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REVIEW

Hypertriglyceridemia and omega-3 fatty acids: Their often overlooked role in cardiovascular disease prevention

M. Arca [a,*], C. Borghi [b], R. Pontremoli [c], G.M. De Ferrari [d], F. Colivicchi [e], G. Desideri [f], P.L. Temporelli [g]

[a] *Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Roma, Italy*
[b] *Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Ospedale Policlinico S.Orsola-Malpighi, Bologna, Italy*
[c] *Dipartimento di Medicina Interna, Università di Genova, Ospedale Policlinico San Martino, Genova, Italy*
[d] *Unità Coronarica e Laboratori Sperimentazione e Ricerca, Centro Clinico di Ricerca Cardiovascolare, IRCCS Fondazione Policlinico San Matteo, Dipartimento di Medicina Molecolare, Università degli Studi di Pavia, Pavia, Italy*
[e] *UOC Cardiologia, Ospedale S. Filippo Neri, ASL ROMA 1, Roma, Italy*
[f] *Facoltà di Medicina e Chirurgia, Università degli Studi dell'Aquila, L'Aquila, Italy*
[g] *Divisione di Cardiologia Riabilitativa, ICS Maugeri, IRCCS, Veruno-NO, Italy*

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Abstract *Aims:* This review aims to describe the pathogenic role of triglycerides in cardiometabolic risk, and the potential role of omega-3 fatty acids in the management of hypertriglyceridemia and cardiovascular disease.
Data synthesis: In epidemiological studies, hypertriglyceridemia correlates with an increased risk of cardiovascular disease, even after adjustment for low density lipoprotein cholesterol (LDL-C) levels. This has been further supported by Mendelian randomization studies where triglyceride-raising common single nucleotide polymorphisms confer an increased risk of developing cardiovascular disease. Although guidelines vary in their definition of hypertriglyceridemia, they consistently define a normal triglyceride level as <150 mg/dL (or <1.7 mmol/L). For patients with moderately elevated triglyceride levels, LDL-C remains the primary target for treatment in both European and US guidelines. However, since any triglyceride level in excess of normal increases the risk of cardiovascular disease, even in patients with optimally managed LDL-C levels, triglycerides are an important secondary target in both assessment and treatment. Dietary changes are a key element of first-line lifestyle intervention, but pharmacological treatment including omega-3 fatty acids may be indicated in people with persistently high triglyceride levels. Moreover, in patients with pre-existing cardiovascular disease, omega-3 supplements significantly reduce the risk of sudden death, cardiac death and myocardial infarction and are generally well tolerated.
Conclusions: Targeting resistant hypertriglyceridemia should be considered as a part of clinical management of cardiovascular risk. Omega-3 fatty acids may represent a valuable resource to this aim.

* Corresponding author. Sapienza Università di Roma, Dipartimento di Medicina Interna e Specialità Mediche, Viale del Policlinico 155, 00161 Rome, Italy. Fax: +39 06 4997 4551.
E-mail address: marcello.arca@uniroma1.it (M. Arca).

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Introduction

Although several studies have associated high plasma triglycerides (TGs) with increased risk of cardiovascular disease (CVD) [1,2], the causal, independent contribution of hypertriglyceridemia to cardiovascular risk remains controversial [3]. The observation that individuals with grossly elevated plasma TGs do not develop atherosclerosis [4], further raised skepticism about the role of TGs in CVD. As interventional studies aimed at reducing TGs have shown inconsistent effects on CVD outcomes, hypertriglyceridemia has received less attention than hypercholesterolemia in the management of cardiovascular risk. However, in the last 10 years, data from Mendelian randomization analyses have brought new attention towards a direct causal association between levels of TG-rich lipoproteins and the risk of CVD [5–7], and there is increasing awareness that TGs may add to a patient's risk profile [8].

TGs are directly affected by the dietary intake of fats and carbohydrate. In particular, the fact that diets rich in omega-3 fatty acids (O3FAs) exert beneficial effect on hypertriglyceridemia and are associated with reduced rates of CVD [9] has raised interest in exploring the potential of O3FAs in the management of hypertriglyceridemia as well as in reducing cardiovascular risk. This review describes the pathogenic role of TGs in cardiometabolic risk, the importance of TGs in cardiovascular risk assessment, and the potential role of O3FAs in the management of hypertriglyceridemia and CVD prevention.

