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JACC Vol. 31, No. 7
June 1998:1561–7



VASCULAR DISEASE

# B-Mode Ultrasound Assessment of Pravastatin Treatment Effect on Carotid and Femoral Artery Walls and Its Correlations With Coronary Arteriographic Findings: A Report of the Regression Growth Evaluation Statin Study (REGRESS)

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***Objectives.*** **In this B-mode ultrasound study we assessed pravastatin treatment effects on carotid and femoral artery walls and investigated the correlations between the state and evolution of peripheral and coronary atherosclerosis.**

***Background.*** **The Regression Growth Evaluation Statin Study (REGRESS) was an 11-center, 2-year, double-blind, placebo-controlled, prospective study of 885 men with coronary artery disease (CAD) (total cholesterol 4 to 8 mmol/liter). The study primarily investigated pravastatin treatment effects on the coronary lumen. This report focuses on the 255 patients who participated in the REGRESS ultrasound study.**

***Methods.*** **Carotid and femoral artery walls were imaged at baseline and at 6, 12, 18 and 24 months. Pravastatin treatment effect was defined as the difference in progression of the combined intima-media thicknesses (IMT) between treatment groups.**

***Results.*** **Pravastatin treatment effects were highly significant (combined IMT: $p = 0.0085$; combined far wall IMT: $p < 0.0001$; common femoral artery far wall IMT: $p = 0.004$). Correlations between the IMTs of the arterial wall segments ranged from −0.17 to 0.81. Baseline correlations between IMT and percent coronary lumen stenoses ranged from 0.23 to 0.36. Baseline IMT correlated with the mean coronary segment diameter ($r = -0.32$, $p = 0.001$) and minimal coronary obstruction diameter ($r = -0.27$, $p = 0.005$). There were no individual correlations between IMT and coronary lumen variables ($p > 0.30$).**

***Conclusions.*** **Pravastatin treatment effects on carotid and femoral artery walls were observed. B-mode ultrasound imaging studies of peripheral arterial walls could not describe the state and evolution of the coronary lumen in the individual patient, but proved to be a highly suitable tool for the assessment of antiatherosclerotic properties of agents.**

**(J Am Coll Cardiol 1998;31:1561–7)**
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In the in vivo assessment of atherosclerotic change, angiography and ultrasound imaging studies are most commonly used. B-mode ultrasound imaging of carotid and femoral artery walls allows recognition of the early stages of atherosclerosis (1–3). Unlike angiography, which investigates the vascular contours and lumen, B-mode ultrasound imaging depicts the structural morphology of the arterial wall itself. As shown by Pignoli et al. (1) in the common carotid artery (CCA) far wall, the leading edges of the B-mode ultrasound double-line patterns represent the lumen-intima interface and the media-adventitia interface of the intima-media complex. Consequently, the distance between these interfaces is called the *intima-media thickness* (IMT). An increase in IMT is regarded as an early sign of atherogenesis (4). IMT increases if vascular walls are exposed to cardiovascular risk factors such as age, serum low density lipoprotein cholesterol, hypertension and smoking (5–16). A reduction of cardiovascular risk factors inhibits IMT progression (17–20). Because B-mode ultrasound imaging of arterial walls is a noninvasive and "patient-friendly" technique, it allows for repeated measurements through time in larger groups of patients. The method has therefore become a powerful tool in studies of atherosclerosis.

In the Regression Growth Evaluation Statin Study (REGRESS) (21), primarily the effect of 2 years of pravastatin treatment on the evolution of the coronary lumen was studied

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Manuscript received April 26, 1997; revised manuscript received February 26, 1998, accepted March 5, 1998.

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0735-1097/98/$19.00
PII S0735-1097(98)00170-3

**Abbreviations and Acronyms**

| | | |
|---|---|---|
| CAD | = | coronary artery disease |
| CCA | = | common carotid artery |
| CFA | = | common femoral artery |
| CI | = | confidence interval |
| IMT | = | intima-media thickness |
| QCA | = | quantitative coronary arteriography |
| MOD | = | minimal (coronary) obstruction diameter |
| MSD | = | mean (coronary) segment diameter |
| REGRESS | = | Regression Growth Evaluation Statin Study |
| SFA | = | superficial femoral artery |

in a randomized fashion. In the B-mode ultrasound substudy of REGRESS, the pravastatin treatment effects on carotid and femoral artery walls were investigated. The studies in the two different vascular beds allowed us to compare the state and changes over time in the coronary lumen with the state and changes over time in the peripheral arterial walls.

