Use of Statins and Fracture

Results of 4 Prospective Studies and Cumulative Meta-analysis of Observational Studies and Controlled Trials

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Background: The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used for the treatment of hyperlipidemia, and recent in vitro and animal data suggest that statins promote bone formation and increase bone strength.

Methods: To determine whether statin use is associated with a reduced risk for fracture, we analyzed statin use and fracture rates in 4 large prospective studies (the Study of Osteoporotic Fractures, the Fracture Intervention Trial, the Heart and Estrogen/Progestin Replacement Study, and the Rotterdam Study). We searched MEDLINE through January 2002 and abstracts from major scientific meetings and performed a cumulative meta-analysis of published and unpublished observational studies and clinical trials. The meta-analysis included 8 observational studies and 2 clinical trials that reported statin use and documented fracture outcomes.

Results: After adjustment for multiple factors, including age, body mass index, and estrogen use, we found a trend toward fewer hip fractures (relative hazards [RHs], 0.19-0.62) and, to a lesser extent, nonspine fractures (RHs, 0.49-0.95) among statin users in each of the 4 prospective studies. The meta-analysis of observational studies was consistent with these findings. The summary odds ratio (OR) for statin use and hip fracture was 0.43 (95% confidence interval [CI], 0.25-0.75), whereas that for nonspine fracture was 0.69 (95% CI, 0.55-0.88). The meta-analysis of clinical trial results did not support a protective effect with statin use for hip fracture (summary OR, 0.87; 95% CI, 0.48-1.58) or nonspine fracture (OR, 1.02; 95% CI, 0.83-1.26).

Conclusions: Observational studies suggest that the risk for hip and nonspine fractures is lower among older women taking statin medications for hyperlipidemia, but post hoc analyses of cardiovascular trials do not. Controlled trials specifically designed to test the effect of statins on skeletal metabolism and fracture are needed.

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THE 3-HYDROXY-3-METHYLglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used medications for the treatment of hyperlipidemia. Recent in vitro and in vivo animal studies have found that these agents promote bone formation, possibly by stimulating osteoblast transcription of bone morphogenetic protein 2 (BMP-2).[1] If such beneficial effects are also found in humans, statins might be clinically useful for the prevention and treatment of osteoporosis.

Although the lipid effects of statins have been widely studied, few human data are available about the skeletal effects of these agents. Several case-control studies have found that statin use is associated with a reduced risk for fracture,[2-4] and other studies have suggested that bone mass is higher among individuals prescribed statin medications.[5,6] However, a recent reanalysis of one of the previously published case-control studies[7] and another large prospective cohort study[8] failed to find any association between statin use and fracture. Furthermore, post hoc analyses from 2 clinical trials designed to assess the cardiovascular effects of statins found no protective effect.[9,10]

We hypothesized that the bone anabolic effects observed in animal models might also be apparent with the clinical use of statins, particularly in postmenopausal women. Therefore, we examined the effect of statin use on bone mass and fracture rates among older women enrolled in 4 large prospective studies. To estimate the overall effect of statin use on hip and nonspine fracture rates, we com-

bined the results from these 4 studies and other existing observational data using meta-analytic techniques and performed a separate meta-analysis of the 2 reported clinical trials.

METHODS

We examined 4 prospective studies with baseline measurements of medication use, including statins, and subsequent fracture outcomes.

SUBJECTS AND MEASUREMENTS

The Study of Osteoporotic Fractures (SOF) is a prospective cohort study of risk factors for hip fracture among 9704 non–African American women older than 65 years.[11] Women were recruited at 4 US clinical centers in 1986 through 1988. During the fourth SOF visit in 1994, dual-energy x-ray absorptiometry (DXA) of the hip (Hologic QDR 2000; Hologic Inc, Bedford, Mass) was performed, and participants were asked to bring in all medications used during the preceding 2 weeks. Fracture end points were documented during a mean follow-up of 4 years.

