Relation of Gemfibrozil Treatment and Lipid Levels With Major Coronary Events: VA-HIT: A Randomized Controlled Trial

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CONSIDERABLE EPIDEMIOLOGIC data show that a low concentration of plasma high-density lipoprotein cholesterol (HDL-C) is a major risk factor for coronary heart disease (CHD).1-4 In the United States, a low HDL-C concentration is the most prevalent lipid abnormality in men with known CHD.5,6 Moreover, a low HDL-C level better distinguishes populations with and without CHD than does a high level of low-density lipoprotein cholesterol (LDL-C).7,8 The VA High-Density Lipoprotein Intervention Trial (VA-HIT) was undertaken to test the hypothesis that drug therapy to increase a low HDL-C level would decrease the incidence of major CHD events.9

A total of 2531 men with known CHD and low levels of HDL-C and LDL-C were recruited for VA-HIT and treated with either the fibric acid derivative gemfibrozil or placebo (FIGURE 1). Treatment with gemfibrozil at a dosage of 1200 mg/d resulted in a 22% reduction in the primary end point, the combined incidence of nonfatal myocardial infarction (MI) and CHD death, during a median follow-up of 5.1 years.9 The relative
trials have also had relatively high concentrations of total cholesterol or LDL-C and, when measured, concentrations of HDL-C that have not been in a distinctly low range. In sharp contrast to subjects in previous trials, participants in VA-HIT who had low LDL-C (≤140 mg/dL [3.63 mmol/L]) as well as low HDL-C (≤40 mg/dL [1.04 mmol/L]) levels. Participants also had a broad range of triglyceride values (≤300 mg/dL [3.38 mmol/L]), representative of triglycerides in 75% to 80% of men with CHD in the United States.9

Gemfibrozil, like other fibric acid derivatives, has a wide range of potentially favorable effects on lipoprotein metabolism.14 The most consistent plasma lipid changes that result from gemfibrozil treatment are an increase in HDL-C and a decrease in triglycerides, changes that are in great part reciprocally related and secondary to the activation by gemfibrozil of the lipolysis of triglyceride-rich lipoproteins. Gemfibrozil may also increase plasma HDL-C by decreasing cholesteryl ester transfer protein–mediated cholesterol exchange from HDL20,21 and by directly stimulating hepatic HDL synthesis and secretion.22 In addition to changes in HDL that are closely linked to triglycerides, like other fibric acids gemfibrozil will activate peroxisome proliferator–activated nuclear receptor that may result in other favorable effects on vascular function, which may be largely independent of changes in HDL concentration.23

The present analysis was performed to determine if the reduction in major CHD events in VA-HIT could be correlated with the concentrations of lipids at baseline, during the trial, and the changes in these lipids with gemfibrozil treatment.

METHODS

The general design and procedures of VA-HIT have been previously reported.24 The trial was conducted from September 1991 through August 1998 in 20 VA medical centers. The primary combined end point, nonfatal MI and CHD death, was adjudicated by an independent committee blinded to treatment assignment. A central laboratory performed all lipid analyses once subjects had been randomized. Laboratory personnel were blinded to treatment and participant identification. This study was approved by the human rights committee of the Cooperative Studies Program Coordinating Center and by each study site’s institutional review board. Each participant gave written informed consent.

Lipid Measurement

Before medication was dispensed, lipid levels were determined twice and averaged to obtain a baseline value. Major lipid concentrations (consisting of HDL-C, triglycerides, and LDL-C) were determined during the trial at 4, 7, 12, 18, 24, 36, 48, and 60 months. Values obtained at the 4- through 18-month visits were averaged and used for trial results in accord with our original protocol design that postulated a 2-year lag in treatment benefit and with the rationale that these earliest samples were obtained before an appreciable number of new CHD events had occurred. If an end point occurred before 18 months, only values up to the time of an end point were averaged to avoid a lipid change that might have been influenced by a new CHD event.

