

**PRIORITY UPDATES FROM THE RESEARCH LITERATURE (PURLs)**

# Shoring Up Osteoporosis Management: A Fresh Start?

Noah Furr, MD, Ansley Ulmer, MD, and Brock Cardon, MD

**Anabolic bone agents, such as parathyroid hormone receptor agonists (teriparatide and abaloparatide) and sclerostin-inhibiting monoclonal antibody (romosozumab), are superior at preventing clinically significant fractures and/or vertebral fractures in women with and without severe osteoporosis compared with bisphosphonates. (J Am Board Fam Med 2024;37:490–493.)**

**Keywords:** Anabolic Bone Agents, Bisphosphonates, Fracture Prevention, Osteoporosis

## Strength of Recommendation: A

Based on a single systematic review with meta-analysis and meta-regression analysis.<sup>1</sup>

## Illustrative Case

A 67-year-old-woman with moderate osteoarthritis presents for follow up from her recent annual preventative medicine examination. A recent dual energy Radiograph absorptiometry (DEXA) scan was diagnostic for osteoporosis with T-scores of  $-2.8$  in her L-spine and  $-2.4$  in bilateral hips. Her calculated Fracture Risk Assessment Tool (FRAX) score predicts a 10-year risk of major osteoporotic fracture of 8.2%. After discussing osteoporosis treatment options, she agrees to pharmacologic treatment. In addition to conservative treatments and nutritional supplementation, what pharmacologic intervention will best reduce the risk

for future osteoporotic fractures in this postmenopausal patient?

## Clinical Context

Osteoporosis is the most prevalent metabolic bone disease worldwide and in the US, claiming fragility fractures in approximately 50% of all women and 20% of all men  $>50$  years of age within the US within their lifetime.<sup>2</sup> Approximately 54 million individuals were affected by low bone mass and osteoporosis in the US in 2010, estimated only to increase as the US population ages, with costs associated with osteoporosis projected to be upward of \$25.3 billion in 2025 alone.<sup>3,4</sup>

The World Health Organization (WHO) defines osteoporosis via a DEXA measurement of bone mineral density (BMD) of either the hip or the spine  $\geq 2.5$  standard deviations below that of healthy sex-adjusted younger adults. This can then be subdivided into primary and secondary causes, primary being menopause and age as main contributors, and secondary stemming from a clear alternate etiology. Considering the subtle and insidious development of osteoporosis, asymptomatic screening is essential in preventing significant morbidity and disability from fragility fractures.<sup>5</sup> The US Preventative Services Task Force (currently under review for edits) recommends all women  $\geq 65$  and all women  $\leq 65$  “at increased risk of osteoporosis” be screened with DEXA imaging with a “Grade B” recommendation, but insufficient data to recommend globally screening men as of 2018.<sup>6</sup>

The 2 main categories of osteoporotic pharmacotherapies are antiresorptive medications (to include

This article was externally peer reviewed.

Submitted 12 February 2024; accepted 19 February 2024.

From the Nellis Family Medicine Residency, Nellis AFB, Las Vegas, NV.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the US Air Force at large, or the Department of Defense.

Funding: None.

Conflict of interest: The authors report no conflict of interest.

FPIN Editor: Rebecca Mullen, MD, MPH, University of Colorado Program, Denver, CO.

Corresponding author: Brock Cardon, MD, Mike O’Callaghan Military Medical Center Family Medicine Residency, 4700 N. Las Vegas Blvd, Nellis AFB, NV 89191 (E-mail: brock.e.cardon.mil@health.mil).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.

bisphosphonates, denosumab, estrogen replacement therapy, and selective estrogen receptor modulators such as raloxifene hydrochloride) and anabolic agents (such as parathyroid receptor agonists and the sclerostin inhibitor, romosozumab).<sup>7</sup> In addition to increasing BMD, treatment is aimed at preventing osteoporotic fragility fractures. Treatment should also be initiated after an osteoporotic fragility fracture occurs, a point of care which primary care physicians seldom initiate.<sup>8</sup>

