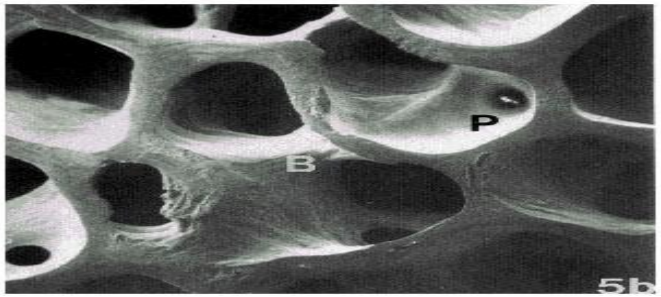
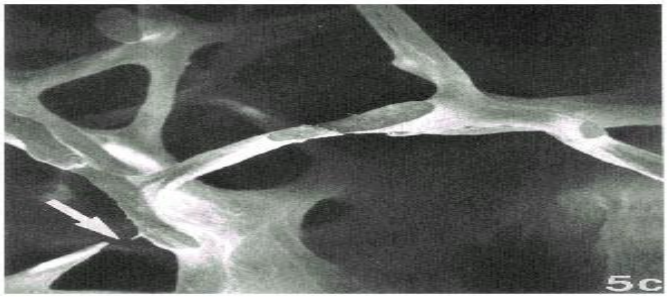
Osteoporosis - Diagnosis and Treatment





"a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture"

Consensus Development Conference

Dr. Elena Segal

Bone changes

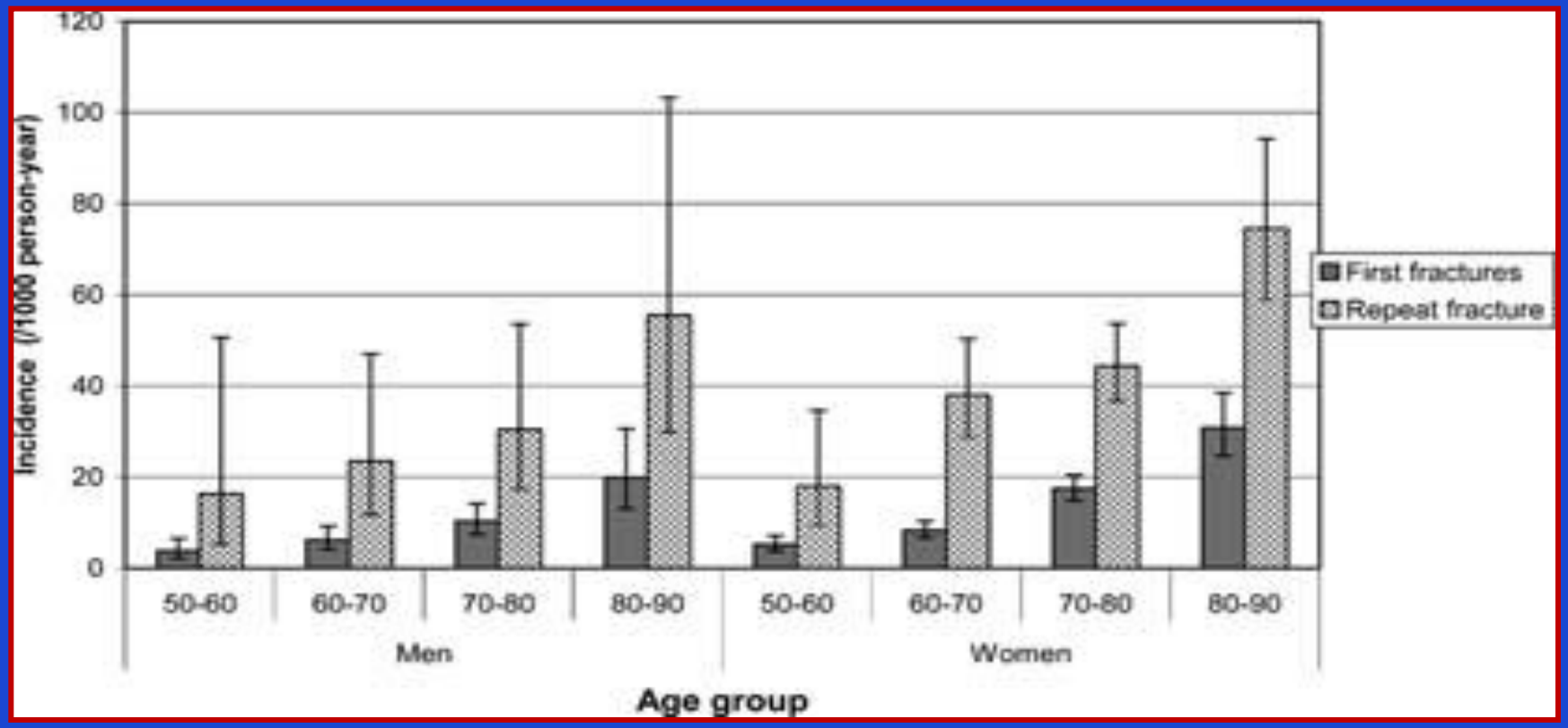
With permission of Lis Mosekilde, Aarhus

- **Young**
- **Age ± Estrogens deficiency**
  - **Age: ↓ *Formation***
  - **Estrogens deficiency:**
    ↑ *Resorption*
- **↓ Bone structure is the essential *pathological* occurrence by Osteoporosis**

Osteoporosis

- Important cause of mortality and morbidity
- A disease that causes bones to lose mass, weaken and fracture
- 1:3 women and 1:7 men are affected
- progression is slow, silent, painless
- Osteoporotic fractures- fractures due to fall from standing height or less, or without fall at all

Incidence of First and Repeat Low-Trauma Fracture in Men and Women by Age Group

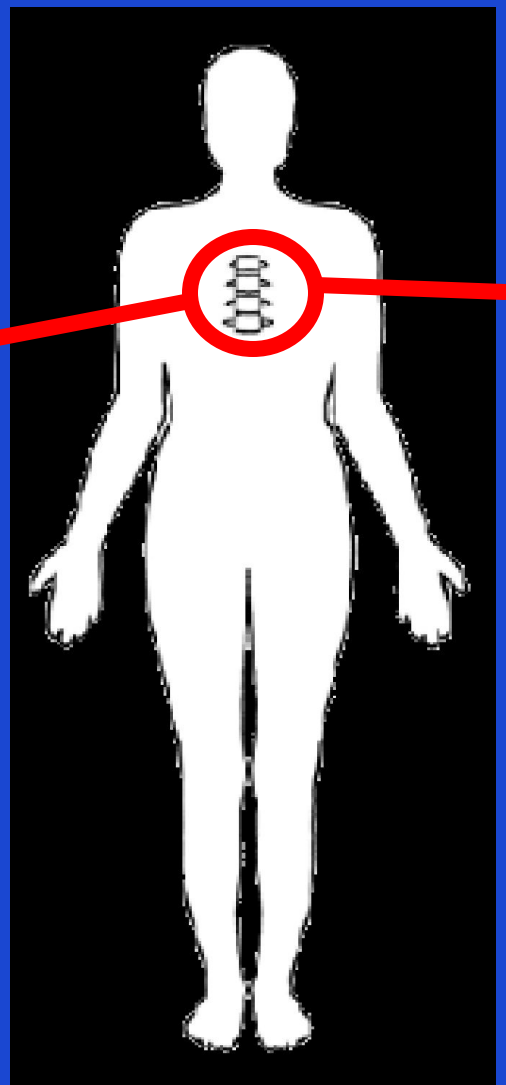


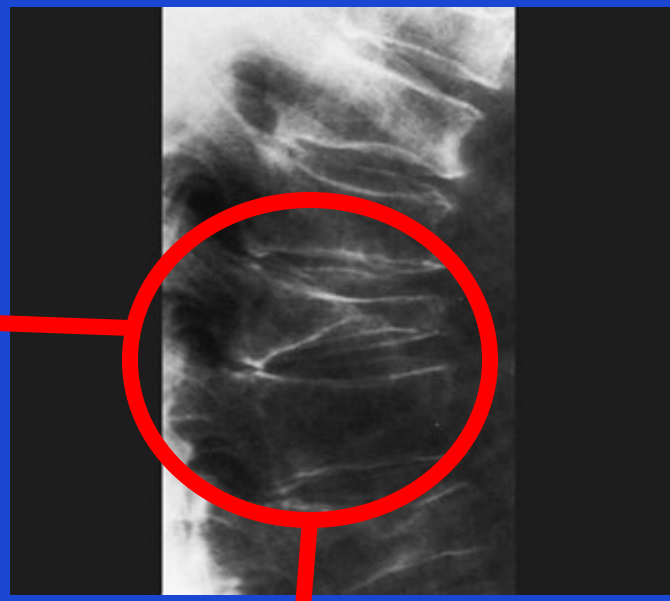
- □ in osteoporotic fractures - 60–70% per decade and similar for first and repeat fractures
- the incidence of repeat fractures was at least double the incidence of first fractures.

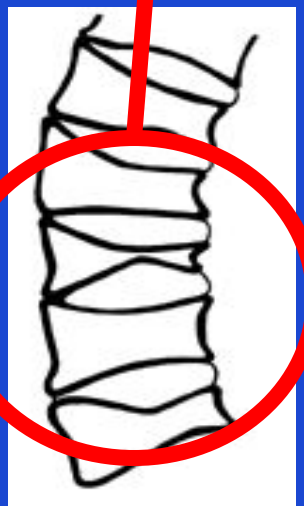
L. Langsetmo et al, JBMR 2009

Osteoporotic fractures

Vertebral fractures







Only 33% of Osteoporotic Vertebral Fractures are Clinically Diagnosed!

