Joint Effects of Serum Triglyceride and LDL Cholesterol and HDL Cholesterol Concentrations on Coronary Heart Disease Risk in the Helsinki Heart Study

Implications for Treatment

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Background. We studied the joint effect of baseline triglyceride and lipoprotein cholesterol levels on the incidence of cardiac end points in the trial group (n=4,081) of the Helsinki Heart Study, a 5-year randomized coronary primary prevention trial among dyslipidemic middle-aged men. The relative risks (RR) were calculated using Cox proportional hazards models with a dummy variable technique that allows simultaneous study of subgroup combinations from the placebo and treatment groups.

Methods and Results. In the placebo group (n=2,045), the low density lipoprotein cholesterol (LDL-C)/high density lipoprotein cholesterol (HDL-C) ratio was the best single predictor of cardiac events. This ratio in combination with the serum triglyceride level revealed a high-risk subgroup: subjects with LDL-C/HDL-C ratio >5 and triglycerides >2.3 mmol/l had a RR of 3.8 (95% CI, 2.2–6.6) compared with those with LDL-C/HDL-C ratio ≤5 and triglyceride concentration ≤2.3 mmol/l. In subjects with triglyceride concentration >2.3 mmol/l and LDL-C/HDL-C ratio ≤5, RR was close to unity (1.1), whereas in those with triglyceride level ≤2.3 mmol/l and LDL-C/HDL-C ratio >5, RR was 1.2. The high-risk group with LDL-C/HDL-C ratio >5 and triglyceride level >2.3 mmol/l profited most from treatment with gemfibrozil, with a 71% lower incidence of coronary heart disease events than the corresponding placebo subgroup. In all other subgroups, the reduction in CHD incidence was substantially smaller.

Conclusions. Serum triglyceride concentration has prognostic value, both for assessing coronary heart disease risk and in predicting the effect of gemfibrozil treatment, especially when used in combination with HDL-C and LDL-C. (Circulation 1992;85:37–45)

A positive association between serum triglyceride concentration and risk of coronary heart disease (CHD) has been observed in most case-control studies and in a number of prospective studies. However, this association has often disappeared when adjustment has been made for other risk factors, particularly the level of high density lipoprotein cholesterol (HDL-C), and it has thus been suggested that serum triglycerides do not have a causal role in atherosclerosis. This conclusion has recently been called into question for several reasons. First, due to multicollinearity, it is not appropriate to adjust for HDL-C when studying the association between serum triglycerides and CHD. Second, an independent association between triglycerides and CHD may have no biological meaning, as the metabolisms of triglyceride-rich very low density lipoprotein (VLDL), and high density lipoprotein (HDL) and low density lipoprotein (LDL) are closely interrelated. Some of the analytical difficulties can be surmounted by studying the joint effects of triglycerides with HDL-C and low density lipoprotein cholesterol (LDL-C) on the risk of CHD and by introducing their interaction into the statistical modeling. The present contribution is based on further analyses of the Helsinki Heart Study data. We have
studied the joint effect of baseline triglycerides and lipoprotein cholesterol concentrations on the risk of CHD and on the risk reduction associated with gemfibrozil treatment.

Methods

The Helsinki Heart Study was a 5-year, placebo-controlled, double-blind clinical trial designed to test the hypothesis that lowering serum LDL-C and triglyceride levels and elevating serum HDL-C level with gemfibrozil, a lipid-modulating drug belonging to the group of fibric acid derivatives, reduces the incidence of CHD in middle-aged dyslipidemic men. The design and execution of the trial have been described in detail elsewhere. Briefly, the participants for the study were selected from 23,531 men aged 40–55 years who were employed by two state agencies and five industrial companies in Finland. Volunteers were eligible for the trial if their serum non-HDL cholesterol (i.e., LDL-C plus VLDL cholesterol) was ≥5.2 mmol/l at two successive measurements and if they had no evidence of CHD or other major disease. The mean baseline cholesterol, LDL-C, HDL-C, and triglyceride levels of the trial population were 6.98, 4.88, 1.23, and 2.02 mmol/l, respectively. The trial participants were randomly allocated either to gemfibrozil (n = 2,046) or placebo (n = 2,035).