## Methods

**Study design and patient selection.** REGRESS was designed as a double-blind, placebo-controlled, multicenter study to assess the 2-year treatment effects of a fixed daily dosage of 40 mg of the 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor, pravastatin, on progression of coronary atherosclerosis as determined by quantitative coronary arteriography (QCA). Eligible for the study were symptomatic men <70 years of age with a serum cholesterol level between 4.0 and 8.0 mmol/liter (155 and 310 mg/dl) and a serum triglyceride level ≤4.0 mmol/liter (354 mg/dl). The coronary angiogram had to show a ≥50% diameter reduction in at least one major coronary artery and had to be of sufficient quality for QCA assessment. In 11 participating hospitals, 885 subjects were included. The primary end points of the study were 1) change in average mean segment diameter (MSD) per subject; and 2) change in average minimal obstruction diameter (MOD) per subject. The study was done under the auspices of the Interuniversity Cardiology Institute, The Netherlands. The coronary angiographic part of the study has been reported previously (21).

**B-mode ultrasound study objectives and end points.** In three REGRESS study centers (St. Antonius Hospital of Nieuwegein and the University Hospitals of Groningen and Nijmegen), subjects participated in B-mode ultrasound studies of carotid and femoral artery walls. Written informed consent was obtained from all subjects. The study was approved by the Institutional Ethics Committees.

The primary end point of the B-mode ultrasound study was the difference in change over time of the mean values of the IMTs of the combined arterial wall segments. Secondary end points included separate analyses of IMT measurement variables, analyses of the combined arterial *near* wall data, analyses of the combined arterial *far* wall data and analyses of the data of the separate arterial wall segments. In addition, the correlations between peripheral IMT measurements and coronary lumen diameters were assessed.

**B-mode ultrasound imaging, off-line video image analysis and quality control.** B-mode ultrasound scans were done at 0 (baseline), 6, 12, 18 and 24 months. Scans were performed by four sonographers. Two similarly calibrated ultrasound machines were used (ACUSON 128 and ACUSON 128XP systems equipped with L7384 7.0-MHz linear array transducers, ACUSON Corporation).

The scans were done as follows. Subjects lay in the supine position. Right and left carotid arteries were imaged from a fixed lateral transducer angle. The left femoral arteries were imaged from a fixed anterior transducer angle. The right femoral artery segments were not imaged, because these were the arteries where the catheters for the coronary arteriographic assessments were introduced. Carotid and femoral artery wall segments were defined by landmarks as represented in the B-mode ultrasound image of the individual subject. The arterial segment 1 cm proximal to the carotid dilation was defined as the CCA segment. The carotid bulb was defined as the arterial segment between the carotid dilation and carotid flow divider. A 1-cm long arterial segment distal to the flow divider was defined as the internal carotid artery (ICA) segment. A 1-cm long arterial segment proximal to the femoral dilation was defined as the common femoral artery (CFA) segment. The 1-cm arterial segment distal to the femoral flow divider was defined as the superficial femoral artery (SFA) segment. Of each arterial wall segment, 5-s real-time image sequences were stored on S-VHS tape.

B-mode ultrasound video images were analyzed off-line (S-VHS Panasonic NV-FS 100 HQ; VCR; Sony GVM-1400 QM multisync monitor; IDEN IVT-7P time base correctors, IPC 80386 personal computers equipped with DT2861 and DT2862 frame grabbers [Data Translation Inc.]). Image analysis software was developed in cooperation with Selzer et al. (22). IMT variables are given in Figure 1.

In a continuous quality-control program before and throughout the study, the contribution of measurement variability of sonographers, image analysts and instrumentation to the total variability in the study group was investigated at regular intervals (23,24).

