Author’s response to reviews

Title: Does Alendronate Reduce the Risk of Fracture in Men? A Meta-analysis Incorporating Prior Knowledge of Anti-Fracture Efficacy in Women

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Author's response to reviews: see over
To the Editor of BioMed Central Musculoskeletal Disorders,

We would like to thank the editorial staff, Drs. Cranney and Heaney for their thoughtful review of our manuscript titled, “Does Alendronate Reduce the Risk of Fracture in Men? A Meta-analysis Incorporating Prior Knowledge of Anti-Fracture Efficacy in Women.” We have responded to all of the comments of the reviewers in the following pages and made requested changes in the revised manuscript. We understand that the former version of figure 1 was not readable (as noted by Dr. Heaney) so we have reconstructed the figure (now Figure 3) and enclosed it as a TIFF file. Please let us know if any of the figures are not acceptable as we are happy to modify them further to the satisfaction of the editorial staff and reviewers.

Please contact Dr. Adachi at the address listed above with any questions or concerns.

Thank you for your consideration.

Sincerely,

A.M. Sawka, MD and J.D. Adachi, MD
Responses to Referee #1:

We would like to thank Dr. Heaney for his thoughtful review and insights. We apologize for the typographic and grammatical errors and have corrected all of them in the revised manuscript. We also apologize for the forest plots shown in the former Figure 1 not being readable. We have reconstructed Figure 1 (now Figure 3) and saved it as a TIFF file so we hope the current version is acceptable. If the current figures are not acceptable, we are happy to modify them further.

1. Pooling Data from all Aminobisphosphonates:

   The Reviewer has presented the very intriguing idea that that the meta-analysis could be extended to include not only alendronate but all aminobisphosphonates. Although this idea is very interesting, we believe it may not be feasible to incorporate in this particular study for several reasons. In order to make the additional assumption that all aminobisphosphonates ‘are created equal’, it would be important to first do a systematic review examining head-to-head superiority, non-inferiority, or equivalence studies comparing the anti-fracture efficacy (or effectiveness) of such drugs in women (the gender with more trial data). If there is evidence that all drugs result in equivalent reductions of fractures in women, bayesian models could then be used to examine the effect of all such drugs in men, incorporating prior information from women. It is also important to note that the aminobisphosphonate class of drugs includes intravenous preparations such as pamidronate as well as oral preparations (such as alendronate and risedronate); it is not clear if it would be appropriate to pool data from trials of drugs administered by different routes. These issues are beyond the scope of the present manuscript but definitely should be considered for future studies.

2. Justification of the Bayesian Approach:

   The Reviewer has requested that we clarify justification for the Bayesian approach so we have done so in the final four sentences in the Background section as follows: “Justification for the use of Bayesian approach in this study is the ability to directly answer the clinically relevant question: how likely is an osteoporotic man treated with alendronate to be protected from fracture given the current evidence in men and prior evidence in women? A classical frequentist analysis does not allow the flexibility to incorporate prior relevant information in
the analysis and all relevant data from women would be ignored in such an analysis. Thus, a Bayesian approach was chosen as the primary analysis method in our study. A simplified representation of our Bayesian model is shown in Figure 1.”

3. Clarification of How Prior Knowledge is Incorporated in a Bayesian Analysis:

We have added a figure (Figure 1) in the revised manuscript depicting how a Bayesian hierarchical model incorporates prior knowledge. We have also added further information to the Methods section under “Statistical Analyses and Assumptions” (second paragraph, second to fourth sentences): “The prior knowledge of treatment effects of alendronate in women (“prior distribution”) was incorporated in a hierarchical model and then the “likelihood function” of data in men was incorporated in this model for the same outcome. In order to transform the “prior” and “likelihood function” data to a “posterior” inference (final result), simulations were performed using Markov chain Monte Carlo Methods (9). For each outcome, we performed 20,000 simulations, with Gibbs sampling of results for posterior distributions started at 2,500. Convergence of the results was achieved in all models. A posterior distribution of the treatment effect of alendronate on the log (OR) and inverse log (OR) scales was obtained for the outcomes of vertebral and non-vertebral fractures, respectively.”

