

Osteoporosis

Susan Ott
January 2020

Disclosures

- I attended a scientific advisory board meeting for Amgen, who paid travel expenses and I declined the honorarium.

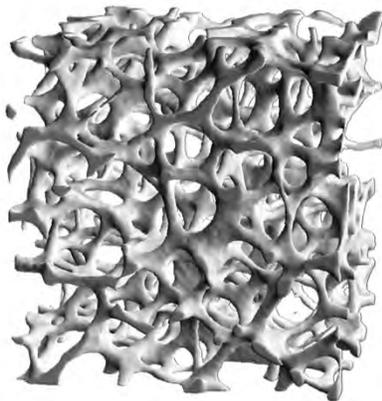
Osteoporosis is common but it's not simple



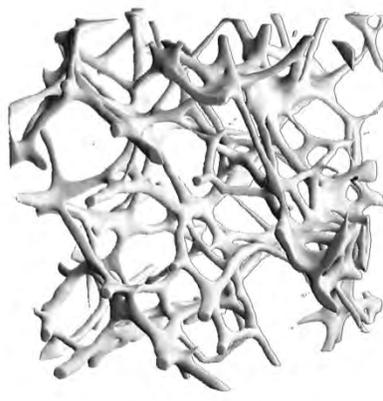
Hip fractures are one of the most important reasons that older patients lose their independence

Lumbar Spine

Young Normal



Osteoporotic



Images courtesy of Ralph Müller, PhD, Switzerland



Topics

- Vertebral fracture assessment and bone density
- Life-style recommendations
- Osteoporosis medications



Vertebral fractures

- ❖ ignored on ~50% of radiology reports
- ❖ risk for a new fracture is 4 times higher than in a person with the same age and BMD without a fracture
- ❖ new fractures cause pain in only 40% of cases
- ❖ patients have higher mortality and disability than patients without fractures
- ❖ should be prescribed medication to strengthen bone!

Vertebral Fracture Assessment



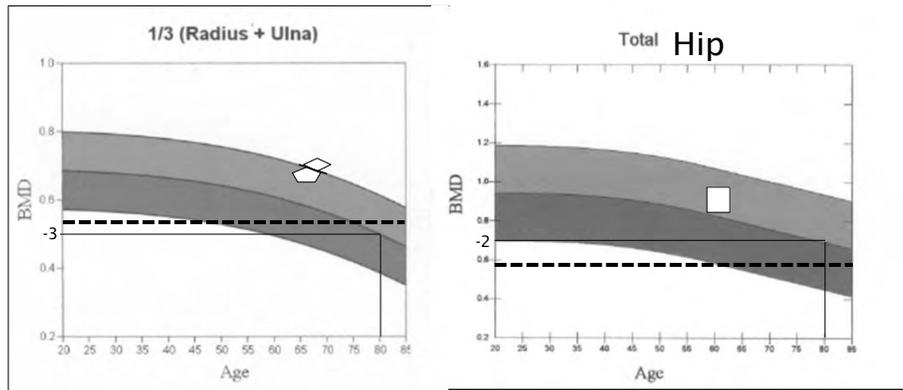
Region ¹	Avg. Ht. (cm)	Z-score	M/P Ratio (%)	Z-score	A/P Ratio (%)	Z-score
T4	1.57	-1.0	92	0.3	104	1.5
T5	1.64	-0.8	83	-1.2	100	1.1
T6	1.62	-1.2	79	-1.7	98	1.3
T7	1.74	-0.5	82	-1.3	91	0.3
T8	1.50	-2.4	66	-3.9	72	-2.8
T9	1.87	-0.4	86	-1.0	100	1.1
T10	2.05	0.0	87	-0.7	103	1.3
T11	1.77	-2.5	70	-3.2	70	-3.6
T12	2.37	-0.1	87	-0.7	94	0.0
L1	2.56	0.1	88	-0.8	96	0.2
L2	2.76	0.6	94	0.2	105	0.9
L3	2.60	-0.4	98	0.4	109	1.2
L4	2.62	-0.3	98	0.0	120	2.4

Moderate Wedge
 Moderate Biconcavity

In NHANES, only 8% of those with a spine fracture by VFA reported a history of spine fracture by questionnaire.

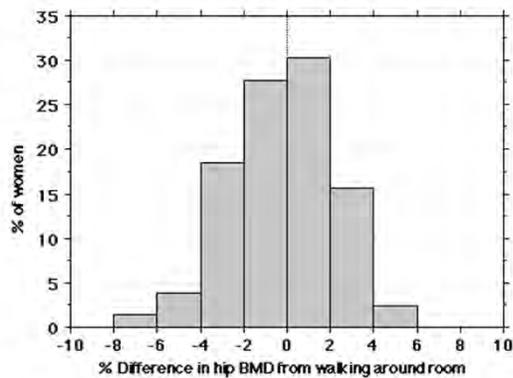
Among those who reported a spine fracture on the questionnaire, only 21% had a fracture by VFA.

Radius T-score does NOT equal Hip T-score



% of 75 y/o women with "osteoporosis" goes from ~20% to ~50%

Reproducibility



0 - 2% change (51%) : Within machine precision
 2 - 4% change (34%) : Mild, non-significant change
 4 - 6% change (6%) : Concerning but can't be sure
 >6% change (1.5%) : Significant change

Bone density does not always predict fractures

Can't measure:

Intrinsic toughness of bone

Brittle bone

Micro-cracks

Micro-architecture

Ability of bone to repair damage

Lifestyle



Calcium: A sacred cow?



- Calcium 1000 mg/day and protein 1-1.2 mg/kg/day (European council)
- Do not use calcium supplements in community-dwelling women to prevent fractures (USPTSF)
- Daily recommended allowance for calcium in adults is 1200mg (Inst. of Medicine)
- It is recommended that a daily calcium intake of between 700 and 1200mg should be advised, if possible achieved through dietary intake (NICE)