The follow-up examinations performed at 3-month intervals included laboratory measurements and an interview on possible adverse effects, hospitalizations, main illnesses, and any symptoms suggesting myocardial infarction. Routine electrocardiograms were taken annually and whenever the participants reported symptoms suggesting myocardial infarction. Definite fatal and nonfatal myocardial infarctions and cardiac death were the end points. The endpoint assessments were made without knowledge of the treatment group.
Fasting serum samples were required only at the second screening and semiannually during the follow-up for serum triglyceride measurement. Total cholesterol concentration was determined from serum, and HDL-C was measured after precipitation of VLDL and LDL with dextran sulphate magnesium chloride by an enzymatic method (Boehringer Mannheim, kit No. 236691). The serum concentration of triglycerides was measured as glycerol after enzymatic hydrolysis with lipase/esterase (Boehringer Mannheim, kit No. 124966). The LDL-C concentration was calculated using the formula LDL-C=total cholesterol minus HDL-C minus triglycerides divided by 2.2.16 Triglyceride values of 8.1 mmol/l or more were excluded from LDL calculations. Computed LDL-C values below 2.6 mmol/l were also excluded. Triglyceride values from the second screening visit were taken to represent the baseline level of serum triglycerides and were also used in calculating baseline LDL-C values. Cholesterol and triglyceride concentrations are given in millimoles per liter. To convert values to milligram per deciliter, they should be divided by 0.02586 and 0.01129, respectively.

Baseline lipid values were dichotomized for the present analyses. The cut-off points were total cholesterol, 7.8 mmol/l; LDL-C, 5.0 mmol/l; triglycerides, 2.3 mmol/l; and LDL-C/HDL-C ratio, 5. These lipid levels follow the Nordic recommendations for drug treatment of hypercholesterolemia.17 Total cholesterol, LDL-C and triglyceride levels, and LDL-C/HDL-C ratio were above these cut-off points in 16, 42, 26, and 21% of the trial population, respectively. The cut-off point for HDL-C was 1.08 mmol/l (the upper limit of the lowest tertile of the baseline HDL-C distribution).

Smoking habits were recorded by an interview at the first screening visit, and a dichotomous variable (current smokers, nonsmokers, and past smokers) was used in the analyses. Statistical Methods

The analyses were done on an "intention to treat" principle. Crude incidence rates are reported when describing the joint effects of lipids and lipoproteins on the incidence of CHD events. To control for confounding variables, the risk patterns were also studied using Cox proportional hazards models18,19 with age, smoking, and systolic blood pressure as covariates. In these analyses, we used categorized variables and a dummy variable technique that allows simultaneous study of several subgroups from the placebo and the gemfibrozil groups.20 For example, when studying the joint effect of treatment and high and low levels of LDL-C and triglycerides (2x2x2 groups), the placebo group with low LDL-C and low triglycerides was chosen as the reference and a system of dummy variables was generated for the remaining seven combinations. These dummy variables were equal to 1 if the combination was present and 0 if the combination was absent.

To study the short-term and long-term predictive power of baseline lipoprotein levels, follow-up time was divided into two periods (the first 2 years and the last 3 years) and the risks were assessed separately for both periods. All analyses reported here are based on baseline lipid and lipoprotein concentrations.

Results

Univariate Association Between Serum Lipid Levels and CHD Incidence

Univariate associations between CHD incidence and the dichotomized lipid and lipoprotein variables are shown in Figure 1. In this selected hyperlipidemic population, both total cholesterol and LDL-C were poor indicators of CHD risk. On the other hand, low HDL-C concentration (<1.08 mmol/l) was associated with high risk (RR 1.73 compared with subjects with HDL-C ≥1.08 mmol/l) (Figure 1, Table 1). Similarly, subjects with serum triglycerides >2.3 mmol/l had a significantly increased risk of CHD (RR, 1.81) (Figure 1, Table 2). Excess CHD risk associated with elevated triglyceride and low HDL-C levels was largely eliminated by gemfibrozil treatment (Table 1).

| TABLE 1. Relative Risk of Cardiac Events in Relation to Baseline Serum High Density Lipoprotein Cholesterol Concentration in the Helsinki Heart Study |
|------------------|------------------|------------------|
|                  | ≥1.08            | <1.08            |
|                  | n=1,384 (placebo), 1,352 (gemfibrozil) | n=651 (placebo), 694 (gemfibrozil) |
| Total 5-year follow-up |                  |                  |
| Placebo          | 1                | 1.73 (1.12–2.66) |
| Gemfibrozil      | 0.79 (0.50–1.23) | 0.92 (0.55–1.54) |
| First 2 years of follow-up |                  |                  |
| Placebo          | 1                | 1.44 (0.68–3.05) |
| Gemfibrozil      | 0.91 (0.44–1.85) | 1.49 (0.72–3.11) |
| Last 3 years of follow-up |                  |                  |
| Placebo          | 1                | 1.90 (1.12–3.22) |
| Gemfibrozil      | 0.72 (0.41–1.28) | 0.60 (0.28–1.26) |