**Statistical analysis.** Baseline characteristics of the treatment groups were compared using the Student *t* test or chi-square test as appropriate. The lipid observations were analyzed using mixed-model analysis of variance for repeated measures under the assumption of a compound symmetry covariance structure. These were compared by using the log-rank test. The IMT analyses were modeled using analysis of variance with a random patient factor, fixed segment and therapy factors. Time since start of therapy was modeled as a linear covariate (25).

In the primary analyses the mean IMT variable was used because in repeatability studies it showed the lowest measurement variability (24). The sensitivity of IMT variables to describe atherosclerotic change was investigated; analyses of

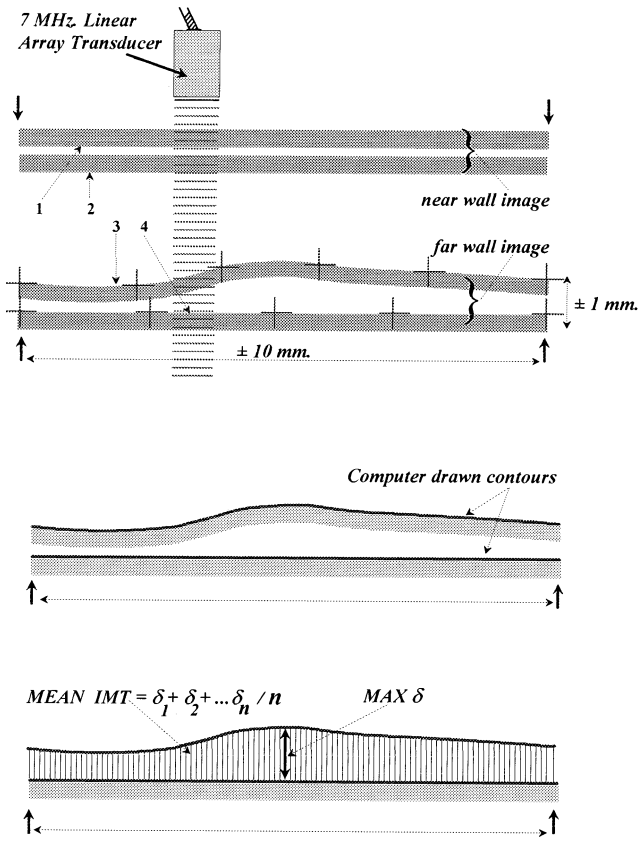



**Figure 1.** B-mode ultrasound image analysis. **Top,** Interfaces are identified with cross-marks. In the near wall, cross-marks identify the trailing edge of the undefined (peri)adventitial-media interface (1) and the gain-dependent trailing edge of the intima-lumen interface (2). In the far wall, the cross-marks identify the well defined leading edges of the lumen-intima interface (3) and media-adventitia interface (4). **Middle,** Analysis software connects the cross-marks (far wall measurement only shown). **Bottom,** Mean IMT is defined as $\delta_1 + \delta_2 + \cdots \delta_n/n$. Maximal IMT is defined as the maximal delta between the two lines. The length of the measurement along the arterial wall is kept as close to 1 cm as possible, but is prone to differ between sites and patients owing to individual anatomy and interference in the ultrasound image.

the IMT data of the combined near wall, of the combined far wall and of each of the arterial wall segments were done for mean and maximal IMT measurements. Relations between the peripheral arterial segment IMTs were described by the Pearson correlation coefficient.

To calculate correlations between coronary arteriographic and ultrasound data, baseline and follow-up mean percent coronary obstruction scores were determined as follows: for each patient the most severe narrowing, expressed as percent lumen diameter reduction, was determined for each analyzable coronary segment; the percentages were summed and the total was divided by the number of contributing segments.

The relations between IMTs and mean percent coronary stenoses were described by the Spearman correlation coefficient.

A p value $\leq 0.05$ was considered statistically significant. In the arterial wall segment analyses, the Bonferroni correction was applied. SPSS, BMDP (5V) and EGRET statistical packages were used.