Lipids were measured after subjects had fasted for 12 to 14 hours. Blood samples were prepared using EDTA as an anticoagulant and plasma was mailed frozen from individual study sites to the central laboratory. Total cholesterol, HDL-C, and triglycerides were determined by standardized automated enzymatic methods25 and LDL-C was calculated by the Friedewald formula.26 Levels of LDL-C were not calculated if triglycerides were higher than 400 mg/dL (4.51 mmol/L). HDL-C was isolated by precipitation with dextran-Mg2+.27 Apolipoprotein (apo) A-I, apoB, HDL2-C, and HDL3-C concentrations were determined at baseline and during the trial at the 12-month follow-up visit.

The mean coefficient of variation for the measurements of cholesterol, triglycerides, and HDL-C was ≤2%, ≤3%, and ≤4%, respectively. Levels of apoA-I and apoB were determined by immunotur...
bidometric precipitation methods and HDL subfractions were separated by differential polyanion precipitation. All results were sent to the VA Cooperative Studies Coordinating Center (West Haven, Conn) and entered into a VA-HIT centralized database.

**Statistical Analysis**

All analyses that relate plasma lipids and apolipoproteins at baseline and during the trial to the development of a new CHD event were performed according to the principle of intention-to-treat and using the combined incidence of nonfatal MI and CHD death, the primary VA-HIT outcome measure. The incidence of CHD events was obtained using the Kaplan-Meier survival method for tertile divisions of baseline and quintile divisions of trial concentrations of HDL-C, triglycerides, and LDL-C. Relative risks (RRs) for concentrations and changes in lipids were calculated from Cox proportional hazards models adjusting for treatment category and the major CHD risk factors of age, diabetes, hypertension, smoking, and body mass index. Compliance with therapy, as assessed by pill counts, did not significantly predict a primary CHD event and was not used in risk modeling. Calculations with baseline and trial lipid levels were separately constructed to assess the significance of individual lipids and apolipoproteins as univariable predictors of risk and, for the major plasma lipids (HDL-C, triglycerides, and LDL-C), as a multivariable set of variables to predict risk. Interaction between treatment and plasma lipids or apolipoproteins at baseline or during the trial were tested 1 at a time using separate Cox models. Relative risks with 95% confidence intervals (CIs) and corresponding P values are shown for all Cox results. Quintile comparisons were performed using log-rank tests to compare survival curves.

**RESULTS**

Lipid data were available for 2521 men at baseline (99.6% of the cohort) and for 2375 subjects from at least 1 of the 4 follow-up visits. The distribution at baseline of plasma HDL-C, triglyceride, and LDL-C values was similar in the placebo and gemfibrozil treatment groups. In this population, selected to have a restricted range of lipid values, mean (SD) values were nearly identical to median values for HDL-C (mean, 31.5 [5.3] mg/dL [1.21 [0.13] mmol/L] and median, 31.7 mg/dL [1.12 mmol/L]) and LDL-C (mean, 111 [22] mg/dL [2.88 [0.57] mmol/L] and median, 112 mg/dL [2.90 mmol/L]), and closely corresponded to median values for triglycerides (mean, 161 [68] mg/dL [1.81 [0.77] mmol/L] and median, 151 mg/dL [1.70 mmol/L]). As previously shown, with treatment the mean values of HDL-C, triglycerides, and LDL-C in both placebo and gemfibrozil groups remained nearly constant from 12 months to the end of the study at 60 months.

**Lipid Changes With Gemfibrozil**

Baseline and trial lipid and apolipoprotein values are shown in Table 1. Most notable was the significant increase in HDL-C, the decrease in triglycerides, and the absence of a change in LDL-C concentrations with gemfibrozil therapy. During the study, plasma apoB concentrations were lower with gemfibrozil therapy than with placebo. In contrast, apoA-I concentrations were the same in both groups. With gemfibrozil, HDL-C, the major subfraction of HDL-C isolated by polyanion precipitation, was increased compared with placebo while HDL3-C, the minor subfraction, was decreased.

