Original Contributions

One-Year Reduction and Longitudinal Analysis of Carotid Intima-Media Thickness Associated With Colestipol/Niacin Therapy

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Background and Purpose: The Cholesterol Lowering Atherosclerosis Study has reported significant reduction of coronary artery disease and of carotid arterial intima-media thickness (IMT) at 2 and 4 years with colestipol/niacin therapy. We now report on treatment effects on carotid IMT at 6 months and 1 year.

Methods: One hundred eighty-eight nonsmoking men, aged 40 to 59 years, with prior coronary artery bypass graft surgery were randomized to colestipol/niacin plus diet therapy or placebo plus diet therapy. Computerized image processing of carotid ultrasound films was used to measure IMT in the right common carotid artery. Treatment group comparisons were made at 6 months and 1 year (46 and 33 subjects, respectively, with baseline and 6-month or 1-year ultrasound measures). The time course of the treatment effect on carotid IMT was estimated using the complete sample of 78 subjects with baseline and on-trial data.

Results: No significant treatment group differences on carotid IMT were found at 6 months. At 1 year, the treated group showed significant reduction of carotid IMT (P=.01 between groups). The placebo group showed continuing progression of IMT during the 4-year study period (estimated progression rate, 0.018 mm/y). The treated group showed reduction of IMT during the first 3 years and a plateau during the remainder of the study.

Conclusions: Reduction of carotid IMT was found with aggressive lipid-lowering therapy. Ultrasound measures of IMT offer a noninvasive and precise measure of early carotid atherosclerosis that will decrease sample size requirements, potentially decrease dropout rates, and widen the study population of antiatherosclerotic clinical trials. (Stroke. 1993;24:1779-1783.)

Key Words • cardiovascular diseases • carotid arteries • clinical trials • lipids • ultrasonics

It has been shown in excised aortas that the two parallel echogenic lines visualized in longitudinal views of the deep wall originate from the blood-intima and the media-adventitia interfaces.1 Pignoli et al1 have shown that the separation between these two lines, intima-media thickness (IMT), is a measure of atherosclerosis at a preinjurious stage of the disease. Carotid IMT has been increasingly recognized as an indicator of arterial wall pathology that can be noninvasively measured from ultrasound images.1-3 In epidemiological studies, carotid IMT has been shown to be correlated with blood pressure.4 Salonen and Salonen5 have shown that carotid intima-media thickening is associated with an increased risk of myocardial infarction; for each millimeter increase in IMT, risk is increased 2.14-fold. Several clinical trials in progress are using IMT as one among several carotid end points, but results have not yet been reported.6,7

The Cholesterol Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled, angiographic trial testing colestipol/niacin plus dietary therapy in nonsmoking men with previous coronary artery bypass surgery.8 We have previously reported clear treatment benefit on coronary arteries at both 2 and 4 years using coronary end point measures based both on panels of human readers and computerized quantitative coronary angiography.9-11 Computerized femoral angiographic results at 2 years have indicated significant, but less consistent, therapy benefits.12

Using fully automated computerized edge-detection algorithms, we have recently reported a significant reduction in carotid arterial wall IMT with colestipol/niacin therapy at 2 and 4 years after randomization to CLAS.13 This analysis also showed significant correlations with angiographic measures of percent diameter stenosis of coronary artery lesions and carotid vessel edge roughness. Thinning of carotid IMT was further shown to correlate with higher levels of high-density lipoprotein cholesterol (HDL-C) and reduced levels of apolipoprotein B.13 We now describe additional analyses of CLAS data to estimate how early treatment benefits of colestipol/niacin therapy may be detected using carotid IMT as an end point.
Subjects and Methods

CLAS Study Design and Ultrasound Methods

Details of the study design have been described.8 CLAS was a randomized, placebo-controlled, angiographic trial testing whether aggressive lipid lowering could retard or reverse atherosclerotic disease. Subjects were 188 nonsmoking men between the ages of 40 and 59, all of whom had had prior coronary artery bypass surgery. Subjects were randomized to colestipol/niacin plus dietary intervention or to placebo plus dietary intervention. Lipids were obtained at baseline and at every on-trial clinic visit (monthly for the first 6 months and bimonthly thereafter). Total cholesterol, HDL-C, and total triglycerides were measured directly. Low-density lipoprotein cholesterol (LDL-C) was obtained by the Friedewald equation: LDL-C = Total-C − HDL-C − (Triglycerides/5). Coronary, femoral, and cervical angiograms were obtained at baseline and at 2 and 4 years after randomization. In addition, carotid B-mode ultrasound images were obtained. Of the 188 randomized subjects, 103 completed 4 treatment years. Subjects with matched carotid B-mode examinations at baseline, 2, and 4 years were selected, resulting in a data set of 78 (39 colestipol/niacin and 39 placebo) subjects. There were no significant differences in baseline or on-trial levels of total cholesterol, HDL-C, LDL-C, triglycerides, or apolipoproteins A-I, B, and C-III between these 78 subjects and the remaining 110 CLAS subjects with ultrasound examinations.13

