Challenging Cases in Osteoporosis

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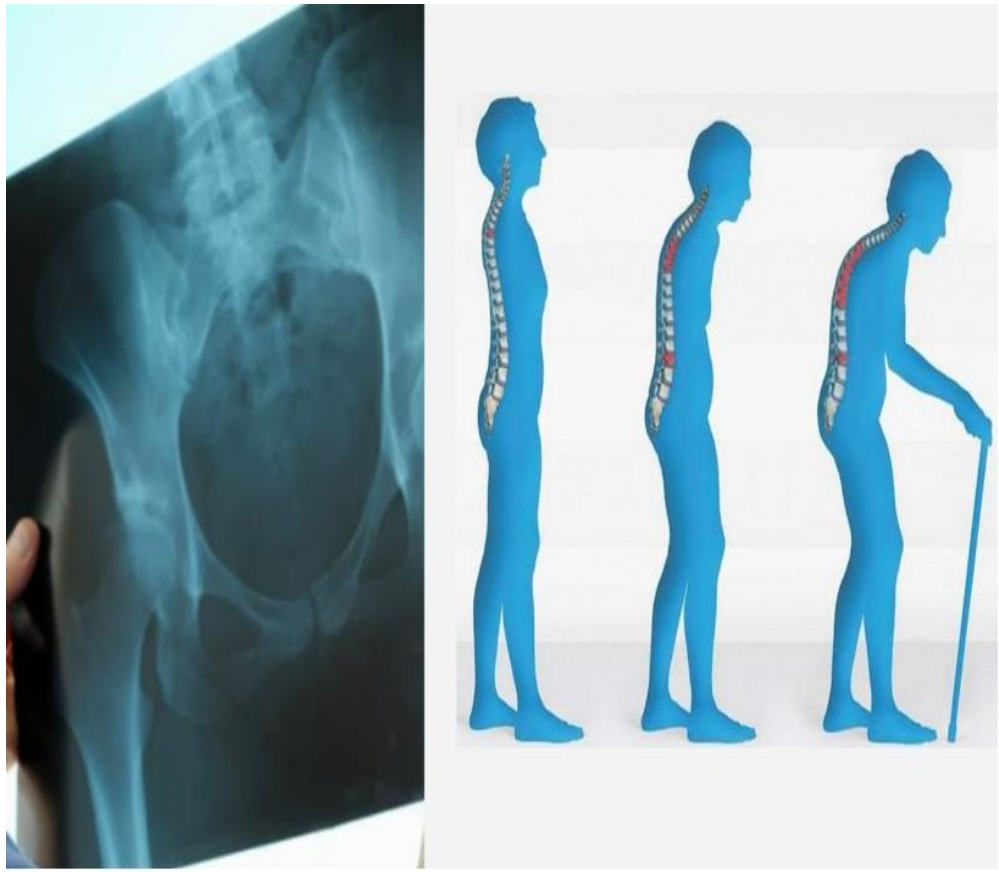

Case presentation

A healthy 70-year-old woman returns for followup of generalized osteoporosis.

She has been **on** Alendronate **, 70 mg by mouth weekly** with excellent compliance for 4 years as well as adequate calcium and vitamin D.

A repeat DXA shows stable values at all sites with T-scores of

Spine : –2.8 (8% increase since baseline)

F Neck: –3.0

T Hip: –2.8 (4.5% increase since baseline).

Case presentation

Two months after seeing you, she she has fallen and **fractured her left humerus**.

Laboratory work-up reveals normal CBC, Ca, Phos, creatinine, 25OHD, serum and urine protein electrophoresis, alk phos, and urinary calcium excretion.

A **fasting serum CTX** comes back in the *lowest 25th percentile* for premenopausal women.

What is the most appropriate management?

A. Stop Alendronate and begin Teriparatide.

B. Stop Alendronate and begin Zoledronic.

C. Stop Alendronate and begin Denosumab

D. Continue Alendronate for now.

What is Osteoporosis Treatment Failure?

Recommends that treatment be changed in any of the following circumstances:

- **Two or more** incident fragility fractures
- **One incident fracture** and elevated CTX or P1NP at baseline with no significant reduction during treatment, a significant decrease in BMD or both
- No significant decrease in serum CTX or P1NP **and** a significant decrease in BMD

What is Osteoporosis Treatment Failure?

