Review Article

Omega-3 Fatty Acids in Cardiovascular Health: Navigating the Duality of Benefits and Risks

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ABSTRACT

Objective: Cardiovascular diseases (CVDs) remain the leading global cause of death and healthcare economic burden. Omega-3 fatty acids (FAs) have been widely advocated for their potential role in improving cardiovascular health, yet emerging evidence questions their efficacy across diverse CVD contexts. This narrative review evaluates the historical and current understanding of omega-3 FAs in CVD management, contrasting their purported benefits with contemporary evidence on risks and outcomes. **Methods**: We conducted a comprehensive synthesis of existing literature, including clinical trials, meta-analyses, and observational studies, to assess the role of omega-3 FAs in primary and secondary CVD prevention. Focus was placed on their effects on hypertension, atherosclerosis, ischemic heart disease, and overall morbidity/mortality. **Results**: Omega-3 FAs demonstrate clear benefits in secondary prevention of certain CVDs, particularly in reducing triglycerides and arrhythmia risk. However, recent studies highlight inconsistent outcomes regarding their impact on overall mortality, stroke prevention, and efficacy in diverse populations. While some trials reaffirm their anti-inflammatory and plaque-stabilizing properties, others suggest negligible effects or even potential risks (e.g., atrial fibrillation in high doses). **Conclusion**: The role of omega-3 FAs in CVD management is nuanced, with evidence supporting selective benefits but also underscoring limitations and unresolved controversies. Clinicians must weigh these findings against individual patient profiles. Further research is needed to clarify optimal dosing, formulations, and target populations to maximize therapeutic potential while mitigating risks.

Key words: cardiovascular diseases, omega-3 fatty acids, antifibrotic, anti-arrhythmic, secondary prevention

The global burden of cardiovascular diseases (CVD) continues to rise, positioning them as the leading cause of mortality worldwide and accounts for 17.9 million deaths annually, a figure representing approximately 31% of all global deaths [1]. In the United States, the total cost of CVD was estimated at $363 billion for the period of 2016-2017. This figure encompasses $216 billion in direct medical costs, including the costs of hospitalizations, medical procedures, and medications, and $147 billion in indirect costs, attributed to lost productivity due to death or disability [2].

Interest in the potential cardiovascular benefits of omega-3 fatty acids (FA) began in the 1940s, Sinclair noted low occurrence of heart-related diseases among Greenland's Indigenous people, who had diets heavily focused on seafood and marine mammals. Over four decades later, Bang and Dyerberg observed that, despite a diet rich in fats and cholesterol and a limited intake of fruits, vegetables, and complex carbohydrates, people in Greenland had healthier blood fat levels compared to their contemporaries in Denmark, and also experienced fewer heart attacks.[3, 4] These observations, along with others, piqued curiosity about the health advantages of consuming more fish, especially due to the positive impacts of certain fats found in fish on heart health, however; in 2020-2021, randomized trials were conducted which did not signify the role of omega-3 fatty acids in CVDs [5, 6]. Approximately 25% of the United States population has elevated triglycerides (≥150 mg/dL), putting them at an increased risk of CVD and having worse health and economic outcomes [7, 8].

FAs are compounds with carbon chains ending in a carboxylic acid, varying in length from 4 to 28 carbon atoms,

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and are classified based on their hydrogen bonding: saturated fatty acids are fully hydrogenated with no double bonds, whereas unsaturated ones have at least one double bond. Within the unsaturated category, polyunsaturated fatty acids (PUFAs) contain multiple double bonds and there are 3 major omega-3 FAs that are essential fats the body cannot produce independently: α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) [9]. ALA is abundant in certain plant foods including olive oil - 0.1, walnuts - 0.7, soybean oil - 0.9, canola oil - 1.3, Walnut oil - 1.4, Flax seed - 2.2, and flaxseed oil - 8.5 grams per tablespoon. Amongst these, the highest amount of omega-3 FA is to be found in flaxseed oil. EPA and DHA are primarily found in marine-based foods that include a variety of fish, such as tuna - 0.73, farmed trout - 0.98, halibut - 1.0, mackerel - 1.57, Pacific herring - 1.81 and Atlantic farmed salmon - 1.83 grams per 3 oz of serving fish. All these fish are rich in omega-3 FAs of which the highest is present in Atlantic farmed salmon, i.e. 1.83 grams of omega-3 FAs per 3 oz. serving size [10-12].

