Comparative Effectiveness of Pharmacologic Treatments to Prevent Fractures: Is This All We Need to Know?

Nearly 75% of all osteoporotic fractures occur among adults aged 65 years or older, contributing significantly to illness and death in the senior population. After age 75 years, hip fractures are the most frequent, and severe fractures cause permanent functional impairment in 50%, loss of autonomy in 30%, and death in 15% to 20% of cases. The exponential increase in hip fractures after age 75 years translates into an estimated 1 in 3 women and 1 in 6 men who will have a hip fracture by their 90th year. Likewise, other osteoporotic fractures, including those of the spine, show a steep increase with age (1).

The strong effect of age on fracture incidence and the aging of the populations in most Western countries warrant the inclusion of persons aged 80 years or older in clinical trials of pharmacologic treatments for the prevention of fractures. However, to date, few clinical trials have included very elderly persons, and in clinical practice, they rarely receive these treatments (2). In general, the systematic exclusion of very elderly persons from clinical trials is driven by the concern that comorbid conditions may camouflage a benefit of the intervention or that medication risks may be increased in persons with an increased likelihood of impaired kidney and gastrointestinal function. For the common pharmacologic treatments to prevent fractures (bisphosphonates, denosumab, and teriparatide), competing nonskeletal risk factors for fractures, such as gait impairment and falls, are a concern because they are not addressed by these treatments. Of note, the primary risk factor for hip fractures and other fragility fractures are falls (3).

The Hip Intervention Program trial with risedronate tested this concern (4) by recruiting a priori 2 groups of postmenopausal women: women aged 70 to 79 years primarily selected on the basis of osteoporosis documented by dual-energy x-ray absorptiometry and women aged 80 years or older selected primarily for the prevalence of nonskeletal risk factors. In both groups combined, a 30% significant reduction of hip fracture was found for risedronate compared with placebo. However, this effect was primarily driven by the first group, which had a significant 40% reduction in hip fracture risk. In the second group, no significant reduction in hip fracture risk with risedronate was demonstrated. Zoledronic acid, a bisphosphonate administered annually, was tested in a subsequent trial, the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Recurrent Fracture Trial, among persons aged 50 to 85 years who had surgical hip fracture repair. One half of the recruited patients were aged 75 years or older, and the study showed a significant 35% reduction in any new clinical fracture. From a clinical perspective, patients in this trial were roughly 10 years younger and had a lower rate of refracture than would be expected in this patient group, leaving clinicians with some uncertainty about the efficacy of the drug in representative patients with hip fractures aged 80 years or older.

Only 30% or fewer of the participants in the pivotal trials with denosumab (5) and teriparatide (6) were postmenopausal women aged 75 years or older, and the prevalence of nonskeletal risk factors was not reported. For both trials, post hoc analyses by age were published by Boonen and colleagues, suggesting a significant benefit of denosumab among women aged 75 years and older (7) or the lack of an interaction by age for teriparatide (8). One clinical trial among osteoporotic men tested fracture prevention with zoledronic acid, but only 18% of its participants were aged 75 years or older (9), and nonskeletal risk factors were not provided.

In a systematic review of the comparative effectiveness of pharmacologic treatments to prevent fractures reported in this issue, Crandall and colleagues (10) point out that too few studies provide head-to-head comparisons of drugs to treat osteoporosis. We agree with this statement but challenge their otherwise-unrestricted conclusion that there is good evidence that bisphosphonates, denosumab, and teriparatide reduce fracture risk. We suggest that this conclusion may not apply to persons aged 75 years or older and especially not to those aged 80 years or older with nonskeletal risk factors for fracture. Because these patients sustain most fragility fractures, their insufficient representation in current clinical trials of pharmacologic treatments against fractures warrants emphasis.

Physicians and patients are concerned about rare major side effects of pharmacologic treatments to prevent fractures. The current review provides practical, useful estimates of the magnitude of effect on the basis of the number needed to treat for each drug attached to a time span, as well as the number of expected individual adverse events per number of persons treated. These findings and their clear reporting lay the groundwork for informed decision making for patients with osteoporosis.

Crandall and colleagues' review provides strong evidence that among postmenopausal women with established osteoporosis, 60 to 89 patients need to be treated with a bisphosphonate, denosumab, teriparatide, or raloxifene to prevent 1 vertebral fracture over 1 to 3 years of treatment, and 50 to 60 patients need to be treated with a bisphosphonate, denosumab, or teriparatide to prevent 1 nonvertebral fracture. If the treatment is a bisphosphonate, low-quality evidence suggests that 2 to 100 of 100 000 treated patients will sustain an atypical subtrochanteric fracture and that 3 to 430 of 10 000 treated patients will develop

osteonecrosis of the jaw. For denosumab, moderate-quality evidence shows that 1 of 118 treated patients will develop an infection. Although this is helpful information to guide clinicians and their patients, we believe that they should recognize that these conclusions may not apply to patients aged 75 years or older, and especially not to those aged 80 years or older with nonskeletal risk factors for falls. Such patients are insufficiently represented in the clinical trials of pharmacologic treatments for fracture prevention included in this careful evidence review.

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References

1. **Bischoff-Ferrari H.** Fragility fractures: the future epidemic and its challenges. Skeletal Radiol. 2013;42:161-3. [PMID: 23188496] doi:10.1007/s00256-012-1549-4
2. **Freedman KB, Kaplan FS, Bilker WB, Strom BL, Lowe RA.** Treatment of osteoporosis: are physicians missing an opportunity? J Bone Joint Surg Am. 2000;82-A:1063-70. [PMID: 10954094]
3. **Nevitt MC, Cummings SR.** Type of fall and risk of hip and wrist fractures: the study of osteoporotic fractures. The Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 1993;41:1226-34. [PMID: 8227898]
4. **McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al; Hip Intervention Program Study Group.** Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333-40. [PMID: 11172164]
5. **Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al; FREEDOM Trial.** Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756-65. [PMID: 19671655] doi:10.1056/NEJMoa0809493
6. **Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al.** Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-41. [PMID: 11346808]
7. **Boonen S, Adachi JD, Man Z, Cummings SR, Lippuner K, Törring O, et al.** Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. J Clin Endocrinol Metab. 2011;96:1727-36. [PMID: 21411557] doi:10.1210/jc.2010-2784
8. **Boonen S, Marin F, Mellstrom D, Xie L, Desaiah D, Krege JH, et al.** Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric perspective. J Am Geriatr Soc. 2006;54:782-9. [PMID: 16696744]
9. **Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, et al.** Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012;367:1714-23. [PMID: 23113482] doi:10.1056/NEJMoa1204061
10. **Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, Booth MJ, et al.** Comparative effectiveness of pharmacologic treatments to prevent fractures. An updated systematic review. Ann Intern Med. 2014;161:711-23. doi:10.7326/M14-0317

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