- Fractures of the hand, skull, digits, feet and ankle are **not** fragility fractures
- A significant bone turnover marker response is a **decline of 25% from baseline for anti-resorptive treatments** and an increase for anabolic agents after 6 months

What is Osteoporosis Treatment Failure?

No evidence is available on the effectiveness of changing treatments when one has been deemed to have failed.

Three general rules recommended:

1. A weaker anti-resorptive is reasonably replaced by a **more potent drug** of the same class.
2. An oral drug is reasonably replaceable by an **injected drug.**
3. A strong anti-resorptive is reasonably replaceable **by an anabolic agent.**

Finding a Better Approach to Osteoporosis Management

Current clinical practice guidelines identify patients at high risk for fracture who are likely to benefit from pharmacological therapy and suggest ways to monitor for effectiveness of therapy.

There is no clear guidance on when fracture risk has been reduced to an acceptably low level.

Finding a Better Approach to Osteoporosis Management

- The current paradigm is—we're happy with the response to therapy; but, in **treat-to-target**—we're not so happy because we believe fracture risk is high

- In considering the treat-to-target approach for osteoporosis, a **patient could technically respond** to **treatment while still having an unacceptably high fracture risk**

Diez-Perez, et. al, Osteoporos Int, 23:2769-, 2012

Finding a Better Approach to Osteoporosis Management

As the ultimate goal of any management strategy in osteoporosis is the prevention of fracture, treating to target implies that there is a **surrogate measure** that confirms a lower fracture risk in the individual osteoporotic patient. Such surrogate measures might include

- BMD
- Bone Turnover Markers (BTMs)
- FRAX® probability

Bone Mineral Density
it's a less than ideal choice for a target

Despite the predictive value of BMD for fracture and the good correlation between fracture risk and BMD:

- Many **fractures arise in BMD that above the osteoporosis** definition
- It is unknown whether switching to another osteoporosis treatment to obtain even **greater increases in BMD** actually translates into **additional fracture benefit.**
- It is not possible to make even reasonably certain estimates in individuals that the **risk of fracture is decreased** to a specific target level with Increases in BMD.

redictive value of BMD for hip and other fractures. J Bone Miner Res. 2005 Jul;20(7):1185-94

Bone Turnover Markers

The decrease in fracture risk on anti-resorptive treatment is associated with significant reductions in BTMs but

- data from clinical and population based studies have proved **difficult to translate into accurate targets** for individuals and the use of BTM targets has not been widely translated into clinical practice.

Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards: osteoporos int 2011;22:391-420. Clin Biochem Rev

FRAX:
No interaction between antifracture efficacy and baseline risk

The FRAX tool produces an estimation of 10-year probability of fracture risk

- Impact of treatment on fracture risk may be difficult to detect by FRAX and that FRAX have a low sensitivity for reduction in fracture risk

Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The assessment of fracture risk. J Bone Joint Surg Am. 2010 Mar;92(3):743-53.

Treat to target as a strategy in osteoporosis

Treat-to-target (**goal-directed therapy**) has been proposed as a strategy to assist clinicians in selecting the most appropriate initial treatment for osteoporosis and guiding subsequent decisions to continue, change, or stop treatment

The **hallmark of successful treatment**, particularly for the patient, is the absence of an intercurrent fracture.

