Cardiovascular disease is the major cause of death for women as well as men, and risk increases markedly in the postmenopausal period. Nonetheless, historically women have received less or delayed attention for coronary heart disease (CHD) than men. Although the benefits of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in women were established in subgroup analyses of major clinical trials, to date there have been very few large prospective studies on the response of women to lipid-lowering therapies. An increasingly attractive means of assessing therapy effectiveness is to evaluate intermediate end points such as disease progression, and this goal preferably should be attained by means of noninvasive imaging modalities. In several small studies, mostly observational and nonrandomized, electron-beam tomography (EBT) was used to assess whether accumulation of coronary artery calcium (CAC), a marker of atherosclerosis, can be slowed with implementation of lipid-lowering therapy. The majority of studies showed that statins can slow and even halt progression of arterial calcification relative to placebo, although some investigators were unable to confirm such findings. It is currently believed that vascular calcification is an active metabolic process that resembles bone formation. Stimulation of fetal aorta smooth muscle cells in vitro with oxidized lipoproteins can induce a phenotypical transformation of these cells into osteoblast-like cells capable of initiating and supporting calcification processes. Hence, it is theoretically conceivable that vascular calcification may be slowed by means of lipid-lowering therapies and that aggressive therapies may be more effective than moderate ones.

**Background**—Women have been underrepresented in statin trials, and few data exist on the effectiveness and safety of statins in this gender. We used sequential electron-beam tomography (EBT) scanning to quantify changes in coronary artery calcium (CAC) as a measure of atherosclerosis burden in patients treated with statins.

**Methods and Results**—In a double-blind, multicenter trial, we randomized 615 hyperlipidemic, postmenopausal women to intensive (atorvastatin 80 mg/d) and moderate (pravastatin 40 mg/d) lipid-lowering therapy. Patients also submitted to 2 EBT scans at a 12-month interval (mean interval 344±55 days) to measure percent change in total and single-artery calcium volume score (CVS) from baseline. Of the 615 randomized women, 475 completed the study. Mean±SD percent LDL reductions were 46.6%±19.9% and 24.5%±18.5 in the intensive and moderate treatment arms, respectively (P<0.0001), and National Cholesterol Education Program Adult Treatment Panel III LDL goal was reached in 85.3% and 58.8% of women, respectively (P<0.0001). The total CVS% change was similar in the 2 treatment groups (median 15.1% and 14.3%, respectively; P=NS), and single-artery CVS% changes and absolute changes were also similar (P=NS). In both arms, there was a trend toward a greater CVS progression in patients with prior cardiovascular disease, diabetes mellitus, and hypertension, whereas hormone replacement therapy had no effect on progression.

**Conclusions**—In postmenopausal women, intensive statin therapy for 1 year caused a greater LDL reduction than moderate therapy but did not result in less progression of coronary calcification. The limitations of this study (too short a follow-up period and the absence of a placebo group) precluded determination of whether progression of CVS was slowed in both arms or neither arm compared with the natural history of the disease. (Circulation. 2005;112:563-571.)

**Key Words:** calcium • imaging • lipids • women
The Beyond Endorsed Lipid Lowering with Electron Beam Tomography (EBT) Scanning (BELLES) trial tested this hypothesis in hypercholesterolemic postmenopausal women who had an indication for lipid-lowering therapy. Treatment-related changes in the extent of CAC at 1 year from initiation of therapy were evaluated by means of sequential EBT scans and quantified with a calcium volume score (CVS).