100 % Patients with vertebral fractures that are visible on X-rays

50 % Symptomatic (dorsalgia)

33 % Clinically diagnosed

8 % Hospitalized

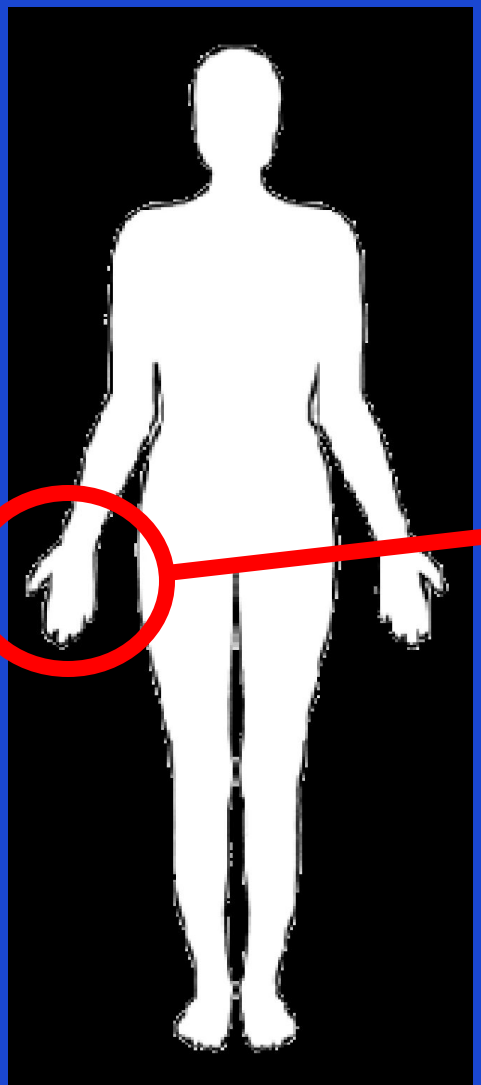
2% Requiring long term care

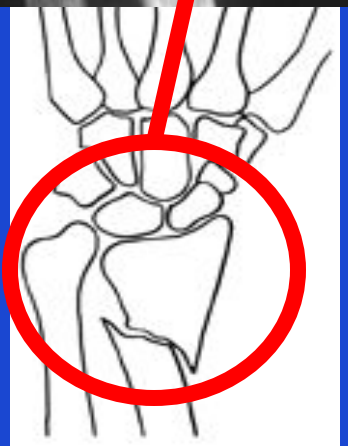
2/3 of patients with vertebral fractures that are visible on X-rays are not diagnosed

Adapted from ROSS PD: Clinical Consequences of Vertebral Fractures: *AM J Med* 1997;103 (2A): 30S-43S

Osteoporotic fractures

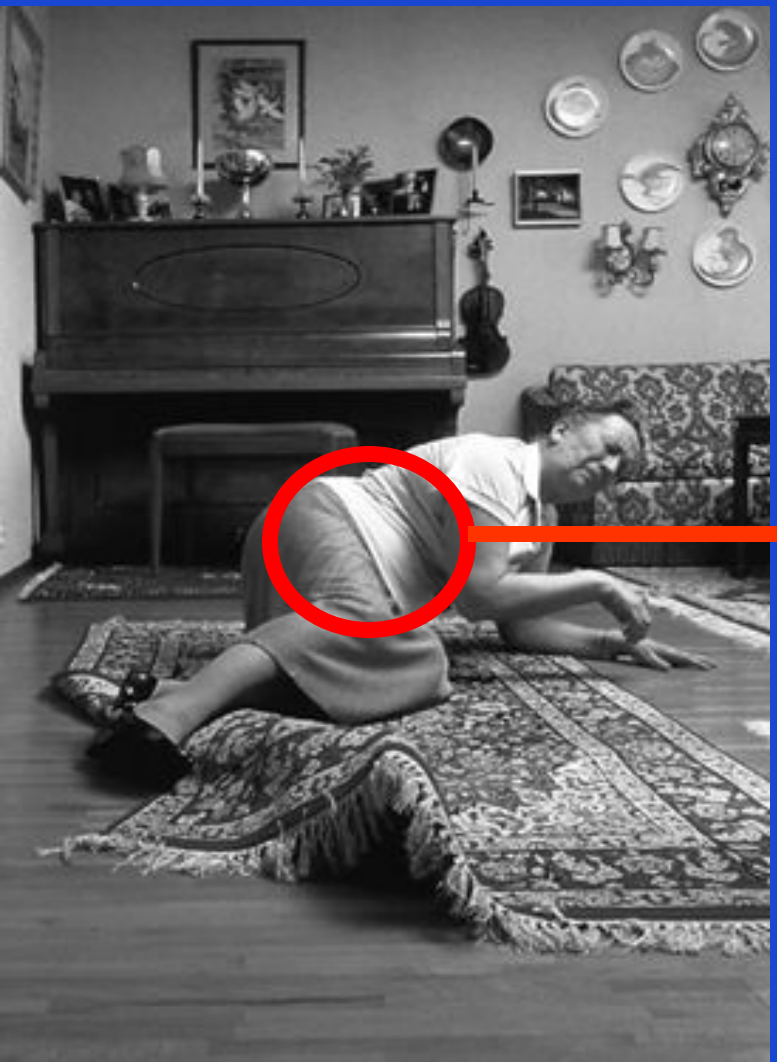
Colle's Fracture

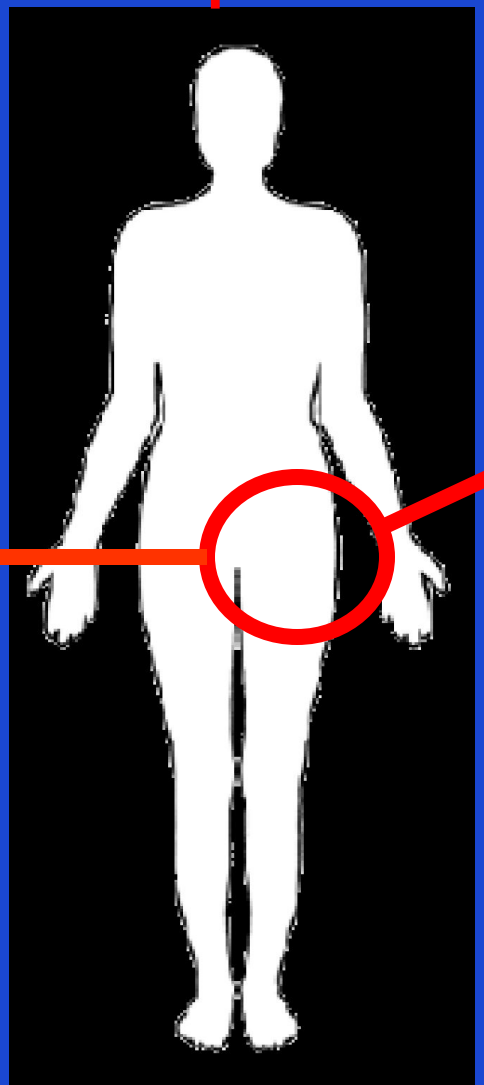


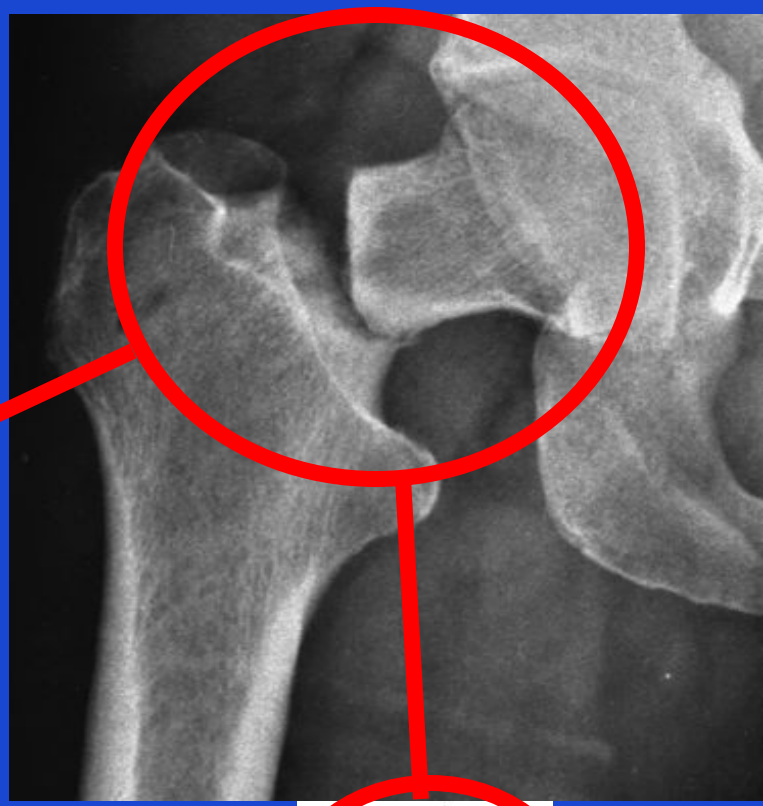


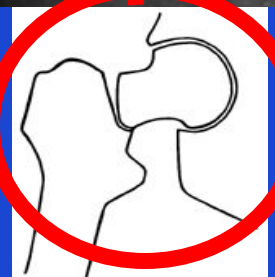
Osteoporotic fractures

Hip fractures









Hip fracture is a deadly condition

Causes of death in men and women aged 45 years or more from Sweden

	Men	Women	Total	Share of all deaths (%)
Acute myocardial infarction	7,113	5,335	12,449	13
Lung cancer	1,761	1,112	2,873	3
Prostate cancer	2,480	0	2,480	3
Breast cancer	11	1,549	1,560	2
Hip fracture	566	854	1,420	2
Transport accident	422	142	564	1

