Non-bisphosphonate Treatments for Osteoporosis: Using Denosumab, Romosozumab, and Others

Joy N. Tsai, M.D.
Assistant Professor, HMS
September 2021

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
ENDOCRINOLOGY

Disclosures:

Research funding - Amgen (Investigator initiated)

Financial interest in Amgen *(spouse is employee of Amgen);* managed by MGH and Partners Healthcare

Learning objectives

- To review fracture efficacy data available for FDA approved postmenopausal osteoporosis treatments
- To discuss clinical outcomes when transitioning between drugs for postmenopausal osteoporosis treatment

Clinical cases

- 80yo woman
- Presents with L2 compression fracture after a fall

- 70yo woman
- Presents with multiple fragility fractures
- Left radius fracture 5 yrs ago
- Rib fracture last year
- T12, L1 fractures this year

- 70yo woman
- History of temporal arteritis and chronic kidney disease
- Screening DXA showed osteoporosis

DXA T-scores: PA Spine -3.1, Total hip -1.6, Femoral neck -2.1

What would you choose?

A) Raloxifene

B) Oral bisphosphonate

- ❑ oral bisphosphonates
  - alendronate
  - risedronate
  - ibandronate

C) Intravenous bisphosphonate

- ❑ IV bisphosphonates
  - zoledronic acid
  - ibandronate

D) Denosumab

E) Anabolic therapy

- teriparatide (parathyroid hormone, PTH 1-34)
- abaloparatide (PTHrP analog)

F) Romosozumab

Teriparatide

- rPTH 1-34
- Intermittent administration increases osteoblastic number and activity
- Also increases osteoclastic activity, but net balance favors bone formation
- Increases new bone formation
- Increases trabecular bone mineral density (BMD) dramatically
- Has variable effects on cortical BMD

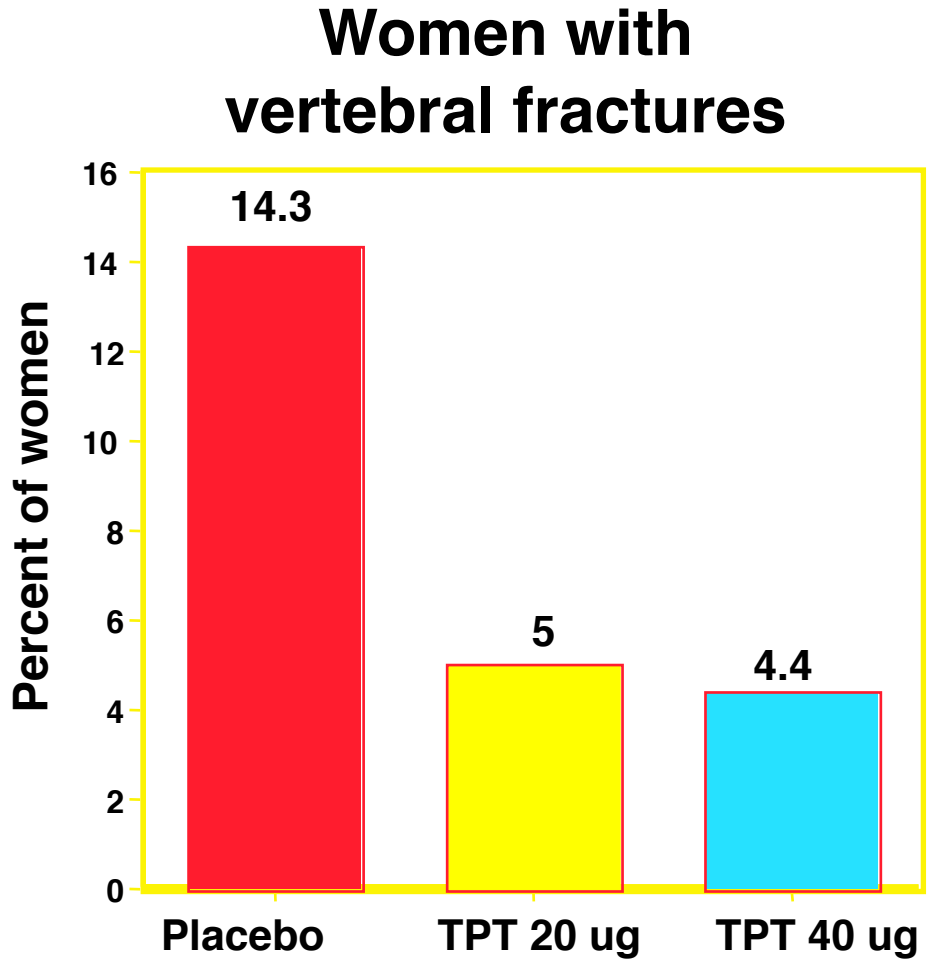
Postmenopausal Osteoporosis Therapy: Teriparatide

Study population

- 1637 women
- Mean age = 70
- At least 1 spine fracture

Randomized to:

- Placebo
- teriparatide 20 ug/day
- teriparatide 40 ug/day



Neer et al., NEJM 344:1434-41, 2001

Slide courtesy of Dr. Joel Finkelstein

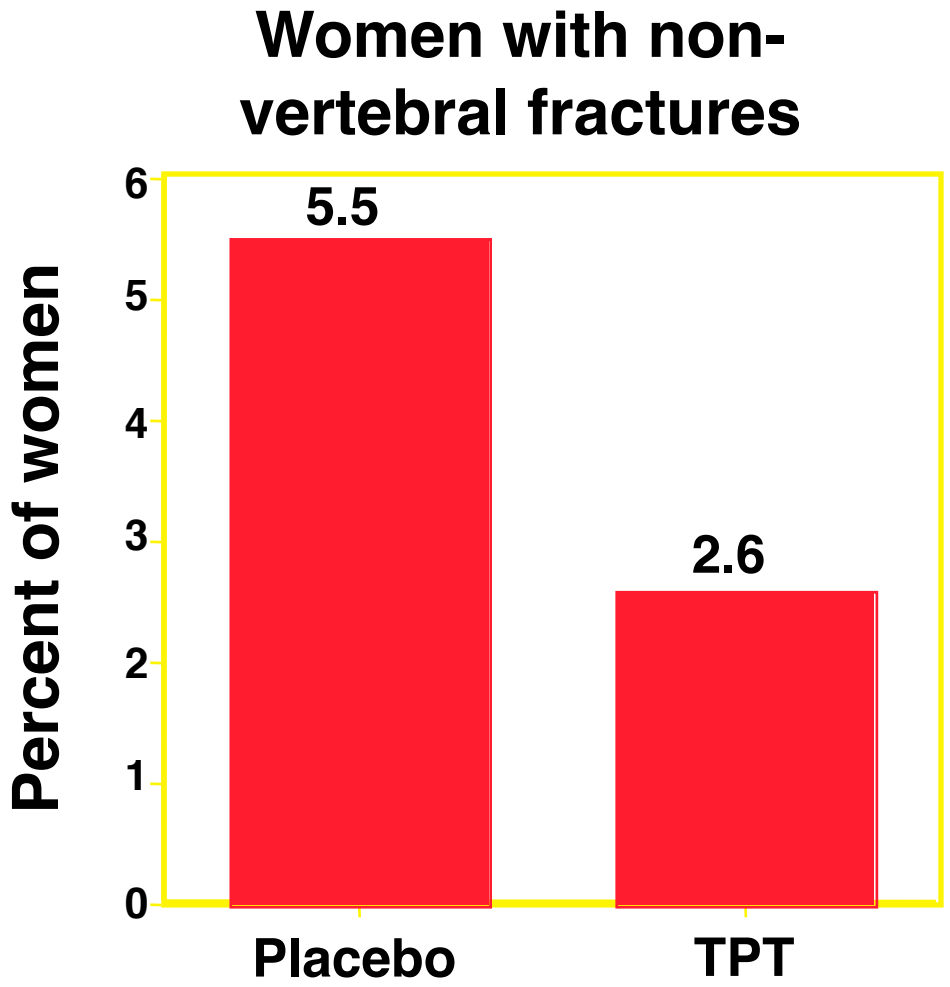
Postmenopausal Osteoporosis Therapy: Teriparatide

Study population

- 1637 women
- Mean age = 70
- At least 1 spine fracture

Randomized to:

- Placebo
- teriparatide



Neer et al., NEJM 344:1434-41, 2001

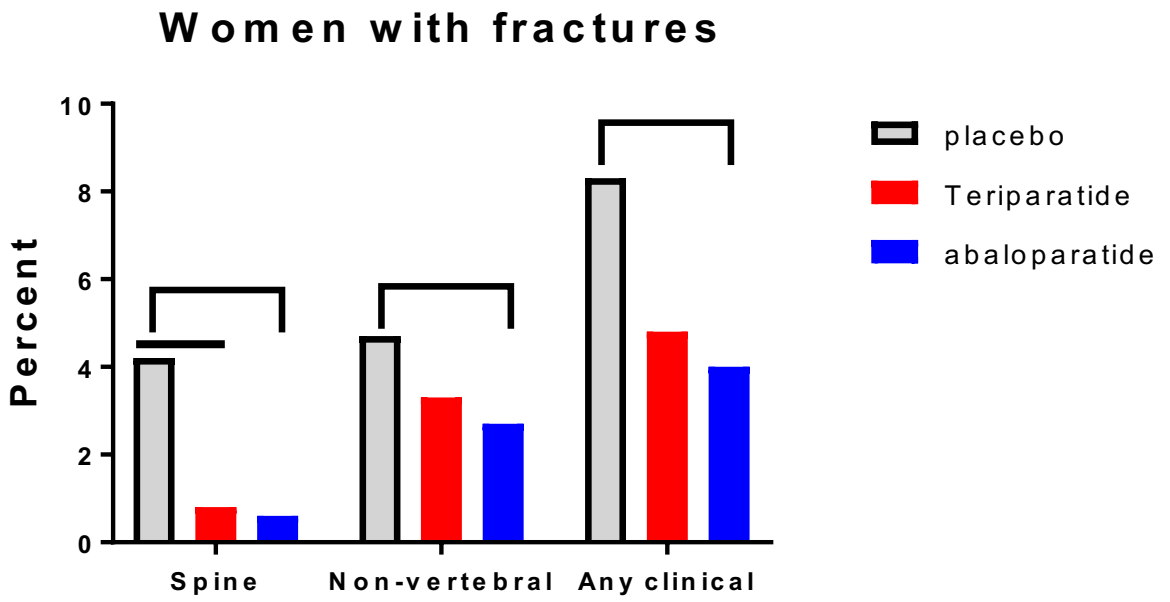
Slide courtesy of Dr. Joel Finkelstein

Abaloparatide

- Parathyroid hormone-related protein analog
- N-terminal of teriparatide and abaloparatide recognized by PTH1 Receptor
- Also increases osteoclastic activity, but net balance favors bone formation

Abaloparatide: ACTIVE (Abaloparatide Comparator Trial in Vertebral Endpoints)

