RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Inaugural National Conference

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VIRTUAL CONFERENCE

RhAPP
RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Osteoporosis Review and Update

Patty Travis CNP
Cleveland Clinic

Disclosure

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Faculty Disclosure

Patty Travis, CNP

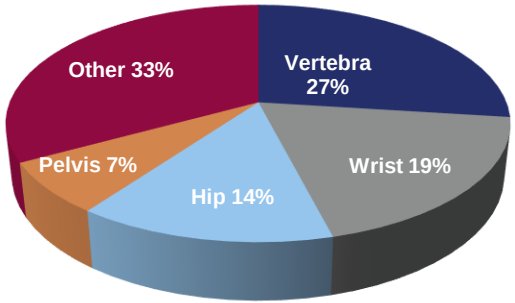
- No conflict of interest related to this presentation
- Speaker Bureau: AbbVie

Learning Objectives

- Gain a better understanding of the societal impact of osteoporosis and the need for appropriate timely treatment
- Be able to apply two different evidence-based assessment recommendations to at-risk patients within one’s practice
- To be more knowledgeable about newer anabolic agents available for treatment of osteoporosis and factors to consider in the decision-making process

Osteoporosis Is a Serious Public Health Problem

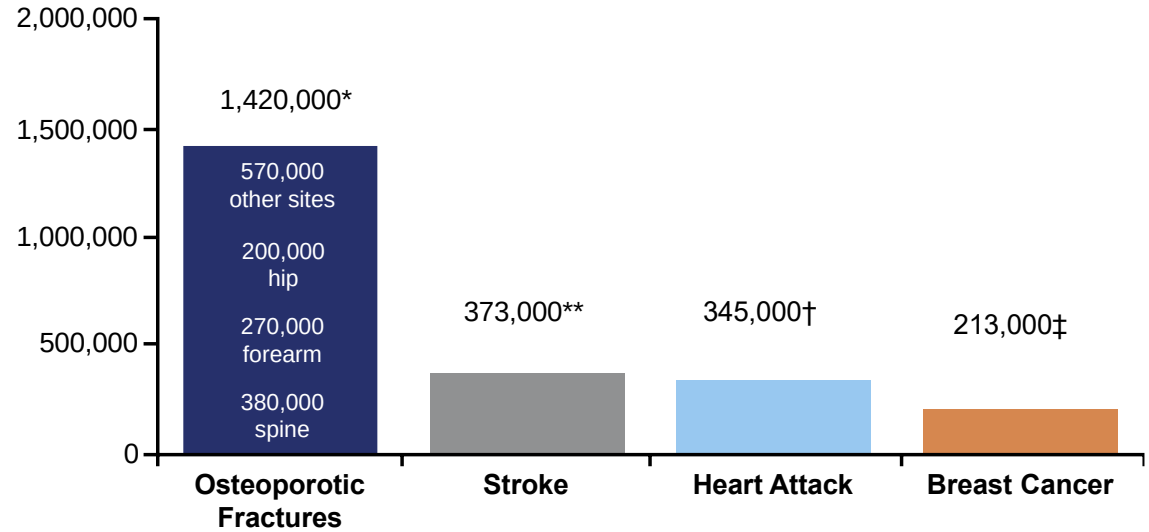
- Affects 10.2 million Americans (80% women)
  - 30% of women and 16% of men age 50 and older have osteoporosis
  - About 1 of every 2 Caucasian women and 1 of every 5 men will have an osteoporotic fracture
- 2 million osteoporotic fractures per year
- Direct healthcare costs about $17-19 billion per year



Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007 Mar;22(3):465-75.
Sözen, T., Özışık, L., & Başaran, N. Ç. (2017). An overview and management of osteoporosis. *European journal of rheumatology*, *4*(1), 46–56.

Common Disease Not as Commonly Treated

Comparative incidences of osteoporosis-related fractures, new strokes, heart attacks, and invasive breast cancer in women in the United States



