

Osteoporosis

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Scope

- **Developments in:**
 - **Fracture risk assessment**
 - **Bone markers**
 - **Treatment**

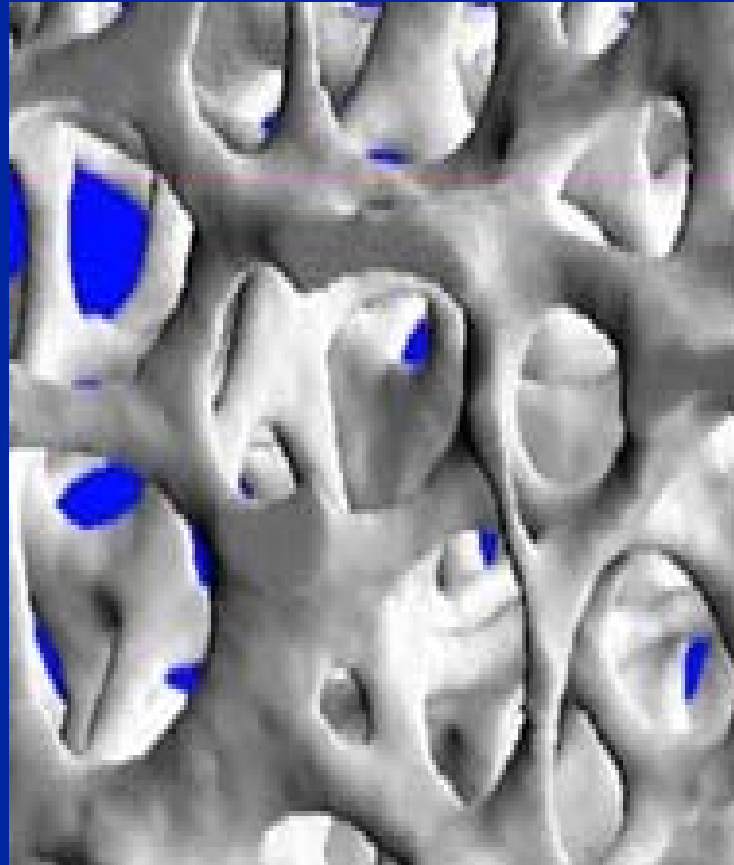
Definition of osteoporosis

- **A systemic skeletal disease characterized by**
 - **low bone mass**
 - and**
 - **microarchitectural deterioration of bone tissue**
 - leading to**
 - **enhanced bone fragility and a consequent increase in fracture risk**



WHO 1994

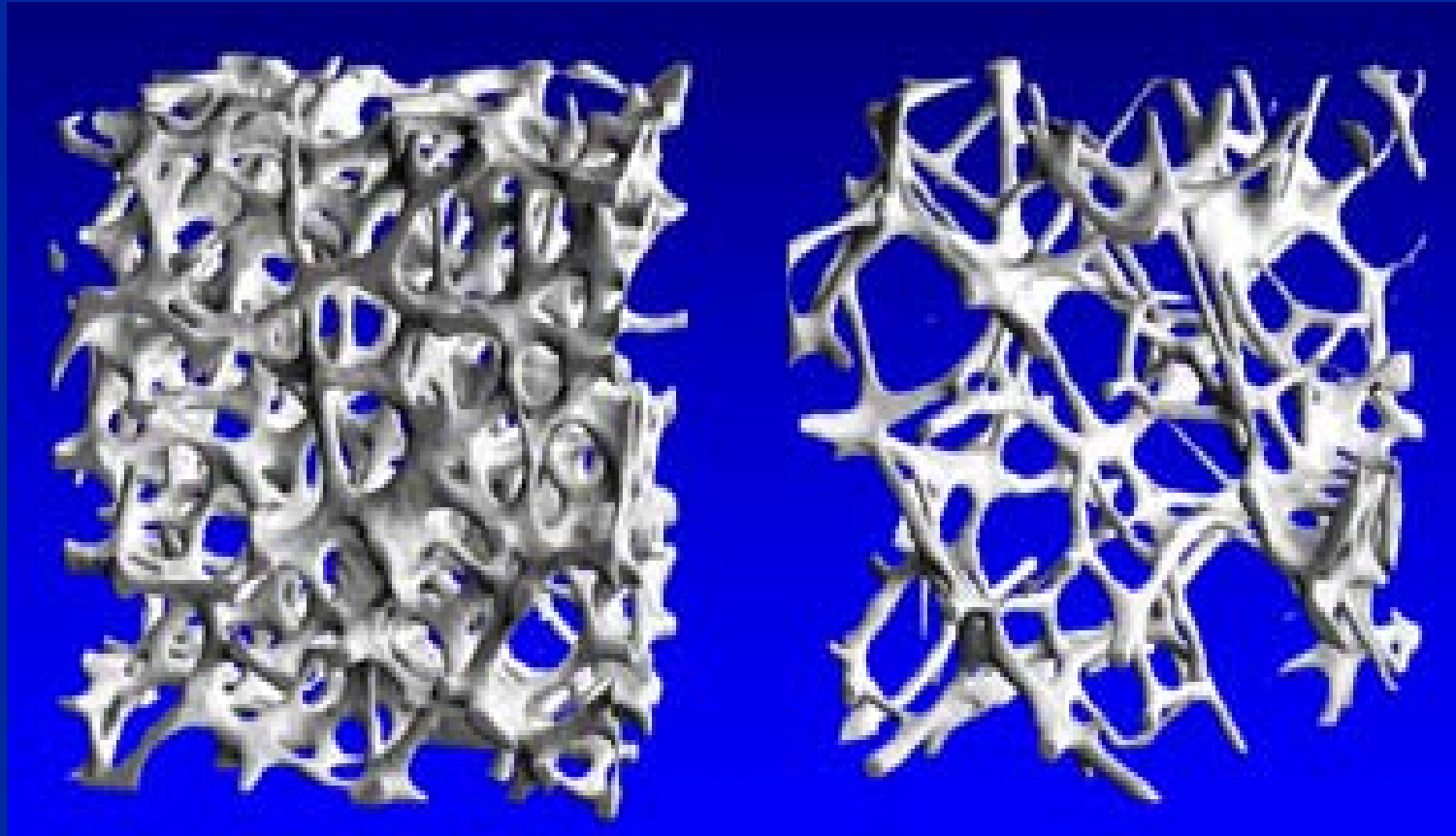
Normal bone architecture



Bone architecture

Normal

osteoporosis



WHO criteria for osteoporosis in women

	T-Score
Normal	-1 and above
Low bone mass	-1 to -2.5
Osteoporosis	< -2.5
Established osteoporosis	< -2.5 and one or more fractures

