Injectable osteoporosis therapies

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Choice of Pharmacologic therapies

Choice of therapy based upon

- Efficacy
- Safety
- Cost
- Convenience
- Individual's fracture risk
  - History of prior fragility fractures, T-score, comorbidities
- Adverse effect profile
- Patient preferences

BMD change

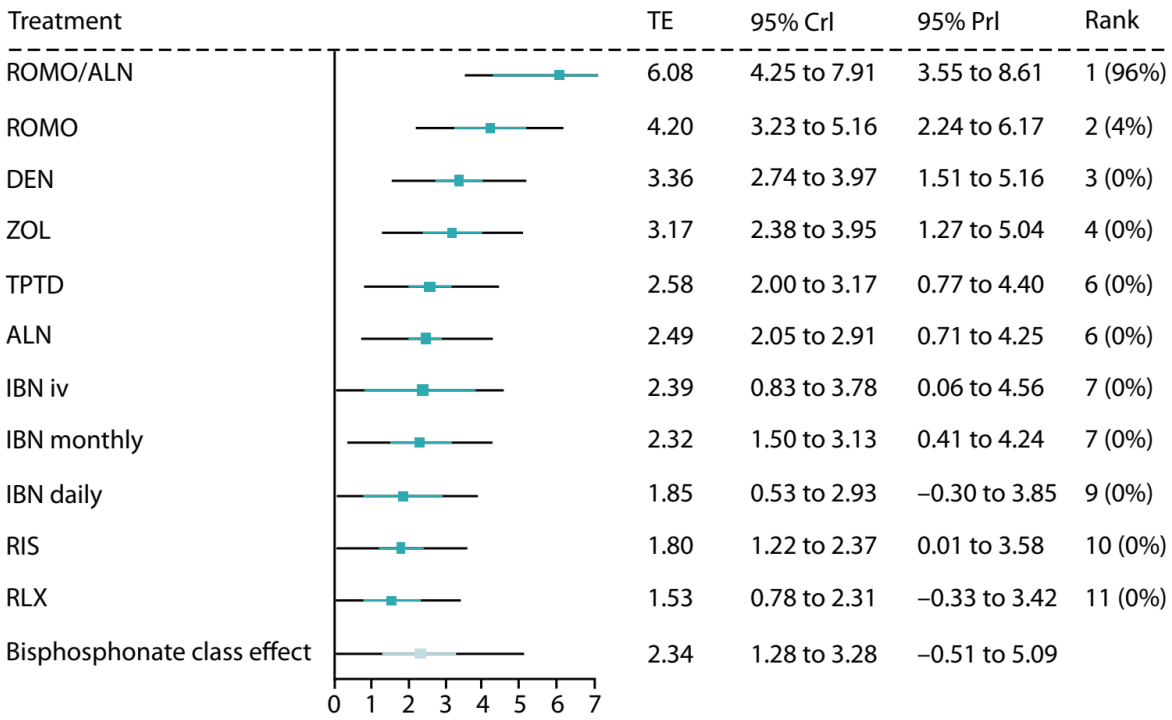


FIGURE 8 Forest plot for percentage change in femoral neck BMD.

Pairwise comparison for vertebral Fx

TABLE 34 Pairwise comparisons, vertebral fractures main analysis

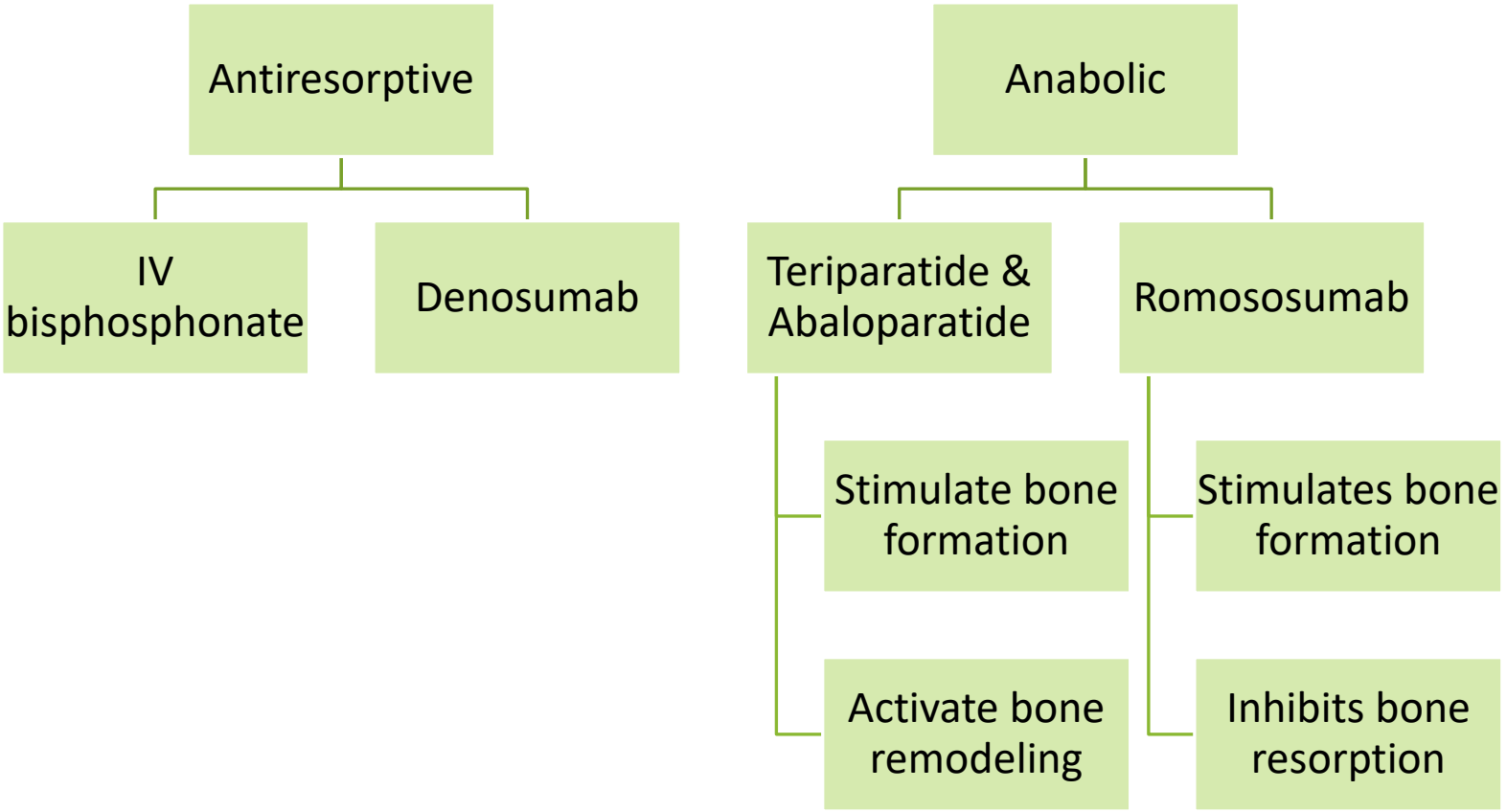
	Placebo	ALN	RIS	ZOL	IBN daily	IBN monthly	DEN	ROMO	TPTD	RLX	ROMO/ALN
Placebo		0.50 (0.32 to 0.81)	0.52 (0.32 to 0.82)	0.39 (0.25 to 0.69)	0.48 (0.28 to 0.83)	0.48 (0.24 to 0.99)	0.31 (0.17 to 0.51)	0.27 (0.12 to 0.57)	0.23 (0.13 to 0.38)	0.62 (0.36 to 0.98)	0.25 (0.13 to 0.50)
ALN	**0.50 (0.40 to 0.64)**		1.06 (0.53 to 1.90)	0.78 (0.42 to 1.61)	0.98 (0.47 to 1.87)	0.96 (0.42 to 2.16)	0.61 (0.29 to 1.20)	0.53 (0.21 to 1.28)	0.47 (0.23 to 0.88)	1.24 (0.60 to 2.29)	0.49 (0.23 to 1.06)
RIS	**0.52 (0.42 to 0.65)**	1.03 (0.77 to 1.39)		0.74 (0.42 to 1.63)	0.93 (0.47 to 1.86)	0.92 (0.41 to 2.17)	0.58 (0.29 to 1.19)	0.51 (0.20 to 1.25)	0.44 (0.23 to 0.85)	1.17 (0.59 to 2.28)	0.47 (0.22 to 1.09)
ZOL	**0.40 (0.29 to 0.55)**	0.81 (0.54 to 1.08)	0.77 (0.52 to 1.08)		1.23 (0.57 to 2.43)	1.19 (0.53 to 2.91)	0.79 (0.34 to 1.50)	0.68 (0.24 to 1.60)	0.60 (0.26 to 1.11)	1.58 (0.68 to 2.90)	0.63 (0.26 to 1.37)
IBN daily	**0.48 (0.33 to 0.71)**	0.98 (0.63 to 1.43)	0.95 (0.61 to 1.37)	1.18 (0.82 to 1.99)		0.99 (0.42 to 2.40)	0.63 (0.29 to 1.32)	0.55 (0.21 to 1.40)	0.48 (0.23 to 0.99)	1.27 (0.59 to 2.56)	0.51 (0.22 to 1.21)
IBN monthly	**0.48 (0.26 to 0.90)**	0.98 (0.51 to 1.75)	0.95 (0.47 to 1.71)	1.14 (0.68 to 2.50)	1.00 (0.49 to 1.98)		0.64 (0.25 to 1.52)	0.55 (0.19 to 1.56)	0.48 (0.19 to 1.13)	1.28 (0.52 to 2.91)	0.51 (0.20 to 1.34)
DEN	**0.30 (0.21 to 0.43)**	**0.61 (0.39 to 0.91)**	**0.58 (0.40 to 0.88)**	0.77 (0.46 to 1.19)	0.63 (0.38 to 1.03)	0.64 (0.31 to 1.26)		0.87 (0.33 to 2.23)	0.76 (0.36 to 1.57)	2.01 (0.95 to 4.14)	0.81 (0.35 to 1.97)
ROMO	**0.27 (0.13 to 0.52)**	0.53 (0.25 to 1.06)	0.51 (0.25 to 1.03)	0.67 (0.30 to 1.35)	0.55 (0.25 to 1.16)	0.55 (0.22 to 1.36)	0.87 (0.40 to 1.86)		0.87 (0.34 to 2.22)	2.31 (0.89 to 5.79)	0.93 (0.33 to 2.71)
TPTD	**0.23 (0.16 to 0.32)**	**0.46 (0.31 to 0.66)**	**0.44 (0.32 to 0.61)**	**0.58 (0.36 to 0.90)**	**0.47 (0.29 to 0.77)**	**0.48 (0.25 to 0.95)**	0.76 (0.46 to 1.20)	0.87 (0.41 to 1.87)		2.65 (1.28 to 5.45)	1.06 (0.48 to 2.61)
RLX	**0.61 (0.44 to 0.80)**	1.23 (0.82 to 1.71)	1.17 (0.82 to 1.68)	1.54 (0.94 to 2.32)	1.26 (0.78 to 1.97)	1.27 (0.65 to 2.47)	2.01 (1.25 to 3.13)	2.30 (1.09 to 4.83)	2.66 (1.72 to 4.11)		0.40 (0.18 to 0.98)
ROMO/ ALN	**0.25 (0.15 to 0.43)**	**0.50 (0.30 to 0.80)**	**0.47 (0.28 to 0.86)**	0.62 (0.33 to 1.11)	**0.51 (0.28 to 0.98)**	0.51 (0.24 to 1.12)	0.81 (0.44 to 1.59)	0.93 (0.40 to 2.29)	1.06 (0.60 to 2.06)	**0.40 (0.23 to 0.78)**	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

