

Triglyceride lowering 2.0: back to the future?

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This editorial refers to ‘Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies’[†], by P.R. Lawler *et al.*, on page 86.

Why the renewed interest in triglyceride?

With the disappointing results of the fibrate–statin combination trials¹ and the long-standing view that the positive association of plasma triglyceride with atherosclerotic cardiovascular disease (ASCVD) risk was irredeemably confounded mainly by its relationship to HDL,^{1,2} the concept that this lipid represented a reasonable target for CVD prevention slowly disappeared over the horizon. However, the requiem may have been premature—a number of current lines of evidence lead to the conclusion that triglyceride lowering may after all be an effective intervention strategy. First, the issue of confounding was addressed in a series of Mendelian randomization studies that demonstrated that genetic variants altering plasma triglyceride levels led to differences in risk of ASCVD.³ In interpreting these studies, however, care must be taken not to assume that raised triglyceride directly causes atherosclerosis since this lipid is not found in abundance in plaque. Rather, perturbations in plasma triglyceride metabolism have consequences for cholesterol-transporting lipoproteins, causing the accumulation of remnant lipoproteins^{2,4} and changes in the structure and metabolism of LDL.^{1,2,5} Second, recent studies have shown the concentration of remnant lipoproteins to be associated with ASCVD outcomes independent of LDL cholesterol (LDLc).^{2,4} The third line of evidence is the remarkably clear, positive result of the REDUCE-IT trial.⁶ This study in ASCVD subjects on background statin therapy with a plasma triglyceride in the range 1.52–5.63 mmol/L (135–499 mg/dL) reported a 25% lower risk in subjects allocated to ethyl eicosapentaenoic acid at 4 g/day vs. placebo.

Epidemiological studies consistently find that triglyceride exhibits a positive association with risk of a first ASCVD event.^{1,2} However,

since statins are known to be able to reduce plasma triglyceride levels especially in individuals with hypertriglyceridaemia,⁷ it has been debatable as to whether in well-treated populations with established ASCVD elevated plasma triglyceride retains a relationship to risk of a further event. This question has been addressed in a number of selected cohorts and in the more general population in the investigation of Lawler *et al.*⁸ reported in the current issue of the *European Heart Journal*. Using a record linkage approach, they explored in 196 717 subjects with prevalent ASCVD drawn from the CANHEART study the relationship of plasma triglyceride to a composite CVD outcome measure. Increasing plasma triglyceride across the range <1.0 to \geq 4.0 mmol/L was associated with a 52% elevated risk of the primary endpoint. Where it could be ascertained (i.e. for subjects \geq 66 years old), most people (>95%) were on statin treatment and it is reasonable to assume (as the authors did) that this would be true of the whole cohort. The value of interrogating health records in this way lies in the fact that they reflect the ‘real world’, and on that basis it was predicted that in clinical practice about a quarter of ASCVD patients will have plasma triglyceride and (moderately well controlled) LDLc in the range used as entry criteria for the REDUCE-IT trial, and hence potentially would be eligible for triglyceride-lowering therapy. This figure, however, is likely to be an upper estimate since it is based on a broad definition of hypertriglyceridaemia. Adopting the more usual threshold of >2.3 mmol/L (200 mg/dL)^{2,9} would identify substantially fewer candidates for this intervention. In REDUCE-IT, subjects were included initially using the full 135–499 mg/dL range, but the lower limit was adjusted to \geq 200 mg/dL about halfway through recruitment. Hence, the mean plasma triglyceride (217 mg/dL) was higher than seen in the CANHEART cohort (177 mg/dL) (table 4 in Lawler *et al.*⁸). Whatever threshold is used, it is clear that a substantial proportion of ASCVD patients will exhibit on statin therapy elevated plasma triglyceride levels that are worth treating, possibly with ethyl eicosapentaenoic acid⁶ or with other high-dose fish oil regimens,⁹ or with a peroxisome proliferator-activated receptor- α (PPAR α) agonist such as pemafibrate which is being investigated in a similar hypertriglyceridaemic population in the ongoing PROMINENT study.¹⁰

