Several large intervention trials have investigated the potential of fibrates to reduce cardiovascular events. The results have varied widely: positive, with gemfibrozil in the primary prevention Helsinki Heart Study (HHS)\(^1\) and the secondary prevention Veterans Administration High Density Lipoprotein Intervention Trial (VA-HIT)\(^2\); positive, with reservations related to an increase in noncardiovascular mortality in the primary prevention World Health Organization trial (clofibrate)\(^3\); and mixed, with bezafibrate in the secondary prevention Bezafibrate Infarction Prevention (BIP) study\(^4\) and with fenofibrate in the combined primary and secondary prevention FIELD study,\(^5\) in which positive outcomes were observed only in certain subgroups. Reasons for the differences between the outcomes of these studies are not immediately apparent.

The observation that the cardioprotective effects of gemfibrozil in the HHS and VA-HIT studies were substantially greater than those found with other fibrates in the World Health Organization, BIP, and FIELD studies may reflect no paradoxical, in view of the fact that the cardiovascular disease (CHD) events attributable to changes in each of the lipids. In an analysis of the HHS, Cox proportional-hazards models were used to estimate the reduction in coronary heart disease (CHD) events attributable to changes in each of the lipid parameters.\(^11\) It was concluded that both the increase in concentration of HDL-C and the decrease in concentration of LDL-C during treatment with gemfibrozil were predictive of benefit. An 8% increase in HDL-C predicted a CHD risk reduction of 23% (P<0.01), whereas a 7% reduction in LDL-C predicted a 15% reduction in CHD events (P<0.04).

The precise mechanism by which gemfibrozil confers its cardioprotection is uncertain and cannot be explained completely in terms of changes in the concentrations of plasma lipids. In an analysis of the HHS, Cox proportional-hazards models were used to estimate the reduction in coronary heart disease (CHD) events attributable to changes in each of the lipid parameters.\(^11\) It was concluded that both the increase in concentration of HDL-C and the decrease in concentration of LDL-C during treatment with gemfibrozil were predictive of benefit. An 8% increase in HDL-C predicted a CHD risk reduction of 23% (P<0.01), whereas a 7% reduction in LDL-C predicted a 15% reduction in CHD events (P<0.04).

In contrast, the large decrease in concentration of serum triglycerides during gemfibrozil treatment in this trial had a relatively small and statistically nonsignificant effect on the rate of CHD events.

The apparent benefits attributable to the increase in HDL-C in the HHS were substantially greater than predicted from population studies in which a 1% increment in HDL-C was equated with an ~1% lower cardiovascular risk.\(^12\) This raised the possibility that gemfibrozil may have cardioprotective properties beyond those predicted by changes in plasma lipid concentration. A similar conclusion has been drawn from analyses of VA-HIT.\(^13\)
In VA-HIT, the baseline concentrations of HDL-C, plasma triglycerides, apolipoprotein (apo) B, apo A-I, and HDL₃-C (but not LDL-C or HDL₂-C) were all significant predictors of CHD events that occurred during the trial. However, in terms of lipid levels during the trial (as distinct from those measured at baseline) and changes in lipid levels from baseline, the only parameter that predicted benefit was the on-treatment concentration of HDL-C. However, even this was able to account for only \( \approx 20\% \) of the event reduction attributable to treatment with gemfibrozil, again supporting a suggestion that gemfibrozil may have cardioprotective properties beyond those explained by its effects on the concentrations of plasma lipids.

The question therefore arises: What is the mechanism of this apparent lipid-independent cardioprotective effect of gemfibrozil in the HHS and VA-HIT studies? This issue has been addressed in a new analysis of VA-HIT reported in the current issue of Circulation.

Otvos et al\(^\text{14}\) describe a nested case-control study from VA-HIT involving 364 cases with a coronary event and 697 age-matched controls. A nuclear magnetic resonance (NMR) technique was used to estimate the size distributions and the particle concentrations of the LDL and HDL fractions. These measures were then related to the risk of having a CHD event. Estimates based on the NMR technique suggested that treatment with gemfibrozil decreased the concentration of small LDL particles and increased that of large LDL particles, with an overall decrease in total LDL particle concentration. Treatment had no effect on HDL particle size (small HDL particles predominated at baseline and in both the active and placebo groups during the trial) but did increase HDL particle concentration, as determined by NMR. The total particle concentration of LDL (positively) and HDL (negatively) and also the particle concentration of small HDL (negatively) both at baseline and on trial were all independently predictive of CHD events that occurred during the trial. In contrast, LDL and HDL particle sizes were unrelated to events. The authors concluded: "The effects of gemfibrozil on NMR-measured LDL and HDL particle subclasses, which are not reflected by conventional lipoprotein cholesterol measures, help explain the demonstrated benefit of this therapy in patients with low HDL cholesterol."

