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MINIREVIEW

Omega-3 Fatty Acids and Cardiovascular Disease Risk: Do We Understand the Relationship?

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Summary

There is a large body of evidence documenting the effects of long-chain polyunsaturated fatty acids with the first double bond at the third position from methyl-terminal (so called omega-3 fatty acids (FAs)) on different components of cardiovascular disease (CVD) risk. However, it may seem the more answers on the topic we learn, the more questions remain to be elucidated. There are three levels of evidence documenting the impact of fish omega-3 FAs on CVD risk. Epidemiological data have shown unequivocally the increased intake of fish is associated with lower CVD morbidity and mortality. Numerous experimental studies have shown (almost always) positive effects of omega-3 FAs on lipoprotein metabolism, coagulation and platelet function, endothelial function, arterial stiffness etc. Most importantly, there are a few prospective clinical endpoint trials (DART, JELIS, GISSI Prevenzione and GISSI-HF) that have examined the impact of omega-3 FAs supplementation on cardiovascular outcomes in different patient populations. Recent meta-analyses of these and other clinical studies have yielded somewhat conflicting results. In this review we will summarize current evidence of omega-3 FAs effects on cardiovascular risk focusing on new data from recent clinical trials as well as possible practical implications for clinical practice.

Key words

Omega-3 fatty acids • EPA • DHA • Cardiovascular risk • Cardiovascular event • Omega-3 index

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Introduction

Long-chain polyunsaturated fatty acids with the first double bond at the third position from the methyl terminal (so called n-3 FAs or omega-3 FAs) can be found in plants and fish. The essential omega-3 FA is alpha-linolenic acid (ALA) that occurs in plants (walnuts, soybean, flaxseed and their oils). This FA is a precursor also for arachidonic acid, which is further metabolised giving rise to eikosanoids with multiple biological functions in the organism. ALA is a substrate for elongation and thus eicosapentaenoic (EPA) and docosaheaxaenoic (DHA) omega-3 FAs are being produced. The latter two can be found in larger quantities in fish meat or fish oil, respectively (salmon, mackerel, trout) (Nettleton 1991). As only less than 5 % of ALA is converted to EPA and DHA in human organism, the dietary sources of these are also considered essential (Brenna 2002, Plourde and Cunnane 2007).

Evidence of cardioprotective effects of omega-3 fatty acids

There have been numerous studies on the impact of fish oil supplementation or fish consumption on the incidence of various forms of atherosclerotic cardiovascular disease. However, many of these studies were poorly designed, lacking proper control group or blinding with ill-defined amount and type of omega-3 FAs used in the intervention arms. Moreover, it is difficult to compare results of trials using dietary advice to those with a precisely defined dose of an omega-3 FAs

Table 1. Documented cardioprotective properties of omega-3 fatty acids.

Omega-3FAs increase	Omega-3 FAs decrease
HDL-cholesterol levels	Triglyceride levels
Arrhythmia threshold	Platelet aggregation and adhesion
Arterial compliance	Adiponectin levels
Endothelium dependent vasodilation	Inflammation (IL-6, TNF alpha)
Atherosclerotic plaque stability	Blood pressure and heart rate
Production of vaso-constrictive eikosanoids	Sympathetic nervous system activity

HDL- high-density lipoprotein, IL-6 – interleukin 6, TNF-alpha-tumour necrosis factor alpha

Table 2. Comparison of EPA and DHA effects on cardiovascular risk factors.

	EPA	DHA
↓ *triglycerides*	++	++
↑ *HDL*	-	+
↓ *small dense LDL*	-	+
↓ *blood pressure*	+/-	+
↑ *endothelial function*	-	+
↓ *heart rate*	-	+
↓ *platelet aggregability*	+	++
↓ *platelet activation*	+	-
↑ *fibrinolysis*	-	-
↑ *glycemia*	+	+/-
↓ *immune response*	-	+/-
↓ *oxidative stress*	+	+

supplement. And (as always when evaluating data from clinical trials) one must take into account the population that was studied and the data refer to. Despite all the above mentioned pitfalls, omega-3FAs belong to the best documented substances in cardiovascular medicine even though still with not entirely understood mechanisms of protective action.

