Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(11): 51183
https://doi.org/10.31083/FBL51183

Review

Analysis of Omega-3 Polyunsaturated Fatty Acids Application in Atherosclerosis Treatment

Alexander Blagov[1,*], Ulyana Rozhkova[2], Olesya Galanova[3], Alexander Orekhov[2]

[1]Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, 125315 Moscow, Russia
[2]Institute for Atherosclerosis Research, 121609 Moscow, Russia
[3]Moscow Center for Advanced Studies, 123592 Moscow, Russia
*Correspondence: al.blagov2014@gmail.com (Alexander Blagov)

Academic Editor: Paramjit S. Tappia
Submitted: 24 February 2026 Revised: 30 April 2026 Accepted: 13 May 2026 Published: 18 November 2026

Abstract

Atherosclerosis manifests as a prolonged inflammatory process within arterial systems, culminating in vascular complications such as ischemic stroke and myocardial infarction. This pathology accounts for considerable healthcare resource utilization, hospital admissions, and mortality globally. Conventional therapeutic approaches—including lipid-modifying agents (statins, ezetimibe), antiplatelet drugs, antihypertensives, anticoagulants, and antihyperglycemic medications—form the cornerstone of atherosclerosis management. However, prevention remains the most effective strategy and should commence at the earliest opportunity. Polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids, have attracted substantial scientific interest due to their diverse biological functions: they participate in inflammatory regulation through direct cellular interactions—including modulation of Toll-like receptor 4 (TLR4) and NOD-like receptor protein 3 (NLRP3) inflammasome signaling—and serve as biochemical precursors for specialized pro-resolving mediators (resolvins, protectins, maresins). Preclinical investigations demonstrate that omega-3 polyunsaturated fatty acids (n-3 PUFAs) reduce atherosclerotic plaque burden, promote plaque stability, and modulate macrophage cholesterol transport. Clinical evidence indicates that high-dose eicosapentaenoic acid (EPA) monotherapy reduces major adverse cardiovascular events and triglyceride levels; however, large-scale randomized trials have produced heterogeneous results, and a dose-dependent increase in atrial fibrillation risk has been established. Future research directions include precision medicine approaches, novel PUFA formulations, specialized pro-resolving mediator (SPM)-based therapies, and investigation of gut microbiota interactions. These findings underscore the need for personalized, biomarker-guided supplementation strategies and adequately powered clinical trials targeting defined patient subpopulations.

Keywords: atherosclerosis; omega-3 polyunsaturated fatty acids; EPA; DHA; cardiovascular disease; inflammation; specialized pro-resolving mediators; resolvins

1. Introduction

Atherosclerosis is fundamentally a lipid-driven pathology resulting from low-density lipoprotein (LDL) and remnant particle accumulation in specific arterial zones, accompanied by inflammatory responses, particularly at sites with disturbed laminar flow near vessel bifurcations [1]. Atherosclerotic vascular disease predominantly affects cardiac and cerebral circulation: coronary artery disease (CAD) and cerebrovascular infarction. CAD and stroke represent the first and third leading mortality causes globally. Established risk factors include: elevated LDL-cholesterol (LDL-C), arterial hypertension, diabetes mellitus, tobacco use, advancing age, and hereditary predisposition. Physical inactivity, excessive body mass, diets enriched in saturated and trans lipids, along with specific genetic variants may further increase risk [2].

Atherogenesis primarily proceeds through intimal lipid entrapment within the extracellular matrix, inducing modifications that initiate chronic inflammation in susceptible arterial regions. This mechanism, operative throughout atherogenic progression stages, commences with nascent lipid streaks in the arterial intima, evolving into fibrous lesions and subsequently into rupture-susceptible atherosclerotic plaques [3].

Atherosclerosis management encompasses interventions promoting regression and inhibiting progression and rupture of atherosclerotic lesions. Risk factor modification including LDL-C reduction, blood pressure control, and glycemic management through dietary optimization, physical activity, smoking cessation, and pharmacotherapy represent fundamental atherosclerosis control strategies [4]. Statins remain the primary therapeutic agents for LDL-C reduction and cardiovascular event prevention. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretic agents, beta-adrenergic blockers, calcium antagonists, and vasodilatory compounds are additionally employed for blood pressure regulation [5].

Polyunsaturated fatty acids (PUFAs) comprise fatty acids containing two or more carbon-carbon double bonds. Classification of PUFAs depends on the initial double bond position relative to the terminal methyl moiety: omega-3 and omega-6 PUFAs feature double bonds at the third and

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

sixth carbon positions from the methyl terminus, respectively. Omega-3 and omega-6 PUFAs possess the greatest biological significance [6]. Clinical interest in PUFAs intensified during the 1970s following publication of epidemiological investigations demonstrating reduced coronary disease and diabetes risk in Greenlandic Inuit populations compared with Danish cohorts, attributed to elevated omega-3 polyunsaturated fatty acid (n-3 PUFA) consumption from marine sources including fish, seals, and marine mammals [7]. These observations highlighted the potential therapeutic utility of PUFAs in cardiovascular pathologies. Consequently, this review evaluates omega-3 fatty acid applications in atherosclerosis treatment.

2. Pathophysiological Mechanisms of Atherosclerosis

Atherosclerosis constitutes a chronic inflammatory disorder. The disease initiates with fatty streak formation, representing lipid-laden foam cell accumulation within the arterial intimal layer [8,9]. Lipid retention marks the initial pathogenic step, followed by chronic inflammation in predisposed regions of major arterial walls, progressing to fatty streaks that advance to fibroatheromas characterized by fibrous composition [10]. Atherosclerosis exhibits continuous progressive development. Fatty streaks emerge at ages 11–12 years, comprising four elements: inflammatory cellular infiltrate, smooth muscle cells, fibrous connective tissue component, and lipid fraction [11].

Endothelial injury initiates the cascade. Turbulent hemodynamics induces endothelial dysfunction, suppresses nitric oxide synthesis, and stimulates adhesion molecule expression attracting inflammatory cells. Additional risk factors contribute at this stage. Consequences include: monocyte and T lymphocyte adhesion to endothelial cells and migration to the subendothelial compartment. Plasma lipids, LDL, and very-low-density lipoprotein (VLDL) bind endothelial cells and undergo oxidation subendothelially [12]. Subendothelial monocytes phagocytose oxidized LDL, forming foam cells. Subsequently, macrophages secrete proinflammatory cytokines, recruiting smooth muscle cells. Smooth muscle cell proliferation and extracellular matrix expansion occur. The lesion culminates in a subendothelial fibrous plaque consisting of a lipid-rich core enveloped by smooth muscle cells and connective tissue fibers [11]. Arterial layers become sequentially involved: intima initially, followed by media, and ultimately adventitia. Arterial wall pathology features a central cholesterol-enriched lipid core surrounded by inflammatory reaction. Each lesion involves lipid accumulation and inflammation. Plaque distorts the media/adventitia interface, expanding arterial caliber while simultaneously reducing luminal dimensions. Neovascularization penetrates the affected intima via vasa vasorum, causing hemorrhage within the arterial wall, producing intramural hemorrhage and fibrous tissue proliferation. Thin fibrous cap rupture precipitates thrombosis and healing. Cyclical healing of clinically silent ruptures produces multilayered tissue repair, culminating in sudden cardiac death. Calcium deposition initially appears as small aggregates, subsequently transforming into large nodular accumulations within the wall. Endothelial erosion triggers thrombosis. Progressive plaque expansion causes stenosis, ultimately leading to fatal ischemia [3].

Plaques exist in two categories: stable and unstable [13]. Stable plaques undergo regression, remain static, or demonstrate slow progression. Unstable plaques develop complications including erosion, fissuring, and rupture, causing stenosis, thrombosis, and infarction. Most clinical manifestations result from unstable plaque complications; therefore, plaque stabilization can diminish atherosclerosis-associated morbidity and mortality. Plaque rupture occurs through enzyme release by activated intraplaque macrophages. Following rupture, plaque contents contact circulating blood, initiating thrombosis [3]. Resultant thrombosis may alter plaque morphology and occlude the vessel lumen. Low-risk plaques contain increased fibrous content, minimal lipid, and cause incomplete blockage, whereas unstable plaques possess extensive lipid cores and thin fibrous caps with narrow lumens. Plaque-induced stenosis culminates in terminal events including acute coronary syndrome, myocardial infarction, fatal arrhythmias, and sudden cardiac death [14].

3. Conventional Therapeutic Approaches to Atherosclerosis

3.1 Lipid-Modifying Pharmaceutical Agents

Statins, including atorvastatin, simvastatin, and rosuvastatin, are universally recognized as fundamental components in atherosclerosis therapeutic management. These compounds function as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, an enzyme that regulates a critical step in cholesterol biosynthesis. Statins primarily reduce LDL-C concentrations. Comprehensive evidence consistently demonstrates their efficacy in decreasing cardiovascular event occurrence and mortality among individuals with atherosclerotic cardiovascular disease [15]. Recommendations from the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) have designated statin therapy as a primary intervention for individuals with atherosclerosis or at elevated cardiovascular event risk [16].

Cholesterol absorption inhibitors, exemplified by ezetimibe, function by targeting Niemann-Pick protein C1-Like 1 (NPC1L1) within the small intestinal brush border. This mechanism prevents dietary cholesterol absorption, producing LDL-C reduction. For enhanced LDL-C lowering, ezetimibe is frequently combined with statins [17].

3.2 Platelet Aggregation Inhibitory Agents

Antiplatelet medications including aspirin and P2Y12 antagonists constitute fundamental interventions

in atherothrombotic event prevention in atherosclerosis. These agents inhibit platelet activation and diminish thrombus formation in atherosclerotic vessels, thereby reducing myocardial infarction and stroke risk. Aspirin irreversibly inhibits cyclooxygenase-1, diminishing thromboxane A2 production, a potent platelet activator. Clopidogrel, ticagrelor, and prasugrel selectively antagonize the platelet P2Y12 receptor, consequently preventing platelet activation and aggregation. Aspirin is widely recommended as first-line antiplatelet therapy for atherosclerosis based on its proven efficacy in reducing cardiovascular events [18].

3.3 Antihypertensive Medications

Antihypertensive pharmaceuticals are extensively utilized in atherosclerosis management, as elevated blood pressure represents a critical risk factor for disease development and progression. These medications function by reducing systemic blood pressure, thereby reducing mechanical stress on arterial walls and decelerating the atherogenic process. Various antihypertensive drug classes, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), calcium channel blockers, and beta-blockers, confer vascular protective effects [5].

ACE inhibitors not only reduce blood pressure but also possess anti-inflammatory characteristics that stabilize atherosclerotic plaques [19]. ACE inhibitors stabilize atherosclerotic plaques primarily by diminishing angiotensin II production, a key mediator of vasoconstriction, inflammation, and oxidative stress contributing to plaque instability. By inhibiting angiotensin I conversion to angiotensin II, these drugs reduce vascular inflammation while enhancing endothelial function through increased nitric oxide availability, a critical vasodilator and anti-inflammatory mediator [20]. This endothelial function improvement further reduces arterial stiffness and maintains vascular integrity. Moreover, decreased angiotensin II concentrations result in a reduction in oxidative stress, protecting the endothelium and diminishing plaque rupture risk. Collectively, these mechanisms render ACE inhibitors effective in promoting plaque stability and preventing cardiovascular events. ARBs similarly reduce angiotensin II action, producing vasodilation and decreased vascular inflammation. Calcium channel blockers improve endothelial function and reduce arterial stiffness, while beta-blockers decrease myocardial oxygen demand and may limit coronary heart disease progression [19].

3.4 Anticoagulant Pharmaceuticals

Anticoagulants serve an important function in atherosclerosis management, particularly in thrombotic event prevention arising from atherosclerotic plaques. These medications prevent blood clot formation, which is crucial for reducing stroke and myocardial infarction risk in individuals with atherosclerosis. Anticoagulants can provide dual benefits in atherosclerosis treatment by stabilizing plaques and reducing blood clot likelihood, potentially offering combined treatment approaches when used with antiplatelet agents [21].

3.5 Glucose Metabolism Regulatory Agents

Antihyperglycemic medications such as metformin exert beneficial atherosclerosis effects through various mechanisms. They reduce insulin resistance, lower blood glucose concentrations, and suppress hepatic glucose production. Metformin additionally possesses anti-inflammatory properties and can inhibit smooth muscle cell proliferation involved in atherosclerotic plaque formation [22].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, another antihyperglycemic drug class, may affect atherosclerosis through various mechanisms. By blocking renal glucose reabsorption, they increase urinary glucose excretion and lower blood glucose levels. SGLT2 inhibitors may also improve endothelial function, reduce oxidative stress, and decrease arterial stiffness, thereby promoting atherosclerosis prevention and regression [23].