**Table 1.** Demographic Data

| | Placebo Group (n = 124) | Pravastatin Group (n = 131) | p Value* |
|---|---|---|---|
| Age (years) | 55.2 ± 7.7 | 56.8 ± 8.1 | 0.10 |
| BMI (kg/m$^2$) | 26.4 ± 2.8 | 26.1 ± 2.7 | 0.27 |
| SBP (mm Hg) | 137.1 ± 17.7 | 133.8 ± 17.3 | 0.13 |
| DBP (mm Hg) | 82.2 ± 11.3 | 79.6 ± 10.0 | 0.06 |
| Hypertension | 39 (32%) | 28 (21%) | 0.07 |
| Familial heart disease | 65 (52%) | 63 (48%) | 0.49 |
| Smoking history | 111 (90%) | 119 (91%) | 0.72 |
| Smoking at randomization | 37 (30%) | 43 (33%) | 0.61 |
| Smoking during study | 39 (32%) | 43 (33%) | 0.81 |
| Previous myocardial infarction | 58 (47%) | 73 (56%) | 0.15 |
| Mean IMT (mm) | | | |
| n + f | 0.86 ± 0.32 | 0.87 ± 0.34 | 0.91 |
| n | 0.82 ± 0.31 | 0.83 ± 0.32 | 0.92 |
| f | 0.88 ± 0.32 | 0.89 ± 0.35 | 0.99 |
| Maximal IMT (mm) | | | |
| n + f | 1.07 ± 0.41 | 1.08 ± 0.45 | 0.78 |
| n | 1.01 ± 0.39 | 1.03 ± 0.42 | 0.97 |
| f | 1.10 ± 0.42 | 1.10 ± 0.47 | 0.82 |

*Significance level obtained from the Student unpaired *t* test or chi-square test. Data presented are mean value ± SD or number (%) of patients. BMI = body mass index; DBP = diastolic blood pressure; IMT = intima-media thickness; n = near wall; f = far wall; SBP = systolic blood pressure.

## Results

In the ultrasound studies 124 subjects were randomized to receive placebo and 131 subjects were randomized to receive active treatment. There were no major differences in clinical variables and study comedication between the randomization groups. Major clinical baseline data are reported in Table 1.

**Pravastatin treatment effect on serum lipid values.** Pravastatin treatment significantly reduced total cholesterol, low density lipoprotein cholesterol and triglycerides and raised high density lipoprotein cholesterol. The maximal effect of pravastatin on lipid values was apparent after 2 months and remained more or less constant afterward. In the placebo group the lipid values remained constant throughout the study. Baseline and intreatment lipid values are reported in Table 2.

**Clinical events.** In the 255-subject ultrasound study group, 38 (14.9%) experienced a total of 46 predefined clinical events. After 2 years of treatment, 79.8% (95% confidence interval [CI] 72% to 88%) of the subjects in the placebo group were without clinical events, whereas 90.1% (95% CI 85% to 95%) of the subjects in the pravastatin group were without clinical events (p = 0.02). These percentages were similar to those of the REGRESS study group as a whole (79% and 89%, respectively) and did not vary among hospitals (p = 0.52) (21).

**B-mode ultrasound findings.** B-mode ultrasound data were available in 254 of the 255 subjects. This amounted to 12,241 arterial wall thickness measurements. Average (±SD) baseline mean IMT was 0.86 ± 0.33 mm (range 0.29 to 3.24).

**Table 2.** Baseline and Treatment Lipid Values

| | Placebo Group (n = 124) | Pravastatin Group (n = 131) | p Value* |
|---|---|---|---|
| Total cholesterol (mmol/liter) | | | |
| Baseline | 6.12 ± 0.88 | 6.18 ± 0.88 | 0.58 |
| Follow-up | 6.14 ± 0.98 | 4.92 ± 1.07 | < 0.001 |
| HDL cholesterol (mmol/liter) | | | |
| Baseline | 0.97 ± 0.22 | 0.99 ± 0.25 | 0.41 |
| Follow-up | 0.95 ± 0.22 | 1.05 ± 0.25 | < 0.001 |
| LDL cholesterol (mmol/liter) | | | |
| Baseline | 4.33 ± 0.79 | 4.36 ± 0.80 | 0.77 |
| Follow-up | 4.30 ± 0.88 | 3.11 ± 0.94 | < 0.001 |
| Triglycerides (mmol/liter) | | | |
| Baseline | 1.82 ± 0.77 | 1.85 ± 0.78 | 0.78 |
| Follow-up | 1.95 ± 0.98 | 1.67 ± 0.93 | 0.01 |

*Significance level obtained from the Student unpaired *t* test. Data presented are mean value ± SD. HDL = high density lipoprotein; LDL = low density lipoprotein.

