Overdiagnosis of osteoporosis: fact or fallacy?

J. Compston¹

Received: 18 June 2015 / Accepted: 19 June 2015 / Published online: 2 July 2015
© International Osteoporosis Foundation and National Osteoporosis Foundation 2015

In their paper in the *British Medical Journal*, “Overdiagnosis of bone fragility in the quest to prevent hip fracture”, Järvinen et al. claim that there is inadequate evidence to support current pharmacological approaches to the prevention of hip fracture [1]. They state, correctly, that the vast majority of hip fractures follow a fall but fail to recognize the obvious connection between the consequence of a fall and bone strength. With the use of selective and misleading presentation of published evidence, they provide a biased critique of current strategies for risk assessment and prevention of hip fracture. Most surprisingly, they fail even to mention Fracture Liaison Services, a model of care that has been shown to be both effective and cost-effective in the secondary prevention of fracture and has been successfully adopted in many parts of the world [2–7].

No one would deny that, as in many fields of medicine, there are gaps in the evidence or that current practice can be improved. Indeed, we know that the majority of elderly people who suffer a hip fracture are not assessed for osteoporosis or offered treatment in the form of lifestyle advice, falls counselling or bone protective therapy [8, 9]. These individuals are at high risk of further fractures and the proven anti-fracture efficacy of pharmacological interventions in this situation provides a strong rationale for their use in secondary prevention. Prevention of the first fracture is another important but more difficult goal, and the efficacy of pharmacotherapy for the primary prevention of fracture has been less well studied. In

much of their analysis, Järvinen et al. fail to make the critical distinction between primary and secondary prevention and by combining figures from studies of both in their meta-analysis, they arrive at a NNT for hip fracture that is too high and meaningless in the context of secondary prevention.

Järvinen et al. acknowledge the large body of published literature demonstrating that the majority of older people whose fracture do not have osteoporosis as defined by the WHO, i.e. a bone mineral density (BMD) T -score ≤ -2.5 , but appear to miss the point that this provides the rationale for fracture risk algorithms which include clinical risk factors that act independently of bone density. In particular, the strong effect of age has been recognized for decades and its inclusion in risk algorithms greatly improves prediction of fracture risk when compared to BMD alone [10, 11]. Furthermore, both in the title and body of their manuscript, the authors use the terms bone fragility and osteoporosis interchangeably. This is incorrect, since factors other than BMD contribute to bone strength and there is not a single BMD T -score threshold that defines bone fragility. The authors claim that estimations of absolute fracture risk are “fundamentally flawed” because fewer than one in three hip fractures is attributable to bone fragility; this statement is based on BMD measurements in a single study in postmenopausal women with a mean age of 71 years [12]. This is misleading, first, because BMD-defined osteoporosis, not bone fragility, was assessed and secondly because (as repeatedly emphasized in other contexts by the authors) over 75 % of hip fractures occur in people over the age of 75 years.

Another major inaccuracy in their analysis is the contention that organisations supporting the development of FRAX have advocated widespread screening for bone fragility (presumably osteoporosis). In contrast to this assertion, both organisations quoted, the National Osteoporosis Foundation and National

✉ J. Compston
jec1001@cam.ac.uk

¹ Cambridge Biomedical Campus, Cambridge, UK

Osteoporosis Guideline Group, recommend a case finding strategy based on the presence of risk factors, a position also supported by, amongst others, the International Osteoporosis Foundation and the National Institute of Health and Care Excellence (NICE) in the UK [13–17]. These organisations have improved awareness of osteoporosis in the general population and amongst healthcare professionals and politicians, empowering individuals who may be at risk of fracture to seek advice and providing guidance on their assessment and management. Rather than imposing an unnecessary “psychological burden”, this strategy provides appropriate access for individuals to information about their risk and the measures that may be taken to reduce it.

The claim by Järvinen et al. that non-pharmacological interventions are overlooked should also be challenged. All guidelines include counselling about life style, including diet, tobacco use and alcohol intake, and promote appropriate levels of physical activity. Whilst adopting these measures may have beneficial effects on bone health, evidence that they prevent fractures is lacking. Guidelines also stress the importance of taking measures to prevent falls. However, although fall prevention programmes have been shown to reduce the frequency of falls, the majority of studies in elderly subjects, not cited by the authors, have failed to show fracture reduction [18, 19]. In the meta-analysis of fall prevention exercise programmes and fracture quoted by Järvinen et al., most women were under the age of 75 years and many did not have risk factors for falling [20]. Extrapolation of these data to the frail elderly population at risk of hip fracture is hazardous, particularly given the difficulties in implementing exercise training in such individuals. Thus, although measures to prevent falls should be a part of secondary fracture prevention programmes, the assertion that they are as effective in reducing fracture as pharmacotherapy is a misrepresentation of current evidence. Notably, in contrast to their critique of pharmacotherapy, Järvinen et al. do not discuss the cost-effectiveness and safety of exercise interventions in the elderly, nor do they consider the likely problems related to low adherence.

