Taking on High-Density Lipoprotein Cholesterol and Triglycerides

Written by Rita Buckley

Dyslipidemia plays a critical role in cardiovascular (CV) risk. Strong evidence supports that lower low-density lipoprotein cholesterol (LDL-C) is better, but there are more questions than answers on what to do about triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Anne Carol Goldberg, MD, Washington University of Medicine, St. Louis, Missouri, USA, addressed high TGs and HDL-C.

TG, lipid fractions used for energy storage, are intrinsically synthesized in the liver and derived from external sources through uptake in the intestine [Sarwar N et al. *Circulation* 2007]. Normal serum TG levels are <150 mg/dL while levels >500 mg/dL increase the risk of pancreatitis [Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001].

TG level is a significant CV disease (CVD) risk factor [Sarwar N et al. *Circulation* 2007]. An estimated 31% of the adult population in the United States has TG levels ≥150 md/dL, with no appreciable change between NHANES 1988–1994 and 1999–2008 [Miller M et al. *Circulation* 2011]. Subgroup analyses suggest that treatment of dyslipidemia defined as TG ≥204 mg/dL and HDL-C ≤34 mg/dL may decrease CV risk [Sacks FM et al. *N Engl J Med* 2010].

HDL is much more complicated than previously appreciated, with roles in lipid transport and exchange, inflammation, immunity, hemostasis, and complement. Recent trials have failed to show that raising HDL-C decreases CVD [Barter PJ et al. *N Engl J Med* 2007; Schwartz GG et al. *N Engl J Med* 2012; The AIM-HIGH Investigators. *N Engl J Med* 2011]. Although some people may have HDL that is proatherogenic [Brewer HB, Jr. *J Clin Endocrinol Metab* 2011], HDL appears to decrease CV risk due to antiatherogenic effects, including regulation of glucose metabolism, endothelial repair, and anti-inflammatory and antithrombotic activities [Chapman MJ et al. *Eur Heart J* 2011].

Robert H. Eckel, MD, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, discussed emerging CVD risk factors. These include apolipoprotein B (apoB), lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and assessment of subclinical atherosclerosis.

Peer-Reviewed Highlights From

A meta-analysis of prospective studies on apoB and coronary heart disease (CHD) gave a relative risk of 1.99 (95% CI, 1.65 to 2.39) in a comparison of individuals in the top third versus those in the bottom third of baseline values [Thompson A, Danesh J. *J Intern Med* 2006]. However, apoB should not replace lipid measurements but might have added value beyond non-HDL-C in patients with low levels of LDL-C ± statin who have elevated TG (>200 mg/dL).

Suk Danik et al. [*JAMA* 2006] found that after adjusting for all pertinent variables, the hazard ratio associated with lipoprotein (a) levels exceeding the 90th percentile (≥65.5 mg/dL) was 1.66 (95% CI, 1.38 to 1.99); 95th percentile (≥83 mg/dL), 1.87 (95% CI, 1.50 to 2.34); and 99th percentile (≥130.7 mg/dL), 1.99 (95% CI, 1.32 to 3.00), with almost no risk gradient at lower levels. Based on these and other findings, the suggested level of additional concern was when the lipoprotein (a) is >30 mg/dL.

Clarke et al. [*Arch Intern Med* 2010] evaluated homocysteine as a marker of CVD risk in a meta-analysis of eight randomized trials involving 37,485 individuals. They found that although dietary supplementation with folic acid yielded an average 25% reduction in homocysteine levels, there were no significant effects on vascular outcomes within 5 years.

In a primary prevention trial, [Antithrombotic Trialists' Collaboration. *Lancet* 2009] aspirin yielded a 12% proportional reduction in serious vascular events (0.51% aspirin vs 0.57% control per year; p=0.0001), mainly due to a reduction of about a fifth in nonfatal myocardial infarction (0.18% vs 0.23% per year; p<0.0001). It also increased major gastrointestinal and extracranial bleeds (0.10% vs 0.07% per year; p<0.0001). According to Dr. Eckel, aspirin reduces CHD in high risk men and ischemic CV accidents in high-risk women. It also has borderline benefit in patients with diabetes without known CVD. Patients with diabetes and CVD should be on aspirin unless contraindicated.

Other emerging CVD risk factors include C-reactive protein (CRP), impaired fasting glucose

(IFG), and subclinical atherosclerosis. CRP concentration has continuous associations with the risk of coronary disease, ischemic stroke, and vascular mortality [Kaptoge S et al. *Lancet* 2010]. Among those with prediabetes, impaired glucose tolerance increases the risk for CVD events, whereas IFG does not. Budoff et al. [*J Am Coll Cardiol* 2007] found that coronary artery calcium was an independent predictor of mortality (model chi-square=2107; p<0.0001).

Thomas P. Bersot, MD, PhD, University of California, San Francisco, San Francisco, California, USA, discussed novel therapeutic strategies for plasma lipid disorders, in particular homozygous familial hypercholesterolemia (HoFH).

HoFH is an extremely rare, refractory, inherited disorder that affects approximately one in a million people in the United States. Those with the disease often suffer myocardial infarction and death before the age of 30. Patients with HoFH respond poorly to currently available therapies.

Treatment strategies focus on reducing very low density lipoprotein (VLDL) and/or LDL levels through the use of novel drugs. Lomitapide is an inhibitor of microsomal TG transfer protein (MTP) in the gut and liver; mipomersen is an antisense oligonucleotide that prevents translation of apoB100 mRNA in the liver. Monoclonal antibodies that neutralize proprotein convertase subtilisin kexin9 (PCSK9), a crucial protein in LDL-C metabolism [Lambert G. *J Lipid Res* 2012], are also being explored.

MTP is required for secretion of VLDL, the precursor to LDL. Lomitapide is an inhibitor of MTP. In a single-arm, open-label, Phase 3 study of the drug, 29 men and women with HoFH, aged ≥18 years, were recruited from 11 centers in 4 countries (USA, Canada, South Africa, and Italy); 23 of 29 enrolled patients completed both the efficacy phase (26 weeks) and the full study (78 weeks) [Cuchel M et al. *Lancet* 2013]. The mean dosage of lomitapide was 40 mg daily.

LDL-C was reduced by a mean of 50% (95% CI, –62 to –39) from baseline (mean 8.7 mmol/L [SD 2.9]) to Week 26 (4.3 mmol/L [2.5]; p<0.0001). Concentrations of LDL-C stayed reduced by 44% (95% CI, –57 to –31; p<0.0001) at Week 56 and 38% (95% CI, –52 to –24; p<0.0001) at Week 78.

Mipomersin sodium, a once-weekly subcutaneous injection, is a first-in-class antisense oligonucleotide inhibitor that targets ApoB-100. Used in addition to maximally tolerated lipid-lowering therapy, it further reduces LDL-C as well as other lipids, including apoB, TG, and non-HDL-C.

PCSK9 inhibition has emerged as one of the most active lines of investigation in cholesterol research, with promising results in a number of Phase 2 trials. Approaches to inhibit PCSK9 include antibodies, RNA interference, and antisense therapy. Currently, 10 pharmaceutical firms have PCSK9-directed therapies in development.