4. Advantages and Limitations of PUFA Application in Atherosclerosis

4.1 PUFAs Sources

Alpha-linolenic acid (ALA; 18:3n-3) is the essential dietary precursor of the long-chain n-3 PUFA(s) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Being "essential" denotes that mammals lack Δ15-desaturase activity and therefore cannot synthesize ALA *de novo*; it must be obtained from plant-based dietary sources such as flaxseed, chia seeds, walnuts, and rapeseed oil [24]. ALA undergoes sequential elongation and desaturation—catalyzed primarily by the fatty acid desaturase 1 (FADS1) (Δ5-desaturase) and FADS2 (Δ6-desaturase) enzymes encoded by genes on chromosome 11q12-13—to yield EPA and subsequently DHA via the Sprecher pathway [25]. However, the overall endogenous conversion efficiency of ALA to EPA in humans is limited (typically <8%), and conversion to DHA is even lower (<0.1–4%), making direct dietary intake of preformed EPA and DHA from marine sources or supplements clinically important, particularly in individuals with reduced FADS enzymatic activity due to common genetic polymorphisms [26]. In addition to free fatty acid forms, n-3 PUFAs are naturally present and biologically active in esterified lipid forms. In particular, n-3 PUFA-containing glycerophospholipids—including phosphatidylcholine (PC), phosphatidylethanolamine (PE), and phosphatidylglycerol (PG)—exhibit superior bioavailability compared with ethyl ester supplements and exert direct anti-inflammatory effects through membrane restructuring and altered eicosanoid signaling [27]. Furthermore, plasmalogens—vinyl ether-linked phospholipids highly enriched in DHA at the sn-2 position—are abundant in car-

diac and vascular tissue and serve both as endogenous antioxidants (protecting membrane polyunsaturated acyl chains from oxidation) and as signaling lipids with anti-inflammatory and anti-atherogenic activity [28]. Reduced plasmalogen levels have been documented in atherosclerotic lesions and in patients with coronary artery disease, implicating plasmalogen deficiency in atherogenesis and suggesting that plasmalogen repletion via dietary krill oil or plasmalogen-enriched supplements may constitute an additional preventive strategy [28].

4.2 Advantages of PUFAs

Polyunsaturated fatty acids demonstrate substantial advantages in cardiovascular disease management through their multifaceted biological activities. The anti-inflammatory properties of n-3 PUFAs represent a primary therapeutic benefit, as these fatty acids suppress production of pro-inflammatory cytokines including tumor necrosis factor-alpha, interleukin-1β, and interleukin-6 through modulation of nuclear factor-kappa B signaling pathways [29]. Furthermore, n-3 PUFAs serve as precursors for specialized pro-resolving mediators, including resolvins, protectins, and maresins, which actively promote inflammation resolution rather than merely suppressing inflammatory responses [30]. Lipid profile modulation constitutes another significant advantage, with extensive evidence demonstrating that EPA and DHA supplementation reduces triglyceride levels by 25–30% in hypertriglyceridemic patients through decreased hepatic very-low-density lipoprotein synthesis and enhanced triglyceride clearance [31]. Additionally, n-3 PUFAs increase high-density lipoprotein cholesterol concentrations and promote a shift from small, dense LDL particles to larger, more buoyant particles with reduced atherogenic potential [32].

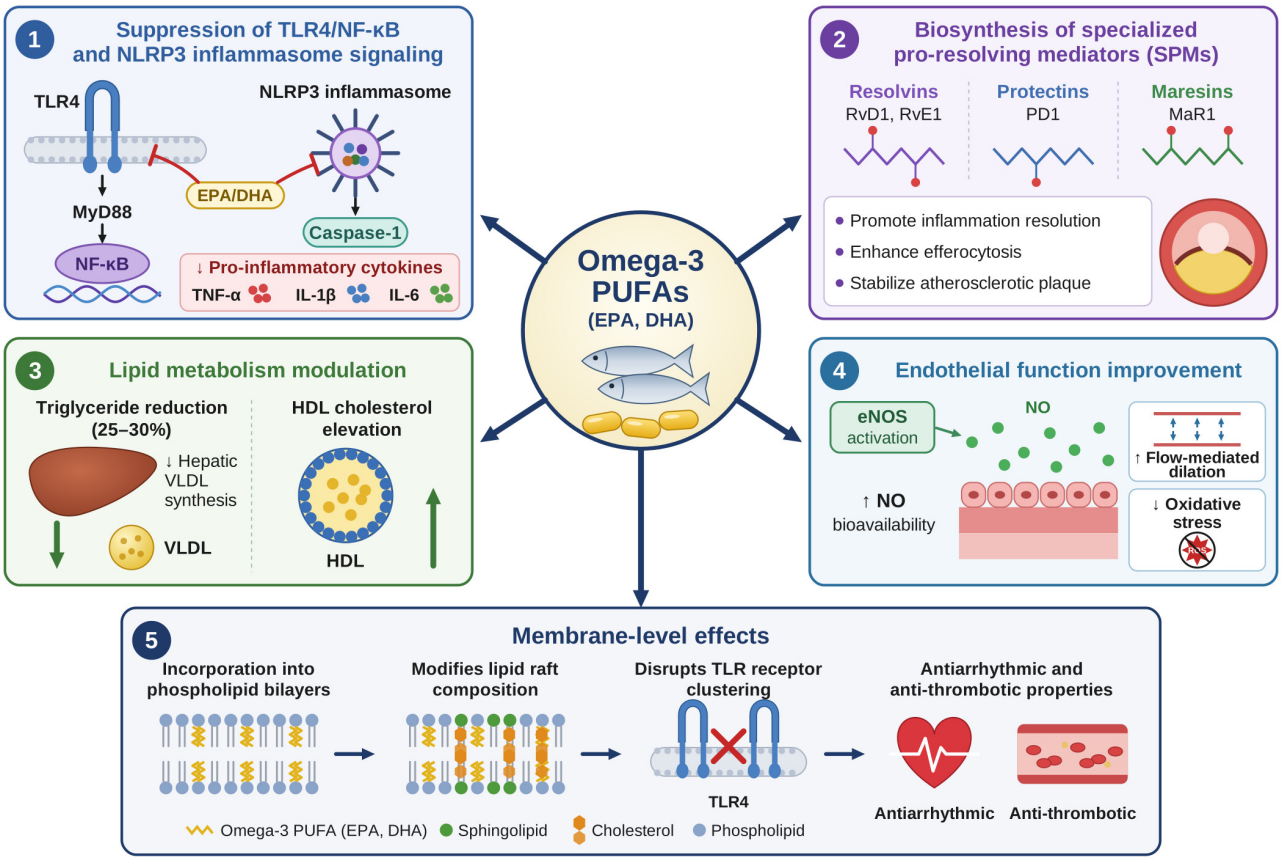
The beneficial effects of PUFAs extend to endothelial function improvement and multiple pleiotropic cardiovascular effects. n-3 PUFA supplementation enhances endothelium-dependent vasodilation through increased nitric oxide bioavailability and reduced oxidative stress, with improvements in flow-mediated dilation observed across diverse patient populations including those with hyperlipidemia, diabetes, and established cardiovascular disease [33]. Membrane incorporation of n-3 PUFAs modifies lipid raft composition and cellular signaling, influencing ion channel function and contributing to antiarrhythmic properties that may reduce sudden cardiac death risk [34,35]. Blood pressure reduction represents another advantage, with meta-analyses demonstrating that n-3 PUFA supplementation produces modest but clinically meaningful reductions in both systolic and diastolic blood pressure, particularly in hypertensive individuals [36]. The favorable safety profile of PUFAs at recommended dosages, coupled with their availability through dietary sources, makes them attractive candidates for long-term cardiovascular disease prevention strategies that complement conventional pharmacological interventions [37].

An important but underappreciated advantage of n-3 PUFAs in atherosclerosis management is their antioxidative activity, which operates through both direct and indirect mechanisms. Directly, DHA and EPA—and particularly their oxidation metabolites such as neuroprostanes and isoprostane F2-like compounds generated non-enzymatically—can act as sacrificial substrates for reactive oxygen species (ROS), thereby reducing the oxidative modification of LDL particles and membrane phospholipids [38]. Indirectly, and arguably more importantly from a sustained therapeutic standpoint, n-3 PUFAs activate the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor pathway. Under basal conditions, Nrf2 is sequestered in the cytoplasm by its inhibitor Kelch-like ECH-associated protein 1 (Keap1). EPA and DHA—and their electrophilic metabolites including 4-hydroxydocosahexaenoic acid (4-HDHA) and nitro-fatty acids—modify critical cysteine residues on Keap1, inducing Nrf2 nuclear translocation [39]. Nuclear Nrf2 binds antioxidant response elements (AREs) in target gene promoters, driving expression of a coordinated antioxidant program including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase (GCL), and thioredoxin reductase [40]. HO-1 induction is of particular relevance to atherosclerosis: HO-1 catalyzes heme degradation to carbon monoxide (CO), biliverdin, and free iron; CO and bilirubin (the product of biliverdin reductase) exert vasodilatory, anti-inflammatory, and anti-thrombotic effects, while HO-1 itself suppresses macrophage activation and promotes efferocytosis of apoptotic cells within plaques [41]. Thus, by simultaneously targeting inflammation (via peroxisome proliferator-activated receptor (PPAR), Toll-like receptor (TLR), nuclear factor kappa B (NF-κB), and NOD-like receptor protein 3 (NLRP3) pathways) and oxidative stress (via Nrf2/HO-1 activation and ROS scavenging), n-3 PUFAs address two of the most fundamental pillars of atherogenesis, reinforcing their rationale as dietary supplements in cardiovascular prevention.

The positive effects of PUFA in atherosclerosis are shown on the Fig. 1. A detailed description of the molecular mechanisms of the influence of PUFA in atherosclerosis is described in section 5.

4.3 Limitations of PUFAs

Despite these mechanistic advantages, substantial limitations constrain the clinical application of PUFAs in atherosclerosis management. The most significant concern involves heterogeneous and often disappointing results from recent large-scale randomized controlled trials. While early observational studies and smaller trials suggested cardiovascular benefit, contemporary mega-trials including STRENGTH, OMEMI, and REDUCE-IT have produced conflicting outcomes, with some studies demonstrating no significant reduction in major adverse cardiovascular



Abbreviations: TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; IL, interleukin; TNF-α, tumor necrosis factor alpha; SPM, specialized pro-resolving mediator; RvD1/RvE1, resolvin D1/E1; PD1, protectin D1; MaR1, maresin 1; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; ROS, reactive oxygen species; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Fig. 1. The positive effects of PUFA in atherosclerosis. n-3 PUFAs exert their atheroprotective effects through five main pathways: (1) Suppression of TLR4/NF-κB and NLRP3 inflammasome signaling, reducing pro-inflammatory cytokine (TNF-α, IL-1β, IL-6) production; (2) Biosynthesis of SPMs—resolvins (RvD1, RvE1), protectins (PD1), and maresins (MaR1)—which actively promote inflammation resolution and plaque stabilization; (3) Lipid metabolism modulation, including triglyceride reduction (25–30%) via decreased hepatic VLDL synthesis, and HDL cholesterol elevation; (4) Endothelial function improvement through increased NO bioavailability, enhanced flow-mediated dilation, and reduced oxidative stress; (5) Membrane-level effects: incorporation into phospholipid bilayers modifies lipid raft composition, disrupts TLR receptor clustering, and confers antiarrhythmic and anti-thrombotic properties. Abbreviations: TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor protein 3; SPM, specialized pro-resolving mediator; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; PUFA, polyunsaturated fatty acid; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1β; RvD1, resolvin D1; RvE1, resolvin E1.

events despite achieving substantial increases in n-3 PUFA blood levels [42,43]. This discordance between mechanistic plausibility and clinical efficacy may reflect inadequate trial design, including insufficient dosing, short follow-up duration, or enrollment of populations already receiving optimal medical therapy with limited room for additional benefit [44,45]. The optimal dosing strategy remains undefined, with uncertainty regarding whether cardiovascular protection requires high-dose prescription formulations (2–4 grams daily) or if lower dietary intake suffices, and whether EPA alone or EPA plus DHA combinations provide superior efficacy [46,47]. Furthermore, the appropriate omega-6 to omega-3 ratio continues to be debated, with some evidence suggesting that high omega-6 intake may antagonize omega-3 benefits, though definitive data supporting specific ratio targets remain lacking [48,49].

Safety concerns have emerged from recent meta-analyses demonstrating a dose-dependent increase in atrial fibrillation risk with high-dose n-3 PUFA supplementation, particularly with EPA doses exceeding 2 grams daily, raising questions about the risk-benefit ratio in certain patient populations [50]. Increased bleeding risk, while generally modest, may be clinically significant when PUFAs are combined with antiplatelet agents or anticoagulants, necessitat-

ing careful monitoring in patients receiving concurrent antithrombotic therapy [51]. Individual variability in PUFA metabolism and response, influenced by genetic polymorphisms in fatty acid desaturase genes, may explain heterogeneous treatment responses and suggests that personalized approaches considering pharmacogenomic factors may be necessary to identify patients most likely to benefit [52]. Gastrointestinal adverse effects including nausea, fishy aftertaste, and dyspepsia, while not life-threatening, contribute to reduced adherence in clinical practice and may limit real-world effectiveness despite efficacy in controlled trial settings [53].

Additional limitations encompass methodological challenges and practical considerations that complicate clinical implementation. The complexity of dietary patterns and potential interactions with other consumed lipids, particularly trans fats, saturated fats, and omega-6 PUFAs, confound interpretation of n-3 PUFA-specific effects in free-living populations [54]. Storage instability and susceptibility to oxidation present practical challenges for supplement formulation and preservation, as oxidized PUFA products may exert pro-inflammatory rather than anti-inflammatory effects, potentially negating therapeutic benefits [55]. The absence of standardized supplementation protocols regarding optimal formulation (triglyceride versus ethyl ester forms), timing of administration, and concurrent food intake creates inconsistency in clinical practice and complicates comparison across studies [56]. Bioavailability variability across different PUFA sources, influenced by formulation characteristics and individual factors including age, sex, and metabolic status, further contributes to unpredictable treatment responses [57,58]. These multifaceted limitations underscore the necessity for personalized approaches informed by biomarker monitoring and continued investigation to identify specific patient populations, dosing strategies, and clinical contexts in which PUFA intervention provides meaningful cardiovascular benefit beyond standard care.

