# Σημαντικότερες ανακοινώσεις των WCO-IOF-ESCEO & ECTS

**Κ. Μαυρουδής**

**16:45 – 17:30**

WORLD CONGRESS ON OSTEOPOROSIS, OSTEOARTHRITIS AND MUSCULOSKELETAL DISEASES

# VIRTUAL CONGRESS

## August 26-28, 2021

IOF International Osteoporosis Foundation

WCO IOF-ESCEO

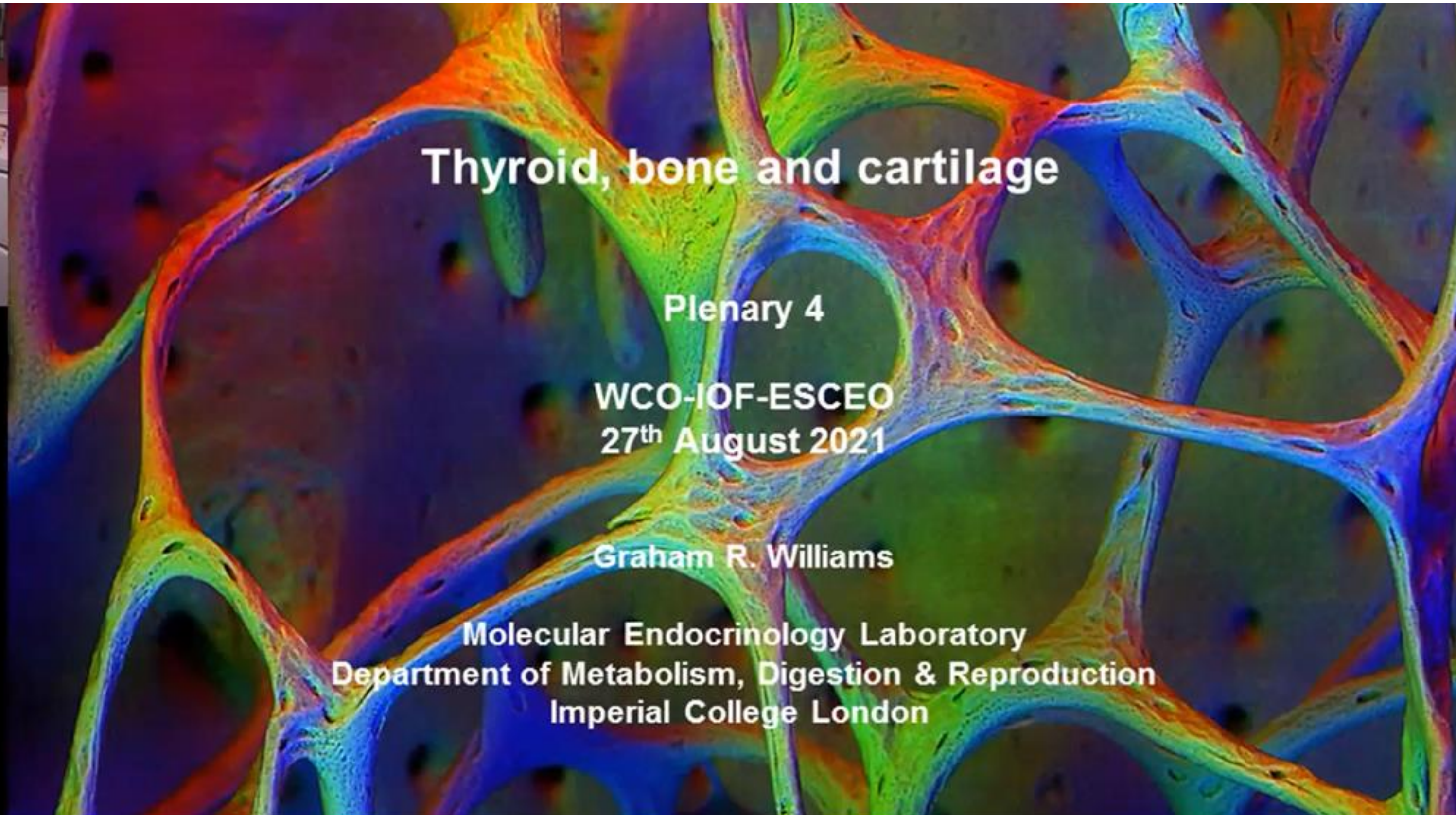
ESCEO

2021 VIRTUAL


**Thyroid, bone and cartilage**
**Calcium-vitamin D** ***(Role of orthopaedic surgeons )***
**The effects of vitamin K on bone**

**LEONIE STUDY**

**PARATHYROIDECTOMY IS ASSOCIATED WITH REDUCED RISK OF FRACTURE AND CVS EVENTS**


Thyroid, bone and cartilage
Plenary 4
WCO-IOF-ESCEO
27th August 2021
Graham R. Williams
Molecular Endocrinology Laboratory
Department of Metabolism, Digestion & Reproduction
Imperial College London

# THYROID, BONE AND CARTILAGE

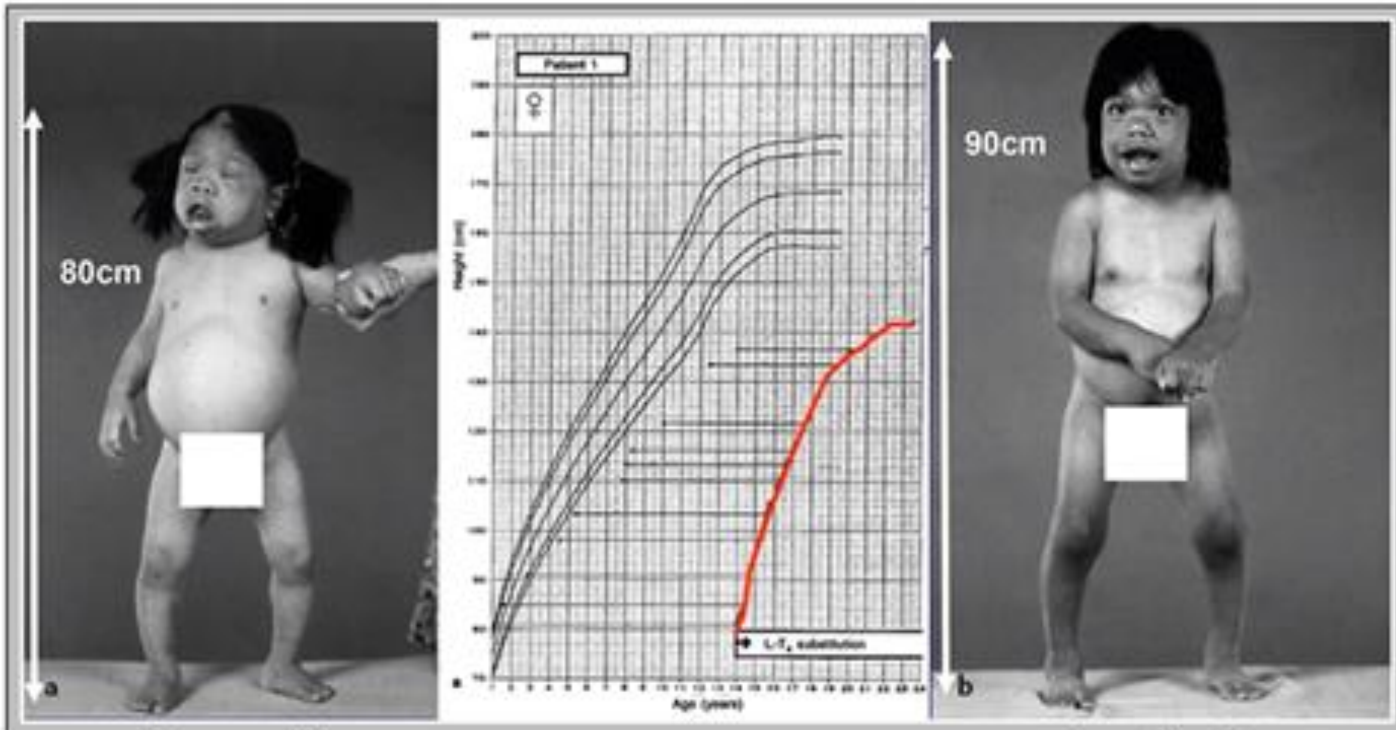
G. R. Williams

Thyroid hormones are essential for skeletal development and are important regulators of bone maintenance .....

**Childhood hypothyroidism** results in delayed skeletal development, retarded linear growth and impaired bone mineral accrual. In severe cases, post-natal growth arrest may result in a complex skeletal dysplasia. Thyroid hormone replacement results in catch-up growth and enhanced bone maturation, but recovery may be incomplete dependent on the duration and severity of hypothyroidism prior to treatment.

**Childhood thyrotoxicosis** is rare and accelerates linear growth. Advanced bone age and premature closure of the growth plates result in short stature, and craniosynostosis may occur in severe cases.

# Hypothyroidism and linear growth




14 years old

6 months Rx

Boersma et al 1996 Eur J Pediatr 155: 362

# Hypothyroidism and bone age


**Treatment with thyroxine**

*Huffmeier et al 2007 Eur J Med Genet 50: 209*

# Thyroid status and skeletal development

## Childhood hypothyroidism

- Delayed skeletal development

**Endochondral ossification**

- Epiphyseal dysgenesis
- Postnatal growth arrest, short stature
- Scoliosis, vertebral immaturity
- Congenital hip dislocation

**Intramembranous ossification**

- Broad flat nasal bridge and face
- Patent fontanelles and sutures

## Childhood hyperthyroidism

- Accelerated skeletal development

**Endochondral ossification**

- Accelerated growth
- Advanced bone age
- Premature fusion of growth plates
- Persistent short stature

**Intramembranous ossification**

- Early closure of cranial sutures
- Craniosynostosis in severe cases

## Thyroid hormone replacement

Induces rapid "catch-up" growth

- Accelerated skeletal maturation
- Long term defect depends on duration of hypothyroidism

Early T4 replacement

- Attain predicted adult height and normal BMD

**Euthyroid status is essential to establish peak bone mass**

*Rivkees 1988 N Engl J Med 318: 599–602, Salerno 2001 Eur J Endocrinol 145:377–383, Salerno 2004 Eur J Endocrinol 151:689–694*
*Hüffmeier 2007 Eur J Med Genet 50:209–215, Segni 1999 Thyroid 9: 871–877, Chawla 2015 Thyroid 25: 1167–1172*

# Summary – thyroid hormones and juvenile skeleton

Thyroid hormones act directly in chondrocytes and osteoblasts

- Regulate intramembranous and endochondral ossification
- Control rate of linear growth and bone maturation
- Stimulate bone formation and mineralization

Hypothyroidism

- Delayed skeletal development
- Catch-up following T4 replacement

Hyperthyroidism

- Accelerated skeletal development
- Short stature

RTHα

- Characteristic skeletal dysplasia typical of congenital hypothyroidism

**Thyroid hormones exert anabolic effects during bone growth**

# PL4 THYROID, BONE AND CARTILAGE (II)
## In adults

**Hypothyroidism** inhibits bone turnover but identification of the effects on bone mass requires long-term follow-up of untreated patients.

**Thyrotoxicosis** is well known to cause severe osteoporosis and fracture, but cases are rare because of prompt diagnosis and treatment. Nevertheless, recent data indicate that **subclinical hyperthyroidism**, in which the serum TSH concentration is suppressed but circulating thyroid hormones are normal, is associated with low bone mineral density and an increased risk of incident fracture. Similar studies have shown that **variation in thyroid status within the reference range in postmenopausal women** is associated with bone loss and an increased risk of fracture.

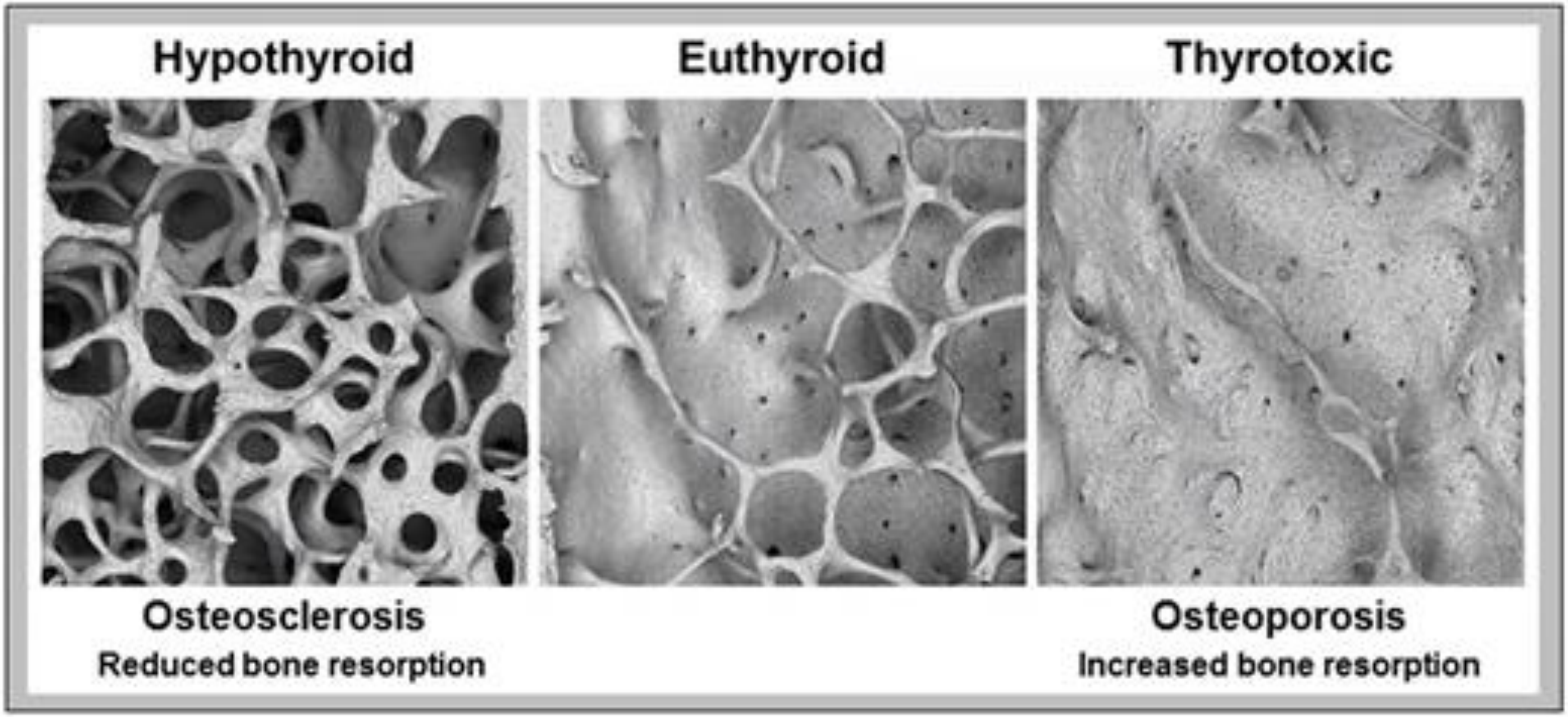
**In summary**, euthyroid status is required for normal post-natal growth and bone mineral accrual and is fundamental for maintenance of the adult skeleton.

# Thyrotoxicosis is a well-established cause of osteoporosis

- Untreated thyrotoxicosis
  - Well known cause of bone loss
    - Osteoporosis
    - Increased fractures
- History of thyrotoxicosis
  - Associated with low BMD and fracture
- Meta-analysis of thyrotoxic patients
  - Increased relative risk of hip fracture

von Recklinghausen 1891 Festschrift Rudolpf Virchow, Berlin 1-89; Moldower & Rabin 1966 Arch Intern Med 118: 379-84
Vestergaard & Mosekilde 2003 Thyroid 13:585-93; Cummings et al 1995 New Engl J Med 332:767-73

# Thyroid hormones increase osteoclastic bone resorption



ESCEO-IOF Symposium   ESCEO-IOF Working Group

**Role of orthopaedic surgeons to ensure optimal Vitamin D levels in patients operated for an osteoporotic fracture**

Chairpersons: *Didier Hannouche, Gerrit Maier*

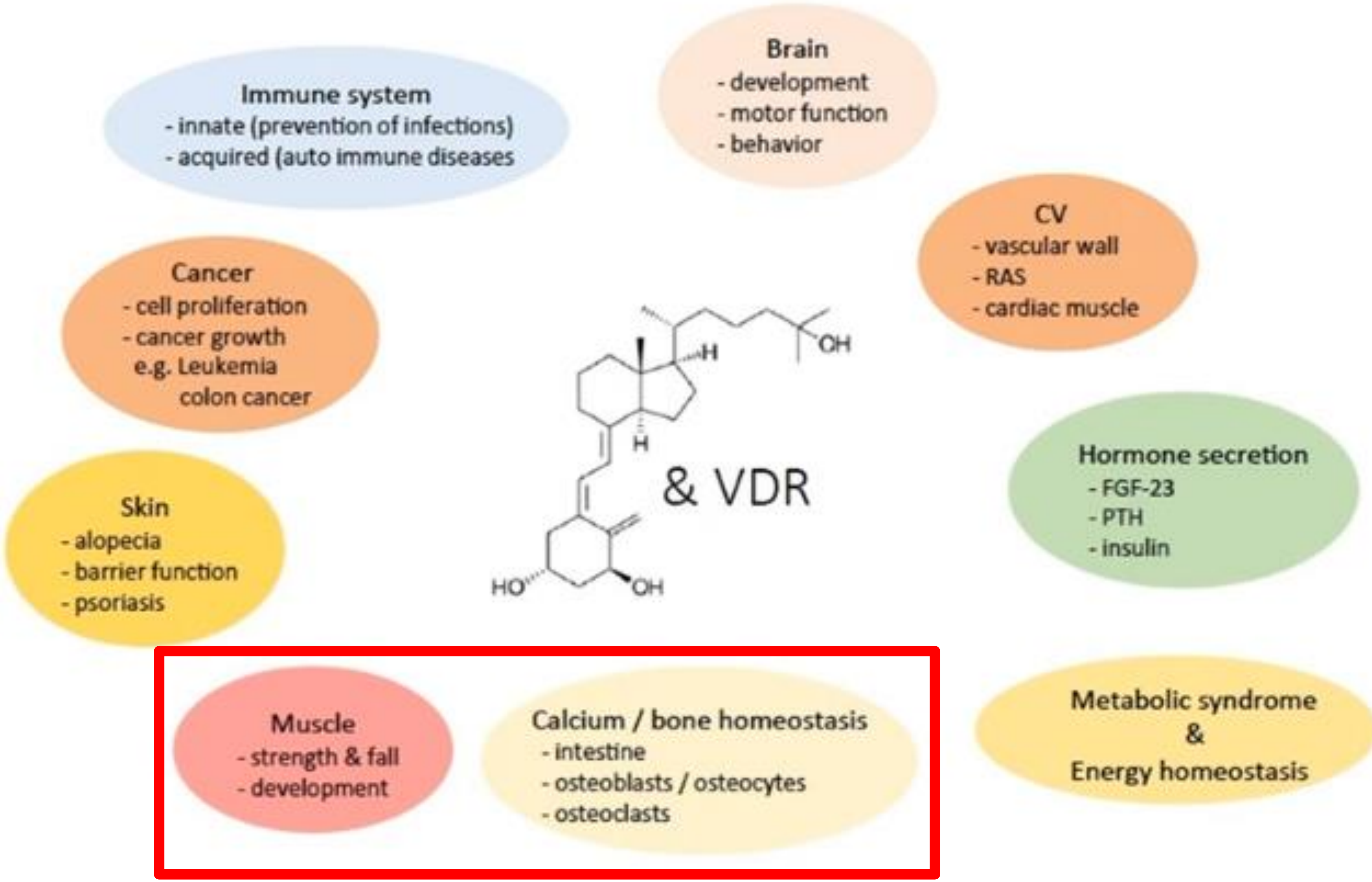
- ***Introduction and scope of the problem***
  *René Rizzoli*
- ***Prevalence of Vitamin D sufficiency/deficiency in patients admitted to the orthopaedic ward***
  *Nicholas Harvey*
- ***Benefits of Vitamin D in patients with fragility fracture***
  *Kyriakos Papavasiliou*
- ***Supplementation with Vitamin D during rehabilitation***
  *Giovanni Iolascon*
- ***Closing remarks*** - *Maria Luisa Brandi*

