Fracture Prevention with Zoledronate in Older Women with Osteopenia

TO THE EDITOR: In the trial reported by Reid et al. (Dec. 20 issue),[1] zoledronic acid led to a lower risk of fragility fractures than placebo among postmenopausal women with osteopenia. We have concerns about the conclusion.

First, nonvertebral fractures were seen in 24% of the participants at screening. A clinical diagnosis of osteoporosis includes the presence of fragility fractures.[2,3] Thus, more than 24% of the participants actually had osteoporosis rather than osteopenia.

Second, if the 10-year risk of major osteoporotic fractures among women with osteopenia is estimated to be 3.9% by the Fracture Risk Assessment Tool (FRAX), a hazard ratio of 0.65 with zoledronate provides a number needed to treat of 74 to prevent the occurrence of a single fragility fracture. We do not think that the absolute effect is similar in higher-risk patients (i.e., those with osteoporosis). Would the authors provide data regarding the incidence of fragility fractures among patients who completely fulfilled the diagnosis of osteopenia?

Third, additional baseline characteristics are important considerations in evaluating the probability of falls. These characteristics include cataracts, glaucoma, dysuria, neurologic disorders (e.g., stroke, Parkinson's disease, and epilepsy), anemia, arrhythmia, frequency of previous falls, and measures of activities of daily living (e.g., with the Barthel scale), all of which might be confounders.

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No potential conflict of interest relevant to this letter was reported.

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1. Reid IR, Horne AM, Mihov B, et al. Fracture prevention with zoledronate in older women with osteopenia. N Engl J Med 2018;379:2407-16.
2. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group. World Health Organ Tech Rep Ser 1994;843:1-129.
3. Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporos Int 2014;25:1439-43.

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TO THE EDITOR: The osteoporotic fracture rate at 6 years was much higher than expected in this trial. Although the baseline expected osteoporotic fracture rate at 10 years was approximately 12.0% in each group, after 6 years of follow-up, 12.2% of the patients in the zoledronate group and 19.0% of those in the placebo group had an osteoporotic fracture (derived from data regarding the number of women with fracture, as presented in Table 2 of their article). However, this was not true for hip fractures, which occurred at a rate that was close to the one expected. A recent study showed an increased risk of falls among older adults receiving doses of vitamin D as low as 60,000 IU per month for 12 months.[1] Given the fact that patients in the two trial groups received 50,000 IU of vitamin D monthly, the increased incidence of falls might have led to increased fracture rates in the two groups. It would be helpful for the authors to present the baseline and follow-up rates of falls, as discussed in their protocol. Caution is appropriate before zoledronate is prescribed in older women with osteopenic bone mineral density values at the hip, because the reportedly lower rate of fractures with zoledronate than with placebo was higher than expected.

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1. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 2016;176:175-83.

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TO THE EDITOR: The results of the trial conducted by Reid et al. are exciting with regard to the lower risk of fracture and may have considerable bearing on morbidity and quality of life in the elderly population. However, clarifications regarding certain aspects of this trial are warranted.

First, the trial design was not pragmatic because it excluded the dominant population at risk for fractures, such as patients with systemic illness, those with metabolic bone disease, and those who use glucocorticoids. Hence the external validity of these data remain questionable.

Second, it would be interesting for the authors to assess the FRAX scores (if available) to know the baseline fracture-risk difference between the two groups. Finally, it would be informative if the authors provided a separate assessment using the T score at the spine, which may be discordantly low in postmenopausal women owing to an estrogen-deficient state, and the difference between the two groups regarding the spine–hip T-score difference, which is a FRAX-independent risk factor for major osteoporotic fracture.[1]

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1. Leslie WD, Kovacs CS, Olszynski WP, et al. Spine-hip T-score difference predicts major osteoporotic fracture risk independent of FRAX(®): a population-based report from CAMOS. J Clin Densitom 2011;14:286-93.

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THE AUTHORS REPLY: Although the women in the trial all had bone densities indicating osteopenia, there was a substantial diversity in baseline risk factors for fracture. The correspondents ask whether particular characteristics identify specific groups of women who benefit more than others from the use of zoledronate. In brief, no interaction between baseline characteristics and the antifracture efficacy of zoledronate was seen (data not shown). Specifically, antifracture efficacy was independent of age (P=0.58) and baseline bone density (P=0.54 for hip; P=0.97 for spine). Thus, zoledronate leads to a lower risk of fracture than placebo among women with T scores in the range of –1.0 to –1.5 (hazard ratios for fragility fracture, 0.52 to 0.58).

Suzuki et al. question whether zoledronate prevents fractures in patients with osteopenia. Our article states that a lower risk of fracture is present among women who have osteopenia according to the most conservative definition, which also excludes women with previous fractures (hazard ratio for nonvertebral fragility fracture vs. placebo, 0.57; 95% confidence interval, 0.37 to 0.86). In this cohort, the risk according to FRAX, shown in Table 1 of our article, underestimated the risk of fragility fractures but overestimated the gradient of risk across the cohort, so we find similarly lower fracture numbers with zoledronate than with placebo across the cohort and a lower number needed to treat than theoretical considerations would have predicted.

Tufan hypothesizes that the vitamin D supplement that was used in our trial may have increased the risk of falls and the incidence of fractures. We think that this is unlikely, since the incidence of hip fracture in the placebo group was as predicted, so the likely explanation for the higher number of fragility fractures is that we used a broader definition of fragility fracture than FRAX does or that FRAX is poorly calibrated for fragility fractures in this particular population. Since vitamin D was given to both groups, this suggestion does not cast doubt on the antifracture efficacy of zoledronate. A total of 21% of the women had a history of falls in the year before recruitment — a percentage that was similar in the two groups and remained unchanged in the last year of the trial.

Contrary to what Chattopadhyay and Jain suggest, most fractures in older women occur in those who do not have overt bone disease or osteoporotic bone density.[1,2] Our trial establishes the antifracture efficacy of a bisphosphonate in that population. The efficacy of bisphosphonates in patients with osteoporosis is already well established.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Tei RMH, Ramlau-Hansen CH, Plana-Ripoll O, Brink O, Langdahl BL. OFELIA: prevalence of osteoporosis in fragility fracture patients. Calcif Tissue Int 2019;104:102-14.
2. Trajanoska K, Schoufour JD, de Jonge EAL, et al. Fracture incidence and secular trends between 1989 and 2013 in a population based cohort: the Rotterdam study. Bone 2018;114:116-24.

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