Pharmacological management of patients with fragility fractures

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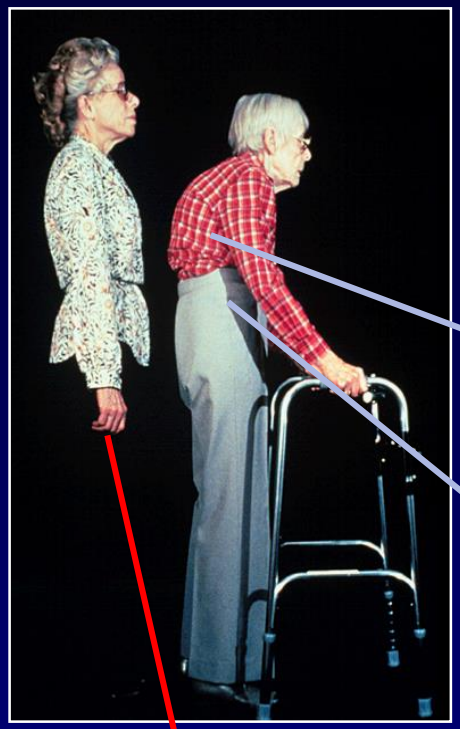
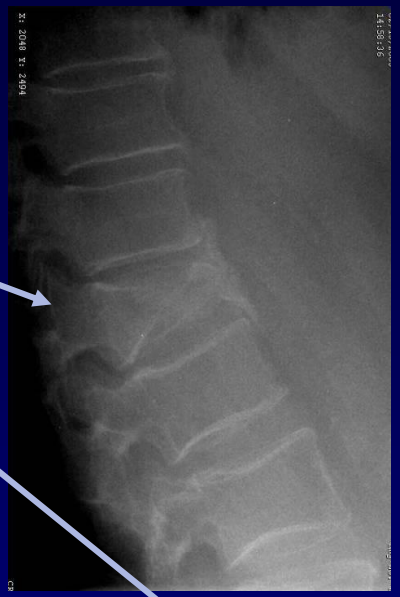
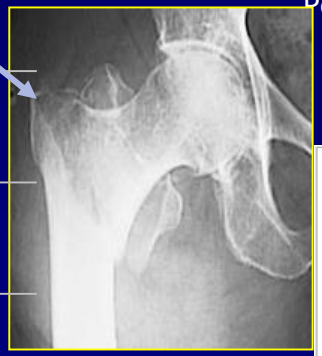
What is the goal of osteoprosis therapy ?

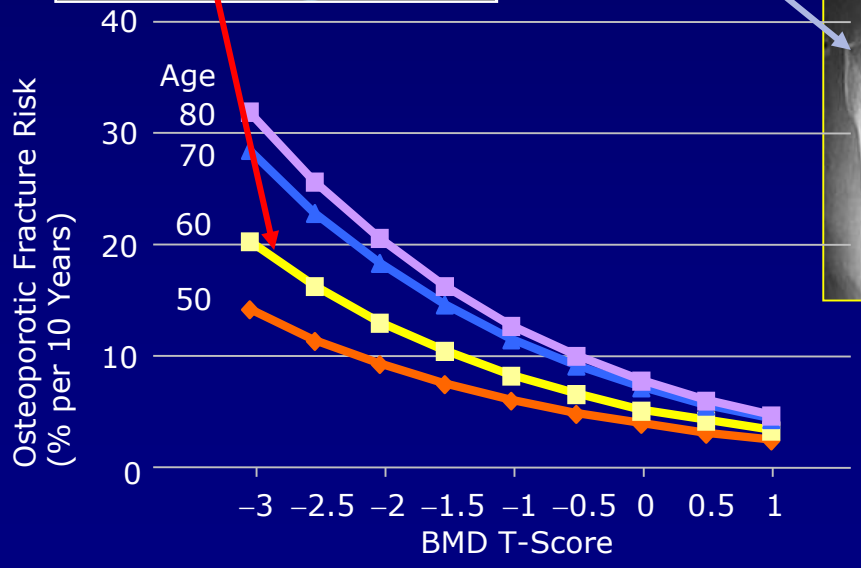
- Rapid reduction of fracture risk, particularly in patients at “imminent” risk
- Long-term restauration of bone mass and strength