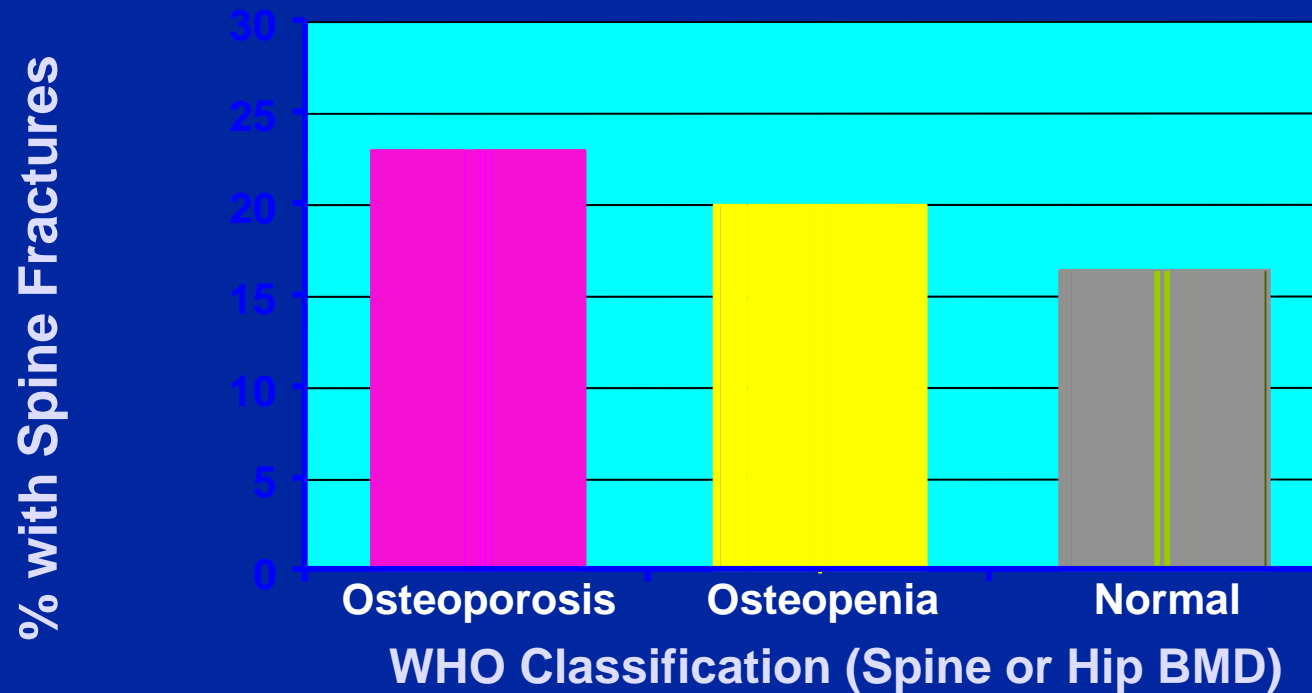
Bone density scanning by DXA

A bone density scan is a low-dose x-ray which checks an area of the body such as the hip, spine or wrist for signs of mineral loss and bone thinning



ADAM.

Classification by T-score alone misses patients with fractures



- ➔ 50% of women with vertebral fracture are not osteoporotic by BMD
- ➔ 1/3 of women needing Rx are missed using BMD alone

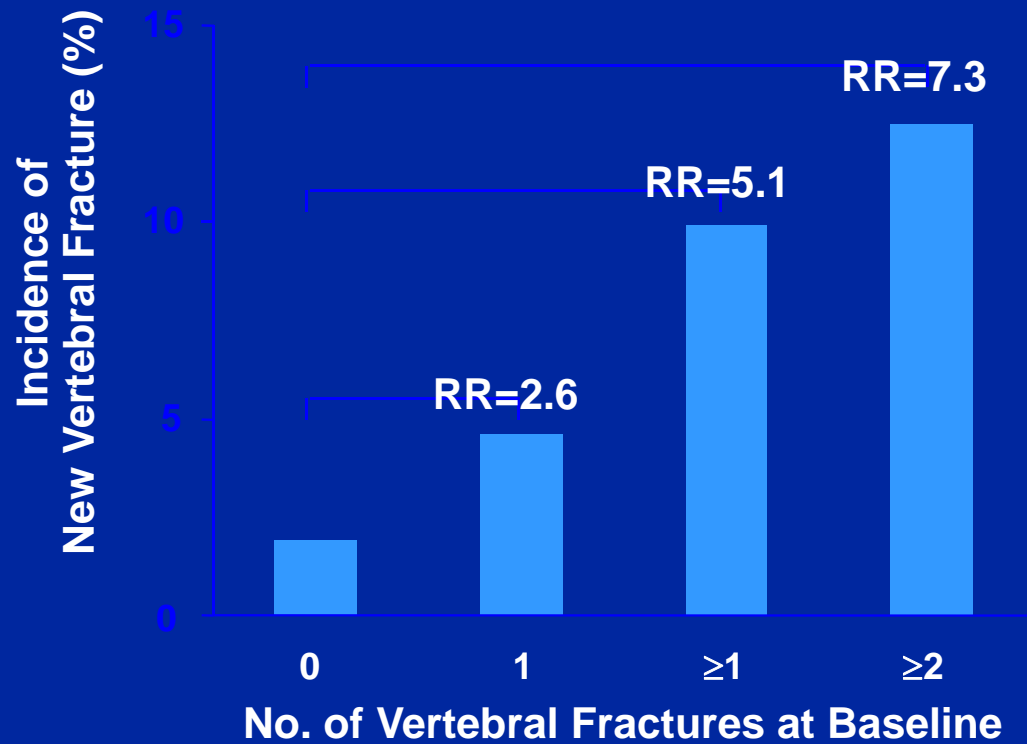
Greenspan S et al, J Clin Densitom 2001;4:373-380

Ten-year probability of hip fracture in Swedish women according to age and BMD at the femoral neck

Kanis and Gluer. *Osteoporos Int.* 2000;26(6):1702-11

	10 year risk of hip fracture	
Age	Among all women	In women with osteoporosis [BMD T score \leq -2.5]
50	0.6	2.9
60	2.3	7.8
70	7.3	18.3
75	11.7	24.6

Effect of Prior Vertebral Fracture on Risk of Subsequent Vertebral Fracture

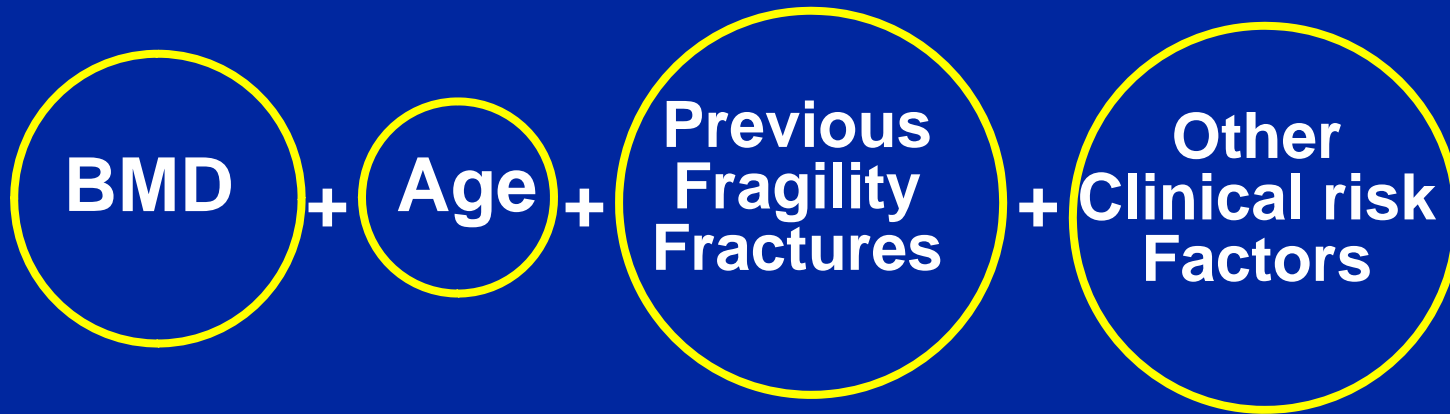


First Year of Study

2725 postmenopausal women randomised to placebo

Adapted from Lindsay R et al., JAMA 2001, 285:320
IOF-ESSR osteoporosis toolkit

Absolute Fracture Risk Calculation



Calculate absolute fracture risk
(10 Year Probability of a Fracture)

