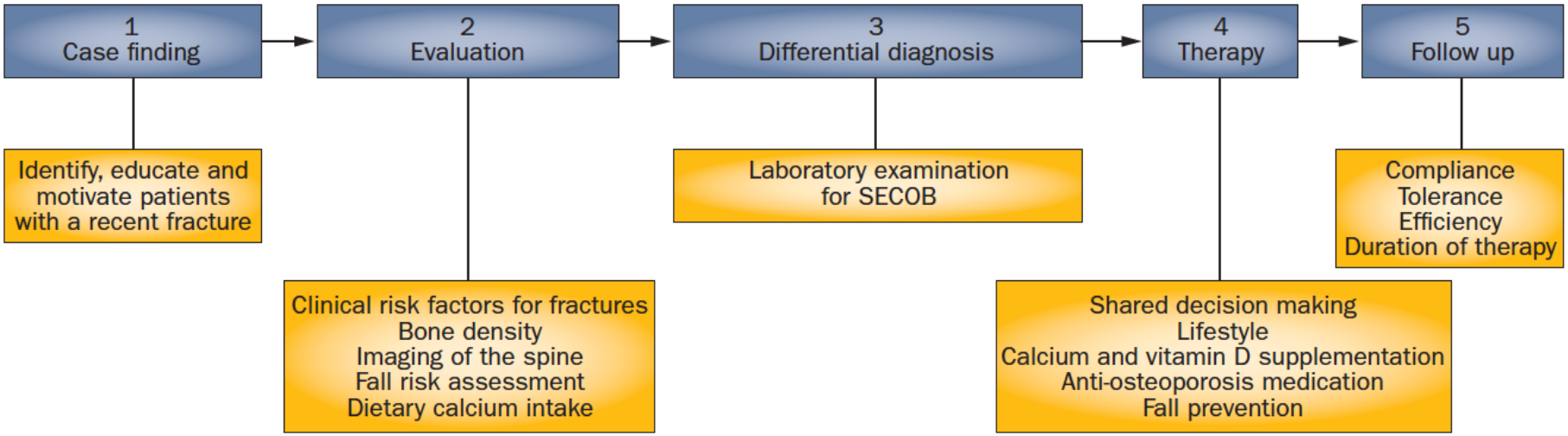
De behandeling van osteoporose: een overzicht.

Joop van den Bergh, internist-endocrinoloog
VieCuri MC Noord-limburg, Maastricht UMC & UHasselt

Fracture prevention: a five-step approach



van den Bergh et al. Nature Reviews. Rheumatol. 2012; 163–172

Fractuurpreventie

- Opsporen van de patiënten met een hoog fractuurrisico
  - Met aandoeningen / risicofactoren maar zonder recente fractuur
  - Na een recente fractuur

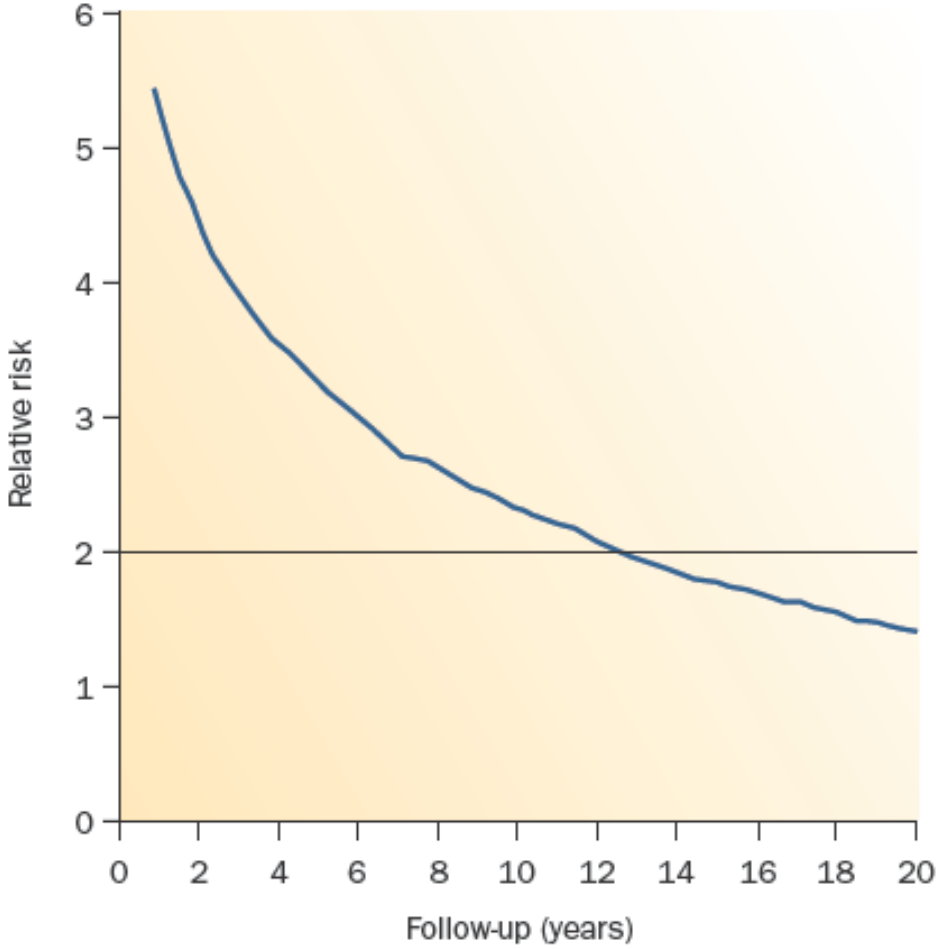
Risicofactoren voor het optreden van een fractuur, met risicoscore:
CBO 2011

Risicofactor	***Risicoscore***
Gewicht <60 kg en/of BMI < 20 kg/m^2	1
Leeftijd > 60 jaar	1
Leeftijd > 70 jaar (>60 jaar niet extra meetellen)	2
Eerdere fractuur na het 50e levensjaar >2 jaar geleden	1
Heupfractuur bij een ouder	1
Verminderde mobiliteit	1
Meer dan 1 keer vallen in het laatste jaar	1
Reumatoïde artritis	1
Aandoening/medicatie met secundaire osteoporose*	1
Gebruik van glucocorticoïden (>3 maanden; ≥7,5 mg/dag)	4

* Aandoening of situatie geassocieerd met secundaire osteoporose:

- Onbehandeld hypogonadisme bij mannen en vrouwen:
  - (bilaterale orchidectomie en ovariëctomie)
  - anorexia nervosa
  - chemotherapie voor borstkanker
  - hypopituitarisme
- Inflammatoire darmziekten: Ziekte van Crohn en colitis ulcerosa.
- Malabsorptie
- Andere chronische inflammatoire aandoeningen zoals spondylartropathie (Ziekte van Bechterew), SLE, sarcoïdose
- Orgaantransplantatie
- Type I Diabetes Mellitus
- Schildklieraandoeningen: onbehandelde hyperthyroïdie of overgesubstitueerde hypothyreoïdie
- Gebruik van anti-epileptica
- Onbehandelde hyperparathyreoïdie
- COPD
- Pernicieuze anemie, lage zonlichtexpositie, diabetes mellitus type 2

Na een recente fractuur:
Risico in de eerste jaren na een fractuur 5 verhoogd



Na 1e fractuur:

23% van alle volgende fracturen binnen 1 jaar

54% binnen 5 jaar

Van Geel et al. Ann Rheum Dis 2009;68:99-102

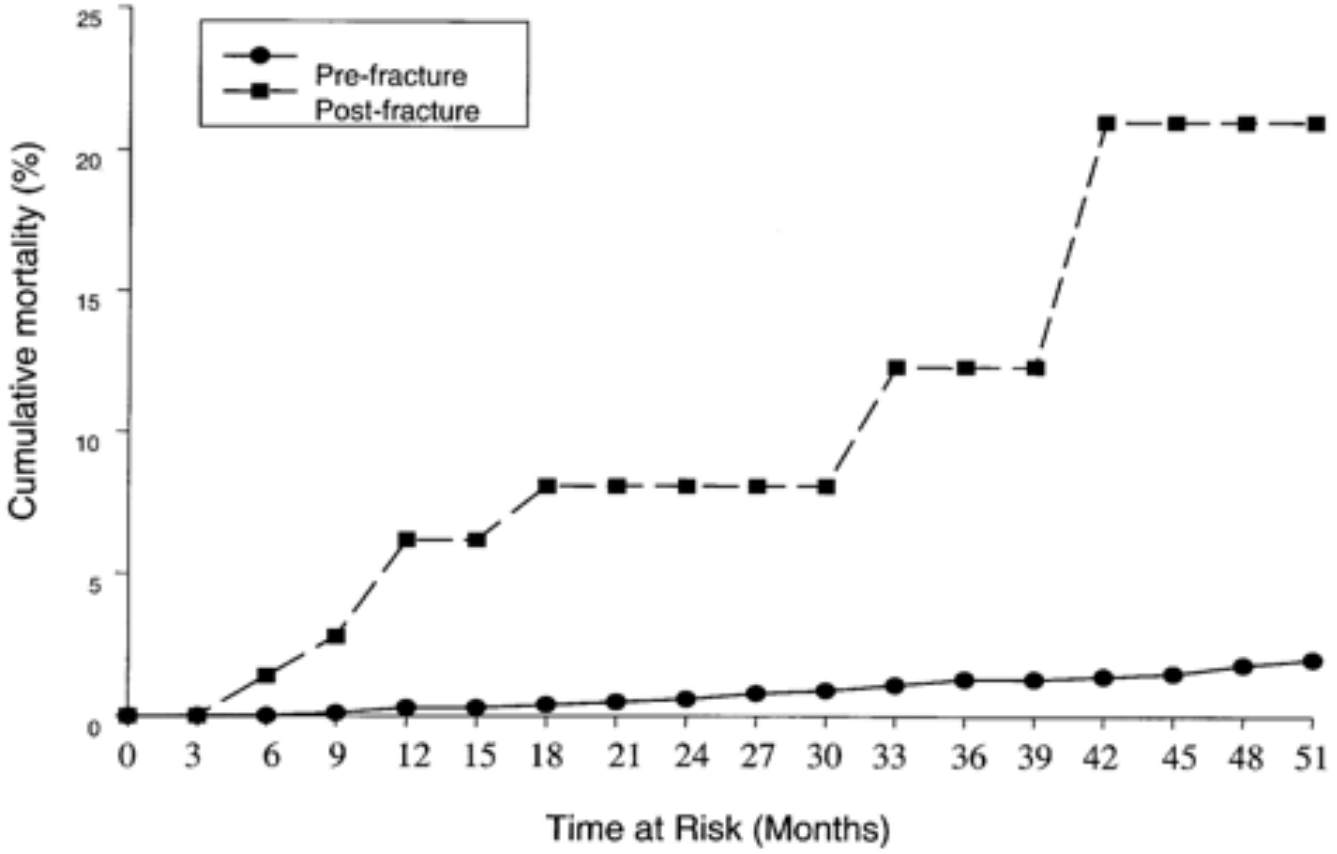
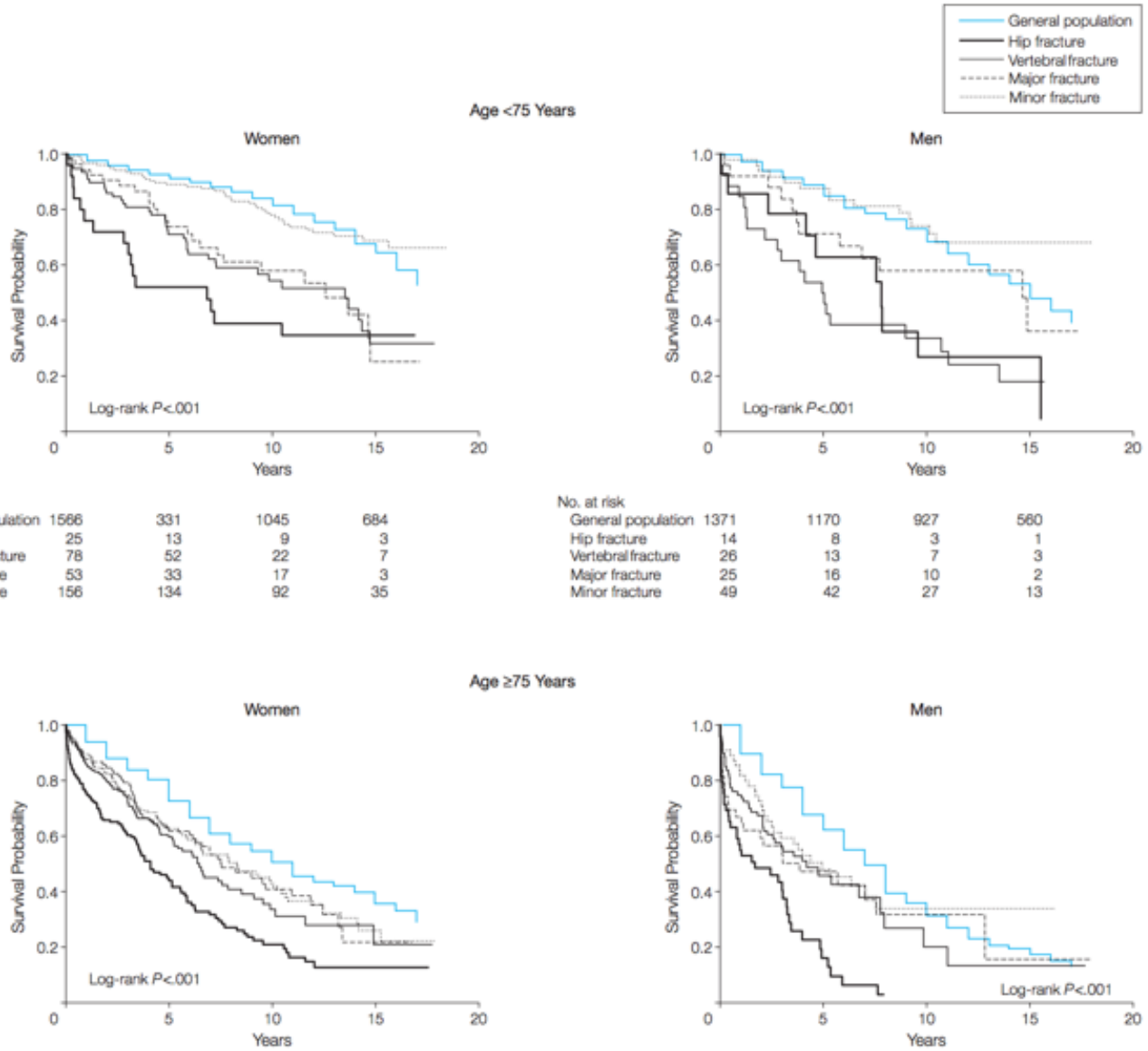


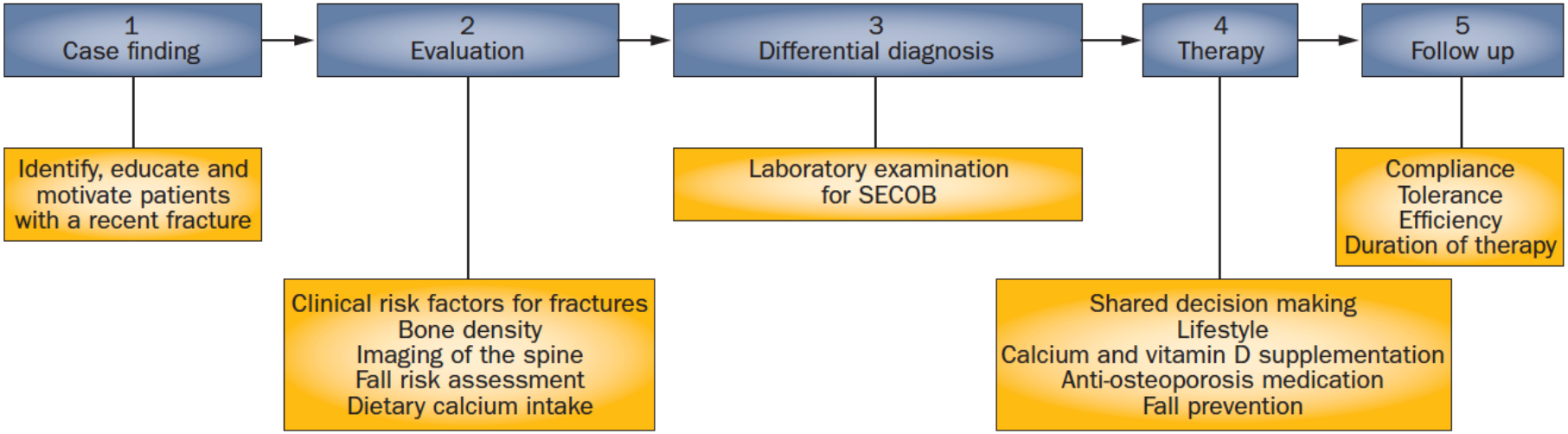
Fig. 2. Cumulative mortality in the pre-fracture and post-fracture period.

