Effects of Intensive Lipid-Lowering Therapy on the Coronary Arteries of Asymptomatic Subjects With Elevated Apolipoprotein B

Xue-Qiao Zhao, MD; B. Greg Brown, MD, PhD; Lynn Hillger, PhD; Dianne Sacco, MS; Brad Bisson, MS; Lloyd Fisher, PhD; John J. Albers, PhD

Background. Do the benefits of intensive lipid-lowering therapy seen in symptomatic patients extend to high-risk subjects who have never had symptoms?

Methods and Results. Of 120 men completing the FATS trial, 91 were symptomatic and 29 asymptomatic. All had apolipoprotein B ≥125 mg/dL, a positive family history, and coronary atherosclerosis. All were counseled in diet and randomized to intensive therapy: colestipol 10 g TID plus either niacin 1 g QID or lovastatin 20 mg BID or to conventional therapy: placebos, or colestipol if low-density lipoprotein cholesterol was elevated. End points included quantitative arteriographic disease change and clinical events over a 2.5-year interval. At baseline, symptomatic and asymptomatic patients had comparable risk profiles, but proximal stenosis severity averaged 36% for symptomatic and 23% for asymptomatic patients (P<.001). Among the 91 symptomatic patients, those in the intensive group experienced definite (≥10%S) proximal lesion progression less frequently than conventional (24% of intensive versus 48% of conventional) and definite regression more frequently (36% of intensive versus 15% of conventional) (P=.009).

Similarly, among the 29 asymptomatic patients, 19% of intensive versus 38% of conventional had progression and 31% of intensive versus 0% of conventional, regression (P=.04). Ischemia on baseline exercise tolerance testing was associated with significantly greater proximal disease progression among the asymptomatic patients. Clinical cardiovascular events (death, infarction, or revascularization) occurred in 10 of 38 symptomatic patients originally assigned to conventional therapy, compared with 5 of 76 asymptomatic patients assigned to intensive (P<.01); no asymptomatic patient had an event.

Conclusions. Asymptomatic subjects with this high-risk profile have less coronary disease at baseline than comparable symptomatic patients, and they have an excellent short-term clinical prognosis. However, asymptomatic subjects are indistinguishable from symptomatic subjects in terms of their arterial disease progression with conventional therapy and their regression with intensive. These findings may justify an active treatment strategy in such subjects, particularly those with provokable ischemia.

(Circulation. 1993;88:2744-2755.)

KEY WORDS • coronary disease • lipids • cardiovascular diseases • lipoproteins

As a consensus of randomized, controlled clinical trials, certain forms of lipid-lowering therapy appear to reduce the frequency of cardiovascular events among patients with established coronary heart disease (secondary prevention) and in subjects with hyperlipidemia but without previously demonstrated coronary disease (primary prevention). Smaller arteriographic trials have determined that progression of atherosclerotic obstructive disease is decreased and its regression enhanced by such therapy; in some of these cases, a significant reduction in clinical events has also been demonstrated. Do subjects who have never experienced any cardiovascular event but who have an otherwise high-risk profile benefit as much from therapy, in terms of arterial changes, as do their "symptomatic" counterparts with established disease? Kane et al have shown that regression of disease occurs with therapy among mostly asymptomatic patients with the uncommon disorder heterozygous familial hypercholesterolemia. But a controlled comparison of the arterial response to therapy between symptomatic and asymptomatic patients with high-risk lipid profiles has not been reported to date. This may prove to be an important issue, since the rate of progression of anatomic coronary disease appears to be a useful harbinger of future clinical events.

