

# TREATING THE OLDEST OLD

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## Conflicts of Interest

Bone Health and Osteoporosis Foundation (formerly NOF): President

Salary support: National Institute of Aging; Amgen-University of Alabama Birmingham

Cofounder and Equity Owner: Faculty Connection, LLC

Co-Inventor US Patent: "Methods for preventing or reducing secondary fractures after hip fracture" Number 20050272707

Inventor US Provisional Patent Application: Compositions and Methods for the Treatment of Infection-Induced Cardiomyopathy

Inventor US Patent: "Medication Kits and Formulations for Preventing, Treating or Reducing Secondary Fractures After Previous Fracture" Number 12532285

Co-Inventor of US Patent: "Bisphosphonate Compositions and Methods for Treating and/or Reducing Cardiac Dysfunction" Number 61/560,328

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## Very Big Problem

- Most patients, many of them older, at high risk for fracture are not evaluated and treated for osteoporosis.
- Most patients who are treated do not take medication long enough to benefit from reduction in fracture risk.
- Most patients do not fully understand the balance of benefits and risk with and without treatment.
- Some clinicians do not understand the risks of procedures they use, problem of missing fractures, or medication complications.

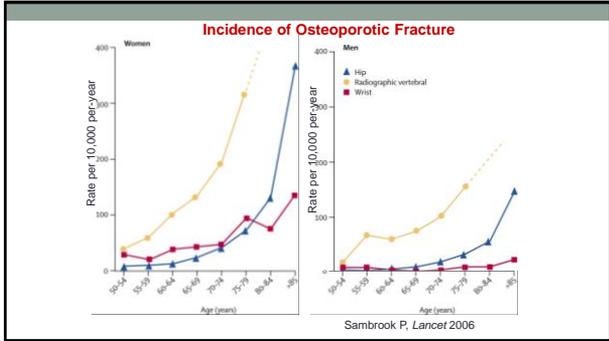
ASBMR. <https://www.asbmr.org/call-to-action.aspx>.

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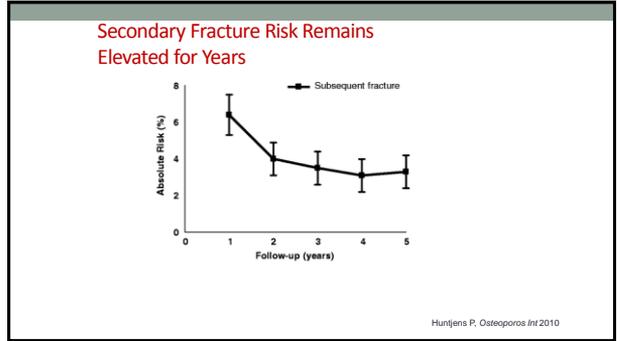
## OBJECTIVES

1. Realize there is a care gap in getting effective, safe therapies to patients who would benefit from osteoporosis therapy.
2. Understand which therapies are effective in improving bone density/reducing fractures in the oldest old.
3. Appreciate osteoporosis practice improvement opportunities for other health care professionals.

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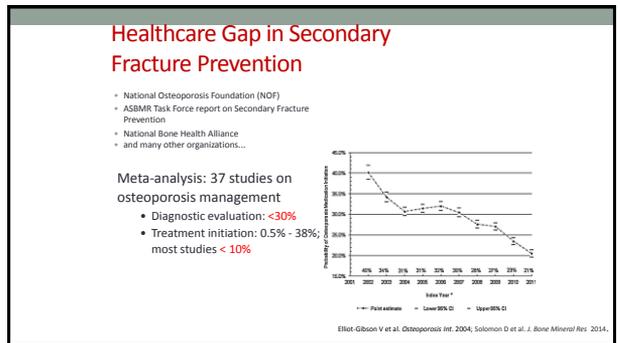
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- ### Risk factors for osteoporosis/fractures
- Increasing age
  - Female
  - Family history of osteoporosis/fractures
  - Smoking
  - Excessive alcohol intake
  - Low body weight
  - History of low impact fractures
  - Loss of height/presence of kyphosis
  - Prolonged glucocorticoid use
  - Chronic neurological diseases that increase risk of falling
  - Frequent fallers