Highest relative efficacy

- Anabolic agents (teriparatide, abaloparatide, romosozumab)
- Denosumab

Injectable therapies



Candidates for Injectable therapies

Initial treatment with an anabolic agent (teriparatide, abaloparatide, romosozumab)

- For patients with **very high fracture risk** we suggest
  - T-score of ≤-2.5 plus a fragility fracture
  - T-score of ≤-3.0 in the absence of fragility fracture
  - history of severe or multiple fractures

Most likely to benefit from anabolic therapy

- The **highest risk** of fracture
  - T-score ≤-3.5 with fragility fracture[s]
  - Tscore ≤-4.0
  - Recent major osteoporotic fracture
  - Multiple recent fractures

Bisphosphonate or denosumab may be appropriate

- Very high fracture risk who cannot be treated with an anabolic agent
- Cost, inconvenience, contraindications, or personal preference

IV bisphosphonate

IV bisphosphonate

Esophageal disorders,

Gastrointestinal intolerance,

History of Rouxen-Y gastric bypass,

Inability to follow the dosing requirements of oral bisphosphonates

- Sit upright for 30 to 60 minutes and/or to swallow a pill

IV zoledronic acid,

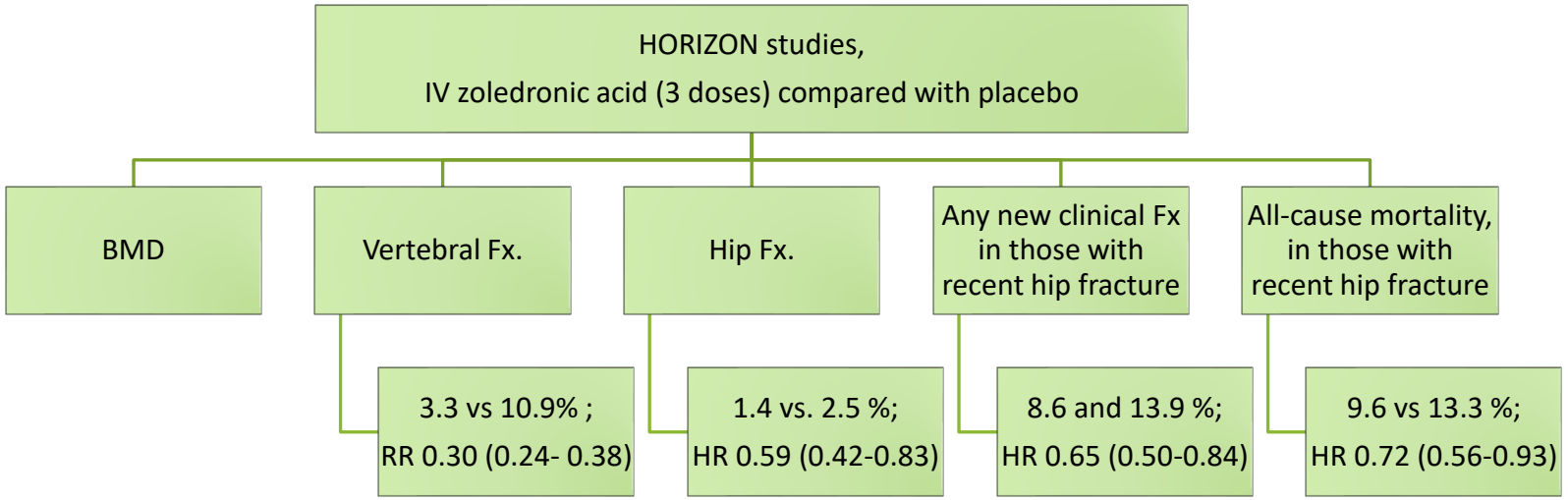
- reduces vertebral and hip fractures

IV ibandronate

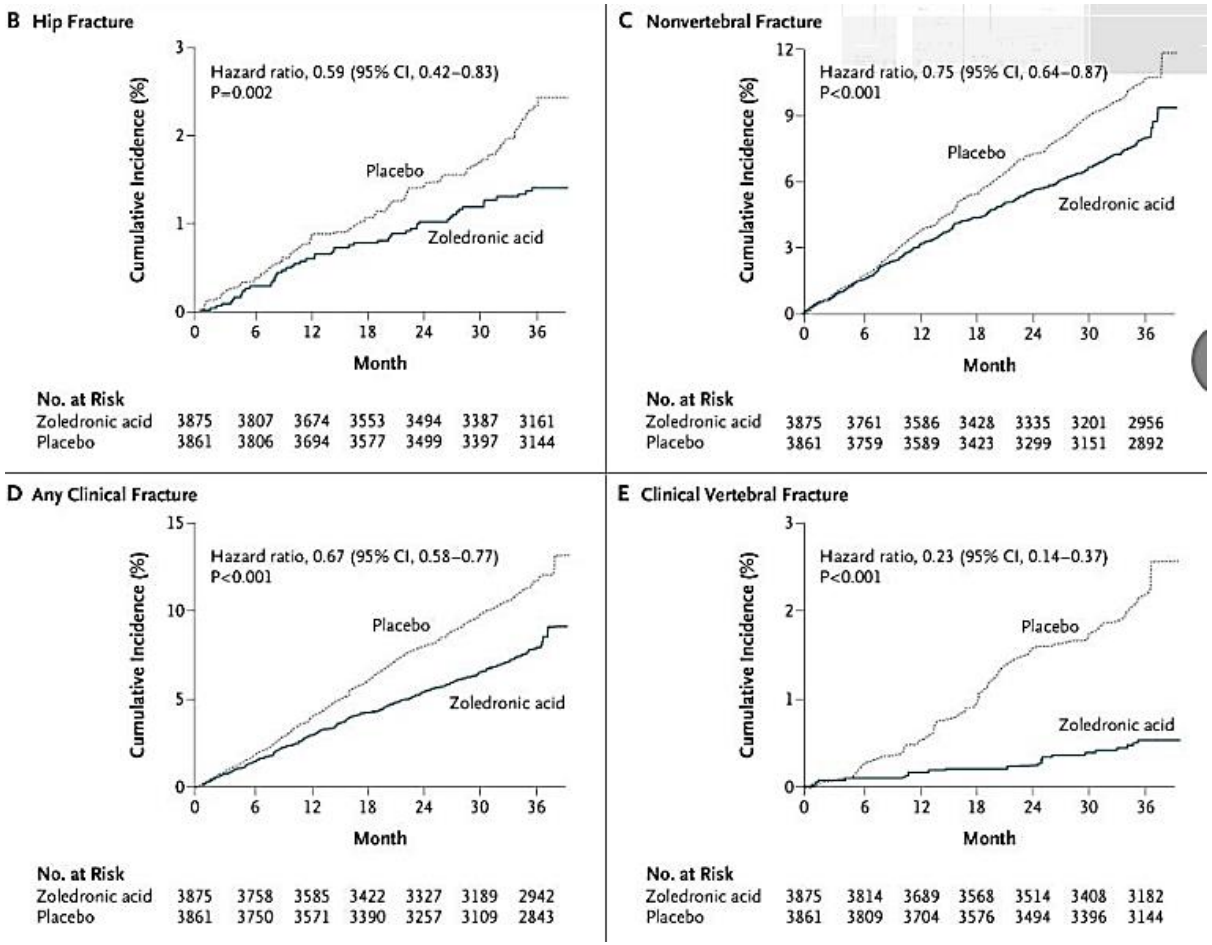
- no direct fracture prevention data

Zoledronic acid

15-minute intravenous infusion once yearly

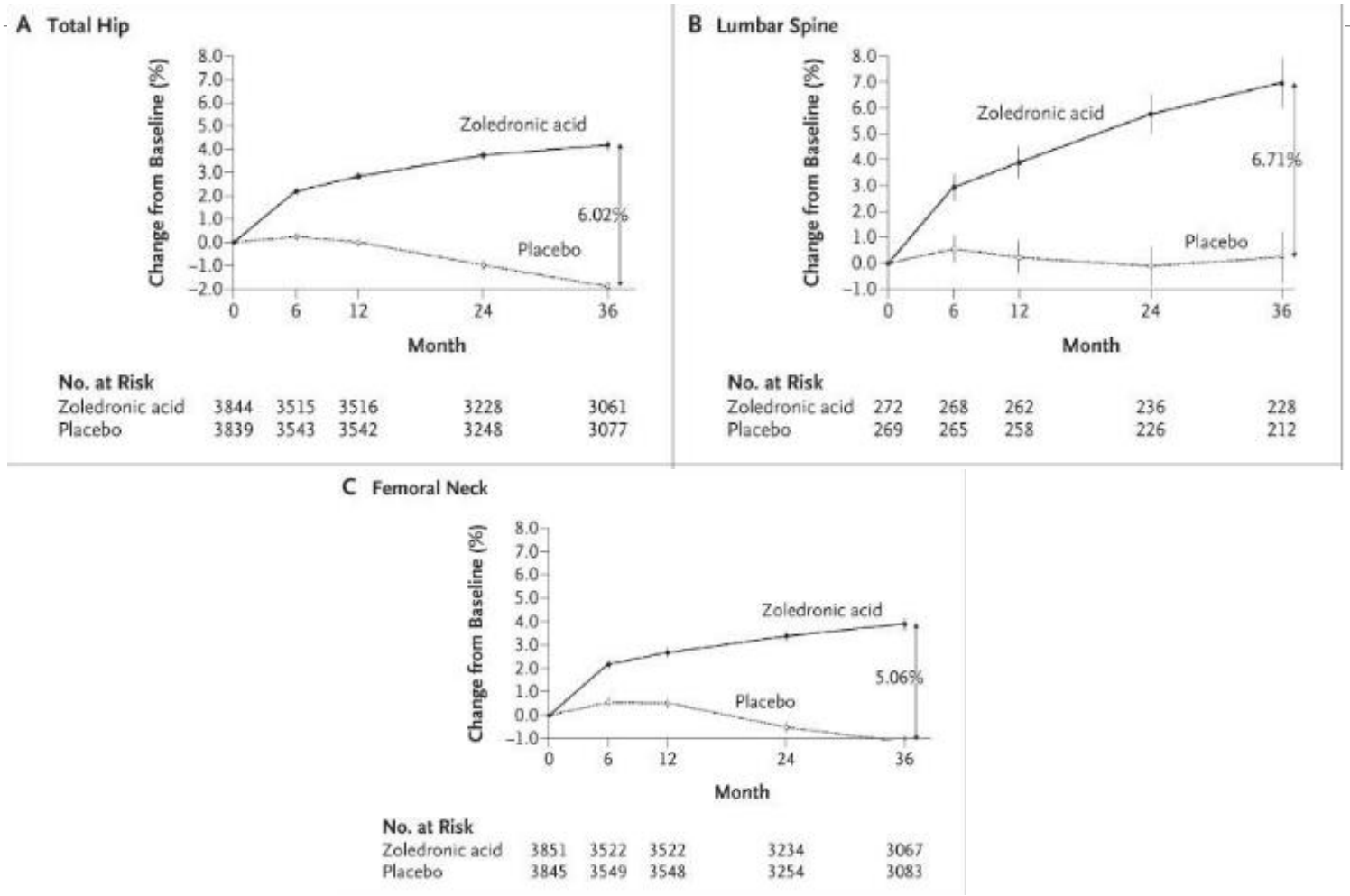


Zoledronic acid and Fx



Black, Dennis M., et al. "Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis." *New England Journal of Medicine* 356.18 (2007): 1809-1822.

Zoledronic acid and BMD



Black, Dennis M., et al. "Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis." *New England Journal of Medicine* 356.18 (2007): 1809-1822.

Combination therapy

Not suggested

- Small additional BMD benefits
- No proven additional fracture benefit
- theoretical concern that combination antiresorptive therapy could over suppress bone turnover and cause increased skeletal fragility
- addition to teriparatide therapy provides little additional benefit for BMD,
  - addition of BP actually reduced the increase in BMD from teriparatide.
  - fracture data are unavailable for combination therapy.


Aclasta
5 mg
solution for infusion
Zoledronic acid
One bottle with 100 ml solution for infusion.
NOVARTIS
Aclasta
5 mg
Solution for infusion
Zoledronic acid
One bottle with 100 ml solution for infusion.
NOVARTIS


1 Bottle
5 mg / 100 mL
Claritoz 5
Zoledronic Acid
Solution for Intravenous Infusion
Sterile - Non pyrogenic
Claritoz 5
Zoledronic Acid

Pretreatment evaluation

Biochemical assessment
- Ca, Cr, 25(OH) vitamin D
- Correction of hypocalcemia and/or vitamin D deficiency (to at least 20 ng/mL [50 nmol/L]) prior to administration

Hypocalcemia
- more likely to occur in those with vitamin D deficiency
- minimized by vitamin D and calcium supplementation.

Prior to each infusion, measure serum creatinine
- adequately hydrated
- infused over at least 15 minutes.
