Update in Osteoporosis

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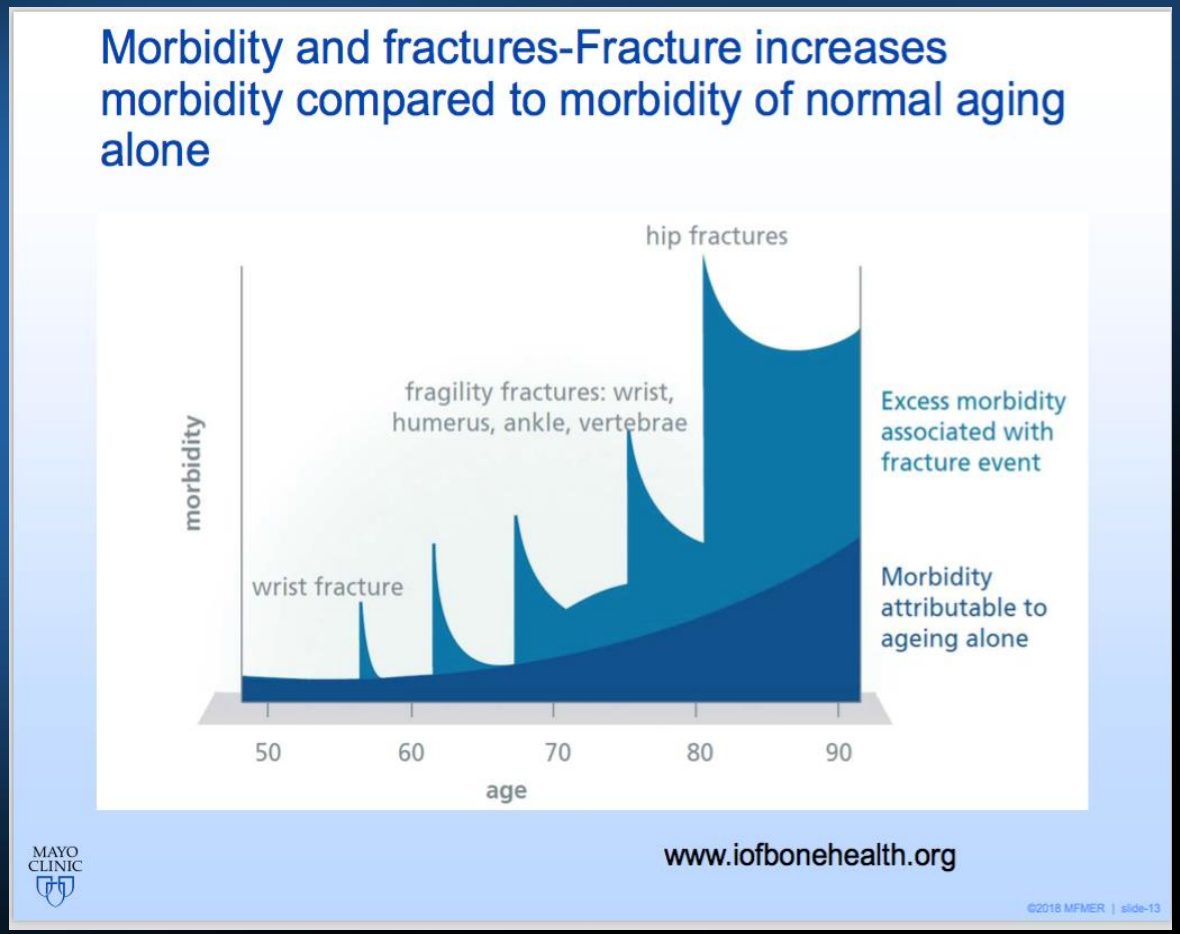
Disclosures

- No Conflicts of interest to disclose

Osteoporosis A Major Public Health Problem

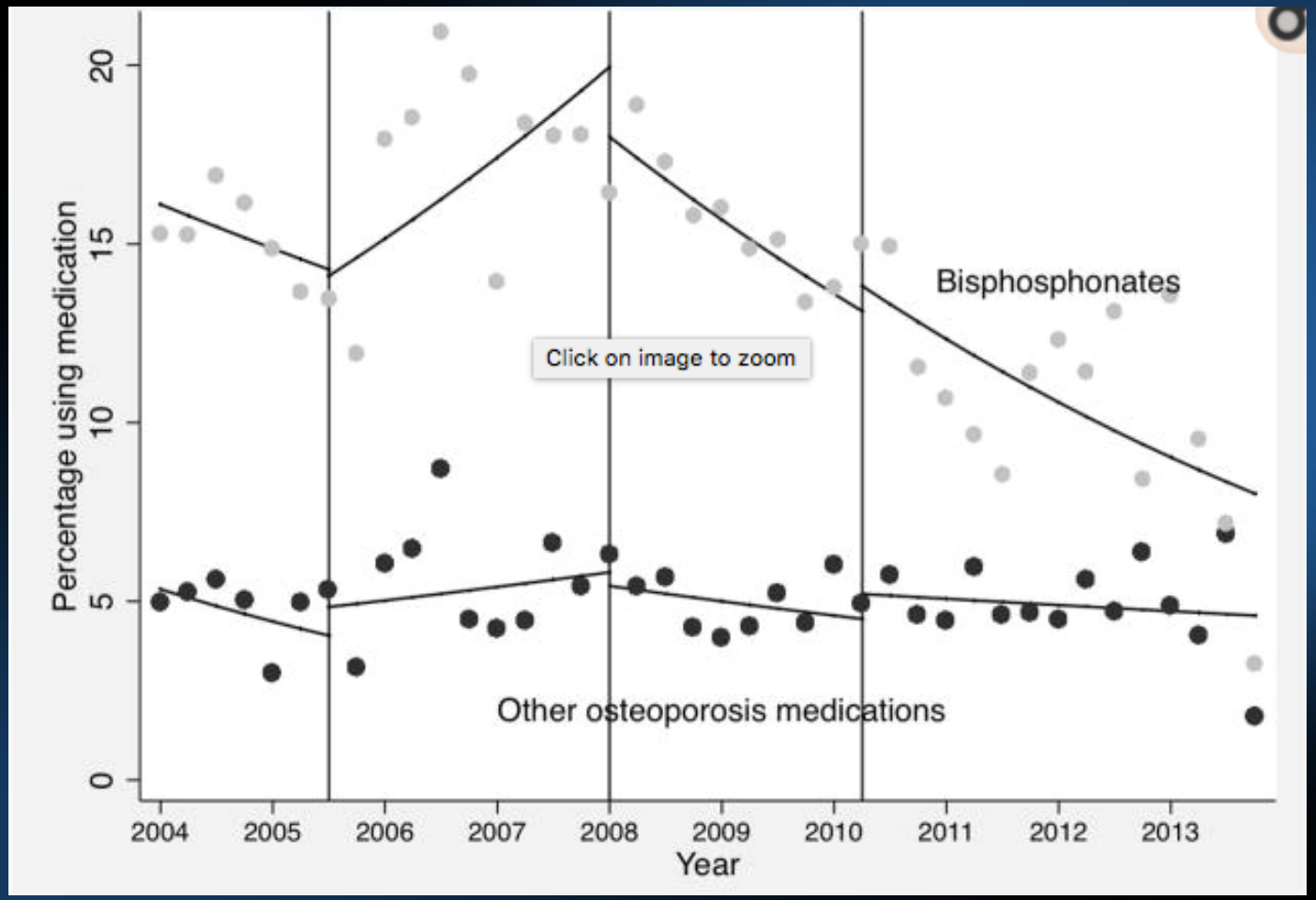
- Osteoporosis is a major and growing public health concern
- Postmenopausal osteoporosis is common . 1:2 women and 1:5 men, aged 50 and older, will have an OP fracture in their lifetime
- Vert. Fxs : A hallmark of the disease and indicate a high risk for future fractures
- Postmenopausal OP is preventable and treatable, but only a small proportion of women at increased risk for fracture are evaluated and treated



Endo. Pract.2016;22:1-41 ; Ost.Int.2011;22:373-390

IOF.bone health.org

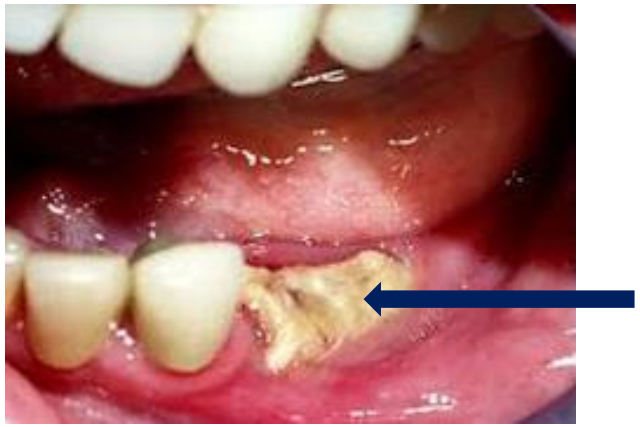
Impact of FDA Announcements on Bisphosphonates Prescriptions



Osteonecrosis of the Jaw (ONJ)

What is ONJ?

- Very delayed healing of a wound inside the mouth usually following a dental extraction
- An area of jaw bone is left exposed
- May be prone to becoming infected



Osteoporosis Dorset

What ONJ is <u>not</u>

- Crumbling jaw bone
- Just jaw pain
- Just a dental infection

Why does ONJ happen?

- It's not clear why it happens

Comparing the risks of fractures vs. ONJ

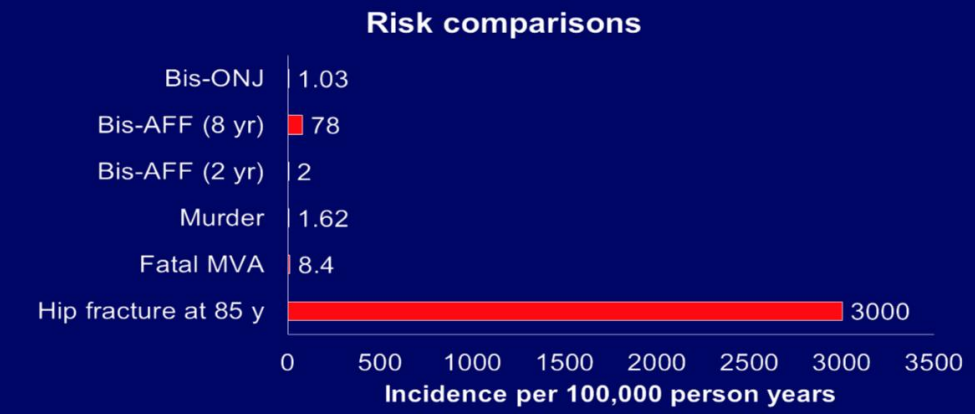
Risk of ONJ ***with*** alendronic acid is between 1 in 1000 & 1 in 10,000

Risk of a major fracture ***without*** alendronic acid is 1 in 4 (28%)

Which risk would you choose?

Overstated Fear of Biphosphonate Use

Relative Risk/Benefit



1. Transportation Canada. 2007 Casualty Rates.
2. Statistics Canada. 2009 Homicide Rate.
3. Khan A, et al. ASMBR, Toronto, 2010. Poster SA0384.
4. Dell R, et coll. JBMR 2010. 25(Suppl1):61. Abstract 1201
5. Johnell O, Oden A, Caulin F, Kanis JA. Osteoporos Int. 2001;12(3):207-14.

Bisphosphonates Prevent Hip Fractures

Expected Hip Fractures in 10,000 Patients at High Risk[1]

Bisphosphonates potentially double subtrochanteric fractures (typical or atypical)[1]

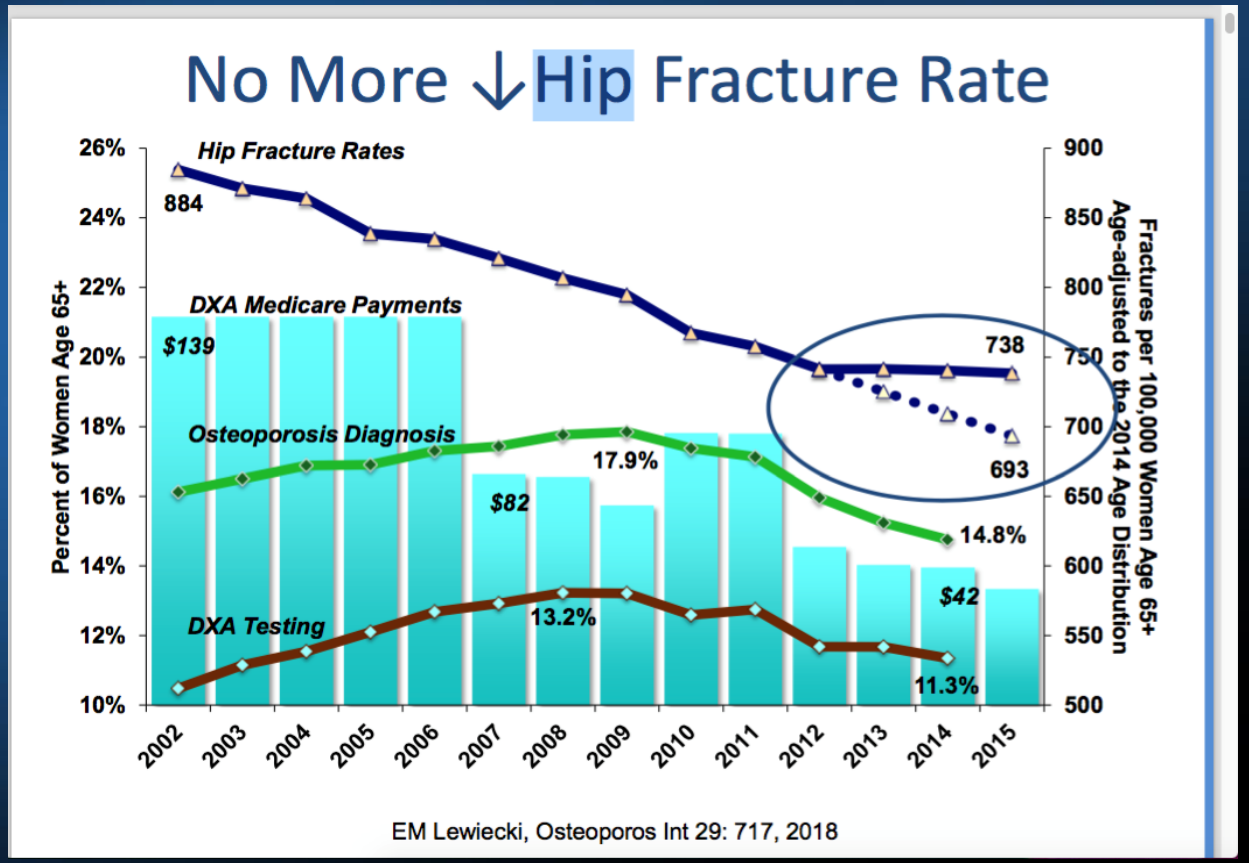
- **Hip fractures cause a high rate of morbidity and mortality[2,3]**
- **Incidence of subtrochanteric fracture very low**

1. Rizzoli R, et al. *Osteoporosis Int* 2011;22:373–390. 2. Cooper C, et al. *Am J Epidemiol* 1993;137:1001–1005. 3. Leibson CL, et al. *J Am Geriatr Soc*. 2002;50:1644–1650.

Ost.Int.2011;22:373

Gap on Osteoporosis Diagnosis and Treatment Stirs Concern

- With ongoing reports of AFFs and ONJ there is uncertainty among postmenopausal women and their HCPs regarding the benefits and risks of different management strategies
  - Who to treat
  - When to monitor
  - Appropriate duration of therapy
  - When to consider a bisphosphonate holiday
- Recent study of Medicare recipients who experienced a hip fracture found that just 19% of them had been receiving bone-active OP treatment before the fracture occurred.
- After the fracture, the % of women receiving treatment barely changed ..21%



Ost. Int. 29:717,2018

Endocrine Society Clinical Practice Guidelines

- Guideline Writing committee commissioned 2 systematic reviews derived from RCTs in postmenopausal women with primary osteoporosis
- Included 107 trials n=193,887 women
- Meta-analyses were done in 2 ways:
  - direct comparison with placebo
  - Combination of direct and indirect comparisons
- Second review was aimed at evaluating values and preferences relevant to the management of osteoporosis in women

JCEM 2019; 104:1595-1622

Evaluation of Values and Preferences Relevant to Management of Osteoporosis

- In general, effectiveness and adverse events considered equally
- Followed by the convenience of taking the drug and impact on daily routines
  - < frequent dosing preferred
  - Oral route preferred
- Injectable route preferred over oral if given< frequently
- Cost (out of pocket) and duration of treatment were less imp. factors for decision-making
- Drug time in market and < drug-drug interactions

JCEM 104:1595-1622,2019

Algorithm for the Management of Postmenopausal Osteoporosis

Lifestyle and nutritional optimization for bone health

Determine the 10 yr fracture risk

high-very high risk

Calcium +vit D as adjunct therapy

BPs reassess fx risk in 3-5 yrs.

5 yrs.for oral; 3 yrs. for IV

teriparatide or abaloparatide for 2 yrs

Denosumab

Reassess fx risk in 5-10 yrs

JCEM 2019;104:1595

Algorithm for the management of Postmenopausal Osteoporosis

bisphosphonates

denosumab

Low-moderate risk
Consider a drug holiday
Reassess fx risk q 2-4 yrs.
If bone loss or pt becomes high risk, consider restarting therapy

High risk
Continue therapy or switch to another Rx

Intolerant to or inappropriate for above therapies

Age >60
Consider SERMs
Low risk of DVT
High risk of breast cancer

High risk
continue therapy or switch to another therapy

JCEM 104:1595-1622,2019

Algorithm for the Management of Postmenopausal Osteoporosis

Lifestyle and nutritional optimization for bone health

Determine the 10 yr fracture risk

Low-moderate risk

Reassess fracture risk in 2-4 yrs.

Or

Bisphoponates

reassess fx risk in 3-5 yrs.