EAT YOUR CALCIUM: 1000mg/day



Cheese 200



Bok Choy: 100



Tofu: 250



Sweet potato: 90



Yogurt: 300



Latte: 300



Kale: 200



Almonds: 100

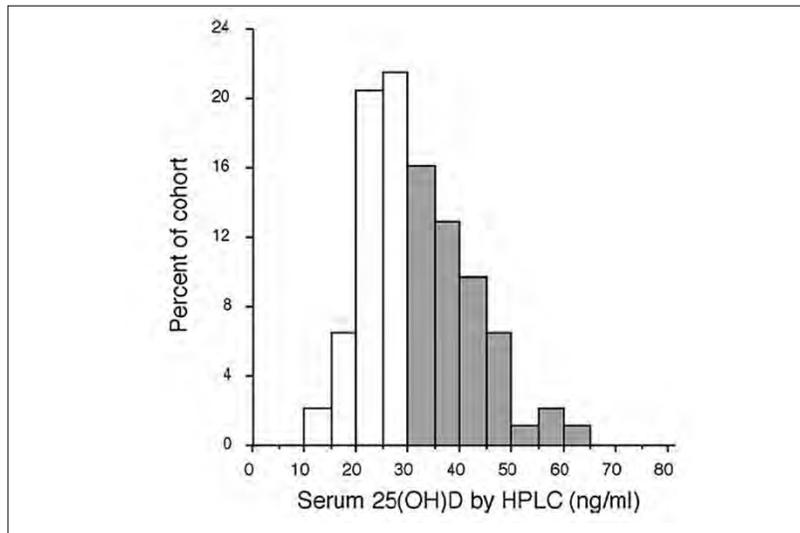
Spinach: zero

Vitamin D levels should be between
20 and 50 ng/ml

To achieve this give
800 to 1000 iu/day of vitamin D

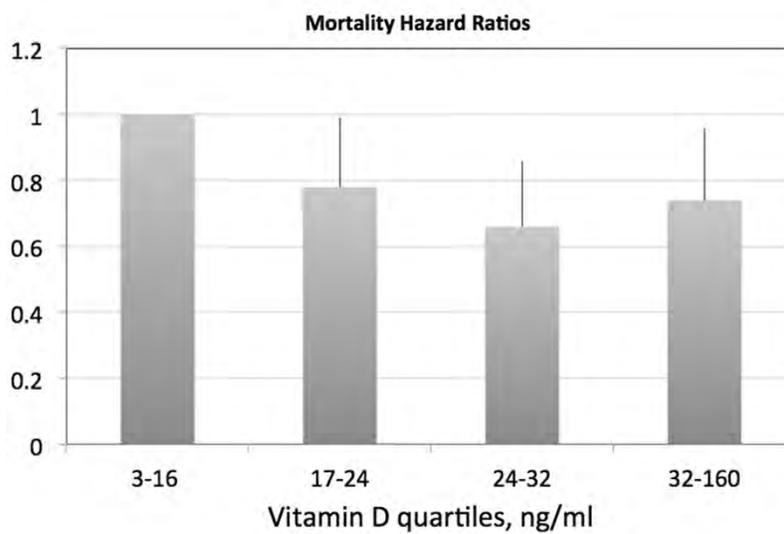
In clinical trials excess vitamin D causes
bone loss and hip fractures

Vitamin D levels in skateboarders from a beach in Hawaii



Binkley 2007

Vitamin D and Mortality



Daraghme, Atherosclerosis, 2016

***Vitamin D, the Sunshine
Supplement, Has
Shadowy Money Behind It***

The doctor most responsible for creating a billion-dollar juggernaut has received hundreds of thousands of dollars from the vitamin D industry.

The New York Times

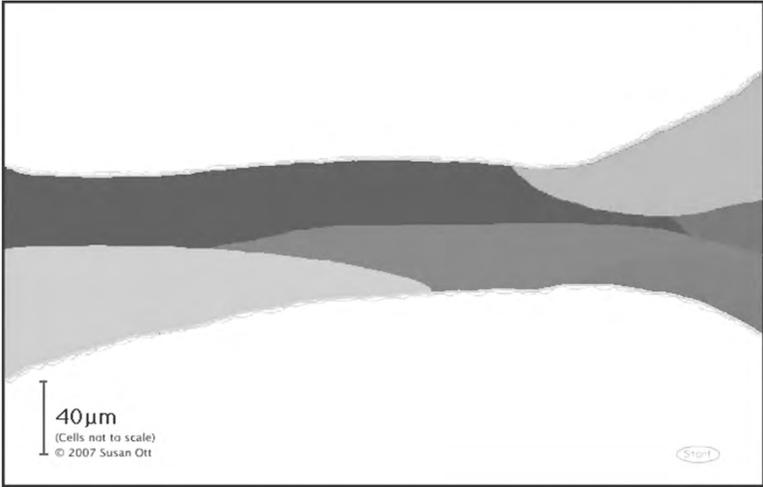
Liz Szabo
Aug 18, 2018

Medicare paid
\$365 million for
Vitamin D tests in 2016

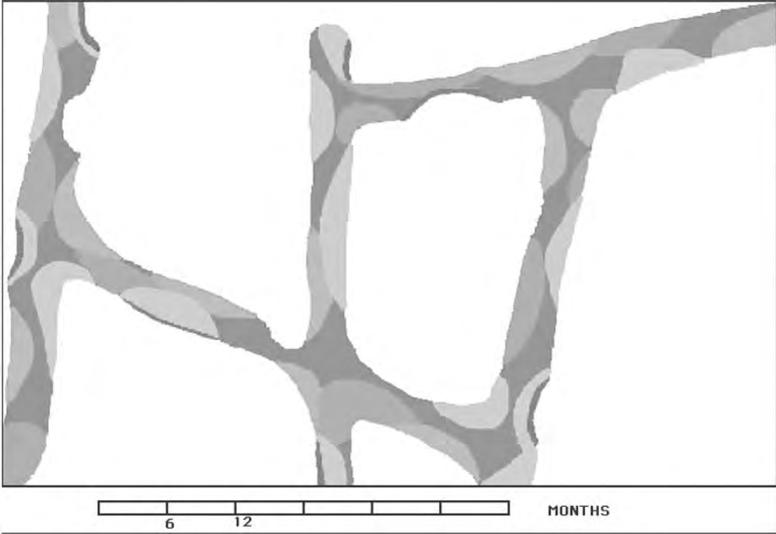


How do medicines work to
strengthen the bone?