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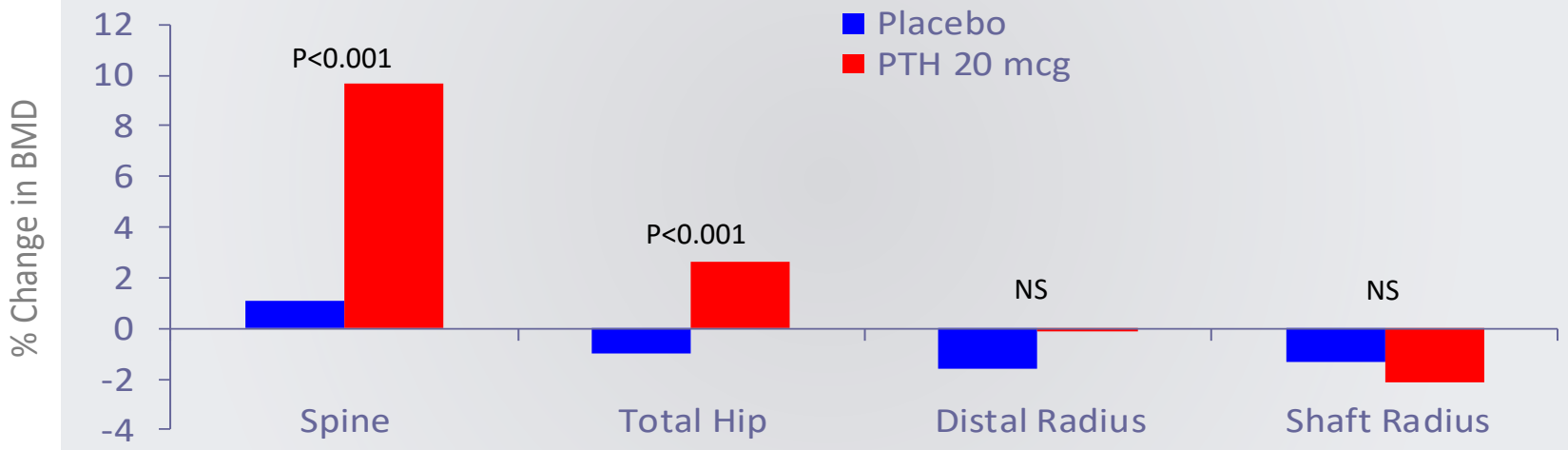
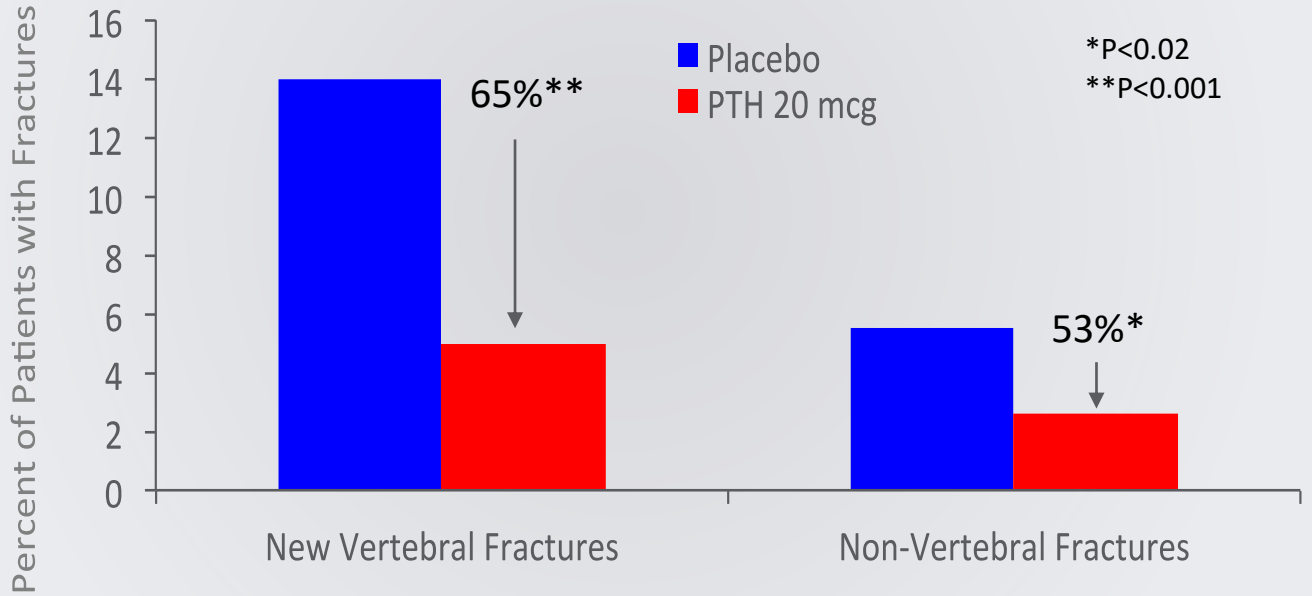
Teriparatide Increases BMD