Methods

Study Population

The design of the BELLES study has been described in detail previously. Patients were recruited at 96 sites in the United States by obstetricians and gynecologists, primary care physicians, internal medicine specialists, and cardiologists. All patients were postmenopausal females aged 55 to 75 years. Menopause was defined as surgical or spontaneous amenorrhea for at least 1 year or receipt of treatment with hormone replacement therapy (HRT) for at least 1 year. HRT was defined as the equivalent of ≥0.625 mg/d of conjugated estrogens given by any route of administration or in combination with progestin therapy. Women not receiving HRT were not allowed to begin such treatment during the study period. In the initial study protocol, designed before the release of the results of the Heart and Estrogen/progestin Replacement Study (HERS) on the negative effects of estrogens on the cardiovascular system, women were asked to continue their current treatment for the remainder of the study. After publication of the data, a letter was sent to the investigators that contained information on HERS and advised them to at least counsel their patients about the potential risks of HRT therapy. Lipid entry criteria were as follows: an LDL cholesterol level ≥130 mg/dL (3.4 mmol/L) for women with CHD, CHD risk equivalents (according to National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] definition), or ≥2 risk factors and a 10-year CHD risk of 10% to 20%; LDL ≥160 mg/dL (4.1 mmol/L) for patients with ≥2 CHD risk factors and 10-year CHD risk of <10%; or patients with 0 to 1 risk factors.

To conform to the recommendation of 2 previously published studies, all patients were required to have a total CVS ≥30 at baseline. This guaranteed the best score reproducibility and the minimization of apparent CVS percentage change over time. Patients were excluded if they presented a known contraindication to the use of HMG-CoA reductase inhibitors (statins), such as known hyper-sensitivity or hepatic dysfunction with aspartate transaminase (AST) or alanine transaminase (ALT) levels ≥1.5 times the upper limit of normal at any time between screening and randomization. Other exclusion criteria included treatment with lipid-lowering drugs other than HRT within 3 months of screening, evidence of secondary hyperlipidemia (as in nephrotic syndrome), renal dysfunction (creatinine ≥1.5 mg/dL), uncontrolled type 1 or type 2 diabetes mellitus (defined by an HbA1c >10%), myocardial infarction ≤6 months before screening, uncontrolled hypothyroidism (defined by thyroid stimulating hormone >1.5 times the upper limit of normal), and plasma triglyceride levels ≥600 mg/dL (6.8 mmol/L). Individuals who had undergone a CABG or PTCA, with or without stent implantation, were included, but the coronary areas that contained clips, stents, and other hardware that might create imaging artifact were excluded. Patients were also excluded if they demonstrated other uncontrolled or concurrent conditions or medication use that may have affected the efficacy or safety comparisons, showed the potential for noncompliance with therapy, or weighed >300 pounds (136.2 kg), because of weight limits imposed by the EBT radiological table. Concurrent therapy with any lipid-regulating medication (eg, niacin, probucol, fibrates, bile-acid sequestering resins, or other statins), drugs known to increase the side effects of statins when prescribed in combination, and systemic steroids was also prohibited.

The randomization process was based exclusively on the presence of clinical characteristics and not the extent of coronary calcification, although all patients were required to have a minimum calcium score of 30. This is the likely explanation for the difference in baseline calcium score noted between the 2 study groups at the end of study when the database was locked and the data were analyzed.

Screening and Follow-Up

Patients underwent an initial screening visit, which included an assessment of medical history, CHD risk factor profile, blood count, lipid profile, and urinalysis. Patients eligible for inclusion in the study after the screening visit were invited to undergo a baseline EBT scan within 3 working days at a designated regional EBT center. An optional second screening visit was allowed for patients who originally failed to qualify because of anomalous clinical laboratory results. If patients met the inclusion/exclusion criteria at their screening visit, they were then eligible to undergo the baseline EBT scan. All baseline scans, as well as follow-up scans, were sent to the EBT core laboratory within 1 week of scanning for prompt evaluation and scoring.

Patients who successfully completed the screening visit and met all inclusion and exclusion criteria were randomized to double-blind treatment with either atorvastatin 80 mg/d and matching pravastatin placebo or pravastatin 40 mg/d and matching atorvastatin placebo, all taken at bedtime. The Clinical Pharmaceutical Operations Department of Pfizer, Ann Arbor, Mich, provided the drugs and matching placebos. Double-blind medication was provided in a double-dummy format as follows: for patients taking active atorvastatin, atorvastatin 40-mg tablets (take 2 daily) and placebo (take 1 daily); for patients taking active pravastatin, pravastatin 40-mg tablets (take 1 daily) and placebo (take 2 daily). Compliance with study medication was calculated as difference in number of active tablets dispensed and returned, divided by number of tablets prescribed between week 0 and week 12 visits, multiplied by 100. Both groups reported similar compliance (average 92.8% for atorvastatin versus 93.4% for pravastatin).

