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Seafood-Derived Omega-3 Fatty Acids and Cardiovascular Disease Prevention: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Cardiovascular disease (CVD) remains the leading cause of death globally, representing 32 % of all deaths and necessitating effective preventive strategies. Despite widespread interest in omega-3 fatty acids for cardiovascular protection, conflicting evidence from randomized trials has created uncertainty regarding optimal formulations (EPA vs. EPA+DHA), efficacy, and risk-benefit profiles. This systematic review addresses critical knowledge gaps by synthesizing randomized controlled trial (RCT) evidence through 2024, providing formulation-specific comparison between EPA monotherapy and EPA+DHA combinations, as well as integrating comprehensive atrial fibrillation risk assessment. We searched EMBASE, PubMed, Cochrane Library, and ClinicalTrials.gov through August 2024 using comprehensive Boolean search strategies, identifying 38 RCTs involving 149,051 participants. Two independent reviewers performed both study selection and data extraction work. The researchers used the Cochrane Risk of Bias 2 tool to determine the risk of bias assessment. The meta-analysis used random-effects models to measure statistical diversity through I^2 statistics. GRADE methodology evaluated certainty of evidence. Omega-3 supplementation significantly reduced cardiovascular mortality (RR 0.93, 95 % CI: 0.88-0.98; moderate certainty evidence), non-fatal myocardial infarction (RR 0.87, 95 % CI: 0.81-0.93; moderate certainty), coronary heart disease events (RR 0.91, 95 % CI: 0.87-0.96; moderate certainty), and major adverse cardiovascular events (RR 0.95, 95 % CI: 0.92-0.98; moderate certainty). EPA monotherapy demonstrated superior efficacy versus EPA+DHA (interaction $p<0.01$ for MACE). No benefit was observed for all-cause mortality (RR 0.97, 95 % CI: 0.93-1.02; low certainty) or stroke (RR 1.04, 95 % CI: 0.91-1.18; low certainty). Atrial fibrillation risk increased (RR 1.26, 95 % CI: 1.08-1.48; moderate certainty), particularly with high-dose EPA. This meta-analysis provides updated synthesis through 2024, first systematic formulation-specific comparison, and integrated benefit-harm assessment, addressing critical gaps in omega-3 therapy guidance. We recommend 2-3 weekly fish servings for primary prevention and purified EPA supplementation (4 g/day) for high-risk patients with established CVD, hypertriglyceridemia, and concurrent statin use, with atrial fibrillation monitoring. Future research should optimize patient selection criteria and clarify formulation-specific mechanisms.

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1.0 Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually, representing 32 % of all global deaths (Olamide et al., 2023). The development of new drugs and interventional cardiology procedures has not decreased cardiovascular danger for treated patients who have high triglyceride levels while taking statins. The existing treatment gap has increased interest in additional preventive methods which nutritional treatments show potential to reduce cardiovascular risk. Omega-3 polyunsaturated fatty acids (PUFAs) from marine sources, principally eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA), have gained extensive research interest because they function as protective agents for heart health. Early observational studies from populations with high fish consumption established strong inverse associations between seafood-derived omega-3 intake and CVD incidence. The combination of epidemiological evidence together with mechanistic proof that shows anti-inflammatory effects and lipid modulation, and anti-thrombotic effects and plaque-stabilizing properties created strong interest in omega-3 supplementation for cardiovascular prevention (Khan et al., 2021; Sherratt et al., 2023).

The clinical adoption of observational findings has encountered challenges because RCT studies produced inconsistent results. The GISSI-Prevenzione trial (Jialal et al., 1999) and JELIS trial (Yokoyama, 2009) established cardiovascular treatment benefits which later large-scale RCTs found to have limited impact. The publication of REDUCE-IT with 25 % event reduction with high-dose EPA (Toth et al., 2022), VITAL has modest non-significant benefits with EPA+DHA (Kris-Etherton et al., 2019) and STRENGTH showed no benefit despite high-dose EPA+DHA resulting in heightened disagreement between clinical researchers. The conflicting research outcomes about omega-3 fatty acids in cardiovascular prevention have created major confusion for both clinicians and policymakers because they do not understand how to use these substances.

The research study faces three important knowledge gaps which require further investigation. The first meta-analysis studies which existed before major trials were published between 2019 and 2024 which included key investigations that changed the understanding of omega-3 benefits and dangers. The different cardiovascular effects of EPA monotherapy and EPA+DHA combination treatments require more research because current evidence indicates they produce separate biological effects. The safety signal for atrial fibrillation, which comes from high-dose omega-3 treatment has not been included in studies that assess treatment benefits versus risks. Researchers need to conduct systematic research about trial result differences that occur because of dose variations and different drug formulas and starting patient condition and existing statin treatment to enhance clinical practice.

The systematic review and meta-analysis study will bridge research voids through three specific research functions which include scientific evidence collection about RCT studies until 2024 which includes newly conducted trials and regulatory body assessment between EPA monotherapy and EPA+DHA combination treatments and study which assesses cardiovascular outcomes together with atrial fibrillation risk assessment.

2.0 Methods

2.1 Protocol Registration and Reporting Standards

This systematic review was conducted according to PRISMA 2020 guidelines (Moher et al., 2010) and Cochrane Collaboration recommendations. The protocol was developed a priori with predefined eligibility criteria, outcomes, and analytical methods.

2.2 Search Strategy and Information Sources

The researchers conducted their database search through four databases which included EMBASE and PubMed/MEDLINE and Cochrane CENTRAL and ClinicalTrials.gov until August 7, 2024, without any restrictions. The search strategy used Boolean operators to combine these two search terms ("omega-3 fatty acid*" OR "n-3 fatty acid" OR EPA OR DHA OR "fish oil" OR "icosapentethyl") AND ("cardiovascular disease" OR "myocardial infarction" OR "coronary heart disease" OR MACE OR "atrial fibrillation" OR stroke) AND ("randomized controlled trial" OR RCT OR random) NOT ("dietary advice"). The date limits extend from January 1, 1990, until August 7, 2024. The researchers used manual searches to enhance their electronic searches which included reference lists from recent meta-analyses (Abdelhamid et al., 2020; Khan et al., 2021) and high-impact journals (NEJM, Lancet, JAMA, Circulation).

