REVIEW ARTICLE

Polyunsaturated fatty acids in cardiovascular diseases: uncertainty prevails

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KEY WORDS

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ABSTRACT

In the late 1970s, a lower incidence of myocardial infarction and favorable hemostatic alterations were reported in Greenland Inuits. This observation prompted investigators worldwide to continue research on the role of a specific diet in this population and sparked an ongoing discussion about the potential use of polyunsaturated fatty acids (PUFAs) in the primary prevention of cardiovascular disease (VITAL), and the secondary prevention of primarily coronary artery disease (JELIS, REDUCE-IT, OMEMI). However, the current evidence to support the preventive value of PUFAs is inconsistent. Seminal clinical trials such as the GISSI-Prevenzione, JELIS, PREDIMED, or ASCEND differed in their approach to the assessment of cardiovascular effects of n–3 PUFAs and reported divergent results. The questions remain whether eicosapentaenoic acid is the only PUFA offering cardiovascular benefits, what is the importance of PUFA dosing, and, finally, who should receive n–3 PUFA treatment. This article discusses the latest insights into n–3 PUFA use in cardiovascular disease prevention.

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Introduction In the late 1970s, a high consumption of n–3 polyunsaturated fatty acids (PUFAs) was reported for the first time to have beneficial cardiovascular effects in Greenland Inuits.[1] Since the publication of this landmark study, numerous investigators worldwide have explored the impact of n–3 PUFAs on various medical conditions, particularly cardiovascular disease (CVD), including coronary artery disease (CAD) and its complications. The initial promising findings in terms of cardiovascular outcomes were not supported by subsequent large meta-analyses. However, it did not reduce the interest in n–3 PUFAs or undermine their role in cardiovascular pharmacotherapy. This review discusses the most recent reports on n–3 PUFA treatment in patients with CVD and points to potential limitations of the clinical trials that provided conflicting evidence on the use of n–3 PUFAs in daily clinical practice.

Lessons learned from basic and translational research

In their groundbreaking study, Dyberg et al[1] demonstrated that the increased proportion of n–3 PUFAs in platelets was associated with a significantly longer clotting time, which could explain the low incidence of atherosclerosis-related mortality, and particularly death from myocardial infarction (MI), in Greenland Inuits. Since then, this concept of the impact of n–3 PUFAs on platelet aggregation and activation, particularly in the acute cardiovascular setting such as MI, has been widely studied.[2,3]

Clinical and experimental studies demonstrated that n–3 PUFAs mediate favorable cardiovascular effects through various mechanisms of action, including vasodilation, antithrombotic properties, and a reduction of local and systemic inflammation, but also antiarrhythmic effects, increased cardiac muscle contraction, and inhibition of cardiac fibrosis (FIGURE 1). This led to a preliminary hypothesis explaining the beneficial effect of n–3 PUFAs on atherosclerosis progression.

Only 2 fatty acids are known to be essential for humans and are easily available in diet: linoleic and α-linolenic acids.[4] To provide full benefits, they have to be metabolized to their long-chain metabolites: linoleic acid to dihomo-γ-linolenic and arachidonic acids, and α-linolenic acid to eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids.[5] Of note, DHA and EPA were shown to be precursors of biochemical components and hormones regulating major physiologic functions, such as the development of the nervous tissue and cardiovascular function.[6] Therefore, these 2