Historical dietary patterns suggest that humans once consumed omega-6 and omega-3 fatty acids in a roughly equal ratio of 1:1. Contrastingly, today's western diets typically present a ratio skewed towards 20:1, favoring omega-6. This shift, largely due to the prevalence of omega-6-rich foods, is problematic because omega-6 FA tends to promote inflammation, unlike omega-3 FA which is known to reduce inflammation and improve cardiovascular health [13].

A particular study highlighted that consuming fish was associated with a reduced risk of mortality from coronary heart disease. Specifically, individuals who ate fish 1 to 3 times a month, once a week, 2 to 4 times a week, and more than 5 times a week experienced a 21%, 29%, 31%, and 34% decrease in risk, respectively, when compared to those who did not consume fish at all [14, 15]. Omega-3 FAs play a vital role in preserving cellular membrane integrity and recent research highlights their significant cardioprotective benefits, including the reduction of triglyceride levels, enhancement of endothelial function, and the lowering of both blood pressure and heart rate. Additionally, their anti-inflammatory, antifibrotic, hypolipidemic, and antiarrhythmic properties make omega-3 FAs a promising supplement for the management and prevention of CVD [16-19].

Significant research over the past two decades has focused on elucidating the mechanisms by which omega-3 FAs exert their cardiovascular benefits. However, the relationship between omega-3 FA intake and cardiovascular outcomes is complex, influenced by factors such as the type and dose of omega-3, baseline nutritional status, and the presence of underlying health conditions. While evidence supports the cardiovascular benefits of omega-3 FAs, the efficacy of supplementation in various contexts, such as primary prevention, secondary prevention, and specific subpopulations, remains a subject of ongoing research and debate [20].

Recognizing the critical role of omega-3 FAs in cardiovascular health and the need for clarity regarding their optimal use, our review aims to discern the precise role of omega-3 FAs in the prevention and management of CVDs. Through a comprehensive review of recent clinical trials, epidemiological studies, and meta-analyses published in the past years, this article seeks to synthesize current knowledge and identify gaps in the literature. Given the potential benefits of omega-3 FAs in cardiovascular health, it is essential to understand the underlying mechanisms by which they exert their effects, which will be discussed in the following sections.

Pathophysiology

Omega-3 FAs have been shown to help prevent inflammation as their metabolism yields specialized pro-resolving lipid mediators like resolvins, maresins, and protectins, which have anti-inflammatory properties [21, 22]. Resolvins can originate from all three omega-3 FAs: EPA gives rise to E-series resolvins, DHA to D-series resolvins, and docosapentaenoic acid (DPA) to resolvin-3DPA whereas protectins and maresins are exclusively produced from precursors of DHA or DPA [23]. Anti-triglyceride, anti-inflammatory, anti-arrhythmic, anti-fibrotic, and anti-thrombotic effects of omega-3 FAs can be attributed to multiple mechanisms as summarized in Figure 1 [22].