Clinical definition of hypertriglyceridemia

Various definitions of what constitutes elevated TGs have been proposed (Table 1). In 2014, the European Atherosclerosis Society consensus panel suggested a definition of normal TGs as <175 mg/dL (<2.0 mmol/L) and severe hypertriglyceridemia as >885 mg/dL (>10.0 mmol/L) [10]. This recommendation is based on genetic studies indicating that TGs in excess of 885 mg/dL probably have a monogenic cause, particularly in younger people (Fig. 1). In people with moderate hypertriglyceridemia (TGs of 175–885 mg/dL [2–10 mmol/L]), TG levels are likely to result from an interaction of several genetic effects and secondary risk factors [10].

Complicating the definition of hypertriglyceridemia is the intraindividual variability in TGs over time [11]. TGs are highest about 4 h after a meal [12], and postprandial levels appear to be affected by the content of the meal, the presence of diabetes, age and body mass index, as well as genetic variants [13]. Taking a fasting sample is thought to reduce the variability of TG measurements. However, a nonfasting sample may more accurately reflect the patient's usual metabolic state because it would reflect the number of atherogenic remnant particles not cleared from the circulation [12]. Importantly, a nonfasting TG level has also been shown to be associated with the risk of CVD [5,7,14–16].

Table 1 Classification of triglyceride levels according to a range of guidelines/definitions [10].

	Triglyceride level	
	mmol/L	mg/dL
NCEP ATP III (2001)		
Normal	<1.7	<150
Borderline-high	1.7–2.3	150–200
High	2.6–5.6	200–500
Very high	>5.6	>500
ESC/EAS guidelines (2011)		
Normal	<1.7	<150
Hypertriglyceridemia	1.7–9.9	150–880
Severe hypertriglyceridemia	≥10	≥880
Endocrine Society guidelines (2012)		
Normal	<1.7	<150
Medium	1.7–2.3	150–200
Moderate	2.3–11.2	200–1000
Severe	11.2–22.4	1000–1980
Very severe	>22.4	>1980
EAS Consensus Panel 2014		
Normal	<2.0	<175
Mild-to-moderate	2.0–10.0	175–885
Severe	>10.0	>885

EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; NCEP ATP, National Cholesterol Education Program Adult Treatment Panel III.

The 2011 statement from the American Heart Association recommends taking a nonfasting TG sample to identify normal or optimal TG levels; a nonfasting level of <200 mg/dL [<2.3 mmol/L] is commensurate with a fasting level of <150 mg/dL [<1.7 mmol/L] [8]. A fasting sample should then be taken in patients with a nonfasting TG level of ≥200 mg/dL [≥2.3 mmol/L] to determine borderline high/high/very high status [8]. Notably, nonfasting TG levels should not be used to calculate LDL-C via the Friedewald method [8] and in patients with high TG levels, the Friedewald formula should not be used to calculate LDL-C levels [17].

Mechanisms of hypertriglyceridemia

In normal conditions, endogenous lipids are packaged in the liver into very low density lipoprotein (VLDL) particles which contain TG as their main component, and dietary lipids absorbed in the intestine are incorporated into chylomicrons (Fig. 2) [18]. Chylomicrons are rapidly cleared as their TG content is hydrolyzed by lipoprotein lipase (LPL) at adipose and muscle tissue capillary beds, releasing free fatty acids (FFA) that are used for cellular metabolic activities [18]. This process leaves behind chylomicron remnants. VLDL is similarly hydrolyzed by LPL, leaving remnants of VLDL particles in the bloodstream and intermediate-density lipoprotein (IDL) particles that are smaller in size and enriched in cholesteryl esters [18]. LPL activity determines the levels of TG-rich lipoproteins in the circulation.

Remnants are primarily cleared by the liver [19]. Receptors for these lipoproteins, including the LDL receptor,

