UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Hôpitaux Universitaires Genève

Bilan et prise en charge de l'ostéoporose et des fractures

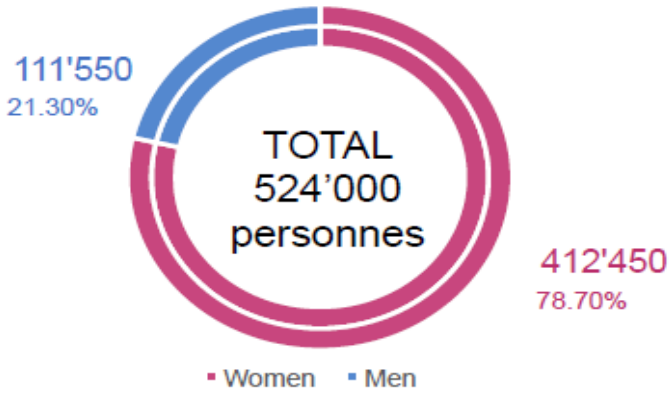
Thierry Chevalley

Congrès de Médecine interne
30 novembre 2023
Hôpital du Jura

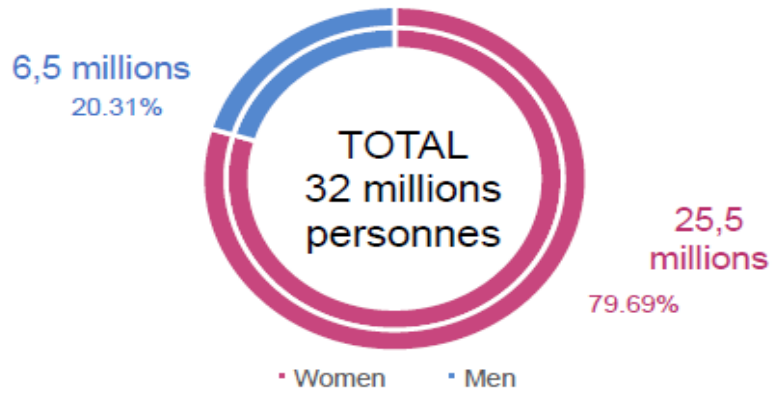
Fardeau de la maladie

Personnes atteintes d'ostéoporose

Suisse



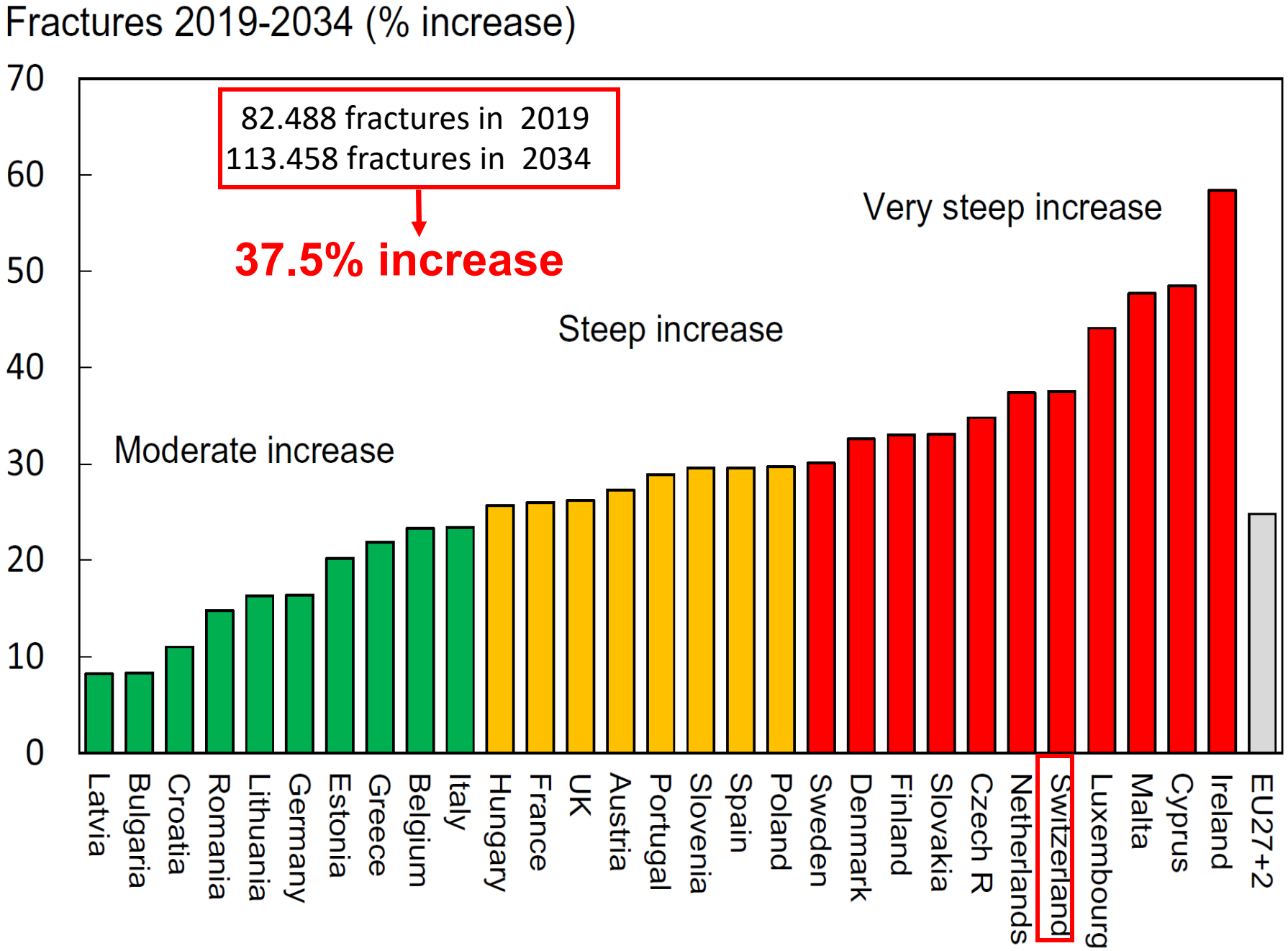
EU 27+2



Prévalence de l'ostéoporose [1]

	Femmes âgées 50+	Hommes âgés 50+	Population totale
Suisse	22.6%	6.6%	6.1%
EU	22.1%	6.6%	5.6%

1. Hernlund JA (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden. Arch Osteoporos 8:136



Kanis JA et al. Arch Osteoporos 2021

Fardeau de la maladie

Coûts des soins de santé liés à l'ostéoporose en 2019

	Suisse	EU 27+2
Coût direct des fractures incidentes	**€2.62 milliards**	**€36.3 milliards**
Coût en cours résultant de fractures survenues avant 2019 (" coûts d'invalidité à long terme ").	**€746 millions**	**€19.0 milliards**
Coût de l'intervention pharmaceutique (évaluation et traitement)	**€60 millions**	**€1.6 milliard**
Coût total (à l'exclusion de la valeur des QALYs* perdues)	**€3.4 milliards (4.5% des dépenses nationales de santé)**	**€56.9 milliards (3.5% des dépenses nationales de santé)**

*QALYs: Quality-Adjusted Life-Year – a multidimensional outcome measure that incorporates both the Quality (health-related) and Quantity (length) of life
Kanis et al., Archives Osteoporos 2021

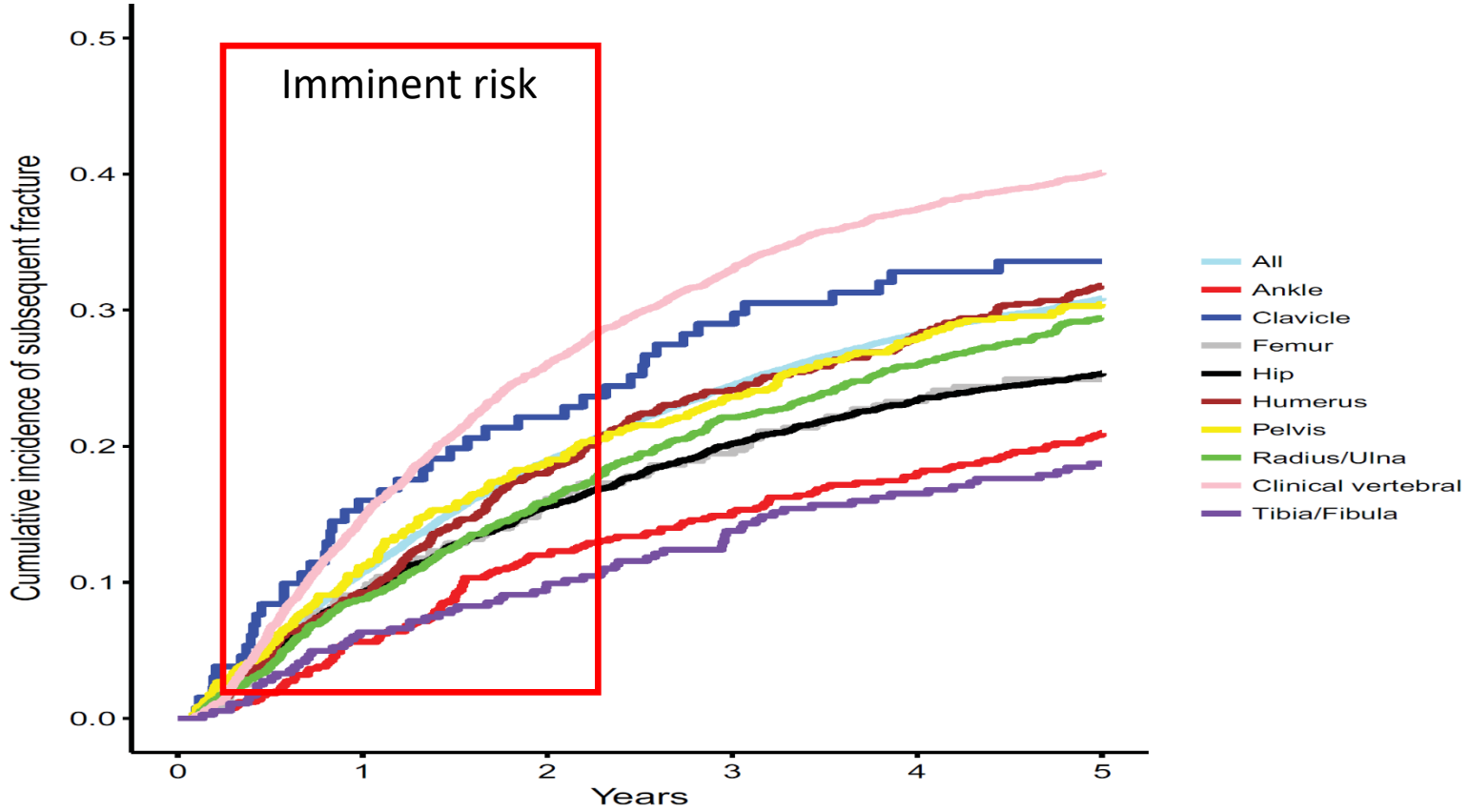
Evolution des coûts directs par habitant entre 2010 et 2019

€190.2/personne (en 2010) → **€402.8**/personne (en 2019) **+ 112%**

€85.7/personne (en 2010) → **€109.1**/personne (en 2019)

Risque de fracture ultérieure après 1ère fracture c/o les femmes âgées

Parmi 377,561 femmes (210,621 and 10,969 pour le résultat à 2 et 5 ans)
- Femmes agées de 65–74 ans avec fracture initiale vertébrale, hanche, bassin, femur ou clavicule &
- Toutes les femmes ≥ 75 ans quelque soit le site de la fracture initiale (sauf cheville et tibia/péroné)



Risque cumulatif de fracture ultérieure

10% (7–14%) à 1 an **18% (15-26%) à 2 ans** **31% (28–42%) à 5 ans**

Balasubramanian A OI 2019

Lacune dans le traitement de l'ostéoporose dans une cohorte prospective de femmes volontaires

Données longitudinales de la cohorte FRISBEE (Fracture Risk Brussels Epidemiological Enquiry) (inclusion 2007-2013)
3560 femmes volontaires âgées de 60 à 85 ans ; 386 premières fractures de fragilité validées, 285 fractures ostéoporotiques majeures (MOF) et 101 fractures « autres majeures » jusqu'en 2018

