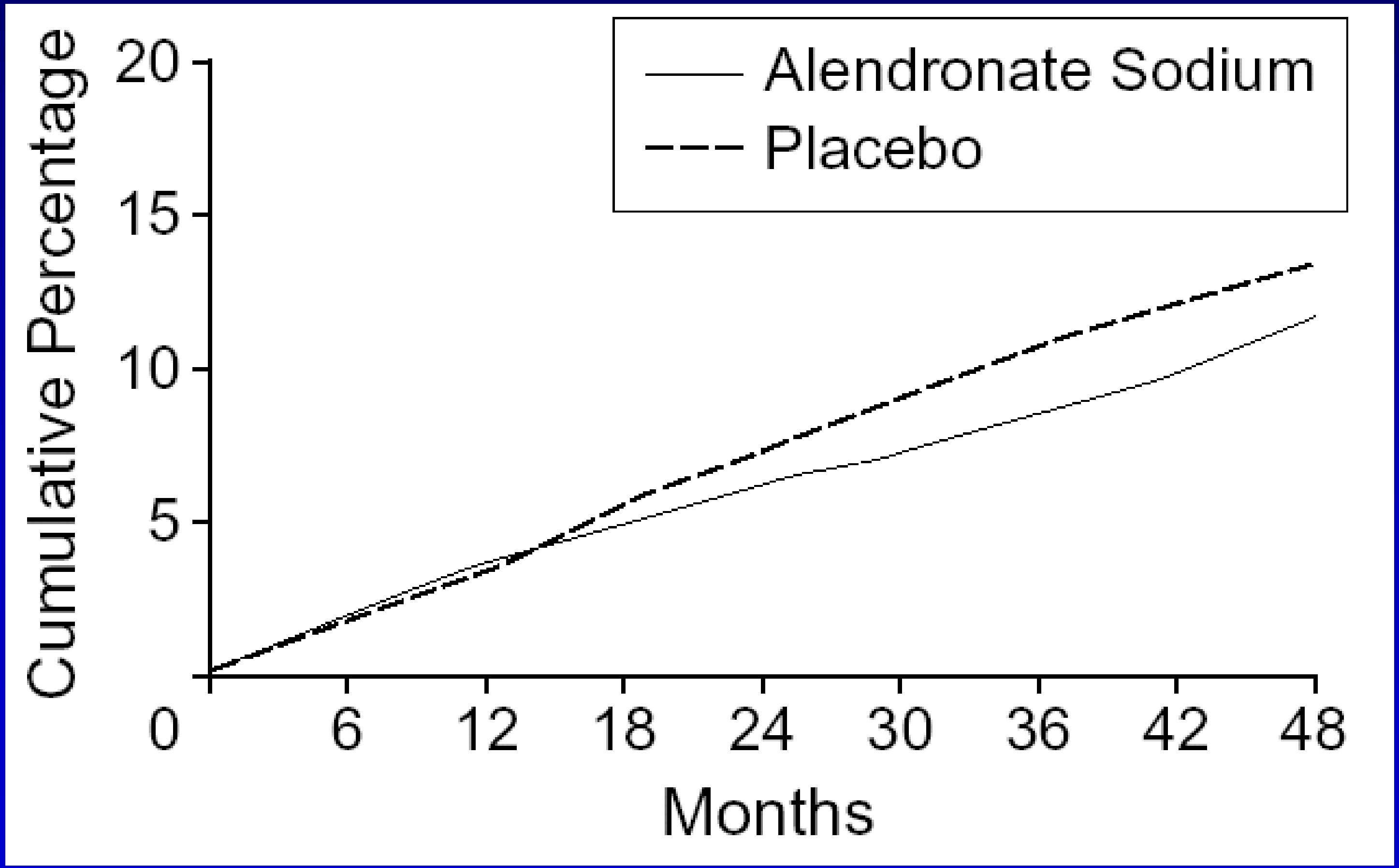
ALENDRONATE - FIT study

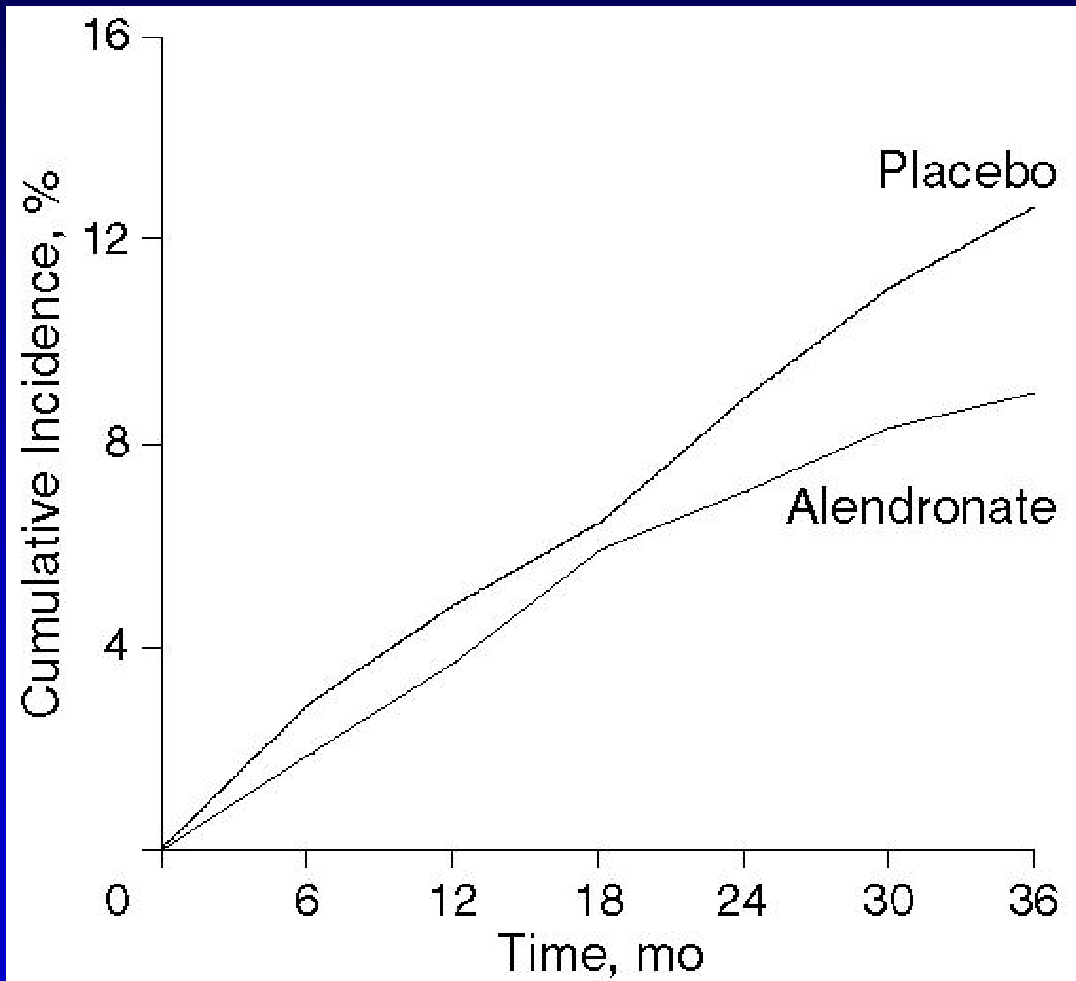
Cummings SR et al., *JAMA*. 1998;280:2077-2082

“non-clinical fracture” arm



ALENDRONATE and NON-VERTEBRAL FRACTURES
A meta-analysys from 5 RCTs

Karpf DB et al., JAMA.277:1159-1164, 1997



ALL NON-VERTEBRAL FRACTURES:

Relative risk =
0.71 (95% C.I = 0.50-0.99.)

Relative risk reduction =
0.29 (95% C.I = 0.02 - 0.49)

Absolute risk reduction=
0.03 (95% C.I = 0.001 - 0.06)

NNT = 34 (17-668)

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ALENDRONATE – O.R.A.G. META-ANALYSIS

Cranney A et al., Endocr Rev 23:508–516, 2002

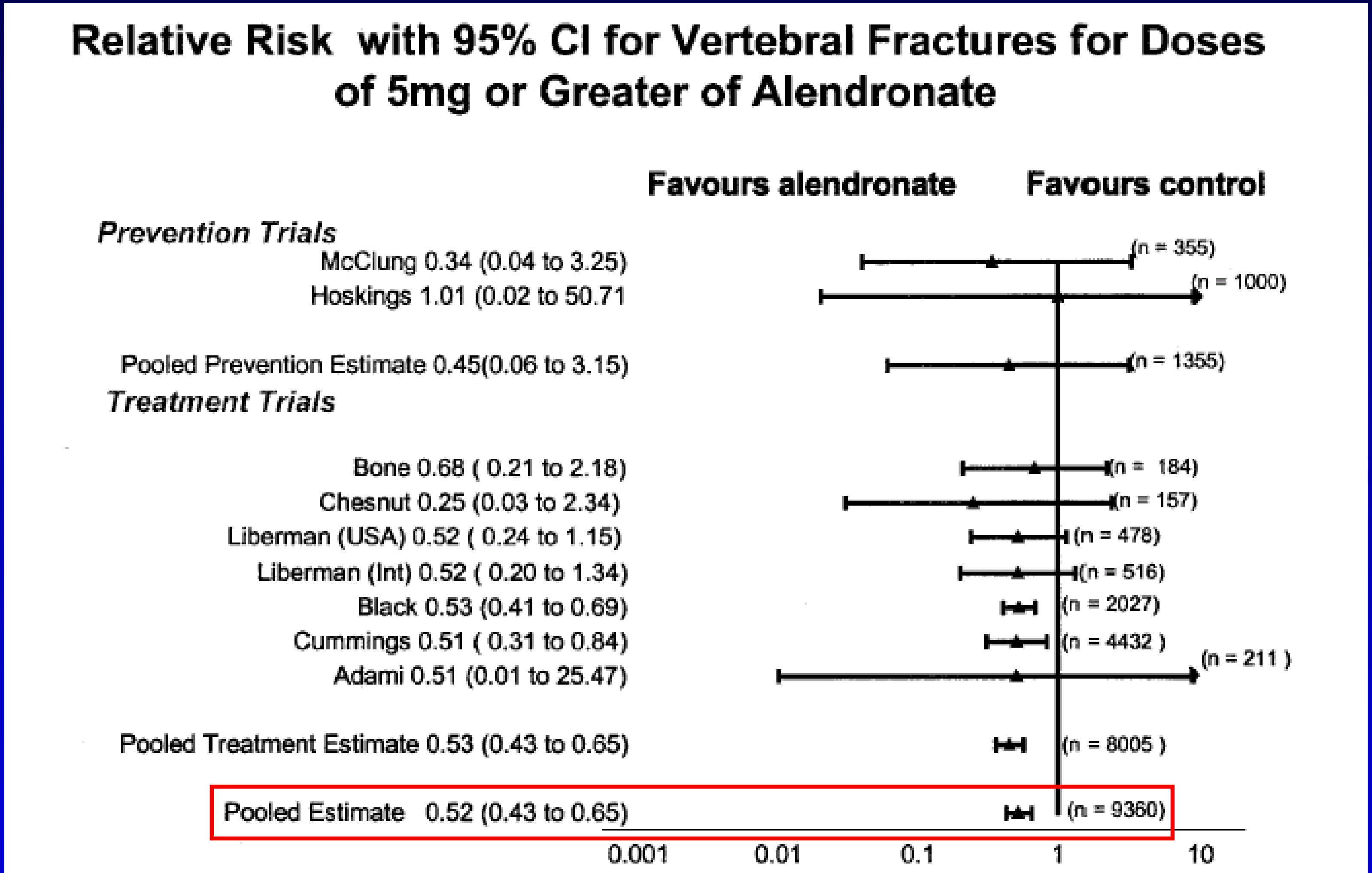

Fig. 2. RR for vertebral fractures with alendronate (5 mg and greater).

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ALENDRONATE – O.R.A.G. META-ANALYSIS

Cranney A et al., Endocr Rev 23:508–516, 2002

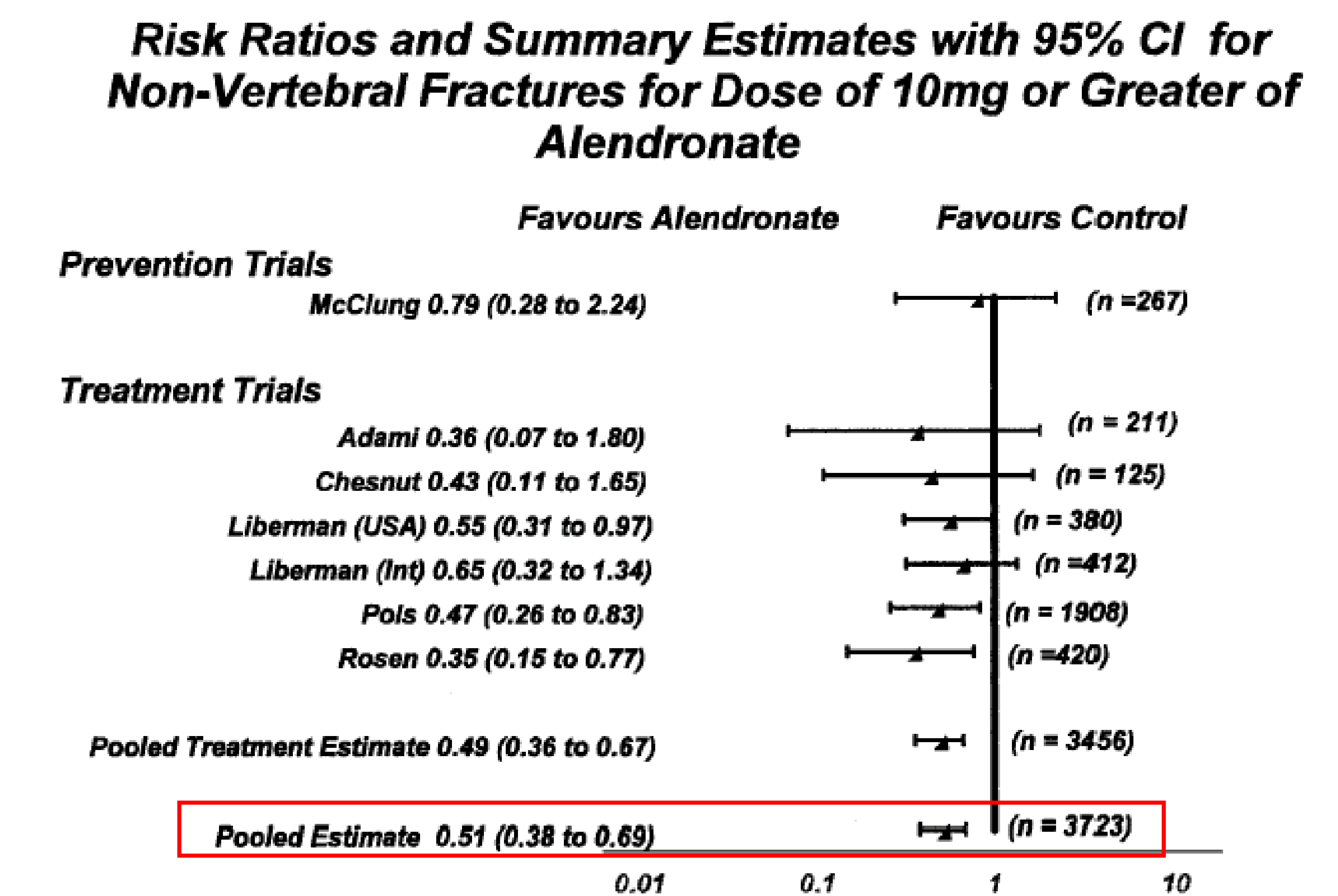

FIG. 3. Risk ratios for nonvertebral fractures with alendronate (10 mg and greater).

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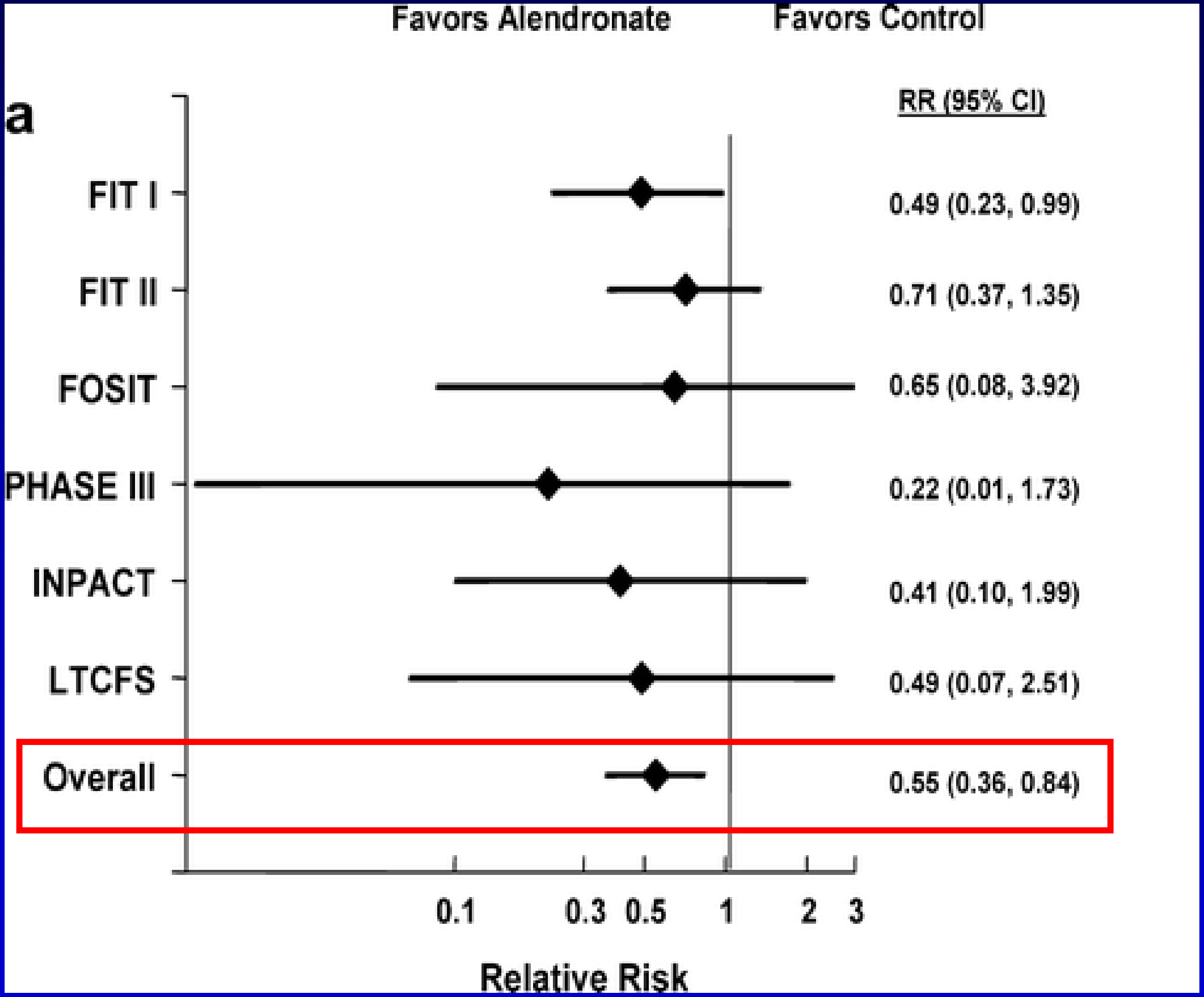
ALENDRONATE – HIP FRACTURES

Papapoulos SE et al., Osteoporos Int. 16: 468-74, 2005



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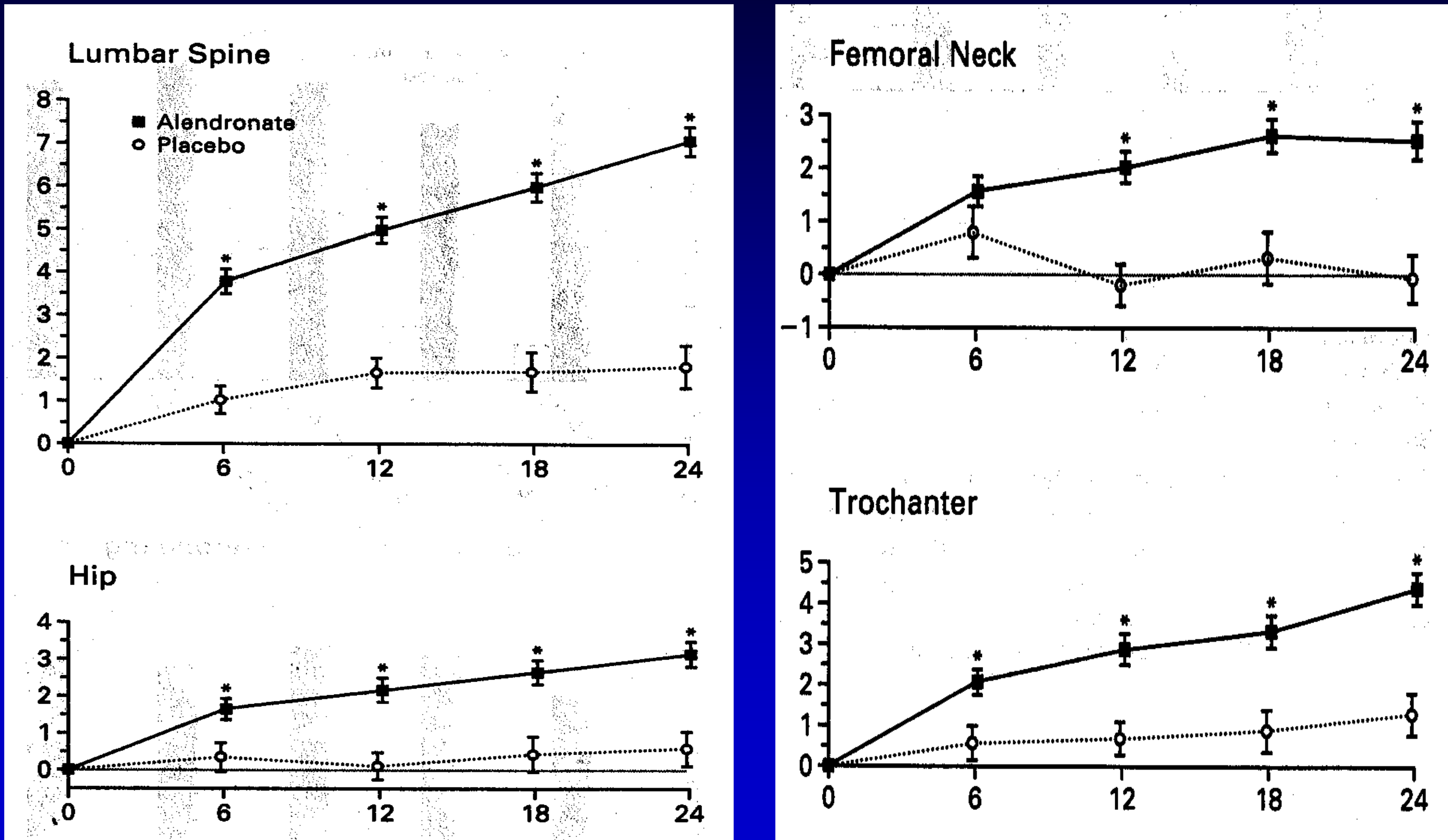
ALENDRONATE in MALE

Orwoll E et al., NEJM 343: 604-610, 2000



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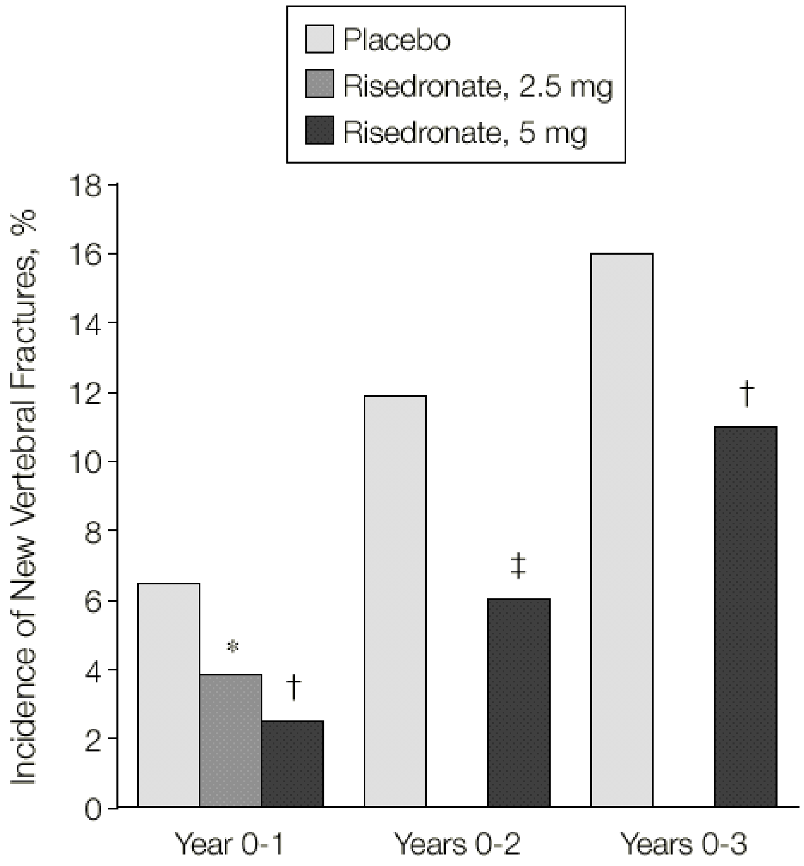
RISEDRONATE – VERT North America study

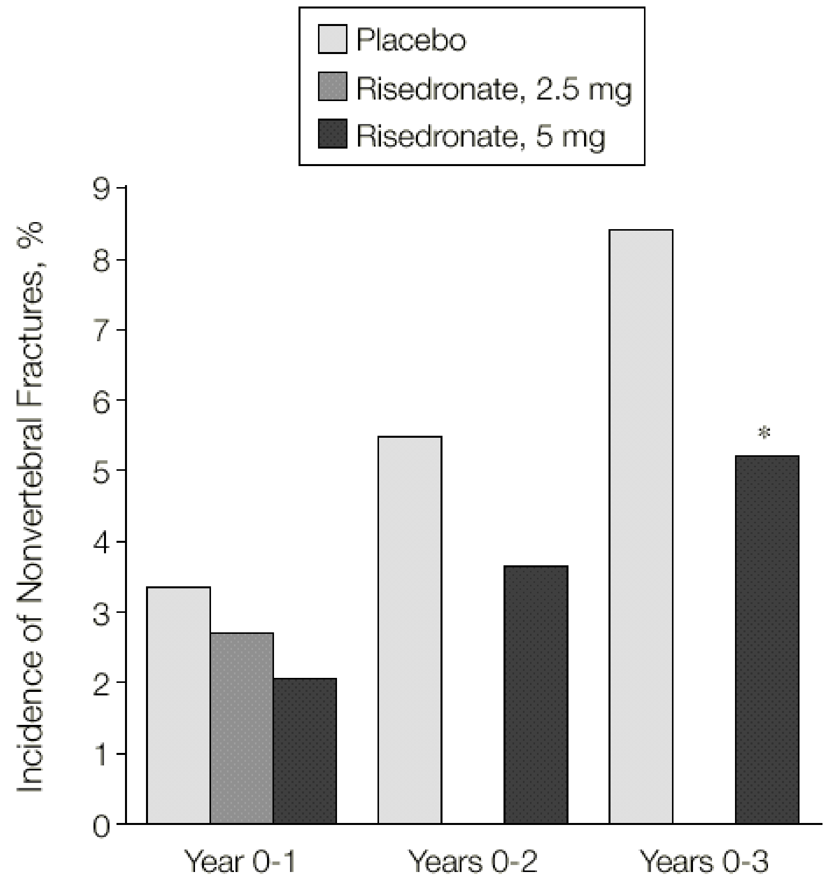
Harris ST et al., JAMA 282: 1344-1352, 1999

Figure 2. Incidence of New Vertebral Fractures by Groups Over Time



Asterisk indicates $P<.05$; dagger, $P<.01$; and double dagger, $P<.001$ vs placebo.

Figure 3. Incidence of Nonvertebral Fractures by Study Group Over Time



Asterisk indicates $P<.05$ vs placebo.

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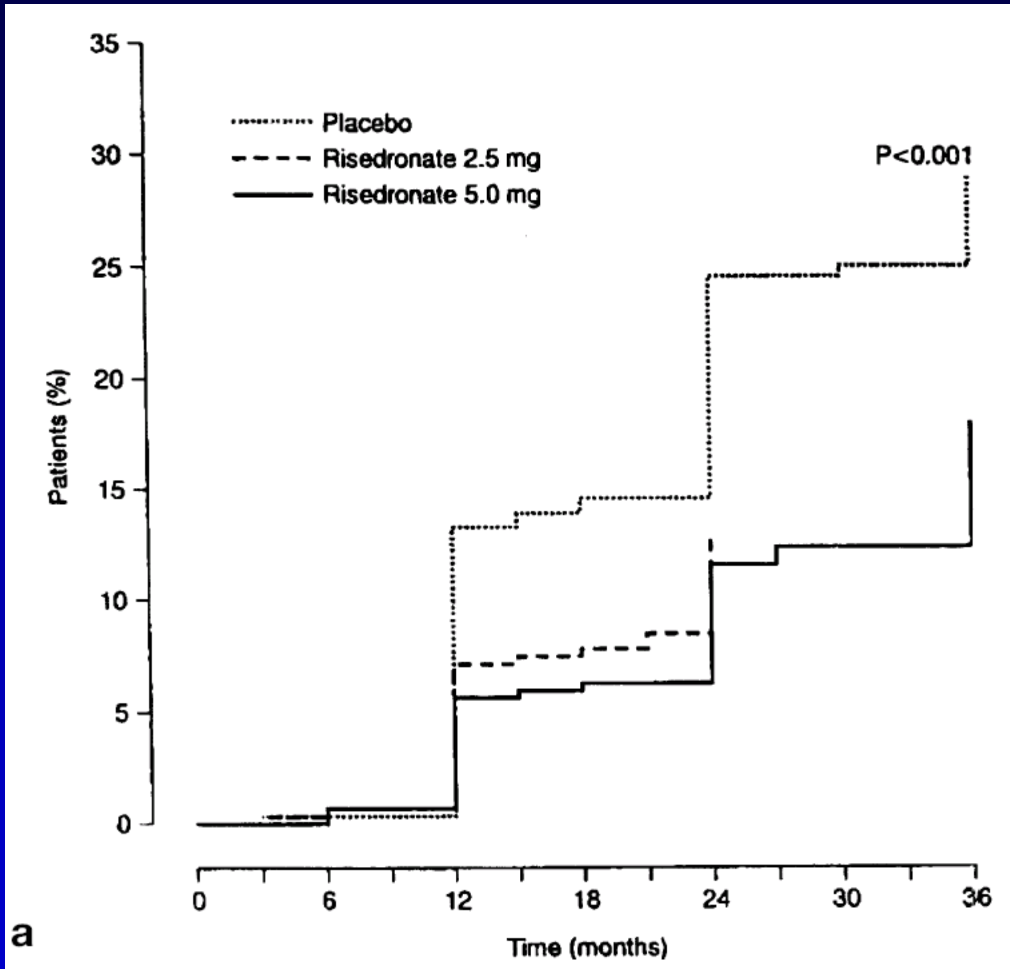
RISEDRONATE – VERT Multinational study

Reginster J-Y et al., Osteoporos Int 11 :83–91, 2000



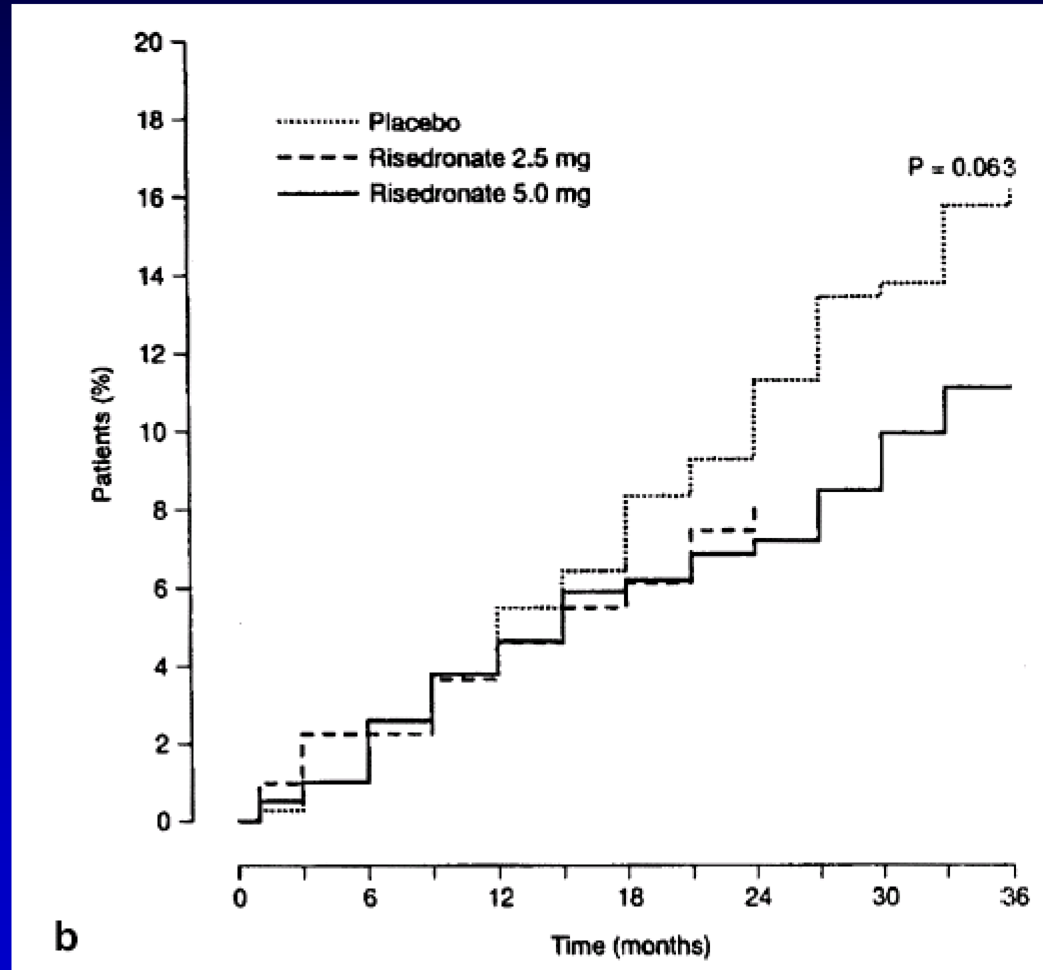


Fig. 2. Incidence of **a** new vertebral fractures and **b** nonvertebral osteoporosis-related fractures, in patients receiving control, risedronate 2.5 mg or risedronate 5 mg.

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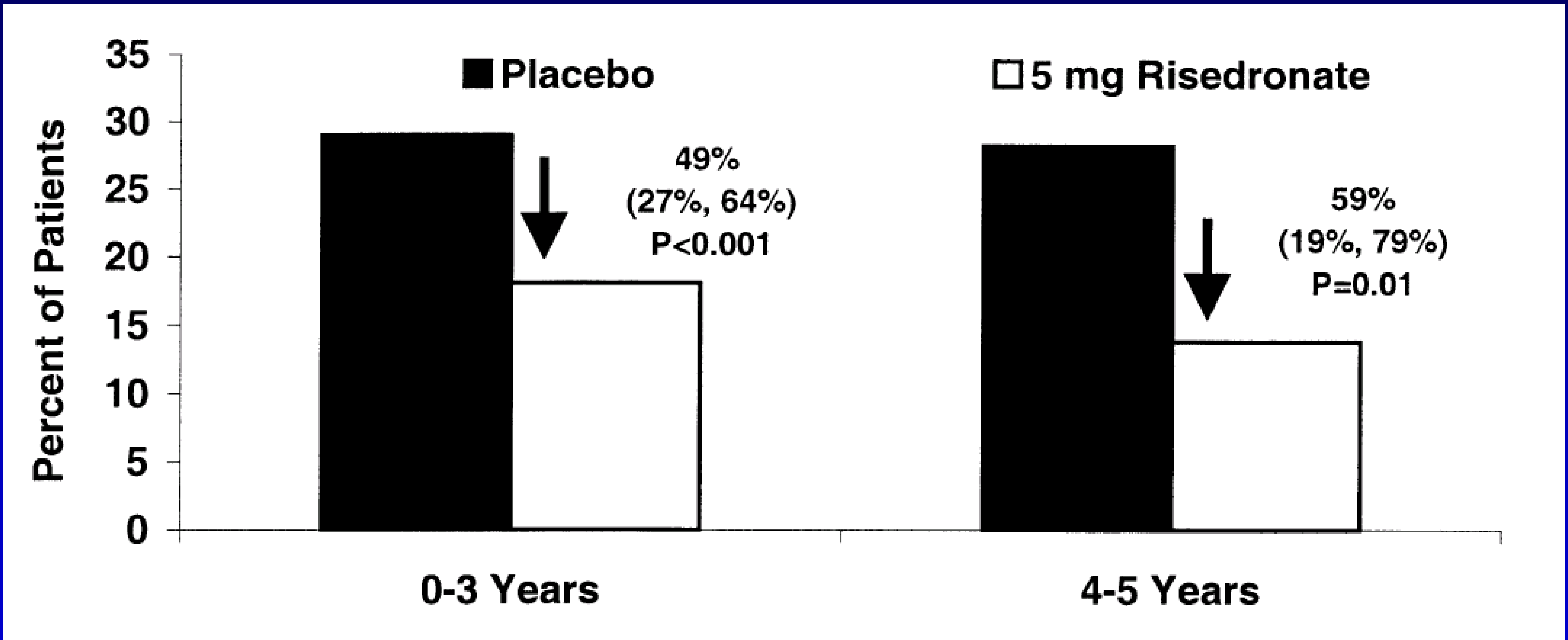
RISEDRONATE – VERT study (5 yrs follow-up)

Sorensen OH et al., Bone 32: 120-126, 2003



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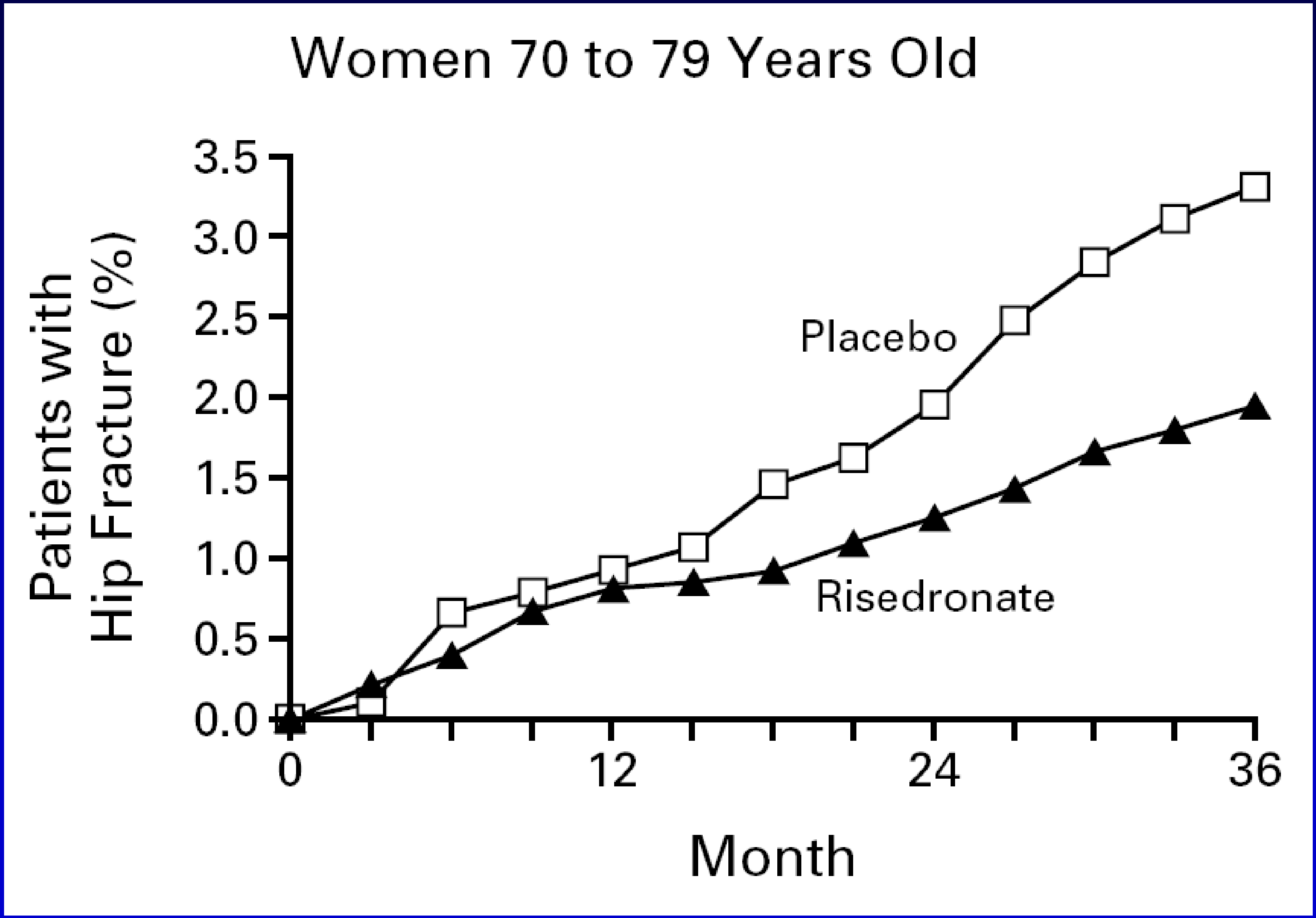
RISEDRONATE – HIP study

McClung MR, N Engl J Med 2001; 344:333-40



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RISEDRONATE
O.R.A.G.
META-ANALYSIS

Cranney A et al.,
Endocr Rev 23: 517–523, 2002

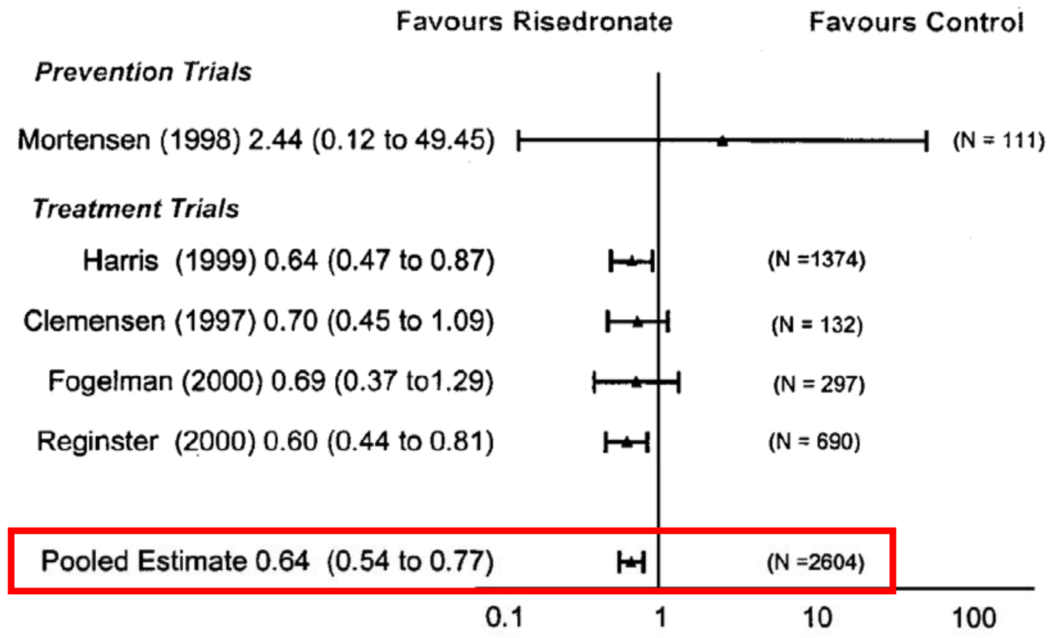

FIG. 2. Relative risk with 95% CI for vertebral fractures after treatment with risedronate.

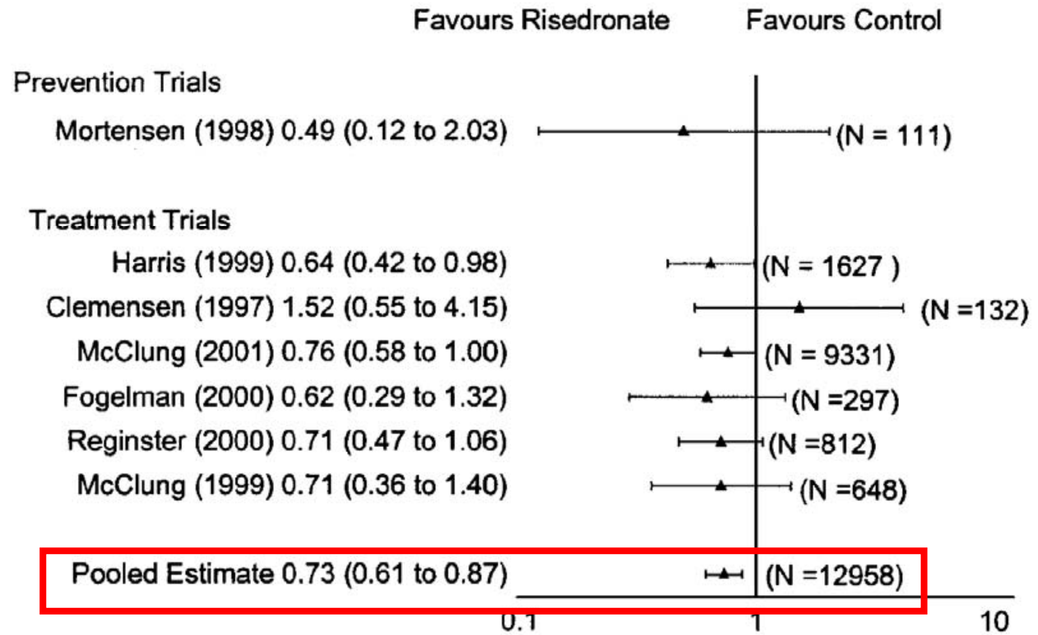

FIG. 3. Relative risk with 95% CI for nonvertebral fractures after treatment with risedronate.

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O.R.A.G. – Osteoporosis Research Advisory Group
META-ANALYSES

Cranney A et al., Endocr Rev 23:570–578, 2002

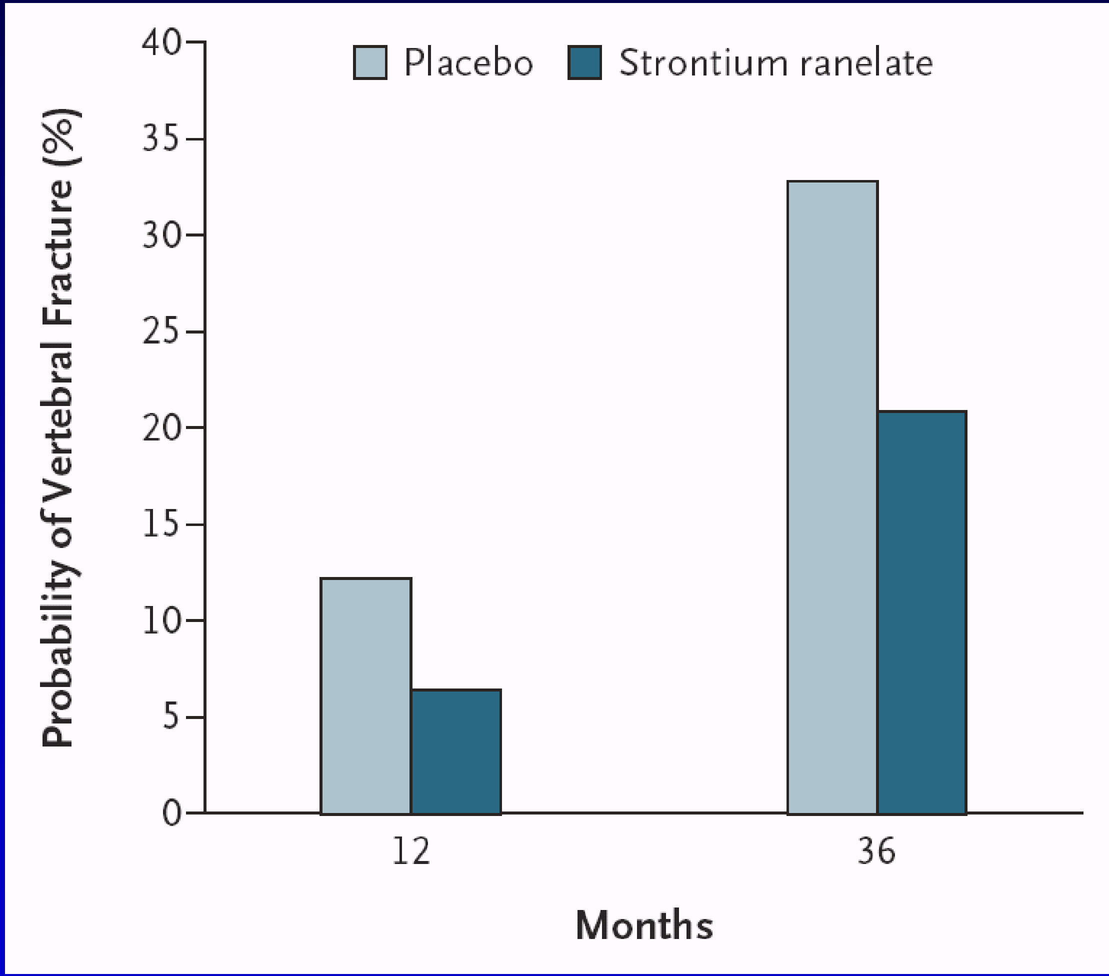
TABLE 4. NNT to prevent a vertebral and nonvertebral fracture over a period of 2 yr

Drug	Vertebral fracture		Nonvertebral fracture
	NNT (95% CI) over 2 yr for low-risk population (risk untreated 0.12%)	NNT (95% CI) over 2 yr for high-risk population (risk untreated 2.88%)	NNT to prevent one fracture (95% CI) for high-risk population (risk untreated 8.65%)
Vitamin D	2252 (1515, 6944)	94 (63, 289)	Effectiveness not established
Alendronate	1790 (1507, 2455)	72 (61, 99)	24 (19, 37)
Etidronate	2252 (1042, 1488)	94 (62, 434)	Effectiveness not established
Risedronate	2315 (1812, 3623)	96 (75, 151)	43 (30, 89)
Raloxifene	2381 (1894, 3472)	99 (79, 145)	Effectiveness not established

Low-risk population defined by BMD.

