

# **FRACTUURPREVENTIE: VERDIEPENDE SCHOLING VOOR PRAKTIJKONDERSTEUNERS**

16 APRIL 2019

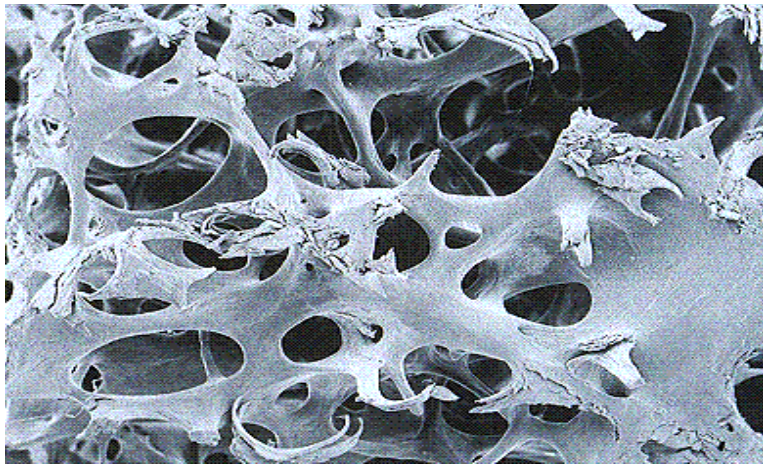
**Behandeling van osteoporose - Math Wijnands**



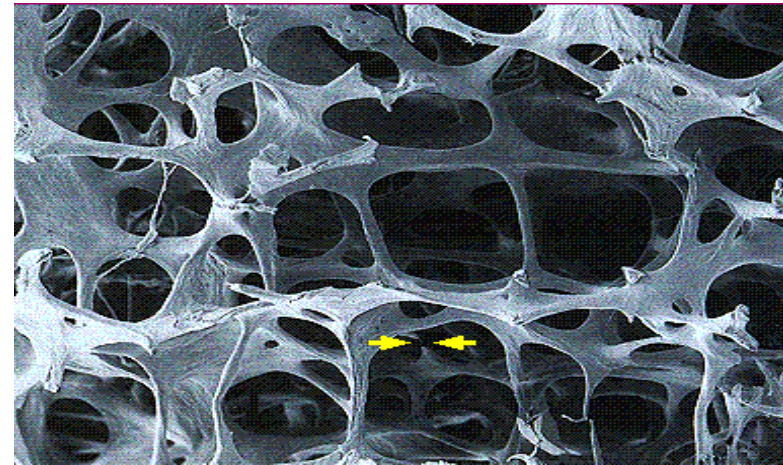


## Definitie osteoporose/botontkalking

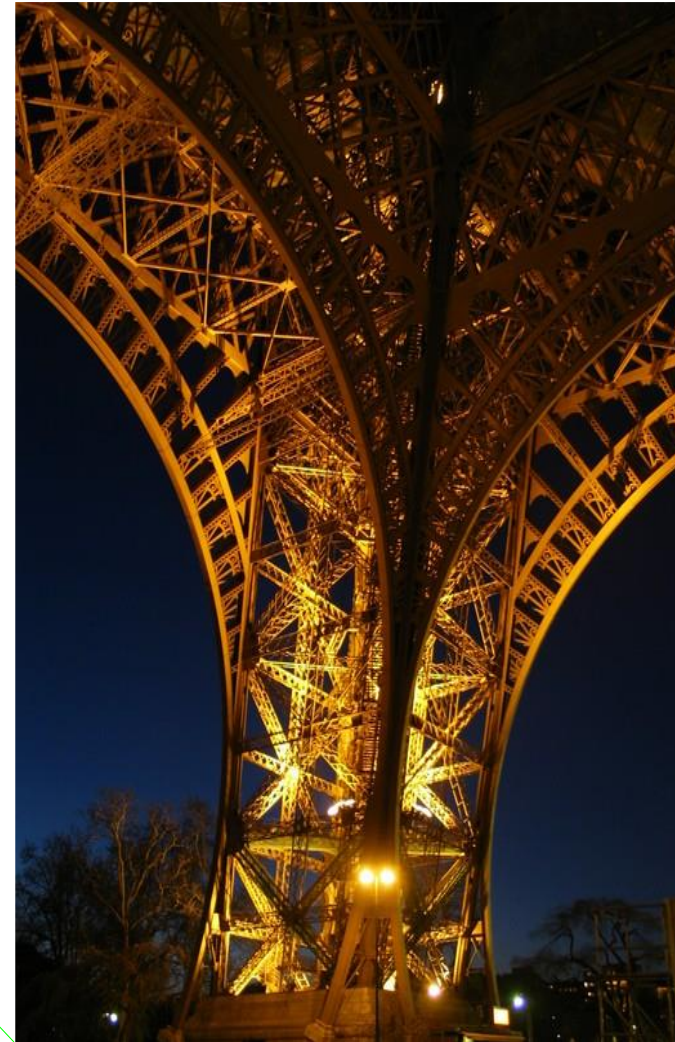
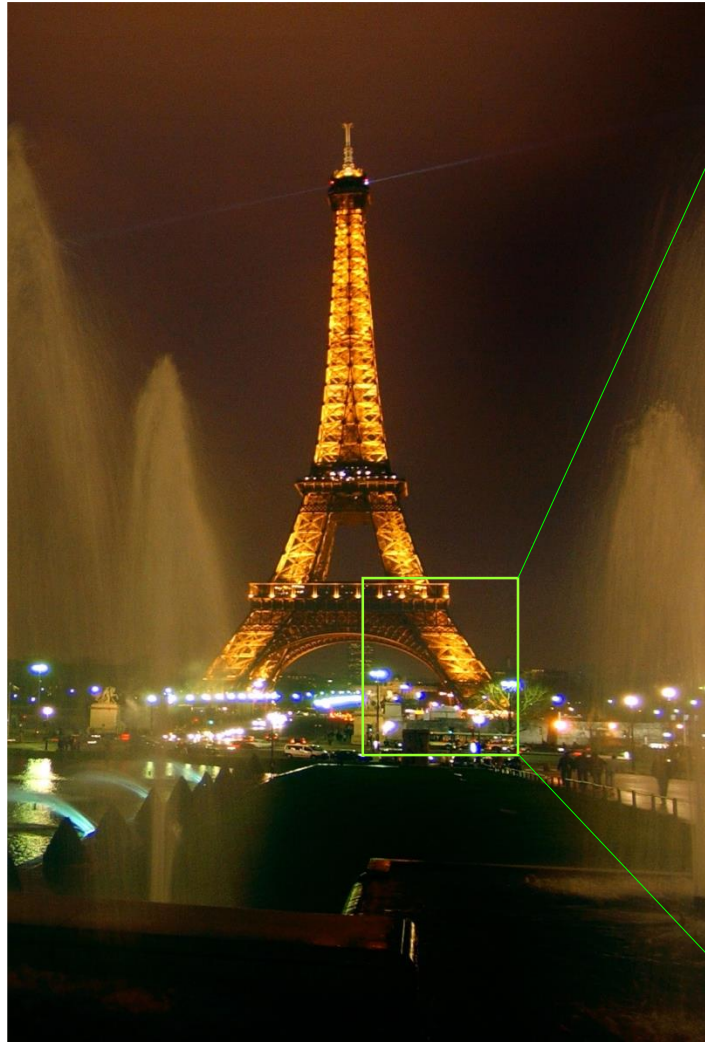
Een systemische aandoening van het skelet die wordt gekarakteriseerd door een lage botmassa en verlies van de microarchitectuur van het bot, met als gevolg een toegenomen risico op fractures.



Normaal



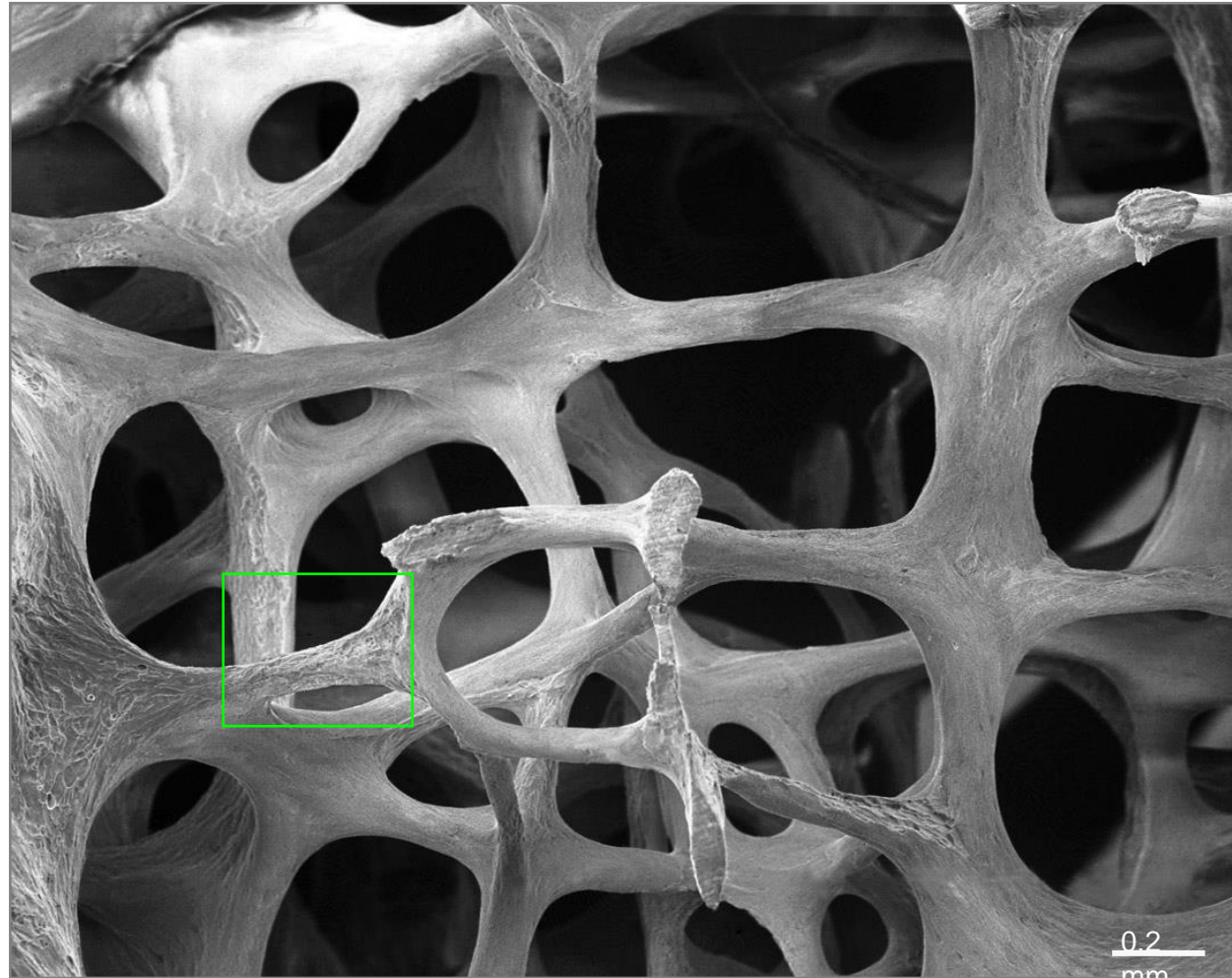
Osteoporose



The Eiffel Tower resists to mechanical stress thanks to its strong construction

This construction consists of an optimal micro architecture

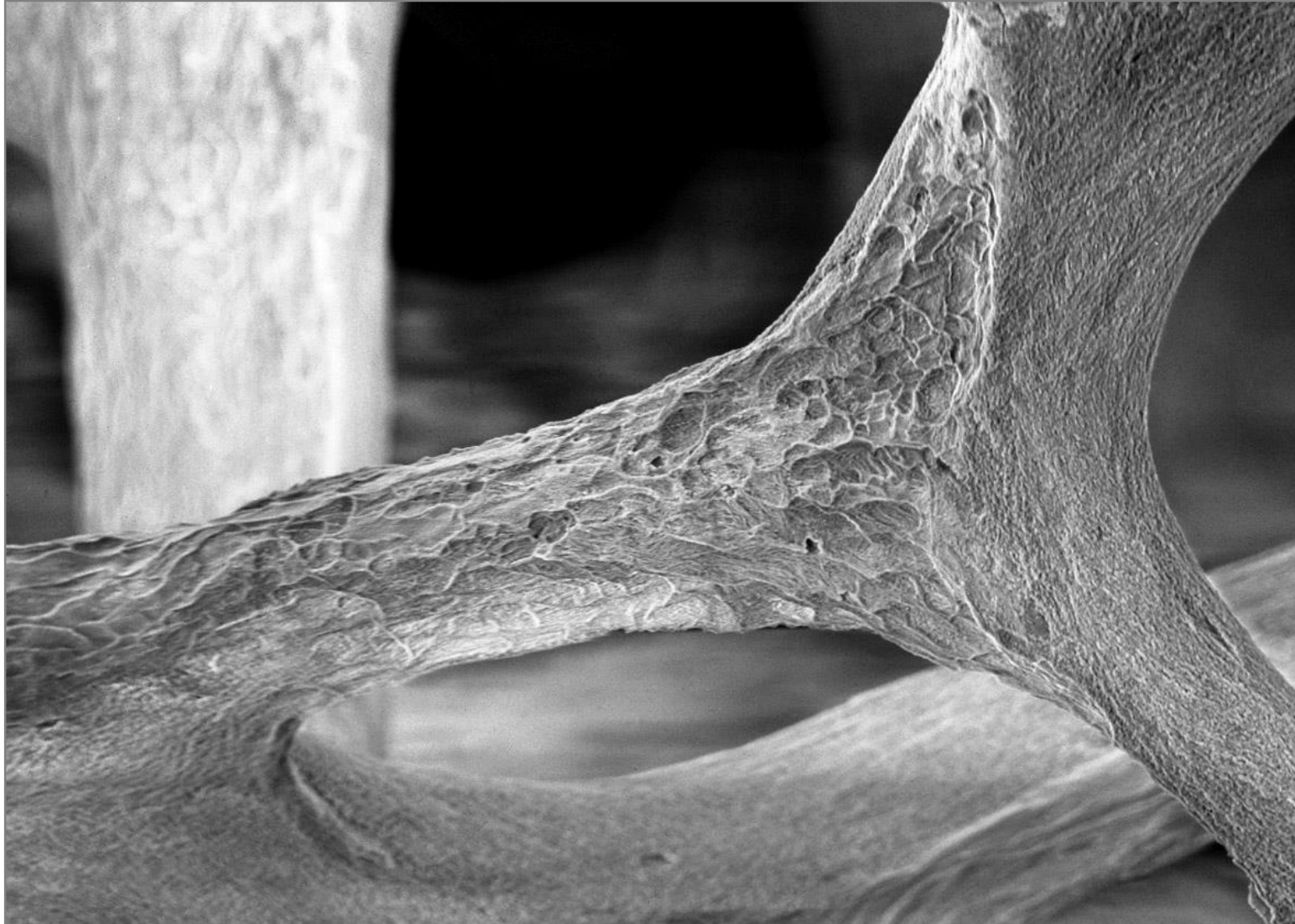
## Bot elektronenmicroscopie I/II



Osteoporotische bot architectuur in de 3<sup>e</sup> lumbale vertebra van een 71 jr oude vrouw

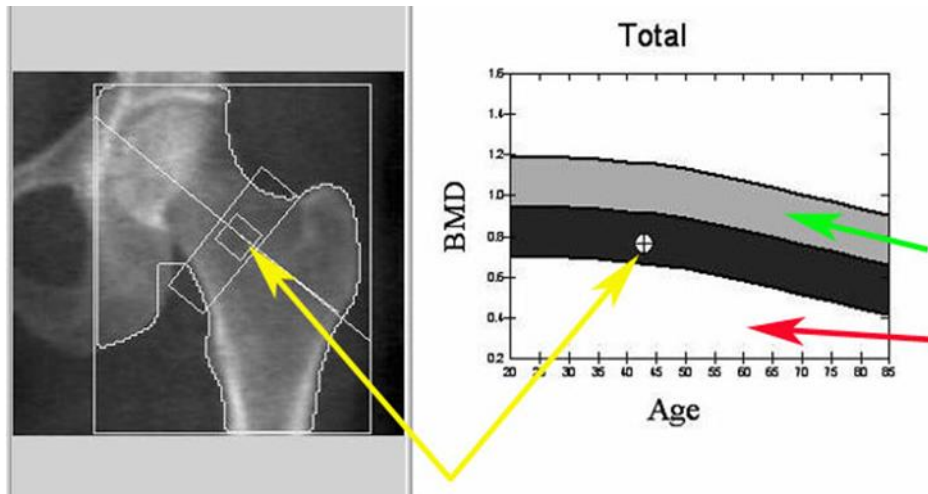
*Merg en andere cellen verwijderd om bot bloot te stellen*