RCT of 1637 women with postmenopausal osteoporosis and ≥1 vertebral fractures treated an average of 18 months with placebo, 20 µg PTH (1-34)

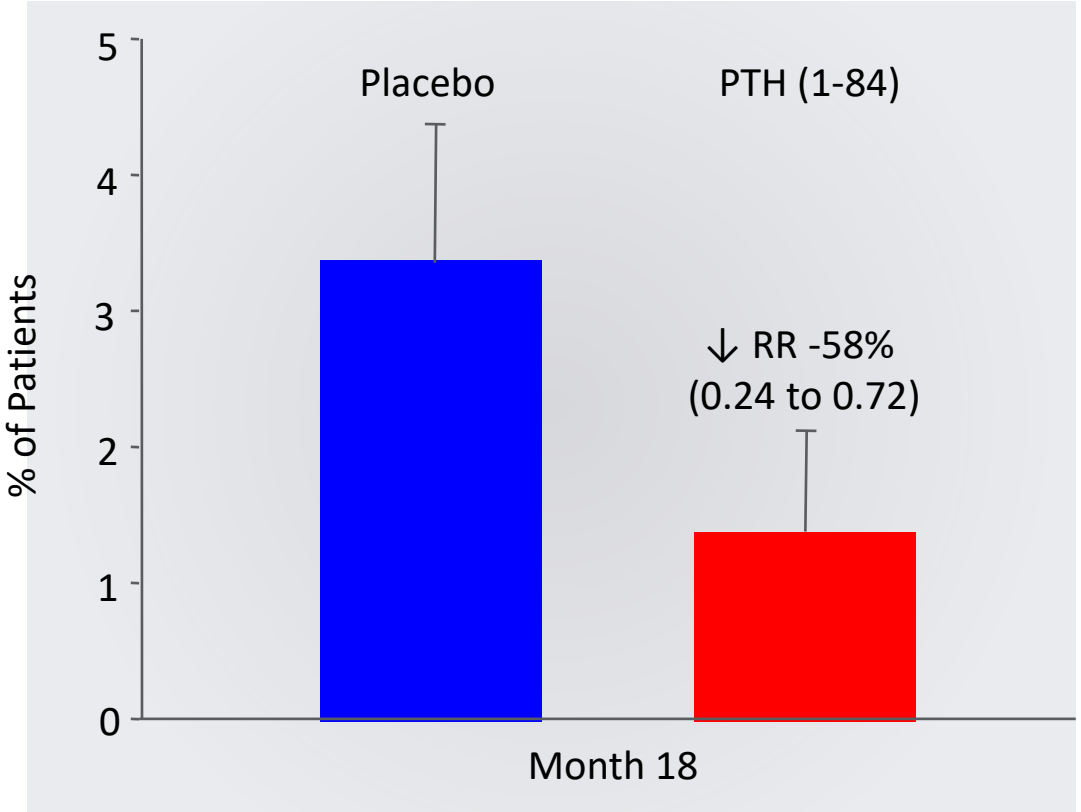


Teriparatide Reduces Fracture Risk

RCT of 1637 women with postmenopausal osteoporosis and ≥1 vertebral fractures treated an average of 18 months with placebo, 20 µg PTH (1-34)



Effect of PTH (1-84) on New or Worsened Vertebral Fractures



Marriott TB; Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med.