J. Kanis et al, 2003

Bone remodelling

Quiescence

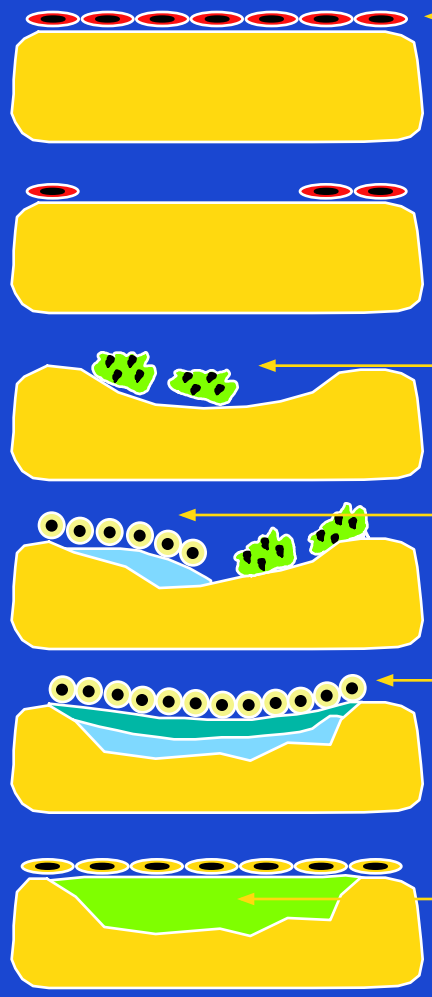
Activation

Resorption

Formation

Mineralization

Quiescence



Lining cells

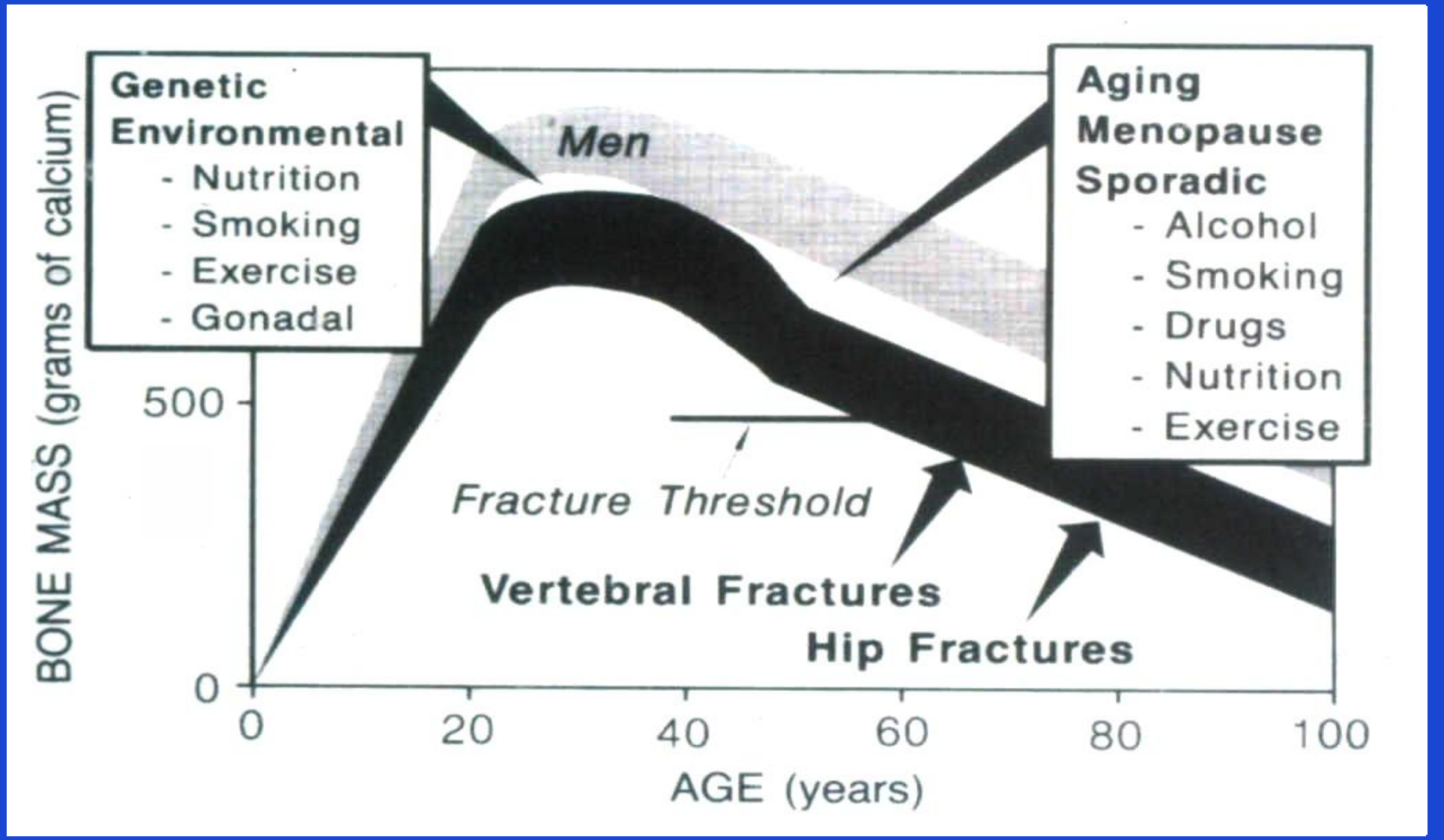
Osteoclasts

Osteoblasts

Mineralized bone

Bone structural unit

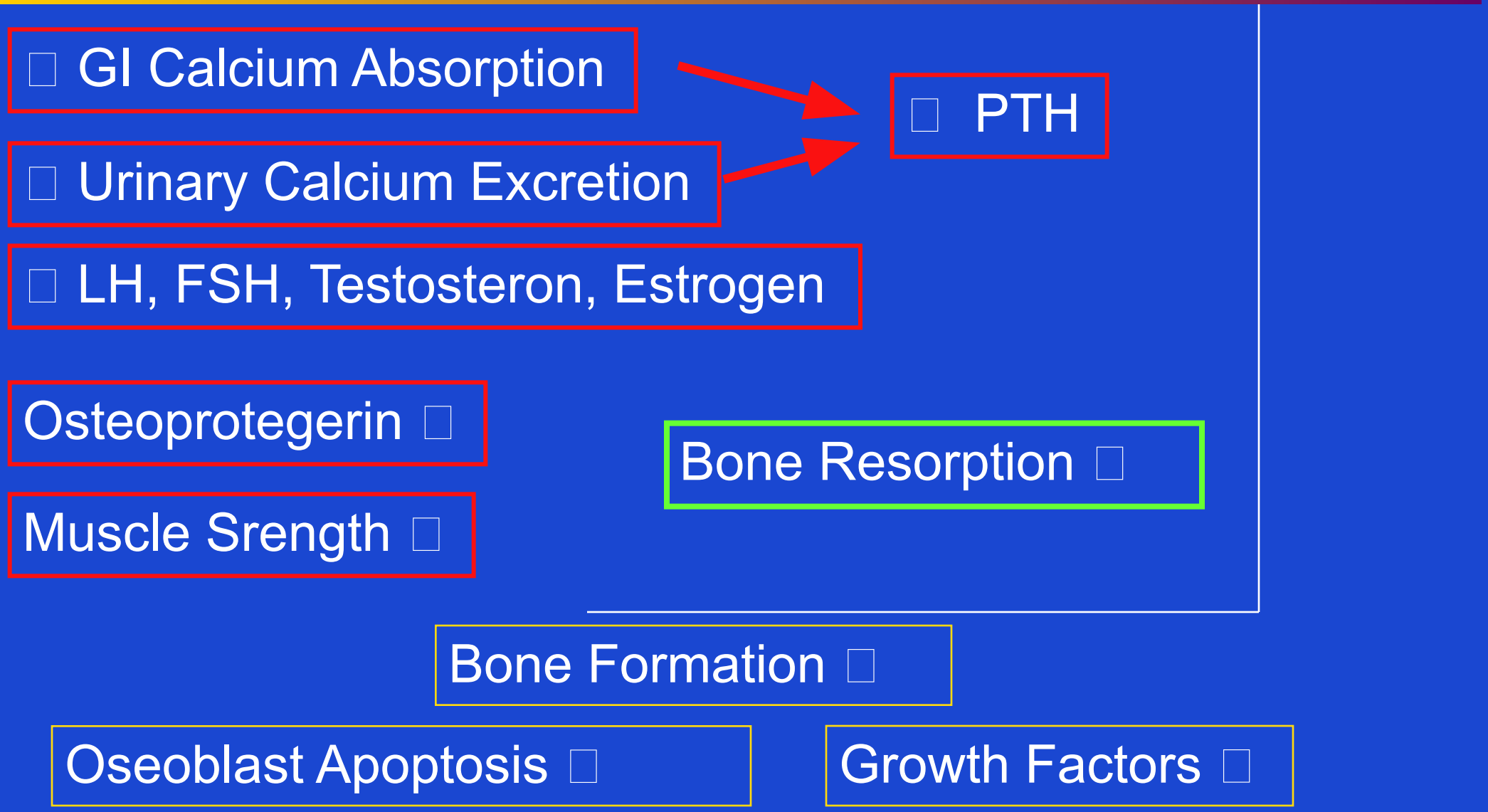
Adapted from Compston 1996


Genetic
Environmental
- Nutrition
- Smoking
- Exercise
- Gonadal
Aging
Menopause
Sporadic
- Alcohol
- Smoking
- Drugs
- Nutrition
- Exercise
Men
Fracture Threshold
Vertebral Fractures
Hip Fractures
BONE MASS (grams of calcium)
500
0
0
20
40
60
80
100
AGE (years)

Osteoporosis - Causes

- **Menstrual status**
  - early menopause (before the age of 45 years)
  - previous amenorrhea (e.g., due to anorexia nervosa, hyperprolactinemia)
- **Drug therapy**
  - glucocorticoids (≥ 7.5 mg/day for > 6 months)
  - antiepileptic drugs (e.g., phenytoin)
  - excessive substitution therapy (e.g., thyroxine)
  - anticoagulant drugs (e.g., heparin, warfarin)

Glucocorticoid Induced Osteoporosis



Osteoporosis - Causes

- **Endocrine disease**
  - primary hyperparathryroidism
  - thyrotoxicosis
  - Cushing's syndrome
- **Rheumatologic diseases**
  - rheumatoid arthritis
  - ankylosing spondylitis