## Bot elektronenmicroscopie II/II

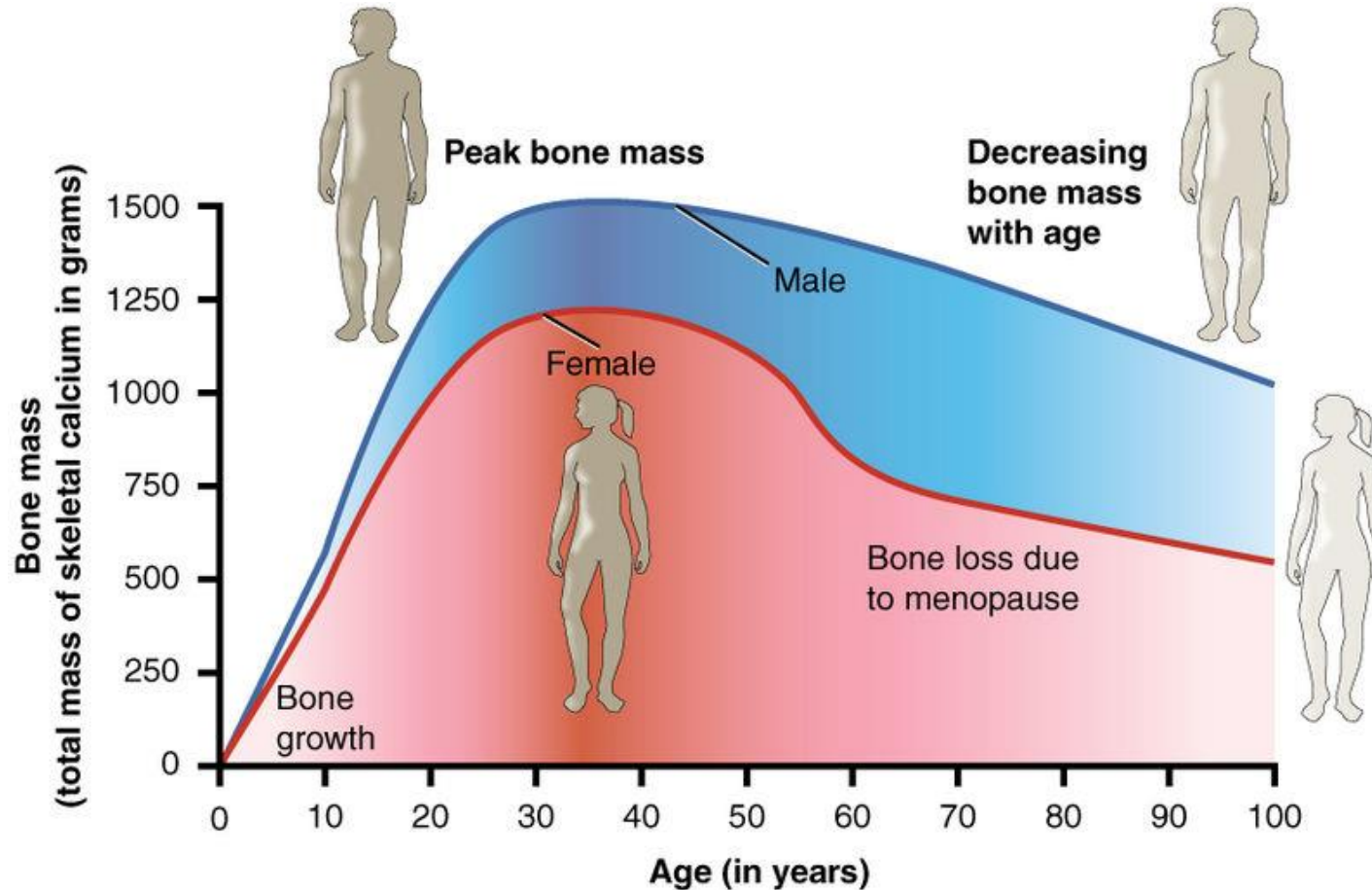


# DEXA: Dual-energy X-ray absorptiometry

- 2 rontgen stralen van verschillend energie level, verschil in absorptie maat voor BMD
- T-score: SD, vergelijking met peak bone mass
- VFA: vertebral fracture assessment



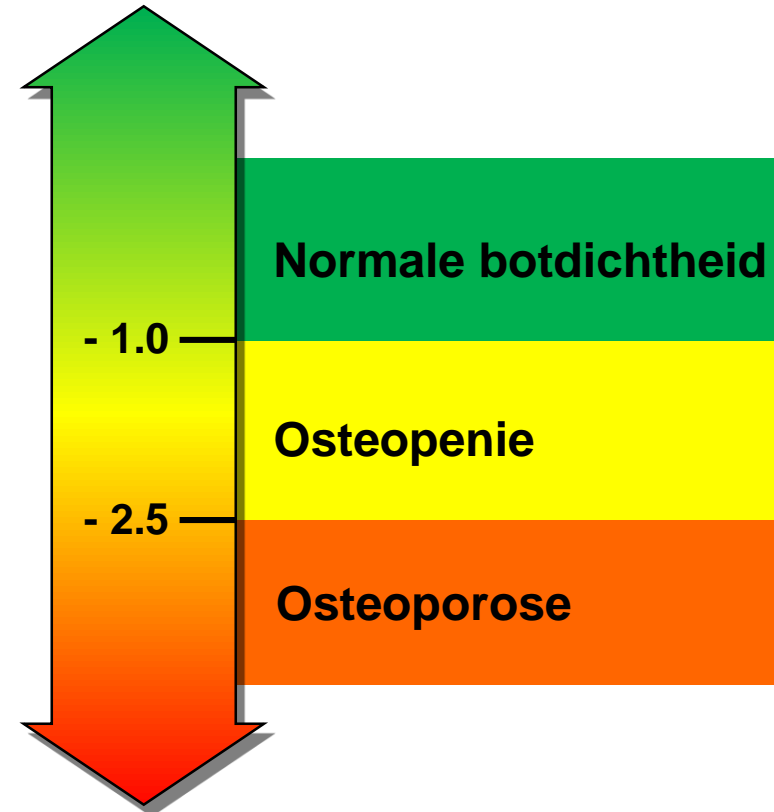
# Botdichtheid (BMD) en leeftijd



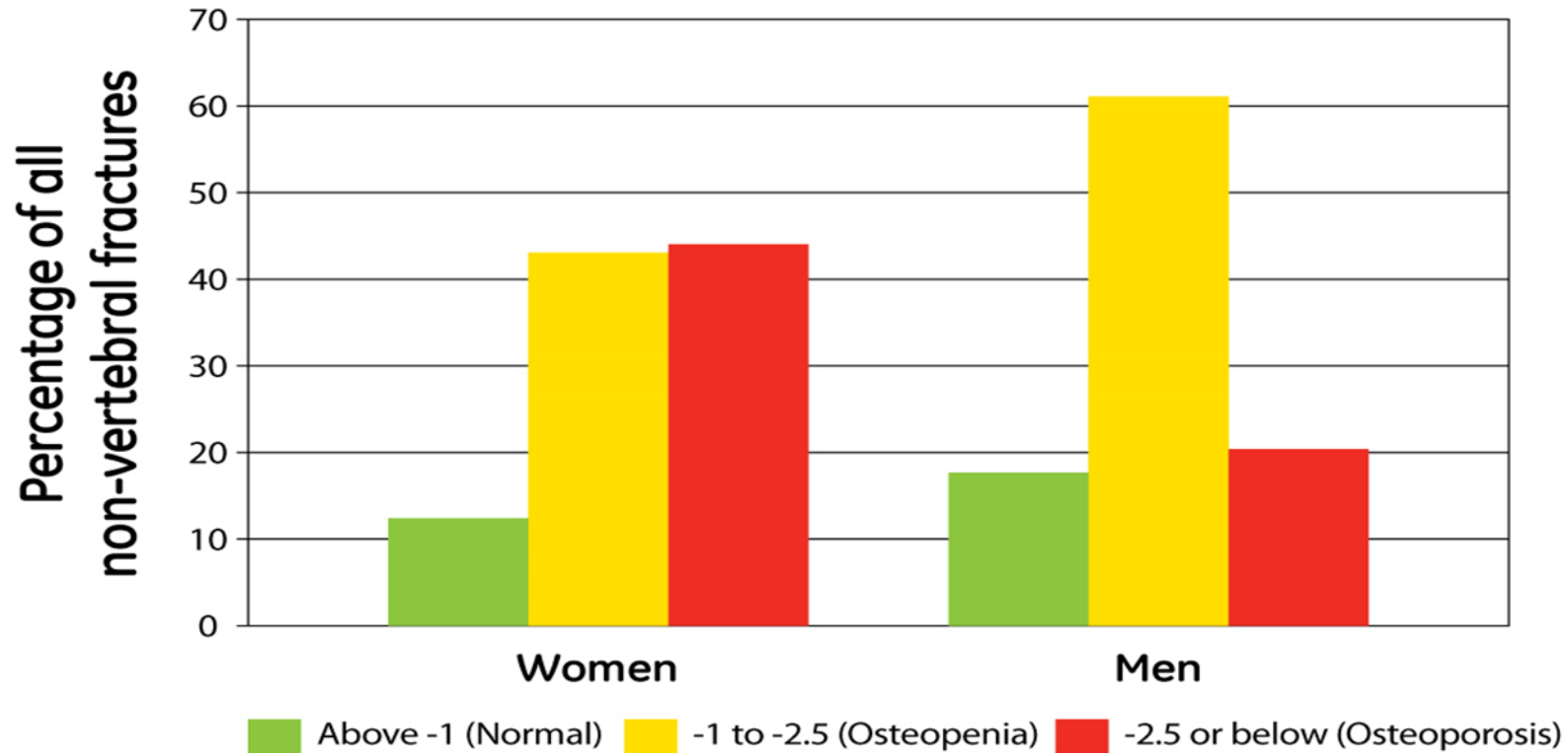


## Diagnose osteoporose middels DXA: definitie van de WHO

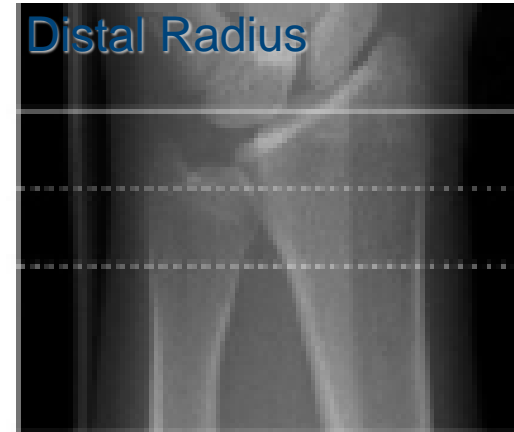
- DXA = **D**ual Energy **X**-ray **A**bsorptiometry
- Wordt in de dagelijkse praktijk gebruikt om de diagnose te stellen
- Meting van de botmineraaldichtheid, m.n. wervelkolom en heup
- T-score geeft de afwijking in standaarddeviaties aan ten opzichte van de gezonde populatie met een piekbotmassa



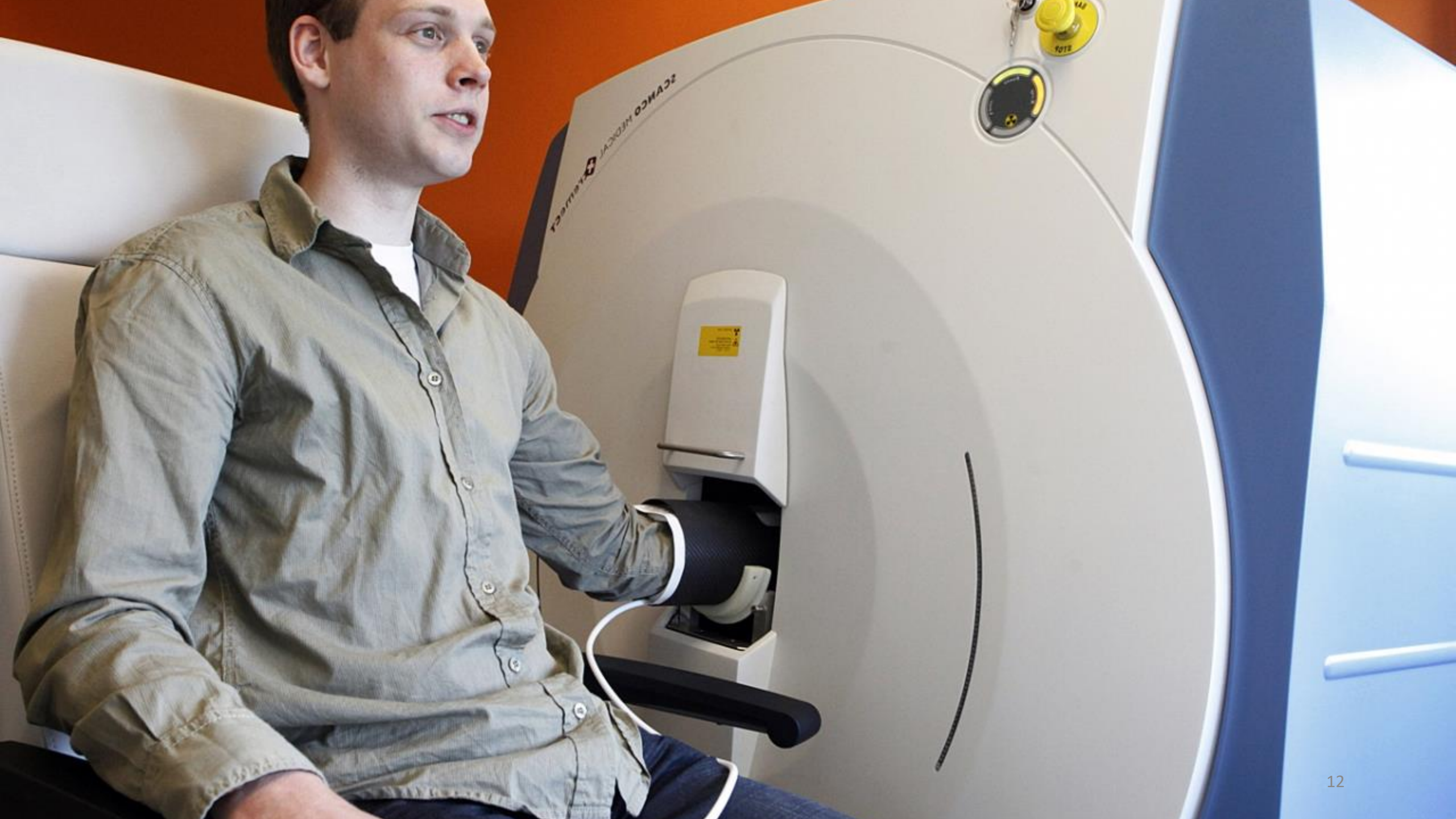
## Prevalence of fractures by osteoporosis risk categories



