# HMG-CoA Reductase Inhibitors and the Risk of Hip Fractures in Elderly Patients

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**Context** Recent animal studies have found that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) lipid-lowering drugs (statins) substantially increase bone formation, but whether statin use in humans results in clinically meaningful bone formation or a reduction in the risk of osteoporotic fractures is not known.

**Objective** To determine whether the use of statins is associated with reduced hip fracture risk.

**Design** Case-control study.

**Setting and Patients** A total of 6110 New Jersey residents aged 65 years or older and enrolled in Medicare and either Medicaid or the Pharmacy Assistance for the Aged and Disabled program. Case patients (n=1222) underwent surgical repair of a hip fracture in 1994. Control patients (n=4888) were identified at a ratio of 4:1 and frequency-matched to case patients for age and sex.

**Main Outcome Measure** Adjusted odds ratio (OR) of hip fracture by statin use in the 180 days and 3 years prior to the index date (the earliest date of admission for surgery), adjusted for demographic and clinical characteristics and health care utilization.

**Results** Use of statins in either the prior 180 days (adjusted OR, 0.50; 95% confidence interval [CI], 0.33-0.76) or prior 3 years (adjusted OR, 0.57; 95% CI, 0.40-0.82) was associated with a significant reduction in the risk of hip fracture, even after controlling for variables such as race, insurance status, psychoactive medications, estrogen and thiazide use, ischemic heart disease, cancer, and diabetes mellitus. No significant relationship was observed between use of nonstatin lipid-lowering agents and hip fracture risk. Clear relationships were observed between the degree of reduction in hip fracture risk and the extent of statin use; there was no evidence of such relationships with nonstatin lipid-lowering agents. After adjusting for extent of statin use in the prior 3 years, current use (on the index date) was associated with a 71% reduction in risk (adjusted OR, 0.29; 95% CI, 0.10-0.81). The relationship between statin use and hip fracture risk persisted after controlling for variables such as the number of medications, the Charlson comorbidity index score, and hospitalization or nursing home stay in the last 180 days, as well as after excluding patients who were in a nursing home prior to their index date or who died in the year after their index date. Use of nonstatin lipid-lowering agents was not observed to be associated with reduction in hip fracture risk in any of these alternative models or analyses.

**Conclusions** These findings support an association between statin use by elderly patients and reduction in the risk of hip fracture. Controlled trials are needed to exclude the possibility of unmeasured confounders.

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OSTEOPOROSIS AFFECTS 20% of women older than 50 years and an even larger proportion of elderly women; fractures attributable to osteoporosis occur in approximately 1.5 million Americans annually.[1-3] Although several recently approved medications effectively prevent and treat osteoporosis, no currently approved drug has been shown to stimulate bone formation activity by osteoblasts.[4]

A recent report suggests that drugs inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) (statins), commonly used to lower lipid levels, may have such potential.[5] Oophorectomized rats given statins in oral dosages comparable to those used in humans (ie, 1-10 mg/kg per day of simvastatin) had a 40% to 90% increase in the trabecular bone volume of the femur and lumbar vertebrae within 35 days, relative to rats given placebo. Statins appear to enhance osteoblast activity through increasing expression of the bone morphogenetic protein 2, a stimulator of osteoblast differentiation. Statins also may be linked to bone metabolism through their ability to inhibit mevalonate synthesis, a mechanism shared with several bisphosphonates.[6] Mevalonate is a precursor necessary for production of cholesterol and 2 lipoids important in the control of osteoclast activity. However, it is not yet clear whether these in vitro and animal findings have clinically useful implications for patient care. Another recent report[7] found that statin use in humans may result in increased bone mineral density. However, it was not evident whether such increases are clinically meaningful or result in a reduction in osteoporotic fractures.