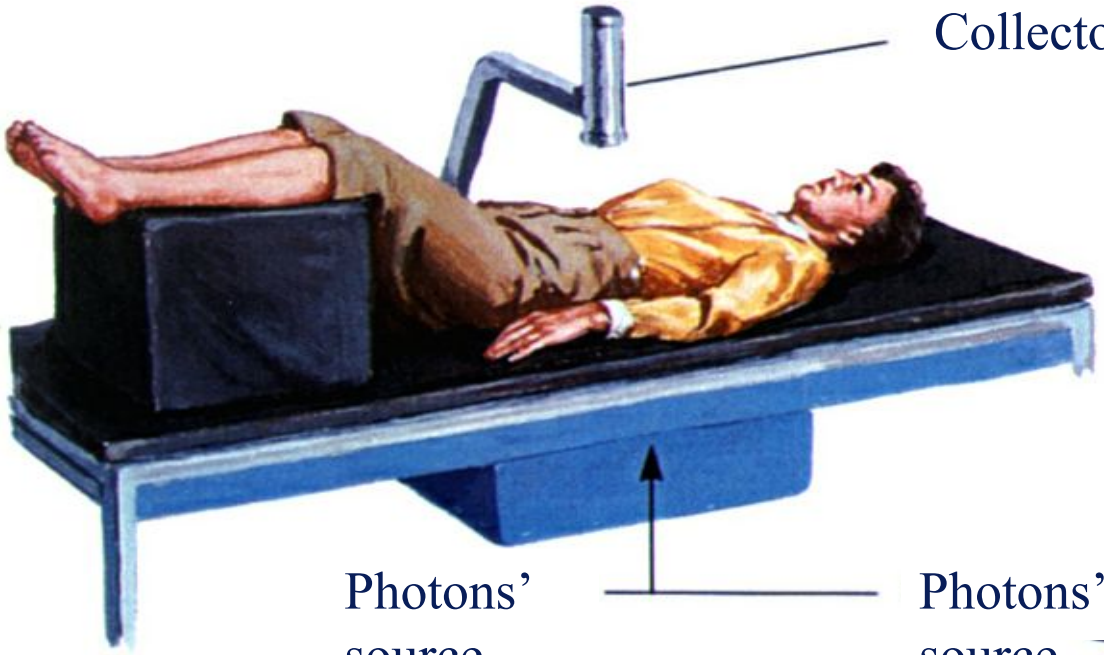
Osteoporosis - Causes

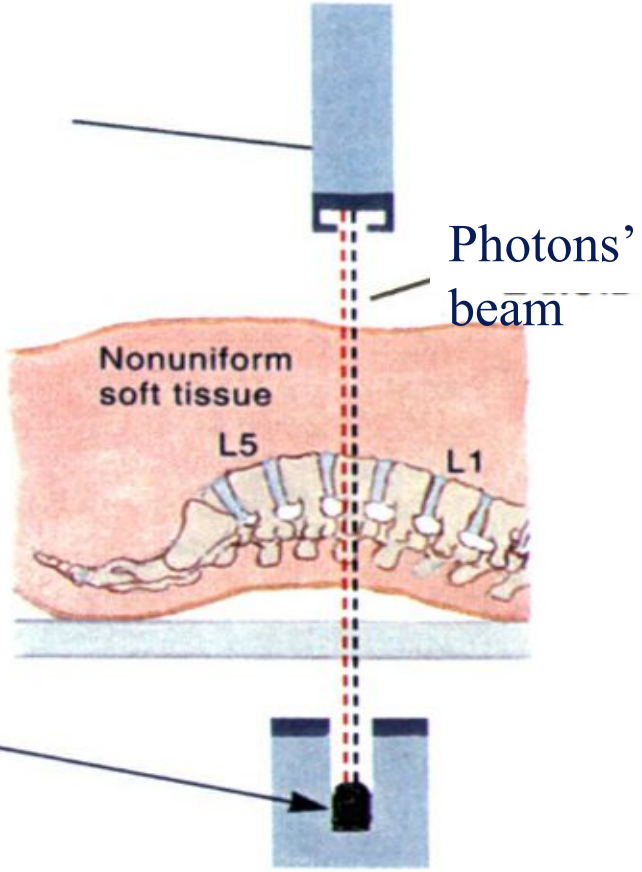
- **Hematologic disease**
  - multiple myeloma
  - systemic mastocytosis
  - lymphoma, leukemia
  - pernicious anemia

Always rule out secondary causes, especially in case of fracture or significant decrease in BMD>5% during one year on treatment

- **Gastrointestinal diseases**
  - malabsorption syndromes (e.g., celiac disease, Crohn's disease, surgery for peptic ulcer)
  - chronic liver disease (primary biliary cirrhosis)

Dual-energy X-ray Absorptiometry - DXA





Definition of Osteoporosis in Women According to WHO (diagnostic criteria)

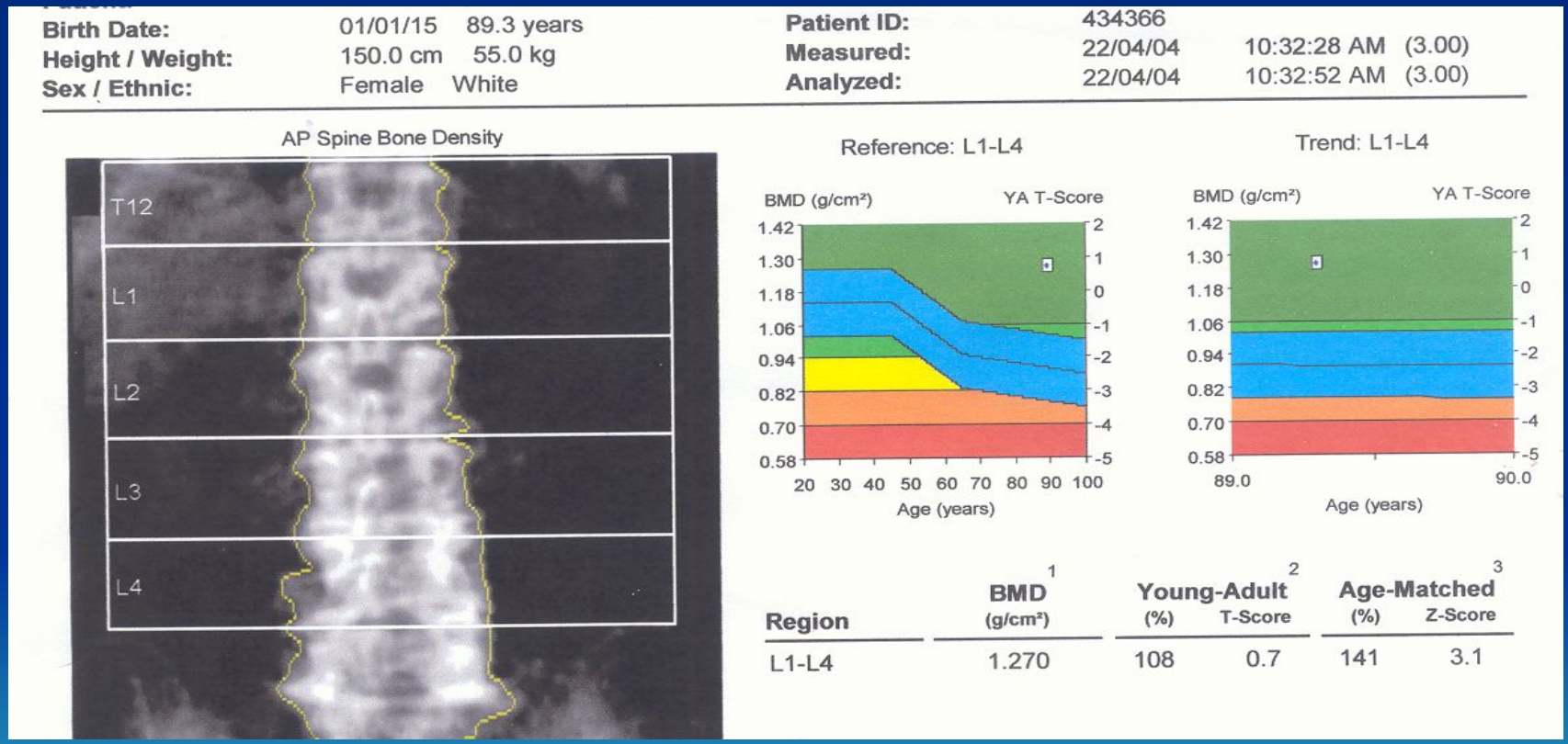
Definition	Bone	Strategy
Normal	T-Score ≥ - 1 SD	Prevention
Osteopenia	-1 SD > T-Score > - 2.5 SD	

.Bone mineral density is only one of risk factors for fracture
Patient who experienced an osteoporotic fracture-definetly has
.osteoporosis, no matter what the BMD results are
In case of decrease in patient's BMD while on treatment- first
.re-evaluate the patient to rule out secondary causes of osteoporosis

nt

Kanis et al Osteoporos Int (1997)7:390-406

Interpretation failure: a “non-osteoporotic” 89 y old lady with a fractured right femoral neck



Fracture Risk Calculator FRAX

Weight Conversion:

pound:

convert

Height Conversion:

inch :

convert

Country Israel Name / ID : About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age: 77 Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg) 68

4. Height (cm) 165

5. Previous fracture No Yes

6. Parent fractured hip No Yes

7. Current smoking No Yes

8. Glucocorticoids No Yes

9. Rheumatoid arthritis No Yes

10. Secondary osteoporosis No Yes

11. Alcohol 3 or more units per day No Yes

12. Femoral neck BMD (g/cm²)

T-Score -2

Clear Calculate

BMI 25.0

The ten year probability of fracture (%)

with BMD

Major osteoporotic	35
Hip fracture	18

Management of osteoporosis: pharmacological therapy

- Calcium
- Vitamin D
- HRT
- SERMs (Raloxifen, Evista)
- Bisphosphonates
- Denosumab

HT (not recommended for osteoporosis, but if used for menopausal symptoms, efficient for osteoporosis)

For young people with normal gonadal status usually calcium and vitamin d replacement are sufficient

Rickets

Vit D deficiency in adults:
Osteomalacia
Fractures
Bone pain
Muscles pain
Difficulties in walking

Recommended Vit D levels for Patients with metabolic bone disorders is about 30 ng/ml=75 nmol/l

Osteomalacia (1)

