

Medical Science

To Cite:

Kapler M, Badura B. The impact of Omega-3 fatty acids on coronary artery disease: A literature review. *Medical Science* 2025; 29: e39ms3537
doi: <https://doi.org/10.54905/disssi.v29i156.e39ms3537>

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Peer-Review History

Received: 10 October 2024

Reviewed & Revised: 14/October/2024 to 13/February/2025

Accepted: 17 February 2025

Published: 21 February 2025

Peer-review Method

External peer-review was done through double-blind method.

Medical Science

pISSN 2321-7359; eISSN 2321-7367



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The impact of Omega-3 fatty acids on coronary artery disease: A literature review

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ABSTRACT

Omega-3 fatty acids (ω -3 FAs) have gained prominence for their potential cardioprotective effects, particularly in coronary artery disease (CAD). Observational findings in high fish-consuming populations suggested reduced cardiovascular events, setting the stage for trials such as GISSI-Prevenzione and JELIS, which linked ω -3 FAs to lowered cardiac risk. Most notably, the REDUCE-IT trial demonstrated that 4 g/day of purified eicosapentaenoic acid (EPA) significantly reduced major adverse cardiovascular events in statin-treated patients with elevated triglycerides. Proposed mechanisms include attenuation of inflammation, plaque stabilization, and triglyceride reduction, although not all research is consistent. Trials like VITAL and STRENGTH showed mixed outcomes, likely reflecting variations in formulations (EPA alone vs. EPA+DHA), dosages, and even placebo oils. Elevated doses of ω -3 FAs carry a small but notable risk of atrial fibrillation, though gastrointestinal side effects remain the most common concern. Overall, high-dose EPA formulations appear effective in reducing residual cardiovascular risk. Further research is warranted to optimize dosing, identify patient subgroups most likely to benefit, and clarify the molecular pathways that underpin these cardioprotective properties.

Keywords: Omega-3 fatty acids, Atherosclerosis, Triglycerides, Coronary artery disease

1. INTRODUCTION

Omega-3 fatty acids (ω -3 FAs) are a heterogeneous group of polyunsaturated fatty acids (PUFAs) with at least one carbon to carbon double bond between the third and fourth carbon atoms from the methyl end, also called the omega end of the fatty acid chain, where the methyl carbon is considered carbon number one (Calder and Yaqoob, 2009). They have been under increasing investigation due to their key role in the human body, mostly in cardiovascular health (Nagao and Yanagita, 2005). PUFAs and ω -3 FAs are fundamental elements of cell membranes. Their role is to influence membrane fluidity, receptor functioning, and the activity of ion channels. By shaping the biophysical properties of

membranes, these fatty acids affect numerous cell signaling pathways, potentially influencing both inflammatory and lipid metabolic processes.

The primary forms of ω -3 FAs include α -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Cholewski et al., 2018). ALA is plant-derived and is found in foods such as flaxseed, chia seeds, and walnuts. EPA and DHA are largely derived from marine sources, including fatty fish such as salmon, mackerel, and sardines. When consumed, EPA and DHA can be incorporated into various tissues, most notably in the phospholipids of cell membranes in the cardiovascular, nervous, and immune systems. The significance of ω -3 FAs first came to prominence in the 1970s when Bang and Dyerberg observed that Greenland Inuit populations, despite a high-fat dietary intake, exhibited markedly low rates of cardiovascular disease (CVD) (Bang and Dyerberg, 1972).

They attributed this paradox to the dietary abundance of marine ω -3 FAs. Since these foundational observations, the scientific community has investigated myriad ways in which ω -3 FAs might confer health benefits, with particular emphasis on their roles in modulating inflammation, maintaining cellular membrane integrity, and regulating lipid metabolism (Calder, 2012; British Nutrition Foundation, 1992). Among cardiovascular diseases, coronary artery disease (CAD) is one of the most studied conditions in relation to ω -3 FA intake (Jain et al., 2015). CAD is one of the leading causes of morbidity and mortality worldwide.

This condition is associated with genetic predispositions and multiple lifestyle risk factors, that include low physical inactivity, diet, smoking, and chronic stress. Considering the global prevalence of CAD and healthcare costs that this causes, research into effective preventive and therapeutic strategies remains a priority (Dalen et al., 2014). Dietary and pharmacological interventions targeting modifiable risk factors—particularly dyslipidemia and chronic inflammation—are essential. Within this context, ω -3 FAs stand out as a potentially valuable component of CAD prevention and management.