STRONTIUM RANELATE – SOTI study

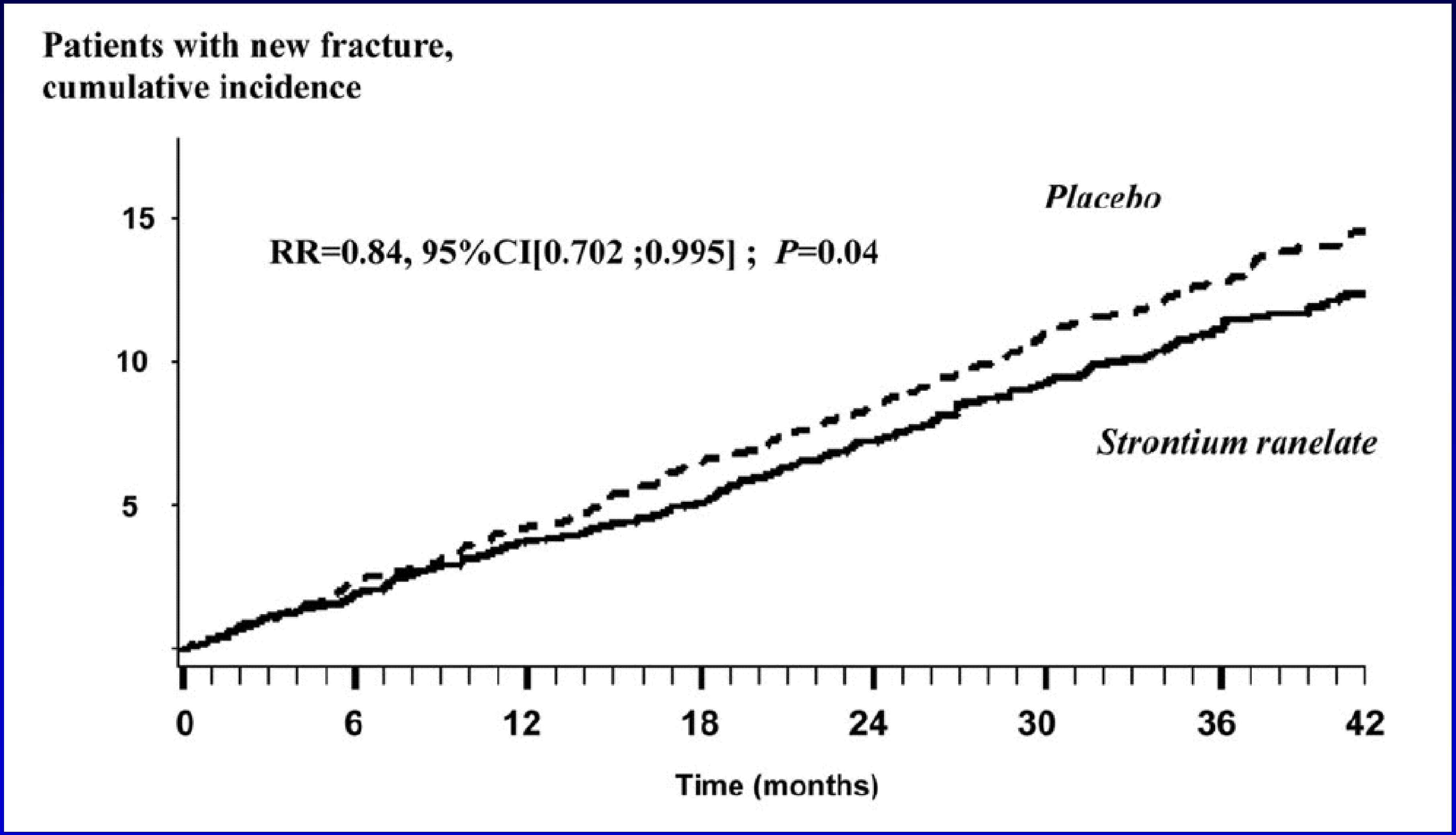
Meunier PJ et al., N Engl J Med 2004;350:459-68



Relative Risk = 0.59 (95% C.I.: 0.48 to 0.73)

STRONTIUM RANELATE – TROPOS study

Reginster JY et al., J Clin Endocrinol Metab 90: 2816–2822, 2005



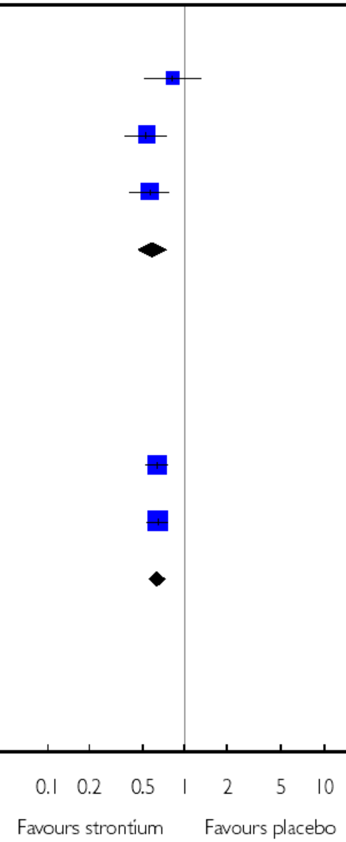
STRONTIUM RANELATE – Cochrane meta-analysis

O'Donnell S et al. Strontium ranelate for preventing and treating postmenopausal osteoporosis.*Cochrane Database of Systematic Reviews* 2006, Issue 3.

Comparison: 01 Fractures

Outcome: 01 Verterbral fractures

Study	Strontium n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 2 g/day - 1 Year					
Meunier 2002	22/85	28/87		22.2	0.80 [0.50, 1.29]
Meunier 2004-1	44/719	85/723		37.6	0.52 [0.37, 0.74]
Reginster 2005	51/1817	93/1823		40.2	0.55 [0.39, 0.77]
Subtotal (95% CI)	2621	2633		100.0	0.59 [0.46, 0.74]
Total events: 117 (Strontium), 206 (Placebo)					
Test for heterogeneity chi-square=2.34 df=2 p=0.31 I?? =14.4%					
Test for overall effect z=4.47 p<0.00001					
02 2 g/day - 3 Years					
Meunier 2004-1	139/719	222/723		43.8	0.63 [0.52, 0.76]
Reginster 2005	202/1817	321/1823		56.2	0.63 [0.54, 0.74]
Subtotal (95% CI)	2536	2546		100.0	0.63 [0.56, 0.71]
Total events: 341 (Strontium), 543 (Placebo)					
Test for heterogeneity chi-square=0.00 df=1 p=0.98 I?? =0.0%					
Test for overall effect z=7.37 p<0.00001					



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STRONTIUM RANELATE – Cochrane meta-analysis

O'Donnell S et al. Strontium ranelate for preventing and treating postmenopausal osteoporosis.*Cochrane Database of Systematic Reviews* 2006, Issue 3.

Comparison: 01 Fractures

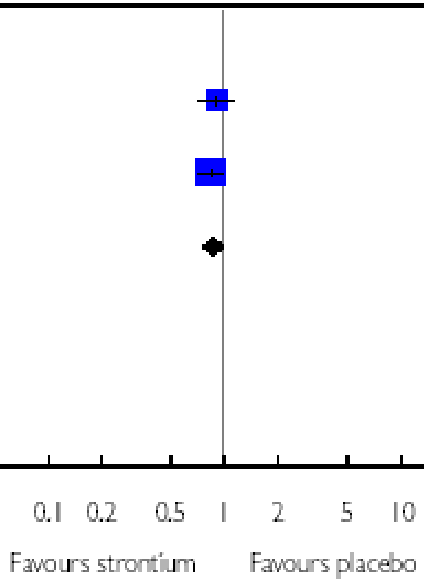
Outcome: 02 Non-vertebral fractures

Study	Strontium ranelate n/N	Placebo n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 2 g/day - 3 Years					
Meunier 2004-I	112/826	122/814		32.6	0.90 [0.71, 1.15]
Reginster 2005	233/2479	276/2453		67.4	0.84 [0.71, 0.99]
Subtotal (95% CI)	3305	3267		100.0	0.86 [0.75, 0.98]

Total events: 345 (Strontium ranelate), 398 (Placebo)

Test for heterogeneity chi-square=0.29 df=1 p=0.59 I?? =0.0%

Test for overall effect z=2.22 p=0.03



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TERIPARATIDE

Neer RM et al., N Engl J Med 344:, 1434-1441, 2001

POPULATION: 1637 postmenopausal women with prior vertebral fractures

TABLE 2. RADIOGRAPHIC EVIDENCE OF NEW VERTEBRAL FRACTURES.*

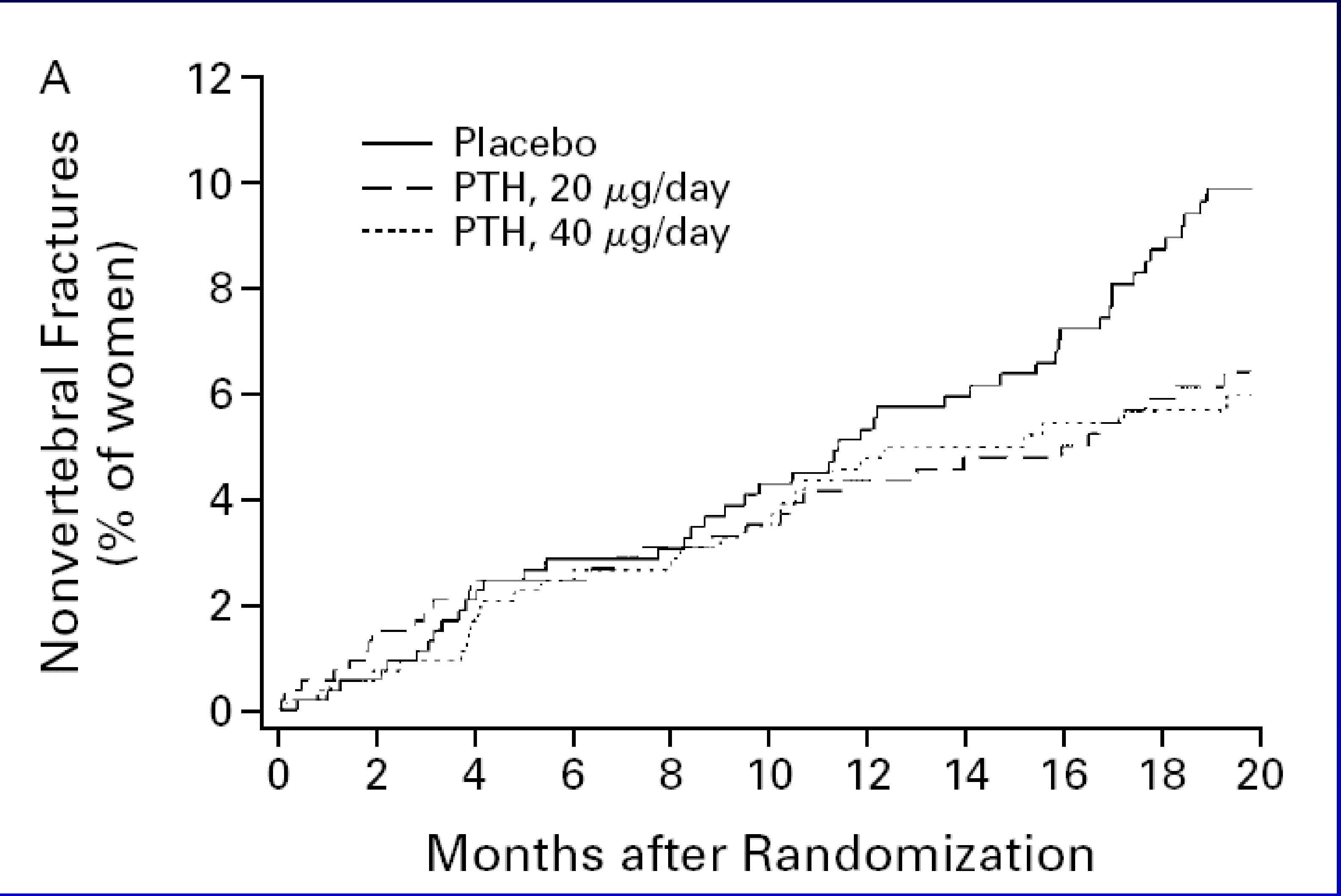
VARIABLE	PLACEBO (N=448)	PTH, 20 μg (N=444)	PTH, 40 μg (N=434)
No. of months at risk (randomization to final radiograph)	21±3	21±3	20±4
≥1 Fracture			
No. of women (%)	64 (14)	22 (5)†	19 (4)†
Relative risk (95% CI) vs. placebo	—	0.35 (0.22–0.55)	0.31 (0.19–0.50)
Percent reduction in absolute risk	—	9	10
>1 Fracture			
No. of women (%)	22 (5)	5 (1)†	3 (<1)†
Relative risk (95% CI) vs. placebo	—	0.23 (0.09–0.60)	0.14 (0.04–0.47)
Percent reduction in absolute risk	—	4	4
≥1 Moderate or severe fracture			
No. of women (%)	42 (9)	4 (<1)†	9 (2)†
Relative risk (95% CI) vs. placebo	—	0.10 (0.04–0.27)	0.22 (0.11–0.45)
Percent reduction in absolute risk	—	9	7

*Plus–minus values are means ±SD. PTH denotes parathyroid hormone (1-34), and CI confidence interval.

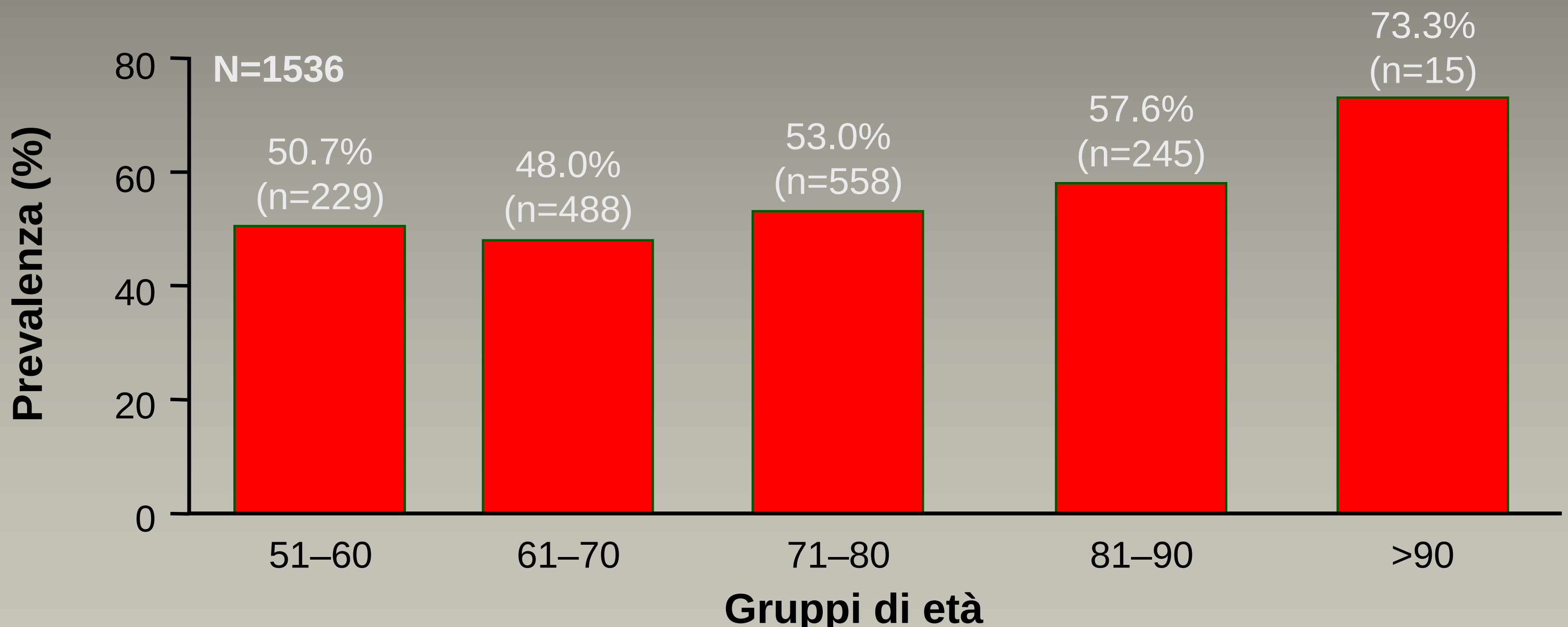
†P≤0.001 for the comparison with placebo.

TERIPARATIDE

Neer RM et al., N Engl J Med 344:, 1434-1441, 2001



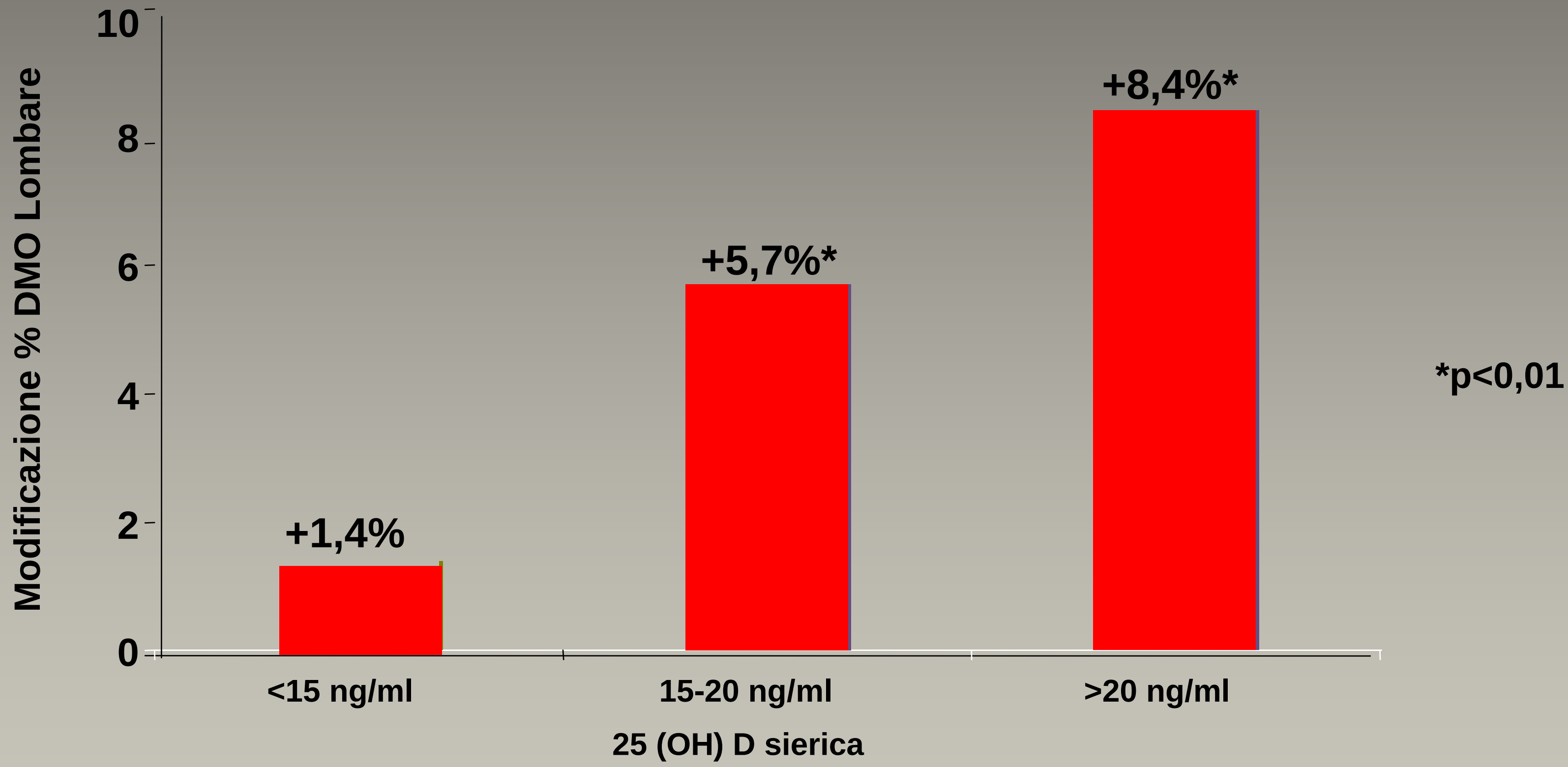
Prevalenza di livelli inadeguati di vitamina D (<30 ng/ml) nelle donne in postmenopausa



p=0.015 per test di tendenza

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

Livelli ematici di vitamina D e risposta all'alendronato



Tratto da; Ishijima M. et al. Abstract SU462 ASBMR 2005

Supplementazione di vitamina D nei vari trial

Studio	Dosaggio Vitamina D (UI/die)
VERT	500
MORE	400/600
TROPOS	400/800
MOBILE	400
FIT	250

IBANDRONATE – BONE study

Chesnut CH III et al., J Bone Miner Res 2004;19:1241–1249

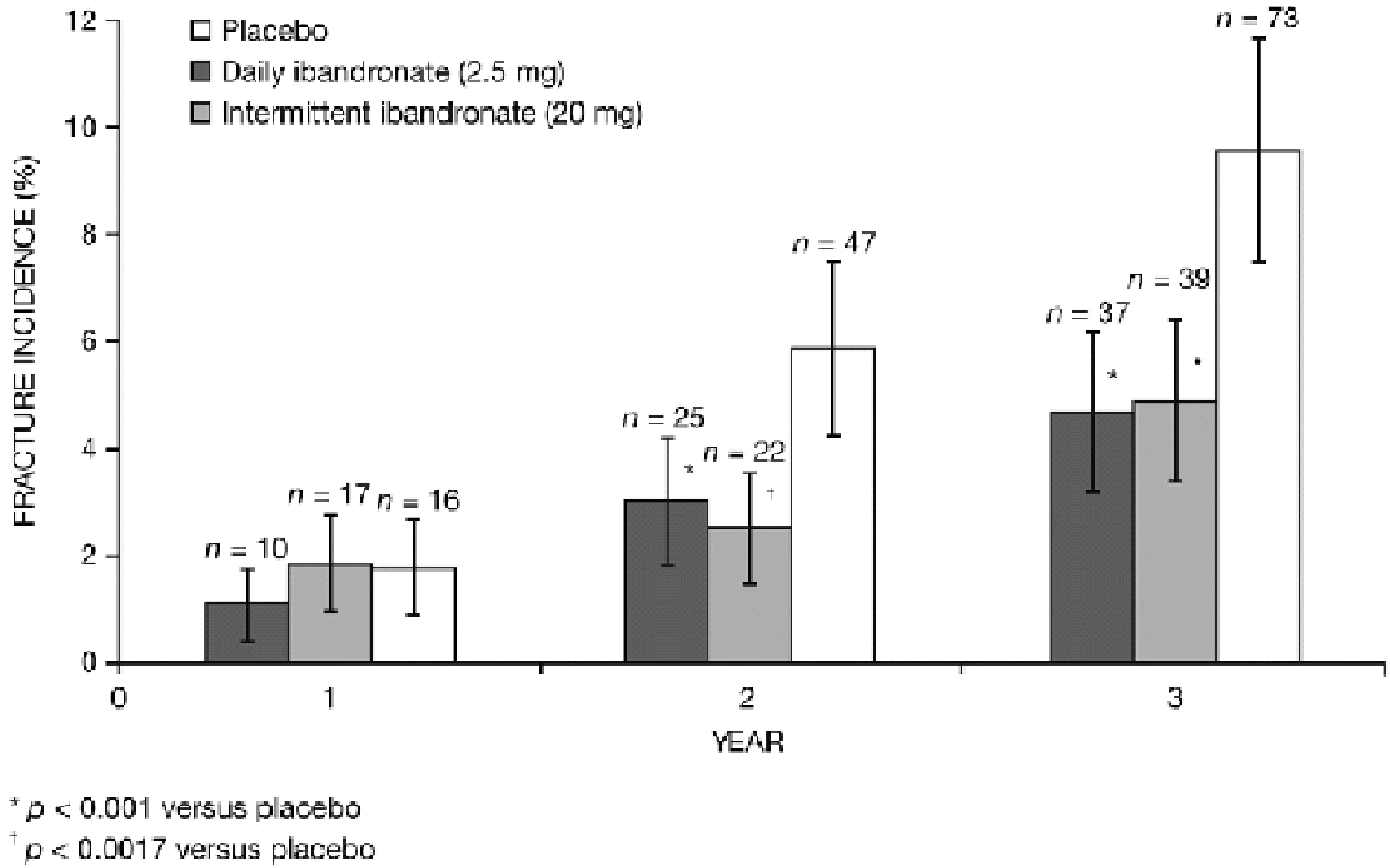


FIG. 2. Cumulative effect of oral daily and intermittent ibandronate on new vertebral fractures during each year of study.

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IBANDRONATE – BONE study

Chesnut CH III et al., J Bone Miner Res 2004;19:1241–1249

Clinical osteoporotic nonvertebral fractures: The incidence of clinical nonvertebral fractures was low and similar between the placebo and active treatment groups (8.2%, 9.1%, and 8.9% in the placebo, 2.5 mg ibandronate, and 20 mg ibandronate groups, respectively).

HORMONE REPLACEMENT THERAPY

Main issues

- antifracture activity
- cardiovascular effects
- breast cancer

HORMONE REPLACEMENT THERAPY

SOFRG
PEPI
HERS
WHI
“One million”

et al.

HORMONE REPLACEMENT THERAPY

Nelson HD et al., *JAMA* 288:872-881, 2002

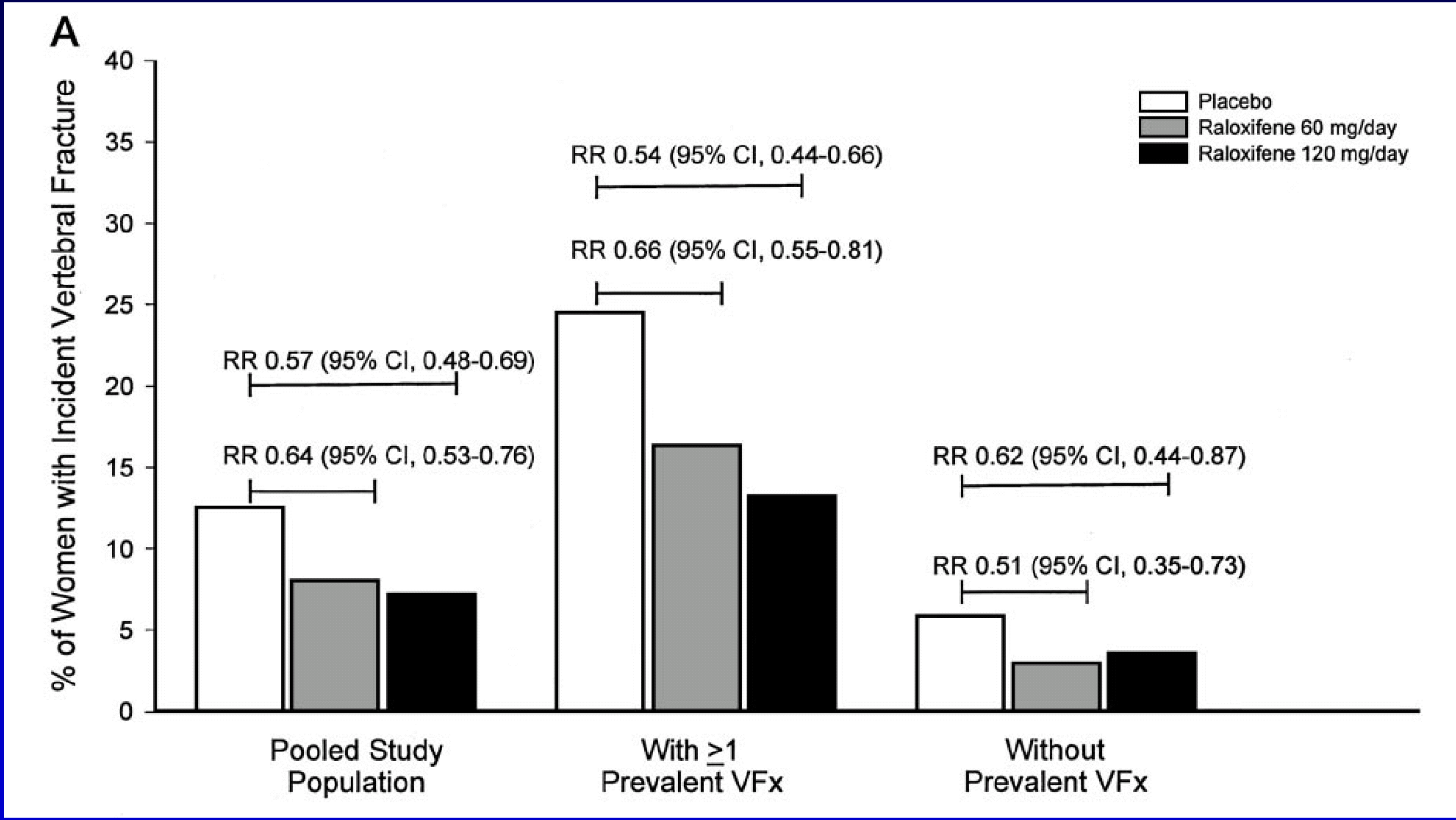
	Relative Risk (95% Confidence Interval [CI]) From Review and Meta-analysis
Benefits (prevention)	
Hip fractures	0.76 (0.56-1.01)
Wrist fractures	0.44 (0.23-0.84)
Vertebral fractures	0.60 (0.36-0.99)
Cases of colon cancer	0.80 (0.74-0.86)
Uncertain benefits	
Cases of dementia prevented	0.66 (0.53-0.82)
Harms (caused)	
Coronary heart disease events	0.91 (0.67-1.33)
Strokes	1.12 (1.01-1.23)
Thromboembolic events	2.14 (1.64-2.81)
Thromboembolic events during first year	3.49 (2.33-5.59)
Breast cancer cases (<5 years' use)	1.0 to 1.14
Breast cancer cases (≥5 years' use)	1.23 to 1.35
Cholecystitis cases (<5 years' use)	1.8 (1.6-2.0)
Cholecystitis cases (≥5 years' use)	2.5 (2.0-2.9)

*WHI indicates Women's Health Initiative; NA, not applicable; and ellipses, data no
heart disease); adjusted CIs, for secondary outcomes.
†Estimates are based on extrapolations.

RALOXIFENE - MORE study

Ettinger B et al., JAMA 282:637-645, 1999

Delmas PD et al., J Clin Endocrinol Metab 87: 3609–3617, 2002 - 4 yrs follow-up



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RALOXIFENE - MORE study

Ettinger B et al., JAMA 282:637-645, 1999

Delmas PD et al., J Clin Endocrinol Metab 87: 3609–3617, 2002

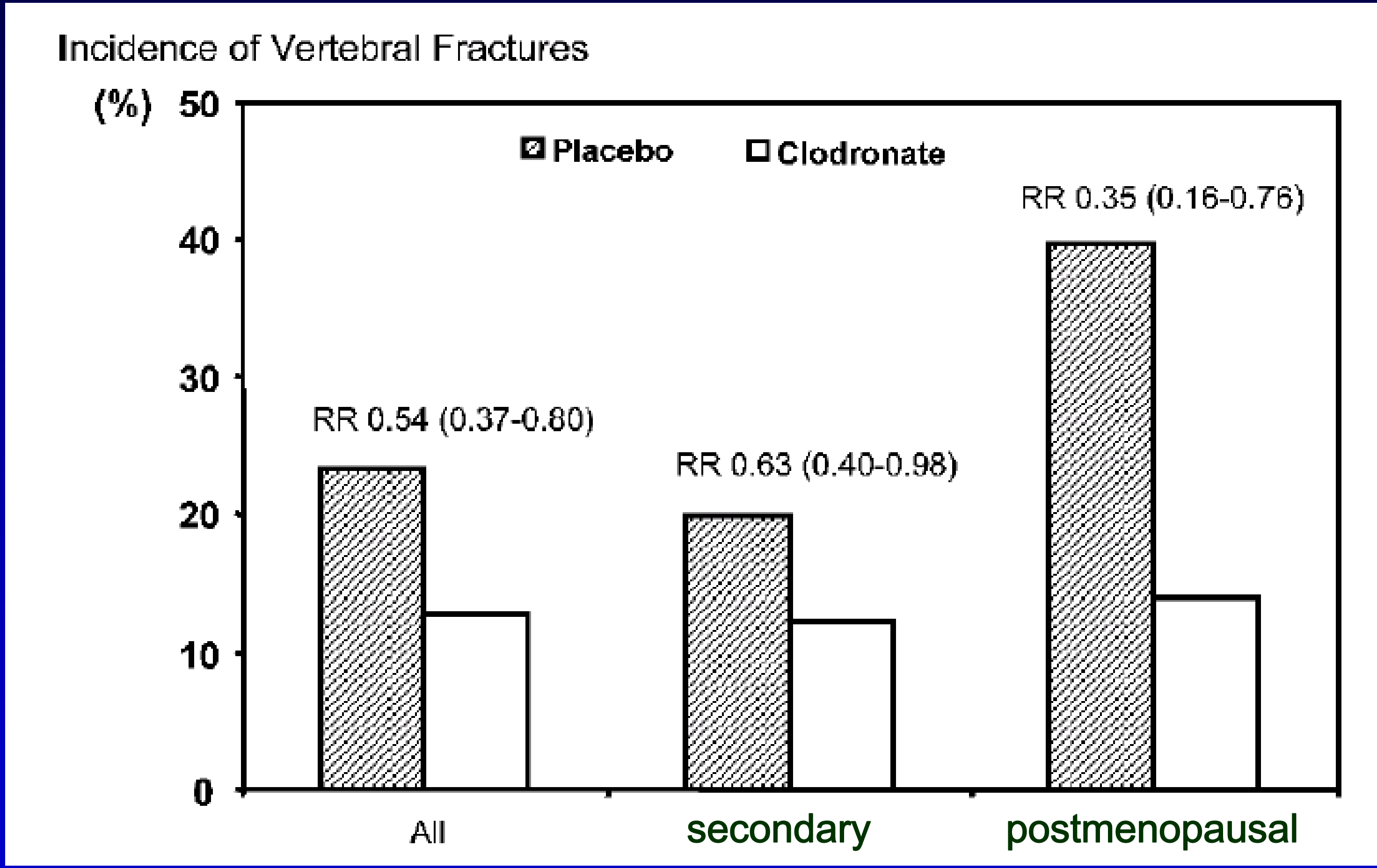
Nonvertebral fractures

Through 4 yr, there was no evidence that raloxifene treatment lowered the risk for nonvertebral fractures.

RR = 0.93 (95% CI: 0.81-1.06)

CLODRONATE

McCloskey E et al., J Bone Miner Res 2004;19:728–736 – 3 years follow-up



Treatment: clodronate 800 mg/day per os

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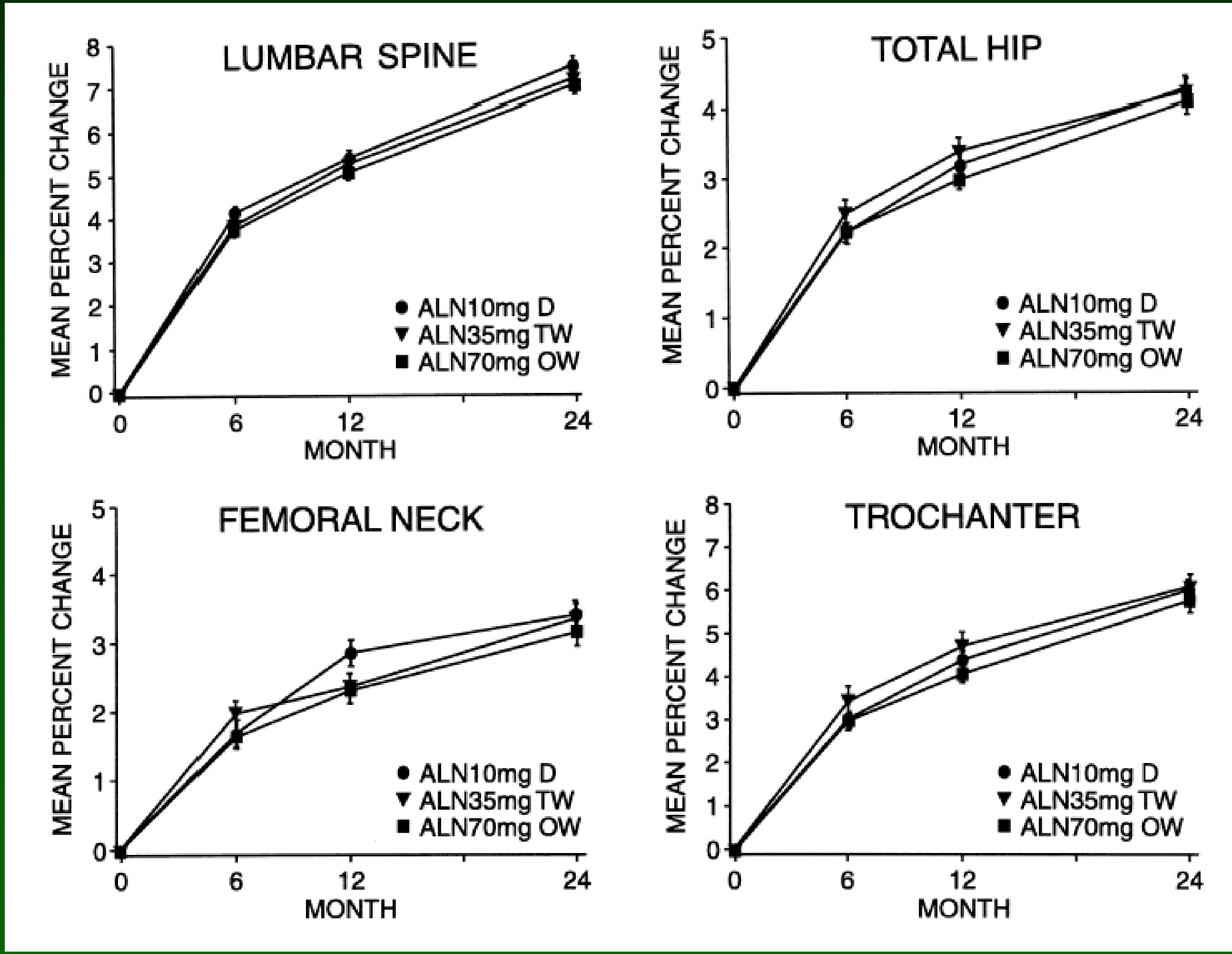
Once-a-week

ALENDRONATE 70 mg/week

Schnitzer T et al., Aging 12: 1-12, 2000

Rizzoli R et al., J Bone Miner Res 17:1988–1996, 2002



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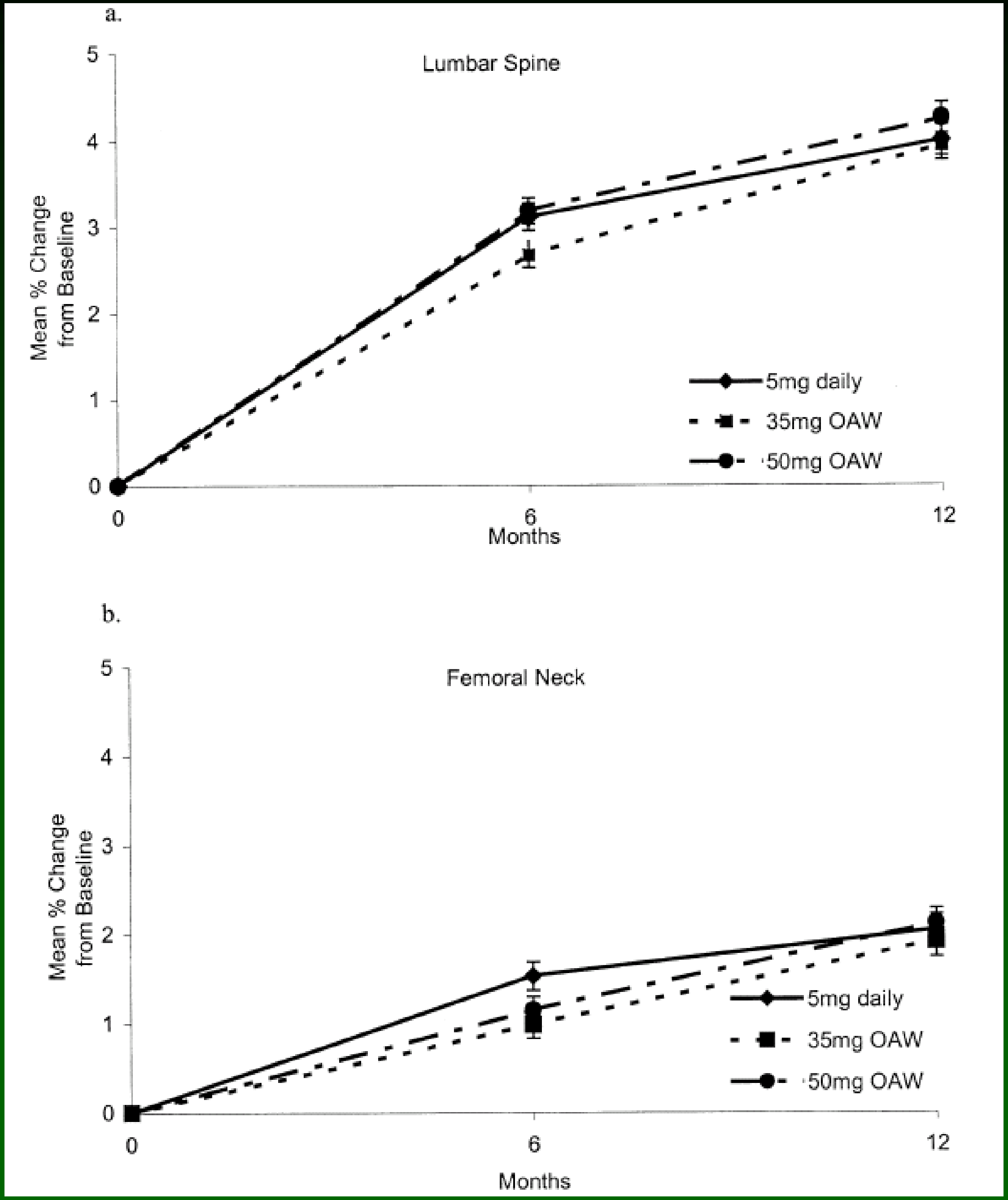
Once-a-week

RISEDRONATE
35 mg/week

Brown JP et al., Calcif Tissue Int 71: 103-111, 2002



Once-a-month

IBANDRONATE 150 mg/month - MOBILE study

Miller PD et al., J Bone Miner Res 20:1315-1322, 2005

Reginster J-Y et al., Ann Rheum Dis 65:654–661, 2006

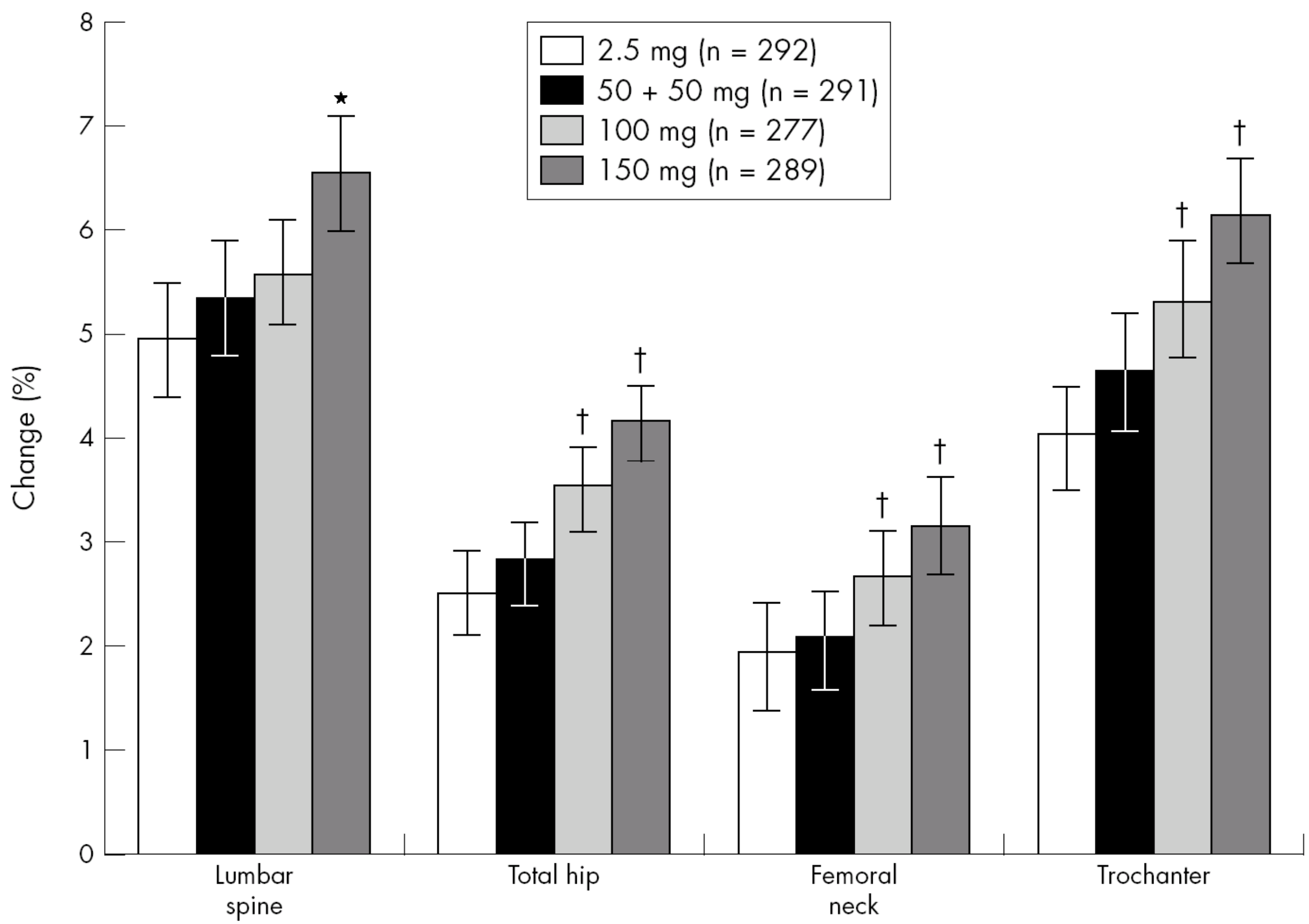


Figure 2 Change (%) from baseline in lumbar spine and proximal femur BMD at 2 years (PP; mean (95% CI)). *p<0.001 versus daily treatment; †p<0.05 versus daily treatment.