After randomization, patients returned for clinic visits at week 6 and at months 3, 6, 9, and 12 for efficacy and safety evaluations. A follow-up EBT scan was scheduled within 1 week of expiration of month 12 (Table 1). If a patient chose to withdraw from the study before completion of 12 months of randomization, a final EBT scan was obtained if at least 9 months of randomized treatment had been provided.

EBT Imaging

EBT imaging was performed at 35 regional sites in the United States with C-150 Imatron scanners (GE/Imatron). A standard imaging protocol was used both at baseline and at follow-up: 36 to 40 continuous slices (slice thickness = 3 mm) were obtained during a single breath hold starting at the level of the carina and extending to the diaphragm. Water and soft tissue phantoms were used daily to flood the systems. Images were acquired at 100-ms scanning time, and prospective triggering at 60% of the RR interval was used. All coronary artery areas that contained calcified foci with a minimum density of 130 HU and a minimum of 3 pixels were included in the total final score. Quantification of coronary artery calcium was performed with a volumetric calcium score (CVS) as described previously. The CVS unit corresponds to 1/1000 mL. Both for simplicity and to adhere to prior style, in this report, we present the numerical value alone without the attached unit symbol. The CVS is reported as the sum of the individual vessels (left main, left anterior descending, left circumflex, and right coronary arteries) score and the single-vessel score.

All scans were interpreted in a core laboratory by 2 independent investigators (PR and TQC) blinded to patients’ treatment and all other clinical data. To guarantee the best score reliability, studies were repeated when they showed excessive artifact due to respiratory motion or ECG misregistration, and all scans were interpreted by 2 experienced EBT investigators (PR and TQC). If the CVS interpretation of the 2 reading physicians was discrepant by ≥15%, a consensus was reached between them before a single score was entered in the database. Given the experience and the utilization of the same workstation and software (NetaMD, Scimage), this occurred in fewer than 10% of the cases. It was decided a priori not to perform 2 EBT scans on every patient at each screening session. This


### TABLE 1. Demographic and Baseline CHD Risk Factors (Safety Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atorvastatin</th>
<th>Pravastatin</th>
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<tbody>
<tr>
<td></td>
<td>80 mg (n=305)</td>
<td>40 mg (n=309)</td>
</tr>
<tr>
<td>Postmenopausal status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>204 (66.9)</td>
<td>212 (68.6)</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>101 (33.1)</td>
<td>97 (31.4)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>64.2 (6.5)</td>
<td>64.5 (6.0)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>279 (91.5)</td>
<td>283 (91.6)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>28.5 (5.4)</td>
<td>29.0 (5.5)</td>
</tr>
<tr>
<td>HRT, n (%)</td>
<td>72 (23.6)</td>
<td>73 (23.6)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>63 (20.7)</td>
<td>51 (16.5)</td>
</tr>
<tr>
<td>Past or nonsmoker</td>
<td>242 (79.3)</td>
<td>258 (83.5)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>138 (45.2)</td>
<td>132 (42.7)</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>42 (13.8)</td>
<td>44 (14.2)</td>
</tr>
<tr>
<td>Cardiovascular history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>10 (3.3)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>CABG</td>
<td>2 (0.7)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>7 (2.3)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>7 (2.3)</td>
<td>10 (3.2)</td>
</tr>
<tr>
<td>Angina</td>
<td>34 (11.1)</td>
<td>24 (7.8)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>21 (6.9)</td>
<td>21 (6.8)</td>
</tr>
</tbody>
</table>

Treatment groups did not differ for any baseline or demographic characteristics (P>NS).

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technique was used in the past when the reproducibility of the calcium score measurements was very low, but based on our (PR and TQC) prior experience, it was clear that it would not provide substantial improvement over a single scan performed with all the careful criteria outlined above. Furthermore, double scanning of each patient would have doubled the radiation dosage administered to asymptomatic individuals, and it was thought that this may have represented an obstacle for approval of the protocol in some institutions.

