

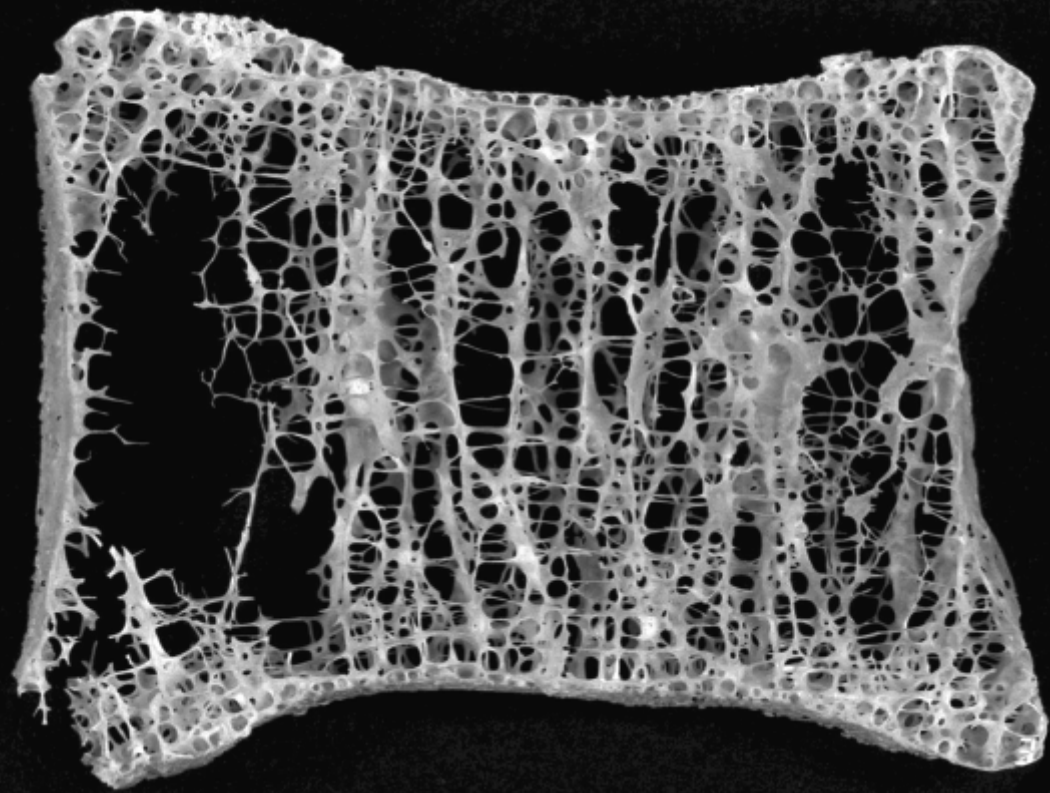
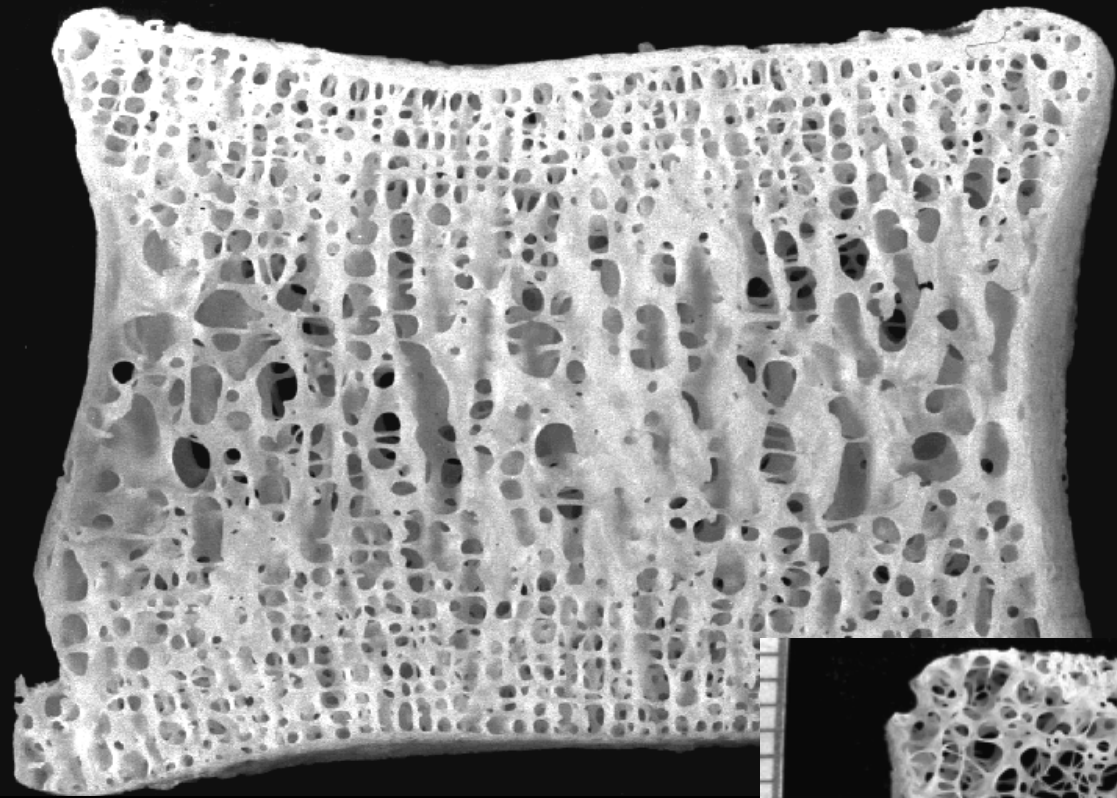
Geneva, March 10, 2005

Osteoporosis

Prof René Rizzoli M.D.

**Division of bone diseases
WHO collaborating center for
osteoporosis prevention**

**Department of rehabilitation and geriatrics
University hospitals
Geneva, Switzerland**



Osteoporosis Definition

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

Consensus Development Conference: *Am J Med* 1991;90:107-110



Osteoporosis: a 2-Stage Disease

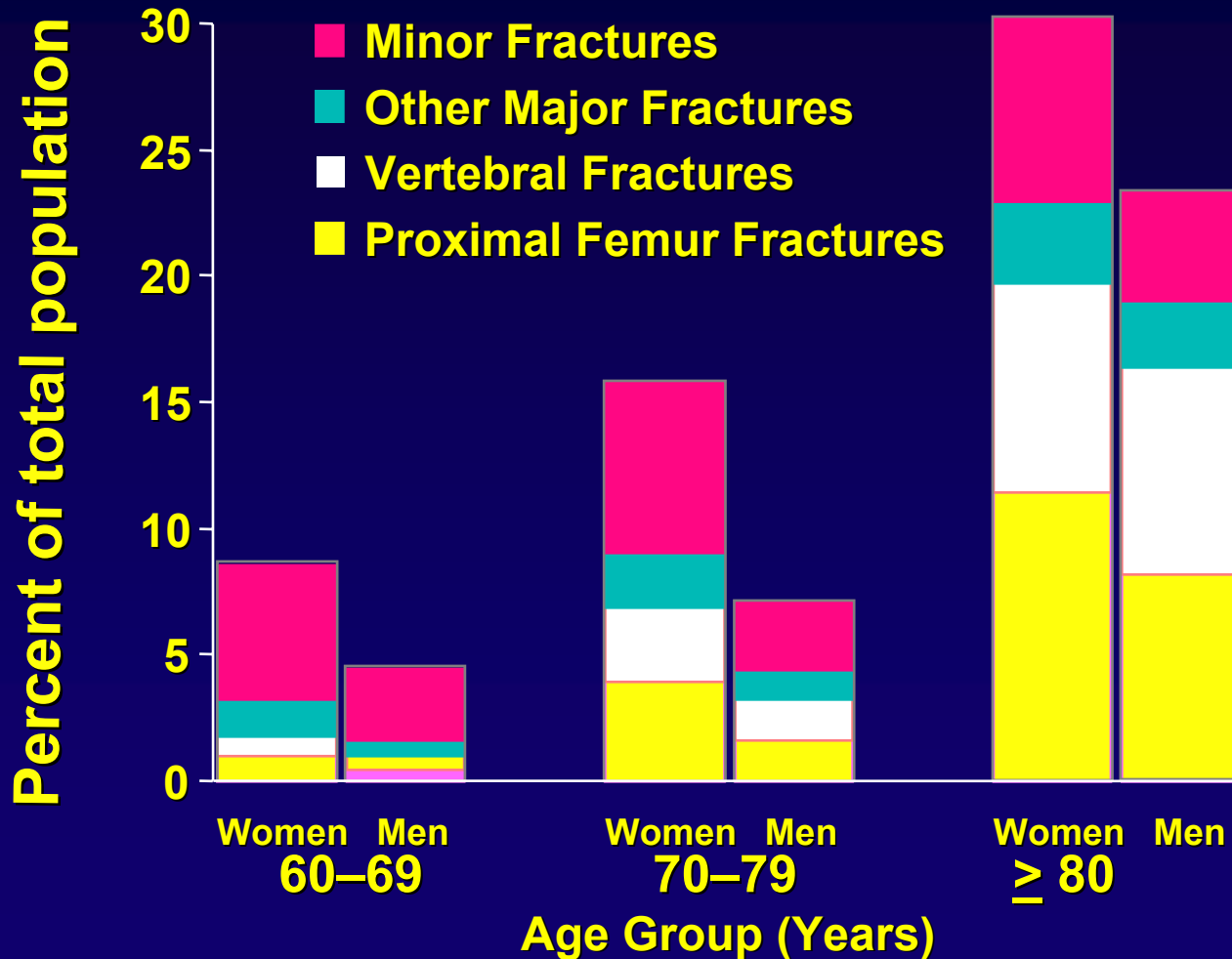
- **With**
- **Without Fracture**



Epidemiology

Fractures by Age and Gender

Dubbo Osteoporosis Epidemiology Study, 1989–1994

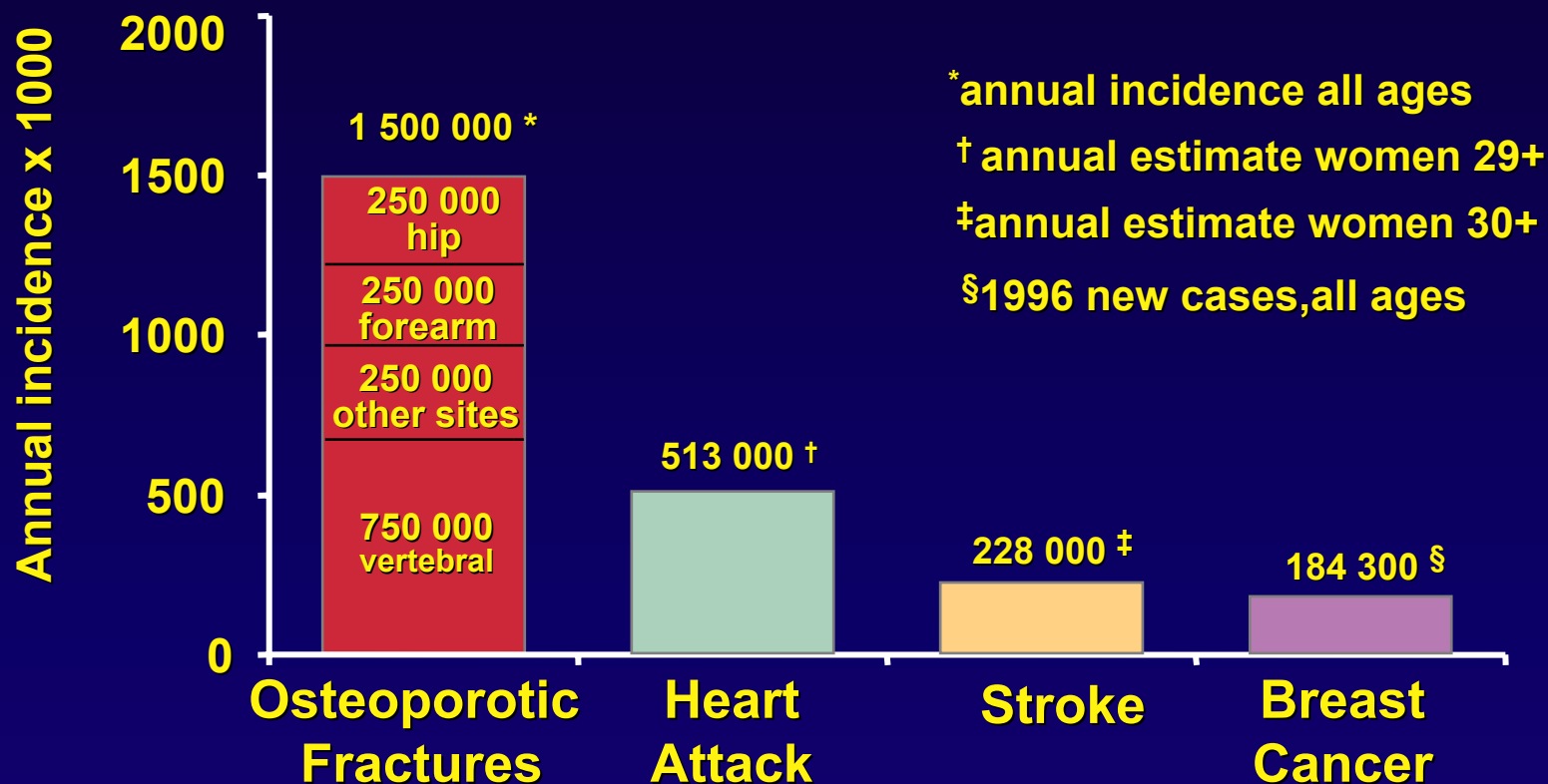


Lifetime risk of fragility fracture in the Swedish population at the age of 50 years (%)

	Women	Men
• Proximal femur	23	11
• Distal forearm	21	5
• Vertebral (clinical)	15	8
• Proximal Humerus	13	5
• Any	46 %	22 %