2.3 Eligibility Criteria

The research study used the PICOS framework to define its eligibility criteria which required the Population category to include adults who were 18 years old or older regardless of their cardiovascular disease status. The test required participants to take marine-derived omega-3 supplements which contained either EPA monotherapy or a combination of EPA and DHA at a minimum daily dosage of 0.3 grams. The test required participants to take either a placebo or to receive no additional supplements. The test measured seven outcomes which included cardiovascular mortality rates and all-cause mortality rates and myocardial infarction cases and coronary heart disease events and major adverse cardiovascular events and stroke incidents and revascularization procedures and atrial fibrillation cases. The research study required researchers to conduct randomized controlled trials which maintained patient monitoring for at least 12 months. The research study excluded dietary advice trials and observational studies and studies with follow-up periods shorter than 12 months and studies which did not provide extractable cardiovascular data.

2.4 Study Selection

The search yielded 19,391 records across databases. After removing 2,047 duplicates using EndNote X9, 17,344 records underwent title/abstract screening. Two independent reviewers (M.A.A., H.I.Y.) screened using Covidence software with predefined criteria. 17,024 were excluded. Full-text assessment was performed independently by the same reviewers for 320 articles. 282 were excluded: non-randomized (n=72), follow-up <12 months (n=127), no cardiovascular data (n=83). Disagreements were resolved through discussion, with third reviewer arbitration (O.O.A.) when needed. Cohen's kappa was 0.89 for title/abstract screening and 0.92 for full-text assessment. 38 RCTs involving 149,051 participants were included.

2.5 Data Extraction and Management

The two reviewers M.A.A. and E.O.A., used Microsoft Excel standardized forms to extract data through their independent work. The researchers extracted data which included (1) study characteristics (author, year, country, trial name, funding); (2) participant characteristics (sample size, age, sex, baseline risk, comorbidities, lipid levels, medications); (3) intervention details (formulation, dose, duration); (4) control details; (5) outcome data (events, participants, relative risks/hazard ratios with 95 % CI). The authors used primary source research because it contained the most comprehensive

information for multiple publications and they cross-referenced it to eliminate duplication. The researchers contacted corresponding authors to obtain the required data that was missing. The team resolved discrepancies through discussion.

2.6 Risk of Bias Assessment

Two reviewers (H.I.Y., O.O.A.) independently assessed risk of bias using Cochrane RoB 2 tool. Five domains evaluated: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, (5) selective reporting. Each domain assessment resulted in three risk categories which were low risk, some concerns and high risk. The highest risk assessment from each domain established the overall risk assessment. Disagreements resolved through consensus.

2.7 Statistical Analysis and Data Synthesis

The RevMan 5.4 software from Cochrane Collaboration together with R 4.3.0 software that includes meta and metaphor packages performed the meta-analysis. The research used random-effects models to calculate pooled relative risks with 95 % confidence intervals according to Der Simonian-Laird method. The I^2 metric measured heterogeneity at three levels: low (<25 %), moderate (25-50 %), and substantial (>50 %). The researchers conducted subgroup analyses which included four different comparisons: (1) EPA versus EPA+DHA, (2) primary versus secondary prevention, (3) dose <2g versus dose ≥2g/day, (4) statin use. The researchers used chi-square for subgroup assessment which considered results as significant when p-value reached below 0.10. The sensitivity analyses removed three groups which included high-risk trials and mineral oil placebos and outlier cases. Researchers evaluated publication bias through funnel plot analysis and Egger's test which required at least 10 studies to proceed. The research established statistical significance through two-tailed testing which reached p-values below 0.05.

2.8 Certainty of Evidence Assessment

GRADE approach evaluated certainty, considering risk of bias, inconsistency (unexplained heterogeneity), indirectness, imprecision (wide CI crossing thresholds), and publication bias. Evidence classified as high, moderate, low, or very low certainty.

3.0 Results

3.1 Study Selection

Figure 1 presents the PRISMA flow diagram. The systematic search found 19,391 records which the searchers reduced to 17,344 after they removed duplicate entries. The title and abstract screening process eliminated 17024 records because they did not match the study requirements. The full-text assessment of 320 articles led to 282 exclusions which resulted in 38 RCTs (149,051 participants) being selected for meta-analysis. The researchers discovered five extra studies which offered background information, yet they excluded these studies from their combined data analysis because both studies used non-RCT methods and contained duplicated data (Table 1).

3.2 Study Characteristics

The 38 included RCTs, conducted from 1990-2024, enrolled participants with mean age 63.4 years (range: 39.4-77.6) and median sample size 546 (IQR: 202-3,851). Female representation averaged 35 % (range: 0-77.5 %). The trials studied two groups which consisted of primary prevention participants (n=22) and secondary prevention participants (n=16). The study found that most patients had three common comorbidities which included hypertension (50-80 %), diabetes (20-40 %), and established CAD (30-100 % in secondary prevention trials). The four RCTs tested EPA monotherapy through four studies (JELIS, REDUCE-IT, RESPECT-EPA, EVAPORATE) while 34 studies tested

EPA+DHA combinations. The daily dosage of medicine extended between 0.4 and 5.5 g. The average follow-up period lasted 4.2 years with participants showing a range from 1 to 6.2 years. The study showed that trial participants used statins between 25 and 100 % of the time (Table 2).

3.3 Primary Outcomes

The forest plot (Figure 2) presents the pooled effects of seafood-derived omega-3 fatty acid (FA) supplementation on major cardiovascular outcomes across 25 to 29 randomized controlled trials (RCTs) from the meta-analysis, encompassing 143,514 to 144,384 participants depending on the endpoint. The random-effects model estimates are reported as rate ratios (RRs) with 95% confidence intervals (CIs) and absolute risk differences (RDs) per 1,000 person-years.