* 2005 annual incidence all ages

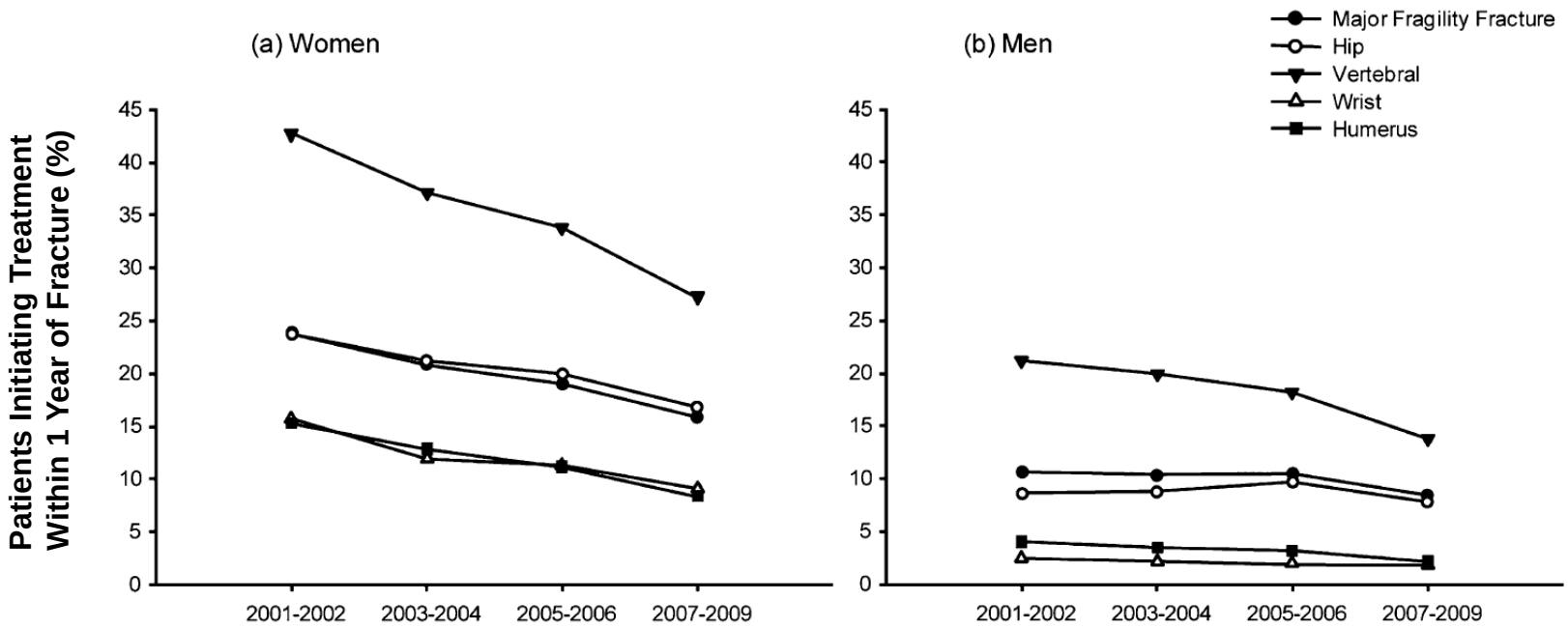
** 2004 estimate

† 2004 estimate, new and recurrent

‡ 2006 new cases, women all ages

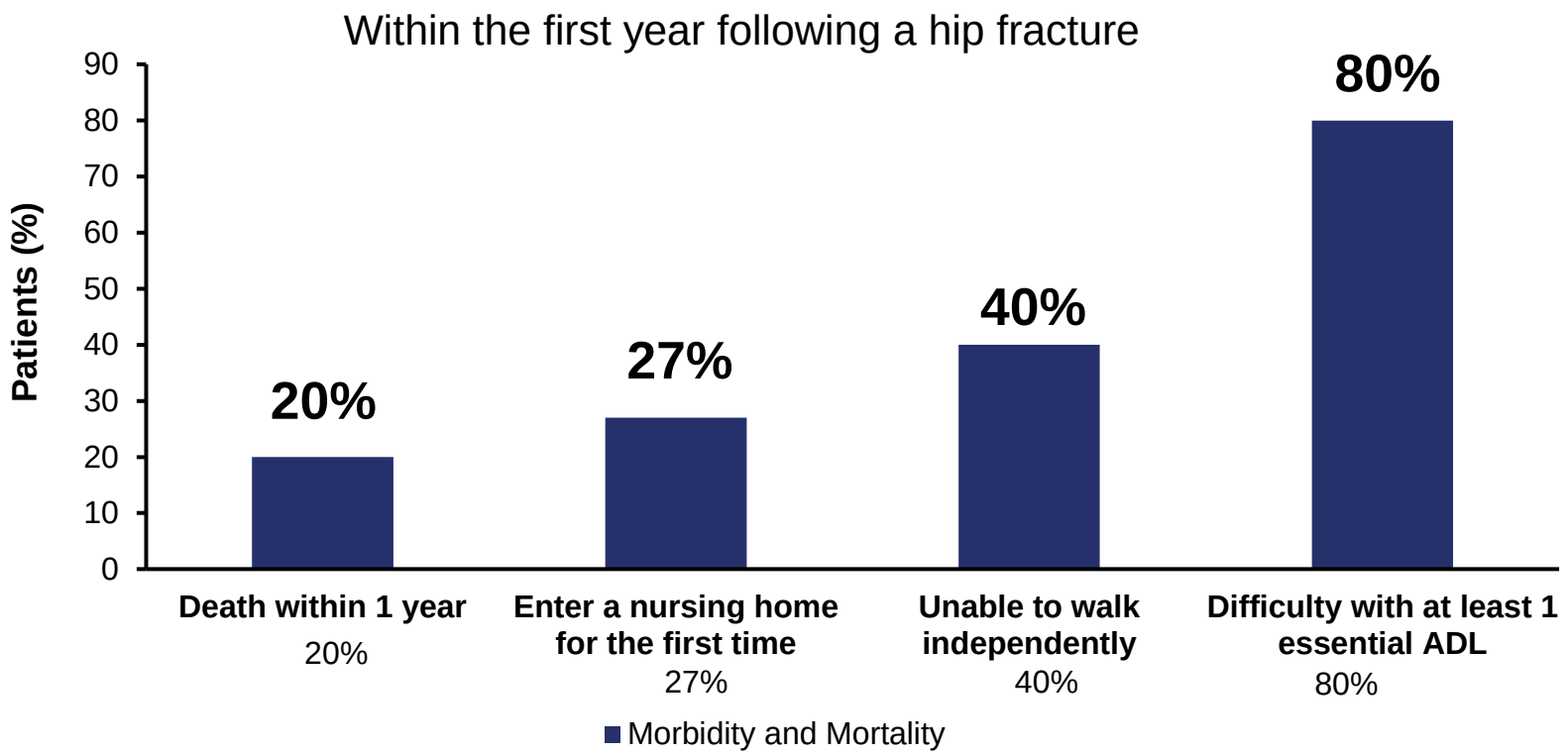
Sözen, T., Özışık, L., & Başaran, N. Ç. (2017). An overview and management of osteoporosis. European journal of rheumatology, 4(1), 46–56.

Treatment Rates Are Declining



Balasubramanian, Akhila et al. Declining Rates of Osteoporosis Management Following Fragility Fractures in the U.S., 2000 Through 2009, The Journal of Bone & Joint Surgery: April 2, 2014 - Volume 96 - Issue 7 - p e52.
Desai RJ, et al. Association of osteoporosis medication use after hip fracture with prevention of subsequent nonvertebral fractures: an instrumental variable analysis. *JAMA Netw Open*. 2018;1(3):e180826

Morbidity and Mortality After Hip Fracture



Cooper C. The crippling consequences of fractures and their impact on quality of life. Am J Med. 1997 Aug 18;103(2A):12S-17S; discussion 17S-19S.

WHO Criteria for Postmenopausal Osteoporosis

The T-score compares an individual's BMD with the mean value for young adults and expresses the difference as a standard deviation score

Category	T-score
Normal	-1.0 and above
Low bone mass (osteopenia)	-1.0 to -2.5
Osteoporosis	-2.5 and below

https://www.who.int/chp/topics/Osteoporosis.pdf Accessed Nov. 2020

FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

- Asia
- Europe
- Middle East & Africa
- North America
  - Canada
  - US
- Latin America
- Oceania

Welcome to FRA

The FRAX® tool has been dev
on individual patient models th
as bone mineral density (BMD

Dr. John A Kanis
Professor Emeritus,
University of
Sheffield

The FRAX® models have been developed from studying population -based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

FRAX Desktop Application

Click here to view the applications available

- US (Caucasian)
- US (Black)
- US (Hispanic)
- US (Asian)