The Fracture Intervention Trial (FIT) was a randomized trial of daily alendronate sodium therapy vs placebo among 6459 women aged 55 to 80 years with low bone mass.[12] Women were recruited from 11 US clinical centers in 1990 through 1992. During the baseline visit, hip DXA (Hologic QDR 2000) was performed, and participants were asked to bring in all medications used during the preceding 2 weeks. All women with low calcium intake received calcium and cholecalciferol (vitamin D) supplementation, and approximately half were randomized to daily alendronate therapy. Fracture end points were documented during a mean follow-up of 3.6 years.

The Heart and Estrogen/Progestin Replacement Study (HERS) was a randomized trial of continuous estrogen plus progestin therapy vs placebo among 2763 women with coronary heart disease who were aged 44 to 79 years.[13] Women were recruited from 20 US clinics in 1993 through 1994. Medication use during the previous 2 weeks was recorded at the baseline visit, and hip DXA (Hologic QDR 2000) was performed on a consecutive sample of women 65 years or older (n=408) at 2 clinics. Approximately half were randomized to daily estrogen/progestin, and the others received matching placebo. Clinical fractures were assessed during a mean follow-up of 4.5 years.

The Rotterdam Study is a population-based prospective cohort study of the determinants of chronic disease in older adults.[14] Participants included 4878 women older than 55 years who were recruited from a defined district in Rotterdam, the Netherlands. During the baseline visit from 1990 through 1993, DXA of the femoral neck (DPX-L; Lunar Corp, Madison, Wis) was performed, and medication use was assessed. Fractures were assessed during a mean follow-up of 5.3 years.

In each study, current medications were brought into the clinics for verification. The strength, dosing, and reason for use were recorded in the SOF and FIT. Other measurements, such as weight and height, were obtained by means of standardized protocols, and health habits, medical history, and previous fractures were collected by questionnaire. Regular exercise was defined as daily walking or other exercise programs in the SOF, FIT, and HERS. Physical activity was not assessed in the Rotterdam Study, but disability in the lower extremities was recorded.

OUTCOMES

After the assessment of medication use, participants in each study were followed up every 4 to 6 months for the occurrence of any fracture. In the SOF, FIT, and HERS, self-reported nonspine fractures were adjudicated by review of radiology reports or, in some cases, by actual review of the radiographs.[11,15,16] In the Rotterdam Study, follow-up for hip fractures was achieved through a link with the computer systems of the general practitioners of the district and on hospital admission data, covering about 80% of the study population. For participants not covered by this system, annual checks were performed on the complete medical records of their general practitioners. Reported fractures in the Rotterdam Study were verified by retrieval and review of the appropriate discharge reports from the patient record.

Incident vertebral fractures were also determined in the FIT by review of lateral lumbosacral and thoracic spine films obtained at baseline and after a mean follow-up of 3.5 years.[12] Each radiograph was analyzed using standard morphometric techniques, and incident vertebral fractures were defined as a greater than 20% reduction in any vertebral height during follow-up. Paired x-rays of the spine were not obtained in the other 3 studies.

ANALYSIS

On the basis of baseline medication use, participants were classified into 1 of the following 3 mutually exclusive categories: current statin use, use of nonstatin agents to lower lipid levels, or no use of medication to lower lipid levels. The relationship between use of medication to lower lipid levels and baseline bone mass density (BMD) was analyzed with linear regression. Hip and nonspine fracture risks were analyzed with Cox proportional hazards models; vertebral fracture was analyzed with logistic models. Except for the Rotterdam Study hip fracture results, all analyses were adjusted for age, body mass index (BMI), physical activity or physical disability, smoking, health status, and use of estrogen or bisphosphonates. In the Rotterdam Study, too few hip fractures occurred among statin users to allow multivariate adjustment, and unadjusted results are presented. In the SOF cohort, the effect of total daily dose for the most commonly used statin (lovastatin) was analyzed by comparing fracture rates among the following 3 groups of women: those taking 20 mg/d or less, those taking more than 20 mg/d, and those reporting no use of medication to lower lipid levels. The effects of alendronate use in the FIT and estrogen/progestin in the HERS were assessed with stratified analyses and inclusion of interaction terms.