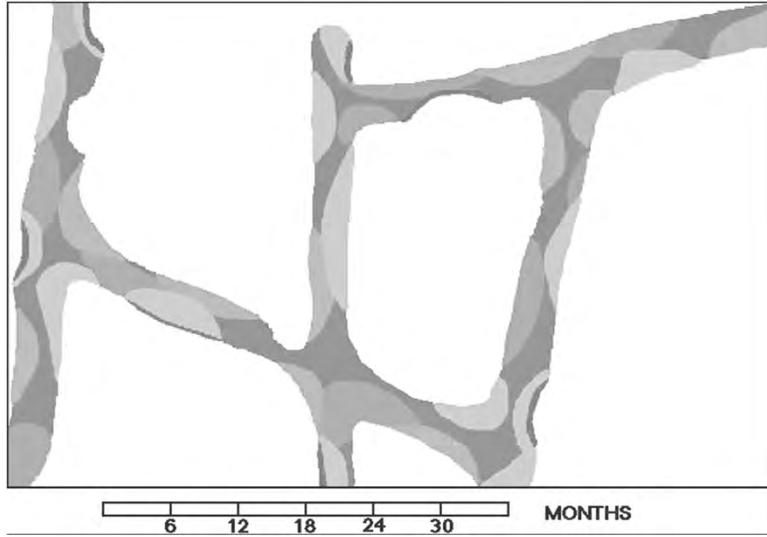
One BMU



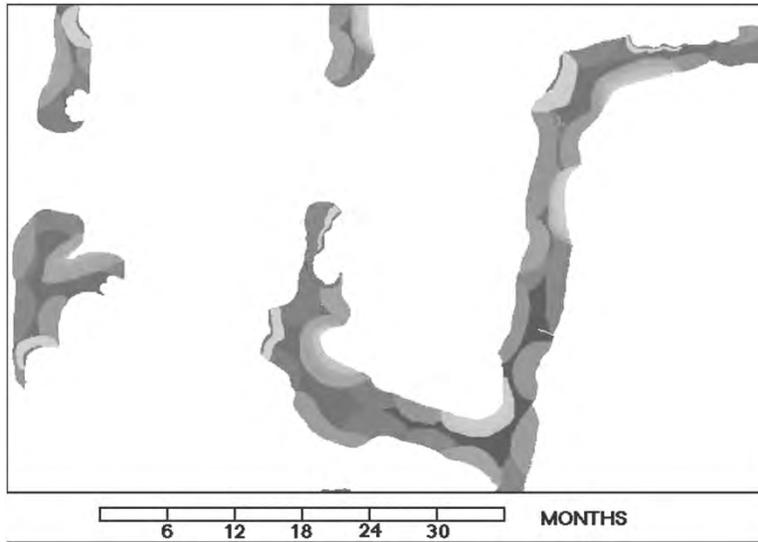
Normal Bone Remodeling



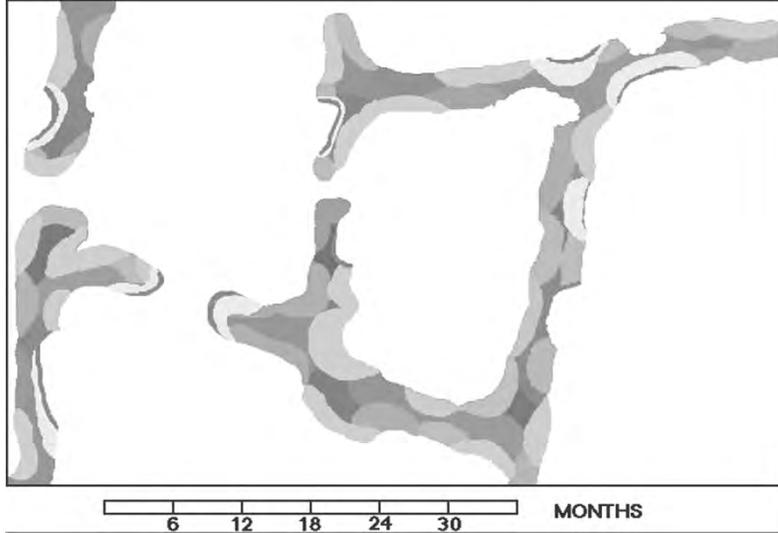
Bone Remodeling at menopause



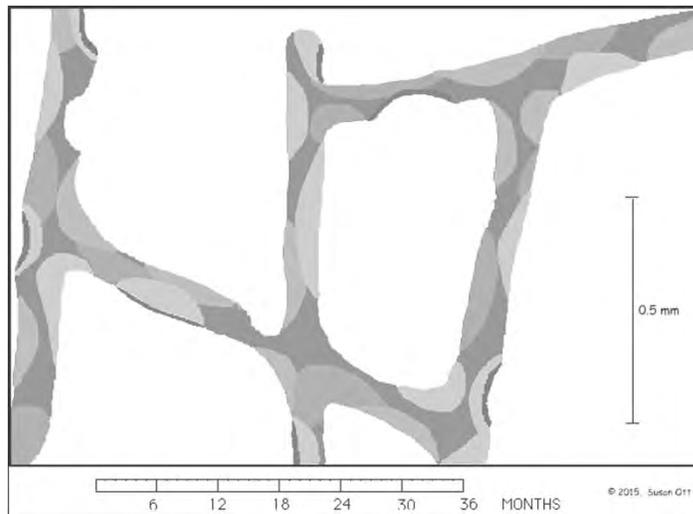
Treatment with estrogen/SERM



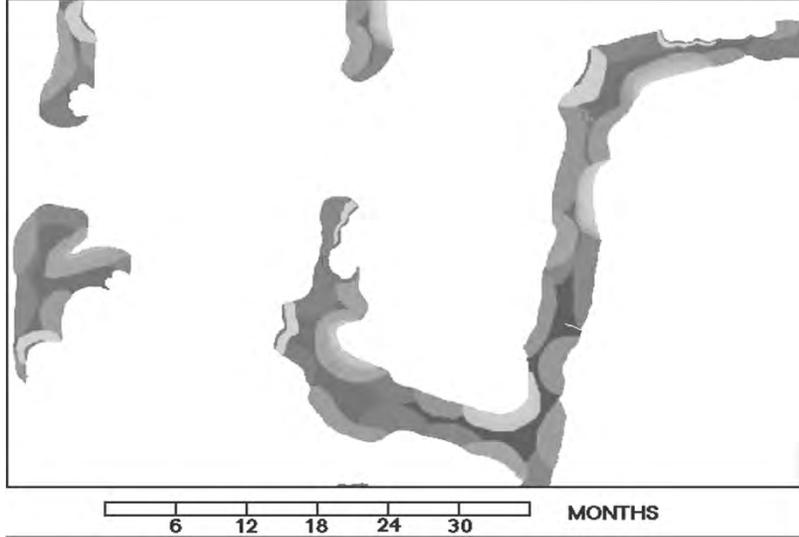
Treatment with bisphosphonate



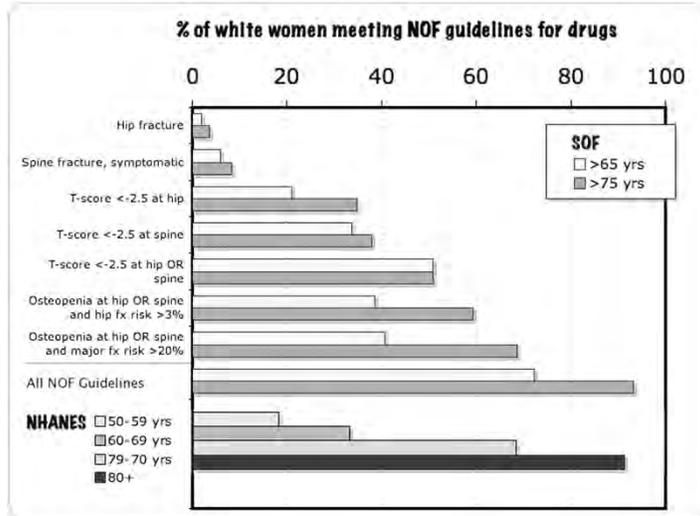
Treatment with denosumab



Treatment with teriparatide



Guidelines may recommend unnecessary treatment



When to start medications?