Cauley JA et al., Osteoporos Int 2000, 11:556

Figure 3. Kaplan-Meier Survival Curves for the General and Fracture Populations According to Type of Fracture and Age Group

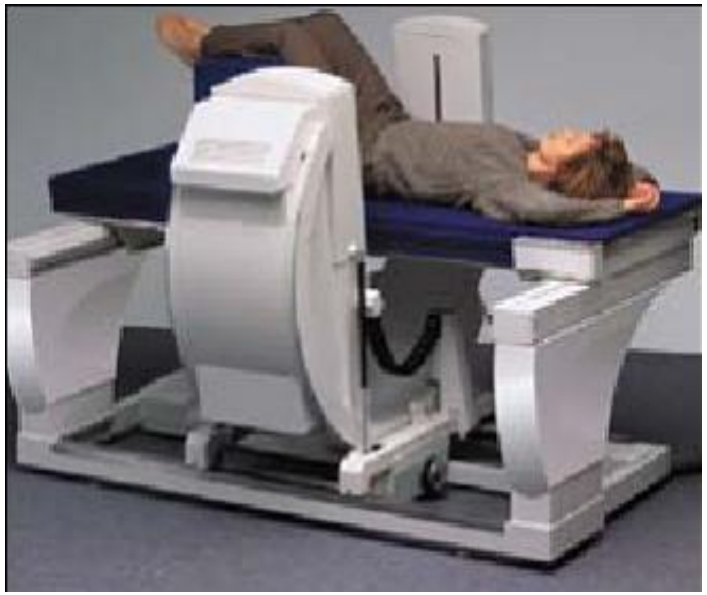


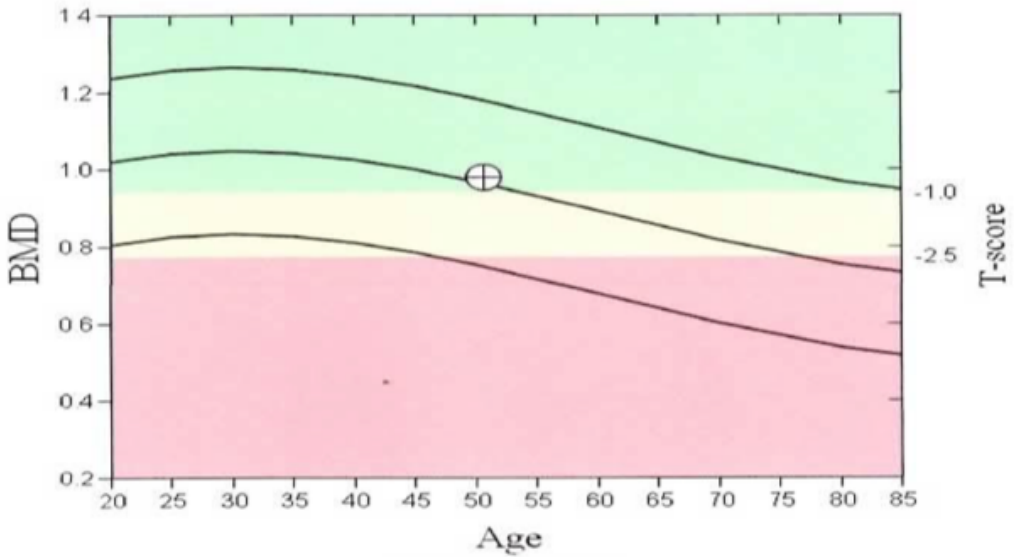
Fracture prevention: evaluation

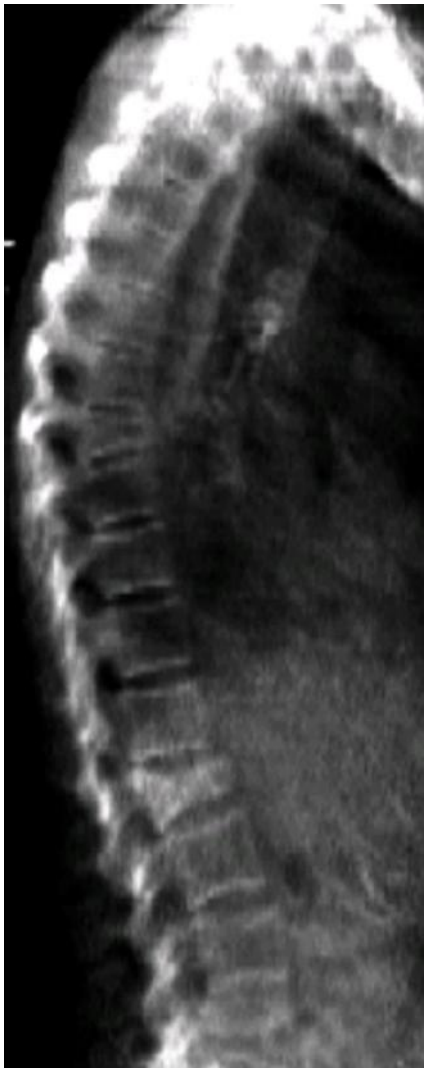


van den Bergh et al. Nature Reviews. Rheumatol. 2012; 163–172

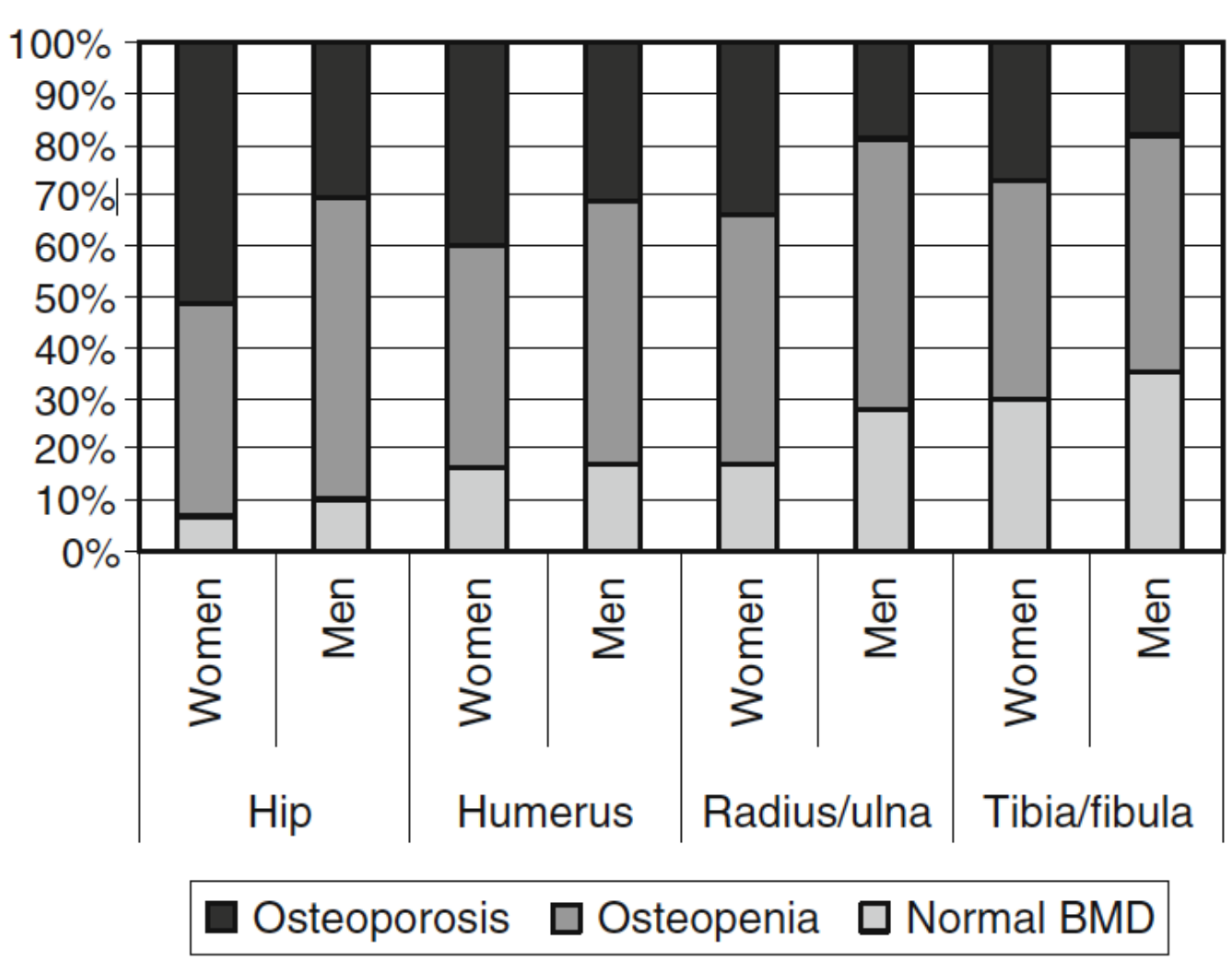
BMD en Vertebral Fracture Assessment (VFA)







