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Commentary: Statins and fracture risk—unresolved questions

Christoph R Meier

In 2000, we found a substantially reduced fracture risk for patients who used hydroxymethyl-glutaryl coenzyme A reductase inhibitors, a class of lipid-lowering drugs also called 'statins'[1] in a retrospective nested case–control analysis using data from the British General Practice Research Database (GPRD). Two large US-based epidemiological analyses reported virtually the same findings.[2,3] These studies were stimulated by an intriguing paper by Mundy *et al.* who screened numerous pharmacological compounds in an animal model. They found a marked increase in bone mass in simvastatin-treated rodents.[4] A recent review article by Bauer[5] nicely summarized these as well as numerous subsequent observational studies: most of them consistently found a reduced fracture risk for human statin users. In 2001, a Dutch group used the GPRD to revisit this issue: they concluded that 'use of statins at dosages prescribed in clinical practice was not associated with a reduction in risk of fracture'.[6]

In the current issue of the *IJE*, Frank de Vries, a co-author of the second GPRD analysis,[6] reports on a re-analysis of GPRD data. The focus is on hip fractures and on explaining the differing results. The first two studies using GPRD data[1,6] differed in four aspects: First, we conducted a nested case–control analysis including 3940 fracture cases and 23 379 controls, all of which came from a study population of users of lipid-lowering drugs, patients with untreated hyperlipidaemia, or a random sample of the GPRD population which had neither hyperlipidaemia nor use of lipid-lowering drugs recorded.[1] Van Staa *et al.* did an open case–control analysis in the GPRD and included virtually all fracture cases >50 years of age: 81 880 fracture cases and the same number of controls.[6] Second, the Dutch group used a larger version of the GPRD, which included data from 683 general practices, while we used a copy of the GPRD with only about half of these practices. We eliminated, independent from this particular study question, all practices for which data quality was uncertain. Third, we a priori excluded participants with cancer, osteoporosis, alcoholism, or previous use of bisphosphonates, while van Staa *et al.* did not make any exclusions. Finally, current statin users in our study had their last statin prescription recorded <30 days prior to the index date, while the Dutch group classified patients as current users if they had a statin prescription recorded within 6 months prior to the index date.

De Vries addresses some of these issues in his re-analysis. The study design ('selected population' vs 'entire population'),

Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Hebelstrasse 2, 4031 Basel, Switzerland. E-mail: meierch@uhbs.ch

Table 1 Current statin use compared with non-use: Results from different analyses of the General Practice Research Database (GPRD)

Study	Odds ratio (95% CI)	Comment
Meier *et al.*[1]	0.12 (0.04–0.41)	Based on 3 exposed cases and 77 exposed controls
Van Staa *et al.*[6]	0.59 (0.31–1.13)	Based on 18 exposed cases and 31 exposed controls
De Vries (in this issue)		
'Selected population'	0.37 (0.27–0.52)	Based on 67 exposed cases and 542 exposed controls, approach similar to Ref. (1)
'Entire population'	0.54 (0.39–0.74)	Based on 58 exposed cases and 106 exposed controls, approach similar to Ref. (6)

however, does not seem to make a substantial difference, since the results for hip fractures are closely similar, and, interestingly, also quite similar to what Meier[1] and van Staa[6] reported a few years ago (Table 1). De Vries explores what may have caused these subtle differences by using various exposure categories for statins and by applying matching for age in different ways. However, none of these modifications made a substantial difference, which is a useful piece of information in its own right. Thus, his re-analysis can be interpreted as providing evidence that modifying certain factors in the design or analysis can shift the odds ratio upwards or downwards, leading to differences in the interpretation of results. On the other hand, one could also argue that unsurprisingly point estimates change slightly when certain conditions are modified, but this change (for example from an odds ratio of 0.4–0.5) is not relevant in the big picture. In contrast to De Vries, I am not impressed by the magnitude of changes in the odds ratios after modifying these parameters, including the age-bands in the matching procedure.

De Vries discusses the possibility that the statin–fracture association may be distorted by socioeconomic status (SES), a parameter which is hard to measure and which was only taken indirectly into account in the GPRD studies by matching on practice. Indeed, it is conceivable, as discussed in our report,[1] that people with higher SES may a priori have a lower fracture risk and a higher likelihood of receiving statins. Unfortunately, the current re-analysis cannot solve this question. Another observation made by de Vries has to be seen in the same context: in our paper[1] as well as his re-analysis, few statin prescriptions were already associated with a reduced fracture risk, even though one might expect an effect only after several months of treatment. One explanation may be bias or substantial confounding, for example by SES: if statin users have a priori a lower fracture risk than non-users, one would expect a reduced fracture risk for all statin users, regardless of exposure timing or duration. However, we also explored whether the fracture risk differed between current statin users and past statin users; for all fractures combined, the OR for current statin use was 0.55 [95% confidence interval (95% CI) 0.44–0.69], and 0.87 (95% CI 0.65–1.18) for past statin use.[1] These results do not rule out bias associated with statin use, but reduce these worries to some degree. Another explanation might be an immediate effect on bones, since bisphosphonates also exert an effect within a few weeks of a therapy initiation. Finally, we may measure a real effect of statins on fracture risk, but this might not be caused by increasing bone strength but by reducing the risk of falls: statins could reduce the risk of falls by improving microcirculation in the brain and thereby co-ordination and propiception. This is not easy to study in an observational setting since falling is not a hard endpoint. To my knowledge, there is only one small study on the risk of falls in relation to statin use which does not support this hypothesis,[7] but nevertheless we need to keep our eyes open for alternative explanations of intriguing und unexpected observations in epidemiological studies.

A reduced fracture risk associated with current statin use has been seen consistently in numerous observational studies, which were done by independent research groups in various health systems and different parts of the world. This surely tells us something, and it seems unlikely that these findings are entirely the result of chance or bias. One important question, however, remains unsolved: why have the various re-analyses of data from randomized trials[8–11] not supported the same conclusions? As much as I support De Vries' attempt to answer some of the open questions I am afraid that the current re-analysis does not help much regarding this key question. Hopefully a future large, well-designed randomized trial, done in an appropriate study population with prospective bone density measurements and fractures as the primary outcome will ultimately provide the answer.

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