Commentary

Osteoporosis: treat and live, or let die twice more likely†

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Patients with fractures have reduced life expectancy (1-3). This is easily understood when death occurs following a hip fracture in an elderly frail individual (4). However, reduced life expectancy is also independently associated with vertebral or forearm fractures (5), rapid bone loss alone (6), and low bone mineral density alone (7).

The most plausible explanation for these less intuitive associations is confounding – when sampling a cohort selected on fractures, low bone mineral density or rapid bone loss, the sampling also selects individuals with coexisting morbidities that confer an increased risk for immobility, bone loss, micro-structural deterioration, muscle loss, propensity for falls, fracture, and the risk of early death. Sampling may also select persons more likely to be receiving treatments and so at risk of adverse events of the drugs (8).

The purpose of treatment is to prolong disease free survival, not just to reduce event rates (9). Identifying and quantifying causal relationships between illness and mortality, illness and fracture, fracture and mortality should make it possible to target each cause of morbidity and mortality; there is no point in reducing fracture risk by reducing survival.

Abrahamsen *et al.* (10) addressed this challenging sea of troubles and attempted to resolve them by using the Danish National Prescription data-base to identify persons commencing treatment for bone fragility, the National hospital discharge database to identify existing comorbidities, and the National Death Register to obtain causes of death. They identified 58,637 women and men starting treatment for bone fragility and 225,084 age- and sex- matched controls. They compared the prevalence of comorbidities and fractures in the two groups and determined life expectancy from

which they then derived the number of life-years lost, and the number of life-years remaining during which effective and safe treatment will be needed for fracture prevention.

The cases had a 4-6 times higher prevalence of comorbidities than controls. In men, 17.5% had a Charlson index of +3 compared to 6.7% of male controls and 7.7% of female cases. The prevalence of fracture was 37.6% in female cases and 20.3% in controls, 27% in male cases and 11% in male controls.

Life expectancy was reduced, more so in men. At 1 year, mortality was 16% in male cases, 3% in male controls, 6.6% in female cases, 4.6% in female controls. At 5 years mortality was 48.2% in male cases, 24.6% in male controls; 28.3% in female cases, 31.9% in female controls. At 10 years, mortality was 69.7% in male cases, 45.4% in male controls, 50.2% in female cases and 50.8% in female controls.

Male cases were more likely to die from pulmonary disease, malignancy and circulatory disease than male controls. In women, pulmonary disease was also a more likely cause of death than in female controls. In men under 80 years and women younger than 60 years the relative risk of dying was high in the first year then declined to stabilize at an elevated level. In women older than about 65 years, risk was only modestly elevated in the first year of treatment then was similar or lower than controls.

The reasons for these patterns of mortality remain uncertain but an two enlightening observations were (i) the modest loss of life years despite the higher prevalence of comorbidities and (ii) the remaining number of life years. The excess mortality was a loss of 1 year of life in men aged 85 but 11.5 years for men aged 50 years. In women, there was no reduction in life expectancy for those over 70 years but there was 1 life year lost for those treated at 65 years and 6.7 years for those

treated at 50 years. As a consequence, the number of life years remaining during which treat against bone fragility will be needed was 18.2 in a 50 year old man, 7.5 years in a 75 year old man, 26.5 years in a 50 year old women and 13.5 years in a 75 year old women.

This study draws attention to several challenges we face as clinicians. The evidence for sustained long term antifracture efficacy is wanting in many areas. Few trials extend beyond 3 years, and trials that report low fracture rates in the 4th though to 8th year of follow-up no longer have a control group. The number of subjects followed is smaller than originally randomized so that the low fracture rates reported may reflect healthy user bias (11, 12). The high morbidity and mortality in men is another lesson; clinical trial data are also wanting in men and the high mortality may be in part the lower compliance with therapy found in men. These are not trivial challenges. Fracture rates appear to be declining during the last few decades but the absolute burden of fractures is increasing because the number of persons living several decades beyond the promise of three score and ten is rapidly increasing (13, 14).

This study could not determine whether anti-osteoporosis treatment improved longevity or shortened it, and could not determine whether reduced survival was the result of comorbidities or fractures. These questions remain and probably require a double-blind randomized controlled trial of antiresorptive therapy with mortality as the outcome. Such a trial is feasible. If the 5-year incidence of mortality is 48% (10) and if bisphosphonates reduces the risk of mortality by approximately 30% (15), then a randomized clinical trial requires ~200 individuals in each treatment arm to have an 80% chance to demonstrate the effect size.

Abrahamsen et al. (10) send several messages. First, their data reinforce that there is a 'window of opportunity'; treat early, within a year of fracture to benefit patients. We need data on long term treatment efficacy and safety in women and men, and to monitor compliance, especially perhaps in

men, and we need to target therapy to the potential causes of mortality such as cardiopulmonary disease.

References

1. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999;353(9156):878-82.
2. Frost SA, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Excess mortality attributable to hip-fracture: a relative survival analysis. Bone 2013;56(1):23-9.
3. Haentjens P, Magaziner J, Colon-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med 2010;152(6):380-90.
4. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301(5):513-21.
5. Pongchaiyakul C, Nguyen ND, Jones G, Center JR, Eisman JA, Nguyen TV. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study. J Bone Miner Res 2005;20(8):1349-55.
6. Nguyen ND, Center JR, Eisman JA, Nguyen TV. Bone loss, weight loss, and weight fluctuation predict mortality risk in elderly men and women. J Bone Miner Res 2007;22(8):1147-54.
7. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Study of Osteoporotic Fractures Research Group. Lancet 1991;338(8763):355-8.
8. Byar DP. Why data bases should not replace randomized clinical trials. Biometrics 1980;36(2):337-42.
9. Seeman E, Eisman JA. 7: Treatment of osteoporosis: why, whom, when and how to treat. The single most important consideration is the individual's absolute risk of fracture. Med J Aust 2004;180(6):298-303.
10. Abrahamsen B, Osmond C, Cooper C. Life expectancy in patients treated for osteoporosis: Observational cohort study using National Danish Prescription data. J Bone Miner Res 2015.
11. Cadarette SM, Solomon DH, Katz JN, Patrick AR, Brookhart MA. Adherence to osteoporosis drugs and fracture prevention: no evidence of healthy adherer bias in a frail cohort of seniors. Osteoporos Int 2011;22(3):943-54.
12. Curtis JR, Larson JC, Delzell E, Brookhart MA, Cadarette SM, Chlebowski R, et al. Placebo adherence, clinical outcomes, and mortality in the women's health initiative randomized hormone therapy trials. Med Care 2011;49(5):427-35.
13. Oden A, McCloskey EV, Kanis JA, Harvey NC, Johansson H. Burden of high fracture probability worldwide: secular increases 2010-2040. Osteoporos Int 2015.
14. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374(9696):1196-208.
15. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357(18):1799-809.