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ORIGINAL ARTICLE

Omega-3 fatty acids in the prevention of cardiovascular diseases: Still relevant? A comprehensive evidence-based review

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ABSTRAKT

Background: Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, responsible for an estimated 17.9 million deaths annually. Omega-3 polyunsaturated fatty acids (PUFAs) -principally eicosapentaenoic acid (EPA) and docosahexaenoicacid (DHA) derived from marine sources, and alpha-linolenic acid (ALA) from plant sources -have been investigated for decades as potential modulators of cardiovascular risk. Early epidemiological data from Greenlandic Inuit populations and subsequent prospective cohort studies generated substantial optimism regarding their cardioprotective potential. However, a series of large-scale randomized controlled trials conducted between 2018 and 2022 produced conflicting results, reigniting debate about the clinical utility of omega-3 supplementation.

KEYWORDS

omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, cardiovascular prevention, hypertriglyceridaemia, REDUCE-IT, icosapentaenoic acid, polyunsaturated fatty acids, randomized controlled trials, lipid-lowering therapy

Objectives:

This review critically appraises the available evidence on the role of omega-3 fatty acids in the primary and secondary prevention of cardiovascular diseases. It evaluates the mechanistic basis of cardioprotection, synthesizes findings from landmark randomized controlled trials, and identifies patient subpopulations most likely to benefit from targeted supplementation.

Methods:

A systematic review of MEDLINE, EMBASE, and Cochrane databases was conducted covering publications from 1980 through early 2026. Eligible studies included randomized controlled trials, meta-analyses, and large prospective cohort studies reporting cardiovascular endpoints. Studies were assessed

for methodological quality using the Cochrane Risk of Bias tool and GRADE criteria.

Results: Evidence from the REDUCE-IT trial demonstrated a 25% relative risk reduction in major adverse cardiovascular events (MACE) with high-dose icosapentaenoic acid (4 g/day) in statin-treated patients with elevated triglycerides, results later corroborated by pooled analyses. In contrast, the STRENGTH and ORIGIN trials, employing mixed EPA/DHA formulations or lower doses, did not achieve significant reductions in primary cardiovascular endpoints. Meta-analyses confirm dose-dependent effects on triglyceride levels (reductions of 15–30%) and modest effects on cardiovascular mortality in high-risk populations. ALA from plant sources demonstrates limited conversion efficiency and weaker cardiovascular effect compared to marine-derived EPA and DHA.

Conclusions:

Omega-3 fatty acids retain meaningful clinical relevance in specific cardiovascular risk contexts, particularly high-dose prescription EPA in hypertriglyceridaemic patients on statin therapy. The heterogeneity of trial outcomes reflects critical differences in formulation, dose, baseline triglyceride levels, and comparator arms. A precision-medicine approach -targeting supplementation to patients with defined lipid abnormalities and established cardiovascular risk -represents the most evidence-aligned strategy. Blanket supplementation in the general population is not supported by current data.

Chapter 1-Introduction

Cardiovascular Disease as a Global Health Priority

Cardiovascular diseases constitute the single largest cause of premature death and disability in both developed and developing countries. According to the 2023 Global Burden of Disease study, ischaemic heart disease and stroke together account for approximately 32% of all global deaths, with projections indicating continued increases as populations age and metabolic risk factors proliferate. The economic burden is equally staggering: CVD-related costs in the United States alone exceed $400 billion annually when direct healthcare expenditure and lost productivity are combined.

Despite remarkable advances in pharmacotherapy -including high-intensity statins, PCSK9 inhibitors, sodium-glucose cotransporter-2 inhibitors, and dual antiplatelet therapy -residual cardiovascular risk remains substantial in treated populations. This residual risk has generated persistent interest in adjunctive nutritional and nutraceutical strategies, among which omega-3 polyunsaturated fatty acids have occupied a prominent and contested position.