5. Multiple Anti-Atherogenic Mechanisms of n-3 PUFAs

5.1 TLR-4 Signaling

The innate immune system performs an essential function in atherogenesis. As part of an evolutionarily conserved system for identifying and responding to pathogen-associated molecular patterns (PAMPs), the innate immune system depends on an extensive family of pattern recognition receptors (PRRs). These receptors, whose atherogenic role is well established, include TLR4, which detects lipopolysaccharide from Gram-negative bacteria. The TLR4 signaling cascade is closely associated with lipid rafts, where TLR4 recruitment occurs upon activation. Fatty acids can modulate these processes. Saturated lauric acid has been demonstrated to induce TLR4 dimerization and recruitment [59].

Unlike saturated fatty acids, unsaturated fatty acids do not activate TLR4. Conversely, docosahexaenoic acid suppresses NF-κB activation and cyclooxygenase-2 (COX-2) expression. Thus, docosahexaenoic acid can inhibit TLR4 activation induced by saturated fatty acids [60]. Furthermore, evidence demonstrates that arachidonic acid can prevent lipopolysaccharide (LPS) binding to MD2 (a TLR4 co-receptor) by binding to MD2, reducing inflammation [61].

5.2 Additional Anti-Inflammatory Signaling Pathways

It also appears significant that while saturated fatty acids can promote NLRP3 inflammasome activation, PUFAs suppress its activity. Dietary PUFAs reduce LPS-induced interleukin-1β (IL-1β) secretion in mice *in vivo*. This is significant given evidence regarding the NLRP3 inflammasome and IL-1β role in atherosclerosis pathogenesis [62]. Beyond direct TLR4 and NLRP3 suppression, n-3 PUFAs orchestrate anti-inflammatory signaling through at least three additional biochemical mechanisms.

First, EPA and DHA function as high-affinity endogenous ligands for peroxisome proliferator-activated receptors alpha and gamma (PPAR-α and PPAR-γ). PPAR-α activation in hepatocytes and macrophages transcriptionally suppresses NF-κB–driven cytokine gene expression (TNF-α, IL-1β, IL-6) while simultaneously upregulating fatty acid β-oxidation genes, reducing the intracellular accumulation of pro-inflammatory lipid intermediates such as diacylglycerol and ceramide [63]. PPAR-γ activation in plaque macrophages induces an anti-inflammatory M2 phenotype, upregulates liver X receptor (LXR) target genes including ATP-binding cassette transporters A1 (ABCA1) and ATP-binding cassette transporters G1 (ABCG1) (facilitating cholesterol efflux), and reduces the production of matrix metalloproteinases responsible for fibrous cap degradation [64].

Second, DHA and EPA competitively displace arachidonic acid (AA; 20:4n-6) from membrane phospholipids and from the active sites of cyclooxygenase (COX-1 and COX-2) and lipoxygenase (5-LOX, 12-LOX, 15-LOX) enzymes [65]. Because AA is the principal precursor for pro-inflammatory eicosanoids—prostaglandin E2 (PGE2), thromboxane A2 (TXA2), and leukotriene B4 (LTB4)—its displacement by EPA and DHA results in substantially reduced biosynthesis of these mediators. In parallel, EPA and DHA serve as alternative COX/LOX substrates, yielding the 3-series prostaglandins and 5-series leukotrienes from EPA, and DHA-derived oxylipins (17-hydroxydocosahexaenoic acid, 14-hydroxydocosahexaenoic acid), which are considerably less potent inflammatory agonists than their AA-derived counterparts [30].

Third, DHA directly suppresses NF-κB nuclear translocation in macrophages and endothelial cells by stabilizing IκBα—the cytoplasmic inhibitor of NF-κB—through a mechanism partly involving G-protein-coupled recep-

tor 120 (GPR120)/beta-arrestin 2 (β-arrestin-2)–mediated transforming growth factor-beta-activated kinase 1 (TAK1) inhibition (described above) and partly through direct effects on inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) kinase activity [66]. The resulting reduction in NF-κB transcriptional activity produces coordinate downregulation of COX-2 protein expression, adhesion molecules (vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), endothelial-leukocyte adhesion molecule-1 (E-selectin)), and chemokines (monocyte chemoattractant protein-1 (MCP-1), IL-8), attenuating monocyte recruitment to the subendothelial space and early atherogenic lesion formation.

5.3 LDL Particle Modification

In the initial Phase I of atherogenesis—characterized by LDL retention and oxidative modification in the subendothelial space—n-3 PUFAs exert direct protective effects by reducing LDL particle size heterogeneity, susceptibility to oxidation, and uptake by macrophage scavenger receptors. Dietary EPA and DHA supplementation promotes a shift from small, dense LDL (sdLDL)—which penetrates the arterial wall more readily and is more susceptible to oxidative modification—toward larger, more buoyant LDL particles that are less atherogenic [67]. Furthermore, EPA incorporation into LDL phospholipids reduces the oxidizability of LDL particles by decreasing their content of arachidonic acid (a readily peroxidizable substrate) and increasing membrane-associated antioxidant capacity [68]. The resulting reduction in oxidized LDL (oxLDL) formation decreases the activation of macrophage scavenger receptors SR-A and CD36, limiting foam cell formation.

5.4 Triglyceride Reduction

EPA and its ester formulations (icosapent ethyl) are the most clinically established agents for reducing plasma triglycerides, achieving 25–30% reductions at therapeutic doses (2–4 g/day) [46]. The underlying mechanisms are multifactorial: (i) n-3 PUFAs accelerate chylomicron triglycerides (TG) clearance in the postprandial state, in part through enhanced apolipoprotein E (ApoE) enrichment of chylomicron remnants, which improves their recognition and uptake by hepatic LDL receptor-related protein (LRP1) [69]; (ii) n-3 PUFAs increase the expression and activity of lipoprotein lipase (LPL), the principal enzyme catalyzing intravascular TG hydrolysis in chylomicrons and VLDL, thereby accelerating TG clearance from the circulation [69]; (iii) importantly, n-3 PUFAs are potent inducers of angiopoietin-like protein 4 (ANGPTL4), a PPAR target gene that acts as an endogenous LPL inhibitor in adipose tissue while promoting LPL activity in the heart [70]. The net consequence of ANGPTL4 induction by n-3 PUFAs is tissue-specific: it may redirect fatty acid delivery from adipose to cardiac muscle, contributing to the anti-obesity effects of n-3 PUFAs, although the net systemic metabolic effect of ANGPTL4 induction requires further characterization [70].

5.5 Membrane Level Effects

The incorporation of EPA and DHA into the phospholipid bilayer of immune and vascular cells fundamentally alters the biophysical properties of membrane microdomains known as lipid rafts. Lipid rafts are cholesterol- and sphingomyelin-enriched ordered membrane domains that serve as platforms for the lateral clustering of signaling receptors, including TLR4 [59]. The substitution of saturated fatty acyl chains in membrane phospholipids with highly unsaturated EPA (20:5n-3) and DHA (22:6n-3) reduces membrane order and disrupts raft integrity, dispersing TLR4 dimers across the disordered membrane and impairing their ability to form the high-order receptor clusters required for efficient signal transduction [59]. This spatial reorganization of TLR4 has direct consequences for Toll/IL-1 receptor (TIR) domain adaptor protein recruitment: the disordered membrane environment diminishes the interaction between the cytoplasmic TIR domain of TLR4 and the TIR domains of the adaptor proteins MyD88 and TRIF (TICAM-1), thereby lowering the efficiency of Myddosome and TRIF complex assembly [59,71]. Reduced adaptor recruitment results in attenuated interleukin-1 receptor-associated kinase (IRAK)1/IRAK4 phosphorylation, diminished TRAF6 activation, and downstream suppression of NF-κB and IRF3 transcriptional activity—collectively reducing the expression of pro-inflammatory cytokines, type I interferons, and endothelial adhesion molecules relevant to atherogenesis [72].

Additionally, DHA-enriched membranes have been shown to suppress ceramide-enriched platform formation, which constitutes an alternative mechanism of TLR4 clustering in response to oxidized LDL and other atherogenic stimuli [59]. These membrane-level effects are thus mechanistically upstream of the intracellular signaling events described above and represent a primary mode by which dietary n-3 PUFAs exert their anti-inflammatory effects in the atherosclerotic arterial wall.

The incorporation of EPA and DHA into sarcolemmal phospholipids in cardiomyocytes directly modulates the function of voltage-gated ion channels. DHA reduces the peak inward sodium current (INa) and the late sodium current (late-INa) in ventricular myocytes, shortening the action potential plateau and reducing triggered arrhythmias [34]. EPA and DHA also modulate L-type calcium channel (ICaL) gating and the transient outward potassium current (Ito), contributing to action potential stabilization, a reduced propensity for early and delayed afterdepolarizations, and reduced risk of ventricular fibrillation [34]. These membrane-electrophysiological effects underlie the anti-arrhythmic properties of n-3 PUFAs and may contribute to the reduction in sudden cardiac death ob-

served in epidemiological studies, independent of effects on atherosclerotic plaque.

5.6 Influence on SPM Synthesis

Experimental evidence convincingly demonstrates n-3 PUFA and metabolite involvement in inflammation resolution in atherosclerosis. Specifically, n-3 PUFAs can downregulate the inflammatory pathway in atherosclerosis both by reducing proinflammatory eicosanoid production and by increasing specialized pro-resolving mediator (SPM) synthesis [30,73,74,75]. Evidence demonstrates that vulnerable regions of human carotid atherosclerotic plaques exhibit significantly lower pro-resolving mediator resolvin D1 (RvD1) levels, along with significantly elevated pro-inflammatory mediator LTB4 levels. Authors also demonstrated that exogenous RvD1 administration to high-fat-fed LDL receptor-deficient (LDLR−/−) mice during atherosclerotic plaque progression restored the RvD1/LTB4 ratio to levels of less advanced atherosclerotic lesions and promoted increased plaque stability (for example, thicker fibrous caps, improved lesion efferocytosis, and reduced oxidative stress and lesion necrosis) [76].

5.7 Modulation of the IRAK Signaling Cascade

A further mechanism by which n-3 PUFAs attenuate vascular inflammation involves indirect modulation of the interleukin-1 receptor-associated kinase (IRAK) signaling cascade. IRAK1 and IRAK4 are serine/threonine kinases that are recruited to the Myddosome complex upon activation of TLRs and IL-1R, and their phosphorylation initiates downstream signaling through TRAF6 ubiquitination, TAK1 activation, and ultimately NF-κB and MAPK pathway engagement [77]. By reducing TLR4 activation through lipid raft restructuring and by suppressing IL-1β production via NLRP3 inflammasome inhibition, n-3 PUFAs diminish the upstream stimuli that drive IRAK1 and IRAK4 recruitment and phosphorylation. This results in attenuated TRAF6-mediated polyubiquitination, reduced TAK1 activation, and consequently decreased NF-κB nuclear translocation and lower expression of pro-inflammatory effectors including TNF-α, IL-6, and MCP-1 [65]. Although the IRAK signaling axis has been most extensively characterized in the context of neuroinflammation in microglial cells [77], the same pathway is operative in macrophages and endothelial cells within the atherosclerotic plaque microenvironment, making it a relevant therapeutic target in cardiovascular disease. The indirect suppression of IRAK-dependent signaling by n-3 PUFAs thus represents an additional mechanism contributing to their anti-inflammatory and plaque-stabilizing effects in atherosclerosis.

5.8 Anti-Thrombotic Effects and Vascular Stiffness

n-3 PUFAs reduce arterial stiffness and atherothrombosis through multiple mechanisms: by shifting eicosanoid production from the pro-thrombotic TXA2 (from AA) toward the weaker TXA3 (from EPA), by increasing the production of prostacyclin (PGI2 and PGI3), which inhibits platelet aggregation and promotes vasodilation, and by reducing platelet membrane arachidonic acid content and the resultant platelet hypersensitivity [78]. Additionally, DHA incorporation into vascular smooth muscle cell membranes reduces large artery stiffness—as measured by pulse wave velocity—through improvement of membrane fluidity and calcium channel function, contributing to lower systolic blood pressure and reduced afterload [79].

5.9 Effect on Cholesterol Transport

Impaired reverse cholesterol transport is considered an important component of atherosclerosis pathogenesis. Substantial evidence indicates a role for ABCA1 and ABCG1 in regulating macrophage cholesterol transport and high-density lipoprotein (HDL) formation. Reduced expression and functional activity of these transporters is associated with foam cell formation and atherosclerosis progression. Unsaturated fatty acids such as palmitoleic, oleic, and linoleic acids have been demonstrated to downregulate ABCA1 expression at both transcriptional and post-transcriptional levels, reducing cholesterol efflux [80]. Eicosapentaenoic and oleic acids also downregulate ABCA1 promoter activity in macrophages. Unsaturated fatty acids also suppress ABCG1 gene expression through a mechanism involving LXR/RXR binding to promoters. Furthermore, membrane incorporation of eicosapentaenoic acid impairs ABCA1-dependent cholesterol efflux via the protein kinase A signaling pathway in primary human macrophages [81].

