

# **Management of postmenopausal osteoporosis in Europe**



**Irene Lambrinoudaki**

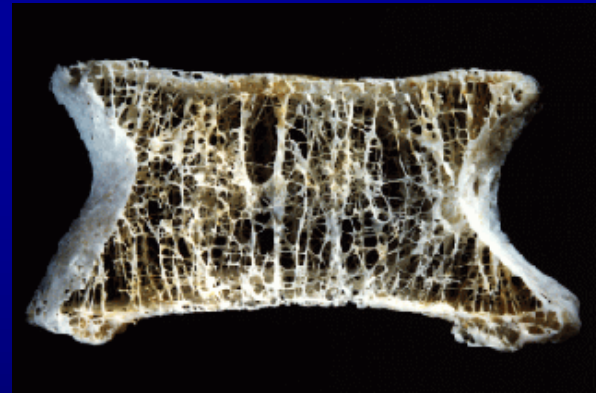
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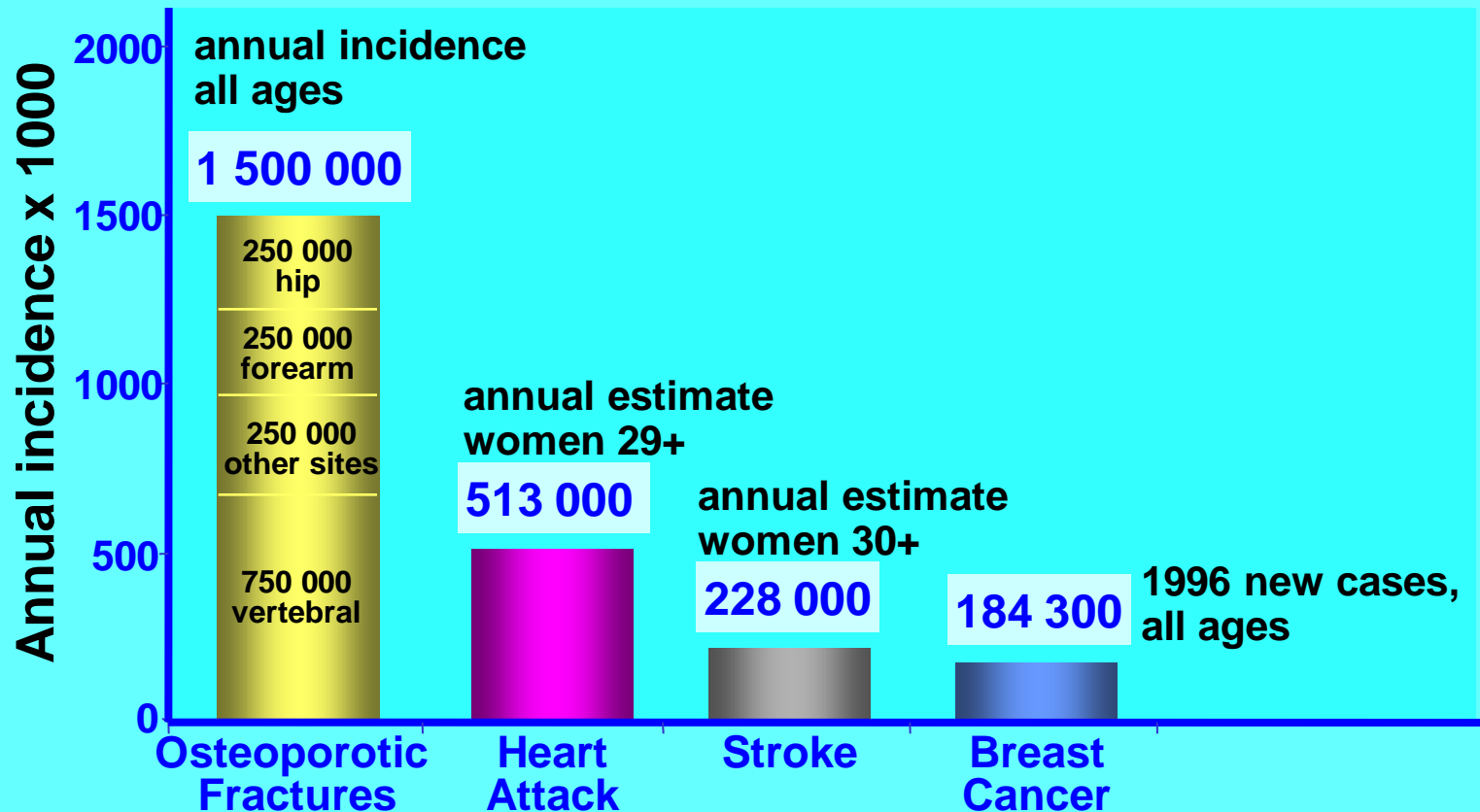
# Osteoporosis

- **Bone disease characterized by low bone mass and reduced mechanical strength leading to low – trauma fractures**



- ✓ **The most frequent menopause – associated disease**

Osteoporotic fractures occur 3 times more often than coronary heart disease and 10 times more often than breast cancer



# Despite increasing awareness fracture rate continues to increase

Germany	2002	2020	2050
Hip fractures	108.341	+44%	+128%
mortality	3.485	+62%	+215%
Lost years with QOL	114.058	+49%	+152%
Cost in million euros	2.736	+47%	+138%

**The health and economic consequences of osteopenia- and osteoporosis-attributable hip fractures**

**in Germany: estimation for 2002 and projection until 2050**

A. Konnopka & N. Jerusel & H.-H. König

Osteoporos Int (2009) 20:1117–1129

# France: although hip fracture mortality declined, vertebral fracture mortality continues to increase

**Table 1.** Standardized Mortality Rates per 100,000 Persons Through the Study Period, by Sex and Site of Osteoporotic Fracture, France, 1968–2004<sup>a</sup>

	1968–1972	1973–1978	1979–1984	1985–1989	1990–1994	1995–1999	2000–2004	% Change <sup>b</sup>
Women								
Hip	294.79	304.9	240.54	196.51	142.8	109.8	102.38	-65.27
Pelvis + vertebrae	5.69	9.01	10.3	9.52	9.38	9.77	9.96	75.01
Skull	3.48	3.45	3.12	3.02	2.82	1.93	1.79	-48.63
Ribs	1.48	2.68	2.68	2.69	2.38	2.45	3.74	152.21
Multiple	2.3	2.41	2.7	2.18	1.53	1.56	4.19	82.34
Others	45.02	50.97	50.35	42.21	36	34.3	42.04	-6.62
All	352.76	373.43	309.69	256.13	194.9	159.8	164.1	-53.48
External causes <sup>c</sup>	361.78	368.03	347.88	341.84	310.29	209.46	176.05	-51.34
General mortality <sup>d</sup>	6,637.04	6,244.72	5,893.97	5,875.37	5,476.01	5,246.21	4,949.3	-25.43

**Population-Level Impact of Osteoporotic Fractures on Mortality and Trends Over Time: A Nationwide Analysis of Vital Statistics for France, 1968–2004**

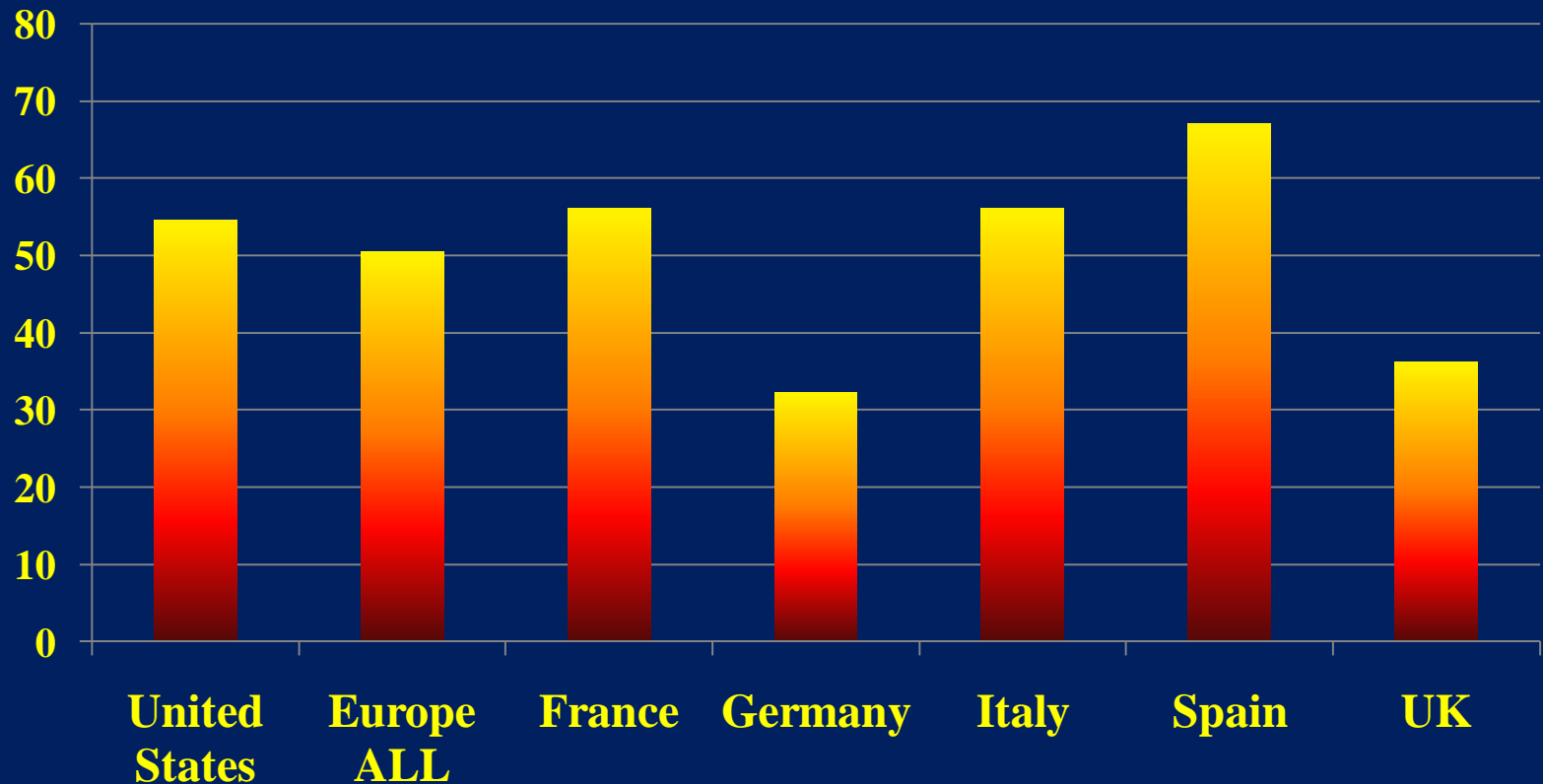
# Europe + USA: less than 50% of women with osteoporosis are diagnosed

