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# Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society

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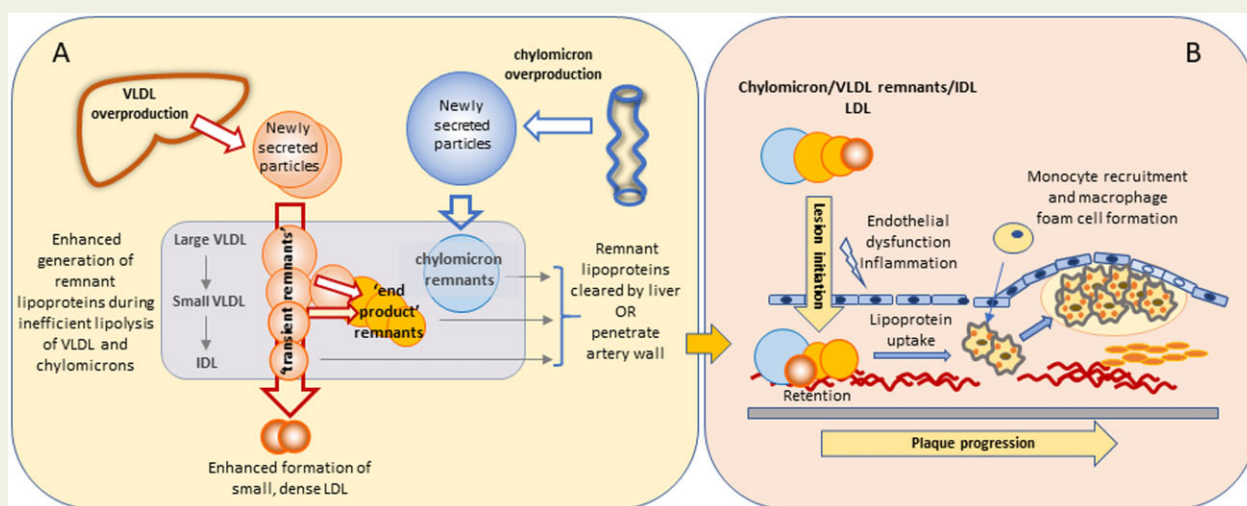
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Recent advances in human genetics, together with a large body of epidemiologic, preclinical, and clinical trial results, provide strong support for a causal association between triglycerides (TG), TG-rich lipoproteins (TRL), and TRL remnants, and increased risk of myocardial infarction, ischaemic stroke, and aortic valve stenosis. These data also indicate that TRL and their remnants may contribute significantly to residual cardiovascular risk in patients on optimized low-density lipoprotein (LDL)-lowering therapy. This statement critically appraises current understanding of the structure, function, and metabolism of TRL, and their pathophysiological role in atherosclerotic cardiovascular disease (ASCVD). Key points are (i) a working definition of normo- and hypertriglyceridaemic states and their relation to risk of ASCVD, (ii) a conceptual framework for the generation of remnants due to dysregulation of TRL production, lipolysis, and remodelling, as well as clearance of remnant lipoproteins from the circulation, (iii) the pleiotropic proatherogenic actions of TRL and remnants at the arterial wall, (iv) challenges in defining, quantitating, and assessing the atherogenic properties of remnant particles, and (v) exploration of the relative atherogenicity of TRL and remnants compared to LDL. Assessment of these issues provides a foundation for evaluating approaches to effectively reduce levels of TRL and remnants by targeting either production, lipolysis, or hepatic clearance, or a combination of these mechanisms. This consensus statement updates current understanding in an integrated manner, thereby providing a platform for new therapeutic paradigms targeting TRL and their remnants, with the aim of reducing the risk of ASCVD.

## Graphical Abstract



Formation of triglyceride-rich lipoprotein remnants and their role in atherosclerosis. Metabolic scheme for the generation and clearance of triglyceride-rich lipoprotein remnant particles (A). In hypertriglyceridaemia, overproduction and inefficient lipolysis of both very low-density lipoprotein and chylomicrons lead to increased remnant formation. Triglyceride-rich lipoprotein remnants contribute to the initiation and progression of atherosclerotic lesions (B). Particle retention in the subendothelial space is followed by inflammation, cholesterol deposition, and macrophage foam cell formation.

## Keywords

Triglycerides • Triglyceride-rich lipoproteins • Lipoprotein remnants • Cardiovascular disease • Residual risk

## Introduction

For decades, triglycerides (TG) have been considered a putative risk factor for atherosclerotic cardiovascular disease (ASCVD).<sup>1,2</sup> Despite mounting evidence from population and genetic studies, controversy persists. Much of this relates to two key questions: first, which is the culprit(s): TG molecules *per se*, TG-rich lipoproteins (TRL), or TRL remnants, and second, for TRL or their remnants, which components give rise to risk: cholesterol contained in these particles, other features, or both? Answers are essential to understand better the pathological consequences of raised TG levels, especially in the context of residual cardiovascular risk when other major factors, particularly low-density lipoprotein cholesterol (LDL-C), are

optimally controlled. This statement aims to define what is known about the structure, function, metabolism, and atherogenicity of TRL and their remnants, and importantly, to identify targeted therapeutic approaches to address residual risk associated with elevated TG levels.

## Search strategy

References (English language only) were identified through searches of PubMed for articles published from 2000 by the use of the terms 'triglycerides'; 'lipoprotein remnants'; 'triglyceride-rich lipoproteins'; in combination with the terms 'cardiovascular disease';

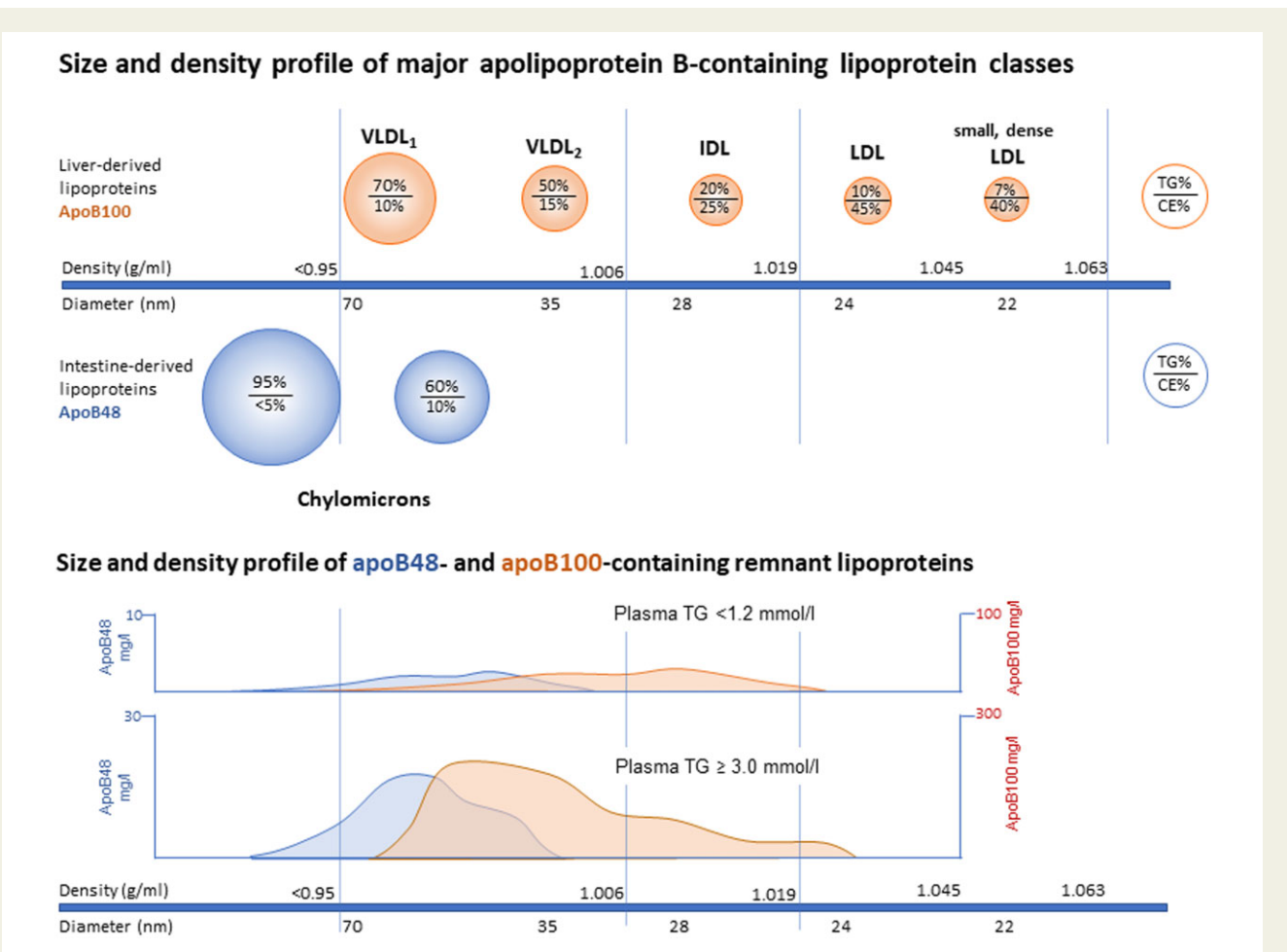
'atherosclerosis'; 'residual risk'; and 'therapeutics'. Relevant articles were also identified through searches of the reference lists of the identified literature.