Definition of Vitamin D Status for Multiple Health Outcomes

25(OH)D ng/ml x 2.5= nmol/l		Vitamin D Status
≤20	≤10	Deficiency
≤50	≤ 25	
		nsufficiency
> 30	>15	Normal
>75	>37.5	

Treatment with vitamin D improves walking, decreases falling and risk of non vertebral fractures

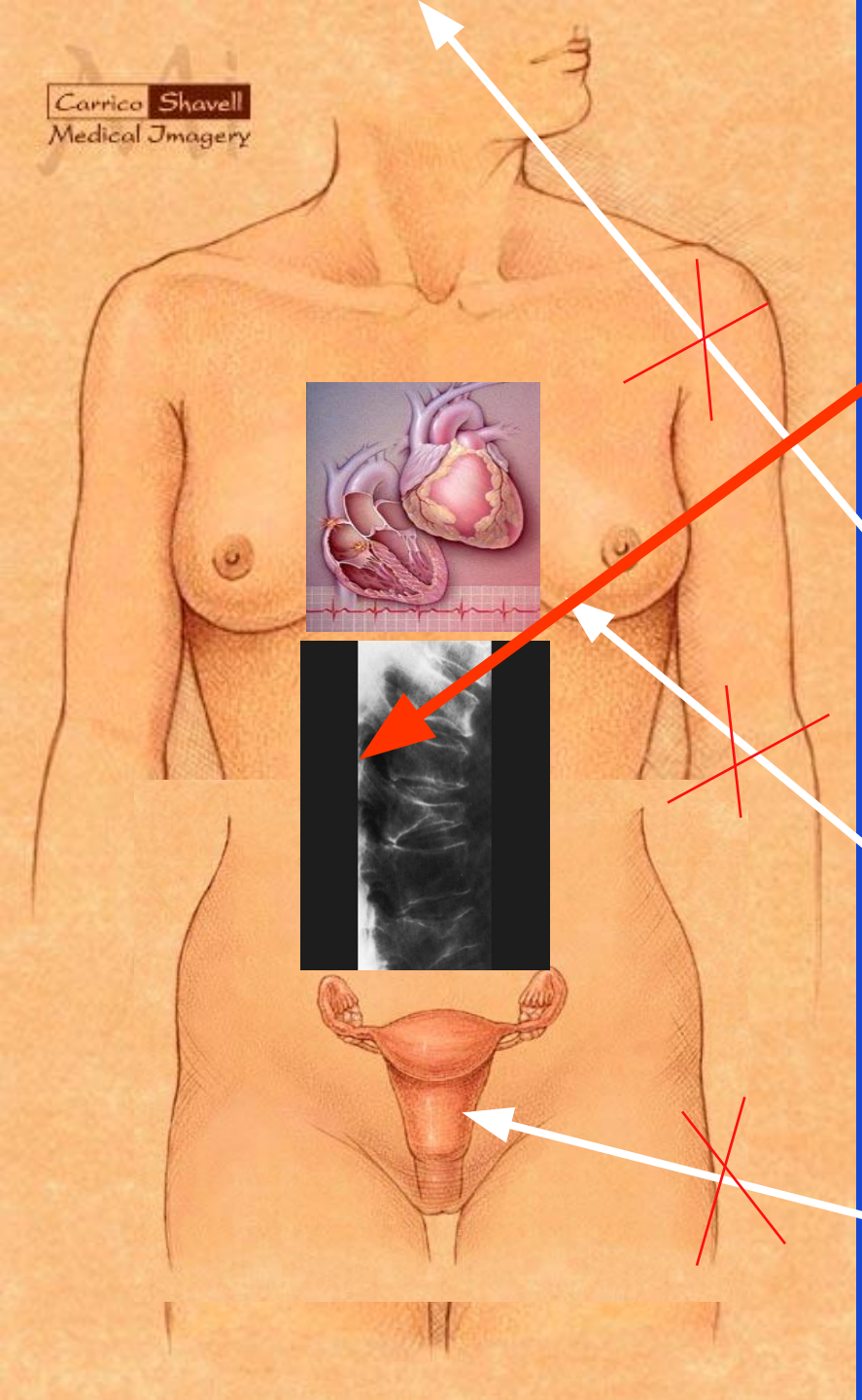
M Parfitt, 1970

M. Holick 2007

Antiresorptive Drugs

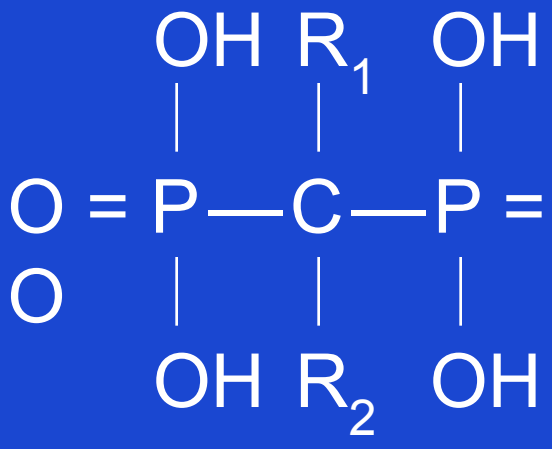
- antiresorptive drugs (estrogen, SERMS, bisphosphonates) ↓ both the rates of bone resorption (in weeks) and formation (in months)
- bone mineral density is ↑ by 3 - 8 % for the first 2-3 years then plateaus; this reduces the risk of fracture by 30 - 50% in various skeletal sites

SERMs- Mechanism of Action



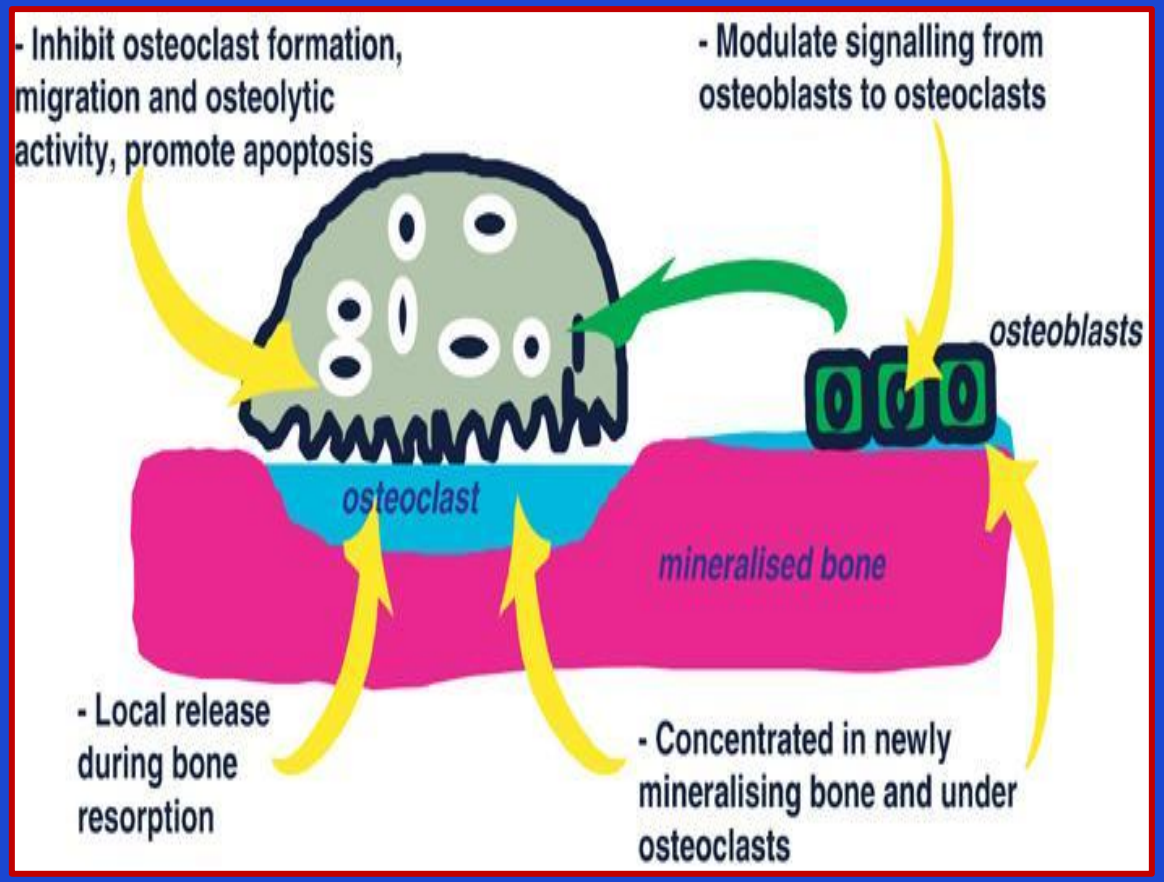
- Acts as Estrogen in bone, decreases incidence of the first vertebral **fracture** from 4.3% for placebo to 1.9% for **Evista** (relative risk **reduction** = 55%)
- Blocks Estrogen action in brain, which can lead to increase in menopausal symptoms
- Blocks Estrogen action in breast, and decreases ER+ breast cancer risk by 80%
- Blocks Estrogen action in uterus, not causes epithelium hyperplasia and bleeding

Bisphosphonates: Pharmacology



- Bone-seeking
- Effective orally or IV
- Poor absorption orally
- Not metabolized, excreted by the kidney
- Long skeletal retention
- Side chain determines potency and side effects

Bisphosphonates: Mechanism of Action



Reduce activity of individual osteoclasts

- inhibit lysosomal enzymes
- inhibit lactate production

Reduce activation frequency

- inhibit recruitment of osteoclast precursors
- inhibit differentiation of osteoclast precursors

