Training Course in Sexual and Reproductive Health Research
Geneva, February 17 2009

Osteoporosis

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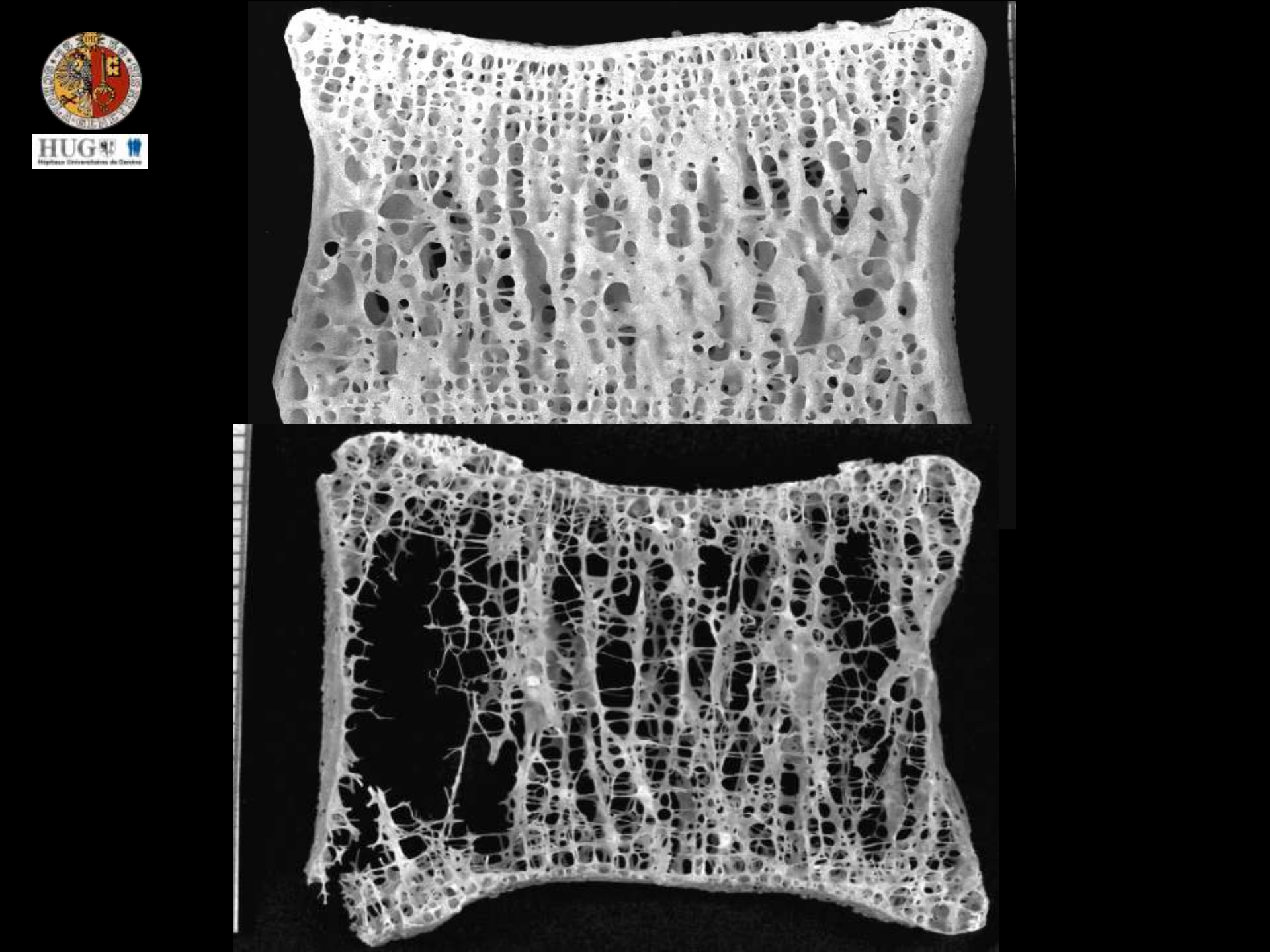


Osteoporosis Definition

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

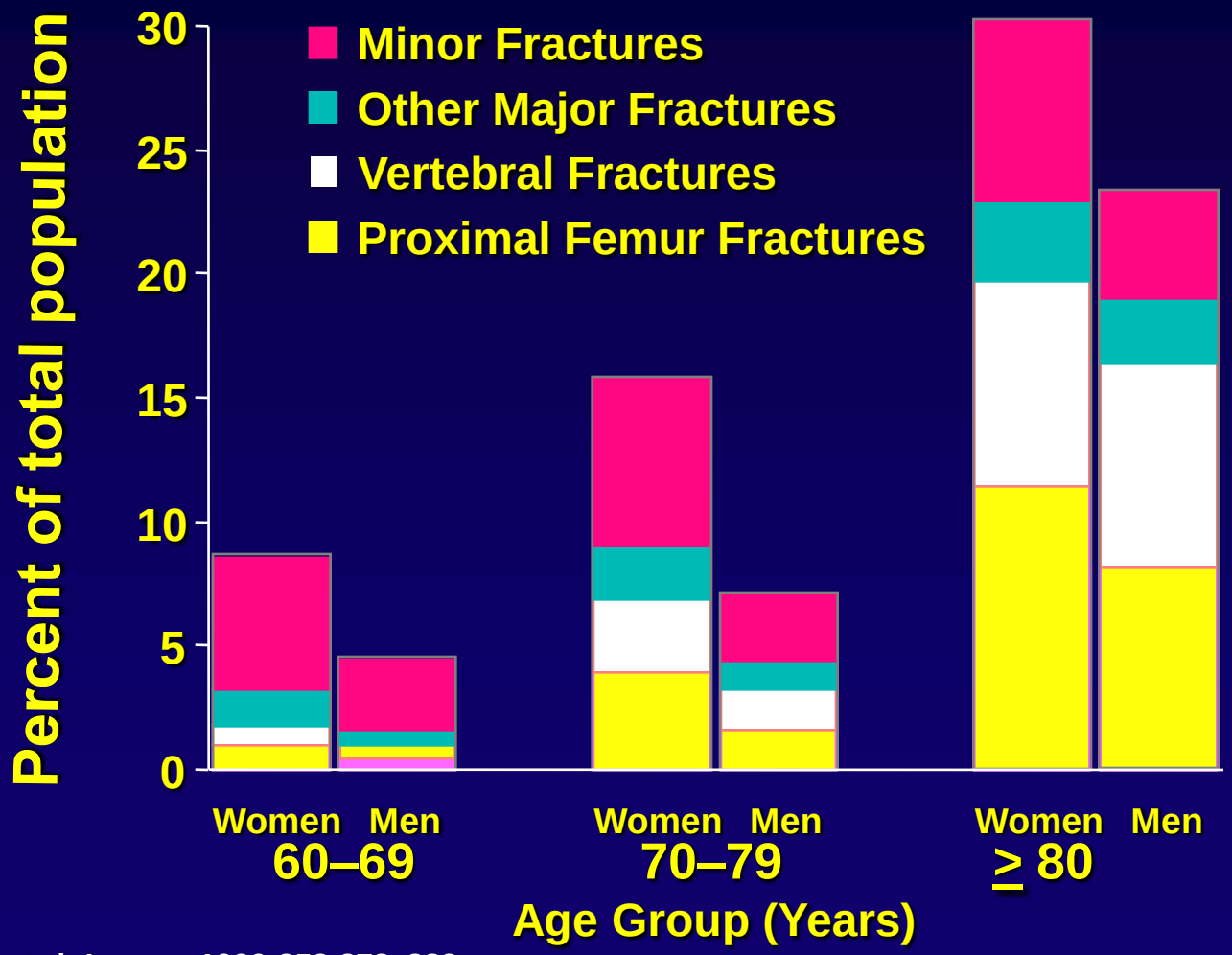
- With
- Without Fracture

Osteoporosis: Lecture Content

- Disease Definition
- Epidemiology
- Burden
- Diagnosis
- Pathophysiology
- Management

Fractures by Age and Gender

Dubbo Osteoporosis Epidemiology Study, 1989–1994



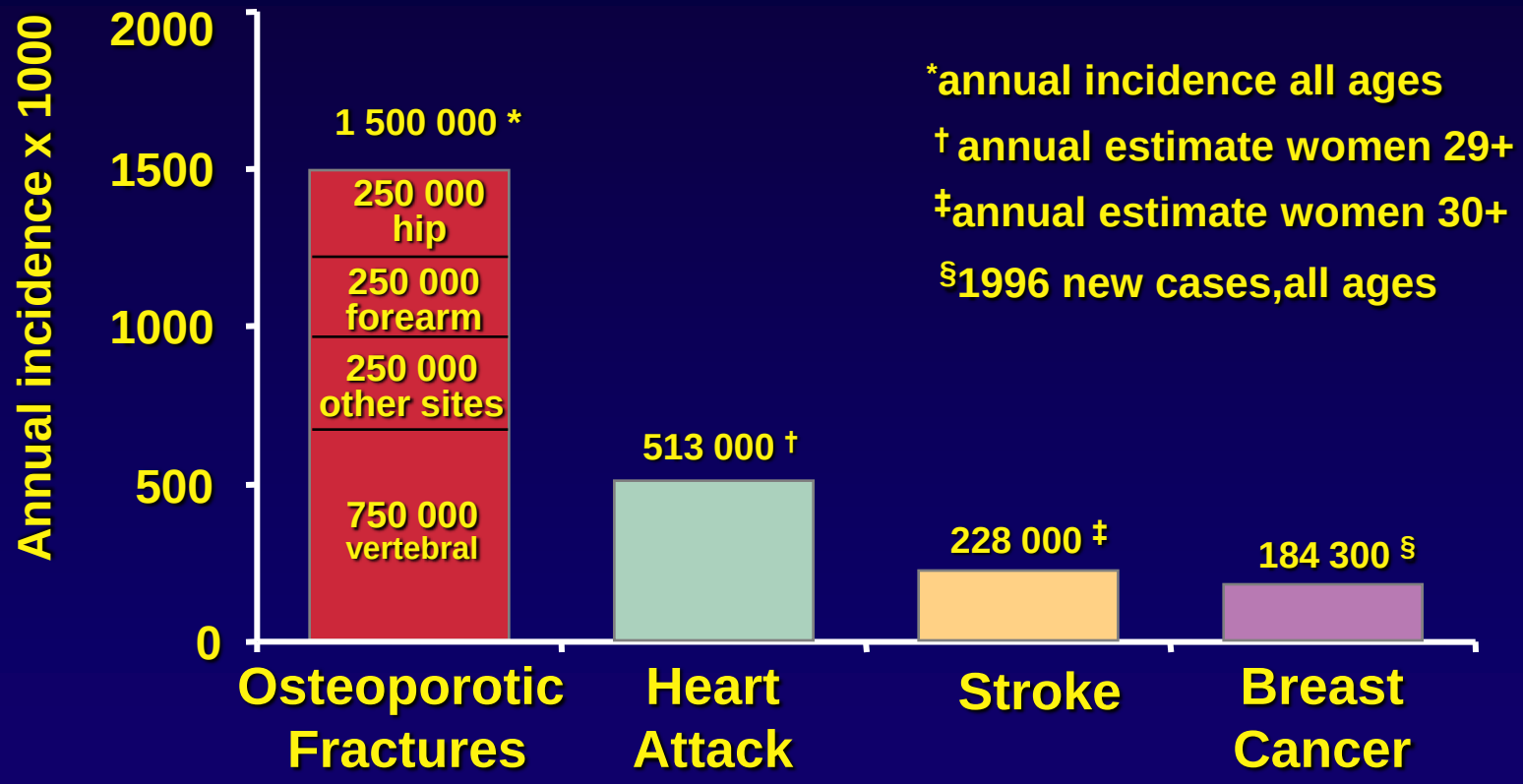
Center J et al. *Lancet.* 1999;353:878–882.

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 %
(Switzerland	51 %	20 %)

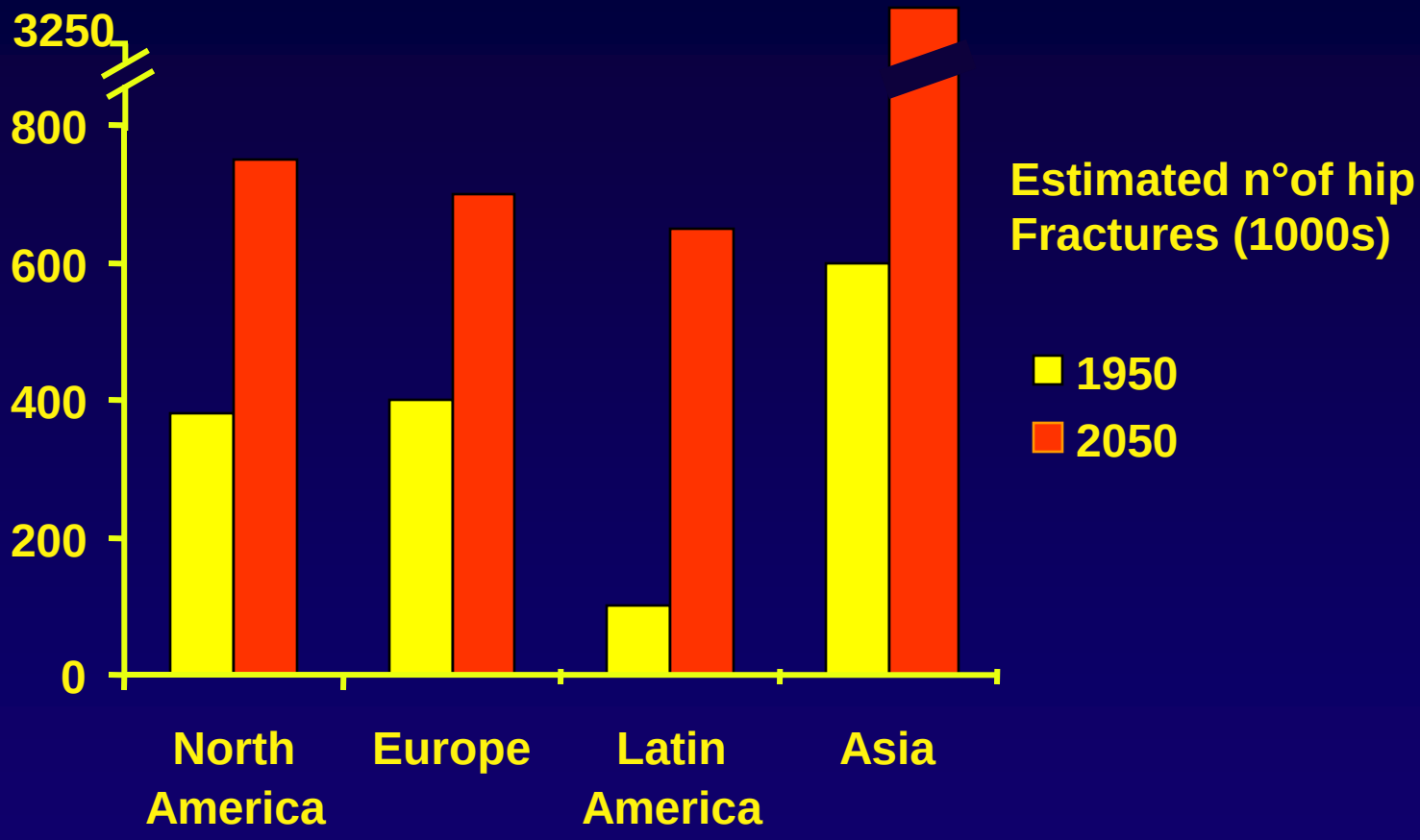
From Kanis et al 2000

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.