DXA evaluation after a fracture



Mean %

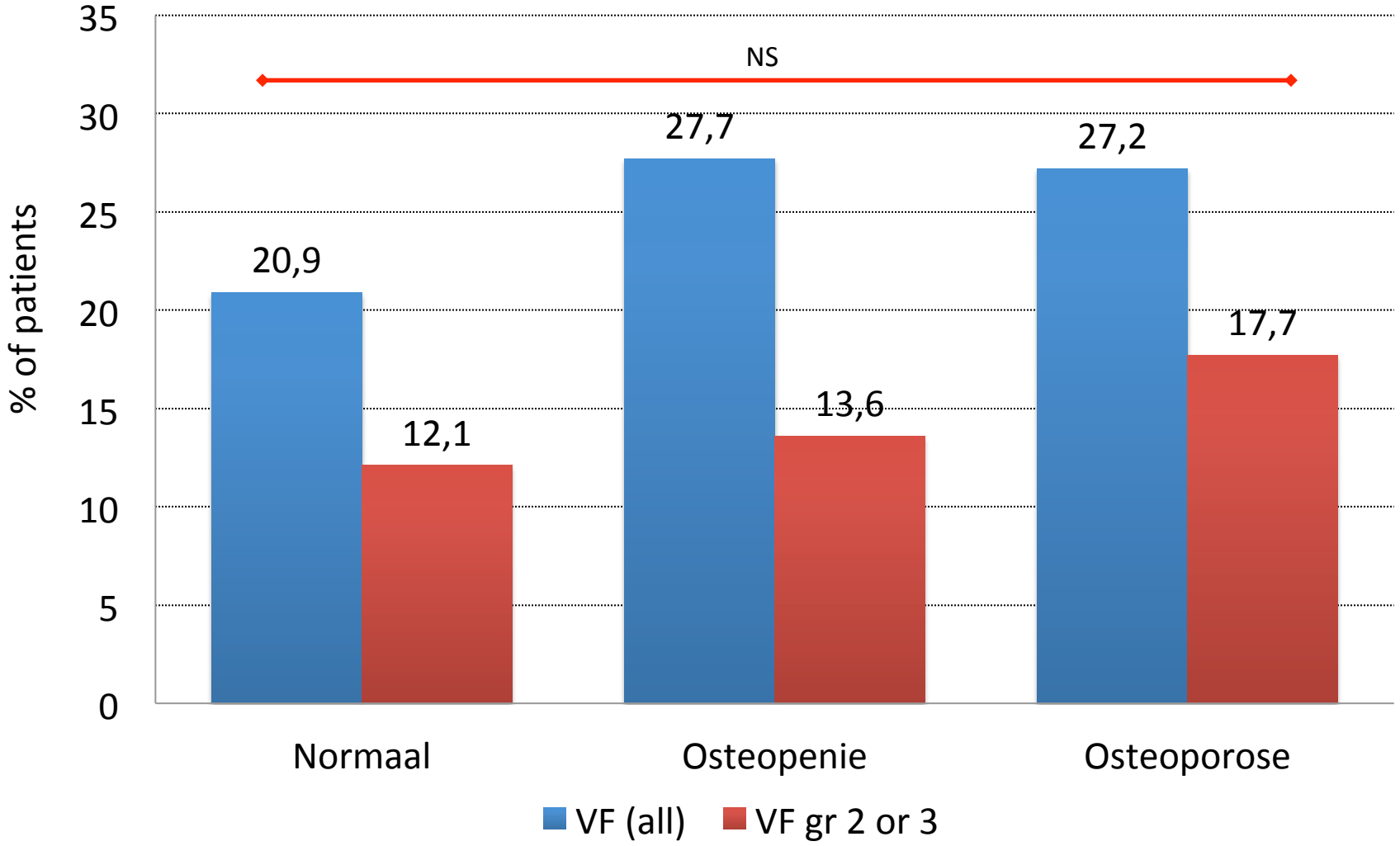
32,2%

46,6%

21,2%

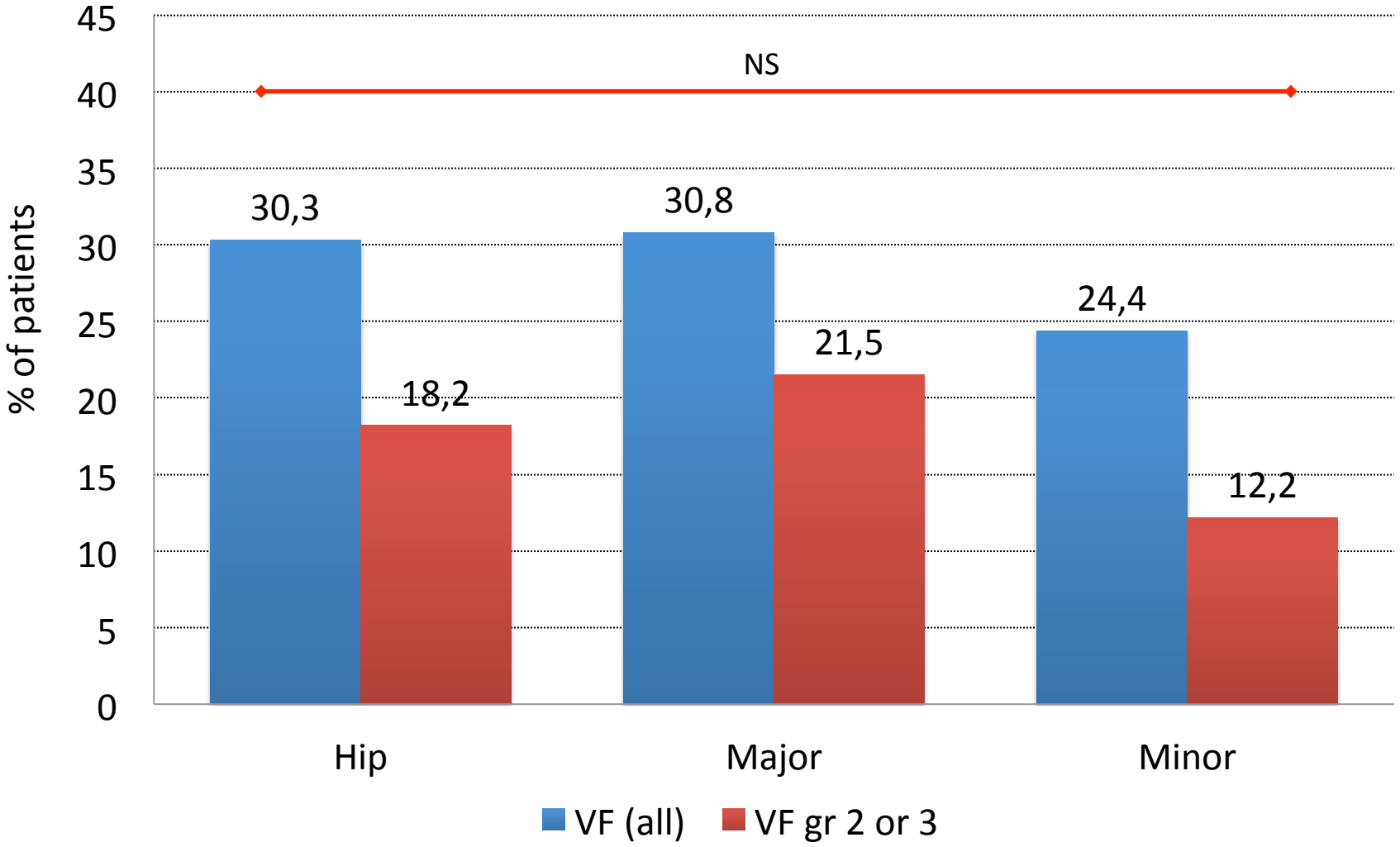
Huntjens et al Osteoporos Int 2011:2129

Percentage of patients with at least one VF



Van der Velde et al. Osteoporos Int 2017:3017

Percentage of patients with at least one VF



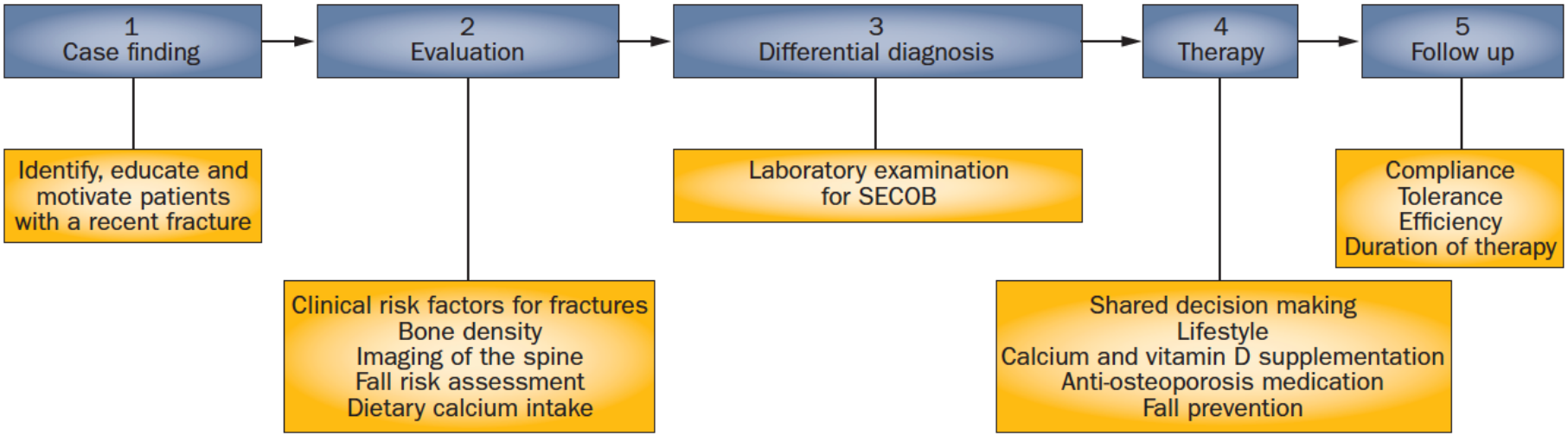
Major: multiple rib, humerus, pelvis, distal femur, and proximal tibia
Minor: all remaining fractures except fingers and toes

Van der Velde et al. Osteoporos Int 2017:3017

Wie behandelen?
50-plussers

	CBO 2011	NHG 2012
• Medicatie		
– *Osteoporose (T<-2.5)*	x	x
– *Wervelfractuur*, onafhankelijk van BMD		
• ≥ 50 jaar	x	
• ≥ 60 jaar		x
– Glucocorticoiden	x	x

Fracture prevention: laboratory examination



van den Bergh et al. Nature Reviews. Rheumatol. 2012; 163–172

Table 1. Overview of SECOBs and other factors that contribute to bone loss or fracture risk or both

Endocrine diseases	*Hematologic and oncologic diseases*	*Medication*
Acromegaly	Hemophilia	Glucocorticoids
Diabetes mellitus	Multiple myeloma	Antidepressants
GH deficiency	MGUS	Antiepileptic drugs
Hypercortisolism	Lymphoma/leukemia	Aromatase inhibitors
Hyperparathyroidism	Systemic mastocytosis	Benzodiazepines
Hyperprolactinemia	Thalassemia	Cyclosporin
Hyperthyroidism	Disseminated carcinoma	Glitazones
Male hypogonadism	Chemotherapy	Gonadotropin-releasing hormone agonists
Premature menopause		Heparin
Central adiposity	*Connective tissue diseases*	Loop diuretics
	Ehlers–Danlos syndrome	Medroxyprogesterone acetate
Gastrointestinal disorders	Marfan's syndrome	Proton-pump inhibitors
Celiac disease	Osteogenesis imperfecta	Thiazolinediones
Chronic biliary tract obstruction	Pseudoxanthoma elasticum	Thyroxine (excessive)
Gastrectomy/gastric bypass		
Inflammatory bowel disease	*Miscellaneous conditions and diseases*	*Other*
Liver cirrhosis	AIDS/HIV	Anorexia nervosa
Malabsorption (other than celiac disease)	Amyloidosis	Osteomalacia
	Chronic metabolic acidosis	
Rheumatic diseases	Chronic obstructive lung disease	*Lifestyle*
Spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis	Congestive heart failure	Alcohol abuse
Rheumatoid arthritis	Depression	Smoking
Systemic lupus erythematosus	End-stage renal disease	Immobilization
Systemic sclerosis	Muscular dystrophy	Low calcium intake
	Sarcoidosis	Low protein intake
	Weight loss	

SECOBs, secondary osteoporosis and other metabolic bone diseases.

Bours et al. Curr Opin Rheumatol 2014, 26:430–439

Contributros

TABLE 2. Prevalence of known contributors to SECOB at presentation with a clinical fracture

Known contributor	Number of patients (percent of total)	Number of Women (percent of all women)	Number of Men (percent of all men)
History of glucocorticoid use	53 (8.5%)	42 (8.7%)	11 (7.6%)
Premature ovarian failure	25 (4.0%)	25 (5.2%)	—
History of alcoholism	16 (2.6%)	4 (0.8%)	12 (8.3%)
History of hyperthyroidism	4 (0.6%)	4 (0.8%)	0
Current anticonvulsant use	6 (1.0%)	5 (1.0%)	1 (0.7%)
History of rheumatoid arthritis or systemic lupus erythematosis	32 (5.2%)	25 (5.2%)	2 (1.4%)
History of COPD	65 (10.4%)	49 (10.2%)	16 (11.1%)
History of CKD	3 (0.5%)	3 (0.6%)	0
History of inflammatory bowel disease or malabsorption	3 (0.5%)	2 (0.4%)	1 (0.7%)
Total (with one or more factors)[a]	144 (23.0%)	115 (23.9%)	29 (20.1%)

COPD, Chronic obstructive pulmonary disease; –, not applicable.

[a] We found a total number of 207 known contributors in 144 patients, and 58 patients had two or more known contributors.

Bours et al. J Clin Endocrinol Metab 2011, 1360-7

TABLE 3. Newly diagnosed contributors to SECOB in men and women with a clinical fracture

	Prevalence of newly diagnosed contributors to SECOB					
	Men (n = 144)		Women (n = 482)		Total (n = 626)	
Disorders	n	%	n	%	n	%
MGUS/myeloma	4/1	2.8/0.7	9/0	1.9/0	13/1	2.1/0.2
CKD						
Stage 3	7	4.9	45	9.3	52	8.3
Stage 4	1	0.7	1	0.2	2	0.3
Hyperparathyroidism (HPT)						
1°[a]	1	0.7	16	3.3	17	2.7
2° due to vitamin D deficiency	11	7.6	38	7.9	49	7.8
2° due to CKD	2	1.4	4	0.8	6	1.0
2° due to vitamin D deficiency and CKD	0	0	9	0.8	9	1.4
Hyperthyroidism[b]	8	5.6	31	6.4	39	6.2
Hypogonadism	12	8.3			12	1.9
Total number of new contributors	47		153		200	
Patients with at least one new contributor[c]	40	27.8	126	26.1	166	26.5

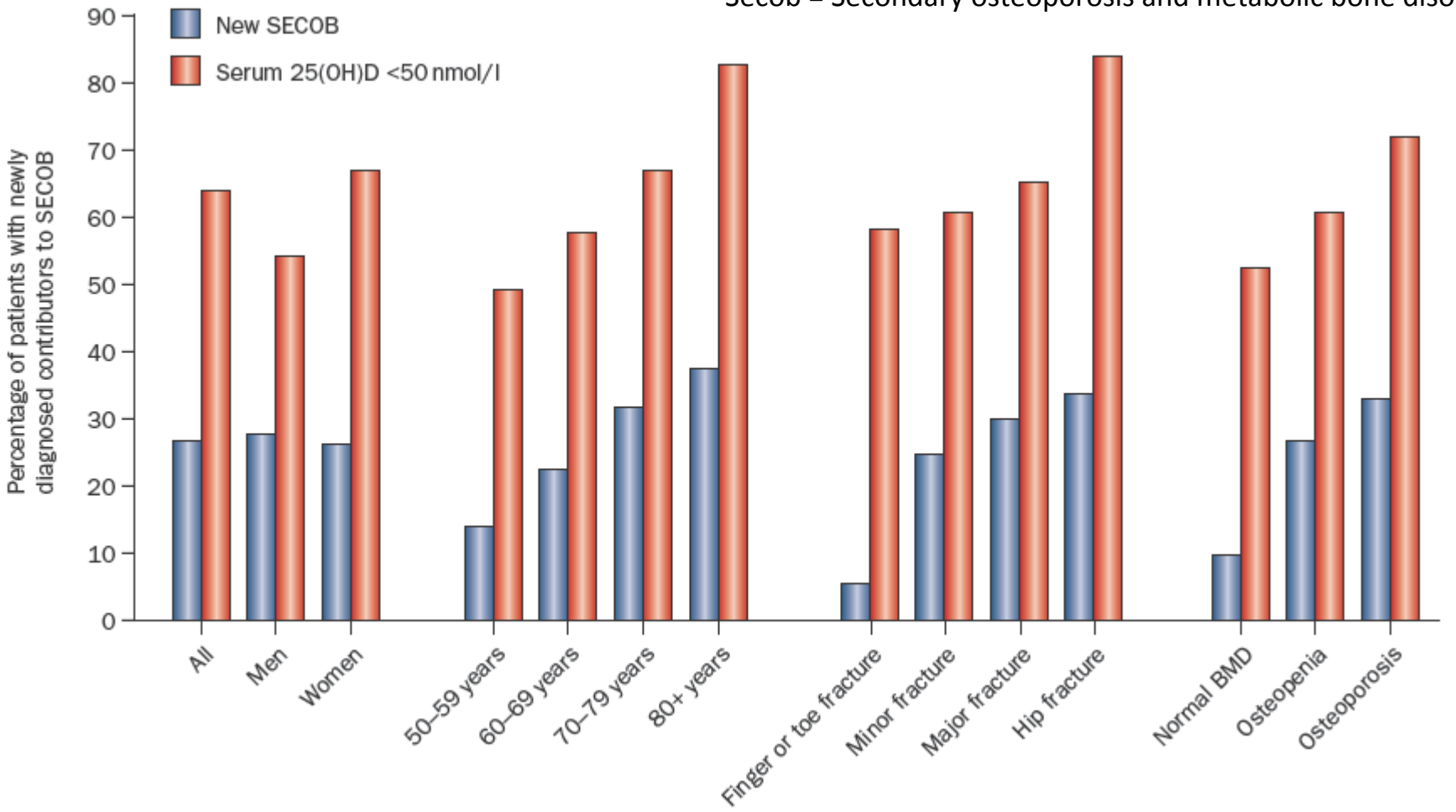
[a] Of the 17 patients with primary hyperparathyroidism (2.7%), 12 (1.9%) had elevated, and five (0.8%) inappropriately normal iPTH levels.

[b] Of the 39 patients with hyperthyroidism (6.2%), 30 (4.8%) were diagnosed with overt and nine (1.4%) with subclinical hyperthyroidism.

Bours, JCM 2011, 1360-7

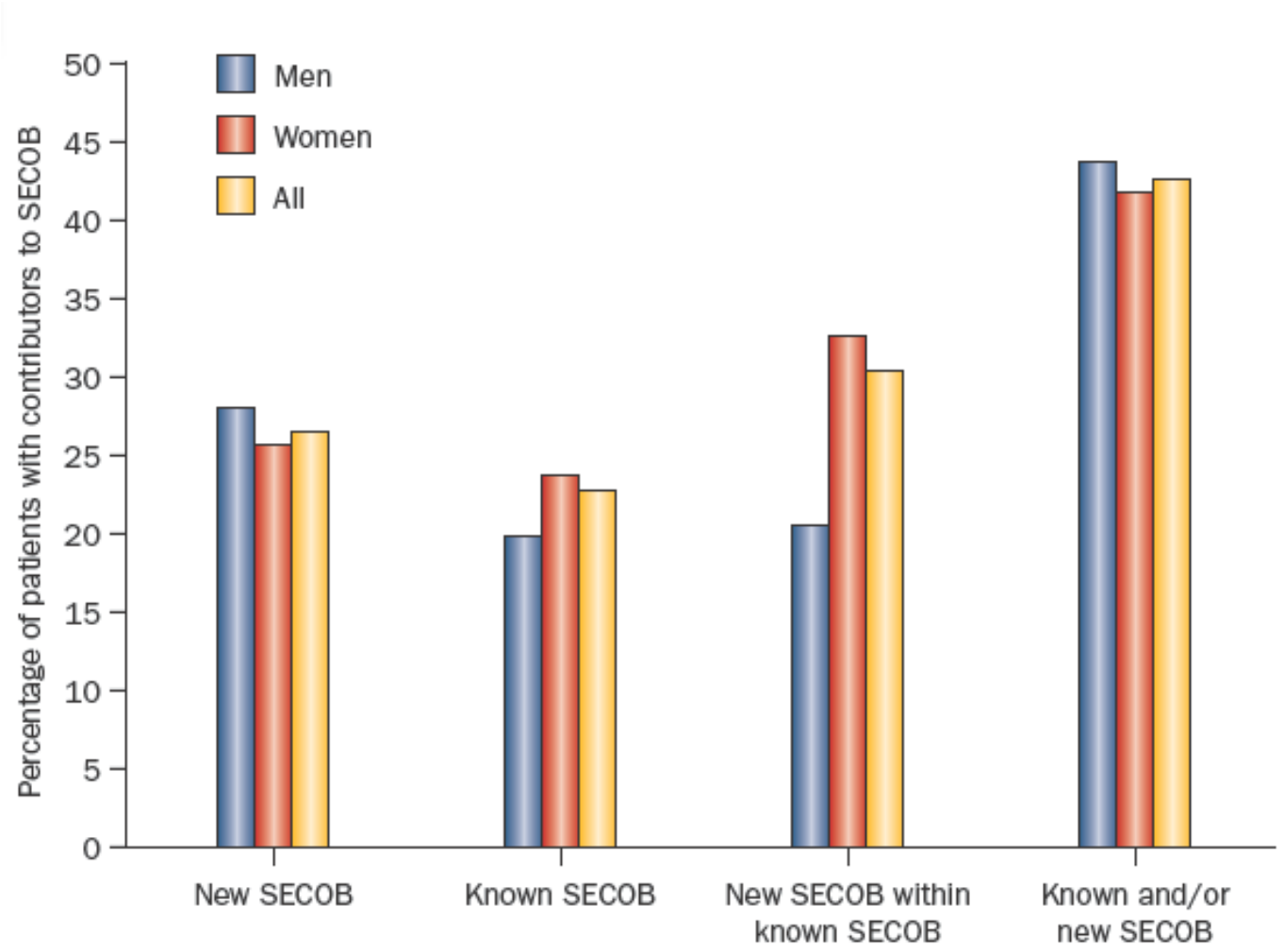
Vitamin D deficiency & SECOB in 50+ patients with a non vertebral fracture