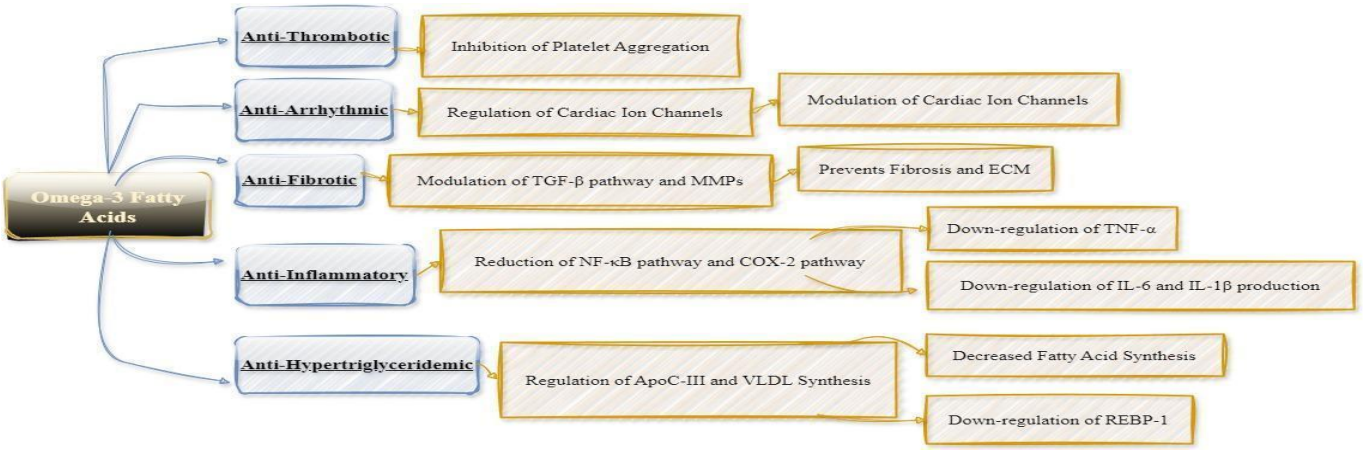

Figure 1: Effects of Omega-3 FAs on different pathophysiologic processes

Omega-3 Fatty Acid Effects as Anti-Hypertriglyceridemic

Omega-3 FAs can regulate gene transcription by interacting with nuclear receptors such as peroxisome proliferator-activated receptors (PPAR) which control lipid, glucose metabolism, and inflammation. PPAR-α is mainly involved in fatty acid metabolism, such as β-oxidation, decreased hepatic triglyceride secretion, increased lipoprotein lipase activity, very low-density lipoprotein (VLDL) clearance, and high-density lipoprotein (HDL) cholesterol production, leading to a favorable hypolipidemic effect [24]. Omega-3 FAs are particularly effective in lowering elevated triglyceride levels, especially at a prescription dose of 4 g/day. This dose has been shown to reduce triglyceride levels by 20% to 30% in patients with levels of 150–500 mg/dL, often accompanied by small reductions in other harmful lipids like non-high-density lipoprotein cholesterol and apolipoprotein B.

In cases of very high triglyceride levels (≥ 500 mg/dL), a prescription of 4 g/day omega-3 FAs is recommended to reduce the risk of pancreatitis, with reductions in triglycerides exceeding 30%. Studies comparing 2 g/day to 4 g/day of prescription omega-3 FAs showed that the lower dose was about half as effective in lowering triglycerides. While recent clinical trials using a 1 g/day dose of omega-3 FAs have not effectively shown to reduce triglyceride levels, but may still influence pathways including arrhythmia, coagulation, vascular health, blood pressure, plaque stability, and inflammation suggesting potential cardiovascular benefits even at lower intake levels. However, in people with fasting triglycerides below 150 mg/dL, these higher doses may not lead to noticeable reductions in triglycerides [25].

Omega-3-Fatty Acid Effects as Anti-Inflammatory

Metabolic treatment utilizing omega-3 FAs has shown benefits in cardiovascular disease management by generating potent anti-inflammatory mediators [22]. HDL isolated from patients treated with EPA significantly increased cholesterol efflux from macrophages and decreased vascular cell adhesion molecule-1 (VCAM-1) expression in endothelial cells as compared with HDL isolated from the patients prior to EPA administration [23]. Notably, individuals taking omega-3 FAs exhibit higher EPA levels in carotid plaque phospholipids, associated with reduced plaque inflammation and increased plaque stability. This has significant implications for reducing the risk of acute cardiovascular events, often precipitated by plaque rupture [26]. Interest has grown in transient receptor potential vanilloid 4 channels (TRPV4), which aid in vasodilation and lowering blood pressure by responding to hemodynamic forces and metabolic signals.

They facilitate vasodilation by increasing intracellular calcium and releasing nitric oxide, leading to smooth muscle cell relaxation [27, 28]. Studies in transgenic models have highlighted the necessity of EPA and its derivative, 17, 18-epoxyeicosatetraenoic acid (17, 18-EEQ), for TRPV4 channel activity. These findings suggest the potential for developing omega-3 FA-like molecules as antihypertensive therapies targeting TRPV4 channels. Additionally, research indicates that omega-3 FAs enhance TRPV4 function in human endothelial cells, supporting their potential clinical utility [28].