***Meet-The-Expert Session 5***

***Calcium-vitamin D, still a role in osteoporosis management?***

Elaine M. Dennison

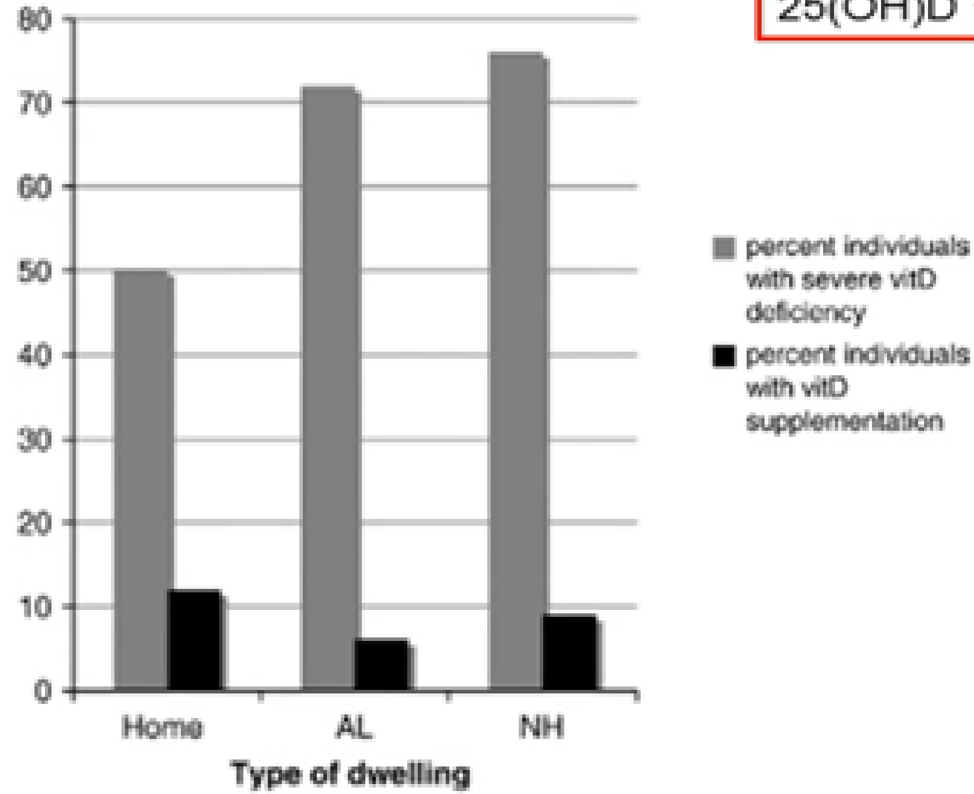
# Vitamin D System: Plurifunctions




*Bouillon & Carmeliet Best Pract Res Clin Endocr Metab 2018*

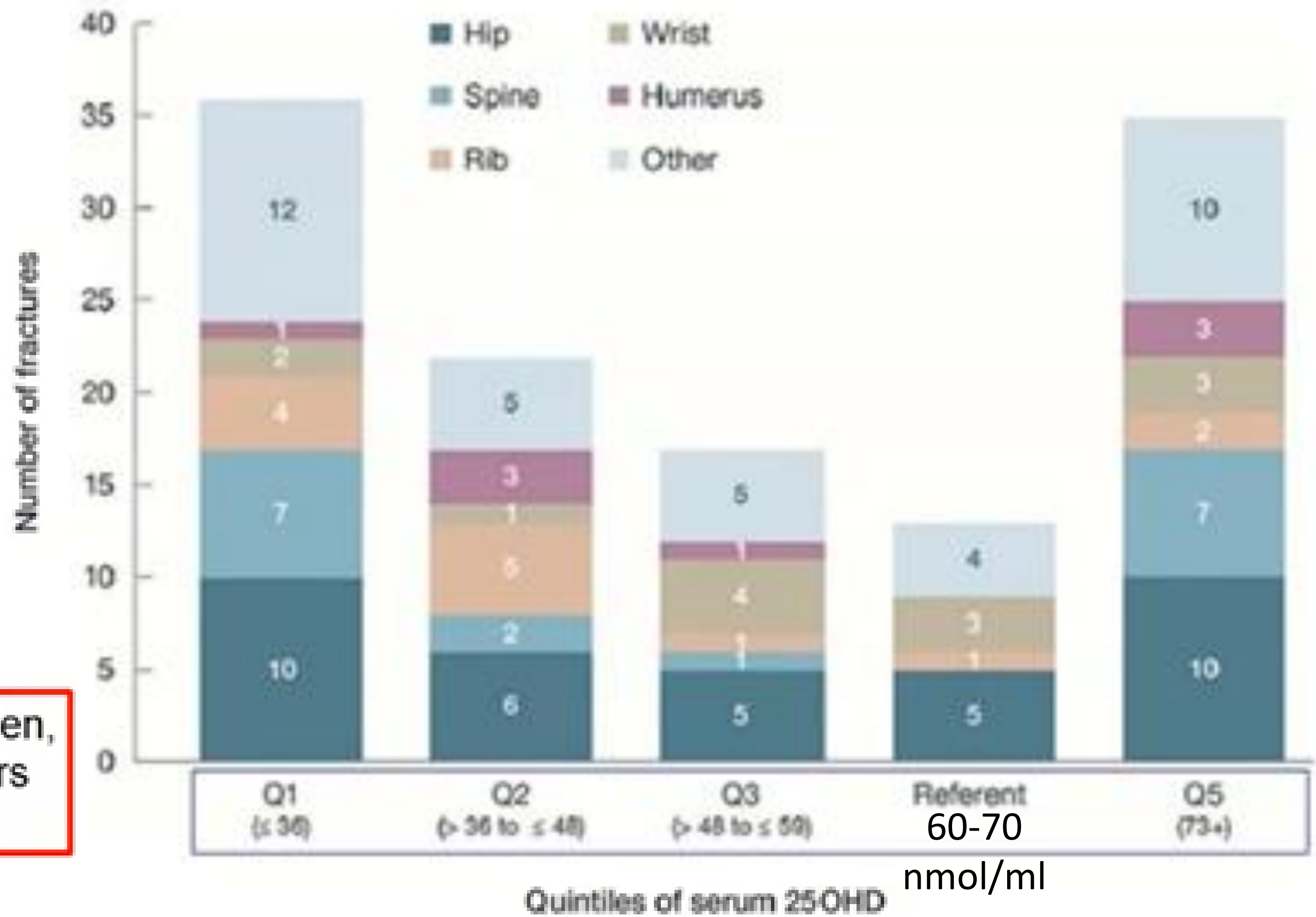
# Severe vitamin D deficiency in Swiss hip fracture patients

Severe 25(OH)D deficiency:
25(OH)D < 30 nmol/l ***(12 ng/ml)***




*Bischoff-Ferrari et al Bone 2008*

## U-Shaped Association Between Serum 25-Hydroxyvitamin D and Fracture Risk in Older Men: Results From the Prospective Population-Based CHAMP Study




1'662 Men,
70-97 Yrs
4.3 Yrs

*Bleicher et al JBMR 2014*

**TABLE 1** Baseline characteristics of patients[1]

| | Values |
|---|---|
| Age, y | 82 ± 7 (65–102) |
| Female sex, % | 73 |
| Caucasian race, % | 93 |
| BMI, kg/m$^2$ | 24.5 ± 4.7 (12.9–50.8) |
| <18.5 (underweight), % | 6 |
| 18.5 to <25.0 (normal weight), % | 54 |
| 25.0 to <30.0 (overweight), % | 30 |
| ≥30 (obese), % | 10 |
| 25-Hydroxyvitamin D, ng/mL | 22.0 ± 9.6 (2.9–57.4) |

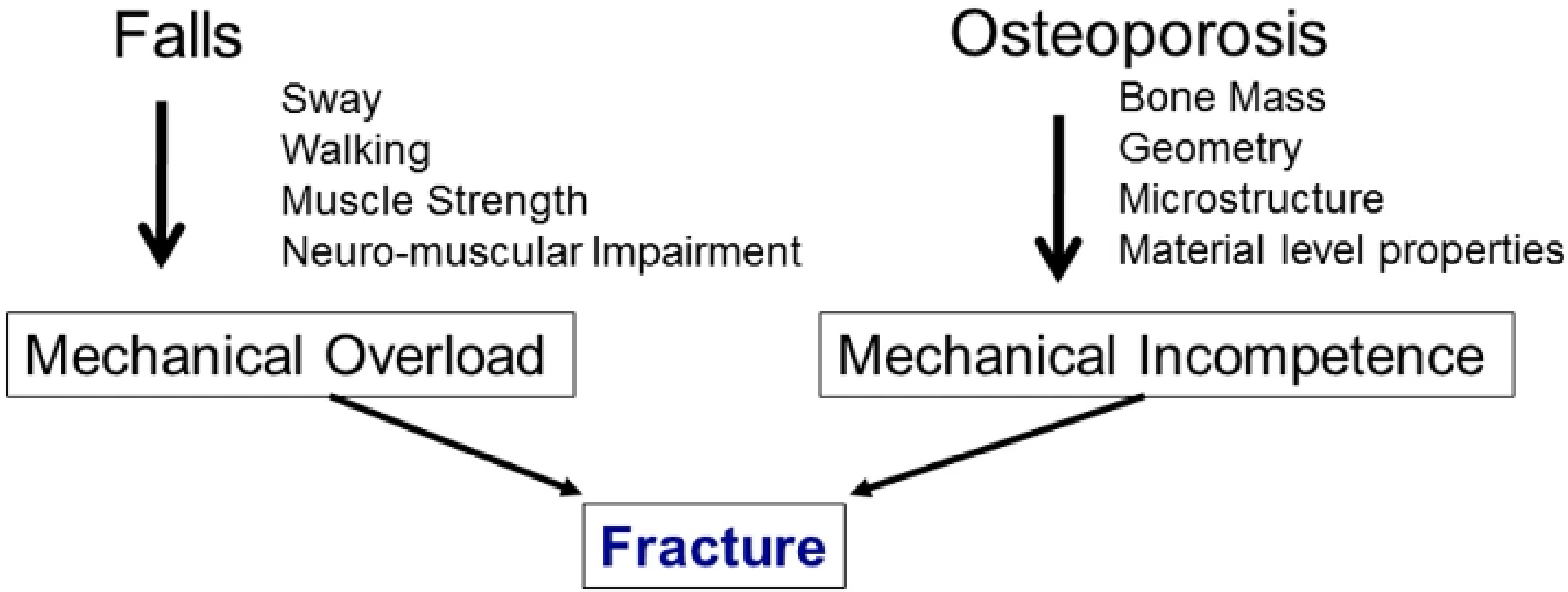
*pses*[1,2,3]

**TABLE 2** Association between preoperative vitamin D status and outcomes after hip fracture surgery[1]

| | Vitamin D concentration | | | | |
|---|---|---|---|---|---|
| | <12 ng/mL | 12 to <20 ng/mL | 20 to <30 ng/mL | ≥30 ng/mL | *P* overall |
| Ability to walk | | | | | |
| 30 d, % who walk | 35 | 56 | 64 | 58 | |
| Unadjusted OR (95% CI) | — | 2.30 (1.03, 5.17) | 3.24 (1.45, 7.26) | 2.57 (1.04, 6.36) | 0.040 |
| Adjusted OR (95% CI) | — | 2.61 (1.13, 5.99) | 3.48 (1.53, 7.95) | 2.84 (1.12, 7.20) | 0.031 |
| 60 d, % who walk | 51 | 67 | 74 | 73 | |
| Unadjusted OR (95% CI) | — | 1.89 (0.86, 4.15) | 2.70 (1.22, 5.95) | 2.62 (1.05, 6.55) | 0.079 |
| Adjusted OR (95% CI) | — | 2.67 (1.14, 6.25) | 3.42 (1.46, 8.00) | 3.67 (1.37, 9.82) | 0.028 |
| Mortality | | | | | |
| 30 d, % who died | 3 | 5 | 2 | 2 | |
| Unadjusted OR (95% CI) | — | 1.85 (0.21, 16.39) | 0.64 (0.06, 7.30) | 0.71 (0.04, 11.72) | 0.582 |
| Adjusted OR (95% CI) | — | 1.44 (0.15, 13.58) | 0.54 (0.04, 6.62) | 0.52 (0.03, 9.22) | 0.631 |
| 60 d, % who died | 11 | 9 | 6 | 2 | |
| Unadjusted OR (95% CI) | — | 0.80 (0.23, 2.79) | 0.46 (0.12, 1.72) | 0.16 (0.02, 1.51) | 0.304 |
| Adjusted OR (95% CI) | — | 0.56 (0.15, 2.08) | 0.34 (0.08, 1.40) | 0.11 (0.01, 1.05) | 0.206 |

[1] *n* = 290 patients in 4 categories: <12 ng/mL (*n* = 35), 12 to <20 ng/mL (*n* = 98), 20 to <30 ng/mL (*n* = 108), ≥30 ng/mL (*n* = 49); ORs were determined by binary logistic regression analysis, unadjusted or adjusted for age and sex.

# Osteoporotic Fracture




*Adapted from Rizzoli, Best Pract Res Clin Endocrinol Metab 2014*

# 25(OH)D decreases post-arthroplasty

| Biomarker | Before | 48 hours | p | Units |
|---|---|---|---|---|
| CRP | 5.0 (5.5) | 116.0 (81.2) | <0.0001 | mg/L |
| 25(OH)D | 56.2 (30.3) | 46.0 (27.6) | 0.0006 | nmol/L |
| VDBP | 334 (43) | 298 (37) | <0.0001 | mg/L |
| uVDBP:Cr | 8 (9) | 20 (25) | 0.0004 | pg/mmol |

Measures taken before and 48 hours post
knee or hip arthroplasty in 30 patients

Waldron et al., J Clinical Pathology 2012;66(7)

# 25(OH)D concentrations in orthopaedic patients

| Study | Country | Population (% female) | Mean (SD) age, years | Mean (SD) 25(OH)D, nmol/l | %25(OH)D <50 nmol/l < 20 ng/ml |
|---|---|---|---|---|---|
| Awal, Au J Ageing 2020 | Australia | 313 | 79.5 | | 34% |
| Hao, AJCN 2020 | USA | 290 (73%) | 82 (7) | 55 (24) | 46% |
| Bischoff-Ferrari, Bone 2008 | Switzerland | 222 (77%) | 86 | 34.6 (community); 24 (NH) | 80% |
| Cher, JBMM 2020 | Singapore | 801 (71%) | 77.7 (8) | - | 47.4% |
| Niikura, J Orthop Surg 2019 | Japan | 360 (78%) | 84.7 (8.2) | 41.3 (18) | 71.7% |
| Papaiannou, BMC MD 2011 | Canada | 65 (56%) | 78.5 (10.3) | 52.3 | |
| Ish-Shalom, JCEM 2008 | Israel | 48 (100%) | 81 (8) | 39.3 (25.3) | |
| Mak, BMCG 2014 | Australia | 218 (77%) | 83.9 (7.2) | 52.7 (23.5) | 47% |
| Moo, BMC MD 2020 | Singapore | 796 (71%) | 77.7 (8) | 50.1 (18.5) | 53.9% |

But variation in assay, population, timing all important
Where examined fewer associations with comorbidity etc than might be expected

Harvey N 2020

# Vitamin D and orthopaedic procedures

- **Arthroplasty:**
  - Low vitamin D levels may result in longer hospital stays following TJA
  - High prevalence of low vitamin D levels in TJA patients
  - Low vitamin D levels (< 20 ng/mL) associated with increased risk of postoperative complications, including periprosthetic joint infection
- **Knee Arthroplasty:**
  - Vitamin D deficient (< 12 ng/mL) patients undergoing TKA have significantly worse outcomes (KSS, alternative step-test, six-meter walk test)
  - Vitamin D deficient mice with intra-articular knee implants have increased bacterial burden and increased neutrophil infiltration in knee joint, reversible with vitamin D3 supplementation
- **Hip Arthroplasty:**
  - Lower pre- and postoperative Harris hip scores in vitamin D deficient THA patients
  - No association between vitamin D levels in THA patients & short-term postoperative outcomes (in-hospital milestones, length of stay, perioperative complications, WOMAC, SF-36, 2-minute walk test, & timed get up-and-go tests)

Moon et al. 2019

Elaine M. Dennison

*Calcium-vitamin D, still a role in osteoporosis management?*

# Conclusions

- Calcium is critical for bone mineralisation and MSK health
- Diet can make an important contribution to calcium requirements, but supplementation may be necessary in some cases
- Latest data are reassuring regarding CVD risk in calcium supplementation
- Requirements vary across the lifecourse
- Online calculators may help patients and physicians assess their dietary intake and requirements
- Physical activity is an important part of benefit, especially in earlier life

# How much calcium and D do you need and why?

The optimal intake of calcium and vitamin D is uncertain. Based upon the meta-analyses discussed below, we suggest 1200 mg of calcium (total of diet and supplement) and 800 international units of vitamin D daily for most postmenopausal women with osteoporosis. Although the optimal intake (diet plus supplement) has not been clearly established in premenopausal women or in men with osteoporosis, 1000 mg of calcium (total of diet and supplement) and 600 international units of vitamin D daily are generally suggested. We recommend **not** administering yearly high-dose (eg, 500,000 international units) vitamin D.

These recommendations are consistent with the Institute of Medicine Dietary Reference Intakes for calcium and vitamin D [1]. The American Geriatrics Society and the National Osteoporosis Foundation recommend a slightly higher dose of vitamin D supplementation (at least 1000 and 800 to 1000 international units daily, respectively), as well as calcium supplements, to older adults (≥65 years) to reduce the risk of fractures and falls [2,3]. (See 'Efficacy' below and "Falls: Prevention in community-dwelling older persons", section on 'Vitamin D supplementation'.)