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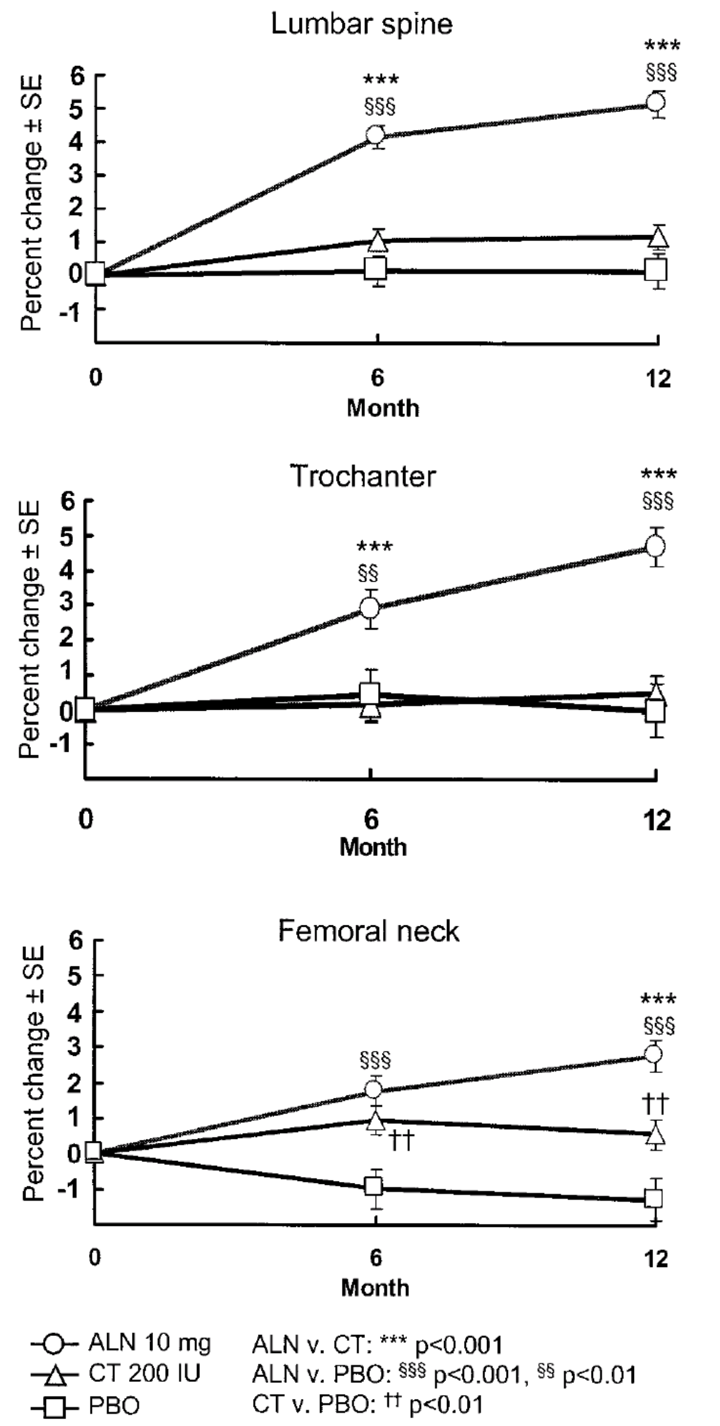
Head-to-Head comparisons

ALENDRONATE vs. CALCITONIN

Downs RW et al., *J Clin Endocrinol Metab* 85: 1783–1788, 2000



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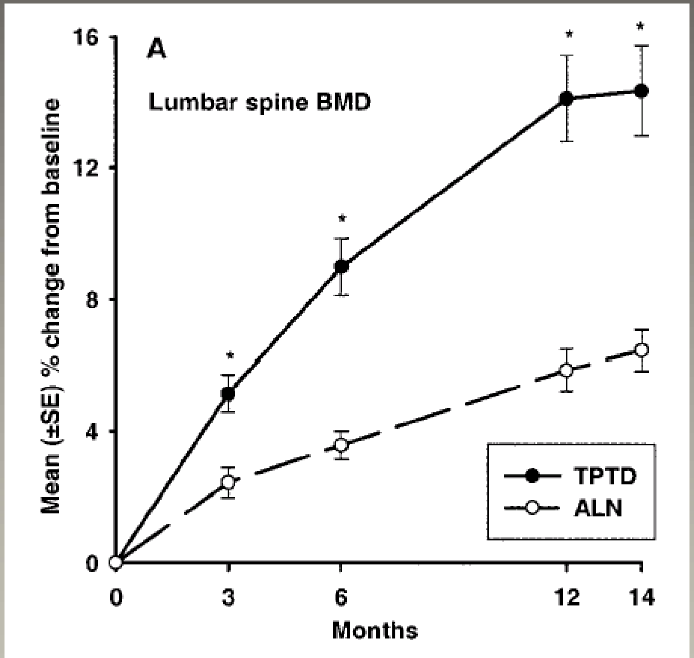
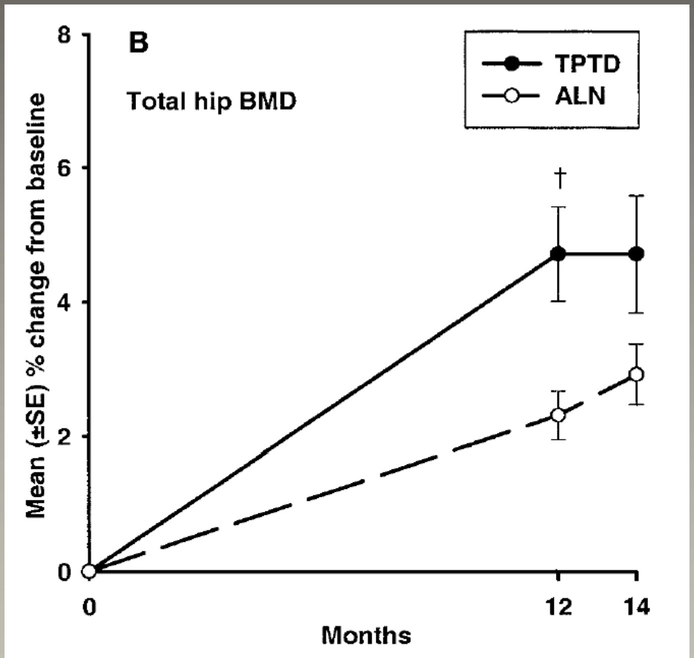
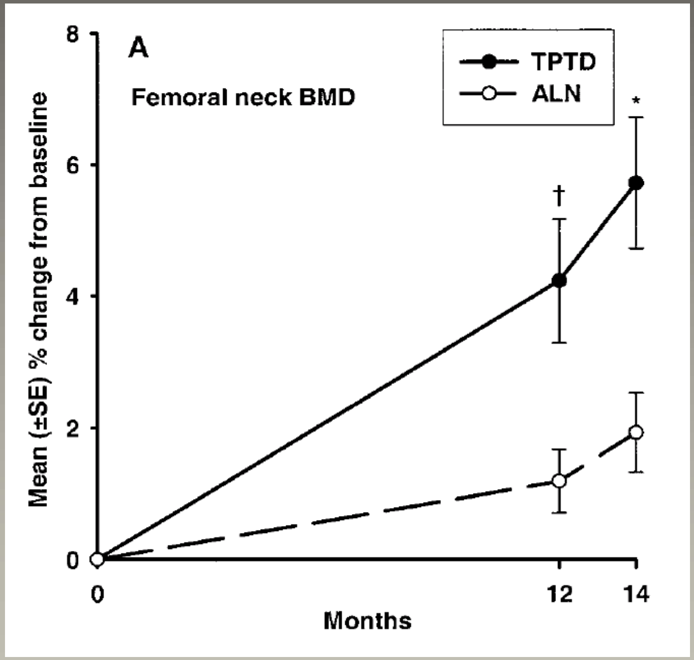
Head-to-Head comparisons

ALENDRONATE vs. TERIPARATIDE

Body J-J et al., *J Clin Endocrinol Metab* 87: 4528–4535, 2002







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Head-to-Head comparisons

ALENDRONATE vs. RALOXIFENE – EFFECT study

Sambrook PN et al., Journal of Internal Medicine 2004; 255: 503–511

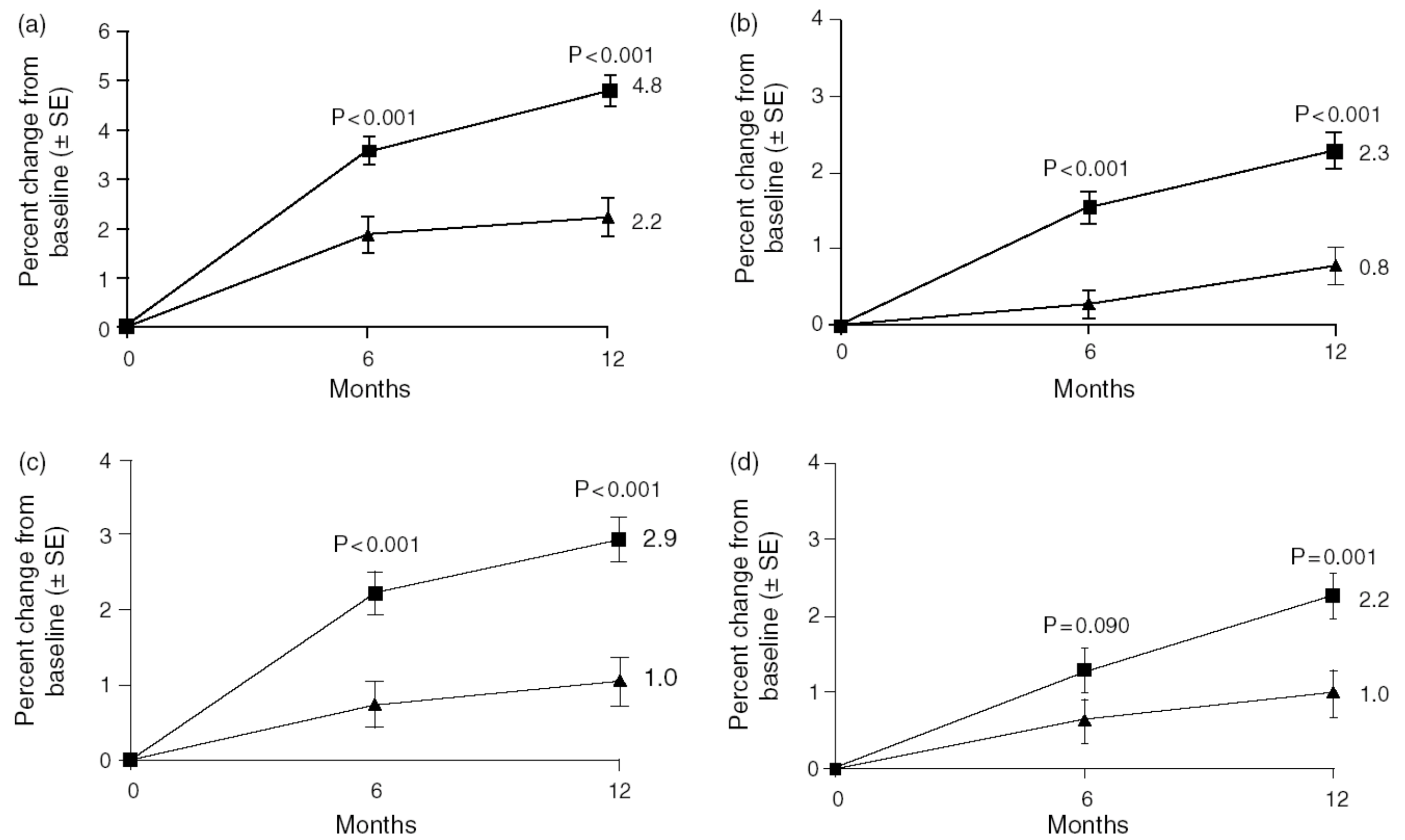

Fig. 2 (a) Changes in bone mineral density (BMD) at lumbar spine. (b) Changes in BMD at total hip. (c) Changes in BMD at hip trochanter. (d) Changes in BMD at femoral neck. The alendronate group experienced greater increases in BMD compared with the raloxifene group at 6 and 12 months at both the hip and spine. ■ alendronate, ▲ raloxifene, *P*-value for between treatment group comparison.

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Head-to-Head comparisons

ALENDRONATE vs. RISEDRONATE – FACT study

Rosen CJ et al., J Bone Miner Res 2005;20:141–151

Bonnick S et al., J Clin Endocrinol Metab. 2006 Apr 24; [Epub ahead of print] – 2 yrs follow-up

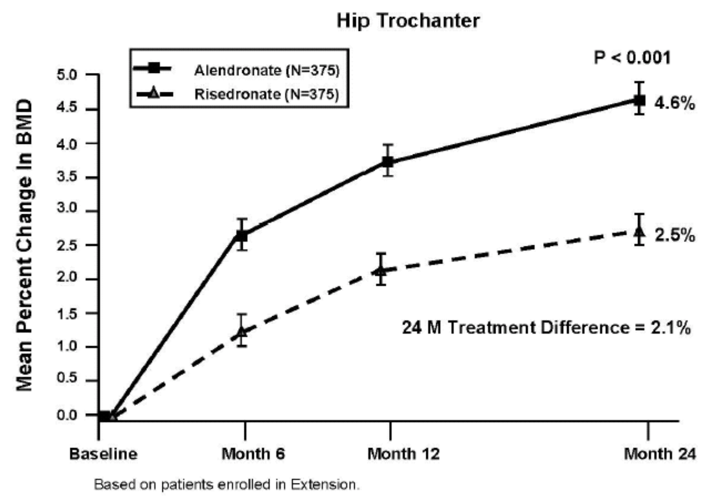
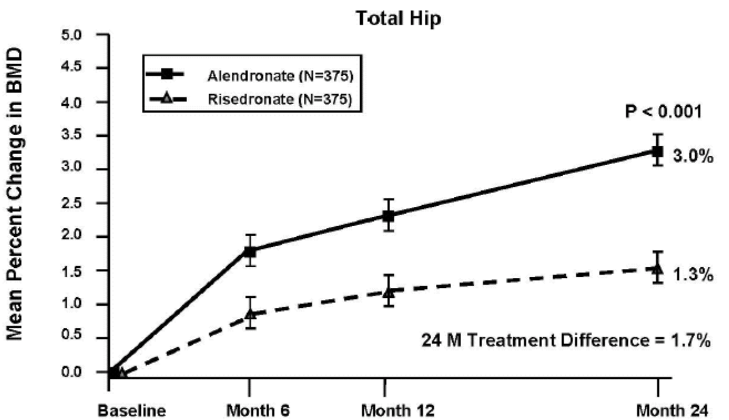


Figure 2b.



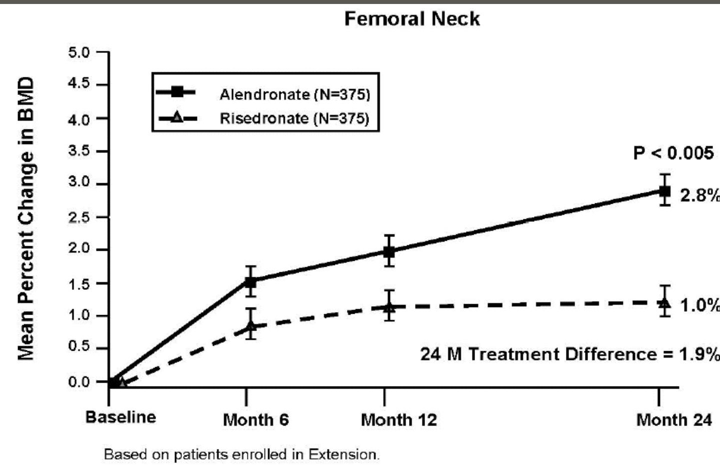
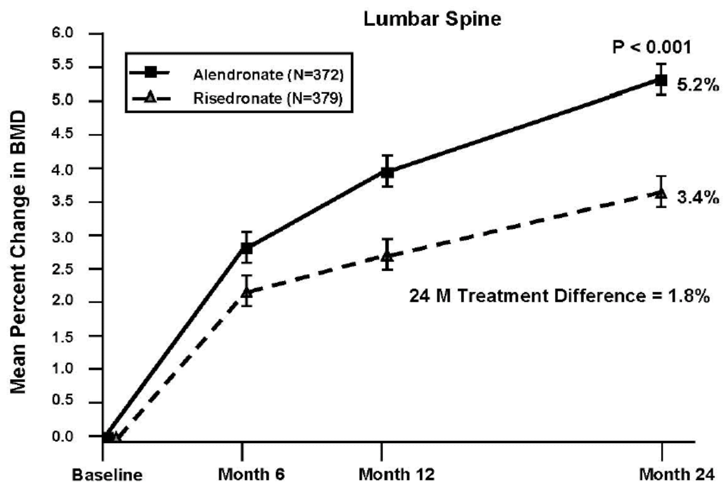


Figure 2d.



THERAPEUTIC PROPOSALS

Alendronate

- First choice drug
- Well suited for all bone types
- Long term administration
- May be associated with estrogen and vit. D
- Gastroesophageal side effects

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THERAPEUTIC PROPOSALS

Risedronate

- First choice drug
- Same effectiveness as alendronate
- Newer drug: less scientific evidence

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THERAPEUTIC PROPOSALS

Strontium ranelate

- Effective on both spinal and non-spinal fractures
- AIFA "nota 79": in case of contraindications or intolerance to alendronate or risedronate

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THERAPEUTIC PROPOSALS

Teriparatide

- Indicated in severe osteoporosis:
  - secondary prevention
  - new fractures occurring during well-conducted therapy with aledronate or risedronate (AIFA “nota 79”)

THERAPEUTIC PROPOSALS

Estrogen

Only for women with

serious climateric syndrome
or
early menopause

THERAPEUTIC PROPOSALS

Other drugs

Many drugs are prescribed due to several non-scientific reasons

- reimbursement by SSN
- patient’s compliance
- associated diseases

clodronate - raloxifene - ibandronate

THERAPEUTIC PROPOSALS

Other drugs

Not indicated:

neridronate

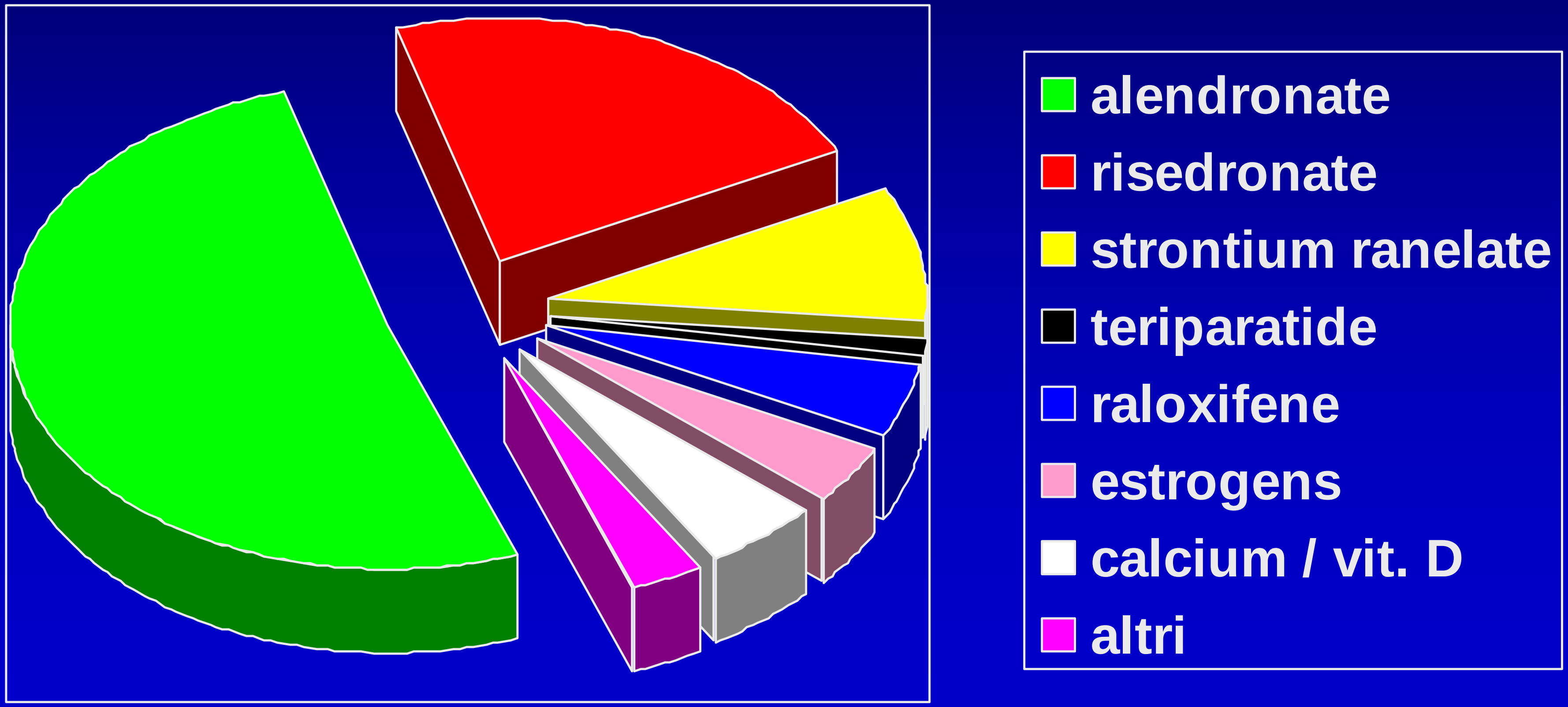
zoledronate

ipriflavone

tibolone

AMBULATORIO OSTEOPOROSI - Endocrinologia, Reggio Emilia

% PATIENTS with ACTIVE CURRENT TREATMENT for OSTEOPOROSIS



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All this was

HOW to treat TODAY

Now:

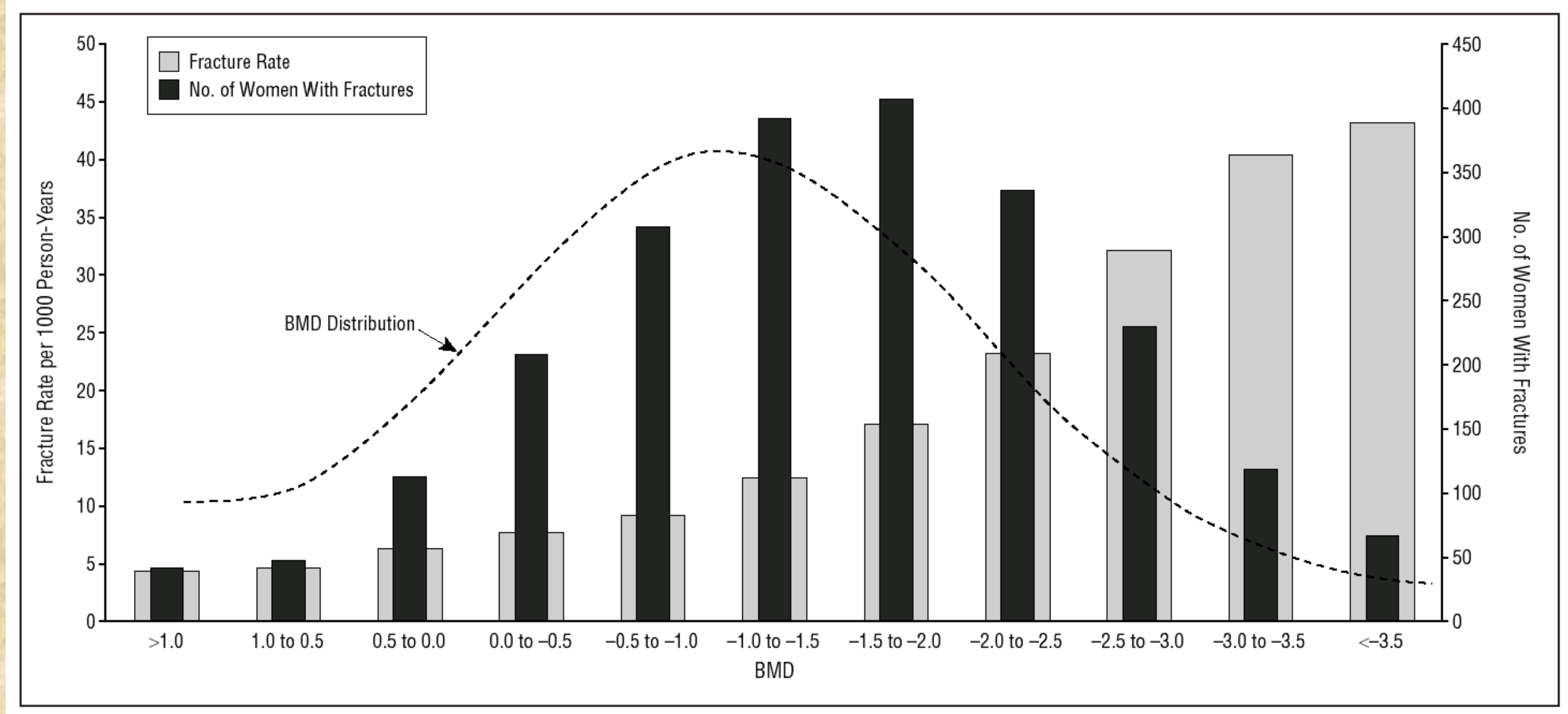
HOW to treat IN THE NEXT FUTURE

And then:

WHO to treat

WHO to treat - NORA study

Siris ES et al., *Arch Intern Med. 164:1108-1112*, 2004



1) Most of fractures occur in osteoPENIC, not in osteoPOROTIC women

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WHO to treat

Andrade SE et al., Arch Intern Med 163: 2052-2057, 2003

Patients Dispensed Drug for Osteoporosis Treatment After a Fracture Among the Population With the Specified Characteristic*	
Overall Population (N = 3492)	Women Not Receiving Treatment Before the Fracture (n = 2605)†
822 (24)	353 (14)

2) Osteoporosis is a largely UNDERTREATED condition

WHO to treat

Carnevale V et al., Osteoporos Int 17: 478–483, 2006

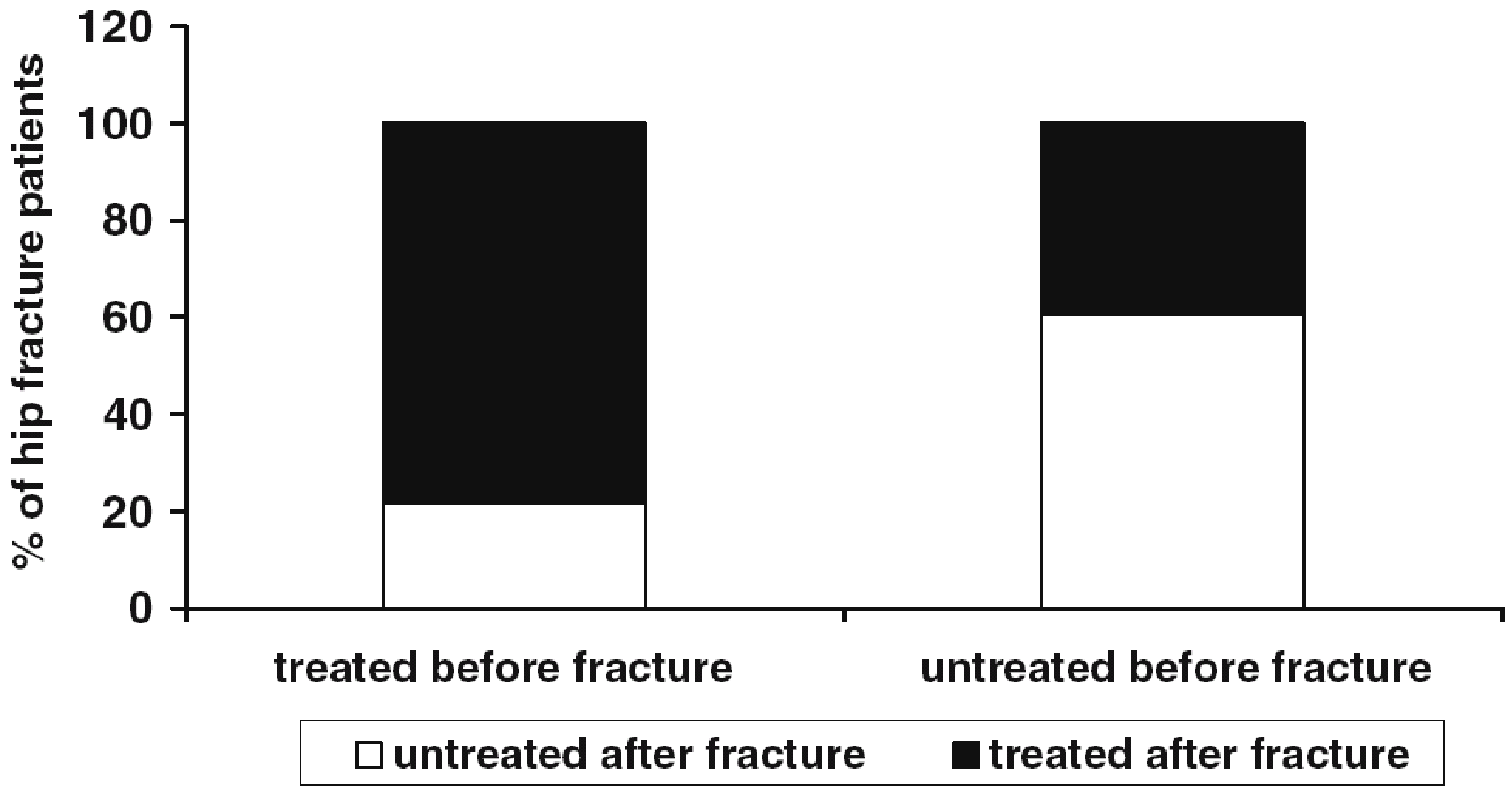


Fig. 2 Use of osteoporosis medication during the six months before and after hip fracture

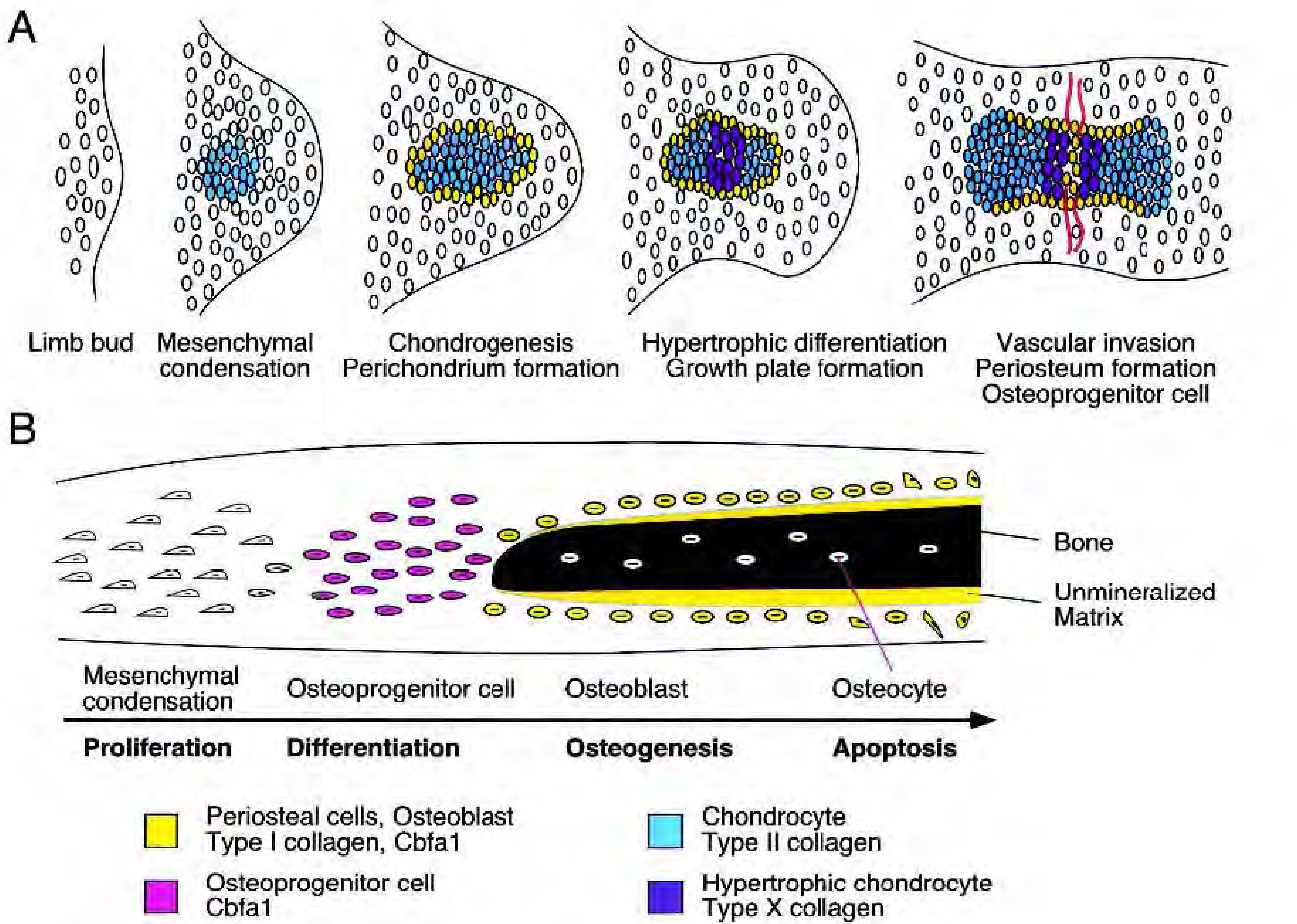
WHO to treat :

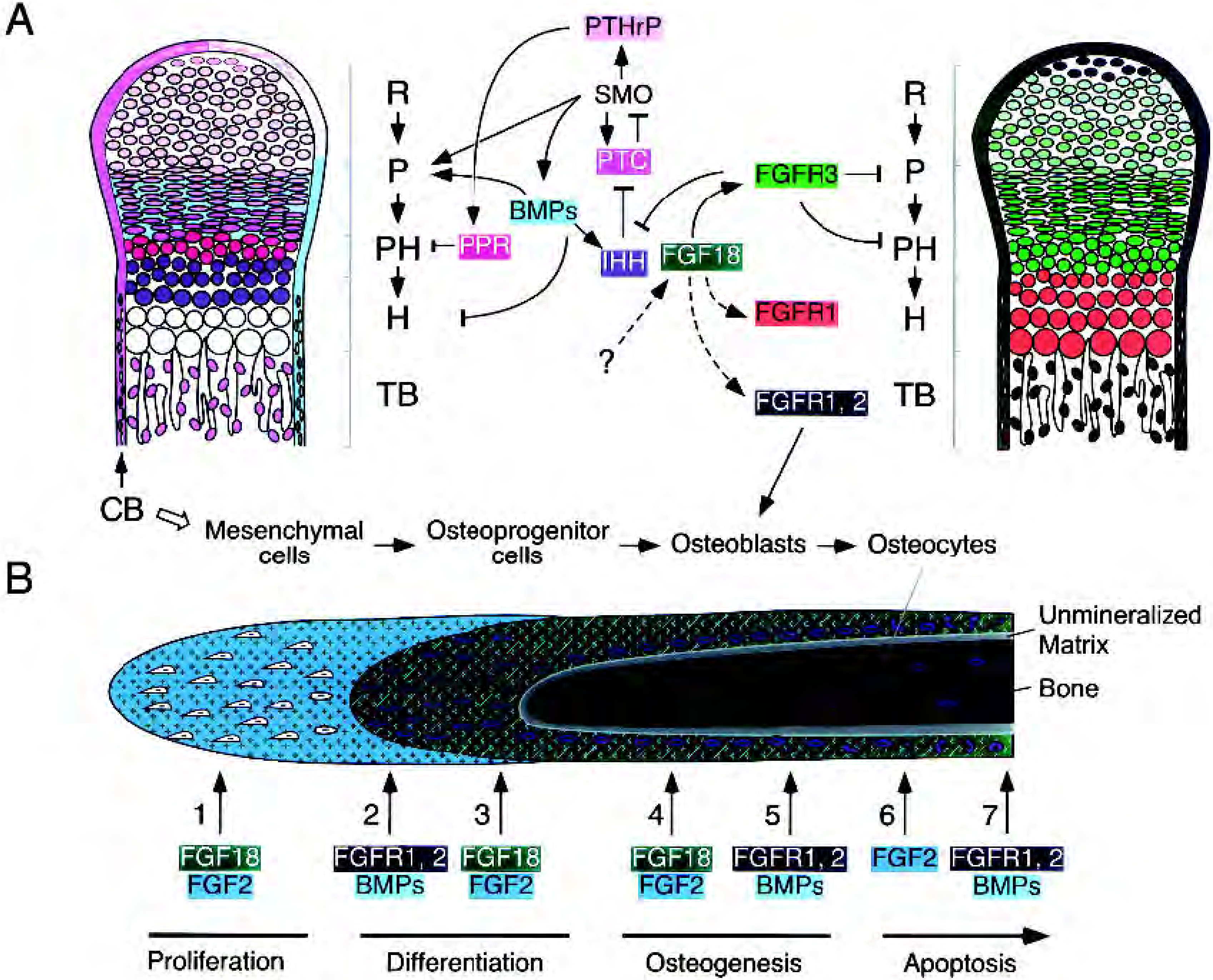
- risk factors assessment
- BMD measurement
- risk fracture definition
- treatment threshold identification

Population-specific RISK TABLES

Review: developmental origins of osteoporotic fracture

Cyrus Cooper · Sarah Westlake · Nicholas Harvey
Kassim Javaid · Elaine Dennison · Mark Hanson


A
Limb bud
Mesenchymal condensation
Chondrogenesis
Perichondrium formation
Hypertrophic differentiation
Growth plate formation
Vascular invasion
Periosteum formation
Osteoprogenitor cell
B
Bone
Unmineralized Matrix
Mesenchymal condensation
Osteoprogenitor cell
Osteoblast
Osteocyte
Proliferation
Differentiation
Osteogenesis
Apoptosis
Periosteal cells, Osteoblast
Type I collagen, Cbfa1
Chondrocyte
Type II collagen
Osteoprogenitor cell
Cbfa1
Hypertrophic chondrocyte
Type X collagen



A
PTHrP
SMO
R
P
PH
H
TB
PTC
BMPs
PPR
IHH
FGF18
FGFR3
FGFR1
FGFR1, 2
?
CB
Mesenchymal cells
Osteoprogenitor cells
Osteoblasts
Osteocytes
B
Unmineralized Matrix
Bone
1
FGF18
FGF2
2
FGFR1, 2
BMPs
3
FGF18
FGF2
4
FGF18
FGF2
5
FGFR1, 2
BMPs
6
FGF2
7
FGFR1, 2
BMPs
Proliferation
Differentiation
Osteogenesis
Apoptosis

Table 1 The essential signalling molecules during fracture healing; their source and targeted cells, and their major functions and expression patterns

Cytokines (IL-1, IL-6, TNF-α)
- Source: macrophages and other inflammatory cells, cells of mesenchymal origin
- Chemotactic effect on other inflammatory cells, stimulation of extracellular matrix synthesis, angiogenesis, recruitment of endogenous fibrogenic cells to the injury site, and at later stages bone resorption
- Increased levels from days 1 to 3 and during bone remodelling

TGF-β
- Source: degranulating platelets, inflammatory cells, endothelium, extracellular matrix, chondrocytes, osteoblasts
- Targeted cells: MSCs, osteoprogenitors cells, osteoblasts, chondrocytes
- Potent mitogenic and chemotactic for bone forming cells, chemotactic for macrophages
- Expressed from very early stages throughout fracture healing

PDGF
- Source: degranulating platelets, macrophages, monocytes (during the granulation stage) and endothelial cells, osteoblasts (at later stages)
- Targeted cells: mesenchymal and inflammatory cells, osteoblasts
- Mitogenic for mesenchymal cells and osteoblasts, chemotactic for inflammatory and mesenchymal cells
- Released at very early stages of fracture healing

BMPs
- Source: osteoprogenitors and mesenchymal cells, osteoblasts, bone extracellular matrix and chondrocytes
- Targeted cells: mesenchymal and osteoprogenitor cells, osteoblasts
- Differentiation of undifferentiated mesenchymal cells into chondrocytes and osteoblasts and osteoprogenitors into osteoblasts
- Various temporal expression patterns (Table 2)

FGFs

- Source: monocytes, macrophages, mesenchymal cells, osteoblasts, chondrocytes
- Targeted cells: mesenchymal and epithelial cells, osteoblasts and chondrocytes
- Angiogenic and mitogenic for mesenchymal and epithelial cells, osteoblasts, chondrocytes
- α-FGF mainly effects chondrocyte proliferation, β-FGF (more potent) involved in chondrocytes maturation and bone resorption
- Expressed from the early stages until osteoblasts formation

IGFs

- Source: bone matrix, endothelial and mesenchymal cells (in granulation stage) and osteoblasts and non-hyperthrophic chondrocytes (in bone and cartilage formation)
- Targeted cells: MSCs, endothelial cells, osteoblasts, chondrocytes
- IGF-I: mesenchymal and osteoprogenitor cells recruitment and proliferation, expressed throughout fracture healing
- IGF-II: cell proliferation and protein synthesis during endochondral ossification

Metalloproteinases

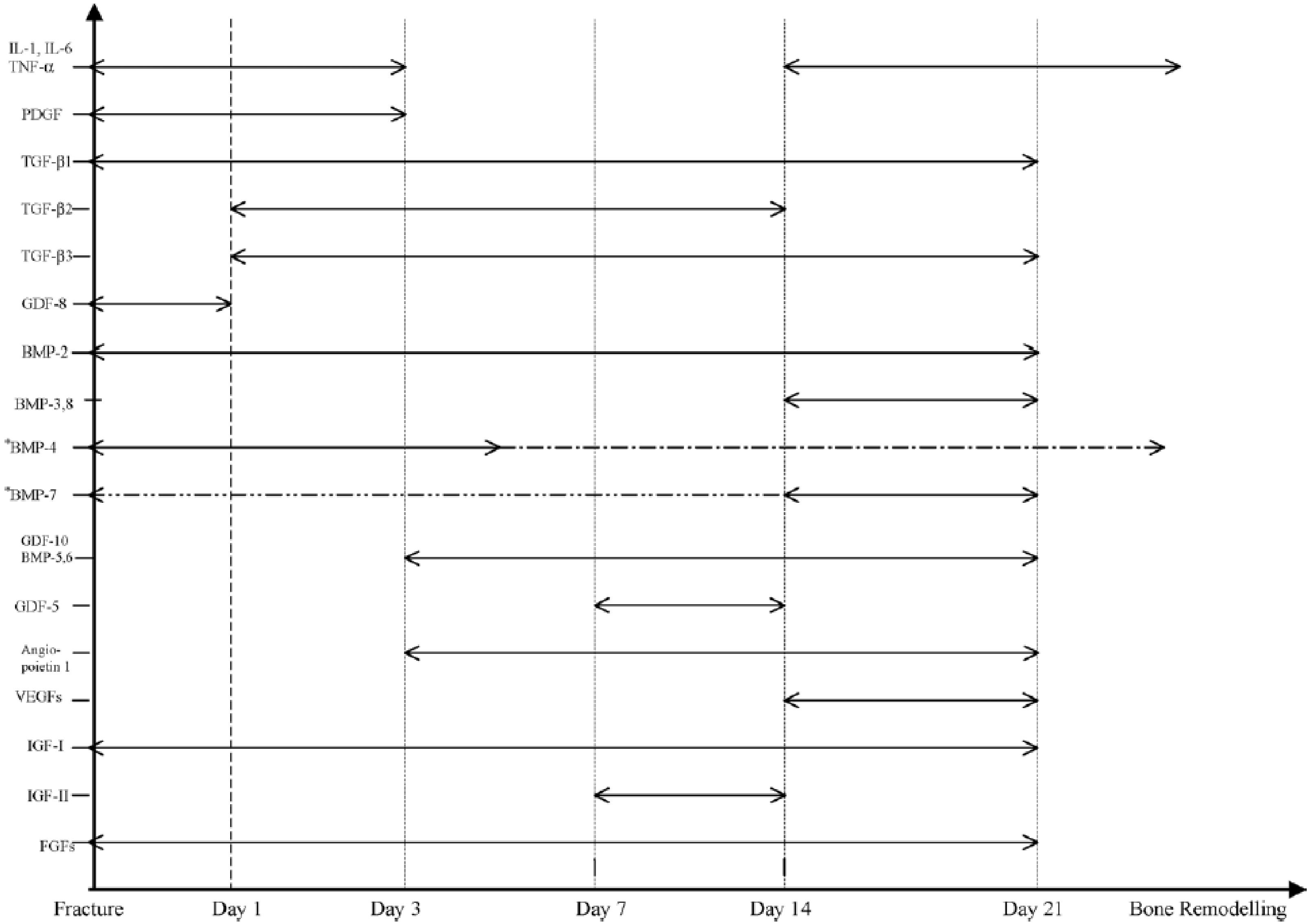
- Source: the extracellular matrix
- Degradation of the cartilage and bone allowing the invasion of blood vessels during the final stages of endochondral ossification and bone remodelling

VEGFs

- Potent stimulators of endothelial cell proliferation
- Expressed during endochondral formation and bone formation

Angiopoietin (1 and 2)

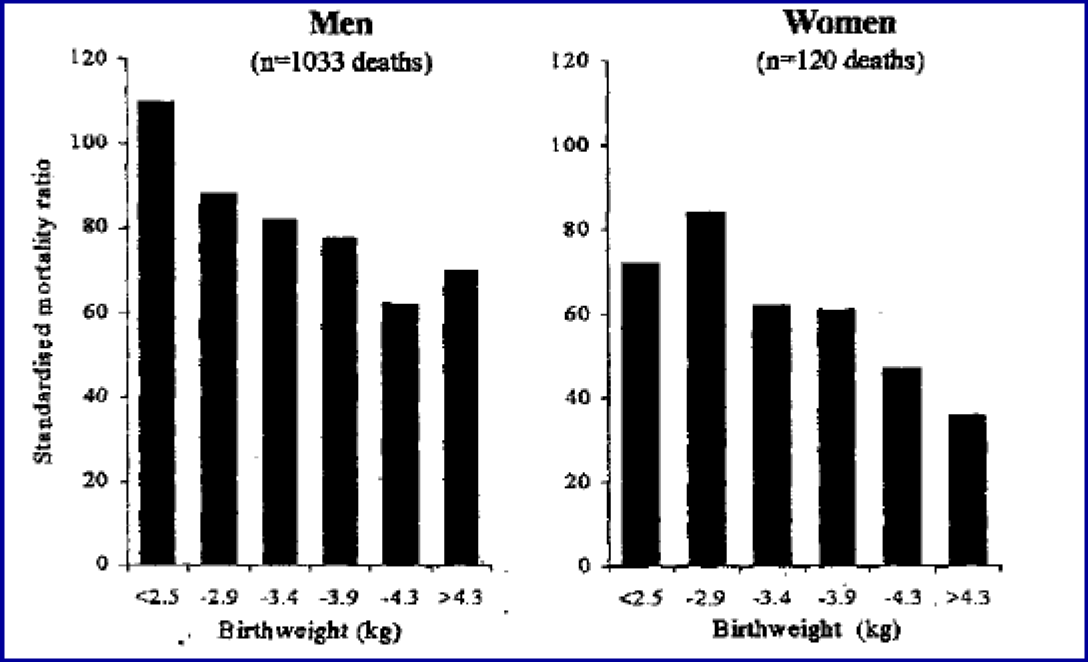
- Formation of larger vessel structures, development of co-lateral branches from existing vessels
- Expressed from the early stages throughout fracture healing



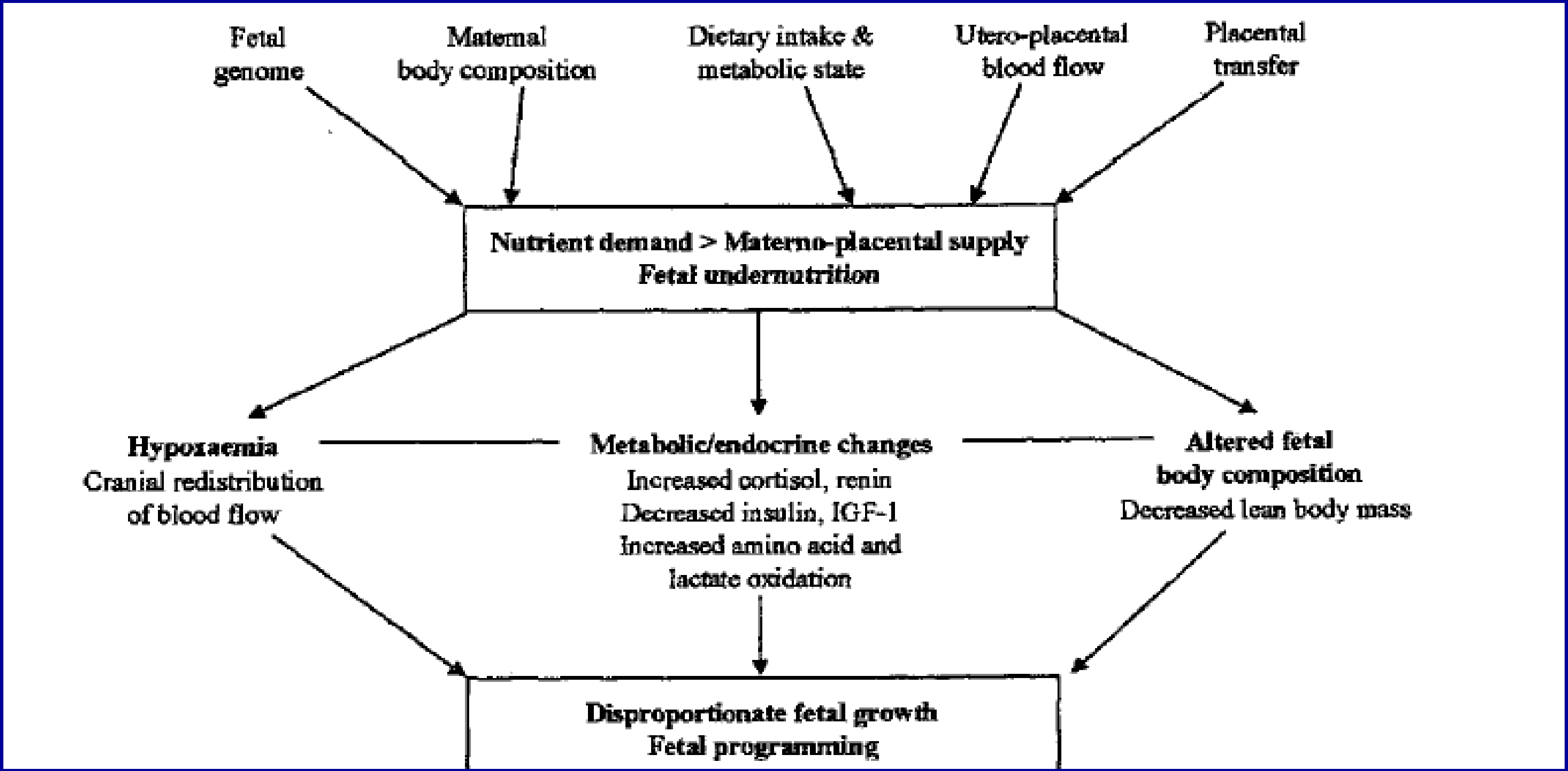
IL-1, IL-6
TNF-α
PDGF
TGF-β1
TGF-β2
TGF-β3
GDF-8
BMP-2
BMP-3,8
*BMP-4
*BMP-7
GDF-10
BMP-5,6
GDF-5
Angio-
poietin 1
VEGFs
IGF-I
IGF-II
FGFs
Fracture
Day 1
Day 3
Day 7
Day 14
Day 21
Bone Remodelling

D J BARKER

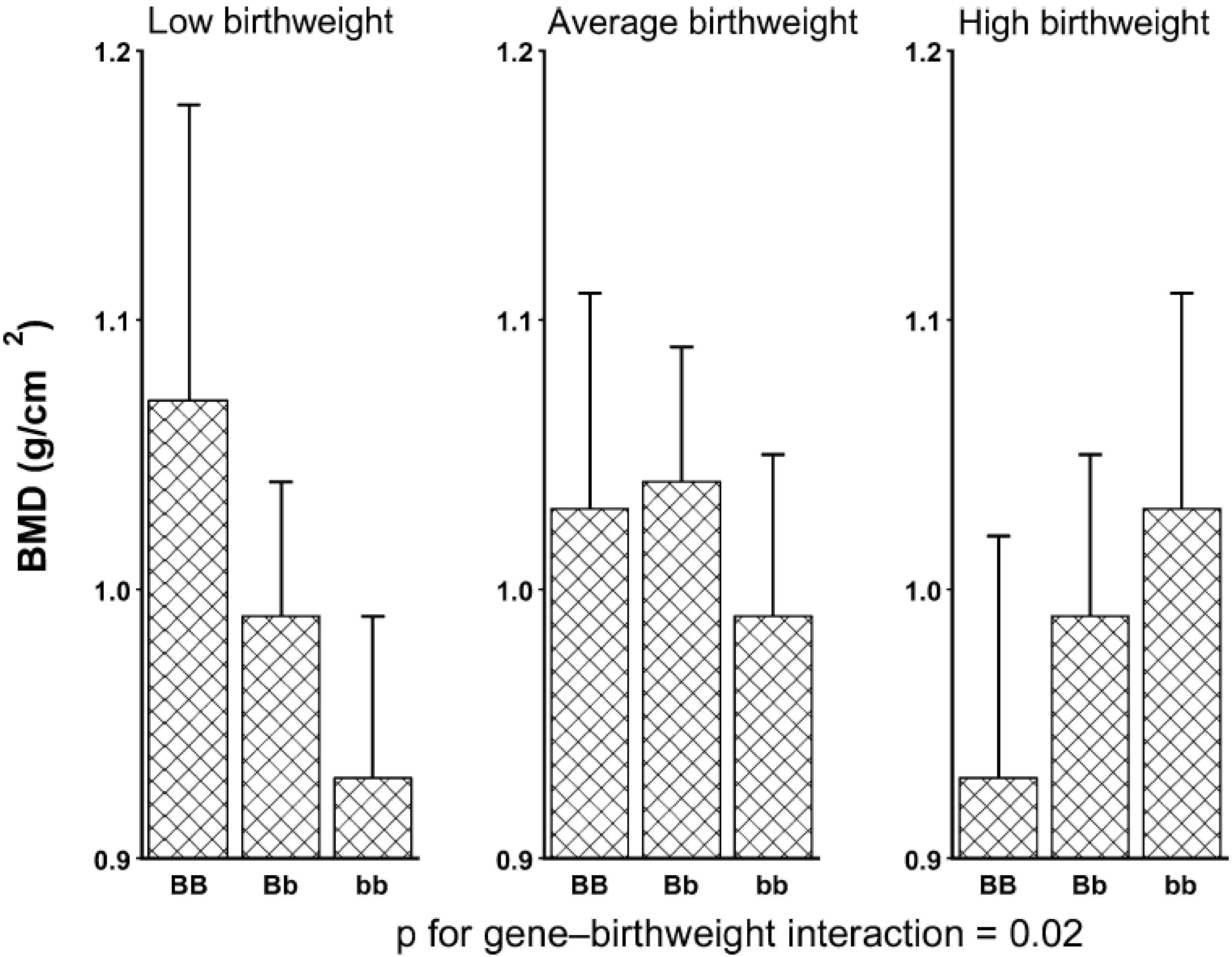
- Low birth-weight and development of metabolic syndrome