%

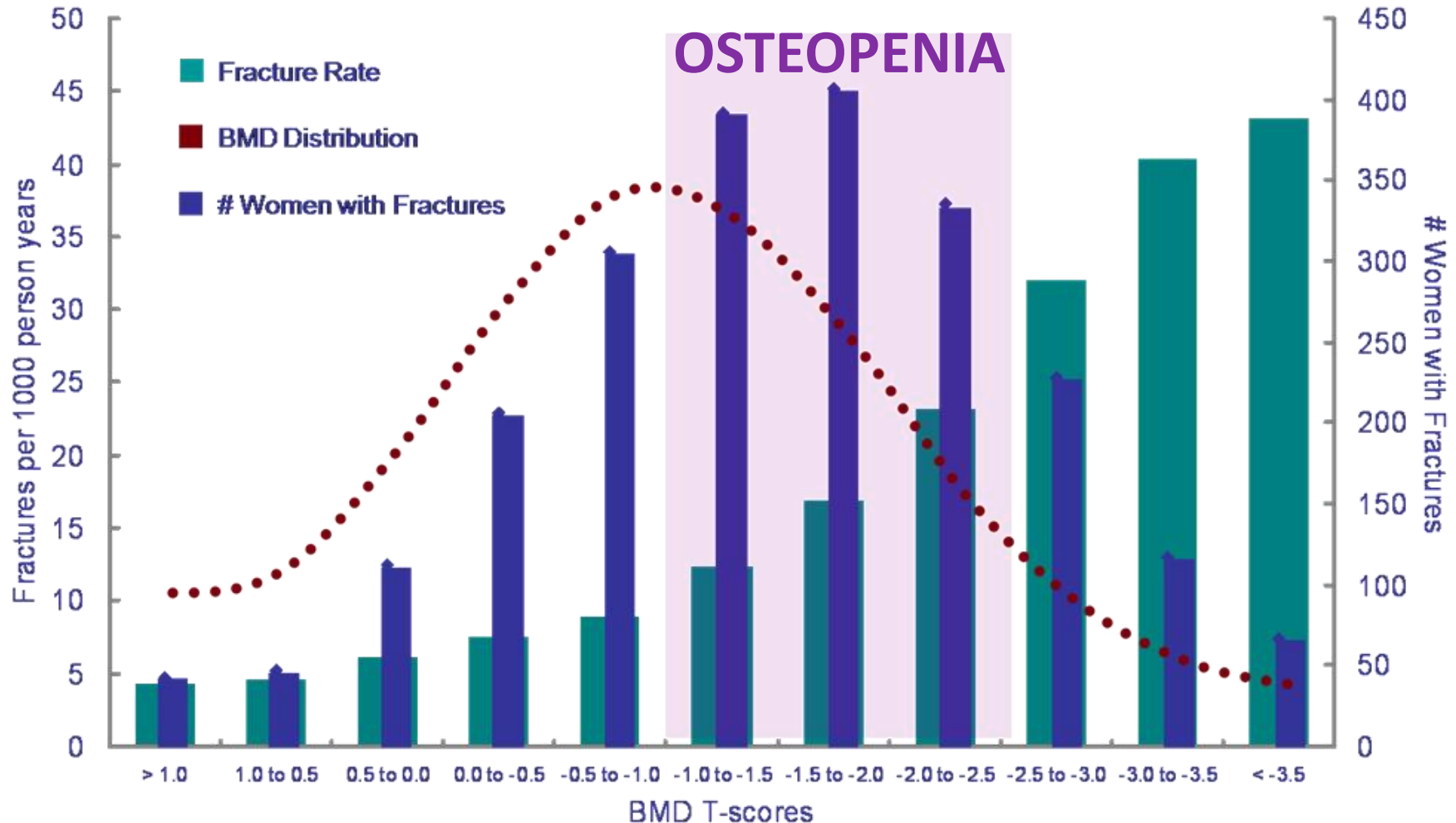
60  
50  
40  
30  
20  
10  
0

# Half of the women with diagnosed osteoporosis receive medical treatment

## % of patients with diagnosed osteoporosis who are drug-treated

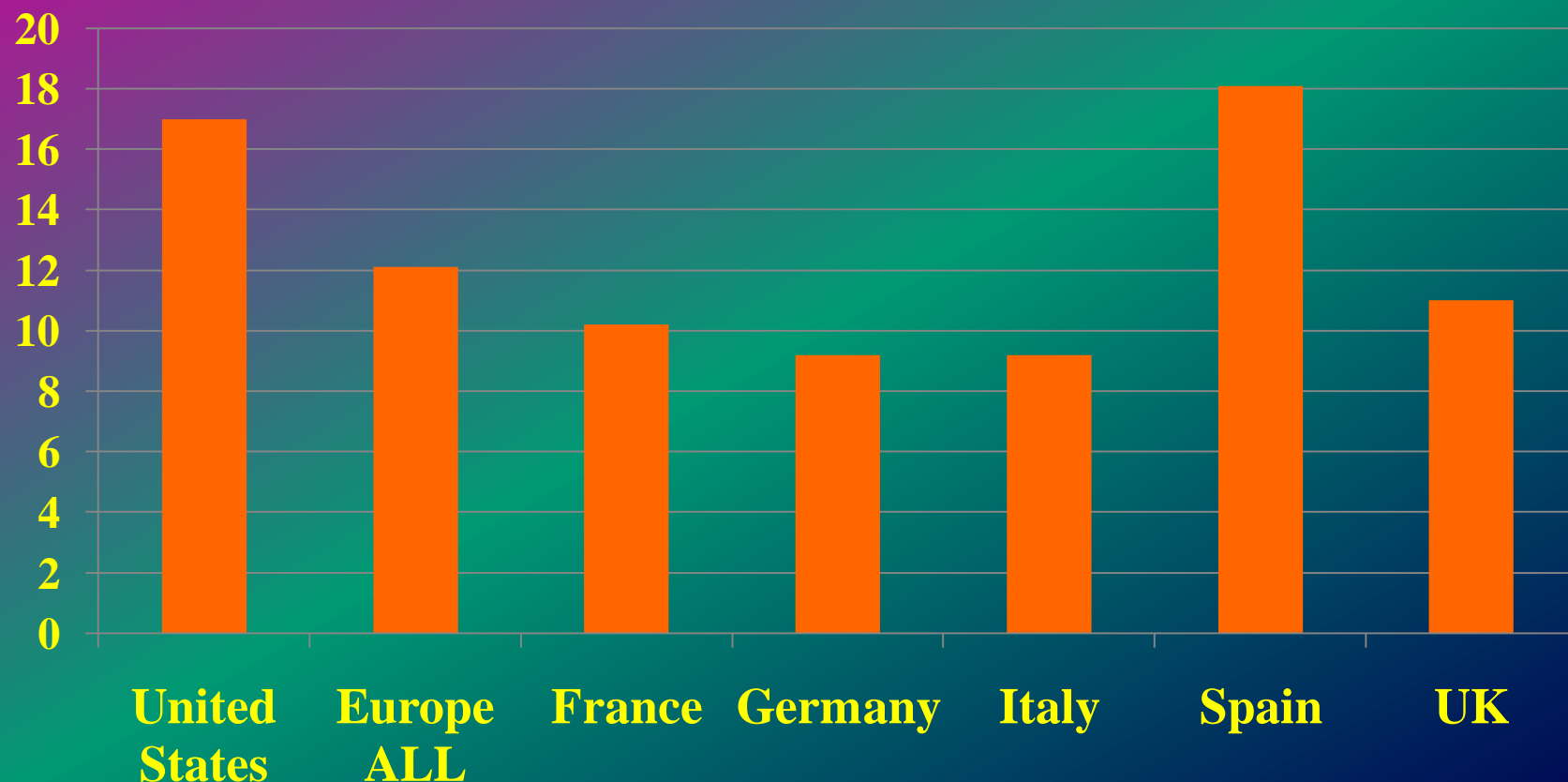


# Most osteoporotic fractures occur in women with osteopenia



# Europe: 12% of women with diagnosed osteopenia receive medical treatment

% of patients with diagnosed osteopenia who are drug-treated



# Increasing the efficacy of osteoporosis management...

## Management targets

- **Women education**
- **Physician education**
- **Identify the high risk patient (case seeking strategy)**
- **Ensure adequate calcium and vitamin D intake**
- **Choose the appropriate treatment**
- **Ensure compliance**
- **Identify treatment failure**