5 yrs.for oral; 3 yrs. for IV

Consider a drug holiday
Reassess fracture risk q 2-4 yrs.
If bone loss or pt becomes high risk ,consider restarting RX

JCEM 2019;104:1595

Case #1 Zoledronic Acid

- Teresa is a 61 y/o female with facial neuralgia and GERD
- She had a T6 vertebral fracture after falling down a stair and clavicle and humerus fracture in another occasion She received zoledronic acid x 3 yrs Last 1/2017. Now on holiday period . Both extension trials, FLEX and HORIZON, checked BMD annually

DXA	T-score (after Zol. Rx)	% decrease since DXA 2016
spine	-2.4	-4%
Total Hip	-1.0	-3.5%

Case # 1 Zoledronic Acid
Bisphosphonate Holiday

- BMD decreased by > than LSC . Decreased by 4.4% spine and 3.5% in TH
- . In Horizon Extension Trial Z3P3 P1NP still remained below premenopausal level (28ng/ml) vs Z6 (25 ng/ml)
- P1NP increased from 13 (2015) to 39 ng/ml . Increased by >than 10 ng/ml which is considered significant
- More studies are needed to determine if BTMs are of clinical utility for guiding drug holiday

- Holiday period must be ended

• Case #1 Zoledronic Acid What Would be your Next Step?

- zoledronic acid for 3 years
- Zoledronic acid for 1 year
- Switch to another treatment
- d/c treatment .She no longer has OP by BMD

Bisphosphonate Drug Holiday

- Guideline 2.2
- A bisphosphonate (BP) drug holiday is considered after 3 yrs with zoledronic acid (or 5 yrs with oral BPs) if BMD is above -2.5
- Women who remain at high risk should continue therapy
- Once a BP holiday is initiated, reassess fracture risk interval and consider reinitiating OP therapy earlier than the 5 -year suggested maximum if:
  - there is a significant decline in BMD ,
  - an intervening fracture,
  - or other factors that alter clinical risk status

Holiday only belongs to bisphosphonates

Candidates for a Drug Holiday ?

- When patient never needed treatment in the first place
  - Retrospective application of NOF guide
- After good response (bone mineral density/bone turnover marker) to at least
  5 years of treatment and fracture risk no longer high
  - No fracture, T-score >-2.5, "young"
- Continue treatment in high-risk patients
  - Previous fractures, T-score <= -2.5

Risk of Clinical Vertebral Fracture and Number Needed to Treat for 5 Years to Prevent One Clinical Vertebral Fracture in the Fracture Intervention Trial Long-Term Extension (FLEX) Study.*

Femoral Neck BMD T Score at Start of Extension†	5-Yr Risk of Clinical Vertebral Fracture		Risk Difference (95% CI)	Number Needed to Trea
	Placebo Group	Alendronate Group‡		
	no./total no. (%)			
All women in study				
All BMD T scores	23/437 (5.5)	16/662 (2.5)	2.9 (0.3–5.4)	34
Less than or equal to –2.5	11/132 (9.3)	9/190 (4.5)	4.8 (0.8–9.2)	21
Greater than –2.5 and less than or equal to –2.0	9/126 (5.8)	3/185 (2.8)	3.0 (0.3–6.7)	33
Greater than –2.0	3/179 (2.3)	4/282 (1.1)	1.2 (0.2–2.8)	81
Women with no prevalent vertebral fracture at start of FLEX study				
Less than or equal to –2.5	6/75 (8.0)	4/109 (3.8)	4.2 (0.6–9.1)	24
Greater than –2.5 and less than or equal to –2.0	3/82 (3.0)	1/121 (1.4)	1.6 (0.2–5.0)	63
Greater than –2.0	2/130 (1.8)	2/203 (0.9)	1.0 (0.1–2.6)	102
Women with prevalent vertebral fracture at start of FLEX study				
Less than or equal to –2.5	5/57 (11.1)	5/81 (5.3)	5.8 (0.8–12.1)	17
Greater than –2.5 and less than or equal to –2.0	6/44 (11.1)	2/64 (5.3)	5.8 (0.8–13.6)	17
Greater than –2.0	1/49 (3.7)	2/79 (1.7)	2.0 (0.3–5.6)	51

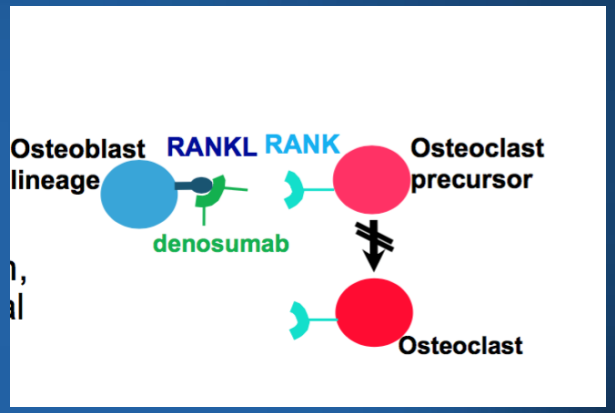
Black D NEJM 2012;361:22

When to End a Bisphosphonate Holiday

- Not clear
- Possible approaches
  - Arbitrarily restart treatment after 1–2 years
  - Monitor BMD/BTM every 6–12 months and restart treatment when significant decrease in BMD or increase in BTM occurs
- Reconsider treatment plan if fracture or change in clinical status

Case #2 Denosumab

- Denise is a 71 yr/o female who has been receiving denosumab q 6 months, without side effects, for the last 5 years . Cost is not an issue
- What is next best step?
  - She's doing great. Stop denosumab
  - She is doing great. Continue with denosumab
  - Change to zoledronic
  - Change to oral bisphosphonates



T-scores	2013	2018	% increase
spine	-2.8	.-2.2	+9.8%
Femoral neck	-2.5	-2.0	+9.3%

Case #2 Denosumab

- GUIDELINE
  - Administration of Denosumab should NOT be delayed or stopped without subsequent antiresorptives (Bisphosphonates, SERMS, HRT)
  - This would prevent the rebound in bone turnover, rapid bone loss (>= 6%) , and risk of vertebral fractures that may occur after stopping denosumab
  - CTX and P1NP increase above baseline values within 3-6 months of d/c denosumab

Stopping Denosumab

- When would you give the antiresorptive if you are planning to stop denosumab?
  - Just before the next expected dose of denosumab ?
  - Wait 1-2 months post last dose of denosumab and then give IV or po antiresorptive (unless she has CKD)

Switch to Other antiresorptive: Summary

- Pros
  - May prevent bone loss observed after stopping denosumab
- Cons:
  - Ideal antiresorptive and preferred timing is unknown
  - If giving Zol. Acid, may need to be given not “too early” or “too late”
- Unkown :
  - Effect on fracture risk

Case 3

- 70 y/o woman, 25 years post menopausal, referred for osteoporosis treatment after a recent painful severe T12 fracture
- No prior treatment for osteoporosis
- Spine T-score -3.5, FN T-score -2.9
- What treatment would you prefer?
  - PO Bisphosphonate
  - IV bisphosphonate
  - Denosumab
  - Teriparatide or abaloparatide

Endocrine Soiciety Guidelines

- In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe or multiple fractures, we recommend teriparatide or abaloparatide treatment for 2 years for the reduction of vertebral and nonvertebral fractures
- In postmenopausal women with osteoporosis who have completed a 2 year course we recommend treatment with antiresorptive therapies to maintain bone density gains

	Vertebral Fracture risk reduction %	**Nonvertebral risk reduction %**
Teriparatide (Forteo)	74	39
Abaloparatide (Tymlos)	87	46

Osteoanabolic Agents for Osteoporosis
PTH Analogs

Trial name	Study drug	Mechanism of action
Fracture prevention Trial N 1637	Teriparatide Forteo 2002	Recombinant human PTH (PTH 1-34 of the N terminal of PTH) Binds to PTH1receptor (2 conformations RG and R0)
Abaloparatide N 2463	Abaloparatide Tymlos 2017	PTH rP (1-34) is a 34 AA synthetic analog of PTHrP .identical to PTHrP at AA 1-22 > Affinity for the RG conformation of PTH 1R

J of the Endoc Soc 2018;922-932

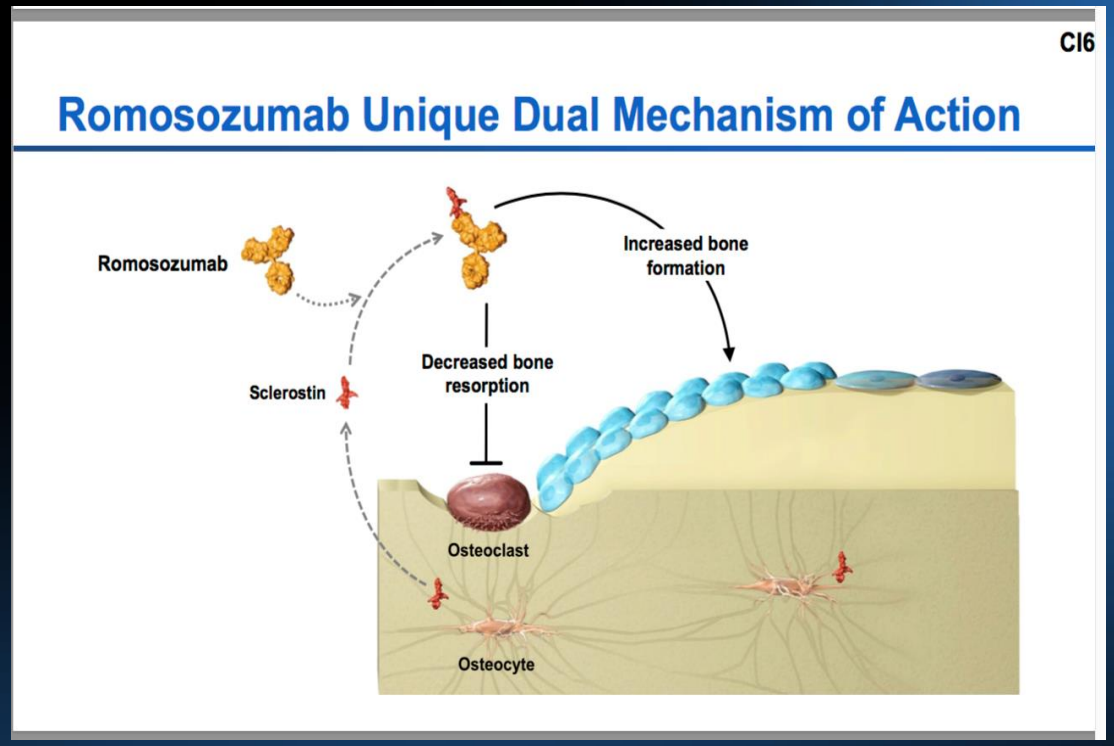
Osteoanabolic Agents for Osteoporosis

Trial name	Study drug	Mechanism of action
Frame N 7180 Evenity vs placebo	Romosozumab Evenity 2019	Humanized monoclonal Ab to sclerostin.
Bridge N 245	romosozumab	
Arch N4093 Aln vs evenity	romosozumab	

J endocr Soc 2018: 922-932

J of the Endoc Soc 2018;922-932

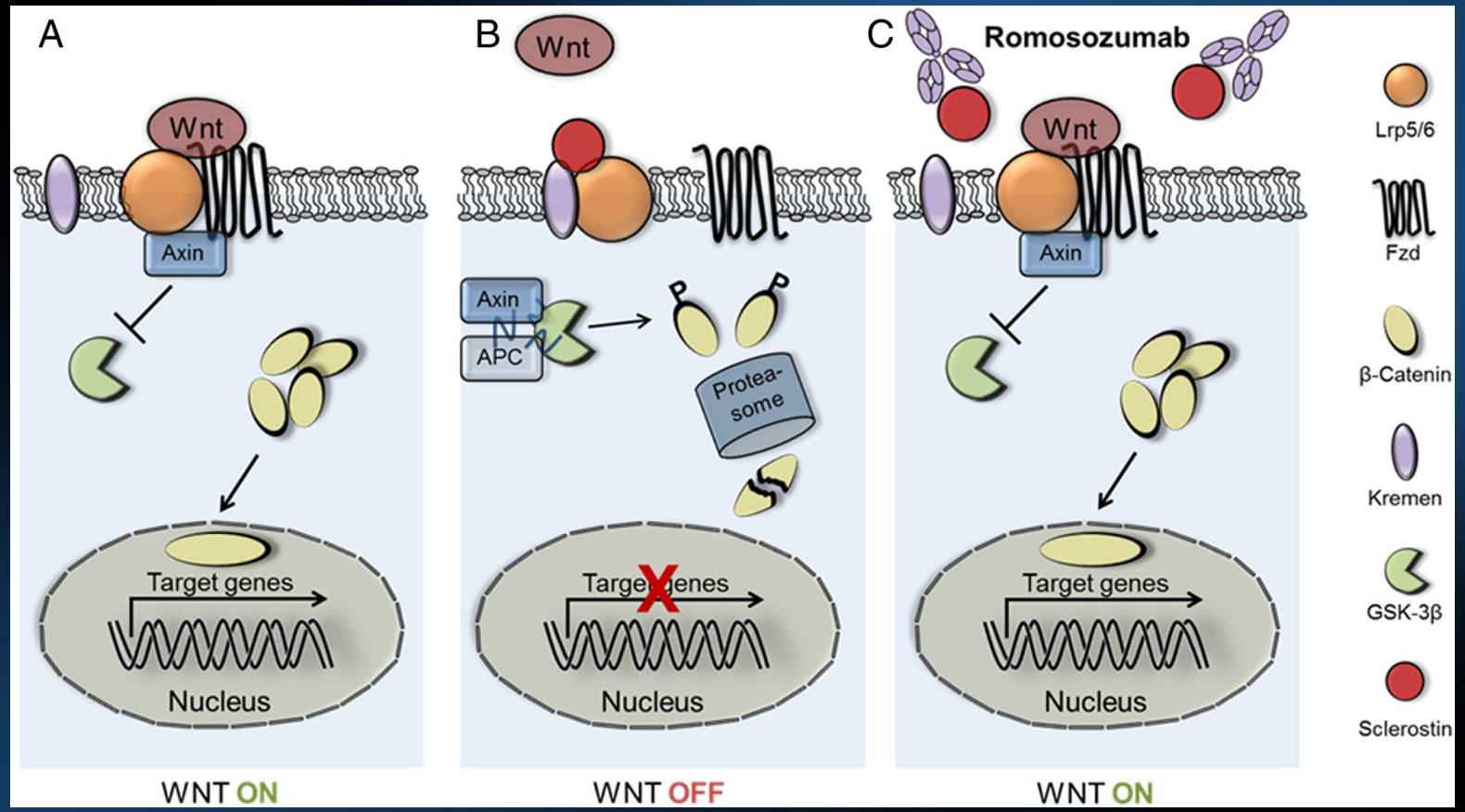
Romosozumab :Dual Mechanism of Action



Prefilled syringe : 105 mg/1.17 ml

Dose 210 mgs

Romosozumab : Humanized Monoclonal Antibody to Sclerostin



Int'l J Women's Health 2015;7:565

FRAME Study

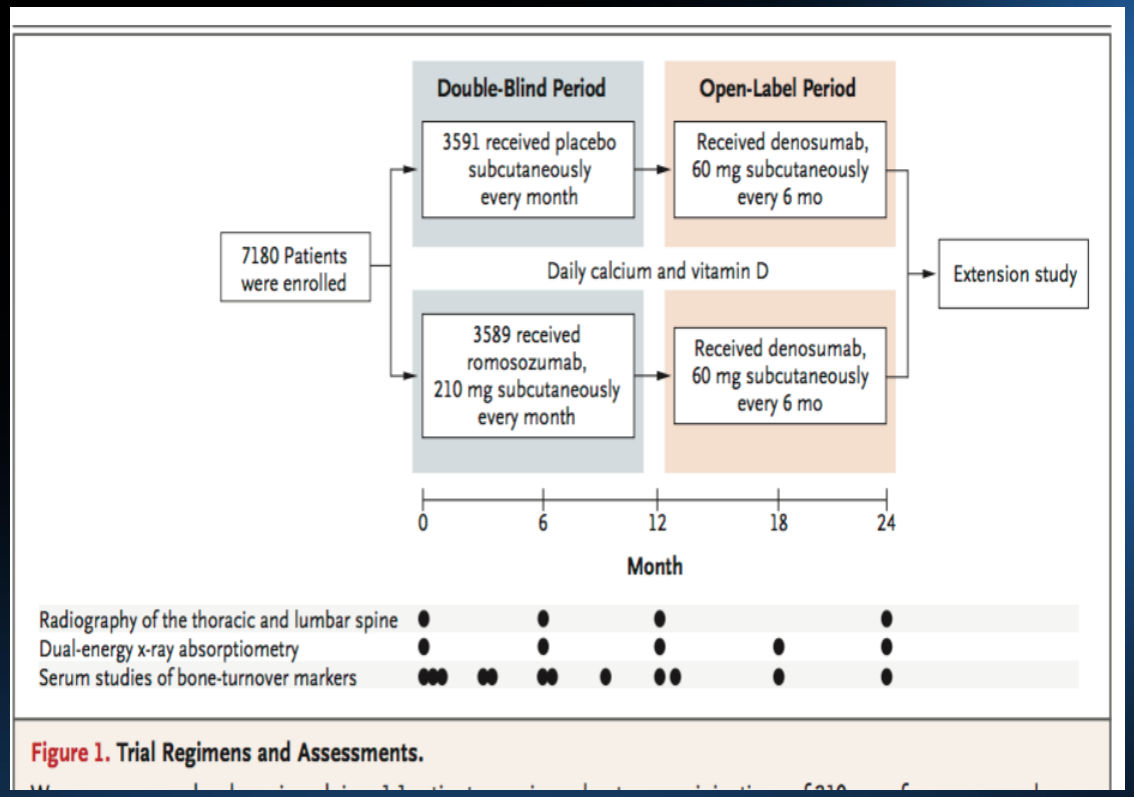
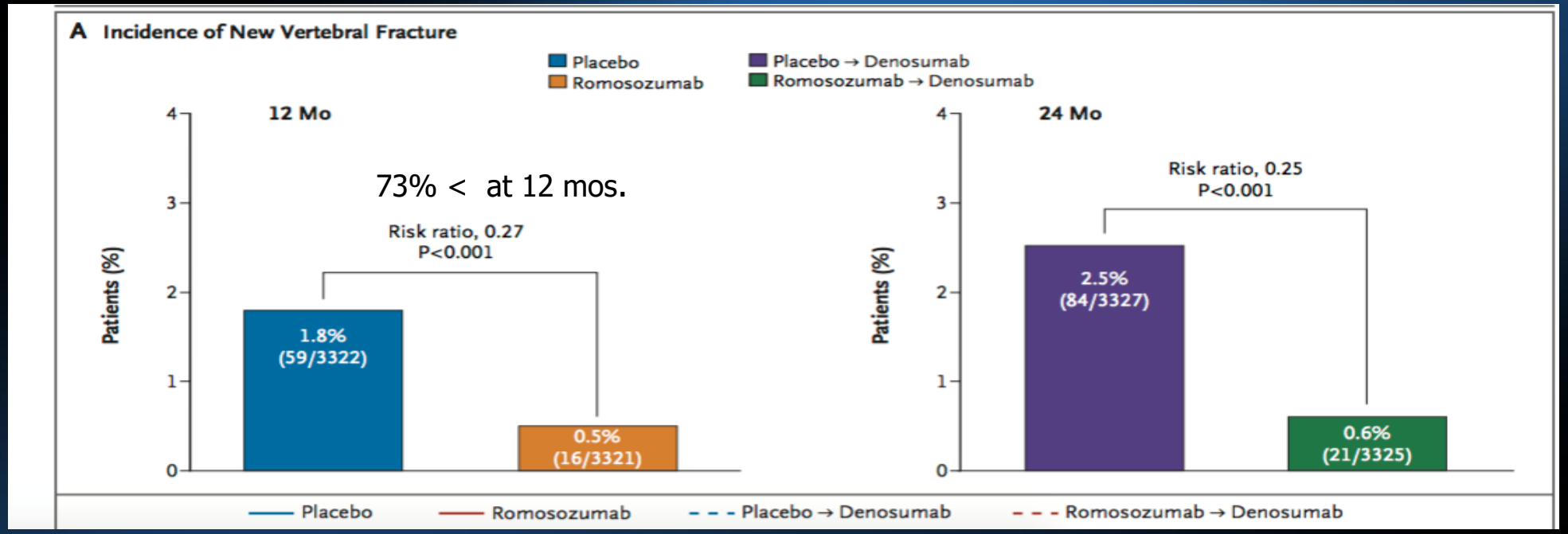


Figure 1. Trial Regimens and Assessments.