The Familial Atherosclerosis Treatment Study (FATS) data have been analyzed to address this question. Of 120 patients who completed the 30-month FATS protocol, 91 were symptomatic patients and 29 were asymptomatic. Symptomatic patients had clinically proven coronary artery disease (CAD). Asymptomatic subjects had comparable baseline risk but had no previous history of myocardial infarction, stroke, claudication, or angina pectoris and were free of chest pain, even during the baseline treadmill test; their CAD was confirmed on protocol arteriogram. In this report, we compare the response of these two groups to lipid-lowering therapy.
Methods

Subjects

Patients enrolled in FATS\textsuperscript{10} were at high risk for premature cardiovascular disease by virtue of (1) an elevated apolipoprotein (apo) B $\geq 125$ mg/dL; (2) at least one coronary lesion $\geq 50\%$ stenosis ($\%S$) or three lesions causing at least $30\%S$, as documented in the baseline angiogram; and (3) a family history of premature cardiovascular events. Family history was called positive if disease had occurred prematurely in at least $20\%$ of those first-degree relatives of the patient's mother or father who had reached middle age.

One hundred forty-six men were enrolled and randomized to one of three therapeutic strategies. Of these, 114 were symptomatic patients with clinically established CAD (angina, myocardial infarction, or effort dyspnea or congestive heart failure due to ischemic left ventricular dysfunction). The remaining 32 had no previous history of clinical CAD. These asymptomatic subjects had come forward because they were aware of abnormal lipids and family history. They were enrolled after eligibility was confirmed by baseline screening and protocol coronary arteriography. An additional 3 such patients underwent catheterization but were found to have less than the required amount of stenosis. Ninety-one symptomatic and 29 asymptomatic patients completed the protocol, including a second coronary arteriogram scheduled for 2.5 years later. This report describes the clinical outcomes of 146 randomized subjects and the angiographic changes among the 120 subjects who completed the study.

Randomization

Each of the three treatment strategies included professional diet counseling\textsuperscript{16} and assessment of diet compliance.\textsuperscript{10,17} Therapy was randomly assigned, doubly blinded, and placebo-controlled and was initiated at the first clinic visit.

\textit{Niacin and colesteolip.} Colesteolip was begun at 5 g TID with meals and was increased to 10 g TID after 10 days unless side effects delayed the increase. Niacin was started at 125 mg BID and progressively increased on a schedule that achieved 500 mg QID (with meals and at bedtime) in 1 month and 1 g QID in 2 months. If low-density lipoprotein cholesterol (LDL-C) did not fall below 120 mg/dL after 3 months, niacin was increased to 1.5 g (three tablets) QID but no further. Of 48 patients assigned to niacin and colesteolip, 18 required increased dosage.

\textit{Lovastatin and colesteolip.} Colesteolip was given as above. Lovastatin was begun at 20 mg BID (morning and bedtime). If LDL-C did not fall below 120 mg/dL after 3 months, lovastatin was increased to 40 mg BID. Of 46 patients assigned to lovastatin and colesteolip, 12 required increased dosage.

\textit{Conventional therapy.} Patients assigned to this control regimen received placebo for colesteolip and for lovastatin, given as above, unless their screening LDL-C exceeded the 90th percentile for age. We felt obliged\textsuperscript{5,6} to provide such patients (43\% of the group) with colesteolip instead of its placebo. For blinding, the lovastatin placebo dose was doubled at the appropriate time in a conventionally treated patient for every dose doubled for a lovastatin/colesteolip-treated patient.

![Diagram showing location of nine standard proximal segments (SEG) of the coronary anatomy. The lesion causing the worst stenosis in each of these segments was measured; the average (Ave) percent stenosis among these segments was computed, and the mean change in this value between the two studies (time points A and B) was determined ($\Delta$). This estimate of the mean change in the severity of proximal stenosis (here 4\%) was made for each patient.]

\textbf{Fig 1.}
sions were classified by consensus as unchanged, definitely changed, or possibly changed. For the latter, a third frame was selected in each view from each film. The borders of each lesion and the catheter were manually traced from the selected frames onto a standard form. For lesions classified as unchanged or definitely changed, the two selected frames were traced once from each view in each film. For possibly changed lesions, three frames were traced from each view by two technicians. All tracings were reviewed for accuracy by an experienced technician and were then digitized and processed by use of techniques developed and validated in our laboratory. Minimum lumen diameter at the point of greatest local narrowing (DM) and nearby normal diameters (DN) were measured, in millimeters, using the catheter as a scaling factor. The two principal disease measures were DM and percent stenosis ($%S = 100 \frac{1 - DM/DN}{DM}$). Intrinsic variability (measurement of six selected frames in a given injection) and short-term variability (repeat measurement of a lesion in an injection 20 minutes later) average 3.4% $S$ for this method. Each estimate of severity was an average over the number of tracings measured, which ranged from 2 to 12 and averaged 3.1 per film. Fig 2 illustrates lesions and their measurements.