- 2,463 women, mean age 69 years
- Spine or total hip T-score <-2.5 and >-5.0 PLUS
  - 2 vertebral fractures or
  - 1 moderate vertebral fracture or
  - Low-trauma fracture
- Randomized to placebo, teriparatide 20mcg daily, or abaloparatide 80mcg daily for 18 months

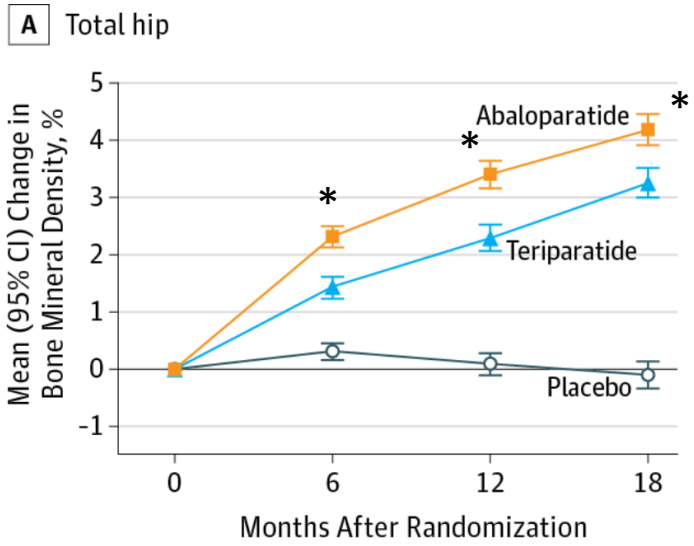


2 hip fractures occurred in placebo group only

Miller P et al JAMA 316:722, 2016

Abaloparatide: ACTIVE

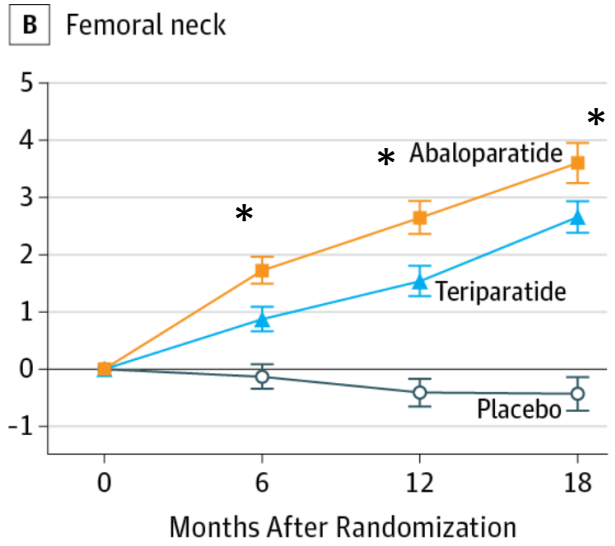
Total hip



No. of participants evaluated

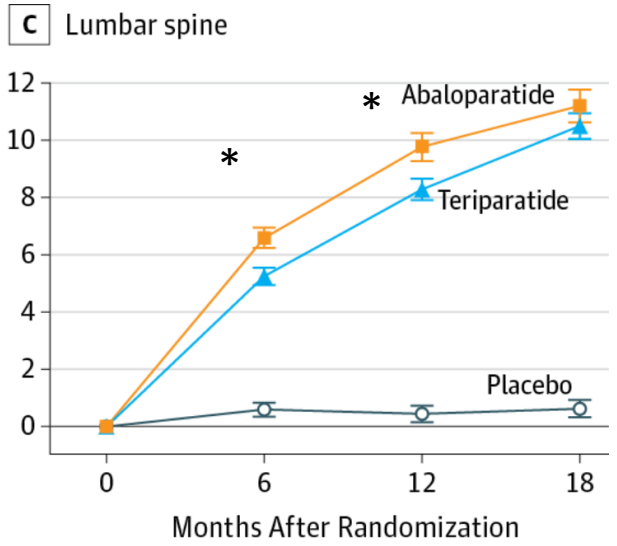
Abaloparatide	822	736	651	615
Placebo	820	762	693	651
Teriparatide	818	754	705	660

Femoral neck



	822	736	651	615
	820	762	693	651
	818	754	705	660

Lumbar spine



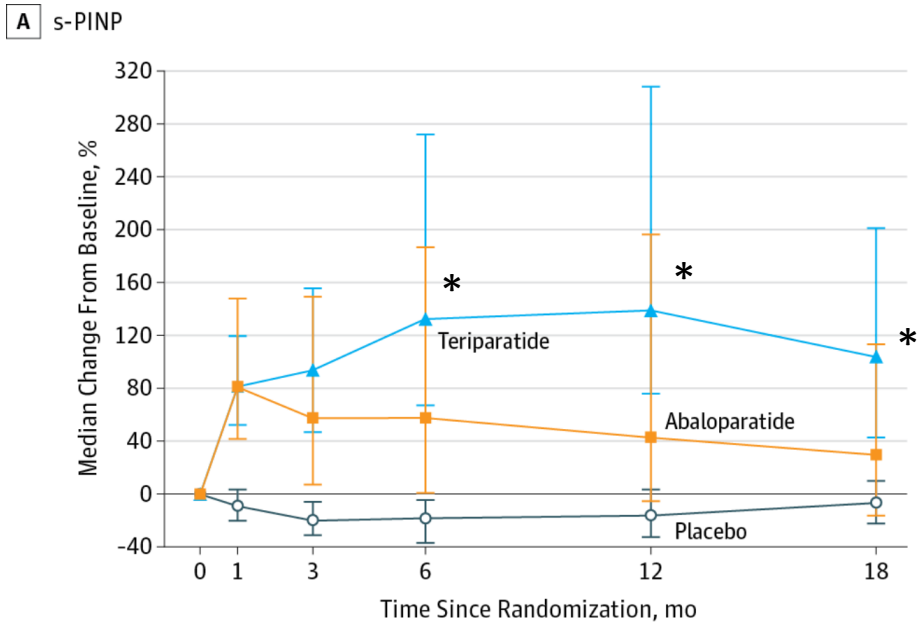
	823	738	652	617
	821	764	694	650
	818	755	704	665

* P<0.05 abaloparatide versus teriparatide

Miller P et al JAMA 316:722, 2016

Abaloparatide: ACTIVE

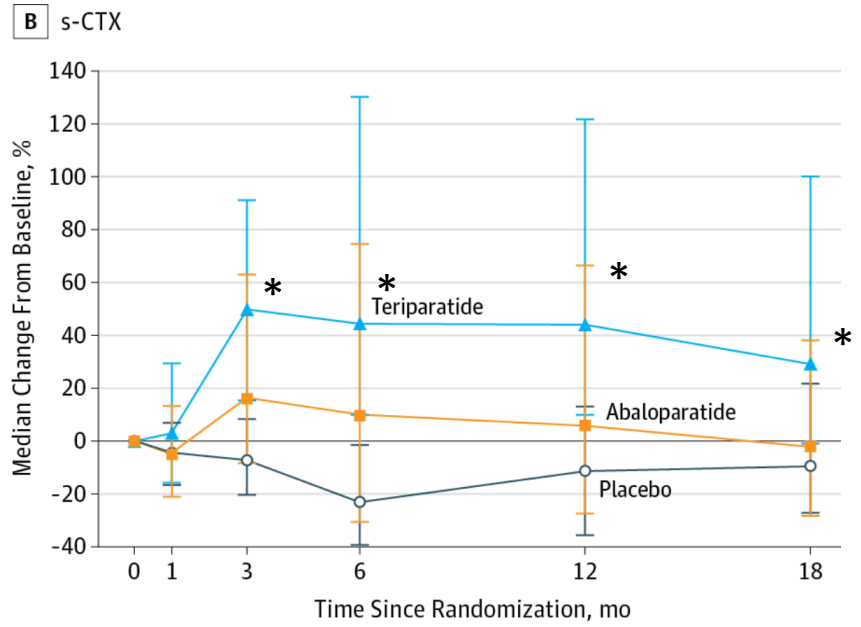
sP1NP (marker of bone formation)



No. of participants evaluated

Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

s-CTX (marker of bone resorption)



	189	187	187	189	189	189
	184	183	181	184	184	184
	227	227	227	227	227	227

Miller P et al JAMA 316:722, 2016

Table 3. Safety and Adverse Events[a]

	Abaloparatide (n = 822)	Placebo (n = 820	Teriparatide (n = 818)
All treatment-emergent adverse events	735 (89.4)	718 (87.6)	727 (88.9)
Serious treatment-emergent adverse events	80 (9.7)	90 (11.0)	82 (10.0)
Deaths[b]	3 (0.4)	5 (0.6)	3 (0.4)
Adverse events leading to discontinuation	81 (9.9)	50 (6.1)	56 (6.8)
Discontinuation due to >7.0% BMD decrease[c]	1/218 (0.5)	12/184 (6.5)	1/160 (0.6)
Most frequently observed adverse events[d]			
Hypercalciuria	93 (11.3)	74 (9.0)	102 (12.5)
Dizziness	82 (10.0)	50 (6.1)	60 (7.3)
Arthralgia	71 (8.6)	80 (9.8)	70 (8.6)
Back pain	70 (8.5)	82 (10.0)	59 (7.2)
Nausea	68 (8.3)	25 (3.0)	42 (5.1)
Upper respiratory tract infection	68 (8.3)	63 (7.7)	73 (8.9)
Headache	62 (7.5)	49 (6.0)	51 (6.2)
Hypertension	59 (7.2)	54 (6.6)	41 (5.0)
Influenza	52 (6.3)	39 (4.8)	34 (4.2)
Nasopharyngitis	48 (5.8)	66 (8.0)	53 (6.5)
Urinary tract infection	43 (5.2)	38 (4.6)	41 (5.0)
Palpitations	42 (5.1)	3 (0.4)	13 (1.6)
Pain in extremity	40 (4.9)	49 (6.0)	42 (5.1)
Constipation	37 (4.5)	42 (5.1)	34 (4.2)
Hypercalcemia (prespecified safety end point)[e]	28/820 (3.4)[f]	3/817 (0.4)	52/816 (6.4)
Adverse events of special interest[g]			
Orthostatic hypotension[h]	140 (17.1)	134 (16.4)	127 (15.5)
Neoplasms, benign, malignant, and unspecified[i]	20 (2.4)	29 (3.5)	31 (3.8)
Fall[j]	4 (0.5)	2 (0.2)	4 (0.5)
Drug hypersensitivity[j,k]	2 (0.2)	2 (0.2)	0
Renal impairment[j]	2 (0.2)	4 (0.5)	3 (0.4)
Myocardial infarction[j]	1 (0.1)	2 (0.2)	2 (0.2)

Practical considerations

- **Daily injections; abaloparatide may be stored at room temperature for up to 30 days**

- **Common side effects**
  - Nausea
  - Dizziness
  - Hypercalcemia

- Black box warning removed from teriparatide regarding risk of osteosarcoma based on 18-yr surveillance data

Gilsenan AW et al JBMR 2020, pp1-8

When I consider PTH analogs:

- **Vertebral fractures or very low spine bone density**

2-yr BMD changes	Lumbar Spine	Total hip
alendronate	5-7%	2.5-4%
teriparatide	8-10%	1.4-2%

When I consider PTH analogs:

- **Vertebral fractures or very low spine bone density**

2-yr BMD changes	Lumbar Spine	Total hip
alendronate	5-7%	2.5-4%
teriparatide	8-10%	1.4-2%

- **Anticipated need for long-term therapy based on history and risk factors**

Does the order of medications make a difference?

