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Effects of Atorvastatin on Bone in Postmenopausal Women with Dyslipidemia: A Double-Blind, Placebo-Controlled, Dose-Ranging Trial

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Context: In preclinical models, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase have been shown to positively affect bone remodeling balance. Observational studies and secondary analyses from lipid-lowering trials have yielded inconsistent results regarding the effect of these agents on bone mineral density and fracture risk.

Objective: Our objective was to determine whether clinically significant skeletal benefits result from hydroxymethylglutaryl-coenzyme A reductase inhibition in postmenopausal women.

Design and Setting: We conducted a prospective, randomized, double-blind, placebo-controlled, dose-ranging comparative clinical trial at 62 sites in the United States.

Participants: Participants included 626 postmenopausal women with low-density lipoprotein cholesterol levels of at least 130 mg/dl (3.4 mmol/liter) and less than 190 mg/dl (4.9 mmol/liter), and lumbar (L1–L4) spine bone mineral density T-score between 0.0 and −2.5.

Intervention: Once-daily placebo or 10, 20, 40, or 80 mg atorvastatin was administered.

Main Outcome Measures: We assessed percent change from baseline in lumbar (L1–L4) spine bone mineral density with each dose of atorvastatin compared with placebo.

Results: At 52 wk, there was no significant difference between each atorvastatin and placebo group or change from baseline at any tested dose of atorvastatin or placebo in lumbar (L1–L4) spine bone mineral density. Nor did atorvastatin produce a significant change in bone mineral density at any other site. Changes in biochemical markers of bone turnover did not differ significantly between each atorvastatin and placebo group. All doses of atorvastatin were generally well tolerated, with similar incidences of adverse events across all dose groups and placebo.

Conclusions: Clinically relevant doses of atorvastatin that lower lipid levels had no effect on bone mineral density or biochemical indices of bone metabolism in this study, suggesting that such oral agents are not useful in the prevention or treatment of osteoporosis.
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BOTH OSTEOPOROSIS AND dyslipidemia are highly prevalent, clinically important, chronic medical problems. Currently, the aminobisphosphonates constitute the most important drug class for the treatment of osteoporosis. These agents act predominantly to decrease bone resorption by inhibition of the farnesyl diphosphate synthase step in the mevalonic acid pathway (1, 2). 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) inhibit the same pathway at an earlier point (3) and may also antagonize osteoclasts by increasing expression of osteoprotegerin (4, 5). Statins may also enhance osteoblast activity by increasing synthesis of bone morphogenetic protein-2 (6, 7). *In vitro* and animal studies have demonstrated that statins, including atorvastatin, can both increase bone formation by osteoblasts and decrease bone resorption by osteoclasts (6, 8–13). However, some experiments in oophorectomized animals have not increased bone mass (14).

The publication of these findings led several groups to examine data from observational studies in which some of the patients took statins. Some of these analyses suggested a possible beneficial effect on osteoporosis or fracture risk (15–28). However, several other studies, including the Women's Health Initiative, failed to demonstrate any such effect (29–32), and one report of early effects was not confirmed by observations extended to 1 yr (33). The possibility of bias in nonrandomized trials is considerable, and one group concluded that the apparent effect of statins was attributable to unmeasured confounding factors (34). Authors of observational studies have consistently called for prospective controlled trials. The authors of a recent metaanalysis found some evidence for reduced hip fracture risk, but not in pro-

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Abbreviations: AE, Adverse event; BMD, bone mineral density; CI, confidence interval; CPK, creatine phosphokinase; DXA, dual-energy x-ray absorptiometry; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; QCT, quantitative computed tomography.

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spective studies, and found little or no effect on biomarkers and bone mineral density (BMD) (35). This analysis was limited by the small size of the controlled trials available. Relatively small prospective studies of the effect of simvastatin have suggested either small effects on BMD or indices of bone turnover (36, 37) or no effect on BMD or bone remodeling biomarkers (38), and a small, short-term study demonstrated no effect of atorvastatin on bone turnover markers (39).

In view of the considerable therapeutic implications of even a modest beneficial effect of atorvastatin or similar drugs on bone metabolism in humans at clinical doses, we undertook a prospective, randomized, double-blind, placebo-controlled trial to determine whether atorvastatin, across the range of clinical doses, compared with placebo had any effects on bone mineral density and biochemical markers of bone turnover in postmenopausal women with modest elevations of low-density lipoprotein cholesterol (LDL-C).

