

# Current and emerging anabolic therapies for the management of osteoporosis

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## Plan for this Presentation:

- What is the extent of the clinical problem?
- Nutritional strategies for prevention of osteoporosis
- Current anabolic therapies
- Emerging anabolic therapies

# Osteoporosis in Australia

- 4.74 million Australians over 50 have osteoporosis or poor bone health
- Direct costs for treatment \$2.75 Bn in 2012
- During 2013 there were approximately 400 fractures per day in Australia due to osteoporosis.
- Poor bone health imposes premature mortality, (2.1-2.6 fold increased mortality risk post-fracture (Bluic D et al J Clin Endocrinol Metab. 2016 Apr 26:jc20161514))
- Premature mortality is reduced with bisphosphonate treatment

# Do we need new drugs for osteoporosis?

Antiresorptive treatments are well documented to reduce the risk of fracture but cannot restore bone mass or deteriorated skeletal architecture with severe disease.

Optimal drugs for osteoporosis would decrease bone resorption and stimulate bone formation at both cortical and trabecular bone sites

# Nutritional Preventative Strategies for Osteoporosis

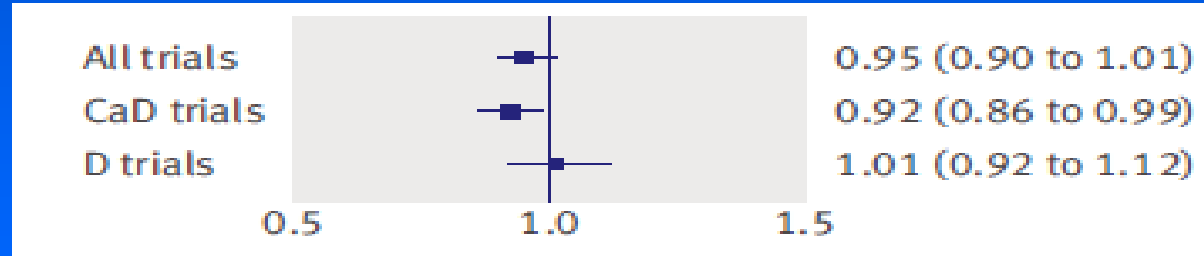
- Adequate vitamin D status and dietary calcium are required for optimal bone health
- Current preclinical data (confirmed by preliminary clinical data) indicate an anabolic action within bone

# Vitamin D plus Calcium or Calcium alone but Not Vitamin D alone protects against Fracture

	Subtotal (n)*	RR (95% CI)	p value
<b>Supplementation</b>			
Calcium	6517	0.90 (0.80-1.00)	0.63
Calcium and vitamin D	46 108	0.87 (0.77-0.97)	
<b>Vitamin D dose</b>			
<800 IU	36 671	0.87 (0.71-1.05)	0.03
≥800 IU	9437	0.84 (0.75-0.94)	

Tang et al Lancet 2007; 370: 657-666

Data from  
68,500 patients



# Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation

Weaver CM et al Osteoporos Int 2016;27(1):367-76.

Per protocol meta-analysis of data from 30,970 subjects showed that calcium plus vitamin D supplementation produced statistically significant:

1. 15% reduced risk of total fractures (SRRE, 0.85; 95% confidence interval [CI], 0.73–0.98)
2. 30% reduced risk of hip fractures (SRRE, 0.70; 95% CI, 0.56–0.87).