Membrane incorporation of eicosapentaenoic acid impairs cholesterol efflux from cholesterol-laden human macrophages also by reducing cholesteryl ester mobilization from lipid droplets. Conversely, membrane incorporation of eicosapentaenoic acid increases ABCA1 functionality in normal cholesterol-laden human THP-1 macrophages, likely through multiple mechanisms. Furthermore, dietary fish and n-3 PUFA intake were associated with leukocyte ABCA1 DNA methylation levels [82].

EPA has been reported to increase lecithin-cholesterol acyltransferase (LCAT) activity, promoting esterification of free cholesterol on nascent HDL particles and thus facilitating HDL maturation [83]. DHA upregulates ApoA-I transcription (the principal apolipoprotein of HDL), and both EPA and DHA increase SR-BI expression in hepatocytes, promoting selective HDL-CE uptake and biliary cholesterol excretion [84]. Furthermore, EPA and DHA have been reported to increase ABCG5 and ABCG8 expression in the enterocyte brush border, promoting intestinal cholesterol excretion and reducing net cholesterol absorption [85]. While data on the net effect of n-3 PUFAs on randomized controlled trial (RCT) in humans remain preliminary, the sum of these effects is directionally consistent with improved reverse cholesterol transport.

5.10 Anti-Obesity Effects, Insulin Resistance, and GLP-1

n-3 PUFAs reduce adiposity and improve insulin sensitivity through PPAR-γ–mediated adipogenesis regulation, reduction of adipose tissue inflammation (via SPM production in adipose macrophages), and inhibition of *de novo* lipogenesis in the liver [66]. Importantly, EPA and DHA—particularly through GPR120 activation in enteroendocrine L-cells—stimulate the secretion of glucagon-like peptide-1 (GLP-1), an incretin hormone that enhances pancreatic β-cell insulin secretion, reduces glucagon secretion, promotes satiety, and decelerates gastric emptying [86]. The relevance of GLP-1 axis activation to cardiovascular risk reduction has been underscored by the cardiovascular outcomes trials of GLP-1 receptor agonists (liraglutide, semaglutide), which demonstrated significant reductions in major adverse cardiovascular events (MACE) in patients with type 2 diabetes and established cardiovascular disease (CVD) [87]. n-3 PUFA–mediated potentiation of endogenous GLP-1 secretion thus represents an additional indirect anti-atherogenic mechanism operating through improvement of glycemic control, body weight reduction, and cardiovascular risk factor modification.

5.11 Experimental Evidence

Moreover, a recent experimental investigation demonstrated that EPA supplementation may reduce diet-induced atherosclerosis in ApoE−/− mice [88]. This investigation also revealed significant n-3 PUFA content increase in various tissues (myocardium, spleen, and skeletal muscle), accompanied by a parallel omega-6 PUFA content decrease at the same level. Furthermore, 18-monohydroxy EPA (a direct precursor for resolvin E1 (RvE1) synthesis) was identified as the most significant circulating EPA-derived metabolite, and RvE1 receptor deletion was associated with pro-atherogenic macrophage signaling, decreased phagocytosis, increased oxidized LDL uptake, increased atherosclerotic plaque size, and necrotic core formation, without changes in serum total cholesterol and triglyceride levels [89]. Overall, these results suggest EPA may exert protective atherosclerosis effects via its derivative SPM RvE1, independent of its effects on total cholesterol and triglyceride levels. Interestingly, RvE1 also attenuates injury-induced vascular neointima formation in mice by inhibiting inflammatory responses and smooth muscle cell migration [90].

An investigation was conducted on LDL receptor-null mice fed various high-saturated fat diets differing only in the omega-6/EPA+DHA ratio. Authors found that mice fed a diet with the lowest omega-6/EPA+DHA ratio (ratio = 1:1) had significantly lower circulating non-HDL cholesterol and IL-6 levels compared to mice fed a diet with the highest omega-6/EPA+DHA ratio [73]. Interestingly, cardiac tissue from mice fed a high-fat diet demonstrated increased arachidonic, linoleic, and docosahexaenoic acids and decreased eicosapentaenoic acid. PUFA incorporation into the cell membrane can alter membrane biophysical properties and affect cardiac function [79]. Key preclinical findings are summarized in Table 1 (Ref. [35,39,40,41,59,62,63,64,65,66,67,69,70,72,76,82,86,91,92,93,94,95,96,97,98,99]).

6. Clinical Investigations of PUFA Utilization in Atherosclerosis Treatment

Accumulating evidence suggests potential n-3 PUFA benefit in cardiovascular disease prevention. Fish oil supplementation in healthy volunteers was associated with improved endothelial function and reduced resting heart rate [36]. Furthermore, n-3 PUFA supplementation significantly improved endothelial function and reduced inflammatory markers in offspring of patients with type 2 diabetes [100]. Dietary supplementation containing marine n-3 PUFAs improved endothelium-dependent dilation of large arteries in patients with hypercholesterolemia but exerted no effect on endothelium-independent dilation. Fish oil supplementation increased endothelial progenitor cell numbers and reduced endothelial microparticle numbers, potentially promoting endothelial integrity [101].

A randomized, placebo-controlled trial including 53 subjects with mild hypertriacylglycerolemia evaluated the potential benefit of daily n-3 PUFA supplementation for improving cardiovascular health. After 10 weeks, subjects taking 3 grams of n-3 PUFA daily had significant increases in plasma and red blood cell n-3 PUFA levels. Additionally, plasma levels of EPA-derived mediators, PGE3, 12-HEPE, 15-HEPE, and 18-HEPE, increased. This was consistent with improvements in cardiovascular risk factors such as HDL levels, triacylglycerides, the arachidonic acid/eicosapentaenoic acid ratio, and the omega-3 index [102].

Results from a recent pooled analysis of 4 international cohort studies including 191,558 people from 58 countries demonstrated that a minimum fish intake of 175 grams (approximately 2 servings) per week was associated with lower major cardiovascular event and mortality risk among patients with pre-existing cardiovascular disease, but not in the general population [53].

A meta-analysis of 13 studies, including a total of 127,477 patients, found that supplementation with marine n-3 PUFAs significantly reduced myocardial infarction, coronary heart disease, and total cardiovascular morbidity risk [54]. A meta-analysis of 38 randomized controlled trials involving 149,051 participants found that n-3 PUFAs reduced cardiovascular mortality and improved cardiovascular outcomes. The cardiovascular risk reduction was greater with eicosapentaenoic acid monotherapy than with docosahexaenoic acid monotherapy. Importantly, n-3 PUFAs increased atrial fibrillation incidence, and eicosapentaenoic acid monotherapy was associated with higher overall bleeding and atrial fibrillation risk compared with the control group [103].

Thus, evidence exists that PUFAs demonstrate promise for clinical use due to their diverse functions. However, data on their clinical efficacy are mixed.

Table 1. Summary of key preclinical findings on PUFAs in atherosclerosis.

Mechanism	PUFA type	Key finding	Reference
TLR4 signaling inhibition	DHA	Suppressed NF-κB activation and COX-2 expression	[92]
NLRP3 inflammasome suppression	n-3 PUFAs	Reduced LPS-induced IL-1β secretion *in vivo*	[62,99]
SPM-mediated inflammation resolution	DHA (RvD1)	Increased plaque stability, thicker fibrous caps, reduced necrosis	[76]
PPAR-α/γ activation and anti-inflammatory gene regulation	EPA, DHA	PPAR-α suppresses NF-κB-driven cytokine genes (TNF-α, IL-1β, IL-6) and upregulates β-oxidation; PPAR-γ promotes M2 macrophage phenotype, upregulates ABCA1/ABCG1, reduces MMP production and fibrous cap degradation	[63,64]
GPR120/β-arrestin-2/TAK1 signaling inhibition	EPA, DHA	GPR120 activation recruits β-arrestin-2, sequesters TAB1, inhibits TAK1 phosphorylation; attenuates NF-κB and MAPK (JNK/p38) activation; reduces VCAM-1, ICAM-1, E-selectin, MCP-1 expression	[66]
Competitive displacement of arachidonic acid from COX/LOX enzymes	EPA, DHA	Displacement of AA reduces PGE2, TXA2, LTB4 biosynthesis; EPA/DHA serve as alternative COX/LOX substrates yielding less potent 3-series prostaglandins and 5-series leukotrienes	[65,93]
Lipid raft remodeling and TIR domain adaptor disruption	EPA, DHA	Incorporation into membrane phospholipids disrupts lipid raft integrity, disperses TLR4 dimers, impairs MyD88/TRIF (TIR domain) recruitment; suppresses ceramide-enriched platform formation; attenuates IRAK1/IRAK4–TRAF6–TAK1–NF-κB and IRF3 signaling	[59,72]
IRAK1/IRAK4 signaling attenuation	EPA, DHA	Reduction of TLR4 activation and IL-1β production decreases upstream stimuli for IRAK1/IRAK4 phosphorylation; attenuates TRAF6 polyubiquitination, TAK1 activation, and downstream NF-κB/MAPK signaling; reduces chronic vascular inflammation	[59,98]
Antioxidative activity: Nrf2/HO-1 pathway activation	EPA, DHA and electrophilic metabolites (4-HDHA, nitro-FAs)	Electrophilic PUFA metabolites modify Keap1 cysteines, inducing Nrf2 nuclear translocation and ARE-driven expression of HO-1, NQO1, GCL; HO-1-derived CO and bilirubin exert vasodilatory, anti-inflammatory, and anti-thrombotic effects; promotes efferocytosis of apoptotic plaque cells	[39,40,41]
LDL particle modification and reduced foam cell formation	EPA, DHA	Promotes shift from small, dense LDL to larger buoyant particles; reduces LDL oxidizability by displacing AA from LDL phospholipids; decreases oxLDL-mediated activation of macrophage scavenger receptors SR-A and CD36, limiting foam cell formation	[67,96]
Triglyceride reduction: LPL upregulation and chylomicron clearance	EPA (icosapent ethyl)	25–30% TG reduction at 2–4 g/day; mechanisms include: ApoE enrichment of chylomicrons accelerating LRP1-mediated hepatic clearance; LPL gene expression upregulation; ANGPTL4 (PPAR target gene) induction redirecting fatty acid delivery; suppression of hepatic VLDL-TG assembly	[69,70,91]
ABCA1 epigenetic regulation and cholesterol efflux	EPA, DHA (dietary fish/omega-3 intake)	Dietary n-3 PUFA intake associated with altered DNA methylation at CpG sites in leukocyte ABCA1 promoter; epigenetic upregulation of ABCA1 expression facilitates macrophage cholesterol efflux and reduces foam cell formation; PPAR-γ activation further upregulates ABCA1/ABCG1 via LXR target gene induction	[82,95]

Table 1. Continued.

Mechanism	PUFA type	Key finding	Reference
Anti-thrombotic effects and vascular stiffness reduction	EPA, DHA	Shifts eicosanoid production from pro-thrombotic TXA2 (from AA) to weaker TXA3 (from EPA); increases PGI2/PGI3 production; reduces platelet AA content and platelet hypersensitivity; DHA incorporation reduces large artery stiffness (pulse wave velocity) via membrane fluidity improvement and calcium channel modulation	[93,94]
Cardiac ion channel modulation and antiarrhythmic effects	EPA, DHA (sarcolemmal incorporation)	Reduces peak INa and late-INa; modulates L-type Ca^{2+} channel (ICaL) gating and Ito; shortens action potential plateau; reduces triggered arrhythmias and propensity for early/delayed afterdepolarizations; reduces ventricular fibrillation risk	[35,97]
Anti-obesity and insulin-sensitizing effects via GPR120/GLP-1 axis	EPA, DHA	GPR120 activation in enteroendocrine L-cells stimulates GLP-1 secretion; GLP-1 enhances β-cell insulin secretion, reduces glucagon, promotes satiety; PPAR-γ-mediated adipogenesis regulation and adipose tissue SPM production reduce adiposity and insulin resistance; indirect anti-atherogenic effect via CVD risk factor reduction	[66,86]

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RvD1, resolvin D1; RvE1, resolvin E1; SPM, specialized pro-resolving mediator; TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; COX-2, cyclooxygenase-2; NLRP3, NOD-like receptor protein 3; IL-1β, interleukin-1β; LPS, lipopolysaccharide; VCAM-1, vascular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; ABCA1/ABCG1, ATP-binding cassette transporters A1/G1; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ApoE−/−, apolipoprotein E-deficient mice; LDLR−/−, LDL receptor-deficient mice; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; ICAM-1, intercellular adhesion molecule-1; E-selectin, endothelial-leukocyte adhesion molecule-1; oxLDL, oxidized LDL; LPL, lipoprotein lipase; ANGPTL4, angiopoietin-like protein 4; TIR, Toll/IL-1 receptor; IRAK, interleukin-1 receptor-associated kinase; PGE2, prostaglandin E2; TXA2, thromboxane A2; LTB4, leukotriene B4; LXR, liver X receptor; GLP-1, glucagon-like peptide-1; HO-1, heme oxygenase-1; AA, arachidonic acid; MMP, matrix metalloproteinase; TRAF6, TNF receptor-associated factor 6; IRF3, interferon regulatory factor 3; PGI2, prostacyclin.

While earlier studies demonstrated predominantly positive effects, more recent studies have revealed no significant clinical effects of PUFA supplementation and, in some cases, negative results. In a large cohort of patients (12,513) with multiple cardiovascular risk factors, daily n-3 PUFA treatment did not reduce cardiovascular mortality or morbidity compared with placebo [104]. Treatment with n-3 PUFAs for 3 months did not improve endothelial function in patients with type 2 diabetes and very high cardiovascular risk. n-3 PUFA intake at a dose of ≤1.8 g/d for 12 months also did not improve endothelial function in healthy adults [56].

