

Commentary

The usefulness of information on HDL-cholesterol: potential pitfalls of conventional assumptions

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Abstract

Treatment decisions related to disease prevention are often based on two conventional and related assumptions. First, an intervention-induced change in a surrogate marker (such as high-density lipoprotein [HDL]-cholesterol) in the desired direction translates into health benefits (such as reduction in coronary events). Second, it is unimportant which interventions are used to alter surrogate markers, since an intervention benefit is independent of the means by which it is achieved. The scientific foundation for these assumptions has been questioned. In this commentary, the appropriateness of relying on low levels of HDL-cholesterol for treatment decisions is reviewed. The Veterans Affairs – HDL-Cholesterol Intervention Trial (VA-HIT) investigators recently reported that only 23% of the gemfibrozil-induced relative reduction in risk of coronary events observed in the trial could be explained by changes in HDL-cholesterol between baseline and the 1-year visit. Thus, 77% of the health benefit to the participants was unexplained. Other possible explanations are that gemfibrozil has multiple mechanisms of action, disease manifestations are multifactorial, and laboratory measurements of HDL-cholesterol are imprecise. The wisdom of relying on levels and changes in surrogate markers such as HDL-cholesterol to make decisions about treatment choices should be questioned. It seems better to rely on direct evidence of health benefits and to prescribe specific interventions that have been shown to reduce mortality and morbidity. Since extrapolations based on surrogate markers may not be in patients' best interest, the practice of medicine ought to be evidence-based.

Keywords clinical trials, coronary heart disease, fibrates, HDL-cholesterol, surrogate markers

Many of the reasonable conclusions and recommendations in Gerald Watts' review of how to treat patients with low levels of high-density lipoprotein (HDL)-cholesterol [1] are based on two conventional and related assumptions. First, an intervention-induced change of a surrogate marker (such as HDL-cholesterol) in the desired direction translates into health benefits (such as reduction in coronary events). Second, it is unimportant which interventions are used to alter surrogate markers, since an intervention benefit is independent of the means by which it is achieved. It seems appropriate to revisit the scientific bases for these common assumptions. Although Watt's review occasioned the following comments, they have broader public health implications.

The investigators of the Veterans Affairs – HDL-Cholesterol Intervention Trial (VA-HIT) [2] were interested in knowing how much of the 22% relative reduction in the risk of the combined incidence of nonfatal myocardial infarction and coronary death could be explained by the individual increases in the surrogate marker, HDL-cholesterol. The investigators included, in a regression analysis, the individual changes in HDL-cholesterol between the baseline and the 1-year visits and the treatment category (gemfibrozil or placebo), and assessed their associations with new coronary events occurring after the 1-year visit. The relative risk of a major coronary event beyond 1 year was 0.78 (95% confidence interval, 0.66–0.94) before and 0.83 (95% confidence interval, 0.68–1.02) after the

adjustment for individual HDL-cholesterol changes. This means that only 23% of the relative reduction in risk of coronary events (relative risk from 0.78 to 0.83) in VA-HIT can be explained by the individual 1-year changes in HDL-cholesterol. In other words, 77% of the benefit of gemfibrozil was unexplained and may be attributable to other mechanisms that are presumably unrelated to HDL-cholesterol. This observation comes as no surprise because drugs have multiple mechanisms of action and disease manifestations are multifactorial.

Several factors could have contributed to the low predictive value of HDL-cholesterol change between baseline and 1 year. The first factor is the variability in the laboratory method for determining HDL-cholesterol. The biologic variability that could have been reduced by averaging measurement over multiple visits is a second factor and, finally, the impact of VA-HIT participants on the gemfibrozil group (who stopped taking the study medication after the 1-year visit) would most probably have lowered the predictive value. If these factors had been adjusted, and the adjustment improved the predictability by 50%, the prediction of the benefit of gemfibrozil in VA-HIT would increase from 23 to 35%. Approximately two-thirds of benefit would, however, still be unexplained. This raises questions about the role of modification of the surrogate marker HDL-cholesterol in prevention of coronary events. In the context of VA-HIT, it appears that information on the change in HDL-cholesterol between baseline and 1 year is only moderately useful as a predictor of coronary events.

Other studies also provide arguments against the HDL-cholesterol hypothesis. Watts contrasts findings from VA-HIT with the Bezafibrate Infarction Prevention (BIP) trial (see Table 1 in [1]). It is puzzling that, despite a threefold greater increase in mean HDL-cholesterol in BIP (+18% in BIP versus +6% in VA-HIT), the reduction in risk of coronary events was about 2.5 times smaller than VA-HIT (-9% in BIP versus -22% in VA-HIT). This observation is not a strong endorsement of the usefulness of HDL-cholesterol in predicting health benefits. One possible explanation of this observation is that gemfibrozil and bezafibrate differ substantially in their non-HDL-cholesterol-mediated mechanism(s) of action. Play of chance and differences in study design and populations could obviously also have contributed to the observed trial differences.

In the Heart and Estrogen/Progestin Replacement Study (HERS), hormone treatment raised HDL-cholesterol by a net 10% compared with placebo [3]. This presumably favorable surrogate effect did not translate into a reduction in major coronary events. Focusing on one intervention effect (the increase in HDL-cholesterol levels) ignores the many other known and unknown actions of hormones, which in HERS appeared to offset any expected benefit attributed to the increase in HDL-cholesterol.

The HERS experience is one more reminder of the limitation of assuming that change in a surrogate marker directly translates into health benefits. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) provided a similar reminder [4]. In spite of a similar drug effect on the surrogate marker blood pressure in the chlorthalidone and doxazosin groups, the risk of cardiovascular events was 25% higher in the latter group. Moreover, the presumed favorable effects of doxazosin on lipids (including a small increase in mean HDL-cholesterol) conveyed no observed benefit on risk of coronary events. The effect of doxazosin on HDL-cholesterol (and low-density lipoprotein-cholesterol) levels, which is very small, seems to be unimportant from a point of view of patient health.

These setbacks to the HDL-cholesterol hypothesis have several potential implications. Clinically, we should recognize that the predictive value of increases in HDL-cholesterol may exist but that the predictability of an agent may depend on the type of treatment and its effects on HDL metabolism, rather than the magnitude of its effect on plasma concentrations of HDL-cholesterol [5,6]. The overall value of clinical monitoring of HDL-cholesterol needs to be considered in the proper perspective. The favorable health effect of gemfibrozil that is attributed primarily to its non-HDL-cholesterol-mediated mechanisms may not be a class effect of fibrates. Treatment guidelines that promote any intervention that raises HDL-cholesterol appear to rest on a soft foundation and would benefit from better scientific evidence. Sound lifestyle modifications are always advisable. A new major scientific challenge is to identify the non-HDL-cholesterol mechanisms of action that contribute to the significant clinical benefits of gemfibrozil. From a regulatory viewpoint, approving drugs based on their actions on surrogate markers (such as HDL-cholesterol) ought to be curtailed [7].

Assessing scientific evidence involves a major component of judgment. It is, in my view, better to rely on scientific evidence and avoid basing decisions on surrogate markers.

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