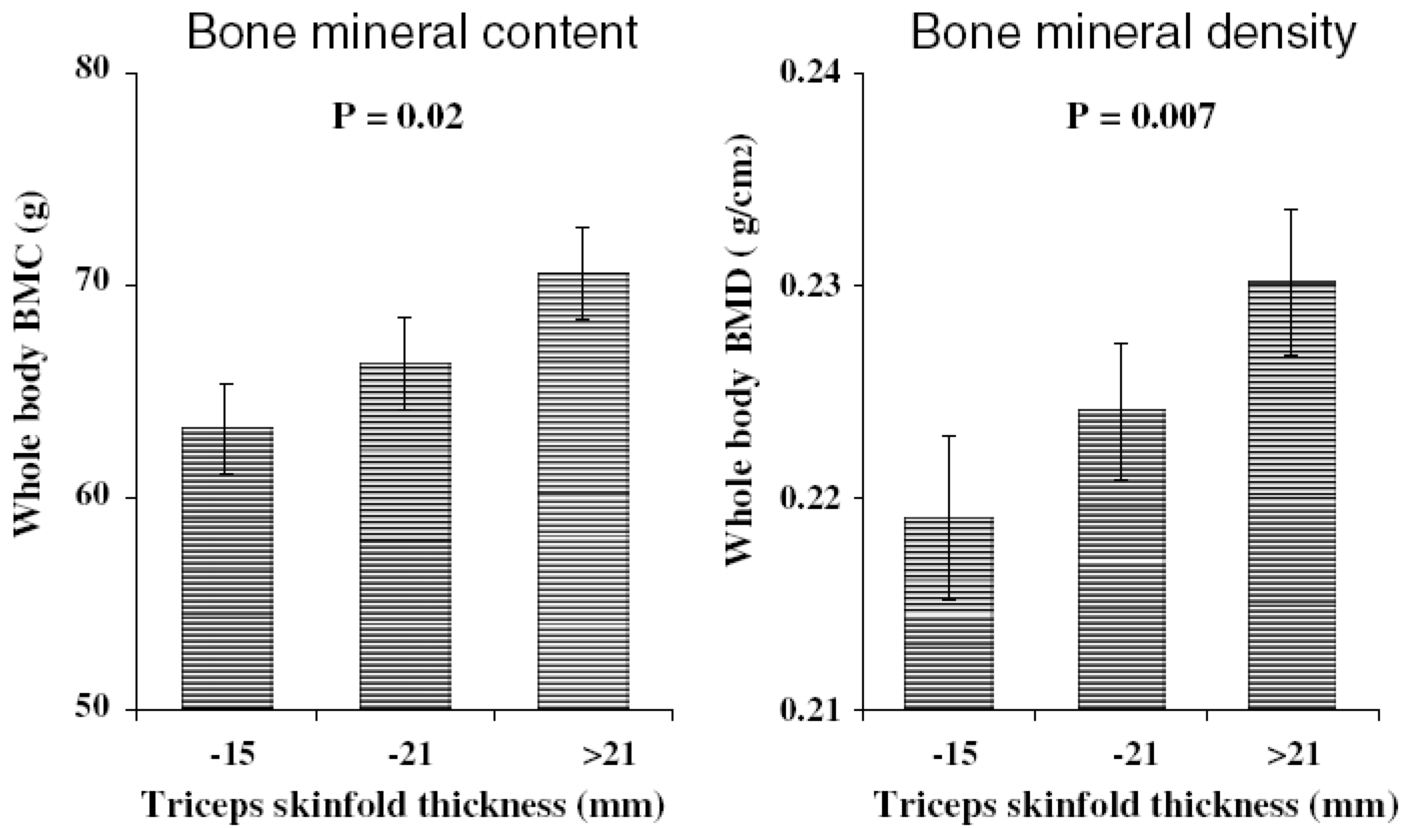
Men
(n=1033 deaths)
Women
(n=120 deaths)
Standardised mortality ratio
0
20
40
60
80
100
120
<2.5
-2.9
-3.4
-3.9
-4.3
>4.3
Birthweight (kg)



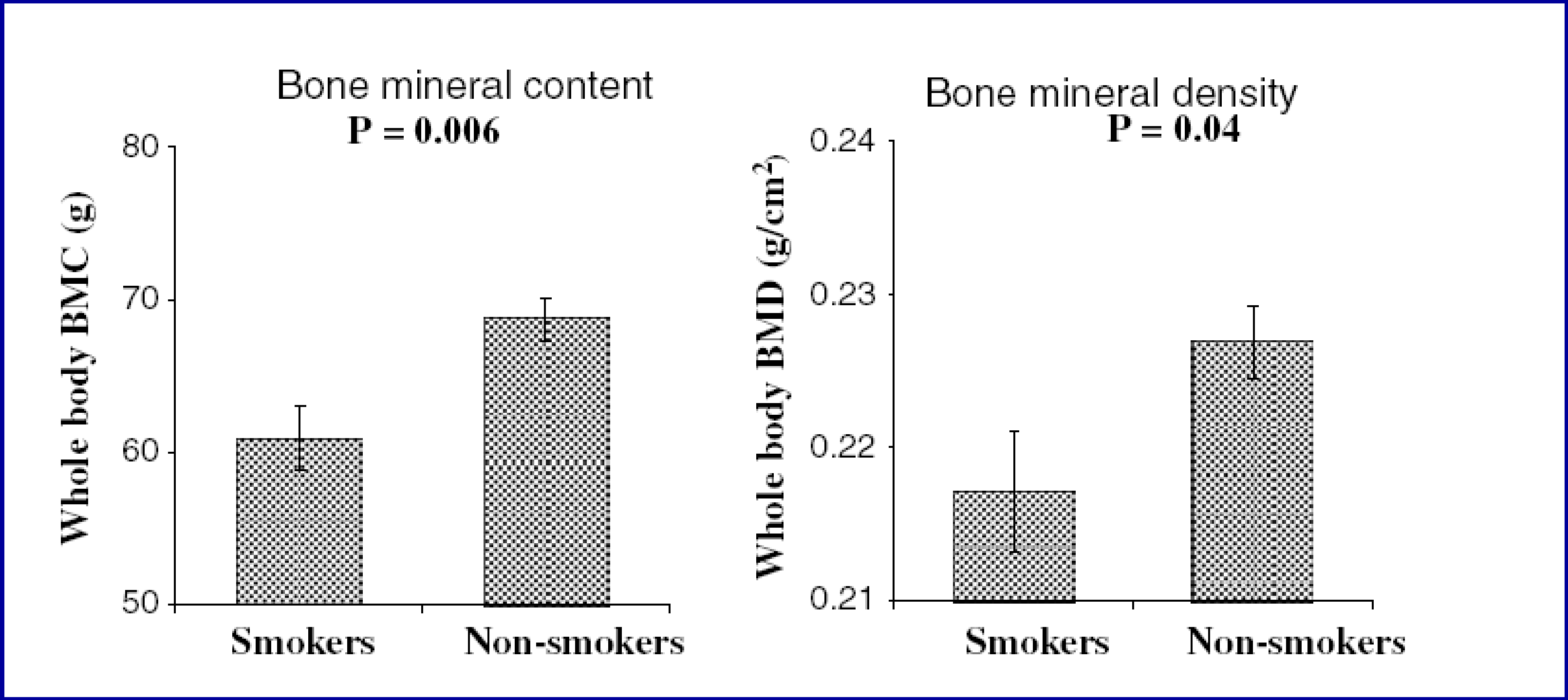
Fetal genome
Maternal body composition
Dietary intake & metabolic state
Utero-placental blood flow
Placental transfer
Nutrient demand > Materno-placental supply
Fetal undernutrition
Hypoxaemia
Cranial redistribution of blood flow
Metabolic/endocrine changes
Increased cortisol, renin
Decreased insulin, IGF-1
Increased amino acid and lactate oxidation
Altered fetal body composition
Decreased lean body mass
Disproportionate fetal growth
Fetal programming



Low birthweight
Average birthweight
High birthweight
BMD (g/cm 2)
1.2
1.1
1.0
0.9
BB
Bb
bb
p for gene–birthweight interaction = 0.02



Bone mineral content
P = 0.02
Whole body BMC (g)
80
70
60
50
-15
-21
>21
Triceps skinfold thickness (mm)
Bone mineral density
P = 0.007
Whole body BMD (g/cm2)
0.24
0.23
0.22
0.21
-15
-21
>21
Triceps skinfold thickness (mm)



Bone mineral content
P = 0.006
Whole body BMC (g)
80
70
60
50
Smokers
Non-smokers
Bone mineral density
P = 0.04
Whole body BMD (g/cm2)
0.24
0.23
0.22
0.21
Smokers
Non-smokers

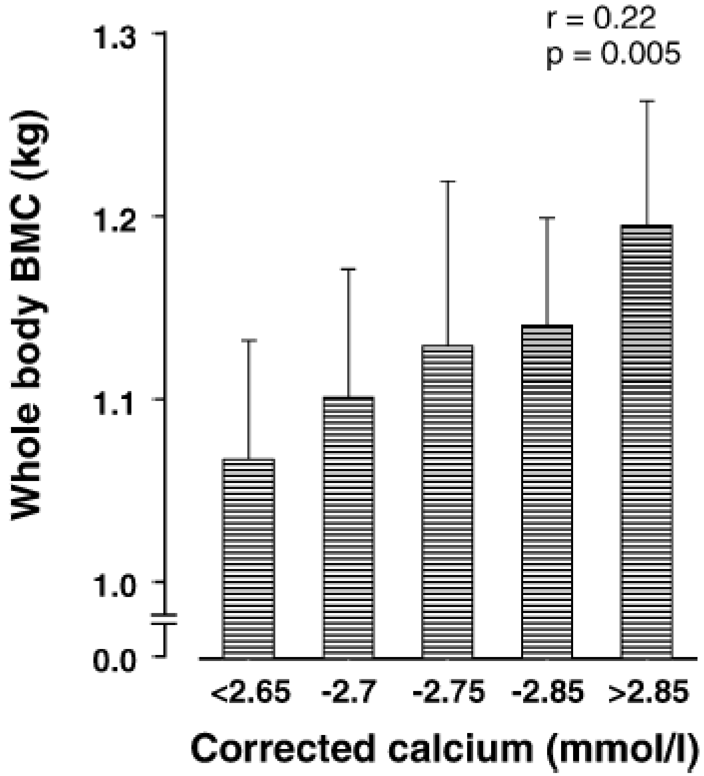


Fig. 7 Nine-year whole body bone mineral content by corrected cord blood calcium. Data derived from Javaid et al. [55]

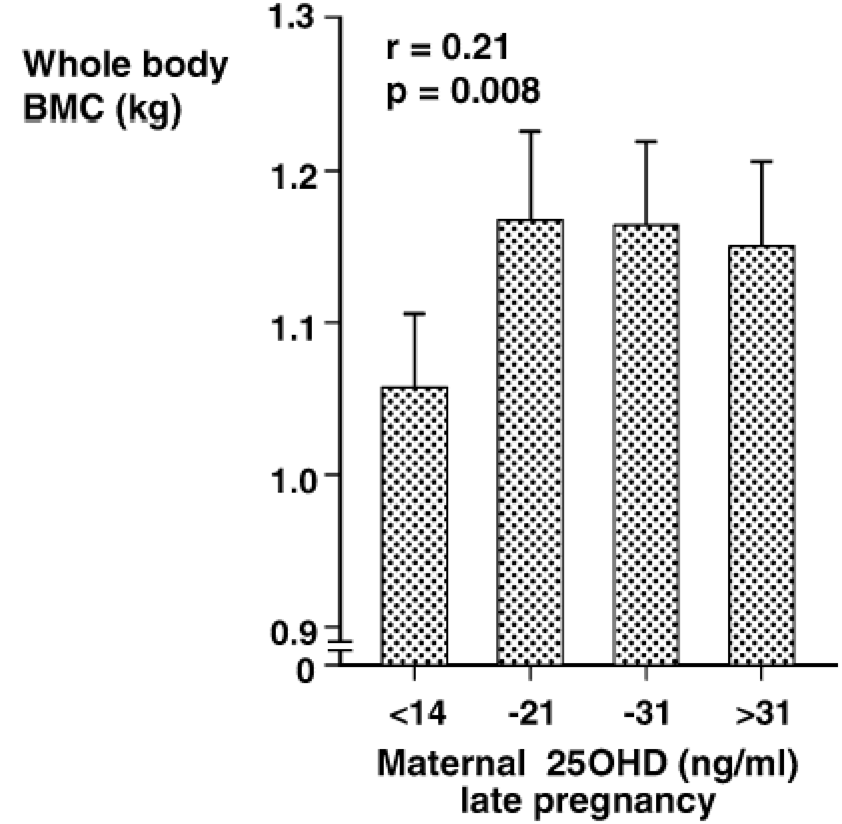


Fig. 8 Maternal 25(OHD) during late pregnancy and whole-body bone mineral content of offspring 9 years later. Data derived from Javaid et al. 2004 [55]

CLINICAL REVIEW 137

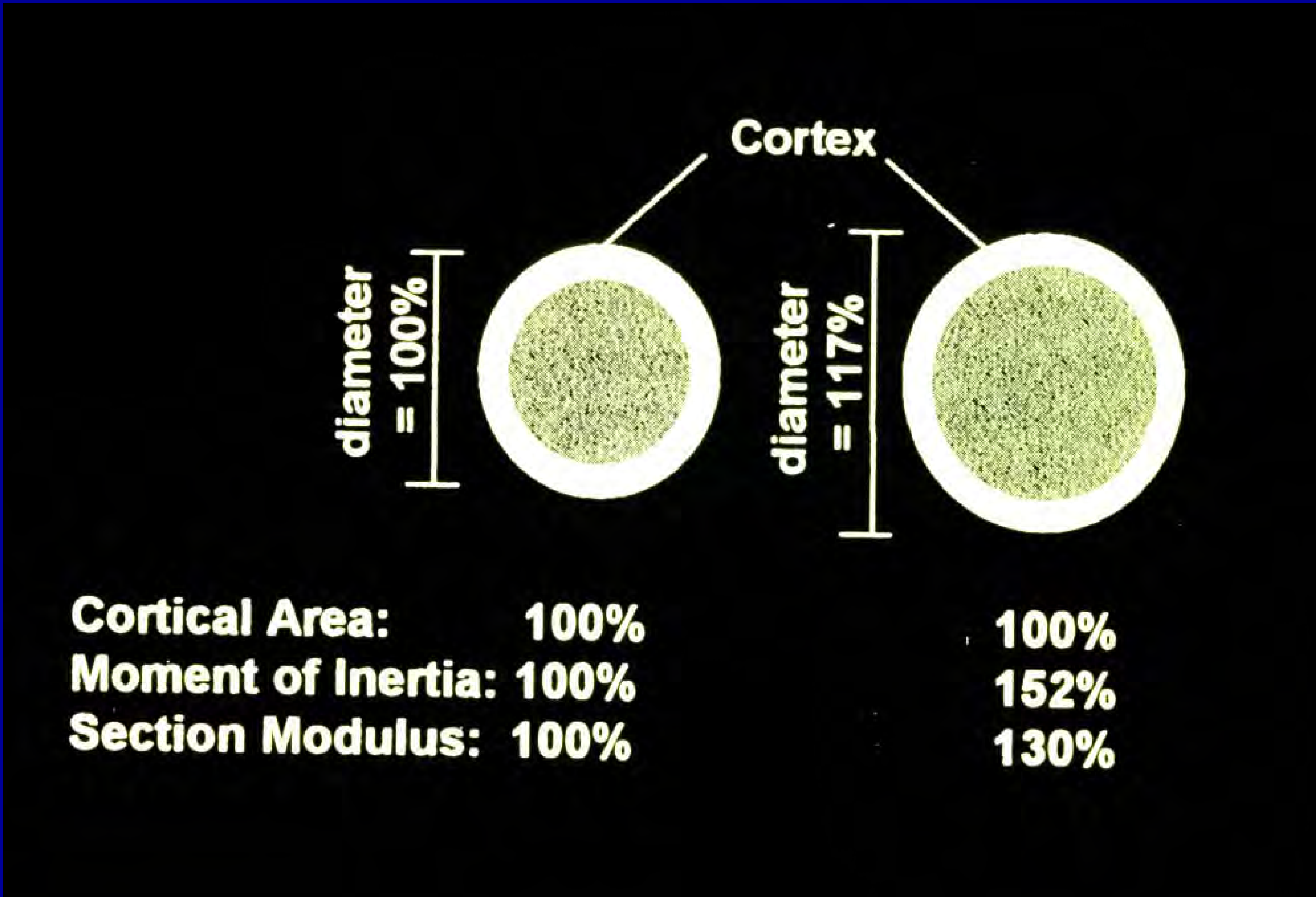
Sexual Dimorphism in Skeletal Size, Density, and Strength

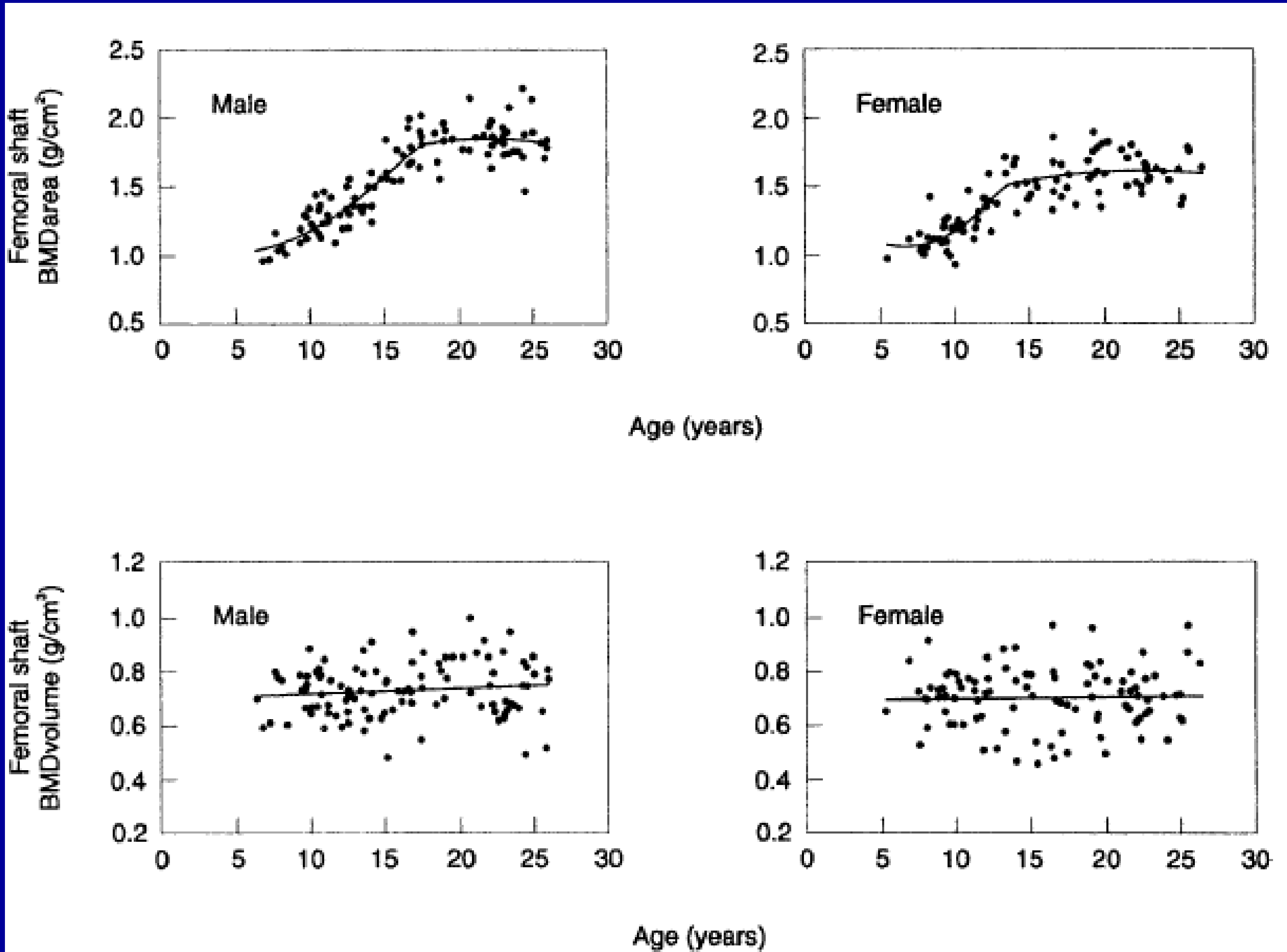
EGO SEEMAN

Department of Endocrinology and Medicine, Austin and Repatriation Medical Centre, University of Melbourne, 3084 Melbourne, Australia

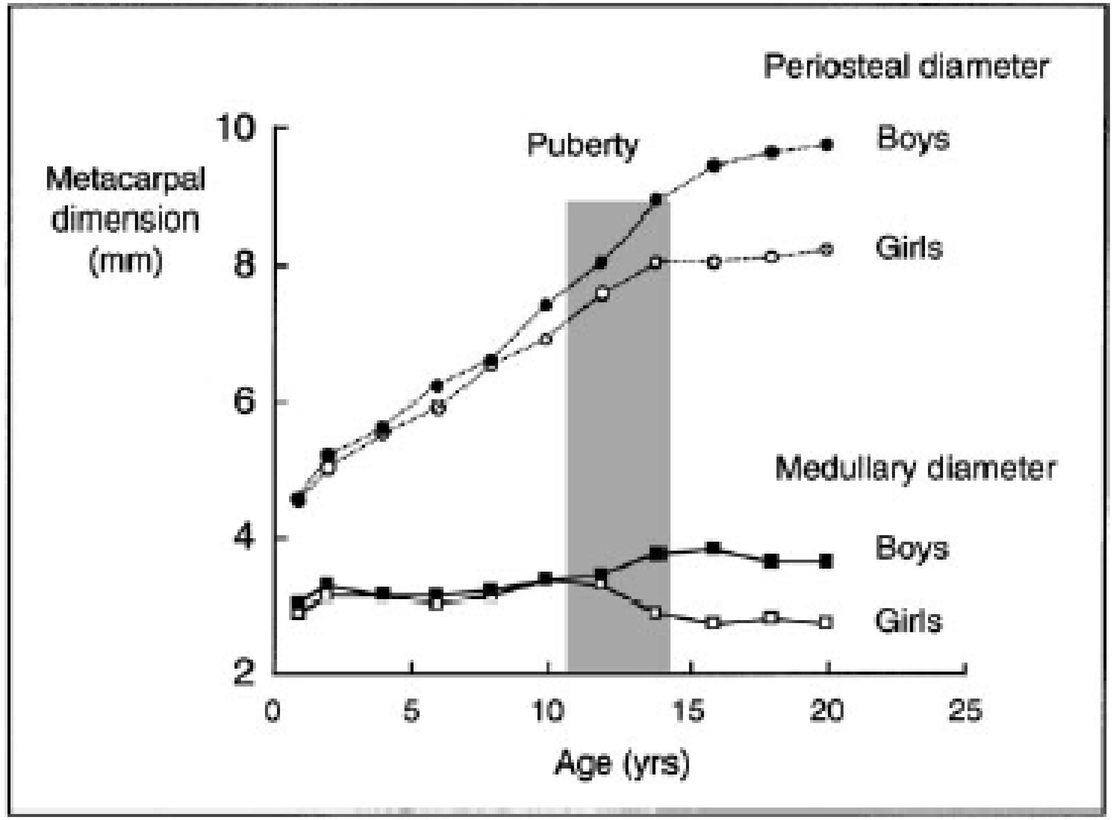
Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?
From *The Rock* by T. S. Eliot

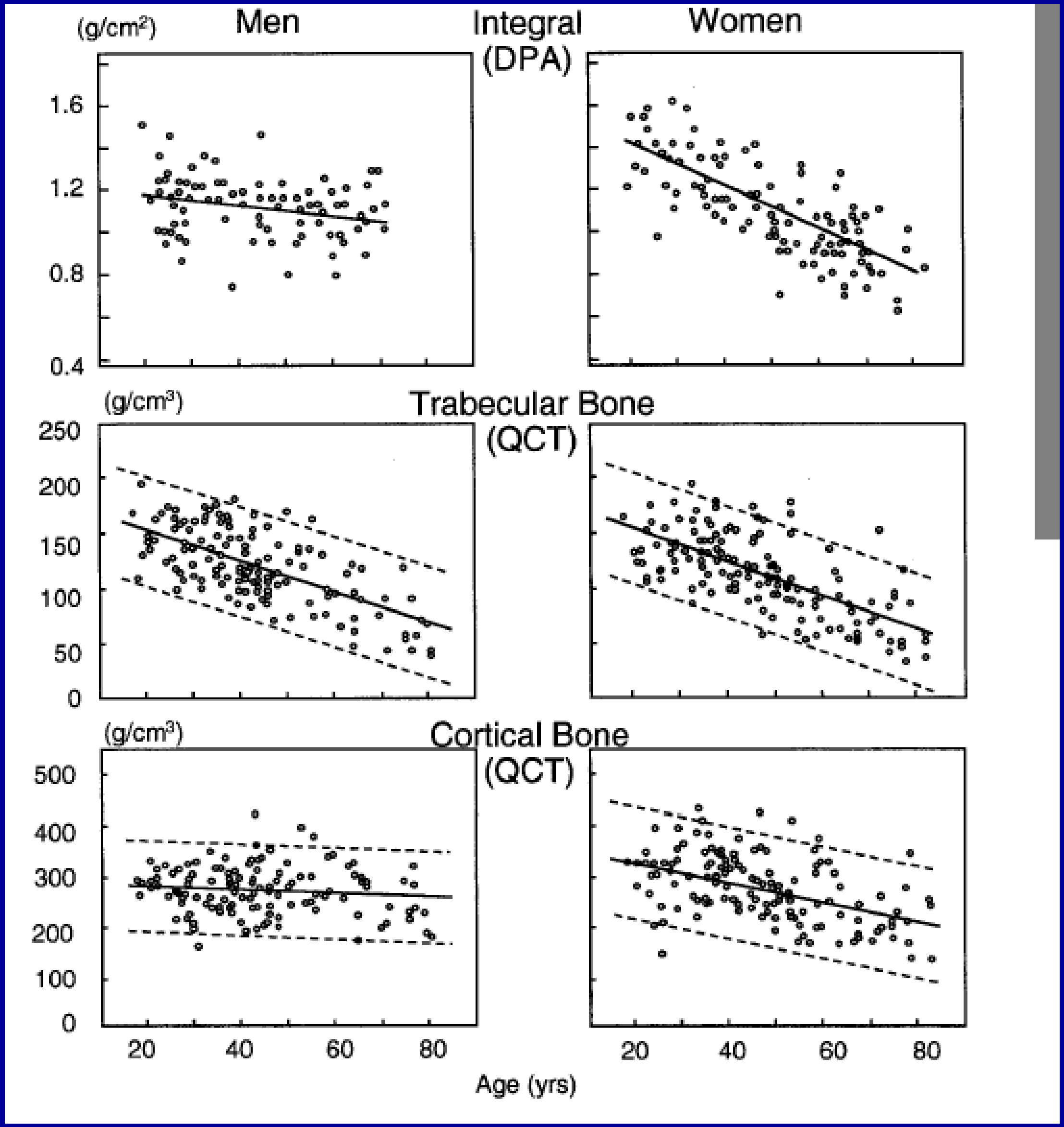
marrow cavity. Only the mineralized mass of bone is seen by the photons so that the degree of attenuation of the photons during their transmission through the bone is a measure of


Cortex
diameter = 100%
diameter = 117%
Cortical Area: 100%
100%
Moment of Inertia: 100%
152%
Section Modulus: 100%
130%



Male
Female
Femoral shaft BMDarea (g/cm²)
Femoral shaft BMDvolume (g/cm³)
Age (years)
Age (years)


Periosteal diameter
Boys
Girls
Puberty
Metacarpal dimension (mm)
10
8
6
4
2
Medullary diameter
Boys
Girls
0
5
10
15
20
25
Age (yrs)

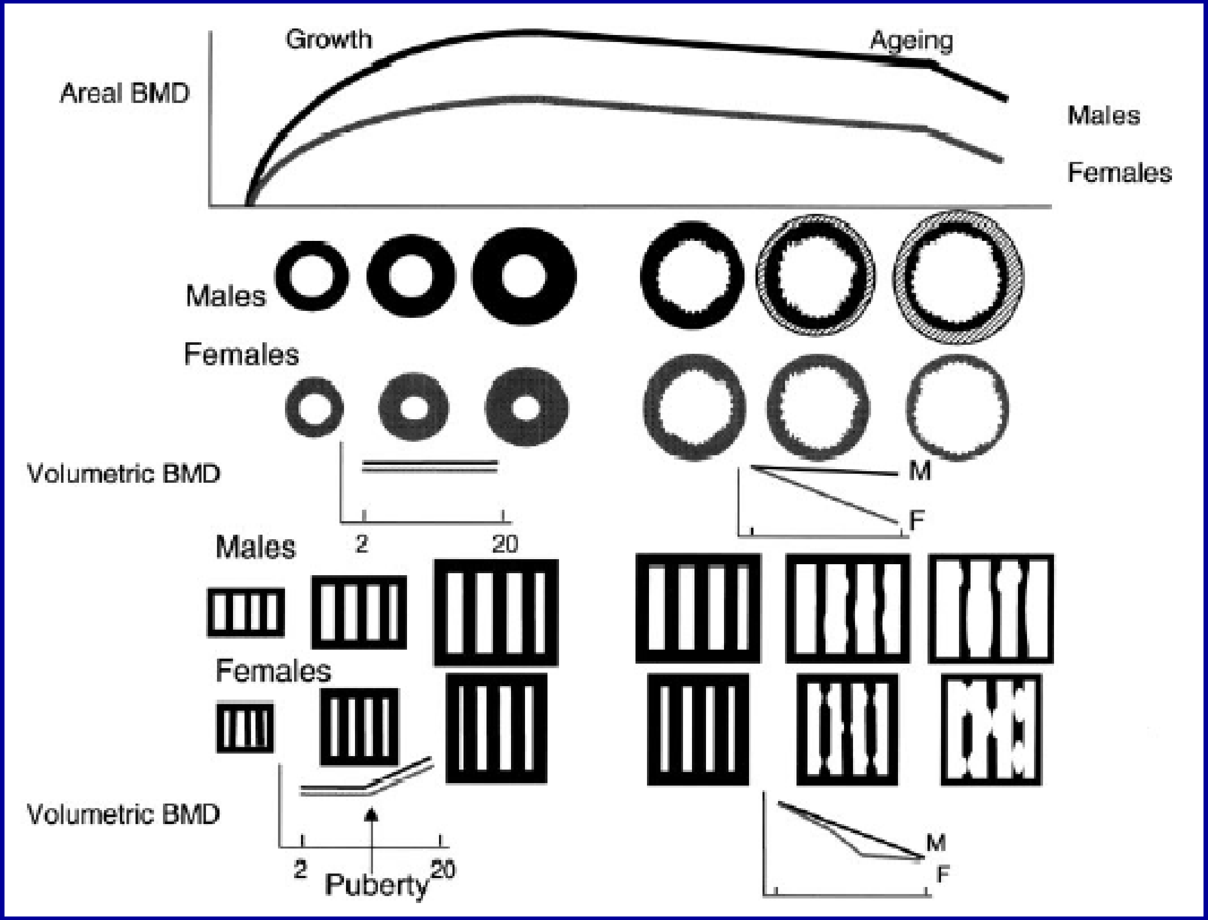

Men
Integral
(DPA)
Women
(g/cm2)
1.6
1.2
0.8
0.4
Trabecular Bone
(QCT)
(g/cm3)
250
200
150
100
50
0
Cortical Bone
(QCT)
(g/cm3)
500
400
300
200
100
0
20
40
60
80
Age (yrs)

Review

Weight-bearing exercise and bone mineral accrual in children and adolescents: A review of controlled trials

K. Hind [a,*], M. Burrows [b]

Results: Twenty-two trials were reviewed. Nine were conducted in prepubertal children (Tanner I), 8 in early pubertal (Tanner II–III) and 5 in pubertal (Tanner IV–V). Sample sizes ranged from $n = 10$ to 65 per group. Exercise interventions included games, dance, resistance training and jumping exercises, ranging in duration from 3 to 48 months. Approximately half of the trials ($n = 10$) included ground reaction force (GRF) data (2 to 9 times body weight). All trials in early pubertal children, 6 in pre pubertal and 2 in pubertal children, reported positive effects of exercise on bone ($P < 0.05$). Mean increases in bone parameters over 6 months were 0.9–4.9% in prepubertal, 1.1–5.5% in early pubertal and 0.3–1.9% in pubertal exercisers compared to controls ($P < 0.05$).



Growth
Ageing
Areal BMD
Males
Females
Males
Females
Volumetric BMD
M
F
2
20
Males
Females
Volumetric BMD
M
F
2
Puberty
20

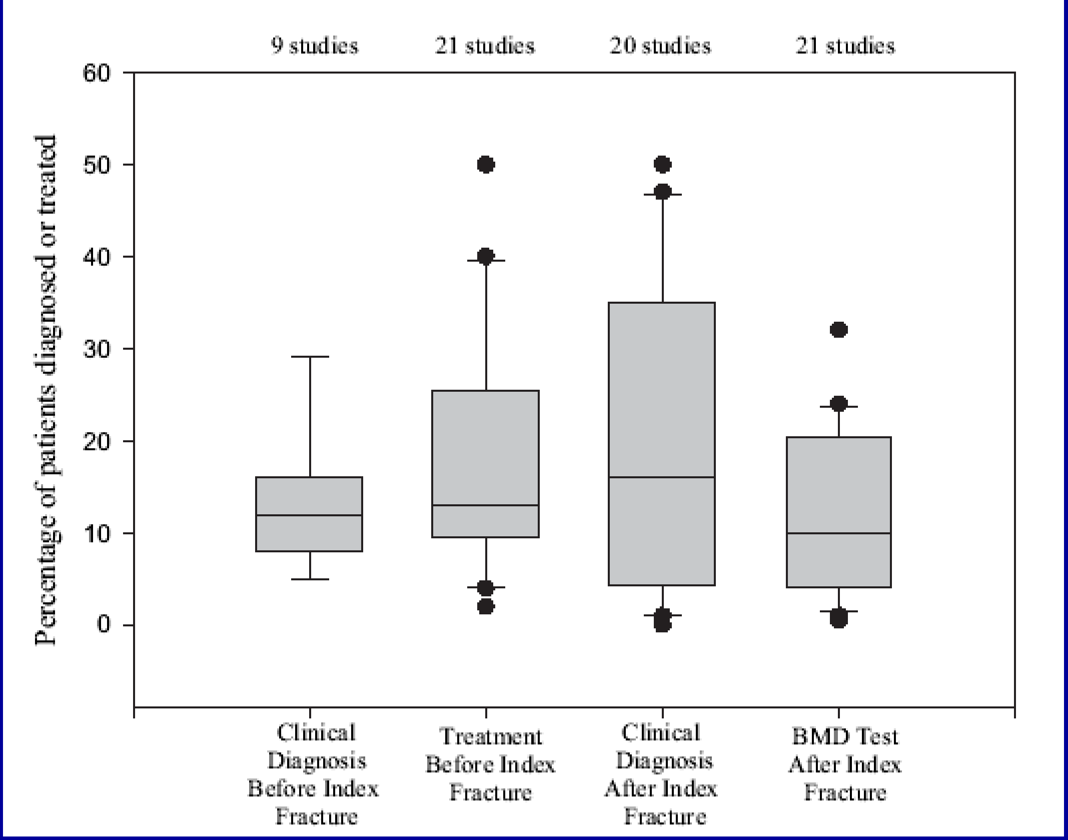
Recommendations for bone densitometry

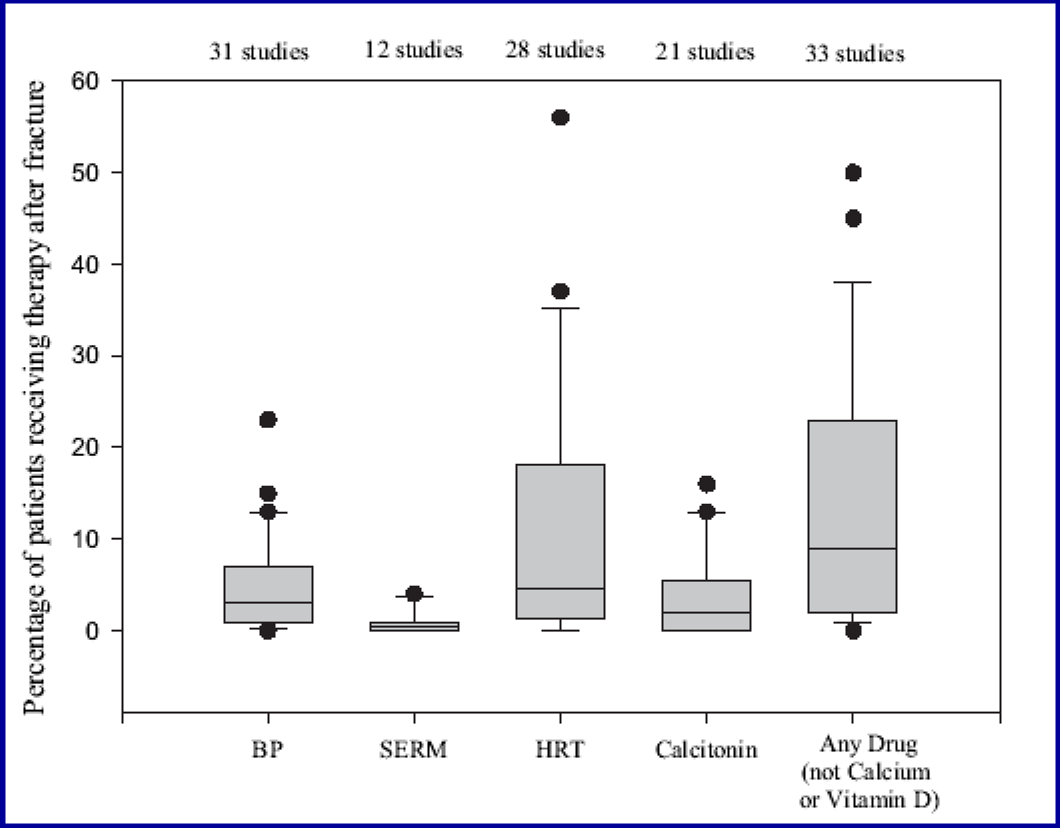
- *Radiographic evidence of osteopenia and/or vertebral deformity*
- *Loss of height, thoracic kyphosis*
- *Previous low-trauma fracture (i.e. a fall from standing height)*
- *Prolonged corticosteroid therapy*
- *Hypogonadism in either sex (possibly to include most menopausal women)*
- *Chronic disorders associated with osteoporosis (e.g. hyperthyroidism and hyperparathyroidism)*
- *A maternal history of hip fracture*
- *A low body mass index*
- *A low calcium intake*

Indicazioni alla misurazione della massa ossea

- *Menopausa prematura (<45 anni)*
- *Amenorrea secondaria > 6 mesi*
- *Ipogonadismo primario*
- *Terapia con corticosteroidi (>7.5 mg/die per 1 anno)*
- *Condizioni associate ad osteoporosi*
  - *Anoressia nervosa*
  - *Malassorbimento*
  - *Iperparatiroidismo primario*
  - *Trapianto*
  - *Insufficienza renale cronica*
  - *Osteogenesi imperfetta*
  - *Neoplasie*
  - *Ipertiroidismo*
  - *Immobilizzazione prolungata*
  - *Sindrome di Cushing*

EFFO Guidelines, 1996

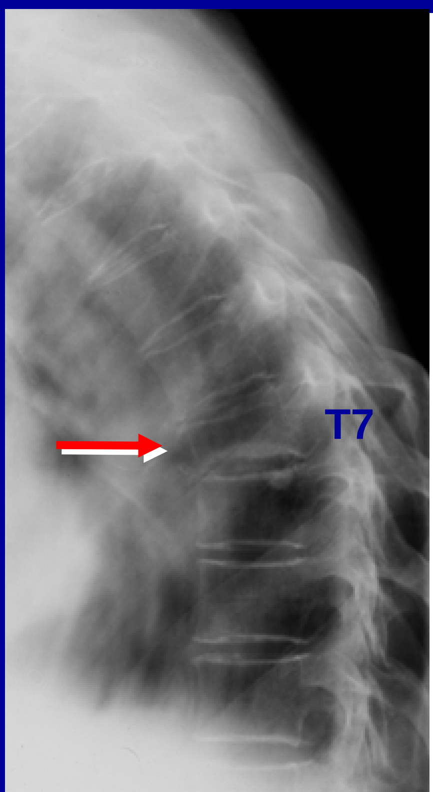

9 studies
21 studies
20 studies
21 studies
Percentage of patients diagnosed or treated
60
50
40
30
20
10
0
Clinical Diagnosis Before Index Fracture
Treatment Before Index Fracture
Clinical Diagnosis After Index Fracture
BMD Test After Index Fracture

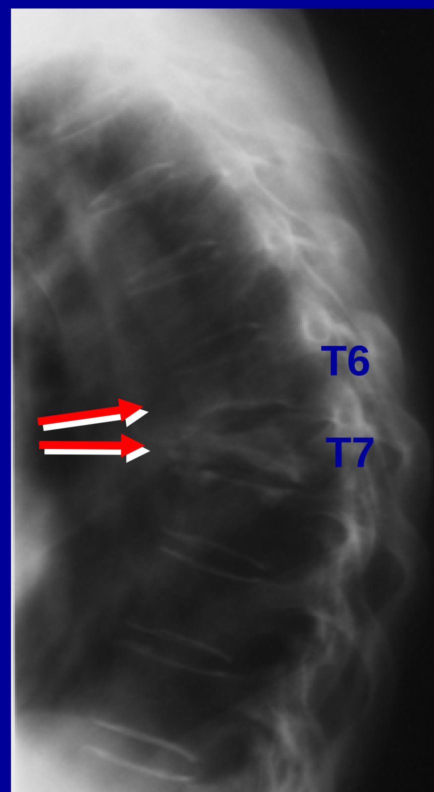

31 studies
12 studies
28 studies
21 studies
33 studies
Percentage of patients receiving therapy after fracture
60
50
40
30
20
10
0
BP
SERM
HRT
Calcitonin
Any Drug
(not Calcium
or Vitamin D)

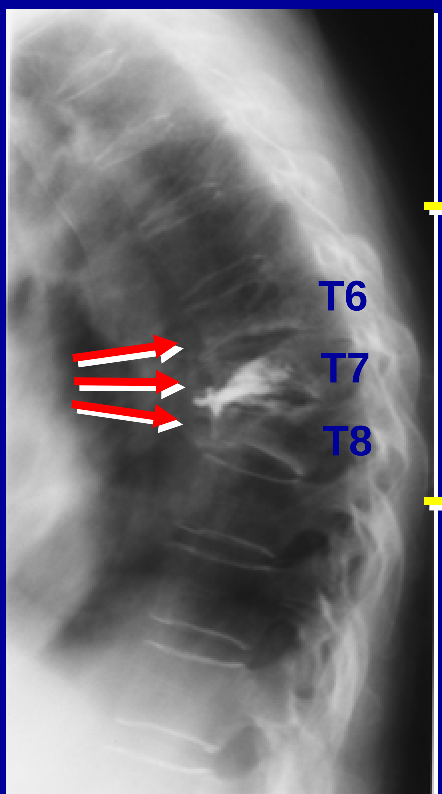
esperienza con pazienti polifratturate

le VCF (vertebral compression fracture) nell'osteoporosi severa

carico assiale e localizzazione delle VCF







Il concetto di normalità della 25-OH-Vitamina D

> 30 ng/ml (70-90 nmol/l) = Normale

12-30 ng/ml (40-70 nmol/l) = Insufficiente

5-12 ng/ml (20-40 nmol/l) = Deficit-Carenza

<5 ng/ml (<20 nmol/l) = Severa carenza

Review

TRENDS in Molecular Medicine Vol.12 No.1 January 2006

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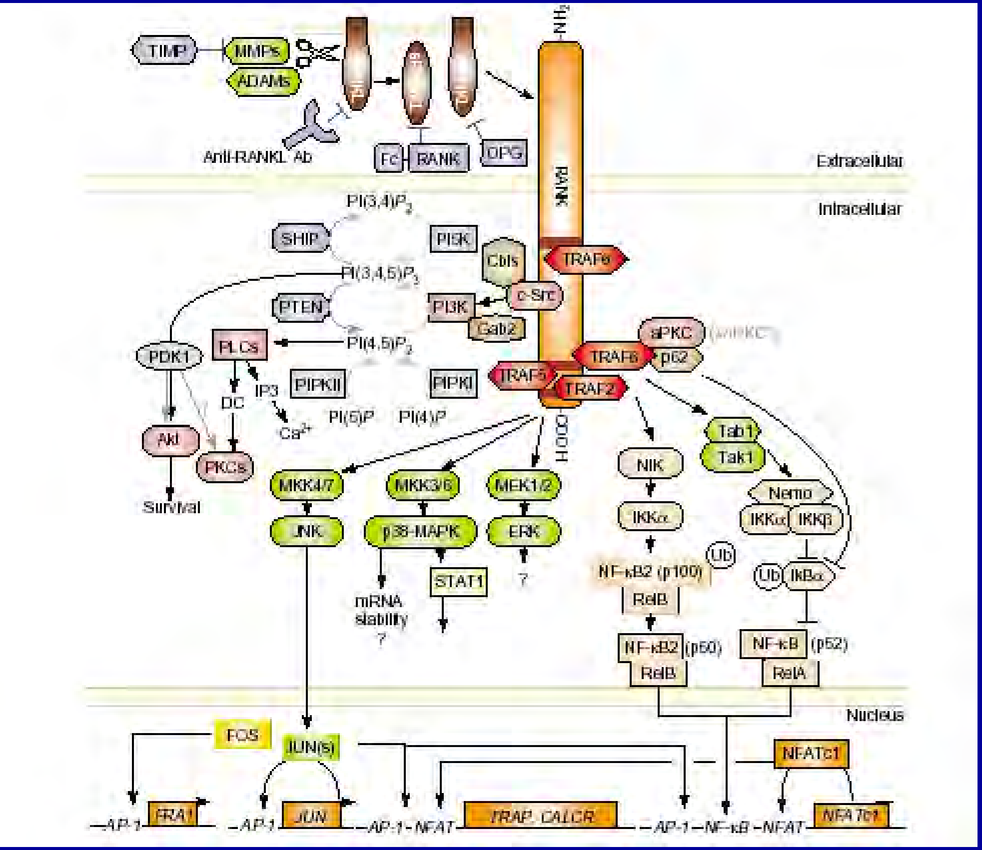
SCIENCE DIRECT

RANKL–RANK signaling in osteoclastogenesis and bone disease

Teiji Wada[1,2], Tomoki Nakashima[1], Nishina Hiroshi[2] and Josef M Penninger[1]

[1]Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA), Dr. Bohrgasse 3, A-1030 Vienna, Austria
[2]Department of Developmental and Regenerative Biology, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8510, Japan



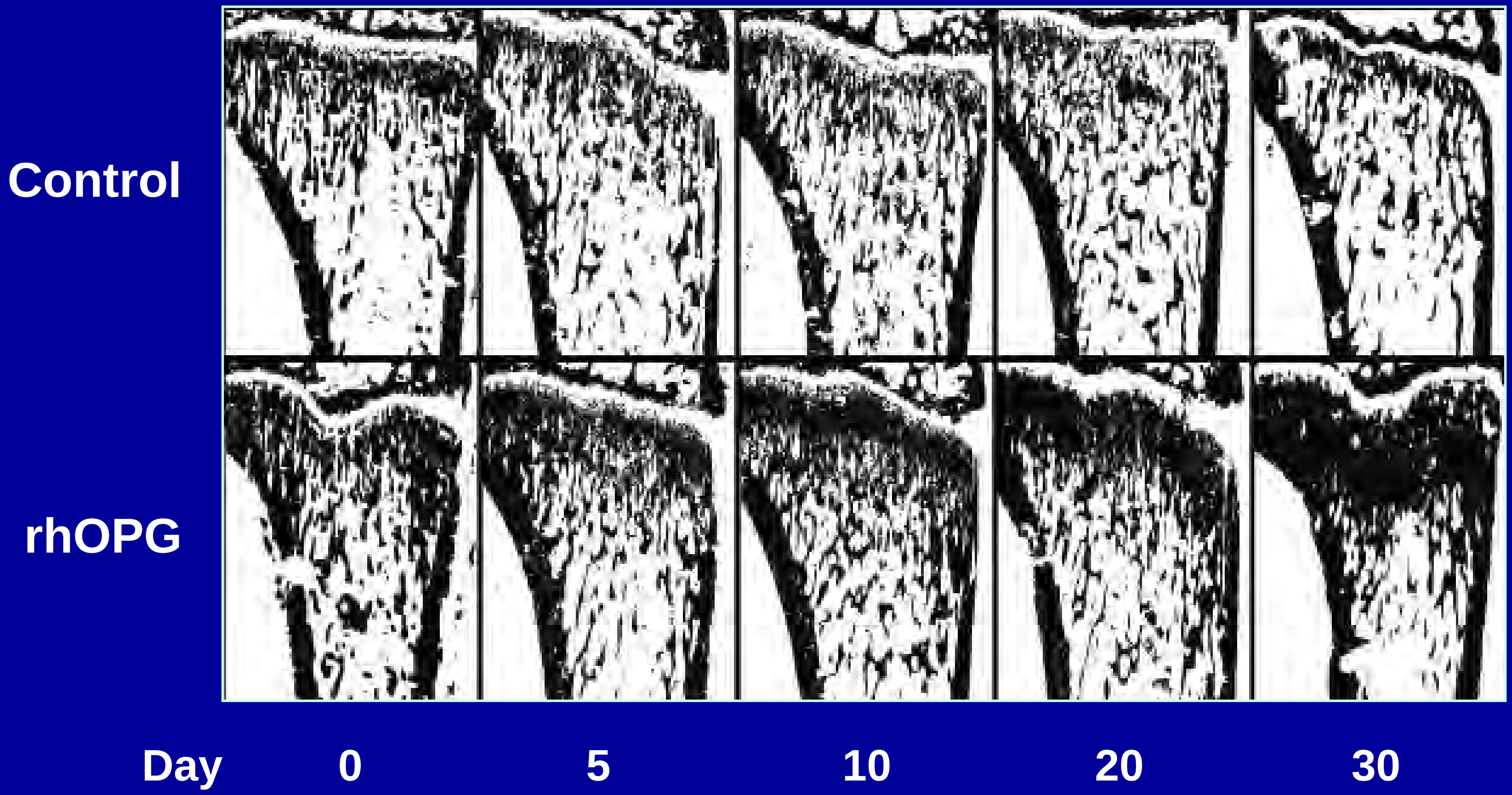
TIMP
MMPs
ADAMs
Anti-RANKL Ab
Fc
RANK
OPG
NH2
RANK
Extracellular
Intracellular
PI(3,4)P2
SHIP
PI5K
Cbls
TRAF6
PI(3,4,5)P3
c-Src
PTEN
PI3K
Gab2
aPKC
p62
PI(4,5)P2
PDK1
PLCs
TRAF6
TRAF5
TRAF2
IP3
PIPKII
PIPKI
DC
Ca2+
PI(5)P
PI(4)P
COOH
Akt
PKCs
Tab1
Tak1
NIK
Survival
MKK4/7
MKK3/6
MEK1/2
Nemo
IKKα
IKKβ
IKKα
JNK
p38-MAPK
ERK
Ub
NF-κB2 (p100)
Ub
IKBα
RelB
STAT1
?
mRNA
stability
?
NF-κB2 (p50)
RelB
NF-κB (p52)
RelA
Nucleus
FOS
JUN(s)
NFATc1
AP-1
FRA1
AP-1
JUN
AP-1
NFAT
TRAP, CALCR
AP-1
NF-κB
NFAT
NFATc1

The Role of RANK Ligand Inhibition in Pathologic Bone Loss

Increased Bone Density Associated with Blockade of RANK Signaling

Radiographs of mouse femur.
Amgen, data on file.