# 1. Patient education

- **GLOW study: to assess the perceived risk of fracture as compared to FRAX-calculated risk**
- **60,000 women from Europe, Australia, USA and Canada were included**

<b>% of women in survey</b>	<b>Perceived risk of fracture</b>
<b>35%</b>	<b>Lower than average</b>
<b>19%</b>	<b>Higher than average</b>
<b>46%</b>	<b>Same as average</b>

# 1. Patient education

- **Women who perceived their risk as higher compared to their peers**



<b>USA</b>	<b>20%</b>
<b>Northern Europe</b>	<b>14%</b>
<b>Southern Europe</b>	<b>20%</b>
<b>Canada</b>	<b>19%</b>
<b>Australia</b>	<b>17%</b>

- **From women with diagnosed osteoporosis**



- **43% perceived themselves at risk of fracture**
- **41% were under medical treatment**

## 2. Physician and care provider education

- **All patients with a previous fragility fracture should receive treatment**

**Brincat M et al. EMAS position statement 2011**

- **505 pts with fragility fractures in Ontario, USA counseled and referred to primary care physicians**

- **51% BMD measurement after Fx**
- **26% initiated treatment**

**Sale JE et al. J Bone Joint Surg Am. 2010 Aug 18;92:1973-80.**

- **France: 349 patients with fragility fracture**
- **Counseled and then referred either to primary care or to hospital osteoporosis Clinic**
- **Interview in six months – management status**



**Only patients receiving care from the hospital  
OP Clinic were under medical treatment**



**Primary care physicians are not alert to the need of  
osteoporosis management**

### 3. Identifying the high-risk patient

- **Based only on BMD, we can prevent 8% of all fractures**

Brinca M et al. EMAS position statement 2011

#### FRAX model: fracture prediction tool

- **Age**
- **Parent with fragility Fx**
- **Glucocorticoid use (> 5mg/d > 3 months)**
- **Previous fragility Fx**
- **Rheumatoid arthritis**
- **Secondary cause of osteoporosis**
- **BMI**
- **smoking**
- **Alcohol use ( $\geq 3$  units/d)**

**10 year  
probability of**

- **Major osteoporotic fx**
- **Hip fx**

**+ hip BMD T-score**

<http://www.shef.ac.uk/FRAX>

### 3. Identifying the high-risk patient

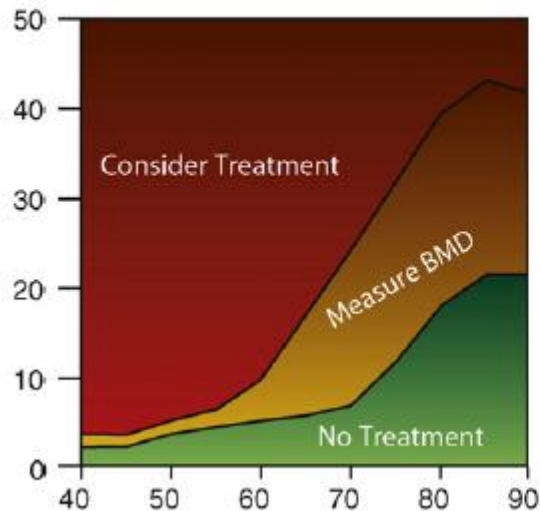
- **Medical treatment is cost-effective when**

- **10-year risk of hip fracture is  $> 3\%$**

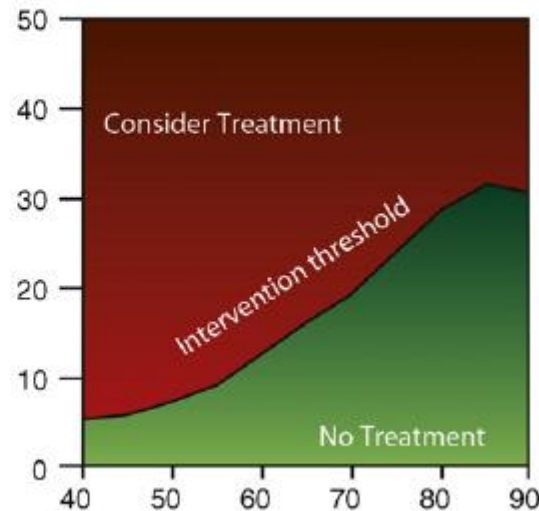
- **10-year risk of major op fracture is  $> 20\%$**

ASSESSMENT WITHOUT BMD

10 year probability of major osteoporotic fracture (%)



ASSESSMENT WITH BMD



**In younger women treatment is considered at a lower threshold**

**Compston J et al, Maturitas 2009;62:105**

**Tosteson AN et al, Osteoporosis Int 2008**

### 3. Case-seeking strategy : increased efficacy, low cost

- 5000 women > 50y in Manitoba, Canada
- Randomization:
- treatment based on

- 
- T-score
  - 10-year fracture risk

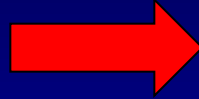
treatment based on fracture risk



- 33% of women reclassified into lower risk categories
- 21% reduction in dispensed medications
- Effect more prominent in women < 65 years

## 4. Calcium and vitamin D supplementation

**Daily requirement  
of postmenopausal  
women**

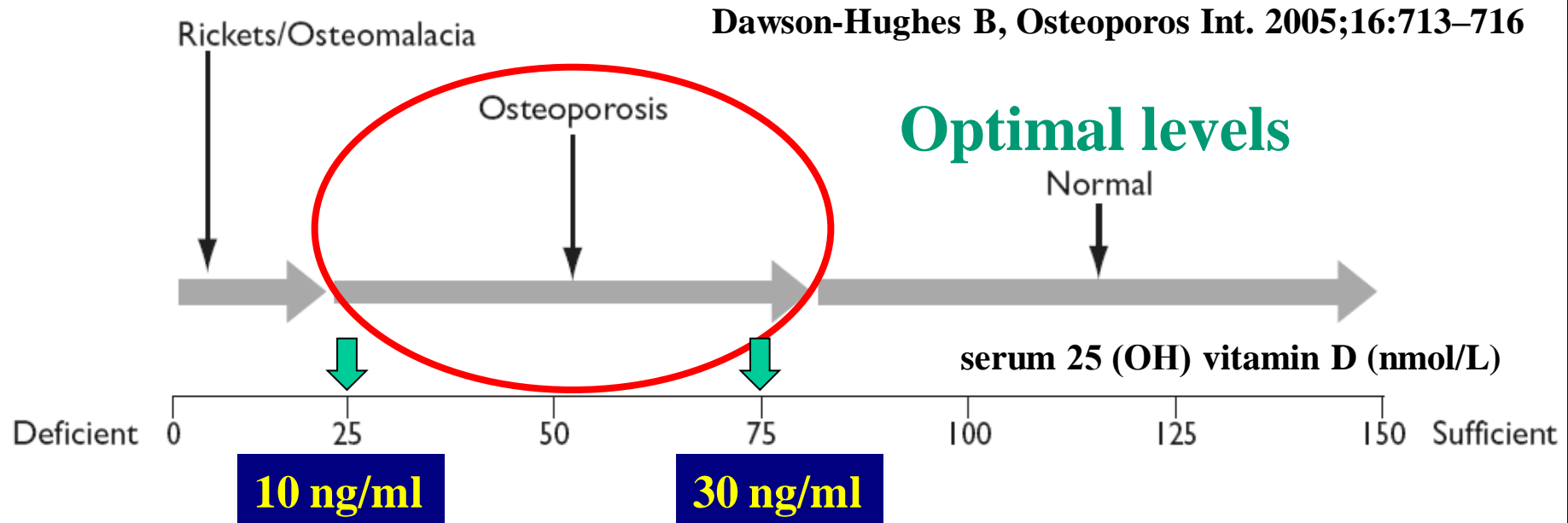


**Ca<sup>++</sup> 1200-1500 mg**

**Vit D 800 IU**

- Intake is almost always lower than recommended
- Lower levels lead to secondary hyperparathyroidism
- Ca / Vit D deficiency attenuates the efficacy of medical treatment
- Ca/ Vit D supplementation alone reduces Fx risk
- Vitamin D promotes muscle strength and decreases the risk of falls