**See also pp 3205 and 3255.**

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While many randomized controlled trials have been performed to test the efficacy of statins in reducing coronary heart disease, fracture outcomes have not been reported, and older patients who would be most likely to demonstrate this effect generally have been excluded.[8,9] One recent report from an observational study identified a statistically nonsignificant decrease in the relative risk of hip fracture for users of statins but not in users of nonstatin lipid-lowering drugs.[10] We examined whether statin use is associated with a reduction in hip fracture rates by analyzing a database containing information on all filled prescriptions, hospital care, surgical procedures, and physician visits for a very large population of older patients.

## METHODS

### Data Sources

**New Jersey Medicaid Program.** We extracted information on all individuals enrolled in the New Jersey Medicaid program from January 1, 1991, to June 30, 1995, including demographic information; dates of enrollment; outpatient, nursing home, and hospital utilization data; and data for all filled prescriptions. The indigent status of Medicaid enrollees results in essentially no out-of-system health care utilization since such utilization would be an out-of-pocket expense.

**New Jersey Pharmacy Assistance for the Aged and Disabled Program.** Additional information on nonindigent patients, the vast majority of whom are aged 65 years and older, was derived for the same time period from the New Jersey Pharmacy Assistance for the Aged and Disabled (PAAD) program, a state-specific program of reimbursement for the drug expenses of nonindigent elderly and disabled citizens.

**New Jersey Medicare.** Medicare data used in the present study included both Medicare Part A data on hospitalizations and nursing home stays, and Medicare Part B data on services and procedures for essentially all New Jersey residents older than 65 years.

We identified all Medicare beneficiaries who were also enrolled in either Medicaid or PAAD (approximately 46%) because the latter 2 programs, but not Medicare, provide comprehensive data on all prescriptions filled. All data on each subject were assembled on a person-specific basis into a relational database to integrate information on prescriptions, procedures, physician encounters, hospitalizations, and long-term care for each individual. All traceable person-specific identifiers were transformed into anonymous, coded study numbers to protect the privacy of program participants.

### Study Population

The study population (TABLE 1) consisted of all patients aged 65 years and older on July 1, 1993, who met program use criteria described below. To ensure complete ascertainment of health care utilization, all patients were required to have had at least 1 medical service during 1994 and to have filled at least 1 prescription for any medication through the Medicaid or PAAD programs in each of 4 consecutive 6-month periods beginning January 1, 1993. We also identified patients who filled 1 or more prescriptions in each of 4 consecutive 6-month periods beginning January 1, 1991, for the analyses of 3-year drug use. Patients who had been hospitalized in the month prior to the index date were excluded.

### Case Definition

Cases of hip fracture were defined as any patient hospitalized between January 1, 1994, and December 31, 1994, for surgical repair of a hip fracture as reflected in a claim for this procedure by a surgeon.[11,12] The index date for cases was the earliest date of admission for this surgery. Four control patients were drawn at random from the study population for each case patient, frequency matched to case patients by year of birth and sex. Each control patient was randomly assigned an index date frequency matched to the index dates of case patients. Case patients and controls were required to have no diagnoses of hip fracture or evidence of hip fracture surgical repairs prior to their index date.

### Exposure to Lipid-Lowering Agents

**Use of Lipid-Lowering Drugs in the 180 Days and 3 Years Prior to the Index Date.** Patients who filled any prescriptions for fluvastatin, lovastatin, pravastatin, or simvastatin in the 180 days prior to their index date were considered to have been exposed to a statin lipid-lowering drug. Patients who filled any prescriptions for cholestyramine, clofibrate, colestipol, gemfibrozil, niacin, or probucol in the 180 days prior to their index date were considered to have been exposed to a nonstatin lipid-lowering agent. We also identified eligible patients who used each of these drugs in the 3 years prior to their index date.

**Extent of Lipid-Lowering Drug Use in the 180 Days and 3 Years Prior to the Index Date.** Using the quantity dispensed and days supply data recorded on prescriptions, we calculated the number of days in the 180 days prior to the index date for which each individual had a filled prescription for a statin drug or a nonstatin lipid-lowering agent. Among eligible subjects, we also calculated the number of such days covered in the 3 years prior to the index date. We used the distributions of days covered to divide individuals exposed to statin and nonstatin lipid-lowering drugs into 4 equal groups (quartiles).

