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SYSTEMATIC REVIEW

Effect of Omega-3 Supplementation on Major Adverse Cardiovascular Events (MACE): A Systematic Review

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Abstract: Major adverse cardiovascular events (MACE) are the most relevant outcome in cardiovascular secondary prevention because they are the main cause of mortality and morbidity in patients with cardiovascular disease. Due to the contrasting results between studies, omega-3 supplementation is believed to have cardioprotective effects, but its significance in reducing MACE is still in question. This study aims to determine the effect of omega-3 supplementation on the prevention of MACE. A literature search was carried out on several databases from September 8–20, 2021. Selection of literature is done through the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. Literature that is eligible was then assessed qualitatively. We compared the hazard ratio of each key outcome of interest, which was included in the primary and secondary end-point of each study. Among 2049 publications found from the initial literature search, 6 publications were included in this study. The analysis showed a significant reduction in cardiovascular risk in participants with a high dose of pure EPA. Studies with a lower dose of omega-3 that contains a combination of EPA and DHA did not provide similar significant results. The use of high-dose omega-3 supplementation with pure EPA content can significantly reduce

Keywords: Major adverse cardiovascular events, omega-3, systematic review

INTRODUCTION

The global intake of omega-3 fatty acids is considered very low, with only less than 20% of the world's population consuming omega-3 more than 250 mg/day, which is far less than the recommended amount by the American Heart Association. Sufficient daily intake is important for the body to function optimally. Omega-3 is an essential fatty acid that cannot be produced by the body, thus sufficient daily intake is important

BULETIN FARMATERA
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for the body to function optimally.[16] Omega 3 is well known for its many benefits, especially for its cardioprotective effects, which has resulted in the soaring demand for fish oil supplementation over the last decade. [17]

Cardiovascular disease is the global leading cause of death. Approximately 17.3% of deaths are caused by cardiovascular conditions each year. [15] With advances in the diagnosis and management of cardiovascular diseases, more patients are able to recover from initial cardiovascular events. Secondary prevention for cardiovascular diseases has also been successful in reducing cardiovascular events and mortality. However, the prognosis is still suboptimal. [5, 14]

Major adverse cardiovascular events (MACE) are the leading cause of morbidity and mortality in patients with cardiovascular disease, which comprises a composite of cardiovascular clinical end points such as stroke, myocardial infarction, coronary revascularization, hospitalization due to heart failure and death. [6] The American Heart Association believes that omega-3 fatty acids play an important role in heart health by lowering plasma triglycerides, thrombocyte aggregation, arrhythmia, and inflammation. [4]

A large epidemiologic study has proven the dosage response association of omega-3 consumption. Higher intake of fish rich in omega-3 is believed to be effective in reducing mortality due to cardiovascular conditions like myocardial infarction.[9] Another study also discovered a reduction of up to 19% in MACE among participants that consumed omega-3 supplementation. with a history of low fish intake.[7] However, there are several new randomized controlled trials that show contrasting results, which give rise to a few debates regarding the significance of omega-3 supplementation in the prevention of MACE.

To explore this potential clinical heterogeneity across omega-3 trials, we performed an updated systematic review with a primary focus on determining the effectiveness of omega-3 supplementation on MACE among patients with cardiovascular risk or cardiovascular disease.

METHOD

The design of this study is a systematic review, which is done by collecting and summarizing all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question (RQ). [2] A comprehensive literature search was performed, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart, using the electronic databases Cochrane Library, PubMed, Science Direct, and Google Scholar through September 8 to September 20, 2021.

The search strategy used was a combination of the following general search terms with Medical Subject Headings: ("omega-3" OR "fish oil") AND ("major adverse cardiovascular events" OR "cardiovascular events"). The pre-determined inclusion criteria were (1) randomized controlled trials from the last 10 years (2011–2021) that compared

BULETIN FARMATERA
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omega-3 supplementation intake (EPA and/or DHA) vs. control (placebo; no supplementation) (2) patients with cardiovascular disease or risk factors (3) Significant adverse cardiovascular events must be reported in trials. (4) trials must have ethical clearance.

There were limitations on language and accessibility to full text. Results with incomplete results or those that are not open access were excluded from the study. Literature that is not in Bahasa Indonesia or English was also excluded. Duplicates were removed and screening of the title and abstract was done on the remaining articles, as well as at full-text level. The study search and selection were performed independently by two reviewers.