## 4. Calcium and vitamin D supplementation



- **Greek postmenopausal women 58 years at risk of osteoporotic Fx**

- **Mean 25OH Vit D: 24.5 ng/ml**
- **22% of women were Vitamin D replete**

## 4. Calcium and vitamin D supplementation

### calcium and vitamin D alone reduce fracture risk

**Table 2.** Results of randomized clinical trials of vitamin D and calcium with fracture as outcome criterion

Reference	Patients	Vitamin D dose	Calcium dose mg/day	Obtained 25(OH)Dnmol/l	PTH decrease	BMD increase	Fracture risk reduction
21	3270	800 IU/day	1200	71	-44%	+6%	Hip:-43%*, nonvert:-32%*
46	2578	400 IU/day		54	-15% (Ref. 57)	+2.2%	Hip: NS, nonvert: NS
47	389	700 IU/day	500	99	-15%	+1%	Nonvert: <i>P</i> = 50%*
45	583	800 IU/day	1200	80	-40%	+5%	Nonvert: <i>P</i> = 0.07
48	569	400 IU/day					Hip: NS, nonvert: NS
49	2686	100,000 IU/4 months		74	-6%		Nonvert: -22%*
50	9605	400 IU/day	1000	47	-15%		Nonvert: -16%*
51	150	800 IU/day	1000	52	-30%	+3%	Nonvert: NS, falls -52%*
52	5292	800 IU/day	1000	62	-20%		Hip: NS, nonvert: NS
53	3454	800 IU/day	1000				Hip: NS, nonvert: NS
33	36,282	400 IU/day	1000			+1%	hip: NS, total fr: NS (hip: per protocol: -29%*)
54	625	1000 IU/day	600				Nonvert: NS, falls: -27%*
55	3440	100,000 IU/4 months		80	-25%		Nonvert: NS
56	242	800 IU/day	1000	84	-20%		Nonvert: NS, falls: -27%*

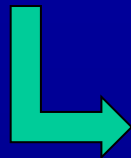
Hip, hip fracture; nonvert, nonvertebral fracture; NS, not significant.

\**P* < 0.05.

## 4. Calcium and vitamin D supplementation

**Patients under medical treatment are Vitamin D-deficient**

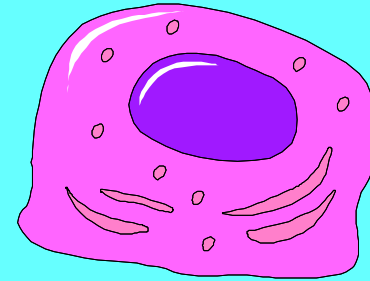
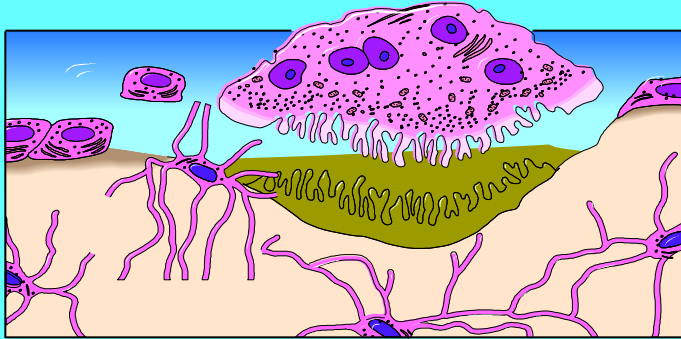
- **258 women in UK at risk of Fx starting medical treatment for osteoporosis**
- **At 6 months: 30% of women vitamin-D deficient**



- **Supplements not prescribed**
- **Low compliance**

**Calcium and vitamin D supplementation should be the first step towards fracture prevention**

# 5. Medical treatment of osteoporosis



## Inhibition of bone resorption

- HRT
- SERMS
- bisphosphonates
- Strontium ranelate
- denosumab

## Stimulation of bone synthesis

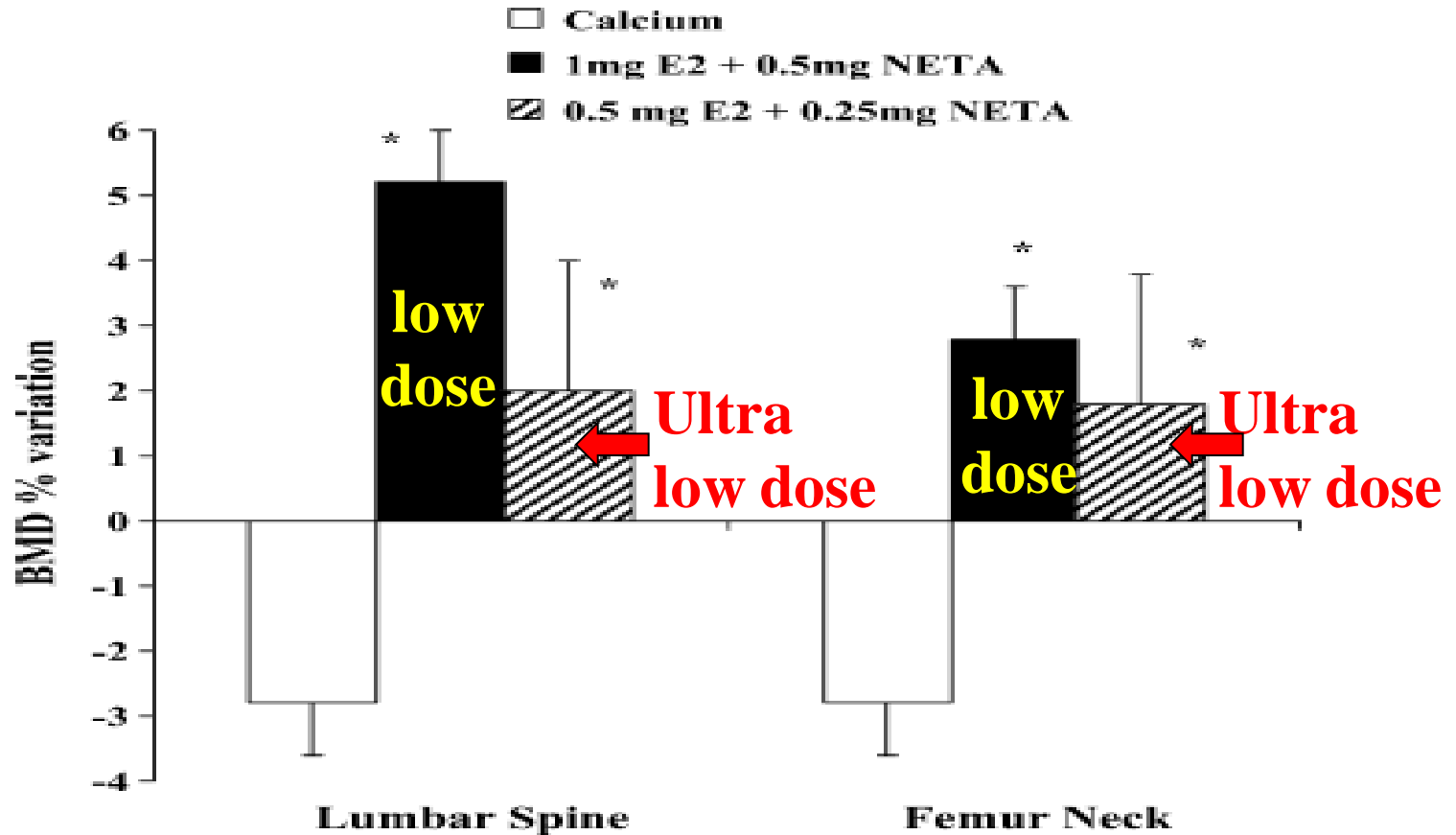
- PTH / teriparatide
- Strontium ranelate

## 5. Medical treatment of osteoporosis

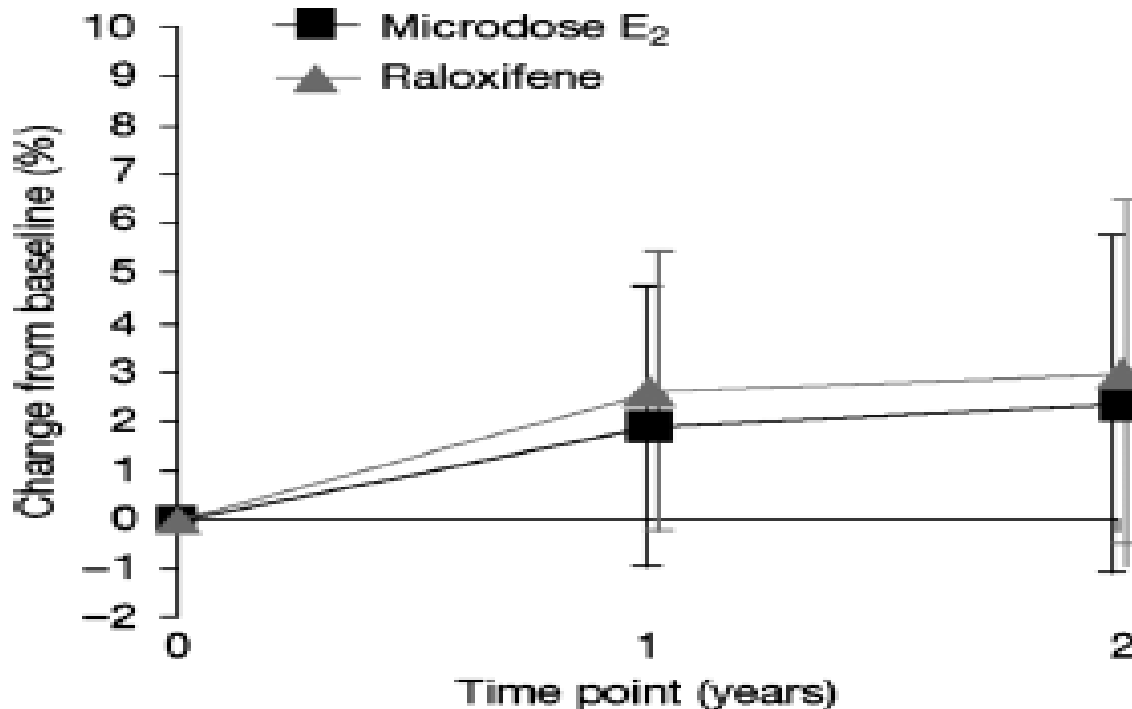
### Hormone replacement therapy

- **Standard doses:**  
(WHI 2002 / 2004)
  - **2-4% increase in BMD**
  - **45% decrease in vertebral and hip Fx**
- **Low doses**
  - **No Fx data**
  - **Same increase in BMD and decrease in bone markers as standard doses**