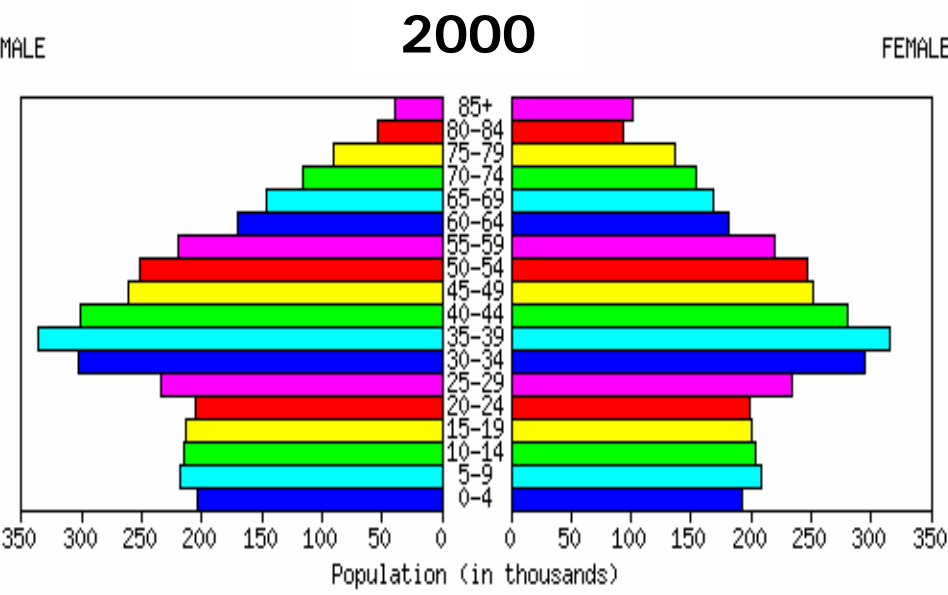
From Kanis et al 2000

Osteoporotic Fractures in Women: Comparison With Other Diseases

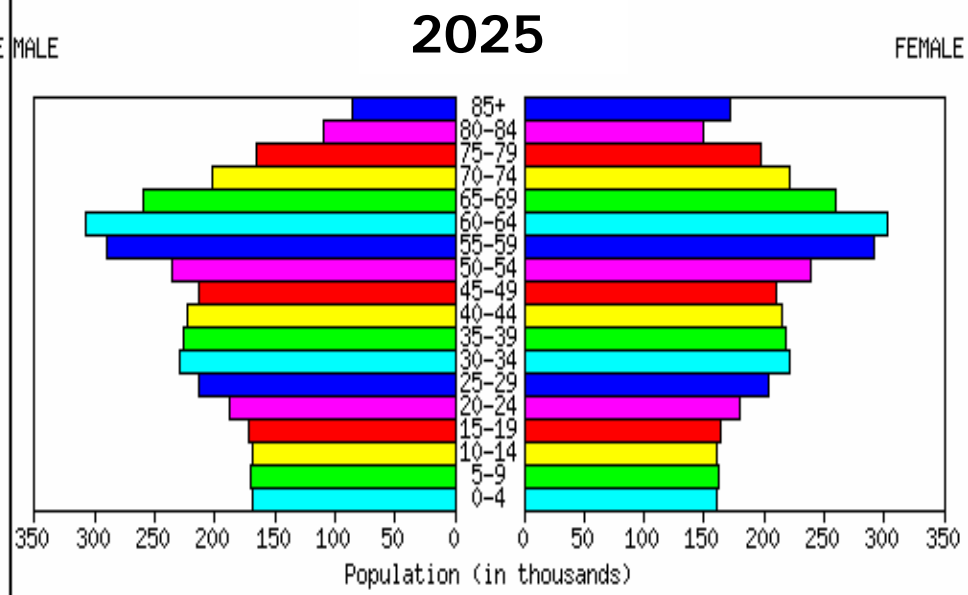


Riggs BL, Melton LJ. *Bone*. 1995.
Heart and Stroke Facts. 1996. American Heart
Association.
Cancer Facts & Figures. 1996. American Cancer Society.

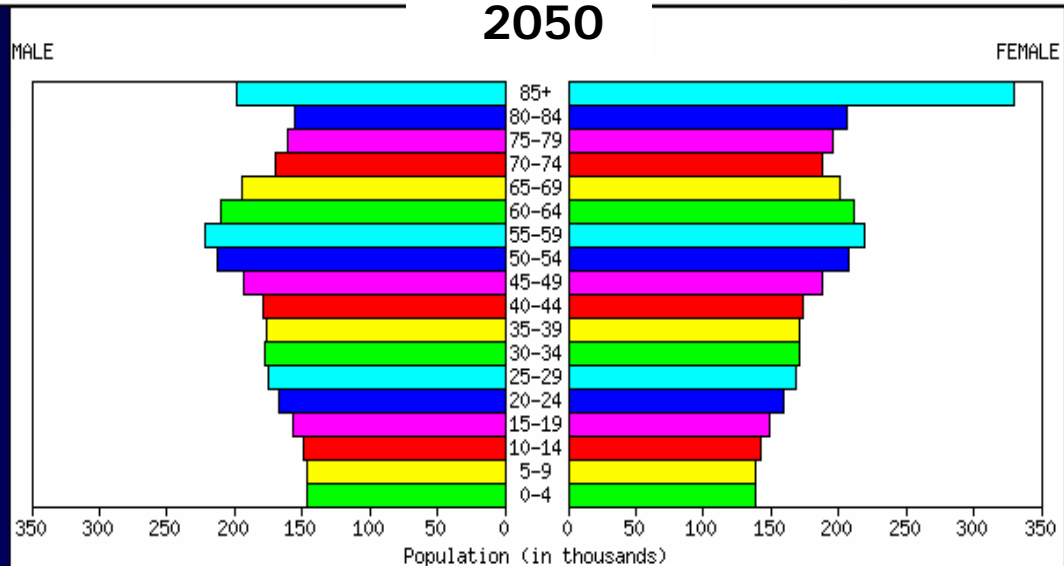
SWITZERLAND 2000, 2025 and 2050



Source: U.S. Census Bureau, International Data Base.

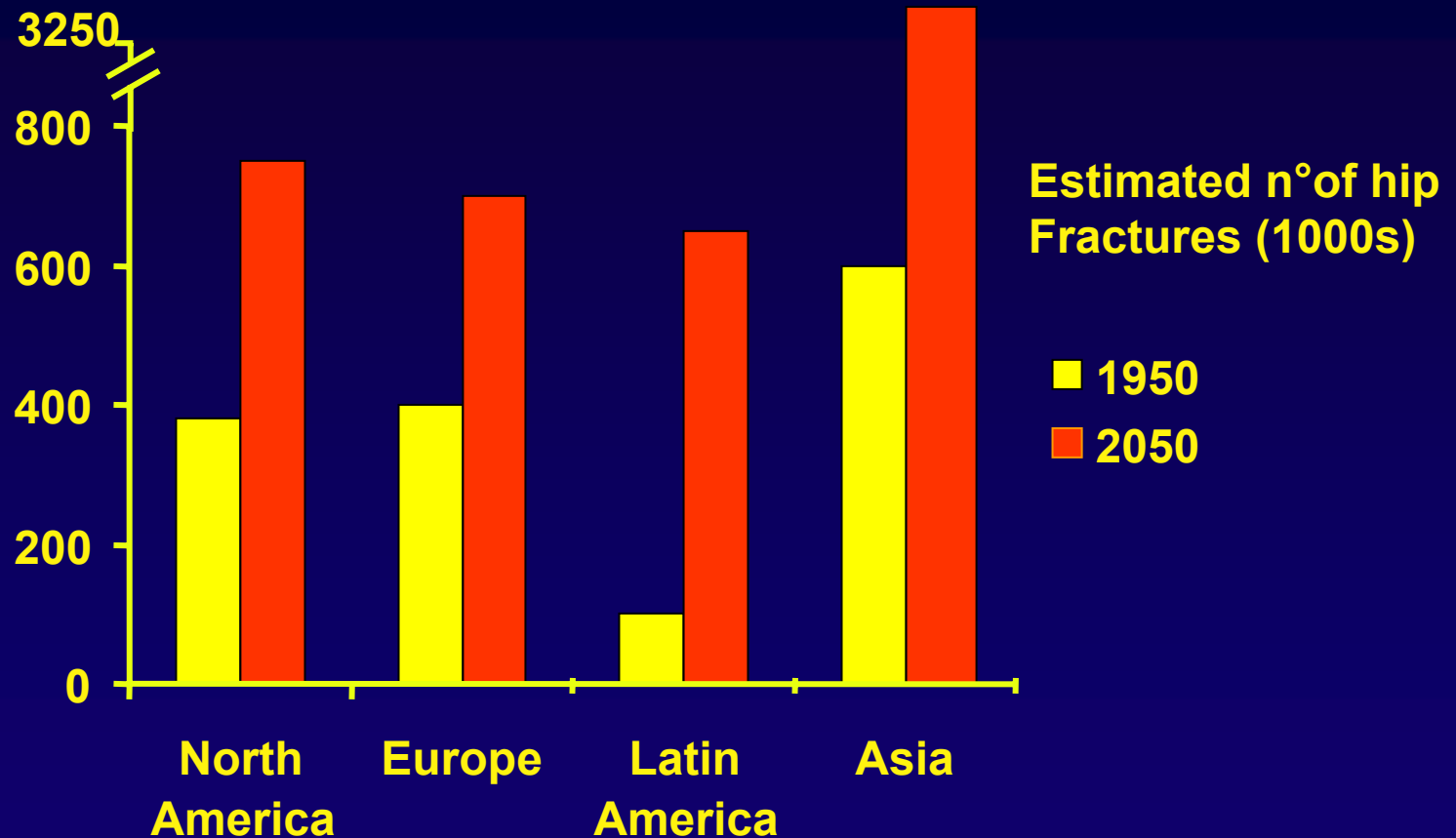


Source: U.S. Census Bureau, International Data Base.



Source: U.S. Census Bureau, International Data Base.

Projected burden of osteoporotic hip fractures worldwide



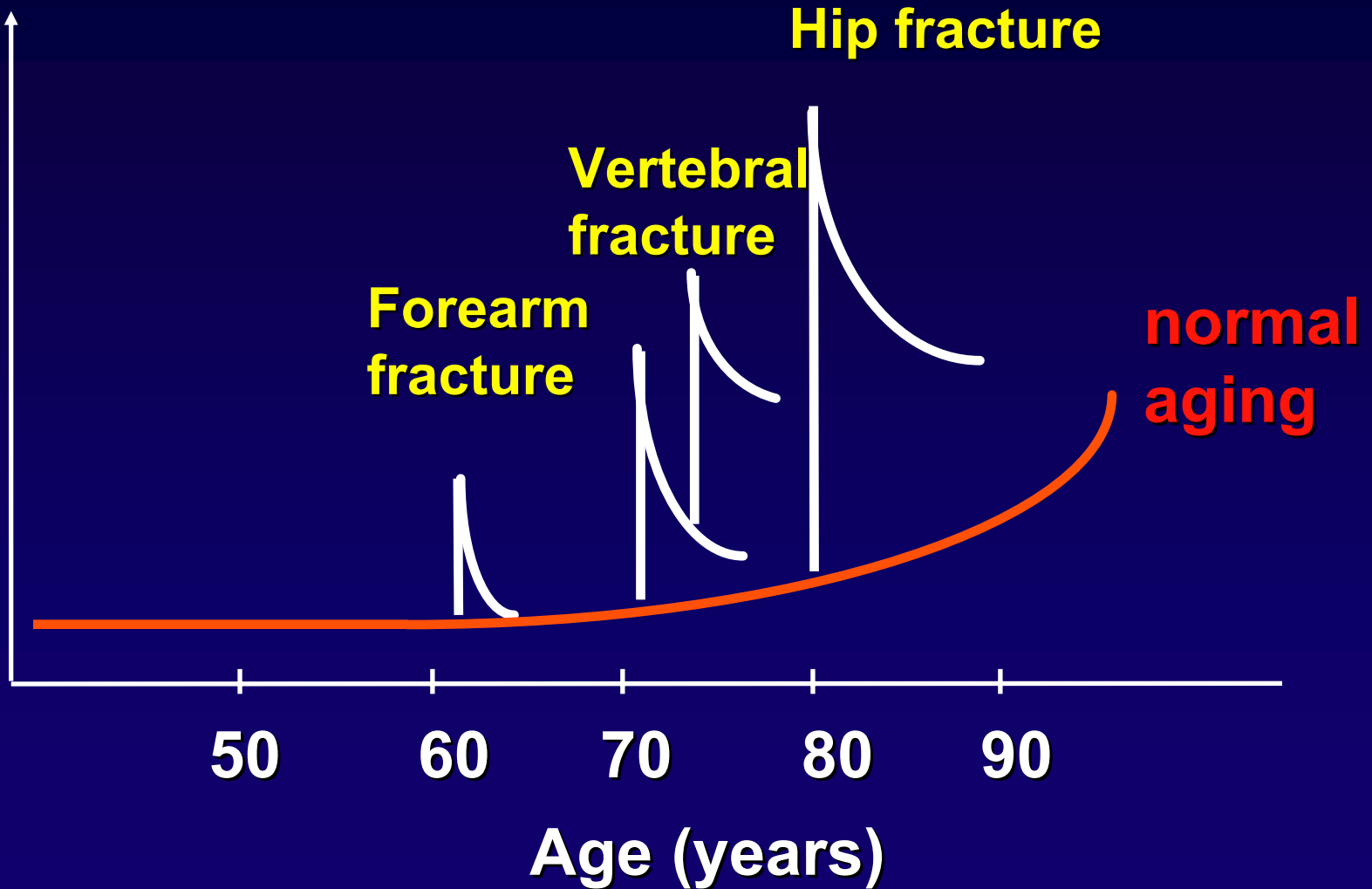
Number of hip fractures: **1990: 1.66 million; 2050: 6.26 million**

Adapted from Cooper C., Melton U, *Osteoporosis Int* 2:285-289, 1992

If the prevalence of hip fracture continues to rise at current rates, it may well be that in the next few decades, orthopaedists will do little else but treat this problem.

