Fracture risk reduction with use of dipeptidyl peptidase-4 inhibitors

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LETTER

Fracture risk reduction with use of dipeptidyl peptidase-4 inhibitors: is there immortal time bias?

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Dear Editor,

Dombrowski et al. [1] report a 33% reduced risk of bone fracture and a 57% reduced risk of hip fracture with use of dipeptidyl peptidase-4 inhibitors (DPP4-Is) and metformin as compared to metformin-only use. The identified protective effect is in contrast with recent literature on this topic, which has not shown an association [2–4]. In view of this difference, we are concerned that the reported relationship may be affected by immortal time bias [5]. Immortal time bias leads to an effect in favour of the studied drug, which corresponds with the results found in the study by Dombrowski et al. [1].

In the study by Dombrowski et al. [1], the start of follow-up is not fully clear. In the methods section, it is mentioned that the index date is defined based on the first DPP4-I (for the DPP4-I users) or the first metformin (for the metformin-only users) prescription, respectively. This suggests that the time between the first metformin prescription and the first DPP4-I prescription is excluded from the analysis. As a consequence, patients have to survive event-free until the time of the first DPP4-I prescription, which causes immortal time bias.

However, the study outcome was defined as rate of bone fractures within 5 years of starting metformin therapy, which suggests that patients (both DPP4-I users and the metformin-only users) were followed from the first metformin prescription onwards. This may only result in immortal time bias if the time from the first metformin prescription until the first DPP4-I prescription is classified as DPP4-exposed instead of unexposed. A time-dependent analysis, in which the time until the DPP4-I prescription is classified as unexposed and the time from the first DPP4-I prescription onwards as exposed, would solve this potential problem.

In conclusion, we would kindly ask the authors to provide some more information on the study design as it is important to know what date was used for both exposure groups to determine start of follow-up. In particular, if the date of the first metformin prescription was used to determine follow-up, it is critical to know whether the time from the first metformin prescription to the first DPP4-I prescription was classified as DPP4-exposed or unexposed.

A response to these comments can be found at doi:10.1007/s00198-017-4139-4.

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Compliance with ethical standards

Conflicts of interest JD, LK, PG and JvB declare that they have no conflicts of interest.

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