## Triglycerides, triglyceride-rich lipoproteins, and remnants: definitions and clinical relevance

Triglycerides are an efficient means of storing excess energy, mainly in adipose tissue. In the blood, TG and cholesteryl esters (CE) circulate within the core of spherical lipoproteins, covered with a monolayer 'shell' of phospholipids and free cholesterol, with apolipoproteins stabilizing the structure. Apolipoprotein (apo) B is the major structural protein in TRL, present as either apoB100, made in the liver, or a truncated form, apoB48, made in the intestine. These isoforms, rather than size or density, best define the TRL class. Very low-density lipoproteins (VLDL), made in the liver, contain apoB100

and are metabolized to VLDL remnants, intermediate-density lipoproteins (IDL), and LDL. Chylomicrons, made in the intestine, are larger and contain apoB48, and are also metabolized to remnant particles but not to IDL and LDL (Figure 1). The intestine also secretes apoB48-containing VLDL-sized particles.<sup>3</sup>

TRL decrease in size during lipolysis; concomitantly, the core content of TG decreases and CE increases due to cholesteryl ester transfer protein (CETP)-mediated exchange of TRL-TG for LDL- and high-density lipoprotein (HDL)-CE. During lipolysis apoB remains with the TRL on which it was secreted. With one apoB molecule per particle, apoB concentration is thus a measure of particle number. Other apolipoproteins (particularly apoCs) transfer mainly to HDL during lipolysis. The spectrum of apoB100- and apoB48-containing remnants varies with plasma TG levels (Figure 1). At optimal levels (<1.2 mmol/L or <100 mg/dL),<sup>4</sup> efficient lipolysis results in limited accumulation of remnant



**Figure 1** Size and density profile of major apolipoprotein B-containing lipoprotein classes. This schematic depicts the spectrum of apolipoprotein (apo) B-containing lipoproteins (VLDL, IDL, LDL—very low-, intermediate-, and low-density lipoproteins, respectively), their density and size (diameter in nm), distribution, and their content of triglyceride and cholesteryl ester (as percent of mass). The stylized distribution of the relative amount of remnant particles in subjects with optimal triglyceride (<1.2 mmol/L) and elevated triglyceride (3.0 mmol/L) is shown for apoB100 (orange) and apoB48 (blue) containing lipoproteins. The profile of 'apoB48 remnants' is based on the apoB48 concentrations in VLDL<sub>1</sub>, VLDL<sub>2</sub>, and IDL in the late (post-peak) phase of lipid absorption and after an overnight fast, whereas that of 'apoB100 remnants' is based on the concentration of apoB100 in VLDL<sub>2</sub> and IDL. Based on data from Björnson *et al.*<sup>3</sup> CE, cholesteryl ester; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very low-density lipoprotein.

particles, predominantly in the small VLDL and IDL size range. At higher TG levels (e.g.  $\geq 3.0$  mmol/L or  $\geq 260$  mg/dL), increased secretion and impaired lipolysis result in the substantial accumulation of chylomicron and VLDL remnants.

Remnant lipoproteins are enriched in cholesterol (both free and esterified) and are depleted in apoC proteins and enriched in apoE (Figure 2).<sup>5–7</sup> The remnant lipoproteins seen in type III hyperlipidaemia ('dysbetalipoproteinaemia' or 'remnant' hyperlipidaemia) are an extreme example of this particle type. Remnants are cleared directly by the liver or converted to IDL and LDL. In most people, remnant lipoproteins (and TRL in general) are highly heterogeneous (Figure 1).<sup>3,6–9</sup> Thus, defining which features confer atherogenicity is challenging.

Extreme elevations of plasma TG levels ( $>10$  mmol/L or  $>880$  mg/dL) increase the risk for acute pancreatitis<sup>10–13</sup> but it is less widely appreciated that fasting levels from as low as  $\sim 1.2$  mmol/L ( $\sim 100$  mg/dL) can be associated with a cluster of metabolic abnormalities that include accumulation of TRL and remnants,<sup>14</sup> as well as increased cardiovascular disease events<sup>15,16</sup> (Figure 1). These lipoprotein particles become more abundant as TG concentrations increase from 'borderline' to 'moderate', 'severe', and 'extreme'. Working consensus definitions for these categories of hypertriglyceridaemia are given in Box 1.<sup>4,14,17–23</sup>

Over the past three decades, epidemiologic and genetic evidence has accumulated to support the concept that elevated levels of plasma TG, TRL, and TRL remnants are causally related to an increased risk of ASCVD-related events—myocardial infarction (MI), stroke, and aortic valve stenosis—and all-cause mortality.<sup>1,2,17,19,20,24–28</sup> Mendelian randomization studies focused on variants in the genes encoding apoAV, apoCIII, lipoprotein lipase (LpL) and the angiopoietin-like proteins 3, 4, and 8 (ANGPTL3, ANGPTL4, and ANGPTL8) have been highly informative.<sup>29–35</sup> Currently, given that no clear signal indicates which features of TRL give rise to risk, and recognizing the need for further study to identify the best index of ASCVD risk, plasma TG levels are a reasonable surrogate. The increase in absolute risk is greatest for MI (approximately four-fold at TG levels  $>5$  mmol/L or  $>440$  mg/dL vs.  $<1$  mmol/L or  $<88$  mg/dL), and less for ischaemic stroke and aortic stenosis (Figure 3).<sup>11,17,27,28</sup> Furthermore, elevated plasma TG levels (with the accumulation of TRL and remnant particles) are related not only to subclinical atherosclerosis and vascular inflammation independently of LDL-C in statin-naïve, apparently healthy subjects, but also equally to residual cardiovascular risk among statin-treated patients, especially those with diabetes mellitus.<sup>2,20,36–38</sup> There is also evidence that reductions in

plasma TG are associated with reduction in the risk of ASCVD events after adjustment for statin-induced LDL-C lowering.<sup>39–42</sup> These findings provide impetus for the development of innovative therapeutics to lower TG and TRL and their remnants for potential cardiovascular benefit.<sup>43</sup>

## Metabolism of triglyceride-rich lipoproteins and their remnants

### Key questions

- What are the major metabolic defects in hypertriglyceridaemia?
- What causes remnant lipoproteins to accumulate?

The primary role of TRL is to transport TG to adipose tissue for storage and to skeletal and cardiac muscle for energy production. The metabolism of apoB-containing lipoproteins is integral to these functions<sup>44–46</sup> (Figure 4), with regulation of the assembly, secretion, and clearance of TRL discussed below.

### What factors regulate the assembly and secretion of triglyceride-rich lipoproteins?

Hormones, nutrients, neural signals, and multiple enzymes and proteins, including CD36, FATP4, FABP1, FABP2, MTP, apoAIV, apoCIII, perilipin, and SAR1B, regulate the assembly and secretion of chylomicrons.<sup>47</sup> These factors direct lipids to storage in cytosolic lipid droplets in enterocytes, or oxidative breakdown, or incorporation into pre-chylomicron particles in the endoplasmic reticulum, which undergo expansion to full-sized chylomicrons.<sup>48</sup> The availability of apoB48—regulated by insulin, gut peptides, neural networks, and nutrient signals [fatty acids (FA) and glucose]—determines the rate of chylomicron formation. Increased numbers of small chylomicrons are secreted by individuals with insulin resistance.<sup>49,50</sup> Intestinal lipid droplets appear to act as temporary lipid stores, modulating the release and size of chylomicrons following meals.<sup>51</sup> Changes in intestinal lymphatic flow may be important in determining how rapidly dietary TG are delivered as TG-FA to peripheral tissues.<sup>52</sup>

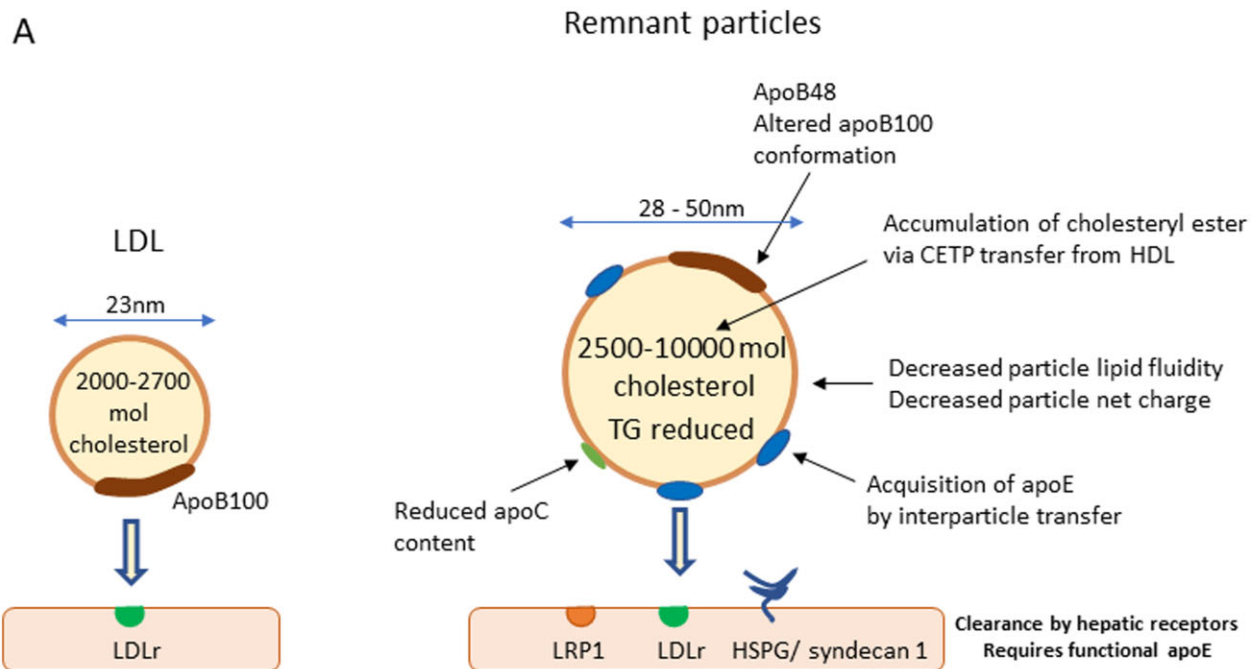
For VLDL, the chronic effects of excess nutrients and insulin resistance are most important, increasing hepatic secretion of larger particles.<sup>53,54</sup> VLDL assembly and secretion are upregulated by (i) the delivery of FA released from insulin-resistant adipocytes, (ii) the increased delivery of remnant TG-FA to the liver due to reduced peripheral lipolysis of chylomicron and VLDL-TG, and (iii) the increased *de novo* lipogenesis<sup>55</sup> (Figure 4).

### What factors regulate the lipolysis of triglyceride-rich lipoproteins?

Clearance of TRL involves two interrelated processes, lipolysis of TG by LpL, and hepatic clearance of remnants. Lipoprotein lipase-mediated hydrolysis of TG was thought to be a relatively simple process regulated by tissue LpL expression, and the content of apoCII (an activator) and apoCIII (an inhibitor) on TRL. However, accumulating

### Consensus key points

- Accumulating evidence from epidemiologic and genetic studies is consistent with a causal relationship between ASCVD risk and elevated plasma levels of TG, TRL, and TRL remnants.
- TRL and TRL remnants accumulate in the plasma at fasting TG levels  $>1.2$  mmol/L ( $>100$  mg/dL).
- At fasting TG levels  $>1.7$  mmol/L ( $>150$  mg/dL), there is consensus that ASCVD risk becomes clinically relevant;<sup>4,20,38</sup> TG levels  $>10$  mmol/L ( $>880$  mg/dL) confer a high risk of pancreatitis with the risk increasing significantly when TG levels are  $>20$  mmol/L.



