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Omega-3 Fish Oil Safety and Efficacy for Cardiac Patients

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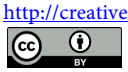

Abstract

Eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] and other omega-3 fatty acids have been extensively studied for their cardiovascular importance. They have anti-inflammatory, antiarrhythmic, and lipid-modulating properties. Omega-3 supplementation has been intensely studied for its effect on cardiac health in relation to its efficacy and safety in preventing cardiac events. Insights into its benefits and associated risks, in particular, are based on randomized controlled trials and systematic reviews, especially when high-dose EPA formulations are recommended. Although there have been conflicting studies, there appears to be some evidence that high-dose EPA formulations may reduce cardiovascular events. Their application is further complicated by safety concerns [increased atrial fibrillation risk and bleeding tendencies]. Nevertheless, tailored omega-3 interventions are likely to be of significant benefit to certain subgroups, such as those with high triglycerides or a high cardiovascular risk. The data suggest that omega-3 supplementation should be taken carefully to avoid the risks of therapeutic benefit. A foundation for advancing personalized cardiovascular therapies and improving clinical outcomes is given by additional insights into dosage, formulation, and patient characteristics.

Subject Areas

Internal Medicine, Cardiology

Keywords

Lipid Modulation, Atrial Fibrillation, Docosahexaenoic Acid [DHA], Eicosapentaenoic Acid [EPA], High-Dose EPA Formulations, Omega-3 Fatty

Acids, Cardiovascular Disease

1. Introduction

Cardiovascular diseases [CVDs] are major causes of mortality worldwide and are mainly influenced by hypertension, diabetes, and hyperlipidemia. Such overlaps between risk factors suggest that comprehensive intervention is required. Omega-3 fatty acids derived from dietary sources such as fish oils have been of interest for their anti-inflammatory, lipid-lowering, and antiarrhythmic properties [1]. Initial studies showed that observational studies have been found to have cardioprotective effects; however, RCTs have resulted in contradictory mixed results [2]. To achieve these, effective interventions are needed to find the right patient subgroups and therapeutic strategies for the profiles. Formulating targeted recommendations requires understanding the biological differences between EPA and DHA and their respective benefits. The supplementation of omega-3 fish oils, mainly eicosapentaenoic acid (EPA) and docosasaenoic acid (DHA), has been widely designed for its potential protective effects against cardiovascular diseases (CVD). Both the EPA and the DHA have distinct biological properties that can differentiate the cardiovascular results in a differentiated way. The EPA is mainly known for its anti-inflammatory effects and the ability to reduce triglycerides, while the DHA is crucial for the integrity of the cell membrane and has been associated with beneficial changes in heart rate and rhythm [3]. Numerous studies have reported the safety and effectiveness of the integration of Omega-3 in heart patients. A full systematic review and a meta-analysis highlighted that Omega-3 fatty acids can significantly reduce cardiovascular events in high-risk populations, although the effects can vary depending on the specific type of fatty acid [4]. A study in 2017 provided further insights, underlining the need for adequate dosage and an adequate formulation to maximize the benefits while minimizing potential adverse effects [5]. In light of these results, the focused research demand formulated for this review is: "How the differential biological effects of the EPA and the DHA in Omega-3 fish oil influence their safety and effectiveness in heart patients"? Tackling this question will not only clarify the roles of these fatty acids but will also help them adapt to future therapeutic approaches for cardiovascular management.

2. Materials And Methods

2.1. Search Strategy and Study Selection

A systematic search of electronic databases, including PubMed, Cochrane Library, and Embase, was conducted to identify peer-reviewed articles published from 2012 to 2025. Search terms included "omega-3 fatty acids," "cardiovascular disease," "EPA," and "DHA."

Inclusion criteria entailed randomized controlled trials (RCTs), meta-analyses, and systematic reviews focused on omega-3 supplementation in cardiac patients. Exclusion criteria included studies on participants with significant co-morbidities unrelated to cardiovascular health, non-peer-reviewed publications, and studies unrelated to human subjects

2.2. Methods

A systematic review of supplementation with omega-3 for CVD outcomes, including RCTs, meta-analyses, and systematic reviews, was conducted on the peer-reviewed articles. The emphasis was on trials of both primary and secondary prevention strategies regarding dosage, formulation, and patient demographics. Study design, participant characteristics, dosage, outcomes, and safety profiles were emphasized for data extraction. Findings were limited to peer-reviewed publications from 2012-2025 to ensure that findings are relevant to current clinical practice. (See Table 1) Studies were also critically appraised to summarize conclusions and to assess the methodological rigor and potential bias. This review synthesized evidence from the literature of studies investigating the reliability and consistency of reported outcomes to provide a comprehensive review of omega-3s and cardiovascular health.

