

**22nd Post ADA / Post ENDO**

**31.08.2023**

# **Bone & Calcium Metabolism**

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# Outline



- An update on FRAX and the clinical use of TBS
- Fracture Liaison Service (FLS) program for secondary fracture prevention
- Do high and very high fracture risk really matter?
- Preventing bone loss after Denosumab
- News on Bisphosphonates and updated guidelines

# An update on FRAX and the clinical use of Trabecular Bone Score (TBS)

# FRAX tool: Calculation of the 10y risk for major osteoporotic and hip fracture

**FRAX<sup>®</sup> Fracture Risk Assessment Tool**

Home Calculation Tool Paper Charts FAQ References English

## Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: **Switzerland** Name/ID:  [About the risk factors](#)

### Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth  
Age:  Y:  M:  D:   
Date of Birth:

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/day  No  Yes

12. Femoral neck BMD (g/cm<sup>2</sup>)  
GE-Lunar  T-score: -2.6

**BMI: 25.0**  
The ten year probability of fracture (%)

with BMD	
Major osteoporotic	27
Hip Fracture	6.3

If you have a TBS value, click here:



### Weight Conversion

Pounds   kg

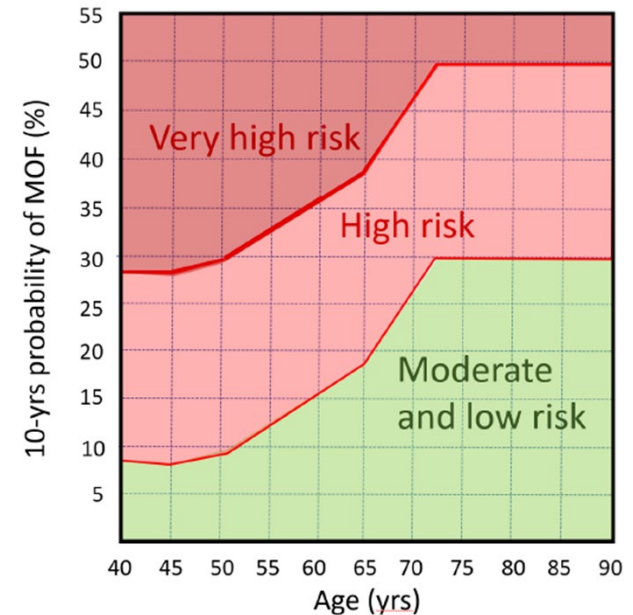
### Height Conversion

Inches   cm

**00214008**  
Individuals with fracture risk assessed since 1st June 2011

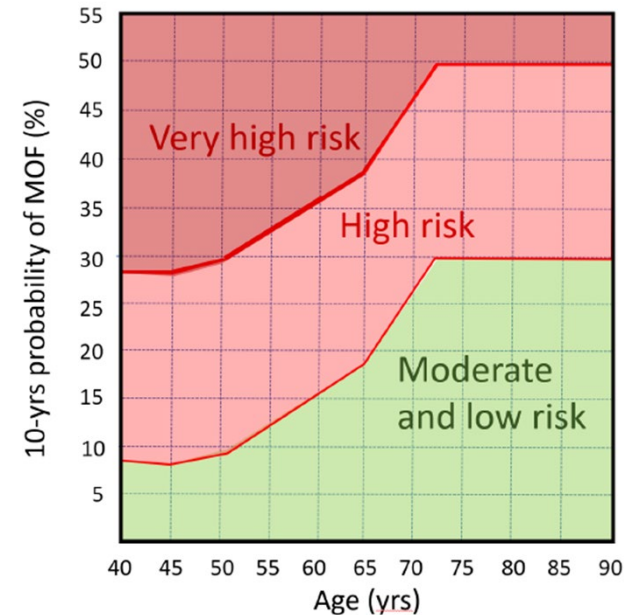
# Strengths and limitations of FRAX

- (+) relatively simple tool with a small number of variables
- (+) incorporated in many guidelines worldwide



# Strengths and limitations of FRAX

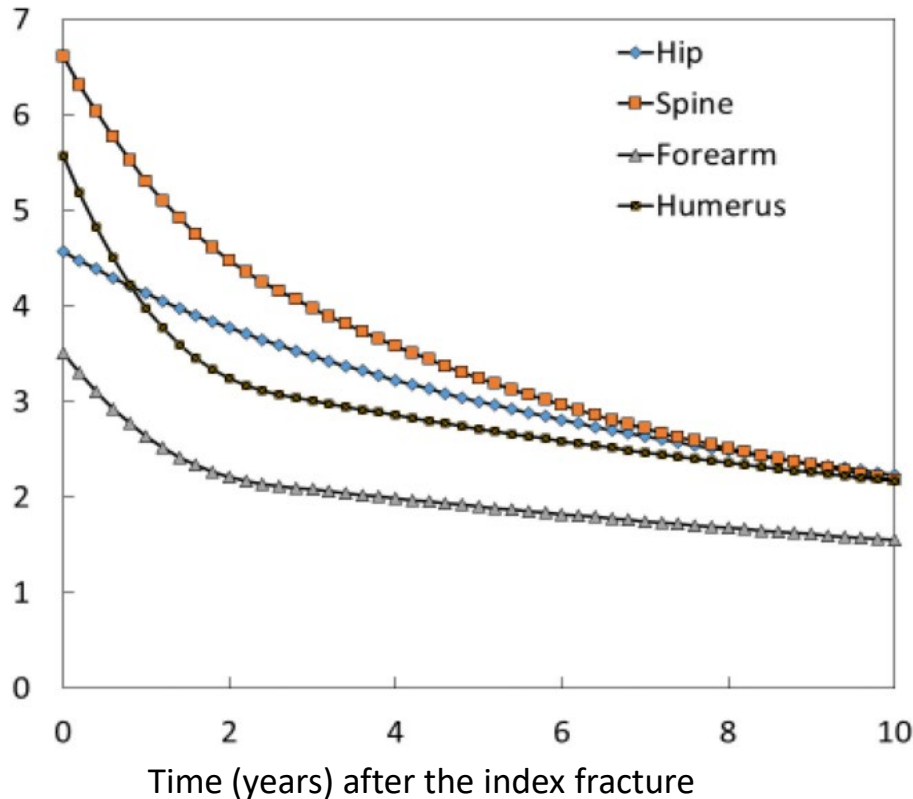
- (+) relatively simple tool with a small number of variables
- (+) incorporated in many guidelines
- (-) some important variables influencing fracture risk are not considered (i.e. falls)
- (-) No «dose response» glucocorticoids
- (-) Number, type, and time since last fracture



# Recency and type of fracture: HR to sustain a MOF after different index fractures

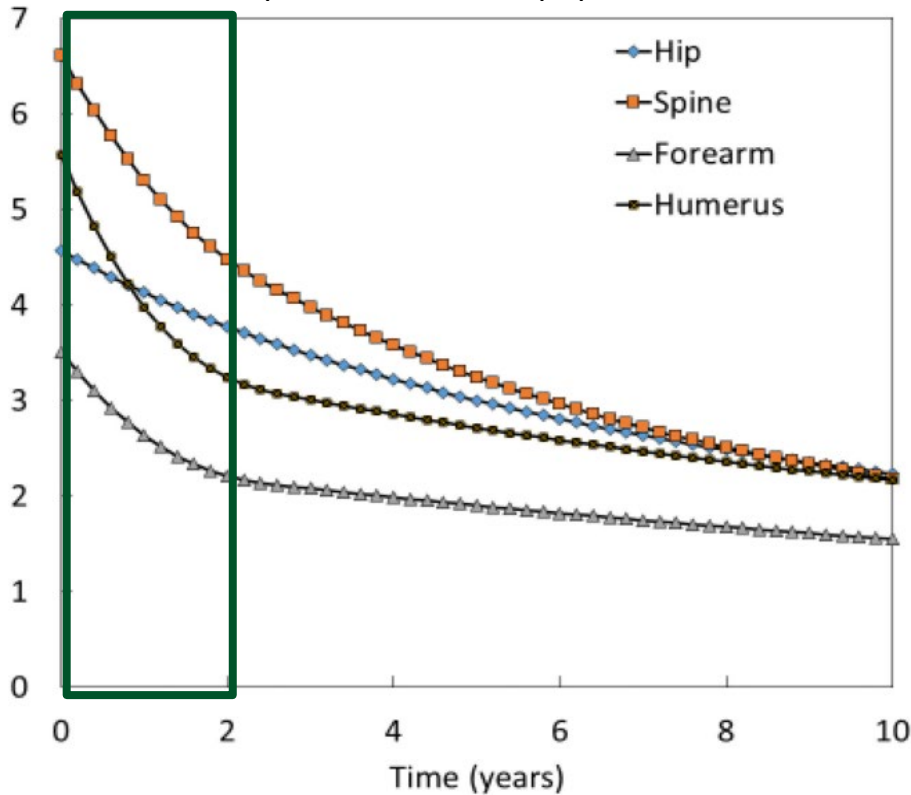


Hazard ratio compared with whole population n=18872



The fracture risk is highest in the first 2 years after a fracture, and remains increased even 10y thereafter

Hazard Ratio compared with whole population n=18872

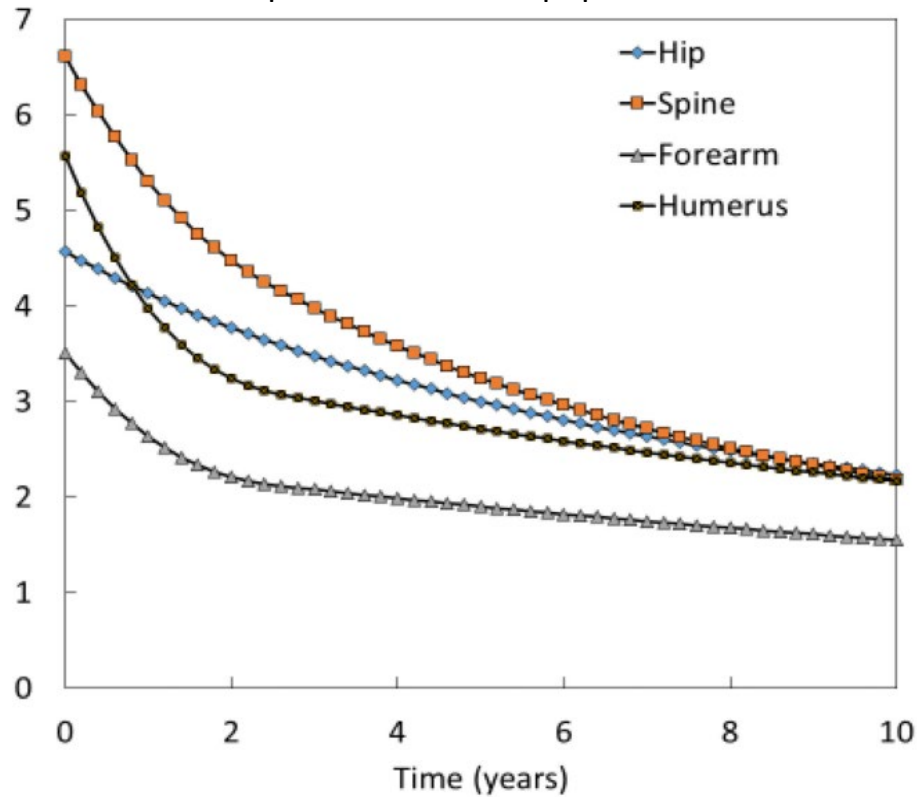


Imminent fracture risk  
= fracture risk within the first 2 years after the fracture



