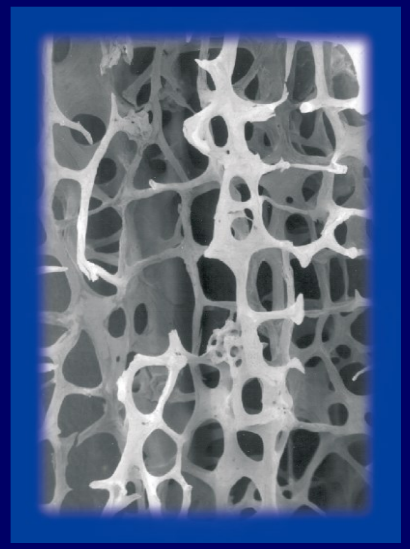
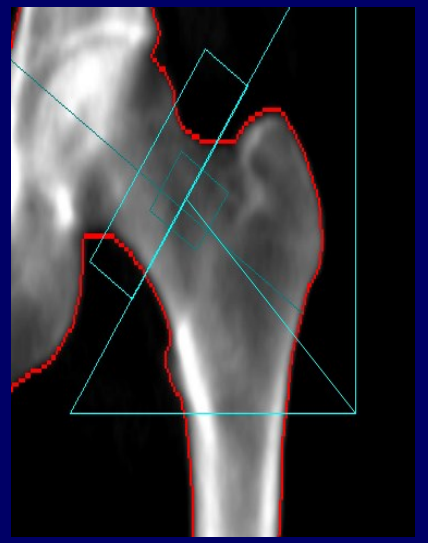
Current Issues in Osteoporosis



Israel Endocrine Society

Winter Conference

November 24, 2022



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DISCLOSURES: I receive consulting fees from Amgen and UCB and honorarium for speaking from Alexion and Amgen

OREGON OSTEOPOROSIS CENTER

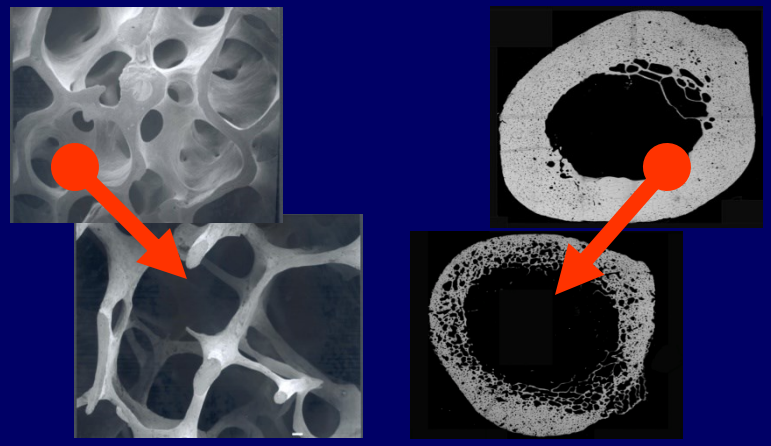
Current Issues in Osteoporosis

- Clinical considerations in choosing OP treatment
- Romosozumab and the CV warning
- Anabolic treatment after hip fracture

Osteoporosis - 2022

Key Points:

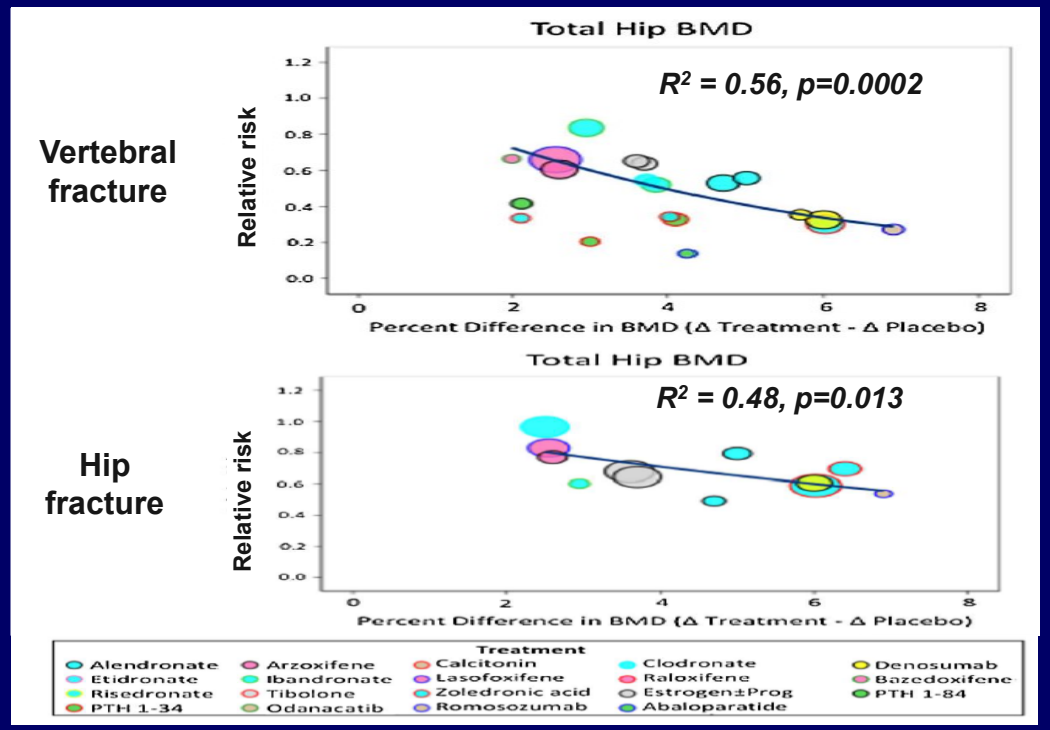
- Osteoporosis is a condition of skeletal fragility due to bone loss resulting in deterioration of bone microarchitecture leading to impaired bone strength
- Osteoporosis is a chronic, incurable condition requiring prolonged management
- None of our drugs “cures” osteoporosis
- Skeletal benefits of all osteoporosis therapies wane upon discontinuation of treatment
  - *It is important to develop a strategy for long-term treatment*
- The sequence with which drugs are given may have important clinical ramifications
- On-treatment hip BMD correlates with current fracture risk
  - *may serve as treatment target*



Images Courtesy of Drs. David Dempster and Roger Zebazi

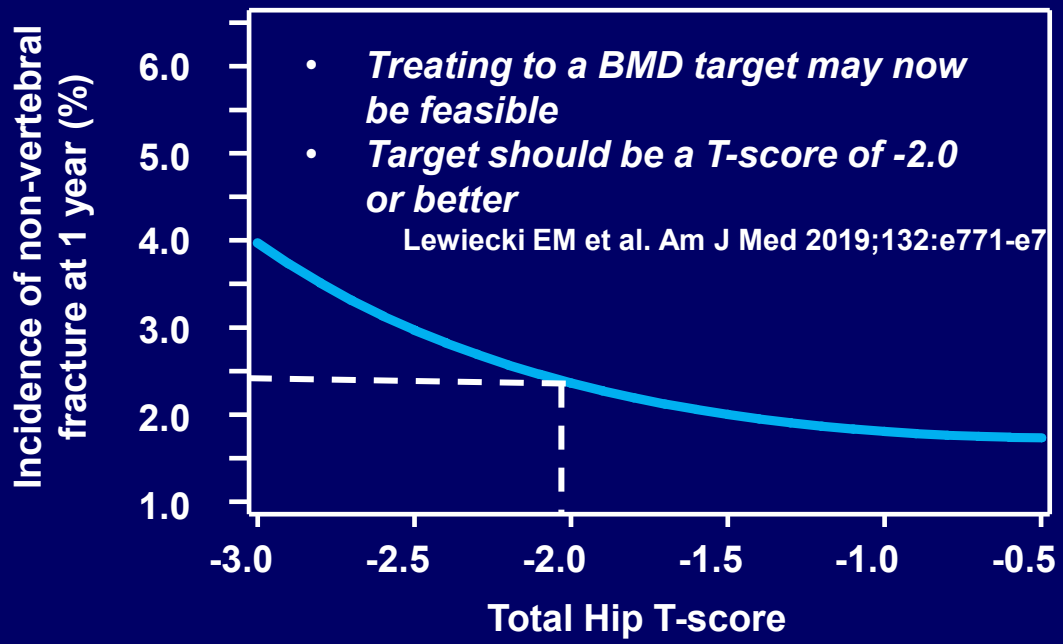
Larger Increases in BMD are Associated with Greater Reduction in Fracture Risk

