HEART OF THE MATTER

Investor Beware

BY SIDNEY GOLDSTEIN, M.D.

Randomized clinical trials are built on the premise that if you know the answer you should not ask the question. With that framework, they are risky business.

The stock market has recently learned all about the downside of those risks. Nevertheless, the scientific community and industry have invested large amounts of time and energy in randomized clinical trials (RCTs) in an attempt to translate bench research to the patient's bedside. They also have required the patient's commitment to participate in these studies. RCTs have exposed the fallacies of many concepts but also have elucidated the benefits of a host of cardiovascular drugs. The success of clinical trials has resulted in the profound decrease in cardiovascular mortality that we have experienced in the last half-century.

It was not too long ago that RCTs provided the proof of the concept that lowering LDL cholesterol could result in improved survival in patients with coronary artery disease. As a result, statins have become established as one of the foundations of contemporary therapy for the treatment of atherosclerotic disease. Prior to statins, there was a variety of drugs that were studied in RCTs in an attempt to prevent coronary disease. The clinical success associated with the lowering of LDL was followed by the tantalizing potential of even greater benefit that might be attained by raising HDL. Supported with both epidemiologic and laboratory data, the pharmaceutical industry responded to the challenge by designing drugs that could specifically raise HDL.

Unfortunately, we still do not have data to support the concept that raising HDL is beneficial to humans. In the last few weeks we have learned, as a result of the ILLUMINATE trial, that our first, and probably not last, foray into the realm of raising HDL was associated with increased mortality in the patients receiving the active drug. We know little else about the trial to explain these findings, with the exception that the drug torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, results in increases not only in HDL but also in systemic blood pressure. Whether the blood pressure response observed in the recent Pfizer trial is inherent in all molecules of this class or unique to torcetrapib remains for further investigation. There also is a suspicion that CETP inhibitors actually may increase cholesterol deposition in the atherosclerotic plaque. Niacin and exercise have been known to increase HDL, but there is little information to suggest that this is beneficial. The results from ILLUMINATE may cause some reflection on the purported benefit of raising HDL.

Other drugs are under investigation in regard to their possible beneficial effects on the progression of plaque formation. Antisense drugs directed at modifying apolipoprotein B and 5-lipoxygenase-activating proteins directed at down-regulation of leukotrienes are in the preliminary phase of clinical studies. In addition, preliminary data suggest that the administration of recombinant apo-A_1 Milano may have a significant effect on decreasing plaque size using intravascular ultrasound imaging.

It is clear that the universality of atherosclerosis speaks to the need for further investigation. The experience with torcetrapib is just one phase in our search for better therapy. It does send a message to the investment community that the buyer should beware: Science is a tricky business. ■

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Statins Lower Risk Of Death Even With Very Low LDL

CHICAGO — Statin therapy is associated with reduced mortality even in patients with very low baseline LDL cholesterol levels—below 60 mg/dL, Dr. Nicholas J. Leeper reported at the annual scientific sessions of the American Heart Association.

He presented an observational study involving 4,295 patients followed for a mean of 724 days after presenting with an LDL cholesterol level below 60 mg/dL. Of these patients, 47% had diabetes; 45% had known ischemic heart disease; and 19% had a prior malignancy, which can cause a marked reduction in LDL.

Statin therapy was prescribed for 60% of patients in the follow-up period, during which there were 510 deaths. After adjustment for age, liver and renal function, and use of other medications, statin therapy was associated with a 34% reduction in the relative risk of mortality.

Among patients with no history of ischemic heart disease, the mortality reduction was 42%.

Moreover, the survival benefit associated with statin therapy also extended to the 623 patients with an extremely low baseline LDL of less than 40 mg/dL. In this group of patients with an ultralow-LDL level, statin users had a 49% reduction in mortality, continued Dr. Leeper of Stanford (Calif.) University.

—Bruce Jancin

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