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Invited Review Article

Assessing the Efficacy of Omega-3 Fatty Acids + Statins vs. Statins Only on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of 40,991 Patients

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ABSTRACT

Background: Clinical guidelines recommend statin use in patients with a vast array of cardiovascular disturbances. However, there is insufficient evidence regarding the concomitant use of omega-3 fatty acids in addition to statins. This meta-analysis aims to uncover the complete effects of this combination therapy on cardiovascular outcomes, lipid biomarkers, inflammatory markers, and plaque markers.

Methods: A detailed literature search was conducted using PubMed, Cochrane, and MEDLINE databases, and all the relevant studies found up to September 2023 were included. The primary outcomes assessed in this meta-analysis was 1) Composite of fatal and non-fatal myocardial infarction, 2) Composite of fatal and non-fatal stroke, 3) Coronary revascularization, 4) Death due to cardiovascular causes, 5) MACE (Major Adverse Cardiovascular Events), 6) Unstable angina, 7) Hospitalization due to unstable angina, 8) and lipid volume index. Secondary outcomes included lipid markers, hsCRP, EPA levels, and EPA/AA ratio.

Results: 14 RCTs were included, featuring a total of 40,991 patients. Patients receiving the omega-3 + statin regimen were associated with a statistically significant decrease in the incidence of MI, MACE, unstable angina, hospitalization due to unstable angina, Total cholesterol levels, triglycerides, hsCRP, and lipid volume index in comparison to their counterparts receiving placebo + statin ($P < 0.05$). In contrast, our analysis found no statistically significant difference in the incidence of fatal and non-fatal stroke, coronary revascularization, and cardiovascular mortality.

Conclusion: Our research reinforces that all patients, regardless of their cardiovascular health, may benefit from adding omega-3 fatty acids to their statin therapy.

INTRODUCTION

Cardiovascular fatalities constitute a staggering annual toll of 17.9 million deaths[1]. To mitigate atherosclerotic cardiovascular events, statins emerge as the foremost pharmacological intervention for reducing low-density lipoprotein cholesterol (LDL-C) levels.

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[#] I take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Table 1
Baseline Demographic and Clinical Characteristics.

Study Name	Trial Name		Sample Size (n)	Dose of Omega 3 mg/day	Gender Male/ Female (n)	Age Mean (SD)	BMI Mean (SD)	Total Cholesterol mg/dL Mean (SD)	Triglycerides mg/dL Mean (SD)	hsCRP mg/dL Mean (SD)	EPA Levels µg/ml Mean (SD)	EPA/AA Ratio Mean (SD)	Drugs for CVDs* (n)
Nosaka K et al, 2016	-	Omega 3 + Statin	119	1800	92/27	70 (11)	23.8 (3.9)	185 (35)	102 (20.18)	-	61.3 (12.41)	0.36 (0..21)	61
		Placebo + Statin	119	-	90/29	71 (12)	24 (3.6)	182 (41)	96 (20.77)	-	62.8 (13.56)	0.38 (0.22)	58
Kita Y et al, 2020	-	Omega 3 + Statin	35	930	28/7	65.8 (3.2)	25 (1.9)	183.5 (21.71)	97.5 (18.48)	0000	47.4 (9.65)	0.31 (0.21)	18
		Placebo + Statin	31	-	27/4	63.5 (5.2)	24.4 (0.89)	186.72 (14.15)	106.5 (19.63)	0000	44.43 (9.62)	0.31 (0.22)	28
Watanabe T et al, 2017	CHERRY	Omega 3 + Statin	97	1800	78/19	67 (10)	23.7 (3.1)	174.9 (40.5)	108.9 (13.75)	0.39 (0.25)	64.4 (14.64)	0.43 (0.23)	42
		Placebo + Statin	96	-	81/15	68 (10)	23.9 (2.9)	165.6 (37.4)	107.9 (17.2)	0.55 (0.46)	64.1 (13.6)	0.48 (0.23)	37
Yokoyama M et al, 2007	JELIS	Omega 3 + Statin	9326	1800	2951/6375	61 (8)	24 (3)	128 (12.1)	32.2 (6.5)	-	-	-	2796
		Placebo + Statin	9319	-	2908/6411	61 (9)	24 (3)	128 (12.2)	32.48 (6.4)	-	-	-	2837
Nicholls SJ et al, 2020	STRENGTH	Omega 3 + Statin	6539	1000	4250/2289	62.5 (9)	32.2 (5.7)	166.3 (14.14)	244.3 (33.2)	0.23 (0.093)	22.2 (6.13)	-	4347
		Placebo + Statin	6539	-	4260/2279	62.5 (9)	32.2 (5.6)	161.5 (14.44)	245 (34.1)	0.23 (0.093)	22.4 (5.9)	-	4348
Bhatt DL et al, 2019	REDUCE-IT	Omega 3 + Statin	4089	4000	2927/1162	63.5 (3.5)	31 (1.94)	-	220.4 (27.58)	0.25 (0.1)	26.1 ()	-	-
		Placebo + Statin	4090	-	2895/1195	63.5 (3.5)	31.1 (2)	-	220.4 (28.4)	0.21 (0.1)	26.1 ()	-	-
Budoff MJ, 2020	EVAPORATE	Omega 3 + Statin	31	4000	17/14	56.5 (8.9)	34.1 (6.5)	-	259.1 (78.1)	-	-	-	-
		Placebo + Statin	37	-	20/17	58.3 (8.6)	33.3 (6.9)	-	259.1 (78.1)	-	-	-	
Sugizaki Y et al, 2020	LINK-IT	Omega 3 + Statin	21	1800	17/4	72.2 (3)	-	158 (13.3)	130.5 (17.3)	0.13 (0.06)	121.5 (22.51)	0.44 (0.23)	-
		Placebo + Statin	21	-	16/5	75 (3.4)	-	148.5 (9.25)	121.5 (15)	0.12 (0.03)	100 (28)	0.41 (0.21)	-
Nishio R et al, 2014	-	Omega 3 + Statin	15	1800	13/2	61 (12.6)	26.4 (3.6)	207.3 (39.1)	161.4 (50.50)	0.24 (0.18)	-	0.32 (0.15)	15