Projected burden of osteoporotic hip fractures worldwide



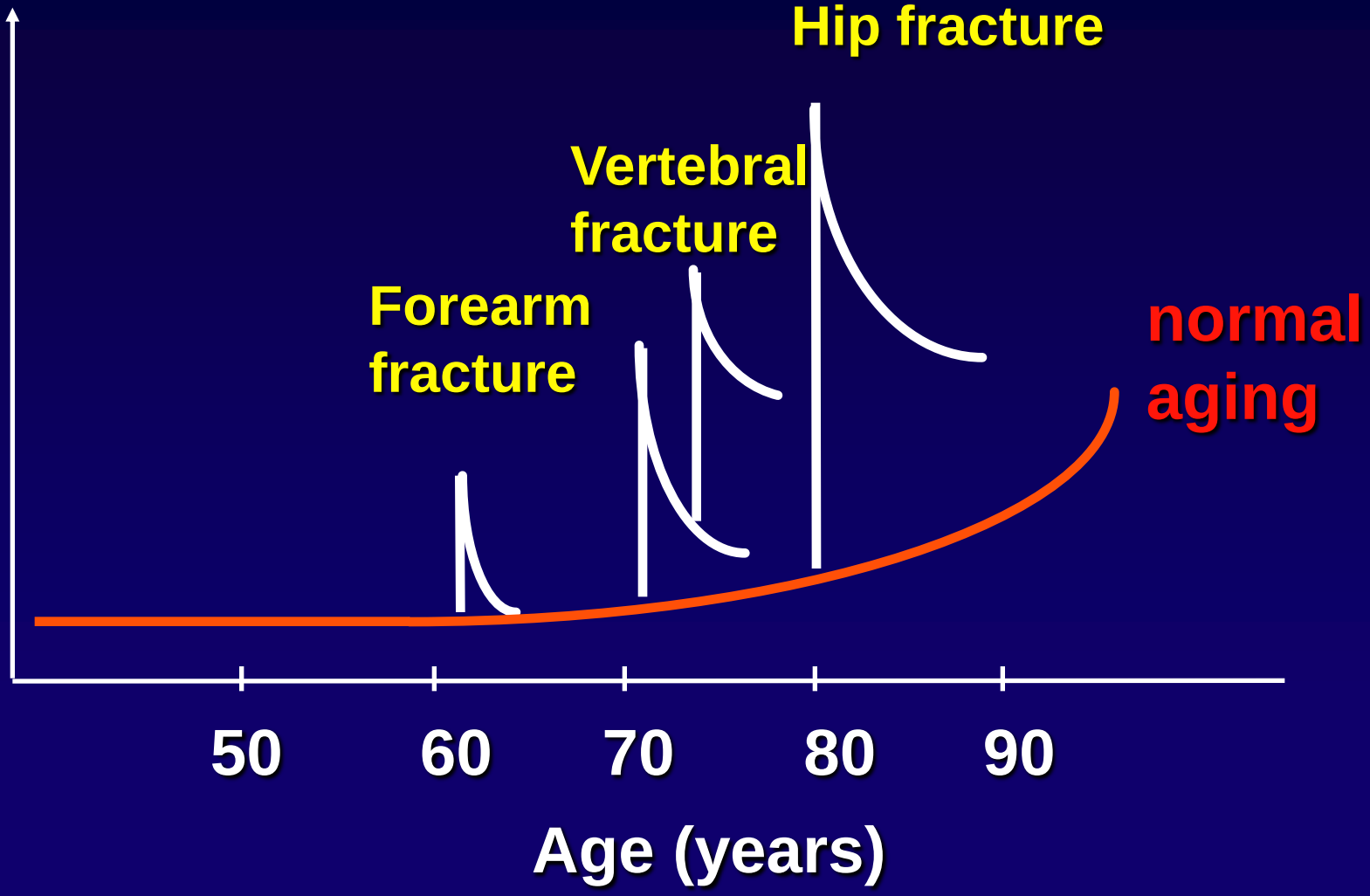
Number of hip fractures: 1990: 1.66 million; 2050: 6.26 million

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

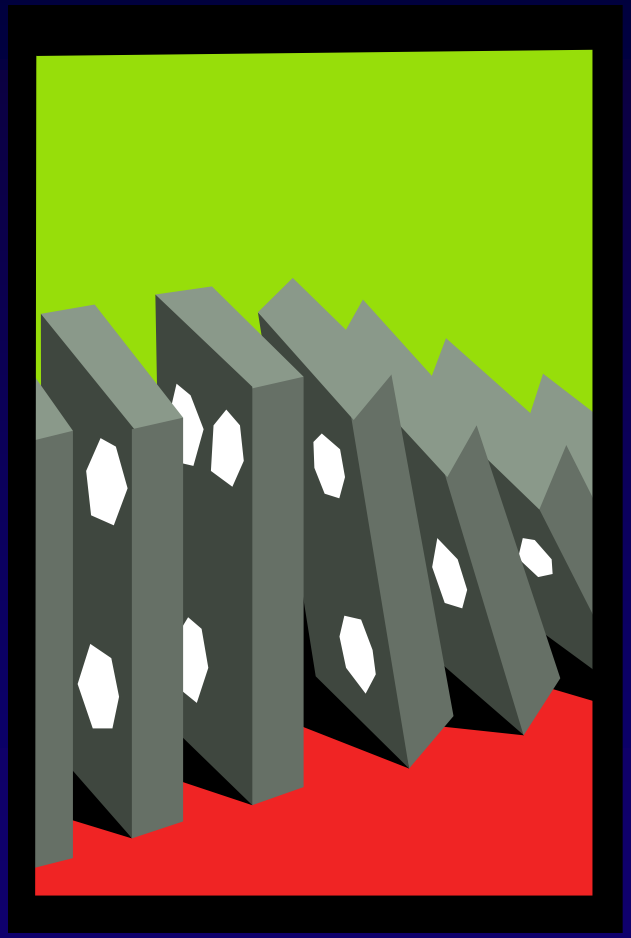
Burden


Degree of dependence
Hip fracture
Vertebral fracture
Forearm fracture
normal aging
50
60
70
80
90
Age (years)

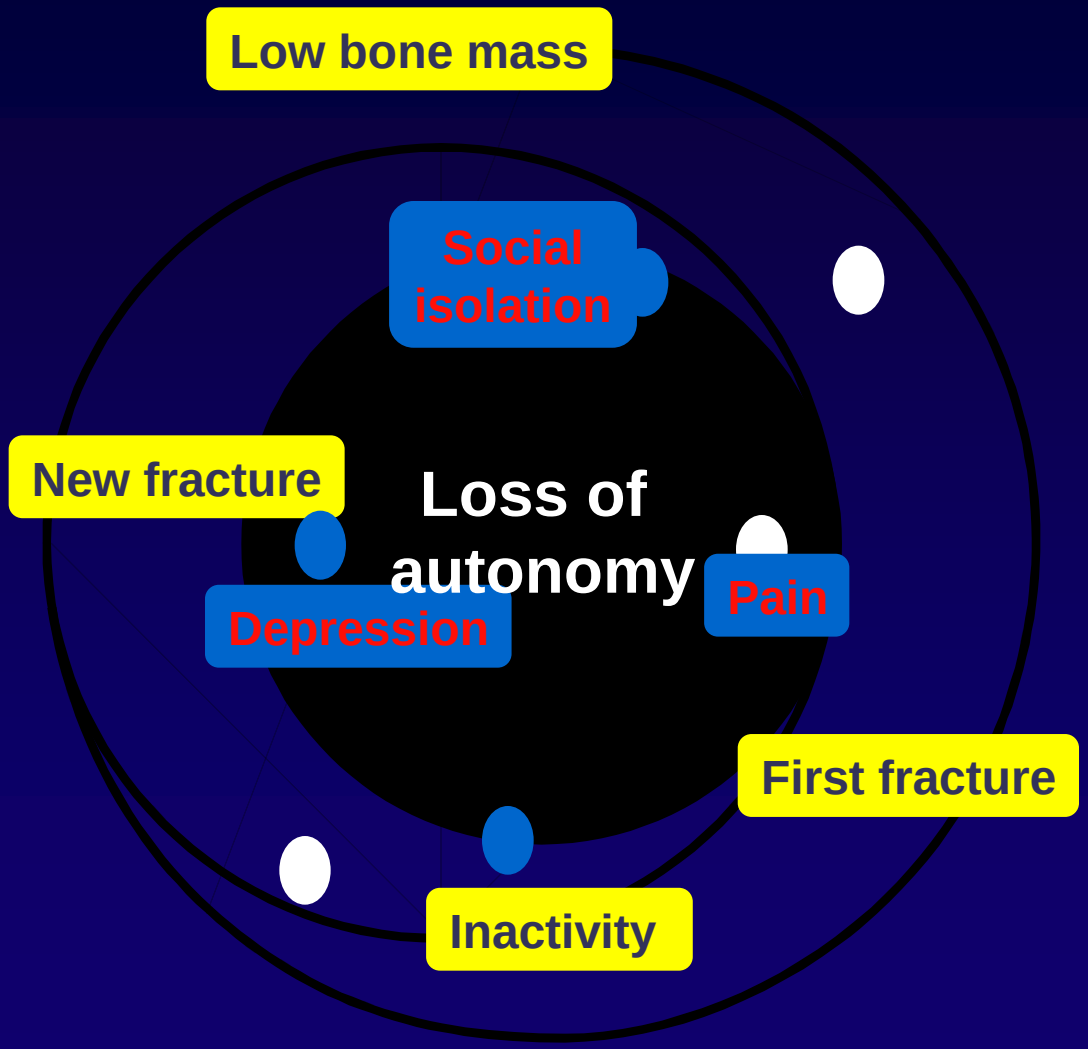
Morbidity After Vertebral Fractures

- 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

A Fragility Fracture -> Fracture



A dangerous vicious circle



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

Center et al, Lancet 1999

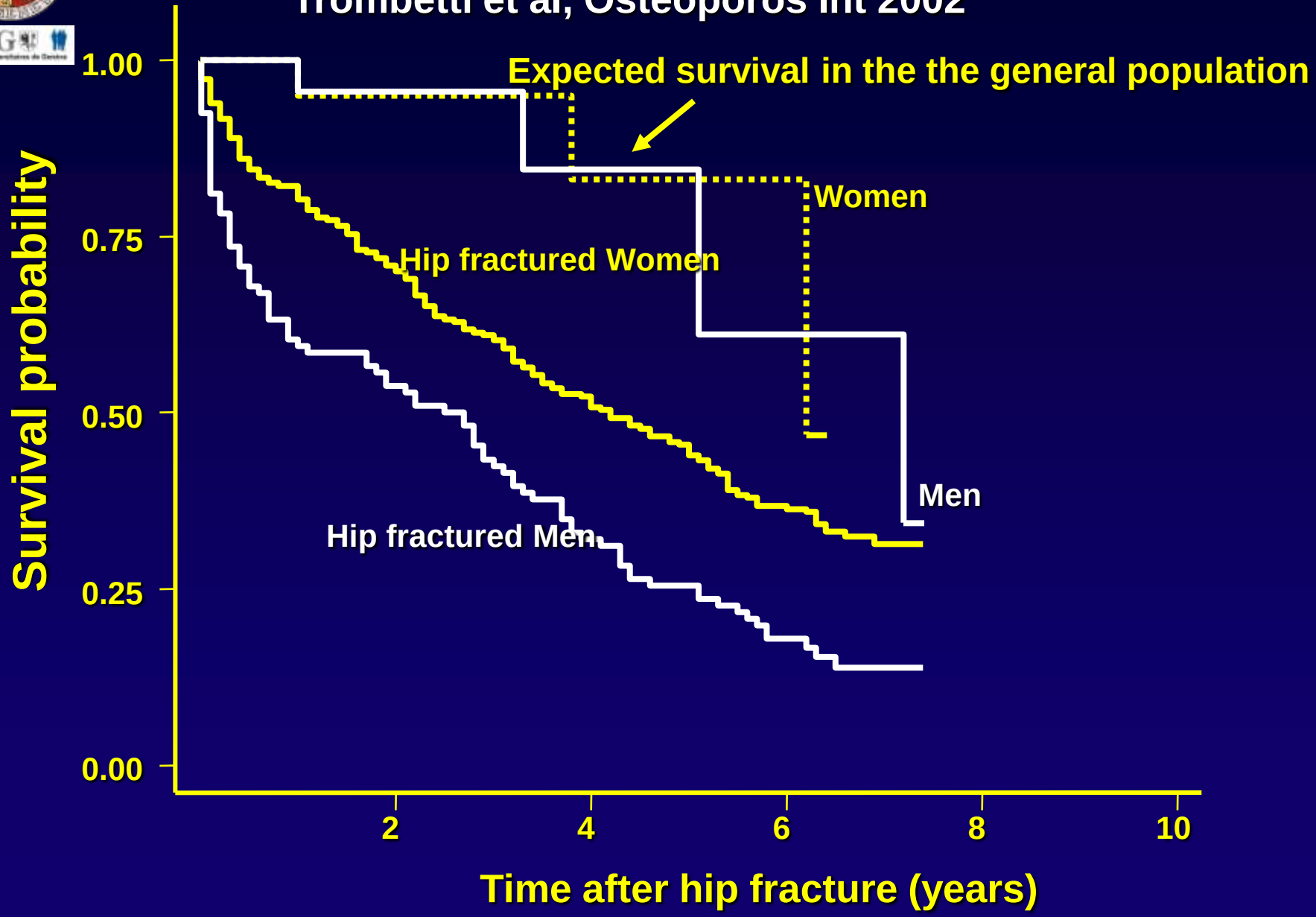
5 - Year Prospective Cohort Study

Age-Standardized Mortality Ratio

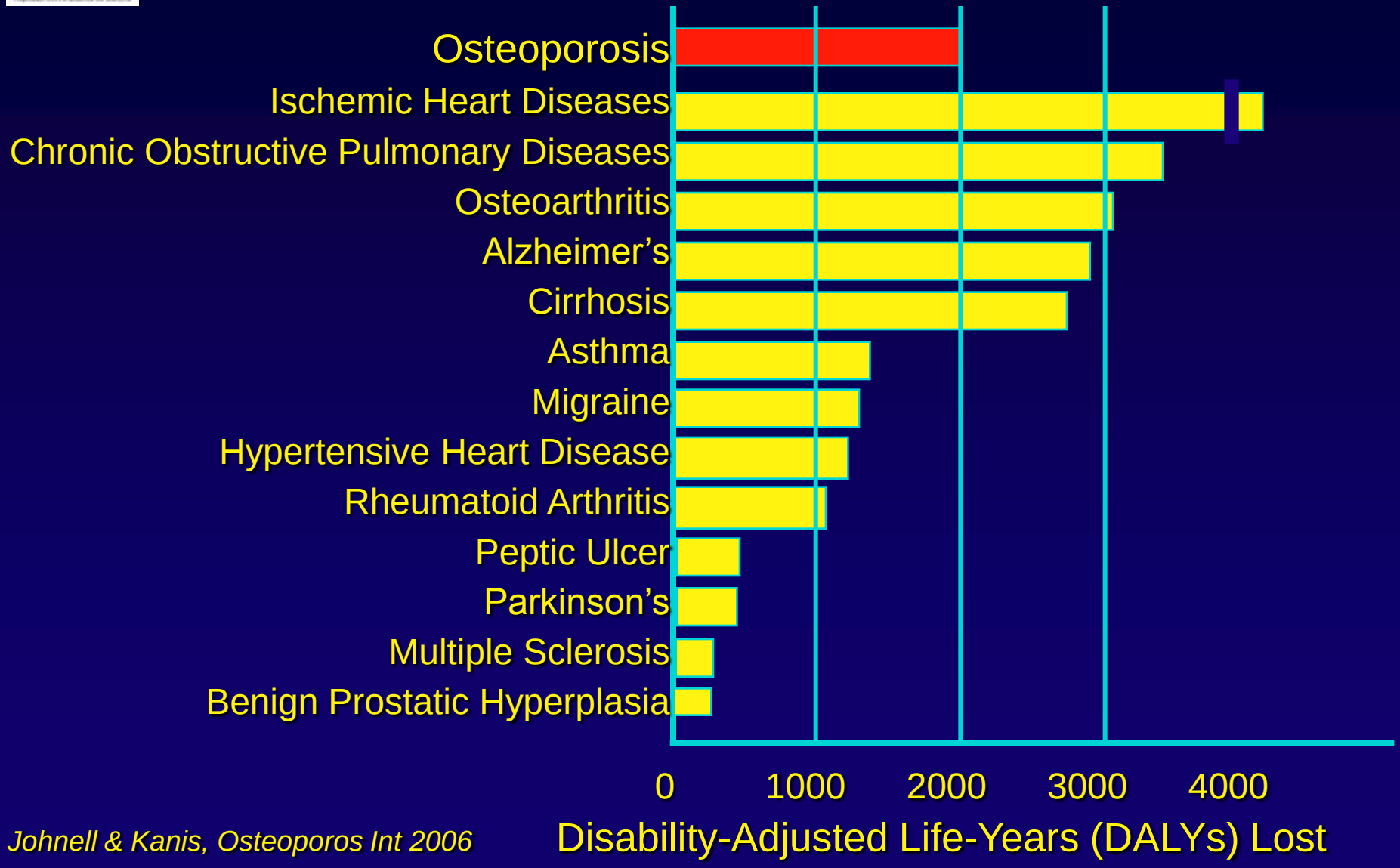
Fracture	Women	Men
Proximal Femur	2.2	3.2
Vertebral	1.7	2.4
Other Major	1.9	2.2
Other Minor	0.8	1.5

Survival after Hip Fracture

Trombetti et al, Osteoporos Int 2002



Disability-Adjusted Life-Years Lost because of Non-communicable Diseases in Europe



Johnell & Kanis, Osteoporos Int 2006

Osteoporosis Results in More Cost than Many Other Diseases

Number of bed days (men and women)

- 701,000 for osteoporosis
- 891,000 for COPD
- 533,000 for stroke
- 328,000 for myocardial infarct
- 201,000 for breast cancer

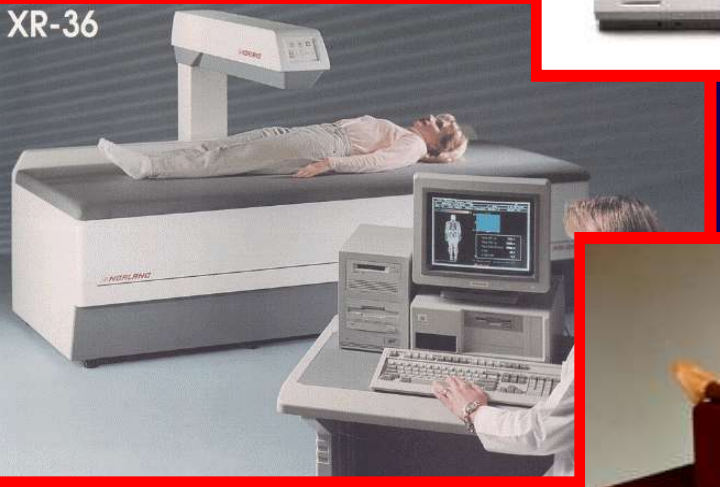
Osteoporosis # 1 when looking at women only