**Consider definitive treatment when fracture risk
high enough to make treatment cost effective**

Risk factors used in the calculation of 10-year risk of fracture

- ◆ Femoral neck T-score
- ◆ Age
- ◆ Previous low trauma fracture
- ◆ Low BMI
- ◆ Ever steroid exposure
- ◆ Family history of hip fracture
- ◆ Current cigarette smoking
- ◆ High alcohol intake (> 2 units/day)*

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

Kanis JA et al, Bone, 2002;30:251-258

Kanis JA et al, Osteoporos Int, 2005;16:581-589

Absolute fracture risk assessment - FRAX™

Country : **Australia** Name / ID : Jane Doe [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

Absolute fracture risk assessment - FRAX™

Country : **Australia**

Name / ID : Jane Doe

About the risk factors 

Questionnaire:

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

Age:

55

Date of birth:

Y:

M:

D:

2. Sex

Male Female

3. Weight (kg)

58.06

4. Height (cm)

162.5

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

-1.8

Clear

Calculate

BMI 21.9

The ten year probability of fracture (%)



with BMD

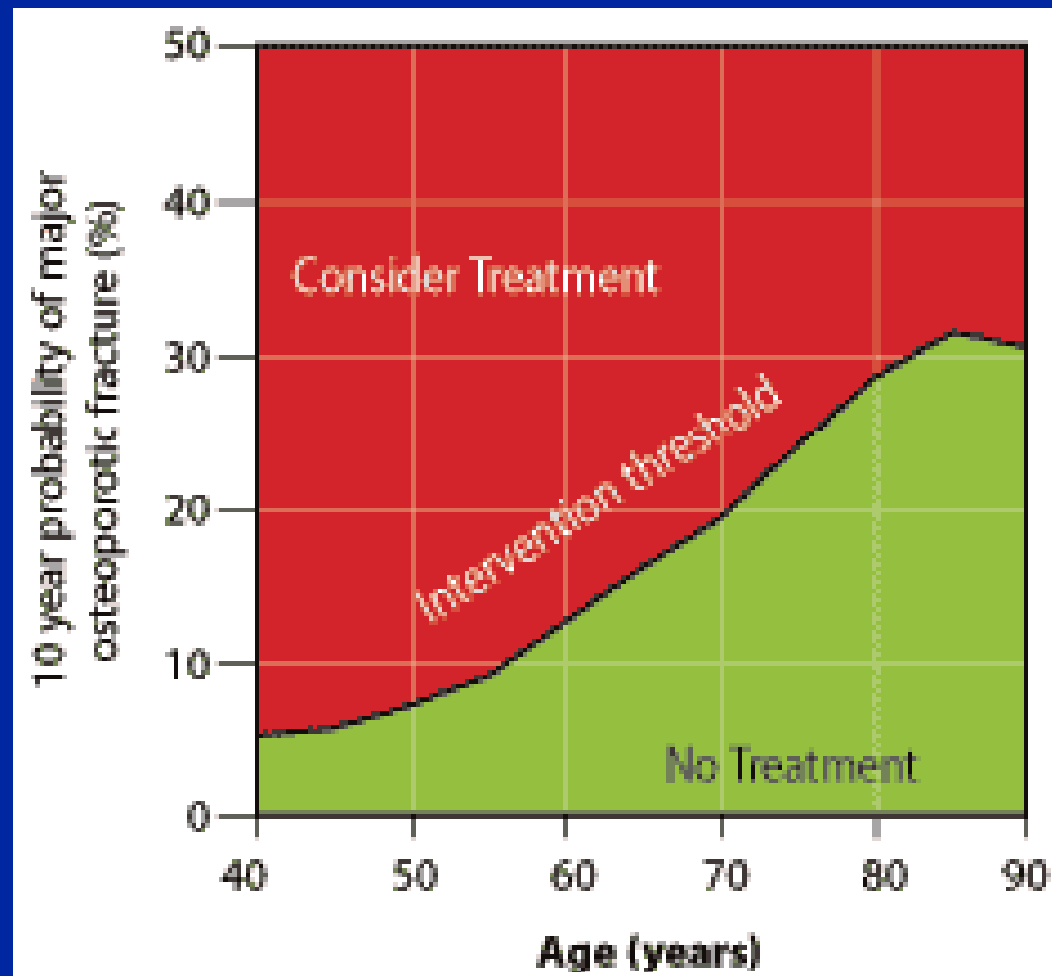
Major osteoporotic

20

Hip fracture

5.7

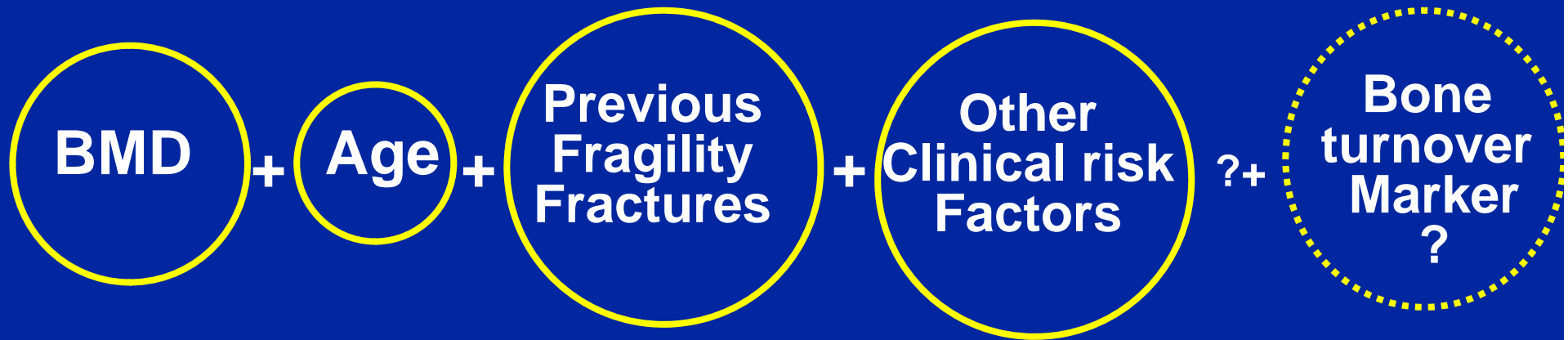
Intervention threshold changes with age



Osteoporosis Guideline Group (NOGG) for the UK.