Ecart de traitement 1 an après une première fracture ostéoporotique majeure

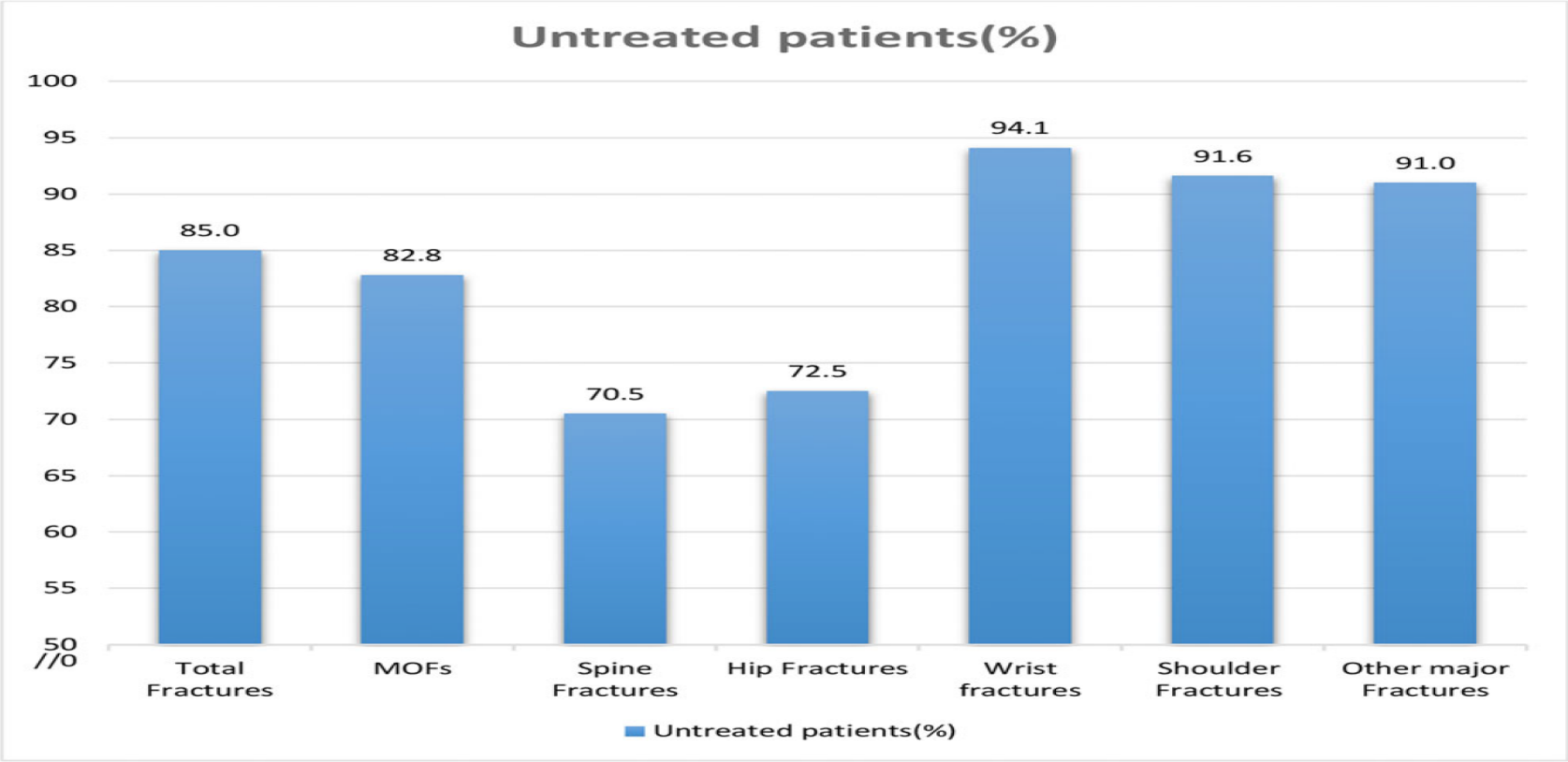
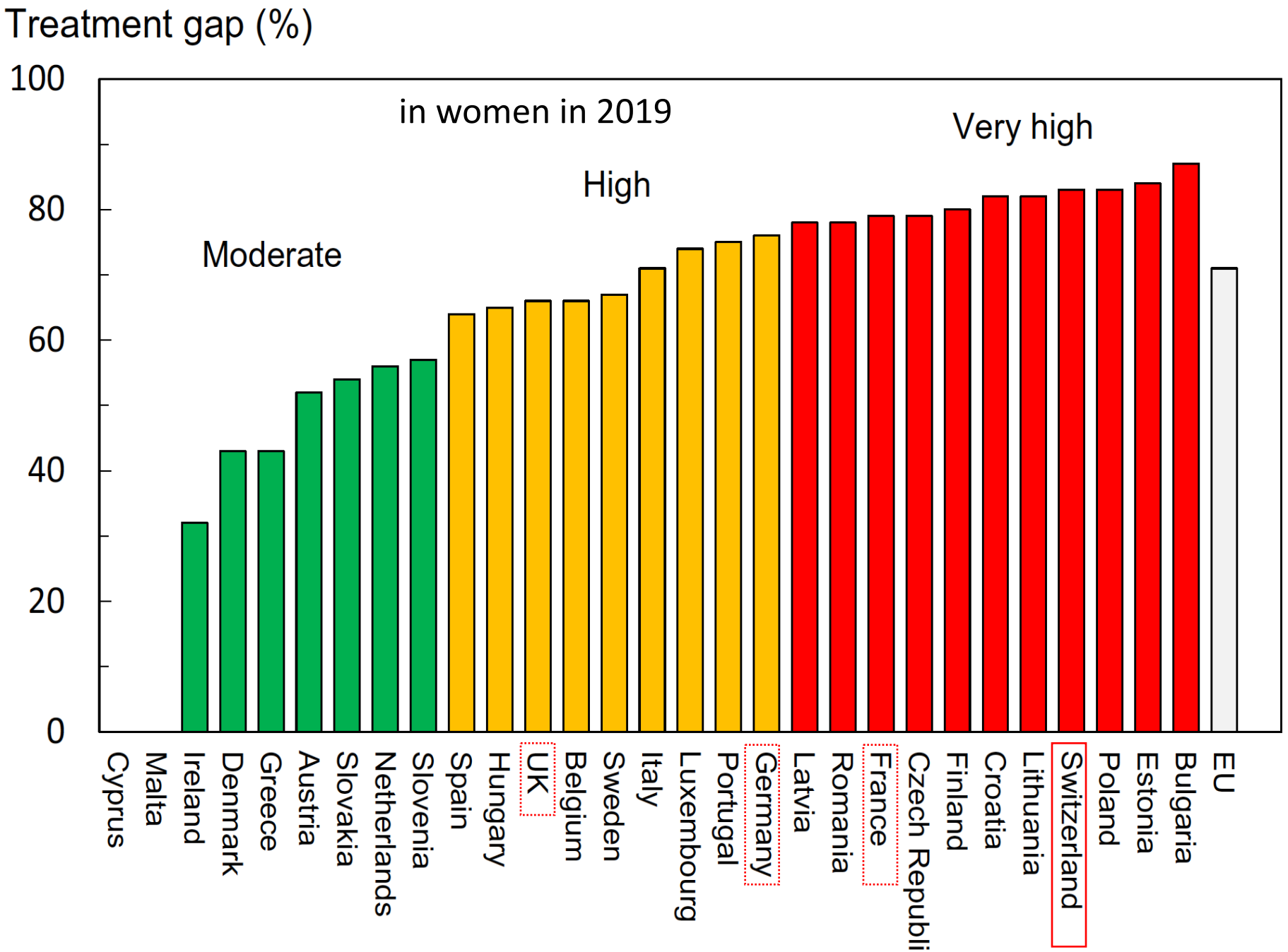


Fig. 1 Untreated women (%) according to the site of the first incident fracture

Iconaru L et al. OI 2020

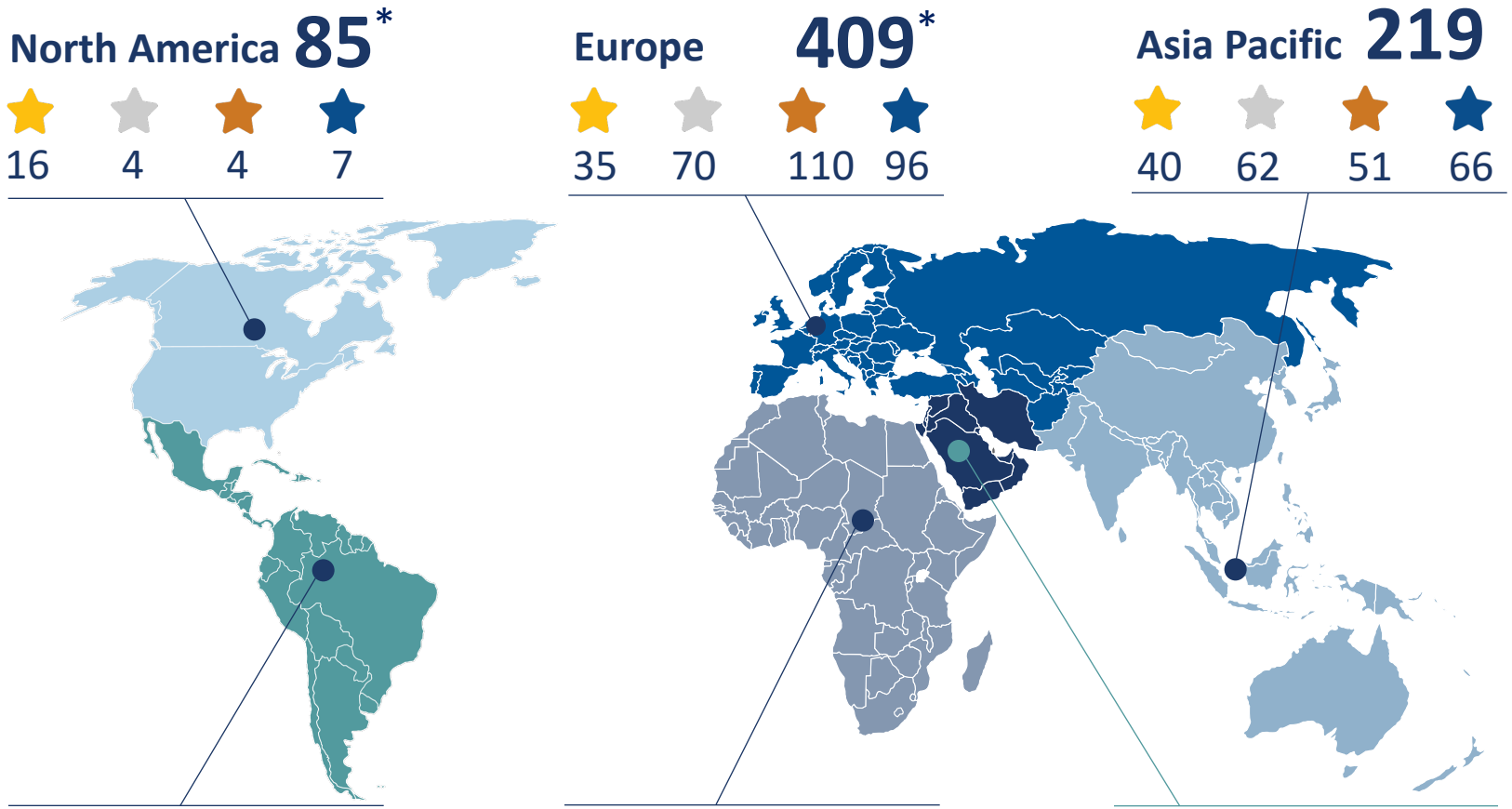


Kanis JA Archives of Osteoporosis 2021

Capture The Fracture® Map of Best Practice

Nov. 2023

886 FLS from 55 countries

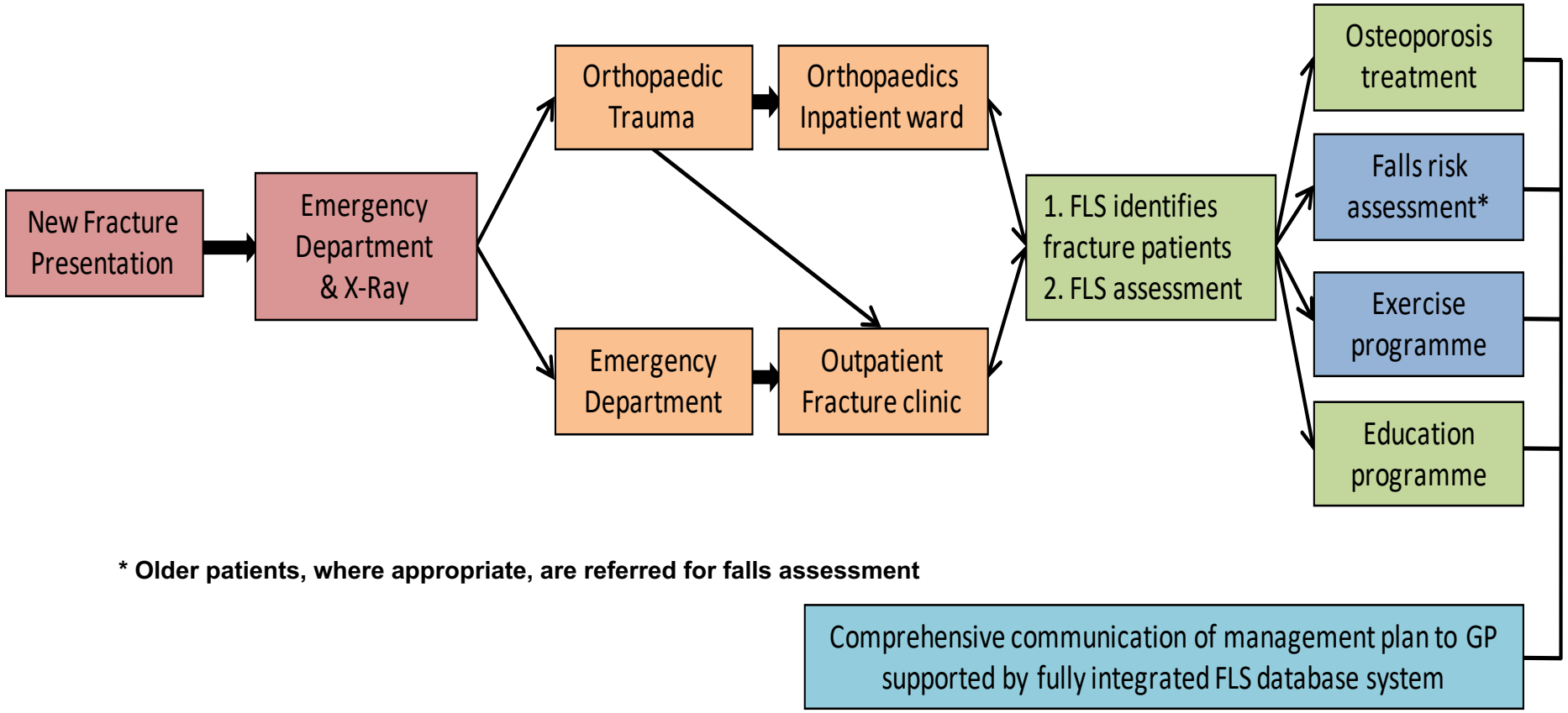


GRAND TOTAL 886 ★98 ★164 ★212 ★260

*Totals include 54 FLS from Osteoporosis Canada and 98 FLS from ROS

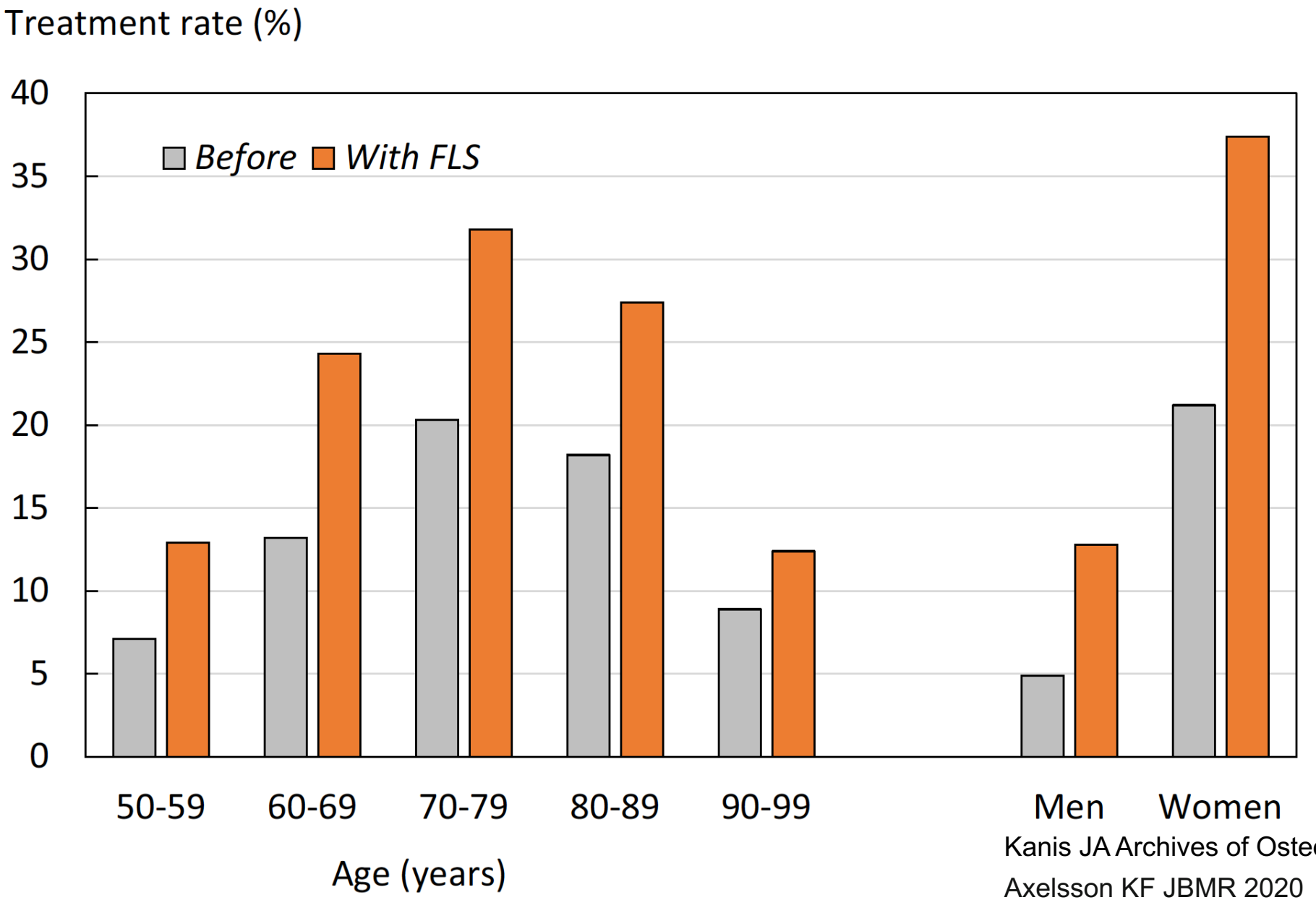
FLS Switzerland 2023

Example care team: The operational structure of a UK-based Fracture Liaison Service (FLS) [1, 2]



1. British Orthopaedic Association, British Geriatrics Society. *The care of patients with fragility fracture* 2007.
2. McLellan AR, Gallacher SJ, Fraser M, McQuillian C. The fracture liaison service: success of a program for the evaluation and management of patients with osteoporotic fracture. *Osteoporos Int.* Dec 2003;14(12):1028-1034.