Harold Rosen, UpToDate 2021

# Up to date 2021

## Calcium and vitamin D supplementation in osteoporosis

Harold N Rosen

The optimal intake of calcium and vitamin D is uncertain. Based upon the meta-analyses discussed below, we suggest:
**calcium 1200 mg** (total of diet and supplement) and
**vitamin D 800 international units daily** for postmenopausal osteoporosis.
Although the optimal intake (diet plus supplement) has not been clearly established in premenopausal osteoporosis (or in males with osteoporosis), **1000 mg of calcium (total of diet and supplement) and 600 international units of vitamin D daily are generally suggested**.
**We recommend not administering yearly high-dose** (eg, 500,000 international units) vitamin D.
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***The effects of vitamin K on bone; beyond coagulation***

Chairperson: *Bo Abrahamsen*

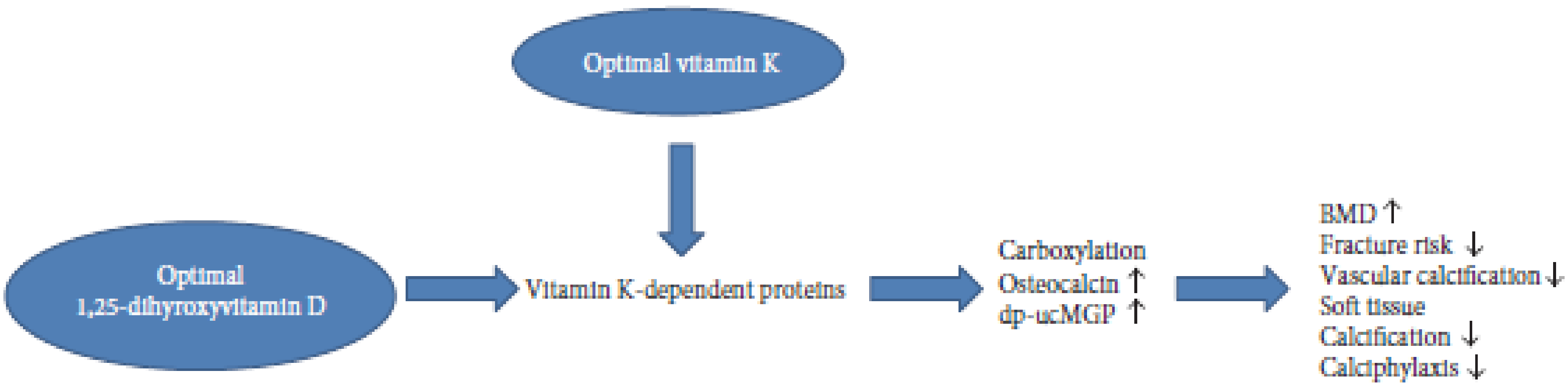
**The biology of the active forms of vitamin K.**

*Dominic Harrington*

**The effects of vitamin K on bone health**

*Geeta Hampson*

# Simplified overview of potential synergy between vitamins D and K and bone and cardiovascular health




International Journal of Endocrinology 2017

# Who's at risk of vitamin K deficiency?

- Those at beginning and end of life / malaborption/ the anorexic patient (stores depleted <3 days)
- Overt deficiency causes bleeding
- Subclinical deficiency (with respect to functionality of extra-hepatic vitamin K-dependent proteins) is common

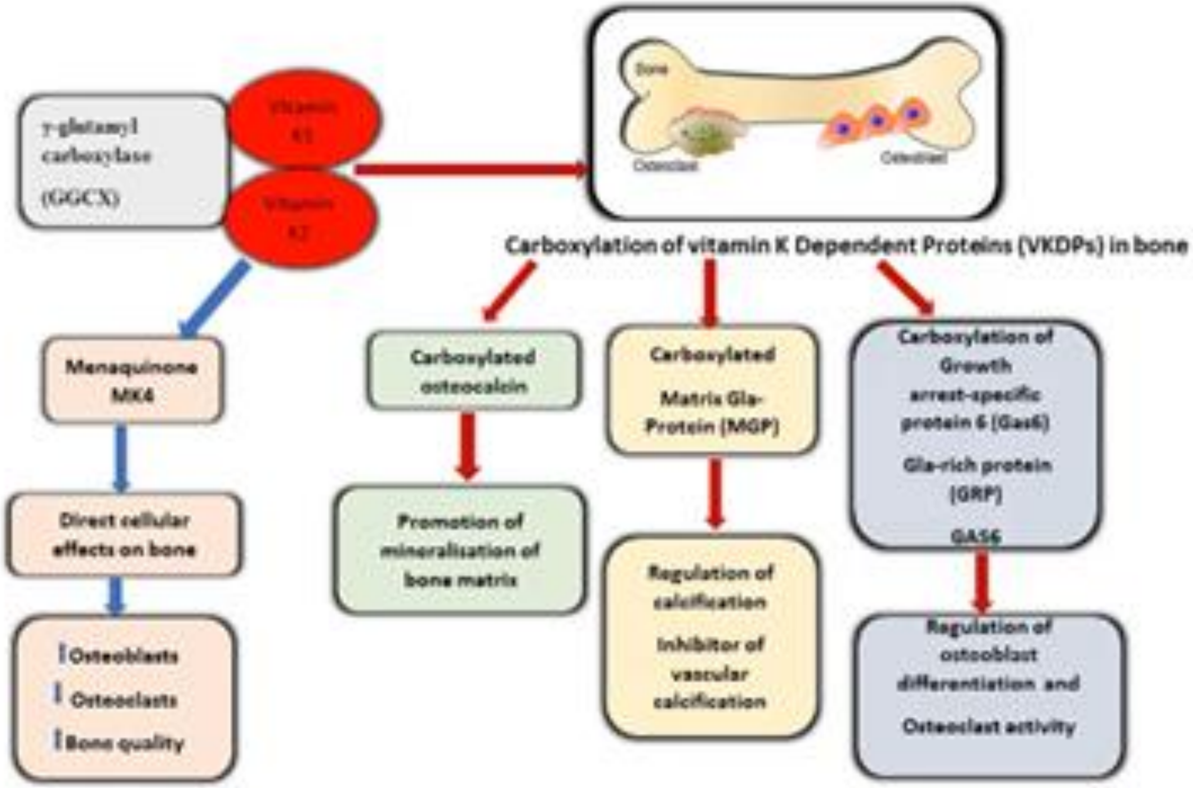
# Risk factors for deficiency

- Suboptimal dietary intake
- Intestinal malabsorption as a consequence of pancreatic insufficiency and bile salt deficiency
- Liver disease, diarrhoea, frequent antibiotic therapy, bowel resection
- Exposure to vitamin K antagonists (warfarin or superwarfarin
- Inborn errors of metabolism – VKCFD1 (carboxylase) and VKCFD2 (KVOR)

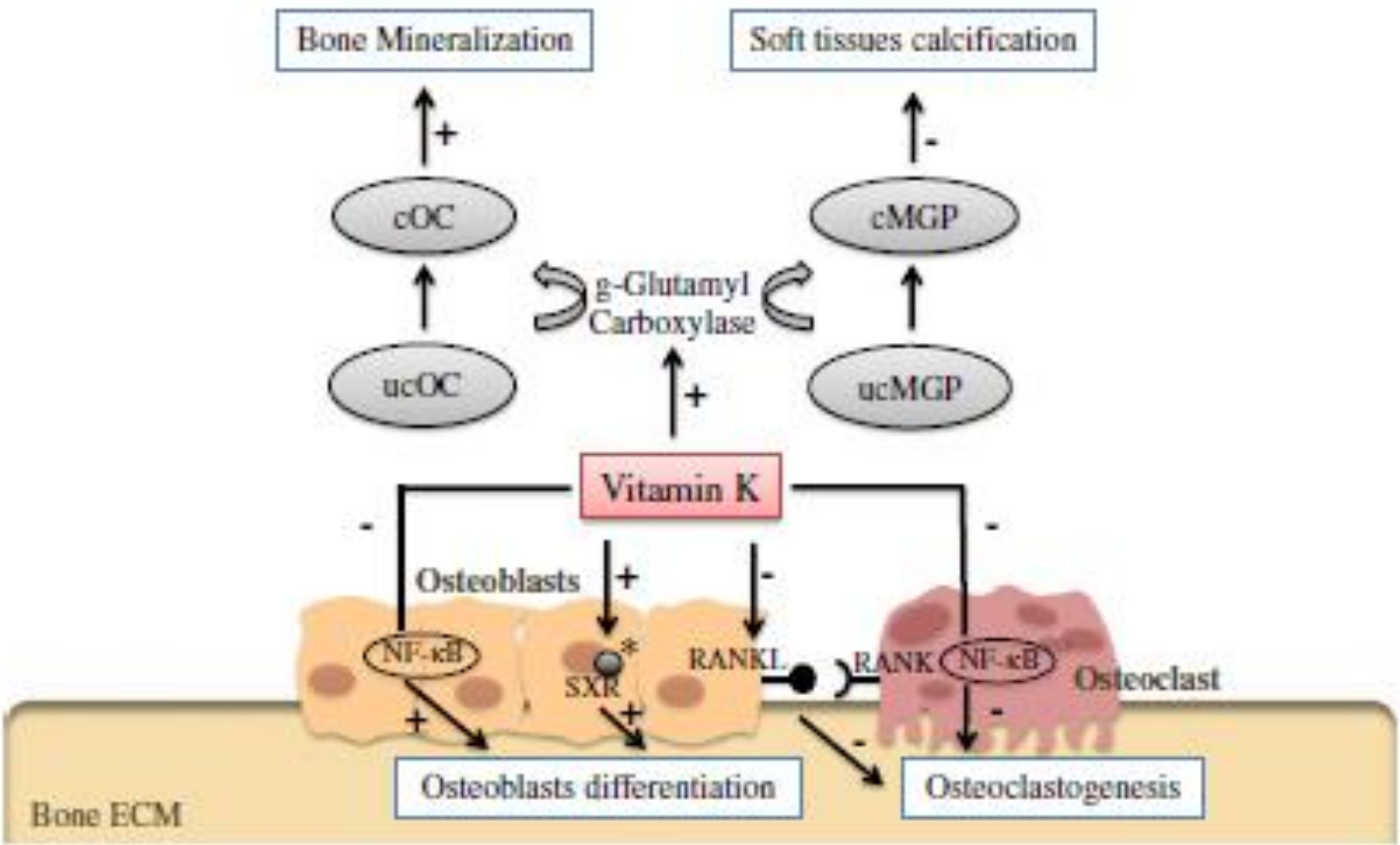
# Summary

- Sub optimal status in 21$^{st}$ Century UK?
- Often missed because laboratory diagnostic tools are insensitive or have poor specificity (or both)
- Biochemical evidence of suboptimal status is common in several cohorts

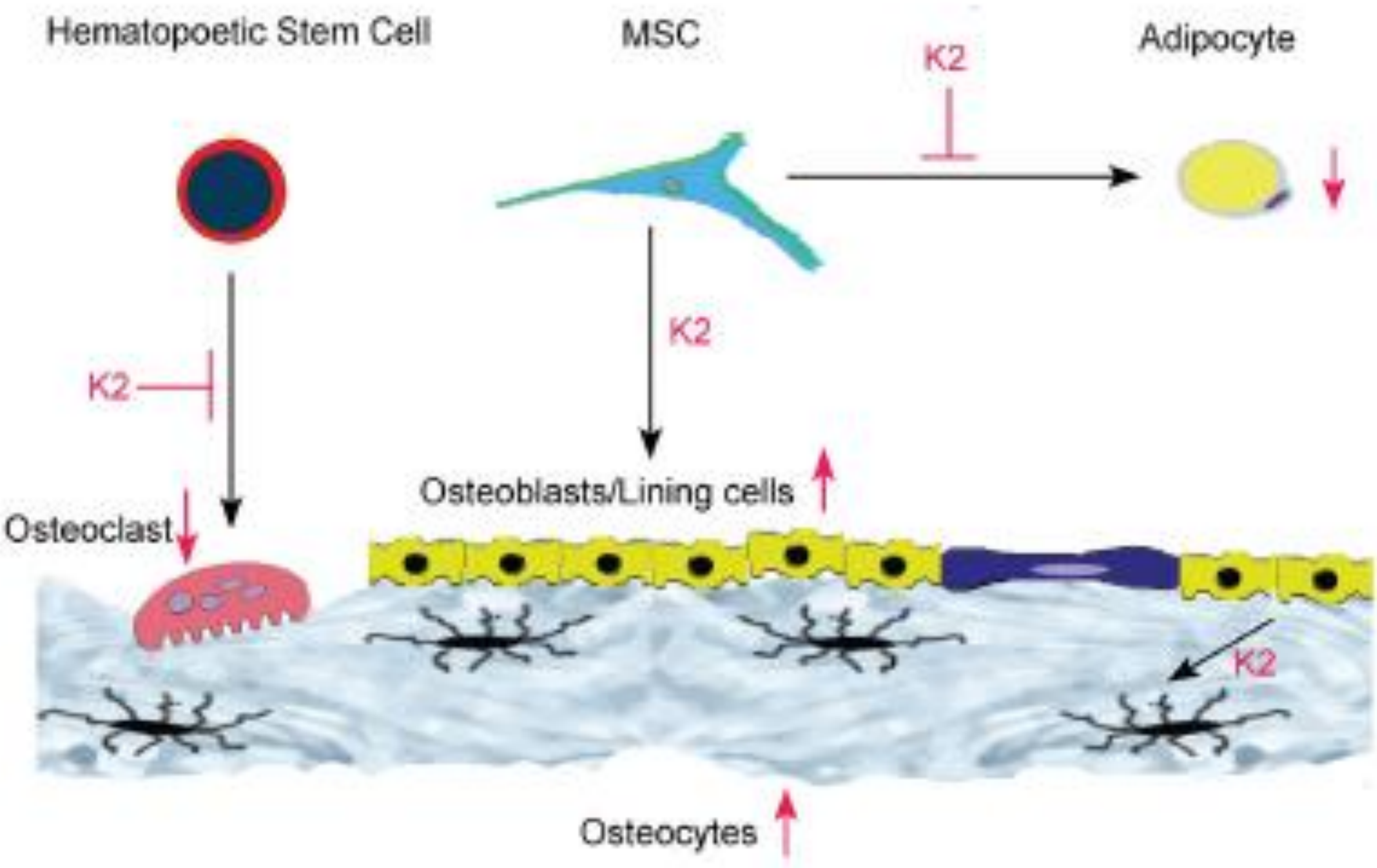
# Vitamin K and skeletal metabolism



# Φυσιολογική δράση της βιταμίνης Κ στα Οστά και Αγγεία (μαλακούς ιστούς)



# Cellular targets of vitamin K2 in bone remodelling




Oral Dis. 2017; 23(8): 1021–1028.

## Summary

- Vitamin K dependent binding proteins (VDBPs) include a number of proteins present in bone such as osteocalcin, matrix-gla protein which are involved in bone formation and mineralization

- Low dietary intake of vitamin K1 and low serum concentrations have been associated with an increased fracture risk which may be independent of bone mineral density

- The recommended nutrient intake (RNI) is 1µg/kg body weight per day of K1. Higher intakes may be required to fully carboxylate the bone-specific VKBPs.

- Intervention trials of vitamin K1 and K2 have shown a potential effect on the reduction of clinical fractures in post-menopausal women but data are inconclusive. Further studies are needed to support this.

# (OP4 - P397) LEONIE STUDY: POOR COMPLIANCE WITH PATIENT INSTRUCTIONS FOR TAKING ORAL BISPHOSPHONATES

K. Briot1 , B. Cortet2 , P. Fardellone3 , T. Thomas4 , F. Tremollières5 1 Rhumatology, Hôpital Cochin, Paris, 2 Rhumatology, CHU de Lille, Lille, 3 Rhumatology, CHU Amiens, Amiens, 4 Rhumatology, Hôpital Nord Saint-Etienne, Saint-Etienne, 5 Menopause, CHU Purpan, Toulouse, France

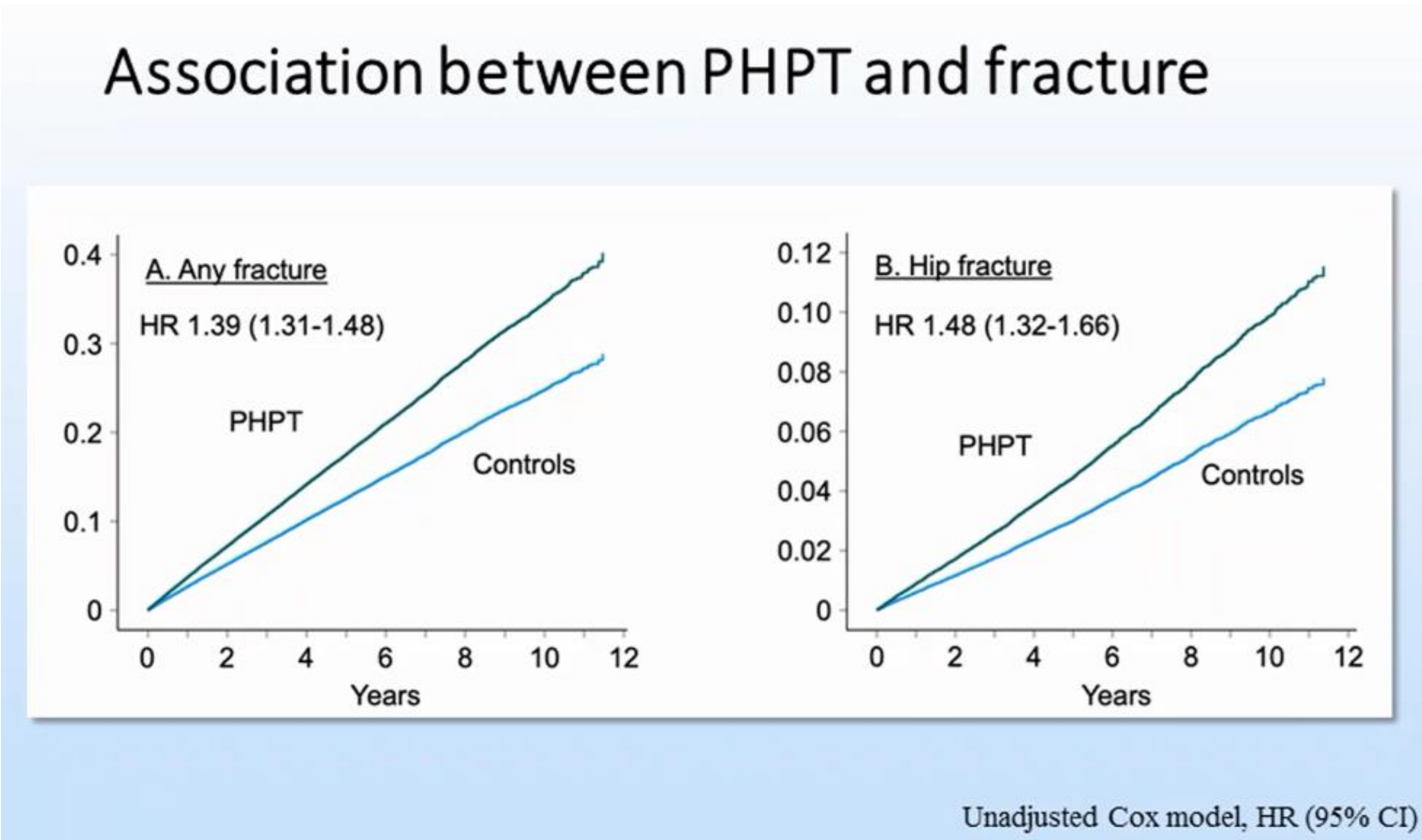
**Conclusion**: The results of the LEONIE study show

- high rate of poor compliance with the patient instructions which are essential for a good absorption of oral BPs
- risk of poor bioavailability of drugs and therefore reduced therapeutic efficacy.
- They strongly suggest that education of physicians, pharmacists and patients to this issue is mandatory.
- The use of gastro-resistant oral forms may also be of interest with the objective of circumvent poor compliance to appropriate drug intake conditions

# OC14

## *PARATHYROIDECTOMY IS ASSOCIATED WITH REDUCED RISK OF FRACTURE AND CARDIOVASCULAR EVENTS IN PATIENTS DIAGNOSED WITH PRIMARY HYPERPARATHYROIDISM - A NATIONAL, RETROSPECTIVE COHORT STUDY*

Presenting author: M. Lorentzon
Authors: K. F. Axelsson, M. Wallander, H. Johansson, N. C. Harvey, L. Vandenput, E. V. McCloskey, L. Enwu, J. A. Kanis, H. Litsne



# Conclusion

- Patients with primary hyperparathyroidism have increased risk for fractures, cardiovascular events and death
- Parathyroidectomy was associated with reduced risk of fractures and cardiovascular events, which could be due to a beneficial effect of surgery or to a bias in the selection of patients for surgery

# ECTS 2021 – Digital Congress
Virtual Lobby

# 48th European Calcified Tissue Society Congress


**ECTS 2021 Digital Congress, 6 – 8 May 2021, followed by the ECTS@Home from 19 – 20 May, 10 – 11 June and on 18 June 2021**

Poster number P159

# Effect of Hormone Replacement Therapy on Bone Formation Quality and Mineralization Regulation Mechanism in Early Postemenopausal Woman

*Gamsjaeger S, Eriksen E, Paschalis EP*

LUDWIG BOLTZMANN INSTITUTE Osteology

07.05.2021

# Materials and Methods

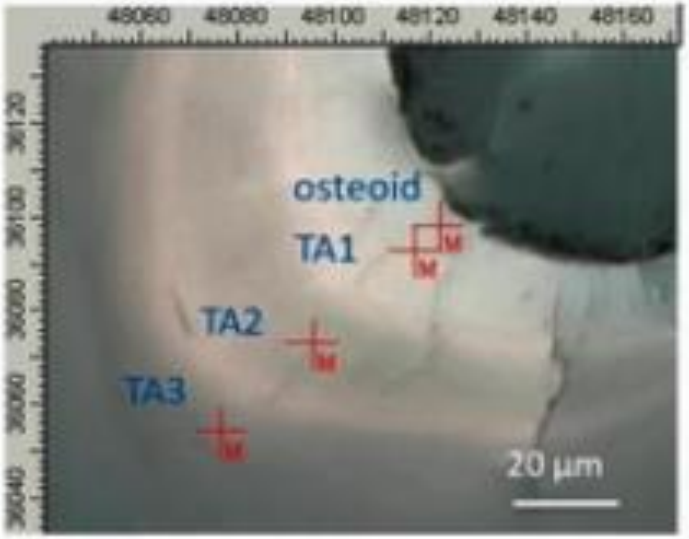
## Patients

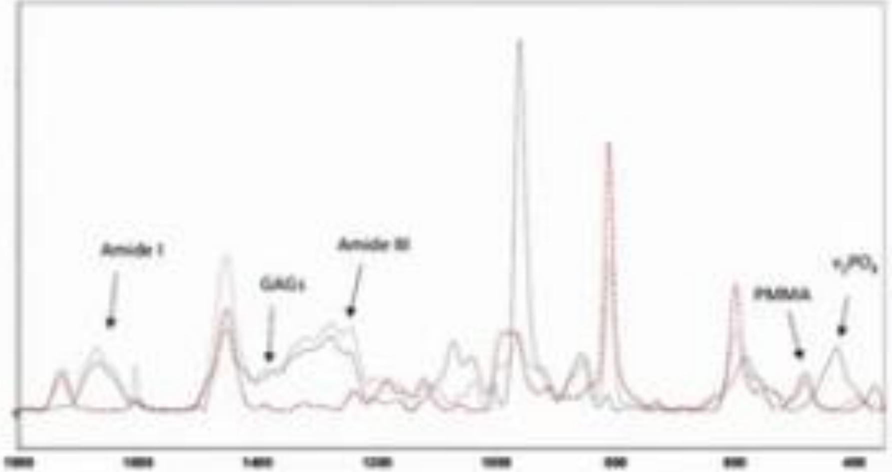
Paired iliac crest biopsies from 10 early postmenopausal woman, total number of biopsies =20, 45-55 years of age and no medication or known influence on calcium metabolism