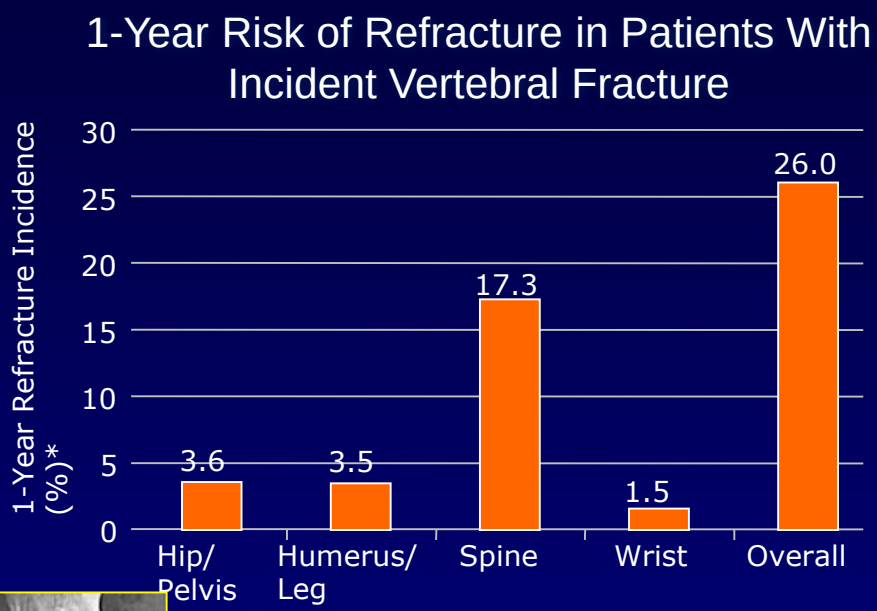
10 yrs vs imminent fracture risk



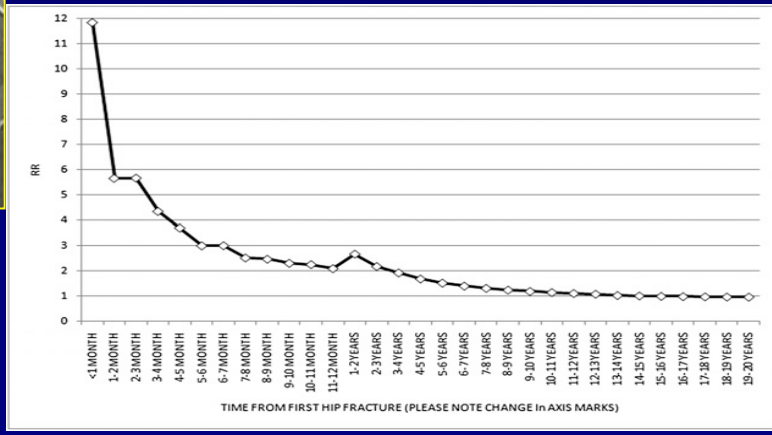




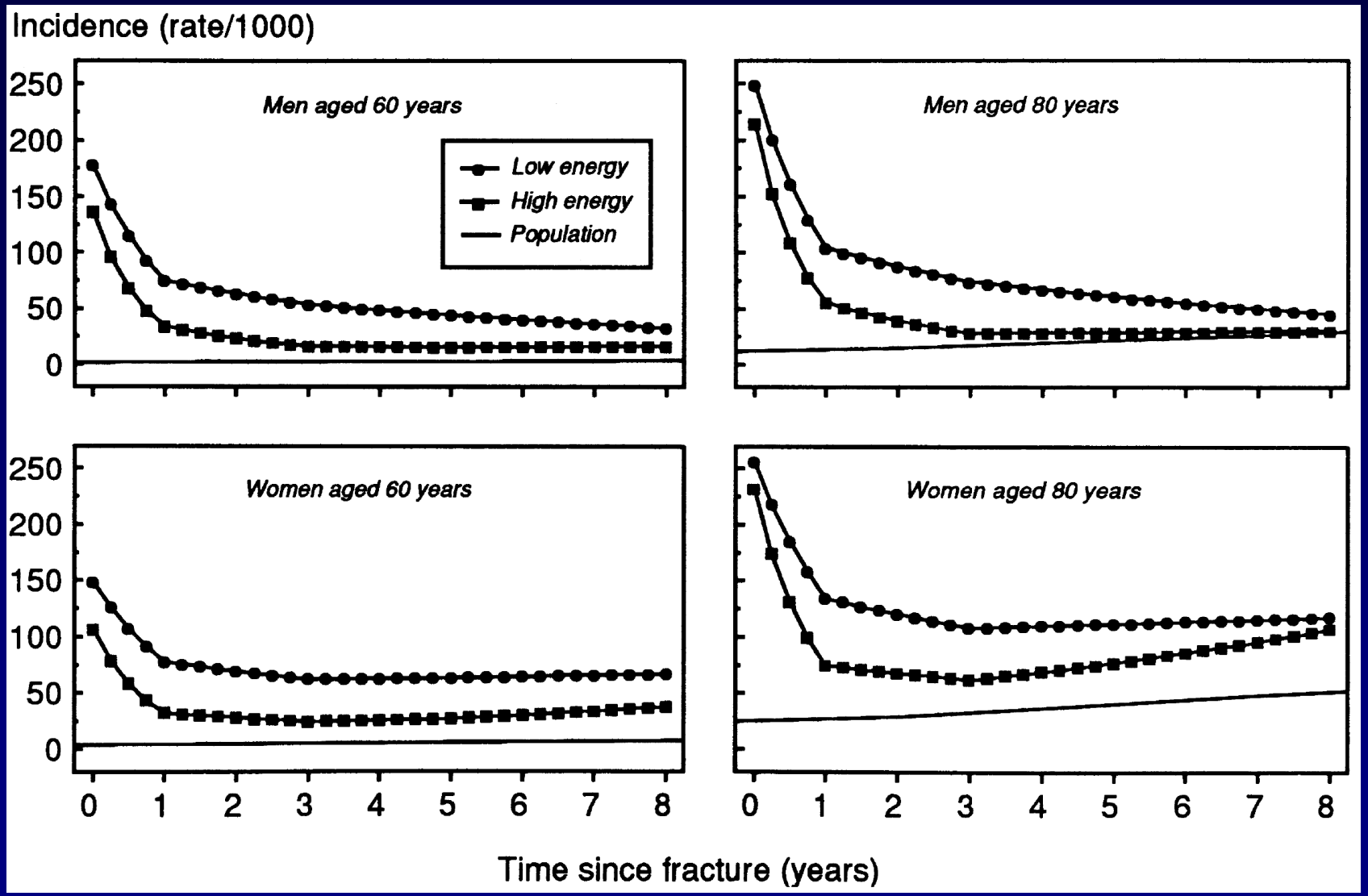




Relative Risk of hip fracture after a hip fracture



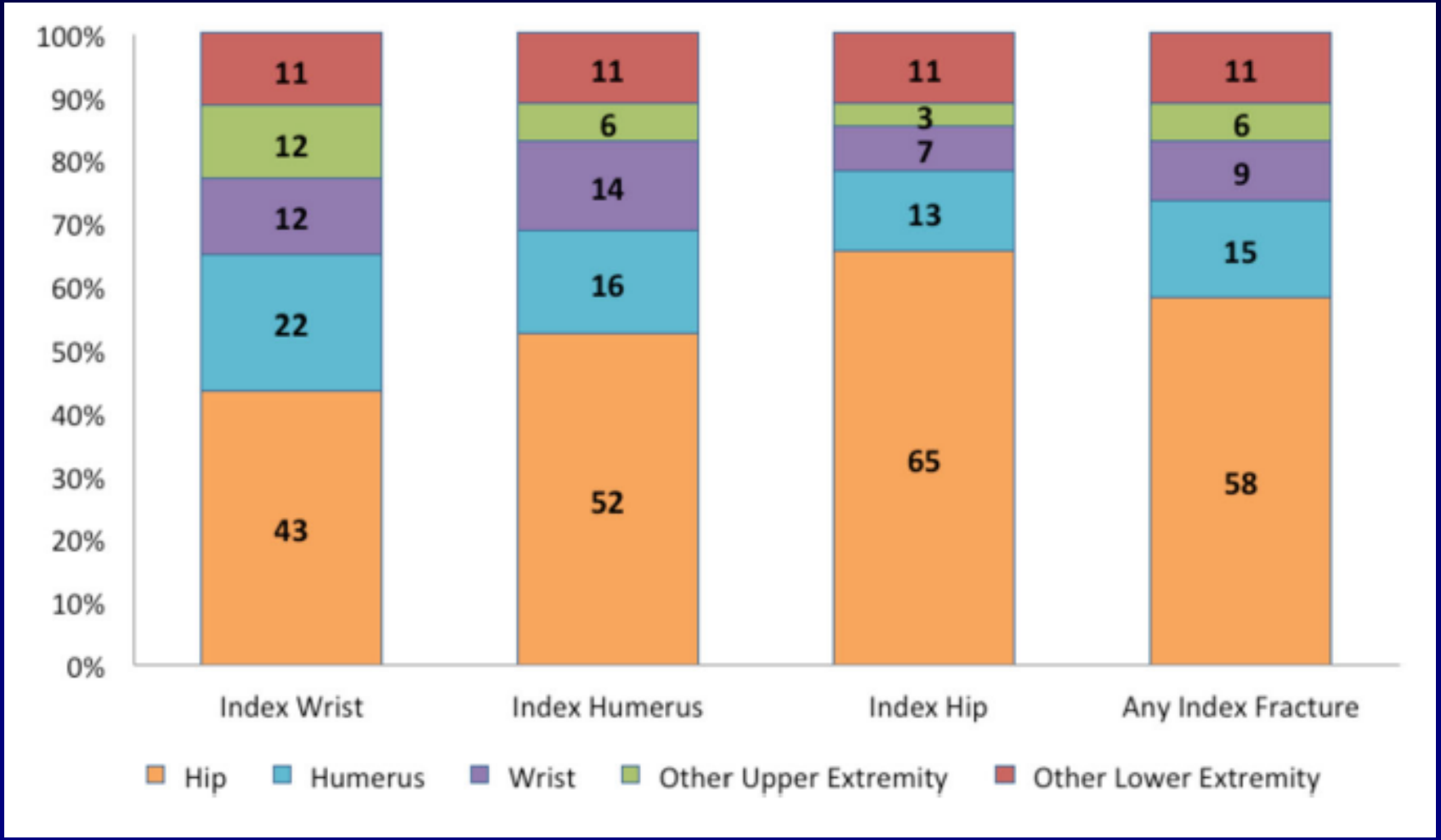
Fracture risk after hospitalization for vertebral fracture



Johnell et al., Osteoporos Int 2001

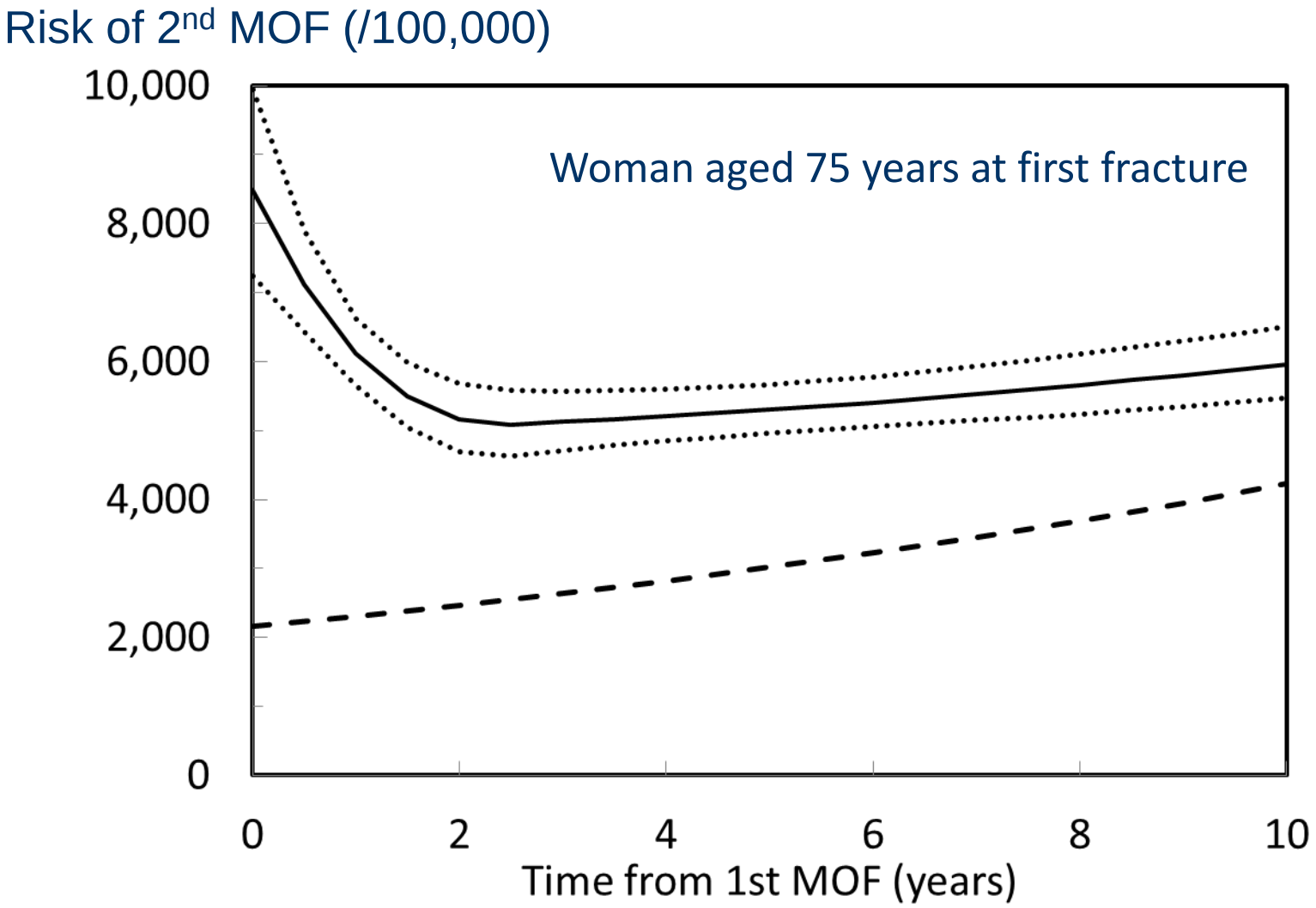
Refracture rates - Medicare

(Women and Men 65+, n=273’000, 1yr rate=4.3%, increases with age, comorbidities, and worst after hip =7.5%)



Bynum, OI 2016

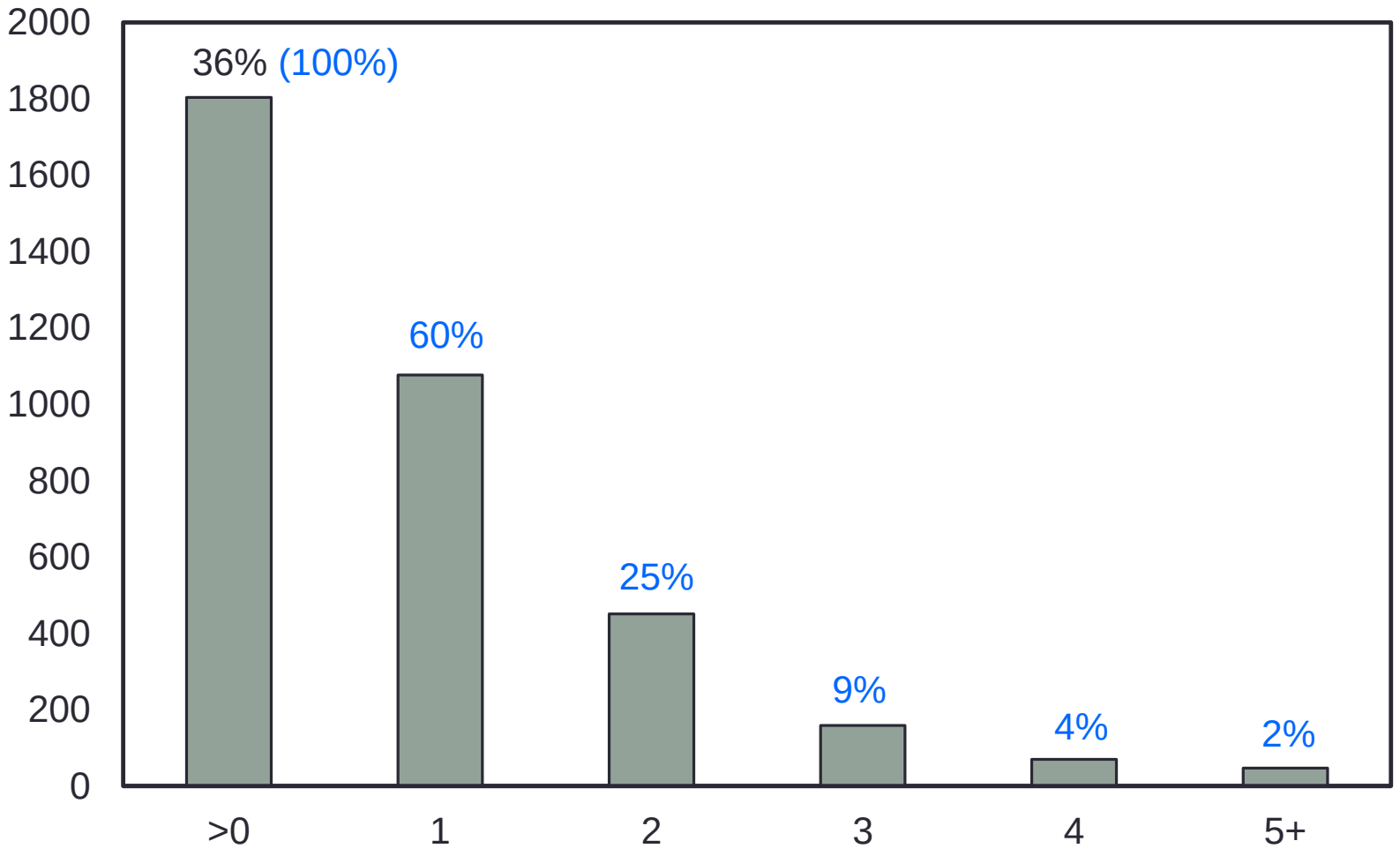
Imminent fracture risk after a first MOF