# HR to sustain another fracture is site-dependent

Hazard Ratio compared with whole population n=18872



# New FRAX model and FRAXplus<sup>®</sup>



Country: **Switzerland** Name/ID:  [About the risk factors](#)

## Questionnaire:

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Age:  Date of Birth: Y:  M:  D:

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GE-Lunar  T-score: -2.6

**BMI: 25.0**  
The ten year probability of fracture (%) 

**with BMD**

Major osteoporotic	<b>27</b>
Hip Fracture	<b>6.3</b>

**Adjust your results, try FRAX plus<sup>®</sup>**



# FRAXplus<sup>®</sup> – Beta version



	FRAX <sup>1</sup>	FRAX2 <sup>2</sup>
Cohorts	9	64
Total	46,340	2,138,428
Person-years	189,852	≈ 20,000,000
% female	68	69
% Europe	56	69
Hip fractures	850	42,468
Osteoporotic fractures	4,168	194,369

# FRAXplus<sup>®</sup> – Beta version



Recency of osteoporotic fracture



Information on trabecular bone score (TBS)



High exposure to oral glucocorticoids



Falls history



Type 2 diabetes mellitus



Concurrent data on lumbar spine BMD



	FRAX <sup>1</sup>	FRAX2 <sup>2</sup>
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# FRAXplus<sup>®</sup> – incorporating type and time since last fracture

**Adjust probability according to recent fractures**

Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. (only available if previous fracture is yes)

Previous fracture	Time since previous fracture
<input type="radio"/> Vertebral	<input type="radio"/> 0 to 1 month
<input type="radio"/> Hip	<input type="radio"/> 1 to 6 months
<input checked="" type="radio"/> Humeral	<input type="radio"/> 6 to 12 months
<input type="radio"/> Forearm	<input checked="" type="radio"/> 12 to 24 months
<input type="radio"/> Other	

**Adjust probability**

# FRAXplus<sup>®</sup> – incorporating type and time since last fracture

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Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. (only available if previous fracture is yes)

**Previous fracture**

- Vertebral
- Hip
- Humeral
- Forearm
- Other

**Time since previous fracture**

- 0 to 1 month
- 1 to 6 months
- 6 to 12 months
- 12 to 24 months

**Adjust probability**

## THE TEN YEAR PROBABILITY OF FRACTURE

Major osteoporotic 17%

Hip Fracture 5%

Adjusted Major osteoporotic 26%

Adjusted Hip Fracture 7.5%

# FRAXplus<sup>®</sup>



**FRAX**

**FRAX plus**

	<b>FRAX</b>	<b>FRAX plus</b>
Web	Free	Credits*
Desktop	Licence	Licence + Credits*
Mobile	Licence	Licence + Credits*
Embedded	Licence	Contact Us
Web Service	Licence	Contact Us

\* 5 free credits when creating new account

\* 50% discount for low and lower-middle income economies according to the World Bank Country Classification

## Buy Credits

(1 credit = 1 FRAXplus<sup>®</sup> adjustment)

Click below

50	<del>100 EUR</del> 50 EUR*
100	<del>200 EUR</del> 100 EUR*
200	<del>400 EUR</del> 200 EUR*

\*50% special discount for the launch of the new FRAX website

If you need to purchase more credits, please [contact us](#).

**1 FRAX Calculation = 1 EUR**

# Trabecular Bone Score (TBS) is a validated index of bone microstructure



Osteoporosis International

<https://doi.org/10.1007/s00198-023-06817-4>

POSITION PAPER



**Update on the clinical use of trabecular bone score (TBS) in the management of osteoporosis: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and the International Osteoporosis Foundation (IOF) under the auspices of WHO Collaborating Center for Epidemiology of Musculoskeletal Health and Aging**

Enisa Shevroja · Jean-Yves Reginster · Olivier Lamy · Nasser Al-Daghri · Manju Chandran · Anne-Laurence Demoux-Baiada, et al. *[full author details at the end of the article]*



- 1) Fracture prediction in postmenopausal osteoporosis  
→ independent of BMD and clinical risk factors



1) Fracture prediction in postmenopausal osteoporosis



2) Fracture prediction in secondary osteoporosis, in which BMD underestimates fracture risk

- Type 2 diabetes
- Chronic kidney disease
- Patients treated with glucocorticoids
- Rheumatologic diseases

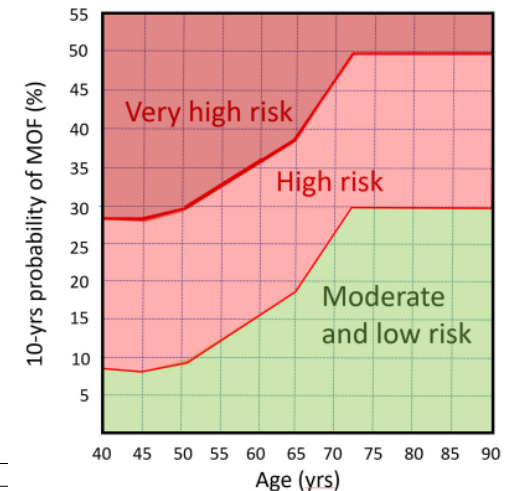
1) Fracture prediction in postmenopausal osteoporosis



2) Fracture prediction in secondary osteoporosis, where BMD underestimates fracture risk

3) Initiating treatment

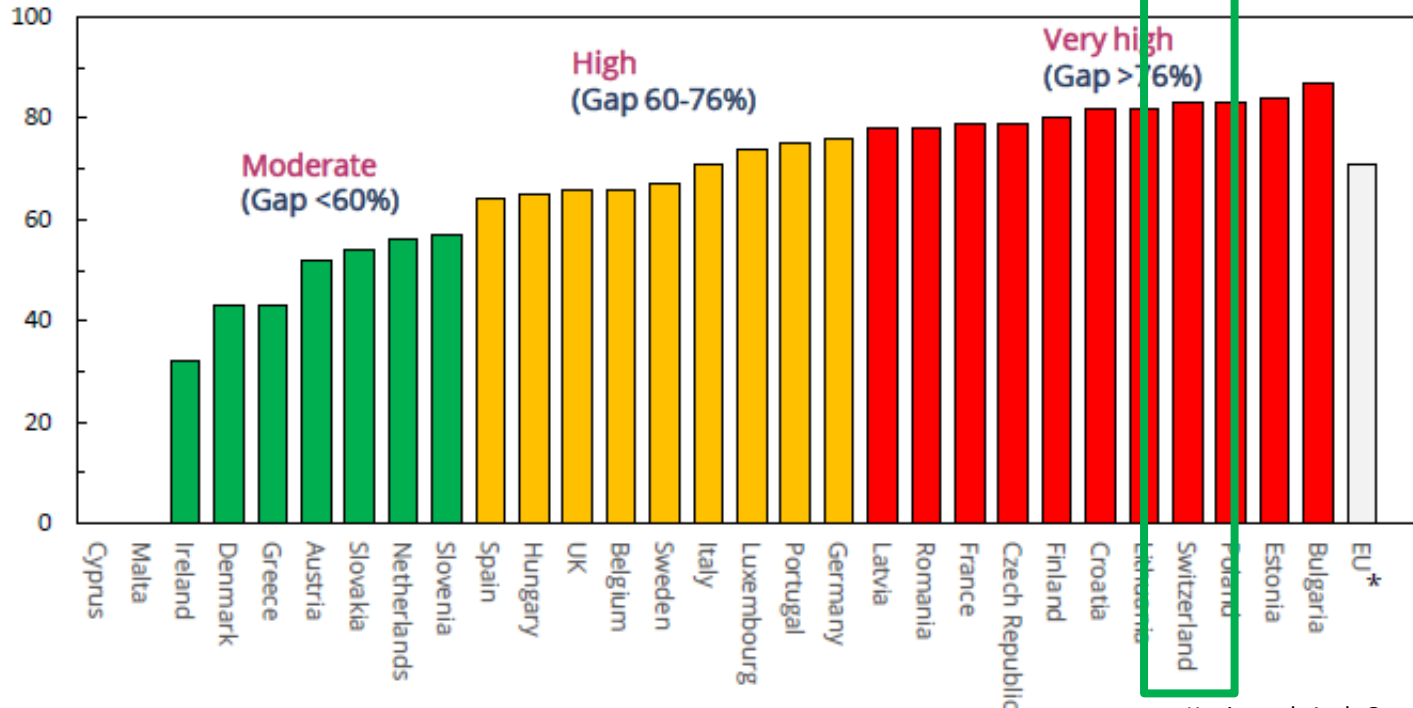
→ greatest utility of TBS in individuals close to a FRAX intervention threshold



# Fracture Liaison Service (FLS) program for secondary fracture prevention

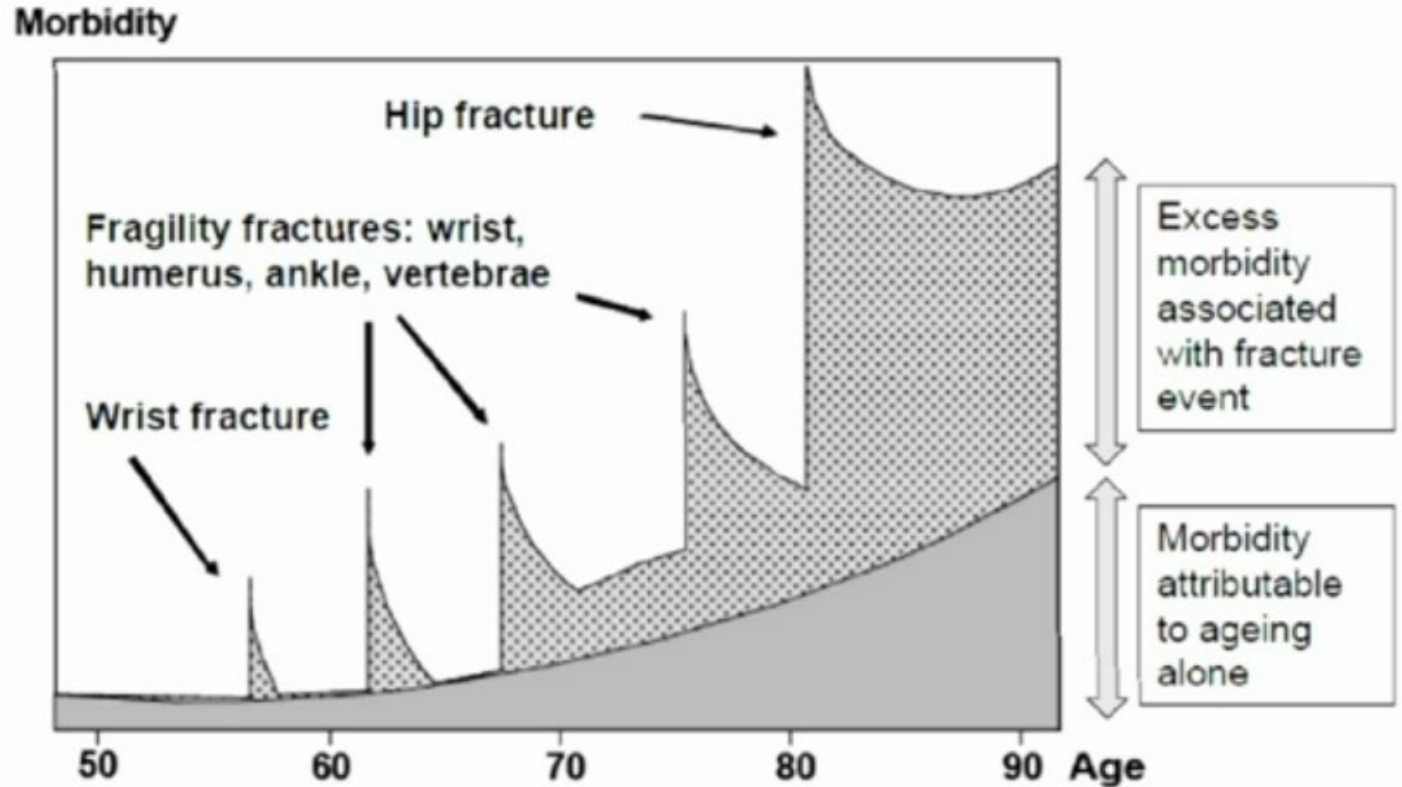
# Osteoporosis treatment gap: How many women with high fracture risk are NOT treated?