4. Comparison of Odds Ratios:

The reviewer has commented that “the odds ratios were somewhat less favorable to alendronate using the Bayesian approach” and has requested clarification of this observation. The odds ratios found using the Bayesian approach were: 0.44 (95% CRI 0.23, 0.83) and 0.60 (95% CRI 0.29, 1.44) for vertebral and non-vertebral fractures, respectively. The odds ratio using the frequentist approach were: 0.36 (95% CI 0.17, 0.77) and OR 0.73 (95% CI, 0.32, 1.67), for vertebral and non-vertebral fracture, respectively. Frankly, given that the credibility and confidence intervals overlap for the same types of fractures, we do not believe that the results of Bayesian and frequentist analyses are clinically or statistically different. We believe that the precision of the odds ratio estimate must be taken in the context of its respective credibility or confidence interval.
Of note, as we stated in the Methods section, in estimating the priors, we noted that in published random effects meta-analyses of postmenopausal women, the relative risk of vertebral fracture with alendronate therapy (≥5 mg daily) was 0.52 (95% confidence intervals [CI], 0.43, 0.65) (9360 women in eight studies); whereas the relative risk of non-vertebral fracture (alendronate ≥10 mg daily) was 0.51 (95% CI, 0.38, 0.69) (3723 women in six studies) (1). Given the high sample sizes, these relative risks would be expected to be similar to odds ratios. It is apparent that although the credibility and confidence intervals overlap, the odds ratios estimated using the Bayesian approach (as compared to the frequentist approach) more closely approach the point estimates observed in women.

Although point estimates (such as odds ratios) using a Bayesian approach would generally not be expected to be significantly different from that obtained using a frequentist approach (if data from prior information and new information is similar), credibility intervals can be narrower using a Bayesian approach than frequentist confidence intervals because of additional data provided by the priors (2). Upon examining our results, the width of the credibility and confidence intervals were 0.6 for Bayesian and frequentist analyses of vertebral fracture data, respectively. The widths of the credibility and confidence intervals were 1.15 and 1.35 for non-vertebral fractures, respectively. Thus, the precision of the results for the outcome of non-vertebral fractures was slightly better for the Bayesian relative to the frequentist approach. In the first paragraph of the Discussion, we have added the following 2 final sentences, “Of note, the numerical estimates of odds ratios and their respective credibility or confidence intervals were similar using Bayesian and frequentist analyses in this study. These findings are not surprising, given that the treatment effects of alendronate in women, from whom prior information was derived, were similar to those observed in men. The precision of our estimate was however slightly improved using a Bayesian approach for the outcome of non-vertebral fractures as seen by the slightly narrower credibility interval than confidence interval for that outcome. Credibility intervals can be narrower using a Bayesian approach than confidence intervals obtained using a frequentist approach because of additional data provided by the priors (reference 2 below).”
5. Use of Intention-to-Treat Approach:

The Reviewer has suggested that the intention-to-treat analysis may be a “knee-jerk” reflex and inquires about its justification. Dr. Heaney also raises the important issue of drug efficacy versus effectiveness of the prescription. We used an intention-to-treat principle to analyze our results as experts in the methodology of randomized controlled trials and systematic reviews have stated the following:

“Patients not adhering to treatments generally differ in respects that are related to prognosis. All randomized patients should therefore be included in the analysis and kept in the originally assigned groups, regardless of their adherence to the study protocol. In other words the analysis should be performed according to the intention-to-treat principle, thus avoiding selection bias.” (reference 3 below)

Of note, upon reviewing our methodology and reasons for exclusion of individual trials, intention-to-treat methodology was not a restriction in our literature search and there was no trial that was excluded solely because of lack of intention-to-treat trial data (for example, the Gonnelli trial lacked any fracture data [4]). We have included justification for focusing on intention to treat analyses in the Methods under “Design of the Systematic Review, Inclusion and Exclusion Criteria” by stating the following in the last sentence of the paragraph, “Our focus was primarily on intention-to-treat data as such analyses are thought to avoid selection bias.” By following recommendations from expert methodologists, we have simply tried to adhere to established principles in the field of trial methodology.