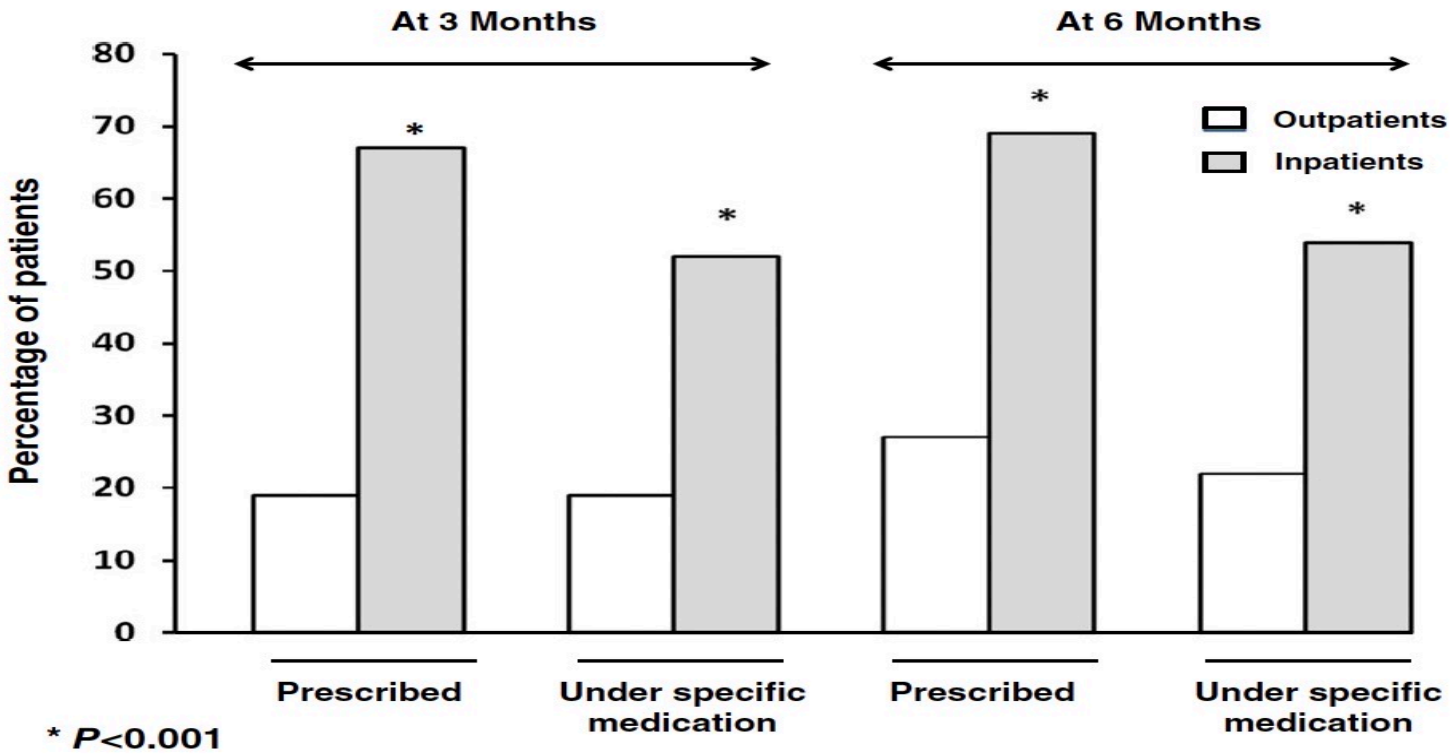
Treatment uptake in the year following a major osteoporotic fracture before and after the institution of FLSs by age and sex



Kanis JA Archives of Osteoporosis 2021

Axelsson KF JBMR 2020

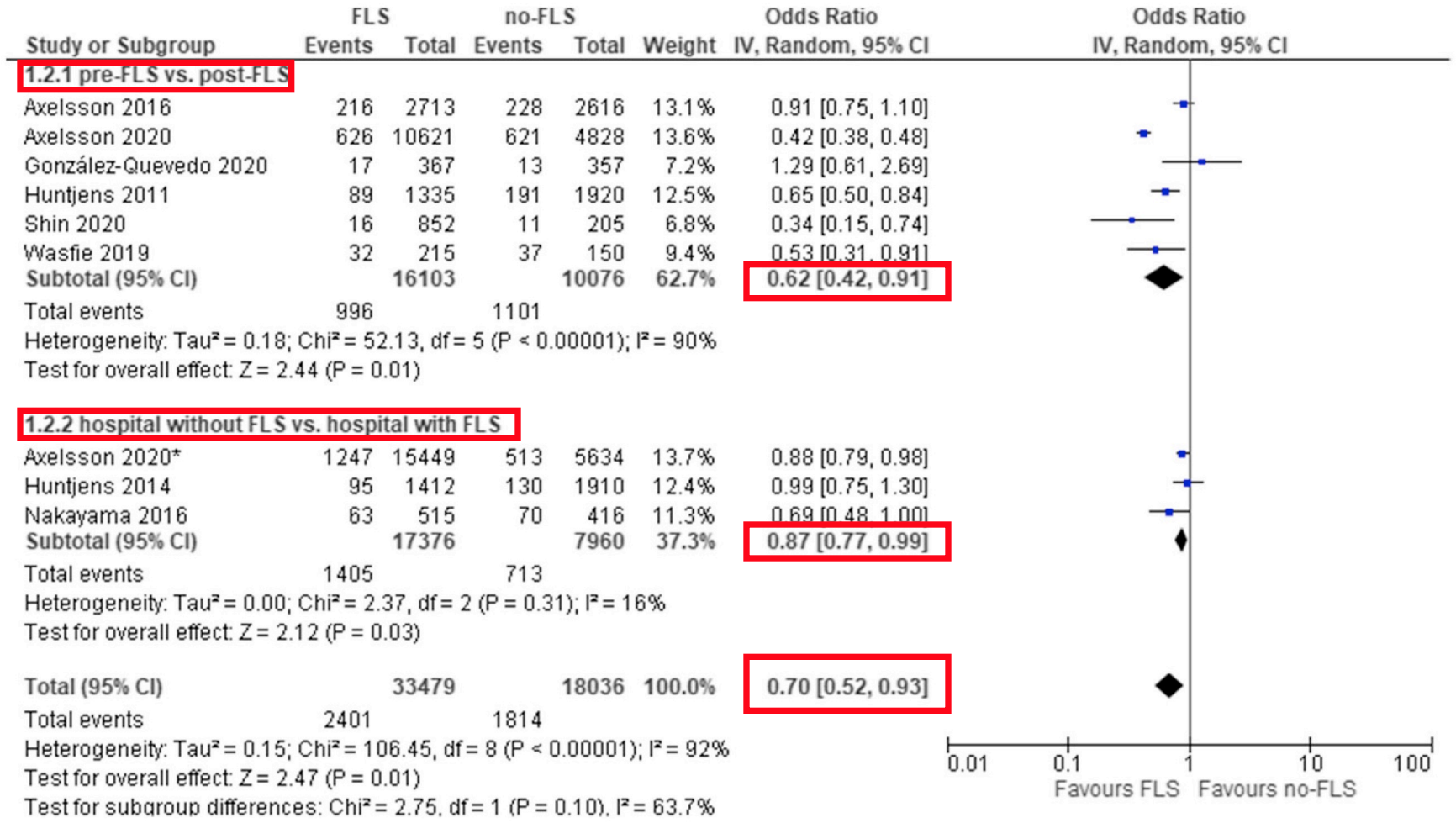
Higher rates of osteoporosis treatment initiation and persistence in patients with newly diagnosed vertebral fracture when introduced in inpatients than later in outpatients



Early patient management after a newly detected vertebral fracture during hospitalization was a more efficacious strategy of secondary fracture prevention than delayed outpatient management following discharge.

Spechbach et al Osteoporos Int 2019

L'impact des «Fracture liaison services» sur les fractures ultérieures
Revue systématique de la littérature & meta-analysis



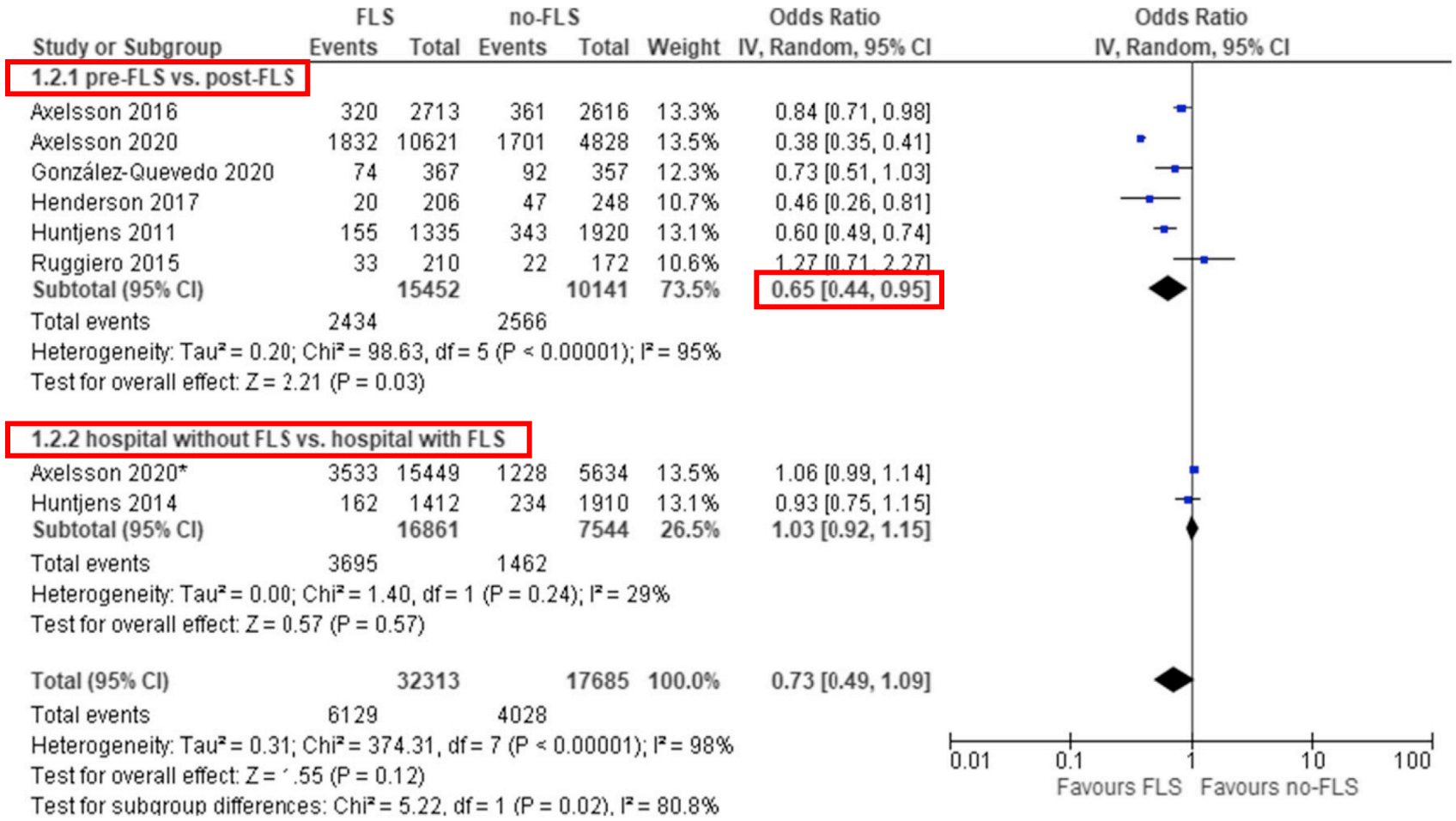
Study or Subgroup	FLS Events	FLS Total	no-FLS Events	no-FLS Total	Weight	Odds Ratio IV, Random, 95% CI
1.2.1 pre-FLS vs. post-FLS						
Axelsson 2016	216	2713	228	2616	13.1%	0.91 [0.75, 1.10]
Axelsson 2020	626	10621	621	4828	13.6%	0.42 [0.38, 0.48]
González-Quevedo 2020	17	367	13	357	7.2%	1.29 [0.61, 2.69]
Huntjens 2011	89	1335	191	1920	12.5%	0.65 [0.50, 0.84]
Shin 2020	16	852	11	205	6.8%	0.34 [0.15, 0.74]
Wasfie 2019	32	215	37	150	9.4%	0.53 [0.31, 0.91]
Subtotal (95% CI)		**16103**		**10076**	**62.7%**	**0.62 [0.42, 0.91]**
Total events	996		1101			
Heterogeneity: Tau² = 0.18; Chi² = 52.13, df = 5 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 2.44 (P = 0.01)						
1.2.2 hospital without FLS vs. hospital with FLS						
Axelsson 2020*	1247	15449	513	5634	13.7%	0.88 [0.79, 0.98]
Huntjens 2014	95	1412	130	1910	12.4%	0.99 [0.75, 1.30]
Nakayama 2016	63	515	70	416	11.3%	0.69 [0.48, 1.00]
Subtotal (95% CI)		**17376**		**7960**	**37.3%**	**0.87 [0.77, 0.99]**
Total events	1405		713			
Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 2 (P = 0.31); I² = 16%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Total (95% CI)		**33479**		**18036**	**100.0%**	**0.70 [0.52, 0.93]**
Total events	2401		1814			
Heterogeneity: Tau² = 0.15; Chi² = 106.45, df = 8 (P < 0.00001); I² = 92%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: Chi² = 2.75, df = 1 (P = 0.10), I² = 63.7%						

Réduction significative de 30% de la probabilité de fractures ultérieures

Etudes avec un suivi > 2 ans : réduction significative de 43%

Li N et al. Osteoporos Int 2021

L'impact des «Fracture liaison services» sur la mortalité
Revue systématique de la litérature & meta-analysis



Mortalité plus faible dans les études pré-versus post-FLS, mais pas dans les études comparant deux hôpitaux différents

Li N et al. Osteoporos Int 2021

Exclure une autre maladie métabolique osseuse ou cause secondaire d'ostéoporose

Interrogatoire
+
Examen clinique

+

Bilan biologique initial:

- FSC
- Calcium
- Phosphate
- Créatinine
- Vitamine D
- Phosphatases alcalines
- EPP
- +- Calciurie des 24h

Si normal, permet d'exclure dans 90% des cas une autre maladie métabolique osseuse ou cause secondaire d'ostéoporose

Lewiecki EM. *Curr Osteoporos Rep*. 2022 Feb;20(1):1-12.
Nuti R et al. *Intern Emerg Med*. 2019 Jan;14(1):85-102.

