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Braunwald's Corner

Triglycerides: the past, the present, and the future

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The past

The relationship between cholesterol (C) and arteriosclerotic cardiovascular disease (ASCVD) emerged early in the 20th century. In 1910, Windaus, a German chemist, found C in atherosclerotic plaques in human aortas. In 1913, Anitschkow, a young Russian experimental pathologist, fed large quantities of pure C to rabbits, causing vascular changes similar to those in developing arteriosclerotic plaques in patients.[1] The importance of LDL-C in the development of ASCVD grew slowly but steadily as a consequence of basic research that was appropriately rewarded by nine separate Nobel Prizes, as well as multiple genetic, epidemiologic, and clinical studies. Drugs to reduce circulating C were developed and found to be effective in both primary and secondary preventions of ASCVD; they have prolonged the lives of millions of people around the world. Taken together, the C story has been one of the medical triumphs of the 20th century.[1]

However, despite these notable advances, lowering LDL-C did not *abolish* ASCVD, and the search was on for other dyslipidaemias that could be responsible for residual atherogenesis. Triglycerides (TG), which provide important sources of energy, became obvious candidates. Indeed, in 1959, Albrink and Mann[2] reported that serum TG was frequently elevated in some persons who had experienced a myocardial infarction. This observation was repeatedly confirmed and extended to other manifestations of ASCVD. For example, in the PROVE IT (TIMI 22) trial, we observed that in statin-treated post-acute coronary syndrome patients, an elevated TG (>150 mg/dL/1.7 mmol/L) was associated with higher cardiovascular risk than those with lower (normal) levels.[3] However, it was observed that TG levels were not independent of LDL-C and other ASCVD risk factors.

The present

Triglycerides, produced in the liver and the intestines, are carried in the bloodstream largely in very low density lipoproteins (VLDLs) and chylomicrons and are hydrolysed by lipoprotein lipase (LpL). In both observational studies and clinical trials, several drugs have been shown to reduce the levels of circulating TGs. Most attention has been focused on fibrates, which act on the cell nucleus to inhibit TG production, but clinical outcomes have been either neutral or inconclusive. For example, a recent well-conducted, large placebo-controlled trial (PROMINENT) studied patients with hypertriglyceridaemia, diabetes, and low levels of LDL-C. A potent fibrate (pemafibrate) reduced TG, VLDL, and VLDL-remnant C (see below) modestly, each by about one-fourth, but did not reduce the risk of cardiac events.[4] As a result of this and other disappointments, the suspicion has grown that while the *association* between TG levels and atherogenesis was clear, a *causal* connection did not appear to be present. This concept was supported by the finding that in contrast to C, TGs *per se* have not been found in atherosclerotic plaques. It was surmised that the TG may carry a culprit substance.

In addition to carrying TGs, partially hydrolysed TG-rich lipoproteins also contain substantial quantities of C in their lipoprotein particles that came from nascent VLDL and chylomicron particles.[5] These are frequently referred to as 'remnant C' (RC) (the term used in this paper) which can be measured directly or calculated by subtracting the sum of LDL-C and HDL-C from total C.[6] In contrast to TG, but like LDL-C, RC can penetrate the arterial intima and play an important role in the development of atherosclerotic plaques. Non-HDL-C, which is calculated by subtracting HDL-C from total C, includes the C in LDL, as well as the C from VLDL, chylomicrons, and RC, while apolipoprotein B (ApoB) is on the surface of all of these atherogenic particles. Both non-HDL-C and ApoB are more accurate predictors of ASCVD risk than LDL-C, which is usually calculated and is widely used.[7]

Nordestgaard and Varbo[6] summarized both pre-clinical and clinical studies as follows: 'High (circulating) TG concentrations are a marker for raised remnant rich in C, which upon entrance into the (arterial) intima, leads to low grade inflammation, atherosclerotic plaques and ultimately cardiovascular disease and increased mortality.' This overview is supported by a large Mendelian randomization trial which demonstrated the adverse effect of RC on cardiovascular outcome.[8] Thus, elevated TGs may be considered to be risk *markers* for ASCVD, while RCs are likely true risk *factors*.

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The future

Apolipoprotein CIII (APOC3) is a glycoprotein produced by the liver that both inhibits LpL and reduces TG removal by the liver and was found to cause hypertriglyceridaemia in transgenic mice.[9] Persons with loss-of-function variants of the *APOC3* gene have low levels of circulating TGs and a low incidence of ASCVD. These findings have made ApoC3 a logical target for the treatment of elevated TG.[5,10] Two approaches for reducing ApoC3 are being studied; the first is antisense oligonucleotides (ASOs), which act on the cell nucleus by inhibiting *APOC3* mRNA and increasing LpL activity. Olezarsen, a drug in this class, has been studied by Bergmark *et al.*[11] in the TIMI 73 trial that studied patients with moderate hypertriglyceridaemia. It reduced APOC3 and circulating TGs by half, accompanied by smaller but significant reductions in VLDL-C, ApoB, and non-HDL-C without exhibiting serious adverse effects; phase 3 trials with this compound are underway.

The second approach to reducing ApoC3 is with ARO-APOC3 (plozasiran), a small interfering RNA (siRNA) which acts in the cytoplasm. It has been studied by Ballantyne *et al.*[12] in a placebo-controlled dose ranging phase 2 trial in persons with combined (mixed) hyperlipidaemia (elevated LDL-C and TG). In addition to markedly reducing APOC3 and serum TG, importantly, it also reduced RC by half and significantly reduced ApoB, non-HDL-C, and LDL-C.

Angiopoietin-like 3 (ANGPTL-3) is a protein that inhibits both LpL and endothelial lipase and reduces hepatic uptake of lipoproteins. Similar to *APOC3*, loss-of-function variants of the *ANGPT* gene increased LpL and endothelial lipase activities and were associated with lower levels of TG, LDL-C, RC, and non-HDL-C, as well as the risk of developing ASCVD. In a trial of patients with combined hyperlipidaemia, Rosenson *et al.*[13] reported that the siRNA zodasiran reduced dose-related ANGPTL3, TGs, RC, LDL-C, ApoB, and non-HDL-C. However, unlike plozasiran, zodasiran did not reduce LDL-C. Both plozasiran and zodasiran were well tolerated but exhibited modest worsening glycaemic control in some patients with diabetes or pre-diabetes, which could be readily controlled.

Conclusions

The unfolding of the TG story has been important, interesting, challenging, and exciting: *important* because early studies showed that elevated concentrations of circulating TGs were frequently present in patients with ASCVD and were considered to be responsible for residual atherogenic risk, especially in statin-treated patients; *interesting* because further work showed that these adverse clinical effects of abnormally elevated TGs appear to be primarily due to our 'old enemy', C, which is increased in partially hydrolysed TG-bearing lipoproteins, i.e. RC; *challenging* because no way to safely reduce RC was possible; and *exciting* because recent research has identified promising approaches that may limit residual atherogenesis in LDL-C treated patients. These include both an ASO and an siRNA that inhibit APOC3 and a second siRNA that blocks ANGPT3. Both siRNAs cause robust reductions of RC, the likely culprit. They also reduce ApoB and non-HDL-C, both of which are predictors of ASCVD risk. The next step will be to determine whether these biochemical improvements will be translated into improved clinical outcomes in patients with hypertriglyceridaemia. It will be interesting to determine whether a combination of the two siRNAs (plozasiran and zodasiran) will have additive actions. Ultimately, editing of the *APOC3* and/or *ANGPTL3* genes may provide more durable inhibition.

Declarations

Disclosure of Interest

The author declares no disclosure of interest for this contribution.

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