**Relation of CHD Events to Baseline Lipid Values**

The relation of CHD events in placebo and gemfibrozil groups to baseline concentrations of HDL-C, triglycerides, and LDL-C is shown in Figure 2. Lipids were stratified as tertiles. In the placebo group, CHD events were higher than the overall mean event rate for this group in the lowest tertile of HDL-C and the highest tertiles of triglycerides and LDL-C. With gemfibrozil, there was a reduction in the RR of a CHD event for each tertile of each lipid, except for the lowest tertile of LDL-C.

**Relation of CHD Events to Lipid Values During the Trial**

Subjects in the placebo and gemfibrozil groups were subdivided into quintiles by trial values of HDL-C, triglycerides, and LDL-C to relate the concentrations of these lipids to the 5-year incidence of nonfatal MI or CHD death (Figure 3). With placebo, the incidence of CHD events was inversely related to trial HDL-C levels (log-rank test, P = .01 comparing quintile 1 with 5) but was unrelated to levels of triglycerides (log-rank test, P = .93) and LDL-C (log-rank test, P = .49 for comparison of quintiles 1 and 5). With gemfibrozil, there was a marked reduction in CHD events compared with
placebo for the second through fourth quintiles of HDL-C levels \((P = .02)\), whereas event rates in the 2 treatment groups did not differ at the lowest and highest HDL-C quintiles. With respect to triglycerides, event rates in the gemfibrozil group did not differ across the lowest 4 quintiles and were decidedly lower than for subjects taking placebo. Only with triglycerides in the highest quintile range with gemfibrozil was the CHD event rate the same as with placebo. Finally, with gemfibrozil, the incidence of CHD events did not differ across the quintile range of LDL-C levels. For all levels of LDL-C, subjects in the gemfibrozil group had a lower CHD event rate than those taking placebo.

**RR of CHD Events From Cox Proportional Hazards Models**

The RR of a new primary CHD event was determined for individual lipid and apolipoprotein variables at baseline and during the trial by Cox models, adjusted for treatment group and for major CHD risk factors (Table 2). At baseline, the concentrations of HDL-C, triglycerides, the HDL3-C subfraction, apoA-I, and apoB were all significant predictors of a new CHD event, whereas during the trial, only concentrations of HDL-C significantly predicted a CHD end point. Neither the change by concentration nor by percentage in HDL-C, the HDL3-C subfraction, triglycerides, LDL-C, or apolipoproteins were significant predictors of CHD risk. Although the trial concentration of HDL3-C did not predict CHD risk \((P = .07)\), the percentage change in the HDL3-C subfraction was significantly related to the probability of a CHD event \((P = .01)\).

**Table 3** shows the results of multivariable analyses performed with the 3 major lipid variables at baseline and during the trial. These models were constructed to exclude apolipoproteins and HDL subfractions because these closely related components of the 3 major lipid variables could be expected to change the predictive relationship of a major lipid. Adjustment was made for treatment category, which showed no significant interaction with any of the major lipids, and for CHD risk factors. There was no significant interaction between HDL-C and triglycerides either at baseline or during the trial. Although HDL-C, triglyceride, and LDL-C concentrations at baseline were not significantly related to the development of a CHD event, the concentration of HDL-C achieved with therapy was strongly related to a reduction in CHD events. The RR reduction in CHD end points for 5-mg/dL (0.13-mmol/L) increase in HDL-C with gemfibrozil was 11%.

We estimated that, together, the concentrations of HDL-C, triglycerides, and LDL-C achieved with therapy made a relatively small contribution to the overall decrease of a primary CHD event with gemfibrozil. That is, the RR of a CHD event with treatment as the only variable in regression analysis was 0.78 (95% CI, 0.66-0.94). The RR of a CHD event attributed to treatment itself should be lessened by the inclusion of other variables in this kind of analysis that would provide explanation for the benefit of treatment. In a regression model that included trial lipid values with treatment category, the RR of a CHD event was 0.83 (95% CI, 0.68-1.02), which would indicate that 77% \((1 - 0.83/[1 - 0.78])\) of the benefit of gemfibrozil was unexplained or that, at most, the lipid concentrations achieved...
with gemfibrozil could account for only 23% of the treatment benefit.

