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ORIGINAL ARTICLE

Lipid-lowering agents and the risk of hip fracture in a Medicaid population

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Context: Three recent nested case-control studies conducted in automated databases suggest that users of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have a risk of hip and other osteoporotic fractures half that of non-users of any lipid-lowering drug. However, this comparison may be biased by unmeasured factors associated with treated hyperlipidemias.

Objective: To compare the risk of hip fracture among users of statins and other lipid-lowering agents, which is less susceptible to bias than the comparisons performed in the previous studies.

Design and setting: Retrospective cohort study conducted in the Tennessee Medicaid program between 1 January 1989 through 31 December 1998.

Subjects: New users of all lipid-lowering drugs and randomly selected non-user controls who at baseline were at least 50 years of age and did not have life threatening illness, nursing home residence, or diagnosed dementia or osteoporosis. There were 12 506 persons with new use of statins, 4798 with new use of other lipid lowering drugs, and 17 280 non-user controls.

Main outcome measure: Fracture of the proximal femur (hip), excluding pathological fractures or those resulting from severe trauma.

Results: During 66 690 person years of follow up, there were 186 hip fractures (2.8 per 1000). Relative to non-users, the adjusted incidence rate ratios (95% confidence interval) were 0.62 (0.45 to 0.85) for statin users and 0.44 (0.26 to 0.95) for other lipid-lowering drugs. When compared directly with the other drugs, the adjusted incidence rate ratio for statins was 1.42 (0.83-2.43).

Conclusion: These data provide evidence that the previously observed protective effect of statins may be explained by unmeasured confounding factors.

Osteoporotic fractures are a major public health problem and of these, hip fracture has the greatest adverse health, social, and economic consequences.¹⁻³ Three recent nested case-control studies reported that users of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), now the most commonly used drugs to treat hyperlipidemias, have lower rates of hip⁴ and other osteoporotic fractures^{5,6} than do persons who receive no lipid-lowering agents. The magnitude of the protective effect was substantial, with estimates of the relative risk for statin users ranging from 0.48⁵ to 0.57⁴ and varied little across the three diverse populations. The effect was consistent with preliminary work in *ex vivo* and rodent models that suggested that statins could retard age related bone loss.⁵ These findings could have major public health implications, given the low risk of adverse effects associated with statins and the large size of the observed protective effect.

These studies all used automated databases of medical care encounters,⁷ which provide an excellent means of tracking statin use and identifying fractures in very large populations. One limitation of these databases is the lack of information on many potential confounding factors. One important such factor for the statin studies is the "healthy drug user" effect, which is similar to the healthy worker effect long known to workers in occupational safety. This term describes the tendency for patients who receive preventive therapy and are good compliers to have fewer illnesses, even after controlling for known risk factors. For example, in the clofibrate clinical trial, patients who were at least 80% compliant with their medication had significantly fewer deaths, even when the medication was placebo.⁸ The behavioral and other factors that presumably underlie this effect are unavailable in automated databases. Another potential confounder is increased body mass, which is present in patients with hyperlipidemias and

protects against hip and some other osteoporotic fractures. This variable was unavailable in two of the studies^{4,5} and missing for 40% of subjects in the third.⁶

Thus, in an automated database study, the best evidence for a protective effect of statins would come from a direct comparison of statin users with those of other lipid-lowering agents. This comparison would remove the "healthy drug user" effect, because both groups would be long term users of similar medications. Similarly, because both groups would have treated hyperlipidemias, the likelihood of confounding by body mass index would be substantially reduced.

When this criterion is used, evidence from the three case-control studies is less convincing. Each study found a protective effect for the non-statin lipid-lowering agents, suggesting the presence of confounding by the factors described above. In two of the three studies, the comparison between this group and the statin users was not statistically significant.^{4,5} However, because these studies had only small numbers of users of other lipid-lowering agents, the power of this comparison was limited. Our study sought to provide information pertinent to this question by conducting a retrospective cohort study of statin use and hip fracture in the Tennessee Medicaid population.⁷ We directly compared risk of hip fractures among users of statins with that among comparable users of other lipid-lowering agents.