The EBT scans were performed purely for research purposes, and therefore, the CVS was not provided to the clinical investigators or patients. This prevented physicians from making therapeutic decisions based on the extent of CVS.

### Outcome Measures

The primary efficacy parameter was defined as the percent change from baseline to month 12 in total coronary CVS, determined by EBT. Efficacy analyses were performed on the modified intention-to-treat population, defined as patients who took at least 1 dose of study medication and who had follow-up EBT data.

There were also 2 secondary efficacy parameters: (1) the percent change from baseline to month 12 in total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides; and (2) absolute change in total CVS and percent change from baseline to month 12 in coronary CVS in each vessel. For the latter purpose, the left main and left anterior descending coronary artery scores were combined in 1 score.

### Safety

At each follow-up visit after screening, all adverse events were recorded, grouped by body system and treatment group. The intensity and relationship of each event to the study drug were summarized. Clinical laboratory evaluations were performed by a central laboratory (Medical Research Laboratories International, Highland Heights, Ky) at screening and at month 12. Additionally, safety laboratory determinations alone (AST, ALT, and creatine kinase [CK] levels) were made at week 6 and at months 3 and 6. A clinically important laboratory abnormality was reported as a serious adverse event and followed until the abnormality resolved or a satisfactory explanation for its occurrence was obtained. Such an abnormality was defined as follows: CK levels >10 times the upper limit of normal on 2 consecutive measurements 4 to 10 days apart, accompanied by muscle tenderness or weakness, or ALT or AST levels >3 times the upper limit of normal on 2 consecutive measurements 4 to 10 days apart. The following outcomes were also recorded as serious adverse events: death; life-threatening adverse event, inpatient hospitalization or prolonged existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect. Safety analyses were performed on the safety population, defined as all patients who took at least 1 dose of study medication.

### Statistical Analysis

A sample size of 259 patients in each treatment group was estimated to have 90% power to detect a difference in mean total coronary CVS values of 10% (the difference between a 10% increase from baseline in total coronary CVS for the pravastatin group and a 0% change in total coronary CVS for the atorvastatin group), with the assumption that the common SD in total coronary CVS is 35% with a 2-group t test with a 0.05 2-sided significance level. These calculations were based on a previous assessment of the effect of statins on coronary artery calcification by EBT.4 In that study, the average yearly CVS progression in untreated patients was 52±36%, whereas progression averaged 25±22% in moderately treated patients and 7±23% in aggressively treated patients. With an anticipated dropout rate of ∼15%, enrollment of ∼300 patients per treatment arm (total of 600) was assessed to be an adequate number of study patients.

All testing was 2-sided and conducted with a 5% type I error rate. Percent changes and absolute changes in EBT efficacy parameters were analyzed with a Cochran-Mantel-Haenszel test based on rank scores, stratified by baseline HRT status (HRT, no HRT). Because >50% of patients had a CVS of zero at baseline for individual arteries (left circumflex and right coronary), the analysis of percent change was not done; absolute changes from baseline were analyzed for these individual arteries. Total CVS and CVS for individual arteries at baseline were compared between treatment groups with Wilcoxon rank sum tests. Additional analyses included a multivariate ANCOVA model to assess treatment differences in percent change in total CVS (rank transformed), with adjustment for the following baseline factors: age, baseline total CVS, baseline HRT status, prior history of cardiovascular disease, diabetes mellitus, smoking status (current/not current), and systemic hypertension. The relationship between percent change in total CVS (rank transformed) and percent change in LDL was further assessed by fitting multivariate regression models, 1 model for each treatment group. Initial models included factors for percent change in LDL cholesterol, age, HRT status, baseline total CVS, prior/current CVD, diabetes, smoking status (current/not current), and hypertension at baseline. The final regression model was determined on the basis of a backward selection method, keeping only those factors in the model determined to be significant at the α=0.10 level but always keeping in the model percent change in LDL cholesterol, baseline total CVS, and baseline HRT status (a stratification variable by design). Analyses of the percent changes from baseline between the 2 treatment groups for the collected lipid parameters were performed with an ANCOVA model, with control for baseline lipid values and baseline HRT status (HRT, no HRT). For patients who discontinued the study before 12 months, the last on-treatment values (CVS, lipid measures) were carried forward. Additional analyses included a comparison of treatment groups in terms of percent of patients reaching the LDL goal, based on NCEP ATP III guidelines,13 with a χ² test. Also, subgroup analyses, based on baseline total CVS categories, baseline HRT, and presence of cardiovascular disease, diabetes mellitus, systemic hypertension, and smoking status, were also performed, with ANCOVA models (on ranked scores), to assess treatment differences in terms of percent change in total CVS within each subgroup. These subgroup analyses were exploratory in nature.
because the study was not designed to detect treatment differences within subgroups; thus, the probability of observing true treatment differences within subgroups was low. No multiplicity adjustments to significance levels were done for any analyses.

