Influence of Low High-Density Lipoprotein Cholesterol and Elevated Triglyceride on Coronary Heart Disease Events and Response to Simvastatin Therapy in 4S

Christie M. Ballantyne, MD; Anders G. Olsson, MD; Thomas J. Cook, MS; Michele F. Mercuri, MD; Terje R. Pedersen, MD; John Kjekshus, MD; for the Scandinavian Simvastatin Survival Study (4S) Group

Background—Patients with low HDL cholesterol (HDL-C) and elevated triglyceride had an increased risk for coronary heart disease (CHD) events and received the greatest benefit with fibrate therapy in substudy analyses of the Helsinki Heart Study and the Bezafibrate Infarction Prevention Study.

Methods and Results—In this post hoc analysis of the Scandinavian Simvastatin Survival Study, which enrolled patients with elevated LDL cholesterol (LDL-C) and CHD, subgroups defined by HDL-C and triglyceride quartiles were compared to examine the influence of HDL-C and triglyceride on CHD events and response to therapy. Patients in the lowest HDL-C (<1.00 mmol/L [39 mg/dL]) and highest triglyceride (>1.80 mmol/L [159 mg/dL]) quartiles (lipid triad; n = 458) had increased proportions of other features of the metabolic syndrome (increased body mass index, hypertension, diabetes), men, prior myocardial infarction, prior revascularization, and β-blocker use than patients in the highest HDL-C (>1.34 mmol/L [52 mg/dL]) and lowest triglyceride (<1.11 mmol/L [98 mg/dL]) quartiles (isolated LDL-C elevation; n = 545). The major coronary event rate was highest in lipid triad patients on placebo (35.9%), and this subgroup had the greatest event reduction (relative risk 0.48, 95% CI 0.33 to 0.69); a significant treatment-by-subgroup interaction (P = 0.03) indicated a greater treatment effect in the lipid triad subgroup than the isolated LDL-C elevation subgroup.

Conclusions—Patients with elevated LDL-C, low HDL-C, and elevated triglycerides were more likely than patients with isolated LDL-C elevation to have other characteristics of the metabolic syndrome, had increased risk for CHD events on placebo, and received greater benefit with simvastatin therapy. (Circulation. 2001;104:3046-3051.)

Key Words: lipids ▪ statins ▪ trials

Although the association between LDL cholesterol (LDL-C) and coronary heart disease (CHD) has been well established in observational studies and clinical trials, the focus on elevated triglycerides and low HDL cholesterol (HDL-C) has increased in regard to risk assessment and pharmacological therapy to reduce risk. In part because of the metabolic interrelation between triglyceride-rich lipoproteins and HDL, hypertriglyceridemia frequently occurs in combination with low HDL-C, and the recent Adult Treatment Panel III (ATP III) guidelines place increased emphasis on identification of patients with the metabolic syndrome, defined by low HDL-C and elevated triglyceride along with truncal obesity, high glucose, and increased blood pressure. In both observational studies and clinical trials, patients with hypertriglyceridemia and an elevated LDL-C/HDL-C ratio had disproportionately high risk for CHD events. In substudy analyses of the Helsinki Heart Study and the Bezafibrate Infarction Prevention (BIP) study, patients with low HDL-C and elevated triglycerides received the greatest benefit on CHD event reduction with fibrate therapy.

The purpose of this analysis was 2-fold: first, to examine whether patients in the Scandinavian Simvastatin Survival Study (4S) with combined abnormalities of increased LDL-C, increased triglyceride, and reduced HDL-C (the lipid triad) had increased risk compared with patients with isolated increased LDL-C (normal triglyceride and HDL-C levels), and second, to examine the comparative benefit of simvastatin therapy in these patients.

Methods

4S studied the effect of simvastatin versus placebo on mortality in CHD patients with elevated LDL-C. Details of the study design...
have been published previously: in general, 4444 men and women 35 to 70 years old with a history of myocardial infarction (MI) and or angina and total cholesterol of 5.5 to 8.0 mmol/L (210 to 310 mg/dL) were randomized to simvastatin 20 to 40 mg/d or placebo and followed up for a median of 5.4 years.