In women at very high risk of fracture, anabolic agents show improved fracture risk reduction compared with antiresorptive medications.<sup>7</sup> In contrast to this emerging evidence, for average risk patients, current clinical practice guidelines of various organizations either support use of bisphosphonates as first-line therapy for primary osteoporosis followed by denosumab, or recommend individualized care within available evidence-based medications.<sup>2,9,10</sup> As such, anabolic agents are only explicitly recommended conditionally in the context of women with primary osteoporosis who are considered “very high-risk” for fracture.<sup>10</sup>

This systematic review, network meta-analysis, and meta-regression analysis compares the safety and efficacy of current osteoporosis therapies to each other and placebo, with evidence to extend anabolic agent use to include all postmenopausal women with osteoporosis regardless of baseline risk factors.<sup>1</sup> This analysis is germane to family physician as we screen for osteoporosis and often initiate pharmacotherapy for fragility fracture prevention.

## Methods

This article was identified as a potential PURL through the standard systematic methodology.<sup>11</sup> An additional literature search was conducted by searching UpToDate and USPSTF with the terms “osteoporosis” and “osteoporosis treatment guidelines” to find additional literature to place this research into the context of current clinical practice.

## Study Summary

This 2023 systematic review, network meta-analysis and meta-regression analysis (69 trials,  $n > 80,000$ ) assessed the comparative effectiveness of osteoporosis

treatments on reducing fracture risk in postmenopausal women. Included studies were randomized controlled trials that included interventions with antiresorptive and anabolic agents. Studies with postmenopausal women, without age restriction, that measured bone mineral density or fractures were included in the analysis. Studies comparing effects with placebo or with an active comparator met eligibility criteria. Trials with sequential treatment or combination treatment were considered and concomitant use of calcium and vitamin-D supplementation was allowed. No restrictions were set on dose or duration of treatment. However, studies completed in exclusively Asian settings were excluded due to differences in dosing guidelines in Asia from the rest of the world. The primary outcome was incidence of all clinical fractures (excluding fingers and toes). Secondary outcomes were vertebral, nonvertebral, hip, and major osteoporotic fractures, as well as all-cause mortality, adverse events, and serious cardiovascular events.

Results illustrated benefit with bisphosphonates (absolute risk reduction [ARR], 14 per 100; 95% CI 7 to 21), parathyroid hormone receptor agonists (PTHrA) (ARR, 35 fewer per 1000; 95% CI, 3 to 39) and romosozumab (ARR, 9 per 1000; 95% CI, 3 to 13) compared with placebo for reducing clinical fractures but did not demonstrate benefit for denosumab or selective estrogen receptor modulators. Network meta-analysis illustrated that bisphosphonates were less effective at reducing clinical fractures compared with PTHrA (odds ratio [OR], 1.5; 95% CI, 1.1 to 2). Denosumab was less effective at reducing clinical fracture risk than PTHrA (OR, 1.9; 95% CI, 1.2 to 2.9) and romosozumab (OR, 1.6; 95% CI, 1 to 2.4).

Secondary outcomes demonstrated that all treatments had protective effects compared with placebo for vertebral fractures. However, in head-to-head comparisons, denosumab (OR, 1.8; 95% CI, 1.1 to 2.9), PTHrA (OR, 2.5; 95% CI, 1.8 to 3.5), and romosozumab (OR, 2.1; 95% CI, 1.4 to 3.0) were more effective than oral bisphosphonates in preventing vertebral fractures. Romosozumab was the only agent more effective than bisphosphonates at preventing hip fracture (OR, 1.6; 95% CI, 1.1 to 2.4). Antiresorptive treatments showed greater reduction of clinical fractures compared with placebo with increasing mean age (studies = 17;

$\beta = 0.98$ , 95% CI 0.96-0.99); otherwise, baseline risk indicators did not affect treatment efficacy. Network analysis could not be completed for nonvertebral fractures.