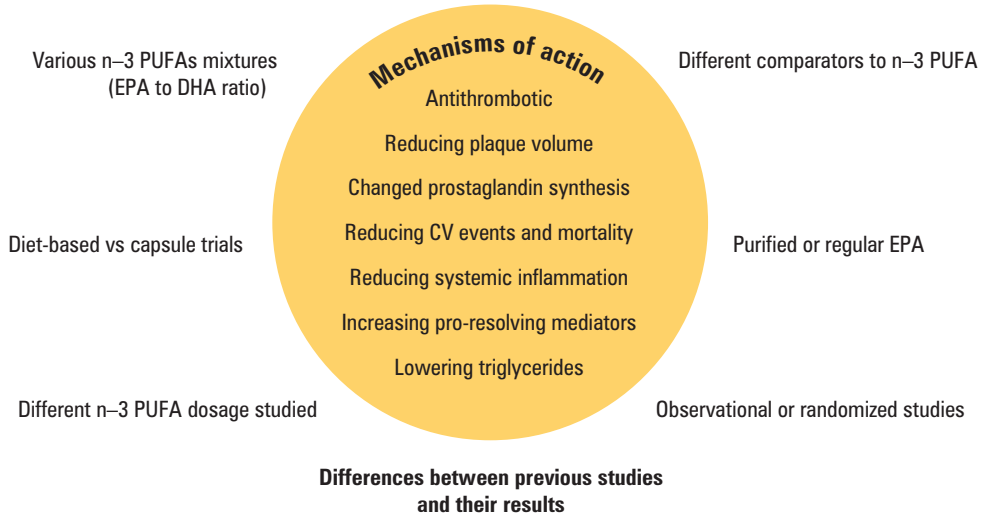

FIGURE 1 Mechanisms of action and differences between various clinical n–3 PUFA studies.

Abbreviations: CV, cardiovascular; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; n–3 PUFA, n–3 polyunsaturated fatty acids

major n–3 PUFAs have attracted the greatest interest in recent cardiovascular research.

Epidemiologic studies and clinical trials showed that n–3 PUFAs could prevent atherosclerosis--related morbidity.[7] It was hypothesized that this outcome was due to the beneficial effect of n–3 PUFAs on endothelial function. Endothelial dysfunction is characterized by reduced vasodilation as well as a proinflammatory and prothrombotic state, and it is present in the early stage of atherosclerosis.[7] The measurement of flow-mediated dilation (FMD) is the gold standard for noninvasive assessment of endothelial dysfunction in the hospital and ambulatory settings. It was reported that improved FMD was associated with a reduced number of cardiovascular events in patients with diagnosed CVD.[7] Moreover, treatment with n–3 PUFAs at a dose of 2 g/d was shown to improve endothelial function and the elastic properties of the arteries in apparently healthy smokers, which was associated with the anti-inflammatory effect.[8] Moreover, the administration of high-dose n–3 PUFAs (4 g/d) for 4 months improved FMD in patients with hypercholesterolemia without altering endothelium-independent dilation.[9] Interestingly, both EPA and DHA were shown to reduce the levels of E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1, which are known for mediating the adhesion of the lymphocytes, monocytes, and macrophages, among other cells, to the vascular endothelium and improve the nitric oxide availability and promote endothelial nitric oxide synthesis.[10,11]

It is well established that type 2 diabetes mellitus (T2D) leads to endothelial dysfunction and atherosclerosis.[7,12] Stirban et al[13] showed that, while fasting FMD remained unchanged, postprandial FMD improved after 6-week n–3 PUFA treatment in patients with well-controlled T2D. Another study did not confirm the effect of n–3 PUFAs on the vascular endothelium in patients with hypertension and T2D.[14] Similarly, 3-month treatment with n–3 PUFAs (2 g/d) did not improve endothelial function, as measured by FMD and nitroglycerin-mediated dilation, in patients with T2D and confirmed atherosclerotic CVD.[15] Therefore, it was speculated that significant metabolic imbalance caused by both atherosclerotic CVD and long-lasting T2D limited the beneficial effect of n–3 PUFAs on the vascular endothelium in these patients.

Systemic inflammation affects the vascular endothelium and was found to be associated with increased levels of soluble adhesion molecules.[16] It also has a negative effect on antiplatelet and antithrombotic properties of the endothelium. It is known that n–3 PUFAs mediate the production of eicosanoids, which enhance anti-inflammatory cytokine production at the site of inflammation, and resolvins, which alleviate the inflammatory process.[10] At the same time, other essential fatty acids, namely, n–6 PUFAs such as arachidonic acid, are considered substrates of proinflammatory eicosanoids, promoting leukocyte activation and vascular permeability by releasing proinflammatory cytokines.[10,17] Moreover, numerous studies in healthy individuals showed a reduced production of 2-series prostaglandins and 4-series leukotrienes by inflammatory cells after supplementation with n–3 PUFAs.[10,17] To maintain homeostasis between proinflammatory and anti--inflammatory responses, an appropriate balance is needed between these 2 fatty acid families.[3]