**W. C. Hayes, In: Bone Formation and Repair
(American Academy of Orthopaedic Surgeons) 1994**

Degree of dependence



Morbidity After Vertebral Fractures

- **Back pain**
- **Loss of height**
- **Deformity (kyphosis, protuberant abdomen)**
- **Reduced pulmonary function**
- **Diminished quality of life: loss of self-esteem, distorted body image, dependence on narcotic analgesics, sleep disorder, depression, loss of independence**

Osteoporosis Results in More Cost Than Many Other Diseases

- **Annual cost of acute hospitalization in Switzerland in 1992: 600 million Swiss francs (US\$350 million)***
 - **Number of bed days (men and women)**
 - **701,000 for osteoporosis**
 - **891,000 for COPD**
 - **533,000 for stroke**
 - **328,000 for myocardial infarction**
 - **201,000 for breast cancer**



Osteoporosis
1 when
looking at
women only

*Lippuner et al. *Osteoporosis Int* 1997; 7: 414-25

Mortality after Major Types of Osteoporotic Fracture in Men and Women: an Observational Study

Center et al, Lancet 1999

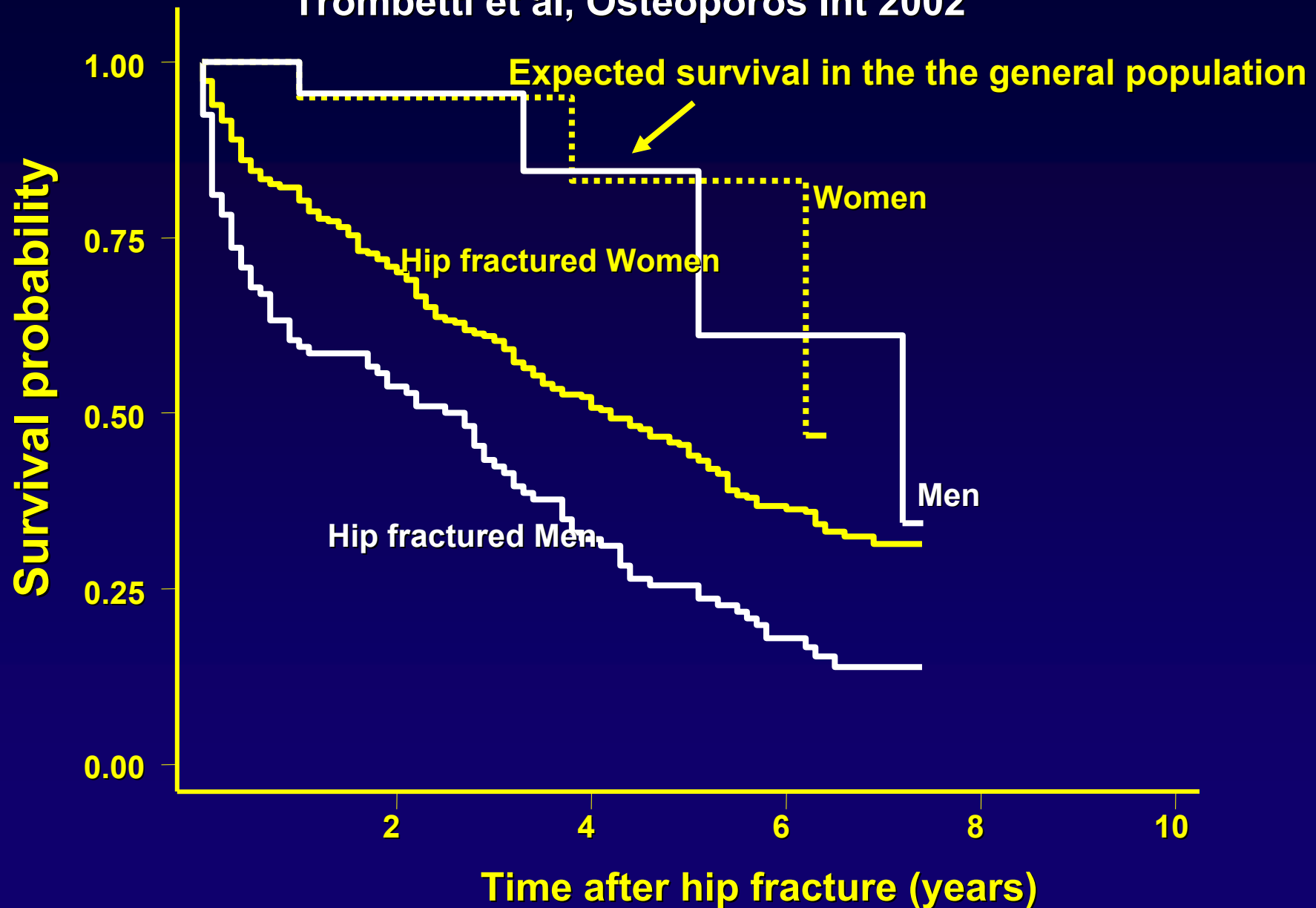
5 - Year Prospective Cohort Study

Age-Standardized Mortality Ratio

Fracture	<u>Women</u>	<u>Men</u>
Proximal Femur	2.2	3.2
Vertebral	1.7	2.4
Other Major	1.9	2.2
Other Minor	0.8	1.5

Survival after Hip Fracture

Trombetti et al, Osteoporos Int 2002



Risk of Death For Hip Fracture in Women Similar to Other Diseases

- **A 50 year old woman's lifetime risk of dying from a hip fracture is equal to her risk of dying from breast cancer and greater than her risk of dying from endometrial cancer**
 - **Hip Fracture: 2.8%**
 - **Breast Cancer: 2.8%**
 - **Endometrial Cancer: 0.7%**

Diagnosis

X-ray techniques

pDXA



XR-36

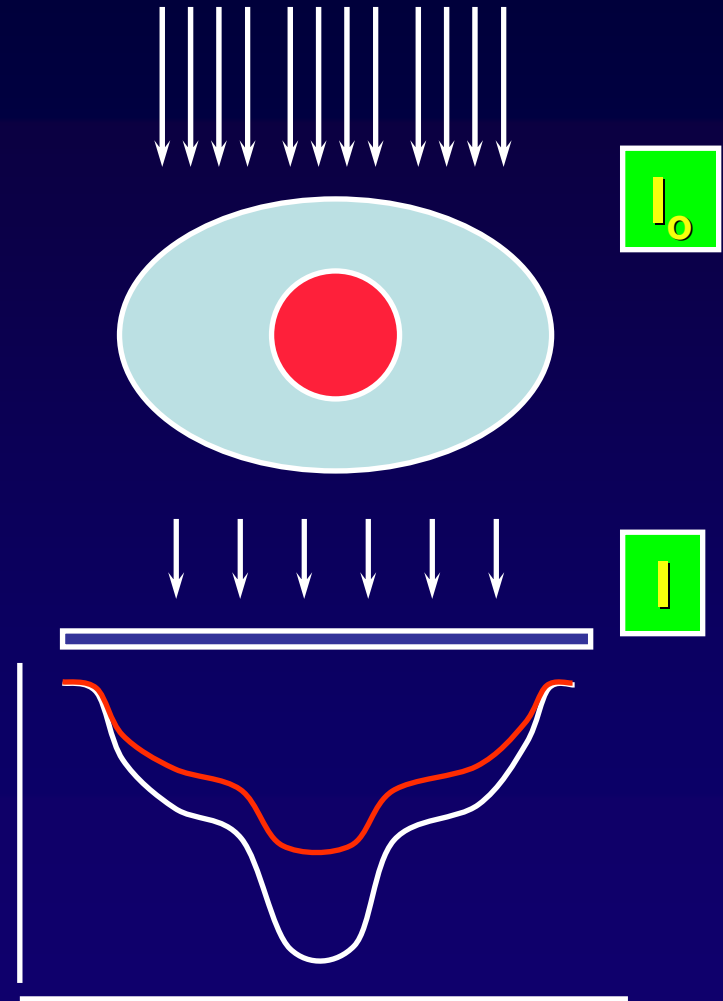


DXA

pQCT

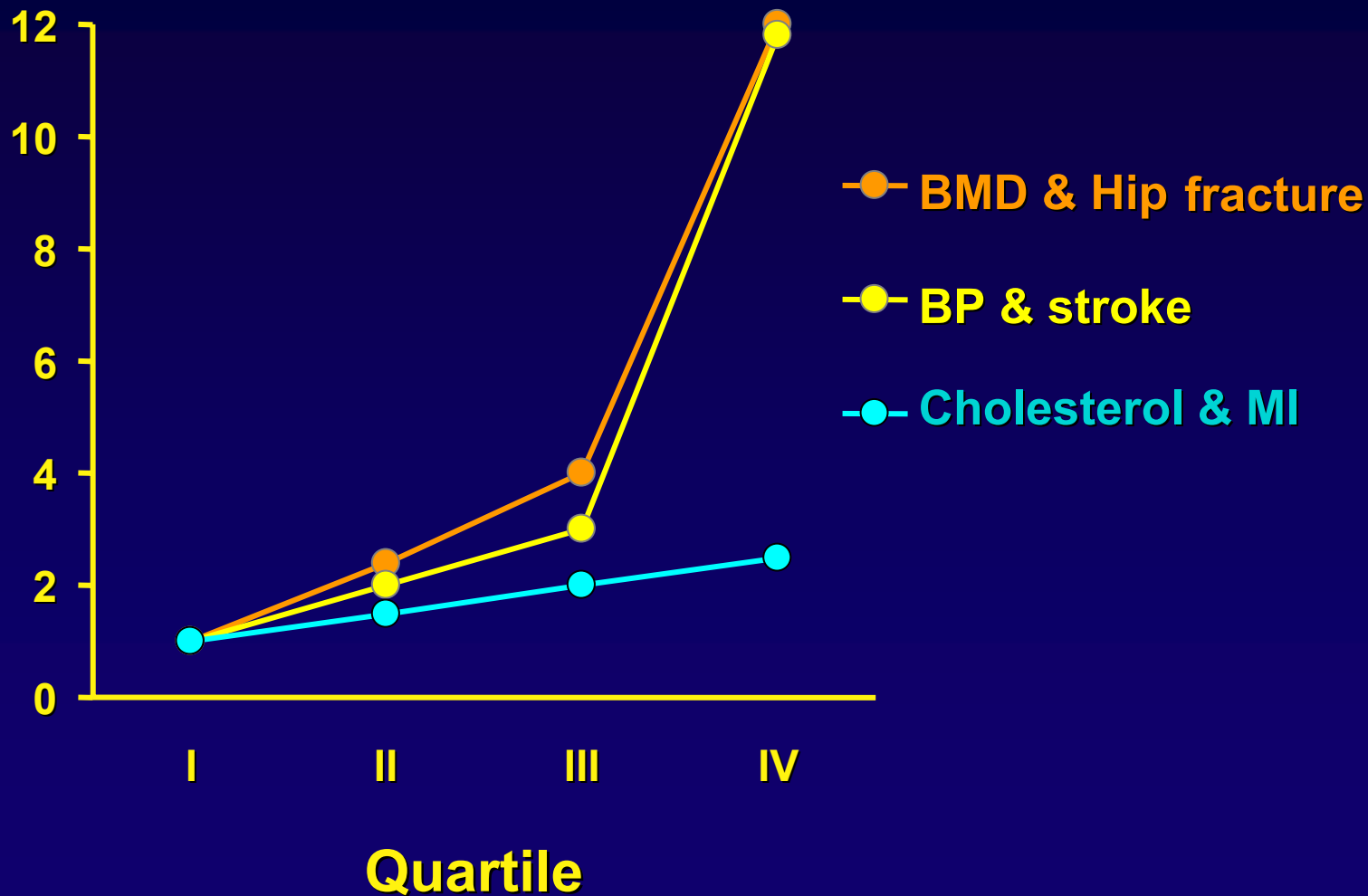
DXA: Principle

- Two attenuation profiles:
 - Low energy X-ray attenuation
 - High energy X-ray attenuation
- Multiply high energy profile by 'k' factor (ratio of soft tissue attenuation at low- & high-energy)
- BMD along scan = Low-energy profile - k-corrected high energy profile



Gradients of risk

Relative risk



Noninvasive Measurement of Bone Mass

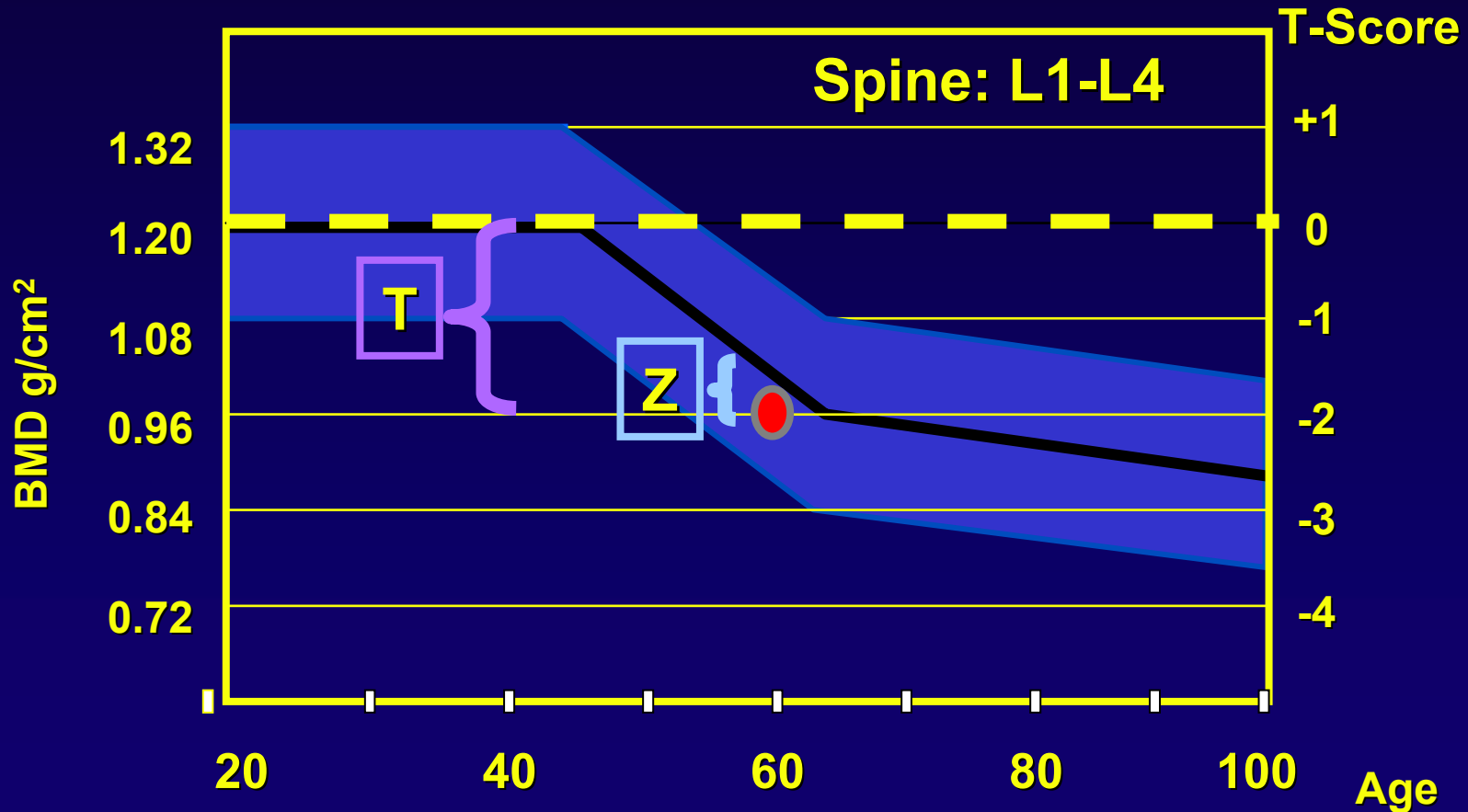
<u>Technique</u>	<u>Site</u>	<u>Precision</u>	<u>Cost Response to Therapy</u>	
SXA	Forearm	++	±	±
	Heel			
DXA	Spine	++	+	++
	Hip	+	+	+
	Tot. Body	++	+	±
QCT	Spine	±	++	+
	Forearm	++	+(+)	±
US	Heel	±	-	-
	+ Fingers			

Medicare Coverage for BMD Tests

<u>Procedure</u>	<u>Site</u>	<u>Fee Schedule Medicare *</u>
DXA	Axial	\$ 128
pDXA	Appendicular	\$ 40
RX Absorptiometry	Appendicular	\$ 38
QUS	Appendicular	\$ 53
SXA	Appendicular	\$ 40
QCT	Axial	\$ 185
pQCT	Appendicular	\$ 40

*** Medicare Allowable Charge = 80% of the Costs**

Example for T-score = - 2.0, 60 year old and Z-Score = - 0.5



Diagnosis of Osteoporosis Using Central DXA

WHO-Definition

	T-score
Normal	≥ -1
Osteopenia	< -1 and > -2.5
Osteoporosis	≤ -2.5
Severe Osteoporosis	≤ -2.5 with Fracture