### What Is New

Current clinical guidelines recommend initial pharmacologic treatment to reduce the risk of fractures in postmenopausal women with primary osteoporosis. Guidelines suggest the use of anabolic agents, followed by bisphosphonate therapy, to reduce the risk of fractures only in women with primary osteoporosis and very high risk of fracture. This study's findings suggest using anabolic agents as initial therapy for osteoporosis in postmenopausal women is more effective at preventing clinical or vertebral fractures, regardless of baseline risk indicators. From a clinical standpoint, this systematic review does not support limiting anabolic agents to only patients at very high risk of fractures.

### Caveats

This study relied on published mean baseline characteristics rather than individual patient data which may increase the risk of aggregation bias. Network meta-analysis and meta-regression analysis were limited due to a large amount of missing data on outcomes and baseline risk indicators and overlap of outcomes and treatment groups. Exclusion of all studies conducted in exclusively Asian settings may affect the generalizability of these recommendations to postmenopausal Asian women. Lastly, assessment of denosumab's effectiveness may be limited by exclusion of the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial, which ostensibly brought denosumab into broad clinical practice and FDA approval, due to it not meeting this meta-analysis's inclusion criteria.

### Challenges to Implementation

Current first line treatments for postmenopausal women with nonsevere osteoporosis, such as bisphosphonates, cost significantly less and have more long-term safety data than anabolic agents. Though this systematic review does not support limiting anabolic agents to only patients at very

high-risk of fractures, these factors will need to be considered by physicians and researchers and may slow implementation of these findings. Direct cost-comparison analyses with current pharmaceutical prices are needed.

To see this article online, please go to: <http://jabfm.org/content/37/3/490.full>.

### References

1. Händel M, Cardoso I, von Bülow C, et al. Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials. *BMJ* 2023;381: e068033
2. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2022;33:2049–102.
3. "Epidemiology: USA." International Osteoporosis Foundation website citing Wright NC, et al., The recent prevalence of osteoporosis and low bone mass at the femoral neck or lumbar spine. *J Bone Miner Res* 2014;29:2520–6. Available at: <https://www.osteoporosis.foundation/facts-statistics/key-statistic-for-north-america>. Accessed on November 13, 2023.
4. "Epidemiology: USA." International Osteoporosis Foundation website citing Berge R, et al. Incidence and Economic Burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 2007;22:465–75. Available at: <https://www.osteoporosis.foundation/facts-statistics/key-statistic-for-north-america>. Accessed on November 13, 2023.
5. Lorentzon M, Cummings SR. Osteoporosis: the evolution of a diagnosis. *J Intern Med* 2015;277: 650–61.
6. Viswanathan M, Reddy S, Berkman N, et al. Screening to prevent osteoporotic fractures: updated evidence report and systematic review for the US Preventative Services Task Force. *JAMA* 2018; 319:2532–51.
7. Akkawi I, Zmerly H. Osteoporosis: current concepts. *Joints* 2018;6:122–7.
8. Bell A, Kendler D, Khan A, et al. A retrospective observational study of osteoporosis management after a fragility fracture in primary care. *Arch Osteoporos* 2022;17:75.
9. Ayers C, Kansagara D, Lazur B, et al. Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: a living systematic review and network meta-analysis for the American College of Physicians. *Ann Intern Med* 2023;176:182–95.

10. Qaseem A, Hicks L, Etzeandia-Ikobaltzeta I, Clinical Guidelines Committee of the American College of Physicians, et al. Pharmacologic treatment of primary osteoporosis or low bone mass to prevent fractures in adults: a living clinical guideline from the American College of Physicians. *Ann Intern Med* 2023;176:224-38.
11. The Priority Updates from the Research Literature (PURLs) methodology. Available at: <https://www.jabfm.org/content/jabfp/37/2/165.full.pdf>.