Fish omega-3 FAs (namely EPA and DHA) posses a lot of properties that can explain their positive impact on cardiovascular events seen both in epidemiological and interventional studies. Table 1 shows some of the most important cardiovascular effects of fish omega-3 FAs. It is noteworthy EPA and DHA differ in their ability to promote various effects of omega-3 FAs supplementation. Obviously, the two occur always together in natural sources – fish meals and fish oil. However, as highly purified EPA and DHA became available, evidence documenting individual effects of EPA and DHA has been accumulated. Comparison of DHA and EPA effects on individual markers of CVD risk is shown in Table 2.

Omega-3 FAs and cell membrane function

There is a solid experimental evidence of different effects of fish omega-3 FAs on individual components of cardiovascular risk. These can be largely explained by very rapid incorporation of omega-3 FAs into cell membranes thus affecting function of cells and tissues with subsequent impact on production of various vasoactive eiosanoids and other mediators (Din *et al.* 2004). These effects can explain for example improvement of endothelial dysfunction or direct influence of omega-3 FAs supplementation on the platelet function (Lee *et al.* 2006). It is also likely the replacement of saturated FAs from cell membranes of cardiomyocytes for omega-3 FAs may account for the antiarrhytmic effect of EPA and DHA observed in some studies (Woodman *et al.* 2003).

Omega-3 FAs and lipid metabolism

Both EPA and DHA play a role in modification of lipid and lipoprotein metabolism. They lower triglycerides by approximately 25 to 35 %. However, in cases of severe hypertriglyceridemia when TG levels exceed 5.5 mmol/l, magnitude of the effect can reach 45 % (Harris *et al.* 1997). Only DHA increases HDL cholesterol shifting the distribution of HDL subclasses towards larger HDL_2 particles that are more active in reverse cholesterol transport (Mori 2000). Although, there is usually no significant change in LDL-cholesterol concentration associated with omega-3 FAs administration, DHA changes the distribution of LDL particle subfractions in favour of less atherogenic, large, buoyant LDLs (Mori 2000). On contrary, especially with high doses of omega-3 FAs used in the treatment of hypertriglyceridemia, LDL levels may rise by 10 %, this effect being even more pronounced in patients with extreme TG elevations at baseline (Harris *et al.* 1997, Harris 1997). This adverse effect of omega-3 FAs may be mediated mostly by DHA as EPA in moderate dose produced 10 % LDL lowering in the JELIS trial (Yokoyama *et al.* 2007). The effects on plasma lipids

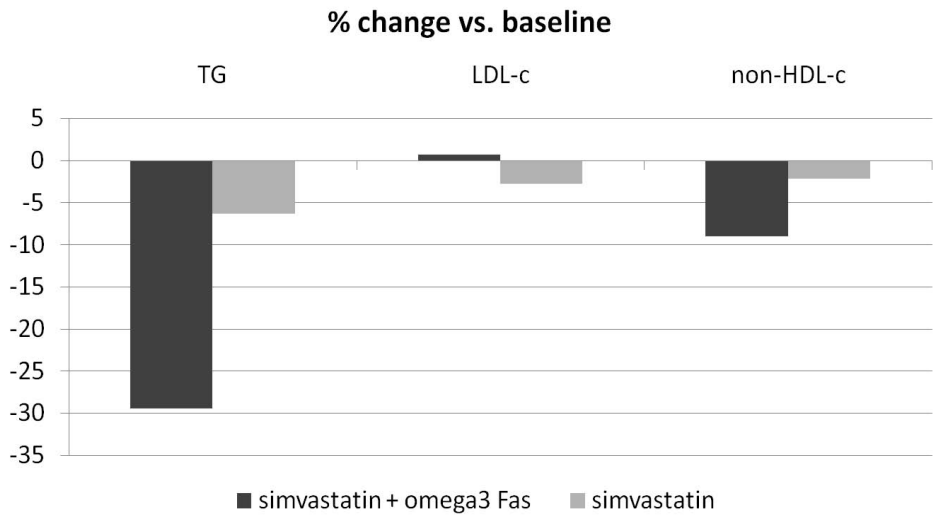

Fig. 1. Effect of 4 g/d omega-3 FAs in combination with simvastatin in patients with elevated triglyceride levels (2.26-5.64 mmol/l) in the COMBOS Trial (data from Davidson *et al.* 2007).

start to occur at daily doses of EPA and DHA of 2 to 4 grams. Very importantly, omega-3 FAs have synergistic and additive effects on plasma lipids when co-administered with statins as depicted by Fig. 1 (Davidson *et al.* 2007). Another practical implication of such studies is the proven safety of omega-3 FAs add on therapy to statins (Davidson *et al.* 2007, Yokoyama *et al.* 2007).