METHODS

Sources of data

The study was conducted among enrollees of the Tennessee Medicaid program,⁷ which has computerized files that permitted cohort assembly and hip fracture identification. These included the enrollment file, a central registry of all enrollees linked with death certificates, the pharmacy file

Table 1 Characteristics of study cohort at baseline

	Statin (n=12506)	Other lipid-lowering (n=4798)	Non-user (n=17280)
Mean study follow up (days)	715.9	684.4	701.5
Mean age (years)	61.8	62.1	61.9
Male (%)	34.6	31.8	33.8
White (%)	75.6	77.3	68.0
Entered cohort (year)	96.0	94.1	95.5
Medicaid enrollment (%)			
Aged	40.8	50.0	45.3
Disabled	18.0	19.8	16.4
Uninsured	41.3	30.3	38.3
Drugs associated with osteoporosis (%)			
Oral corticosteroids	10.8	9.8	11.1
Replacement estrogens, in women	29.6	27.3	26.3
Thiazide diuretic	32.2	38.1	27.7
Drugs associated with falls (%)			
Hypnotic, anxiolytic, muscle relaxant	37.7	40.9	34.1
Antidepressant	27.3	28.0	20.8
Anticonvulsant	5.7	5.9	6.5
Antiparkinsonian agent	0.4	0.5	0.8
Mean number of cardiovascular drugs*	1.8	1.7	1.0
Mean number of other drugs†	2.1	2.2	2.0
Hospitalization or emergency room (%)	13.7	17.2	15.4

*Includes antiarrhythmics, angiotensin converting enzyme inhibitors, anticoagulants, antidiabetics, β -blockers, calcium channel blockers, digitalis, loop diuretics, other antihypertensives, nitrates, or platelet inhibitors.

†Includes antimicrobials, bronchodilators, non-steroidal anti-inflammatory drugs, opioid analgesics, or gastrointestinal drugs.

consisting of records of prescriptions filled at the pharmacy, the inpatient file, with the records of hospitalizations for Medicaid enrollees, the outpatient file with encounter records for emergency room, hospital outpatient department, outpatient surgical facility, and physician visits for Medicaid enrollees and the nursing home file.

Cohort

The study period was 1 January 1989 through 31 December 1998. The cohort consisted of persons during this period who began use of statins or other lipid-lowering agents or were in a random sample of controls not using these drugs. We identified all persons with one or more prescriptions for statins (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin) or other lipid-lowering agents (gemfibrozil, clofibrate, fenofibrate, colestipol, cholestyramine, niacin, nicotinate, probucol). The date the first such prescription was filled was denoted t₀. To assure that the cohort included persons likely to remain on lipid-lowering drugs for a long enough period to affect bone mass, we further required that during the 90 days after t₀ the persons were enrolled and had two additional prescriptions for a lipid-lowering agent of the same type as that started at t₀ with no prescription for an agent of a different type.

There were several other cohort membership requirements to assure that the information necessary for the study was available and that there was the possibility of benefiting from a protective effect of statins. Cohort members had to have at least 365 days of prior enrollment and had no prescription for a lipid lowering agent in the preceding 365 days. They also had to have a known date of birth and gender and on t₀ be 50 years of age or older (the age at which age related bone loss begins to accelerate, particularly for women³). Because persons with severe illness, disability, or dementia would have been poor candidates for lipid-lowering therapy, we excluded patients who on t₀ or in the past 365 days had a life threatening illness (cancer, HIV, renal failure, heart failure, liver injury, respiratory failure, or other serious immunologic disorders), were in a nursing home, or had diagnosed dementia (medical encounter diagnosis or prescription for antipsychotic, tacrine, or donepezil). The cohort was further restricted to patients

with no evidence of clinically treated osteoporosis (use of bisphosphonates, calcitonin, fluoride, vitamin D metabolites, diagnosis of osteoporosis or osteomalacia) or osteoporotic fractures in the 365 days preceding t₀,⁹ as patients with such advanced disease would have less opportunity to benefit from a treatment that prevented age related bone loss.

The control non-users of lipid-lowering agents were a demographically matched, random sample of Medicaid enrollees with no use of a lipid lowering agent any time during the study period. For each lipid-lowering drug user in the cohort, we selected one non-user control, matched on gender, birth year, and t₀. Non-user controls had to have been eligible on t₀ and the preceding 365 days and to have had at least one filled prescription for any medication in this period, which assured some medical care utilization. Furthermore, all non-users had to have at least 90 days of enrollment after t₀, and satisfy all of the other cohort membership criteria. If more than one person met these criteria, one was selected at random.