Larger increases in hip BMD were associated with greater reduction in vertebral and hip fracture risk
Strong correlations between change in BMD and fracture risk reduction
R^2 0.41 – 0.73; p values 0.0001 - 0.014



Bouxsein M et al. *J Bone Miner Res* 2019;34:632-42

Total hip T-score achieved on treatment with denosumab predicted fracture risk during the following year



Ferrari S et al. *J Bone Miner Res* 2019;34:1033-40

Osteoporosis Treatment Options - 2022

- Anti-remodeling agents *(inhibit bone turnover)*
  - Estrogen (approved for prevention only)
  - Estrogen agonists/antagonist (raloxifene)
  - Bisphosphonates (oral and IV)
  - RANK ligand inhibitor (denosumab)

- Osteoanabolic agents *(activate bone formation)*
  - Remodeling stimulators (*increase formation and resorption*)
    - Parathyroid hormone receptor activators
      - teriparatide
  - Modeling stimulator *(increase formation, decrease resorption)*
    - Sclerostin inhibitor
      - romosozumab

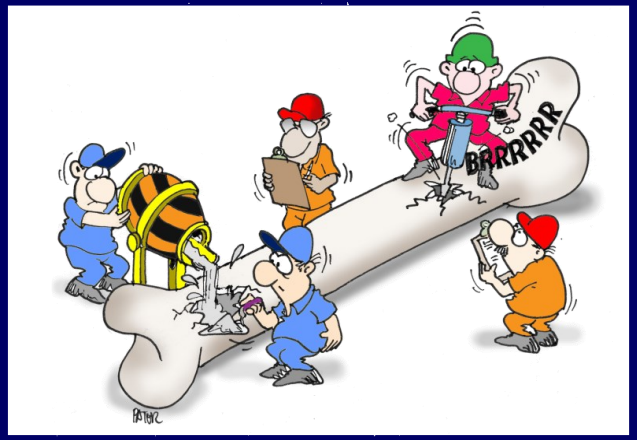
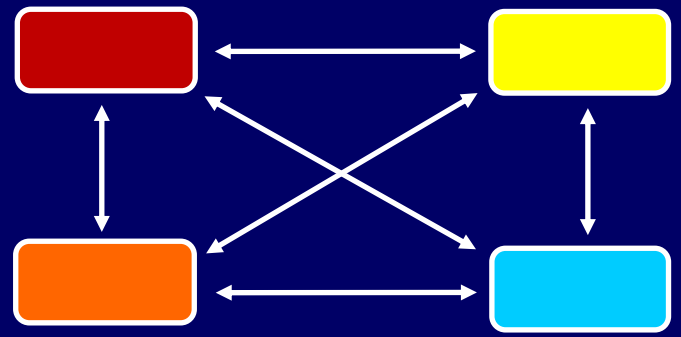


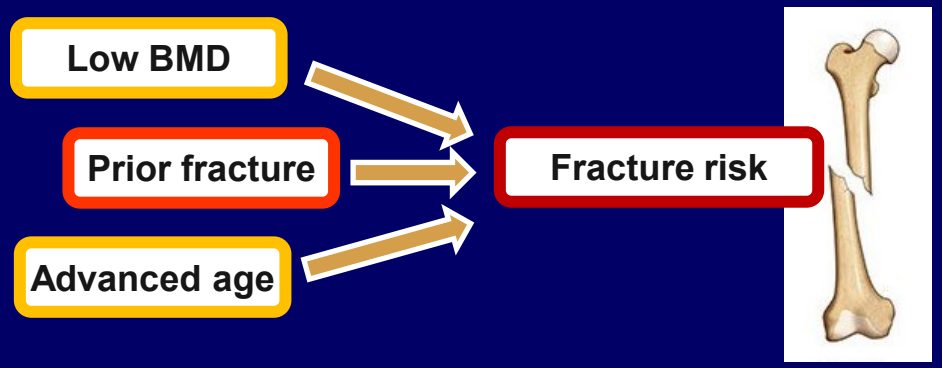
Image Courtesy of
Dr. Sergio Ragi

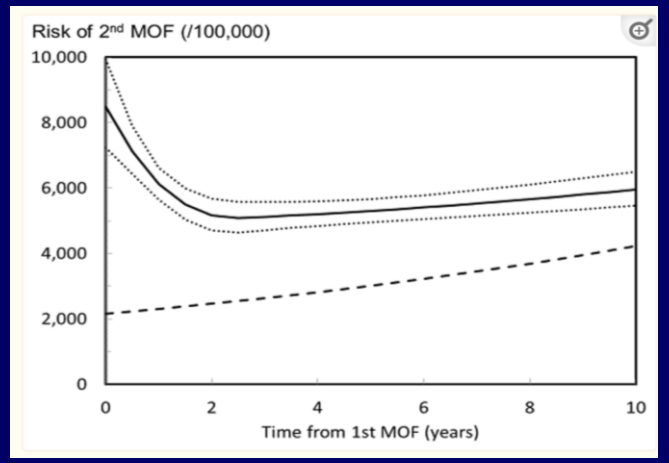
Optimal therapy involves the use of drugs in various sequences



Assessing Fracture Risk

- Recent guidelines recommend choosing initial therapy based on the patient's risk of fracture





Johansson H, *Osteoporos Int* 2017;28:775–70

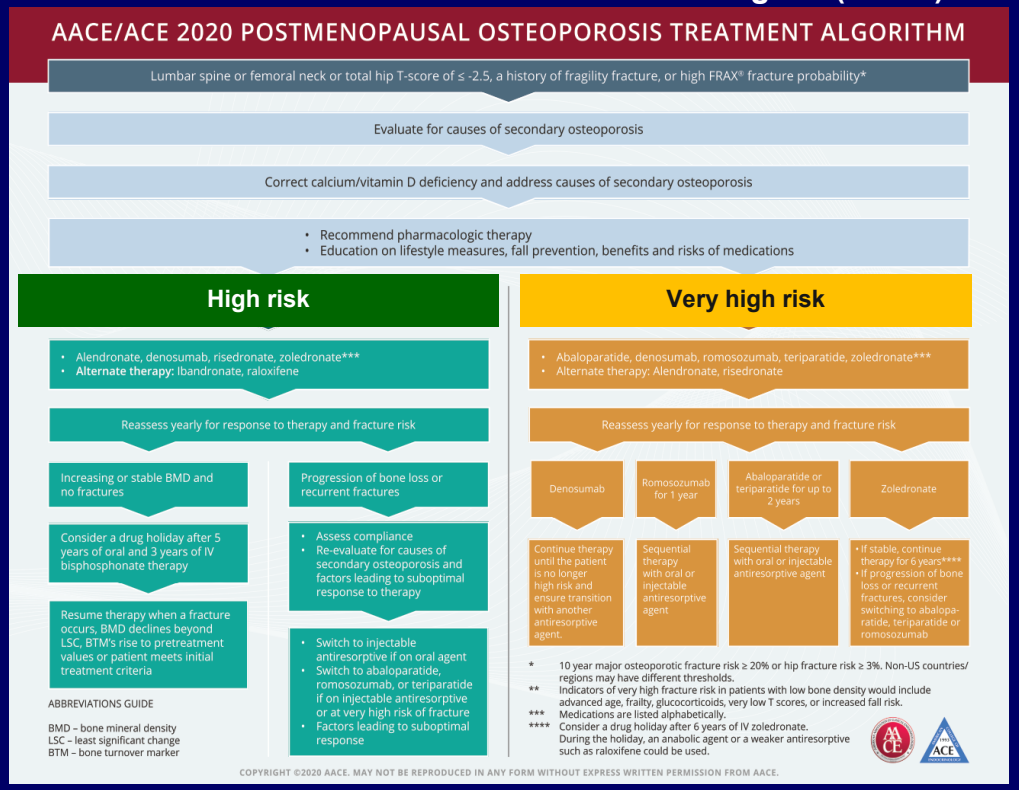
- The recency of a fracture is now recognized as an important determinant of fracture risk
  - 5-8 fold increase in relative risk in first 2 years after incident fracture
  - 10-20% incidence of fracture over 2 years after incident fracture
  - 19% incidence of another vertebral fracture after an incident vertebral fracture

Lindsay R et al. *JAMA* 285:320–23
Balasubramanian A et al. *Osteoporos Int* 2019;30:79–92
Banefelt J et al. *Osteoporos Int* 2019;30:601–9
Kanis JA et al. *Osteoporos Int* 2018;29:1747–57