- If on nephrotoxic drugs or diuretics, periodic postinfusion measurement of Cr
- not recommended for GFR ≤35 mL/min

Flu-like symptoms,
- minimized by longer infusion times (45 to 60 minutes)
- acetaminophen or ibuprofen

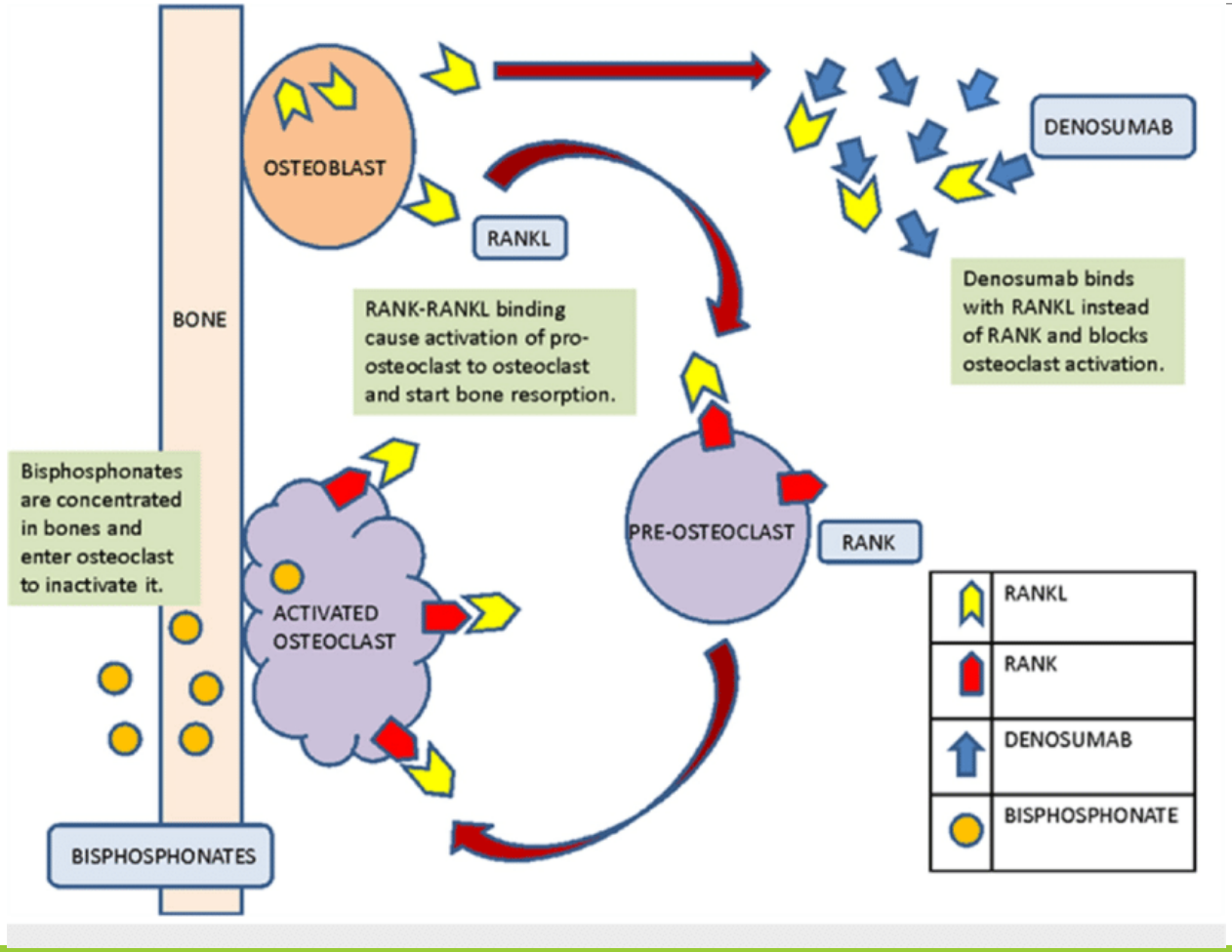
Invasive dental procedures

Invasive dental procedures (extractions, implants) and risk factors for ONJ

- If a dental implant or extraction already planned, delay bisphosphonate therapy for a few months until healing of the jaw is complete.
- If already taking bisphosphonates, approach is uncertain
  - Some discontinue bisphosphonates and resume again when healing is complete,
  - others suggest not stopping bisphosphonates.
- Guidelines from the American Association of Oral and Maxillofacial Surgeons
  - <4 years with no clinical risk factors: dentoalveolar surgery, such as extractions and implants, as usual
  - >4 years or concomitant glucocorticoids: discontinuing bisphosphonates

Denosumab

Denosumab



RANK/RANKL: Activation, migration, differentiation, and fusion of hematopoietic cells of the osteoclast lineage the process of bone resorption

Candidates of denosumab

- ✓Difficulty with the dosing requirements of oral BP
- ✓Intolerant of or unresponsive to any BP
- ✓Impaired kidney function
- ✓Those in whom desired increases in BMD exceed typical gains achieved with oral BP therapy
- ❑Concerns:
  - ❑Increased risk of vertebral fracture after discontinuation
  - ❑Need for indefinite administration discussed with patients prior to initiation
  - ❑If DC, begin alternative therapy to prevent rapid bone loss and vertebral fracture

Dosing and administration

60 mg SQ once every six months (upper arm, thigh, abdomen)
Single-use, prefilled syringe or a single-use vial
Stored in the refrigerator until 15-30 min before administration
Not renally excreted, no dose adjustments for CKD
Maintenance of BMD with continued use for 10 years

Pretreatment evaluation

Risk of hypocalcemia

- All patients
  - Ca, 25(OH)D prior
  - Hypocalcemia: not receive until corrected
  - vitamin D deficiency: replaced prior to administration.
  - all patients adequately supplemented with calcium and vitamin D while taking denosumab.
- Patients with advanced kidney disease
  - Significant risk of severe hypocalcemia, greater caution and increased monitoring

Suppression of bone remodeling

- Denosumab suppresses bone remodeling
- may contribute to adverse outcomes, such as ONJ

Posttreatment

Monitoring of serum calcium

- Not required in patients without risk factors for hypocalcemia
- 10 days after denosumab in high risk:
  - **CKD** with GFR<30 including patients receiving dialysis
    - serious outcomes of severe hypocalcemia,
    - hospitalization and death
  - Predisposing conditions to hypocalcemia (**malabsorption** syndromes)
    - a greater risk of hypocalcemia if becomes ill and cannot take oral calcium after having received denosumab,
    - Monitor Calcium levels more frequently in this setting