Risks were estimated using Cox regression models with age, smoking status, and systolic blood pressure as covariates. Risk in subjects in the placebo group with high density lipoprotein cholesterol (HDL-C) concentration ≥1.08 mmol/l was set at 1. In parentheses, 95% confidence intervals are given.
The risk associated with low HDL-C level in the placebo group was similar during the first 2 years and the last 3 years of follow-up (Table 1). The pattern seen in the gemfibrozil group was quite different. Here, subjects with low baseline HDL level had an increased risk only during the first 2 years but not during the last 3 years, suggesting that the gemfibrozil-induced elevation of HDL-C level had eliminated the extra risk after 2 years of treatment. High baseline triglyceride concentration (>2.3 mmol/l) predicted the risk of CHD only during the first 2 years in the placebo group (Table 2). This extra risk was eliminated by gemfibrozil treatment.

The association between baseline triglyceride concentration and CHD incidence in the placebo group was J-shaped, with the lowest incidence in subjects with triglyceride levels between 1.2 and 1.5 mmol/l (Figure 2). The incidence of cardiac end points in the two highest quintiles was approximately 2.5 times greater than that in the second quintile but only approximately 1.5 times higher than the incidence in the lowest quintile. Despite the lack of monotony, the relative risk of CHD was significantly higher in the two highest quintiles of triglycerides (>1.9 mmol/l) than in the three lowest quintiles (Table 3). When adjusted for age, smoking, hypertension, and either total cholesterol or LDL-C, using Cox models, the subjects in the two highest quintiles had approximately 75% higher CHD risk than subjects in the three lowest quintiles. When HDL-C was added to the models, relative risk decreased and was no more statistically significant (NS). Essentially similar results were obtained when serum triglyceride concentration was used as such and after a logarithmic transformation. At first sight, these results would imply that baseline triglyceride concentration was not an independent risk factor for CHD. However, because the correlation between baseline values of HDL-C and triglycerides (after a logarithmic transformation) was not negligible ($r=-0.44$), further analyses were carried out in an attempt to eliminate the effects of multicollinearity.

**Joint Effects of Serum Triglycerides and Lipoprotein Cholesterol on CHD Incidence**

Analysis of the joint effect of triglycerides and total cholesterol demonstrated that a high level of total

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**TABLE 2. Relative Risk of Cardiac Events in Relation to Baseline Serum Triglycerides Concentration in the Helsinki Heart Study**

<table>
<thead>
<tr>
<th>Triglyceride concentration (mmol/l)</th>
<th>(\leq2.3)</th>
<th>(&gt;2.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 5-year follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
<td>1.81 (1.16–2.81)</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>0.83 (0.55–1.25)</td>
<td>0.76 (0.43–1.36)</td>
</tr>
<tr>
<td>First 2 years of follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
<td>3.97 (1.85–8.33)</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>1.84 (0.91–3.75)</td>
<td>1.10 (0.49–3.51)</td>
</tr>
<tr>
<td>Last 3 years of follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
<td>1.17 (0.65–2.10)</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>0.52 (0.31–0.90)</td>
<td>0.60 (0.29–1.24)</td>
</tr>
</tbody>
</table>

Risks were estimated using Cox regression models with age, smoking status, and systolic blood pressure as covariates. Risk in subjects in the placebo group with high density lipoprotein cholesterol concentration \(\geq1.08\) mmol/l was set at 1. In parentheses, 95% confidence intervals are given.

