Triglycerides and residual risk

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Purpose of review
To review the recent evidence from observational/genetic/interventional studies addressing triglycerides and residual cardiovascular risk (CVRisk).

Recent findings
Large population-based and secondary prevention studies consistently show an association of higher triglycerides with increased CVRisk. This is compounded by genetic studies demonstrating an independent relationship between triglyceride raising or lowering genetic variants affecting triglyceride-rich lipoproteins (TRL) metabolism and CVRisk. Mendelian randomization analysis suggests the benefit of genetic lowering of triglycerides and LDL-cholesterol is similar per unit change in apolipoprotein-B. Among cholesterol-lowering trials, more intensive statin therapy produced greater CVRisk reductions in patients with higher TRL-cholesterol or triglycerides; proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition led to similar triglycerides reduction but greater non-HDL-C or apolipoprotein-B reductions than fibrates or fish oils. Regarding n-3 fatty acids, A Study of Cardiovascular Events in Diabetes (ASCEND) and Vitamin D and Omega-3 Trial (VITAL) primary prevention trials with eicosapentaenoic acid (EPA) and docosahexaenoic acid failed to demonstrate cardiovascular benefits, Conversely, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) using high-dose icosapent-ethyl (purified EPA) in primary (diabetes) and secondary prevention with hypertriglyceridemia showed significant cardiovascular events reductions (greater than expected by the observed triglycerides or apolipoprotein-B reductions, suggesting potential benefits through non-lipid pathways).

Summary
Evidence suggests higher triglycerides are a marker of CVRisk and may help identify patients who benefit from intensification of therapy. Moreover, genetic studies support a causal link between TRL/triglycerides and cardiovascular disease. Treatment with high-dose EPA may be of benefit in high-risk patients with hypertriglyceridemia to reduce CVRisk.

Keywords
cardiovascular disease, non-HDL-cholesterol, residual risk, triglyceride-rich lipoproteins, triglycerides

INTRODUCTION

Low-density lipoprotein-cholesterol (LDL-C) is the primary target for lipid-lowering therapy (LLM) to reduce atherosclerotic cardiovascular disease (ASCVD) risk, supported by a large body of evidence demonstrating that LDL-C is both a causal and cumulative risk factor for ASCVD [1]. However, despite patients being treated effectively with cholesterol-lowering medication, including intensive statin therapy [2] or combination therapy [3–5], a significant residual risk may persist. Reduction of residual ASCVD risk may additionally require attainment of non-high-density lipoprotein-cholesterol (non-HDL-C), which captures not only LDL-C but also the other proatherogenic apolipoprotein-B-containing lipoproteins, including triglyceride-rich lipoproteins (TRLs) (comprising intermediate-density and very low-density lipoproteins, chylomicrons and their remnants) and lipoprotein(a) [6,7▪]. In fact, non-HDL-C levels have been more strongly associated with ASCVD risk than LDL-C [8,9] and, it is recommended by guidelines as a secondary lipid target to attain residual risk persisting after LDL-C lowering [10▪▪]. This seems of particular importance in certain conditions such as diabetes, obesity, or metabolic syndrome, where a so-called

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KEY POINTS

- Non-HDL-C (which also captures the cholesterol in triglyceride-rich lipoproteins [TRLs]) has been more strongly associated with cardiovascular risk than LDL-C and is recommended as a secondary target to attain residual risk, particularly in certain conditions (e.g., diabetes, obesity, metabolic syndrome) with an 'atherogenic dyslipidemia' profile (including high non-HDL-C and triglycerides and low HDL-C).
- Large epidemiological population-based studies and secondary prevention studies in statin-treated coronary patients suggest that higher triglycerides are a marker of cardiovascular risk and may help identify a subgroup of patients who may benefit from intensification of therapy.
- Genetic evidence reveals a relationship between triglyceride-raising or lowering genetic variants affecting TRLs metabolism and cardiovascular risk, and supports a causal link with cardiovascular disease.
- Guidelines recommend statins as first-line drug to reduce cardiovascular risk in high-risk individuals with hypertriglyceridemia.
- Although ASCEND and VITAL n-3 fatty acids trials in primary prevention with EPA and DHA failed to demonstrate cardiovascular benefits, REDUCE-IT using high-dose icosapent ethyl (purified EPA) in primary (diabetes) and secondary prevention with hypertriglyceridemia showed a significant 25% relative risk reduction in adverse cardiovascular events.

atherogenic dyslipidaemia is frequently described, including elevations of non-HDL-C and triglycerides and low HDL-C [10▪▪,11].