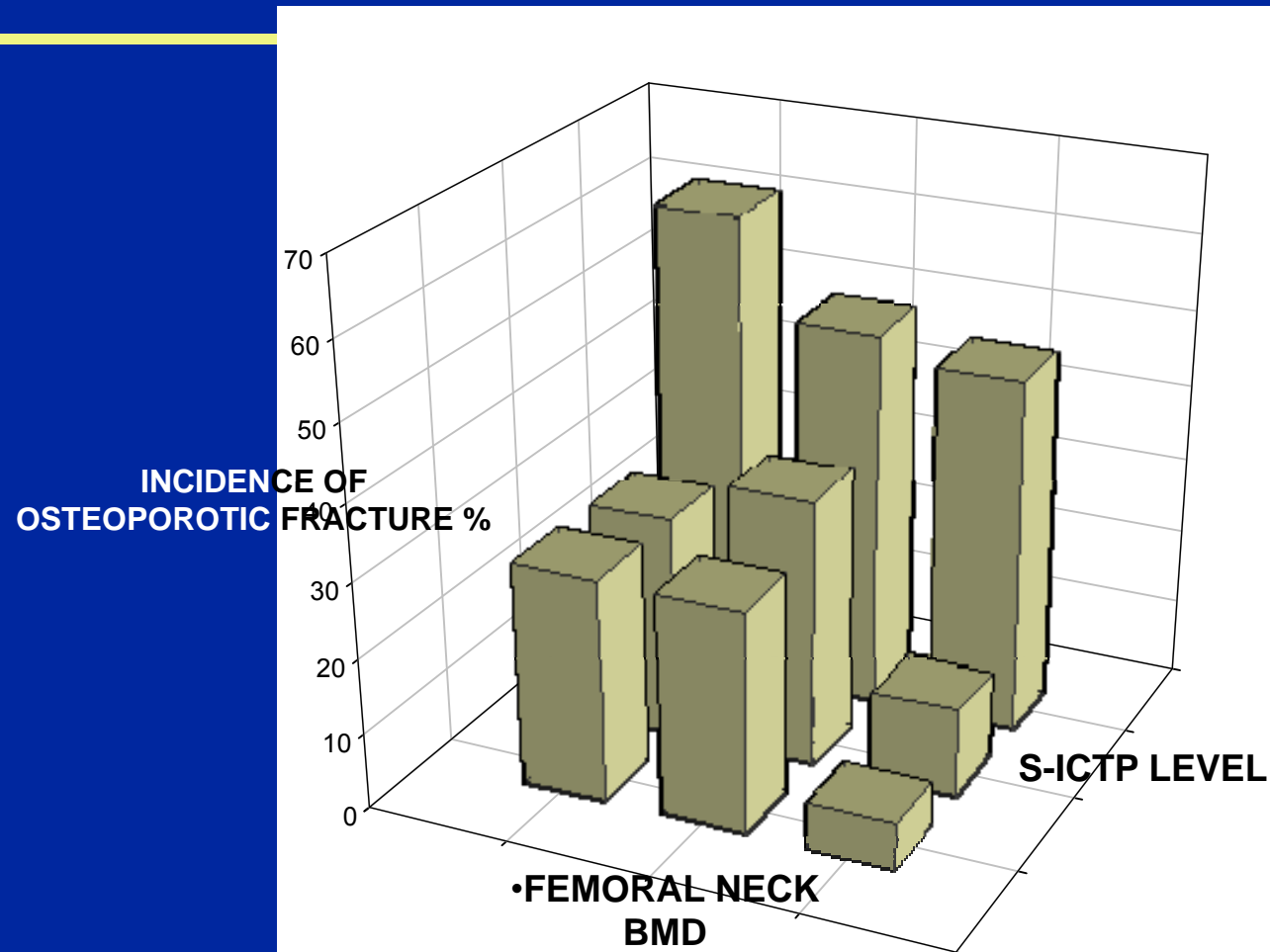
Absolute Fracture Risk Calculation

Is there a role for bone markers?



Calculate absolute fracture risk
(10 Year Probability of a Fracture)

The additive effects of bone turnover marker and BMD on fracture risk



Patients with raised bone resorption markers have an increased risk of future fractures

This is independent of the current BMD

Patients with low BMD and high resorption markers have a 4-5-fold higher risk of future fractures

Case-cohort control study of 151 older men from the Dubbo Study followed prospectively over 6.3 years.

Utility of Biochemical Markers of Bone turnoverin osteoporosis

Vasikaran SD *CRCLS* 2008; 45: 221-258

- ◆ Bone markers show promise for fracture risk assessment and monitoring treatment
- ◆ Proliferation of various bone turnover markers and methods
 - a source of confusion
- ◆ Need for international agreement on a standard bone turnover marker
 - to focus efforts to study the role of bone turnover markers in osteoporosis ...and
 - to arrive at guidelines on their use
- ◆ Bone resorption marker specific to bone collagen
 - NTX or CTX (urine/serum)
- ◆ Bone formation marker
 - serum B-ALP or serum PINP

IFCC Working Group on Bone Marker Standards in Osteoporosis


- ◆ Aim of the WG:

- ◆ To define Bone Marker Standards

- a reference standard bone resorption marker and
- a reference standard bone formation marker

- to be used in all future clinical trials in order to accumulate data to help expedite their incorporation into clinical practice.

- ◆ In collaboration with
the International Osteoporosis Foundation (IOF)



IOF-IFCC Bone Marker Standards WG

October 2010


POSITION PAPER

**Markers of bone turnover for the prediction of fracture risk
and monitoring of osteoporosis treatment:**

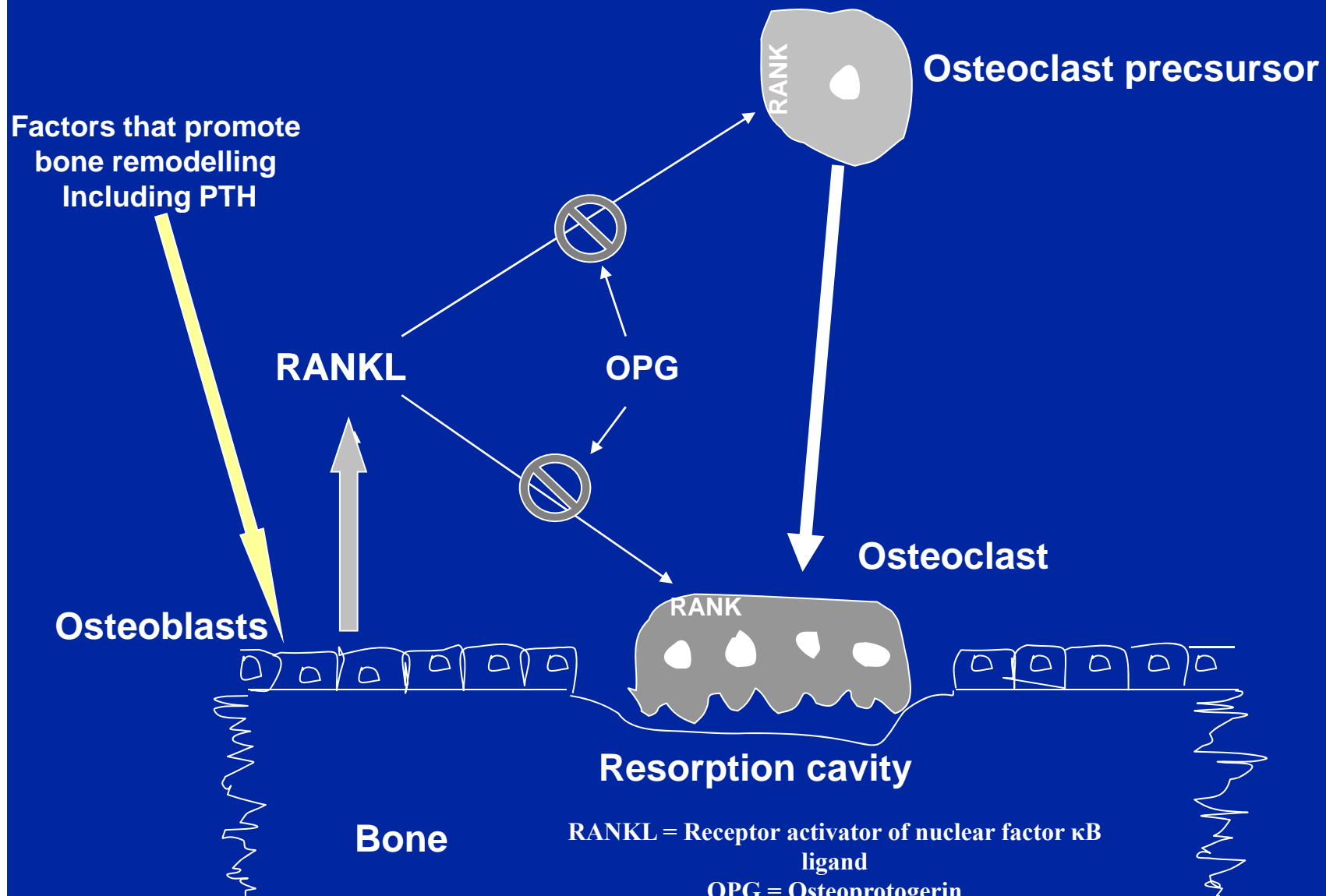
A need for international reference standards