**Statistical Analysis**

Baseline differences in key variables between asymptomatic and symptomatic patients were compared by $\chi^2$ tests for categorical variables and pooled $t$ tests for continuous variables. Patients given lovastatin/colestipol or given niacin/colestipol were considered intensively treated; their data were combined for statistical analysis. This combination yielding 58 symptomatic and 16 asymptomatic intensively treated patients seems justified because of the absence of any significant differences between these two drug groups in lesion change, LDL/high-density lipoprotein (HDL) response, or clinical event rate either in the overall study or in the two subgroups of symptom status. Differences between conventionally and intensively treated patients and between asymptomatic and symptomatic patients in mean proximal disease change were compared by one-way or two-way ANOVA as appropriate; in cases in which the changes were not normally distributed, the Kruskall-Wallis ANOVA was used.

Group differences in frequencies of regression and progression were compared by $\chi^2$ testing and in clinical events by Fisher's exact test. A difference was considered statistically significant if the two-sided probability of the observed result under the null hypothesis was $\leq .05$.

**Results**

**Patient Characteristics**

Table 1 shows baseline risk factors for asymptomatic and symptomatic patients who completed the study. The 29 asymptomatic subjects, aged 46±10 years, had a relatively high-risk profile for coronary heart disease, with mean±SD total cholesterol 286±45 mg/dL, LDL-C 199±54 mg/dL, HDL-C 41±9 mg/dL, and apo B 161±42 mg/dL. Twenty-four percent had a history of hypertension, 62% were past smokers, and 21% were current smokers. On average, 33% of the middle-aged or older first-degree relatives of their father or their mother had experienced a premature cardiovascular
**TABLE 1. Comparison of Baseline Risk Factors Between Symptomatic and Asymptomatic Patients**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Symptomatic, n=91</th>
<th>Asymptomatic, n=29</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>48±8</td>
<td>46±10</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>History of smoking, %</td>
<td>84</td>
<td>62†</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Premature disease index*</td>
<td>0.39</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Lipid risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>264±41</td>
<td>286±45†</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>183±44</td>
<td>199±54</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>37±8</td>
<td>41±9†</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>5.0±1.2</td>
<td>5.0±1.6</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>152±23</td>
<td>161±42</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>37±35</td>
<td>31±28</td>
</tr>
<tr>
<td><strong>CAD evidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>53</td>
<td>0‡</td>
</tr>
<tr>
<td>Angina at entry, %</td>
<td>89</td>
<td>0†</td>
</tr>
<tr>
<td>ETT positive (ST ↓ ≥1 mm); %</td>
<td>59</td>
<td>35</td>
</tr>
<tr>
<td>Mean % proximal stenosis</td>
<td>36±11</td>
<td>23±11‡</td>
</tr>
<tr>
<td>Mean %S of the single worst proximal lesion</td>
<td>77±24</td>
<td>45±15$‡</td>
</tr>
<tr>
<td>Mean No. of proximal lesions ≥50%S</td>
<td>1.6±0.9</td>
<td>0.8±0.6†</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; Lp(a), lipoprotein(a); CAD, coronary artery disease; and ETT, exercise tolerance test.

*Proportion of first-degree relatives of the patient's father and mother who had premature cardiovascular disease (angina, myocardial infarction, sudden death, stroke, or claudication) when they had reached middle age (defined as 45 years of age for men and 55 for women).

†P<.05, ‡P<.01 compared with symptomatic patients.