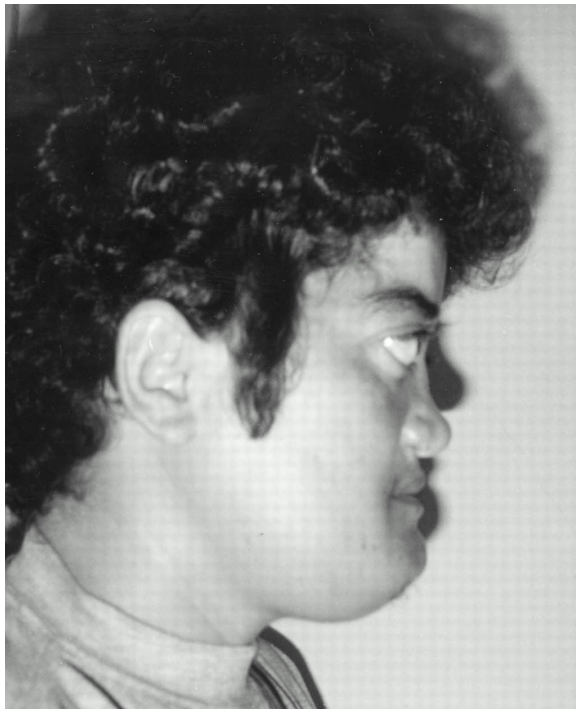
- Switching from a bisphosphonate to an anabolic drug may result in transient cortical bone loss and blunted bone density gains at predominantly trabecular bone sites
- In subgroup of postmenopausal women, mean 24-mo spine BMD gain was greater in treatment-naïve group (n=84, 13.1%) versus prior antiresorptive treatment group (n=134, 10.2%, p<0.005).*[Obermayer-Pietsch BM et al]*

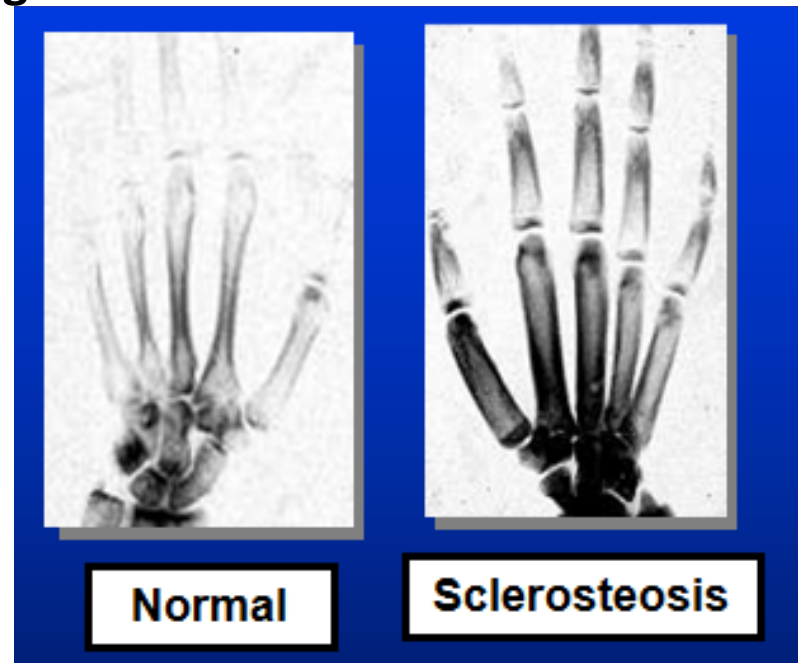
		% change total hip BMD during TPTD			
		6mo	12mo	18mo	24mo
Boonen et al (N=107)	Alendronate (29 mo) to TPTD (24 mo)	-1.2%	-0.6%	+0.6%	+2.1%

Obermayer-Pietsch BM et al JBMR 2008; Cosman F et al JCEM 2009; Boonen et al JCEM 2008; Ettinger B et al JBMR 2004; Miller PD et al JCEM 2008

Sclerostin Inhibitor: romosozumab

- Human disease: Sclerostiosis
  - Good quality, fracture resistant bone
  - Bone overgrowth in skull causes clinical problems
  - Caused by gene defect in *sost* gene



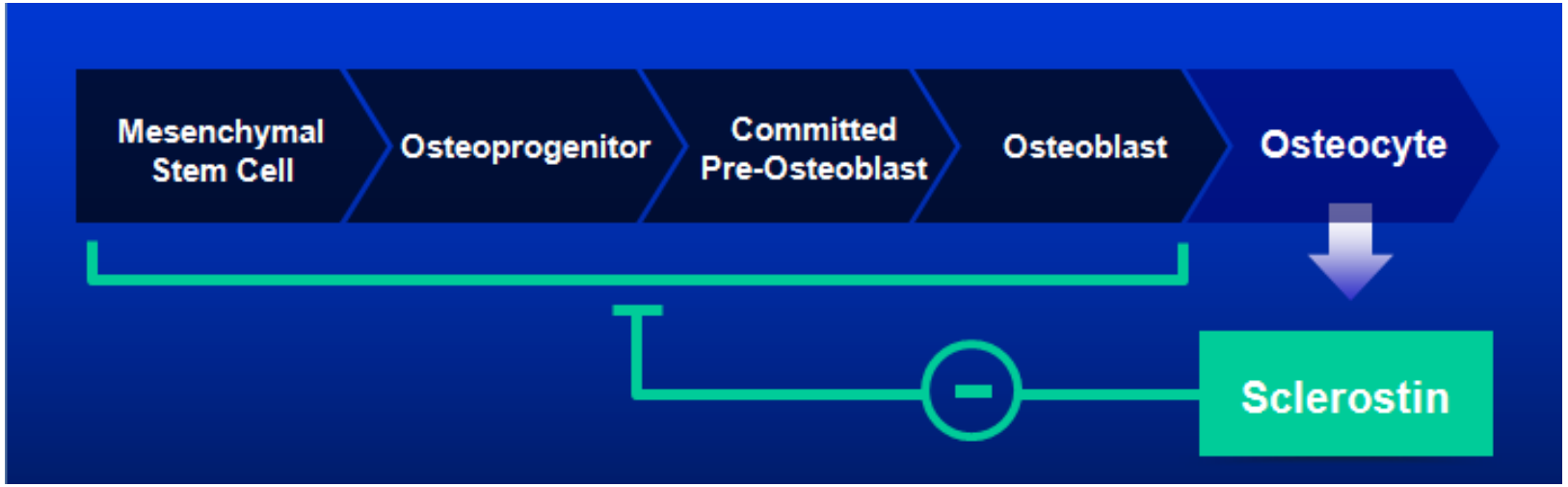


(Balemans et al, Hum Mol Gen 2001)

Heterozygote family members have dense, fracture resistant bone but no apparent negative health consequences

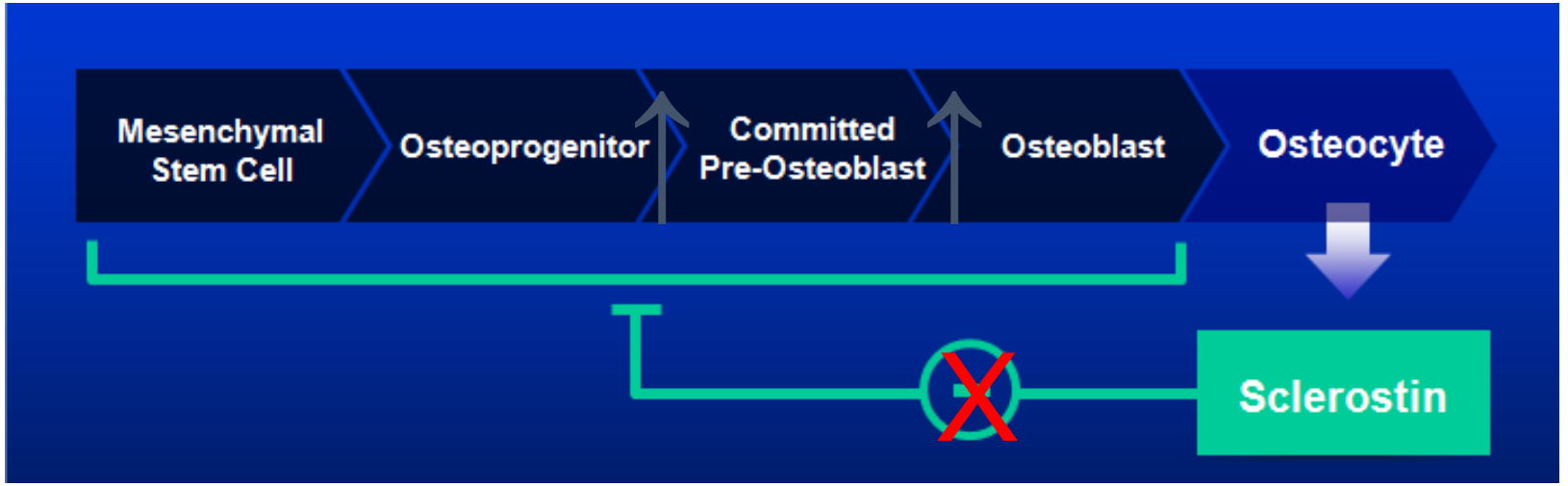
Targeting Wnt Signaling

- **Sclerostin (*sost*) is a Wnt antagonist**
- **Wnts are growth factors that bind to a receptor complex (Fz, LRPs) initiating signaling cascades that control osteoblast function**
- **Wnt signaling is ubiquitous but <u>sost is expressed only in osteocytes</u>**



