

Statin Use, Clinical Fracture, and Bone Density in Postmenopausal Women: Results from the Women's Health Initiative Observational Study

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Background: 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been shown to stimulate bone formation in laboratory studies, both *in vitro* and *in vivo*. While early epidemiologic studies showed lower risk for hip fracture among statin users than nonusers, subsequent studies have produced mixed results.

Objective: To examine the association of statin use with incidence of hip, lower arm or wrist, and other clinical fractures and with baseline levels of bone density.

Design: Prospective study.

Setting: Women's Health Initiative Observational Study conducted in 40 clinical centers in the United States.

Participants: 93 716 postmenopausal women ages 50 to 79 years.

Measurements: Rates of hip, lower arm or wrist, and other clinical fractures were compared among 7846 statin users and 85 870 nonusers over a median follow-up of 3.9 years. In 6442 women enrolled at three clinical centers, baseline levels of total

hip, posterior–anterior spine, and total-body bone density measured by using dual-energy x-ray absorptiometry were compared according to statin use.

Results: Age-adjusted rates of hip, lower arm or wrist, and other clinical fractures were similar between statin users and nonusers regardless of duration of statin use. The multivariate-adjusted hazard ratios for current statin use were 1.22 (95% CI, 0.83 to 1.81) for hip fracture, 1.04 (CI, 0.85 to 1.27) for lower arm or wrist fracture, and 1.11 (CI, 1.00 to 1.22) for other clinical fracture. Bone density levels did not statistically differ between statin users and nonusers at any skeletal site after adjustment for age, ethnicity, body mass index, and other factors.

Conclusion: Statin use did not improve fracture risk or bone density in the Women's Health Initiative Observational Study. The cumulative evidence does not warrant use of statins to prevent or treat osteoporosis.

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The long-term efficacy and safety of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been established in large multicenter trials of cholesterol-lowering for preventing coronary events in both sexes (1–4). Recent laboratory studies have shown that statins stimulate bone formation in cultured osteoblasts, neonatal murine calvaria, and the cortical bone of mice (5). Statins administered orally increased the trabecular bone volume of female rats by 90%. These findings raise the possibility that statin treatment might prevent both coronary and fracture events, two major causes of morbidity in older women, later in life.

Early epidemiologic studies examining the association of statin use with risk for hip fracture produced encouraging results (6–9). These studies were limited, however, by either small numbers of fractures (6) or lack of data on important potential confounders (7–9). More recent studies had mixed results (10–12), with some showing no association (11, 12). Few studies have examined associations with both fracture rates and bone density in the same study group. Therefore, we examined the association of statin use with levels of bone density and rates of hip, lower arm or wrist, and other clinical fractures in the Women's Health Initiative (WHI) Observational Study cohort of postmenopausal women.

METHODS

Study Group

The study group for this paper is the WHI Observational Study, a prospective cohort study that enrolled 93 716 women ages 50 to 79 years from 1994 to 1998 at 40 clinical centers throughout the United States. Study methods have been described in detail elsewhere (13). Briefly, women were eligible if they were postmenopausal, were unlikely to relocate or die within 3 years, were not enrolled in the WHI Clinical Trial, and were not participating in any other clinical trial. At baseline, women completed screening and enrollment questionnaires by interview and self-report, physical examination, and blood specimen collection. Human subjects review committees at each participating institution reviewed and approved the study.

Follow-up and Outcome Ascertainment

Women are sent questionnaires annually to report any hospitalization and a wide variety of outcomes, including clinical fractures of any type. Follow-up time ranged from 2 to 6 years per participant as of February 2001 (median duration, 3.9 years). At that time, 2.8% of participants ($n = 2632$) had withdrawn or were lost to follow-up (2.7% of statin users and 2.8% of nonusers). Hip fractures are confirmed by central review of radiology reports. Other

Context

Some observational studies have shown fewer fractures in patients receiving statins, but other studies have shown no effect. The studies have been small and had limited ability to adjust for potential confounders.