**TABLE 2. Details of Baseline Lesion Frequency and Severity in Four Different Ranges of Stenosis Severity for All Lesions Observed and Measured, Per Patient, in the Proximal Coronary Segments of Fig 1**

<table>
<thead>
<tr>
<th>Baseline Stenosis Range</th>
<th>Minimal, ≥10% to &lt;30%</th>
<th>Mild, ≥30% to &lt;50%</th>
<th>Moderate, ≥50% to &lt;70%</th>
<th>Severe, ≥70% to 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of lesions per patient in given range at baseline</td>
<td>4.0±2.0</td>
<td>4.9±1.9</td>
<td>.02</td>
<td>3.9±2.4</td>
</tr>
<tr>
<td>No. of patients with lesions measured in each range</td>
<td>104</td>
<td>32</td>
<td>107</td>
<td>25</td>
</tr>
<tr>
<td>Mean severity of these lesions per patient</td>
<td>21.7±3.3</td>
<td>20.8±3.1</td>
<td>NS</td>
<td>38.2±3.2</td>
</tr>
</tbody>
</table>

Plus/minus values are mean±SD.
Patients and 41 for asymptomatic (P<.03). It rose 4% and 8%, respectively, with conventional therapy, 17% and 12% with lovastatin/colestipol, and 42% and 43% with niacin/colestipol. Thus, major lipid, lipoprotein, and apolipoprotein changes occurred only during intensive treatment, and the amounts of change were independent of symptom status.

Frequencies of Patient Regression and Progression

A 10-point difference in the measured percent stenosis value was considered a criterion for definite lesion change in this study.10,23,24 As shown in Fig 3, among asymptomatic subjects, regression only (at least one of the nine proximal lesions improved by ≥10% stenosis without any such worsening) occurred in none of the conventionally treated patients; by comparison, it occurred in 31% of the intensively treated patients. See Fig 2 for examples of lesion regression. Progression only (converse of above) occurred in 38% of asymptomatic conventional therapy subjects but only half as frequently (19%) among the intensively treated patients (conventional versus intensive for asymptomatic patients, P=.043). Similar results were observed among symptomatic patients; regression only occurred in 15% of conventional therapy patients and 36% of patients in the two intensive treatment groups; progression only occurred in 48% of conventionally treated patients and 24% of intensively treated patients (conventional versus intensive for symptomatic patients, P=.009).

Fig 3 also shows that there is no significant difference in frequencies of patient regression and progression between symptomatic and asymptomatic patients.

Thirty-two percent of 91 symptomatic and 52% of 29 asymptomatic patients had no change ≥10% S in any of their nine proximal segments. “Mixed change,” progression of at least one lesion and regression of at least one other lesion by ≥10% S, was uncommon, occurring in 7% of symptomatic patients and 3% of asymptomatic.

Change in Proximal Coronary Lesions

Table 4 provides the average patient change per therapy group in lesion percent stenosis for the nine proximal lesions. For the 29 asymptomatic patients, the average severity of stenosis for the worst lesion in each of the nine proximal segments was 23%S at baseline. After 2.5 years of treatment in the conventional therapy subgroup, it increased by 1.4±3.5%S; by comparison, it decreased by −0.7±3.1%S among intensively treated patients (P=.10). For 91 symptomatic patients, baseline severity of proximal disease averaged 36%S. Two and one half years later, it worsened by 2.4±4.1%S in those patients given conventional therapy; in contrast, it improved by −0.8±4.9%S in intensively treated patients (P=.002). The beneficial effect of intensive therapy on stenosis severity among symptomatic patients was not significantly different from that among asymptomatic (P=.57 by two-way ANOVA).

All lesions. In addition to the worst lesion measured in each of the nine standard proximal segments, milder lesions, when obvious, were measured in these same
segments and also in the more distal segments and in other branches. In all, excluding catheter tip lesions, 24 11.0±2.4 lesions were measured per patient. There was a significant difference (P<.003) among the symptomatic patients and a favorable trend (P=.10) among the asymptomatic subjects, between those treated conventionally and intensively, in the average change in all lesions.

Lesion subsets. Per-patient average change among significant (≥50%S) and among mild (<50%S) lesions was determined for the four combinations of symptom status and therapy (symptomatic, asymptomatic; conventional, intensive). Results similar to the overall analysis above are documented in Table 4.