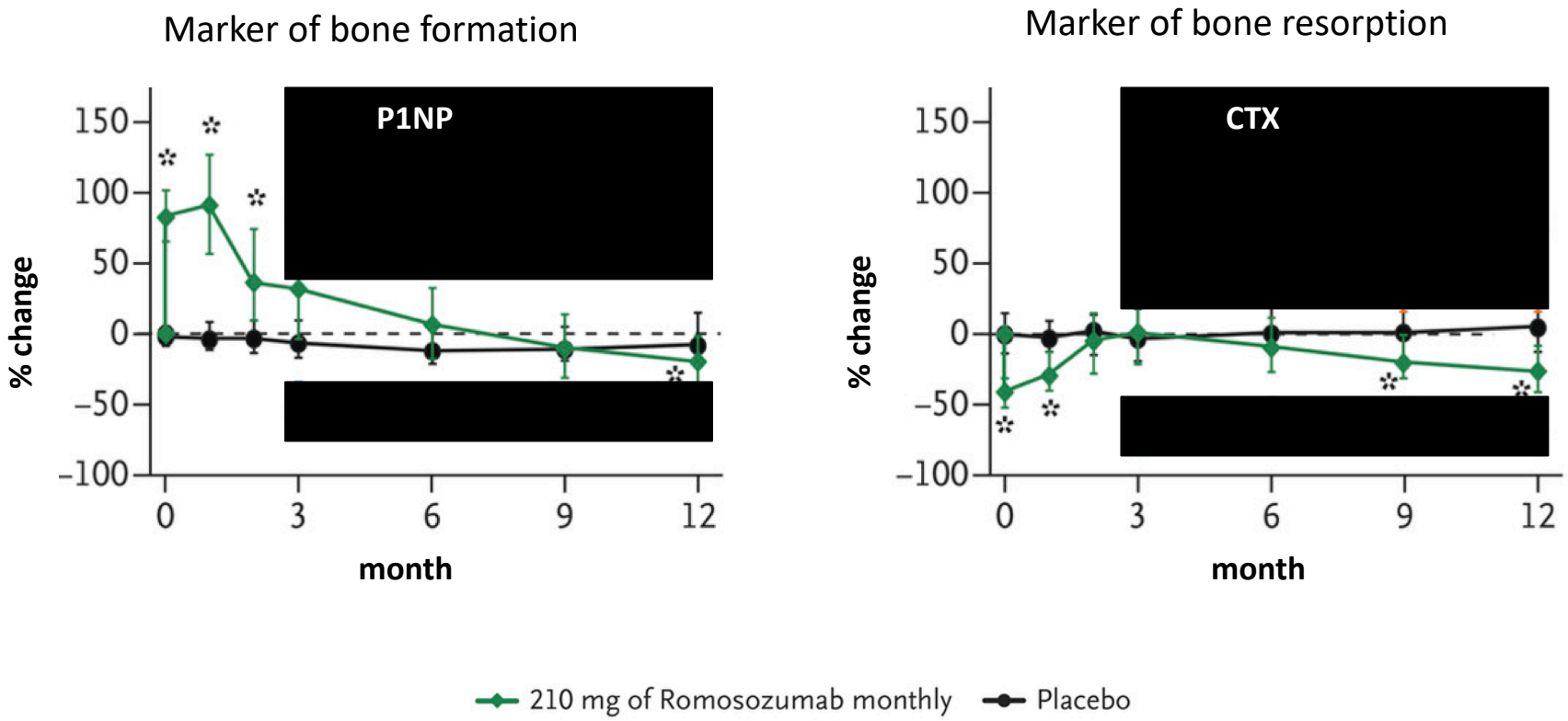
Targeting Wnt Signaling

- Sclerostin (*sost*) is a Wnt antagonist
- Wnts are growth factors that bind to a receptor complex (Fz, LRPs) initiating signaling cascades that control osteoblast function
- Wnt signaling is ubiquitous but <u>sost is expressed only in osteocytes</u>



Romosozumab: Bone Turnover Markers

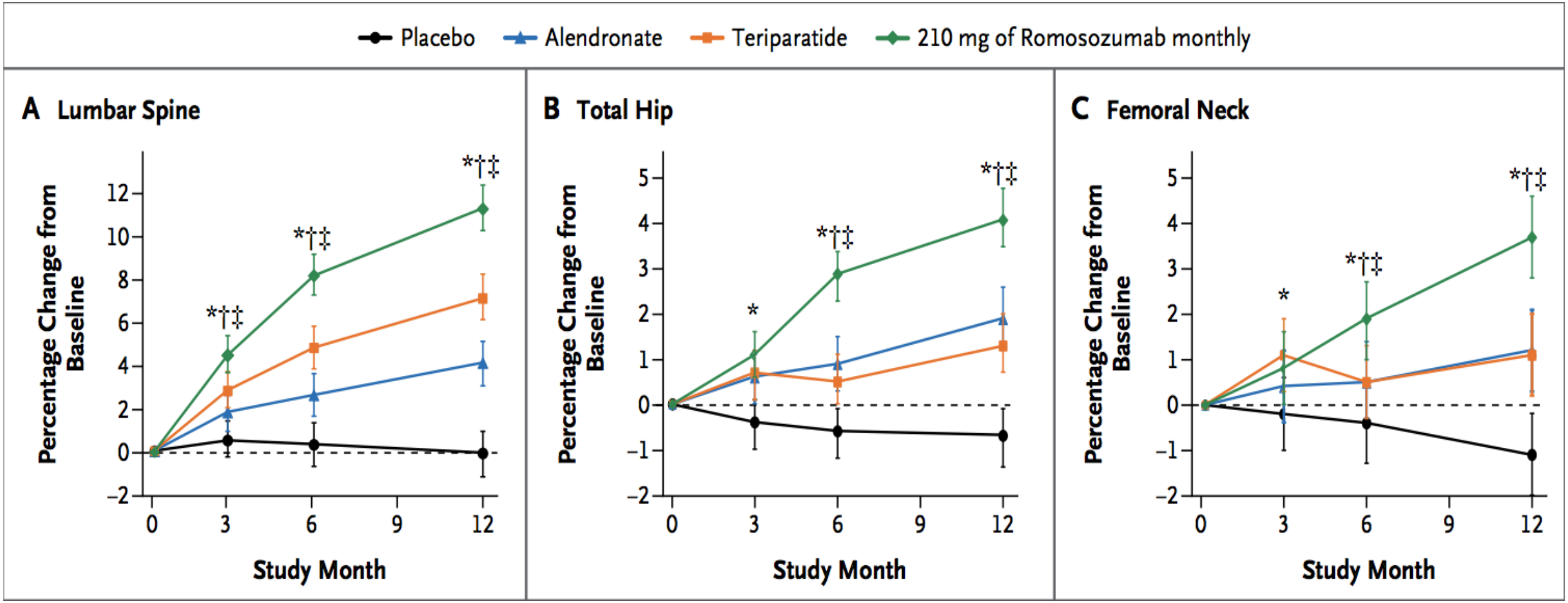
- **1-year trial of sclerostin antibody romosozumab in 419 post-menopausal women.**



McClung et al, NEJM 2014

Romosozumab: BMD

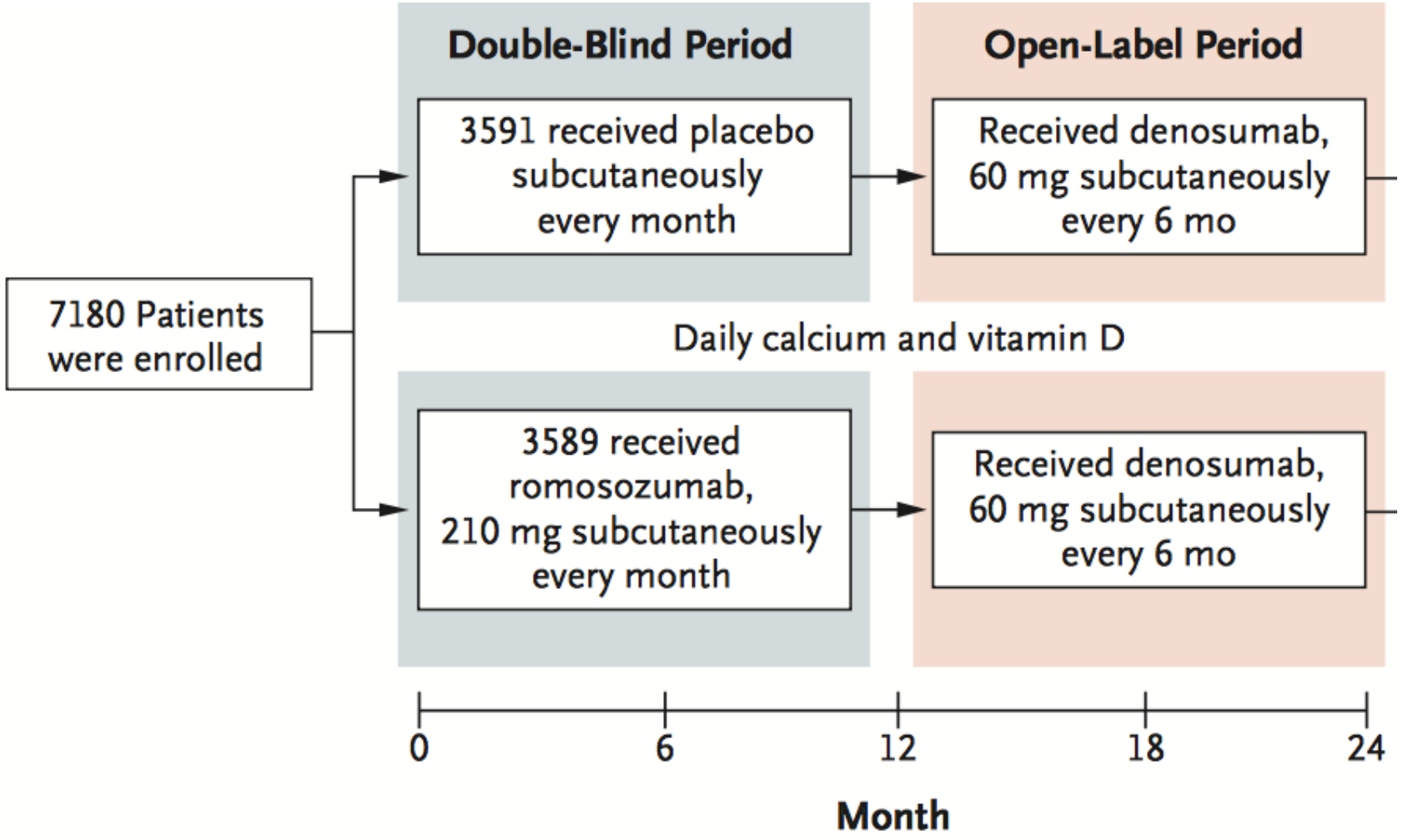
- 1-year trial of sclerostin antibody romosozumab in 419 post-menopausal women.