Omega-3 FAs and hemodynamics

In all studies of omega-3 FAs a decrease of heart rate has been described in the active treatment arms. The average fall of heart rate ranged from 3 to 3.7 beats per minute being more pronounced in DHA (Morris *et al.* 1993). In a study assessing the impact of omega-3 FAs on blood pressure control using 24-hour monitoring the average decrease of 5.8 and 3.3 mm Hg for systolic and diastolic blood pressure, respectively, were observed (Mori *et al.* 1999). The mechanisms beyond this effect include membrane stabilizing effect, lowering the sensitivity of beta-adrenergic receptors as well as that of sympathetic nervous tone (Grimsgaard *et al.* 1998).

Omega-3 FAs and platelet function

Both DHA and EPA have profound effect on platelet function. Not only membrane stabilizing effect but also competition of omega-3 FAs for cyklooxygenase activity with arachidonic acid (more pronounced in DHA), which lowers production of platelet activating eicosanoids (e.g. tromboxane A_2) play an important role (Larson *et al.* 2008). In a study in diabetic patients Woodman and co-workers demonstrated administration of highly purified EPA/DHA was associated with a decrease in platelet aggregability by 30 % (Woodman *et al*. 2003). The platelet function modification effects are dose dependent and start with doses of omega-3 FAs greater than 2 g per day (Woodman et al, 2003). The platelet effects seem to be mediated mostly by EPA (Din *et al.* 2007).

Omega-3 FAs and inflammation

Another possibly cardioprotective action of omega-3 FAs can be modulation of immune response and anti-inflammatory properties. As demonstrated in vitro, DHA lowers cytoadhesive molecules expression on endothelial cells and monocytes (Mori and Beilin 2004). Similarly, levels of interleukin 6, interleukin 1β and tissue necrosis factor α decrease after EPA/DHA administration (Bhatnagar and Durrington 2003). However, in another work of the same authors no impact of omega-3 FAs supplementation on hsCRP in a cohort of diabetics was observed (Mori *et al.* 2003). Very high doses of omega-3FAs (i.e. 8 g/d) were associated with a significant reduction of inflammatory marker levels in patients with severe heart failure (Mehra *et al.* 2006).

There are a few other documented effects of omega-3 FAs supplementation on different pathways playing a role in the development of cardiovascular disease, e.g. fat tissue metabolism and adipokine production, insulin resistance, fibrinolysis etc. (Itoh *et al.* 2007, Mori *et al*. 2003, Grimsgaard *et al*. 1998) The evidence is usually less robust and sometimes inconsistent.

As we reviewed above, there exists very large documentation of mechanisms by which omega-3 FAs can protect arteries from development of atherosclerosis. Nevertheless, one must bear in mind that even the best experimental evidence of benefit associated with a therapy is not a proof of its impact on clinical events. Thus, for any treatment the most important is the data from well organized, randomised, placebo-controlled clinical trials and omega-3 FAs are not an exception.