Infections and skin reactions

Anabolic agents

Anabolic therapy

Reserved for individuals with **very high risk** of fracture

- Very high risk of fracture
- Prior fragility fracture **and** contraindications or intolerance to any BP
- Fragility fracture and/or decline in BMD on other osteoporosis agent(s) despite treatment adherence

May be used in **less severe** osteoporosis (T-score ≤-2.5 without a fragility fracture)

- Unable to tolerate oral or IV BP

After initial therapy with an anabolic agent is discontinued:

- treated with an antiresorptive agent (typically a BP) to preserve the gains in BMD
- If unable to tolerate oral or IV BP: denosumab or raloxifene

Selection of anabolic agent

Teriparatide

- Long track record of safety
- Daily SQ
- Limited to 18 to 24 months
- > 24 months in selected individuals if risk remains high

Abaloparatide

- Daily SQ injection
- Limited to 18 to 24 months

Romosozumab

- Greater BMD response
- Limited clinical experience
- Uncertain long-term side effects
- Administered by a health care professional
- Once monthly two SQ injections
- 12 monthly doses

PTH and PTHrP analogs

PTH and PTHrP analogs

Chronic exposure to elevated PTH or PTHrP

- Bone resorption

Intermittent administration of recombinant human PTH or PTHrP in normal individuals

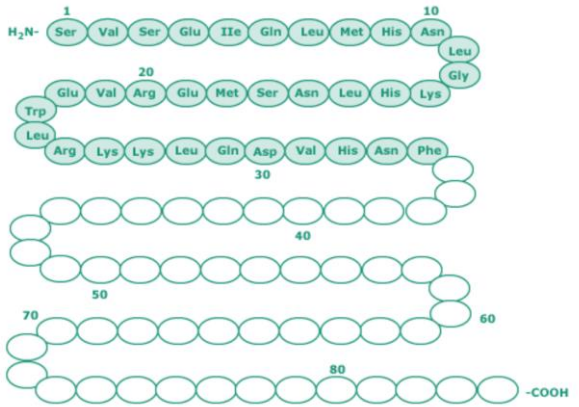
- Stimulate bone formation more than resorption.

Teriparatide (PTH [1-34])

- Form of PTH, consisting of amino acids 1-34.
- Retains all of the biologic activity of the intact peptide (1-84).
- Available since 2002

Abaloparatide (PTHrP [1-34])

- Synthetic analog of PTHrP with 76 % homology
- Binds more selectively to the PTH type 1 receptor
- More transient response,
  - Favoring bone formation
  - Minimizing the effects of more prolonged activation (eg, bone resorption, hypercalcemia).
- Available in the US since 2017.



Effect of teriparatide on skeletal architecture

Site specific actions

Enhances **trabecular** more than cortical bone mass.

- Trabecular thickness, number, and connectivity are all increased by PTH
- Qualitative changes in trabecular microarchitecture

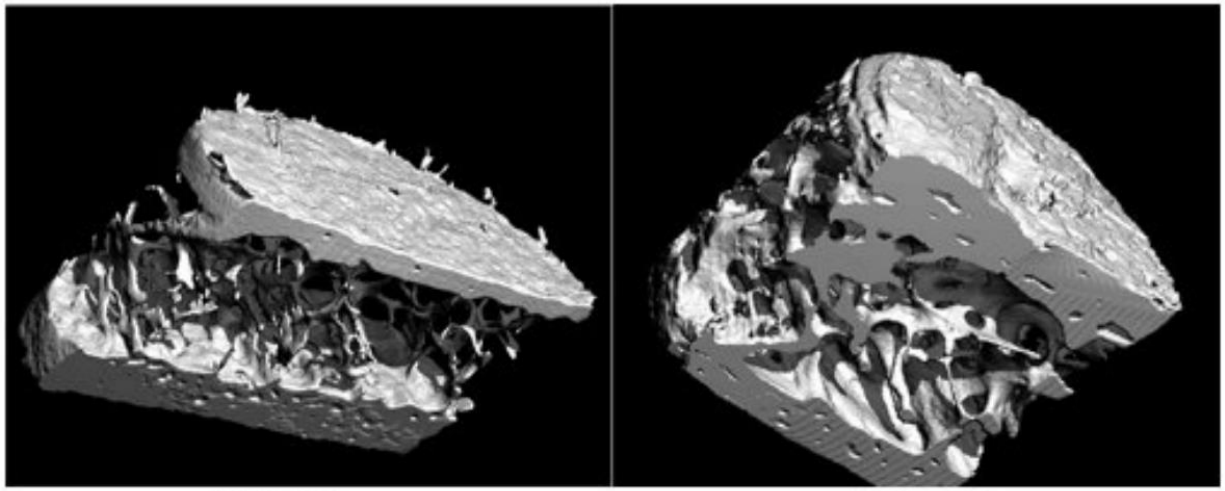
Cortical compartment,

- Periosteal circumference may increase
- Decrease in secondary mineralization in the cortical skeleton

BMD

Fx risk

Bone strength



Patient selection

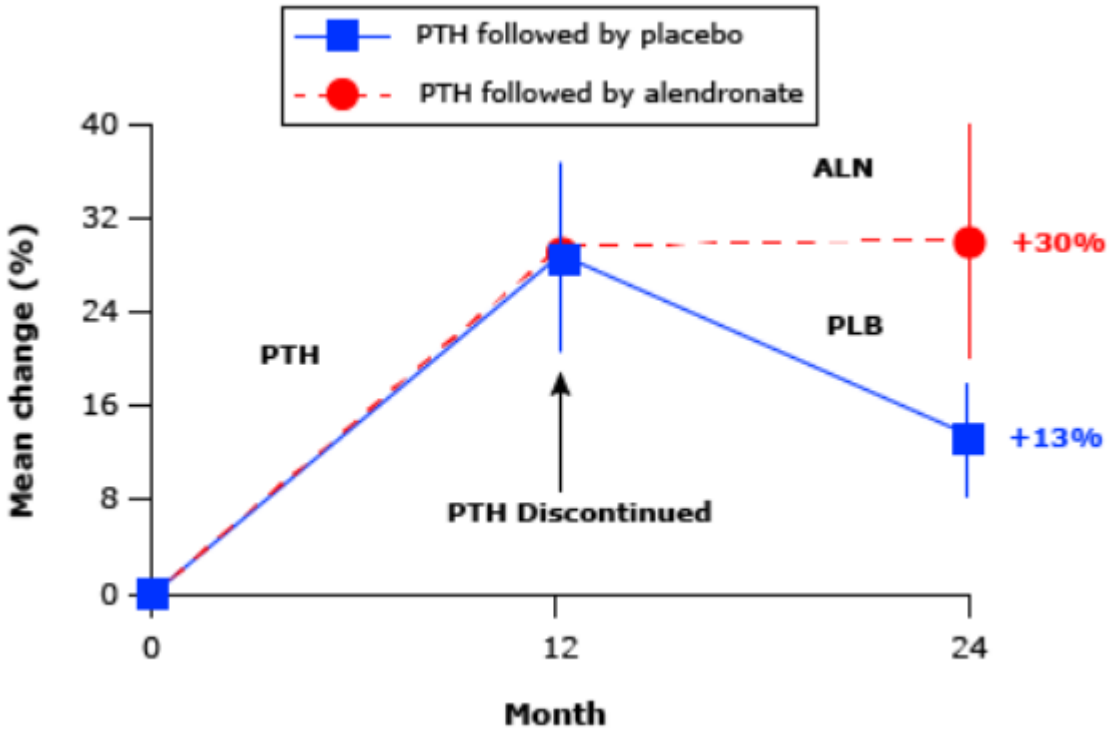
Not first-line

- cost, subcutaneous, limited long-term safety data, availability of other agents

Potential candidates:

- Very high risk for fracture
  - T-score of ≤-3.0 even in the absence of fractures,
  - T-score of -2.5 or below plus a fragility fracture,
  - history of multiple fractures,
  - advanced age
- Unable to tolerate bisphosphonates
- Relative contraindications to oral bisphosphonates
  - achalasia,
  - scleroderma esophagus,
  - esophageal strictures).
- No benefit from other therapies in spite of adherence
  - fracture and/or loss of BMD

PTH (1-84) followed by placebo or alendronate



Contraindications/precautions

Primary or secondary **hyperparathyroidism**, even if they have low BMD

Other **hypercalcemic** disorders
- chronic granulomatous disorders,
- hypercalcemia of malignancy
- possibility of exacerbating hypercalcemia

Increased baseline risk for **osteosarcoma**,
- **Paget** disease of bone
- unexplained elevation of **ALkP**,
- bone metastases or skeletal **malignancies**,
- history of prior **radiation** therapy involving the skeleton
- pediatric/young adult patients with open **epiphyses**.

In patients with preexisting nonskeletal malignancies, kidney stones, or impaired kidney function,
- PTH/PTHrP analogs should not be considered
- unless other drugs have not prevented fractures and benefits outweigh potential risks