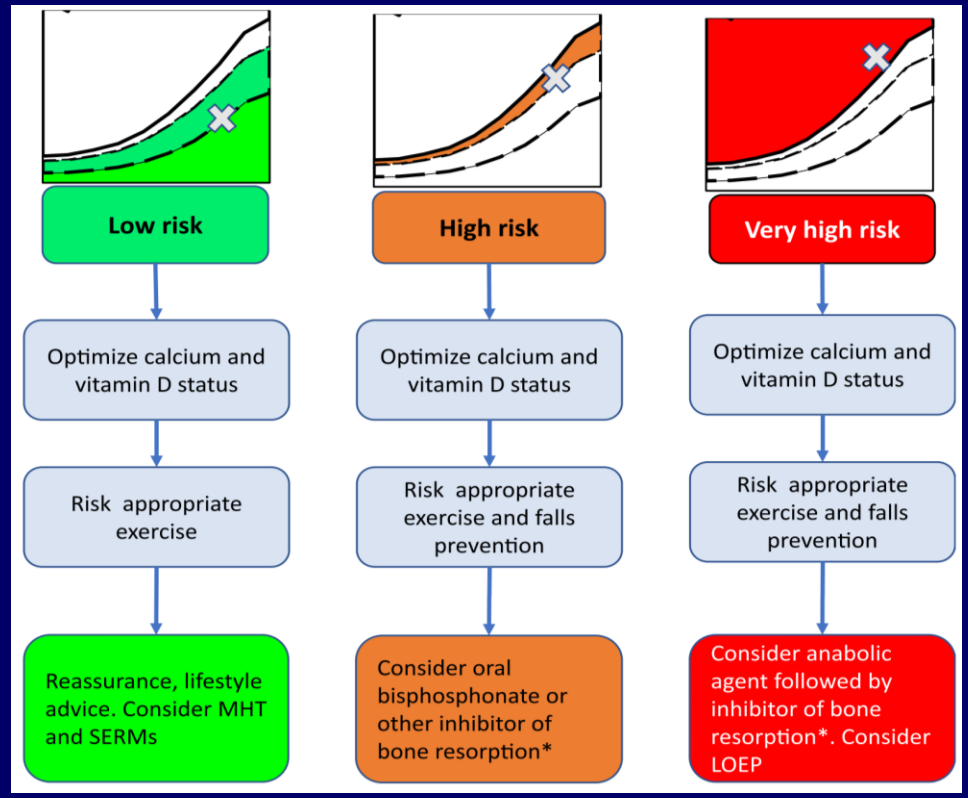
Very High Fracture Risk

Key Point: **Recent guidelines have defined a category of "very high" fracture risk**

American Association of Clinical Endocrinologists (AACE)



International Osteoporosis Foundation (IOF)



1. Camacho PM et al. AACE Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2020 Update. *Endocr Pract* 2020;26(Suppl 1):1-46
2. Kanis JA et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporos Int* 2020;31:1-12

Very High Fracture Risk

Defining "very high" fracture risk

- Examples of patients at very high fracture risk
  - AACE (1): patients with
    - fracture within the past 12 months
    - multiple fractures
    - fractures while on approved osteoporosis therapy
    - very low T-score (e.g., less than −3.0)
    - FRAX™ estimates of fracture risk of >30% for major osteoporotic fracture or >4.5% for hip fracture
  - IOF (2): patients with
    - recent clinical vertebral fracture
    - previous fracture and age 80 or older
    - previous fracture and parental history of hip fracture

1. Camacho PM et al. AACE Clinical Practice. *Endocr Pract* 2020;26(Suppl 1):1-46
2. Kanis JA et al.. *Osteoporos Int* 2020;31:1-12

Initial Treatment Based on Fracture Risk

Treatment recommendations depending on fracture risk

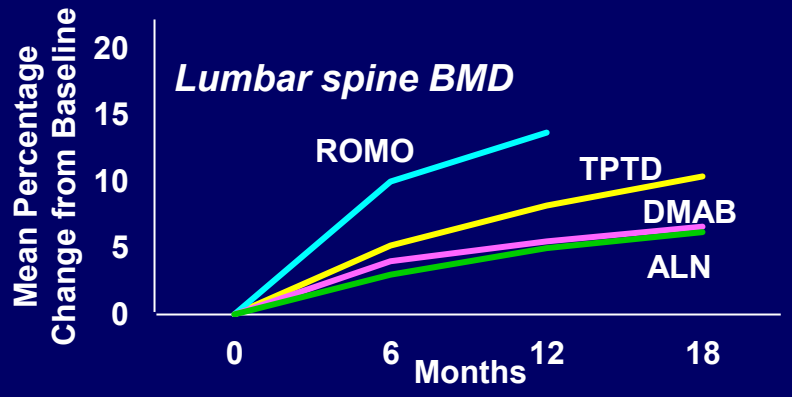
RISK CATEGORIES			
Low	**Moderate**	**High**	**Very High**
Postmenopausal women with low BMD but few or no other risk factors, especially if they are recently estrogen deficient, are candidates for prevention therapy	Younger postmenopausal women with lumbar spine BMD consistent with osteoporosis without prior fracture; low risk for hip fracture	Osteoporosis in spine or hip; low bone mass with remote history of non-spine, non-hip fracture or multiple other risk factors	Recent (within 1-2 years) fracture; very low BMD (<-3.0) or very high fracture probability by FRAX (>30% MOF or 4.5% hip fracture) hip region
RECOMMENDED DRUGS			
Hormone therapy	Raloxifene	Bisphosphonates	Osteoanabolic agents *
Low-dose bisphosphonates		Denosumab	Teriparatide Abaloparatide Romosozumab

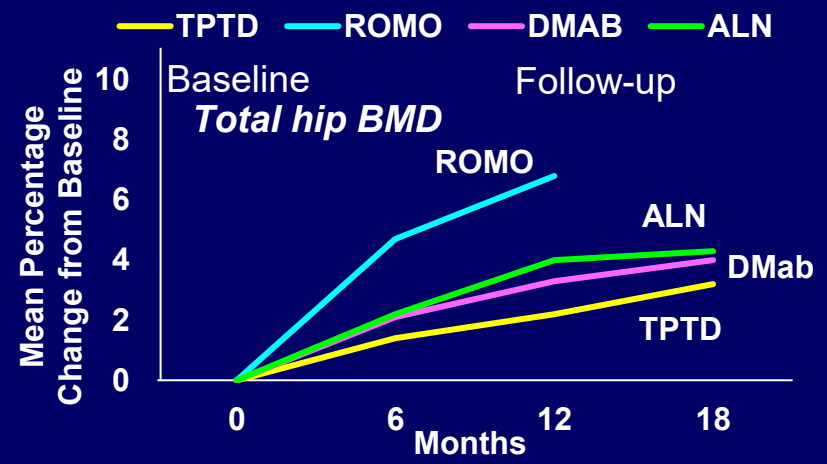
* to be followed by an anti-remodeling drug

Camacho PM et al.. *Endocr Pract* 2020;26(Suppl 1):1-46
Kanis JA et al. *Osteoporos Int* 2020;31:1-12
McClung MR et al. *Menopause* 2021:28:973-97