# Adequate vitamin D status and dietary calcium are required for optimal bone health

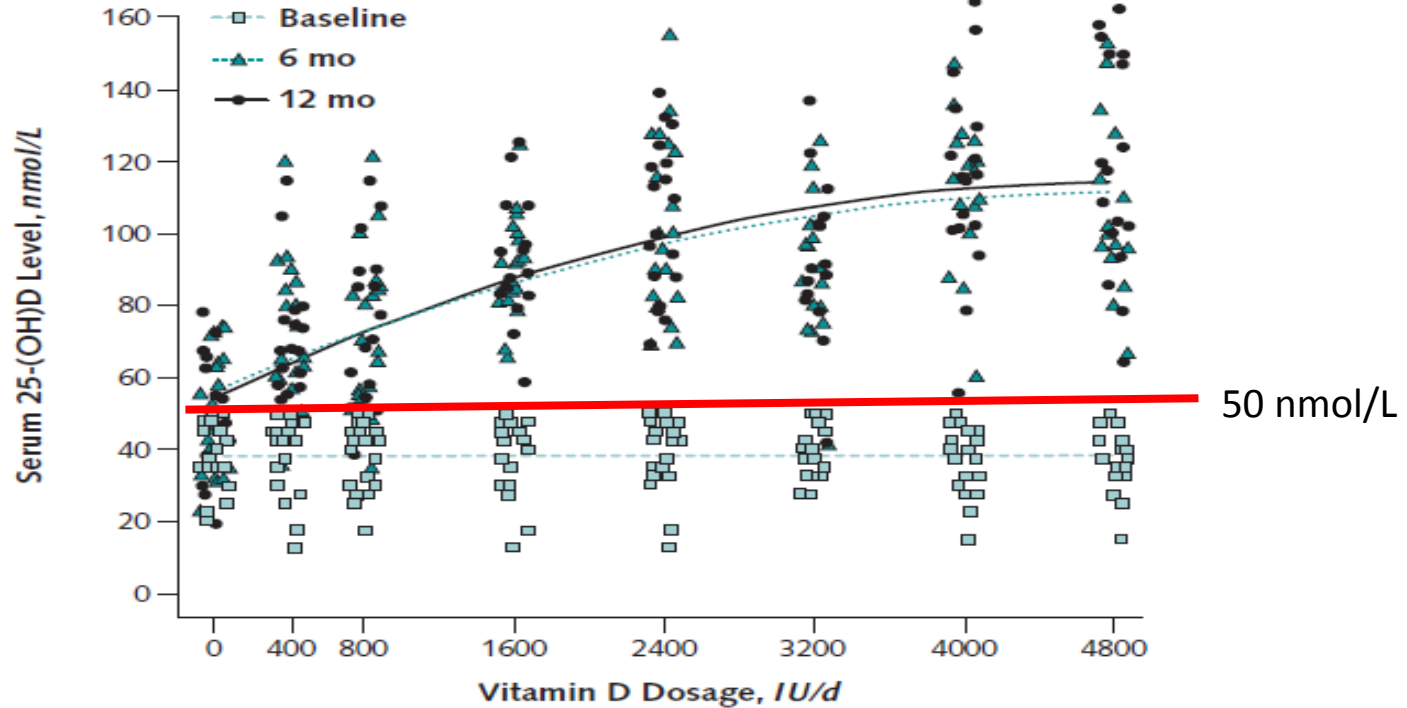
- What is adequate dietary calcium intake?

Wide agreement (US, Australia, NZ, Europe, International Osteoporosis Foundation, etc)

Age	Estimated Average requirement	Recommended Daily Intake
<b>Men</b>		
19-30 yr	840 mg/day	1,000 mg/day
31-50 yr	840 mg/day	1,000 mg/day
51-70 yr	840 mg/day	1,000 mg/day
>70 yr	1,100 mg/day	1,300 mg/day
<b>Women</b>		
19-30 yr	840 mg/day	1,000 mg/day
31-50 yr	840 mg/day	1,000 mg/day
51-70 yr	1,100 mg/day	1,300 mg/day
>70 yr	1,100 mg/day	1,300 mg/day