Table 1. Summary of included studies.

Study	Design	Participants	Dosage	Key findings	Quality assessment
Kotwal *et al.* (2012)	Meta-analysis	77,917 individuals	Varies	Omega-3s may reduce cardiovascular risk	High
Aung *et al.* (2018)	Meta-analysis	77,917 individuals	Varies	No significant reduction in major CV events	High
Yan *et al.* (2024)	Systematic review & meta-analysis	Mixed population	Varies	Confirms benefits in CVD prevention	High
Khan *et al.* (2021)	Systematic review & meta-analysis	Mixed population	Varies	Omega-3s linked to lower CV risk	Moderate
Siscovick *et al.* (2017)	Science advisory	General population	1 - 4 g/day	AHA recommends Omega-3s for CV health	High
Jaca *et al.*	Review	Mixed population	Varies	No clear primary/secondary prevention benefit	High
Abdelhamid *et al.*	Review	Mixed population	Varies	No strong evidence for prevention	High
Rawat *et al.*	Observational study	Cardiac patients	Varies	Suggests safety and efficacy in heart patients	Moderate

Continued

Skulas-Ray *et al.* (2019)	**Science advisory**	**Hypertriglyceridemia patients**	**2 - 4 g/day**	**AHA supports Omega-3s for lowering triglycerides**	**High**
Bernasconi *et al.* (2020)	Meta-analysis	Mixed population	Varies	High-dose Omega-3s improve outcomes	High
Sherratt *et al.* (2023)	Review	General population	Varies	Ongoing debate on effectiveness	Moderate
Abdelhamid *et al.* (2021)	Meta-analysis	Atrial fibrillation patients	Varies	Omega-3s linked to increased AF risk	High
Glück & Alter (2016)	Review	Heart failure and arrhythmia patients	Varies	Discusses mechanisms and clinical	Moderate
Kotwal *et al.* (2012)	Meta-analysis	77,917 individuals	Varies	Omega-3s may reduce cardiovascular risk	High
Aung *et al.* (2018)	Meta-analysis	77,917 individuals	Varies	No significant reduction in major CV events	High
Yan *et al.* (2024)	Systematic review & meta-analysis	Mixed population	Varies	Confirms benefits in CVD prevention	High
Khan *et al.* (2021)	Systematic review & meta-analysis	Mixed population	Varies	Omega-3s linked to lower CV risk	Moderate
Siscovick *et al.* (2017)	Science advisory	General population	1 - 4 g/day	AHA recommends Omega-3s for CV health	High
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Sherratt *et al.* (2023)	Review	General population	Varies	Ongoing debate on effectiveness	Moderate
Abdelhamid *et al.* (2021)	Meta-analysis	Atrial fibrillation patients	Varies	Omega-3s linked to increased AF risk	High
Glück & Alter (2016)	Review	Heart failure and arrhythmia patients	Varies	Discusses mechanisms and clinical	Moderate

2.3. Quality Assessment

The methodological quality of included studies was evaluated using the Cochrane Risk of Bias Tool, considering factors such as randomization, blinding, and size of sample. Studies were classified as high, moderate, or low quality based on these criteria.

2.4. Data Analysis

Overall, the best evidence was chosen based on how consistent, important, and high-quality the evidence was that omega-3 prevented primary or secondary CVD. The extracted statistical outcomes included relative risk [RR], confidence intervals [CI], and incidence rates in order to gain insight into cardiovascular outcomes from extraction, interpretation, and understanding of the statistics. The objective was to measure the benefits and detriments of EPA compared to EPA and DHA formulations. A critical review of safety profiles of adverse events of different supplementation regimens was also made regarding atrial fibrillation and bleeding risk. Systematic reliability assessment was applied to methodological rigor in sample study size, duration, and control variables. The factors considered here were baseline triglyceride levels, the current treatments being given, and individual patient characteristics, and that was sorted so we could get a little bit more nuanced information. This meticulous investigation was performed to determine the efficacy and safety of omega-3 supplementation given the divergent function omega-3 supplementation plays among different populations and clinical settings

3. Results

3.1. Primary Prevention

Omega-3 fatty acids showed little efficacy in primary prevention studies in reducing major cardiovascular events. The Cochrane Review, which included 112,059 participants in 37 RCTs, found no effect of omega-3 on all-cause mortality, cardiovascular mortality, or major vascular events [6]. However, subgroups with high triglyceride levels or starting baseline low in omega were found to have very small benefits [7]. That implies that although omega-3 supplementation has no general benefit in people at low risk, some benefits might be measurable in targeted intervention. For example, patients with metabolic syndrome or prediabetes who received modest reductions in cardiovascular events on high doses of EPA [2]. However, these findings do not generalize and suggest that omega-3 may address particular risk profiles.