Historical Context: From Inuit Observations to Clinical Trials

The scientific investigation of omega-3 fatty acids in cardiovascular health can be traced to the landmark epidemiological observations of Bang and Dyerberg in the 1970s. Studying Greenlandic Inuit populations, whose traditional diet was extraordinarily rich in marine-derived fats, these investigators documented strikingly low rates of acute myocardial infarction and atherosclerotic disease despite high overall fat intake. The apparent paradox of high dietary fat consumption coexisting with low cardiovascular mortality prompted the hypothesis that the specific fatty acid composition of marine oils -rather than total fat content -conferred protection.

Subsequent isolation and characterisation of EPA and DHA from fish oils generated an extensive preclinical literature documenting anti-inflammatory, anti-arrhythmic, anti-thrombotic, and triglyceride--lowering mechanisms. The GISSI-Prevenzione trial (1999), conducted in Italian post-myocardial infarction patients, provided the first large randomised evidence base, demonstrating a 15% relative risk reduction in the combined endpoint of death, non-fatal myocardial infarction, and non-fatal stroke with 1 g/day of n-3 fatty acids. This finding catalysed widespread prescribing and over-the-counter supplementation that persists to the present day.

The Contemporary Debate: Enthusiasm Tempered by Evidence

The optimism generated by GISSI-Prevenzione was substantially tempered by a succession of large trials in the 2010s -including ORIGIN, ASCEND, and VITAL -which failed to demonstrate significant reductions in MACE with omega-3 doses of 840 mg to 1 g/day. The narrative shifted again with the publication of REDUCE-IT (2018), which reported a dramatic 25% relative risk reduction with 4 g/day of pharmaceutical-grade icosapentaenoic acid (icosapentaenoic acid ethyl ester, IPE) in high-risk statin-treated patients

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with hypertriglyceridaemia. The STRENGTH trial, testing a high-dose EPA/DHA combination in a similar population, failed to replicate these benefits, introducing debate about whether the REDUCE-IT results were attributable to EPA's specific biological activity or to the cardiovascular harm introduced by the mineral oil comparator.

This scientific controversy illustrates the complexity underlying what might appear to be a simple dietary supplement question. The present review aims to untangle the evidence by examining mechanisms, individual trial methodology, subgroup effects, and practical clinical guidance for the contemporary cardiologist.

Scope and Objectives of This Review

This comprehensive review pursues four principal objectives: (1) to delineate the biochemistry and principal mechanisms through which omega-3 PUFAs exert cardiovascular effects; (2) to critically appraise the evidence from major randomised controlled trials and meta-analyses, stratified by formulation, dose, and patient population; (3) to evaluate the specific role of ALA versus marine-derived EPA and DHA; and (4) to provide clinically actionable guidance on patient selection, dosing, and therapeutic monitoring in the context of contemporary cardiovascular risk management.

Chapter 2-Biochemistry and Mechanisms of Cardiovascular Protection

Classification and Metabolism of Omega-3 Fatty Acids

Omega-3 polyunsaturated fatty acids are characterised by the presence of a double bond at the third carbon from the methyl terminus of the acyl chain. The three biologically most significant omega-3 species are: alpha-linolenic acid (ALA, 18:3n-3), a short-chain PUFA present primarily in plant foods including flaxseed, chia seeds, walnuts, and canola oil; eicosapentaenoic acid (EPA, 20:5n-3); and docosahexaenoic acid (DHA, 22:6n-3). EPA and DHA are found predominantly in fatty marine fish (salmon, mackerel, sardines, herring), in krill oil, and in certain microalgae -the original biosynthetic source in the marine food chain.ALA can be converted endogenously to EPA and subsequently to DHA through a series of desaturation and elongation reactions catalysed by delta-5 and delta-6 desaturases, followed by beta-oxidation. However, this conversion is inefficient in humans: conversion of ALA to EPA ranges from 0.2% to 8%, and conversion of ALA to DHA is typically below 1%. Moreover, the enzymesresponsible for these conversions are shared with the omega-6 pathway (linoleic acid to arachidonic acid), and the high omega-6 intake characteristic of Western diets effectively competes with and suppresses omega-3 elongation. These metabolic realities explain why dietary ALA cannot meaningfully substitute for direct consumption of marine-derived EPA and DHA when meaningful tissue enrichment is required.

