Secondary Prevention of Coronary Heart Disease
The Role of Fibric Acids
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A reduction in low-density lipoprotein (LDL) cholesterol lowers coronary heart disease (CHD) by 24% to 31% in subjects with prevalent CHD; this reduction occurs with the use of several statins, including simvastatin and pravastatin. Additional reductions in CHD could come from further reductions in LDL cholesterol, as was suggested by the Post Coronary Artery Bypass Graft clinical trial (POST CABG). An alternative approach is to attempt to reduce triglyceride levels and to raise levels of high-density lipoprotein (HDL) cholesterol.

The role of triglyceride levels in relation to CHD and the possible use of fibric acids in the reduction of CHD are controversial. Although initial meta-analyses challenged the possible independent role of triglycerides in relation to CHD, one recent carefully performed meta-analyses supported triglyceride levels as an independent predictor of CHD. Another potential issue is that the atherogenicity of elevated triglycerides may vary. Brunzell et al reported that subjects with familial hypertriglyceridemia are at a reduced risk for CHD than subjects with familial combined hyperlipidemia. In the Mevacor Atherosclerosis Regression Study (MARS), subjects with elevated levels of triglycerides rich in apoCIII had a very rapid progression of atherosclerosis. The misclassification of key variables, such as triglyceride levels, reduces the significance of relations in longitudinal studies, and it may also affect clinical trials by allowing the inclusion of subjects with, for example, elevated triglyceride levels but a low risk of CHD. The direct measurement of apoB may improve the selection of patients in clinical trials.

The use of fibric acids in the treatment of CHD has been controversial, both because of questions of safety and because of questions of efficacy. In a World Health Organization (WHO) study, clofibrate therapy was associated with a significant reduction in major coronary events; however, the overall mortality was higher in the clofibrate group, principally because of an increase in noncardiovascular mortality (especially gastrointestinal disorders). In the Helsinki Heart Study, gemfibrozil significantly reduced major coronary events by 34%; however, after the conclusion of the trial, a nonsignificant increase in overall mortality was observed. Both the WHO and Helsinki studies were primary prevention studies. As a result, the question of the safety of fibric acids has been raised.

In the past year, 2 important secondary prevention trials, the Veterans Affairs HDL Intervention Study (VAHIT) with gemfibrozil and the Bezafibrate Infarction Prevention (BIP) study have provided important new information on both the safety and efficacy of fibric acids in subjects with low HDL cholesterol and normal triglyceride levels. Both large studies showed no increase in overall or noncardiovascular mortality; thus, these studies provide strong data on the safety of fibric acids and lessen concerns (especially regarding gemfibrozil) raised by earlier studies.

The VAHIT and BIP studies provided different answers with respect to efficacy. In VAHIT, a 22% reduction occurred in major CHD (P=0.006), whereas in the BIP study (reported in this issue), there was a 9.4% reduction (P=0.26) that was restricted to nonfatal events. Both the VAHIT and BIP studies were large (2531 and 3090 subjects, respectively), had similar follow-up times (5.1 and 6.2 years, respectively), and had the same primary end point. The baseline levels of triglycerides (VAHIT versus BIP, 161 versus 147 mg/dL) and HDL cholesterol (VAHIT versus BIP, 32 versus 34.6 mg/dL) were very similar in both trials; however, LDL cholesterol levels were lower at baseline in the VAHIT study (111 versus 148 mg/dL). The lipid changes in the BIP study may have actually been more favorable (LDL, −6.5%; HDL, 18%; and triglycerides, −21%) than those in the VAHIT trial (LDL, 0%; HDL, 6%; and triglycerides, −31%). The proportion of diabetic subjects was higher in VAHIT than in BIP (25% versus 10%), but this is unlikely to affect results because the effectiveness of gemfibrozil in reducing CHD in VAHIT was identical in diabetic and nondiabetic subjects.

The dilemma is why the 2 studies had different results. One possible but relatively unpalatable answer (in large randomized trials) is chance. Although no confidence intervals are presented for the major primary end point in the BIP study, the 95% confidence intervals in the VAHIT study were 7% to 35%; thus, they include the percent reduction in CHD observed in the BIP study. A previous very small regression trial (n=81), the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT), showed a 73% reduction in CHD (P=0.049). However, such small studies would have relatively little effect on a meta-analysis compared with the much larger BIP study. A possible consequence of the higher LDL cholesterol in the BIP study is that more subjects received additional medications (resins) to reduce LDL cholesterol (15%...
in placebo and 11% in the bezafibrate group). The greater percentage of adjunct lipid-lowering in the placebo group might have reduced the relative effectiveness of bezafibrate, although the LDL level achieved during the trial remained lower in the bezafibrate group than in the control group throughout the trial. In contrast, only 1% to 2% of subjects in the VAHIT study received other lipid-lowering drugs. Finally, one can question whether gemfibrozil and bezafibrate have other effects not currently understood (do fibric acids actually form a “class”).