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

Diagnosis

X-ray techniques

pDXA

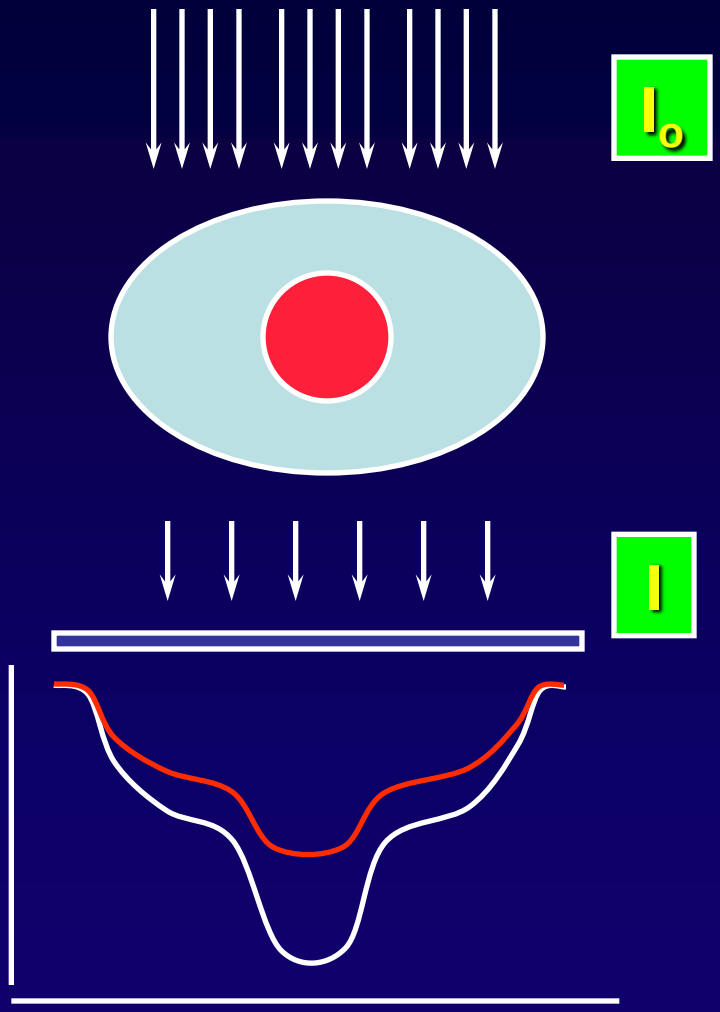


DXA

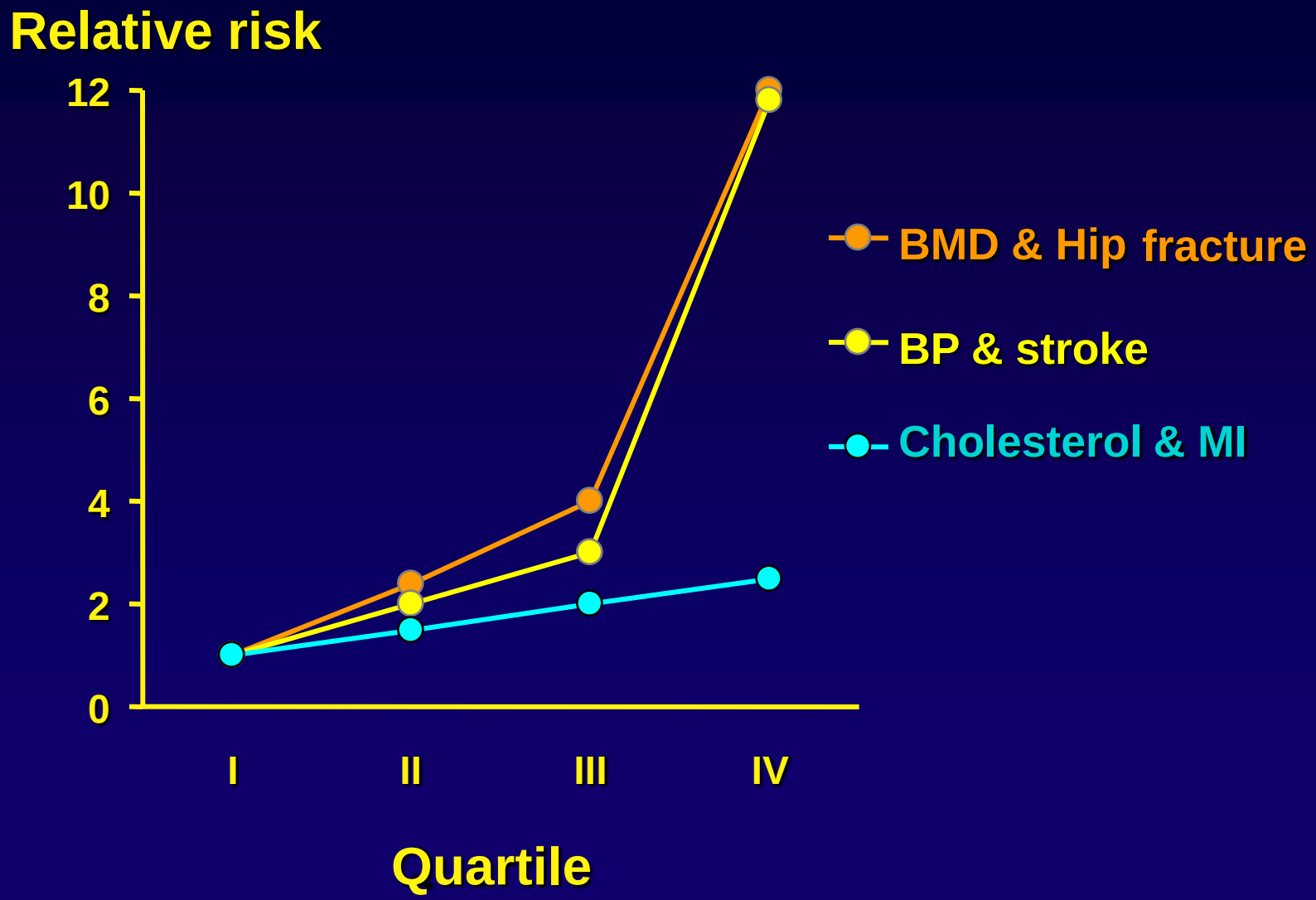
pQCT

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



Noninvasive Measurement of Bone Mineral Mass

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

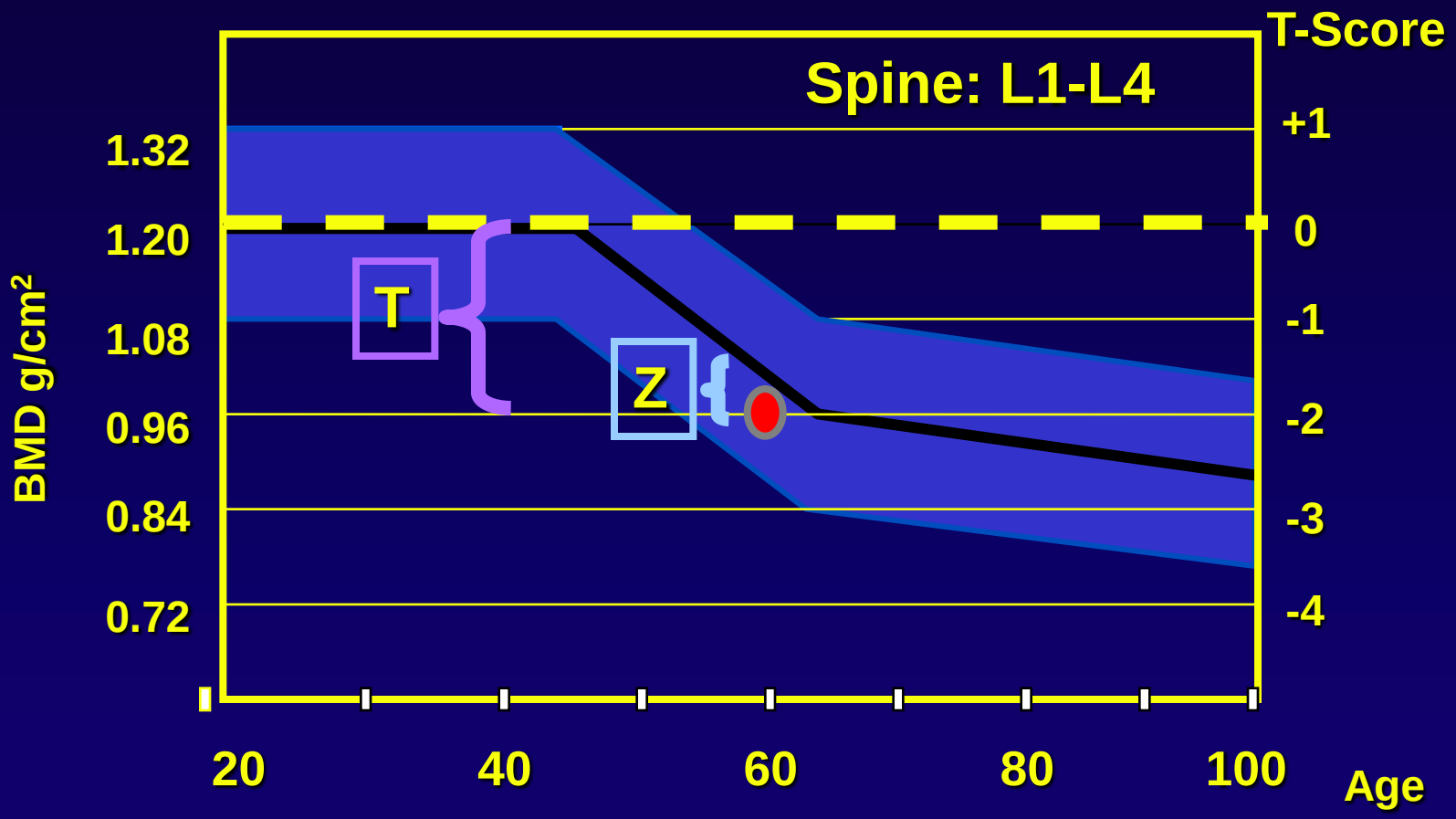
Medicare Coverage for BMD Tests

Procedure	Site	Fee Schedule Medicare *
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

JAMA 288:1889-1897,2002

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

↓

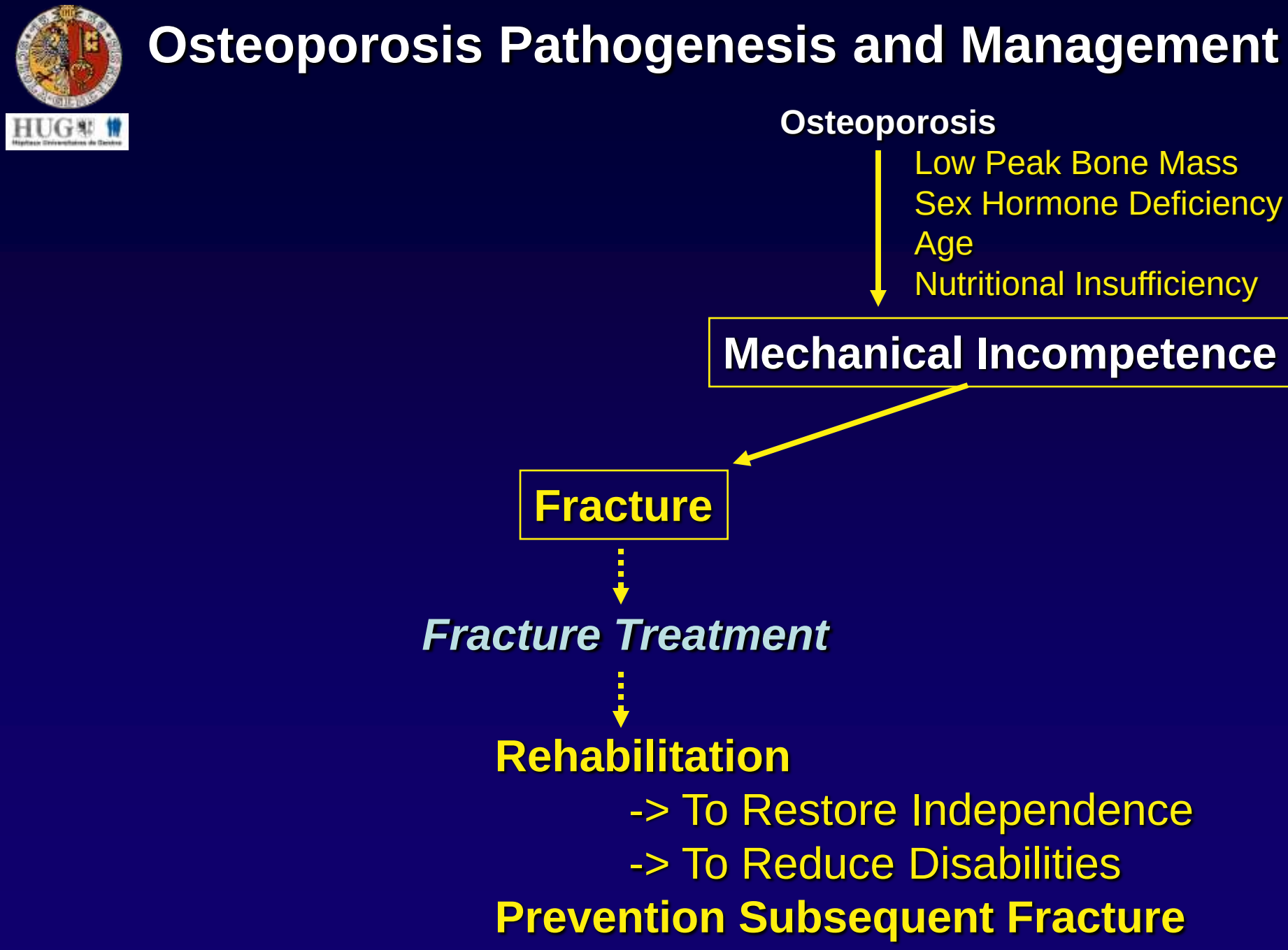
Rehabilitation

-> To Restore Independence

-> To Reduce Disabilities

Prevention Subsequent Fracture

Osteoporosis Pathogenesis and Management



Osteoporosis Pathogenesis and Management

Falls

- Sway
- Walking
- Muscle Strength
- Neuro-muscular Impairment

Mechanical Overload

Osteoporosis

- Low Peak Bone Mass
- Sex Hormone Deficiency
- Age
- Nutritional Insufficiency

Mechanical Incompetence

Fracture

Fracture Treatment

Rehabilitation

-> To Restore Independence

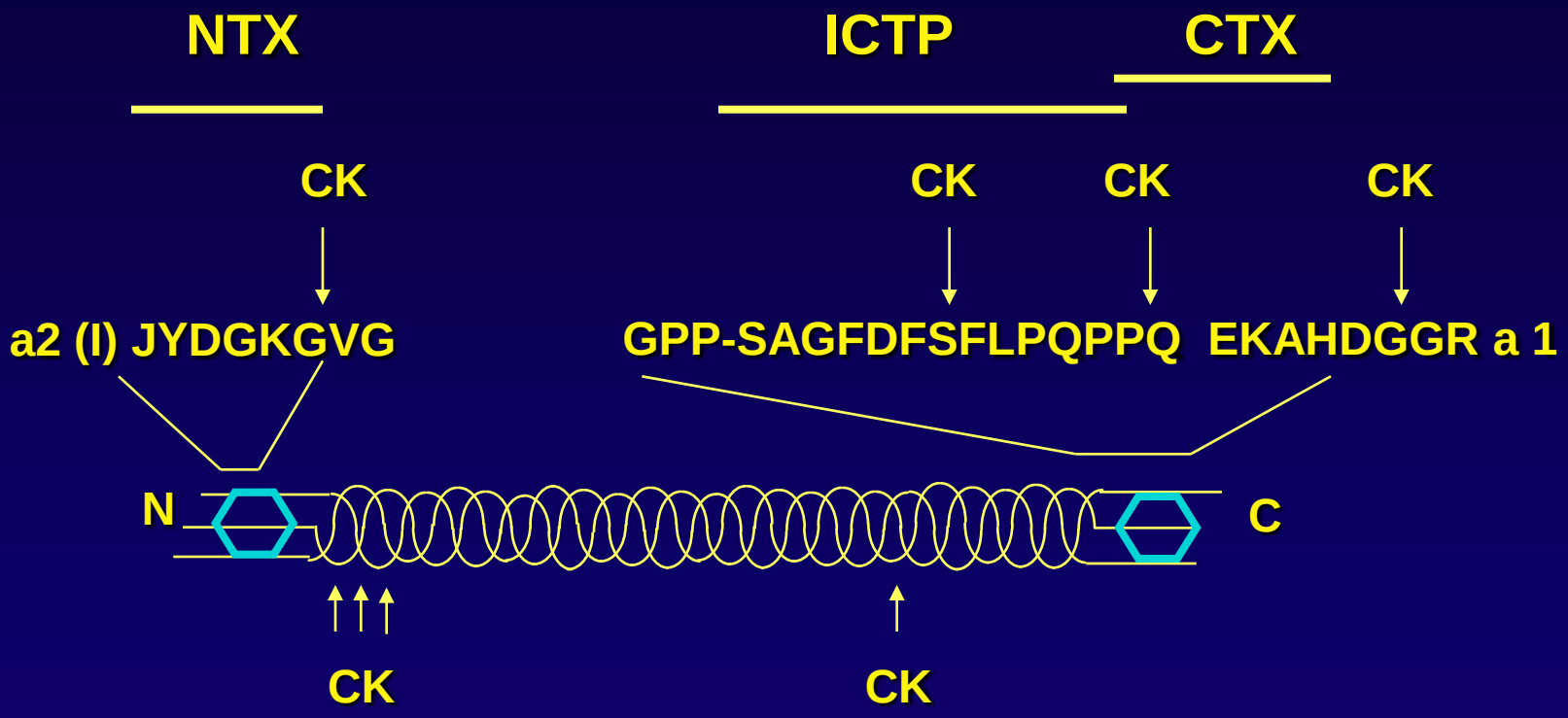
-> To Reduce Disabilities

Prevention Subsequent Fracture

Determinants of Fracture Risk

1. Age
2. Prevalent Fracture
3. Family history of Fracture
4. Glucocorticoid
5. Low BMI
6. Alkohol, Smoking
7. Baseline BMD
8. Baseline Turnover