- Mean age 70.9 yrs.
- Mean BMD -2.72 LS; -2.47 TH,-2.75 FN
- 18.3% had a prevalent vertebral fracture (most mild to moderate)
- 21.7% had a previous nonvertebral fracture

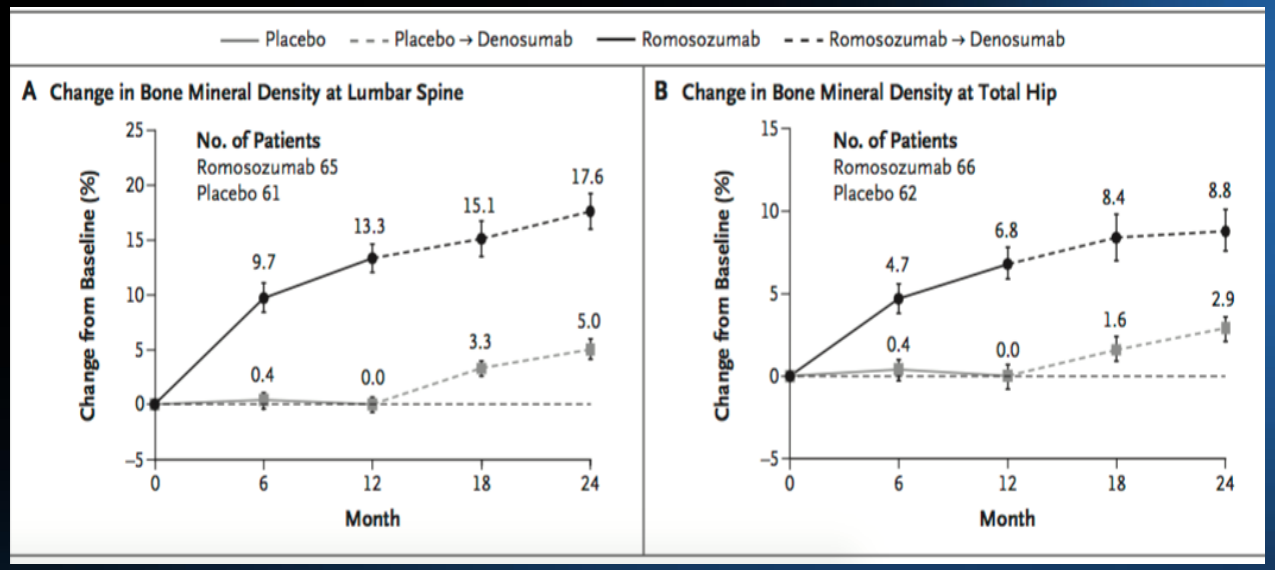
Cosman F NEJM 2016 ;375:1532

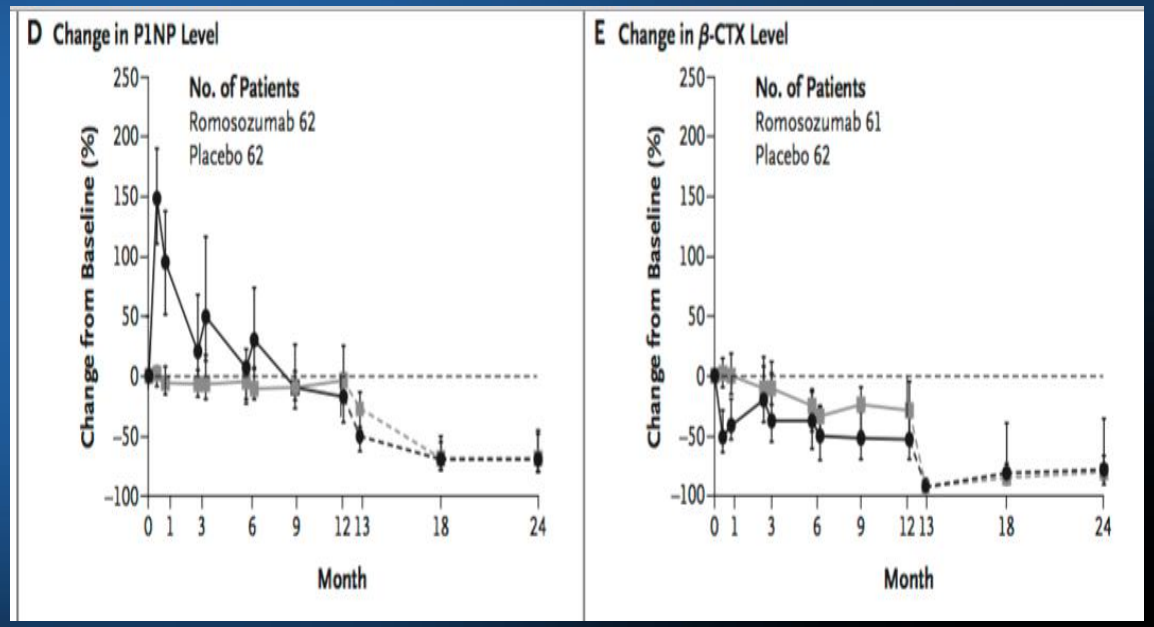
Romozumab in Postmenopausal Women With Osteoporosis
Incidence of New Vertebral Fractures



Cosman F NEJM 2016 ;375:1532

% Changes From Baseline in BMD and in BTMs





Cosman F NEJM 2016 ;375:1532

Fracture Efficacy Summary : Non Vertebral Fractures

- Clinical and nonvertebral fractures nominally significant at 12-24 months p<.05
- Subgroup analysis (post Hoc) : Larger nonvertebral fracture reductions outside of Latin America
- Not LA 57% HR 0.58%
- Latin America 43% HR 1.25
  - Incidence of nonvertebral fractures in LA
    - In those using placebo risk of NV fractures 1/3 of expected
    - Romosozumab no detectable treatment effect

BMD T-score increases in FRAME vs FREEDOM and FREEDOM Extension

D

LS

TH

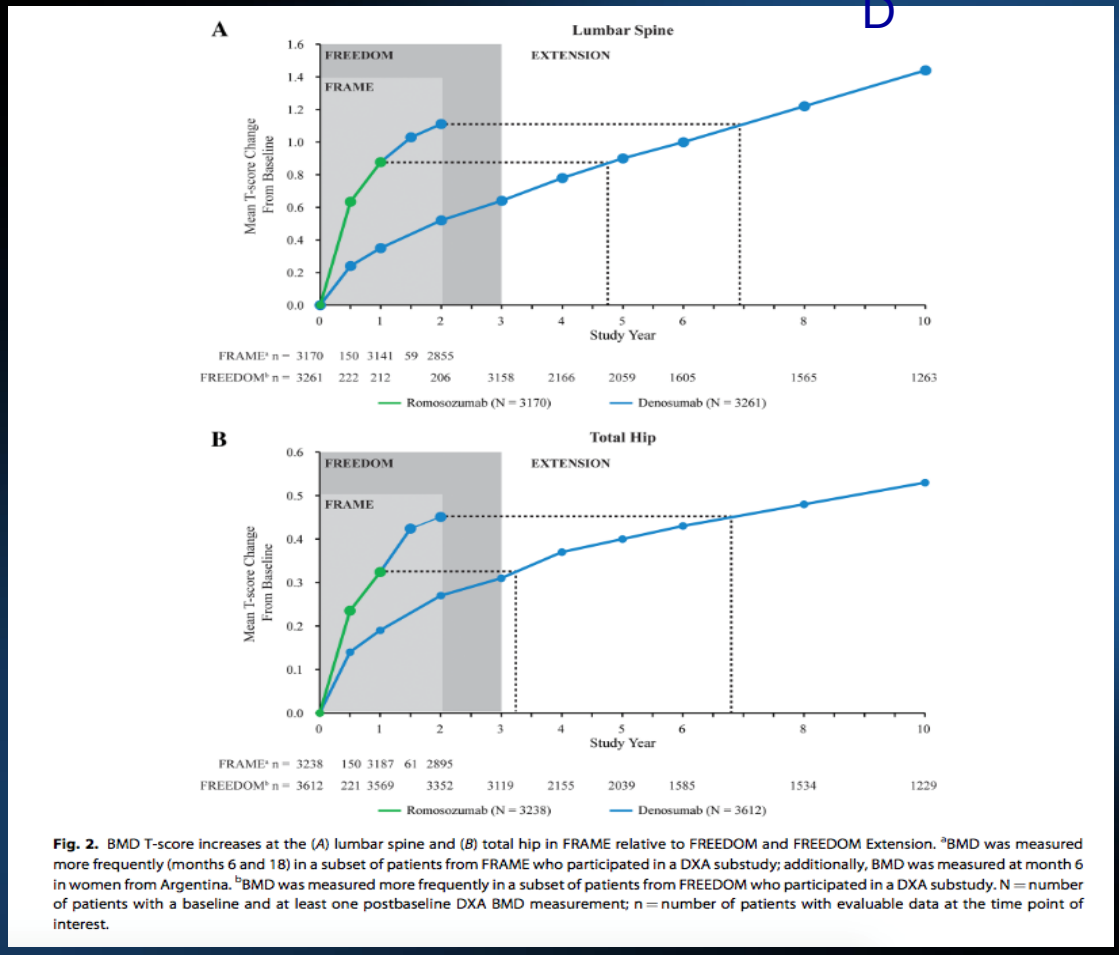
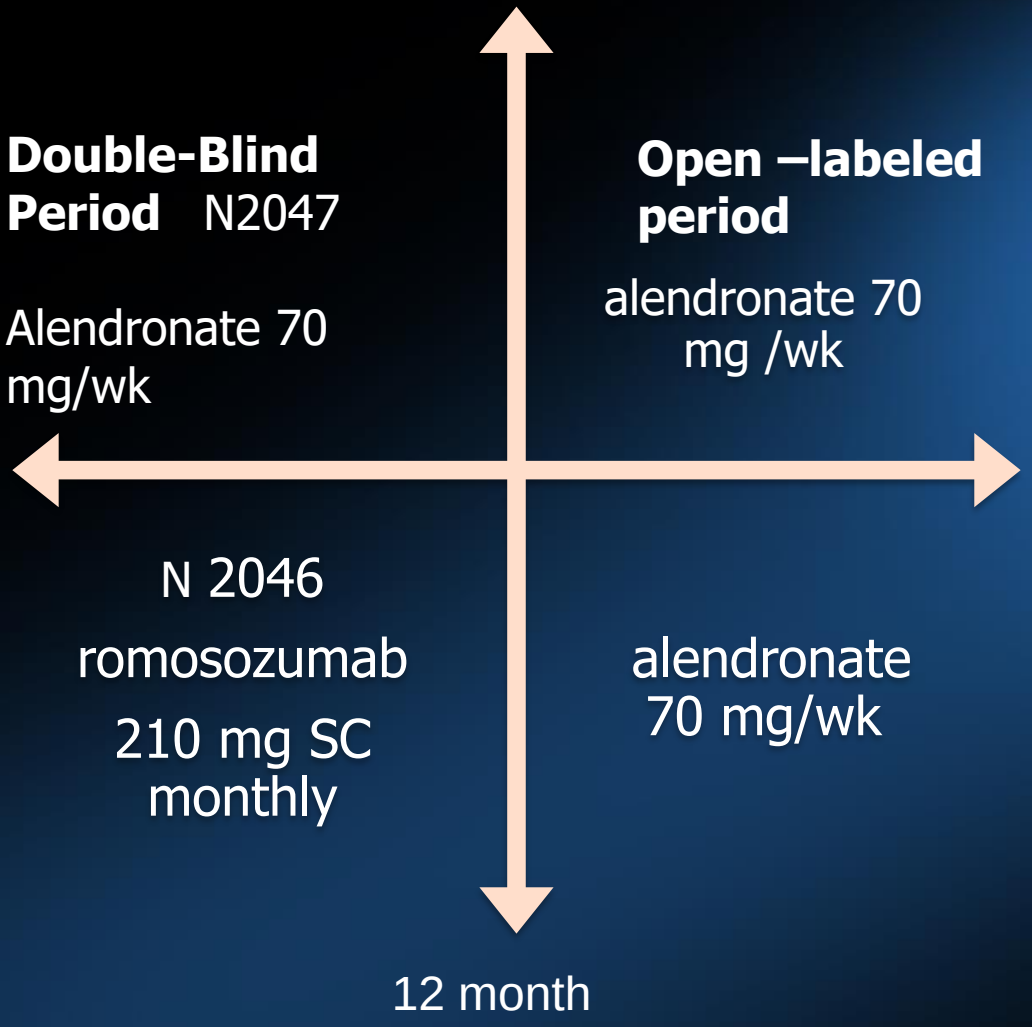


Fig. 2. BMD T-score increases at the (*A*) lumbar spine and (*B*) total hip in FRAME relative to FREEDOM and FREEDOM Extension. [a]BMD was measured more frequently (months 6 and 18) in a subset of patients from FRAME who participated in a DXA substudy; additionally, BMD was measured at month 6 in women from Argentina. [b]BMD was measured more frequently in a subset of patients from FREEDOM who participated in a DXA substudy. N = number of patients with a baseline and at least one postbaseline DXA BMD measurement; n = number of patients with evaluable data at the time point of interest.

JBMR 2018;33:1219

ARCH Study Trial Schema

(Active-Controlled Fracture Study in PM Women with Osteoporosis)



- Treatment groups were similar in age, ethnicity, and fracture history Mean age 74 y/o. 50% >/= 75 y/o
- Majority non-Hispanics >60%
- 99% had a previous osteoporotic fracture
- 96% had a prevalent vertebral fracture
- >/= 1 moderate or severe vert. fx or >/=2 mild vert fractures
- Mean BMD
  - -2.96 LS
  - -2.80 TH
  - -2.90 FN

Saag K NEJM 2017;377:1417

Primary Outcome: New Vertebral, Clinical, and Nonvertebral Fractures

47%

27%

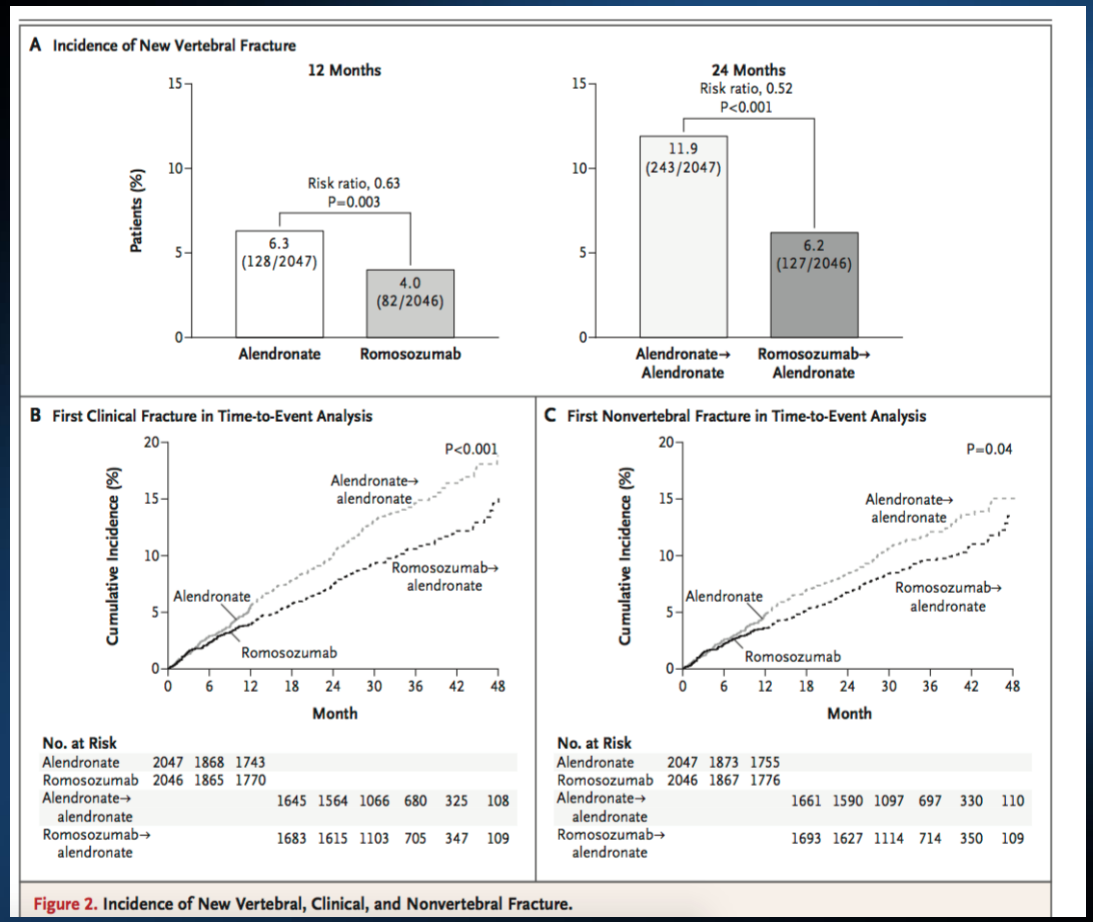


Figure 2. Incidence of New Vertebral, Clinical, and Nonvertebral Fracture.