*MOF Major Osteoporotic Fracture

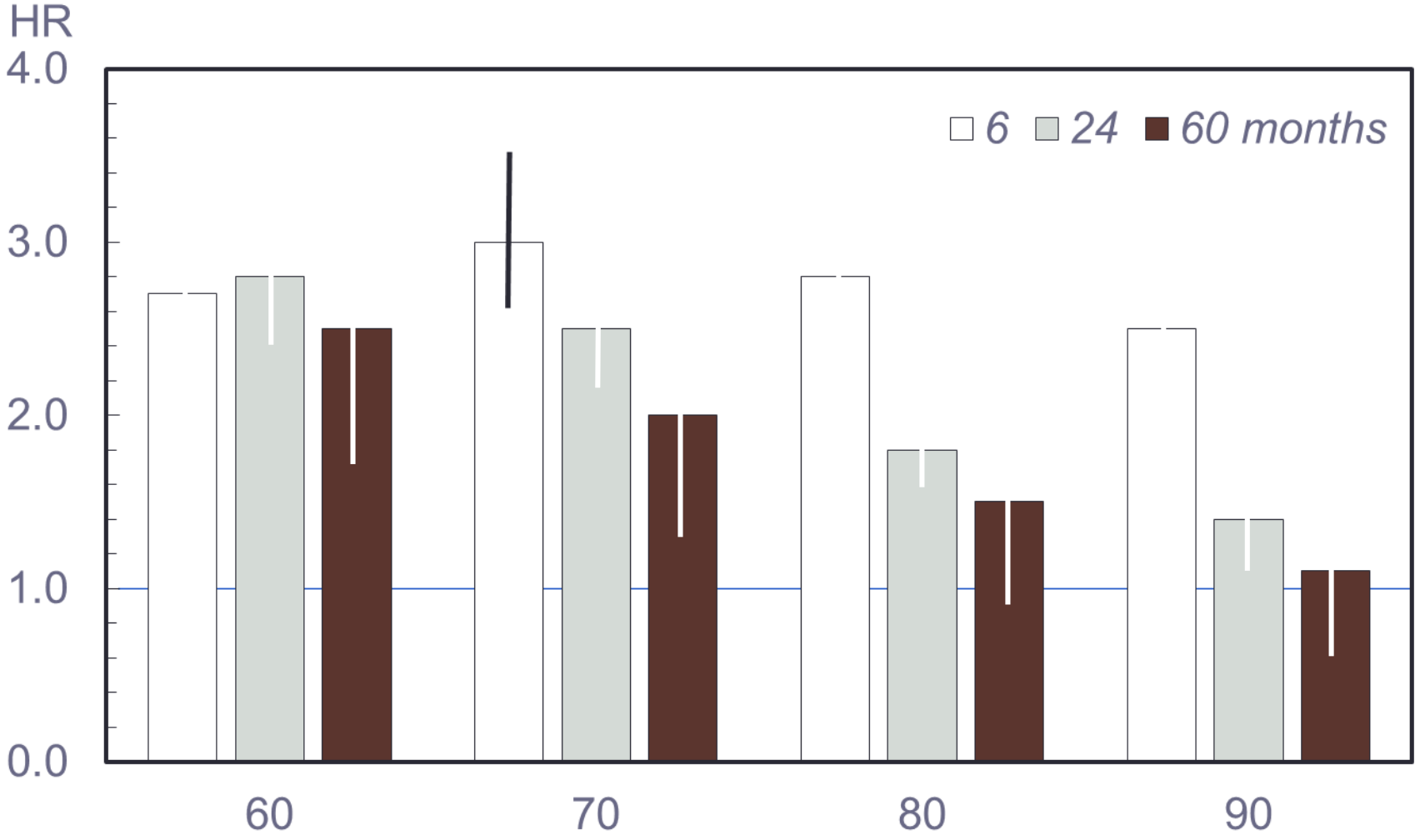
Johansson et al, Reykjavik Study

Numbers of fractures in the 10 years after an index fracture (in 5039 individuals)



Johansson et al, Reykjavik Study

Age and risk of subsequent MOF* following a first MOF.



*MOF Major Osteoporotic Fracture

Johansson et al, Reykjavik Study

Hip fracture prevention

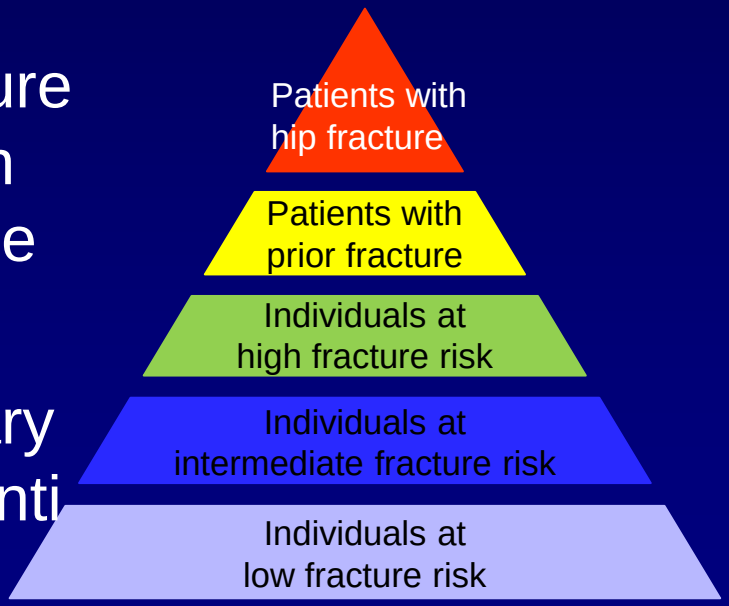
1. Target selected patients at high risk for fracture

2. Treat with pharmacological therapy to prevent fracture

Identifying patients

Fracture liaison service

Primary prevention

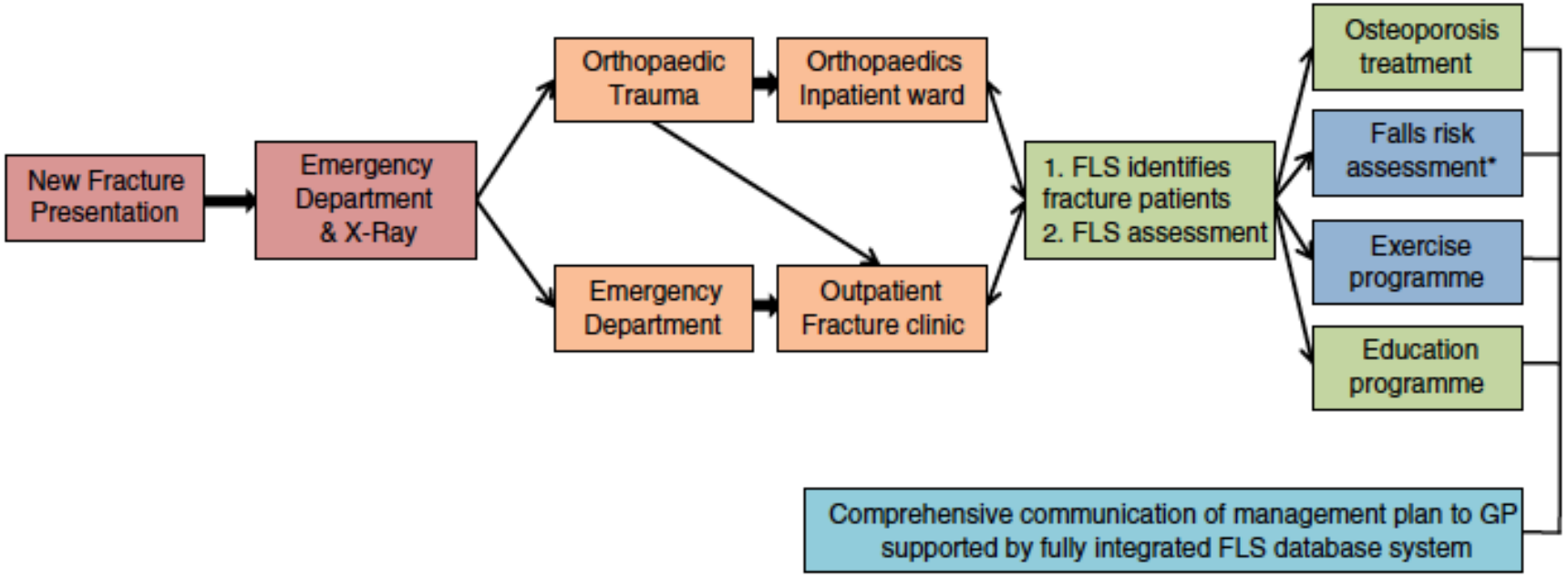


*"The ultimate goal of any management strategy in osteoporosis is the **prevention of fracture**"**

Adapted from Brankin E et al. *Curr Med Res Opin* 2005;21:475-82.
IOF – Capture the Fracture Campaign and Slide Kit
www.capturethefracture.org/slide-kits-reports

* Kanis J et al. *Osteoporos Int* 2014;25:2533-43.
Lewiecki EM et al. *J Clin Endocrinol Metab* 2013;98:946-53.

Secondary prevention: Fracture liaison service



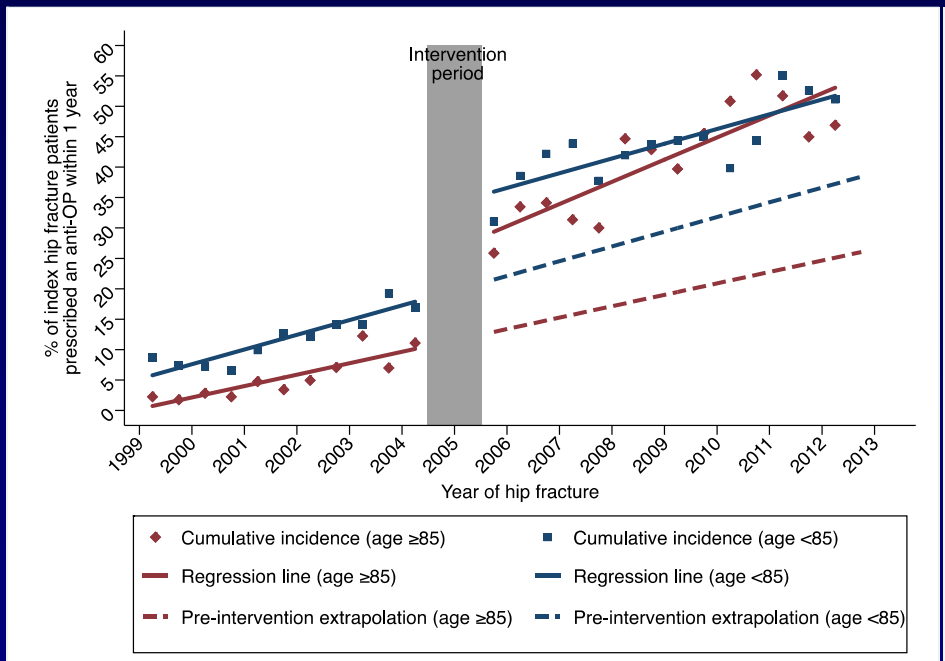
* Older patients, where appropriate, are identified and referred for falls assessment

Akesson, OI 2013

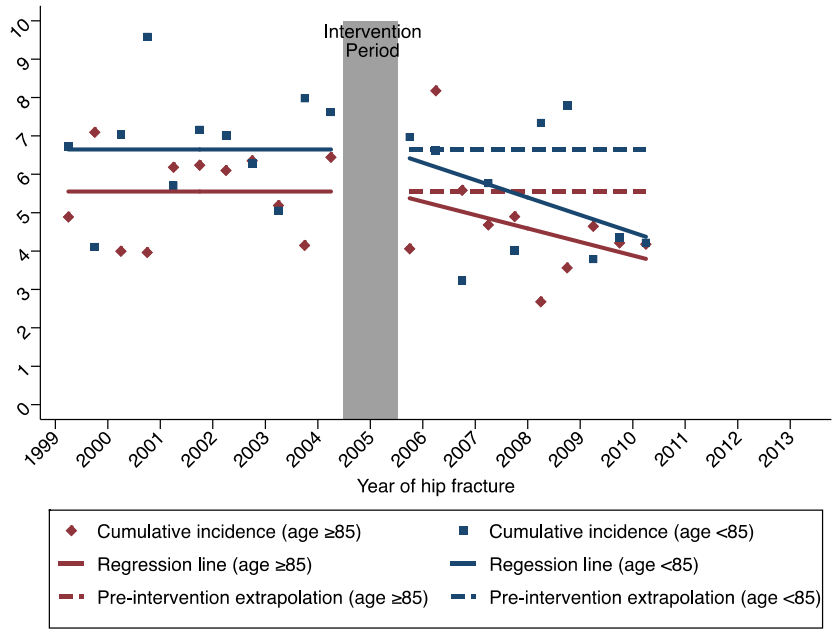
ANTI-OSTEOPOROSIS MEDICATION PRESCRIPTIONS AND INCIDENCE OF SECONDARY FRACTURE AMONGST HIP FRACTURE PATIENTS IN ENGLAND AND WALES: AN AGE STRATIFIED INTERRUPTED TIME SERIES ANALYSIS