Lipids were measured in fasting serum obtained at baseline and periodically thereafter. Simvastatin was titrated from 20 to 40 mg if needed to reduce total cholesterol to <5.2 mmol/L (200 mg/dL). Total cholesterol, HDL-C, and triglycerides were measured enzymatically, and LDL-C concentration was calculated by the Friedewald formula. Apolipoprotein (apo) B concentration was measured by an immunoturbidity method (Orion Diagnostics).

Major coronary events were defined as coronary death, definite or probable hospital-verified nonfatal acute MI, resuscitated cardiac arrest, and definite silent MI verified by ECG.

Subgroups compared in this analysis were patients in the lowest quartile for HDL-C and the highest quartile for triglycerides and patients in the highest quartile for HDL-C and the lowest quartile for triglycerides. Baseline characteristics except age and lipids were analyzed by the Cochran-Mantel-Haenszel test. Age and lipids (baseline value, 1-year value, and 1-year change) were analyzed by ANOVA with treatment, subgroup, and treatment-by-subgroup interaction as the independent categorical variables. Major coronary events, total mortality, and revascularization rates were analyzed with a Cox proportional hazards model to assess subgroup differences and treatment-by-subgroup interactions.

Results
In the subgroup with the lipid triad, ie, patients in the lowest quartile for HDL-C (<1.00 mmol/L [39 mg/dL]) and the highest quartile for triglycerides (>1.80 mmol/L [159 mg/dL]), 221 patients received simvastatin and 237 received placebo. In the subgroup with isolated LDL-C elevation, ie, patients in the highest quartile for HDL-C (>1.34 mmol/L [52 mg/dL]) and the lowest quartile for triglycerides (<1.11 mmol/L [98 mg/dL]), 261 patients received simvastatin and 284 received placebo.

Comparison of the 2 subgroups at baseline (Table 1) indicated that patients with the lipid triad were older, were more likely to be male, were more obese, and had increased incidence of hypertension, diabetes mellitus, prior MI, prior revascularization, and β-blocker use. By definition, the subgroups had significantly different baseline HDL-C and triglyceride concentrations, and the lipid triad subgroup also had significantly higher total cholesterol, LDL-C, apo B, and non-HDL cholesterol concentrations.

At 1 year, percent changes in LDL-C and apo B with simvastatin were nearly identical in both subgroups (Table 2), but in the lipid triad subgroup, only 35.7% of simvastatin patients were titrated from 20 to 40 mg, whereas 44.8% of simvastatin patients with isolated LDL-C elevation required titration (P=0.051 for differences between groups). LDL-C decreased by 37.5% in the lipid triad subgroup compared with 36.0% in the subgroup with isolated LDL-C elevation, and apo B decreased by 28.8% and 29.6% in the respective subgroups. Total cholesterol reduction was significantly greater in the lipid triad subgroup, 29.7% compared with 25.6% in the subgroup with isolated LDL-C elevation (P=0.01). There were trends toward more benefit with simvastatin on HDL-C and triglyceride concentrations in the lipid triad subgroup, but the differences were not statistically significant and may have been partially due to regression to the mean. HDL-C increased by 10.3% in the lipid triad subgroup, compared with a decrease of 0.6% in the subgroup with isolated LDL-C elevation, and triglycerides decreased by 24.1% and 6.7% in the respective subgroups.

Event-free survival was significantly lower in lipid triad patients receiving placebo than in the other treatment subgroups (Figure 1). The major coronary event rate at 5 years was 35.9% in lipid triad patients on placebo, and lipid triad patients had the greatest event reduction with simvastatin (0.48 relative risk, 95% CI 0.33 to 0.69) (Table 3). The significant treatment-by-subgroup interaction for major coronary events (P=0.03) indicated a greater treatment effect in the lipid triad subgroup than in the isolated LDL elevation subgroup (Figure 2A). Similar trends toward greater benefit with simvastatin among patients in the lipid triad subgroup were seen for total mortality (Figure 2B), coronary mortality (Figure 2C), and revascularization (Figure 2D), but the treatment-by-subgroup interactions were not statistically significant.