**Low dose and ultra-low dose hormone replacement therapy is effective in increasing BMD at the lumbar spine and at the hip in postmenopausal women**

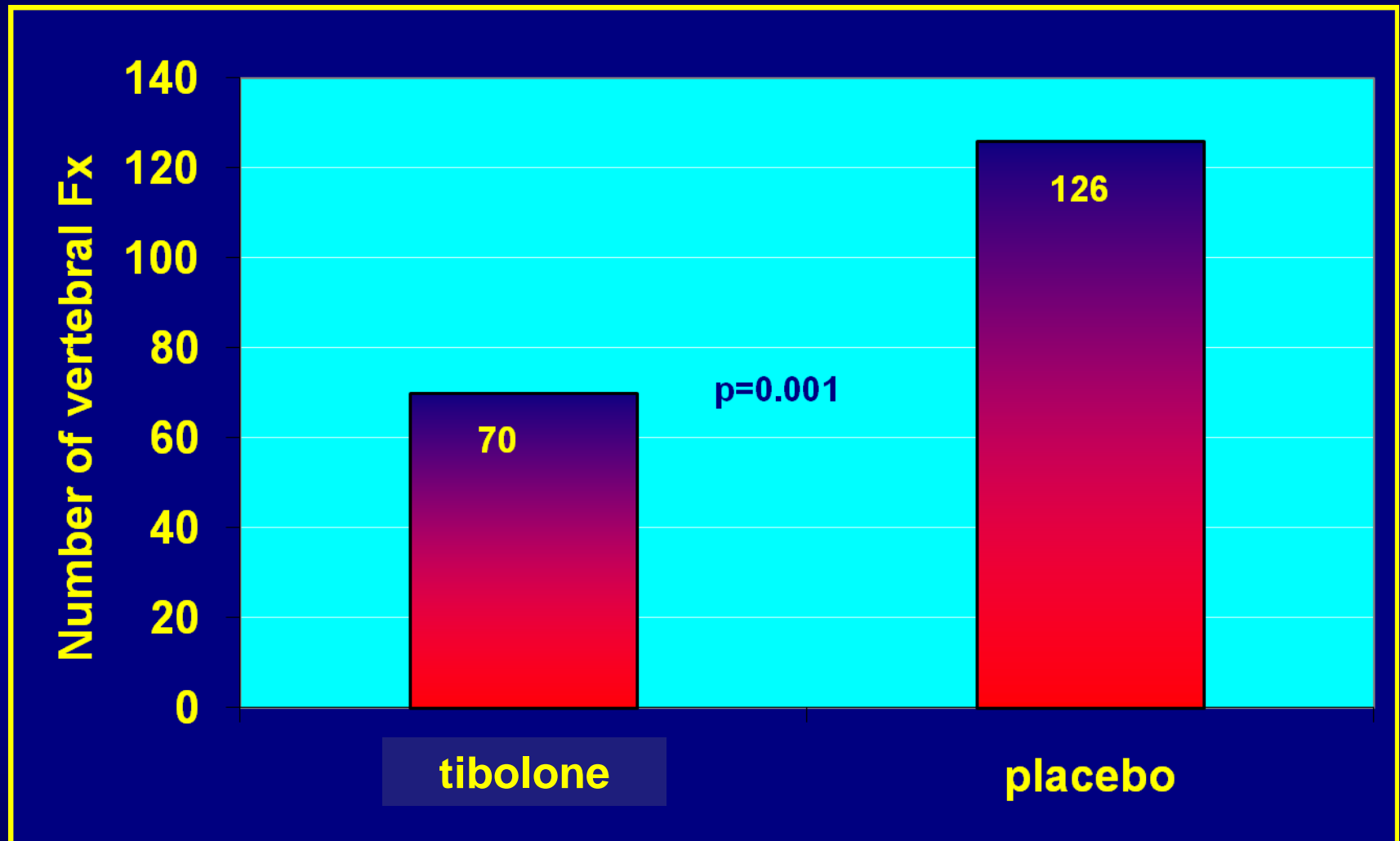


## Ultra-low dose of estrogen therapy increases BMD at the lumbar spine in a similar manner to raloxifene



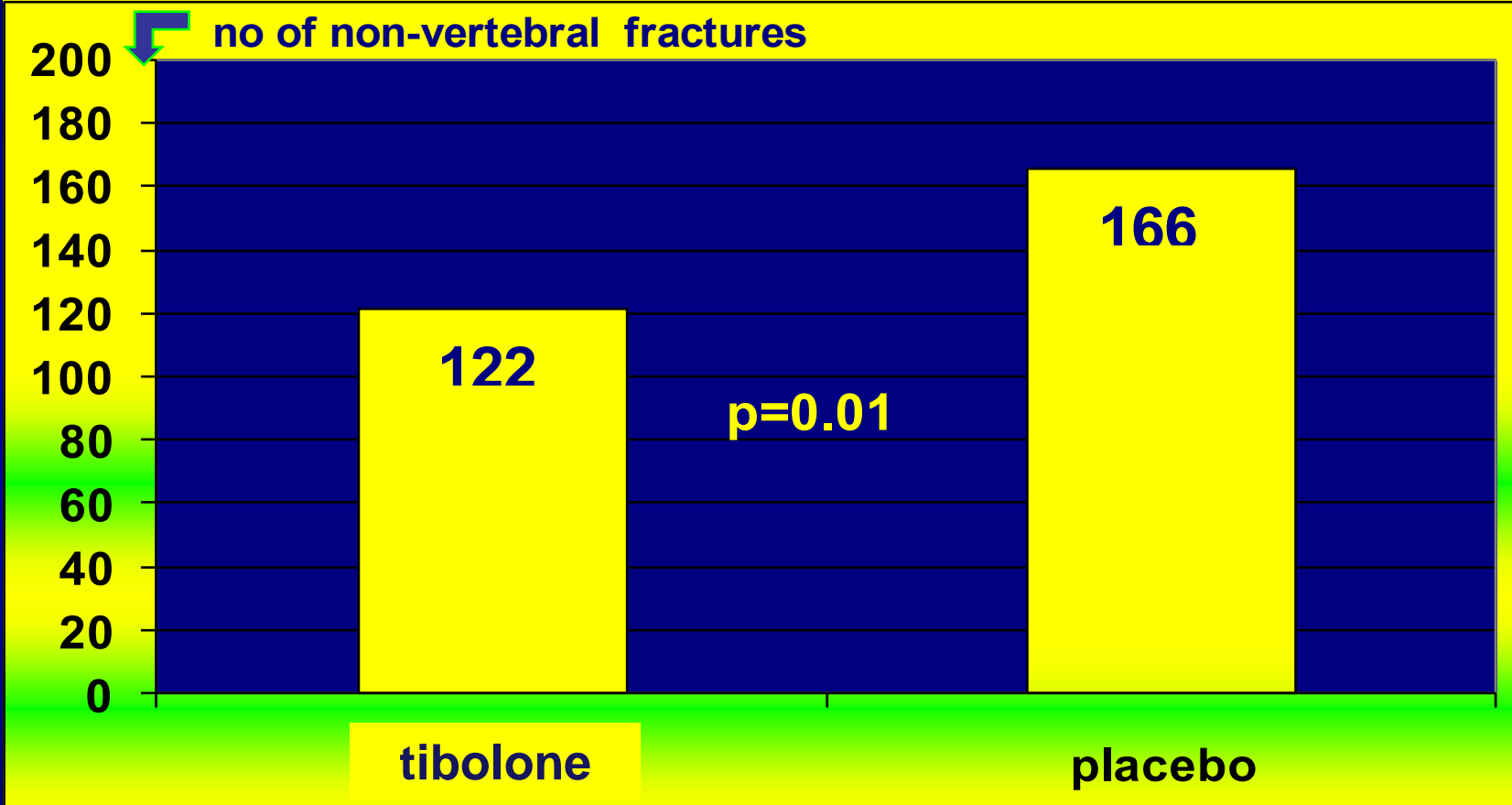
**FIG. 2.** Relative percent change (mean  $\pm$  SD) from baseline in bone mineral density at the lumbar spine, per protocol set, in postmenopausal women receiving treatment with either microdose E<sub>2</sub> 0.014 mg/day or raloxifene 60 mg/day. E<sub>2</sub>, 17 $\beta$ -estradiol.