B-mode scanning was performed with a BioDynamics Biosound instrument (BioDynamics, Inc. Indianapolis, Ind) using a transducer with 9-MHz central frequency. Longitudinal views were recorded in anterior and lateral positions of both the near and far walls of the distal 1 cm of the right common carotid artery. Minimum gain required for clear visualization of structures was used. Ultrasound images were recorded at 30 frames per second on ¼-inch videotape. A tissue phantom was examined monthly to ensure instrument quality control. The distance between characteristic echoes arising from blood-intima interface and media-adventitia interface was taken as a measure of combined IMT.1 With treatment assignment masked, an image analyst measured IMT and carotid vessel diameter using a 386/33 personal computer and Data Translation DT 2862 image processing board. The computer program involved three steps. First, the analyst used a computer mouse to approximately identify three to six points of the blood-intima boundary, and the program then fit a smooth curve to these points as a guide for edge tracking. Next, a computer search was made along paths perpendicular to the curve for conditional edge points of maximum intensity change. Last, the gradient value for each conditional edge was compared with the maximum gradient of all conditional edge points, and those with gradients less than 20% of the maximum were eliminated. This three-step process was repeated to obtain the coordinates of the media-adventitia boundary. IMT in the distal right common carotid was computed as the average distance, over 120 boundary points (representing 1 cm along the carotid wall), between the far wall lumen-intima boundary and the far wall media-adventitia boundary.

Statistical Analysis

Of the 78 CLAS subjects with matched baseline, 2-, and 4-year ultrasound examinations, 46 (23 drug, 23 placebo) had baseline/month (±8 weeks) ultrasound data, 33 (14 drug, 19 placebo) had baseline/year (±8 weeks) data, and 19 (8 drug, 11 placebo) had complete baseline, 6-month, and 1-year ultrasound data.

Drug- and placebo-treated subjects were compared for baseline carotid IMT, vessel diameter, and levels of lipids and lipoproteins using two-sample t tests. Treatment group comparisons of 6-month and 1-year change in carotid IMT and vessel diameter were also tested with a two-sample t test. Two- and 4-year treatment group differences in IMT change have been previously reported.13 To estimate the temporal characteristics of IMT change over the entire 4 years of the CLAS study, we used data from the entire set of CLAS baseline and on-trial IMT measurements. This resulted in a data set of 78 subjects contributing 78 baseline and 224 on-trial IMT measurements. The variable TIME (number of months since the baseline ultrasound exam) was regressed on IMT, with both linear and quadratic effects of TIME tested. A single regression model was fit to the two groups simultaneously. To estimate treatment group differences in IMT change over time, two interaction terms between TIME and treatment group (TX=0 if in placebo and 1 if in drug group) were tested: (1) TX TIME to test whether there was a differential linear progression of IMT between treatment groups and (2) TX TIME2 to test whether there was a differential quadratic trend in IMT between treatment groups. Because the two treatment groups did not significantly differ on baseline IMT, a common intercept term, a (estimating IMT at baseline, or TIME=0), was fit for both treatment groups. The regression models were fit using a recently developed extension of general linear models for dependent responses, since subjects contributed more than one IMT measure to the analysis.14

Results

Lipids and Lipoproteins: Baseline Comparability and On-Trial Changes

Baseline levels of serum lipids and lipoproteins are displayed in Table 1. In the group of 46 CLAS subjects with baseline/6-month ultrasound examinations, the drug group had significantly higher total cholesterol at baseline than the placebo group (average±SD, 253±32 mg/dL versus 232±35 mg/dL, P=.04). All other lipids were not significantly different between the two treatment groups. The colestipol/niacin group showed a significant reduction in total cholesterol (−25% at 6 months; −28% at 1 year), LDL-C (−38% at 6 months; −47% at 1 year), and triglycerides (−34% at 6 months; −27% at 1 year), with a concomitant increase in HDL-C (+35% at 6 months; +41% at 1 year). For the placebo group, milder decreases were noted in total cholesterol (−6% at 6 months; −3% at 1 year), LDL-C (−5% at 6 months; −4% at 1 year), and total triglycerides (−18% at 6 months; −0.4% at 1 year). HDL-C did not change in the placebo group (+1% at 6 months; −1% at 1 year). All lipid changes were significantly different between treatment groups.
6-Month and 1-Year Carotid End Points
In the 46 CLAS subjects with baseline and 6-month examinations, there were no baseline differences in carotid far wall IMT (Table 2). Within each treatment group, there was no significant change in IMT from baseline to 6 months, and the IMT change was also not significantly different between treatment groups.