## Raman microspectroscopy outcomes

- Mineral / matrix ratio (MM)
- Tissue water content (TW)
- Glycosaminoglycan content
- Relative sulfated protegoglycan content
- Pyridinoline content (PYD)
- Mineral maturity/ crystallinity (MMC)

Area selection criteria

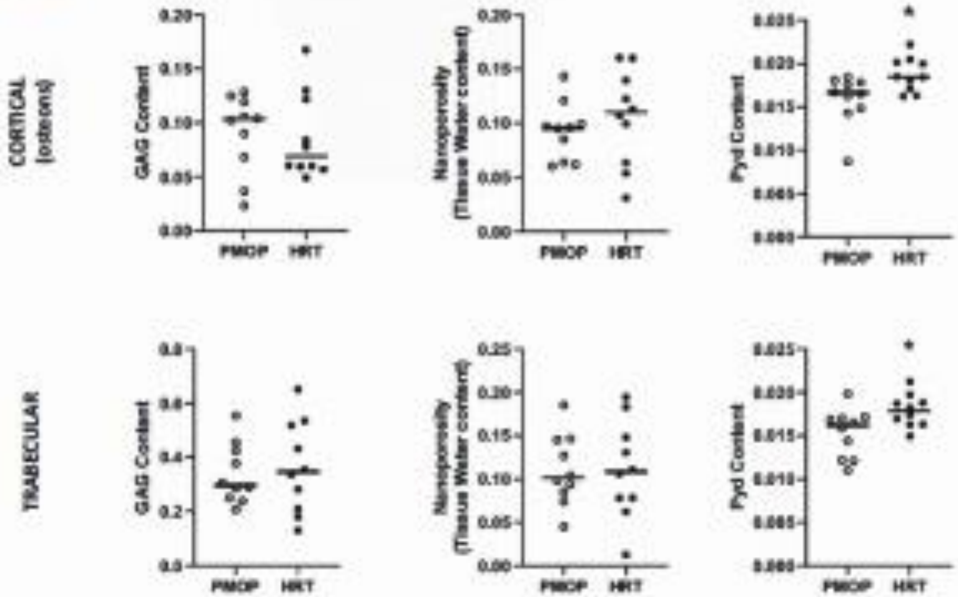



LUDWIG BOLTZMANN INSTITUTE Osteology

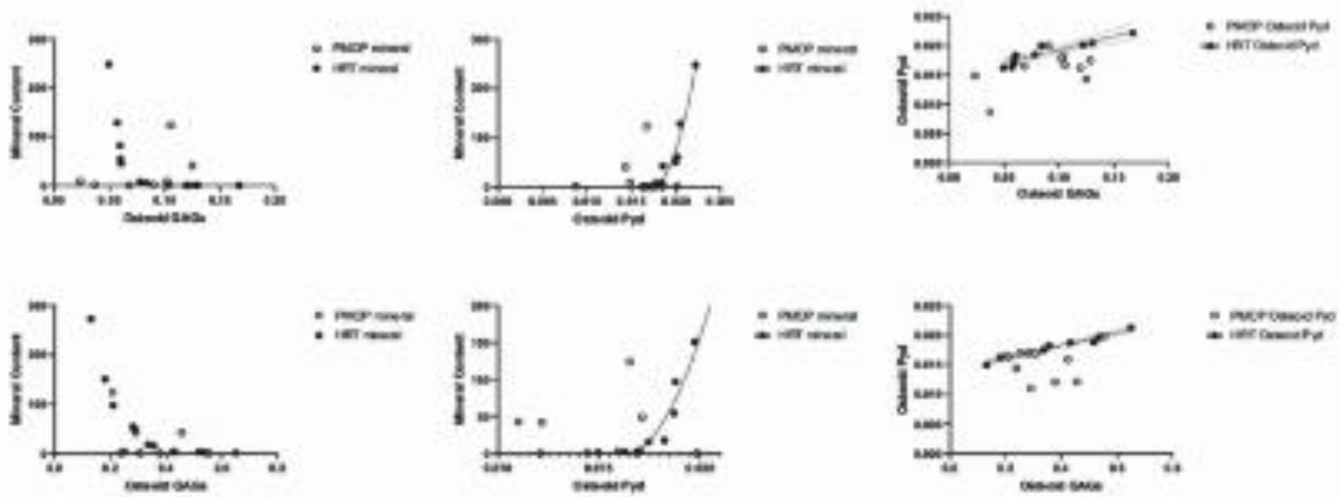

1. Paschalis et al. 2003 Effect of hormone replacement therapy on bone quality in early postmenopausal women. JBMR
2. Paschalis et al. 2016 Aging versus postmenopausal osteoporosis: bone composition and maturation kinetics at actively-forming trabecular surfaces of female subjects aged 1 to 84 years. JBMR
3. Paschalis et al. 2017 Ovarianhormone depletion affects cortical bone quality differently on different skeletalenvelopes. Bone
4. Paschalis et al. 2019 Estrogen depletion alters mineralization regulation mechanisms in an ovariectomized monkey animal model. Bone

# Results



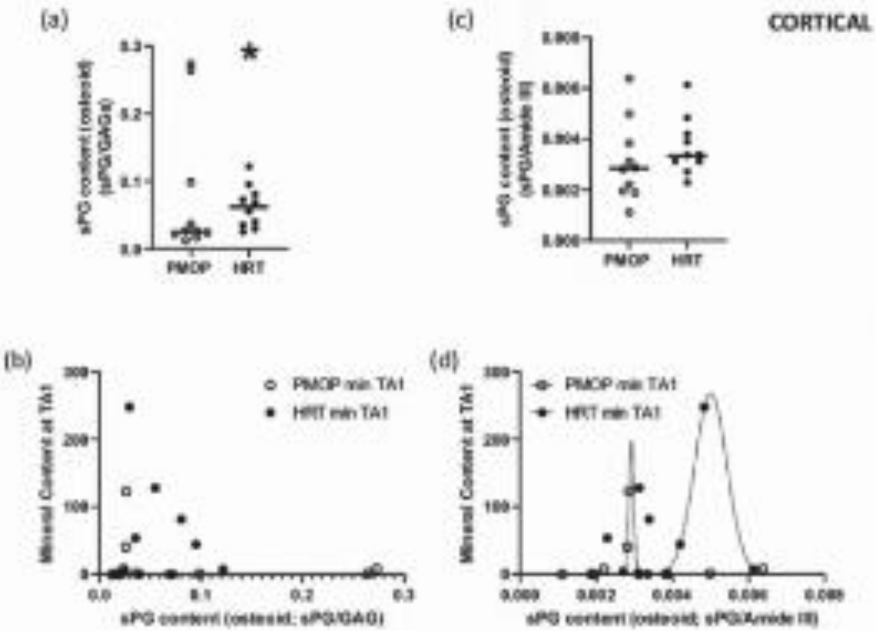

Osteoid of forming cortical and trabecular surfaces

Correlation between osteoid and earliest formed mineral



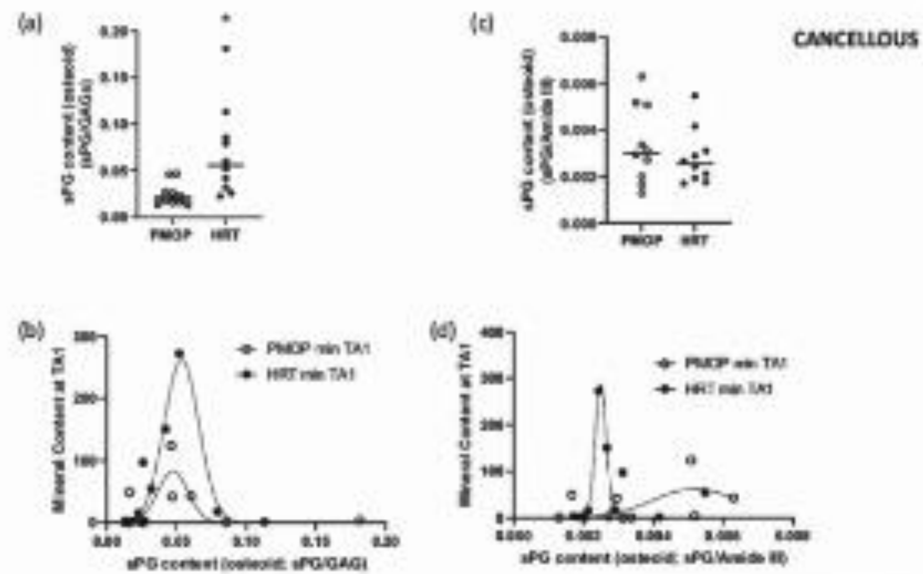

LUDWIG BOLTZMANN INSTITUTE
Osteology

# Results




**Sulfated proteoglycans in the cortical (osteons) forming surfaces**

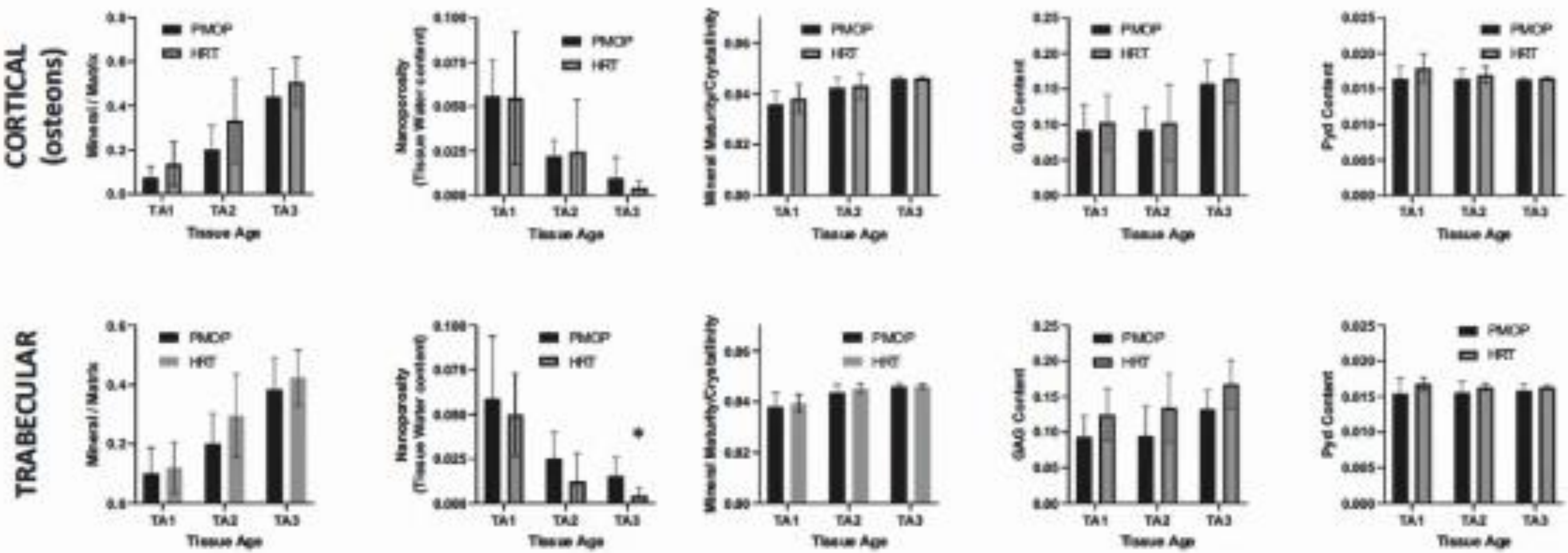
**Sulfated proteoglycans in the trabecular forming surfaces**




LUDWIG BOLTZMANN INSTITUTE
Osteology

# Results

**Bone quality of youngest mineralized tissue**

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Osteology

# Summary

- Early postemopausal women exhibit limited correlations between osteoid composition and earliest deposited mineral content.
- HRT administration for two years affects the osteoid composition.
- HRT administration for two years affects mineralization regulation mechanisms.

LUDWIG BOLTZMANN INSTITUTE Osteology

COP30

# Bone analysis revealed high bone resorption in Idiopathic Osteoporosis in young adults

Bastien Leger, Agnès Ostertag, Thomas Funck-Brentano, Caroline Marty, Corinne Collet and Martine Cohen-Solal

INSERM U1132 et Paris Université
Rheumatology department, hôpital Lariboisière
Paris

## Background

- Idiopathic osteoporosis (IO) is uncommon disorder in young adults before the age <50-55 years.
- The pathogenesis is reported as an osteoblast dysfunction. (Cohen JCEM 2011) However, the mechanism remains unclear.

- The aim of the study was to **describe the histomorphometric and microarchitecture profile in IO**.

# Methods

- Bone biopsy (BB) collection from Lariboisiere hospital included 19 biopsies from **19 IO patients,** performed after exclusion of any secondary causes (i.e. endocrine, GI, treatment, eating disorders)

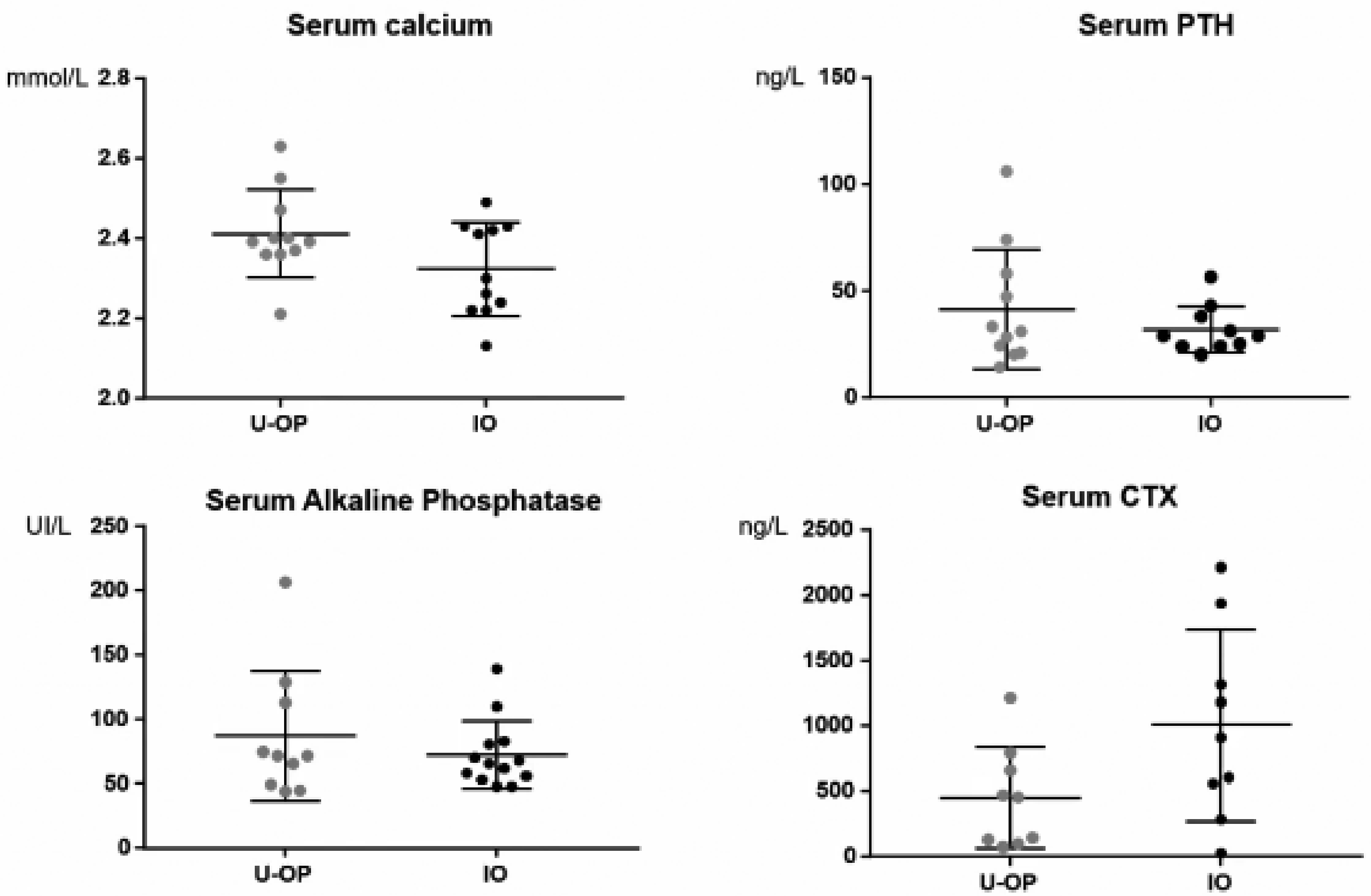
- **BB of IO were compared to 2 groups** :
  - 16 postmenopausal controls without osteoporosis (Ctrl) (De Vernejoul 1981)
  - 31 untreated postmenopausal osteoporotic (U-OP)
  - Mean range of literature was also reported (Recker Bone 2018)

- Microarchitecture of BB was analyzed using microcomputed tomography
- Histomorphometric analysis for the quantification of the cellular profiles
- DXA, serum bone biomarkers were collected

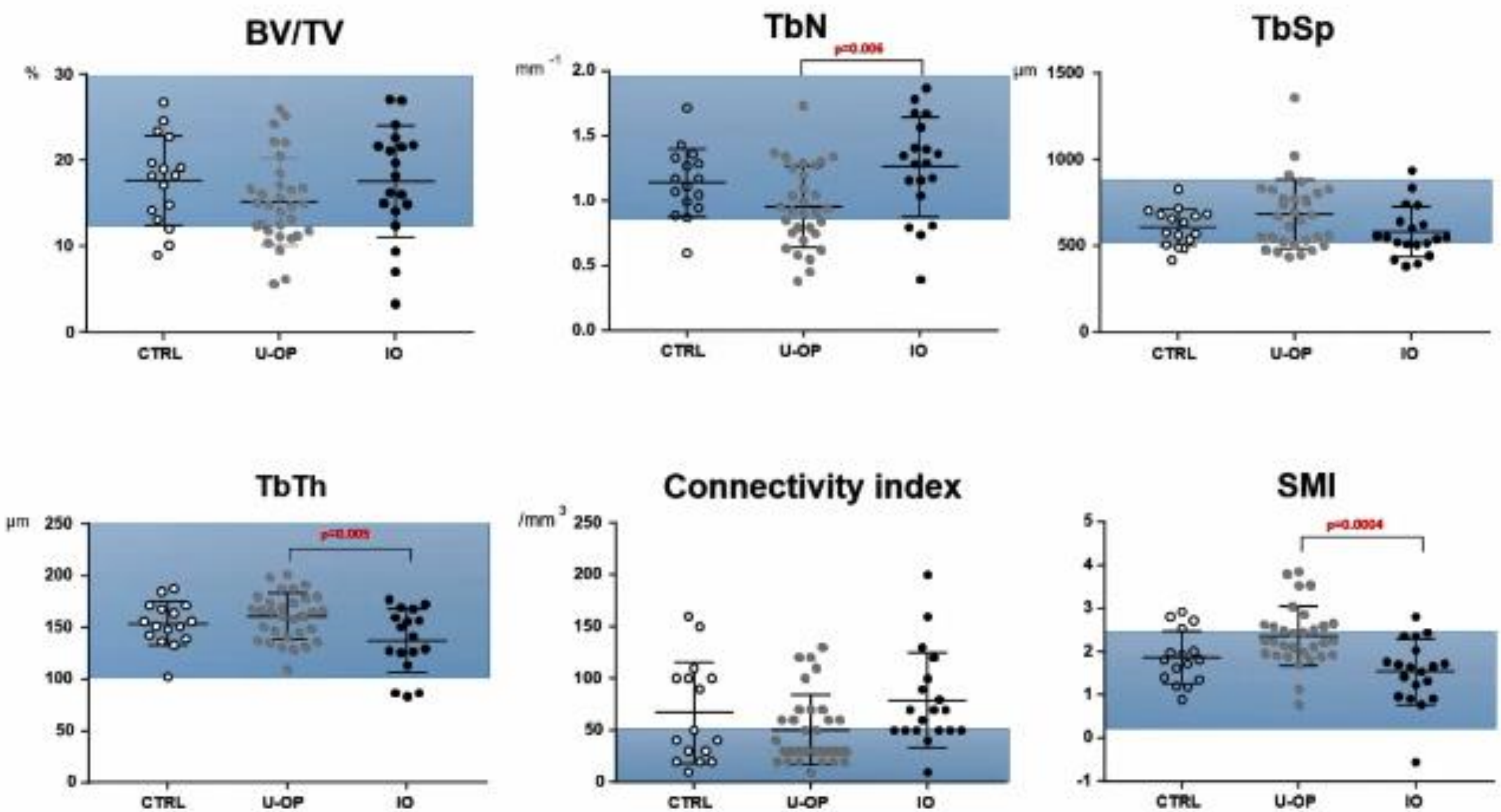
# Table : Clinical, DXA, and biological parameters

| | Control | U-OP | IO | p-value |
|---|---|---|---|---|
| | n=16 | n=31 | n=19 | |
| | mean ± SD | mean ± SD | mean ± SD | |
| **Clinical** | | | | |
| Female (n) | 100% (16) | 87% (27) | 63,2% (12) | <0.05 |
| Age (years) | 61.9 ± 7.7 | 63.3 ± 9.3 | 34.2 ± 8.5 | <0.0001 |
| BMI (kg/m²) | NA | 25.8 ± 6.5 | 24.0 ± 5.1 | 0.465 |
| **DXA** | | | | |
| Lumbar Spine density (g/cm²) | NA | 0.921 ± 0.192 | 0.893 ± 0.171 | 0.743 |
| Total hip density (g/cm²) | NA | 0.786 ± 0.093 | 0.769 ± 0.112 | 0.724 |
| **Biology** | | | | |
| Ca2+ (mmol/L) | NA | 2.4 ± 0.1 | 2.3 ± 0.1 | 0.080 |
| Phosphorus (mmol/L) | NA | 1.08 ± 0.280 | 0.98 ± 0.18 | 0.325 |
| Vitamine D (ng/mL) | NA | 40.4 ± 18.6 | 35.5 ± 12.7 | 0.464 |
| PTH (ng/L) | NA | 41.5 ± 28.0 | 32.0 ± 11.0 | 0.560 |
| ALP (UI/L) | NA | 87.2 ± 50.5 | 71.6 ± 27.2 | 0.366 |
| Osteocalcine (µg/L) | NA | 27.3 ± 13.7 | 24.6 ± 15.6 | 0.702 |
| Crosslaps (ng/L) | NA | 447.6 ± 387.7 | 1002.8 ± 733.6 | 0.167 |