Minimum lumen diameter. DM is another index of disease severity for the nine proximal lesions. It averaged 2.24 mm for asymptomatic subjects at baseline; after 2.5 years of treatment, DM decreased (worsened) −0.054±0.14 mm in the conventional group and increased (improved) 0.026±0.14 mm in the intensive group (P=.13), as seen in Table 4. Among symptomatic patients at baseline, DM averaged 1.80 mm (P<.001 versus asymptomatic); at the end of the study, DM worsened −0.049±0.15 mm during conventional therapy and improved 0.023±0.15 mm with intensive therapy (P=.02).

A comparison of the therapeutic benefit (difference between conventional and intensive therapy outcomes) between symptomatic and asymptomatic patients was performed in terms of average percent stenosis change in nine proximal lesions, in proximal lesions ≥50%S or <50%S, and in all measured lesions and in terms of the average change in DM for nine proximal coronary segments. Significant differences were not found; in other words, the natural progression of coronary lesions was changed favorably and comparably by intensive treatment in both symptomatic and asymptomatic patient groups, as shown in Table 4.

**Treadmill Ischemia, a Correlate of Increased Disease Progression Rate**

There were 10 of 29 asymptomatic and 54 of 91 symptomatic patients with at least 1 mm horizontal ST depression at peak effort on baseline treadmill test. Regardless of the therapy, the 64 with a “positive” ischemic response (but no angina among the asymptomatic group) had significantly greater disease progression (mean change in severity of proximal stenosis, Δ%S̄prox=1.2±4.5%S for positive and −0.6±4.4%S for negative; P=.03). This was also true for the 10 asymptomatic subjects with a positive ischemic response and 19 asymptomatic subjects without it (1.9±3.7%S versus −0.6±3.0%S; P=.05). As seen in Table 4, a positive ST segment response appears to identify a subset of the asymptomatic population that, on average, experiences substantial progression with conventional and does not regress with intensive therapy, although small patient numbers preclude a definitive conclusion.

**Correlates of Change in Proximal Stenosis**

Among the 120 patients completing the FATS trial, the “best” multivariate model for the estimation of change in mean proximal stenosis severity included the percent change (%Δ) from baseline to the average during therapy in apo B, in HDL-C, and in systolic blood pressure (SBP). Also included was the ST segment shift at peak effort on baseline treadmill exercise testing (ΔST), a sign of the presence of severe stenoses, which are known to be more likely to progress than milder lesions.

In Fig 4, these 120 men were classified as symptomatic (open symbols) and asymptomatic (solid symbols). Their observed Δ%S̄prox were plotted against a value estimated from the following “best” multivariate predictive expression (Δ%S̄̃prox) obtained for the entire cohort:

**Table 4. Average Per-Patient Change in Lesion Percent Stenosis for Nine Proximal Lesions, for Those Lesions ≥50%S, or Those <50%S for All 11.0±2.4 Lesions Measured Per Patient**