The impact of Omega 3 fish oil on cardiac health is analyzed, with major findings. The supplementation of Omega-3 reduces the risk of myocardial infarction by 13% and coronary heart disease [8]. In addition, the Omega-3 index plays a significant role, as patients with higher Omega-3 levels still had a 4.6% extended lifespan and a 10-fold risk reduction of sudden cardiac death compared to those with lower Omega-3 levels. But side effects like atrial fibrillation happen in 13%

of regular fish oil supplement users, which underscores the need for medical guidance before you start taking it safely and effectively.

3.2. Secondary Prevention

The outcomes were more varied in secondary prevention settings. EPA [icosapent ethyl] high dose was shown to reduce cardiovascular events [25% reduction in relative risk] in statin-treated patients in the REDUCE-IT trial [9]. This suggests that omega-3 supplementation adds to existing therapies for high-risk individuals. In contrast, the STRENGTH trial did not show cardiovascular benefits with a mixed EPA/DHA formulation [10]. However, these discrepancies underscore the need to carefully select formulations and customize treatment to patient-derived risk profiles [11]. Further analysis revealed that outcomes, in this instance, are determined by the degree to which patients adhered to the therapy and that their initial triglyceride baseline is unstable. Similarly, the efficacy of omega-3 supplementation was also found to differ according to whether or not the participants were taking concurrent statin therapy, consistent with current meta-analyses. In contrast, MACE was reduced in patients also receiving high-dose EPA when compared to omega-3 alone [9]. This suggests that there may be synergy between omega-3 and lipid-lowering drugs and warrants further study.

3.3. Mechanistic Insights

EPA and DHA have different biological activities. While DHA's role in plaque stability remains unclear [11], EPA improves endothelial function, reducing plaque lipid content, potentially making the plaque more stable [11]. These differences may account for the superiority of pure EPA products such as icosapentethyl in some but not all trials [12]. EPA's anti-inflammatory and antioxidant properties also help to confer its cardiovascular benefits. Optimal therapeutic strategies depend on the understanding of these mechanisms. EPA has also been demonstrated to modulate lipid metabolism, decrease oxidative stress and inhibit platelet aggregation, and decrease the risk of atherosclerosis [10]. While less well studied, DHA also may have potential in neural and endothelial cell signaling, but the effect on cardiovascular outcomes is inconsistent. Future research may focus on DHA's potential to improve autonomic regulation and enhance vascular reactivity. However, inconsistencies in study design and endpoints prevent definitive conclusions on the role DHA might have for cardiovascular health.

3.4. Safety Concerns

3.4.1. Atrial Fibrillation

Meta-analysis has consistently reported an increased risk of AF with omega-3 supplementation. A 2021 study showed a 37% increase in cases of AF in omega-3 patients compared to placebo, with increased levels of omega-3 linked to increased risk [12]. Its use in patients at risk for arrhythmia should raise concern, and careful consideration of dosage and patient selection ensues. However, the REDUCE-

IT and STRENGTH trials showed a dose-dependent incidence of AF in patients who received more than 4 g/day of omega-3 [9]. Omega-3 supplements triglyceride reduction comes with potential arrhythmic risks, and clinicians must balance the two. The analysis also suggests that patients who have prior arrhythmias or structural heart abnormalities are more likely to develop AF while on omega-3 therapy. This finding highlights the need for pretreatment assessment and monitoring of supplemented patients.

3.4.2. Bleeding Risks

Omega-3 fatty acids have anticoagulant properties and increase the risk of bleeding when combined with antiplatelet or anticoagulant therapies at high doses [10]. Of course, this is rare, but it points out the need to monitor patients with coagulopathy or concomitant anticoagulant therapy. Isolated cases of great bleeding events were reported, such as in elderly patients with comorbidities [2]. Where no risk assessments can be done, prior patient education and omega-3 therapy must also occur.