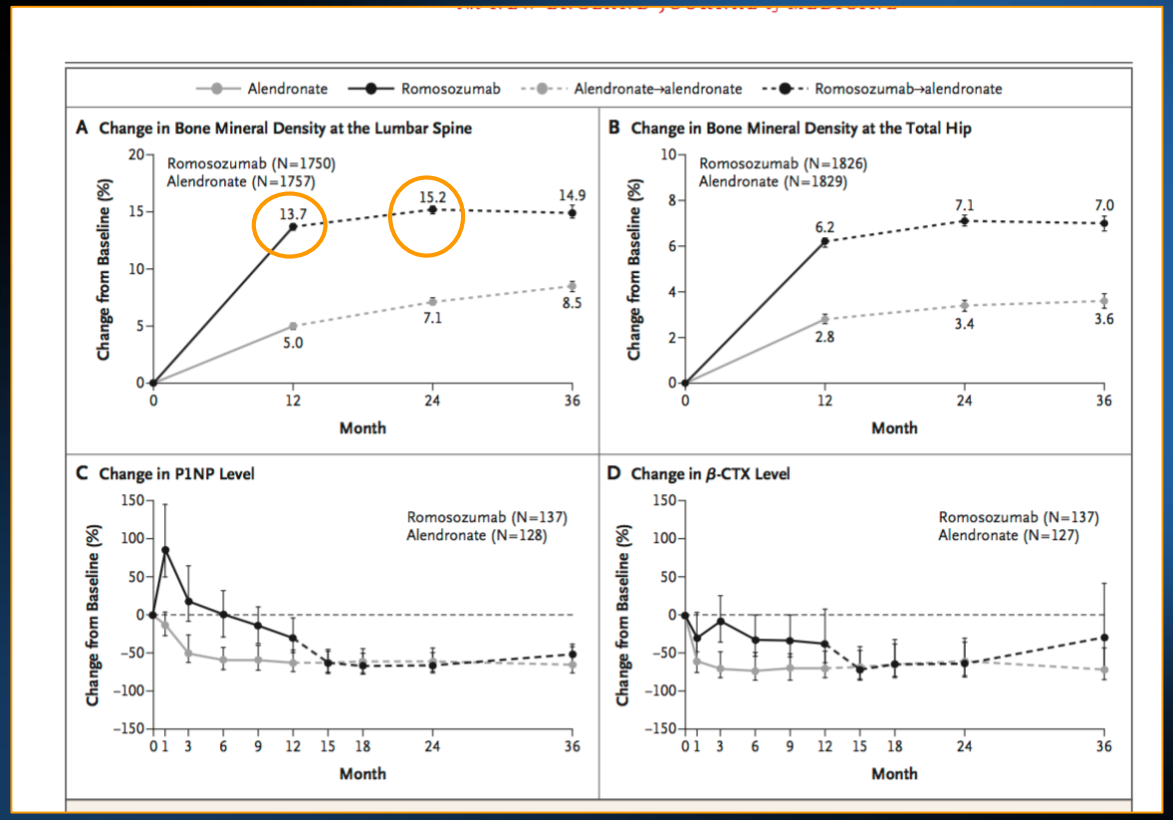
48%

19%

Hip Fractures
38% lower risk with Romosozumab (2% vs 3.2%)

Saag K NEJM 2017; 377:1417

% Change from Baseline in BMD and Levels Of BTMs



Saag K NEJM 2017;377:1417

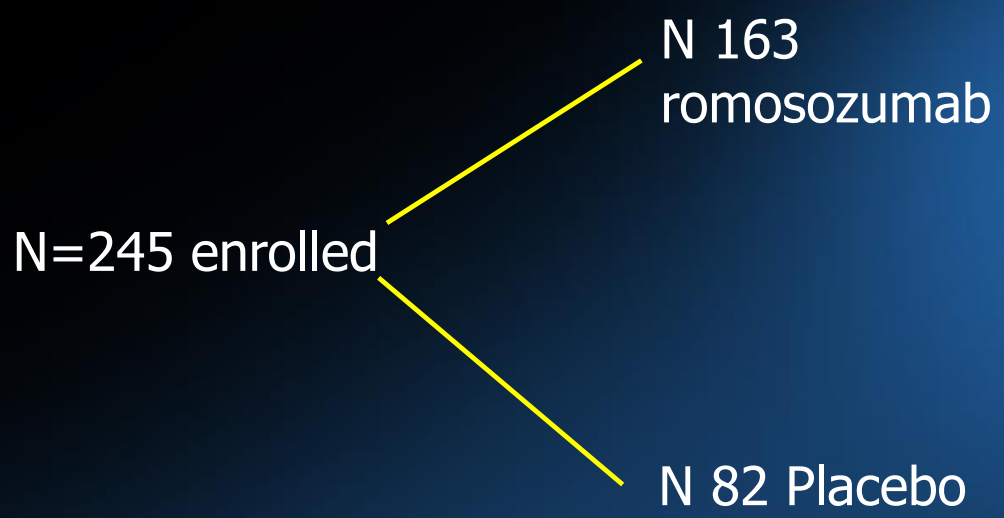
Adverse Events

- Adverse events and serious adverse event rates were similar between the 2 treatment groups during the double- blind period with 2 exceptions :
- Injection- site reactions 4.4% vs 2.6%
- Increased incidence of adjudicated serious CV events during the double-blind period
  - 2.5% (50/2040) vs 1.9% (38/2014)
  - Included cardiac ischemic events, Cerebrovascular events, heart failure
  - Difference remained stable during the second 12 months after all patients were switched to alendronate (6.5% vs 6.1%)

J of Clinical Outcomes 2018 march

Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men with Osteoporosis

- **Study Design**



- **Baseline characteristics**
  - Balanced between the 2 groups
  - Overall, mean age was 72→7.3 yrs. With 40% >75 y/o
- **Baseline T-score**
  - -2.3 +- 1.3 LS
  - -1.9 +- 0.6 TH
  - -2.3 +- 0.5 FN
- **Similar fracture risk**
  - 53% and 56% had a previous fracture, respectively

Lewiecki M JCEM 103: 3183,2019

Phase III Trial in Men : Bridge

- Romosozumab significantly increased BMD in LS and TH N 245
- Bone biobsy in 20 patients Parameters of bone reorption had decreased and those of bone formation were unchanged
- However, there was an increase in adjudicated serious CVEs : 4.9% vs 2.5%
  - Cardiac ischemic events 1.8% vs 0%
  - Cerebrovascular events 1.8% vs 1.2%

Lewiecki M JCEM 103:3183-3193,2018

Cardiovascular Outcomes of Romosozumab

- Slight increase in CV outcomes in ARCH and Bridge study
- Important to mention that the Frame Study (Fracture Study in Postmenopausal women with Osteoporosis) a larger, N 7180, placebo controlled trial didn't show significant differences in adjudicated serious cv events. Enrolled a somewhat younger population with < advanced osteoporosis
- In a 12 month trial including 436 pm women with osteoporosis, who were transitioning from bisphosphonates to romosozumab or teriparatide the incidence of serious adverse events 8% vs 11% were lower in the romosozumab group
- Another important contrast with FRAME , is the comparison drug. (Placebo vs bisphosphonate)
- Alendronate has been associated with a reduction in the risk of CVD in some studies but not in 2 meta-analysis.
- Further evaluation is needed to determine the cause of the observed imbalance in CV events

Arterioscler Thromb Vasc Biol 2019;39:1343

Arterioscler Thromb Vasc Biol 2019;39:1343

Sclerostin, Bone, and Vessels

- Osteocytes are a major source of sclerostin though chondrocytes, liver, kidney, and vascular wall (aorta)may also secrete it.
- There are theoretical considerations that sclerostin inhibition could be associated with CV risk
- Sclerostin is expressed in the aorta and up-regulated in foci of vascular and valvular calcification
- Although sclerostin (inhibitor of WnT canonical pathway) may function as a negative regulator of vascular calcification and sclerostin inhibition could promote vascular calcification studies have shown conflicting results
- The unclear relationship between sclerostin and vascular calcification or CVEs is likely due to the inconsistency of published data on sample size, underlying conditions, anatomic site of investigation, and different methods of analysis
- Sclerosteosis; Van Buchem's disease

Arterioscler Thromb Vasc Biol 2019;39:1343

Arterioscler Thromb Vasc Biol 2019;39:1343

Making Choices Among Anabolic Therapies

- Administration
  - Monthly in-office injections 12 monthly vs
  - Daily self injection for 18-24 months
  - Cost
  - Patient or physician preference
- Safety
  - PTH analogues possible osteosarcoma : unlikely
  - Sclerostin inhibitor, Romosozumab : possible but small ↑ in CVEs
- Efficacy
  - All reduce vertebral and nonvertebral fractures; but no head to head studies
  - Larger early↑ in hip BMD with romosozumab . May be considered for patients at very high risk of hip or nonvertebral fractures

Endocrine Society Guidelines :Essential Points

- Treat high risk individuals –particularly those with previous fracture
- Consider bisphosphonates as the first line therapeutic choice for postmenopausal women at high risk of fracture
- Reassess fracture risk after patient has been on bisphosphonates for 3-5 yrs.
- Following reassessment, prescribe "bisphosphonate holiday" for women who are on bisphosphonate and have a low-to-moderate risk of fracture
- In post menopausal women with osteoporosis who are at high risk of fractures, consider using denosumab as an alternative INITIAl treatment
- Consider anabolic therapy, teriparatide or abaloparatide, in postmenopausal women with osteoporosis at very high risk of fracture
- There is no drug holiday for denosumab or anabolic therapy

Thank You !

Incidence of clinical and Nonvertebral Fractures

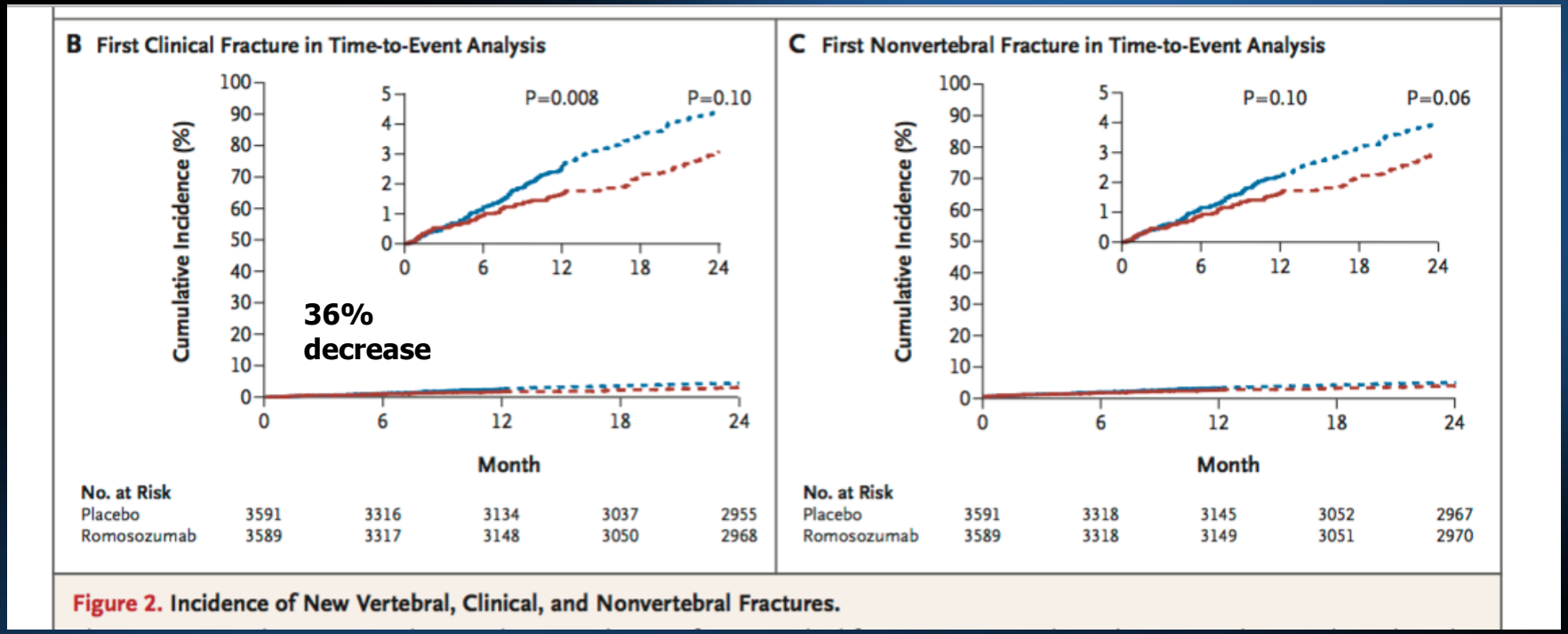
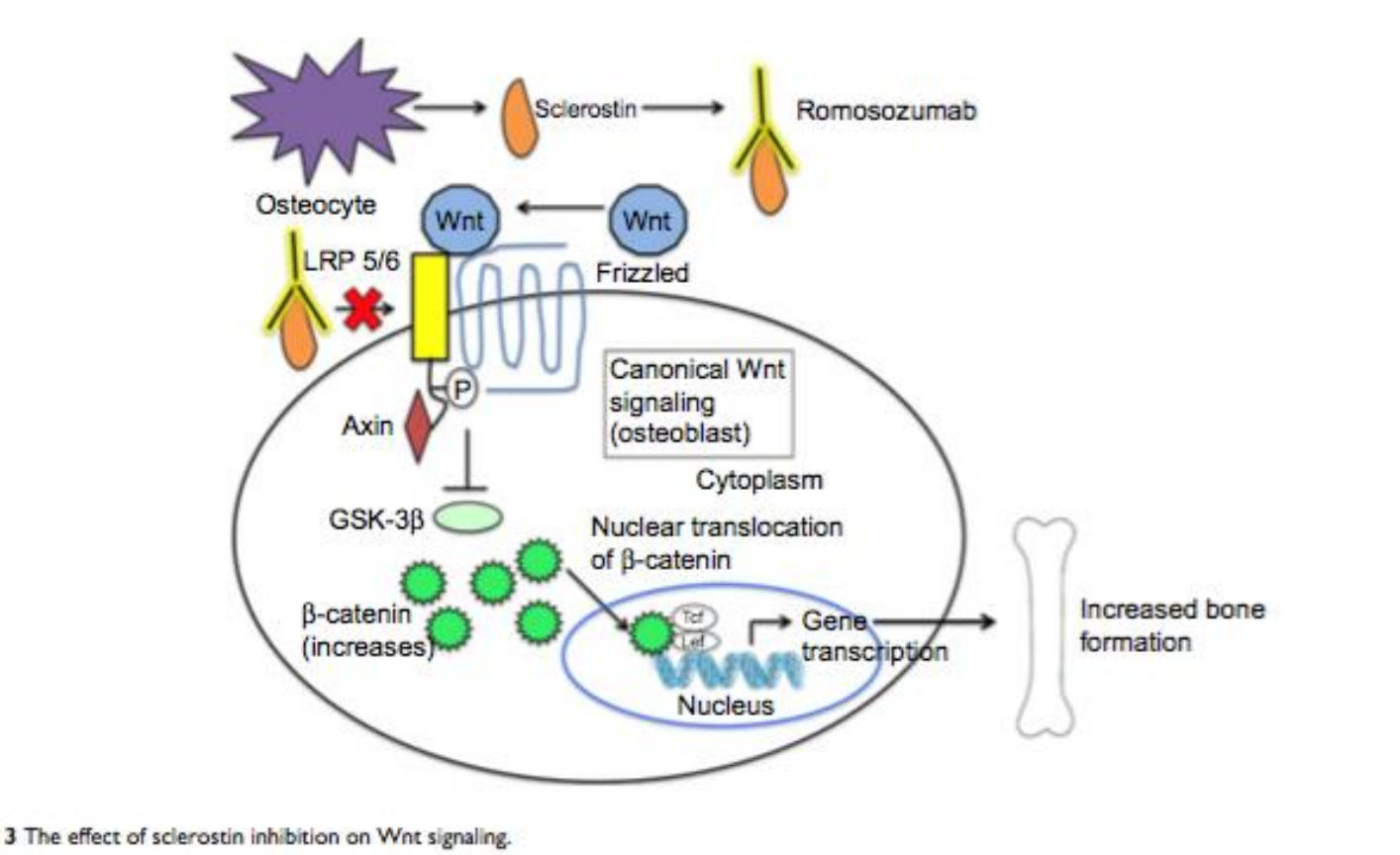


Figure 2. Incidence of New Vertebral, Clinical, and Nonvertebral Fractures.

