The case against triglycerides

By Lev Osherovich, Senior Writer

Although the harmful effects of certain lipids such as low-density lipoprotein cholesterol on the cardiovascular system are well established, the role of triglycerides in heart disease has been suspected but less clear. Now, a large-scale epidemiological study provides evidence that increased triglycerides are indeed associated with a greater risk of coronary artery disease.¹ The question now is whether the converse is true: Can lowering triglycerides protect against CAD?

Triglycerides are lipids consisting of several fatty acids linked to a glycerol molecule. They are the primary source of lipid-derived energy in the body and are transported through the blood in cholesterol-rich lipoprotein particles. In CAD, these particles accumulate as atherosclerotic plaques within the walls of the coronary artery, leading to myocardial infarction (MI).

The physical association between triglycerides and cholesterol has confounded previous efforts to distinguish whether high levels of triglycerides are themselves harmful. For example, CAD patients with high triglycerides also typically have high low-density lipoprotein (LDL) cholesterol.

"There has been uncertainty for 50 years as to whether elevated triglycerides can cause heart disease," said Nadeem Sarwar, university lecturer in cardiovascular epidemiology at the **University of Cambridge** and corresponding author of the study, which was published in *The Lancet*.

"Because triglyceride levels are correlated with other lipid levels," testing the effect of triglycerides alone on CAD risk has been difficult, noted Sarwar. Getting an answer from an interventional trial of compounds that lower triglycerides is "impossible," he added, because medications that affect triglycerides also affect other lipids, such as LDL and high-density lipoprotein (HDL) cholesterol.

Thus, Sarwar's group decided to study the natural variation in triglyceride levels using a combination of genetic and epidemiological methods. "We found that people who carried a genetic variant that elevated triglycerides had higher risk of coronary heart disease," he said.

Tri and tri again

To unravel the effect of triglycerides on CAD, Sarwar's team turned to a relatively common genetic variant in apolipoprotein A-V (APOA5), the protein component of the very low-density lipoprotein (VLDL) particles that carry most triglycerides through the blood. Prior work identified a SNP in the *APOA5* promoter that alters VLDL particles and increases the circulating concentration of triglycerides.²

Sarwar's team used data from the Triglyceride Coronary Disease Genetics Consortium and the Emerging Risk Factors Collaboration to test the link between *APOA5* mutations, triglycerides and CAD risk. The two academic consortia pool genetic and physiological measurements from epidemiological and interventional studies of cardiovascular disease.

First, the team examined genetic data from 73,252 individuals enrolled in 39 epidemiological studies to confirm that the *APOA5* variant correlated with higher levels of triglycerides. Indeed, carriers of a single copy of the defective *APOA5* gene had a 16% increase in triglyceride levels compared with noncarriers. Individuals with two defective copies had about 32% more triglycerides than noncarriers.

Importantly, the *APOA5* variant did not affect the concentration of cholesterol or the size of LDL particles. The mutation modestly decreased the size and concentration of HDL particles compared with those in noncarriers.

Next, the team tested whether the *APOA5* polymorphism was more common in CAD patients. In about 56,000 cases and controls drawn from previous studies, each copy of the defective *APOA5* allele corresponded with an 18% increase in the prevalence of CAD.

Finally, Sarwar and colleagues compared their theoretical prediction of triglyceride-associated disease with actual CAD incidence in 68 prospective trials involving 302,430 individuals. The predicted risk of CAD agreed well with real-world findings, suggesting that *APOA5*-associated changes in triglyceride levels could potentially account for new cases of CAD.

Maker or marker?

Despite these results, it's unclear whether lowering triglycerides should be a goal or whether triglyceride levels are instead a surrogate marker of disease risk.

Sarwar said that the findings are supportive of causality between triglycerides and CAD, but noted that the mechanism by which the *APOA5* variant leads to higher CAD risk remains unknown. One possibility is that triglyceride-bearing VLDL particles are to blame, but it's also possible that the modest decrease in HDL caused by the mutation contributes to disease.

An Australian group's meta-analysis of prospective trials of lipid-lowering fibrate drugs does support the causality hypothesis. That report, also published this month in *The Lancet*, showed an overall 13% reduction in MIs and sudden deaths due to coronary events in 18 trials of fibrates involving 45,058 patients.³

Fibrates lower triglycerides and raise HDL by turning on peroxisome proliferation-activated receptor- α (PPARA; PPAR α), a transcriptional regulator of lipid metabolism.

Vlado Perkovic, associate professor of medicine at **The University of Sydney**, co-director of the renal and metabolic division at **The George Institute of International Health** and lead author of the meta-analysis, said much of the benefit of fibrates is likely due to reductions in triglyceride levels.