Contribution

In this subanalysis of the Women's Health Initiative, postmenopausal women had similar rates of hip, lower arm or wrist, and other fractures whether or not they used statins. The authors adjusted for many potential confounders, and the estimates of fracture rates were very precise.

Implications

Statin use does not seem to prevent fractures in postmenopausal women.

—The Editors

fractures are counted on the basis of self-report. Nonetheless, in the WHI Clinical Trial, in which all fractures are adjudicated, 81% of self-reported nonhip clinical fractures are confirmed by physician review of medical records, suggesting that the self-report of such fractures is reasonably accurate. For this report, we classified fractures into three mutually exclusive categories: 1) hip fractures, 2) lower arm or wrist fractures, and 3) other clinical fractures. Clinically recognized vertebral fractures were classified as "other clinical fractures."

Bone mineral density at the total hip, posterior-anterior spine, and total body was measured at baseline in three clinical centers among 6442 women (97% of participants enrolled in Pittsburgh, Pennsylvania; Birmingham, Alabama; and Phoenix and Tucson, Arizona) with dual-energy x-ray absorptiometry using a Hologic QDR densitometer (Hologic, Inc., Waltham, Massachusetts). Standard protocols for positioning and analysis were used by technicians who were trained and certified by the University of California, San Francisco, Bone Density Coordinating Center, San Francisco, California. The ongoing quality assurance program includes monitoring spine and hip phantom scans; reviewing a random sample of all scans and flagging scans with specific problems; hardware or software change control, including *in vitro* and *in vivo* cross-calibration; and scanning calibration phantoms across instruments and clinical sites.

Statin Exposure and Potential Confounders

Participants were asked to bring all current prescription medications to their first screening interview. Clinic interviewers entered each medication name directly from the containers into the WHI database, which assigned drug codes using Medispan software (First DataBank, Inc., San Bruno, California). Women reported duration of use for each current medication. Information on dose was not recorded. Current medication use was ascertained by using identical methods at the year 3 clinic visit.

Current statin medication use was defined as use of any HMG-CoA reductase inhibitor. Duration of use was examined in three categories (<1 year, 1 to 3 years, or >3 years). Statin medications were further categorized into three groups according to their demonstrated potency for lipid-lowering on the basis of a dose-efficacy trial (14): low potency (fluvastatin and lovastatin), medium potency (pravastatin), and high potency (atorvastatin, simvastatin). Other lipid-lowering medications were fibrates, colestipol, probucol, cholestyramine, niacin, or nicotinic acid.

All covariates were ascertained at baseline. Current use of thiazide diuretics, alendronate, corticosteroid, and sedative or hypnotic medications was recorded by using the same procedures described. Current and previous use of hormone replacement therapy was ascertained by interview using a detailed questionnaire that measured type, route of administration, number of pills per day or week, and duration for each hormonal preparation ever taken. For the purposes of this report, hormone replacement therapy was defined as current use of any estrogen with or without progestin.

Dietary supplements, including calcium preparations, taken at least twice weekly for the past 2 weeks were also entered into the database. Dietary intake of calcium was measured by using a semi-quantitative food-frequency questionnaire (15). Total calcium intake was defined as the sum of calcium from diet and supplements.

Baseline questionnaires ascertained information on race or ethnicity, history of fracture or coronary heart disease (history of myocardial infarction or angina), current and past smoking, coffee consumption (cups per day), and time spent walking outside the home for more than 10 minutes without stopping (minutes per week). Alcohol consumption was estimated from the food-frequency questionnaire. Physical function was measured by using the 10-item Medical Outcomes Study scale (16). Weight was measured to the nearest 0.1 kg on a balance-beam scale with the participant dressed in indoor clothing without shoes. Height was measured to the nearest 0.1 cm by using a wall-mounted stadiometer. Body mass index was calculated as weight in kg/height in m².