S HAWLEY ET AL

Anti-OP prescription within 1 year after hip fracture



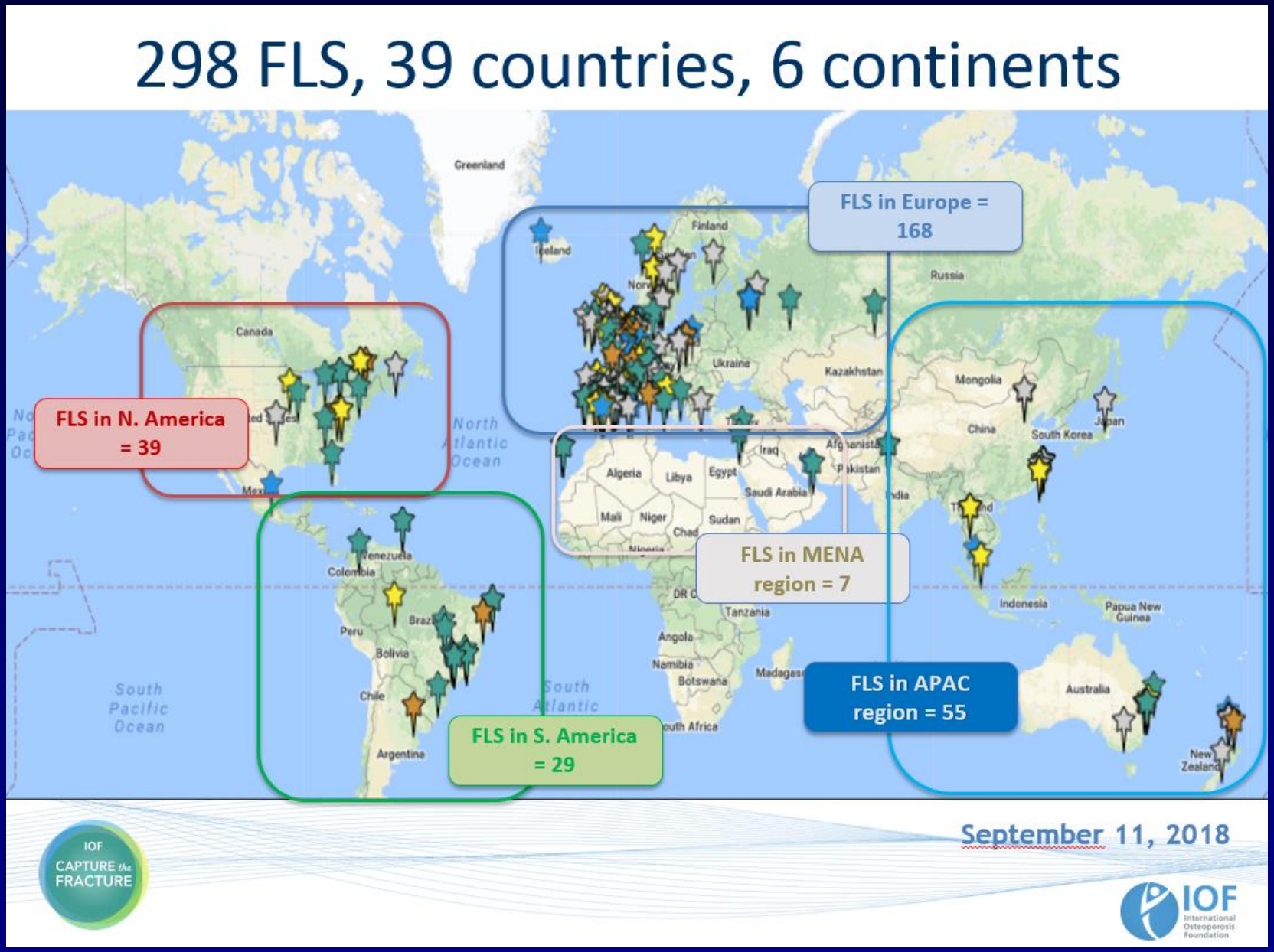
Major fracture within 3 year after hip fracture



CONCLUSION

Prescriptions of ALN after hip fracture increase and subsequent fractures decrease suggesting clinical effectiveness of alendronate for secondary fracture prevention. This effect is preserved in very elderly patients.

CTF Map of Best Practice



Running an FLS?
Join the Capture the Fracture® Programme

Why join?

- Showcase your achievements
- Learn from the BPF to improve your service
- Get international recognition with a Gold, Silver, or Bronze star
- Be part of a global invitiative to prevent secondary fractures

Who can participate?

- Coordinator-based models of care
- All type of facilities
- At any stage in development
- Any size worldwide

IOF International Osteoporosis Foundation

The Process

Step 1

FLS submits online application

Step 2

FLS marked in green on the map while being reviewed

Step 3

BPF achievement level assigned

Step 4

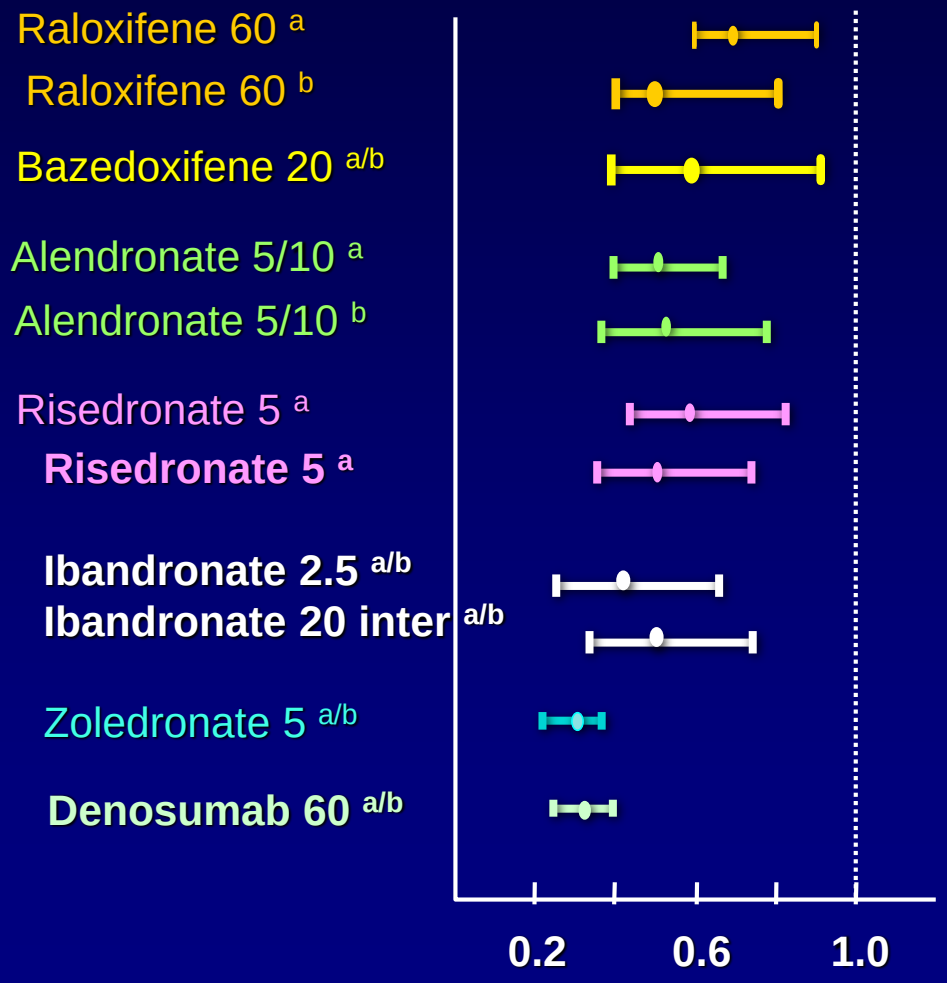
FLS is scored and recognized on the map

https://youtu.be/gpAAvvukjQw

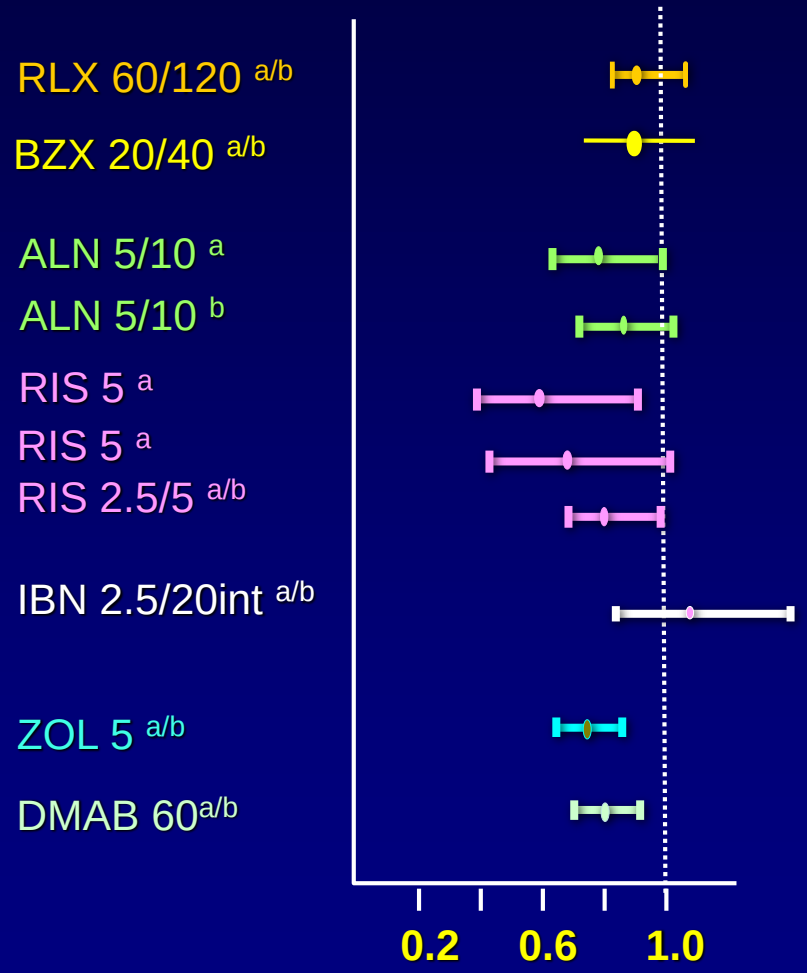
VIDEO!

Fracture risk reduction with anti-resorptives

RR of new vertebral fracture ± IC 95% - RCT (3-4 yrs)



RR of new non-vertebral fracture ± IC 95% - RCT (3-4 yrs)



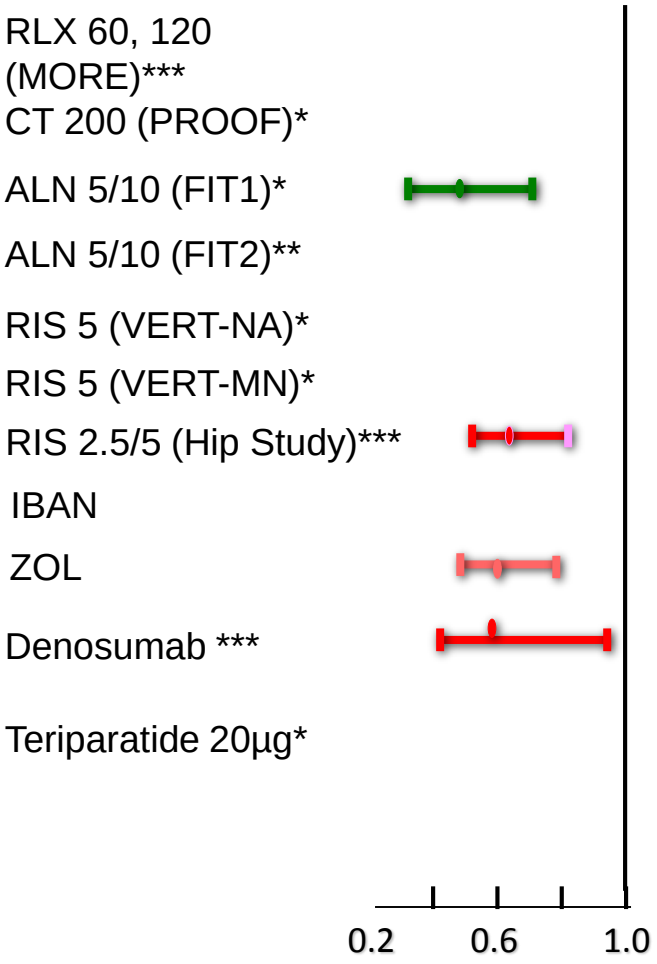
[a] with prevalent vert fx [b] without prevalent vert fx [a/b] with or without prevalent vert fx

Hip fracture risk reduction (RR ± 95% CI)