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## Tailor Evaluation and Management for each Patient

### Estimate fracture risk

- Consider additional fall/fracture risk factors outside of FRAX

### Estimate life expectancy

- Lag time to benefit only ~1 year
- Longer life expectancy → more fracture risk

### Consider goals of care

- Trade-off between present comfort/convenience and future harm prevention
- Serious adverse events caused by osteoporosis drugs are very rare, but patient concern for rare events and burden of polypharmacy should be considered

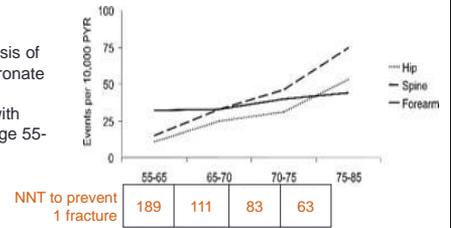
### Address fall risk in all patients

Berry, S. JAMA, 2019

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## Post-hoc Analysis-Benefits of Alendronate Increase with Age

- Post-hoc analysis of FIT trial (alendronate vs placebo)
- 3658 women with osteoporosis age 55-80



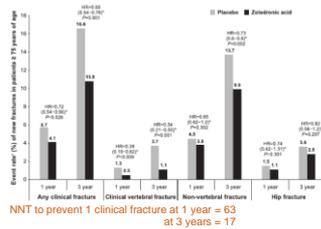
Hockberg, M. J Bone Mineral Res, 2005

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## Post-hoc Analysis-Benefits of Zoledronic Acid Persist Old Age

Post-hoc analysis of HORIZON trial (zoledronic acid vs placebo)

3887 women with osteoporosis age ≥75 (mean age 79)



Boonen, S. J Amer Geriatrics Soc, 2010

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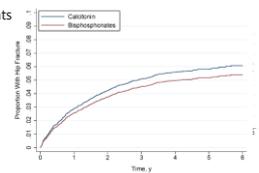
## Bisphosphonates Reduces Fractures in LTC Patients

Retrospective cohort of 10,418 LTC residents

Mean age 85, mean follow-up 2.5 years

New bisphosphonate use vs calcitonin use (active comparator)

28 more fracture-free days in bisphosphonate group



Zullo D., J Amer Geriatrics Soc, 2019

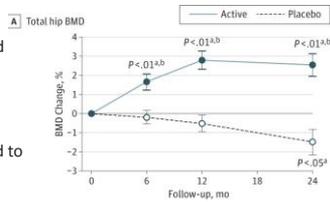
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## Bisphosphonates improve BMD in a LTC population

ZEST trial: RCT of zoledronic acid vs. placebo

181 women in ALF or NH, mean age 85

2-year follow up, underpowered to detect fracture reduction



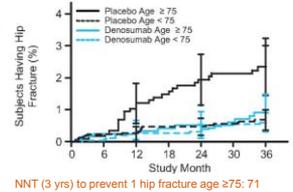
Greenspan, S. JAMA Intern Med 2015

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## Denosumab Reduces Fractures in Older Patients

Post-hoc analysis of FREEDOM trial (denosumab vs placebo)

7808 women with osteoporosis age 60-90, stratified above/below 75yo



Boonen, S. J Clin Endocrinol Metab, 2011

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## American Association of Clinical Endocrinologist Fracture Risk Stratification

### Patients at High Risk for Fracture

- Had recent fracture in last 12 months
- Had fracture while on approved anti-fracture treatment
- Had fractures while on drugs that may cause skeletal harm
- Experienced multiple fractures
- Very low T-score <-3.0
- High risk for falls or history of injurious falls
- Very high fracture probability per FRAX
  - Major osteoporosis fracture risk ≥30%
  - Hip fracture risk ≥4.5%

teriparatide, abaloparatide, romosozumab

denosumab, zoledronic acid, alendronate, risedronate

Modified from American Academy of Clinical Endocrinologists, June 9, 2009

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## Teriparatide Fracture Reduction Efficacy

Teriparatide reduced the risk of vertebral fractures by 65-73%, hip fractures by 56%, and non-vertebral fractures by 38-53% in patients with osteoporosis, after an average of 18 months of therapy.