### Covariates

The variables for all case and control patients used to calculate the crude and adjusted odds ratios (ORs) were obtained as follows. Program enrollment information was used to determine the sociodemographic characteristics of age, sex, race, and insurance status (Medicaid vs PAAD). We determined other specific medication use by examining all prescriptions filled in the 180 days prior to the index date and recording use of estrogen replacement therapy, oral corticosteroids, thiazide diuretics, or any psychoactive medication. Additional drugs were studied as markers of specific clinical conditions. We scanned all epi-

sodes of inpatient and outpatient care and filled prescription data in the 180 days prior to the index date to identify evidence of the following comorbidities: ischemic heart disease (based on diagnoses,[11] procedures such as angioplasty or bypass surgery,[11,12] hospitalization codes,[13] and prescriptions for nitrates); congestive heart failure (based on diagnostic codes and hospitalization codes); hypertension (based on diagnoses and hospitalization codes); diabetes mellitus (based on diagnoses, hospitalization codes, and prescriptions for insulin or oral hypoglycemics); and cancer excluding nonmelanoma skin cancer (based on diagnoses). We also used diagnostic information from all inpatient and outpatient encounters in the 180 days prior to the index date to calculate a modified Charlson comorbidity index score, a commonly used measure of the extent of comorbid illness.[14] Finally, we recorded whether patients died in the 365 days following their index date.

The extent of health care utilization was assessed in the 180 days prior to the index date as the number of medications (different generic entities) used, days hospitalized, days spent in a nursing home, and physician visits.

## Analyses

We initially measured the demographic, clinical, and health care utilization characteristics of case and control patients. Crude ORs of hip fracture were then calculated for any statin use in the 180 days prior and in the 3 years prior to the index date relative to no use. The statistical significance of relationships was assessed using $\chi^2$ statistics and 95% confidence intervals (CIs).

We next constructed multivariable unconditional logistic regression models of the risk of hip fracture using SAS, version 6.12 (SAS Institute, Cary, NC) to control for possible confounding by patients' clinical or sociodemographic characteristics. Variables representing the use of statins as well as nonstatin lipid-lowering drugs (separately for the prior 180 days or the prior 3 years), and estrogen replacement therapy were introduced into the model, as were age and sex. Remaining covariates representing specific clinical conditions, other medication use, and demographic characteristics were then subjected to a forward, stepwise selection procedure with a selection criterion of $P \leq .20$. To assess the robustness of the findings and test for the possibility of other confound-

**Table 1.** Characteristics of Case Patients and Control Patients With Hip Fracture in the 180 Days Prior to the Index Date*

