Triglyceride-rich Lipoprotein Cholesterol (TRL-C)

The Ugly Stepsister of LDL-C

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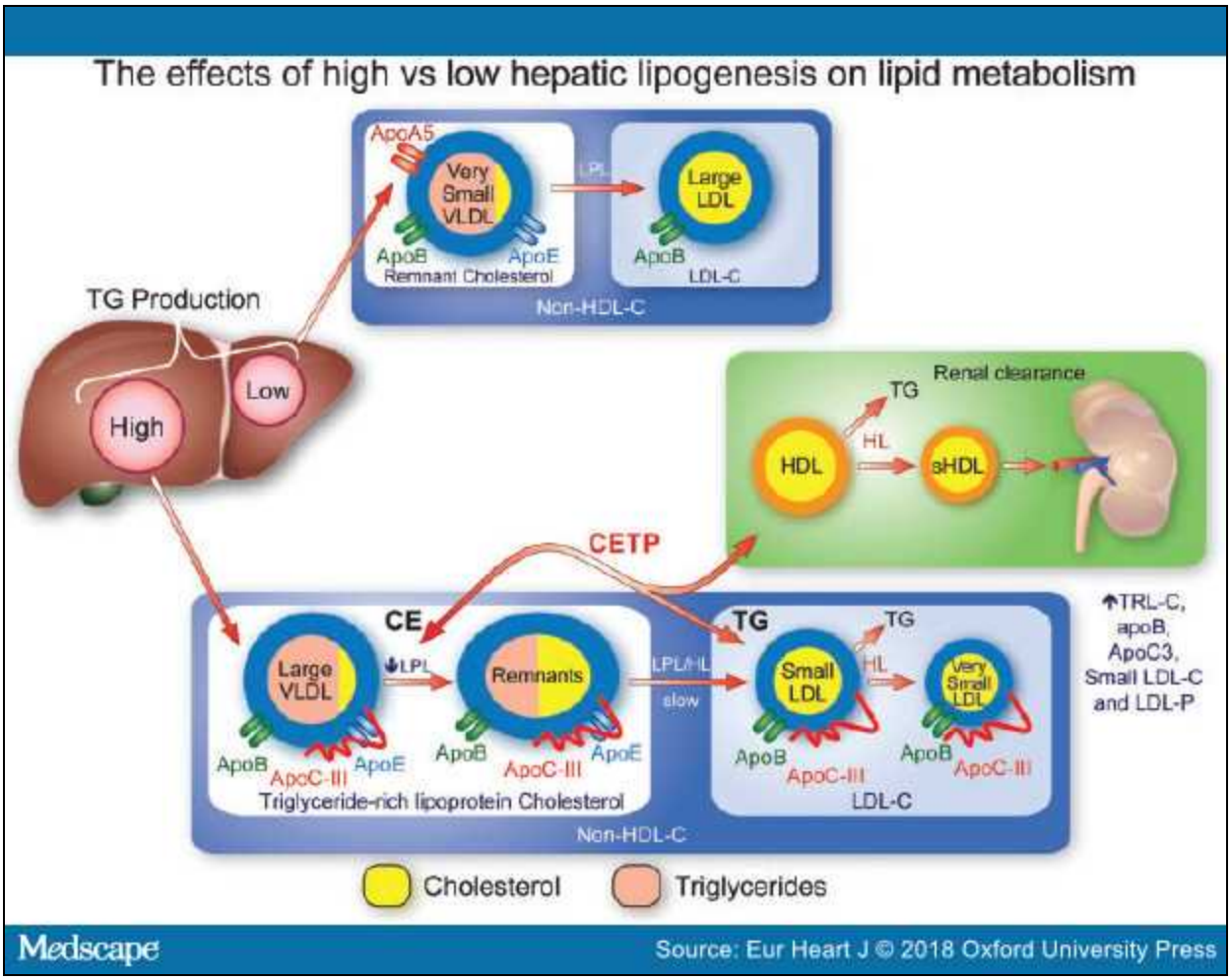
Lowering LDL-C for reducing cardiovascular risk has been a key therapeutic strategy for >30 years. This strategy has been adopted globally primarily by recommending statin therapy to lower LDL-C. There is a general consensus that the lower the LDL-C, the better the clinical outcomes.[1,2] However, there is growing evidence that triglycerides are not just a marker of increased cardiovascular (CV) risk but rather a causal factor that rivals LDL-C.[3] Madsen *et al*. in this issue of the journal[4] have added to the evidence base that targeting patients with hypertriglyceridaemia with statins or other triglyceride-lowering therapies may significantly reduce CV events in patients without pre-existing atherosclerotic cardiovascular disease (ASCVD) and therefore represents a population that deserves special attention for the primary prevention of coronary heart disease.