Statistical Analysis

The characteristics of women taking a statin medication at baseline were compared with those of women not taking statin medication by using chi-square tests to determine the statistical significance of the differences. Age-adjusted incidence rates of hip, lower arm or wrist, and other clinical fractures per 1000 person-years were calculated according to duration of statin use by the direct method, using the age distribution of the full cohort as the standard population. Women contributed follow-up time until the occurrence of fracture, death, or the end of follow-up, whichever came first. The *a priori* analysis plan specified selected stratified analyses to determine whether associations between statin use and fracture were apparent

Table 1. Descriptive Characteristics of Postmenopausal Women Enrolled in the Women's Health Initiative Observational Study

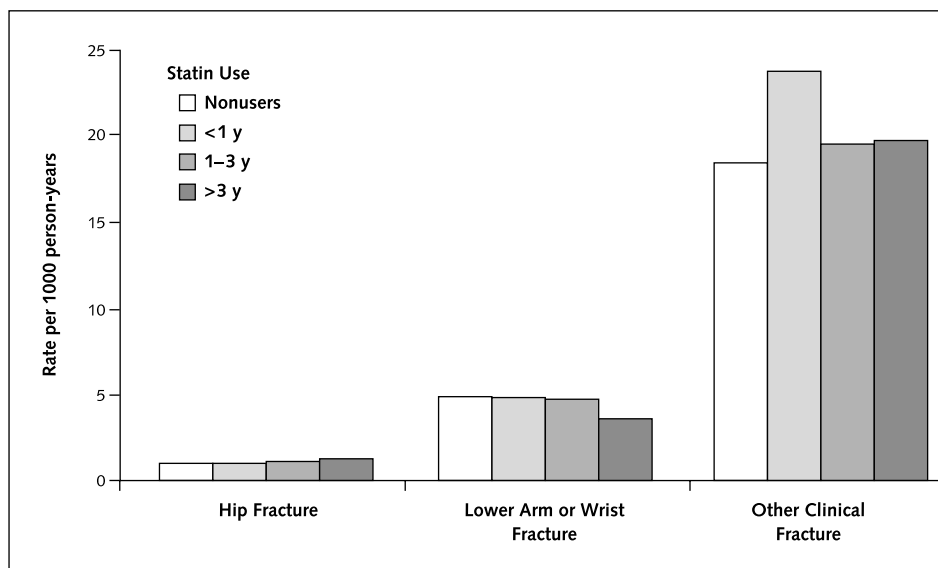
Characteristic	Statin Users, n (%)	Nonusers, n (%)	P Value
Total	7846 (100.0)	85 870 (100.0)	
Age group			<0.001
50–59 y	1407 (17.9)	28 300 (33.0)	
60–69 y	3971 (50.6)	37 244 (43.4)	
70–79 y	2468 (31.5)	20 326 (23.7)	
Race or ethnicity			<0.001
White	6455 (82.3)	71 565 (83.3)	
Black	696 (8.9)	6945 (8.1)	
Hispanic	250 (3.2)	3403 (4.0)	
Asian or Pacific Islander	300 (3.8)	2371 (2.8)	
American Indian or Alaskan Native	33 (0.4)	390 (0.5)	
Other or unspecified	112 (1.4)	1196 (1.4)	
Body mass index			<0.001
Underweight (<18.5 kg/m ²)	31 (0.4)	1076 (1.3)	
Normal (18.5–24.9 kg/m ²)	2172 (28.0)	34 522 (40.7)	
Overweight (25.0–29.9 kg/m ²)	3136 (40.4)	28 339 (33.4)	
Obesity I (30.0–34.9 kg/m ²)	1612 (20.8)	12 979 (15.3)	
Obesity II (35.0–39.9 kg/m ²)	540 (7.0)	4916 (5.8)	
Extreme obesity (≥40 kg/m ²)	270 (3.5)	3023 (3.6)	
History of fracture	3057 (39.4)	32 591 (38.6)	0.2
History of myocardial infarction or angina	1467 (18.8)	3978 (4.7)	<0.001
Years of hormone replacement therapy use among current users			<0.001
Never or past user	4669 (59.6)	46 319 (54.0)	
<5 y	903 (11.5)	11 610 (13.5)	
5 to <10 y	721 (9.2)	9658 (11.3)	
10 to <15 y	564 (7.2)	7341 (8.6)	
≥15 y	976 (12.5)	10 807 (12.6)	
Years of thiazide use			<0.001
Nonuser	7189 (91.6)	81 349 (94.7)	
<10 y	482 (6.1)	3204 (3.7)	
≥10 y	175 (2.2)	1315 (1.5)	
Alendronate use	281 (3.6)	1865 (2.2)	<0.001
Corticosteroid use	92 (1.2)	1113 (1.3)	>0.2
Psychoactive drug use	690 (8.8)	5093 (5.9)	<0.001
Nonstatin antihyperlipidemic use	199 (2.5)	1201 (1.4)	<0.001
Alcohol intake			<0.001
Nondrinker*	972 (12.5)	9505 (11.2)	
Past drinker	1730 (22.2)	15 827 (18.6)	
<1 drink/mo	930 (11.9)	9803 (11.5)	
<1 drink/wk	1608 (20.6)	17 122 (20.1)	
1 to <7 drinks/wk	1770 (22.7)	22 076 (25.9)	
≥7 drinks/wk	789 (10.1)	10 921 (12.8)	
Cigarette smoking			<0.001
Never	3767 (48.8)	43 261 (51.1)	
Past	3525 (45.6)	35 993 (42.5)	
Current	435 (5.6)	5356 (6.3)	
Coffee (caffeinated) intake			<0.001
None	3719 (47.9)	36 656 (43.2)	
1 cup/d	1313 (16.9)	13 648 (16.1)	
2–3 cups/d	2158 (27.8)	25 916 (30.5)	
≥4 cups/d	568 (7.3)	8642 (10.2)	
Daily calcium intake			<0.001
<600 mg/d	1672 (22.8)	17 053 (21.0)	
600–1500 mg/d	3823 (52.1)	42 314 (52.0)	
>1500 mg/d	1850 (25.2)	21 951 (27.0)	
Walking			<0.001
None	3504 (44.7)	35 472 (41.3)	
1–150 min/wk	3138 (40.0)	36 355 (42.3)	
>150 min/wk	1204 (15.3)	14 043 (16.4)	
Physical function score (>90)	2105 (27.4)	32 736 (38.9)	<0.001