**B**

	Borderline	Moderately elevated	Type III
Plasma TG (mmol/L)	1.2	4.50	4.59
RLP-C (mmol/l)	0.21	0.40	1.13
RLP-C/apoB molar ratio	3306	2878	7633
RLP apoB48/B100	0.02	0.11	0.95
TRL-sized particles RLP-C/apoB	trace	2920	9801
Intermediate-size RLP-C/apoB	3251	2674	5055

**Figure 2** Physicochemical characteristics of remnant lipoproteins. (A) Remnant lipoproteins are partially lipolysed products of lipoprotein lipase action. They have a triglyceride-depleted core and are enriched in cholesteryl esters. The main structural protein is apolipoprotein (apo)B48 in chylomicron remnants and apoB100 in very low-density lipoprotein remnants. A typical normal-sized low-density lipoprotein particle is shown for comparison. (B) Comparison of the cholesterol/apoB molar ratios in remnant-like particles isolated by immunoaffinity gel from the plasma of fasting subjects with Type III dyslipoproteinaemia, in which remnant particles accumulate, or borderline or moderately elevated triglyceride levels (data extracted from ref<sup>5</sup>). Only traces of remnant particles were detected in subjects with borderline elevated triglyceride levels. apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; HSPG, heparan sulphate proteoglycans; LDLr, low-density lipoprotein receptor; LRP1, low-density lipoprotein receptor-related protein 1; mol, molecules; RLP, remnant-like particle; RLP-C, remnant-like particle cholesterol; TG triglyceride; TRL, triglyceride-rich lipoproteins.

### Box 1 Consensus definitions of normo- and hypertriglyceridaemia

Category	Triglyceride level mmol/L (mg/dL)
Optimal	<1.2 (<~100)
Borderline	1.2–1.7 (100–150)
Moderately elevated	1.7–5.7 (150–500)
Severe	5.7–10.0 (500–880)
Extreme	>10 (>880)

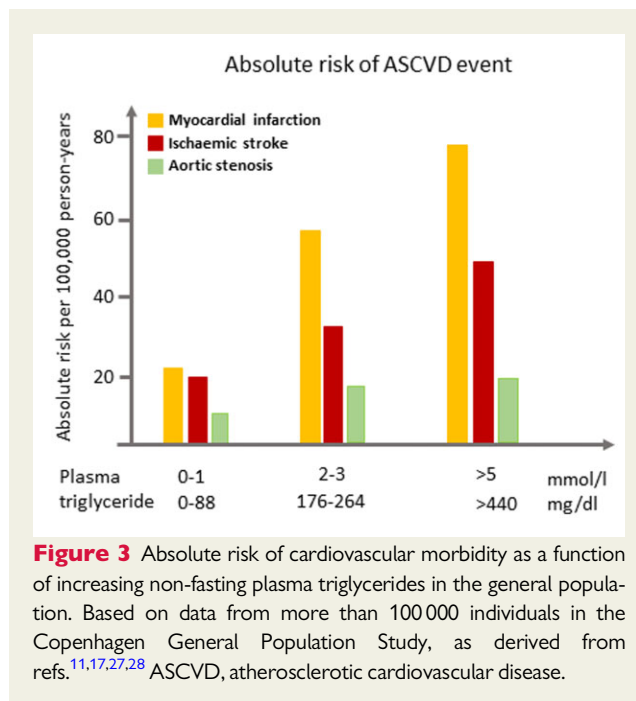
Plasma TG varies over a wide range in the population, and as levels rise, the risk of atherosclerotic cardiovascular disease increases continuously. For this reason, as with LDL-C, it is inappropriate to use classical percent thresholds (5th, 95th percentile) to define 'normal' and 'abnormal'. The cut-points here are derived from previous guidelines, epidemiological surveys and studies of TG metabolism. Extreme elevation is the threshold for high risk of acute pancreatitis. The division between 'optimal' and 'borderline' is based on recommendations from previous guidelines and the findings that remnant populations begin to be detectable using the remnant-like particle assay above this level and small, dense LDL formation is concomitantly enhanced. These cut-points are arbitrary but in the view of the Consensus Panel may serve as a working definition that has clinical utility. There is no distinction by gender.<sup>4,14,17–23</sup> LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

evidence indicates greater complexity, involving apoAV, ANGPTL3, 4 and 8, lipase maturation factor-1 (LMF1), and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein (GPIHBP1)<sup>18,56</sup> (Figure 4). Complete loss-of-function (LOF) mutations in genes encoding several of these proteins can cause severe hypertriglyceridaemia (LpL, apoCII, apoAV, LMF1, and GPIHBP1) or hypolipidaemia (apoCIII, ANGPTL3, and ANGPTL4). Heterozygous LOF has also been identified in some patients with polygenic severe hypertriglyceridaemia.<sup>13,57</sup>

Two of these proteins, apoCIII and ANGPTL3, have emerged as key therapeutic targets. ApoCIII is a major determinant of how efficiently TG are cleared from the plasma.<sup>58</sup> Loss-of-function variants of *APOC3* that result in reduced synthesis of the protein are associated with absent or low circulating apoCIII levels, increased efficiency of TG removal from TRL, and lower plasma TG levels,<sup>59,60</sup> whereas increased apoCIII levels, as seen in insulin resistance and obesity, result in reduced clearance and higher plasma TG<sup>61–63</sup> (Figure 4). ANGPTL3, 4, and 8 are inhibitors of LpL and play important roles in targeting chylomicrons and VLDL to white adipose tissue or skeletal muscle, depending on nutritional and hormonal status at any time.<sup>45</sup> Loss-of-function variants in *ANGPTL3* have been associated with reduced plasma levels of TG, LDL-C, and HDL-C.<sup>32,64,65</sup>

### Which factors regulate the generation and clearance of chylomicron and very low-density lipoprotein remnants?

Remnant formation is enhanced by overproduction of TRL or by genetic or physiological factors that limit lipolysis, or both. At moderately elevated plasma TG levels, there is increased secretion of large TG-enriched VLDL and chylomicrons from the liver and small intestine that, when combined with suboptimal LpL action in obesity, insulin resistance, and/or diabetes mellitus, results in remnant accumulation.<sup>36</sup> Variants in the LpL gene that cause partial LOF of the LpL enzyme, or in other genes affecting LpL activity, also lower the rate of

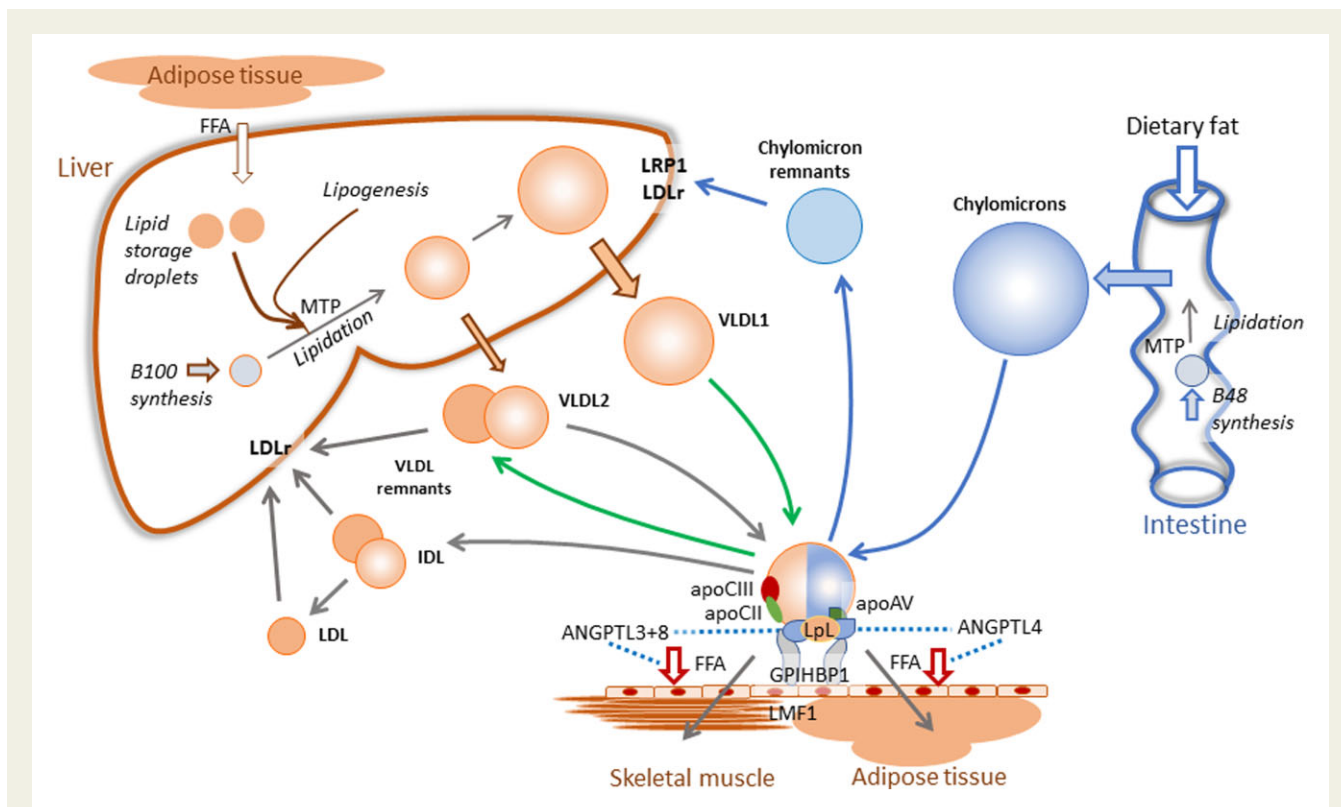


**Figure 3** Absolute risk of cardiovascular morbidity as a function of increasing non-fasting plasma triglycerides in the general population. Based on data from more than 100 000 individuals in the Copenhagen General Population Study, as derived from refs.<sup>11,17,27,28</sup> ASCVD, atherosclerotic cardiovascular disease.

TG removal from VLDL and chylomicrons, resulting in elevated plasma TG levels and remnant accumulation even when TRL secretion is normal (Figure 5).<sup>5,44,66</sup> The absence of lipolysis (i.e. complete LpL deficiency) results in the extreme elevation of large 'nascent' TRL without any concomitant increase in remnants,<sup>36,67,68</sup> here, pancreatitis rather than ASCVD is the major risk.