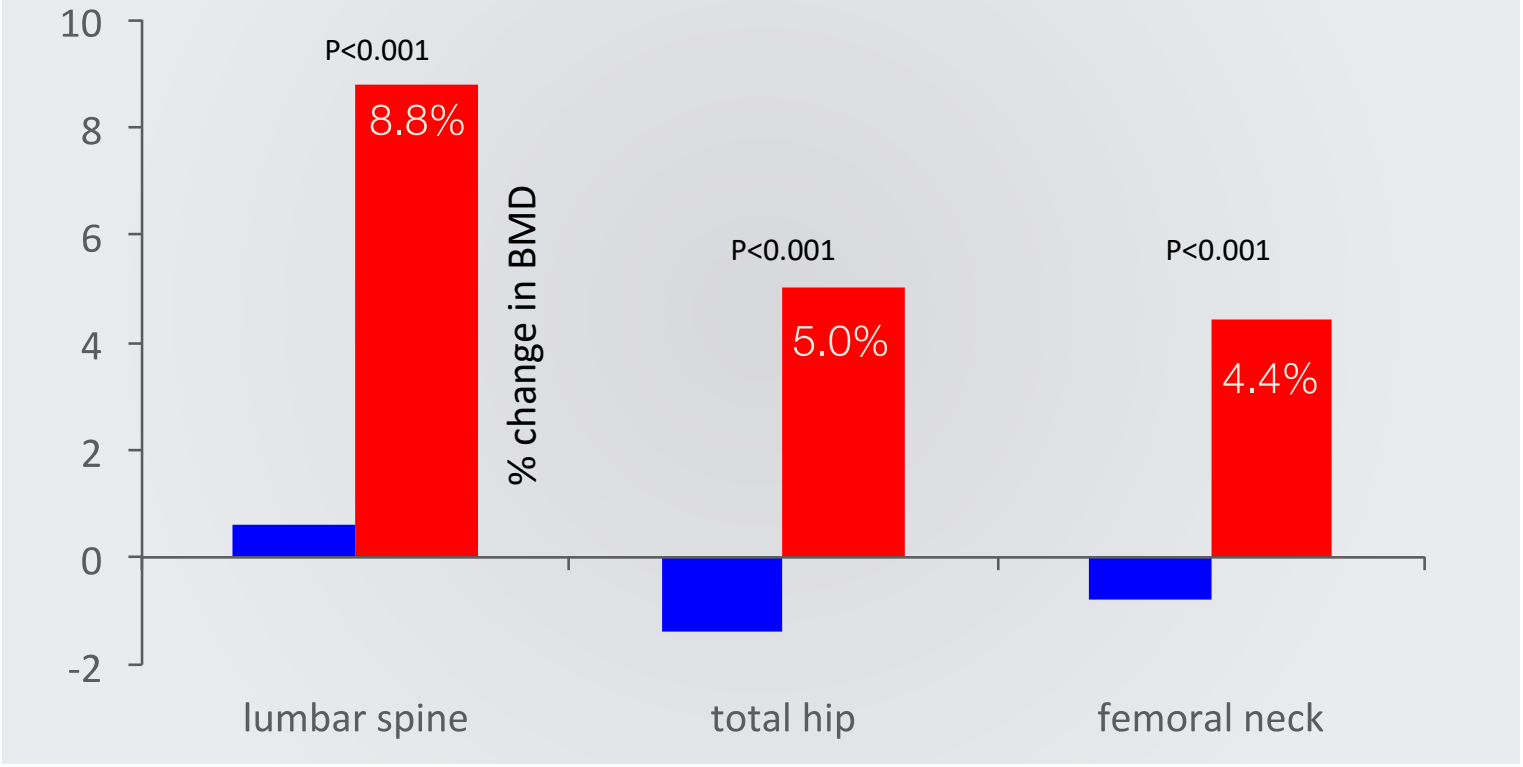
Need to Balance Benefits vs. Disadvantages

- **BENEFITS**
- increases BMD (spine and hip)
- decreases Fractures (spine & nonvertebral)

