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PERSPECTIVES

Fracture Prevention in Frail Older Adults: Why, When and How

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Abstract

Frail, older adults are at the highest risk of fracture, but osteoporosis treatment decisions are complicated by this group's limited life expectancy, co-morbidities, and under-representation in clinical trials. This *Perspective* attempts to review the rationale for fracture prevention, provide a framework for making individual osteoporosis treatment decisions, and discuss practical issues in preventing fractures in frail older adults. While clinical trial evidence is not optimal, available data does suggest that osteoporosis therapies have similar safety, efficacy, and cost-effectiveness even at older ages and in the presence of common co-morbidities. Using life tables and validated fracture prediction tools, fracture risk in the remaining years can be estimated. Considering the lag time to efficacy, patient compliance and preference, and incorporating non-pharmacologic fracture prevention strategies such as fall prevention, appropriate treatment decisions can be made for this high risk population. *IBMS BoneKEy*. 2008 November;5(11):426-435.

Background

Deciding when and how to treat frail, older patients for osteoporosis can be a challenging problem in clinical practice. Although the prevalence of osteoporosis and risk of fracture increase exponentially with age (1), frail older adults also have a lower life expectancy that may limit the benefit of treatment. In addition, co-morbidities accumulate with age and impact both screening and treatment options. Finally, frail, older patients have been under-represented in osteoporosis clinical trials (2), and the efficacy of treatment in frail populations is unclear. In short, determining the risk-benefit ratio for such patients is difficult.

Not surprisingly, then, frail, older patients are generally less likely to be evaluated and treated for osteoporosis than younger patients, although there is substantial variation within and between practice settings (3;4). For example, in a study of Medicaid beneficiaries in Kansas, female nursing home residents were less likely to receive anti-resorptive therapies than community-dwellers, except in the subgroup of women over 85 years of age, who were more likely to receive therapy if they resided in a nursing home (3). Osteoporosis treatment rates for patients in nursing homes with known osteoporosis or recent hip fracture vary from 0-85% (4). This variation suggests that a better understanding of the risks and benefits of treating populations with limited life expectancies or multiple co-morbidities is needed.

The purpose of this *Perspective* is to review the rationale for considering osteoporosis therapy in older and frailer populations, to provide a framework for individual decision-making in elderly or chronically ill individuals, and to review the evidence supporting various fracture prevention options for older adults.

Rationale for Treating Frail, Older Populations

The prevalence of osteoporosis increases steadily beginning at approximately 50 years of age in women, and 60 years of age in men (1). Similarly, the incidence of falls rises steadily in older adults at roughly the same ages (5). These conditions together lead to the exponential increase in fracture risk that has been noted in multiple previous epidemiologic studies (6). The prevalence of co-morbidities associated with an increased risk of falls and fractures also increases with

age, including stroke, Parkinson's disease, peripheral neuropathy, prostate cancer, cognitive impairment, sensory impairment, and psychotropic medication use. The frailest subset of our population that resides in nursing homes is at roughly a 2- to 6-fold higher risk of fracture than similarly aged community-dwellers (7).

Not only are older and frailer individuals at higher risk of fracture, but they also suffer more morbidity and mortality when a fracture does occur (8-10). For example, fractures in frail nursing home residents are more likely to result in functional status declines, pain, depression, higher cost, and mortality than in community populations (8-12). Thus, older and frailer patients are in fact at the highest risk of suffering fractures and morbidity from fractures, and potentially have the most to gain from effective fracture prevention strategies.