Omega-3 Fatty Acids Effects as Antithrombotic

Omega-3 FAs, including EPA and DHA, influence platelet aggregation and exhibit antithrombotic effects which contribute to cardioprotection and the prevention of blood clot formation [29]. Consumption of EPA leads to the production of 3-series prostaglandins [B3, D3, E3, I3, and thromboxane A3 (TXA3)], which are metabolized by cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX). These compounds, including prostaglandin I3 (PGI3) and thromboxane A3, possess potent vasodilatory effects, reduce platelet aggregation, diminish cardiac ischemic injury, mitigate arteriosclerosis, and promote angiogenesis.

EPA competes with arachidonic acid for cell membrane phospholipid synthesis, thus reducing thromboxane A2 production and favoring TXA3 production. Additionally, EPA generates anti-inflammatory 5-series leukotrienes (B5, C5, and D6) [30]. Omega-3 FAs also demonstrate potential in preventing thrombus formation and thromboembolism in atrial fibrillation patients by suppressing factor VII activating protease [31]. Consumption of omega-3 FAs results in the downregulation of inflammation, platelet function, platelet-endothelium interactions, and tissue factor expression, consequently reducing the risk of venous thromboembolism and recurrent venous thromboembolism.

Omega-3 Fatty Acids Effect as Anti-Fibrotic

Omega-3 FAs play a crucial role in regulating oxidative stress and protecting the heart from fibrosis, a significant contributor to heart failure. Heart failure (HF) is associated with decreased availability of ATP (adenosine triphosphate), altered handling of Na+ and Ca2+, and oxidatively stressed myocytes. Resolvin D1 (RvD1) can activate nuclear factor erythropoietin 2 related factor 2 (NRF2), which plays a crucial role in regulating oxidative stress and consequently, mitigating the onset of HF. EPA interaction with free fatty acid receptor 4 (Ffar4) receptor, or the G-protein coupled receptor 120 (GPR120) fibroblast receptors inhibit cardiac fibrosis by activating the anti-fibrotic endothelial nitric oxide synthase (eNOS)/cyclic guanosine monophosphate (cGMP)/cGMP/protein kinase G (PKG) signaling pathway [22]. The cGMP/protein kinase G (PKG) signaling pathway prevents TGF-β1-induced cardiac fibrosis [33].

Omega-3 Fatty Acid Effects as Antiarrhythmic

Omega-3 FAs have anti-arrhythmic capabilities that involve modulating ion channel properties, membrane composition, and fluidity and modulating the sympatho-vagal balance. In some pathological situations, direct blockage of sarcolemmal ion channels (Na+, Ca2+, and different K+ currents) may

stabilize electrical activity and extend the cardiomyocytes' relative refractory time. Arrhythmia triggers may be eliminated or diminished by an omega-3 FA-mediated control of intracellular calcium handling, which includes suppression of sarcoplasmic reticulum ryanodine receptors (RyR) channels and avoidance of calcium overload [31]. Omega-3 FAs also diminish adrenergic stimulation by reducing the rise in cAMP levels in myocytes [34]. While they typically exhibit antiarrhythmic properties, they might paradoxically promote reentrant arrhythmias, recent research has shed light on the role of PIEZO proteins in mediating the effect of omega-3 FAs on atrial fibrillation (AF). PIEZO 1/2 proteins are large ion channels found in cell membranes, which respond to mechanical forces by opening and allowing the influx of positively charged ions like calcium. Specifically, DHA slows down the inactivation of PIEZO1, while EPA speeds it up. The balance between these effects, determined by the DHA: EPA ratio, can ultimately influence calcium influx and other processes.

Increased calcium influx due to altered PIEZO channel activity can prolong the action potential, increase the likelihood of delayed after-depolarizations, and ultimately promote AF [35]. In a recent study, the role of omega-3 FAs was found to mediate the heart's electrical activity, including long QT syndrome [36]. Figure 2 provides an overview of the various mechanisms by which omega-3 FAs alter AF risk. Omega 3 FAs modulate various pathways, such as reducing inflammation through specialized pro-resolving lipid mediators and regulating gene transcription via nuclear receptors. Additionally, omega-3 FAs lower triglyceride levels and improve vascular function, contributing to cardiovascular health. Their ability to modulate ion channels and membrane composition further enhances their anti-arrhythmic potential, making them promising therapeutic agents for CVD management.

