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## Statins and Fracture Risk

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LOSS OF BONE MASS ACCOMPANIES THE AGING PROCESS and increases risk of fracture, particularly in women. The principal sites of osteoporotic fractures are the forearm, vertebral body, and hip.<sup>1</sup> Pharmacological theory<sup>2</sup> and in vivo<sup>3</sup> and animal<sup>4</sup> model observations have suggested that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may increase bone mineral density, raising the hope that these drugs also may be useful in reducing risk of osteoporotic fractures.

With the publication of the article by van Staa and colleagues<sup>5</sup> in this issue of THE JOURNAL, there are now at least 7 studies reported in full publication or abstract form that have measured the association between statin use and fracture risk.<sup>5-11</sup> Of these, 6 used observational designs<sup>5-10</sup> and 1 reanalyzed data from a randomized trial that was performed to evaluate cardiovascular end points.<sup>11</sup> At first glance, these studies appear inconsistent, with 3 positive studies and 4 that did not show a statistically significant protective effect. However, closer examination shows some consistency across studies. For example, although these studies have examined different primary outcomes, all reported results for hip fracture. A statistically significant inverse association with hip fracture risk was reported in 3 of the 7 studies,<sup>7-9</sup> and point estimates for relative risks (RRs) and odds ratios (ORs) for 6 of the 7 studies are less than 0.8 (we calculated the RR to be 0.77 [95% confidence interval {CI}, 0.34-1.75] for the study by Reid et al<sup>11</sup> based on data presented in their article). Unfortunately, this type of analysis could not be performed for

other osteoporotic fracture sites, since not all the studies presented the necessary data.

However, because all 3 "positive" studies are observational, it is important to consider the possibility that bias or confounding, rather than a true protective effect of statins, may be responsible for the observed inverse associations. In particular, if statins are preferentially prescribed to persons who have a lower fracture risk, and the factors responsible for this lower risk are not adequately measured and accounted for, then any observed associations could be due to bias or confounding rather than being causal. Importantly, the only randomized clinical trial among the 7 studies<sup>11</sup> failed to show a protective effect of statins on fracture risk, although it was primarily a study of men and had sufficiently few hip fracture outcomes that its results remain statistically compatible with the results of the nonrandomized studies.

van Staa et al<sup>5</sup> argue that the associations observed in their study are most likely to be due to confounding by body mass index (BMI), since high BMI is associated with both elevated serum cholesterol levels and a reduction in risk of osteoporotic fractures. Although this concern is entirely reasonable on its face, van Staa et al provided no empirical evidence for its support, such as evidence that the RR in their study was

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attenuated after controlling for BMI among those for whom BMI data were available. The observation that BMI was controlled for in 2 studies that showed a significant or almost significant association argues against confounding by BMI as a source of the association,<sup>6,8</sup> although the study by Meier et al<sup>8</sup> had substantial missing data on BMI. In addition, in the 2 studies that presented both BMI-adjusted and -unadjusted results, adjusting for this variable did not shift the RR toward the null value.<sup>5,8</sup> Regardless, the possibility of confounding by BMI probably has not been examined closely enough to consider the issue settled. Furthermore, there might be other uncontrolled confounding factors (eg, differences in physical activity or dietary intake of calcium or vitamin D) contributing to the observed association in nonrandomized studies.

Adding to the uncertainty of the suggestive findings is the inconsistency in the results of supplemental analyses that would support the hypothesis of a protective effect of statins. For example, a causal argument would be bolstered if nonstatin lipid-lowering drugs did not show a protective association, because current pharmacological theory would not predict such an effect of these agents. However, such analyses have been equivocal, with at least a trend toward an inverse association for nonstatin lipid-lowering drugs in 2 studies.<sup>8,9</sup> Monotonic relationships between risk of fracture and duration of statin use and number of statin prescriptions, if found, would also bolster the argument that the observed associations are causal. However, such a relationship was found in 1 study<sup>9</sup> but not in others,<sup>5,7,8</sup> adding to the uncertainty that the observed association is causal.

Interestingly, 2 of the observational studies took place within the UK General Practice Research Database (GPRD)<sup>5,8</sup> yet arrive at quantitatively and, apparently, qualitatively different results. As replicability is a hallmark of science, one would hope that 2 groups studying the same association within the same population would arrive at the same results. However, van Staa et al reported an OR of 0.59 (95% CI, 0.31-1.13) for the association between statin use and hip fracture, whereas Meier et al reported an OR of 0.12 (95% CI, 0.04-0.41). Although these estimates are consistent with an inverse association between statin use and hip fracture, the results of van Staa et al, but not of Meier et al, are also consistent with no association. For the larger set of fractures studied by the 2 research groups, the ORs appeared even less consistent: 1.01 (95% CI, 0.88-1.16) for van Staa et al vs 0.55 (95% CI, 0.44-0.69) for Meier et al, although the latter includes fractures of unspecified sites, which are not included in the former. Another potential source of the difference in results is that current statin use was defined by van Staa et al as a prescription within the past 6 months and by Meier et al as a prescription within the past 30 days. This argument is weakened, however, by the analysis by van Staa et al of statin use within the past 3 months, which had an RR of 0.99 (95% CI, 0.86-1.14).

However, there were many other differences between the 2 studies. For example, van Staa et al used the entire GPRD data set: 683 general practices and data from 1987 through

July 1999. In contrast, Meier et al analyzed data from only 300 GPRD practices and only through September 1998. Thus, the latter analyzed a subset of the former. Furthermore, GPRD records its diagnosis information using the OXMIS (Oxford Medical Indexing System) and Read coding systems. Meier et al appear to have mapped the GPRD codes to *International Classification of Diseases, Eighth Revision (ICD-8)* codes, while van Staa et al mapped them to *ICD-9* codes. Thus, although these studies appear to be using the same database, they are studying different patients and, depending on how this mapping was performed, may have studied different outcomes.

In summary, the available evidence seems consistent with a protective effect of statins on risk of hip fracture but this finding also could have been caused by uncontrolled confounding. A definitive answer will probably require evidence from randomized trials. Fortunately, large randomized trials of the effect of these drugs on cardiovascular outcomes have been performed, and these trials should be available for reanalysis, as was the study by Reid et al.<sup>11</sup> Because these trials were designed to detect differences in the rates of cardiovascular events, the studies, taken individually, may not have enough statistical power to detect clinically meaningful reductions in risk of osteoporotic fractures. However, this limitation could be addressed by performing a meta-analysis, and the investigators of these studies should be encouraged to combine their individual-level patient data to conduct a meta-analysis of this question. Such a reanalysis should focus on fractures at sites usually associated with osteoporotic fractures because statins should be most likely to have a protective effect on these sites. However, until convincing data from randomized trials have demonstrated a protective effect of statins on risk of osteoporotic fractures, the evidence supports the conclusion of the editorialists who commented on the first such article in this journal: "In the meantime, patients with osteoporosis should be treated with agents that have been proven to reduce the risk of fractures."<sup>2</sup>

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