COMMENT

VA-HIT was undertaken to determine if raising HDL-C concentrations would decrease major coronary events in a high-risk group of men with low HDL-C. Treatment with gemfibrozil resulted in a significant reduction in CHD events during a 5-year period of follow-up in conjunction with an increase in HDL-C, a decrease in triglycerides, and no change in LDL-C levels. We now show that in VA-HIT the reduction in nonfatal MI and CHD death was strongly correlated with treatment concentrations of HDL-C but not triglycerides or LDL-C. In multivariable analysis, adjusting for the CHD risk factors of diabetes, hypertension, smoking, age, and body mass index, the only major lipid to predict a significant reduction in CHD events was HDL-C.

A notable finding of VA-HIT was that with multivariable analysis, neither baseline nor treatment triglyceride levels predicted CHD events (Table 3). A similar conclusion was reported in the Helsinki Heart Study, which found equally profound reductions in triglycerides with gemfibrozil as in VA-HIT (on the order of 30%) but no independent benefit of triglyceride reduction. Furthermore, even as a single lipid variable, VA-HIT triglyceride concentrations during treatment were not significantly related to the occurrence of a coronary event (Table 2).

Contrary to these trial results, we did find that baseline triglycerides as a single

![Figure 3. Relation of the 5-Year Incidence of CHD Events to HDL-C, Triglyceride, and LDL-C Values Achieved With Placebo or Gemfibrozil](image)

Incidence rates were obtained from Kaplan-Meier survival curves for each quintile of values. The median event rates with interquartile ranges are plotted for the quintiles of the average of lipid values at 4 through 18-month follow-up. To obtain near-even numbers of subjects in each quintile, the placebo and gemfibrozil groups were separately subdivided. The relation of the incidence of coronary heart disease (CHD) events to trial values of high-density lipoprotein cholesterol (HDL-C), triglycerides, and low-density lipoprotein cholesterol (LDL-C) is shown by best-fit curves. To convert mg/dL to mmol/L, multiply HDL-C and LDL-C values by 0.02586 and triglycerides by 0.01127.

### Table 2. Plasma Lipids and Apolipoproteins as Predictors of Nonfatal MI and CHD Mortality*

<table>
<thead>
<tr>
<th>Variable (Change)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C (5.0 mg/dL)</td>
<td>0.91 (0.83-0.99)</td>
<td>.047</td>
</tr>
<tr>
<td>Triglycerides (50 mg/dL)</td>
<td>1.07 (1.01-1.15)</td>
<td>.045</td>
</tr>
<tr>
<td>LDL-C (25 mg/dL)</td>
<td>1.07 (0.96-1.19)</td>
<td>.22</td>
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<tr>
<td>Apolipoprotein B (10 mg/dL)</td>
<td>1.06 (1.01-1.11)</td>
<td>.01</td>
</tr>
<tr>
<td>Apolipoprotein A-I (10 mg/dL)</td>
<td>0.92 (0.86-0.98)</td>
<td>.01</td>
</tr>
<tr>
<td>HDL-C (2.0 mg/dL)</td>
<td>0.99 (0.91-1.08)</td>
<td>.70</td>
</tr>
<tr>
<td>LDL-C (5.0 mg/dL)</td>
<td>0.80 (0.71-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C (5.0 mg/dL)</td>
<td>1.09 (0.81-1.07)</td>
<td>.01</td>
</tr>
<tr>
<td>Triglycerides (50 mg/dL)</td>
<td>1.05 (0.98-1.14)</td>
<td>.16</td>
</tr>
<tr>
<td>LDL-C (25 mg/dL)</td>
<td>1.07 (0.96-1.20)</td>
<td>.19</td>
</tr>
<tr>
<td>Apolipoprotein B (10 mg/dL)</td>
<td>1.04 (0.99-1.10)</td>
<td>.15</td>
</tr>
<tr>
<td>Apolipoprotein A-I (10 mg/dL)</td>
<td>0.95 (0.89-1.01)</td>
<td>.07</td>
</tr>
<tr>
<td>HDL-C (2.0 mg/dL)</td>
<td>0.99 (0.90-1.09)</td>
<td>.84†</td>
</tr>
<tr>
<td>LDL-C (5.0 mg/dL)</td>
<td>0.92 (0.84-1.01)</td>
<td>.07</td>
</tr>
</tbody>
</table>