# In vivo evaluation of Bone Micro-structure by high-resolution HR-pQCT

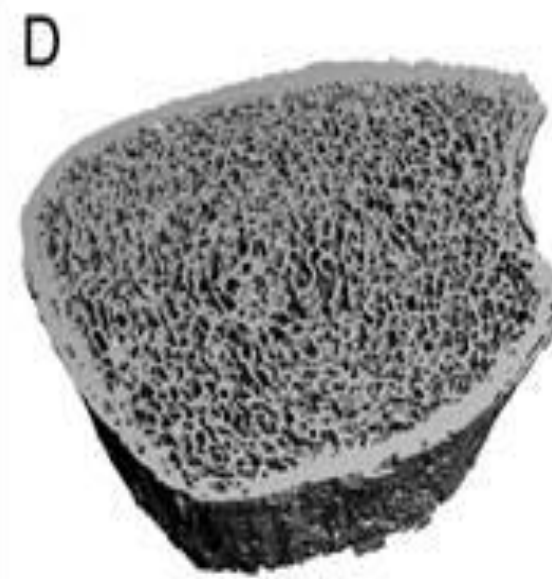
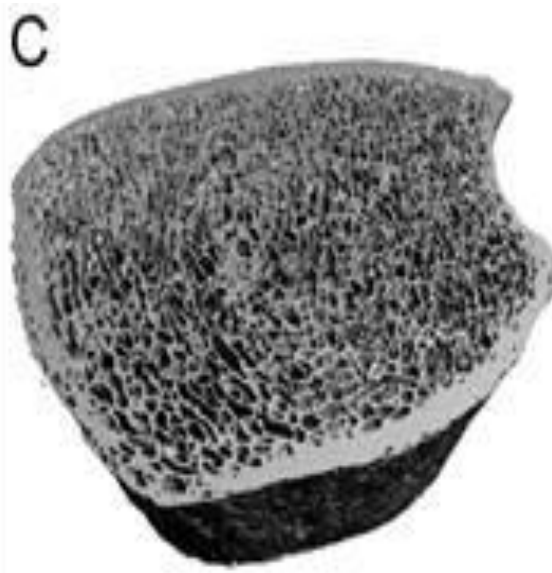
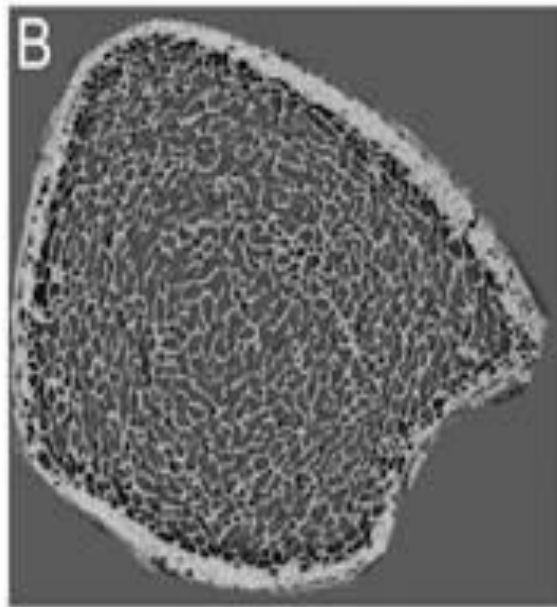
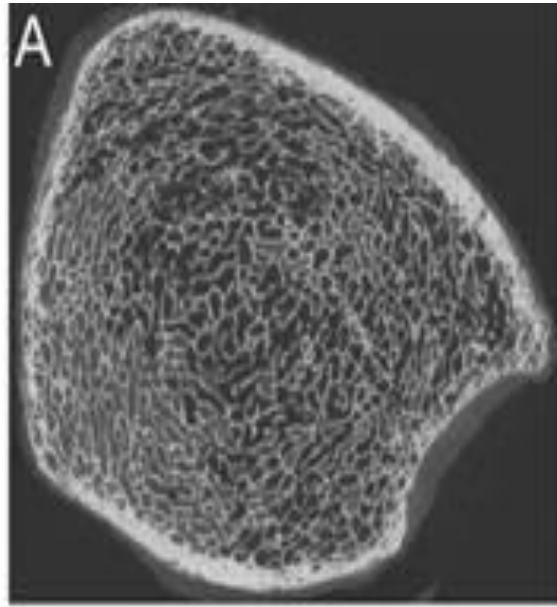


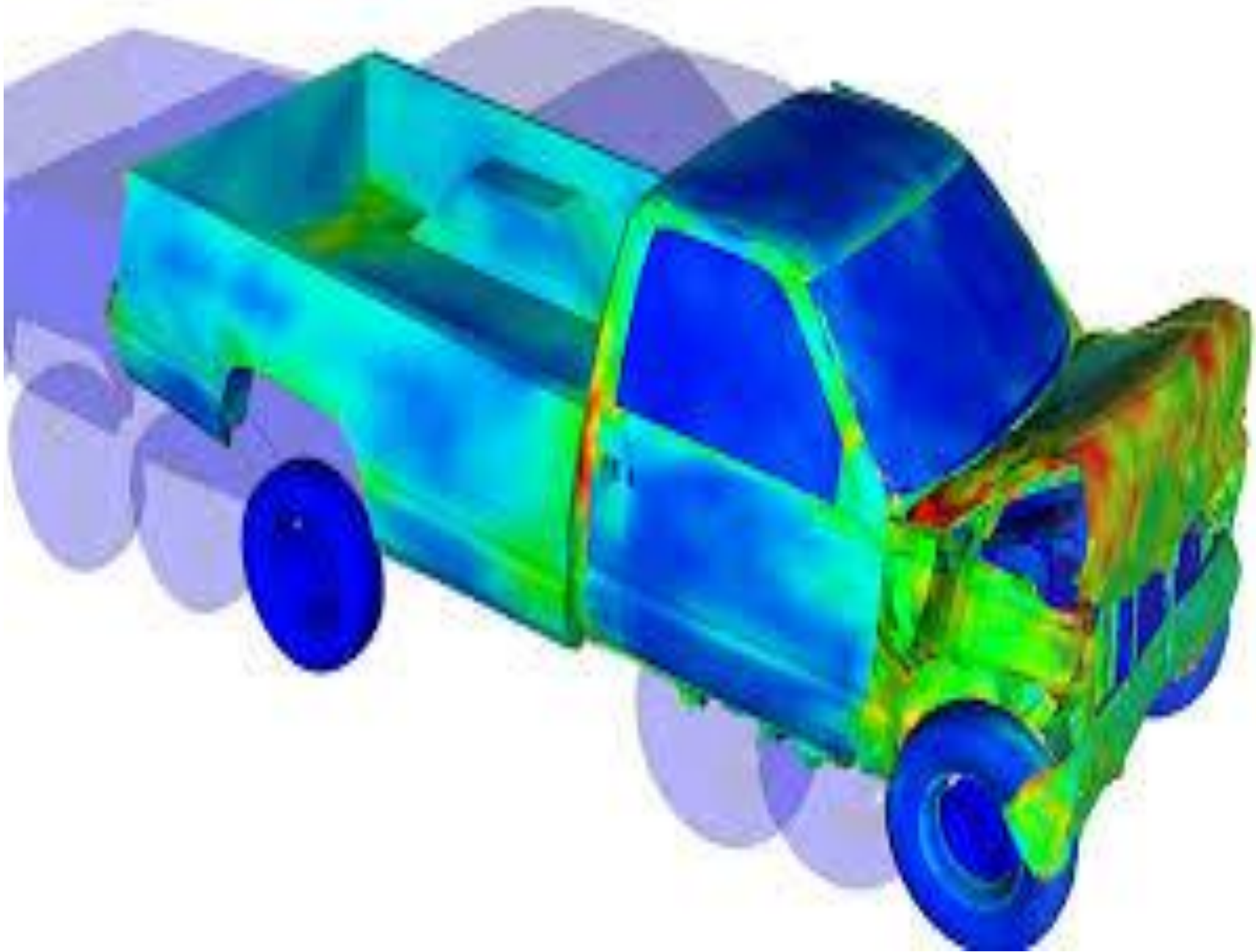
- 82  $\mu\text{m}$  resolution (HR-pQCT)
- 2.6 min acquisition time
- $< 5\mu\text{ Sv}$  radiation dose