Cosman F NEJM 2016 ;375:1532

Sclerostin Inhibition on WnT Signal



3 The effect of sclerostin inhibition on Wnt signaling.

Int'l J of Women's Health 2015;7:565

Sclerosteosis /Van Buchem Disease

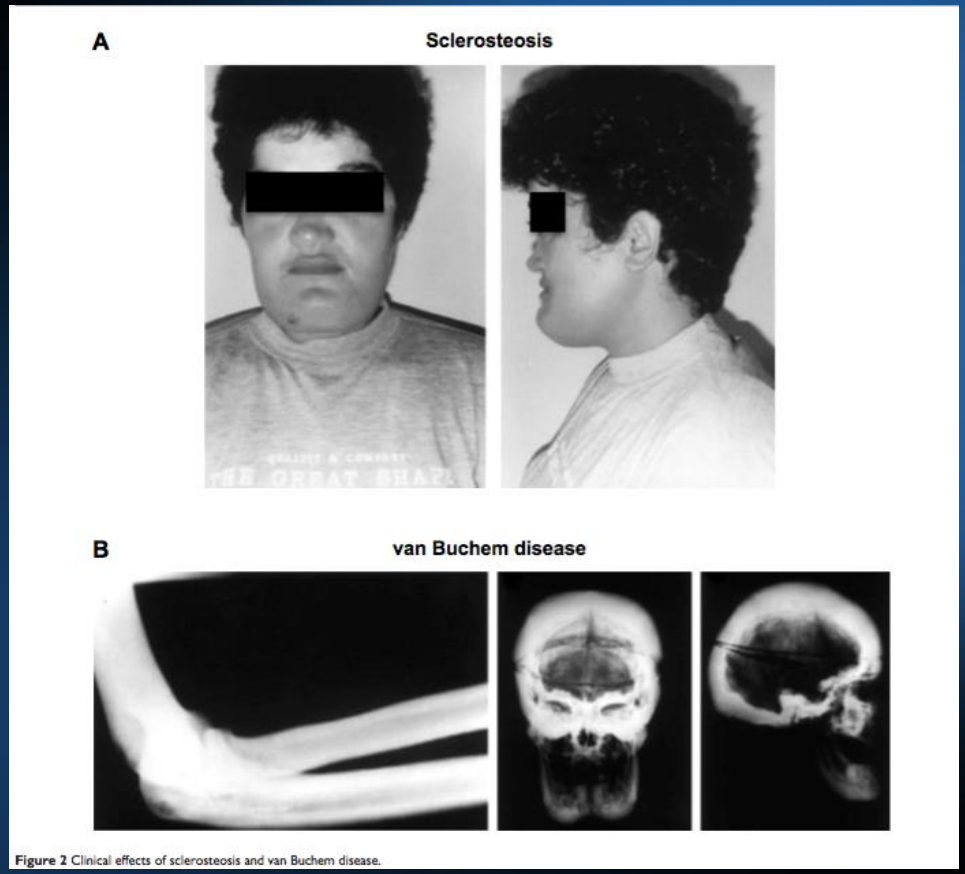


Figure 2 Clinical effects of sclerosteosis and van Buchem disease.

Am J of Human Genetics 62:1661

Potential explanations for CV outcomes

- There are theoretical considerations that sclerostin inhibition could be associated with CV risk
- Sclerostin is expressed in the aorta and up-regulated in foci of vascular and valvular calcification
- WnT pathway-shared mechanism of bone and cv system
- Wnt in cardiovascular disease
  - Family that carried a missense mutation in LRP6 gene, results in hyperlipemia, early CAD as well as osteoporosis
  - Mutations in LRP6 gene cause an impairment in canonical WnT signaling
  - Indicating that WnT has a protective role in atherosclerosis
  - Taken altogether, although there is evidence to support both adverse and beneficial roles of WnT in CVD, the weight of evidence favors that canonical WnT-B –catenin signaling may have a net beneficial role

Arterioscler Thromb Vasc Biol 2019;39:1343

Incidence of Fractures
placebo-denosumab vs romosozumab –denosumab

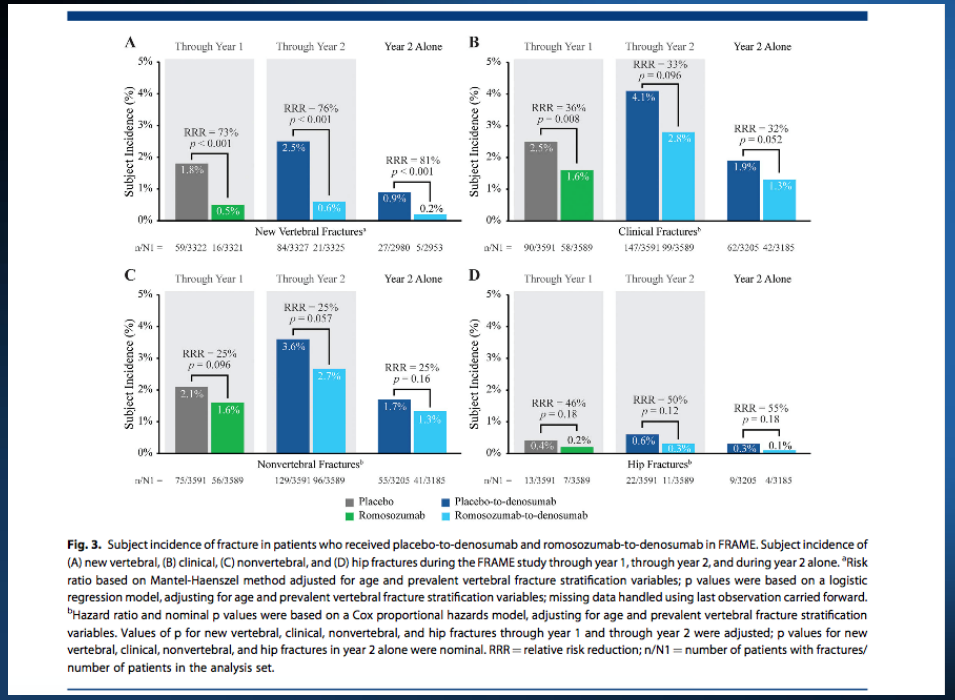


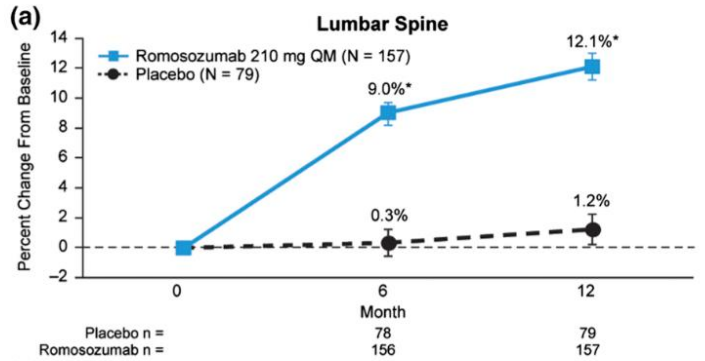
Fig. 3. Subject incidence of fracture in patients who received placebo-to-denosumab and romosozumab-to-denosumab in FRAME. Subject incidence of (A) new vertebral, (B) clinical, (C) nonvertebral, and (D) hip fractures during the FRAME study through year 1, through year 2, and during year 2 alone. [a]Risk ratio based on Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables; p values were based on a logistic regression model, adjusting for age and prevalent vertebral fracture stratification variables; missing data handled using last observation carried forward. [b]Hazard ratio and nominal p values were based on a Cox proportional hazards model, adjusting for age and prevalent vertebral fracture stratification variables. Values of p for new vertebral, clinical, nonvertebral, and hip fractures through year 1 and through year 2 were adjusted; p values for new vertebral, clinical, nonvertebral, and hip fractures in year 2 alone were nominal. RRR = relative risk reduction; n/N1 = number of patients with fractures/number of patients in the analysis set.

Adverse Events and Safety

Table 2. Summary of Subject Incidence of Treatment-Emergent Adverse Events Through Month 12

Adverse event, n (%)	Romosozumab 210 mg QM (N = 163)	Placebo (N = 81)
Any adverse event	123 (75.5)	65 (80.2)
Serious adverse event	21 (12.9)	10 (12.3)
Adjudicated cardiovascular serious adverse event[a]	8[b] (4.9)	2 (2.5)
Cardiac ischemic event	3 (1.8)	0 (0.0)
Cerebrovascular event	3 (1.8)	1 (1.2)
Death[c,d]	2[e] (1.2)	1 (1.2)
Heart failure	1 (0.6)	0 (0.0)
Death	1 (0.6)	1 (1.2)
Leading to discontinuation of investigational product	5 (3.1)	1 (1.2)
Events of interest		
Hypocalcemia	0 (0.0)	0 (0.0)
Hypersensitivity	8 (4.9)	4 (4.9)
Injection-site reaction[f]	9 (5.5)	3 (3.7)
Malignancy	3 (1.8)	2 (2.5)
Hyperostosis	0 (0.0)	0 (0.0)
Osteoarthritis	8 (4.9)	4 (4.9)
Atypical femoral fracture[a]	0 (0.0)	0 (0.0)
Osteonecrosis of the jaw[a]	0 (0.0)	0 (0.0)
Incident fracture[g]	3 (1.8)	2 (2.5)
Subject incidence of anti-romosozumab antibody formation		
Binding antibodies	28 (17.2)	NA
Neutralizing antibodies	1 (0.6)	NA

Cosman F NEJM 2016;375: 1532


(a)
Lumbar Spine
Romosozumab 210 mg QM (N = 157)
Placebo (N = 79)
Percent Change From Baseline
9.0%*
12.1%*
0.3%
1.2%
Month
Placebo n = 78 79
Romosozumab n = 156 157
(b)
Total Hip
Romosozumab 210 mg QM (N = 158)
Placebo (N = 79)
Percent Change From Baseline
1.6%*
2.5%*
0.2%
−0.5%
Month
Placebo n = 78 79
Romosozumab n = 157 158

Fracture Efficacy Summary

- Significant reductions for vertebral fractures at 12 and 24 months (primary)
- Clinical and non-vertebral fracture reductions nominally significant at 12 and 24 months
  p>.05 after adj for mult. comparisons, 3 of 4 > 0.05
- All 24 month comparisons against active control (PBO→D'Mab)
- Subgroup analysis (post-hoc): larger reductions outside of S. America.

  Non-vertebral fractures, 12 months

  Not S. America (57%) HR=0.58 (0.37, 0.89)

  S. America (43%) HR=1.25 (0.68, 2.27)

Making Choices Among Anabolic Therapies: Romosozumab vs. (Abaloparatide or Teriparatide)

Administration

- Monthly in-office injections 12 monthly (Romo) vs. daily self-injections for 18-24 mos (TPTD, abalo)
- Cost
- Patient or physician preference

Safety

- PTH/analogs: possible osteosarcoma (unlikely)
- Romo: Possible but small increase in cardiovascular events

Efficacy

- All reduce vertebral and non-vertebral, but no head-to-head studies
- Larger early increase in hip BMD for Romo vs. Teriparatide (also vs. Abalo) and may be considered for patients at very risk of hip or non-vertebral fx.

Cardiovascular Outcomes of Romosozumab

Interpretation of Cardiovascular Safety

Summary

- No excess events in Romo vs. placebo in FRAME 2016 trial
- Slight increase in ischemic and cerebrovascular events in Romo vs. ALN in ARCH 2017 trial (decrease in heart failure). None were statistically significant.

Potential Explanations

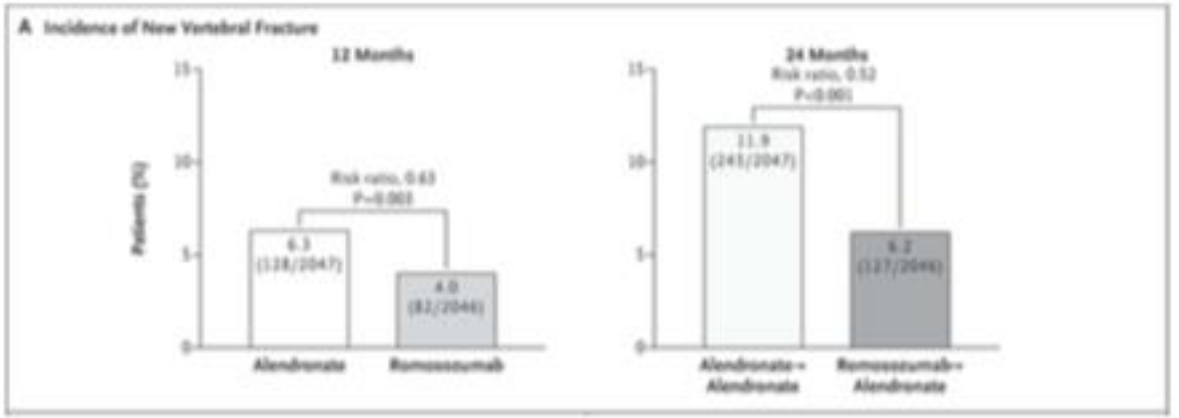
1. Random Difference
2. ALN (comparator to Romo) decreases cardiovascular events, especially cerebrovascular
   - Evidence varies in individual ALN studies or meta-analyses
3. Romo increases (slightly) cardiovascular event risk

Interpretation by Regulators

- FDA: after initial review, asked for more information on cardiovascular. Approved 2019, but with black box warning*
- European: Initial review (6/21/19). Did not approve due to cardiovascular concerns. Sponsors can reapply

*may increase the risk of heart attack, stroke and cardiovascular death and should not be used in patients who have had a heart attack or stroke within the previous year or very high risk.

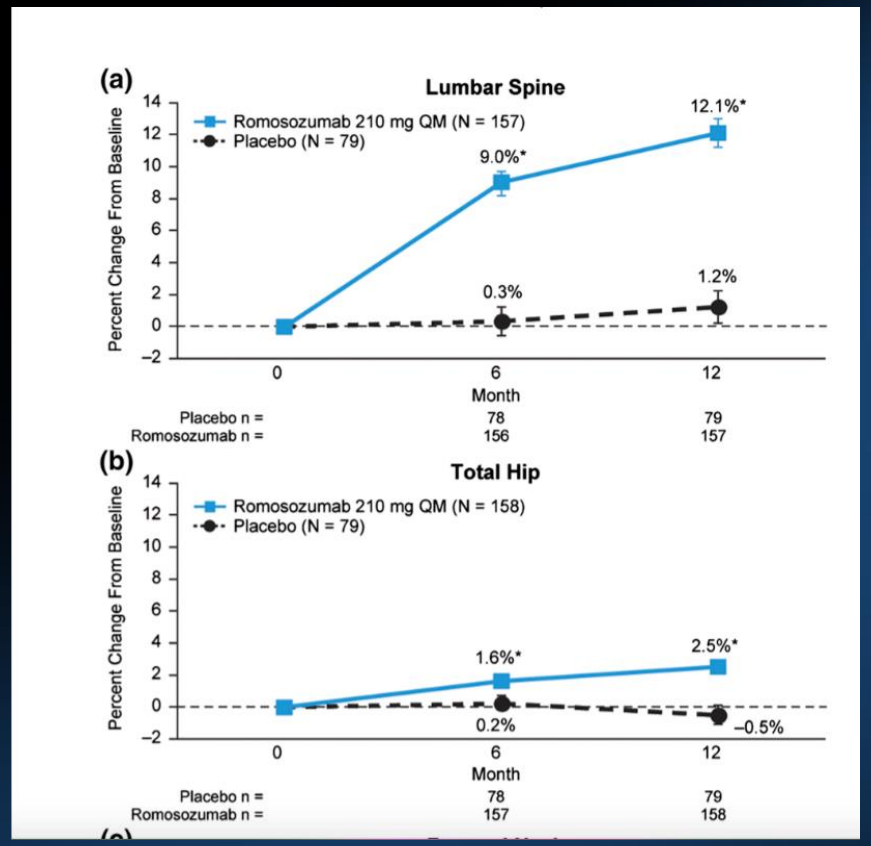
Incidence of New Vertebral, Clinical, and Nonvertebral Fracture
Romo/ALN Compared to 2 years ALN

