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Effects of eicosapentaenoic acid and docosahexaenoic acid on lipoproteins in hypertriglyceridemia

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Purpose of review
The treatment of hypertriglyceridemia (HTG) with ω-3 fatty acid preparations adds a novel therapy to reduce cardiovascular disease. This review examines the effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid on lipoproteins and the cardioprotective effects in HTG.

Recent findings
The evidence that ω-3 fatty acid therapy at prescription strength is effective and safe at lowering triglyceride levels is growing. Although EPA/docosahexaenoic acid formulations did lower triglyceride levels, an increase in low-density lipoproteins was observed and outcome data were mixed. More recent trials have shown that decreased levels of low-density lipoprotein can be achieved with EPA preparations. Although the cardiovascular outcomes data are not fully available, meta-analysis of available data reports protection against vascular disease.

Summary
The addition of ω-3 fatty acid treatment should be considered in patients with severe HTG as well as high-risk patients for atherosclerotic disease. Emerging data are supportive, but long-term outcome studies are still underway.

Keywords
hypertriglyceridemia, lipoproteins, ω-3 fatty acids

INTRODUCTION

Cardiovascular disease (CVD) remains to be a prominent focus of research worldwide [1]. Indicators that lead to CVD and the strategies for prevention and treatment remain the central components. Major clinical factors of CVD risk include high-plasma cholesterol and high triglycerides. Due in part to the definitive link between raised concentrations of low-density lipoprotein (LDL) cholesterol and CVD, decades of research has been focused on approaches to lower plasma LDL cholesterol [2,3]. The result has been the highly effective use of statins in CVD treatment and prevention [4]. We now understand that the treatment of LDL cholesterol alone, however, does not completely reduce CVD risk [5,6].

Hypertriglyceridemia (HTG) represents a risk factor for atherosclerotic CVD although, contrasting observations has been reported [7–9]. The National Cholesterol Education Program – Adult Treatment Panel III defined normal triglyceride level as less than 150 mg/dl, borderline high as 150–199 mg/dl, high as 200–499 mg/dl, and very high triglyceride as at least 500 mg/dl [10]. A growing body of evidence links HTG with CVD [11]; however, the role of triglyceride in the CVD risk assessment remains controversial. The 2013 American College of Cardiology/American Heart Association Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults did not directly address triglyceride, as the panel felt that concrete data are still lacking to make formal recommendations [12]. Owing to the interrelationship of triglyceride with other lipoproteins such as low levels of high-density lipoprotein (HDL) and increased levels of LDL,

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KEY POINTS

- ω-3 fatty acid consistently lowers triglyceride levels.
- Treatment of HTG protects against vascular disease.
- ω-3 fatty acids add a novel therapy to at risk patients.

elevated triglyceride levels have been felt to represent a marker rather than an independent risk factor for CVD [13]. Recent theories suggest that elevated triglyceride is a reflection of triglyceride in atherogenic triglyceride-rich lipoprotein remnants, which consists of chylomicron remnants and very low-density lipoprotein (VLDL) remnant particles [13]. The triglyceride-rich lipoproteins remnants are thought to generate toxic substances and damage the endothelium when in contact with endothelial lipoprotein lipase [14]. Owing to the limitation of statin therapy on triglyceride and the recognition of the possible role of triglyceride on CVD, an interest is now focused on ω-3 fatty acid preparations [15].

The two ω-3 fatty acids of focus are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are essential in human physiology. Both EPA and DHA are mostly obtained by consuming oily fish, such as salmon, albacore tuna, mackerel, herring, and sardines or by fish oil supplements [16]. Numerous studies are reporting the potent triglyceride-lowering effects and potential benefits to protect against CVD [17]. We intend to review the effects of EPA and DHA on lipoproteins in HTG.

HYPERTRIGLYCERIDEMIA

The causes of HTG can be classified into two major categories, primary and secondary. Primary HTG results from genetic defects leading to disordered triglyceride metabolism, such as familial combined hyperlipidemia and familial HTG, familial dysbetalipoproteinemia, apolipoprotein C-2 deficiency, and lipoprotein lipase deficiency [13]. Secondary HTG is most commonly caused by diets high in carbohydrates or high glycemic index content, high alcohol consumption, uncontrolled diabetes mellitus, and hypothyroidism. Medications such as nonselective β-blockers, tamoxifen, oral estrogens, glucocorticosteroids, thiazide diuretics, propofol, and antiretroviral drugs have been implicated as well [13,18]. High levels of triglyceride ($\geq$500 mg/dl) have been well established as a risk factor for pancreatitis, and currently is the third leading cause after alcohol and gallstones [19]. In the presence of triglyceride levels (200–499 mg/dl), treatment is recommended to reduce CVD risk [20].

Many therapeutic strategies to lower triglyceride levels are recommended but must be in conjunction with changes in dietary habits such as restriction to caloric intake, reduction of fat ingestion, and abstinence from alcohol. The current pharmacological interventions to lower triglyceride levels include statins, fibrates, nicotinic acid, and ω-3 fatty acids [13,21].