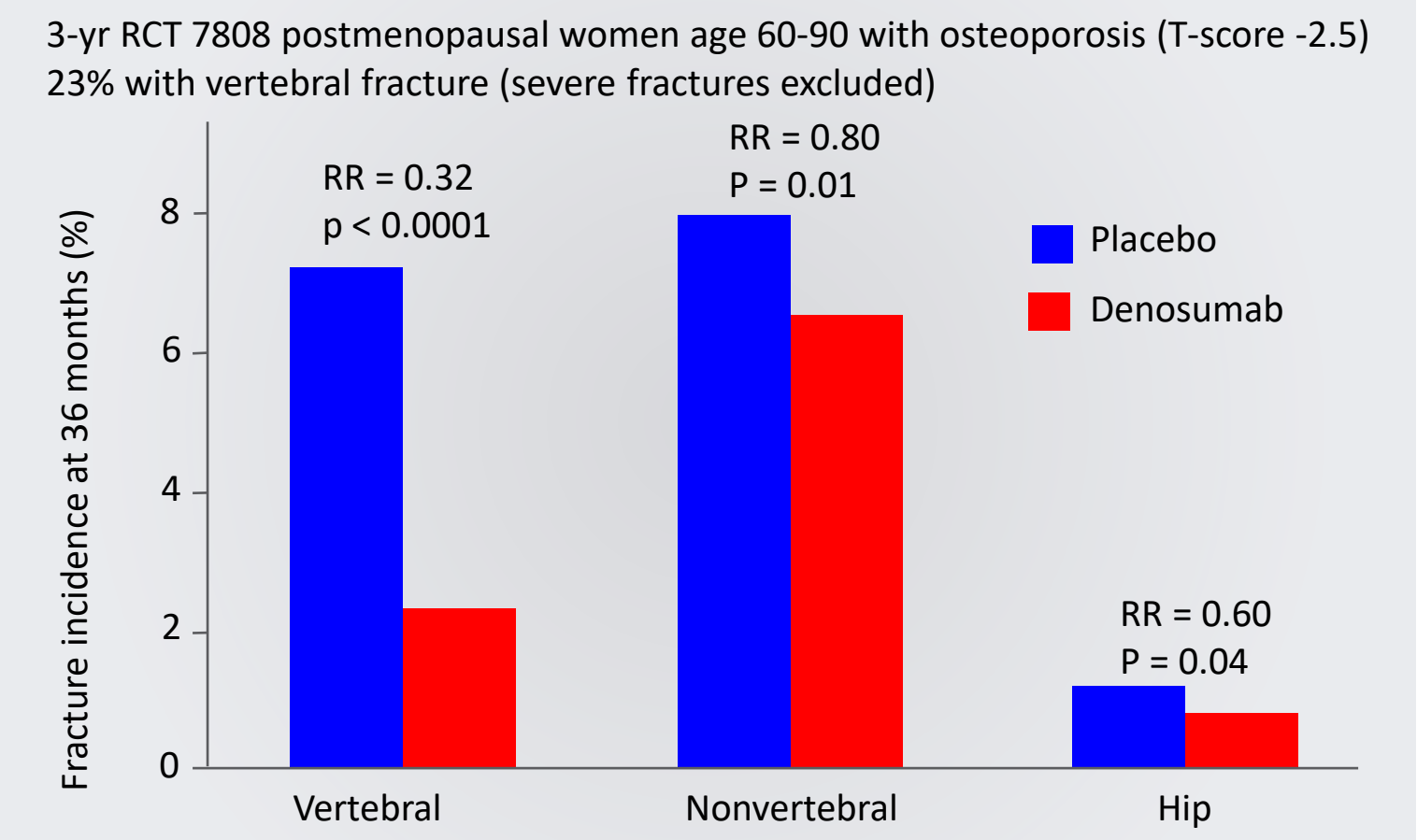
- **Disadvantages**
- limit of 2 years of therapy
- Daily Injection
- no proven benefit for hip Fx

Denosumab Increases BMD

3-yr RCT 7808 postmenopausal women age 60-90 with osteoporosis (T-score -2.5)
23% with vertebral fracture (severe fractures excluded)