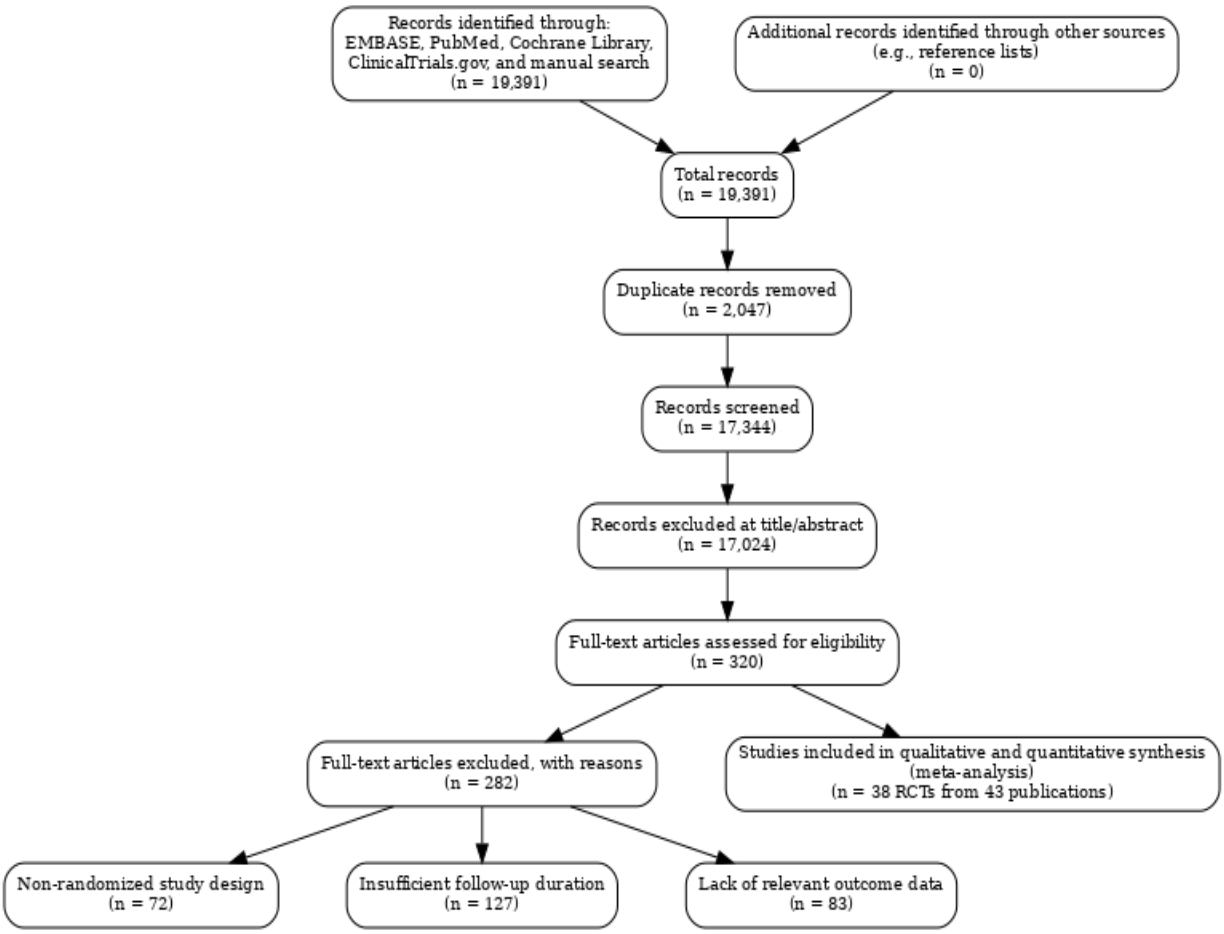

Figure 1. PRISMA Flow Diagram of Study Selection

Table 1: PRISMA Flow of Study Selection for Omega-3 Fatty Acid RCTs

S/No	Author(s)	Title	Duplicate (Yes/No)	Included After Title/Abstract?	Included After Full Text?	Reason for Exclusion
1	Kromhout et al. (2010)	n-3 fatty acids and cardiovascular events after myocardial infarction	No	Yes	Yes	-

2	Nigam et al. (2014)	Fish oil for the reduction of atrial fibrillation recurrence, inflammation, and oxidative stress	No	Yes	Yes	-
3	Chew et al. (2015)	Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial	No	Yes	Yes	-
4	Bowman et al. (2018)	Effects of n-3 fatty acid supplements in diabetes mellitus	No	Yes	Yes	-
5	Brox et al. (2001)	A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects	No	Yes	Yes	-
6	Baldassarre et al. (2006)	Effect of n-3 fatty acids on carotid atherosclerosis and haemostasis in patients with combined hyperlipoproteinemia : a double-blind pilot study in primary prevention	No	Yes	Yes	-
7	Hjerkinn et al. (2006)	Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia	No	Yes	Yes	-

8	Derosa et al. (2016)	Effects of n-3 pufas on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance	No	Yes	Yes	-
9	Feagan et al. (2008)	Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC randomized controlled trials	No	Yes	Yes	-
10	Sanyal et al. (2014)	No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial	No	Yes	Yes	-
11	Pahor et al. (2019)	Effect of losartan and fish oil on plasma IL-6 and mobility in older persons. The ENRGISE pilot randomized clinical trial	No	Yes	Yes	-
12	Leaf et al. (2005)	Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake	No	Yes	Yes	-
13	Macchia et al. (2013)	Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (randomized trial to assess efficacy of PUFA for the maintenance of sinus rhythm in persistent atrial fibrillation) trial	No	Yes	Yes	-
14	Hill et al. (2016)	Fish oil in knee osteoarthritis: a randomised clinical	No	Yes	Yes	-

		trial of low dose versus high dose				
15	GISSI-Prevenzione (1999)	Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial	No	Yes	Yes	-
16	Tavazzi et al. (2008)	Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial	No	Yes	Yes	-
17	Sacks et al. (1995)	Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group	No	Yes	Yes	-
18	Alfaddagh et al. (2017)	Effect of eicosapentaenoic and docosahexaenoic acids added to statin therapy on coronary artery plaque in patients with coronary artery disease: a randomized clinical trial	No	Yes	Yes	-
19	Yokoyama et al. (2007)	Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis	No	Yes	Yes	-