Although the frequency of diabetes mellitus was increased in patients with the lipid triad, exclusion of the patients with diabetes defined by either clinical history or glucose ≥126 mg/dL (n=73, 16%) did not substantially alter the findings (Figure 3).

To determine whether the greater treatment effect of simvastatin in the lipid triad subgroup was due to sex-related

### Table 1. Baseline Characteristics of 1003 Patients by Baseline HDL-C and Triglyceride Quartiles*

<table>
<thead>
<tr>
<th>Age, y (mean±SD)</th>
<th>Lipid Triad (n=458)</th>
<th>Isolated ↑ LDL-C (n=545)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>425 (93)</td>
<td>360 (66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Qualifying diagnosis, n (%)</td>
<td>79 (17)</td>
<td>138 (25)</td>
<td>0.002</td>
</tr>
<tr>
<td>Angina only</td>
<td>280 (61)</td>
<td>334 (61)</td>
<td>0.96</td>
</tr>
<tr>
<td>Angina and MI</td>
<td>99 (22)</td>
<td>73 (13)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Previous PTCA or CABG, n (%)</td>
<td>42 (9)</td>
<td>25 (5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus: history, n (%)</td>
<td>31 (7)</td>
<td>11 (2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Diabetes mellitus: glucose ≥126 mg/dL, n (%)</td>
<td>42 (9)</td>
<td>23 (4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Impaired fasting glucose: glucose 110–125 mg/dL, n (%)</td>
<td>80 (17)</td>
<td>67 (12)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>145 (32)</td>
<td>116 (21)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (mean±SD)</td>
<td>137.1±20.0</td>
<td>140.0±20.7</td>
<td>0.44</td>
</tr>
<tr>
<td>Body mass index, kg/m^2 (mean±SD)</td>
<td>26.9±3.1</td>
<td>24.5±3.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nonsmokers, n (%)</td>
<td>101 (22)</td>
<td>89 (31)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Concomitant therapy, n (%)</td>
<td>164 (36)</td>
<td>192 (35)</td>
<td>0.85</td>
</tr>
<tr>
<td>Aspirin</td>
<td>337 (74)</td>
<td>200 (37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>129 (28)</td>
<td>184 (34)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Lipid triad indicates lowest HDL-C quartile (<1.00 mmol/L [39 mg/dL]) and highest triglyceride quartile (>1.80 mmol/L [159 mg/dL]); isolated ↑ LDL-C, highest HDL-C quartile (>1.34 mmol/L [52 mg/dL]) and lowest triglyceride quartile (<1.11 mmol/L [98 mg/dL]).
differences, data on the men in both subgroups were analyzed separately. Similar results were found: with simvastatin, relative risk for a major coronary event was 0.47 (0.32 to 0.70) in the lipid triad subgroup and 0.91 (0.59 to 1.41) in the subgroup with isolated LDL-C elevation (P = 0.03 for treatment-by-subgroup interaction). Respective relative risks for total mortality were 0.44 (0.24 to 0.81) and 0.81 (0.44 to 1.51), but as in the overall subgroup analysis, the treatment-by-subgroup interaction was not statistically significant.

**Discussion**

In this post hoc analysis of 45 data, patients with the lipid triad (elevated LDL-C, low HDL-C, elevated triglycerides) had increased comorbidity at baseline, increased major coronary event rate on placebo, and significantly greater reduction of major coronary events with simvastatin compared with patients with isolated LDL-C elevation.

In post hoc analyses of the Helsinki Heart Study and the BIP study, patients with the lipid triad had increased risk for CHD events and greater benefit with fibrate therapy. In the Helsinki study, which included 4081 men without known CHD who had non-HDL cholesterol >200 mg/dL, the subgroup defined by LDL-C/HDL-C ratio >5 and triglyceride level >205 mg/dL had a relative risk for a cardiac event of 3.8 compared with patients with LDL-C/HDL-C ratio ≤5 and triglyceride level ≤2.3 mmol/L. This high-risk subgroup also had the largest reduction in cardiac events with gemfibrozil, 71%, compared with 34% in the study overall. In BIP, which studied 3090 men and women with previous MI or angina, HDL-C ≤45 mg/dL, triglycerides ≤300 mg/dL, and LDL-C ≤180 mg/dL, the subgroup with HDL-C <35 mg/dL and triglycerides ≥200 mg/dL had a 6.2-year CHD event rate of 22.3% on placebo and a statistically significant 41.8%
reduction in CHD events with bezafibrate; in contrast, in the study overall, CHD event reduction with bezafibrate was 7.3%, which was not statistically significant. These post hoc analyses have been used to support fibrate treatment in patients with the lipid triad.