The quality of each randomized trial that was selected will be evaluated using the Jadad Criteria. Literature that is eligible was then collected and assessed qualitatively. We compared the Hazard Ratio (HR) with 95% confidence intervals of each key outcome of interest, which were included in the primary and secondary end-point of each study. Each factor that was predicted to affect the efficacy of omega-3 towards cardiovascular risk factors or cardiovascular disease was also analyzed.

RESULT

A total of 1878 studies were screened after removing duplicates, and 8 studies were reviewed for eligibility. From those 8 studies, 2 further studies were removed because of having limited presentation of findings and being methodologically weak compared to the other 6 studies based on Jadad Criteria. The literature search, which was reported in the form of a PRISMA flowchart, can be found in Figure 1. A total of 6 trials encompassing 76.235 participants were then included in this study. The quality of each randomized trial was evaluated through the Jadad Criteria and 5 out of 6 trials received a perfect score, indicating an overall excellent quality of RCT included in this study.

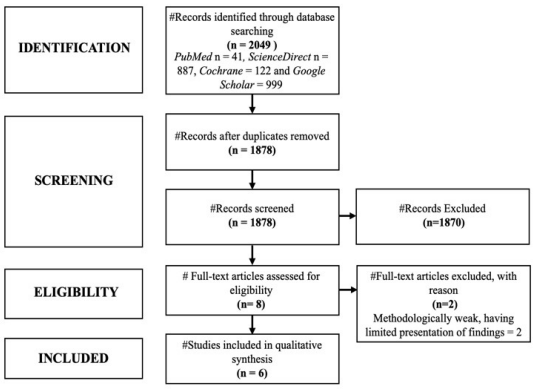

Figure 1 PRISMA flowchart

The characteristics of each trial and its participants are reported in Table 1 and Table 2. From the selected 6 trials, 5 trials compared EPA + DHA vs control and 1 trial compared pure EPA vs control. Most of the trials studied both secondary and primary prevention. Some trials used statins as an adjunct to omega-3 intervention. Three trials used the recommended amount of omega-3, which is 1 g/day, and the other three used a higher amount of omega-3, including the EPA trial that used 4 g/day of omega-3. The population ranges from those with high cardiovascular risk, low cardiovascular risk and those with a diagnosis of cardiovascular disease. Most

BULETIN FARMATERA
E-ISSN: 2528-410X

of the trials included are multinational. Follow-up of each trial varied from 2 years to as long as 7.5 years. Some were terminated early due to the low probability of demonstrating any clinical benefit.

The results from the trials were analyzed using the Cox proportional hazard model with a 95% confidence interval (CI). The hazard hari (HARI) and p value obtained from each finding were then compared. End points, hazard hari and p value of each trial are reported in Table 3. Two of the six trials were very similar, with the only difference being the omega-3 content and the placebo used; both trials also used statins as an adjunct treatment. The STRENGTH trial used 4g of carboxylic acid as an intervention, which contained a mixture of EPA and DHA, while the REDUCE-IT trial used 4g of icosapent ethyl that only contained pure EPA. Theoretically, carboxylic ci dis believed to produce a similar amount of plasma EPA as icosapent ethyl, but the results obtained were quite different. In the REDUCE-IT trial, the incidence of the primary end point was 25% lower in patients with omega-3 than in placebo, with p value <0.001 and HARI 0.75 [95% CI, 0.68–0.83] with a 4.8% absolute difference between the two groups. The secondary end-point also showed the same significant difference.

The consistent result in the REDUCE-IT trial showed that supplementation of omega-3 containing a high dose of pure EPA has a significant effect on cardiovascular events. The STRENGTH trial, on the other hand, found no significant difference in the primary and secondary end-points of omega-3 and control groups. With HR 0.99 [95% CI, 0.90 – 1.19] for the primary end-point and HR 1.05 [95% CI, 0.93 – 1.19] for the secondary end-point that's comprised of stoke, myocardial infarction, and cardiovascular death. From these 2 trials, the incidence of cardiovascular events is lower in patients that consume high-intensity statins.