McClung et al, NEJM 2014

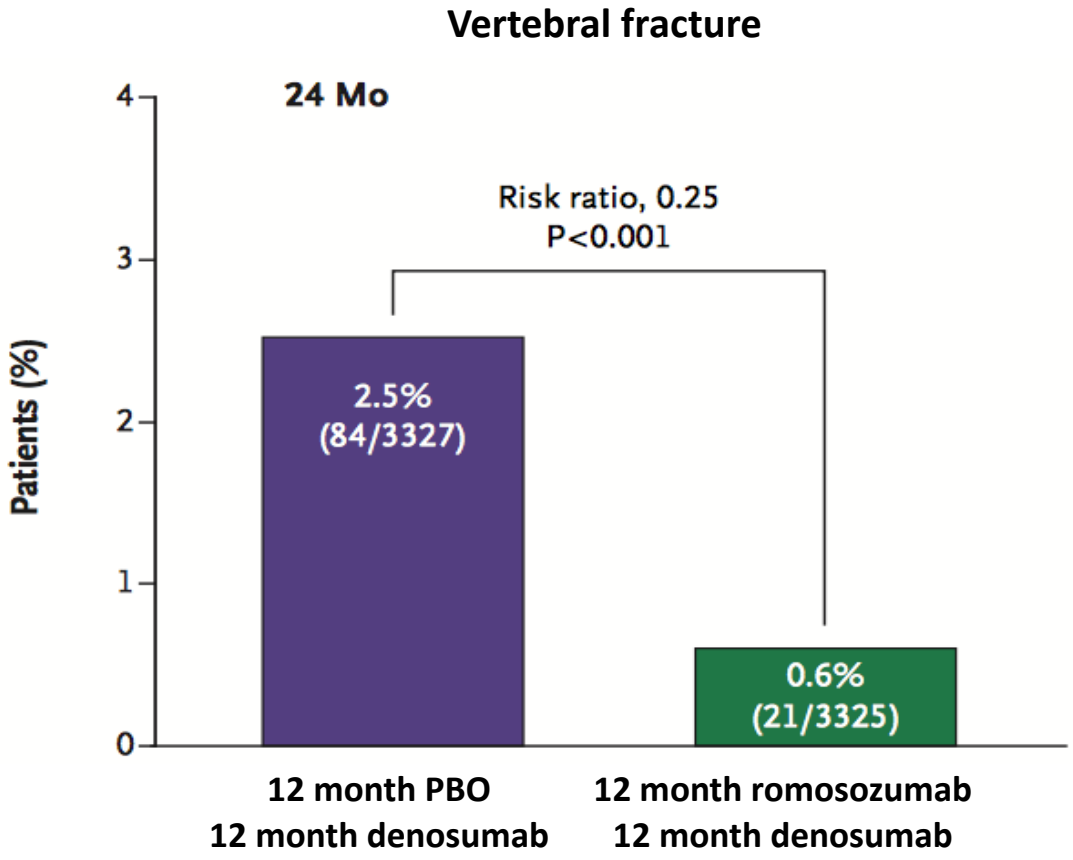
Romosozumab: FRAME

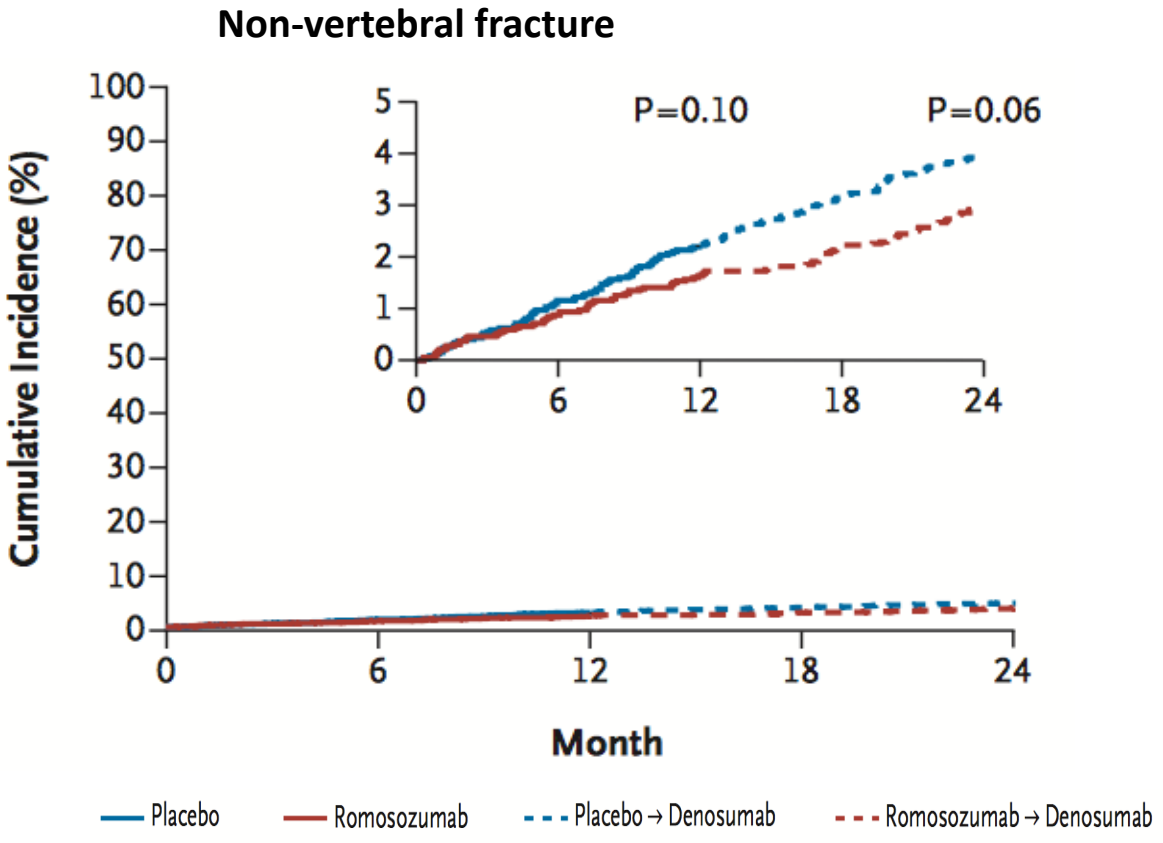
- **Placebo Controlled Phase 3 study (210-mg = 3 70-ml injections)**