Baseline IMT data are included in Table 1. The combined mean IMT data showed a highly significant pravastatin treatment effect: IMT decreased 0.05 ± 0.20 (SE) mm in the pravastatin group, whereas the IMT in the placebo group remained unchanged (p = 0.0085). Analyses of the maximal IMT data showed similar results. Average (±SD) baseline maximal IMT was 1.07 ± 0.43 mm (range 0.46 to 3.28). IMT decreased 0.05 ± 0.22 (SE) mm in the pravastatin group, but increased 0.01 ± 0.21 mm in the placebo group (p = 0.0024). Near wall data and far wall data were analyzed separately. In 254 subjects 5,122 *near* wall arterial segments and 7,119 *far* wall arterial segments were measured. With respect to the near wall mean IMT data, no effect of pravastatin was noticed (p = 0.89). The far wall mean IMT data showed a highly significant treatment effect (p < 0.0001) (Table 3). Therefore, the pravastatin treatment effect on the combined near and far wall arterial segments was practically entirely accounted for by the differential change in far wall IMT. Analyses of the separate arterial wall segments revealed that a major pravastatin effect was seen in the CFA far wall arterial segment: the placebo group showed an IMT increase of 0.13 ± 0.05 (SE) mm, whereas in the pravastatin group showed a decrease of 0.06 ± 0.05 mm in mean IMT (p = 0.004) (Table 4 and Fig. 2). Analyses of the maximal IMT data in the CFA far wall segment showed similar results: no treatment effect was observed in the near wall (p = 0.83); in the far wall, IMT decreased 0.12 ± 0.05 (SE) mm more in the pravastatin group than in the placebo group (p < 0.0001).

**Correlations in peripheral and coronary arteries.** *Peripheral arterial IMT measurements within subjects.* The observed intrapatient Pearson correlation coefficients of the peripheral arterial wall segments varied between −0.17 and 0.81, with a mean intraclass correlation of 0.20.

*Baseline peripheral IMT measurements and coronary artery stenosis.* The combined baseline maximal IMT correlated with the baseline MSD (r = −0.32, p = 0.001) and MOD (r = −0.27, p = 0.005). The Spearman correlation coefficients between the baseline IMTs of the separate arterial wall segment measurements and the baseline percent coronary lumen stenosis varied from 0.23 to 0.36. It appeared that the IMT measurements of the far wall CFA and of the far wall SFA segments correlated moderately positively with the percent coronary stenosis (p = 0.33 and p = 0.36, respectively; both p < 0.01).

*Pravastatin treatment effect between IMT measurements and coronary artery stenosis.* In the REGRESS study complete sets of repeated QCA data on 653 subjects were available. Analyses of the two primary coronary end points—differences between the mean values of the MSD and the median values of the MOD—showed a significant pravastatin treatment effect (δMSD 0.04 mm, p = 0.02; δMOD 0.06 mm, p = 0.001) (21). The analysis of the QCA data of the 255 subjects who participated in the B-mode ultrasound study showed a similar, statistically nonsignificant trend in the change of coronary lumen diameter (δMSD 0.02 mm, p = 0.43; δMOD 0.03 mm, p = 0.23).

There were no significant correlations between the change in the mean percent coronary stenosis (nor in any of the other variables of coronary diameter change) and change in IMT in any of the arterial wall segments (all p > 0.30).

## Discussion

In the REGRESS B-mode ultrasound study pravastatin treatment effect on combined carotid and femoral artery IMT were highly significant. The participants of the ultrasound study received coronary arteriograms, as did all REGRESS patients. The correlations between peripheral wall thickness and coronary lumen measurements were low to moderate, and no correlations in treatment effects between the two vascular beds were observed.