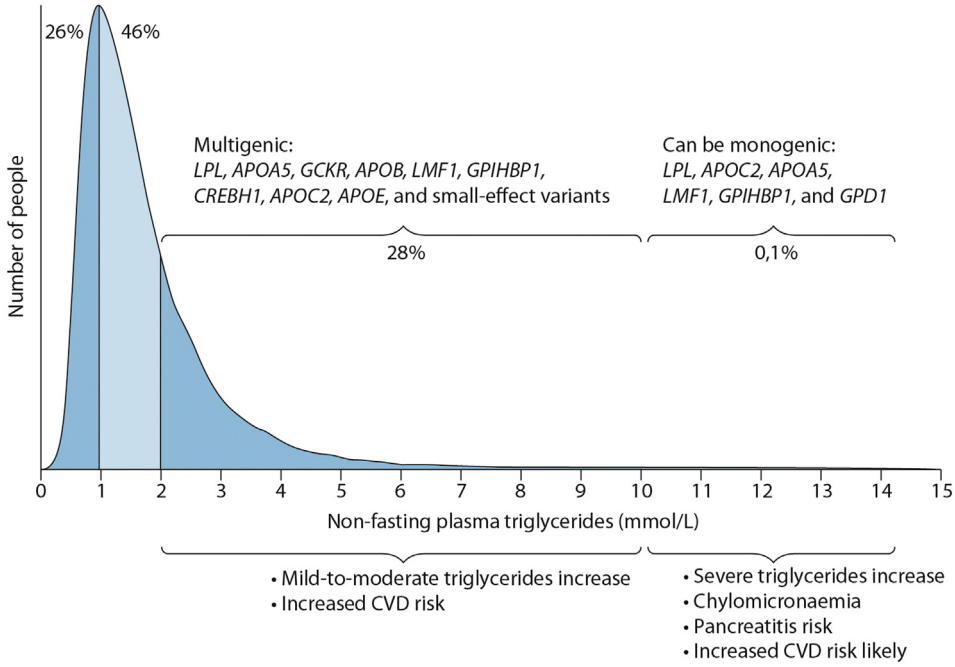

Figure 1 Distribution of triglyceride levels within the population, and the likely genetic contribution of elevated triglyceride levels [10]. Reprinted from Lancet Diabetes Endocrinol, Vol. 2, R.A. Hegele, H.N. Ginsberg, M.J. Chapman, B.G. Nordestgaard, J.A. Kuivenhoven, M. Averna et al., The polygenic nature ofhypertriglyceridaemia: implications for definition, diagnosis, and management, pp. 655–66, 2014, with permission from Elsevier.

VLDL receptor, LDL receptor-related protein 1 (LRP1) and heparan sulfate proteoglycans (HSPGs), are present on the surface of hepatocytes where they facilitate hepatic clearance of these lipoproteins [19]. Knockout mouse models have shown that the LDL receptor is not rate limiting in remnant clearance, and that TG-rich protein clearance also requires LRP1. Another pathway for lipoprotein clearance involves syndecan 1, a core component of HSPG, which is essential for both the binding and degradation of VLDL remnant particles [19].

Any disruption that causes increased production of chylomicrons and/or VLDL particles or a reduction in their metabolic breakdown will result in elevated TG levels [8]. Hypertriglyceridemia may be primary or secondary [20]. Primary causes of hypertriglyceridemia include familial hyperchylomicronemia (a deficiency of LPL, leading to increased chylomicron levels); familial hypertriglyceridemia, characterized by an isolated elevation of VLDL; combined hyperlipoproteinemia, characterized by increased levels of VLDL and LDL; and familial dysbetalipoproteinemia, characterized by increased IDL [20]. Secondary hypertriglyceridemia is often associated with lifestyle factors, such as alcohol use, poor diet or physical inactivity, and commonly occurs in patients with obesity, metabolic syndrome or type 2 diabetes [20]. However, it may also occur as a result of medication use; common culprit agents are corticosteroids, estrogens, tamoxifen, isotretinoin and the cardioselective β-blockers [20]. Many patients with secondary hypertriglyceridemia have more than one condition that increases their risk of elevated TGs [20].

The genetic architecture of hypertriglyceridemia is complex (Fig. 1). On the basis of recent genetic data, it is thought that severe hypertriglyceridemia (TGs >10 mmol/L) is likely to have a monogenic cause where loss-of-function mutations in genes that regulate catabolism of TG-rich lipoproteins (eg, *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*) play a major role. Conversely, the more common mild-to-moderate hypertriglyceridaemia (TGs 2–10 mmol/L) is typically multigenic, and results from the cumulative burden of common and rare variants in more than 30 genes [10]. However, even in patients with monogenic hypertriglyceridemia non-genetic, susceptibility factors are likely to still play a role [20].