www.iofbonehealth.org

www.nof.org

www.jpof.or.jp

www.esceo.org

FRAX available as iPhone App

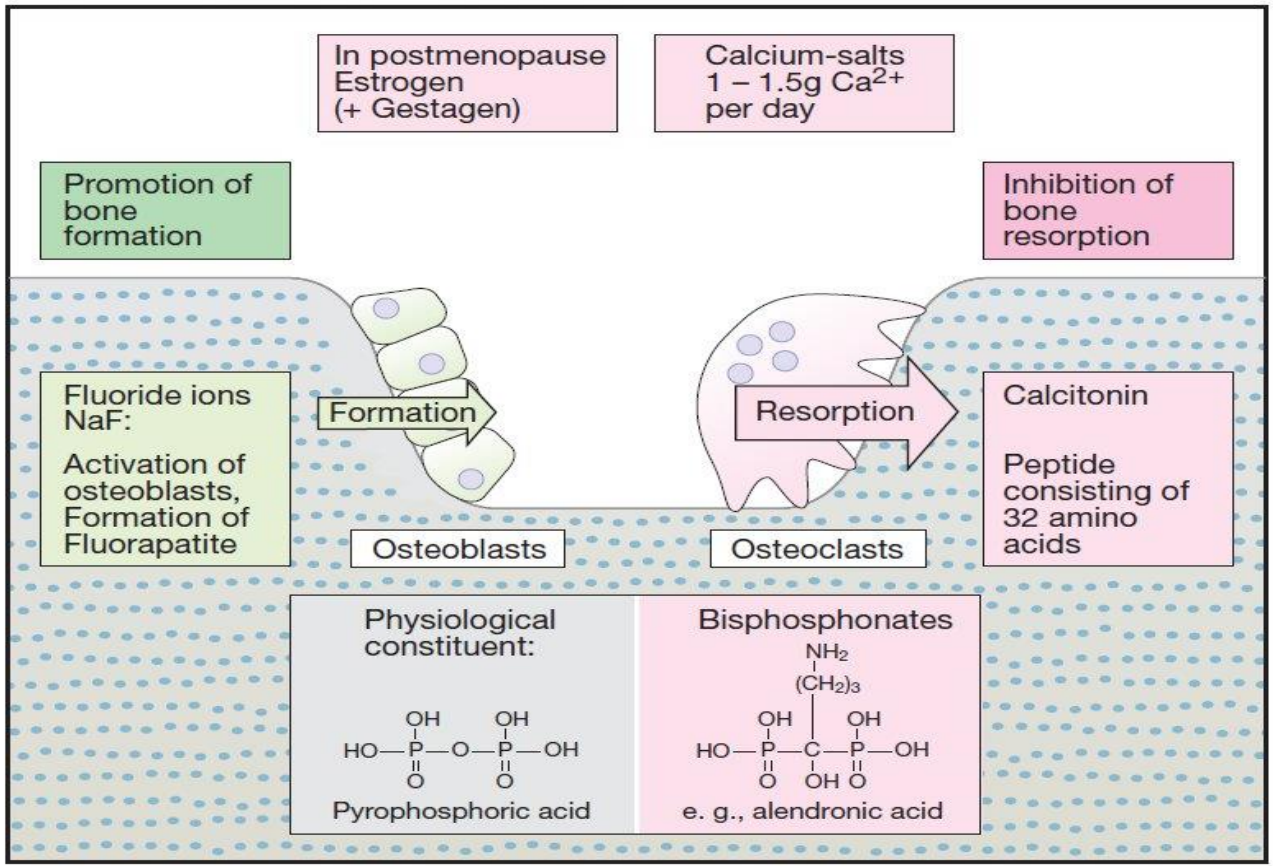
country=9


FRAX®
WHO Fracture Risk Assessment Tool
Home
Calculation Tool
Paper Charts
FAQ
References
English
Calculation Tool
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: US (Caucasian)
Name/ID:
About the risk factors
Questionnaire:
1. Age (between 40-90 years) or Date of birth
Age:
Date of birth:
63
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
59.87
4. Height (cm)
160.02
5. Previous fracture
No
Yes
6. Parent fractured hip
No
Yes
7. Current smoking
No
Yes
8. Glucocorticoids
No
Yes
9. Rheumatoid arthritis
No
Yes
10. Secondary osteoporosis
No
Yes
11. Alcohol 3 or more units per day
No
Yes
12. Femoral neck BMD (g/cm²)
Hologic
0.580
T-score: -2.3
Clear
Calculate
BMI 23.4
The ten year probability of fracture (%)
with BMD
Major osteoporotic
19
Hip fracture
3.5
11
2.0
Weight Conversion
Pounds
kg
132
Convert
Height Conversion
Inches
cm
63
Convert
01640703
Individuals with fracture risk assessed since 1st June 2011

Benefits of FRAX	Limitations of FRAX
Derives 10-year probability of clinical event from measurable parameters	Not valid to monitor patients on treatment
Internationally recognized and validated	Only femoral neck BMD is considered
Based on data from multiple cohorts	Risk is “yes/no” – there is no consideration of “dose” (e.g., fractures, glucocorticoids, smoking, alcohol)
Easily accessible on the Internet or DXA software	Not all risk factors are included (eg, risk of falling)
Helps identify patients who need treatment	Clinical judgment is required
Can be used to reassure low-risk patients	Do patients with high FRAX scores benefit from medication? (Unknown)

Sözen, T., Özışık, L., & Başaran, N. Ç. (2017). An overview and management of osteoporosis. European journal of rheumatology, 4(1), 46–56.

Bone Formation and Bone Resorption

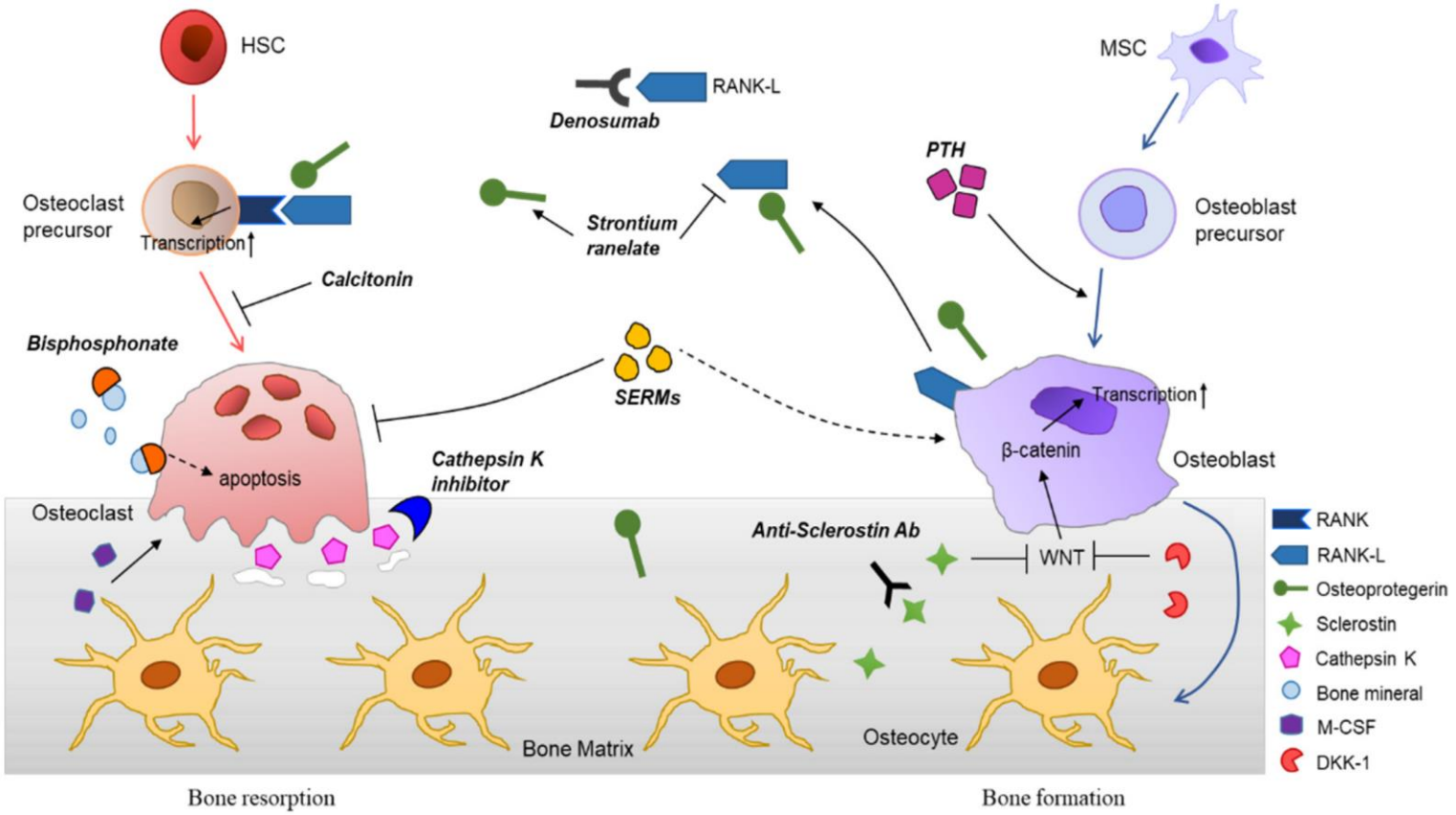


Sözen T, Özışık L, & Başaran NÇ. 2017. An overview and management of osteoporosis. *European Journal of Rheumatology*. 4(1), 46–56.