The IOF-IFCC Bone Marker Standards Working Group

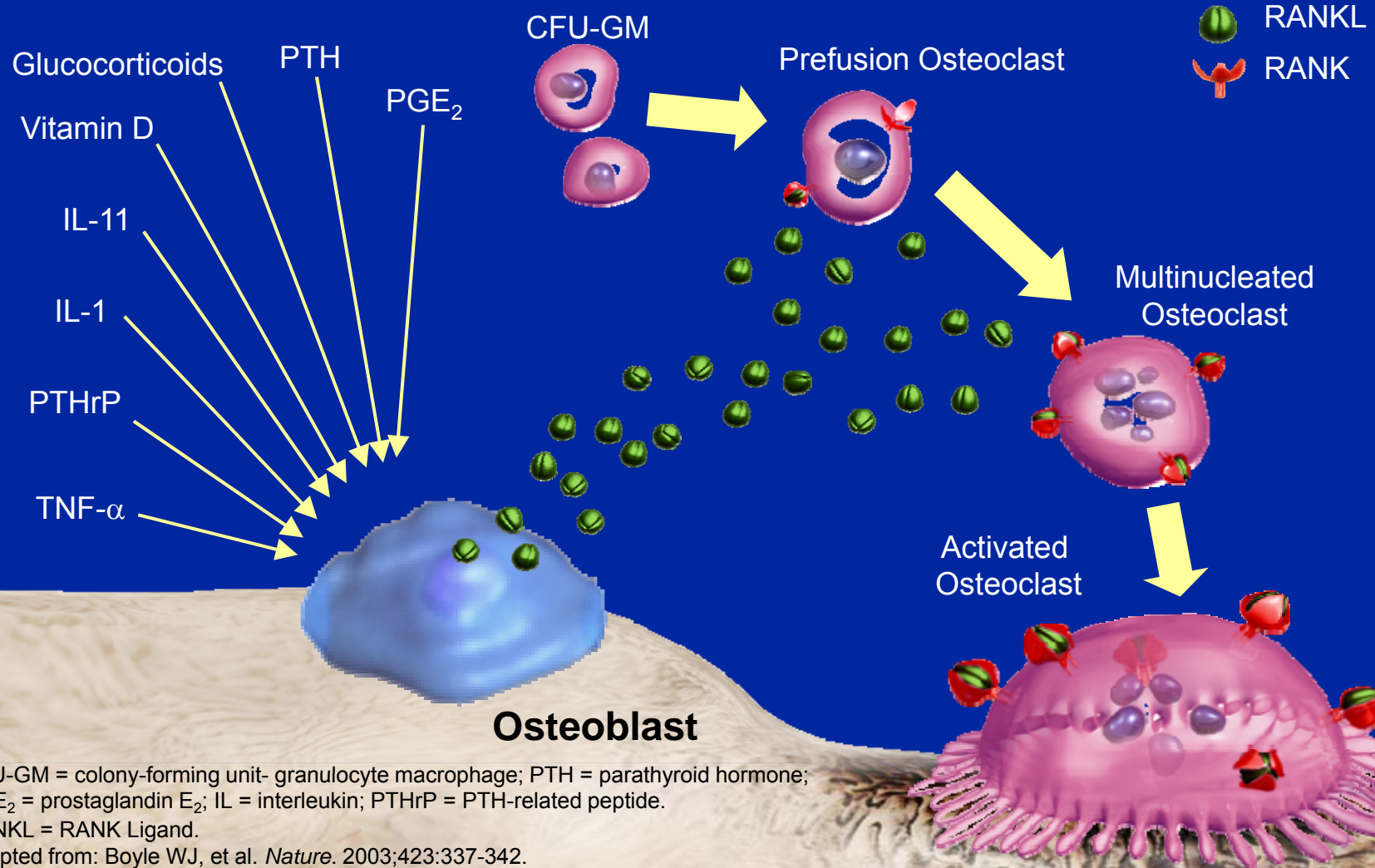
International Osteoporosis Foundation and the International Federation of Clinical
Chemistry and Laboratory Medicine



Regulation of bone remodelling



Factors that Stimulate Osteoblast Expression of RANK Ligand



CFU-GM = colony-forming unit- granulocyte macrophage; PTH = parathyroid hormone; PGE₂ = prostaglandin E₂; IL = interleukin; PTHrP = PTH-related peptide.

RANKL = RANK Ligand.

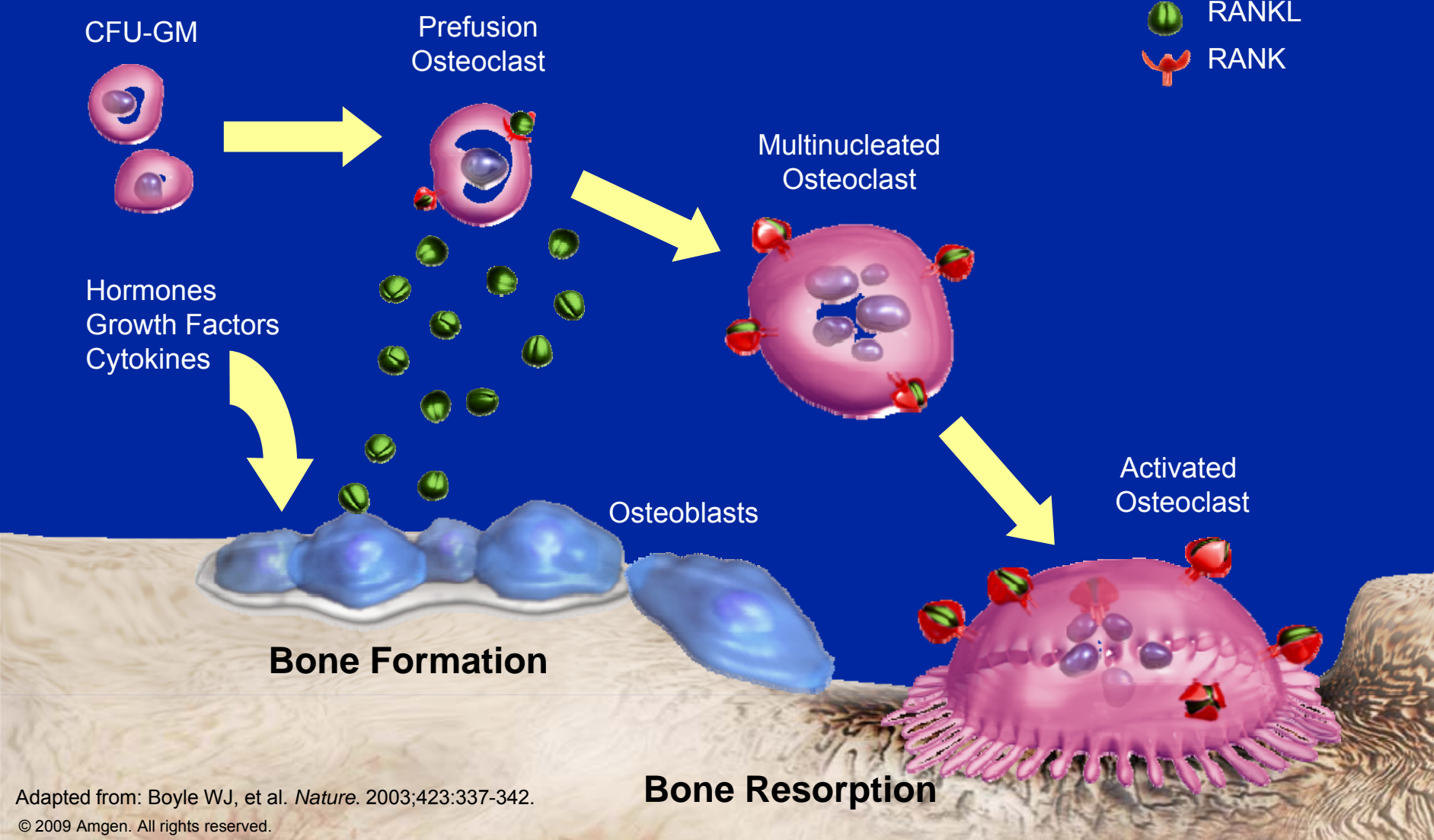
Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342.