In 33 subjects with baseline and 1-year carotid examinations, there were no treatment group differences in baseline IMT (Table 2). At 1 year, the colestepliol/niacin group showed an average decrease in IMT of -0.02 mm (within-group P=.002), while the placebo group showed nonsignificant thickening of IMT from baseline (mean change, 0.01 mm). These IMT changes were significantly different between treatment groups (P=.01; Table 2).

Analyses using the 19 subjects with complete baseline, 6-month, and 1-year IMT measures yielded results similar to Table 2. The mean±SD baseline IMT was 0.62±0.09 mm in drug-treated and 0.60±0.16 mm in placebo-treated subjects (P=NS). Six-month change averaged 0.00±0.01 mm in drug-treated and 0.00±0.02 mm in placebo-treated subjects (P=NS between groups); 1-year change averaged -0.02±0.02 mm in drug-treated and -0.01±0.02 mm in placebo-treated subjects (between-group P=.009).

Change in Intima-Media Thickness Over Time
Using data from all 78 subjects with baseline and at least one on-trial ultrasound examination in the 4 years of the CLAS study, carotid IMT was regressed on TIME (months since the baseline ultrasound examination). A test for equality of intercepts between the two groups was not rejected, indicating that the two groups had equal IMT at baseline (TIME=0). There was a significant linear trend in IMT over time. Furthermore, the TX\times TIME interaction term was statistically significant (P<.05), indicating that the linear trend of IMT over time was not equal between the two groups. While the quadratic effect of TIME was not significant for the whole sample, the TX\times TIME2 interaction term was significant, indicating that there was a significant quadratic relation between IMT and time in the drug group but not the placebo group. For this reason, the resulting treatment group–specific regression equations include a quadratic term for the drug group but not for the placebo group. Letting TIME represent the number of months since the baseline ultrasound examination, the resulting regression equation for the placebo group was IMT=0.628+(0.00147\times TIME). The slope coefficient corresponds to an estimated IMT increase of 0.018 mm/y in the placebo group during the 4-year study period. For the drug group, the estimated regression equation was IMT=0.628−(0.0027\times TIME)+(0.00004\times TIME2). By mathematical derivation of the time point at which the slope of this regression equation equals 0, IMT thinning is estimated to occur over the first 3.2 study years and then plateaus during the remaining third and fourth years. Assuming a completely linear relation between time and IMT for the drug group for the first 3.2 study years, the estimated slope coefficient (-0.0022) corresponds to an annual decrease in IMT of 0.026 mm/y. The left panels of the Figure display the fitted regression line by treatment group together with the observed IMT means and SDs during the trial period. For display

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Lipids and Lipoproteins in CLAS Subjects With 6-Month and 1-Year Carotid Ultrasound Measures</th>
<th>All Subjects (n=60)</th>
<th>Baseline/6-Month Subjects (n=46)</th>
<th>Baseline/1-Year Subjects (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>244±35</td>
<td>243±35</td>
<td>244±32</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>170±29</td>
<td>167±31</td>
<td>172±27</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>44±8</td>
<td>43±7</td>
<td>45±8</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>151±81</td>
<td>158±82</td>
<td>132±67</td>
</tr>
</tbody>
</table>

Values are mean±SD. CLAS indicates Cholesterol Lowering Atherosclerosis Study; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

<table>
<thead>
<tr>
<th>TABLE 2. Carotid Intima-Media Thickness in CLAS Subjects at 6 Months and 1 Year</th>
<th>Drug</th>
<th>Placebo</th>
<th>P (between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Month IMT, mm (n=23 drug, 23 placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.61±0.09</td>
<td>0.59±0.14</td>
<td>.52</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.61±0.09</td>
<td>0.59±0.13</td>
<td>.55</td>
</tr>
<tr>
<td>6 Months–baseline</td>
<td>0.00±0.02</td>
<td>0.00±0.03</td>
<td>.76</td>
</tr>
<tr>
<td>P (within group)</td>
<td>.66</td>
<td>.90</td>
<td></td>
</tr>
<tr>
<td>1-Year IMT, mm (n=14 drug, 19 placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.64±0.08</td>
<td>0.61±0.13</td>
<td>.46</td>
</tr>
<tr>
<td>1 Year</td>
<td>0.63±0.08</td>
<td>0.62±0.12</td>
<td>.85</td>
</tr>
<tr>
<td>1 Year–baseline</td>
<td>-0.02±0.02</td>
<td>0.01±0.03</td>
<td>.01</td>
</tr>
<tr>
<td>P (within group)</td>
<td>.002</td>
<td>.42</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD. CLAS indicates Cholesterol Lowering Atherosclerosis Study; IMT, intima-media thickness.
purposes, the intercept term representing average IMT at baseline is fitted separately for each treatment group (intercept=0.647 mm for the colestipol/niacin and 0.612 mm for the placebo group). The top right panel of the Figure presents the fitted regression lines with the intercepts constrained to be equal, with the continued progression of IMT in the placebo group during the 4-year study period at a rate of 0.018 mm/y and the IMT thinning during the first 3.2 years in the drug group.