Medications for Osteoporosis

Stimulate Bone Formation	Inhibit Bone Resorption
Teriparatide (Forteo) – PTH analog	Alendronate (Fosamax) – bisphos
Abaloparatide (Tymlos) – PTH analog	Risedronate (Actonel, Atelvia) – bisphos
Romosozumab (Evenity) – monocloncal antibody	Ibandronate (Boniva) – bisphos
	Zoledronate/ Zoledronic Acid (Reclast) – bisphos
	Denosumab (Prolia) – monoclonal antibody
	Raloxifene (Evista) – selective estrogen receptor modulator (SERM)
	Calcitonin (Miacalcin, Fortical) – hormone
	Estrogen (various) – hormone

Medications Effects on Osteoblasts and Osteoclasts



Noh J-Y, Yang Y, Jung H. Molecular Mechanisms and Emerging Therapeutics for Osteoporosis. *Int. J. Mol. Sci*. 2020, 21, 7623.

PTH Analogs

<u>Abaloparatide</u> (PTHrp 1-34)

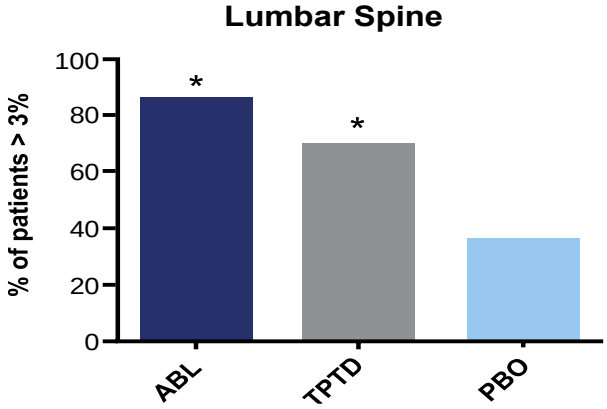
- Daily sc injection
- Binds to PTH 1 receptor
  - R^G conformation
- cAMP signaling short
  - **Bone resorption : lower**
- **Hypercalemia : less**
  - <1,25 vit D
- Cortical porosity : less
- Bone mass : > increase
- Higher dose trials
  - 80mcg

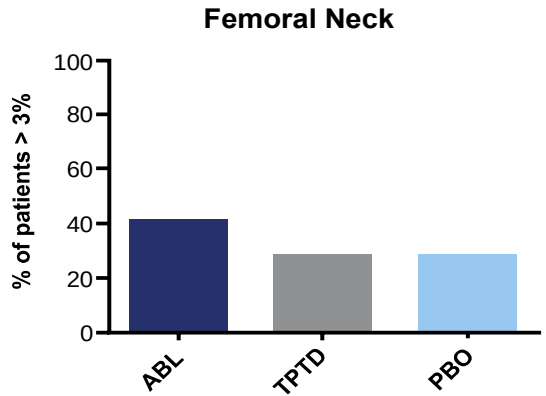
<u>Teriparatide</u> (rhPTH 1-34)

- Daily sc injection
- Binds to PTH 1 receptor
  - R^O conformation
- cAMP signaling prolonged
  - **Bone resorption : higher**
- **Hypercalcemia : more**
  - >1,25 vit D (intestinal Ca)
- Cortical porosity : more
- Bone mass : < increase
- Lower dose trials
  - 20mcg

Hattersley, Gary, et al. “Binding Selectivity of Abaloparatide for PTH-Type-1-Receptor Conformations and Effects on Downstream Signaling.” *Endocrinology*. vol. 157,1 (2016): 141-9;
P.D. Miller, et al. Bone mineral density response rates are greater in patients treated with abaloparatide compared with hose treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial. *Bone*. Volume 120, 2019, Pages 137-140.

Abaloparatide vs Teriparatide





n= 222 postmenopausal women
24 week trial

		% > 3% increase BMD	
		LS	***Hip***
ABL:	**80mcg sq qd**	**86%**	**37%**
TPTD:	**20mcg sq qd**	**70%**	**16%**
PBO:		**36%**	**15%**

Primary Endpoint LS BMD

ABL:	**6.7%**
TPTD:	**5.5%**
PBO:	**1.6%**

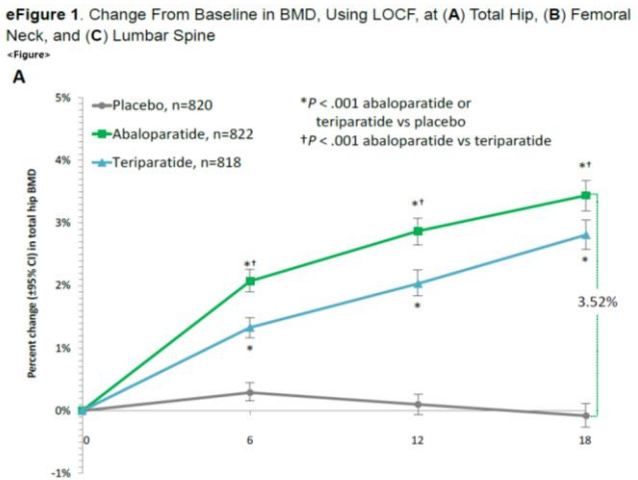
	Formation	***Resorption***
ABL:	**P1NP +52%,**	**CTX +23%**
TPTD:	**P1NP +98%,**	**CTX +76%**

Hypercalcemia: 4 hr ABL 11%, TPTD 40%
24 hr ABL 9%, TPTD 16%

Leder B. *JCEM*. 2015: 100: 697.

Active: Abaloparatide
The Abaloparatide Comparator Trial In Vertebral Endpoints

2463 postmenopausal women with osteoporosis



Primary Endpoint

Percentage of participants with new vertebral fracture in the abaloparatide vs placebo groups. Sample size was set to detect a 4% difference (57% risk reduction) between treatment groups.