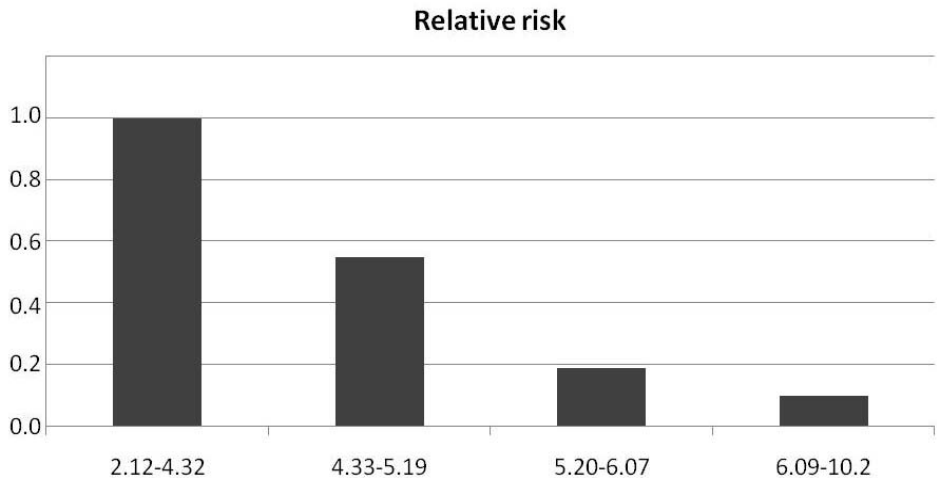

Fig. 2. Relative risk of sudden cardiac death according to omega-3 FAs blood concentration as a percentage of all fatty acids (data from Block *et al.* 2007).

Omega-3 fatty acids and cardiovascular risk in the light of clinical trials

Since the original epidemiological observations of low CVD mortality in populations with high consumption of fish there has been continuous interest of scientific and medical communities in the possibility of lowering CVD risk by omega-3FAs (Zhang *et al.* 1999). Thus, it is not surprising that the medical literature to date contains thousands of papers on the topic. As stated in the beginning of this review, the studies are frequently difficult to compare due to methodological and statistical issues, which also hamper the efforts of authors of meta-analyses.

In the past three years, at least four major meta-analyses of omega-3 FAs and their relationship to cardiovascular morbidity and mortality were published with not entirely concordant conclusions (Hooper *et al.* 2006, Wang *et al.* 2006, León *et al.* 2008, Lee *et al.* 2008). While three of them concluded that fish oils supplementation is associated with a decrease of the risk of cardiovascular events and CVD death rates, the newest and largest meta-analysis by León and co-workers failed to prove any benefits of omega-3 FAs on cardiovascular prognosis. A logical question would be, how it was possible the meta-analyses using the same data ended up with a different conclusion? The most likely reason is the selection of studies included into the subsequent analyses and new data that could not have been assessed previously.

In terms of cardiovascular efficacy and safety of omega-3 FAs there are three most important clinical studies: the DART study, the GISSI Prevenzione and GISSI-HF trials and the JELIS study.

In the Diet and Reinfarction Trial (DART), 2033 men after myocardial infarction were followed for two years. These were randomly assigned to a group instructed to increase fish intake to achieve daily consumption of EPA and DHA of approximately 900 mg or to a control group that received no specific information. The intervention group experienced 29 % reduction in all cause mortality and the incidence of reinfarction was reduced by 32 % (Burr *et al.* 1989). The authors performed another analysis of the original cohort ten years after the initiation of the study. Surprisingly, despite the intervention group still had slightly higher intake of fish (not significantly compared to the controls in the follow-up), the positive impact of fish diet disappeared and the patients from the original intervention group showed even greater risk of cardiovascular death than original controls (unadjusted hazard 1.31). Authors themselves speculate this was likely due to the fact omega-3 FAs offer rather acute cardioprotection mediated by platelet function modification, anti-oxidative and anti-inflammatory properties and thus long term benefit could not have been demonstrated. Moreover, the intake of fish was similar in the two groups after the original DART study was terminated, which also attenuated any possible differences (Ness *et al.* 2002).

The second study that usually belongs to the core evidence in any meta-analysis is the Japan EPA Lipid Intervention Study (JELIS) (Yokoyama *et al.* 2007). It was a very large trial following 18 645 patients with hyperlipidemia (more than 3500 of which had a history of a vascular event). The study subjects were randomly assigned to either statin alone or a combination of statin and 1.8 g of EPA daily. After 5 years, the combination treatment was associated with a significant reduction of the primary composite endpoint comprising death, revascularisation, myocardial infarction and unstable

angina by 19 % compared to the statin alone group. A post hoc analysis of the secondary prevention subgroup revealed similar benefit of the statin+EPA combination of cardiovascular outcomes in this subgroup in which relative risk was reduced by 23 %(Matsuzaki *et al.* 2009). The greatest relative risk reduction of 53 % experienced patients in primary prevention with increased triglyceride and decreased HDL-cholesterol levels (Saito *et al.* 2008).