Type I collagen epitopes and Cathepsin K cleavage sites

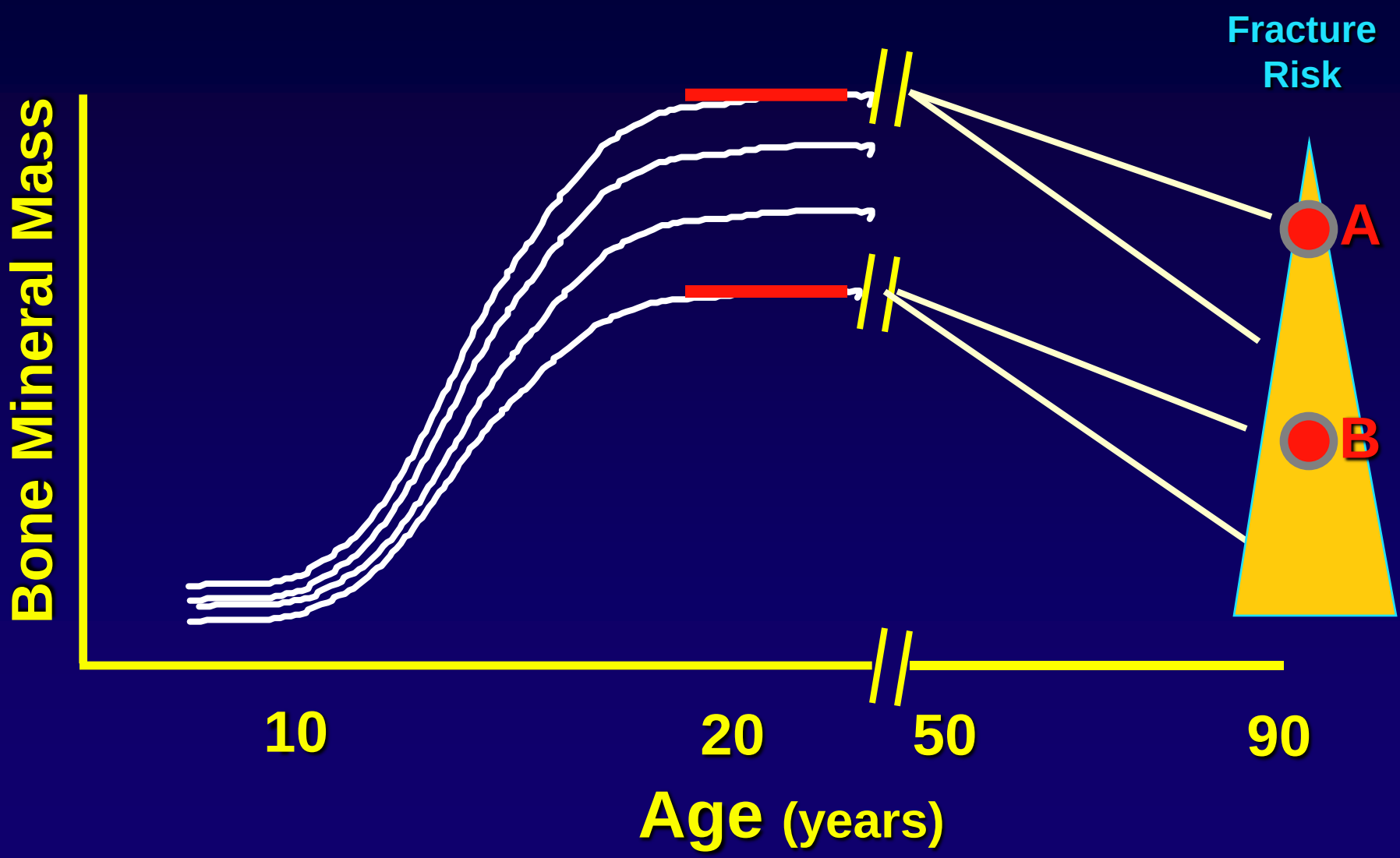


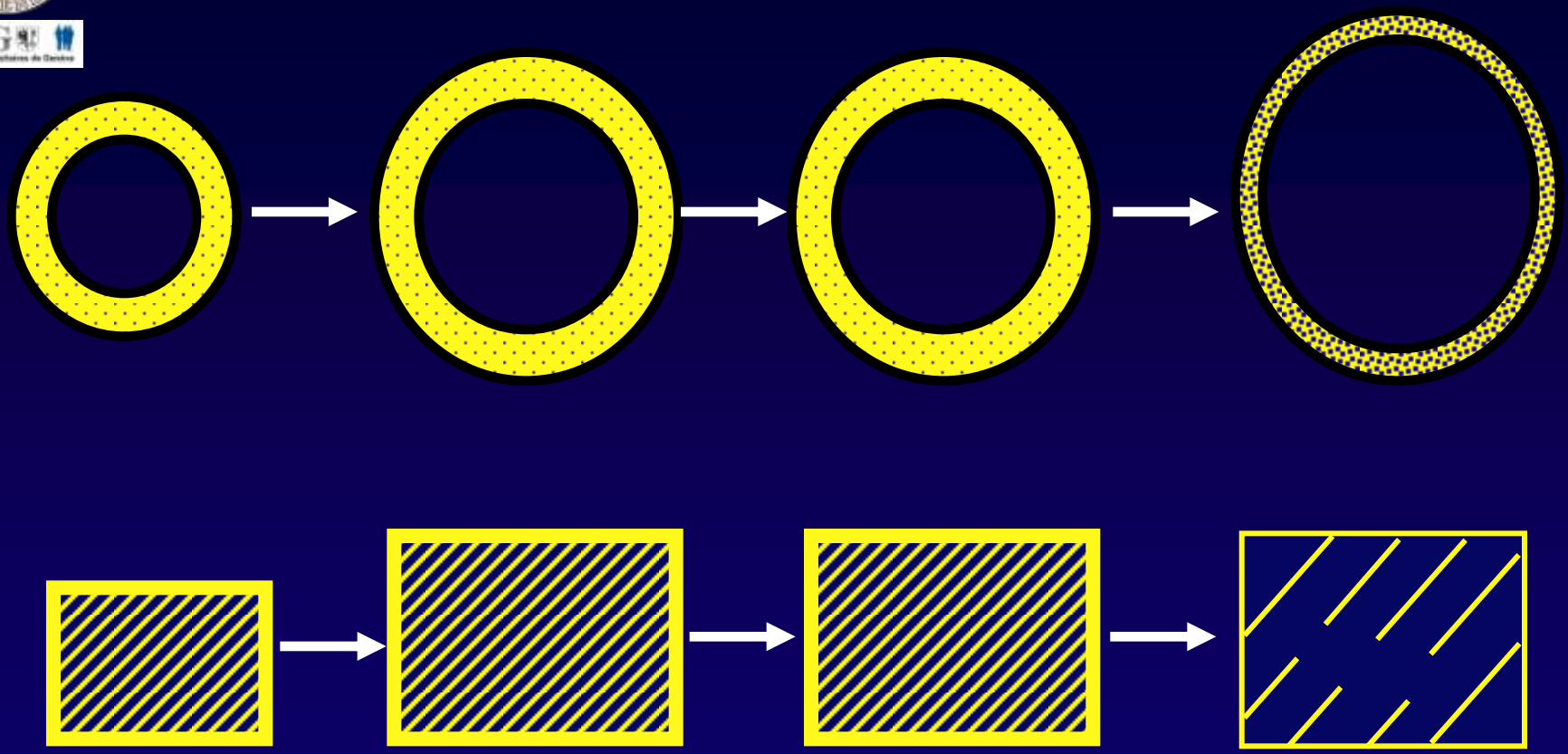
Deoxypyridinoline
Pyridinolines

Garnero et al., JBC, 1998

Sassi et al., Bone, 2000

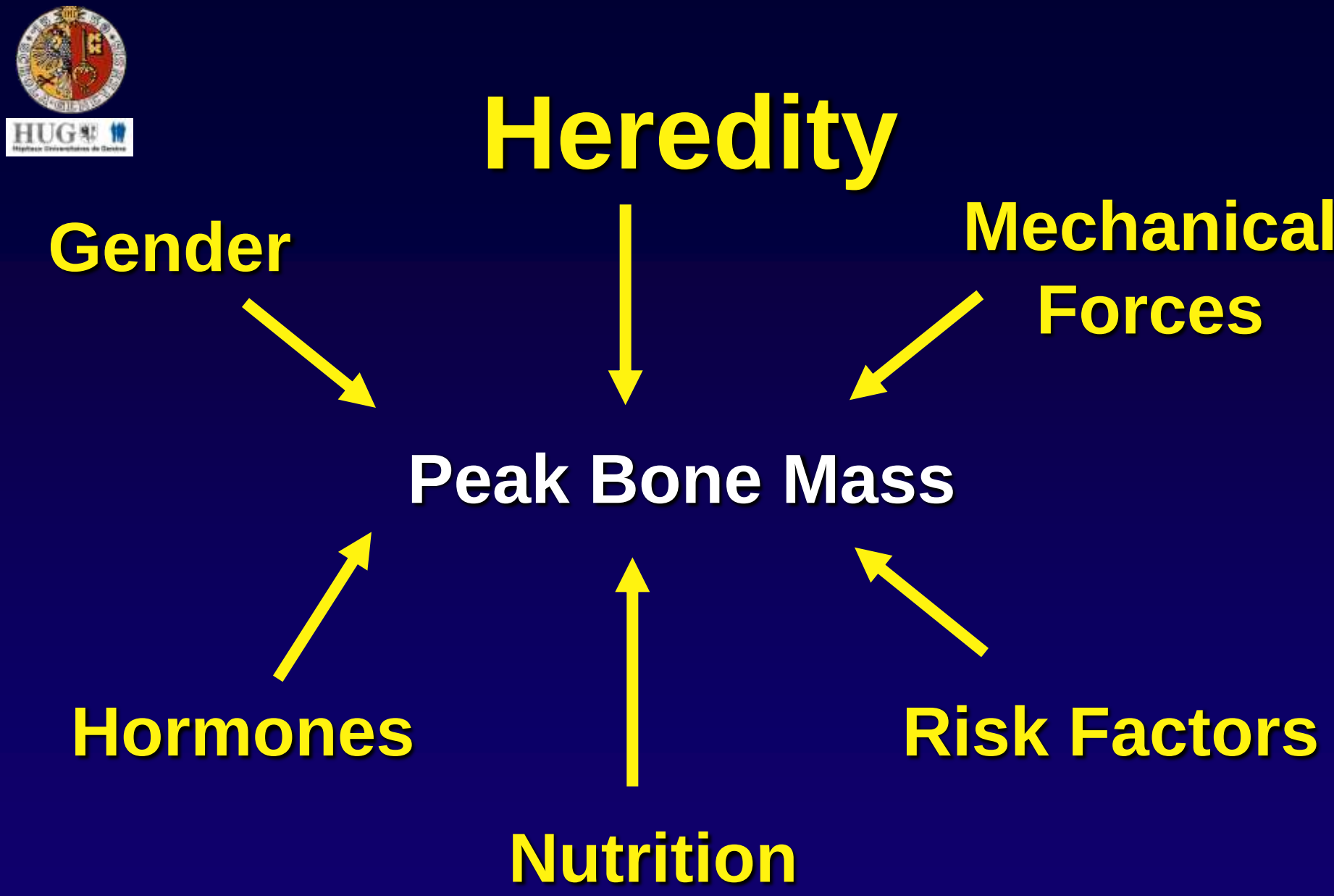
Tracking of Bone Mineral Mass

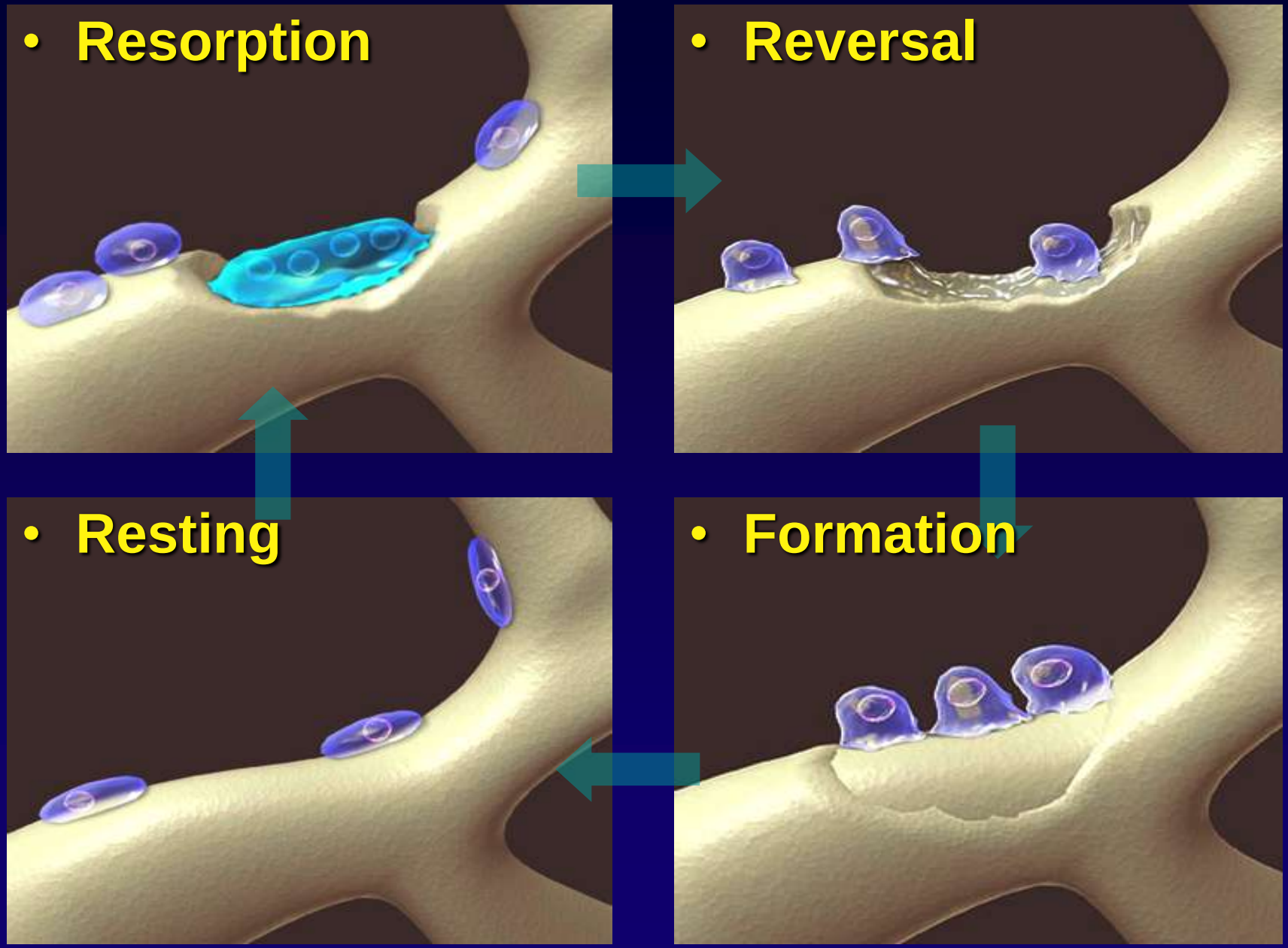




Age: 10 20 40 70

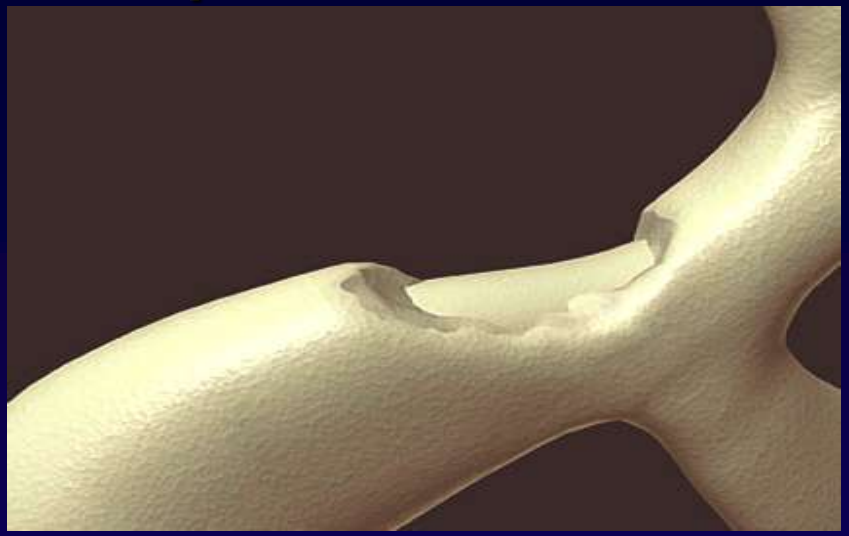
Rizzoli et al.,J Mol Endocrinol 2001


Heredity
Gender
Mechanical Forces
Peak Bone Mass
Hormones
Risk Factors
Nutrition


• Resorption
• Reversal
• Resting
• Formation

•Coupled and balanced

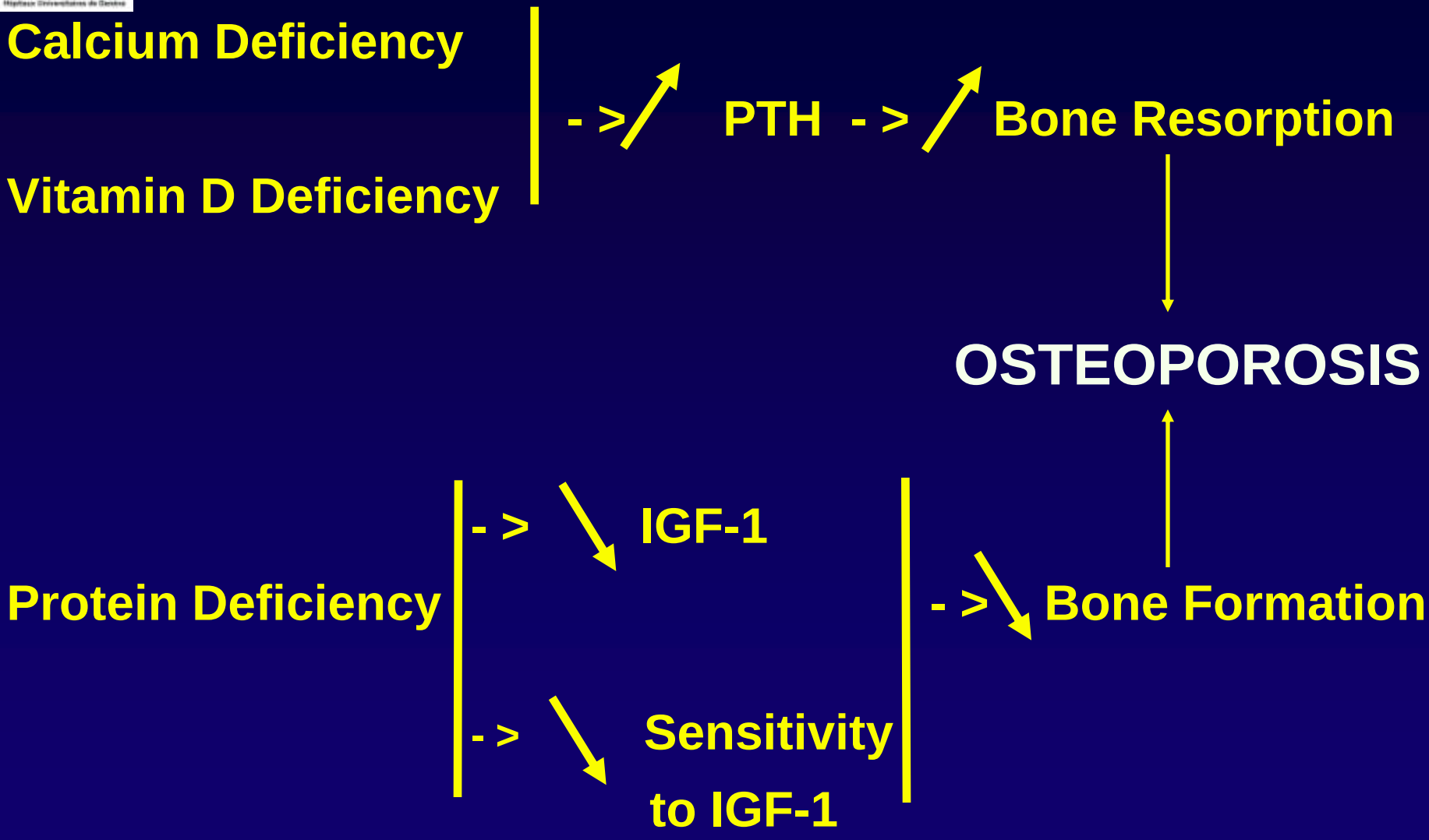
•Coupled but imbalanced



•Uncoupled but balanced

•Uncoupled and imbalanced

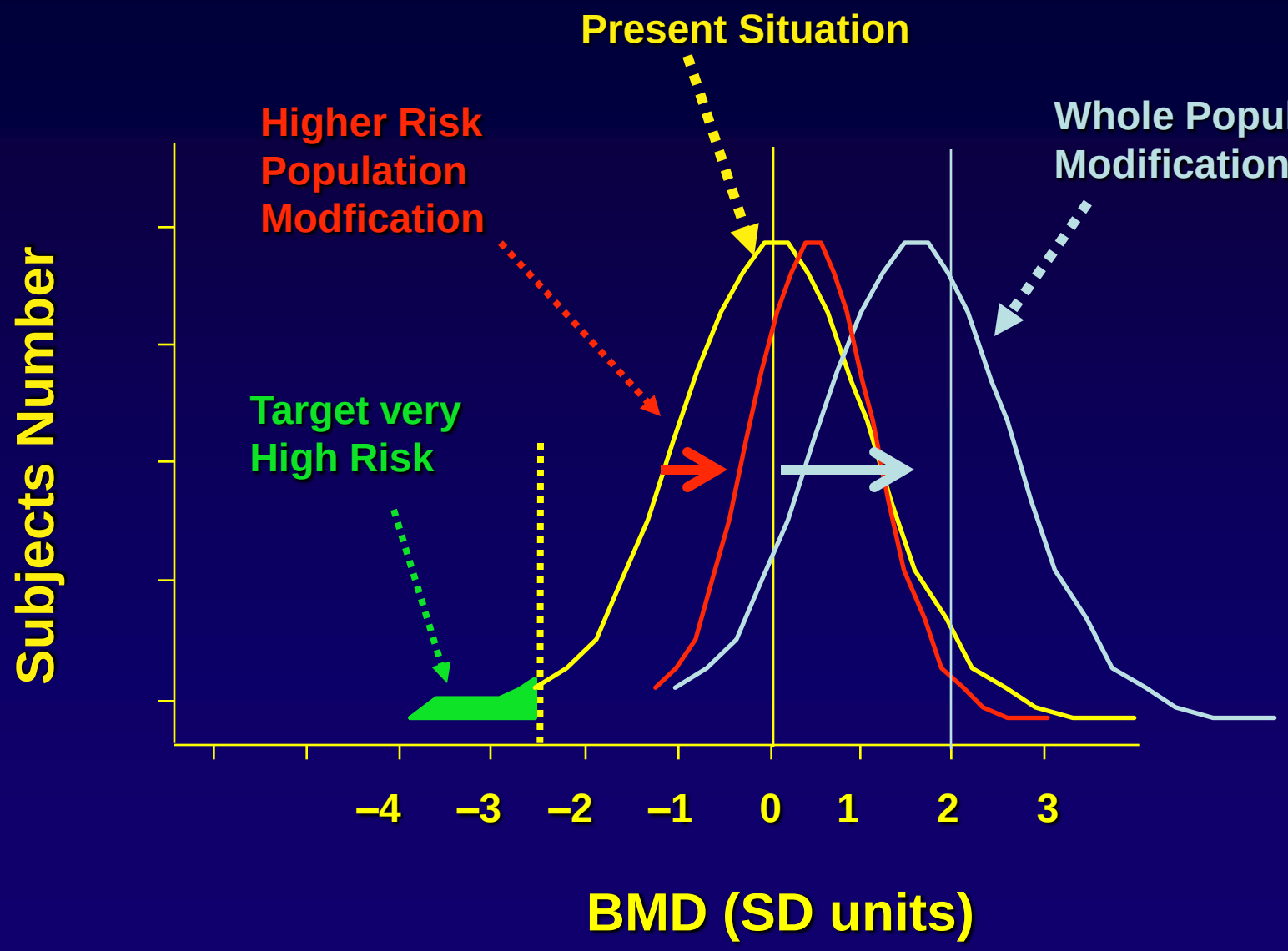
MALNUTRITION IN ELDERLY



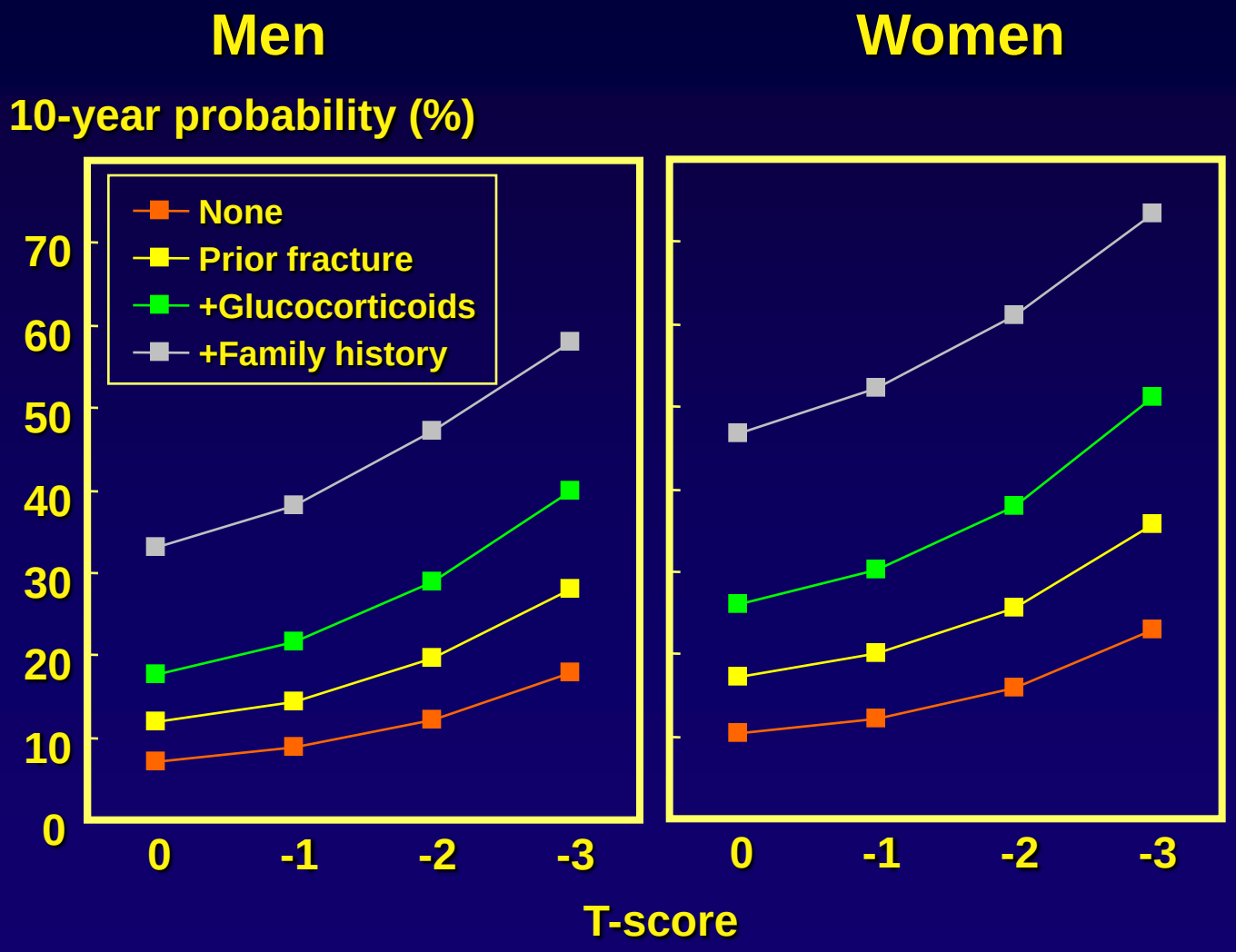
Management

- Indication to treatment
- Treatment possibilities