- Estrogen: Peri-menopause
- Raloxifene: When tolerated after menopause (localized spine disease)
- Bisphosphonates: Hip T-score < -2.5 OR a fragility fracture (age independent)
- Calcitonin: Anytime (safe but 2nd choice)
- Teriparatide: Severe disease, any adult
- Denosumab: Patients with cancer
- Romosozumab: Severe ($T < -3.5$ for now)

For each medicine you start, you should have a plan for duration and follow-up

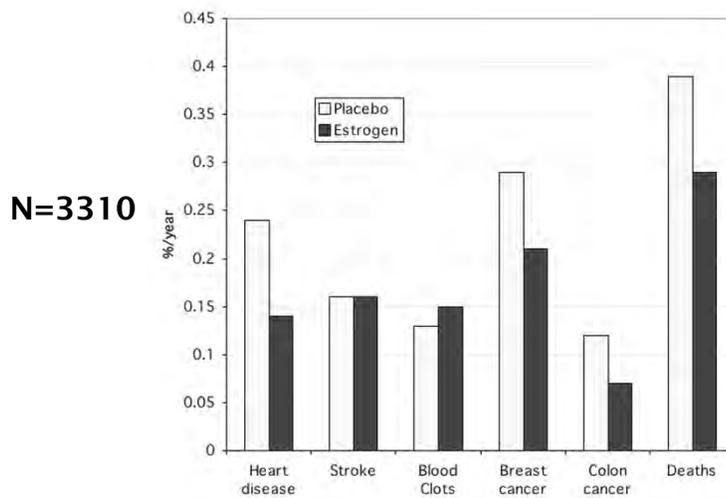
This is critical for the injectables.



“When indicated among women aged <60 years or within 10 years after menopause, HRT may be recommended for additional benefit to musculoskeletal health”

ESCEO

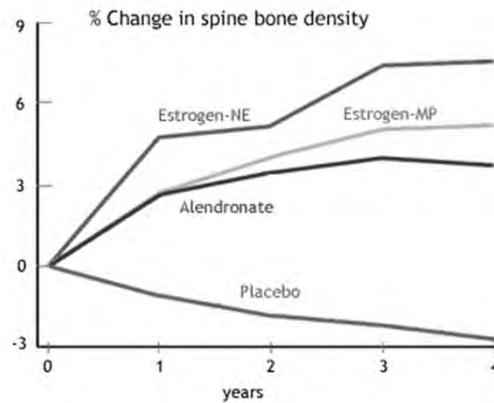
Estrogen in women aged 50-59



WHI, JAMA 04

Estrogen vs Alendronate

**N=1609
Women younger
than 60**



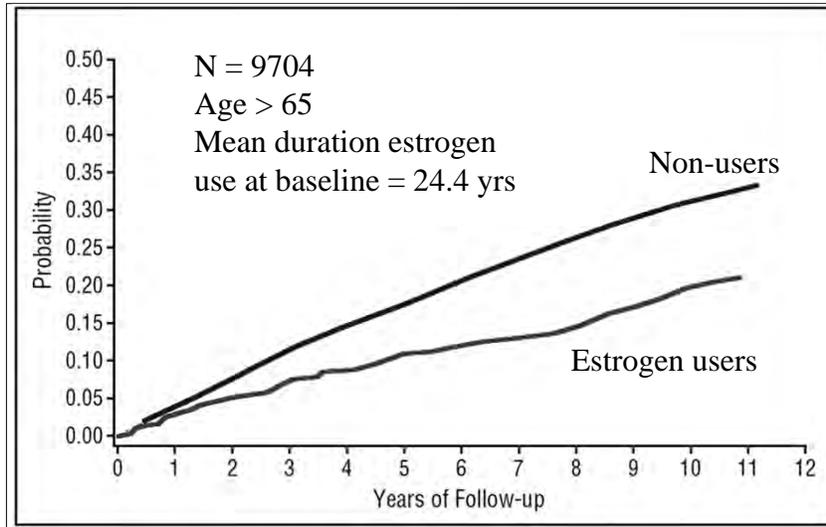
Ravn, Ann Intern Med 99

Estrogen vs. bisphosphonate

% Change in lumbar spine bone density

Author	Yr	N	Estrogen	Bisphosphonate	Both	Placebo	Comment
Wimalawansa	98	72	7	7.3	10.4		Established osteoporosis; 4 yrs; etidronate
Bone	00	425	6	6	8.3	-0.6	hysterectomized women; 2yrs; alendronate
Greenspan	03	373	7.1	7.7	10.4	1.1	elderly women; 3yrs; alendronate
Evio	04	90	10	9.1	11.2		osteoporosis; 2yrs; alendronate
Ravn	99	1609	7.5	4		-2.8	perimenopausal; 4yr; alendronate

Non-vertebral fracture incidence



Nelson, Arch Intern Med 2002

Raloxifene

- Good choice for woman with osteoporosis at the spine but not the hip
- Improves the quality of bone (like estrogen but unlike bisphosphonates)
- Reduces breast cancer. Over 8 years:

Placebo	4.2 per 1000/yr
Raloxifene	1.4 per 1000/yr

Raloxifene

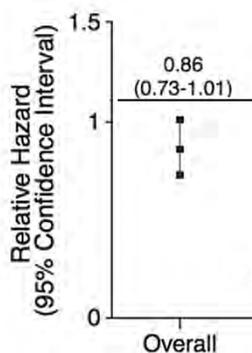
- ❖ May make hot flashes worse
- ❖ Not effective in premenopausal women
- ❖ No effect on uterus
- ❖ Acts like estrogen on bone
- ❖ Decreases LDL cholesterol like estrogen
- ❖ Increases blood clotting like estrogen
- ❖ In women with serious coronary artery disease, same number of strokes but more were fatal. No difference in strokes in the 8 year osteoporosis trial
- ❖ Give at different time of day than thyroxine