The next major end point trial with fibric acid that will be reported will be the Diabetic Atherosclerosis Intervention Study (DAIS). This study is a 3-year coronary angiography regression trial evaluating 200 mg of (micronized) fenofibrate in 418 patients with type 2 diabetes; the results will be presented at the International Atherosclerosis Society meeting in Stockholm in June 2000. The larger Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial involving 8000 diabetic subjects, including 2000 subjects with prevalent CHD, and evaluating fenofibrate and placebo for 5 years will be reported in 2005.

In summary, although it is uncertain why the effectiveness (but not the safety) differed between the VAHIT and BIP studies, the two most likely possibilities are chance (overlapping confidence intervals) or inherent differences in the agents. If the differences between VAHIT and BIP are due to chance, then we could conclude that fibric acids might produce an ≈16% reduction in CHD risk (which represents the mean reduction by combining data from both clinical trials); furthermore, both gemfibrozil and bezafibrate seem to be safe.

The BIP investigators suggest in a subgroup analysis that bezafibrate reduced the incidence of major CHD by 39.5% (P = 0.02). A number of caveats should be made, including that the inferences from subgroup analyses are always weaker than the primary analyses. An example of the controversy surrounding subgroup analyses can be seen in the issue of whether the relation between LDL cholesterol and CHD is linear in statin trials. First, a statistical test of heterogeneity should be performed to test whether the subgroups are significantly different (as was done in the Long-term Intervention with Pravastatin in Ischaemic Disease [LIPID] study). A second caveat is that the number of subjects with triglyceride levels ≥200 mg/dL was small (n = 459; 14.9%). Furthermore, in the VAHIT study, the effectiveness of gemfibrozil for CHD reduction was similar in subjects with triglyceride levels above and below 151 mg/dL (28% and 27%, respectively). The VAHIT investigators, in a preliminary communication presented at the 1999 American Heart Association Scientific Sessions, suggested that the benefit of gemfibrozil was due to a rise in HDL more than a fall in triglyceride levels, but this is difficult to assess without a full report. Nevertheless, a case can be made for concentrating on subjects with high triglyceride levels because in the Helsinki Heart Study subgroup analyses, gemfibrozil was particularly effective in subjects with high triglyceride levels; thus, a “prior” hypothesis exists.

In the LIPID trial, pravastatin showed a benefit in subjects with low HDL levels (24% reduction in CHD in subjects with HDL <39 mg/dL) and high triglyceride levels (24% reduction in CHD in subjects with triglycerides >239 mg/dL). Thus, it might be argued that even in patient types that are likely to benefit from fibric acids (high triglyceride and low HDL cholesterol levels), similar benefits may be seen with statins. The subjects in the LIPID trial and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)10 had baseline lipoprotein levels similar to those of subjects in the BIP study, and yet patients in the former studies had significant reductions in CHD (22% and 36%, respectively).

Given the complexity of the available fibric acid trials, what therapy recommendations might currently be made? For most CHD patients, statins will remain the initial drug of choice, although fibric acids may be useful in a subset of subjects. For subjects with LDL cholesterol ≥130 mg/dL and triglyceride levels <500 mg/dL, a statin should be the first choice. If LDL cholesterol is <130 mg/dL, a statin might be used after appropriate nutrition therapy if HDL levels are high (ie, ≥40 mg/dL). If LDL cholesterol is <130 mg/dL and HDL cholesterol is low (ie, <40 mg/dL), either a statin or fibric acid may be useful. The results of the BIP study suggest that perhaps a triglyceride level ≥200 mg/dL or perhaps ≥175 mg/dL might be suggested as an additional requirement for fibric acid use as well.

The more important issue is whether statins and fibric acids might be used in combination. Although there is a risk of myositis, many experts use this combination. Furthermore, a primary prevention trial in diabetic subjects (Lipids in Diabetes Study [LDS]) is currently testing this hypothesis in a 2 × 2 factorial design with 200 mg of (micronized) fenofibrate as one main effect and 0.4 mg of cerivastatin as the other main effect. A total of 5000 subjects will be followed for 5 years, and the trial is scheduled to end in 2005. Thus, this study will directly compare the effectiveness of a statin versus a fibric acid. Additionally, 1250 subjects will be on both a fibric acid and a statin. This trial, thus, provides an interesting alternative to the clinical trials in CHD patients testing whether more LDL lowering is better (Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine [SEARCH] and Treating to New Targets trial [TNT]).

In the next 5 to 7 years, we will know the results of both “more is better statin” trials (TNT and SEARCH) and the new generation of fibric acid trials (DAIS, FIELD and LDS). This new information will allow more precise recommendations for the treatment of dyslipidemia.

References


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