Osteoporosis Preventive Strategies



Probability of osteoporotic fracture* at age 65



US Caucasian, no CRF, BMI=24

**Hip, spine, humerus, forearm*

Weight Conversion:

pound: [ ]

convert

1 pound = 0.453592 kg

Height Conversion:

inch : [ ]

convert

1 inch = 2.54 cm

FRAX WHO Fracture Risk Assessment Tool

HOME | CALCULATION TOOL | FAQ | REFERENCE

Your Country : UK Name / ID : [ ] About the risk factors

Questionnaire:

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

   Age: [ ] Date of birth: Y: [ ] M: [ ] D: [ ]

2. Sex ○ Male ○ Female

3. Weight (kg) [ ]

4. Height (cm) [ ]

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 more units per day ○ No ○ Yes

12. Femoral neck BMD

    T-score [ ]

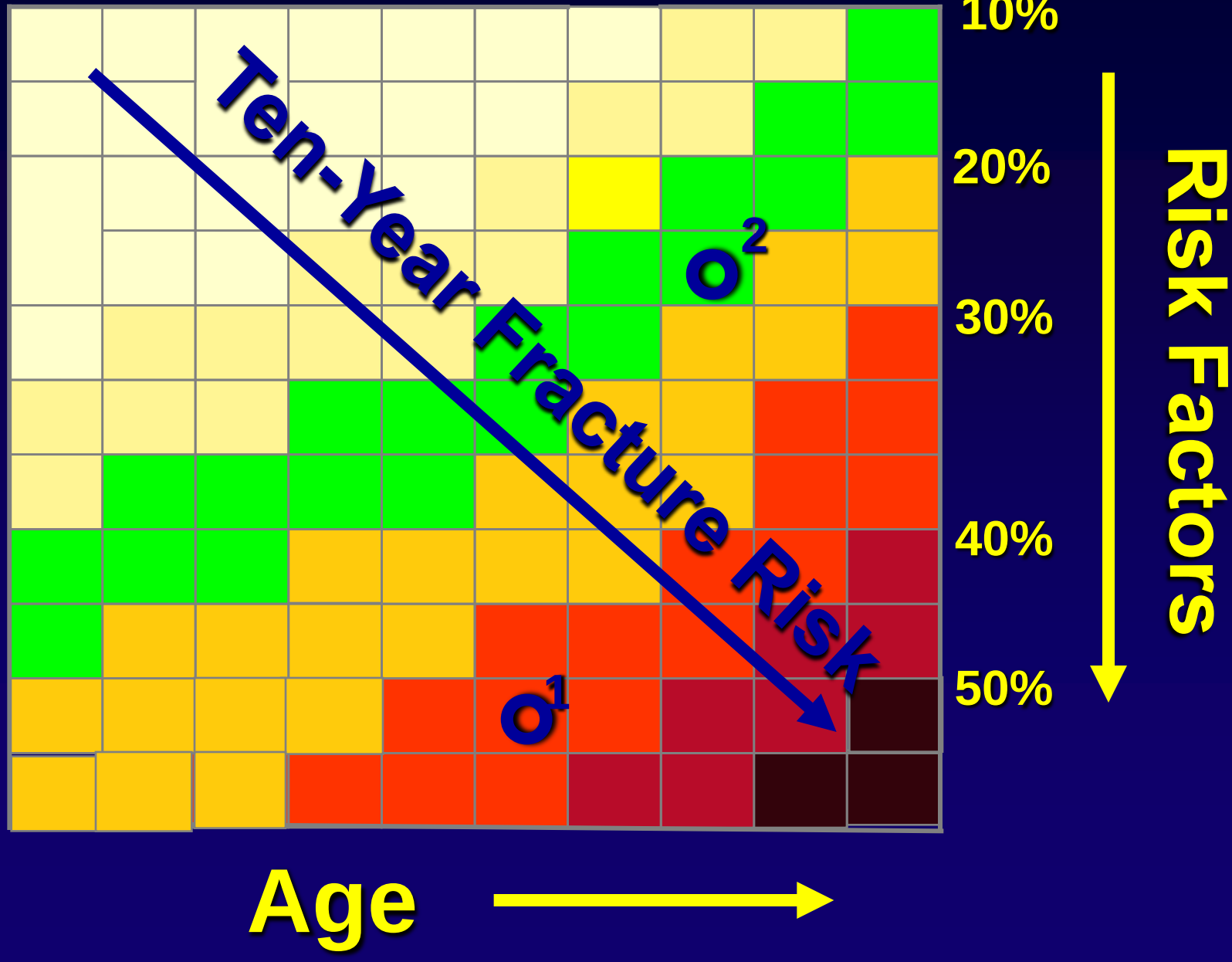
Clear Calculate

BMI: 24

The ten year probability of fracture (%) with BMD

Major osteoporotic fracture	23.9
Hip fracture:	8.0

10-Year Risk:



General Management

- Treatment of any Disease Causing Bone Loss
- Ensure Dietary Calcium Intake ≥ 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)

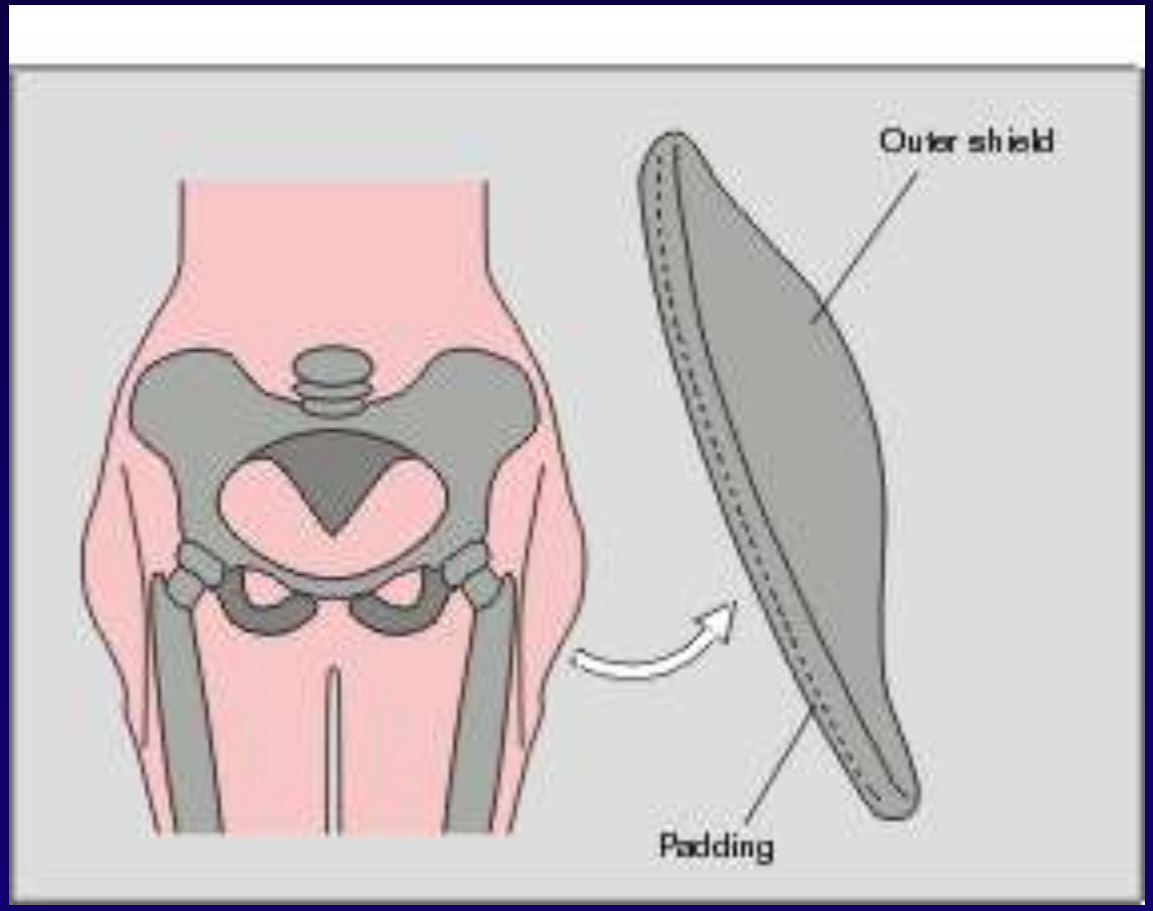
Risk Factors Associated with Falls

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

Hip Fracture Prevention



- RCT in Community: No

- RCT in Nursing Homes:
  Cluster Random.: Yes
  Individual Random.: No
  Left vs Right: No

- Problems
  Compliance
  Persistence

Therapeutic Agents Used in Osteoporosis

Anticatabolic Agents

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

Anabolic Agents

- (Fluoride)
- Parathyroid Hormone

Complex Action

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

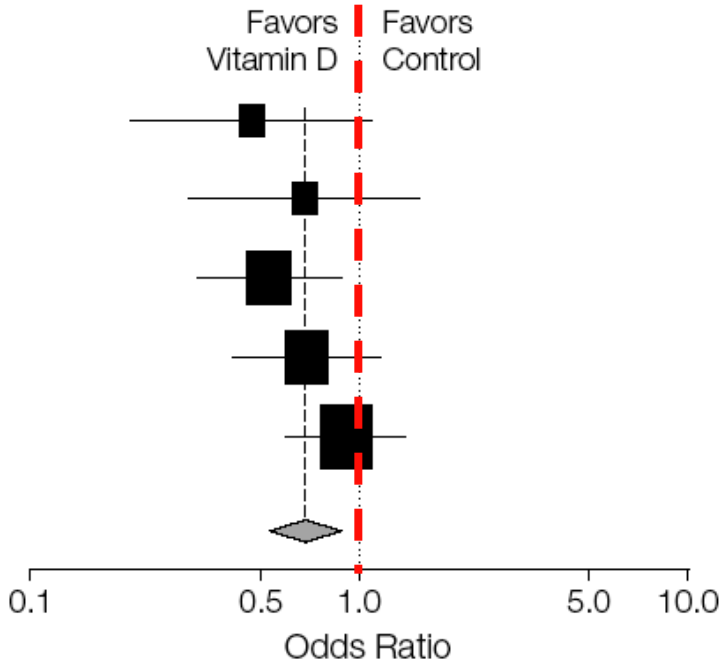
Mixed Action

- Strontium Ranelate

Vitamin D and Risk of Falling

Primary Analysis

Source	Odds Ratio (95% CI)
Pfeifer et al,[11] 2000	0.47 (0.20-1.10)
Bischoff et al,[12] 2003	0.68 (0.30-1.54)
Gallagher et al,[17] 2001	0.53 (0.32-0.88)
Dukas et al,[18] 2004	0.69 (0.41-1.16)
Graafmans et al,[19] 1996	0.91 (0.59-1.40)
Pooled (Uncorrected)	**0.69 (0.53-0.88)**



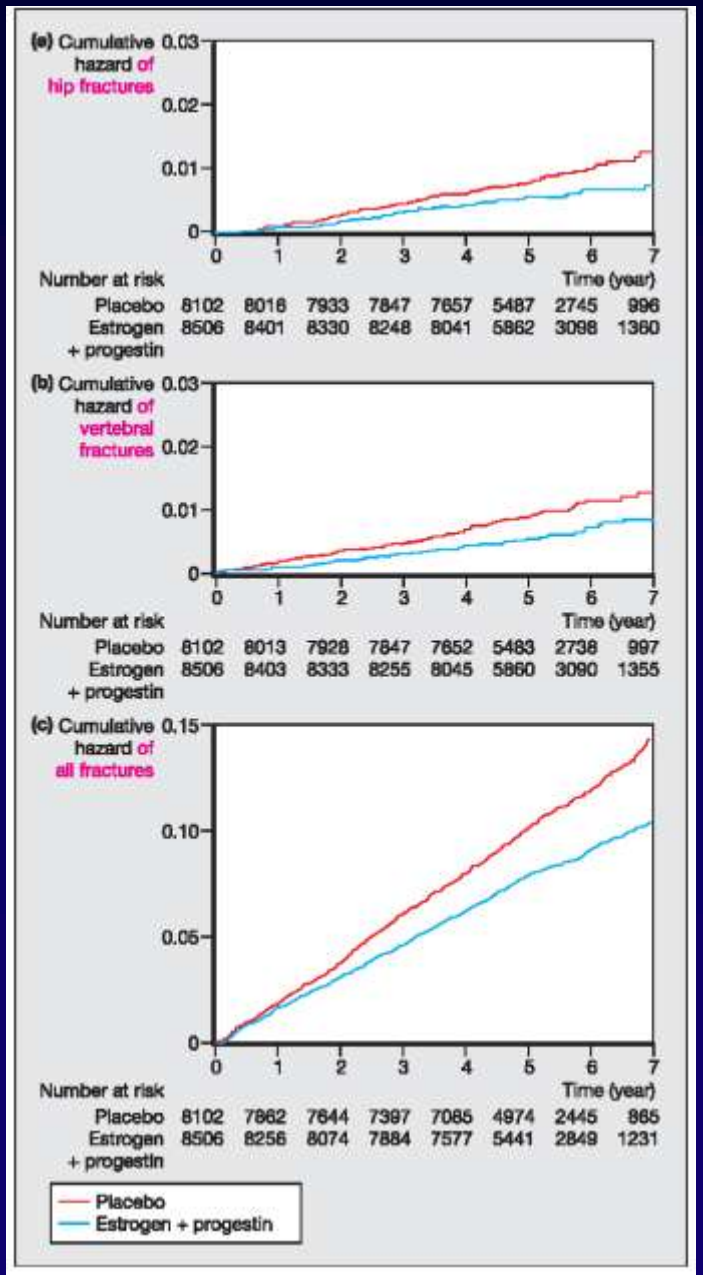
H. Bischoff-Ferrrari et al JAMA 2004

Hormone Replacement Therapy and Fracture Risk

Hip

Vertebral

All Fractures

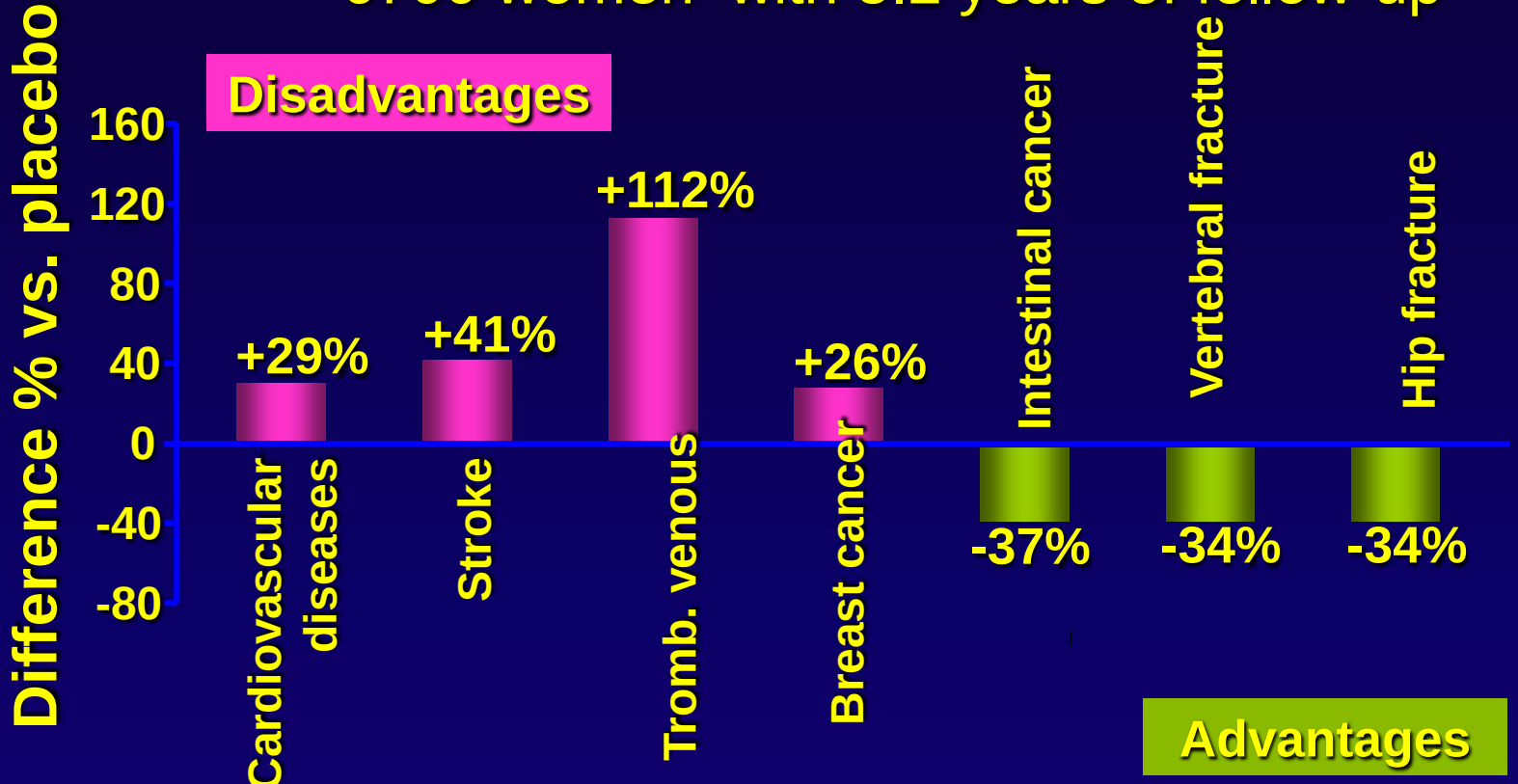


Placebo
HRT

WHI Study,
Cauley et al, 2003

Women's Health Initiative - First randomized, controlled trial in women (50-79 years) treated with HRT

6700 women with 5.2 years of follow-up



Manson JE at al, N Engl J Med, 2003;349:523-534

Anti -fracture efficacy (RR ± 95% CI)

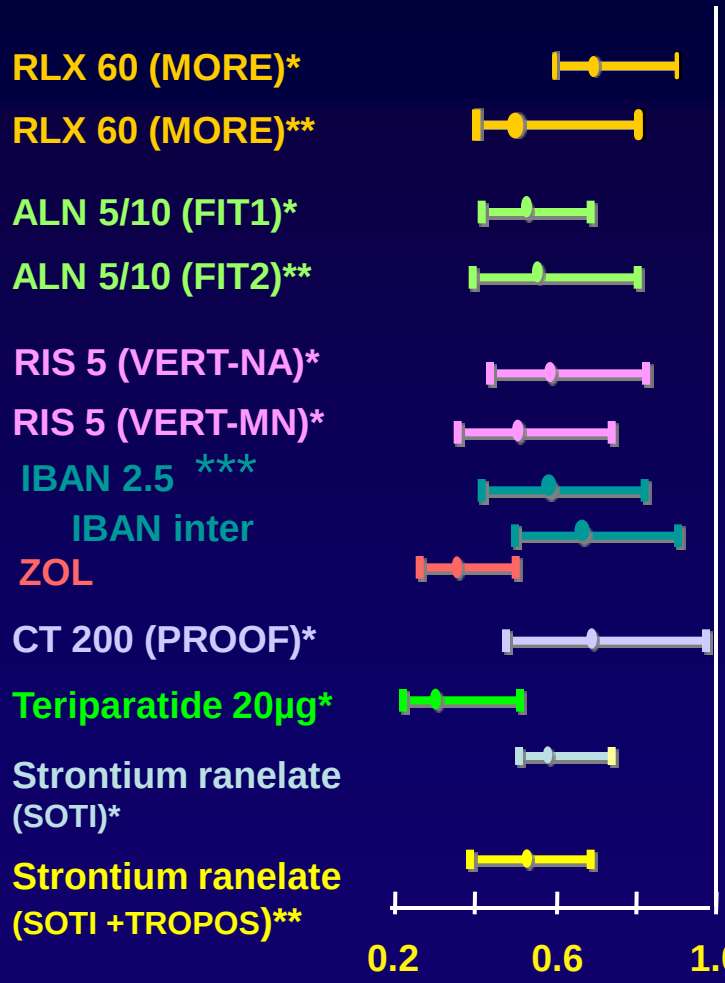
Vertebral Fx

* with prev vert fracture(s) ** without prev vert fractures *** with or without prev vert fractures

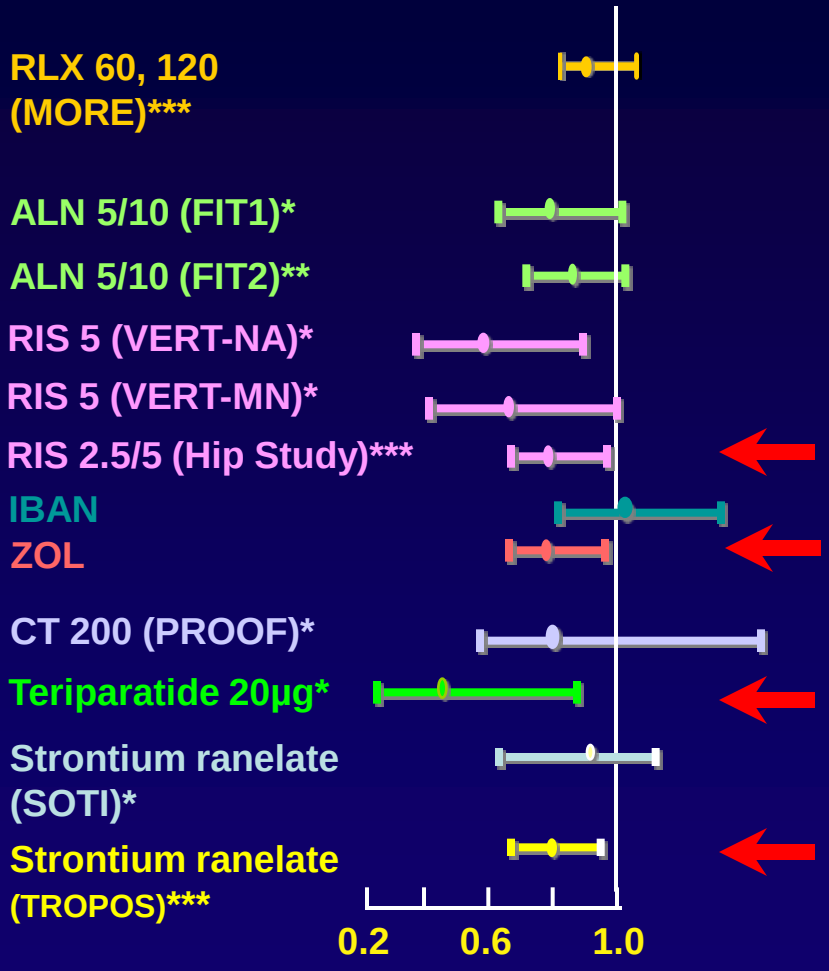
Update from Delmas 2002

Anti -fracture efficacy (RR ± 95% CI)