# LIFT study: Low-dose tibolone decreases vertebral fracture risk by 45% in postmenopausal women at risk of fracture.



Cummings SR et al, N Engl J Med, Aug 2008

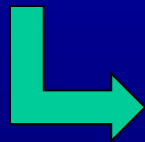
# LIFT study: Low-dose tibolone decreases non-vertebral fracture risk by 26% in postmenopausal women at risk of fracture.



Cummings SR et al, N Engl J Med, Aug 2008

## 5. Choosing the appropriate treatment

- **Hormone Replacement Therapy is a first-line option for the young recently postmenopausal woman at risk of fracture**



- **Osteoporosis prevention**
- **Quality of life**

## 5. Choosing the appropriate treatment

### SERMS

- **Raloxifene (available since 1998)**
- **Bazedoxifene (recently available)**
  - **2-3% BMD increase at the lumbar spine and hip**
  - **40-45% reduction of vertebral Fx risk**
  - **No effect on hip Fx in primary analysis**
  - **Post-hoc analysis in high risk subgroup: 50% reduction of non-vertebral Fx with bazedoxifene and 22% with raloxifene**

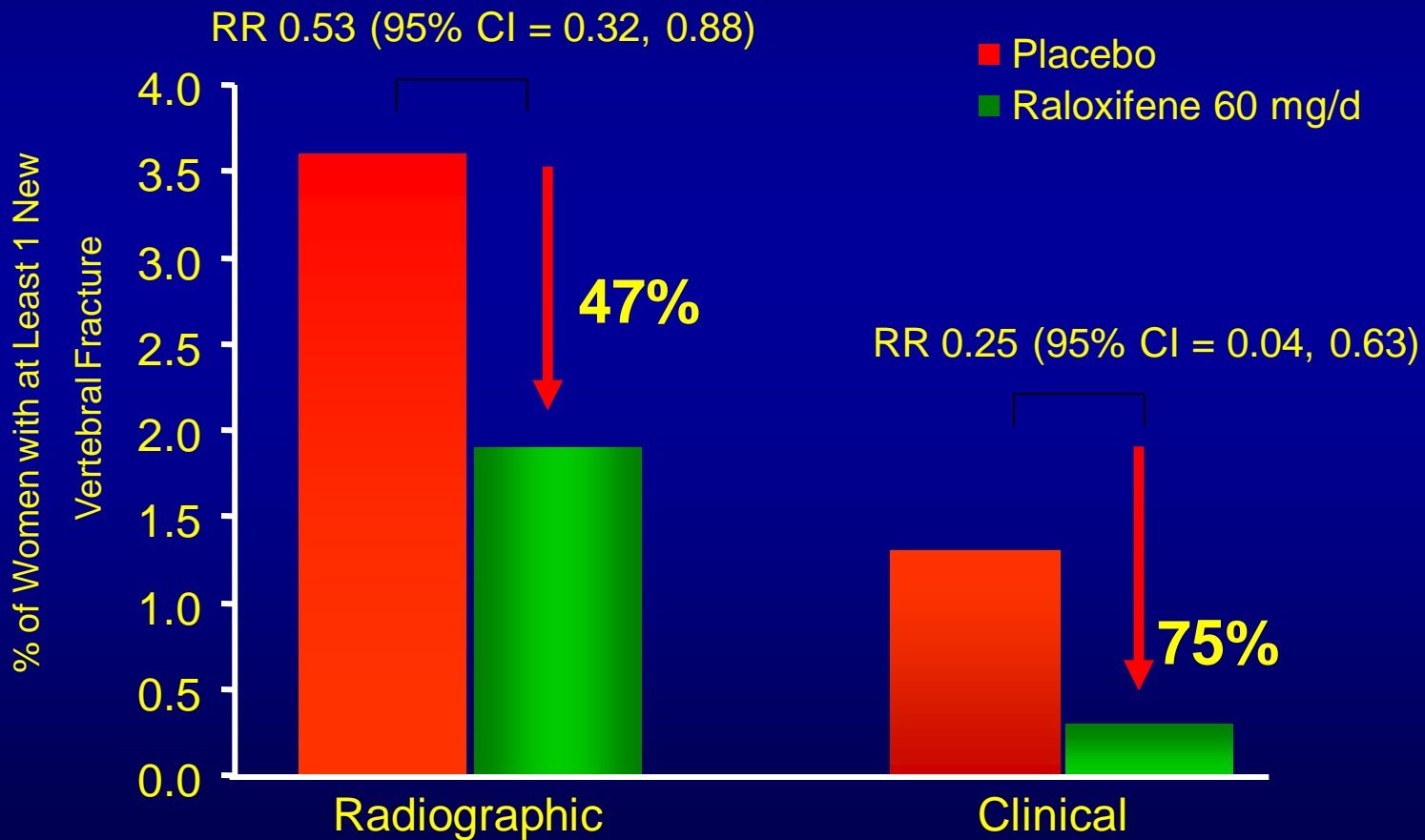
**Siris ES et al, J Bone Miner Res. 2005;20:1514-24**

**Silverman S et al, J Bone Miner Res 2008;23:1923**

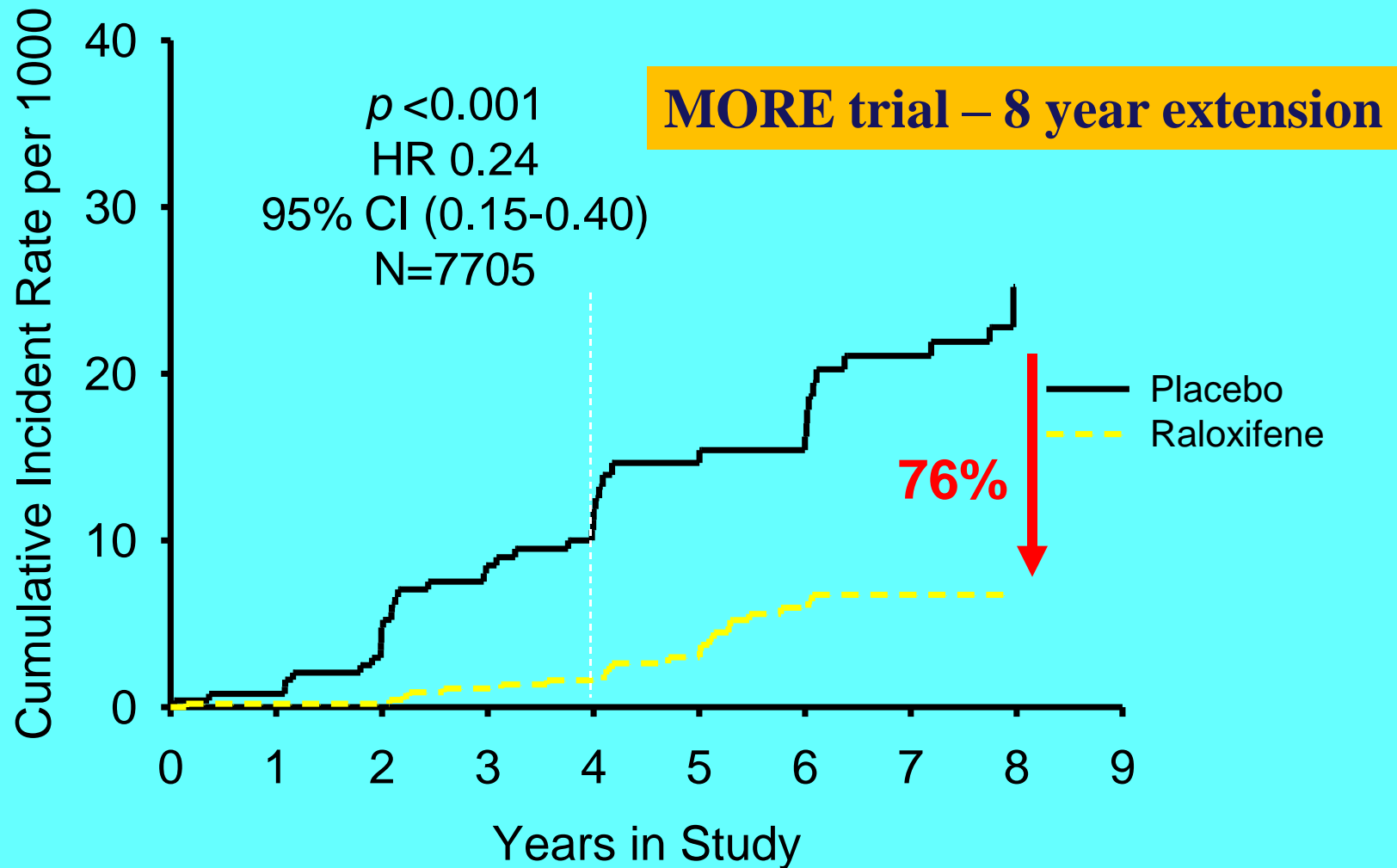
**Delmas PD, et al. J Clin Endocrinol Metab. 2002;87:3609-3617**

# Raloxifene reduces the risk of the 1<sup>st</sup> vertebral fracture in postmenopausal women with osteopenia

## MORE Trial - 3 Years



# Raloxifene reduces the risk of primary breast cancer in postmenopausal women at risk of fracture



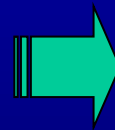
## 5. Choosing the appropriate treatment

### SERMS

- Postmenopausal women with low BMD at risk of fracture
- Asymptomatic, low / average risk of VTE