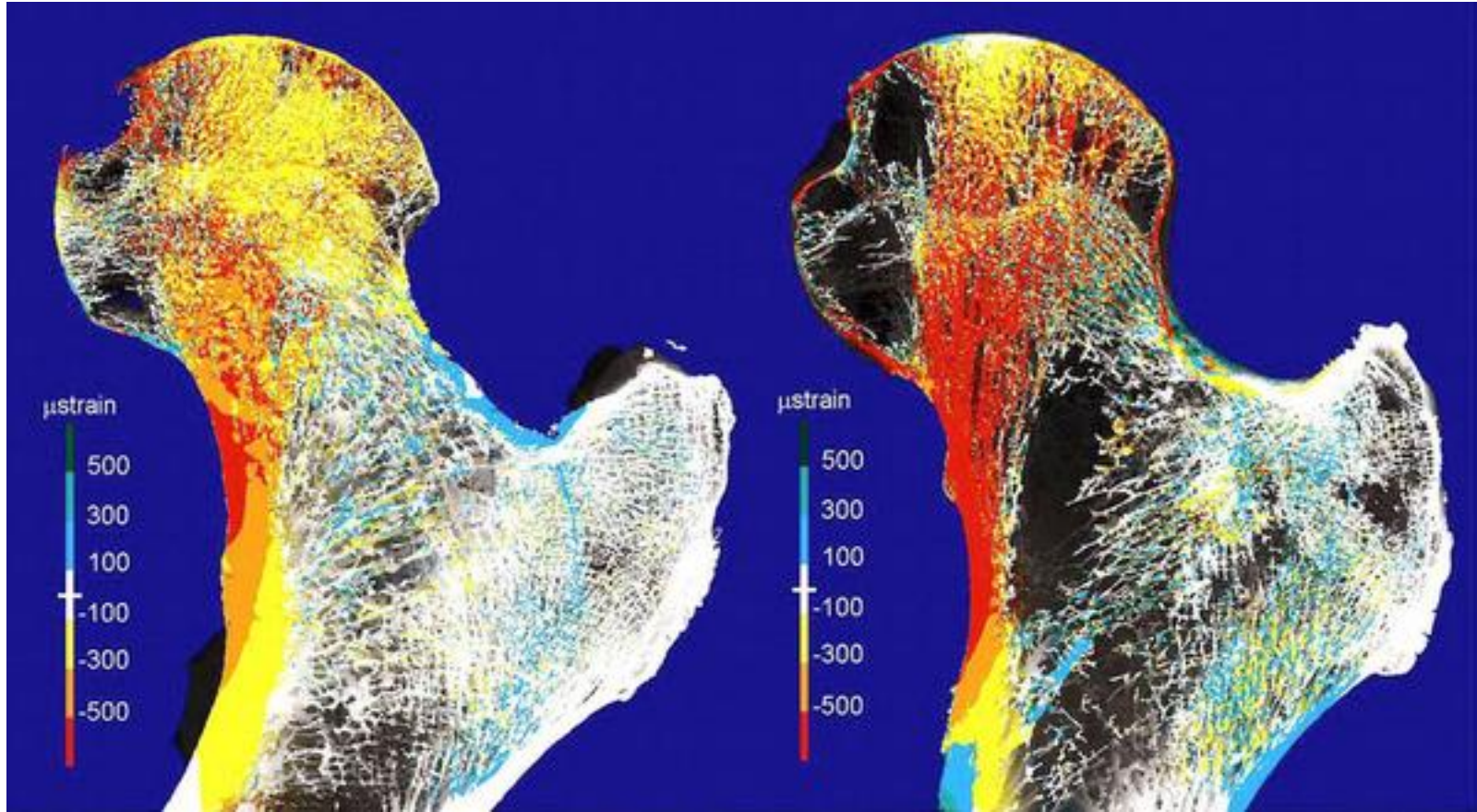


SCANCO MEDICAL SYSTEMS











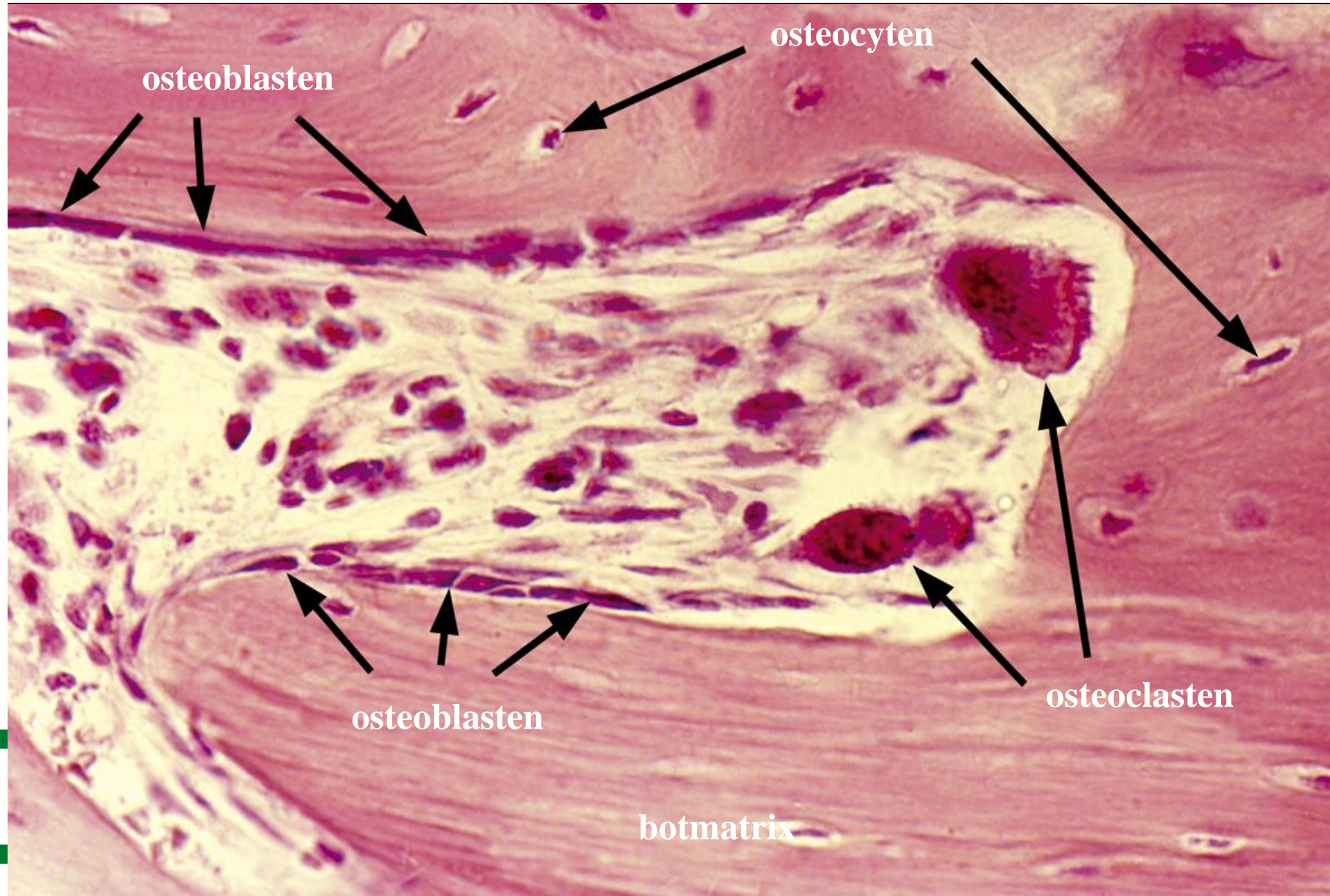
# Fysiologie van het bot



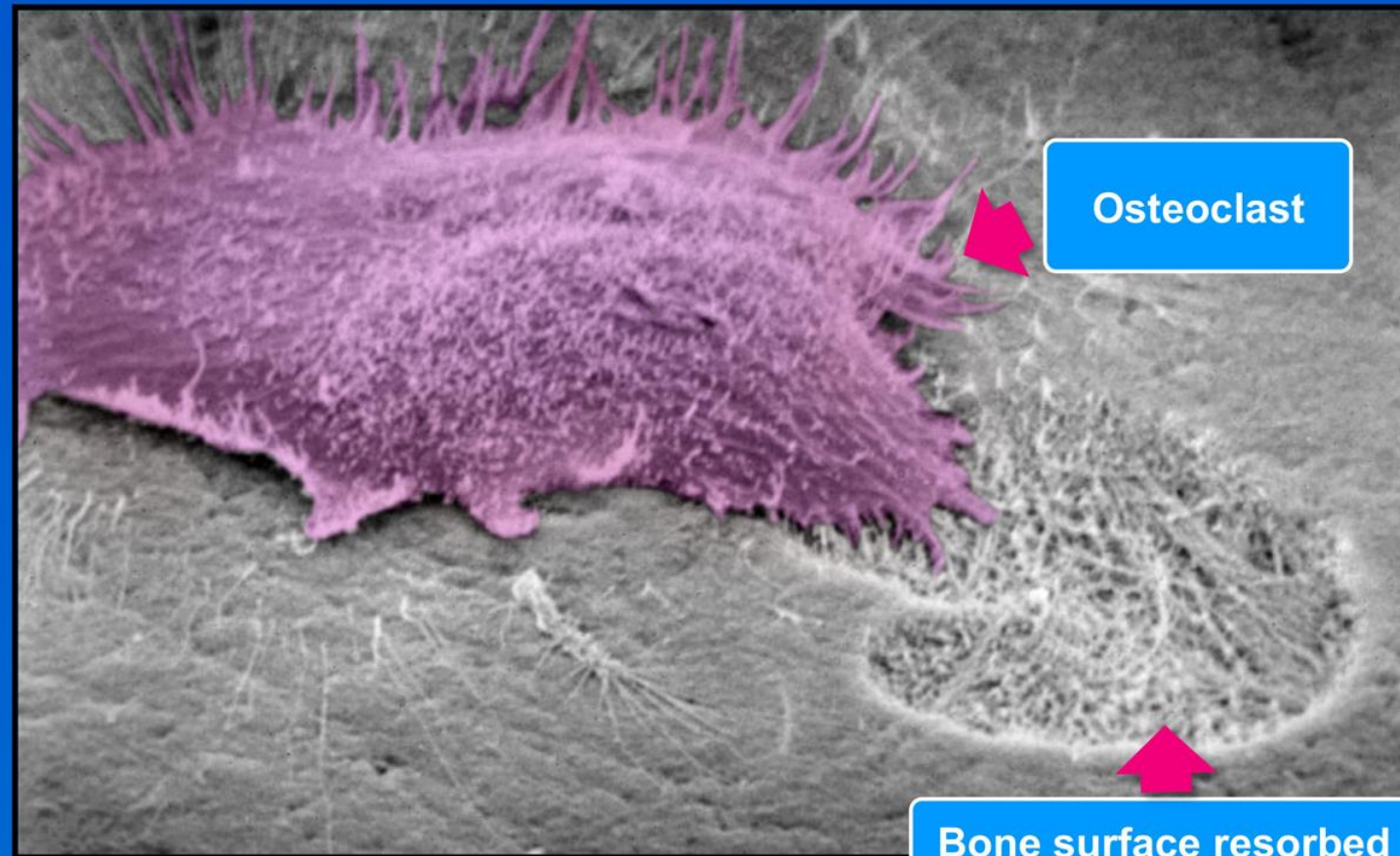
# Werk aan de weg



# Bot is levend, dynamisch weefsel



# Osteoclasts Are the Cells that Resorb Bone

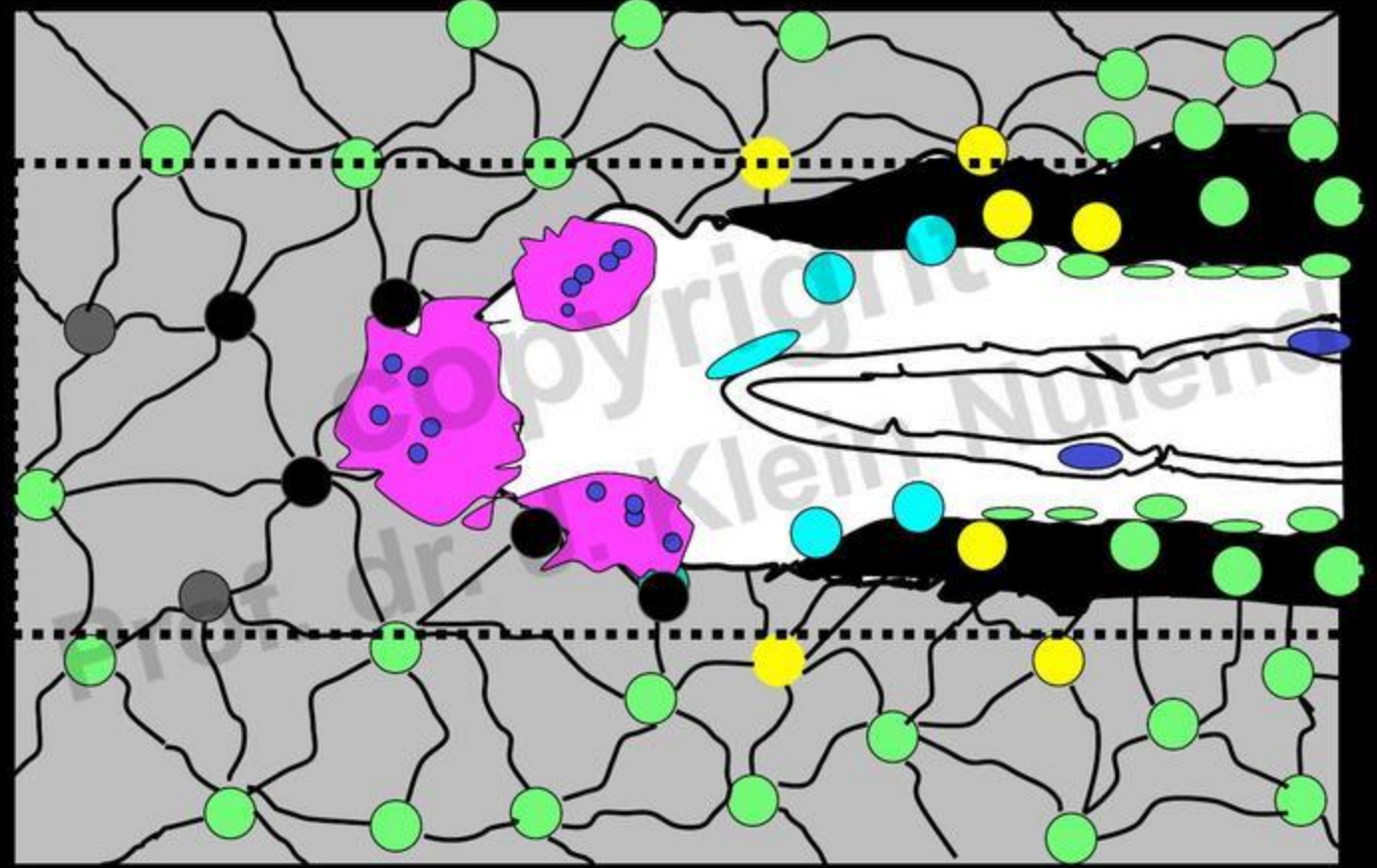


Osteoclast

Bone surface resorbed  
by osteoclast

Adapted from: [http://www.brsoc.org.uk/gallery/arnett\\_osteoclast.jpg](http://www.brsoc.org.uk/gallery/arnett_osteoclast.jpg).  
Electron micrograph photo reproduced with permission. © Tim Arnett, The Bone Research Society.

# ADAPTIVE BONE REMODELING



Macrofagen of  
monocyt precursors

Mesenchymale  
progenitoren

Osteoclasten en osteoblasten



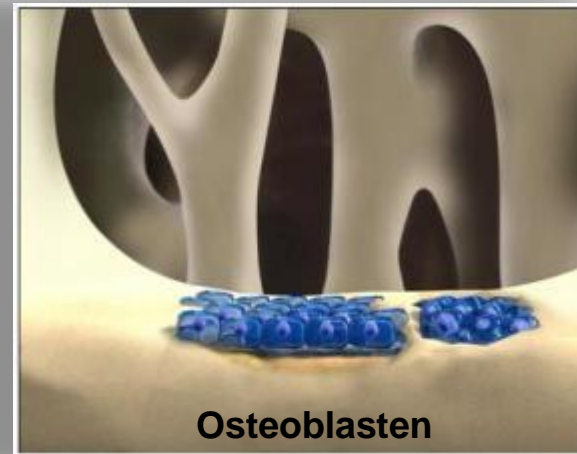
Bot afbraak



Bot formatie



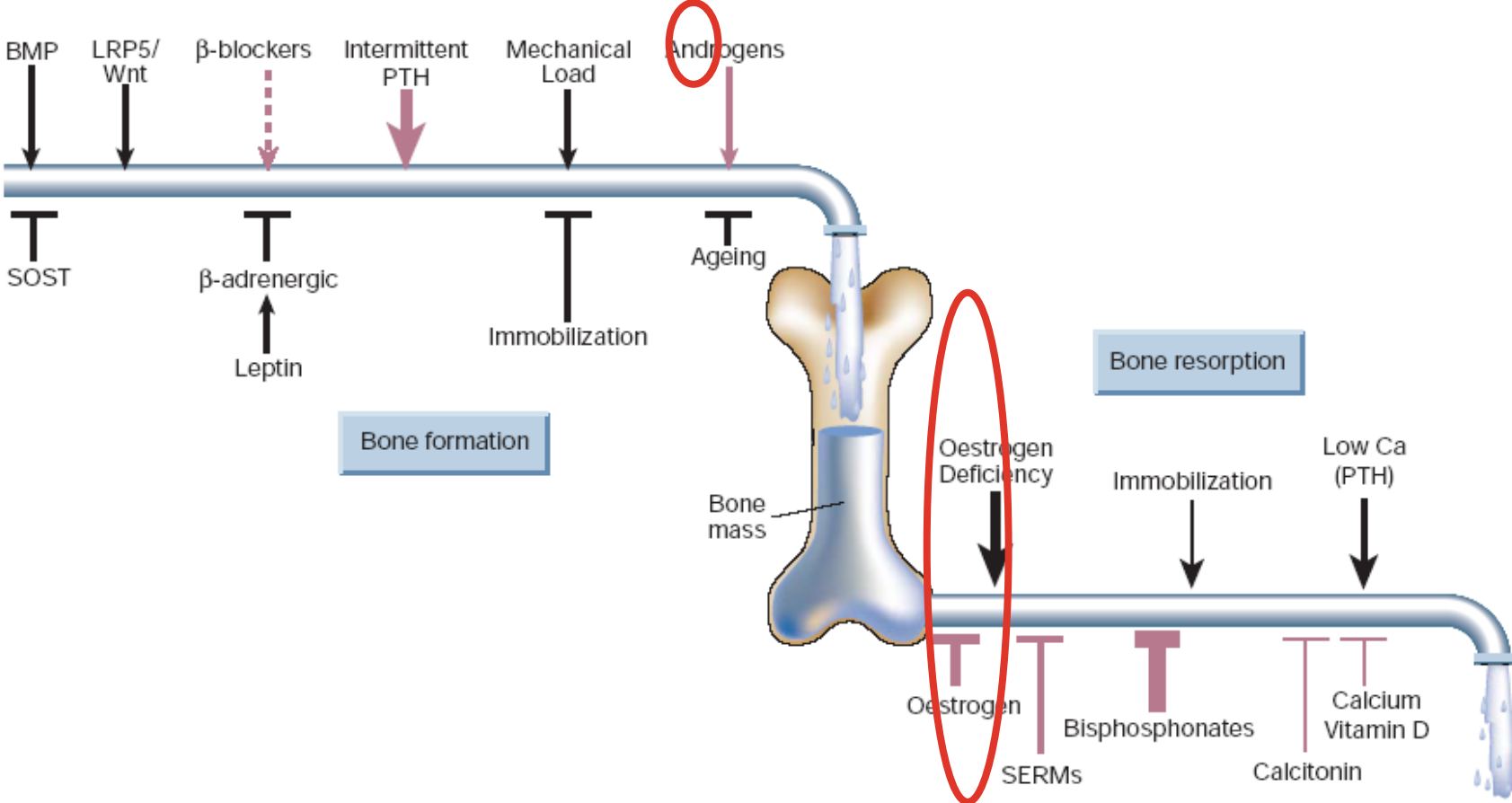
Osteoclasten



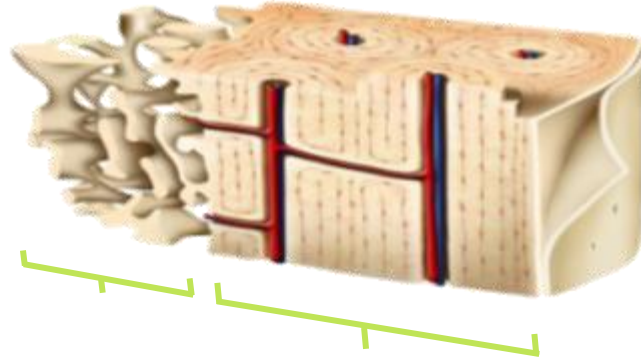
Osteoblasten



# Regulatie bot remodelering: multifactorieel



# Bot turnover rate: 10% botmassaverlies / jaar

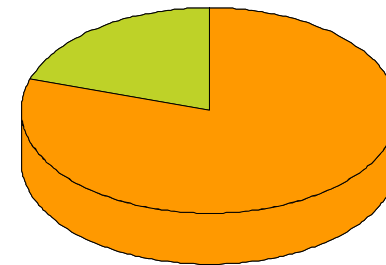
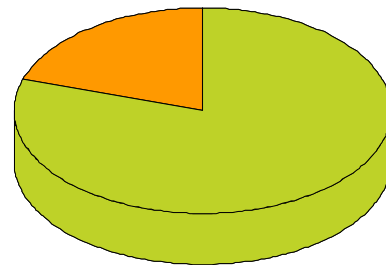


## Trabeculair bot

- 20% van de botmassa
- 80% van bot turnover

## Corticaal bot

- 80% van de botmassa
- 20% van bot turnover



Vertebrale fracturen !



# Fracture Calculation Tool (FRAX)

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

Country: **Netherlands** 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 or more units per day  No  Yes

12. Femoral neck BMD (g/cm<sup>2</sup>)

T-Score

**BMI 18.8** 

**The ten year probability of fracture (%)**

**with BMD**

|                      |            |
|----------------------|------------|
| ■ Major osteoporotic | <b>17</b>  |
| ■ Hip fracture       | <b>8.5</b> |

# Fracture Risk Calculator van Garvan

<http://www.garvan.org.au/bone-fracture-risk/>

Fill out the following to estimate your fracture risk

Full Name (optional)

Sex?  Male  Female

Age  ▼

Fractures since the age of 50 (excluding major trauma, e.g. car accidents)  ▼

Falls over last 12 months  ▼

Do you have a Bone Mineral Density (BMD) measurement?  Yes  No

T-scores

OR

Densitometer  by DXA GE Lunar  by DXA Hologic

# Fractuur risico: FRAX en Garvan

**BMI 18.8**  
**The ten year probability of fracture (%)**

**with BMD**

|                    |            |
|--------------------|------------|
| Major osteoporotic | <b>17</b>  |
| Hip fracture       | <b>8.5</b> |

FRACTURE RISK CALCULATOR

5 & 10 year Fracture Risk For

Prepared 16-Jun-11

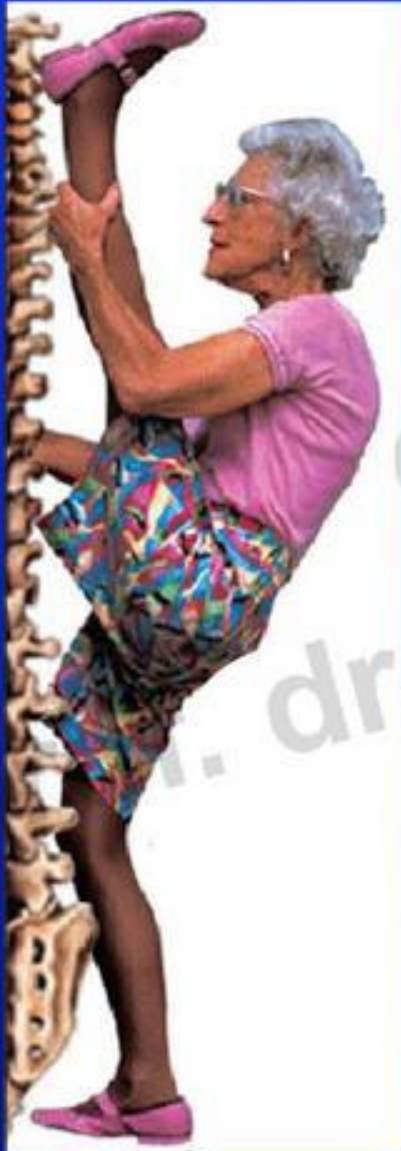
|                     |              |  |              |
|---------------------|--------------|--|--------------|
| <b>Hip Fracture</b> |              | <b>Any Osteoporotic / Fragility Fracture</b> |              |
| <b>27%</b>          | <b>46.7%</b> | <b>35.3%</b>                                 | <b>60.7%</b> |
| 5 year risk         | 10 year risk | 5 year risk                                  | 10 year risk |

# Behandelplan

- Leefstijladviezen
- Calcium en vitamine D suppletie\*
- Valpreventie
- Medicatie : keuze uit verschillende mogelijkheden\*
  - Therapietrouw
  - Maagklachten
  - Voorkeur van patiënt



# BASIC PREVENTION



**Vitamin**



**alcium**



**Prevent**



**xercise**



**alls**



**ain weight**

**Stop**



**moking**





# Screenen valrisico

- **Hoe vaak bent u het afgelopen jaar gevallen?**
- Wat was daarvan de oorzaak volgens u?
- **Bent u bang om te vallen?**
- Kunt u uw evenwicht goed bewaren?
- Bent u vaak duizelig?
- Heeft u problemen met zien / ogen?