(*continued on next page*)

Table 1 (*continued*)

Study Name	Trial Name		Sample Size (n)	Dose of Omega 3 mg/day	Gender Male/ Female (n)	Age Mean (SD)	BMI Mean (SD)	Total Cholesterol mg/dL Mean (SD)	Triglycerides mg/dL Mean (SD)	hsCRP mg/dL Mean (SD)	EPA Levels µg/ml Mean (SD)	EPA/AA Ratio Mean (SD)	Drugs for CVDs* (n)
		Placebo + Statin	15	-	13/2	63.8 (9.5)	24.6 (3.5)	196.3 (40.3)	146.8 (37.4)	0.22 (0.15)	-	0.27 (0.13)	17
Toyama K et al, 2014	-	Omega 3 + Statin	40	1800	35/5	65.9 (8.2)	24.3 (2.9)	-	150.7 (92.9)	0.08 (0.10)	62.5 (38.1)	0.45 (0.34)	64
		Placebo + Statin	40	-	32/8	68.7 (10.6)	24.8 (2.9)	-	135 (74.6)	0.20 (0.36)	64 (30.2)	0.42 (0.26)	77
Chan DC et al, 2016	-	Omega 3 + Statin	10	-	-	-	27 (1.3)	-	-	-	-	-	-
		Placebo + Statin	10	-	-	-	27 (1.4)	-	-	-	-	-	-
Niki T et al, 2012	-	Omega 3 + Statin	29	1800	21/8	68.1 (10.1)	-	-	151.3 (73.2)	0.02 (0.04)	59.9 (23.5)	0.3 (0.2)	37
		Placebo + Statin	30	-	19/11	69.4 (10.7)	-	-	128.6 (58.9)	0.01 (0.02)	71.6 (38.7)	0.4 (0.2)	40
Alfaddagh A et al, 2017	-	Omega 3 + Statin	122	3360	104/18	62.4 (7.8)	30.9 (3.8)	153.7 (34.6)	125.5 (27.4)	0.2 (0.24)	-	-	202
		Placebo + Statin	97	-	84/13	62.6 (7.5)	30.5 (3.5)	152.2 (38.4)	119.87 (22.95)	0.18 (0.25)	-	-	170
Ahn J et al, 2016	-	Omega 3 + Statin	38	3000	24/14	59.6 (9.1)	24.8 (2.4)	205.53 (42.09)	127.77 (19.76)	-	-	-	64
		Placebo + Statin	36	-	26/10	60.7 (0.8)	24.5 (2.5)	183.50 (47.21)	135.62 (31.03)	-	-	-	64

Drugs for CVDs*: ACE Inhibitors + ARBs + Beta Blockers + Calcium Channel Blockers