Fibrates are often recommended as first-line with ω-3 fatty acids as adjunct therapy. Most common fibrates include fenofibrate and gemfibrozil. Although they are not benign therapies and the rate of adverse events observed are dependent on the choice of fibrate administered. Gemfibrozil increases risk of myopathy when used with a statin and fibrates are associated with increased gallstones [22]. Niacin has been shown to increase HDL, decrease triglyceride, and reduce rate of CVD events but the most common adverse effect of cutaneous vasodilatation or flushing is reported in up to 70% of patients receiving therapy [23]. This prevents dose titration or it decreases adherence by patients [24]. In contrast, the frequency of adverse effects observed has generally been similar in ω-3 fatty acids treatment group and the placebo group [25,26]. The most common adverse events being gastrointestinal (nausea, diarrhea, and mild gastrointestinal disturbances) and no serious safety issues were identified [25,26]. The ω-3 fatty acids (EPA and DHA) are thought to reduce triglyceride levels primarily by promoting fatty acid degrading via peroxisomal β-oxidation, inhibiting lipogenesis in the liver, and accelerating clearance triglyceride from the plasma by increasing fractional clearance rate of VLDL [27]. Various types of ω-3 in prescription form currently exist on the US market, ω-3 fatty acid in ethyl ester formulation with both EPA and DHA, ω-3 fatty acid with mostly pure ethyl ester of EPA termed icosapent ethyl and lastly the ω-3 fatty acid in free fatty acid form of EPA and DHA [28].

EFFECTS OF EICOSAPENTAENOIC ACID AND DOCOSAHEXAENOIC ACID ON LIPIDS

The pharmacological doses of ω-3 fatty acids (at least 2 g/day) significantly reduce triglyceride levels, but appear to affect other lipoproteins, including LDL [29]. The increase in LDL was observed in patients with very high triglyceride levels and following the use of DHA alone compared with studies using EPA alone [28].

The initial available pharmaceutical formulation of ω-3 was composed of EPA 47% and DHA 38% in their ethyl ester form. It was used as an adjunct to diet

Table 1. Effects of eicosapentaenoic acid and docosahexaenoic acid on triglyceride and low-density lipoprotein in hypertriglyceridemia patients [25–27,31,34]

	EPA + DHA (ethyl esters)		EPA + DHA (free fatty acid form)		EPA (ethyl esters)		EPA (ethyl esters)	
	4 g/day	4 g/day	2 g/day	4 g/day	2 g/day	4 g/day	2 g/day	4 g/day
TG	−45.0%	−38.9%	−25.9%	−30.9%	−19.7%	−33.1%	−10.1%	−21.5%
LDL	+31.0%	+16.7%	+19.2%	+19.4%	−1.1%	−16.3%	−3.6%	−6.2%

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HTG, hypertriglyceridemia; LDL, low-density lipoprotein; TG, triglyceride.

for the treatment of severe HTG, triglyceride at least 500 mg/dl [30,31]. A 4 g/day formulation taken for 16 weeks significantly reduced triglyceride levels by 45%, VLDL by 32%, and increased HDL by 13%, but it also significantly increased LDL by 31% ($P = 0.0014$) [30]. In another study involving patients with severe HTG taking 4 g/day for 6 weeks reduced triglyceride levels by 38.9%, VLDL by 29.2%, and increased HDL by 5.9%, but also seen was a significant increase in LDL by 16.7% ($P = 0.007$) [31].

A recently Food and Drug Administration-approved ω-3 in the free fatty acid formulation containing EPA 55% and DHA 20% was used for the treatment of adults with severe HTG. In the double-blinded, randomized trial of Epanova for lowering very high triglycerides, patients with severe HTG (triglyceride ≥ 500 mg/dl but ≤2000 mg/dl) were tested at three doses: 2, 3, and 4 g/day versus olive oil as the control [32]. Serum triglyceride levels were decreased significantly in all three doses compared with controls by 25.9, 25.5, and 30.9%, respectively. Non-HDL cholesterol was decreased as well by 7.6, 6.9, and 9.6%, respectively. LDL was significantly increased with 2 g/day by 19.2% ($P < 0.01$) and by 19.4% with 4 g/day ($P < 0.001$) compared with controls, but not with 3 g/day [32]. The multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension study studied the triglyceride-lowering effect of icosapent ethyl, which is an ω-3 fatty acid with 96% pure ethyl ester of EPA [25,33]. The study specifically looked at the effect of icosapent ethyl in severe HTG patients who had triglyceride levels at least 500 mg/dl and the impact on other lipoproteins, which included LDL, VLDL, HDL, non-HDL, total cholesterol, and lipoprotein-associated phospholipase A3 [34]. The study included 229 patients (24.9% with triglyceride ≥ 500 mg/dl and 39.3% with triglyceride > 750 mg/dl) who were randomized to icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or placebo over a 12-week period. The results reported that 2 g/day reduced triglyceride by 24.9% and 4 g/day reduced triglyceride levels by 35.7% in patients with triglyceride at least 500 mg/dl. In patients with triglyceride higher than 750 mg/dl, 2 g/day reduced triglyceride levels by 32.9%, whereas 4 g/day reduced triglyceride levels by 45.4%. Overall, icosapent ethyl 2 g/day decreased triglyceride levels by 19.7% ($P = 0.0051$) and 4 g/day decreased triglyceride levels by 33.1% ($P < 0.0001$) [25]. Further reductions were reported in patients with baseline triglyceride higher than 750 mg/dl and with concurrent statin therapy. Icosapent ethyl 2 g/day with statin decreased triglyceride levels by 40.7% ($P = 0.0276$) and 4 g/day reduced triglyceride levels by 65% ($P = 0.0001$). This suggests a possible synergistic relationship between icosapent ethyl and statins. Icosapent ethyl did not simultaneously increase LDL levels [25].