In addition to studying the n-3 PUFA role, there is growing interest in finding the optimal omega-6/n-3 PUFA ratio [50]. The importance of omega-6 PUFAs for cardiovascular disease has also been the subject of many studies over a long period. Linoleic acid is an essential omega-6 fatty acid because it cannot be synthesized by humans. It is the most abundant PUFA in the human diet, as significant amounts of linoleic acid are present in vegetable oils [105].

Linoleic acid has been demonstrated to lower LDL cholesterol levels. And higher linolenic acid intake has been associated with lower atherosclerotic plaque risk in the carotid arteries. A meta-analysis of 30 prospective studies involving 68,659 people found that higher linolenic acid concentrations were significantly associated with lower total cardiovascular disease, cardiovascular mortality, and ischemic stroke risks [106]. An analysis of 13 cohort studies with a total of 310,602 participants found that dietary linoleic acid intake was inversely associated with coronary heart disease risk in a dose-dependent manner [107]. Conversely, an assessment of reconstructed data from the Sydney Dietary Heart Study and an updated meta-analysis found that dietary linoleic acid intake from safflower oil increased coronary heart disease and cardiovascular disease death risk [108]. A study of 20,000 middle-aged men and women in the Netherlands found that linoleic acid intake was not associated with the total cholesterol to HDL cholesterol ratio, and no association was found between linoleic acid intake and coronary heart disease (CHD) incidence over a 10-year follow-up period [109].

The heterogeneity of clinical outcomes across large-scale trials is well illustrated by a series of landmark randomized controlled trials that differ markedly in their results depending on the dose, formulation, and patient population studied. The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) enrolled 8179 statin-treated patients with established cardiovascular disease or diabetes mellitus plus elevated triglycerides (≥135 mg/dL) and randomized them to icosapent

ethyl (pure EPA ethyl ester) 4 g/day or mineral oil placebo. After a median follow-up of 4.9 years, icosapent ethyl produced a 25% relative risk reduction in the primary composite endpoint of major adverse cardiovascular events (MACE: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina hospitalization; HR 0.75; 95% CI 0.68–0.83; $p < 0.001$) [42]. However, the trial was criticized for the use of mineral oil as placebo, which may have artificially inflated the apparent benefit by increasing LDL-C in the control group.

In contrast, the Statin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial enrolled 13,078 high-risk statin-treated patients with hypertriglyceridemia and randomized them to a high-dose omega-3 carboxylic acid formulation (EPA+DHA, 4 g/day) or corn oil placebo. The trial was terminated early for futility after a median follow-up of 3.5 years, with no significant difference in MACE between groups (HR 0.99; 95% CI 0.90–1.09) and an increased incidence of new-onset atrial fibrillation in the omega-3 group [43]. The divergent results of REDUCE-IT and STRENGTH have generated considerable debate regarding whether the cardiovascular benefit observed with icosapent ethyl is attributable to EPA-specific biological effects (including its superior membrane incorporation, unique antioxidant properties, and lack of LDL-C raising compared with DHA) or to the choice of comparator [44].

The question of atrial fibrillation risk was specifically addressed by the Vitamin D and Omega-3 Trial — cardiac rhythm substudy (VITAL-Rhythm) substudy of the VITAL trial, which enrolled 25,119 participants without a prior history of atrial fibrillation (AF) and randomized them to 1 g/day marine n-3 PUFAs (EPA+DHA in a 1.2:1 ratio) or placebo over a median follow-up of 5.3 years. No significant reduction in incident AF was observed in the omega-3 group overall (HR 0.93; 95% CI 0.84–1.03), although a subgroup analysis suggested a potential increased risk among participants with baseline triglycerides ≥150 mg/dL [110]. A subsequent pooled analysis and updated meta-analysis by Gencer et al. [50] involving data from multiple trials confirmed that the AF risk with n-3 PUFAs is dose-dependent, with higher doses (≥2 g/day) associated with statistically significant increases in AF incidence, while lower doses (≤1 g/day) did not demonstrate this signal. These findings have important implications for patient selection and risk-benefit assessment in clinical practice, particularly in patients with pre-existing susceptibility to AF.

With respect to effects on coronary atherosclerotic plaque burden, the Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE) trial provided imaging-based evidence of icosapent ethyl's anti-atherosclerotic action. In this double-blind, randomized trial, 80 patients with coronary artery disease and elevated triglycerides were assigned to icosapent ethyl 4 g/day or placebo for 18 months, with serial coronary computed tomography angiography (CCTA) performed at baseline and follow-up. Icosapent ethyl produced a significant regression in low-attenuation plaque volume (−17% vs. +109% in the placebo group; $p < 0.001$) and total plaque volume, providing direct imaging evidence of plaque-stabilizing effects beyond triglyceride lowering [111]. These results are mechanistically consistent with EPA's anti-inflammatory, antioxidative, and membrane-stabilizing properties described in Section 5, and with the clinical outcomes benefit observed in REDUCE-IT.

A systematic review and meta-analysis by Khan et al. [103] synthesizing data from 38 randomized controlled trials involving 149,051 participants evaluated the comparative efficacy and safety of different n-3 PUFA formulations across cardiovascular outcomes. This analysis confirmed that high-dose EPA monotherapy was the most effective intervention for reducing major cardiovascular events and cardiovascular mortality, while combined EPA+DHA formulations at equivalent doses produced a less consistent reduction. The network meta-analysis further documented a dose-dependent increase in atrial fibrillation risk across all n-3 PUFA formulations, with EPA monotherapy carrying a numerically higher AF incidence than EPA+DHA combinations — a finding that has prompted ongoing investigation into the mechanisms underlying EPA-specific proarrhythmic risk. Taken together, these large-scale trials demonstrate that the clinical impact of n-3 PUFAs on atherosclerosis-related outcomes is critically dependent on the specific fatty acid composition, dose, and patient risk profile, and that EPA monotherapy at pharmacological doses represents the most evidence-supported approach for cardiovascular risk reduction in statin-treated patients with residual hypertriglyceridemia [103].

Clinical trial results on n-3 PUFAs have been inconsistent, and this heterogeneity may be explained by several key factors. First, differences in study population stratification are important, because trials enrolling patients with established cardiovascular disease, hypertriglyceridemia, or high residual risk may be more likely to show benefit than studies involving lower-risk or more heterogeneous populations. Second, intervention dosage and formulation can substantially affect outcomes, since low-dose supplements, EPA-only preparations, and EPA/DHA combinations may not produce equivalent biological effects. Third, follow-up duration may influence the ability to detect changes in hard cardiovascular endpoints, as shorter studies may capture biomarker changes without sufficient time to demonstrate clinical benefit. In addition, background therapy, adherence, dietary intake, and the choice of primary endpoint may further contribute to discrepant findings. Therefore, the overall evidence suggests that the clinical impact of n-3 PUFAs depends strongly on the studied population, intervention characteristics, and trial design

Table 2. Summary of key clinical studies on PUFAs in cardiovascular disease.

Study type	Population	Intervention	Key outcome	Reference
RCT	Healthy volunteers	Fish oil supplementation	Improved endothelial function, reduced heart rate	[114]
RCT	Hypertriacylglycerolemia (n = 53)	3 g omega-3 daily, 10 weeks	Improved HDL, triglycerides, omega-3 index	[102]
Pooled cohort	191,558 from 58 countries	≥175 g fish/week	Lower CV events in CVD patients only	[53]
Meta-analysis	127,477 patients	Marine n-3 PUFAs	Reduced MI, CHD, CV morbidity	[54]
Meta-analysis	149,051 (38 RCTs)	n-3 PUFAs	Reduced CV mortality; increased AF risk	[103]
RCT	12,513 high CV risk	Daily omega-3	No reduction in CV mortality/ morbidity	[104]
Meta-analysis	68,659 (30 studies)	Linolenic acid	Lower CVD, CV mortality, stroke risk	[106]
RCT (VITAL-Rhythm)	25,119 participants, 5.3 y	1 g EPA+DHA daily	No AF reduction; potential increase in high TG	[110]
RCT (REDUCE-IT)	8179 CVD/DM + high TG	4 g icosapent ethyl (EPA) daily	25% reduction in CV events; ↑AF, bleeding	[42]
RCT (STRENGTH)	13,078 high-risk patients	4 g omega-3 CA (EPA+DHA)	No CV benefit; terminated early for futility	[43]
RCT (EVAPORATE)	80 CAD + high TG, 18 mo	4 g icosapent ethyl daily	Plaque regression: –17% vs +109% (CCTA)	[111]
Network meta-analysis	149,051 (38 trials)	Various omega-3 formulations	High-dose EPA most effective; dose-dependent AF	[50,103]

Abbreviations: RCT, randomized controlled trial; CV, cardiovascular; CVD, cardiovascular disease; AF, atrial fibrillation; TG, triglycerides; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; MI, myocardial infarction; CHD, coronary heart disease; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; HDL, high-density lipoprotein; CA, carboxylic acid formulation; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; STRENGTH, Statin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridemia; EVAPORATE, Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy; VITAL-Rhythm, Vitamin D and Omega-3 Trial — cardiac rhythm substudy.

[112,113]. Thus, the clinical significance of PUFAs in cardiovascular diseases is controversial and further research is needed. Key clinical studies are summarized in Table 2 (Ref. [42,43,50,53,54,102,103,104,106,110,111,114]).

7. Fish Consumption vs. Fish Oil Supplementation

A practical dimension that is critical for translating the evidence on n-3 PUFAs into dietary guidance concerns the distinction between whole fish consumption and fish oil supplementation as vehicles for n-3 PUFA delivery, since these two approaches differ substantially in their nutritional composition, bioavailability, and evidence base for cardiovascular outcomes. Whole oily fish—including salmon, mackerel, sardines, herring, anchovies, and trout—deliver EPA and DHA in the form of membrane-bound phospholipids and intact triglycerides within a complex food matrix that also provides high-quality protein, vitamin D, selenium, astaxanthin (a potent antioxidant carotenoid), and other micronutrients with independent cardiovascular relevance [115]. The phospholipid form of n-3 PUFAs in fish is generally more bioavailable than the ethyl ester form used in many supplements, and the food matrix may enhance lymphatic absorption and reduce lipid oxidation during transit [57]. Large prospective cohort studies and a pooled analysis of 191,558 individuals from 58 countries demonstrated that consumption of at least 175 g of fish per week (approximately 2 servings) was associated with significantly lower major cardiovascular event and mortality risk in patients with pre-existing cardiovascular disease, though associations in the general primary prevention population were less robust, consistent with a greater absolute benefit in higher-risk individuals. Fish oil supplements—available as ethyl esters (icosapent ethyl, omega-3-acid ethyl esters), re-esterified triglycerides, free fatty acids, or phospholipid-bound formulations (krill oil)—offer the advantage of precise dosing, suitability for individuals who cannot or do not eat fish, and the capacity to achieve pharmacological plasma concentrations (2–4 g EPA+DHA/day) not readily attained through diet alone [116]. However, ethyl ester formulations exhibit lower bioavailability than triglyceride or phospholipid forms in the fasted state, and supplement qual-

ity varies considerably with respect to EPA:DHA ratio, degree of oxidation, and contamination with heavy metals or persistent organic pollutants [55,115]. Importantly, clinical trial evidence demonstrates that cardiovascular benefits are dose-dependent and formulation-specific: high-dose pure EPA (icosapent ethyl, 4 g/day; REDUCE-IT) produced a 25% relative risk reduction in MACE, while high-dose EPA+DHA carboxylic acid (STRENGTH) showed no benefit, suggesting that the two formulations may have distinct biological mechanisms and that EPA monotherapy may offer particular advantages in statin-treated patients with residual hypertriglyceridemia. For practical dietary guidance, current evidence supports the following approach: (i) for the general population, consumption of 2 or more servings of oily fish per week is recommended by major cardiovascular societies as a primary prevention measure; (ii) for patients with established CVD, hypertriglyceridemia (TG $\geq$150 mg/dL), or statin-treated residual risk, prescription-grade high-dose EPA (icosapent ethyl 4 g/day) should be considered as a pharmacological intervention with demonstrated outcomes benefit; (iii) for individuals with fish allergy or dietary restrictions, high-quality re-esterified triglyceride omega-3 supplements (with standardized EPA+DHA content $\geq$90%) taken with meals represent a reasonable alternative to dietary fish, though evidence for reduction in hard cardiovascular endpoints with non-prescription supplements remains less consistent [117]. Monitoring the omega-3 index (erythrocyte EPA+DHA as a percentage of total fatty acids; target $\geq$8%) provides a validated biomarker of tissue n-3 PUFA status and can guide therapeutic decisions regarding adequacy of dietary or supplemental intake [118].

8. Future Perspectives

The future of PUFA research in atherosclerosis management necessitates several key investigative directions. First, precision medicine approaches utilizing genetic and metabolomic profiling may identify specific patient subpopulations most likely to benefit from PUFA supplementation [119,120]. Characterization of genetic polymorphisms affecting PUFA metabolism, particularly in fatty acid desaturase genes (FADS1 and FADS2), could enable personalized supplementation strategies based on individual conversion efficiency of alpha-linolenic acid to EPA and DHA [52,121]. Integration of multi-omic data, including genomics, transcriptomics, and lipidomics, with machine learning algorithms may facilitate development of predictive models for PUFA response, enabling targeted therapy for individuals with the greatest potential for cardiovascular benefit [119,122].