* Refers to women whose lifetime alcohol consumption is less than 12 drinks of any kind of alcoholic beverage.

in key subgroups of women. For these analyses, women were stratified according to age group (50 to 64 years versus ≥65 years), current hormone replacement therapy use, body mass index (<25 kg/m² versus ≥25 kg/m², the standard threshold for overweight) (17), history of fracture,

and history of coronary disease. Hazard ratios adjusted for age and corresponding 95% CIs were calculated by using Cox proportional hazards survival models for each fracture category using PHREG in SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina). To control for

Figure. Age-adjusted rates of fracture per 1000 person-years according to duration of statin use among postmenopausal women 50 to 79 years of age in the Women's Health Initiative Observational Study.



potential confounding factors, hazard ratios and corresponding 95% CIs for categories of duration and potency of statin use were calculated by using multivariate Cox proportional hazards survival models, using the forced entry approach for variable selection. The multivariate models adjusted for age; race or ethnicity; body mass index; previous fracture; previous coronary disease; current and past hormone replacement therapy use; thiazide, alendronate, corticosteroid, or psychoactive drug use; calcium intake; walking; current and past smoking; coffee intake; and physical function. The multivariate models included individual clinical center as a stratification (or blocking) variable to allow the underlying hazard to be estimated separately for each clinical center. Interaction by clinical center was evaluated by comparing log likelihood statistics (chi-squares) for a model with interaction terms for each clinical center and a reduced model without these terms. Tests for the proportional hazards assumption were conducted by examining plots of the baseline hazard by statin duration categories and by testing interaction terms of statin use by time. Multivariate models were based on 81 896 individuals after exclusion of participants with missing values. The models for potency of statin medications are based on 81 876 participants because some statin medications could not be classified according to potency. To evaluate the effects of change in statin use over time on the results, final models were repeated by entering statin use as time-dependent exposure, using updated information gathered at the year 3 clinic visit.

