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OMEGA-3 FATTY ACIDS AND CARDIOVASCULAR DISEASE: A DECADE OF EVIDENCE

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ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide. Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid EPA) and docosahexaenoic acid (DHA), have been proposed as cardioprotective agents through anti-inflammatory, antithrombotic, and plaque- stabilizing mechanisms. This review synthesizes evidence from randomized controlled trials (RCTs) and meta- analyses over the past decade, examining the effects of omega-3 supplementation on cardiovascular outcomes. High-dose purified EPA (4g/day icosapent ethyl) consistently reduces major adverse cardiovascular events (MACE) in high-risk populations [1,2]. Conversely, low-dose or mixed EPA+DHA formulations show variable or neutral results [3,4]. Mechanistic, biomarker, and imaging studies support biological plausibility of benefit [5], while safety signals- particularly increased risk of atrial fibrillation- should be considered [2,6]. Formulation, dosing, and patient selection are critical for optimizing cardiovascular outcomes.

KEYWORDS

Omega-3 Fatty Acids, Cardiovascular Disease, EPA, DHA, Atherosclerosis, Arrhythmia, Meta-Analysis, Supplementation, Triglycerides

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1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, accounting for nearly 18 million deaths annually according to the World Health Organization [7]. The global burden of ischemic heart disease, stroke, and heart failure continues to rise, largely due to population aging, unhealthy diets, and sedentary lifestyles. Despite major advances in pharmacotherapy and preventive cardiology, residual cardiovascular risk persists even among patients receiving optimal statin therapy [8]. Therefore, identifying safe and effective nutritional or pharmacological interventions remains a public health priority.

On area of increasing scientific interest involves the potential cardioprotective role of omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapenthaenoic acid (EPA) and docosahexaenoic acid (DHA). These long-chain fatty acids are primarily obtained from marine sources such as fatty fish (e.g., salmon, sardines, mackerel) and certain algae [9]. α-Linolenic acid (ALA), a plant-derived omega-3 fatty acid found in flaxseed and walnuts, can be endogenously converted to EPA and DHA, though the conversion rate in humans is inefficient (typically <10%) [10]. Biochemically, EPA and DHA are incorporated into cellular membranes, influencing membrane fluidity, ion channel function, and eicosanoid synthesis. They serve as precursors for anti-inflammatory and pro-resolving lipid mediators - resolvins, protectins, and maresins - which modulate inflammation, platelet aggregation, and endothelial function [11]. These mechanisms suggest several potential pathways through which omega-3 fatty acids might reduce cardiovascular risk.

The hypothesis that omega-3 fatty acids confer cardiovascular protection originated from early observational studies in the 1970s. Research among Greenlandic Inuit populations revealed low rates of coronary heart disease despite hugh dietary fat intake, leading to the seminal work of Dyerberg and Bang [12]. Subsequent clinical trials, including the DART (Diet and Reinfarction Trial,1989) and GISSI-Prevenzione (1999) studies, demostrated reductions in mortality and sudden cardiac death among patients who consumed fish oil supplements after myocardial infraction [13,14]. These early finding shaped the perception of omega-3 fatty acids as cardioprotective nutrients.

However, more recent randomized controlled trials (RCTs) have yielded conflicting results, challenging the university of those early conclusions. Large, contemporary trials such as REDUCE-IT (Bhatt et al., 2019), STRENGTH (Nicholls et al.,2020) and VITAL (Manson et al., 2019) producted heterogeneous outcomes

despite similar study design. While REDUCE-IT demonstrated a 25% reduction in major adverse cardiovascular events (MACE) with high- dose purified EPA (4g/day of icosapent ethyl) [1], the STRENGTH and VITAL studies - using mixed EPA+DHA formulations - found no significant benefit [2,3]. Such discrepancies have reignited debate regarding the differential biological activity of EPA versus DHA, the optimal dosing strategy, and the influence of background statin therapy or baseline triglyceride levels.

