ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol
A Randomized Trial Comparing the Effects of Atorvastatin and Pravastatin on Carotid Intima Media Thickness

Allen J. Taylor, MD; Steven M. Kent, MD; Patrick J. Flaherty, DO; Louis C. Coyle, DO; Thor T. Markwood, MD; Marina N. Vernalis, DO

Background—Whether marked LDL reduction to levels well below 100 mg/dL would further reduce the burden of cardiovascular disease is controversial. We compared the effects of 2 statins with widely differing potencies for LDL reduction (pravastatin 40 mg/d and atorvastatin 80 mg/d) on carotid intima-media thickness (CIMT).

Methods and Results—This was a single-center, randomized, clinical trial of 161 patients (mean age, 60 years; 71.4% male; 46% with known cardiovascular disease) that met National Cholesterol Education Program (NCEP) II criteria for lipid-lowering therapy. The effects of atorvastatin (80 mg/d; n = 79) and pravastatin (40 mg/d; n = 82) on CIMT were compared using blinded, serial assessments of the far wall of the distal common carotid artery. Baseline CIMT and other characteristics were similar between study groups. As anticipated, atorvastatin was substantially more potent for LDL reduction after 12 months: in the atorvastatin group, LDL cholesterol was 76 ± 23 mg/dL after 12 months (48.5%); LDL cholesterol was 110 ± 30 mg/dL in the pravastatin group (27.2%; P < 0.001). Atorvastatin induced progressive CIMT regression over 12 months (change in CIMT, −0.034 ± 0.021 mm), whereas CIMT was stable in the pravastatin group (change of 0.025 ± 0.017 mm; P = 0.03).

Conclusions—Marked LDL reduction (<100 mg/dL) with a high-potency statin provides superior efficacy for atherosclerosis regression at 1 year. This early effect on CIMT, a surrogate for clinical benefit, suggests that marked LDL reduction with synthetic statins may provide enhanced reduction in clinical coronary event rates. (Circulation. 2002;106:2055-2060.)

Key Words: atherosclerosis  ■  lipids  ■  risk factors  ■  hydroxymethylglutaryl coenzyme A reductase inhibitors

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have been established by definitive primary and secondary cardiovascular prevention trials as the cornerstone of pharmacoprevention of atherosclerotic vascular disease.

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Consequently, these trials have led to the growing use of statin medications in a broader range of patients with progressively lower cardiovascular risk profiles. Despite the rapid growth in knowledge on the clinical use of statins obtained from clinical trials, whether marked cholesterol reduction to levels below 100 mg/dL would further reduce the incidence of coronary heart disease is controversial. Furthermore, the 5 currently available statins are chemically different compounds that possess a wide range of efficacy for LDL reduction,1,2 possible minor differences in their HDL effects,3,4 and wide variability in other nonlipid effects.5 Thus, the assumption of a class effect for statins in coronary heart disease prevention is premature until head-to-head clinical trials are completed. We compared the effects of pravastatin and atorvastatin on carotid intima-media thickness (CIMT), a validated surrogate cardiovascular end point,6–9 in a single-center, prospective, randomized trial.

Methods

Study Population

This trial was independently funded by Walter Reed Army Medical Center, a university-affiliated, suburban, tertiary-care military medical center, and was approved by the institution’s Department of Clinical Investigation. After providing informed consent, volunteer adult patients (at least 18 years of age) who met National Cholesterol Education Program (Adult Treatment Panel II; NCEP) criteria for pharmacological lipid-lowering therapy were randomized in a 1:1 fashion to either pravastatin 40 mg daily or atorvastatin 80 mg daily.10 Exclusion criteria included the current use of lipid-lowering
drug therapy, known intolerance to statins, and prior carotid endarterectomy.