META-ANALYSIS METHODS

Using MEDLINE, we searched the English-language medical literature through January 2002 for studies examining the relationship between statin use and fracture risk. As only a small number of studies were found, we systematically searched for abstracts from major meetings about osteoporosis, rheumatology, and endocrinology and contacted investigators about unpublished data. Studies of men or women that assessed statin use at baseline and documented hip or any nonspine fracture outcomes were included. Including the 4 previously unpublished studies reported herein, we found a total of 8 observational studies that met our inclusion criteria. The summary estimate was based on the reported relative hazards (RHs) or odds ratios (ORs) and 95% confidence intervals (CIs), using the most adjusted risk estimate available. One study did not report adjusted hip fracture results, and we calculated the unadjusted risk from the published data.[4] Similar methods were used to combine unadjusted results from the 2 existing cardiovascular trials, both randomized and placebo controlled, that have reported fracture end points.

The summary estimates and 95% CIs were calculated using a random-effects model and the general variance–based

Table 1. Prevalence of Use of Statins and Other Medication to Lower Lipid Levels

	No. (%) of Users at Baseline			
	SOF (n = 8422)	Rotterdam Study (n = 4878)	FIT (n = 6459)	HERS (n = 3763)
Statins	314 (3.7)	40 (0.8)	290 (4.5)	1002 (26.6)
Lovastatin	243 (2.9)	0	238 (3.7)	622 (16.5)
Pravastatin sodium	38 (0.5)	4 (0.1)	32 (0.5)	227 (6.0)
Simvastatin	32 (0.4)	38 (0.8)	20 (0.3)	138 (3.7)
Fluvastatin sodium	1 (0.01)	0	0	15 (0.4)
Nonstatins	331 (3.9)	NA	336 (5.2)	426 (11.3)
Niacin	129 (1.5)	NA	177 (2.7)	163 (4.3)
Gemfibrozil	119 (1.4)	NA	83 (1.3)	173 (4.6)
Bile acid resins	67 (0.8)	NA	66 (1.0)	88 (2.3)
Probucol	16 (0.2)	NA	10 (0.2)	2 (0.05)

Abbreviations: FIT, Fracture Intervention Trial; HERS, Heart and Estrogen/Progestin Replacement Study; NA, not available; SOF, Study of Osteoporotic Fractures.

method.[17] To search for heterogeneity between the studies results, we used a χ^2 test; P values of less than .10 were considered statistically significant. For studies with multiple published results,[2,7] we tested the effect of each of the differing results on our summary estimate. To determine the independent effects of sex, multivariate adjustment, and differing study designs, we repeated the meta-analysis including only women, multiply adjusted studies, and prospective cohort studies.

ROLE OF THE FUNDING SOURCE

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RESULTS

STATIN USE AND FRACTURE IN 4 PROSPECTIVE STUDIES

The prevalence of statin use in the SOF, FIT, HERS, and Rotterdam Study ranged from less than 1% in the Rotterdam Study to greater than 26% in the HERS (**Table 1**). Lovastatin was the most commonly used medication to lower lipid levels in the SOF, FIT, and HERS, whereas simvastatin was the most commonly reported statin in the Rotterdam Study. The prevalence of nonstatin medications to lower lipid levels is also listed in Table 1. The most commonly used nonstatins included niacin, gemfibrozil, and bile acid resins.

The baseline characteristics of statin users and nonusers in each of the 4 studies are shown in **Table 2**. Compared with women not taking medication to lower lipid levels, statin users in the SOF were significantly younger and had a higher BMI. Statin users in the SOF, FIT, and HERS were less likely to report a previous fracture, but statin users in the Rotterdam Study were more likely to report previous fractures. Hip BMD was higher among statin users in each of the studies, and these differences were statistically significant in the SOF, HERS, and Rotterdam Study. After adjustment for age, BMI, exercise or physical disability, smoking, health status, and use of estrogen and bisphosphonates, hip BMD remained significantly higher among statin users in the HERS (0.78 vs 0.75 g/cm^2; P=.03), but not in the other 3 studies.