Subjects and Methods

This was a multicenter, randomized, double-blind, placebo-controlled study conducted at 62 sites in the United States. Institutional review board approval was obtained for each site, and each participant gave written informed consent.

Subjects

The study enrolled 626 women, aged 40–75 yr, with LDL-C levels of at least 130 mg/dl (3.4 mmol/liter) and less than 190 mg/dl (4.9 mmol/liter). At screening, lumbar spine BMD was required to be between 0.0 and 2.5 SD below the mean for young adult Caucasian women (>0.772 g/cm^2 and <1.047 g/cm^2 by Hologic densitometers). All individuals were postmenopausal, as demonstrated by serum estradiol levels of less than 110 pmol/liter (30 pg/ml) and FSH levels of more than 30 IU/liter.

Patients were excluded if they were treated with any of the following within 3 months (or as specified) before screening: any lipid-lowering medication, systemic hormone therapy (6 months), or other drugs affecting bone metabolism, including vitamin D (more than 1000 IU daily), calcitonin, hormone therapy or selective estrogen receptor modulators, bisphosphonates (within 12 months), sodium fluoride, or chronic systemic or inhaled glucocorticoids. Patients with a clinical history of diabetes mellitus, coronary heart disease, or any medical disease known to be associated with development of metabolic bone disease (*e.g.* bone marrow disease, hereditary disorders of calcium or mineral metabolism, untreated or inadequately treated endocrine disorders, severe rheumatoid arthritis, or a history of malignancy within the past 5 yr) were also excluded. After publication of the third National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines in 2001 (40), patients who presented with two or more cardiovascular risk factors and an LDL-C of at least 160 mg/dl (4.1 mmol/liter) were not included.

Study design

The study incorporated a 2-wk screening phase, followed by 52 wk of randomized treatment. Eligible participants were randomly assigned to receive once-daily doses of atorvastatin (10, 20, 40, or 80 mg) or matching placebo according to a computer-generated pseudo-random code using the method of random permuted blocks. Patients in each group received calcium and vitamin D supplementation in the form of tablets containing 500 mg elemental calcium and 200 IU vitamin D, taken twice daily. All patients were instructed to follow the NCEP ATP III Step I (40) or a comparable diet.

The primary endpoint was percent change in areal lumbar spine BMD (L1–L4, following International Society of Clinical Densitometry official positions for skeletal site selection) (41), measured by dual-energy x-ray absorptiometry (DXA) at baseline and at wk 52 or completion. Secondary endpoints included percent change in femoral neck, trochanter, and total proximal femoral areal BMD measured by DXA at baseline and wk 52. In addition, lumbar spine L1–L2 volumetric BMD was measured by quantitative computed tomography (QCT) in a subset of patients at selected investigative sites. Percent changes from baseline to wk 26 were also evaluated. All centers used Hologic densitometers (models QDR-1000, QDR-2000, 2000, 4500, or Delphi). Centralized bone density interpretation and quality control were carried out by Synarc Inc. (Portland, OR).

Biochemical and safety measurements

Serum samples for biochemical markers of bone metabolism and lipid biomarkers and second-void urine specimens were collected after a 10- to 14-h fast. To minimize variability due to diurnal variation, subjects were instructed to report between 0600 and 1000 h at all visits. Bone biomarkers included serum N-telopeptide of type I collagen (Ostex International, Seattle, WA; now Wampole, MA), serum C-telopeptide of type I collagen (Elecsys 2010; Roche Diagnostics, Indianapolis, IN), osteocalcin (Elecsys 2010; Roche Diagnostics), bone-specific alkaline phosphatase (Quidel, San Diego, CA), N-terminal propeptide of procollagen type I (Elecsys 2010; Roche Diagnostics), and urinary deoxypyridinoline (Quidel). Samples for bone biomarkers were stored at or below −70 C until they were analyzed in batches, including all samples from each subject. Serum lipid markers included total cholesterol, LDL-C [by Friedewald estimation unless triglycerides were >400 mg/dl (4.5 mmol/liter), then determined directly by ultracentrifugation], triglycerides (glycerol blanked), and high-density lipoprotein cholesterol (HDL-C) (chemical precipitation by dextran sulfate/$MgCl_2$). Cholesterol and triglyceride measurements employed Centers for Disease Control and Prevention (CDC) standardized enzymatic methods on the Hitachi 911 analyzer (Roche Diagnostics). All bone marker and lipid measurements were performed at Pacific Biometrics, Inc. (Seattle, WA). In addition, standard hematological and biochemical safety measurements were performed.