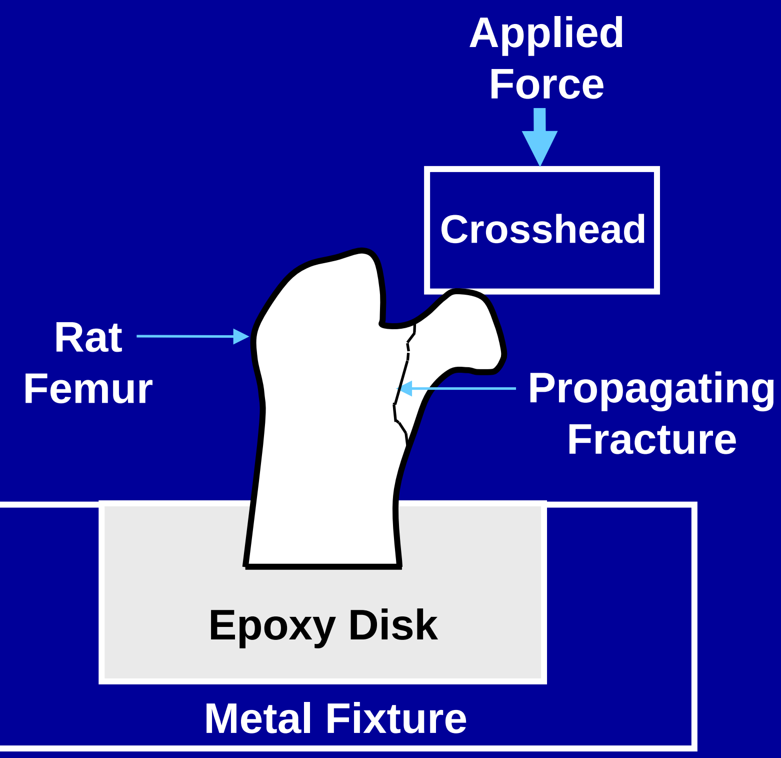
Bone Formed During RANK-L is Well Mineralized

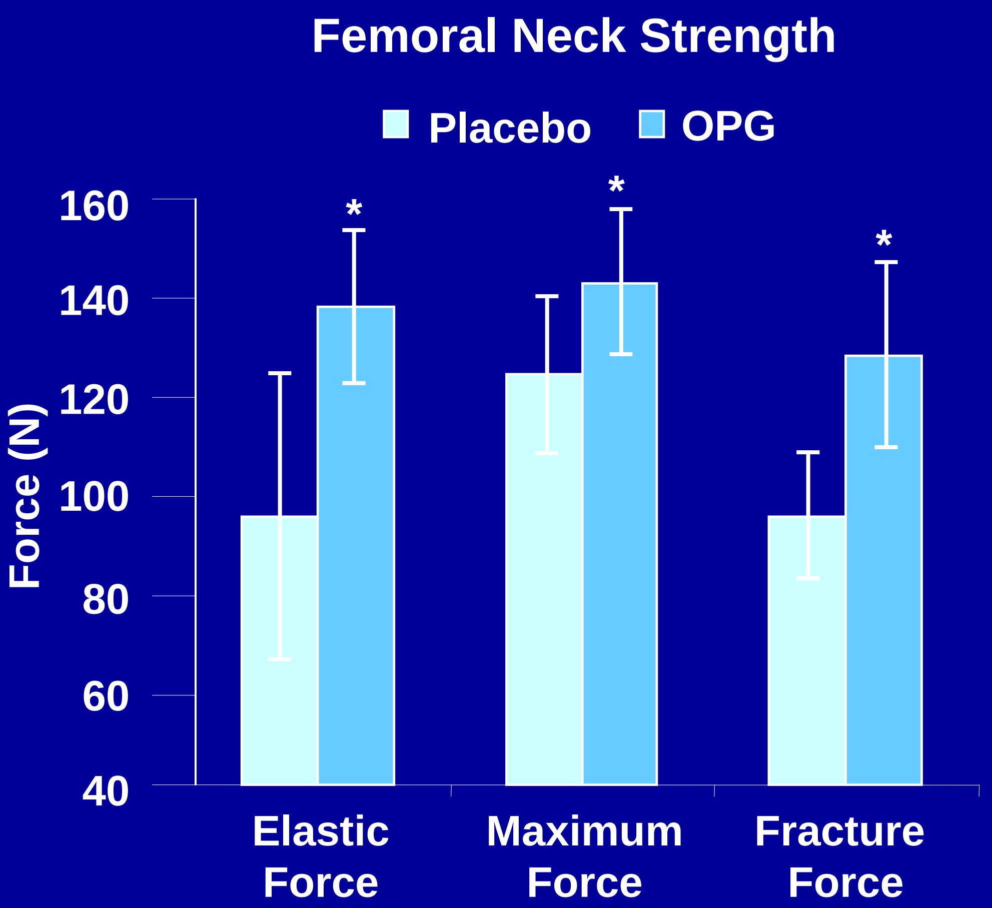


rhOPG = recombinant human OPG

Reproduced from Capparelli C, et al. *J Bone Miner Res.* 2003;18:852-8 with permission of the American Society for Bone and Mineral Research.

RANK-LInhibition and Neck Strength in Rats





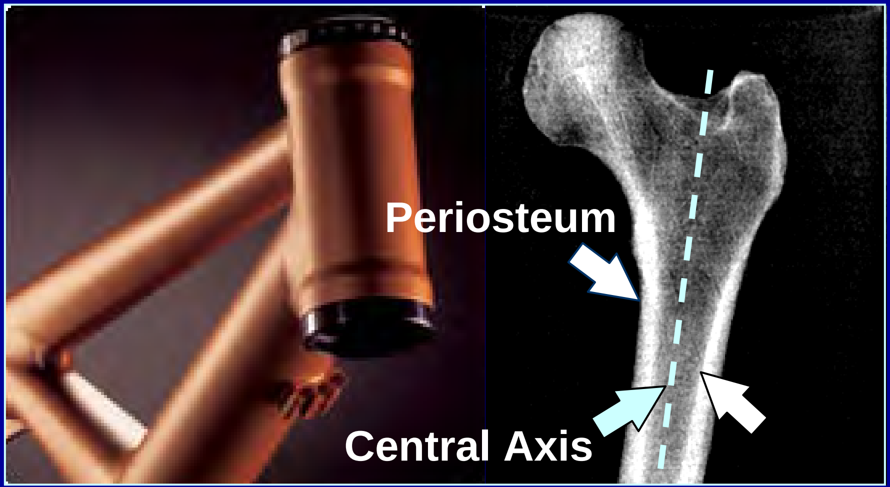
*Significantly greater than placebo, $P < 0.05$

Reproduced from Ross AB, et al. *J Mater Sci Mater Med.* 2001;12:583-8 with kind permission of Springer Science and Business Media.

The Importance of Bone Geometry for Cortical Strenght

- In general, wide tubes are stronger than narrow tubes due to a greater cross-sectional moment of inertia (CSMI)
- CSMI is an index of bone strength[1]
- Bone strength can be predicted by multiplying CSMI X BMD[1]

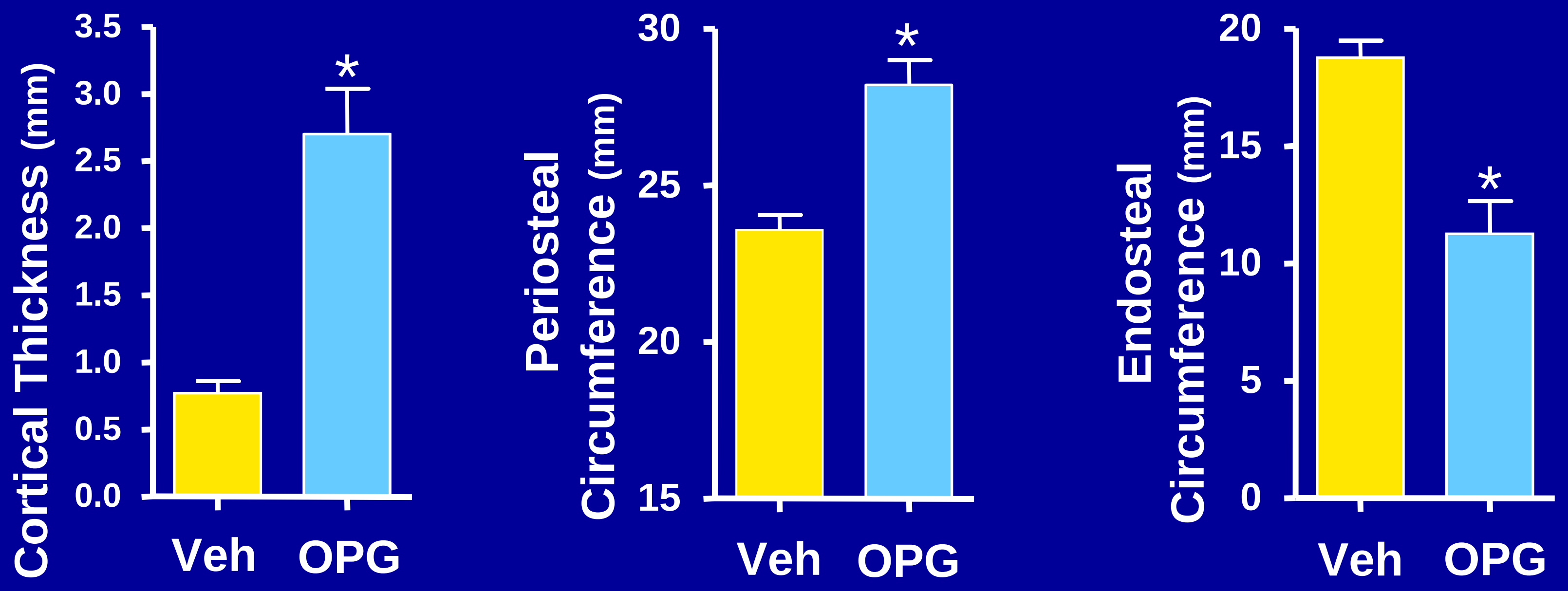
Bike frames are strong due to wide tubing



Periosteal expansion helps to maintain bone strength as we age

1. Ferretti JL, et al. *Bone. 1996;*18:97-102.

RANK Ligand Inhibition Increases Cortical Bone Area and Thickness in the Radius of Female Monkeys



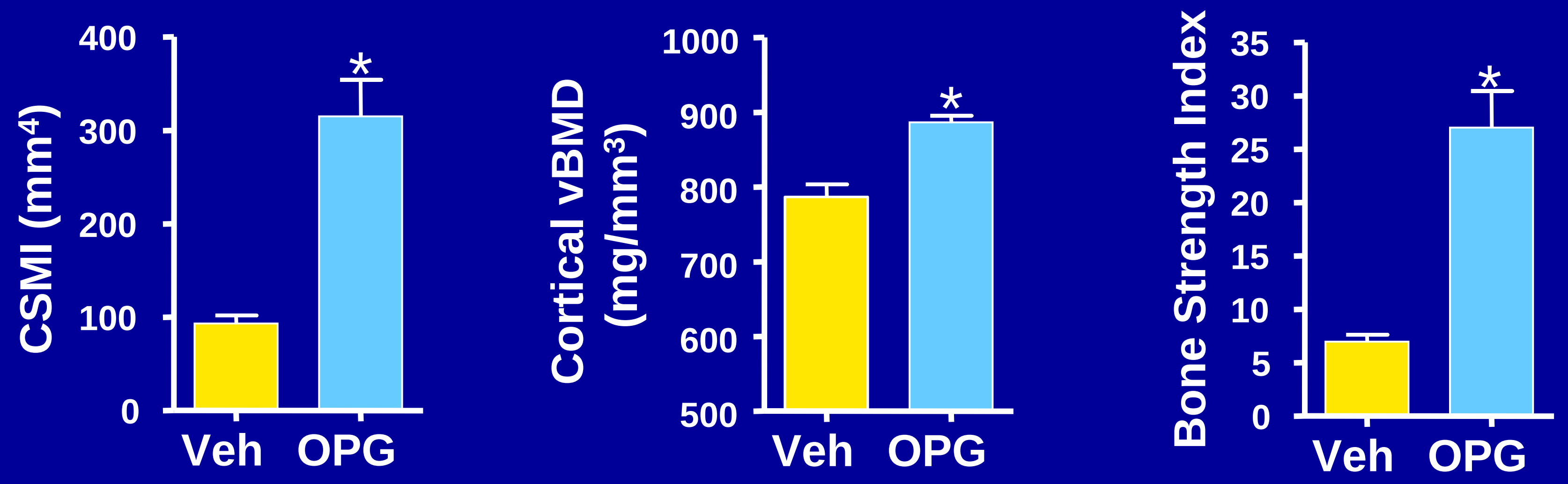
Veh = vehicle

*Significantly different from vehicle, $p<0.05$

Kostenuik PJ, et al. *Osteoporosis International.* 2005;16(Suppl 3):S68. Abstract P268

(BSI) in the Radius of Female Monkeys

CSMI x BMD = Bone SI

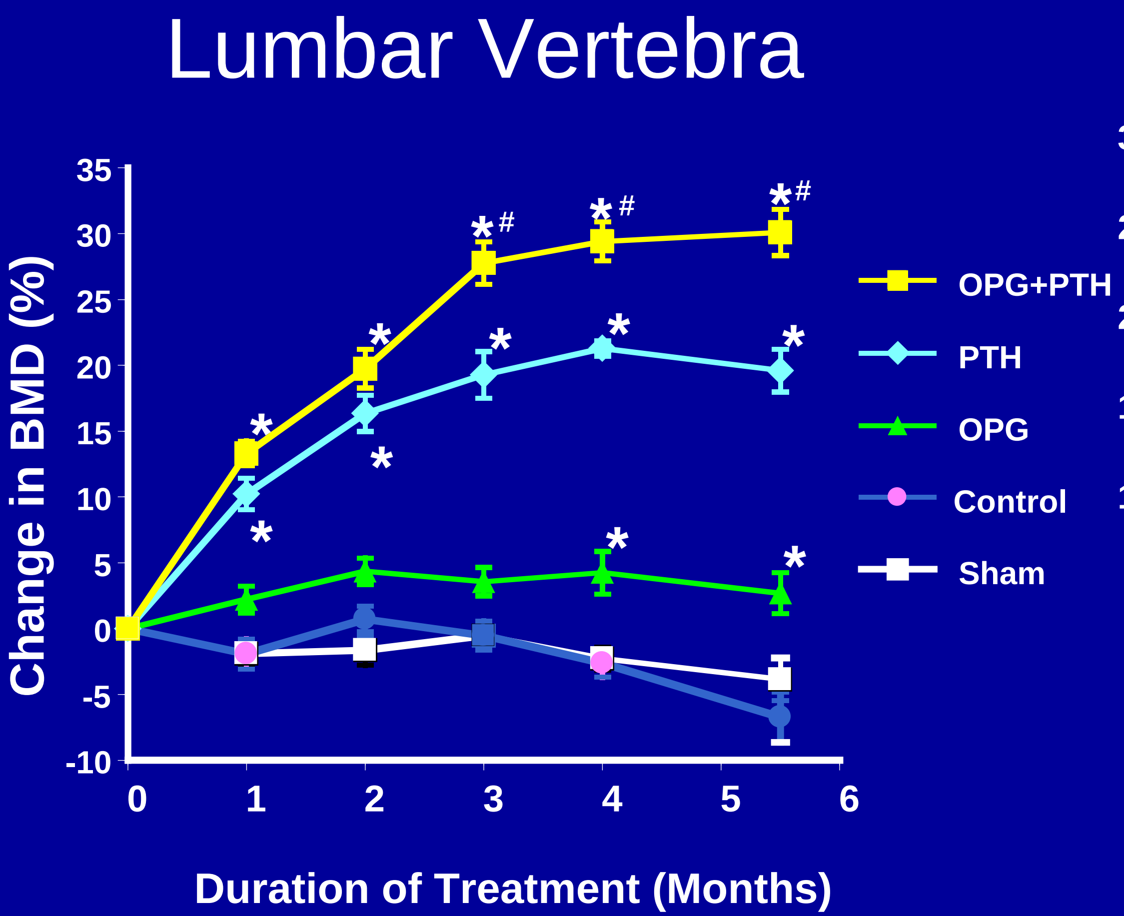


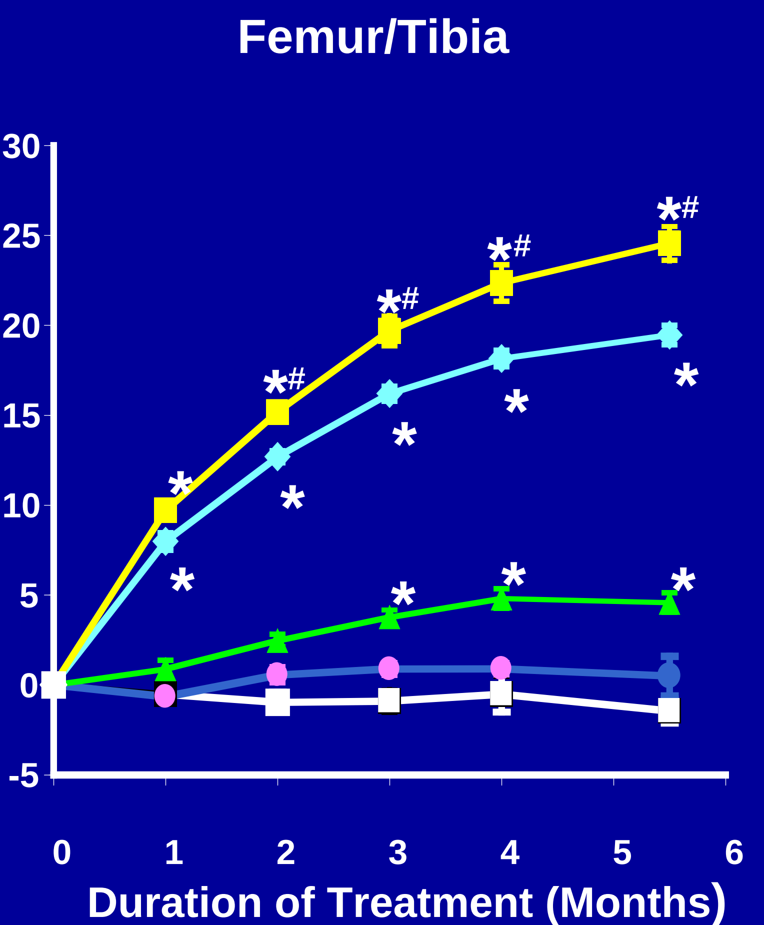
Veh = vehicle

*Significantly different from vehicle, $p<0.05$

Kostenuik PJ, et al. *Osteoporosis International.* 2005;16(Suppl 3):S68. Abstract P268.

RANK Ligand Inhibition and PTH have Additive Effects on BMD in Aged OVX Rats





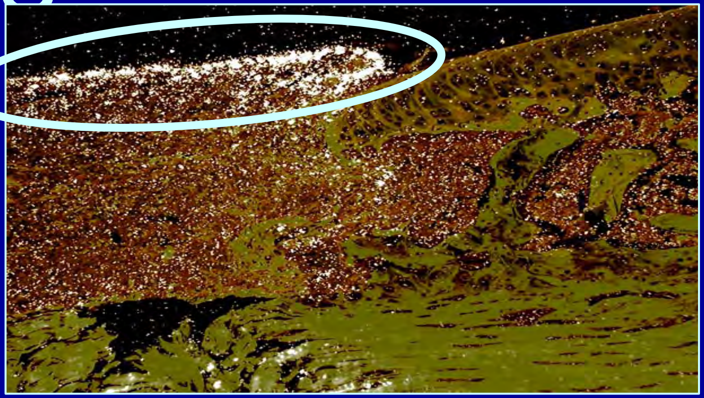
* = significant difference from vehicle-treated OVX
# = significant difference from PTH-treated OVX (by Tukey-Kramer test, $P < 0.05$).

Adapted from Kostenuik PJ, et al. *Endocrinol.* 2001;142:4295-304.

The Role of RANK Ligand Inhibition in Bone Erosions

RANK Ligand is Required for Bone Erosions in Rheumatoid Arthritis

RANK Ligand mRNA detected in Arthritic Synovium



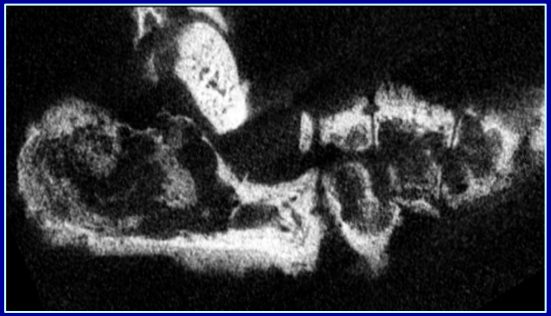
RANK Ligand in arthritic synovium[1]

- RANK Ligand gene expression is significantly elevated by activated T cells and synoviocytes in the inflamed synovium[1,2]
- Cytokines differentially regulate RANK Ligand and OPG, thereby altering the RANK Ligand/OPG ratio to favor bone resorption[1,2]

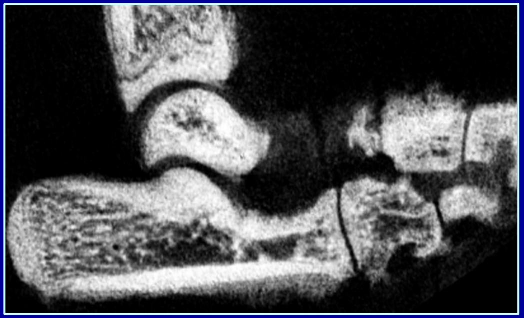
1. Amgen, data on file.
2. Kong Y-Y, et al. *Nature*. 1999;402:304-9.

RANK-L inhibition in Preclinical Models of Arthritis

Normal Healthy Rat Paw[1]



Arthritic Rat Paw[1]

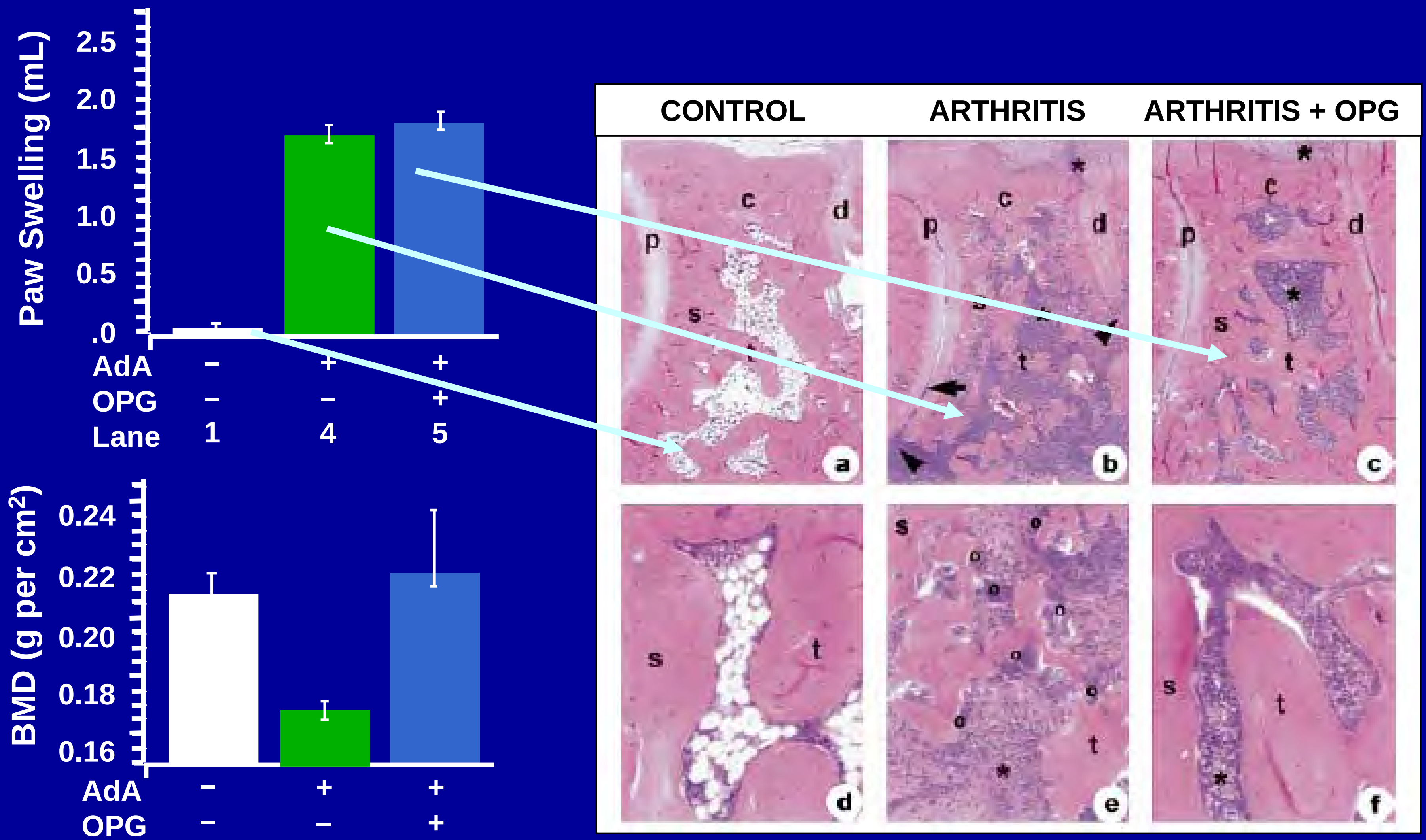


Arthritic Rat Paw + OPG[1]

- Adjuvant arthritis-induced excess RANK Ligand leads to focal osteolytic lesions and significant bone loss
- RANK Ligand inhibition appears to prevent loss of bone mineral density in adjuvant arthritis

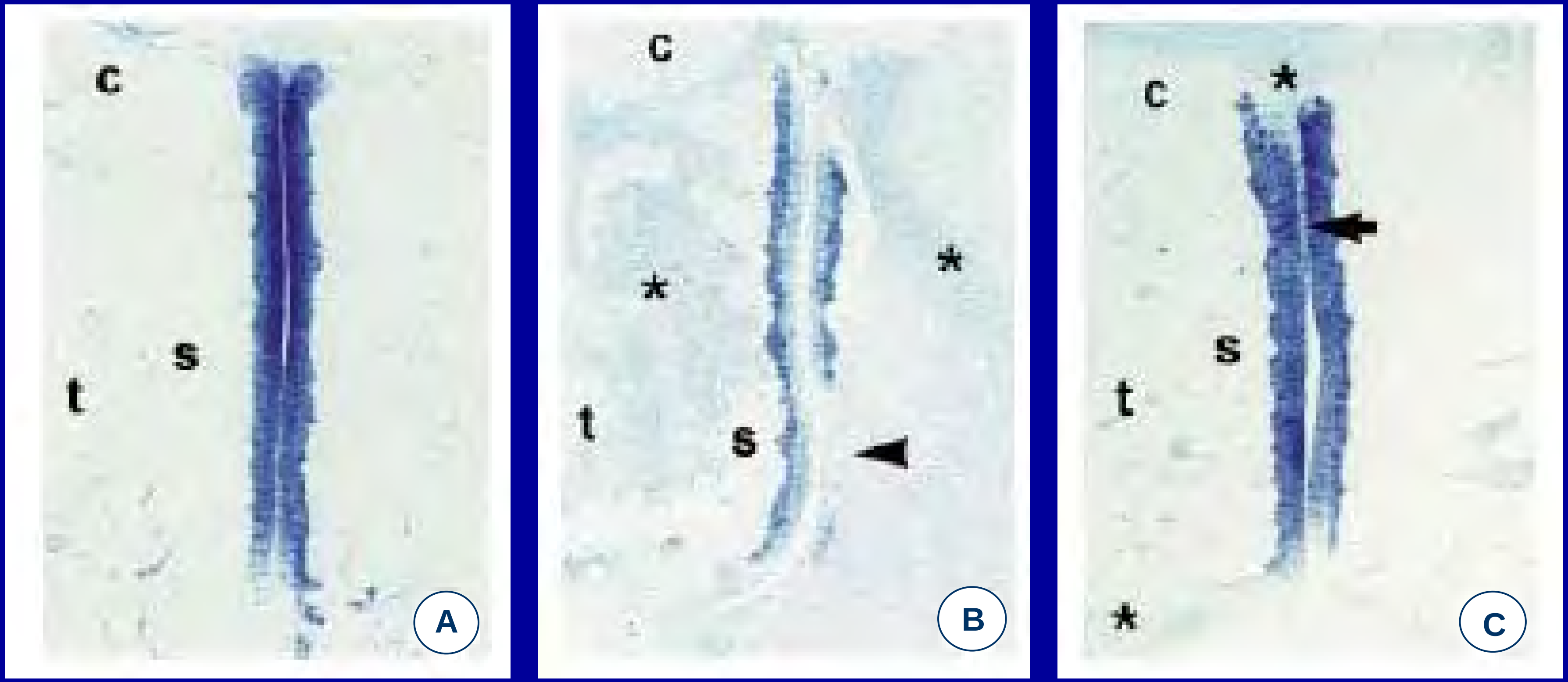
1. Kostenuik PJ, et al. *J Bone Min Res.* 2004;19(Suppl 1):S189. Abstract SA510

RANK Ligand Inhibition in Arthritic Rats Prevents Loss of BMD, but Does Not Inhibit Inflammation



RANK Ligand Inhibition Can Prevent Cartilage Destruction in Rats

Normal	Arthritic	RANK Ligand Inhibition



Reproduced from Kong Y-Y, et al. *Nature.* 1999;402:304-9
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The Role of RANK Ligand Inhibition in Treatment-Induced Bone Loss

RANK Ligand and Bone Loss in Glucocorticoid Osteoporosis

- Glucocorticoid exposure enhances RANK Ligand expression and inhibits OPG production by osteoblasts[1-2]
- This alteration increases the OPG/RANK Ligand ratio and results in osteoclast-driven bone resorption

1. Hofbauer LC, et al. *Endocrinol.* 1999;140:4382-9.

2. Sasaki N, et al. *Nephrol Dial Transplant.* 2001;16:479-82.

Cancer Treatment-Bone Loss

- Women with breast cancer treated with aromatase inhibitors
  - In this patient population, there was a more than 1.5- to 2-fold higher risk of experiencing vertebral fracture[1,2]
- Men with prostate cancer treated with androgen deprivation therapy (ADT)
  - Estimated 1 in 4 men who undergo androgen deprivation therapy will experience skeletal complications, such as fracture, within 2 years[3,4]

1. Baum M, et al. *Lancet.* 2002;359:2131-39.
2. Arimidex® (anastrazole) prescribing information
3. Melton LJ, et al. *J Urol.* 2003;169:1747-50.
4. Smith M, et al. *N Engl J Med.* 2001;345:948.

Cancer Treatment-Bone Loss

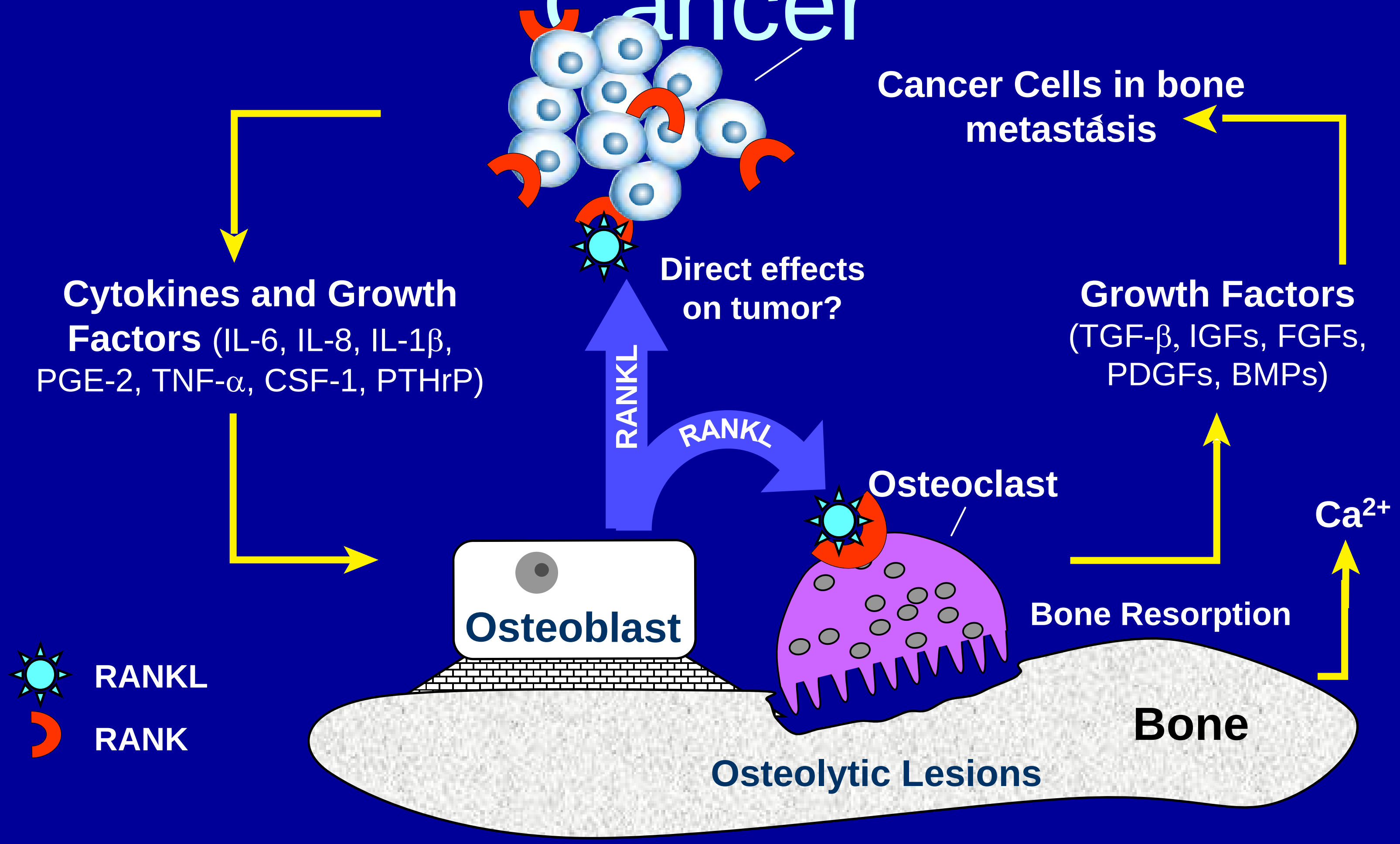
- Hormone ablative therapies enhance RANK Ligand expression and inhibit OPG production by osteoblasts
- This alteration increases the RANK Ligand/OPG ratio and results in osteoclast-driven bone resorption

	Cancer Treatment	
	ADT [3,4]	**Aromatase Inhibitor** [1,2]
Increase in bone turnover markers	✓	✓
Rapid bone loss	✓	✓
Increased risk of fracture	✓	✓

1. Theriatult RL. *Oncol.* 2004;18(Suppl 3):11-5. 2. Coleman RE. *Oncol*. 2004;18(Suppl 3):16-20. 3. Stoch SA, et al. *J Clin Endocrinol Metab.* 2001;86:2787-91. 4. Smith M, et al. *N Engl J Med.* 2001;345:948.

The Role of RANK Ligand Inhibition in Cancer-Related Bone Disease

"Vicious Cycle" of Bone Destruction in Metastatic Cancer



Adapted from Roodman GD. *N Engl J Med.* 2004;350:1655-64.

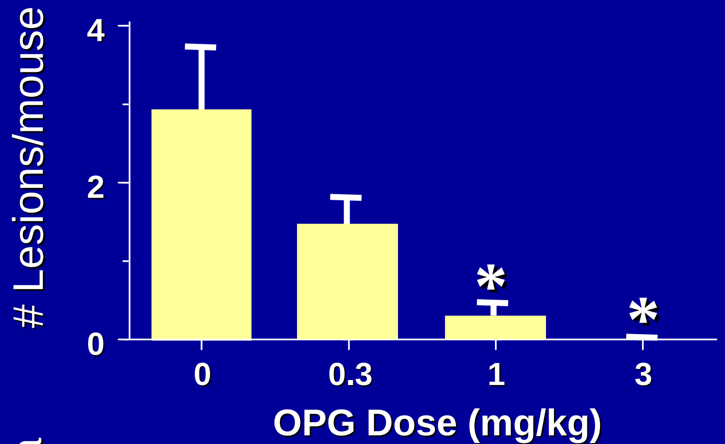
Tumor-Induced Osteolysis in Breast Cancer Model

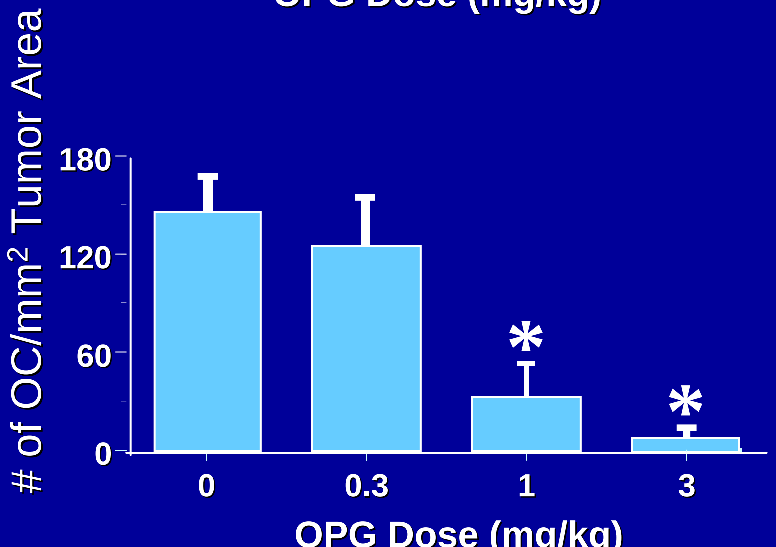
MDA-231
Intracardiac Model

Radiographic lesions

Control

RANK Ligand Inhibition



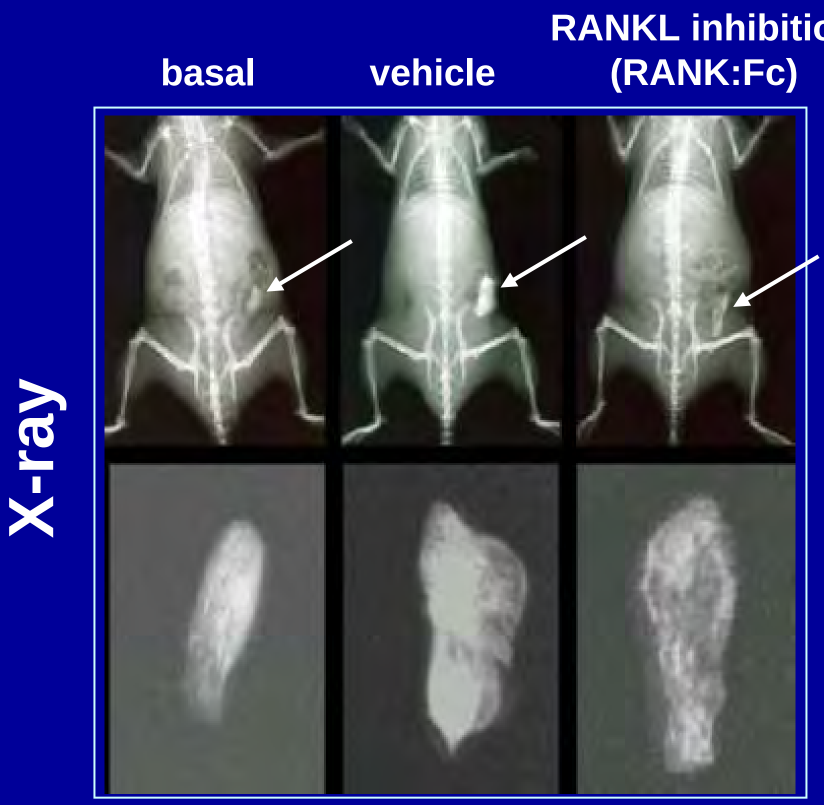


* Significantly different from 0 mg/kg OPG

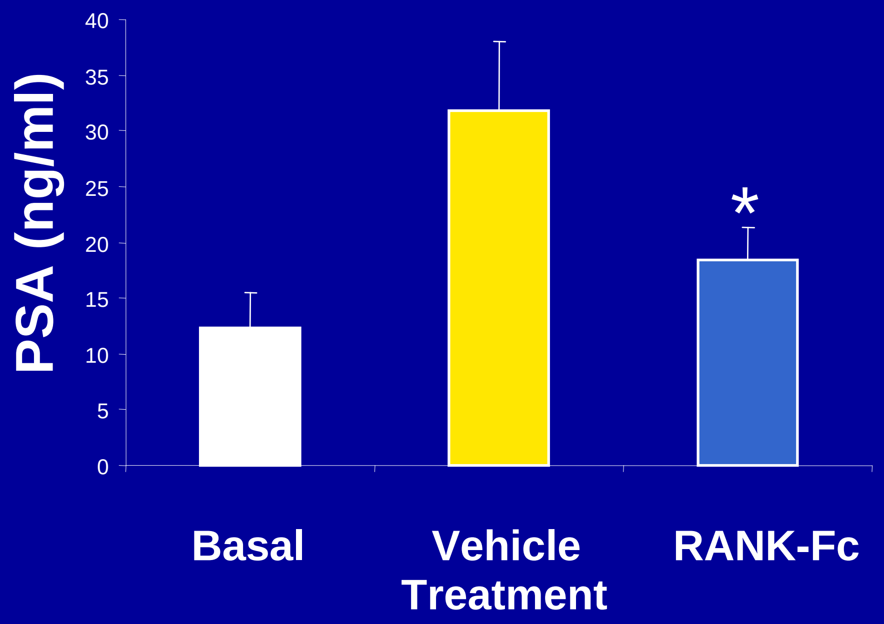
Adapted from Morony S, et al. *Cancer Res*. 2001;61(11):4432-6.

Prostate Cancer-induced Osteoblastic Bone Lesions

Prostate Cancer LuCaP 35 HU/SCID model, Rx initiated at 6 weeks



Serum PSA as surrogate marker for prostate tumor burden



Zhang J, et al. *Cancer Res.* 2003;63:7883-90.

* P <0.01 as compared with vehicle treated group

FGFs

- Source: monocytes, macrophages, mesenchymal cells, osteoblasts, chondrocytes
- Targeted cells: mesenchymal and epithelial cells, osteoblasts and chondrocytes
- Angiogenic and mitogenic for mesenchymal and epithelial cells, osteoblasts, chondrocytes
- α-FGF mainly effects chondrocyte proliferation, β-FGF (more potent) involved in chondrocytes maturation and bone resorption
- Expressed from the early stages until osteoblasts formation

IGFs

- Source: bone matrix, endothelial and mesenchymal cells (in granulation stage) and osteoblasts and non-hyperthrophic chondrocytes (in bone and cartilage formation)
- Targeted cells: MSCs, endothelial cells, osteoblasts, chondrocytes
- IGF-I: mesenchymal and osteoprogenitor cells recruitment and proliferation, expressed throughout fracture healing
- IGF-II: cell proliferation and protein synthesis during endochondral ossification

Metalloproteinases

- Source: the extracellular matrix
- Degradation of the cartilage and bone allowing the invasion of blood vessels during the final stages of endochondral ossification and bone remodelling

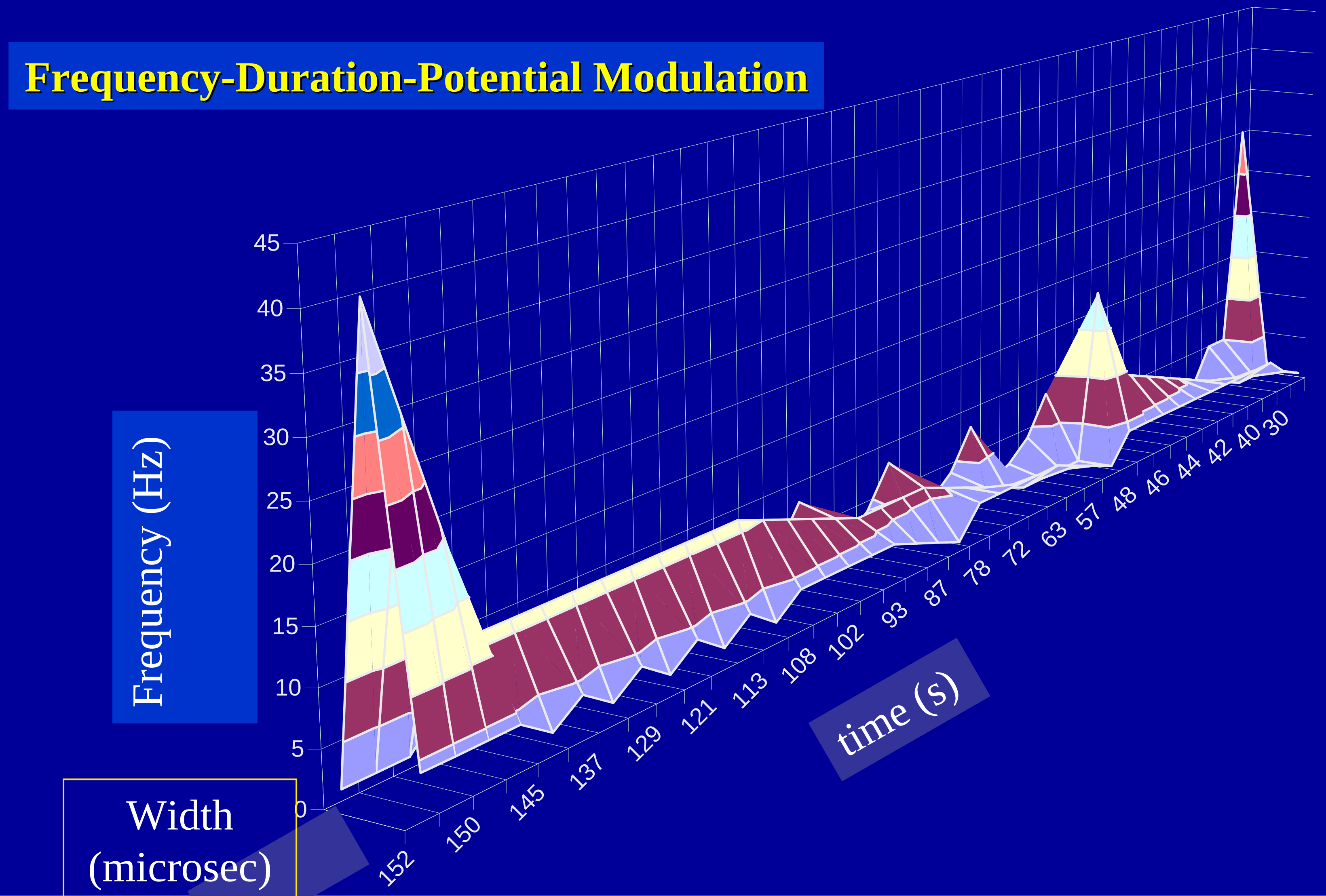
VEGFs

- Potent stimulators of endothelial cell proliferation
- Expressed during endochondral formation and bone formation

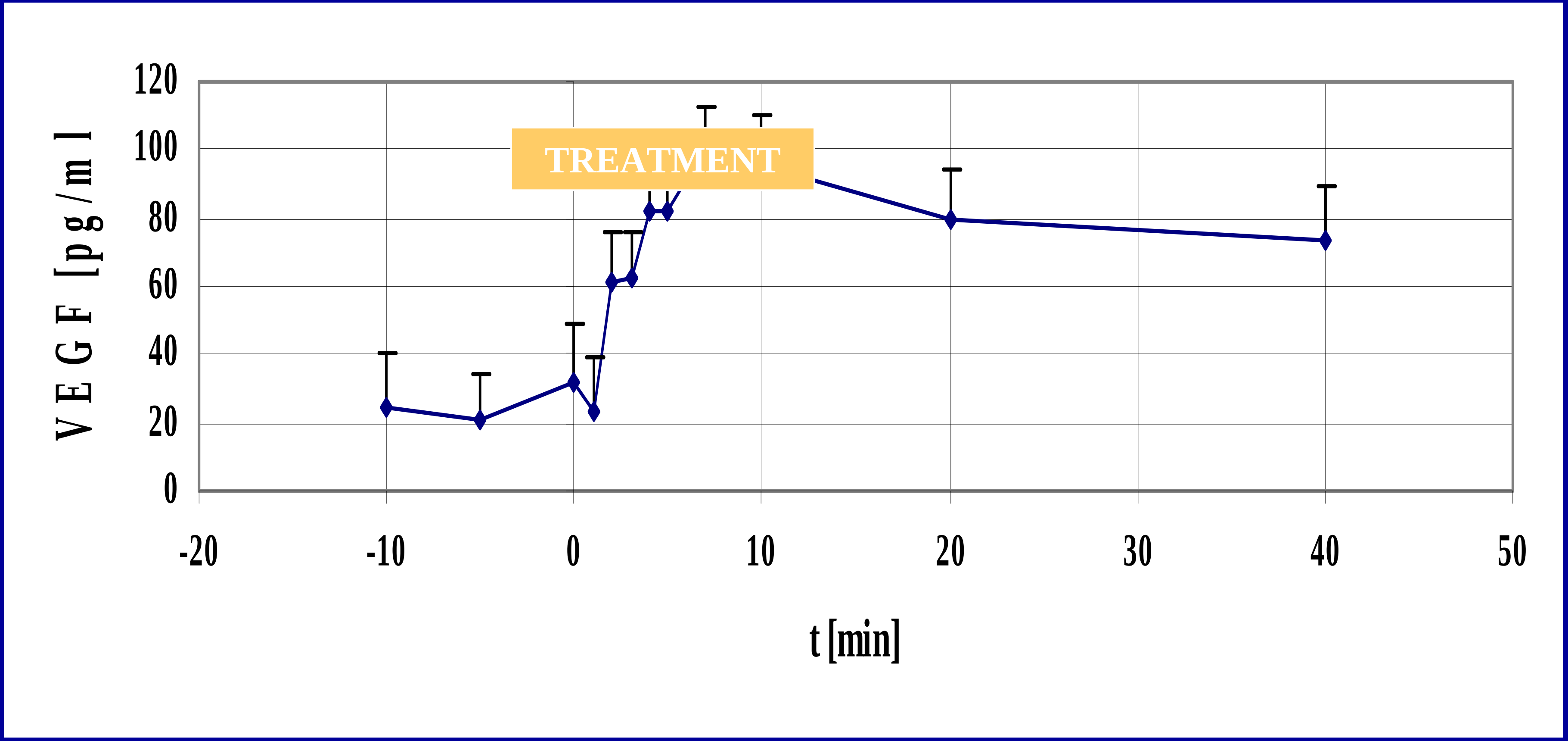
Angiopoietin (1 and 2)