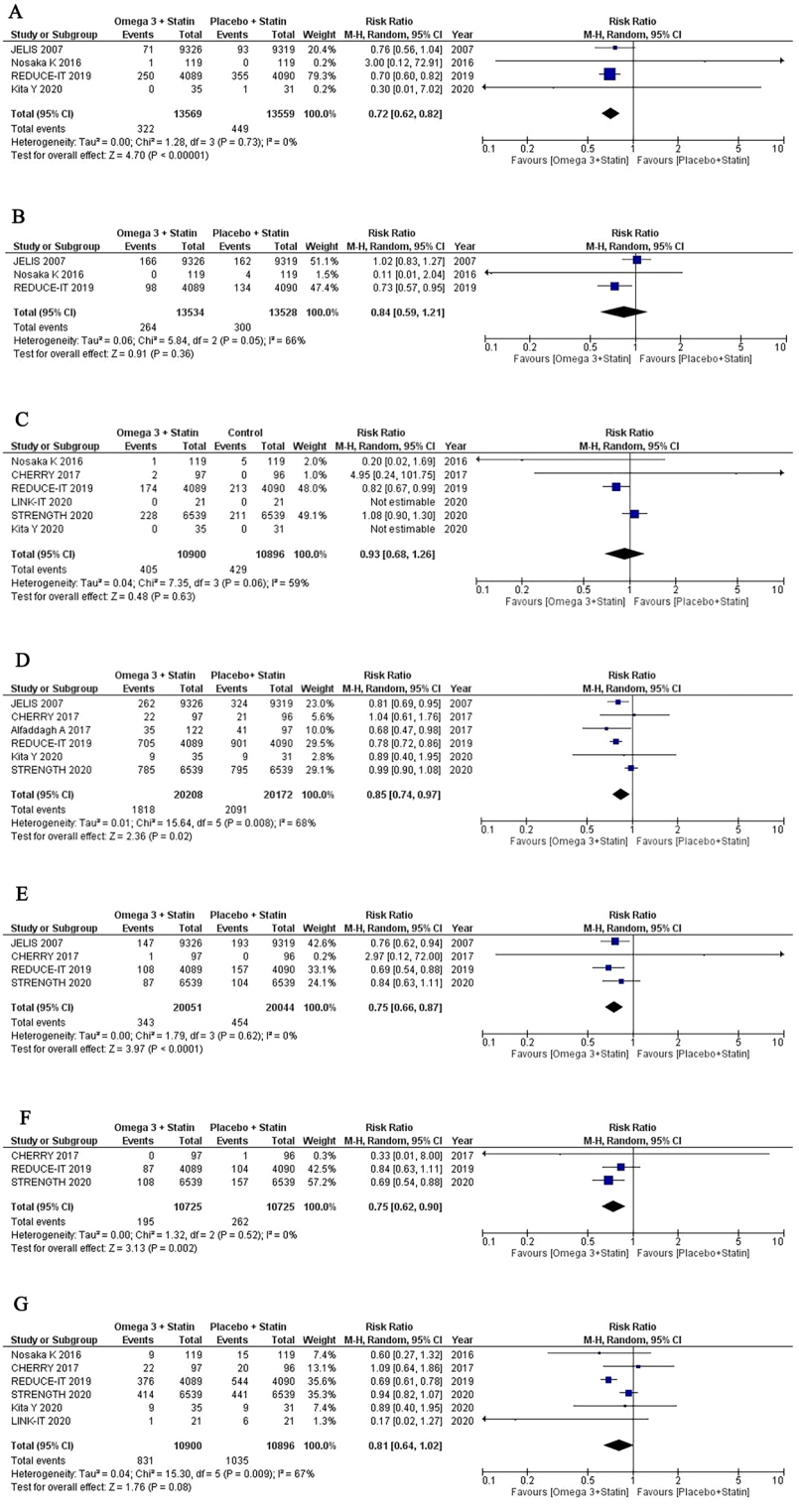

Fig. 1. (A) Forest plot of composite fatal and non-fatal MI (B) Forest plot of composite fatal and non-fatal stroke (C) Forest plot of Cardiovascular deaths (D) Forest plot of MACE (E) Forest plot of unstable angina (F) Forest plot of hospitalization for unstable angina (G) Forest plot of coronary revascularization.

The rate of occurrence of major cardiovascular events during 5-year follow-up in patients undergoing statin therapy was 21.7% for