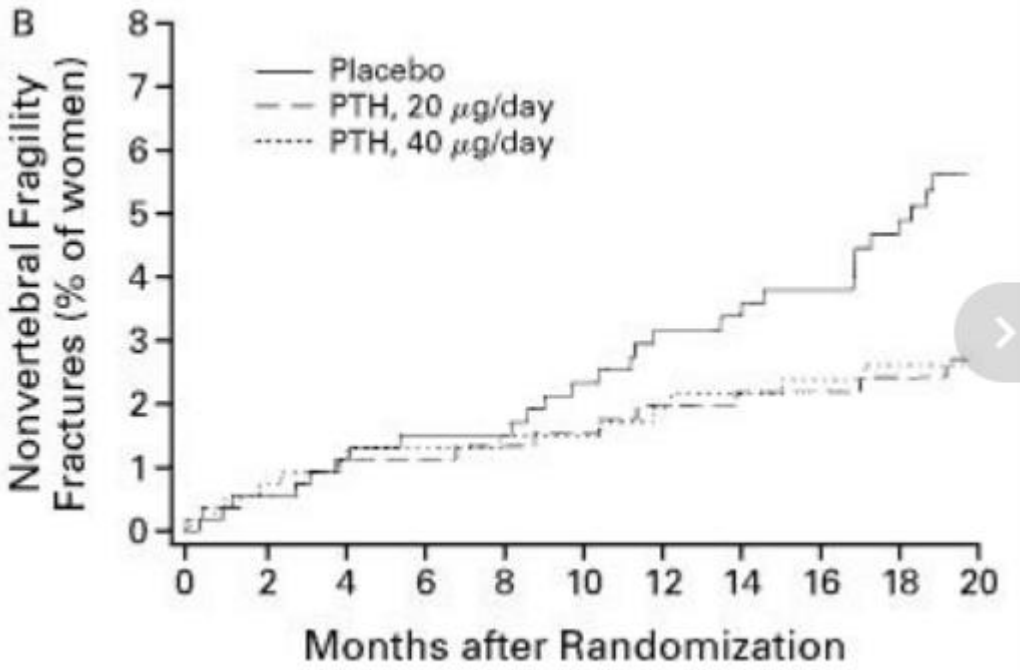
Teriparatide

1637 postmenopausal women with previous vertebral fractures

After 18 months of treatment

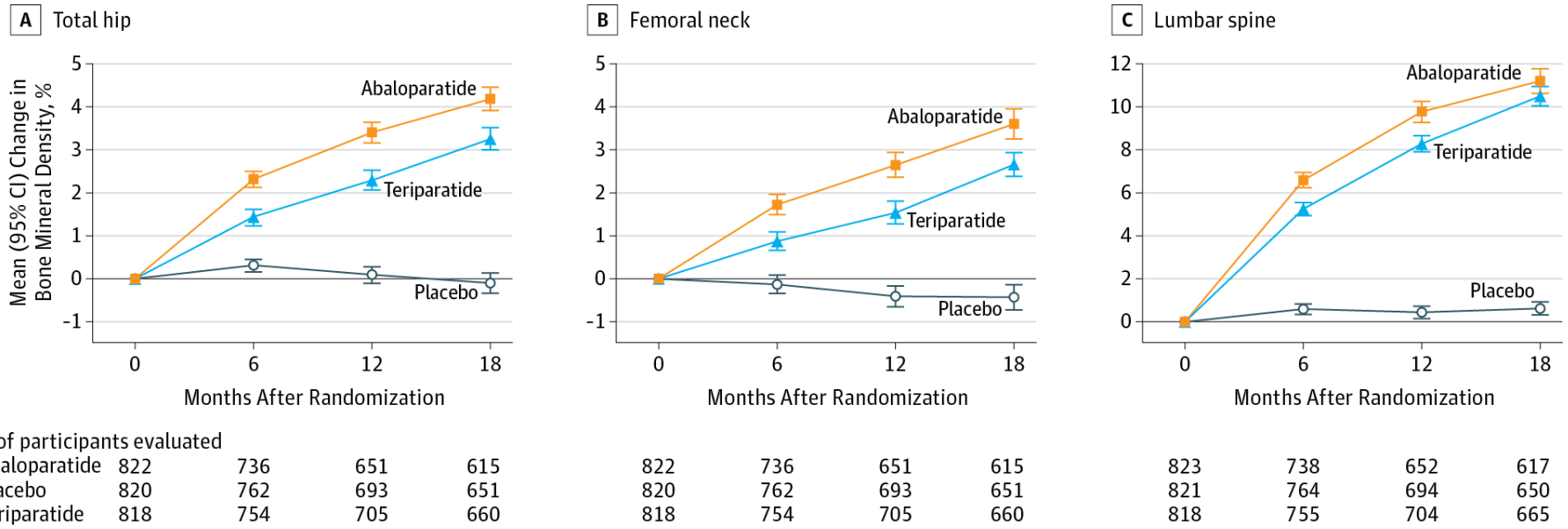
- Spine and hip BMD increase dose-dependently
- Vertebral and nonvertebral fracture risk reduction did not differ by dose

Beneficial effects independent of age, baseline BMD, and prevalent vertebral fractures



Neer, Robert M., et al. "Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis." *New England journal of medicine* 344.19 (2001): 1434-1441.

Change From Baseline in BMD



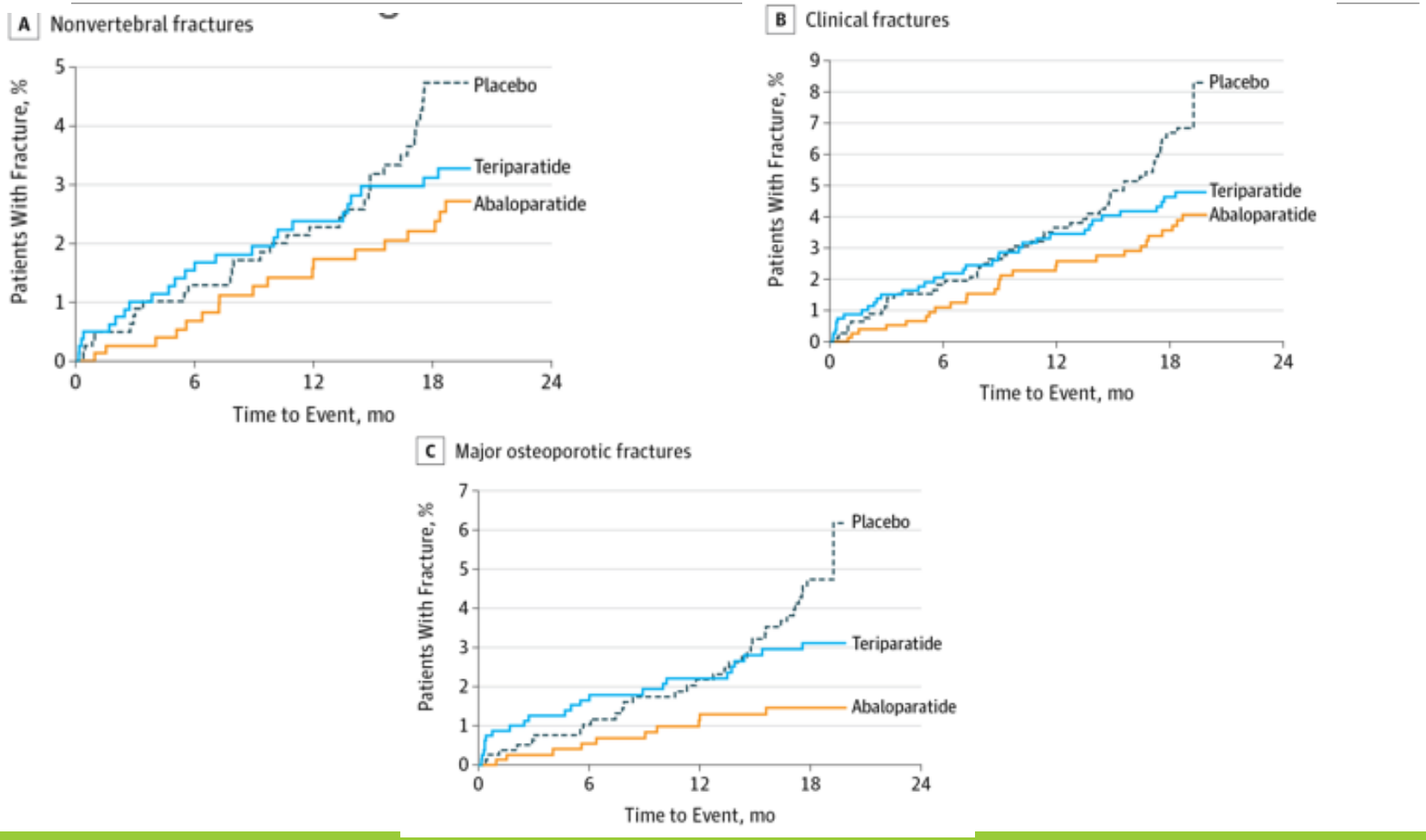
No. of participants evaluated

Abaloparatide	822	736	651	615	822	736	651	615	823	738	652	617
Placebo	820	762	693	651	820	762	693	651	821	764	694	650
Teriparatide	818	754	705	660	818	754	705	660	818	755	704	665

Improvement in BMD and reduction in fracture rates similar in abaloparatide and teriparatide.
Incidence of **hypercalcemia** lower with abaloparatide

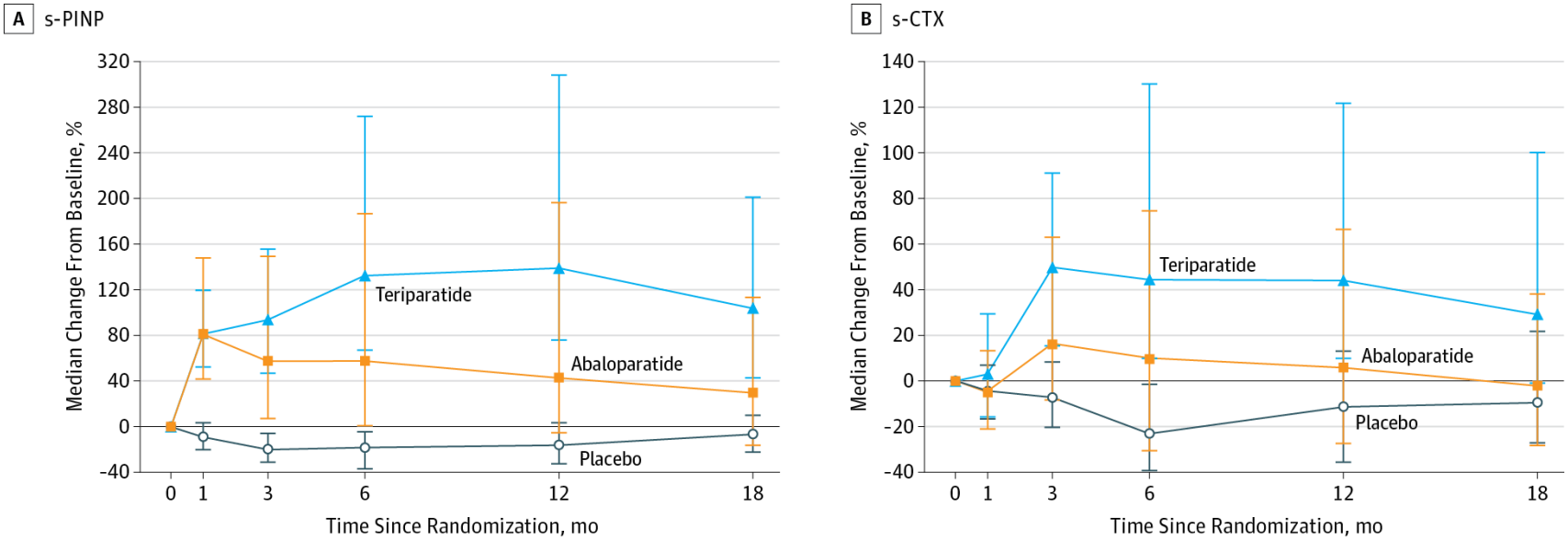
Miller, Paul D., et al. "Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial." *Jama* 316.7 (2016): 722-733.