Mainly for Spine and Hip in Women

Pathophysiology

Osteoporosis Pathogenesis and Management

Fracture



Fracture Treatment



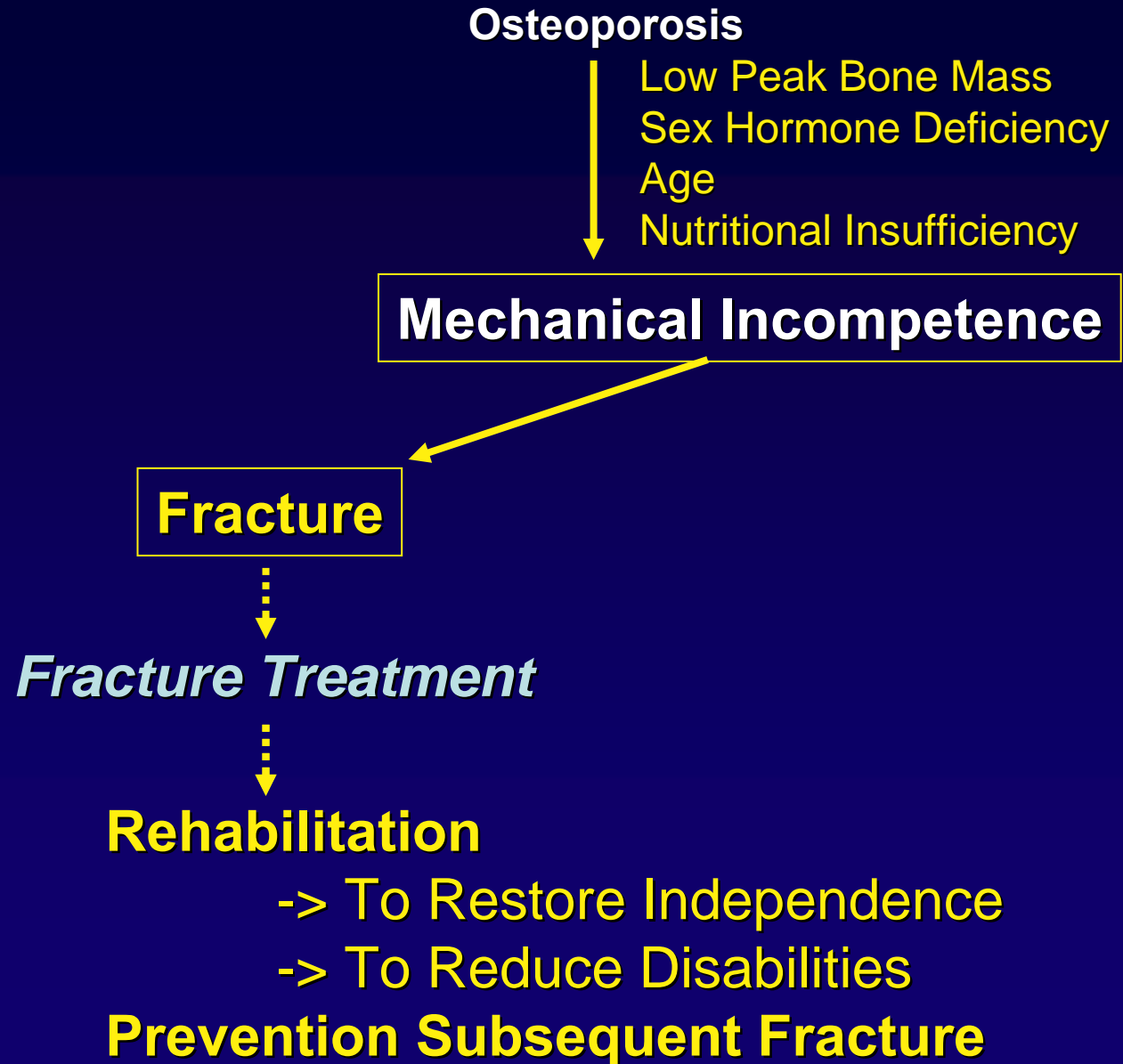
Rehabilitation

-> To Restore Independence

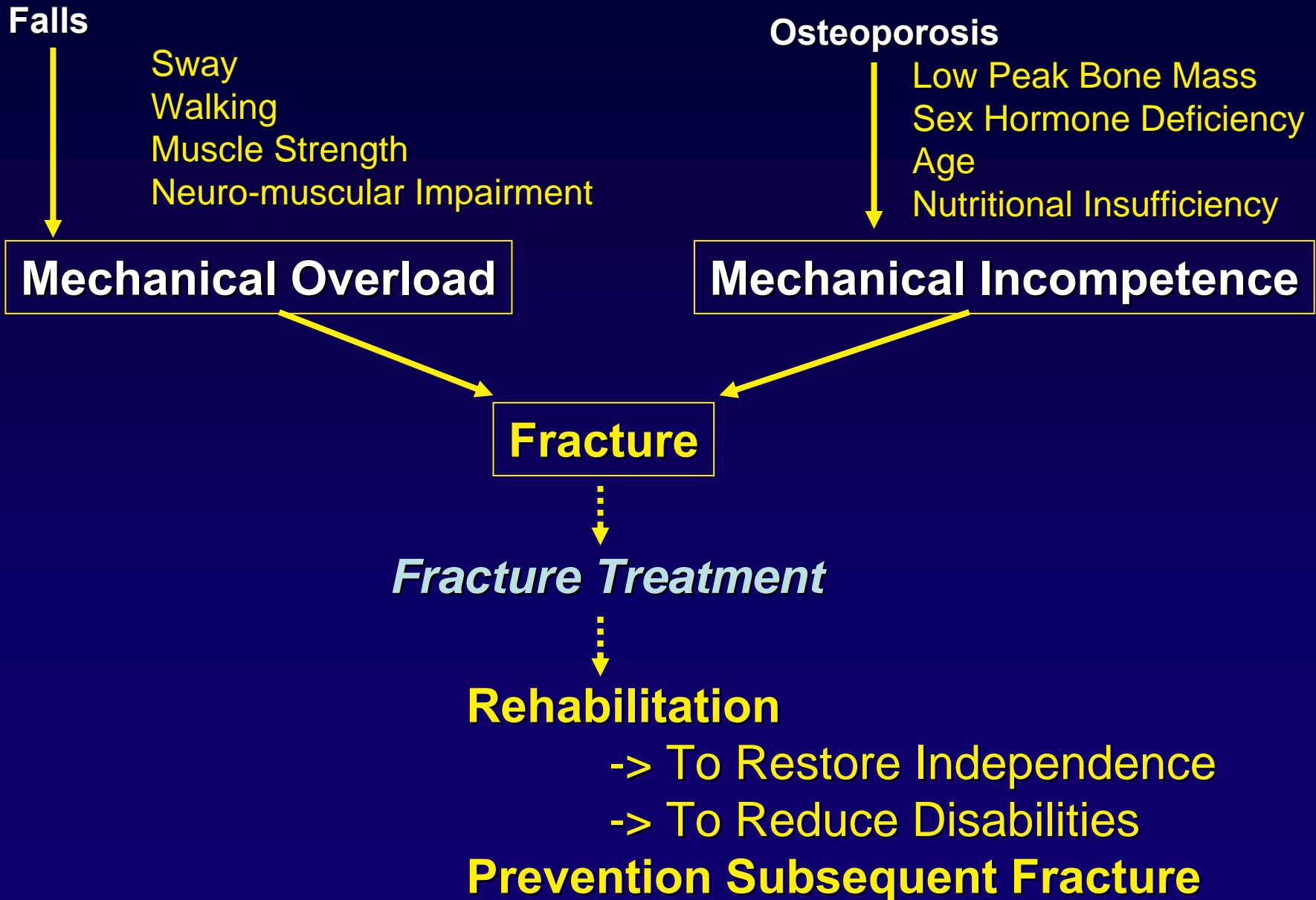
-> To Reduce Disabilities

Prevention Subsequent Fracture

Osteoporosis Pathogenesis and Management



Osteoporosis Pathogenesis and Management



Determinants of Fracture Risk

1. Age

2. Prevalent Fracture

3. Baseline BMD

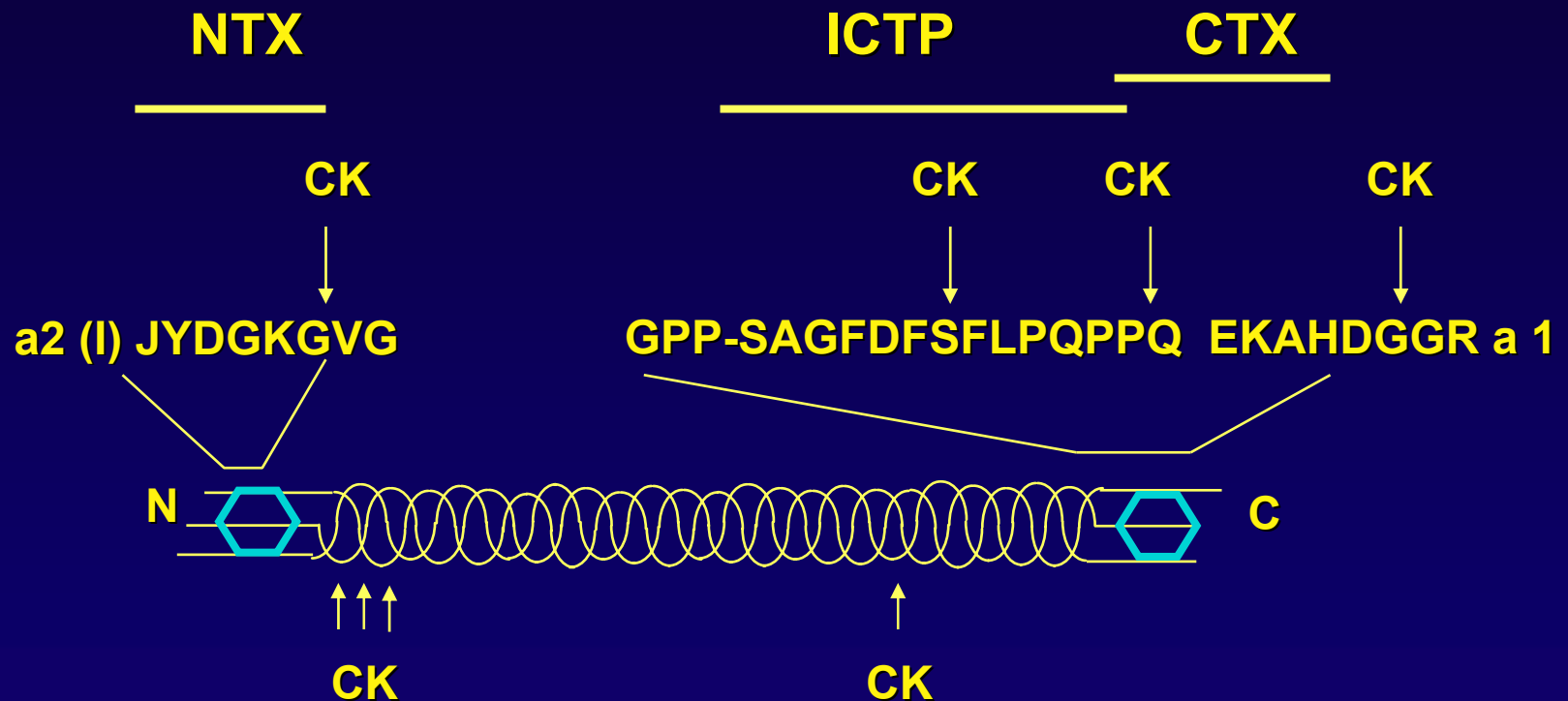
4. Baseline Turnover

5. Changes in BMD

6. Changes in Turnover

7. Fall-related Risk

Type I collagen epitopes and Cathepsin K cleavage sites

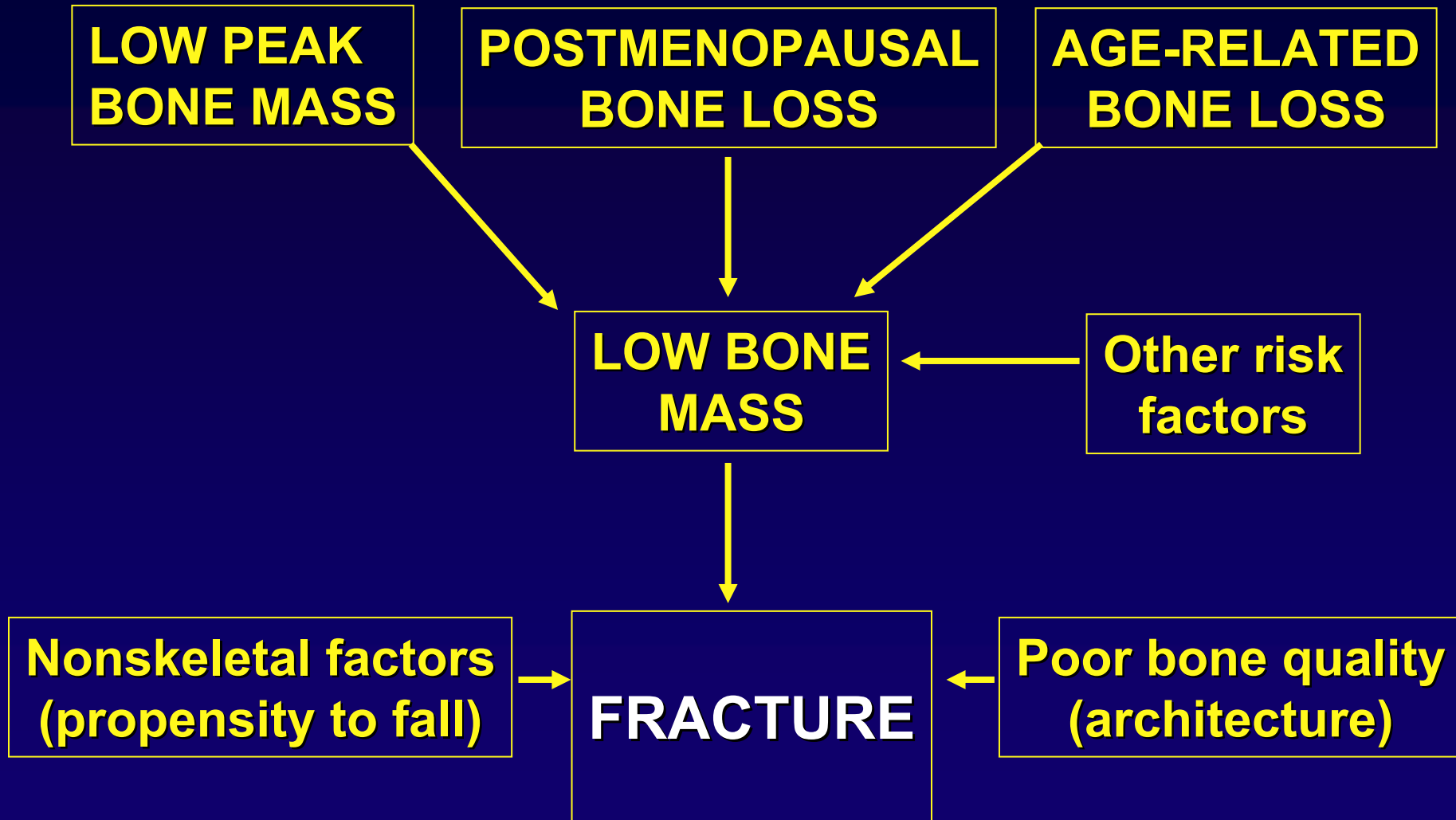


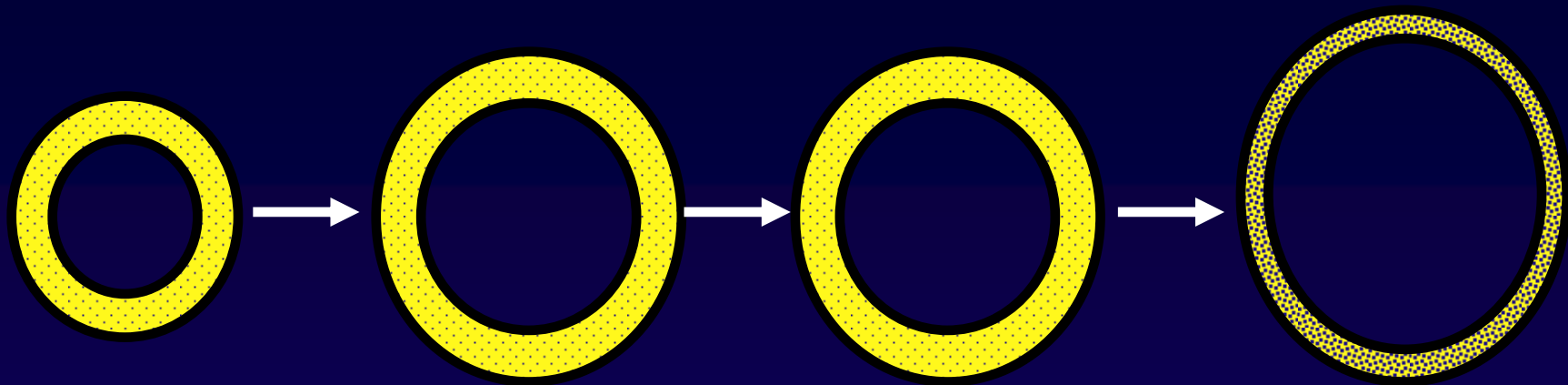
Deoxypyridinoline
Pyridinolines

Garnero et al., JBC, 1998