Triglycerides are carried by TRLs particles in blood. A strong correlation between TRL-C and triglycerides, and between non-HDL-C and triglycerides exists [6,7▪,12]. Additionally, it has been shown that attainment of non-HDL-C targets in patients with diabetes correlates inversely with triglyceride levels [12]. As such, patients with elevated triglycerides may represent a subgroup exposed to higher risk who may require more intensive therapy to further clear proatherogenic lipoproteins in an attempt to further reduce their residual risk. In the present review, we assess the recent evidence from observational, genetic and interventional studies addressing triglycerides and ASCVD (residual) risk.

EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

Large prospective, population-based studies suggest that people in the general population who have higher triglycerides, even within the range considered as the 'usual' levels, are at higher risk of incident ASCVD. Early analysis in more than 262 500 general population individuals from 29 prospective studies, with a median triglycerides of 1–2 mmol/l, showed that, after a 12.1-year median follow-up (~10 200 incident cases of coronary artery disease [CAD]), individuals in the top third of triglyceride levels had more than 70% higher risk of CAD compared with those in the bottom third [13].

These results were later confirmed in analysis from the Emerging Risk Factors Collaboration (ERFC) and Triglyceride Coronary Disease Genetics Consortium (TG-CDGC) in more than 300 000 people free from vascular disease at baseline from multiple long-term prospective studies [8,14], and more recently in about 75 700 participants in the Copenhagen General Population and Copenhagen City Heart study over a shorter (4-year) period of follow-up [15]. In these studies, the risk of ASCVD, particularly for CAD, but also for ischaemic stroke, was significantly associated with triglyceride levels in a 'dose-dependent' manner, after adjusting for age, sex and other risk factors [8,14,15]. For instance, in the Danish studies combined, and comparing to individuals with triglycerides at least 4.00 mmol/l at baseline, the risk progressively decreased with lower triglycerides, from about 20 to 30%, 50 and up to 60% among those with triglycerides 3.00–3.99, 2.00–2.99, 1.00–1.99 and less than 1 mmol/l, respectively ($P < 0.001$ across triglyceride levels) [15]. Of interest, in the ERFC/TG-CDGC, the association between CAD and ischaemic stroke with triglycerides disappeared after further adjustment for non-HDL-C and HDL-C [8,14]. However, the close association between triglycerides, non-HDL-C and HDL-C, and, in particular, non-HDL-C which captures the cholesterol in TRLs particles, may explain, at least partly, the lack of association when adjusting by HDL-C and particularly non-HDL-C, as adjustment for the causal exposure attenuates the relationship with the exposure.

TRL-C levels have also been associated with subclinical coronary atherosclerosis: in the ELSA-Brasil Study in about 3800 individuals without history of CAD not using LLM, fasting TRL-C levels were independently associated with the presence and severity of calcium coronary score [16]. In secondary prevention in patients with established CAD on a background of statins, fasting triglycerides are related with an unfavourable ASCVD prognosis [7▪,17,18]. Observational analysis in postacute coronary syndrome, statin-treated patients from Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), Myocardial Ischemia Reduction with Acute Cholesterol Lowering trial (MIRACL), or dal-OUTCOMES trials (the latter with a median LDL-C of 73 mg/dl) revealed that those with higher triglycerides at study entry associated

significantly higher cumulative rates of events in the short and long-term after adjustment for triglyceride-related risk factors, HDL-C and LDL-C [17,18]. More recently, posthoc analysis of the Treating to New Targets trial (TNT) trial in stable CAD patients receiving atorvastatin 10 mg/day showed that increasing TRL-C levels were associated with progressively higher five-year rates of cardiovascular events (Fig. 1) [7▪].