Clinical fractures in Alendronate Trial

FIT trial

N = 4000
Without
baseline
vertebral
fracture

Duration
4.5 yrs



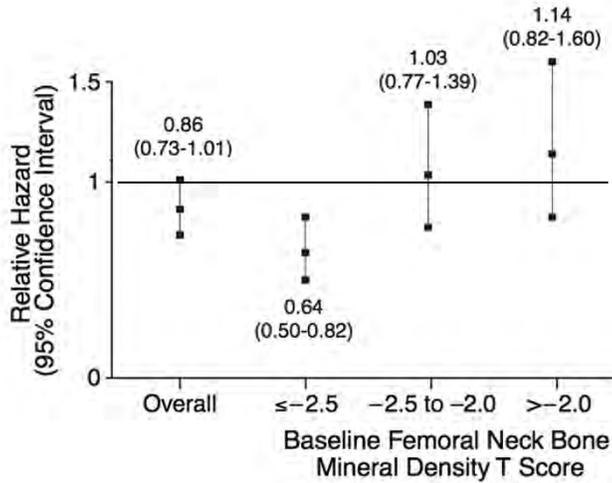
Cummings, JAMA 1998

Clinical fractures in Alendronate Trial

FIT trial

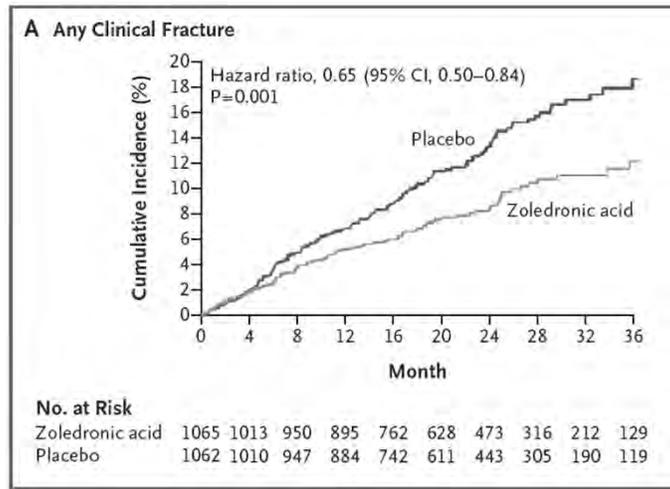
N = 4000
Without
baseline
vertebral
fracture