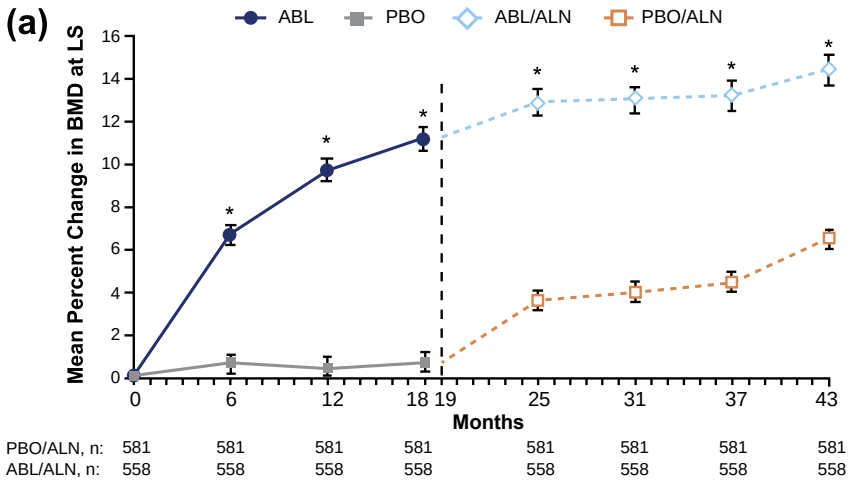
Secondary Endpoint

- The Kaplan-Meier estimated event rate for nonvertebral fracture was 2.7% for abaloparatide, 4.7% for placebo
- Nonvertebral fractures
  - Exclude spine, sternum patella, toes, fingers, skull, major trauma
- Abaloparatide vs PBO
  - HR 0.57 (p = 0.049)
- Teriparatide vs PBO
  - HR 0.72 (p = 0.22)
- TPTD vs ABL
  - HR 0.79 (p = 0.44)

Leder B. *JCEM*. 2015 :100: 697; Miller P, et al. *JAMA*. 2016; 316:722.
P.D. Miller, et al. Bone mineral density response rates are greater in patients treated with abaloparatide compared with hose treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial. *Bone*. Volume 120, 2019, Pages 137-140.

Foundational Effect Abaloparatide

Vertebral Fractures
Bone Density



Based on Treatment Period

- Active (86% RRR)
- Month 0-18: Vertebral Fx
  - PBO
    - N=30
  - ABL
    - N=4
- ACTIVExtend only (Aln)
- Month 19-43 : Vertebral Fx RRR 87%
  - PBO/ALN
    - N=16 (BMD gains =)
  - ABL/ALN
    - N=2

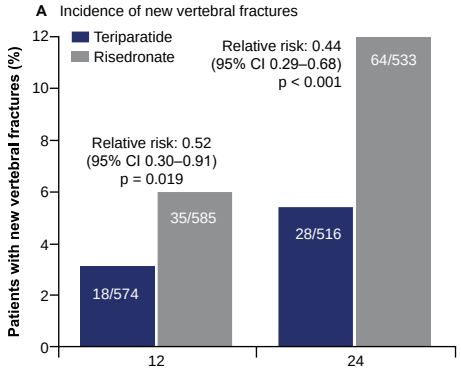
Leder B. *JCEM*. 2015: 100: 697;
P.D. Miller, et al. Bone mineral density response rates are greater in patients treated with abaloparatide compared with hose treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial. *Bone*. Volume 120, 2019, Pages 137-140.

VERO Trial

Inclusion Criteria Endpoints

- Post-menopausal OP
  - TPTD n = 680
  - Risedronate n = 680
- Entry Vertebral fracture
  - 2 moderate, 1 severe
  - 25-40%, > 40%
- T-score < -1.5
- Primary endpoint
  - Vertebral fracture
- Seconday endpoints
  - New/worsening vert fx
  - Clinical fx
  - Non-vert fx

Fracture Endpoints



- First Clinical Fracture
  - 5% vs 10% (rr 0.48, p = 0.0009)
- First non-vertebral fracture
  - 4% vs 6% (rr 0.66 (p = 0.10)
- New moderate or severe vert fx
  - 5% vs 12% (rr = 0.42 p = 0.001)
- New multiple vert fx
  - <1% vs 2% (rr = 0.16, p = 0.007)

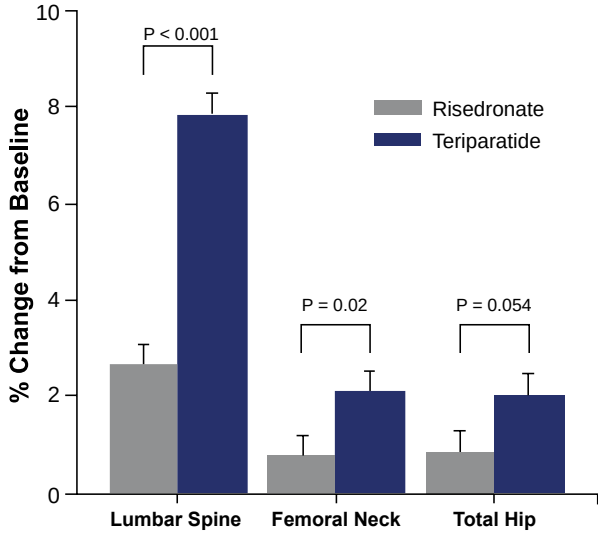
Kendler DL, et al. *Lancet*. 2018. 391:230.

Teriparatide vs Risedronate
Back Pain

Clinical Trial

- RCT back pain (1^0 endpoint)
  - n = 350 Risedronate (35mg/wk)
  - n = 360 Teriparatide (20mcg/d)
  - T-score <-2.0, 1 moderate VFx
  - 1 Vfx 35%, ≥ 2 60%
- 18 month data
- BMD increase 18 months (lumbar spine)
  - Risedronate: 2.6%
  - Teriparatide: 7.8% (p < .001)
- Vertebral fracture
  - Risedronate: 9.4%
  - Teriparatide: 4.4% (p = 0.01)
- VFx Severity (moderate/severe)
  - Risedronate: n=27
  - Teriparatide: n=8 (p=0.04)
- Non-vertebral fragility fracture
  - Risedronate 8.3%,
  - Teriparatide 7.8% (p = ns)

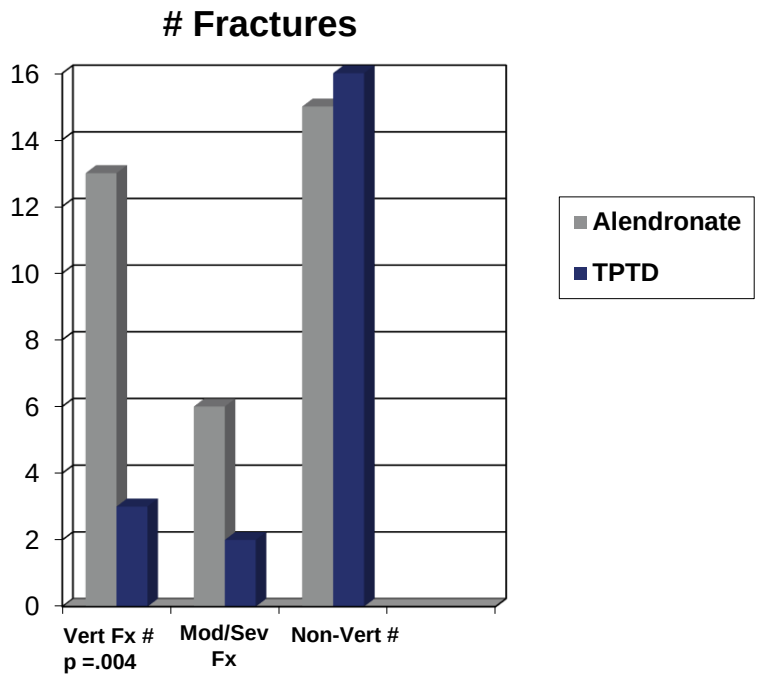
Bone Density (18m)



Hadji P, et al. *OI*. 2012; 23(8), 2141.