It was established that CAD and invasive coronary interventions are associated with an increased systemic inflammation and thrombotic risk.[18,19] In the CHERRY trial[20] (Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography), a combined treatment with EPA and statins significantly reduced the coronary plaque volume

as compared with statin therapy alone in patients with CAD. Atherosclerotic plaques were reported to easily incorporate EPA.[18] Cawood et al[21] revealed that patients awaiting carotid endarterectomy who were treated with n–3 PUFA capsules had a lower number of foam cells than patients receiving control capsules. Moreover, in the n–3-PUFA group, plaques were more stable and less inflamed. Tanaka et al[22] showed that oral administration of EPA increased antioxidant and anti-inflammatory activity of high-density lipoprotein (HDL). Similarly, EPA was reported to enhance the antiatherosclerotic functions of HDL particles. Finally, the authors demonstrated that the antioxidative and anti-inflammatory functions of HDL promoted the cholesterol efflux from macrophages in patients with dyslipidemia.[22] The addition of n–3 PUFAs to standard-of--care treatment improved response to antiplatelet therapy after percutaneous coronary interventions.[23,24] Moreover, it was shown that the addition of n–3 PUFAs to optimal guideline-based pharmacotherapy significantly reduced thrombin formation and oxidative stress as well as favorably altered fibrin clot properties.[25] However, a recent study also demonstrated that 3-month supplementation with EPA and DHA in patients with concomitant CAD and T2D did not reduce thrombin generation or platelet activation.[26] Therefore, it is speculated that the effects of n–3 PUFA treatment might be unfavorably altered by glucose metabolism disorders, especially in patients with long-lasting T2D.[15,26-29]

Results from early clinical trials The strong position of n–3 PUFAs in the treatment of cardiovascular patients was supported by randomized controlled trials already more than 20 years ago. The most famous GISSI-Prevenzione trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione) was one of the first to show that even a low dose of n–3 PUFAs (1 g/d) resulted in a significant reduction of major adverse cardiovascular events.[30] In the JELIS (Japan EPA Lipid Intervention Study), patients with hypercholesterolemia were randomly assigned to receive pure EPA ethyl ester with 10 mg of pravastatin or 5 mg of simvastatin once daily.[31] As in the GISSI-Prevenzione study, the authors observed a significant reduction of major adverse cardiovascular events, especially nonfatal coronary events. The JELIS study was also one of the first to use pure EPA instead of a combination of EPA and DHA. However, in line with the results of basic and translational research,[15,26,27] no significant association was found between n–3 PUFA supplementation (1 g/d) and the rate of cardiovascular events in T2D patients either with[32] or without established CVD.[33] Both trials confirmed that impaired glucose metabolism limits the potential benefits of n–3 PUFA supplementation.

In 2020, the OMEMI study (Omega-3 Fatty Acids in Elderly Patients with Myocardial Infarction) investigated the effect of daily supplementation with n–3 PUFA at a moderate dose (930 mg/d of EPA and 660 mg/d of DHA) in patients with a recent acute MI. It failed to show any benefit on the primary endpoint, which was a composite of nonfatal acute MI, unscheduled revascularization, stroke, all-cause death, and hospitalization for heart failure, at 2-year follow-up.[34] Moreover, in the ORIGIN trial (Outcome Reduction with Initial Glargine Intervention), the administration of 1 g of n–3 PUFAs daily did not reduce the rate of cardiovascular deaths or other outcomes during 6 years in patients with dysglycemia and additional cardiovascular risk factors.[32] Similarly, in the ASCEND trial (A Study of Cardiovascular Events in Diabetes) including patients with T2D without evidence of CVD, there was no significant difference in the risk of serious vascular events between patients assigned to receive n–3 PUFA supplementation and those assigned to receive placebo.[33] Furthermore, a low-dose supplementation with a combination of EPA and DHA did not significantly reduce the rate of major cardiovascular events among patients after MI who received state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy.[35] Finally, a recent large primary prevention study, VITAL (Vitamin D and Omega-3 Trial), also did not demonstrate any additional benefit of n–3 PUFAs for reducing the risk of major cardiovascular events.[36]