Denosumab Reduces Fractures



Need to Balance Benefits vs. Disadvantages Denosomab

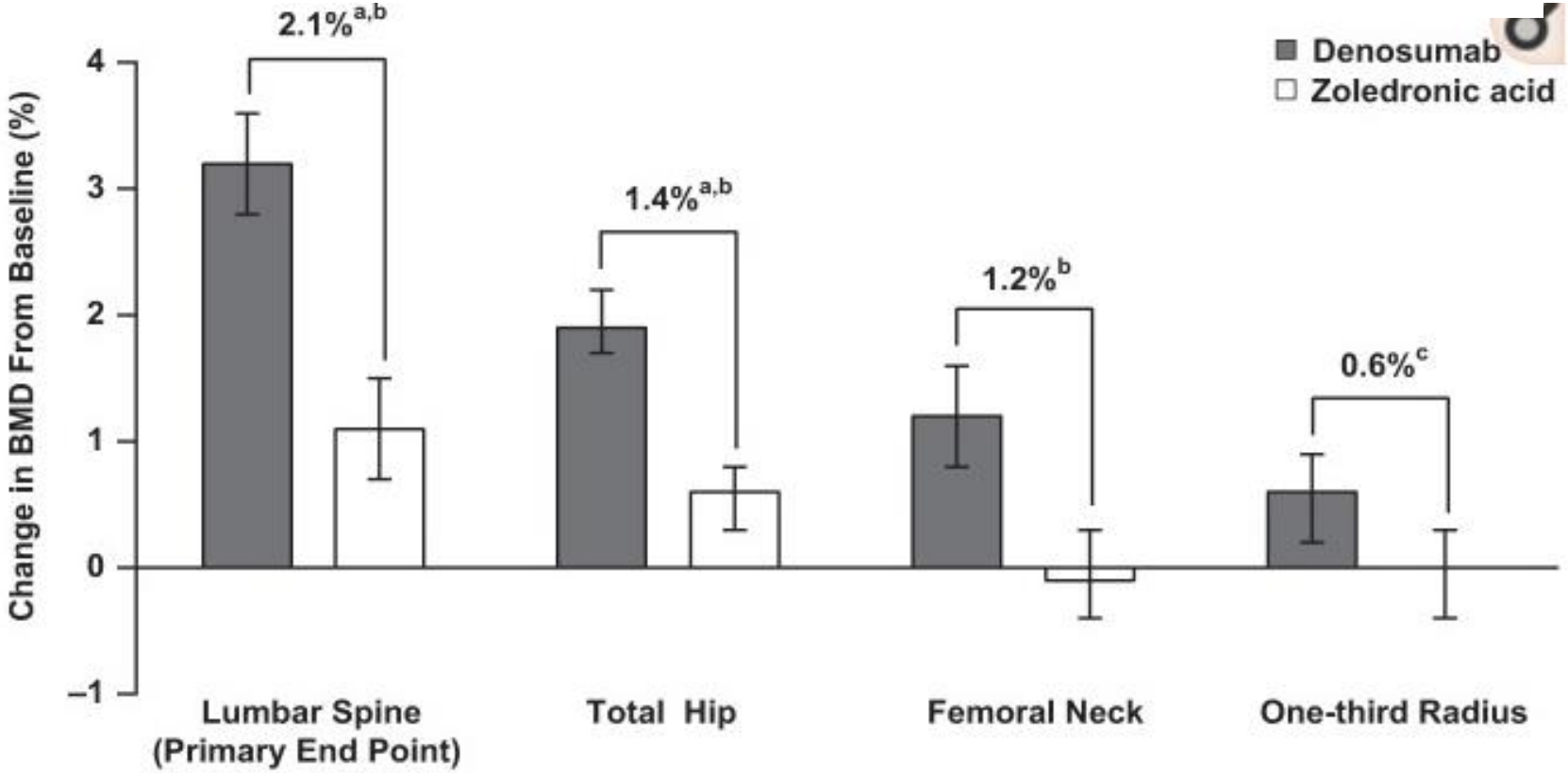
- **BENEFITS**
- **Increase BMD (spine and hip)**
- **Reduces Fracture (spine, hip & nonvertebral)**
- **SQ injection Q 6 m**

Disadvantages

In patients coming off of long-term ALN **no fracture outcomes**

Effect on bone resorption= **reversible**

Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates.



Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. The Journal of Clinical Endocrinology & Metabolism. 2016 Aug 1;101(8):3163-70.

Denosumab or Zoledronic Acid

After 8 years on DMAB, BMD continues to increase at both spine and hip while TH BMD plateaus at a lower level after only 4.5 years on ZA

Intravenous ZA will not increase BMD in patients already responding to ALN.

McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, Zhou W, Adera M, Davis J. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone1;41(1):122-8.

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Worldwide, an Osteoporosis-Related Fracture Occurs
Every 3 Seconds
Is Your Patient Next?