<table>
<thead>
<tr>
<th>Lesion Category</th>
<th>Conventional Therapy</th>
<th>Intensive Treatment</th>
<th>P</th>
<th>n</th>
<th>n</th>
<th>P</th>
<th>P†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>All proximal lesions, %S</td>
<td>2.4±1.1</td>
<td>0.8±1.4</td>
<td>.002</td>
<td>13</td>
<td>1.4±3.5</td>
<td>0.7±3.1</td>
<td>.10</td>
<td>.45</td>
</tr>
<tr>
<td>With (+) ST segment on ETT§</td>
<td>2.8±3.6</td>
<td>0.2±4.9</td>
<td>.06</td>
<td>4</td>
<td>4.0±3.8</td>
<td>0.6±3.2</td>
<td>.16</td>
<td>.55</td>
</tr>
<tr>
<td>With (−) ST segment on ETT</td>
<td>2.0±4.7</td>
<td>2.6±4.5</td>
<td>.006</td>
<td>9</td>
<td>0.3±2.9</td>
<td>1.4±2.9</td>
<td>.23</td>
<td>.32</td>
</tr>
<tr>
<td>Proximal lesion &gt;50%S</td>
<td>1.2±8.1</td>
<td>5.0±14.4</td>
<td>.02</td>
<td>3</td>
<td>1.8±1.2</td>
<td>6.8±8.1</td>
<td>.13</td>
<td>.90</td>
</tr>
<tr>
<td>Proximal lesions &lt;50%S</td>
<td>2.8±3.8</td>
<td>0.38±4.0</td>
<td>.01</td>
<td>13</td>
<td>1.5±4.8</td>
<td>0.3±3.2</td>
<td>.18</td>
<td>.33</td>
</tr>
<tr>
<td>All lesions, %S</td>
<td>2.2±3.8</td>
<td>0.72±4.7</td>
<td>.003</td>
<td>13</td>
<td>1.5±3.6</td>
<td>0.54±2.9</td>
<td>.10</td>
<td>.55</td>
</tr>
</tbody>
</table>

*Also, change in minimum diameter for nine proximal lesions. Comparison of symptomatic patients and asymptomatic subjects in terms of their arterial response to lipid-lowering therapy.
†P values for symptomatic vs asymptomatic patients with conventional therapy.
‡P values for symptomatic vs asymptomatic patients with intensive therapy.
§(+ ) ST segment response is ≥1 mm depression, at peak effort, on the baseline exercise tolerance test (ETT).
Fig 4. Scatterplot showing results of the original multivariate statistical analysis. These 120 men in the original FATS study were classified as symptomatic (○, □, and △) and asymptomatic subjects (■, ●, and ▲). Their observed mean changes in the severity of proximal stenosis (ΔSprog) were plotted against a value estimated with the following predictive expression: ΔSprog = -0.07 (%Δapo B) - 0.03 (%ΔHDL-C) + 0.14 (%ΔSBP) - 0.7 ΔST + 1.5, where SBP is systolic blood pressure and ST is ST segment. The observed mean change in proximal stenosis in these patients correlated highly with change predicted by this expression. For symptomatic patients, r = .53, P = .0001; for asymptomatic patients, r = .42, P = .022. Squares indicate conventional therapy; triangles indicate niacin plus colesterol; circles indicate lovastatin plus colesterol.

Clinical Events

Death, myocardial infarction, or newly refractory unstable ischemic symptoms that required either bypass surgery or angioplasty were considered as hard clinical cardiovascular end points. Among 38 symptomatic (SX) patients randomized to the conventional (CONV) group, 10 (26%) had clinical events, as did only 5 (7%) of 76 symptomatic patients treated intensively (INT) (P < .01). None of the 32 asymptomatic (ASX) patients, regardless of therapy, had clinical events during the 2.5 years.

10-fold greater risk of dying within 6 to 10 years from cardiac causes than subjects who have never manifested ischemic symptoms.27-29 This added risk attributable to the symptomatic state occurs at all levels of LDL-C and HDL-C.27 Current opinion favors the idea that high-risk patients with clinically manifest coronary disease, particularly in cases of elevated LDL-C or apo B and/or a positive family history, should be treated with an intensive approach to lipid lowering.30 There is less consensus regarding this therapeutic approach in patients with a comparably abnormal risk factor profile but without previous cardiovascular symptoms.31,32 Simply put, should these asymptomatic "high-risk" subjects be treated with comparable intensity?

The selection of patients for the FATS trial resulted in a mixed population, with about three fourths having clinically established disease and one fourth having no previous symptoms suggestive of ischemia. Although most of the FATS patients were first found to have elevated apo B at the time of a clinically indicated catheterization, a certain number came forward simply because of known hypercholesterolemia and a positive family history. Among 35 who so identified themselves and went on to a protocol cardiac catheterization, 32 had the minimal anatomic disease required to continue in the study; of these, 29 completed the 2.5-year protocol. Thus, the majority of middle-aged men selected for high apo B and for a positive family history will have at least one 50% stenosis or three 30% lesions. This subgroup, although small, permits thoughtful assessment of certain issues related to the above question about intensive therapy in asymptomatic high-risk subjects. We found that, despite an identical LDL/HDL ratio (5.0), comparable Lp(a) levels, and generally comparable conventional risk factors (although, overall, slightly more benign in the asymptomatic subjects), the baseline disease severity in each of nine proximal

Discussion

Patients who have established coronary artery disease (myocardial infarction, angina) are at fivefold to
coronary segments averaged 13% stenosis greater in the symptomatic group (36% versus 23%, P<.001).