Significant hip fracture risk Reduction: 4 studies

Only studies with preplanned analysis:

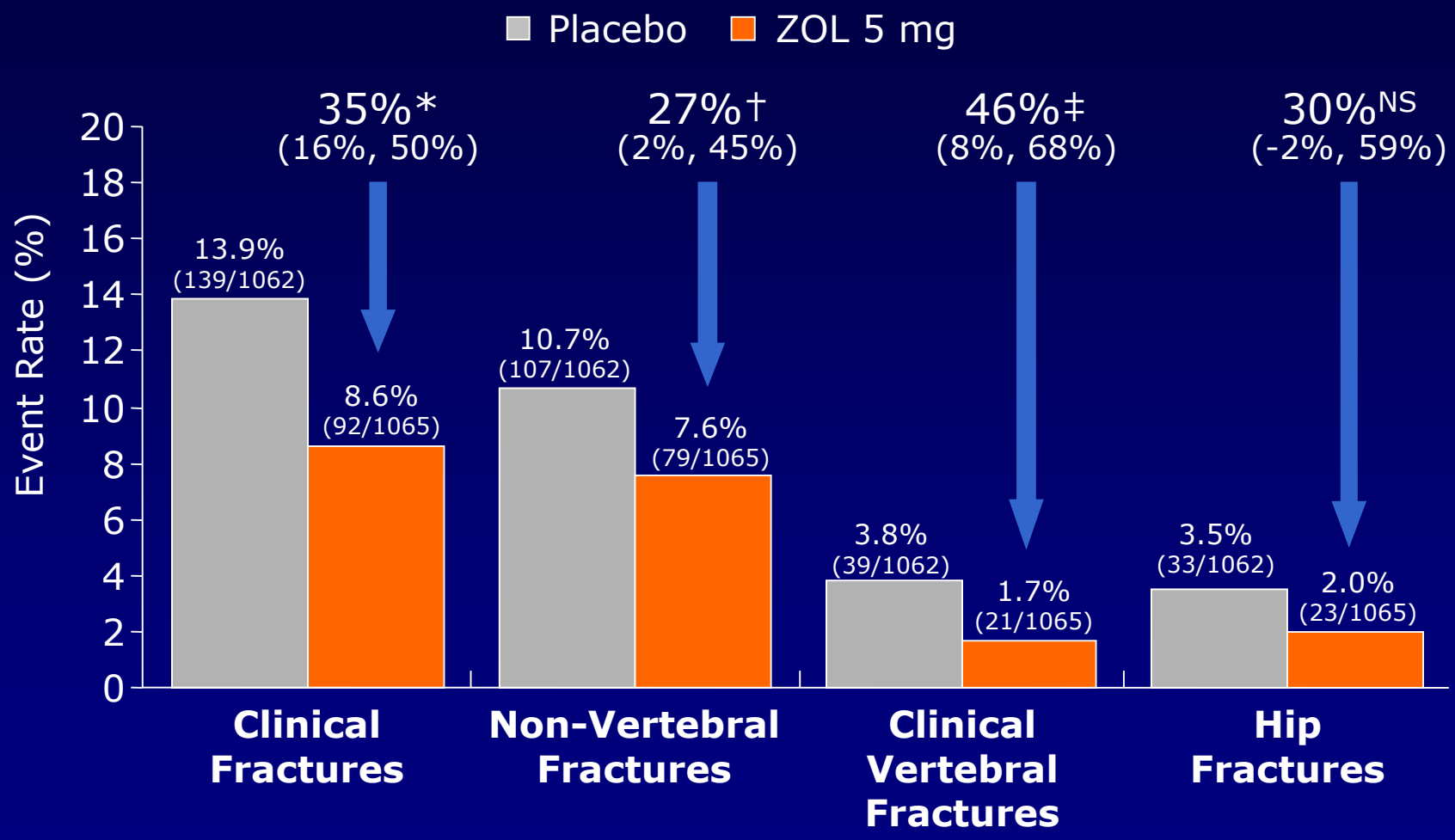
- RIS 2.5/5 (Hip Study)
- ZOL 5 mg (Horizon Study)
- Denosumab (Freedom Study)



* with prev vert

*** with or without prev vert fractures

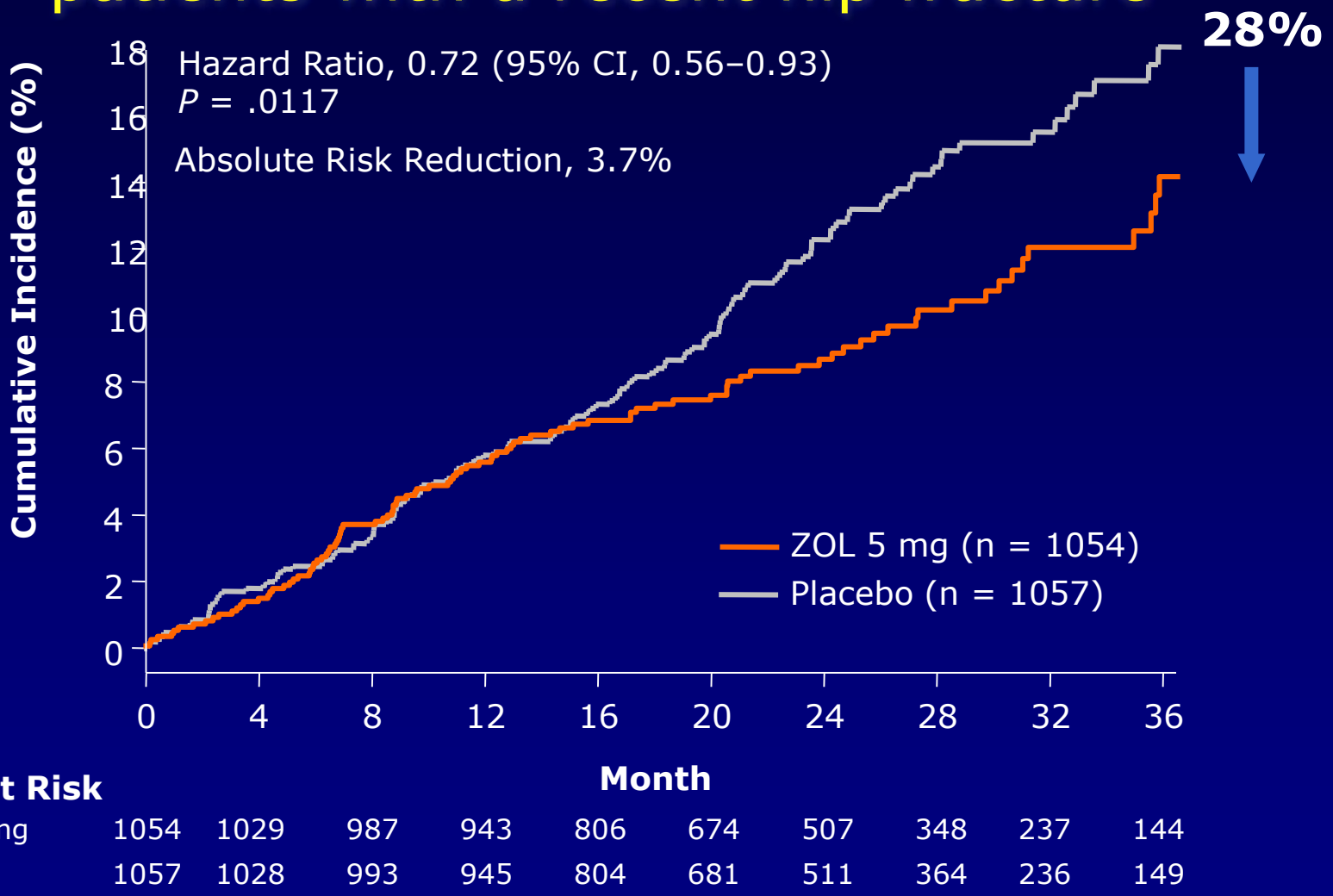
Zoledronic Acid 5 mg Reduced Subsequent Fracture Risk in post-hip fracture patients



*P = .0012; †P = .0338; ‡P = .0210, relative risk reduction vs placebo; NS = not significant.
Values above bars are cumulative event rates based on Kaplan-Meier estimates at Month 24.

Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at www.nejm.org]

Zoledronic Acid 5 mg Reduced Risk of All-Cause Mortality by 28% Over Time in patients with a recent hip fracture



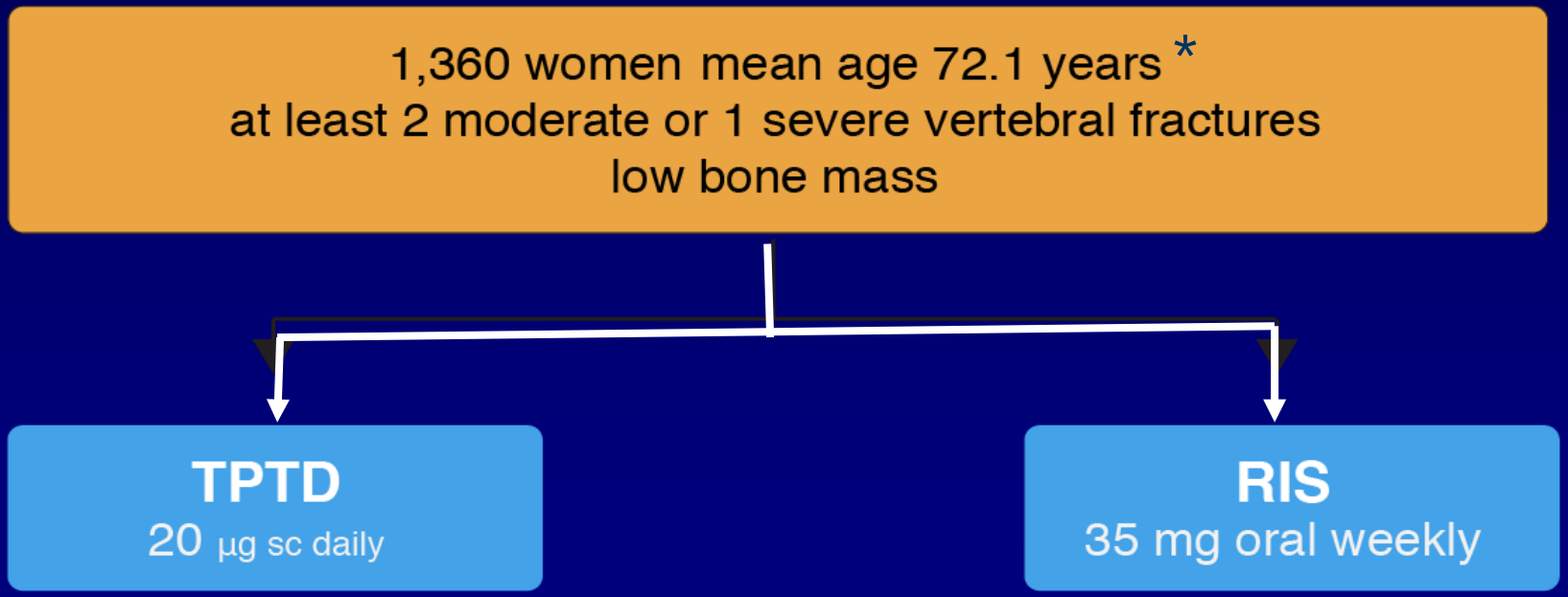
No. at Risk										
ZOL 5 mg	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at www.nejm.org]

EFFECTS OF 24 MONTHS TREATMENT OF TERIPARATIDE COMPARED WITH RISEDRONATE ON NEW FRACTURES IN POSTMENOPAUSAL WOMEN

- Compare the anti-fracture efficacy of teriparatide (TPTD) with risedronate (RIS) in postmenopausal women with severe osteoporosis (VERO study)