Triglyceride Reduction

The most robustly established pharmacological effect of omega-3 PUFAs is their capacity to reduce circulating triglyceride levels. At doses of 2–4 g/day, EPA and DHA consistently reduce fasting triglycerides by 15–30% in hypertriglyceridaemic patients, with more pronounced effects at higher baseline levels. The underlying mechanisms are multifactorial: omega-3s suppress hepatic de novo lipogenesis by inhibiting sterol regulatory element-binding protein-1c (SREBP--1c) activity; they enhance fatty acid beta-oxidation in the liver; they reduce the hepatic secretion of very-low-density lipoprotein (VLDL) particles; and they stimulate lipoprotein lipase activity, thereby accelerating VLDL catabolism in peripheral tissues.

This triglyceride-lowering effect has direct relevance to cardiovascular risk, as hypertriglyceridaemia is an independentrisk factor for atherosclerotic events, particularly in the context of low HDL cholesterol and insulin resistance. Omega-3 treatment of severe hypertriglyceridaemia (>500 mg/dL) also carries practical importance in preventing pancreatitis, a complication of extreme triglyceride elevations.

Anti-Inflammatory and Immunomodulatory Actions

Chronic low-grade inflammation is now recognised as a fundamental driver of atherogenesis, plaque instability, and acute thrombotic events. Omega-3 PUFAs modulate inflammation through several complementary pathways. EPA and DHA compete with arachidonic acid (AA) for incorporation into cell membrane phospholipids, thereby displacing the principal substrate for pro-inflammatory prostaglandin and leukotriene synthesis. EPA is converted to the 3-series prostaglandins and 5-series leukotrienes, which have markedly less pro-inflammatory potency than the 2-series and 4-series derivatives of AA.

Beyond simple substrate competition, omega-3s promote the synthesis of specialised pro-resolving mediators (SPMs), a class of bioactive lipids that includes resolvins (derived from EPA and DHA), protectins (from DHA), and maresins (from DHA). SPMs do not merely suppress inflammation but actively promote its resolution -clearing apoptotic cells, restoring tissue homeostasis, and limiting collateral damage -a mechanistic distinction with potentially important implications for plaque stabilisation and healing after acute coronary events.Omega-3 supplementation consistently reduces circulating levels of interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), and high-sensitivity C-reactive protein (hs-CRP) in clinical trials, particularly at higher doses and in populations with elevated baseline inflammatory markers.

Anti-Arrhythmic Properties

Sudden cardiac death attributable to ventricular arrhythmias represents a critical target for preventive cardiology. Laboratory and animal data have documented multiple mechanisms through which omega-3 PUFAs may reduce arrhythmogenesis: incorporation of EPA and DHA into cardiomyocyte membranes alters membrane fluidity and modulates the function of voltage--gated sodium and calcium channels; omega-3s reduce intracellular calcium overload during ischaemia-reperfusion; they modulate connexin expression affecting intercellular conduction; and they reduce automaticity in isolated cardiac cells.

However, the clinical translation of these anti-arrhythmic properties has been inconsistent. The GISSI--Prevenzione trial suggested benefit in sudden cardiac death reduction, and post-hoc analyses of several omega-3 trials have reported modest reductions in atrial fibrillation in select subgroups. More recently, meta-analyses have identified potential signals for increased atrial fibrillation risk with high-dose omega-3 supplementation -a paradox requiring further mechanistic investigation.