Another study called the OMEMI trial that used a lower dosage of omega-3 supplementation, which is 1.59 g/day, on the elderly with recent acute myocardial infarction didn't result in a significant difference between the omega-3 and placebo group. The HR obtained for the primary end-point was 1.08 [95% CI, 0.82–1.41] after 2 years of follow-up. Three other studies, which are the VITAL, ORIGIN, and ASCEND trials, followed the recommended dosage of daily omega-3 intake by the AHA, which is 1 g/day, but the results showed a similar insignificant difference as the OMEMI trial. The primary end point in the VITAL trial had an HR of 0.92 [95% CI, 0.80-1.06], but the omega-3 group had a lower incidence of myocardial infarction with an HR of 0.72 [95% CI, 0.59-0.90].

E-ISSN: 2528-410X

Table 1 Characteristics of studies

No.	Trial	Location	Participants	Number of participants	Follow up	Jadad score
1.	Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH)	Multicenter multinational	Patients with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C).	13078	3.5 years	5
2.	Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial (REDUCE – IT)	Multicenter multinational	Patients with established cardiovascular disease or with diabetes and other risk factors.	8179	4.9 years	5
3.	Omega-3 Fatty acids in Elderly with Myocardial Infarction (OMEMI)	Norway	Patients aged 70 to 82 years with recent (2–8 weeks) AMI.	1027	2 years	5
4.	A Study of Cardiovascular Events in Diabetes (ASCEND)	Great Britain	Patients with diabetes but without evidence of atherosclerotic cardiovascular disease.	15480	7.4 years	5
5.	Outcome Reduction with an Initial Glargine Intervention (ORIGIN)	Multicenter multinational	Patients who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance, or diabetes.	12611	6.2 years	5
6.	The Vitamin D and Omega-3 Trial (VITAL)	United States of America	Men >50 and women >55 in the United States	25871	5.3 years	4

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Table 2 Characteristics of participants

Trial	Age	No. (%)			Intervention	Participants	Dosage g/day	mg/dL	Control	Participants	mg/dL	Combination
		Coronary Heart Disease	Hypertension	Diabetes				TG			TG	
STRENGTH, 2020	62.5	6,035 (46.1)	11420 (87.4)	9170 (70.2)	EPA + DHA	6539	4.0	239.0	Corn oil	6539	240.0	Statin (50% high intensity statin)
REDUCE-IT, 2018	64	5785 (70.7)	-	4787 (58.5)	EPA	4089	4.0	216.5	Mineral oil	4090	216.0	Statin
OMEMI, 2020	74	1014 (100)	611 (60.3)	210 (20.7)	EPA + DHA	505	1.59	115.4	Corn oil	509	107.4	-
ASCEND, 2018	63.3	0	9536 (62.6)	15480 (100)	EPA + DHA	7740	0.84	-	Olive oil	7740	-	-
ORIGIN, 2012	63.5	-	9962 (79.5)	-	EPA + DHA	6281	0.84	142	Olive oil	6255	140	-
VITAL, 2018	67.1	0	12884 (49.8)	3459 (13.7)	EPA + DHA	12933	0.84	-	Vitamin D3	12938	-	-

STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; VITAL, Vitamin D and Omega-3 Trial; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; ASCEND, A Study of Cardiovascular Events in Diabetes; OMEMI, Omega-3 fatty acids in Elderly with Myocardial Infarction; EPA, eicosapentaenoic acid; DHA. Docosahexaenoic acid; TG, Triglyceride

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Table 3 Clinical end points and result of each trials.