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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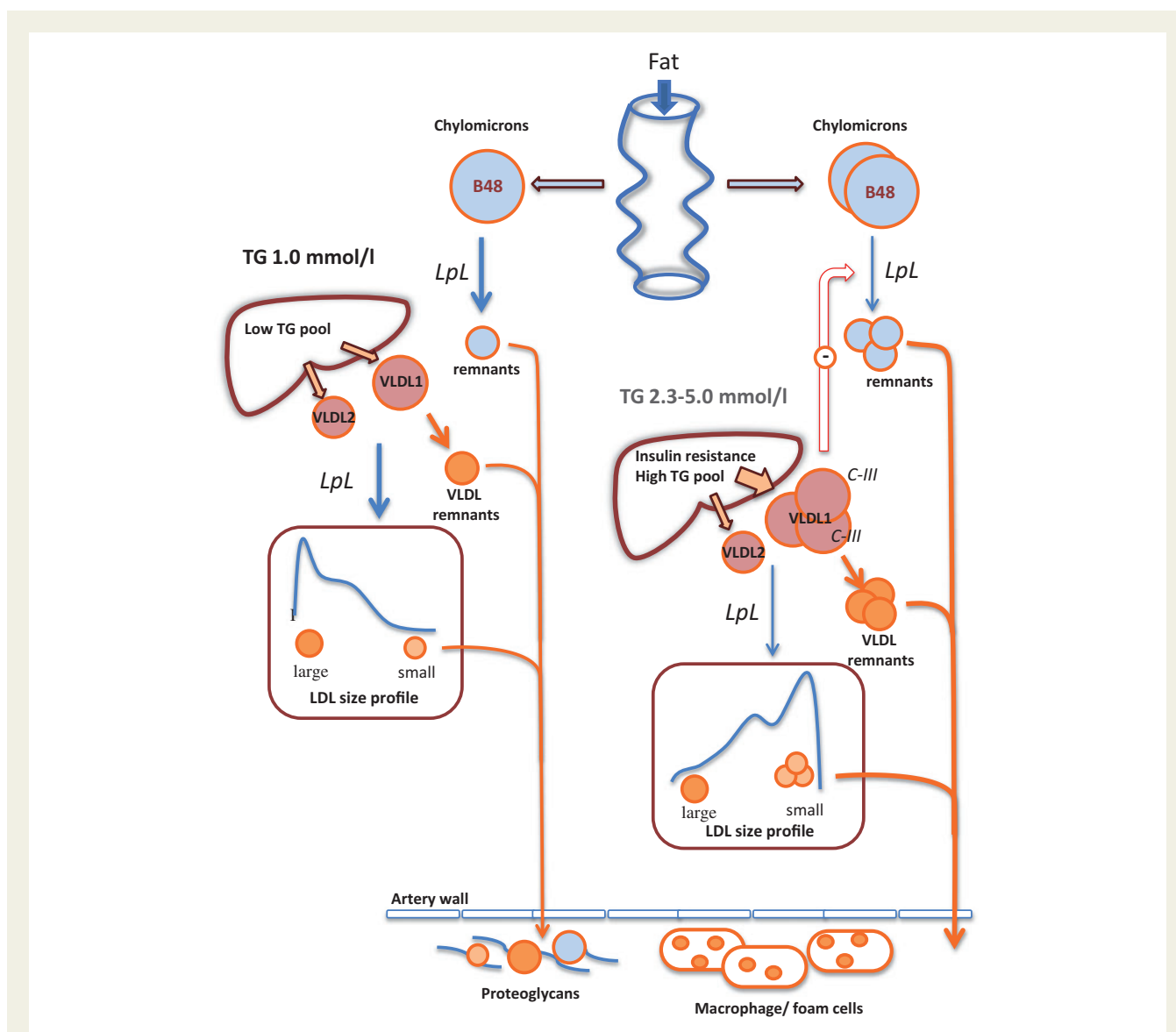


Figure 1 The impact of triglyceride (TG) levels on the apoB-containing lipoprotein spectrum is depicted schematically for those with an optimal level (TG 1.0 mmol/L) and those with moderate hypertriglyceridaemia (TG 2.3–5.0 mmol/L). The liver generates triglyceride-carrying lipoproteins associated with apoB100 that vary in size from large VLDL₁ to smaller VLDL₂. Lipoprotein lipase acts on VLDL to hydrolyse the core TG and convert the particles to LDL as the terminal product of lipolysis. Subjects with optimal TG levels make few remnants and the LDL formed is mostly large. Chylomicrons containing apoB48 as the main structural protein released from the intestine during lipid absorption are rapidly converted to smaller particles (remnants) that are cleared by the liver. Subjects with elevated plasma TG levels overproduce VLDL₁ due to high fat content in the liver and a failure of insulin to suppress VLDL₁ synthesis.¹¹ Lipolysis is also delayed due to the presence high levels of apoCIII, an inhibitor of lipoprotein lipase. Inefficient lipolysis leads to prolonged circulation times and increased cholesterol (cholesteryl ester) acquisition by VLDL that in turn favours formation of VLDL remnants. In those with high TG, remodelling of LDL leads to the generation of high amounts of small, dense LDL.⁵ Chylomicron metabolism is also compromised, with increased formation of apoB48-containing remnants. The relatively long-lived remnants and small LDL are available to bind to arterial wall proteoglycan and promote foam cell^{4,12} formation.

What are the metabolic causes and consequences of hypertriglyceridaemia?