Duration
4.5 yrs



Cummings, JAMA 1998

Zoledronic acid in hip fx patients



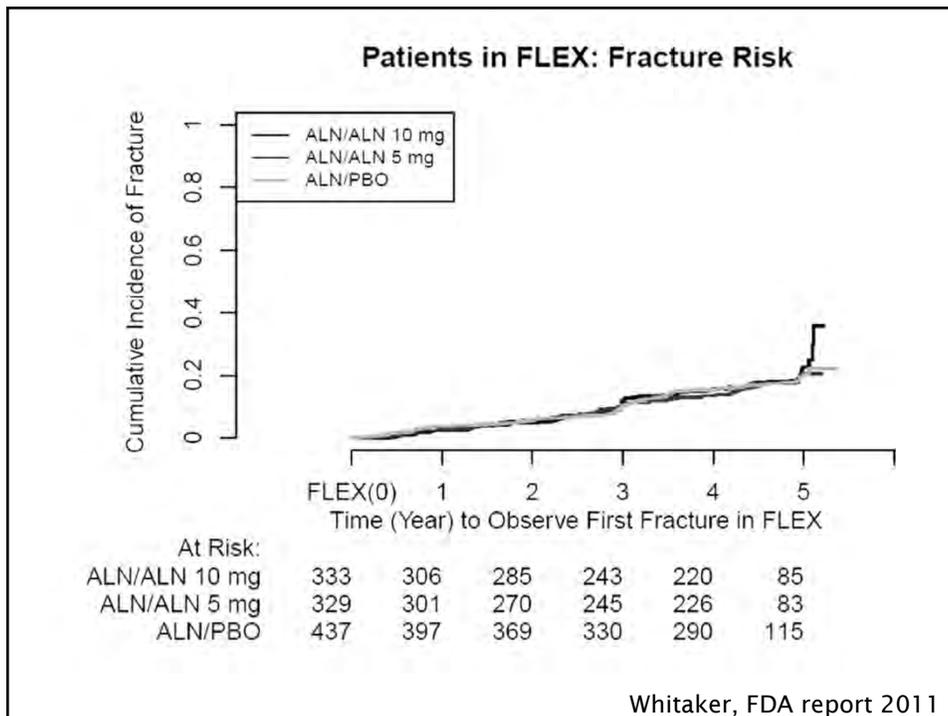
Lyles NEJM 2007

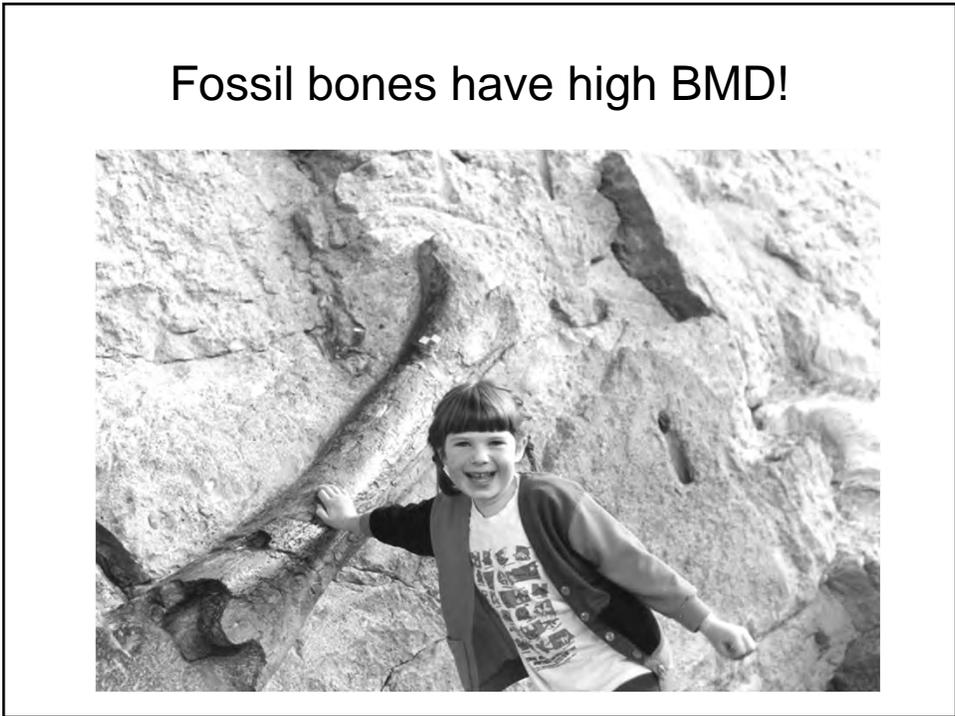
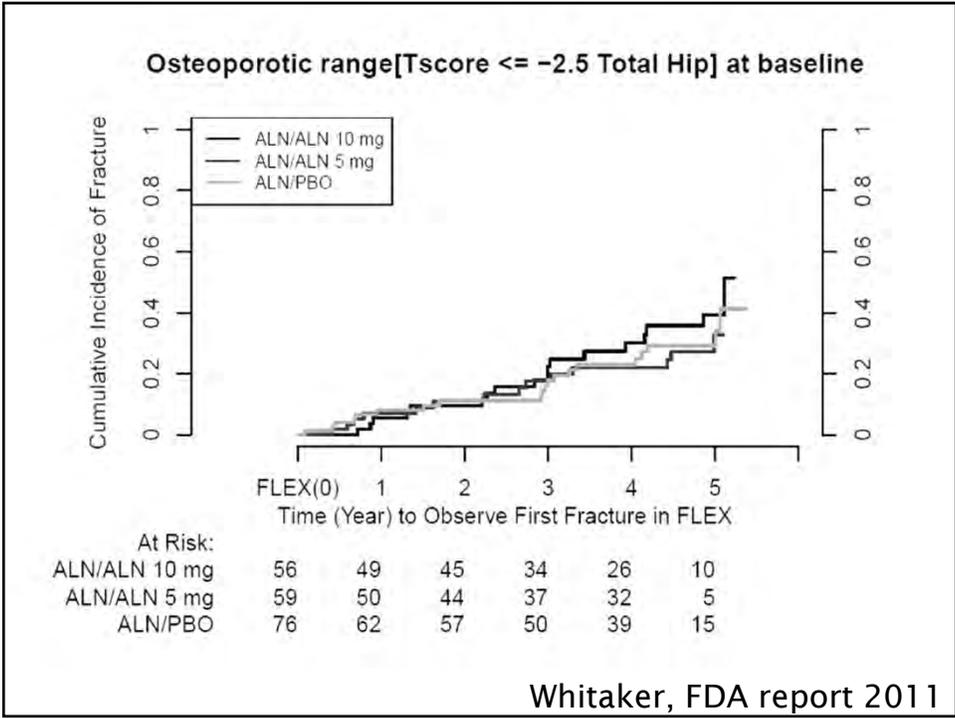
Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R. Reid, M.D., Anne M. Horne, M.B., Ch.B., Borislav Mlikov, B.Phty., Angela Stewart, R.N., Elizabeth Garratt, B.Nurs., Sumwai Wong, B.Sc., Katy R. Wiessing, B.Sc., Mark J. Bolland, Ph.D., Sonja Bastin, M.B., Ch.B., and Gregory D. Gamble, M.Sc.

Zoledronate reduced fractures in patients with osteopenia

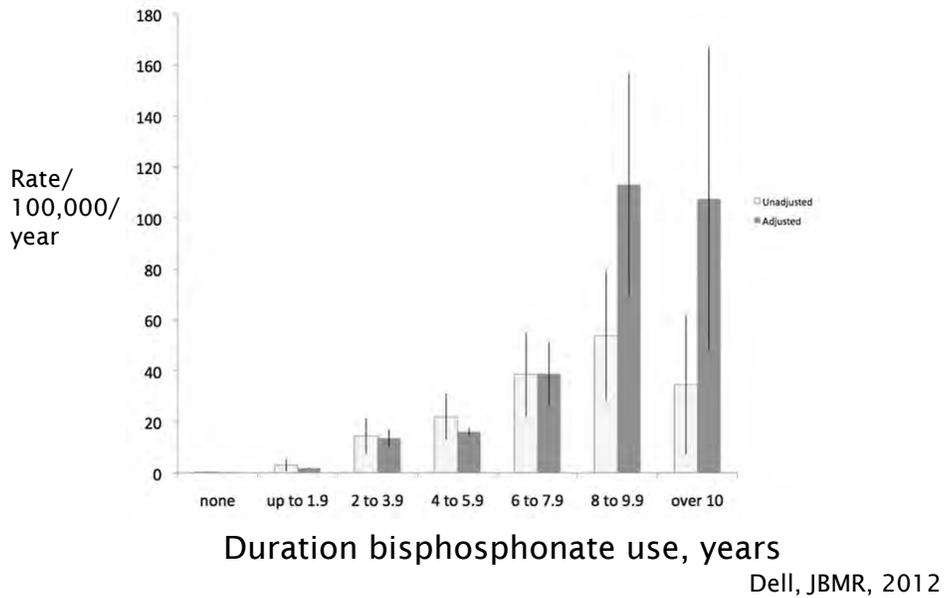
- New study from New Zealand
- N = 2000, 6 years (Q 2yr doses)
- >65 yrs, women, mean 71, T-score of one hip between -1 and -2.5 (but other hip could be lower). Median fx risk was 12%.
- Prevalent fracture in 23%
- **RESULT**
- 190 vs 122 women with fractures
- (no difference for hip fractures)







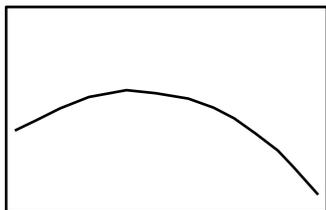
Incidence of atypical femur fracture



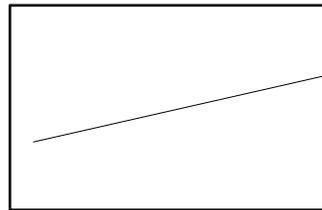
Long-term bisphosphonates

Bone biopsies from ordinary osteoporotic patients on bisphosphonates from 1 to 17 years found strength peaked at 7 years and then declined to levels below baseline. Crack density increased progressively.

STRENGTH



CRACK DENSITY



*Pienkowski, Wood, Malluche.
ASBMR 2019*

Teriparatide
Abaloparatide
Denosumab
Romosozumab

- ✧ Should be used only in severe cases.
- ✧ Should be given by practitioner with experience and knowledge of these drugs.
- ✧ Rebound bone loss with discontinuation means there must be a long-range plan and compliant patient.

Denosumab

- Increases bone density
- Reduces clinical fractures
- Stops bone resorption and also completely stops bone formation
- Some cases of atypical fractures and jaw osteonecrosis
- Rebound loss after it wears off in 6 mo.

