Treating osteoporosis in the oldest old

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With more than 13 million US citizens now 80 years old or over, it is more important than ever that we are able to provide robust advice and guidance regarding the pros and cons of treating osteoporosis in the old or very old. This age group counts for a large proportion of the societal fracture burden. Hence, 1 in 6 fractures in Denmark occur in patients aged 80 or over, although this age group accounts for a little over 5% of the population (Figure 1). If treatment truly is equally effective in this age group, then the societal business case is strong given the large number of fractures sustained in this age group. However, managing osteoporosis in the oldest old is often challenging because of coexisting illnesses and frailty and concerns about lifetime expectancy and time to onset of treatment effect. Health professionals will carefully need to think about the pros and cons of every chronic treatment and have a meaningful discussion with their patient about what can be gained in terms of quality of life. We clearly need the best possible trial data to help our decision making.

Even with limited life expectancy, osteoporotic fractures can add pain and disability to what might have been fairly comfortable months or years. It can be argued that a high competing risk of death may not be a sound reason for withholding treatment for osteoporosis. The competing risk argument is really based on the assumption that survival itself is not also improved by osteoporosis agents. Although controversial, there may be meaningful extra-skeletal benefits of potent anti-osteoporosis medications that could improve survival and supporting randomized controlled trial (RCT) data exist.\textsuperscript{1-3} If osteoporosis medications reduce the risk of death, directly or through reducing fracture risk, should such treatment then not be actively targeted to patients with increased mortality risk? At least if it is affordable and well tolerated?

In this issue of the Journal of Bone and Mineral Research, Schini and co-authors\textsuperscript{4} from the FNIH-ASBMR-SABRE collaboration present a very timely individual patient data analysis of data from 23 RCTs of osteoporosis pharmaceuticals including 11 bisphosphonate trials. In the primary analysis, stratification by age 70 was used because this was close to the median age in the trials and hence provided good statistical power with roughly equal numbers of patients in both groups. In brief, this analysis of more than 120 000 participants found...

\textbf{Figure 1.} Contribution to total societal fracture burden (line) in Denmark by age group compared with size of the population at risk (bars). The 80+ age category contributes 1 in 6 fractures but accounts for only 5.4% of the population. Fractures before age 50 are included in the total number of fractures but not included graphically. Calculated from fracture events and population statistics from Driessen et al.\textsuperscript{9}.

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no overall significant interactions—that is, no loss of effect—with age on fracture outcomes. There were overlapping risk reductions for the 2 age groups. When restricted to bisphosphonate trials, a somewhat greater mean risk reduction was seen in the younger age group (hazard ratio [HR], 0.44) while the risk reduction was significantly smaller for ages 70 and over (HR, 0.79; P for interaction = .02). This contrasted with greater absolute BMD gains at both the hip and spine in the older age group. Perhaps age alone does not degrade the integrity of osteoporotic bone to an extent that interferes with BMD increases on re-filling of resorbing surfaces, at least not over the age span covered by the trials. In essence, even larger BMD improvements look to be needed to offset the increases in fracture risk explained by other aspects of increasing age, such as poor balance and muscle function, so we need to address issues such as vertigo and sarcopenia. Perhaps falls-inducing medications can be discontinued or their dose reduced and multidisciplinary falls intervention is helpful if available. Hip fractures aside, both the younger and the older age groups had significant and clinically important reductions in both vertebral and non-vertebral fractures, with no discernible interaction with age. The authors conducted a sensitivity analysis with an age cutoff of 75 years and found similar results but with lower statistical power. There were not enough trial data to justify a separate analysis for age 80 years and over, although such an analysis would have been particularly welcome, as it would firm up the evidence for efficacy in the oldest group of patients. Few if any healthcare providers today would hesitate to treat a 70-year-old for osteoporosis on the grounds of age.

Even if a handful of trials had been available with substantial numbers of patients aged 80 years and older, one could raise concerns that study participants would not be representative of most patients of that age group who present with osteoporosis. This issue is not even confined to the older age group but is present at all ages: for alendronate use in women, for example, 35% of Spanish and 44% of Danish users had conditions or other clinical characteristics that would have precluded them from being included in the original licensing trials. Observational studies also support osteoporosis treatment in the oldest old. Swedish register data on fracture outcomes in tertiary prevention at 80 years or older are reassuring, with risk reductions closely mirroring what was found in RCTs in younger age groups. More recently, Ström et al reported on BMD changes and fracture risk reductions with osteoporosis medications and found the same BMD improvements in women aged 80 or over as in women aged 60–79 and a significant fracture risk reduction.

With the new combined RCT data from the FNIH collaboration there is little to support the hypothesis that osteoporosis medications work less well in the oldest old. In the absence of a signal suggesting that older patients benefit less from treatment, can we reasonably call for large-scale placebo-controlled trials in the oldest old where those in the placebo arm are placed at an unacceptable risk of harm?

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References