Teriparatide Versus Alendronate in the Treatment of Glucocorticoid Induced Osteoporosis (GIOP)

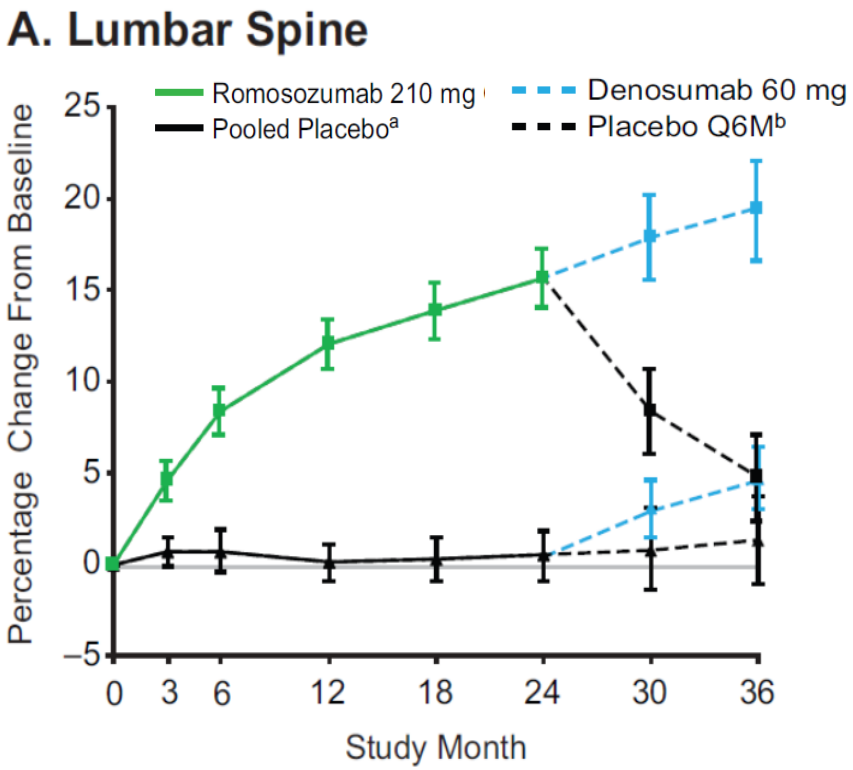
- RCT steroid osteoporosis
  - n = 214 Alendronate (10mg/d)
  - n = 214 Teriparatide (20mcg/d)
  - T<2.0, <1.0 with fx
- *36 month data*
- Average steroid dose 7.5 mg
- Average duration 1.3 years
- Primary End Point: BMD 36m (DXA)
  - Alendronate: 5.3%
  - Teriparatide: 11.0% (p<.001)
- Not prespecified end points
  - Vertebral fracture
    - Alendronate: 13
    - Teriparatide: 3 (p = 0.007)
- Non-vertebral fragility fracture
  - Alendronate 15, TPTD 16 (p = ns)



Moderate 26-40%;
Severe >40% height reduction

.Saag K, et al. *Arth Rheum*. 2009;60(11):3346.

Romosozumab
Monoclonal Sclerostin Antibody



Phase 2: n = 419 postmenopausal women
Treatment: 12 months of 24 month trial

Romo: 210mg sq qm
TPTD: 20mcg sq qd
ALN: 70mg po qwk
PBO: calcium

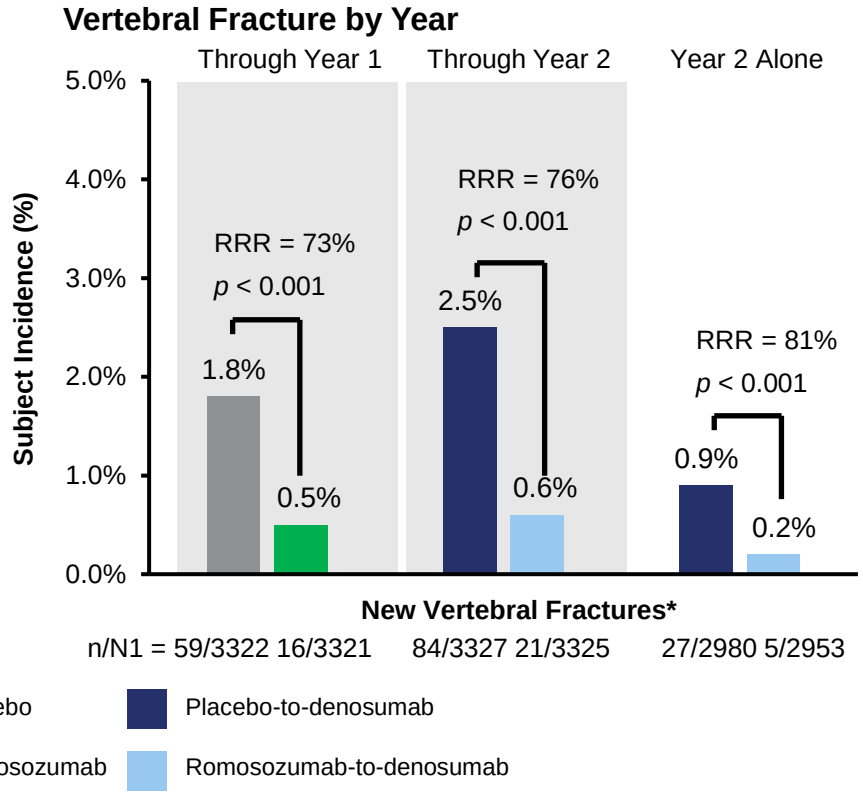
Primary Endpoint :	**LS BMD**
Romo:	**11.3%**
TPTD:	**7.0%**
ALN:	**4.0%**
PBO:	**0.1%**

McClung, MR, et al. *NEJM.* 2014;
McClung MR, et al. *JBMR*. 2018:33;1397.