**Sociale kaart** bestaat uit gecertificeerde fysio- en oefentherapeuten met een valpreventief oefenprogramma die vergoeding krijgen vanuit CZ en VGZ:

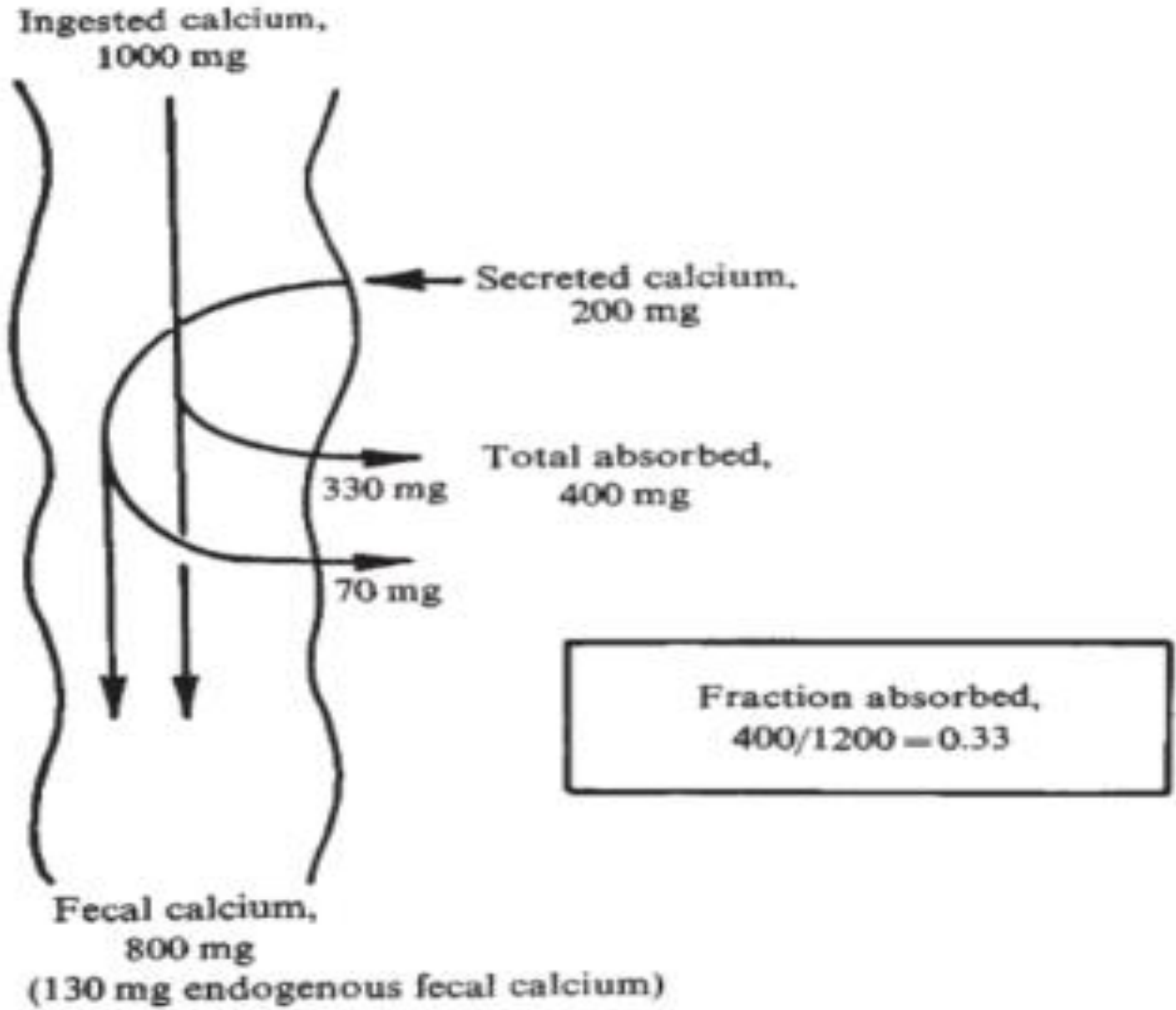
- 1) Zicht op Evenwicht
- 2) Vallen Verledentijd
- 3) OTAGO
- 4) In Balans



→ **Behandeling op maat!**

- Groepssessie in praktijk of op locatie
- Individuele sessie in praktijk of bij patiënt thuis





# Calcium absorptie

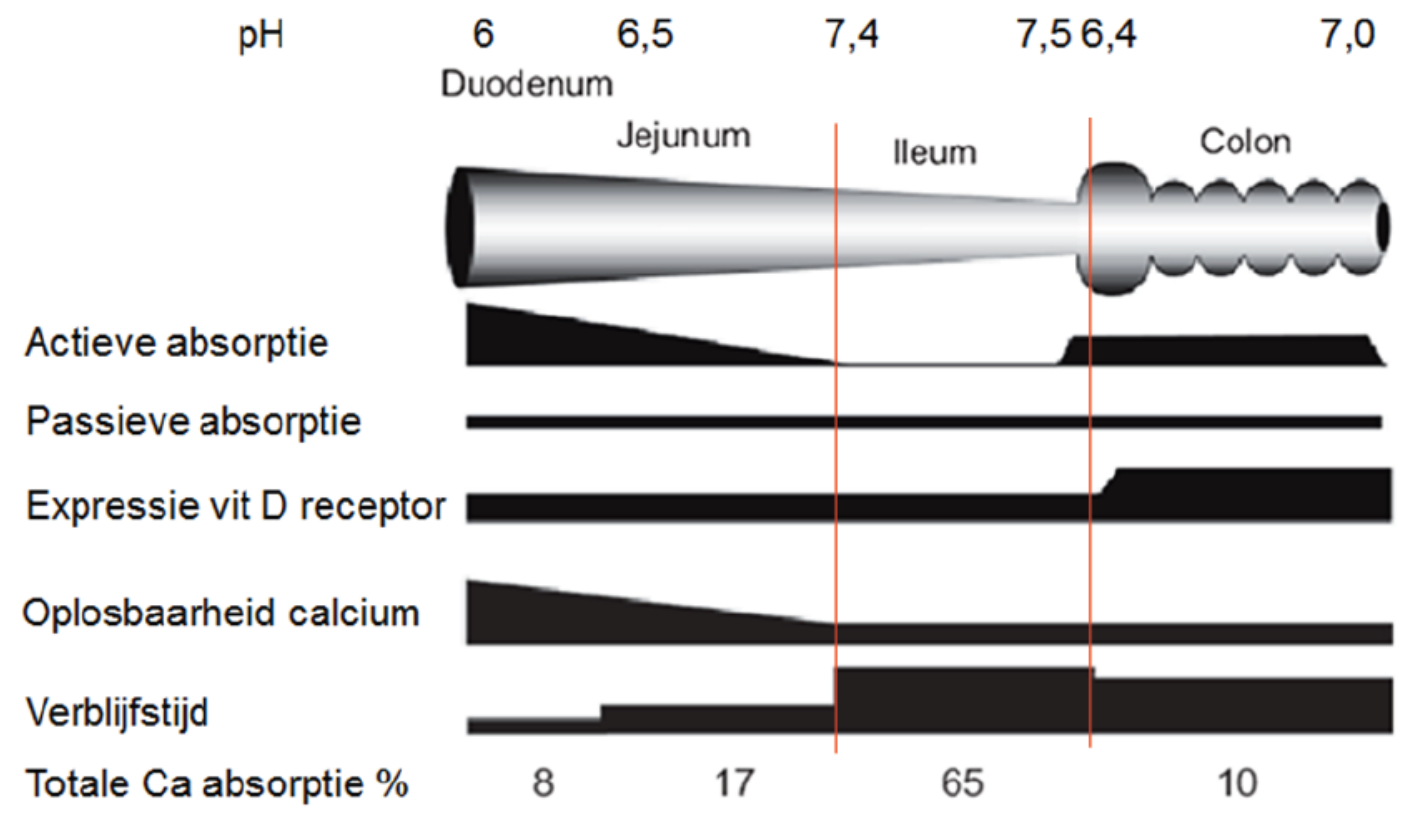
- Actief, transcellulair

- Vit D afhankelijk
- Verzadigbaar
- 75%

- Passief, paracellulair

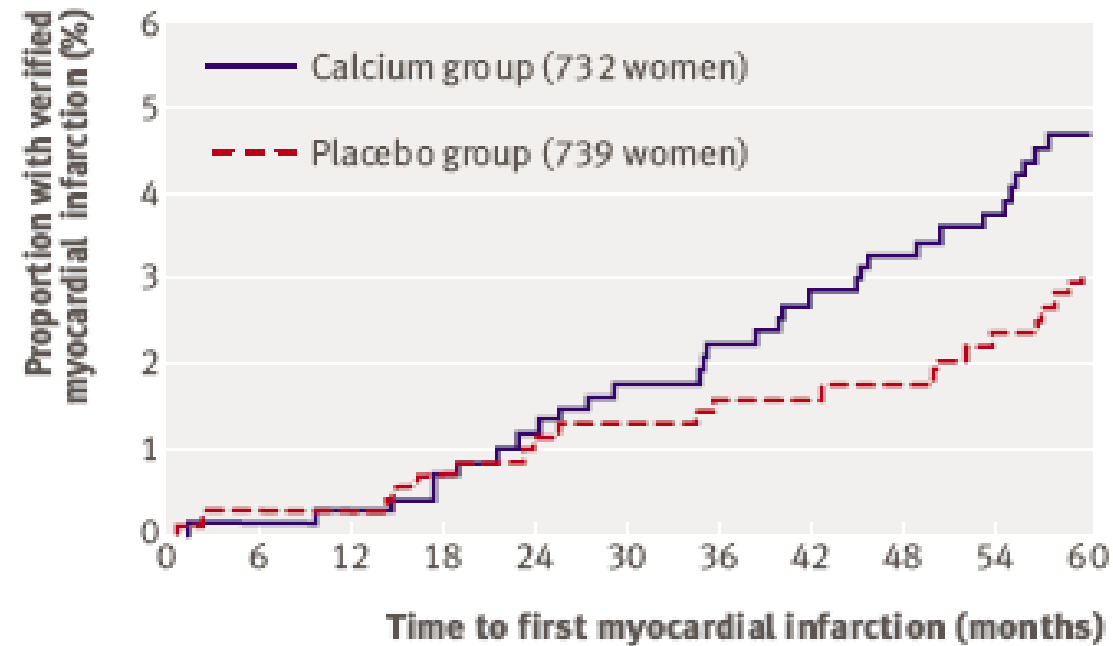
- Onafhankelijk vit D
- Onverzadigbaar
- 25%



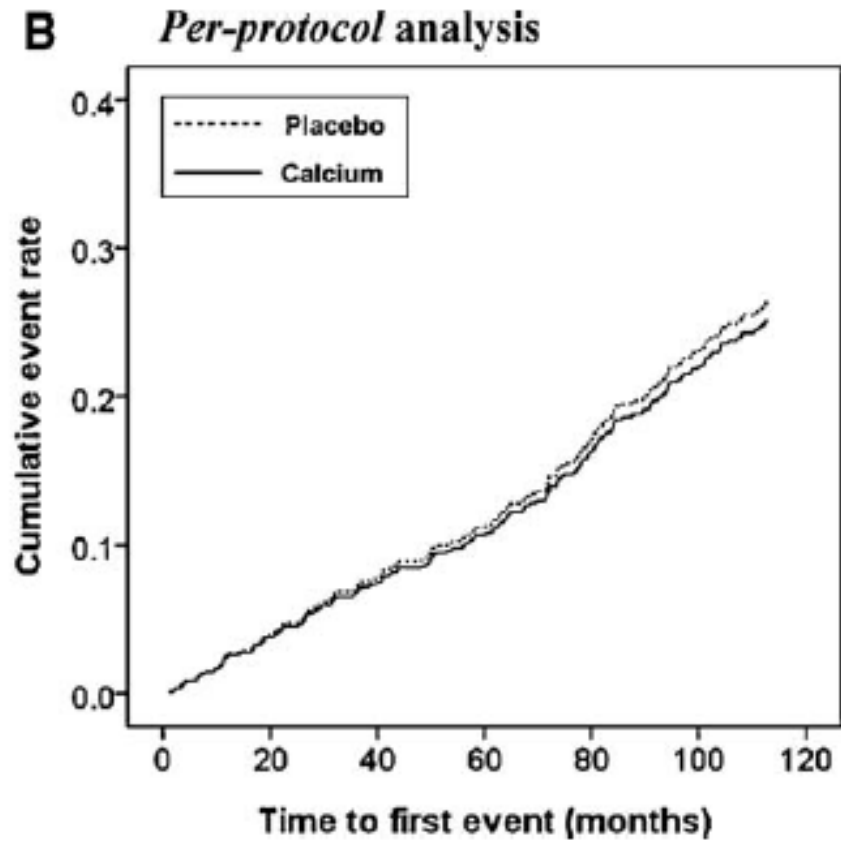
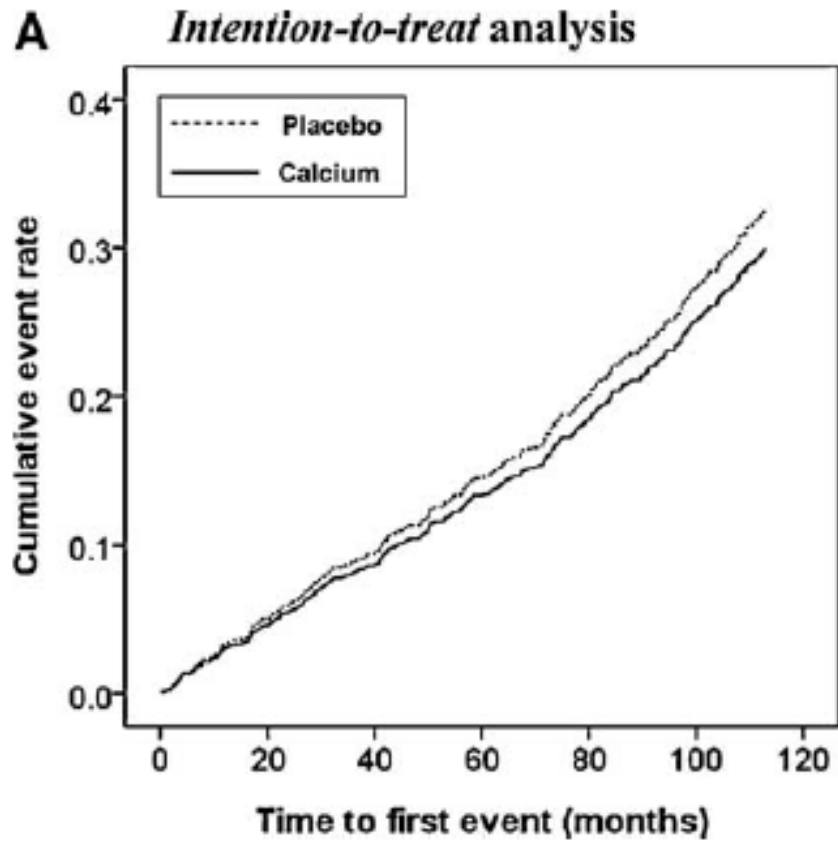


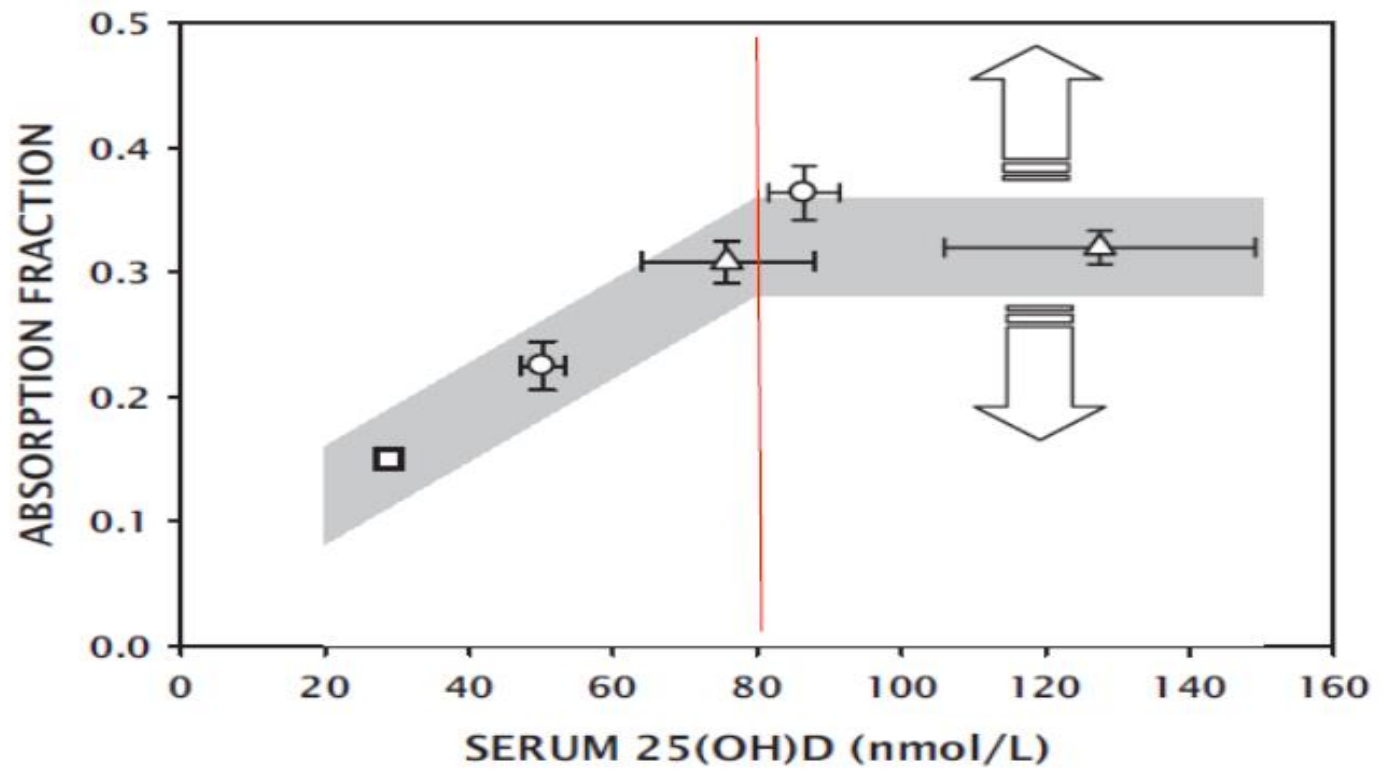
## Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial

Mark J Bolland, research fellow, P Alan Barber, senior lecturer, Robert N Doughty, associate professor, Barbara Mason, research officer, Anne Horne, research fellow, Ruth Ames, research officer, Gregory D Gamble, research fellow, Andrew Grey, associate professor, Ian R Reid, professor



Downloaded from [bmj.com](http://bmj.com) on 31 January 2008







# Calcium en vitamine D suppletie

| Calcium suppletie | NHG                         | CBO                       |
|-------------------|-----------------------------|---------------------------|
| 1000 mg/dag       | Geen zuivelinname           | Geen zuivelinname         |
| 500 -1000 mg/dag  |                             | Inname <1000-1200 mg/dag  |
| 500 mg/dag        | 1-3 Porties zuivelproducten |                           |
| Geen suppletie    | 4 Porties zuivelproducten   | 4 Porties zuivelproducten |

| Vitamine D suppletie | NHG                          | CBO   | GR (GezondheidsRaad)    |
|----------------------|------------------------------|---|-------------------------|
| 800 IE               | Matig en hoog fractuurrisico | Patiënten met osteoporose of in verzorgingstehuis | Ouderen ≥ 70 jaar       |
| 400 IE               |                              |   | Vrouwen van 50 -70 jaar |



# Medicamenteuze behandeling

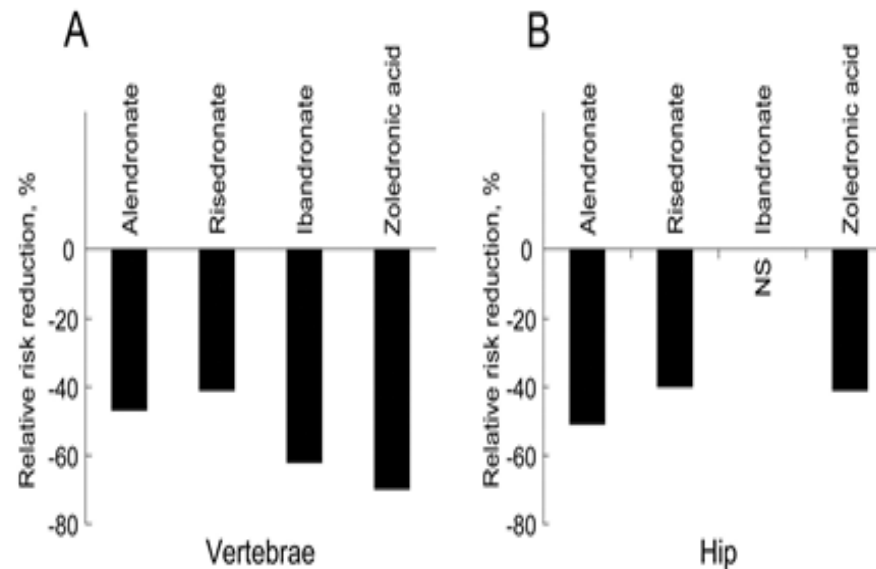
| CBO richtlijn osteoporose fractuurpreventie <sup>1</sup>   |  | NHG standaard fractuurpreventie <sup>2</sup> |                                     |
|--|--|--|-------------------------------------|
| Eerste keus<br>Wervel, niet-wervel en heup fractuurpreventie   | Alendronaat PO of Risedronaat PO   | Eerste keus                                  | Alendronaat PO of Risedronaat PO    |
| Tweede keus<br>1. Wervel, niet-wervel en heup fractuurpreventie<br>2. Wervel en niet-wervel fractuurpreventie<br>3. Wervel fractuurpreventie | 1. Denosumab SC of Zoledronaat IV<br>2. Strontiumranelaat PO<br>3. Ibandronaat PO/ IV of Raloxifeen PO | Tweede keus                                  | Denosumab SC of Zoledronaat IV      |
| Derde keus<br>1. Wervel en niet-wervel fractuurpreventie<br>2. Wervel fractuurpreventie  | Teriparatide SC  | Derde Keus                                   | Geen andere medicamenten aanbevolen |

# Overzicht kenmerken van medicamenten

|  | Aangetoonde fractuurpreventie met hoog bewijs |             |      | Gebruik   |
|--|---|-------------|------|---|
|  | wervel  | niet-wervel | heup |   |
| <b>Alendronaat</b>   | X   | X           | X    | <b>Tabletten dagelijks 10 mg of wekelijks 70 mg</b>                         |
| <b>Risedronaat</b>   | X   | X           | X    | <b>Tabletten dagelijks 5 mg of wekelijks 35 mg of maandelijks 2 x 75 mg</b> |
| <b>Ibandronaat</b>   | X   |             |      | <b>Maandelijks 150 mg tabletten of 3-maandelijks met 15 sec IV injectie</b> |
| <b>Zoledronaat</b>   | X   | X           | X    | <b>Jaarlijks 5 mg tijdens 15 min IV injectie</b>                            |
| <b>Raloxifeen</b>  | X   |             |      | <b>Jaarlijks 5 mg tijdens 15 min IV injectie</b>                            |
| <b>Teriparatide (rhPTH-1-34)</b>                                 | X   | X           |      | <b>SC 1/d</b>   |
| <b>PTH (1-84) (rhPTH-1-84)</b>                                   | X   |             |      | <b>SC 1/d</b>   |
| <b>Strontiumrelanaat</b>   | X   | X           |      | <b>2 g sachet per dag</b>   |
| <b>Denosumab</b> <small>SC = subcutaan, IV = intraveneus</small> | X   | X           | X    | <b>SC 2 x 60 mg/jaar</b>  |

# Vershil in effect bisfosfonaten

## Fractuurpreventie



Relative risk reduction for vertebral (A) and hip (B) fractures in postmenopausal women with known osteoporosis after 3 yr of bisphosphonate treatment.

*Khosla S et al, JCEM 2012*

# Prijzen medicatie (incl. afleverkosten)

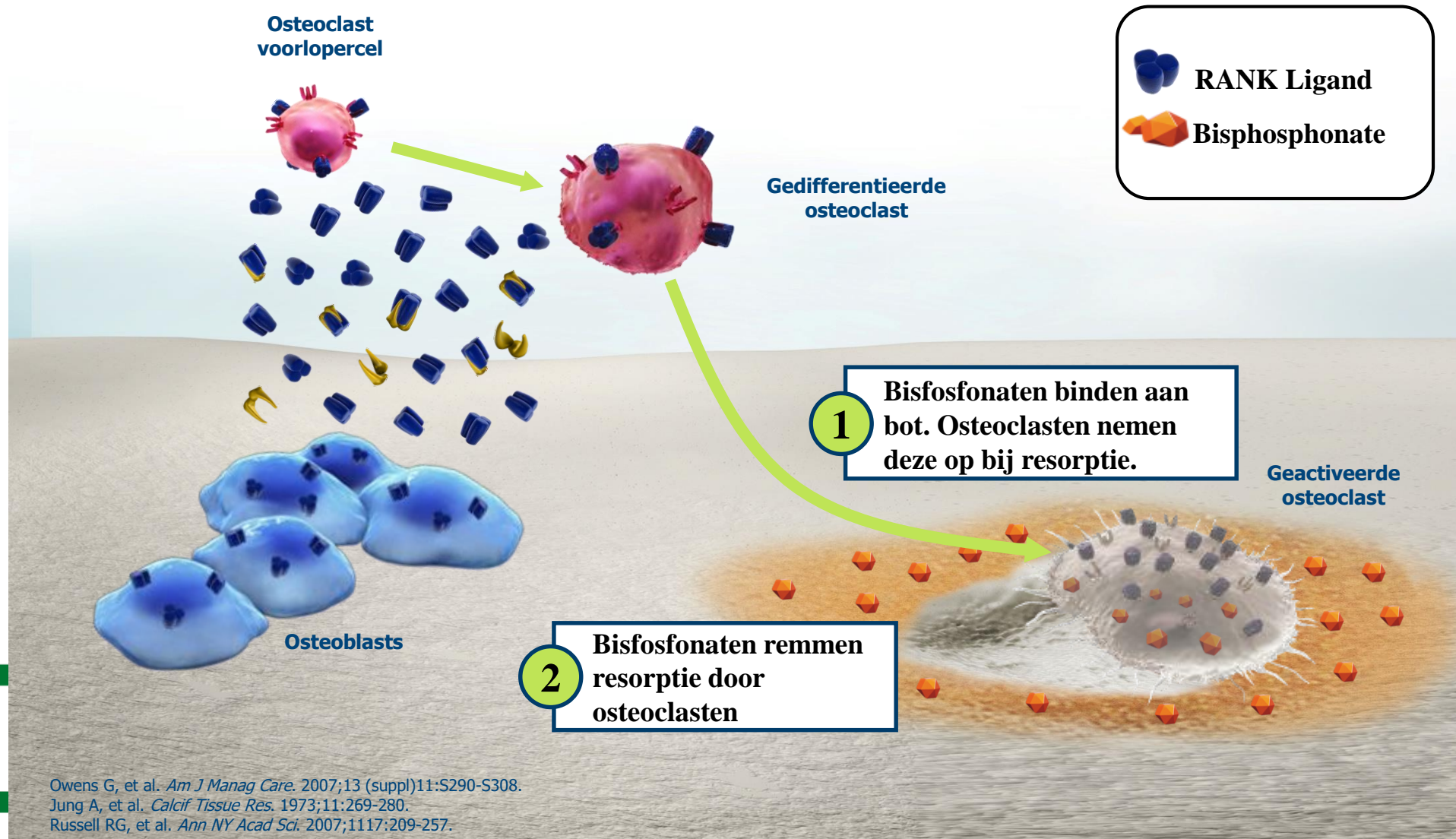
| Geneesmiddel                  | Toediening  | Doseerfrequentie | Prijs/jaar |
|-------------------------------|-------------|------------------|------------|
| Alendroninezuur 70 mg         | Oraal       | 1x per week      | € 41,69    |
| Risedroninezuur 35 mg         | Oraal       | 1x per week      | € 43,51    |
| Ibandroninezuur 150 mg        | Oraal       | 1x per maand     | € 57,36    |
| Ibandroninezuur<br>(Bonviva)  | Iv injectie | 1x per 3 maanden | € 299,64   |
| Zoledroninezuurg<br>(Aclasta) | Iv injectie | 1x per jaar      | € 312,73   |
| Denosumab (Prolia)            | Sc injectie | 1x per 6 maanden | € 431,86   |

# Werking bisfosfonaten

- Bone turnover
  - Remming activiteit, rijping osteoclasten
  - Apoptose osteoclasten
  - Aanvankelijk meer botformatie, echter volgt botresorptie
- Bone mineral density (BMD)
  - Behoud/verbetering van microarchitectuur bot
  - Mineralisatie
- Met name trabeculair bot



# Bisfosfonaten binden aan bot en remmen osteoclasten op het botoppervlak





# Interacties Bisfosfonaten

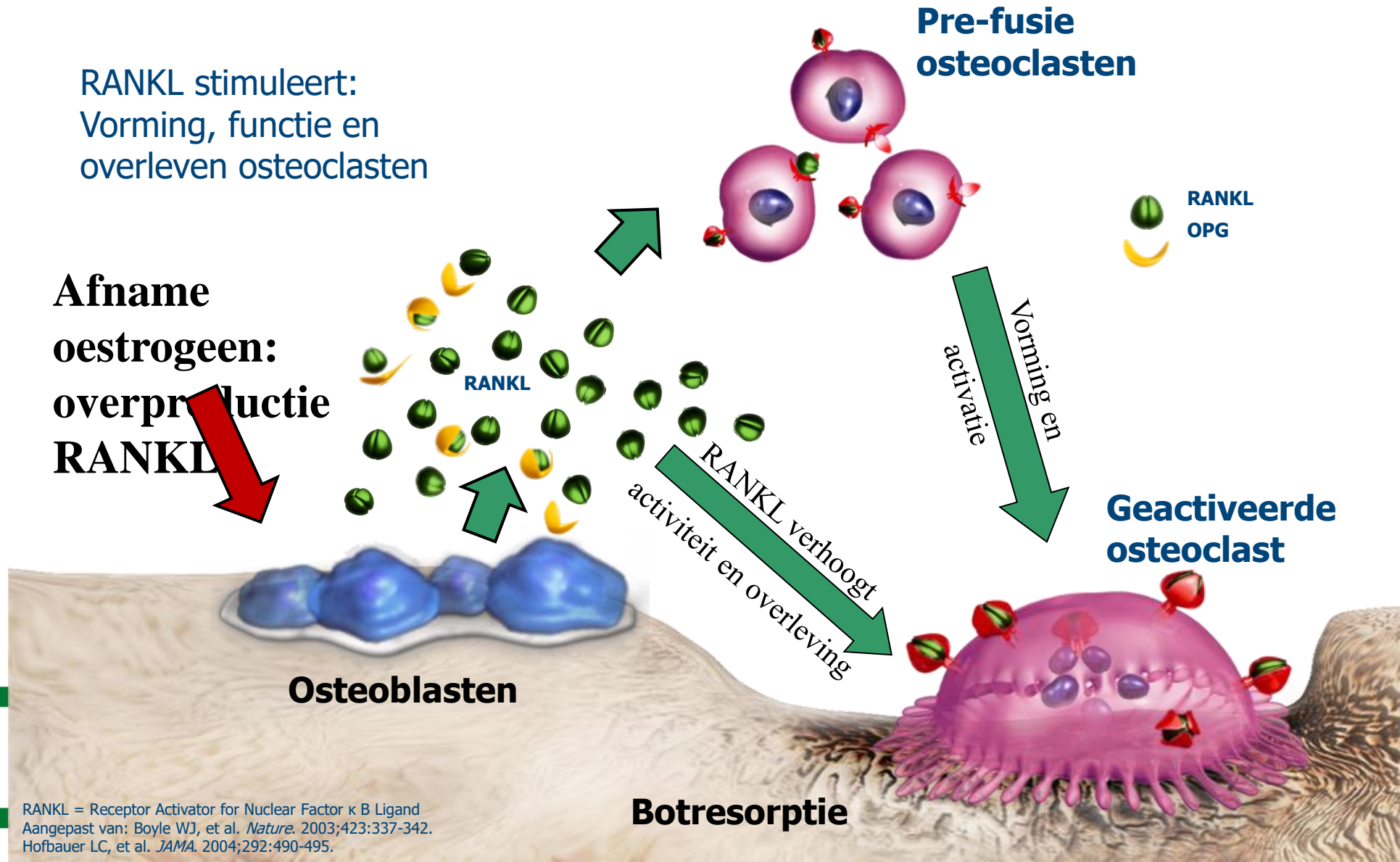
- Inname met calciumpreparaten, antacida
- NSAIDs: GI effecten
- Medicatie met effect op maagontleding