# Dose response to Vitamin D Supplementation in Postmenopausal Women



# Current anabolic therapies

- Parathyroid hormone peptides
- Strontium ranelate

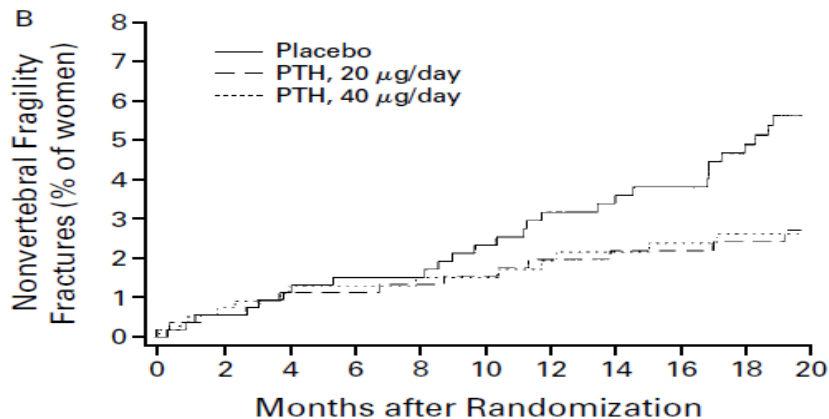
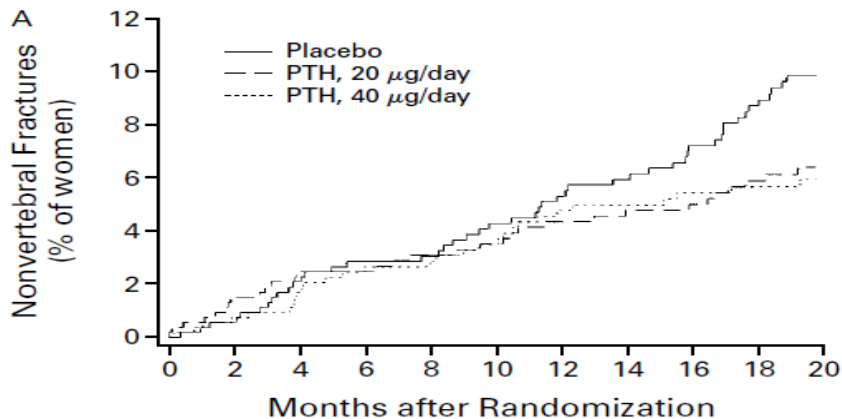
# Parathyroid hormone peptides

- Continuous endogenous production or exogenous administration of PTH is deleterious for bone stimulating bone resorption
- Intermittent PTH (eg daily subcut. injections) with 1-84 PTH or 1-34 PTH (teriparatide) are in current clinical use for anabolic actions.
- PBS approved for severe established osteoporosis in people at very high risk of fracture who develop one or more new symptomatic fractures despite at least 12 months of continuous antiresorptive therapy. Use is limited to a lifetime duration of 18 months

# Efficacy of Teriparatide to increase BMD and reduce risk of non-vertebral fractures

Change in Bone Mineral Density (mean 21 months)

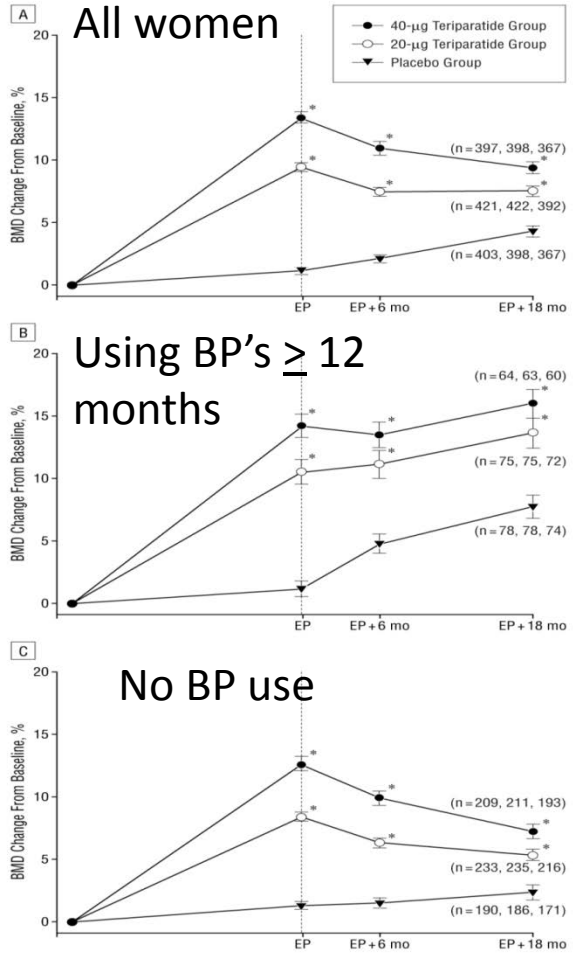
	Placebo	PTH 20 $\mu\text{g}/\text{d}$	40 $\mu\text{g}/\text{d}$
Lumbar spine	1.1%	9.7%	13.7



# Bone mineral density changes at the lumbar spine during and after treatment with teriparatide

BMD gained through the use of teriparatide can be maintained only with the use of anti-resorptive agents.