One issue that affects the clinician's understanding of the role of triglycerides in assessing CV risk is the nomenclature. Non-HDL-C is very simple to calculate: total cholesterol minus HDL-C (both total cholesterol and HDL-C are directly measured). Non-HDL-C is superior to LDL-C as a CV risk predictor and, in the statin trials when non-HDL-C and LDL-C are discordant, risk follows non-HDL-C.[5] The reason that non-HDL-C is a better risk predictor than LDL-C is because the cholesterol content in the triglyceride-rich lipoproteins [very low-density lipoprotein (VLDL), VLDL remnants, intermediate-density lipoprotein (IDL), and chylomicrons] is also atherogenic. The cholesterol content in these triglyceride-rich lipoproteins has been estimated by the Freidwald formula as approximately triglyceride levels divided by five, because these lipoproteins have ~60% triglyceride and 12% cholesterol (a 5:1 ratio).[6] The confusion arises as to what to call this "other" cholesterol (non-HDL-C minus LDL-C). The most accurate term is triglyceride-rich lipoprotein cholesterol (TRL-C) but it has also been called 'remnant cholesterol'[7] and most commonly VLDL-C.

Defining the cholesterol content in these triglyceride-rich lipoproteins is clinically important because this is the substrate for development of the atherosclerotic plaque rather than the triglycerides. In fact, a study suggests that ~50% of the cholesterol found in atherosclerotic plaque is derived from TRL-C even though, in most patients, TRL-C levels are much lower than calculated LDL-C.[8] Another area of confusion is that hypertriglyceridaemia is associated with a myriad of lipoprotein modifications and it is unclear which of these changes (if not all) are causal for atherosclerosis. In the setting of increased hepatic lipogenesis (Take Home Figure), the liver secretes enlarged VLDL which is enriched but results in delayed peripheral lipolysis and clearance of these triglyceride-rich particles. Therefore, there is delayed conversion of VLDL to LDL, resulting in elevation in TRL-C. Since lipolysis is impaired, LDL particles are also enriched in apoCIII and triglycerides which ultimately transform into smaller and more numerous particles. The end result is that hypertriglyceridaemia is associated with elevated TRL-C (and hence non-HDL-C), ApoB, ApoCIII, small dense LDL-C, and LDL particles (LDL-Ps) in the setting of a normal or low level of LDL-C. All of these lipoprotein changes are associated with increased CV risk[9–12] and, based on genome-wide association trials, are more casually validated than the accompanying low HDL-C for the development of atherosclerosis.[13] If triglycerides are lowered by lifestyle changes, fibrates, or omega-3 fatty acids, there is a reduction in TRL-C, apoB, and apoCIII, and this shifts from small dense LDL particles (and hence small dense LDL-C) to larger LDL particles.[14,15] Statins effectively lower TRL-C, ApoB, ApoCIII, small dense LDL-C, and LDL-Ps, and therefore represent the best therapeutic option to affect CV risk in the hypertriglyceridaemic patient.[16,17]



Take Home Figure.

The effects of high vs. low hepatic lipogenesis on lipid metabolism.

Madsen *et al*.[4] raise two important clinical issues in regards to the management of CV risk in patients with hypertriglyceridaemia. They have identified, through the Copenhagen Heart Study which has provided a plethora of insights into the role of triglyceride levels and CV risk, a primary prevention population with hypertriglyceridaemia (>3 mmol/L) that is not statin eligible as defined according to the 2016 ESC/EAS guidelines, but has a ASCVD risk equivalent to statin-eligible patients. Therefore, the hypertriglyceridaemic patient represents an unmet need for primary prevention and may potentially be a population that could be enrolled with equipoise in a placebo-controlled outcome trial with a statin or triglyceride-lowering therapy such as omega-3 fatty acids or fibrates.