*MI indicates myocardial infarction; CHD, coronary heart disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Individual lipid and apolipoprotein relative risk values were adjusted for treatment and CHD risk factors of age, smoking, diabetes, hypertension, and body mass index. Trial lipid values are the average of values at 4, 7, 12, and 18 months of follow-up or to the time of an index end point; apolipoprotein and HDL-C subfractions are values at the 12-month visit. To convert HDL-C and its subfractions and LDL-C to mmol/L, multiply by 0.02586. To convert triglycerides to mmol/L, multiply by 0.01127.

†The interaction between treatment group and HDL2-C was significant (P = .02).

### Table 3. Major Plasma Lipids as Multivariable Predictors of Nonfatal MI and CHD Mortality*

<table>
<thead>
<tr>
<th>Variable (Change)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C (5.0 mg/dL)</td>
<td>0.93 (0.85-1.02)</td>
<td>.13</td>
</tr>
<tr>
<td>Triglycerides (50 mg/dL)</td>
<td>1.06 (0.99-1.14)</td>
<td>.11</td>
</tr>
<tr>
<td>LDL-C (25 mg/dL)</td>
<td>1.06 (0.96-1.17)</td>
<td>.26</td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C (5.0 mg/dL)</td>
<td>0.89 (0.81-0.97)</td>
<td>.01</td>
</tr>
<tr>
<td>Triglycerides (50 mg/dL)</td>
<td>1.08 (0.98-1.18)</td>
<td>.16</td>
</tr>
<tr>
<td>LDL-C (25 mg/dL)</td>
<td>1.07 (0.96-1.20)</td>
<td>.19</td>
</tr>
</tbody>
</table>

*MI indicates myocardial infarction; CHD, coronary heart disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Individual lipid and apolipoprotein relative risk values were adjusted for treatment and CHD risk factors of age, smoking, diabetes, hypertension, and body mass index. Trial lipid values are the average of values at 4, 7, 12, and 18 months of follow-up or to the time of an index end point. To convert HDL-C and its subfractions and LDL-C to mmol/L, multiply by 0.02586. To convert triglycerides to mmol/L, multiply by 0.01127.
l lipid variable had a significant relationship to the development of CHD events (Table 2) and that the event rate was highest at the highest tertile level of triglycerides at baseline (Figure 2). Moreover, at this highest tertile level of baseline triglycerides, gemfibrozil resulted in a significant reduction in CHD events (RR reduction of 28%). This observation is consistent with the Bezafibrate Infarction Prevention Study28 that, like VA-HIT, found a higher event rate and also a significant benefit of fibrate therapy in the subgroup of patients with the highest baseline values of triglycerides.

In VA-HIT we found that the subfraction HDL$_2$-C, but not HDL$_3$-C, at baseline and as a percentage change with therapy was significantly related to the development of new CHD events. Fibrates selectively increase HDL$_3$ and the subfraction of HDL that is smaller and relatively poorer in free cholesterol than HDL$_2$ and, consequently, more likely to initiate free cholesterol efflux from peripheral tissue sites than HDL$_2$ in the process of reverse cholesterol transport.29,30 Although HDL$_3$-C and total HDL-C are strongly correlated, 4 angiographic intervention trials have shown HDL$_3$-C to be a better predictor of coronary lesion progression than total HDL-C.31-33 Those results coincide with our finding in VA-HIT that baseline concentrations of HDL$_3$-C were more strongly related to a CHD event than total HDL-C (Table 2).