Justification for Osteoanabolic Therapy as Initial Therapy

increases BMD more and more quickly than do other drugs



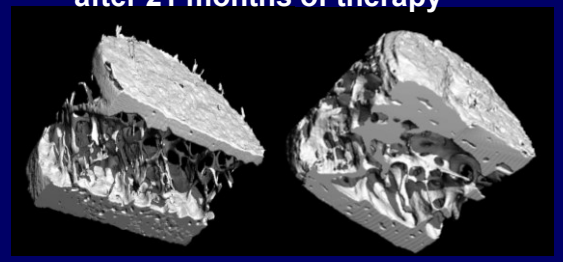


TPTD = teriparatide; ROMO = romosozumab; DMab = denosumab; ALN = alendronate

McClung MR. *Aging Clin Exp Res* 2021;33:775-91

improves trabecular microarchitecture

Iliac crest biopsies taken at baseline and after 21 months of therapy



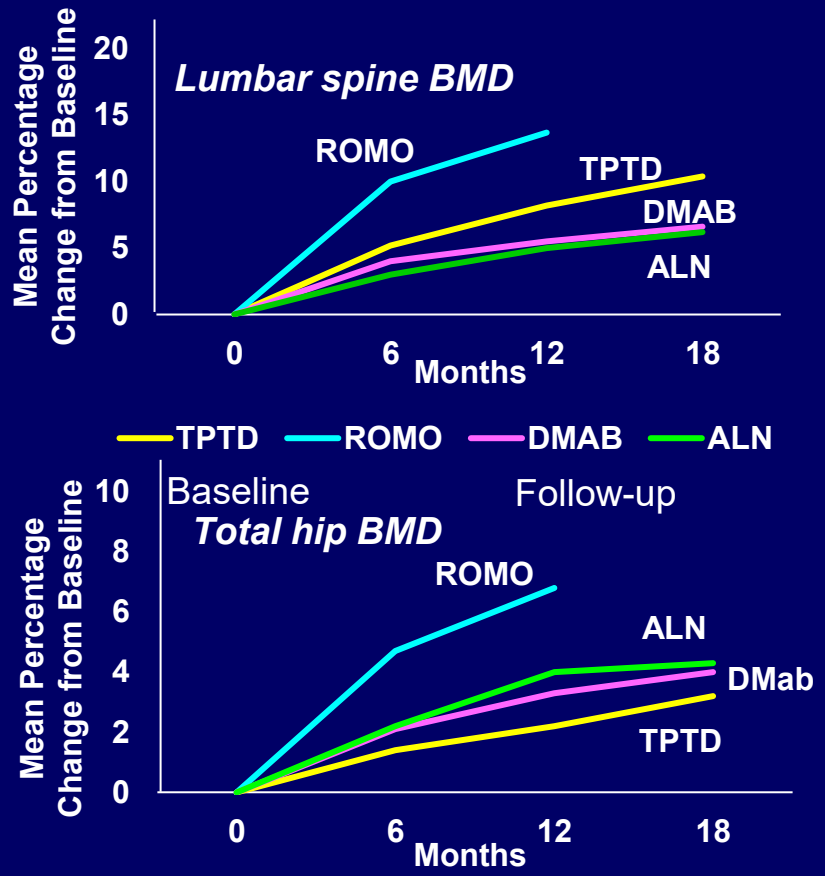
Dempster DW et al. *J Bone Miner Res* 2018;33:627-33
Jiang Y et al. *J Bone Miner Res* 2003;18:1932-41

Iliac crest biopsies after 12 months of therapy

Chavassieux P et al. *J Bone Miner Res* 2019;34:1597-1608

Justification for Osteoanabolic Therapy as Initial Therapy

increases BMD more and more quickly than do other drugs



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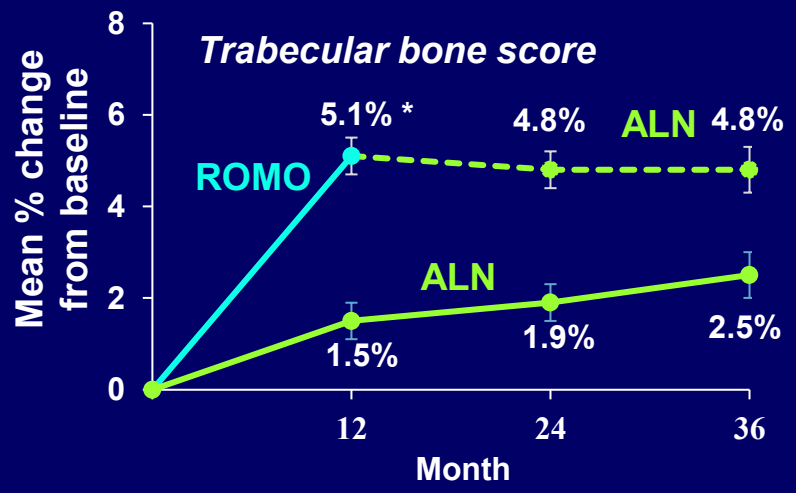
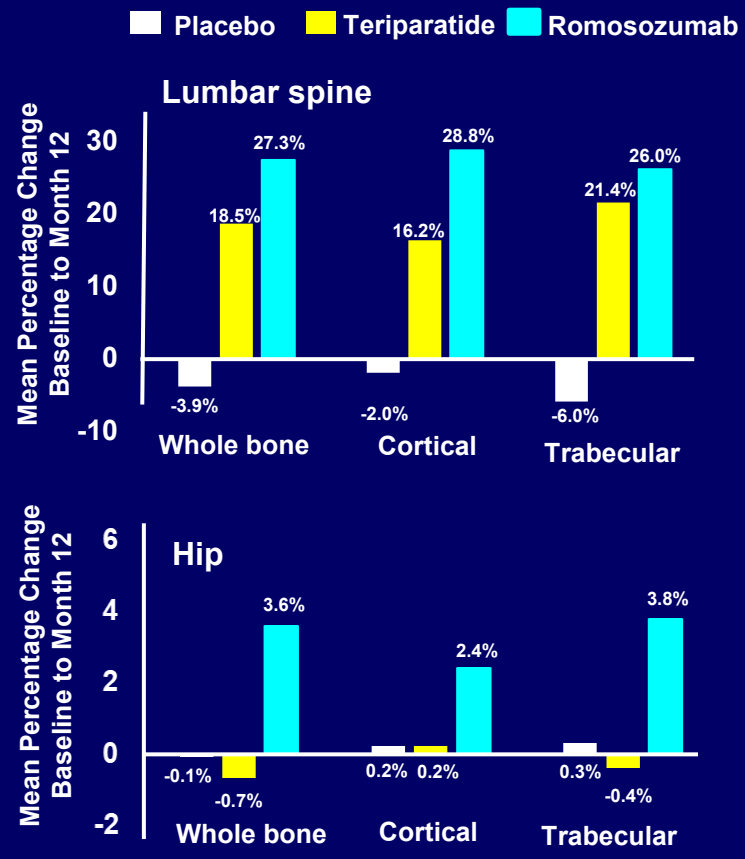


McClung MR et al. ASBMR 2022

increases estimated bone strength by finite element analysis over 12 months

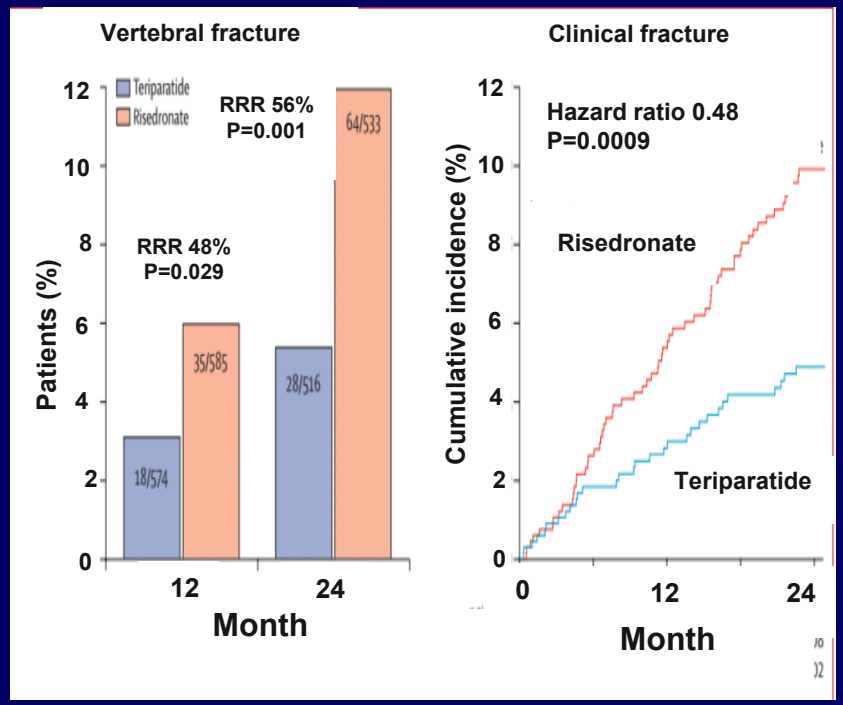


Keaveny T et al. *J Bone Miner Res* 2017;32:1956-62

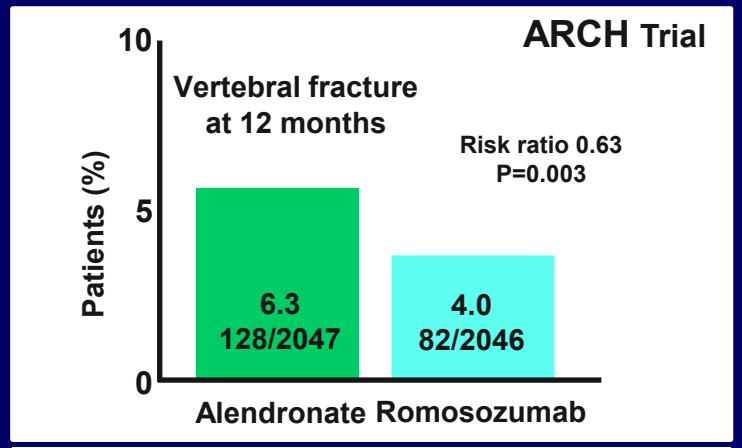
Justification for Osteoanabolic Therapy as Initial Therapy