No.	Author, Year, Trial	Population	Type of prevention	Clinical end points	Hazard Ratio (95% CI)	P value	Result
1.	Nicholls *et al*., (2020) STRENGTH	Patients with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C).	Primary and secondary prevention	Primary end-point: a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.	Primary end point: 0.99 (0.90 - 1.19)	0.84	No significant effect.
				Secondary end-point: (1) composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina in patients with established cardiovascular disease at baseline, (2) composite of cardiovascular death, nonfatal myocardial infarction, and non-fatal stroke in the whole cohort (3) composite of cardiac death, nonfatal myocardial infarction, coronary revascularization, and hospitalization for unstable angina in the whole cohort (4) cardiovascular death in the whole cohort (5) all-cause death in the whole cohort	Secondary end point: 1.05 (0.93 - 1.19)	0.40	
2.	Bhatt *et al*., (2018) REDUCE-IT	Patients with established cardiovascular disease or with diabetes and other risk factors.	Primary and secondary prevention	Primary end-point: a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis.	Primary end point: 0.75 (0.68 - 0.83)	0.001	Reduction in cardiovascular risk up to 25%
				Secondary end-point: a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis.	Secondary end point: 0.74 (0.65 - 0.83)	0.001	
3.	Kaldstad *et al*., (2021) OMEMI	Patients aged 70 to 82 years with recent (2–8 weeks) AMI.	Secondary prevention	Primary end-point: A composite of nonfatal AMI, unscheduled revascularization, stroke, all-cause death, heart failure hospitalization after 2 years.	Primary end point: 1.07 (0.82 - 1.40)	0.62	No significant effect
				Secondary end-point: New atrial fibrillation.	Secondary end point: 1.84 (0.98 - 3.44)	0.056	

BULETIN FARMATERA

E-ISSN: 2528-410X

Table 3 Continued

No.	Author, Year, Trial	Participants	Type of prevention	Clinical end points	Hazard ratio (95% CI)	P value	Result
4.	Bowman *et al.*, (2018) ASCEND	Patients with diabetes but without evidence of atherosclerotic cardiovascular disease.	Primary prevention	Primary end-point: A first serious vascular event Secondary end-point: A first serious vascular event or any arterial revascularization.	Primary end point: 0.97 (0.87 - 1.08) Secondary end point: 1.00 (0.91 - 1.09)	0.55 -	No significant effect
5.	Bosch *et al.*, (2012) ORIGIN	Patients who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance, or diabetes.	Primary and secondary prevention	Primary end-point: Death from cardiovascular causes Secondary end-point: Composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; death from any cause; and death from arrhythmia.	Primary end point: 0.98 (0.87 - 1.10) Secondary end point: 1.01 (0.93 - 1.10)	0.72 0.81	No significant effect
6.	Manson *et al.*, (2018) VITAL	Men >50 and women >55 in the United States.	Primary prevention	Primary end-point: Major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type. Secondary end-point: Individual components of the composite cardiovascular end point, the composite end point plus coronary revascularization (expanded composite of cardiovascular events), site-specific cancers, and death from cancer.	Primary end point: 0.92 (0.80 - 1.06) Secondary end point: 0.93 (0.82 - 1.04) Myocardial infarction 0.72 (0.59 - 0.90) Cardiovascular death 0.96 (0.76 - 1.21) Stroke 1.04 (0.83 - 1.31)	0.24 -	No significant effect

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STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; VITAL, Vitamin D and Omega-3 Trial; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; ASCEND, A Study of Cardiovascular Events in Diabetes; OMEMI, Omega-3 fatty acids in Elderly with Myocardial Infarction; CI, Confidence interval.

BULETIN FARMATERA
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The ASCEND trial used a population of diabetic patients but no significant difference was found with HR 0.97 [CI 95%, 0.87–1.08]. Lastly, another study called the ORIGIN trial, which used the same omega-3 dosage but with 90% EPA content in a population with high cardiovascular risk, showed no significant difference in cardiovascular events with HR 1.01 [95%, 0.93–1.10] at 6-year follow-up.

A significant increase in atrial fibrillation incidence was found in the omega-3 group of 3 different trials with a higher dosage of omega-3. The first is from the STRENGTH trial that used 4 g of carboxylic acid with a HR of 1.69 [95% CI, 1.29–2.21] and a p value <0.001. The REDUCE-IT trial that used 4 g of icosapent ethyl and the OMEMI trial with 1.59 of omega-3 also resulted in the same finding with p value <0,004 and <0.006.

DISCUSSION

In this systematic review of six trials comprising 76.235 participants, we noted that omega-3 supplementation is associated with cardiovascular events, but the significance of its effect depends on the dosage, composition, statin intensity, ethnicity, and cardiovascular risk of each participant. Overall, high-dose EPA monotherapy trials showed significant reductions in cardiovascular events when compared to EPA + DHA combination trials. However, it is found that monotherapy of high-dose omega-3 is associated with a higher risk of atrial fibrillation.