### raloxifene

- Women with risk factors for breast cancer



- Family history of breast ca
- Obesity
- Benign breast disease
- Increased breast density
- Daily alcohol intake
- nulliparity

## 5. Choosing the appropriate treatment

### Oral Bisphosphonates

- Alendronate 70mg weekly
- Risedronate 35 mg weekly  
or 75mg monthly
- Ibandronate 150 mg monthly

### I.V. bisphosphonates

- Ibandronate 3mg every 3 months
- Zoledronic acid 5mg annually

### Efficacy

- 5-7 % increase in BMD
- 40-70% reduction of vertebral fractures
- 25-50% reduction of non-vertebral fractures

**Low cost  
(aln / ris)**

## 5. Choosing the appropriate treatment

### Concerns about bisphosphonates

- **Gastric irritation (oral) / esophageal cancer ?**
- **Acute phase reaction (IV)**
- **Bone turnover oversuppression (frozen bone)**



- **Osteonecrosis of the jaw (rare / cancer pts)**
- **Atypical fractures (subtrochanteric)**

- **Associated with prolonged use (> 5 years)**
- **Drug holiday ??**

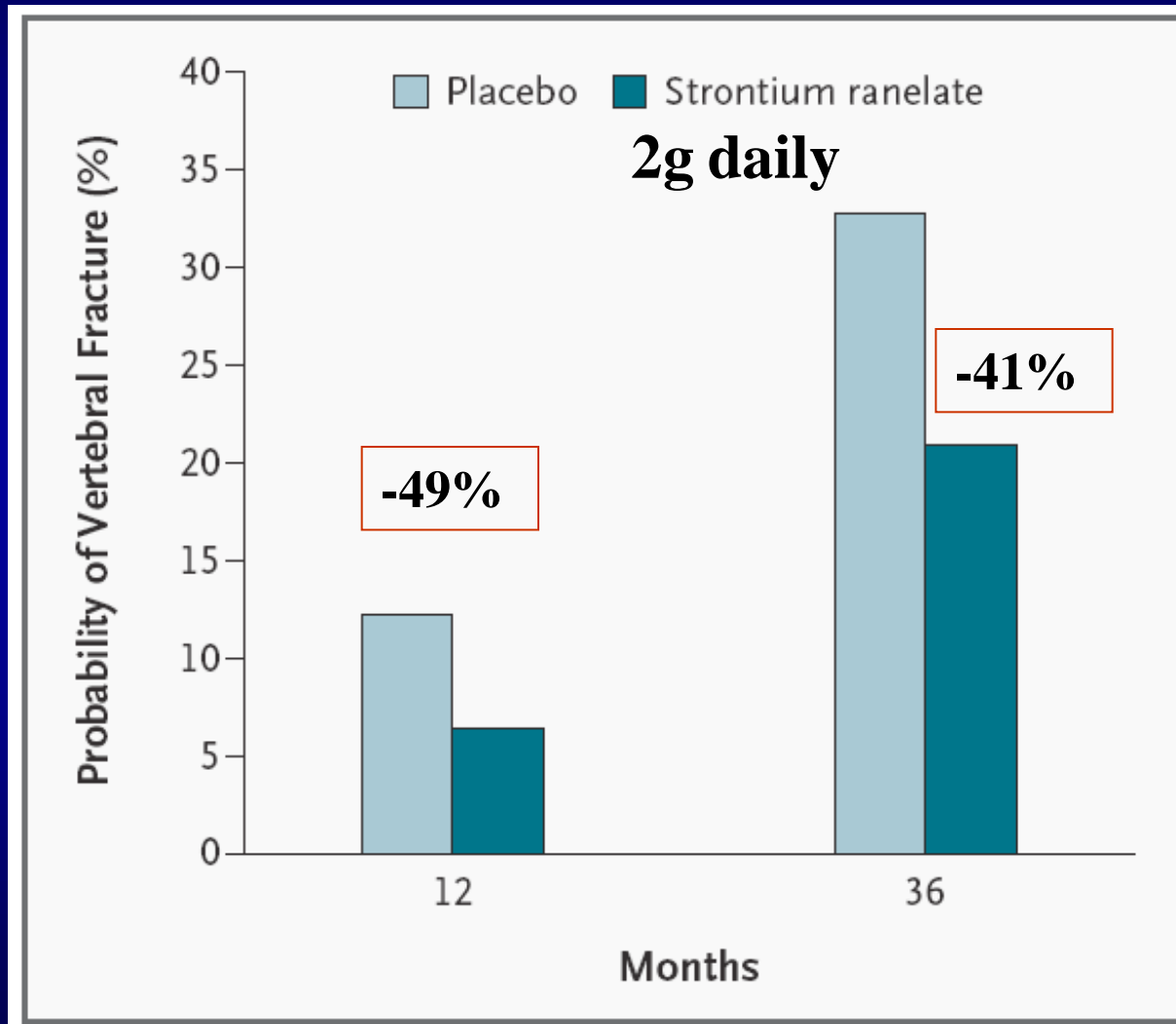
Schilcher J et al. N Engl J Med. 2011;364:1728-37

Giusti A et al. Bone 2011 May 1;48:966-71

Park-Wyllie LY et al JAMA. 2011 Feb 23;305(8):783-9.

## 5. Choosing the appropriate treatment

### Strontium ranelate



- **16% reduction in non-vertebral Fx**

- **5% increase in femoral neck**

- **BMD**

- **nausea, diarrhea, skin rash**

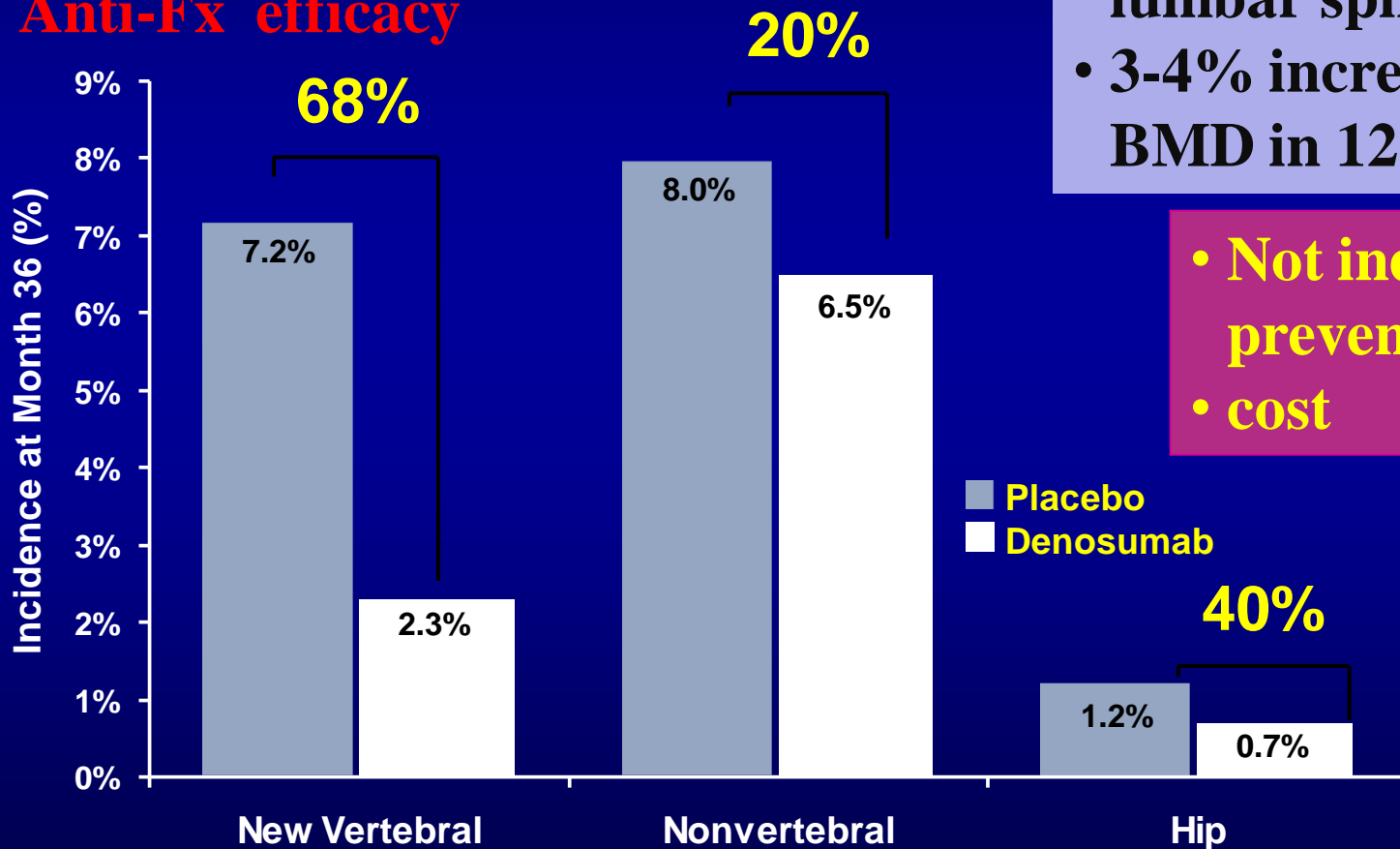
- **cost**

## 5. Choosing the appropriate treatment

- **Denosumab: monoclonal antibody against RANK-L**
- **1 sc injection every 6 months**