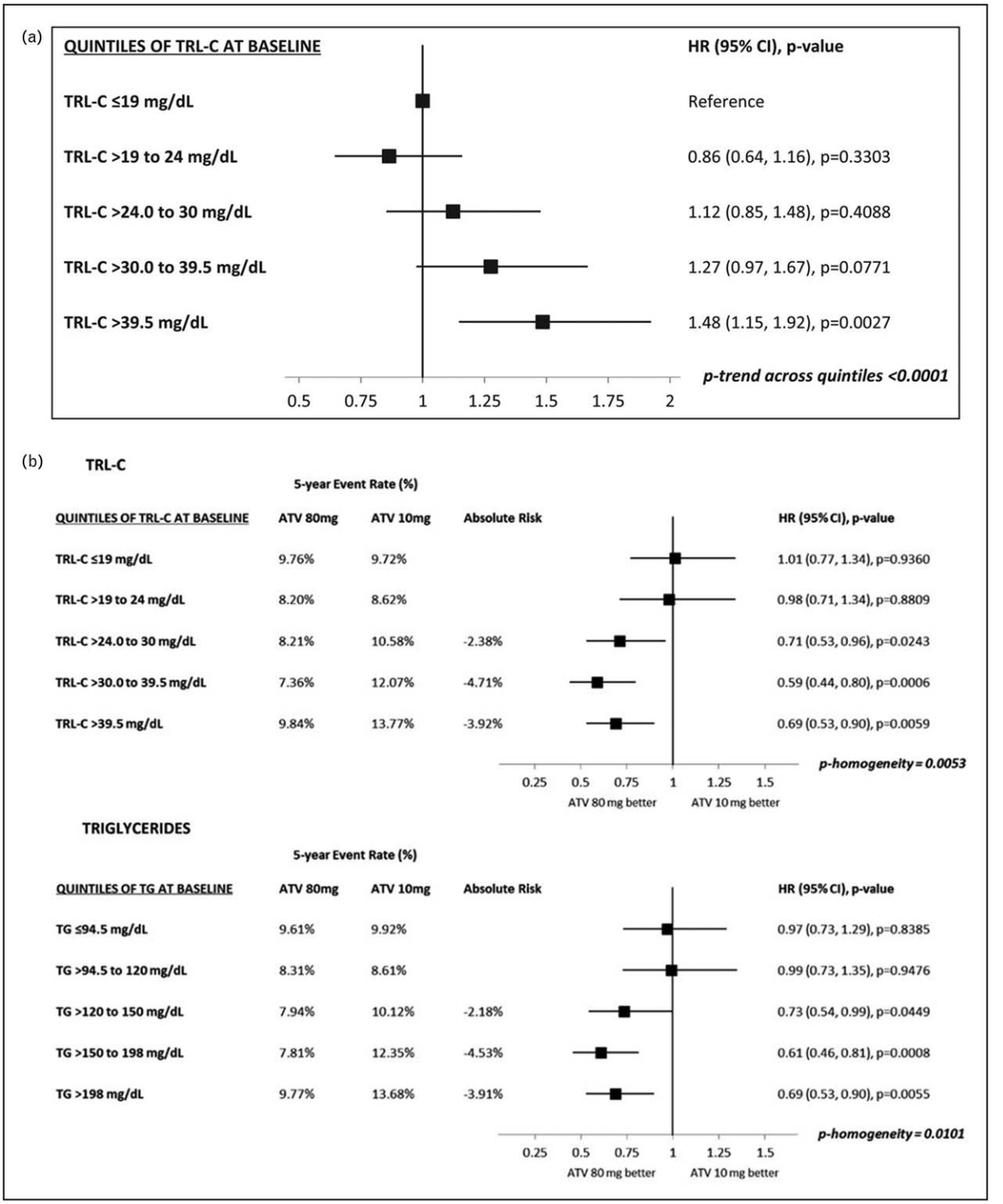

FIGURE 1. Risk of major cardiovascular events among patients on atorvastatin 10 mg/day by quintiles of TRL-C (a), and effect of atorvastatin 80 versus 10 mg/day on the risk of major cardiovascular events by quintiles of TRL-C and of triglycerides at baseline in the TNT trial (b). ATV, atorvastatin; CI, confidence interval; HR, hazard ratio; TG, triglycerides; TNT, Treating to New Targets trial; TRL-C, triglyceride-rich lipoprotein cholesterol. Reproduced with permission from [7▪].