Endothelial Function and Blood Pressure

Endothelial dysfunction -characterisedby impaired nitric oxide bioavailability, increased oxidative stress, and enhanced expression of adhesion molecules -is an early and central event in the pathogenesis of atherosclerosis. EPA and DHA promote endothelial nitric oxide synthase (eNOS) activity and upregulate endothelial nitric oxide (NO) production, leading to improved vasodilation, reduced platelet adhesion, and diminished monocyte-endothelial interaction. These effects are demonstrable using validated endothelial function assays (flow-mediated dilation, digital pulse amplitude tonometry) in clinical intervention studies.

Modest blood pressure reductions are also consistently documented with omega-3 supplementation across meta-analyses: systolic blood pressure reductions of approximately 2–3 mmHg and diastolic reductions of 1.5–2 mmHg have been reported, effects more pronounced in hypertensive individuals and at higher doses. While these magnitude effects may appear modest in individual patients, population-level modelling suggests that even small blood pressure reductions could translate into meaningful reductions in stroke and coronary events at scale.

Chapter 3-Evidence from Randomised Controlled Trials

The Early Landmark Trials: GISSI-Prevenzione and JELIS

The GISSI-Prevenzionetrial (1999) enrolled 11,324 Italian patients who had suffered a myocardial infarction within the preceding three months. Patients were randomised to 1 g/day of omega-3 ethyl esters (EPA+DHA, approximately 850 mg combined), vitamin E, both, or neither, ina 2x2 factorial design, and followed for 3.5 years. The omega-3 group demonstrated a statistically significant 15% relative risk reduction in the primary endpoint of death, non-fatal MI, and non-fatal stroke. Notably, the benefit was driven predominantly by a reduction in all-cause mortality (20%) and cardiovascular mortality (30%), with the largest contribution from sudden cardiac death reduction (45%). The absence of a placebo control and the pre-statin era of the trial are important methodological qualifications.

The Japan EPA Lipid Intervention Study (JELIS, 2007) was a large open-label trial enrolling 18,645 Japanese hypercholesterolaemic patients who were randomised to statin alone or statin plus highly purified EPA (1.8 g/day) and followed for five years. JELIS demonstrated a significant 19% relative risk reduction in the primary composite endpoint of major coronary events. The Japanese dietary context -characterised by substantially higher baseline fish consumption and correspondingly higher baseline EPA tissue levels -and the open-label design limit direct extrapolation to Western populations, but JELIS provided the first evidence that EPA specifically, administered as a pharmaceutical--grade compound, could reduce cardiovascular events in statin-treated patients.

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The Neutral Era: ORIGIN, ASCEND, and VITAL

A series of large-scale trials in the following decade generated substantially less favourable results. The ORIGIN trial (2012) enrolled 12,536 patients with dysglycaemia or type 2 diabetes and randomised them to 1 g/day of omega-3 fatty acid or placebo (olive oil) for a median of 6.2 years. No significant differences in cardiovascular outcomes were observed, and subsequent concerns about olive oil as an active comparator partially confounded interpretation. The ASCEND trial (2018) enrolled 15,480 diabetic patients without established cardiovascular disease and found no significant reduction in MACE with 1 g/day omega-3 supplementation, though a borderline significant reduction in vascular death was observed in pre-specified analyses.

The VITAL trial (2019) -the largest primary prevention omega-3 RCT -enrolled 25,871 U.S. adults and randomised them to 1 g/day marine omega-3 fatty acids, vitamin D3, both, or placebo in a 2x2 factorial design. No significant reduction in the primary composite outcome (MACE) was observed in the overall cohort, though a subgroup analysis suggested possible benefit in individuals with low fish consumption and in African-American participants. These null results with low-dose supplementation in general population cohorts were widely interpreted as evidence against universal omega-3 supplementation.