Lindsay R et al Arch Intern Med. 2004;164:2024-2030



EP indicates end point of the Fracture Prevention Trial

# Strontium ranelate (SR)

- European Medicines Agency (2013) warned that SR should be avoided in patients with ischaemic heart disease (IHD), peripheral vascular disease (PVD) or cerebrovascular disease (CVD), and in patients with uncontrolled hypertension.
- Now indicated in patients with severe osteoporosis for whom treatment with other osteoporosis treatments is not possible and without contraindications

# Strontium ranelate (contd)

- Considered an anabolic agent with increased bone formation associated with reduced bone resorption
- SR (2g/d) over 10 years ↑ lumbar BMD ( $34 \pm 20$  %) with reduction of vertebral fractures (RR 0.6, 95% CI 0.53-0.69) and non-vertebral fractures (RR 0.85, 0.74-0.99)

# Emerging anabolic therapies

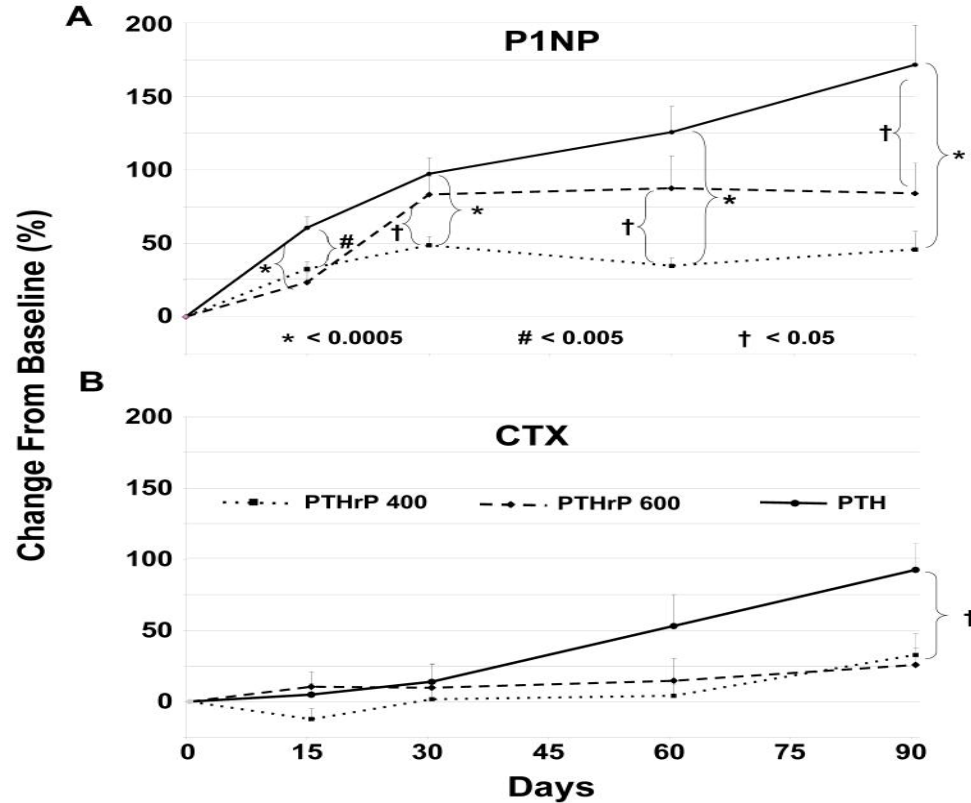
- Parathyroid hormone-related peptide
- Anti-sclerostin antibody



# Parathyroid hormone-related peptide

- PTHrP (1-36) and analogues (abaloparatide) are now being assessed
- Bind to same receptor as PTH peptides
- Similar anabolic action compared to PTH but reduced bone resorption by an unknown mechanism
- Adverse actions currently less than teriparatide