**Table 3.** Pravastatin Treatment Effects in the REGRESS B-Mode Ultrasound Study Group (n = 255): Change in Coronary Lumen and Peripheral Intima-Media Thickness

| | Placebo Group | Pravastatin Group | p Value* |
|---|---|---|---|
| Coronary lumen variables | | | |
| MSD (mm) | 0.06 ± 0.16 | 0.04 ± 0.15 | 0.43 |
| MOD (mm) | 0.08 ± 0.18 | 0.05 ± 0.24 | 0.23 |
| %S | 0.9 ± 5.4 | 1.2 ± 5.9 | 0.76 |
| Peripheral IMT (mm) | | | |
| Mean | 0.00 ± 0.20 | 0.05 ± 0.20 | 0.0085 (n: 0.89; f: < 0.0001) |
| Maximal | −0.01 ± 0.21 | 0.05 ± 0.22 | 0.0024 (n: 0.83; f: < 0.0001) |

*Significance level obtained from the Student *t* test; p < 0.05 considered significant. *Change* is defined as baseline value minus value of variables after 2 years (positive values indicate an increase in coronary lumen and a decrease in wall thickness). Data presented are mean value ± SE. MOD = minimal (coronary) obstruction diameter; MSD = mean (coronary) segment diameter; %S = mean percent stenosis (mean values of per patient percent lumen reduction of analyzable segments divided by number of contributing segments); other abbreviations as in Table 1.

**Table 4.** Pravastatin Treatment Effect on Carotid and Femoral Artery Intima-Media Thickness

| Arterial Wall Segments | Near Wall | | | Far Wall | | |
|---|---|---|---|---|---|---|
| | Placebo | Pravastatin | p Value* | Placebo | Pravastatin | p Value |
| CCA | | | | | | |
| Right | 0.02 ± 0.02 | 0.00 ± 0.02 | 0.40 | 0.02 ± 0.02 | −0.01 ± 0.02 | 0.35 |
| Left | 0.00 ± 0.02 | 0.00 ± 0.02 | 0.88 | 0.05 ± 0.02 | 0.04 ± 0.02 | 0.67 |
| CB | | | | | | |
| Right | 0.15 ± 0.06 | 0.21 ± 0.06 | 0.47 | 0.09 ± 0.04 | 0.06 ± 0.04 | 0.62 |
| Left | 0.11 ± 0.05 | 0.09 ± 0.05 | 0.73 | 0.08 ± 0.04 | 0.01 ± 0.04 | 0.23 |
| ICA | | | | | | |
| Right | −0.10 ± 0.08 | −0.06 ± 0.07 | 0.62 | −0.07 ± 0.05 | −0.06 ± 0.04 | 0.92 |
| Left | −0.07 ± 0.07 | 0.06 ± 0.06 | 0.12 | −0.06 ± 0.04 | 0.01 ± 0.04 | 0.23 |
| CFA, left | 0.01 ± 0.04 | 0.05 ± 0.04 | 0.49 | −0.13 ± 0.05 | 0.06 ± 0.05 | 0.004 |
| SFA, left | 0.04 ± 0.03 | 0.04 ± 0.03 | 0.94 | 0.04 ± 0.02 | 0.01 ± 0.02 | 0.40 |

*Significance level obtained from the Student *t* test; $p < 0.005$ considered significant. *Change* is defined as baseline intima-media thickness minus that after 2 years (positive values indicate a decrease in intima-media thickness in millimeters). Data presented are mean value ± SE. CB = carotid bulb; CCA = common carotid artery; CFA = common femoral artery; ICA = internal carotid artery; SFA = superficial femoral artery.

**Mean and maximal IMT as arterial wall thickness variables.** Analyses of MEAN IMTs and maximal IMTs showed similar results. Both IMT variables are suitable for use in carotid and femoral artery wall thickness studies.

**Near and far wall IMT measurements.** The ultrasound interfaces in the B-mode ultrasound image near and far walls have different origins (as shown in Fig. 1). The distances between the interfaces of the far wall represent the borders of the intima-media complex; those of the near wall *do not* (25). The value and validity of B-mode ultrasound arterial near wall thickness measurements are therefore a topic of debate (26–28).