Although observational studies cannot demonstrate causality, but rather association, the current evidence from these large epidemiological studies suggest that higher triglycerides represent a marker of ASCVD risk and may help identify a subgroup who benefit from intensification of therapy.

EVIDENCE FROM GENETIC STUDIES

During the last few years, a number of studies have provided insights into the relationship between genes related to the triglycerides metabolism, triglyceride levels and ASCVD risk. Overall, genetic evidence suggests that TRLs, assessed by plasma triglycerides levels, represent a causal risk factor for ASCVD, particularly for CAD [19]. In a large study assessing the effects of genetic variants on the risk of myocardial infarction (~20 000 cases of myocardial infarction and ~50 000 controls), the investigators found that those loci associated with an effect on triglycerides were associated with CAD, with the strength of the Single nucleotide polymorphism (SNP's) effect on triglyceride levels correlating with the magnitude of its effect on CAD risk [19,20]. In multivariable Mendelian randomization models to account for the effects of LDL-C and HDL-C, a 1-SD increase in triglyceride levels in people with triglyceride-raising alleles was significantly and independently associated to a 54% increase risk of myocardial infarction [19,20].

Lipoprotein-lipase (LPL) hydrolyses triglycerides carried by circulating lipoproteins, reducing the levels of triglycerides. Consequently, genetic variants that ultimately affect LPL activity alter the levels of triglycerides. *LPL* or *APO-A5* loss-of-function genetic variants result in a reduction of LPL activity, what has been related to increased concentrations of and prolonged exposure to TRLs particles, increased triglycerides levels, and increased ASCVD risk [21–23]. For instance, a recent study in about 47 000 individuals found that heterozygous carriers of *LPL* loss-of-function and missense pathogenic variants had higher triglyceride levels (~20 mg/dl) and an increased risk of premature CAD [odds ratio 1.84; 95% confidence interval (CI), 1.35–2.51] [23]. On the contrary, *angiopoietin-like 3 (Angiopoietin-like 3 (ANGPTL3))*, *ANGPTL4* or *APOC3* loss-of-function genetic variants lead to an increased LPL activity, resulting in lower triglycerides levels, and that translated into an ASCVD risk reduction [15,22,24,25–27]. For instance, *APOC3* loss-of-function mutations have been associated with 39–44% lower triglycerides levels compared with noncarriers, which translated into a 60% risk reduction of ischaemic vascular disease among carriers versus noncarriers [15,24,28].

Together, these genetic studies make a strong case to support a causal link between TRLs/triglycerides and ASCVD, particularly CAD. Since genetic variants are present from birth, genetic findings may also suggest a cumulative effect of altered TRL/triglyceride levels over time.

Finally, recent Mendelian randomization analysis provides important insights on the effect of triglycerides and LDL-C on CAD risk [29▪▪]. On the basis that each atherogenic lipoprotein contains a single apoB, the authors compared the benefit of genetic lowering of triglycerides and LDL-C by estimating their effects per unit change in apoB. For each 10-mg/dl lower apoB, carriers of LPL variants associated with lower triglyceride levels and carriers of LDL-receptor variants associated with lower LDL-C levels had a similar lower CAD risk despite the differences in individual lipid levels (Fig. 2). These findings suggest that the benefit of lowering triglycerides and LDL-C are similar per unit change in apoB and proportional to the absolute reduction in apoB [29▪▪]. As TRLs approximate triglycerides divided by five and assuming that apoB-containing lipoproteins have similar atherogenic effects, the authors discussed that a five-fold higher reductions in triglycerides (~200 mg/dl) would be required to achieve the same 20% CAD risk reduction observed by reducing LDL-C about 40 mg/dl [29▪▪,30]. As current available drugs are unable to reach that level of triglycerides reductions, this may partly explain the failure of some triglyceride-lowering drugs to consistently reduce ASCVD risk.