A similar strategy was used to examine cross-sectional associations of statin use and bone density measured at the total hip, posterior–anterior spine, and total body. Mean bone density for each category of duration and potency of statin use was estimated by using general linear regression

models, first adjusting for age and body mass index and then adjusting for the same covariates, using the uniform forced entry criteria for variable selection. Indicator variables for the three clinical centers were included in all models.

Role of the Funding Source

This study was funded through National Institutes of Health contracts with the WHI Clinical Centers and the Clinical Coordinating Center. Representatives from the National Institutes of Health participated in the design and monitored the conduct of the WHI Observational Study. The National Institutes of Health Project Office reviewed and approved the final manuscript.

RESULTS

Among the 93 716 women in the total cohort, 7846 (8.4%) were currently using statin medication at baseline; 1844 (2%) had used their current statin medication for more than 3 years, 3416 (3.6%) for 1 to 3 years, and 2586 (2.8%) for less than 1 year. The prevalence rates of use of statin agents were simvastatin (2.6%), lovastatin (2.1%), pravastatin (1.9%), fluvastatin (1.0%), and atorvastatin (0.8%). According to potency classification, 2526 women (3.1%) used a low-potency statin, 1516 (1.9%) used a medium-potency statin, and 2720 (3.3%) used a high-potency statin. Women currently using statin medication at baseline were older than nonusers (mean age, 65.8 years vs. 63.4 years, respectively), had higher body mass index (28.4 kg/m² vs. 27.2 kg/m², respectively), and were more likely to have a history of myocardial infarction or angina (Table 1). Concurrent use of thiazide diuretics was also more common among statin users. Hormone replacement therapy was used slightly less often among statin

users than nonusers (40.4% vs. 46.0%, respectively). Among current hormone users, the duration of hormone use was similar for statin users (8.4 years) and nonusers (8.3 years). Other baseline characteristics were similar for statin users and nonusers, including race or ethnicity, history of fracture, alcohol consumption, smoking, time spent walking, and total daily calcium intake (Table 1). Although the differences by statin use were small, many of these comparisons were nonetheless statistically different because of the large number of women in the cohort.

During 335 384 person-years of follow-up, 321 hip fractures, 1582 lower arm or wrist fractures, and 5864 other clinical fractures occurred. Age-adjusted incidence rates of fracture were similar for statin users and nonusers regardless of duration of statin use (Figure). The age-adjusted rates of hip fracture were 0.97/1000 person-years for nonusers and 1.04/1000 person-years for statin users of any duration (data not shown).

Statin use was not statistically associated with a reduced hazard of fracture among women in any stratum of age, body mass index, current hormone replacement therapy use, history of fracture, or history of coronary disease (data not shown). In these stratified analyses, the hazard ratios associated with 3 years or less or more than 3 years of statin use did not vary consistently above or below 1.0. Few hip fractures occurred in any stratum among the women with 3 or more years of statin exposure, and no statistically significant associations were observed. Statin use was associated with small increased hazards of lower

arm or wrist and other clinical fractures, and CIs excluded 1.0 in some strata (data not shown).

In the multivariate analysis (Table 2), the adjusted hazard ratios associated with more than 3 years of statin use were 1.20 (95% CI, 0.59 to 2.45) for hip fracture, 1.09 (CI, 0.75 to 1.59) for lower arm or wrist fracture, and 1.12 (CI, 0.92 to 1.35) for other clinical fracture. In these multivariate models, older age, white ethnicity, lower body mass index, previous fracture, previous coronary disease, current smoking, and corticosteroid use were associated with greater hazards of hip fracture, while current hormone replacement therapy use, walking, and higher physical function were associated with reduced hazards of hip fracture. As indicated by the CIs in Table 2, the largest decreases in fracture rates for current statin users that are statistically compatible with the study data at the 0.05 error level are 17% for hip fracture and 15% for lower arm or wrist fracture. No decrease in risk for other clinical fracture was statistically compatible with the data. The largest increases in fracture rates for current statin users that are statistically compatible with the study data at the 0.05 error level are 81% for hip fracture, 27% for lower arm or wrist fracture, and 22% for other clinical fracture. Thus, for most of the comparisons in Table 2, the direction of the hazards ratios is more consistent with an increased risk for fracture than with a decreased risk.