| Characteristic | Cases, No. (%) (n = 1222) | Controls, No. (%) (n = 4888) |
|---|---|---|
| Age, y† | | |
| 65-74 | 200 (16.4) | 785 (16.1) |
| 75-84 | 506 (41.4) | 2033 (41.6) |
| ≥85 | 515 (42.1) | 2066 (42.3) |
| Sex† | | |
| Women | 1014 (83.0) | 4081 (83.5) |
| Men | 208 (17.0) | 807 (16.5) |
| Race | | |
| White | 1103 (90.3) | 4123 (84.3) |
| Nonwhite | 119 (9.7) | 765 (15.7) |
| Insurance status | | |
| Medicaid | 517 (42.3) | 1710 (35.0) |
| PAAD | 705 (57.7) | 3178 (65.0) |
| Medication use | | |
| Statins in prior 180 days | 27 (2.2) | 213 (4.4) |
| Statins in prior 3 years | 39 (4.1) | 261 (7.0) |
| Nonstatins in prior 180 days | 17 (1.4) | 81 (1.7) |
| Nonstatins in prior 3 years | 39 (4.1) | 174 (4.7) |
| Estrogens | 19 (1.6) | 78 (1.6) |
| Thiazides | 169 (13.8) | 878 (18.0) |
| Oral corticosteroids | 55 (4.5) | 192 (3.9) |
| Any psychoactive medication | 359 (29.4) | 820 (16.8) |
| No. of medications | | |
| 0-4 | 399 (32.7) | 1934 (39.6) |
| 5-9 | 509 (41.7) | 2095 (42.9) |
| ≥10 | 314 (25.7) | 859 (17.6) |
| Specific diagnoses | | |
| Ischemic heart disease | 509 (41.7) | 1784 (36.5) |
| Congestive heart failure | 354 (29.0) | 1368 (28.0) |
| Hypertension | 805 (65.9) | 3488 (71.4) |
| Diabetes mellitus | 255 (20.9) | 930 (19.0) |
| Cancer | 101 (8.3) | 310 (6.3) |
| Charlson comorbidity index score | | |
| 0 | 467 (38.2) | 2617 (53.5) |
| 1 | 371 (30.4) | 1243 (25.4) |
| ≥2 | 384 (31.4) | 1028 (21.0) |
| Hospitalization in prior 180 days | | |
| Yes | 346 (28.3) | 771 (15.8) |
| No | 876 (71.7) | 4117 (84.2) |
| Physician visits in prior 180 days | | |
| 0-1 | 249 (20.4) | 1110 (22.7) |
| 2-5 | 375 (30.7) | 1600 (32.7) |
| 6-9 | 269 (22.0) | 1090 (22.3) |
| ≥10 | 329 (26.9) | 1088 (22.3) |
| Nursing home stay in prior 180 days | | |
| Yes | 392 (32.1) | 957 (19.6) |
| No | 830 (67.9) | 3831 (80.4) |

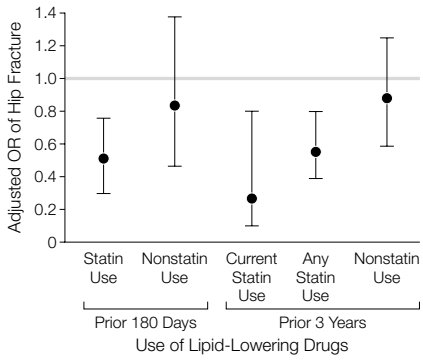
*For 3-year analyses of statin and nonstatin lipid-lowering drug use, numbers and percentages were calculated for the subset of 950 cases and 3714 controls eligible for this entire period. PAAD indicates New Jersey Pharmacy Assistance for the Aged and Disabled program.
†Controls were frequency matched to cases by age and sex.

**Table 2.** Crude and Adjusted Odds Ratios of Hip Fracture From Models Controlling for Comorbid Conditions, Medication Use, and Other Patient Characteristics*

| Characteristic | Crude Odds Ratios (95% CI) | Adjusted Odds Ratios (95% CI) |
|---|---|---|
| Any statin use in prior 180 days | 0.50 (0.33-0.74) | 0.50 (0.33-0.76) |
| Any statin use in prior 3 years | 0.57 (0.40-0.80) | 0.57 (0.40-0.82) |
| Any nonstatin use in prior 180 days | 0.84 (0.49-1.42) | 0.81 (0.47-1.38) |
| Any nonstatin use in prior 3 years | 0.87 (0.61-1.24) | 0.87 (0.60-1.26) |
| Nonwhite race | 0.59 (0.48-0.72) | 0.56 (0.45-0.69) |
| Medicaid | 1.36 (1.20-1.55) | 1.27 (1.11-1.46) |
| Psychoactive medication use | 2.06 (1.79-2.38) | 1.88 (1.62-2.18) |
| Estrogen use | 0.97 (0.59-1.61) | 0.92 (0.55-1.54) |
| Thiazide use | 0.73 (0.61-0.88) | 0.87 (0.72-1.05) |
| Ischemic heart disease | 1.24 (1.09-1.41) | 1.20 (1.05-1.38) |
| Hypertension | 0.78 (0.68-0.89) | 0.83 (0.72-0.96) |
| Cancer | 1.33 (1.05-1.68) | 1.22 (0.96-1.55) |
| Diabetes mellitus | 1.12 (0.96-1.31) | 1.14 (0.97-1.34) |

*CI indicates confidence interval. Adjusted odds ratios and 95% CIs are based on a multivariable logistic regression models including all the factors listed plus age and sex. The 180-day and 3-year assessments of statin and nonstatin drug use were calculated in separate models. Values for the other variables listed came from the model containing 180-day lipid-lowering drug use. For the smaller number of individuals available for study for 3 years prior to the index date (950 cases and 3714 controls), the values for all these variables were virtually identical. Referent is the absence of drug use or disease state for all characteristics except race and insurance status: for race the referent is white; for insurance status, New Jersey Pharmacy Assistance for the Aged and Disabled program.