This variability in clinical outcomes highlights a critical research gap: the need to clarify the conditions under which omega-3 fatty acids exert cardioprotective effects, the relative efficacy of different formulations, and the mechanistic basis of their action. Furthermore, emerging data suggest potential adverse effects, such as a higher incidence of atrial fibrillation at very high doses, warranting careful re-evaluation of safety profiles [15].

Therefore, the aim of this reviewis to systematically evaluate the most recent clinical and mechanistic evidance regarding the effects of omega-3 fatty acid supplementation on cardiovascular diseases. Special attention is given to distinguishing the roles of EPA and DHA, exploring potential dose-response relationships, and identifying patient populations that may derive the greatest benefit.

2. Materials and Methods

A systematic search was conducted in PubMed, Scopus, Web of Science and Cochrane Library for studies published between January 2015 and October 2025. Search terms included: “omega-3 fatty acids”, “EPA”, “DHA”, “icosapent ethyl”, “cardiovascular disease”, “myocardial infarction,” “stroke,” “heart failure,” “atrial fibrillation,” “randomized controlled trial,” and “meta-analysis.”

Inclusion criteria:

- RCTs, systematic reviews or meta-analyses
- Adults ≥18 years with or at risk for CVD
- Intervention: omega-3 supplementation (EPA, DHA, or combination)
- Comparator: placebo or standard therapy
- Outcomes: MACE, myocardial infraction, stroke, heart failure, arrhythmia
- English language, full text

Exclusion criteria:

- Observational studies, editorials, abstracts
- Non-cardiovascular outcomes
- Animal or in vitro studies

3. Research Results

3.1. REDUCE-IT Trial (2019)

The REDUCE-IT trial enrolled 8,179 statin-treated patients with elevated triglycerides (135-499 mg/dL) and either established cardiovascular disease or diabetes with additional risk factors. Participants received icosapent ethyl (4 g/day of highly purified EPA) or mineral-oil placebo for a median of 4.9 years.

Icosapent ethyl reduced the risk of the composite primary endpoint- cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina- by 25% compared with placebo (HR 0.75; 95% CI 0.68-0.83; $p < 0.001$) [1].

Subsequent analyses confirmed consistent benefits across subgroups and a 30% reduction in total (first+recurrent) events [16,17].

3.2. STRENGHT Trial (2020)

The STRENGTH trial randomized 13,078 high-risk patients receiving statins to omega-3 carboxylic acids (4 g/day, a mixture of EPA+DHA) or corn-oil placebo. After 42 months of follow-up, the study was terminated for futility. There was no significant difference in major adverse cardiovascular events (HR 0.99; 95% CI 0.90-1.09; $p = 0.84$) [2].

A higher incidence of atrial fibrillation was observed in the omega-3 group, suggesting a possible dose-related pro-arrhythmic effect [2].

3.3. VITAL Trial (2019)

In the VITAL primary-prevention trial, 25,871 healthy adults were assigned to 1 g/day of omega-3 (460 mg EPA+380 mg DHA) or placebo for 5.3 years. Supplementation did not significantly reduce major cardiovascular events (HR 0.92; 95% CI 0.80-1.06) [3].

However, subgroup analysis indicated potential benefit for individuals with low baseline fish intake and for African-American participants [3].

3.4. JELIS Trial (Post-hoc Analyses, 2020 Update)

The Japan EPA Lipid Intervention Study (JELIS) originally demonstrated that 1.8 g/day EPA added to statin therapy reduced major coronary events by 19% among Japanese patients with hypercholesterolemia [18].

Recent re-analyses confirmed long-term benefit, particularly in patients with elevated triglycerides and low HDL cholesterol, highlighting the synergistic role of purified EPA in high-risk dyslipidemic populations [19].

3.5. OMENI Trial (2020)

The OMEMI trial evaluated 1.8 g/day of combined EPA+DHA in 1,027 elderly post-myocardial infarction patients (mean age = 75 years). After 24 months, there was no reduction in composite cardiovascular events, but a trend toward increased atrial fibrillation [20].

3.6. EVAPORATE Trial (2020)

The EVAPORATE mechanistic imaging study investigated the effect of icosapent ethyl (4 g/day) on coronary atherosclerotic plaque progression using serial coronary CT angiography.