However, these patients have also been under-represented in osteoporosis clinical trials, and questions remain about whether available treatments are equally safe and effective in the frailest patients (2). When direct evidence is lacking, it is useful to examine *post-hoc* analyses, meta-analyses, and cohort studies that include a substantial number of patients with advanced age. Subgroup analyses of clinical trials of several bisphosphonates, teriparatide and raloxifene suggest that these agents have similar fracture relative risk reduction and adverse event profiles in older participants (13-17). Moreover, since the incidence of fracture increases with age, older clinical trial participants experience a larger absolute fracture risk reduction. For example, the number needed to treat to prevent 1 additional fracture with oral bisphosphonates in an overall clinical trial population is approximately 25; for those over age 80 it is only 12 (13). A handful of clinical trials have included substantial numbers of frail older adults, although these trial participants may still be healthier than the general population. A trial of risedronate in more than 3800 women aged 80 years or older showed a similar safety profile to that of younger participants, and fracture reduction efficacy in those with T scores -2.5 or lower, although not in those selected on the basis of risk factors for falling alone (18). A trial of zoledronic acid after hip fracture included patients with prior nursing home residence, cognitive impairment, and advanced age; this study demonstrated reduction in both clinical fractures and mortality across all age subgroups (19). A study of alendronate in nursing home residents showed significant improvement in bone density, and a favorable safety profile, compared to placebo (20). Thus, available evidence is reassuring that pharmacologic treatment is likely to be both safe and efficacious in older populations.

Co-morbidities associated with aging may also impact the safety and efficacy of osteoporosis therapy. Small clinical trials of bisphosphonates have been completed on patients with stroke (21-22), type 2 diabetes (23), Parkinson's disease (24), and prostate cancer (25), and suggest a similar bone density effect and safety in the presence of these conditions. Renal function declines with advancing age, and clinical trials have generally excluded patients with glomerular filtration rates (GFR) less than 30 ml/min. However, subgroup analyses of bisphosphonate trials have consistently demonstrated safety and efficacy down to GFR 30-45 ml/min, and although the numbers of subjects is quite small, even in those with GFR less than 30 ml/min (26). Although the subjects included in some of these studies may be younger or healthier than the frail, older population discussed here, it appears that there is not an interaction between these common conditions of older age and the efficacy and safety of osteoporosis therapy. Therefore, the presence of these co-morbidities does not preclude consideration of osteoporosis therapy.

Finally, advancing age and limited life expectancy may impact the cost-effectiveness of osteoporosis therapy for frail older populations. Although assumptions and calculations differ, most studies have suggested that the cost-effectiveness of bisphosphonates and teriparatide either remain stable or actually improve with older age, due to the substantially higher absolute risk of fractures in this group (27;28). When limited life

expectancy is considered, the cost per quality adjusted life year becomes less attractive, but the cost per fracture averted remains stable (29), suggesting that treatment may be reasonable in some patients with limited life expectancies but very high fracture risk.

In summary, the oldest subset of our population is at the highest risk of fracture. Although this group has been under-represented in clinical trials, available evidence is reassuring that available therapies are likely to be safe, effective, and cost-effective for carefully selected patients, even at advanced age and in the presence of multiple co-morbidities. However, deciding when and how to treat an individual patient requires additional considerations.

Approach to Decision-Making in Individual Patients

Most economic analyses, fracture risk assessment tools, and clinical practice guidelines assume that the patient will receive 5-10 years of therapy, and do not account for competing causes of mortality that may limit the benefit accrued by a patient with a shorter life expectancy. Thus, deciding whether the benefit of a particular strategy is likely to outweigh the risks and costs for an individual patient requires consideration of the lag time prior to efficacy of the strategy being considered, the patient's remaining life expectancy, and an estimation of the risk of suffering a fracture in that remaining lifetime.