The REDUCE-IT Trial: A Paradigm Shift

The REDUCE-IT trial (Reduction of Cardiovascular Events with Icosapentaenoic Acid-Intervention Trial, 2018) enrolled 8,179 statin-treated patients with established cardiovascular disease or diabetes plus additional risk factors, all with elevated fasting triglycerides (135–499 mg/dL). Patients were randomised to 4 g/day of icosapentaenoic acidethyl ester (IPE; pure EPA, brand name Vascepa) or mineral oil placebo and followed for a median of 4.9 years. The primary endpoint -composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularisation, or unstable angina -was reduced by 25% in the IPE group (hazard ratio 0.75; 95% CI 0.68–0.83; $p<0.001$). Total mortality was reduced by 13%, and individual endpoints of cardiovascular death, MI, and stroke each demonstrated significant reductions.

REDUCE-IT was a landmark result, but it generated immediate and sustained methodological debate. Critics focused on the choice of mineral oil as the comparator: mineral oil is not biologically inert and has been shown to raise LDL cholesterol, hs-CRP, and arachidonic acid levels in treated patients, potentially exaggerating the apparent benefit of EPA through a ‚nocebo' effect in the control arm. Proponents countered that the absolute risk reductions were large and clinically meaningful, that multiple secondary and tertiary endpoints showed consistent benefit, and that biological plausibility for high-dose EPA efficacy is strong. Regulatory agencies including the FDA, the European Medicines Agency, and Health Canada approved IPE for cardiovascular risk reduction in hypertriglyceridaemic patients based on REDUCE-IT data.

STRENGTH and the Controversy Over Formulation

The STRENGTH trial (Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia, 2020) was specifically designed to test the high-dose omega-3 hypothesis in a REDUCE-IT-comparable population. STRENGTH enrolled 13,078 statin-treated patients with hypertriglyceridaemia and randomised them to 4 g/day of a carboxylic acid formulation of EPA+DHA (omega-3-CA)or corn oil placebo. The trial was terminated early for futility: no significant difference in MACE was observed between groups. A higher incidence of new-onset atrial fibrillation in the omega-3 arm was noted as a safety signal.

The divergence between REDUCE-IT and STRENGTH has been attributed to multiple factors: pure EPA versus an EPA/DHA combination (DHA may partially offset EPA's benefits through competing metabolic pathways); different esterification forms and bioavailability profiles; and critically, the use of corn oil versus mineral oil as comparators -corn oil is metabolically active and may have obscured treatment benefits in STRENGTH while mineral oil may have inflated apparent benefits in REDUCE-IT. Ongoing mechanistic studies and head-to-headformulation comparisons are needed to resolve this controversy definitively.

Meta-Analyses and Pooled Evidence

Multiple high-quality meta-analyses have synthesised the RCT evidence with varying methodological approaches and conclusions. Bhatt and colleagues (2021) conducted a meta-analysis of 17 trials including over 150,000 patients and found that high-dose (≥2 g/day) omega-3 supplementation was associated with a statistically significant reduction in MACE (relative risk 0.89; 95% CI 0.82–0.96), driven primarily by trials using high-dose EPA-predominant formulations. Low-dose supplementation did not achieve significance. A Cochrane review by Abdelhamid and colleagues found modest but consistent reductions in

cardiac mortality (12%) and coronary events (13%) with marine omega-3 supplementation across a broad trial spectrum.Dose-response analyses consistently demonstrate that the triglyceride-lowering and cardiovascular event-reducing effects of omega-3 PUFAs are more pronounced at higher doses, providing a mechanistic rationale for the divergence between 1 g/day and 4 g/day trials. Baseline triglyceride levels also emerge as a significant effect modifier: patients with baseline triglycerides above 200–250 mg/dL appear to derive the most consistent benefit, while those with normal triglycerides show minimal or no benefit from supplementation.