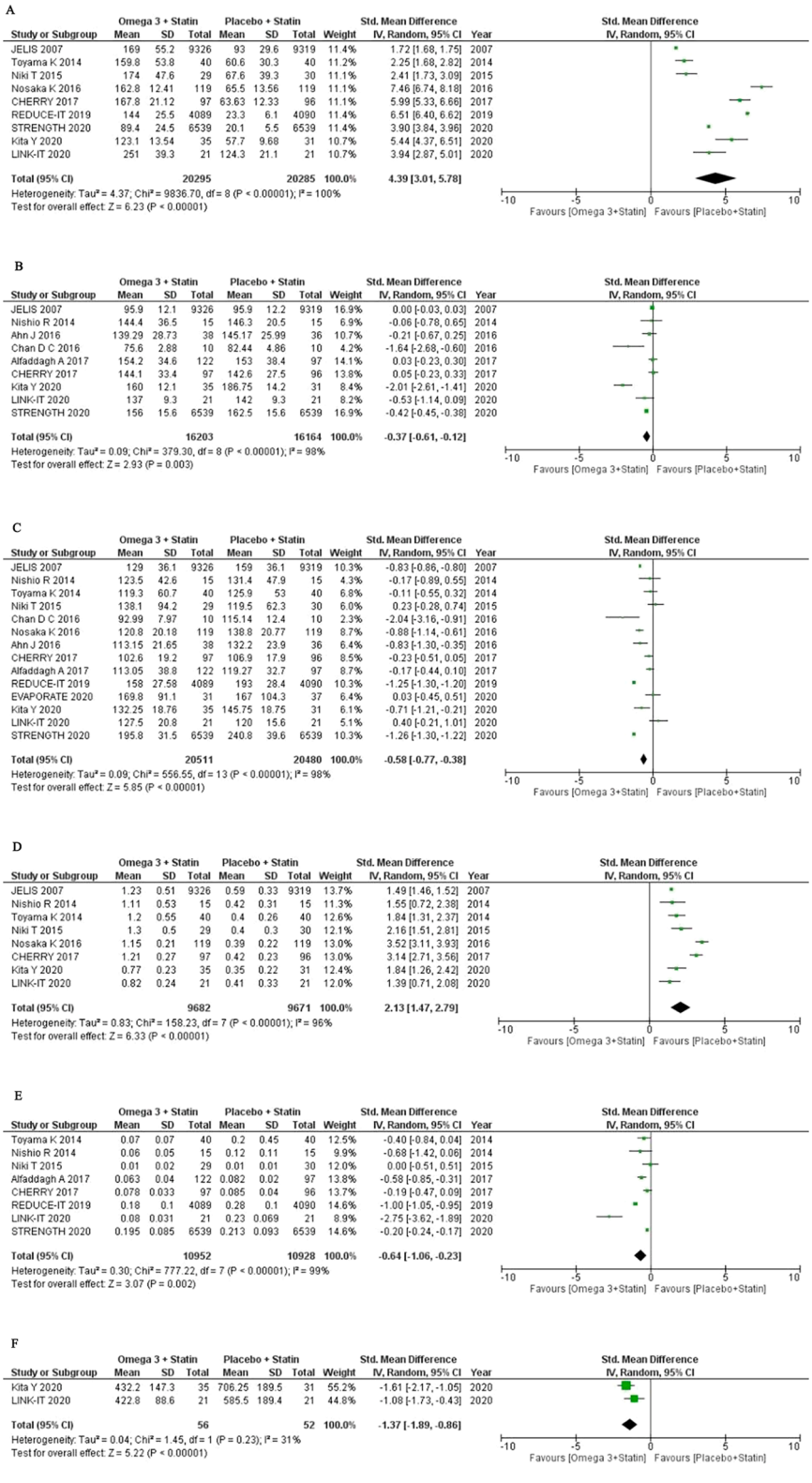

Fig. 2. (A) Forest plot of EPA levels (B) Forest plot of total cholesterol levels (C) Forest plot of triglyceride levels (D) Forest plot of EPA/AA ratio (E) Forest plot of serum hs-CRP (F) Forest plot of lipid volume index.

patients with previous CVD diseases and 9.5% for those who were not[2]. Lowering LDL-C levels to less than 70 mg/mol has also resulted in disease progression[2,3]. This is attributed to "residual risk" that somewhat remains even after statin therapy[1-5]. Reduction of this residual risk is extremely important to prevent the progression of ischemic cardiovascular events.

Consequently, there is an increased inclination towards combination regimens involving statins and w-3 PUFA. W-3 PUFA include Eicosapentaenoic Acid (EPA)[6], Docosahexaenoic Acid (DHA)[7-9] and Alpha Linolenic Acid.

Rupture of vulnerable plaques, marked by thin fibrous cap, large lipid core, and high macrophage content, are responsible for ACS development[2]. ACS encompasses STEMI, NSTEMI, and angina pectoris and can lead to major adverse cardiovascular effects such as death, hospitalization, and revascularization. ACS has a 5.6% hospital mortality rate and a 15% 1-year mortality rate[10]. Certain biomarkers may assist in identifying endothelial dysfunction, the underlying cause of ACS. These include hsCRP[11], LDL-C, and EPA/AA ratio[12].

There has been increasing epidemiological evidence that intake of omega-3 fatty acid is protective against morbidity related to cardiovascular diseases[7]. It has been reported that W-3 PUFA reduces CVD by incorporating HDL, increasing its anti-inflammatory anti-oxidative functions, and increasing cholesterol efflux[3,8,9,12]. They have also been shown to decrease inflammatory and apoptotic activity in the plaques while simultaneously increasing collagen and smooth muscle cells[2]. EPA decreased unstable angina, platelet aggregation, and lipid action while increasing vasodilation, anti-proliferation, and plaque stabilization[7].

The EVAPORATE study showed a reduction in plaque volume, calcification, and fibrosis of plaque[13]. Still, the reports are conflicting. Ahn et al. showed that there was no regression of atherosclerosis in patients undergoing PCI[14]. Previous studies either didn't have patients already on statin therapy[15] or were only concerned with plaque volume and character[16].

Our study includes a large and diverse sample size. We have studied the combined effects of omega-3 fatty acids and statins. Our study incorporates CVD outcomes, lipid markers, plaque characteristics, and inflammatory markers for refined analysis.

METHODS

Data Search and Study Strategy

This meta-analysis was conducted per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[17]. A detailed literature search was conducted using PubMed, Cochrane, and MEDLINE databases, and all the relevant studies found up to September 2023 were included. A more detailed picture of the search strategy is attached in Supplemental table 1.

Study Selection and Eligibility Criteria

Articles from the systematic search were screened for any duplicates found to be eliminated. All the remaining selected articles were initially screened based on their title and abstract, and subsequently, the studies underwent a full-text screening to assess their relevance. TWO reviewers (A.I. and S.H.H.) independently carried out the screening process, and any discrepancies found during this process were resolved through detailed discussion till a consensus was reached.

The selected articles were in accordance with the following eligibility criteria: 1) Randomized Control Trials with a follow-up for at least 8 weeks, 2) Studies involving patients on statin therapy, 3) Studies in which omega 3 fatty acids were compared with Placebo, 4) Studies in which cardiovascular outcomes or lesion markers were reported as the primary outcomes. All case series, case reports, non-English articles, and articles in which patients took omega-3 fatty acids without statins or did not report any cardiovascular outcomes were excluded from the study.