Metabolic processing of newly secreted TRL by LpL generates a partially lipolysed heterogeneous population of remnant particles. Some of the apoB100 remnants are efficiently further lipolysed by LpL and hepatic lipase (HL) to LDL; they can be viewed as 'transient' remnants. Other apoB100 remnants, and all apoB48 remnants, undergo remodelling that renders them resistant to further lipolysis, remaining in the VLDL–IDL density range as 'end-product' remnants, until they are removed directly from the circulation by the liver. The underlying basis for these alternative pathways of TRL remnant metabolism is not well understood (Figure 5). The longer a remnant remains in the circulation, the more it becomes enriched with CE; the cholesterol content in these end-product remnants can exceed 7500 molecules per particle (vs. 2000–2700 in LDL). Several factors, including activating or inhibitory apolipoproteins (apoCII and apoCIII, respectively) on the TRL surface, and LpL availability, influence residence time in the circulation and the potential entry and retention of remnants within the arterial subendothelial space.<sup>5</sup>

As stated above, all chylomicron remnants and variable amounts of VLDL remnants undergo direct hepatic clearance (Figures 2 and 4), mainly involving the LDL receptor, although studies in mice suggest putative roles for LDL receptor-related protein 1 and heparan sulphate proteoglycans (particularly syndecan 1).<sup>69,70</sup> For chylomicron remnants, functional apoE on the particle is required (apoB48 is not a ligand).<sup>71</sup> In type III hyperlipidaemia, patients are homozygous for the *APOE2* variant that lacks the ability to bind to lipoprotein receptors; however, only a minority develop 'remnant' dyslipidaemia, implying

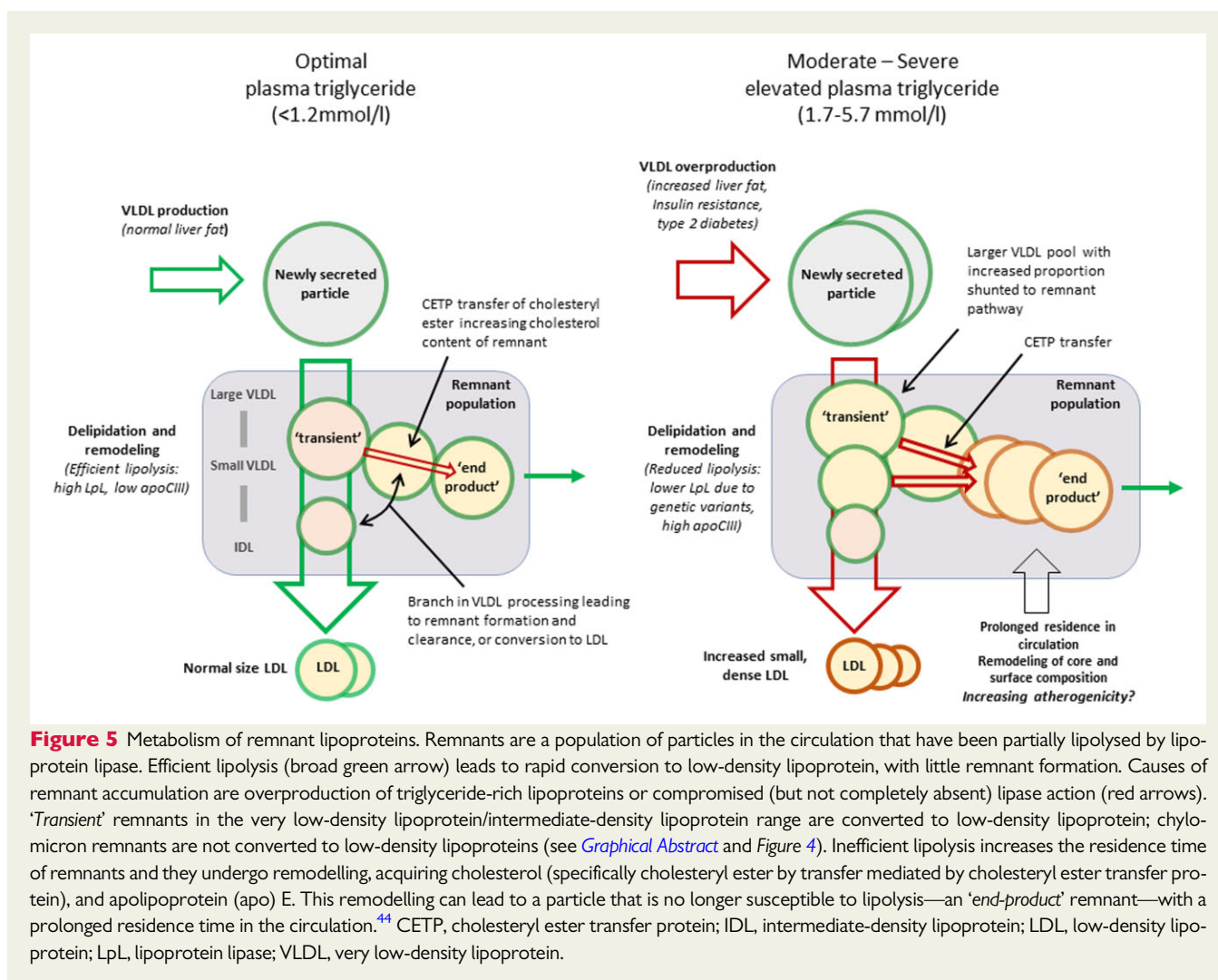


**Figure 4** Overview of apolipoprotein B lipoprotein metabolism. During absorption of fat from the diet, chylomicrons are generated by the enterocytes in the small intestine, travel via lymphatics, and appear in the bloodstream. Lipidation of a primordial apolipoprotein (apo) B48-containing particle (apoB48, a truncated form of apoB100 made solely in the intestine) is mediated by microsomal triglyceride transfer protein using triglyceride synthesized from absorbed fatty acids. In a similar assembly process, a large triglyceride-rich, apoB100-containing very low-density lipoprotein (VLDL)<sub>1</sub> is made in the liver using a variety of sources for triglyceride synthesis—*de novo* lipogenesis, fatty acids released from intracellular storage droplets, free fatty acids taken up from the circulation after their release from adipose tissue, and triglyceride fatty acids present in VLDL chylomicron remnants. Chylomicrons and VLDL<sub>1</sub> (and to an extent VLDL<sub>2</sub>) compete for the same lipolytic mechanism. Lipoprotein lipase is anchored to the luminal surface of the capillary endothelium in skeletal muscle and adipose tissue by glycoposphatidylinositol-anchored high-density lipoprotein-binding protein-1. This enzyme hydrolyzes triglyceride in the core of the particle releasing fatty acids into the underlying tissue bed. Lipase maturation factor 1 is essential for the secretion of functional lipase from adipose tissue and muscle. ApoCII is an activator (essential cofactor) of lipoprotein lipase, whereas apoCIII is an inhibitor of the enzyme and of remnant particle uptake. The angiopoietin-like proteins 3, 4, and 8 (ANGPTL3, 4, 8) have a tissue-specific role in modifying (inhibiting) lipoprotein lipase action, whereas apoAV increases lipoprotein lipase-mediated lipolysis. Lipolysis of chylomicrons leads to the formation of remnant particles, which are cleared by the liver via the low-density lipoprotein receptors and, based on mouse studies, the low-density lipoprotein receptor-related protein 1. Likewise, VLDL<sub>1</sub> is delipidated to VLDL<sub>2</sub>, remnants, and intermediate-density lipoproteins, which are either removed by liver receptors or converted to low-density lipoprotein as the final product. Smaller VLDL<sub>2</sub> is also made by the liver and can be delipidated to intermediate-density lipoprotein and low-density lipoprotein (for more detail see refs.<sup>43–45</sup>). It should be noted that lipolysis of both chylomicrons and VLDL in adipose tissue and skeletal muscle is neither equally divided nor randomly apportioned but is determined by insulin mediated regulation of lipoprotein lipase in each tissue, with insulin stimulating lipoprotein lipase in adipose tissue and inhibiting it in skeletal muscle. In addition, ANGPTL3 and ANGPTL8 inhibit lipoprotein lipase activity in skeletal muscle in the fed state and ANGPTL4 inhibits lipoprotein lipase activity in white adipose tissue during fasting.<sup>45</sup> FFA, free fatty acids; GPIHBP1, glycoposphatidylinositol-anchored high-density lipoprotein-binding protein-1; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLr, low-density lipoprotein receptor; LMF1, lipase maturation factor 1; LRP1, low-density lipoprotein receptor-related protein 1; MTP, microsomal triglyceride transfer protein; VLDL, very low-density lipoprotein.

that secondary acquired or inherited factors (e.g. insulin resistance) are needed to increase VLDL and chylomicron secretion or impair lipolysis, resulting in hyperlipidaemia. An identifying feature is a grossly elevated cholesterol/TG ratio in TRL, due to marked accumulation of VLDL and chylomicron ‘end-product’ remnants highly enriched in cholesterol (up to 10 000 molecules per particle)<sup>5</sup> (Figure 5). The elevated ASCVD risk in this dyslipidaemia is *prima facie* evidence for the role of remnant lipoproteins in atherogenesis, as LDL levels are typically low.<sup>72</sup>

Hepatic clearance of VLDL remnants is mediated by either apoB100 or apoE through receptor-dependent and receptor-independent pathways;<sup>7,17,71,73</sup> 25–75% of these particles are removed directly rather than converted to LDL. Which factors determine the fate of a remnant particle (in the VLDL or IDL density range) remains incompletely defined, although apoCIII inhibits whereas apoE and possibly HL facilitate hepatic remnant uptake.<sup>74,75</sup> In mice, apoCIII impacts plasma TG levels and remnant accumulation when LpL activity is reduced, but not when normal.<sup>75</sup> Additional





**Figure 5** Metabolism of remnant lipoproteins. Remnants are a population of particles in the circulation that have been partially lipolysed by lipoprotein lipase. Efficient lipolysis (broad green arrow) leads to rapid conversion to low-density lipoprotein, with little remnant formation. Causes of remnant accumulation are overproduction of triglyceride-rich lipoproteins or compromised (but not completely absent) lipase action (red arrows). 'Transient' remnants in the very low-density lipoprotein/intermediate-density lipoprotein range are converted to low-density lipoprotein; chylomicron remnants are not converted to low-density lipoproteins (see *Graphical Abstract* and *Figure 4*). Inefficient lipolysis increases the residence time of remnants and they undergo remodelling, acquiring cholesterol (specifically cholesteryl ester by transfer mediated by cholesteryl ester transfer protein), and apolipoprotein (apo) E. This remodelling can lead to a particle that is no longer susceptible to lipolysis—an 'end-product' remnant—with a prolonged residence time in the circulation.<sup>44</sup> CETP, cholesteryl ester transfer protein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LpL, lipoprotein lipase; VLDL, very low-density lipoprotein.

studies in mice suggest that endothelial lipase may play a role in remnant removal independent of LpL and LDL receptors.<sup>76</sup>

The preceding discussion illustrates the difficulty inherent in defining remnants. Identifying a proteomic or lipidomic signature specific for a sub-population of TRL that contributes to atherogenesis is crucial; lacking this, a looser concept is necessary, as discussed below.