Multiples causes d'ostéoporoses secondaires

Endocrines

Hyperthyroïdies
Hypogonadismes
Hyperparathyroïdie
Hyperprolactinémies
Hypercortisolismes
Insuffisance somatotrope
Acromégalies
Diabète

Médicamenteuses

- Corticoïdes
- Inhibiteurs de l'aromatase
- Anti-androgènes
- …

Maladies inflammatoires chroniques

Toxiques

Alcool
Tabac

CKD-MBD

Infections virales chroniques

VIH

Nutritionnelles

Anorexie mentale
Malnutrition
Malabsorptions
Apports insuffisants en calcium, protéines…

Gastro-intestinales

Maladie cœliaque
MICI
Hépatopathies chroniques

….

Hématologiques

MGUS
Mastocytoses
Thalassémies

Indication à la densitométrie osseuse: évaluation des facteurs de risque

Recommandations 2020: avant d'effectuer une densitométrie, une évaluation du risque d'ostéoporose est proposé en utilisant les facteurs de risque évalués dans le FRAX

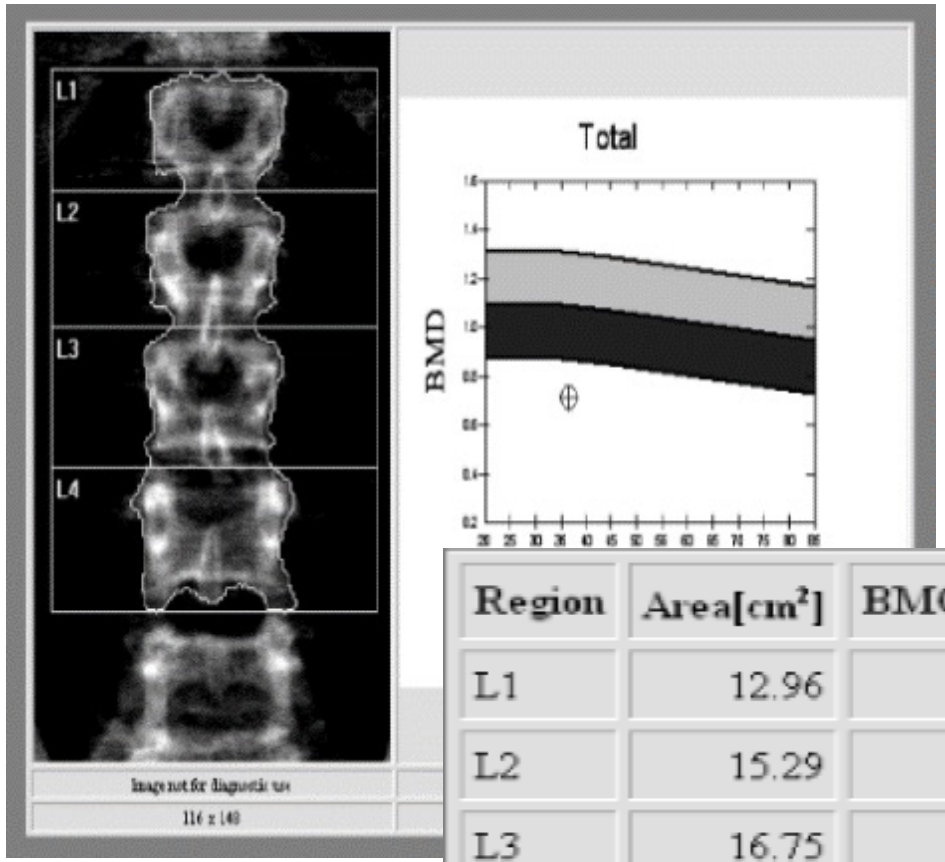
Table 1: Clinical risk factors for fractures in FRAX.

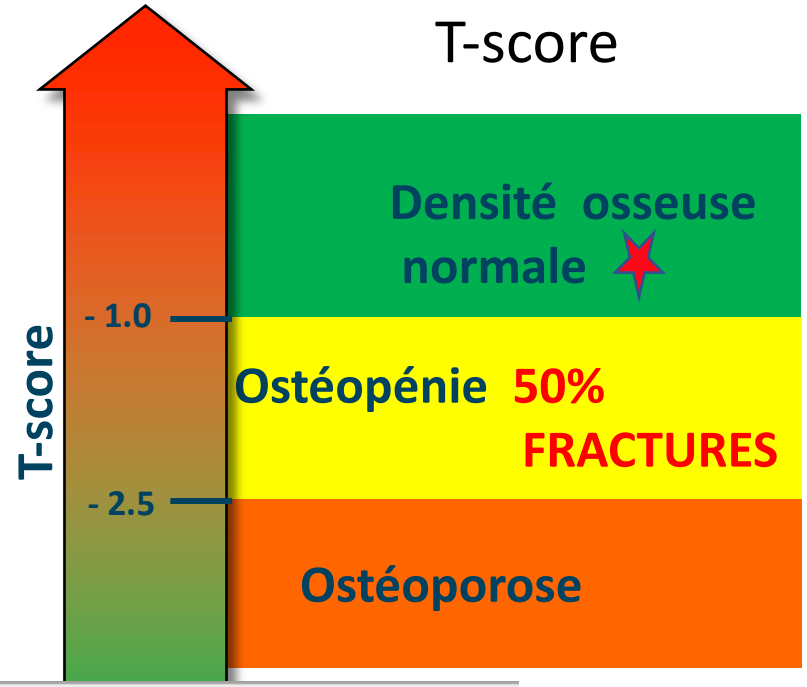
Age
Sex
Body mass index
Previous fracture
Parental hip fracture
Current smoking
Alcohol >3 units/d
Glucocorticoids
Rhumatoid arthritis
Secondary osteoporosis (type 1 diabetes, malabsorption, chronic liver disease, hypogonadism, untreated hyperthyroidism, adult osteogenesis imperfecta)

Ostéodensitométrie - par absorptiométrie double énergie à rayons X (DEXA)	Oui	– Ostéoporose cliniquement manifeste et après une fracture provoquée par un traumatisme minime – Corticothérapie de longue durée ou hypogonadisme – Maladies du système digestif avec syndrome de malabsorption (en particulier la maladie de Crohn, la rectocolite hémorragique et la maladie cœliaque) – Hyperparathyroïdie primaire (lorsque l'indication chirurgicale n'est pas nette) – Ostéogenèse imparfaite – VIH – En cas de thérapie à base d'inhibiteurs de l'aromatase (après la ménopause) ou de l'association analogues de la GnRH + inhibiteurs de l'aromatase (avant la ménopause)	1.3.1995/ 1.1.1999/ 1.7.2010/ 1.7.2012/ 1.1.1999/ 1.7.2010/ 1.1.2015/ 1.7.2019/ 1.4.2020
		Examens de l'évolution tant que dure la situation à risque prédisposante, en principe tous les deux ans au maximum.	1.3.1995/ 1.4.2020

OPAS, 1.1.2021

La mineralométrie
… son interprétation

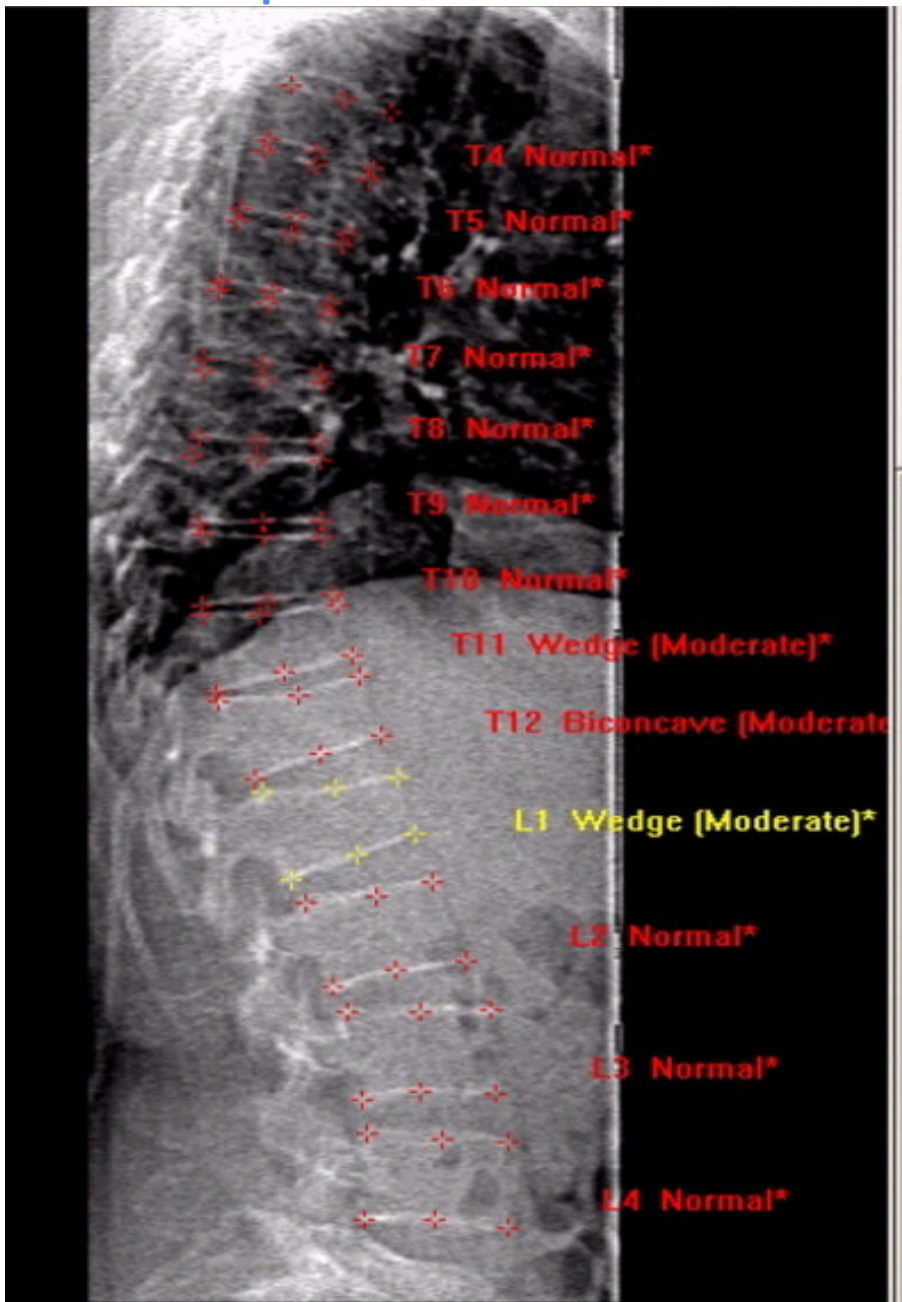


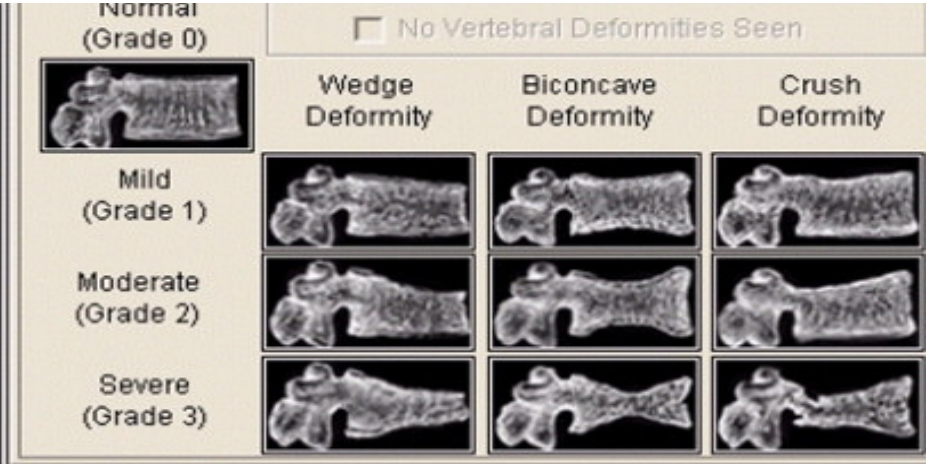


Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score
L1	12.96	7.86	0.607	-3.6
L2	15.29	11.48	0.751	-3.1
L3	16.75	12.60	0.752	-3.2
L4	18.82	13.58	0.722	-3.8
Total	**63.82**	**45.52**	**0.713**	**-3.4**

Sauf si troubles dégénératifs du rachis : **La DMO est sur-estimée = ininterprétable**

