Zoledronate Prevents Fracture in Postmenopausal Women with Osteopenia

Physician Focus Series
What are the criteria for osteoporosis?

Osteoporosis is a systemic skeletal condition characterized by loss of bone mass, deterioration of bone microarchitecture, and reduced bone strength, all of which increase the risk of fractures.¹ Osteoporosis is generally designated when bone mineral density DEXA measurements show a T score of − 2.5 or less at the spine or hip, or when a fragility fracture has occurred.² The category of osteopenia is defined exclusively in terms of bone mineral density using a T-score range between − 1 and − 2.4 SD below the mean of peak bone mass in healthy young women.³

Who should be treated to prevent fractures?

Fracture risk is sufficiently high in most postmenopausal women with osteoporosis (T scores − 2.5 or lower or those who have experienced fragility fractures) to warrant treatment. An extensive body of high-quality evidence shows that pharmacologic treatment using antiresorptive or anabolic drugs in postmenopausal women who have osteoporosis is effective for preventing further bone loss and reducing the risk for initial or subsequent fractures.⁴ However, data on drug therapy to prevent fractures in women with osteopenia has been inconsistent⁵,⁶ and this, along with hesitation about long-term adverse effects of bisphosphonates,⁷ has led to equivocal endorsement of treating low bone mass alone.⁸ While the incidence of fractures in women with osteopenia is lower than that of patients with osteoporosis, more than 50% of fragility fractures occur in women with bone mineral density scores within the “osteopenia” range.⁹ In fact, solely from a total prevalence standpoint, most fractures occur in women with osteopenia.¹⁰

Thus, to be useful in preventing the majority of fractures, treatment should be considered for some patients whose bone mineral density measurements fall within the osteopenia range.

What new evidence exists supporting treatment of osteopenia?

Recently published results of a trial of bisphosphonate therapy demonstrating fracture reduction in women with osteopenia has the potential to change practice. A double-blind randomized controlled trial involving 2000 postmenopausal women with osteopenia compared the incidence of fracture after receiving IV zoledronate or placebo at 18-month intervals.¹¹ Participants in both groups were considered at relatively high risk for a future fracture based on the median FRAX (Fracture Risk Assessment Tool) score, which predicted a 10-year risk of osteoporotic fracture at 12% and 10-year risk of hip fracture of 2.3%. The women were followed for 6 years for the primary endpoint, which was time to first occurrence of a fragility fracture. In an intention-to-treat analysis, 122 women assigned to zoledronate experienced a fracture versus 190 on placebo, corresponding to a 37% relative risk reduction (hazard ratio with zoledronate 0.63; 95% CI, 0.50-0.79; P < .001). The number needed to treat with zoledronate to prevent one fracture was 15. Women who received zoledronate had a lower risk of nonvertebral fragility fractures, symptomatic fractures, vertebral fractures, and height loss. Osteonecrosis of the jaw and atypical femur fractures are rare adverse effects that have previously been associated with bisphosphonate use; neither were reported in any participants.
The study is of interest to practicing clinicians for a few reasons:

- First, this study was conducted in a population of women defined as having osteopenia, for whom drug therapy was successful not only in increasing bone mass but also in reducing vertebral and nonvertebral fractures. Statistically, the benefit of treatment was substantial, and particularly meaningful because the endpoint used in the trial extends the benefit to fracture outcome. On a relative basis, the degree of benefit is comparable to that seen with use of zoledronate given yearly for the treatment of osteoporosis.\textsuperscript{12, 13}

- Second, benefits were observed using an infrequent dosing regimen of 18-month intervals, and this, along with the IV route of administration, favors convenience and facilitates compliance with therapy.

- Third, serious adverse effects were uncommon over the lengthy trial, which can relieve safety concerns and mitigate inertia that often restrains clinicians from prescribing therapy, particularly with bisphosphonates. Interestingly, an analysis of the occurrence of adverse effects showed that women in the treatment group appeared to gain protection against cancer and cardiovascular events, and a trend toward reduced mortality. These were not prespecified primary endpoints, however, and require additional trials to confirm and fully explore the nature of these associations.

How can clinicians apply these results to patient care?

With these current data, clinicians may wish to reconsider the role of drug therapy for low bone mass in some postmenopausal women whose bone mineral density values fall short of the traditional osteoporosis T-score range, especially if fracture risk is high due to other conditions. The newly available evidence substantiates the benefit of such treatment in a potentially broad group of women but should not encourage indiscriminate prescription of bisphosphonates or other osteoporotic drugs to all patients with osteopenia. In addition to T scores, decisions on when to initiate therapy are based on a combination of both bone mineral density scores and an assessment of clinical risk factors.\textsuperscript{14-17} Selection of the most appropriate agent and duration of therapy require consideration as well. The present study offers formal evidence that starting zoledronate therapy in older postmenopausal women with osteopenia—perhaps earlier on—can reduce fractures in that population. Armed with the evidence, clinicians can proceed confidently with an individualized risk assessment and engage in a shared decision-making discussion with their patients regarding expectations, benefits, and harms of treatment.\textsuperscript{18, 19}

For more information, see the \textbf{Osteoporosis Clinical Overview} in ClinicalKey.
References