Thus, two related questions arise: Do patients who have reached the symptomatic threshold have, by nature, an inherently greater tendency to develop obstructive disease than asymptomatic subjects? And if so, why? Data provided in this report may be pertinent to these questions. When symptomatic patients are compared with asymptomatic, the amount of disease progression among either the intensively or the conventionally treated patients was not significantly different (see Table 4 and Fig 3), although there was a suggestive trend among those treated conventionally (symptomatic, Δ%Spos = +2.4%S versus asymptomatic, 1.4% S; P=.45). One interpretation of these control group observations is that the presence of symptoms at baseline can be explained by more severe occlusive disease in the symptomatic group because of a somewhat more rapid rate of progression over the years in these patients who have a somewhat less favorable risk factor profile. However, another set of observations, which may lead to a different interpretation, better explains the presence or absence of symptoms. That is, a much greater number of the 91 symptomatic patients had at least one significant (≥50%), severe (≥70%), or totally occluded lesion (69, 56, and 39, respectively) in comparison with the same estimates among the 29 asymptomatic subjects (7, 2, and 0, respectively; P<.0001 in each case).

It is now becoming understood that the more severe lesions are often formed by certain disruptive transformations of the lipid-rich atherosclerotic plaque.33-36 This raises the possibility that symptomatic patients in FATS had not only an adverse risk factor profile but also a propensity for such structural plaque disruption. Conversely, the asymptomatic group, despite a similar risk factor profile, may have plaques that are less susceptible to this disruptive transformation that leads to severe stenosis and ischemia. In other words, there may be "tissue" characteristics of the arterial wall or the plaques that are additional risk factors for progressing to the symptomatic threshold. These questions cannot be answered with certainty by a retrospective analysis of these data. But Table 2 does suggest that the symptomatic patients entered the study with a greater number of significant or severe lesions, whereas the lesion frequency in the milder range of lesions (10% to 30% and 30% to 50% S) is, if anything, greater among the asymptomatic group. The 30% to 50% S range is particularly telling, since all proximal lesions in this range of severity are almost certain to have been visualized and measured. The data in Table 2 suggest that high-risk asymptomatic subjects have a distribution of lesions in the lesser ranges of stenosis severity that is similar to that of their symptomatic counterparts, but somehow they are significantly less likely to have experienced progression into the more severe ranges.

In summary, this evidence can be interpreted to support two distinctly different hypotheses regarding the presence of symptoms among these high-risk subjects. One hypothesis is that the presence of symptoms may be due to greater baseline disease severity that is, in turn, due to the cumulative effects of somewhat more rapidly progressive (Table 4) and significantly more advanced disease progression (Table 2) associated with a somewhat more adverse risk profile (Table 1). An alternative hypothesis is that symptoms may be explained by a selective increase in the presence of significant (≥50%S) or severe (≥70%S) lesions; this may be explained by a greater tendency for plaque disruption among the patients with symptoms. That is, an arterial, or plaque, risk factor(s) may contribute importantly to the distinction between the symptomatic and the symptom-free state. Indeed, it has been shown that lesions likely to undergo disruptive changes contain more core lipid and more foam cells and have a paucity of smooth muscle cells in the thin fibrous cap of the atheroma.33-39 Thus, the answer to whether to treat the asymptomatic high-risk subject intensively may depend, in part, on whether he or she has an independent arterial risk factor predictive of plaque disruption. It is important to emphasize independence, since the lipid content of a lesion may not be independent of serum cholesterol. Lacking such a factor, the subject with an apparently high-risk profile may, in fact, be naturally protected against formation of severe stenosis. In that case, intensive treatment might safely be avoided in such a favored subject.