All treatment-emergent adverse events (AEs), including adverse drug reactions, illnesses with onset during the study, or exacerbation of preexisting illnesses, were reported, regardless of treatment group or suspected causal relationship to study drug. Serious AEs, regardless of treatment group or suspected relationship to drug, were reported immediately and were defined as any adverse drug experience that was life-threatening or resulted in death, inpatient hospitalization, or significant disability/incapacity. Events that required medical or surgical intervention to prevent one of these outcomes could also be classed as serious AEs. Safety was also assessed by clinical laboratory measurements [including hemograms, aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase (CPK)]) in addition to physical examinations, vital signs, and electrocardiograms.

Statistical methods

The *a priori* sample size projection of 575 participants (115 per treatment group) was estimated to provide approximately 90% power to detect a 2.0% treatment-related difference in lumbar spine BMD between atorvastatin and placebo, assuming a SD of 3.5% and a dropout rate of approximately 20%. Hypothesis testing was controlled for multiple comparisons (four active treatments and a placebo) via Dunnett's method, and all tests were two sided and were conducted at a 5% significance level. All analyses, tables, listings, and plots were produced using the SAS statistical software.

Three patient populations were identified for purposes of analysis: the efficacy-evaluable (per-protocol) population consisting of subjects who met all evaluability criteria determined before unblinding and database lock, those for whom follow-up data were obtained within 1 month of the scheduled wk-52 visit, and those who took at least 80% of their study drug. Because the purpose of this study was to optimize the ability to detect differences between groups rather than evaluate overall therapeutic effect, efficacy results for the per-protocol population were considered to be of primary interest and are presented herein. The modified intent-to-treat (ITT) population comprised all individuals who received at least one dose of study medication and had both a baseline and at least one post-baseline BMD measurement. The results for all efficacy endpoints were similar for both the per-protocol and modified ITT populations. The safety population included all subjects that received at least one dose of study medication.

The principal analyses of efficacy were comparisons of the differences in percent changes from baseline to the end of the study (52 wk) between each atorvastatin treatment group and the placebo group; percent changes from baseline to wk 26 were also evaluated. For BMD measurements, an analysis of covariance model adjusted for treatment, center, and baseline value was used to assess treatment differences from placebo at each visit, based on comparisons of least squares (LS) means. Percent responders (defined as those patients with any positive change in BMD from baseline) and dose response (linear regression) were also assessed. For bone markers, 10% trimmed means of percent changes and 95% confidence intervals (CI) are reported. Further comparisons were carried out on rank-transformed percent changes from baseline, using linear model methodology, including O'Brien's procedure to determine the overall treatment effect on multiple markers combined and separate analysis on each bone marker alone. Blood lipid parameters were analyzed using the same methods used for BMD on percent change data. The proportion of patients with LDL-C of 130 mg/dl (3.4 mmol/liter) or less was compared between each treatment *vs.* placebo using Pearson's χ^2 test. Due to the exploratory nature of the study, no adjustments were made for multiple endpoints, except that multiple comparisons of atorvastatin *vs.* placebo LS means in linear models were performed using Dunnett's method.

For reporting purposes, investigator terms describing AEs were coded to standard preferred terms based on the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary and were characterized by intensity and relationship to study drug. Consistent with usual practice, abnormal laboratory values of more than three times the upper limit of normal for hepatic transaminases (aspartate aminotransferase and alanine aminotransferase) and more than 10 times the upper limit of normal for CPK at two consecutive measurements obtained 4–10 d apart were predefined as clinically important.

