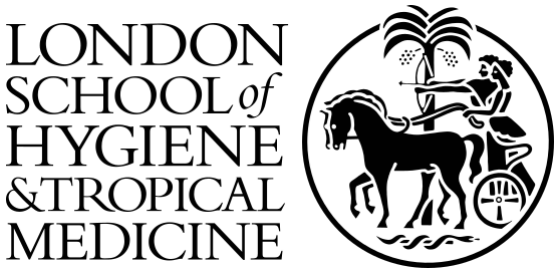

Reply to: Association between alendronate and all-cause mortality and cardiovascular mortality among hip fracture: an alternative explanation

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To the Editor:

We are thankful to Prof. Nguyen and Dr. Tran for their interest in our study and we appreciate the opportunity to respond to their comments. As Prof. Nguyen and Dr. Tran suggested that censoring patients at the time of switching medications might have inflated the effect size, we investigated this potential bias by excluding patients with switching of medications. Of the 3,081 alendronate-treated patients, 281 patients (9.1%) switched the therapy during the study period. After excluding these patients, we observed similar findings (Table), suggesting that bias due to treatment of censoring data should be minimal in our study.

Table: Association of alendronate and cardiovascular morality after excluding patients switching therapy.

Follow-up years	Hazard ratio (95% CI)	P
1-year	0.35 (0.18-0.67)	0.002
3-years	0.5 (0.34-0.72)	<0.001
5-years	0.57 (0.42-0.78)	<0.001
10-years	0.61 (0.45-0.82)	0.001

Prof. Nguyen and Dr. Tran performed a Bayesian analysis to investigate the probability that alendronate reduces cardiovascular mortality risk by more than 50%. However, the estimation was based on two meta-analysis, which included only a few studies (4 out of 110), conducted in patients with hip fracture. Given that hip fracture is associated with an increased risk of cardiovascular events [1], the estimation may not be comparable to our study. In addition, only RCTs were included in these two meta-analyses. While RCTs are considered the highest level of evidence, valuable data can be obtained from larger less selective population derived samples, and may not always agree with RCTs. One example is the association between the anti-diabetic agent SGLT2 and cardiovascular death. A recent meta-analysis of RCTs showed that SGLT2 was associated with a reduced risk of cardiovascular death (HR 0.77; 95% CI 0.6-0.98) [2], whereas a multinational observational analysis (CVD-REAL Nordic study) using propensity score matching (a similar approach to our study) obtained similar findings with a larger effect size (HR 0.53; 95: CI 0.40-0.71) [3]. As discussed in our study and other literatures [4, 5], the intention-to-treat analysis may underestimate treatment effect due to the misclassification of exposure in RCTs. Besides, results from the highly selected population in RCTs may be less generalizable to "real-world" conditions. Therefore, the result for cardiovascular mortality using Bayesian analysis is unlikely to reflect the real world clinical setting and potentially be underestimated.

More importantly, a previous population-based study in Taiwan also showed that the use of bisphosphonates was associated with a lower risk of coronary heart disease (adjusted HR 0.37; 95% CI 0.32-0.43) [6]. The effect size was similar to the results in our study. However, we do acknowledge that unmeasured confounding factors in observational studies could lead to over-estimation of effect. Therefore, we suggest further studies in other populations with robust control for confounders to validate the effect of alendronate on cardiovascular events.

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