Genetic Score	Δ Triglycerides (95% CI)	*P* Value	Δ Low-Density Lipoprotein Cholesterol (95% CI)	*P* Value	Odds Ratio for Coronary Heart Disease (95% CI)	*P* Value
LPL	-69.9 (-71.6 to -68.3)	7.1×10^{-1363}	0.7 (0.0 to 1.4)	.04	0.771 (0.741 to 0.802)	3.9×10^{-38}
LDLR	-1.9 (-3.9 to -0.1)	.04	-14.2 (-14.8 to -13.6)	1.4×10^{-465}	0.773 (0.747 to 0.801)	1.1×10^{-46}

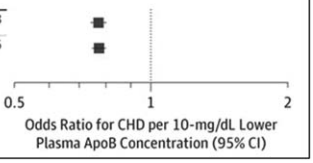

FIGURE 2. Association between lipoprotein lipase gene (LPL) and LDL receptor gene (LDLR) genetic scores with levels of triglycerides and LDL-C, and risk of coronary heart disease per 10-mg/dl lower plasma concentration of apolipoprotein B-containing lipoproteins. ApoB, apolipoprotein B; CHD, coronary heart disease; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase. Reproduced with permission from [29▪▪].

EVIDENCE FROM CLINICAL TRIALS

Low-density lipoprotein-cholesterol lowering

Although the effects of statins on triglycerides are limited (~10–20% reduction) [10▪▪], as patients with elevated triglycerides have higher absolute risk, guidelines recommend statins as first-line drug to reduce ASCVD risk in high-risk individuals with hypertriglyceridemia [10▪▪]. This is supported by recent posthoc analyses from the TNT trial on about 10 000 participants with stable CAD, where intensive treatment with atorvastatin 80 mg/day, versus 10 mg/day, resulted in significantly greater ASCVD risk reductions among patients with higher TRL-C or triglycerides (Fig. 1b) [7▪]. In relative terms, the benefit was 31% with almost 4% absolute benefit among those with triglycerides at least 199 mg/dl [7▪].

PCSK9 inhibitors have shown to significantly reduce not only LDL-C but also non-HDL-C, apoB and triglycerides as well as increasing HDL-C and apolipoprotein A-I, in both diabetic and nondiabetic patients [31,32]. Among patients with elevated triglycerides, Alirocumab was similar to fibrates or fish oils with respect to triglycerides lowering and HDL-C raising but produced statistically greater reductions in non-HDL-C, apoB and LDL particle number [33▪]. If risk relates to apoB rather than triglycerides, as discussed above, then this study suggests that increasing clearance of apoB and thus triglyceride-containing lipoproteins may be more favourable than reducing triglycerides synthesis (e.g., fibrates, n-3 fatty acids).

Fibrates

Although some trials in the pre-statin era showed some benefit on ASCVD risk reduction [10▪▪,34], after the introduction of statins fibrates have only demonstrated some benefit in post-hoc subgroup analysis of patients with high triglycerides and low HDL-C from trials where the primary endpoint was not reduced overall [34]. Consequently, the use of fibrates is not routinely recommended in most guidelines for ASCVD prevention as first-line LLM [10▪▪]. A large placebo-controlled trial (PROMINENT, ~10 000 participants) with pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator, is currently ongoing [35]; this trial, aiming to target residual risk after LDL-C lowering in type-2 diabetes with mild-to-moderate hypertriglyceridemia and low HDL-C, may provide further insights on the effects of fibrates on ASCVD prevention.

n-3 fatty acids

A renewed interest in n-3 fatty acids (n3FAs) has been raised since the recent results from REDUCE-IT showing a reduction on ASCVD adverse outcomes with n3FAs [36▪▪]. These findings, however, contrast with other past and recent n3FAs trials, which, contrarily to REDUCE-IT, failed to demonstrate benefit on cardiovascular endpoints. In this sense, a Cochrane review in 2018 concluded that the consumption of n3FAs (eicosapentaenoic [EPA]/docosahexaenoic [DHA] acids) decreases triglycerides but this was not translated into benefit for all-cause mortality or ASCVD events [37]. Similar conclusions resulted from a 2018 meta-analysis of 10 studies (>77 000 individuals), which failed to demonstrate any cardiovascular benefit with n3FA supplementation [38].