Increase osteoclast apoptosis

Bisphosphonates: Indications and Contraindications

Indications

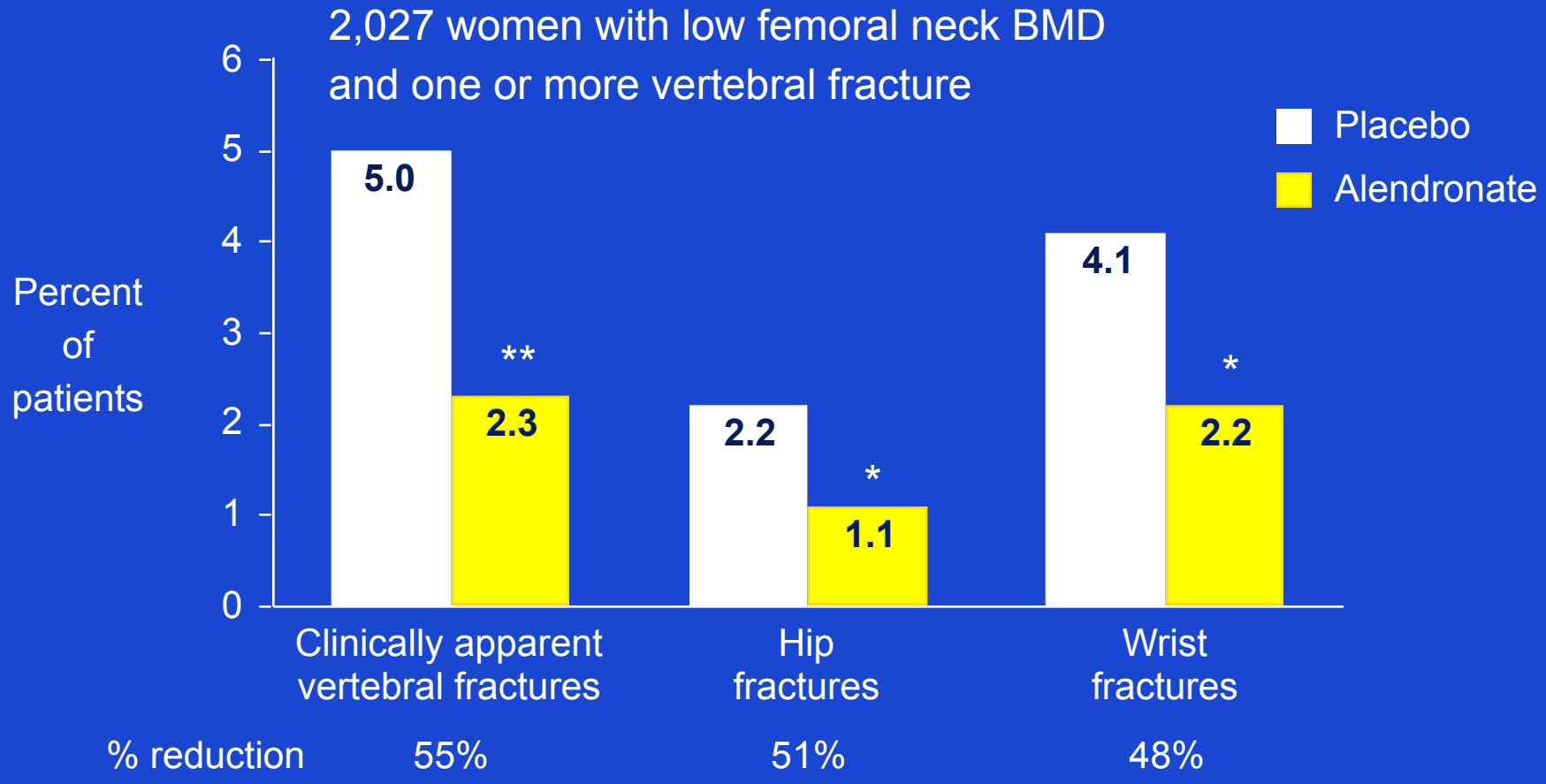
- Prevention of bone loss in recently menopausal women
- Treatment of established osteoporosis
- May have benefits in many conditions characterized by increased bone remodeling (eg, Paget's disease, hypercalcemia of malignancy)

Contraindications

- Active upper GI disease (some
- bisphosphonates cause esophageal
- irritation)
- Hypocalcemia
- Renal insufficiency

In patients reated with glucocorticoids for a long time- antiresorptive treatment recommended if BMD is≤-1.5

Fracture Intervention Trial (FIT)



**$P < 0.001$; *$P < 0.05$

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

ACLASTA® HAS PROVEN FRACTURE RISK REDUCTION AT ALL 3 KEYS OSTEOPOROSIS SITES DURING 3 YEARS[2]

MORPHOMETRIC VERTEBRAL FRACTURE

70%

(ARR 7.6%)
P<0.001

NONVERTEBRAL FRACTURE^

25%

(ARR 2.7%)
P<0.001

HIP FRACTURE

41%

(ARR 1.1%)
P=0.002

*Relative to placebo. ^ Nonvertebral fracture ia a composite endpoint excluding finger, toe and facial fractures.
ARR: Absolute Risk Reduction.

Annually infused ACLASTA® provides a significant and sustained fracture protection[2]

.Black DM, et al.N Engl J Med. 2007; 356(18): 1809-1822. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis .2

ACLASTA HAS PROVEN TO REDUCE NEW CLINICAL FRACTURES DURING 3 YEARS AND ALL-CAUSE MORTALITY AFTER A RECENT, LOW-TRAUMA HIP FRACTURE

: Hip Fracture Patients

: The HORIZON Recurrent Fracture Trial (RFT)

After a recent low-trauma hip fracture[3]

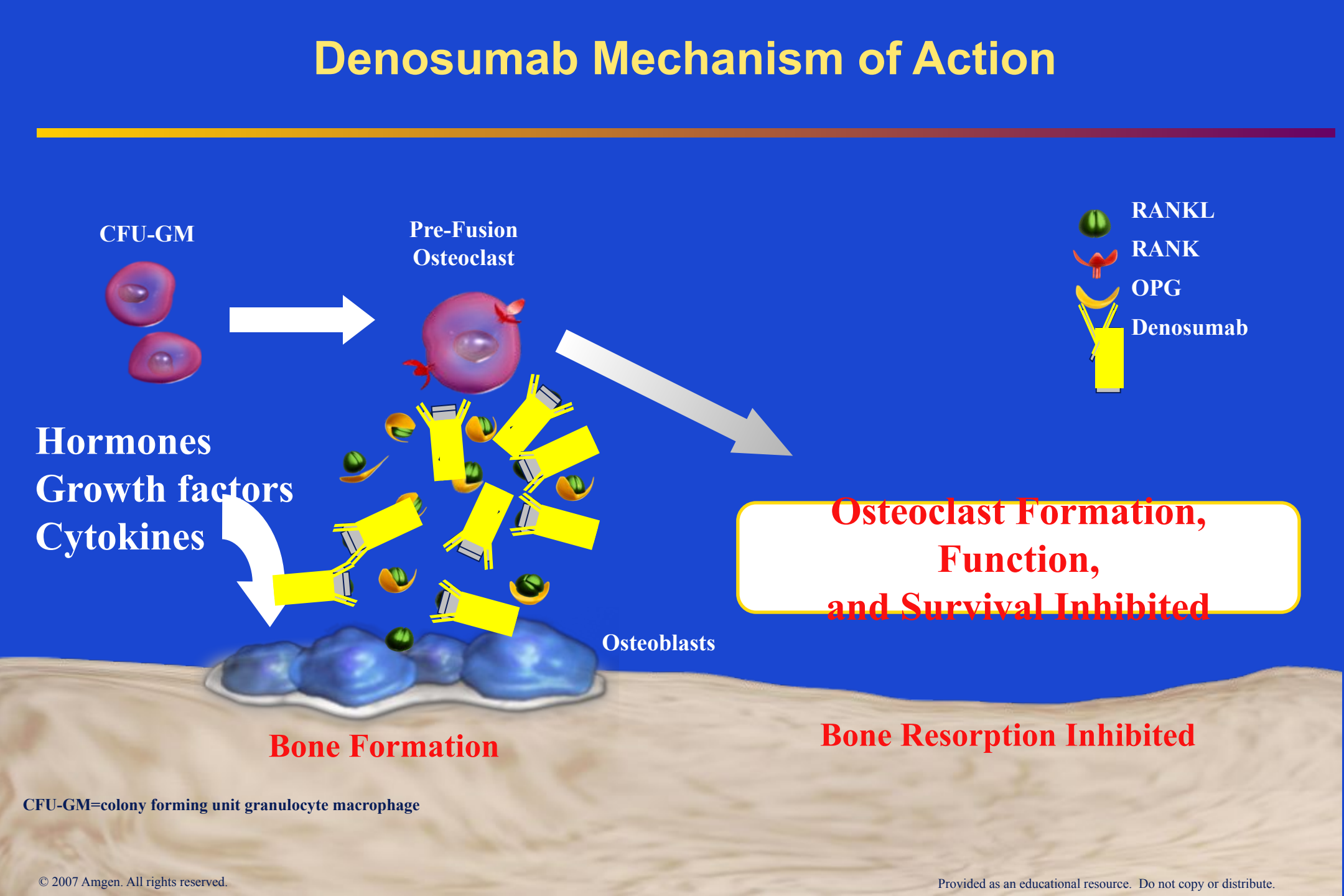
Give vitamin D supplementation-75000-100000 IU in !!one dose before the Zoledronic acid infusion

Hazard ratio,
0.65 (95% CI,0.50-0.84).
Zoledronic Acid (n = 1065) vs.
Placebo (n = 1062)
Death-No.(%):
Zoledronic Acid 92 (8.6) vs.
Placebo 139 (13.9) .