Morphométrie

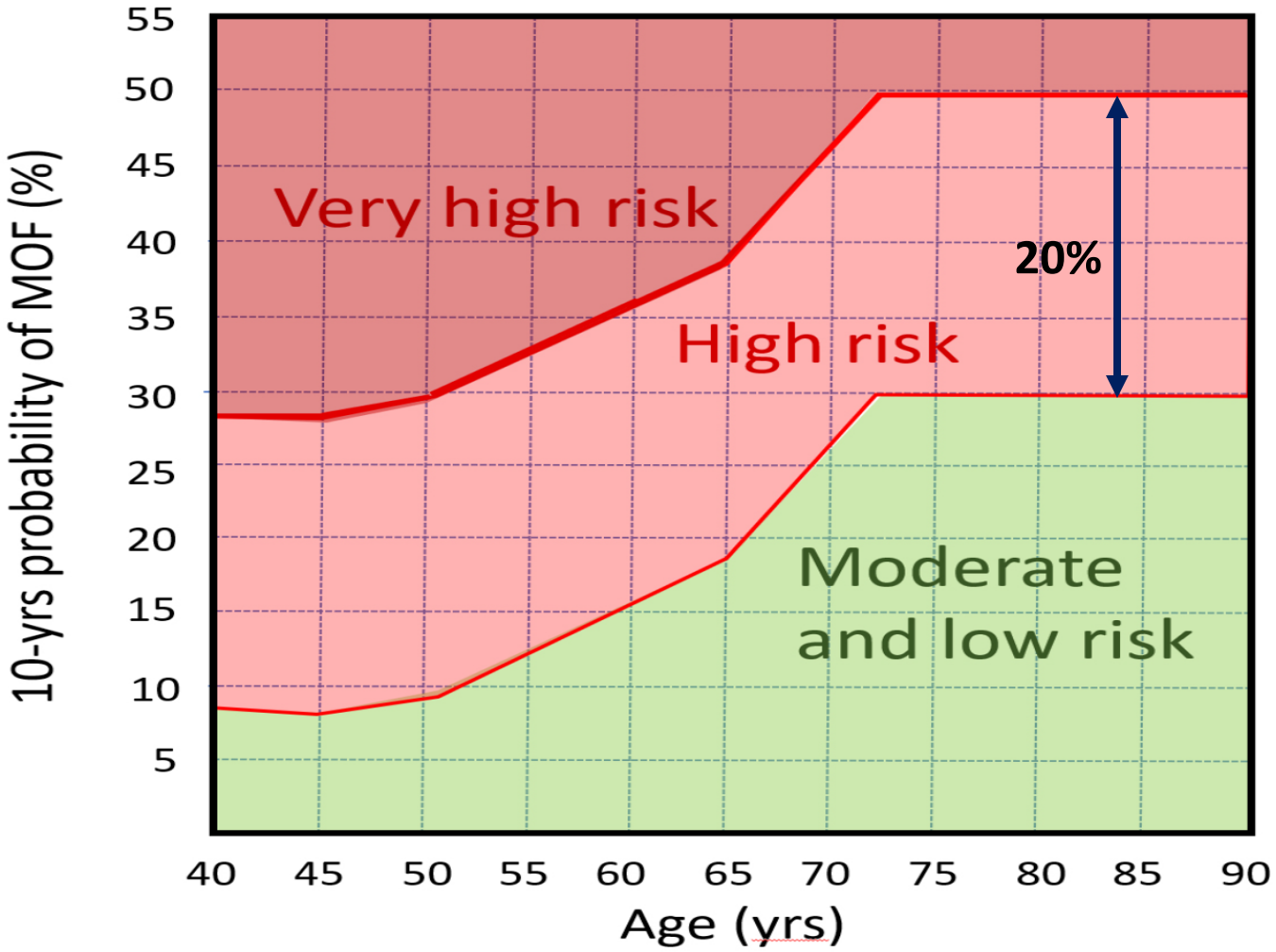




Vertebral Assessment

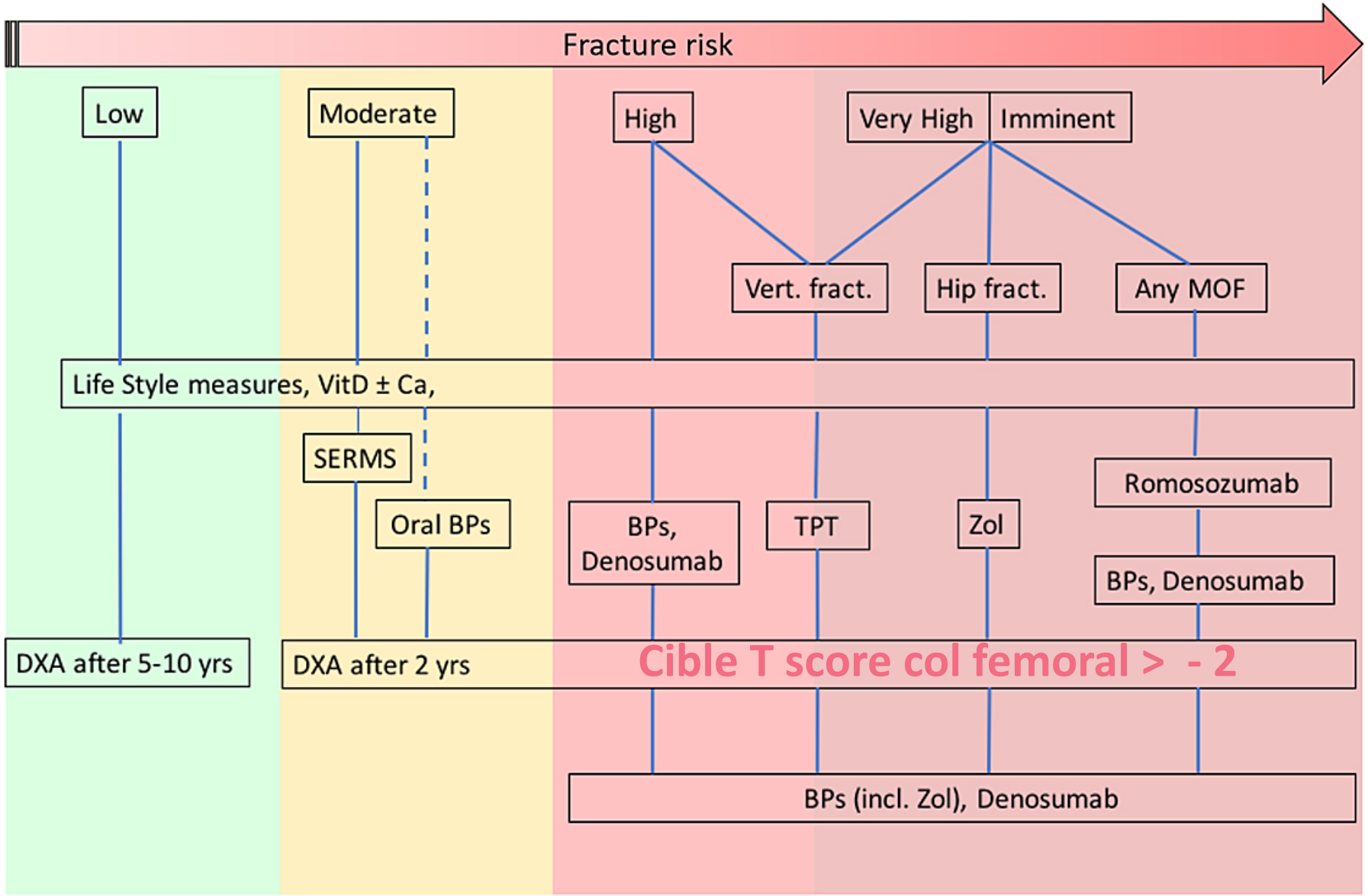
Label	Height (mm) Post	Mid	Ant	Percent Deformation Wedge	Biconcave	Crush
	Deformity (Grade)					
T4	17.8	18.3	18.2	0.0%	-3.1%	2.5%
	Normal					
T5	19.9	17.9	18.5	6.8%	9.9%	0.0%
	Normal					
T6	19.4	18.1	19.2	1.1%	6.7%	0.0%
	Normal					
T7	21.1	19.6	18.5	12.3%	6.8%	0.0%
	Normal					
T8	20.9	19.4	18.7	10.5%	7.0%	0.0%
	Normal					
T9	21.1	20.2	19.5	7.3%	4.3%	0.0%
	Normal					
T10	22.4	20.2	18.3	18.5%	9.9%	0.0%
	Normal					
T11	24.3	18.8	16.1	33.7%	22.5%	0.0%
	Wedge (Moderate)					
T12	26.3	19.4	19.4	26.2%	26.5%	0.0%
	Biconcave (Moderate)					
L1	28.9	22.5	18.1	37.6%	22.4%	0.0%
	Wedge (Moderate)					
L2	27.0	23.7	27.1	0.0%	12.2%	0.5%
	Normal					
L3	27.8	25.4	26.4	5.2%	8.8%	0.0%
	Normal					
L4	27.3	25.1	26.7	2.2%	8.3%	0.0%

Seuils d'intervention pour le TT anti-ostéoporotique basés sur le risque à 10 ans de fracture ostéoporotique majeure



Ferrari S et al. Swiss Med Wkly 2020

Recommendations de traitement par niveau de risque



Ferrari S et al. Swiss Med Wkly. 2020

Zol: Zoledronate (ACLASTA)- Denosumab (PROLIA)- TPT : teriparatide

Efficacy of Bisphosphonates in Reducing Fracture Risk In Postmenopausal Osteoporosis

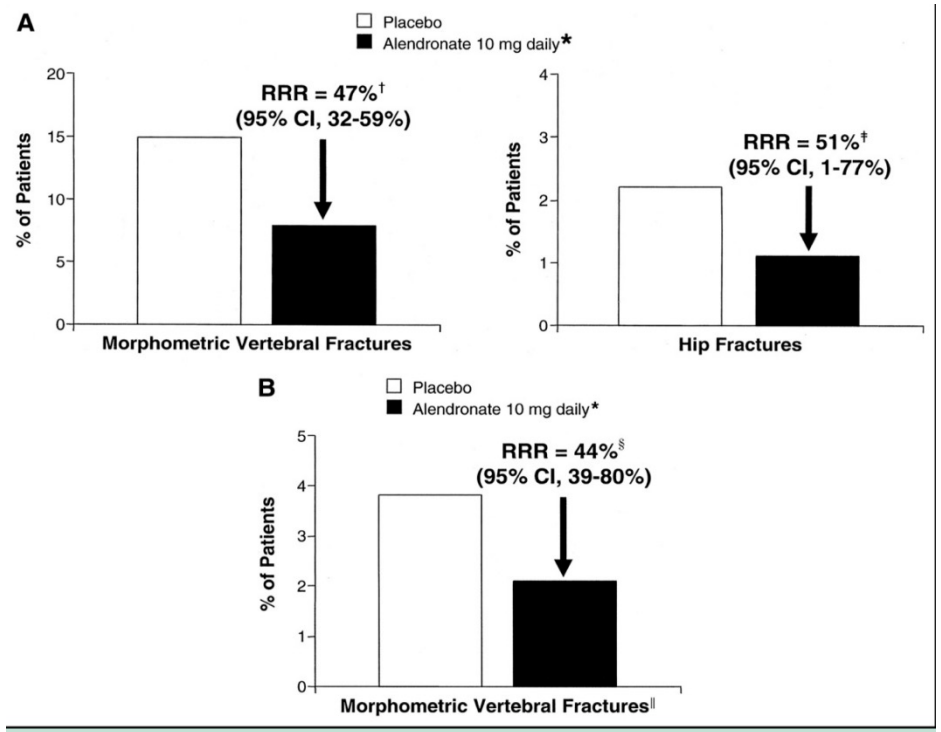


Figure 1 Rate of fractures in postmenopausal women receiving alendronate or placebo in (*A*) Fracture Intervention Trial (FIT)–1 after 3 years and (*B*) FIT-2 after a mean of 4.2 years. CI = confidence interval; RRR = relative risk reduction. *Alendronate 5 mg/day for the first 2 years of study. †P <0.001 vs. placebo; ‡P = 0.047 vs. placebo; §P = 0.002 vs. placebo. ‖Morphometric fractures defined as fractures diagnosed by a clinician. (Data from *Lancet*[10] and *JAMA*.[11])

Black DM et al. Lancet 1996
Cummings SR et al. JAMA 1998

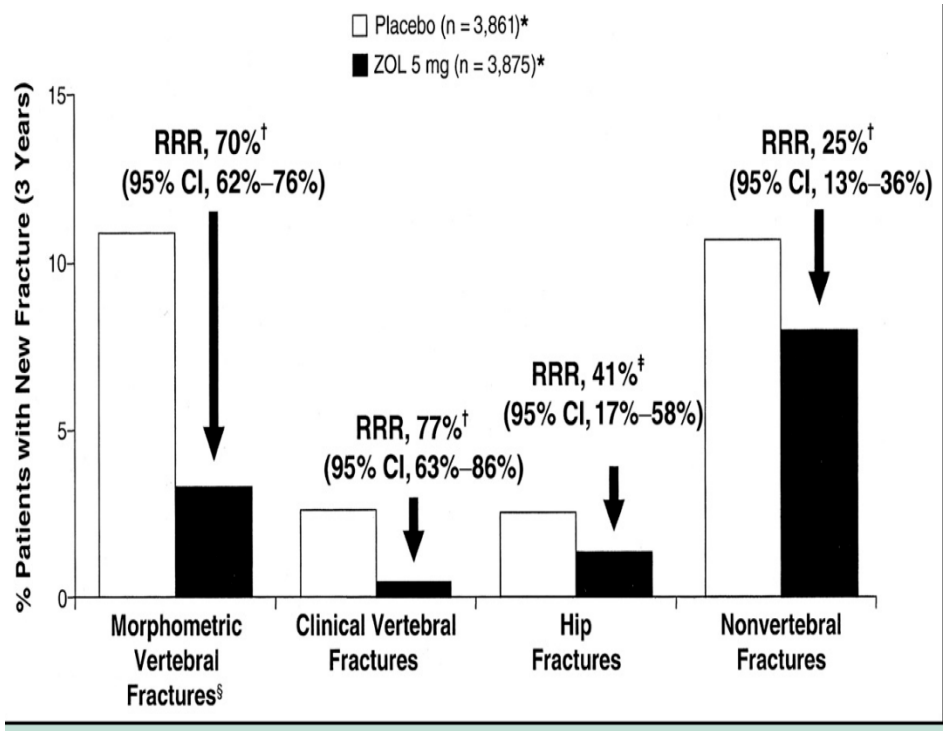


Figure 4 Rates of fractures over 3 years in postmenopausal women treated with zoledronic acid 5 mg (ZOL) or placebo infusions every 12 months in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)–Pivotal Fracture Trial. Values for hip fractures, clinical vertebral fractures, and nonvertebral fractures are cumulative event rates based on Kaplan-Meier estimates at month 36. *P*-values are based on an adjusted logistic-regression analysis. *A total of 14 patients in the zoledronic acid group and 15 in the placebo group were excluded from all analyses because the participation of their clinical center was terminated, owing to issues associated with reliability of data. †P <0.001 vs. placebo; ‡P = 0.002 vs. placebo. §Includes stratum 1 patients only (no concomitant therapy). CI = confidence interval; RRR = relative risk reduction. (Adapted from *N Engl J Med*.[26])