Results

Baseline characteristics

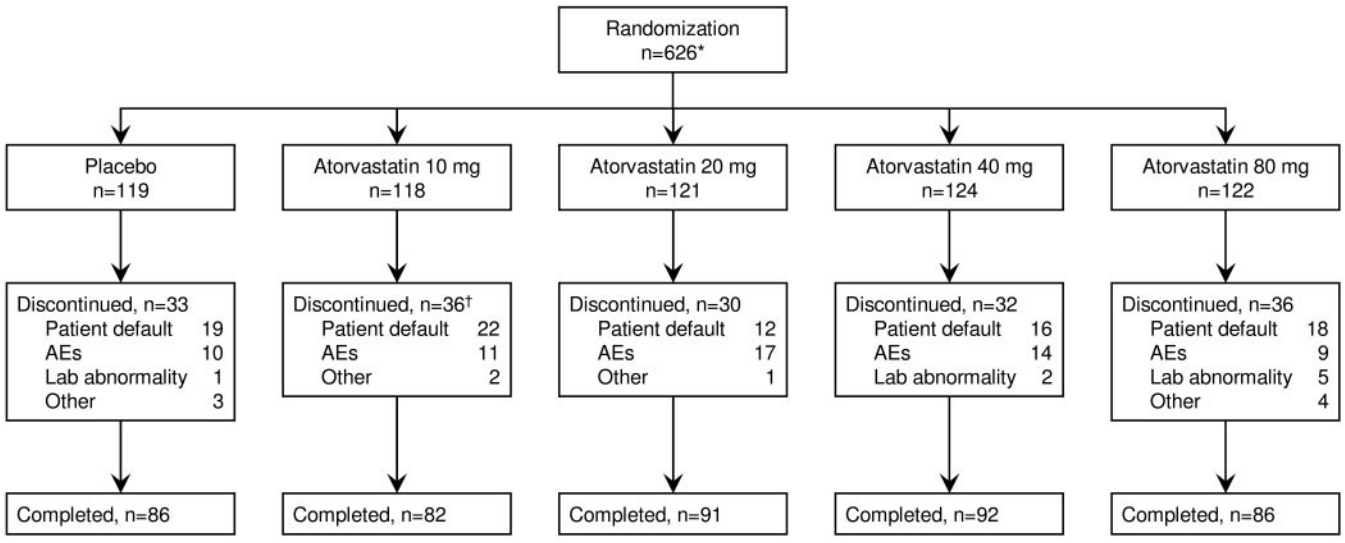
As shown in Fig. 1, a total of 626 women were randomized to one of the five treatment groups, of whom 604 actually received at least one dose of study medication. Of these, 167 (27.6%) discontinued prematurely and 437 (72.4%) completed the study through the final visit. The most common reason for discontinuation was withdrawn consent or loss of the subject to follow-up (n = 87, 13.9%). The per-protocol, modified ITT, and overall safety populations comprised 318, 482, and 604 individuals, respectively. Patient demographics and baseline characteristics are presented in Table 1. There were no clinically important differences between groups in any of the baseline characteristics. Medications taken before study start and during the study were similar between treatment groups.

Effect on BMD

There were no significant differences between any dose of atorvastatin and placebo for percent changes in the lumbar spine (L1–L4) BMD measured by DXA from baseline to 52 wk (Fig. 2 and Table 2). Furthermore, there was no significant difference between treatments at wk 26 and no significant change from baseline to wk 26 or 52 for any treatment group. Approximately 39–53% of patients in each treatment group were responders (positive change in lumbar spine, L1–L4, BMD). However, there was no significant difference between atorvastatin and placebo responder rates, and the overall dose-response relationship was not significant. Furthermore, there were no significant differences between groups with respect to changes in secondary BMD endpoints, including LS volumetric BMD (QCT) and the femoral DXA measurements from baseline to 26 or 52 wk. There were no significant within-group changes, with the exception of a borderline decrease in total proximal femur BMD within the placebo group at wk 52 (Table 2).

Effects on biochemical markers of bone metabolism

Measurements of the biochemical markers of bone metabolism failed to demonstrate any significant differences between the atorvastatin and placebo groups for percent change from baseline to wk 52 (Table 2) or wk 26. Within individual groups, some reductions (95% CI < 0) were observed, but there was no clear pattern of dose dependence.



*22 patients were randomized but did not receive the allocated treatment
†1 patient withdrew due to an AE that was present 12 days prior to study start

FIG. 1. Study flow chart.