This is an interesting conclusion, although it should be interpreted with caution for several reasons. For example, the magnitude of the gemfibrozil-induced reduction in LDL particle concentration as measured by NMR was of the same order as the reduction in apo B, as would be predicted from the fact that apo B is well documented as a measure of LDL particle concentration. However, in contrast to the results from NMR, the concentration of apo B in this analysis did not predict events. The question arises: Why was the NMR-generated value of LDL particle concentration so highly predictive of events, whereas that of apo B was not? The authors explain this anomaly by suggesting poor precision in the measurement of apo B. If true, this is rather disturbing. There would have been a much greater confidence in this new analysis if the relation of CHD events with NMR-generated LDL particle concentration had been at least similar to the relation of events with the concentration of apo B.

Another note of caution concerns the apparent relation between CHD events and the NMR-estimated HDL particle concentration. Given that there was no evidence in this study that gemfibrozil changed HDL particle concentration, it follows that the concentration of HDL-C should closely match that of HDL particle concentration. The question therefore arises: Why was the predictive power of HDL particle concentration (as measured by NMR) so much greater than that of HDL-C? There is no obvious answer to this, beyond casting doubt on the validity of the measurement of either HDL-C or HDL particle concentration by the NMR technique.

The relations between CHD events and the NMR-generated particle concentrations of HDL and LDL in VA-HIT are presented by Otvos et al\(^\text{14}\) in terms of the change in relative risk associated with a 1–standard deviation increment in each of the variables. These numbers do not provide any sense of how much the changes in LDL and HDL particle concentration may have contributed to the benefits associated with gemfibrozil therapy in this trial. It is possible (and perhaps likely) that HDL and LDL particle concentrations do predict events, but as was the case with HDL-C in the earlier publication, changes in lipoprotein particle concentrations may account for only a fraction of the observed benefits derived from treatment with gemfibrozil. It should also be noted that this new analysis suggesting a relation between lipoprotein particle concentration and CHD risk does not explain why people with diabetes, insulin resistance, obesity, or dyslipidemia derive a disproportionately large benefit from treatment with gemfibrozil, as was observed in both VA-HIT\(^\text{7}\) and the HHS.\(^\text{6}\) It would have been interesting to discover whether the NMR-derived changes in LDL and HDL particle concentrations in VA-HIT were greater in the subgroups (those with diabetes or with features of the metabolic syndrome) that derived the greatest event reduction during treatment with gemfibrozil.

So, what does this new analysis of VA-HIT tell us? It does provide evidence that LDL and HDL particle concentrations (as measured by NMR) are predictive of cardiovascular risk. This is consistent with what has been reported previously with the much simpler measurements of LDL-C, HDL-C, and apo B. However, it does not establish that changes in lipoprotein particle concentration are the main mechanism by which gemfibrozil reduces cardiovascular risk. In fact, the precise mechanism by which gemfibrozil in particular and fibrates in general reduce cardiovascular risk continues to be a major challenge for future research.

However, regardless of mechanism, it is a proven fact that gemfibrozil (and possibly also bezafibrate) is extremely effective in reducing cardiovascular risk in people with features of the metabolic syndrome. This robust and consistent finding should remain a powerful stimulus for conducting research designed to understand the true mechanism. Such understanding will provide the rationale for continuing the investigation of PPAR-\(\alpha\) activation as a strategy for reducing cardiovascular risk in people with insulin resistance or other features of the metabolic syndrome. Such research should not be derailed by the unexpected results of the recently reported FIELD trial that may conceivably have
reflected issues with fenofibrate that are not necessarily shared by other PPAR-\(\alpha\) agonists.

**Disclosures**

None.

**References**


Cardioprotective Properties of Fibrates: Which Fibrate, Which Patients, What Mechanism?
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