Available fracture prevention strategies vary as to the lag time between initiating therapy and the onset of fracture reduction benefit. Although the efficacy of external hip protectors remains controversial (30), theoretically they should provide immediate protection. Although clinical trials are generally not designed to identify the time to onset of significant fracture protection in an individual patient, insights into the lag time can be found by examining the first separation of survival curves in a proportional hazards analysis, or first time point with a significantly different fracture rate than placebo. Vitamin D supplementation (31) (which also reduces falls in older adults (32)) and intravenous bisphosphonates (19) significantly decrease fracture rates as early as 6 months after the first dose. Oral bisphosphonates and teriparatide reduce vertebral fractures within 12 months of therapy, and recent secondary analyses and cohort studies with teriparatide and risedronate suggest a non-vertebral fracture benefit within 6-7 months (33-35). Significant reductions in vertebral fractures were seen after 24 months of therapy in trials of calcitonin and raloxifene (36;37), although *post-hoc* analyses suggest that the benefit may begin earlier. Thus, treating a patient with a 2-3 year life expectancy with an agent that requires 2 years before a benefit is seen is not likely to be useful, while consideration of therapies with shorter lag time, such as hip protectors, vitamin D supplementation, or some bisphosphonates, may be reasonable if the absolute fracture risk is high.

While determining the lag time to benefit of the proposed therapy is fairly straightforward, estimation of the patient's remaining life expectancy may not be. Many patients do not have a single life-threatening illness with clear prognostic markers, but rather multiple chronic illnesses or impaired functional status for which prognostic tools are imprecise or nonexistent. In this situation, the approach of Walter (38) and colleagues is particularly useful in estimating a patient's remaining life expectancy. The clinician simply determines whether, in his or her judgment, the patient's health and functional status is in the healthiest quartile, the sickest quartile, or in the 2 middle quartiles for the patient's age. Using U.S. life tables, the average remaining life expectancy for an older adult at his or her age and quartile of health can be determined (Fig. 1). The clinician can then decide whether his or her individual patient is likely to have sufficient remaining life expectancy to benefit from fracture prevention therapies.

The final consideration in deciding whether to initiate fracture prevention strategies in an older individual is estimating the absolute risk of suffering a fracture in his or her remaining life expectancy. Validated tools such as the World Health Organization

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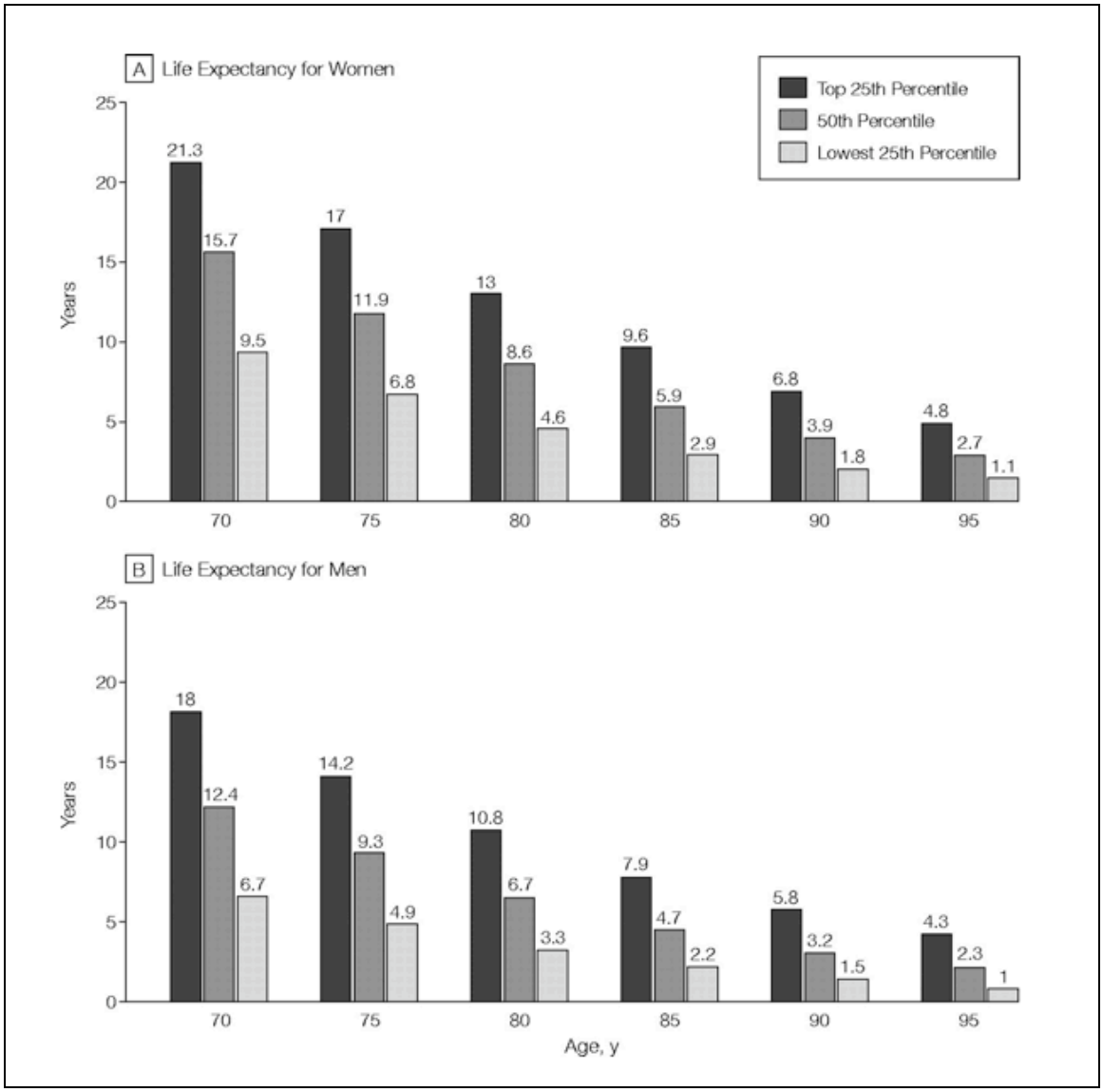