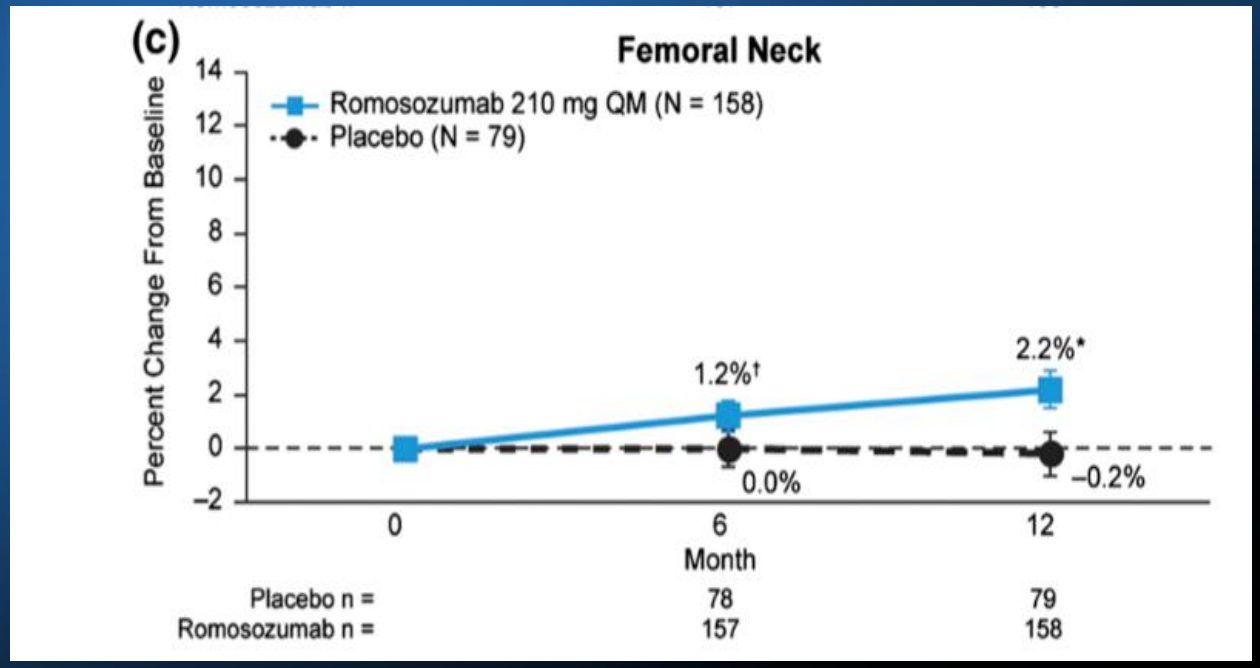


Saag NEJM 2016

BRIDGE Study Romosozumab in Men with Osteoporosis

BMD % Change from Baseline

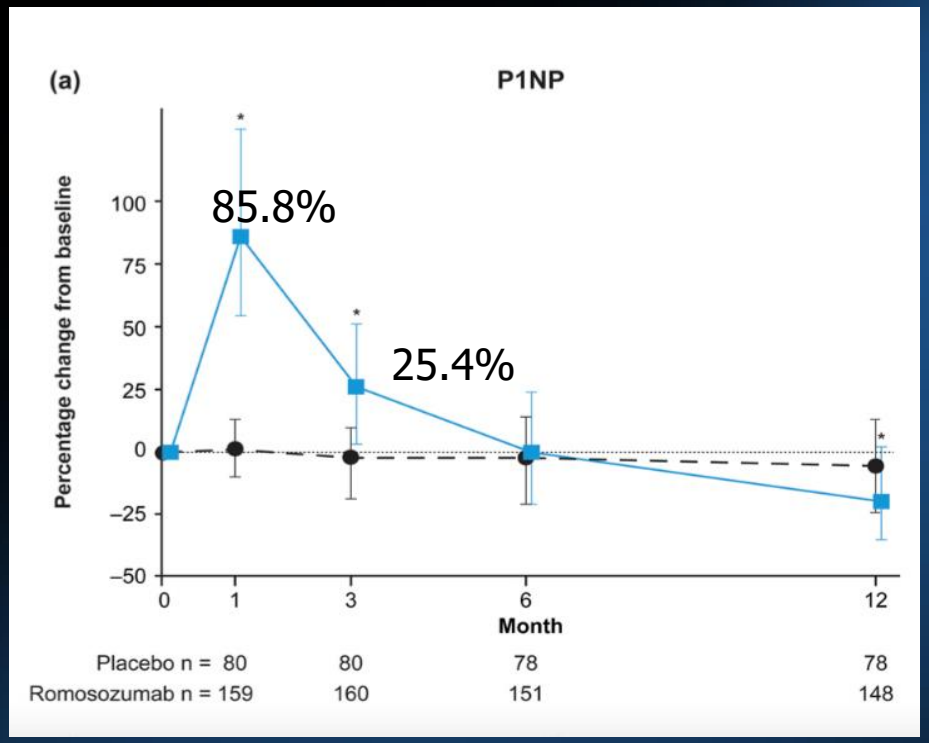


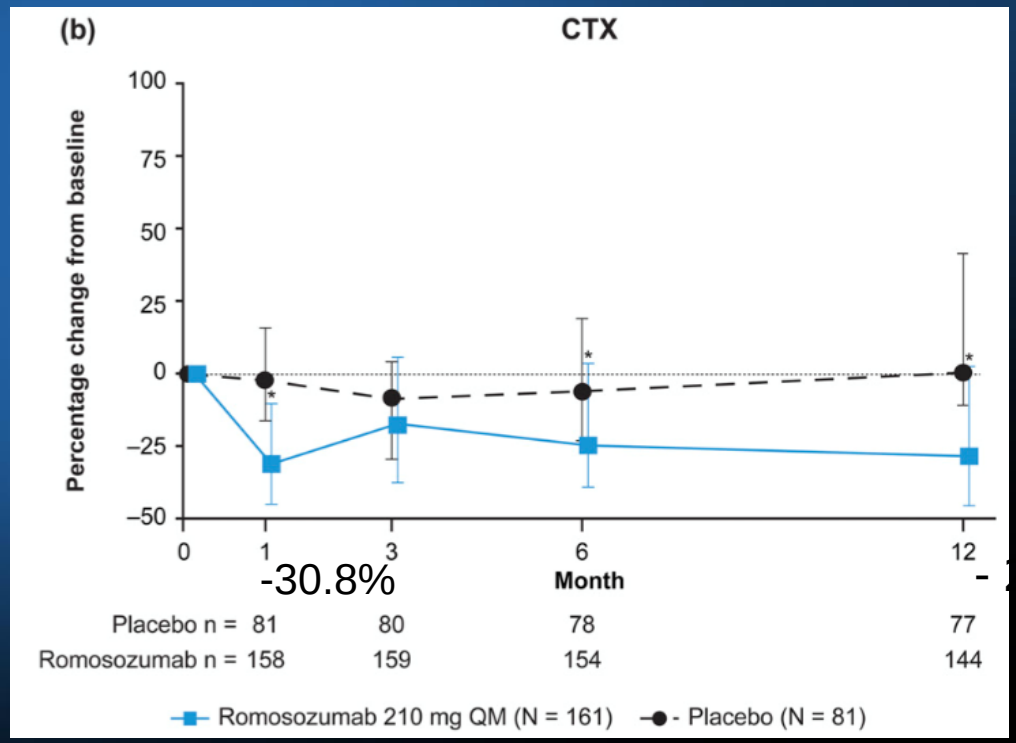


JCEM 103:3183,2018

BRIDGE Study Romosozumab in Men with Osteoporosis

BTMs % Change from Baseline

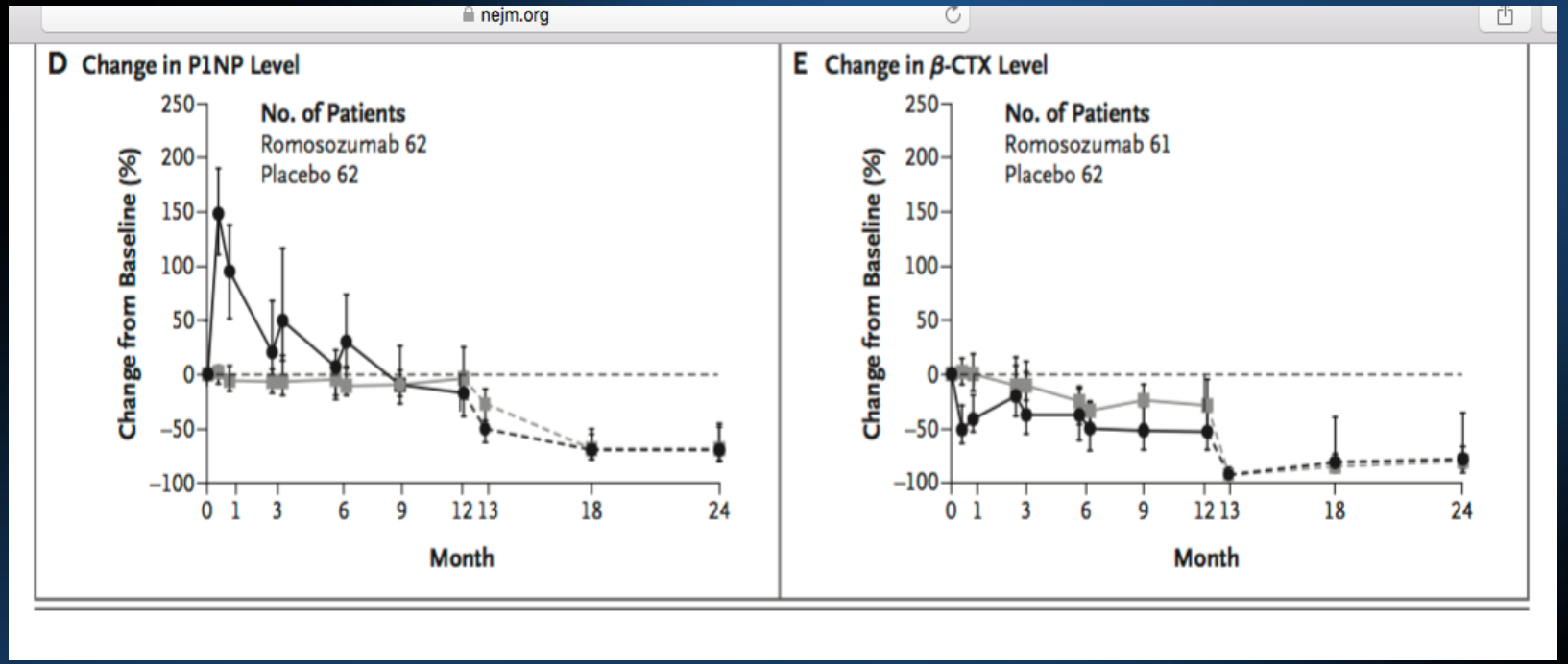




Bone biobsy N20 at 12 months
Parameters of bone resorption had decreased and those of bone formation were unchanged

JCEM 103:3183,2018

% Change from Baseline in Levels of BTMs



NEJM 2016;375: 16

FRAME Study

The NEW ENGLAND JOURNAL of MEDICINE

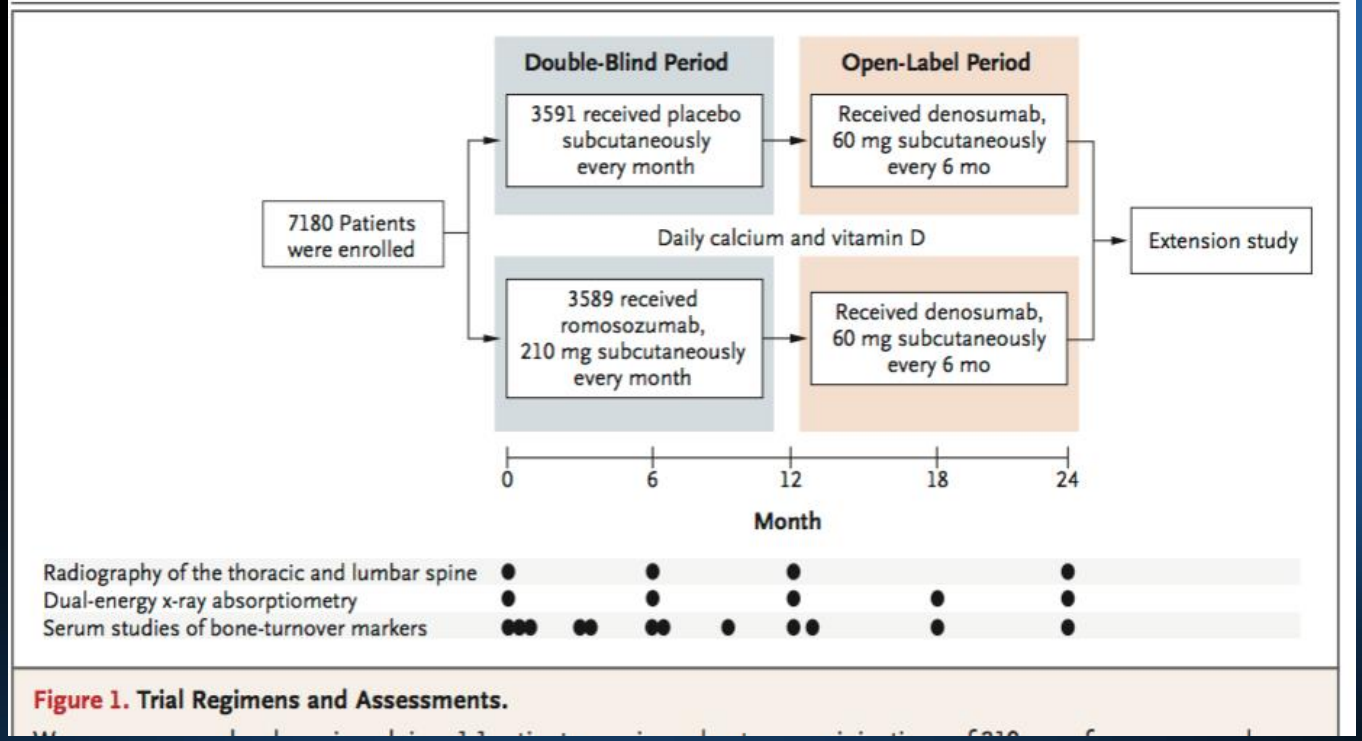
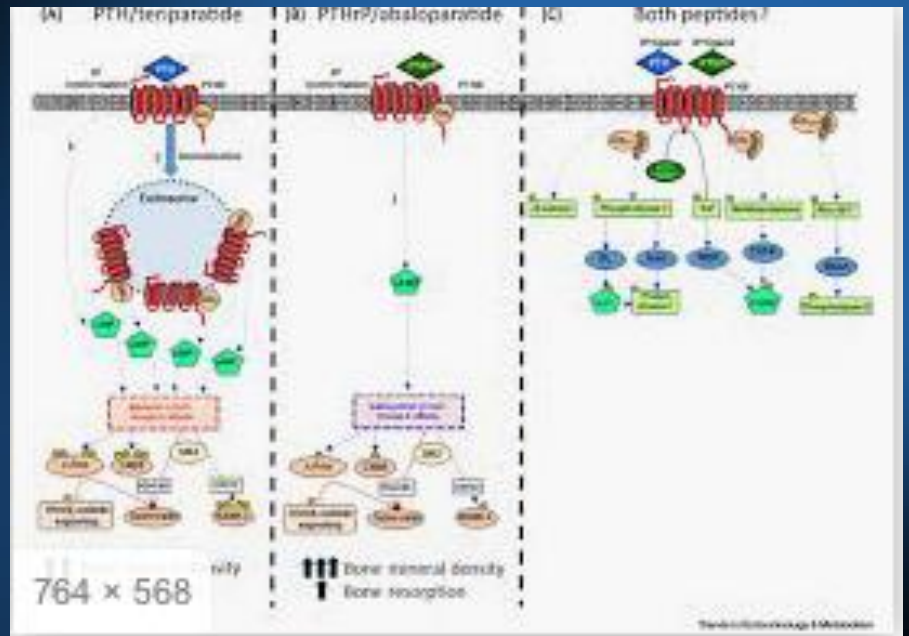
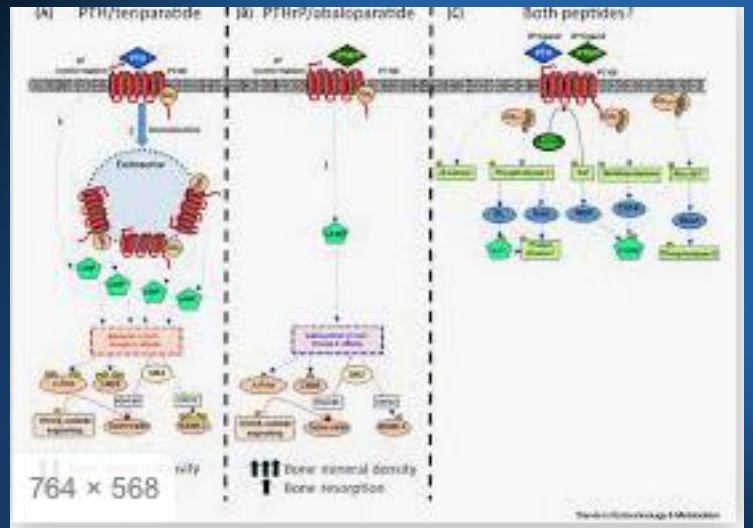


Figure 1. Trial Regimens and Assessments.

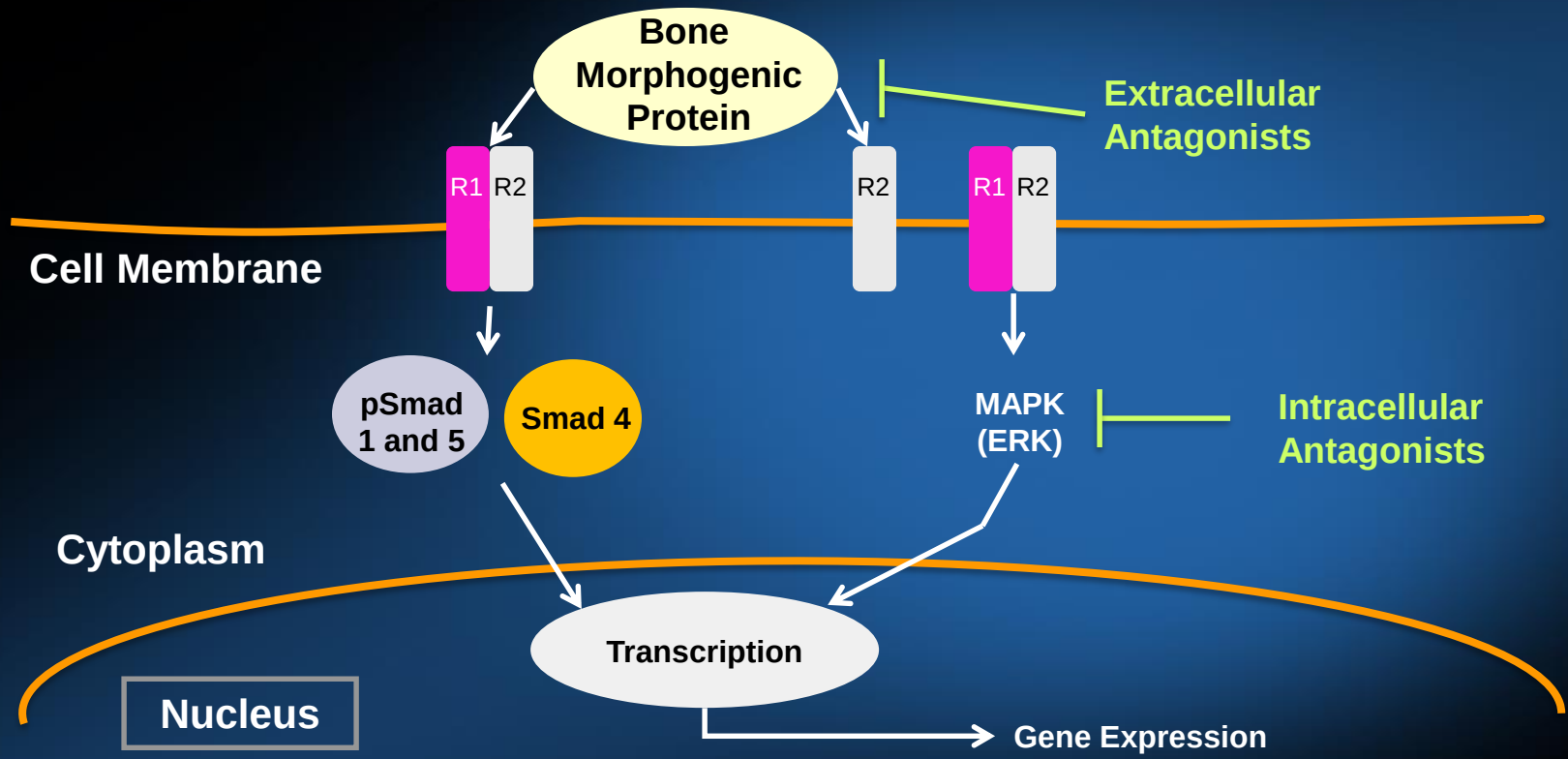


Handling Parathormone Receptor Type 1 ...