Time to Event



Miller, Paul D., et al. "Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial." *Jama* 316.7 (2016): 722-733.

Change in Serum Bone Metabolism Markers



- The bone formation marker s-PINP and the resorption marker s-CTX showed significant increases among abaloparatide- and teriparatide-treated participants compared with placebo at 3, 6, and 12 months
- For bone formation, initial increases in the first month were similar, but by 3 months, bone formation began to decrease in the abaloparatide group compared with the teriparatide group.
- Similarly, the increase in s-CTX was less in the abaloparatide group than in the teriparatide group.

Miller, Paul D., et al. "Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial." *Jama* 316.7 (2016): 722-733.

Dosing

Teriparatide (PTH [1-34])

- 20 mcg/day SQ into the th… …ominal wall.
- A … …d pen (containing 28 doses)

Abaloparatide

- 80 mcg/day SQ the periumbilical region.
- A multidose, prefilled pen (containing 30 doses)
- … the patient can sit or lie flat, in case …static hypotension occur.
- Usually max…

Pretreatment

DXA (if not performed in the past two years)

Ca, P, Cr, AlkP, 25(OH)D

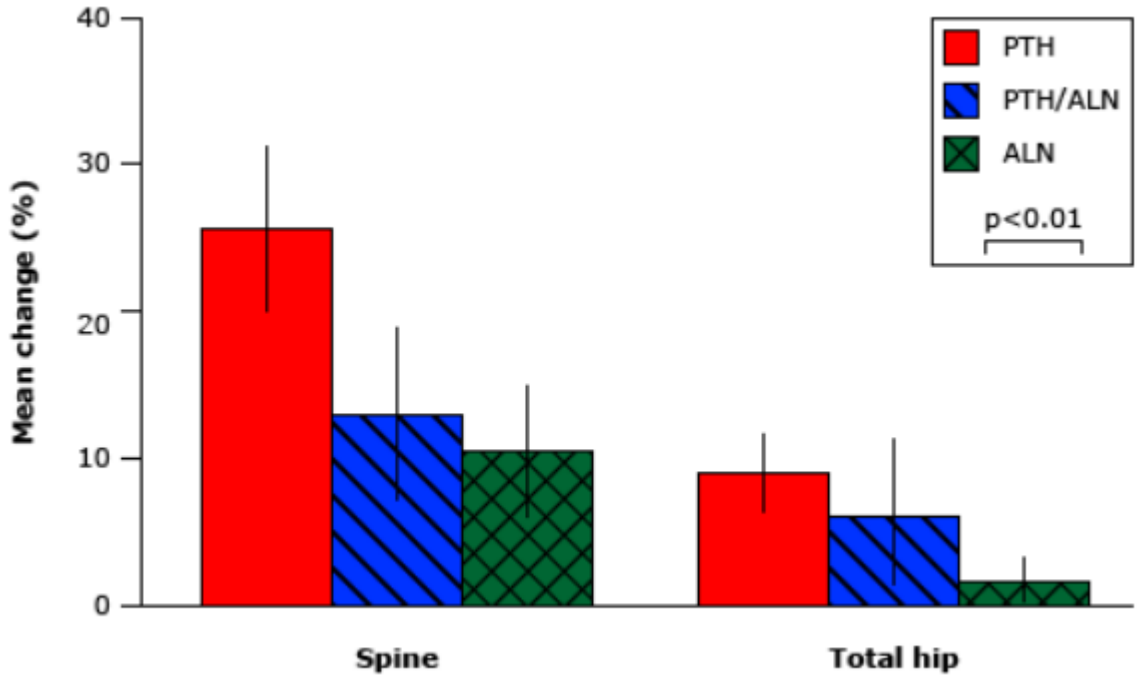
Evaluate for baseline **hypercalciuria**: 24hUrine (Ca, Cr) or fasting specimen ratio

- Vitamin D deficiency: replaced until normal prior to therapy
- Hypercalcemia or hypercalciuria (urinary Ca >300 mg/24 hours in females or >400 mg/24 hours in males)
  - Further evaluation for primary hyperparathyroidism or other hypercalcemic disorder prior
  - Contraindicated in patients with hypercalcemic disorders unless fully resolved.
  - Isolated hypercalciuria: not start unless resolved

If hypercalcemia develops,

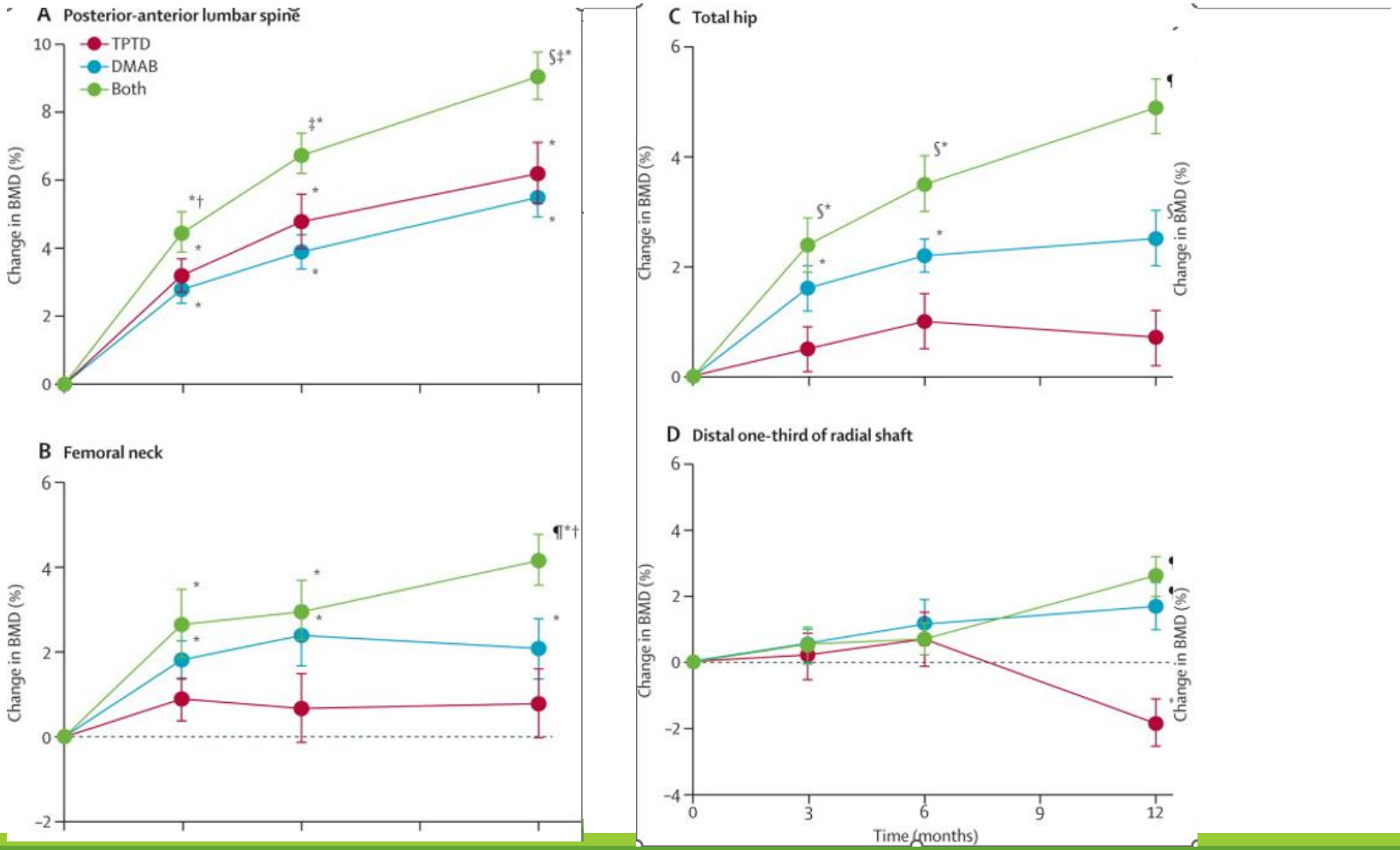
- The first step: reduction in calcium supplementation (no >500 mg daily)
- and/or temporary cessation of vitamin D with repeat measurement of Ca 24 h after the last dose of PTH/PTHrP analog.
- If hypercalcemia persists, dosing adjusted to alternate-day therapy.
- If clinically significant hypercalcemia does not resolve, discontinued.