Results

Patient Population

The flow chart of patient screening and enrollment is presented in Figure 1. Between September 1999 and May 2002, 4739 postmenopausal women completed a screening visit. A total of 615 patients were randomized at 96 centers in 18 geographic areas in the United States. One randomized patient withdrew consent and returned the study medication unused. Most women were excluded from the study after the first screening visit because of failure to meet lipid (63%) and/or CVS (42%) criteria for inclusion. A total of 475 women (218 in the atorvastatin group and 257 in the pravastatin group) underwent both a baseline and a follow-up EBT scan (mean interval between scans 344 ± 55 days) and constitute the modified intention-to-treat population. The remaining 139 women (87 atorvastatin patients and 52 pravastatin patients) were excluded from the modified intention-to-treat population because they had missing follow-up EBT data. Four of these excluded patients (3 atorvastatin patients and 1 pravastatin patient) also had invalid or missing baseline EBT data. Overall, clinical and demographic characteristics at baseline were similar in the 2 treatment arms and are summarized in Table 1. There were no differences in demographic characteristics and baseline risk factors between the 139 women who did not undergo a follow-up scan and those who completed the study and were included in the final modified intention-to-treat analyses.

Change in Serum Lipid Levels

By study completion, mean ± SD LDL cholesterol levels had decreased by 46.6% ± 19.9% to 92 ± 36.1 mg/dL (2.4 mmol/L) in the atorvastatin group and by 24.5% ± 18.5% to 129 ± 31.1 mg/dL (3.3 mmol/L) in the pravastatin group (P < 0.0001; Table 2). Women receiving atorvastatin also experienced significantly greater reductions in total cholesterol, triglycerides, and apolipoprotein B than women receiving pravastatin (all P < 0.0001). Increases in HDL cholesterol were moderate in both groups, and the differences between groups did not reach significance (P = 0.06). Serum LDL goal, based on recommended NCEP ATP III guidelines, was reached more frequently in the intensive-therapy group than in the moderately treated patients (85.3% versus 58.8%; P < 0.0001).

Change in CVS

CVS measurements for the 2 treatment groups in the modified intention-to-treat analysis are presented in Table 3. At baseline, total CVS was significantly higher in the pravastatin group than in the atorvastatin group (P = 0.04). After 12 months of treatment, the median percent increase in total CVS was similar among women receiving atorvastatin and those receiving pravastatin (15.1% versus 14.3%, respectively, P = 0.64). After adjustment for age and other baseline factors, the treatment difference in percent change in total CVS was not significant (P = 0.97). Absolute changes in total CVS were also similar in both treatment groups (P = 0.21). Further analyses demonstrated that there was no correlation between percent change in total CVS and percent change in LDL cholesterol in either treatment arm or in the overall study population (Figures 2 and 3). Fitting multivariate regression models, which initially included baseline risk factors and eliminated factors deemed to be insignificant (P > 0.10), did not show percent change in LDL cholesterol to be a significant predictor of percent change in total CVS in...
Subgroup Analyses