In age-adjusted analyses, the risk for new hip and nonspine fractures was lower among women who reported statin use at baseline compared with women who did not use agents to lower lipid levels (data not shown). After adjustment for age, BMI, physical activity or physical disability, smoking, health status, and use of estrogen and bisphosphonates, these relationships were similar but were no longer statistically significant (**Table 3**). For example, in the SOF, the RH for hip fracture among statin users was 0.19 (95% CI, 0.03-1.38), and the RH for nonspine fractures was 0.76 (95% CI, 0.50-1.16). Compared with those not reporting statin use, the risk for nonspine fractures was lowest among women reporting use of more than 20 mg/d of lovastatin (RH, 0.34; 95% CI, 0.08-1.41), with little apparent reduction among those taking 20 mg/d (RH, 0.87; 95% CI, 0.51-1.48) (P=.14 for trend). Results regarding nonspine and spine fractures were similar in the FIT when analyses were limited to women in the placebo group.

To examine the possibility that the reduced risk for fracture among statin users was in some way related to factors other than statin use, we also examined the risk for fracture among women who were taking nonstatin agents to lower lipid levels in the SOF, FIT, and HERS. After adjustment for age, BMI, physical activity, smoking, health status, and use of estrogen and bisphosphonates, we found no evidence that the use of nonstatin agents to lower lipid levels was associated with a reduced risk for fracture (**Table 4**).

META-ANALYSIS RESULTS

Observational Studies

To better assess the effect of statin use on fracture risk, we combined data from the 4 studies reported herein and 4 previously reported observational studies[2-4,7,8] (**Table 5**). The primary hip fracture analyses included a total of 151 500 subjects, 9946 statin users, and 2814 hip fractures, whereas the nonspine fracture analyses included 57 621 subjects, 2893 statin users, and 9384 nonspine fractures.

The summary ORs for hip fracture among statin users compared with women not taking medications to lower lipid levels in all 8 studies was 0.43 (95% CI, 0.25-0.75) and the summary estimate for nonspine fracture risk was 0.69 (95% CI, 0.75-0.88) (**Figure 1** and **Figure 2**, respectively). Heterogeneity was present among the finding of the hip fracture studies (P=.04), but there was no evidence of heterogeneity among the findings of the nonspine fractures (P=.60). Further analysis revealed that the hip fracture summary estimate was no longer heterogeneous without the results of the Womens' Health Initiative (WHI) study (P=.50), and excluding the WHI study from the meta-analysis had little effect on the results (summary OR, 0.39; 95% CI, 0.27-0.58).

Table 2. Baseline Characteristics of Statin Users and Nonusers

Variable	SOF		Rotterdam Study		FIT		HERS	
	Statin User (n = 324)	Statin Nonuser (n = 8098)	Statin User (n = 82)	Statin Nonuser (n = 4796)	Statin User (n = 284)	Statin Nonuser (n = 6175)	Statin User (n = 1001)	Statin Nonuser (n = 1762)
Age, mean (SD), y	75.1 (3.5)*	77.2 (5.1)	66.4 (6.0)*	71.8 (10.3)	68.6 (3.5)	68.6 (5.1)	66.1 (6.1)	66.5 (6.9)
BMI, mean (SD)	27.4 (4.3)*	26.4 (4.8)	26.8 (4.0)	26.7 (4.1)	25.7 (3.9)	25.1 (4.0)	28.5 (5.3)	28.6 (5.6)
Regular exercise, %	5.2	4.7	NA	NA	47.5	53.4	14.6	12.4
Current smoker, %	4.8	6.0	22.5*	17.4	9.9	10.7	9.6	15.1
Poor-fair self-reported health, %	22.3	21.2	10.4	11.2	5.1	6.3	22.0	25.3
Bisphosphonate use at baseline %	0	0	0	0	0	0	0	0
Estrogen use at baseline, %	14.7	16.6	1.2	2.6	0	0	0	0
Previous fracture, %	31.2	36.2	24.4*	15.2	38.4*	42.5	38.4*	42.5
Hip BMD, mean (SD), g/m^2†	0.77 (0.12)*	0.73 (0.13)	0.85 (0.13)*	0.81 (0.13)	0.70 (0.09)	0.69 (0.09)	0.79 (0.12)*	0.76 (0.13)