Aim of the Study

This review aims to evaluate current research on the effectiveness of ω -3 FAs in preventing and managing CAD, with a primary focus on atherosclerosis. By examining optimal dosages, formulations (e.g., EPA vs. EPA+DHA), and underlying mechanisms of action, this review provides a comprehensive overview of how ω -3 FAs may influence the pathophysiology of CAD, reduce major adverse cardiovascular events (MACE), and balance potential risks such as bleeding complications or atrial fibrillation.

2. METHODOLOGY

A targeted literature review was conducted using PubMed, Google Scholar, and the Cochrane Library. Publications from 1970 to September 2024 were reviewed using search terms such as “omega-3 fatty acids”, “EPA”, “DHA”, “cardiovascular disease”, “REDUCE-IT”, and “coronary artery disease”. Human studies—including randomized trials, observational data, and meta-analyses—examining the role of ω -3 FAs in CAD prevention or treatment were primarily selected. Non-English or unrelated studies were excluded. Key findings were synthesized to present an updated overview of ω -3 FAs in CAD.

3. RESULTS AND DISCUSSION

Coronary Artery Disease (CAD)

Pathophysiology

Coronary artery disease (CAD), also referred to as ischemic heart disease, is a condition in which the coronary arteries are narrowed or blocked. This often occurs as a result of atherosclerosis—a chronic progressive disease of the arterial wall characterized by plaque buildup (Libby and Theroux, 2005). In earlier decades, atherosclerosis was viewed purely as a cholesterol storage issue, wherein elevated serum lipids would accumulate in arterial walls. However, it is now widely recognized as a dynamic inflammatory process. Inflammatory signals, endothelial dysfunction, and dyslipidemia converge to facilitate the subendothelial deposition of lipid-laden macrophages (foam cells), eventually leading to the formation of atherosclerotic plaques (Moore et al., 2013; Stary et al., 1994).

The atherosclerotic process can be triggered by several factors, including hypertension, hyperlipidemia, smoking, diabetes mellitus, and other stressors on the vascular endothelium. These stressors promote the subendothelial accumulation of apolipoprotein B-containing lipoproteins (ApoB-LPs)—primarily low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Over time, smooth muscle cells migrate from the media to the intima, proliferate, and synthesize extracellular matrix components that form the

fibrous cap of the plaque (Moore and Tabas, 2011; Williams and Tabas, 1995). The plaque can either slowly enlarge, impeding blood flow, or become unstable and prone to rupture.

In the event of rupture, prothrombotic components (e.g., tissue factor) are exposed to circulating platelets and coagulation factors, which can result in an acute thrombus and possible myocardial infarction (Morita, 2016; Pirillo et al., 2023). Along with lipid infiltration, inflammatory mediators, such as cytokines (IL-6, TNF- α) and chemokines, further exacerbate plaque progression and instability (Jonasson et al., 1986). Endothelial dysfunction, indicated by impaired nitric oxide production, is another factor that contributes to CAD pathogenesis. The complexity of CAD pathophysiology highlights the need for strategies that can modify lipids and reduce chronic inflammation.

Symptoms

Clinically, CAD primarily causes symptoms such as pressure, tightness, or pain in the chest, which may radiate to the arms, neck, jaw, or back. These symptoms collectively called angina pectoris are typically triggered by increased myocardial oxygen demand (e.g., physical exertion) or other stress factors such as emotional upset (Epstein, 1971, Kelemen, 2006). Stable ischemic heart disease (SIHD) presents with predictable, exertion-induced angina relieved by rest or nitroglycerin. In contrast, acute coronary syndrome (ACS), encompassing unstable angina, non-ST-elevation MI (NSTEMI), and ST-elevation MI (STEMI), is characterized by more severe, persisting or sudden onset symptoms, often occurring at rest and potentially including dyspnea or syncope.

Management strategies for SIHD often rely on risk factor control—lifestyle modifications (diet, exercise, smoking cessation), medications (including β -blockers, ACE inhibitors, statins, and antiplatelet agents), and sometimes revascularization procedures. In ACS, prompt assessment and timely intervention—either percutaneous coronary intervention (PCI) or surgical coronary artery bypass grafting (CABG) - can be lifesaving (Shahjehan et al., 2024).