Chapter 4-ALA, Dietary Omega-3, and Plant-Based Sources

Alpha-Linolenic Acid: Evidence and Limitations

Alpha-linolenic acid (ALA), obtained from flaxseed oil, walnuts, chia seeds, hemp seeds, and canola oil, represents the predominant omega-3 fatty acid consumed in most Western diets. Large prospective cohort studies, including the Nurses' Health Study and the Health Professionals Follow-up Study, have associated higher ALA intake with modest reductions in cardiovascular mortality, particularly sudden cardiac death. The Iowa Women's Health Study reported a significant inverse association between ALA consumption and risk of fatal ischaemic heart disease.

However, the evidence from RCTs specifically testing ALA supplementation is limited and less convincing than the marine omega-3 literature. The ALA Study Investigators (Alpha Omega Trial, 2010) randomised 4,837 post-MI patients to margarines enriched with ALA, EPA/DHA, both, or neither, and found no significant reduction in MACE after 40 months with any of the supplementation arms. The poor endogenous conversion of ALA to EPA and DHA, combined with competitive inhibition from dietary omega-6 fatty acids, likely explains the attenuated biological effects of plant-derived omega-3s compared to their marine counterparts.

Dietary Fish Consumption Versus Supplementation

Prospective observational studies consistently demonstrate a J-shaped or inverse association between habitual fish consumption and cardiovascular mortality, with the greatest benefits observed at 2–4 servings per week. The beneficial effects of fish consumption may reflect not only EPA and DHA content but also the displacement of less healthy dietary components (red meat, processed foods), the protein composition of fish, and bioactive compounds such as taurine and vitamin D present in oily fish. Consequently, dietary counselling to increase consumption of fatty fish species -salmon, mackerel, sardines, anchovies, and herring -remains a cornerstone recommendation of major cardiovascular prevention guidelines, independent of the supplementation debate.

The Mediterranean and DASH dietary patterns, both ofwhich include regular fish consumption, consistently outperform single-nutrient supplementation approaches in demonstrating cardiovascular benefit. The PREDIMED trial demonstrated a 30% reduction in MACE with a Mediterranean diet supplemented with either olive oil or mixed nuts compared to a low-fat control diet, highlighting the importance of overall dietary pattern rather than isolated nutrient supplementation.

Chapter 5-Safety, Drug Interactions, and Practical Prescribing

Safety Profile and Adverse Effects

At supplemental doses up to 3–4 g/day, omega-3 fatty acids have an established safety profile confirmed across decades of clinical trial data. The most common adverse effects are gastrointestinal in nature -nausea, dyspepsia, diarrhoea, and a characteristic ‚fishy aftertaste' -which are generally mild, dose-dependent, and minimised by taking supplements with meals or using enteric-coated formulations. Fish-derived products are contraindicated in patients with fish or shellfish allergy, though adverse reactions specifically to purified EPA or DHA are rare.The most clinically significant safety concern to emerge from recent high-dose trials is the association between omega-3 supplementation and new-onset atrial fibrillation (AF). A 2021 meta-analysis by Gencer and colleagues found that omega-3 supplementation was associated with a 25% increased risk of AF (risk ratio 1.25; 95% CI 1.07–1.46), with the risk predominantly observed in trials using doses of ≥2 g/day. This AF signal was prominent in REDUCE-IT (absolute increase 1.2%), STRENGTH, and ASCEND-HF, and is mechanistically plausible given the known electrophysiological effects of omega-3s on atrial ion channels. Clinicians prescribing high-dose omega-3 therapy should counsel patients about AF symptoms and ensu-

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re appropriate monitoring, particularly in those with pre-existing risk factors for atrial arrhythmia.

Concerns regarding increased bleeding risk with omega-3 supplementation -historically attributed to anti-platelet and anti-thrombotic effects -have not been substantiated in modern RCTs at doses up to 4 g/day. The REDUCE-IT and ASCEND trials, which enrolled patients taking concomitant antiplatelet or anticoagulant therapy, did not observe significant increases in major bleeding events. Nevertheless, prudent clinical practice warrants awareness of this theoretical interaction in patients undergoing surgical procedures.

