Packard, C. J. (2020) Triglyceride lowering 2.0: back to the future? *European Heart Journal*, 41(1), pp. 95-98. (doi:10.1093/eurheartj/ehz810)

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

http://eprints.gla.ac.uk/204813/

Deposited on: 06 January 2020

Triglyceride lowering 2.0: Back to the future?

Chris J Packard

Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland, G12 8TA

Corresponding author:

Professor Chris J Packard
Email chris.j.packard@gmail.com
Phone (44) 141 330 2677
Institute of Cardiovascular and Medical Sciences
Glasgow University
126 University Place
Glasgow G12 8TA

Why the renewed interest in triglyceride?

With the disappointing results of the fibrate-statin combination trials (1) and the longstanding 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 faded 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 randomisation 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 to 5.63 mmol/l (135 to 499 mg/dl) reported a 25% lower risk in subjects allocated to ethyl eicosapentanoic acid at 4g/day versus 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 hypertriglyceridemia (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. 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 >=4.0 mmol/l was associated with a 52% elevated risk of the primary endpoint. Where it could be ascertained (i.e. for subjects >=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 hypertriglyceridemia. Adopting the more usual threshold of >2.3mmol/l (200mg/dl) (2,9) would identify substantially fewer candidates for this intervention. In REDUCE-IT subjects were included initially using the full 135-499mg/dl range but the lower limit was adjusted to >=200mg/dl about halfway through recruitment. Hence, the mean plasma triglyceride (217mg/dl) was higher than seen in the CANHEART cohort (177mg/dl) (Table 4 in (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 eicosapentanoic acid (6) or with other high dose fish oil regimens (9), or with a PPARα agonist such as pemafibrate which is being investigated in a similar hypertriglyceridemic population in the ongoing PROMINENT study (10).

What are the metabolic causes and consequences of hypertriglyceridemia?
The range of triglyceride concentration used to define the cohort of subjects in REDUCE-IT (6) 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 hypertriglyceridemia (2.3 to 5.0 mmol/l) (2,9). As triglyceride rises over this range the distribution of lipoprotein particles changes (Figure1). Large very low density lipoproteins (VLDL$_1$) 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 resistance (11) - about half of the subjects in the CANHEART cohort (8) and REDUCE-IT (6) were diabetic) and decreased lipolytic efficiency likely caused by high rates of apoC-III synthesis; apoCIII has long been recognised as an inhibitor of lipoprotein lipase (11). The presence of high levels of VLDL$_1$ 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 VLDL$_1$ 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 hypertriglyceridemic 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 hypertriglyceridemia (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 VLDL$_1$. In hypertriglyceridemia, chylomicron metabolism is compromised due possibly to high levels of apoCIII and the presence of abundant VLDL$_1$ 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 behavior of triglyceride-rich particles from these two tissue sources. In a recent study (13) we were able to show that apoB48-containing particles in hypertriglyceridemic 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 cholesterol (8) 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 – PPARα 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 chylomicronemia following a fat meal and hence the generation of apoB48-conting 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 around 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 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-lipopotein 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 discussion of potentially additional, non-lipoprotein mediated mechanisms in (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.

References

1. Fruchart JC, Santos RD, Aguilar-Salinas C, Aikawa M, Al Rasadi K, Amarenco P, Barter PJ, Ceska R, Corsini A, Després JP, Duriez P, Eckel RH, Ezhov MV, Farnier M, Ginsberg HN, Hermans MP, Ishibashi S, Karpe F, Kodama T, Koenig W, Krempf M, Lim S, Lorenzatti AJ, McPherson R, Nuñez-Cortes JM, Nordestgaard BG, Ogawa H, Packard CJ, Plutzky J, Ponte-Negretti CI, Pradhan A, Ray KK, Reiner Ž, Ridker PM, Ruscica M, Sadikot S, Shimano H, Sritara P, Stock JK, Su TC, Susekov AV, Tartar A, Taskinen MR, Tenenbaum A, Tokgözoğlu LS, Tomlinson B, Tybjærg-Hansen A, Valensi P, Vrablík M, Wahli W, Watts GF, Yamashita S, Yokote K, Zambon A, Libby P.The selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) paradigm: conceptual framework and therapeutic potential : A consensus statement from the International Atherosclerosis Society (IAS) and the Residual Risk Reduction Initiative (R3i) Foundation. Cardiovasc Diabetol. 2019;18:71. doi: 10.1186/s12933-019-0864-7.

2. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group . 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019 Aug 31. pii: ehz455. doi: 10.1093/eurheartj/ehz455. [Epub ahead of print] No abstract available.

3. Tall AR. Increasing Lipolysis and Reducing Atherosclerosis. New Engl. J Med. 2017;377:280-3.

4. Nordestgaard BG. Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease: New Insights From Epidemiology, Genetics, and Biology.Circ Res. 2016;118:547-63

5. Packard CJ, Shepherd J. Lipoprotein heterogeneity and apolipoprotein B metabolism. Arterioscler Thromb Vasc Biol. 1997;17:3542-56

6. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. New Engl. J. Med. 2019;380:11-22.

7. Caslake MJ, Packard CJ. Phenotypes, genotypes and response to statin therapy. Curr Opin Lipidol. 2004;15:387-92.

8. Lawler PR, Kotrri G, Koh M, Goodman SG, Farkouh ME, Lee DS, Austin PC, Udell JA, Ko DT. Real world risk of cardiovascular outcomes associated with hypertriglyceridemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies. Europ. Heart J. (2019) x;xx-xx.

9. Skulas-Ray AC, **Wilson** PWF, Harris WS, **Brinton** EA, Kris-Etherton PM, Richter CK, Jacobson TA, Engler MB, Miller M, Robinson JG, Blum CB, Rodriguez-Leyva D, de Ferranti SD, Welty FK; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-

3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. Circulation. 2019;140:e673-e691.

10. Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, Ginsberg H, Hiatt WR,Ishibashi S, Koenig W, Nordestgaard BG, Fruchart JC, Libby P and Ridker PM. Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients withDiabetes (PROMINENT) study. Am Heart J. 2018;206:80-93.

11. Borén J, Watts GF, Adiels M, Söderlund S, Chan DC, Hakkarainen A, Lundbom N, Matikainen N, Kahri J, Vergès B, Barrett PH, Taskinen MR. Kinetic and Related Determinants of Plasma Triglyceride Concentration in Abdominal Obesity: Multicenter Tracer Kinetic Study. Arterioscler Thromb Vasc Biol. 2015;35:2218-24

12. Dallinga-Thie GM, Kroon J, Borén J, Chapman MJ. Triglyceride-Rich Lipoproteins and Remnants: Targets for Therapy? Curr Cardiol Rep. 2016;18:67. doi: 10.1007/s11886-016-0745-6.

13. Björnson E, Packard CJ, Adiels M, Andersson L, Matikainen N, Söderlund S, Kahri J, Sihlbom C, Thorsell A, Zhou H, Taskinen MR, Borén J. Investigation of human apoB48 metabolism using a new, integrated non-steady-state model of apoB48 and apoB100 kinetics. J Intern Med. 2019;285:562-577

14. Wong AT, Chan DC, Ooi EM, Ng TW, Watts GF, Barrett PH. Omega-3 fatty acid ethyl ester supplementation decreases very-low-density lipoprotein triacylglycerol secretion in obese men. Clin Sci (Lond). 2013;125:45-51.

15. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, Laufs U, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Nicholls SJ, Bhatt DL, SabatineMS and Catapano AL. Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. JAMA. 2019;321:364-373.

Figure legend

The impact of triglyceride 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 hypertriglyceridemia (TG 2.3-5.0mmol/l). The liver generates triglyceride-carrying lipoproteins associated with apoB100 that vary in size from large $VLDL_1$ to smaller $VLDL_2$. Lipoprotein lipase acts on VLDL to hydrolyse the core triglyceride and convert the particles to LDL as the terminal product of lipolysis. Subjects with optimal triglyceride 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 triglyceride levels overproduce $VLDL_1$ due to high fat content in the liver and a failure of insulin to suppress $VLDL_1$ 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 triglyceride, remodeling of LDL leads to the generation of high amounts of small, dense LDL (5). Chylomicron metabolism too is 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 formation (4,12).

Figure 1