The identification of rare and common variants that confer an increased risk of developing high TG levels or high remnant cholesterol levels have been used to test the hypothesis whether elevation of plasma TG might also be associated with an increased risk of developing coronary artery disease (CAD). This approach, usually defined as Mendelian randomization, is aimed at determining the prevalence or incidence of CAD in carriers versus non carriers of each genetic variant or their combination. This approach appears to be particularly interesting in investigating the relation between TG and CAD risk as it minimizes problems with confounding and reverse causation. For example, 10 genotype combinations determined by three different TG-raising variants in the *APOA5* gene increased the risk of myocardial infarction (MI) by around 40% [5,6]. More recently, it has been reported that, compared with 46,703 non-carriers, 188 heterozygous carriers of an LPL-damaging mutation had higher TGs and higher CAD risk (odds ratio 1.84; 95% CI 1.35–2.51; $p < 0.001$). An analysis of six common LPL variants demonstrated an odds ratio for CAD of 1.51 per 1 standard deviation increase in TG [21]. In addition, some genetic polymorphisms work in the opposite direction to reduce the risk of developing elevated TG

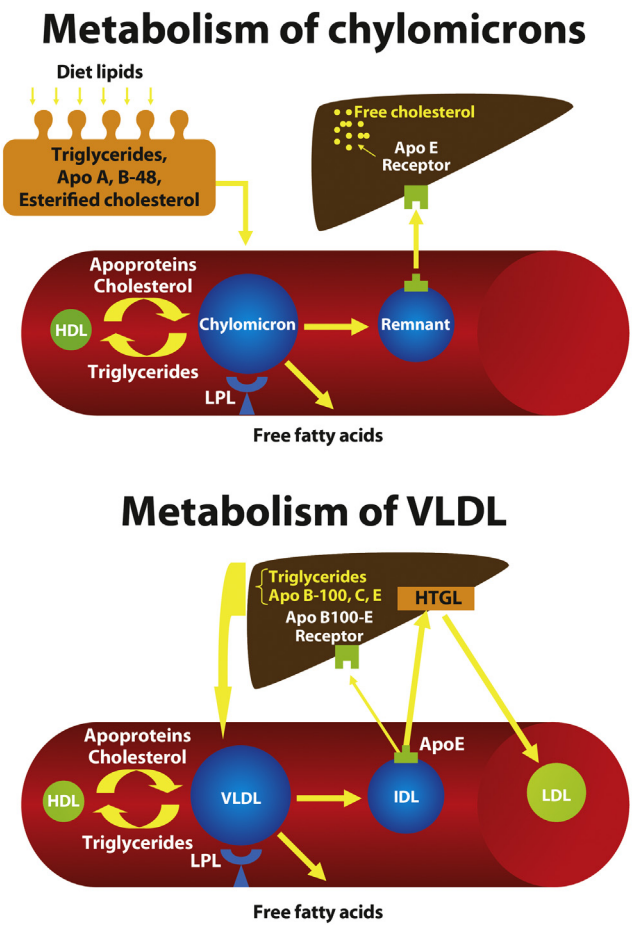

Figure 2 Triglyceride metabolism. Apo, apolipoprotein; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.

levels and CAD, including loss-of-function alleles in the *ANGPTL4* and *APOC3* genes [15,22,23]. This wealth of genetic data on TG metabolism and CAD risk provides a new and strong support to the notion that TG-rich lipoproteins are causally associated with CAD.

Clinical complications of hypertriglyceridemia

In patients with TG levels >1000 mg/dL (>11.3 mmol/L), the usual pathway for lipid hydrolysis is overwhelmed, and many more chylomicrons circulate in plasma, even in the fasting state, instead of being cleared [8,24]. Chylomicrons are too large to enter the arterial intima, and are therefore not considered to be atherogenic until they are converted to chylomicron remnants [25].

As a result of chylomicrons' remnants depositing in tissue, patients with primary chylomicronemia often present with xanthomas on the trunk, buttocks, shoulders and extremities [4]. Xanthomas are raised yellow papules on the skin, which are histologically characterized by lipid-containing macrophages. Other features of primary chylomicronemia include lipemia retinalis (accumulation of lipids in the retinal vessels) and hepatosplenomegaly secondary to macrophage infiltration of the liver and spleen [4]. However, pancreatitis remains the most potentially serious complication of chylomicronemia [4], especially when levels exceed 1000 mg/dL [11.3 mmol/L] [26].

For most patients with TG levels <1000 mg/dL (<11.3 mmol/L), acute pancreatitis is less of a concern than CVD. At these TG levels, the predominant lipid particles are not chylomicrons, but chylomicron remnants and other atherogenic particles. In both men and women, the risk of CVD (MI, ischemic heart disease, and mortality) increases significantly with increasing levels of nonfasting TGs ($p < 0.001$) [16].