In follow-up analysis the reported effects of icosapent ethyl on lipoprotein particle concentration and size showed that 4 g/day significantly reduced the concentration of the large VLDL particles by 27.9% ($P = 0.0211$), small LDL by 25.6% ($P < 0.0001$), total LDL by 16.3% ($P = 0.0006$), and total HDL by 7.4% ($P < 0.0063$). However, the 2 g/day did not have the statistically significant reductions on these lipoprotein parameters [34].

In another multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial named the ANCHOR study; it assessed the safety and efficacy of icosapent ethyl in patients who were at high risk for CVD. The study included 702 patients who had adequate control of LDL on statin therapy and persistently elevated triglyceride level at least 200 mg/dl but less than 500 mg/dl [26]. The ANCHOR study patients were randomized to icosapent ethyl 4 g/day, 2 g/day, or placebo and the primary end point was triglyceride level change from baseline to the end of the 12-week period. The secondary included percentage change in LDL, non-HDL, VLDL, apolipoprotein-B, and phospholipase A2. Selected exploratory end points included total cholesterol, HDL, and high-sensitivity C reactive protein. The 2 g/day group had a reduction in triglyceride levels by 10.1% and the 4 g/day group had a reduction in triglyceride levels by 21.5%. Icosapent ethyl 4 g/day decreased LDL by 6.2% ($P = 0.0067$), whereas the 2 g/day group did not significantly reduce LDL. In addition 4 g/day

decreased total cholesterol (12.0%), apolipoprotein B (9.3%), very-low density lipoprotein cholesterol (24.4%), lipoprotein-associated phospholipase A2 (19.0%), and high-sensitivity C-reactive protein (22.0%) versus placebo ($P < 0.001$ for all comparisons) [26].

The current formulations of ω-3 fatty acids in the studies mentioned report the effects of different doses. The higher dose of 4 g/day had the greatest effect on triglyceride levels compared to the 2 g/day formulation. The initial formulation of EPA and DHA studied the 4 g/day effects, whereas the randomized trial of Epanova for lowering very high triglycerides, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12 week study with an open label extension, and ANCHOR studied and reported the effects of both doses (Table 1).

CARDIOVASCULAR DISEASE OUTCOMES

Cardiovascular outcome trials of ω-3 fatty acids have resulted in inconsistent results [35]. The Japan EPA Lipid Intervention Study observed a decrease of 19% in major cardiovascular events (MACE) [36] and in an Italian study, the GISSI Prevenzione Investigators a 10% decrease of MACE was seen [37]. Although the Risk and Prevention study, the Outcome Reduction With Initial Glargine Intervention study and the OMEGA trial did not report significant reduction in rate of MACE [38–40]. A meta-analysis consisting of 20 clinical trials of which included 63 030 participants reported that ω-3 fatty acid treatment may protect against vascular death, but did not significantly affect the rate of arrhythmia, cerebrovascular events or sudden death [41]. It is important to note that combination ω-3 fatty acids (EPA + DHA) have consistently failed to prevent atherosclerotic cardiovascular disease in the presence of statins. Currently, underway are two large international cardiovascular outcome studies to evaluate the clinical efficacy of ω-3 fatty acid therapy: the reduction of cardiovascular events with EPA – intervention trial (REDUCE-IT) and the statin residual risk reduction with EpaNova in high cardiovascular risk patients with hypertriglyceridemia (STRENGTH) [42,43]. They are expected to complete December 2017 and June 2019, respectively. Both studies are designed to evaluate the safety and efficacy of ω-3 fatty acids in combination with statin therapy, particularly in high-risk patients with HTG.

CONCLUSION

The reduction of high or very high triglyceride with EPA or DHA is associated with different effects on LDL. Treatment with either lowered triglyceride levels, but DHA was more often associated with an increases in LDL and EPA on the other hand, decreased LDL or resulted in no significant change of LDL. Ongoing trials are currently underway to evaluate the efficacy of ω-3 fatty acids on the prevention of CVD.

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Conflicts of interest

There are no conflicts of interest.

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