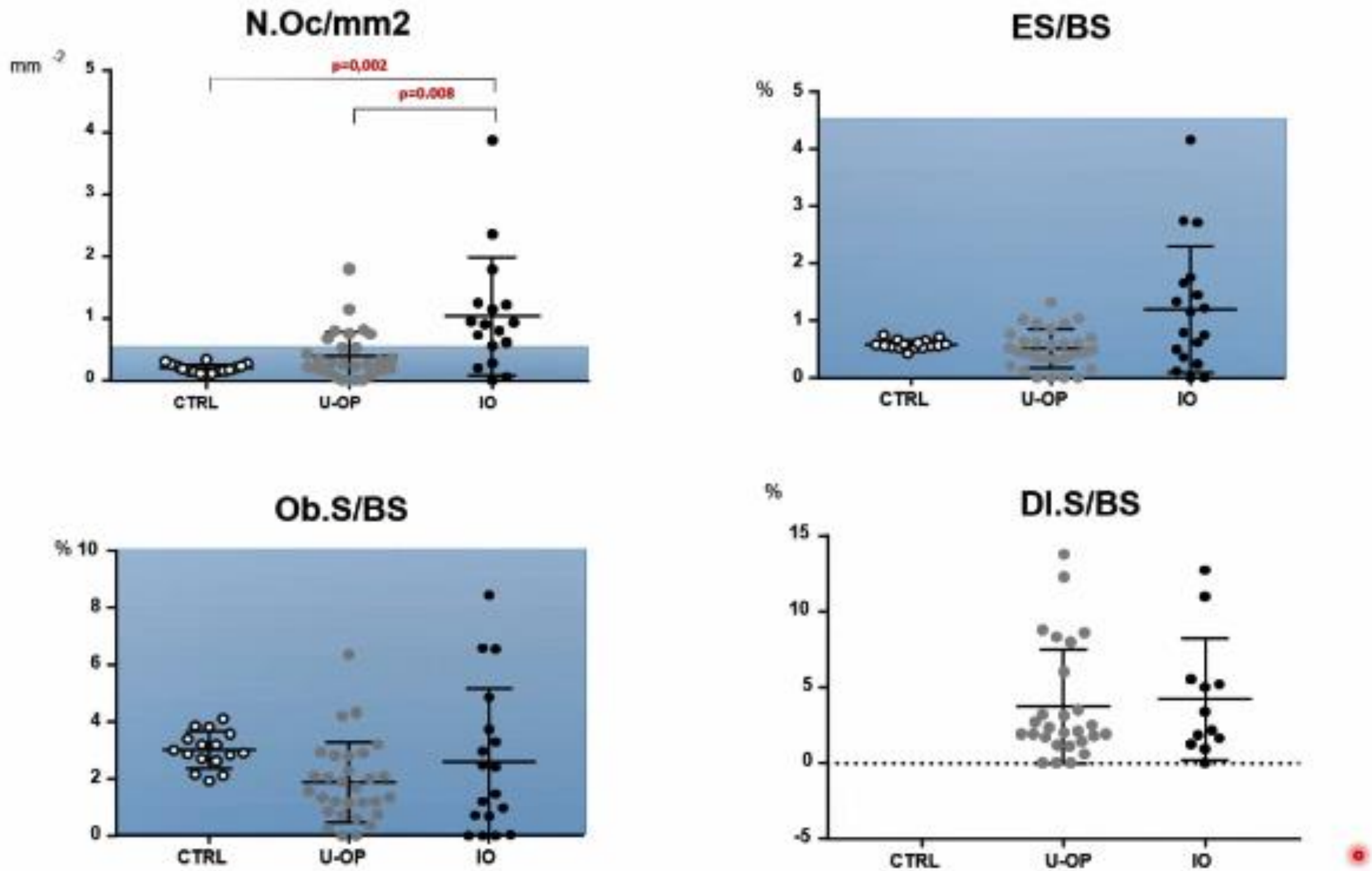
## Biochemical markers of bone remodeling



## Microarchitecture analysis



# Histomorphometric analysis



## Conclusion

BB profile of IO patients showed :

- no differences in terms of bone volume, but lower TbTh, indicating reduced bone formation
- **A large variation** in osteoclast and osteoblast parameters.
- **Low bone formation** and **unexpected high bone resorption** compared to U-OP and controls women despite younger age.

The persistent bone resorption in IO might be responsible to bone fragility in addition to reported reduction in bone formation.

**ECTS**

**Thursday, May 6th, 10:30 - 11:30, Stream 1**

**Session code:**10

**Session title:** Plenary Symposium 1: What is New (WIN)?

**Session type:** Plenary Symposium

**Track:** Clinical & Basic

# PS1-2- New therapeutic strategies

## *Kenneth Saag*

***Congratulations to Kenneth Saag recipient of the 2021 Excellence in Research Award***

# Approach to Selection of Topics

- Predominately articles published in 2020 and 2021
- Emphasis on RCTs and ancillary studies on what's new or controversial
    - Bisphosphonates?
    - Denosumab?
    - Anabolics?
- Focus on romosozumab
- Review of quality improvement RCTs

# What's New/Controversial with Bisphosphonates?

# Bisphosphonate Potential Safety Issues

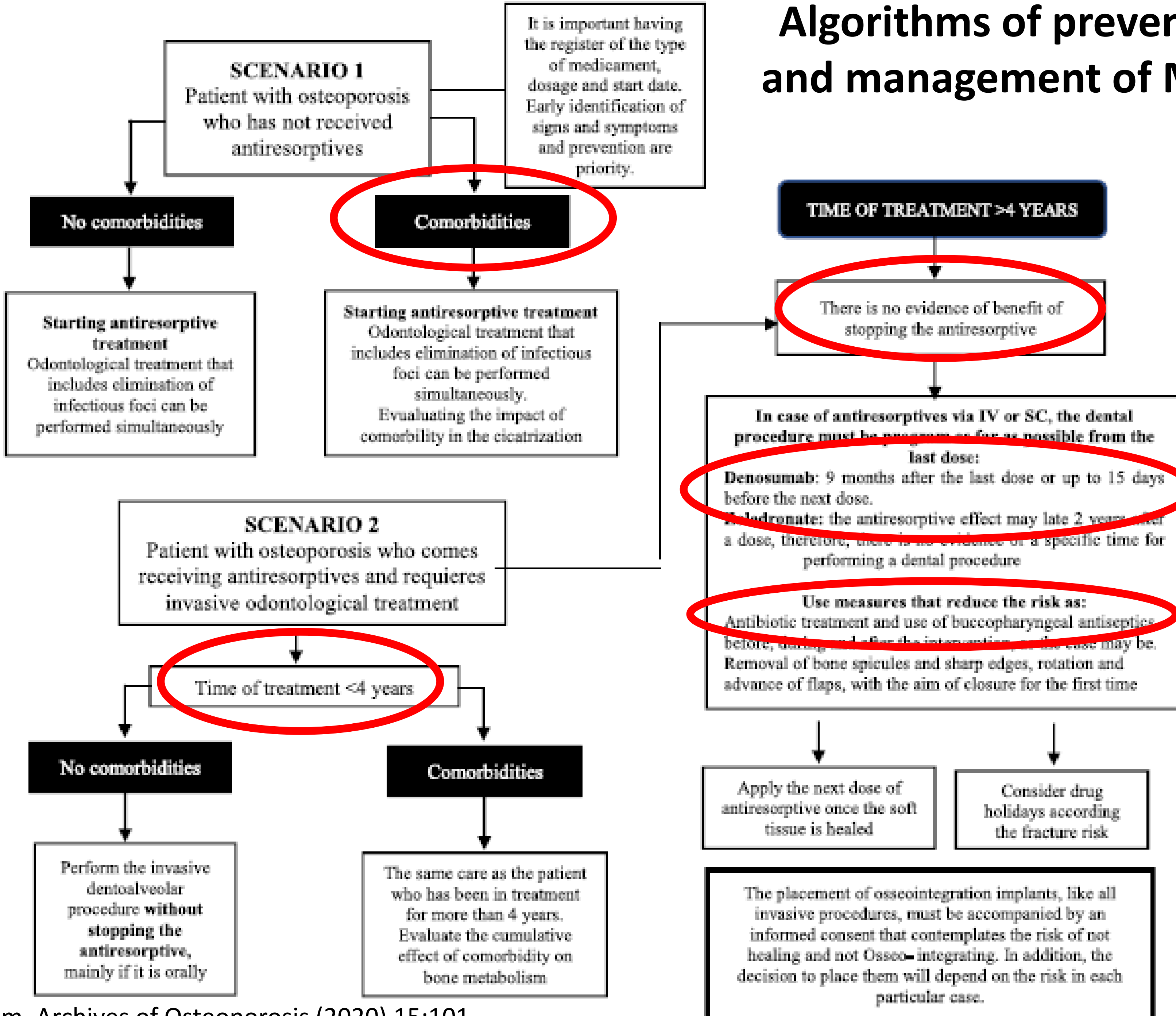
- Osteonecrosis of the Jaw (ONJ)
- Atypical Fractures
- Acute phase reactions
- Esophageal Cancer
- Atrial Fibrillation
- Fracture Non-union
- Uveitis

# Prevention of ONJ

- **Prior to Anti-resorptive Treatment**
  - Remove oral infection, pathology and use antibiotics
  - Extract partially embedded or very poor teeth
  - Periodontal stabilization for teeth with excessive mobility in patients with good dental hygiene
  - Anti-resorptives deferred until surgical sites mucosalized (2–3 weeks)
  - Inadequate dentures modified, rebased, or replaced, especially along lingual flange region or at mandibular tori
- **After anti-resportive treatment- Prior to invasive dental treatments**
  - Bone turnover markers (CTX/NTX) generally <u>not</u> helpful
  - Debate over bisphosphonate discontinuation- consider 2 month break


Marx RE. *J Oral Maxillofac Surg* 2005;63:1567
Hellstein JW. *J Am Dent Assoc* 2011;142:1243
Vandone AM. *Ann Oncol* 2012;23:193
Ruggiero SL. *J Oral Maxillofac Surg* 2014;72:1938

# Algorithms of prevention and management of MONJ




M Chalem, Archives of Osteoporosis (2020) 15:101

# Duration of Bisphosponates (BPs) and Atypical Femoral Fractures (AFF)

## (n = 87,820 women)

- 16,180 continued BP for ≥ 3 years
- Forty-six confirmed AFFs occurred during follow-up
- AFF-free survival significantly greater for BP treatment < 3 years compared to treatment ≥3 years (p = 0.004)

**Risk of AFF per 100,000**

| | < 3 years BP | ≥ 3 yrs BPs |
|---|---|---|
| At 5 Years | 27 | 120 |
| At 10 years | 27 | 363 |

Lo JC. *BMC Musculoskel Dis* 2020;21:801

# What Happens After a Drug Holiday of > 2 yrs ?

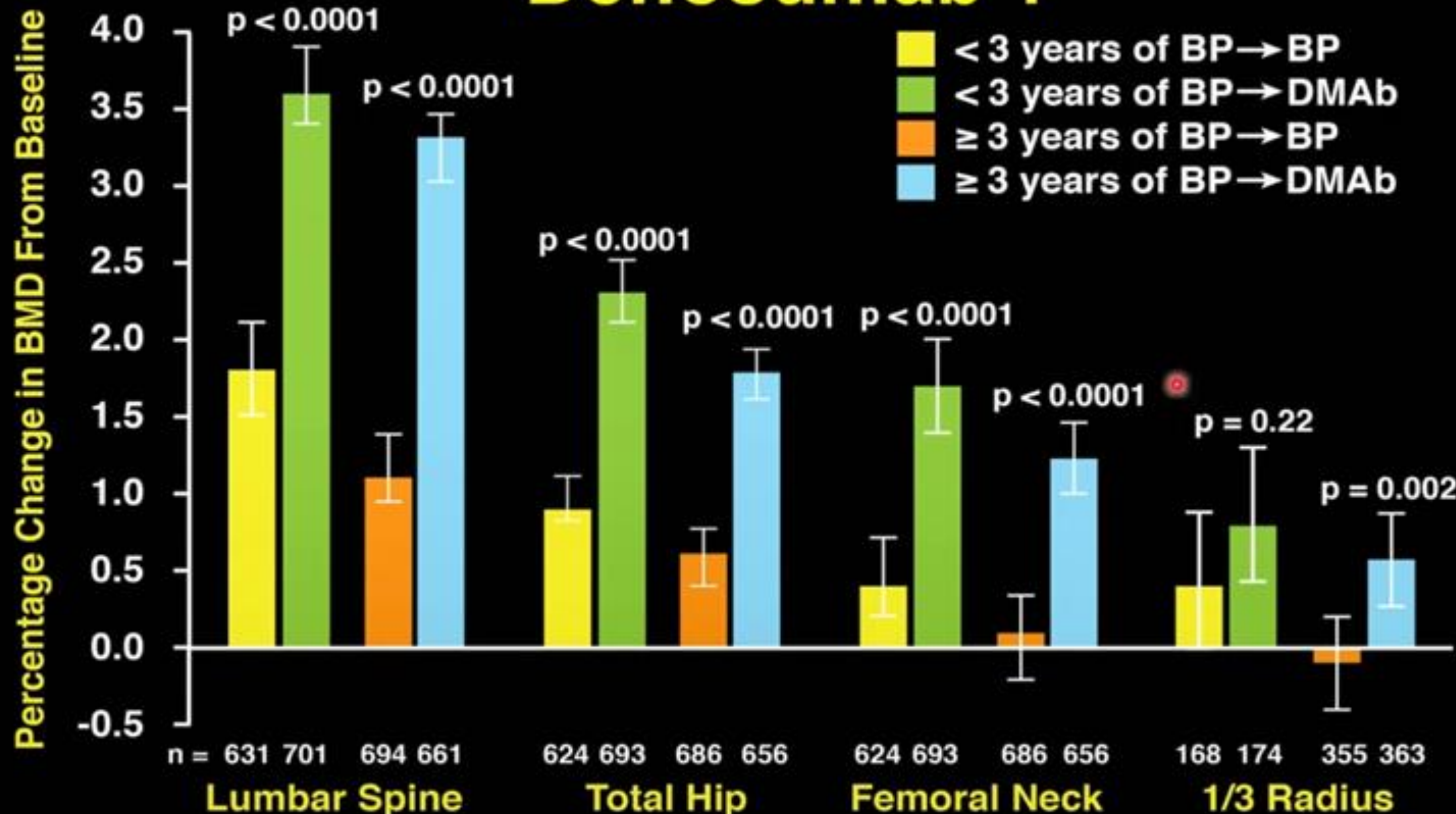
## US Medicare Data Summary (n = 74K)

- Hip fracture (fx)
  - Alendronate- 30% ↑
  - Risedronate- 50% ↑
  - Zoledonic acid- 30% ↑
- Vertebral fractures
  - Alendronate- 20% ↑
  - Risedronate- 60% ↑
  - Zoledronic acid - 40% ↑
- Other fracture types
  - 0-40% ↑ depending on fracture site

Curtis J. *Medical Care* 2020; 58:1 doi
Black DM. *J Clin Endocrinol Metab* 2000;85:4118

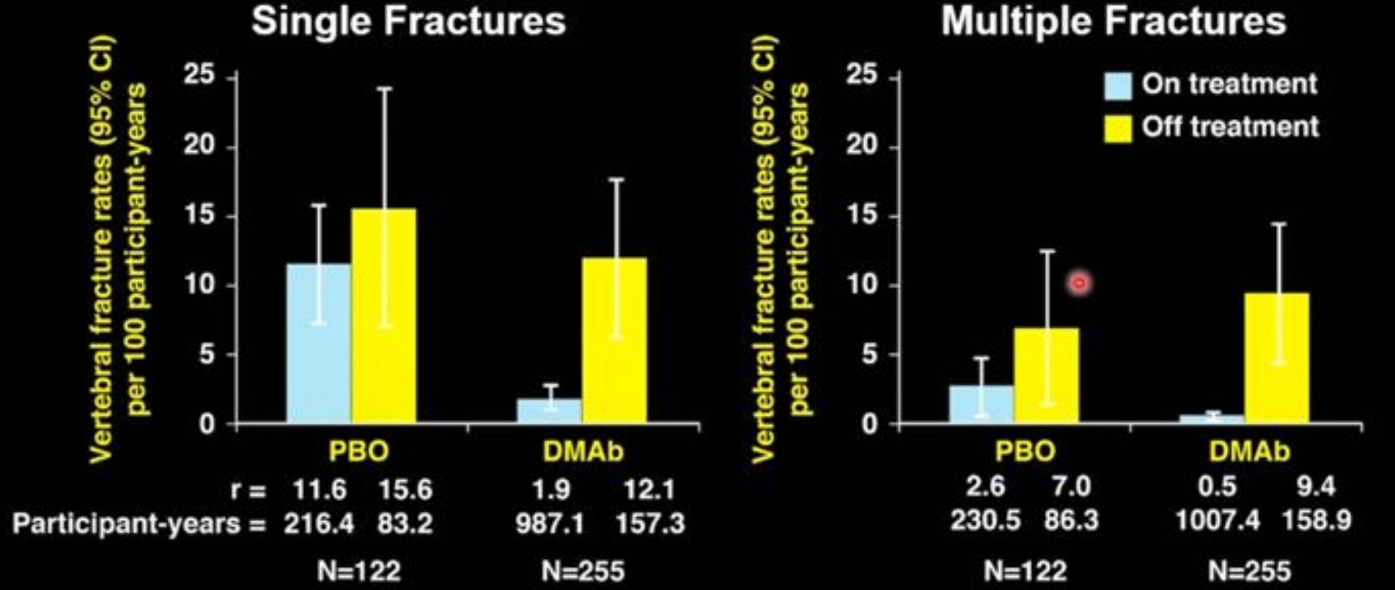
# What's New/Controversial with Denosumab?