Trials with the recommended daily dose of omega-3 showed no significant effect on cardiovascular events. The STRENGTH trial, which used a high dosage of EPA and DHA, also showed no significant result. Subgroup analyses of several trials showed the least reduction of cardiovascular events in participants that were white compared to participants that were Asian or black. This finding can be associated with the observation of Greenland Inuits, which proved that gene variability has an effect on the bioavailability and metabolism of omega-3 fatty acids and coronary risk. [9.] An observation on 3 different trials regarding the association of cardiovascular risk and omega-3 supplementation showed a reduction in cardiovascular events for participants with higher cardiovascular risk than those with lower or no cardiovascular risk.

From all 6 trials, the most substantial scientific evidence came from the REDUCE-IT trial, which showed a 20% reduction in cardiovascular events. However, another trial with the same dose of omega-3 but a different composition, which is the STRENGTH trial, yielded different results. A few factors might cause the difference in cardiovascular outcomes. Both trials used the same amount of omega-3 per day, but the REDUCE-IT trial used pure EPA content, whereas the STRENGTH trial used an EPA+ DHA combination. Other trials that used the EPA + DHA combination also produced insignificant results, thus proving that EPA has more significant cardioprotective effects than the EPA + DHA combination. We couldn't

BULETIN FARMATERA
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determine the effect of DHA monotherapy because none of the trials tested it.

Another factor is the difference in control used. The STRENGTH trial used corn oil as control, which is an inert comparator and doesn't cause any effect on cardiovascular risk, while the REDUCE-IT trial used mineral oil as control, whose neutrality is still in question because an increase in CRP of as much as 30% was found in the mineral oil group and there were also some adverse effects that might have contributed to the increase in cardiovascular risk among participants. However, for these reasons alone, the significant difference in the REDUCE-IT trial cannot be entirely justified. Different characteristics of participants in each trial might also contribute to the difference in outcome.

Regarding the association between baseline omega-3 and cardiovascular events, a post hoc analysis study from the STRENGTH trial showed no association between the concentration of plasma EPA and DHA content with cardiovascular events after 12 months of consuming omega-3. Another trial, such as the ASCEND and ORIGIN trials, also didn't find the correlation between baseline omega-3 and cardiovascular events. However, in the subgroup analyses of the VITAL trial, a lower incidence of cardiovascular events is found in the group of participants with a history of low fish intake (<112.5 g/week). Further investigation should be done into this matter.

There was no discussion in any of the trials regarding the effect of omega-3 on clinical improvement in participants with cardiovascular disease. However, several trials had found significant findings on biochemical parameters, especially in plasma triglyceride level and LDL-C level. The STRENGTH trial reported a reduction in apolipoprotein CIII, hs-CRP, and non-HDL-C and an increase in LDL, HDL, and plasma triglyceride levels. In the REDUCE-IT study, a reduction of 18.3% in plasma triglycerides was found in the omega-3 group. OMEMI and ORIGIN trials also had similar reductions in plasma triglyceride levels. Although the REDUCE-IT trial has proven that there's no association between plasma triglyceride and LDL-C on any of the end-points after one year of observation, This leads to the notion that the reduction of ischemic events in this trial might be from metabolic effects and not from a reduction in plasma triglycerides.

This study has a large number of participants with different characteristics, and thus the data obtained is quite varied and representative in evaluating omega-3 as a primary or secondary prevention. Biochemical parameters were also evaluated in some of the trials, which helped in supporting the rationale of the results obtained. Every trial that was included in this trial also received a great score in quality based on the Jadad Criteria for RCT. However, this study also has various limitations. Firstly, after screening through the databases, only a few trials matched the inclusion criteria of this study, and the selection of databases and keywords is only based on the author's subjective consideration, which may increase the possibility of bias.

BULETIN FARMATERA
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Secondly, over the 6 trials included in this study, each and every trial only used a fixed amount of omega-3 supplementation throughout the trial, thus the dose-response effect of omega-3 cannot be assessed. Lastly, none of the trials evaluated the effect of DHA monotherapy on cardiovascular events, thus its effect on cardiovascular risk is still in question.

CONCLUSION

The use of high-dose omega-3 supplementation with pure EPA content can significantly reduce MACE compared to the EPA+DHA combination.

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BULETIN FARMATERA
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