Handling Parathormone Receptor Type 1 ...

Signaling Pathways Used by BMPs in Osteoblasts

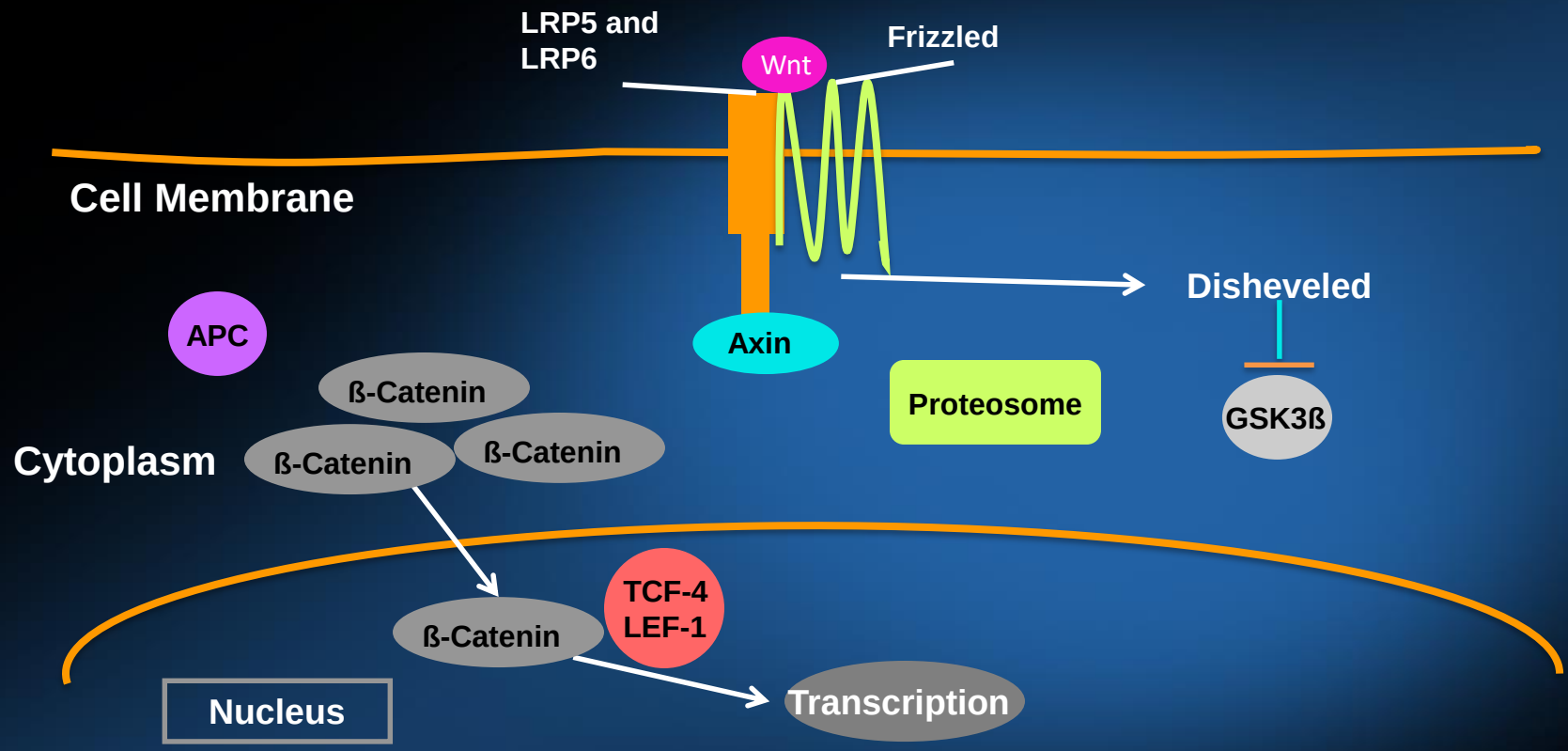


After BMP binds to its predimerized types I and II receptors (RI and RII), Smad 1 and 5 proteins are phosphorylated (pSmad), associate with Smad 4, and translocate to the nucleus to regulate transcription.

Another pathway used by BMP involves binding to its type II receptor, an intrinsic kinase that activates the type I receptor; the newly dimerized receptor complex activates the mitogen-activated protein kinase (MAPK) extracellular regulated kinase (ERK) pathway to regulate transcription.

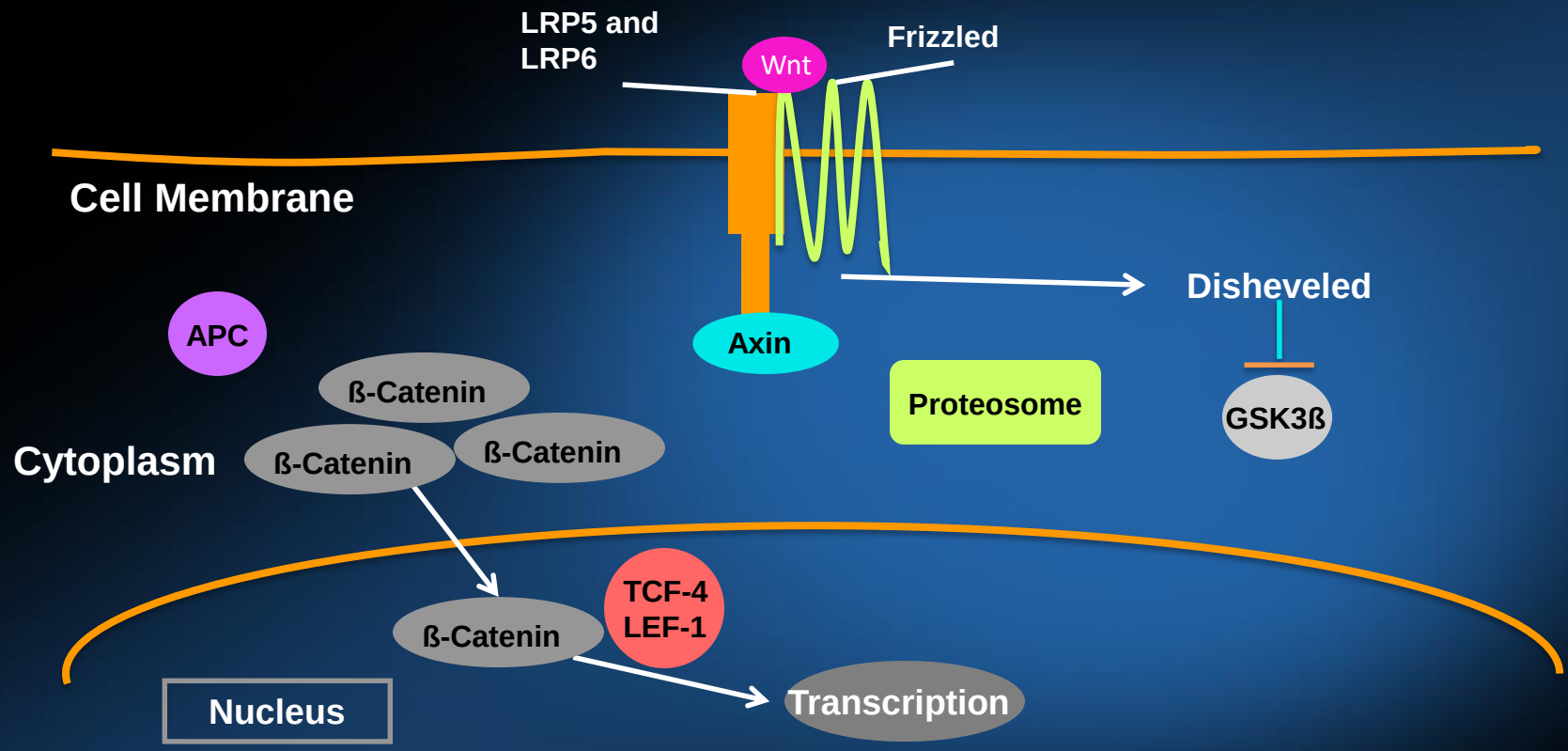
Extracellular antagonists bind BMP and prevent signal transduction.

Wnt Signal



After Wnt binding to its receptor (frizzled) and coreceptors (low density lipoprotein receptor-related proteins 5 and 6 [LPR5 and LPR6]), disheveled, an intracellular protein is induced to degrade GSK-3β. In addition, the cytoplasmic tails of LRP5 and LRP6 bind and anchor axin. These 2 events lead to the stabilization of β-catenin and its translocation to the nucleus, where it binds to T-cell factor 4 (TCF-4) or lymphoid enhancer binding factor1 (LEF-1) to regulate transcription.

Wnt Signal



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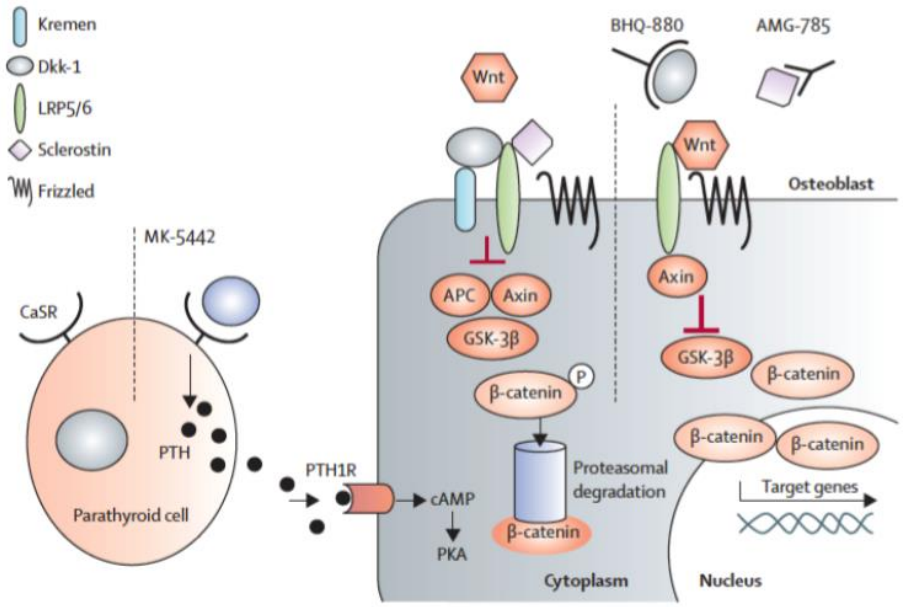
- "It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.

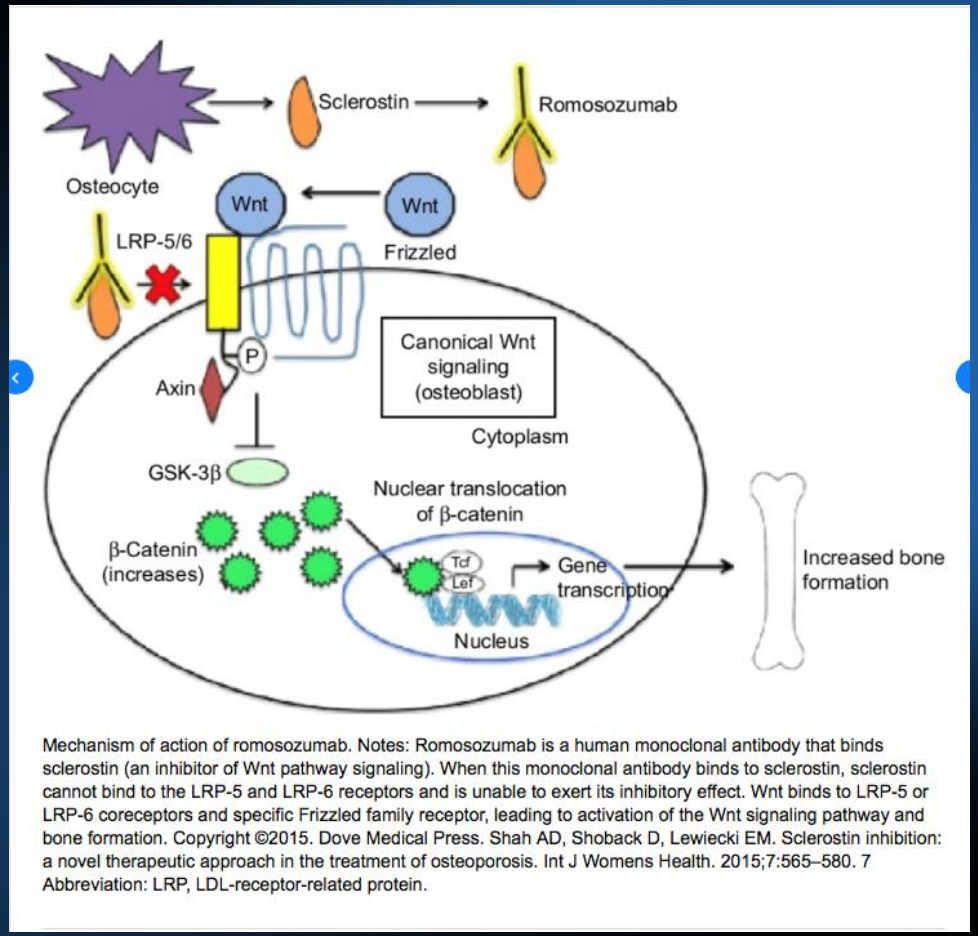
- ..Mark Twain

Therapeutic Targets in Osteoblast Physiology



Rachner TD et al Lancet 2011 377: 1276–87.

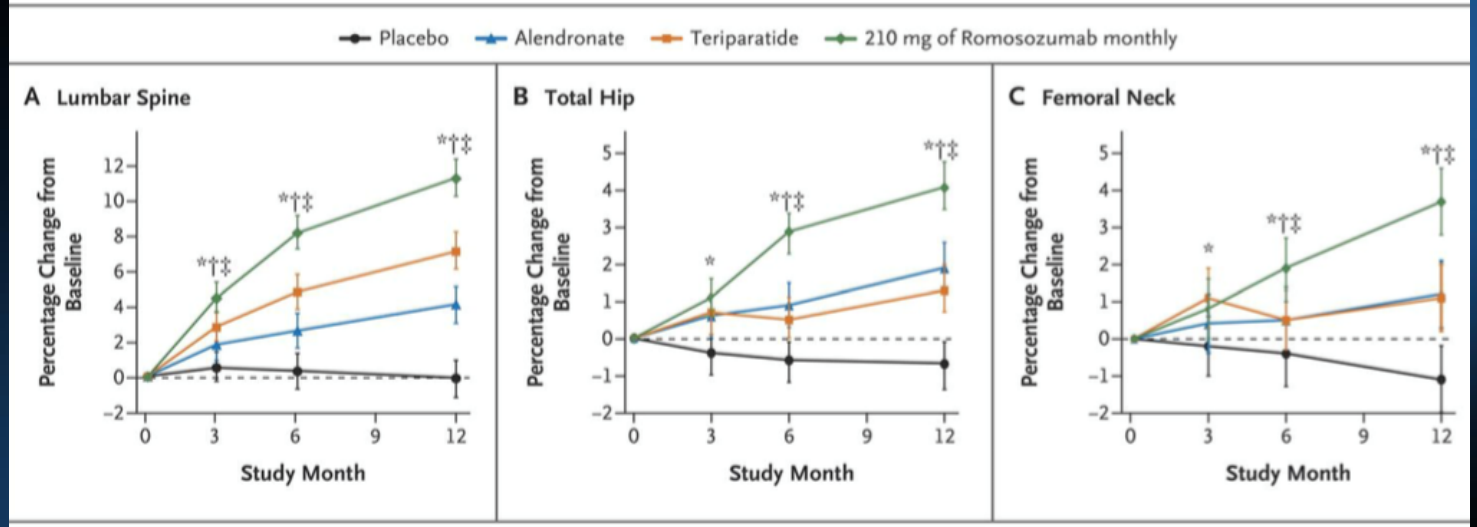
Mechanism of Action of Romosozumab



Mechanism of action of romosozumab. Notes: Romosozumab is a human monoclonal antibody that binds sclerostin (an inhibitor of Wnt pathway signaling). When this monoclonal antibody binds to sclerostin, sclerostin cannot bind to the LRP-5 and LRP-6 receptors and is unable to exert its inhibitory effect. Wnt binds to LRP-5 or LRP-6 coreceptors and specific Frizzled family receptor, leading to activation of the Wnt signaling pathway and bone formation. Copyright ©2015. Dove Medical Press. Shah AD, Shoback D, Lewiecki EM. Sclerostin inhibition: a novel therapeutic approach in the treatment of osteoporosis. Int J Womens Health. 2015;7:565–580. 7
Abbreviation: LRP, LDL-receptor-related protein.

