Hotline Editorial

The VA HDL Intervention Trial: clinical implications

Clinical trials have clearly shown that low density lipoprotein (LDL)-cholesterol lowering reduces coronary heart disease morbidity and mortality in patients with established coronary heart disease and LDL-cholesterol above 3·4 mmol . l$^{-1}$. However, about 40% of coronary heart disease patients do not have elevated levels of LDL-cholesterol and many of them have low levels of high density lipoprotein (HDL) cholesterol as their primary lipid abnormality. Overall, about 25% of patients with coronary heart disease have low HDL-cholesterol in the absence of elevated LDL-cholesterol. Low HDL-cholesterol, even in the absence of elevated total LDL-cholesterol, has been shown to be an important risk factor for the development of new or recurrent coronary heart disease events in observational epidemiological studies. However, there have been no clinical trial data to guide therapeutic decisions in these patients. Therefore, we initiated the VA (Veterans Affairs) HDL Intervention Trial (VA-HIT) in order to determine whether coronary heart disease patients whose primary lipid abnormality is a low level of HDL-cholesterol benefit from lipid therapy designed primarily to raise their HDL-cholesterol.

VA-HIT: design and major results

VA-HIT was a randomized controlled clinical trial conducted in 20 VA medical centres throughout the United States. Men with established coronary heart disease with low levels of HDL-cholesterol ($\leq$1·03 mmol . l$^{-1}$) and low levels of LDL-cholesterol ($\leq$3·6 mmol . l$^{-1}$) were eligible to enter the trial unless they had a serious underlying illness expected to limit their life expectancy within 5 years. Patients were assigned to receive either gemfibrozil 1200 mg . day$^{-1}$ or matching placebo and were followed for an average of 5 years. The primary end-point was the combined incidence of non-fatal myocardial infarction and coronary heart disease death. At baseline, the 2531 enrolled patients tended to be elderly (mean age 64 years), overweight (mean body mass index 29 kg . m$^{-2}$), and to have a high prevalence of hypertension (57%) and diabetes (25%). Sixty-one percent had a history of myocardial infarction, 82% were on aspirin and 43% were taking a beta-blocker. The mean LDL-cholesterol was 2·87 mmol . l$^{-1}$ and the mean HDL-cholesterol was 0·83 mmol . l$^{-1}$.

As compared with those on placebo, patients assigned gemfibrozil had no change in their LDL-cholesterol during the study, whereas HDL-cholesterol was increased by 6% and triglycerides were reduced by 31%. For the primary outcome of coronary heart disease death and non-fatal myocardial infarction, gemfibrozil resulted in a 22% relative risk reduction (95% confidence interval 7 to 35, $P=0·006$) or a 4·4% absolute risk reduction. Strokes, transient ischaemic attacks, carotid endarterectomy and hospitalization for congestive heart failure were significantly reduced in those assigned gemfibrozil (relative risk reductions of 29%, 59%, 65%, and 22%, respectively). There were also fewer coronary revascularization and peripheral vascular procedures, although these differences were not statistically significant. The rate of hospitalization for unstable angina did not differ between the two treatment groups. Patients tolerated gemfibrozil well and were no more likely to discontinue medication by the end of the study than patients assigned placebo. All-cause mortality and incidence of cancer were slightly lower in patients assigned gemfibrozil (220 and 198 deaths and 138 and 125 incident cancers, in placebo and gemfibrozil groups respectively).

Summary of VA-HIT

The uniqueness of this trial lies in the population studied and the lipid effects of the intervention. VA-HIT is the first major clinical trial to examine the benefits of lipid therapy in patients whose primary lipid abnormality is a low level of HDL-cholesterol and the first trial to show that raising HDL-cholesterol and lowering triglycerides, in the absence...
of LDL-cholesterol lowering, results in clinical benefit. The 22% reduction in non-fatal myocardial infarction and coronary heart disease death observed in VA-HIT is comparable to the 23 to 24% reduction seen in statin trials in coronary heart disease patients with moderate levels of LDL-cholesterol [6,7]. Similarly, the 29% reduction in investigator-designated stroke is comparable to the 30% stroke reduction reported in recent statin trials [6].

Metabolic syndrome in VA-HIT

The patients in this trial had a high prevalence of features of the metabolic syndrome, a cluster of abnormalities including low HDL-cholesterol, high triglycerides, and small dense LDL particles; insulin resistance, glucose intolerance or diabetes; hypertension; and obesity [8]. This syndrome, which has also been called the insulin resistance syndrome is considered by some to rival hypercholesterolemia in atherogenic potential [9]. Over 80% of VA-HIT patients had two or more features of this syndrome and over 50% had three or more. Subgroup analyses from the Helsinki Heart Study, a primary prevention trial in men with high levels of LDL-cholesterol, showed that the treatment effect of gemfibrozil was largely confined to patients who were overweight and had low HDL-cholesterol and high triglycerides [10]. This subgroup analysis and the results of VA-HIT suggest that patients with features of the metabolic syndrome may be particularly likely to benefit from gemfibrozil.