TABLE 1. Demographic and baseline characteristics

	Placebo, n = 119	Atorvastatin			
		10 mg, n = 118	20 mg, n = 121	40 mg, n = 124	80 mg, n = 122
Age (yr)	58.8 (7.6)	58.6 (6.5)	59.2 (6.7)	59.4 (7.0)	57.8 (6.7)
Race					
No. of white subjects (%)	107 (89.9)	108 (91.5)	98 (81.0)	110 (88.7)	105 (86.1)
No. of years menopausal	13.3 (8.3)	11.8 (8.2)	11.6 (8.1)	12.8 (8.7)	11.3 (7.9)
Weight (kg)	73.8 (15.3)	72.7 (15.0)	72.6 (13.5)	74.6 (15.0)	73.0 (12.6)
Ex-smoker or current smoker, n (%)	55 (46.2)	56 (47.5)	50 (41.3)	62 (50)	62 (50.8)
Lumbar spine (L1–L4) BMD (g/cm^2) by DXA[a]	0.91 (0.087)	0.92 (0.084)	0.92 (0.079)	0.93 (0.083)	0.91 (0.086)
Lumbar spine (L1–L2) BMD (g/cm^3) by QCT[b]	111.88 (29.500)	127.52 (22.932)	124.13 (21.992)	120.64 (21.195)	125.21 (18.523)
Total hip BMD (g/cm^2) by DXA[a]	0.84 (0.109)	0.87 (0.100)	0.85 (0.108)	0.87 (0.099)	0.87 (0.103)
Total cholesterol[a]					
mg/dl	244.8 (21.7)	241.2 (19.8)	242.2 (21.0)	245.2 (21.8)	242.4 (23.0)
mmol/liter	6.3 (0.6)	6.2 (0.5)	6.3 (0.5)	6.3 (0.6)	6.3 (0.6)
LDL-C[a]					
mg/dl	159.1 (16.9)	154.8 (16.5)	158.0 (17.9)	155.4 (17.0)	155.6 (15.5)
mmol/liter	4.1 (0.4)	4.0 (0.4)	4.1 (0.5)	4.0 (0.4)	4.0 (0.4)
Triglycerides[a]					
mg/dl	141.2 (61.6)	124.7 (53.1)	139.9 (59.5)	143.2 (70.3)	152.6 (83.3)
mmol/liter	1.6 (0.7)	1.4 (0.6)	1.6 (0.7)	1.6 (0.8)	1.7 (0.9)
HDL-C[a]					
mg/dl	57.5 (11.0)	61.6 (14.7)	56.2 (13.9)	61.1 (15.2)	56.4 (12.3)
mmol/liter	1.5 (0.3)	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)	1.5 (0.3)

Numbers represent mean (SD) values unless specified otherwise.
[a] Mean (SD) values for the efficacy evaluable population.
[b] Mean (SD) values for the efficacy-evaluable population (from selected sites only) (total n = 47; placebo, n = 11; atorvastatin 10 mg, n = 11; 20 mg, n = 11; 40 mg, n = 6; 80 mg, n = 8).

Multivariate analysis of the overall treatment effect of all markers compared with placebo was nonsignificant for all doses of atorvastatin.

In exploratory analyses, we found no evidence of differential treatment effects on bone markers between patients younger and older than 62 yr (data not shown).

Effect on lipids

As anticipated from the well-characterized effects of atorvastatin, the mean total cholesterol, LDL-C, and triglyceride levels decreased from baseline to wk 52 for each of the atorvastatin groups in terms of percent change, and these differences were statistically significant compared with the placebo group (Fig. 3). The mean HDL-C levels were not significantly different in terms of percent change between baseline and wk 52 within treatment groups or between atorvastatin and placebo groups (Fig. 3).