Abbreviations: BMD, bone mass density; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); FIT, Fracture Intervention Trial; HERS, Heart and Estrogen/Progestin Replacement Study; SOF, Study of Osteoporotic Fractures.

*$P<.05$ compared with nonusers.

†Total hip BMD was measured in the SOF, FIT, and HERS (in a subset of 139 statin users and 269 nonusers); the femoral neck was measured in the Rotterdam Study.

Table 3. Multivariate Analyses of Statin Use and Fracture*

Fracture Site	SOF		Rotterdam Study		FIT†		HERS‡	
	No.	RH (95% CI)	No.	RH (95% CI)	No.	RH (95% CI)	No.	RH (95% CI)
Hip	186	0.19 (0.03-1.38)	180	0.31 (0.04-2.25)	76	0.53 (0.07-3.82)	23	0.62 (0.16-2.35)
Any nonspine	897	0.76 (0.50-1.16)	546	0.49 (0.15-1.57)	825	0.95 (0.59-1.52)	248	0.92 (0.64-1.32)
Vertebral		NA		NA	340	0.60 (0.26-1.39)§		NA

Abbreviations: CI, confidence interval; FIT, Fracture Intervention Trial; HERS, Heart and Estrogen/Progestin Replacement Study; NA, not applicable; RH, relative hazard; SOF, Study of Osteoporotic Fractures.

*Cox proportional hazards models were adjusted for age, body mass index, physical activity (physical disability in the Rotterdam Study), smoking, health status, and use of estrogen. Numbers indicate number of fractures.

†Further adjusted for allocation to alendronate or placebo.

‡Further adjusted for allocation to estrogen/progestin or placebo.

§Odds ratio (95% CI), calculated from a multiply adjusted logistic regression model.

Table 4. Multivariate Analyses of Use of Nonstatin Medication to Lower Lipid Levels and Fracture*

Fracture Site	SOF		FIT†		HERS‡	
	No.	RH (95% CI)	No.	RH (95% CI)	No.	RH (95% CI)
Hip	186	1.30 (0.63-2.70)	76	2.74 (0.36-20.76)	23	0.62 (0.18-2.14)
Any nonspine	897	1.19 (0.85-1.66)	825	1.14 (0.28-4.59)	248	0.97 (0.69-1.38)
Vertebral		NA	340	0.95 (0.50-1.79)§		NA

Abbreviations: CI, confidence interval; FIT, Fracture Intervention Trial; HERS, Heart and Estrogen/Progestin Replacement Study; NA, not applicable; RH, relative hazard; SOF, Study of Osteoporotic Fractures.

*Cox proportional hazards models were adjusted for age, body mass index, physical activity (physical disability in the Rotterdam Study), smoking, health status, and use of estrogen. Numbers indicate number of fractures.

†Further adjusted for allocation to alendronate sodium or placebo.

‡Further adjusted for allocation to estrogen/progestin or placebo.

§Odds ratio (95% CI), calculated from a multiply adjusted logistic regression model.