Fig. 1. Average remaining life expectancy by age and quartile of health, from U.S. life tables. Reproduced from Walter *et al*. *JAMA*. 2001 Jun 6;285(21):2751. Copyright © 2001, American Medical Association. All rights reserved.

Fracture Risk Assessment Tool (FRAX®, available at http://www.shef.ac.uk/FRAX/) provide risk estimates in a 10-year period that are adjusted for average life expectancy. As seen from the life tables, however, there is substantial variation in the remaining life expectancy among older adults based on their underlying health status. Thus, FRAX® is likely to underestimate the absolute fracture risk for the healthiest quartile of older adults, and over-estimate the risk for the sickest quartile. For example, FRAX® estimates that an 85-year-old white woman in the U.S. with a BMI of 25 has a 27% risk of suffering a major osteoporotic fracture in 10 years. If she is in the highest quartile of health for her age, then life tables indicate that her average life expectancy is about 10 years, and her fracture risk is at least 27% or greater. This patient is highly likely to benefit from pharmacologic osteoporosis therapy. If she is in the sickest quartile of health, her average life expectancy is only 3 years, or approximately half of the average life expectancy for her age group, and her risk of fracture is therefore roughly half of the FRAX® estimate, or 13%. This figure can be used as a starting point from which to further refine the estimate of the woman's risk for

the purposes of clinical decision-making. If she resided in a nursing home or had frequent falls, her risk is likely to be higher. It should be emphasized that these numbers are only estimates and have not been validated in prospective studies. Nevertheless, this approach does provide a useful framework when faced with deciding whether an individual's lifetime fracture risk warrants consideration for osteoporosis evaluation and treatment, in the face of advanced age or multiple chronic illnesses.

Fracture Prevention Options for Older Populations

Once the clinician and patient decide that it is sensible to intervene to reduce fracture risk, there are a number of options from which to choose. While a full review of fracture prevention therapies is beyond the scope of this article, the following discussion briefly reviews evidence that is particularly applicable to older adults, and discusses practical considerations for their use in frail populations.