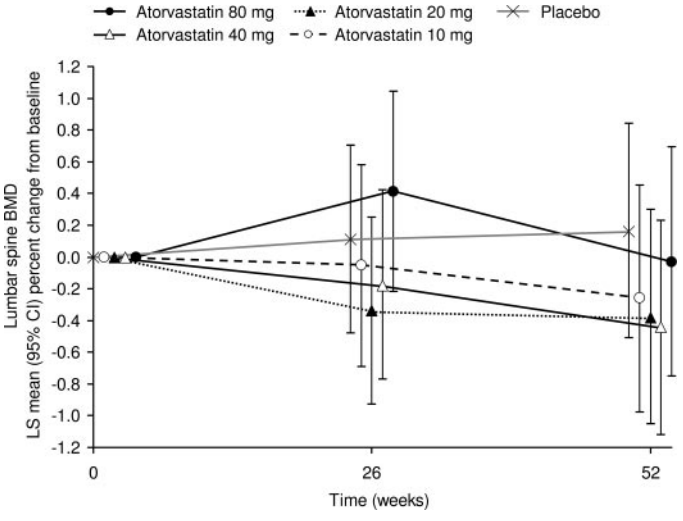


FIG. 2. Lumbar spine (L1–L4) BMD by DXA: mean percent change from baseline (efficacy evaluable population).

Safety evaluation

Overall, atorvastatin was well tolerated, consistent with the product labeling and previous publications. Serious AEs were reported in 12 patients (placebo, n = 3; atorvastatin 10 mg n = 1, 20 mg n = 4, 40 mg n = 2, 80 mg n = 2), of which none was considered to be related to study treatment, and only one led to permanent study drug discontinuation (atorvastatin 80 mg, hemorrhagic stroke). There were no deaths or cases of rhabdomyolysis during the study.

The incidences of the most frequently reported treatment-emergent AEs are summarized in Table 3. The most frequently reported treatment-related AE was myalgia (four, five, 10, five, and three cases reported for 10, 20, 40, and 80 mg atorvastatin and placebo, respectively). We did not observe CPK elevations above the predefined threshold in any patient. Hepatic transaminase elevations exceeding the predefined thresholds were observed in two patients, both of whom were receiving atorvastatin (40 and 80 mg), and both discontinued treatment. All laboratory abnormalities were followed up and resolved by the end of the study.

Discussion

We found no evidence that systemic atorvastatin administration produced any significant effect on bone mass or markers, despite highly provocative reports that statins, when used in experimental systems, affected both bone formation and bone resorption in the direction of a positive remodeling balance (6, 8–12). Although the orally adminis-

TABLE 2. Percent change from baseline to wk 52 (last observation carried forward[a]) in BMD and markers of bone metabolism (per-protocol population)

	% change from baseline				
	Placebo, n = 67	Atorvastatin			
		10 mg, n = 59	20 mg, n = 65	40 mg, n = 67	80 mg, n = 60
Lumbar spine (L1–L4) BMD by DXA, LS mean (95% CI)	0.16 (−0.51, 0.84)	−0.26 (−0.98, 0.45)	−0.38 (−1.05, 0.30)	−0.44 (−1.12, 0.23)	−0.03 (−0.75, 0.69)
Lumbar spine (L1–L2) BMD by QCT,[b] LS mean (95% CI)	2.36 (−2.96, 7.68)	−3.95 (−8.97, 1.06)	−1.93 (−7.17, 3.30)	0.11 (−6.74, 6.96)	−3.43 (−9.41, 2.54)
Total femoral BMD by DXA, LS mean (95% CI)	−0.74 (−1.43, −0.04)	−0.58 (−1.31, 0.15)	−0.55 (−1.25, 0.15)	−0.51 (−1.20, 0.19)	−0.06 (−0.81, 0.68)
sNTX, 10% trimmed mean (95% CI)	−3.68 (−8.54, 1.18)	−3.50 (−8.24, 1.24)	0.02 (−5.86, 5.89)	−6.54 (−10.05, −3.03)	−5.04 (−9.98, −0.09)
sCTX, 10% trimmed mean (95% CI)	−4.18 (−14.77, 6.41)	−1.92 (−8.58, 4.74)	3.96 (−6.45, 14.36)	−4.47 (−12.25, 3.31)	−1.14 (−10.50, 8.22)
Osteocalcin, 10% trimmed mean (95% CI)	−4.38 (−10.39, 1.64)	−4.44 (−10.52, 1.64)	−2.88 (−8.78, 3.02)	−5.32 (−10.88, 0.24)	−10.56 (−15.70, −5.43)
BSAP, 10% trimmed mean (95% CI)	−2.74 (−6.44, 0.97)	0.55 (−3.25, 4.35)	−1.34 (−6.06, 3.38)	−0.80 (−4.76, 3.16)	−1.18 (−5.41, 3.05)
P1NP, 10% trimmed mean (95% CI)	−7.04 (−12.89, −1.19)	−0.25 (−7.15, 6.64)	−1.20 (−8.86, 6.45)	−1.63 (−9.53, 6.27)	−10.29 (−16.65, −3.92)
DPD, 10% trimmed mean (95% CI)	0.83 (−5.19, 6.85)	−3.44 (−9.37, 2.48)	1.88 (−3.62, 7.38)	−1.19 (−6.70, 4.32)	−5.81 (−10.62, −1.01)