**Figure 1.** Adjusted Odds of Hip Fracture With Lipid-Lowering Drug Use




Adjusted relative odds of hip fracture associated with statin and nonstatin lipid-lowering drug use in the 180 days or 3 years prior to the index date, compared with nonuse in each category. The adjusted odds ratios (ORs) were derived from multivariable logistic regression models containing covariates listed in Table 2. Error bars represent 95% confidence intervals.

ers, we then constructed alternative multivariable models in which comorbid disease severity scores (categorized as 0, 1, and ≥2) and health care utilization variables were subjected to a forward selection procedure.

To address the possibility that statins might be preferentially prescribed to healthier patients (who would also be at lower risk of hip fracture), we studied 2 subsamples of patients: one that excluded any individuals who were in a nursing home in the 180 days prior to their index date and another that excluded all those who died in the 365 days after the index date.

To examine whether the extent of use of lipid-lowering drugs was associated with hip fracture risk, we measured hip fracture risk in relation to the number of days of use of statin and nonstatin lipid-lowering drugs, as reflected in the quantities dispensed in all filled prescriptions for these agents. The adjusted risks associated with quartiles of use during the prior 180 days as well as the 3 years prior to the index date were calculated. Finally, as an additional test of the biological relevance of any statin–hip fracture relationship, we examined the effect of current statin use (as of the index date) in a model controlling for the extent of statin use in the previous 3 years.

## RESULTS

Characteristics of the study population (n = 1222 cases and n = 4888 controls) are presented in Table 1. The patient population was mostly aged 75 years or older and female. In keeping with previous findings,[15-24] case patients were more likely than control patients to be white and users of corticosteroids or psychoactive medications but less likely to be thiazide users. Case patients were somewhat more likely than control patients to have ischemic heart disease, diabetes mellitus, or cancer but were less likely to have hypertension.

TABLE 2 presents the crude and adjusted ORs from logistic regression models of factors associated with the risk of hip fracture. In unadjusted analyses, statin use in the 180 days prior to the index date was associated with a 50% reduction in hip fracture risk. Controlling for a wide range of clinical variables, other medication use, and demographic characteristics had essentially no effect on this finding, with statin use in the prior 180 days still associated with a 50% reduction in the risk of hip fracture (FIGURE 1). By contrast, use of nonstatin lipid-lowering agents in the prior 180 days did not have a statistically significant association with hip fracture rates in either crude or multivariable analyses.

Statin use in the prior 3 years also was associated with a 43% reduction in the crude and adjusted risk of hip fracture (Table 2 and Figure 1). No significant associations were observed for use of nonstatin lipid-lowering drugs over this period, despite a substantial increase in the number of subjects exposed to these drugs. The model presented in Table 2 also supports other epidemiologic associations with hip fracture reported in previous studies.[15-24]

In alternative models, statin use in both the prior 180 days and the prior 3 years continued to be significantly associated with a reduction of comparable magnitude in risk of hip fracture, while no significant associations were observed between use of nonstatin lipid-lowering agents and hip fracture risk. TABLE 3 presents results of models containing comorbidity scores and health care utilization variables rather than specific diagnoses, with essentially the same findings.