Hazard ratio,
0.72 (95% CI,0.56-0.93),
Zoledronic Acid (n = 1054) vs.
Placebo (n = 1057) ;P=0.01.
Death-No.(%):
Zoledronic Acid 101 (9.6) vs.
Placebo 141 (13.3)

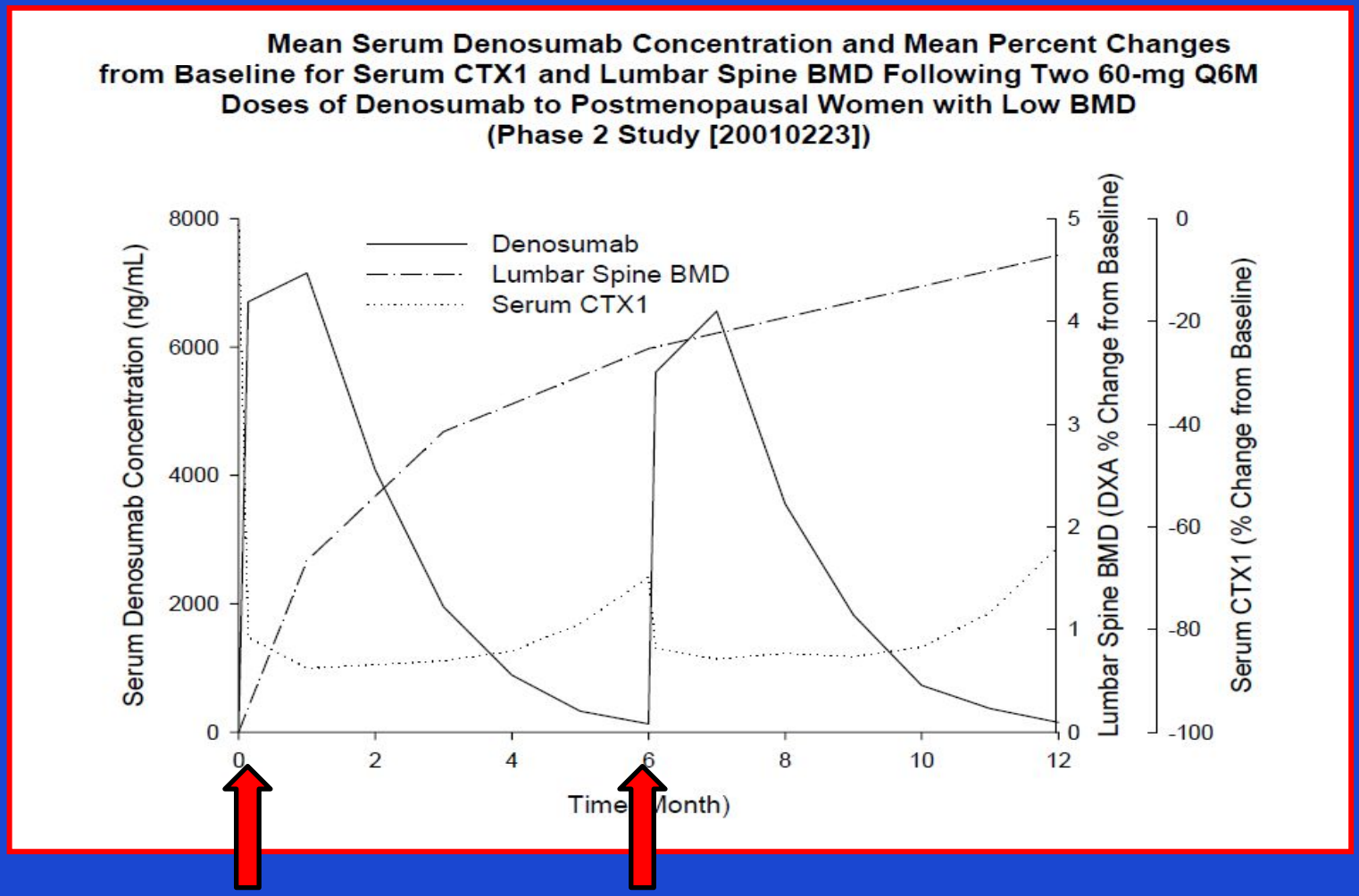
.Lyles KW, et al. N Engl J Med. 2007; 357: 1799-1809. Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

Denosumab Mechanism of Action



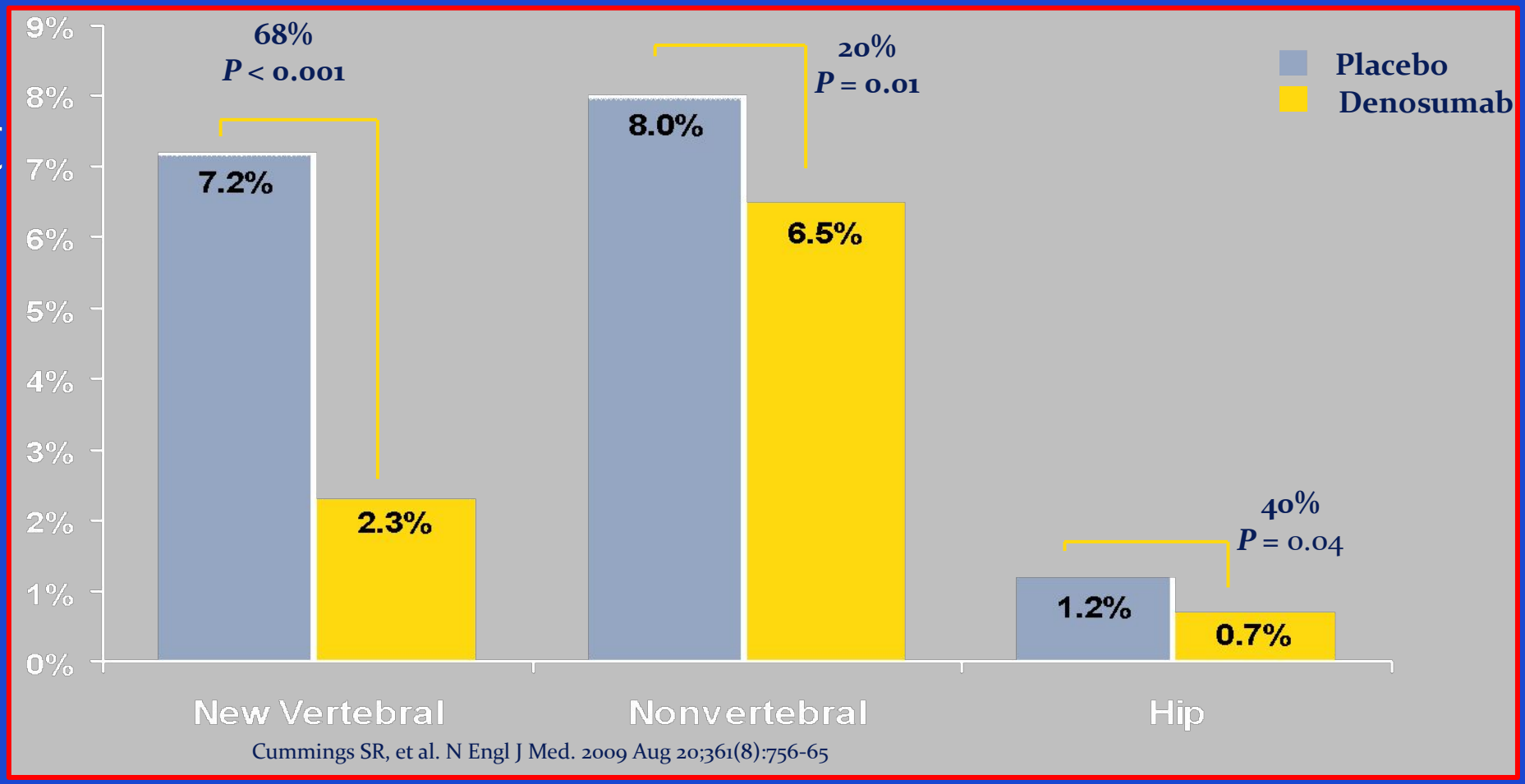
CFU-GM=colony forming unit granulocyte macrophage

Bone Turnover Markers with Denosumab



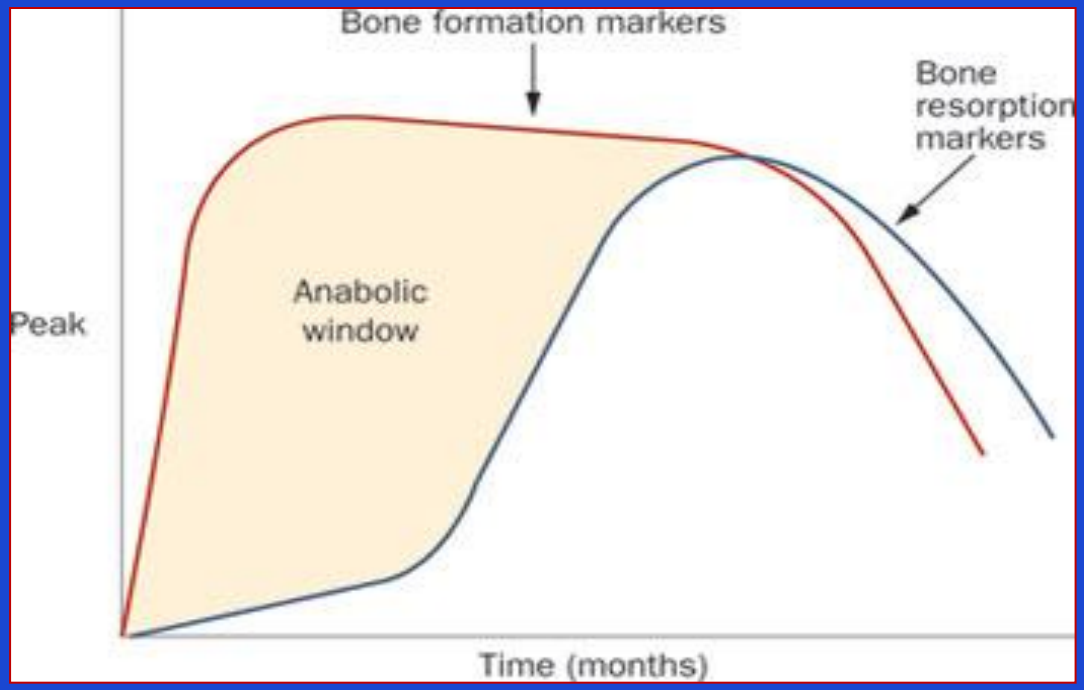
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM176623.pdf

The Effect of Denosumab on Fracture Risks at 36 Months *Phase 3: The FREEDOM Trial*