Treatment gap (%) in 2019



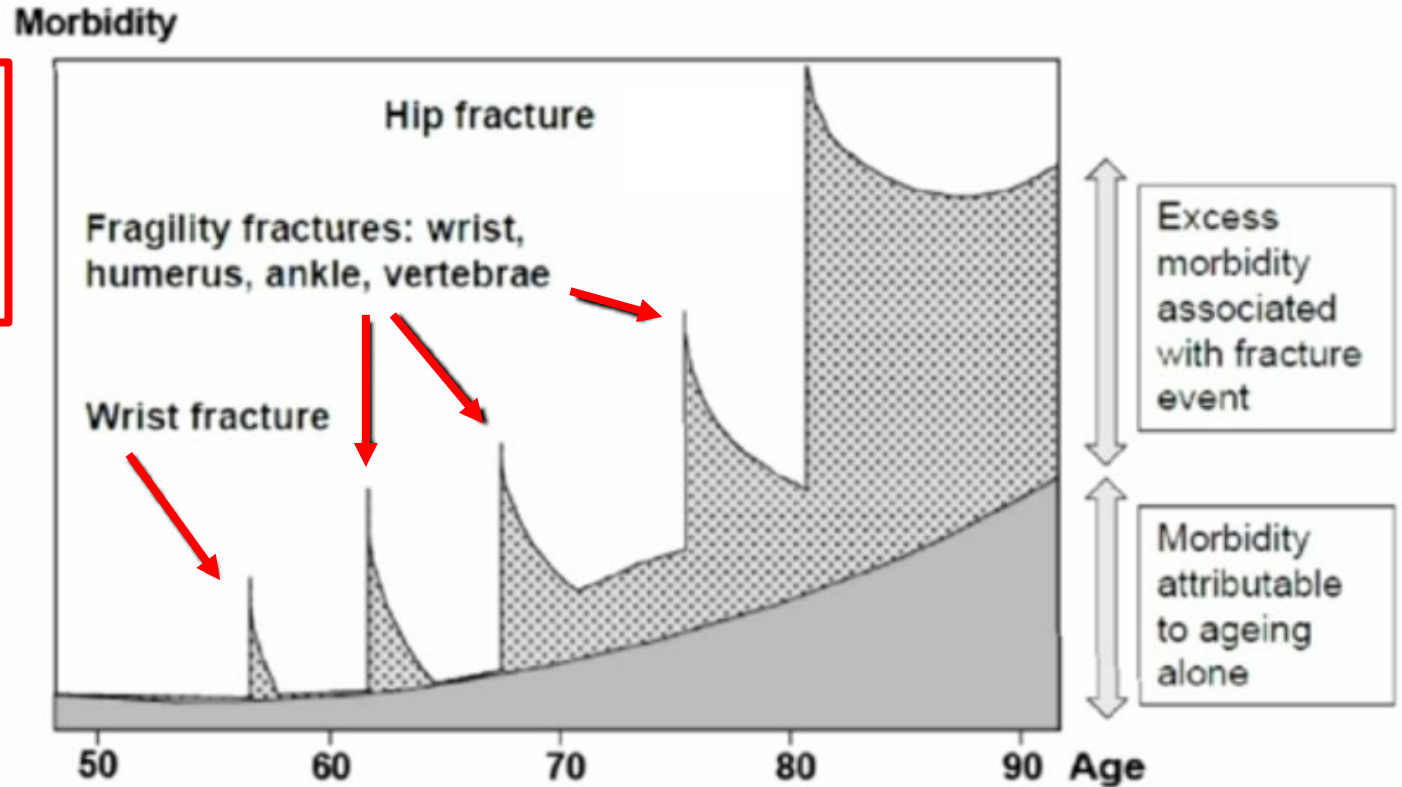
Kanis et al, Arch Osteoporos 2021

# The «osteoporosis career»: 50% of all patients with a hip fracture have had another fracture before



# The «osteoporosis career»: 50% of all patients with a hip fracture have had another fracture before

(missed)  
Opportunities for  
intervention



# Global Burden of Disease Fracture Study 1990-2019

## Global, regional, and national burden of fractures in 204 countries and territories



- **178 million** new fractures, an increase of 33.4% since 1990
- **455 million** prevalent cases of acute or long-term symptoms of a fracture, an increase of 70.1% since 1990
- **25.8 million** years lived with disability, an increase of 65.3% since 1990
- The majority of fractures occurred in older adults, with increases in age-specific incidence becoming evident around age 50 to 54 years in females and 65 to 69 years in males
- Substantial increases in age-specific incidence occurred from age 80 years onwards for both sexes



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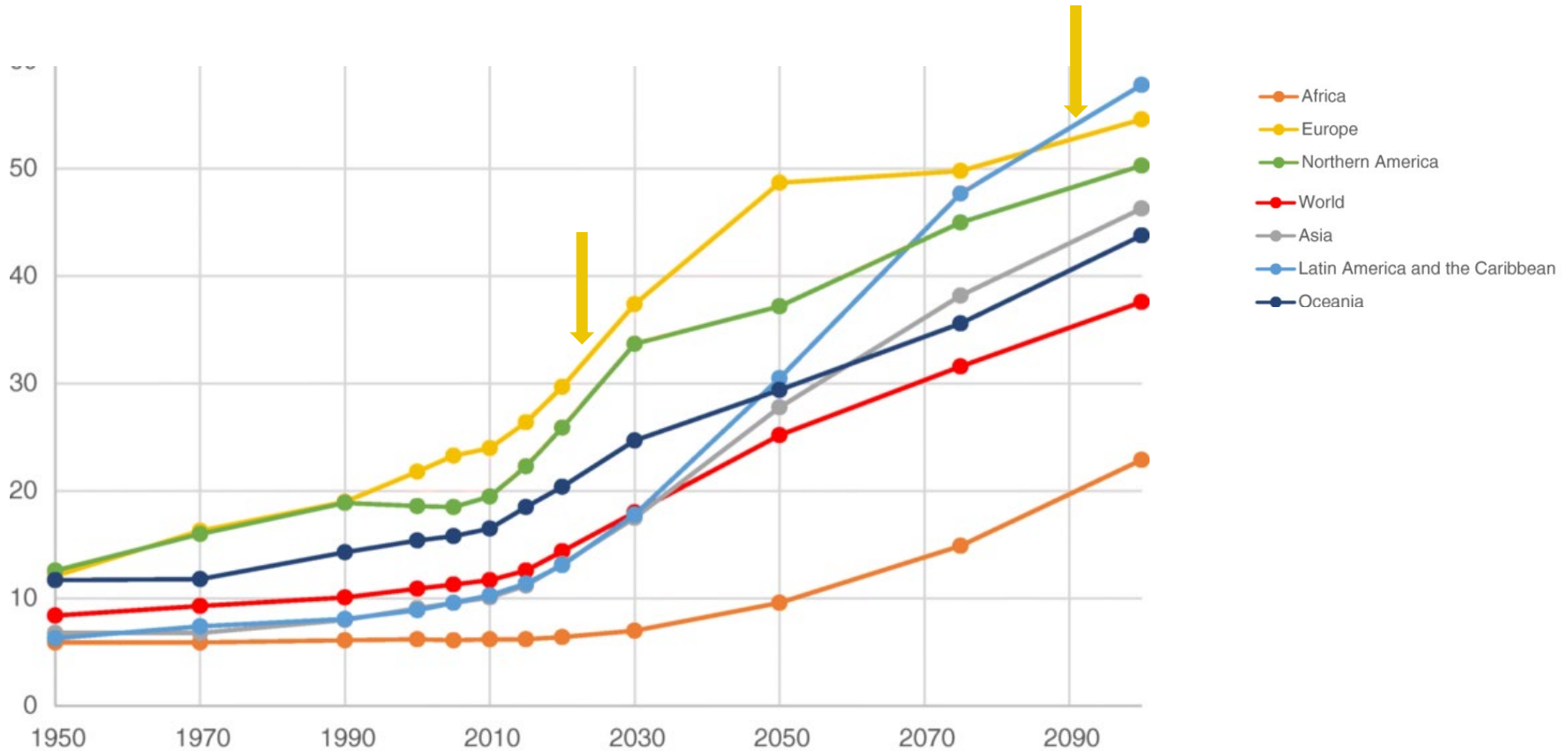
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- Substantial increases in age-specific incidence occurred from age 80 years onwards for both sexes

## The proportion of older adults will further increase

Old-age dependency ratio = ratio of population aged  $\geq 65$ y to the population aged 15-64 y



## Approach: Fracture Liaison Service (FLS)



International program for secondary fracture prevention – Capture the fracture

→ «Making the first fracture the last fracture»





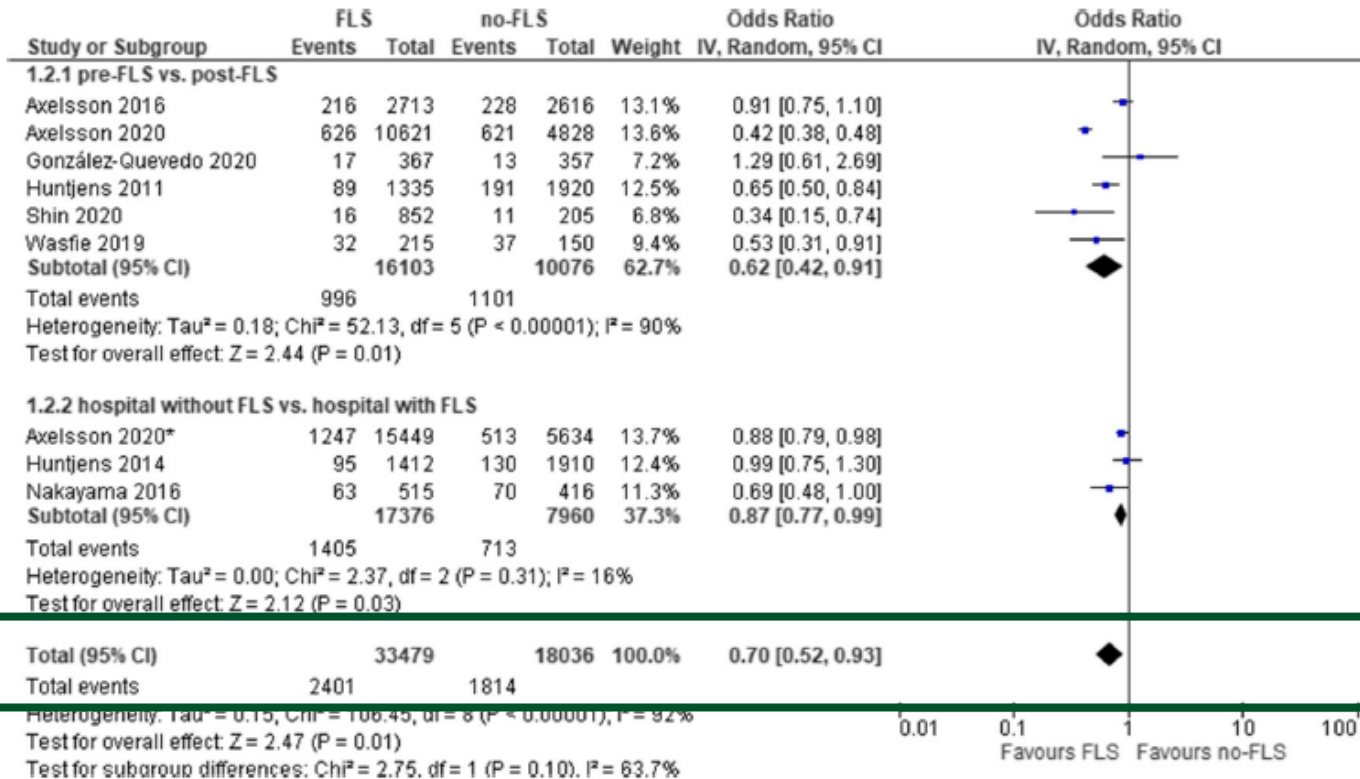
## Fracture Liaison Service (FLS)