Prevalence

CAD is a significant public health concern because of its high prevalence and mortality rates. In the United States, one in every four deaths is still caused by CAD (Benjamin et al., 2019). After decades of decline in cardiovascular mortality, recently researchers observe the reverse trends. This emphasizes the persistent challenge of controlling CAD risk factors. Approximately 20.5 million (7.1%) adults aged 20 and older in the U.S. are estimated to have CAD (Martin et al., 2024). In Europe overall CVD-related mortality is estimated to cause about 45% of all deaths (Townsend et al., 2016).

Despite some improvements over the years in Western Europe, CAD-related events are responsible for around 20% of all deaths in Europe annually (Nichols et al., 2014). With a multitude of risk factors across many countries and cultures, strategies tailored to regional health systems and dietary practices are crucial. Because of the sheer scale of the disease, interventions that can reduce even a small percentage of CAD risk translate to substantial population-level benefits. Within that framework, exploring adjunctive therapies such as ω -3 FAs to complement standard treatments offers a valuable avenue to further reduce mortality and morbidity.

Omega-3 Fatty Acids (ω -3 FAs)

Overview

PUFAs supplementation, including ω -3 FAs, is essential for human health as the body cannot synthesize them de novo in sufficient quantities. Chemically, ω -3 FAs feature a double bond at the third carbon from the methyl end ($-\text{CH}_3$), leading to multiple degrees of unsaturation (Burdge and Calder, 2015). This structure profoundly affects the fluidity of cell membranes, influencing receptor conformation, ion channel function, and the generation of lipid mediators. There are three primary ω -3 FAs:

α -Linolenic Acid (ALA, 18:3n-3)

ALA is a short-chain ω -3 FA found predominantly in plants such as flaxseed, canola oil, and walnuts. In humans, ALA can be endogenously converted into longer-chain ω -3 FAs—EPA and DHA—but this conversion rate tends to be relatively low, especially in men (Burdge and Calder, 2005). A study by Burdge and Wootton, (2002) suggests young women may have a somewhat higher conversion rate, potentially providing them with relatively more endogenous EPA and DHA.

Eicosapentaenoic Acid (EPA, 20:5n-3)

EPA is a long-chain ω -3 FA found primarily in marine sources. EPA plays a significant role in reducing inflammation and has various cardiovascular benefits (Oliver et al., 2020). Its structure, which includes five double bonds, contributes to its biological activity in reducing the production of inflammatory eicosanoids.

Docosahexaenoic Acid (DHA, 22:6n-3)

DHA, another long-chain ω -3 FA primarily obtained from marine sources, is crucial for neurological and visual development and function. It is abundant in the brain and retina, and its deficiency is associated with cognitive decline and vision problems (Lauritzen et al., 2001). DHA has six double bonds, which makes it highly unsaturated and essential for maintaining the fluidity of cell membranes (Innis, 2007).

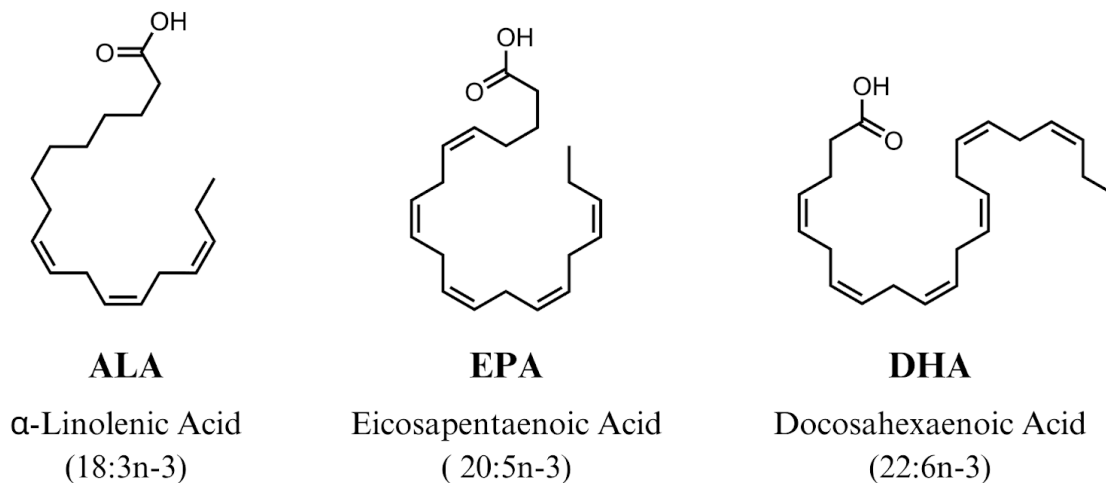


Figure 1 Structure of n-3 polyunsaturated fatty acids (PUFAs)