Miller and colleagues demonstrated that, in patients who had experienced an MI and were receiving statins, TG levels above normal (150 mg/dL [1.7 mmol/L]) were associated with an increased risk of a recurrent ischemic event (Fig. 3) [27]. In this study, every 10 mg/dL decrement in TGs was associated with a 1.8% reduction in the risk of a cardiovascular event, and this significant relationship ($p < 0.001$) remained statistically significant after adjustment for other risk factors, including LDL-C and HDL-C [27].

The mechanisms by which elevated TG levels may cause atherosclerosis are complex. TG-rich lipoproteins (in particular those of relatively small size like the remnants) can enter into the arterial wall where they are trapped. It is interesting that TG-rich lipoproteins, unlike LDL particles, can be taken up directly by macrophages, turning these cells into foam cells, the hallmark cells of the atherosclerotic plaque. It has also been speculated that once TG-rich lipoproteins penetrate the arterial intima, the release of FFAs and monoacylglycerols by TG hydrolysis may cause severe inflammation and necrosis [28]. People with fasting hypertriglyceridemia have abnormal postprandial lipid profiles, which are characterized by hyperlipidemia that is more pronounced and persists for longer than in normolipedemic individuals [29,30]. Hypertriglyceridemia activates the plasma cholesteryl ester transfer protein (CETP), which is responsible for intravascular lipid remodeling.

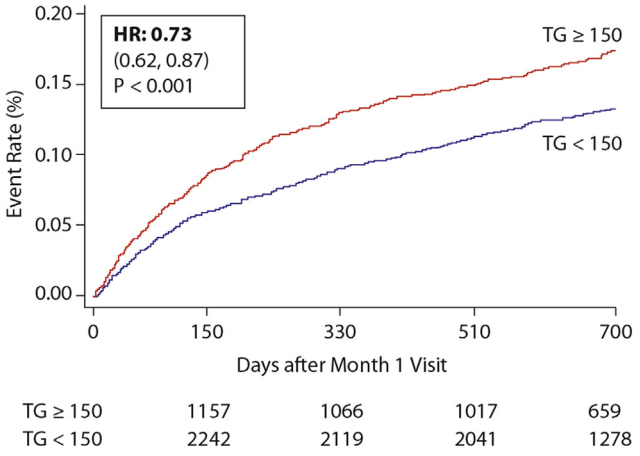

Figure 3 Kaplan–Meier estimate of the risk of death, MI or recurrent ACS in patients with normal (<150 mg/dL [1.7 mmol/L]) or elevated (≥150 mg/dL [1.7 mmol/L]) triglyceride levels after acute MI; all patients were receiving statins [27]. HR, hazard ratio; TG, triglycerides.

CETP transfers triglycerides from triglyceride-rich lipoproteins, such as VLDL and chylomicrons, to HDL and LDL in exchange for cholesteryl esters [31,32]. Triglyceride-rich HDL is then rapidly metabolized, while triglyceride-rich LDL is converted to small dense LDL [32], which appears to be involved in the atherogenic process [33].

Implications for patient management

As described earlier, patients with very high or severely elevated TG levels are at risk of pancreatitis, and require intensive lifestyle interventions including strict recommendations about abstaining from alcohol and limiting dietary fat intake [34]. Depending on the local guidelines, this usually applies to patients with TGs >500 mg/dL (5.6 mmol/L) or 885 mg/dL (10 mmol/L). Guidelines also recommend pharmacological treatment with TG-lowering therapy in patients who have TGs >500 mg/dL (5.6 mmol/L) [34].

For patients with moderately elevated TG levels, LDL-C remains the primary target for treatment in patients with most types of dyslipidemia in both European and US guidelines [17,26]. Nevertheless, the fact that any TG level in excess of normal (150 mg/dL [1.7 mmol/L]) increases the risk of CVD even in patients with optimally managed LDL-C [27,35] highlights the importance of TG as a secondary target in both assessment and treatment. The ESC/EAS guidelines note that TGs should be taken into account as part of a complete risk assessment and when determining treatment for patients with dyslipidemia [17]. They also recommend initiating treatment for patients with TGs >200 mg/dL (2.3 mmol/L) [17].

