Statin Use and Fracture Risk

Study of a US Veterans Population

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Background: Whether statins reduce the risk of fractures is still contested. Several studies support a favorable association, whereas post hoc analyses of statin-randomized trials have failed to find a benefit. We sought to assess this possible relationship in a large population of elderly, predominantly male veterans.

Methods: We established the study population using all health care encounters and services from patients who received care in the New England Veterans Affairs health care system between January 1998 and June 2001. According to evidence from the literature, covariates that would affect the risk of fractures were included in the final model, as were medications that were clinically meaningful and significant in univariate models and the Charlson Comorbidity Index as a surrogate for general health. We also conducted a similar analysis among new statin users. We used pooled logistic regression to assess for significant associations.

Results: Of the 91,052 patients in the final cohort, 28,063 were prescribed statins and 2195 were prescribed non-statin lipid-lowering medications. In the adjusted analyses, statin use was associated with a 36% (odds ratio, 0.64; 95% confidence interval, 0.58-0.72) reduction in fracture risk when compared with no lipid-lowering therapy and a 32% (odds ratio, 0.67; 95% confidence interval, 0.50-0.91) reduction when compared with nonstatin lipid-lowering therapy. Similar findings were found for the new statin user group.

Conclusions: We have provided yet another study in a unique population of mostly male veterans that found a significant reduction in fractures among statin users. More studies need to be performed to confirm or refute our findings.

This retrospective study was approved by the Boston VA institutional review board. The study population was created from a database that contained all health care encounters and services for the population of patients who received care in the New England VA health care system between January 1, 1998, and June 30, 2001 (n = 385 037). Use of the VA health care system consisted of use of the pharmacy, laboratory, inpatient, or outpatient facilities. Patients who died or were admitted to long-term care before the study end (June 30, 2001) or before the occurrence of a fracture (n = 47 057) were excluded. We required study participants to be active users of the VA health care system as evidenced by at least 1 visit to a facility every 12 months after entry into the cohort (159 166 excluded). Patients with inconsistent ages (n = 927) and those who did not have anthropomorphic data collected routinely at primary care visits (n = 61 345) were also excluded. In addition, patients with a recorded diagnosis of cancer, except skin cancers, were excluded because these individuals may not have been prescribed preventive care such as statins and may have markedly different risk factor profiles for fracture (n = 16 855).

Among this population of interest, we identified 94 364 patients who received more than 1 prescription for the statins atorvastatin calcium, cerivastatin sodium, fluvastatin sodium, lovastatin, pravastatin sodium, or simvastatin; more than 1 prescription for the nonstatin lipid-lowering agents cholestryramine resin, clofibrate, colestipol hydrochloride, fenofibrate, gemfibrozil, niacin, or niacinamide; or none of these medications during the study period. We then excluded 3095 people who had received prescriptions for both statins and nonstatin lipid-lowering agents. Finally, we excluded 217 people with a diagnosis of a fracture during their first month in the VA health care system because we did not have adequate longitudinal information on these people. Our final study population consisted of 91 052 mostly male participants (only 4321 women).

Our primary outcome of interest was an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis of fracture in the inpatient or outpatient records. To improve the accuracy of this diagnosis, rib and unspecified fractures were excluded and ankle fractures were included only if they were accompanied by an orthopedic visit within 30 days of the diagnosis.

Potential covariates collected include sex, age, race, and body mass index (BMI). The Charlson Comorbidity Index was also derived for each participant. Since illnesses that contribute to the Charlson Comorbidity Index are rarely diagnosed at entry into the system, the cumulative score covered the period from the start of the study window until the occurrence of a fracture or the end of the study window. To quantify preexisting fracture risk, we collected diagnoses of osteoporosis (ICD-9 code = 733.0x) and prescriptions for calcium or a bisphosphonate. Prescriptions for medications believed to be associated with an increased risk of falls in elderly individuals, including benzodiazepines, barbiturates, muscle relaxants, antidepressants, and antipsychotics, were also collected, as were prednisone, antiparkinsonian agent, and anticonvulsant prescriptions.

Covariates thought to affect the risk of fractures according to evidence from the literature were included in the final model (age, BMI, and sex). The Charlson Comorbidity Index was included as a surrogate for general health. All medications that were clinically meaningful and statistically associated with fracture based on univariate models were included in the model. Pooled logistic regression with repeated observations was used to compare the number of incident fractures among those using only statins as a lipid-lowering therapy with those using other lipid-lowering therapies or no therapy. Person-time was attributed to the non–lipid-lowering group on a monthly basis from entry into the VA health care system until the initiation of a lipid-lowering medication, the first occurrence of fracture, or the end of the study window. Exposed person-months began when the first lipid-lowering medication was dispensed and continued until the first occurrence of fracture or the end of the study window. A generalized additive model was used to determine the best fit for nonlinear factors such as age and BMI, which were squared in the final models.