After 18 months, patients receiving EPA exhibited significant regression of low-attenuation plaque volume (-17%) versus progression in the placebo group (+109%) [6].

These findings support plaque-stabilizing and anti-inflammatory mechanisms of EPA beyond triglyceride lowering.

3.7. ASCEND Trial (2018)

The ASCEND trial enrolled 15,480 patients with diabetes but no known CVD. Participants received 1 g/day omega-3 (460 mg EPA+380 mg DHA) or placebo for 7.4 years. There was no significant difference in serious vascular events (8.9% vs 9.2%; $p = 0.55$) [21].

3.8. Meta-analyses (2020-2024)

3.8.1 Aung et al., 2018 (JAMA Cardiology)

A pooled analysis of 10 RCTs ($n = 77,917$) found no significant reduction in fatal or nonfatal coronary heart disease with standard-dose omega-3 supplementation [22].

3.8.2 Bernasconi et al., 2020 (JAHA)

A meta-analysis of 40 studies ($n > 135,000$) concluded that omega-3 supplementation was associated with a 13% lower risk of myocardial infarction and 8% lower risk of coronary death, with greater benefits at doses ≥ 1 g/day [5].

3.8.3 Hu et al., 2022 (Eur Heart J)

A dose-response meta-analysis of 149,051 participants showed progressive risk reduction for cardiovascular events with increasing omega-3 intake, especially for EPA-only interventions [5].

3.8.4 Qi et al., 2023 (Eur J Prev Cardiol)

An updated meta-analysis of 17 RCTs reported that high-dose omega-3 supplementation (>4 g/day) was linked to reduced ischemic events but higher risk of atrial fibrillation [23].

4. Discussion

The current body of evidence indicates that omega-3 fatty acids, particularly high dose purified EPA, confer meaningful cardiovascular benefits in specific high-risk populations. The REDUCE-IT Trial demonstrated a 25% reduction in major adverse cardiovascular events (MACE) among statin-treated patients with elevated triglycerides, confirming the clinical relevance of targeted omega-3 therapy [1]. Conversely, trials using mixed EPA+DHA formulations, such as STRENGTH and VITAL, have produced neutral or variable outcomes, suggesting that formulation and dosage are critical determinants of efficacy [2,3].

4.1 Mechanistic Consideration

EPA and DHA, while both long-chain omega-3 fatty acids, differ in biochemical properties and mechanisms of action. EPA is more potent in producing anti-inflammatory lipid mediators (resolvins, protectins, maresins) and exhibits superior plaque-stabilizing effects, potentially explaining the robust outcomes in REDUCE-IT compared to trials using EPA+DHA mixtures [5,6]. DHA, while beneficial for membrane fluidity and triglyceride reduction, may partially counteract EPA's anti-inflammatory signaling, which could account for the less consistent results in mixed formulations [24].

Mechanistic studies, including the EVAPORATE trial, support EPA's ability to slow low-attenuation plaque progression and promote regression independent of LDL-C lowering, suggesting pleiotropic cardiovascular effects that go beyond lipid modification [5,25]. Systematic reviews and meta-analyses further corroborate that high-dose EPA reduces coronary events and revascularization, whereas mixed formulations provide more modest benefits [10,27].

4.2 Safety Profile

High-dose omega-3 supplementation, particularly EPA, is generally well tolerated, but recent trials report a modest increase in atrial fibrillation (AF) [1,2,5]. In REDUCE-IT and STRENGTH, AF incidence was higher in the intervention groups, although most episodes were non-severe. Clinicians should weigh this risk, especially in patients with pre-existing AF or high arrhythmia risk and monitor accordingly [4].

4.3 Population Considerations

Efficacy appears greatest in secondary prevention populations- patients with established ASCVD, diabetes with additional risk factors, or persistent hypertriglyceridemia despite statin therapy [1,5]. In primary prevention trials like VITAL, the benefit was limited to subgroups with low baseline fish intake, highlighting the importance of baseline dietary exposure and residual risk profile [3,13]. This indicates that omega-3 therapy should be personalized, targeting those most likely to derive cardiovascular benefit.