Both US and European guidelines highlight the importance of lifestyle measures as the first step to reducing TG levels, in particular weight loss, limiting alcohol intake and avoiding too much sugar/fructose or saturated fat in the diet [8,17]. Following a Mediterranean diet (which is rich in monounsaturated fatty acids) also significantly reduces TG levels, as well as increasing HDL-C [36]. Consumption of fish is an important factor associated with cardiovascular risk reduction, and the higher the O3FA level of the fish, the greater the effect [37].

Guidelines acknowledge that a TG level of <150 mg/dL (<1.7 mmol/L) is desirable, and if elevated TG or non-HDL-C levels persist after lifestyle intervention and statin therapy, a number of guidelines recommend the use of TG-lowering agents, primarily fibrates or O3FAs [17,38].

Fibrates decrease TGs by ~36%, non-HDL-C by ~6%–16%, and LDL-C by ~8%, and increase HDL-C by ~10% [39]. However, fibrate-induced increases in LDL-C may occur in patients with severe hypertriglyceridemia. To date, cardiovascular outcome studies of fibrates have produced varied results, with some studies suggesting a benefit only in hypertriglyceridemic patients with low HDL-C. In a meta-analysis of 7389 patients with high TGs (>200 mg/dL [2.3 mmol/L]), fibrate therapy decreased vascular events by 25%, and in the 5068 patients with both high TGs and low HDL-C (<40 mg/dL [1 mmol/L]), a 29% decrease in vascular events was observed [40]. Fibrate therapy is associated with a number of adverse effects, including increases in creatinine levels, myopathy, and, in rare cases, rhabdomyolysis, especially when used in combination with other lipid-lowering therapies [41]. Therefore, additional therapeutic options must be considered.

O3FAs reliably reduce TGs by 20%–50% [8,42], and affect both fasting and nonfasting levels. For this reason, O3FAs supplements are one of the pharmacological therapies recommended for patients with elevated TGs [17,26].

The role of omega-3 fatty acids in the management of hypertriglyceridemia

Effects of omega-3 fatty acids on triglyceride metabolism and their role in atheroprotection

Very long-chain O3FAs include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [43]. A number of likely mechanisms contribute to the effect of O3FAs on TG levels [34,44]. Firstly, O3FAs downregulate hepatic VLDL production. They also reduce the amount of non-esterified fatty acids that is delivered to the liver by upregulating β-oxidation of fatty acids in the liver, adipose tissue, heart and skeletal muscle, so fewer fatty acids are stored intracellularly or released back into the circulation [44]. In peripheral tissues, O3FAs increase fatty acid uptake by adipocytes, cardiac and skeletal muscle cells, and counteract the lipolytic release of non-esterified fatty acids from adipose tissue by suppressing inflammation [44]. O3FA have been shown to reduce postprandial hypertriglyceridemia [45–47], as well as remnant lipoprotein cholesterol and the TG content of chylomicrons and VLDLs [47].

A recent review of interventional studies supported the notion that O3FAs supplementation has relevant effect neither on total or LDL-C though, in some cases, fish oil consumption led to a slight increase in LDL-C levels, especially when high PUFA doses were used [48]. However, it is noteworthy that different O3FAs might have divergent effects on atherogenic lipoproteins when administered alone. In fact, in a meta-analysis of randomized controlled studies, DHA, but not EPA, was found to significantly increase plasma LDL-C and HDL-C concentrations [49].

O3FA have been shown to have anti-atherogenic and cardioprotective effects. O3FA decrease the levels of apolipoprotein CIII, thereby reducing the inflammatory changes associated with atherosclerosis and CVD [50]. Furthermore, both DHA and EPA improve endothelial function [51,52] and reduce the biomarkers of platelet activation [53].

Effects of diets rich in omega-3 fatty acid-rich on hypertriglyceridemia

A study conducted in 20 healthy people showed that a diet rich in fish decreased the concentrations of TG-rich lipoproteins, LDL-C and HDL-C over the course of 24 weeks [54]. Furthermore, in a double-blind, randomized,

Table 2 Clinical trials of at least 1 year's duration and published in the past 20 years, which have assessed the effect of omega-3 fatty acids on cardiovascular endpoints (other treatment arms in these studies not included).