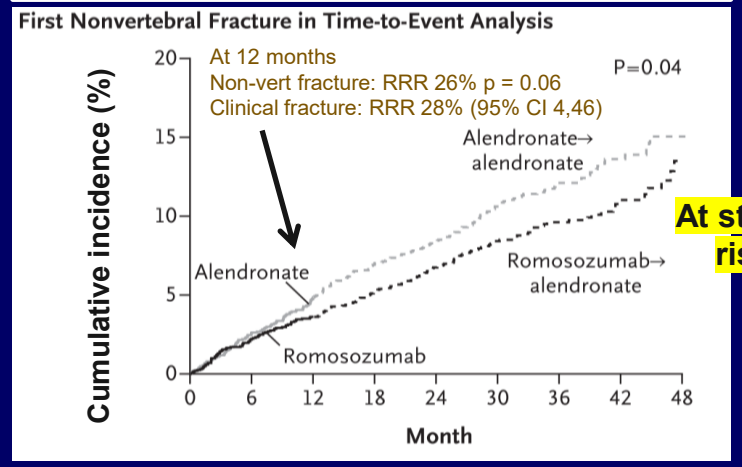
Key Point: **Teriparatide and romosozumab reduce fracture risk more effectively than do bisphosphonates**

VERO Study



Kendler DL et al. *Lancet* 2017 Nov 9. pii: S0140-6736(17)32137-2



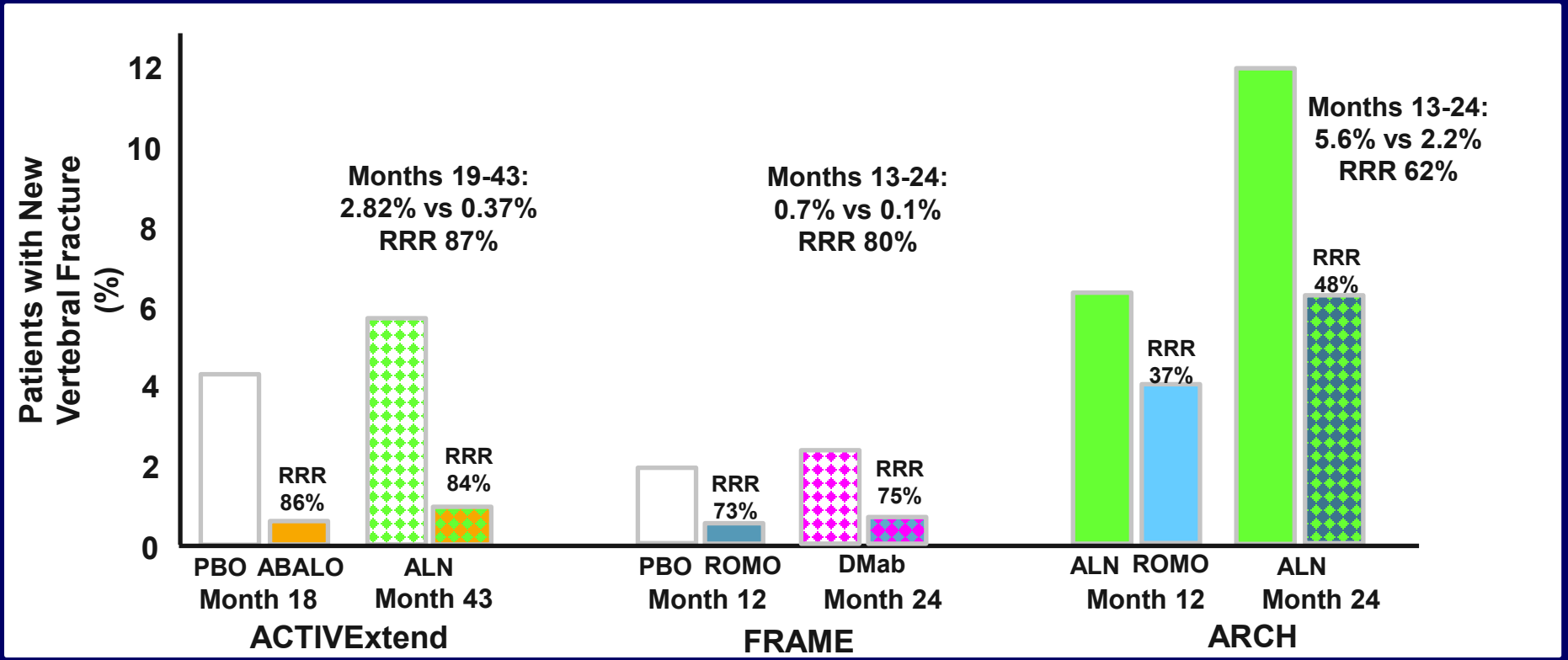


At study end, hip fracture risk reduced by 38%

Saag K et al. *N Engl J Med* 2017;377:1417-27

Justification for Osteoanabolic Therapy as Initial Therapy

Key Point: **The fracture protection afforded by a course of osteoanabolic therapy persists for at least two years after transition to an anti-remodeling drug**

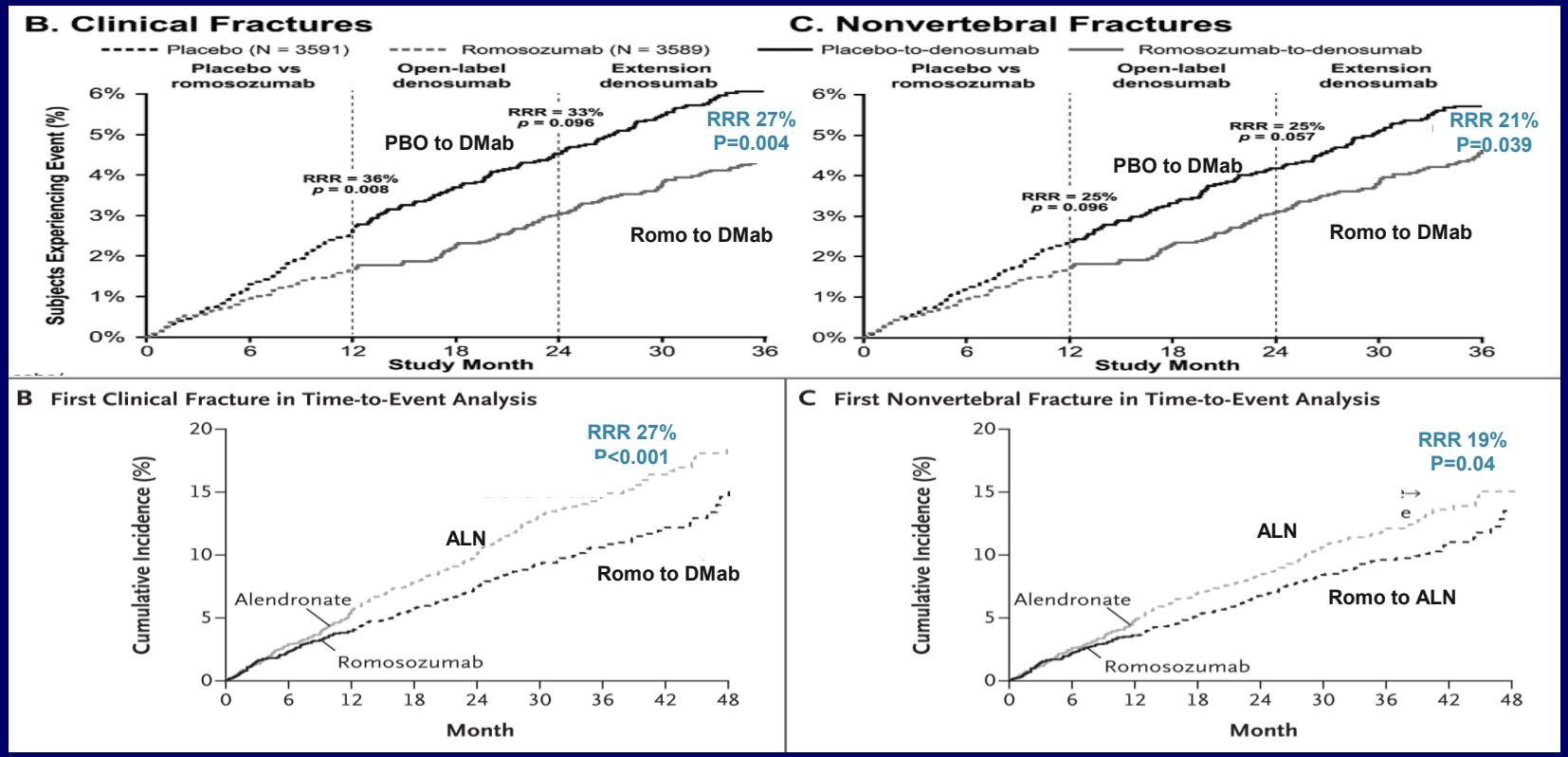


PBO = placebo; ABALO = abaloparatide; ROMO = romosozumab; DMab = denosumab; RRR = relative risk reduction