The range of triglyceride concentration used to define the cohort of subjects in REDUCE-IT⁶ and the study of Lawler *et al.*⁸ is wide,

including those in the upper end of what clinical chemists term the normal range (up to 2.3 mmol/L) and those with classically defined moderate hypertriglyceridaemia (2.3–5.0 mmol/L).^{2,9} As triglyceride rises over this range, the distribution of lipoprotein particles changes (Figure 1). Large very low-density lipoproteins (VLDL₁) become the major triglyceride-rich species due to a combination of increased production from the liver (that in many is the result of high levels of

liver fat and central insulin resistance¹¹—about half of the subjects in the CANHEART cohort⁸ and REDUCE-IT⁶ were diabetic) and decreased lipolytic efficiency probably caused by high rates of apolipoprotein CIII (apoCIII) synthesis; apoCIII has long been recognized as an inhibitor of lipoprotein lipase.¹¹ The presence of high levels of VLDL₁ with a prolonged residence time in the circulation greatly increases the propensity to form remnants, so called because they are partially lipolysed triglyceride-rich lipoproteins that are no longer able to be efficiently delipidated. These particles are enriched in cholesterol, particularly cholesteryl esters, and are believed to be at least as atherogenic as LDL on a per particle basis.^{4,12} A further consequence of elevated levels of VLDL₁ is the enhanced generation of small dense LDL that again is thought to be particularly atherogenic since it has reduced affinity for the LDL receptor and is more likely to bind to arterial wall proteoglycans.^{2,5} The hypertriglyceridaemic patient is therefore in double jeopardy in terms of lipoprotein pathophysiology. Statins are able to induce accelerated clearance of VLDL remnants and LDL from the bloodstream, and hence lower the incidence of ASCVD in hypertriglyceridaemia,⁷ but there appears to be a residual risk that is amenable to targeted triglyceride reduction.^{1,2,9}

Of course, the liver is not the only organ involved in triglyceride transport. The intestine when presented with dietary fat generates a wave of chylomicrons that enter the bloodstream and undergo rapid lipolysis using the same enzymatic pathway as VLDL₁. In hypertriglyceridaemia, chylomicron metabolism is compromised due possibly to high levels of apoCIII and the presence of abundant VLDL₁ particles that compete for available lipoprotein lipase (Figure 1). The result is a greater peak triglyceride concentration during lipid absorption and the generation of high levels of chylomicron remnants.^{1,9} Since the intestine makes a short form of apoB (B48), whereas the liver makes full-length apoB100, it is possible to track the behaviour of triglyceride-rich particles from these two tissue sources. In a recent study,¹³ we were able to show that apoB48-containing particles in hypertriglyceridaemic subjects are released across the entire chylomicron–VLDL size range, persist for many hours, and accumulate to high levels, thus adding to the circulating remnant particle population. It is worth noting that ‘remnant’ is primarily a metabolic term describing partially lipolysed, cholesteryl ester-rich, slowly metabolized particles and, as such, these particles are a subset of the spectrum of triglyceride-transporting lipoproteins found in the circulation (Figure 1). Thus, use of total VLDL cholesterol⁸ is a surrogate measure for remnant cholesterol that is probably proportionate to the amount of remnants present but is not an accurate quantification of this subfraction.

What happens when you lower triglyceride?

Two therapeutic modalities are commonly used for the specific reduction of elevated plasma triglyceride levels—PPAR α agonists/fibrates^{1,2} and high doses of fish oil/omega-3 fatty acids.^{2,9} Their mechanisms of action have been well studied over many years; fibrates act mainly to increase VLDL clearance,¹ whereas omega-3 fatty acids have been found to lower VLDL production in the liver.^{9,14} The impact of these drugs on the entirety of lipoprotein metabolism is a function of the basal plasma triglyceride level.^{1,5,9} Both classes of

agents reduce the extent of chylomicronaemia following a fat meal and hence the generation of apoB48-containing remnants, and by their effects on VLDL metabolism decrease the levels of VLDL (apoB100-containing) remnants. It is known that plasma triglyceride is the major factor controlling LDL particle size, so, as the concentration of this lipid falls, LDL size will increase and the amount of small, dense LDL in the circulation will be reduced.^{1,4,9} The response in terms of LDLc concentration for most individuals will be little change,^{2,9} whereas those with initial triglyceride of \sim 5.0 mmol/L may experience a moderate increase in LDLc.^{5,9} Thus, as stated above, if the influence of dysregulation of plasma triglyceride on ASCVD risk is primarily through the impact on the apoB-containing lipoprotein spectrum (Figure 1), then the benefits of lowering this lipid will be a function of the net effect on remnants and LDL. The importance of understanding the impact of triglyceride-lowering strategies on the whole apoB-containing lipoprotein spectrum is further emphasized in a recent investigation demonstrating that the ASCVD risk reduction associated with genetic variants that lower triglyceride is dependent on the associated reduction in apoB.¹⁵ Thus, relating change in triglyceride to change in risk may not be straightforward and in this context it is of interest to note that in the REDUCE-IT trial there was no obvious relationship between basal triglyceride and reduction in risk (prompting consideration of possible non-lipoprotein mechanisms of benefit by Bhatt *et al.*⁶

In conclusion, triglyceride lowering may have a new lease of life now that the focus has moved to subjects who are likely to receive the greatest benefit from this intervention. However, given the impact of raised triglyceride on the metabolism of the whole spectrum of apoB-containing lipoproteins, we should not expect interpretation of the relationship between lipid reduction and decreased ASCVD risk to be as straightforward as it has been for LDL cholesterol.

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