# Continue Bisphosponates or Switch to Denosumab ?




Miller P. *Osteoporosis Int* 2020;31:181

# Fractures After Stopping Denosumab (DMAb)




Cummings S. *JBMR* 2018;33:190

# Infectious Risk with Denosumab Meta-analysis

| Comparison | RR (95% CI) | Studies (nr) | Patients |
|---|---|---|---|
| Serious Infectious Adverse Event | 1.21 (1.04- 1.4) | 30 | 21, 179 |
| More than 12 M of Rx | 1.24 (1.05- 1.46) | 16 | 15, 283 |
| ENT infection | 2.66 (1.2- 5.91) | 17 | 15,387 |
| GI infection | 1.43(1.02- 2.01) | 20 | 16,656 |

Diker-Cohen T. *JCEM* 2020;105:1

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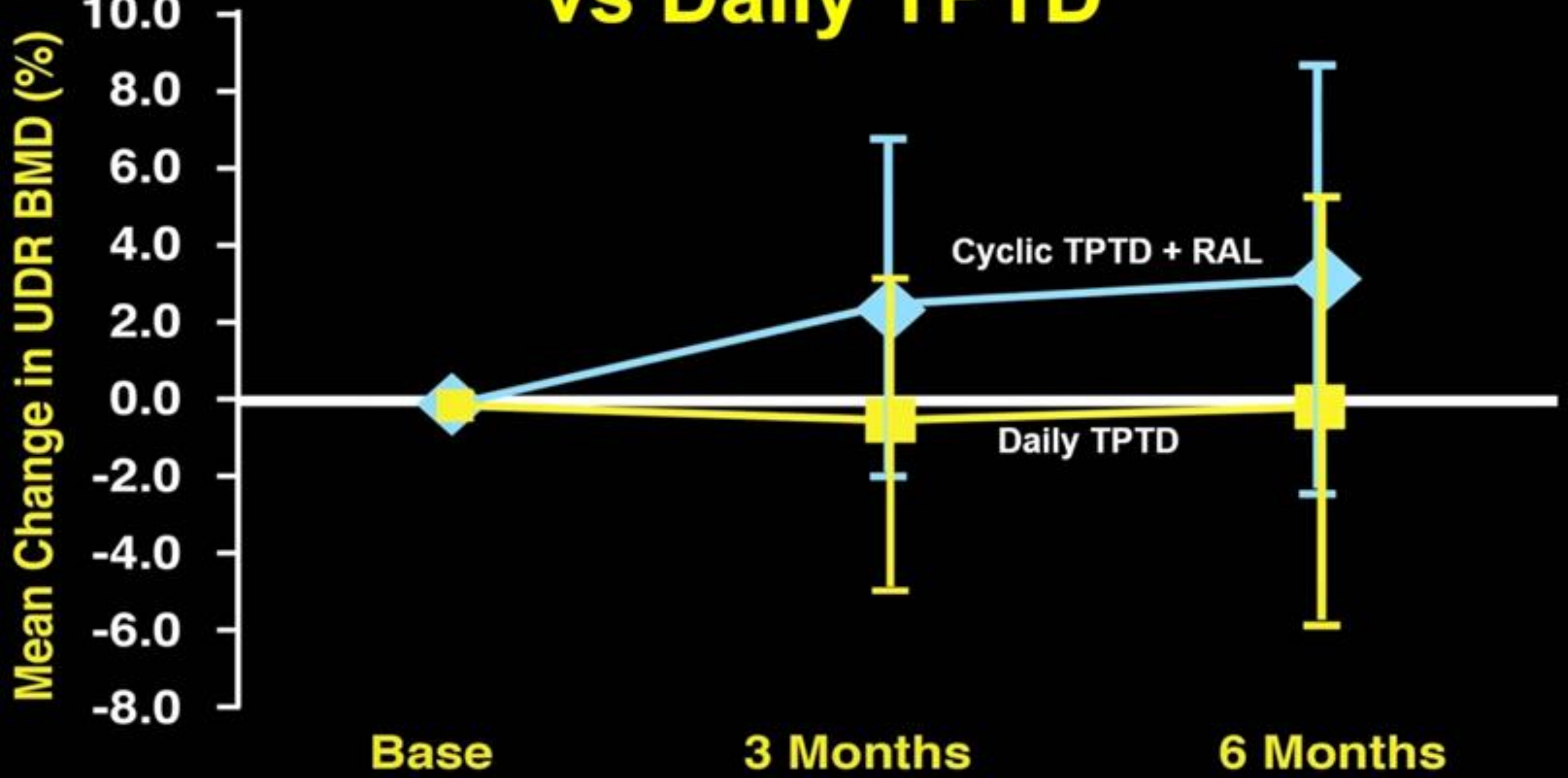
Diker-Cohen T. *JCEM* 2020;105:1

# What's New/Controversial with Anabolic Approaches?

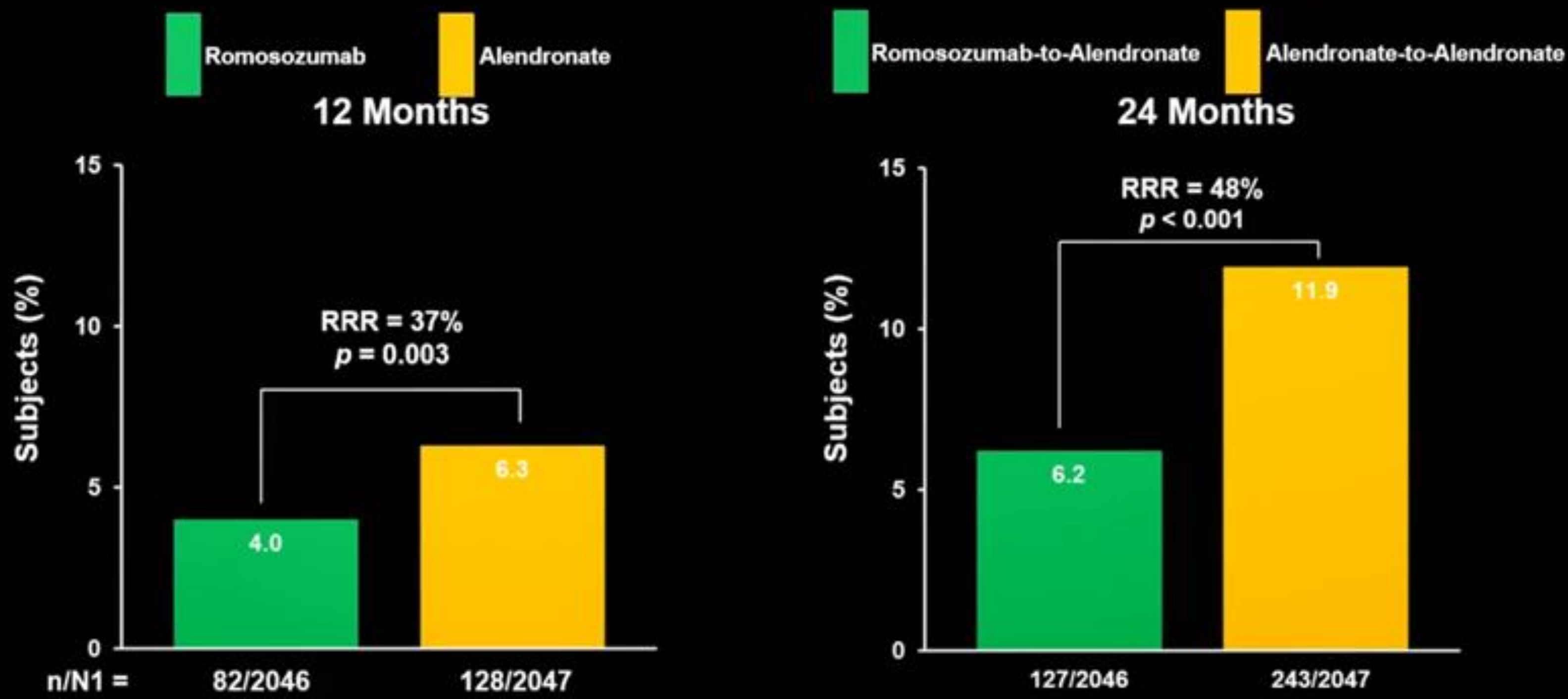
# Cyclic Teriparatide (TPTD) + Raloxifene vs Daily TPTD




Heenam G. *Arch Osteo* 2021;15;16:70

# Romosozumab ARCH Study

## Primary Endpoint: New Vertebral Fracture Through 24 mos

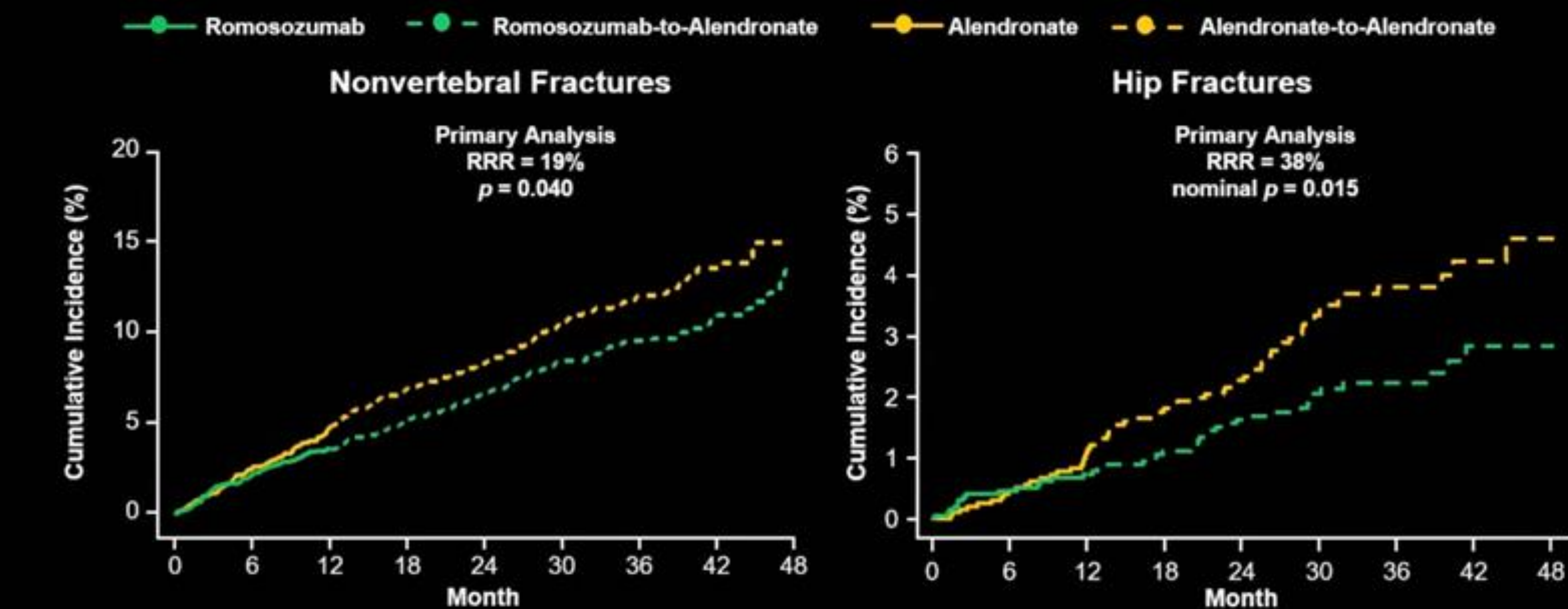



n/N1 = Number of subjects with fractures/Number of subjects in the primary analysis set for vertebral fractures. Missing fracture status was imputed by multiple imputation for patients without observed fracture at an earlier timepoint. n and % are based on the average across 5 imputed datasets. RRR = relative risk reduction.

Saag K. *NEJM* 2017; 377:1417

# Romosozumab ARCH Study

## Secondary Endpoints: Nonvertebral Fracture and Hip Fracture




**Nonvertebral Fractures**

| Month | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|---|---|---|---|---|---|---|---|---|---|
| Aln to Aln (n=) | 2047 | 1873 | 1755 | 1661 | 1590 | 1097 | 697 | 330 | 110 |
| Romo to Aln (n=) | 2046 | 1867 | 1776 | 1693 | 1627 | 1114 | 714 | 350 | 109 |

**Hip Fractures**

| Month | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|---|---|---|---|---|---|---|---|---|---|
| Aln to Aln (n=) | 2047 | 1914 | 1821 | 1750 | 1690 | 1182 | 755 | 364 | 124 |
| Romo to Aln (n=) | 2046 | 1900 | 1829 | 1766 | 1715 | 1195 | 772 | 379 | 125 |

n = number of subjects at risk for event at time point of interest. Aln = alendronate; Romo = romosozumab.

Saag K. *NEJM* 2017; 377:1417

# Serious Adverse Events in ARCH

| | Month 12 Double-Blind Period | |
|---|---|---|
| | Romosozumab N = 2040 | Alendronate N = 2014 |
| All adverse events | 1544 (75.7) | 1584 (78.6) |
| Serious adverse events | 262 (12.8) | 278 (13.8) |
| Adjudicated serious cardiovascular event[a] | 50 (2.5) | 38 (1.9) |
| Cardiac ischemic event | 16 (0.8) | 6 (0.3) |
| Cerebrovascular event | 16 (0.8) | 7 (0.3) |
| Heart failure | 4 (0.2) | 8 (0.4) |
| Cardiovascular death | 17 (0.8) | 12 (0.6) |
| Non-coronary revascularization | 3 (0.1) | 5 (0.2) |
| Peripheral vascular ischemic event not requiring revascularization | 0 (0.0) | 2 (< 0.1) |
| Death | 30 (1.5) | 21 (1.0) |

Data are n (%). N = number of subjects who received ≥ 1 dose of investigational product. [a]Adverse events adjudicated positive by an independent adjudication committee. Cardiovascular deaths includes fatal events adjudicated as cardiovascular-related or undetermined (presumed cardiac-related). [b]Incidence rates through primary analysis were cumulative and included all events in the double-blind and open-label period in subjects who received ≥ 1 dose of investigational product.

Saag K. *NEJM* 2017; 377:1417

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Saag K. *NEJM* 2017; 377:1417

# Romosozumab BRIDGE Study in Men
# Treatment-Emergent Adverse Events

| | Romosozumab 210 mg QM<br>N = 163<br>n (%) | Placebo<br>N = 81<br>n (%) |
|---|---|---|
| Any adverse event | 123 (75.5) | 65 (80.2) |
| Serious adverse event | 21 (12.9) | 10 (12.3) |
| Adjudicated cardiovascular event[a] | 8 (4.9) | 2 (2.5) |
| Death | 1 (0.6) | 1 (1.2) |
| Adjudicated cardiovascular death[b] | 1 (0.6) | 1 (1.2) |
| Leading to discontinuation of investigational product | 5 (3.1) | 1 (1.2) |
| Events of interest | | |
| Hypocalcemia | 0 (0.0) | 0 (0.0) |
| Hypersensitivity | 8 (4.9) | 4 (4.9) |
| Injection site reactions | 9 (5.5)[c] | 3 (3.7) |
| Malignancy | 3 (1.8) | 2 (2.5) |
| Hyperostosis | 0 (0.0) | 0 (0.0) |
| Osteoarthritis | 8 (4.9) | 4 (4.9) |
| Atypical femoral fracture[a] | 0 (0.0) | 0 (0.0) |
| Osteonecrosis of the jaw[a] | 0 (0.0) | 0 (0.0) |
| Subject incidence of anti-romosozumab antibody formation | | |
| Binding antibodies | 29 (18.0) | NA |
| Neutralizing antibodies | 0 (0.0) | NA |

N = number of subjects who received ≥ 1 dose of investigational product. n = number of subjects with ≥ 1 event. NA = not applicable; QM = once monthly. [a]Only includes events adjudicated positive by independent adjudication committee. [b]Adjudicated cardiovascular death events include fatal events adjudicated as cardiovascular-related or undetermined. [c]Most reactions were reported as mild in severity.

EM Lewiecki *JCEM* 2018;103:3183

# Regulatory Action on Romosozumab

- FDA Advisory Committee (1/19)- Recommended approval of Romosozumab (19 yes vs 1 no)
- Cardiovascular signal in trials 20110142 and 20110174 → "FDA Black Box" Warning (Warning and Precaution for cardiac risk)
- EC approval late 2019

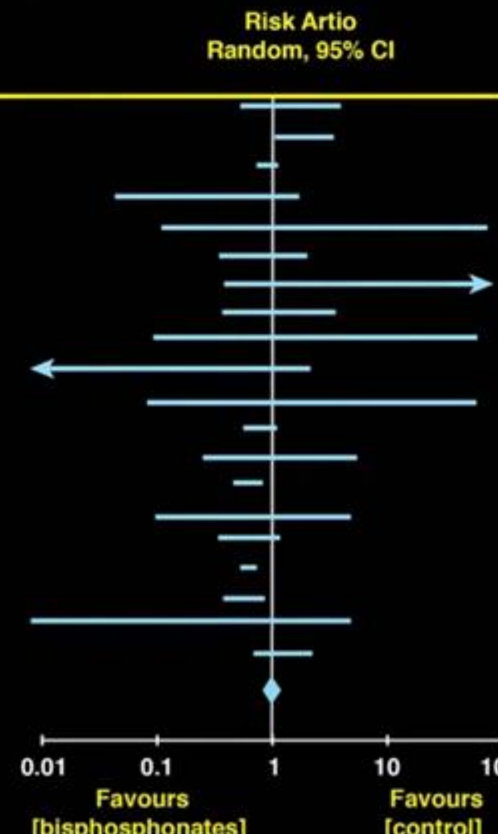
# Romosozumab - Adverse Effects Summary

- Overall Safety in FRAME, ARCH, STRUCTURE, BRIDGE
  - Most adverse events balanced between treatment arms
  - 5% injection site reactions, 2 ONJs and 1 AFF by 24 months in FRAME, none during double blind period of ARCH, or in STRUCTURE, BRIDGE
- Small numerical differences in CV AEs in ARCH, BRIDGE
  - Possibly due to alendronate being cardioprotective
  - Possibly due to chance since not seen in larger FRAME
  - Possibly real and just not seen in a lower risk population (FRAME)

Cosman F. *NEJM* 2016; 375:1532
Sing CW. *J Bone Miner Res* 2018. doi: 10.1002/jbmr.3448
Liu Y. *Climateric* 2018;21:189