McClung MR et al. *Postgrad Med* 2022;May 30:1-11

Justification for Osteoanabolic Therapy as Initial Therapy

Key Point: **The fracture protection afforded by a 12 month course of romosozumab persists for at least two years after transition to alendronate or denosumab**

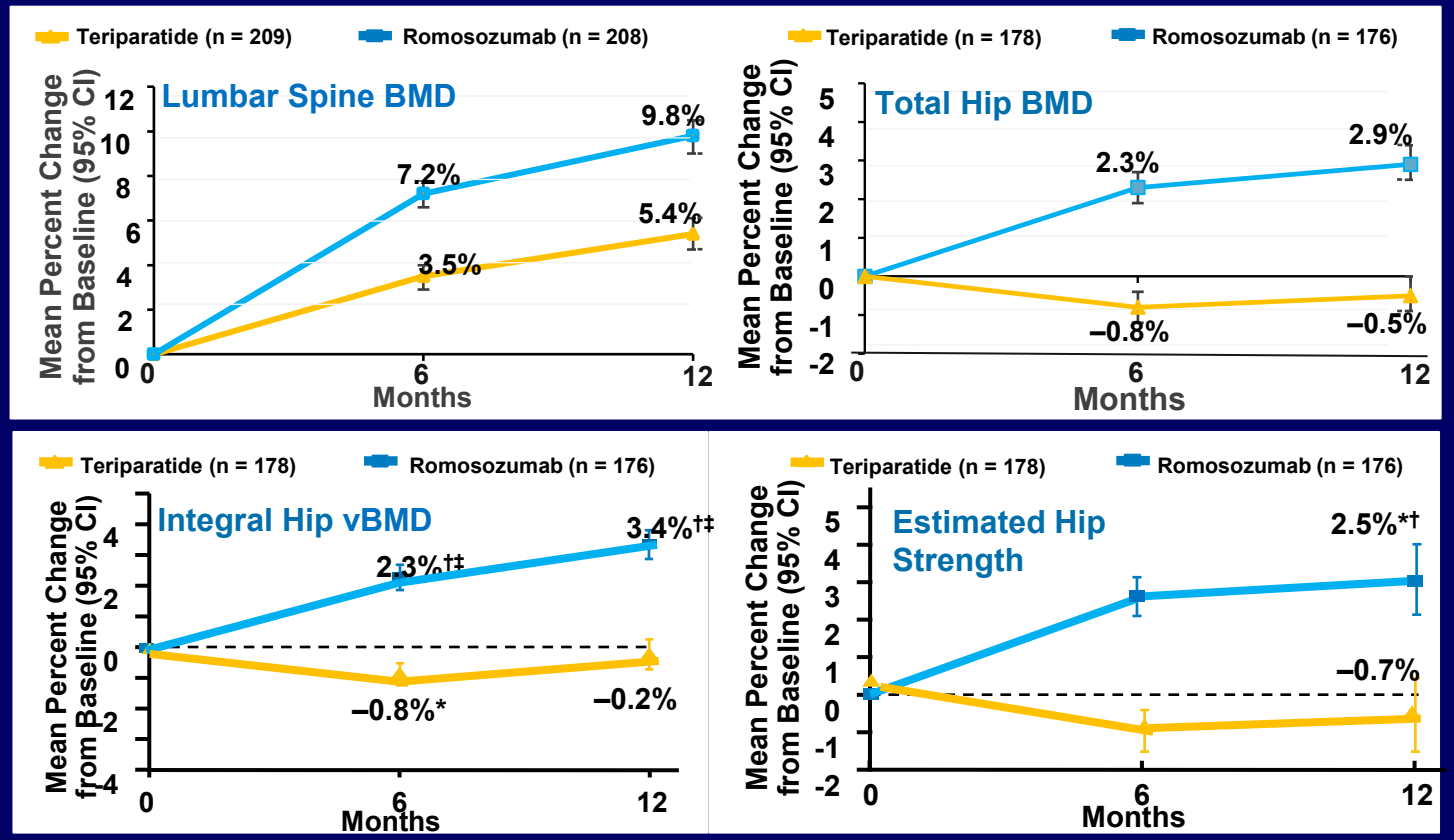


ALN = alendronate; PBO = placebo;
Romo = romosozumab; RRR = relative risk reduction

Saag K et al. *N Engl J Med* 2017;377:1417-27
Lewiecki EM et al. *J Bone Miner Res* 2019;34:419-28

Osteoanabolic Therapy After Bisphosphonates

- Some patients who have been treated with bisphosphonates remain at very high fracture risk
- In patients previously treated with alendronate, BMD and estimated bone strength increased more with romosozumab than with teriparatide



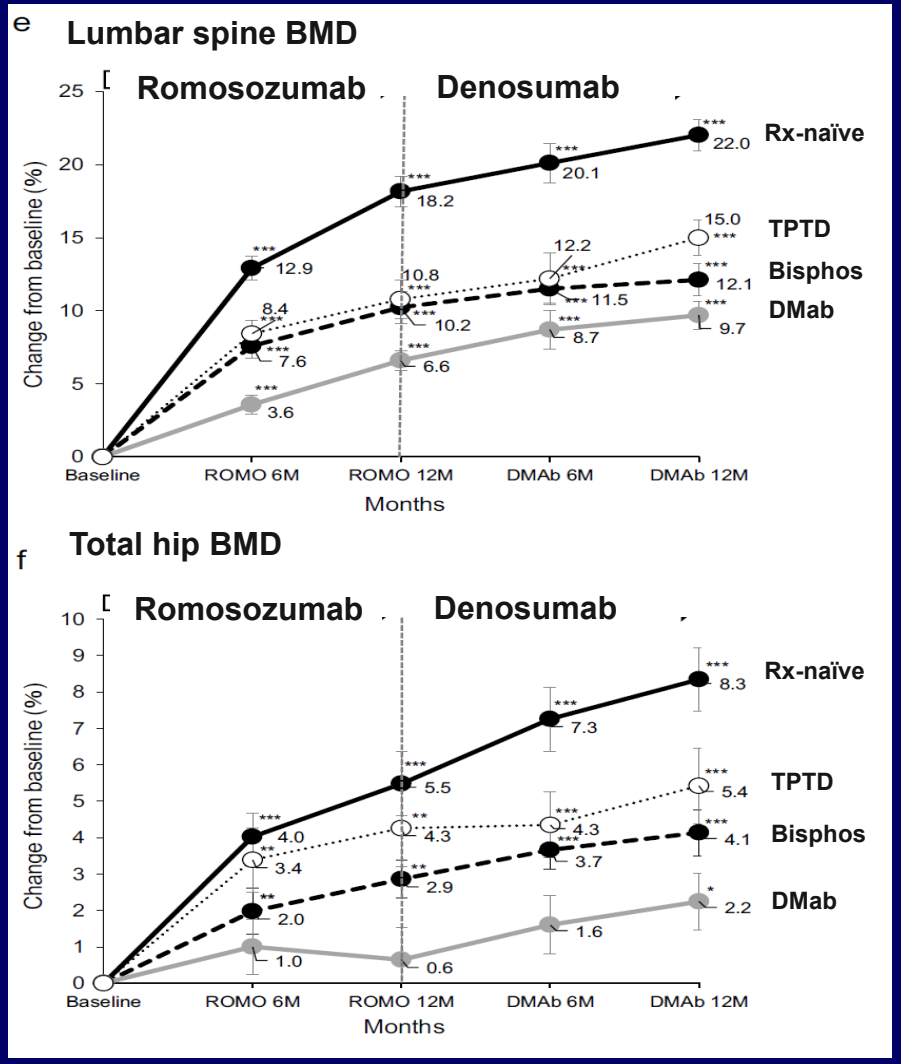
Langdahl B et al. *Lancet* 2017;390:1585–94