**FREEDOM: phase 3 trial**

**Anti-Fx efficacy**



- **6-7% increase in lumbar spine BMD**
- **3-4% increase in hip BMD in 12 months**

- **Not indicated for prevention**
- **cost**

Cummings SR, et al. *N Engl J Med.* 2009;361:756-65

Bone HG, et al. *J Clin Endocrinol Metab.* 2008;93:2149-2157

## 5. Choosing the appropriate treatment

- **Anabolic agents: teriparatide / PTH (1-84)**
- **1 sc injection daily for 18-24 months**

	teriparatide	PTH 1-84
Lumbar spine BMD	+9%	+7%
Hip BMD	+3%	+2%
Vertebral fractures	-65% (in women with prevalent vertebral Fx)	-40% (in women with mean T-score -3)
Non-vertebral fractures	-53% (in women with prevalent vertebral Fx)	Evidence not available
hypercalcemia	11%	23%

- **High cost !!**
- **Consider in cases of failure of antiresorptive therapy**
- **Established osteoporosis**

## 5. Choosing the appropriate treatment

### Cost - effectiveness

- **White women aged 55-75 years with osteopenia and no additional risk factors**



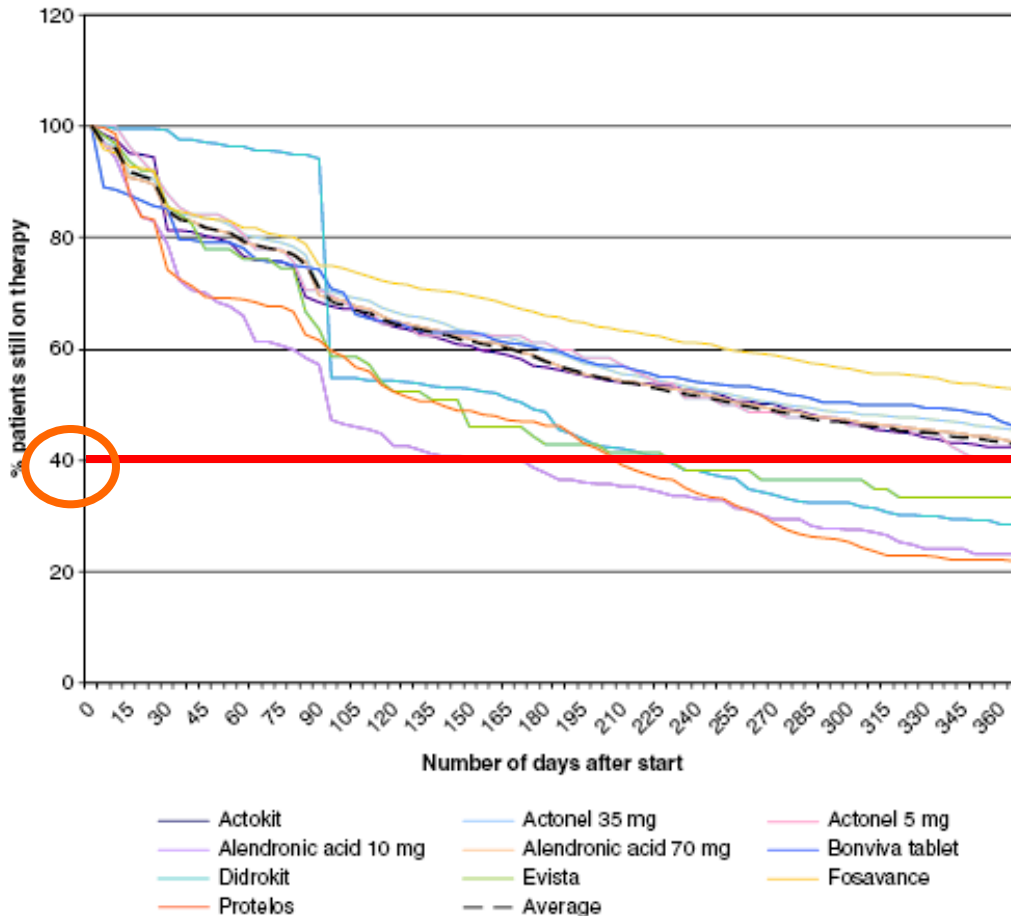
**Alendronate not cost-effective**

**Schousboe JT et al. Ann Intern Med. 2005;142:734-41.**

- **Cost-effectiveness of medical treatment should be carefully evaluated especially in young postmenopausal women**

## 6. Ensure compliance

- 40% of women still receive their treatment after 12 months



### Risk factors for low compliance

- Young age
- Urban dense – populated area
- Daily regimens

Netelenbos JC et al,  
Osteoporos Int. 2011  
May;22(5):1537-46

## 7. Identify treatment failure

- **BMD is not a criterion of response to treatment**
- **Treatment failure: incident fracture while on treatment**

### Before deciding to switch treatment...

- **Is it a low-trauma Fx?**
- **Is it due to postmenopausal osteoporosis?**
- **Was the patient compliant?**
- **Did the patient receive adequate calcium and Vitamin D?**
- **Is the drug known to be effective on the type of fracture sustained ? (hip Fx)**
- **Was the drug taken long enough to be effective?**

Nadia Mehsen

Joint Bone Spine 77 (2010) S133-S138

# Conclusions

- **Despite improvements in diagnosis and treatment, osteoporotic fracture rate continues to increase**
- **Identification of the high-risk patient is the best strategy to improve cost-effectiveness of medical treatment**
- **Hormone replacement therapy should be considered in the young recently menopausal woman, being the best option to address both osteoporosis prevention and quality of life**

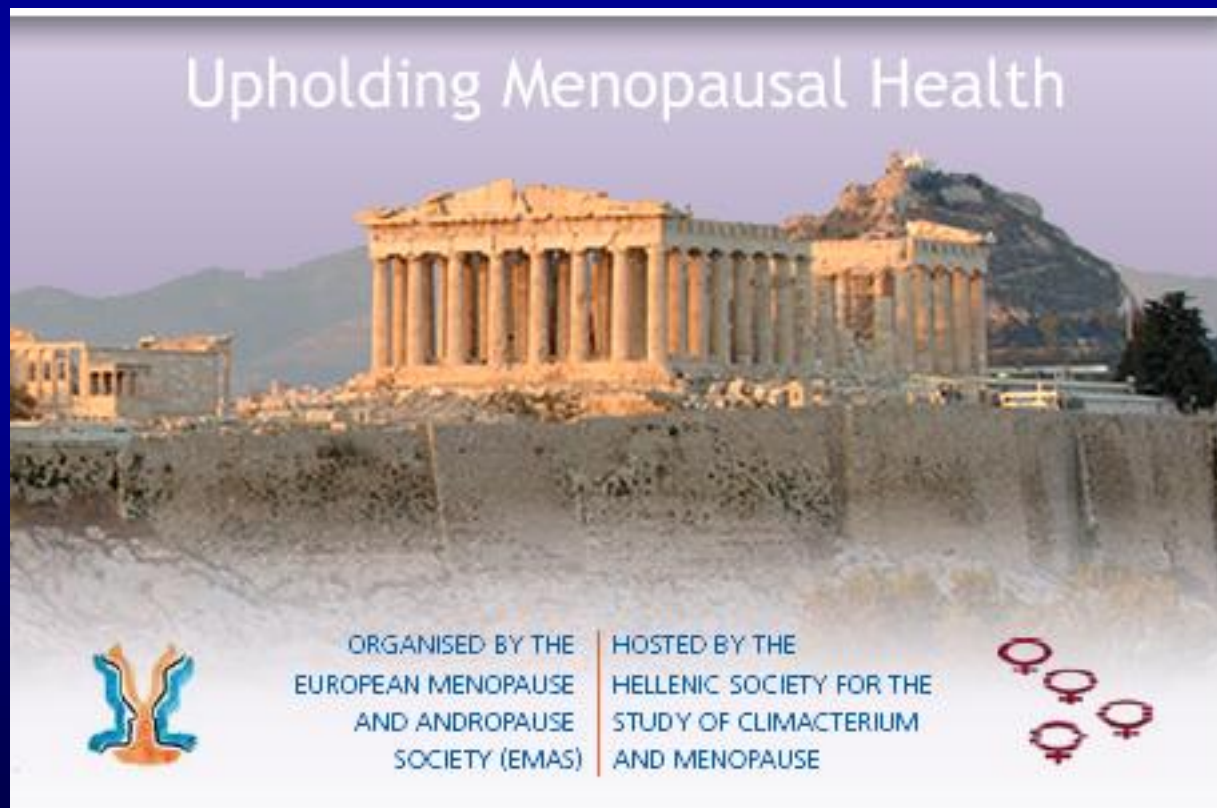
.... see you in Athens in 2012



9TH EUROPEAN CONGRESS ON  
**MENOPAUSE AND ANDROPAUSE**  
ATHENS, GREECE, 28-31 MARCH, 2012



Upholding Menopausal Health



ORGANISED BY THE  
EUROPEAN MENOPAUSE  
AND ANDROPAUSE  
SOCIETY (EMAS)

HOSTED BY THE  
HELLENIC SOCIETY FOR THE  
STUDY OF CLIMACTERIUM  
AND MENOPAUSE