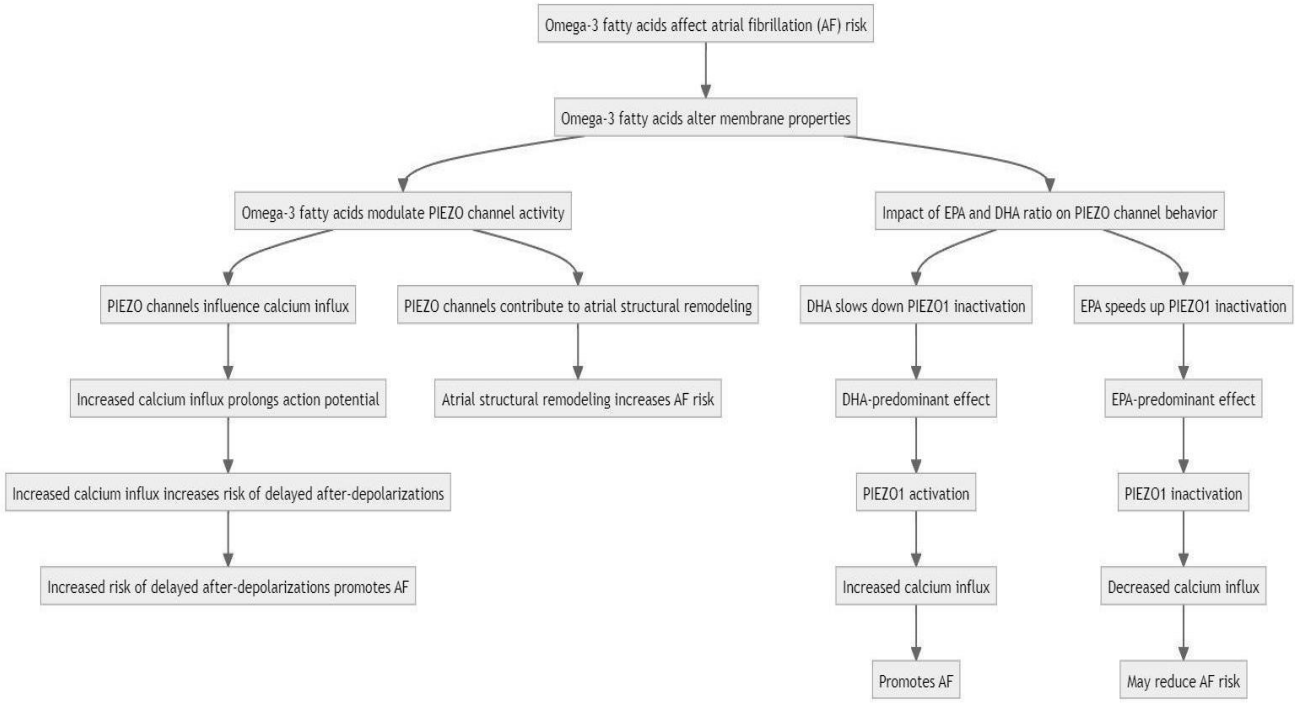

Figure 2: Mechanism by which omega-3 fatty acids affect atrial fibrillation risk.

DISCUSSION

The study that first forayed into the world of omega-3 FAs was one carried out on the population in Greenland in 1971, suggesting that omega-3 FAs, or fish oil had a significant effect on patients with atherosclerotic disease [37]. This has led to the discovery of the role of omega-3 FAs in a lot of pathologic conditions, including but not limited to atherosclerotic cardiovascular disease, arrhythmia, congestive heart disease, carcinogenesis, and neurologic conditions like dementia [38].