A significant reduction in hip fracture incidence in postmenopausal women has been reported for several interventions including alendronate, risedronate, zoledronic acid and denosumab [21–24]. Järvinen et al. question the relevance of these studies to the very elderly, since the power in many trials was inadequate to demonstrate efficacy in sub-group analyses. In their meta-analysis, they include three studies of women aged ≥ 75 years and conclude that none of these showed a significant effect on hip fracture reduction. In the first of these, failure to show a significant effect of risedronate in women aged ≥ 80 years may have been because these women were not selected for treatment on the basis of high fracture risk but were included, without knowledge of BMD in the majority, if they had at least one non-skeletal risk factor for fracture [22]. The second study quoted is a sub-group analysis of

women aged ≥ 75 years in the HORIZON trial; contrary to the assertion in the footnote of Fig. 3 in the article of Järvinen et al., this analysis did not have sufficient power to demonstrate reduction in hip fracture in the older women (as clearly stated in the publication), but it is noteworthy that no statistically significant interactions between hip fracture reduction and age were observed [25]. In the trial reported by Lyles et al., hip fracture reduction was not a primary endpoint [26]. Nevertheless, in the latter two publications, a non-significant reduction in hip fracture was observed. Finally, the authors quote the paper of Greenspan et al. as further evidence against an effect of pharmacotherapy on hip fracture. However, this study included only 191 women and was obviously underpowered to show an effect on hip fracture [27]. The conclusion from these data that individuals most prone to hip fracture do not benefit from bisphosphonate treatment is therefore not justifiable; absence of evidence does not constitute evidence for absence of an effect.

By focusing only on hip fracture, Järvinen et al. greatly undervalue the overall benefits of pharmacotherapy. Spine fractures and non-vertebral non-hip fractures constitute the vast majority of fragility fractures in the elderly and are associated with significant morbidity and, in some cases, mortality [28]. These fractures often precede or follow hip fractures and are reduced by pharmacotherapy in postmenopausal women, including the very elderly. In an analysis of pooled data from randomized controlled trials containing 1392 osteoporotic women aged 80 years or more, risedronate therapy was associated with an 81 % reduction in new vertebral fractures after only 1 year of treatment [29]. Analysis of data from 3658 postmenopausal women with osteoporosis treated with alendronate demonstrated that the relative risk reductions for hip, clinical spine and wrist fractures were constant across age groups; importantly, because of the increasing age-related increase in fracture risk in the placebo group, the absolute fracture risk reduction increased with age [30]. In a pooled analysis of data from women aged ≥ 75 years ($n=3887$) enrolled in the HORIZON fracture prevention and recurrent fracture prevention trials, Boonen et al. reported a significant reduction of 35 % in the incidence of all new clinical fractures; significant decreases in clinical vertebral fractures (66 %) and clinical non-vertebral fractures (27 %) were also demonstrated [31]. These reductions were comparable to those seen in women aged <75 years and no significant treatment-by-age group interactions were observed.

The statement that evidence for cost-effectiveness of pharmacotherapy in the reduction of fracture is completely lacking provides another example where a large body of published evidence has been totally disregarded [32, 33]. The broader approach championed by Fracture Liaison Services that includes pharmacotherapy has also been shown to be cost-effective [2–7]. Intervention thresholds based both on cost-effectiveness and clinical appropriateness are provided for

guidance by national guidelines but always with the explicit caveat that they do not replace the need for clinical judgment in the management of individual patients.

Editors of academic journals have a responsibility to ensure that published papers are balanced and reflect the available evidence. This is particularly true of a journal such as the *British Medical Journal*, which is widely read by primary care practitioners and healthcare commissioners who cannot be expected to have in-depth knowledge of specialist topics. Even the title of the Järvinen paper is misleading; it is not an analysis, it is a biased and misrepresentative viewpoint. When such extreme views are expressed in the published literature, they should at the very least be counterbalanced by simultaneous publication of alternative opinions. Publication of this misleading and nihilistic view of pharmacotherapy for osteoporosis does a disservice to the many millions of elderly people worldwide who suffer fragility fractures and to the scientific and patient organizations that have worked tirelessly over many years to improve their management.

Conflict of interest Professor Compston is Chairman of the National Osteoporosis Guideline Group.