Real World Experience with Romosozumab

- Average BMD responses to romosozumab for 12 months followed by denosumab for 12 months was evaluated in patients with various previous treatment

- As seen in previous studies, BMD response was greater in treatment-naïve patients than in those pre-treated with bisphosphonates, denosumab or teriparatide

Ebina K et al. *Osteoporos Int* 2022 33;1807-13



Current Issues in Osteoporosis

Clinical considerations in choosing OP treatment

Initial choice of therapy should be based on an assessment of the patient's fracture risk and the probability of a specific treatment (or sequence of therapies) achieving one's treatment target

Beginning therapy with a bone forming agent makes intuitive sense, especially for patients at very high risk of fracture

After bisphosphonates or denosumab, romosozumab appears to induce larger changes in BMD than does teriparatide

The remainder of the patient's health status (e.g., renal function, etc.) and her objectives and preferences must be considered

Current Issues in Osteoporosis

Romosozumab and the CV warning

In the Phase 3 romosozumab studies, all serious CV events were reviewed and adjudicated by a cardiology research group at Duke University. They were blinded to the study and to treatment allocation.

	ARCH[1]				FRAME[2]			
	Alendronate	Romosozumab	HR	95% CI	Placebo	Romosozumab	HR	95% CI
Number	2014	2040			3576	3587		
Serious CV AEs	1.9%	2.5%	1.32	(0.87, 2.01)	1.1%	1.2%	1.00	(0.66, 1.50)

AE = adverse event; CV = cardiovascular; HR = hazard ratio; CI = confidence interval

1. Saag K et al. *N Engl J Med.* 2017;377:1417-27
2. Cosman F et al. *N Engl J Med* 2016;375:1532-43

Current Issues in Osteoporosis

Romosozumab and the CV warning

In the Phase 3 romosozumab studies, all serious CV events were reviewed and adjudicated by a cardiology research group at Duke University. They were blinded to the study and to treatment allocation.

When the imbalanced in serious CV adverse events was seen, they performed a post-hoc analysis confining the cases to Major Adverse CV Events (MACE)

	ARCH[1]				FRAME[2]			
	Alendronate	Romosozumab	HR	95% CI	Placebo	Romosozumab	HR	95% CI
Number	2014	2040			3576	3587		
Serious CV AEs	1.9%	2.5%	1.32	(0.87, 2.01)	1.1%	1.2%	1.00	(0.66, 1.50)
MACE	1.1%	2.0%*	1.87	(1.11, 3.14)	0.8%	0.8%**	1.03	(0.62, 1.72)

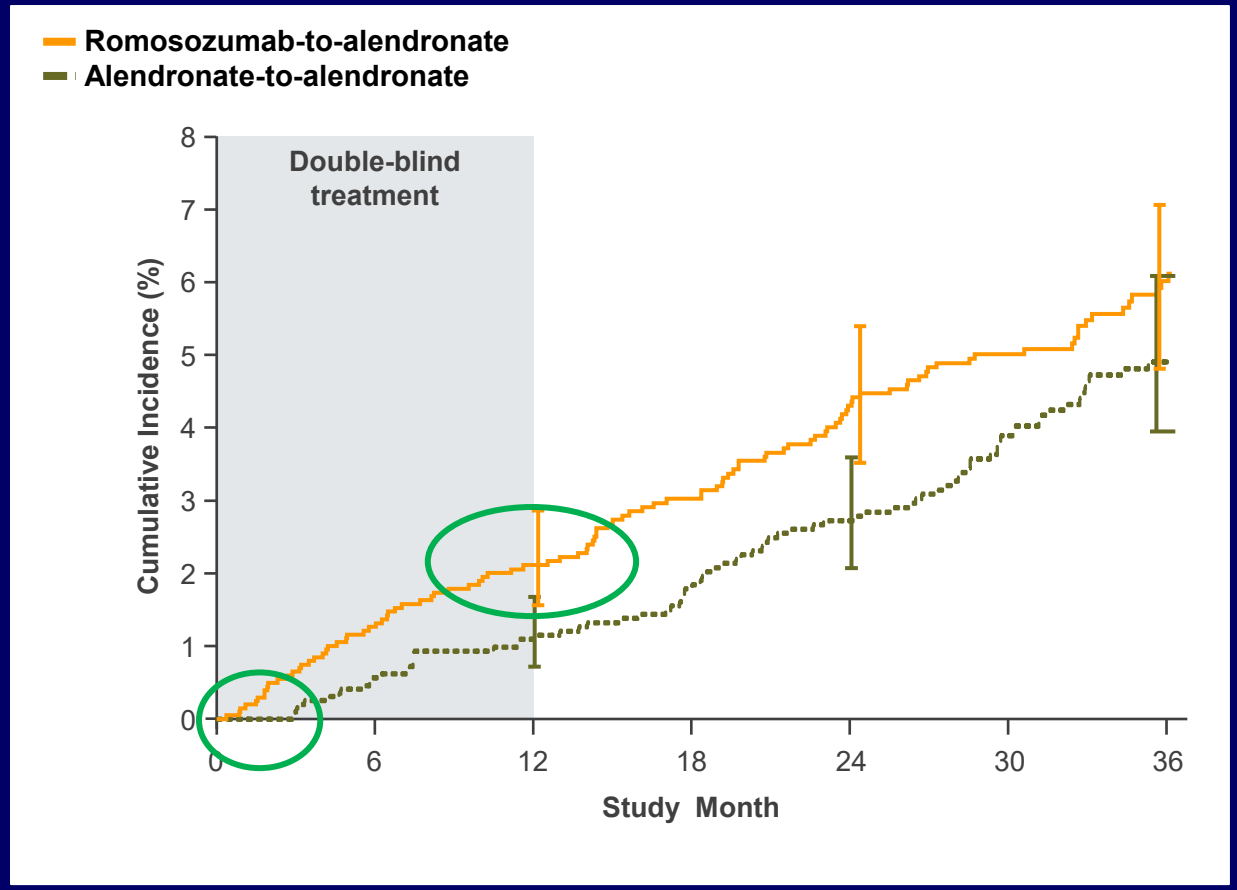
AE = adverse event; CV = cardiovascular; HR = hazard ratio; CI = confidence interval

1. Saag K et al. *N Engl J Med.* 2017;377:1417-27
2. Cosman F et al. *N Engl J Med* 2016;375:1532-43

Romosozumab and Cardiovascular Safety

- The disparity in results between the two studies is not explained.
- Very few events in alendronate group during first 3 months
- Effect seen early without progression
- No inflection in the romosozumab-to-alendronate curve
- *The cumulative incidence plot is not suggestive of either an adverse effect of romosozumab or a protective effect of alendronate*
- No genetic or animal model evidence for adverse CV effects of sclerostin deficiency or antisclerostin therapy

Time to First Positively Adjudicated MACE in the ARCH Study



Cummings SR, McCulloch C.. Osteoporos Int. 2020;31:1019-21
Langdahl BL et al. J Clin Endocrinol Metab 2021;106:1845-53

Romosozumab and Cardiovascular Safety

- A separate analysis of that same FAERS pharmacovigilance database for the years 2019-2020 reported 1948 romosozumab-related adverse events

	Results
Total AE reports	1948 (US 39.3%, Japan 59.7%
Average age (years)	Not given
% female	76.6%
Adverse events with increased risk	Reporting odds ratio (95% confidence interval)
injection site pain	6.89, (5.60, 8.48)
cardiac failure	12.62, (9.85, 16.17)
renal impairment	9.11, (6.98, 11.89)
pneumonia	1.53, (1.10, 2.21
elevated alkaline phosphatase	14.60, (9.28, 22.97)

NOTES:

No mention of MACE events

Heart failure in ARCH:

0.4% with alendronate

0.2% with romosozumab

Increased alkaline phosphatase is an expected finding

Chen Z et al. *Expert Opinion on Drug Safety* 2022. Online Oct 5

Romosozumab and Cardiovascular Safety

- In a Japanese study, the reported incidences of stroke and ischemic heart disease per 100 person-years in patients receiving romosozumab were calculated and were lower than the reported incidence of those events in a general population cohort of Japanese adults.