Foundational Effect Romosozumab Frame (vs Placebo)

Vertebral Fracture

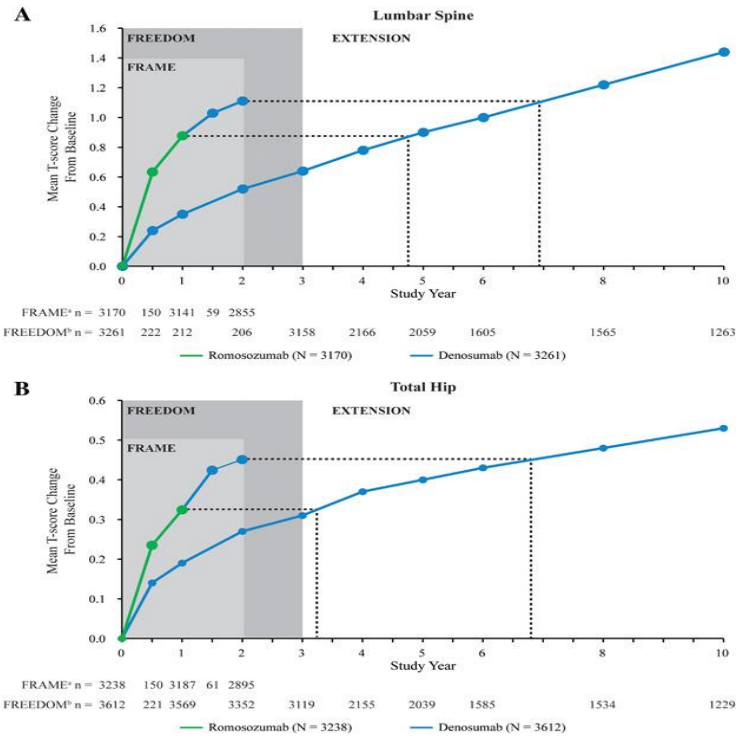
- Year 1#'s
  - PBO 59
  - Romo 16 (RRR 73%)
- Year 1-2
  - PBO/Dmab 84
  - Romo/Dmab 21 (RRR 76%)
- Year 2 (Dmab)
  - PBO/Dmab 27
  - Romo/Dmab 5 (RR 81%)
  - Similar BMD increase year 2



Cosman F. *JBMR*. 2018;33(7):1219.

BMD Increases

Freedom (Denosumab) vs FRAME (Romozosumab)



BMD Increases

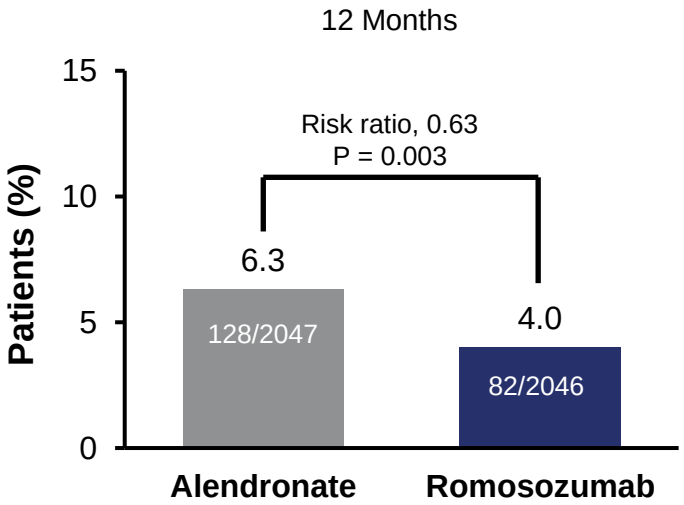
- <u>BMD Changes LS</u>
  - Romo 1 years
  - Dmab >4.5 years
- <u>BMD Changes LS</u>
  - Romo-Dmab 2 years
  - Dmab alone 7 years
- <u>BMD Changes Hip</u>
  - Romo-Dmab 2 years
  - Dmab alone >6.5 years

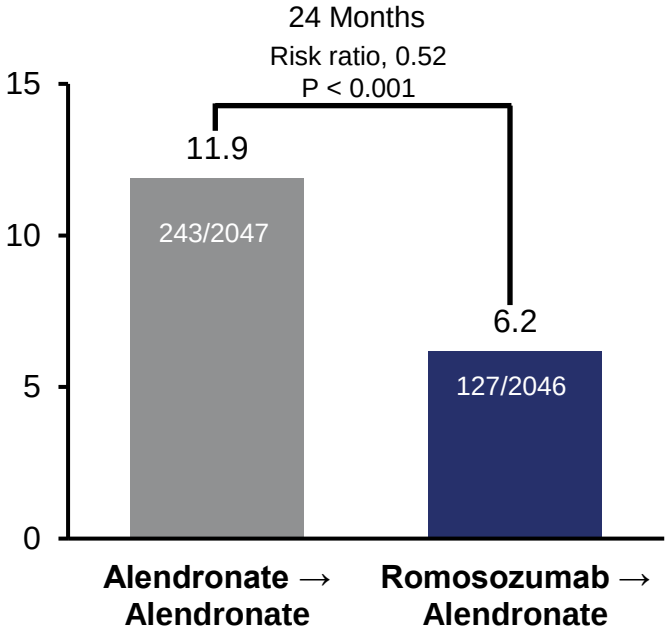
Cosman F. *JBMR*. 2018;33(7):1219.

ARCH: Romosozumab vs Alendronate

Vertebral Fracture

Incidence of New Vertebral Fracture



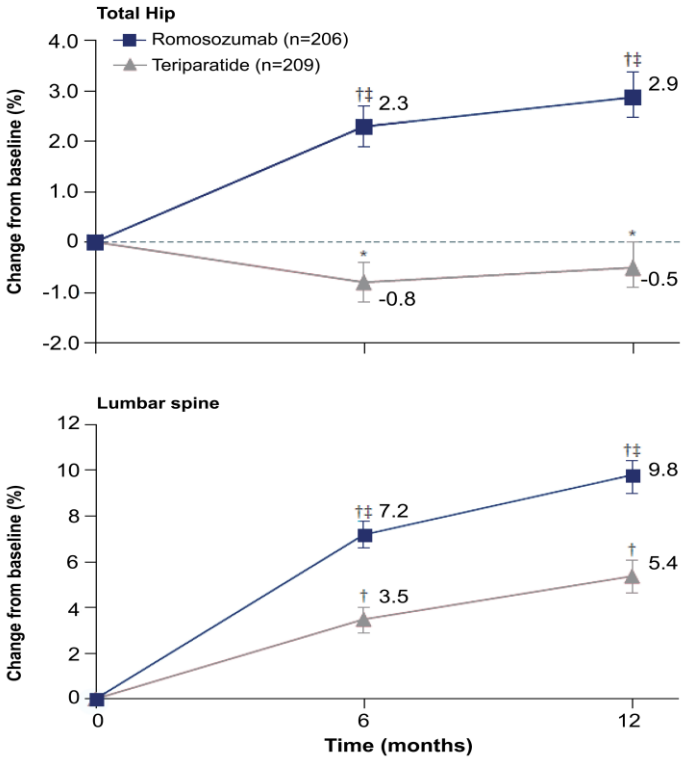


- Year 1: Romo vs ALN RRR = -37%
- Year 1-2: Romo/ALN vs ALN/ALN RRR = -48%

Saag KG, et al. *NEJM*. 2017;277:141.