Hofbauer LC, et al. *JAMA*. 2004;292:490-495.

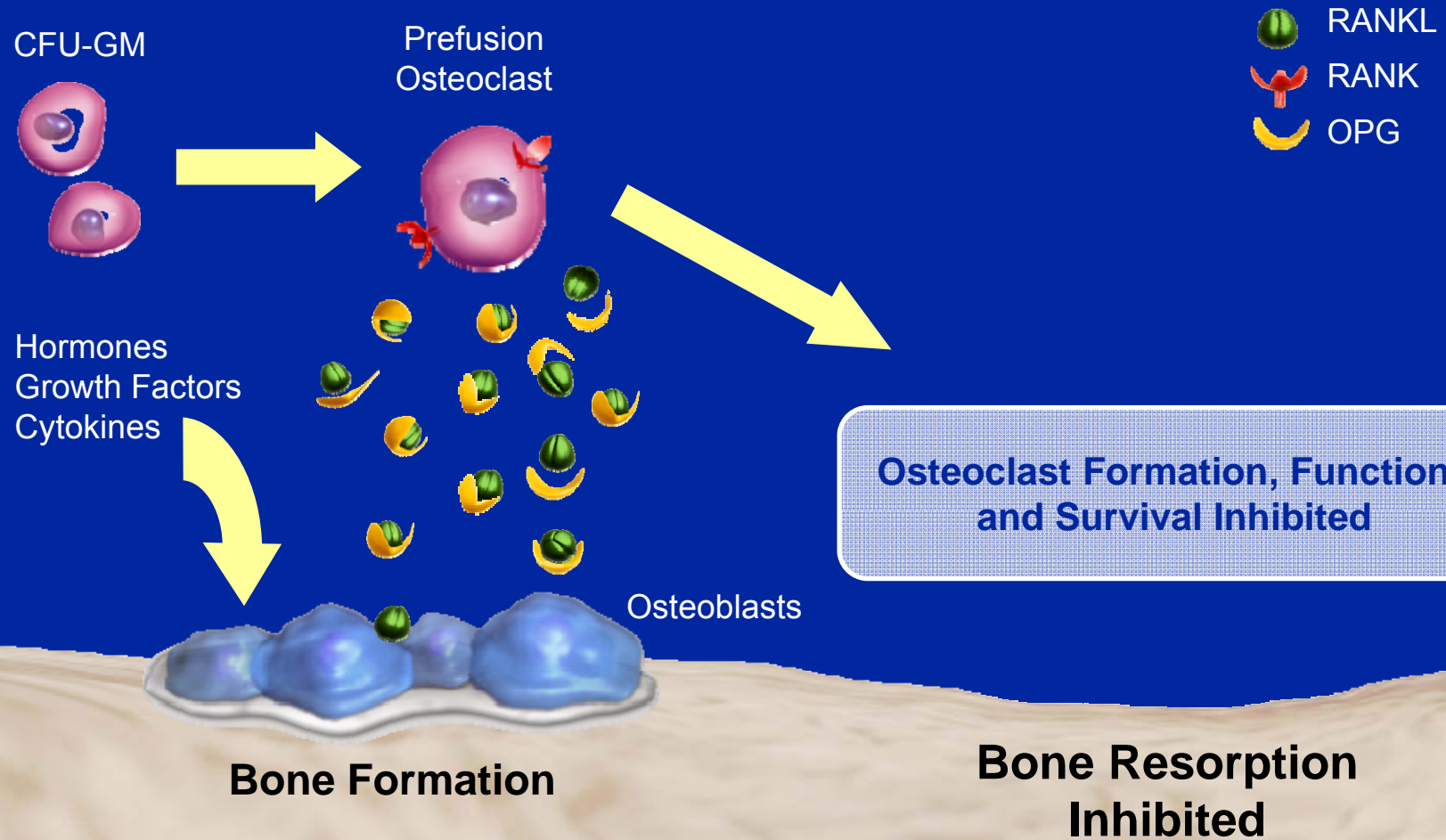
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RANK Ligand