One of the first extensive clinical assessments of fish consumption and cardiovascular events was the Chicago Western Electric Study, which showed a significant inverse association between baseline fish intake and the 30-year risk of fatal MI.[37] Moreover, the most important dietary study conducted in the recent years, PREDIMED (Prevención con Dieta Mediterránea), compared 2 dietary strategies to ultimately determine optimal dietary habits for cardiovascular patients.[38] The authors compared a low-fat diet (at that time widely recommended to patients with established CVD) with the Mediterranean diet (rich in n–3 PUFAs) supplemented with either extra-virgin olive oil or nuts.[38] Contrary to the primary prevention study,[36] the Mediterranean diet rich in PUFAs substantially reduced the rate of major adverse cardiovascular events.[38]

Subsequent meta-analyses Similar to major clinical trials, available meta-analyses also provide discrepant results. In 2004, Whelton et al[39] compared 19 observational studies (14 cohort and 5 case-control) investigating fish intake in patients with CAD. The authors demonstrated a significant reduction (by 20%) in the risk of fatal CAD, which led them to conclude that fish consumption may be an essential component of lifestyle modification in the prevention of CAD.[39] Del Gobbo et al[40] conducted a meta-analysis of 19 cohort studies with a total of 45 000 participants to determine the potential benefit of n–3 PUFAs for the primary prevention of CAD by evaluating

the biomarkers of seafood-derived PUFAs for incident CAD. The study showed that higher levels of n–3 PUFAs, especially DHA and EPA, were significantly associated with a more favorable cardiovascular risk profile, and thus with a lower incidence of fatal CAD.[40] However, contradictory results were reported by 2 most recent meta-analyses.[41,42] Aung et al[41] assessed the risk of fatal and nonfatal CAD events, but also other major vascular events, in 77 917 high-cardiovascular-risk patients from 10 large randomized clinical trials. The analysis showed no significant association of n–3 PUFA use with fatal or nonfatal CAD and major vascular events.[41] Therefore, the authors concluded that there is no evidence to support the recommendation for using n–3 PUFA supplements in patients with CAD.[41] The other meta-analysis included study-level data from 13 trials.[42] Interestingly, a meta-regression was conducted to determine a dose-response relationship between n–3 PUFA dose and the risk of each prespecified outcome (MI, cardiovascular death, CAD death, total CAD, stroke, and CVD events, as well as major cardiovascular events). The authors reported that n–3 PUFA supplementation reduced the risk of MI, CAD, and CVD death, as well as total CAD and CVD events. The effect was observed even after the exclusion of the REDUCE-IT trial (Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial), which demonstrated the most favorable results for n–3 PUFAs to date.[42,43] Interestingly, in a recent pooled analysis including data from 17 prospective cohort studies, Harris et al[44] demonstrated that over a median follow-up of 16 years, the risk of death from any cause was significantly reduced (by 15%–18%) in patients in the highest quintile (vs the lowest quintile) of n–3 PUFA (20–22 carbon) concentrations in blood. In another meta-analysis, the use of EPA and DHA was found to reduce the risk of cardiovascular outcomes, especially CAD and MI.[45] The authors reported that the association was dose dependent for CVD and MI, with significantly greater beneficial effects observed with an increase in the dose of n–3 PUFA.[45]