Results from three large trials have been released during the last two years and are summarized in Table 1. The ASCEND [39▪] and VITAL [40▪] trials were conducted in primary prevention patients not selected on the basis of their levels of triglycerides (ASCEND in diabetic patients); they compared 840 mg/day of EPA and DHA versus placebo, with a variable percentage of participants on a background of other LLM, but failed to demonstrate a benefit of n3FAs treatment over long-term follow-up (Table 1) [39▪,40▪]. However, REDUCE-IT trial [36▪▪] changed our perception of this class and highlighted the likely importance of dose on potential benefits. This study investigated high-dose (4 g/day) icosapent ethyl (purified EPA) versus placebo in patients with hypertriglyceridemia (150–499 mg/dl) and LDL-C 41–100 mg/dl (on statin) and either cardiovascular disease (secondary prevention) or diabetes with additional risk factors (primary prevention). Over a 4.9-year median follow-up icosapent ethyl, versus placebo, reduced triglycerides by 44 mg/dl, resulting in a significant 25% relative risk reduction in adverse cardiovascular events, with an absolute between-group difference of 4.8% (95% CI, 3.1–6.5) (Number Needed to Treat (NNT) 21; 95% CI, 15–33) [36▪▪]. The benefit was consistent on several cardiovascular outcomes, including risk of cardiovascular death (Hazard Ratio (HR) 0.80; 95% CI, 0.66–0.98). Importantly, risk reductions were unrelated to baseline triglycerides or the magnitude of triglycerides lowering and greater than it would be expected by the reductions in triglycerides or apoB. This raises the possibility of potential cardiovascular benefits through nonlipid pathways, perhaps related to platelet function or cell-membrane stabilization [41].

The ongoing A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial evaluates the effect of Epanova (n-3 carboxylic acids EPA and DHA) 4 g/day in high-risk statin-treated patients with hypertriglyceridemia and low HDL-C, with results expected in 2020 (Table 1) [42].

Table 1. Comparison of recent trials with n-3 fatty acids

Trial	ASCEND [39▪]	VITAL [40▪]	REDUCE-IT [36▪▪]	STRENGTH [42]
Participants	$n = 15\,480$	$n = 25\,871$	$n = 8179$	$n > 13\,000$
n3FA type	EPA + DHA	EPA + DHA	Icosapent ethyl (purified EPA ethyl ester)	Epanova (omega-3 carboxylic acids EPA + DHA)
n3FA dose	840 mg/day	840 mg/day	4 g/day	4 g/day
Control	Placebo (olive oil)	Placebo	Placebo (mineral oil)	Placebo (corn oil)
Population	Primary prevention in patients with diabetes	Primary prevention	Hypertriglyceridemia 150–499 mg/dl and LDL-C 41–100 mg/dl on statins, in primary prevention of patients with diabetes (plus additional risk factor/s) or in secondary prevention	Hypertriglyceridemia 180–499 mg/dl and low HDL-C on statin, in high-risk primary prevention (based on age, diabetes and other risk factors assessment) or in secondary prevention
Age	63 years (mean)	67 years (mean)	64 years (median)	≥18 years
Men	63%	49%	71%	–
White race	96%	71%	90%	–
Diabetes	100%	14%	59%	–
Current smoking	8.3%	7.2%	NR	–
Body mass index	31 kg/m^2 (mean)	28 kg/m^2 (mean)	31 kg/m^2 (median)	–
Statins	75%	37.5% on cholesterol-lowering drugs	100%	100%
LDL-C at baseline	NR (mean TC 161 mg/dl)	NR	75 mg/dl (median)	<100 mg/dl, or ≥100 if on maximally tolerated statin dose
Non-HDL-C at baseline	113 mg/dl (mean)	NR	118 mg/dl (median)	–
ApoB at baseline	82 mg/dl (mean)	NR	82 mg/dl (median)	–
HDL-C at baseline	49 mg/dl (mean)	NR	40 mg/dl (median)	<42 mg/dl in men/<47 in women
TG at baseline	NR	NR	216 mg/dl (median)	≥180 to <500 mg/dl
Follow-up	Mean 7.4 years	Median 5.3 years	Median 4.9 years	Expected 3–5 years
LDL-C change from baseline	NR	NR	+6.6% (+5.0 mg/dl) with control versus n3FA	–
TG change from baseline	NR	NR	−19.7% (−44.5 mg/dl) with n3FA versus control	–
Primary endpoint	Serious vascular event (composite of nonfatal MI, nonfatal ischaemic stroke, TIA or vascular death)	Major CV events (composite of MI, stroke or CV death)	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization or hospitalization for unstable angina
Effect of n3FA (versus control) on primary endpoint	RR 0.97 (95% CI 0.87, 1.08), $P = 0.55$	HR 0.92 (95% CI 0.80, 1.06), $P = 0.24$	HR 0.75 (95% CI 0.68, 0.83), $P < 0.001$	–