Secob = Secondary osteoporosis and metabolic bone disorders



van den Bergh et al. Nature Reviews. Rheumatol. 2012; 163–172

Onderliggende aandoeningen bij patiënten > 50 jaar met een recente fractuur



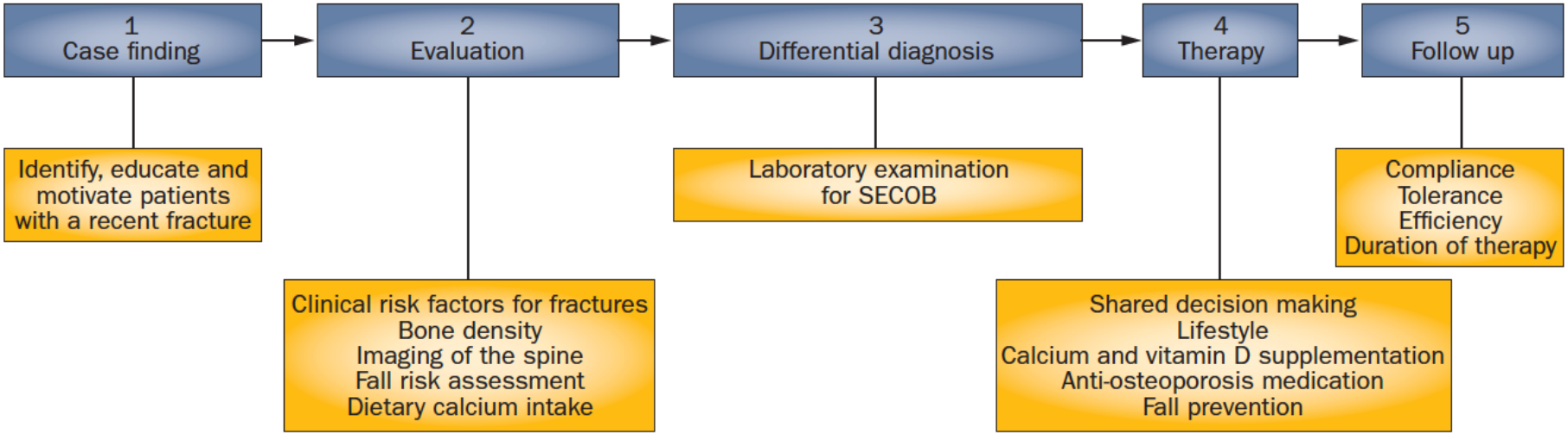
van den Bergh et al. Nature Reviews. Rheumatol. 2012; 163–172

Table 2 Prevalence of secondary factors for bone fragility in patients with a recent fracture grouped according to gender and BMD

	Male ($n=182$)	Female ($n=504$)	Normal BMD ($n=102$)	Osteopenia ($n=385$)	Osteoporosis ($n=199$)	Total number patients ($n=686$)
FRAX clinical risk factors:						
Smoking (%)	42 (23)	80 (16)	15 (16)	64 (17)	43 (22)	122 (18)
Use of >3 IU alcohol (%)	30 (17)	49 (10)	13 (13)	44 (11)	22 (11)	79 (12)
Glucocorticoids (%)	14 (8)	66 (13)	11 (11)	42 (11)	27 (14)	80 (12)
Rheumatoid arthritis (%)	2 (1)	20 (4)	3 (3)	11 (3)	8 (4)	22 (3)
Early menopause (%)	–	96 (19)	13 (13)	45 (12)	38 (19)	96 (14)
Laboratory-based factors						
Chronic kidney disease (%)	15 (8)	77 (15)	10 (10)	53 (14)	29 (15)	92 (13)
MGUS (%)	25 (14)	65 (13)	5 (5)	46 (12)	39 (20)	90 (13)
1° hyperparathyroidism (%)	–	7 (1)	1 (1)	4 (1)	2 (1)	7 (1)
2° hyperparathyroidism (%)	7 (4)	35 (7)	3 (3)	25 (7)	14 (7)	42 (6)
Hyperthyroidism (%)	1 (1)	12 (2)	1 (1)	7 (2)	5 (3)	13 (2)
Hypogonadism (%)	8 (4)	–	1 (1)	6 (2)	1 (1)	8 (1)
Patients with >1 factor (%)	93 (51)	297 (59)	48 (47)	219 (57)	123 (62)	390 (57)

Malgo et al. Arch Osteoporos (2016) 11: 12

Fracture prevention: therapy



van den Bergh et al. Nature Reviews. Rheumatol. 2012; 163–172

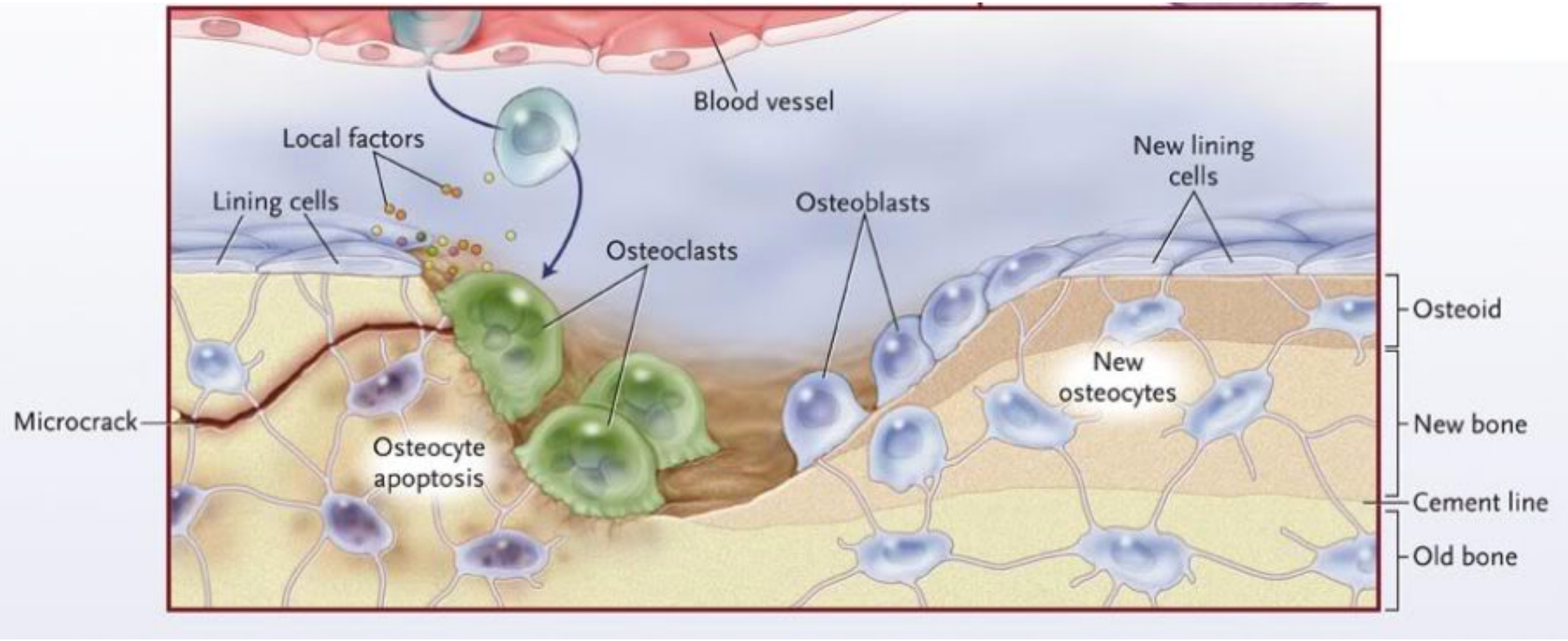
Behandeling met Calcium en vitamin D

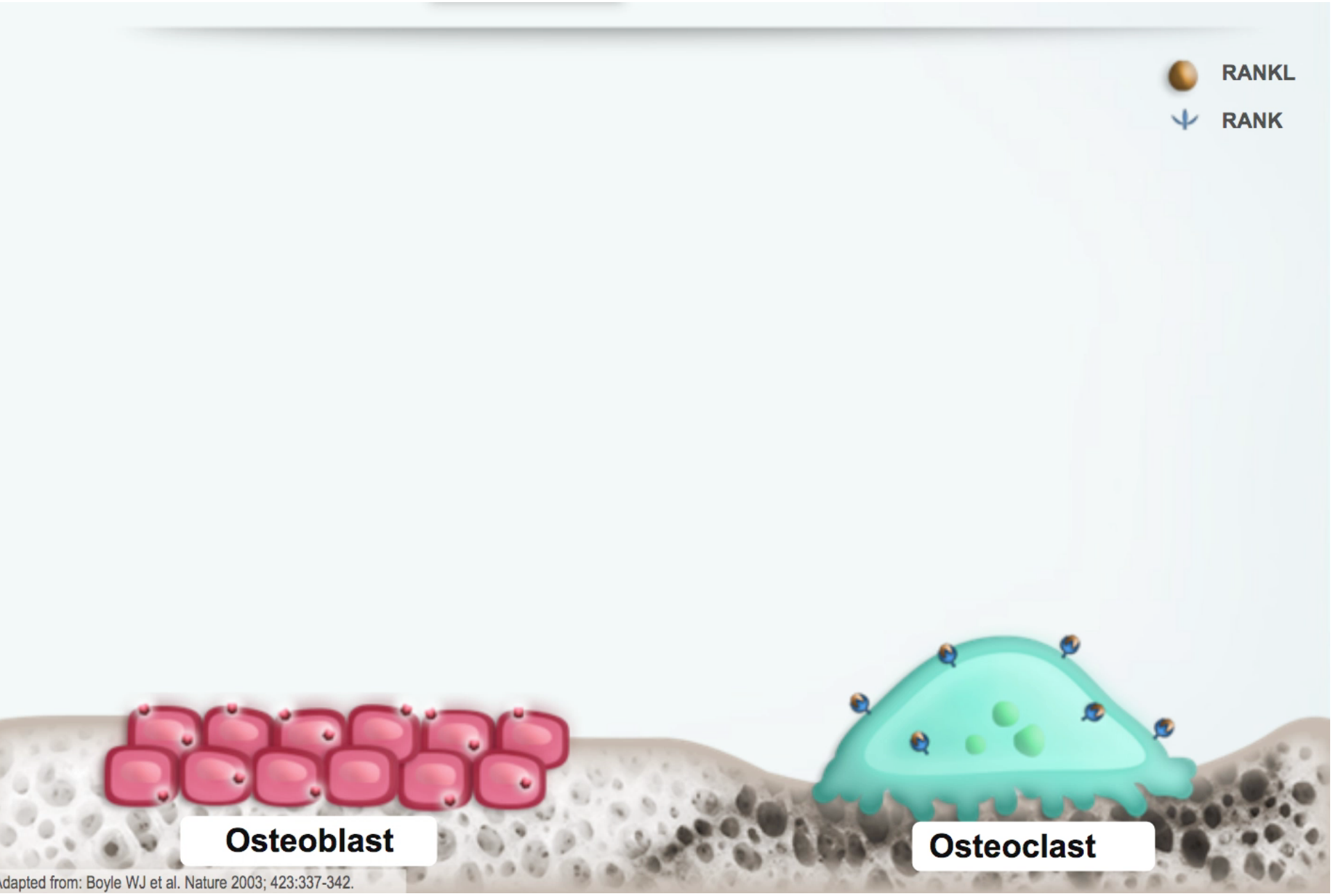
- Streef naar totale calcium inname 1000-1200mg/dag
  - Geen zuivelproducten — 1000 mg supplement
  - 1-2 zuivelproducten — 500 mg supplement
  - 3-4 zuivelproducten — geen aanpassing nodig

- Standaard suppletie met 1000 mg wordt niet aanbevolen vanwege het (mogelijk) toegenomen risico op CV aandoeningen

- Vitamine D suppletie: 800 IU/dag
  - Bij osteoporose
  - Mensen in verpleeg- of verzorgingshuis
  - Bij fractuur > 50 jaar

Botstofwisseling



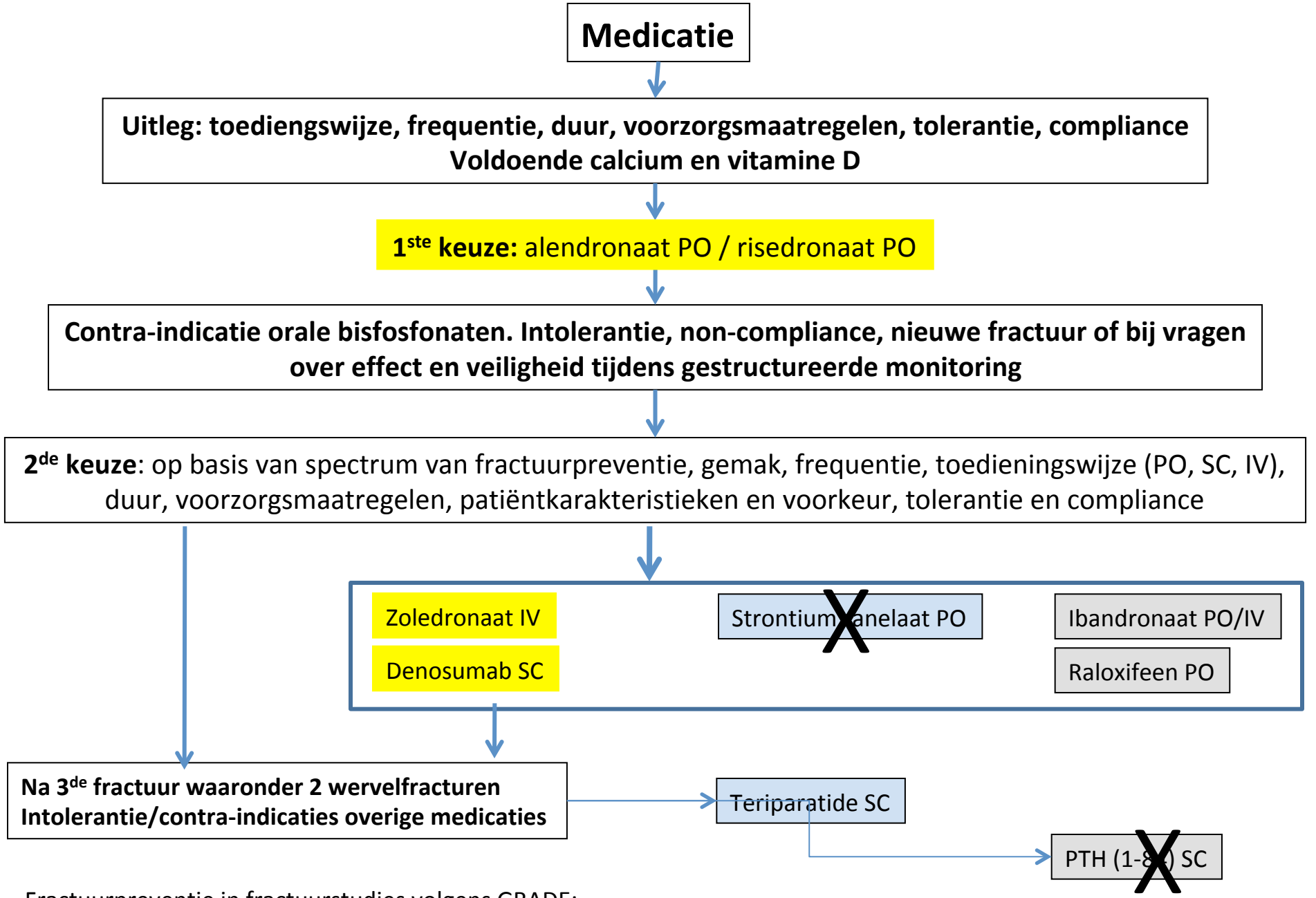


Adapted from: Boyle WJ et al. Nature 2003; 423:337-342.