### Why do fasting plasma triglyceride levels vary widely?

Plasma TG range from 0.33 to 120 mmol/L (30 to 10 000 mg/dL)<sup>13,17</sup> (Figure 6), reflecting variability in the rates of secretion and clearance of TG and apoB in VLDL and chylomicrons.<sup>61,77</sup>

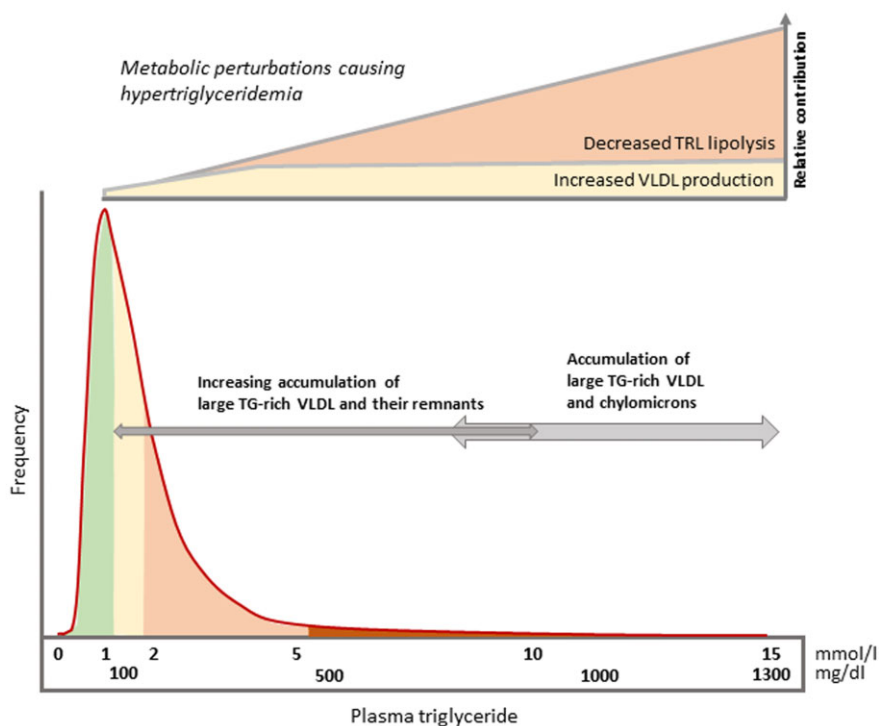
With borderline to moderately elevated plasma TG, overproduction is typically the main contributor, whereas reduced LpL-mediated lipolysis of TG is the dominant abnormality when plasma TG is severely elevated. The two- to four-fold range of secretion and several-fold range of clearance underlie the observed population variability.

Another reason for the wide range of plasma TG levels is variability in the non-fasting (postprandial) state. Whether fasting or non-fasting plasma TG levels provide a better index of ASCVD risk is

pertinent,<sup>78,79</sup> the role of postprandial lipaemia in atherosclerosis is discussed in *Box 2*.<sup>3,25,80–92</sup>

### Consensus key points

- Chylomicrons and VLDL (TRL) are assembled in the small intestine and liver, respectively, and transport TG and cholesterol in the circulation.
- Plasma levels of TRL are determined by the rate of production, the efficiency of removal of TG content by lipolysis, and hepatic clearance.
- Several enzymes, lipid transfer proteins, and the lipid and protein composition of TRL and remnants all contribute to the regulation of lipolysis and hepatic clearance of these lipoproteins.
- In severe hypertriglyceridaemia, a reduced TRL clearance rate is the dominant metabolic abnormality.
- Partial removal of TG from chylomicrons or VLDL creates remnants. Remnant levels depend on the extent of lipolysis, conversion of VLDL remnants to LDL, and the efficiency of hepatic removal of both VLDL and chylomicron remnants.
- Remnant particles may contain up to four-fold greater cholesterol content per particle than LDL.



**Figure 6** Causes of hypertriglyceridaemia in the population. This schematic representation illustrates the distribution of plasma triglyceride levels in a population (adapted from a survey of >100 000 individuals in the Copenhagen General Population Study).<sup>17</sup> The distribution is segmented by colours according to the triglyceride cut-points in *Box 1*, i.e. optimal triglyceride <1.2 mmol/L (green), borderline elevated, 1.2–1.7 mmol/L (yellow), moderately elevated, 1.7–5.7 mmol/L (pink), and severe or extreme hypertriglyceridaemia, >5.7 mmol/L (brown). (Note plasma samples in this survey were non-fasting whereas cut-points in *Box 1* are for fasting values). Increased production of very low-density lipoprotein in the liver is the primary abnormality leading to higher levels of triglyceride-rich lipoproteins and remnants in individuals with borderline/moderately increased plasma triglyceride, whereas decreased lipolysis is the predominant feature at higher triglyceride concentrations, with accumulation of both very low-density lipoprotein and chylomicrons. Individuals with the most severe forms of hypertriglyceridaemia, particularly those with monogenic causes, may have normal production rates and extremely low levels of lipolysis. TG, triglyceride; VLDL, very low-density lipoprotein.

## Does abnormal triglyceride-rich lipoprotein metabolism impact other lipoprotein classes?

As LDL is the terminal product of the VLDL delipidation and remodelling cascade, changes in VLDL metabolism impact LDL structure, function, and metabolism. Plasma TG modifies LDL size and composition;<sup>66,93</sup> higher levels result in small, dense LDL generated via CETP-mediated lipid exchange of LDL-CE with TRL-TG and subsequent lipolysis. These particles may be enriched in bioactive inflammatory lysolipids and are more likely to be retained in arterial atherosclerotic lesions because of their longer plasma residence time.<sup>66,93</sup>

Circulating HDL are highly heterogeneous in their physicochemical properties and biological activities, reflecting the complexity of metabolic processes underlying their production, intravascular remodelling, and catabolism.<sup>2,94-96</sup> Hypertriglyceridaemia leads to significant perturbations in HDL metabolism, and in direct

consequence, to subnormal HDL-C levels.<sup>2,94,95,97,98</sup> This involves major modification of the HDL proteome and lipidome,<sup>99,100</sup> resulting in attenuated vasculoprotective functions including reverse cholesterol transport, inhibition of oxidation, and anti-inflammatory activities.<sup>96,101,102</sup> The relevance of these alterations to increased ASCVD risk in hypertriglyceridaemia is unclear due to physiologically interrelated pathways.

### Consensus key points

- Changes in VLDL metabolism impact the structure, composition, metabolism, and function of LDL and HDL particles.
- Hypertriglyceridaemia favours the formation of small, dense LDL with potentially increased atherogenicity and smaller, denser HDL particles with a perturbed lipidome and proteome and defective vasculoprotective functions. The degree to which these alterations contribute to cardiovascular risk is unclear.

**Box 2 Postprandial lipid metabolism****Supporting refs**

- Most individuals are in a postprandial state, ingesting several fat-rich meals during the day. Plasma TG levels peak after bedtime and the nadir is in the early morning after an overnight fast. In a 'real-world' setting, random non-fasting (postprandial) TG is on average 20–25% higher than fasting values. This difference is, however, determined significantly by the fasting value 81,82
- Fasting plasma TG is strongly predictive of TG responses after eating 83
- Population and genetic studies identify non-fasting (postprandial) hypertriglyceridaemia, occurring 8 h or more after a meal, as an important but neglected risk factor for premature ASCVD 25,84–86
- Postprandial accumulation of TRL, typically detected as area under the curve for TG, is driven by overproduction and/or decreased catabolism of these particles. Predisposing genetic variations and clinical conditions such as obesity and insulin resistance often underlie such accumulation 25
- Large TRL are not atherogenic, in contrast to cholesterol-rich remnants that are formed after removal of TG from TRL by lipoprotein lipase-mediated lipolysis 86
- Clinical recognition of postprandial hypertriglyceridaemia is hampered by technical difficulties and the lack of established clinical protocols for its characterization 87,88
- While ~80% of the rise in TG levels after a fat-load meal is due to intestinally derived B48-containing lipoproteins, apoB100-containing VLDL account for most (~80%) of the increase in particle number 3,87–89
- Intestinal lipoprotein metabolism is more complex than previously recognized. Chylomicron production is linked to a taste–gut–brain axis. In both fasting and postprandial states, apoB48-containing particles are secreted not only as chylomicrons but also as smaller TRL particles resembling VLDL 51,90–92

ASCVD, atherosclerotic cardiovascular disease; TG, triglyceride; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein.

## Role of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease

### Key questions

- How are elevated TRL linked to cardiovascular risk?
- Do we need new tools to evaluate cardiovascular risk associated with hypertriglyceridaemia?