Recent cardiovascular outcome trials Recently, numerous large randomized controlled trials investigating the effects of n–3 PUFAs have been conducted. Interestingly, the latest trials—REDUCE-IT and STRENGTH (Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia)—yielded conflicting results on the role of n–3 PUFAs in cardiovascular patients.[43,46] The REDUCE-IT trial demonstrated a highly significant reduction in the risk of major cardiovascular events by 25%, including a lower risk of cardiovascular death (by 20%).[43] On the contrary, the STRENGTH trial failed to show any benefit of n–3 PUFAs and was stopped for futility.[46] A direct comparison of these trials is challenging because of numerous significant differences (TABLE 1). The REDUCE-IT focused on higher-cardiovascular-risk patients with a higher prevalence of established CVD (over 70% of secondary prevention cases) and included more men than women. Moreover, elevated triglyceride levels were one of the key inclusion criteria, unlike in the STRENGTH trial. There is a bulk of evidence justifying the use of n–3 PUFAs in the treatment of hypertriglyceridemia.[47] Inclusion of patients with elevated triglycerides levels might have favorably affected the results of the REDUCE-IT trial. Moreover, as described above, basic and translational research[15,26,27] confirmed that dysglycemia hampers the positive cardiovascular effects of n–3 PUFAs, which was also supported by at least 2 major randomized clinical trials—ORIGIN and ASCEND.[32,33] On the other hand, in the STRENGTH trial, a vast majority of patients were diagnosed with T2D at baseline, which possibly reduced the positive effects of n–3 PUFA in the interventional group. The studies also differ considerably in the percentage of patients on high-dose statin treatment. As described previously, adding n–3 PUFAs on top of high-dose statin treatment significantly inhibits plaque volume progression[48] and improves the lipid profile.[49,50] Therefore, a lower percentage of patients receiving high-dose statins in the REDUCE-IT trial may have resulted in cardiovascular benefits being more easily observed with icosapent ethyl ester in this very high-risk population.

In addition to the above discrepancies, also the assessed active compounds differed between studies. In REDUCE-IT, the authors used highly purified EPA ethyl ester (icosapent ethyl ester) as compared with a mixture of EPA and DHA carboxylic acid formulations. A purified version of EPA ethyl ester alone (1.8 g/d) was also used in the JELIS study in Japanese patients with hypercholesterolemia.[31] Compared with statin treatment, EPA ethyl ester reduced the risk of major coronary events. Interestingly, a subanalysis of the JELIS study found that in patients with impaired glucose metabolism and hypercholesterolemia, treatment with pure EPA reduced the risk of coronary events by 22%.[51] It is likely that the addition of DHA to this mixture of carboxylic acids weakened the beneficial effect of EPA in the STRENGTH study. Finally, different comparators were used in both trials—mineral oil in REDUCE-IT and corn oil in STRENGTH. The neutral results of the STRENGTH trial sparked a discussion about the use and safety of mineral oil. It was speculated that the surprisingly positive results of REDUCE-IT might be attributed to the theoretical adverse effects of mineral oil rather than to the clinical benefits of icosapent ethyl ester. However, the authors of the REDUCE-IT trial pointed out that mineral oil was previously frequently used in other clinical trials with no significant cardiovascular safety concerns reported. They concluded that oral mineral oil is essentially inert, with no systemic impact in humans other than a lubricating laxative effect in the gastrointestinal tract.[52]