Although this is one of the first analyses of a trial of statin therapy to examine specifically the benefit of statin therapy in patients with the lipid triad, substantial evidence from previous clinical event and angiographic trials supports the use of a statin in such patients. Previous analyses of 4S and other clinical trials of statin therapy have demonstrated that patients with lower HDL-C had higher coronary event rates on placebo and significant reductions in event rates with statin therapy. Treatment with simvastatin in 4S; pravastatin in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS); and lovastatin in the West of Scotland Coronary Prevention Study,9 the Cholesterol and Recurrent Events trial,10 and the Long-Term Intervention with Pravastatin in Ischaemic Disease trial11; and lovastatin in the Veterans Affairs High-Density Lipoprotein Intervention Study with gemfibrozil also showed benefit in patients with low HDL-C, more than half of whom had the metabolic syndrome; in multivariable analysis, only on-treatment HDL-C was predictive of CHD events.15

Angiographic trials have also found that patients with lower HDL-C are at increased risk and receive the greatest benefit from treatment. In the Lipoprotein and Coronary Atherosclerosis Study,12 patients with low HDL-C (<35 mg/dL) had the greatest CHD progression with placebo and the greatest treatment effect with fluvastatin, both on reduced CHD progression and prolonged event-free survival.16 These patients also had increased triglyceride levels and increased body mass index, also components of the metabolic syndrome. In other angiographic trials, increased IDL and VLDL concentrations17 or increased small, dense LDL18 have been used to identify high-risk subgroups, which were also characterized by low HDL-C, elevated triglyceride, and other aspects of the metabolic syndrome. Indeed, the cutoff points defined for the metabolic syndrome in the ATP III guidelines are very similar to the quartile thresholds in this 4S analysis: HDL-C <1.03 mmol/L (40 mg/dL) in men, triglyceride ≥1.69 mmol/L (150 mg/dL).1

Previous substudy analyses of 4S have identified patients by use of criteria that are also relevant to the metabolic syndrome. Individuals with baseline fasting glucose ≥126 mg/dL (n=483) had a 37.5% incidence of major CHD events with placebo and a relative risk reduction of 42% with simvastatin,19 which is similar to the 35.9% incidence of CHD events in lipid triad patients on placebo and the 52% relative risk reduction with simvastatin in the present analysis. Excluding the 16% of lipid triad patients with either a clinical history of diabetes or glucose ≥126 mg/dL did not alter the findings. Miettinen et al20,21 previously stratified the Finnish participants of 4S by the ratio of cholestanol to cholesterol at baseline. Individuals with a low cholestanol/cholesterol ratio were considered to have low absorption and were noted to have high levels of lathosterol, consistent with high production of cholesterol.21 These “low absorbers” also had increased body mass index, increased triglycerides, and decreased HDL-C20; low cholesterol absorption and high cholesterol synthesis have been associated with glucose and insulin levels and postulated to be a component of the metabolic syndrome.22 Patients in 4S with low absorption/high production had the greatest benefit on events, with a 38% relative risk reduction, whereas no benefit was observed in patients who were high absorbers/low producers.20 Low absorbers also had slightly but significantly greater cholesterol reduction at 6 weeks compared with high absorbers (29.4±0.9% versus 25.6±0.9%, P<0.001),21 which is similar to the greater 1-year cholesterol reduction in lipid triad patients in the present study (29.7±11.2% versus 25.6±10.6% in patients with isolated LDL-C elevation, P=0.01); the lipid triad subgroup also tended to require less titration. Thus, these different studies, which identified individuals with the metabolic syndrome by 3 different criteria (glucose; triglyceride and HDL-C levels; and cholestanol/cholesterol ratio), have all shown remarkable efficacy of statin therapy in patients with facets of the metabolic syndrome and high LDL-C.

