Low High-Density Lipoprotein Cholesterol and Response to Simvastatin Therapy in Scandinavian Simvastatin Survival Study (4S)

To the Editor:

Ballantyne et al. compared the coronary heart disease (CHD) event rate and the response to simvastatin therapy in a subgroup of approximately 500 individuals from the Scandinavian Simvastatin Survival Study (4S) study with “isolated increased LDL-C” with a similarly-sized subgroup that had not only an increased LDL cholesterol (LDL-C), but also the lowest levels of HDL cholesterol (HDL-C) and highest levels of triglycerides (“the lipid triad”) in 4S. The group with the lipid triad was found to have a higher CHD event rate and a greater reduction in CHD events with simvastatin therapy than those with an isolated increased LDL-C.

Those patients with isolated increased LDL-C were said to have “normal triglyceride and HDL-C levels.” Although individuals with isolated increased LDL-C did have highly favorable triglycerides with a mean (SD) of 80±12 mg/dL, this group had not only “normal” levels of LDL-C, but also a high enough HDL-C level at a mean of 63±11 mg/dL to have a “protective” effect from HDL-C. Indeed, in the GISSI-Prevenzione report of a European cohort followed for 4 years after myocardial infarction (which seems to be the only published predictive algorithm for secondary prevention to date), there was a relative 3% reduction of CHD death for each mg/dL increment of HDL-C that was greater than 55 mg/dL in men (with an even greater reduction of CHD death in women). With CHD, an HDL-C value greater than 55 mg/dL is distinctly unusual. In the GISSI report, which examined >11,000 men and women with CHD, only 11% of the men had HDL-C >55 mg/dL. To more fairly judge the contribution of a low HDL-C to the risk associated with a high LDL-C would require that a group with HDL-C in a range closer to the median range of HDL-C, with CHD of about 40 to 45 mg/dL, be compared with a lower HDL-C. It is possible that the risk and response to statin therapy in the 4S low HDL-C subgroup is so profoundly influenced by the high LDL-C (which is characteristic of the 4S patient population in general) that no differences would be apparent if a comparison were to be made between the 4S subgroup with a low HDL-C level and a HDL-C subgroup with an average HDL-C rather than a subgroup with an unusually high and protective level of HDL-C.

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Response

In response to Dr. Robins, we agree that the observations of markedly increased risk for coronary heart disease (CHD) events and response to simvastatin observed in the Scandinavian Simvastatin Survival Study (4S) may not be applicable to groups with average or low levels of LDL cholesterol (LDL-C). The levels of HDL cholesterol (HDL-C) observed in the highest quartile (>1.32 mmol/L [52 mg/dL]) are higher than are commonly seen in men with CHD: that is why women made up ~34% of this group. In the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI) Prevenzione study, 28% of the women had an HDL-C level >1.42 mmol/L (55 mg/dL). It is not clear that the results from GISSI-Prevenzione can be used to support the argument that the influence of HDL-C would be any different for men with average versus high HDL-C. Indeed, there was no significant difference in GISSI in relative risk for death among men with HDL-C of 1.06 to 1.42 mmol/L (41 to 55 mg/dL) versus >1.42 mmol/L (55 mg/dL) in the fully adjusted model, and therefore no difference in the risk points for men with HDL-C in either of these strata. We believe that the most important clinical issue is not whether there is a differential response to statins in patients with low versus high levels of HDL-C, but “whether optimal therapy for these high-risk individuals should consist of high-dose statin monotherapy, fibrate monotherapy, or combination therapy with statin plus fibrate” or other agents to raise HDL-C.

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