Denosumab in CKD

High incidence of serious hypocalcemia

Seizures, laryngospasm,
arrhythmias, tetany

No randomized trials in patients with chronic kidney disease

Unknown effects on vascular calcifications;
case report of rapid development

Denosumab rebound

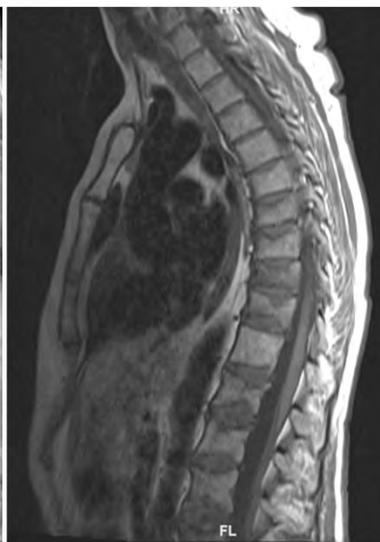
- In one study, subjects gained 12% over ten years
- After stopping they lost 13% during the next year

Discontinuation of Denosumab and Associated Fracture Incidence

Conclusion: Discontinuation of DMAb is associated with an increase in VFx rate to levels comparable to PBO.

Among subjects who sustained new VFx after DMAb cessation, there was a greater incidence of multiple new VFx than in PBO

Brown ASBMR 2016



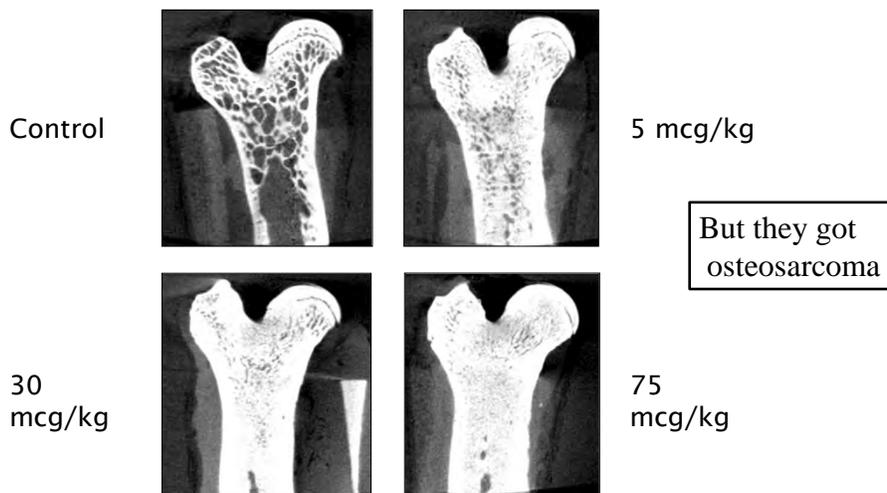
Before
and after
skipping a
dose of
denosumab



48 yr old woman with breast cancer treated with AI from 2010 to 2015 and denosumab from 2012-2015 with improvement in BMD. Within 6 months after stopping she developed multiple spine fractures.

Popp, Osteoporosis Int 2016

Exaggerated Increases in Bone Mass 2-Year Rat Study of PTH



Vahle. *Tox Path.* 2002;30(3):312.

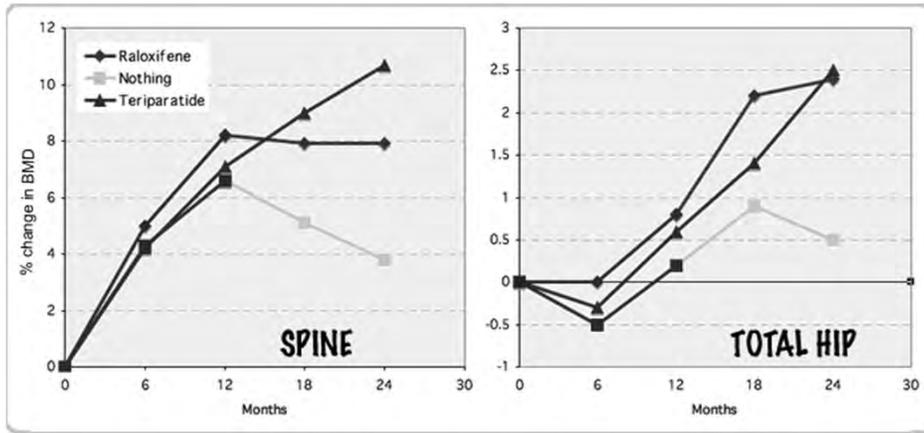
Teri/abalo-paratide Contraindications

History of malignancy / radiation / Paget's
Abnormal SPEP or UPEP
High alkaline phosphatase
Hypercalcemia
Hypercalciuria
Vitamin D level >45ng/dl
Hyperparathyroidism
Hepatic disease
Chronic Kidney Disease grade 4-5
High uric acid
Noncompliance

Adverse effects or teriparatide

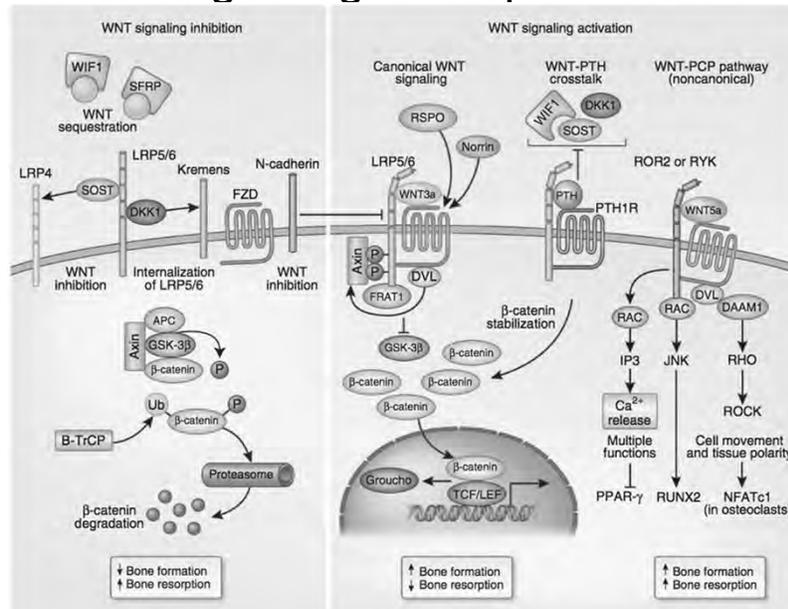
Hypercalcemia in 11%
Hypercalciuria or kidney stones
Gout
8% nausea/ dizziness / bone aches