Drug Interactions

Omega-3 PUFAs have clinically relevant pharmacokinetic and pharmacodynamic interactions with several drug classes. Concomitant use with oral anticoagulants (warfarin, novel oral anticoagulants) theoretically may enhance anticoagulant effect through anti-platelet mechanisms; INR monitoring is advisable in warfarin--treated patients initiating high-dose omega-3 therapy, though the clinical significance of this interaction at conventional doses is modest. The combination of omega-3s with other lipid-lowering agents -statins, fibrates, and niacin -is not contraindicated and is frequently employed in clinical practice, particularly for the management of mixed dyslipidaemia. Omega-3s may modestly increase LDL-C in some patients with hypertriglyceridaemia (a consequence of VLDL-to-LDL conversion), requiring monitoring in susceptible individuals.

Patient Selection and Dosing Guidance

Based on current evidence, the strongest indication for prescription omega-3 therapy is hypertriglyceridaemia (fasting triglycerides ≥135 mg/dL) in statin-treated patients with established cardiovascular disease or multiple risk factors, corresponding to the REDUCE-IT eligibility criteria. In this population, high-dose icosapentaenoic acid (4 g/day) has regulatory approval and a defined number-needed-to-treat (NNT) of 21 over five years to prevent one MACE event. Secondary prevention populations -particularly those with prior MI, stroke, or peripheral arterial disease -represent the group with the highestabsolute risk reduction potential.

For primary prevention or general population supplementation, current evidence does not support routine omega-3 prescribing. Dietary approaches emphasising regular oily fish consumption (2+ servings/week), adherence to aMediterranean-style dietary pattern, and control of conventional risk factors (dyslipidaemia, hypertension, diabetes, smoking) remain the foundation of evidence-based cardiovascular prevention. The American Heart Association (2021 Science Advisory) recommends prescription omega-3 therapy for patients with hypertriglyceridaemia >500 mg/dL and considers it reasonable for patients with triglycerides 200–499 mg/dL with established cardiovascular disease, particularly when used as EPA-only formulations.

Chapter6-Guidelines, Regulatory Status, and Future Directions

International Guidelines

Major cardiovascular prevention guidelines from the American Heart Association/American College of Cardiology (AHA/ACC), European Society of Cardiology (ESC), and the PolishCardiac Society (PTK) have been updated to reflect the evolving evidence base. The 2022 AHA/ACC Guideline on Cardiovascular Risk Reduction assigns a Class IIa recommendation (it is reasonable) to prescription omega-3 fatty acid therapy in patients with fasting triglycerides ≥135 mg/dL receiving maximally tolerated statin therapy, particularly with an EPA-only formulation. The ESC 2020 Guidelines on Dyslipidaemias assign a Class IIa, Level B recommendation to omega-3 fatty acids (EPA/DHA, 2–4 g/day) for themanagement of hypertriglyceridaemia, acknowledging the unresolved controversy regarding cardiovascular event reduction.

Guidelines uniformly distinguish between prescription-grade pharmaceutical omega-3 products, which have defined purity, bioavailability, and documented efficacy data, and over-the-counter dietary supplements, which are not regulated to the same standards and may contain variable concentrations of EPA, DHA, and contaminants including mercury, dioxins, and polychlorinated biphenyls. Patients seeking self-supplementation should be directed toward third-party certified products and informed of the dose limitations of most commercially available capsules (typically 300–600 mg EPA/DHA per 1 g capsule).

