The Evolving Role of HDL in Reducing Cardiovascular Risk*

A high-density lipoprotein (HDL) cholesterol level has consistently been shown to be inversely associated with coronary artery disease (CAD) events in epidemiologic studies. Low HDL cholesterol is a common lipid abnormality in individuals with CAD and is a major risk factor in the National Cholesterol Education Program's algorithm for risk stratification of patients in primary prevention. Consequently, physicians may be uncertain whether to target HDL cholesterol or low-density lipoprotein (LDL) cholesterol to reduce CAD risk in the high-risk patient with low HDL cholesterol.

Recent clinical trials have provided new data on the effects of lipid-regulating therapy on CAD progression and clinical events in patients with low HDL cholesterol levels. Several trials of statin therapy have demonstrated benefit in patients with low HDL cholesterol levels. Both angiographic and clinical event trials have consistently shown that statin therapy provides the greatest benefit in patients with low HDL cholesterol levels at baseline. Trials of fibrate therapy, which may have been expected to produce greater increases in HDL cholesterol, have reported mixed results, with benefit demonstrated in the Veterans Affairs HDL Intervention Trial but not in the Bezafibrate Infarction Prevention trial. Recent trials with simvastatin have shown that higher doses of simvastatin can raise HDL cholesterol levels by approximately 16%, which is a greater increase than was previously recognized. In addition, recent trials have shown that pharmacologic differences in 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors may influence the efficacy of these agents on HDL and LDL cholesterol. For example, comparative studies have shown that high-dose simvastatin provides significantly greater increases in HDL cholesterol and apolipoprotein A-I levels than does high-dose atorvastatin. Further studies are needed to understand the mechanisms whereby statins increase HDL cholesterol levels and the physiologic relevance of such changes.

In summary, HDL cholesterol levels play an important role in identifying patients at high risk for CAD, and therapy for these patients should reduce LDL cholesterol and raise HDL cholesterol. The clinical trial data support using a statin as first-line pharmacologic therapy for patients with low HDL cholesterol levels and mildly to moderately elevated LDL cholesterol levels. More information is needed to inform clinicians whether patients with combined abnormalities of LDL cholesterol, HDL cholesterol, and/or triglyceride are best treated by high-dose statin therapy or by adding a second agent, such as nicotinic acid or a fibrate, to the statin. Finally, the current HDL cholesterol cut points used in screening are outdated; it must be recognized that less than 40 mg/dL is low for a man and less than 45 mg/dL is low for a woman.

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