Black DM et al. NEJM 2007

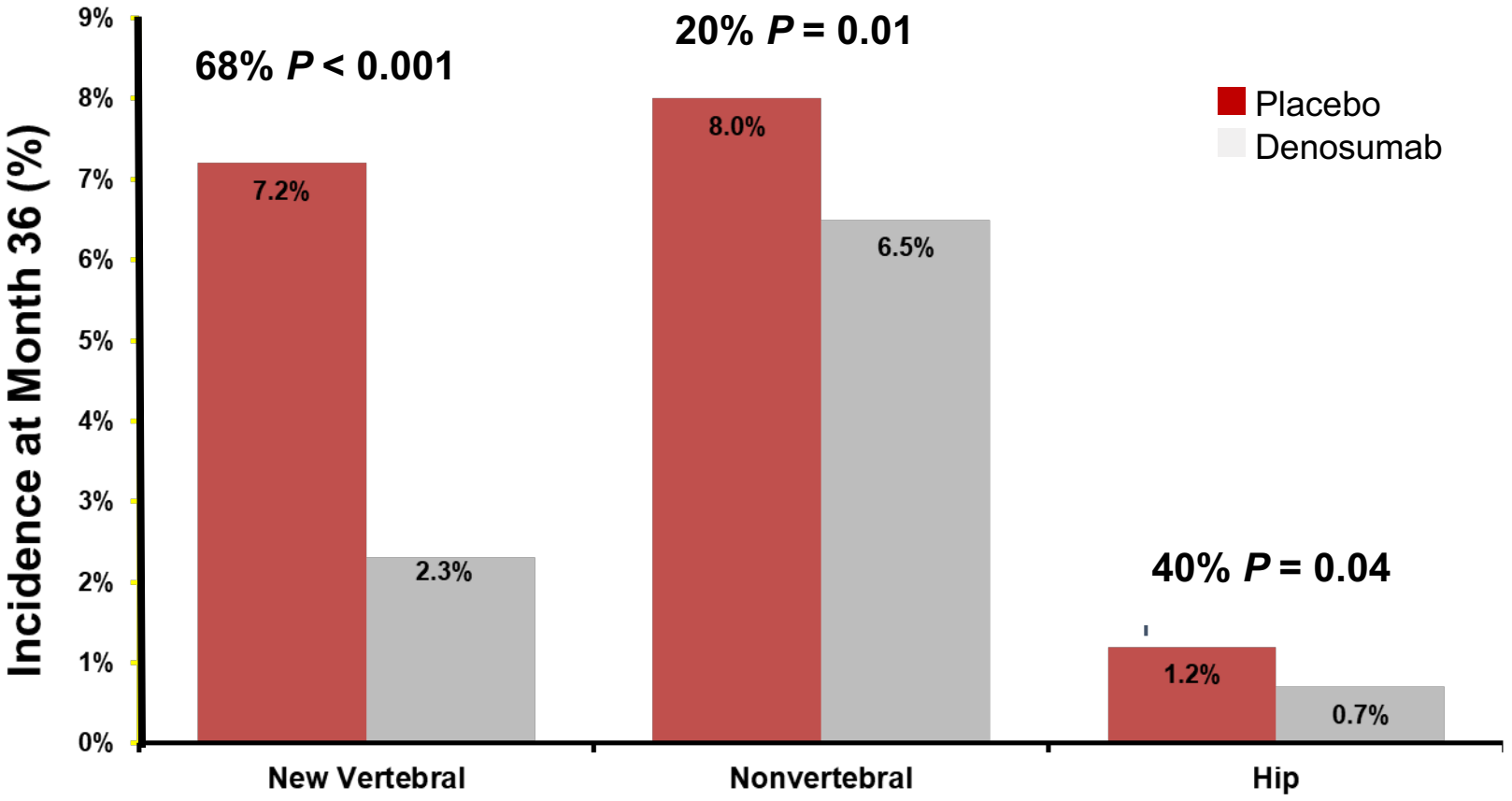
Bilezikian JP Am J Med 2009

Effect of Denosumab on Fracture Risks at 36 Months

Phase 3: The FREEDOM Trial

- Fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts

- 7868 women (60 to 90 yrs); -4.0 <T score BMD <−2.5 at the lumbar spine or total hip

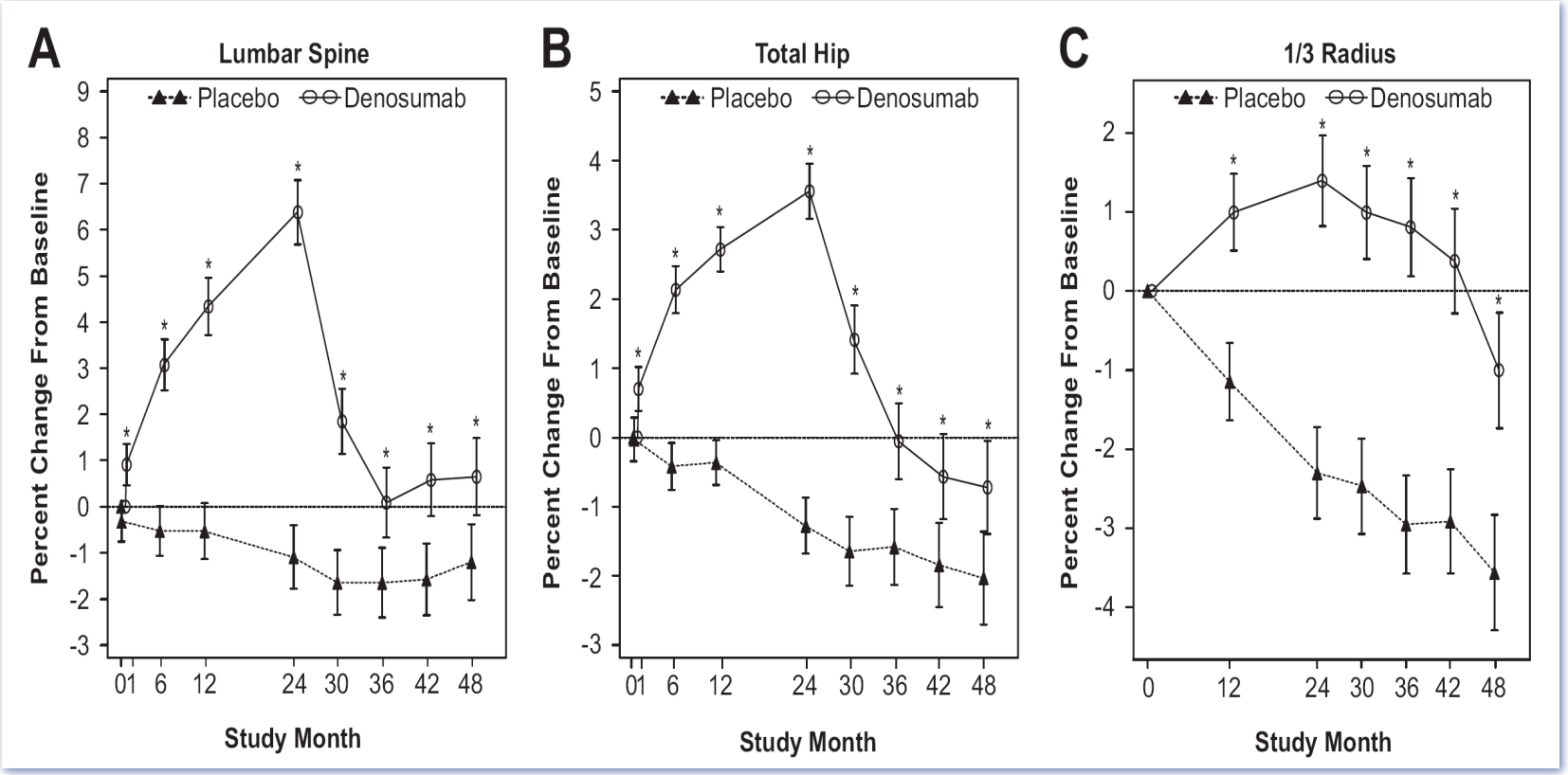


Cummings SR, et al. N Engl J Med. 2009 Aug 20;361(8):756-65

Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density in Postmenopausal Women with Low Bone Mass

- 256 postmenopausal women, mean age of 59 yrs, mean lumbar spine T-score of -1.61

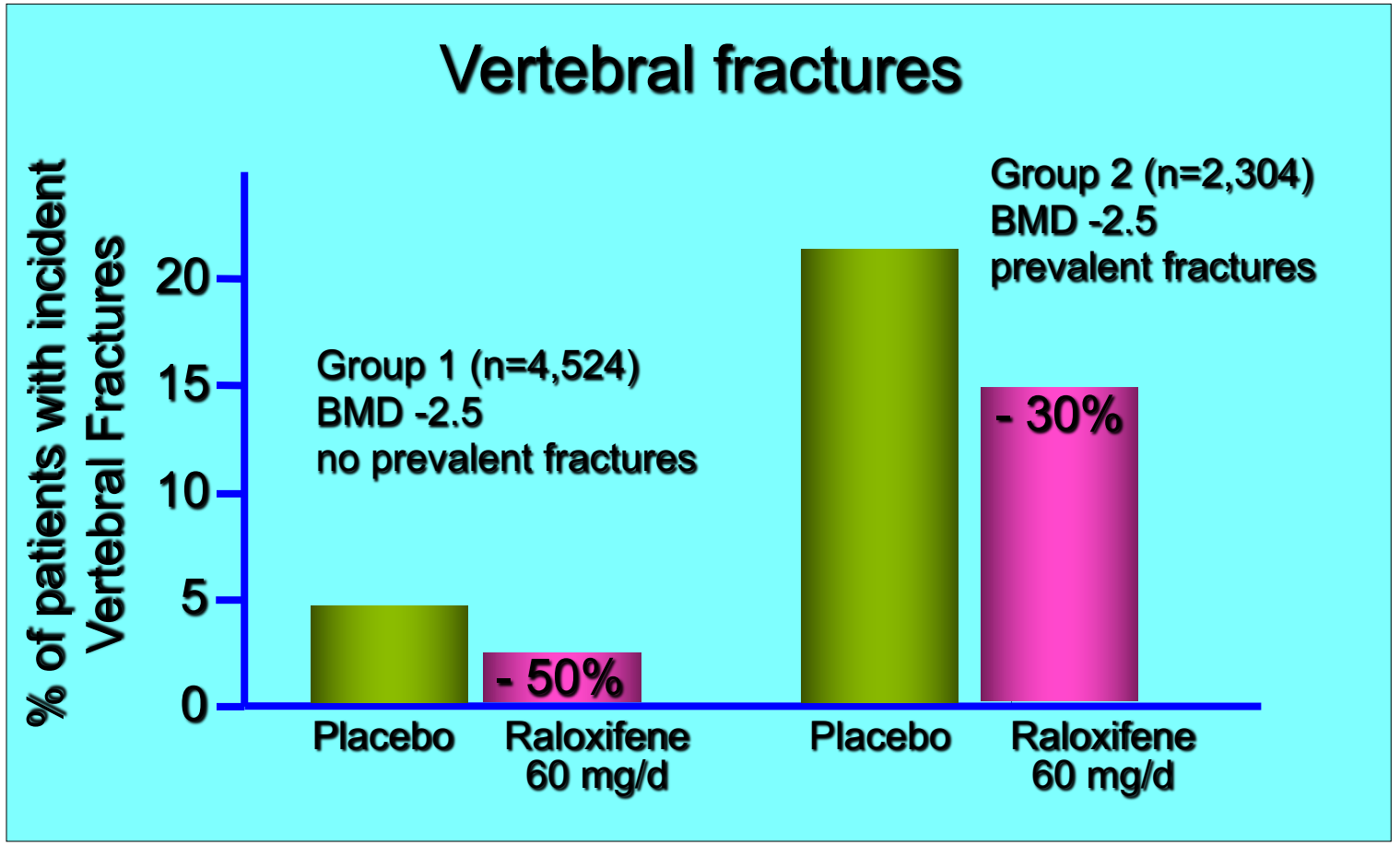
- Placebo or 60 mg denosumab every 6 months for 24 months, followed by 24 months off treatment



Bone HG et al. JCEM 2011

Effets du raloxifene sur les fractures vertébrales (MORE study)

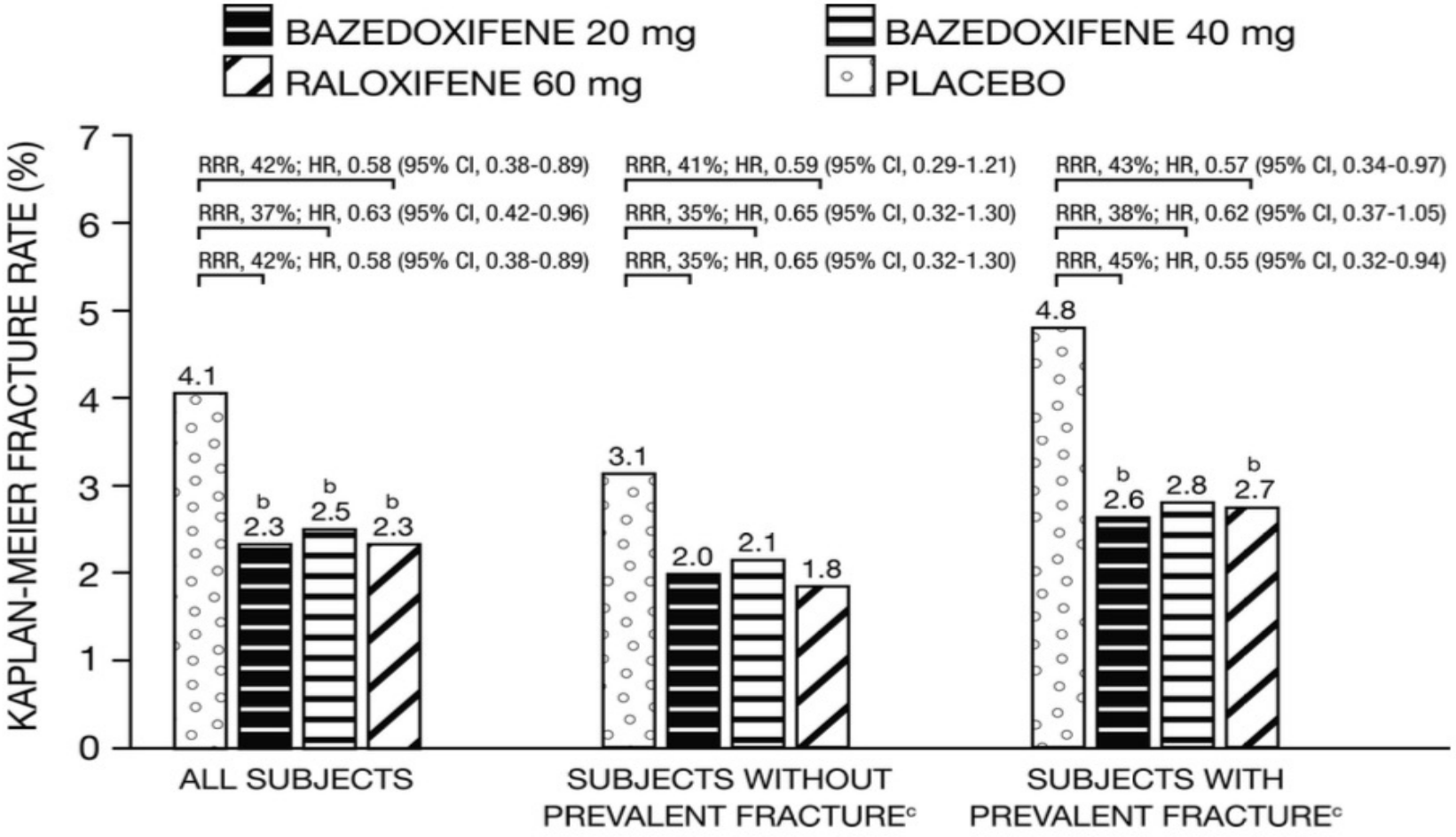
7705 osteoporotic women aged 31 to 80 yrs in 25 countries; postmenopausal ≥ 2 yrs



Ettinger B et al, JAMA, 1999;282:637-645

Efficacy of Bazedoxifene in Reducing New Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis: Results From a 3-Year, Randomized, Placebo-, and Active-Controlled Clinical Trial*