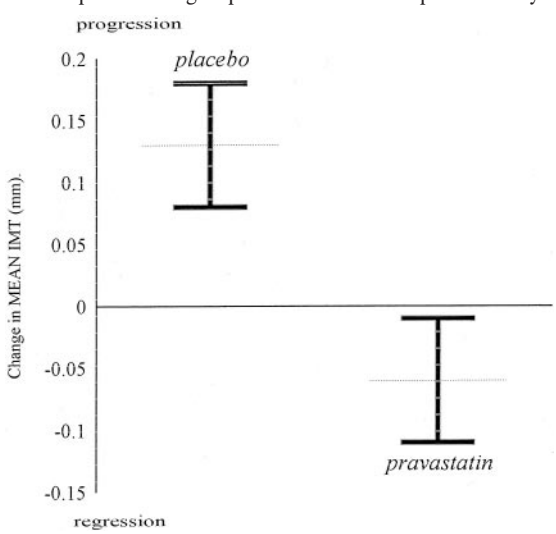
In this study we observed treatment effects in the far wall segments only. This finding strongly suggests that in medical intervention trials, where small differences in the progression of the intima-media complex are observed, far wall IMT measurements are more sensitive than near wall thickness measurements in detecting change.

For epidemiologic purposes it is suggested to include near wall measurements at baseline of a clinical trial and to proceed solely with far wall measurements in follow-up.

**Finding a major treatment effect in the far wall of the CFA.** Analyses of the IMT data of the separate arterial wall segments showed a highly significant treatment effect on the far wall of the CFA. A reason for this finding may be that the highest maximal IMT (1.37 mm) and the highest standard deviation (0.69 mm) were observed in this arterial wall segment (baseline data). The high standard deviation may indicate a high prevalence of arterial wall irregularities. It may be hypothesized that a pronounced treatment effect in this arterial wall segment was observed because arterial walls with a high incidence of lesions have a higher arterial wall thickness progression rate. As a fast progressor, the CFA far wall may be more sensitive to low density lipoprotein cholesterol and triglyceride reduction. A treatment effect in the far wall of the CFA may therefore be more readily observed (18,20).

**Comparison with other studies.** In several atherosclerosis regression studies, B-mode ultrasound imaging has been used for investigation and demonstration of treatment effects of cholesterol reduction. The 4-year Cholesterol Lowering Atherosclerosis Study (CLAS) tested the treatment effects of colestipol-niacin plus diet therapy in 46 nonsmoking men with previous coronary bypass surgery (19). B-mode ultrasound scans were done in four carotid artery far wall segments. There were significant treatment effects after 2 and 4 years ($p < 0.0001$). The Asymptomatic Carotid Artery Progression Study (ACAPS) was a 3-year trial in which the treatment effect of a daily dosage of 20 to 40 mg of lovastatin, in a factorial design with warfarin or placebo, or both, was investigated (17). In this trial, 12 (near and far) carotid artery wall segments were scanned in asymptomatic men and women with early carotid atherosclerosis (as assessed with B-mode ultrasound imaging).

**Figure 2.** Change in CFA far wall IMT in millimeters (±SE) for the placebo and pravastatin groups after a treatment period of 2 years.



A lovastatin treatment effect on the combined maximal IMT was observed ($p < 0.001$). Pravastatin treatment effects on peripheral IMT have been described in the B-mode ultrasound components of the Pravastatin, Lipids, and Atherosclerosis in the Carotid arteries trial (PLAC-2) (29,30) and Kuopio Atherosclerosis Prevention Study (KAPS) (20). In the 3-year PLAC-2 trial, 151 men and women with coronary artery disease (CAD), diet-resistant elevated low density lipoprotein cholesterol and the presence of at least one carotid lesion were randomized to receive placebo or 20 to 40 mg of pravastatin daily. The primary outcome measure—that is, the change in the mean value of the maximal IMT measurements over time in 12 carotid (near and far wall) arterial segments, was not significantly different between the placebo and treatment group ($p = 0.44$). However, a subanalysis of the separate arterial segments showed a significant treatment effect in the CCA ($p = 0.03$). KAPS investigated the 3-year treatment effect of a daily dosage of 40 mg of pravastatin in 447 hypercholesterolemic men (low density lipoprotein cholesterol >4.0 mmol/liter) using six carotid and femoral artery far wall segments. The treatment effect for the combined segment IMT was significant ($p = 0.02$).

