New targets for treating hypertriglyceridemia

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Purpose of review
Elevated fasting and postprandial plasma triglyceride concentrations are associated with an increased risk for atherosclerotic cardiovascular disease in patients on and off low-density lipoprotein (LDL) lowering therapy.

Recent findings
This association is not mediated by triglycerides directly. Other components of triglyceride rich lipoproteins, such as cholesterol and apolipoproteins B and -CIII can directly induce and enhance atherosclerosis. In addition, an elevated concentration of triglyceride rich lipoproteins affects the concentration, composition, function, and metabolism of LDL and high-density lipoprotein (HDL), which contributes to the risk. Especially in patients with hypertriglyceridemia, apolipoprotein B and non-HDL-cholesterol (encompassing cholesterol of all atherogenic lipoproteins) predict risk better than LDL-cholesterol and/or triglycerides. Therefore, current guidelines have stated secondary goals relating to non-HDL-cholesterol and apolipoprotein B (in addition to the primary goal relating to LDL-cholesterol). These secondary goals can be achieved by further reducing LDL-cholesterol or by decreasing triglyceride rich lipoproteins. However, only further LDL reduction has so far proven to be beneficial in outcome trials. In addition, high dose eicosapentaenoic acid (EPA) can reduce atherosclerotic cardio-vascular disease risk in patients with hypertriglyceridemia, although benefit is not (or not only) related to apolipoprotein B or non-HDL-cholesterol reduction.

Summary
Non-HDL-cholesterol and apoB represent novel targets for patients with hypertriglyceridemia, but achieving LDL-cholesterol targets remains the first step for cardio-vascular risk reduction.

Keywords
apolipoprotein B, cholesterol, non-high-density lipoprotein-cholesterol, remnant, triglyceride-rich lipoproteins

INTRODUCTION

Changes in triglyceride levels and/or metabolism are important in a number of clinically relevant conditions. Thus, elevated triglyceride levels are a defining criterion for the metabolic syndrome, can cause acute pancreatitis, are typical in metabolic dysfunction associated liver disease, and are associated with dementia, aortic stenosis, and atherosclerotic cardiovascular disease (ASCVD) [1–6]. The exact role of triglycerides in these disease entities is not always clear. In some conditions, elevated triglyceride concentrations may be causal (i.e. acute pancreatitis), in others it is unknown if triglycerides represent a marker or are causal (dementia, aortic stenosis) and in again others elevated triglyceride concentrations may be the consequence of the disease (metabolic dysfunction associated liver disease).

From a clinical perspective, the most important finding is the association between elevated fasting and postprandial triglyceride levels with ASCVD, which will be the focus of this review.

TRIGLYCERIDES/TRIGLYCERIDE-RICH LIPOPROTEINS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Even with very strong and consequent low-density lipoprotein (LDL) lowering only a certain fraction (30–50%) of cardiovascular events can be prevented [7–9]. The term residual risk is being used to describe this phenomenon. Although residual risk may obviously relate to the presence of other risk factors, such as diabetes, smoking, etc., additional lipid abnormalities also play an important role. Elevated triglyceride concentrations, dysfunctional high-density lipoprotein (HDL) and elevated lipoprotein(a) concentrations must be discussed in this

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KEY POINTS

- Patients with hypertriglyceridemia have an increased risk for atherosclerotic cardiovascular risk.
- Non-high-density lipoprotein-cholesterol and apolipoprotein B are secondary lipid goals in patients with hypertriglyceridemia.
- These goals can be achieved by further low-density lipoprotein-cholesterol lowering or by the reduction of triglyceride rich lipoproteins.

context. In this review, the focus will be on hypertriglyceridemia, whereas HDL dysfunction will be covered in a separate manuscript and lipoprotein(a) has been discussed recently in detail [10].

A number of studies show that elevated fasting and postprandial triglyceride concentrations are an independent risk factor for ASCVD [11,12]. This has been shown in patients without lipid lowering therapy but also in patients on statin therapy [13].