Reference	Design	Type of patients	Treatments	N	Duration (years)	Primary endpoint	Difference vs placebo or control (95% CI)	P-value
Primary intervention studies								
Yokoyama et al., 2007 [58]	PROBE	Hypercholesterolemic Japanese pts on a statin	EPA 1.8 g/day No EPA	9326 9319	Mean 4.6	Any major fatal or nonfatal coronary event	HR 0.81 (0.69–0.95)	0.011
ORIGIN investigators 2012 [56]	R, DB	High CV risk and dysglycemia	n-3 PUFA 900 mg/day Placebo	6281 6255	Median 6.2	Cardiovascular death	HR 0.98 (0.87–1.10)	0.72
Risk and Prevention Study Collaborative Group, 2013 [64]	R, DB	Multiple CV risk factors of atherosclerotic vascular disease (not MI)	n-3 PUFA 1 g/day Placebo	6244 6269	Median 5	Composite of death, nonfatal MI, nonfatal stroke	HR 0.97 (0.88–1.08)	0.58
AREDS2 Research Group 2014 [67]	R, DB	Age 50–85 years with age-related macular degeneration	n-3 PUFA (EPA + DHA) 1 g/day No PUFA	2056 2147	Median 4.8	Composite outcome of time to the first occurrence of CVD mortality or morbidity	HR 0.95 (0.78–1.17)	0.64
Secondary intervention studies								
Singh et al., 1997 [65]	R, DB	Post acute MI	Fish oil (EPA + DHA) 1.8 g/day Placebo	122 118	1	Total cardiac events	RR 0.70 (0.29–0.90)	<0.05
GISSI investigators 1999 [59]	R, OL	Recent MI (≤3 months)	n-3 PUFA No PUFA	5666 5668	3.5	Cumulative rate of all-cause death, nonfatal MI, and non-fatal stroke	RR 0.90 (0.82–0.99)	0.048
Nilsen et al., 2001 [62]	R, DB	Post acute MI	Fish oil (EPA + DHA) 3.4–3.5 g/day Placebo	150 150	2	At least one cardiac event	Incidence: 28% Incidence: 24%	>0.05
Svensson et al., 2006 [66]	R, DB	Hemodialysis pts with CVD	n-3 PUFA 1.7 g/day Placebo	103 103	2	Composite of acute MI, angina requiring coronary intervention, stroke, TIA, PVD requiring surgical intervention, or death	HR 1.04 (0.72–1.48)	0.85
Galan et al., 2010 [61]	R, DB	History of CVD	n3-PUFA (EPA + DHA) 600 mg/day Placebo	633 626	Median 4.7	First major CV event	HR 1.08 (0.79–1.47)	0.64
Kromhout et al., 2010 [60]	R, DB	History of MI	n-3 PUFA (EPA + DHA) 400 mg/day Control	2404 2433	3.3	Major CV event	HR 1.01 (0.87–1.17)	0.93
Rauch et al., 2010 [63]	R, DB	Recent acute MI	n-3 PUFA (EPA + DHA) 1 g/day Placebo	1925 1893	1	Sudden cardiac death	OR 0.95 (0.56–1.60)	0.84

CAD, coronary artery disease; CI, confidence intervals; CV, cardiovascular; CVD, cardiovascular disease; DB, double-blind; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio; MI, myocardial infarction; OL, open-label; OR, odds ratio; PROBE, prospective, randomized, open-label, blinded endpoints; pts, patients; PUFA, polyunsaturated fatty acids; R, randomized; RR, relative risk.

crossover, interventional study where 16 men (aged 35–75 years old) substituted 80 g of their normal dietary fat intake with one of two test fat diets, the first one containing 5 g/100 g long chain (n-3) fatty acids and the second with matched oleic acid, it was shown that, after 21 days, the omega-3 enriched diet lowered plasma triglycerides by 27% and VLDL-TG by 32% [55].

The effects of supplementation with omega-3 fatty acids on hypertriglyceridemia

An alternative way to employ O3FA in the treatment of patients with hypertriglyceridemia is to use pharmacological preparations. These preparations usually contain DHA + EPA as ethyl esters [43]. Data from use of these agents suggest that they may be effective in a number of clinical conditions characterized by TG elevation. For example, in patients with impaired glycemic control, supplementation with O3FA produced significant reductions in plasma TGs [56]. In addition, a meta-analysis of 20 randomized controlled trials has shown that in patients with diabetes, supplementation with O3FA reduces plasma TG by 21.3 mg/dL (0.24 mmol/L) [57]. Also in people at risk of CVD, supplementation with EPA has been shown to reduce triglyceridemia [58]. The effects of O3FA supplementation in patients with existing CVD are less certain, with one study reporting significant reductions in TGs in patients who had a MI [59], while in another study no such reductions were observed [60].