PTH 1-84 + alendronate



Changes in trabecular volumetric BMD in the lumbar spine and total hip by QCT (g/cm) after 12 months of treatment

PTH analog plus denosumab

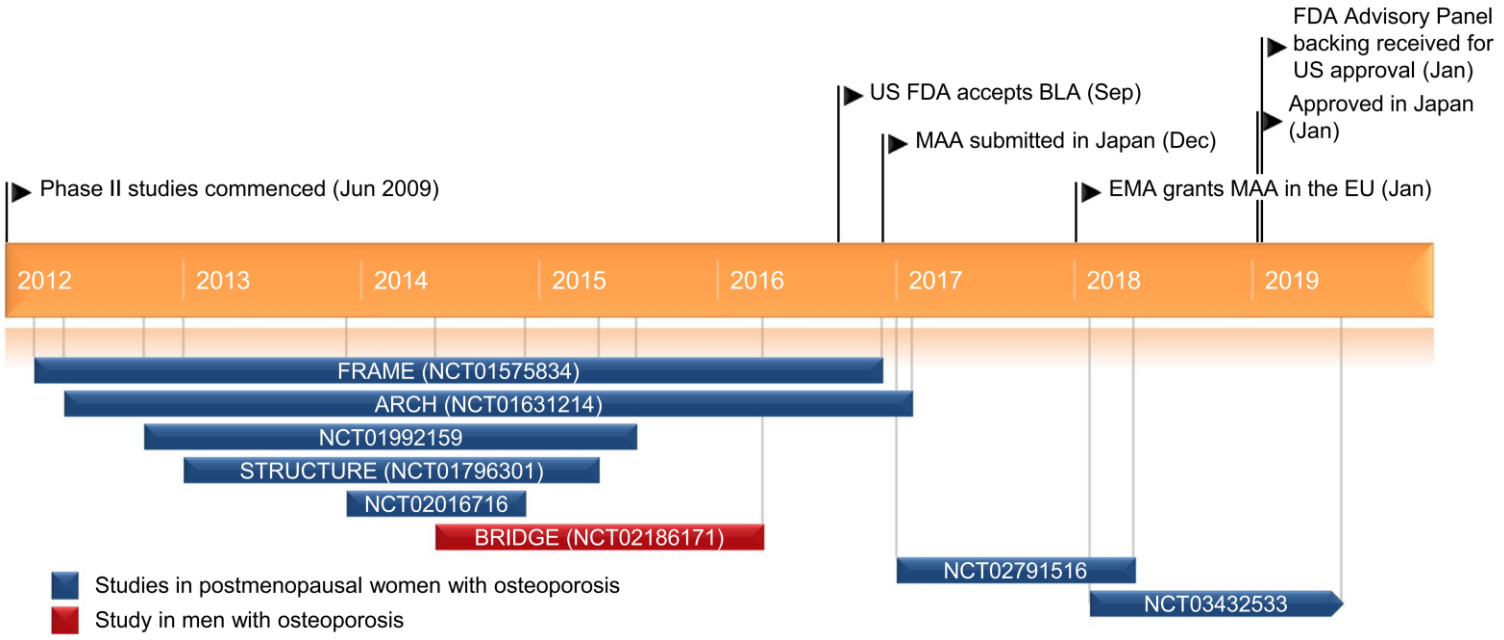


Tsai, Joy N., et al. "Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial." *The Lancet* 382.9886 (2013): 50-56.

Romosozumab

Key milestones in the development of romosozumab

FDA April 2019 & Health Canada June 2019

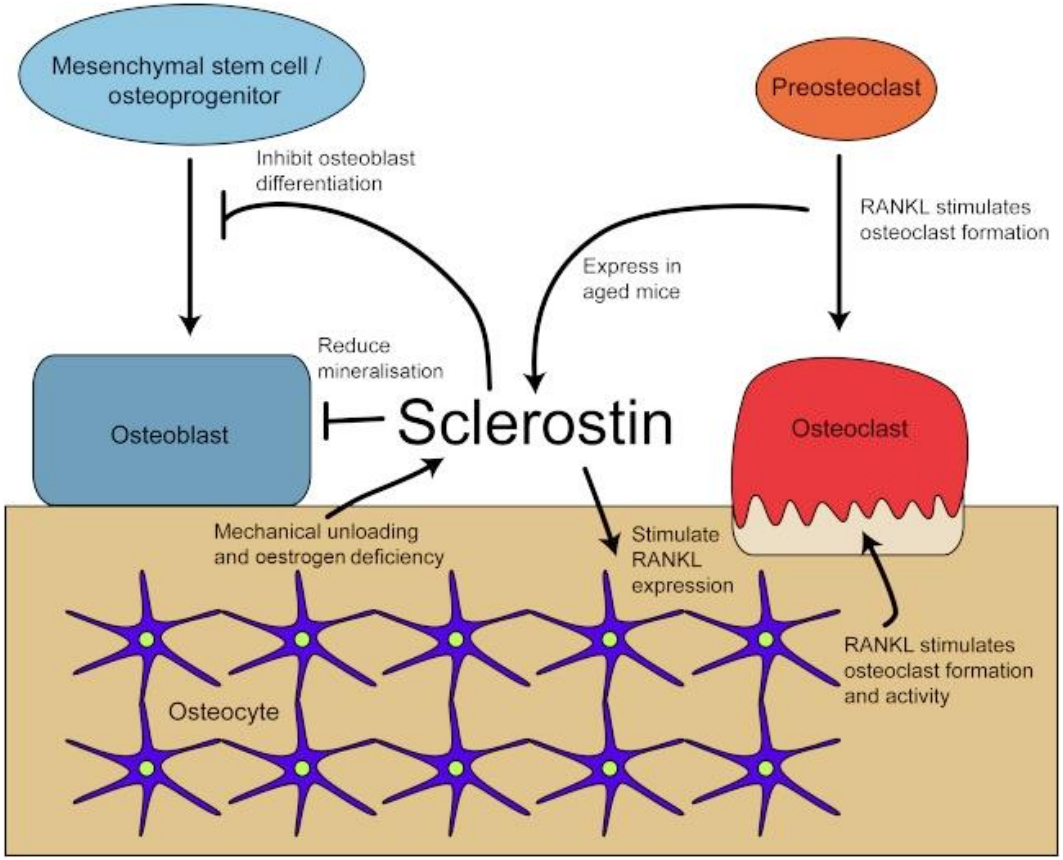


Romosozumab

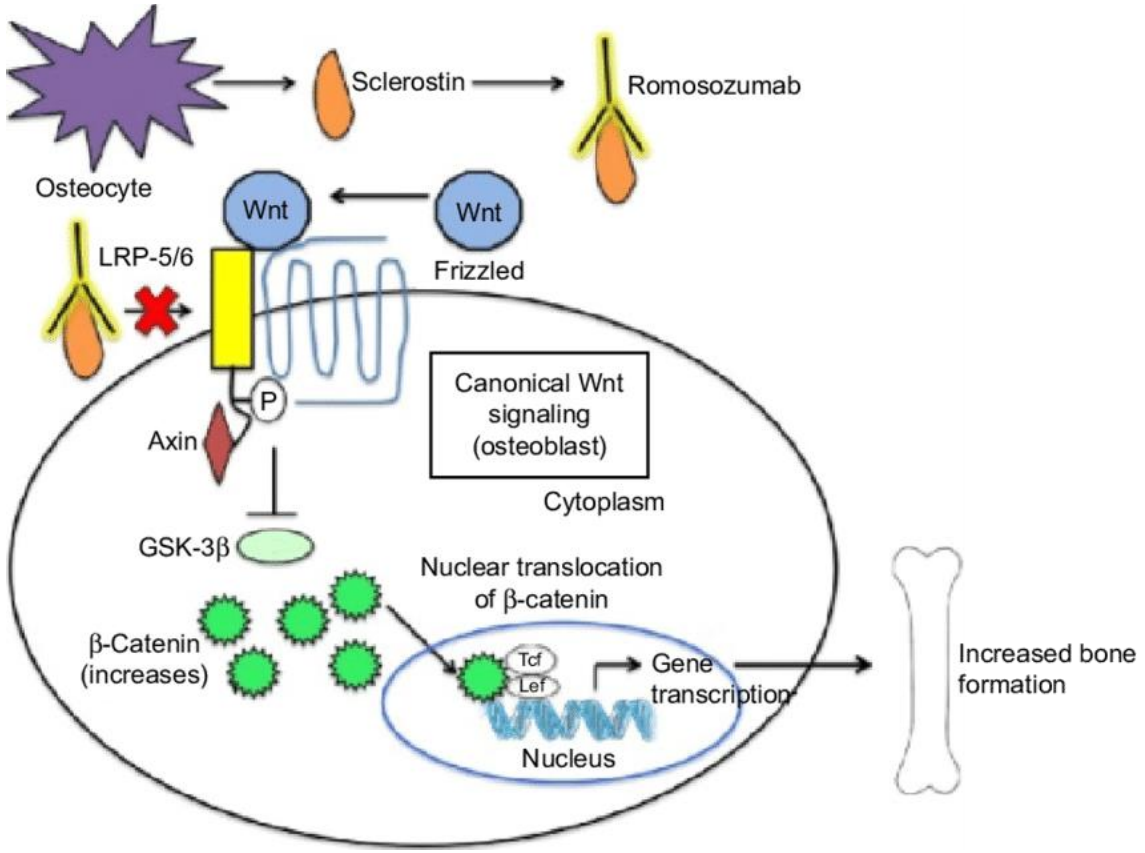
Humanised monoclonal antibody IgG2 against sclerostin

Increases bone formation

Suppresses bone resorption



Romosozumab



Romosozumab Rx.