To understand the role of triglycerides in ASCVD, it is important to understand the metabolism of triglyceride rich lipoproteins (TRL), which is more complex than that of LDL. TRL may be of intestinal (chylomicrons) or hepatic (VLDL) origin [14▪▪]. Although all TRL contain one molecule of apolipoprotein (apo) B, those of intestinal origin have one molecule of apoB-48, while those of hepatic origin have one molecule of apoB-100. Depending on the state of delipidation, they contain various amounts of triglycerides but similar amounts of cholesterol and apoC-III. In normolipidemic subjects freshly secreted TRL are rapidly delipidated resulting in the formation of LDL (from VLDL) and chylomicron remnants (from chylomicrons). Although LDL have a longer half-life in plasma, chylomicron remnants are rapidly taken up by the liver. Hypertriglyceridemia results if the production of TRL is increased (as in diabetes mellitus type 2) or catabolism is delayed (as with variants of lipoprotein lipase). In many situations, such as metabolic syndrome, a combination of both disturbances (overproduction and delayed catabolism) contribute to hypertriglyceridemia [14▪▪].

Since triglycerides are not transported isolated in plasma but in form of lipoproteins, which contain as outlined above additional components, the question arises which is the link between elevated triglyceride concentrations and ASCVD. Potential candidates are:

(1) Triglycerides themselves
(2) Other components transported in TRL such as cholesterol, oxidized lipids, apoB, apoC-III, etc.
(3) TRL as particles
(4) Triglyceride induced changes in LDL and HDL composition, function, and metabolism
(5) A combination of the above

There is currently no evidence that triglycerides themselves are atherogenic [15]. In this context, it is also important to look at the epidemiological association between triglyceride levels and ASCVD [16]. The data indicate that risk does not increase linearly with increasing triglyceride concentrations, but 'levels off' meaning that in subjects with severely elevated triglyceride levels risk is not significantly higher than in subjects with moderately elevated triglyceride concentrations. This is different when other components of triglyceride rich lipoproteins are considered [15]. Risk increases linearly or curvilinearly with increasing concentrations of remnant cholesterol, apoB, and apoC-III. It is important to realize that remnant cholesterol, apoB and apoC-III concentrations are more or less directly related to particle number, while triglycerides are not. With severely elevated triglyceride concentrations, particle number does not further increase but the load of triglycerides per particle increases (usually indicating less efficient delipidation). These observations make it unlikely that triglyceride molecules can directly induce atherosclerosis.

At the same time, there is good evidence from epidemiological and genetic data that the number of apoB containing particles is directly linked to ASCVD and that the apoB plasma concentration is a better predictor of risk than the concentration of triglycerides or LDL-cholesterol [17▪▪,18]. Especially, the genetic data indicate that an elevated concentration of apoB is a predictor of risk irrespective of whether the concentration is elevated because of an increased concentration of LDL or TRL. A recent cohort study using data from the UK Biobank and two large international clinical intervention trials confirms that ASCVD risk can be captured best by the number of apoB containing particles (irrespective of their lipid content) [19▪▪].

Thus, ASCVD risk is related to the TRL particle number. It is however largely unclear, whether individual components of TRL or the particle as a whole induces ASCVD [14▪▪]. Cholesterol transported by any lipoprotein into the arterial wall can precipitate as crystals and induce inflammation [20]. Similarly, apoC-III has been directly linked to endothelial inflammation [21▪]. Therefore, it is likely that apoB containing lipoproteins are responsible for transporting these components into the arterial wall, where inflammation is then induced.

However, it should also be noted that an elevated concentration of TRL is associated with

important changes in LDL and HDL composition, function and metabolism, which may significantly contribute to the observed association between TRL and ASCVD [22▪,23,24]. In the presence of an elevated concentration of TRL, there is predominance of small dense LDL, which are known to be more atherogenic because they contain more oxidized and modified components have a longer half-life and interact not as well with the LDL-receptor. In addition, with an increased concentration of TRL, HDL-cholesterol concentration is typically decreased and more important from an atherosclerosis point of view HDL function is impaired. To which extent these changes in LDL and HDL composition, function and metabolism contribute to the increased risk for ASCVD seen with elevated TRL is being debated.