For all measurements, the *P* value for the difference between each atorvastatin group and placebo was nonsignificant using Dunnett's method in linear models. BSAP, Bone-specific alkaline phosphatase; DPD, urinary deoxypyridinoline; P1NP, procollagen type I N propeptide; sCTX, serum C-telopeptide; sNTX, serum N-telopeptide.

[a] No values were imputed due to the definition of the per-protocol population, who required follow-up data within 1 month of the wk-52 visit.

[b] A subset of the efficacy evaluable population from selected sites only was analyzed for lumbar spine (L1–L2) BMD by QCT (total n = 47; placebo, n = 11; atorvastatin 10 mg, n = 11; 20 mg, n = 11; 40 mg, n = 6; 80 mg, n = 8).

tered doses employed in humans result in much lower exposure than the relatively high concentrations that were used in those experiments, and orally administered statins undergo a first-pass effect, the reports of a possible clinical benefit from such medications, although not consistent, warranted a prospective controlled trial. We conducted such a study using the entire clinical dosage range of atorvastatin (10–80 mg), the most widely prescribed of these medications, to determine whether an effect on any measurement of BMD or an effect on bone metabolism could be detected and, if so, to determine whether a dose-response relationship existed. As far as we are aware, this prospective, randomized controlled clinical trial is unique in employing a range of doses to determine whether there is an effect of HMG-CoA reductase inhibition on bone metabolism. We found no such effects over 52 wk of treatment on lumbar (L1–L4) spine BMD by DXA, lumbar (L1–L2) spine BMD by QCT, total hip BMD by DXA, or biochemical markers of bone metabolism, although the expected lipid-lowering effect was apparent. Although we could not exclude the possibility of subtle effects over many years, all medications that have been shown to be beneficial for the prevention or treatment of osteoporosis have produced measurable effects on several of these endpoints.

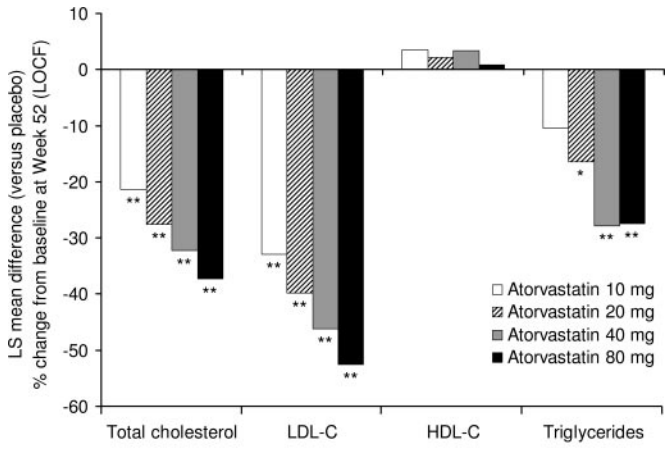


FIG. 3. Serum lipids: mean difference (atorvastatin *vs.* placebo) percent change from baseline at wk 52 (efficacy evaluable population).

Case-control analyses have suggested potential benefits of statins in reducing the risk of fracture (17–19, 23, 28). However, the association between fracture risk and the level of statin exposure differed across these studies, and in two of the studies, potentially confounding factors such as body mass index were inadequately controlled (17, 18). In addition, either the effects of statins on BMD or bone turnover were not assessed in these studies or changes in BMD were not associated with the risk of fracture (23). Subsequent studies have not supported this association between fracture risk reduction and statin use (29–31, 42).