### How do triglyceride-rich lipoproteins and remnants exert atherogenic effects at the arterial wall?

While LDL-C is an established major causal factor for ASCVD,<sup>93,103,104</sup> the causality of TG, TRL, or TRL remnants for ASCVD is contentious.<sup>17,36,105–107</sup> Partly, this relates to variable TRL composition (Figures 2 and 4 and Box 3).<sup>2,7,17,44,73,95,108–111</sup> While there is no evidence that TG directly exert atherogenic effects,<sup>17</sup> free FA liberated during lipolysis of TRL–TG (in the subendothelial space or at the endothelial surface) can exert proinflammatory effects on endothelial cells and monocyte-derived macrophages.<sup>112–114</sup> This is evident with saturated FA, but not polyunsaturated forms (e.g. omega-3 free FA).<sup>112,115</sup> Lipid-loaded foam cells and smooth muscle cells in lesions, abundant sources of LpL, promote endothelial activation and permeability (Box 4).<sup>112–119</sup> LpL in arterial macrophages may also directly promote atherogenesis.<sup>120</sup>

The TRL delipidation cascade generates subpopulations (remnants, IDL) differing in atherogenic potential.<sup>2,3,5,44,73,86,93,121</sup> Particles below ~70 nm diameter (which excludes most newly secreted, non-lipolysed chylomicrons and very large VLDL) traverse the endothelium by active transcytosis<sup>93</sup> and are retained in the subendothelial layer of the artery wall, contributing to lesion initiation and progression mainly by mechanisms involving cholesterol deposition, inflammation, and prothrombotic effects (Figure 7 and Box 4).<sup>2,17,25,36,73,108,112–119,122</sup> Remnant particles in the small VLDL and IDL range, with at least 30% cholesterol by weight, may contain up to four-fold more cholesterol molecules than an LDL particle (up to 10 000 vs. 2000–2700 cholesterol molecules per lipoprotein particle, respectively).<sup>123,124</sup> VLDL and remnants are also enriched in apoE and apoCIII, both implicated in binding and retention in the artery wall.<sup>5,71,125</sup> These factors enhance remnant cholesterol deposition in the plaque;<sup>71,126,127</sup> indeed, unlike LDL, remnant particle entry exceeds efflux.<sup>127–129</sup> Similar to LDL, denaturation of cholesterol-rich remnant particles in the subendothelial environment may give rise to cholesterol microdomains,<sup>130</sup> favouring the formation of cholesterol monohydrate crystals.<sup>93,131,132</sup> Crystal formation may also occur upon VLDL or remnant uptake by macrophages, with activation of the NLRP3 inflammasome and an inflammatory response.<sup>130,133–135</sup> Cholesterol crystals induce macrophage apoptosis, with major implications for plaque instability and rupture.<sup>136</sup> Indeed, cholesterol crystals are typical of the

### Box 3 The proteome and lipidome of triglyceride-rich lipoproteins and their remnants

#### Supporting refs

- The proteomes of TRL and remnant particles contain a single copy of either apoB48 or apoB100, together with other, smaller apolipoproteins (CIII, CII, CI, AIV, AV, E, and traces of AI and II) and ANGPTL-3, -4, and -8. The proteome of remnant particles is enriched in apoE and apoCIII <sup>7,17,44,108–111</sup>
- The lipidomes of TRL and their remnants undergo dynamic intravascular metabolic remodelling, reflecting the activities of LpL, HL, CETP, and PLTP. Remnant particles are enriched in cholesteryl esters and deficient in TG (Figure 2). Proteomic components modulate rates of lipolysis, cholesteryl ester enrichment, and hepatic clearance of TRL and remnants <sup>44,73,95,110</sup>
- In atherogenic dyslipidaemia (TG levels >2.3 mmol/L or >200 mg/dL), the lipidome of the VLDL + IDL fraction (density <1.019 g/mL) comprises >20 distinct lipid classes, representing >500 individual molecular species (Meikle PJ, and Chapman MJ, unpublished data). Among the fasting apoB-containing lipoproteins under dyslipidaemic conditions, TRL and their remnants are the predominant plasma transporter of neutral lipids (triacylglycerols, diacylglycerols, and cholesteryl esters: 28, 110, and 190 nmol/mL plasma, respectively), specific phospholipids (phosphatidylethanolamine and phosphatidylinositol: 5.8 and 10.1 nmol/ml plasma respectively), and ceramides (0.9 nmol/mL plasma) <sup>66</sup>
- Based on these findings, is there a lipidomic signature for remnant particles? And if so, is this specific to apoB48, rather than apoB100-containing remnants?

ANGPTL3, 4, 8: angiopoietin-like proteins 3, 4, 8; apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LpL, lipoprotein lipase; PLTP phospholipid transfer protein; TG, triglyceride; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein.

necrotic core of atherosclerotic plaques, enhancing vulnerability and propensity to rupture. <sup>137,138</sup>

ApoE-mediated macrophage uptake of VLDL and remnants promotes an inflammatory (M1) phenotype, <sup>2,17,139</sup> enhances inflammation, increases phagocytosis and foam cell formation, exerts defective efferocytotic activity, and favours fibrous cap thinning due to activation of metalloprotease expression <sup>140</sup> (Figure 7). On a per particle basis, cholesterol-rich remnant particles are more potent inducers of macrophage foam cells than LDL and do not need structural modification to trigger uptake. <sup>36,93,141</sup> Arterial retention of TRL and their remnants induces maladaptive responses central to plaque initiation and progression (Box 4). Studies suggest that elevated TG and

### Box 4 Putative effects of triglyceride-rich lipoproteins and their remnants on vascular wall biology and their relevance to atherothrombosis

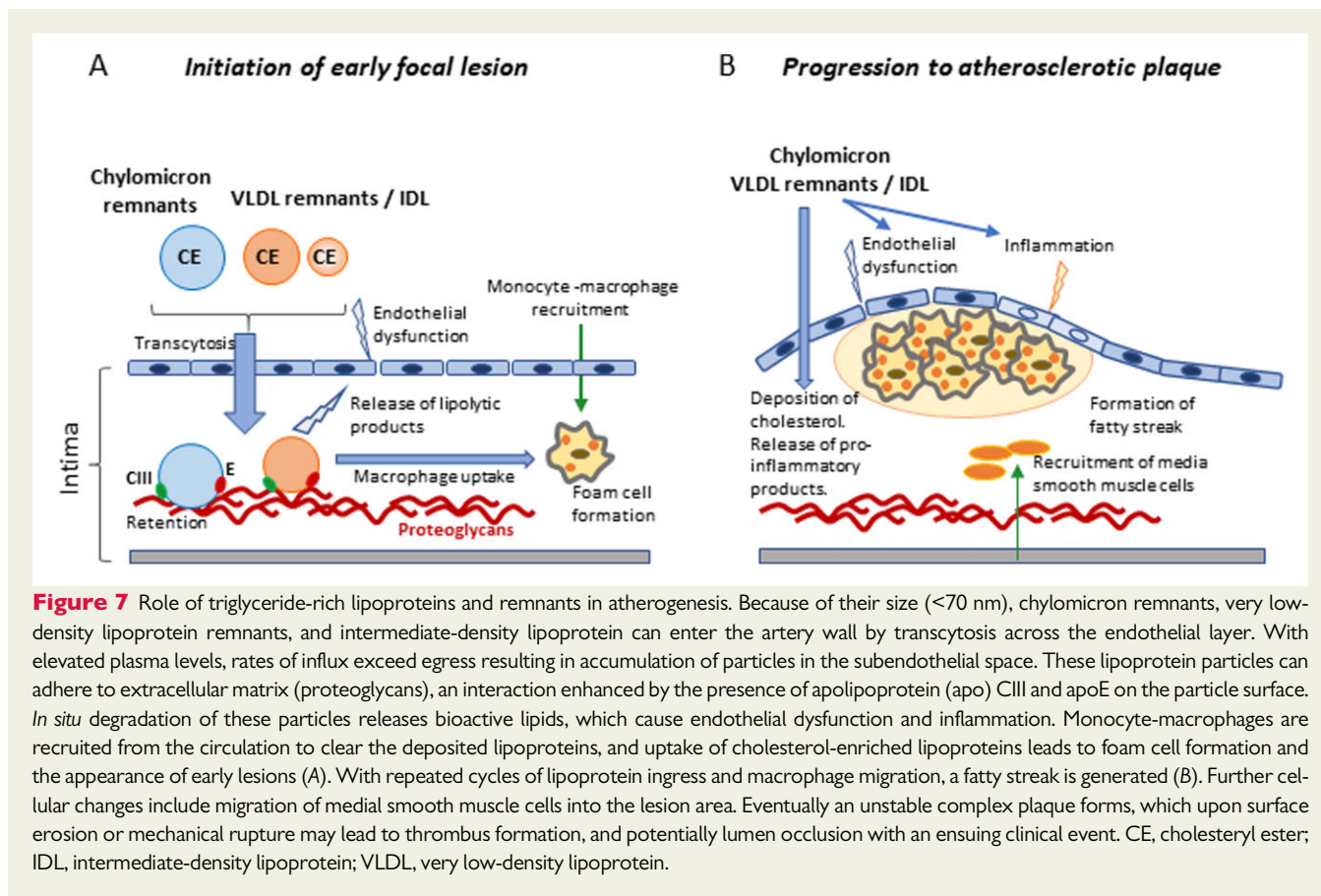
#### Supporting refs

- Acute elevation of TRL and their remnants in the postprandial phase induces impaired vasodilation, upregulates production of proinflammatory cytokines, enhances an endothelial inflammatory response, and upregulates expression of vascular cell adhesion molecule-1 and monocyte activation. This involves both direct and indirect mechanisms. <sup>116</sup>
- Lipolytically released saturated fatty acids and phospholipids containing oxidized fatty acids activate toll-like receptors of subendothelial macrophages, producing reactive oxygen species (ROS) and proinflammatory lipids and proteins. <sup>112,113</sup>
- TRL-associated apolipoprotein (apo) CIII activates the NLRP3 inflammasome in human monocytes by inducing an alternative NLRP3 inflammasome via caspase-8 with dimerization of toll-like receptors 2 and 4. This process involves production of ROS. ApoCIII-activated human monocytes impede endothelial regeneration *in vivo* <sup>117</sup>
- TRL and their remnants are implicated in plaque rupture and thrombus formation via redox-sensitive mechanisms, tissue factor secretion from the endothelium, and stimulation of monocytes and thrombin generation. Coagulation factors VII and X are specifically bound and transported by chylomicrons and very low-density lipoproteins <sup>118,119</sup>

TRL, triglyceride-rich lipoproteins.

remnant cholesterol levels are causally related to whole body low-grade inflammation, in contrast to LDL-C. <sup>12,142</sup> Recently, the PESA (Progression of Early Subclinical Atherosclerosis) study reported a significant association of vascular inflammation with TG levels  $\geq 1.7$  mmol/L. <sup>38</sup>

Given the greater abundance of LDL particles (estimated particle numbers for LDL are 3–10 greater than for TRL in most individuals), and longer plasma residence time (on average, 2.5–3.5 days for LDL vs. 4–13 h for chylomicrons and VLDL in subjects with raised TG), <sup>92</sup> then LDL is clearly the primary atherogenic lipoprotein target for ASCVD prevention. This comparison of numbers of remnant particles vs. LDL is an approximation given current limitations in our ability to precisely define the nature of remnant particles. Published studies suggest that up to 30% of the cholesterol load in apoB-containing lipoproteins can be transported by remnant particles when calculated as the cholesterol content of the VLDL + IDL fraction. <sup>143–145</sup> In this context, it should be noted that TG-rich particles



