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LETTER

Proton pump inhibitors, fracture risk and selection bias: three studies, same database, two answers

F. de Vries · T.-P. van Staa · H. G. M. Leufkens

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Dear Editor,

Two studies in 2000 and 2001, both conducted using the UK General Practice Research Database (GPRD), reported conflicting results on the potential beneficial effects of statin use and fracture risk. An extensive reanalysis of the results showed that selection bias in one study largely explained the discrepant findings and that the results did not support a hypothesis of beneficial effects on bone. The reanalysis showed that the risk of hip fractures was halved almost instantly after starting statins and waned thereafter, which is difficult to reconcile with a bone effect. The biological mechanism assumed in 2000 was that statins affected the mevolanate pathway as do the bisphosphonates. Rather than emphasising the summary relative risks (RRs) in the original statin analyses, the absence of a durable response should have limited the interpretation of the findings since the data did not support a biological mechanism for statins to increase the quality or quantity of bone [1].

Does history repeat itself? On 25 May 2010, the Food and Drug Administration (FDA) decided to add a warning of a possible increased risk of fractures to the labelling of proton pump inhibitors (PPIs), drugs that are widely used for the treatment of gastroesophageal reflux disease [2]. This decision was based on the FDA's internal review of seven epidemiological studies, including two studies that used GPRD, but again with conflicting results [3, 4]. Two recently published papers were not included in this review, including a third GPRD study [5]. The FDA review showed that only few studies have evaluated the duration of any effect between use of PPIs and risk of fracture. The two recent studies in GPRD [5] and the Dutch PHARMO database (which has been published as an abstract since mid 2009, but which is now in press in Osteoporosis International) showed that the association between PPI use and fracture risk at various fracture sites was highest during the first year of treatment (a 1.3-fold increased risk of hip fracture), and then attenuated with prolonged use (with a 0.9-fold increased risk of hip fracture in patients who had used PPIs for >7 years [6]). Similar to findings with statins and fracture risk, selection bias could explain this pattern of risk with duration of use [1]. These data are not supportive of a hypothesis that PPIs modify the quality or quantity of bone.

The FDA review considered that the biological mechanisms for an increased risk of fractures with PPIs are not known. Despite this, the FDA review concluded that the available data suggested a possible increased risk of fractures with PPI use. In our view, evidence for drug effects should not be used on an assessment of deviations of summary RRs from unity but rather on an assessment on whether specific hypotheses of biological mechanisms of drug effects are supported by evidence. Given the weak and

F. de Vries · T.-P. van Staa · H. G. M. Leufkens
Utrecht Institute for Pharmaceutical Sciences,
Universiteit Utrecht,
Utrecht, Netherlands

F. de Vries · T.-P. van Staa
General Practice Research Database (GPRD),
Medicines and Healthcare Products Regulatory Agency,
London, UK

F. de Vries (✉)
Division of Pharmacoepidemiology and Clinical Pharmacology,
Utrecht Institute for Pharmaceutical Sciences,
Sorbonnelaan 16,
3584 CA Utrecht, Netherlands
e-mail: f.devries@uu.nl

F. de Vries
MRC Epidemiology Resource Centre,
Southampton General Hospital,
Southampton, UK

conflicting evidences, not only from epidemiological studies, but also for a pharmacological effect of PPIs on bone mineral density in humans, we feel that the label change of PPIs is premature.

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