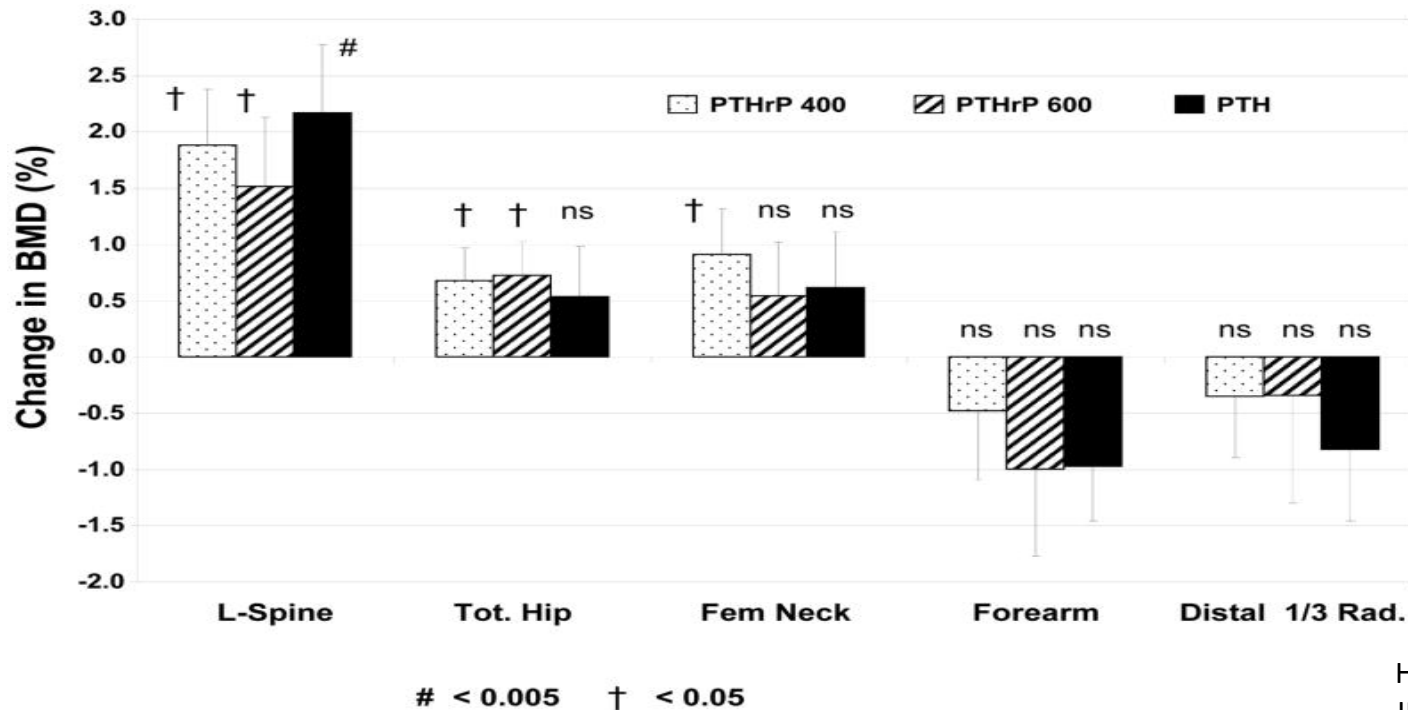
# Comparison of PTHrP and PTH on bone turnover markers