- Coordinator-based program in a clinic
- Goal: To capture patients aged > 50/60y who present with a fracture by an FLS-coordinator
- If it's a fragility fracture, screening for osteoporosis and treatment are offered
- The patient is followed-up to ensure further treatment / adherence

# Fracture Liaison Service: successful and cost-effective

- Increase in osteoporosis treatment and adherence
- Significant reduction of further fractures

# Significant reduction of further fractures after an index fracture



**-30%**

# Fracture Liaison Service: successful and cost-effective

- Increase in osteoporosis treatment and adherence
- Significant reduction of further fractures
- Significant reduction of mortality



# Significant reduction of mortality after a fracture



Study or Subgroup	FLS		no-FLS		Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
	Events	Total	Events	Total			
<b>1.2.1 pre-FLS vs. post-FLS</b>							
Axelsson 2016	320	2713	361	2616	13.3%	0.84 [0.71, 0.98]	
Axelsson 2020	1832	10621	1701	4828	13.5%	0.38 [0.35, 0.41]	
González-Quevedo 2020	74	367	92	357	12.3%	0.73 [0.51, 1.03]	
Henderson 2017	20	206	47	248	10.7%	0.46 [0.26, 0.81]	
Huntjens 2011	155	1335	343	1920	13.1%	0.60 [0.49, 0.74]	
Ruggiero 2015	33	210	22	172	10.8%	1.27 [0.71, 2.27]	
<b>Subtotal (95% CI)</b>		<b>15452</b>		<b>10141</b>	<b>73.5%</b>	<b>0.65 [0.44, 0.95]</b>	
<b>Total events</b>	<b>2434</b>		<b>2566</b>				

Heterogeneity: Tau<sup>2</sup> = 0.20; Chi<sup>2</sup> = 98.63, df = 5 (P < 0.00001); I<sup>2</sup> = 95%

Test for overall effect: Z = 2.21 (P = 0.03)

**-35%**

## Decreased Mortality and Subsequent Fracture Risk in Patients With a Major and Hip Fracture After the Introduction of a Fracture Liaison Service: A 3-Year Follow-Up Survey

Lisanne Vranken,<sup>1,2</sup> Irma J.A. de Bruin,<sup>1,2</sup> Annemariëk H.M. Driessen,<sup>3</sup> Piet P.M. Geusens,<sup>4,5</sup> John A. Eisman,<sup>6,7,8</sup> Jacqueline R. Center,<sup>6,7</sup> Robert Y. van der Velde,<sup>1,2</sup> Heinrich M.J. Janzing,<sup>9</sup> Sjoerd Kaarsemaker,<sup>10</sup> Joop P. van den Bergh,<sup>1,2</sup> and Caroline E. Wylers<sup>1,2</sup>

### Further fractures **-33%**

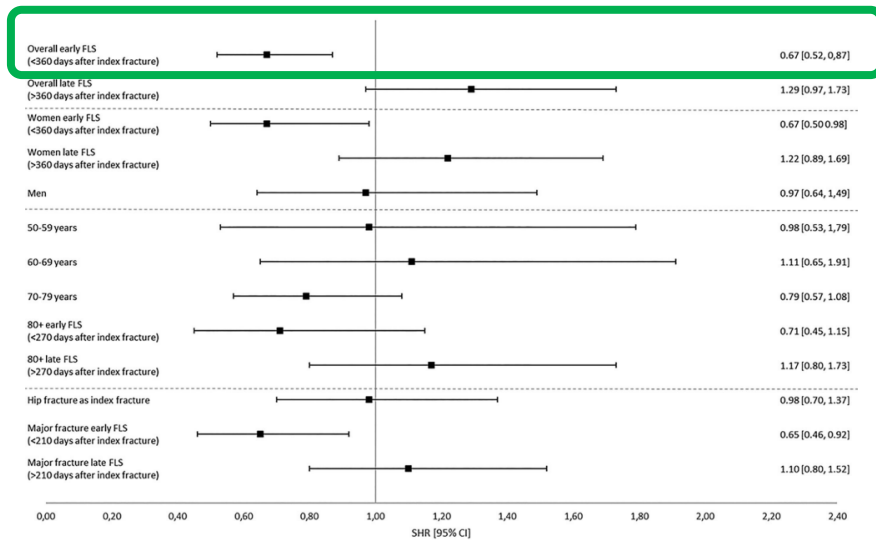


Fig. 2. Subsequent major or hip fracture risk after a major or hip index fracture during 3 years of follow-up, starting from date of index fracture.

### Mortality **-16%**

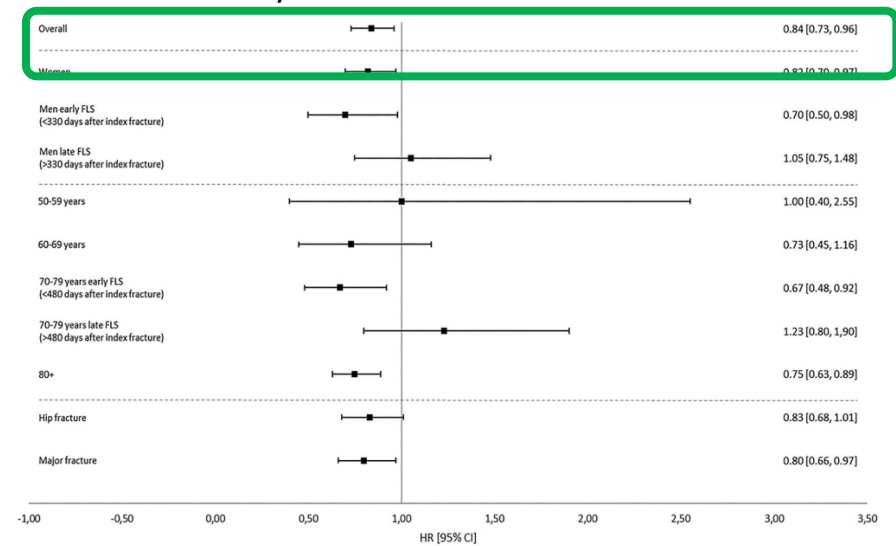


Fig. 1. Mortality risk after a major or hip index fracture during 3 years of follow-up, starting from date of index fracture.

# Fracture Liaison Service: successful and cost-effective

- Increase in osteoporosis treatment and adherence
- Significant reduction of further fractures
- Significant reduction of mortality
- Cost-effective in all age ranges

Wu et al, Osteopor Int, 2018  
Cooper et al, Osteopor Int, 2012  
McLellan et al, Osteopor Int, 2011  
Vranken et al, submitted

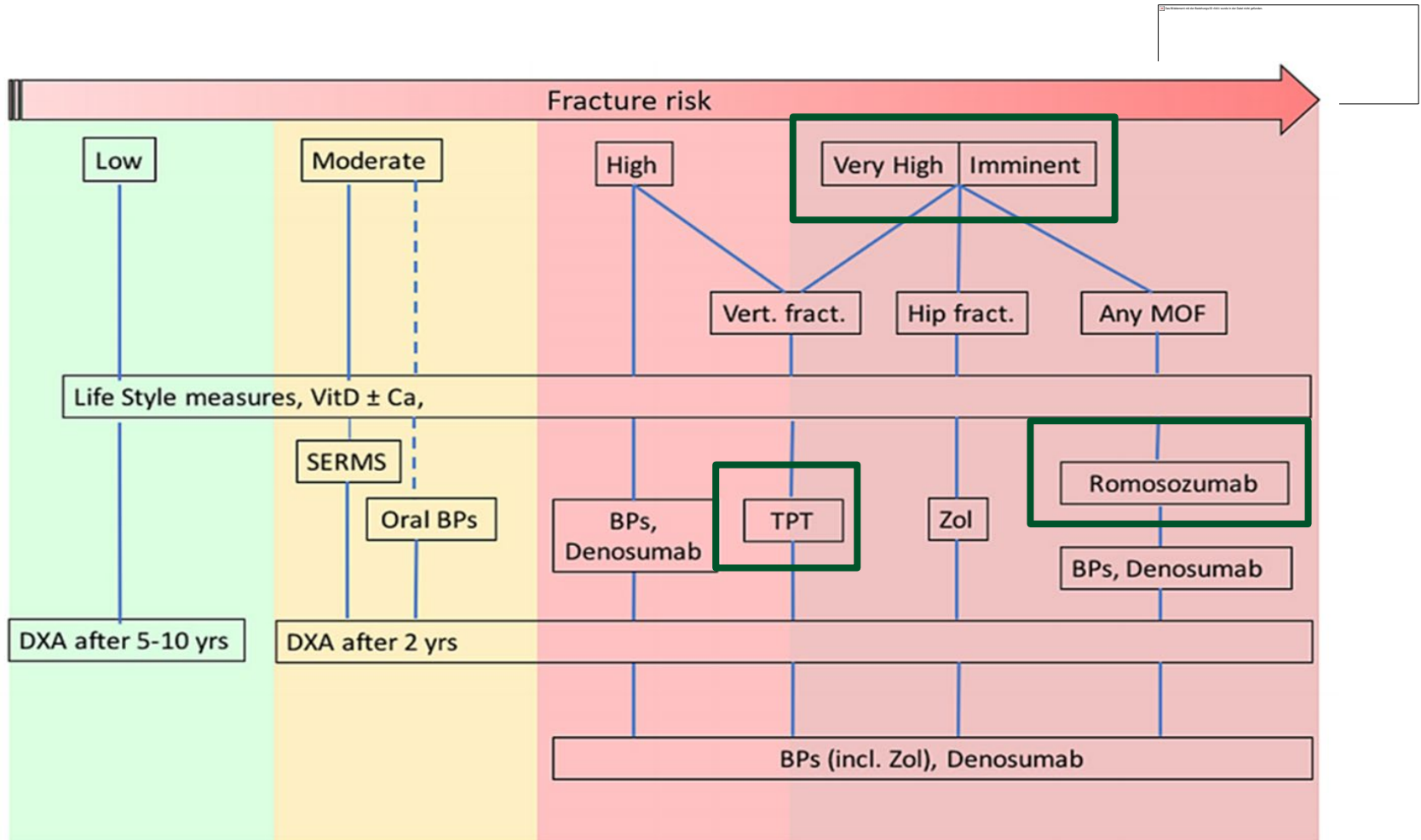
# «Map of best practice» of the IOF: 860 FLS from 54 countries