2 year randomized (1:1), double blind, double-dummy trial



* 36% with recent clinical VFx; 72% previously on AR (mean 4.5 yrs); 10% on GC

Kendler et al, Lancet 2017

EFFECTS OF 24 MONTHS TREATMENT OF TERIPARATIDE COMPARED WITH RISEDRONATE ON NEW FRACTURES IN POSTMENOPAUSAL WOMEN

KENDLER ET AL., UNIVERSITY OF BRITISH COLUMBIA, CA

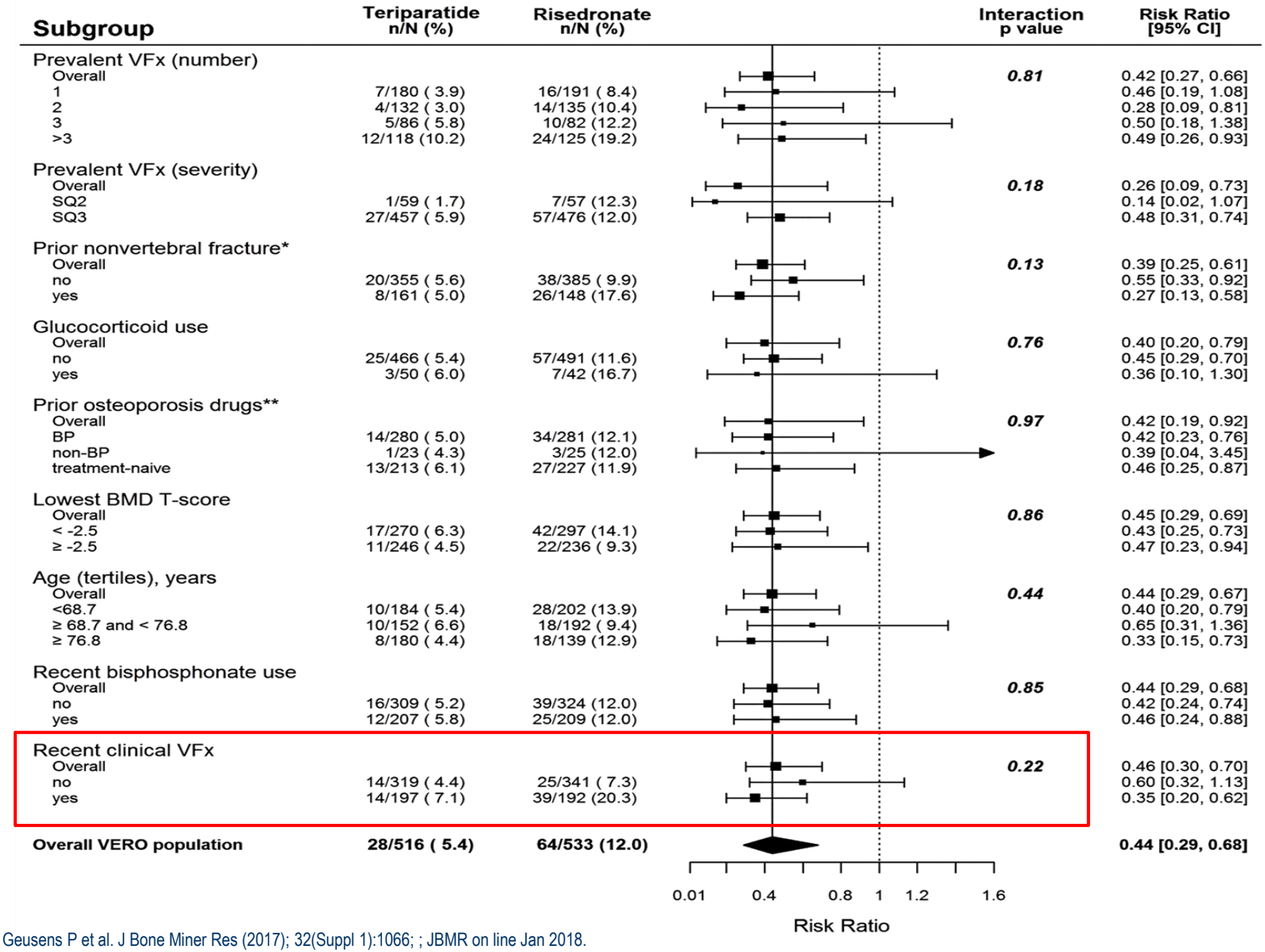
	TPTD (n=680)	RIS (n=680)	Relative Risk or Hazard Ratio (95% CI) vs RIS
Vertebral fracture (≥1)	28 (5.4)	64 (12.0)	0.44 (0.29; 0.68)
Moderate/severe vertebral fractures (≥1)	26 (5.0)	63 (11.8)	0.42 (0.27; 0.65)
Multiple vertebral fractures (≥2)	2 (0.4)	12 (2.3)	0.16 (0.04; 0.74)
Clinical fractures	30 (4.8)	61 (9.8)	0.48 (0.32; 0.74)
Non vertebral fragility fractures	24 (4.0)	38 (6.1)	0.66 (0.39; 1.10)

Conclusions

- In postmenopausal women with severe osteoporosis, the risk for new vertebral and clinical fractures was significantly reduced in patients randomized to TPTD compared to RIS
- There was a trend to fewer NVF in patients on TPTD compared to RIS
- These results support TPTD as 1st line treatment for women with severe osteoporosis, superior to RIS antiresorptive therapy

Kendler et al, Lancet 2017
Ferrari, Lancet (editorial) 2017

Risk Ratios for New Vertebral Fractures: stratification by risk subgroups

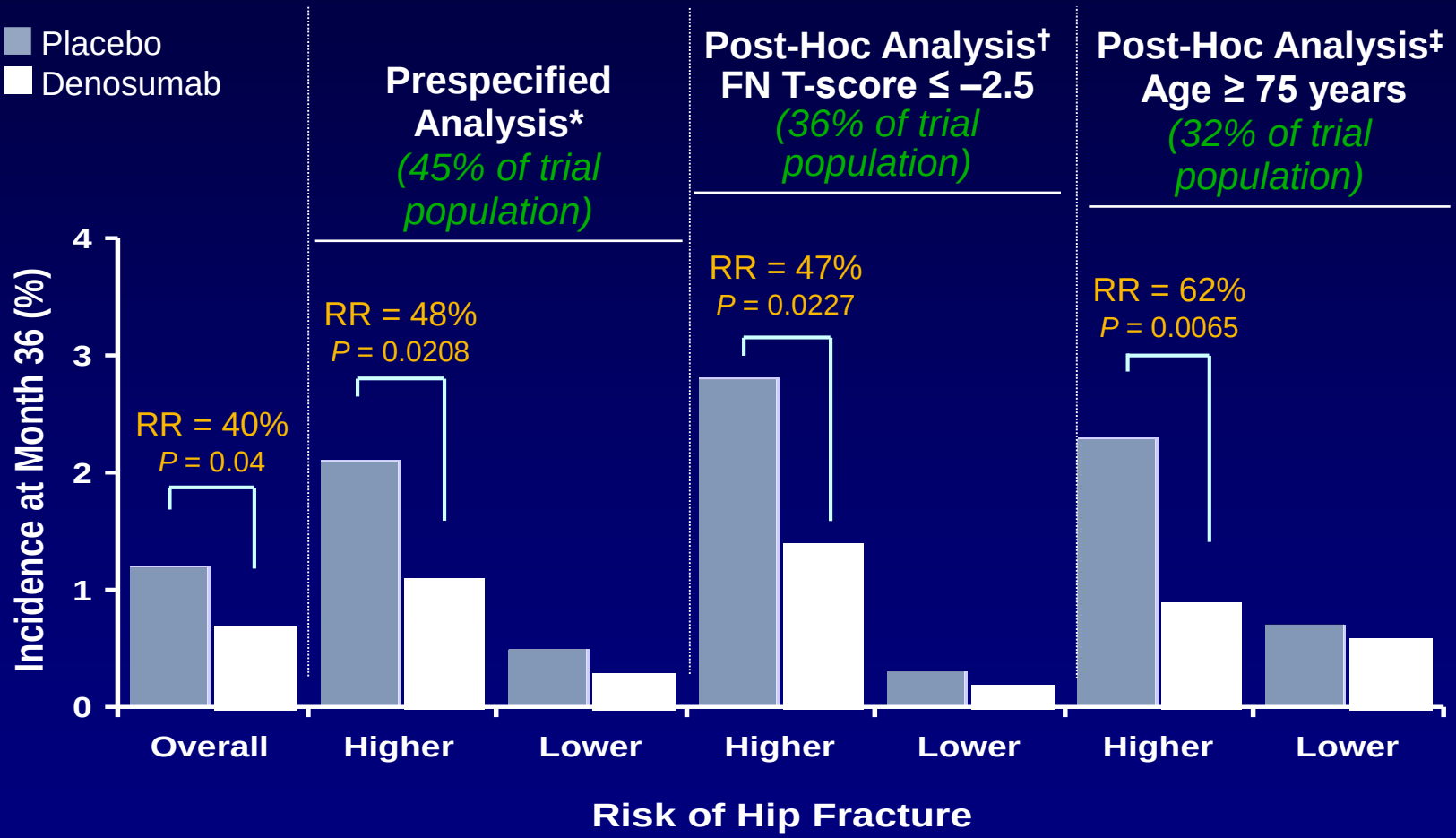


*Hip, radius, humerus, ribs, pelvis, tibia and femur
**Prior BP users, non-BP users, treatment naïve

Geusens P et al. J Bone Miner Res (2017); 32(Suppl 1):1066; ; JBMR on line Jan 2018.

The Effect of Denosumab on New Hip Fractures in Higher Risk Populations

Phase 3: The FREEDOM Trial – Higher Risk Sub-analysis



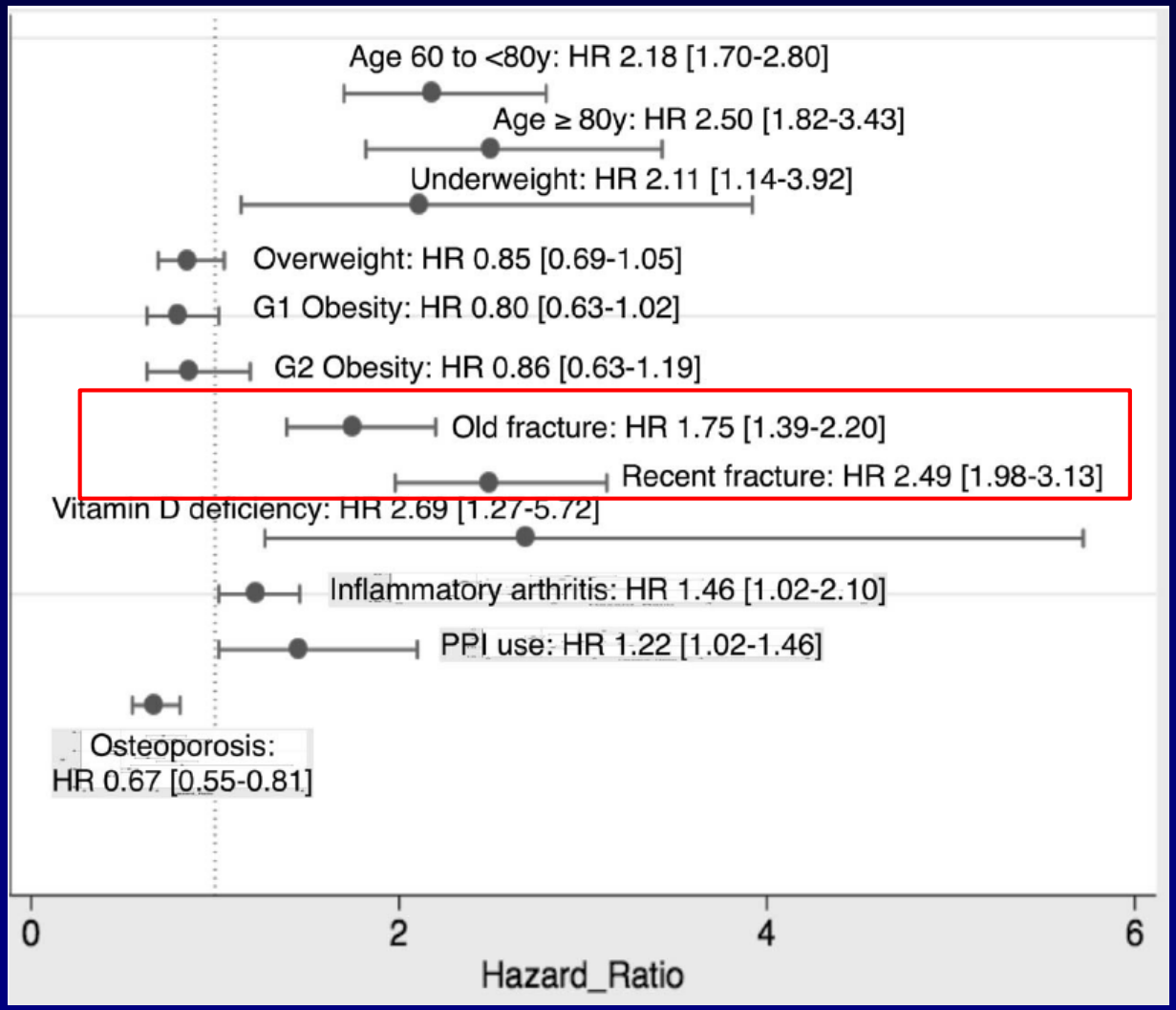
*In a subset of higher risk patients with ≥ 2 of the following: (a) age > 70 years, (b) baseline BMD T-score ≤ –3.0 at lumbar spine, total hip, or femoral neck, (c) prevalent vertebral fracture at baseline