There was no significant difference in treatment effect (percent CVS change from baseline to month 12, atorvastatin versus pravastatin) across 4 subgroups stratified by baseline CVS (30 to 61, 62 to 115, 116 to 255, and >255; Table 4). The percentage of subjects who stopped HRT during the study (both before and after publication of scientific studies demonstrating a negative cardiovascular impact of this therapy) was similar between the 2 treatment groups (6.1% in the atorvastatin group and 8.7% in the pravastatin group). Furthermore, HRT had no influence on progression of total CVS in either treatment group. Similarly, subgroup analyses based on presence of prior cardiovascular disease, presence of diabetes mellitus, systemic hypertension, and smoking status indicated no differences between treatment arms in percent change in total CVS. Interestingly, however, in both treatment arms, there was a trend toward a greater increase in total CVS in women with preexisting cardiovascular disease and those with the risk factors listed above than their counterparts without these conditions, with the exception of smoking status in the pravastatin arm, in which the trend was in the opposite direction. However, owing to the small number of patients in each of the subgroups, the probability of detecting true treatment differences within subgroups is low.

Safety

The overall incidence of adverse events reported by the study investigators was similar between the 2 treatment groups (82.6% atorvastatin; 83.8% pravastatin). Seven atorvastatin-treated patients (2.7%) had clinically important elevations in ALT and AST (ALT/AST >3 times the upper limit of normal for 2 consecutive measurements 4 to 10 days apart). No patient receiving pravastatin experienced clinically important elevations of ALT and AST, and no patient in either treatment arm had increased CK levels >10 times the upper limits of normal for 2 consecutive measurements 4 to 10 days apart.

There was a single case of rhabdomyolysis in the atorvastatin arm in a 67-year-old woman with multiple comorbidities and concurrent medications. Elevations in AST, ALT, and CK were preceded by a febrile illness and occurred after discontinuation of atorvastatin.

Discussion

Statins are widely used to prevent primary and secondary CHD events. Coronary artery calcification is a sensitive surrogate measure of atherosclerotic plaque burden and has been shown to be an excellent indicator of risk of future CHD events. Monitoring the progression of CAC has been proposed as a means of monitoring atherosclerosis progression and treatment efficacy, and in observational studies, greater CAC progression has been associated with increased risk of myocardial infarction and death.

BELLES was the first randomized, double-blind clinical trial to test the hypothesis that 2 statin regimens with substantially different lipid-lowering activities can affect progression of coronary artery calcification as assessed by sequential EBT imaging. BELLES was also the first large randomized trial of 2 dose regimens of statins in women only. Despite the observed and expected differences in impact on lipid profile, there was no difference in the progression of total CVS between intensive lipid lowering with 80 mg of atorvastatin and moderate lipid lowering with 40 mg of pravastatin. The change in CVS observed in individual coronary vessels was also similar between groups, and the relative change in total CVS was not correlated with the relative change in LDL levels over time. The majority of previous EBT studies investigating the association between lipid lowering and changes in CAC suggested that statin therapy can retard CAC progression over time compared with untreated patients. In the absence of a placebo group in BELLES, it was impossible to draw any conclusion about the absolute treatment effect of either regimen and to ascertain whether slowing of disease was attained.

The possibility that the lack of difference in progression might have been due to a randomization bias, given the difference between treatment arms in baseline CVS, was
excluded by verifying that the treatment effect on progression was similar among quartiles of baseline CVS. We also discounted the possibility that there may have been subtle differences in response within subgroups that were not detectable by comparison of the 2 overall treatment arms. In fact, subgroup analyses based on presence of prior or current cardiovascular disease, diabetes mellitus, systemic hypertension, and smoking status indicated no difference between the atorvastatin and pravastatin arms in percent change in total CVS. Nonetheless, the ability of EBT to detect a difference in progression in risk subsets of the population was illustrated by the trend to greater progression of CVS in patients with risk factors and prior cardiovascular disease than in those risk and/or disease naïve. Hence, EBT imaging may not be sensitive enough to detect differences in CVS progression between 2 active treatments but may be sufficiently accurate to detect a difference in progression in selected risk groups.