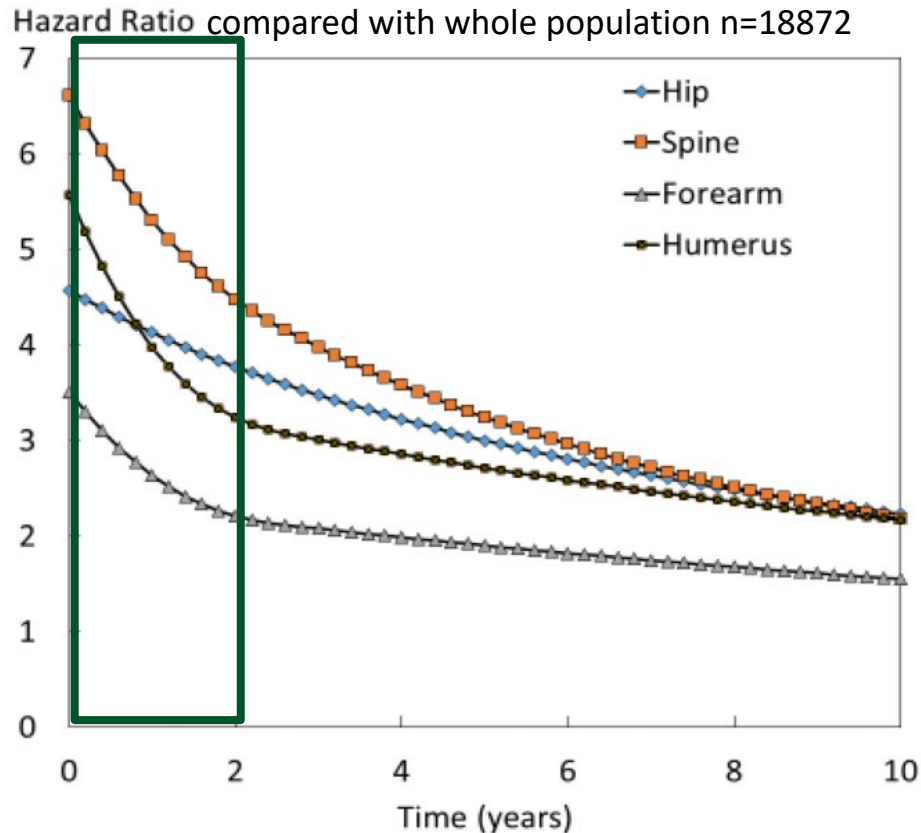
**SWISS FLS**  
Fracture Liaison Services

**SVGO**  
Schweizerische  
Vereinigung  
gegen die  
Osteoporose

**Do high and very high fracture risk  
really matter ?**



The risk of another fracture is very high especially in the first 2 years after the index fracture



Imminent fracture risk  
= fracture risk within the first 2 years after the fracture

# Greater improvements in BMD are strongly associated with greater reductions in vertebral and hip fractures

Meta-regression of 38 placebo-controlled trials

**Table 5.** Estimated Fracture Risk Reduction Associated With BMD Improvement

	Vertebral fracture	Hip fracture	Nonvertebral fracture
<b>Δ Total hip BMD</b>			
2%	28%	16%	10%
4%	51%	29%	16%
6%	66%	40%	21%
<b>Δ Femoral neck BMD</b>			
2%	28%	15%	11%
4%	55%	32%	19%
6%	72%	46%	27%
<b>Δ Lumbar spine BMD</b>			
2%	28%	22%	11%
8%	62%	38%	21%
14%	79%	51%	30%



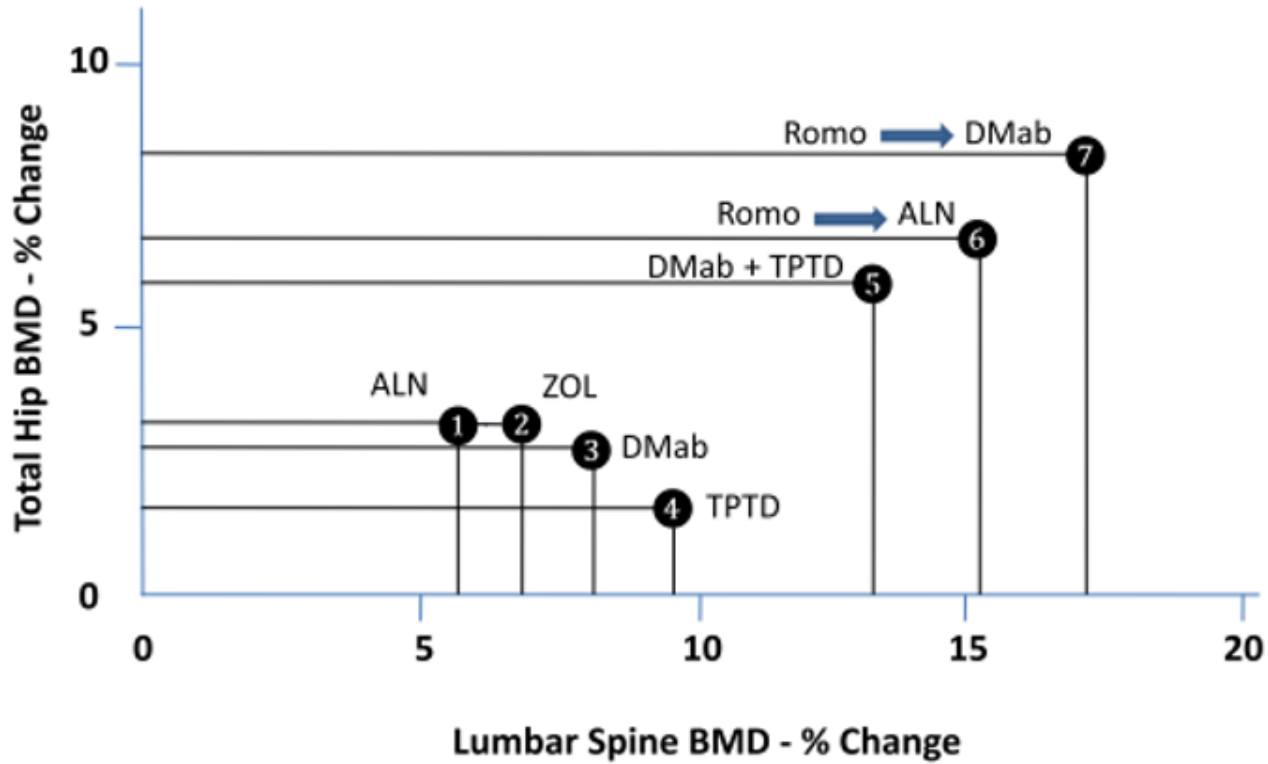
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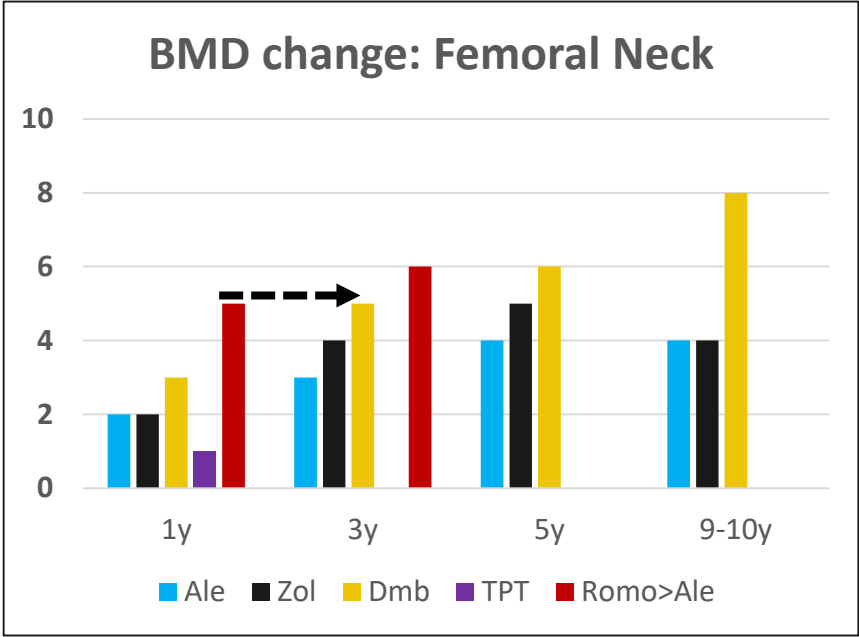
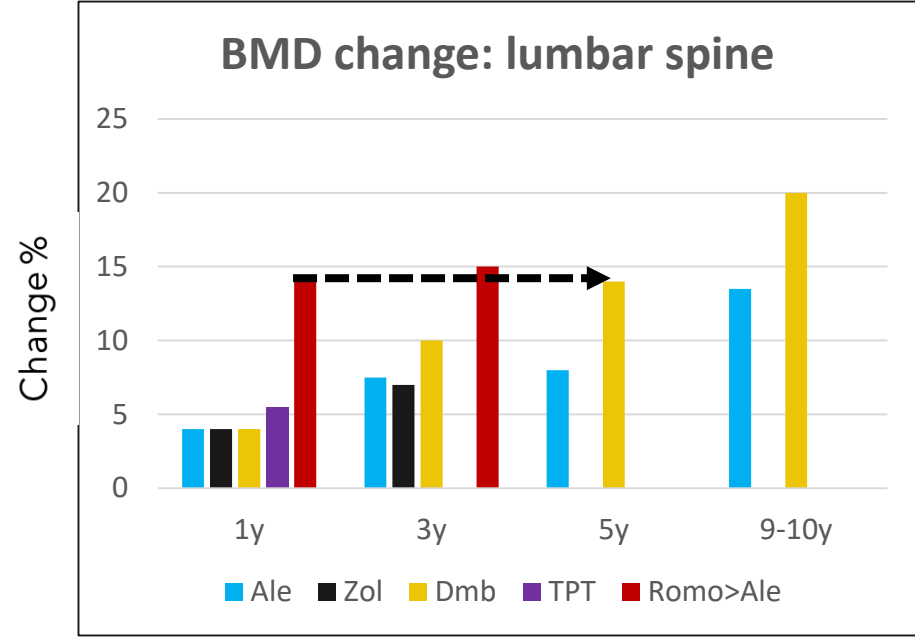
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# BMD changes after 2 years of different agents