Additional analyses were conducted to adjust for the possibility that statins may be preferentially withheld from frail patients or those in long-

term care facilities, who might also have higher fracture rates. The significant association between statin use and reduction in hip fracture risk remained virtually unchanged when the population studied was restricted to case and control patients who had not been in a nursing home in the 180 days prior to the index date (any statin use in 180 days prior vs no use: adjusted OR, 0.57; 95% CI, 0.37-0.87), as well as in a subgroup of patients restricted to those who did not die in the year after the index date (adjusted OR, 0.45; 95% CI, 0.28-0.71).

If the relationship between statin use and fracture was causal, a greater protective effect with greater use would be expected. After controlling for the possible confounders described above, we observed a clear use-response relationship when we examined the risk of hip fracture associated with quartiles of statin use in the prior 180 days. FIGURE 2 presents the adjusted relative odds of hip fracture for quartiles of days of statin use in the 3 years prior to the index date. It demonstrates a clear use-response relationship between statin use and decrease in hip fracture risk, with risk significantly reduced to 0.37 for the highest quartile of use relative to no use (95% CI, 0.17-0.82). By contrast, there was no use-response relationship for nonstatin lipid-lowering agents in either time period.

Finally, we determined the effect of current statin use (as of the index date), as well as prior, but not current, statin use, from a model controlling for total use over the previous 3 years. Current statin use was associated with an even greater (71%) reduction in the risk of hip fracture (current statin use vs no use: adjusted OR, 0.29; 95% CI, 0.10-0.81 [Figure 1]) while past use in the absence of current use did not show a significant association (prior-only statin use vs no use: adjusted OR, 0.60; 95% CI, 0.29-1.25), even after adjusting for total number of days of use during the 3-year period.

## COMMENT

In this study of 1222 elderly patients with hip fracture and 4888 controls, the use of statin lipid-lowering medication was associated with a 50% reduction in the risk of hip fracture, even after controlling for comorbidity, extent of health care utilization, age, sex, race, and insurance status. Three findings provide evidence that this relationship may be both causal and related to the biological activity of statins. First, we did not observe any significant protective effect for nonstatin lipid-lowering agents—a therapeutic class with the same indications but with different underlying mechanisms of action. Second, we observed clear use-response relationships between both short-term (prior 180 days) and longer-term (prior 3 year) statin use and reduction in hip fracture risk. This finding of a short-term use-response relationship suggests that the protection conferred by statin use may begin after a relatively short period and is consistent with the time frame in which new bone formation has been shown to occur in both in vivo and in vitro rodent models.[5] Alternatively, extensive short-term statin use in our study population also may have been a marker of patients with more extensive long-term use. Finally, we observed the lowest risks with current statin use rather than prior use, even after adjusting for the total extent of statin use.

The fact that the medical community and patients were unaware of any potential association between statin use and bone density in 1991-1994 and the highly variable nature of the use of these drugs in older patients during this period provided a good context in which to explore this relationship retrospectively. However, it is important to consider several potential limitations of this study and whether they could provide an alternative explanation for its findings.

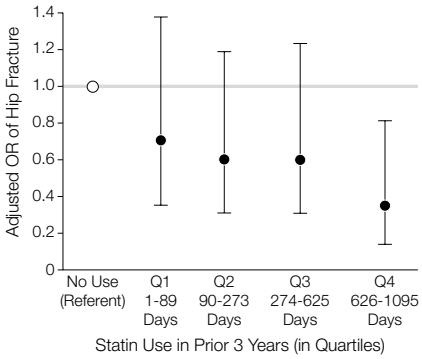
First is the possibility that statins may have been given preferentially to less frail patients or those otherwise at lower risk of hip fracture. However, the approximately 50% reduction in risk did not change when we adjusted for the presence of a wide variety of comorbid conditions, such as ischemic heart