Outcomes of Interest, Data Extraction, and Quality Assessment

The primary outcomes assessed in this meta-analysis were 1) Composite of fatal and non-fatal myocardial infarction, 2) Composite of fatal and non-fatal stroke, 3) Coronary revascularization, 4) Death due to cardiovascular causes, 5) MACE (Major Adverse Cardiovascular Events), 6) Hospitalization due to unstable angina, 7) and lipid volume index. Additionally, some secondary outcomes were also analyzed, which include lipid markers, hsCRP, EPA levels, and EPA/AA ratio. An Excel spreadsheet was designed to extract the included studies' study characteristics, baseline demographics, outcome data, and safety data. The quality assessment was then carried out utilizing the Cochrane Risk of Bias tool, independently by two reviewers (A.I. and S.H.H.), and any disparity during this process was concluded via in-depth discussion between the reviewers[18].

The Statistical Analysis

In conducting the analysis, Review Manager (RevMan version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) was used to conduct all the statistical analyses. A random-effects model was chosen to account for any expected heterogeneity in study design and certain outcome definitions. While continuous outcomes were evaluated by Standard Mean Differences with a 95% confidence interval, the Higgins I2 statistic was opted to assess statistical heterogeneity, and it was deemed significant when it exceeded 50%. In the allocation of study weights, an inverse variance method was used. Moreover, in an effort to identify the trial-causing heterogeneity of >50%, sensitivity analysis was conducted by employing the leave-one-out analysis. Lastly, publication bias was visually assessed by funnel plots for outcomes that were reported by more than 13 studies. A p-value of equal to or less than 0.05 signifies a result of practical importance.

RESULTS

Literature Search and Characteristics of Studies

The systematic search initially revealed 1,374 records, dating from inception to September 2023. After the removal of duplicate records, there were 785 articles remaining, which were subject to a rigorous screening at the title-and-abstract level, followed by a subsequent full-text screening of 149 articles. Ultimately, there were 14 studies eligible for inclusion into this qualitative and quantitative synthesis[2,3,6-9,12-14,19,20,21,22,23], after the exclusion of 97 articles with no relevant outcomes of interest, and 38 articles that did not have study or patient characteristics that complied with our eligibility criteria. Further details regarding the screening process are depicted in the PRISMA flowchart, illustrated in Supplementary Figure 1

This comprehensive systematic review and meta-analysis featured a total of 40,991 patients, including 20,511 patients receiving the omega 3 + statin regimen, and 20,480 patients receiving the placebo + statin regimen. The average age of the included study population for the omega 3 + statin cohort was 64.3 years, whereas the average age of the placebo + statin cohort was 65.2 years. Most studies administered omega-3 fatty acids at a dose of 1,800 mg per day; however, certain trials administered doses as low as 930 mg per day, whereas other trials administered doses as high as 4,000 mg per day. Further details on the baseline demographic and clinical characteristics of the included study population are available in Table 1.

Quality of Assessment and Risk of Bias

The quality and risk of bias of included studies was evaluated using the Cochrane Risk of Bias Tool for Randomized Controlled Trials. In general, the studies demonstrated a moderate quality of assessment and risk of bias, with several studies faltering in the blinding aspect (performance bias) of the evaluation. The risk of bias graph is illustrated in Supplementary Figure 2, with the summary of evaluation available in Supplementary Figure 3.