A meta-analysis carried out by Gelejinse et al concluded that fish oil supplementation caused a modest lowering of blood pressure, which was thought to be due to the increased production of nitric oxide through the consumption of omega-3 Fas [39, 40]. This claim was substantiated in another study by Tousoulis et al which reported that in patients with metabolic syndrome, endothelial function was improved by omega-3 FA via flow-mediated dilation, arterial stiffness by carotid-femoral pulse-wave velocity (PVW), in addition to an anti-inflammatory component [41]. A study conducted on 31 subjects with ischemic heart failure who were treated with 2g of omega-3 FAs per day for a period of eight weeks indicated that the omega-3 FAs increased the left ventricular ejection fraction. The levels of soluble interleukin-1 receptor-like 1 (sST2), an established marker of inflammation and myocardial fibrosis, and high-sensitivity C-reactive protein (hs-CRP) also

decreased, while flow-mediated dilation increased. All of this indicates an improvement in inflammation, fibrosis, endothelial function, and ventricular systolic and diastolic performance as a consequence of the omega-3 FAs' actions [42].

The anti-platelet effect of omega-3 FAs has been confirmed by a meta-analysis of 15 randomized controlled trials which concluded that omega-3 FAs have a role in inhibiting platelet aggregation [43]. In another study, administration of 3g of omega-3 FAs for four weeks has also been proven to lower fibrinogen, factor V, and thrombin levels in healthy, borderline overweight men, although these benefits were seen mainly in those subjects with high fibrinogen-carrying alpha-chain fibrinogen polymorphism [44]. Thus, there is some substantial research backing these claims of omega-3 FAs on thrombus formation, but the data surrounding it is quite outdated, and newer, prospective studies need to be carried out in order to fully understand the extent of its effect on platelet aggregation and clot formation.

Hypercholesterolemia is another important component of predicting cardiovascular morbidity and mortality, and has been studied extensively in the WOSCOPS, 4S and MEGA studies, which highlighted the importance of low-density lipoprotein (LDL) reducing statins in primary and secondary prevention of heart diseases [45]. In addition to LDLs, triglycerides are also considered to be conducive to the pathological process in CVD patients, and can be atherogenic, and controlling their levels is imperative in order to achieve better lipid control [46]. Omega-3 FAs have been shown to reduce triglycerides in patients with hypertriglyceridemia, and lead to an increase in LDL as well as HDL. However, the increase in LDL is smaller than the decrease observed in VLDL, and there is a net decrease in non-HDL cholesterol [47]. A randomized clinical study carried out on Japanese subjects concluded that these effects of omega-3 FAs on triglycerides depend on the dose, rather than the type of omega-3 FAs, and that higher amounts of omega-3 FA consumption are associated with higher reductions in triglycerides [48].

Studies carried out on different preparations of omega-3 FAs, such as EPA and DHA have also had promising findings. The Japan EPA Lipid Intervention Study (JELIS) trial evaluated the effect of highly purified EPA in CVD patients taking statins, and concluded that high-purity EPA administration lowered CVD risk by a modest 19%, and that adherence to the supplements is also associated with lower CVD events [49, 50]. A study carried out in Italy highlighted the effect of EPA/DHA preparations in secondary prevention in post-myocardial infarction (MI) patients, showing lowered total death, sudden death, and CVD-related death [37].

This claim has been challenged by a randomized controlled trial on 13,078 patients carried out by Nicholls et al, in which the administration of a carboxylic acid formulation of EPA and DHA was compared to the administration of corn oil, with no studied cardiovascular benefits. The study did not find a significant reduction in cardiovascular death, MI, coronary revascularization, stroke, or hospitalization for unstable angina [6]. This study also pointed out the loopholes in the JELIS trial, claiming that the trial did not adhere to contemporary standards of care. The effects of omega-3 FAs in arrhythmia are even more conflicting. There have been earlier studies on animal models that show that omega-3 FAs have antiarrhythmic properties [51].

On another occasion, a meta-analysis of population-based cohort studies as well as randomized controlled trials found no significant effects of omega-3 FAs on the secondary prevention of AF after cardioversion [52]. On the contrary, recent large-scale randomized control trials suggest that omega-3 FAs might also be associated with an increased risk of AF [35]. The Vitamin D and Omega-3 (VITAL) rhythm study randomized 12,542 patients to receive either standard-dose EPA and DHA combination or placebo, and after a median period of follow-up for 5.6 years, it was found that AF incidence in patients receiving the omega-3 formulation was 7.2 per 1000 person-years, and the incidence in patients receiving placebo was 6.6 per 1000 person-years, with a p- value of 0.19 [5].