| TABLE 3. Absolute and Relative Benefits of Simvastatin on Major Coronary Events by Baseline HDL-C and Triglyceride Quartiles |
|---------------------------------|-----------------|-----------------|
|                                 | Lipid Triad     | Isolated ↑ LDL-C | 4S Overall |
|                                 | (n=458)         | (n=545)         | (n=4444)   |
| Placebo event rate, n (%)       | 85/237 (35.9)   | 59/284 (20.8)   | 622/22223 (28) |
| Simvastatin event rate, n (%)   | 42/221 (19.0)   | 47/261 (18.0)   | 431/2221 (19) |
| Relative risk (95% CI)          | 0.48 (0.33–0.69)| 0.86 (0.59–1.26)| 0.66 (0.59–0.75) |
| Relative risk P value*          | 0.00009         | 0.44            | <0.00001   |
| Absolute benefit per 100 subjects treated | 16.96 | 2.85 | 9.08 |
| No. needed to treat             | 6               | 36              | 11         |

*There was also a statistically significant difference between the relative risks for the 2 subgroups (P=0.03).
The mechanism for benefit in these patients may be related to the effects of simvastatin on atherogenic lipoproteins overall, with a reduction in both LDL and triglyceride-rich lipoproteins (VLDL remnants and IDL), which together compose non-HDL cholesterol, recommended as a secondary target of therapy by ATP III. Higher doses of simvastatin have even greater effects on reducing non-HDL cholesterol and increasing HDL-C and apo A-I than the doses used in 4S.

In this study, patients with isolated LDL-C elevation had less treatment benefit than patients with the lipid triad (relative risk 0.86 [0.59 to 1.26] versus 0.48 [0.33 to 0.69]). Patients with high LDL-C and high HDL-C, however, also had a lower event rate on placebo, and in light of the wide CIs, the limited power with a small sample size to detect a difference of 20% to 25%, and the post hoc design of the analysis, this finding must be interpreted with caution and may be due to chance. The previous studies by Miettinen, which also showed less benefit in patients with similar features (lower body mass index, higher HDL-C, lower triglycerides), suggest a hypothesis. These patients, who had no risk reduction with simvastatin, had a worsening of the ratio of plant sterols, especially campesterol, to cholesterol during the course of the study and increased serum levels. The molecular mechanism for these findings may include the influence of 2 genes, \( \text{ABCG5} \) and \( \text{ABCG8} \), which in tandem secrete cholesterol and plant sterols out of cells and may be regulated by cellular sterol levels. Mutations that lead to a loss of function of \( \text{ABCG5} \) and \( \text{ABCG8} \) cause \( \text{H Gilbert syndrome} \), characterized by high levels of cholesterol and plant sterols. Statins reduce cholesterol levels in hepatocytes and thus may downregulate expression of \( \text{ABCG5} \) and \( \text{ABCG8} \), which would reduce hepatic excretion of plant sterols, such as campesterol, and worsen the ratios in “high absorbers.” As suggested by Miettinen et al., patients who are high absorbers of cholesterol (and more likely to have isolated elevated LDL-C) may benefit from a combination of statin plus therapy that blocks cholesterol absorption (high-dose resins, plant stanol ester, or ezetimibe).

In summary, patients in 4S who had elevated LDL-C, reduced HDL-C, and elevated triglycerides—either by history or glucose \( \geq 126 \text{ mg/dL} \), or both—had a major coronary event rate that was similar to that in patients without lipid triad and without diabetes. By comparison, event rates on placebo were similarly high in patients with lipid triad and patients without diabetes and in patients without lipid triad.
previous trials of fibrates, patients with the lipid triad also had
greater benefit with drug therapy, which in 4S was simvasta-
tin. These findings support aggressive lifestyle and pharma-
cological therapy in patients with the metabolic syndrome, as
suggested by the ATP III guidelines.1 The results of this post
hoc analysis provide a rationale for designing future clinical
trials to determine whether optimal therapy for these high-
risk individuals should consist of high-dose statin mono-
therapy, fibrate monotherapy, or combination therapy with
statin plus fibrate.

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