**Figure 7** Role of triglyceride-rich lipoproteins and remnants in atherogenesis. Because of their size (<70 nm), chylomicron remnants, very low-density lipoprotein remnants, and intermediate-density lipoprotein can enter the artery wall by transcytosis across the endothelial layer. With elevated plasma levels, rates of influx exceed egress resulting in accumulation of particles in the subendothelial space. These lipoprotein particles can adhere to extracellular matrix (proteoglycans), an interaction enhanced by the presence of apolipoprotein (apo) CIII and apoE on the particle surface. *In situ* degradation of these particles releases bioactive lipids, which cause endothelial dysfunction and inflammation. Monocyte-macrophages are recruited from the circulation to clear the deposited lipoproteins, and uptake of cholesterol-enriched lipoproteins leads to foam cell formation and the appearance of early lesions (A). With repeated cycles of lipoprotein ingress and macrophage migration, a fatty streak is generated (B). Further cellular changes include migration of medial smooth muscle cells into the lesion area. Eventually an unstable complex plaque forms, which upon surface erosion or mechanical rupture may lead to thrombus formation, and potentially lumen occlusion with an ensuing clinical event. CE, cholesteryl ester; IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.

secreted from the intestine and liver become ‘transient’ remnants very soon after entering the plasma compartment due to their exposure to remodelling enzymes, metabolically active apolipoproteins, and lipid transfer factors and hence are included in the overall remnant particle count.

When considering the clinical relevance of particle abundance, it is noteworthy that despite the predominance of LDL particle numbers in fasting and postprandial states, the relative danger of ‘remnants’ cannot simply be equated with their particle number, as multiple factors are implicated in a comparison of the relative atherogenicity of these two sets of particles. Such factors include plasma residence time, cholesterol load, rates of penetration and retention in the arterial intima, susceptibility to modification *in situ*, rates of uptake in macrophages, and propensity to form proinflammatory foam cells.<sup>93</sup> Thus, even with uncertainty regarding the exact proportion of cholesterol carried in remnants, in part due to methodological issues,<sup>146</sup> the long duration of elevated levels during the postprandial period ( $\geq 8$  h) results in the arterial wall being extensively exposed to remnant particles.<sup>3,86</sup> Both apoB48- and apoB100-containing remnant particles have been identified in human atherosclerotic lesions.<sup>147,148</sup>

Taken together, there is evidence for interactive and complementary mechanisms for apoB48- and apoB100-containing remnants in atherogenesis. Since first proposed,<sup>149</sup> increased levels of intestinal-derived postprandial lipoproteins have been increasingly recognized as key players in the development of ASCVD.<sup>86,150</sup>

### Consensus key points

Based on evidence from several sources particularly preclinical studies, we conclude the following:

- Arterial retention of TRL and their remnants is linked to maladaptive responses central to plaque initiation and progression.
- The apoE and apoCIII content of VLDL and chylomicron remnant particles is critical to mechanisms of arterial retention.
- LpL expressed by arterial wall macrophages and smooth muscle cells may directly promote atherogenesis.
- Cholesterol-rich remnant particles induce macrophage foam cell formation more potently than LDL.<sup>36,93,141</sup>
- Macrophage uptake of remnant particles in native or modified forms elicits an inflammatory response, thereby promoting atherosclerosis.<sup>151,152</sup>
- Emerging pathophysiological and metabolic evidence supports the putative atherogenicity of apoB48- and apoB100-containing remnants during the postprandial period, with apoB100-containing particles predominating.

### How is the risk associated with triglyceride-rich lipoproteins assessed?

Currently, there is no definitive measure that captures the independent atherogenic potential of TRL and their remnants, their structural and metabolic variability, or the changes in their number and

composition after dietary fat absorption.<sup>150</sup> Fasting/non-fasting plasma TG measurement provides a basis for guideline thresholds for hypertriglyceridaemia.<sup>13,20</sup> Non-fasting TG is equivalent, if not superior, to fasting TG in assessing potential ASCVD risk.<sup>78,79</sup> If TRL promote plaque development and inflammation predominantly due to their cholesterol content (either fasting or non-fasting), then TRL cholesterol might be a superior index of ASCVD risk, either assayed directly or estimated (Box 5).<sup>66,153,154</sup> Estimation of VLDL cholesterol concentration by nuclear magnetic resonance (NMR) spectroscopy analysis was recently proposed as a surrogate for remnant lipoproteins.<sup>155</sup> Prospective evaluation of its relationship to MI risk concluded that VLDL cholesterol influenced ASCVD risk similarly to LDL-C, although as suggested, further validation of NMR-based particle measurement is needed before wider adoption.<sup>146</sup>

Non-HDL-C, which by definition includes the cholesterol in LDL-C, remnants, and lipoprotein(a),<sup>79,156</sup> is a simple, robust index of the total concentration of potentially atherogenic particles in the circulation. Widely recommended by guidelines, non-HDL-C highlights elevated remnants in type 2 diabetes mellitus.<sup>20,157</sup> Subtracting directly measured LDL-C from non-HDL-C provides a crude estimate of remnant cholesterol content<sup>78</sup> but includes cholesterol in TRL not yet processed to remnants. Assays that specifically measure the cholesterol content of remnant particles have revealed significant associations with ASCVD.<sup>17,86</sup> These include the remnant-like particle assay<sup>68,158,159</sup> and a direct assay of TRL cholesterol. Among emerging approaches, assays of total apoB, apoB100, and apoB48 would offer direct measures of TRL particle number. In addition, several studies have indicated that TRL ceramide species may be predictive of cardiovascular events and mortality<sup>66,160–162</sup> (Box 5). Finally, readers should note that the proposed cut-points (Box 1) reflect current knowledge; further studies are necessary to more accurately relate each category of hypertriglyceridaemia to risk for ASCVD and/or pancreatitis. It is reasonable, therefore, to continue to use TG, which is routinely measured in all clinical laboratories, as a surrogate biomarker.

## Strategic approaches to lowering of triglyceride-rich lipoproteins and remnants for atherosclerotic cardiovascular disease prevention

### Key questions

- Are the proatherogenic mechanisms of TRL sufficiently understood for therapeutic targeting in ASCVD patients with residual risk?
- What are the optimal strategies for reducing ASCVD risk in hypertriglyceridaemia?
- Are currently available therapeutics targeting pathways that will result in reduction of cardiovascular risk? What does the future offer?

Available and novel therapies that target TG metabolism can reduce TRL plasma concentration but need to be evaluated individually for impact on atherogenic lipoproteins. Baseline TG level (fasting or non-fasting), as a reflection of the underlying metabolic abnormality

(Figure 6), as well as concomitant medications, especially LDL-lowering drugs, may also influence the potential impact of any therapy on ASCVD outcomes. For example, fibrates effectively lower TG across the range of TG levels but only modestly reduce apoB levels. Their effects on LDL-C differ between moderate hypertriglyceridaemia (LDL-C is decreased or shows no change) and severe hypertriglyceridaemia (LDL-C is increased, albeit from a low baseline level).<sup>163,164</sup>

Guideline-recommended first steps for managing hypertriglyceridaemia are diet modification and weight loss. Dietary goals include (i) avoiding highly refined carbohydrate foods;<sup>4,165</sup> (ii) incorporating seafood, particularly fatty fish;<sup>166</sup> (iii) increasing fibre-rich foods (fruits, vegetables and whole grains);<sup>4</sup> (iv) avoiding excess alcohol;<sup>167</sup> and (v) substituting mono- and polyunsaturated fat (mostly from plant oils and nuts) for animal fat (meat and dairy).<sup>168</sup> Dietary trans FA increase TG levels minimally but should be avoided because they significantly raise LDL-C and lower HDL-C.<sup>169</sup> Energy intake should be adjusted to achieve and maintain a healthy body weight.

The 2019 ESC/EAS guidelines for dyslipidaemia management recognize that ASCVD risk is increased at TG levels >1.7 mmol/L (>150 mg/dL), but only recommend initiating pharmacotherapy in high-risk patients if >2.3 mmol/L (>200 mg/dL) after excluding secondary causes.<sup>20</sup> There are also no treatment goals, either for plasma TG or indices of remnant abundance, given limited evidence from randomized controlled trials that lowering TG or TRL reduce ASCVD risk.<sup>20</sup> Thus, strategic approaches to lowering TRL warrant discussion. This point is especially pertinent given that PESA reported the presence of peripheral atherosclerotic plaques in 58% of middle-aged individuals with elevated TG levels ( $\geq 1.7$  mmol/L), low-to-moderate cardiovascular risk, and high or normal LDL-C.<sup>38</sup>

### Inhibiting lipoprotein production

Inhibiting secretion of apoB100- and apoB48-lipoproteins may be the optimal approach for achieving the reduction of all atherogenic lipoproteins. Drugs such as mipomersen [an antisense oligonucleotide (ASO) inhibitor of apoB translation] and lomitapide (an inhibitor of microsomal triglyceride transport protein activity) block either apoB synthesis or the addition of lipid during chylomicron and VLDL assembly in the intestine and liver, respectively. Both also promote hepatic TG accumulation and possible development of non-alcoholic fatty liver disease, limiting their use to severe hypercholesterolaemia.<sup>170–173</sup> Novel or combination therapies that inhibit the assembly of apoB-lipoproteins and protect against excess intracellular lipid by promoting FA oxidation or decreasing TG synthesis are, therefore, needed.