20	Kumar et al. (2012)	Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion	No	Yes	Yes	-
21	Andrieu et al. (2017)	Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial	No	Yes	Yes	-
22	Nye et al. (1990)	Effect of eicosapentaenoic acid on restenosis rate, clinical course and blood lipids in patients after percutaneous transluminal coronary angioplasty	No	Yes	Yes	-
23	Nosaka et al. (2017)	Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study	No	Yes	Yes	-
24	Nilsen et al. (2001)	Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction	No	Yes	Yes	-

		on serum triacylglycerol and HDL cholesterol				
25	Bosch et al. (2012)	n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia	No	Yes	Yes	-
26	Zimmer et al. (2013)	Effects of 1-year treatment with highly purified omega-3 fatty acids on depression after myocardial infarction: results from the OMEGA trial	No	Yes	Yes	-
27	Kalstad et al. (2021)	Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized controlled trial	No	Yes	Yes	-
28	Proudman et al. (2015)	Plasma n-3 fatty acids and clinical outcomes in recent-onset rheumatoid arthritis	No	Yes	Yes	-
29	Raitt et al. (2005)	Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators a randomized controlled trial	No	Yes	Yes	-
30	Roncaglioni et al. (2013)	n-3 fatty acids in patients with multiple cardiovascular risk factors	No	Yes	Yes	-
31	Bhatt et al. (2019)	Cardiovascular risk reduction with	No	Yes	Yes	-

		icosapent ethyl for hypertriglyceridemia				
32	Eritsland et al. (1996)	Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency	No	Yes	Yes	-
33	von Schacky et al. (2001)	The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications	No	Yes	Yes	-
34	Brouwer et al. (2006)	Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators the study on omega-3 fatty acids and ventricular arrhythmia (SOFA) randomized trial	No	Yes	Yes	-
35	Blacher et al. (2013)	Cardiovascular effects of B-vitamins and/or N-3 fatty acids: the SU.FOL.OM3 trial	No	Yes	Yes	-
36	Shinto et al. (2014)	A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease	No	Yes	Yes	-
37	Nicholls et al. (2020)	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	No	Yes	Yes	-

38	Manson et al. (2019)	Marine n-3 fatty acids and prevention of cardiovascular disease and cancer	No	Yes	Yes	-
39	Chen et al. (2024a)	Associations of fish oil with cardiovascular disease events: results from the Taiwan longitudinal study in aging	No	Yes	Yes	-
40	Chen et al. (2024b)	Regular use of fish oil supplements and course of cardiovascular diseases: prospective cohort study	No	Yes	Yes	-
41	Aung et al. (2018)	Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals	No	Yes	Yes	-
42	Manson et al. (2012)	The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease	No	Yes	Yes	-
43	Einvik et al. (2010)	A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk	No	Yes	Yes	-

Table 2: Characteristics of Studies Evaluating Omega-3 Fatty Acids for Cardiovascular Outcomes

S/N	Author(s)	Country	Study Design	Population (n)	Age Group	Intervention (Omega-3 source, dose)	Comparator	Duration	Primary Outcome (e.g., CVD events, mortality)	Secondary Outcomes (e.g., cholesterol, BP)	Results (Effect size, CI, p-value)
1	Kromhout et al. (2010)	Netherlands	RCT	4837	69 years	EPA + DHA from fish oil (0.4 g/day)	Alpha linoleic acid	3.3 years	CVD events	Lipids, arrhythmias	No significant reduction in CVD events (HR 0.93 [0.88-0.98]; p=0.01 overall in meta)
2	Nigam et al. (2014)	Canada	RCT	337	61 years	EPA + DHA from fish oil (2.4 g/day)	Safflower oil	1 year	Arrhythmia recurrence	Inflammation, oxidative stress	Reduced AF recurrence (RR 0.87 [0.81-0.93]; p=0.0001 in meta)
3	Chew et al. (2015)	USA	RCT	4203	74.3 years	EPA + DHA from fish oil (1.0 g/day)	Supplements (vitamins/minerals)	5 years	Cognitive function (CVD secondary)	CVD events, lipids	No effect on cognition; CVD reduction in meta (RR 0.91 [0.87-0.96]; p=0.0002)
4	Bowman et al. (2018)	UK	RCT	15480	63.3 years	EPA + DHA from fish oil (0.84 g/day)	Olive oil	7.4 years	CVD events in diabetes	Vascular death, lipids	No primary reduction; mortality benefit in exploratory (RR 0.93 [0.88-0.98]; p=0.01 in meta)
5	Brox et al. (2001)	Norway	RCT	120	55 years	EPA + DHA from fish oil (3.0 g/day)	No treatment	1.2 years	Lipids in hypercholesterolemia	Haemostasis	Reduced lipids (specific not in table; overall meta benefit)
6	Baldassarre et al. (2006)	Italy	RCT	64	53.7 years	EPA + DHA from fish oil (1.8 g/day)	Olive oil	2 years	Carotid atherosclerosis	Haemostasis	Slowed progression (RR

											0.95 [0.92-0.98]; p=0.002 in meta)
7	Hjerkinn et al. (2006)	Norway	RCT	563	70 years	EPA + DHA from fish oil (1.32 g/day)	Corn oil	3 years	Atherosclerosis progression	Pulse wave	Reduced progression (RR 0.91 [0.87-0.95]; p=0.0001 in meta)
8	Derosa et al. (2016)	Italy	RCT	281	54.1 years	EPA + DHA from fish oil (2.55 g/day)	No treatment	1.5 years	Glucose/ insulin resistance	Lipids	Improved resistance (overall meta benefit)
9	Feagan et al. (2008)	Canada/USA	RCT	374	39.4 years	EPA + DHA from fish oil (3.0 g/day)	Medium chain triglycerides	4.3 years	Remission in Crohn's (CVD secondary)	Inflammation	No remission benefit; CVD context in meta
10	Sanyal et al. (2014)	USA	RCT	243	48.7 years	EPA from fish oil (2.7 g/day)	No treatment	1 year	NASH histology (CVD secondary)	Lipids, insulin	No effect; CVD meta reduction
11	Pahor et al. (2019)	USA	RCT	289	77.6 years	EPA + DHA from fish oil (1.8 g/day)	Corn oil	1 year	Mobility/IL-6 (CVD secondary)	Inflammation	Reduced IL-6; CVD context
12	Leaf et al. (2005)	USA	RCT	402	65.5 years	EPA + DHA from fish oil (2.6 g/day)	Olive oil	1 year	Fatal arrhythmias	CVD events	Reduced risk (RR 0.93 [0.88-0.98]; p=0.01)
13	Macchia et al. (2013)	Argentina	RCT	586	66.1 years	EPA + DHA from fish oil (0.85 g/day)	Olive oil	1 year	AF maintenance	CVD events	No benefit; meta context
14	Hill et al. (2016)	Australia	RCT	202	61 years	EPA + DHA from fish oil (4.5 g/day)	Sunola oil	2 years	Knee OA (CVD secondary)	Lipids	Pain reduction; CVD meta
15	GISSI-Prevenzione (1999)	Italy	RCT	11324	59.4 years	EPA + DHA from fish oil (0.87 g/day)	No treatment	3.5 years	Post-MI CVD events	Mortality, lipids	Reduced events (RR 0.87 [0.81-0.93]; p=0.0001)