Bone formation

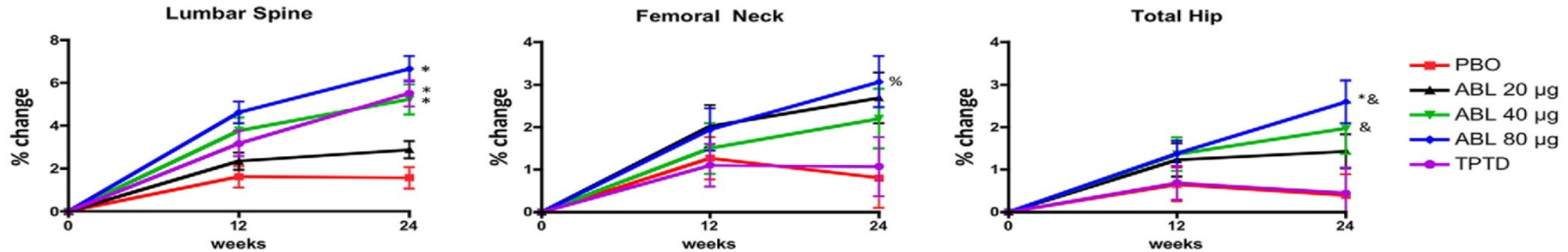
Bone resorption

# Effects of PTHrP and PTH on BMD in Postmenopausal Women over 90 days



No significant difference in BMD change between groups at any site.  
# and † symbols refer to statistical significance compared baseline values

# Comparison of Abaloparatide with Teriparatide on BMD in postmenopausal women



ABL, abaloparatide; TPTD, teriparatide. \*,  $P < .01$  vs placebo; %,  $P < .05$  vs placebo; &,  $P < .05$  vs teriparatide.

Abaloparatide is a synthetic peptide analog of PTH-related protein selected to retain potent anabolic activity with decreased bone resorption, less calcium-mobilizing potential, and improved room temperature stability

Published in: B. Leder; L. O'Dea; J. R. Zanchetta; P. Kumar; K. Banks; K. McKay; C. Lyttle; G. Hattersley;

*The Journal of Clinical Endocrinology & Metabolism* 2015, 100, 697-706.

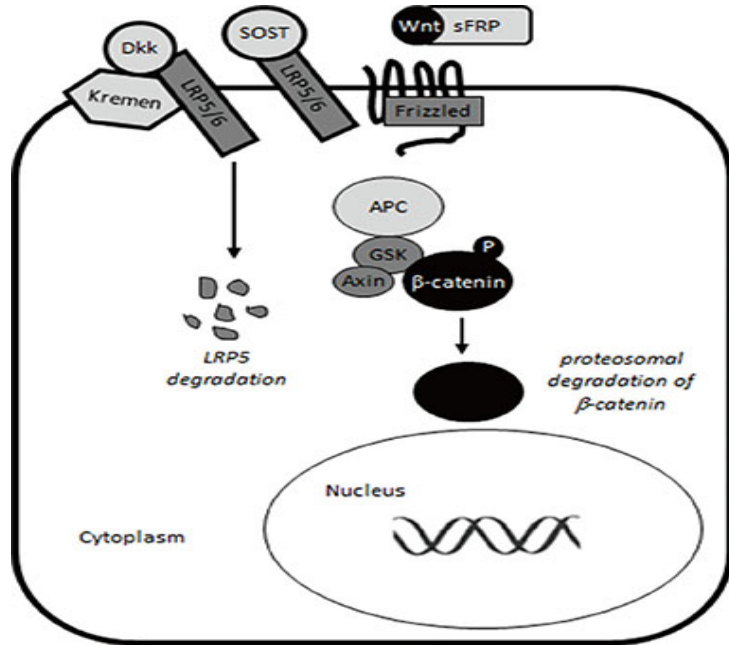
DOI: 10.1210/jc.2014-3718

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# Actions of Sclerostin: the role for anti-sclerostin antibody