To address the possible relationship between dose and length of statin exposure, we conducted a nested retrospective cohort study. Participants with at least 3 months of observation before a statin prescription were considered new statin users. Prevalent statin users and users of other lipid-lowering therapies were excluded. The comparison group was VA health care system users who did not receive a statin prescription during the previous year. Statin users who had stopped therapy for 1 year or longer were reclassified as nonusers. However, any fractures that occurred within the 12 months before reclassification were attributed to the statin group.

In addition, the mean statin dose for the study period was determined for each month and converted to a simvastatin equivalent dose and then divided into tertiles. The equivalent simvastatin doses were determined by dividing the lovastatin or pravastatin dose by a factor of 2, dividing the fluvastatin dose by 4, and multiplying the cerivastatin dose by 10 and the atorvastatin dose by 2. We used pooled logistic regression with repeated observations to compare the number of incident fractures among new users of statins with nonusers.

Of the 91 052 patients in the final cohort, 28 063 were prescribed only statins, 2195 were prescribed nonstatin lipid-lowering medications alone, and the remaining 60 794 were not prescribed any lipid-lowering medications during the study window. Table 1 gives the characteristics of the cohort. Statin users were older than veterans not using lipid-lowering therapy (65.1 years of age compared with 59.3 years; P < .001) and those receiving other lipid-lowering therapies (61.0 years of age; P < .001). The BMI was higher among those receiving lipid-lowering therapies. The mean scores on the Charlson Comorbidity Index were higher in the other lipid-lowering group (mean score, 1.4) and statin group (mean score, 1.3) compared with the no lipid-lowering group (mean score, 0.9).

In Table 2, the number and types of fractures in each group are given. There were a total of 394 fractures among the statin-only users, 2018 fractures in the non–lipid-lowering group, and 51 fractures in the group receiving other lipid-lowering therapies. Table 3 gives the crude and adjusted logistic regression models for the risk of fracture for individuals taking statins compared with those receiving nonstatin lipid-lowering therapies or no lipid-lowering therapy and a comparison between individu-
als receiving nonstatin lipid-lowering therapies and those not receiving lipid-lowering therapies. In the adjusted analyses, the use of statins compared with no lipid-lowering therapy was associated with a 36% reduction in fracture risk and a 32% risk reduction compared with nonstatin lipid-lowering therapy. However, no significant difference occurred in the risk of fractures between users of nonstatin therapies compared with those not receiving lipid-lowering therapy.

In the new statin user analysis, there was a 162 463 person-year exposure history for the nonstatin comparison group compared with an 18 776 person-year exposure history for statin users. The fracture incidence rate per 1000 person-years was 12.35 for the nonstatin group compared with 7.35 for all simvastatin equivalent doses. Table 4 gives the odds of developing fractures between new statin users and the nonstatin comparison group, with the statin dose divided into tertiles. In all models there is a significant reduction in the risk of fractures, with a greater benefit for those in the upper tertile of statin dose (multivariate adjusted odds ratio [OR], 0.50; 95% confidence interval [CI], 0.37-0.70).
Our goal was to ascertain whether statins were associated with fewer fractures in a large, elderly, mostly male veteran population with numerous comorbid conditions. More than 28 000 of these individuals were using statins, making this study one of the largest to evaluate the association between statins and fractures. The use of statins in this study was associated with a 36% reduction in fracture risk when compared with no lipid-lowering therapy. These findings did not deviate significantly after adjustment for various covariates, including BMI.

Our findings are similar to those of other large cohort studies. In the nested case-control study by Meier et al,15 the use of statins was associated with a reduced risk of fractures (OR, 0.55; 95% CI, 0.44-0.69), and Wang et al14 found similar reductions (OR, 0.50; 95% CI, 0.33-0.76). If these findings are true, there are more than 30 million Americans at risk for osteoporosis who could benefit from the use of statins.22,23