In summary, triglycerides are a marker of an atherogenic lipid constellation. The ASCVD risk is mediated via TRL (or components thereof) and probably by changes in LDL and HDL composition, function and metabolism induced by an increased number of TRL. Therefore, it may be better to use parameters other than triglycerides to estimate ASCVD risk and as treatment goals.

APOLIPOPROTEIN B

Since all atherogenic lipoproteins (chylomicron remnants, VLDL, IDL, LDL, lipoprotein(a)) contain one (and only one) molecule of apoB, the apoB concentration directly reflects the number of atherogenic particles in plasma. Consistent with this, it has also been shown that the apoB plasma concentration is a better predictor of ASCVD risk than LDL-cholesterol and has been proposed as a risk estimator and treatment goal for many years [18]. In fact, the recent 2019 ESC/EAS guidelines suggest apoB as a secondary treatment goal (Table 1) [25▪]. In contrast, the 2021 ACC Expert Consensus on the management of patients with persistent hypertriglyceridemia, does not mention apoB or non-HDL cholesterol as a treatment target but focuses on LDL-cholesterol lowering for ASCVD risk reduction [26].

There are several advantages to using the apoB plasma concentration to estimate risk and as a treatment goal. If the number of apoB containing particles is the link to ASCVD, then measuring the apoB concentration is measuring the culprit. It is also attractive to capture all lipid associated risk by one parameter, instead of considering LDL-cholesterol, HDL-cholesterol and triglyceride concentrations separately. The apoB concentration can be determined with great precision and less variability than LDL-cholesterol. ApoB measurements are widely available (but significantly more expensive than cholesterol measurements).

But, there are also several disadvantages to be mentioned. Most importantly, this approach assumes that all apoB containing particles convey the same risk. Although all apoB containing particles are atherogenic, it is unclear, whether this is true. Thus, it is unclear whether an elevated apoB concentration because of elevated plasma LDL is associated with the same risk as an elevated apoB because of an elevated TRL concentration in plasma. In fact chylomicrons which also contain one apoB molecule are probably not atherogenic because they are 'too large' to enter the arterial wall. Finally, it must be acknowledged that most of our intervention data are LDL-cholesterol based (concerning inclusion criteria and outcome parameters), therefore the results of these studies cannot simply be extrapolated to apoB.

NON-HIGH DENSITY LIPOPROTEIN-CHOLESTEROL (NON-HIGH DENSITY LIPOPROTEIN-C; NON-HIGH DENSITY LIPOPROTEIN-CHOLESTEROL = TOTAL-CHOLESTEROL – HIGH DENSITY LIPOPROTEIN-CHOLESTEROL)

Non-HDL-C is an approximate for apoB, as it captures all cholesterol on atherogenic lipoproteins (again: chylomicrons, chylomicron remnants, VLDL, IDL, LDL, lipoprotein(a)). In contrast to

Table 1. Primary and secondary lipid goals for prevention of ASCVD (according to ESC) [25▪]

Risk category[a]	LDL-cholesterol	Non-HDL-cholesterol	apoB
	Primary goal	Secondary goal	Secondary goal
Very high risk	<55 mg/dl/<1.4 mmol/l and ≥50% reduction from baseline	<85 mg/dl/<2.2 mmol/l	<65 mg/dl
High risk	<70 mg/dl/<1.8 mmol/l and ≥50% reduction from baseline	<100 mg/dl/<2.6 mmol/l	<80 mg/dl
Moderate risk	<100 mg/dl/<2.6 mmol/l	<130 mg/dl/<3.4 mmol/l	Not defined
Low risk	<115 mg/dl/<3.0 mmol/l	<145 mg/dl/<3.8 mmol/l	Not defined

apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]As defined in the ESC guidelines [25▪].

triglyceride levels, which may increase disproportionally to the increase in particle number (TRL), the cholesterol content is a better reflection of TRL. Thus, the increase in TRL-cholesterol parallels the increase in apoB and thus particle number. Although this is generally true different apoB containing lipoprotein classes may contain a different amount of cholesterol (but always only one apoB).