2(105 mg): 210 mg SQ
once monthly for 12 m

Romosozumab
Evenity

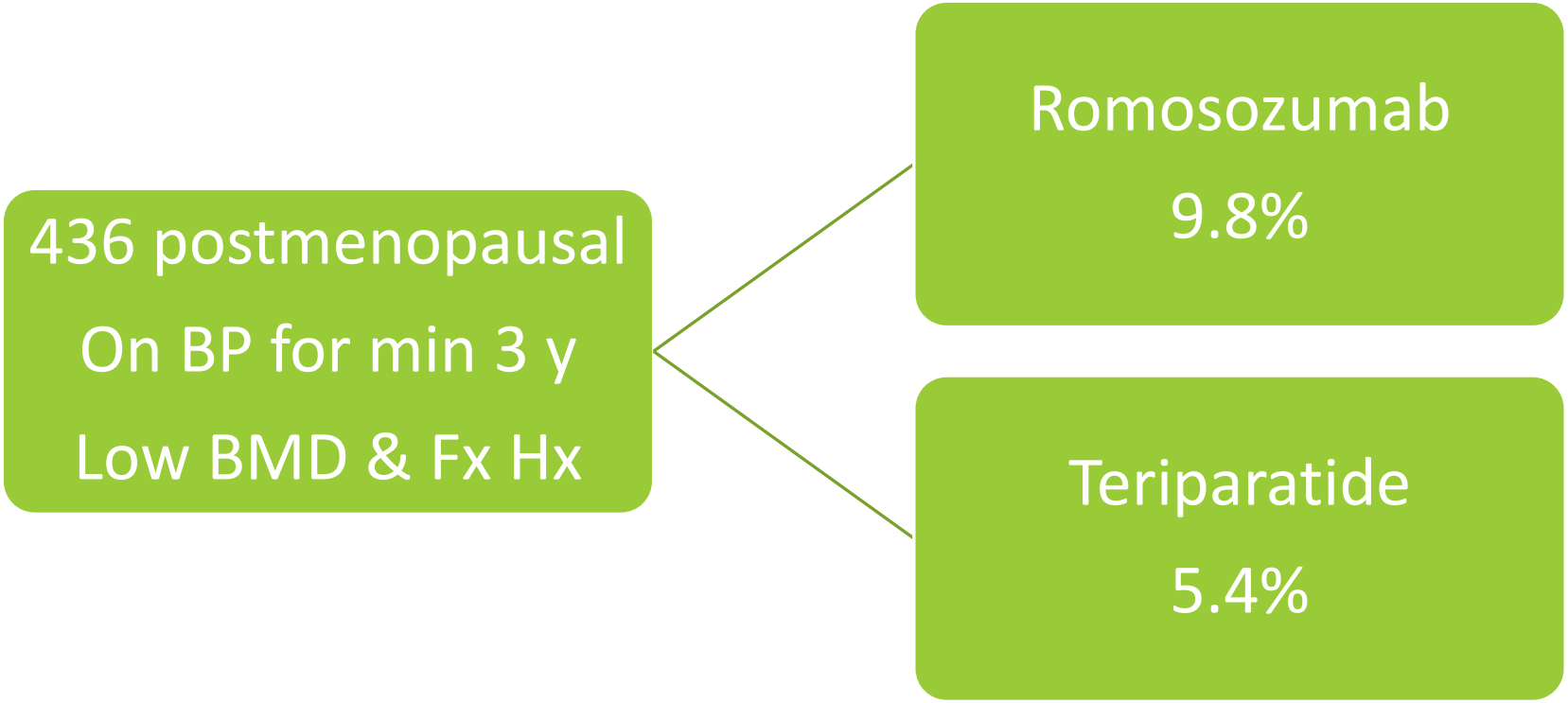
Romosozumab candidates

Not considered initial therapy for most

Possible candidates include

- Multiple fragility fractures
- High risk for fracture who cannot tolerate any other osteoporosis therapies
- Fail other osteoporosis therapies
  - Fracture with loss of BMD in spite of compliance

Romosozumab and BMD



BMD change

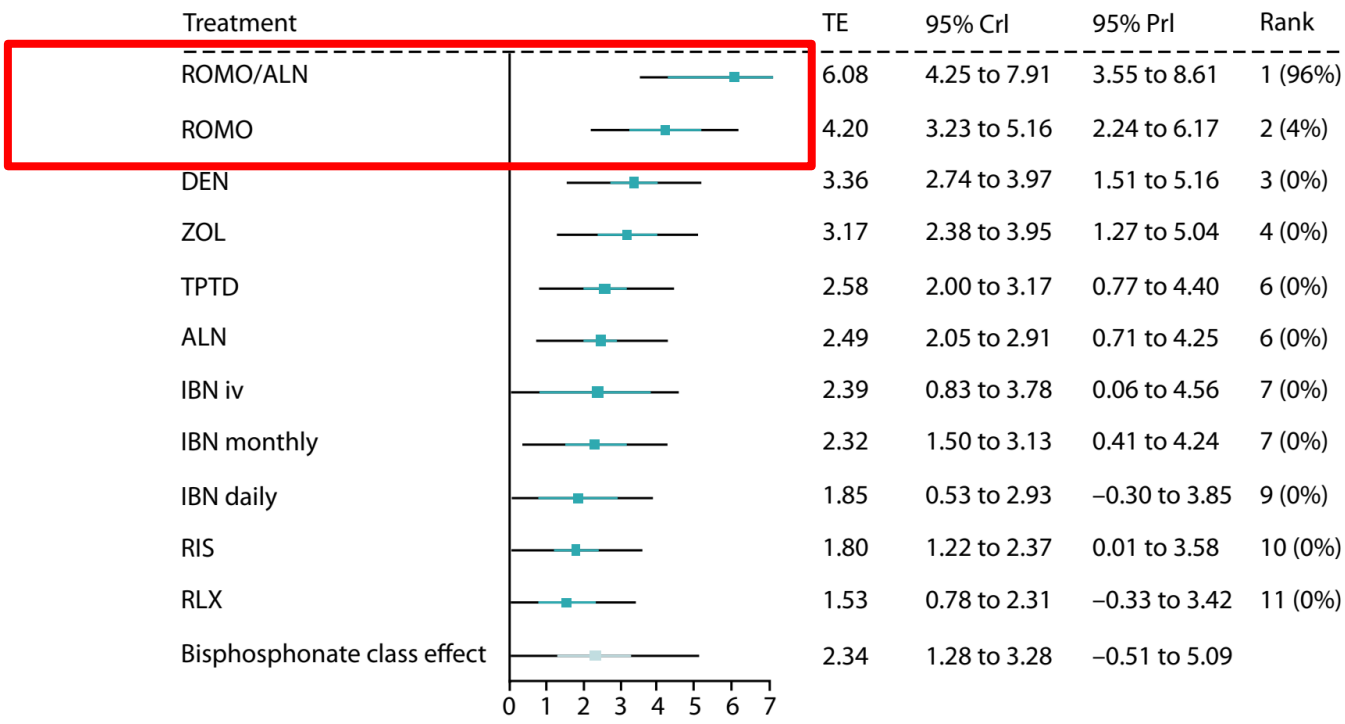


FIGURE 8 Forest plot for percentage change in femoral neck BMD.

Pairwise comparison for vertebral Fx

TABLE 34 Pairwise comparisons, vertebral fractures main analysis

	Placebo	ALN	RIS	ZOL	IBN daily	IBN monthly	DEN	ROMO	TPTD	RLX	ROMO/ALN
Placebo		0.50 (0.32 to 0.81)	0.52 (0.32 to 0.82)	0.39 (0.25 to 0.69)	0.48 (0.28 to 0.83)	0.48 (0.24 to 0.99)	0.31 (0.17 to 0.51)	0.27 (0.12 to 0.57)	0.23 (0.13 to 0.38)	0.62 (0.36 to 0.98)	0.25 (0.13 to 0.50)
ALN	**0.50 (0.40 to 0.64)**		1.06 (0.53 to 1.90)	0.78 (0.42 to 1.61)	0.98 (0.47 to 1.87)	0.96 (0.42 to 2.16)	0.61 (0.29 to 1.20)	0.53 (0.21 to 1.28)	0.47 (0.23 to 0.88)	1.24 (0.60 to 2.29)	0.49 (0.23 to 1.06)
RIS	**0.52 (0.42 to 0.65)**	1.03 (0.77 to 1.39)		0.74 (0.42 to 1.63)	0.93 (0.47 to 1.86)	0.92 (0.41 to 2.17)	0.58 (0.29 to 1.19)	0.51 (0.20 to 1.25)	0.44 (0.23 to 0.85)	1.17 (0.59 to 2.28)	0.47 (0.22 to 1.09)
ZOL	**0.40 (0.29 to 0.55)**	0.81 (0.54 to 1.08)	0.77 (0.52 to 1.08)		1.23 (0.57 to 2.43)	1.19 (0.53 to 2.91)	0.79 (0.34 to 1.50)	0.68 (0.24 to 1.60)	0.60 (0.26 to 1.11)	1.58 (0.68 to 2.90)	0.63 (0.26 to 1.37)
IBN daily	**0.48 (0.33 to 0.71)**	0.98 (0.63 to 1.43)	0.95 (0.61 to 1.37)	1.18 (0.82 to 1.99)		0.99 (0.42 to 2.40)	0.63 (0.29 to 1.32)	0.55 (0.21 to 1.40)	0.48 (0.23 to 0.99)	1.27 (0.59 to 2.56)	0.51 (0.22 to 1.21)
IBN monthly	**0.48 (0.26 to 0.90)**	0.98 (0.51 to 1.75)	0.95 (0.47 to 1.71)	1.14 (0.68 to 2.50)	1.00 (0.49 to 1.98)		0.64 (0.25 to 1.52)	0.55 (0.19 to 1.56)	0.48 (0.19 to 1.13)	1.28 (0.52 to 2.91)	0.51 (0.20 to 1.34)
DEN	**0.30 (0.21 to 0.43)**	**0.61 (0.39 to 0.91)**	**0.58 (0.40 to 0.88)**	0.77 (0.46 to 1.19)	0.63 (0.38 to 1.03)	0.64 (0.31 to 1.26)		0.87 (0.33 to 2.23)	0.76 (0.36 to 1.57)	2.01 (0.95 to 4.14)	0.81 (0.35 to 1.97)
ROMO	**0.27 (0.13 to 0.52)**	0.53 (0.25 to 1.06)	0.51 (0.25 to 1.03)	0.67 (0.30 to 1.35)	0.55 (0.25 to 1.16)	0.55 (0.22 to 1.36)	0.87 (0.40 to 1.86)		0.87 (0.34 to 2.22)	2.31 (0.89 to 5.79)	0.93 (0.33 to 2.71)
TPTD	**0.23 (0.16 to 0.32)**	**0.46 (0.31 to 0.66)**	**0.44 (0.32 to 0.61)**	**0.58 (0.36 to 0.90)**	**0.47 (0.29 to 0.77)**	**0.48 (0.25 to 0.95)**	0.76 (0.46 to 1.20)	0.87 (0.41 to 1.87)		2.65 (1.28 to 5.45)	1.06 (0.48 to 2.61)
RLX	**0.61 (0.44 to 0.80)**	1.23 (0.82 to 1.71)	1.17 (0.82 to 1.68)	1.54 (0.94 to 2.32)	1.26 (0.78 to 1.97)	1.27 (0.65 to 2.47)	2.01 (1.25 to 3.13)	2.30 (1.09 to 4.83)	2.66 (1.72 to 4.11)		0.40 (0.18 to 0.98)
ROMO/ALN	**0.25 (0.15 to 0.43)**	**0.50 (0.30 to 0.80)**	**0.47 (0.28 to 0.86)**	0.62 (0.33 to 1.11)	**0.51 (0.28 to 0.98)**	0.51 (0.24 to 1.12)	0.81 (0.44 to 1.59)	0.93 (0.40 to 2.29)	1.06 (0.60 to 2.06)	**0.40 (0.23 to 0.78)**	

Pairwise HR and 95% CrIs (lower triangle, not shaded), predictive effects in a new study and 95% PrI (upper triangle, shaded).
Bold font shows comparisons that indicate a statistically significant difference between interventions.

Romosozumab and side effects

Most frequent: Joint pain, injection site pain, injection site erythema, nasopharyngitis

Infrequent: Hyperostosis, hypocalcaemia, cardiovascular and cerebrovascular events

(cardiac ischemic, and cerebrovascular accidents [0.8 versus 0.3 percent])

Contraindicated in patients with hypocalcaemia

Caution in high risk for ischemic heart disease or cerebrovascular disorder