Cosman et al, NEJM 2016

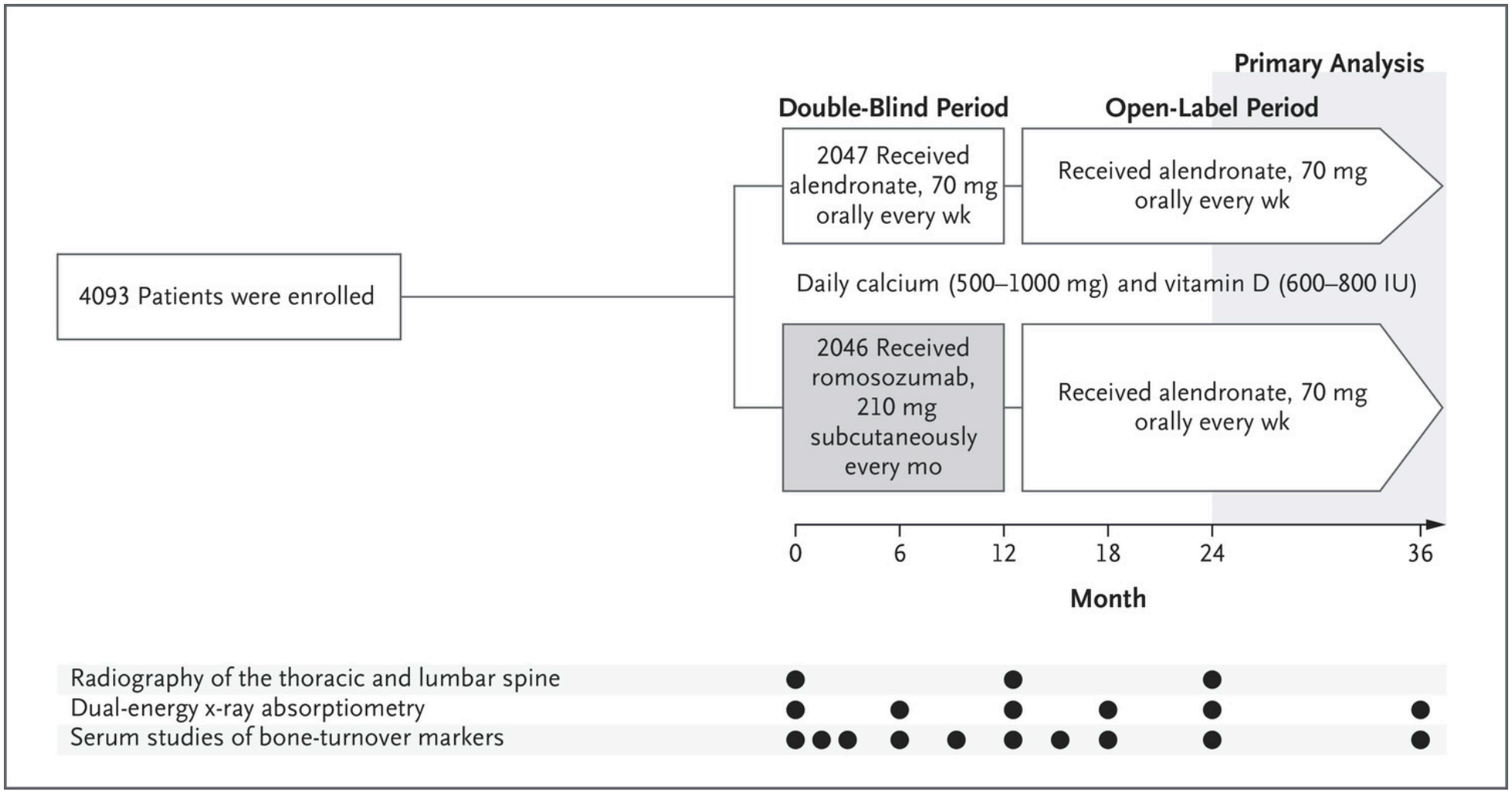
Romosozumab: FRAME





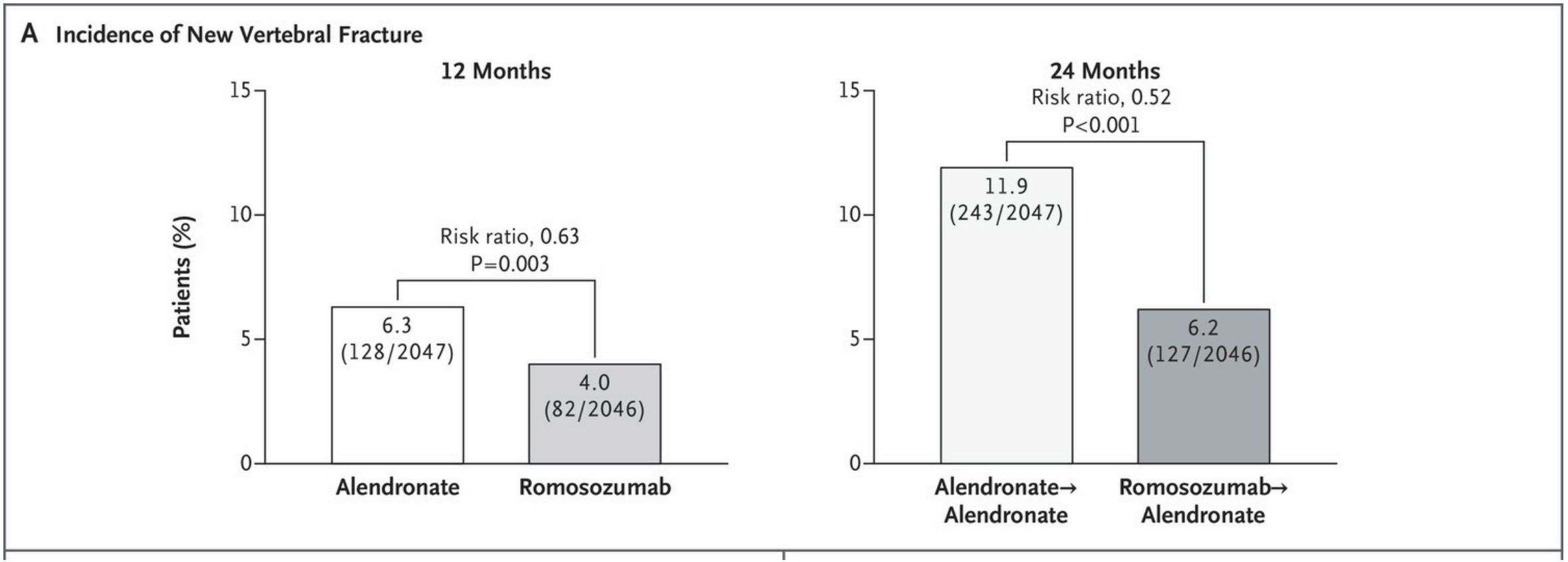
Cosman et al, NEJM 2016

Romosozumab: ARCH



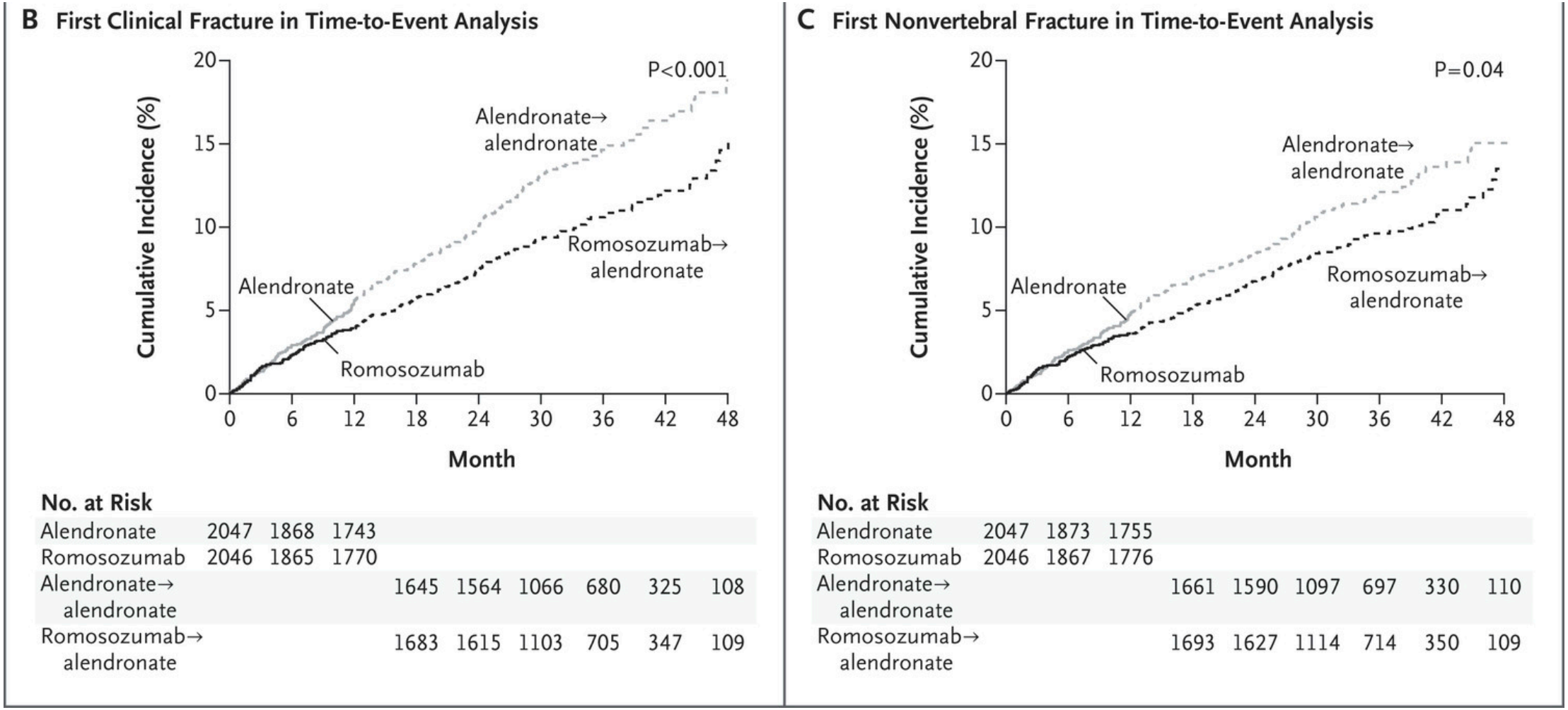
Saag et al, NEJM 2017

Romosozumab: ARCH



Saag et al, NEJM 2017

Romosozumab: ARCH



Saag et al, NEJM 2017

Romosozumab: ARCH

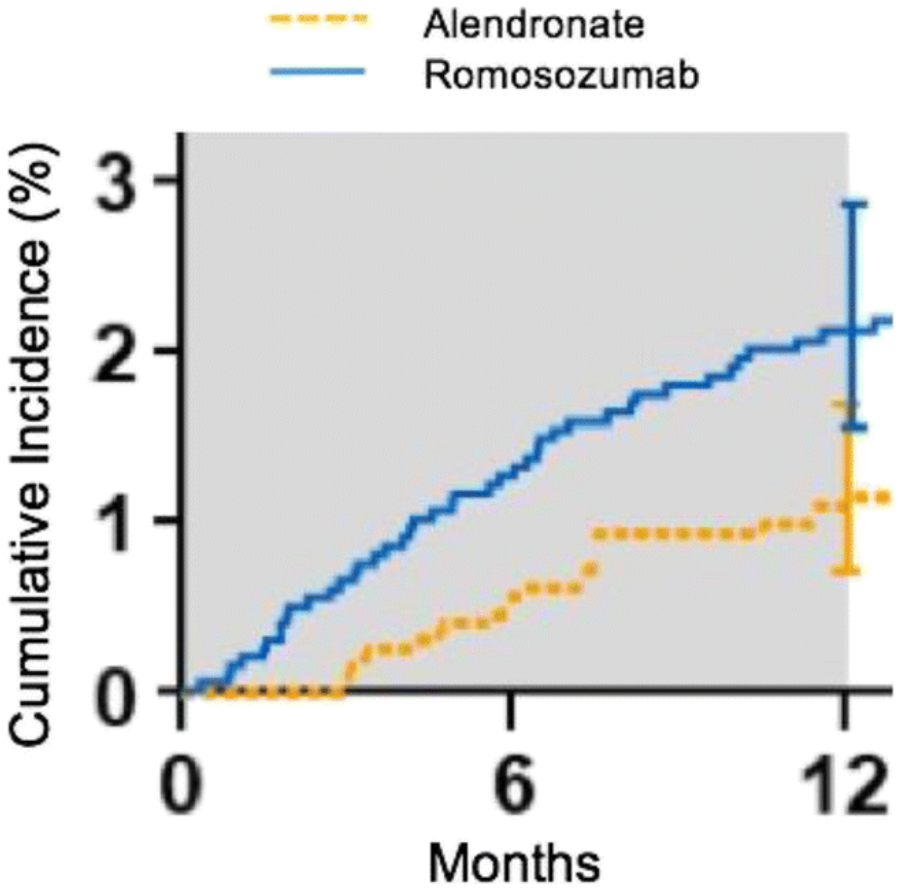
Table 2. Adverse Events.

Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period*	
	Alendronate (N = 2014)	Romosozumab (N = 2040)	Alendronate to Alendronate (N = 2014)	Romosozumab to Alendronate (N = 2040)
	number of patients (percent)			
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Back pain†	228 (11.3)	186 (9.1)	393 (19.5)	329 (16.1)
Nasopharyngitis†	218 (10.8)	213 (10.4)	373 (18.5)	363 (17.8)
Serious adverse event	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Adjudicated serious cardiovascular event‡	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0	5 (0.2)	2 (<0.1)
Death	21 (1.0)§	30 (1.5)	90 (4.5)§	90 (4.4)
Event leading to discontinuation of trial regimen	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Event leading to discontinuation of trial participation	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)

Saag et al, NEJM 2017

Romosozumab: CV risks

- Black box warning:
  - May increase risk of myocardial infarction, stroke and cardiovascular death
  - Should not be initiated in patients who have had a MI or stroke in the preceding year
  - If a patients experiences a MI or stroke during therapy, romosozumab should be discontinued



Cumulative 12-month incidence of MACE CVD events in the alendronate and romosozumab groups in the ARCH Trial

Rare side effects

Osteonecrosis of the jaw (ONJ)

- In FRAME (N=7,180):
  - 2 cases ONJ
- In ARCH (N=4,093):
  - 0 cases during romosozumab period
  - 1 event in each group during open-label alendronate

Atypical femur fracture (AFF)

- In FRAME (N=7,180):
  - One case of AFF
- In ARCH (N=4,093):
  - 2 AFF in romosozumab-to-alendronate
  - 4 AFF in alendronate-to-alendronate

Practical Considerations

- FDA approved dose is 210 mg SC monthly
- Injection sites include upper arm, abdomen, and thigh
- 210 mg = two injections, 105 mg/1.17 ml single-use prefilled syringe

COVID considerations

- **2021 Joint Guidance on COVID-19 Vaccination and Osteoporosis Management from the ASBMR, AACE, Endocrine Society, ECTS, IOF, and NOF**

“Romosozumab (Evenity®)

- We recommend an interval of 4-7 days between provision of these injections, or consideration for injection in the abdomen (except for a two-inch area around the navel) or thigh if administered concomitantly.”