†In a subset of higher risk patients with femoral neck BMD T-score ≤ –2.5; ‡In a subset of higher risk patients age ≥ 75 years

FN = femoral neck

Boonen S, et al. *JCEM 2011 ; McClung et al., JBMR 2011*

Risk factors for oral BP failure in Spain (fract. on Tx, > 80% compliance)



Prieto, JBMR 2013

Real world effectiveness of OP therapies

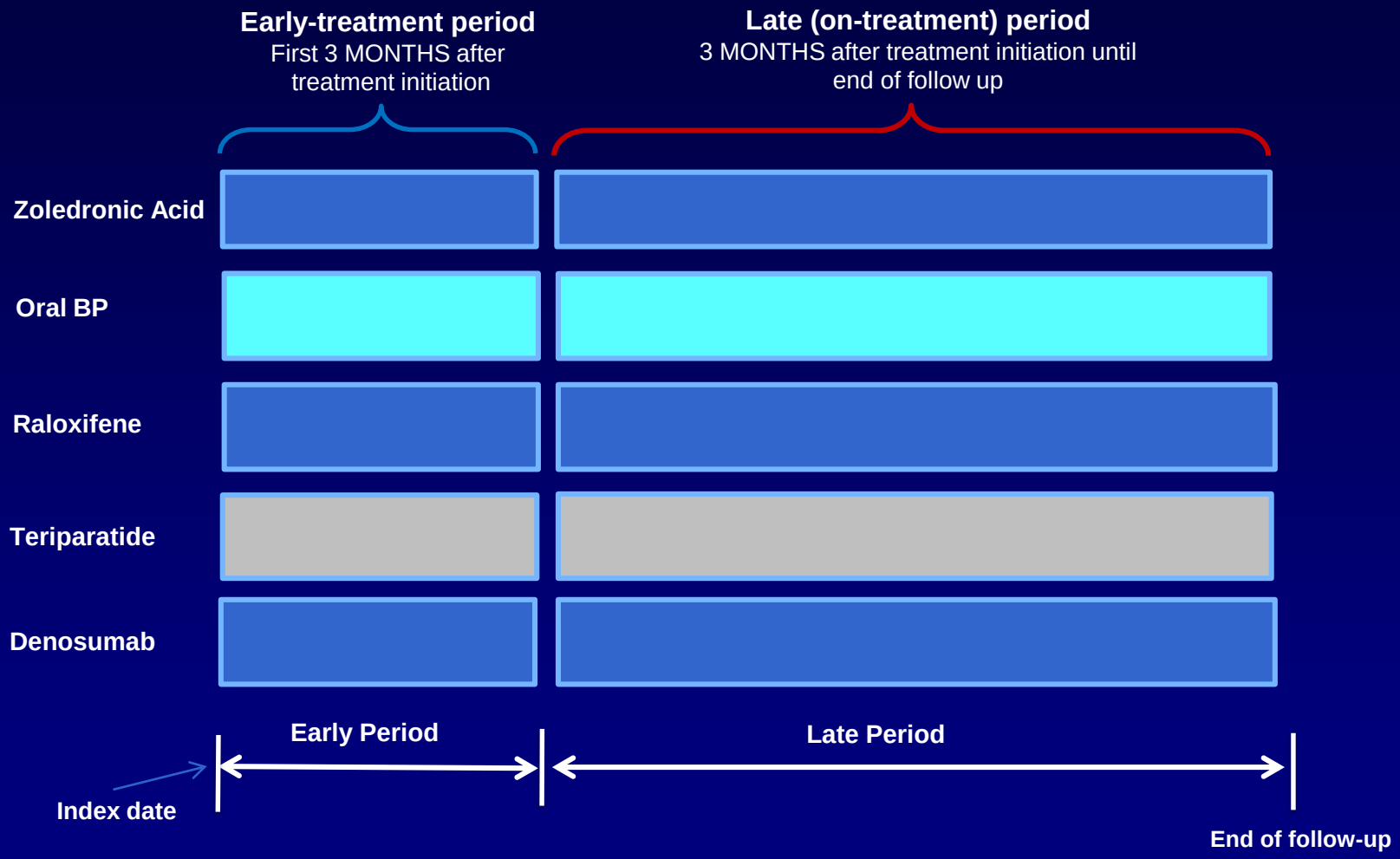
Eligibility Criteria

- Women age ≥ 65 years receiving treatment with:
  - Denosumab
  - Oral bisphosphonates (alendronate, risedronate, ibandronate)
  - IV bisphosphonates (IV ibandronate, zoledronic acid)
  - Teriparatide
  - Raloxifene
- Period 01/01/2009 to 06/30/2012
- Available data for at least 12 months prior to index prescription date and at least 4 months after
- Excluded patients with baseline diagnoses of Paget's disease or malignancy
- Excluded patients who switched study medications or received calcitonin within 3 months following treatment index date

1.3mio women, Mean age 78 years

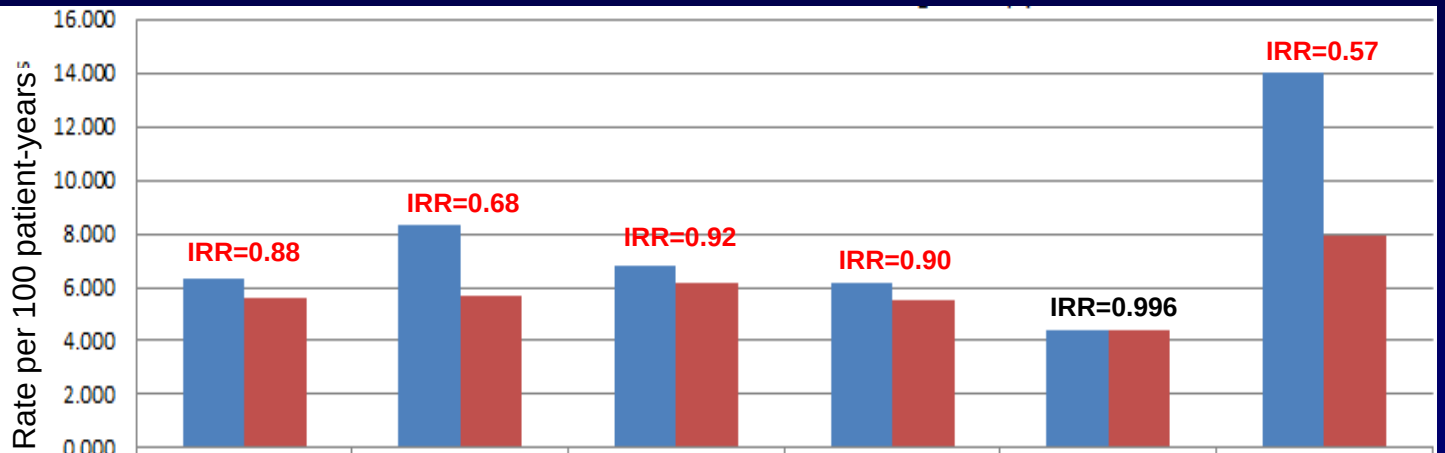
Yusuf, Archives Osteop 2018

Within-patient analytic approach used to evaluate fracture risk reduction with denosumab and other OP pharmacotherapies



For each patient, fracture risk during early period is compared to the risk during on-treatment period

Incidence of all fracture endpoint during early and late periods, by treatment cohort



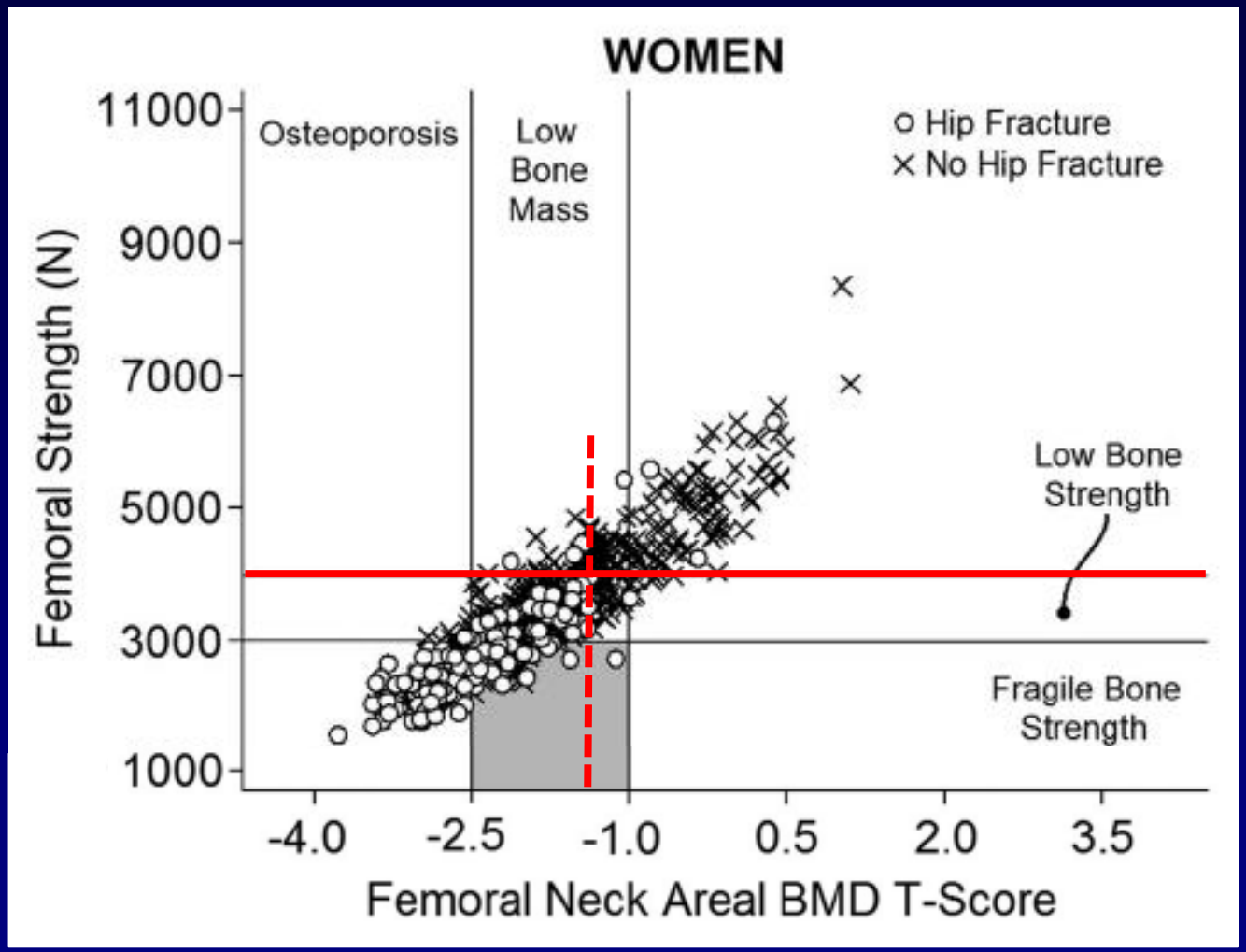
	All	Denosumab	IV Zoledronic acid	Other bisphosphonates	Raloxifene	Teriparatide
	Late: early 95% CI = 0.884 (0.870,0.898)	Late: early 95% CI = 0.683 (0.624,0.747)	Late: early 95% CI = 0.915 (0.871,0.961)	Late: early 95% CI = 0.896 (0.880,0.913)	Late: early 95% CI = 0.996 (0.931,1.064)	Late: early 95% CI = 0.566 (0.516,0.620)
Early (Initial) therapy period	6.299	8.320	6.772	6.201	4.429	14.036
Late (Subsequent) therapy period	5.566	5.679	6.194	5.559	4.409	7.940

Yusuf, Archives Osteop 2018

What is the goal of osteoprosis therapy ?