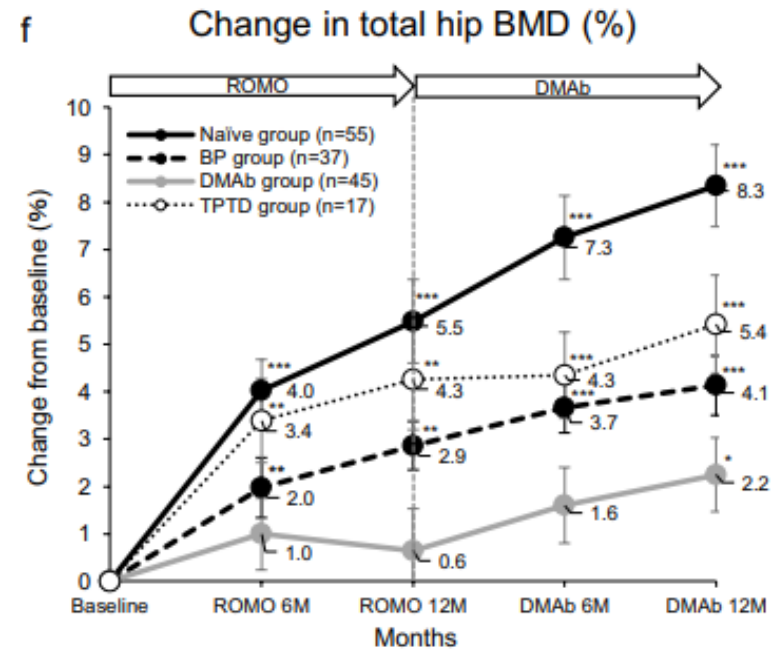
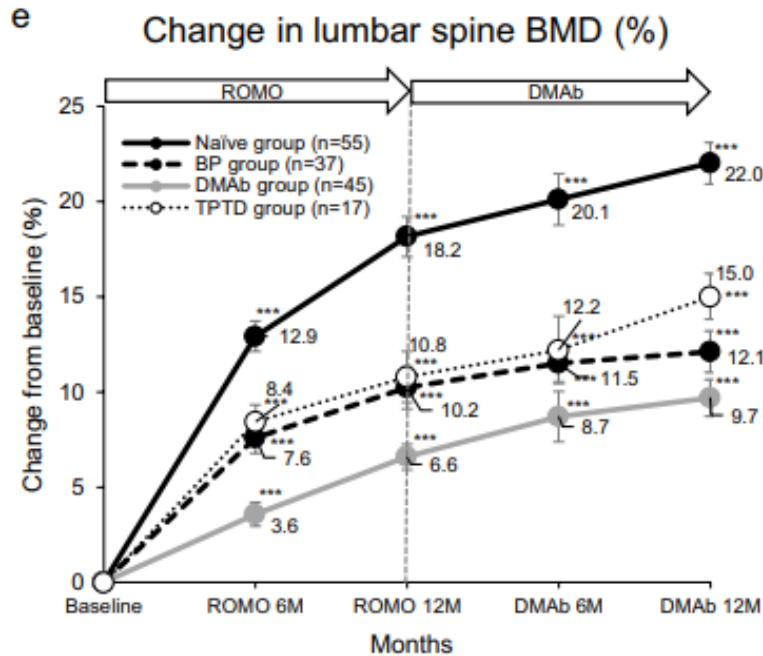
# Overview on Speed & Magnitude of different treatment effect on BMD



Approach: «Anabolics first» in very high fracture risk patients

Black JAMA 2006  
 Harris JAMA 1999  
 Black JBMR 2015  
 Black NEJM 2007  
 Saag 2017  
 Neer 2001

# Observational study investigating the effect of prior treatment on the treatment response of Romosozumab followed by Denosumab



Approach: «Anabolics first» in very high fracture risk patients

# Preventing bone loss / rebound after Denosumab

# Predictors of bone loss after stopping Denosumab



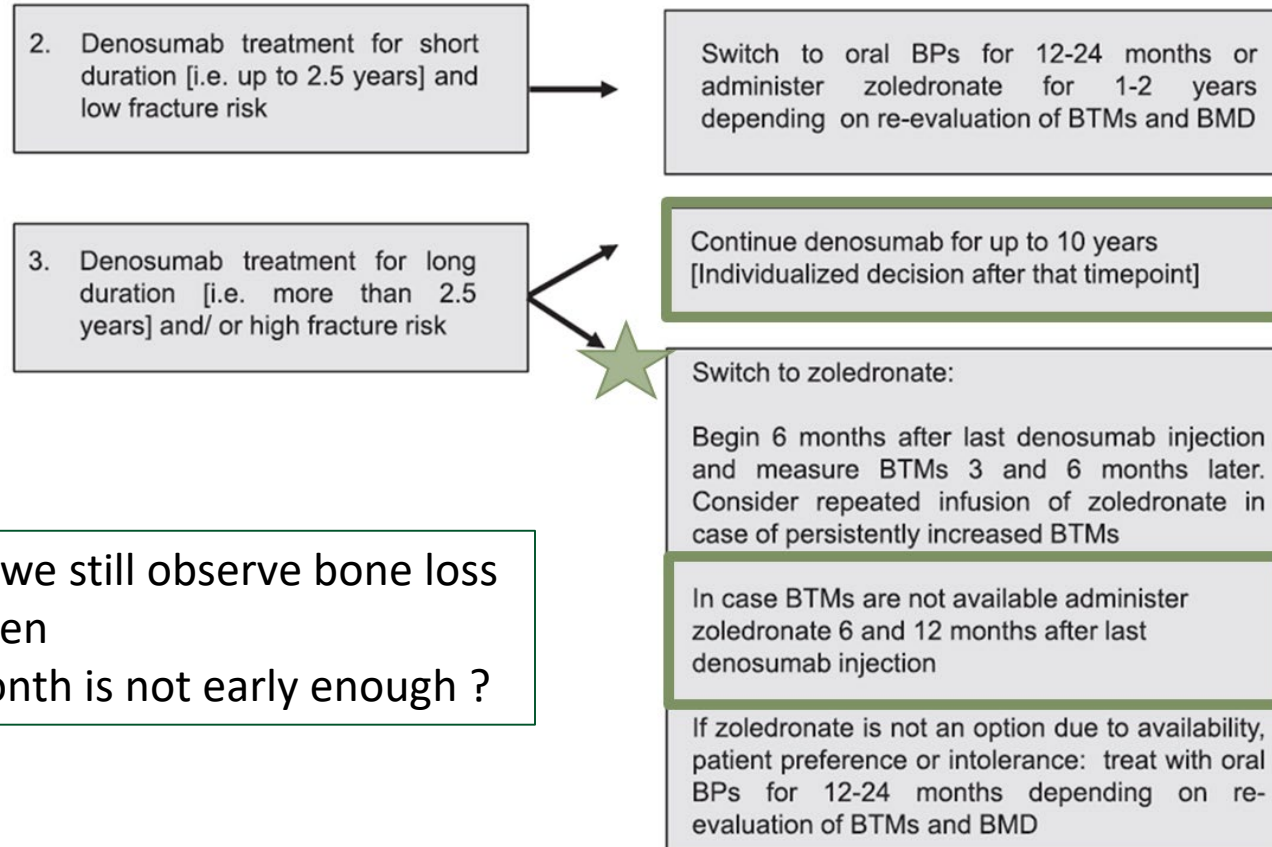
- Duration of treatment (> 3y) – Cosman et al, 2022
- Good BMD response to Denosumab – several studies
- Prevalent vertebral fractures – Burckhart et al, 2021
- No previous oral BP's - Burckhart et al, 2021
- Bone turnover markers ? - Liebich et al, 2023

# Preventing bone loss after Denosumab cessation



- Zoledronate infusions – many studies
- Alendronate ? – Tutaworn et al, 2023
  
- NOT Risedronate – Tutaworn et al, 2023
- NOT Raloxifene – Ha et al, 2022

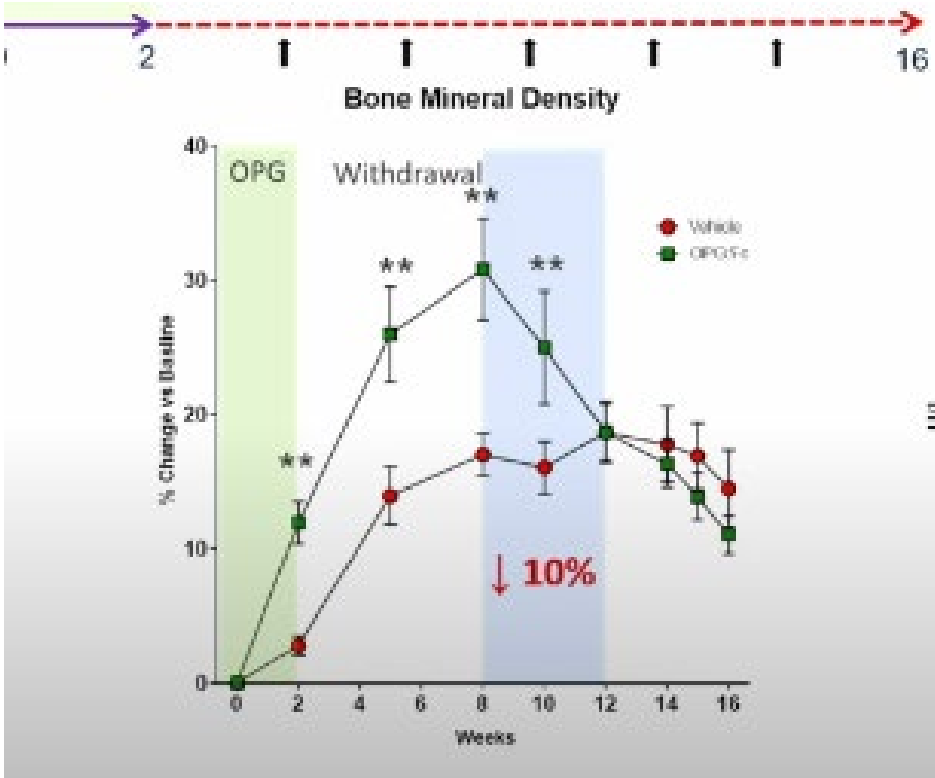
# ECTS position statement, JCEM 2021



Unfortunately, we still observe bone loss with this regimen  
→ maybe 6 month is not early enough ?

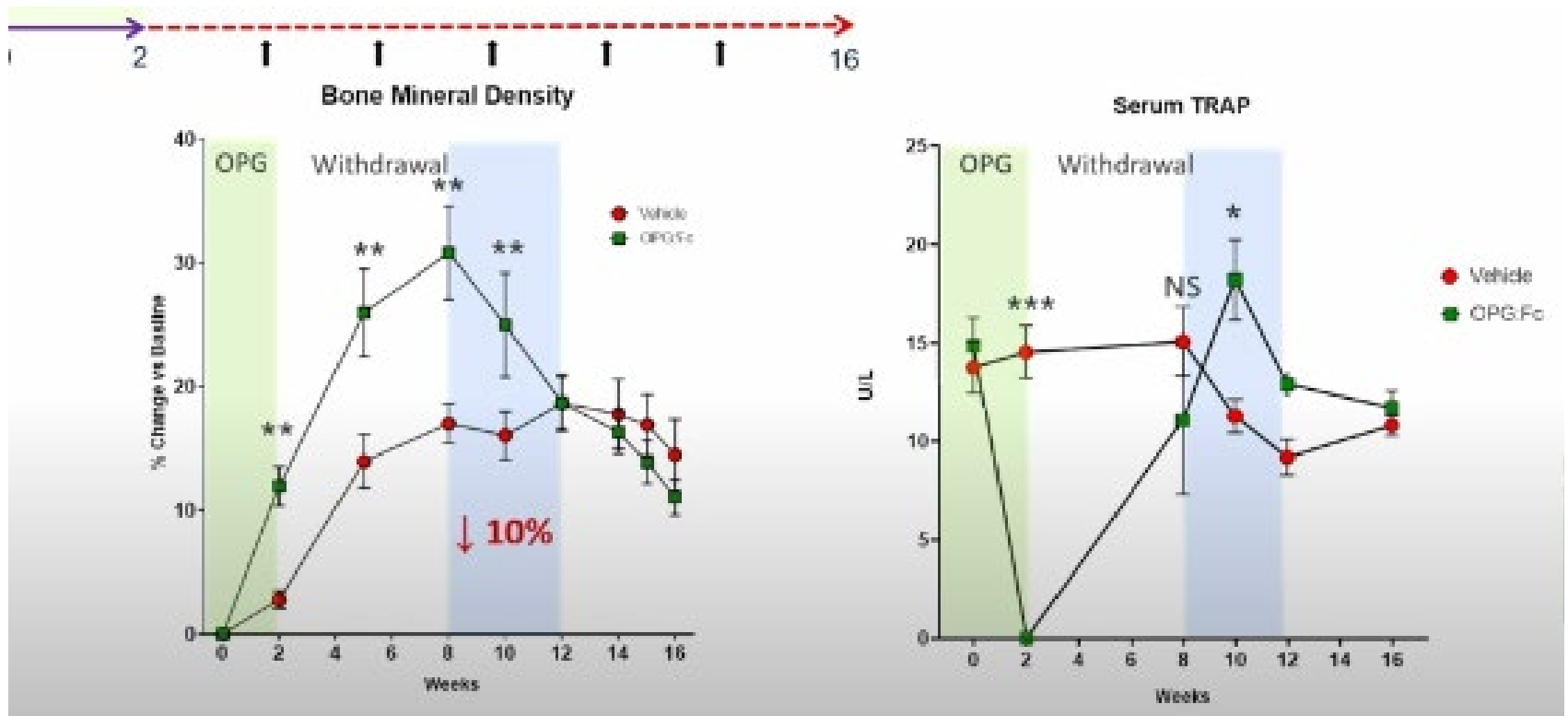


OPG (RANKL inhibition) given for 2 weeks increases BMD in mice, followed by a loss similar to rebound after dmab