Sassi et al., Bone, 2000

Pathogenesis of Osteoporotic Fracture





Age: 10

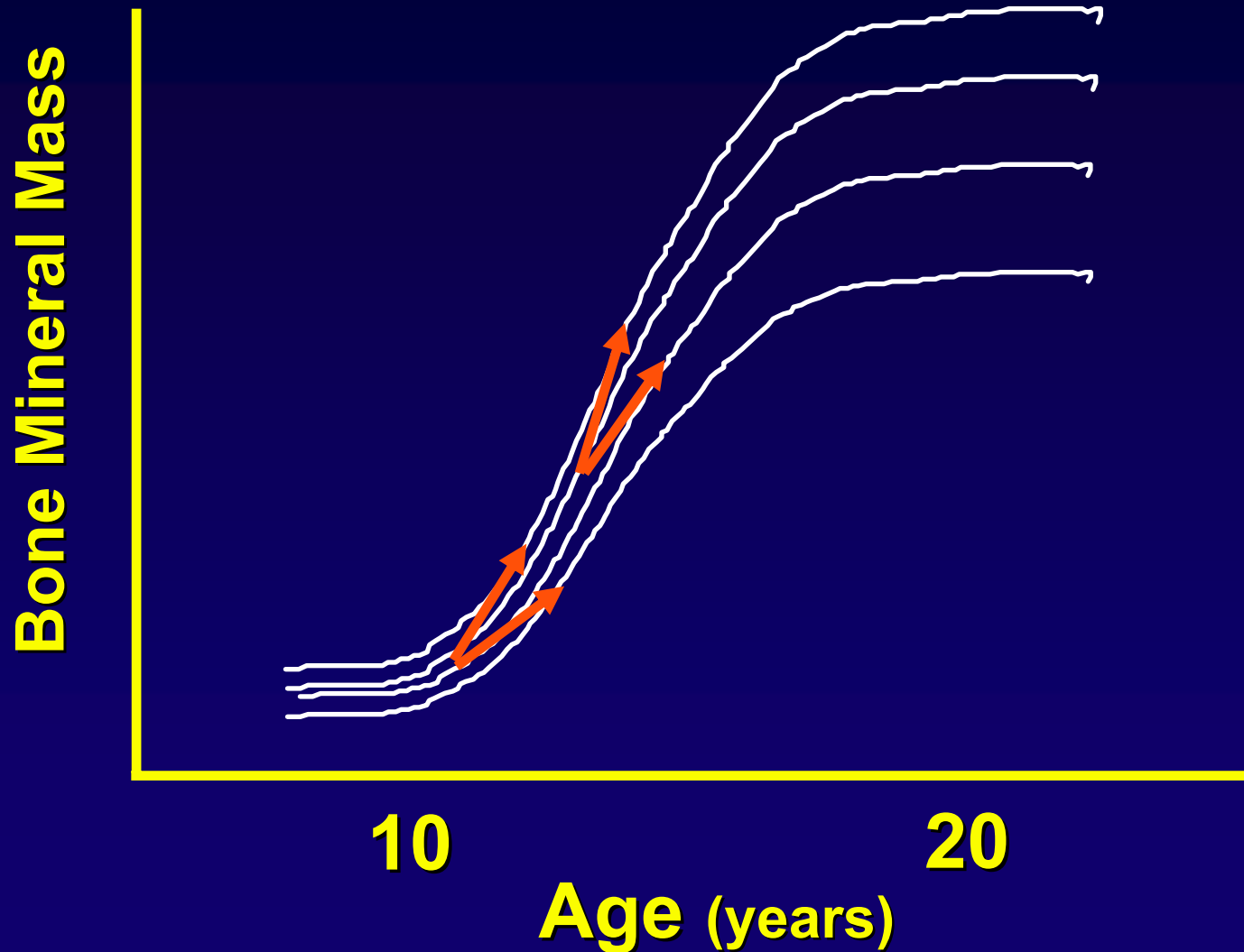
20

40

70

Rizzoli et al., J Mol Endocrinol 2001

Tracking of Bone Mineral Mass Accrual



Heredity

Gender

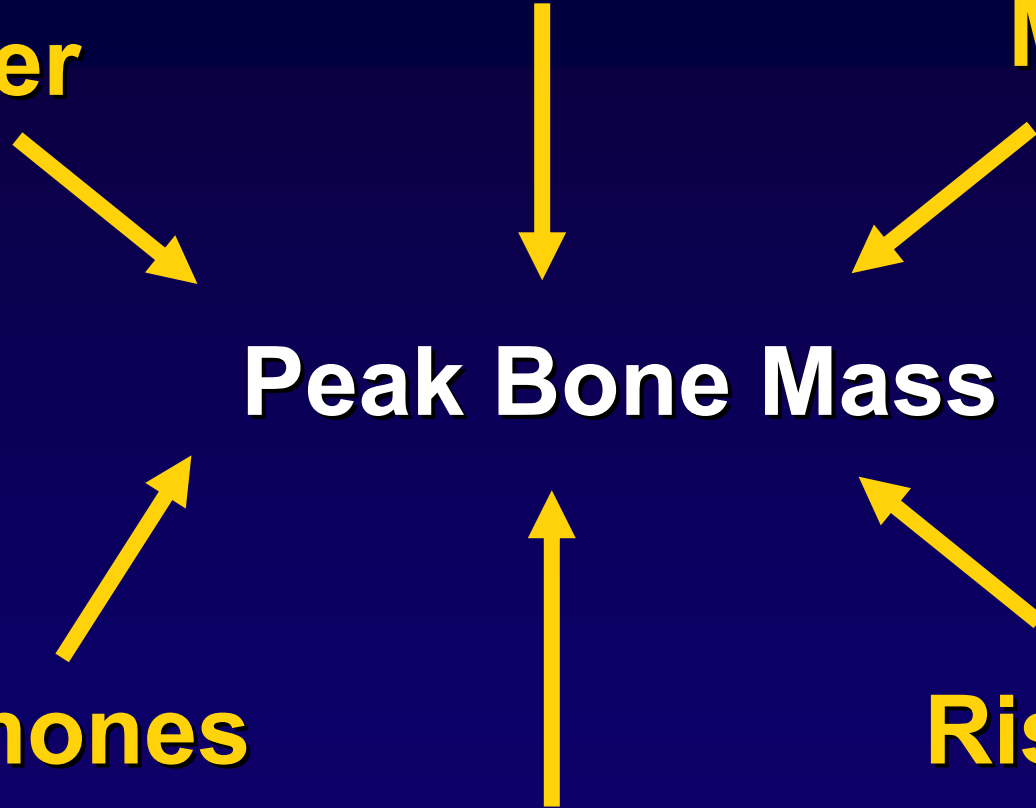
**Mechanical
Forces**

Peak Bone Mass

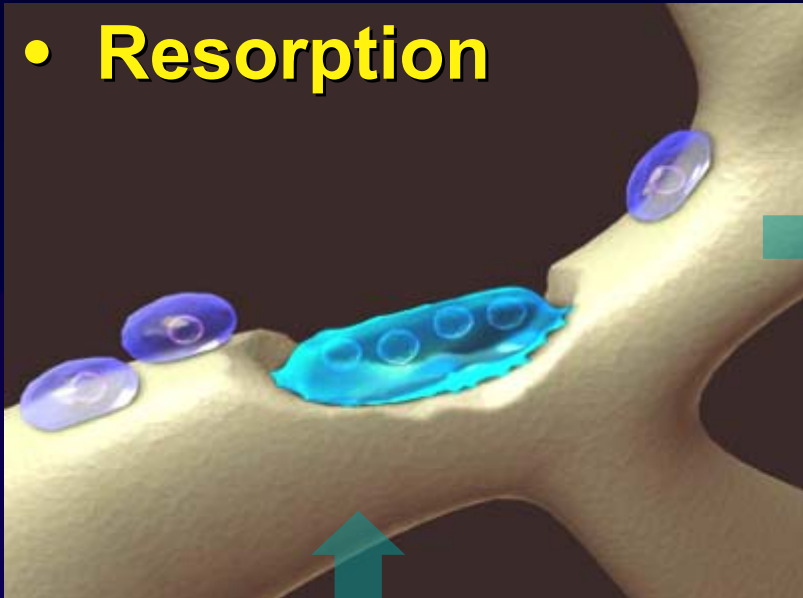
Hormones

Risk Factors

Nutrition



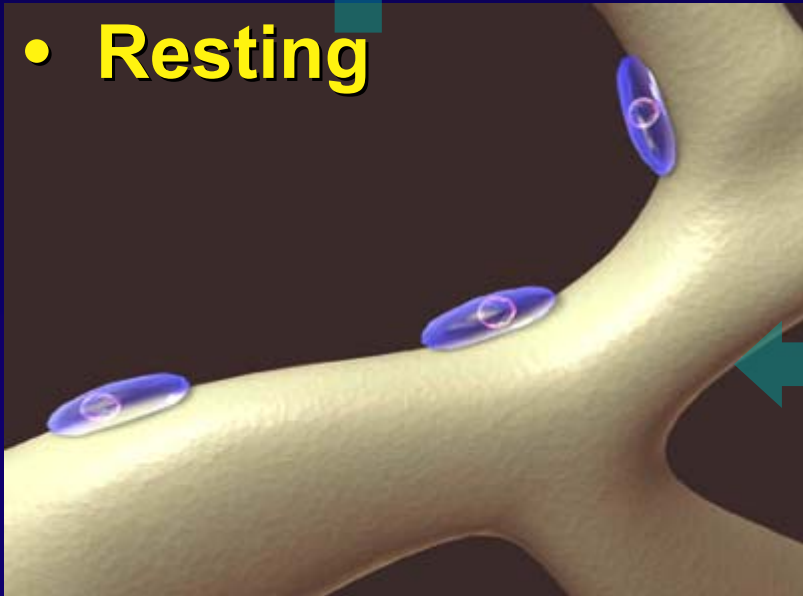
- **Resorption**



- **Reversal**



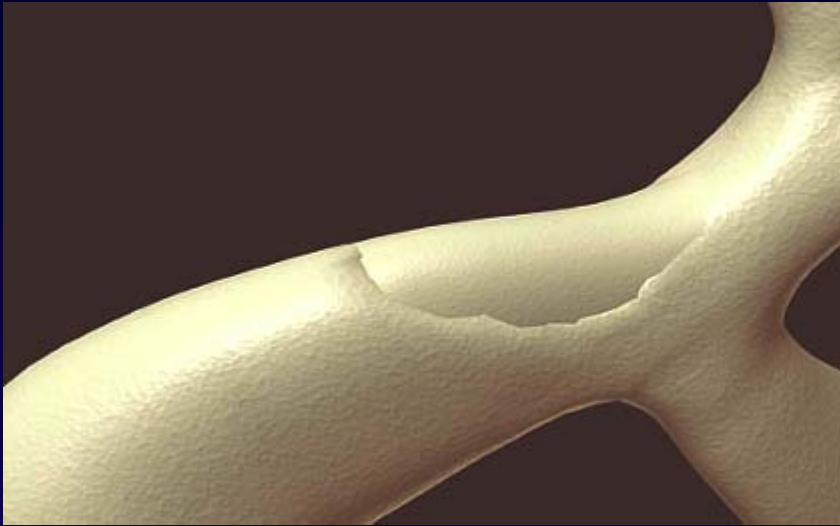
- **Resting**



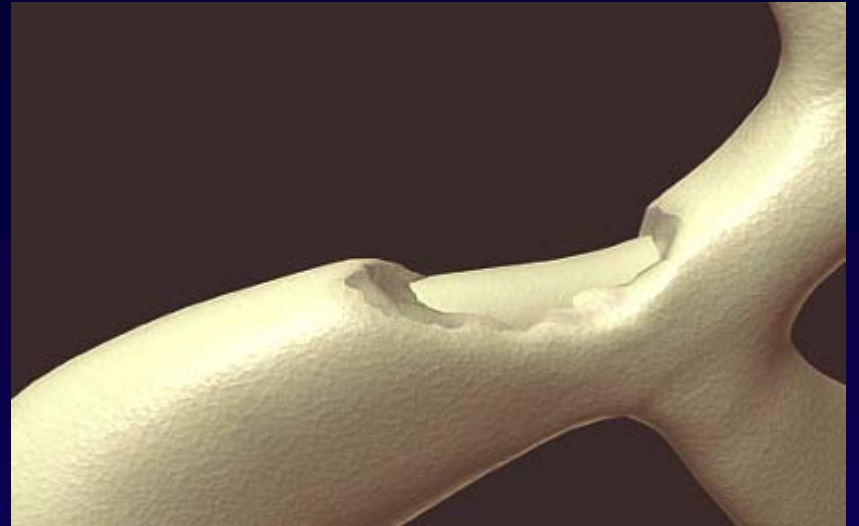
- **Formation**



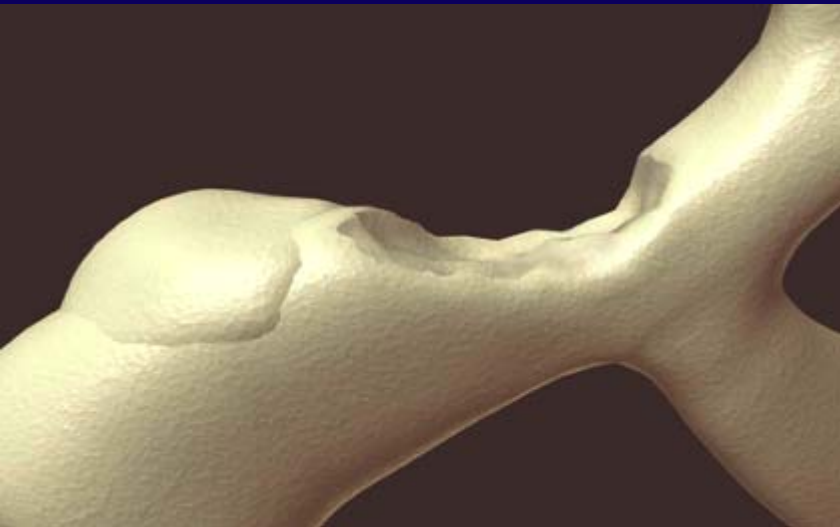
•Coupled and balanced



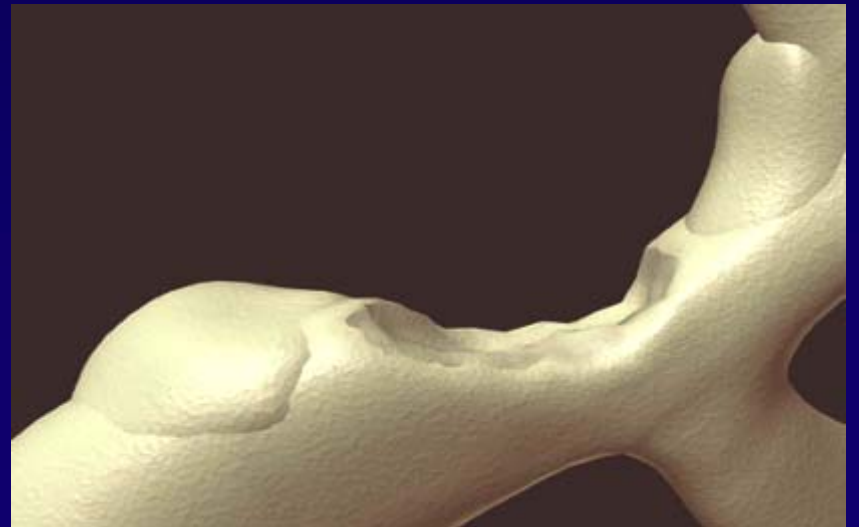
•Coupled but imbalanced



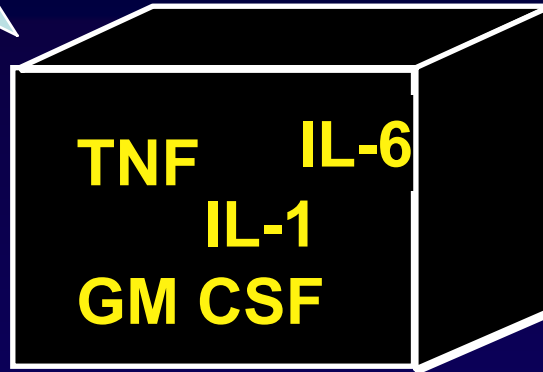
•Uncoupled but balanced