References

- Järvinen TL, Michaëlsson K, Jokihaara J, Collins GS, Perry TL, Mintzes B et al (2015) Overdiagnosis of bone fragility in the quest to prevent hip fracture. *BMJ* 350:h2088
- Sander B, Elliot-Gibson V, Beaton DE, Bogoch ER, Maetzel A (2008) A coordinator program in post-fracture osteoporosis management improves outcomes and saves costs. *J Bone Joint Surg Am* 90:1197–1205
- Majumdar SR, Lier DA, Beaupre LA, Hanley DA, Maksymowych WP et al (2009) Osteoporosis case manager for patients with hip fractures: results of a cost-effectiveness analysis conducted alongside a randomized trial. *Arch Intern Med* 169:25–31
- Greene D, Dell RM (2010) Outcomes of an osteoporosis disease-management program managed by nurse practitioners. *J Am Acad Nurse Pract* 22:326–329
- McLellan AR, Wolowacz SE, Zimovetz EA, Beard SM, Lock S, McCrink L et al (2011) Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. *Osteoporos Int* 22:2083–2098
- Cooper MS, Palmer AJ, Seibel MJ (2012) Cost-effectiveness of the concord minimal trauma fracture liaison service, a prospective, controlled fracture prevention study. *Osteoporos Int* 23:97–107
- Solomon DH, Patrick AR, Schousboe J, Losina E (2014) The potential economic benefits of improved post-fracture care: a cost-effectiveness analysis of a fracture liaison service in the US health-care system. *J Bone Miner Res* 29:1667–1674
- Liu SK, Munson JC, Bell JE, Zaha RL, Mecchella JN, Tosteson AN et al (2013) Quality of osteoporosis care of older Medicare recipients with fragility fractures: 2006 to 2010. *J Am Geriatr Soc* 61:1855–1862
- Kanis JA, Svedbom A, Harvey N, McCloskey EV (2014) The osteoporosis treatment gap. *J Bone Miner Res* 29:1926–1928
- Hui SL, Slemenda CW, Johnston CC Jr (1988) Age and bone mass as predictors of fracture in a prospective study. *J Clin Invest* 81:1804–1809
- Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B (2001) Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int* 12:989–995
- Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, Osteoporotic Fractures Research Group et al (2003) BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res* 18:1947–1954
- National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. NOF 2104. Available at (<http://nof.org/files/nof/public/content/file/2791/upload/919.pdf>)
- National Osteoporosis Guideline Group. Osteoporosis: clinical guideline for prevention and treatment. Available from www.shef.ac.uk/NOGG
- World Health Organization (2004) WHO scientific group on the assessment of osteoporosis at primary health care level L Summary Meeting Report Brussels, Belgium, 5–7 May 2004 <http://www.who.int/chp/topics/Osteoporosis.pdf?ua=1>. Accessed 16th June 2015
- Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) (2013) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 24:23–57
- National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. NICE 2012. Available at www.nice.org.uk/nicemedia/live/13857/60399/60399.pdf
- Silva RB, Eslick GD, Duque G (2013) Exercise for falls and fracture prevention in long term care facilities: a systematic review and meta-analysis. *J Am Med Dir Assoc* 14:685–689
- Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM et al (2012) Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 9:CD007146
- El-Khoury F, Cassou B, Charles MA, Dargent-Molina P (2013) The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. *BMJ* 347:f6234
- Black D, Cummings S, Karpf D, Cauley JA, Thompson DE, Nevitt MC et al (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 348:1535–1541
- McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C et al (2001) Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 344:333–340
- Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA et al (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 356:1809–1822
- Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, FREEDOM Trial et al (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 361:756–765
- Eastell R, Black DM, Boonen S, Adami S, Felsenberg D, Lippuner K, HORIZON Pivotal Fracture Trial et al (2009) Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. *J Clin Endocrinol Metab* 94:3215–3225
- Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, for the HORIZON Recurrent Fracture Trial et al (2007)

- Zoledronic acid in reducing clinical fracture and mortality after hip fracture. *N Engl J Med* 357:nihpa40967
27. Greenspan SL, Perera S, Ferchak MA, Nace DA, Resnick NM (2015) Efficacy and safety of single-dose zoledronic acid for osteoporosis in frail elderly women: a randomized clinical trial. *JAMA Intern Med* 175:913–921
 28. Roux C, Wyman A, Hooven FH, Gehlbach SH, Adachi JD, Chapurlat RD, GLOW investigators et al (2012) Burden of non-hip, non-vertebral fractures on quality of life in postmenopausal women: the Global Longitudinal study of Osteoporosis in Women (GLOW). *Osteoporos Int* 23:2863–2871
 29. Boonen S, McClung MR, Eastell R, El-Hajj Fuleihan G, Barton IP, Delmas P (2004) Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: implications for the use of antiresorptive agents in the old and oldest old. *J Am Geriatr Soc* 52:1832–1839
 30. Hochberg MC, Thompson DE, Black DM, Quandt SA, Cauley J, Geusens P, FIT Research Group et al (2005) Effect of alendronate on the age-specific incidence of symptomatic osteoporotic fractures. *J Bone Miner Res* 20:971–976
 31. Boonen S, Black DM, Colón-Emeric CS, Eastell R, Magaziner JS, Eriksen EF et al (2010) Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. *J Am Geriatr Soc* 58:292–299
 32. Kanis JA, Hiligsmann M (2014) The application of health technology assessment in osteoporosis. *Best Pract Res Clin Endocrinol Metab* 28:895–910
 33. Hiligsmann M, Evers SM, Ben Sedrine W, Kanis JA, Ramaekers B, Reginster JY et al (2015) A systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis. *Pharmacoeconomics* 33:205–224