Mediator of Osteoclast Formation, Function, and Survival



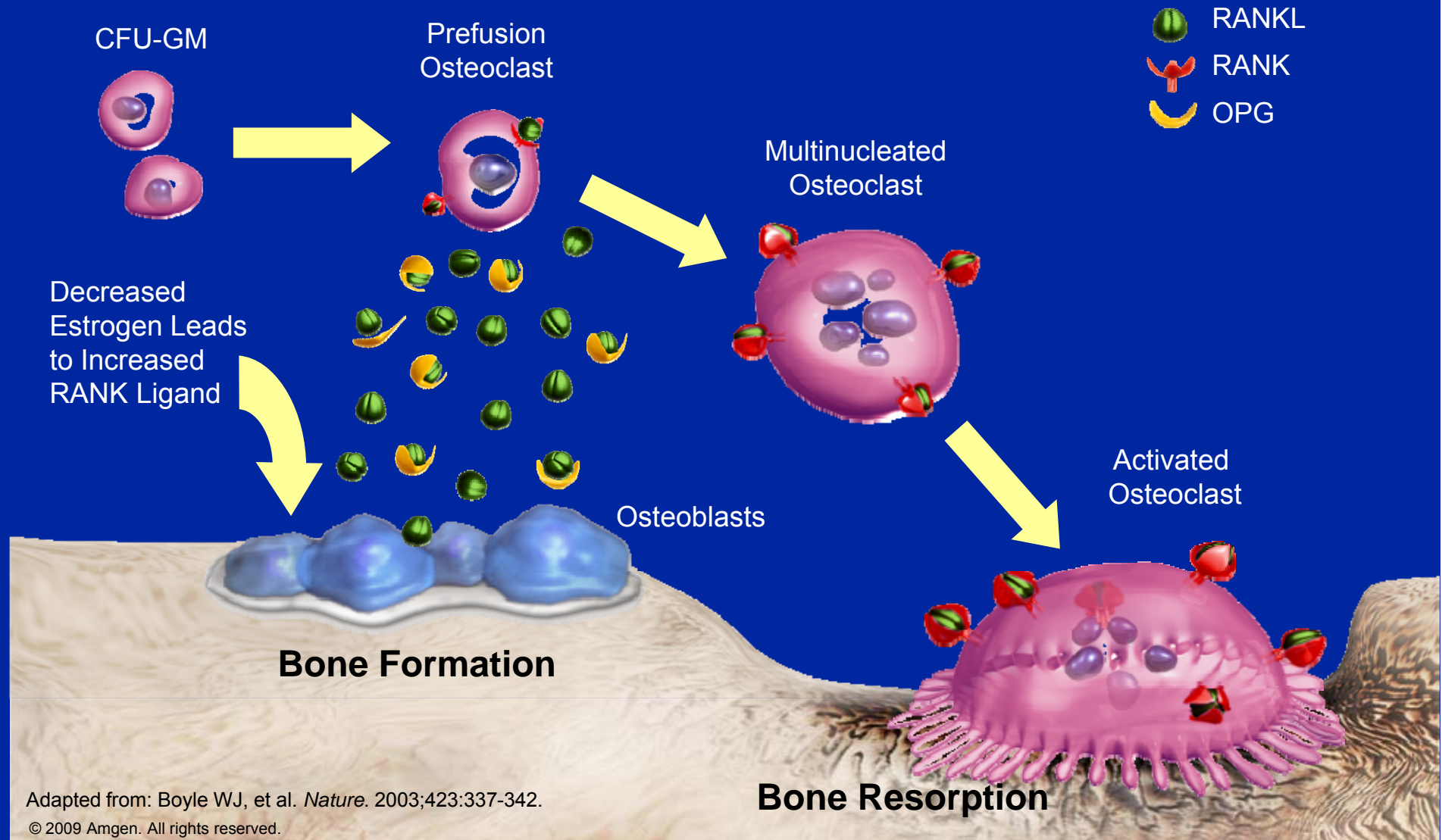
OPG a Decoy Receptor for RANK



Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342.

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Excess RANK Ligand Can Increase Bone Resorption Leading to Osteoporosis



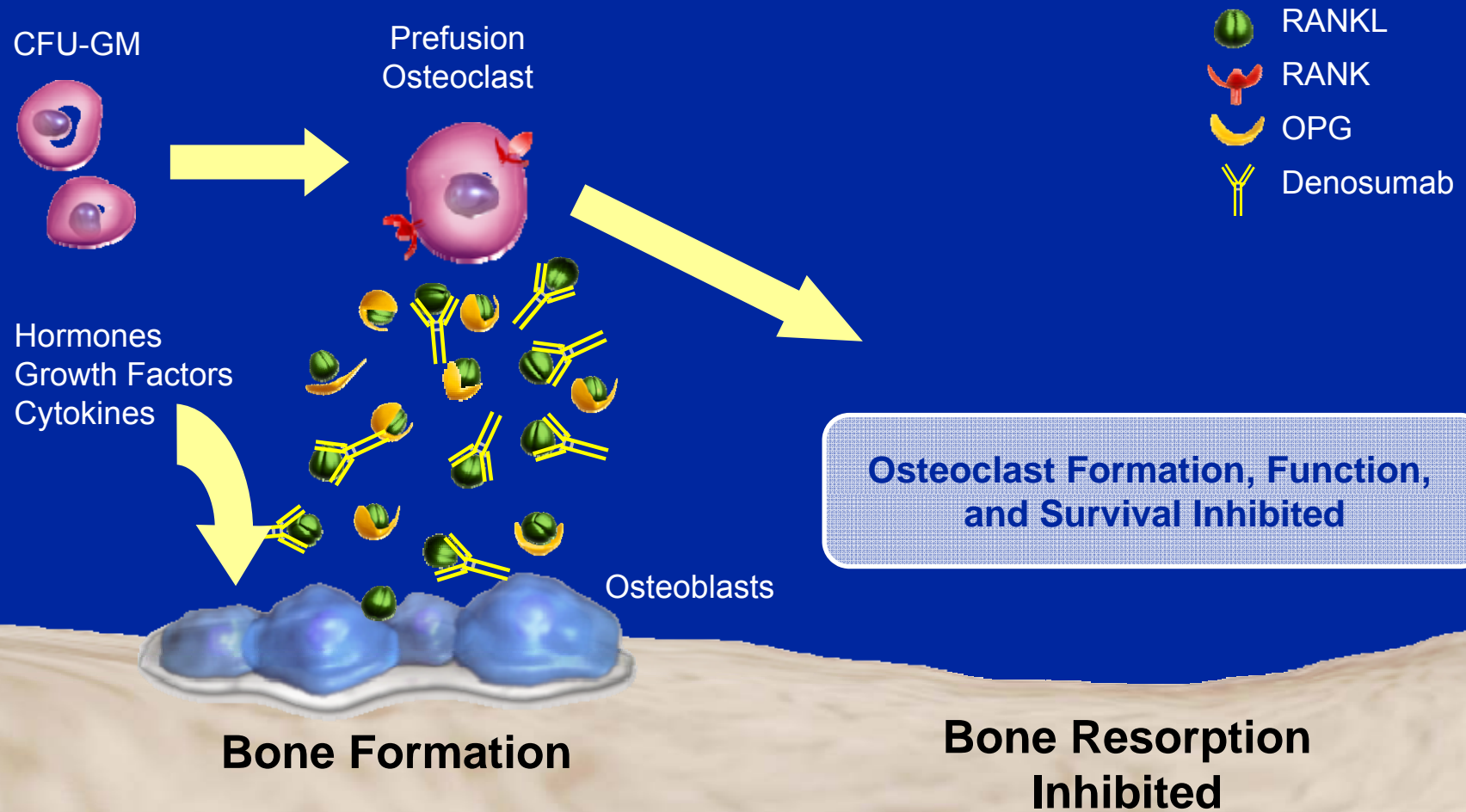
Denosumab

RANK Ligand antibody

- ◆ Fully human monoclonal antibody
 - High specificity for RANK Ligand
 - High affinity for human RANK Ligand

Ig = immunoglobulin; TNF = tumor necrosis factor; TRAIL = TNF- α -related apoptosis-inducing ligand.
Bekker PJ, et al. *J Bone Miner Res.* 2004;19:1059-1066.
McClung MR, et al. *N Engl J Med.* 2006;354:821-831.
Cummings SR, et al. *N Engl J Med.* 2009;361:756-765.

Denosumab Binds RANK Ligand and Inhibits Osteoclast Formation, Function, and Survival



Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342

McClung ER, et al. *N Engl J Med*. 2006;354:821-831.

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The Percent Change in Bone Turnover Markers Over 36 Months With Denosumab