**Discussion**

Ultrasonographic carotid end points obtained in CLAS indicate that a significant treatment benefit of lipid-lowering therapy on carotid IMT was detected at 1 year. Although there was a trend of therapeutic benefit at 6 months after randomization, this did not attain statistical significance (Figure). These results confirm our initial findings of significant treatment benefits at 2 and 4 years and indicate the value of early examination for treatment effects in the carotid artery. Reduction of carotid IMT occurred in the presence of 1-year reductions of 28% in total cholesterol, 47% in LDL-C, 27% in triglycerides, and an increase of 41% in HDL-C. This level of lipid change contributed to significant reversal of atherosclerosis in coronary arteries at 2 and 4 years and mild reduction of femoral atherosclerosis at 2 years.

Combining the two treatment groups to determine which treatment-related changes in lipids and apolipoproteins were correlated with IMT thinning, higher on-trial levels of HDL-C and lower levels of apolipoprotein B were independently associated with thinning of IMT at 2 years. Similar analyses on 6-month and 1-year IMT change, including total cholesterol, LDL-C, HDL-C, triglycerides, and apolipoproteins A-I, B, and C-III as potential correlates, revealed that there were no significant correlates of IMT change at 6 months. In contrast, an increase from baseline in HDL-C was the single significant correlate of IMT thinning at 1 year ($r=-.46, P<.01$). These results provide support for the role of HDL-C in the early reversal of preintrusive lesions in the carotid artery.

Clinical trials of lipid-lowering therapies to date have focused on mortality and/or morbidity end points or have used angiographic end points. CLAS is the first controlled lipid-lowering trial to report treatment benefit on carotid artery atherosclerosis using a noninvasive end point obtained from ultrasound images.

The use of carotid IMT as a noninvasive end point measure in clinical trials has several important implications. First, it offers the potential for increased recruitment and reduced dropout rates from reluctance to undergo repeat angiography. Second, it allows for repeated on-trial sampling of trial end points rather than the two typically obtained at baseline and study completion in angiographic trials. Multiple noninvasive measures of atherosclerosis provide information about the onset and stability of treatment benefits. In addition, repeat ultrasound scans obtained in close temporal proximity allow estimation of the degree of measurement error inherent in these end point data and adjustment for such error in estimating treatment group differences. Finally, carotid IMT end points offer the opportunity to study treatment effects at the level of the arterial wall in asymptomatic subjects, children, and the elderly.

CLAS carotid IMT results have additional implications for the design of atherosclerosis intervention.
trials. Because of the precision of our automated measure of IMT in the distal centimeter of the common carotid artery,13 the sample size required to detect treatment group differences is drastically reduced relative to angiographic and other carotid ultrasound end point measures. A second implication of CLAS carotid results is that treatment group differences may be detected in shorter trials at reduced cost. Although randomized coronary angiographic trials have primarily reported coronary artery lesion change after 2 or 4 years of treatment, there is evidence that coronary artery lesion change may occur as early as 1 year.21 The data reported here, along with our previous report on 2- and 4-year IMT treatment effects,13 indicate that IMT change in response to lipid-lowering therapy is detectable at 1 year, is maximal at approximately 3 years, levels off between 3 and 4 years, and is maintained for 4 years. CLAS data additionally indicate that in placebo-treated CLAS subjects, IMT progressively thickens at an estimated annual rate of 0.018 mm, or 2.8%/y, during the 4 years of the study.

Our estimate of a 0.018-mm annual IMT change in untreated subjects is much lower than the 0.06 mm reported by Furberg et al22 in the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-2) Trial. Subjects for PLAC-2 were recruited with specific IMT eligibility criteria (at least one carotid arterial lesion with IMT of 1.3 mm or greater) in addition to a history of coronary disease.7 CLAS subjects were recruited only on the basis of coronary disease, with all subjects having had prior coronary bypass graft surgery.8 In addition, PLAC-2 end point data include measures of IMT in the carotid bulb and internal carotid. Our IMT measurement was confined to the distal 1 cm of the far wall of the common carotid artery.

In summary, we report treatment benefit of colestipol-niacin therapy on common carotid IMT beginning within 1 year and becoming significant at 1 year after randomization. Our findings suggest that this noninvasive measure of early atherosclerosis can be of important utility in future atherosclerosis trials. Common carotid arterial wall IMT end point measurement offers increased efficiency by reducing the required sample size and trial length. It will also increase recruitment rates and decrease trial dropouts.

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References


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