- Formation of larger vessel structures, development of co-lateral branches from existing vessels
- Expressed from the early stages throughout fracture healing

NEW TREATMENT:
ELECTRICAL NEURO-MODULATION

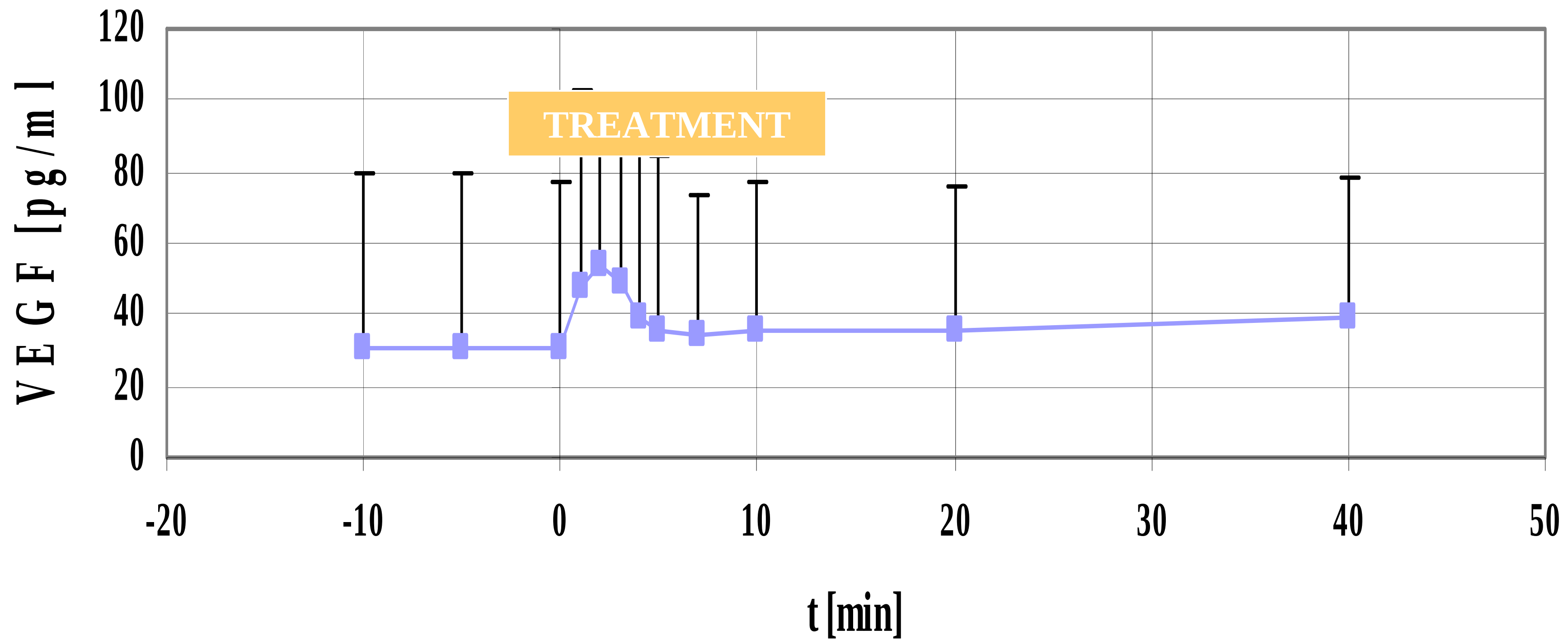


RESULTS



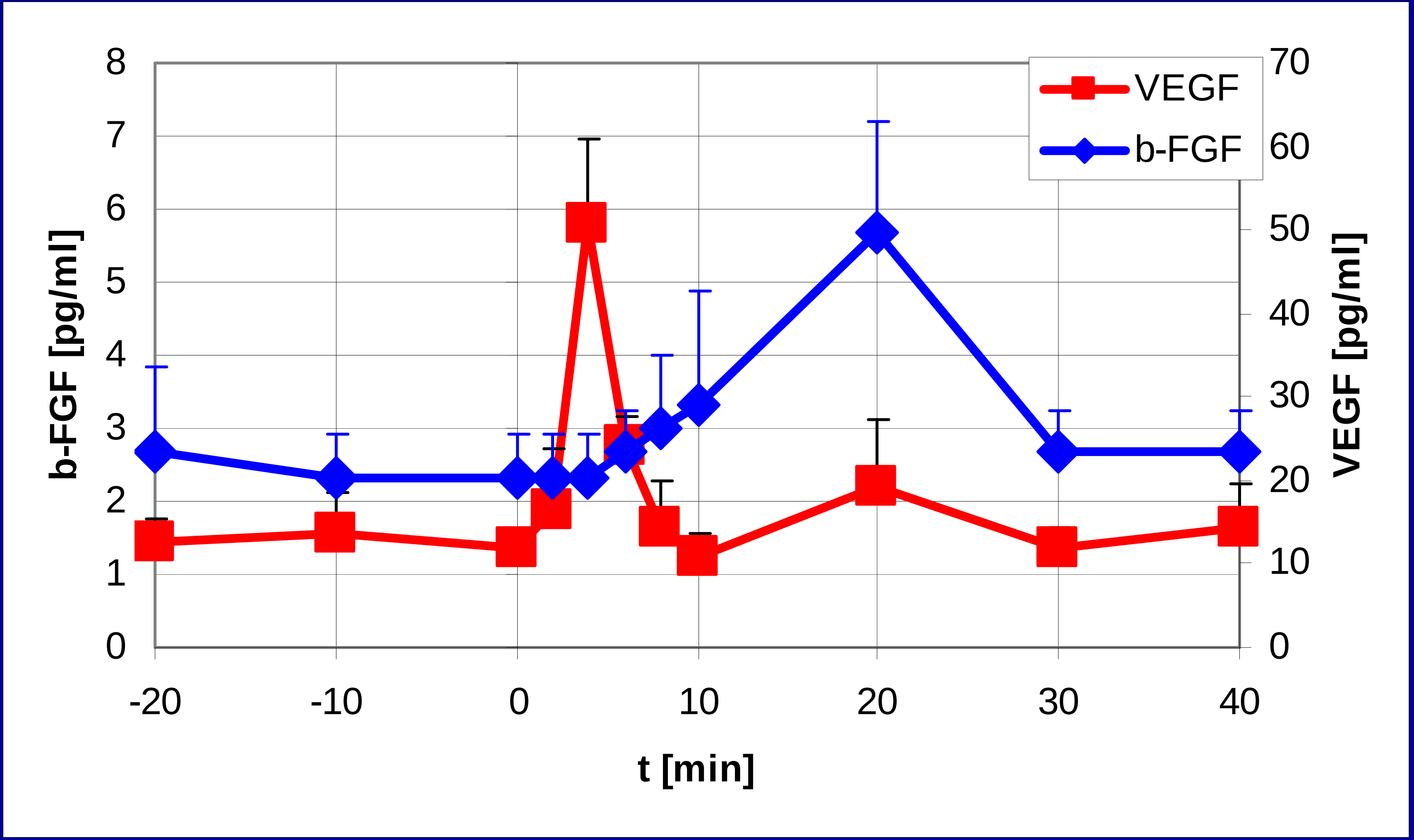
CONTROLS (n=10; mean and standard deviation)

RESULTS



OSTEOPOROTIC FRACTURES (n=10; mean and standard deviation)

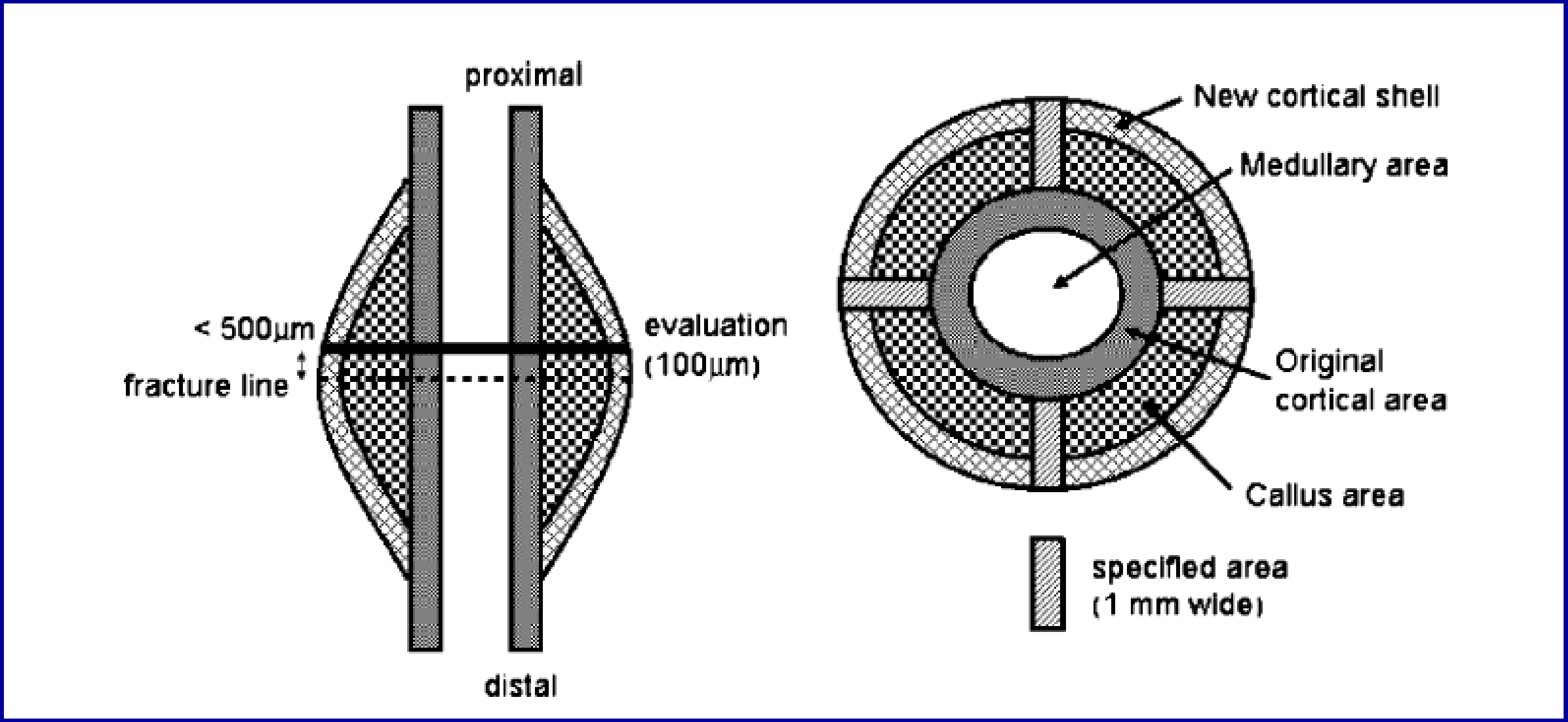
ANGIOGENIC GROWTH FACTORS



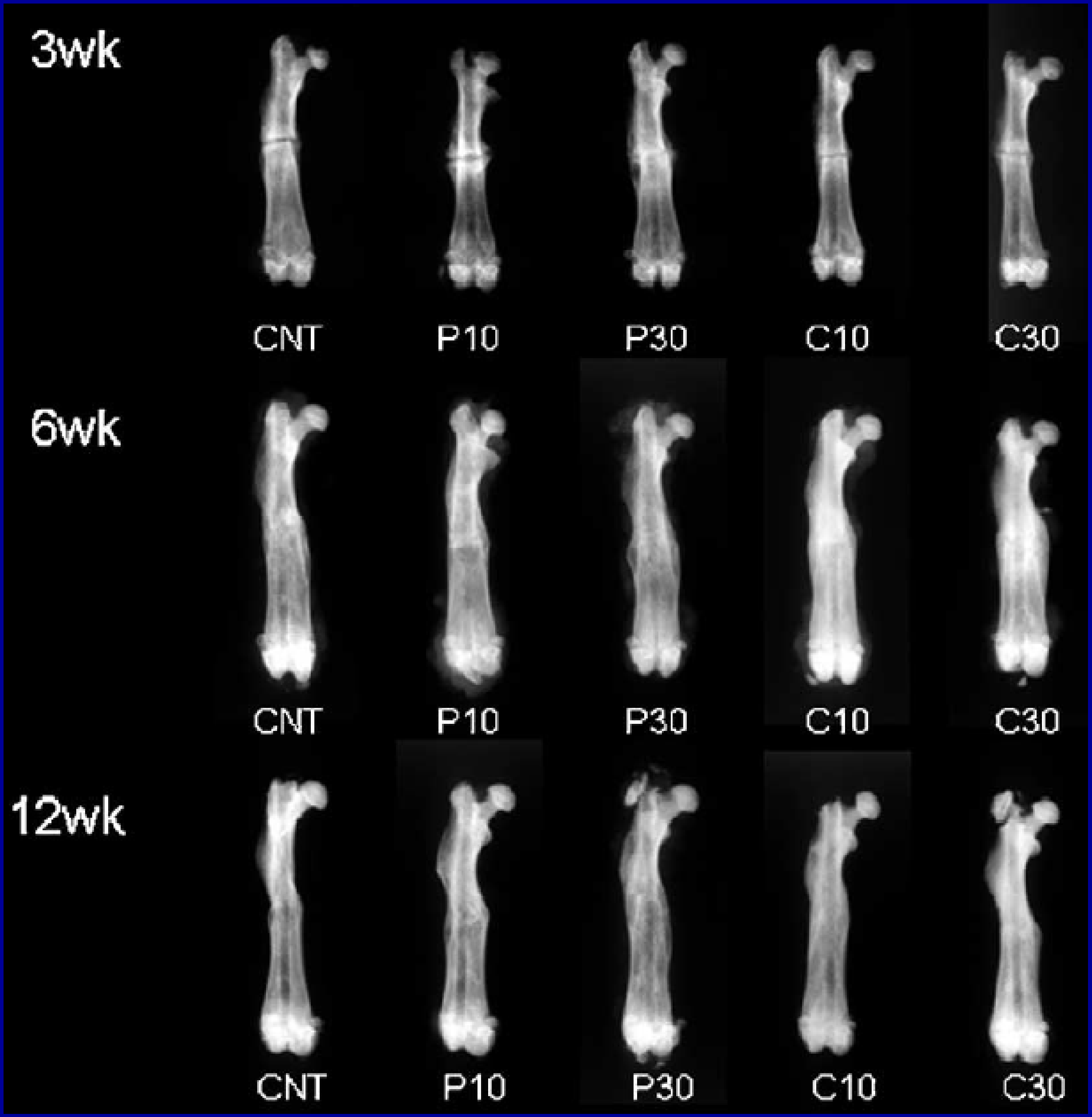
Human parathyroid hormone (1–34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora

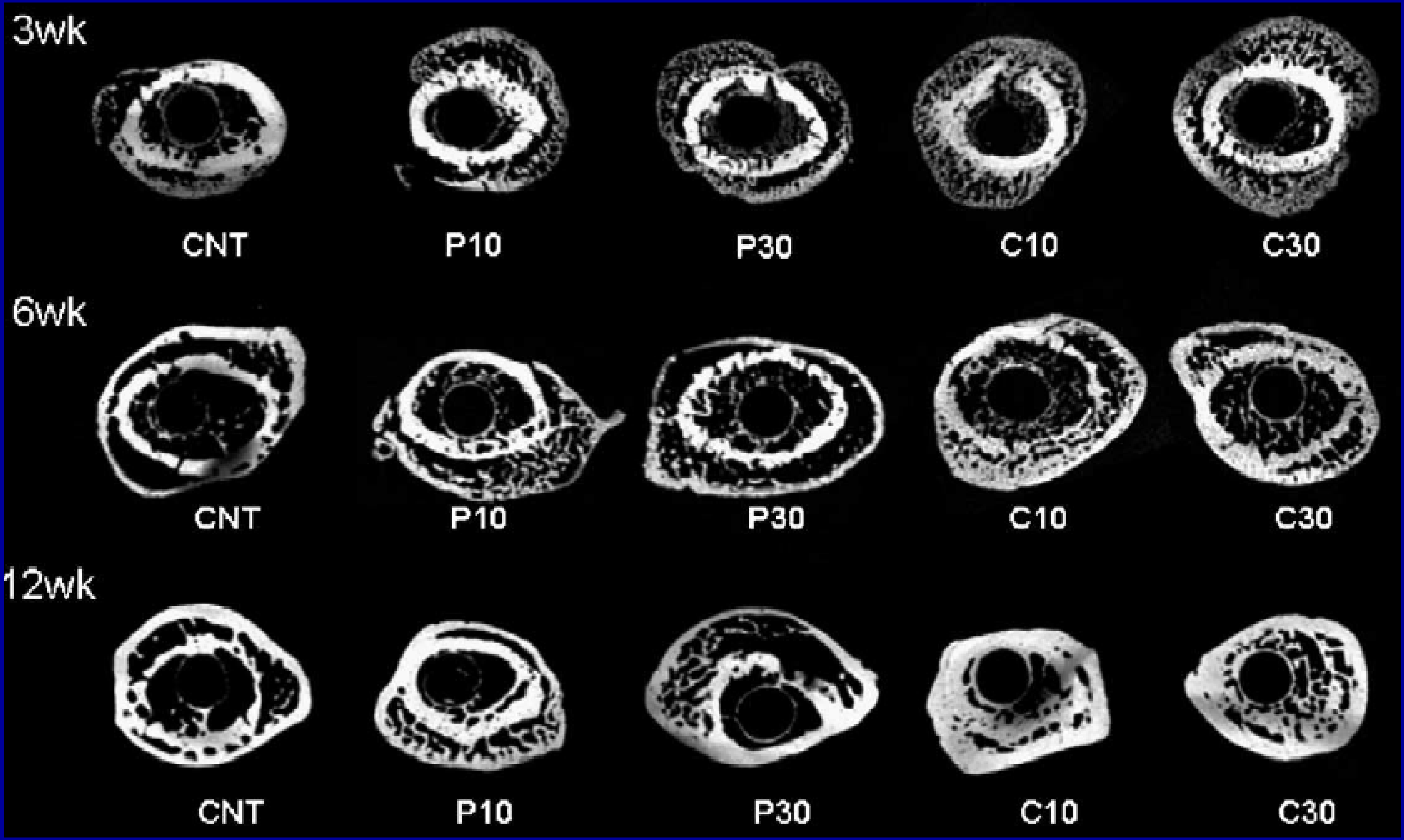
Satoshi Komatsubara[a], Satoshi Mori[a,*], Tasuku Mashiba[a], Kiichi Nonaka[b], Azusa Seki[c], Tomoyuki Akiyama[a], Kensaku Miyamoto[a], Yongping Cao[a], Takeshi Manabe[a], Hiromichi Norimatsu[a]

[a]*Department of Orthopedic Surgery, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa, Japan*
[b]*Section of Pharmacology, Department of Hard Tissue Engineering, Division of Bio-Matrix, Graduate School, Tokyo Medical Dental University, Tokyo, Japan*
[c]*Hamri Corporation, Tokyo, Japan*



proximal
< 500µm
fracture line
evaluation
(100µm)
distal
New cortical shell
Medullary area
Original
cortical area
Callus area
specified area
(1 mm wide)


3wk
CNT
P10
P30
C10
C30
6wk
CNT
P10
P30
C10
C30
12wk
CNT
P10
P30
C10
C30


3wk
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12wk
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C10
C30

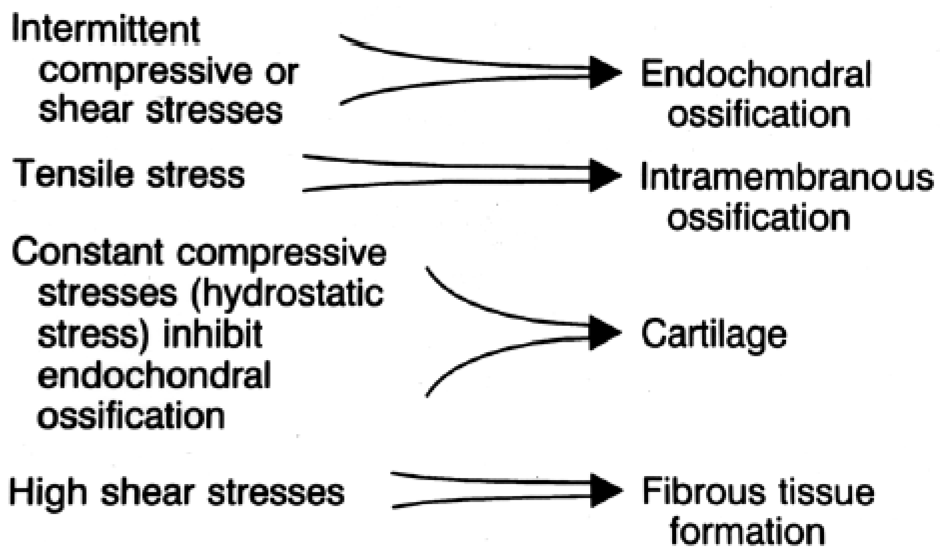


Figure 7. Hypothetical bone formation mechanism under different types of physical stresses.

GATTI DAVIDE
Riabilitazione Reumatologica
Valeggio S/M
Università di Verona

ITALIAN CRITERIA

for the treatment of

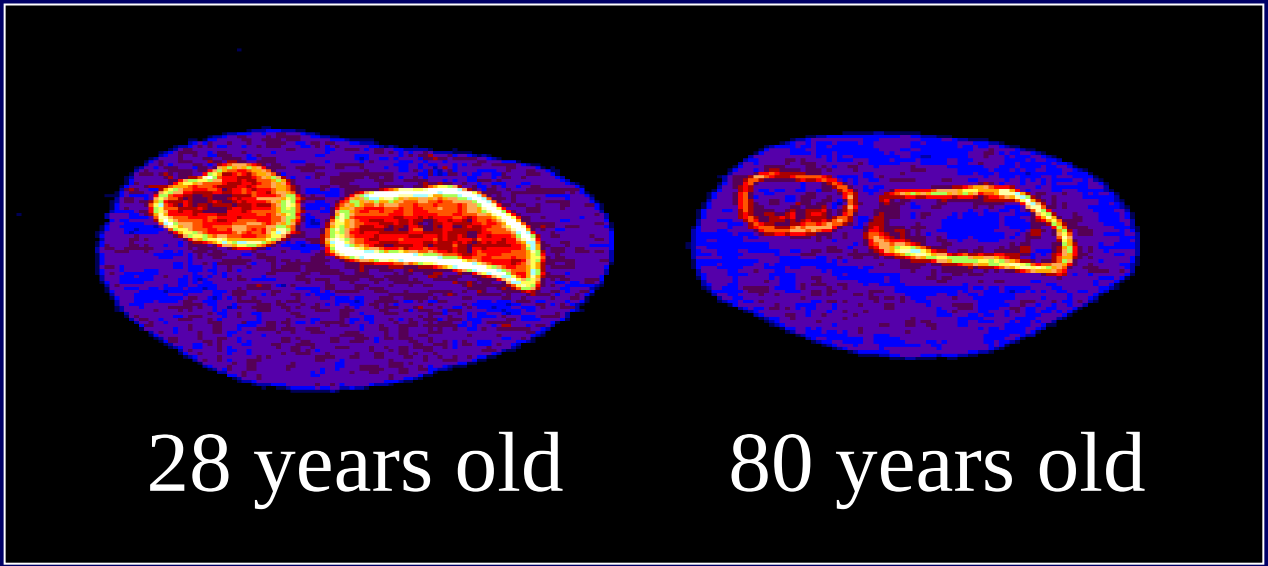
OSTEOPOROSIS

OSTEOPOROSIS

SKELETAL DISORDER CHARACTERIZED BY COMPROMISED BONE STRENGTH PREDISPOSING TO AN INCREASED RISK OF FRACTURE.

BONE STRENGTH REFLECTS THE INTEGRATION OF TWO MAIN FEATURES: BONE DENSITY AND BONE QUALITY.

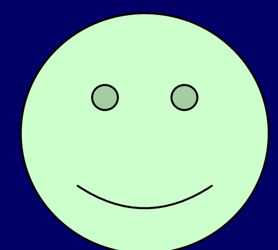
Consensus Conference 2001



Who should be treated with bone active agents?

OSTEOPORSIS PREVENTION ?

FRACTURE PREVENTION ?



MOST RELEVANT RISK FACTORS OF OSTEOPOROTIC FRACTURES

BONE STENGTH = BONE DENSITY + BONE QUALITY

FRACTURE RISK FACTORS

LOW BMD

?

BONE STENGTH = **BONE DENSITY** + **BONE QUALITY**

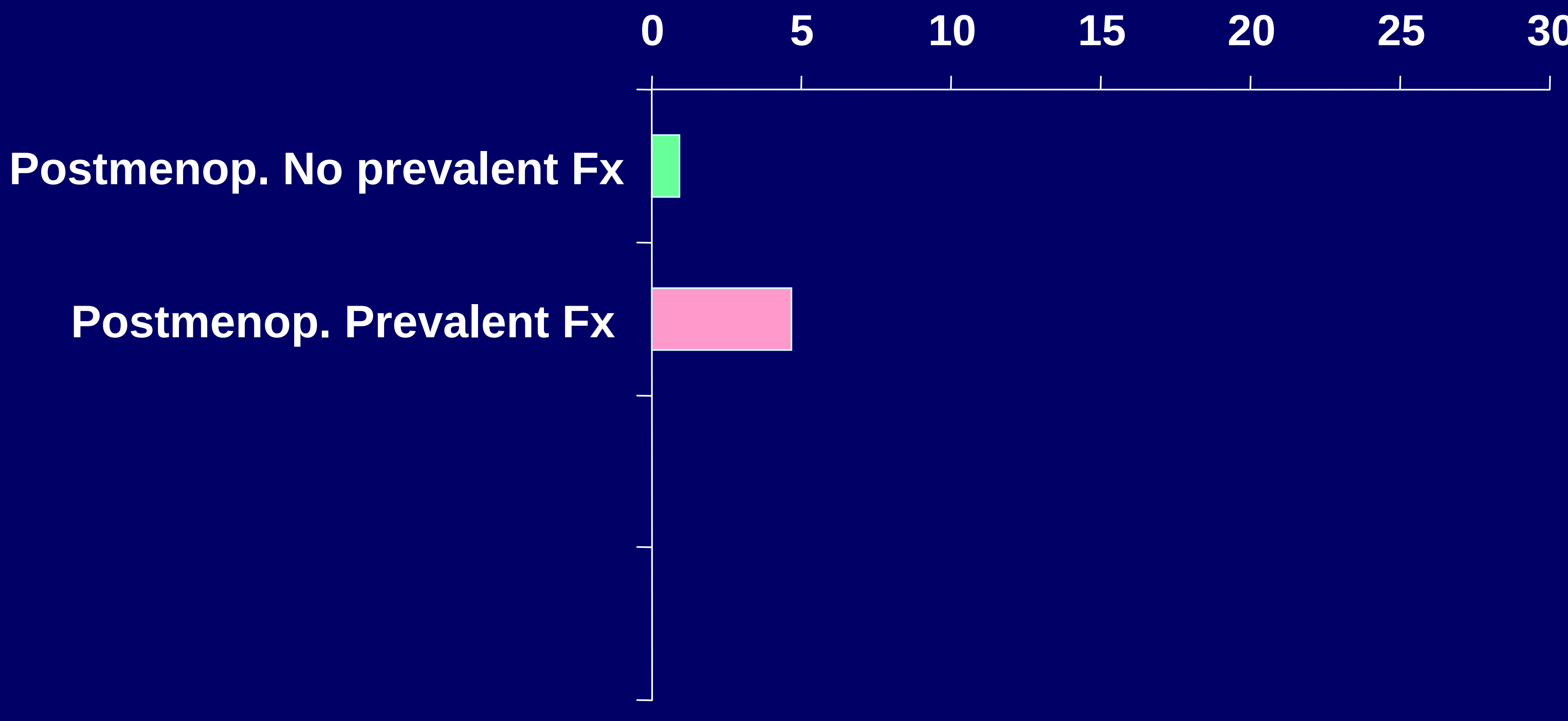
anything
you
can
measure
.....

DXA = QUANTITATIVE EVALUATION

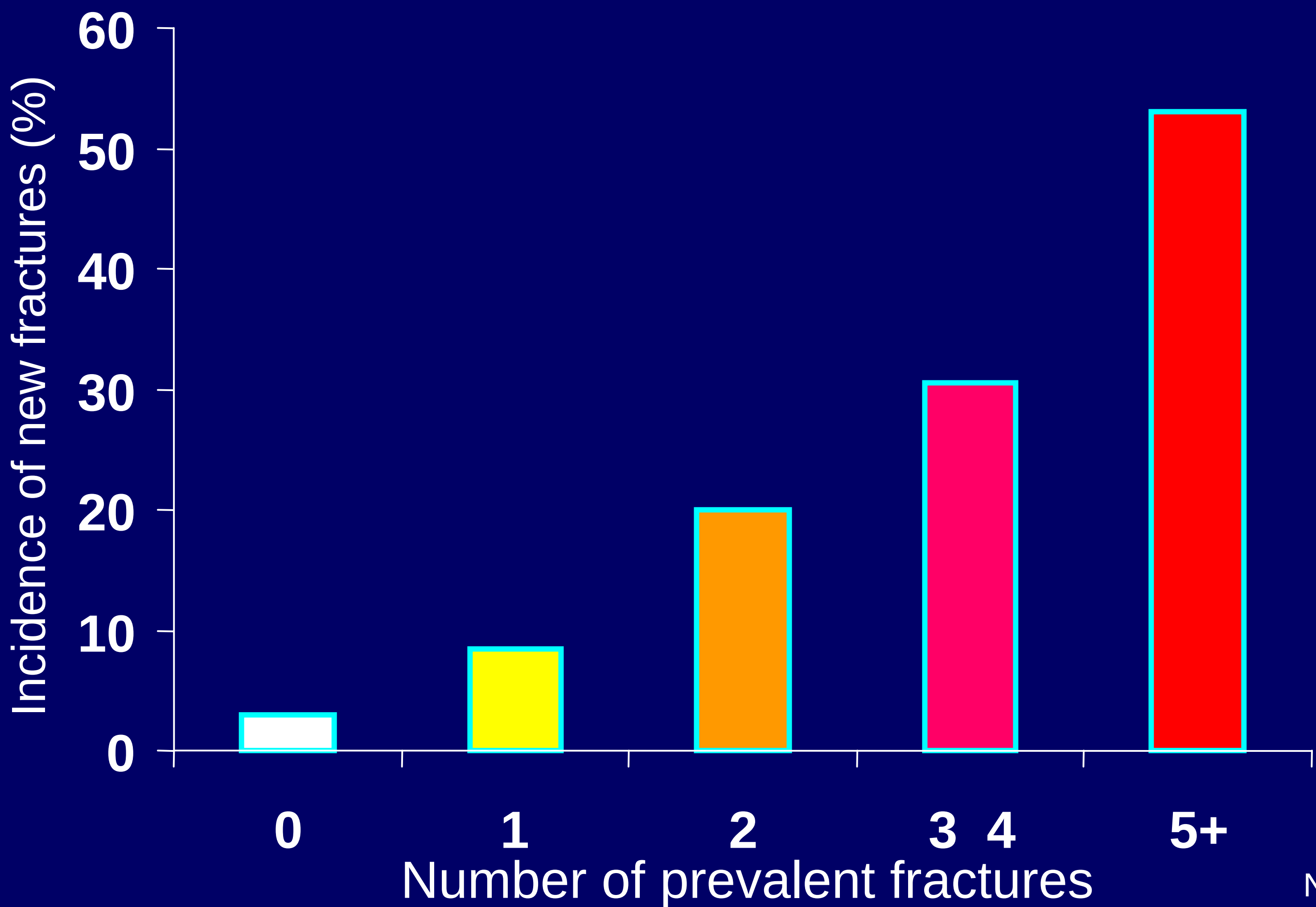
DXA CANNOT ALWAYS PREDICT FRACTURE RISK…

VERTEBRAL FRACTURE RELATIVE RISK

ADJUSTED FOR -2.5 SD T-SCORE (SPINE BMD)



Incidence of new vertebral fractures during follow-up, by number of prevalent fractures



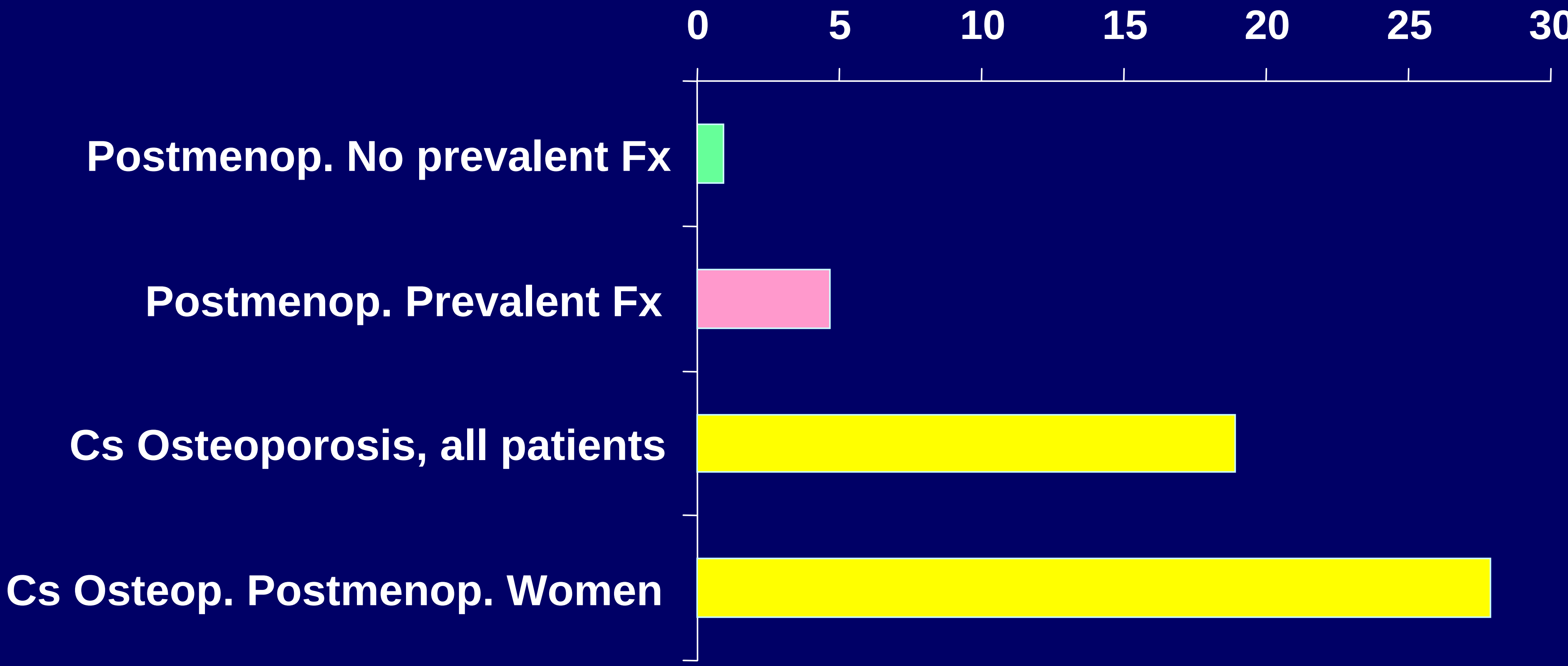
Nevitt et al 1999

MOST RELEVANT RISK FACTORS OF OSTEOPOROTIC FRACTURES

1. **PREVIOUS OSTEOPOROTIC FRACTURES** ***old*** **NOTA 79**

VERTEBRAL FRACTURE RELATIVE RISK

ADJUSTED FOR -2.5 SD T-SCORE (SPINE BMD)



Incidence of new vertebral fractures during 1 year follow-up

	T-SCORE (SPINE BMD)	FRACTURE INCIDENCE
POSTMENOPAUSAL OSTEOPOROSIS	< -2,5	**4,5 %**
G.I.OP	= -1,2	**16,1 %**

Ettinger et al. 1999 Wallach et al. 2000

MOST RELEVANT RISK FACTORS OF OSTEOPOROTIC FRACTURES

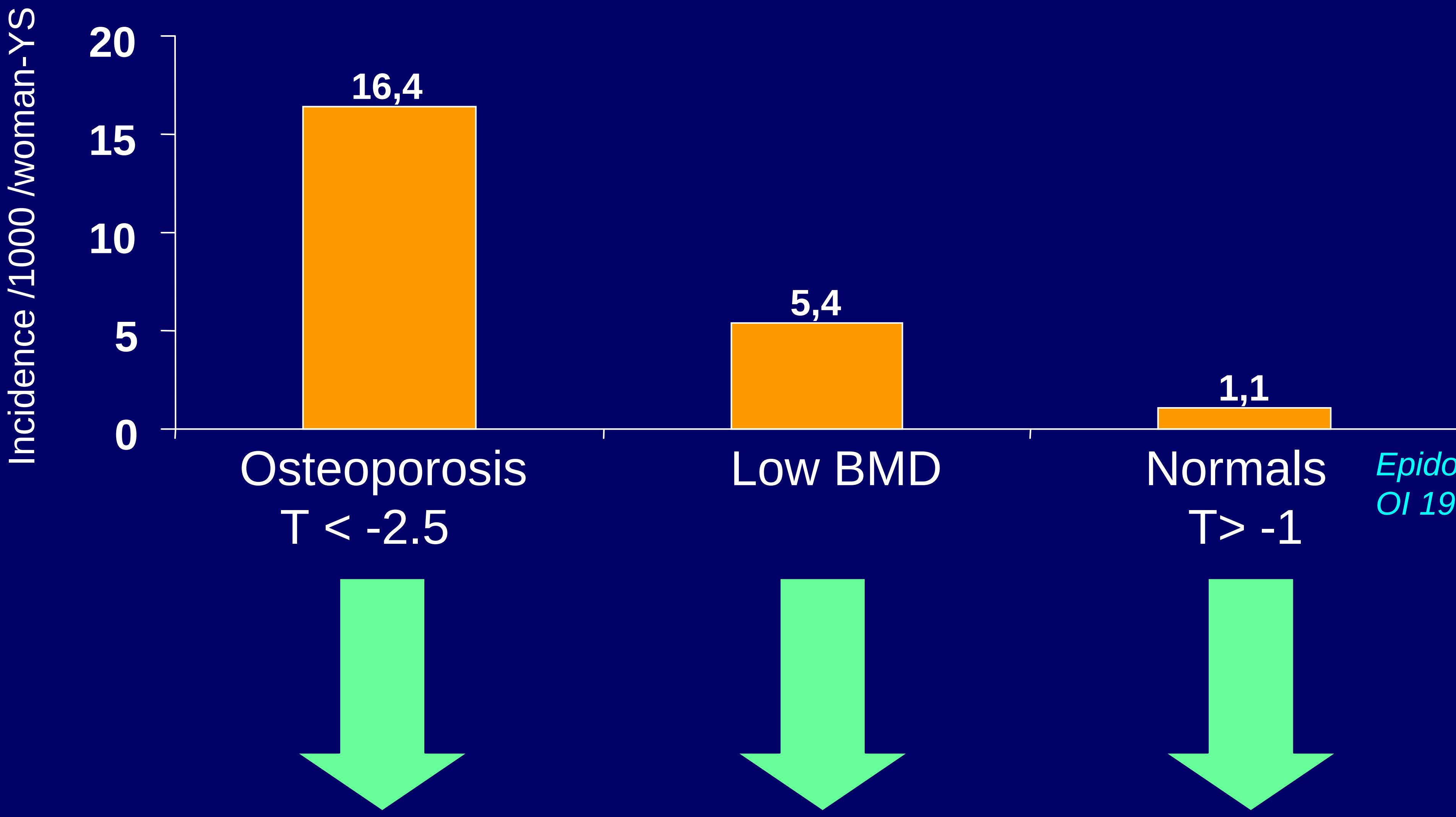
1. **PREVIOUS OSTEOPOROTIC FRACTURES** — ***old* NOTA 79**

2. **GLUCOCORTICOID THERAPY** — ***new* NOTA 79**

MOST RELEVANT RISK FACTORS OF OSTEOPOROTIC FRACTURES

1. PREVIOUS OSTEOPOROTIC FRACTURES — *old* NOTA 79
2. GLUCOCORTICOID THERAPY — *new* NOTA 79
3. LOW BMD

THERAPY → RR 0,50



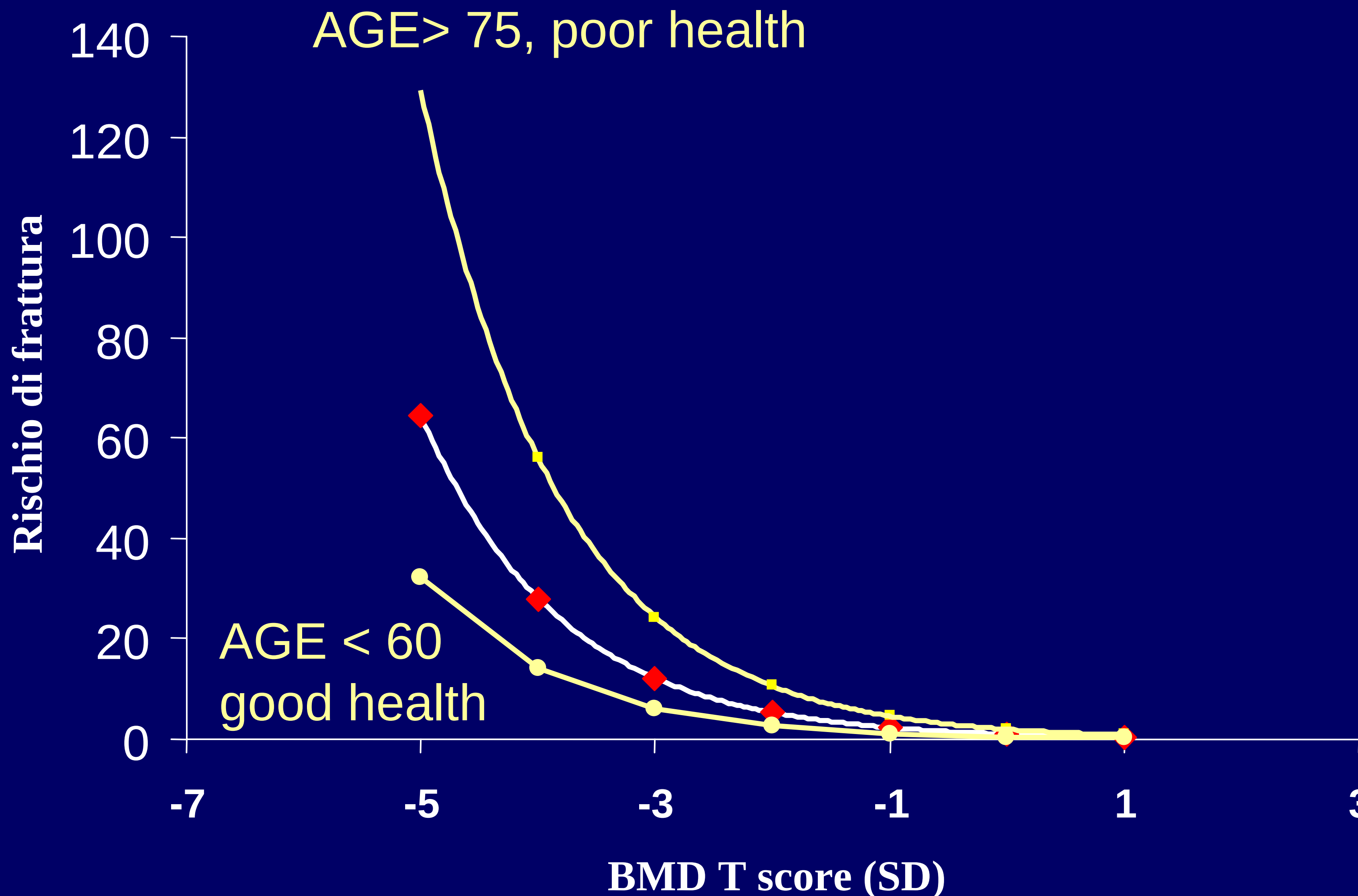
Epidos study, OI 1998

NNT 122 370 1818

IN ITALY: WOMEN > 50 YS OLD = 11.000.000

T-SCORE	n° (Milioni)	hip-fx (incidenza)	hip-fx
<-2,5	1.1	(16/1000)	**17.600**
>-2,5	9.9	(2/1000)	**19.800**

Other fracture risk factors amplify the effect of low BMD



Treatment threshold
NOF Guidelines

age < 65: T score < -2.5

age > 65: T score < -2.0

Treatment threshold

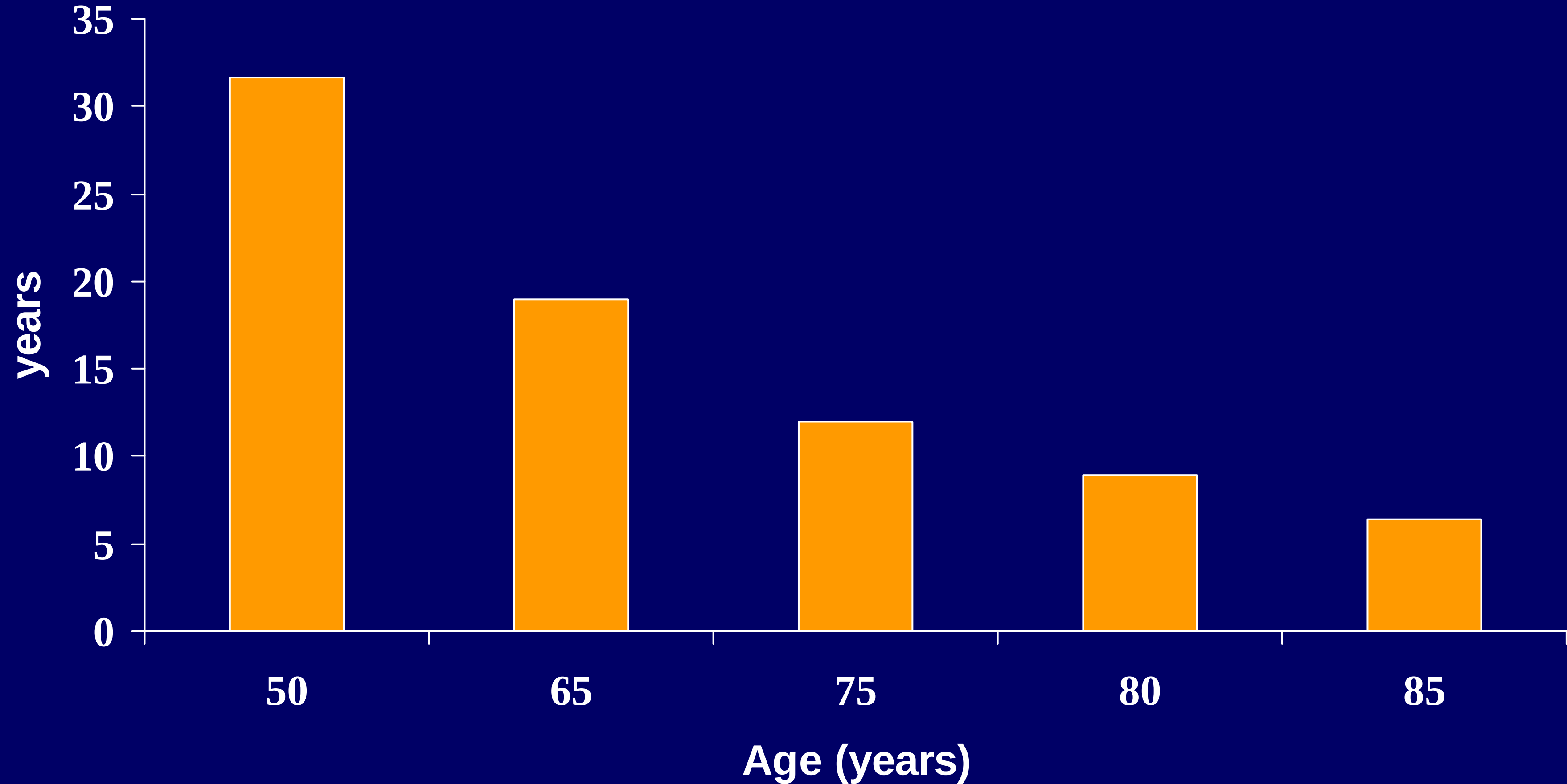
NOF Guidelines

age < 65: T score < -2.5 = 0.8 % of the population

age > 65: T score < -2.0 = 85% of the elderly

<u>Rational: treating absolute risk of fracture!</u>

REMAINING LIFE EXPECTANCY IN WOMEN



Ten year probability (%) of any fracture in women by T-score

	T – s c o r e									
Age	1	0.5	0	-0.5	-1	-1.5	-2	-2.5	-3	-4
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	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	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

LINEE GUIDA ANNO 2005

per la diagnosi, prevenzione e terapia dell'osteoporosi

ALGORITMO PER LA STIMA DEL RISCHIO DI FRATTURA VERTEBRALE CLINICAMENTE MANIFESTA A 10 ANNI

1,12 (età-anni)-0.008 (età-anni)²-2,3 (BMD hip T-score)-0,24 (BMI kg/m²) -33

se fuma >10 sigarette +12%

se storia familiare

se artrite Reumato

se pregresse frattu

se menopausa prin

L'Alg

e vita

ALGORITMO PER LA STIMA DEL RISCHIO DI FRATTURA VERTEBRALE A 10 ANNI

1,12 (età-anni)-0.008 (età-anni)²-0,80 (AD-SoS T-score falange) – 0,24 (BMI kg/m²) -33

di calcio

ALGORITMO PER LA STIMA DEL RISCHIO FRATTURA DI FEMORE A 10 ANNI

0,33 (età-anni)-4,31 (BMD hip T-score)-0,25 (BMI kg/m²)-20,7

se fuma > 10 sigarette	+21%
se storia familiare per fx femore	+102%
se artrite Reumatoide	+46%
se pregresse fratture op a polso	+33%
se menopausa prima di 46 anni	+7%

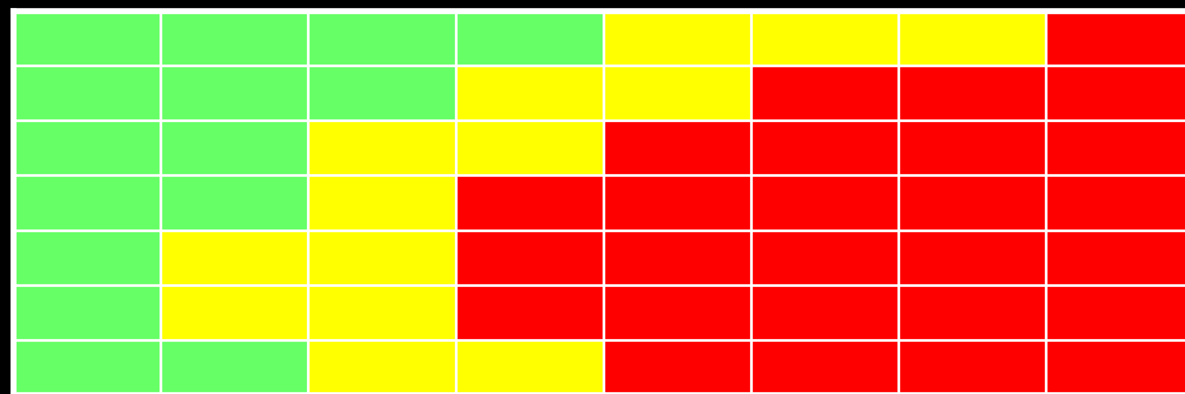
L'*Algoritmo si riferisce a donne con un normale apporto di calcio e vitamina D (livelli sierici di 25OH vitamina D >12 ng/ml)*

BMD + age

BMD + age

+

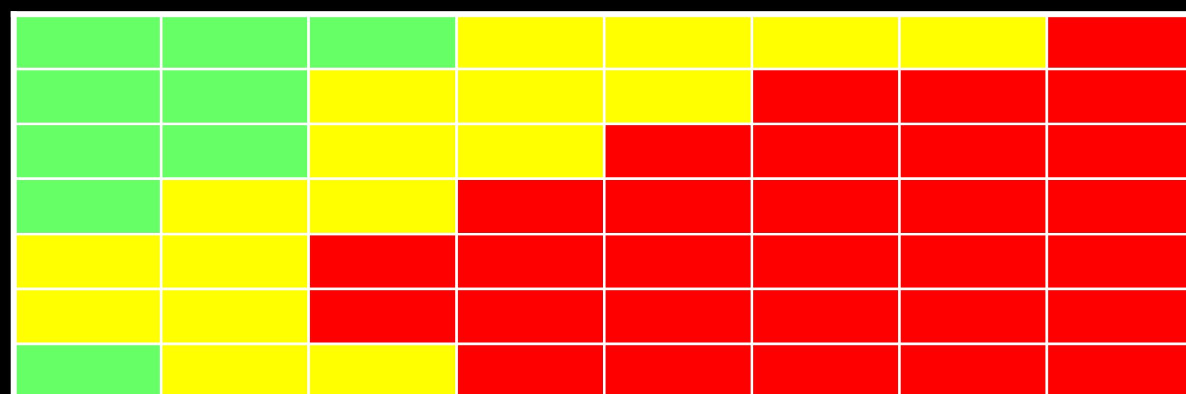
smoke o low BMI



BMD + ETA’

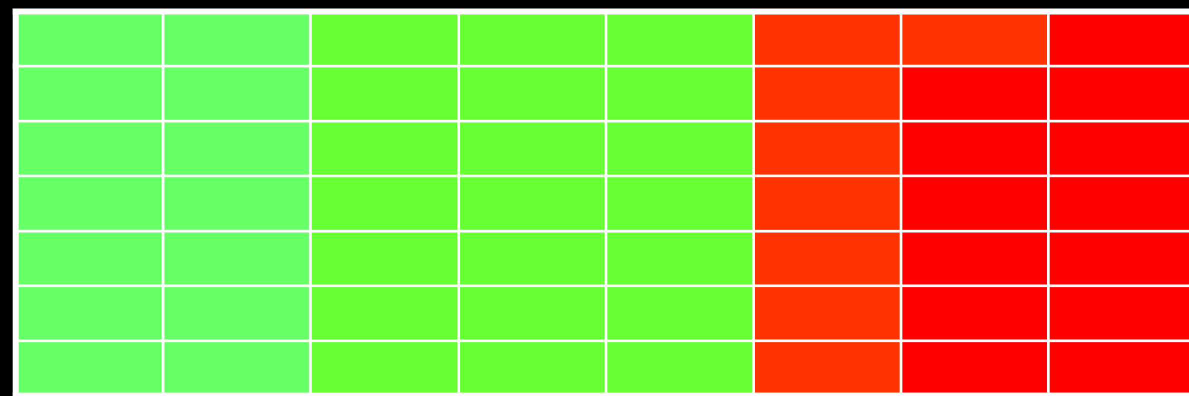
+

smoke + low BMI



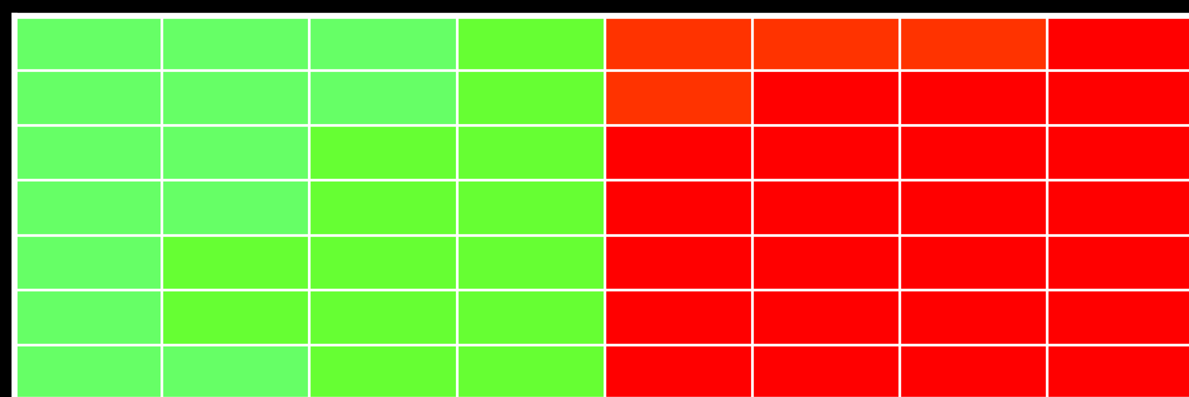
NEW..... NOTA 79

BMD



BMD +

RISK FACTORS



NEW..... NOTA 79

RISK FACTORS ?