Response of TH and FN BMD to Romosozumab

Response of Spinal, Total Hip and Femoral Neck BMD to 210 mg Monthly Romosozumab



McClung MR et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1305224

Risk of Subsequent Fractures

Prior Fracture Increases the Risk of Subsequent Fracture

	Site of Subsequent Fracture		
Site of Prior Fracture	Wrist	Vertebra	Hip
Wrist	3.3	1.7	1.9
Vertebra	1.4	4.4	2.3
Hip	NA	2.5	2.3

About ½ of hip fractures are preceded by another fracture

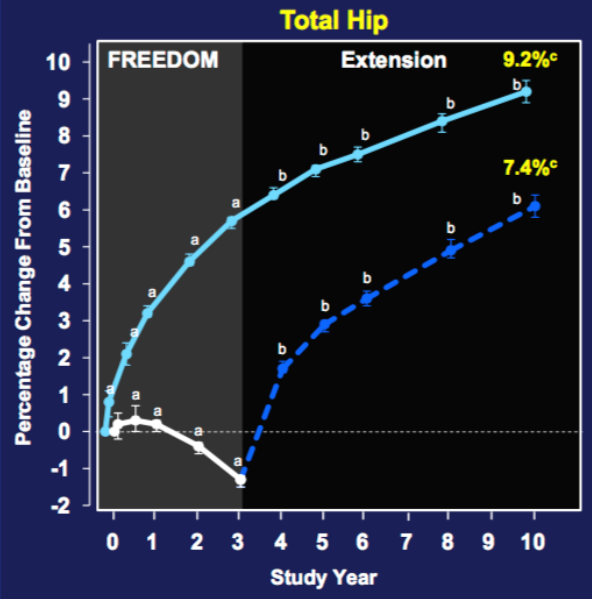
Klotzbuecher CM et al. J Bone Miner Res. 2000;15:721-739.
Port L et al. Osteoporos Int. 2003;14:780-784.

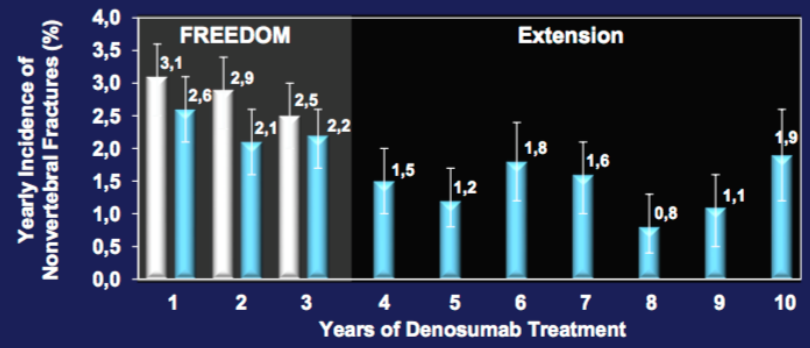
JBMR 2000;15:721

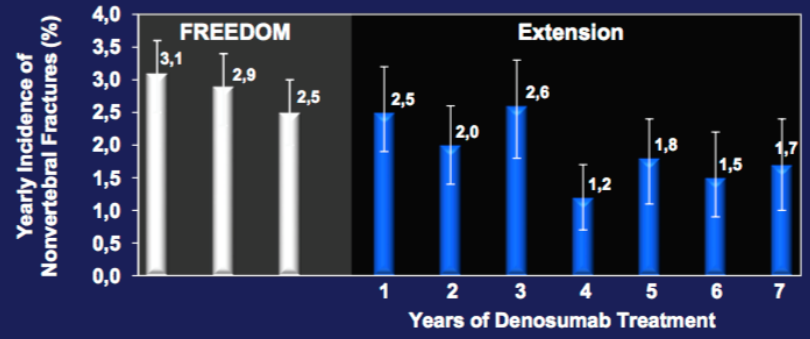
Freedom Extension Trial

Effects of Denosumab Treatment on Total Hip BMD and Nonvertebral Fractures Through 10 Years

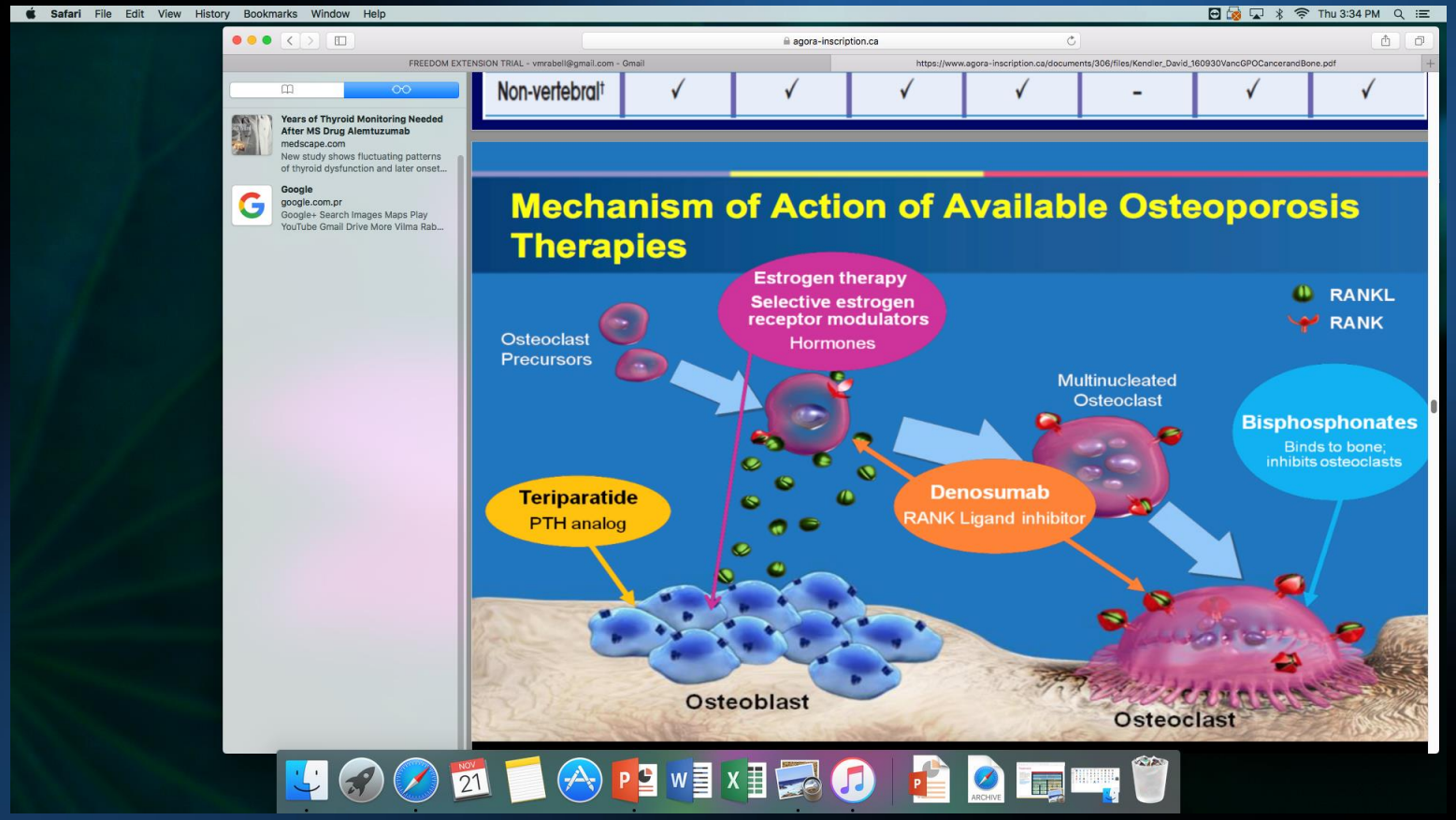
Placebo Long-term Denosumab Cross-over Denosumab







BMD data are LS means and 95% confidence intervals. [a]$P < 0.05$ vs FREEDOM baseline. [b]$P < 0.05$ vs FREEDOM and Extension baselines. [c]Percentage change while on denosumab treatment. Percentages for nonvertebral fractures are Kaplan-Meier estimates.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Years of Thyroid Monitoring Needed After MS Drug Alemtuzumab
medscape.com
New study shows fluctuating patterns of thyroid dysfunction and later onset...
Google
google.com.pr
Google+ Search Images Maps Play YouTube Gmail Drive More Vilma Rab...
Non-vertebral†
Mechanism of Action of Available Osteoporosis Therapies
Estrogen therapy
Selective estrogen receptor modulators
Hormones
RANKL
RANK
Osteoclast Precursors
Multinucleated Osteoclast
Bisphosphonates
Binds to bone; inhibits osteoclasts
Teriparatide
PTH analog
Denosumab
RANK Ligand inhibitor
Osteoblast
Osteoclast

Adverse Events ARCH Study

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)
Event of interest¶				

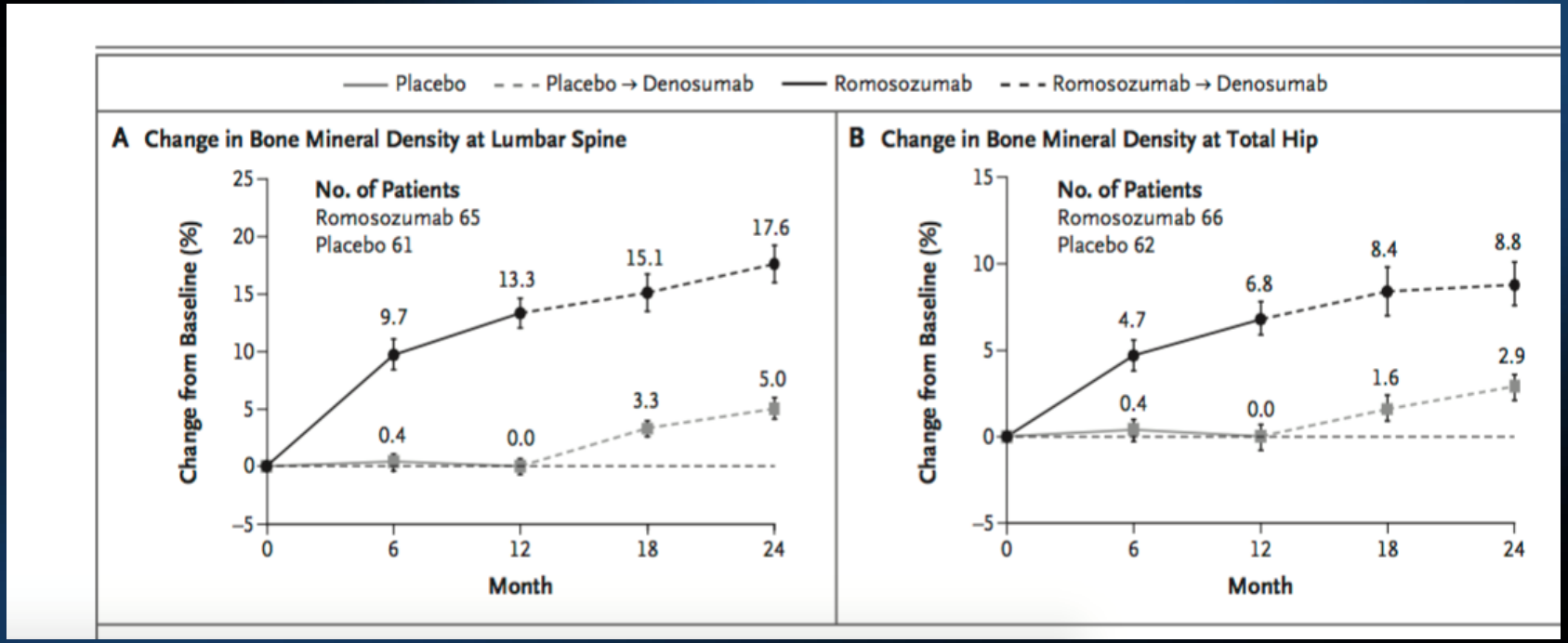
OR 2.27

OR 1.31

OR 2.65

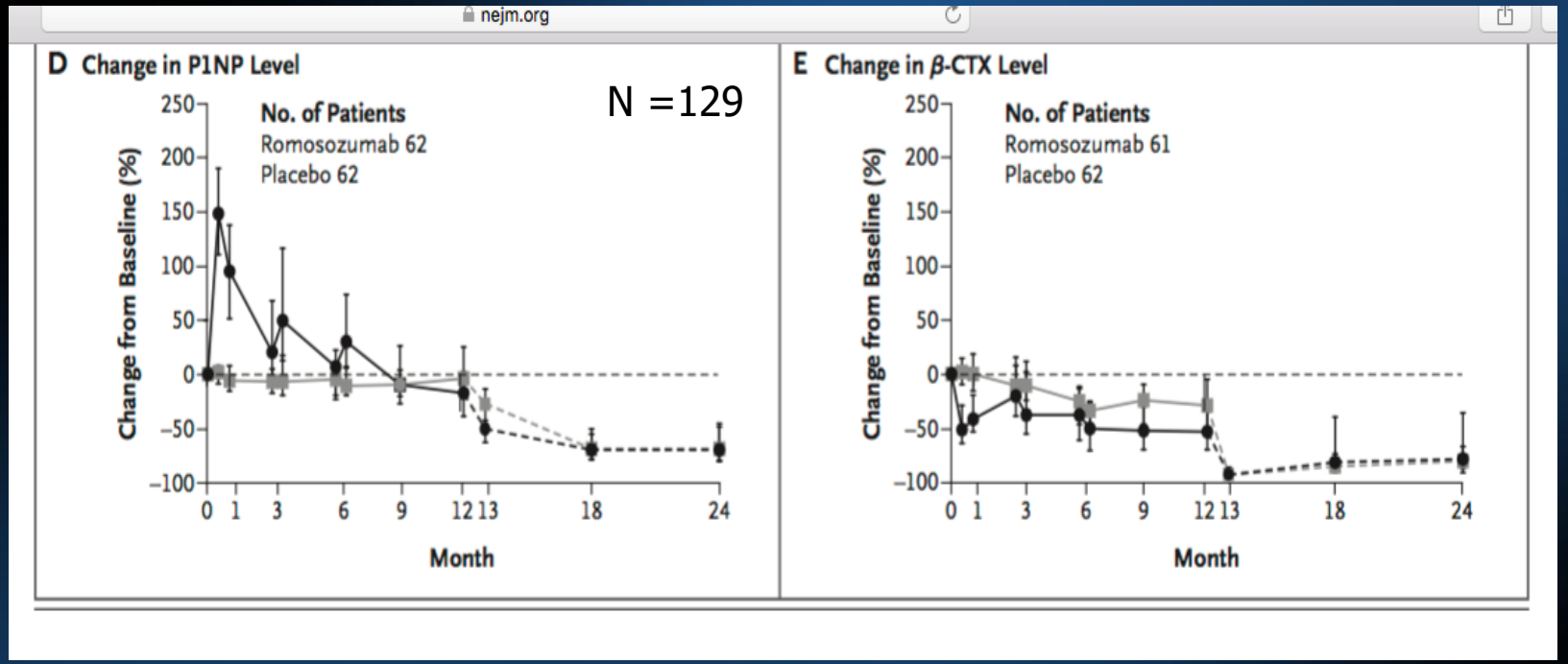
Saag K NEJM 2017;377:1417

Changes in Bone Mineral Density



NEJM 2016; 375:16

% Change from Baseline in Levels of BTMs



NEJM 2016;375: 16

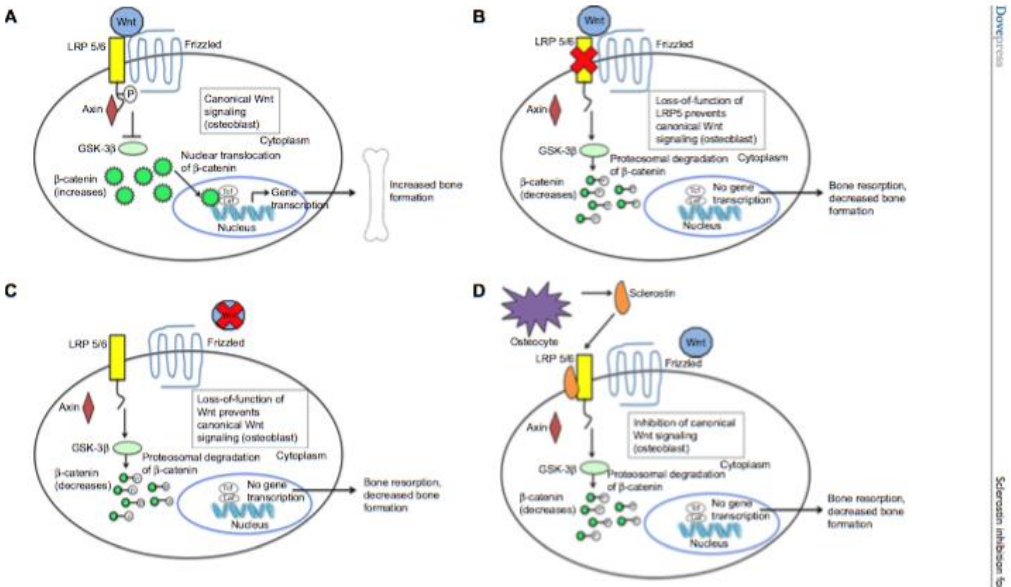


Figure 1 Wnt signaling pathways and the biology of sclerostin.

Notes: (A) Canonical Wnt signaling: in the absence of sclerostin, Wnt binds to LRP 5/6 and its co-receptor, frizzled. This results in phosphorylation of the cytoplasmic tail of LRP 5/6, which allows axin to bind the receptor complex. Axin binding leads to inhibition of GSK-3β, which normally functions to target β-catenin for degradation. Therefore, cytoplasmic levels of β-catenin increase and are translocated to the nucleus, where they bind to DNA binding proteins and activate target gene promoters. This results in osteoblast differentiation, proliferation and survival and hence, increased bone formation. **(B** and **C)** Loss-of-function of LRP5 and Wnt prevent canonical Wnt signaling: Loss-of-function of LRP5 and Wnt prevent formation of the active Wnt-LRP 5/6-frizzled complex and prevent Wnt signaling. The cytoplasmic tail of LRP 5/6 remains unphosphorylated. Therefore, axin does not bind the receptor complex. GSK-3β activity is uninhibited and therefore leads to phosphorylation of β-catenin, targeting it for degradation. Cytoplasmic levels of β-catenin decrease. Therefore, there is less translocation of the protein to the nucleus. Target gene promoters of the Wnt signaling pathway are not activated. This results in decreased bone formation and increased bone resorption and hence, skeletal fragility and fractures. **(D)** Inhibition of canonical Wnt signaling by sclerostin: sclerostin is secreted by osteocytes. It binds to LRP 5/6, which prevents Wnt from binding to LRP 5/6 and its co-receptor, frizzled. Therefore, Wnt signaling is inhibited. Through the mechanisms described above (**B** and **C**), this results in decreased bone formation and increased bone resorption.