The Role of Omega-3 Fatty Acids in Coronary Artery Disease

One of the most consistently observed effects of ω -3 FAs is the favorable modulation of lipid profiles, particularly a reduction in triglycerides (TGs). Hypertriglyceridemia is an independent risk factor for CAD, and reducing TG levels can help slow down the atherosclerotic process. The ω -3 FAs are involved in reducing hepatic VLDL secretion and enhancing the clearance of TG-rich lipoproteins, resulting in significant triglyceride lowering. Decreasing TG levels can directly reduce the presence of small, dense LDL particles—a known atherogenic lipoprotein subtype—and can also help lower the overall presence of atherogenic remnant particles. In addition to lowering TGs, EPA in particular may exert a modest effect on other lipid parameters.

Anti-Inflammatory and Plaque-Stabilizing Effects

Chronic inflammation is central to the development and progression of atherosclerosis. Elevated cytokines (e.g., IL-6) and adhesion molecules can promote monocyte recruitment, foam cell formation, and plaque destabilization. ω -3 FAs, especially EPA, have been shown to reduce the production of pro-inflammatory eicosanoids (e.g., leukotriene B4) by competing with arachidonic acid for cyclooxygenase (COX) and lipoxygenase enzymes (Calder, 2012; GISSI-Prevenzione Investigators, 1999).

Additionally, specialized inflammation-resolving mediators such as resolvins, protectins, and maresins, derived from EPA and DHA, help regulate the resolution phase of inflammation. By favoring these anti-inflammatory pathways, ω -3 FAs can contribute to a more stable plaque phenotype with a thicker fibrous cap and reduced necrotic core. The JELIS study in Japan (patients with hypercholesterolemia) offered clinical support for these mechanisms, demonstrating that purified EPA (1.8 g/day) significantly lowered the risk of major coronary events when combined with statin therapy (Yokoyama et al., 2007).

Triglyceride-lowering and Lipid Metabolism

Elevated triglycerides (TGs) are an independent risk factor for cardiovascular disease. High-dose ω -3 FA supplementation (2–4 g/day) has been shown to significantly lower TG levels (15–30% reduction or more), which in turn can reduce the risk of atherogenic remnant lipoproteins (Bhatt et al., 2019; Manson et al., 2019). The mechanism of action of ω -3 FAs involves reducing the hepatic production and secretion of very low-density lipoprotein (VLDL) particles while simultaneously enhancing their clearance.

Antithrombotic Properties

ω -3 FAs may offer mild antithrombotic benefits through multiple routes. First, they can reduce platelet aggregation by lowering the synthesis of thromboxane A₂, a potent platelet agonist. Second, by improving endothelial function, partly via enhanced nitric oxide bioavailability, ω -3 FAs potentially contribute to vasodilation and decreased platelet adhesion (Calder, 2012; Nicholls et al., 2020). Although these effects are not as robust as those seen with dedicated antiplatelet drugs, such as aspirin and P2Y₁₂ inhibitors, they may still modestly lower the tendency for plaque thrombosis and subsequent myocardial infarction.

Clinical Evidence of Omega-3 FAs in CAD Prevention and Management

Observational studies in Greenland Inuit populations formed the initial basis for investigating the cardioprotective properties of marine ω -3 FAs (Bang and Dyerberg, 1972). Subsequent research expanded upon these findings in Western populations. The GISSI-Prevenzione trial examined post-myocardial infarction (MI) patients and found that supplementation with 0.85g per day of ω -3 FAs was associated with a reduction in both all-cause mortality and cardiovascular mortality (GISSI-Prevenzione Investigators, 1999). Despite some limitations, this trial reinforced the case for ω -3 FAs supplementation following acute MI. The JELIS trial, focusing on Japanese patients with hypercholesterolemia, further highlighted the benefit of EPA.

