

**COMMENT & RESPONSE**

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parator with warfarin, and so the potential for confounding by indication cannot be ignored.<sup>2</sup> However, at the time the studies were conducted, no comparator with similar indications existed because warfarin was the only treatment choice available. With the availability of NOACs, there will be opportunities for reliable comparisons with warfarin with respect to fracture risk. Further comparisons between different NOACs, as suggested by Sugiyama, will provide further insights into any mechanistic differences between NOACs with respect to fracture risk, as well as inform the choice of oral anticoagulant prescribed in clinical practice.

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1. Fusaro M, Dalle Carbonare L, Dusso A, et al. Differential effects of dabigatran and warfarin on bone volume and structure in rats with normal renal function. *PLoS One*. 2015;10(8):e0133847.
2. Veronese N, Bano G, Bertozzo G, et al. Vitamin K antagonists' use and fracture risk: results from a systematic review and meta-analysis. *J Thromb Haemost*. 2015;13(9):1665-1675.

**In Reply** Dr Sugiyama suggested some possible mechanisms for our results and directions for further research. We agree that it is worth investigating whether dabigatran could reduce the risk of falls in future studies. We were unable to look in detail at hip and vertebral fractures separately because of the small number of events; even the composite outcome was rare (<1.0 per 100 person-years). Additional studies that examine the risk of falls, as well as fall-related and fall-unrelated fractures, are therefore warranted to evaluate the possible roles of dabigatran and warfarin in association with fracture risk, especially among patients receiving short-term treatment (<1 year).

Although the lower risk of fractures with short-term treatment may be less likely to result from changes in bone fragility, we think that this might not necessarily preclude any biological effects of dabigatran or warfarin on bone because we also observed a lower risk for long-term use ( $\geq 1$  year). Further, an animal study reported that dabigatran use was associated with higher bone volume, reduced trabecular separation, and lower bone turnover rate compared with warfarin use.<sup>1</sup> It would be useful to determine the effect on bone, together with the risk of falls and individual types of fractures, with the use of dabigatran vs warfarin in future studies.

Although some studies suggest that warfarin may not cause fragility fractures,<sup>2</sup> previous evidence was mainly derived from studies using untreated or unmatched patients as the com-