Clinical Implications: Who Merits Intensive Treatment?

The purpose of this discussion has been to briefly explore certain issues related to whether apparently high-risk but presently asymptomatic individuals should be treated with the same intensity as symptomatic patients with a comparably adverse risk factor profile. The evidence is strong that clinically established cardiovascular disease greatly increases the likelihood of a future cardiac event; therefore, intensive lipid-lowering therapy may not be indicated as strongly in the absence of symptoms. Alternatively, we may need to search for independent arterial properties such as vasomotor dysfunction40,41 or plaque composition by magnetic resonance imaging42 or by intravascular ultrasound43,44 to identify for treatment the patients or plaques that are truly at high risk for progression to severe stenosis or to clinical events. One such variable for risk stratification appears to be the ST segment response during treadmill testing, which, if positive, is associated with increased disease progression among the asymptomatic subjects. This observation is based on small numbers and needs further confirmation.

Because all symptomatic patients were at one time asymptomatic, one cannot necessarily infer protection for a patient from absence of symptoms. In the absence of identifiable features that better distinguish those at greatest risk for a premature cardiac event, a physician may take comfort that, regardless of treatment, his or her asymptomatic patient is relatively unlikely to be so afflicted in the short term. And should the physician and patient elect to undertake intensive lipid modification, they may be encouraged by the knowledge that the patient’s arterial obstruction is more likely to improve and is less likely to worsen. Two recent publications44,45 have demonstrated that measured progression of arteriographic disease over a given time interval is a strong risk factor for subsequent cardiac events. Buchwald et al14 reported that the Global Change Score assessed visually from 695 pairs of films obtained at baseline and at 3 years in POSCH was significantly associated with subsequent overall and atherosclerotic coronary heart
disease mortality \(P<0.01\) in these patients. Waters et al\(^5\) reported that measured progression by 15% stenosis of at least one coronary lesion per patient, which was seen in 141 (42%) of 335 patients studied over a 2-year interval, conveyed a 7.3-fold relative risk of future (within 6 to 10 years) cardiac death. Sixteen of the 19 such deaths were in “progressors” \(P<0.001\). If a comparable relation applies to high-risk asymptomatic subjects, then therapy that favorably alters disease progression, as seen in our asymptomatic FATS patients, may protect against these untoward events. For the present, adequate data are not available, and the effect of such therapy on mortality in the asymptomatic subject, particularly on all-cause mortality, and its cost-effectiveness remain the subject of ongoing controversy,\(^31,32,45,46\) although there is evidence that cardiovascular events can be reduced.\(^5,6\)

After deliberating the above considerations and data, our recommendation is to follow a strategy of moderate intervention for these high-risk (high LDL or apo B and positive family history) asymptomatic patients, especially among those with treadmill ischemia. One such strategy is to follow the current National Cholesterol Education Program (NCEP) guidelines, taking a target LDL-C of <130 mg/dL among such men and women, with an even greater commitment to achieving that target if other risk factors are present.

Acknowledgments

This study was supported in part by National Institutes of Health (NIH) grants RO1-HL-19451, PO1-HL-30006, and RO1-HL-42419 from the National Heart, Lung, and Blood Institute, in part by a grant from the John L. Locke, Jr Charitable Trust, Seattle, Wash, in part by the University of Washington Clinical Research Center (NIH RR-37), and in part by a grant (DK-35816) to the Clinical Nutrition Research Unit from the National Institute of Diabetes and Digestive and Kidney Disorders. We express our thanks to Ellen Zincavage in preparing the manuscript.

References


Effects of intensive lipid-lowering therapy on the coronary arteries of asymptomatic subjects with elevated apolipoprotein B.

X Q Zhao, B G Brown, L Hillger, D Sacco, B Bisson, L Fisher and J J Albers

Circulation. 1993;88:2744-2753
doi: 10.1161/01.CIR.88.6.2744

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/88/6/2744

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/