Effect van medicatie in de primaire analyses van RCTs met fractuurpreventie als eindpunt

Medicament		Wervel-fracturen	Niet wervel-fracturen	Heupfracturen
	Follow-up	Relatief effect	Relatief effect	Relatief effect
Alendronaat	1-4 jaar	0.55 (0.45-0.67)	0.84 (0.74-0.94)	0.61 (0.4-0.92)
Risedronaat	2-3 jaar	0.63 (0.51-0.77)	0.80 (0.72-0.90)	0.74 (0.59-0.94)
Zoledronaat	2 jaar	0.30 (0.24-0.38)	0.75 (0.64-0.87)	0.59 (0.42-0.83)
Denosumab	3 jaar	0.32 (0.26-0.41)	0.80 (0.67-0.95)	0.60 (0.37-0.96)
Etidronaat	2-4 jaar	0.59 (0.36-0.96)	1.07 (0.72-1.06)	1.20 (0.37-3.88)
Strontiumranelaat	3 jaar	0.63 (0.56-0.71)	0.86 (0.75-0.98)	Niet te bepalen
Teriparatide	1.5 jaar	0.36 (0.28-0.47)	0.62 (0.48-0.82)	Niet te bepalen
Raloxifen	3 jaar	0.60 (0.50-0.70)	0.91 (0.79-1.06)	Niet te bepalen
Ibandronaat	3 jaar	0.50 (0.34-0.74)	Niet te bepalen	Niet te bepalen

CBO Osteoporose en Fractuurpreventie, 2011


Medicatie
Uitleg: toediengswijze, frequentie, duur, voorzorgsmaatregelen, tolerantie, compliance
Voldoende calcium en vitamine D
1ste keuze: alendronaat PO / risedronaat PO
Contra-indicatie orale bisfosfonaten. Intolerantie, non-compliance, nieuwe fractuur of bij vragen over effect en veiligheid tijdens gestructureerde monitoring
2de keuze: op basis van spectrum van fractuurpreventie, gemak, frequentie, toedieningswijze (PO, SC, IV), duur, voorzorgsmaatregelen, patiëntkarakteristieken en voorkeur, tolerantie en compliance
Zoledronaat IV
Denosumab SC
Strontium ranelaat PO
Ibandronaat PO/IV
Raloxifeen PO
Na 3de fractuur waaronder 2 wervelfracturen
Intolerantie/contra-indicaties overige medicaties
Teriparatide SC
PTH (1-84) SC
Fractuurpreventie in fractuurstudies volgens GRADE:
Wervel, niet-Wervel en Heup
Wervel,niet-Wervel
Wervel

Nieuwe ontwikkelingen

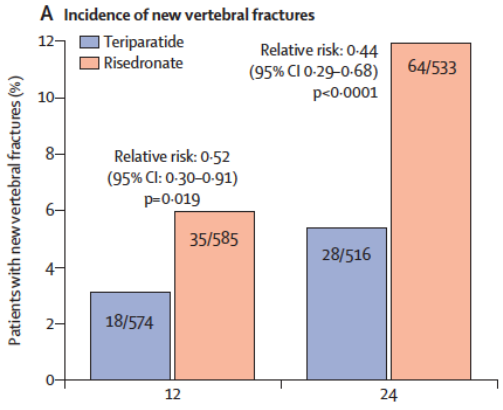
- **Teriparatide vs Risedronaat**
- Abaloparatide
- Romosozumab vs Alendronaat

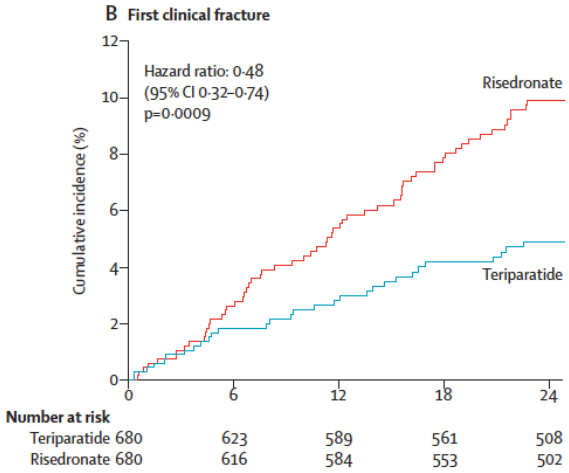
Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial

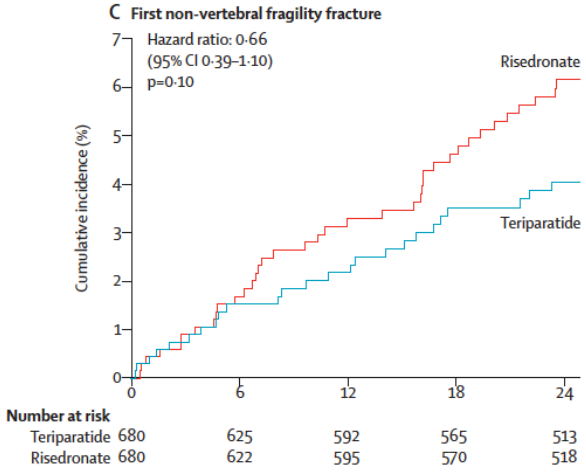
David L Kendler, Fernando Marin, Cristiano A F Zerbini, Luis A Russo, Susan L Greenspan, Vit Zikan, Alicia Bagur, Jorge Malouf-Sierra, Péter Lakatos, Astrid Fahrleitner-Pammer, Eric Lespessailles, Salvatore Minisola, Jean Jacques Body, Piet Geusens, Rüdiger Möricke, Pedro López-Romero

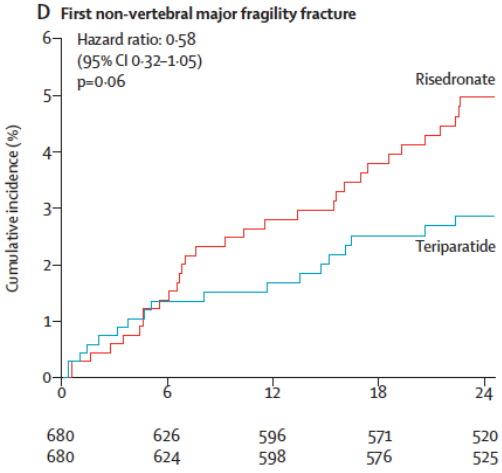
Lancet
Published Online
November 9, 2017
http://dx.doi.org/10.1016/
S0140-6736(17)32137-2

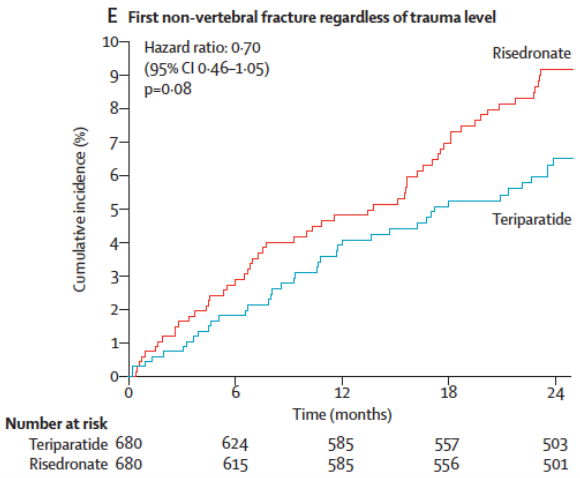
Post-menopausal women > 45 years, T score <–1.50
At least two moderate or one severe prevalent vertebral fragility fracture











Nieuwe ontwikkelingen

- Teriparatide vs Risedronaat
- **Abaloparatide**
- Romosozumab vs Alendronaat

JAMA | Original Investigation

Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis
A Randomized Clinical Trial

Paul D. Miller, MD; Gary Hattersley, PhD; Bente Juel Riis, MD; Gregory C. Williams, PhD; Edith Lau, MD; Luis Augusto Russo, MD, PhD; Peter Alexandersen, MD; Cristiano A. F. Zerbini, MD; Ming-yi Hu, PhD; Alan G. Harris, MD; Lorraine A. Fitzpatrick, MD; Felicia Cosman, MD; Claus Christiansen, MD; for the ACTIVE Study Investigators

JAMA. 2016;316(7):722–733

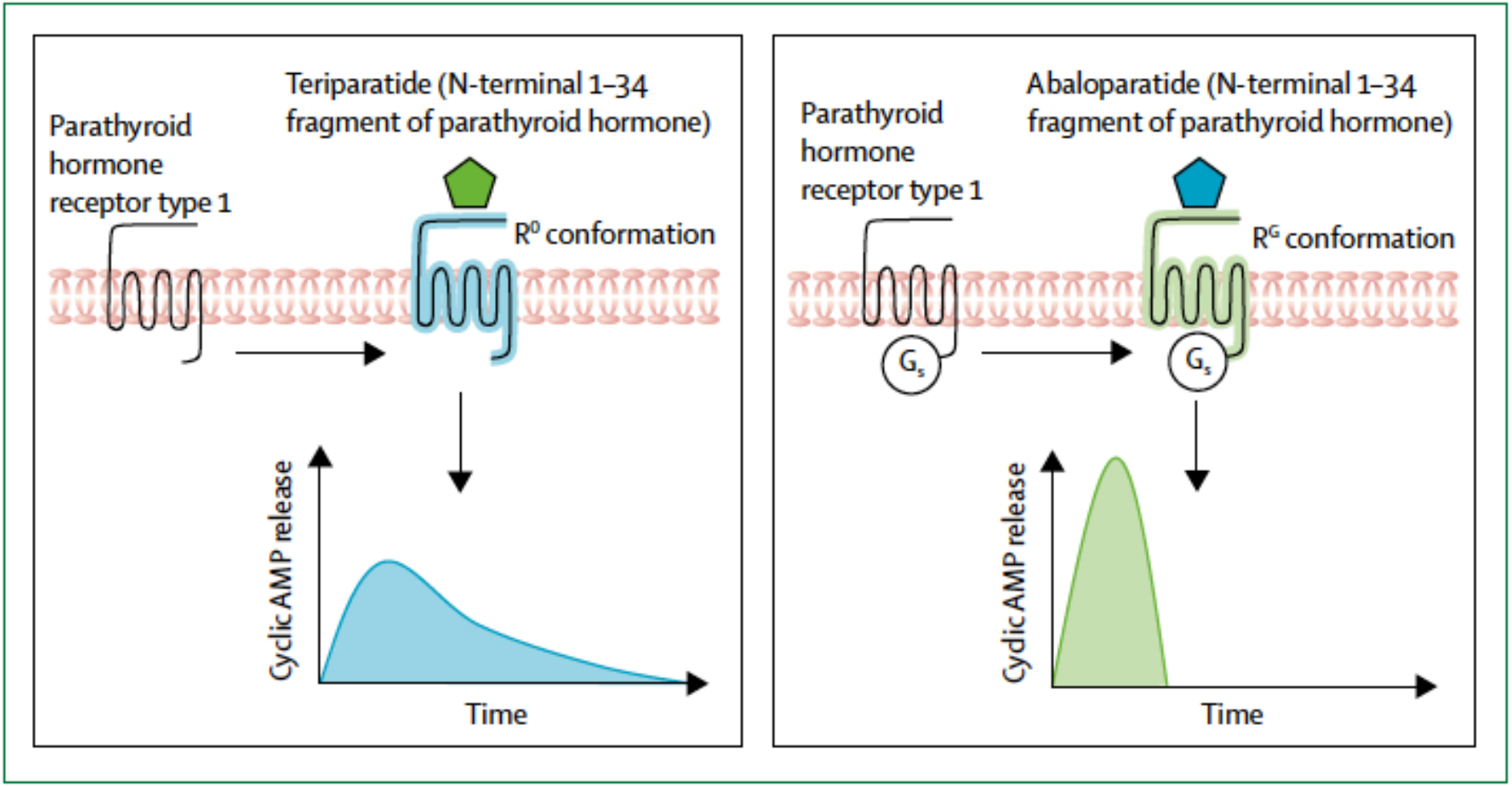


***Figure 1*: Differential effects of teriparatide (parathyroid hormone 1–34) versus abaloparatide (parathyroid hormone-related peptide 1–34) on parathyroid hormone receptor 1 signalling**

(A) Teriparatide activates parathyroid hormone receptor 1 towards the R^0 conformation, which results in intracellular release of the second messenger cyclic AMP. (B) By contrast, abaloparatide activates the receptor towards the R^G conformation with a more transient cyclic AMP increase. AMP=adenosine monophosphate.

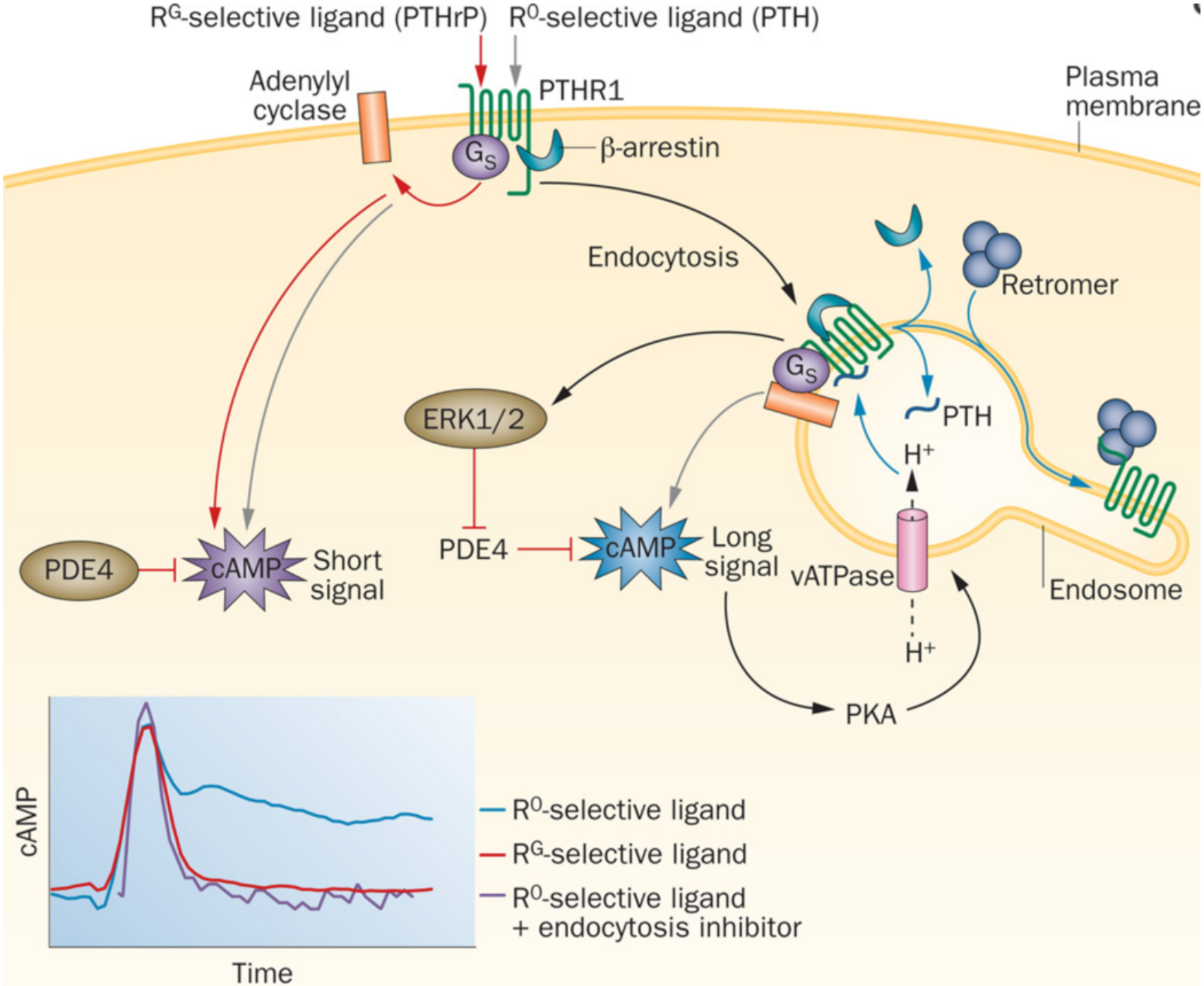

R^G-selective ligand (PTHrP)
R^0-selective ligand (PTH)
Adenylyl cyclase
PTHR1
Plasma membrane
β-arrestin
G_S
Endocytosis
Retromer
PTH
H+
ERK1/2
PDE4
cAMP
Short signal
PDE4
cAMP
Long signal
vATPase
Endosome
H+
PKA
cAMP
Time
R^0-selective ligand
R^G-selective ligand
R^0-selective ligand + endocytosis inhibitor