**Table 3.** Adjusted Odds Ratios of Hip Fracture From Alternative Models Controlling for Medication Use, Comorbid Illness Severity, Health Care Utilization, and Other Patient Characteristics*

| | Adjusted Odds Ratio (95% CI) |
|---|---|
| Any statin use in prior 180 days | 0.54 (0.36-0.82) |
| Any statin use in prior 3 years | 0.61 (0.42-0.87) |
| Any nonstatin use in prior 180 days | 0.81 (0.47-1.39) |
| Any nonstatin use in prior 3 years | 0.88 (0.60-1.27) |
| Nonwhite race | 0.57 (0.46-0.70) |
| Any psychoactive medication use | 1.63 (1.39-1.90) |
| Estrogen use | 0.89 (0.53-1.49) |
| Thiazide use | 0.86 (0.72-1.04) |
| No. of medications | |
| 0-4 | 1.00 |
| 5-9 | 0.98 (0.84-1.14) |
| ≥10 | 1.19 (0.98-1.44) |
| Charlson Comorbidity Index score | |
| 0 | 1.00 |
| 1 | 1.40 (1.19-1.64) |
| ≥2 | 1.30 (1.08-1.57) |
| Hospitalization in prior 180 days | 1.66 (1.40-1.97) |
| Nursing home stay in prior 180 days | 1.50 (1.28-1.76) |

*CI indicates confidence interval. Adjusted odds ratios and 95% CIs are based on multivariable logistic regression models controlling for the factors listed plus age and sex. The 180-day and 3-year assessments of statin and nonstatin drug use were calculated in separate models. Values for the other variables listed came from the model containing 180-day lipid-lowering drug use. For the smaller number of individuals available for study for 3 years prior to the index date (950 cases and 3714 controls), the values for all these variables were virtually identical. Referent is the absence of drug use or health care utilization.

**Figure 2.** Use-Response Curve for Hip Fracture and 3-Year Statin Use




Adjusted odds ratio (OR) of hip fracture relative to number of days of statin use in the 3 years prior to the index date based on filled prescriptions, compared with nonuse and adjusted for the variables listed in Table 2. All subjects who used any statin in the 3 years prior to their index date were divided into 4 quartiles based on the distribution of days of statin use. Error bars represent 95% confidence intervals.

disease, hypertension, congestive heart failure, diabetes mellitus, or cancer, as well as for other measures of chronic illness such as days spent in hospital, number of physician visits, Charlson comorbidity index score, number of medications taken, nursing home residency, and death in the following year.

Another possibility is that statins were used preferentially in patients (or prescribed by physicians) who might have been more "prevention-oriented"; such an orientation may in turn have been associated with a higher baseline health status and/or use of other measures that would lower the risk of fracture. In 1991-1994, apart from estrogen replacement therapy, use of other medications specifically for osteoporosis was uncommon. Introduction into the multivariate model of a variable describing the use of estrogen replacement therapy had no effect on the statin–hip fracture relationship. Most importantly, in no analysis did we observe a significant protective effect for nonstatin lipid-lowering agents, which are prescribed for the same indications, including analyses of use during the prior 3 years, which provided considerable additional statistical power to observe a relationship if it were present.

Third, because we could not measure weight or body mass index in our data, it is possible that obesity might be associated with both statin use and a reduced risk of hip fracture. However, a recent observational study by Bauer and colleagues[10] did attempt to assess the effect of statin use on hip fracture risk among 2 cohorts of elderly women in whom data were available on body mass index, exercise history, smoking, and other clinical characteristics. After controlling for these variables, Bauer et al[10] reported a reduction in the relative risk of hip fracture among statin users, but these findings did not reach statistical significance, perhaps because the number of fractures was too small. In the present study, greater body mass index probably explains some of the modest reduction in hip fracture rates seen among hypertensive patients; controlling for the presence of hypertension in our analysis did not alter the observed statin effect. The drug use data were based on filled prescription claims rather than directly observed drug use, and the outcome assessment was based on claims filed by surgeons for performing a surgical repair of a hip fracture. It is conceivable that these assessments may have led to misclassification in some instances,[25] but it is not clear how this would have introduced any systematic bias. Finally, it is possible that some of the observed reduction in fracture risk may be attributable to prevention of stroke and myocardial infarction, which, in theory, could have precipitated falls resulting in fracture. However, this is unlikely to explain more than a small fraction of the observed risk reduction, particularly since the reduction in fracture rates was larger than the previously reported rates of reduction in myocardial infarction or stroke events.