TABLE 1 Head-to-head comparison of REDUCE-IT and STRENGTH trials

Characteristic		REDUCE-IT	STRENGTH
Key inclusion criteria		• Age ≥45 years and established CVD or age ≥50 years and T2D and 1 additional cardiovascular risk factor • Fasting triglycerides: 150–499 mg/dl • LDL-C: 41–100 mg/dl • Stable statin dose ≥4 weeks	• Age ≥18 years and high cardiovascular risk • High cardiovascular risk: established atherosclerotic CVD; T1D or T2D and age ≥40 years (men) or ≥50 years (women) with at least 1 additional risk factor; high-risk primary prevention patients ≥50 years (men) or ≥60 years (women) with at least 1 additional risk factor
Age, y		64	62.5
Female sex, %		28.8	35
Number of participants (randomized)	Interventional group	4089	6539
	Placebo group	4090	6539
Daily n–3 PUFA dose		4g (2 × 2 g)	4 g
n–3 PUFA composition		Icosapent ethyl (highly purified and stable EPA ethyl ester)	Carboxylic acid formulation of omega-3 fatty acids (EPA and DHA)
Comparator		Mineral oil	Corn oil
Primary prevention cohort, %	Interventional group	29.3	44.4
	Placebo group	29.3	43.8
Secondary prevention cohort, %	Interventional group	70.7	55.6
	Placebo group	70.7	56.2
High-intensity statin treatment, %	Interventional group	31.5	49.8
	Placebo group	30	50.1
T2D at baseline, %	Interventional group	57.9	70.5
	Placebo group	57.8	69.8
BMI, kg/m^2, mean	Interventional group	30.8	32.2
	Placebo group	30.8	32.2
Primary efficacy endpoint		A composite of cardiovascular death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization or unstable angina in a time-to-event analysis	A composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, hospitalization for unstable angina; major cardiovascular events included cardiovascular death, nonfatal MI, and nonfatal stroke
Key secondary endpoint		A composite of cardiovascular death, nonfatal MI, or nonfatal stroke in a time-to-event analysis	• A composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina in patients with established CVD at baseline • A composite of cardiovascular death, nonfatal MI, and nonfatal stroke in the whole cohort and patients with established CVD at baseline • Composite of cardiac death, nonfatal MI, coronary revascularization, and hospitalization for unstable angina in the whole cohort and in patients with established CVD at baseline • Cardiovascular death in the whole cohort and in patients with established CVD at baseline • All-cause death in the whole cohort and in patients with established CVD at baseline
Outcomes		• Reduction of the primary efficacy endpoint by 25% (HR, 0.75; 95% CI, 0.68–0.83) • Reduction of the key secondary endpoint by 26% (HR, 0.74; 95% CI, 0.65–0.83)	• Nonsignificant 1% reduction of the primary efficacy endpoint (HR, 0.99; 95% CI, 0.90–1.09) • Nonsignificant increase by 5% of the major cardiovascular events (HR, 1.05; 95% CI, 0.93–1.19) • Reduction of coronary events in patients with established CVD at baseline by 15% (HR, 0.85; 95% CI, 0.75–0.97)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; others, see FIGURE 1

Possible mechanisms underlying cardiovascular protection Despite the enormous success of low-density lipoprotein (LDL)–lowering therapies in cardiovascular risk reduction, patients still have residual cardiovascular risk, associated to some extent with increased triglyceride levels.[18] It was reported that EPA at a dose from 2 to 4 mg/d reduces triglyceride levels without increasing LDL-cholesterol levels.[53,54] This effect can be explained by a reduced production and faster clearance of triglyceride-rich lipoproteins in line with a prompt clearance of LDL particles and a slower generation of very-LDL particles.[31,51,54] Triglyceride-rich lipoproteins were found to damage vascular function and promote atherosclerosis progression by several mechanisms.[18] Their favorable effects on other residual risk factors were also confirmed by some cardiovascular outcome trials. These risk factors included inflammation (COLCOT [Colchicine Cardiovascular Outcomes Trial][55] and CANTOS [Canakinumab Anti-Inflammatory Thrombosis Outcome Study][56]) and increased thrombotic risk (COMPASS [Cardiovascular Outcomes for People Using Anticoagulation Strategies][57] and THEMIS [Ticagrelor Versus Placebo in Patients With Type 2 Diabetes Mellitus][58]). Interestingly, n–3 PUFAs, and EPA in particular, exhibit both anti-inflammatory and antithrombotic properties targeting the residual cardiovascular risk. They were also shown to induce the production of the proresolving lipid mediators, such as resolvins, maresins, and protectins, which are highly coordinated metabolites that help restore homeostasis following acute inflammation.[18,59] Cardioprotective effects of EPA and DHA can be also attributed to antithrombotic metabolites via the increased production of prostacyclin.[18] Unlike n–3 PUFAs, n–6 PUFAs are metabolized mainly to the more prothrombotic thromboxane A2, a platelet activator contributing to atherothrombosis.[18] Interestingly, because n–3 and n–6 PUFAs compete for the same enzyme, cyclooxygenase, a proper balance between them is needed to show pro- or antithrombotic properties.[18]