•Uncoupled and imbalanced



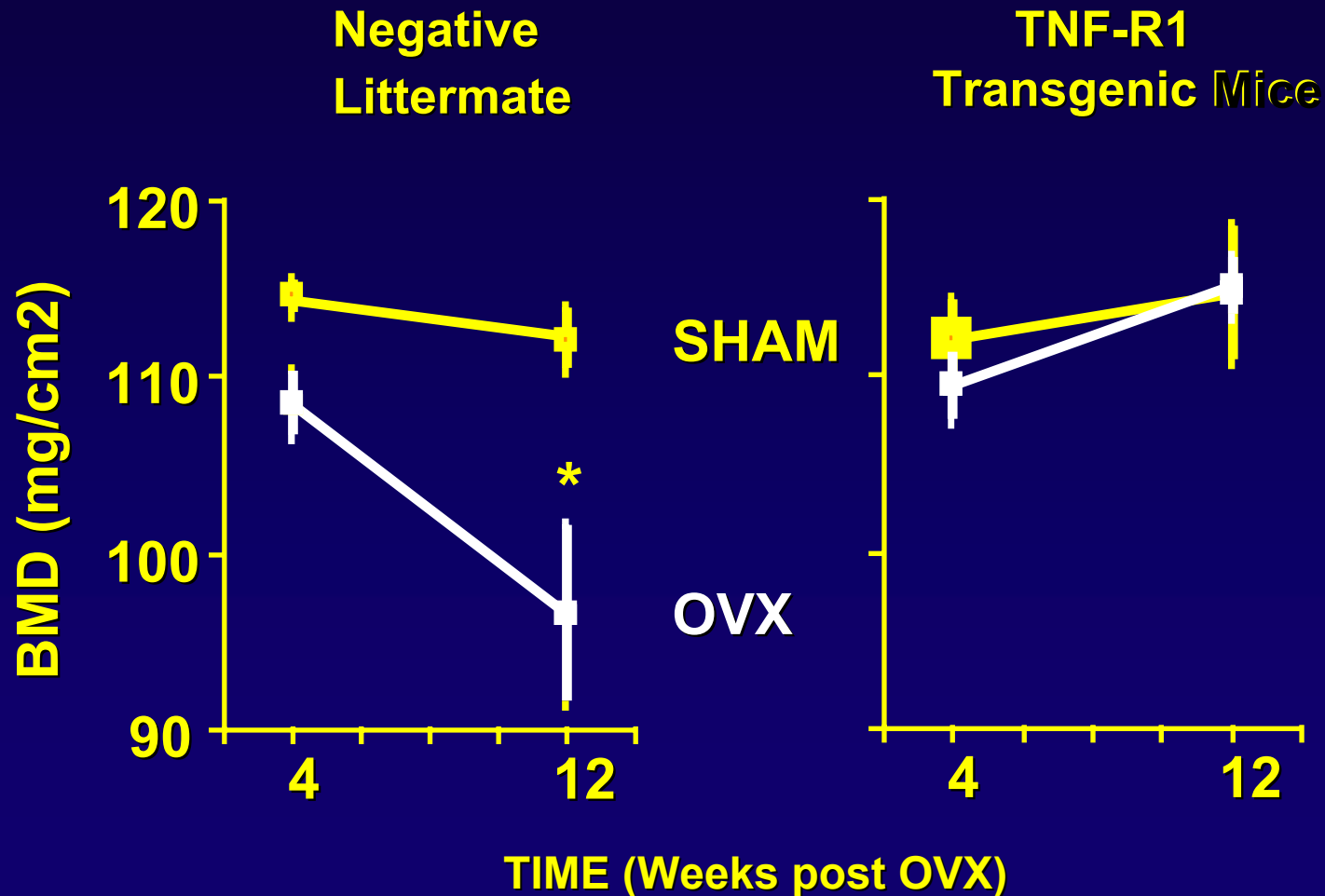
Estrogen Deficiency



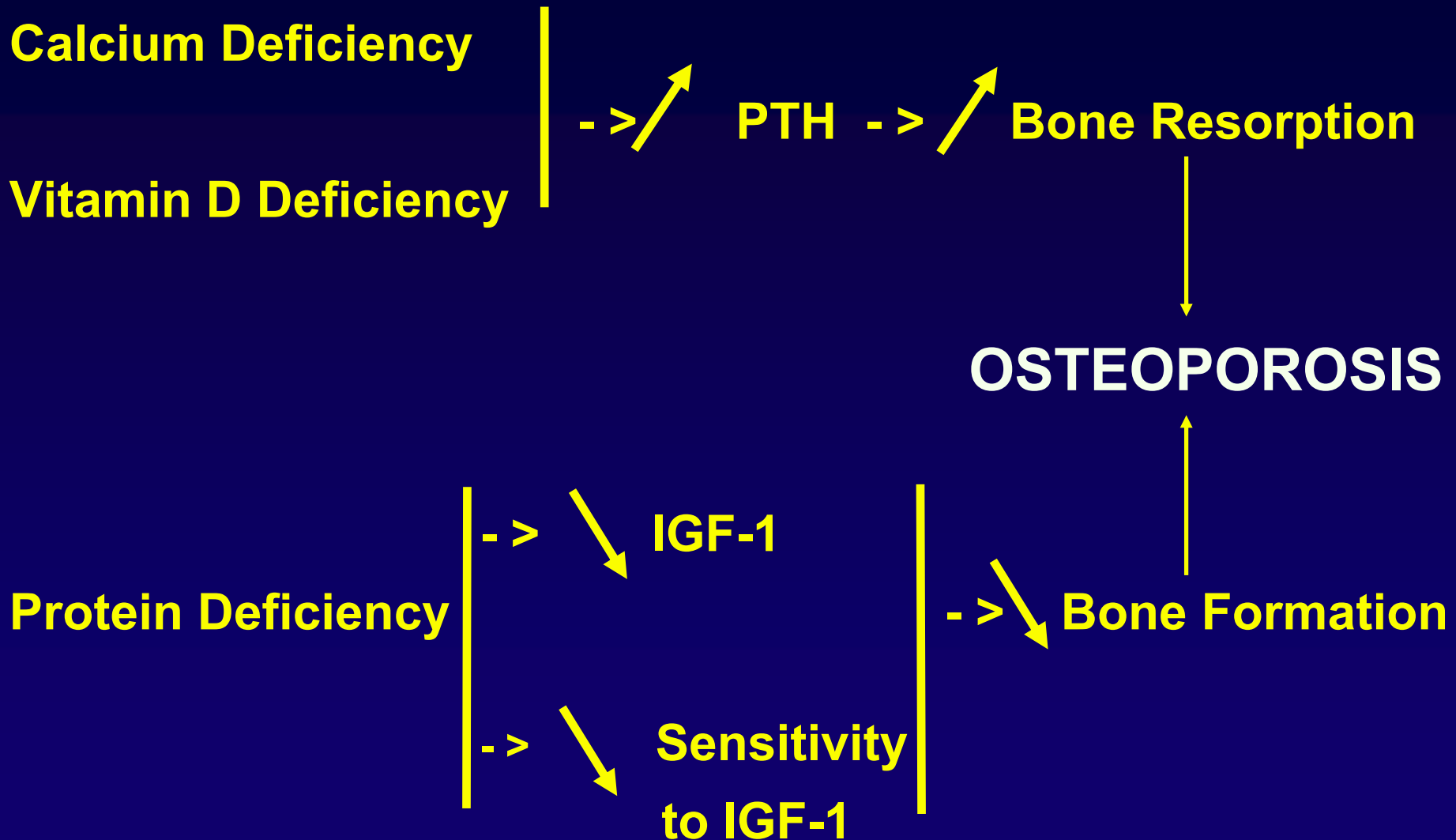
Increased Bone Turnover

Bone Loss

Effects of OVX in Mice overexpressing sTNFR1-IgG3 Fusion Protein and in Negative Littermate



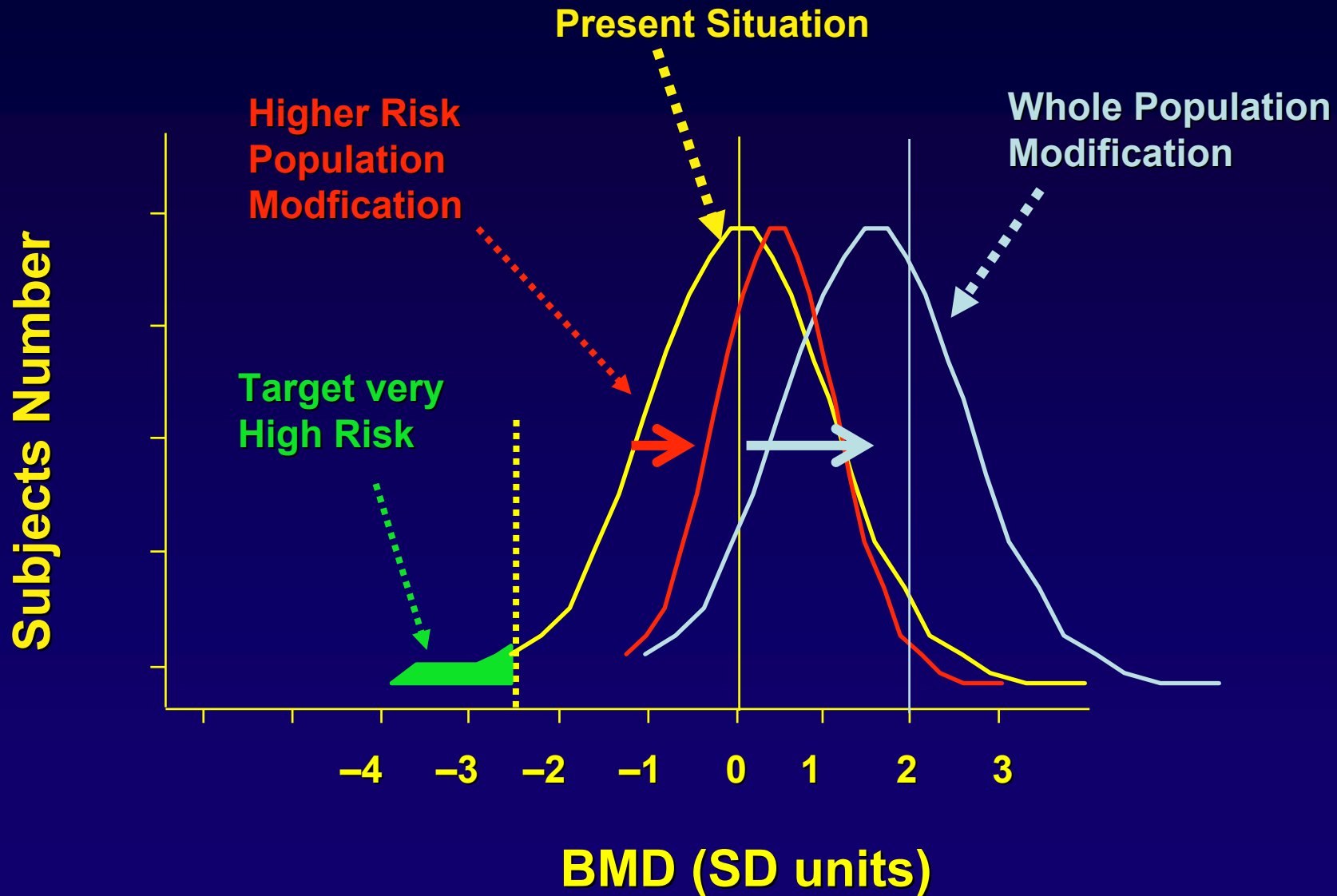
MALNUTRITION IN ELDERLY



Management

- **Indication to treatment**
- **Treatment possibilities**

Osteoporosis Preventive Strategies



General Management

- **Treatment of any Disease Causing Bone Loss**
- **Ensure Dietary Calcium Intake \geq 1000 mg /d**
- **Ensure Adequate Dietary Protein Intake**
- **Correct or Prevent Vitamin D Insufficiency (800 IU/d)**
- **Promote Weight-Bearing Physical Exercise**
- **Reduce Falling Risk**
- **Reduce Fall Consequences (Hip Protectors)**