# Rol van RANKL bij postmenopauzale osteoporose

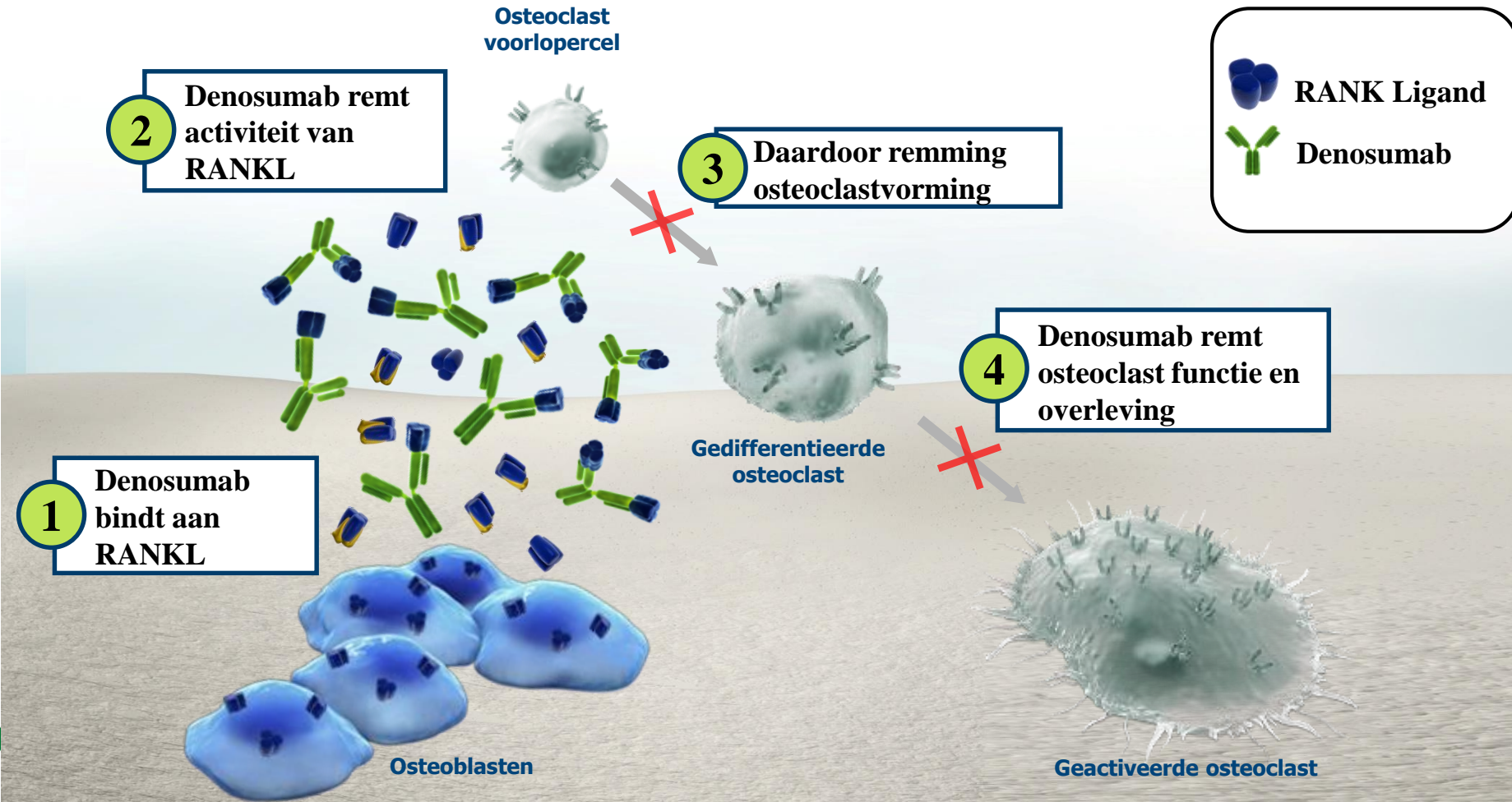
RANKL stimuleert:  
Vorming, functie en  
overleven osteoclasten

**Afname  
oestrogeen:  
overproductie  
RANKL**



RANKL = Receptor Activator for Nuclear Factor  $\kappa$  B Ligand  
Aangepast van: Boyle WJ, et al. *Nature*. 2003;423:337-342.  
Hofbauer LC, et al. *JAMA*. 2004;292:490-495.

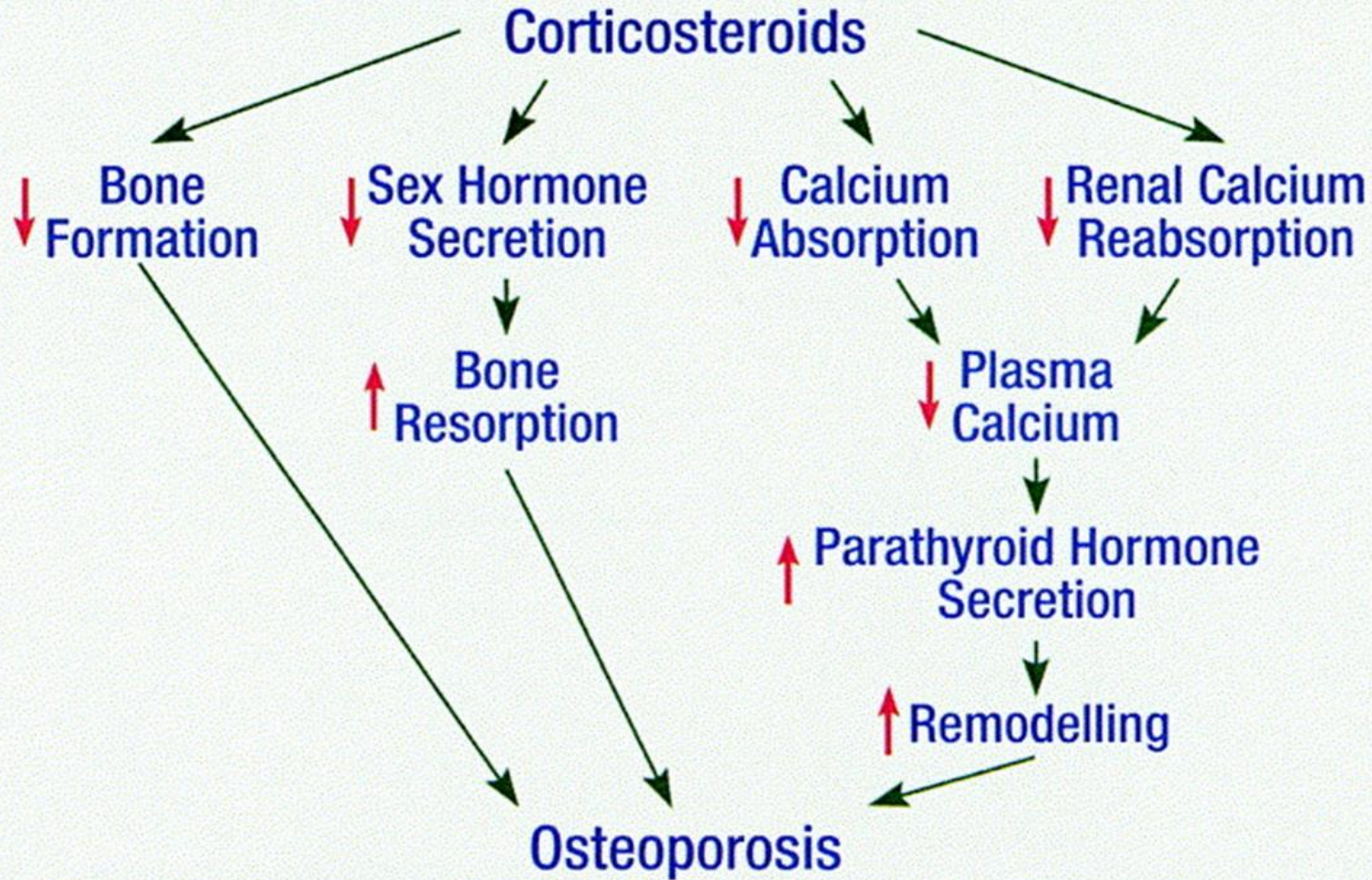
# Denosumab remt vorming, functie en overleven osteoclasten



# Teriparatide (Forsteo)

- rhPTH 1-34
- Anabool
- Max 2 jaar (eenmalige cyclus)
- Subcutaan 20 mug per dag

## Effect of Corticosteroids on Bone Metabolism



# Wanneer osteoporose profylaxe?

- Glucocorticoïd gebruik langer dan 3 maanden:
- Dosering  $> 7.5$  mg per dag en  $< 15$  mg
  - Leeftijd  $< 70$  jaar: advies DEXA scan
  - Leeftijd  $> 70$  jaar: advies behandelen
- Dosering  $> 15$  mg per dag: advies behandelen



Bisfosfonaten moeten na 5 jaar behandeling worden gestopt???



# Complicaties botresorptieremmers

- Hypocalciëmie (vitamine D!)
- Acute inflammatoire respons ~20%
- Nierfunctiestoornissen
  - Klaring < 30 ml/min contra-indicatie
- Atypische femurfracturen
  - NNT harm: 1 : 1500
  - NNT treat: 1 : 38
- Osteonecrose kaak
  - Osteoporose: 1:10.000 – 1:100.000
  - Maligniteiten: 1: 10 - 1:100



# Atypische fracturen



TYPICAL Subtrochanteric Fracture

- Spiral pattern
- Substantial comminution
- Thin cortices



ATYPICAL Subtrochanteric Fracture

- Transverse or short oblique orientation
- No comminution
- Thick cortices – focal or generalized

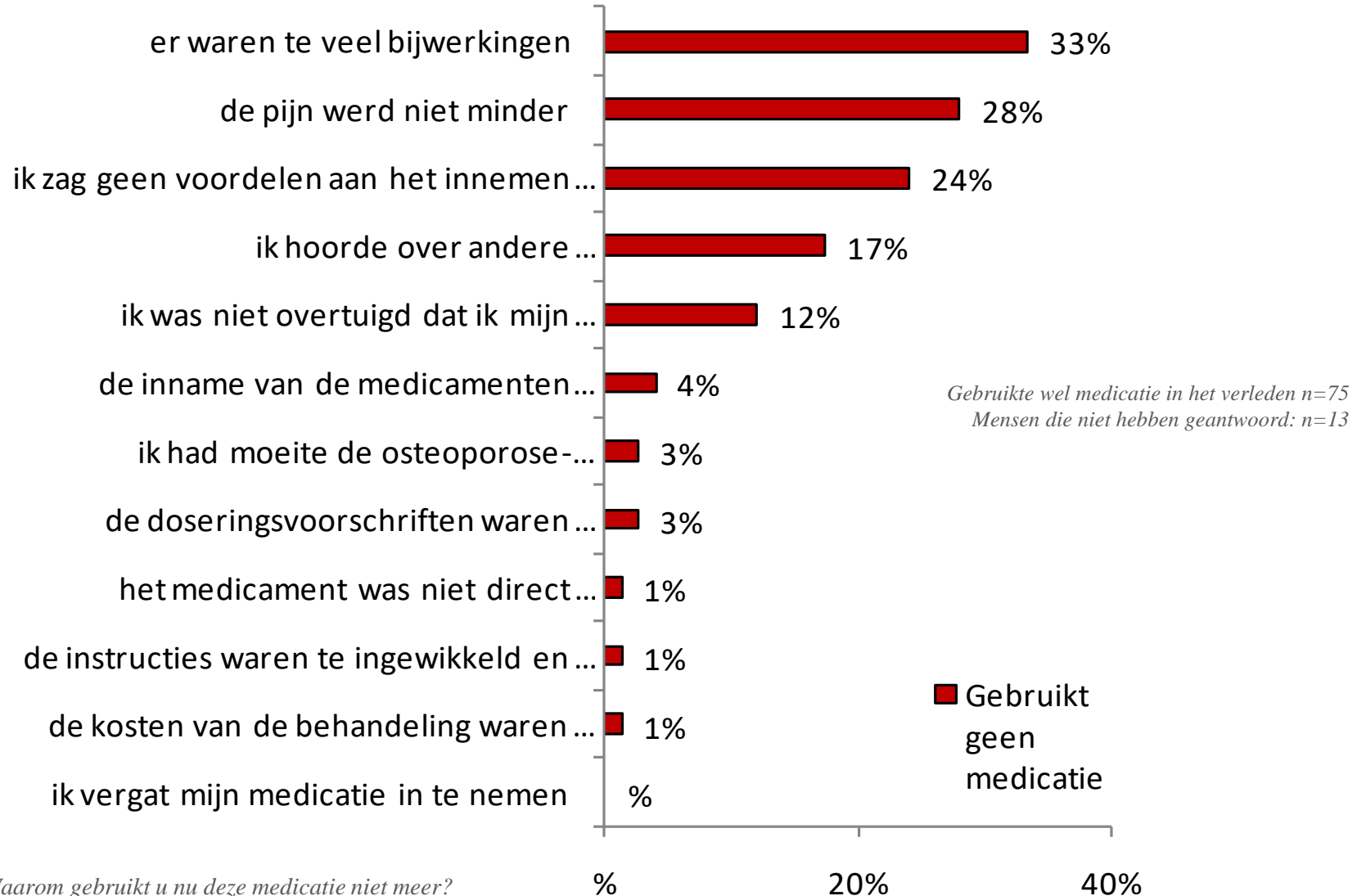
# Osteonecrose van de kaak



“ONJ”



## Bijwerkingen meest voorkomende reden

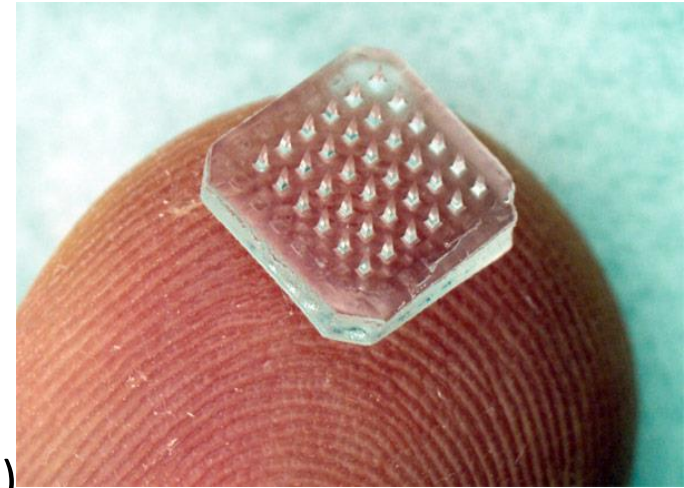


B05. Waarom gebruikt u nu deze medicatie niet meer?