Reducing TG availability for VLDL assembly represents another approach. For example, high-dose omega-3 FA [3–4 g/day, usually the combination of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] reduces VLDL-TG and apoB secretion by ~25–30%, with variable changes in fractional clearance rate.<sup>174,175</sup> Some studies showed an increase in conversion of VLDL to IDL and LDL, although no change in plasma IDL and LDL levels. Thus, omega-3 FA may have limited impact on remnant populations or the total number of atherogenic lipoproteins. In REDUCE-IT (Reduction of Cardiovascular Events with EPA—Intervention Trial), high-dose EPA reduced

### Box 5 Approaches to assessment of atherosclerotic cardiovascular disease risk associated with triglyceride-rich lipoproteins and their remnants

Index	Measurement
TG	<ul style="list-style-type: none"> <li>Fasting or non-fasting measurement</li> </ul>
Non-HDL-C	<ul style="list-style-type: none"> <li>Directly measured total cholesterol minus HDL-C</li> </ul>
TRL cholesterol	<ul style="list-style-type: none"> <li>Direct assay, after isolation of the VLDL (density &lt;1.006 g/mL) or VLDL + IDL (density &lt;1.019 g/mL) fractions (Figure 1)</li> <li>Estimated, multiply plasma TG by the ratio of cholesterol to TG in VLDL (relatively constant for fasting samples on a population basis, 0.46 mmol cholesterol/mmol TG or 0.2 mg/mg). Modifications are available for severe hypertriglyceridaemia or very low LDL-C levels<sup>153,154</sup></li> </ul>
Remnant particles	<ul style="list-style-type: none"> <li>'Remnant-like particle' assay, based on immunoaffinity separation of lipoprotein particles with the characteristics of chylomicron and VLDL remnants<sup>158</sup></li> <li>Direct assay, measuring cholesterol content in chylomicrons and VLDL and their remnants (including IDL), i.e. 'TRL cholesterol'. This was developed with standardization against the equivalent ultracentrifugally isolated fraction (density &lt;1.019 g/mL). TRL that are not remnants are also captured in this assay<sup>159</sup></li> </ul>
Emerging approaches	
Total apoB	<ul style="list-style-type: none"> <li>With one copy of apoB, either apoB48 or apoB100, per particle of TRL and remnants, immunological assay of total apoB in the fraction comprising chylomicrons, VLDL, and remnants (density &lt;1.019 g/mL) would provide a measure of total TRL (i.e. particle numbers of chylomicrons, VLDL and their remnants)</li> <li>This assay could be refined by complementary estimation of intestinally derived apoB48- and liver-derived apoB100-containing particles</li> <li>With standardization and clinical evaluation, the molar ratio of cholesterol/apoB in this fraction may indicate the degree of cholesterol enrichment and, thus, remnant content and potential atherogenicity</li> </ul>
Ceramide species	<ul style="list-style-type: none"> <li>There is robust evidence for plasma ratios of ceramide species (e.g. [d18:1/16:0]/ [d18:1/24:0]) as predictors of cardiovascular events and mortality</li> <li>Given their lipotoxic properties and increased content in the TRL and remnant fraction (density &lt;1.019 g/mL lipoproteins) in dyslipidaemic subjects, mass spectrometric assay of ceramides in this fraction may inform the putative atherogenicity of the liposome of TRL and remnants<sup>66,160–162</sup></li> </ul>

apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TRL, triglyceride-rich lipoproteins; VLDL, very low-density lipoprotein.

ASCVD risk, although it was suggested that only a modest part of this benefit was due to changes in TRL levels.<sup>176</sup> The lack of benefit in STRENGTH (Outcomes Study to Assess S-Tatin Residual Risk Reduction with EpaNova in High CV Risk Patients with Hypertriglyceridaemia) with a DHA/EPA combination suggests that DHA and EPA may differ in their effects on ASCVD.<sup>177</sup>

### Reducing cholesteryl ester enrichment of remnants

As CE transfer from HDL to TRL is a key step in remnant lipoprotein formation, inhibiting CETP should decrease remnants. Studies with evacetrapib or anacetrapib showed a marked decrease in the cholesterol/TG ratio in VLDL using measures that include remnants.<sup>178,179</sup> While anacetrapib treatment led to a small risk reduction, putatively linked to a decrease in LDL-C, greater LDL-C reduction with evacetrapib did not confer cardiovascular benefit.<sup>180,181</sup>

### Stimulating lipolysis

This approach lowers plasma TG in a range of patients, underlining the role of inefficient lipolysis in the aetiology of hypertriglyceridaemia

(Figure 6). Fibrates are the archetypal agents, promoting lipolysis by increasing LpL activity<sup>182</sup> and decreasing the synthesis of apoCIII (Figure 4), thereby enhancing the efficiency of VLDL clearance. Whether stimulating lipolysis lowers remnant concentration and ASCVD risk depends on the efficiency of hepatic uptake pathways. It is equally uncertain as to whether more efficient lipolysis and increased conversion of remnants to LDL may be beneficial. Using a Mendelian randomization approach for LPL variants indicated that those associated with TG-lowering were linked to reductions in ASCVD.<sup>26</sup> The LPLS447X variant that increases enzyme activity has also been linked to lower ASCVD.<sup>183</sup>

Outcomes trials with fibrates, other than gemfibrozil, failed to show clear evidence of reduction in cardiovascular events, although there was benefit in patient subgroups with raised TG with or without low HDL-C, patients who would be expected to have elevated remnant levels.<sup>184,185</sup> Further insights are awaited from the PROMINENT trial, in which pemafibrate is being compared to placebo on a background of statin therapy.<sup>186</sup>

ApoCIII is a known inhibitor of LpL (Figure 4). Indeed, individuals with LOF APOC3 variants have low plasma TG levels<sup>59,60,187</sup> and

markedly increased *in vivo* fractional turnover of VLDL–TG with efficient conversion of VLDL apoB to LDL, indicating increased lipolysis.<sup>59,187</sup> Of note, an ASO targeting *APOC3* markedly reduced plasma TG levels in severe hypertriglyceridaemia, an effect equally evident in the absence of LpL activity.<sup>188,189</sup>

ANGPTL3 is another known inhibitor of LpL activity (Figure 4) and individuals with *ANGPTL3* LOF variants have low levels of TG, LDL-C, and HDL-C.<sup>32,65</sup> Effects on LDL-C, HDL-C, and apoB levels in hypertriglyceridaemic subjects have varied in early trials of a monoclonal antibody directed against *ANGPTL3*<sup>190</sup> and an ASO therapy that reduced the synthesis of the protein.<sup>191</sup> A single dose of an *ANGPTL3* inhibitor reduced plasma TG levels ~40% in a patient deficient in *APOC2*; this effect persisted for 90 days, implying LpL-independent lowering of TG.<sup>192</sup>

## Enhancing remnant clearance

Increasing the efficiency of removal pathways for atherogenic lipoproteins should, theoretically, reduce ASCVD risk. Statins up-regulate the LDL receptor and would be expected to decrease remnant particles by accelerating their catabolism.<sup>145,193</sup> Statin-mediated TG-lowering is limited at optimal levels of TG (Box 1), but more effective at higher levels (>2.3 mmol/L), with similar percent reductions in TG and LDL-C.<sup>194</sup> Statins also promote chylomicron remnant clearance and reduce lipaemia following a fat-rich meal.<sup>195</sup> Thus, statins can reduce remnant abundance, providing further support for optimizing their use in individuals most at risk. However, stimulating receptor-mediated clearance alone is unlikely to address fully the residual remnant-associated risk of ASCVD.

PCSK9 inhibitors increase the activity of LDL receptors and the clearance rate of IDL in healthy subjects.<sup>196</sup> Effects on VLDL clearance are less than with statins, with only modest TG lowering in hypertriglyceridaemia,<sup>197</sup> implying a capacity to reduce plasma levels of smaller-sized remnants at lower TG levels, but not remnants at higher TG levels. PCSK9 inhibitors appear to have little effect on chylomicronaemia and apoB48 metabolism.<sup>198,199</sup>

As previously noted, apoCIII inhibits lipolysis and based on studies in rodents may also inhibit the hepatic uptake of remnant-like lipid emulsions.<sup>74,200,201</sup> An ASO directed against apoCIII markedly reduced plasma TG levels in subjects lacking LpL activity,<sup>188,189</sup> thus providing indirect support for improved hepatic uptake at low plasma apoCIII levels. In contrast, kinetic studies in humans with either complete<sup>60</sup> or partial<sup>187</sup> LOF of *APOC3* showed markedly increased fractional clearance of VLDL–TG and apoB and increased conversion of VLDL to LDL without increased hepatic uptake of remnants. In a mouse model, the effect of reducing apoCIII on hepatic remnant removal was significant only when LpL activity was markedly reduced,<sup>75</sup> possibly explaining the lack of apoB reduction with an apoCIII ASO in moderate hypertriglyceridaemia.<sup>202</sup> These findings offer insights as to whether simply improving lipolysis—without increasing remnant removal—will reduce ASCVD risk in people with high TRL levels.

ANGPTL3, another confirmed inhibitor of LpL-mediated lipolysis, also appears to play a role in non-LpL-mediated clearance of TRL, as suggested by lowering of TG levels with *ANGPTL3* inhibition in a patient lacking *APOC2*.<sup>192</sup> Studies in mice also implicate a role for dis-inhibited endothelial lipase in stimulating remnant removal by the liver, independent of the LDL receptor.<sup>76,203</sup> Further support is

provided by evidence that an *ANGPTL3* monoclonal antibody increased the LDL fractional clearance rate and reduced plasma LDL-C and apoB levels in patients with homozygous familial hypercholesterolaemia.<sup>204,205</sup>

## Consensus key points

- Regulation of plasma levels of TG, TRL, and remnants is complex. Developing therapeutics that reduce the levels of one or more of these lipoproteins and concomitantly reduce ASCVD risk is challenging.
- Improved understanding of the pathways that determine circulating levels of TG, TRL, and remnants is needed.
- A key question is whether targeting lipolysis and clearance of TRL and remnants rather than remnant production itself is more effective for reducing ASCVD risk.
- For existing therapies, clinical trials that use validated specific assays are essential to inform whether lowering levels of TG and TRL and/or remnants can reduce ASCVD risk.
- Determining the relative atherogenicity of TRL and remnants vs. LDL is critical and will require specific assays for these lipoprotein species.

## Conclusions

Our knowledge of TG metabolism and the aberrations leading to elevated plasma TG levels is substantial. However, understanding the pathobiology of remnant lipoproteins (overviewed in the [Graphical Abstract](#)), the atherogenic potential of their lipidomic and proteomic composition, and their measurement is very much a ‘work-in-progress’ that is key to the development of optimal targeted therapies. This statement highlights two important unmet needs: (i) a standardized, readily applicable assay to measure remnants and (ii) therapeutic options to lower circulating levels of remnants to reduce residual ASCVD risk in patients on maximal LDL-C-lowering treatment. With several promising candidates, the answer will likely involve combination therapy targeting both remnant formation and clearance pathways and avoiding attendant increases in LDL particles. The latter is key, because any proatherogenic effects of TRL and remnants will be synergistic to those of other apoB-containing lipoproteins, particularly LDL and lipoprotein(a).<sup>17,25,93,104,206</sup>

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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