Comparison in the interpretation of the results of this substudy and the overall REGRESS B-mode ultrasound study may be difficult because study group selection, study duration, scanning and off-line video image analysis procedures and statistical analyses differ for each of the studies. In all of the aforementioned studies, different approaches to the different methodologic components were used. However, whatever methodology was chosen, the common denominator for all of these studies was demonstration of treatment effects in peripheral arterial walls. The REGRESS B-mode ultrasound study has some distinctly different characteristics when compared with the aforementioned studies. The study group was selected based on the presence of proven CAD and not on risk factors. Also, no attempt was made to select the B-mode ultrasound study group based on increased cardiovascular risk factors or increased IMT.

Others have investigated correlations between peripheral and coronary atherosclerosis (29,31,32). In our study a univariate approach was taken because it most closely describes the ability of peripheral B-mode ultrasound IMT measurements to predict coronary atherosclerosis in screening procedures. Our results of this approach are in agreement with those of Adams et al. (31). Multivariate correlation models were described by Adams et al. (31), Craven et al. (32), and Crouse et al. (29). These last three models add little to the predictive value of IMT for patients with CAD.

**Potential and limitations of B-mode ultrasound atherosclerotic studies.** From epidemiologic studies it is known that increased IMT is positively related to atherosclerotic risk factors and CAD (6,8–10,12,17,28). In lipid intervention studies treatment effects were shown in peripheral arteries (19,20,29,30) and coronary arteries (21,33,34). In this study pravastatin treatment effects were shown on peripheral *and* coronary arteries.

Ideally, one would like to individually predict the status and treatment effects in the coronary arteries by means of noninvasive peripheral B-mode ultrasound imaging of peripheral arterial walls. However, because our studies showed treatment effects in the study group as a whole but not on an individual basis, and also lacked correlation between peripheral and coronary measurements, this is not a goal likely to be achieved. Several reasons for the low correlations can be mentioned. First, there is a great variability in the manifestation of atherosclerosis within and between vascular beds (18,31). The general association between sites is in agreement with the systemic nature of atherosclerosis, whereas the lack of tight agreement between the sites is an expression of the focal nature of the atherosclerotic lesion formation. Second, 7-MHz B-mode ultrasound imaging has a relatively low axial resolution (0.3 to 0.4 mm) (1,12,13,29) in comparison with the size of the intima-media complex (0.6 to 1.4 mm) and the treatment effect of statins (0.05 to 0.1 mm). Third, B-mode ultrasound can image the full range of atherogenesis in arterial walls. In contrast, coronary arteriography focuses on plaques through visualization of the arterial lumen (29), which results in an underestimation of the extent of (especially early) atherosclerosis.

Therefore, even if the resolution of B-mode ultrasound imaging and coronary angiography were enhanced, the variability of the genesis of atherosclerotic lesion formation (31,35,36) throughout the different sites of the vascular beds is such that a peripheral observation of an arterial wall is unable to predict coronary lumen stenosis. As a consequence, within the individual, an IMT measurement of a given peripheral arterial wall segment cannot be used to predict the state of atherosclerosis in the coronary arteries, let alone the prediction of even smaller individual treatment effects.

**Clinical implications.** The findings of this study are evidence of the important contribution of statin treatment to the reduction of cardiovascular risk factors.

**Conclusions.** Our results confirm that pravastatin therapy inhibits the progression of peripheral atherosclerosis. In that sense, peripheral arteries and coronary arteries showed parallel trends.

The low correlation of the state and evolution of atherosclerosis between peripheral arterial wall thickness measurements and coronary artery lumen measurements reflect the great morphologic variety of atherosclerosis within and between vascular beds within and between individuals. Consequently, peripheral arterial wall thickness measurements are unsuitable as a screening tool for CAD or as a test for individual medication treatment effects on coronary arteries.

The B-mode ultrasound study showed highly significant pravastatin treatment effects. Indeed, B-mode ultrasound imaging was more sensitive than QCA in detecting treatment effects. Therefore, B-mode ultrasound measurements of the carotid and femoral artery intima-media complex are highly suitable to assess the antiatherosclerotic properties of agents.

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