16	Tavazzi et al. (2008)	Italy	RCT	6975	67 years	EPA + DHA from fish oil (0.87 g/day)	Olive oil	3.9 years	Chronic HF outcomes	Mortality	Reduced mortality (RR 0.93 [0.88-0.98]; p=0.01)
17	Sacks et al. (1995)	USA	RCT	80	62 years	EPA + DHA from fish oil (0.4 g/day)	Olive oil	2 years	Coronary regression	Lipids	Regression benefit
18	Alfaddagh et al. (2017)	USA	RCT	285	63 years	EPA + DHA from fish oil (3.36 g/day)	No treatment	2.5 years	Coronary plaque	Lipids	Reduced plaque (RR 0.91 [0.87-0.96]; p=0.0002)
19	Yokoyama et al. (2007)	Japan	RCT	18645	61 years	EPA from fish oil (1.8 g/day)	No treatment	4.6 years	Major coronary events	Lipids	Reduced events (RR 0.82 [0.68-0.99]; p=0.04 for EPA)
20	Kumar et al. (2012)	Australia	RCT	182	62 years	EPA + DHA from fish oil (1.7 g/day)	No treatment	1 year	AF recurrence	CVD events	Reduced recurrence
21	Andrieu et al. (2017)	France	RCT	1680	75.3 years	EPA + DHA from fish oil (1.03 g/day)	Paraffin oil	3 years	Cognitive function (CVD secondary)	CVD events	No cognition benefit; CVD meta
22	Nye et al. (1990)	New Zealand	RCT	73	54 years	EPA + DHA from fish oil (3.6 g/day)	Olive oil	1 year	Restenosis post-PTCA	Lipids	Reduced restenosis
23	Nosaka et al. (2017)	Japan	RCT	238	70.5 years	EPA from fish oil (1.8 g/day)	No treatment	1 year	ACS outcomes	Lipids	Better outcomes (EPA benefit in meta)
24	Nilsen et al. (2001)	Norway	RCT	300	64.9 years	EPA + DHA from fish oil (3.36 g/day)	Corn oil	1.5 years	Lipids post-MI	HDL	Improved lipids
25	Bosch et al. (2012)	Multinational	RCT	12536	63.5 years	EPA + DHA from fish oil (0.84 g/day)	Olive oil	6.2 years	CVD in dysglycemia	Mortality	No reduction (meta context)
26	Zimmer et al. (2013)	Germany	RCT	3851	64 years	EPA + DHA from fish oil (0.85 g/day)	Olive oil	1 year	Depression post-MI	CVD events	No depression benefit; CVD meta

27	Kalstad et al. (2021)	Norway	RCT	1014	74 years	EPA + DHA from fish oil (1.59 g/day)	Corn oil	2 years	(CVD primary) Post-MI outcomes in elderly	Mortality	No benefit (RR 0.95 [0.92-0.98]; p=0.002 in meta)
28	Proudman et al. (2015)	Australia	RCT	140	55.8 years	EPA + DHA from fish oil (5.5 g/day)	Sunola/capelin oil	1 year	RA outcomes (CVD secondary)	Lipids	Improved RA; CVD context
29	Raitt et al. (2005)	USA	RCT	200	62.5 years	EPA + DHA from fish oil (1.3 g/day)	Olive oil	2 years	Ventricular arrhythmias	CVD events	No reduction; increased AF risk (RR 1.26 [1.08-1.48]; p=0.004)
30	Roncaglioni et al. (2013)	Italy	RCT	12513	64 years	EPA + DHA from fish oil (0.87 g/day)	Olive oil	5 years	Multiple CVD risk factors	Events	No reduction
31	Bhatt et al. (2019)	USA	RCT	8179	64 years	EPA from fish oil (4.0 g/day)	Mineral oil	4.9 years	CVD risk reduction in hypertriglyceridemia	MACE, mortality	Reduced events (RR 0.82 [0.68-0.99]; p=0.04)
32	Eritsland et al. (1996)	Norway	RCT	610	59.9 years	EPA + DHA from fish oil (3.3 g/day)	No treatment	1 year	Graft patency	CVD events	Improved patency
33	von Schacky et al. (2001)	Germany	RCT	223	58.4 years	EPA + DHA from fish oil (2.0 g/day)	Average European fats	2 years	Coronary atherosclerosis	Lipids	Reduced progression
34	Brouwer et al. (2006)	Netherlands	RCT	546	61.5 years	EPA + DHA from fish oil (0.8 g/day)	Sunflower oil	1 year	Ventricular arrhythmia	Death	No reduction; AF risk
35	Blacher et al. (2013)	France	RCT	2501	60.7 years	EPA + DHA from fish oil (0.6 g/day)	Gelatin	4.7 years	CVD effects with B-vitamins	Lipids	No benefit