Table 2. Fracture Efficacy End Points After 18 Months of Treatment

	Study Participants With Fracture, No. (%)[a]			Abaloparatide vs Placebo		
	Abaloparatide (n = 824)	Placebo (n = 821)	Teriparatide (n = 818)	RD (95% CI)[b]	HR (95% CI)[c]	*P* Value[d]
Primary End Point						
New vertebral fracture	4 (0.6)	30 (4.2)	6 (0.8)	−3.64 (−5.42 to −2.10)	RR, 0.14 (0.05 to 0.39)[e]	<.001
Secondary End Point						
Nonvertebral fracture	18 (2.7)	33 (4.7)	24 (3.3)	−2.01 (−4.02 to −0.00)	0.57 (0.32 to 1.00)	.049
Exploratory End Points						
Major osteoporotic fracture	10 (1.5)	34 (6.2)	23 (3.1)	−4.73 (−8.07 to −1.40)	0.30 (0.15 to 0.61)	<.001
Clinical fracture	27 (4.0)	49 (8.3)	35 (4.8)	−4.24 (−7.93 to −0.54)	0.57 (0.35 to 0.91)	.02

Table 2. Fracture Efficacy End Points After 18 Months of Treatment

	Study Participants With Fracture, No. (%)[a]			Abaloparatide vs Placebo		
	Abaloparatide (n = 824)	Placebo (n = 821)	Teriparatide (n = 818)	RD (95% CI)[b]	HR (95% CI)[c]	*P* Value[d]
Primary End Point						
New vertebral fracture	4 (0.6)	30 (4.2)	6 (0.8)	−3.64 (−5.42 to −2.10)	RR, 0.14 (0.05 to 0.39)[e]	<.001
Secondary End Point						
Nonvertebral fracture	18 (2.7)	33 (4.7)	24 (3.3)	−2.01 (−4.02 to −0.00)	0.57 (0.32 to 1.00)	.049
Exploratory End Points						
Major osteoporotic fracture	10 (1.5)	34 (6.2)	23 (3.1)	−4.73 (−8.07 to −1.40)	0.30 (0.15 to 0.61)	<.001
Clinical fracture	27 (4.0)	49 (8.3)	35 (4.8)	−4.24 (−7.93 to −0.54)	0.57 (0.35 to 0.91)	.02

Nieuwe ontwikkelingen

- Teriparatide vs Risedronaat
- Abaloparatide
- **Romosozumab vs Alendronaat**

Original Article

Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

Kenneth G. Saag, M.D., Jeffrey Petersen, M.D., Maria Luisa Brandi, M.D., Andrew C. Karaplis, M.D., Ph.D., Mattias Lorentzon, M.D., Ph.D., Thierry Thomas, M.D., Ph.D., Judy Maddox, D.O., Michelle Fan, Ph.D., Paul D. Meisner, Pharm.D., and Andreas Grauer, M.D.

N Engl J Med
Volume 377(15):1417-1427
October 12, 2017

The NEW ENGLAND JOURNAL of MEDICINE

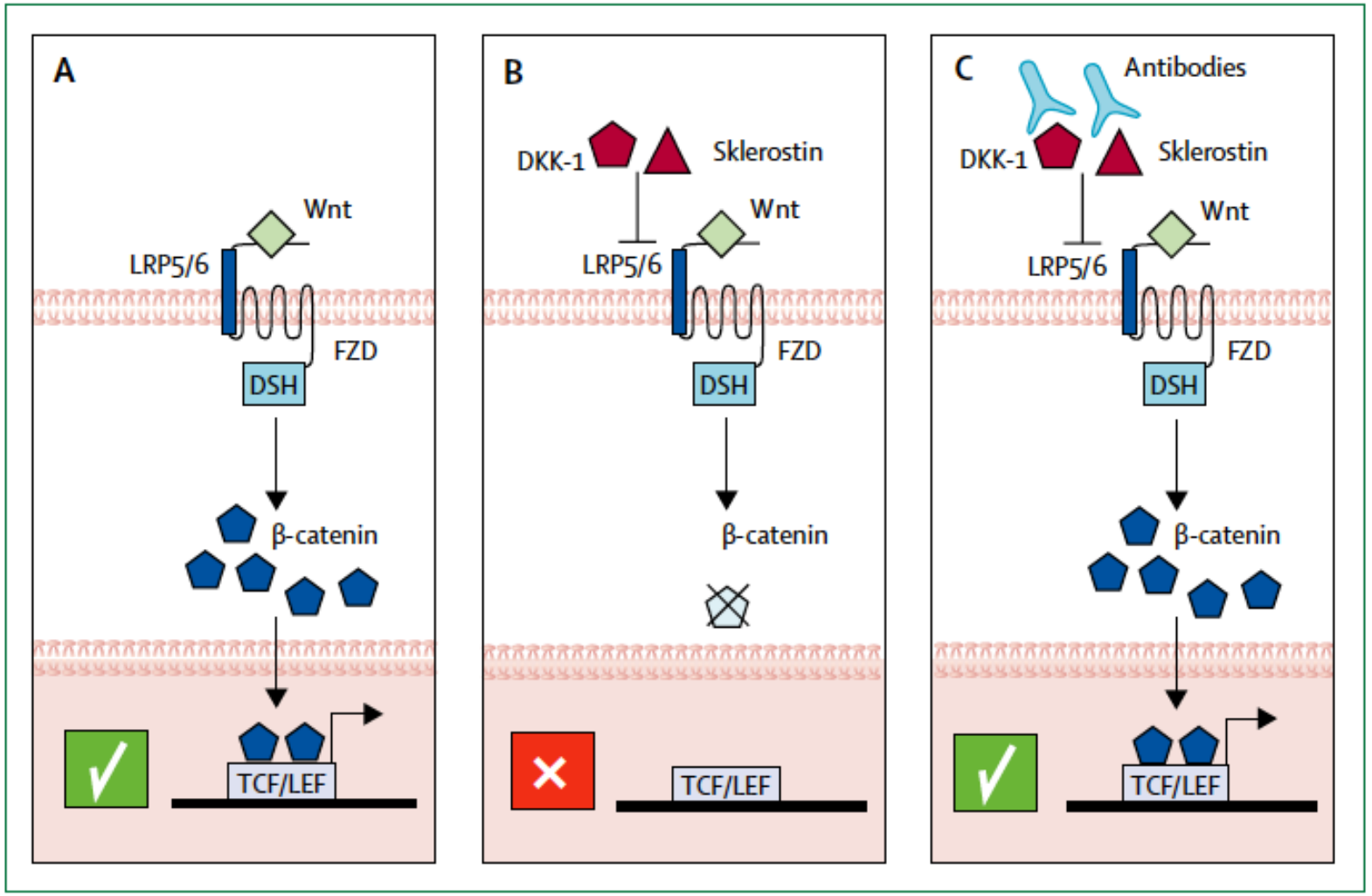
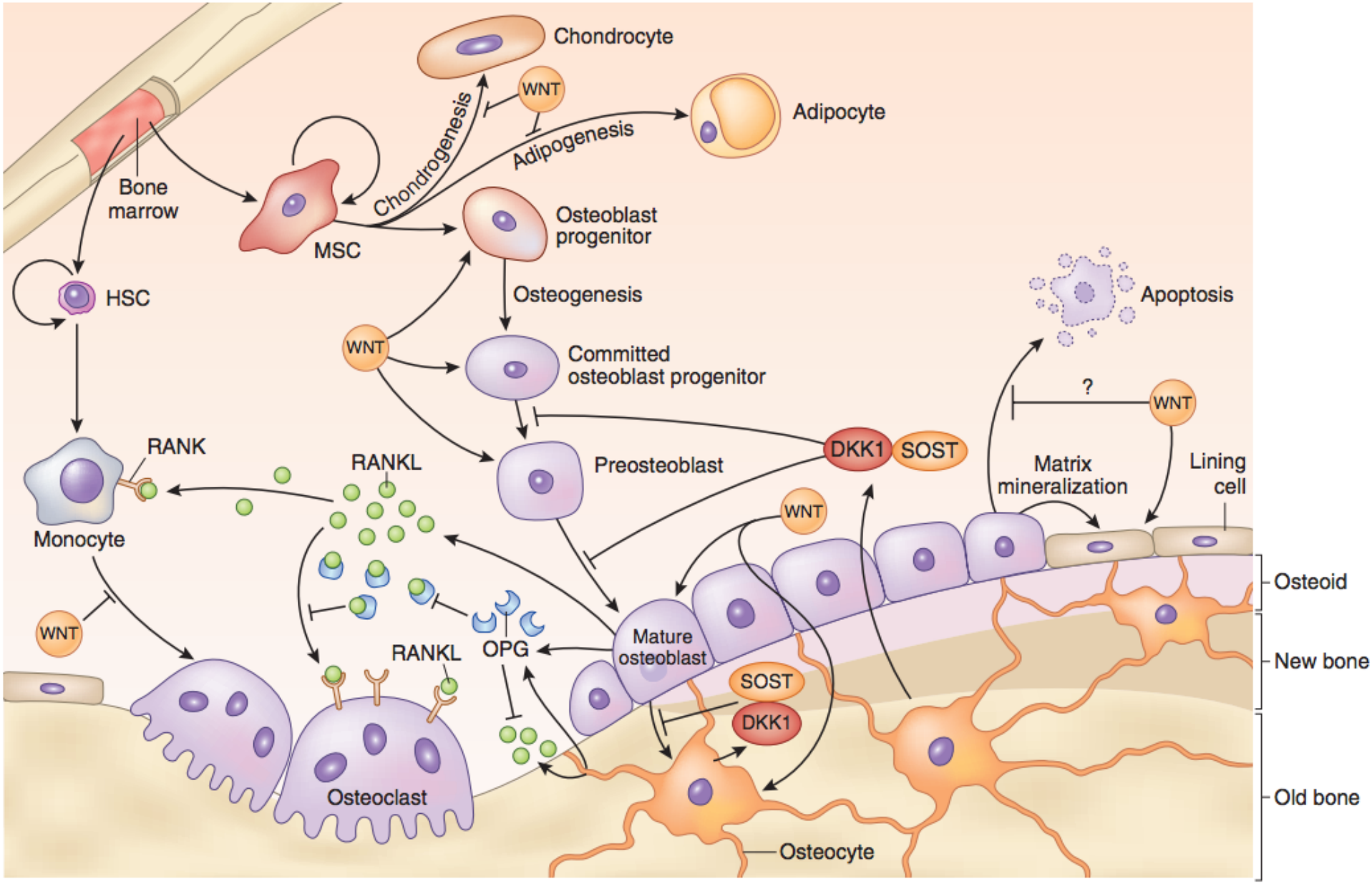
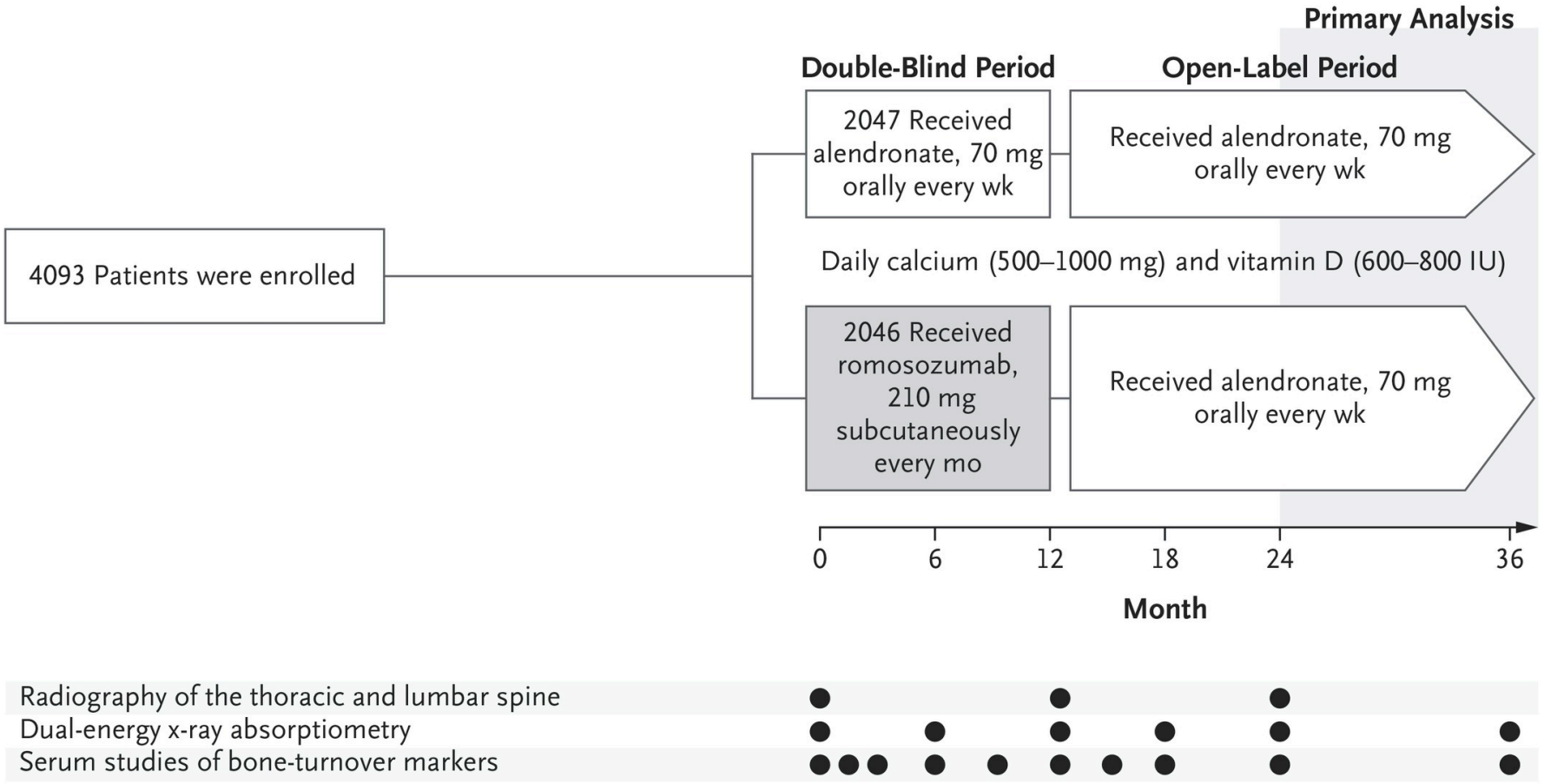