Randomization

Patients were randomly assigned to open-label treatment with either pravastatin or atorvastatin using a computer-generated random number sequence. Allocation was concealed in sealed study folders that were held in a central, secure location until after informed consent was obtained. The use of supplemental lipid-lowering medications was not permitted. The statin medication was initiated and maintained at the target study dose throughout the duration of the study. Dose titrations were not permitted, except when temporary and in response to possible statin side effects. All patients received standard dietary counseling by a study investigator in accord with the dietary recommendations of the American Heart Association. All 139 patients who completed the 12-month study demonstrated compliance with the treatment program through return visits for prescription refills and clinic visits for laboratory analysis. Compliance was enhanced through central control of study medication and prescriptions and mailed reminders for the timing of study-related procedures.

Between December 1999 and February 2001, 161 patients were enrolled in the trial. Figure 1 shows the flow of patients through the trial. A total of 138 patients (85.7%) completed the 12-month study. The last follow-up occurred in February 2002.

End Points

The predefined primary end point of this study was the change in mean common CIMT after 1 year. Secondary end points included a composite of clinical cardiovascular events, including hospitalization for an acute coronary syndrome (unstable angina or myocardial infarction), stroke, or an arterial revascularization procedure (percutaneous coronary revascularization, coronary bypass surgery, or peripheral vascular revascularization).

Carotid B-Mode Ultrasound

Measurements were obtained from the far wall of the distal common carotid arteries (immediately proximal to the carotid bulb) and reported as the average value for the bilateral measurement. This location was chosen a priori because of its demonstrated reproducibility compared with measurements of CIMT at other sites. All studies were performed on a single ultrasound machine (ACUSON Sequoia) using a linear array 8-MHz scan head (8L5C) with standardized image settings, including resolution mode, depth of field, gain, and transmit focus. Ultrasound studies (at baseline and 6

and 12 months) were performed in a standard fashion by a group of sonographers who were specifically trained to perform the prescribed study examination. All sonograms were obtained with patients in the supine position and their head turned slightly to the contralateral side. DICOM images from a diastolic frame of the cine-loop recording were electronically stored and transferred via optical disk to an off-line work station for quantitation. Each ultrasound examination was performed as an independent study, without knowledge of the previous CIMT results. Images from an individual patient’s prior ultrasound exams were not used to guide their follow-up evaluations. Both patients and providers were blinded to the CIMT results until the 1-year follow-up examination was completed.

An independent observer who was blinded to treatment group and trained in the interpretation of CIMT images performed off-line analysis of B-mode ultrasound images using a custom script for CIMT analysis (Prosolv Echo Analyzer, Problem Solving Concepts, Indianapolis, IN). The near (intimal-luminal surface) and far (medial-adventitial) field arterial wall borders were manually traced for measurement of mean and maximal CIMT. The mean length of CIMT evaluated was 1.26±0.23 cm and was similar in the atorvastatin and pravastatin groups. The precision and reliability of the ultrasound method was tested in a randomly selected subgroup of 32 arteries with paired images obtained on the same day. The mean difference in CIMT between these images was 0.017 mm, and the intraclass correlation coefficient (random effects model) was 0.92 (P<0.001). Paired CIMT measurements in these same arteries showed a high degree of reproducibility, with a mean difference in CIMT of 0.020 mm, and an intraclass correlation coefficient of 0.97 (P<0.001).

Laboratory Analysis

Laboratory measurements included serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein (CRP), liver-associated enzymes, and plasma fibrinogen at baseline and 3 and 12 months. LDL cholesterol was measured using a direct assay. CRP was measured with a high-sensitivity, commercially available immunoturbidimetric assay that uses monoclonal antibodies to CRP (Roche Cobas Integra, Switzerland). Plasma fibrinogen was measured using a commercially available, validated assay that uses an electromechanical determination of clotting time (STA-Fibrinogen, Diagnostic Stago, France).