	Romosozumab	Shiga Cohort Study
Cohort size	39,352 person-years	689,859 followed for 1 year
Number of strokes	not given	2956
Mean age of stroke patients	77.0 years	76.2 years
% female	76.1% (15% unknown)	53.4%
Incidence of ischemic cardiac event per 100 person-years	0.1007	0.17
Incidence of stroke per 100 person-years	0.164	0.40

Takeuchi Y et al. *Osteoporos Sarcopenia* 2021;7:89-91

Romosozumab and Cardiovascular Safety

- **The uncertainty of the relationship between EVENITY and CV risk is reflected in the Warning in the Prescribing Information**

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH

See full prescribing information for complete boxed warning.

- **EVENITY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)**
- **EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)**
- **If a patient experiences a myocardial infarction or stroke during therapy, EVENITY should be discontinued. (5.1)**

Until we know more about this CV risk, it is prudent to use EVENITY in patients at very high risk of fracture and to avoid its use in patients at very high risk for myocardial infarction and stroke

Romosozumab and Cardiovascular Safety

Personal opinion:

- **Examples of patients who would not be candidates for romosozumab because of high cardiovascular risk would include patients with :**
  - **recent myocardial infarction or stroke**
  - **active coronary artery syndromes (angina, etc.)**
  - **poorly controlled diabetes or hypertension**

- **Examples of patients I would feel comfortable beginning therapy with romosozumab after discussion of CV risks with the patient:**
  - **Well controlled diabetes or hypertension**
  - **Remote history of myocardial infarction or stroke**
  - **Women over age 80**

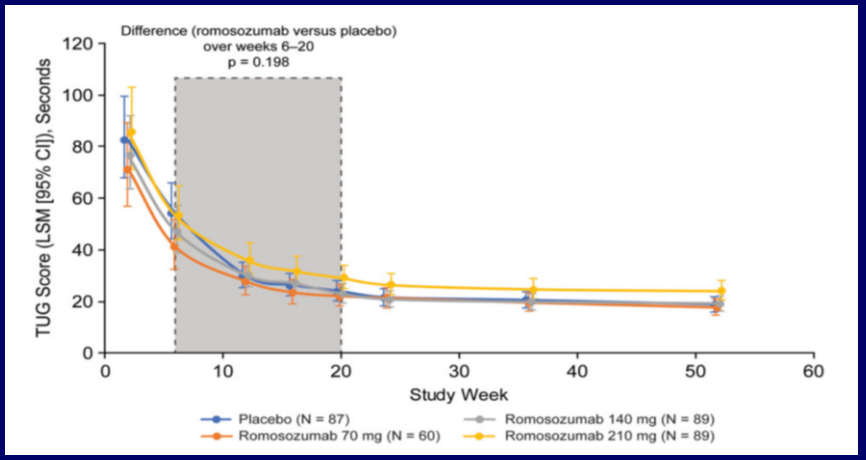
Current Issues in Osteoporosis

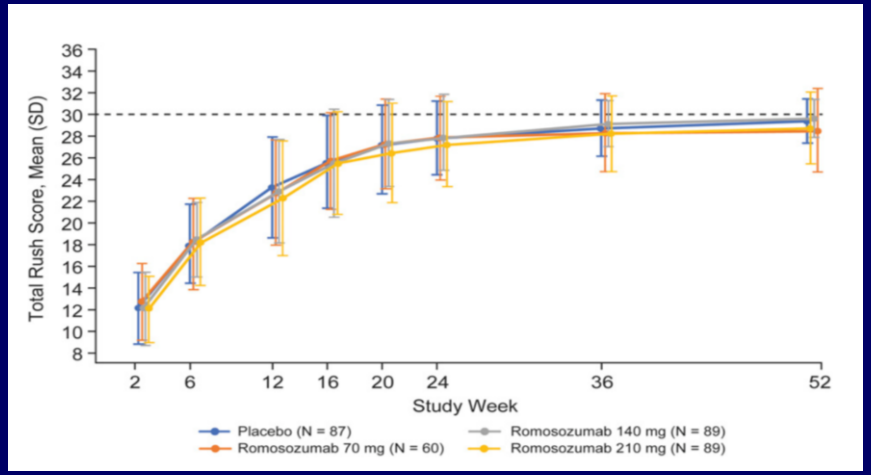
Osteoanabolic Therapy After Hip Fracture

- Having a hip fracture is a strong risk factor for having additional fractures and for death.
- Pharmacological treatment is recommended for all postmenopausal women and older men who experience a hip fracture.
- The only study to evaluate the effects of treatment on recurrent fracture risk was the HORIZON Post Hip Fracture Study
  - Annual infusions of zoledronate reduced fracture risk by 35% and overall mortality by 28% in elderly men and women with a recent hip fracture
- Studies of osteoanabolic agents after hip fracture have only evaluated changes in bone mineral density, fracture healing and/or functional outcomes

Romosozumab After Hip Fracture

- A Phase 2 study randomly assigned 352 patients with a recent low-energy intertrochanteric or femoral neck fracture to receive placebo or romosozumab in doses of 70, 140 or 210 mg per month for 12 months
- *Primary endpoints:*
  - TUG score, a validated measure used to assess functional mobility of persons with impaired mobility and which correlates well with activities of daily living
  - RUSH score, a validated tool to objectively assess hip (femoral neck) fracture-healing after surgical repair
- *RESULTS:* Both scores improved in all groups with no differences in outcomes among the treatment groups. Three hip fractures occurred - all in the romosozumab groups





Teriparatide After Hip Fracture

- Several studies evaluating the effects of teriparatide (TPTD) after hip fracture have produced inconsistent results
  1. An observational study compared 60 patients treated with TPTD after an intertrochanteric (IT) hip fracture with 52 other patients. In the TPTD group, Harris Hip Score was significantly increased ($p = 0.02$) and VAS pain scores were reduced ($p = 0.008$). The mean time to fracture healing was 14.8 weeks (SD 7.1) without TPTD and 12.1 weeks (SD 6.4) with TPTD ($p = 0.002$). Frequency of postoperative complications was reduced in the TPTD-treated group ($p = 0.028$).
  2. 31 patients with IT hip fracture did or did not receive TPTD according to the patient's preference. All fractures had healed by 24 weeks. At 12 weeks, fractures had healed in 56% of TPTD group and 13% in the control group.
  3. 30 men and women (average age 73 years) with intertrochanteric fracture, were randomly assigned to receive teriparatide or placebo. Mean healing time was significantly shorter (13.3 vs 15.5 weeks ($P = 0.001$) with TPTD. Slightly better function at 6 months in TPTD group.
  4. Authors of a meta-analysis concluded that current limited evidence did not support the use of TPTD to improve fracture healing of hip fractures due to study heterogeneity and various sources of biases.

Kim S-J et al. Injury 2019;50:1364-70
Mishra S et al. Cureus 14: e26190
Rana A et al. Int J Burn Trauma 2021;11:234-44

Current Issues in Osteoporosis

Osteoanabolic Therapy After Hip Fracture

Summary:

- **There is not yet solid evidence that anabolic agents hasten fracture healing or rehabilitation following a hip fracture**
- **There is no evidence of impaired fracture healing or other harm when using an osteoanabolic agent after a hip fracture**
- **Bone mineral density increases with osteoanabolic therapy in patients with hip fracture, but there is no current evidence that the risk of subsequent hip fracture is reduced**
- **Head-to-head studies demonstrate faster and larger increases in BMD and bone strength with romosozumab vs teriparatide in women with osteoporosis**
- ***OPINION: If the patient with a recent hip fracture meets the criteria of "very high risk", I would be very comfortable prescribing an anabolic agent.***

Thank you

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Current Issues in Osteoporosis

Final thoughts:

- **There is not yet solid evidence that anabolic agents hasten fracture healing or rehabilitation following a hip fracture**
- **There is no evidence of impaired fracture healing or other harm when using an osteoanabolic agent after a hip fracture**
- **Bone mineral density increases with osteoanabolic therapy in patients with hip fracture, but there is no current evidence that the risk of subsequent hip fracture is reduced**
- **Head-to-head studies demonstrate faster and larger increases in BMD and bone strength with romosozumab vs teriparatide in women with osteoporosis**
- ***OPINION: If the patient with a recent hip fracture meets the criteria of "very high risk", I would be very comfortable prescribing an anabolic agent.***