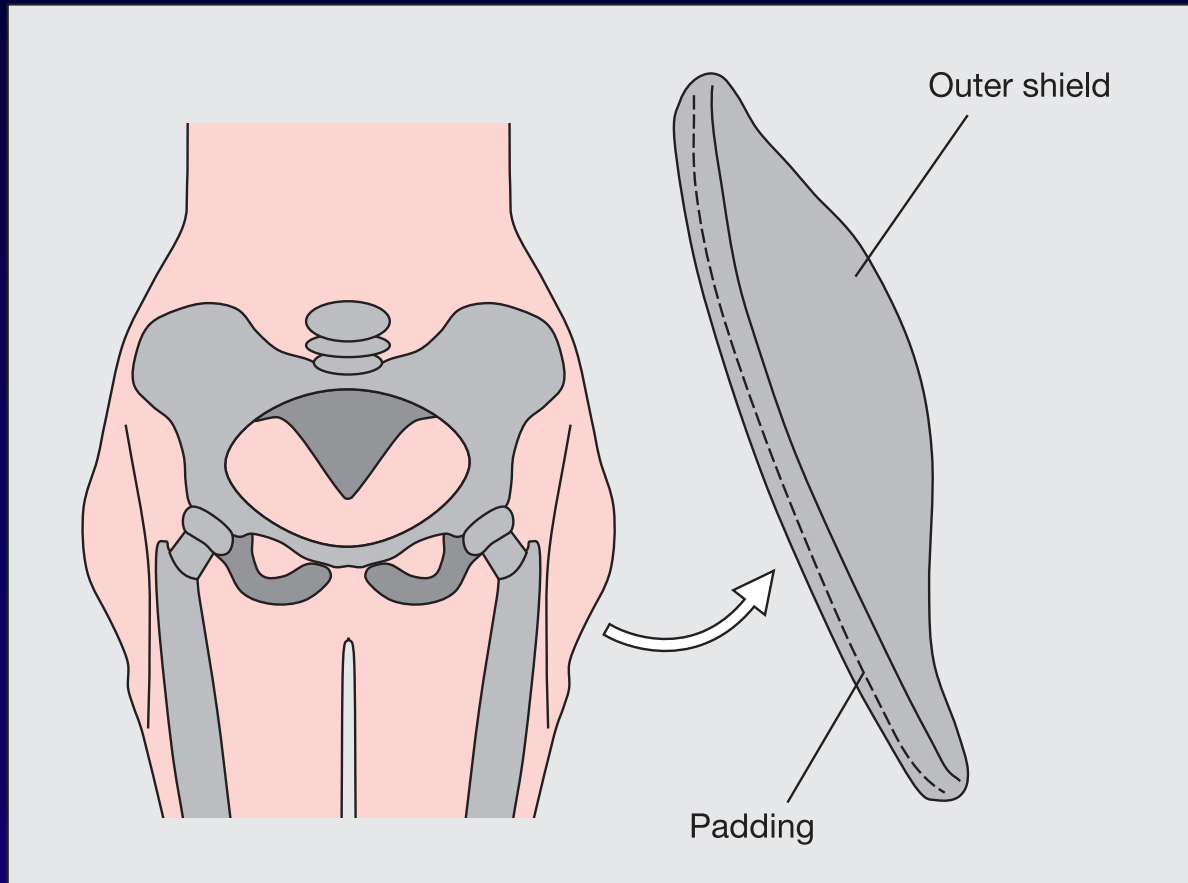
Risk Factors Associated with Falls

- 1. Impaired Mobility, Disability**
- 2. Impaired Gait and Balance**
- 3. Neuromuscular or Musculoskeletal Disorders**
- 4. Age**
- 5. Impaired Vision**
- 6. Neurological, Heart Disorders**
- 7. History of Falls**
- 8. Medication**
- 9. Cognitive Impairment**

After Myers et al., Bone 1996

The Hip Protector

The hip protector



Prevention of Hip Fracture in Elderly People with Use of Hip Protector

Kannus et al., New Engl J Med 2000

1725 Elderly, 82 yrs, 650 with Hip Protectors vs 1075 Controls

	<u>Hip Protectors</u>	<u>Controls</u>
Hip Fracture (/1000 person-years)	21.3	46.0
Relative Hazard	0.4	
Hip Fracture * (/100 Falls)	0.39	2.43

Arms Fracture

(/1000 person-years)	16.4	19.9
(/100 Falls) *	0.68	0.81

* According to Use of the Protector

Therapeutic Agents Used in Osteoporosis

Anticatabolic Agents

- *Estrogens ± Progestagens*
- *SERMs*
- *Bisphosphonates*
- *Calcitonin*
- *Calcium*

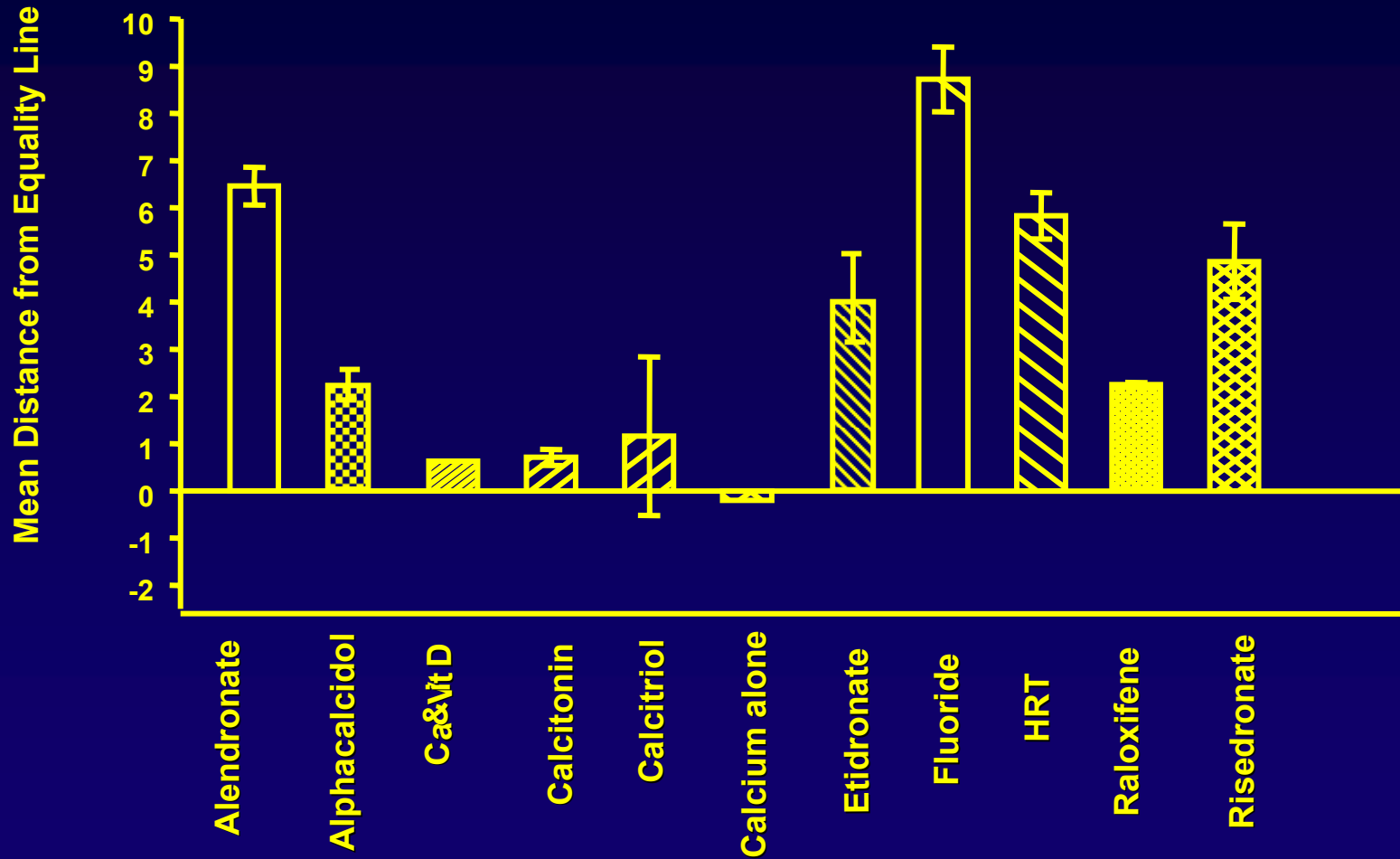
Complex Action

- *Vitamin D and Derivatives*
- *Anabolic Steroids*
- *(Ipriflavone)*
- *Tibolone*