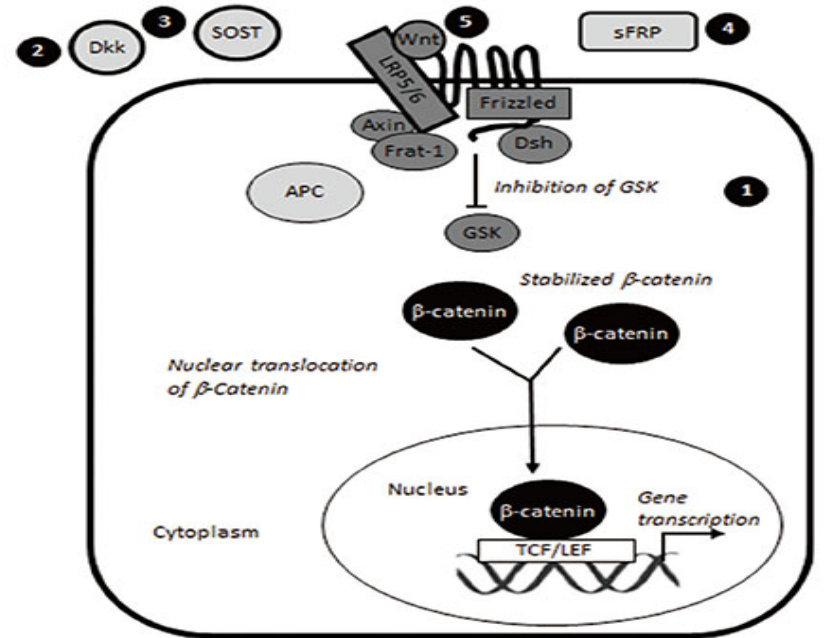
- Sclerostin is one of a number of inhibitors of the canonical Wnt signalling pathway
- Wnt signalling pathway in osteoblasts is responsible for stimulating bone formation in response to mechanical loading by stimulating osteoblast proliferation.
- Sclerostin is synthesized by osteocytes when bone is unloaded, inhibiting bone formation
- Sclerostin also activates osteoclastogenesis and bone resorption reducing bone mineral content.

# Wnt signalling pathway to stimulate osteoblast proliferation



Inhibition by sclerostin (SOST), dickkopf (Dkk) or secreted frizzled-related protein (sFRP)

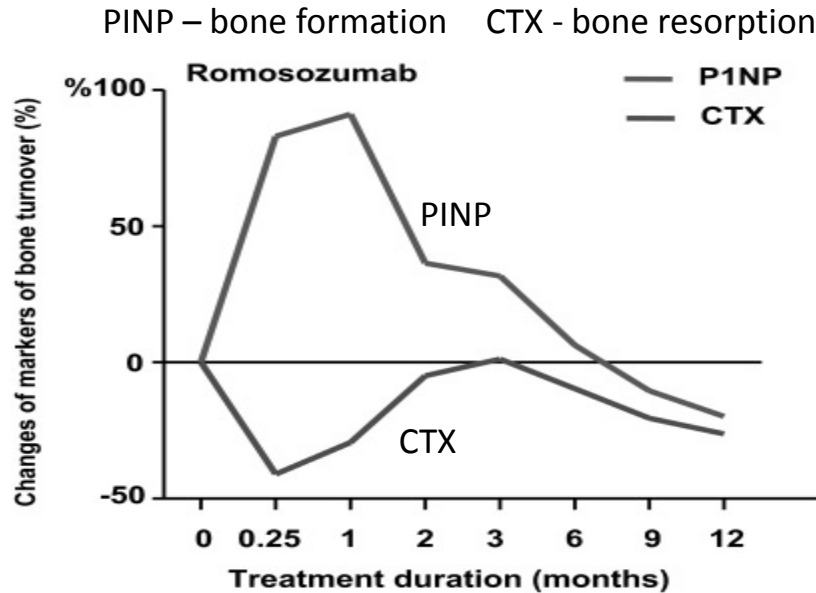
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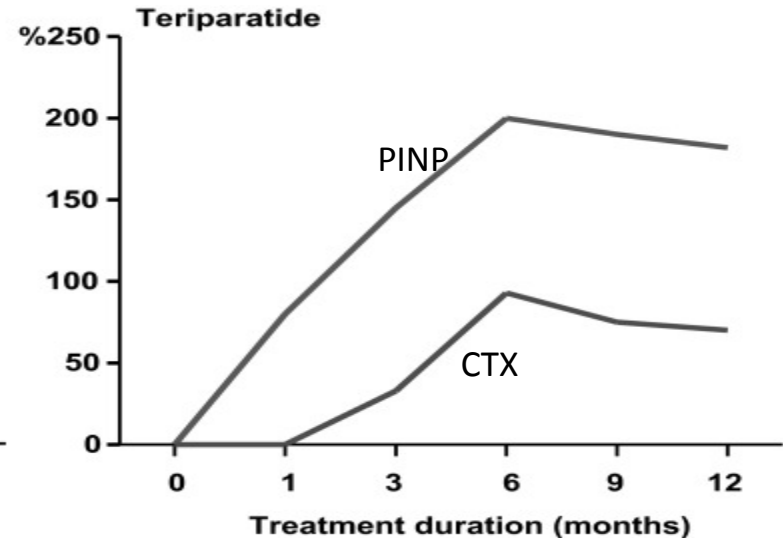
Activation by removal of the inhibitory factors