The VERO Trial compared teriparatide and risedronate in postmenopausal women with severe osteoporosis, reporting ~50% fewer new vertebral fractures and ~25% fewer non-vertebral fractures in the teriparatide group after 24 months.

Neer R. N Engl J Med, 2001; Diaz-Perez A, Bone, 2019; Kendler D. Lancet 2018

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## Teriparatide Adverse Effects

Can cause nausea, arthralgia and pain. Hypotension and tachycardia can occur with the initial doses. Transient hypercalcemia and hypercalcuria can occur, that is usually corrected by reducing calcium intake.

Treatment should not be used in patients with hypercalcemia, bone metastases, skeletal malignancies, Paget's Disease of bone, an elevated alkaline phosphatase, or prior skeletal radiation.

Labeling includes a boxed warning about a risk of osteosarcoma based on animal studies. In a post-marketing surveillance study, none of the 1448 cases of osteosarcoma in the US in a 7-year period were associated with use of teriparatide.

Lexicomp, Accessed 3-17-21; The Medical Letter vol 62, 2021

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## Abaloparatide Fracture Reduction Efficacy

Abaloparatide reduced the risk of new vertebral fractures by **-86%** and non-vertebral fractures by **-43%** in postmenopausal women with osteoporosis, after an average of 18 months of treatment.

In the extension study (ACTIVE-Extend) after 18 months of abaloparatide or placebo the addition of oral alendronate for 6 months for a total of up to 24 months, resulted in a relative risk reduction of radiographic spine fractures by **87%**, non-vertebral fractures by **52%**, and major osteoporotic fractures by **58%**.

Miller P, JAMA 2016; Cosman F, Mayo Clin Proc, 2017

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## Abaloparatide Adverse Effects

Can cause injection-site reactions, nausea, headaches, dizziness, palpitations, tachycardia, orthostatic hypotension, hypercalcemia, hypercalcuria, and hyperuricemia. Reducing calcium intake usually corrects hypercalcemia and hypercalcuria.

As with teriparatide, abaloparatide labeling includes a boxed warning about a risk of osteosarcoma based on animal data.

Lexicomp, Accessed 3-17-21; The Medical Letter 62, 2020

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## Romosozumab Fracture Reduction Efficacy

Romozozumab compared to placebo for 12 months reduced risk of new vertebral fractures by **73%** and clinical fractures by **36%** in the pivotal FRAME Trial. In the ARCH trial high risk postmenopausal women had significantly fewer fractures when receiving romosozumab compared to alendronate: **48%** fewer new vertebral fractures, **19%** fewer non-vertebral fractures, and **38%** fewer hip fractures after 12 months.

Extension studies have shown bone density trending towards pretreatment levels after stopping therapy. Treatment with denosumab, and to a smaller degree alendronate, preserve or increase bone density following romosozumab therapy.

Cosman F, N Engl J Med 2016; Saag K, N Engl J Med 2017; McClung M, J Bone Miner Res 2018

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## Romsozumab Adverse Effects

Arthralgia and headache, most common adverse effects in the registration trials. Can cause hypocalcemia so this should be corrected prior to initiation of therapy. Can cause hypersensitivity reactions.

In the two registration trials, FRAME and ARCH (11,273 patients) 3 atypical femoral fractures and 3 cases of osteonecrosis of the jaw occurred in patients receiving romosozumab.

