REPLY LETTER TO THE EDITOR

JBMR®

Complementarity of Cohort Studies and Randomized Controlled Trials

John A Eisman,[1,2,3] Piet Geusens,[4,5] and Joop van den Bergh[4,6,7]

[1]Bone Biology, Garvan Institute of Medical Research, Sydney, Australia
[2]St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, Sydney, Australia
[3]School of Medicine Sydney, University of Notre Dame Australia, Sydney, Australia
[4]Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands
[5]Biomedical Research Centre, Hasselt University, Hasselt, Belgium
[6]Department of Internal Medicine, VieCuri Medical Center, Venlo, The Netherlands
[7]Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium

To the Editor,

Nordstrom and colleagues essentially reiterate but in no way refute the biases to which we refer. Our point about potential benefits and mortality risk reduction is that if there are very low mortality rates, it is difficult for any study or any agent to demonstrate a mortality benefit. Their comment that the mortality rate was low for hip fracture patients receiving placebo emphasizes this point. The entire rationale for meta-analyses is that these represent a way of combining data from different studies to get a more precise estimate of true effects, which the meta-analysis demonstrates.

Nordstrom and colleagues then suggest that reductions in fracture incidence from 27% to 43% are similar. These 27% to 43% risk reductions represent a 60% range in fracture risk reduction, which we do not consider to be similar. In any case, this also makes the point that different studies in different populations result in different outcomes, including benefits. In this context, anyone who has recruited subjects for randomized controlled trials knows that people entering the study are a small subset of the total community of individuals to whom the outcomes may be extrapolated.

With regard to the input from observational studies, some are indeed limited by potential biases as we addressed. However, we argue that some observational study analyses, such as the one we performed on the Glasgow fracture liaison service outcomes,[1] can largely reduce these biases. In some cohort studies, some biases such as selection by indication may be relevant. However, in the Glasgow analysis, only those who attended the fracture liaison service were included and recommended treatment (bisphosphonate or calcium and vitamin D alone) were examined (equivalent to intention-to-treat). Thus, any suggestion of healthy user bias is irrelevant.

Denying a potentially beneficial outcome is just as bad as ignoring a potentially adverse outcome. This is not about failure of the primary outcomes in pivotal study but rather about ignoring the potential secondary benefits. We suggest that if the zoledronic acid post–hip fracture study had *not* shown the 28% benefit in mortality[2] but rather even a 1% adverse mortality outcome, zoledronic acid would have been withdrawn. As an example of the reality of this imbalance, the development of a novel cathepsin K inhibitor, odanacatib, was abandoned after it had completed its pivotal randomized controlled trial (RCT) studies with clear fracture risk reduction comparable to other antiresorptive agents.[3] This decision was based on an unexplained and unexpected risk of death from stroke. Importantly, there was no overall higher stroke risk, nor was there any overall increased death risk. More recently, the FDA approval of romosozumab carried with it the cardiovascular risk warning.[4] If, as the FDA announcement acknowledges, the cohort data are correct, it is most likely true not that romosozumab carries any cardiovascular risk but rather that it does not carry the benefit of alendronate.

Nordstrom and colleagues ultimately suggest that one has to be safe in assessing outcomes but then assume that an adverse outcome must be treated as likely true whereas a beneficial outcome must be treated as likely untrue. Our argument is that such a position, even when argued from an ethical (or even legalistic) viewpoint, is scientifically and statistically invalid. We consider that this is scientifically inappropriate, even though it is certainly true that the potential mortality benefit of osteoporosis treatment is ignored in guidelines. Just as some adverse events are identified not from the pivotal RCTs but from observational studies, unexpected benefits, particularly for mortality, should not be ignored in the extensive observational studies that consistently show this same important benefit.

Disclosures

The authors have nothing to disclose.

References

1. vanGeel T, Bliuc D, Geusens PPM, et al. Reduced mortality and subsequent fracture risk associated with oral bisphosphonate

Received in original form April 24, 2019; accepted April 28, 2019. Accepted manuscript online July 11, 2019.

Journal of Bone and Mineral Research, Vol. 34, No. 9, September 2019, pp. 1769–1770
DOI: 10.1002/jbmr.3809

recommendation in a fracture liaison service setting: a prospective cohort study. PLoS One. 2018;13:e0198006.

2. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357:1799–1809.
3. Mullard A. Merck & Co drops osteoporosis drug odanacatib. Nat Rev Drug Discov. 2016;15:669.
4. FDA. FDA approves new treatment for osteoporosis in postmenopausal women at high risk of fracture [Internet]. 2019 Apr 9. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635653.htm.