Teriparatide discontinuation

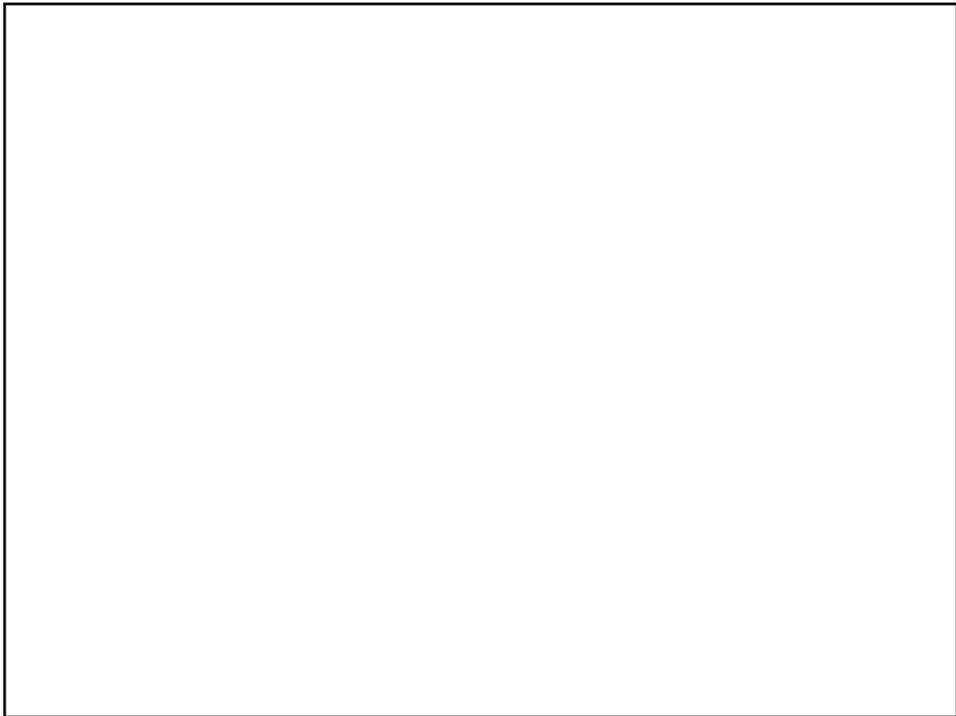
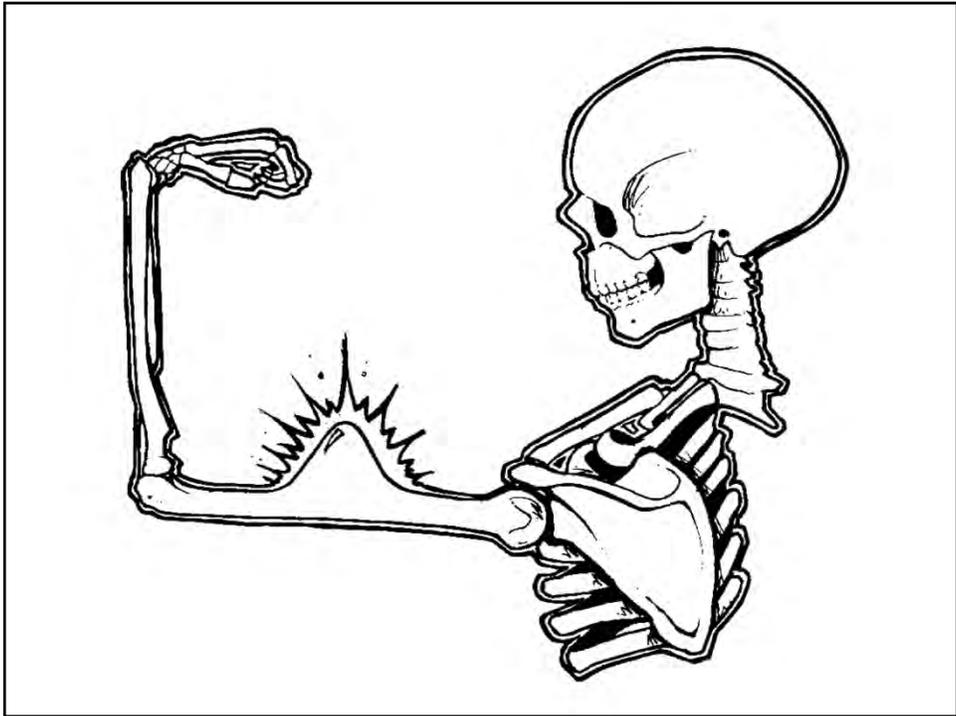


Eastell, JBMR 2009

WNT signaling: a simplified view



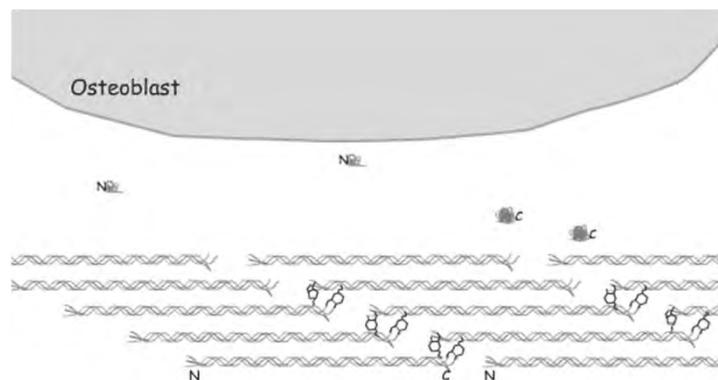
Baron, Nature Med, 2013



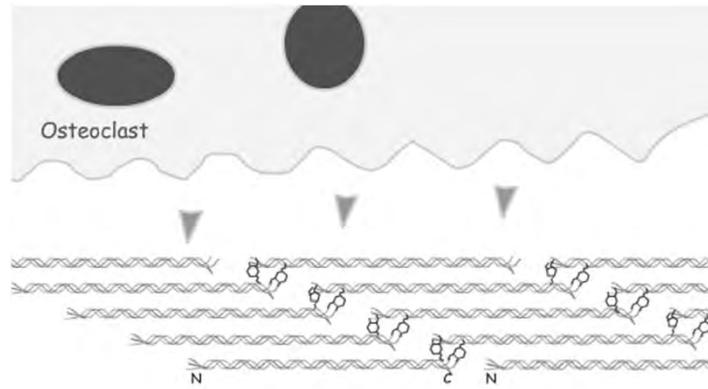
Markers of bone formation



Markers of bone resorption



Markers of bone resorption



Markers of bone resorption