Results were qualitatively similar when the meta-analysis was limited to studies with multiply adjusted results or prospective cohort studies, or limited to women. For example, in analyses limited for multiply adjusted studies (n=6, including the WHI), the summary estimate for hip fracture among statin users was 0.46 (95% CI, 0.26-0.83), and when the results were limited to women (6 studies, including the WHI), the summary estimate was 0.65 (95% CI, 0.04-1.10). Lastly, differing results from the General Practice Research Database have been published,[2,7] but our hip fracture results were similar when the initial (summary OR, 0.43; 95% CI, 0.25-

Table 5. Other Observational Studies of Statin Use and Fracture

Study (Design)	Population (No. of Subjects)	Statin Use (No. of Subjects)	Fracture Site (No. of Subjects)	RR (95% CI)	Adjustments
NJ Medicaid[3] (CC)	Men and women aged >65 y (6110)	Any Rx in preceding 6 mo (230)	Hip (1222)	0.50 (0.33-0.76)	Age and sex matched, adjusted for HRT, other medications, other diseases, and Charlston index
HMO[4] (CC)	Women aged >65 y (3675)	≥13 Rx filled in previous 2 y (109)	Hip (262) Hip, spine, arm (928)	0.22 (0.03-1.66) 0.48 (0.27-0.83)	Unadjusted Adjusted for age, No. of hospitalizations, chronic disease, and other lipid drugs
WHI[8] (PC)	Women aged 50-79 y (93 724)	Current use at baseline (7847)	Hip (187)	0.98 (0.73-1.62)	Adjusted for age, race, BMI, history of fracture, HRT and other medications, other diseases, walking, and coffee drinking
GPRD-1[2] (CC)	Men and women aged 50-89 y (27 319)	Current use at baseline (1030)	Hip (678) Nonspine (3949)	0.12 (0.04-0.41) 0.55 (0.44-0.66)	Age, sex, and practice matched; and adjusted for BMI, smoking, physician visits, HRT/steroid use
GPRD-2[7] (CC)	Men and women aged 50-90 y (163 760)	Any use in preceding 6 mo (950)	Hip (12 965) Hip, vertebrae, clavicle, humerus, forearm, ankle, foot (81 880)	0.59 (0.31-1.13) 1.01 (0.88-1.16)	Age, sex, and practice matched; and adjusted for smoking, other medications, other diseases, and BMI if available (60%)

Abbreviations: BMI, body mass index; CC, case-control study; CI, confidence interval; GPRD, General Practice Research Database; HMO, health maintenance organization; HRT, hormone replacement therapy; NJ, New Jersey; PC, prospective cohort study; RR, relative risk; Rx, prescription; WHI, Women's Health Initiative study.

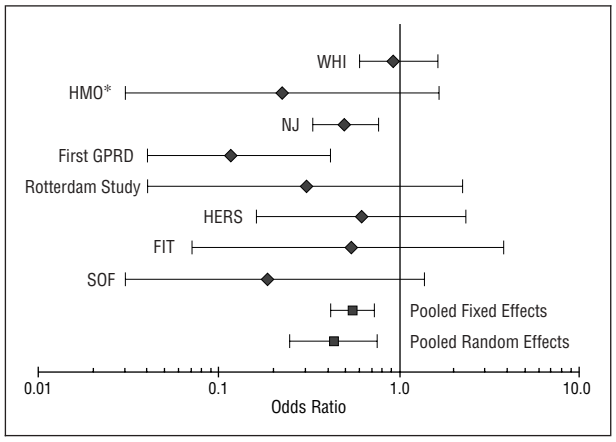

Figure 1. Odds ratios (diamonds) and 95% confidence intervals (horizontal lines) from studies of risk for hip fracture in women receiving statins in observational studies. Asterisk indicates unadjusted results; WHI, Womens' Health Initiative (WHI) study; HMO, health maintenance organization; NJ, New Jersey; GPRD, General Practice Research Database; HERS, Heart and Estrogen/Progestin Replacement Study; FIT, Fracture Intervention Trial; and SOF, Study of Osteoporotic Fractures.