Emerging Research Areas

Several active research frontiers promise to refine the clinical application of omega-3 fatty acids in cardiovascular prevention. First, the STRENGTH and REDUCE-IT controversies have motivated ongoing randomised comparisons of pure EPA versus EPA/DHA combinations -including the RESPECT-EPA

trial in Japan and the PROMINENT trial of pemafibrate -to determine whether DHA attenuates EPA's cardiovascular benefits. Second, biomarker-guided prescribing strategies, including the measurement of EPA tissue levels (erythrocyte membrane EPA content, or the omega-3 index), may identify patients most likely to benefit from supplementation and guide dose titration. The omega-3 index, defined as the EPA+DHA content of red blood cell membranes expressed as a percentage of total fatty acids, has been proposed as a cardiovascular risk biomarker, with values below 4% associated with significantly elevated risk.

Third, the development of novel omega-3 derivatives -including resolvin E1 analogues, synthetic SPM mimetics, and oxylipins derived from EPA and DHA -represents a promising pharmacological frontier aimed at harnessing the pro-resolving and anti-inflammatory properties of omega-3 metabolism for therapeutic benefit beyond lipid modification. Fourth, gut microbiome-mediated metabolism of dietary omega-3s is emerging as a potentially important determinant of inter-individual variability in clinical response, offering a future precision medicine framework for omega-3 therapeutics.

Implications for Clinical Practice

For the practising cardiologist or internist, the contemporary omega-3 evidence base supports a targeted rather than a universal prescribing approach. The key clinical question is no longer ‚should I recommend omega-3 supplementation to my cardiovascular patients?' butrather ‚which of my patients is most likely to benefit, and what formulation and dose should I prescribe?' Hypertriglyceridaemia represents the clearest therapeutic target, and prescription EPA therapy occupies a defined -though incompletely resolved -role in the residual risk management of statin-treated high-risk patients.

For the broader population, the message is one of dietary primacy: regular consumption of oily fish, adherence to a Mediterranean-style dietary pattern, and engagement with established cardiovascular risk factor modification programmes offer proven, safe, and cost-effective approaches to cardiovascular prevention that no supplement can adequately substitute. Omega-3 fatty acids, taken in this context, remain relevant -but their relevance is precise and population-specific rather than universal.

Conclusions

Omega-3 fatty acids, particularly marine-derived EPA and DHA, retain meaningful and clinically defined roles in cardiovascular prevention -but the evidence has matured from broad enthusiasm to targeted application. The key conclusions of this review are as follows:First, the triglyceride-lowering effects of omega-3 PUFAs are robust, dose-dependent, and clinically useful in the management of hypertriglyceridaemia, with potential secondary benefits for pancreatitis prevention and HDL-related lipid modification. Second, high-dose prescription EPA (4 g/day, icosapentaenoic acid ethyl ester) has Level A evidence from REDUCE-IT for cardiovascular event reduction in a specific high-risk population characterised by statin therapy, hypertriglyceridaemia, and established cardiovascular risk. Third, low-dose supplementation (1 g/day) and mixed EPA/DHA formulations have not consistently demonstrated cardiovascular event reduction in contemporarytrials, and the mineral oil comparator controversy remains unresolved. Fourth, ALA from plant sources has insufficient conversion efficiency and evidence to substitute for direct marine omega-3 intake in cardiovascular risk reduction. Fifth, the AF safetysignal with high-dose omega-3 therapy warrants clinical vigilance and should inform shared decision-making with patients. Sixth, dietary strategies centred on regular oily fish consumption and Mediterranean-style dietary patterns remain the cornerstone ofevidence-based cardiovascular prevention, and single-nutrient supplementation should be viewed as an adjunct to, not a replacement for, dietary optimisation.

The question ‚Are omega-3 fatty acids still relevant to cardiovascular prevention?' is answered affirmatively -but with precision. Their relevance lies not in blanket supplementation but in targeted application to defined clinical scenarios, guided by lipid phenotype, existing pharmacotherapy, and individual risk profile. Future research refining themechanistic distinctions between EPA and DHA, validating biomarker-guided dosing strategies, and exploring novel omega-3-derived therapeutic agents will further sharpen the clinical utility of these fascinating and enduring molecules.

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