We agree with Dr. Heaney that it would be informative to do a sensitivity analysis of per protocol data (results from patients who adhered to therapy), but upon re-examining the primary papers, such data were not published and we did not have access to primary individual patient data. Thus, we were unable to perform per-protocol analyses of the efficacy of the drug in patients who were compliant. We have added a sentence describing this limitation to the first paragraph of the Discussion (second sentence): “We were also unable to perform a per protocol sensitivity analysis of the anti-fracture efficacy of
alendronate in men who were compliant with therapy as these data were not published in the primary trials.”

Responses to Referee #2:

We would also like to thank Dr. Cranney for her thoughtful review and suggestions. We apologize for the typographic and grammatical errors and have corrected them in the revised manuscript.

1. The Reviewer has requested more detail about Bayesian methodology and we have provided more information on Bayesian hierarchical modeling in the Methods under “Statistical Analyses and Assumptions” (second paragraph, second to fourth sentences) – see 3rd response to Reviewer #1. We have also added a simplified diagram of our Bayesian hierarchical model (Figure 1 in revised manuscript).

2. The Reviewer has suggested that the prevalence of vertebral fractures in men and women from CaMos be quoted. We have provided this information in the second sentence of the first paragraph of the Background section in the revised manuscript: “In a population-based study of Canadians age 50 years by the Canadian Multicenter Osteoporosis Study Group, the prevalence of vertebral fractures was found to be 23.5% in men and 21.5% in women” (reference 5 below).

3. The Reviewer has requested further information on the search strategy and suggested that this could be added to an Appendix. We have added an Appendix with details of the electronic search strategy.

4. The Reviewer has asked whether unpublished data was included. We did not include any unpublished data and we have added this limitation to the third sentence of the first paragraph of the Discussion.

5. The Reviewer has suggested moving results of the search to the Results section and we have done so in a section titled, “Results of Search for Relevant Studies” (first paragraph of the Results). We have added details of the total number of eligible trials (one hundred and three) to this paragraph as well as to figure (Figure 2 in revised manuscript).
6. The Reviewer has asked if we contacted authors to clarify details of randomization. We did not contact authors inquiring about such information and we have added this limitation to the third sentence of the Discussion.

7. The Reviewer has inquired whether vertebral fractures were assessed in the same fashion in both trials. We have added the following sentences (4th and 5th sentences in Results, under “Summary of Alendronate Trials in Men”: In the Orwoll study, an incident vertebral fracture was defined using the semi-quantitative method of Genant (reference 6 below), as assessed by a radiologist blinded to treatment assignment at the University of California in San Francisco. In the Ringe study, a vertebral fracture was defined by a new decrease in vertebral height of at least 20%, as assessed by a radiologist blinded to treatment assignment.”

8. The Reviewer has suggested that use of alfacalcidol in the Ringe trial could be considered an active comparator compared to the vitamin D preparation used in the Orwoll trial. We agree with this observation, and have modified the first sentence of the Discussion as follows: “Limitations of our systematic review include the paucity of trial data from men, the small sample sizes in trials, the variations in trial duration between studies, and the inconsistency of calcium and vitamin D formulations between trials (with the possibility that the alfacalcidol used in the Ringe study could be considered a form of active therapy [reference 7 listed below]).” Unfortunately, given the paucity of trials in this area, we were not able to make restrictions on calcium or vitamin D preparations for exclusion of studies, nor perform a meaningful sensitivity analysis of the effect of different vitamin D preparations.

References