Second, development of novel PUFA derivatives and formulations with enhanced bioavailability and oxidative stability may overcome current limitations of conventional supplements [123]. Advanced delivery systems, including nanoparticle encapsulation, liposomal formulations, and structured phospholipid carriers, warrant investigation to improve absorption and tissue targeting while minimizing oxidative degradation [57].

Third, comprehensive investigation of specialized pro-resolving mediators derived from n-3 PUFAs represents a promising therapeutic avenue [74]. Direct administration of resolvins, protectins, and maresins may provide more targeted anti-inflammatory effects compared with parent PUFA supplementation, potentially achieving therapeutic benefits at lower doses with improved safety profiles [124]. Understanding the mechanisms regulating SPM biosynthesis, including the roles of lipoxygenases, cyclooxygenases, and cytochrome P450 enzymes, could identify novel therapeutic targets for modulating endogenous resolution pathways [124]. Investigation of SPM receptor pharmacology and development of small molecule agonists may enable pharmaceutical approaches to harness resolution biology without requiring PUFA supplementation [125]. Fourth, large-scale, adequately powered randomized controlled trials with longer follow-up periods (5–10 years) are essential to definitively establish PUFA efficacy in specific atherosclerosis populations, including primary prevention in high-risk individuals, secondary prevention in established coronary disease, and patients with metabolic syndrome or diabetes [58].

Such trials should incorporate comprehensive biomarker assessments, including advanced lipidomic profiling to characterize PUFA metabolite patterns, inflammatory markers (high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha), and imaging outcomes using coronary computed tomography angiography or intravascular ultrasound to quantify plaque burden and composition changes [126]. Fifth, investigation of combination therapies integrating PUFAs with conventional pharmacological interventions may reveal synergistic effects [127]. Potential combinations include n-3 PUFAs with statins for enhanced lipid-lowering and anti-inflammatory effects, with antiplatelet agents for optimized antithrombotic protection, or with novel anti-inflammatory therapeutics targeting the NLRP3 inflammasome or interleukin-1β pathway [128]. Understanding potential interactions between PUFAs and emerging cardiovascular therapies, including PCSK9 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists, could optimize therapeutic regimens for multifactorial risk reduction [23,87,129].

Sixth, standardization of PUFA supplementation protocols, including optimal dosing regimens (considering both total dose and EPA:DHA ratio), duration of treatment for achieving steady-state tissue incorporation, and formulation specifications (triglyceride versus ethyl ester versus free fatty acid forms), requires establishment through rigorous comparative effectiveness research [130]. Development of reliable biomarkers for monitoring PUFA status beyond simple plasma levels, such as the omega-3 in-

dex (erythrocyte EPA+DHA as percentage of total fatty acids) or comprehensive fatty acid profiling, would facilitate clinical implementation and therapeutic monitoring [111]. Finally, elucidation of the complex interactions between dietary PUFA intake, endogenous fatty acid metabolism, gut microbiota composition and function, and cardiovascular outcomes represents a critical research frontier [131,132,133]. The gut microbiome influences PUFA metabolism through production of bioactive metabolites, modulation of host lipid metabolism, and effects on inflammatory tone, suggesting that microbiome-targeted interventions (probiotics, prebiotics, or synbiotics) combined with PUFA supplementation might enhance therapeutic efficacy [132,133]. Understanding how dietary patterns (Mediterranean, plant-based, or ketogenic diets) and lifestyle factors (exercise, sleep, stress management) modulate PUFA effects could inform comprehensive preventive strategies that optimize cardiovascular health through multiple complementary mechanisms [79]. These future directions hold promise for translating the mechanistic insights gained from preclinical investigations into clinically meaningful therapeutic interventions for atherosclerosis prevention and treatment, moving beyond the one-size-fits-all approach toward personalized, mechanistically-informed cardiovascular care [134].

9. Discussion

Previous fundamental research has demonstrated that n-3 PUFAs can exert beneficial anti-inflammatory and antioxidant effects, improve endothelial function, prevent thrombosis, lower blood lipid levels, improve left ventricular remodeling, stabilize cellular electrical activity, and regulate autonomic nervous system function [135].

In clinical settings, n-3 PUFAs can prevent atherosclerosis and stabilize or reduce plaque. Accumulating evidence suggests that the cardioprotective properties of n-3 PUFAs are associated with their anti-inflammatory effects, involvement in plasma membrane biophysical property regulation, signaling pathway and cardiac ion channel modification, and endothelial function improvement. Despite numerous studies, many obtained data are contradictory and, when analyzed comprehensively, do not provide confidence in the full therapeutic efficacy of n-3 PUFAs. Moreover, analysis of many recent studies has demonstrated that PUFA benefits in cardiovascular event prevention may be exaggerated. Specifically, increased atrial fibrillation risk has been demonstrated with PUFA intake [50].

Simultaneously, it should be noted that many studies do not account for covariate influence, including physical activity level and patient treatment attitudes. Furthermore, the importance of other dietary factors, including other oils consumed by patients, which could have influenced study results, must be considered. Interestingly, salmon, a good dietary PUFA source, is itself affected by coronary atherosclerosis. A cholesterol-rich diet led to worsening lipid parameters and lesion progression [136,137]. These and other data highlight the need for comprehensive assessment of various factors. Thus, PUFAs are involved in regulating numerous mechanisms with complex cross-talk and associated with cardiovascular disease. This necessitates new research that will expand our understanding of vascular wall processes and how these processes can be effectively influenced.

10. Conclusions

The problem of atherosclerosis remains one of the most pressing issues in contemporary medicine. The large patient population, significant impact on quality of life, productivity, and prognosis, pose a substantial economic and social burden for patients, their families, society, and healthcare systems in many countries. The problem's importance is also underscored by the fact that a significant number of cardiovascular diseases today have limited therapeutic prospects. This and other information reinforce the importance of preventive measures that can reduce cardiovascular complication risk. n-3 PUFAs have long been considered promising agents for the prevention and treatment of numerous cardiovascular diseases. Numerous studies highlight the importance of increasing absolute n-3 PUFA intake to reduce cardiovascular disease risk. The beneficial cardiovascular effects of n-3 PUFAs may be based on their anti-inflammatory and anti-atherosclerotic properties. However, given recent conflicting results, further research in this area is needed.

Author Contributions

AB and AO designed the research study. UR, OG analyzed the collected information. All authors wrote the original manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by Russian Science Foundation, grant number 25-15-00082.

Conflicts of Interest

Given his role as the Guest Editor, Alexander Orekhov had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Paramjit S. Tappia.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT-3.5 in order to collect some information, check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

References

[1] Mohd Nor NS, Al-Khateeb AM, Chua YA, Mohd Kasim NA, Mohd Nawawi H. Heterozygous familial hypercholesterolaemia in a pair of identical twins: a case report and updated review. BMC Pediatrics. 2019; 19: 106. https://doi.org/10.1186/s12887-019-1474-y

[2] Dichgans M, Pulit SL, Rosand J. Stroke genetics: discovery, biology, and clinical applications. The Lancet. Neurology. 2019; 18: 587–599. https://doi.org/10.1016/S1474-4422(19)30043-2

[3] Kowara M, Cudnoch-Jedrzejewska A. Pathophysiology of Atherosclerotic Plaque Development-Contemporary Experience and New Directions in Research. International Journal of Molecular Sciences. 2021; 22: 3513. https://doi.org/10.3390/ijms22073513

[4] Spannella F, Giulietti F, Di Pentima C, Sarzani R. Prevalence and Control of Dyslipidemia in Patients Referred for High Blood Pressure: The Disregarded "Double-Trouble" Lipid Profile in Overweight/Obese. Advances in Therapy. 2019; 36: 1426–1437. https://doi.org/10.1007/s12325-019-00941-6

[5] Alradwan I, Al Fayez N, Alomary MN, Alshehri AA, Aodah AH, Almughem FA, et al. Emerging Trends and Innovations in the Treatment and Diagnosis of Atherosclerosis and Cardiovascular Disease: A Comprehensive Review towards Healthier Aging. Pharmaceutics. 2024; 16: 1037. https://doi.org/10.3390/pharmaceutics16081037

[6] Schunck WH, Konkel A, Fischer R, Weylandt KH. Therapeutic potential of omega-3 fatty acid-derived epoxyeicosanoids in cardiovascular and inflammatory diseases. Pharmacology & Therapeutics. 2018; 183: 177–204. https://doi.org/10.1016/j.pharmthera.2017.10.016

[7] Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. Lancet (London, England). 1971; 1: 1143–1145. https://doi.org/10.1016/s0140-6736(71)91658-8

[8] Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of Atherosclerosis. International Journal of Molecular Sciences. 2022; 23: 3346. https://doi.org/10.3390/ijms23063346

[9] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011; 473: 317–325. https://doi.org/10.1038/nature10146

[10] Morrison AM, Sullivan AE, Aday AW. Atherosclerotic Disease: Pathogenesis and Approaches to Management. The Medical Clinics of North America. 2023; 107: 793–805. https://doi.org/10.1016/j.mcna.2023.04.004

[11] Gusev E, Sarapultsev A. Atherosclerosis and Inflammation: Insights from the Theory of General Pathological Processes. International Journal of Molecular Sciences. 2023; 24: 7910. https://doi.org/10.3390/ijms24097910

[12] Ajoolabady A, Pratico D, Lin L, Mantzoros CS, Bahijri S, Tuomilehto J, et al. Inflammation in atherosclerosis: pathophysiology and mechanisms. Cell Death & Disease. 2024; 15: 817. https://doi.org/10.1038/s41419-024-07166-8

[13] Xu Y, Zeng X, Tu WJ. Editorial: Pathophysiology, treatment and rehabilitation of atherosclerosis-related diseases in geriatric population. Frontiers in Medicine. 2024; 11: 1358769. https://doi.org/10.3389/fmed.2024.1358769

[14] Björkegren JLM, Lusis AJ. Atherosclerosis: Recent developments. Cell. 2022; 185: 1630–1645. https://doi.org/10.1016/j.cell.2022.04.004

[15] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 139: e1082–e1143. https://doi.org/10.1161/CIR.0000000000000625

[16] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 139: e1046–e1081. https://doi.org/10.1161/CIR.0000000000000624

[17] Omidi F, Rahmannia M, Shahidi Bonjar AH, Mohammadsharifi P, Nasiri MJ, Sarmastzadeh T. Ezetimibe and atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Frontiers in Cardiovascular Medicine. 2023; 10: 1269172. https://doi.org/10.3389/fcvm.2023.1269172

[18] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 140: e596–e646. https://doi.org/10.1161/CIR.0000000000000678

[19] Yurdagul A, Jr. Crosstalk Between Macrophages and Vascular Smooth Muscle Cells in Atherosclerotic Plaque Stability. Arteriosclerosis, Thrombosis, and Vascular Biology. 2022; 42: 372–380. https://doi.org/10.1161/ATVBAHA.121.316233

[20] Ancion A, Tridetti J, Nguyen Trung ML, Oury C, Lancellotti P. A Review of the Role of Bradykinin and Nitric Oxide in the Cardioprotective Action of Angiotensin-Converting Enzyme Inhibitors: Focus on Perindopril. Cardiology and Therapy. 2019; 8: 179–191. https://doi.org/10.1007/s40119-019-00150-w

[21] Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanas F, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2018; 391: 205–218. https://doi.org/10.1016/S0140-6736(17)32458-3

[22] Deng M, Su D, Xu S, Little PJ, Feng X, Tang L, et al. Metformin and Vascular Diseases: A Focused Review on Smooth Muscle Cell Function. Frontiers in pharmacology. 2020; 11. https://doi.org/10.3389/fphar.2020.00635

[23] Liu Z, Ma X, Ilyas I, Zheng X, Luo S, Little PJ, et al. Impact of sodium glucose cotransporter 2 (SGLT2) inhibitors on atherosclerosis: from pharmacology to pre-clinical and clinical therapeutics. Theranostics. 2021; 11(9): 4502–4515. https://doi.org/10.7150/thno.54498

[24] Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical implications in cardiovascular prevention. Biochemical Pharmacology. 2009; 77: 937–946. https://doi.org/10.1016/j.bcp.2008.10.020

[25] Park HG, Park WJ, Kothapalli KS, Brenna JT. The fatty acid desaturase 2 (FADS2) gene product catalyzes Δ4 desaturation to yield n-3 docosahexaenoic acid and n-6 docosapentaenoic acid in human cells. FASEB journal: official publication of the Federation of American Societies for Experimental Biology, 2015; 29: 3911–3919. https://doi.org/10.1096/fj.15-271783

[26] Emken EA, Adlof RO, Gulley RM. Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. Biochimica et Biophysica Acta. 1994; 1213: 277–288. https://doi.org/10.1016/0005-2760(94)00054-9

[27] Murru E, Banni S, Carta G. Nutritional properties of dietary omega-3-enriched phospholipids. BioMed Research International. 2013; 2013: 965417. https://doi.org/10.1155/2013/965417

[28] Wallner S, Schmitz G. Plasmalogens the neglected regulatory and scavenging lipid species. Chemistry and Physics of Lipids. 2011; 164: 573–589. https://doi.org/10.1016/j.chemphyslip.2011.06.008

[29] Kotlyarov S, Kotlyarova A. Clinical significance of polyunsaturated fatty acids in the prevention of cardiovascular diseases. Frontiers in Nutrition. 2022; 9: 998291. https://doi.org/10.3389/fnut.2022.998291

[30] Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nature Reviews. Immunology. 2008; 8: 349–361. https://doi.org/10.1038/nri2294