B

# Effects of romosozumab, a humanized monoclonal antibody against sclerostin, on bone turnover markers



romosozumab 210 mg once-monthly

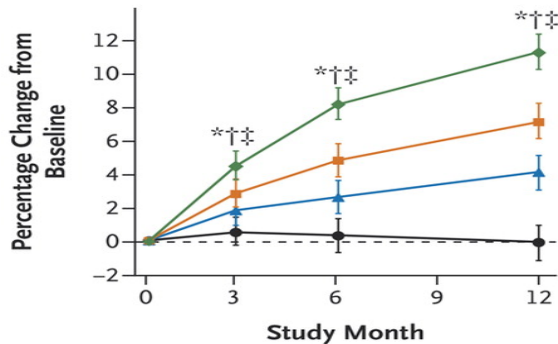


teriparatide 20 µg daily

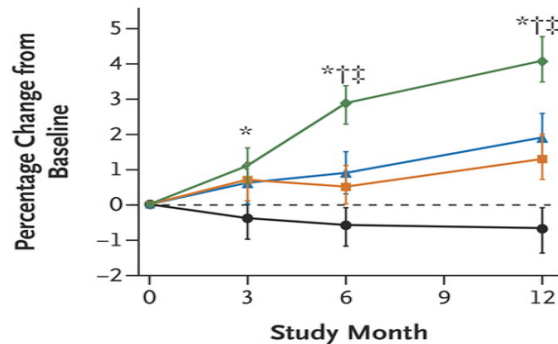
# Effect of Romosozumab on Bone Mineral Density as Percentage Change from Baseline

—●— Placebo    —▲— Alendronate    —■— Teriparatide    —◆— 210 mg of Romosozumab monthly

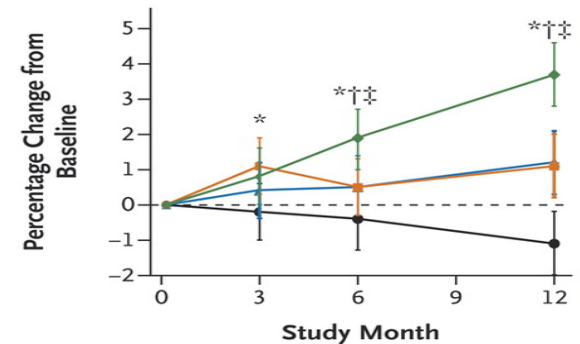
**A Lumbar Spine**



**B Total Hip**



**C Femoral Neck**



419 postmenopausal women were randomly assigned to receive subcutaneous romosozumab monthly (at a dose of 70 mg, 140 mg, or 210 mg) or every 3 months (140 mg or 210 mg), subcutaneous placebo, or an open-label active comparator--oral alendronate (70 mg weekly) or subcutaneous teriparatide (20 µg daily).



# Summary:

Vitamin D and dietary calcium are essential nutrients: they are both necessary to reduce fracture risk in the elderly

Teriparatide is markedly anabolic for bone and reduces risk of fracture but its use is limited

Strontium ranelate reduces risk of fracture but use is limited by contraindications

PTHrP analogs and sclerostin antibody treatments offer markedly anabolic effects as demonstrated by increased bone mineral density

Romosozumab phase 3 trial data will be available by the end of 2016

# Conclusions:

Antiresorptive treatments are well documented to reduce the risk of fracture but cannot restore the mass and deteriorated skeletal architecture with severe disease.

Optimal drugs for osteoporosis would decrease bone resorption and stimulate bone formation at both cortical and trabecular bone sites

Current data on these emerging anabolic agents suggest they may meet this need however antifracture efficacy and long-term tolerability remain to be established in phase 3 clinical studies

Thankyou