Therapy and clinical trials

Rachel Elkin[a,b] and Richard A. Krasuski[a]

The link between triglyceride levels and cardiovascular disease was first described several decades ago. Several high-quality observational studies and clinical trials [1,2▪,3–5,6▪▪,7,8] have since demonstrated that elevated levels of triglycerides are associated with an increased risk of cardiovascular disease, myocardial infarction, stroke and all-cause mortality, even after LDL cholesterol (LDL-C) therapeutic goals have been achieved. This evidence base was recently bolstered by two large genetic studies [9,10] that linked loss-of-function or missense mutations in apolipoprotein C3 [APOC3; a protein that normally inhibits lipoprotein lipase (an enzyme responsible for the hydrolysis of triglyceride-rich lipoproteins)] to reduced cardiovascular risk.

The first of these studies [9] utilized data from individuals enrolled in two large Danish observational studies (the Copenhagen City Heart Study and the Copenhagen General Population Study; 75 725 individuals in total). Using DNA sequencing and mutational analysis, Jørgensen and colleagues identified three key loss-of-function or missense mutations in the APOC3 gene: R19X, IVS2+1G→A and A43T. Heterozygote carriers of any of these mutations (occurring at a frequency of 1 in 290 patients) had, on average, 44% lower plasma triglyceride levels than noncarriers [9]. Moreover, the risk of developing coronary or vascular disease in APOC3 heterozygotes was significantly lower than that observed in noncarriers [hazard ratio (HR) 0.64 (95% confidence interval (CI) 0.41–0.99) and 0.59 (0.41–0.86), respectively].

Similar findings were obtained in the second study [10], which drew on data from the Exome Sequencing Project and 15 large cohort studies. In addition to the three loss-of-function mutations reported by Jørgensen and colleagues, exome sequencing identified a fourth APOC3 mutation, IVS3+1G→T, which also was associated with reduced plasma triglyceride levels. Carriers of any of the four APOC3 mutations had significantly lower triglyceride levels than noncarriers (~39%), and a lower risk of coronary disease (HR 0.60, 95% CI 0.47–0.75) [10]. An analysis of the relationship between APOC3 levels and incident cardiovascular disease yielded similar conclusions, with every 1 mg/dl decrease in plasma levels of APOC3 associated with a 4% decrease in risk (HR 0.96, 95% CI 0.94–0.98).

The findings of both studies are in accordance with the results of Mendelian randomization studies [11▪▪,12▪], which offer additional evidence supporting the association of elevated levels of triglycerides with cardiovascular disease and all-cause mortality and suggest a causal role for triglycerides in the atherogenic process. Taken together, the results of these studies also suggest that APOC3 could be a valuable pharmacologic target for lowering triglyceride levels and cardiovascular risk in patients who are not mutation carriers. Indeed, antisense oligonucleotide inhibition of APOC3 effectively lowers triglyceride levels in healthy subjects [13] and hypertriglyceridemic patients, and an antisense inhibitor of APOC3 (ISIS-APOCIII$_{Rx}$) has recently entered phase III study. Whether or not such a medication will be able to reduce the risk of cardiovascular disease, however, remains to be determined.

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Conflicts of interest

Dr Krasuski has served as a consultant to Actelion and Bayer, and is on the speaker's bureau of Roche and the scientific advisory board of Ventripoint.

[a]Division of Cardiovascular Medicine, Cleveland Clinic Foundation and [b]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA

Correspondence to Richard A. Krasuski, MD, Desk J2-4, Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195, USA. E-mail: krasusr@ccf.org

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Nordestgaard BG, Benn M, Schnohr P, *et al.* Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 2007; 298:299–308.
2. ■ Athyros VG, Tziomalos K, Karagiannis A, *et al.* Genetic, epidemiologic and clinical data strongly suggest that fasting or nonfasting triglycerides are independent cardiovascular risk factors. Curr Med Res Opin 2014; 1–4. [Epub ahead of print]

A succinct review of the genetic, observational and clinical trial data on triglycerides that has been published in recent years, with particular emphasis on the associations amongst triglycerides, cardiovascular disease, adverse cardiovascular outcomes and mortality.

3. Freiberg JJ, Tybjærg-Hansen A, Jensen JS, *et al.* Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA 2008; 300:2142–2152.
4. Varbo A, Nordestgaard BG, Tybjærg-Hansen A, *et al.* Nonfasting triglycerides, cholesterol, and ischemic stroke in the general population. Ann Neurol 2011; 69:628–634.
5. Sarwar N, Danesh J, Eiriksdottir G, *et al.* Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 western prospective studies. Circulation 2007; 115:450–458.
6. ■■ Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet 2014; 384:626–635.

An excellent review of the epidemiologic and genetic evidence linking elevated levels of triglycerides to cardiovascular disease and poorer overall survival, with brief sections devoted to the diagnosis and treatment of patients with hypertriglyceridemia.