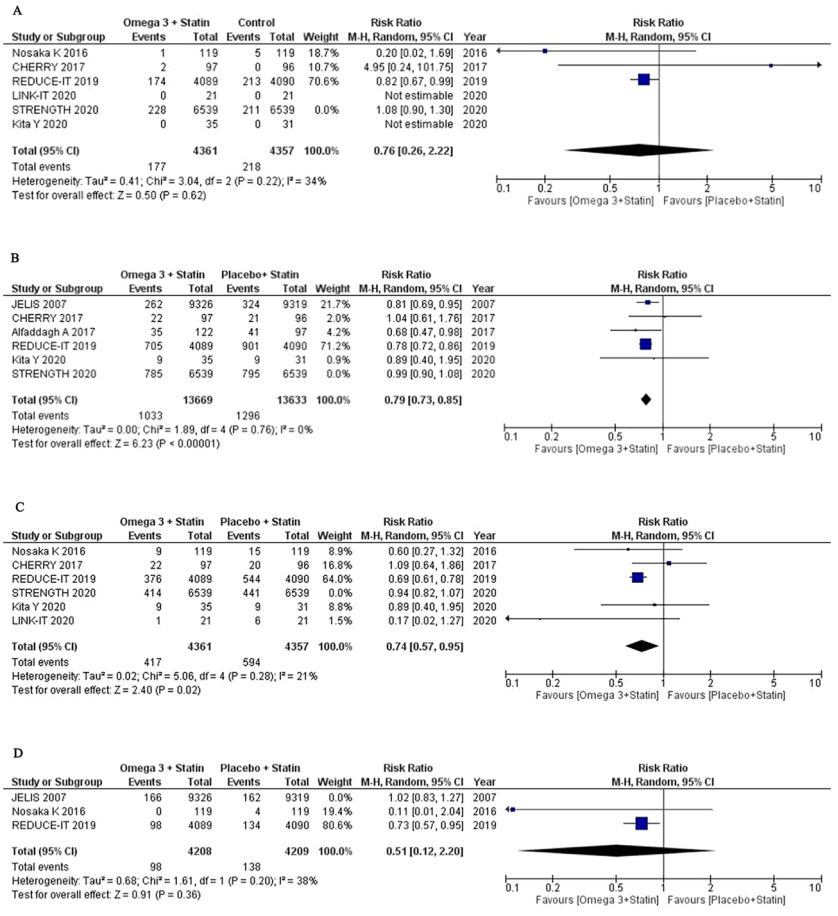

Fig. 3. (A) Post-sensitivity analysis forest plot of Cardiovascular deaths (B) Post-sensitivity analysis forest plot of MACE (C) Post-sensitivity analysis forest plot of coronary revascularization (D) Post-sensitivity analysis forest plot of composite fatal and non-fatal stroke

Comparison of Clinical Outcomes

This comprehensive systematic review and meta-analysis explored the following clinical outcomes, including: (i) cardiovascular mortality, (ii) incidence of MACE, (iii) incidence of MI, (iv) incidence of stroke, (v) incidence of unstable angina, (vi) hospitalization due to unstable angina, (vii) use of coronary revascularization. The incidence of composite fatal and non-fatal MI was reported by 4 studies, where it was observed that patients receiving the omega-3 + statin regimen were associated with a statistically significant decrease in the incidence of MI, in comparison to their counterparts receiving a placebo + statin (RR: 0.72; 95% CI [0.62 to 0.82]; P < 0.00001; Fig. 1A). The incidence of composite fatal and non-fatal stroke was reported by 3 studies, where no statistically significant differences were observed between patients receiving the omega-3 + statin regimen, and the patients receiving a placebo + statin only (RR: 0.84; 95% CI [0.59 to 1.21]; P = 0.36; I^2 = 66%; Fig. 1B). The incidence of cardiovascular mortality was reported by 6 studies, where no statistically significant differences were observed between patients receiving the omega-3 + statin regimen, and the patients receiving a placebo + statin only (RR: 0.93; 95% CI [0.68 to 1.26]; P = 0.63; I^2 = 59%; Fig. 1C). The incidence of MACE was reported by 6 studies, where it was observed that patients receiving the omega-3 + statin regimen were associated with a statistically significant decrease in the incidence of MACE, in comparison to their counterparts receiving a placebo + statin (RR: 0.85; 95% CI [0.74 to 0.97]; P = 0.02; I^2 = 68%; Fig. 1D). The incidence of unstable angina was reported by 4 studies, where it was observed that patients receiving omega-3 + statin regimen were associated with a statistically significant decrease in the incidence of unstable angina, in comparison to their counterparts receiving a placebo + statin (RR: 0.75; 95% CI [0.66 to 0.87]; P < 0.0001; Fig. 1E). The incidence of hospitalization for unstable angina was reported by 3 studies, where it was observed that patients receiving omega-3 + statin regimen were associated with a statistically significant decrease in the hospitalization for unstable angina, in comparison to their counterparts receiving a placebo + statin (RR: 0.75; 95% CI [0.62 to 0.90]; P = 0.002; Fig. 1F). The use of coronary revascularization was reported by 6 studies, where no statistically significant differences were observed between patients receiving the omega-3 + statin regimen, and the patients receiving a placebo + statin only (RR: 0.81; 95% CI [0.64 to 1.02]; P = 0.08; I^2 = 67%; Fig. 1G).

Comparison of Laboratory Parameters

This comprehensive systematic review and meta-analysis explored the following laboratory parameters, including: (i) serum EPA levels, (ii) total cholesterol levels, (iii) triglyceride levels, (iv) AA ratio, (v) serum hsCRP levels, and (vi) lipid volume index. The differences in serum EPA levels were reported by 9 studies, where it was observed that patients receiving omega-3 + statin regimen were associated with a statistically significant increase in serum EPA levels in comparison to their counterparts receiving a placebo + statin (SMD: 4.39; 95% CI [3.01 to 5.78]; P < 0.00001; I^2 = 100%; Fig. 2A). The differences in total cholesterol levels were reported by 9 studies, where it was observed that patients receiving omega-3 + statin regimen were associated with a statistically significant decrease in total cholesterol levels in comparison to their counterparts receiving a placebo + statin (SMD: -0.37; 95% CI [-0.61 to -0.12]; P = 0.003; I^2 = 98%; Fig. 2B). The differences in triglyceride levels were reported by all 14 studies, where it was observed that patients receiving omega-3 + statin regimen were associated with a statistically significant decrease in triglyceride levels in comparison to their counterparts receiving a placebo + statin (SMD: -0.58; 95% CI [-0.77 to -0.38]; P < 0.00001; I^2 = 98%; Fig. 2C). The differences in the EPA/AA ratio were reported by 8 studies, where it was observed that patients receiving the omega-3 + statin regimen were associated with a statistically significant increase in the EPA/AA ratio in comparison to their counterparts receiving a placebo + statin (SMD: 2.13; 95% CI [1.47 to 2.79]; P < 0.00001; I^2 = 96%; Fig. 2D). The serum hsCRP levels were reported by 8 studies, where it was observed that patients receiving the omega-3 + statin regimen were associated with a statistically significant decrease in serum hsCRP levels in comparison to their counterparts receiving a placebo + statin (SMD: -0.64; 95% CI [-1.06 to -0.23; P = 0.002; I^2 = 99%; Fig. 2E). The lipid volume index was reported by 2 studies, where it was observed that patients receiving the omega-3 + statin regimen were associated with a statistically significant decrease in lipid volume index in comparison to their counterparts receiving a placebo + statin (SMD: -1.37; 95% CI [-1.89 to -0.86]; P < 0.00001; Fig. 2F).

Assessment of Heterogeneity

In order to address the significant levels of heterogeneity observed within certain outcomes, the sensitivity analysis technique using the leave-one-out method was performed. In the outcome of cardiovascular mortality, the exclusion of the STRENGTH (2020) trial led to a considerable reduction of heterogeneity, from I^2 = 59% to I^2 = 34%[20] (Fig. 3A). Moreover, in the outcome of MACE, the exclusion of STRENGTH (2020) trial led to the complete eradication of all heterogeneity, from I^2 = 68% to I^2 = 0%[20] (Fig. 3B). Furthermore, in the outcome of coronary revascularization, the exclusion of STRENGTH (2020) trial led to a considerable reduction of heterogeneity, from I^2 = 67% to I^2 = 21%[20] (Fig. 3C). The results of these sensitivity analyses outline a distinct pattern involving the STRENGTH trial, which may be attributable to several factors. Firstly, the trial featured the exclusive inclusion of patients with a high cardiovascular risk, predisposing the sample population to worsened clinical outcomes and parameters. Secondly, this trial featured one of the largest patient populations of the included studies, increasing the possibility of skewed and unreliable results of the meta-analysis paired with the subsequent heightened levels of heterogeneity, as the majority of other trials included are considerably smaller with respect to sample sizes. Thirdly, the use of “corn oil” as a placebo comparator may induce innate differences when compared to other trials, as other studies have reported the use of mineral oil instead.

In the outcome of stroke, the exclusion of JELIS (2007) trial led to a considerable reduction of heterogeneity, from I^2 = 66% to I^2 = 38%[7] (Fig. 3D). This may be attributed to the trial’s immensely longer follow-up duration, averaging at a mean follow-up of 4.6 years. Several implications arise from this, as this study holds the longest follow-up duration out of other included studies. Although other

studies, with a comparatively shorter follow-up duration feature the benefit of the omega-3 + statin regimen, there may be a lack of long-term benefit with respect to the intervention, and hence sets the stage for future trials in including comprehensive subgroup analyses on the basis of follow-up duration, in order to effectively gauge the efficacy of omega-3 acids in improving clinical outcomes and laboratory parameters.

Other outcomes, including (i) AA ratio, (ii) EPA levels, (iii) hsCRP levels, (iv) total cholesterol, (v) and triglyceride levels featured significant levels of heterogeneity that could not be diminished or eradicated via sensitivity analyses using the leave-one-out method. The persistent heterogeneity may arise from several causative factors, such as the exclusive use of the random-effects model throughout the meta-analyses, paired with high variability within the patient population. The included outcomes are heavily influenced by variations in genetics, weight, and ethnicity. In order to address such heterogeneity, future studies are encouraged to conduct comprehensive subgroup analyses and explore the differences within short-term and long-term clinical and laboratory outcomes with regards to the efficacy of omega-3 acids.

Assessment of Publication Bias

Visual assessment of publication bias was evaluated using a funnel plot, generated on the random-effects model, for the outcome of triglyceride levels. It was visually observed that no significant publication bias was present within this outcome, justified by the symmetry of the funnel plot, illustrated in (Supplementary figure 4).

DISCUSSION

Our meta-analysis, involving 40,991 patients, found several noteworthy advantages in adding omega-3 fatty acids to statin therapy for cardiovascular prevention. "Residual Risk" is the cardiovascular risk that persists after statin therapy[24]. Our study computed the changes in residual risk by the addition of omega-3 fatty acids to the conventional statin therapy. This analysis documented a diminished incidence of MACE, unstable angina, Non-fatal MI, and hospitalization due to unstable angina with the use of statin and Omega-3 fatty acids in high-risk populations. Our study also gauged alterations in the level of biomarkers used for assessing cardiovascular risk, in particular cholesterol, TGs[24,25], hsCRP[26], lipid volume, and EPA/AA ratio[27]. Analysis revealed a decline in cholesterol, TGs, HsCRP, and lipid volume, implying that the overall risk was reduced by administering omega-3 fatty acids alongside statins. Moreover, an increased EPA/AA ratio was noticed, suggesting plaque stabilization[12].

It has been speculated that acute inflammation after MI is responsible for the progression of systemic atherosclerosis. Omega-3 fatty acids decrease pro-inflammatory signals and increase resolution, thus decreasing adverse CVD outcomes. Nosaka et al. reported a decrease in ventricular arrhythmias after early initiation of treatment by EPA after PCI[7]. Omega-3 fatty acids have also shown antioxidative properties that lead to plaque stabilization[3]. This entire situation leads to a good prognosis in terms of CV health. A reduction in lipid volume with PTV/EPA therapy has also been noticed[21]. An improvement in endothelial dysfunction was also found by the administration of omega-3 fatty acid therapy. Endothelial dysfunction is a clinical marker for CAD[7]. This can also be one manner through which omega-3 fatty acids decrease cardiac outcomes like fatal MI, unstable angina, and subsequent hospitalization.

Our results were concurrent with many previous trials. The JELIS trial demonstrated that statin + EPA therapy decreased CVD by 19% over a 5-year follow-up[13]. Another trial, CHERRY, showed that combining ezetimibe and atorvastatin decreased LDL-C levels and atheroma plaque volume[21]. The EVAPORATE trial demonstrated a decline in plaque regression associated with statins + Omega-3 fatty acids[19]. Coinciding with our findings, A study conducted by Yokoyama M et al. also discussed a decrease in fatal MI and SCD[7]. Hypertriglyceridemia is an important independent marker of ischemic progression[24,25]. Furthermore, non-fasting high serum levels of triglycerides are a hallmark of triglyceride remnants. These TRL remnants have stronger atherogenic potential due to their large cholesterol-carrying capacity. Hypertriglyceridemia is also associated with increased endothelial dysfunction which can be mediated by impaired vasodilation[2]. Adjuvant therapy with Omega-3 fatty acids along with statins may succeed in lowering this residual risk.

There is increasing evidence that the residual risk is due to TR lipoproteins and cholesterol levels. HsCRP derived by endothelial IL-6 is considered a strong biomarker of atherogenic inflammation. Elevated levels of hs-CRP are found in unstable angina and MI[26,28]. This explains the decrease in MACE, Unstable angina, and hospitalization in the population treated by statins and Omega-3 fatty acids.

AA is the precursor of many inflammatory mediators involved in atheroma formation[27]. Omega-3 fatty acids have been reported to disrupt membrane phospholipids, ultimately preventing inflammatory actions of AA metabolites[29]. Niki et al. reported studies that found low serum EPA/AA ratio to be a marker of high plaque rupture. He also reported that low serum EPA levels are an independent biomarker of increased mortality in AMI settings[12]. EPA is reported to influence arterial elasticity by NO release or production[29]. A high EPA/AA ratio leads to a lower incidence of SCD or MI[7].

In stark contrast, we also found that there was no change in fatal or non-fatal stroke incidence. This could point a finger toward the fact that PUFA effects might not be fully antiatherosclerotic[22]. Similarly, there wasn't any notable difference in the need for coronary revascularization between these two variables. This may further the hypothesis that the protection from cardiovascular events is not due to the anti-thrombogenic effects of Omega-3 fatty acids. However, the association our analysis revealed between a significant decrease in cardiovascular ailments and the concomitant usage of Omega-3 fatty acids and statins is far more authoritative, ultimately suggesting the cardioprotective effects of the combination therapy.

There were a few limitations in our study, though they have a minimal influence on the outcomes, that we could not neutralize. Our patient population was diverse and comprised of a wide variety of patients having variable baseline parameters. Although this was done to assess the action of statins Omega-3 fatty acids on a larger scale, it brought about some heterogeneity. Another limitation we faced was that the trials we used had differences in follow-up durations, dosages, and placebo interventions. The difference in these

parameters may have an influence on the outcomes, but not significant enough.

This study is the first to analyze the combined effect of Omega-3 fatty acids and statins on Cardiovascular Outcomes and Plaque markers simultaneously. Additionally, our study analyzes the lipid markers, plaque characteristics, and inflammatory markers, all in synchrony, to give a better, more nuanced interpretation of the outcomes. No previous meta-analysis had studied the combined effect of omega-3 and statins on cardiovascular outcomes. We have included a large sample size comprising a diverse patient population consisting of patients with coronary syndrome, CHD, hypercholesterolemia, high-risk CVD, hypertriglyceridemia, dyslipidemia, and patients with in-stent neoatherosclerosis.

Future studies that examine the safety of Omega-3 fatty acid treatment, in addition to its efficacy, are welcomed. Examining the effects of this combination therapy in patients undergoing stent interventions can also be explored more streamlined to provide insights for a better recovery rate. Finally, clinical studies are required to assess the combined impact of Omega-3 fatty acids and statins on the patients' quality of life after a cardiovascular illness has been diagnosed.

CONCLUSION

Our systematic review and meta-analysis of 40,991 patients with dyslipidemia, ACS, CHD, and high-risk CVD assessed the efficacy of Omega-3 fatty acids and statin therapy on CVD outcomes, lipid markers, inflammatory markers, and plaque characteristics. The result shows that adding omega-3 fatty acids to statin therapy significantly reduces the incidence of MACE, MI, unstable angina, and hospitalization for unstable angina. Our analysis also found a decrease in levels of total cholesterol, triglycerides, and hs-CRP. An increase in levels of EPA and EPA/AA ratio was also a significant finding. This analysis reported no significant increase in the risk of adverse outcomes. Our research reinforces that all patients, regardless of their cardiovascular health, may benefit from adding omega-3 fatty acids to their statin therapy.

AUTHORS' APPROVAL

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Declarations

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cpcardiol.2023.102245.

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