The non-HDL-C targets parallel the LDL-cholesterol targets being always 30 mg/dl or 0.8 mmol/l higher than the LDL-cholesterol targets (Table 1) [25▪]. This reflects the fact that in fasting all TRL are VLDL where the ratio between TG and cholesterol is 5:1 (in mg/dl) or 2.2:1 (in mmol/l) (Friedewald formula). If a TG level of 150 mg/dl (1.7 mmol/l) is considered the upper normal limit, then theoretically 30 mg/dl (0.8 mmol/l) is the upper limit for VLDL-cholesterol.

The advantage of using non-HDL-C lays in its simplicity of determination, as it requires only one calculation step using parameters that are very widely available. It may also be considered as an advantage that many patients and physicians are used to cholesterol as an important parameter and therefore less 'education' is required to introduce this parameter.

As a disadvantage it must be mentioned that it is only a surrogate for apoB. Similar to using apoB, the underlying assumption that cholesterol on any apoB containing particle conveys the same ASCVD risk may be an oversimplification. As an example may serve that small dense LDL are more atherogenic than normal sized LDL. A certain LDL-cholesterol level (as part of non-HDL-C) may thus represent more or less particles (depending on the subtype distribution) and thus different levels of risk.

ACHIEVING LIPID GOALS IN PATIENTS WITH HYPERTRIGLYCERIDEMIA/ COMBINED DYSLIPIDEMIA

In many patients with hypertriglyceridemia, there is a concomitant elevation of LDL-cholesterol. Although most guidelines define an absolute threshold for fasting triglycerides (such as 150 mg/dl, 200 mg/dl, 1,7 mmol/l or 2 mmol/l) to define 'elevated' triglycerides, no such absolute values exist for LDL-cholesterol. LDL-cholesterol thresholds and goals are defined on the basis of absolute ASCVD risk and may vary from 55 mg/dl (1.4 mmol/l) to 115 mg/dl (3 mmol/l). Therefore, apoB and non-HDL-C goals also vary.

Without doubt achieving the LDL-cholesterol goal should be the first step and the primary goal, as this reflects numerous high quality randomized controlled trials [25▪]. Achieving secondary goals, either apoB or non-HDL-C may then follow. These secondary goals clearly do not have the same weight as the primary goals, as they are not based on the results of outcome trials testing these parameters. Secondary goals (apoB or non-HDL-cholesterol) may be reached by different strategies.

As non-HDL-C mostly reflects LDL-cholesterol and TRL-cholesterol (remnant cholesterol) one approach is to further decrease LDL-cholesterol (Table 2). As it is well known further decreasing

Table 2. Approaches to achieve non-HDL-cholesterol and/or apoB targets once LDL-cholesterol goals are achieved with statin or combination therapy

Approach	Strategy	Outcome trial without concomitant statin therapy[a]	Outcome trial with concomitant statin therapy[a]	Comment
Increase of statin dose	Further decrease of LDL	NA	+	Limited effect on non-HDL-cholesterol/apoB
Ezetimibe	Further decrease of LDL	0	+	Limited effect on non-HDL-cholesterol/apoB
PCSK9-inhibitors	Further decrease of LDL	0	+	Limited effect on non-HDL-cholesterol/apoB
Fibrates	Decrease of remnant-cholesterol	+	–	Consistent triglyceride reduction; unclear if negative outcome trials relate to methodological aspects or to true failure
Niacin	Decrease of remnant-cholesterol	+	–	Triglyceride reduction, but no cardio-vascular benefit in combination with statins
Omega 3 fatty acids (DHA/EPA)	Decrease of remnant-cholesterol; lipid independent effects	0	–	Triglyceride reduction, but no cardiovascular benefit
Omega-3 fatty acids (high dose EPA)	Decrease of remnant-cholesterol; lipid independent effects	0	+	Benefit which seems to be independent of triglyceride reduction

apoB, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]'0', no outcome trial available; '–', outcome trial(s) did not show benefit; '+', outcome trial(s) show benefit.