In JELIS, patients receiving 1.8g/day of purified EPA alongside a statin, saw fewer major coronary events compared to those on statin therapy alone (Yokoyama et al., 2007). Notably, the study involved a largely Japanese cohort, traditionally high fish consumers, yet still demonstrated an incremental benefit from additional EPA supplementation. Among the most pivotal and contemporary trials is REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial) (Bhatt et al., 2019). This trial specifically examined icosapent ethyl (IPE), a highly purified EPA derivative, at a dose of 4 g/day in patients with elevated triglycerides (≥ 135 mg/dL and < 500 mg/dL) despite stable statin therapy.

Over 8,000 participants, encompassing those with established cardiovascular disease and those at high cardiovascular risk, were randomly assigned to receive IPE or a mineral oil placebo. Primary Endpoint: A composite of major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. Key Findings include a 25% relative risk reduction for MACE in the IPE group compared to placebo and robust effects on triglyceride reduction and markers of inflammation. An absolute risk reduction of approximately 4.8%, yielding a number needed to treat (NNT) of 21 over a median of 4.9 years.

Crucially, REDUCE-IT used a pure EPA formulation, distinguishing it from other trials that employed a mix of EPA and DHA or lower dosages. This feature has led to discussions around the possibility that high-dose purified EPA exerts unique benefits beyond mere triglyceride lowering—potentially via plaque stabilization and anti-inflammatory actions. Other studies, including VITAL and STRENGTH, offered insights into the complexities of ω -3 FA supplementation:

- VITAL (Vitamin D and Omega-3 Trial) evaluated 1 g/day of marine ω -3 (EPA+DHA) in a primary prevention population. It did not find a statistically significant reduction in major cardiovascular events but did note some secondary benefits, such as reduced myocardial infarction risk in certain subgroups (Manson et al., 2019).
- STRENGTH which employed a mixed EPA+DHA carboxylic acid formulation at 4 g/day in high-risk patients, failed to demonstrate cardiovascular benefit compared to a corn oil placebo (Nicholls et al., 2020). Several explanations have been proposed for these divergent results, including differences in placebo composition (mineral oil vs. corn oil), variations in the ratio and purity of EPA to DHA, and differences in the baseline risk levels of study populations.
- This body of evidence underscores the critical role those specific formulations (e.g., pure EPA vs. EPA+DHA), dosages (4 g/day vs. lower doses), and patient characteristics (presence or absence of hypertriglyceridemia, background statin use) can play in determining clinical outcomes.

Safety Profile and Notable Adverse Effects

Most patients tolerate ω -3 FAs well at standard or moderate dosages. The most common minor adverse effects are gastrointestinal disturbances—such as a fishy aftertaste or mild gastrointestinal upset. Some of the effects can be alleviated by taking supplements with meals or using enteric-coated capsules. Because ω -3 FAs can have a mild antiplatelet effect, there is a theoretical concern about increasing bleeding risk, especially at higher dosages or in combination with anticoagulants. In clinical practice, however, clinically significant bleeding events tied directly to ω -3 FA use appear uncommon. Nonetheless, patients on antiplatelet or anticoagulant therapy should be monitored closely.

The potential association between high-dose ω -3 FAs and an increased incidence of atrial fibrillation (AF) has attracted growing attention. In REDUCE-IT, the incident AF rate was higher in the icosapent ethyl group than in the placebo group (5.3% vs. 3.9%, respectively) (Bhatt et al., 2019). The exact mechanism behind this observation remains under investigation. It may involve changes in atrial membrane electrophysiology or subtle shifts in inflammation and ion handling. While AF risk elevation was moderate, it was statistically significant and should be considered, mainly for patients with known paroxysmal AF or other atrial disorders of conduction.

Optimal Dosage Considerations

Public health guidelines usually recommend 1–2 servings of fatty fish per week that contain roughly 250–500 mg/day of EPA+DHA for the general population (Innis, 2007). This level of intake is generally considered beneficial for overall health and may offer modest cardioprotection. However, individuals with higher cardiovascular risk or established CAD often require pharmacologic doses (2–4 g/day) of ω -3 FAs to achieve therapeutic benefits in triglyceride reduction and potential anti-inflammatory effects. Evidence from trials such as REDUCE-IT points toward the unique advantages of a pure EPA formulation. Compared to combined EPA+DHA supplements, EPA-only therapies appear less likely to increase LDL-C and may yield more pronounced anti-inflammatory effects. While DHA possesses important roles in neurological and retinal health, its potential to elevate LDL-C or interfere with the cardiometabolic actions of EPA is a topic of ongoing debate.