Among the 63 227 women who had completed a year 3 clinic visit as of February 2001 (67.5% of the cohort), 83% of current statin users at baseline were still using a

Table 2. Adjusted Hazard Ratios Relating Duration of Statin Use, Statin Use versus Use of Other Lipid-Lowering Medications, and Potency of Statin Use to Risk for Hip, Lower Arm or Wrist, and Other Clinical Fractures: Women’s Health Initiative Observational Study, 1994–1999*

Variable	Participants, n	Hazard Ratio (95% CI)†		
		Hip Fracture	Lower Arm or Wrist Fracture	Other Clinical Fracture
Current statin use				
Nonuser	75 114	1.00	1.00	1.00
User	6782	1.22 (0.83–1.81)	1.04 (0.85–1.27)	1.11 (1.00–1.22)
Years of statin medication use				
Nonusers	75 114	1.00	1.00	1.00
<1 y	2249	1.06 (0.52–2.16)	0.90 (0.63–1.29)	1.16 (0.99–1.37)
1–3 y	2930	1.35 (0.78–2.34)	1.12 (0.85–1.48)	1.05 (0.91–1.22)
>3 y	1603	1.20 (0.59–2.45)	1.09 (0.75–1.59)	1.12 (0.92–1.35)
Potency of statin medication				
Nonusers	75 114	1.00	1.00	1.00
Low (fluvastatin, lovastatin)	2526	1.04 (0.57–1.92)	0.84 (0.61–1.16)	1.13 (0.98–1.31)
Medium (pravastatin)	1516	1.27 (0.60–2.72)	1.43 (1.01–2.02)	1.11 (0.91–1.36)
High (atorvastatin, simvastatin)	2720	1.42 (0.79–2.57)	1.04 (0.75–1.44)	1.07 (0.90–1.26)
Current statin use vs. other lipid-lowering medications				
Nonusers	74 056	1.00	1.00	1.00
Statin medication	6607	1.21 (0.81–1.80)	1.05 (0.86–1.28)	1.12 (1.01–1.24)
Other lipid-lowering medications	1058	0.83 (0.31–2.25)	0.84 (0.52–1.36)	1.20 (0.97–1.48)
Both	175	1.43 (0.20–10.32)	0.67 (0.17–2.68)	0.83 (0.44–1.54)

* Hazard ratios derived from multivariate Cox proportional hazards regression analysis adjusted for age, race or ethnicity, body mass index, history of fracture, history of myocardial infarction or angina, years of hormone replacement therapy use (<5 years, 5 to <10 years, 10 to <15 years, or ≥15 years), years of thiazide use (<10 years or ≥10 years), current alendronate use, total calcium intake, time spent walking, current and past smoking, alcohol consumption, coffee consumption, oral corticosteroid use, psychoactive medication use, nonstatin lipid-lowering medication use (except in last set of models), and physical function; stratified by clinical center. Hazard ratios above 1 correspond to more fractures for statin users.

† Multivariate models were based on 81 896 observations with the exception of the models for “potency of statin medications,” which were based on 81 876 observations.