Evidence from randomized controlled trials (RCTs) of interventions to treat such elevations is limited by the fact that no large-scale trial has been completed in which subjects were selected on the basis of triglyceride elevation and treated with an agent that substantially lowers triglycerides and TRL-C. Three such trials are underway for secondary prevention in patients with pre-existing ASCVD on statin therapy: REDUCE-IT, STRENGTH, and PROMINENT. These trials are similarly addressing the high residual risk population with hypertriglyceridaemia, but also have important differences that may lead to discordant results. REDUCE-IT [Reduction of Cardiovascular Events Outcomes trial (ClinicalTrials number NCT01492361)], which will probably be completed first of the three, is targeting high-risk patients with hypertriglyceridaemia without a HDL-C criterion. This trial with 8000 patients treated with either 4 g of icosopentyl ester or control is trying to replicate the benefits of the JELIS trial in which the subset of patients with triglycerides >150 mg/dL and HDL-C <40 mg/dL had a dramatic 53% reduction in CV events in combination with a low dose of pravastatin.[18] The JELIS trial was conducted in Japan, and whether REDUCE-IT can demonstrate a CV benefit in a population with a much lower baseline of omega-3 fatty acid levels and in an era of higher statin dosing with aspirin is eagerly anticipated. The STRENGTH trial [Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia (NCT02104817)] has a much larger sample size (n = 13 000) in which omega-3 carboxylic acid 4 g per day containing both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with increased bioavailability is utilized compared with corn oil in a population selected to have a much higher atherogenic

residual risk due to a combination of hypertriglyceridaemia paired with low HDL-C. In the ACCORD trial, this cohort had an ~70% greater CV event rate compared with the rest of the study population and appeared to benefit with an ~8–9 mg/dL decrease in TRL-C.[19] PROMINENT (pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in diabetic patients) will recruit an estimated 10 000 high-risk diabetic patients worldwide who have hypertriglyceridaemia paired with low HDL-C to determine the effects of treatment with pemafibrate, a potent PPAR-α (peroxisome proliferator-activated receptor-α) agent, on cardiovascular outcomes in a randomized placebo-controlled trial.[20] Therefore, this trial will attempt to replicate the ACCORD subgroup findings with fenofibrate utilizing a novel, more potent PPAR-α agent and a much larger sample size. While these CV outcome trials are under way, subgroup analyses of data from previous RCTs are suggestive of a reduction in coronary artery disease and ASCVD event rates with lipid-altering therapies that lower triglyceride and TRL-C, including statins, fibrates, omega-3 fatty acid concentrates, and niacin in patients with elevation of triglycerides, particularly if accompanied by a low HDL-C concentration.[19] If any of these three secondary prevention trials are positive, then a primary prevention trial in patients with hypertriglyceridaemia may not be necessary. The evidence for treatment for patients with hypertriglyceridaemia and therefore elevated non-HDL-C without clinical ASCVD is based on the following assertions.

i. Non-HDL-C, which contains the cholesterol carried in LDL-Ps (including IDLs) plus that carried in triglyceride-rich lipoproteins (VLDL and chylomicron particles), has consistently been a stronger predictor of CV disease (CVD) risk than LDL-C in observational studies and clinical trials of lipid-altering therapies.

ii. The superiority of non-HDL-C over LDL-C as an indicator of CVD risk is based, in part, on recent findings from studies of genetic variants that influence TRL-C or LDL-C levels that they are both causally associated with CVD.

iii. Each mg/dL elevation of VLDL-C is associated with at least as large an increase in CVD risk as is observed per mg/dL of LDL-C elevation, thus supporting a causal role for TRL-C elevation in atherosclerotic CVD.

iv. In RCTs, lowering TRL-C with fibrates, niacin, and an omega-3 fatty acid (EPA) in participants with elevated triglycerides, or elevated triglycerides and low HDL-C, has produced reductions in CV events, with a degree of risk reduction similar to that which would be predicted based on observational evidence.

v. In the cardiovascular outcomes trials with drugs that lower triglycerides and TRL-C, but do not lower (and, in some cases, elevate) LDL-C, there is a high correlation between TRL-C reduction and the magnitude of the CV event benefit.

Therefore, there is compelling evidence that lowering elevated non-HDL-C in the patients with hypertriglyceridaemia with 'low' levels of LDL-C who are considered not statin eligible will provide a clinical benefit. Statins are most probably the preferred therapeutic options based on the ability to lower TRL-C, apoB, LDL-Ps, and small dense LDL-C, which are residual atherogenic factors despite a low level of LDL-C. Combination therapy with more than one potent triglyceride-lowering therapy such as omega-3 fatty acids and PPAR-α agents may provide further risk reduction in a patient population at high CV risk that has not received the attention it deserves due to the failure to recognize the potent atherogenicity of TRL-C.

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