- FAMILIAR HISTORY OF VERTEBRAL FRACTURES
- RHEUMATOID ARTHRITIS
- COLLES FRACTURE
- EARLY MENOPAUSE
- CORTICOSTEROID THERAPY

OSTEOPOROSIS
Who should be treated with bone active agents?

1. **PREVIOUS OP FRACTURES** — ***old* NOTA 79**

2. **GIOP** — ***present* NOTA 79**

3. **LOW BMD** — ***new* NOTA 79**

evidence based medicine 

.. IL FARMACO E' COSI' EFFICACE

CHE L'HO DATO A MIA MADRE …

EVIDENZA

MAMMA

.. IL FARMACO E' EFFICACE….

NELLA MIA ESPERIENZA …………..

EVIDENZA

PERSONALE

EBM LEVELS OF EVIDENCE

1. RCT:
2. Cohort Study:
3. Case-control study:
4. Case - series:
5. Expert Opinion:

LINEE GUIDA

Anno 2005

per la diagnosi, prevenzione e terapia dell'osteoporosi

Approvato dalle seguenti Società Scientifiche:

Collegio dei Reumatologi Ospedalieri (CROI)
Società Italiana dell'Osteoporosi e delle Malattie del Metabolismo Minerale e Scheletrico (SIOMMMS)
Società Italiana di Medicina Fisica e Riabilitativa (SIMFER)
Società Italiana di Medicina Interna (SIMI)
Società Italiana di Ortopedia e Traumatologia (SIOT)
Società Italiana di Radiologia Medica (SIRM)
Società Italiana di Reumatologia (SIR)

LINEE GUIDA

per la diagnosi, prevenzione e terapia dell'osteoporosi

ANNO 2005

GRADI DI RACCOMANDAZIONE PER LE LINEE GUIDA DELLA PRATICA CLINICA

Grado	*Criteri*
A	Richiede la presenza del livello di evidenza 1a o 1b più il consenso*
B	Richiede la presenza del livello di evidenza 2 o 2b più il consenso*
C	Richiede la presenza del livello di evidenza 3 di più il consenso
D	Qualsiasi livello più basso di evidenza più il consenso

**Un adeguato livello di evidenza è stato necessario, ma non sufficiente per assegnare un grado nella raccomandazione; è stato inoltre richiesto il consenso.*

LINEE GUIDA

Linee guida 2005 SIOMMMS, CROI, SIMFER, SIMI, SIOT, SIRM, SIR

GRADO DI RACCOMANDAZIONE PER LA TERAPIA

	Donne prevenzione	Donne terapia	OP cortisone prevenzione	OP cortisone terapia	Maschi
• alendronate	A	A	A	A	A
• risedronato	A	A	A	A	A
• clodronato	B	B	/	/	/
• paratormone	/	A	C	C	C
• Stronzio ranelato	A	A	/	/	/
• Raloxifene	A	A	/	/	/
• Terapia ormonale sostitutiva	A	A			

** l'efficacia antifratturativa va considerata alla luce degli effetti potenzialmente negativi;*

Ibandronato	**/**	**A**	**/**	**/**	**/**

CHI TRATTARE

EVIDENZA + PRESCRIVIBILITA'

TERAPIA EFFICACE
PER LA
SUOCERA

TERAPIA EFFICACE
PER LA
MAMMA

LINEE GUIDA

2005 SIOMMMS, CROI, SIMFER, SIMI, SIOT, SIRM, SIR

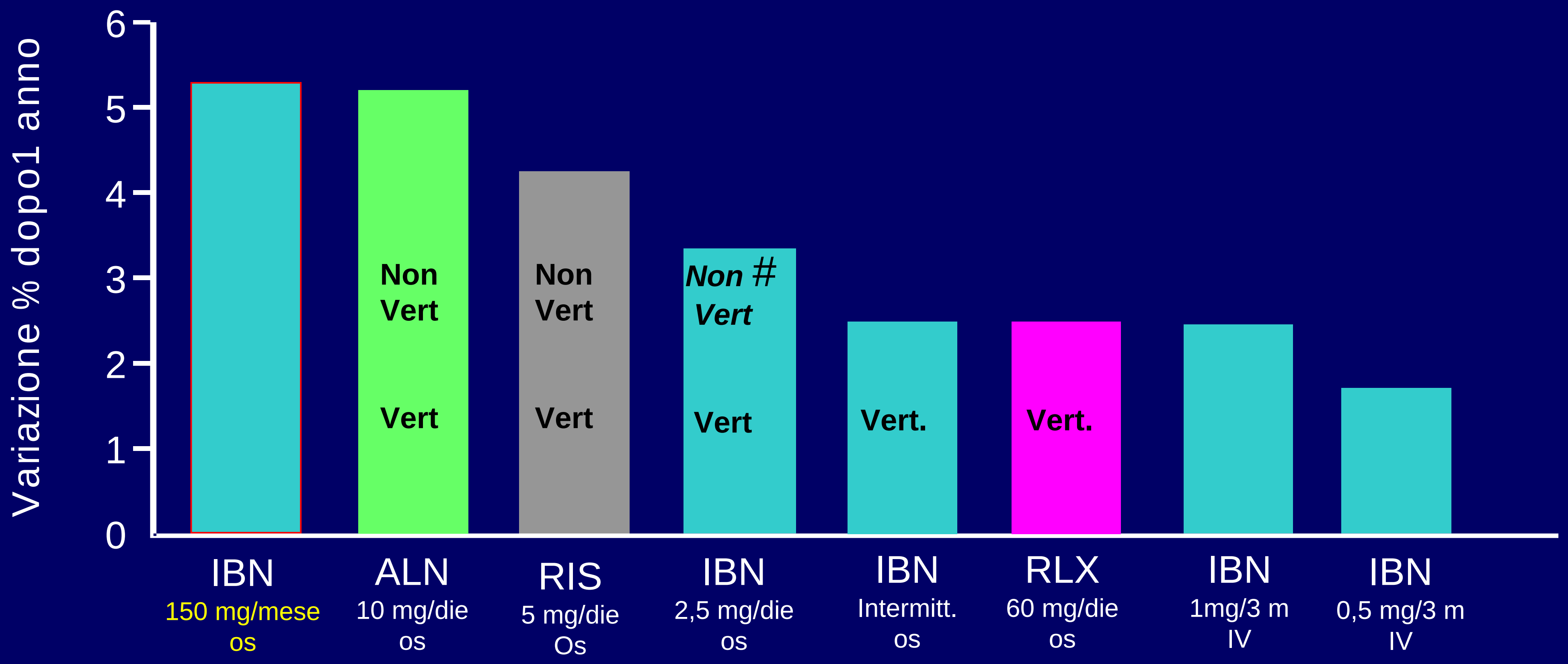
Intervento farmacologico	*Obiettivo terapeutico* *Fx -vert*	*Fx- non vert*	*Fx- Femorali*
• alendronato	1a	1b	1a
• risedronato	1a	1b	1a
• clodronato	2	3	3
• paratormone	1a	1a	//
• stronzio ranelato	1a	1b	$1b^3$
• Terapia ormonale sostitutiva	1a	1a	1a
• Raloxifene	1b	--	--
Ibandronato	1a	$1b^3$	/

EFFETTO SULLA BMD

EVIDENZA 1

EFFETTO SULLE FRATTURE

EVIDENZA 1



= sottogruppo ad alto rischio

“Male osteoporosis”

Alfredo Scillitani
Unit of Endocrinology
Ospedale “Casa Sollievo della Sofferenza”
San Giovanni Rotondo

3rd Joint Meeting AME-AACE - Verona 27-29 October 2006

Epidemiology

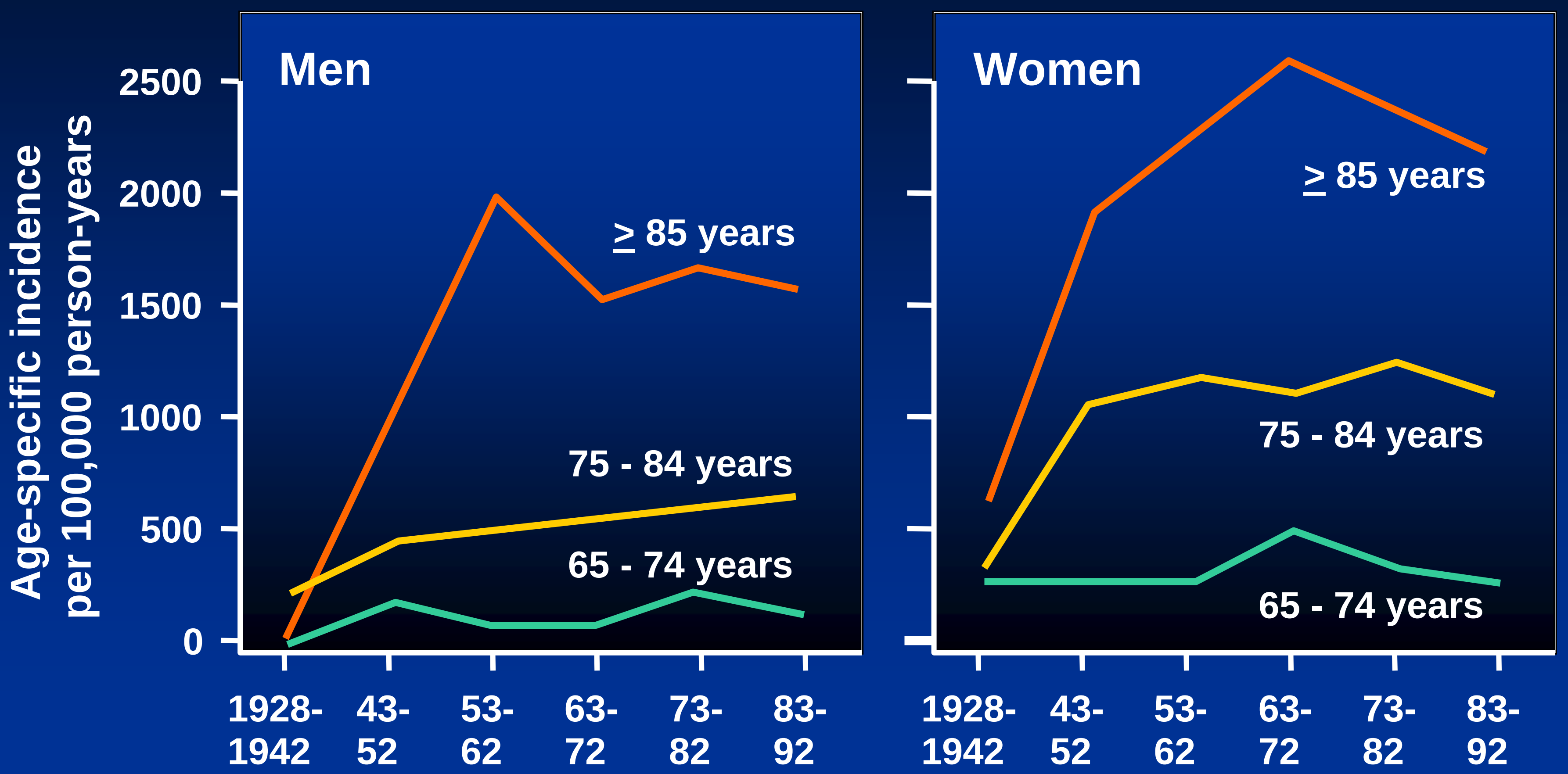
Age adjusted prevalence (%):

	women	men
Osteopenia	50	47 (33)*
Osteoporosis	18	6 (4)*

* when utilizing cut-off for women

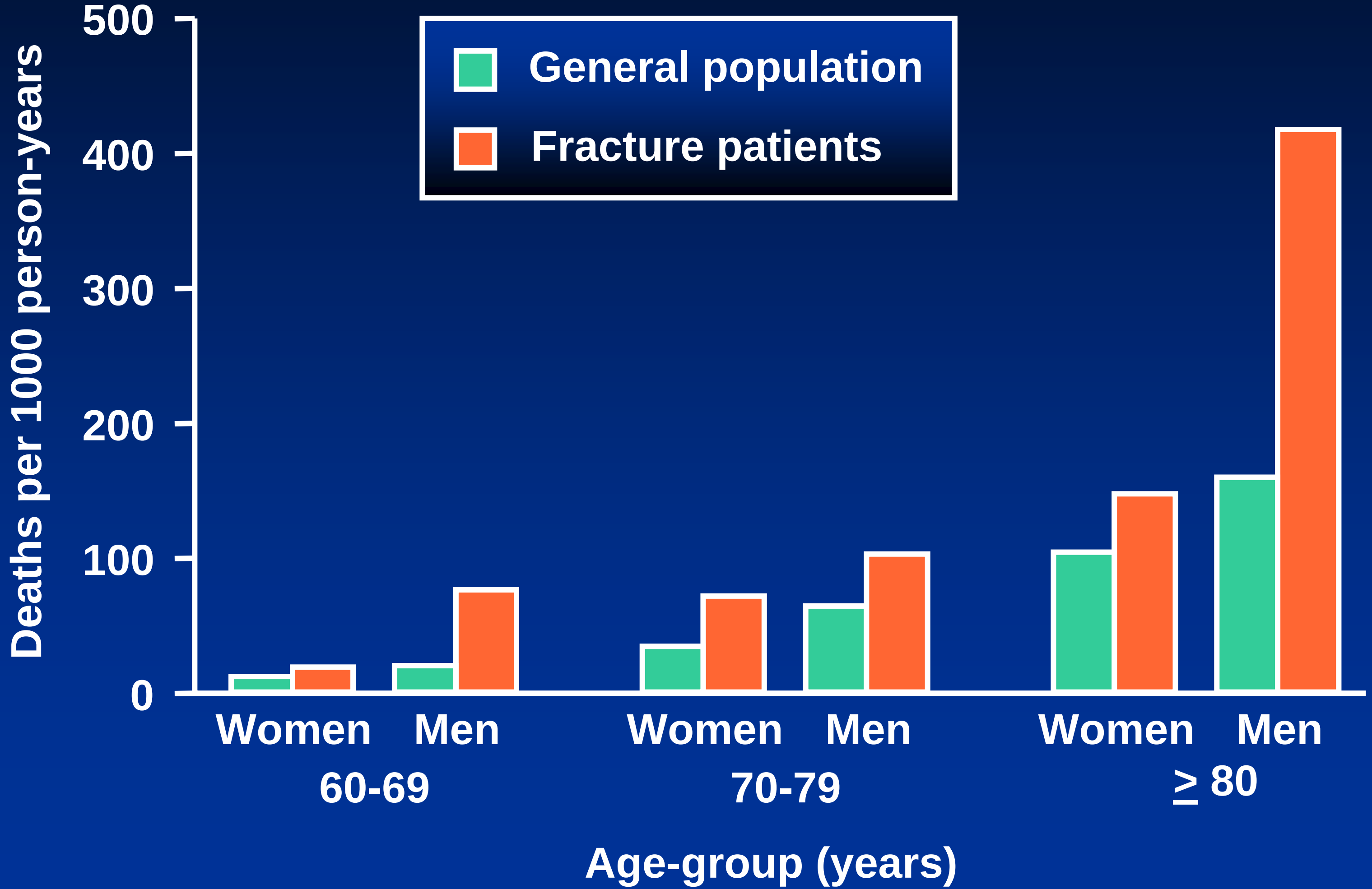
Bilezikian J.P., J.C.E.M., 1999

Age-specific incidence of hip fractures



Melton L.J. III et al., Public Health Rep., 1996

Mortality rates for fracture patients and general population by sex and age-group



Center J.R. et al., Lancet, 1999

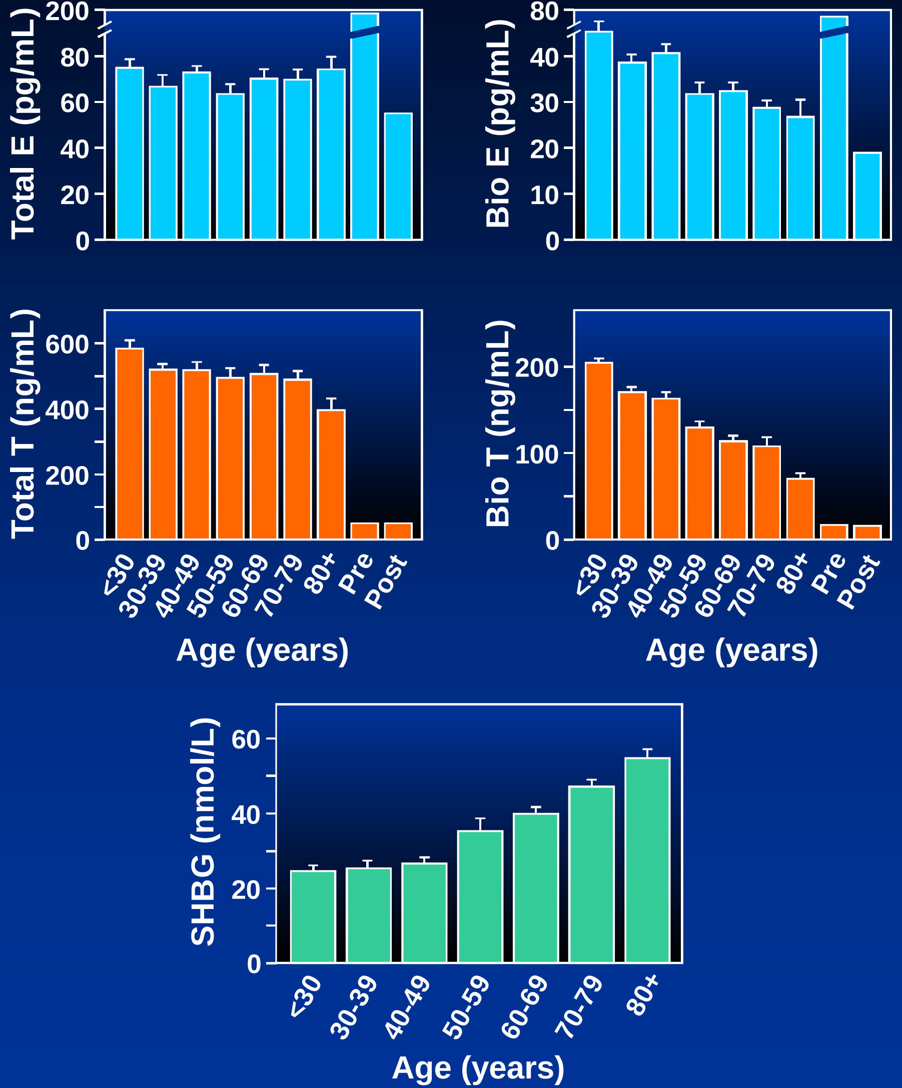
Estrogens as key factors in the establishment of peak bone mass in men

Chronological age (yrs)	28	24, 3/12
Karyotype	46, XY	—
Phenotype	normal male	normal male
Bone age (yrs)	15	14
Testosterone	=	–
Dihydrotestosterone	=	–
Estradiol	–	‡
Estrone	–	‡
Radial BMD	—	0.570 (-4.65 SDS)
Lumbar BMD	0.745 (<2.0 SD for bone age)	0.931 (-1.68 SDS)
Height (cm)	204	204 (+3.7 SDS)
Weight (kg)	127	135.1 (+2.1 SDS)
Estrogen therapy	Ineffective	Effective
Defect	Estrogen resistance	Aromatase deficiency

Smith E.P. et al., N.E.J.M., 1994

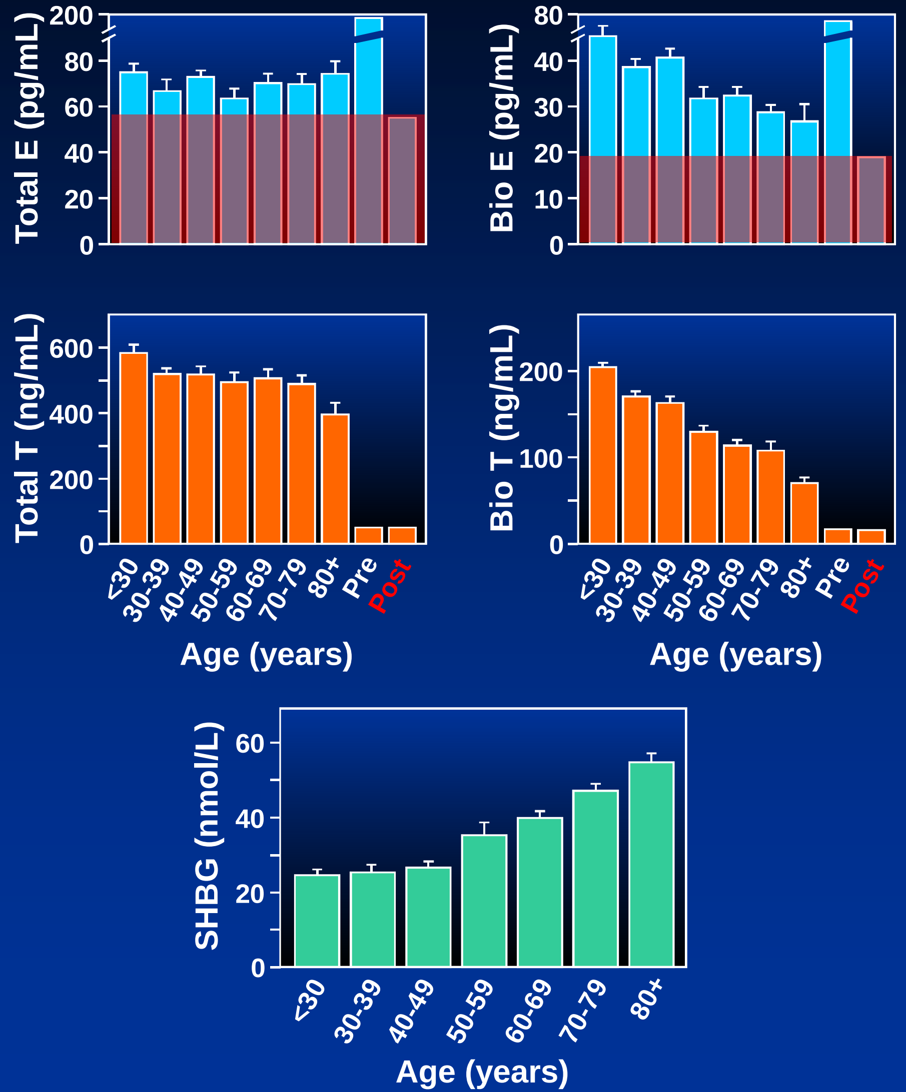
Morishima A. et al., J.C.E.M., 1995

Changes in serum estrogen (top), testosterone (middle) and sex hormone binding globulin (bottom) in aging men



Khosla S. et al., J.C.E.M. 1998

Changes in serum estrogen (top), testosterone (middle) and sex hormone binding globulin (bottom) in aging men



Khosla S. et al., J.C.E.M. 1998

Possible causes of higher bone fragility in women

- Smaller bone size at peak bone mass

- Trabecular bone loss causes a deeper architectural damage

- Lower periostal bone apposition with aging

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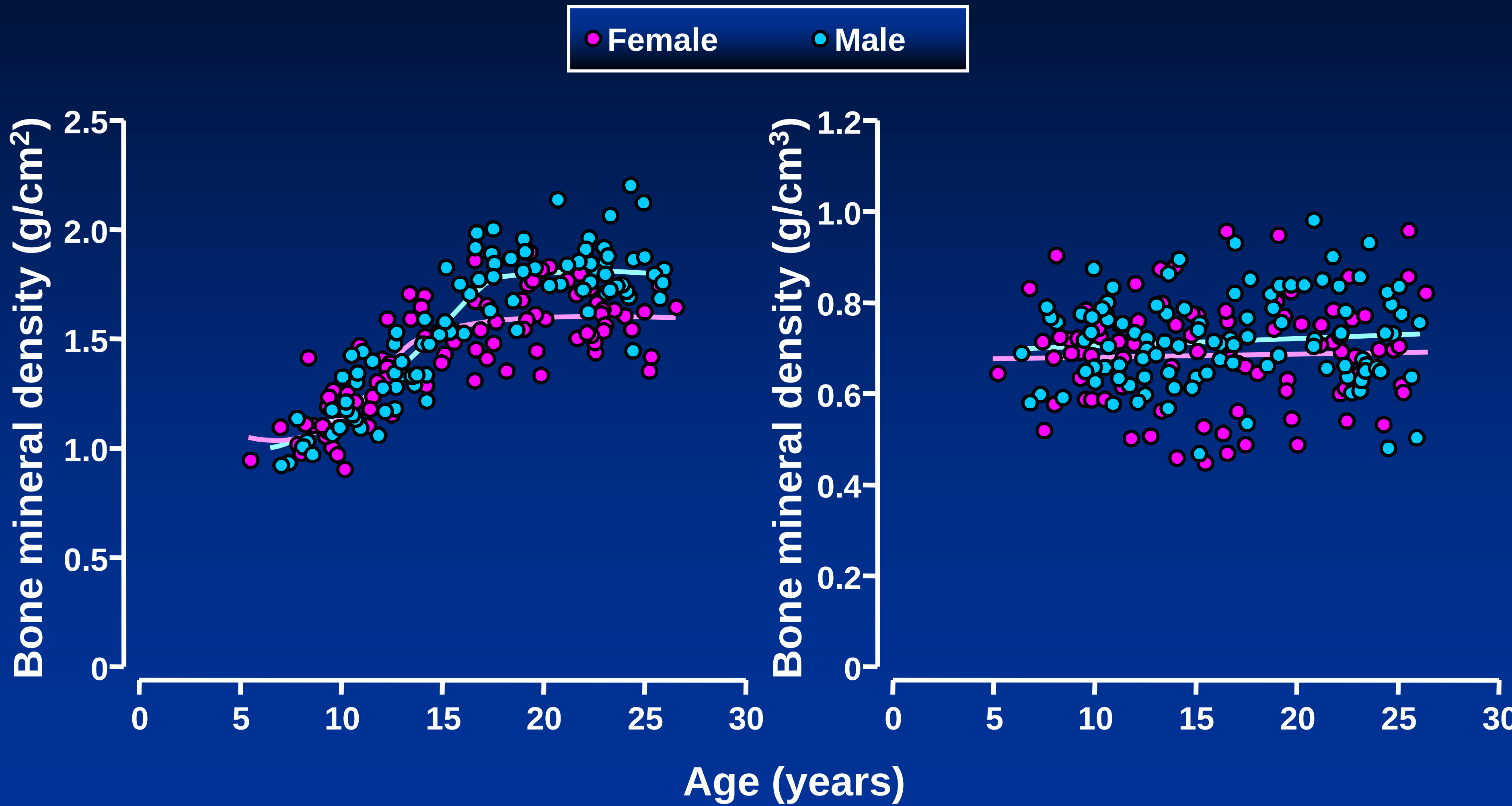
Growing: areal (left) and volumetric (right) bone mineral density at femural shaft



Lu P.W. et al., J.C.E.M., 1996

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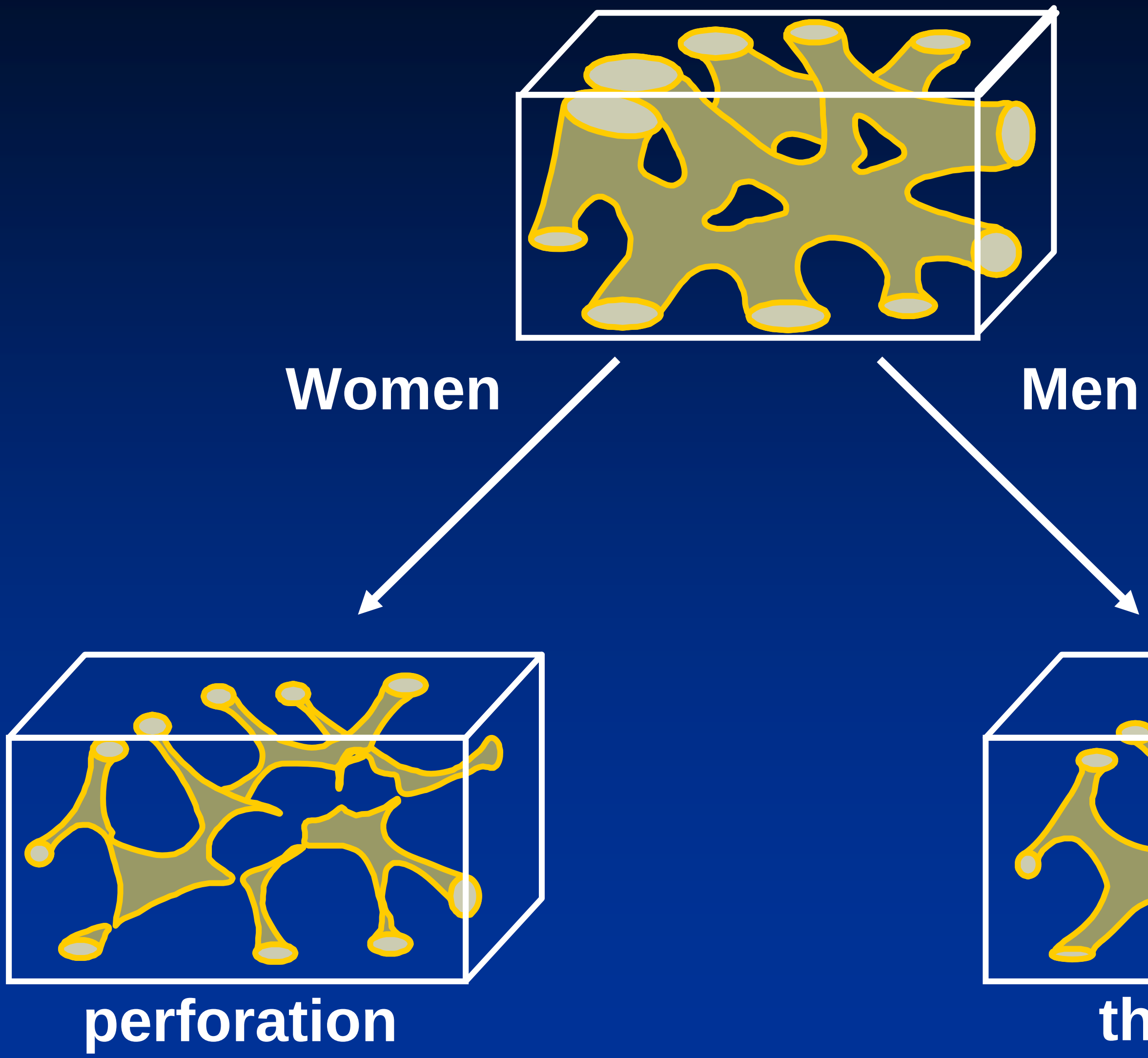
Mechanisms of loss of trabecular bone in women and trabecular thinning in men



Seeman E., Lancet, 2002

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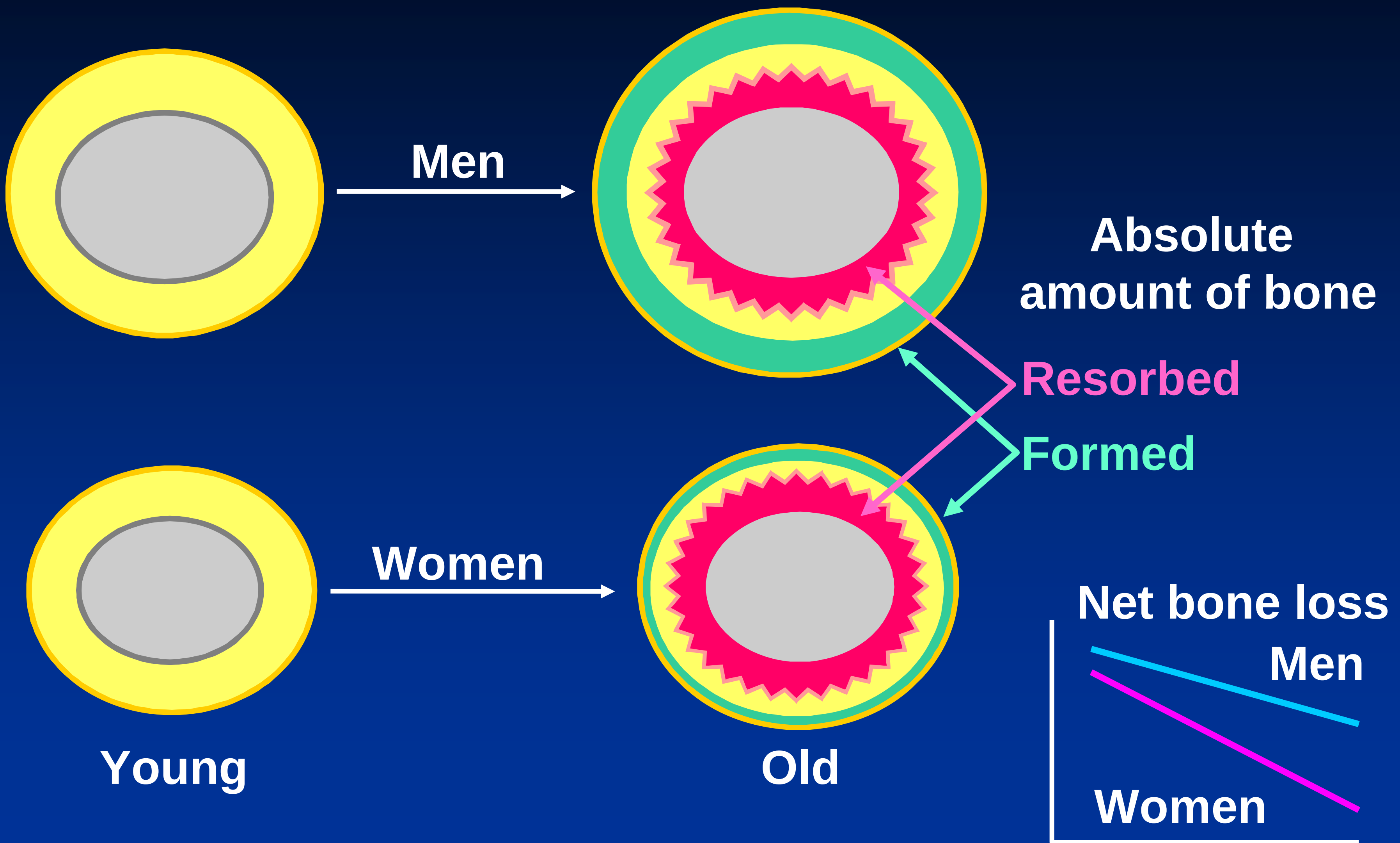
Ageing: position and extent of bone loss in men and women



Seeman E., Lancet, 2002

CAUSES OF SECONDARY OSTEOPOROSIS

Hypogonadal states
- Turner syndrome
- Klinefelter syndrome
- Anorexia nervosa
- Hypothalamic amenorrhea
- Hyperprolactinemia
- Other primary/secondary hypogonadal states

Endocrine disorders
- Cushing’s syndrome
- Hyperparathyroidism
- Thyrotoxicosis
- Insulin-dependent diabetes mellitus
- Acromegaly
- Adrenal insufficiency

Nutritional and gastrointestinal disorders
- Malnutrition
- Parenteral nutrition
- Malabsorption syndromes
- Gastrectomy
- Severe liver disease, especially biliary cirrhosis
- Pernicious anemia

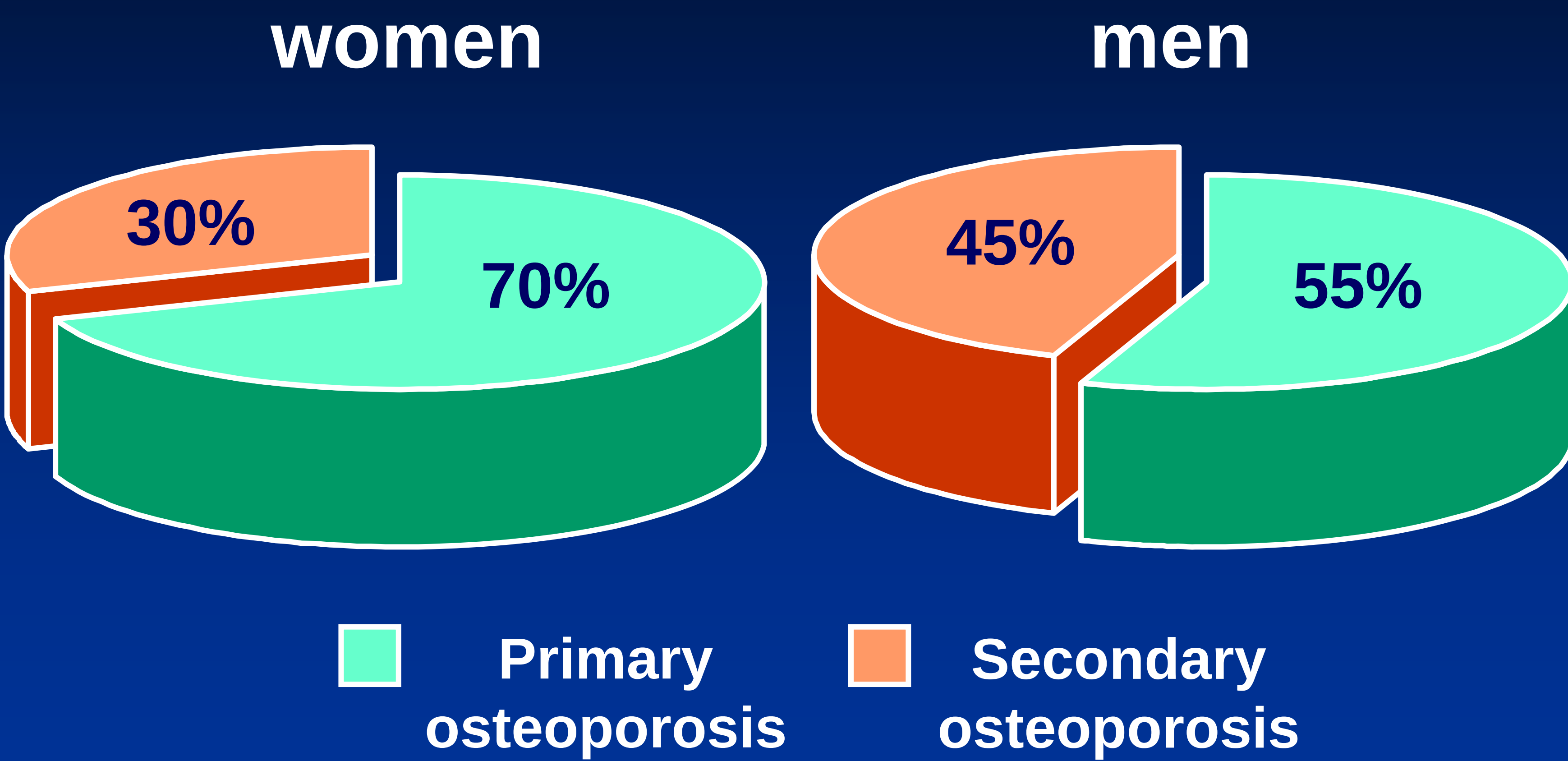
Rheumatologic disorders
- Rheumatoid arthritis
- Ankylosing spondylitis

Hematologic disorders/malignancy
- Multiple myeloma
- Lymphoma and leukemia
- Malignancy-associated parathyroid hormone related (PTHrP) production
- Mastocytosis
- Hemophilia
- Thalassemia

Selected inherited disorders
- Osteogenesis imperfecta
- Marfan syndrome
- Hernochromatosis
- Hypophosphatasia
- Glycogen storage diseases
- Homocystinuria
- Ehlers-Danlos syndrome
- Porphyria
- Menkes’ syndrome
- Epidermolysis bullosa

Other disorders
- Immobilization
- Chronic obstructive pulmonary disease
- Pregnancy and lactation
- Scoliosis
- Multiple sclerosis
- Sarcoidosis
- Amyloidosis

Rate of primary and secondary osteoporosis in women and men



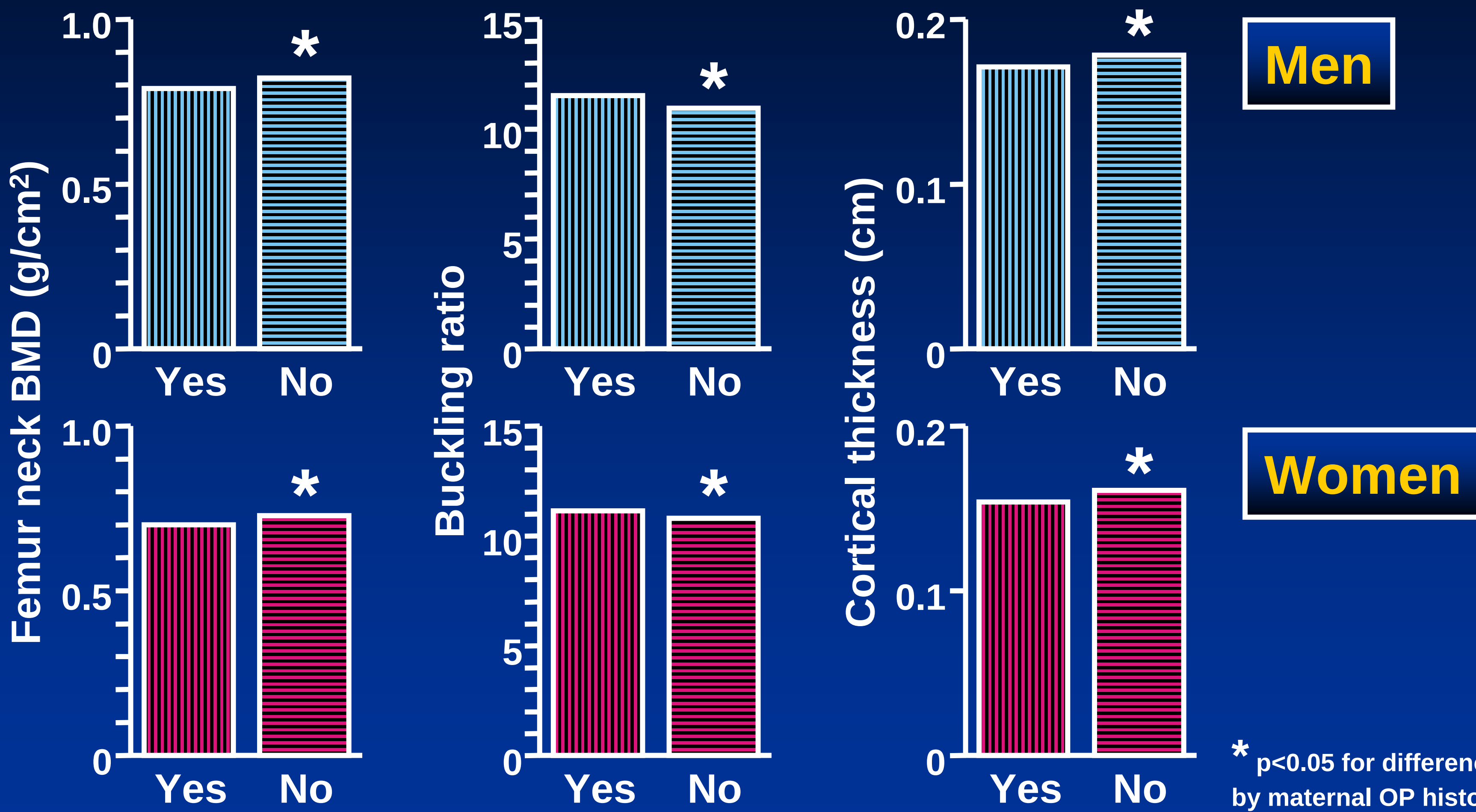
- Patient history
- Physical examination

Risk Factors

- familial
- nutritional
- environmental
- social
- medical
- pharmacological
- ....