# Bisphosphonates Meta-analysis of CV Outcomes

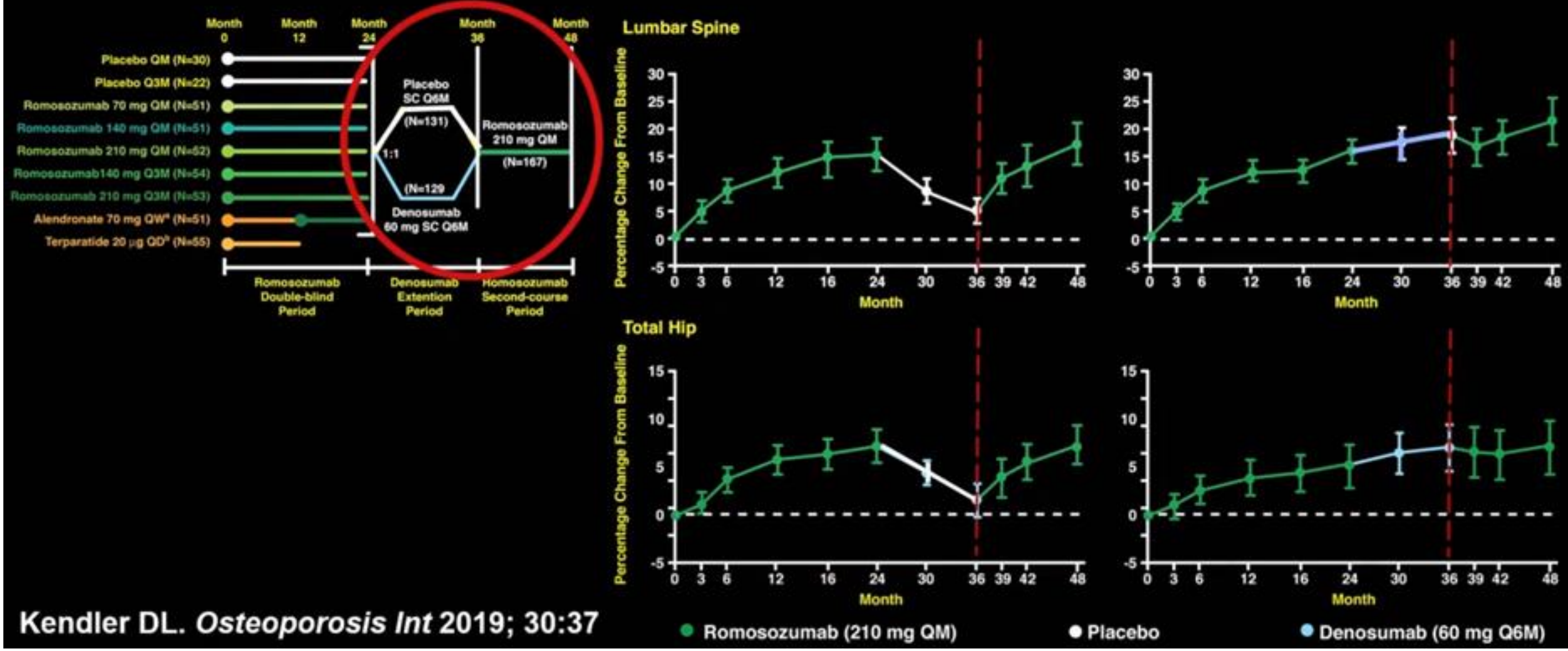
| | Bisphosphonates | | Control | | | Risk Ratio Random, 95% CI |
|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | Weight | |
| Adami 2004 | 23 | 392 | 5 | 128 | 1.7% | 1.50 [0.58, 3.87] |
| Atula 2003 | 35 | 538 | 18 | 541 | 4.5% | 1.96 [1.12, 3.41] |
| Black 2007 | 164 | 3852 | 166 | 3862 | 18.7% | 0.99 [0.80, 1.22] |
| Boonen 2009 | 2 | 191 | 3 | 93 | 0.5% | 0.32 [0.06, 1.91] |
| Chevrel 2006 | 1 | 31 | 0 | 33 | 0.2% | 3.19 [0.13, 75.43] |
| Dalbeth 2014 | 9 | 50 | 9 | 50 | 2.1% | 1.00 [0.43, 2.31] |
| Deamaley 2003 | 4 | 155 | 0 | 54 | 0.2% | 9.06 [0.49, 166.82] |
| Eastell 2011 | 7 | 57 | 5 | 57 | 1.3% | 1.40 [0.47, 4.15] |
| Eggelmeijer 1996 | 1 | 54 | 0 | 54 | 0.2% | 3.00 [0.12, 72.05] |
| Ernst 2003 | 0 | 104 | 3 | 105 | 0.2% | 0.14 [0.01, 2.76] |
| Greenspan 2013 | 1 | 94 | 0 | 93 | 0.2% | 2.97 [0.12, 71.951] |
| Hosking 1998 | 99 | 997 | 47 | 502 | 10.5% | 1.06 [0.76, 1.48] |
| Klotz 2013 | 4 | 77 | 3 | 90 | 0.7% | 1.56 [0.36, 6.75] |
| Lyles 2007 | 95 | 1054 | 107 | 1057 | 14.4% | 0.89 [0.68, 1.16] |
| McClung 2006 | 2 | 46 | 2 | 46 | 0.4% | 1.00 [0.15, 6.80] |
| Orwoll 2000 | 23 | 146 | 16 | 95 | 4.1% | 0.94 [0.52, 1.68] |
| Recker 2004 | 455 | 1911 | 240 | 949 | 27.2% | 0.94 [0.82, 1.08] |
| Reginster 2000 | 68 | 815 | 38 | 407 | 8.5% | 0.89 [0.61, 1.31] |
| Tee 2012 | 0 | 22 | 1 | 22 | 0.2% | 0.33 [0.01, 7.76] |
| von Minckwitz 2013 | 61 | 1996 | 15 | 998 | 4.4% | 2.03 [1.16, 3.56] |
| Total (95% CI) | | 12582 | | 9338 | 100.0% | 1.03 [0.91, 1.17] |
| Total events | 1054 | | 678 | | | |




Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 22.51$, df = 19 (P = 0.26); $I^2 = 16\%$
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: No applicable

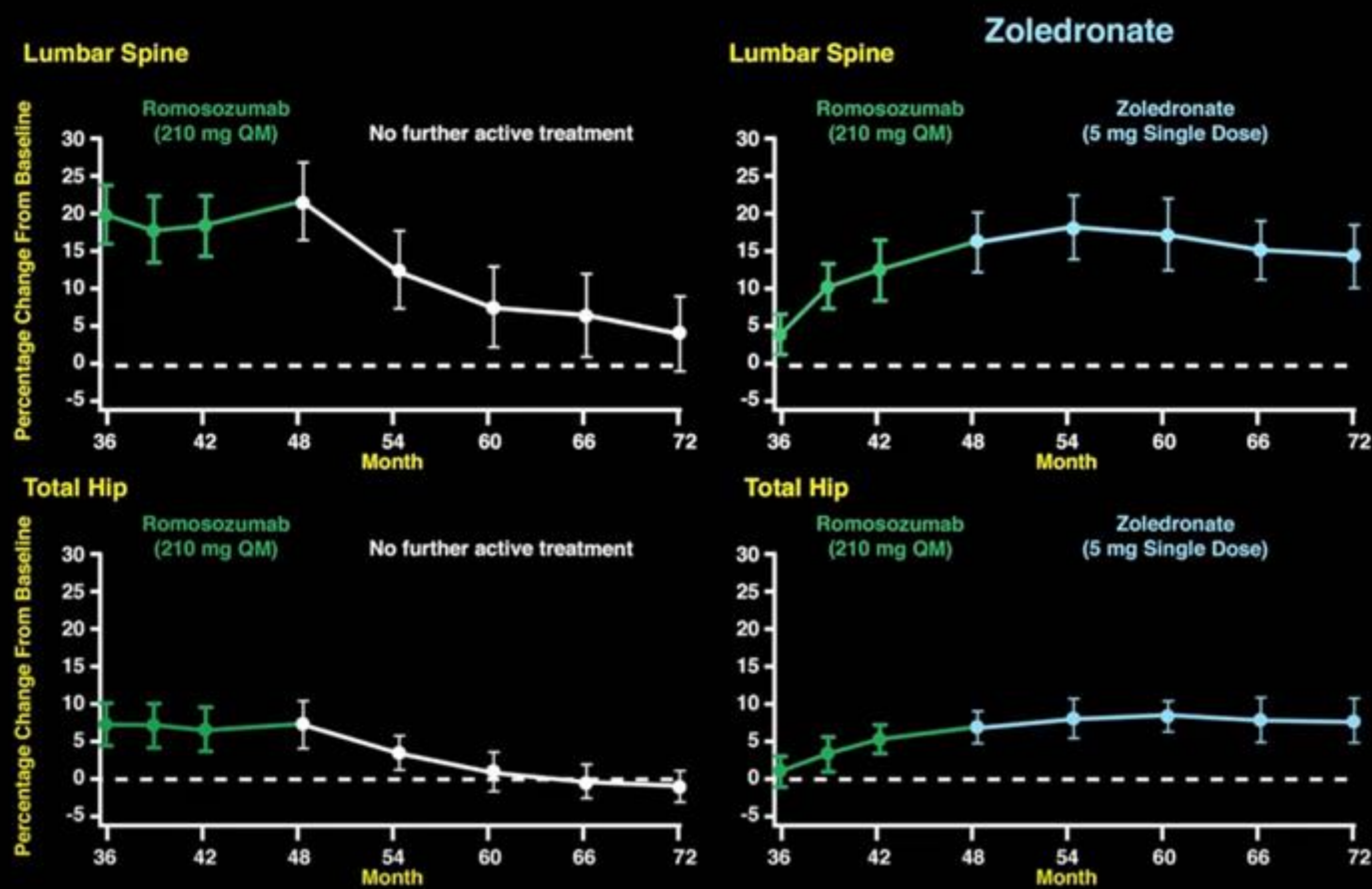
Kranenburg G. *Atherosclerosis* 2016;252:106

# Second Course of Romosozumab Following Placebo or Denosumab

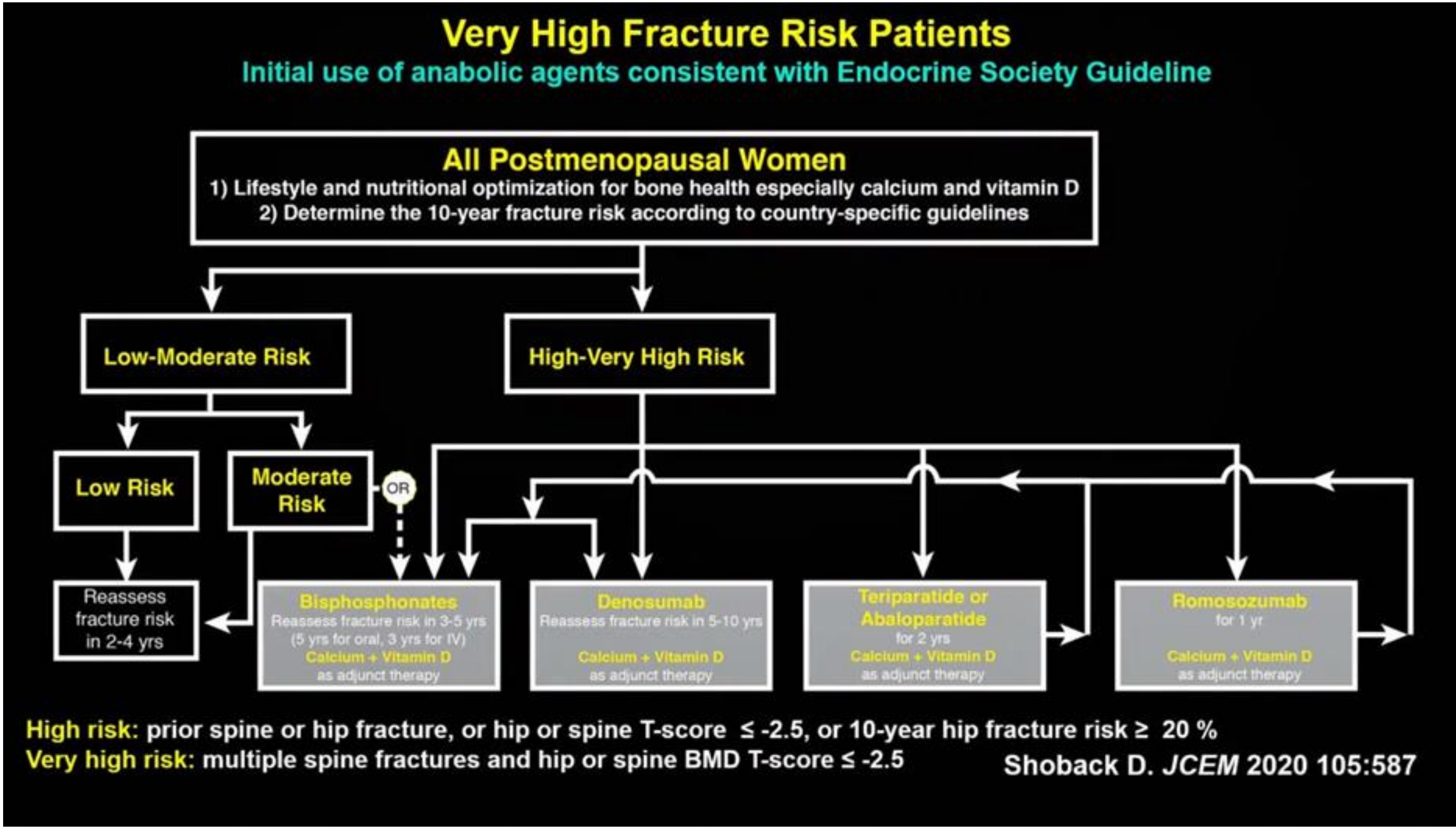



Kendler DL. *Osteoporosis Int* 2019; 30:37

# Zoledronate after Romosozumab




McClung M et al., Osteoporos Int 2020 31:2231-41


Very High Fracture Risk Patients
Initial use of anabolic agents consistent with Endocrine Society Guideline
All Postmenopausal Women
1) Lifestyle and nutritional optimization for bone health especially calcium and vitamin D
2) Determine the 10-year fracture risk according to country-specific guidelines
Low-Moderate Risk
High-Very High Risk
Low Risk
Moderate Risk
OR
Reassess fracture risk in 2-4 yrs
Bisphosphonates
Reassess fracture risk in 3-5 yrs
(5 yrs for oral, 3 yrs for IV)
Calcium + Vitamin D
as adjunct therapy
Denosumab
Reassess fracture risk in 5-10 yrs
Calcium + Vitamin D
as adjunct therapy
Teriparatide or Abaloparatide
for 2 yrs
Calcium + Vitamin D
as adjunct therapy
Romosozumab
for 1 yr
Calcium + Vitamin D
as adjunct therapy
High risk: prior spine or hip fracture, or hip or spine T-score ≤ -2.5, or 10-year hip fracture risk ≥ 20 %
Very high risk: multiple spine fractures and hip or spine BMD T-score ≤ -2.5
Shoback D. JCEM 2020 105:587

# Conclusions

- ONJ and AFF rare, but better understanding of risk factors and possible prevention rx
- Denosumab needs an exit strategy, likely a bisphosphonate (?alendronate)
- Anabolics may reduce fractures more than anti-resorptives in some high risk patients
- Romosozumab
  - Potent dual mechanism “niche” therapy
  - CV safety questions persist
  - May follow Dmab, benefits from Zol or Dmab after
- Final Frontier – Translating Research into Practice

# Long-term Osteoporosis Treatment: The personalised approach

***CSS1-3: Identification and treatment of osteoporosis based on individual fracture risk***

*Speaker:* Felicia Cosman, United States

# Objectives

- Long-term treatment considerations and risk stratification
  - Identification of the very-high-risk patient
- Treatment strategies for highest risk patients
  - Anabolic first treatment
    - Rapid and sustained fracture risk reduction
    - Optimal BMD gain
- Recent osteoporosis treatment guidelines
- Simple case studies

BMD, bone mineral density.

# Risk Stratification

| Low Risk | Moderate Risk | High Risk | Very High Risk |
|---|---|---|---|
| **No prior fracture, T-Score ≥ -1, and 10-year FRAX probabilities < 20% MOF, < 3% hip** | **No prior fracture, and T-Score between -1 and -2.5 and FRAX 10-year probabilities < 20% MOF, < 3% hip** | **Prior fracture (more than 2 years earlier), *or* T-Score ≤ -2.5, or T-Score between -1 and -2.5 with FRAX 10-year probabilities ≥ 20% MOF or ≥ 3% hip** | High imminent risk > 10% over 2 years **Who are these patients?** |
| No pharmacologic treatment needed | **Goal: Maintain BMD**<br>Some benefit from sequential antiresorptive monotherapy esp those with BMD close to -2.5<br>• Estrogens in early menopause<br>• Raloxifene 50s to late 60s<br>• Bisphosphonates mid/late 60s | **Goal: Improve BMD/reduce fracture risk**<br>• Younger women may benefit from estrogens/raloxifene especially if spine T-Score low and hip > -2.5<br>• Usually bisphosphonates or denosumab<br>• Anabolic agents appropriate for some | **Goal: Reduce fracture risk rapidly and potently; increase BMD quickly and potently** |

Modified from Camacho PM, et al. Endocr Pract 2020;26:1–46,
Shoback D, et al. J Clin Endocrinol Metab 2020;105:587–94 and
Ferrari S et al, Swiss Med Wkly 2020;150:w20352

FRAX, fracture risk assessment tool; MOF, major osteoporotic fracture.

# Patients at Very High Imminent Risk (≥ 10% in 2 years)

- Recent clinical or radiographic vertebral fracture[1,2]
- History of multiple prior fractures[3]
- TH T-Score ≤ -3, especially with additional factors[4]
  - Single fracture occurring more than 1 year ago
  - Advanced age
  - Chronic diseases/meds
  - Poor physical function and falls
- Treatment goals for these patients:
  - Improve skeletal strength and BMD rapidly to reduce risk of both vertebral and non-vertebral fractures[5,6]
  - Can we accomplish this faster or to a greater extent with anabolic medication?

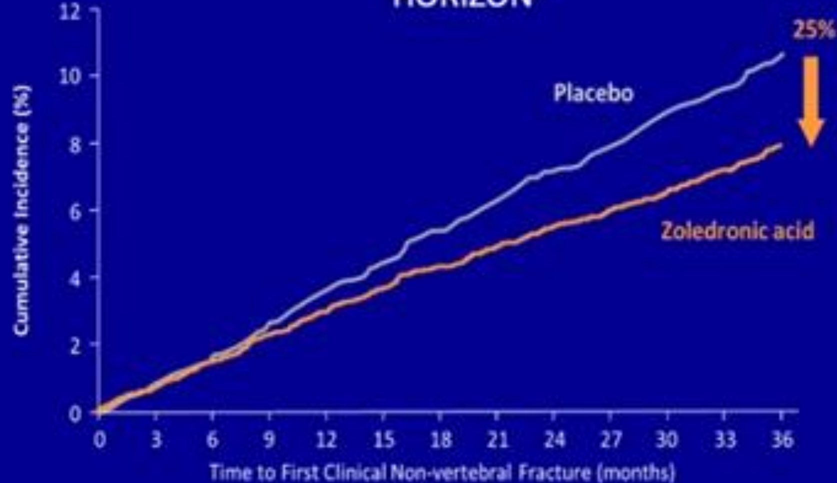
1. Balasubarmanian A, et al. Osteoporos Int 2019; 30:79–92; 2. Lindsay R, et al. JAMA 2001;285:320–3;
3. Gehlbach SH, et al. Osteoporos Int 2007;18:805–10; 4. Adachi JD, et al. Arch Osteoporos 2019;14:53;
5. Thomas T, et al. Osteoporosis Int 2020;31:2303–11; 6. Black DM, et al. Lancet Diabetes Endocrinol2020;8:672–82.

TH, total hip.

