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Protective Effects of HDL-C and Need to Raise Low Levels Explored

ANAHEIM—Because of its various protective effects against atherosclerosis and cardiovascular risk, raising levels of high-density lipoprotein cholesterol (HDL-C) is a viable therapeutic strategy, said Daniel J. Rader, MD, Associate Professor of Medicine and Director

of the Preventive Cardiovascular Medicine and Lipid Clinic at the University of Pennsylvania Medical School in Philadelphia.

HDL-C protects against atherosclerosis by promoting reverse cholesterol transport, a process in which excess cholesterol is effluxed

from cells in the arterial wall and returned to the liver for excretion into the bile and, ultimately, the feces. HDL-C also protects against atherosclerosis and reduces cardiovascular risk by mechanisms that are independent of reverse cholesterol

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transport—namely, its antioxidant, anti-inflammatory, and anticoagulant effects.

Numerous reports of in vitro and in vivo studies demonstrate the antioxidant, anti-inflammatory, and anticoagulant properties of HDL-C, Dr. Rader pointed out. Data have shown that HDL-C inhibits low-density lipoprotein cholesterol (LDL-C) aggregation and that mixing HDL-C with LDL-C protects against LDL-C oxidation. Other studies have shown that HDL-C blunts the endothelial inflammatory response by inhibiting the expression of adhesion molecules. Still other investigations have shown that HDL-C inhibits thrombin-induced platelet aggregation and fibrinogen binding and, when combined with protein S and activated protein C, substantially increases prothrombin time.

Although much of the data supporting the protective role of HDL-C have come from animal experiments, epidemiologic studies such as the Framingham Heart Study demonstrate that low levels of HDL-C are associated with high risk for cardiovascular disease and

high levels are associated with low risk, Dr. Rader said. Low HDL-C levels are commonly seen in people who smoke, are sedentary, are overweight or obese, are insulin resistant or diabetic, have high triglyceride levels, or have chronic inflammatory disorders.

HDL-C protects against atherosclerosis by promoting reverse cholesterol transport and by its antioxidant, anti-inflammatory, and anticoagulant effects.

—Daniel J. Rader, MD

In fact, low HDL-C is a risk factor even when LDL-C is well controlled, he continued, citing Framingham data that show a similar risk for car-

diovascular disease in people with LDL-C levels of about 100 mg/dL but HDL-C levels in the 20s and low 30s and in those with LDL-C levels of about 220 mg/dL but HDL-C levels in the 40s.

Moreover, the increased risk conferred by low HDL-C prompted the National Cholesterol Education Program, in its most recent set of guidelines, to raise the cutoff point for target HDL-C from 35 to 40 mg/dL. This markedly increases the number of patients who can now be officially classified as having low HDL-C.

Raising HDL-C begins with therapeutic lifestyle changes: smoking cessation, weight loss, and increased exercise. Clearly, optimal control of type 2 diabetes is also essential.

Although alcohol raises HDL-C and moderate alcohol intake is associated with reduced risk, actually “prescribing” alcohol or increased alcohol intake for patients with low HDL-C is a judgment call, Dr. Rader said. Similarly, the prescription of hormone replacement therapy, which raises levels of HDL-C and its major protein apoA-I, is also a judg-

ment call because its role in reducing cardiovascular risk is not certain.

Pharmacologic approaches to revising HDL-C include statins in patients who also have elevated LDL-C, fibrates in patients with elevated triglycerides, niacin in patients with isolated low HDL-C, and combination therapy in patients with combined dyslipidemia.

Animal studies have suggested several new approaches to raising HDL-C levels. These include upregulating the transcription of ABCA1, a cellular protein that mediates cholesterol efflux in reverse cholesterol transport, through nuclear receptors such as LXR and RXR; promoting reverse cholesterol transport by mechanisms that have yet to be elucidated; and raising HDL-C and apoA-I levels by inhibiting cholesterol ester transfer protein (CETP), the protein that transfers HDL-C to apo B-containing lipoproteins.

“We have known for more than a decade that a deficiency of CETP results in very high levels of HDL-C,” Dr. Rader observed. “As a result, there has been considerable interest in inhibiting CETP as a strategy to raise HDL-C.” ■