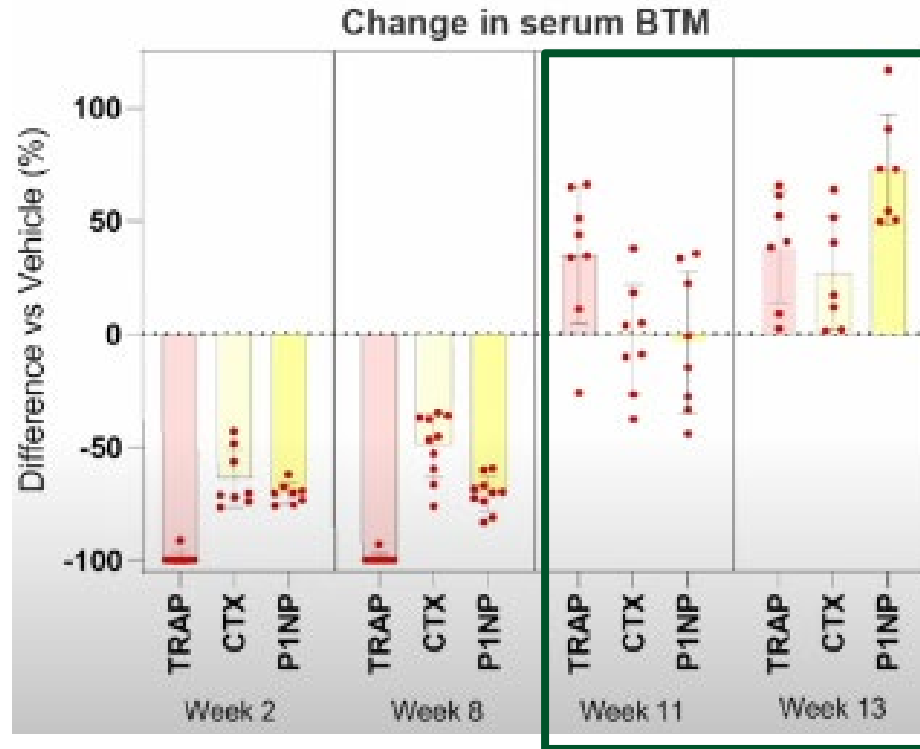


OPG: Osteoprotegerin

Serum TRAP (marker of osteoclast activity) decreases rapidly during OPG, and immediately overshoots to levels above baseline with OPG-withdrawal



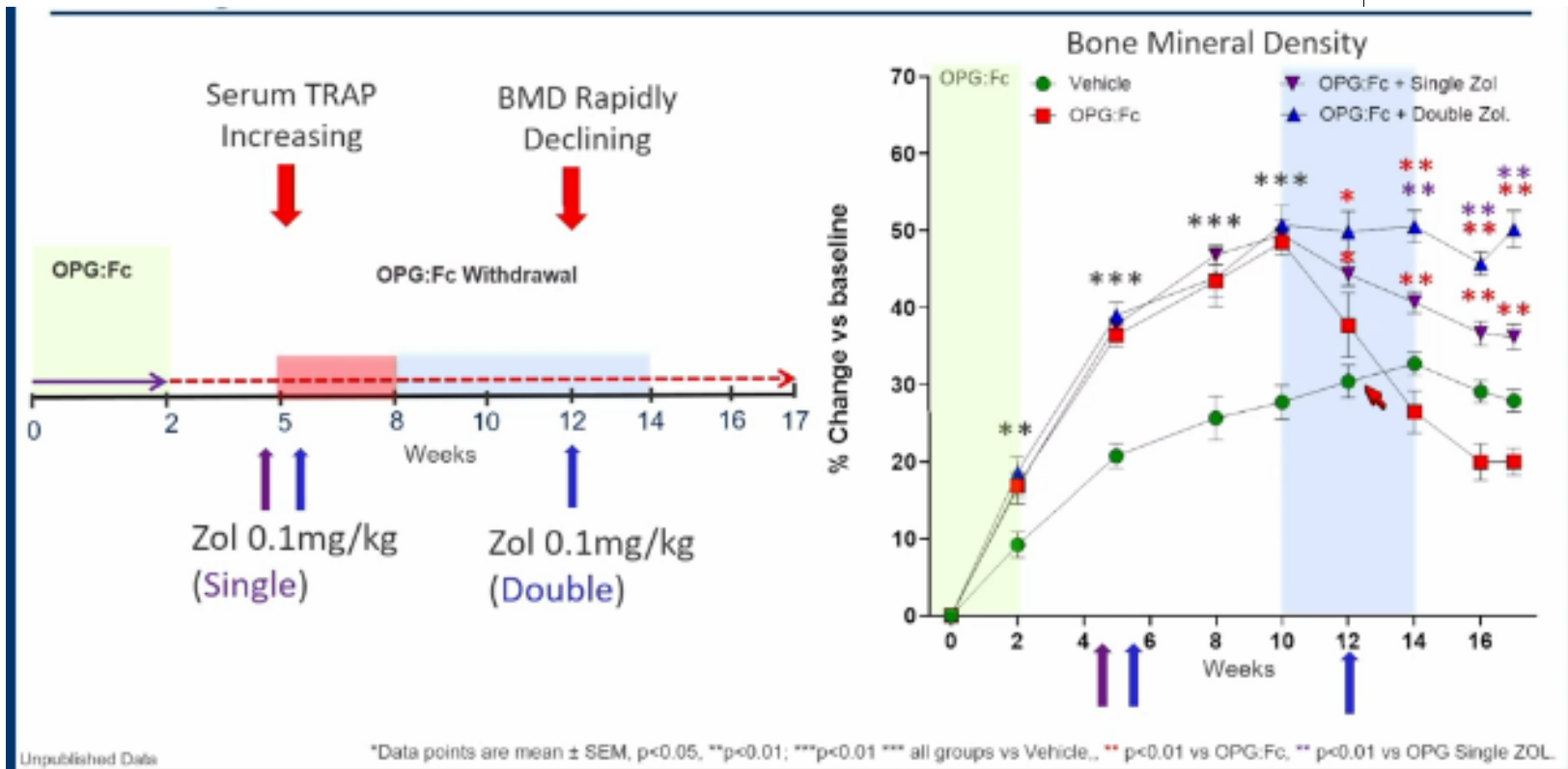
# Increase in serum TRAP levels precedes the rise in the currently used serum markers of bone turnover P1NP and CTX



TRAP = Tartrate-resistant acid phosphatase (TRAP 5b)

31.08.2023

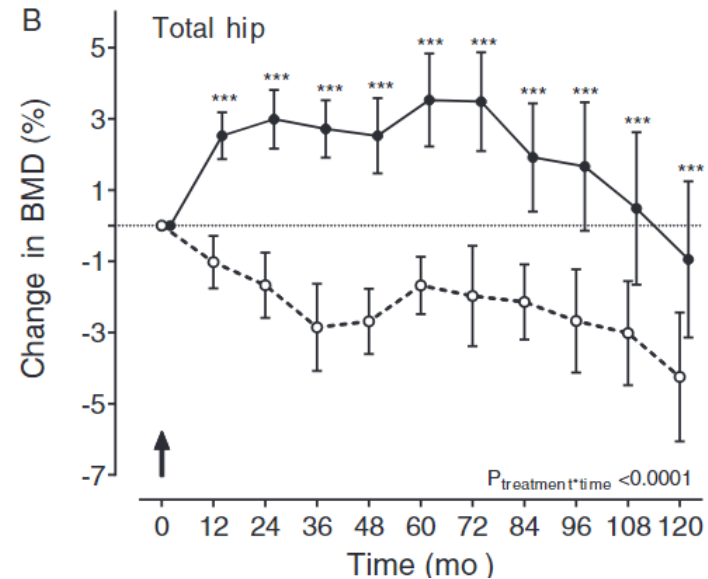
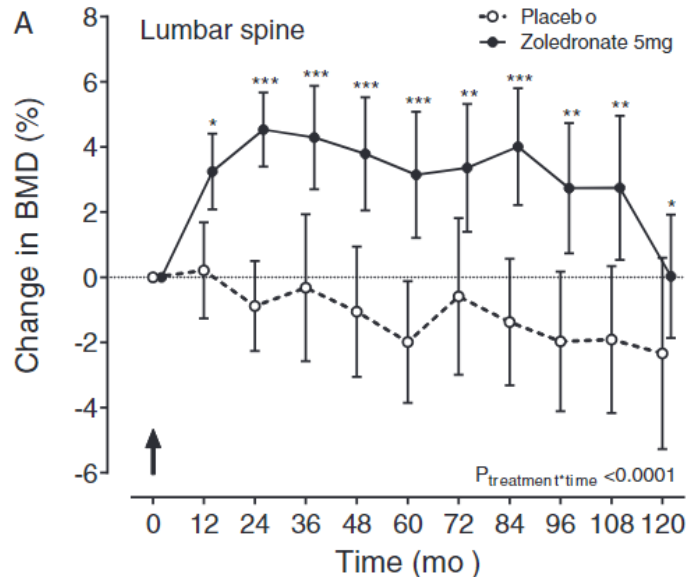
McDonald et al., oral Presentation 2023



→ Early and multiple dosing of ZOL may provide an improved strategy to prevent bone loss for patients stopping denosumab