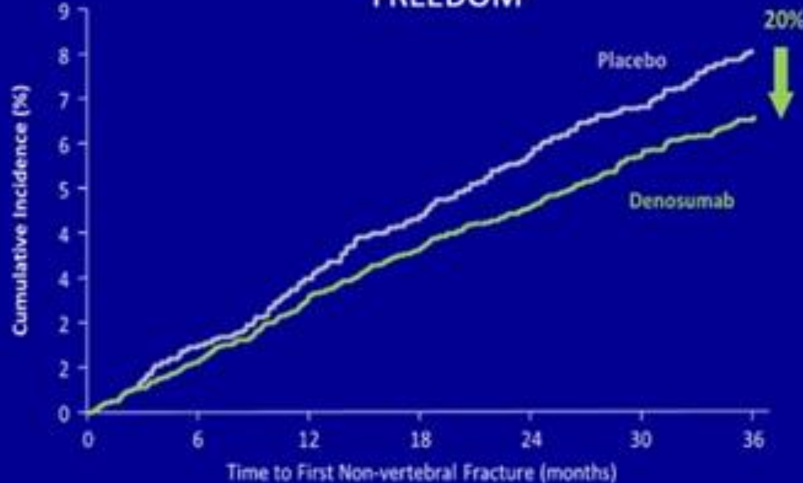
# Treatment of High-risk Patients: Efficacy with Highest Potency Antiresorptives

- Vertebral fracture risk reductions 60–70% within 1 year[1,2]
- Non-vertebral fracture risk reductions at best 20–25% and not seen before 3 years[1,2]

HORIZON[1*]

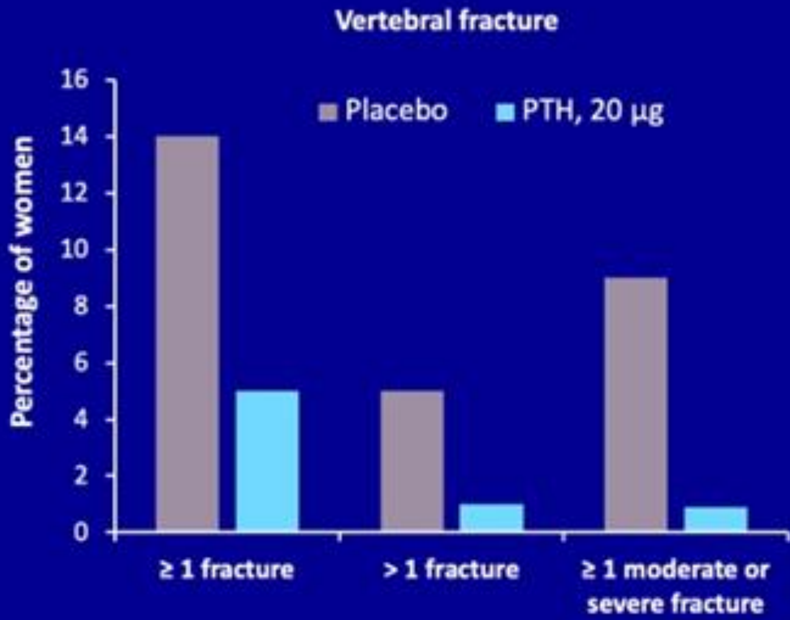


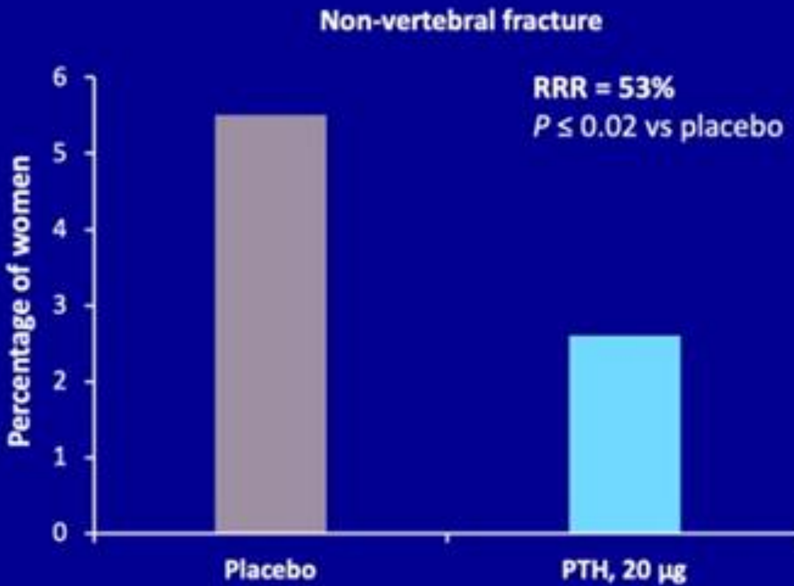

FREEDOM[2]




1. Black DM, et al. N Eng J Med 2007;356:1809; 2. Cummings SR, et al. N Engl J Med 2009;361:756–65.

# Pivotal Teriparatide Fracture Trial
# Fracture Effects Over 19 Months

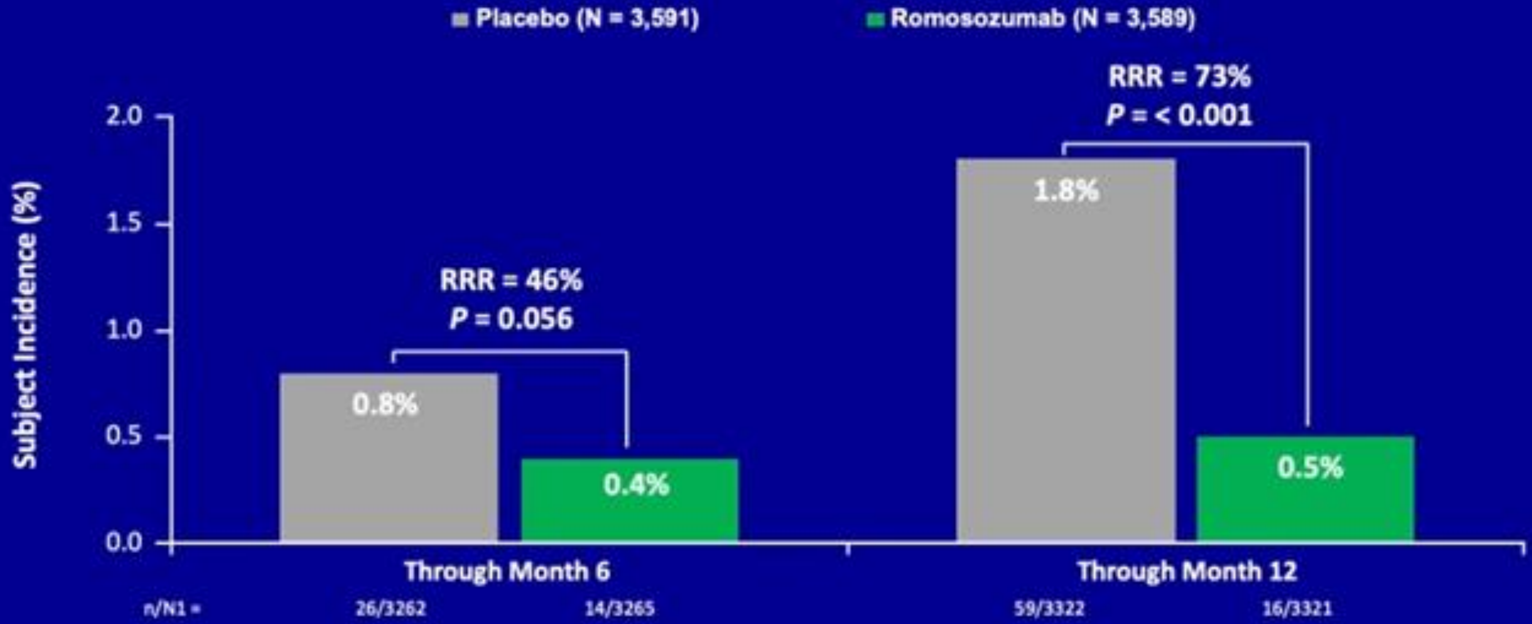



Neer RM, et al. N Engl J Med 2001;344:1434–41.

PTH, parathyroid hormone; RRR, relative risk reduction.

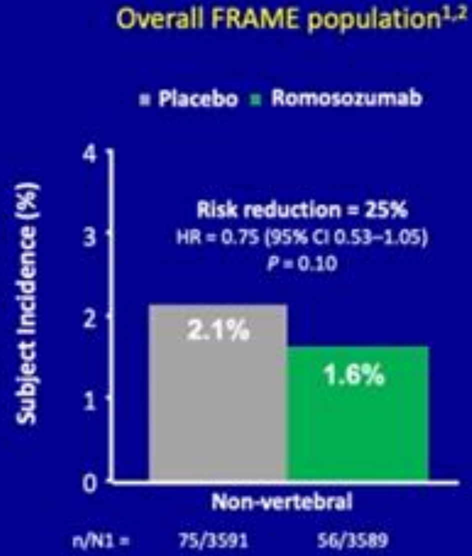
# FRAME: New Vertebral Fracture Incidence Through Month 12 (Co-primary Endpoint)

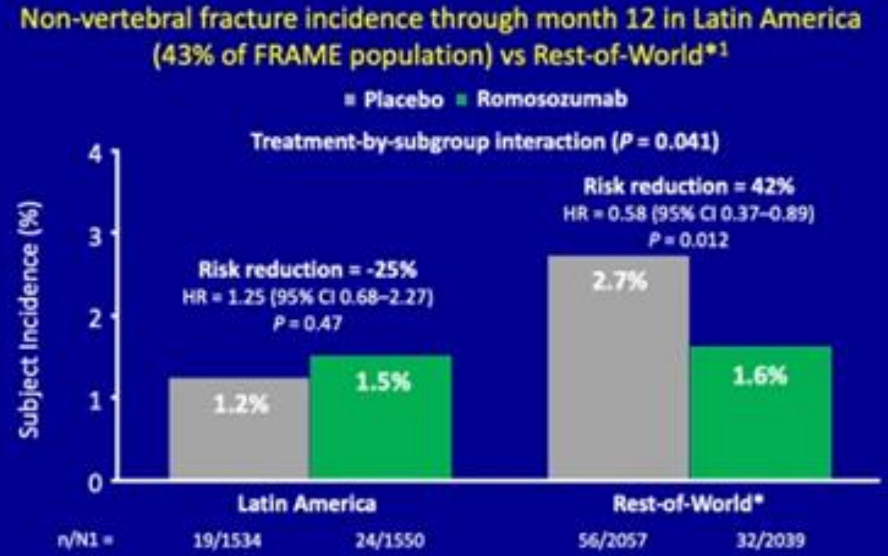



n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures
*P*-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture

Cosman F, et al. N Engl J Med 2016;375:1532–43; Cosman F, et al. ASBMR 2016 (oral presentation): 1096.

# FRAME: Non-vertebral Fracture Outcomes Through Month 12




*Regions excluding Latin America grouped post hoc. n/N1 = number of subjects with fractures/number of subjects in the full analysis set.
Non-vertebral fractures exclude fractures of the skull, face, metacarpals, fingers, and toes, pathologic fractures and those due to high trauma

1. Cosman F, et al. N Engl J Med 2016;375:1532–43; 2. Cosman F, et al. J Bone Miner Res 2018;33:1219–26.

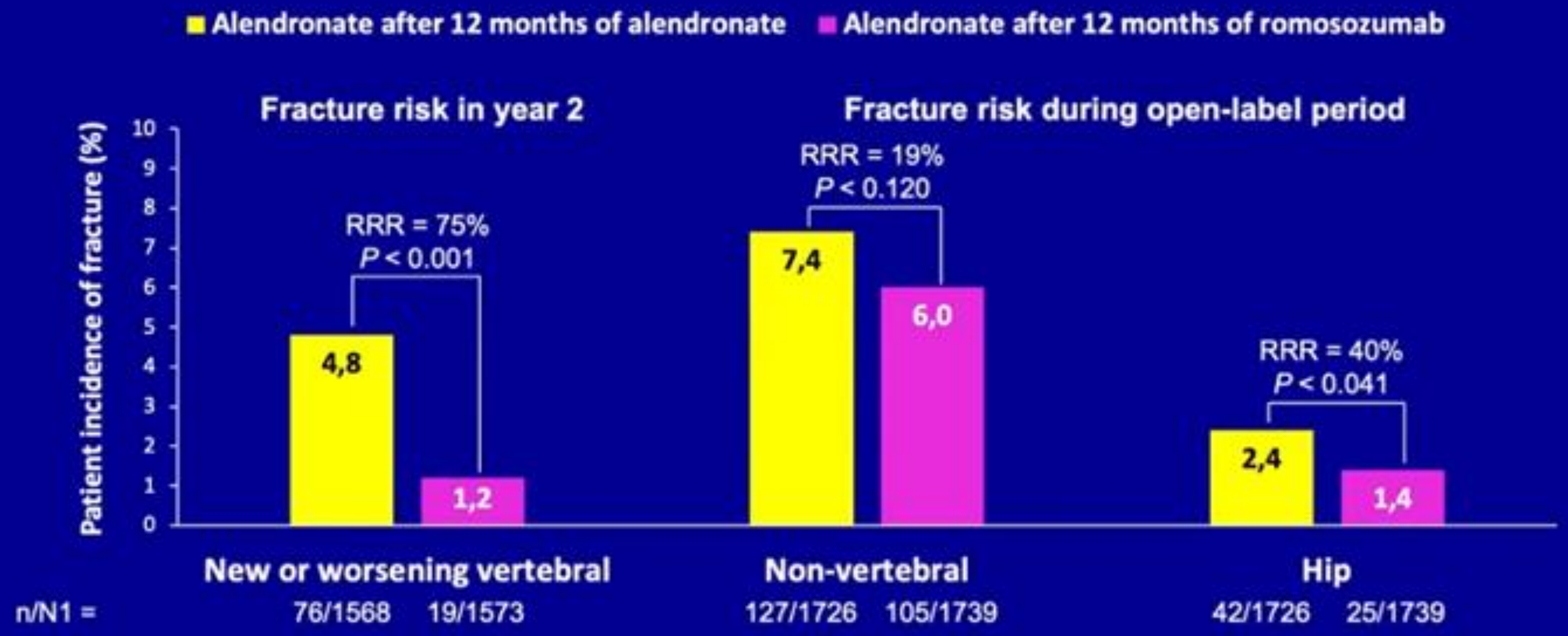
# ARCH: Incidence of New Vertebral Fracture Through Month 24 (Co-primary Endpoint)


n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures.
*Missing fracture status was imputed by multiple imputation for patients without an observed fracture at an earlier time point. n and % are based on the average across 5 imputed data sets; †RRR at 12 months by LOCF: 36% (nominal $P = 0.008$): romosozumab 3.2% (55/1696) vs alendronate 5.0% (85/1703); ‡RRR at 24 months by LOCF: 50% (nominal $P < 0.001$): romo-to-ALN 4.1% (74/1825) vs ANL-to-ALN 8.0% (147/1843)

Saag K, et al. N Engl J Med 2017;377:1417–27.

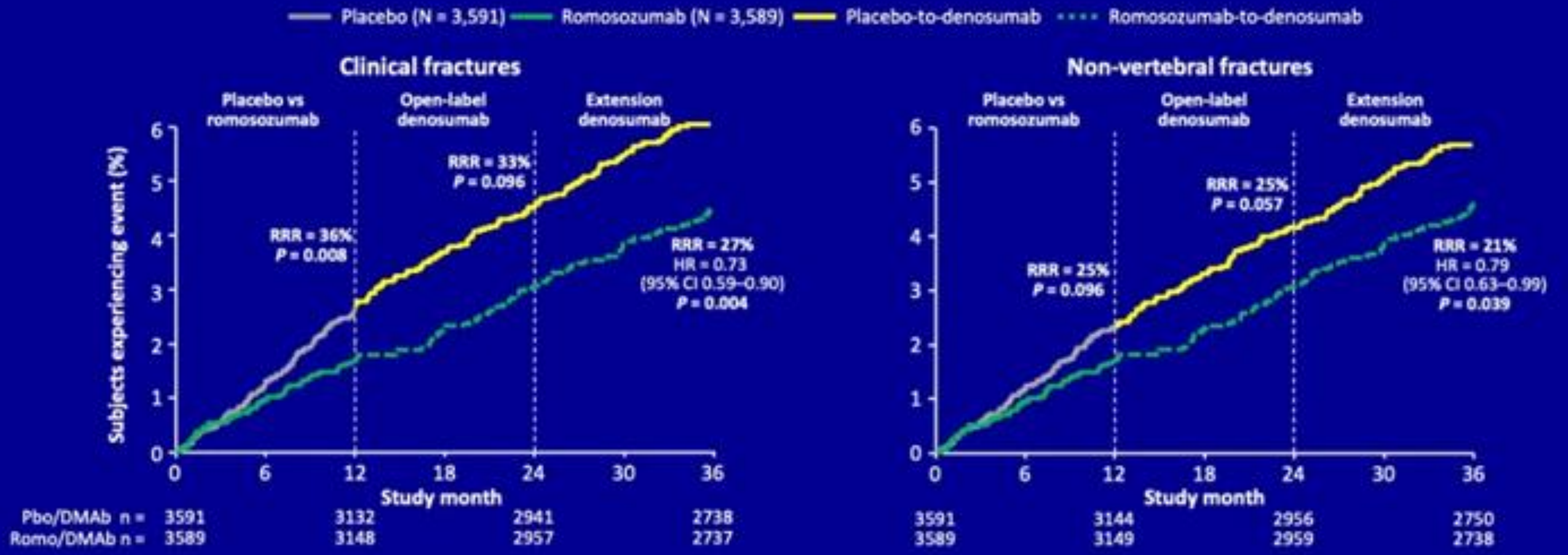
LOCF, last observation carried forward.

# ARCH: Sustained Fracture Risk Reductions During Antiresortive Treatment




Cosman F, et al. J Bone Miner Res 2020;35:1333–42.

# FRAME Extension: Time to First Clinical and Non-vertebral Fracture Through Month 36




Non-vertebral fractures comprised the majority (more than 85%) of clinical fractures. n = number of subjects at risk for event at time point of interest. Relative risk reduction and *P*-values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure as reported for the primary analysis. *P*-values for month 36 are nominal

Lewiecki EM, et al. J Bone Miner Res 2019;34:419–28.

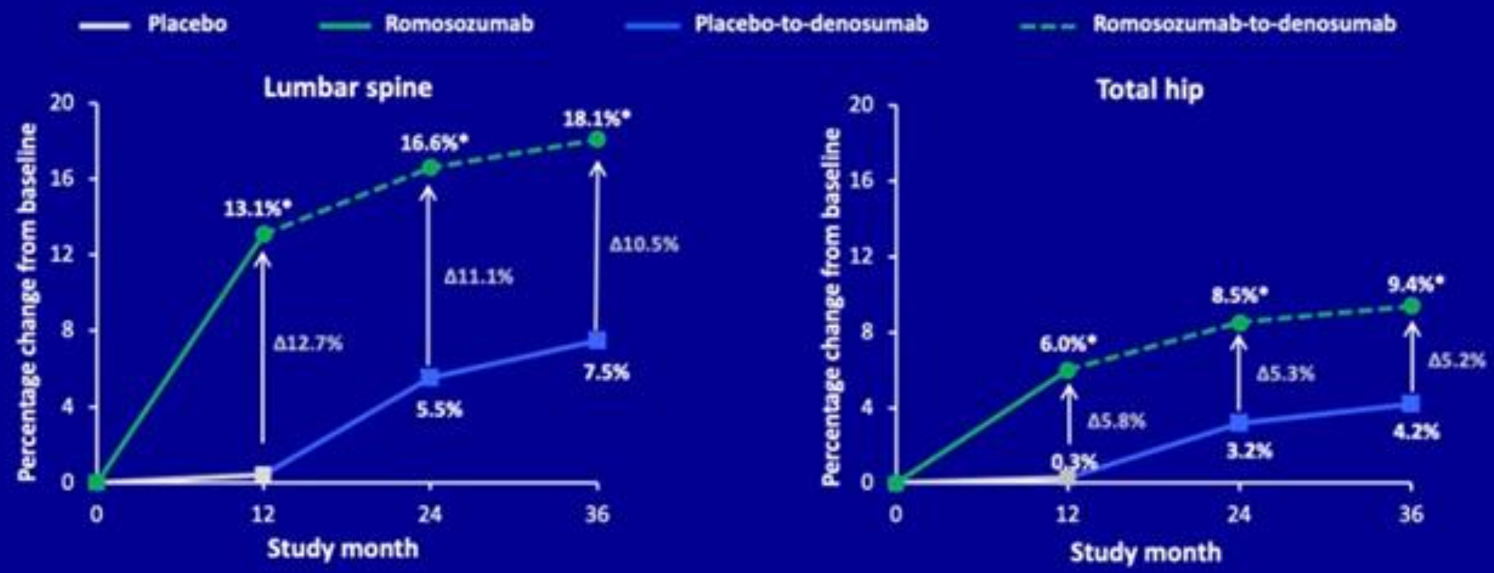
DMAb, denosumab; Pbo, placebo.

# Very-high-risk Patients: Optimal Treatment Sequences

- **First treatment goal**
  - Preventing incident fracture can be accomplished faster and to a greater extent with anabolic agents[1]
  - Antifracture effects are sustained after transition to antiresorptive therapy[1-3]
  - Optimal approach is to begin with an anabolic agent[4-6]
- **Second treatment goal *to increase BMD T-Score to > -2.5***
  - What is the evidence that BMD on treatment is associated with bone strength and how can we best achieve the treatment target?

1. Saag K, et al. N Engl J Med 2017;377:1417–27; 2. Cosman F, et al. J Bone Miner Res 2020;35:1333–42; 3. Cosman F, et al. J Bone Miner Res 2018;33:1219–26; 4. Lewiecki EM, et al. J Bone Miner Res 2019;34:419–28; 5. Cosman F. Endocr Pract 2020;26:777–86; 6. Kanis JA, et al. Osteoporos Int 2020;31:1–12.

# FRAME Extension: Spine and Hip BMD Through Month 36




*Nominal $P < 0.001$. Data are least-square mean (95% CI) based on ANCOVA model adjusting for treatment, age, and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction. For subjects with a baseline and at least one post baseline DXA, n = 3176 for placebo and n = 3169 for romosozumab at the lumbar spine, and n = 3256 for placebo and n = 3237 for romosozumab at the total hip

Lewiecki EM, et al. J Bone Miner Res 2019;34:419–28.

ANCOVA, analysis of covariance; DXA, dual-energy X-ray absorptiometry.

# AACE Guidelines: Very-high-risk Patients Definition and Management

- **R23.** Consider patients with a **recent fracture** (e.g. within the past 12 months), fractures while on approved osteoporosis therapy, **multiple fractures**, fractures while on drugs causing skeletal harm (e.g. long-term glucocorticoids), **very low T-Score (e.g. less than -3.0)**, high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (e.g. major osteoporosis fracture > 30%, hip fracture > 4.5%) or other validated fracture risk algorithm to be at very high fracture risk

- **R25.** **Abaloparatide**, denosumab, **romosozumab**, **teriparatide**, and zoledronate should be considered for patients unable to use oral therapy and as **initial therapy for patients at very high fracture risk, as defined in R23**

Camacho PM, et al. Endocr Pract 2020;26:1–46.