Mechanisms

Gemfibrozil is known to have several effects on lipid metabolism and on the coagulation system [11,12]. Gemfibrozil increases plasma HDL by two major mechanisms. First, it activates lipolysis which not only results in the formation of smaller triglyceride-rich lipoprotein particles, but also results in the generation of an excess of apoproteins and lipids which are used to form new HDL. Activation of lipolysis leads to a reduction of fasting and postprandial triglyceride levels, which, in turn, are accompanied by a reduction in the fraction of small, dense, highly oxidizable LDL particles. Second, gemfibrozil directly increases the hepatic synthesis of the major protein constituents of the HDL particle, apoA-I and apoA-II. Although some fibrates reduce fibrinogen, gemfibrozil does not. However, gemfibrozil has been reported to decrease clotting factor VII, prothrombin fragment F1+2, and platelet activity as well as plasminogen activator inhibitor-1, an inhibitor of fibrinolysis. There are thus many potential mechanisms by which gemfibrozil might improve the atherothrombotic process, and it is impossible to definitively ascribe the favourable clinical effect observed in VA-HIT to one or more putative mechanisms. Nevertheless, preliminary analyses from VA-HIT that examined the major lipid parameters, suggest that an increase in HDL-cholesterol level is the predominant predictor of clinical benefit.

Extrapolation to other interventions

It is tempting to speculate that interventions that have a more potent effect on HDL-cholesterol might be even more effective than gemfibrozil at reducing major coronary events in patients whose primary lipid abnormality is a low level of HDL-cholesterol. Niacin, for example, is known to raise HDL-cholesterol by 15 to 30% [13]. However, we do not believe that there is sufficient clinical trial data at the present time to support the conclusion that raising HDL-cholesterol, by whatever means, will lower clinical event rates. This kind of generic conclusion, now established for blood pressure reduction and lowering elevated levels of LDL-cholesterol, is generally reached only after many clinical trials conducted in multiple populations with a variety of interventions yielding consistent conclusions.

Gemfibrozil vs statins

VA-HIT enrolled a population of coronary heart disease patients chosen specifically for low levels of HDL-cholesterol and low levels of LDL-cholesterol. Although the average LDL-cholesterol in this study (2.87 mmol.1⁻¹) was substantially lower than in any other primary or secondary prevention trial reported to date, the average LDL-cholesterol was still higher than 2.59 mmol .1⁻¹, the target LDL-cholesterol level for coronary heart disease patients according to some expert groups [15]. This raises the question of whether coronary heart disease patients with LDL-cholesterol levels between 2.59 and 3.36 mmol.1⁻¹, who clearly benefited from treatment in VA-HIT, should receive gemfibrozil or, instead, should be treated with a statin to lower their LDL-cholesterol to less than 2.59 mmol.1⁻¹. The answer to this question hinges on the strength of the evidence that statins reduce coronary events in patients who present with an initial LDL-cholesterol less than 3.6 mmol.1⁻¹. There are no clinical trial data that specifically address this question. However, subgroup
analyses from two large scale secondary prevention trials of pravastatin that enrolled patients with a broad range of LDL-cholesterol do not support the benefits of statins in this population.

In the Cholesterol and Recurrent Events (CARE) study, the relative risk reduction associated with pravastatin use in the 825 patients with LDL-cholesterol <3.23 mmol . l⁻¹ at baseline, was minus 3% (95% confidence interval, −38% to 23%). In other words, patients assigned pravastatin had a non-significant 3% increase in coronary events relative to placebo⁶. Among 2637 patients with initial LDL-cholesterol <3.49 mmol . l⁻¹ enrolled in the Long Term Intervention with Pravastatin in Ischemic Disease study (LIPID), pravastatin was associated with a non-significant 16% relative risk reduction (95% confidence interval, −4% to 32%)⁷. Thus these subgroup analyses suggest that statins are not beneficial in patients with initial LDL-cholesterol of <3.36 mmol . l⁻¹. Future clinical trials, such as the British Heart Protection Study, will likely provide definitive information on this point.

Conclusions

As the first major clinical trial to demonstrate that lipid therapy targeting HDL-cholesterol and triglycerides benefits coronary heart disease patients whose primary lipid abnormality is a low level of HDL-cholesterol, VA-HIT has introduced new possibilities for the secondary prevention of coronary heart disease that extend beyond the established benefits of lowering elevated levels of LDL-cholesterol. This trial also suggests that fibrates may be effective agents for the secondary prevention of coronary heart disease in patients with the metabolic syndrome who do not have high-risk LDL-cholesterol.

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References