Statistical Analysis

The trial was powered to the primary end point (change in CIMT), as previously described. Changes in lipids, CRP, and fibrinogen over time were evaluated using either a paired t test or Wilcoxon signed-rank test, as appropriate. Comparison of the treatment effect between experimental groups for the primary end point (change in CIMT at 12 months) was performed with a z test for independent groups. Further, the change in mean CIMT between treatment groups was compared using a general linear model for repeated measures for the baseline and 6- and 12-month CIMT assessments. The χ² statistic was used to compare the 2 groups with regard to proportion that demonstrated stabilization or progression of mean CIMT. All statistical analyses were performed using SPSS software (version 10.05, SPSS Inc, Chicago, Ill). Values are reported as mean±SD, except where indicated. A 2-sided probability value of ≤0.05 was considered statistically significant.

Results

The mean patient age was 60 years, 71.4% were men, and 46% had known cardiovascular disease. The mean baseline total cholesterol was 232±42 mg/dL, and the mean LDL cholesterol was 152±34 mg/dL. Baseline mean CIMT was 0.627±0.189 mm (range, 0.32 to 1.36 mm). The 2 experimental groups (pravastatin and atorvastatin) had similar demographic characteristics (Table 1) and similar baseline measured serological and CIMT variables. There were no
At 12 months, the on-therapy LDL cholesterol in the atorvastatin group was 76 (30.8), H11006 compared to 23 mg/dL (48.5% decrease) in the pravastatin arm. Similarly, the triglyceride levels were lower in the atorvastatin group (137 (0.34) mg/dL) compared to 30 (0.21) mg/dL in the pravastatin group. The HDL cholesterol levels also showed a difference, with 50 (14) mg/dL in the atorvastatin group compared to 49 (16) mg/dL in the pravastatin arm. The C-reactive protein levels were significantly lower in the atorvastatin group (0.32 mg/dL) compared to 0.40 mg/dL in the pravastatin group. The Fibrinogen levels were also lower in the atorvastatin group (374 (73) mg/dL) compared to 369 (76) mg/dL in the pravastatin arm. These differences were statistically significant (P values below 0.001).

### TABLE 1. Baseline Characteristics of 161 Patients Randomly Assigned to Either Atorvastatin or Pravastatin

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n=82)</th>
<th>Atorvastatin (n=79)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>61 (74.4)</td>
<td>54 (68.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±12</td>
<td>56±11</td>
<td>0.18</td>
</tr>
<tr>
<td>History of coronary artery disease, n (%)</td>
<td>35 (42.7)</td>
<td>39 (49.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Family history of coronary heart disease, n (%)</td>
<td>24 (29.3)</td>
<td>30 (38.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td>6 (7.3)</td>
<td>11 (13.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (10.4)</td>
<td>9 (14.3)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>56 (68.3)</td>
<td>56 (70.9)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>234±42</td>
<td>229±42</td>
<td>0.43</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>155±34</td>
<td>148±32</td>
<td>0.19</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49±14</td>
<td>49±16</td>
<td>0.97</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>203±107</td>
<td>211±135</td>
<td>0.66</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.40±0.33</td>
<td>0.43±0.45</td>
<td>0.34</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>397±102</td>
<td>374±73</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%).

### Differences between groups in the use of other cardiovascular medications, including β-blockers, calcium-channel blockers, aspirin, angiotensin-converting enzyme inhibitors, or hypoglycemic agents, either at the beginning or the end of the study.

### Primary and Secondary End Points

Table 2 shows the serological measurements at 3 and 12 months for the 2 experimental groups. As expected, atorvastatin resulted in significantly greater reductions in total cholesterol, LDL cholesterol, and triglyceride concentrations. At 12 months, the on-therapy LDL cholesterol in the atorvastatin group was 76±23 mg/dL (48.5% decrease) compared with 110±30 mg/dL (27.2% decrease) in the pravastatin arm (P<0.001 for between-group comparison). Atorvastatin also resulted in a continued reduction in CRP values at 3 and 12 months, which were also significantly lower than those observed in the pravastatin group at 12 months.