With a few exceptions,
7
8
the majority of prior EBT studies on the relationship between lipid lowering and changes in CAC suggested that statin therapy can retard CAC growth. All of those studies included primarily men, and there is a possibility that the pathobiological events connected with plaque development and progression might be different in women than in men. Although the latter idea remains speculative, it is of interest that women harboring CAC demonstrate a considerably more severe outcome than men,24 which

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**TABLE 3. Changes in Coronary CVS**

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin 80 mg (n=218)</th>
<th>Pravastatin 40 mg (n=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
</tr>
<tr>
<td>Total CVS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>204.7 (297.1)</td>
<td>107.1</td>
</tr>
<tr>
<td>12-Month follow-up</td>
<td>233.2 (350.1)</td>
<td>118.6</td>
</tr>
<tr>
<td>Absolute change</td>
<td>28.5 (87.4)</td>
<td>14.2</td>
</tr>
<tr>
<td>Percentage change</td>
<td>20.1 (30.8)</td>
<td>15.1</td>
</tr>
<tr>
<td>Left main and left anterior descending coronary arteries (combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>116.3 (152.4)</td>
<td>74.6</td>
</tr>
<tr>
<td>12-Month follow-up</td>
<td>130.6 (178.9)</td>
<td>85.9</td>
</tr>
<tr>
<td>Absolute change</td>
<td>14.4 (73.8)</td>
<td>8.7</td>
</tr>
<tr>
<td>Percentage change</td>
<td>21.0 (47.4)</td>
<td>12.3</td>
</tr>
<tr>
<td>Left circumflex coronary artery†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23.1 (57.4)</td>
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</tr>
<tr>
<td>12-Month follow-up</td>
<td>29.7 (86.4)</td>
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</tr>
<tr>
<td>Absolute change</td>
<td>6.6 (59.5)</td>
<td>0.0</td>
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<tr>
<td>Right coronary artery†</td>
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<tr>
<td>Baseline</td>
<td>65.2 (144.9)</td>
<td>7.2</td>
</tr>
<tr>
<td>12-Month follow-up</td>
<td>72.8 (154.5)</td>
<td>13.1</td>
</tr>
<tr>
<td>Absolute change</td>
<td>7.7 (31.2)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*For comparison between the 2 treatment groups, in terms of percent and absolute change from baseline, P value based on Cochran-Mantel-Haenszel test, stratified by baseline HRT status (HRT, no HRT). For treatment comparison of baseline CVS, P value based on Wilcoxon rank sum test.

†Percent change not analyzed because >50% of patients had CVS of 0 at baseline.

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**Figure 2.** Percent change in total CVS vs percent change in LDL after 12 months, pravastatin 40 mg. LDL-C indicates LDL cholesterol.

**Figure 3.** Percent change in total CVS vs percent change in LDL after 12 months, atorvastatin 80 mg. LDL-C indicates LDL cholesterol.
Previous studies using measurements of carotid intima-media thickness or measures of coronary atherosclerotic plaque volume have demonstrated significant benefits with atorvastatin 80 mg compared with less efficacious statin regimens. Nonetheless, significant differences separate BELLES from those studies, all based on ultrasound technologies. The spatial resolution of transcutaneous, and especially intravascular, ultrasound is several-fold greater than that of the EBT technology used for the present study. It remains to be seen whether newer CT technologies with a tomographic slice thickness of 0.5 to 0.75 mm (compared with the 3-mm slice thickness used in the present study) will improve the detection of small changes in plaque burden. Furthermore, both Smilde et al25 and Nissen et al27 focused their research efforts on higher-risk individuals (familial hypercholesterolemia and patients with chest pain with an indication for coronary angiography, respectively) than the patients enrolled in BELLES. In both studies, the interval between scans was longer (2 years and 18 months, respectively) than in BELLES. A longer follow-up in BELLES, in which 2 active treatments were used, might have allowed the surfacing of a difference in treatment effect. Finally, the ultrasound technique is exquisitely sensitive to the noncalcified component of the atherosclerotic plaque, which may undergo a greater and earlier rearrangement in the course of aggressive therapy for atherosclerosis than the calcified portion. It is also possible that the calcification process of the atherosclerotic plaque may not be entirely stopped or reversed by lipid-lowering therapy.