[31] Bays HE, Braeckman RA, Ballantyne CM, Kastelein JJ, Otvos JD, Stirtan WG, et al. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on lipoprotein particle concentration and size in patients with very high triglyceride levels (the MARINE study). Journal of Clinical Lipidology. 2012; 6: 565–572. https://doi.org/10.1016/j.jacl.2012.07.001

[32] Bäck M, Hansson GK. Omega-3 fatty acids, cardiovascular risk, and the resolution of inflammation. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2019; 33: 1536–1539. https://doi.org/10.1096/fj.201802445R

[33] Arabi SM, Bahari H, Chambari M, Bahrami LS, Mohaildeen Gubari M I, Watts GF, et al. Omega-3 fatty acids and endothelial function: A GRADE-assessed systematic review and meta-analysis. European journal of clinical investigation. 2024; 54: e14109. https://doi.org/10.1111/eci.14109

[34] Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation. 2003; 107: 2646–2652. https://doi.org/10.1161/01.CIR.0000069566.78305.33

[35] Moreno C, Macías A, Prieto A, de la Cruz A, González T, Valenzuela C. Effects of n-3 Polyunsaturated Fatty Acids on Cardiac Ion Channels. Frontiers in physiology. 2012; 3: 245. https://doi.org/10.3389/fphys.2012.00245

[36] Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. American Journal of Hypertension. 2014; 27: 885–896. https://doi.org/10.1093/ajh/hpu024

[37] Simonetto M, Infante M, Sacco RL, Rundek T, Della-Morte D. A Novel Anti-Inflammatory Role of Omega-3 PUFAs in Prevention and Treatment of Atherosclerosis and Vascular Cognitive Impairment and Dementia. Nutrients. 2019; 11: 2279. https://doi.org/10.3390/nu11102279

[38] Kanner J, Lapidot T. The stomach as a bioreactor: dietary lipid peroxidation in the gastric fluid and the effects of plant-derived antioxidants. Free Radical Biology & Medicine. 2001; 31: 1388–1395. https://doi.org/10.1016/s0891-5849(01)00718-3

[39] Gao L, Wang J, Sekhar KR, Yin H, Yared NF, Schneider SN, et al. Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3. The Journal of Biological Chemistry. 2007; 282: 2529–2537. https://doi.org/10.1074/jbc.M607622200

[40] Kobayashi M, Yamamoto M. Molecular mechanisms activating the Nrf2-Keap1 pathway of antioxidant gene regulation. Antioxidants & Redox Signaling. 2005; 7: 385–394. https://doi.org/10.1089/ars.2005.7.385

[41] Ayer A, Zarjou A, Agarwal A, Stocker R. Heme Oxygenases in Cardiovascular Health and Disease. Physiological Reviews. 2016; 96: 1449–1508. https://doi.org/10.1152/physrev.00003.2016

[42] Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. The New England Journal of Medicine. 2019; 380: 11–22. https://doi.org/10.1056/NEJMoa1812792

[43] Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. JAMA. 2020; 324: 2268–2280. https://doi.org/10.1001/jama.2020.22258

[44] Zhang W, Gan D, Huo S, Chen P. Unraveling the discrepancies between REDUCE-IT and STRENGTH trials with omega-3 fatty acids: new analytical approaches. Frontiers in Nutrition. 2024; 11: 1490953. https://doi.org/10.3389/fnut.2024.1490953

[45] Michaeloudes C, Christodoulides S, Christodoulou P, Kyriakou TC, Patrikios I, Stephanou A. Variability in the Clinical Effects of the Omega-3 Polyunsaturated Fatty Acids DHA and EPA in Cardiovascular Disease-Possible Causes and Future Considerations. Nutrients. 2023; 15: 4830. https://doi.org/10.3390/nu15224830

[46] Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. Circulation. 2019; 140: e673–e691. https://doi.org/10.1161/CIR.0000000000000709

[47] Bradberry JC, Hilleman DE. Overview of omega-3 Fatty Acid therapies. P & T: a Peer-reviewed Journal for Formulary Management. 2013; 38: 681–691.

[48] Shramko VS, Polonskaya YV, Kashtanova EV, Stakhneva EM, Ragino YI. The Short Overview on the Relevance of Fatty Acids for Human Cardiovascular Disorders. Biomolecules. 2020; 10: 1127. https://doi.org/10.3390/biom10081127

[49] Mariamenatu AH, Abdu EM. Overconsumption of Omega-6 Polyunsaturated Fatty Acids (PUFAs) versus Deficiency of Omega-3 PUFAs in Modern-Day Diets: The Disturbing Factor for Their "Balanced Antagonistic Metabolic Functions" in the Human Body. Journal of Lipids. 2021; 2021: 8848161. https://doi.org/10.1155/2021/8848161

[50] Gencer B, Djousse L, Al-Ramady OT, Cook NR, Manson JE, Albert CM. Effect of Long-Term Marine ω-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. Circulation. 2021; 144: 1981–1990. https://doi.org/10.1161/CIRCULATIONAHA.121.055654

[51] Bozbas E, Zhou R, Soyama S, Allen-Redpath K, Mitchell JL, Fisk HL, et al. Dietary n-3 polyunsaturated fatty acids alter the number, fatty acid profile and coagulatory activity of circulating and platelet-derived extracellular vesicles: a randomized, controlled crossover trial. The American Journal of Clinical Nutrition. 2024; 119: 1175–1186. https://doi.org/10.1016/j.ajcnut.2024.03.008

[52] Mathias RA, Pani V, Chilton FH. Genetic Variants in the FADS Gene: Implications for Dietary Recommendations for Fatty Acid Intake. Current Nutrition Reports. 2014; 3: 139–148. https://doi.org/10.1007/s13668-014-0079-1

[53] Mohan D, Mente A, Dehghan M, Rangarajan S, O'Donnell M, Hu W, et al. Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With

or Without Vascular Disease From 58 Countries. AMA internal medicine, 2021; 181: 631–649. https://doi.org/10.1001/jamainternmed.2021.0036

[54] Hu Y, Hu FB, Manson JE. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. Journal of the American Heart Association. 2019; 8: e013543. https://doi.org/10.1161/JAHA.119.013543

[55] Mason RP, Sherratt SCR. Omega-3 fatty acid fish oil dietary supplements contain saturated fats and oxidized lipids that may interfere with their intended biological benefits. Biochemical and Biophysical Research Communications. 2017; 483: 425–429. https://doi.org/10.1016/j.bbrc.2016.12.127

[56] Siniarski A, Haberka M, Mostowik M, Gołębiowska-Wiatrak R, Poręba M, Malinowski KP, et al. Treatment with omega-3 polyunsaturated fatty acids does not improve endothelial function in patients with type 2 diabetes and very high cardiovascular risk: A randomized, double-blind, placebo-controlled study (Omega-FMD). Atherosclerosis. 2018; 271: 148–155. https://doi.org/10.1016/j.atherosclerosis.2018.02.030

[57] Dyerberg J, Madsen P, Møller JM, Aardestrup I, Schmidt EB. Bioavailability of marine n-3 fatty acid formulations. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2010; 83: 137–141. https://doi.org/10.1016/j.plefa.2010.06.007

[58] Ghasemifard S, Turchini GM, Sinclair AJ. Omega-3 long chain fatty acid "bioavailability": a review of evidence and methodological considerations. Progress in Lipid Research. 2014; 56: 92–108. https://doi.org/10.1016/j.plipres.2014.09.001

[59] Wong SW, Kwon MJ, Choi AMK, Kim HP, Nakahira K, Hwang DH. Fatty acids modulate Toll-like receptor 4 activation through regulation of receptor dimerization and recruitment into lipid rafts in a reactive oxygen species-dependent manner. The Journal of Biological Chemistry. 2009; 284: 27384–27392. https://doi.org/10.1074/jbc.M109.044065

[60] Weatherill AR, Lee JY, Zhao L, Lemay DG, Youn HS, Hwang DH. Saturated and polyunsaturated fatty acids reciprocally modulate dendritic cell functions mediated through TLR4. Journal of Immunology (Baltimore, Md.: 1950). 2005; 174: 5390–5397. https://doi.org/10.4049/jimmunol.174.9.5390

[61] Zhang Y, Chen H, Zhang W, Cai Y, Shan P, Wu D, et al. Arachidonic acid inhibits inflammatory responses by binding to myeloid differentiation factor-2 (MD2) and preventing MD2/toll-like receptor 4 signaling activation. Biochimica et Biophysica Acta. Molecular Basis of Disease. 2020; 1866: 165683. https://doi.org/10.1016/j.bbadis.2020.165683

[62] Shen L, Yang Y, Ou T, Key CC, Tong SH, Sequeira RC, et al. Dietary PUFAs attenuate NLRP3 inflammasome activation via enhancing macrophage autophagy. Journal of lipid research, 2017; 58: 1808–1821. https://doi.org/10.1194/jlr.M075879

[63] Kersten S. Integrated physiology and systems biology of PPARα. Molecular Metabolism. 2014; 3: 354–371. https://doi.org/10.1016/j.molmet.2014.02.002

[64] Varga T, Czimmerer Z, Nagy L. PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation. Biochimica et Biophysica Acta. 2011; 1812: 1007–1022. https://doi.org/10.1016/j.bbadis.2011.02.014

[65] Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochemical Society Transactions. 2017; 45: 1105–1115. https://doi.org/10.1042/BST20160474

[66] Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell. 2010; 142: 687–698. https://doi.org/10.1016/j.cell.2010.07.041

[67] Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. Journal of Lipid Research. 2002; 43: 1363–1379. https://doi.org/10.1194/jlr.r200004-jlr200

[68] Sherratt SCR, Juliano RA, Copland C, Bhatt DL, Libby P, Mason RP. EPA and DHA containing phospholipids have contrasting effects on membrane structure. Journal of lipid research. 2021; 62: 100106. https://doi.org/10.1016/j.jlr.2021.100106

[69] Harris WS. n-3 fatty acids and lipoproteins: comparison of results from human and animal studies. Lipids. 1996; 31: 243–252. https://doi.org/10.1007/BF02529870

[70] Kroupa O, Vorrsjö E, Stienstra R, Mattijssen F, Nilsson SK, Sukonina V, et al. Linking nutritional regulation of Angptl4, Gpihbp1, and Lmf1 to lipoprotein lipase activity in rodent adipose tissue. BMC Physiology. 2012; 12: 13. https://doi.org/10.1186/1472-6793-12-13

[71] Chen W, Jump DB, Esselman WJ, Busik JV. Inhibition of cytokine signaling in human retinal endothelial cells through modification of caveolae/lipid rafts by docosahexaenoic acid. Investigative Ophthalmology & Visual Science. 2007; 48: 18–26. https://doi.org/10.1167/iovs.06-0619

[72] Shaikh SR, Rockett BD, Salameh M, Carraway K. Docosahexaenoic acid modifies the clustering and size of lipid rafts and the lateral organization and surface expression of MHC class I of EL4 cells. The Journal of Nutrition. 2009; 139: 1632–1639. https://doi.org/10.3945/jn.109.108720

[73] Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. The Journal of Clinical Investigation. 2018; 128: 2657–2669. https://doi.org/10.1172/JCI97943

[74] Salazar J, Pirela D, Nava M, Castro A, Angarita L, Parra H, et al. Specialized Proresolving Lipid Mediators: A Potential Therapeutic Target for Atherosclerosis. International journal of molecular sciences, 2022; 23: 3133. https://doi.org/10.3390/ijms23063133

[75] Recchiuti A, Serhan CN. Pro-Resolving Lipid Mediators (SPMs) and Their Actions in Regulating miRNA in Novel Resolution Circuits in Inflammation. Frontiers in Immunology. 2012; 3: 298. https://doi.org/10.3389/fimmu.2012.00298

[76] Fredman G, Hellmann J, Proto JD, Kuriakose G, Colas RA, Dorweiler B, et al. An imbalance between specialized pro-resolving lipid mediators and pro-inflammatory leukotrienes promotes instability of atherosclerotic plaques. Nature Communications. 2016; 7: 12859. https://doi.org/10.1038/ncomms12859

[77] Avivar-Valderas A, Conti MJ. The Activation of TLR or IL-1R in Microglia Mediates Neuroinflammation Through IRAK. European Journal of Neurodegenerative Diseases. 2025; 14: 58–61.