3.4.3. Gastrointestinal Effects

Adverse effects across studies included mild gastrointestinal symptoms such as nausea and diarrhea [1]. However, these side effects are usually mild and transient and can lead to patient noncompliance with long-term supplementation regimens. Formulating omega-3 products to improve palatability and mitigate these two issues will improve patient compliance and therapeutic outcomes.

Microencapsulation techniques and combined formulations are emerging and are thought to provide gastrointestinal comfort without losing efficacy [11].

3.5. Analyzing Discrepancies in Findings

The discrepancies between study findings regarding omega-3 supplementation can be attributed to several factors, including differences in:

- Study Design: Variations in RCT vs. observational studies and single vs. multicenter trials.
- Population Characteristics: Differences in demographics—the age, baseline health status, and pre-existing conditions of study subjects.
- Dosage and Formulation: Variability in the types and amounts of omega-3 products used in trials, particularly distinctions between EPA and DHA concentrations. For example, the REDUCE-IT trial utilized high-dose EPA, whereas the STRENGTH trial employed a mixed formulation that did not yield significant benefits.

Further exploration into these factors can shed light on why certain studies demonstrate positive outcomes while others exhibit neutrality or adverse effects.

3.6. Biological Pathways and Clinical Implications

EPA and DHA exert their effects through various biological mechanisms. EPA primarily influences cardiovascular health by:

- **Improving Endothelial Function:** EPA enhances nitric oxide availability, leading to vasodilation and improved blood flow.
- **Anti-Inflammatory Effects:** It alters the production of pro-inflammatory cytokines and inhibits leukocyte adhesion, potentially reducing atherosclerotic plaque formation.
- **Platelet Aggregation Inhibition:** EPA reduces thromboxane A2 levels, leading to decreased platelet aggregation and thus lower thrombotic risk.

DHA, while similarly beneficial, also participates in neural signaling, which may influence cardiac rhythm and autonomic regulation, further needing exploration in clinical outcomes observed in varying research studies.

4. Discussion

Differences in study design, patient characteristics, and omega-3 formulations are the reasons for heterogeneity in trial outcomes. The positive findings of icosapent ethyl in the REDUCE-IT trial, and the marked formulation-specific effects, are especially observed in high-risk patients with elevated triglycerides [6]. The results of this trial underscore the importance of using high-purity EPA formulations to elicit meaningful cardiovascular benefits. In contrast to this, mixed EPA/DHA formulations lacked benefits in the STRENGTH trial and emphasize that selection of patients and treatment protocols needs precision [10]. Future research should seek to find biomarkers or genetic profiles that predict responsiveness to omega-3 supplements. Caution must be used regarding the safety profile of omega-3 supplementation. Its use is limited by increased AF risk, especially at high doses in patients with arrhythmogenic predisposition [7]. However, its triglyceride-lowering properties support the use of it in the treatment of hypertriglyceridemia [9]. The dual profile of benefits and risks of this therapy requires a tailored use of therapy, taking both efficacy and potential adverse events into account. Together with targeted dosing strategies, patient monitoring may be enhanced in order to achieve optimal outcomes and minimize risk.

Omega-3 fish oil has drawn considerable attention regarding its potential advantages for heart health thanks to various biological mechanisms. The main routes involve anti-inflammatory effects, modulation of lipid metabolism, and impact on heart rate. A study in 2022 elucidated the complex biological justification of the disparate effects observed in omega-3 fatty acids, stressing their role in the results of cardiovascular disease [11]. In addition, Glück and Alter. In 2016, the implications of highly unsaturated fatty acids on heart failure and arrhythmia were discussed. These studies collectively highlight the need for more in-depth exploration of omega-3 fatty acids to solidify their therapeutic roles in cardiovascular health. [13]

5. Conclusions

High-dose EPA supplementation for omega-3 fatty acids may have cardiovascular benefits in certain populations but is not universally effective. Personalized treat-

ment approaches are needed for safety concerns, e.g., AF and bleeding risks. Future research is needed to understand the mechanistic differences between EPA and DHA and to identify patient subgroups that will most benefit. Yet, since the potential benefits and risks of omega-3 supplementation vary with individual patient profiles, clinicians should carefully consider the benefits and risks for each patient. Omega-3 therapies may have a key role in managing cardiovascular disease by improving the use of high-quality evidence and precision techniques, thereby mitigating the global burden of cardiovascular events.

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All authors contributed equally to the article.

Conflicts of Interest

The authors declare no conflicts of interest.

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