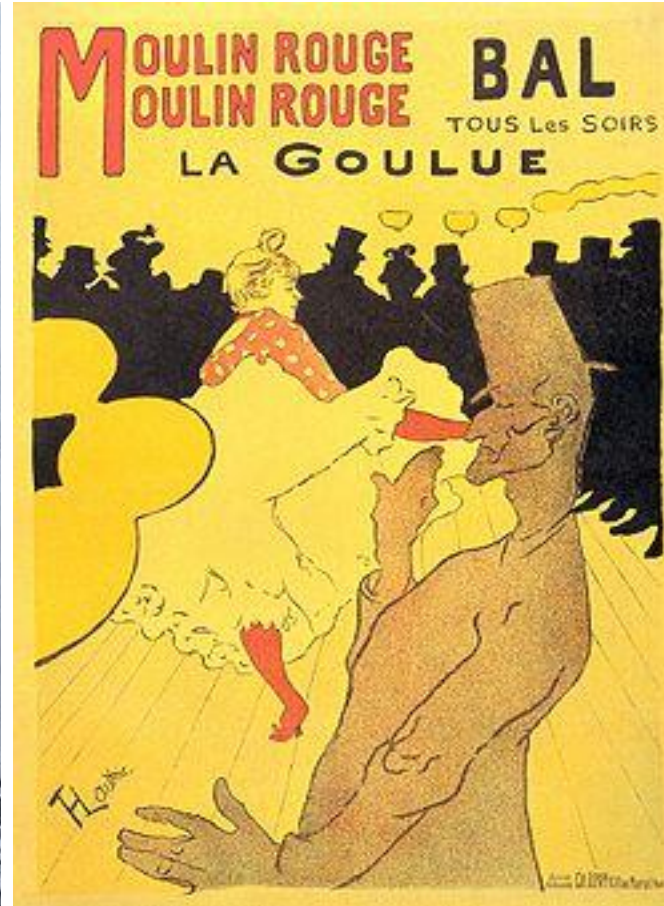
# Nieuwe ontwikkelingen PTH

- \* Nieuwe toedieningsvormen:
  - Transdermaal (microneedle patch)
  - Wekelijkse dosering
- \* PTH-RP (related protein)
- \* Calciumreceptorantagonist  
(stimuleert endogene aanmaak PTH)



# Pycnodysostosis

Henri de Toulouse-Lautrec (1864-1901)



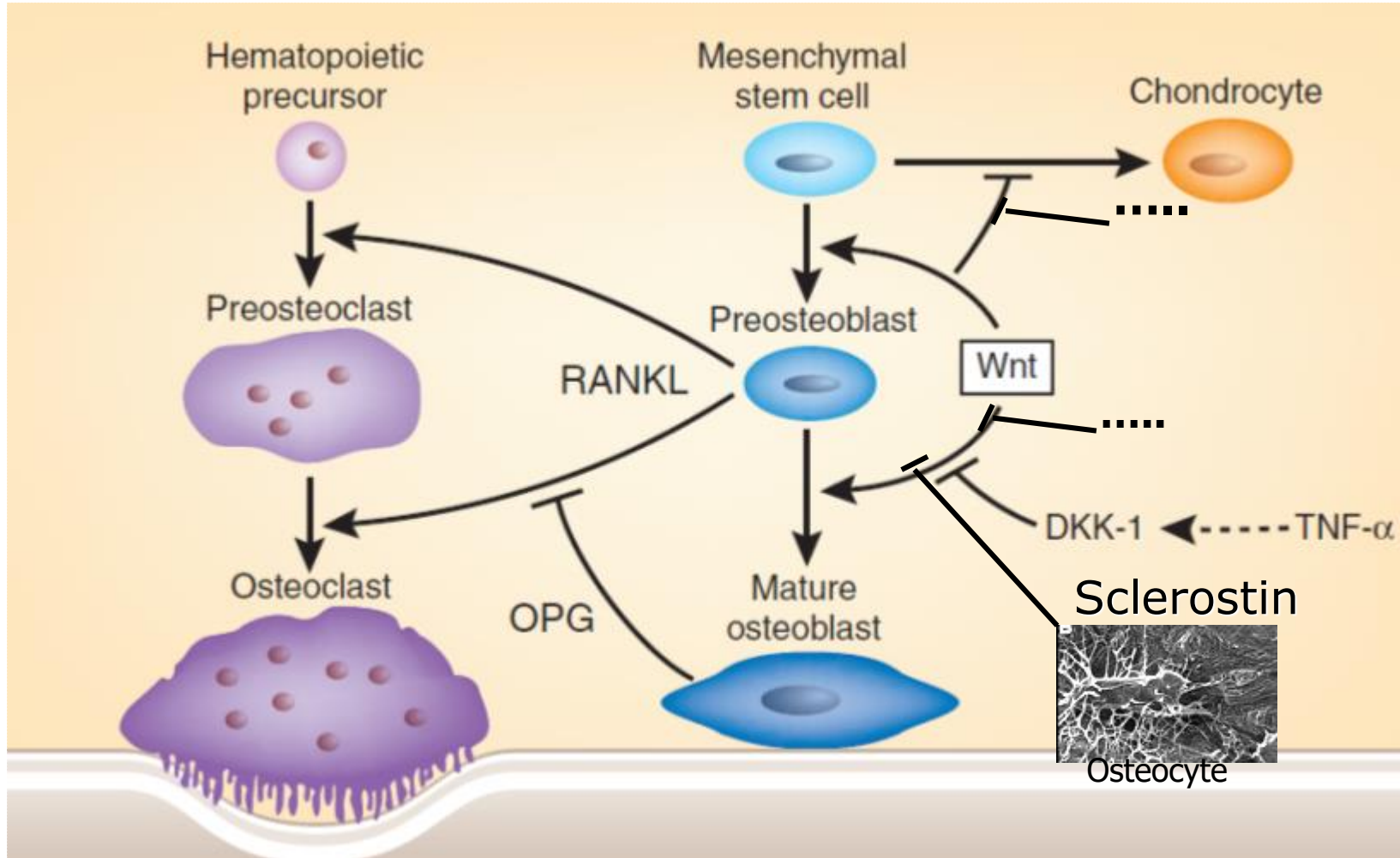
# Pycnodysostosis

- Cathepsine K-deficientie
- Cathepsine K remmer:
  - Odanacatib





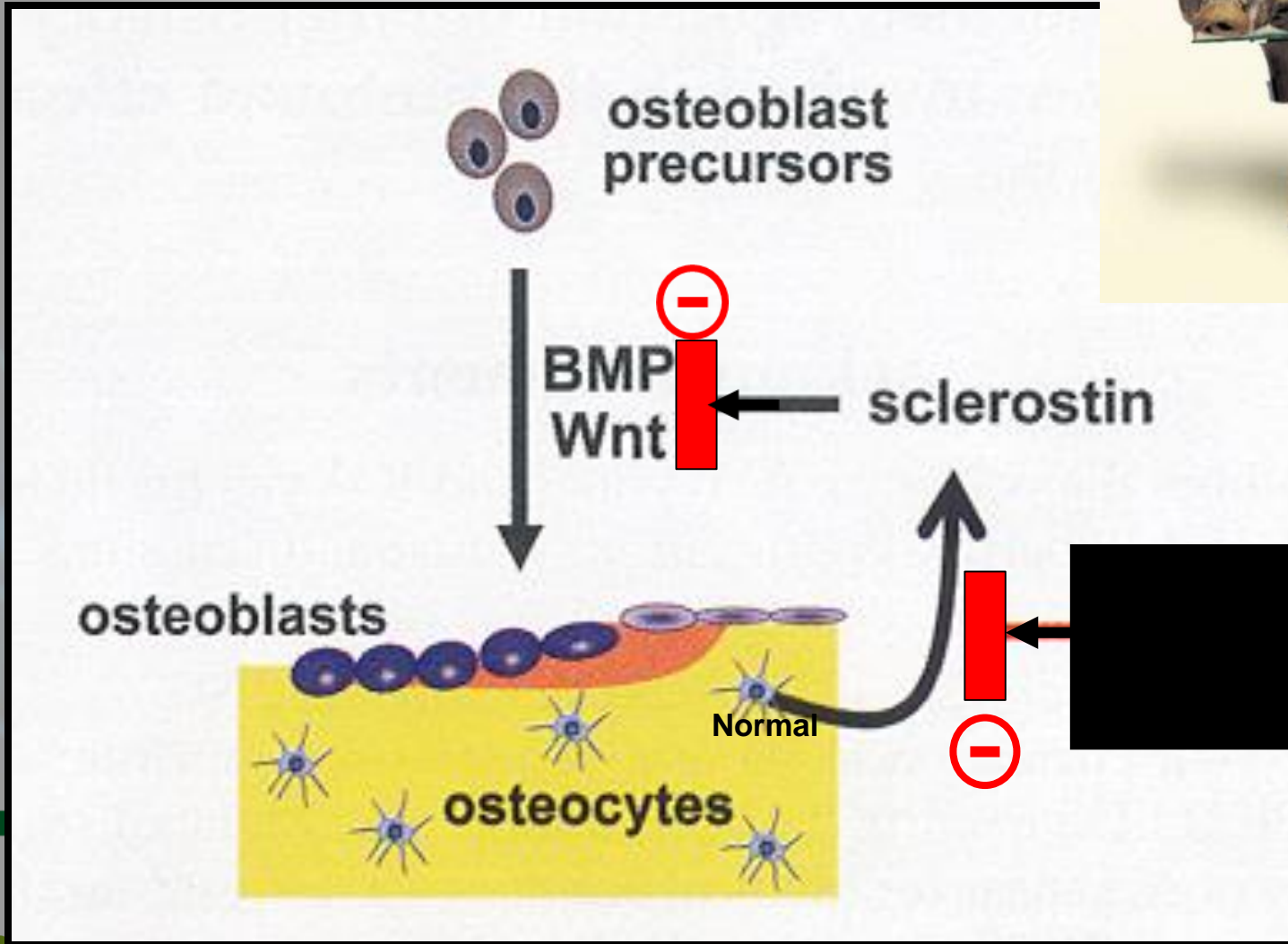
# RANKL OPG & Wnt System resorption formation



*hAB against RANKL*  
*denosumab*

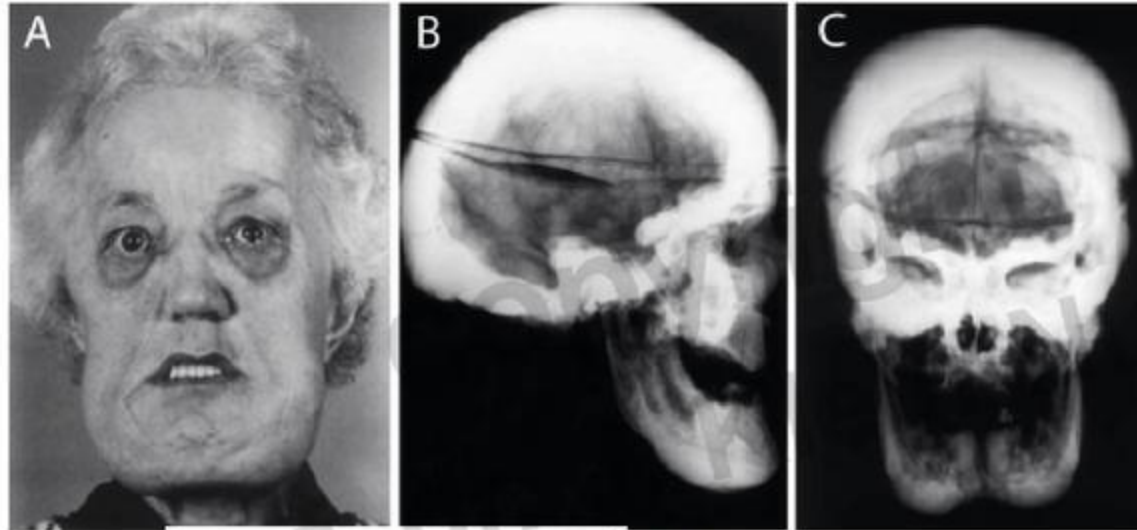
*hAB against*  
*sclerostin*

# Sclerostin (SOST)



**Sclerosteosis /  
van Buchem's**

# Van Buchem Disease - Clinical features



-Thickened skull

- Thickened mandible, elongation and deformity

-Diaphyseal cortex of long bones → narrowed medullary cavities

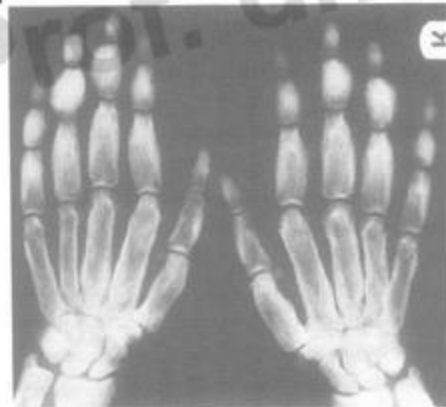


TABLE 1. Measured values from the metacarpals in adult Van Buchem-affected, Van Buchem carriers, and normal subjects

|                                | Van Buchem affected (n = 6) | Van Buchem carriers (n = 9) | Normal subjects (n = 5) |
|--------------------------------|-----------------------------|-----------------------------|-------------------------|
| Age (yr)                       | 51.0 ± 5.8                  | 45.8 ± 5.2                  | 51.7 ± 5.9              |
| Length (mm)                    | 68.4 ± 3.1                  | 71.4 ± 3.1                  | 62.5 ± 2.3              |
| Epiphysis diameter (mm)        | 16.3 ± 0.7                  | 18.0 ± 0.6 <sup>a</sup>     | 14.9 ± 0.9              |
| Diaphyseal outer diameter (mm) | 12.83 ± .69 <sup>b</sup>    | 9.45 ± .33                  | 8.20 ± .37              |
| Diaphyseal inner diameter (mm) | 6.45 ± .76 <sup>c</sup>     | 4.52 ± .36                  | 3.85 ± .39              |
| Thickness (mm)                 | 3.19 ± 0.31 <sup>c</sup>    | 2.46 ± 0.12                 | 2.18 ± .13              |

Values are the mean ± SE of combined digits and sexes. Data were analyzed by three-way ANOVA and *post hoc* testing with Tukey's highest significant difference test.

<sup>a</sup>  $P < 0.05$  vs. normal subjects.

<sup>b</sup>  $P < 0.001$  vs. normal subjects and carriers.

<sup>c</sup>  $P < 0.01$  vs. normal subjects;  $P < 0.05$  vs. carriers.

- Spine

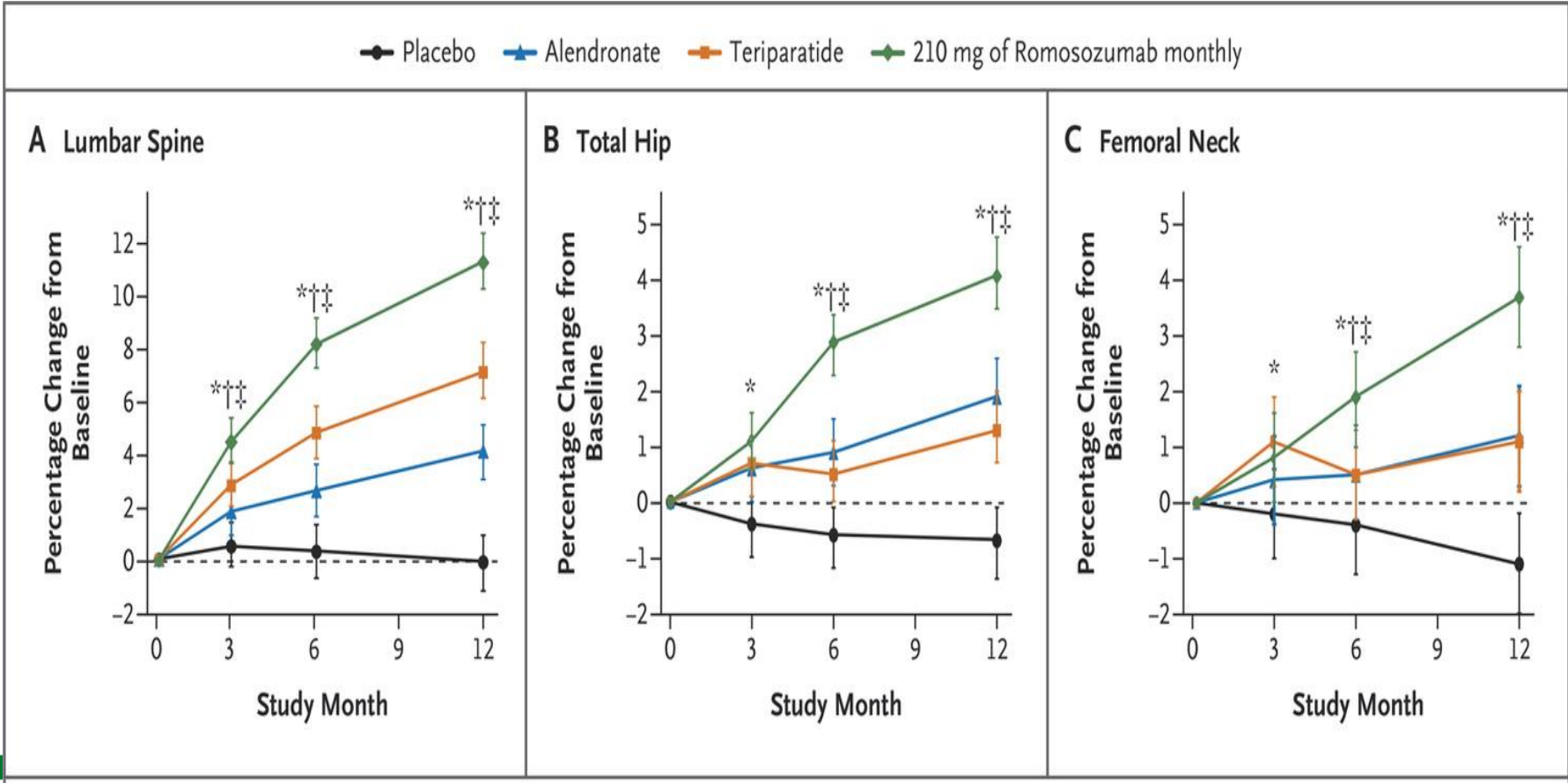
- Pelvic bone



**Chronological portraits of a patient with sclerosteosis from the age of 3 years onward.**

**She was born with syndactyly at both hands and developed facial palsy, deafness, facial distortion, and maxillary overgrowth during childhood.**

**By the age of 30, she had developed proptosis and elevated intracranial pressure due to overgrowth of the calvaria. Craniectomy was performed, but she died nevertheless because of elevated intracranial pressure at the age of 54 years**





**STRONG**  
**STRONG**  
**FUTURE**  
**BONES**