Adjusted bone variable means according to maternal osteoporosis history

Maternal history of osteoporosis



* p<0.05 for differences by maternal OP history within sex category

Looker A.C. & Beck T.J., C.T.I., 2004

Bone related toxic effects before and after diagnosis of prostate cancer

	12 Mo before diagnosis (%)	P value	12 to 60 Mo after diagnosis	P value
OSTEOPOROSIS				
Androgen deprivation therapy	0.59	0.19	6.92	<0.001
No androgen deprivation therapy	0.46		3.69	
ANY FRACTURE				
Androgen deprivation therapy	3.41	0.01	19.37	<0.001
No androgen deprivation therapy	2.80		12.63	
FRACTURE RESULTING IN HOSPITALIZATION				
Androgen deprivation therapy	0.26	0.49	5.19	<0.001
No androgen deprivation therapy	0.21		2.35	

Shahinian V.B. et al., N.E.J.M., 2005

Physical signs

- Height loss
- Armspan-Height difference
- Weight ⟵
- Kyphosis ⟵
- Wall-Occiput distance ⟵
- Rib-Pelvis distance ⟵
- Grip strength
- Hand skinfold
- Tooth count ⟵

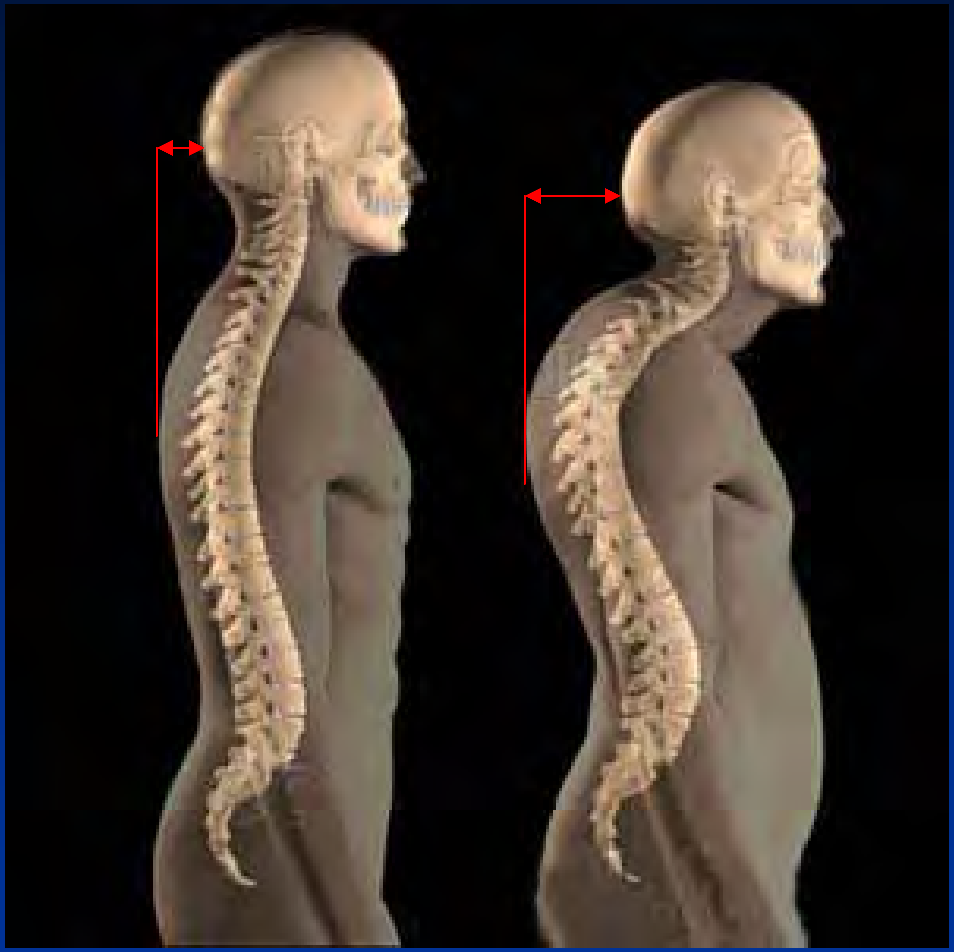
Physical signs and osteoporosis: anthropometric variables

	MEN with fractures	WOMEN with fractures
Sitting height *	‡	‡
Leg length *	=	‡
Arm span *	=	‡

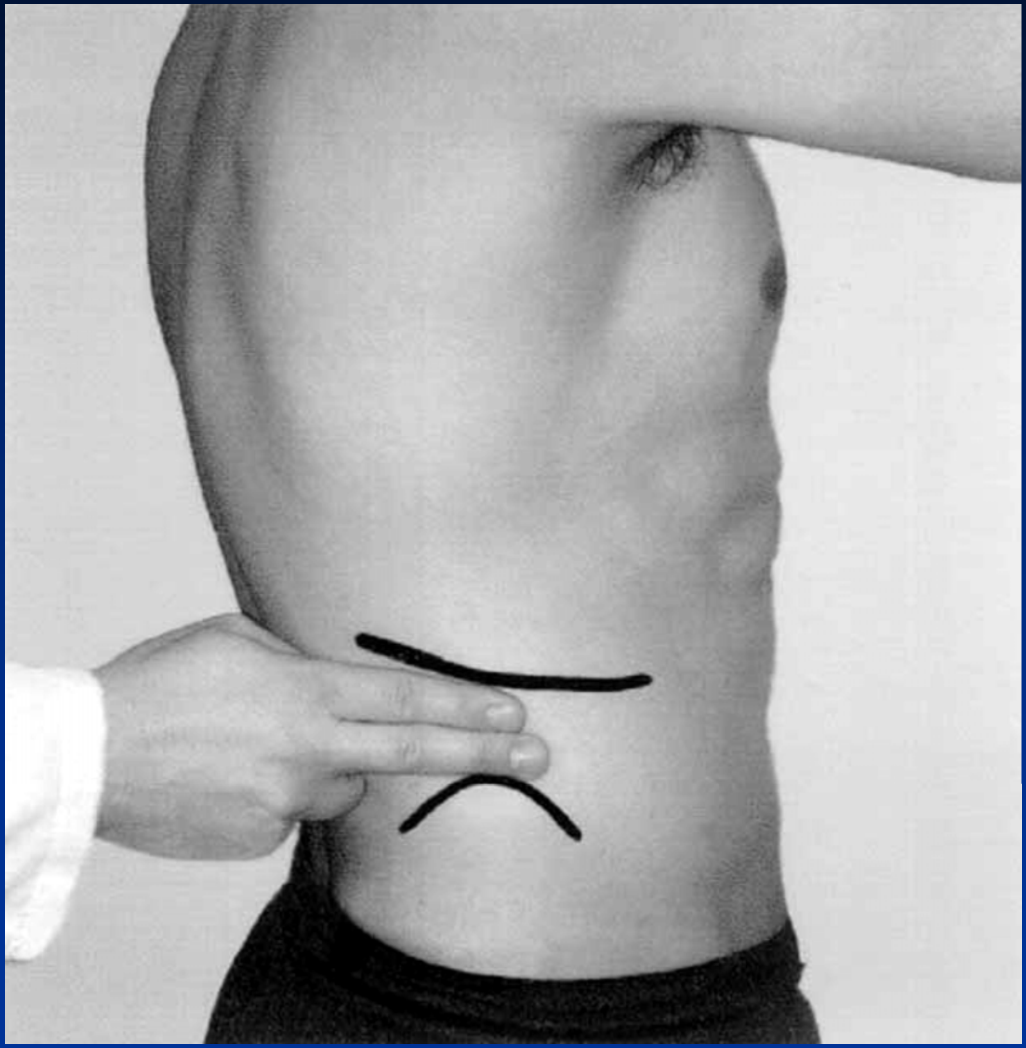
* relative to age-matched controls

Wang X.F. et al., Osteoporos. Int., 2004

Wall-occiput test for occult thoracic vertebral fractures



Rib-pelvis distance test for occult lumbar vertebral fractures



Siminoski K. et al., Am. J. Med., 2003

Physical examination

- **Genetic forms of osteoporosis**

  Pathognomic manifestations of diseases

Ehlers-Danlos syndrome

by permission of Prof. P. Filipponi

Physical examination

Genetic forms of osteoporosis

- Pathognomic manifestations of diseases

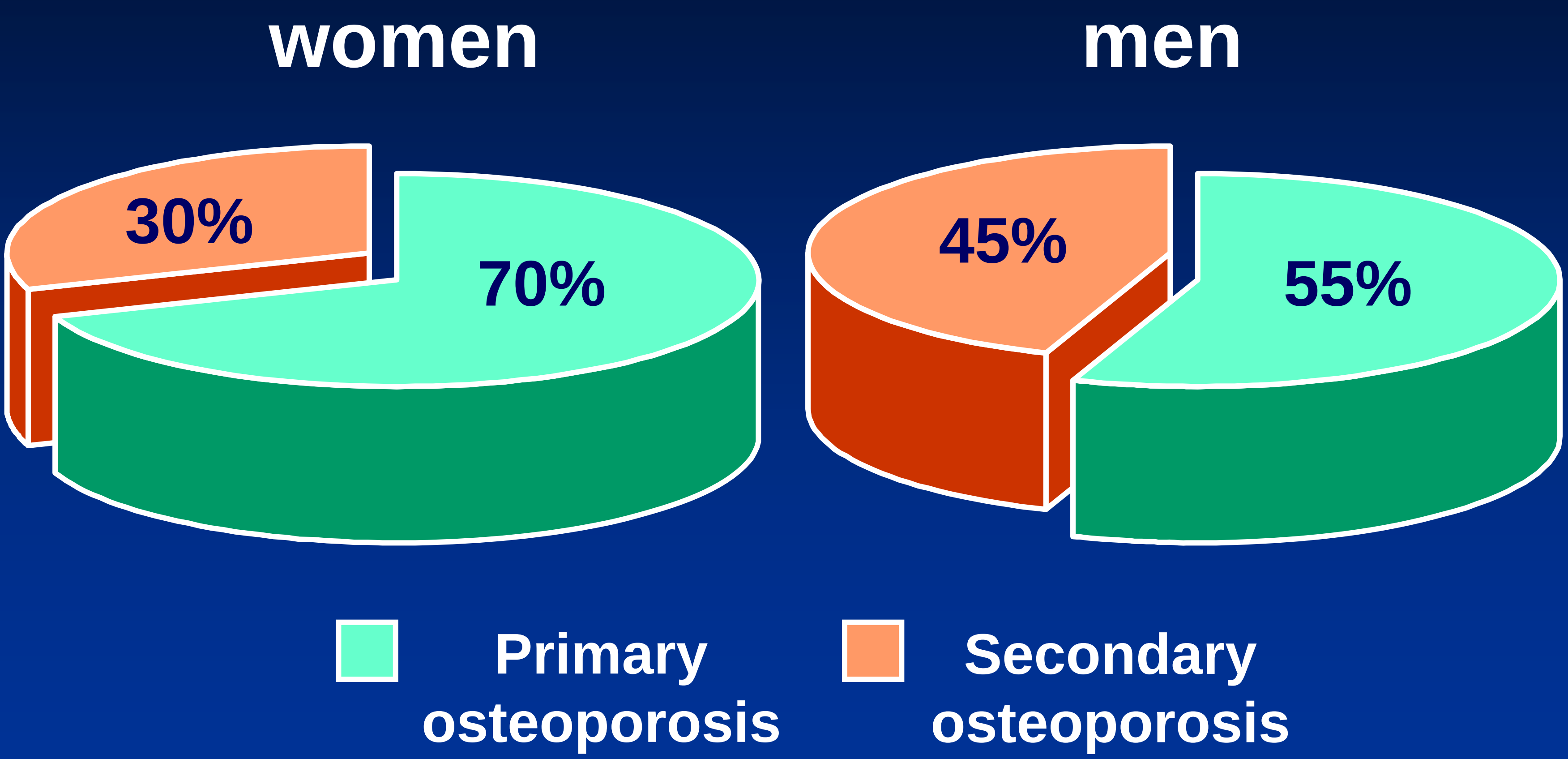
Hyperthyroidism

Routine laboratory tests

- E.S.R.
- Complete blood count
- Calcium
- Phosphorus
- Creatinine
- Alkaline phosphatase
- Liver function tests (i.e. serum protein electrophoresis, γGT...)
- 24-h urine calcium

If on the basis of these tests (or in relation to the physical examination), there is evidence of medical conditions associated with bone loss a definitive diagnosis should be pursued with appropriate testing

Rate of primary and secondary osteoporosis in women and men



More focused laboratory testing
(to uncover “occult” secondary causes of osteoporosis)

- s. ionized calcium
- s. parathyroid hormone
- s. 25(OH)D
- hormones (s. testosterone, s. TSH, 24-hour urine cortisol)
- s. anti-(gliadin), -tissue transglutaminase and -endomysial antibody
- s. total tryptase
- biochemical marker of bone remodelling
- bone marrow aspiration
- bone biopsy

Celiac disease among patients with osteoporosis

	All	Males	Females
Patients with osteoporosis	266	25	241
Patients with celiac disease	9 (3.4%)	2 (8.0%)	7 (2.9%)

Stenson W.F. et al., Arch. Intern. Med.,2005

BMD and fractures in alcoholics

	Alcoholics (n = 51)	Controls (n = 31)	*p*
BMD at lumbar spine (g/cm^2)	1,025 ± 0,135	1,055 ± 0,152	ns
BMD at femoral neck (g/cm^2)	0,843 ± 0,121	0,854 ± 0,191	ns
BMD at total neck (g/cm^2)	0,968 ± 0,122	1,005 ± 0,173	ns
Vertebral fractures (n,%)	16 (31,4%)	3 (9,7%)	<0,021
Peripheral fractures (n,%)	21 (41,2%)	0	<0,000
All fractures (n,%)	28 (54,9%)	3 (9,7%)	<0,000

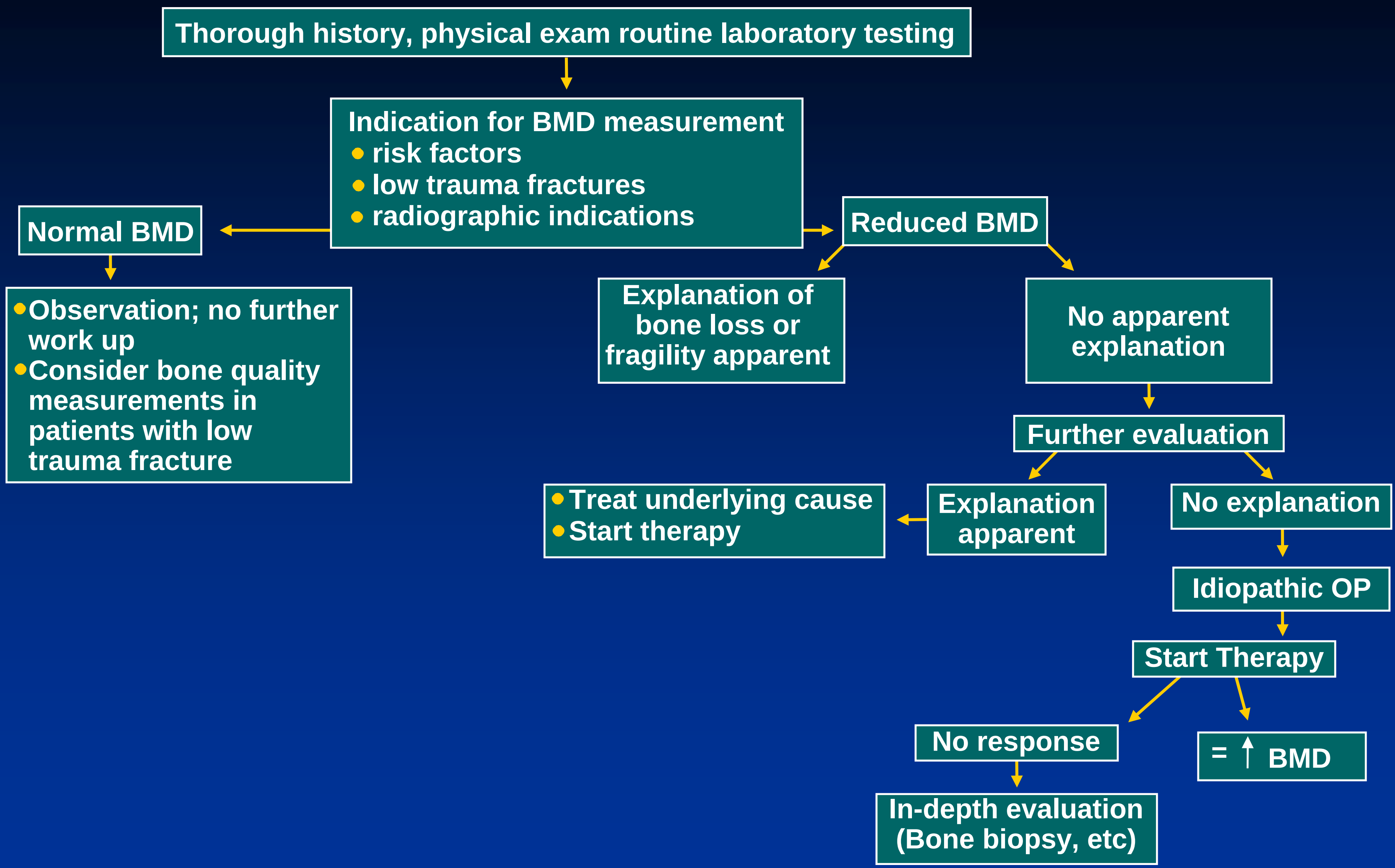
Santori C. et al., (unpublished data)

Fractures in alcoholics according to WHO BMD criteria

	Alcoholics with vertebral fractures (n 16)	Alcoholics with vertebral and non vertebral fractures (n 28)
Normali (n/%)	7 (43,7%)	16 (57,2%)
Osteopenia (n/%)	8 (50%)	9 (32,1%)
Osteoporosis (n/%)	1 (6,3%)	3 (10,7%)

Santori C. et al., (dati non pubblicati)

Clinical evaluation of osteoporosis in men



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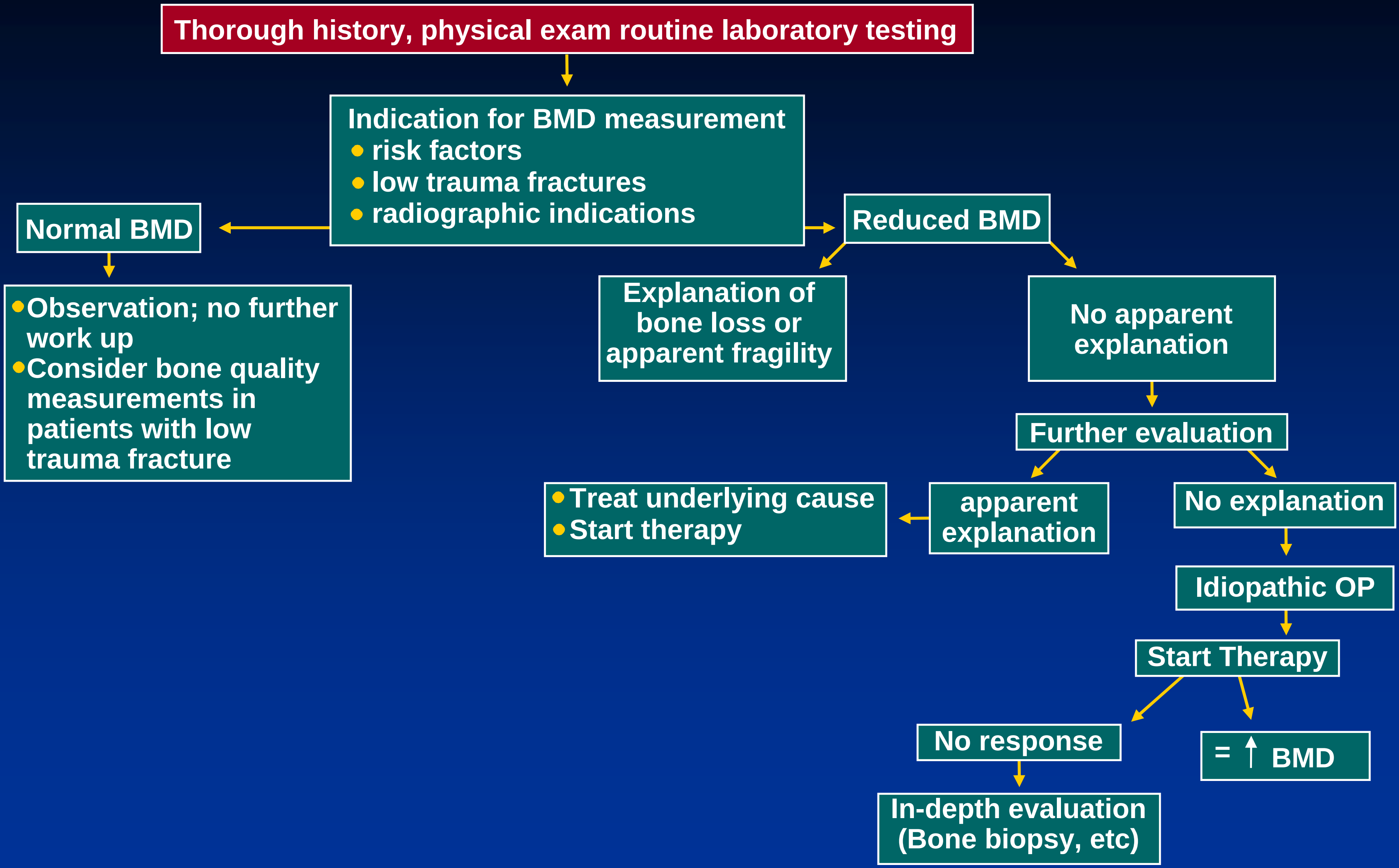

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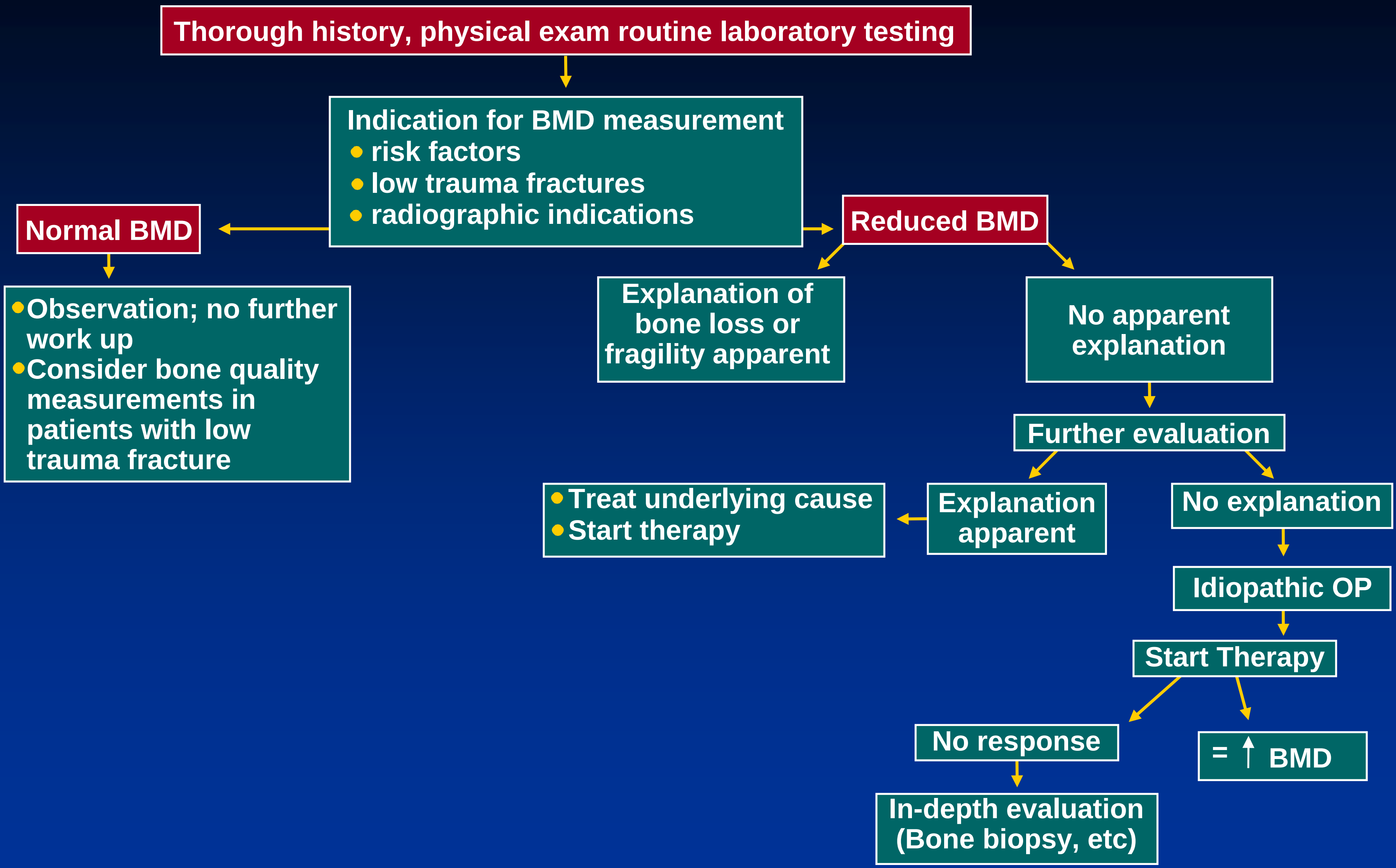

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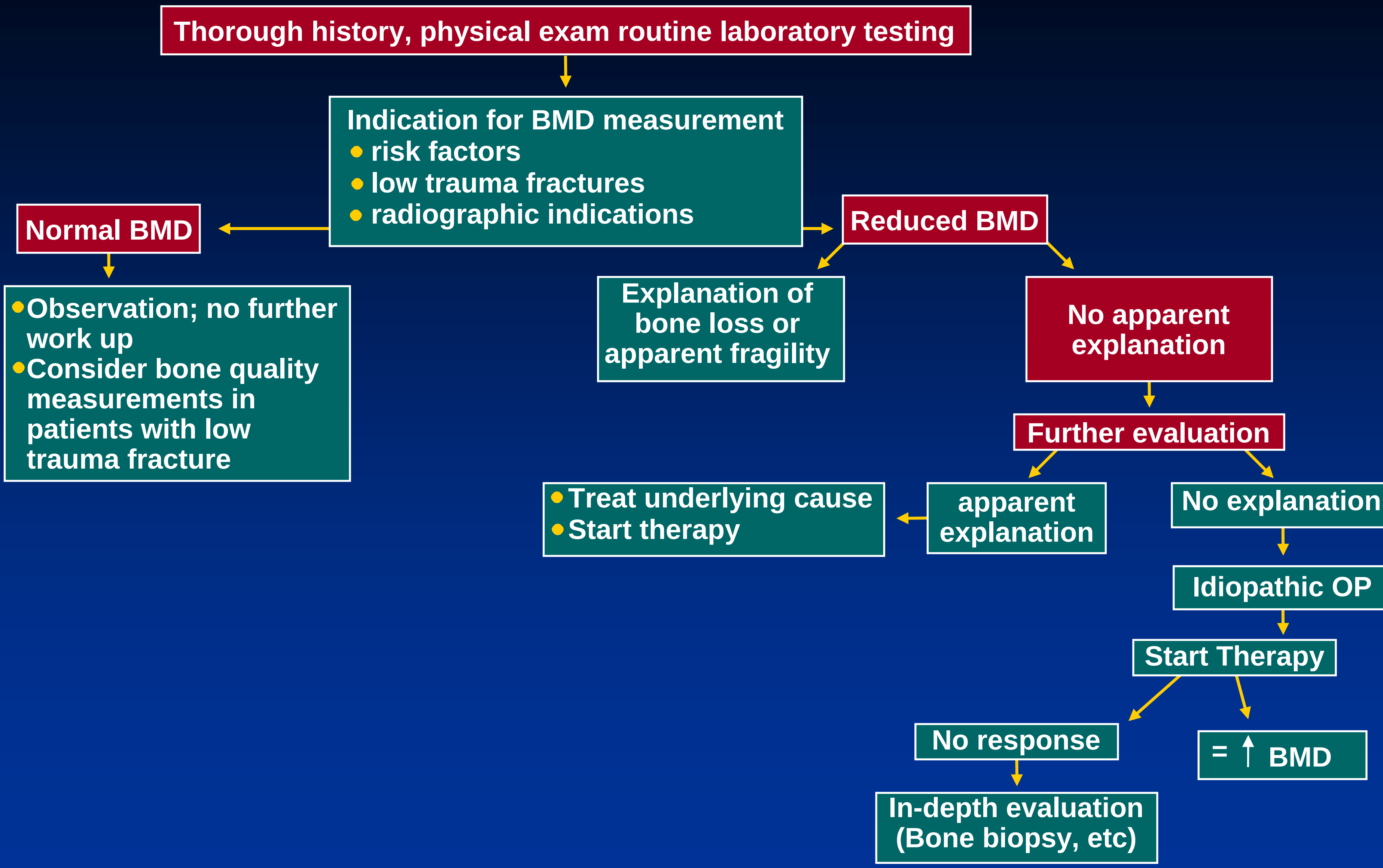
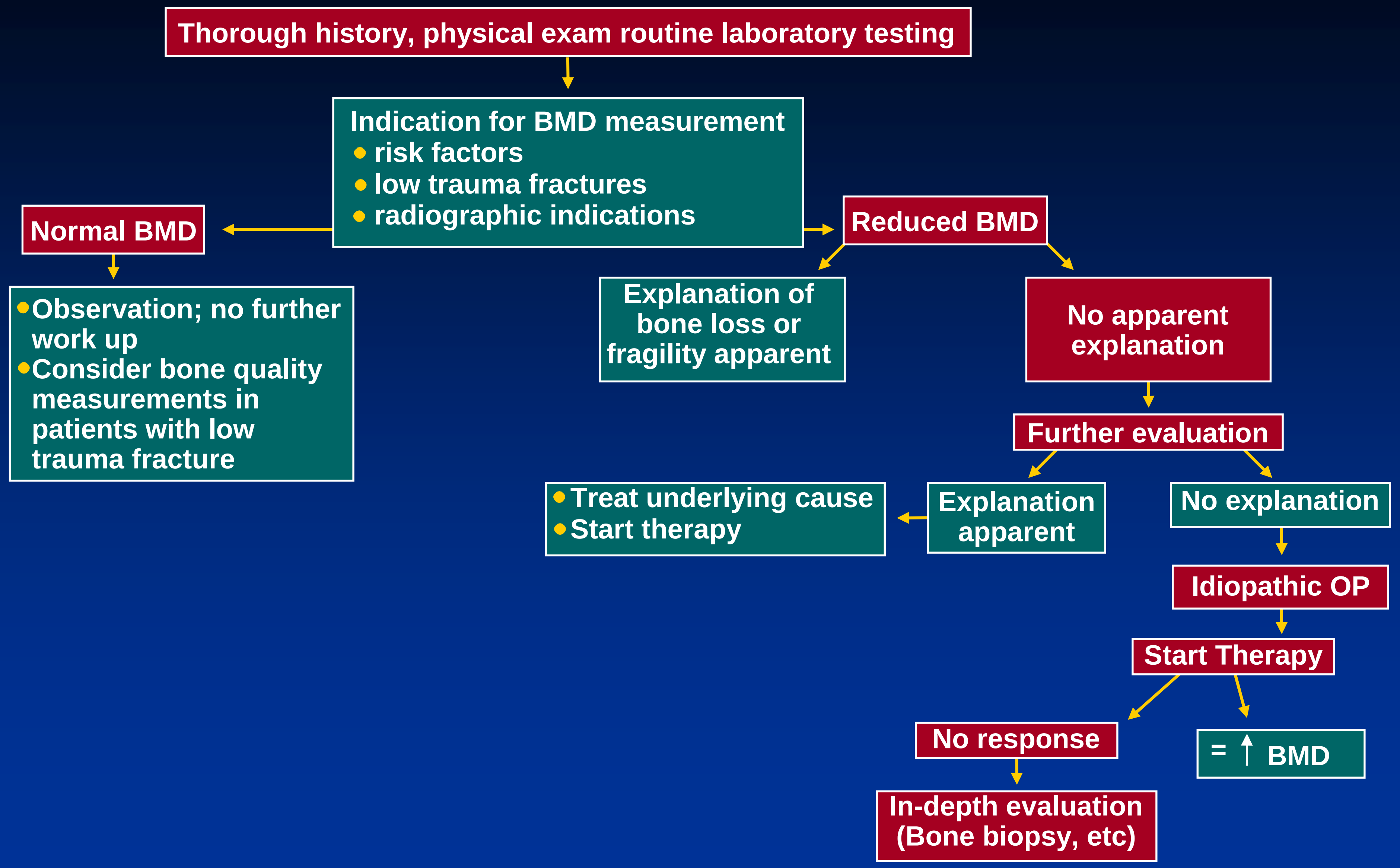
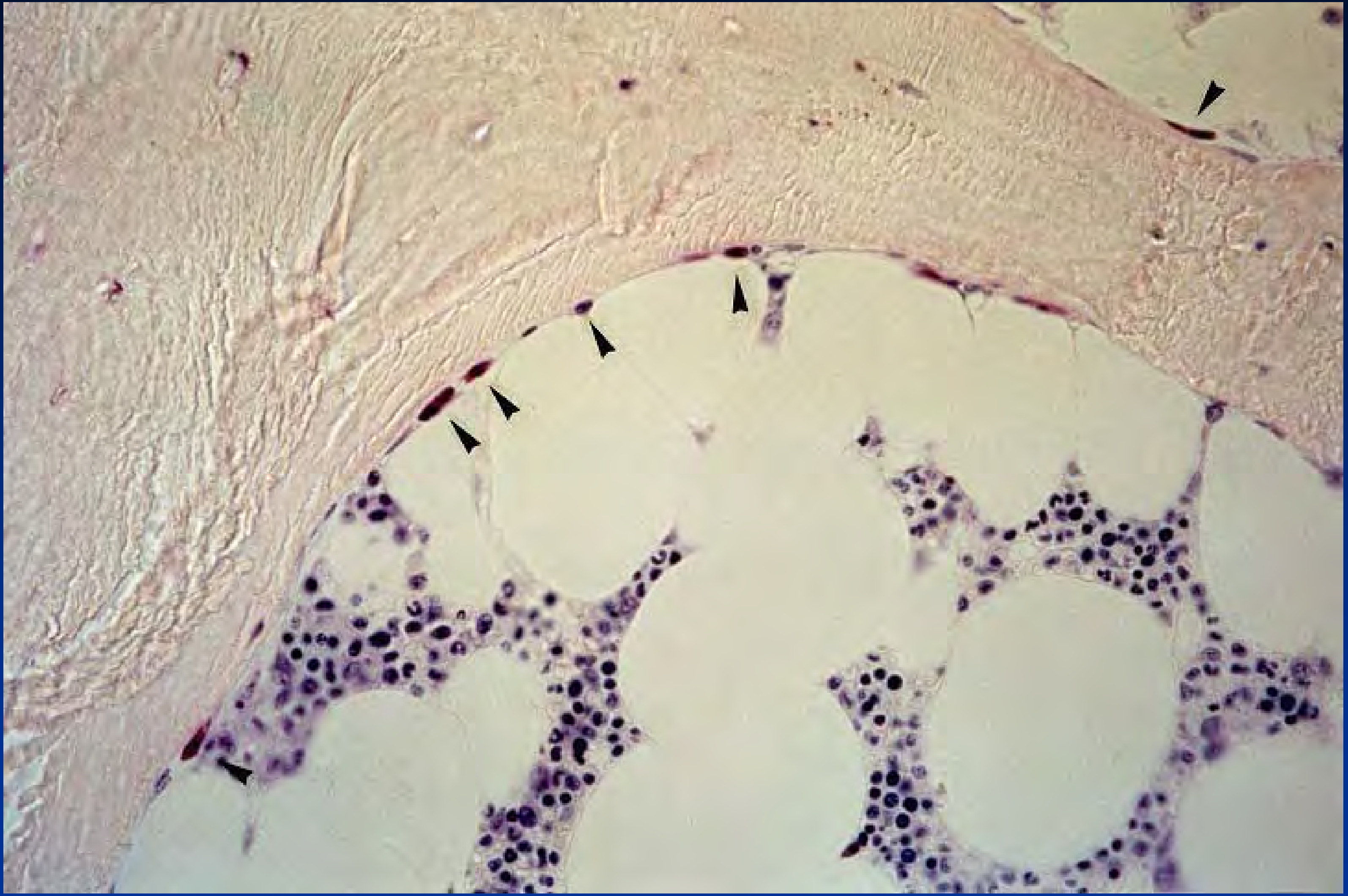


Clinical evaluation of osteoporosis in men

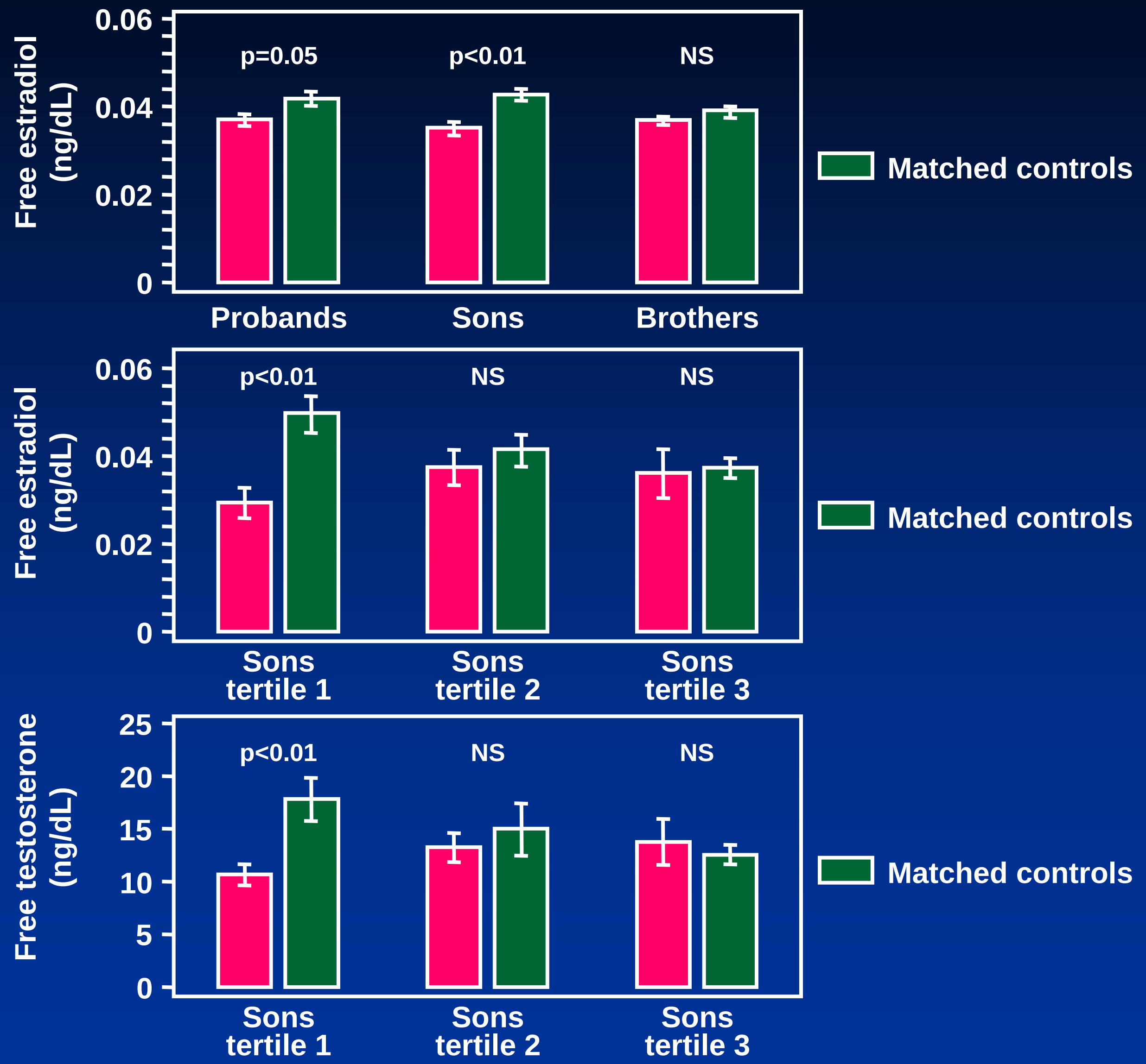


Systemic mastocytosis



Is there a role for estrogen determination?

Sex steroids in male idiopathic osteoporosis

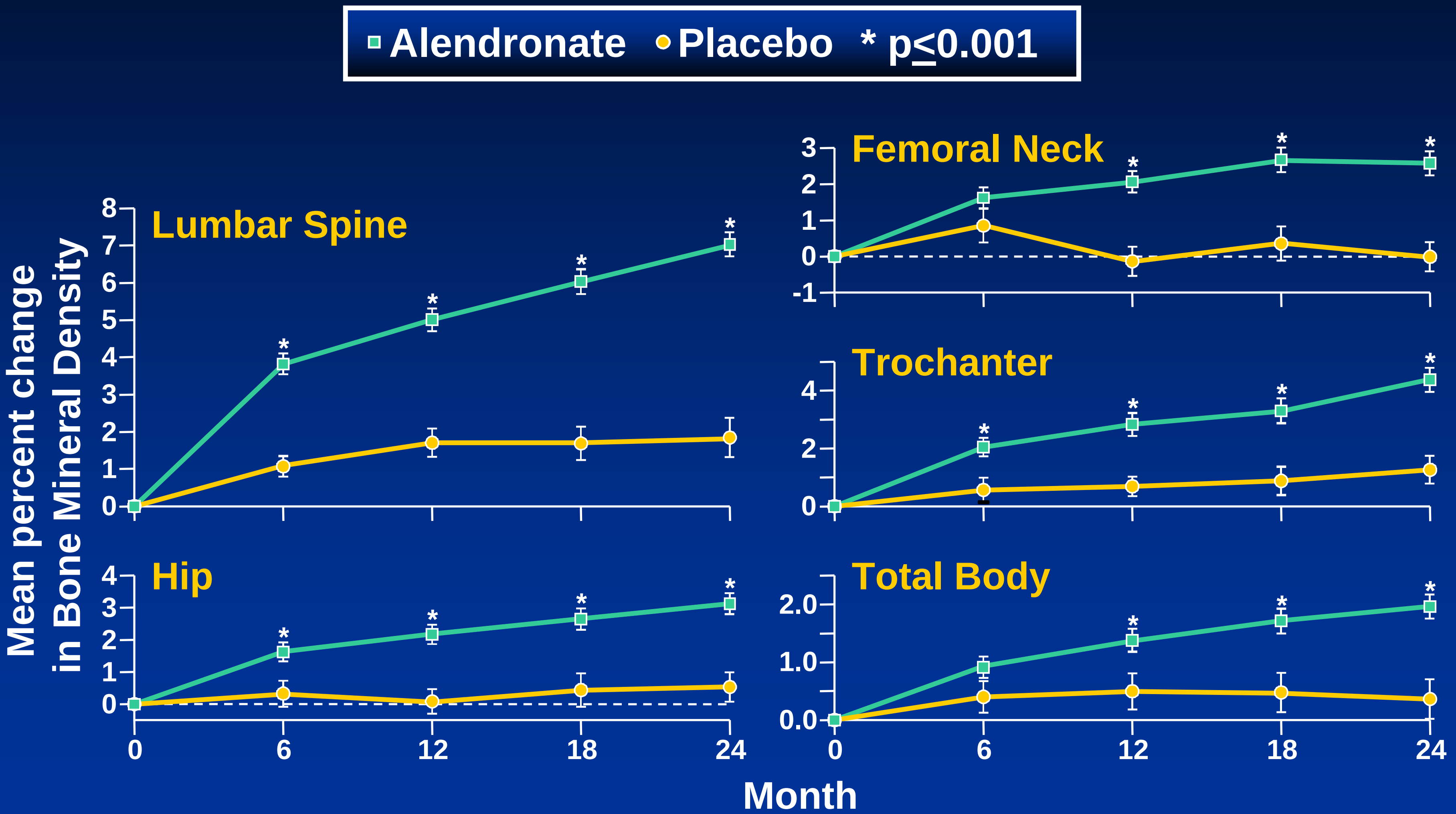


Van Pottelbergh et al., J. Clin. Endocrinol. Metab., 2004

Male osteoporosis: Therapy

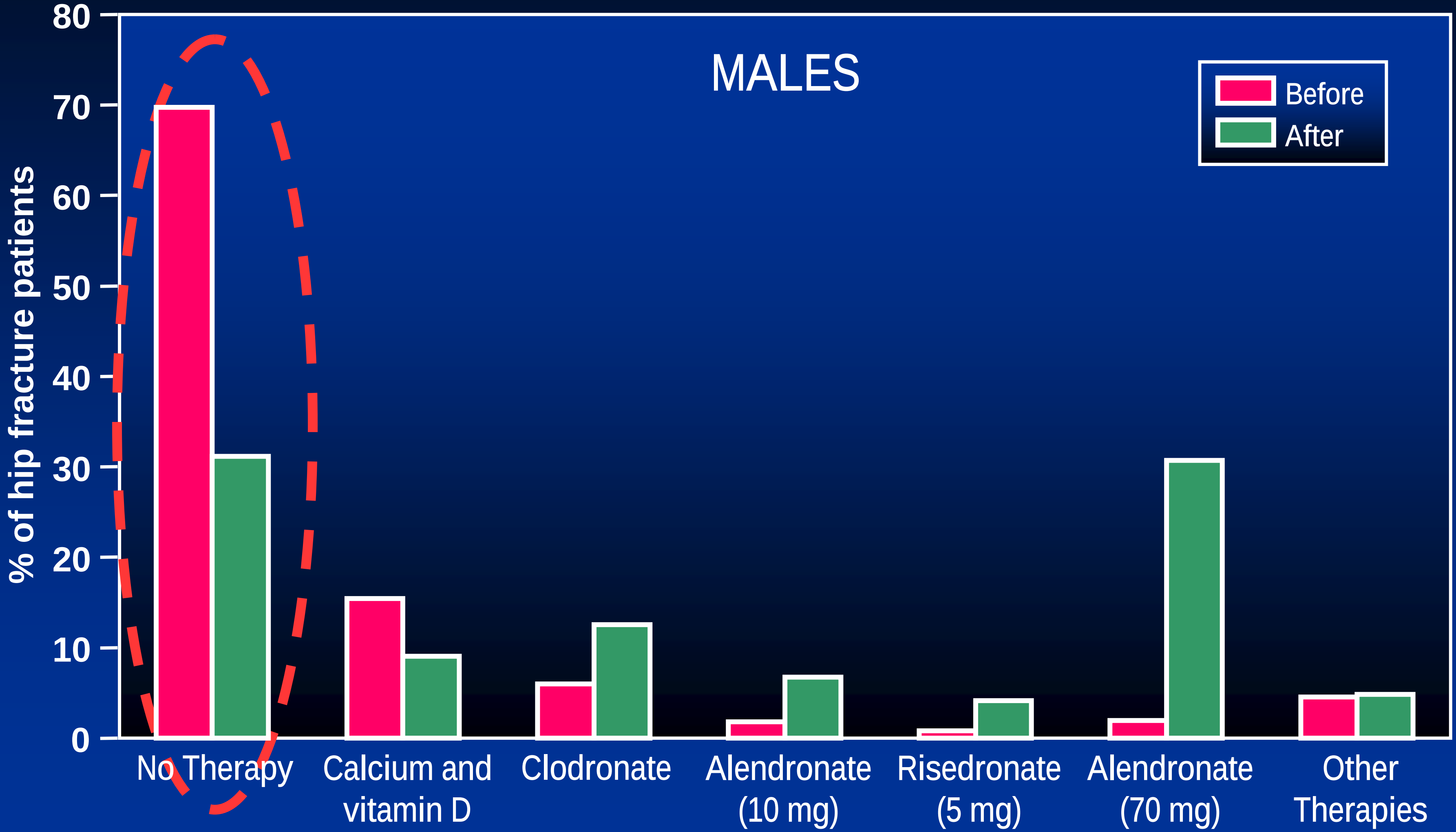
- life-style modification (stop smoking, alcohol, etc.)
- Physical activity
- Adequate calcium intake (1200-1500 mg)
- Adequate vitamin D supplementation (400-800 UI/die)
- Drugs:
  - hormonal replacement therapy (hypogonadism)
  - Alendronate
  - (Risedronate, PTH, …)

Alendronate for the treatment of osteoporosis in men



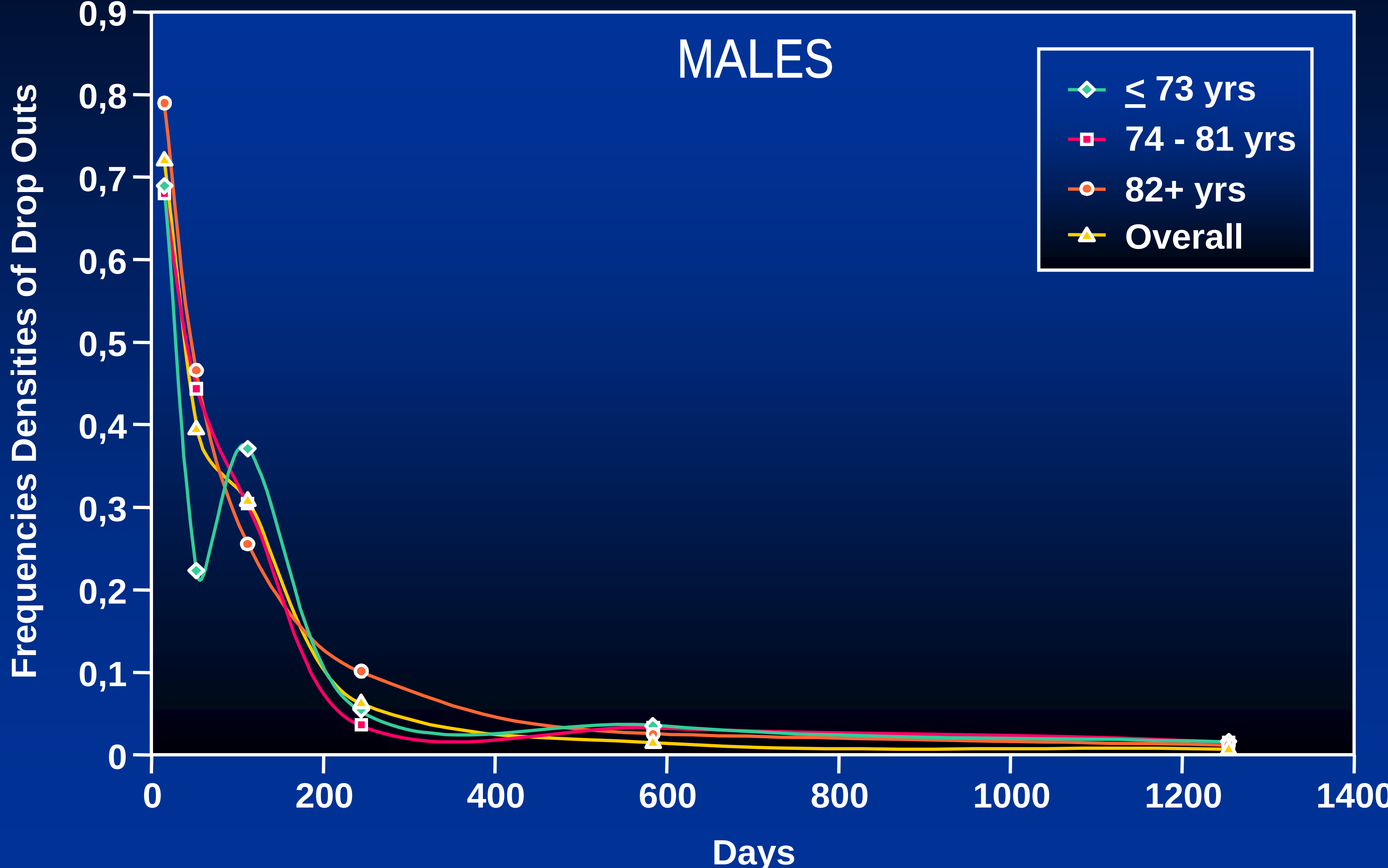
Orwoll E. et al., N.E.J.M., 2000

Use of osteoporosis medication before and after hip fracture



Carnevale V. et al., Osteoporos. Int., 2006

Dropout curves with time of those patients who stopped therapy, with respect age in classes



Carnevale V. et al., Osteoporos. Int., 2006