Invited Commentary

Considering the Risks and Benefits of Osteoporosis Treatment in Older Adults

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Hip fractures increase exponentially beyond the seventh decade of life, as does the risk of their devastating consequences, which include functional decline, institutionalization, mortality, and destitution. Clinicians are often hesitant to start pharmacologic treatment in older adults, particularly those with multiple comorbidities, polypharmacy, and frailty. This reluctance stems in part from the concern that these patients with a shorter life expectancy may not experience the same risk-benefit profile as healthier adults when prescribed preventive therapies.

Related article

In the study by Ensrud et al,[1] the authors examined the incidence of hip fracture among older women with osteoporosis or at high risk for fracture as part of the Study of Osteoporotic Fractures (SOF). Cumulative incidence functions were used to describe the 5-year incidence of hip fracture, accounting for the competing risk of death. Results were stratified according to the number of baseline comorbidities and the validated Lee prognostication index. Many of the women in this study with multiple comorbidities were frail: the mean gait speed of women with 3 or more comorbidities was 0.77 m/s, less than the threshold of 0.8 m/s used to identify individuals with frailty and increased mortality. Furthermore, 45% reported fair or poor health, 57% reported difficulty walking 2 or more blocks, and 37% reported difficulty with household chores. Nonetheless, the authors found that the incidence of hip fracture increased in women with osteoporosis who also had 3 or more comorbidities and in women with a worse prognosis after accounting for the competing risk of death. In contrast, in women without osteoporosis but at risk for fracture, the incidence of hip fracture remained low, and mortality over 5 years far exceeded fracture risk, particularly in women with multiple comorbidities.

These findings are of great clinical importance given the ongoing recognition that clinical guidelines should consider multimorbidity. Presently, the guidelines for screening and treating adults for osteoporosis offer no consideration of age, comorbidities, or frailty. In contrast, guidelines for cancer screening caution against routine screening in older adults of advanced age or with limited life expectancy given the diminishing value of cancer screening and prevention therapies in the eighth and ninth decades of life. This study by Ensrud et al[1] suggests that the risk-benefit calculation for fracture prevention in older adults differs from that of cancer. If medications to prevent fracture are equally effective in older women with multiple comorbidities as they are in younger women, then older women with comorbidities are the individuals most likely to benefit from osteoporosis treatment.

Unfortunately, older adults with multiple comorbidities were typically excluded from the pivotal osteoporosis randomized clinical trials (RCTs), and data to support treatment efficacy in this population are sparse. Nonetheless, post hoc analyses suggest osteoporosis medications are probably effective: subgroup analyses have consistently demonstrated efficacy among the oldest individuals[2] and those with neurologic impairment.[3] Furthermore, smaller trials of patients living in a nursing home or assisted living suggest that these medications may prevent fractures. In a study by Greenspan et al,[4] 327 women (mean age, 78.5 years) with low bone mineral density residing in a retirement community or nursing home were randomized to alendronate vs placebo. After 2 years of follow-up, there were numerically fewer fractures in women receiving alendronate (13 fractures among 13 women) compared with placebo (28 fractures among 18 women), although the difference was not statistically significant. In a second trial by Greenspan,[5] 181 women (mean age, 85.5 years) living in an assisted living facility or nursing home were randomized to a single intravenous bisphosphonate infusion (zoledronic acid) vs placebo. After 2 years of follow-up, there were numerically fewer vertebral fractures in women receiving zoledronic acid compared with placebo (6 vs 8), although the total number of fractures was greater in the zoledronic acid group (18 vs 15).

Conducting a large randomized trial of bisphosphonates in older adults with multimorbidity that is powered to detect a difference in fracture and adverse events is improbable. Therefore, well-conducted observational studies are necessary to understand whether osteoporosis medications are effective and safe in this population. A large, observational study comparing the incidence of hip and nonvertebral fracture in nursing home residents newly prescribed a bisphosphonate vs calcitonin (n = 10 418)[6] found, over a mean follow-up period of 2.5 years, that new bisphosphonate users were less likely than calcitonin users to experience hip fracture (5.1% vs 5.8%; hazard ratio, 0.83; 95% CI, 0.71-0.98). The reduction in fractures with bisphosphonate treatment was observed within 6 months. However, the average gain in survival without hip fracture associated with bisphosphonate treatment instead of calcitonin was modest over 6 years: only 28 days. As a comparison, the average gain in cardiovascular event-free survival among older adults treated for the same time period with a statin for primary prevention was 19 days.[7] Despite the modest reduction in hip fracture observed, it may still be reasonable to treat older adults with established osteoporosis and multimorbidity who also have at least a 2-year life expectancy, given the morbidity and expenses associated with a single hip fracture.

Competing risk of death is a key consideration when weighing the risks and benefits of treatment in older adults with multimorbidity. Clinicians may rely on validated prediction

models, such as the FRAX tool and the Lee index, to compare the absolute risk of fracture with risk of death. It is notable that both the FRAX tool and the Lee prognostic index, while well validated, do not include some risk factors that clinicians may consider important to evaluate the risk-benefit profile of pharmacologic treatment in an older patient with osteoporosis. For example, history of falls is not included in either model. Although difficulty bathing is included in the Lee index, other important functional measures, such as difficulty with transfers, are not. Finally, both models fail to risk stratify with very advanced age: the Lee index assigns the same number of points to anyone aged 85 years or older, whereas the FRAX tool assumes a maximum age of 90 years. Thus, for very old patients with the highest risk of fracture, it is unclear how the FRAX model performs, and the Lee index likely underestimates mortality. New models to predict fracture and mortality specifically in adults with advanced age and multimorbidity are needed.

Patient preference is another important consideration when assessing the risks and benefits of treatment. Preventing fractures is a priority for many older adults: in a survey of older women, 80% reported that they would prefer death as opposed to a hip fracture leading to institutionalization.[8] At the same time, older adults and their clinicians are concerned with polypharmacy and rare but serious adverse events associated with osteoporosis treatment. Guidelines for osteoporosis treatment should encourage a discussion of patient preference.

Despite the obvious challenges of treating osteoporosis in older adults with multimorbidity, the study by Ensrud et al[1] reminds us of the dangers in ignoring the problem. Older patients with established osteoporosis and multiple comorbidities are at the greatest risk for hip fracture. We encourage additional research that will guide treatment in this growing patient population, and we hope that future guidelines for osteoporosis treatment will include recommendations for older patients with multimorbidity.

ARTICLE INFORMATION

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Published Online: June 17, 2019. doi:10.1001/jamainternmed.2019.0688

Conflict of Interest Disclosures: Dr Berry reported royalties for a chapter in UpToDate from Wolters Kluwer outside the submitted work. Dr Kiel reported royalties for a chapter in UpToDate from Wolters Kluwer, grants from the Dairy Council, grants from Radius Health, and personal fees from Springer outside the submitted work. No other disclosures were reported.

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