Vertebral Fx



Non-Vertebral Fx



* with prev vert fracture(s) ** without prev vert fractures *** with or without prev vert fractures

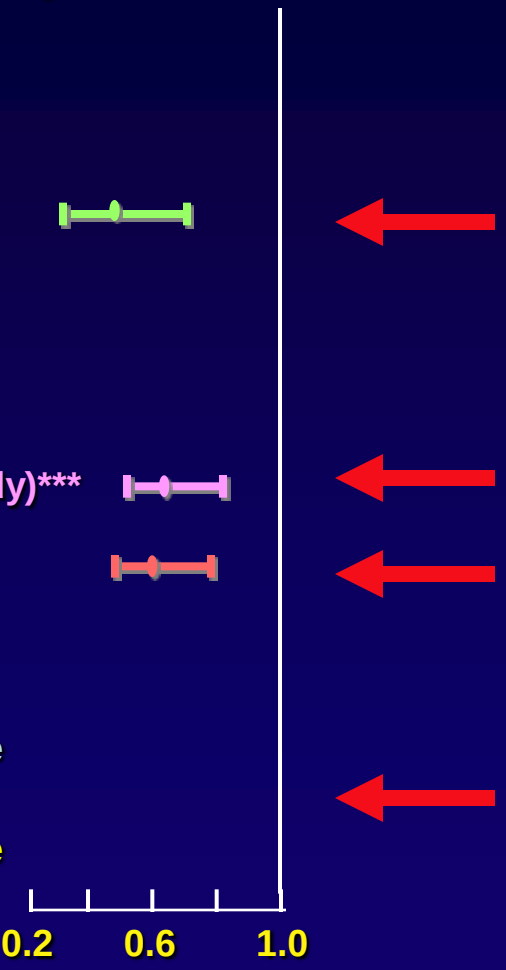
Update from Delmas 2002

Anti -fracture efficacy (RR ± 95% CI)

Hip Fx

Significant hip fracture risk Reduction: 3 studies

Only studies with preplanned analysis:
- RIS 2.5/5 (Hip Study)
- ZOL 5 mg (Horizon Study)



* with prev vert

*** with or without prev vert fractures

Bisphosphonate New Schedules of Administration

1. Weekly (Alendronate, Risedronate)
   -> Monthly Oral Administration
   - Ibandronate
   - Risedronate

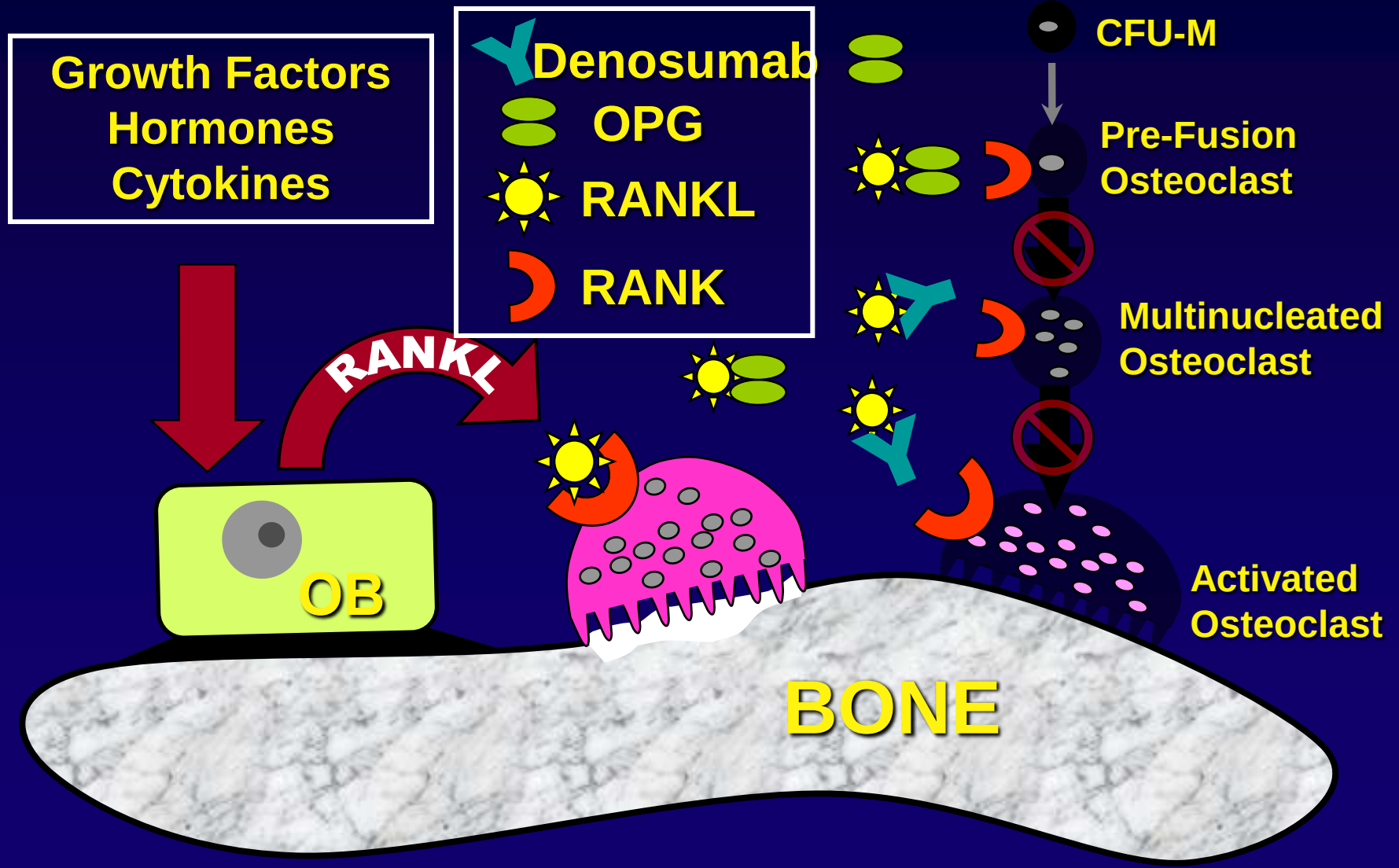
2. Trimonthly Intravenous Administration - Ibandronate

3. Annual Intravenous Administration - Zoledronate *

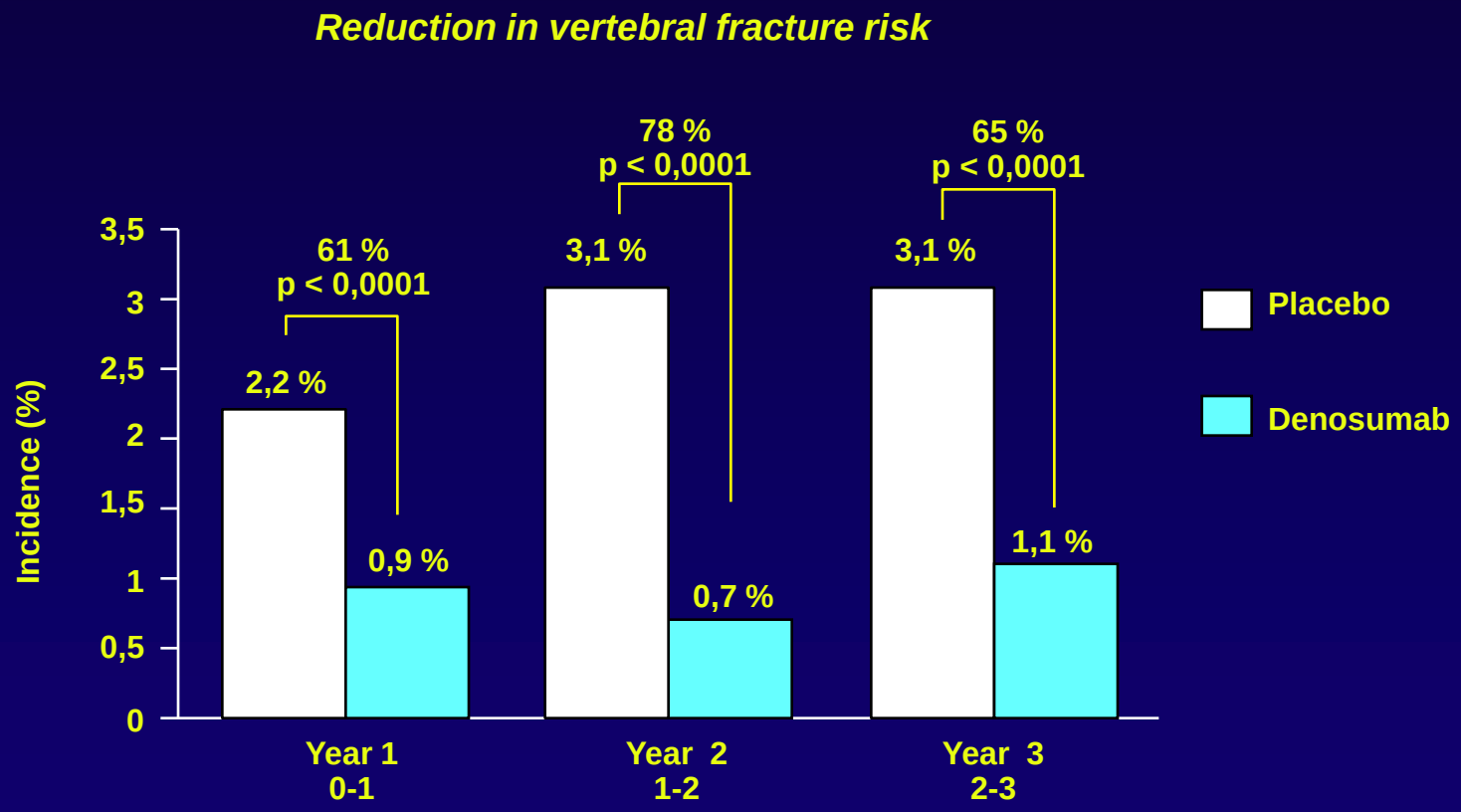
4. Sequential Regimen (PTH -> ALN, RIS or ALN -> PTH)

***: Fracture Data**

Mechanism of Action of Denosumab

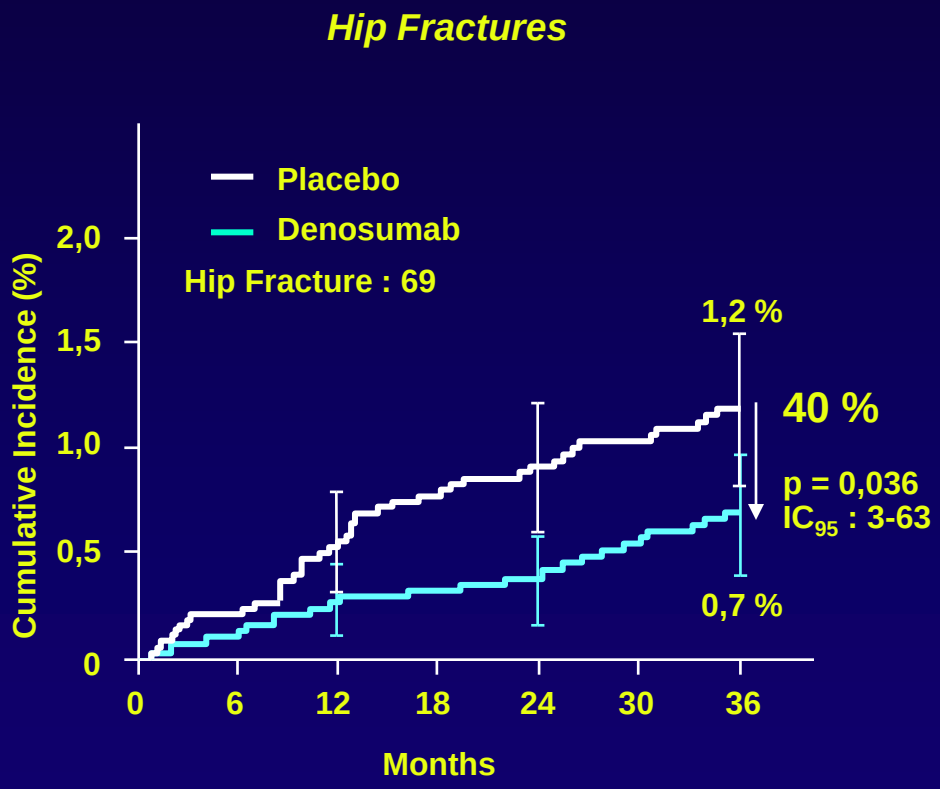


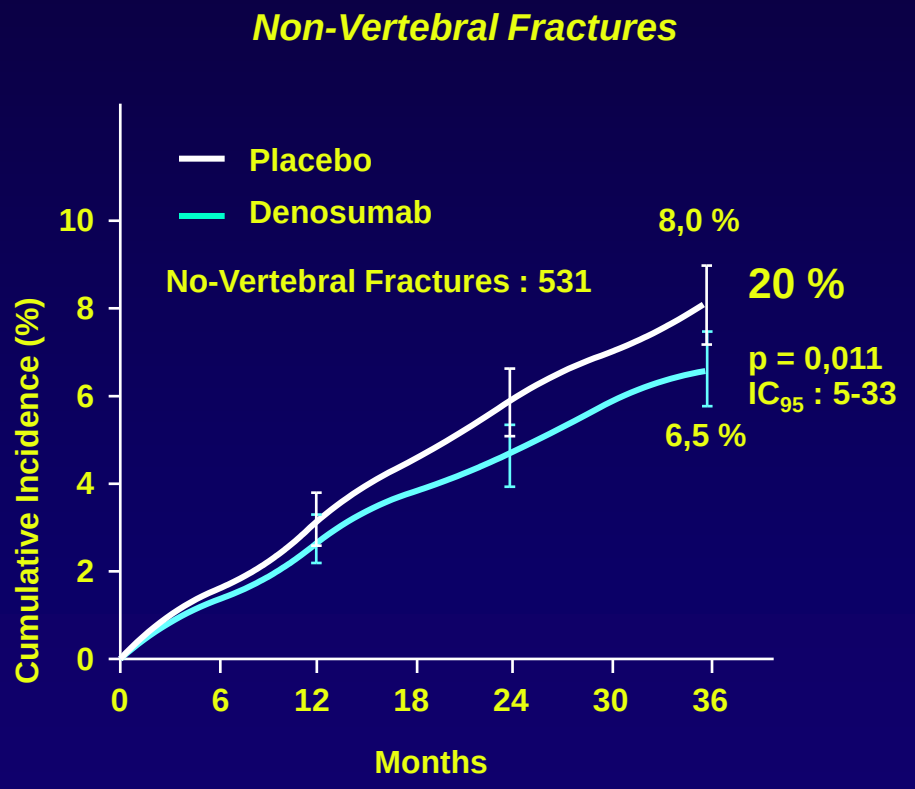
Phase III Trial on the Effects of Denosumab on Vertebral Fracture Risk in Women with Postmenopausal Osteoporosis



ASBMR 2008 - D'après Cummings S.R. et al., San Francisco, États-Unis, abstract 1286,

Phase III Trial on the Effects of Denosumab on Non-Vertebral Fracture Risk in Women with Postmenopausal Osteoporosis