On the basis of the data presented herein, it could be concluded that EBT is not sensitive enough to reliably detect longitudinal changes in calcification, and therefore, it may be of no or limited utility to follow progression of disease. However, the findings of the present study are also reassuring in view of recent observations that individuals with greater CVS progression are at greater risk of myocardial infarction than those with slower progression, even when treated with statins to the same level of LDL. In fact, during a 2.5-year follow-up, patients with significantly greater progression (42±23% versus 17±25%, P<0.001) had a 17-fold increase in risk of events in spite of similar LDL control. Furthermore, 98% of the patients who had a myocardial infarction during therapy with statins showed a CVS progression ≥15% per year. Hence, progression of CAC appears to matter and can be assessed prospectively by EBT, although this older technology may not be sensitive enough to compare treatment effects.

Two recent clinical trials demonstrated the superiority of aggressive lipid-lowering strategies compared with moderate ones in patients at high risk of cardiovascular disease. Both hard clinical end points and highly accurate surrogate indexes of therapeutic effectiveness (plaque volume seen on

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Atorvastatin 80 mg (n=218)</th>
<th>Pravastatin 40 mg (n=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–61 (n=55 atorvastatin, n=63 pravastatin)</td>
<td>27 (32.5)</td>
<td>23 (47.9)</td>
</tr>
<tr>
<td>62–115 (n=64 atorvastatin, n=54 pravastatin)</td>
<td>24 (38.5)</td>
<td>23 (30.3)</td>
</tr>
<tr>
<td>116–255 (n=56 atorvastatin, n=64 pravastatin)</td>
<td>18 (22.9)</td>
<td>22 (30.3)</td>
</tr>
<tr>
<td>&gt;255 (n=42 atorvastatin, n=75 pravastatin)</td>
<td>8 (20.7)</td>
<td>11 (17.2)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease.
*Raw data mean (SD).
†Treatment-by-subgroup interactions: P>0.10, based on ANCOVA (with ranked scores).
intravascular ultrasound) were reduced by an intensive regimen that lowered the average LDL level to \( \approx 70 \text{ mg/dL} \). The results of BELLES should not and cannot limit the importance of those findings, which, along with other recent data, stimulated the modification of the most current guidelines of NCEP to recommend new LDL targets of 100 mg/dL and 70 mg/dL for moderate- and high-risk individuals, respectively. Whether attaining a lower LDL target in BELLES similar to that reached in the above trials might have resulted in a greater CVS reduction in the intensive- than in the moderate-treatment arm remains speculative.

The baseline difference in CVS between treatment groups was a serendipitous consequence of patient randomization based on clinical criteria alone. Indeed, this represents a good example of the fact that traditional risk factors do not entirely help predict the development of atherosclerosis. Although more frequent clinically important elevations in ALT and AST were observed in the atorvastatin group than in the pravastatin group, these rates were similar to those reported in pooled safety analyses and previous clinical studies using high-dose atorvastatin.

There were limitations to this study. The duration of the follow-up was chosen to be 1 year on the basis of prior experience. Whether a longer duration of follow-up might have brought up a difference in drug effect on CVS is unknown. The use of sequential EBT imaging to test the effects of statins (specifically atorvastatin and pravastatin) on CVS had not been tested in dyslipidemic postmenopausal women before the design of the present study. Indeed, most prior studies had included a majority of male patients.

In summary, despite significantly greater LDL reduction, intensive therapy with atorvastatin did not slow progression of coronary artery calcification more than moderate therapy with pravastatin as measured by EBT. Changes in total coronary CVS did not correlate with changes in LDL levels in either treatment group or in the overall study population. Further findings included a trend toward a greater CVS progression in women with prior cardiovascular disease than disease naïve patients and in patients with than in those without risk factors. In the absence of a placebo group, it was impossible to verify whether progression of CVS was slowed in both arms or neither compared with the natural history of the disease.

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**References**


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