4.4 Clinical Implications

The evidence suggests that high-dose, purified EPA supplementation (4 g/day) should be considered as an adjunct to standard therapy in high-risk patients with elevated triglycerides [1,5]. Mixed EPA+DHA formulations at lower doses, often available over-the-counter, may not confer the same level of cardiovascular protection, emphasizing the distinction between prescription-grade and nutraceutical omega-3 products [26].

Key clinical considerations include:

- Patient risk profile (primary vs secondary prevention)
- Baseline triglycerides and residual lipid risk
- Choice of omega-3 formulation (EPA-only vs EPA+DHA)
- Potencial for adverse events, particularly atrial fibrillation

4.5 Summary

In summary, high-dose purified EPA demonstrates consistent cardiovascular benefit, mechanistically linked to anti-inflammatory, anti-thrombotic, and plaque-stabilizing effects [1,5,25]. Mixed EPA+DHA formulations and lower doses show less consistent efficacy, reinforcing the need for targeted, evidence-based supplementation. Careful patient selection, dosing, and monitoring of arrhythmia risk are essential to optimize outcomes [2,5,4].

5. Conclusions

The accumulated evidence from the past decade indicates that omega-3 polyunsaturated fatty acids (PUFAs) exert clinically relevant but context-dependent effects on cardiovascular health [1, 5, 9, 24-26]. The strongest and most consistent benefit is observed with high-dose pure eicosapentaenoic acid (EPA) formulations, particularly icosapent ethyl (4 g/day), which significantly reduce major adverse cardiovascular events in patients with established atherosclerotic cardiovascular disease (ASCVD) or elevated triglyceride levels despite statin therapy [1, 6, 16-18].

In contrast, formulations combining EPA and docosahexaenoic acid (DHA), typically administered at lower doses, have demonstrated neutral or inconsistent cardiovascular outcomes in large-scale randomized controlled trials [2-4, 20-22]. This divergence likely reflects differences in molecular actions, pharmacokinetics, and interactions between the two fatty acids [8,9,11]. EPA primarily mediates anti-inflammatory, anti-thrombotic, and plaque-stabilizing effects, while DHA may raise LDL cholesterol or interfere with EPA's incorporation into membrane phospholipids [9,24,25].

Mechanistically, omega-3 fatty acids reduce vascular inflammation, stabilize atherosclerotic plaques, and modulate lipid metabolism and cardiac electrophysiology [8, 9, 11, 24]. However, recent data indicate a modest increase in atrial fibrillation (AF) risk at high doses (>4 g/day), emphasizing the need for careful patient selection and dose optimization in clinical practice [23, 24, 26].

From a public health perspective, omega-3 intake remains an essential component of a cardioprotective diet, especially through the consumption of oily fish or algal sources [7, 9, 10, 12-14]. Nevertheless, the use of pharmacological omega-3 supplementation should be reserved for individuals with residual cardiovascular risk despite guideline-directed medical therapy [1, 5, 15, 17, 18].

5.1 Clinical Implications

- High-dose purified EPA (icosapent ethyl) is recommended as adjunct therapy for high-risk patients with elevated triglycerides on statins [1, 6, 16-18].
- Low-dose mixed EPA+DHA supplements are not indicated for primary prevention of cardiovascular disease [2-4, 20-22].

- Physicians should monitor for atrial fibrillation and tailor therapy to patient-specific risk profiles [23, 25, 26].

5.2 Limitations

This review is based primarily on published RCTs and meta-analyses, most of which were conducted in North American and Asian populations; extrapolation to other ethnic or dietary contexts should be made with caution [2-4, 18, 20, 22]. Furthermore, variability in formulations, background diet, and placebo oils complicates direct comparisons between trials [3-5, 21, 25].

In conclusion, omega-3 fatty acids - particularly high dose, purified EPA- represent a valuable adjunct to modern cardiovascular prevention, with clear benefits in appropriately selected patients. Future research focusing on personalized omega-3 strategies will be crucial to optimize outcomes on minimalize risks in cardiovascular care.

DISCLOSURE

Authors' contribution:

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