The difference in clinical outcomes between REDUCE-IT and studies like STRENGTH further accentuates the importance of investigating the ratio and purity of ω -3 FA formulations for specific cardiovascular endpoints (Bhatt et al., 2019; Nicholls et al., 2020). Statins remain the cornerstone of dyslipidemia management in CAD. The addition of ω -3 FAs, particularly high-dose EPA, seems to reduce residual cardiovascular risk in patients who have persistent hypertriglyceridemia despite statin therapy. This complementarity suggests a mechanistic synergy where statins primarily reduce LDL-C and systemic inflammation, while EPA specifically addresses high TG levels and some inflammatory processes not fully suppressed by statins alone. Key findings from the reviewed studies are summarized in (Table 1).

Table 1 Summary of the key points.

Aspect	Key Findings
Population Evidence	Observational studies in Inuit populations linked high ω -3 FA consumption to low CAD prevalence.
Clinical Trials	GISSI-Prevenzione: ω -3 FAs reduced cardiovascular and all-cause mortality in post-MI patients. JELIS: EPA supplementation with statins reduced major coronary events. REDUCE-IT: High-dose EPA significantly reduced MACE by 25% in statin-treated, high-risk populations.
Mechanisms of Action	Triglyceride reduction, anti-inflammatory effects, plaque stabilization, and antithrombotic properties.
Safety Concerns	High doses linked to a small but notable risk of atrial fibrillation.
Optimal Dosage	Therapeutic doses: 2–4 g/day for CAD prevention; EPA

	formulations show superior outcomes.
Controversial Findings	Mixed results in trials like VITAL and STRENGTH due to differences in formulations and populations.

Future Directions and Research Gaps

Despite the promising data from high-dose EPA trials, several unanswered questions remain. **Mechanistic Studies:** Although anti-inflammatory and plaque-stabilizing mechanisms are proposed, additional in-depth studies are needed to fully elucidate how EPA exerts its plaque-regressing or stabilizing effects at the molecular and cellular levels. **Biomarkers and Personalized Medicine:** Certain populations may benefit more from ω -3 FA supplementation than others. Future investigations could focus on identifying biomarkers that predict response to therapy—such as baseline TG levels, inflammatory markers, or specific genetic polymorphisms.

Long-Term Safety: The link between high-dose ω -3 FAs and atrial fibrillation warrants ongoing surveillance. Large-scale registries and post-marketing studies could provide further clarity on the incidence, risk factors, and management of ω -3 FA-related arrhythmias. **Optimal Formulation and Combination:** Whether a specific EPA: DHA ratio (or purely EPA) is definitively superior for all high-risk patients needs continued investigation. Additionally, the role of combining ω -3 FAs with emerging lipid-lowering therapies (e.g., PCSK9 inhibitors) is an area of active exploration.

4. CONCLUSION

Omega-3 fatty acids, especially when administered as high-dose EPA formulations, have emerged as a promising tool for the primary prevention and management of coronary artery disease. Several studies, from early Inuit population studies to randomized controlled trials like REDUCE-IT, underline ω -3 FA's capacity to significantly reduce major adverse cardiovascular events when used alongside other well-established therapies. These benefits extend beyond just triglyceride-lowering and include anti-inflammatory, antithrombotic, and plaque-stabilizing abilities that can slow down the atherosclerotic process. However, clinicians must be mindful of potential side effects, notably a slightly increased risk of atrial fibrillation with high-dose regimens, as well as mild gastrointestinal complaints.

The choice of ω -3 FA formulation—especially the distinction between pure EPA and combinations of EPA+DHA—also appears to be pivotal in achieving favorable cardiovascular outcomes. Going forward, further research is expected to refine optimal dosing regimens, clarify patient subgroups most likely to benefit, and explore additional synergistic effects with novel lipid-lowering and anti-inflammatory interventions. Continued collaboration between researchers, clinicians, and public health experts will be key to translating these insights into safe, targeted, and broadly accessible strategies for preventing and managing coronary artery disease worldwide.

Author's Contributions

Conceptualization: Marta Kapler

Methodology: Marta Kapler

Formal analysis: Barbara Badura

Data curation and investigation: Marta Kapler, Barbara Badura

Original draft: Marta Kapler

Review & editing: Barbara Badura

All authors have read and agreed with the final, published version of the manuscript.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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