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**FIGURE 2. Bar graph shows incidence of coronary heart disease by quintiles of baseline triglyceride values in the placebo group. Cut-off points of quintiles were 1.20, 1.51, 1.90, and 2.50 mmol/l, respectively. Number of events in each subgroup are shown by numbers at the base of each bar.**
cholesterol was associated with elevated CHD risk only when the triglyceride level was also high (>2.3 mmol/l) (Figure 3). Similar results were seen when the risks were calculated using LDL-C instead of total cholesterol (Figure 3). Data obtained after adjustment for age, smoking, and hypertension using Cox models confirmed the visual impression from the crude incidence rates. Relative risk was highest for subjects with both LDL-C and triglycerides above the cut-off points (RR, 2.37) and was not elevated in subjects with high LDL-C and low triglyceride level (RR, 1.06) (Table 4). The joint effects of HDL-C and triglycerides on CHD incidence are shown in Figure 3 and Table 5. The risk was particularly high in subjects with high triglyceride and low HDL-C levels.

As shown in Table 6 and Figure 3, the LDL-C/HDL-C ratio was a strong predictor of CHD risk, especially in subjects with high triglyceride levels; thus, the highest risk in any of the subgroups examined in this report was observed in subjects with LDL-C/HDL-C ratio >5 and triglyceride concentration >2.3 mmol/l. This group also benefitted most from gemfibrozil treatment; the incidence was reduced by more than 70% compared with the placebo group (p<0.005). No difference was observed in all-cause mortality between the gemfibrozil- and placebo-treated subjects in this subgroup. The all-cause mortality in the placebo group was 5.82 per 1,000 person-years, with four deaths (all cardiovascular) and 3.88 per 1,000 person-years in the gemfibrozil group, with three deaths (two cardiovascular deaths and one accident).

Finally, we analyzed the LDL-C/HDL-C ratio in subjects with this ratio >5 and serum triglycerides
TABLE 3. Relative Risk of Cardiac Events by Baseline Levels of Serum Triglycerides in Placebo Group of the Helsinki Heart Study

<table>
<thead>
<tr>
<th>Serum triglyceride concentration (mmol/l)*</th>
<th>Covariates</th>
<th>≤1.9 (n=1,217)</th>
<th>&gt;1.9 (n=818)</th>
<th>≤2.3 (n=1,529)</th>
<th>&gt;2.3 (n=506)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Model A: triglycerides, age, smoking, systolic blood pressure</td>
<td>1</td>
<td>1.75</td>
<td>1</td>
<td>1.86</td>
<td>(1.19–2.91)</td>
</tr>
<tr>
<td>Model A plus total cholesterol</td>
<td>1</td>
<td>1.72</td>
<td>1</td>
<td>1.80</td>
<td>(1.15–2.83)</td>
</tr>
<tr>
<td>Model A plus LDL cholesterol</td>
<td>1</td>
<td>1.85</td>
<td>1</td>
<td>2.01</td>
<td>(1.27–3.18)</td>
</tr>
<tr>
<td>Model A plus HDL cholesterol</td>
<td>1</td>
<td>1.29</td>
<td>1</td>
<td>1.40</td>
<td>(0.87–2.25)</td>
</tr>
</tbody>
</table>

Risks were estimated using Cox regression model with age, smoking status, and systolic blood pressure as covariates. In each model, the lower category was used as the reference group with unity risk. In parentheses, 95% confidence intervals are given. LDL, low density lipoprotein; HDL, high density lipoprotein.

*The two cut points used in categorization (1.9 and 2.3 mmol/l) were chosen based on quintile analysis of the present cohort (cut point between the third and fourth quintile, see also Figure 2) and the Nordic recommendations for drug treatment of hypertriglyceridemia (see Reference 17).

below or above 2.3 mmol/l. Although the ratio was slightly higher in the hypertriglyceridemic subgroup (6.2 versus 5.9), the difference was not large enough to explain the observed difference in the CHD risk. As an LDL-C/HDL-C ratio >5 may result either from a high LDL-C level or from a low HDL-C level (or both), the distributions of baseline LDL-C, HDL-C, and triglycerides were examined in the groups formed on the basis of the LDL-C/HDL-C ratio and triglyceride concentration (Table 7). Ninety percent of the subjects in the group with LDL-C/HDL-C ratio >5 and triglycerides >2.3 mmol/l had low levels of HDL-C, whereas 49% in that group had high LDL levels. These data suggest that both the elevated risk of CHD and the treatment effect depend more on the level of HDL-C than on the level of LDL-C in this hyperlipidemic population.