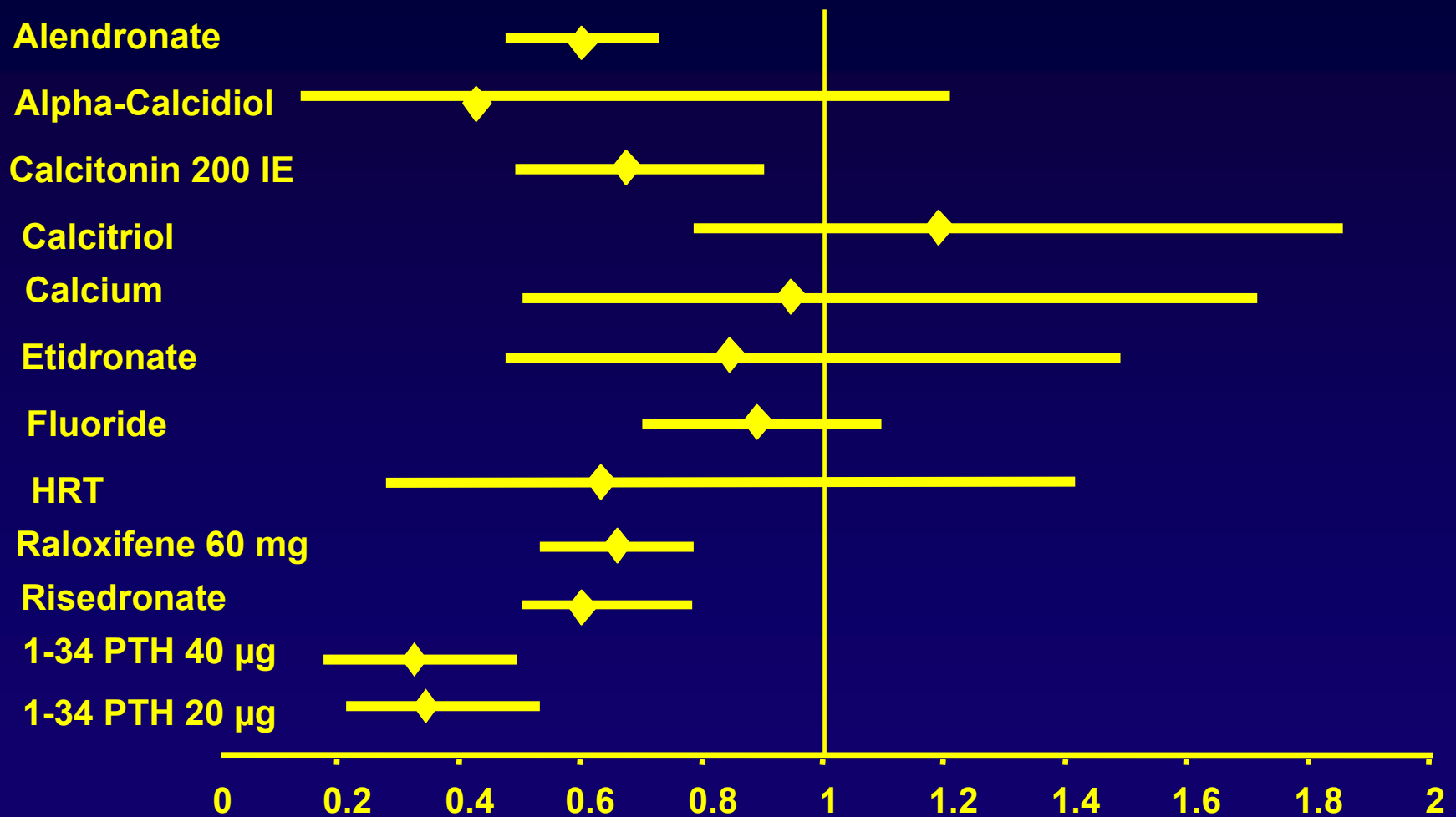
Anabolic Agents

- *(Fluoride)*
- *Parathyroid Hormone*
- *Growth Hormone*
- *IGF-I*

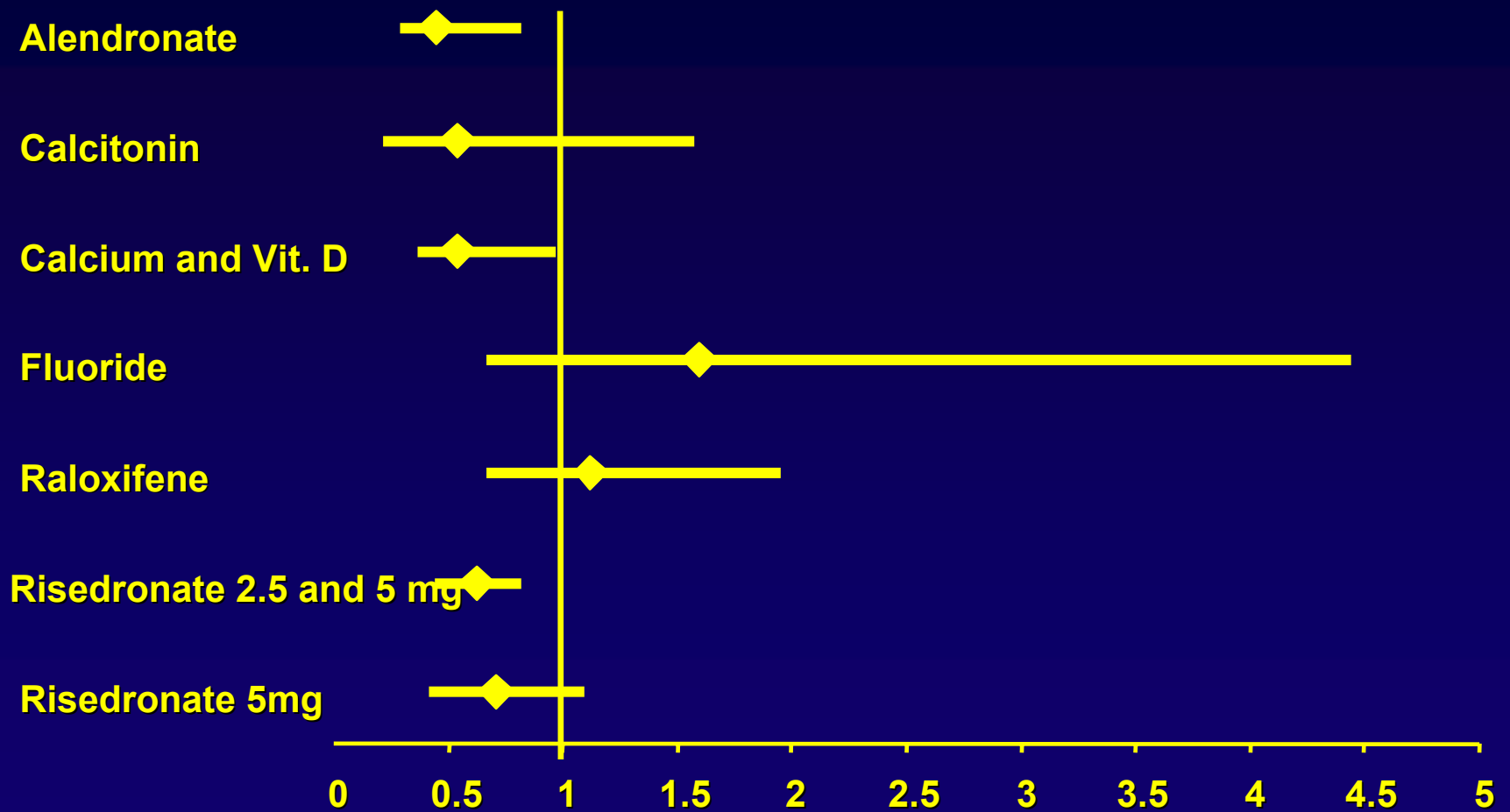
Mean Distance From the Equality Line for Spine BMD



Morphometric Vertebral Fractures: Summary of Relative Risk and 95% Confidence by Therapy



Hip Fracture: Summary of Relative Risk and 95% Confidence Intervals by Therapy

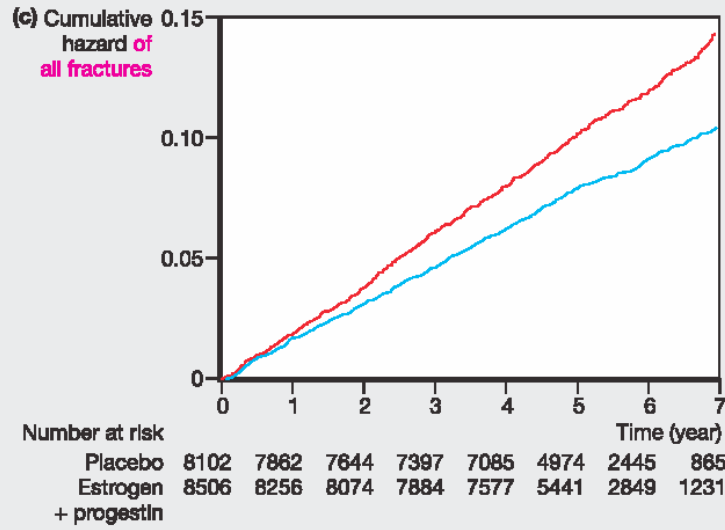
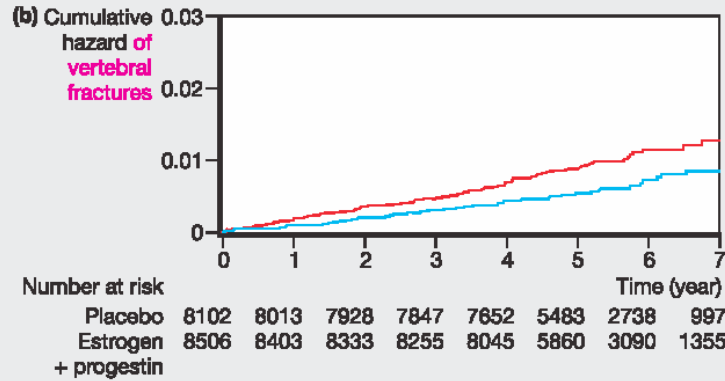
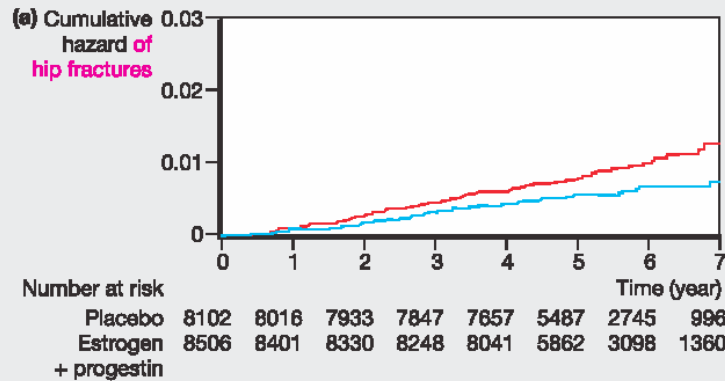


Fracture:

Hip

Vertebrae

All



— Placebo
— Estrogen + progestin

Placebo
HRT

Hormone Replacement Therapy and Fracture Risk

WHI Study, Cauley et al, 2003

Drugs

Reduction in Fracture Risk

(Randomized Controlled Trials)

Vertebral Fracture

Non-Vertebral

Fracture

Estrogens

+

+

Cyclic Etidronate

±

0

Alendronate

++

+

Raloxifene

+

0

Risedronate

++

+

Nasal Calcitonin

+

0

Calcium-Vitamin D

?

+

Fluoride Salts

±

0

Tibolone

?

?

PTH

++

±

Strontium Ranelate

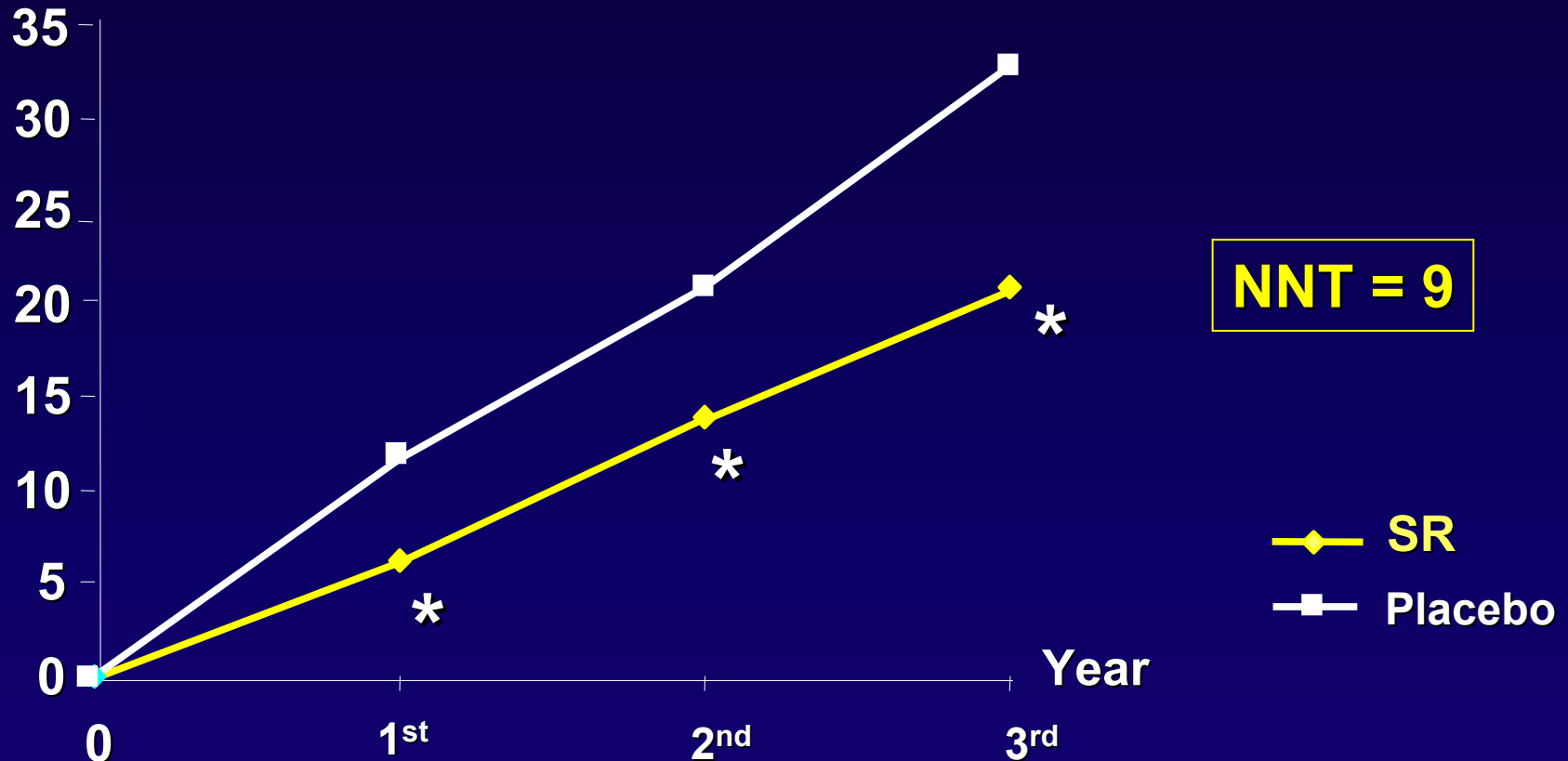
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+

SOTI: CUMULATIVE INCIDENCE OF PATIENTS WITH NEW VERTEBRAL FRACTURE

% patients

Risk of vertebral fracture: - 41%



NNT = 9

◆ SR
■ Placebo

* P < 0.001

Over 3-year: Relative Risk = 0.59, 95% CI [0.48; 0.73]

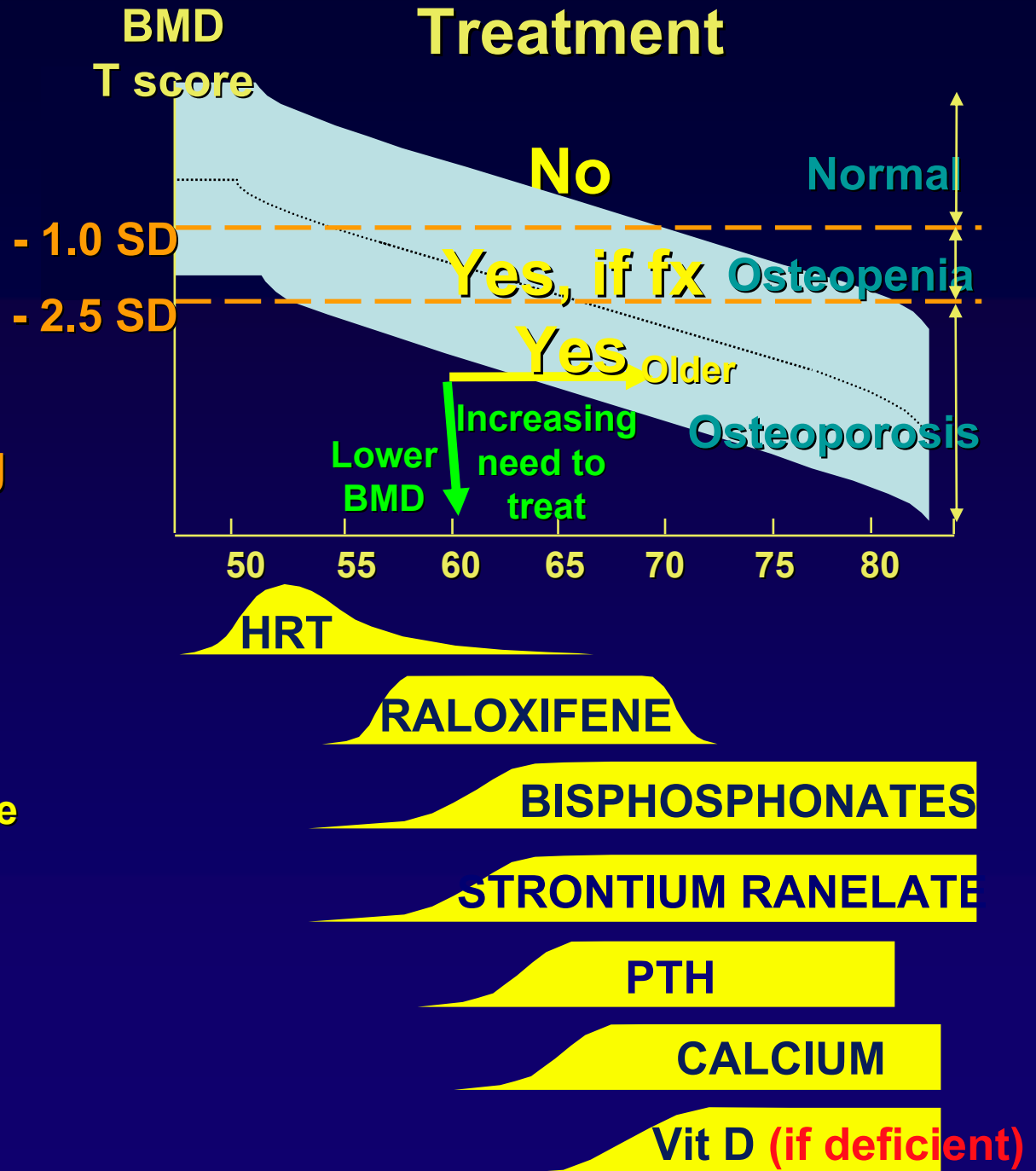
Meunier PJ et al., NEJM 2004

Kaplan-Meier; RR: Cox model

Adapted from
E. Seeman
(2004)

Factors Influencing Treatment Decision

- Advancing age
- Lower BMD
- Presence of Fracture
- Risk factors or disease causing continued bone loss
 - Leanness
 - Family history



Fractures are not Unavoidable Expenses to Pay as a Consequence of Increased Life-Expectancy

Because of

- **Better Identification of Risk Factors for Osteoporosis**
- **Early Diagnosis, before the First Fracture**
- **A Larger Use of Preventive and Therapeutical Strategies, whose Efficacy has been Demonstrated in Randomized Controlled Trials, with Fracture Incidence as Primary End-Point**

1. Aim of Therapy

**≠ Treatment of
Osteoporosis**

**= Treatment of Patients
with Osteoporosis**

2. Never Too Late