The third study providing a substantial part of the data in the meta-analyses is the Gruppo Italiano per lo Studio della Sopravivenza nell´Infarto Miocardico (GISSI)-Prevenzione study (GISSI-Prevenzione Investigators 1999). 11 323 survivors of myocardial infarction were randomized to 850 mg of DHA/EPA daily or usual care. Treatment significantly reduced risk of death from any cause by 28 % after only 4 months, being driven mainly by the lowering of sudden cardiac death risk by 45 %. The differences remained significant for the whole 3.5 year duration of the study. Effects of omega-3 FAs were studied by the same group in a population of heart failure patients (GISSI-HF Investigators 2008). 3494 patients with heart failure were randomized to 850 mg of omega-3 FAs daily and 3481 received matching placebo. DHA/EPA administration reduced the risk of death from any cause by 9 % (p=0.041) and hospitalization for cardiovascular reasons by 8 % (p=0,009), which means 56 patients needed to be treated for 3.9 years to prevent one death.

The three cited studies clearly demonstrate the pitfalls of meta-analyses. The DART, JELIS and GISSI studies enrolled different patient populations with large differences in baseline cardiovascular risk. In the trials different types and doses of omega-3 FAs as well as different study designs were used. It is also noteworthy, that the follow-up analysis of the DART study reported increased risk of cardiovascular events, which attenuates the positive findings from the JELIS and GISSI trials when evaluated together.

Omega-3 FAs: navigating the maze of evidence

Even though the meta-analyses of omega-3 FAs impact on cardiovascular risk are sometimes controversial, the evidence of cardiovascular benefit associated with omega-3 FAs consumption is unequivocal. This fact is being reflected by guidelines of various expert societies including American Heart Association (Kris-Etherton *et al.* Circulation 2003), American Diabetes Association (Buse *et al.* 2007) as well as the joint guidelines on cardiovascular prevention of nine European societies (Graham *et al.* 2007). All the guidelines in line with most meta-analyses and reports from well conducted clinical trials agree the evidence is particularly well-proven in secondary prevention and (although less robust) it is reliable in primary prevention setting, too.

For the primary prevention of cardiovascular events it is currently recommended to maintain the daily intake of DHA and EPA in the range of 300-600 mg. In secondary prevention higher dose of 900 to 1200 mg a day is well supported by the evidence. For the reasons of triglyceride lowering even higher dose between 3000 and 4000 mg of DHA and EPA is suggested.

The recommended intake of omega-3 FAs can be achieved by increased oily fish consumption; however, for the purpose of triglyceride lowering dietary supplements of concentrated EPA/DHA are usually necessary. A standardized capsulated concentrate of EPA and DHA as a prescription drug is also available in the USA and some European countries (Brunton and Collins 2007).

The future direction might be individualizing the recommendation according to the actual need of a particular patient based on the measurement of plasma concentration of omega-3 FAs. As reviewed by Albert and co-workers concentrations of omega-3 FAs in plasma are strong predictors of sudden cardiac death (Albert *et al.* 2002). Therefore, Harris has proposed a new marker of cardiovascular risk – an omega-3 index (Harris 2007). This index reflects the proportion of omega-3 FAs in the membrane of red blood cells. Omega-3 index exceeding 8 % is associated with the lowest risk of cardiovascular events while levels below 4 % are typically found in coronary artery disease patients (Block *et al*. 2007) (Fig. 2). Thus, omega-3 index may help identify those who would benefit most from omega-3 FAs supplementation.

Conclusions

Omega-3 FAs take part in a number of processes influencing the course of atherosclerotic vascular disease from initial functional changes to severe structural damage. Despite sometimes conflicting results of individual clinical trials as well as meta-analyses of omega-3 FAs impact on cardiovascular outcomes, the current evidence is sufficient to

encourage intake of 500 and 1000 mg of EPA/DHA daily in primary and secondary prevention of cardiovascular disease, respectively. In the future, more personalized recommendation based on assessment of individual omega-3 FAs needs (using e.g. omega-3 red blood cell index) would be possible.

Conflict of Interest

There is no conflict of interest.

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