Discussion

The main finding in the present report was the strong interdependence of LDL-C, HDL-C, and triglyceride concentrations as predictors of CHD risk and treatment benefit due to gemfibrozil. The risk associated with the levels of HDL-C and LDL-C was dependent on the level of triglycerides, and vice versa. The LDL-C/HDL-C ratio had more prognostic value than LDL-C and HDL-C alone, and hypertriglyceridemia was a strong indicator of the short-term CHD risk, especially when the LDL-C/HDL-C ratio was also high.

Our results are compatible with several earlier studies. The CHD risk associated with serum triglyceride concentration disappeared in most studies when adjustment was made for other CHD risk factors, especially HDL-C.6–8 On the other hand, an independent effect of triglycerides on CHD risk was observed both in the Framingham7 and Milwaukee8 Cardiovascular Data Register cohorts when triglyceride level was considered jointly with HDL-C or with the total cholesterol HDL-C ratio. In the Paris prospective study,12 interaction of the effects of total cholesterol and triglycerides on CHD risk was significant, suggesting that the effects of triglyceride and total cholesterol levels are interdependent. All these observations suggest that much information is lost if the independent association between serum triglycerides or lipoprotein cholesterol levels and the risk of CHD is evaluated without taking into account their joint effects.

Extensive evidence from animal studies, clinical trials, and observational epidemiological studies has confirmed the causal role of LDL-C in atherosclero-

TABLE 4. Relative Risk of Cardiac Events in Combined Categories of Baseline Serum Low Density Lipoprotein Cholesterol and Triglycerides

<table>
<thead>
<tr>
<th>LDL-C ≤5.0 (mmol/l)</th>
<th>LDL-C &gt;5.0 (mmol/l)</th>
<th>TG ≤2.3 (mmol/l)</th>
<th>TG &gt;2.3 (mmol/l)</th>
<th>TG ≤2.3 (mmol/l)</th>
<th>TG &gt;2.3 (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 5-year follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.06 (0.62–1.80)</td>
<td>2.37 (1.21–4.63)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>841</td>
<td>687</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>1.07 (0.62–1.84)</td>
<td>1.50 (0.71–3.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>819</td>
<td>686</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risks were estimated using Cox regression models with age, smoking status, and systolic blood pressure as covariates. Those in the placebo group who had low density lipoprotein cholesterol (LDL-C) ≤5.0 mmol/l and triglycerides (TG) ≤2.3 mmol/l were the reference group with unity risk. In parentheses, 95% confidence intervals are given.
TABLE 5. Relative Risk of Cardiac Events in Combined Categories of Baseline Serum High Density Lipoprotein Cholesterol and Triglycerides

<table>
<thead>
<tr>
<th></th>
<th>HDL-C ≥1.08 (mmol/l)</th>
<th></th>
<th>HDL-C &lt;1.08 (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TG ≤2.3 (mmol/l)</td>
<td>TG &gt;2.3 (mmol/l)</td>
<td>TG ≤2.3 (mmol/l)</td>
</tr>
<tr>
<td>Total 5-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>RR 1</td>
<td>1.31 (0.63–2.72)</td>
<td>1.33 (0.74–2.40)</td>
</tr>
<tr>
<td></td>
<td>n 1,166</td>
<td>218</td>
<td>363</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>RR 0.82 (0.50–1.35)</td>
<td>0.86 (0.38–1.94)</td>
<td>1.10 (0.59–2.04)</td>
</tr>
<tr>
<td></td>
<td>n 1,106</td>
<td>246</td>
<td>400</td>
</tr>
</tbody>
</table>

Risks were estimated using Cox regression models with age, smoking status, and systolic blood pressure as covariates. Those in the placebo group with triglycerides (TG) ≤2.3 mmol/l and high density lipoprotein cholesterol (HDL-C) ≥1.08 mmol/l were the reference group with unity risk. In parentheses, 95% confidence intervals are given. RR, relative risk.

points chosen are to some extent arbitrary: lower values of triglycerides and LDL-C/HDL-C ratio would also have defined a high-risk group, although not as marked as the present one. For example, subjects with triglycerides >1.9 mmol/l and LDL-C/HDL-C ratio >4.5 comprise a 17% subgroup of the trial population that has a 53% reduction in CHD incidence as a result of treatment with gemfibrozil. Caution is also necessary in the interpretation of these findings, as they are based on a post hoc analysis of subgroups not defined in the original study plan. It is important to note that our conclusions are based on a cohort of initially healthy, hyperlipidemic middle-aged men and are not necessarily generalizable to other populations.