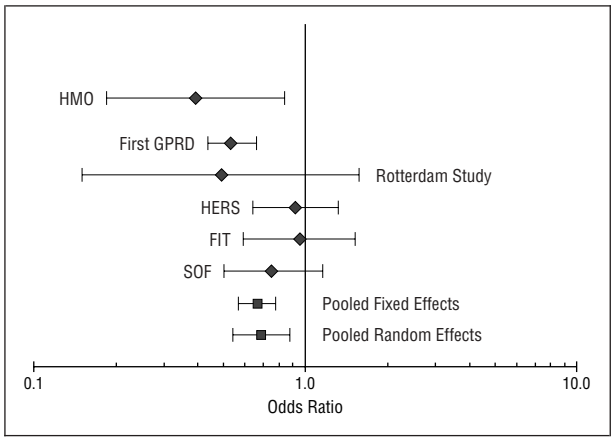

Figure 2. Odds ratios (diamonds) and 95% confidence intervals (horizontal lines) from studies of risk for nonspine fracture in women receiving statins in observational studies. HMO indicates health maintenance organization; GPRD, General Practice Research Database; HERS, Heart and Estrogen/Progestin Replacement Study; FIT, Fracture Intervention Trial; and SOF, Study of Osteoporotic Fractures.

0.75) or subsequent (summary OR, 0.61; 95% CI, 0.45-0.81) results were included in the meta-analysis.

Clinical Trials

Two placebo-controlled clinical trials with cardiovascular end points have performed post hoc analyses of self-reported fractures (**Table 6**). The LIPID study (Long-term Intervention with Pravastatin in Ischaemic Disease)[9] was a multicenter controlled trial of pravastatin sodium (40 mg/d) vs placebo among 9014 individuals (17% women) with known coronary artery disease. The 4S Study (Scandinavial Simvastatin Survival Study)[10] was a multicenter controlled trial of simvastatin (20-40 mg/d) vs placebo among 4444 subjects (19% women) with known coronary artery disease.

The summary OR for hip fracture among subjects allocated to statin vs those allocated to placebo was 0.87 (95% CI, 0.48-1.58). The summary estimate for nonspine fracture risk was 1.02 (95% CI, 0.83-1.26). Heterogeneity was not present when these 2 trials were combined.

COMMENT

Well-tolerated and effective agents for the prevention and treatment of osteoporosis are needed.[18,19] Our analyses of 4 large prospective studies suggest that statins may prevent osteoporotic fractures. Each study found a strong trend toward fewer hip fractures among women who reported the use of statin medications, even after adjusting for a number of other factors. We also observed a trend toward fewer incident vertebral fractures among statin

Table 6. Previously Reported Cardiovascular Trials With Fracture Outcomes

Study/Design	Population	Statin Used	Fracture Site (No.)	RR (95% CI)
4S[10]	4444 Subjects with CV disease (19% women)	Simvastatin, 20-40 mg/d, vs placebo	Hip (20) Nonspine (155)	1.0 (0.12-2.42)* 1.11 (0.81-1.52)*
LIPID[9]	9014 Subjects with CV disease (17% women)	Pravastatin sodium, 40 mg/d, vs placebo	Hip (23) Nonspine (358)	0.77 (0.34-1.75)* 0.94 (0.77-1.16)

Abbreviations: 4S, Scandinavian Simvastatin Survival Study; CI, confidence interval; CV, cardiovascular; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; RR, relative risk.
*Calculated from the authors' data.

users in the FIT. Associations between statin use and other nonspine fractures were less consistent. Fracture risk was not reduced among women treated with nonstatin agents to lower lipid levels, suggesting that the observed effects among statin users were not a result of bias or confounding. Overall, these data are consistent with existing in vitro and animal data and support a beneficial effect of statins on the skeleton.

Our study did not elucidate the mechanism by which statins reduce fracture risk. After adjustment for confounding factors, we observed a relatively small effect on BMD with statin use, insufficient to account for the observed reductions in fractures. Other mechanisms, such as an alteration of bone turnover or beneficial effects on bone microarchitecture or geometry, may be responsible. Further studies of these surrogate effects are needed.