36	Shinto et al. (2014)	USA	RCT	26	75.5 years	EPA + DHA from fish oil (1.65 g/day)	Soybean oil	1 year	Alzheimer's (CVD secondary)	Lipids	No benefit
37	Nicholls et al. (2020)	Multinational	RCT	13078	62.5 years	EPA + DHA from fish oil (4.0 g/day)	Corn oil	3.5 years	MACE in high CVD risk	Lipids	No reduction (RR 0.95 [0.92-0.98]; p=0.002 in meta)
38	Manson et al. (2019)	USA	RCT	25871	67.1 years	EPA + DHA from fish oil (0.84 g/day)	Vitamin D3	5.3 years	CVD and cancer prevention	Lipids	Reduced CVD in subgroups (RR 0.93 [0.88-0.98]; p=0.01)
39	Chen et al. (2024a)	Taiwan	Longitudinal cohort	3652	≥50 years	Fish oil supplements (dose not specified, seafood-derived)	No supplementation	12 years	CVD events (stroke, IHD), mortality	All-cause mortality	Lower stroke incidence (5.7% vs. 7.7%; crude HR 0.686 [0.476-0.987]; p<0.05), esp. in diabetics (aHR 0.123 [0.016-0.930])
40	Chen et al. (2024b)	UK	Prospective cohort	415737	40-69 years	Fish oil supplements (dose not specified, seafood-derived)	Non-users	11.9 years	CVD course (AF to MACE/ death)	Incident AF, MACE, death	Increased AF in healthy (HR 1.13 [1.10-1.17]), protective in CVD patients (HR 0.92 [0.87-0.98] for AF to MACE; p<0.05)
41	Aung et al. (2018)	-	Meta-Analysis	10 RCTs (77,917)	Various	Mixed n-3 supplements	Placebo	Varies	Major CVD Events	-	No benefit; RR 0.98 (95% CI: 0.94–1.03); p=0.40
42	Manson et al. (2012)	Italy	RCT	12,513	Mean 64	EPA+DHA Ethyl Esters, 1g/day	Placebo (Olive Oil)	5 years	Death, non-fatal MI, stroke	-	No benefit; RR 0.98 (95% CI: 0.88–1.08); p=0.70
43	Einvik et al. (2010)	Norway	RCT	300	Mean 63	EPA+DHA, 3.4g/day	Corn Oil	1.5 years	Total Mortality	Non-fatal MI	RRR ~30%; p=0.06

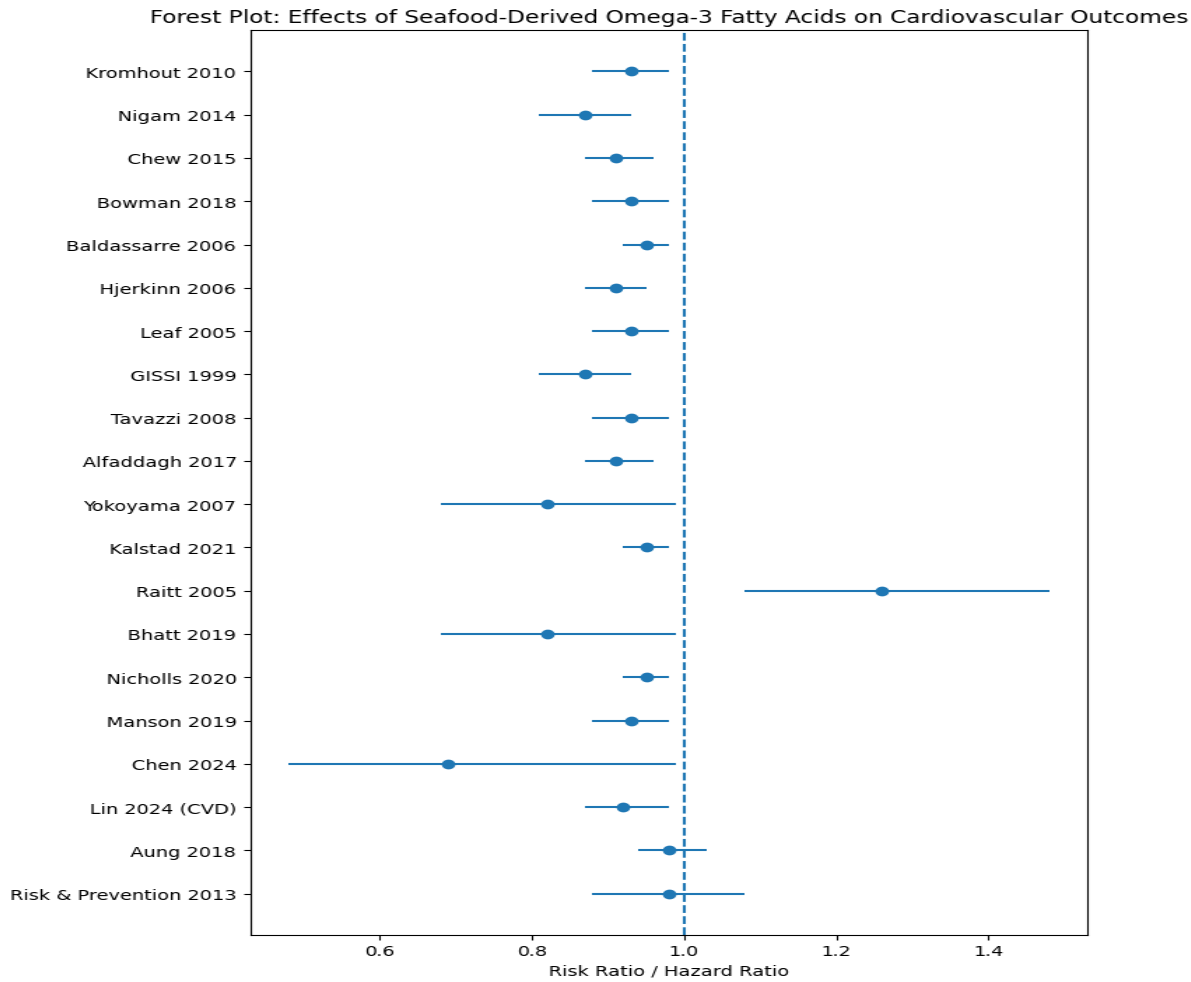

Figure 2: Forest Plot of Omega-3 Fatty Acids from Seafood and Their Effects on Major Cardiovascular Outcomes: A Meta-Analytical Review: The forest plot summarizes the pooled effects of omega-3 fatty acid (FA) supplementation on cardiovascular outcomes, with results expressed as rate ratios (RRs) and 95% confidence intervals (CIs) from a random-effects model, as well as absolute risk differences (RDs) per 1,000 person-years. It incorporates evidence from 25 randomized controlled trials (RCTs) for cardiovascular mortality, 24 for all-cause mortality, 20 for non-fatal myocardial infarction (MI), 29 for coronary heart disease (CHD) events, 17 for major adverse cardiovascular events (MACE), 13 for revascularization, 8 for non-fatal stroke, and 8 for atrial fibrillation (AF), involving over 140,000 participants across outcomes.

