Letter to the Editor

Title: Vitamin K Antagonist Use and Fracture

Running title: Vitamin K Antagonist Use and Fracture

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Word count: 400

No. of References: 5

No. of Tables: 2

Keywords: fracture, osteoporosis, non-vitamin K antagonist oral anticoagulant

We read with interest the article by Fiordellisi and colleagues, who reported findings of a systematic review and meta-analysis on the association between vitamin K antagonist (VKA) use and fracture.[1] The results provide an important contribution to better understand the risk of fractures associated with VKA use, which is still controversial and not well described in clinical practice.

One of the key findings of Fiordellisi et al was that there was no association between a higher risk of fracture and the use of VKA versus non-vitamin K antagonist oral anticoagulant (NOAC). The finding was supported by a pooled estimate of 0.95 (95% confidence interval: 0.78-1.15) with respect to *VKA versus NOAC users*. In reviewing this finding, we looked at the data presented in the forest plot (Figure 3 in the article). We found that the data for three of the included studies: Lucenteforte et al,[2] Norby et al,[3] and Steffel et al,[4] matched with the adjusted hazard ratios of *NOAC versus VKA users* reported in these studies *(*Lucenteforte: dabigatran versus warfarin; Norby: rivaroxaban versus warfarin; Steffel: edoxaban versus warfarin). As Fiordellisi et al defined the reference group as NOAC users in their meta-analysis, the *inverse* of these hazard ratios should have been used. Interestingly, when we re-calculated the pooled estimate by using the inverse of these figures, the result would suggest an association between a higher risk of fractures and the use of VKA versus NOAC (Table 1).

Further, in Fiordellisi et al, the data for Lau et al[5] was derived from the unadjusted event counts, whereas for all other three studies,[2-4] the adjusted data were used. It is important that the adjusted estimates for all studies are used when pooling the data, not only for consistency, but also for the robustness of the pooled estimate. When the adjusted estimates were used, the result would, again, suggested an association of a higher risk of fracture with VKA versus NOAC (Table 2).

Our findings contradict with Fiordellisi et al. and might raise questions on the validity of their results, and the foundation of the study conclusion regarding whether fracture risk should be considered when choosing an oral anticoagulant. We hope that the relevance of our findings would be considered by Fiordellisi and colleagues, and further work would be taken in addressing these issues. As such, the validity and the impact of the influential findings of the article would be greatly enhanced.

Acknowledgements

Funder: None

Conflict of interest: ICKW has received research funding outside the submitted work from the Hong Kong Research Grants Council, the Hong Kong Health and Medical Research Fund, Bristol-Myers Squibb, Pfizer, Janssen, and Bayer; KKCM is supported by the CW Maplethorpe Fellowship and has received personal fees outside the submitted work from IQVIA Holdings. No other disclosures were reported.

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Table 1. Pooled Results for Vitamin K antagonists (VKAs) versus Non-vitamin K antagonist oral anticoagulant (NOAC) when the inverse of the original result estimates are used in the meta-analysis

Study or Subgroup	Log [Result Estimates]	SE	Weight	Result Estimates IV, Random, 95%CI
Lau 2017	0.414	0.214	7.0%	1.51 [0.99, 2.30]
Lucenteforte 2017	0.039	0.272	4.3%	1.04 [0.61, 1.77][1]
Norby 2017	0.182	0.088	41.5%	1.20 [1.01, 1.43][1]
Steffel 2016	0.131	0.082	47.2%	1.14 [0.97, 1.34][1]
Total (95% CI)			**100%**	**1.18 [1.06, 1.32]**

Abbreviations: SE: standard error; CI: confidence interval.
Notes: Reviewer Manager 5.3 was used to conduct the analysis. The figures are rounded by Review Manager.
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.78$, df = 3 (P = 0.62); $I^2 = 0\%$; Test for overall effect: Z = 2.97 (P = 0.003).
[1]Obtained by taking the inverse of the adjusted hazard ratios of fracture risk with NOAC versus VKA reported by the source articles.

Table 2. Pooled Results for Vitamin K antagonists (VKAs) versus Non-vitamin K antagonist oral anticoagulant (NOAC) when the inverse of the adjusted estimates are used for all studies

Study or Subgroup	Log [Result Estimates]	SE	Weight	Result Estimates IV, Random, 95%CI
Lau 2017	0.967	0.280	13.0%	2.63 [1.52, 4.55][1]
Lucenteforte 2017	0.039	0.272	13.5%	1.04 [0.61, 1.77][2]
Norby 2017	0.182	0.088	36.3%	1.20 [1.01, 1.43][2]
Steffel 2016	0.131	0.082	37.2%	1.14 [0.97, 1.34][2]
Total (95% CI)			**100%**	**1.28 [1.01, 1.62]**

Abbreviations: SE: standard error; CI: confidence interval.
Notes: Reviewer Manager 5.3 was used to conduct the analysis. The figures are rounded by Review Manager.
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.53$, df = 3 (P = 0.04); $I^2 = 65\%$; Test for overall effect: Z = 2.06 (P = 0.04)
[1]Obtained by taking the inverse of the adjusted incidence rate ratio of fracture risk with NOAC versus warfarin reported by the source article.
[2]Obtained by taking the inverse of the adjusted hazard ratios of fracture risk with NOAC versus warfarin reported by the source articles.