We designed VA-HIT to exclude patients with a high concentration of LDL-C. With gemfibrozil, concentrations of LDL-C were not changed compared with placebo nor were CHD events significantly related to baseline or trial LDL-C concentrations. Moreover, concentrations of apoB, the component of LDL that has been found to be strongly correlated with a reduction in CHD risk when LDL-C is decreased with therapy,34 had no significant relation to the development of a CHD event.

The absence of any discernible effect on LDL-C concentrations distinguishes VA-HIT from previous lipid intervention trials that have demonstrated a reduction in CHD end points or improvement in angiographic end points with drug therapy. In other trials in which changes in HDL-C (or a major subfraction of HDL) could be statistically shown to contribute to a reduction in CHD or angiographic events, subjects have had higher than desirable LDL-C (or higher total cholesterol) at entry and/or reductions in LDL-C (or total cholesterol) with drug therapy that clearly played a part in CHD event reduction. These include the Helsinki Heart Study,17 the only other large clinical end point trial that has shown a significant benefit of increasing HDL-C, AFCAPS/TexCAPS,35 which showed a significant benefit of increasing apoA-I, and a number of trials in which drug therapy improved angiographic end points.36-40,44-46

Our analyses have several potential limitations. First, our trial was confined to men with CHD and a lipid profile of those excluded those with either a high LDL-C (> 140 mg/dL [3.6 mmol/L]) or a high level of triglycerides (> 300 mg/dL [3.4 mmol/L]). We have previously justified our exclusion of women on the basis of finding relatively few women with CHD and low HDL-C levels in the VA health care system when this trial was begun.24 We also have justified our exclusion of persons with a high LDL-C level to avoid the possibility that these individuals might be treated with another active drug to lower those levels. Our exclusion of persons with high triglyceride levels was based on the relative infrequency of triglycerides higher than 300 mg/dL in a survey that we conducted of 8000 men with known CHD,9 in which only 12.8% had triglycerides higher than 300 mg/dL and only 4.1% had triglycerides higher than 300 mg/dL together with a low level of LDL-C.

We believe that our analyses have many strengths that prominently include our exclusive use of the primary adjudicated end point of this trial, the combined incidence of nonfatal MI and CHD death, to define a new CHD event and our adherence to analyses by intention-to-treat, which preserved our strict randomization scheme.

An important practical issue relates to the extent to which the results of VA-HIT can be extrapolated to other kinds of therapy that also have the property of increasing HDL-C levels. For example, would statins, niacin, or certain lifestyle changes such as weight loss, which also increase HDL-C, be anticipated to have the same beneficial effect as gemfibrozil in the clinical context of VA-HIT? The data we have presented would strongly argue that it is not possible to assume that based on only an HDL-C response, a clinical outcome comparable to VA-HIT could be achieved with another kind of therapy. First, we have shown that at the same trial levels of HDL-C and in a relatively low range of HDL-C, there were fewer CHD events with gemfibrozil than with placebo. Second, we have shown that trial lipid levels as variables in a multivariable model can explain only 23% of the favorable effect of gemfibrozil. Although the results of VA-HIT clearly show that clinical benefit is correlated with higher values of HDL-C, fibrates produce a variety of other potentially favorable metabolic changes mediated in part through the activation of peroxisome proliferator–activated receptors.23

In summary, VA-HIT, which was conducted with the fibric acid derivative gemfibrozil, is the first lipid intervention trial to show that raising HDL-C concentrations in persons with established CHD and both a low HDL-C and a low LDL-C level will significantly reduce the incidence of major coronary events. We have demonstrated that a reduction in new coronary events is at least partly dependent on the concentration of HDL-C achieved with gemfibrozil and that the benefit of this therapy is independent of changes in the concentration of triglycerides or LDL-C.
Los Angeles, Calif (Dr Hershan). Cincinnati, Ohio (Dr Wexler) and Minneapolis, Minn (Dr Rubins).

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