Table 3. Adjusted Mean Bone Mineral Density according to Duration and Potency of Statin Use and Other Lipid-Lowering Medications: Women's Health Initiative Observational Study*

Variable	Participants	Mean Bone Mineral Density					
		Total Hip		Posterior–Anterior Spine		Total Body	
		Age- and BMI-Adjusted	Multivariate-Adjusted†	Age- and BMI-Adjusted	Multivariate-Adjusted†	Age- and BMI-Adjusted	Multivariate-Adjusted†
<i>n</i>	<i>g/cm²</i>						
Current statin use							
Nonuser	6020	0.84	0.84	0.98	0.98	1.01	1.01
User	422	0.86‡	0.85	0.98	0.98	1.01	1.01
Years of statin medication use							
Nonusers	6020	0.84	0.84	0.98	0.98	1.01	1.01
<1 y	126	0.85	0.85	0.98	0.98	1.02	1.03
1–3 y	217	0.86	0.85	0.98	0.98	1.01	1.01
>3 y	79	0.87	0.85	1.00	0.99	1.01	1.01
Potency of statin medication							
Nonusers	6020	0.84	0.84	0.98	0.98	1.01	1.01
Low (fluvastatin, lovastatin)	134	0.85	0.85	0.98	0.98	1.01	1.01
Medium (pravastatin)	117	0.86	0.85	0.98	0.97	1.01	1.01
High (atorvastatin, simvastatin)	169	0.86§	0.86	0.99	0.99	1.02	1.02
Current use of statin vs. other lipid-lowering medications							
Nonusers	5913	0.84	0.84	0.98	0.98	1.01	1.01
Statin medication	417	0.85	0.85	0.98	0.98	1.01	1.01
Other lipid-lowering medications	107	0.85	0.85	1.00	0.99	1.02	1.01
Both	5	0.92	0.91	0.94	0.94	1.02	1.01

* BMI = body mass index.

† Mean bone mineral density adjusted for age, race or ethnicity, body mass index, history of fracture, history of myocardial infarction or angina, years of hormone replacement therapy use (<5 years, 5 to <10 years, 10 to <15 years, or ≥15 years), years of thiazide use (<10 years or ≥10 years), current alendronate use, total calcium intake, time spent walking, current and past smoking, alcohol consumption, coffee consumption, oral corticosteroid use, psychoactive medication use, nonstatin lipid-lowering medication use (except in last set of models), physical function, and clinical center.

‡ *P* = 0.0193.

§ *P* = 0.0446.

|| *P* = 0.0268.

statin medication (3777 of 4550) 3 years later. Among the 85 870 women not using a statin medication at baseline, 5471 (6.4%) were taking a statin medication at the year 3 clinic visit. Hazard ratios for statin use derived from time-dependent Cox proportional hazards models were 1.08 (CI, 0.74 to 1.58) for hip fracture, 1.16 (CI, 0.98 to 1.37) for lower arm or wrist fracture, and 1.18 (CI, 1.08 to 1.29) for other clinical fracture.

No category of statin potency (low, medium, or high) was statistically associated with occurrence of hip, lower arm or wrist, or other clinical fractures (Table 2). Because the high-potency statin medications are newer and have been used for shorter durations than the low- and medium-potency statins, we added indicator variables for duration of statin use to the models examining potency; the hazard ratios for high-potency statin use did not change appreciably (data not shown). Examination of the individual statin medications did not reveal any associations with fracture (data not shown). There were no statistically significant associations between the use of other lipid-lowering medications and fracture (Table 2). Tests of interaction for statin use by time and across clinical centers were not statistically significant for any fracture category.

Bone mineral density at the total hip was slightly, but statistically significantly, higher among statin users than

nonusers after adjustment for age and body mass index (Table 3). Use of a high-potency statin was also statistically associated with higher mean total-hip bone density compared with nonusers after adjustment for age and body mass index. Neither difference persisted after adjustment for the many potential confounders in the multivariate models. No statistically significant differences were observed by statin use in bone density at the posterior–anterior spine or total body regardless of duration or potency of statin use. Use of other lipid-lowering medications was not associated with bone density at any skeletal site.