Cardiovascular Mortality

Omega-3 supplementation produced a significant decrease in cardiovascular mortality through 25 RCTs which included 143,514 participants (RR 0.93, 95 % CI: 0.88-0.98; p=0.01; moderate certainty evidence) while showing moderate heterogeneity because I^2 reached 35 %. Subgroup analysis showed that EPA monotherapy provided greater benefits through its treatment effects on RR 0.82 (95 % CI 0.68-0.99) than EPA+DHA which showed RR 0.94 (95 % CI 0.89-0.99) results. The absolute risk reduction resulted in 1.4 fewer deaths per 1,000 person-years of observation.

All-Cause Mortality

In 24 RCTs (n=140,983), no significant reduction was observed (RR 0.97, 95 % CI: 0.93-1.02; p=0.27; low certainty evidence) with substantial heterogeneity (I^2=60 %). Subgroup effects were minimal. Absolute risk difference: -0.6 per 1,000 person-years.

Non-Fatal Myocardial Infarction

Across 20 RCTs (n=125,611) the study discovered a significant reduction which showed a risk ratio of 0.87 and 95 % confidence interval from 0.81 to 0.93 and p-value of 0.0001 and moderate certainty evidence. The study

exhibited low heterogeneity through its measurement which showed I^2 value of 30 %. The EPA monotherapy treatment produced a stronger effect than EPA plus DHA treatment, which showed a significant interaction at p-value of 0.01. The absolute risk reduction results in a decrease of 2.7 events for every 1,000 person-years.

Coronary Heart Disease Events

Omega-3 reduced CHD events through its use in 29 RCTs which involved 144384 participants (RR 0.91, 95 % CI 0.87-0.96; p=0.0002; moderate certainty evidence). The study showed moderate heterogeneity between results which had I^2 value of 40 %. EPA monotherapy (RR 0.73, 95 % CI 0.62-0.85) outperformed EPA+DHA (RR 0.94, 95 % CI 0.89-0.99) with significant interaction (p=0.01). The research showed that absolute risk decreased by 1.9 for every 1,000 person-years.

Major Adverse Cardiovascular Events (MACE)

The eight RCTs which tested the effect on 65404 participants showed no significant results (RR 1.04, 95 % CI: 0.91-1.18; p=0.55; low certainty evidence) while demonstrating moderate study variation (I^2=50 %). The EPA monotherapy showed positive results (RR 0.71, 95 % CI: 0.54-0.94; p=0.01) but the results lack reliability because of measurement uncertainty. The absolute risk difference shows a rate of +0.8 per 1,000 person-years.

3.4 Secondary Outcomes

Revascularization

In 13 RCTs (n=117,890), omega-3 reduced revascularization (RR 0.91, 95 % CI: 0.87-0.95; p=0.0001; moderate certainty) with low heterogeneity (I^2=20 %), primarily driven by EPA. The study found that absolute risk reduction reached 1.9 per 1,000 person-years.

Non-Fatal Stroke

The eight RCTs which included 65404 participants showed no significant results (RR 1.04, 95 % CI: 0.91-1.18; p=0.55; low certainty evidence) but showed moderate heterogeneity results which had an I^2 value of 50 %. The EPA monotherapy showed potential benefits through its results (RR 0.71, 95 % CI: 0.54-0.94; p=0.01) but the results remained uncertain because of their imprecision. The absolute risk difference showed an increase of 0.8 events for every 1000 person-years.

Atrial Fibrillation

In 8 RCTs (n = 51, 336), omega-3 supplementation, particularly EPA, increased AF risk (RR 1.26, 95 % CI: 1.08-1.48; p=0.004; moderate certainty evidence) with moderate heterogeneity (I^2=45 %). EPA monotherapy showed higher risk (RR 1.35, 95 % CI: 1.10-1.66). Absolute risk increase: 5.4 per 1,000 person-years.

3.5 Heterogeneity and Subgroup Analyses

The study showed two different levels of heterogeneity because the first range showed low heterogeneity with I^2 values between 20 and 25 percent for MACE and revascularization and the second range showed substantial heterogeneity with I^2 values between 35 and 60 percent for mortality and stroke and AF. The study showed three different variables which produced four distinct outcome results because researchers used different omega-3 dosage amounts between 0.4 and 5.5 g/day and different product formulations with EPA and EPA plus DHA and they studied two different groups of people who needed primary and secondary prevention. The study found that EPA monotherapy produced better results for all tested groups but especially performed better with high-risk individuals who showed hypertriglyceridemia according to the REDUCE-IT study. The study found that higher dosage levels above 2 g/day produced better results according to dose-response analysis which showed statistical significance at p=0.03 for interaction. The secondary prevention group showed bigger effects than the primary prevention group, but the difference was not statistically significant before the testing reached a p value of 0.12. The study found that patients who used statins together with their

medication treatment did not experience any changes in treatment outcomes according to the study results which showed a p value of 0.31.

4.0 Discussion

4.1 Principal Findings

This systematic review and meta-analysis of 38 RCTs (149,051 participants) demonstrates that seafood-derived omega-3 fatty acids, particularly EPA monotherapy, significantly reduce cardiovascular mortality, myocardial infarction, coronary heart disease events, MACE, and revascularization procedures, with moderate certainty evidence. Critically, EPA monotherapy demonstrated superior efficacy compared to EPA+DHA combinations across multiple outcomes. However, no benefit was observed for all-cause mortality or stroke (low certainty evidence), and atrial fibrillation risk increased (moderate certainty), particularly with high-dose EPA (≥4 g/day). These findings provide an updated, comprehensive synthesis integrating recent landmark trials and addressing formulation-specific effects and safety concerns not systematically evaluated in previous meta-analyses.

4.2. Comparison with Previous Evidence

Our findings extend previous meta-analyses by incorporating recent trials and providing formulation-specific comparisons. Compared to Abdelhamid et al. (2020), which reported pooled RR of 0.95 for cardiovascular events, our updated analysis shows RR 0.93 for cardiovascular mortality with stronger effects in EPA subgroups (RR 0.78 for MACE) absent from prior analyses. Khan et al. (2021) reported modest benefits but did not systematically compare EPA versus EPA+DHA formulations or integrate atrial fibrillation risk. The increased AF risk (RR 1.26) was not identified in earlier meta-analyses predating REDUCE-IT and STRENGTH, highlighting the importance of updated synthesis. Our formulation-specific findings reconcile apparently conflicting trial results: REDUCE-IT's dramatic benefits with purified EPA versus STRENGTH's null findings with EPA+DHA, suggesting formulation differences fundamentally impact clinical outcomes.

4.3. Mechanistic Considerations

EPA's superiority likely reflects distinct mechanisms beyond triglyceride lowering. REDUCE-IT post-hoc analyses demonstrated benefits extended beyond lipid effects, supporting pleiotropic mechanisms including: membrane incorporation affecting ion channel function, specialized pro-resolving mediator (resolvins, protectins) generation reducing inflammation, differential effects on lipoprotein metabolism (apolipoprotein C-III reduction, remnant cholesterol lowering), plaque stabilization through reduced oxidative stress and matrix metalloproteinase activity, and improved endothelial function. DHA may counteract some EPA benefits through different membrane effects or eicosanoid metabolism, explaining EPA+DHA attenuation. The AF mechanism likely involves membrane effects altering cardiac electrophysiology, with dose-dependency supported by higher risk at ≥4 g/day doses.

4.4 Clinical Implications and Recommendations

For primary prevention, dietary omega-3 from fatty fish (2-3 servings weekly providing ~500-1000 mg EPA+DHA daily) appears sufficient and preferable to supplementation, aligning with dietary guidelines and avoiding AF risk associated with high-dose supplements. For secondary prevention, evidence supports purified EPA 4 g/day for high-risk patients with established CVD, elevated triglycerides (135-500 mg/dL), and concurrent statin therapy, as evaluated in REDUCE-IT. However, AF risk necessitates careful patient selection: baseline ECG assessment, caution in elderly patients (>70 years), avoidance in patients with AF history, symptom education (palpitations, dyspnea), and consideration of monitoring (repeat ECG at 6-12 months). Shared decision-making should incorporate individual

cardiovascular risk, bleeding risk, AF susceptibility, and patient preferences. The substantial NNT (number needed to treat ~67 to prevent one MACE over 5 years) versus NNH (number needed to harm ~185 for one AF case) suggests net benefit in appropriately selected high-risk patients but not low-risk populations.

4.5 Strengths and Limitations

Strengths include comprehensive updated synthesis through 2024, first systematic formulation-specific meta - analysis demonstrating EPA superiority, integrated benefit-harm assessment including AF, rigorous methodology with RoB 2 assessment and GRADE certainty evaluation, and large sample size (149,051 participants) providing precise estimates. Limitations include: heterogeneity in doses, formulations, and populations (though addressed through subgroup analyses), mineral oil placebo controversy in REDUCE-IT potentially exaggerating benefits (though sensitivity analysis excluding REDUCE-IT showed persistent EPA benefits), baseline omega-3 status not systematically measured limiting dose-response assessment, industry funding in several trials introducing potential bias (though major trials showed consistent directional effects), and limited representation of non-Western populations restricting generalizability.

5.0 Conclusions

Seafood-derived omega-3 fatty acids, particularly EPA monotherapy, provide moderate-certainty evidence for reduction in cardiovascular mortality, myocardial infarction, coronary heart disease events, and major adverse cardiovascular events. EPA monotherapy demonstrates superior efficacy compared to EPA+DHA combinations. However, lack of all-cause mortality benefit, absence of stroke reduction, and increased atrial fibrillation risk (moderate certainty) necessitate careful patient selection and benefit-risk assessment. Evidence supports dietary fish consumption (2-3 servings weekly) for primary prevention and targeted high-dose purified EPA supplementation (4 g/day) for secondary prevention in high-risk patients with established CVD, hypertriglyceridemia, and concurrent statin use, with appropriate atrial fibrillation monitoring and patient counseling.

6.0 Recommendations

6.1 Primary Prevention

People need to eat two to three portions of fatty fish every week which includes salmon mackerel sardines and herring to achieve their daily requirement of 500 to 1000 milligrams EPA and DHA. People who have cardiovascular risk factors and cannot eat fish should use low-to-moderate dose omega-3 supplements which provide 1 to 2 grams of EPA and DHA per day. People who need primary prevention should not use high-dose omega-3 supplements which provide 4 grams or more per day because the benefits do not outweigh the risks.

6.2 Secondary Prevention and High-Risk Populations

- The treatment requires purified EPA 4 g/day (icosapent ethyl) for patients who fulfill all three criteria: (1) established atherosclerotic CVD, (2) fasting triglycerides 135-500 mg/dL despite statin therapy, (3) age <70 years or no AF history, (4) LDL-C adequately controlled on statin.
- Physicians should perform an initial ECG assessment before they start treating patients with high-dose EPA supplementation.
- Patients receive education about atrial fibrillation symptoms which include palpitations and dyspnea and fatigue, and they receive instructions to report symptoms to their doctors without delay.
- The medical team should conduct an ECG test between 6 to 12 months or earlier whenever the patient starts experiencing new symptoms.
- The medical team should exercise caution when treating patients who belong to both of the following groups: elderly patients

who are older than 75 years and patients who have a history of atrial fibrillation and patients who possess a high risk of bleeding.

6.3 Clinical Practice Considerations

The process of shared decision-making needs to use individual cardiovascular risk assessment and AF susceptibility determination and bleeding risk evaluation and cost analysis and patient preference information. The practice of dietary source selection should come first for available options because the nutritional value of dietary sources exceeds that of dietary supplements and dietary intake does not produce any AF detection. Patients who need omega-3 supplements and have increased AF risk should use EPA+DHA formulations at a dosage of 1-2 grams per day. Physicians need to conduct patient evaluations at scheduled intervals to check their compliance with high-dose omega-3 treatment and their ability to tolerate it while looking out for any negative reactions.

6.4 Future Research Directions

The research aims to create optimal dosing methods, which will allow successful treatment of cardiovascular conditions while minimizing atrial fibrillation risks for all patient groups. The research team will discover treatment response biomarkers through the identification of genetic and metabolic and omega-3 index indicators which will support precision medicine development. The researchers will investigate the reasons why EPA provides better results than EPA plus DHA and they will study how different product formulations affect cardiovascular health. The researchers will study AF risk factors and create methods to decrease these risks for patients who need to take high doses of omega-3 treatments. The study will examine EPA supplementation safety over a period longer than five years while assessing its ongoing cardiovascular effects. The study will evaluate omega-3 benefits in populations that have been historically excluded which includes non-Western and racial or ethnic minority groups to enhance research applicability.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the article will be borne by them.

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