The role of omega-3 fatty acids in the management of cardiovascular risk

Relevant studies of O3FAs were identified by conducting a PubMed search of randomized controlled trials published since January 1, 1997, with “omega-3”, “n-3”, “eicosapentaenoic acid”, “docosahexaenoic acid”, or “icosapent ethyl” in the title or abstract. Primary and secondary intervention studies that examined cardiovascular endpoints, lasted for at least 1 year, and included a control arm were considered.

To date, the long-term placebo-controlled clinical trials with O3FAs have produced inconclusive data on their effects on cardiovascular outcomes (Table 2), but the variability is likely to result from the different patient populations, endpoints, and doses used in these studies [56,58–67]. Studies in which patients have received O3FAs for primary prevention of cardiovascular events tended to show no significant benefit [56,64,67], with the exception of the JELIS study which showed a significant reduction in cardiovascular events in hypercholesterolemic Japanese patients who took O3FAs in addition to a statin [58]. Meta-analyses of the placebo-controlled studies in patients with pre-existing CVD have shown that O3FAs significantly reduce the risk of sudden death, cardiac death and MI [68,69]. This is consistent with data from a retrospective analysis of outcomes among real-world (unselected) Italian patients prescribed O3FAs when discharged from hospital after acute MI [70]. The risk of all-cause mortality or recurrent MI was significantly reduced in the cohort receiving O3FAs (n = 2425) compared with those not receiving them (n = 8844), after adjustment for patient characteristics and concurrent therapies [70]. O3FAs reduced the risk of all-cause mortality by 24% (adjusted hazard ratio 0.76 [95% CI 0.59–0.97]) and the risk of recurrent MI by 35% (adjusted hazard ratio 0.65 [95% CI 0.49–0.87]) [70].

With the exception of the JELIS study in Japanese patients [58], there are limited data on the impact of adding O3FAs to statin therapy in patients who require TG lowering in addition to LDL-C lowering. Two trials, the REDUCE-IT study (NCT01492361) and the STRENGTH study (NCT02104817), are underway to investigate this. The REDUCE-IT study is examining the effects of icosapent ethyl on cardiovascular events in high-risk patients with hypertriglyceridemia who are taking a statin, and is expected to be completed in December 2017. The STRENGTH study is investigating the effect of O3FAs, in addition to a statin, in individuals with hypertriglyceridemia, low HDL-C levels who are at high risk for CVD. The estimated completion date of the STRENGTH study is November 2019.

Despite the current lack of randomized controlled data, the European Heart Association recommends treating elevated TGs (>200 mg/dL [2.3 mmol/L]) in patients with controlled LDL-C [17] by using fibrates as the first choice and O3FAs in case of controindications [17].

Conclusions

Mendelian randomization analyses strongly implicate elevated TGs levels in the development of CVD. Consumption of a diet rich in O3FAs can help to mitigate this risk. Pharmacological doses of O3FAs lower TG levels and may have other beneficial physiological effects on lipid transport and atherosclerosis development. Meta-analyses of clinical trials with these agents indicate a significant reduction in the risk of recurrent MI when used as secondary prevention. Their role in primary prevention of CVD is less clear, but data from large-scale clinical trials will help to answer this question in the coming years.

Conflicts of interest

M. Arca has received research grant support from Aegerion, Amgen, IONIS, Akcea Therapeutics, Chiesi, Pfizer, Regeneron and Sanofi, has served as a consultant for Amgen, Aegerion, Akcea Therapeutics, Regeneron, Sanofi and Sigma-Tau and received lecturing fees from Amgen, Aegerion, Merck, Pfizer, Sanofi and Sigma Tau; C. Borghi has received lecturing fees from Menarini, Servier, Roche, Novartis, MSD, Sanofi, BMS, Takeda, Tejin, and has been an advisory board member for Menarini, Servier, Novartis, Alfa-Sigma, Bonomelli, Sanofi, Grunenthal; R. Pontremoli has received consulting and speaking honoraria from Sigma Tau, MSD, Novartis, Astrazeneca, Boehringer-Ingelheim, Lilly, Teijin Pharma and Algorytm SAS; G.M.

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Author contributions

All authors read, revised and approved the outline and the subsequent drafts of the manuscript.

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