Bisphosphonates are currently the most frequently prescribed osteoporosis therapy for older adults in the U.S (3). Particular considerations for this class of medication include poor oral absorption and the risk of esophageal ulceration, requiring that the drug be given after fasting and with the patient sitting upright for some time after the dose. This may be problematic for older patients with mobility or cognitive impairment, unless assistance with adherence to safe drug administration is available. The efficacy of these drugs is reduced substantially with poor compliance (39) and therefore careful follow-up to ensure adequate dosing is indicated. Another concern is the high prevalence of vitamin D deficiency in older patients (40). It is particularly important to ensure adequate 25(OH) vitamin D serum levels or to provide empiric vitamin D repletion prior to initiating bisphosphonates, especially intravenous agents, due to the risk of clinically significant hypocalcemia (41). Side effects such as reflux symptoms increase in prevalence with age, however, in at least some trials of frail older adults, reflux symptoms were not different between placebo and bisphosphonate-treated subjects (20). The prevalence of acute phase reaction symptoms with I.V. zoledronic acid was substantially lower in a trial of older hip fracture patients, compared to trials in younger, postmenopausal women (19;42).

Other pharmacologic therapies have less evidence to support their use in frail older populations. Nevertheless, calcitonin, selective estrogen receptor modulators, and teriparatide are potential alternatives to bisphosphonates in those who cannot tolerate or who have failed bisphosphonates. The increased risk of thromboembolism warrants caution with the use of the selective estrogen receptor modulators in patients with recent fractures (37). Strontium ranelate (43) and tibolone (44) are options outside of the U.S. Of particular concern for older patients is the 2-fold increased risk of stroke seen with tibolone, given the higher risk of and morbidity associated with strokes in older age.

Calcium and vitamin D supplementation are particularly important both for bone health and for fall prevention. Vitamin D supplements appear to reduce fall risk in a dose-dependent manner at a minimum of 800 IU daily (32). Patients with significant vitamin D deficiency, however, need replacement doses in addition to daily vitamin D supplements, and a target 25(OH) vitamin D level of at least 30 ng/ml is generally recommended. It may be less expensive in high prevalence populations to empirically replete patients who have low or normal serum calcium with high dose vitamin D for 6-12 weeks, rather than to measure 25(OH) vitamin D levels. Clinicians should keep in mind significant drug-drug interactions with calcium supplements that commonly occur in older adults, including proton pump inhibitors (45) (decrease calcium absorption), fluoroquinolone antibiotics (46) (decrease antibiotic absorption), and for formulations that contain vitamin K such as some chewable calcium supplements, warfarin (decreased INR level).

External hip protectors are a theoretically attractive, but still controversial strategy for

fracture prevention in older adults. Clinical trials have yielded conflicting results, and meta-analyses have not resulted in a definitive answer about their efficacy (30). Evidence is most compelling for use in nursing home residents, and their effect in community dwellers is unknown. Heterogeneity in the biomechanical properties of the hip protectors may have contributed to these disparate results (47), and if a hip protector is used it seems wise to recommend brands with supporting clinical trial evidence. If effective, hip protectors are likely to be highly cost-effective (48). With the immediate onset of fracture risk reduction and limited side effects, hip protectors remain a reasonable option for some high risk patients.

Finally, fall prevention is an important way to reduce fractures in older adults and must not be neglected. Falls generally result from multiple factors interacting in a susceptible individual, and therefore multi-factorial risk reduction interventions have the best evidence in reducing falls and fractures (49-51). These interventions include measuring orthostatic blood pressure, reducing psychoactive or other medications that increase fall risk, optimizing vision and hearing, teaching lower extremity balance and strengthening exercises, eliminating environmental hazards, and prescribing appropriate assistive devices. Collaboration with physical and occupational therapists, or referral to a multidisciplinary fall reduction program, is helpful in completing these time-consuming tasks.

Summary

Fracture prevention in frail, older adults requires careful consideration of the fracture risk in remaining lifetime, the risks and benefits of treatment, the lag time to onset of efficacy, and patient goals and preferences. Many older patients who are appropriate candidates for osteoporosis therapy are not currently being treated and would benefit from consideration of the full range of osteoporosis treatment and fall prevention options currently available.

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