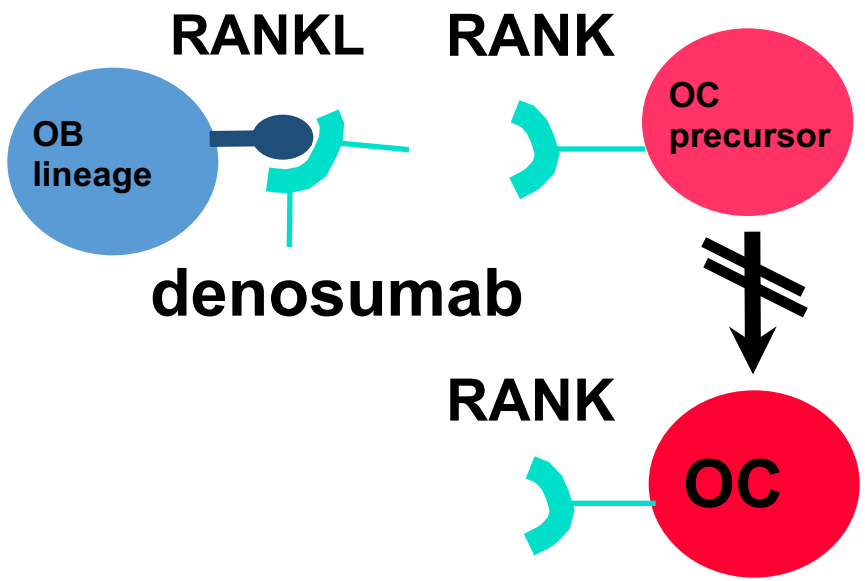
When I consider romosozumab:

- **Very high fracture risk patients**

2-yr BMD changes	**Lumbar Spine**	**Total hip**
alendronate	5-7%	2.5-4%
teriparatide	8-10%	1.4-2%
Romosozumab **(12-months)**	10%	4%

Denosumab

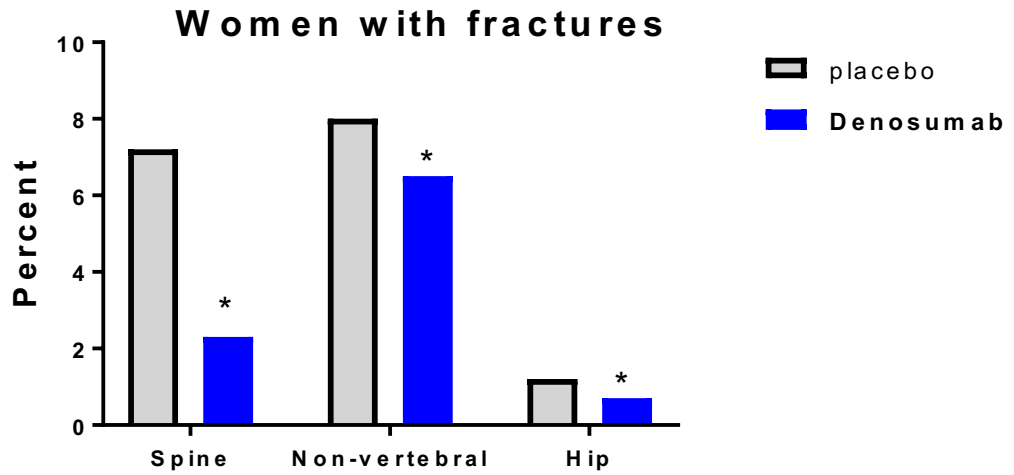
- A monoclonal antibody that binds to RANK-ligand and therefore blocks binding to RANK
- Inhibits bone resorption by inhibiting osteoclast differentiation, proliferation, function, and survival



Lacey DL et al. Cell 1998;93:165-76

Denosumab: FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months)

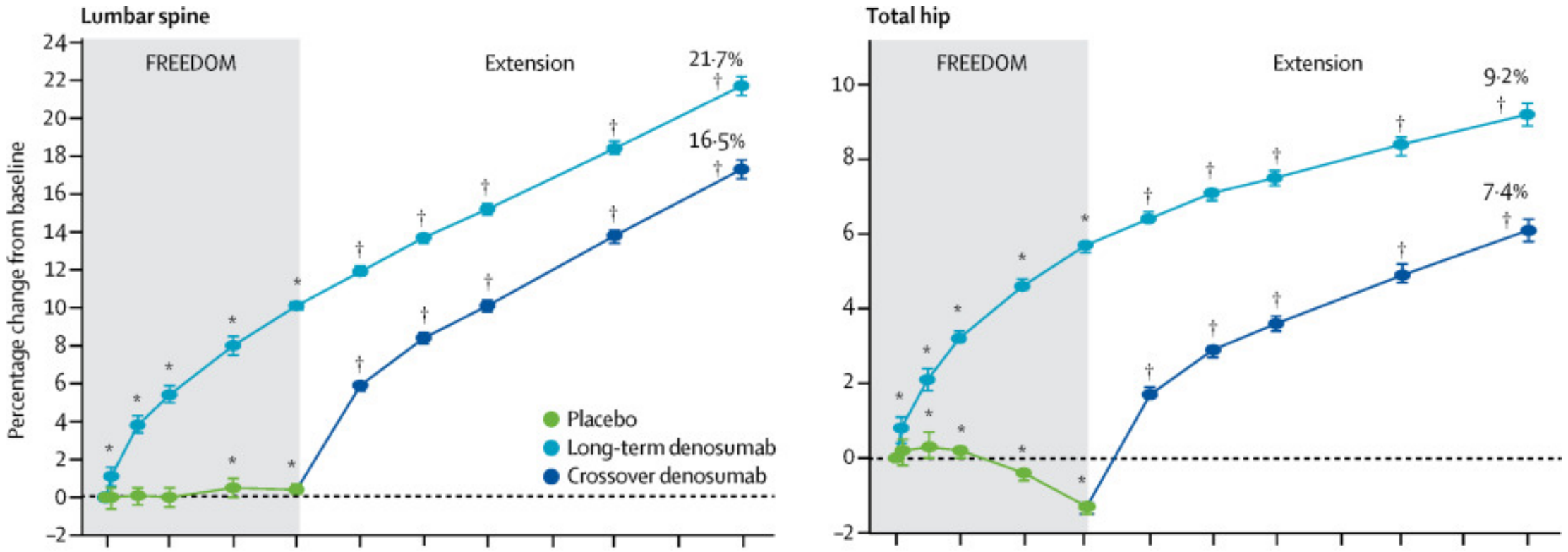
- 7,808 women, mean age 72
- Spine or total hip T-score <-2.5 and >-4.0
- Randomized to denosumab 60mg every 6 months or placebo for 3 years



*significantly different from placebo

Cummings et al., NEJM 361:756, 2009

Long term denosumab use



N=2,626 completed extension

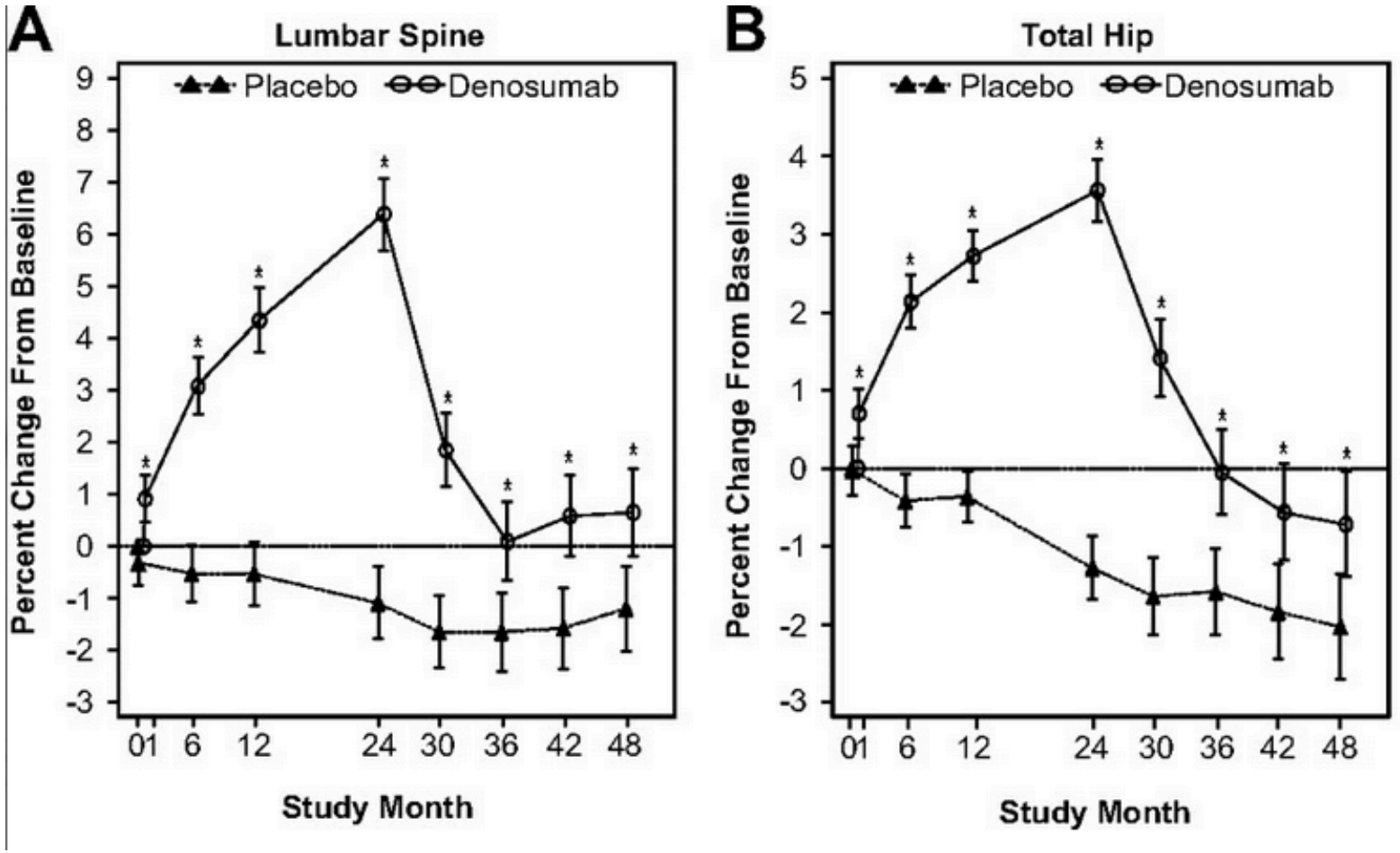
Papapoulos, S., Lippuner, K., Roux, C. et al. Osteoporos Int (2015)

Risks and Benefits of Denosumab

- **Benefits**
  - Can be used in renal failure (but caution hypocalcemia, nadir day 10 in those with normal renal function)

- **Risks**
  - **Common:**
    - Eczema, myalgias
  - **Less common**
    - Hypocalcemia
    - Osteonecrosis of the jaw (rare)
    - Atypical femoral fractures (rare)

Rapid bone loss after discontinuing denosumab



Bone H et al. 2011 JCEM

Increased risk of multiple vertebral fractures after stopping denosumab

- Bone density rapidly decreases after discontinuation of denosumab and multiple case reports of vertebral fractures after discontinuing denosumab

- From FREEDOM trial and extension:
  - Vertebral fracture rate increased
  - Proportion of multiple vertebral fractures greater in those who discontinued denosumab versus those who received placebo (3.4% versus 2.2%)
  - Greatest risk in those who had a prior vertebral fracture