Several studies have investigated the effects of statins on BMD in hyperlipidemic patients but were limited by the absence of a randomized, controlled design and have yielded inconsistent findings (29, 30, 36, 43–45). The data from the current trial are consistent with those of a smaller randomized, controlled trial in which simvastatin showed no benefit on BMD and biochemical bone markers in a similar population of women (38). Both studies enrolled postmenopausal women with low BMD and moderately elevated LDL-C and randomized them in a double-blind fashion to either a statin or placebo. The potential effects of statins on bone turnover were thereby assessed prospectively in a well-characterized target population using a well-matched control group.

At the time of study initiation, no clinical data were available on the effects of atorvastatin (or statins in general) on BMD; therefore, statistical considerations were based on information available from selective estrogen receptor modulators. After controlling for multiple comparisons (four active treatments *vs.* placebo), approximately 90 patients per treatment group were calculated to have 90% power to detect an assumed difference of 2.0% between active and placebo, with a SD of 3.5% and a dropout rate of approximately 20%. However, this was a conservative assumption regarding the SD for the distribution of percent change from baseline val-

TABLE 3. All-cause, treatment-emergent AEs occurring in at least 10% of patients in any treatment group

	No. of patients experiencing AE (%)				
	Placebo, n = 119	Atorvastatin			
		10 mg, n = 118	20 mg, n = 121	40 mg, n = 124	80 mg, n = 122
Any AE	102 (86)	98 (83)	109 (90)	104 (84)	102 (84)
Respiratory infection	20 (17)	20 (17)	13 (11)	27 (22)	25 (20)
Arthralgia	14 (12)	16 (14)	21 (17)	20 (16)	14 (11)
Myalgia	8 (7)	10 (8)	8 (7)	19 (15)	16 (13)
Urinary tract infection	12 (10)	5 (4)	12 (10)	14 (11)	13 (11)
Headache	10 (8)	10 (8)	8 (7)	14 (11)	11 (9)
Dyspepsia	10 (8)	10 (8)	11 (9)	9 (7)	12 (10)
Constipation	12 (10)	8 (7)	11 (9)	10 (8)	8 (7)
Pain	9 (8)	7 (6)	9 (7)	15 (12)	8 (7)
Accidental injury	9 (8)	5 (4)	4 (3)	14 (11)	8 (7)
Asthenia	6 (5)	4 (3)	13 (11)	9 (7)	6 (5)
Sinusitis	8 (7)	12 (10)	5 (4)	5 (4)	5 (4)

ues, and based on the results obtained, the actual SD was in the range 2.5–2.8%. Recalculating the power assuming a SD of 3% with 60 subjects in each treatment group (as in the per-protocol analysis) yields a power of more than 85% for each comparison. Therefore, the power to detect a treatment difference of 2.0% in the per-protocol analysis with a SD of 2.8% would be consistent with the original power estimate.

As expected, consistent with data from previous studies (46), atorvastatin therapy decreased total cholesterol, LDL-C, and triglycerides in a dose-dependent fashion in this population of postmenopausal women with dyslipidemia. No changes in HDL-C were observed in any treatment group, although HDL-C levels were relatively high in all groups at baseline. Atorvastatin was well tolerated at all doses, and overall safety was comparable to placebo. The reported incidence of serious AEs did not increase significantly with higher doses, and only two patients were reported to have clinically meaningful abnormal laboratory liver function tests with atorvastatin treatment, which were resolved by the end of the study. Thus, our findings were generally consistent with labeled product-safety information.

Despite the *in vitro* data suggesting that statins inhibit bone-resorption and enhance osteoblast activity (6), no effects on bone metabolism were observed in our study. After absorption, statins are biotransformed in the liver with a high hepatic first-pass clearance, resulting in a substantial lipid-lowering effect but a low systemic exposure to unbound pharmacologically active drug (47). The observed lack of effect of atorvastatin on BMD and bone biomarkers may therefore have been the result of low statin uptake into bone tissue. The maximum doses of the currently available medications in this class are limited by tolerability and safety considerations. Therefore, it is unlikely that substantially higher systemic doses of oral HMG-CoA reductase inhibitors could be employed clinically. Thus, our findings do not support a role for conventional doses of atorvastatin in the prevention or treatment of postmenopausal osteoporosis.

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