LDL-cholesterol translates into cardio-vascular benefit as it was shown in the PCSK9-inhibitor outcome trials [8,9]. However, there is obviously a limit to how much apoB and/or non-HDL-C can be reduced by lowering LDL-cholesterol.

Alternatively, TRL-cholesterol can be reduced, which effectively means reduction of TRL. This can be achieved by fibrates, high dose omega-3 fatty acids and most importantly be life-style modification [27▪]. Although these approaches reduce triglycerides, convincing outcome data showing that this will translate into clinical benefit are lacking. It is currently unclear whether the failure of these trials to show benefit relates to the fact that this approach does not work or to methodological issues with the available trials. However, it should be noted that these approaches decrease TRL-cholesterol (and apoB) to a lesser extent than triglycerides.

New approaches (antibodies and or oligonucleotides) addressing apoC-III and angiopoietin-like 3 (and other angiopoietin like proteins) are also being developed to decrease elevated triglyceride concentrations. Although these approaches are very promising with respect to triglyceride reduction, it is unclear whether this also translates into clinical benefit with respect to ASCVD risk reduction. In addition, most of these new approaches currently focus on patients with very severe hypertriglyceridemia as observed in familial chylomicronemia syndrome although promising results were also shown in mild to moderate hypertriglyceridemia [28,29].

Finally, approaches not directly addressing TRL can be applied. In this context, high dose EPA as used in the REDUCE-IT trial is of interest [30]. In this trial patients with high ASCVD risk and hypertriglyceridemia (triglycerides 150–500 mg/dl) on statin therapy (and LDL-cholesterol at or close to goal) dramatically benefitted from the addition of 4 g EPA per day. Interestingly, this ASCVD risk reduction cannot be explained by triglyceride (or TRL-cholesterol or apoB) reduction alone, indicating that additional mechanism are relevant. The interpretation of the REDUCE-IT trial is further complicated by the findings of the STRENGTH study, which also tested the effect of high dose omega-3 fatty acids on the prevention of ASCVD and showed no benefit [31]. However, the two studies differ in study populations [high risk (REDUCE-IT) vs. moderate-high risk (STRENGTH)), omega-3 fatty acids (EPA (REDUCE_IT) vs. EPA/DHA (STRENGTH)] and comparator (mineral oil (REDUCE-IT) vs. corn oil (STRENGTH)). The most common interpretation to explain the observed differences between the studies relates to the differences in active oils (EPA vs. EPA + DHA) [32]. However, recently a provocative interpretation has been presented: based on a simulation using data from the Copenhagen General Population Study it was hypothesized that the contrasting results of the two studies do not relate to different effects of EPA and DHA on lipid levels or CRP but to different effects of the comparator oils on these parameters and on lipid independent effects of EPA [33▪]. [XX] Anti-inflammatory effects protecting the endothelial wall from damage induced by TRL are probably of key importance.

CONCLUSION

Although there is convincing evidence that patients with elevated triglyceride concentrations have an elevated risk for ASCVD, it is currently unclear how this risk is best addressed. Achieving secondary goals, such as apoB and/or non-HDL-cholesterol (besides LDL-cholesterol as the primary goal) by either further reducing LDL or by reducing TRL is one strategy. Of these approaches, only further LDL lowering has so far been successful in outcome trials. Another strategy is the use of high dose EPA, as this reduced the ASCVD risk in statin treated patients with hypertriglyceridemia (and LDL-cholesterol on or close to goal).

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Conflicts of interest

Dr Parhofer reports personal fees from Akcea, Amarin, Amgen, Daiichi-Sankyo, Ionis, MSD, Novartis, and Sanofi, outside the submitted work.

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