7. Faergeman O, Holme I, Fayyad R, *et al.* Plasma triglycerides and cardiovascular events in the Treating to New Targets and Incremental Disease in Endpoints Through Aggressive Lipid Lowering trials of statins in patients with coronary artery disease. Am J Cardiol 2009; 104:459–463.
8. Miller M, Cannon CP, Murphy SA, *et al.* Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008; 51:724–730.
9. Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG, *et al.* Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med 2014; 371:32–41.
10. The TG and HDL Working Group of the Exome Sequencing Project; National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med 2014; 371:22–31.
11. ■■ Holmes MV, Asselbergs FW, Palmer TM, *et al.* Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J 2014. [Epub ahead of print]

Holmes and colleagues report the results of a Mendelian randomization study drawing on genetic and clinical data from 62 199 participants in 17 studies. Because offspring genotypes are, in effect, randomly assigned at conception (without regards to extraneous variables), the use of genetic variants as dependent variables avoids issues such as reverse causation or confounding that often make observational studies difficult to interpret. Indeed, by simulating a randomized study design, Mendelian randomization studies – unlike observational studies – can suggest causal relationships. In their study, Holmes and colleagues conducted three types of analyses to evaluate the relationship between the various lipid fractions [high-density lipoprotein cholesterol (HDL-C), triglycerides, and LDL-C] and coronary heart disease: an unadjusted, unrestricted analysis, using all genetic variants associated with the lipid fraction of interest as predictors; a restricted analysis, using only genetic variants associated with levels of a single lipid fraction (e.g. HDL-C, but not triglycerides or LDL-C) as predictors; and an adjusted, unrestricted analysis, which took the unrestricted model and sequentially adjusted for the other two lipid fractions and statin use. In two of the analytic approaches (unadjusted, unrestricted and restricted), elevated triglyceride levels were significant predictors of coronary heart disease risk [odds ratio (OR) 1.62, 95% CI 1.24–2.11 and 1.61, 95% CI 1.00–2.59, respectively, for every 1 log unit increase in plasma triglyceride levels], suggesting that triglycerides may be causally related to atherogenesis and coronary heart disease. With respect to the other lipid fractions assessed, only one of the analytic approaches used to evaluate the relationship of HDL-C with coronary heart disease risk was significant, while all three analyses for LDL-C were significant.

12. ■ Thomsen M, Varbo A, Tybjærg-Hansen A, *et al.* Low nonfasting triglycerides and reduced all-cause mortality: a Mendelian randomization study. Clin Chem 2014; 60:737–746.

Using a Mendelian randomization approach and data from the Copenhagen City Heart Study, Thomsen *et al.* studied the effects of genetic variants in lipoprotein lipase (associated with reduced circulating triglyceride levels) on all-cause mortality. They showed a progressively lower risk of all-cause mortality with decreasing levels of nonfasting plasma triglycerides (OR for triglycerides 177–265 mg/dl, 0.84, 95% CI 0.73–0.96; for 89–176 mg/dl, 0.67, 95% CI 0.60–0.76; and for <89 mg/dl, 0.51, 95% CI 0.44–0.58; all compared with nonfasting triglycerides 266–442 mg/dl). Additionally, Thomsen and colleagues demonstrated a cumulative mortality benefit with increasing numbers of triglyceride-decreasing alleles (OR for four alleles, 0.86, 95% CI 0.76–0.97; for five alleles, 0.81, 95% CI 0.71–0.93; and for six alleles, 0.77, 95% CI 0.55–1.08; all compared with zero to three triglyceride-decreasing alleles).

13. Graham MJ, Lee RG, Bell TA, *et al.* Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. Circ Res 2013; 112:1479–1490.

FURTHER RECOMMENDED READING

Roberts R. Genetics of coronary artery disease. Circ Res 2014; 114:1890–1903. ■

Looking more broadly at cardiovascular disease, Roberts reviews the common variants (about half of which are found in >50% of the population) associated with coronary artery disease or myocardial infarction risk, with particular focus on the 9p21 and PCSK9 variants.

Cui G, Li Z, Li R, *et al.* A functional variant in APOA5/A4/C3/A1 gene cluster ■ contributes to elevated triglycerides and severity of CAD by interfering with microRNA 3201 binding efficiency. J Am Coll Cardiol 2014; 64:267–277.

Using functional analysis, Cui *et al.* demonstrate that a genetic variant, rs2266788∗C, located in the 3′ untranslated region (UTR) of the *APOA5* gene, destroys the microRNA 3201 binding site in the 3′ UTR. Because microRNA 3201 binding to the 3′ UTR promotes degradation of APOA5 mRNA, destruction of this binding site increases the translation of APOA5 transcripts, thereby increasing plasma levels. This, in turn, is associated with increased plasma triglyceride levels. Moreover, Cui and colleagues showed that coronary artery disease severity is tracked with the number of copies of the rs2266788∗C variant, such that a higher gene dosage was associated with a greater coronary artery disease severity. This again provides support for the relationship between plasma triglyceride levels and coronary artery disease.

Do RQ, Nicholls SJ, Schwartz GG. Evolving targets for lipid-modifying therapy. ■ EMBO Mol Med 2014; 6:1215–1230.

Along with an overview of cholesterol metabolism, the authors provide a thorough review of potential therapeutic targets within this metabolic pathway, highlighting both currently utilized medications and agents that are still being tested in the process. Therapeutic strategies aimed at lowering lipoprotein(a), LDL-C and triglyceride-rich lipoprotein levels or raising HDL-C levels are discussed.

Sahebkar A, Chew GT, Watts GF. Recent advances in pharmacotherapy for ■■ hypertriglyceridemia. Prog Lipid Res 2014; 56:47–66.

An excellent discussion of the clinical efficacy of several hypotriglyceridemic agents, with emphasis on newer therapeutics in various stages of development or clinical testing (e.g. dual peroxisome proliferator-activated receptor α/γ agonists, diacylglycerol acyltransferase-1 inhibitors, angiopoietin-like protein 3, APOC3-targeted antisense oligonucleotides). Of note, although all of the agents discussed appear effective in lowering plasma triglyceride levels, most have yet to demonstrate reductions in adverse cardiovascular events or prevention of cardiovascular disease.