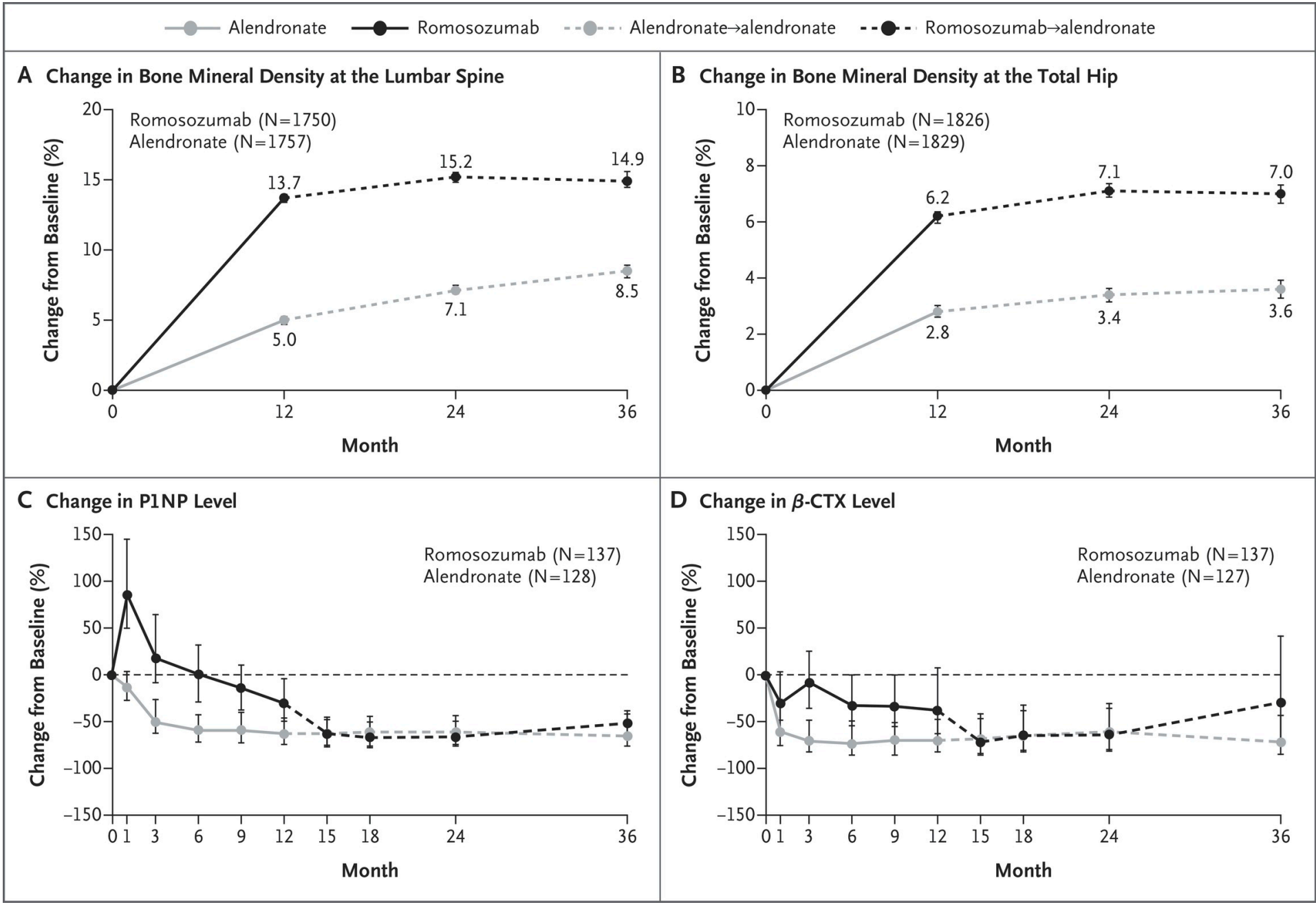
***Figure 2*: Overview of the Wnt signalling pathway—effects of ligands, inhibitors, and targeted therapies**
(A) After binding of Wnt to the LRP5/6 receptor, β-catenin translocates into the nucleus, binds to TCF/LEF transcription factors, and stimulates transcription of osteoblast genes, which results in enhanced bone formation. (B) The endogenous Wnt inhibitors sclerostin and DKK-1 interfere with Wnt signal transduction, resulting in less β-catenin translocation into the nucleus. Osteoblastic functions and bone formation is reduced. (C) Antibodies against sclerostin or DKK-1, or both, neutralise the Wnt inhibitors, thus restoring the scenario of unopposed Wnt signalling as depicted in panel A, which leads to enhanced osteoblastic bone formation. LRP5=low-density lipoprotein receptor-related protein 5. FZD=frizzled. DSH=dishevelled. DKK-1=dickkopf-related protein 1.



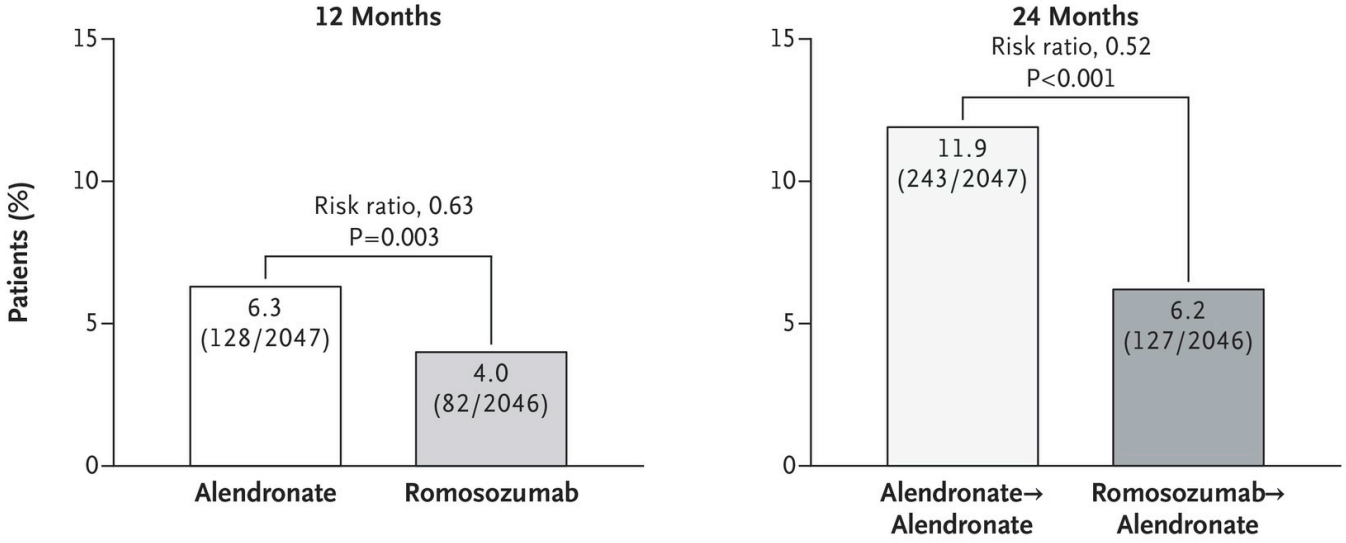
Baron et al. Nature Medicine 2013: 179



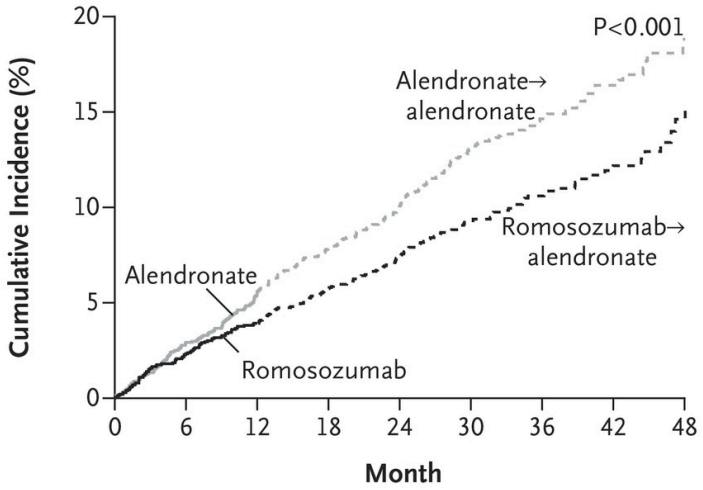
Saag KG et al. N Engl J Med 2017;377:1417-1427


Alendronate
Romosozumab
Alendronate→alendronate
Romosozumab→alendronate
A Change in Bone Mineral Density at the Lumbar Spine
Romosozumab (N=1750)
Alendronate (N=1757)
Change from Baseline (%)
20
15
10
5
0
13.7
15.2
14.9
8.5
7.1
5.0
0
12
24
36
Month
B Change in Bone Mineral Density at the Total Hip
Romosozumab (N=1826)
Alendronate (N=1829)
Change from Baseline (%)
10
8
6
4
2
0
6.2
7.1
7.0
3.6
3.4
2.8
0
12
24
36
Month
C Change in P1NP Level
Romosozumab (N=137)
Alendronate (N=128)
Change from Baseline (%)
150
100
50
0
−50
−100
−150
0 1 3 6 9 12 15 18 24 36
Month
D Change in β-CTX Level
Romosozumab (N=137)
Alendronate (N=127)
Change from Baseline (%)
150
100
50
0
−50
−100
−150
0 1 3 6 9 12 15 18 24 36
Month

A Incidence of New Vertebral Fracture

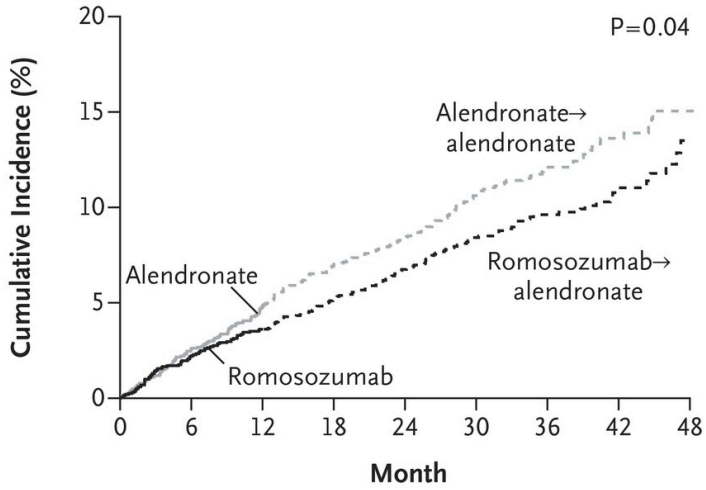


B First Clinical Fracture in Time-to-Event Analysis



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

C First Nonvertebral Fracture in Time-to-Event Analysis

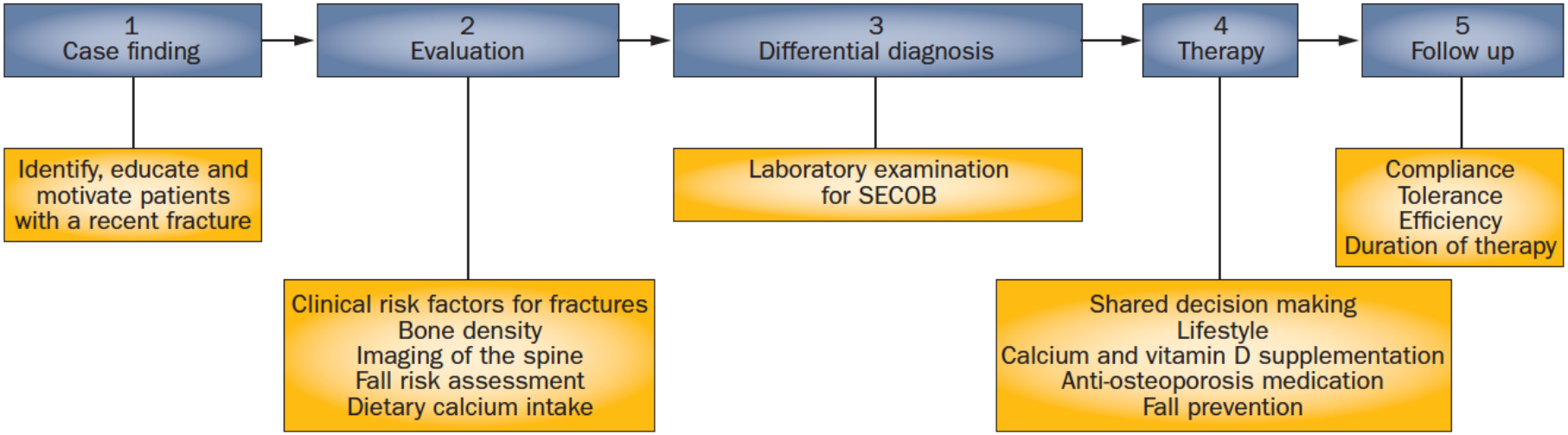


No. at Risk									
Alendronate	2047	1873	1755						
Romosozumab	2046	1867	1776						
Alendronate→ alendronate				1661	1590	1097	697	330	110
Romosozumab→ alendronate				1693	1627	1114	714	350	109

Event	Month 12: Double-Blind Period	
	Alendronate (N=2014)	Romosozumab (N=2040)
	number of pati	
Adjudicated serious cardiovascular event‡	38 (1.9)	50 (2.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)
Cerebrovascular event	7 (0.3)	16 (0.8)
Heart failure	8 (0.4)	4 (0.2)
Death	12 (0.6)	17 (0.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0

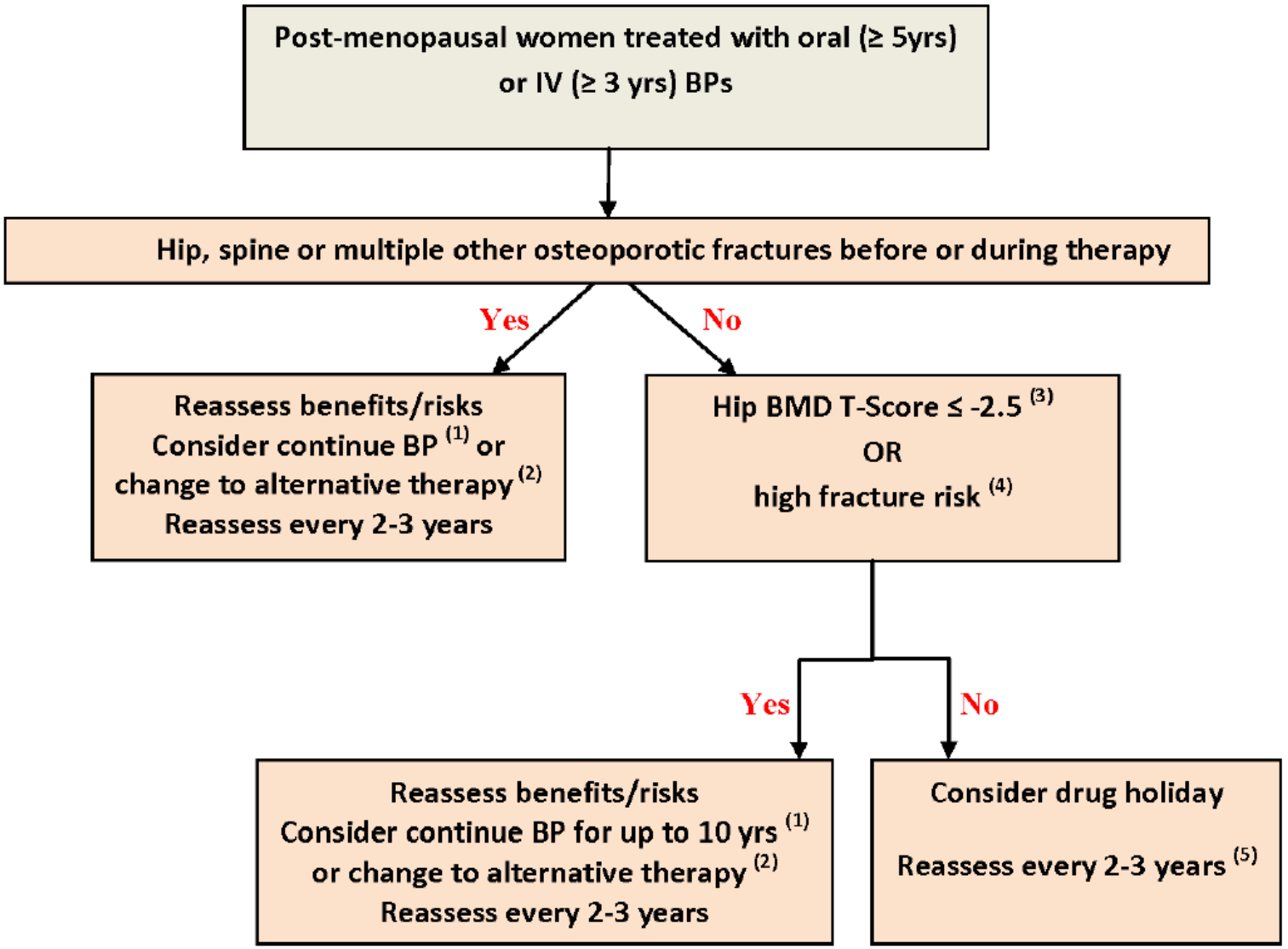
Event	12 Months	
	Placebo (N=3576)	Romosozumab (N=3581)
		number
Adverse event during treatment†	2850 (79.7)	2806 (78.4)
Arthralgia	429 (12.0)	467 (13.0)
Nasopharyngitis	438 (12.2)	459 (12.8)
Back pain	378 (10.6)	375 (10.5)
Serious adverse event	312 (8.7)	344 (9.6)
Adjudicated serious cardiovascular event‡	41 (1.1)	44 (1.2)

Fracture prevention: follow-up



van den Bergh et al. Nature Reviews. Rheumatol. 2012; 163–172

Approach for Management of Postmenopausal Women on Long Term Bisphosphonate Therapy