Follow up for each cohort member began on t₀ and extended through the end of the study follow up (12/31/1999), end of enrollment, death, 90 days after cessation of lipid-lowering agent use, change from a non-statin lipid lowering agent to a statin (at least 90 days of use), or a study endpoint, whichever was first. If a user of a lipid-lowering agent had follow up censored because drug use ceased or changed to a statin, follow up also was censored for the corresponding matched control.

Study outcome

The study outcome was a fracture of the proximal femur (hip), as identified from a previously developed algorithm for identifying fractures from Medicaid data that was validated through review of 1440 charts.⁹ When compared with medical chart review, this algorithm had a positive predictive value of 98% and a sensitivity of 97%. From potential cases thus identified, we excluded those with evidence of pathological fracture or severe trauma (diagnosis codes E800–E848, except E824).

Analysis

Unadjusted rates of hip fracture were calculated by dividing the number of cases by person time of study follow up.

Table 2 Occurrence of hip fractures, by study group

	Person years	Hip fractures	Rate /1000	Adjusted IRR	95% CI
Non-user	33189	120	3.62	1.00	Reference
Statin	24512	49	2.00	0.62	0.45 to 0.85
Other lipid-lowering drug	8990	17	1.89	0.44	0.26 to 0.72

CI, confidence interval; IRR, incidence rate ratio.

Estimates of rate ratios adjusted for potential differences between the three study groups were calculated from proportional hazards models. Covariates in the model, defined at the time of cohort entry, included demographic characteristics, calendar year, reason for Medicaid enrollment (aged, disabled or blind, or uninsured, a group that became eligible under a special program initiated in Tennessee in 1994¹⁰), use in the past 365 days of medications associated in the literature with osteoporosis (oral corticosteroids, replacement estrogens, thiazide diuretics) or falls (hypnotics, anxiolytics, skeletal muscle relaxants, antidepressants, anticonvulsants, antiparkinsonian agents),¹¹ and hospitalization or emergency room visit in the past 365 days. The latter factor served as measures of general poor health, which is associated with increased risk of falls and fractures.^{12–13}

All analyses were performed with SAS version 8.0. All p values are two sided. The study was approved by the Vanderbilt University Committee for the Protection of Human Subjects.

RESULTS

The cohort included 12 506 persons with qualifying new use of statins, 4798 with new use of other lipid lowering drugs (for 3846, or 80%, gemfibrozil), and 17 280 control non-users of lipid-lowering drugs (table 1). Cohort members had a mean age of 62 years and 66% were female. Among users of either type of lipid-lowering agent, 76% were white, in contrast with 68% of non-user controls. Users of statins entered the cohort a mean of two years after users of other lipid-lowering drugs. Since Medicaid enrollment of persons lacking health insurance also increased over the study period, statin users were more likely to have qualified for Medicaid because of lack of health insurance (41%) than were users of other lipid-lowering drugs (30%). Statin users and users of other lipid-lowering agents were comparable with respect to use of medications at baseline; non-users had slightly lower baseline use of other drugs.

There were 186 hip fractures that occurred during the 66 690 person years of study follow up, for a rate of 2.8 hip fractures per 1000 person years. The rate among non-users of any lipid-lowering agent was 3.6 per 1000 person years (table 2). When compared with non-users, the adjusted incidence rate ratio (95% confidence interval) for users of statins was 0.62 (0.45 to 0.85) and that for users of other lipid-lowering drugs was 0.44 (0.26 to 0.95). When users of statins were compared with other lipid-lowering agents, the adjusted incidence rate ratio was 1.42 (0.83–2.43).

Because persons 65 years of age or older have the greatest risk of osteoporotic hip fracture, we performed a subgroup analysis of the 11 416 cohort members of this age at baseline. There were 22 164 person years of follow up and 121 hip fractures in this group, or 5.5 fractures per 1000 person years. The adjusted incidence rate ratios among users of statins and other lipid-lowering agents were 0.68 (0.46–1.00) and 0.42 (0.22–0.80), respectively.

DISCUSSION

If, as suggested in the findings of three recently published case-control studies,^{4–6} widely used and well tolerated medications such as the statins halve the rate of osteoporotic

fractures, the public health implications would be enormous. Thus, before these widely publicized findings lead patients to seek statins for osteoporosis or researchers to embark on expensive prospective studies, it is important to assemble as much evidence relevant to this question as is possible from available data. In this regard, the large automated databases of medical encounters are important, because they track use of statins for large numbers of patients and can be used to identify hip and other osteoporotic fractures.

