Clinical Significance of Statin Pleiotropic Effects
Hypotheses Versus Evidence

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he word “pleiotropic” usually is applied to genetics, referring to the multiple actions of a single gene. Regarding drug therapy for dyslipidemia, however, the term has become synonymous with clinical benefits beyond the effects of the drug on lipoproteins. HMG-CoA reductase inhibitors (statins), as the most widely prescribed drugs in the world, have been extensively evaluated for effects independent of lipid alterations. Mice and rats are relatively good models to evaluate potential pleiotropic effects of HMG-CoA reductase inhibitors because statins do not lower circulating cholesterol concentrations in these species. Statin administration results in greater nitric oxide bioavailability, increased ability to recruit endothelial progenitor cells, inhibition of cardiac hypertrophy, and reductions in the size and severity of strokes. Despite a failure to lower blood cholesterol, however, these drugs may influence cell membrane lipid levels. In rodent models, statins have been shown to decrease mitogen-activated protein kinase activation, enhance nitric oxide synthase expression, and reduce LOX-1 transcription by reducing oxidized low-density lipoprotein (LDL) uptake in endothelial cell membranes. Accordingly, the pleiotropic effects in animals may not be independent of the cellular uptake of lipids.

In humans, the purported clinical benefits of statins have ranged from improved bone density to reduced occurrence of Alzheimer disease, as well as enhanced cardiovascular benefits beyond blood lipid modification. Numerous studies have demonstrated that statins improve endothelial function, most likely by increasing nitric oxide bioavailability and reducing oxidant stress. Statins also may have “negative pleiotropic” effects because they may downregulate cholesterol efflux from nonloaded human macrophages by inhibiting synthesis of an oxysterol ligand for liver X receptor. In this issue of Circulation, Landmesser et al report that with equal lowering of LDL-cholesterol by simvastatin or ezetimibe, only simvastatin improved endothelial function (as measured by flow-dependent dilation in the radial artery) in patients with congestive heart failure (CHF). This study supports the view that statins provide clinical cardiovascular benefits beyond lipid modification.

From a historical perspective, the hypothesis that statins may reduce coronary heart disease (CHD) events to a degree greater than expected from lipoprotein modification was first suggested by the results of the West of Scotland Coronary Prevention Study Group (WOSCOPS) trial. This “overlap analysis” compared event rates in pravastatin and placebo subjects whose on-trial LDL-cholesterol values were in a range that occurred with high frequency in both groups, 3.62 to 4.65 mmol/L (140 to 180 mg/dL). The investigators found a significant reduction in event rate associated with pravastatin therapy after adjustment for lipoprotein cholesterol and triglyceride levels during treatment. A similar finding also was demonstrated in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFFCAPS/TexCAPS), although, after correction for apolipoprotein B and A1 levels, no difference was noted in event rate for subjects on lovastatin versus placebo. Because of the lack of available outcome trial results for all statins at the time, the use of statins with proven benefits on event rates, including pravastatin, lovastatin, and simvastatin, all fungal metabolites or “natural statins,” was advocated in part for their presumed ability to provide additional clinical benefits resulting from their pleiotropic effects.

As findings from more outcomes trials have been published, it has become obvious that all statins, whether fungal metabolites or synthetic, confer similar CHD event reduction if adjusted for differences in lipid changes (Figure). These additional trials, especially the Heart Protection Study (HPS) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) also verified the hypothesis that “lower is better” regarding LDL-cholesterol, especially for high-risk CHD patients. The ALLHAT trial, although flawed because of the high frequency of crossover between treatments, failed to demonstrate a clinical benefit for pravastatin beyond lipid lowering. This effectively disproved the hypothesis that pravastatin provided unique pleiotropic benefits different from other statins.

Other lipid-altering drugs such as bile acid sequestrants, niacin, and fibrates have been demonstrated to lower CHD events to an extent similar to statin therapy if adjusted for cholesterol lowering, although this provides only indirect evidence against clinical pleiotropic benefits of the statin drugs. Statins have been shown to lower inflammatory markers such as C-reactive protein (CRP), but the degree of CRP reduction correlates with the extent of lipid lowering, and this effect is not unique to statins. The
cholesterol absorption inhibitor, ezetimibe, enhances CRP reduction when added to a statin, and equal lowering of LDL-cholesterol by a low-dose statin plus ezetimibe or a high-dose statin provides equivalent CRP reduction.11

Pleiotropic statin enthusiasts argue that in statin trials, clinical event reductions appear more rapidly than in nonstatin trials. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL)12 and PROVE-IT trials, significant benefits, mostly driven by reductions in the incidence of unstable angina, occurred within the first month of treatment, whereas in nonstatin trials, the clinical benefits required multiple years for the Kaplan-Meier curves to separate. The MIRACL and PROVE-IT trials, however, enrolled patients with acute coronary syndromes who had much higher event rates than the subjects in the nonstatin trials. Significant stroke reduction appears to have been present only in statin trials, but the nonstatin trials, which provided less cholesterol reduction, trended toward stroke reduction as well. Therefore, the idea that statins provide unique benefits attributable to factors other than modification of the lipoprotein profile compared with other classes of lipid-altering medications remains speculative.

Landmesser et al have provided convincing evidence that simvastatin improved endothelial function in patients with CHF, whereas ezetimibe did not. Improved endothelial function alone may not translate into fewer events, however. Estrogen therapy was documented to markedly improve endothelial function and provide many other cardiovascular benefits,13 but clinical trials failed to demonstrate a reduction in CHD events. The potential pleiotropic benefits of statins for improving outcomes are presently being tested in 2 large trials in patients with CHF: CORONA and Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI-HF).

Therefore, it is important to distinguish potential pleiotropic benefits of specific lipid therapies from improvements in proven surrogate endpoints such as LDL-cholesterol, non-HDL-cholesterol, and ApoB. The National Cholesterol Education Program Adult Treatment Panel III guidelines do not recommend specific drugs to reduce CHD events but rather lipoprotein target goals based on the weight of clinical evidence. Among clinicians the pleiotropic benefits of statins have reached almost mythical proportions. Although research and debate regarding this issue should continue, in the absence of evidence for benefits on events from randomized clinical trials, the focus must remain on achieving the recommended goals of therapy established by national guidelines.

References


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In the editorial by Davidson, “Clinical Significance of Statin Pleiotropic Effects: Hypotheses Versus Evidence,” which appeared in the May 10, 2005, issue of the journal (Circulation. 2005;111:2280–2281), several errors were detected in the figure. A revised figure and legend appear below.

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Meta-Regression Analysis
CHD (Nonfatal MI + CHD Death)

Relation of total cholesterol (TC) differential in active treatment (TRT) versus control group (CTL) to percentage change in cardiovascular events versus placebo. Gray circles indicate nonstatin therapy; gray diamonds, statin therapy. Trials: VA-HIT indicates Veterans Affairs High-Density Lipoprotein Intervention Trial; LRC-CPPT, Lipids Research Clinics Coronary Primary Prevention Trial; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Lipid Lowering Trial; CDP, Coronary Drug Project; A to Z, Aggrastat to Zocor; HHS, Helsinki Heart Study; TNT, Treat to New Target; Post-CABG, Post-Coronary Artery Bypass Graft trial; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; CARE, Cholesterol and Recurrent Events; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; HPS, Heart Protection Study; WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; POSCH, Program on the Surgical Control of the Hyperlipidemias; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; LIPS, Lescol Intervention Prevention Study; and 4S, Scandinavian Simvastatin Survival Study.