- Rapid reduction of fracture risk, particulaly in patients at “imminent” risk
- Long-term restauration of bone mass and strength

Femoral strength and BMD threshold for hip fractures



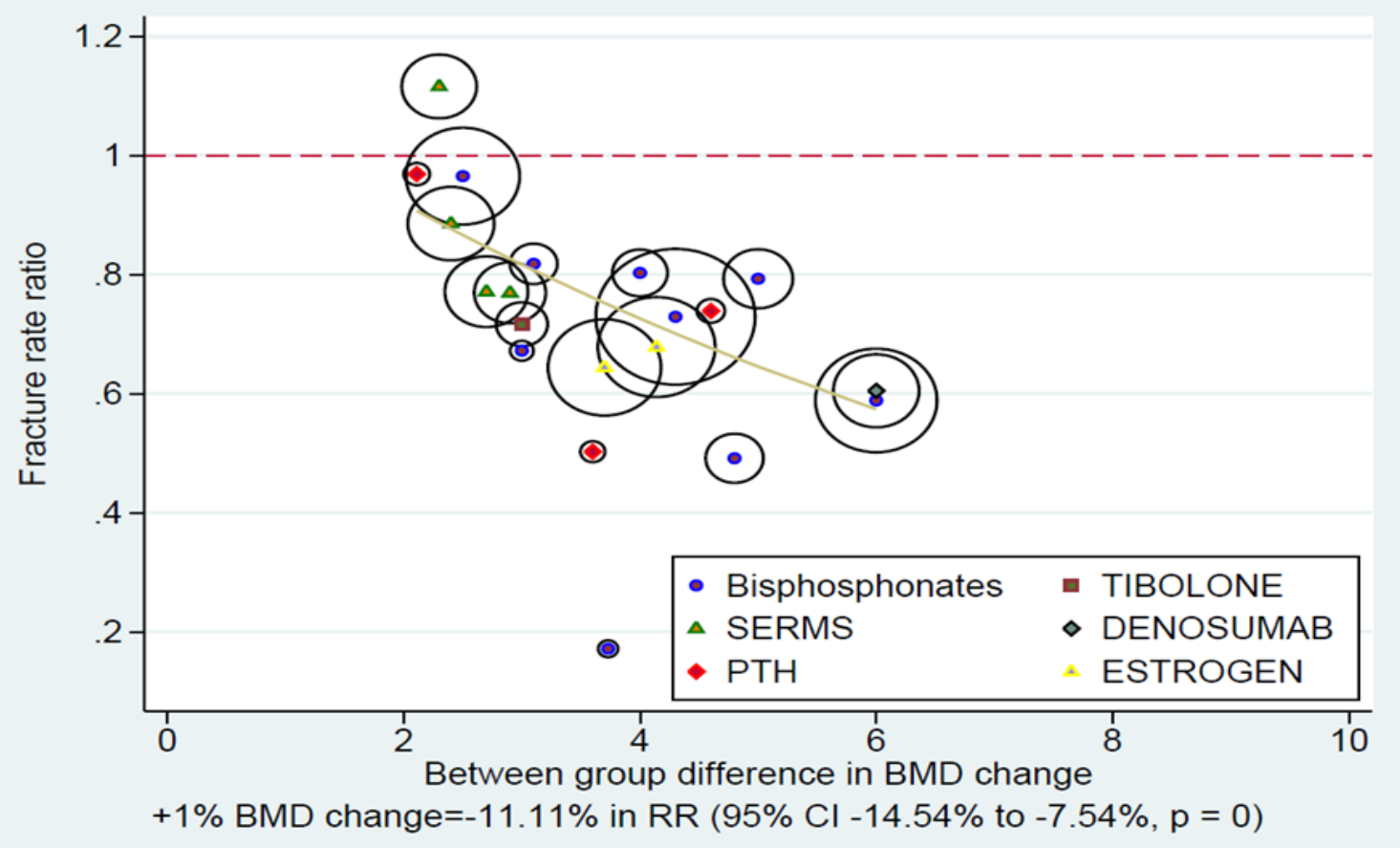
Case-control study, 5 yrs follow-up, from the AGES-Reykjavik cohort

BMD = bone mineral density.

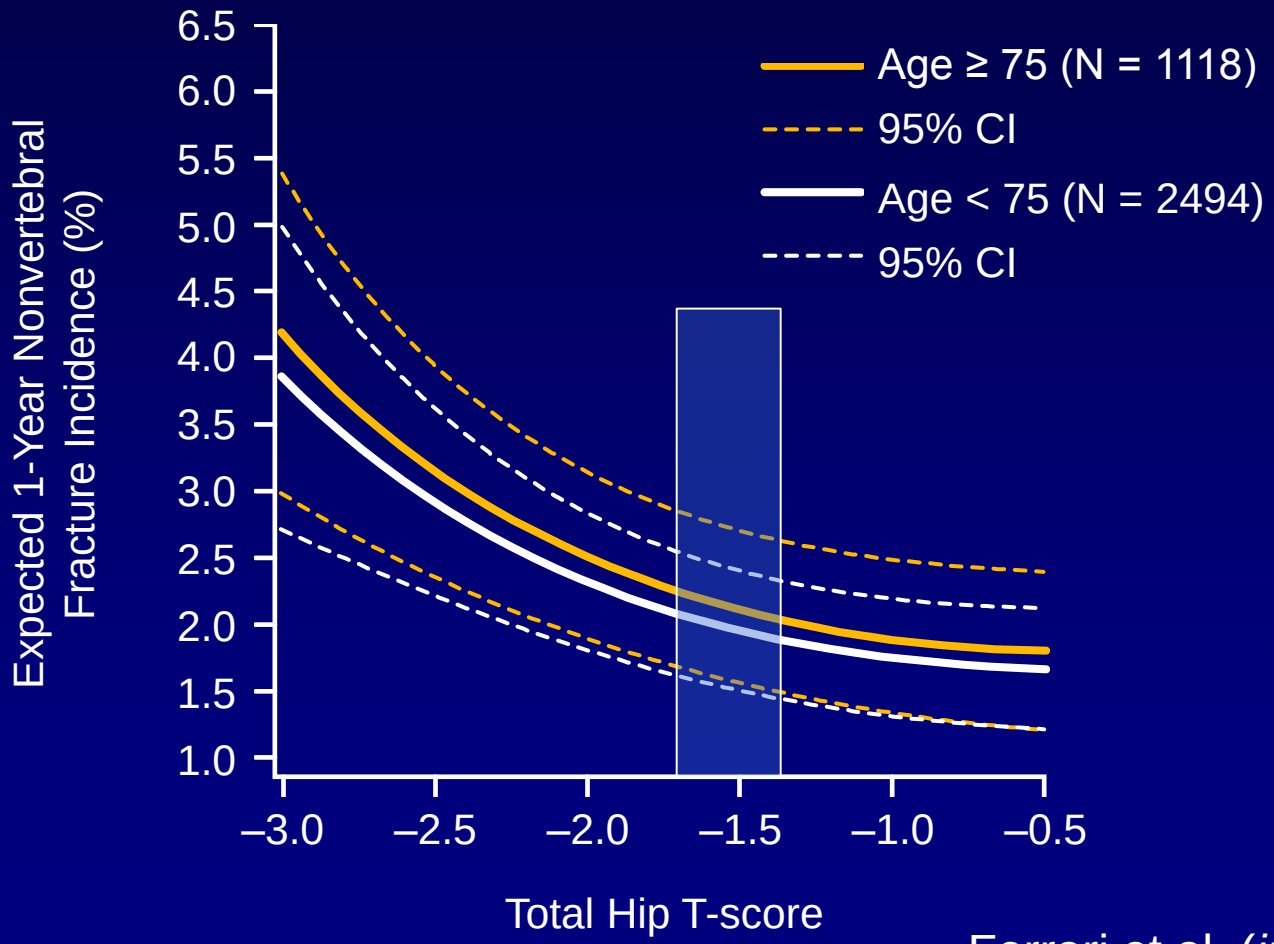
Kopperdahl DL *et al. JBMR* 2014; **29**:570–580.

Greater Hip BMD gains = Greater Reduction in Hip Fracture Risk in Osteoporosis Trials: A Meta-Regression

DENNIS BLACK, ERIC VITTINGHOFF, RICHARD EASTELL, MARY BOUXSEIN, ET AL.

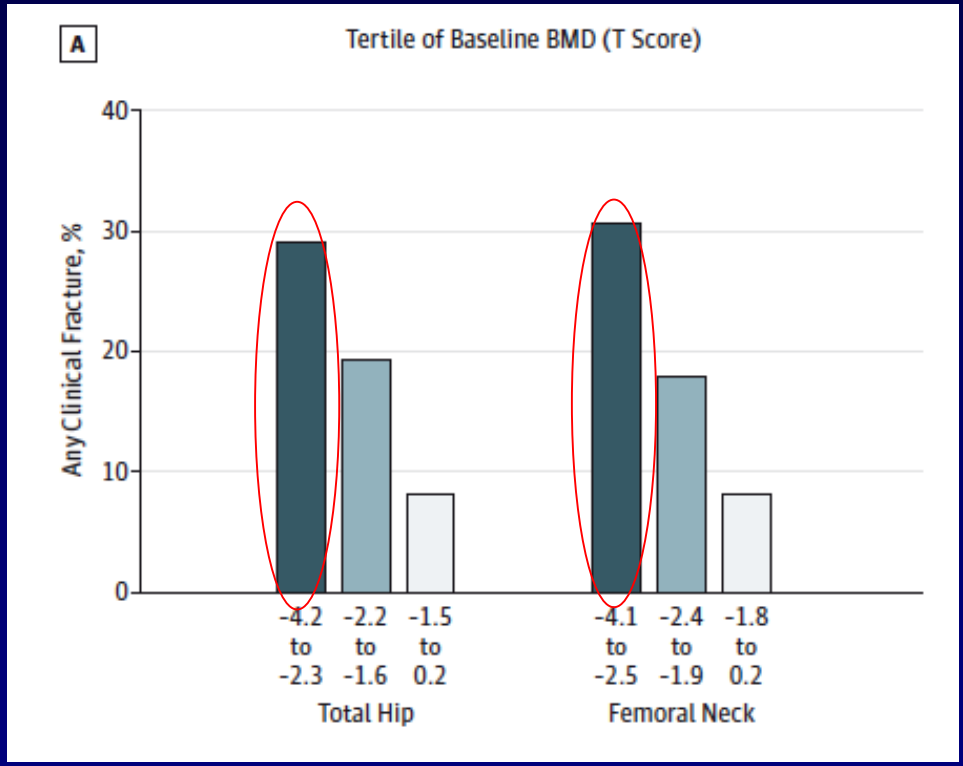


Relationship Between Total Hip T-score and Nonvertebral Fracture in the FREEDOM & Extension (denosumab) trial



Ferrari et al. (*in revision*)

FLEX Trial: Non-vertebral fracture risk by T-score after ALN is stopped (> 5yrs)



Bauer JAMA 2014

Conclusions

- Patients with recent fractures are at imminent risk of refracturing (5-20% in one year)
- Identification and immediate treatment of osteoporosis is mandatory in these patients
  - FLS
- There is good evidence that OP drugs reduce fracture risk, including in these high risk / imminent risk patients, particularly with ZOL, Dmab and TPT
- Treatment should be pursued at least until bone mass is restored to near optimal bone strength levels (T-scores ≥-2)