Unfortunately, these databases provide little information on two important potential confounders: the “healthy drug user” effect and body mass. Patients who receive therapy for lipid-lowering agents, and who are compliant for long periods of time are likely to be different from other patients with regard to several factors that lower risk for hip fractures. There are substantial data indicating that hip fracture is associated with unstable health and frailty,^{12–13} which could discourage long term statin use. That it may be difficult to measure the multiple factors underlying this effect is evidenced by the protective effects of similar magnitude consistently seen in observational studies of β -carotene and cancer,^{14–15} and replacement estrogens and coronary heart disease,^{16–18} which have not been confirmed in clinical trials. Patients with raised lipids also tend to have increased body mass, which would protect against hip and some other osteoporotic fractures.

Thus, except in the unlikely case that all presently available lipid-lowering agents protect against osteoporosis, the best way to address this question in automated databases is to directly compare users of statins and other lipid-lowering medications. This provides substantial (although not necessarily complete) control for factors such as those described above associated with long term treatment of hyperlipidemias.

In the present cohort study, adjusted rates of hip fracture among statin users did not differ significantly from those among users of other lipid-lowering agents. This is compatible with the findings of two of the three previous case-control studies,^{4–5} which also failed to report a significant difference between statin users and users of other lipid-lowering drugs. Like the previous case-control studies,^{4–6} statin users in our study had an adjusted rate of hip fractures 38% lower than that for the controls not using lipid-lowering drugs. Taken together, these findings thus suggest that the statin protective effect may reflect confounding by factors associated with the use of any lipid-lowering drug.

Our study had several characteristics that complement previous work. The study outcome was fracture of the hip, which has major adverse medical, social, and economic consequences^{1–3} and which can be prevented by reducing age related bone loss. It was conducted in a Medicaid population, which has greater homogeneity with regard to potential confounders such as income and education. We excluded some of the frailest patients, those in nursing homes or those with evidence of dementia, because these patients have very high risk of hip fracture and would be unlikely to receive lipid-lowering agents.

However, our study shared many of the limitations of the previous reports. We had no information on body mass index and smoking, which might be potential confounders. However, it seems unlikely that these factors differed systematically between statin users and users of other lipid-lowering agents. Like the other studies, our study had limited sample

Key points

- Osteoporotic fractures are a major public health problem for older persons and of these, hip fracture has the greatest adverse consequences.
- Three recent studies report that users of the popular "statin" medications have approximately a 50% reduction in fracture of the hip than do persons taking no lipid-lowering drugs.
- However, these studies may not have fully controlled for the possibility that patients receiving statins are healthier than other patients with similar level of cardiovascular disease.
- The present retrospective cohort study focused on a comparison between new users of statins with new users of other lipid lowering drugs, primarily gemfibrozil.
- Although users of both types of medication had lower rates of hip fracture than did non-users; the rate for statins was very similar to that of other lipid-lowering agents.
- Thus, our data provides evidence that the previously observed protective effect of statins may be explained by unmeasured confounders.

size for the comparison of statins with other lipid-lowering drugs. The numbers of events among this latter group, which is a critical factor determining the precision of comparisons, was low in each of the studies. Our study included 17 hip fractures in the other lipid-lowering agent cohort, which compares to 17 (drug in past 180 days), six (current drug use), and six (all fractures, drug for 12+ months) in the studies of Wang *et al.*,⁴ Meier *et al.*,⁶ and Chan *et al.*,⁵ respectively. Either larger studies or meta-analysis may be required to quantify differences between the specific types of lipid-lowering agents.

Thus, our data provide evidence that it is premature to use statins for prevention of osteoporotic fractures. This caution is reinforced by the recently reported data on fractures from the Scandinavian Simvastatin Survival Study clinical trial,¹⁹ in which there was no evidence of even a trend towards a protective effect for statin users. Similarly, a recent analysis²⁰ using much of the same data of the Meier *et al* study suggested the beneficial effect of statins, particularly for hip fracture, was smaller than previously stated. Ultimately, randomized clinical trials with fracture endpoints would be required to demonstrate that statins prevent fractures. However, before undertaking such lengthy and expensive trials, it would be useful to obtain further support for the hypothesis that statins prevent fractures. This could be provided by either larger observational studies that better quantify the differences between users of statins and other lipid-lowering agents or clinical trials of statin effects on bone quality.

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