Mean CIMT progressively decreased in the atorvastatin group, which was significantly different from the results with pravastatin (P=0.030; Table 3). Atorvastatin induced progressive mean CIMT regression over 12 months (change in CIMT, −0.034±0.021 mm), whereas mean CIMT was stable in the pravastatin group (change of 0.025±0.017 mm; between-group comparison, P=0.03; Table 3 and Figure 2). Similar results were found for both the right and left CIMT when analyzed separately. A similar trend was observed at 12 months in the change in maximum CIMT between treatment groups (Table 3). CIMT regression, defined as a net decrease in mean CIMT at 12 months, was observed in 27 of 70 pravastatin patients (38.6%), and 37 of 68 atorvastatin patients (54.4%; P=0.062). There were no differences observed between treatment groups in any of the 6-month CIMT measurements.

### Side Effects and Clinical Coronary Heart Disease Events

No patient experienced significant (3 times upper limit of normal) elevations of liver-associated enzymes or had myositis. During the study period, 6 patients had a cardiovascular event (4.3%). This included 3 patients in each treatment group (total of 10 events) [(pravastatin: unstable angina (n=3), arterial revascularization procedure (n=2), stroke (n=1), arterial revascularization procedure (n=1))].
Atherosclerosis.7 the principal reduction in cardiovascular events associated with atorvastatin 80 mg/d.

...during treatment with either pravastatin 40 mg/d or colestipol and niacin on carotid atherosclerosis,6 found that reduction. Prior studies, including the Cholesterol Lowering Atherosclerosis Study (CLAS) that evaluated the effect of regression in the coronary and carotid arteries is a validated surrogate end point for the clinical benefit of cholesterol lowering. This randomized trial demonstrated enhanced regression of CIMT within 1 year in the setting of marked LDL reduction. This study supports, but does not prove, the potential of high-potency, synthetic statins such as atorvastatin to prevent adverse cardiovascular events on the basis of effects on CIMT. Whereas natural statins, such as pravastatin, have been definitively proven to reduce cardiovascular event rates,27–29 fewer outcome data are available for newer, synthetic statins such as atorvastatin. Our results offer the first insight into the possible results of ongoing cardiovascular outcome trials investigating the head-to-head effects of different statins, but they require cautious interpretation because they cannot discern the relative contributions of LDL cholesterol reductions from other drug effects because of the many real and postulated differences among statin drugs in their potency for LDL reduction and their pleiotropic effects. Of note, 3 industry-sponsored trials are ongoing that are evaluating pravastatin and atorvastatin in the same doses evaluated in this study. These studies include the Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES) trial (coronary calcium progression), REVERSAl of Atherosclerosis with Lipitor (REVERSAL) (intravascular ultrasound), and PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE IT) (clinical events). These trials will provide important additional insights into the clinical relevance of marked reductions in LDL cholesterol with atorvastatin.

Discussion

This randomized trial demonstrated enhanced regression of CIMT within 1 year in the setting of marked LDL reduction with atorvastatin 80 mg compared with more modest LDL reduction achieved with pravastatin 40 mg. Atherosclerosis regression in the coronary and carotid arteries is a validated surrogate end point for the clinical benefit of cholesterol reduction. Prior studies, including the Cholesterol Lowering Atherosclerosis Study (CLAS) that evaluated the effect of colestipol and niacin on carotid atherosclerosis,6 found that the principal reduction in cardiovascular events associated with cholesterol reduction occurred in patients with stabilized atherosclerosis.7–9 Thus, our demonstration of mean atherosclerosis regression with marked LDL lowering implies that an LDL of 76 versus 110 mg/dL could lead to a further reduction in cardiovascular event rates. This novel finding extends the results of the post-Coronary Artery Bypass Graft Trial, which reported atherosclerosis regression in both saphenous vein grafts13 and the native left main coronary artery14 during treatment to an LDL cholesterol of ~100 mg/dL versus 130 mg/dL. Although our study is a significant initial demonstration of the potential benefits of marked reductions in LDL cholesterol, further studies are necessary to determine whether LDL lowering to values far below the NCEP-defined “optimal” value of 100 mg/dL15 could lead to further reductions in coronary event rates.