STRUCTURE: Romosozumab vs TPTD

BMD: Areal

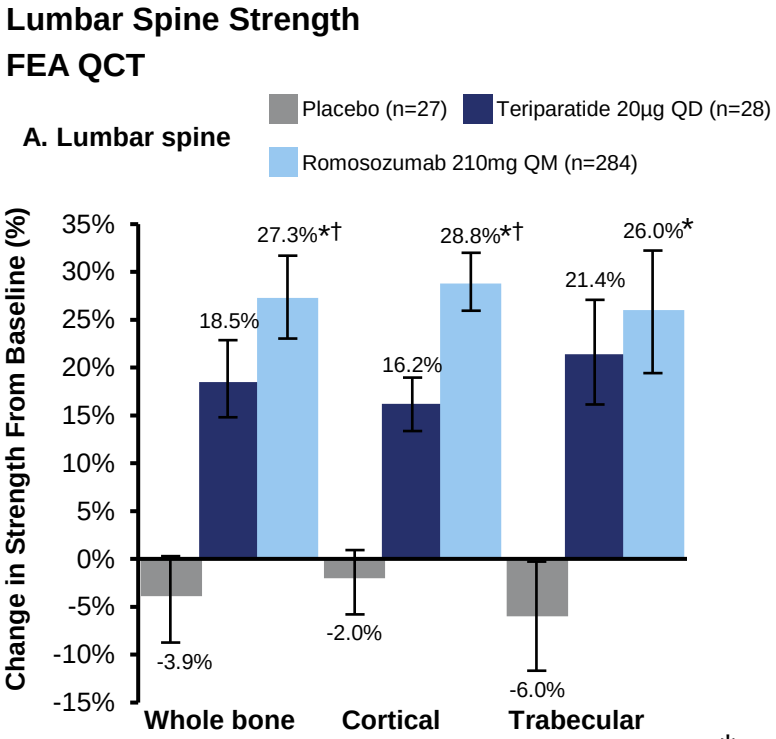


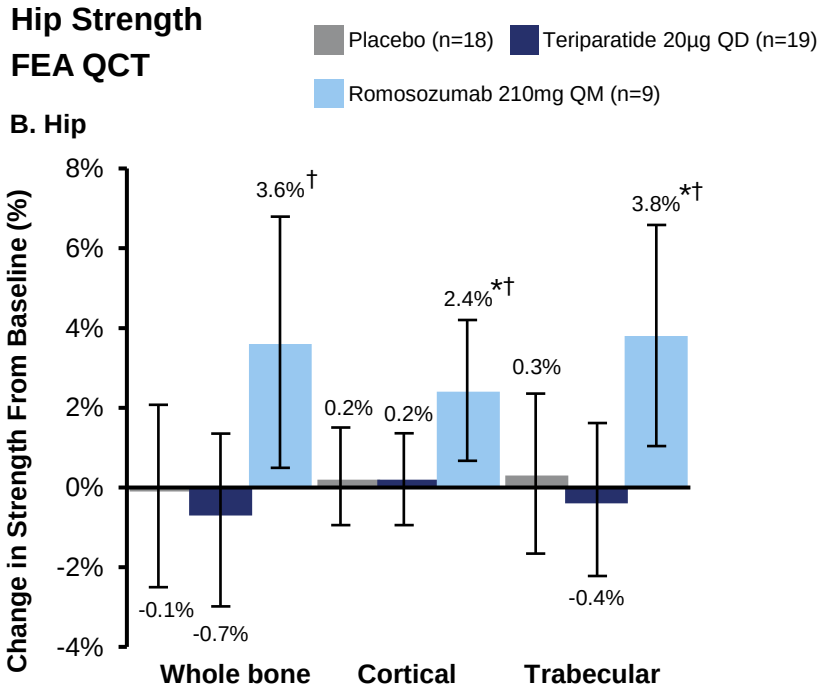
Trial

- PMO
- n = 436
- Age 55-90 years (mean 71)
- T≤-2.5 TH, FN or LS
- Nonvertebral or vertebral fx
- Oral bisphosphonate >3 years
- Treatment
  - Romo vs TPTD 12m

Langdahl BL, et al. *Lancet*. 2017;390:1585.

Structure: Romosozumab vs TPTD



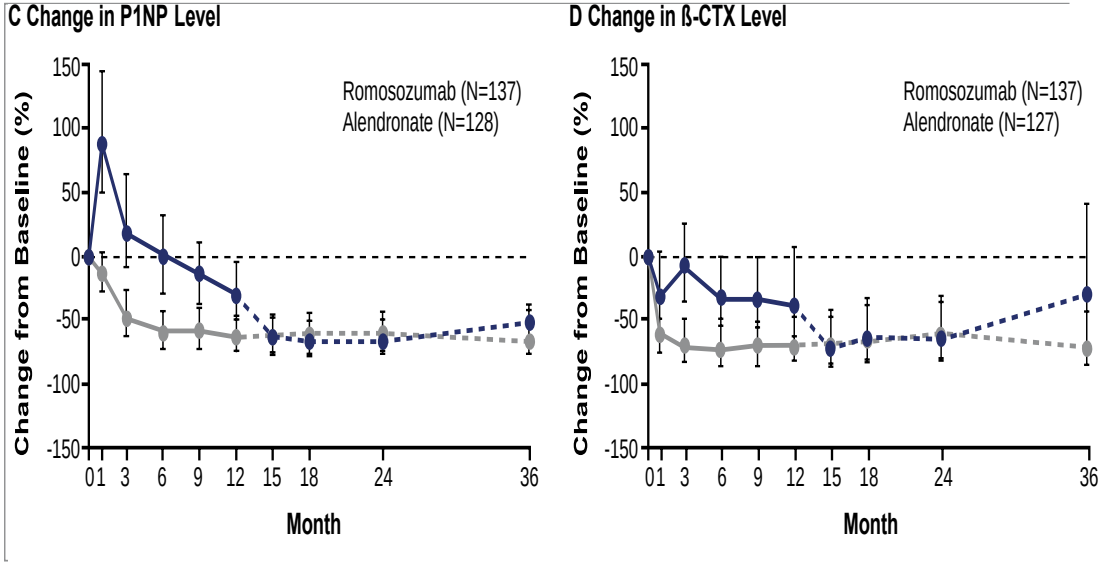


*p <0.05

Keaveny, et al. *JBMR.* 2017;32;1956.

Bone Turnover Markers
Romosozumab vs TPDP

Formation (P1NP) **Resorption (CTX)**



Paradigm

Anabolic agents

- Romosozumab
  - Pro modeling (70%)
  - Antiresorptive
    - RANKL effects
- Teriparatide (TPTD)
  - Pro modeling (30%)
  - Resorptive
    - PTH T1 receptor
    - **abaloparatide (PTHrP) less stimulation resorption**

Saag KG, et al. *NEJM*. 2017;377:1417; Appelman-Dijkstra NM, et al. *CTI*. 2016; 98:370.

Anabolic Choice

Romosozumab

- Higher risk hip fracture
  - Low hip T-score
  - Hip fracture
- High resorption markers
- After ALN (Structure)
- Previous XRT
- Previous PTH therapy

PTH Analogs

- Higher spine fracture risk
- Fracture healing, nonunion
- CV patient, CV risk factors
- After Romosozumab
  - **Best sequence PTH then Romo**
- Home vs office (12 visits)
- Travel (abaloparatide)

Conclusion

Anabolic

- Larger BMD gains
  - PTH underestimated by DXA
  - Romo 1-yr hip +6%
- Fracture advantage vs ALN
  - Vertebral
  - Non-vertebral and hip
- Foundational effect
  - Lower fx rates with AR agent after anabolic

Antiresoptive

- Easy to use
- Less expensive
- No limitation on duration
- Extention trials
  - 10 yrs denosumab
  - 10 yrs for alendronate
- Duration
  - 3-10 yrs, holiday, retreat

RhAPP
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Thank You.