The risk and prevention (RP) trial of 2013 looked at hospitalizations with AF without excluding pre-existing AF and found that the percentage of AF in patients taking the omega-3 supplement vs. placebo was 1.8% vs. 1.5% respectively, with a p-value of 0.15 [53]. To substantiate these claims, a recent meta-analysis of six randomized controlled trials concluded that omega-3 FAs were associated with an increased risk of incident AF when compared to placebo (incidence rate ratio 1.29, $p = 0.0002$) [54]. Another meta-analysis of 7 randomized controlled trials found a 25% increase in AF incidence in patients on omega-3 fatty acids vs. placebo [55]. Table 1 illustrates the outcomes of different studies and meta-analyses highlighting the effect of omega-3 FAs on CVD. While the triglyceride-lowering effects of omega-3 FAs demonstrate their potential role in improving lipid profiles, their impact on cardiac arrhythmias remains controversial, warranting closer examination.

Thus, in spite of previous studies showing positive correlations between the administration of omega-3 FAs and CVD risk, this information has to be taken with a grain of salt, since new and emerging studies suggest otherwise. In spite of such differing conclusions from studies, there have been significant revelations regarding the positive effects of omega-3 FAs in lowering triglycerides, and reducing CVD risk. Additional studies and investigations into the molecular mechanisms causing these effects on different physiological and pathological processes need to be carried out in order to gain a clear understanding of the benefits and risks associated with regular omega-3 FA consumption.

Table 1: Different studies showing Omega-3 Fatty Acids effects on cardiovascular health

Study	Year	Study design	Population / Participants	Intervention / Exposure	Key Findings
Zhang et al. [56]	2022	Meta-analysis	4973 adults across 71 trials	Combined EHA+DPA dose of 2.8g/day (Interquartile range 1.3-3.6g/day)	Significant decrease in systolic as well as diastolic BP with doses between 2-3g/day
Bischoff-Ferrari et al. [57]	2020	Randomized control trial	2157 adults, mean age 74.9 years	Randomized to treatment with vitamin D3, omega 3 or strength-training exercise program	No significant changes in systolic and diastolic blood pressure
Liu et al. [58]	2023	Meta-analysis	387 participants across 8 trials	Not specified	Significant reduction in systolic and diastolic blood pressure
Abdelhamid et al. [59]	2020	Meta-analysis	162,796 participants across 86 Randomized controlled trials	Unspecified supplementation/increased intake of Long-chain omega-3 (LC-3)and ALA	Increased LC-3 reduces coronary heart disease mortality and reduces serum Triglycerides, increasing ALA causes reduction in cardiovascular events and arrhythmia
Nicholls et al.[6]	2020	Randomized Control Trial	13,078 patients across 675 academic and community hospitals	Randomization to 4g/day of omega-3 FA or corn oil	No significant change in outcome of cardiovascular death, nonfatal MI, nonfatal stroke, or coronary revascularization among attain-treated patients at high cardiovascular risk
Bhatt et al.[60]	2019	Randomized Control Trial	8179 patients	2g/day of icosapent ethyl twice daily	Hypertriglyceridemic patients using statins had a significantly lower risk of ischemic events on supplementation of omega-3 FA compared to placebo
JELIS trial, Yokoyama et al.[49]	2007	Randomized Control Trial	18645 patients with total cholesterol of 6.5 mmol/L or greater	1800 mg/day of EPA+statin or statin daily	Significant reduction in LDL cholesterol, unstable angina, and non-fatal coronary events
Albert et al.[5]	2021	Randomized Control Trial	25119 patients $\geq$ 50 years	460 mg/day of EPA and 380 mg/day of DHA vs vitamin D3 and placebo	No significant difference in the incidence of Atrial fibrillation amongst the groups

CONCLUSION

At present, the information delineating the exact role of omega-3 FAs on the cardiovascular system is quite conflicted, and this paper was an attempt to understand the pathological processes that are being affected by supplementing omega-3 FAs in the diet of patients. While it has shown promising results in patients with hypertension, ischemic heart disease, and thrombus formation, there have been no studies that prove its effects on cardiovascular mortality, MI, arrhythmias, and rates of stroke and hospitalizations due to cardiovascular diseases. Thus, in order to understand this dichotomy, more prospective studies need to be carried out in order to understand the full spectrum of effects of omega-3 FAs in patients with CVD.

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