"We did a subgroup analysis to see if we could identify any trial parameters associated with more or less benefit" from fibrate therapy, he said. "We looked at people with higher and lower HDL at baseline, as well as total cholesterol, and this didn't appear to influence the

results. The only thing we found was that in patients with higher triglycerides, the benefit of fibrate treatment was stronger.”

Thus, said Perkovic, the fact that his group’s paper and Sarwar’s findings “come to the same conclusions from multiple directions supports the hypothesis that triglycerides are a driver of coronary risk.”

Andrew Plump, VP and head of cardiovascular disease discovery at **Merck & Co. Inc.**, said Sarwar’s work firmly links APOA5 to higher triglycerides and CAD risk, but he wants to see further genetic and interventional studies uncover the underlying cause.

“The part that’s ironclad is the association of APOA5 to risk. When you perturb that gene, you also perturb disease risk,” said Plump. Although it is possible that triglycerides themselves directly lead to CAD, he noted that “it could also be that APOA5 affects something else that affects triglycerides.”

Merck’s anacetrapib (MK-0859), an inhibitor of cholesteryl ester transfer protein (CETP), is in Phase III trials for dyslipidemia and atherosclerosis. Plump said the compound works by raising HDL but doesn’t affect triglycerides.

“It could be that APOA5 is just a bad protein that also happens to increase triglycerides,” said Steven Zelenkofske, CMO and SVP of clinical and medical affairs at **Regado Biosciences Inc.**

Regado’s REG1 two-component Anticoagulation System is in Phase II testing to treat blood clots in acute coronary syndrome. The system consists of RB006, an inhibitor of activated Factor IX, and RB007, a control agent that neutralizes RB006.

Lipid trials

Ultimately, said Sarwar, the question of whether triglycerides cause CAD can only be resolved with an interventional trial of triglyceride-lowering agents.

This may be easier said than done, however. Although there is no shortage of enzymes involved in triglyceride metabolism, finding a target that primarily affects triglycerides—and not LDL or HDL—may be a challenge.

“As far as I know, there are no agents in development whose sole effect is on triglycerides,” said Plump. “Most mechanisms that affect triglycerides also affect LDL and HDL.”

“There are a number of targets in the lipid pathway that modify triglycerides,” said Rebecca Taub, SVP of R&D at **Via Pharmaceuticals Inc.** “It’s a very complex area involving triglyceride biosynthesis, absorption and clearance.”

Via Pharmaceuticals is developing an inhibitor of diacylglycerol O-acyltransferase-1 (DGAT1), an enzyme that links fatty acids to glycerol at the time of dietary absorption. The company acquired the preclinical compound from **Roche**.

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**—Andrew Plump,
Merck & Co. Inc.**

Further complicating efforts to unravel the role of triglycerides, Taub said, is that inhibiting early steps in triglyceride metabolism has indirect effects on intestinal secretion of peptide hormones that affect appetite, blood sugar and insulin sensitivity. These side effects, though desirable when treating type 2 diabetes, can complicate interpretation of the effect of manipulating triglycerides on CAD.

One marketed drug, a formulation of ω -3 fatty acid ethyl esters refined from fish oil, lowers levels of both triglycerides and inflammatory lipids. **GlaxoSmithKline plc** markets the drug in the U.S. as Lovaza to treat severe hypertriglyceridemia that leads to pancreatitis and gall bladder disease. Lovaza is used off-label in patients with moderately increased triglycerides.

Pronova Biopharma ASA licensed the U.S. rights to the fish oil formulation to Reliant Pharmaceuticals, Inc., which was acquired by GSK in 2007. Pronova is also developing the formulation under the name Omacor in partnership with **Takeda Pharmaceutical Co. Ltd.** The collaborators have Phase III trials ongoing in MI and CAD.

The most immediate value of the *Lancet* study may be to help stratify high-risk patients in future CAD trials.

“If you can convince the FDA that you have a population with a physiological defect that leads to a poor outcome,” it would allow a study to preselect a population of patients most likely to benefit from a triglyceride-lowering drug, said Zelenkofske.

Finding a benefit to lowering triglycerides in mutant APOA5 carriers also could set the stage for prophylactic trials of triglyceride-lowering agents in a broader population of hypertriglyceridemic individuals who do not yet show symptoms of CAD, he added.

Sarwar said the findings have not been patented.

Oshervich, L. *SciBX* 3(21); doi:10.1038/scibx.2010.637
Published online May 27, 2010

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Pronova Biopharma ASA (OSE:PRON), Lysaker, Norway
Regado Biosciences Inc., Basking Ridge, N.J.
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