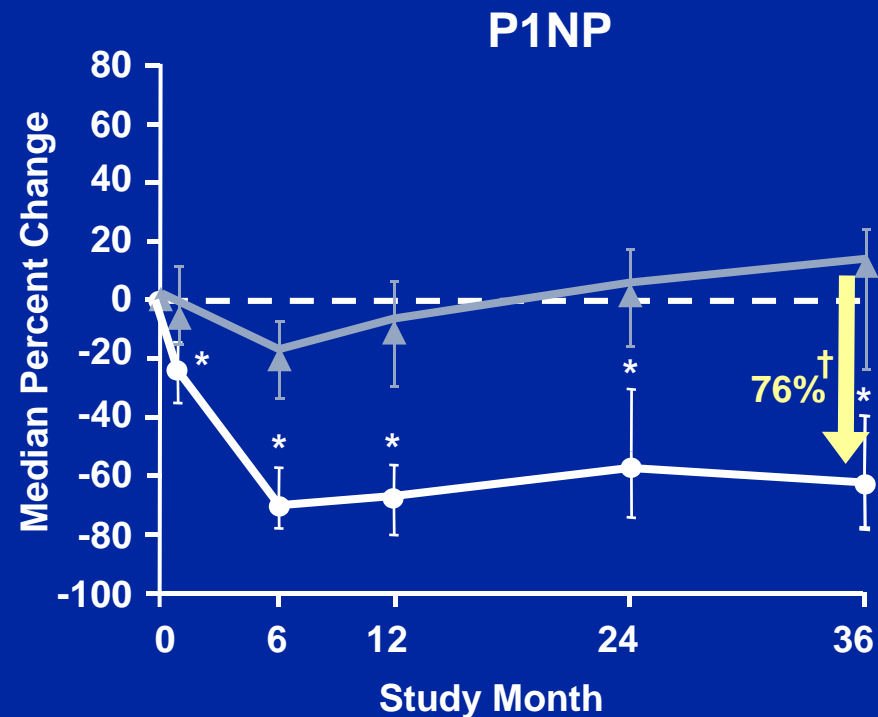
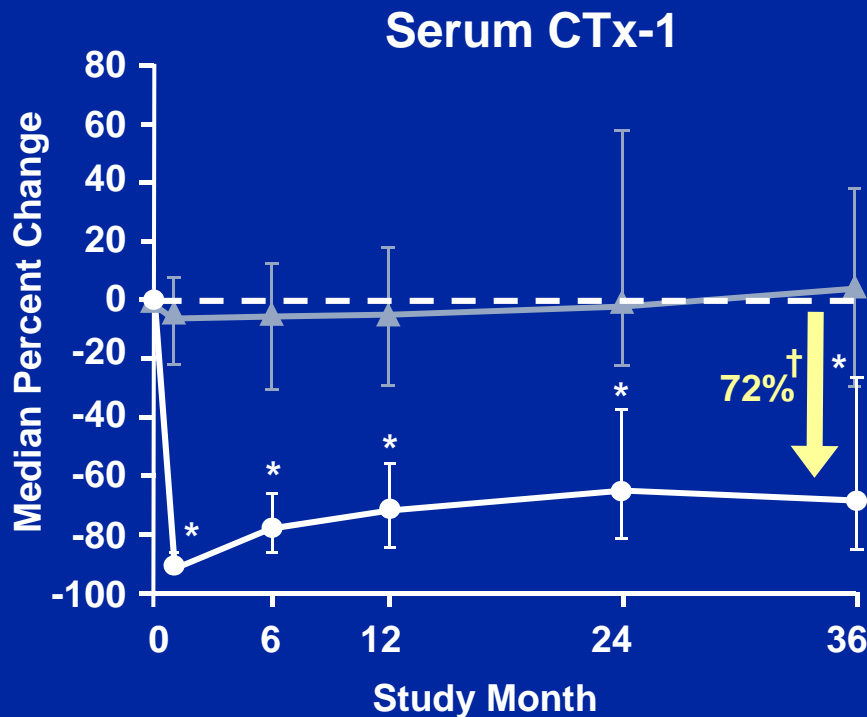
Phase 3: The FREEDOM Trial

Bone Turnover Markers Substudy

n = 160

▲ Placebo

● Denosumab 60 mg Q6M



*P < 0.001 for denosumab vs placebo

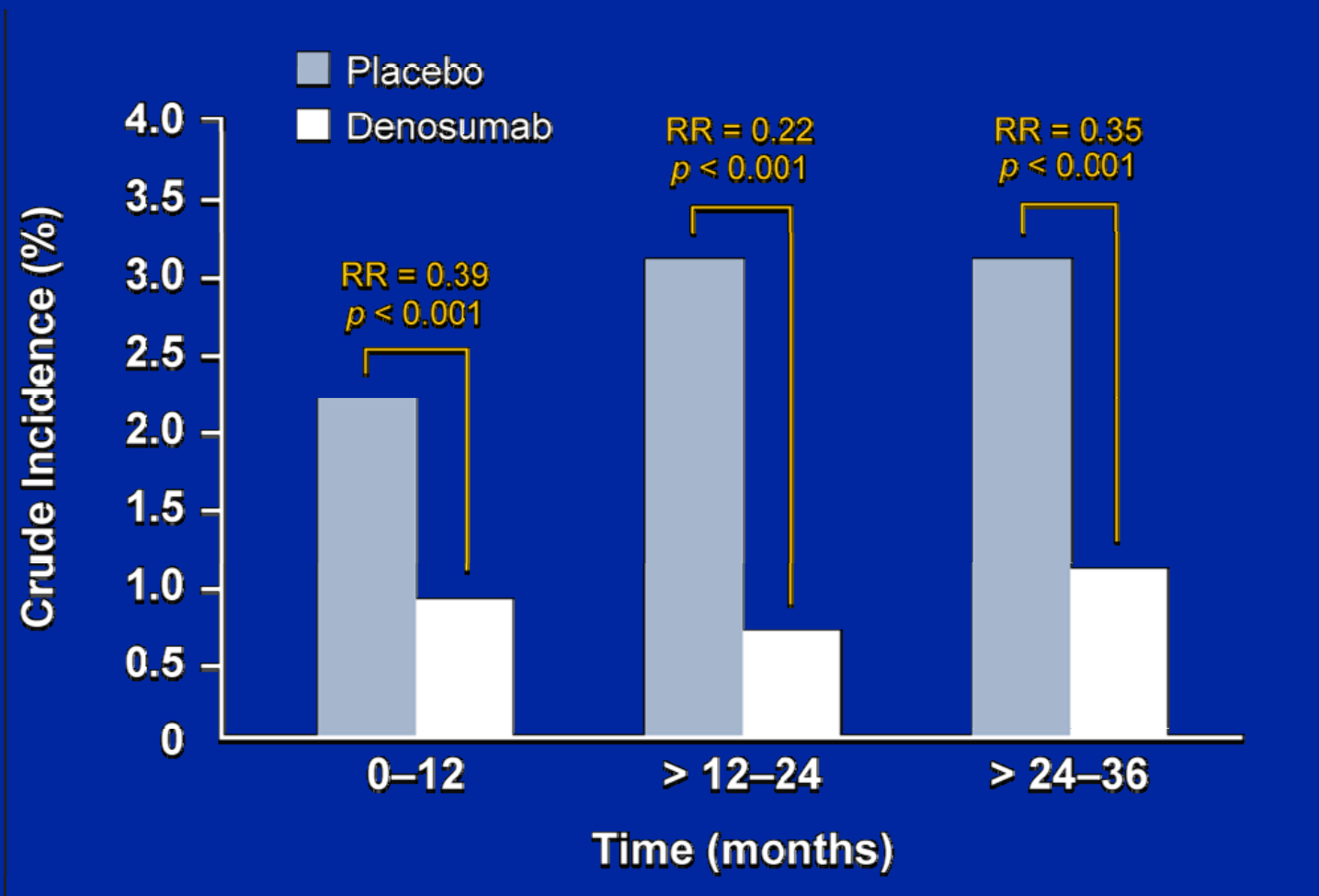
† denosumab group relative decrease vs placebo at month 36

CTx-1 = type 1 C-telopeptide; P1NP = intact N-terminal propeptide of type I procollagen

Cummings SR, et al. *N Engl J Med.* 2009;361:756-765. Copyright © 2009 Massachusetts Medical Society. All rights reserved.

The Effect of Denosumab on New Vertebral Fractures During Each Year of Study

Phase 3: The FREEDOM Trial



Intent-to-treat, last observation carried forward analysis
Cummings SR, et al. *N Engl J Med.* 2009;361:756-765.

Drugs used in osteoporosis treatment

- **HRT**
- **SERM/Raloxifene**
- **Bisphosphonates**
 - Alendronate
 - Risedronate
 - Zoledronic acid
- **Denosumab**

- **Parathyroid hormone (PTH)**

- **Strontium ranelate**