DISCUSSION

In this prospective study of 93 716 women, there was no statistically significant association of statin use with reduced hazard of hip, lower arm or wrist, or other clinical fractures. Among statin users at baseline, the hazard ratio for hip fracture was 1.22 and the CIs indicate that the true hazard ratio may be as low as 0.83 or as high as 1.81. No protective associations were detected in any subgroup of women classified by age, body mass index, current hormone use, or history of fracture. Neither longer duration of statin use nor use of higher-potency statin medications was statistically associated with reduced hazards of any type of

fracture. A small, statistically significant association between current statin use and higher risk for other clinical fractures was observed. Current statin use, regardless of duration or potency, was not statistically associated with bone mineral density at the hip, posterior–anterior spine, or total body after adjustment for age, body mass index, race or ethnicity, and other correlates of bone density.

Early reports from epidemiologic studies suggested impressive reductions (30% to 50%) in hip fracture risk associated with current and longer-term statin use (6–9). In one report of three prospective studies, statin use was associated with large reductions in risk for hip fracture, but the CIs included 1.0 because of small numbers of hip fracture (6). In two other case–control studies, findings of a reduced risk for fracture associated with statin use were limited because the available administrative data did not permit adjustment for important potentially confounding factors, such as body mass index (8, 9). In one observational study (7), the original report showed a 45% reduction in hip fracture risk in a British sample of more than 91 000 participants; whereas in a second analysis of the same database by other researchers using different epidemiologic methods, there was no association between statin use and hip fracture (10). In a randomized trial of 9014 men and women, 40 mg of pravastatin taken daily for an average of 6.1 years had no effect on occurrence of fractures (11). The latter trial, while in agreement with the findings presented here, was based predominantly on male participants and examined a single agent, pravastatin, which has shown “very little” effect on bone in laboratory studies (18).

Laboratory studies, both in vitro and in mice, have shown that statin medications stimulate bone formation through increasing the synthesis of bone morphogenic protein-2 (5). This activity was attributed to HMG-CoA reductase inhibition since addition of mevalonate, a downstream metabolite of HMG-CoA, blocked new bone formation. There has been progress in determining the intermediate steps that involve inhibition of prenylation, increased endothelial nitric oxide synthetase expression, and blocking of Rho activity (19). Statins can also inhibit osteoclast function and may reduce bone resorption (18).

If the statins most commonly used in current clinical practice affect bone formation in humans, it is reasonable to postulate that an effect on bone mineral density might be observed before (or concomitant with) a beneficial effect on fracture. Three cross-sectional studies (12, 20, 21) and a 1-year prospective study of 20 patients (22) have observed higher bone mineral density levels among statin users. Similar to our findings, slightly higher hip bone density levels were observed among women using statin medications in two large epidemiologic cohorts; however, these differences were not statistically significant after adjustment for potential confounders (6). Our findings do not support an association between the statins in current use and bone density at any skeletal site.

This study was limited by the relatively low prevalence of statin use in the study sample, particularly long-term statin use. We could not account for statins used in the past that were no longer being taken at baseline. Lack of information on dose of statin medication was another limitation, although the available data did allow examination of duration and potency. Reliance on self-report of non-hip clinical fractures is a third limitation, but the accuracy of self-report in the WHI Clinical Trial suggests that occurrence of fracture is reliably reported, particularly when broad categories of fracture sites are aggregated for analysis. Finally, spine radiographs were not obtained, so we could not examine associations with subclinical vertebral fractures.

Strengths of the present study include the size and diversity of the study group, the large number of fracture events, the availability of data on numerous confounding factors, and the ability to assess associations with bone mineral density and fracture in the same study group. Statin medications have been used for relatively short periods, less than 5 years for most people to date. Longer duration of statin use merits further study. Development of new statin agents that specifically target the mechanisms responsible for enhancing bone formation may offer greater promise than the currently marketed statins metabolized by the liver.

No associations between statin use and increased bone mineral density or reduced risk for fracture were observed in this large prospective study of postmenopausal women. Moreover, a substantial reduction in fracture risk from statin use is statistically incompatible with these data. At present, the epidemiologic data relating statin use to fracture are equivocal. The cumulative evidence does not warrant the use of statins as agents to prevent or treat osteoporosis.

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