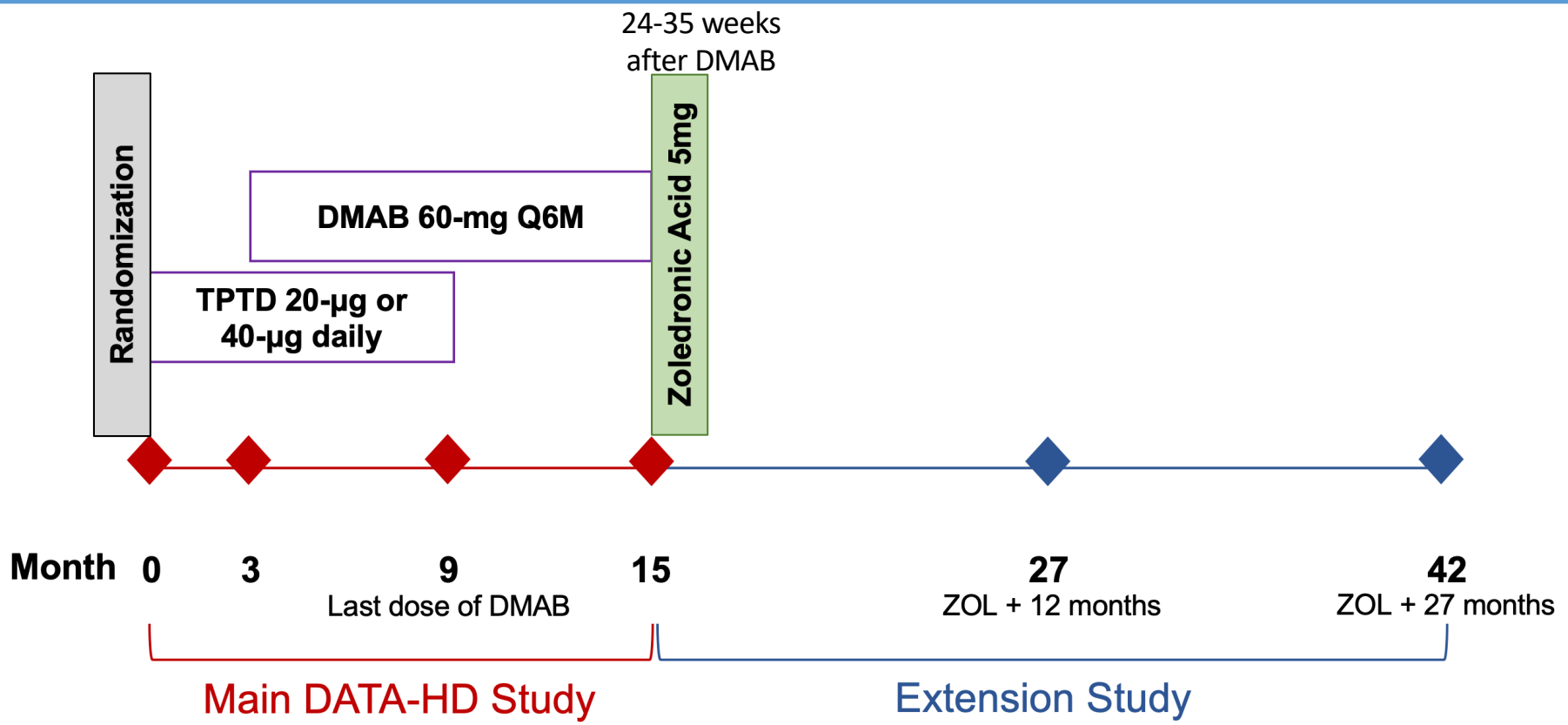
Bone HG et al JCEM 2011
Cummings SR et al. JBMR 2017
Anastasilakis AD et al JBMR August 2019
Reid IR et al Calcif Tissue Int 2017
Freemantle N et al Osteopor Int 2012

Choice of antiresorptive after discontinuing denosumab

- Ideal therapy after denosumab not defined
  - Inconsistent reports of effect of bisphosphonates after denosumab

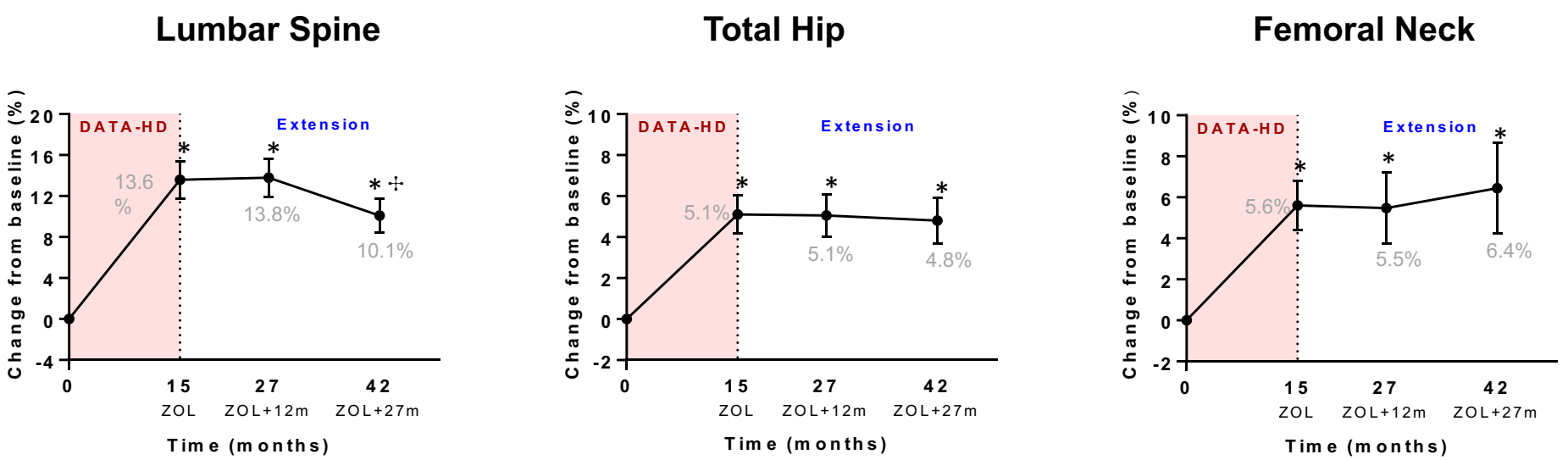
Reid IR et al Calcif Tissue Int 2017
Reid IR et al Calcif Tissue Int 2018
Athanasios D et al JBMR August 2019
Kendler D et al JCEM March 2020
Solling S,Langdahl B JBMR October 2020

Denosumab and High-dose Teriparatide Administration Extension Schema



Tsai, JN, Leder BZ 2019 Lancet Diab and Endo (15-month results)
Ramchand SK, Leder BZ ASBMR 2021 (27-month results)

Changes in Areal BMD - DXA



Data are mean percent change from baseline and 95% confidence interval
*P < 0.05 versus month 0, ✢P < 0.05 versus month 15

Ramchand SK, Leder BZ JBMR 2021

Zol did not maintain BMD after DMAB

- 61 postmenopausal women with osteopenia
- 2-yr RCT open label
- Mean DMAB 4.6 years
  - ZOL at 6 months (6M group, n=20)
  - ZOL at 9 months (9M group, n=20)
  - ZOL when BTM increased (OBS group, n=20) or after additional 6 months

		6M N=20	9M N=20	OBS N=20
12-months after ZOL	Lumbar spine Total hip	-4.8% (0.7) -2.6% (0.5)	-4.1% (1.1) -3.2% (0.8)	-4.7% (1.2) -3.6% (0.8)

Solling S, Harslof T, Langdahl B J Bone Miner Res Vol 35, No 10, October 2020, pp 1858-1870

DAPS (Denosumab Adherence Preference Satisfaction) study

- Postmenopausal women (N=250)
- 24-mo randomized, crossover comparison of 1-yr denosumab and 1-yr alendronate
- Baseline T-scores of -2.0, -2.6, and -2.0 at LS, TH and FN

		Denosumab-to-alendronate N=115
Month 0 to 12	Lumbar spine Total hip Femoral neck	5.6% 3.2% 3.1%
Month 12 to 24	Lumbar spine Total hip Femoral neck	0.6% 0.4% -0.1%

Freemantle N et al Osteopor Int 2012 Jan
Kendler D et al J Clin Endocrinol Metab 2020 Mar 1;105(3)

When I consider denosumab:

- **Abnormal renal function precludes use of other medications**
- **Patient preference**
- **I typically aim to limit use to approximately 5 years in order to avoid rare side effects**
- **Choice of antiresorptive after discontinuing denosumab would be either alendronate or zoledronic acid with close monitoring of DXA**

Clinical cases

- 80yo woman
- Presents with L2 compression fracture after a fall

- 70yo woman
- Presents with multiple fragility fractures
- Left radius fracture 5 yrs ago
- Rib fracture last year
- T12, L1 fractures this year

- 70yo woman
- History of temporal arteritis and chronic kidney disease
- Screening DXA showed osteoporosis

DXA T-scores: PA Spine -3.1, Total hip -1.6, Femoral neck -2.1

Summary: Expected BMD changes

2-yr BMD changes	Lumbar Spine	Total hip
alendronate	5-7%	2.5-4%
zoledronic acid	7-8%	4%
denosumab	8%	4%
teriparatide	8-10%	1.4-2%
raloxifene	1-2%	1-2%
Romosozumab **(12-months)**	10%	4%

Summary

- Several FDA-approved medications for postmenopausal osteoporosis available for patients at **high** risk of fracture
- Given many practical issues regarding administration, the final choice is dependent on clinician/patient shared preferences.
- Osteoporosis is a chronic disease, so the sequence and follow-up plan of therapy is a more prominent consideration now.
  - Clinicians and patients need to be aware of the increased fracture risk when discontinuing denosumab

Thank you

Questions?

- **Key Points:** While oral bisphosphonates are often first-line therapy for postmenopausal osteoporosis, non-bisphosphonate treatments may be considered for patients at very high risk of fracture. Use of these medications may offer the following advantages: 1) Parathyroid hormone analogs (teriparatide and abaloparatide) increase trabecular bone significantly and reduce risk of vertebral fracture. PTH analogs may be considered for patients with vertebral fractures. 2) Romosozumab – This monoclonal antibody to sclerostin is uniquely both anabolic and antiresorptive. Romosozoumab improves bone density at both the spine and hip dramatically in 12 months and was shown to reduce risk of vertebral fractures. 3) Denosumab – A potent antiresorptive that may be used in patients with abnormal renal function. Given the increased risk of multiple vertebral fractures when denosumab is stopped, an alternate antiresorptive must be used upon discontinuation of denosumab.
- **Next Best Steps:** Non-bisphosphonate therapy may be considered in patients at very high risk of fracture. Notably, each anabolic medication may be used for a limited time period and there is a risk of vertebral fracture after stopping denosumab. As such, patients and providers should be aware that use of an antiresorptive should be considered after discontinuing non-bisphosphonate therapy.