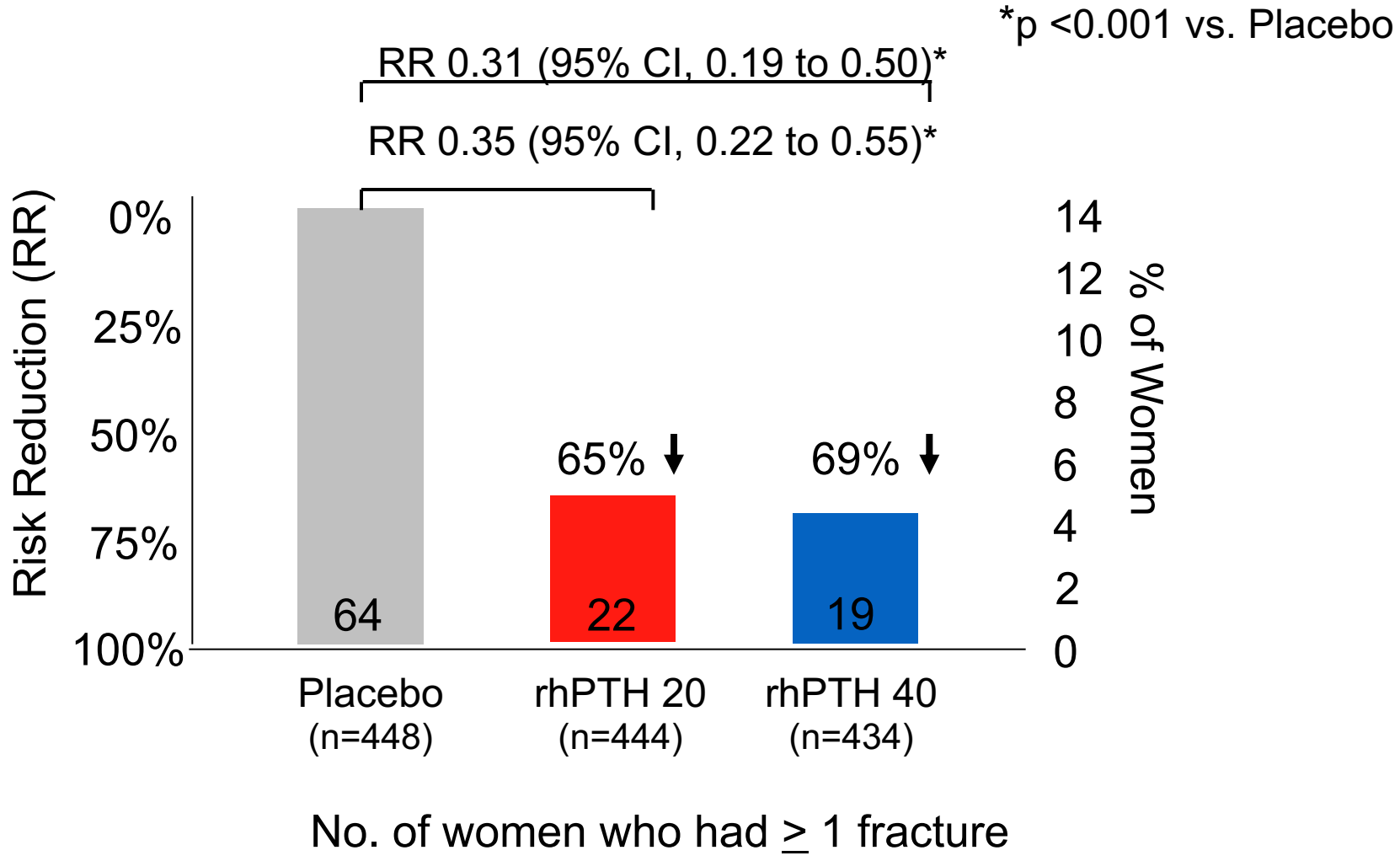
6847 healthy postmenopausal women with osteoporosis (55–85 yr of age)



Silverman et al. J Bone Miner Res 2008;23:1923–1934

Effect of rhPTH (1-34) on the Risk of New Vertebral Fractures

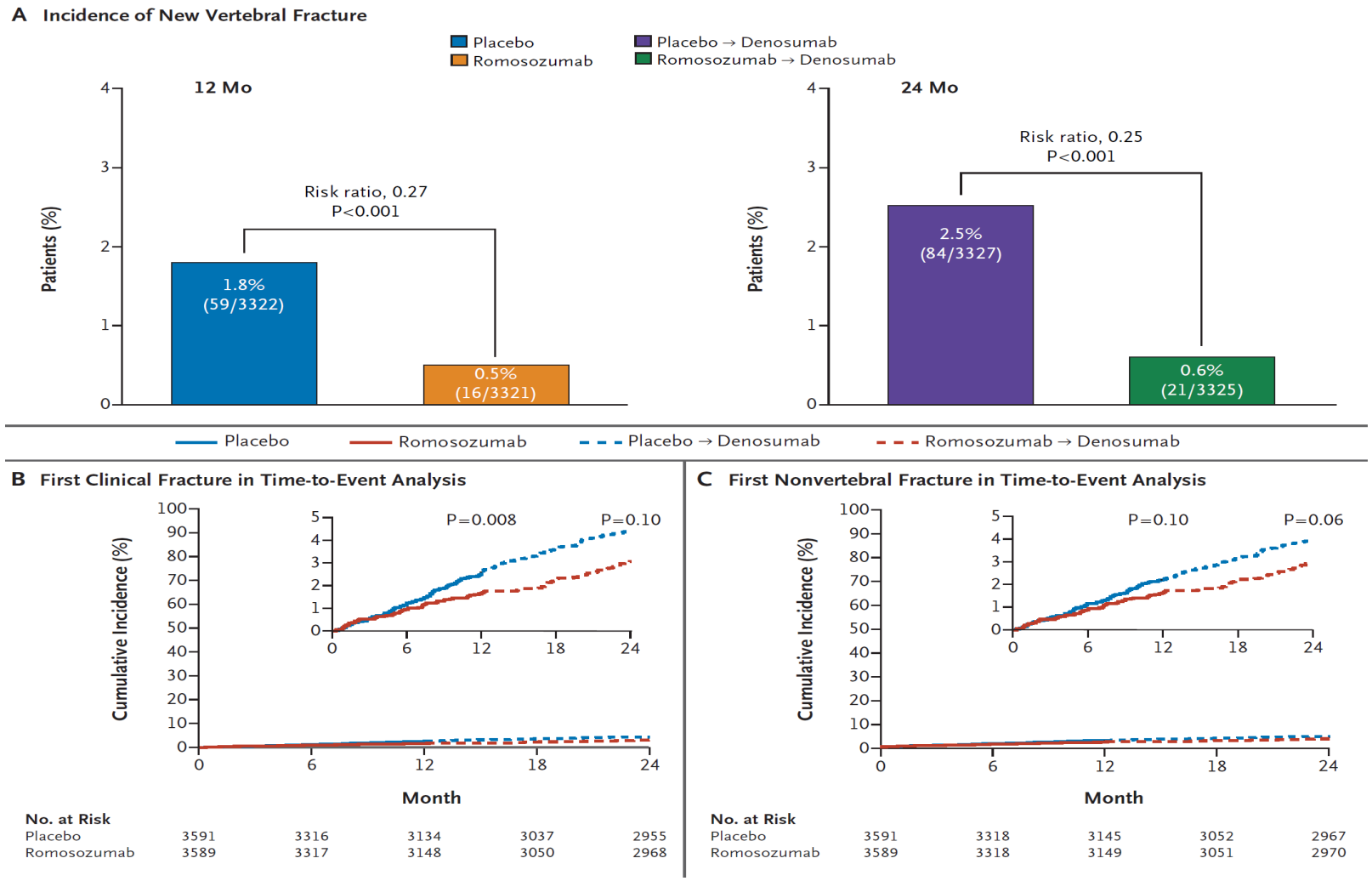
1637 postmenopausal women with prior vertebral fractures



Neer et al 2001

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

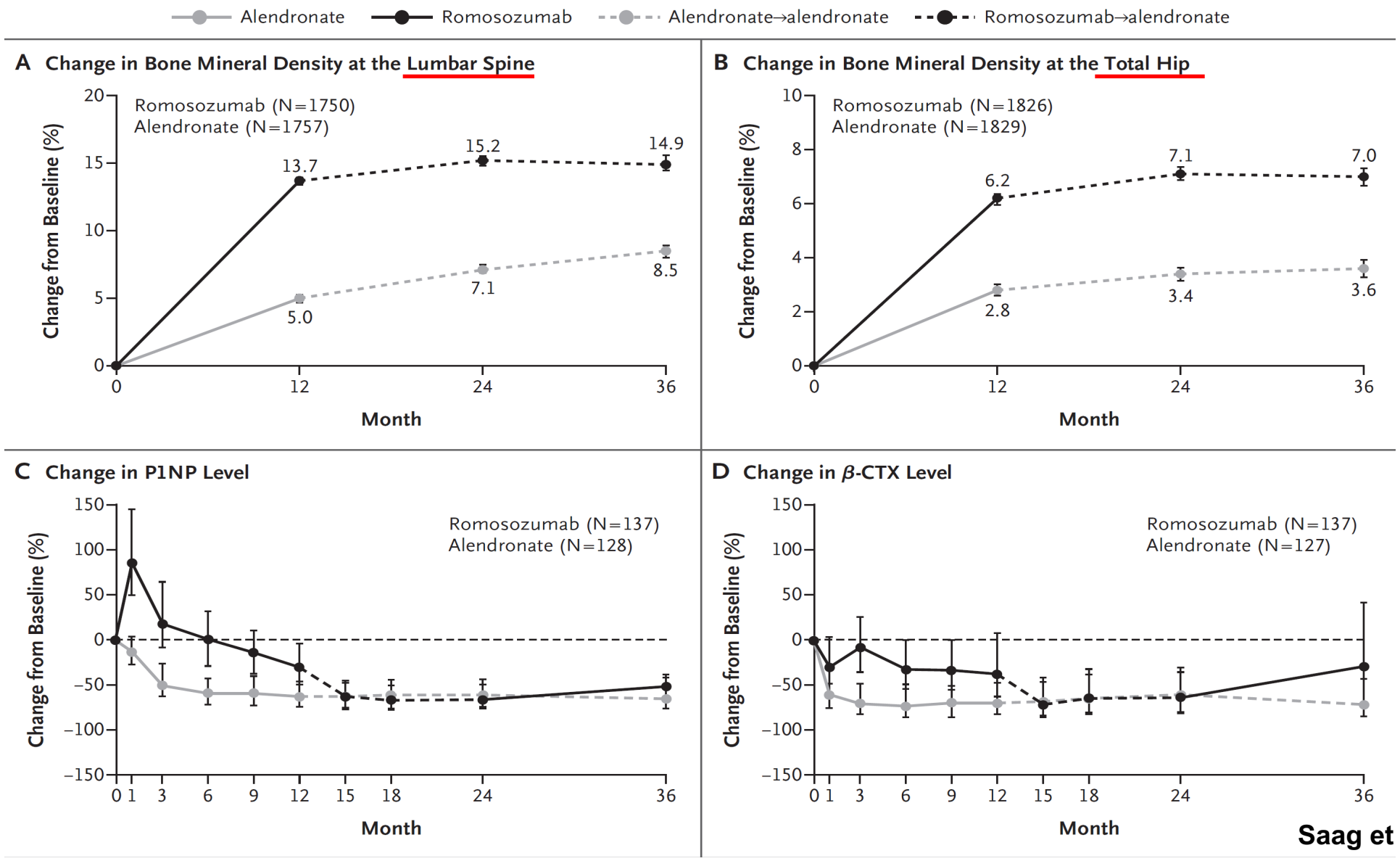
- **Monoclonal antibody that binds sclerostin (protein expressed by osteocytes that downregulates osteoblastic bone formation)**
- **7180 postmenopausal women, -3.5 < T score < –2.5 at the total hip or femoral neck.**
- **Monthly s.c romosozumab (210 mg) or placebo for 12 months and then denosumab (60 mg) s.c every 6 M for 12 months**



Cosman F et al., NEJM 2016

Romosozumab or Alendronate for Fracture Prevention in Women

- 4093 postmenopausal women with osteoporosis and a fragility fracture
- Randomized to monthly s.cut romosozumab (210 mg) or weekly oral alendronate (70 mg) for 12 months, followed by open-label alendronate in both groups.



Saag et al. NEJM 2017

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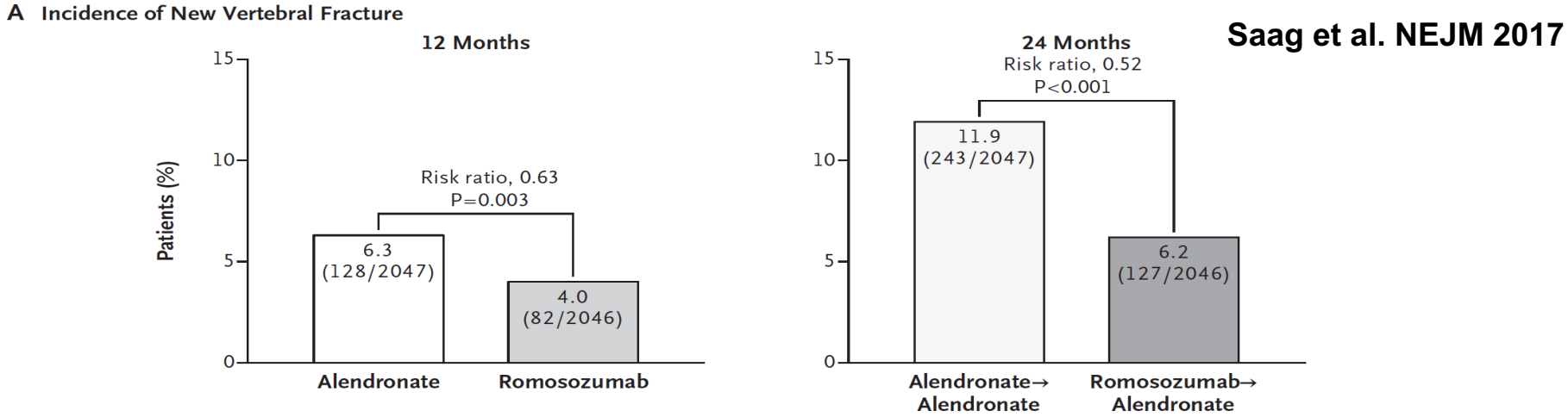
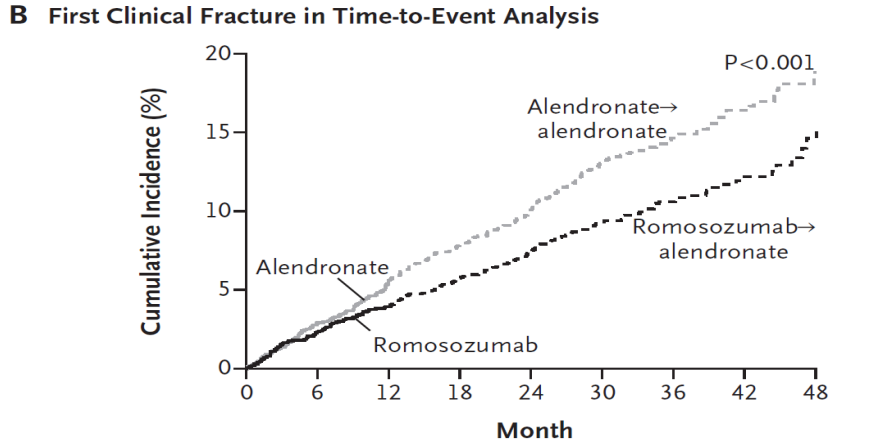
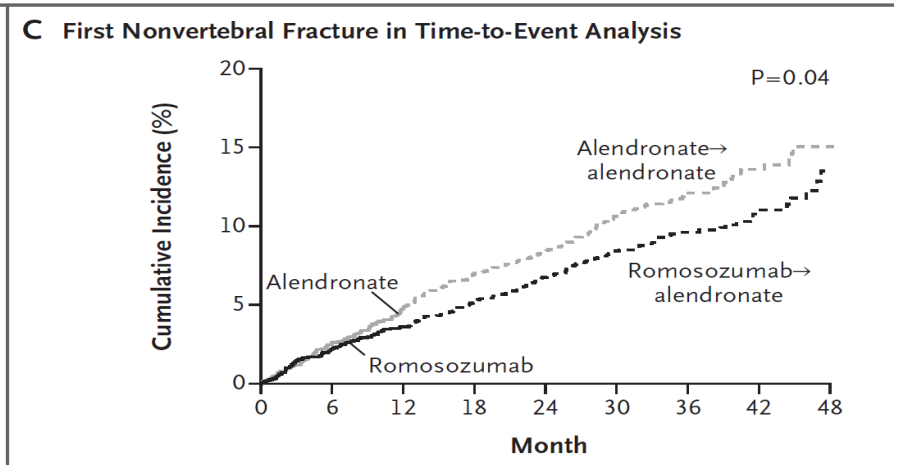