The analyses of statin use and fracture in the SOF, FIT, HERS, and Rotterdam Study had several important strengths. Each study collected medication data prospectively, and fracture outcomes were rigorously adjudicated without knowledge of medication use. Unlike some previous studies, we accounted for important confounding factors, such as weight and estrogen use. The results were consistent across the 4 studies, despite differences in subject recruitment (both population based and among those with established osteoporosis or heart disease) and study design. Despite these strengths, our analyses have several limitations. We examined only baseline medication use and had no information about longitudinal statin use. As prescription medication use may change over time, it is likely that ascertainment of longitudinal statin use would result in even stronger associations with fracture. Although our analyses were adjusted for age, BMI, physical activity, smoking, health status, and use of estrogen or bisphosphonates, we cannot exclude the possibility that statin users differ from nonusers in other important ways that may influence fracture risk. However, we found no protective effect with the use of nonstatin medications to lower lipid levels. Because of small numbers, our dose-response analyses were limited to lovastatin users in the SOF, and the most commonly used statins in these studies were older, less potent compounds. Future studies should assess the individual effect of newer, more potent HMG-CoA reductase inhibitors.

The trend toward fewer fractures among statin users in the SOF, FIT, HERS, and Rotterdam Study were confirmed by our cumulative meta-analysis of observational studies. Using standard techniques, we summarized the results from 8 studies and found that statin use was associated with a reduced risk for hip and nonspine fractures. The summary estimates for hip (a 57% reduction among statin users) and nonspine (a 31% reduction among statin users) fractures were statistically significant and clinically important. We found no evidence that the protective effect of statins was limited to unadjusted studies, a specific sex, or a specific study design. Although there was evidence of heterogeneity among the findings of the hip fracture studies, it disappeared when the WHI results were omitted. We were unable to determine the cause of this heterogeneity, and could not attribute it to differences in the WHI subjects, study design, duration of follow-up, or statistical adjustments. Therefore, we chose to retain the WHI results in our final analysis despite the observed heterogeneity, but the results were similar when it was excluded.

Conversely, 2 placebo-controlled clinical trials with cardiovascular end points have performed post hoc analyses of self-reported fractures, and neither found a protective effect. When these 2 studies were combined using meta-analytic techniques, we found no evidence of fewer nonspine or hip fractures among individuals randomized to statins, although the CIs for hip fracture were wide (95% CI, 0.48-1.58). A number of potential explanations exist for these 2 negative trials, including insufficient numbers of high-risk subjects, inadequate power for hip fracture, lack of objective fracture adjudication, and in the LIPID trial, use of a statin that appears to have little effect on bone in vitro. It is likely that statin trial participants are more compliant than statin users in observational studies. Adequately powered trials specifically designed to test the effects of statins on fracture rates in high-risk individuals are needed.[20,21]

Lastly, the beneficial skeletal effects of statins are supported by an increasing number of laboratory studies.[22] The biological effects of statins on bone metabolism were first reported in 1999, when Mundy et al[1] found that statins were potent stimulators of bone formation in vitro. Lovastatin and subsequently other lipophilic statins such as simvastatin, mevastatin, and fluvastatin sodium were noted to increase BMP-2 messenger RNA and the production of BMP-2 by osteoblast cell lines. Osteoblast differentiation is enhanced by members of the BMP family, including BMP-2. The effect of statin on BMP-2 activity was abolished by addition of a downstream metabolite (mevalonate), confirming that inhibition of HMG-CoA reductase was responsible for the observed effects on BMP-2. Others have found beneficial skeletal effects with statin exposure in vitro and in animal models.[23-25] In vitro studies suggest that pravastatin, which is more water-soluble than other statins, has virtually no effect on BMP-

2.[23] We were not able to separately examine the effects of pravastatin in our analyses.

CONCLUSIONS

We found that use of HMG-CoA reductase inhibitors was associated with a consistent and clinically meaningful but nonsignificant reduction in hip and vertebral fractures in 4 prospective observational studies of older women. A similar trend was not observed with the use of nonstatin agents to lower lipid levels. When these results were quantitatively combined with other studies of statin use and fracture, we observed a significant reduction in hip and nonspine fracture risk among statin users. These findings build on the recent reports that statins increase bone formation in rodents and suggest that statins may be useful agents for osteoporosis. Clinical trials are needed to test the ability of potent statins to prevent fracture.

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