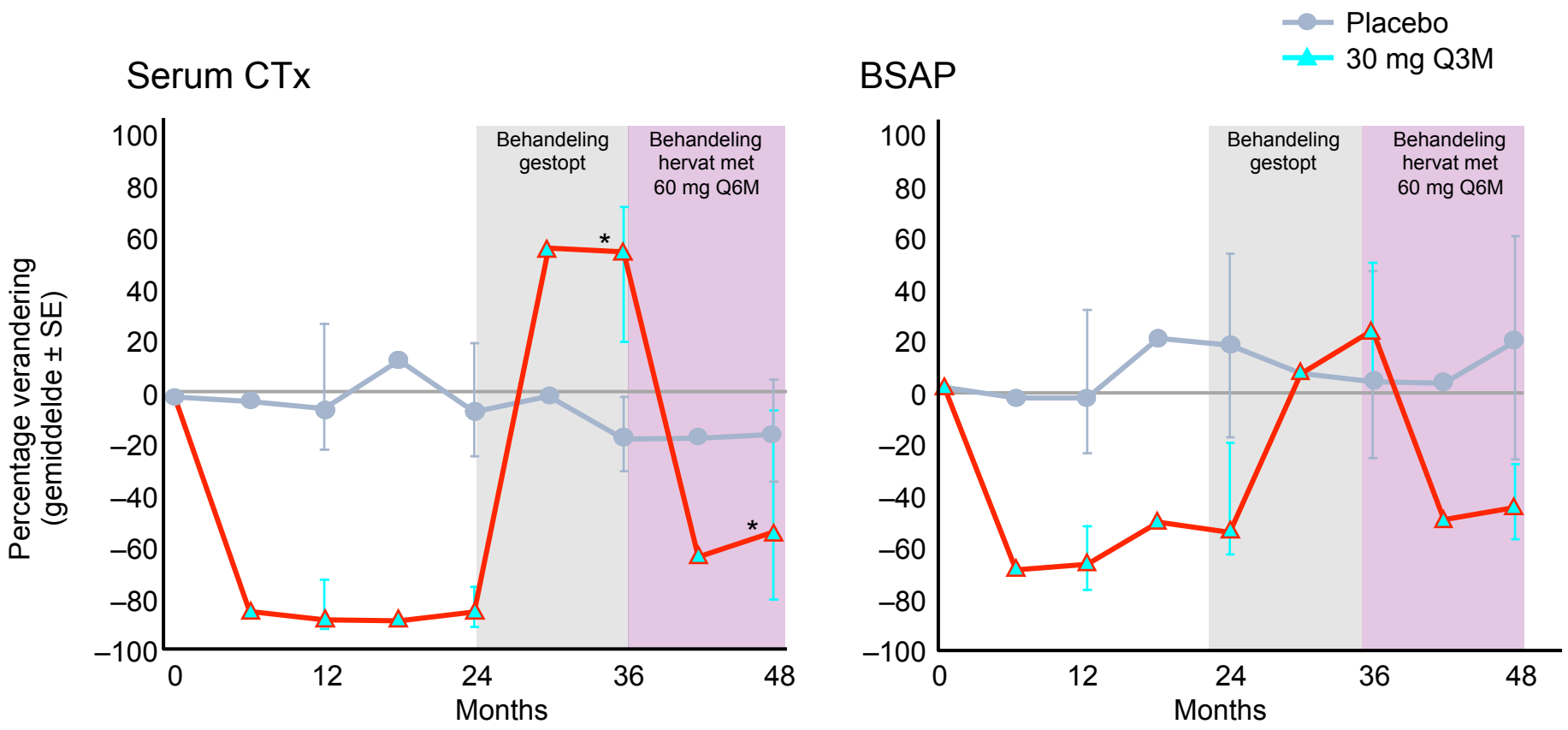
JBMR Date Final Disposition Set September 7, 2015

Severe rebound-associated vertebral fractures after denosumab discontinuation

- These 9 cases are unusual and disturbing for several reasons
- All VFs were spontaneous and most patients had a high number of VFs (mean = 5.5) in a short period of time.
- Their VFs occurred rapidly after last denosumab injection (9 to 16 months)

Lamy et al. JCEM October 6, 2016

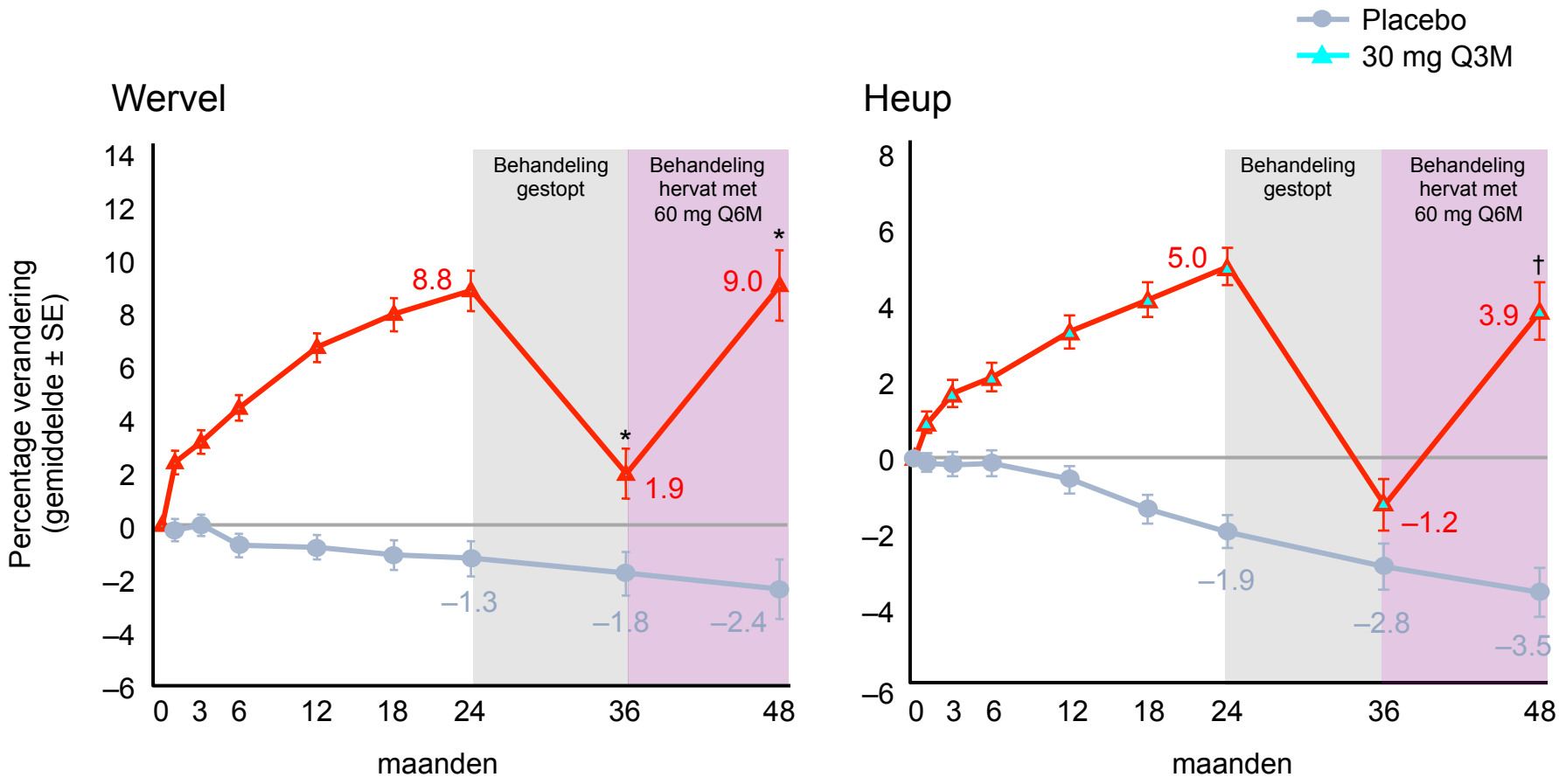
Denosumab behandeling gestopt en hervat: effecten op botmarkers



*P < 0.001 op maand 36 en = 0.05 op maand 48 vs. placebo.
†P = 0.01 vs. placebo.
Miller PD et al. Bone (2008); 43(2), 222-229

Miller PD et al. Bone (2008); 43(2), 222-229

Denosumab behandeling gestopt en hervat: effect op BMD van wervel en heup



*P = 0.004 op maand 36 en < 0.001 op maand 48 vs. placebo.

Miller PD et al. Bone (2008); 43(2), 222-229

(Multiple) Vertebral fracture rate after discontinuation of denosumab

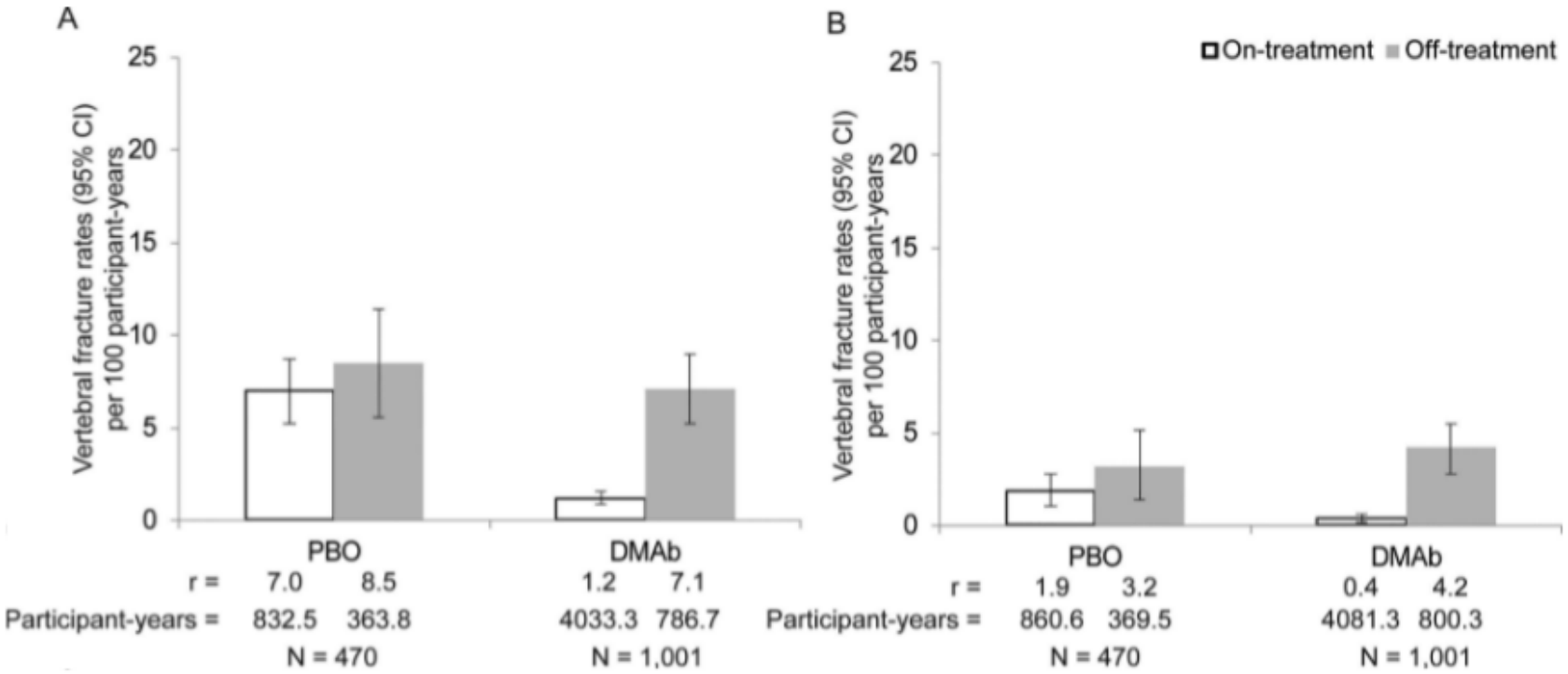


Fig. 2. Exposure-adjusted rates of (*A*) any and (*B*) multiple vertebral fractures in participants who received placebo or denosumab in the FREEDOM study and denosumab in the Extension before (white bar) and after (gray bar) discontinuing treatment. DMAb = denosumab; PBO = placebo; r = rate per 100 participant-years.

Cummings et al. JBMR 2017 online

(Multiple) Vertebral fracture rate after discontinuation of denosumab

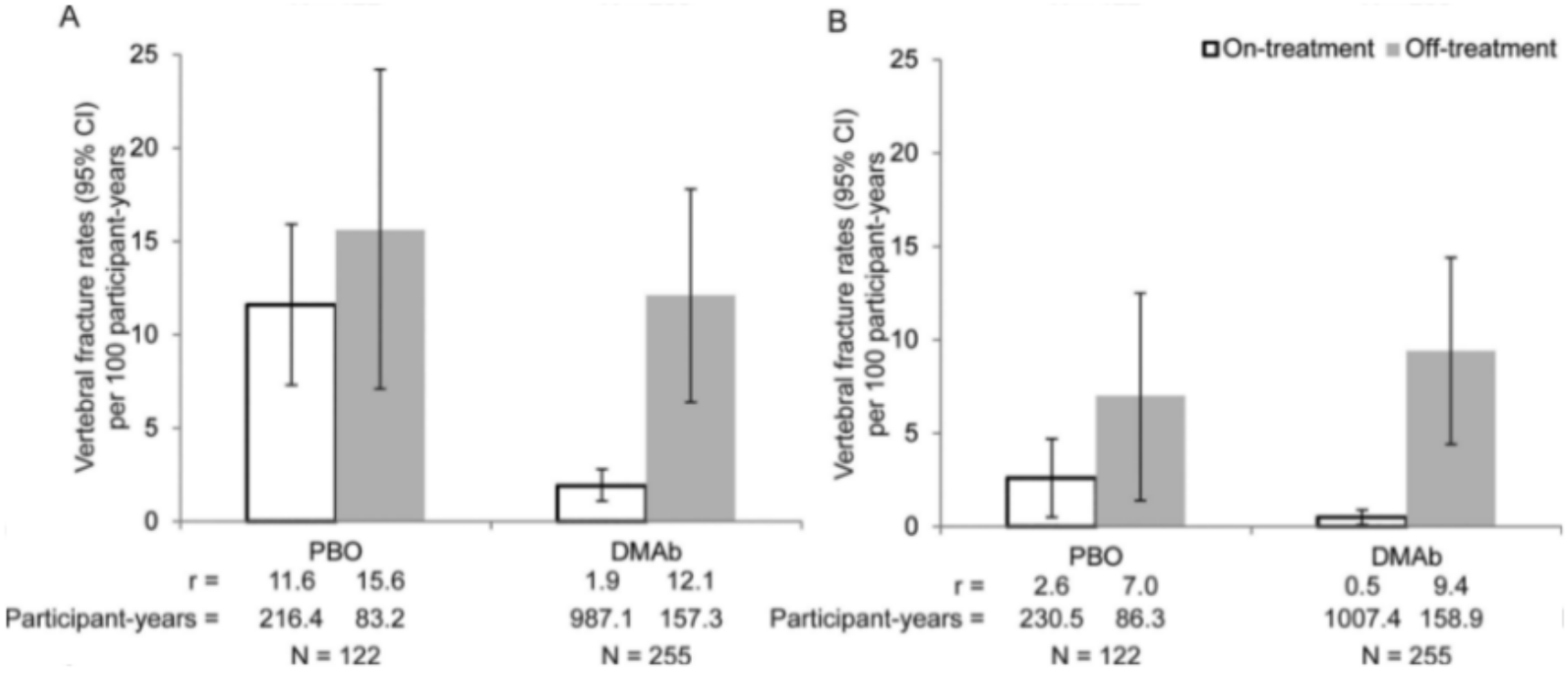


Fig. 3. Exposure-adjusted rates of (*A*) any and (*B*) multiple vertebral fractures in participants with prevalent vertebral fractures who received placebo or denosumab in the FREEDOM study and denosumab in the Extension before (white bar) and after (gray bar) discontinuing treatment. DMAb = denosumab; PBO = placebo; r = rate per 100 participant-years.

Cummings et al. JBMR 2017 online

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS

- Re-evaluation after 5 years of denosumab treatment
- high fracture risk
  - continue denosumab therapy for up to 10 years or be switched to an alternative treatment
- low fracture risk
  - bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover

➢ denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk