Impact of Omega-3 Fatty Acids on Cardiovascular Disease Prevention: an updated Meta-analysis of RCTs

Abstract

This meta-analysis evaluated the impact of omega-3 fatty acids on cardiovascular disease prevention by synthesizing data from 17 randomized controlled trials (RCTs) involving 82,592 patients. The analysis found that omega-3 fatty acid supplementation significantly reduced triglyceride levels and modestly decreased LDL levels. Additionally, the supplementation was associated with a lower risk of major cardiovascular events and cardiac mortalities. These findings support the use of omega-3 fatty acids as a preventive strategy in cardiovascular care, though further research is needed to optimize their use and understand the mechanisms of action.

Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVDs) are one of major causes of death in the world, claiming 17.9 million lives a year These diseases include conditions such as coronary artery disease, heart failure, and stroke due to risk factors like hypertension, smoking cigarettes, diabetes mellitus or being overweight. With the significant contribution of CVD in healthcare burden and disability, an effective preventive measure is needed on a priority basis.[1, 2]

Omega-3 fatty acids, largely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been extensively investigated for potential cardiovascular benefits. These long-chain polyunsaturated fatty acids, largely found in fish oils, are thought to have a multitude of beneficial effects including anti-inflammatory [3], anti-thrombotic and lipid-lowering properties. Omega-3 fatty acids supposedly lowers triglyceride levels through inhibition of hepatic triglyceride synthesis and increased clearance of lipoproteins containing TG by modifying this process mechanism. They also can enhance endothelial function, reduce arterial stiffness and stabilize atherosclerotic plaques, with the potential to lower CVD risk as well [4,5].

Although these mechanisms are promising, in clinical practice the efficacy of omega-3-polyunsaturated fatty acids as supplemental treatment to reduce CV events remains a matter of debate. Omega-3 fatty acids were originally associated with a significant risk reduction in CVDs [6], as reported early from observational studies. However, later randomized controlled trials (RCTs) produced conflicting results with most of them reporting either cardiovascular benefits or no significant effects [7]. There was potential of these discrepancies being the result of differences in study design, populations studied, the dose and duration[8[.

The use of omega-3 fatty acids for the prevention of CV events and modification in clinical outcomes in patients with CVD still lacks solid evidence. Many of these allow publications on similar types of studies having major methodological weaknesses like small sample size, short follow-up duration or various definitions for cardiovascular outcomes [9].. Moreover, the changing clinical trial landscape requires ongoing refinement to integrate new evidence with clarity in recommendations for real-world care [10,11].

This updated meta-analysis sets out to provide a comprehensive and up-to-date assessment of the effects of omega-3 fatty acids in cardiovascular disease prevention. This study aims to recapitulate the effect of omega-3 fatty acids on clinical outcomes related with cardiovascular diseases through systematic review and meta-analysis by combining evidences from RCTs which have so far been published until June 2024, concentrating particularly on important endpoints as change in serum triglyceride, Low density lipoprotein [LDL] levels, Rates for major adverse cardiac events (secondary prevention) and Cardiac mortalities.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards were adhered to in the latest meta-analysis [12]. Since the latest study was predicated on a systematic review and meta-analysis of previously published RCT trials, no extra ethical review was necessary.

PICO Framework

Among patients with cardiovascular diseases, what are the clinical outcomes of Omega-3 Fatty Acids in comparison to placebo? The recent study used the Population Intervention Control Outcome (PICO) framework to guide the search (Table 1)[13].

Table no. 1: *PICO framework for research question of recent study*

PICO	**Description**
Population	Adult Patients diagnosed with cardiovascular diseases
Intervention	Omega-3 Fatty Acids
Control/ comparison	Placebo
Outcome	Triglycerides levels, LDL, incidence of major cardiovascular events, cardiac mortalities

Search Strategy

Using Mesh keywords, a collection of research articles about the "Impact of Omega-3 Fatty Acids on Cardiovascular Disease Prevention" was gathered from several databases. Four electronic databases—PubMed, EMBASE, Clinicaltrials.gov, and the Cochrane Library—were utilized in a recent systematic review and meta-analysis to locate studies addressing the effects of omega-3 fatty acids on individuals with cardiovascular illnesses. ("cardiovascular diseases" OR "cardiac patients" OR "CVD" OR "patients with cardiac risk") AND ("omega-3 fatty acids" OR "n-3 fatty acids") AND ("incidence of cardiovascular events" OR "major cardiac events" OR "MACE" OR "all cause mortalities" OR "cardiac deaths" "triglycerides levels" OR "TG" OR "LDL"). Both MeSH keywords were used for data extraction. The research timeframe was scheduled to run from June 2024 to 2000.

Study Selection & Eligibility Criteria

PRISMA principles were followed in the selection and screening of research articles. The screening of research articles was aided by the predetermined selection criteria. Following a complete text review, each study was screened separately by two authors in accordance with the selection criteria.

Inclusion Criteria: Only those research studies were included in the recent systematic review and meta-analysis that met the following criteria: 1). Discussing the study population with heart failure and cardiac risk 2). Discussing the clinical outcomes of omega-3 fatty acids 3). Studies discussing clinical outcomes such as triglycerides levels (TG), LDL levels, incidence of cardiovascular events or MACE, all cause mortalities or adverse events (deaths) 4). Studies based on randomized controlled trials, 5). Studies with full text and published in English.

Exclusion Criteria: Only the following studies were not included: 1. addressing the population affected by hypoglycemia and diabetes 2. talking about other medications or using omega-3 in conjunction with other medications, including vitamin D, to lower the risk of cardiovascular illness 3. Studies that provided results instead of triglyceride levels (TG), low-density lipoprotein (LDL) levels, the frequency of cardiovascular events (MACE), all-cause mortality, or adverse events (deaths) 4 were also eliminated. Systematic reviews, meta-analyses, scoping reviews, literature reviews, conferences, and case studies have all already been published (5). Studies with duplicate publications or non-full-text papers were published in languages other than English.

Data Extraction

A pre-made table was used to retrieve data from the listed research. Relevant data were taken from every study that two authors included. The extracted data included author names, year of publication, country, study population & sample size, study follow-up or duration, type of intervention and outcomes such as Triglycerides levels, LDL, incidence of major cardiovascular events, and cardiac mortalities.

Primary Outcomes

In recent meta-analysis, the primary outcomes were Triglycerides levels, LDL, incidence of major cardiovascular events, cardiac mortalities and adverse cardiac events or death after intervention by omega-3 fatty acids among heart failure patients.

Risk of Bias Assessment

The Cochrane risk of bias tool was applied to assess the risk bias of included RCT's. The risk bias of included studies was evaluated on the basis of seven domains; allocation concealment, blinding of participants, Selection bias, blinding of outcome assessment, selective reporting and other bias. The score or level of each included study was categorized into Low risk, unclear and high risk[14].

Statistical Analysis

In recent meta-analysis, the pooled analysis was conducted by using RevMan (Review Manager) software version 5.4. The Mantel-Hansel (M-H) random effect model was applied (12) for evaluation of mean difference, odds ratio and risk ratio of expected outcomes after omega-3 fatty acids. Furthermore, the I2 statistics was used to measure the heterogeneity. A significant difference was considered if the p-value > 0.05. If the I2 value was >50%, heterogeneity was considered significant [15].

RESULTS

Included Studies

The selection and screening of research articles related to the study aims "Impact of Omega-3 Fatty Acids on Cardiovascular Disease Prevention" was conducted by following PRISMA guidelines in recent meta-analysis [12]. From three prescribed electronic databases, about 18600 research articles were extracted after implication of search strategy. Only 5630 papers were screened, and 1065 articles were excluded before screening. The eligibility criteria was applied to only 2605 articles and the final number of research articles that met inclusion criteria was 17, as mentioned in Fig no 1.

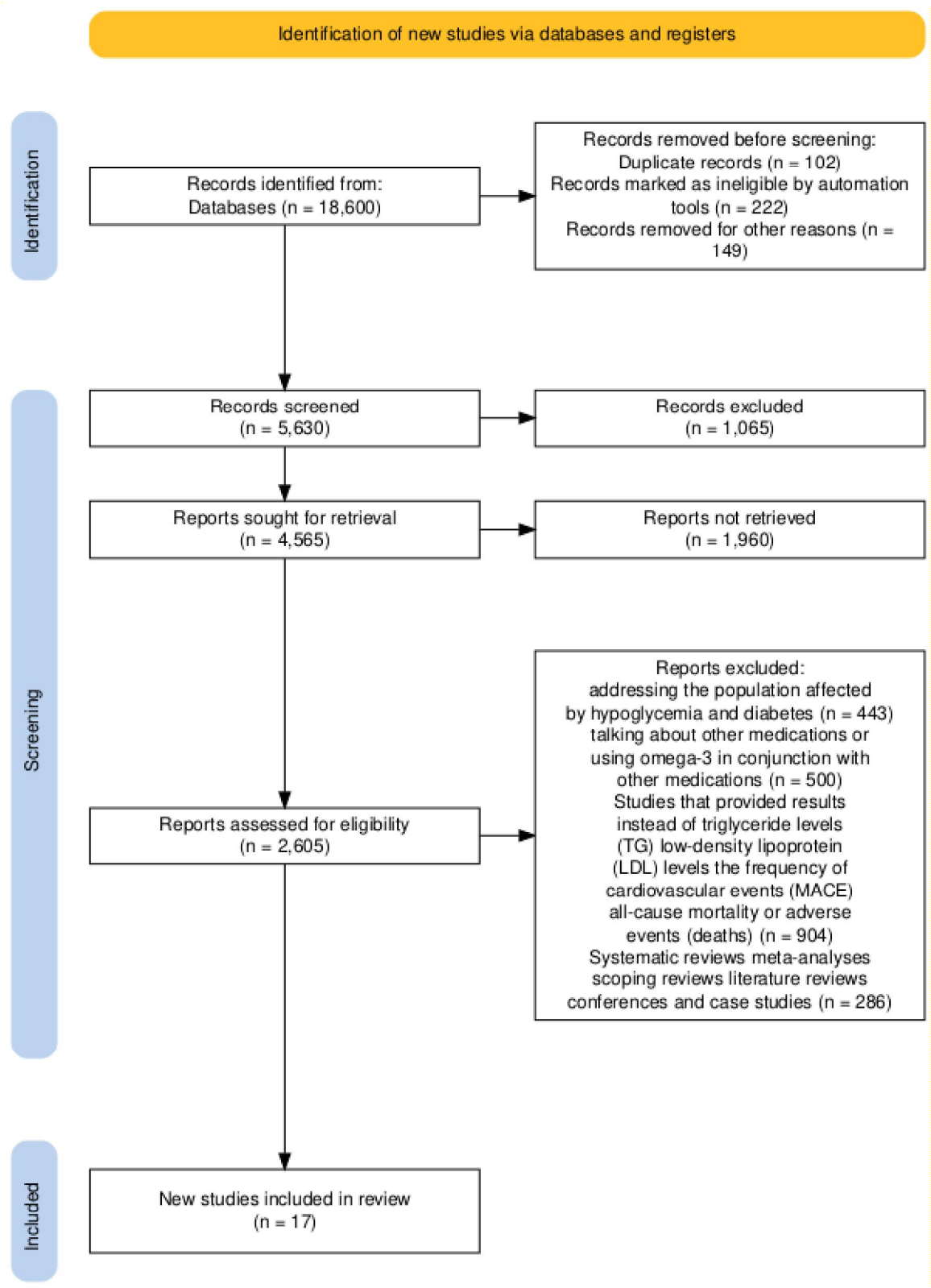

Fig no. 1: ***Screening and selection of included studies by PRISMA Guidelines***

Risk of Bias Assessment

The Cochrane risk of bias tool was used to assess the studies, and the findings are presented in Fig. 2 and 3. All our studies were considered to have minimal risk of bias, indicating a high level of reliability.

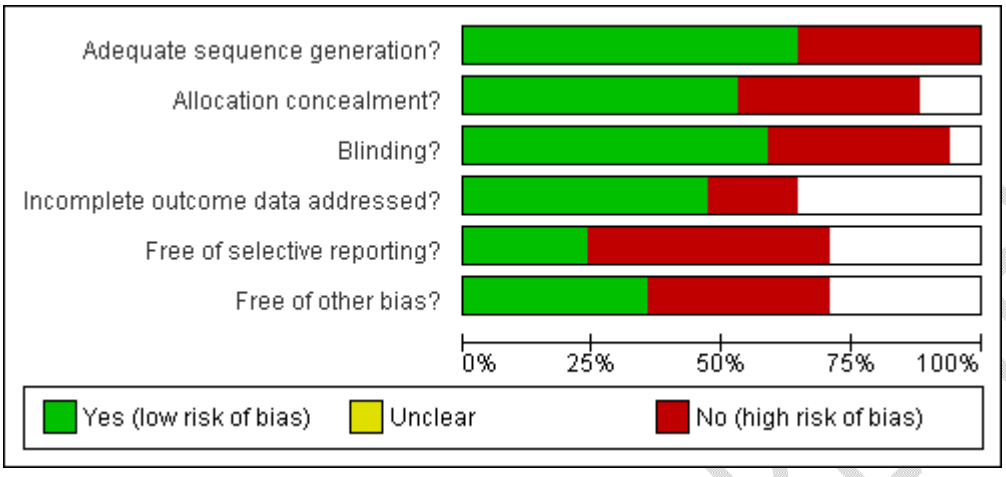

Fig no. 2: Graph of Risk bias of included studies

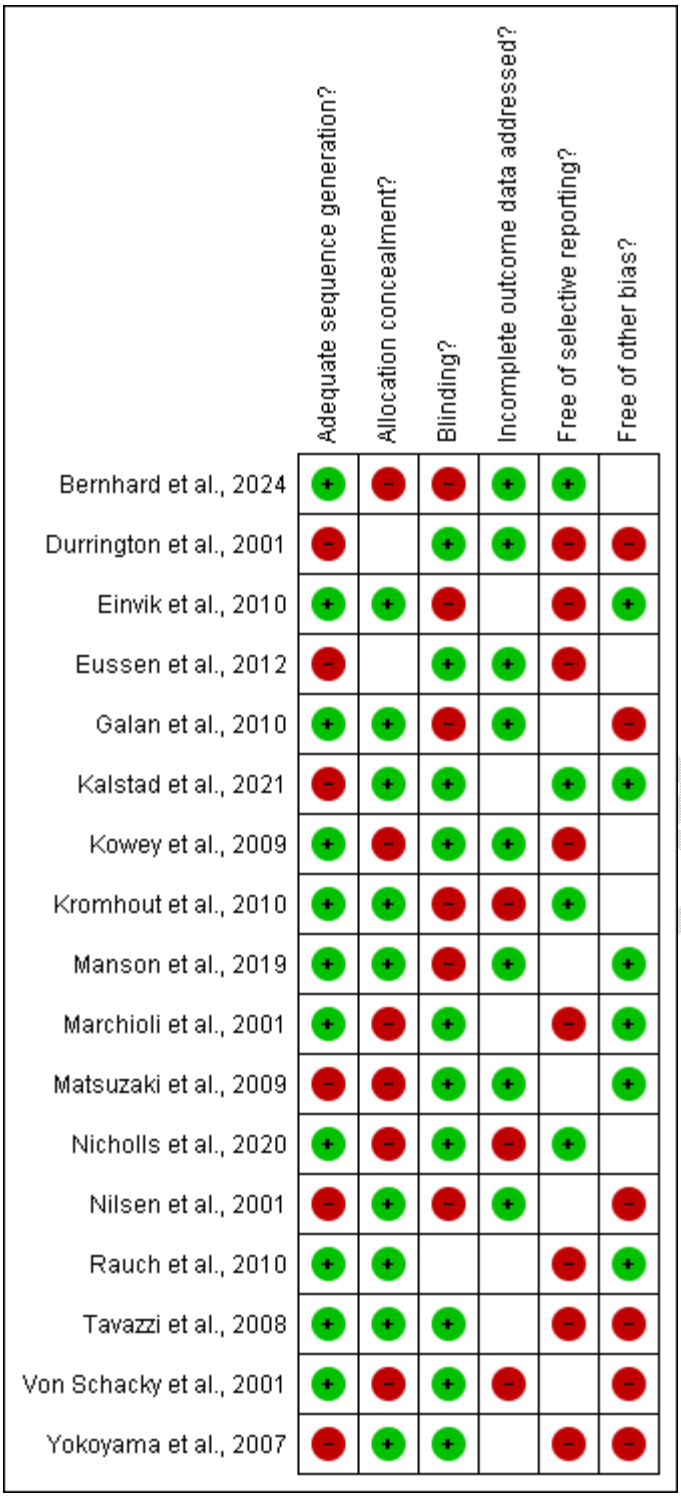

Fig no. 3: Graph of risk bias summary of included studies [16-32]

Characteristics of Included Studies

About 82,592 CVD patients from 17 RCT's were analyzed. In recent meta-analysis of RCT's, the interventions used to reduce the rates of cardiovascular events, was omega-3 fatty acids among patients with cardiovascular disease or cardiac risk to evaluate its clinical outcomes. About To produce heterogeneity, 17 RCT's were taken from 9 different countries such as 2 from USA [16, 28], 2 from Italy [17, 23], 2 from Japan [18, 27], 2 from Netherlands [19,29], 2 from United Kingdom [21, 30], 2 from Germany [20,32], 2 from Norway [22, 25], 1 from France [24] and 2 from Netherland [19, 29].

Table 1: ***Characteristics of included studies***

Author, Year	Country	Study population & Sample size	Study follow up	Treatment or intervention	Dose (g/day)	Triglycerides (mg/dl)	LDL (Low-density lipoprotein-cholesterol)	Cardiovascular events	Mortalities
Kowey et al., 2009 [16]	USA	584 patients with arterial fibrillation: 233 in treatment group & 246 in placebo	6 months	EPA + DHA	4 g/d of prescription omega-3 (465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid)			T: 135 P: 129	
Tavazzi et al., 2008 [17]	Italy	6,975 patients with CHD 3494 in treatment or 3481 in placebo	3.9 years	n-3 polyunsaturated fatty acids (PUFA)	n-3 PUFA 1 g daily			T: 955 P: 1014	T: 96 P: 92
Matsuzaki et al., 2009 [18]	Japan	3644 patients of coronary artery disease (CAD) 1823 EPA group & 1841 control group	4.6 years	EPA + Statin	1,800 mg of EPA	T:(-16.5) P:(-9)	T: 2.5 (0.9) P: 2.4 (0.9)	T: 158 P: 197	T: 178 P: 145
Kromhout et al., 2010 [19]	Netherlands	4837 patients: 2389 in treatment & 2448 in placebo	40.8 months	EPA + DHA	226 mg of EPA combined with 150 mg of DHA			T:227 P: 245	T: 19 P: 31
Rauch et al., 2010 [20]	Germany	3851 patients of acute myocardial infraction	12 months	EPA + DHA	1 g/d of omega-3-acid ethyl esters-90	T: -24.68 P:- 25.7		T: 182 P: 149	T: 28 P: 29

		1919 in treatment, 1885 in placebo							
Durrington et al., 2001 210]	United Kingdom	59 patients of CHD 30 in treatment 29 in placebo	48 weeks	Omacor	10 mg of omega-3 PUFA	T: -28.8 P: -34.23	T: -0.7 P: -0.5		T: 0 P: 1
Nilsen et al., 2001 [22]	Norway	300 with MI 150 in treatment 150 in placebo	12 months	n−3 Fatty acids	4 g highly concentrated n−3 fatty acids		T: −11.14 P: −6.18	T: 42 P: 36	T: 8 P: 8
Marchioli et al., 2001 [23]	Italy	5663 CVD patients 2835 in treatment 2828 in placebo	4 years	EPA / DHA	1-g capsule daily ofomega-3 PUFA			T: 266 P: 330	T: 239 P: 299
Galan et al., 2010 [24]	France	2501 patients with MI 1253 in treatment 1248 in placebo	4.7 years	EPA / DHA	600 mg of eicosapentanoic acid and docosahexaenoic acid	T: 1.2 P: 1.1		T: 81 P: 76	T: 58 P: 59
Kalstad et al., 2021 [25]	Norway	1027 patients with MI 505 in treatment 509 in placebo	8 weeks	EPA/ DHA	1.8 g n-3 PUFA	T: -8.1 P: 5.1	T: 0 P: 0.7	T: 108 P: 102	T: 28 T: 28
Nicholls et al., 2020 [26]	Australia	6539 in treatment 6539 in placebo	12 months	EPA / DHA	4 g/d of omega-3 CA	T: -19 P: -0.9	T; 1.2 P: -1.1	T: 785 P: 795	T: 228 P: 211
Yokoyama et al., 2007 [27]	Japan	9326 in EPA group & 9319 in placebo	5 years	EPA / DHA	1800 mg of EPA	T; -22.7 P:-19.88		T; 262 P: 324	

Bernhard et al., 2024 [28]	USA	358 patients with MI 180 in treatment 178 in placebo	6.6 years	O3-FA	4 g/ day of Omega-3 polyunsaturated fatty acids (O3-FA)			T: 6 P: 12	
Eussen et al., 2012 [29]	Netherlands	3740 in treatment 413 in placebo	3.7 years	EPA/ DHA	400 mg eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA)	T: -1.07 P: -3.06	T: 0.14 P: 0.45	T: 495 C: 62	T: 9 P: 18
Manson et al., 2019 [30]	United Kingdom	25,871 patients 15,200 in treatment 10, 571 in placebo	5.3 years	EPA / DHA	1g / day marine n-3 fatty acids			T: 386 P: 419	T: 300 P: 678
Einvik et al., 2010 [31]	Norway	563 patients: 283 in treatment 280 in placebo	3 years	n-3 PUFA	2.4 g n-3 PUFA supplementation			T: 24 P: 44	T: 11 P: 27
Von Schacky et al., 2001 [32]	Germany	162 patients 82 in treatment 80 in placebo	2 years	n-3 fatty acids	1.5 g/d n−3 fatty acids			T: 2 P: 7	T: 1 P: 3

PRIMARY OUTCOMES

1. **Triglyceride levels (mg/dl)**

Among 17 included studies, 8 RCT's [18, 21 24, 25, 26, 27, 29] discussed the triglycerides level as outcome of omega-3 fatty acids and recorded the difference between baseline and after intervention values with varying follow up (min. 8 weeks and max. 6 years). The pooled analysis showed that TG levels decreased significantly after omega-3 fatty acids [mean difference= -4.41 (-10.16 to 1.88) Cl: 95%) and heterogeneity reported was (df= 7, I^2 = 100%, p<0.000001).

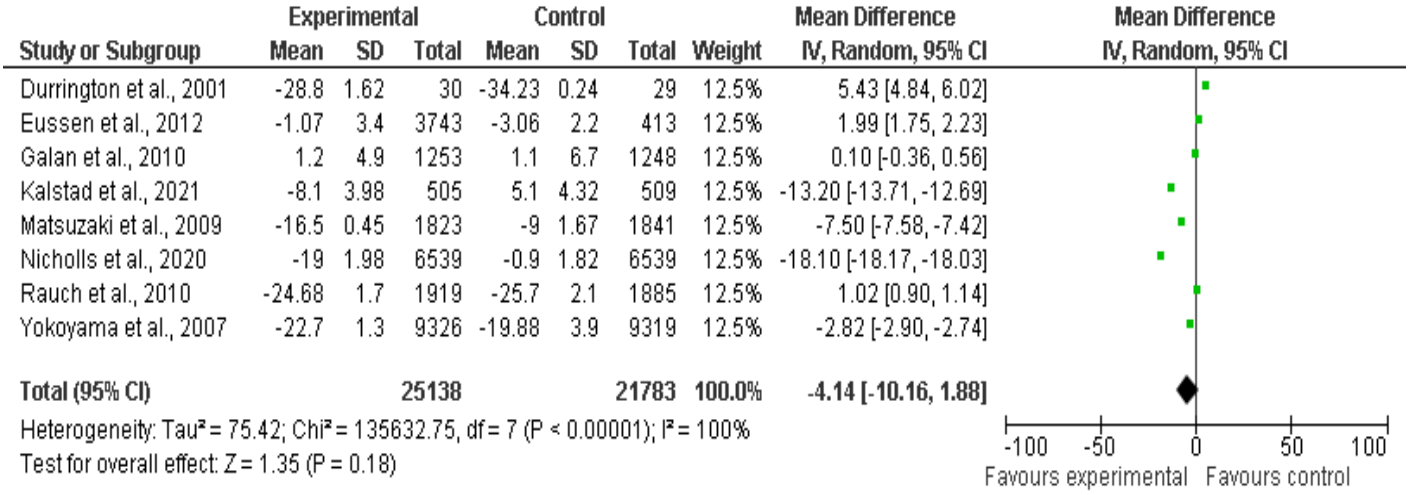

Figure no. 4: Forest plot of mean difference of TG levels among treatment and placebo groups[18, 21 24, 25, 26, 27, 29]

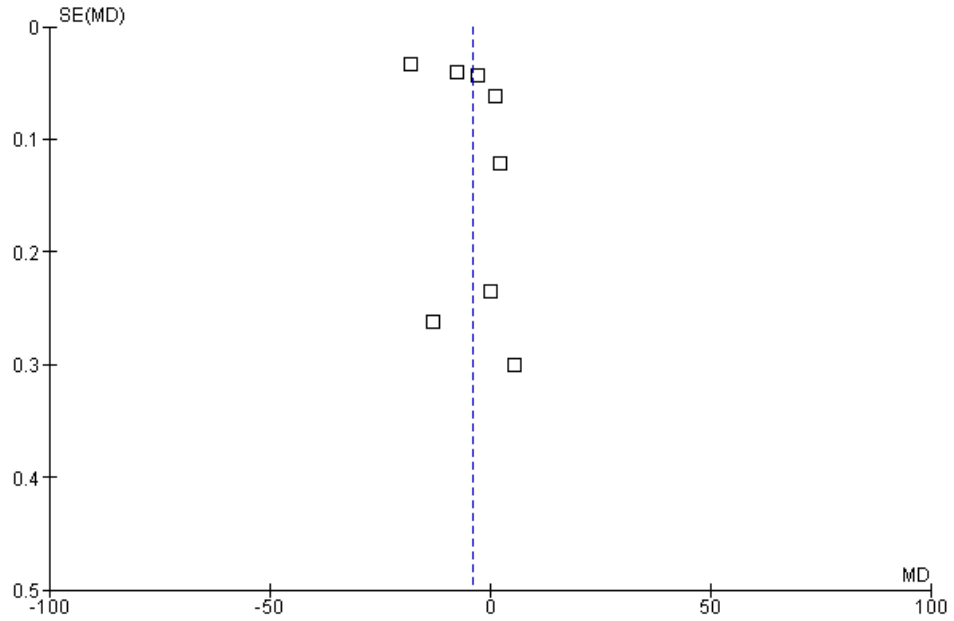

Figure no. 5: Funnel plot of mean difference of TG levels among treatment and placebo groups [18, 21 24, 25, 26, 27, 29]

2. LDL (mg/dl)

Among 17 included studies, 6 RCT's [18, 21,,, 11, 14, 15, 18] discussed the LDL level as outcome of omega-3 fatty acids and recorded the difference between baseline and after intervention values with varying follow up (min. 8 weeks and max. 6 years). The pooled analysis showed that LDL levels decreased slightly after omega-3 fatty acids [mean difference= -0.70 (-2.12 to 0.72) Cl: 95%) and heterogeneity reported was (df= 5, I^2 = 100%, p<0.000001).

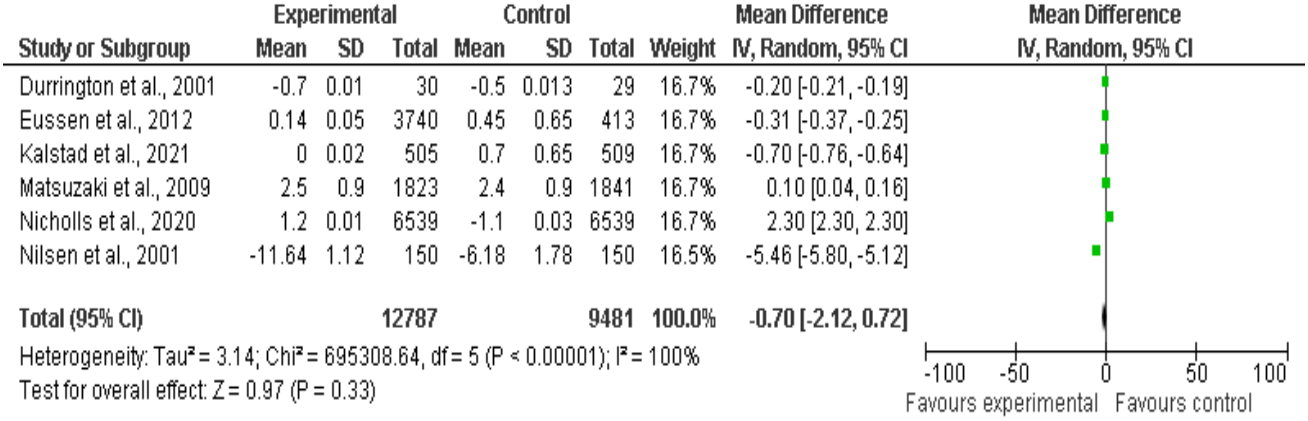

Figure no. 6: Forest plot of mean difference of LDL levels among treatment and placebo groups [18, 21,,, 11, 14, 15, 18]

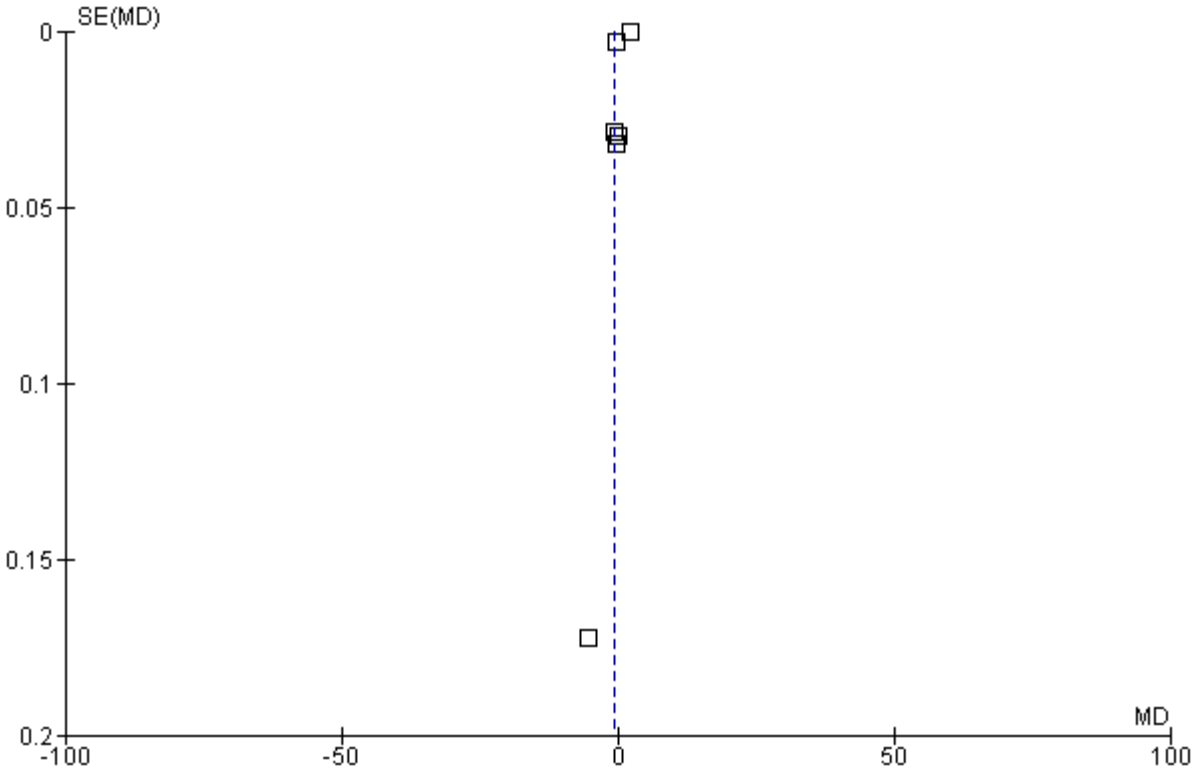

Figure no. 7: Funnel plot of mean difference of LDL levels among treatment and placebo groups [18, 21,,, 11, 14, 15, 18]

3. Cardiovascular events or MACE (major cardiovascular events)

Among 17 included studies, 16 RCT's [16-20, 22- 32] discussed the cardiovascular events as outcome of omega-3 fatty acids and recorded among treatment and placebo groups with varying follow up (min. 8 weeks and max. 6 years). The pooled analysis showed that risk ratio favored

the group receiving omega-3 fatty acids [risk ratio= 0.90 (0.82 to 0.99) Cl: 95%) and heterogeneity reported was (df= 15, I^2 = 76%, p<0.000001).

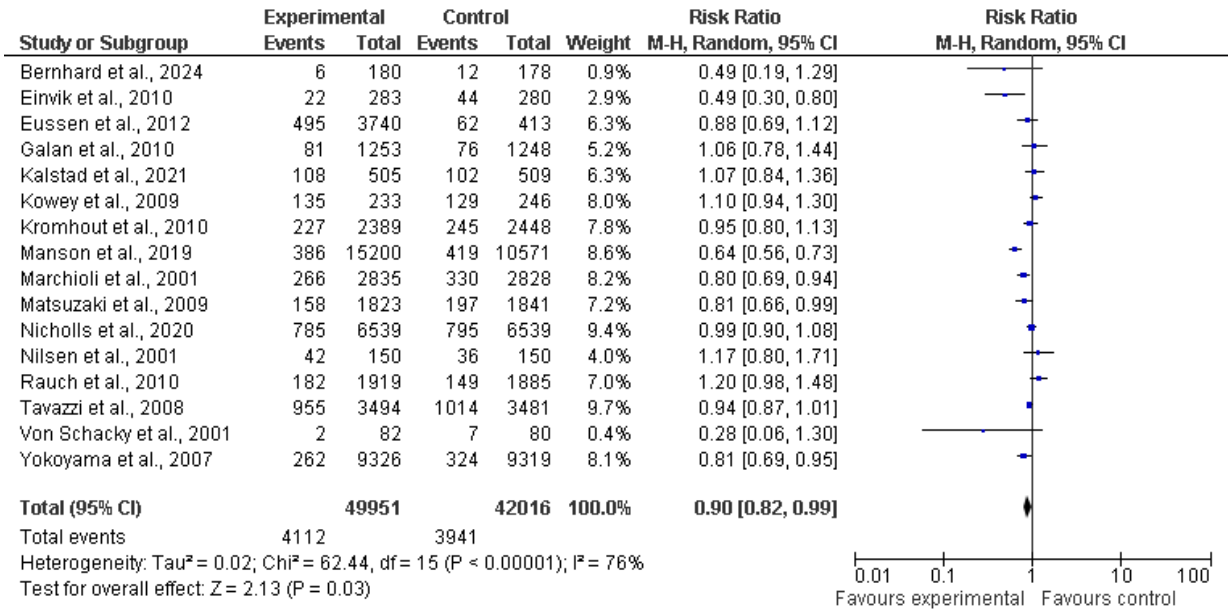

Figure no. 8: Forest plot of risk ratio of cardiovascular events among treatment and placebo groups [16-20, 22- 32]

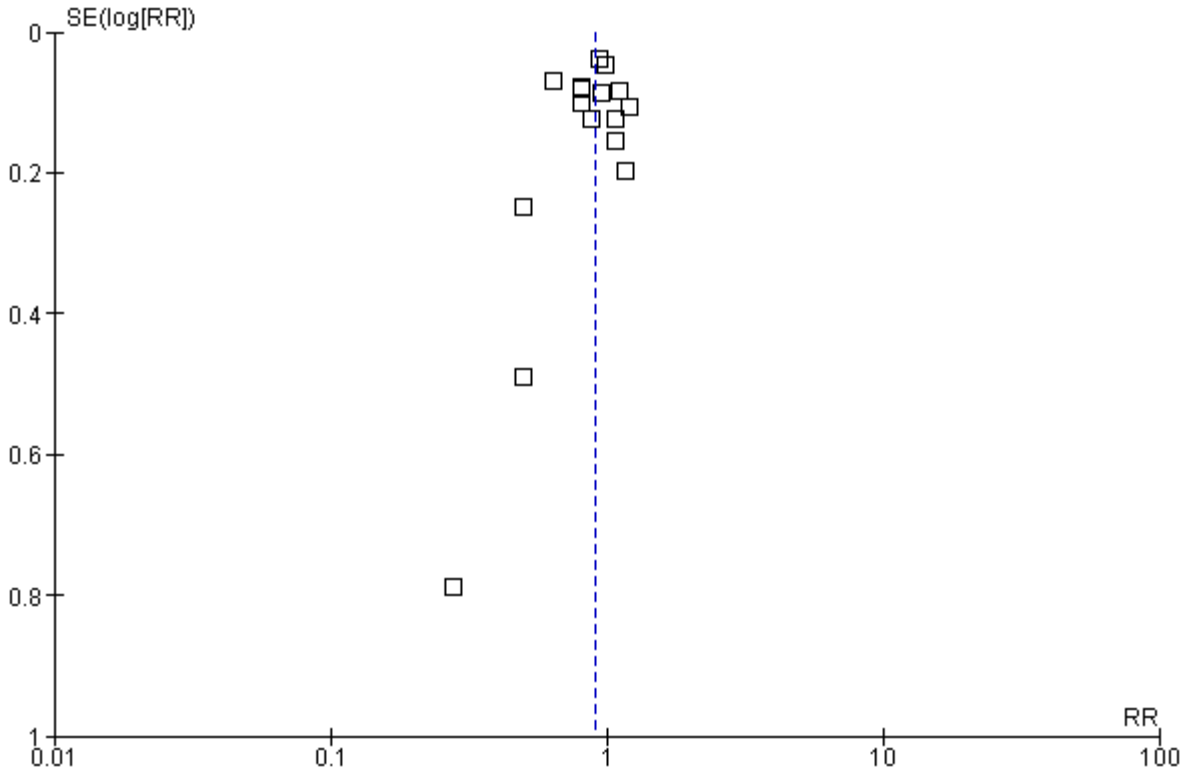

Figure no. 9: Funnel plot of risk ratio of cardiovascular events among treatment and placebo groups[16-20, 22- 32]

4. Cardiac mortalities

Among 17 included studies, 14 RCT's [16-20, 22- 32] discussed the cardiovascular deaths as outcome of omega-3 fatty acids and recorded among treatment and placebo groups with varying follow up (min. 8 weeks and max. 6 years). The pooled analysis showed that risk ratio favored the group receiving omega-3 fatty acids [risk ratio= 0.65 (0.44 to 0.95) Cl: 95%) and heterogeneity reported was (df= 13, I^2 = 95%, p<0.000001).

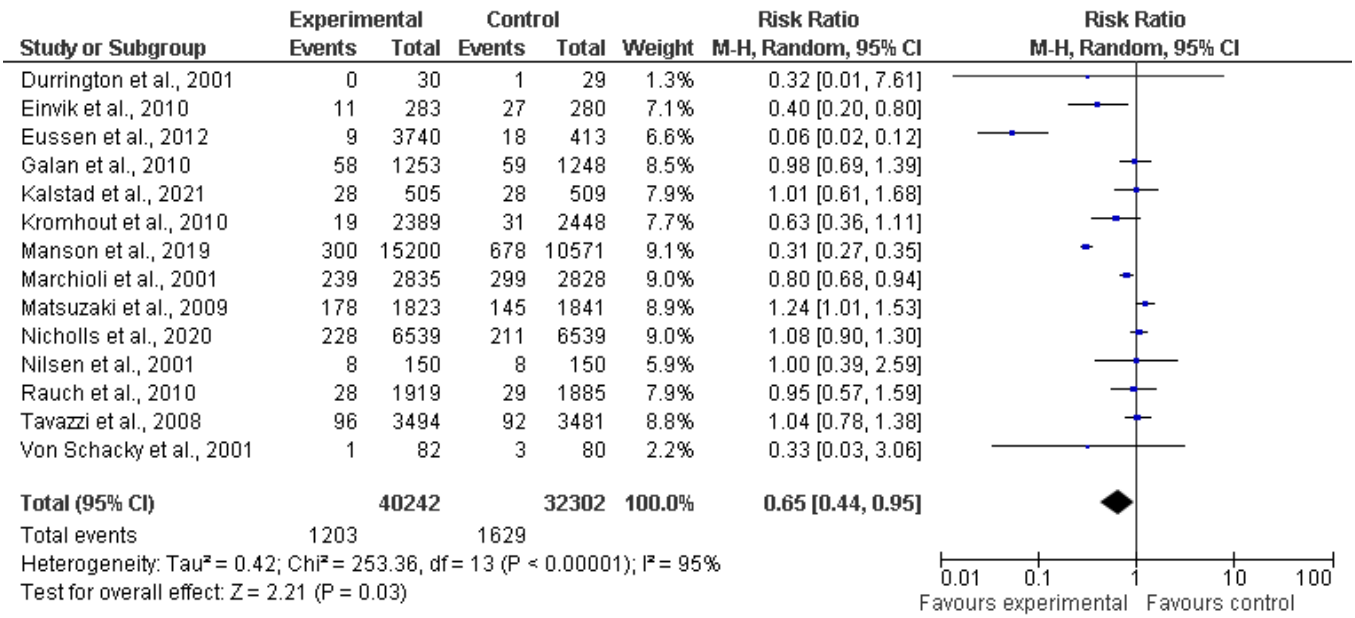

Figure 10 risk ratio of group receiving omega-3 fatty acids [16-20, 22- 32]

Discussion

The outcomes of this most recent meta-analysis enable researchers to gain critical information with regard to protective features of omega-3 PUFAs on CVD. The results thus obtained are consistent with the prior literature, but the differences are also discussed as follows.

Triglyceride Levels

The second component of the lipid profile which was triglyceride level was also found to have been lowered by omega-3 fatty acids with an overall mean difference of -4. 41 mg/dl (95% CI: In terms of the Effect Estimate (EQ; range = -10. 16 to 1. 88) of the included studies, the meta-analysis found that the results were relatively consistent. This decrease can also be congruent with Balk's et al. , [33] and Mozaffarian and Rimm's [34] meta-analysis where omega-3s were associated with a reduction of triglyceride levels. Inhibition of hepatic triglyceride synthesis and increase in lipoprotein lipase-mediated removal of triglyceride-rich lipoproteins is said to be responsible for the lipid-lowering effects and more specifically the decrease in triglyceride level by omega-3 fatty acids [35].

The large amount of heterogeneity published in our analysis (I^2 = 100%, p < 0. 000001) makes us think that the effects vary among some studies because of methodological differences, population characteristics, and administration of omega-3 doses. This size of heterogeneity suggests that more research to determine the predictors that determine the size of the effect of triglyceride in different groups of people is required.

LDL Cholesterol Levels

The results concerning omega-3 fatty acids were less distinctive as to the LDL cholesterol with a mean difference of -0. 70 mg/dl (95% CI: Exceeded: Below the proliferation threshold of -2. 12 to 0. 72. This is in line with other studies in which omega-3 has been largely found to have a minimal reducing or non-reducing role on the total cholesterol 'LDL' [36, 38]. This may be so because omega-3 fatty acids differently affect the various lipid fractions, and their main advantage is in the context of the triglycerides rather than affecting the LDL.

Thus, the high level of statistical heterogeneity for LDL outcomes (I^2 = 100%, p < 0. 000001) suggests that treatment effects of omega-3 might depend on baseline lipid levels, presence of comorbidities and type and dose of omega-3 used. Further research directions have to be oriented on the identification of the circumstances in which omega-3 supplements may have a greater impact on LDL cholesterol.

Major Cardiovascular Events (MACE)

In our meta-analysis, omega-3 fatty acids were related to a small but still significantly lower risk of MACE, with a risk ratio of 0. 90 (95% CI: 0. 82 to 0. 99 among the different groups of participants or clients. This result is in agreement with that observed in the GISSI-Prevenzione trial [36] which showed that omega-3 supplements are protective against cardiac events. Thus, the anti-inflammatory and anti-thrombotic actions, together with the stabilizing impact on plaques of omega-3 PUFAs are probably implicated within this setting [35].

However, the proven variability of the influence (I^2 = 76%, p < 0. 000001) proves that omega-3 is not effective in all the populations of patients studied. Many of these differences might be due to differences in the populations in the studies, the length of the interventions, and the baseline cardiovascular risk factors of patients in the trials. Further research should aim at establishing

patient characteristics that would help to determine which patients obtain the most benefit from supplementation with omega-3.

Cardiac Mortalities

In the present meta-analysis, we found the number of cardiac mortalities decreased with a risk ratio of 0. 65 (95% CI: The effects of omega-3 fatty acid on total mortality, cardiovascular mortality, sudden cardiac death and myocardial infarction are shown in a meta-analysis from 13 studies (0. 44 to 0. 95), and underlines the role of omega 3 fatty acid in high risk cardiovascular groups. This result is consistent with findings of other major randomized trials like the JELIS trial [40] and the GISSI-Prevenzione trial conducted in 1999 wherein it was found that omega-3 supplementation lowered deaths from cardiac causes.

Yet, a notable level of heterogeneity in this outcome (I^2 = 95%, p < 0. 000001) indicates that the size of the effect may depend on the amount of omega-3 used, the time of follow up and the kind of cardiovascular events studied. More studies must be conducted to define these lagers and to identify the best approach to the adaptive use of omega-3 fatty acids in minimizing cardiac mortality in patient studies.

Implications

These results of the present meta-analysis support the idea that omega-3 fatty acids can serve as only preventive agents in patients with cardiovascular disease especially in lowering triglyceride levels, occurrence of major cardiovascular events and cardiac deaths. From these findings it can be deduced that omega-3 can be included in patients' management protocols for individuals characterized by increased risk of developing CVDs. But more often, the effects of omega-3 fatty acids in various population samples and settings recommend the careful personalization of these recommendations and, in effect, the cardiovascular prevention interventions that utilize it.

Limitations

However, several limitations of this meta-analysis can still be highlighted because they are an important part of recognising the general methodology of the research, which is the analysis of randomized controlled trials: A high level of heterogeneity across the studies suggests variation

of effects for outcomes, which may not allow the generalization of the results. However, variations of dosage, formulation, and duration of omega-3 supplementation across the studies are other issues that make direct comparisons and conclusions rather difficult. In addition, there is a possibility of publication bias and a limitation of the analysis in that they only included studies published in English. Further research should endeavor to overcome these limitations by performing more comparative and standardized controlled trials.

Conclusion

Based on this systematic review of randomized controlled trials, omega-3 fatty acids have significant reductions in triglyceride levels, risk of major cardiovascular events and cardiac mortalities. The outcome supports the underlying use of omega-3 supplementation as the part of primary prevention for persons with risk factors for cardiovascular diseases. Nevertheless, the differences between the studies appear to warrant more investigation in order to further optimize the dosage and particularly to assess patients who could benefit the most from omega-3 fatty acids. Despite the statistically positive findings, preliminary discussion of the evidence highlights the fact that the available data is not readily generalizable, and there are variations in the impact of omega-3 on cardiovascular health. More research on the system of action and the consequences of omega-3 fatty acid in long-term usage will help in coming up with better guidelines in the use of omega-3 fatty acids for CV patients.

References

1. World Health Organization: Cardiovascular diseases (CVDs) (2020). Accessed: July 28, 2024:https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
2. Roger VL, Go AS, Lloyd-Jones DM, et al.: Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012, 125: 10.1161/CIR.0b013e31823ac046.
3. Benjamin EJ, Muntner P, Alonso A, et al.: Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation. 2019, 139: 10.1161/CIR.0000000000000659.
4. Mozaffarian D, Wu JH: Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011, 58:2047-2067. 10.1016/j.jacc.2011.06.063.
5. Calder PC: Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. BiochimBiophys Acta. 2015, 1851:469-484. 10.1016/j.bbalip.2014.08.010.
6. Harris WS, Miller M: Efficacy of omega-3 fatty acids in reducing triglycerides in patients with mixed dyslipidemia. J Clin Lipidol. 2018, 12:718-724. 10.1016/j.jacl.2018.03.002.
7. Mori TA, Woodman RJ: The independent effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans. Curr Opin Clin NutrMetab Care. 2006, 9:95-104. 10.1097/01.mco.0000200321.66057.58.
8. Saravanan P, Davidson NC, Schmidt EB, Calder PC: Cardiovascular effects of marine omega-3 fatty acids. Lancet. 2010, 376:540-550. 10.1016/S0140-6736(10)60445-X.
9. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR: Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis?. Lancet. 1978, 312:117-119. 10.1016/S0140-6736(78)91505-2.
10. Manson JE, Cook NR, Lee IM, et al.: Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med. 2019, 380:23-32. 10.1056/NEJMoa1811403.
11. Nicholls SJ, Lincoff AM, Garcia M, 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. 10.1001/jama.2020.22258.

12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021, 88:105906.
13. Sarkis-Onofre R, Catalá-López F, Aromataris E, Lockwood C: How to properly use the PRISMA Statement. Syst Rev. 2021, 10:1-3.
14. Schardt C, Adams MB, Owens T, et al.: Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007, 7:16. 10.1186/1472-6947-7-16.
15. Higgins JP, Altman DG, Gøtzsche PC, et al.: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011, 343 . 10.1136/bmj.d5928.
16. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM: Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. JAMA. 2010, 304:2363-2372.
17. Tavazzi L, Maggioni AP, Marchioli R, et al.: Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2008, 372:1223-1230.
18. Matsuzaki M, Yokoyama M, Saito Y, et al.: Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease secondary prevention analysis from JELIS. Circ J. 2009, 73:1283-1290.
19. Kromhout D, Giltay EJ, Geleijnse JM: n–3 Fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010, 363:2015-2026.
20. Rauch B, Schiele R, Schneider S, et al.: OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010, 122:2152-2159.
21. Durrington PN, Bhatnagar D, Mackness MI, et al.: An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. Heart. 2001, 85:544-548.

22. Nilsen DW, Albrektsen G, Landmark K, et al.: Effects of a high-dose concentrate of n− 3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. Am J Clin Nutr. 2001, 74:50-56.
23. Marchioli R, Schweiger C, Tavazzi L, Valagussa F: Efficacy of n- 3 polyunsaturated fatty acids after myocardial infarction: results of GISSI- prevenzione trial. Lipids. 2001, 36
24. Galan P, Kesse-Guyot E, Czernichow S, et al.: Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomisedplacebo controlled trial. BMJ. 2010, 341
25. Kalstad AA, Myhre PL, Laake K, et al.: Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized, controlled trial. Circulation. 2021, 143:528-539.
26. Nicholls SJ, Lincoff AM, Garcia M, 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.
27. Yokoyama M, Origasa H, Matsuzaki M, et al.: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007, 369:1090-1098. 10.1016/S0140-6736(07)60527-3.
28. Bernhard B, Heydari B, Abdullah S, et al.: Effect of six month's treatment with omega-3 acid ethyl esters on long-term outcomes after acute myocardial infarction: The OMEGA-REMODEL randomized clinical trial. Int J Cardiol. 2024, 399:131698. 10.1016/j.ijcard.2023.131698.
29. Eussen SR, Geleijnse JM, Giltay EJ, et al.: Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. Eur Heart J. 2012, 33:1582-1588. 10.1093/eurheartj/ehr499.
30. Manson JE, Cook NR, Lee IM, et al.: Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2019, 380:23-32. 10.1056/NEJMoa1811403.

31. Einvik G, Klemsdal TO, Sandvik L, Hjerkinn EM: A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. Eur J Cardiovasc Prev Rehabil. 2010, 17:588-592.
32. Von Schacky C, Baumann K, Angerer P: The effect of n− 3 fatty acids on coronary atherosclerosis: Results from SCIMO, an angiographic study, background and implications. Lipids. 2001, 36
33. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J: Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006, 189:19-30. 10.1016/j.atherosclerosis.2006.01.007.
34. Mozaffarian D, Rimm EB: Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006, 296:1885-1899. 10.1001/jama.296.15.1885.
35. Lee JH, O'Keefe JH, Lavie CJ, Harris WS: Omega-3 fatty acids: cardiovascular benefits, sources and sustainability. Nat Rev Cardiol. 2009, 6:753-758. 10.1038/nrcardio.2009.188.
36. GISSI-Prevenzione Investigators: Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet. 1999, 354:447-455. 10.1016/S0140-6736(99)07072-5.
37. Bhatt DL, Steg PG, Miller M, et al.: Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019, 380:11-22. 10.1056/NEJMoa1812792.
38. Yokoyama M, Origasa H, Matsuzaki M, et al.: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007, 369:1090-1098. 10.1016/S0140-6736(07)60527-3.
39. Mozaffarian D, Wu JH: Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011, 58:2047-2067. 10.1016/j.jacc.2011.06.063.
40. Calder PC: Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. BiochimBiophys Acta. 2015, 1851:469-484. 10.1016/j.bbalip.2014.08.010.