ApoB, apolipoprotein B; ASCEND, A Study of Cardiovascular Events in Diabetes; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; n3FA, omega-3 fatty acids; NR, not reported; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial; RR, rate ratio; STRENGTH, Statin Residual Risk Reduction with Epanova in High Risk Patients with Hypertriglyceridemia; TC, total cholesterol; TG, triglycerides; TIA, transient ischaemic attack; VITAL, Vitamin D and Omega-3 Trial.

Novel therapeutic approaches under investigation

Novel approaches, directed toward new potential targets (as supported by studies on genetic variants related to TRL/triglycerides metabolism), have emerged in the last years. This is the case of Volanesorsen, a second-generation antisense oligonucleotide that lowers ApoC3 levels by binding to its messenger-RNA, ultimately resulting in triglyceride reductions of 31–71% [43]; its use is currently restricted to familial chylomicronemia syndrome [10▪▪]. Two novel compounds targeting ANGPTL3 through different mechanisms (monoclonal antibody Evinacumab; antisense anti-RNA oligonucleotide IONIS-ANGPTL3Rx) are also being evaluated; by inhibiting ANGPTL3 these compounds, achieve profound reductions in triglycerides and LDL-C but also HDL-C [26,44]. Although promising drugs, ASCVD outcome trials are yet required to assess whether these larger reductions in TRL/triglycerides translate into ASCVD risk reduction.

RECOMMENDATIONS FROM NEW GUIDELINES

New 2018 American College of Cardiology/American Heart Association (ACC/AHA) and 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for management of dyslipidaemia have been published [10▪▪,45▪▪]. Although the ACC/AHA guidelines did not lower LDL-C targets, the ESC/EAS guidelines have recommended more aggressive and lower LDL-C goals for those at very high risk such as established ASCVD, diabetes or high Systematic Coronary Risk Estimation (SCORE) risk. No specific goals are set for triglycerides, but it is recognized that low levels indicate lower risk, whereas persistent hypertriglyceridemia may identify patients with higher risk and/or the need of further risk assessment [10▪▪]. Both guidelines highlight persistent hypertriglyceridemia as a case to consider initiation or intensification of statins in high-risk individuals to reduce ASCVD risk (Table 2).

Table 2. 2018 American (AHA/ACC) and 2019 European (ESC/EAS) guidelines recommendations for pharmacological treatment in patients with high triglycerides

2018 ACC/AHA guidelines on the management of blood cholesterol [45▪▪]		**2019 ESC/EAS guidelines for the management of dyslipidaemias [10▪▪]**	
Recommendations for pharmacological treatment in patients with high triglycerides			
Adults ≥20 years with moderate hypertriglyceridemia (TG 175–499 mg/dl)	Address and treat lifestyle and secondary factors and medications that increase TG (COR I, LOE B-NR)	High-risk individuals with TG > 200 mg/dl	Statin treatment is recommended as the first drug of choice to reduce CVD risk (class I, level B)
Adults 40–75 years with moderate (TG 175–499 mg/dl) or severe (TG ≥ 500 mg/dl) hypertriglyceridemia and ASCVD risk of ≥7.5%	Reevaluate ASCVD risk after addressing lifestyle and secondary factors, and consider persistently elevated TG as a factor favouring initiation or intensification of statin therapy (COR IIa, LOE B-R)	High-risk (or above) individuals with TG between 135 and 499 mg/dl despite statin treatment	n-3 PUFAs (icosapent ethyl 2 × 2 g/day) should be considered in combination with a statin (class IIa, level B)
Adults 40–75 years with severe hypertriglyceridemia (TG ≥ 500 mg/dl) and ASCVD risk of ≥7.5%	Address reversible causes of high TG and initiate statin therapy (COR IIa, LOE B-R)	Primary prevention of patients at LDL-C goal with TG > 200 mg/dl	Fenofibrate or bezafibrate may be considered in combination with statins (class IIb, level B)
Adults with severe hypertriglyceridemia (TG ≥ 500 mg/dl), especially fasting TG ≥ 1000 mg/dl, with persistently elevated TG after addressing other causes of hypertriglyceridemia	Implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy (COR IIa, LOE B-NR)	High-risk patients at LDL-C goal with TG > 200 mg/dl	Fenofibrate or bezafibrate may be considered in combination with statins (class IIb, level C)