From the beginning, the primary benefit of n–3 PUFAs was reported mainly for patients with very high cardiovascular risk, particularly those with CAD. Targeting a reduction of other endpoints such as cardiovascular death, stroke, or other vascular events can be challenging, especially with constantly changing pharmacotherapy that constitutes the standard of care at the time of the trial. Interestingly, despite the high dose of n–3 PUFA, the STRENGTH trial reported negative results in terms of reducing major adverse cardiovascular events. A significant reduction was reported only for coronary events in the secondary prevention group.[46] Similarly, in the REDUCE-IT trial, there was a shift in favor of icosapent ethyl efficacy in patients with established CVD.[43] Selection of appropriate patients to receive n–3 PUFA treatment remains a crucial issue. Most evidence suggests that the best possible benefit of n–3 PUFA is observed when given as secondary prevention in patients with hypertriglyceridemia and very high risk of atherosclerosis. This definitely leaves room for future research.

Therapy with EPA alone seems to contribute significantly to residual cardiovascular risk reduction and to confer additional protection on top of the current standard-of-care treatment with statins.[18,59] The interim analysis of the EVAPORATE trial (Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy) revealed a favorable effect of high-dose icosapent ethyl ester on the reduction of total plaque volume progression.[60] Therefore, purified EPA appears to have a higher potential to reduce plaque volume and improve plaque composition, possibly leading to a significant reduction in the risk of coronary events, as demonstrated by the REDUCE-IT study. Clinical studies with high-dose EPA (2–4 g/d) provided mechanistic insights into dose-dependent changes of various biomarkers.[18,59] Treatment with purified EPA vs placebo was shown to reduce the ratio of arachidonic acid to EPA as well as the levels of high-sensitivity C-reactive protein, remnant-like particle cholesterol, and oxidized LDL cholesterol in patients with highly elevated triglyceride levels.[18,59] Therefore, in order to reduce the residual risk of cardiovascular events and mortality, especially in the most challenging patient populations (with established CVD, long-lasting T2D, and metabolic syndrome), it seems that the use of high-dose purified EPA is preferable.

Conclusions The current European Society of Cardiology guidelines recommend using purified n–3 PUFA (icosapent ethyl) at a dose of 4 g daily as second-line treatment after statins in patients at high or very high cardiovascular risk with triglycerides ranging from 1.5 to 5.6 mmol/l (135–499 mg/dl) despite statin treatment.[47] Moreover, the guidelines recommend the Mediterranean diet in a wide range of patients in both primary and secondary prevention of CVDs.[61] It was demonstrated that CAD is reduced by 2% to 3% when 1% of the energy from saturated fatty acids is replaced by PUFAs. Therefore, the European Society of Cardiology guidelines indicate that patients should 1) avoid trans unsaturated fatty acids, 2) consume a maximum of 10% of the total energy intake from the unsaturated fatty acids, and 3) consume fish once or twice per week, including at least one oily fish, particularly rich in PUFAs.[61] There is a body of evidence showing that patients with established cardiovascular disease or with T2D and at least one additional risk factor including high triglycerides levels benefit the most from the high dose (4 g daily) of icosapent ethyl ester EPA. That is why despite optimal statin therapy, the icosapent ethyl ester EPA should be considered in those patients to reduce the risk of cardiovascular events and mortality.

There are currently many clinical trials underway with n–3 PUFAs. In the field of cardiovascular

diseases, they mainly concern the treatment of patients with severe hypertriglyceridemia, treatment of residual systemic inflammation, obesity, metabolic syndrome, and glucose metabolism abnormalities. Additionally, there are many basic science studies such as the IPE-PREVENTION (Icosapent Ethyl and Prevention of Vascular Regenerative Cell Exhaustion Study), which will provide further molecular and cellular insights into the mechanisms underlying the cardiovascular benefits of highly purified EPA; or the EPA&LDL (Effect of E-EPA on Circulating LDL and Plasma Lipid Metabolism) in which the investigators will focus on LDL aggregation susceptibility, lipid composition, and proteoglycan binding affinity. Finally, to clarify whether icosapent ethyl is actually better than a high-dose combination of EPA and DHA (as in the STRENGTH study), the experts mentioned the need to compare highly purified EPA in patients with high cardiovascular risk with placebo in the form of corn oil. Therefore, despite the long history of research on n–3 PUFAs, recent studies show that it is by no means complete.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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