Several mechanisms could explain the strong joint effect of LDL-C/HDL-C ratio and hypertriglyceridemia on the rate of CHD. Based on what is known about the physiological functions of lipoproteins, the high LDL-C/HDL-C ratio is likely to affect the progression of atherosclerosis. On the other hand, there is increasing evidence that hypertriglyceridemia influences various hemostatic functions and may therefore be involved in events leading to thrombosis formation.26 The remarkably strong treatment effect in the group defined by high LDL-C/HDL-C ratio and hypertriglyceridemia may be due to the effects of gemfibrozil on both processes.27

Further support for the hypothesis that serum triglycerides and HDL cholesterol do not influence

TABLE 6. Relative Risk of Cardiac Events in Combined Categories of Baseline Serum Low Density Lipoprotein Cholesterol to High Density Lipoprotein Cholesterol Ratio and Triglycerides

<table>
<thead>
<tr>
<th></th>
<th>LDL-C/HDL-C ≤5.0</th>
<th></th>
<th>LDL-C/HDL-C &gt;5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TG ≤2.3 (mmol/l)</td>
<td>TG &gt;2.3 (mmol/l)</td>
<td>TG ≤2.3 (mmol/l)</td>
</tr>
<tr>
<td>Total 5-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>RR 1</td>
<td>1.05 (0.56–2.00)</td>
<td>1.19 (0.61–2.32)</td>
</tr>
<tr>
<td></td>
<td>n 1,262</td>
<td>341</td>
<td>266</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>RR 0.76 (0.47–1.22)</td>
<td>0.72 (0.35–1.47)</td>
<td>1.24 (0.65–2.35)</td>
</tr>
<tr>
<td></td>
<td>n 1,201</td>
<td>356</td>
<td>304</td>
</tr>
</tbody>
</table>

Risks were estimated using Cox regression models with age, smoking status, and systolic blood pressure as covariates. Those in the placebo group with serum low density lipoprotein cholesterol (LDL-C) to high density lipoprotein cholesterol (HDL-C) ratio ≤5.0 mmol/l and triglycerides (TG) ≤2.3 mmol/l were the reference group with unity risk. In parentheses, 95% confidence intervals are given. RR, relative risk.
the same mechanisms in the development of myocardial infarction was obtained from differences in risk patterns during the first 2 and the last 3 years of the present trial. Low HDL-C level predicted the risk in the placebo group, especially during the last 3 years. Moreover, gemfibrozil-induced reduction in risk in subjects with low HDL cholesterol was seen only during that last part of the intervention. In contrast, high serum triglyceride level predicted the risk in the placebo group only during the first 2 years of the study. This extra risk was totally eliminated by gemfibrozil treatment. Although based on relatively small numbers, these observations are compatible with the hypothesis that serum triglycerides are involved in thrombus formation in already-compromised coronary arteries.26

It is interesting to note that the lipid criteria used to identify the subgroup with high risk are closely similar to the lipoprotein pattern described for the syndrome with small dense LDL.28 These criteria include moderately elevated LDL-C and VLDL levels and low HDL-C levels. This pattern is common among subjects with myocardial infarction and appears to be influenced by a common allele at a single gene locus.29 Whether gemfibrozil treatment specifically reduces the risk associated with this syndrome remains to be studied.

Summary

The present data suggest that elevated serum triglyceride concentration is a marker of elevated CHD risk, especially in subjects with a high LDL-C/HDL-C ratio. Moreover, our findings suggest that by using LDL-C/HDL-C ratio and fasting triglyceride concentration as criteria, it is possible to define a subgroup with an over-70% reduction in CHD risk during gemfibrozil therapy. In fact, most of the effect associated with gemfibrozil treatment was confined to this subgroup comprising about 10% of the trial population. These observations have important clinical implications, as they suggest that relatively simple laboratory measurements can be used to identify a small patient group that is likely to benefit from long-term drug intervention. Such tailoring of drug therapy is particularly important in the light of potential adverse effects associated with life-long treatment with lipid-lowering drugs.

Acknowledgments

We thank Dr. Bjarne Hansen for inspiring discussions and Laura Fellman and Marja Nordberg for skillful technical assistance in preparation of the manuscript.

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KEY WORDS • triglycerides • low density lipoprotein •
high density lipoprotein • risk factors • clinical trials

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Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment.
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Circulation. 1992;85:37-45
doi: 10.1161/01.CIR.85.1.37

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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