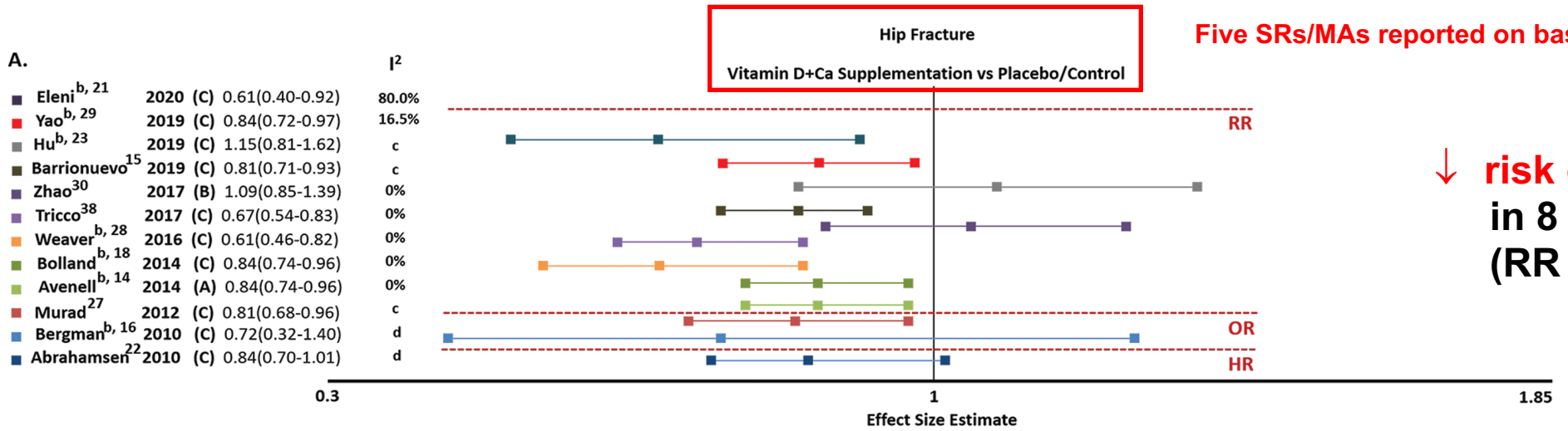


No. at Risk									
Alendronate	2047	1868	1743						
Romosozumab	2046	1865	1770						
Alendronate→ alendronate				1645	1564	1066	680	325	108
Romosozumab→ alendronate				1683	1615	1103	705	347	109



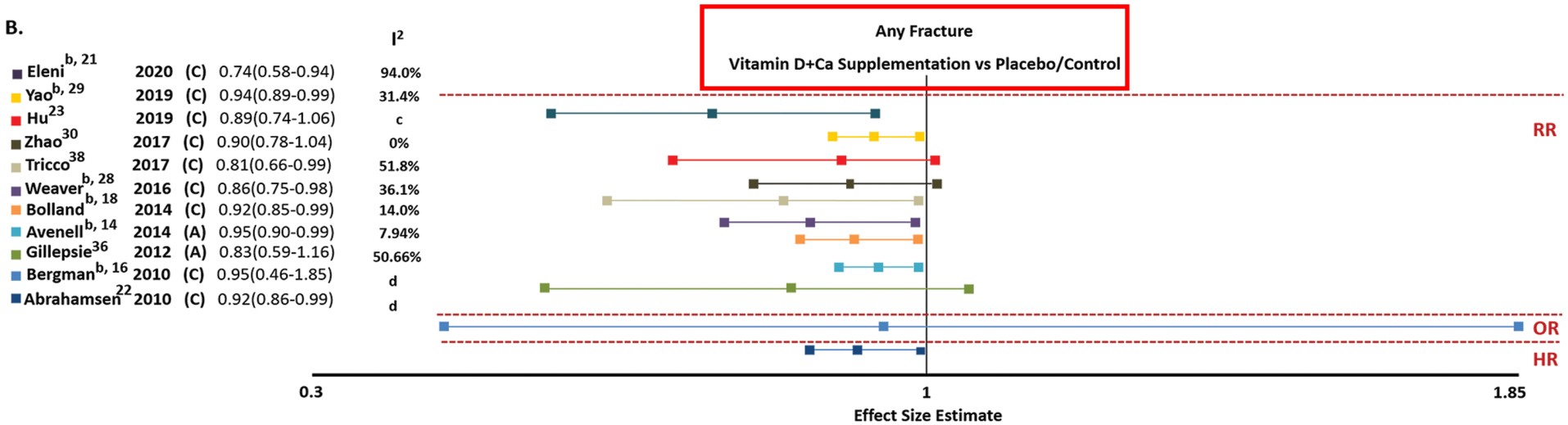
No. at Risk									
Alendronate	2047	1873	1755						
Romosozumab	2046	1867	1776						
Alendronate→ alendronate				1661	1590	1097	697	330	110
Romosozumab→ alendronate				1693	1627	1114	714	350	109

Vitamin D Supplementation and Fractures in Adults: A Systematic Umbrella Review of Meta-Analyses of Controlled Trials



Five SRs/MAs reported on baseline 25(OH)D (20.9-83.8 nmol/L)

↓ **risk of hip fractures** in 8 of 12 SRs/MAs (RR 0.61-0.84)



↓ **any fractures** in 7 of 11 SR/MAs (RR 0.74-0.95)

Quality Assessment Using the AMSTAR-2 Tool: (A)-Moderate Quality; (B)-Low Quality; (C)-Critically Low Quality
a: Abbreviations: RR: Risk Ratio, OR: Odds Ratio, HR: Hazard Ratio
b: Meta-Analysis including institutionalized trials
c: Network Meta-Analysis
d: Not available

Conclusion: Ca/D reduces the risk of hip and any fractures, possibly driven by findings from institutionalized individuals.

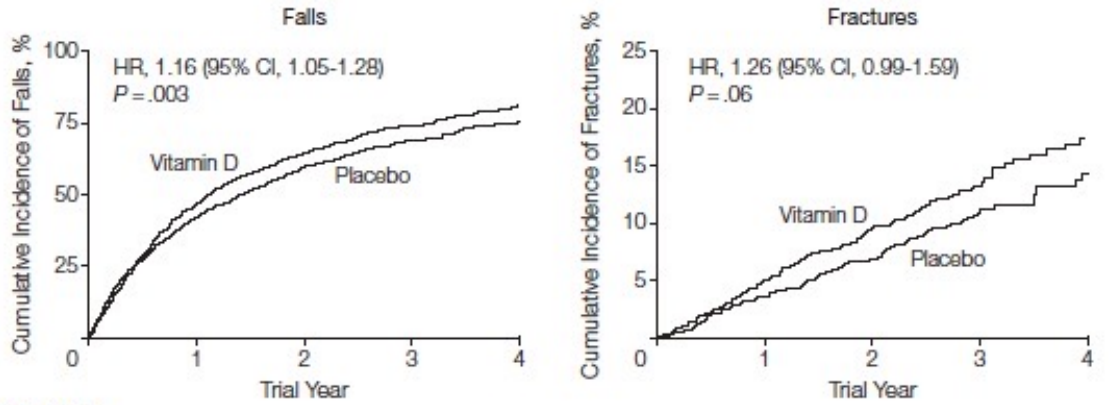
Chahktoura M et al. JCEM 2022

Vitamin D: 500’000 IU Annually

2256 community-dwelling W, aged ≥ 70 yrs, high risk of fracture (maternal hip fracture, past fracture, or self reported faller)

25(OH)D) ~ 50 nmol /l

Figure 2. Kaplan-Meier Plots of Cumulative Incidence of Time to First Fracture and First Fall



No. of women

Vitamin D	1131	588	382	77	22
Placebo	1125	635	429	87	33

1131	1048	963	236	106
1125	1050	985	253	115

This analysis censors data after first fall or fracture. Time to first fracture and fall was analyzed using Cox proportional hazards models. CI indicates confidence intervals; HR, hazard ratio.

Table 4. Temporal Pattern of Risk in Falls and Fracture 0 to 3 Months and 4 to 12 Months After Treatment

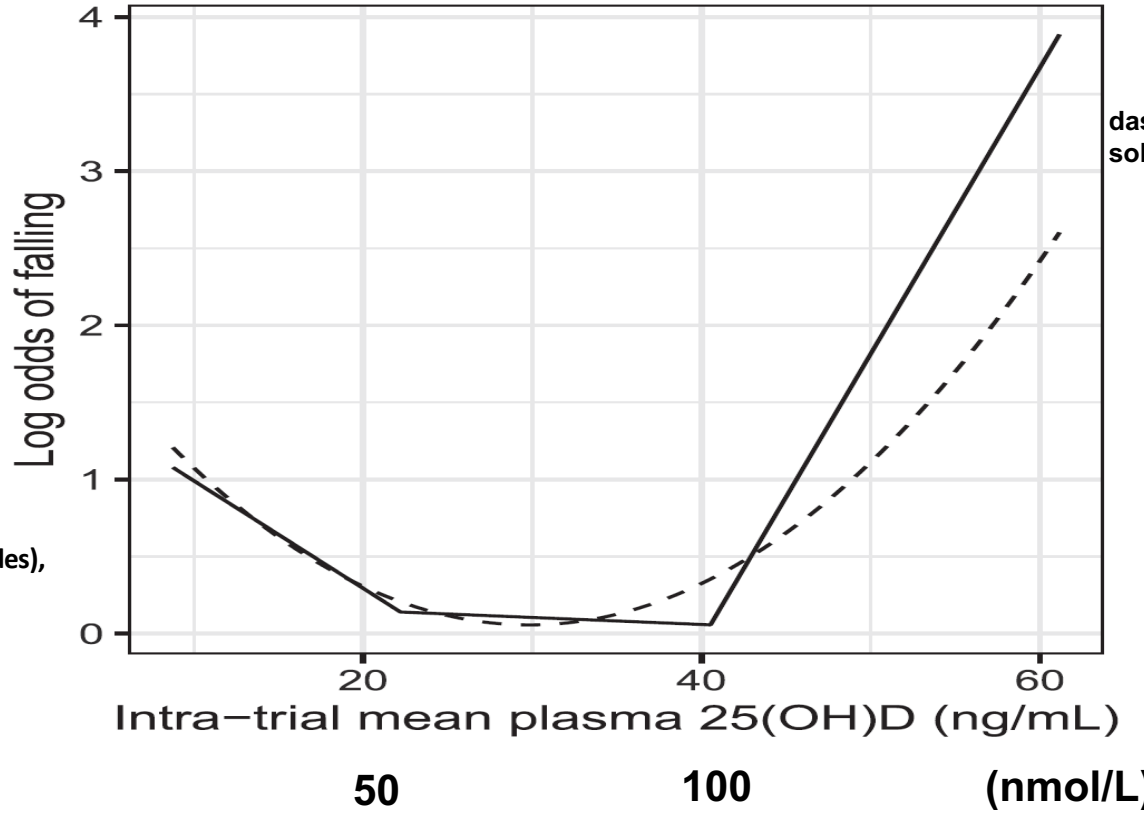
	Incidence Rate Ratio for Vitamin D Group, Estimate (95% Confidence Interval)[a]	*P* Value
Time after treatment, mo		
Falls		
Within 3	1.31 (1.12-1.54)	.001
After 3	1.13 (0.99-1.29)	.08
Fracture		
Within 3	1.53 (0.95-2.46)	.08
After 3	1.18 (0.91-1.54)	.21

Results similar after adjustment for baseline calcium intake

Sanders et al JAMA 2010

STOP IT: Intra-trial mean 25(OH)D and risk of falling
410 men and women ≥ 65 yrs, baseline 25(OH)D 55 nmol/L
700 UI vit D3 plus calcium for 3 yrs

- Serum 25(OH)D measured every 6 months
- Intra-trial mean 25(OH)D defined as the mean of all measurements from 6 M to time to first fall
- Careful falls assessments made every 6M for 3 yrs



dashed line is a quadratic and
solid line is a 3-piecewise regression

adjusted for age (half decades), sex, and calcium intake,

The U-shaped pattern of falling was similar in men and women

Dawson-Hughes B JCEM 2022

Take Home Messages (1)

- **Les patients avec fracture de fragilité sont à haut risque de nouvelles fractures survenant surtout dans les premiers 6 à 24 mois.**
- **La majorité de ces patients ne sont pas évalués ou traités.**
- **Plusieurs traitements anti-ostéoporotiques spécifiques réduisent l'incidence de nouvelles fractures vertébrales, non-vertébrales et de hanche.**
- **Les Fracture Liaison Service avec un coordinateur permettent de diminuer le taux de refractures et la mortalité, ceci avec un rapport coût-bénéfice favorable.**
- **Ces filières de prévention secondaire des fractures sont considérées actuellement comme standard de soins dans le monde.**

Take Home Messages (2)

- **Une dose quotidienne de 700-800 UI vit D avec un apport adéquat de calcium réduit le risque de chutes et de fractures chez les patients âgés carencés/insuffisants.**

- **La supplémentation en vit D chez des sujets âgés avec des taux adéquats de 25(OH)D n'améliore pas la performance musculaire et ne diminue pas les chutes.**

- **Une supplémentation pour atteindre un taux de 25(OH)D ≥ 100 nmol/l semble augmenter le risque de chutes.**

- **Des bolus importants de vit D peuvent aussi augmenter le risque de chutes.**

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