Despite these striking findings, it remains possible that some aspect of physicians' selection of patients for statin therapy, unaddressed in the present analysis, might confound the relationship observed. Future observational studies or randomized trials will be required to address this possibility and to further our understanding of the potential effects of statins in relation to fractures in elderly patients.

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**REFERENCES**

**1.** Looker AC, Johnston CC, Wahner HW, et al. Prevalence of low femoral bone density in older US women from NHANES III. *J Bone Miner Res*. 1995;10:796-802.
**2.** Melton LG, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? *J Bone Miner Res*. 1992;7:1005-1010.
**3.** Riggs BL, Melton LJ. Involutional osteoporosis. *N Engl J Med*. 1986;314:1676-1686.
**4.** Russell RG, Rogers MJ, Frith JC, et al. The pharmacology of bisphosphonates and new insights into their mechanisms of action. *J Bone Miner Res*. 1999; 14(suppl 2):53-65.
**5.** Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. *Science*. 1999;286:1946-1946.
**6.** Luckman SP, Hughes DE, Coxon FP, Russell RG, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including RAS. *J Bone Miner Res*. 1998;13:581-589.
**7.** Chung YS, Lee MD, Lee SK, Kim HM, Fitzpatrick LA. HMG-CoA reductase inhibitors increase BMD in type 2 diabetes mellitus patients. *J Clin Endocrinol Metab*. 2000;85:1137-1142.
**8.** Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
**9.** Scandinavian Simvastatin Survival Study (4S) Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet*. 1994;344: 1383-1389.
**10.** Bauer DC, Mundy GR, Jamal SA, et al. Statin use, bone mass and fracture: an analysis of two prospective studies [abstract]. *J Bone Miner Res*. 1999;14 (suppl 1):S179.
**11.** *International Classification of Diseases, Ninth Revision, Clinical Modification.* Washington, DC: Public Health Service, US Dept of Health and Human Services; 1988.
**12.** *Physicians' Current Procedural Terminology*. 4th ed. Chicago, Ill: American Medical Association; 1989.
**13.** *St Anthony's Diagnosis Related Group Working Guidebook*. Alexandria, Va: St Anthony Publishing Inc; 1993.
**14.** Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with *ICD-9-CM* administrative databases. *J Clin Epidemiol*. 1992;45:613-619.
**15.** Silverman SL, Madison RE. Decreased incidence of hip fracture in Hispanics, Asians, and Blacks: California hospital discharge data. *Am J Public Health*. 1988;78:1482-1483.
**16.** Hofer TP, Katz SJ. Healthy behaviors among women in the United States and Ontario: the effect on use of preventive care. *Am J Public Health*. 1996; 86:1755-1759.
**17.** Gregg EW, Cauley JA, Seeley DG, Ensrud KE, Bauer DC. Physical activity and osteoporotic fracture risk in older women. *Ann Intern Med*. 1998;129:81-88.
**18.** Orwoll ES, Bauer DC, Vogt TM, Fox KM. Axial bone mass in older women. *Ann Intern Med*. 1996; 124:187-196.
**19.** Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med*. 1998;339: 875-882.
**20.** Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ III. Psychotropic drug use and the risk of hip fracture. *N Engl J Med*. 1987;316:363-369.
**21.** Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA*. 1989;262:3303-3307.
**22.** Herings RC, Stricker BH, de Boer A, Bakker A, Sturmans A. Benzodiazepines and the risk of falling leading to femur fractures. *Arch Intern Med*. 1995;155: 1801-1807.
**23.** Cumming RG, Klineberg RJ. Psychotropics, thiazide diuretics and hip fractures in the elderly. *Med J Aust*. 1993;158:414-417.
**24.** LaCroix AZ, Wienpahl J, White LR, et al. Thiazide diuretic agents and the incidence of hip fracture. *N Engl J Med*. 1990;322:286-290.
**25.** Baron JA, Lu-Yao G, Barrett J, McLerran D, Fisher ES. Internal validation of Medicare claims data. *Epidemiology*. 1994;5:541-544.