Recent decades have witnessed an increasing awareness of the importance of lowering triglyceride concentrations in conjunction with lowering LDL cholesterol (LDL-C)\(^1\) to achieve optimal reduction of the risk for coronary heart disease (CHD). Historically, LDL-C was the only target of pharmacologic therapy in CHD prevention. Thus the first Adult Treatment Panel (ATP I) of the National Cholesterol Education Program published in 1988 used only LDL-C cutoffs as guidelines. Since then, there have been incremental changes with regard to the importance of lowering triglyceride concentrations in addition to LDL-C. In ATP II, triglycerides was still not recognized as an independent risk factor, but the upper limit considered healthy for triglycerides was lowered from 250 to 200 mg/dL. ATP II also discussed triglycerides as a risk factor and the treatment of patients with increased triglycerides with either nonpharmacologic or pharmacologic therapies. ATP III, published in 2001, further lowered the normal range of triglycerides to <150 mg/dL. Whereas ATP III maintains that lowering of LDL-C should be the primary target of therapy, it also recommended that non-HDL cholesterol (LDL + VLDL) be used as the secondary target of therapy.

In part, the increased recognition of the importance of lowering triglycerides has been a result of increased recognition of the metabolic syndrome (MS). Although the diagnosis of MS is based on meeting at least 3 of the 5 criteria (increased triglycerides, low HDL-C, abdominal obesity, high blood pressure, and increased fasting glucose concentrations), by far the majority of individuals with MS have increased triglycerides. ATP III also contained explicit guidelines on the management of MS, by treating the underlying cause through diet and exercise, through specific pharmacological therapies which lower triglycerides and hypertension, or both.

The fact that increased serum triglyceride concentrations are positively associated with risk for CHD has long been recognized. The debate has always focused on whether it is an independent risk factor. Increased triglycerides affect both HDL and LDL. For example, it has long been demonstrated that increased serum triglycerides are associated with lowered HDL-C concentrations and decreased HDL and LDL particle sizes. Moreover, treatment of patients with triglyceride-lowering therapies such as fibric acid derivatives not only lowers serum triglycerides but also increases HDL-C concentrations. In particular, reducing serum triglycerides is known to be associated with increased HDL\(_2\), the larger HDL particles thought to be more protective than the smaller HDL\(_3\) particles. Similarly, although increased triglycerides may not be the only mechanism for decreased average particle size of LDL, it is a major mechanism involved in increasing the proportion of small, dense LDL particles. Lowering triglycerides is almost always associated with the reduction of small, dense LDL particles, thereby further rendering an individual’s lipid profile to be less atherogenic (1).

Early publications argued that the risk associated with increased triglycerides is secondary to its influence on the HDL-C concentration and/or the qualitative changes in LDL and HDL particles. More recent studies have demonstrated that increased triglycerides are an independent risk factor. In particular, postprandial studies have now demonstrated that increases in triglyceride-rich chylomicron or VLDL remnant particles are associated with increased atherogenicity, and this effect is independent of the atherogenic effect of triglycerides on LDL and HDL particles (2).

The recent study of Pollin et al. (3) has now further confirmed the importance of triglycerides as an independent risk factor for CHD. In an attempt to discover human mutations that are responsible for variations in human triglyceride concentrations, Pollin et al. performed a high-fat feeding intervention and a genome-wide association study (GWAS) in 809 Old Order Amish individuals as part of the Heredity and
Phenotype Intervention Heart Study (HAPI) (4). Along with the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), in which 1200 individuals were subjected to a fat challenge meal, the HAPI study is 1 of the 2 largest studies focusing on the understanding of genetics of fasting and postprandial triglyceride concentrations. The HAPI GWAS study eventually led to the discovery of a single nucleotide polymorphism (SNP), rs10892151, which is in linkage disequilibrium with a loss-of-function mutation in APOC3. Sequencing of the coding region of APOC3 led to the discovery of a C-to-T substitution on the 55th nucleotide of the APOC3 gene that results in a premature stop-codon substituting for an arginine residue at the 19th position of the protein. The premature stop codon, when present in the APOC3 gene, results in the complete lack of production of apoC-III peptide. Thus carriers of this loss-of-function mutation have half the apoC-III protein concentrations, and they have reduced fasting and postprandial triglyceride concentrations. The finding that a loss-of-function mutation in APOC3 is associated with reduced triglyceride concentration is in agreement with the well-known function of apoC-III as an inhibitor of lipoprotein lipase. Moreover, apoC-III may activate vascular endothelial cells through increased expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1).

Electron-beam computed tomography has in the past decade been used to quantify coronary artery calcium (CAC) in many multicenter studies, such as NHLBI Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development In Young Adults (CARDIA). It is thought to be a very good marker of subclinical atherosclerosis. By measuring the CAC score on the study participants, Pollin et al. (3) showed that individuals who were carriers of the R19X mutation in the APOC3 gene were significantly less likely to have any CAC (odds ratio (OR) 0.35, P = 0.002), and for those with CAC, they were likely to have lower CAC scores compared to the reference ranges established in the MESA cohort (OR 0.40, P = 0.01 for carriers to have CAC >100 Agatston units).

The discovery of the R19X mutation, which lowers the fasting and postprandial triglyceride concentrations and is associated with lowered risk of CHD, implies that a lifelong reduction in triglycerides reduces an individual’s risk of CHD. The study is interesting in 2 other respects. First, the mean triglyceride concentration of 57 mg/dL in participants who do not carry the R19X mutation is already very low. For carriers of the mutation, the mean triglyceride concentration was only 31 mg/dL; in contrast, the healthy triglyceride concentration in ATPIII is defined as <150 mg/dL. Second, the mutation in the APOC3 in the Amish population is associated not only with lowered triglyceride, but also with increased HDL-C and lowered LDL-C. Whereas lowering triglycerides from relatively high concentrations (>150 mg/dL) is known to be associated with increased concentrations of HDL-C, not much is known about whether lowering of triglyceride to <100 mg/dL is always associated with increased HDL-C. Most of the therapies used in lowering triglycerides, such as niacin, fish oil, and fibrates, are also associated with a decrease in APOC3 expression. Fibric acid derivatives such as fenofibrate and gemfibrozil are known to bind to peroxisome proliferator-activated receptor α (PPARα) receptors, leading to the down-regulation of APOC3. In GOLDN, SNPs in APOC3 have been shown to be significantly associated with the lowering of triglycerides by fenofibrate (4). Further studies are needed to elucidate whether downregulation of APOC3 expression is linked to upregulation of genes involved in HDL metabolism.

The results from the study Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) demonstrated that aggressive lowering of LDL to 62 mg/dL, compared with lowering LDL to 95 mg/dL, resulted in reduction of a recurring event or death from 26.3% to 22.6% during a 30-month follow-up (5). The relatively high percentage of a recurring event at an LDL concentration of 62 mg/dL could mean other therapeutic targets used in combination with LDL-C reduction may be of further benefit in secondary prevention.

If the results from the Lancaster Amish can be extrapolated to the general population, the question arises, could secondary prevention of CHD benefit from an aggressive reduction of LDL-C (to 60 mg/dL) and reduction of triglycerides to below that of the current target of 150 mg/dL? In view of the interesting finding from the HAPI study, more research on the reduction of triglycerides, either singly or in combination with reduction of LDL-C, may contribute to improved clinical outcome in both primary and secondary prevention of CHD in the future (3).
References