In the ARCH Trial serious adverse cardiovascular events occurred more frequently with romosozumab than alendronate (2.5% vs. 1.9%). In the FRAME Trial, the rate was not higher with romosozumab than placebo. The drug should not be used in patients with a myocardial infarction or stroke within the previous year.

Neutralizing antibodies to romosozumab have developed, and it is unknown if they reduce efficacy.

Lexicomp, Accessed 3-17-21; *The Medical Letter* 62, 2020

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## When bone forming therapy is completed

Upon completion of a course of teriparatide, abaloparatide or romosozumab, patients should receive a one to two year course of a bisphosphonate or denosumab to preserve the new bone created and reduce the risk of subsequent fractures.

Greenspan, *S Menopause*, 2020; Leder, B, *J Bone Miner Res* 2019; ACCE, June 9, 2020

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## Average Monthly Wholesale Price of Bone Formation Agents

<u>Teriparatide (Lilly)</u>	\$4,531.20
Daily subcutaneous injections (24 months)	
<u>Biosimilar Teriparatide</u>	\$2,968.56
Daily subcutaneous injections (24 months)	
<u>Abaloparatide</u>	\$2,546.06
Daily subcutaneous injections (24 months)	
<u>Romsozumab</u>	\$2,318.94
Two subcutaneous injections monthly for 12 months	

Lexicomp, Accessed, 3-17-21

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## Lyles' Osteoporosis Practice Improvement Opportunities

- Some Radiologists do not diagnose vertebral deformities on lateral chest or abdominal radiographs.
- Some Interventional Radiologists perform kyphoplasties or vertebroplasties and without initiating therapy.
- Some Dentists or Oral Surgeons quote an incorrect risk of osteonecrosis of the jaw from antiresorptive therapy prior to dental procedures.

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“Degenerative change again seen in the spine”



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Radiologists underreport rates of prevalent vertebral fractures

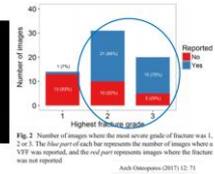
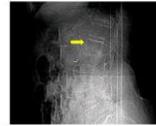


Fig 2. Number of images where the most severe grade of fracture was 1, 2, or 3. The blue part of each bar represents the number of images where a VCF was reported, and the red part represents images where the fracture was not reported. Arch Osteoporos (2017) 12: 71

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**Pain, Quality of Life, and Safety Outcomes of Kyphoplasty for Vertebral Compression Fractures (VCF)...**

Individuals with painful VCFs experienced symptomatic improvement compared with baseline with all interventions. The clinical importance of greater improvements with BK versus NSM is unclear, may be due to placebo effect, and may not counterbalance short-term AE risks. Outcomes appeared similar between BK and other surgical interventions. Well-controlled randomized trials comparing BK with sham would help resolve remaining uncertainty about relative benefits and harms of BK.

A task force of the American Society of Bone and Mineral Research reviewed 10 published trial with 1837 subjects comparing balloon kyphoplasty (BK) and nonsurgical management (NSM) after VCFs.

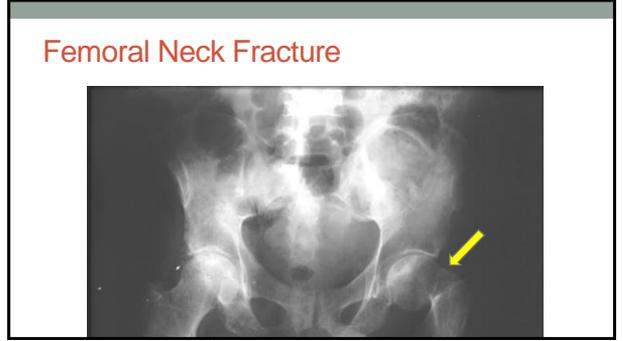
Rodriguez AJ. J Bone Mineral Research. 2017

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