Cummings SR, et al. N Engl J Med. 2009 Aug 20;361(8):756-65

Anabolic Window with Teriparatide



Biosynthetic PTH

stimulate bone formation

overfill resorption cavities

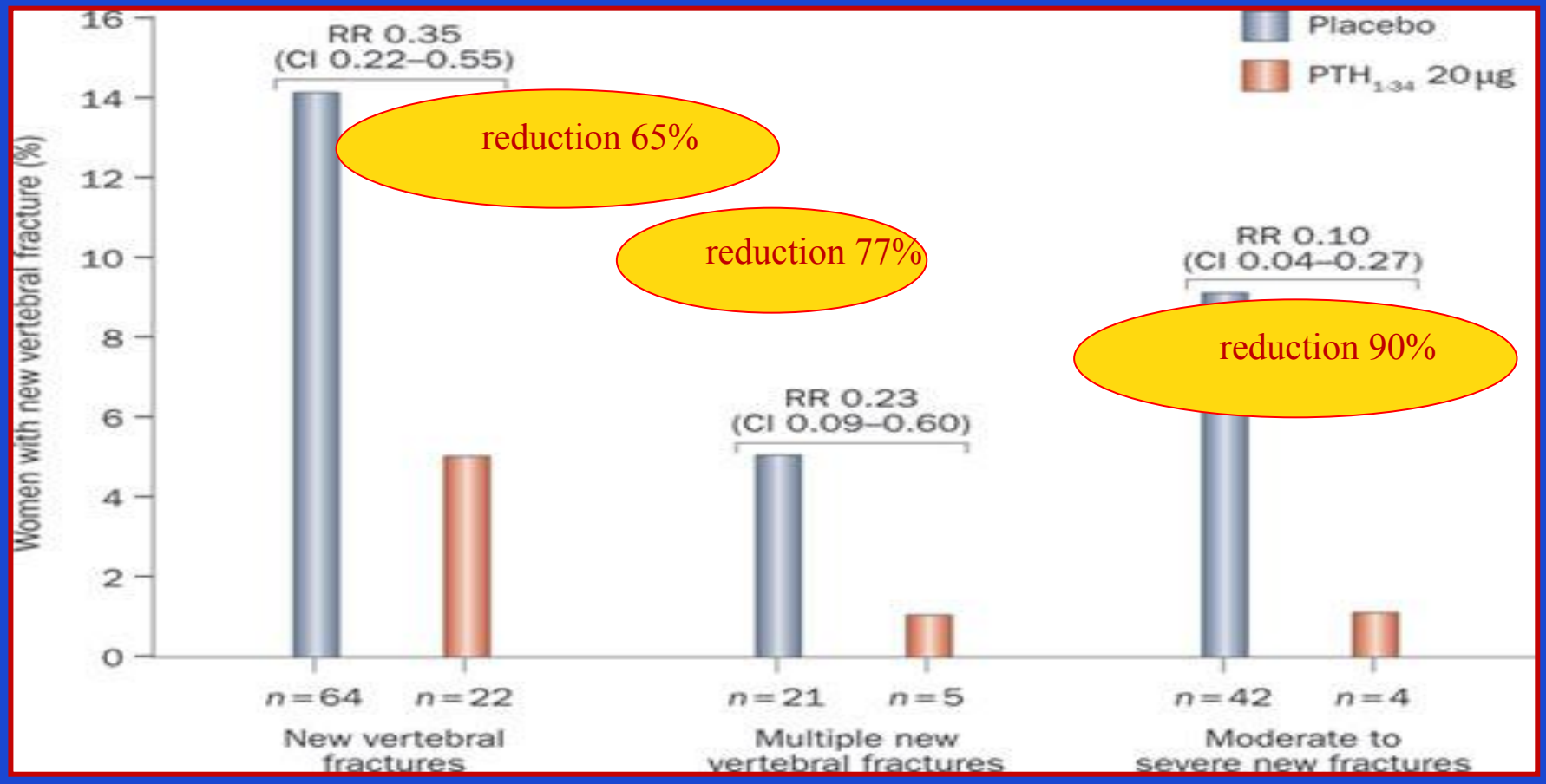
the increase in bone density continues beyond two years

.Rubin, Bilezikian, 2003

Comparison of BMD Changes During Treatment with PTH 1-34 or Fosalan

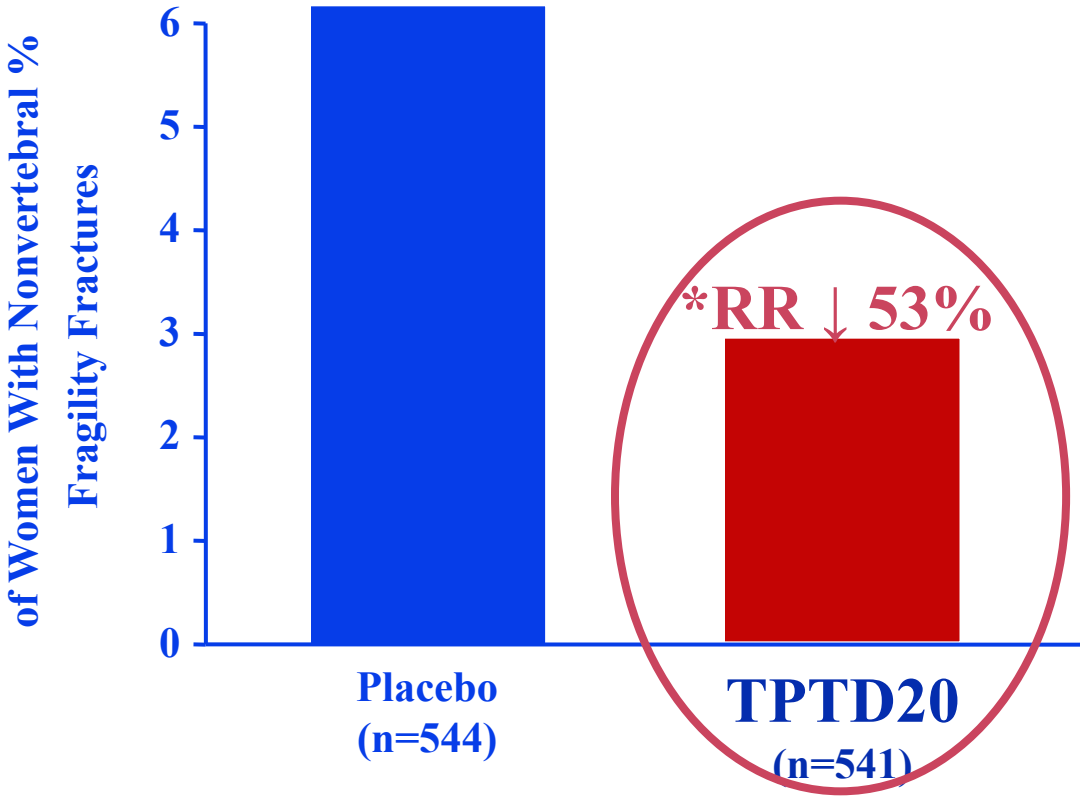
Measurement Site	PTH	Fosalan
Lumbar spine	12.2±9.4*	5.6±5.0
Total hip	4.0±5.7*	2.5±3.2
Femoral neck	4.8±6.5*	1.7±4.3
Ultradistal radius	0.2±6.6	1.4±5.1

Effect of $PTH_{1–34}$ on Vertebral Fracture Risk



Kraenzlin, M. E. & Meier, C. (2011) Parathyroid hormone analogues in the treatment of osteoporosis
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2011.108

Teriparatide Reduces the Risk of Nonvertebral Fragility Fractures*



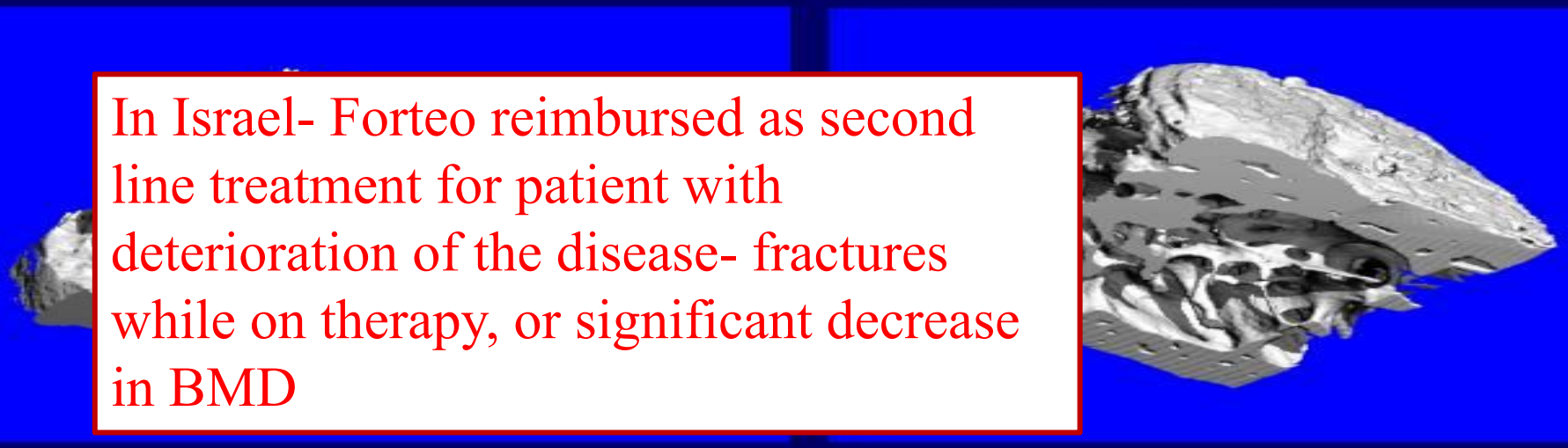
.Defined as occurring with minimal trauma*

.P<.05†

.N Engl J Med. 2001;344:1434-1441

Teriparatide Improves Skeletal Architecture

In Israel- Forteo reimbursed as second line treatment for patient with deterioration of the disease- fractures while on therapy, or significant decrease in BMD



Jiang UCSF

Baseline

Patient treated with teriparatide 20µg

Follow up

Female, age 65
Duration of therapy: 637 days (approx 21 mos)

BMD Change:
⇒Lumbar Spine: +7.4% (group mean = 9.7 ± 7.4%)
⇒Total Hip: +5.2% (group mean = 2.6 ± 4.9%)

Data from Jiang et al. JBMR 2003 (in press)

!Thank you