Information in this table does not intend to be exhaustive and the original guidelines should be consulted for the management of patients and to follow any recommendation and action. In the 2018 ACC/AHA guidelines, the class of recommendation (COR) refers to the estimated magnitude and certainty of benefit in proportion to risk (I, strong benefit over risk; IIa, moderate; IIb, weak; III, no benefit; IV, harm, higher risk than Benefit), and the level of evidence (LOE) corresponds to the quality of evidence supporting the recommendation (A, high quality; B-R, moderate, randomized; B-NR, moderate, nonrandomized); C-LD, limited data; C-EO, expert opinion) [45▪▪]. In the 2019 ESC/EAS guidelines, the class of recommendation refers to the evidence and/or agreement supporting the benefit/usefulness/effectiveness of a treatment or procedure (I, recommended or indicated; IIa, should be considered; IIb, may be considered; III, not recommended), and the level of evidence supporting the recommendations is graded from A (multiple randomized trials or metaanalyses) to B (single randomized trial or large nonrandomized studies) and C (expert opinion and/or small studies, retrospective studies or registries) [10▪▪]. ACC/AHA, American Heart Association/American College of Cardiology; ASCVD, atherosclerotic cardiovascular disease; COR, class of recommendation; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; HTG, hypertriglyceridemia; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; PUFA, polyunsaturated fatty acid; TG, triglycerides.

Guidelines have reiterated the relevance of atherogenic lipoproteins and total atherogenic cholesterol content by supporting the notion that non-HDL-C and apoB are considered stronger biomarkers of atherogenicity than LDL-C alone, as they reflect all the circulating atherogenic lipoproteins [10▪▪,45▪▪,46]. This may be of particular relevance in conditions associated with high triglycerides. Non-HDL-C or apoB are considered secondary objectives of therapy [10▪▪,45▪▪].

Both guidelines recommend lifestyle interventions in all categories of hypertriglyceridemia as pivotal strategies for controlling plasma triglycerides, and addressing underlying causes leading to increased triglycerides (e.g., diabetes, chronic kidney disease, metabolic syndrome, hypothyroidism, medications increasing triglycerides) [10▪▪,45▪▪]. The criteria to initiate pharmacological treatments, however, differ between both guidelines. The AHA/ACC guidelines consider two categories of hypertriglyceridemia in adults: moderate (fasting or nonfasting triglycerides 175–499 mg/dl) and severe (fasting triglycerides ≥500 mg/dl) [45▪▪]; in moderate hypertriglyceridemia, nonpharmacological strategies are usually preferred according to this guideline [45▪▪]. Table 2 summarizes the recommendations for the pharmacological treatment of patients with elevated triglycerides.

CONCLUSION

Current evidence supports a role of triglycerides in the assessment of residual cardiovascular risk. Persistent higher triglycerides are not only a marker of cardiovascular risk but it also may help identify patients who benefit from intensification of therapy. Moreover, genetic studies support a causal link of TRL, as assessed by triglyceride levels, and ASCVD. These genetic studies have also helped identify potential new treatment targets, some of which are already under investigation using novel therapeutic approaches beyond small molecules. Current guidelines recommend statins as first-line drug to reduce cardiovascular risk in high-risk individuals with hypertriglyceridemia. Although more data are needed to understand the mechanism of action and confirm the effects of icosapent ethyl, the significant and consistent benefit on several cardiovascular outcomes observed in REDUCE-IT adds this drug to the therapeutic arsenal for cardiovascular prevention in high-risk individuals with hypertriglyceridemia. Whether this benefit is related to the class (n3FAs) or specific of this compound, or to the dose, is yet unclear.

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Conflicts of interest

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- ▪ of special interest
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