CIMT is a validated measure of atherosclerosis burden and is most reproducibly evaluated in the far wall of the distal common carotid artery.11,12 However, CIMT is modulated by multiple cardiovascular risk factors that, taken together, explain only a minority of the interpatient variance in plaque burden.16–20 Nonetheless, the magnitude and time course of changes in CIMT observed in this study in association with marked versus moderate LDL reductions mirror those seen in placebo-controlled atherosclerosis regression trials with statins.21–25 A previously completed randomized trial comparing atorvastatin and simvastatin for familial hypercholesterolemia26 also found greater reductions in CIMT in association with a greater degrees of LDL reduction. As in previous studies with pravastatin (taken as a daily dose of 40 mg), CIMT stabilized or slowed in its progression, but regression was uncommon.21

This study supports, but does not prove, the potential of high-potency, synthetic statins such as atorvastatin to prevent adverse cardiovascular events on the basis of effects on CIMT. Whereas natural statins, such as pravastatin, have been definitively proven to reduce cardiovascular event rates, 27–29 fewer outcome data are available for newer, synthetic statins such as atorvastatin. Our results offer the first insight into the possible results of ongoing cardiovascular outcome trials investigating the head-to-head effects of different statins, but they require cautious interpretation because they cannot discern the relative contributions of LDL cholesterol reductions from other drug effects because of the many real and postulated differences among statin drugs in their potency for LDL reduction and their pleiotropic effects. Of note, 3 industry-sponsored trials are ongoing that are evaluating pravastatin and atorvastatin in the same doses evaluated in this study. These studies include the Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES) trial (coronary calcium progression), REVERSAl of Atherosclerosis with Lipitor (REVERSAL) (intravascular ultrasound), and PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE IT) (clinical events). These trials will provide important additional insights into the clinical relevance of marked reductions in LDL cholesterol with atorvastatin.
CRP has been directly related to the rate of progression of carotid atherosclerosis in patients not receiving lipid-lowering therapy. The Cholesterol and Recurrent Events (CARE) trial found that pravastatin-associated declines in CRP were strongly associated with reduced risk from future cardiovascular events. Our study, with the finding of greater reductions in CRP and CIMT in atorvastatin-treated patients with lower LDL cholesterol, differs from previous assertions that the effect of statins on CRP is independent of an effect on LDL lowering. These data support the need for further clinical outcomes studies on the utility of targeting both CRP and LDL as metrics of the success of lipid-lowering treatments.

Limitations
There are several notable limitations to this trial. This randomized clinical trial used open-label administration of study drug, although the results are strengthened by the concealment of allocation and the use of an objective, blinded, end point assessment. Although mean CIMT changes were different for atorvastatin and pravastatin over the 12-month study period, mean CIMT stabilization was observed in pravastatin-treated patients. The clinical implications of CIMT regression with atorvastatin compared with those occurring with either pravastatin-induced early CIMT stabilization or delayed (≥12 months) regression are currently unknown. Finally, this study used 2 statin treatments with significantly different potencies for LDL reduction and thus cannot discern the potential role of pleiotropic differences between agents. It is likely that the LDL reduction alone has an important role in determining serial changes in CIMT. However, whether other drug effects unrelated to LDL reduction (eg, as reviewed by Rosenson and Tangney) positively or negatively modulate the relationship between LDL reduction and CIMT regression for either atorvastatin or pravastatin will require randomized trials in which the drug administered is the independent variable and the extent of LDL reduction is equivalent between treatment groups.

Conclusions
Marked LDL reduction to values substantially below 100 mg/dL with atorvastatin provides superior efficacy for atherosclerosis regression in the distal common carotid artery at 1 year compared with an LDL of 110 mg/dL achieved with pravastatin. This early effect on CIMT, a surrogate for clinical benefit of cholesterol lowering therapies, supports the hypothesis currently being tested in ongoing randomized clinical trials that marked LDL reduction with synthetic statins may provide enhanced reduction in clinical coronary event rates.

References


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Circulation. 2002;106:2055-2060
doi: 10.1161/01.CIR.0000034508.55617.65

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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