[78] Gao LG, Cao J, Mao QX, Lu XC, Zhou XL, Fan L. Influence of omega-3 polyunsaturated fatty acid-supplementation on platelet aggregation in humans: a meta-analysis of randomized controlled trials. Atherosclerosis. 2013; 226: 328–334. https://doi.org/10.1016/j.atherosclerosis.2012.10.056

[79] Mozaffarian D, Wu JHY. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. Journal of the American College of Cardiology. 2011; 58: 2047–2067. https://doi.org/10.1016/j.jacc.2011.06.063

[80] Ku CS, Park Y, Coleman SL, Lee J. Unsaturated fatty acids repress expression of ATP binding cassette transporter A1 and G1 in RAW 264.7 macrophages. The Journal of Nutritional Biochemistry. 2012; 23: 1271–1276. https://doi.org/10.1016/j.jnutbio.2011.07.007

[81] Phillips MC. Molecular mechanisms of cellular cholesterol efflux. The Journal of Biological Chemistry. 2014; 289: 24020–24029. https://doi.org/10.1074/jbc.R114.583658

[82] Fujii R, Yamada H, Munetsuna E, Yamazaki M, Mizuno G, Ando Y, et al. Dietary fish and ω-3 polyunsaturated fatty acids are associated with leukocyte ABCA1 DNA methylation levels. Nutrition (Burbank, Los Angeles County, Calif.). 2021; 81: 110951.

https://doi.org/10.1016/j.nut.2020.110951
[83] Pizzini A, Lunger L, Demetz E, Hilbe R, Weiss G, Ebenbichler C, et al. The Role of Omega-3 Fatty Acids in Reverse Cholesterol Transport: A Review. Nutrients, 2017; 9: 1099. https://doi.org/10.3390/nu9101099
[84] Morton AM, Furtado JD, Mendivil CO, Sacks FM. Dietary unsaturated fat increases HDL metabolic pathways involving apoE favorable to reverse cholesterol transport. JCI Insight. 2019; 4: e124620. https://doi.org/10.1172/jci.insight.124620
[85] Yu L, Li-Hawkins J, Hammer RE, Berge KE, Horton JD, Cohen JC, et al. Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol. The Journal of clinical investigation. 2002; 110: 671–680. https://doi.org/10.1172/JCI16001
[86] Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, et al. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. Nature Medicine. 2005; 11: 90–94. https://doi.org/10.1038/nm1168
[87] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England Journal of Medicine. 2016; 375: 311–322. https://doi.org/10.1056/NEJMoa1603827
[88] Zang T, Chen H, Shen S, Xu F, Wang R, Yin J, et al. Highly Purified Eicosapentaenoic Acid Alleviates the Inflammatory Response and Oxidative Stress in Macrophages during Atherosclerosis via the miR-1a-3p/sFRP1/Wnt/PCP-JNK Pathway. Oxidative Medicine and Cellular Longevity. 2022; 2022: 9451058. https://doi.org/10.1155/2022/9451058
[89] Laguna-Fernandez A, Checa A, Carracedo M, Artiach G, Petri MH, Baumgartner R, et al. ERV1/ChemR23 Signaling Protects Against Atherosclerosis by Modifying Oxidized Low-Density Lipoprotein Uptake and Phagocytosis in Macrophages. Circulation. 2018; 138: 1693–1705. https://doi.org/10.1161/CIRCULATIONAHA.117.032801
[90] Liu G, Gong Y, Zhang R, Piao L, Li X, Liu Q, et al. Resolvin E1 attenuates injury-induced vascular neointimal formation by inhibition of inflammatory responses and vascular smooth muscle cell migration. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2018; 32: 5413–5425. https://doi.org/10.1096/fj.201800173R
[91] Shearer GC, Savinova OV, Harris WS. Fish oil – how does it reduce plasma triglycerides? Biochimica et Biophysica Acta. 2012; 1821: 843–851. https://doi.org/10.1016/j.bbalip.2011.10.011
[92] Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, Bray G, et al. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. Journal of Lipid Research. 2003; 44: 479–486. https://doi.org/10.1194/jlr.M200361-JLR200
[93] Adili R, Hawley M, Holinstat M. Regulation of platelet function and thrombosis by omega-3 and omega-6 polyunsaturated fatty acids. Prostaglandins & Other Lipid Mediators. 2018; 139: 10–18. https://doi.org/10.1016/j.prostaglandins.2018.09.005
[94] Pase MP, Grima NA, Sarris J. Do long-chain n-3 fatty acids reduce arterial stiffness? A meta-analysis of randomised controlled trials. The British Journal of Nutrition. 2011; 106: 974–980. https://doi.org/10.1017/S0007114511002819
[95] Chawla A, Boisvert WA, Lee CH, Laffitte BA, Barak Y, Joseph SB, et al. A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. Molecular Cell. 2001; 7: 161–171. https://doi.org/10.1016/s1097-2765(01)00164-2
[96] McLaren JE, Michael DR, Guschina IA, Harwood JL, Ramji DP. Eicosapentaenoic acid and docosahexaenoic acid regulate modified LDL uptake and macropinocytosis in human macrophages. Lipids. 2011; 46: 1053–1061. https://doi.org/10.1007/s11745-011-3598-1
[97] Zhao Z, Wen H, Fefelova N, Allen C, Guillaume N, Xiao D, et al. Docosahexaenoic Acid reduces the incidence of early afterdepolarizations caused by oxidative stress in rabbit ventricular myocytes. Frontiers in Physiology. 2012; 3: 252. https://doi.org/10.3389/fphys.2012.00252
[98] Huang CY, Sheu WHH, Chiang AN. Docosahexaenoic acid and eicosapentaenoic acid suppress adhesion molecule expression in human aortic endothelial cells via differential mechanisms. Molecular Nutrition & Food Research. 2015; 59: 751–762. https://doi.org/10.1002/mnfr.201400687
[99] Liu YH, Li XY, Chen CY, Zhang HM, Kang JX. Omega-3 fatty acid intervention suppresses lipopolysaccharide-induced inflammation and weight loss in mice. Mar Drugs. 2015; 13: 1026–1036. https://doi.org/10.3390/md13021026
[100] Li R, Wang Y, Xu J, Yu J, Li B. Effects of n-3 Polyunsaturated Fatty Acid Supplementation on Cardiovascular Indices in Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials. Reviews in Cardiovascular Medicine. 2025; 26: 25882. https://doi.org/10.31083/RCM25882
[101] Wu SY, Mayneris-Perxachs J, Lovegrove JA, Todd S, Yaqoob P. Fish-oil supplementation alters numbers of circulating endothelial progenitor cells and microparticles independently of eNOS genotype. The American Journal of Clinical Nutrition. 2014; 100: 1232–1243. https://doi.org/10.3945/ajcn.114.088880
[102] Dawczynski C, Massey KA, Ness C, Kiehntopf M, Stepanow S, Platzer M, et al. Randomized placebo-controlled intervention with n-3 LC-PUFA-supplemented yoghurt: effects on circulating eicosanoids and cardiovascular risk factors. Clinical Nutrition (Edinburgh, Scotland). 2013; 32: 686–696. https://doi.org/10.1016/j.clnu.2012.12.010
[103] Khan SU, Lone AN, Khan MS, Virani SS, Blumenthal RS, Nasir K, et al. Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis. EClinicalMedicine. 2021; 38: 100997. https://doi.org/10.1016/j.eclinm.2021.100997
[104] Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, Caimi V, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. The New England Journal of Medicine. 2013; 368: 1800–1808. https://doi.org/10.1056/NEJMoa1205409
[105] Saini RK, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance - A review. Life Sciences. 2018; 203: 255–267. https://doi.org/10.1016/j.lfs.2018.04.049
[106] Marklund M, Wu JHY, Imamura F, Del Gobbo LC, Fretts A, de Goede J, et al. Biomarkers of Dietary Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality. Circulation. 2019; 139: 2422–2436. https://doi.org/10.1161/CIRCULATIONAHA.118.038908
[107] Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, et al. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. Circulation. 2014; 130: 1568–1578. https://doi.org/10.1161/CIRCULATIONAHA.114.010236
[108] Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ (Clinical Research Ed.). 2013; 346: e8707. https://doi.org/10.1136/bmj.e8707
[109] de Goede J, Geleijnse JM, Boer JM, Kromhout D, Verschuren WM. Linoleic acid intake, plasma cholesterol and 10-year incidence of CHD in 20,000 middle-aged men and women in the Netherlands. The British Journal of Nutrition. 2012; 107: 1070–

1076. https://doi.org/10.1017/S0007114511003837
[110] Albert CM, Cook NR, Pester J, Moorthy MV, Ridge C, Danik JS, et al. Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation: A Randomized Clinical Trial. JAMA. 2021; 325: 1061–1073. https://doi.org/10.1001/jama.2021.1489
[111] Budoff MJ, Bhatt DL, Kinninger A, Lakshmanan S, Muhlestein JB, Le VT, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. European Heart Journal. 2020; 41: 3925–3932. https://doi.org/10.1093/eurheartj/ehaa652
[112] DiNicolantonio JJ, O'Keefe JH. The Benefits of Omega-3 Fats for Stabilizing and Remodeling Atherosclerosis. Missouri Medicine. 2020; 117: 65–69.
[113] Kris-Etherton PM, Harris WS, Appel LJ, American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002; 106: 2747–2757. https://doi.org/10.1161/01.cir.0000038493.65177.94
[114] Shah AP, Ichiuji AM, Han JK, Traina M, El-Bialy A, Meymandi SK, et al. Cardiovascular and endothelial effects of fish oil supplementation in healthy volunteers. Journal of Cardiovascular Pharmacology and Therapeutics. 2007; 12: 213–219. https://doi.org/10.1177/1074248407304749
[115] Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006; 296: 1885–1899. https://doi.org/10.1001/jama.296.15.1885
[116] Kris-Etherton PM, Grieger JA, Etherton TD. Dietary reference intakes for DHA and EPA. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2009; 81: 99–104. https://doi.org/10.1016/j.plefa.2009.05.011
[117] Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. Journal of the American College of Nutrition. 2001; 20: 5–19. https://doi.org/10.1080/07315724.2001.10719008
[118] Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Preventive Medicine. 2004; 39: 212–220. https://doi.org/10.1016/j.ypmed.2004.02.030
[119] Shaikh SR, Bazinet RP. Heterogeneity in the response to n-3 polyunsaturated fatty acids. Current opinion in clinical nutrition and metabolic care. 2023; 26: 284–287. https://doi.org/10.1097/MCO.0000000000000930
[120] Phillips CM, Tierney AC, Roche HM. Gene-nutrient interactions in the metabolic syndrome. Journal of Nutrigenetics and Nutrigenomics. 2008; 1: 136–151. https://doi.org/10.1159/000112461
[121] Lemaitre RN, Tanaka T, Tang W, Manichaikul A, Foy M, Kabagambe EK, et al. Genetic loci associated with plasma phospholipid n-3 fatty acids: a meta-analysis of genome-wide association studies from the CHARGE Consortium. PLoS Genetics. 2011; 7: e1002193. https://doi.org/10.1371/journal.pgen.1002193
[122] Piening BD, Zhou W, Contrepois K, Röst H, Gu Urban GJ, Mishra T, et al. Integrative Personal Omics Profiles during Periods of Weight Gain and Loss. Cell Systems. 2018; 6: 157–170.e8. https://doi.org/10.1016/j.cels.2017.12.013
[123] Homroy S, Chopra R, Singh PK, Dhiman A, Chand M, Talwar B. Role of encapsulation on the bioavailability of omega-3 fatty acids. Comprehensive reviews in food science and food safety. 2024; 23: e13272. https://doi.org/10.1111/1541-4337.13272
[124] Chiang N, Serhan CN. Specialized pro-resolving mediator network: an update on production and actions. Essays in biochemistry. 2020; 64: 443–462. https://doi.org/10.1042/EBC20200018
[125] Pirault J, Bäck M. Lipoxin and Resolvin Receptors Transducing the Resolution of Inflammation in Cardiovascular Disease. Frontiers in pharmacology. 2018; 9. https://doi.org/10.3389/fphar.2018.01273
[126] Norris PC, Dennis EA. Omega-3 fatty acids cause dramatic changes in TLR4 and purinergic eicosanoid signaling. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109: 8517–8522. https://doi.org/10.1073/pnas.1200189109
[127] Dalli J, Colas RA, Serhan CN. Novel n-3 immunoresolvents: structures and actions. Scientific Reports. 2013; 3: 1940. https://doi.org/10.1038/srep01940
[128] Chandrasekharan JA, Sharma-Walia N. Lipoxins: nature's way to resolve inflammation. Journal of Inflammation Research. 2015; 8: 181–192. https://doi.org/10.2147/JIR.S90380
[129] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England Journal of Medicine. 2017; 376: 1713–1722. https://doi.org/10.1056/NEJMoa1615664
[130] Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet (London, England). 2007; 369: 1090–1098. https://doi.org/10.1016/S0140-6736(07)60527-3
[131] Costantini L, Molinari R, Farinon B, Merendino N. Impact of Omega-3 Fatty Acids on the Gut Microbiota. International Journal of Molecular Sciences. 2017; 18: 2645. https://doi.org/10.3390/ijms18122645
[132] Hutchinson AN, Tingö L, Brummer RJ. The Potential Effects of Probiotics and ω-3 Fatty Acids on Chronic Low-Grade Inflammation. Nutrients. 2020; 12: 2402. https://doi.org/10.3390/nu12082402
[133] Miyamoto J, Igarashi M, Watanabe K, Karaki SI, Mukouyama H, Kishino S, et al. Gut microbiota confers host resistance to obesity by metabolizing dietary polyunsaturated fatty acids. Nature communications, 2019; 10: 4007. https://doi.org/10.1038/s41467-019-11978-0
[134] Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clinical Therapeutics. 2007; 29: 1354–1367. https://doi.org/10.1016/j.clinthera.2007.07.018
[135] Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. The American Journal of Clinical Nutrition. 2008; 87: 1991S–1996S. https://doi.org/10.1093/ajcn/87.6.1991S
[136] Dalum AS, Kristthorsdottir KH, Griffiths DJ, Bjørklund K, Poppe TT. Arteriosclerosis in the ventral aorta and epicarditis in the bulbus arteriosus of Atlantic salmon (Salmo salar L). Journal of Fish Diseases. 2017; 40: 797–809. https://doi.org/10.1111/jfd.12561
[137] Farrell AP, Saunders RL, Freeman HC, Mommsen TP. Arteriosclerosis in Atlantic salmon. Effects of dietary cholesterol and maturation. Arteriosclerosis. 1986; 6: 453–461. https://doi.org/10.1161/01.atv.6.4.453