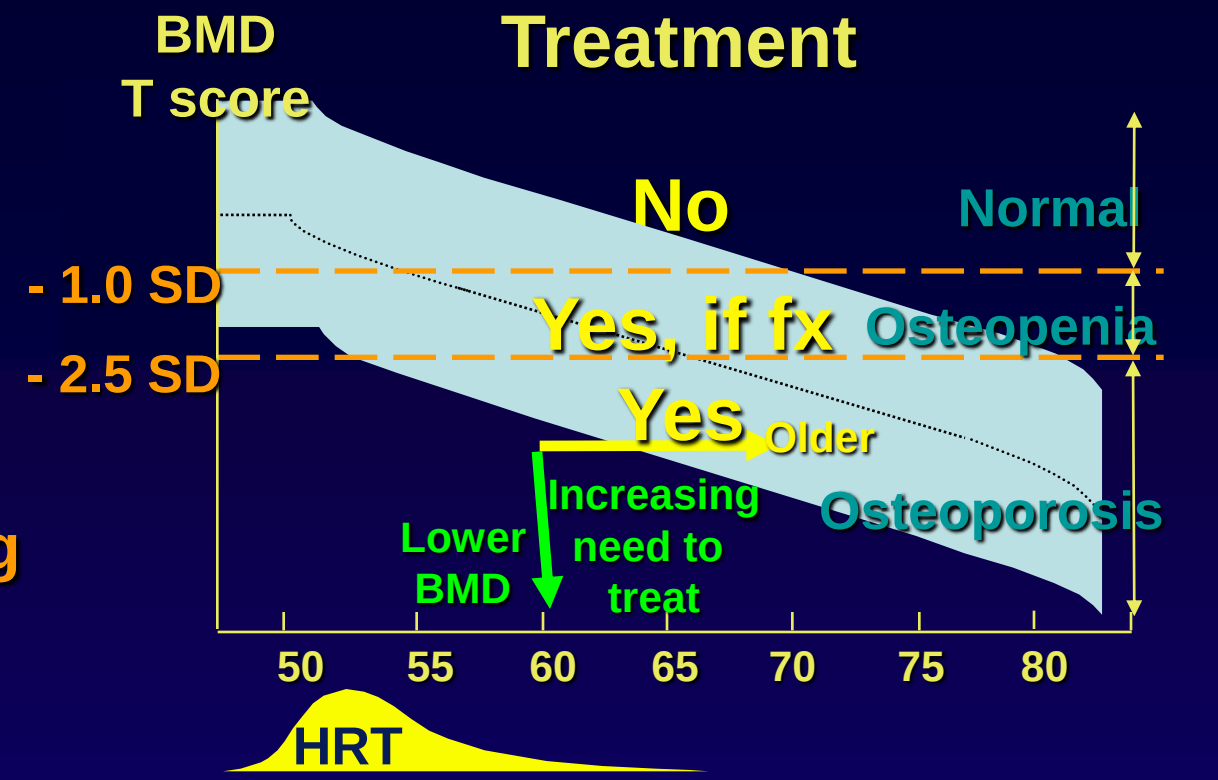


ASBMR 2008 - D'après Cummings S.R. et al., San Francisco, États-Unis, abstract 1286,

Osteoporosis Treatment in 2009 Summary

- HRT: ↓ spine fx; ↓ hip fx
- SERMS: ↓ spine fx; no effect on peripheral fx
- Calcitonin: possible ↓ spine fx; no hip data
- Alendronate: ↓ spine fx; ↓ hip fx
- Risedronate: ↓ spine fx; ↓ hip fx
- Ibandronate: ↓ spine fx; no effect on hip
- Zoledronate: ↓ spine fx; ↓ hip fx
- PTH: ↓ spine fx
- Strontium Ranelate: ↓ spine fx; ↓ hip fx
- Denosumab: ↓ spine fx; ↓ hip fx

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

1. Aim of Therapy

≠ Treatment of Osteoporosis

= Treatment of Patients with Osteoporosis

2. Never Too Late

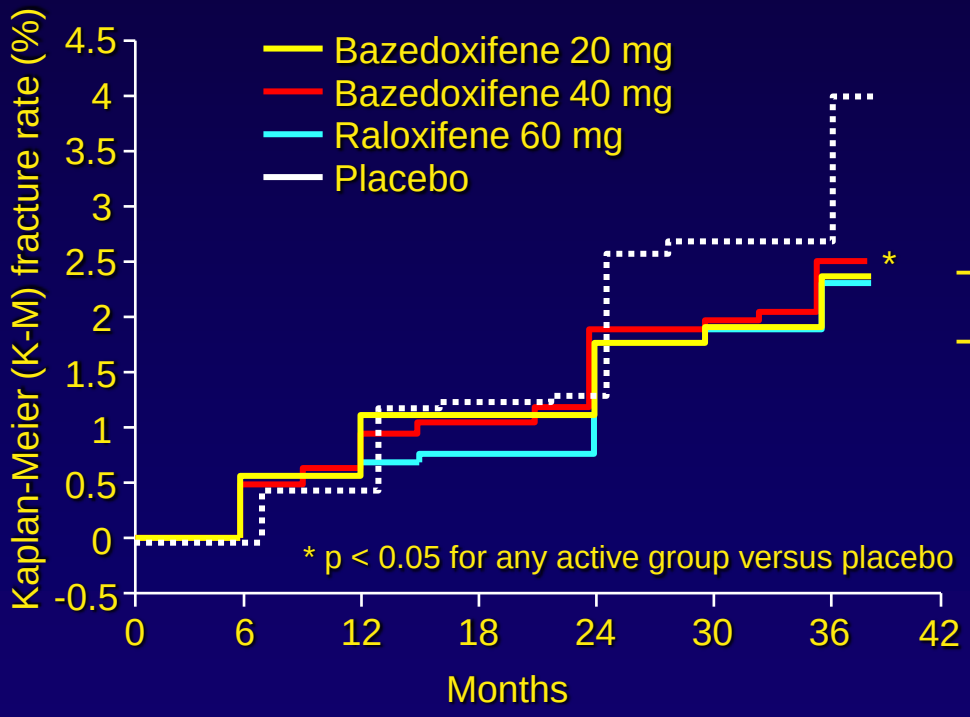
Fractures are not Unavoidable Expenses to Pay as a Consequence of Increased Life-Expectancy

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 Controled Trials, with Fracture Incidence as Primary End-Point

Effect of Bazedoxifene on Vertebral Fracture in Postmenopausal Women with Osteoporosis

Incidence of new vertebral fracture (intent-to-treat population 0-36 months)



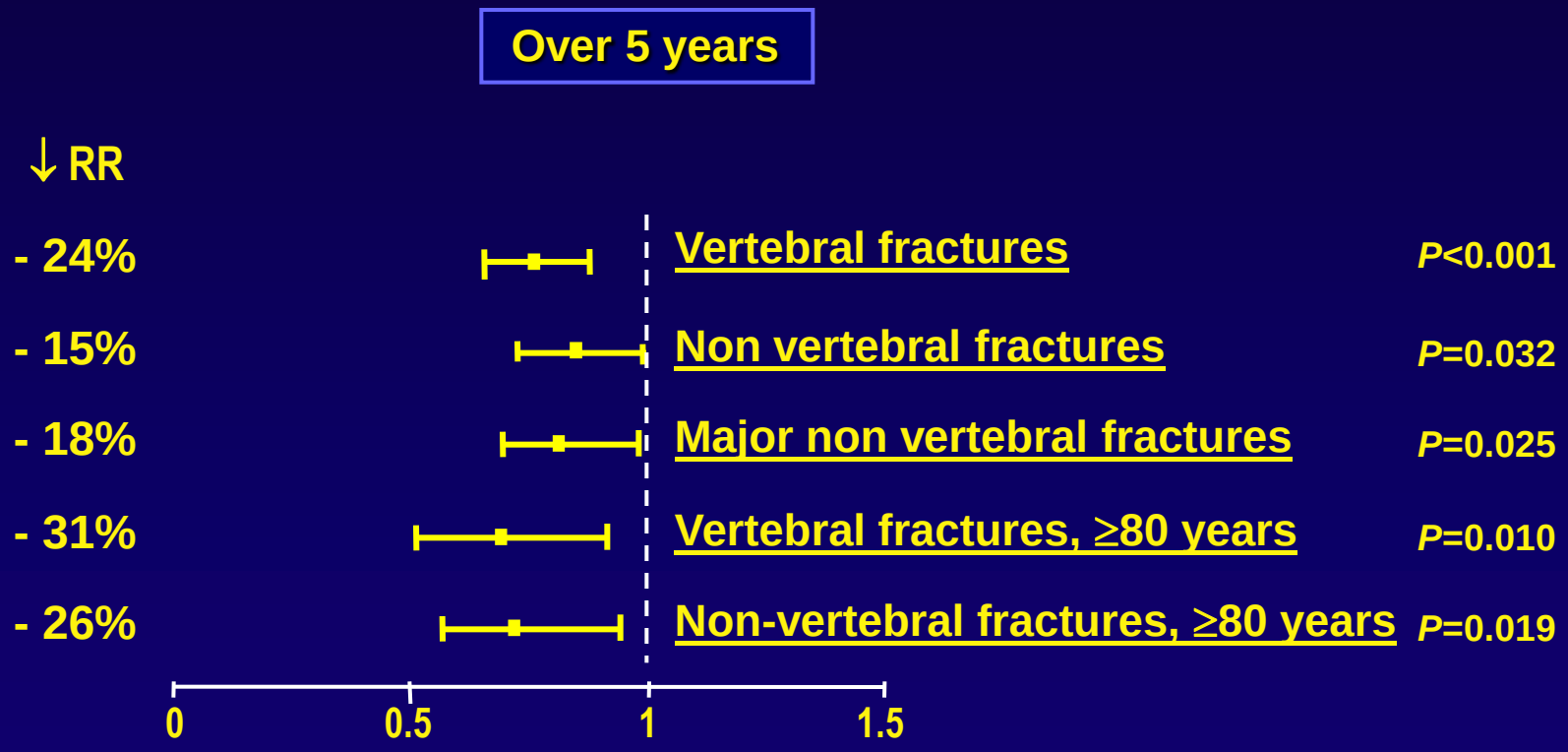
- Results
  - the reduction in the incidence of new vertebral fractures was (as compared to placebo)
    - - 42% in group I
    - - 37% in group II
    - - 42% in group III
  - there was no treatment effect on NVF
  - there was no difference between the different groups with regard to adverse effects

Bazedoxifene significantly reduces the risk of new vertebral fracture in postmenopausal women with osteoporosis

ASBMR 2007 – From Silverman SL et al., Beverly Hills, USA, abstract 1206, updated

Long-Term Vertebral and Non-vertebral FractureRisk Reduction with Strontium Ranelate

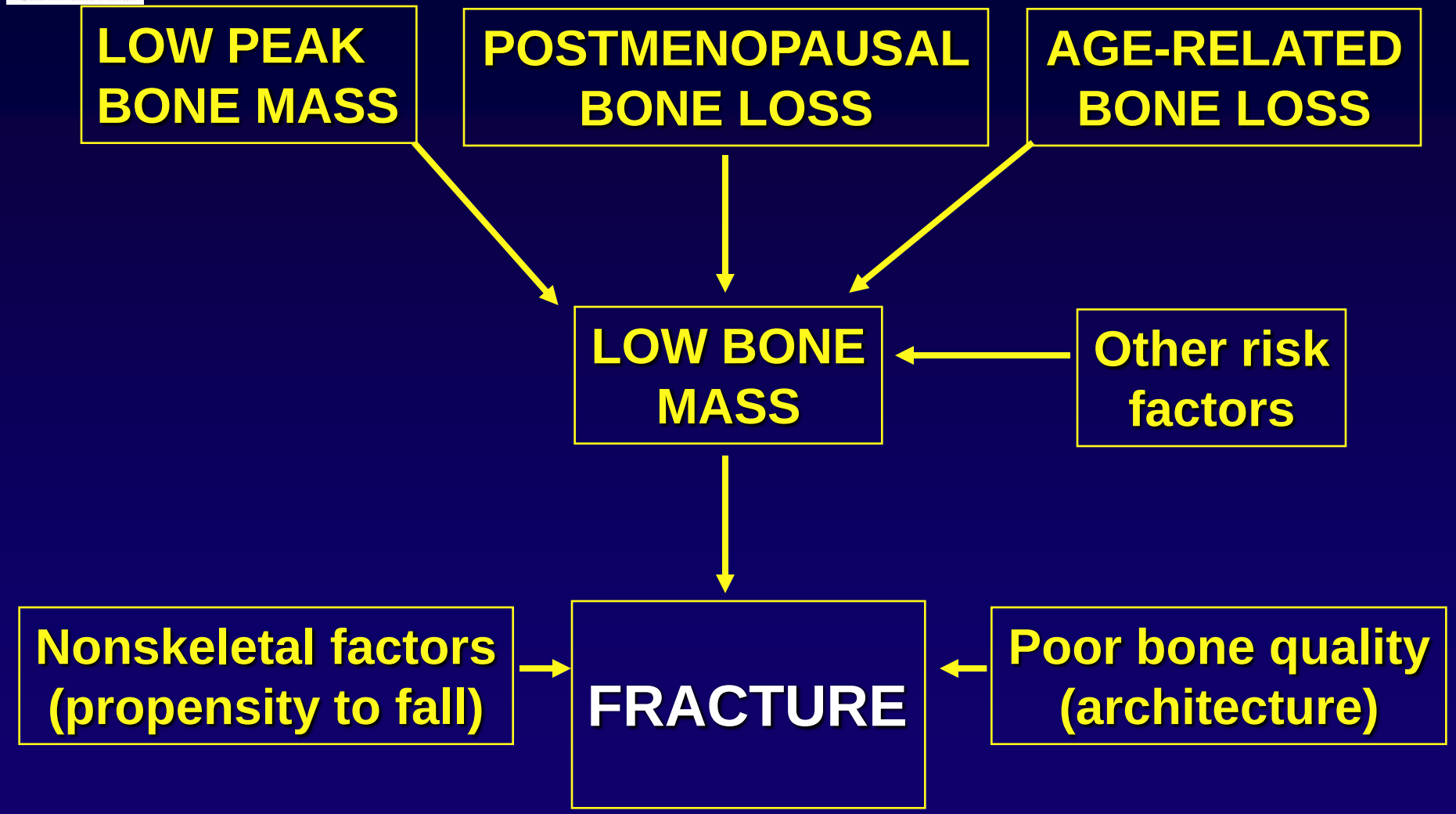
Favors Strontium ranelate



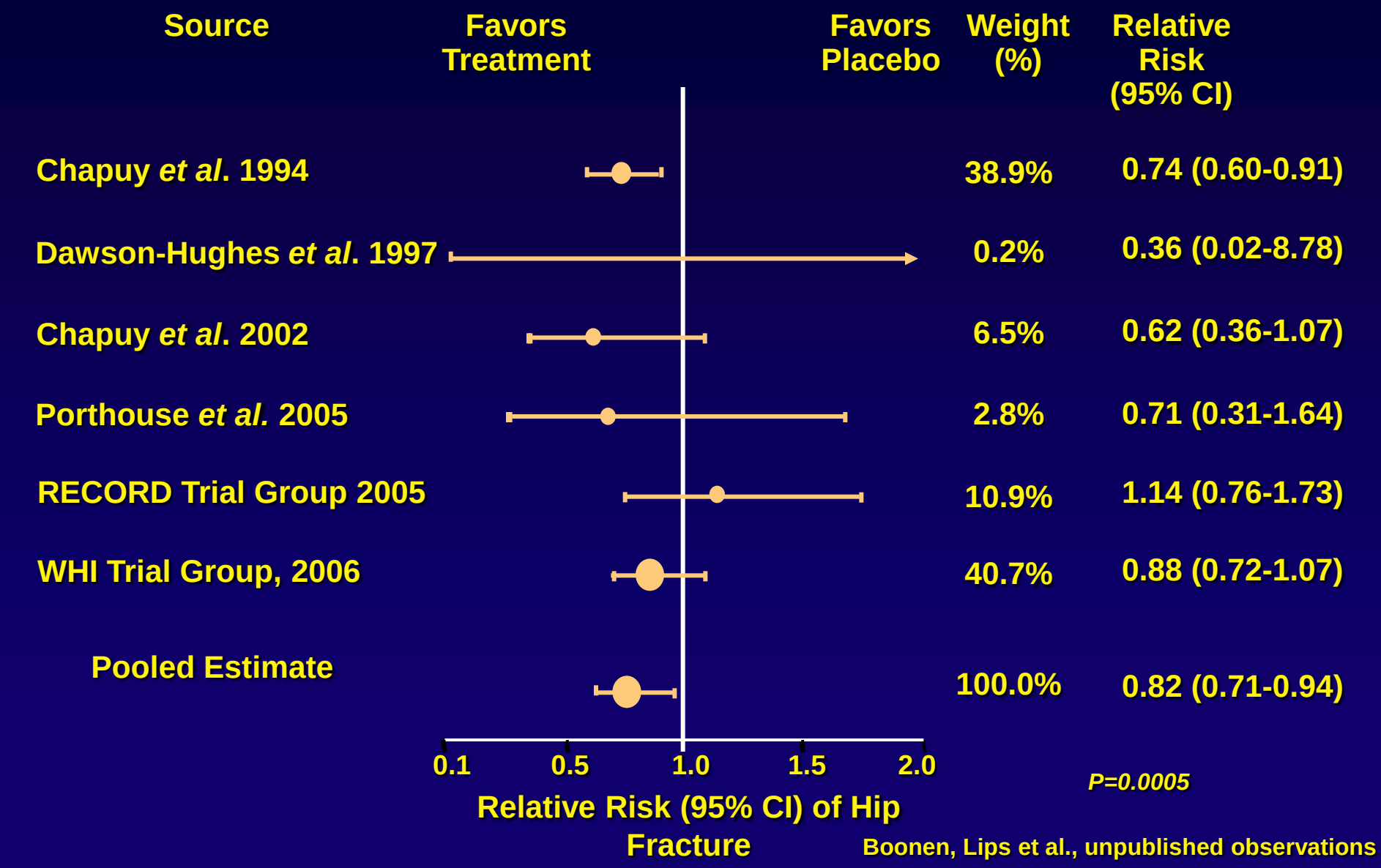
Reginster et al 2007

RELATIVE RISKS AND 95% CI

Pathogenesis of Osteoporotic Fracture



Hip Fracture Risk – *Vitamin D & Calcium* Versus Placebo/No Treatment



Boonen, Lips et al., unpublished observations

Tracking of Bone Mineral Mass Accrual