In our study, we included several factors that based on historical data and crude analysis were associated with both statin use and outcome fracture. Two likely confounders not included were alcohol and tobacco use. Neither is accurately coded for in health care claims data. In addition, we were unable to adjust for physical inactivity.24 It is possible that statin users are counseled to a greater extent than nonusers to stop smoking and to exercise. As a result of this healthier lifestyle, fracture risk would be reduced, yet this should also be the case for those receiving other lipid-lowering therapies. However, there was a favorable reduction in fractures among statin users compared with those receiving other lipid-lowering therapies. In addition, scores on the Charlson Comorbidity Index24 (an index of underlying burden of comorbid conditions) were higher among statin users, suggesting that this group is not necessarily healthier. It is also unclear how strong an effect exercise would have on fracture risk in this population. In an examination of osteoporosis risk factors in the Framingham Osteoporosis Study,24 factors associated with a lower bone mineral density in men were smoking and thinness. Gain- ing weight was associated with an increase in bone mineral density, whereas physical activity had no effect.25-27

We adjusted for several other potential confounders, such as selective serotonin reuptake inhibitors28,29 and tricyclic antidepressants. These agents serve as surrogates for clinically significant depression, which in some studies was shown to be associated with fractures.30 We also adjusted for other medications shown to increase the
risk of falls.\textsuperscript{27,31-33} We did not adjust for nitrates\textsuperscript{34} or thiazide diuretics\textsuperscript{35,36} because they were not significantly associated with both the exposure and the outcome and the evidence of their association is limited.

In our primary analysis, we did not discern among different doses of statins or duration of statin use. Prevalent statin users may have had years of statin exposure, which would be problematic if a long history of use also served as a marker of a healthier patient. Ray\textsuperscript{37} addressed this concern in a recent article in which he proposed evaluating new users in comparison analyses. Therefore, we conducted a nested cohort analysis in which we considered only individuals with at least 3 months of observation before receiving a statin. We also determined the mean monthly dose of statin (converted to an equivalent dose of simvastatin) and divided the dose into tertiles. The subsequent analysis revealed a greater benefit with higher doses of statin ($P$ for trend $<.001$). We had to make several assumptions to conduct this analysis. For instance, if participants stopped therapy for more than 12 months, we no longer considered them statin users and they then became nonusers. It is possible that statins have an effect that lasts beyond 1 year, which would mean that we underestimated the benefit. Despite the limitations of this analysis, the results support our overall findings that statins are associated with fewer fractures and hint to the possibility of a dose effect. Unfortunately, we had insufficient variation in the types of statin (formulary restriction to mainly lovastatin or simvastatin) to evaluate any potential differences between them.

Whether statins reduce fractures continues to be debated. Numerous epidemiologic studies and a proposed biological mechanism provide evidence that statins may reduce fractures. However, failure to find a favorable association in statin-randomized clinical trials and concerns for residual confounding in epidemiologic studies or classification suggest that caution is warranted in interpreting the results of observational studies. The BMI is one possible confounder and is the reason why we confined our observational cohort to patients with weight recorded. Studies\textsuperscript{27,38} in men have reported that increased weight protects against fractures, whereas other studies\textsuperscript{39} have not. However, if increases in BMI are protective, the mechanism is uncertain but may include increased bone mineral density\textsuperscript{40} due to greater circulating endogenous estrogen levels.\textsuperscript{41,42}

Another possible explanation is that elevated cholesterol levels, which are often higher among obese individuals, are protective against fracture. In this case, an elevated BMI would be a surrogate for an elevated cholesterol level. Adami et al\textsuperscript{33} reported that in 2 cohorts of healthy women and men, bone mineral density was significantly related to serum lipids: negatively for high-density lipoprotein cholesterol and positively for triglycerides and low-density lipoprotein cholesterol. If these findings are true, then it may explain why the statin clinical trials fail to find an association, whereas the observation trials that compare populations with high cholesterol levels (group receiving statins) vs the controls with lower cholesterol levels (nonstatin group) find a difference that favors statins. In this scenario, statins are a surrogate for higher cholesterol levels, which are protective against fractures.

This finding contradicts other evidence that suggests that osteoporosis and CVD share many of the same risk factors. Greater oxidative stress, inflammation, and endothelial dysfunction that results in poor bone health suggest a common pathway of CVD and fractures. Known CVD risk factors, such as diabetes, smoking, and physical inactivity, are also associated with a lower bone mineral density.\textsuperscript{44,45}

It is evident that more studies need to be performed to address this controversy. The potential public health impact is too great to leave this question unanswered. We have provided yet another study in a unique population. In our large cohort of mostly male veterans, statin therapy was associated with a reduction in fractures. Our study represents one of the largest studies to date of individuals receiving statins and the evaluation of fracture risk. Although we were limited in adjusting for all known confounders, this study provides additional information that fuels the debate of whether statins protect individuals against fractures. Further research is necessary to confirm or refute our findings.

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