# News on Bisphosphonates and Updated guidelines

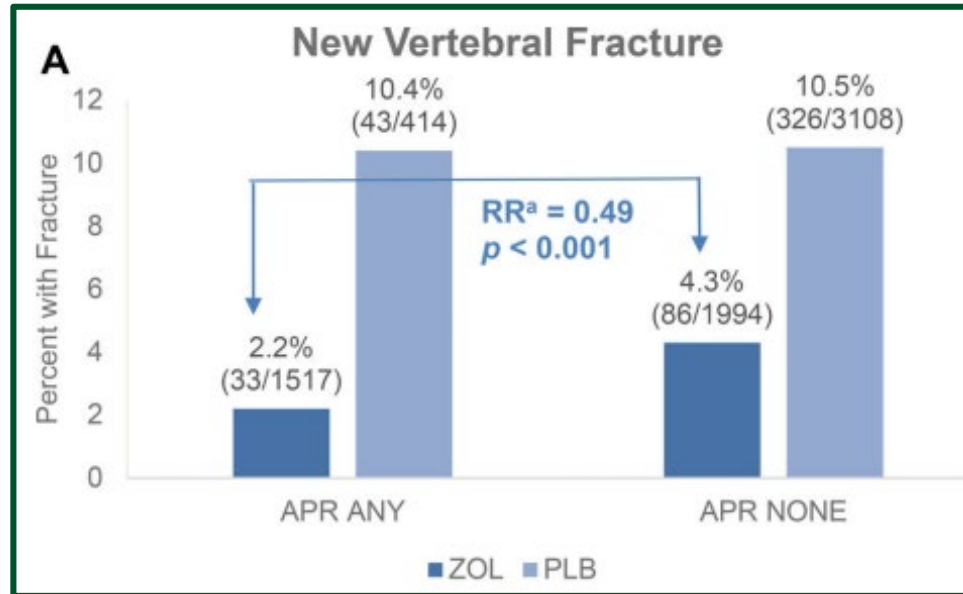
## Bone Mineral Density and Bone Turnover 10 Years After a Single 5 mg Dose or Two 5-Yearly Lower Doses of Zoledronate in Osteopenic Older Women: An Open-Label Extension of a Randomized Controlled Trial



BMD after one dose of Zoledronate 5mg is stable for almost 10 years  
 → potential value in the strategies to prevent osteoporosis

## The Interaction of Acute-Phase Reaction and Efficacy for Osteoporosis After Zoledronic Acid: HORIZON Pivotal Fracture Trial

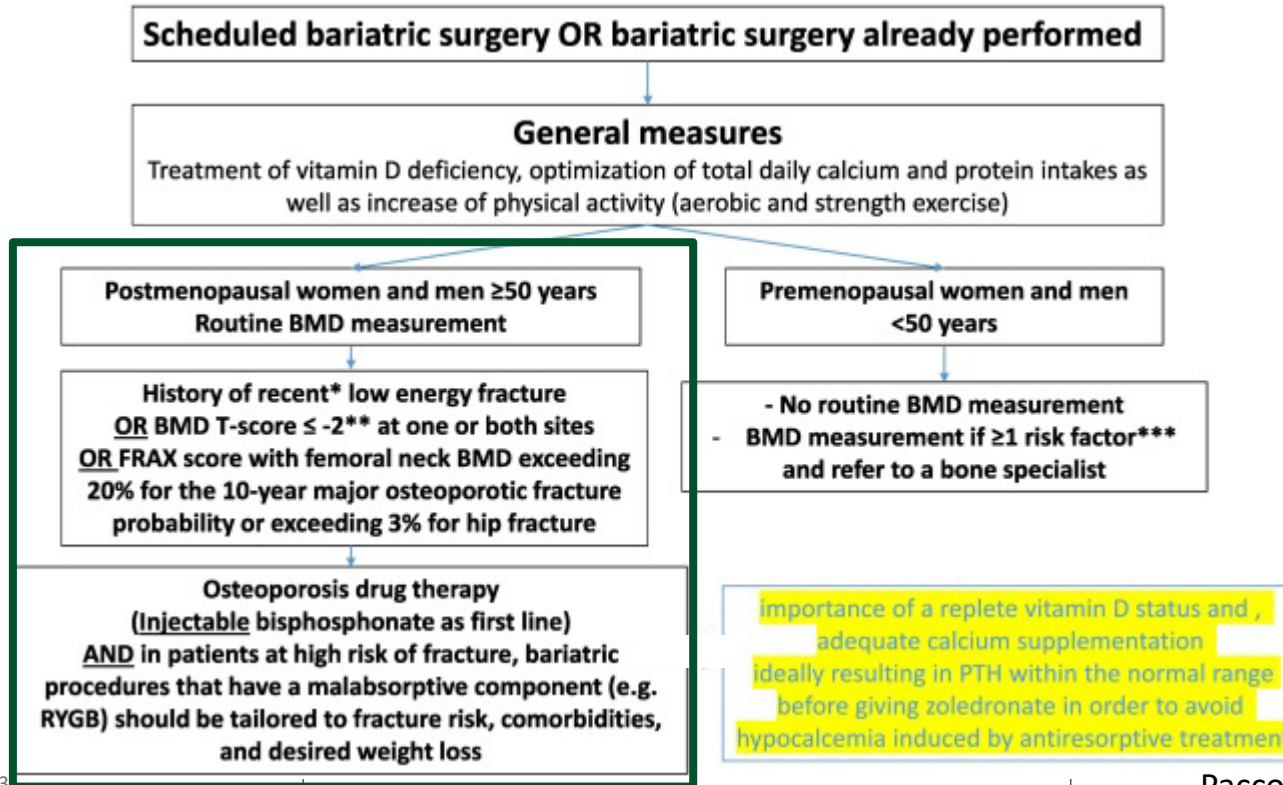
Dennis M. Black,<sup>1</sup> Ian R. Reid,<sup>2</sup> Nicola Napoli,<sup>3,4</sup> Susan K. Ewing,<sup>1</sup> Masataka Shiraki,<sup>5</sup> Toshitaka Nakamura,<sup>6</sup> Yasuhiro Takeuchi,<sup>7,8</sup> Anne L. Schafer,<sup>1,9,10</sup> Tiffany Y. Kim,<sup>9,10</sup> and Jane A. Cauley<sup>11</sup>



Women starting ZOL who experience an Acute-Phase-Reaction have a larger treatment-related reduction in vertebral fracture risk compared to those without

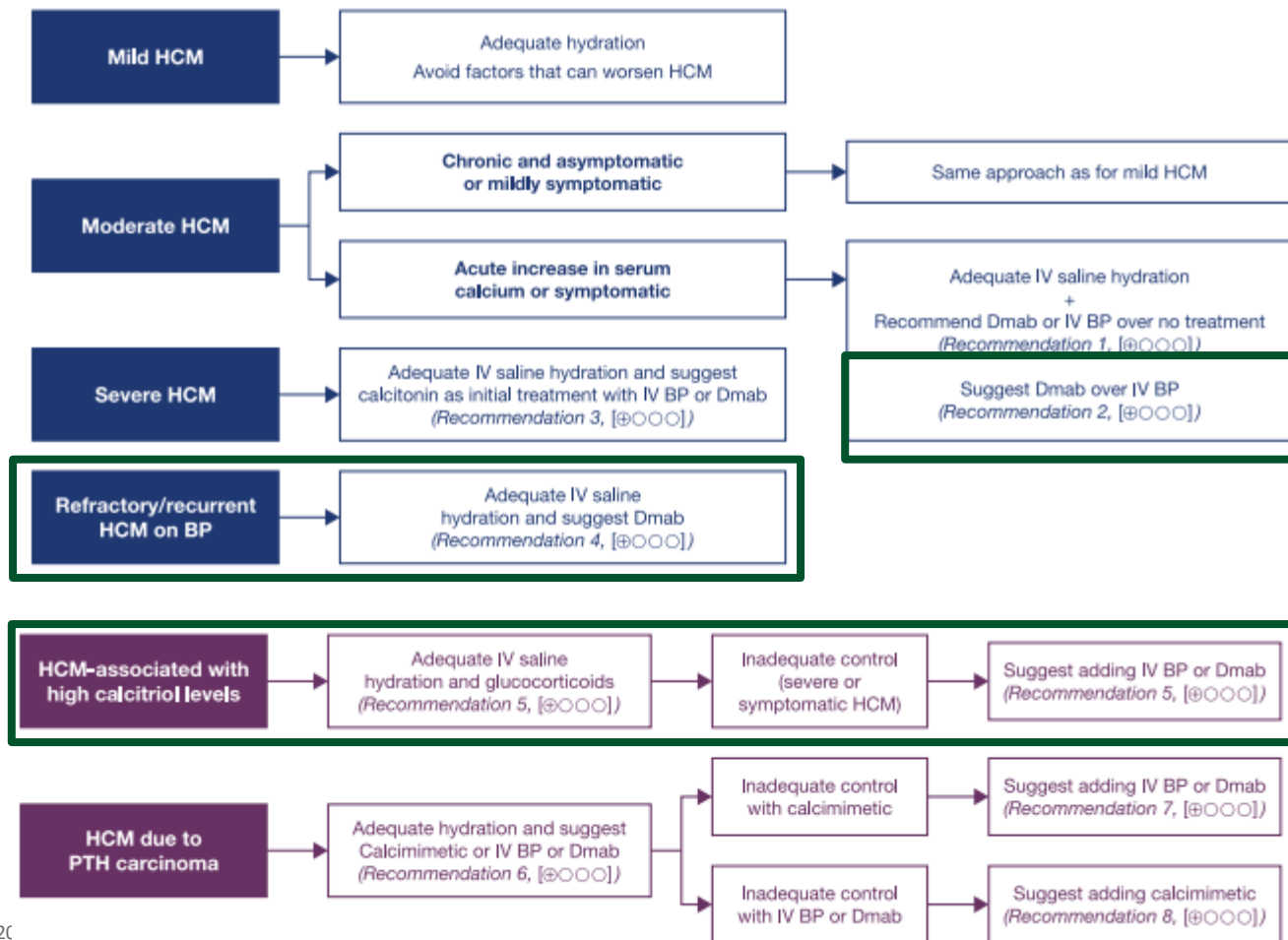
# Bariatric surgery and skeletal health: A narrative review and position statement for management by the European Calcified Tissue Society (ECTS)

Julien Paccou<sup>1</sup>, Elena Tsoardi<sup>2</sup>, Christian Meier<sup>3</sup>, Andrea Palermo<sup>4</sup>, Jessica Pepe<sup>5</sup>, Jean-Jacques Body<sup>6</sup>, M Carola Zillikens<sup>7</sup>





# Treatment of Hypercalcemia of Malignancy in Adults: An Endocrine Society Clinical Practice Guideline



# Updated guidelines / Position statements in 2022

*The Journal of Clinical Endocrinology & Metabolism*, 2022, **107**, 1441–1460  
<https://doi.org/10.1210/clinem/dgab888>  
Advance access publication 18 December 2021  
Reports and Recommendations



## Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS

Athanasios D. Anastasilakis,<sup>1,\*</sup> Jessica Pepe,<sup>2,\*</sup> Nicola Napoli,<sup>3,\*</sup> Andrea Palermo,<sup>3,Ⓞ</sup> Christos Magopoulos,<sup>4</sup> Aliya A. Khan,<sup>5</sup> M. Carola Zillikens,<sup>6</sup> and Jean-Jacques Body<sup>7</sup>

> *J Bone Miner Res.* 2022 Dec;37(12):2568–2585. doi: 10.1002/jbmr.4691. Epub 2022 Nov 14.

## Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop

Aliya A Khan<sup>1</sup>, John P Bilezikian<sup>2</sup>, Maria Luisa Brandi<sup>3</sup>, Bart L Clarke<sup>4</sup>, Neil J Gittoes<sup>5</sup>,


## World guidelines for falls prevention and management for older adults: a global initiative

Manuel Montero-Odasso , Nathalie van der Velde, Finbarr C Martin, Mirko Petrovic,



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John P. Bilezikian , Aliya A. Khan, Shonni J. Silverberg, Ghada El-Hajj Fuleihan,



Thank you

