

## ORIGINAL RESEARCH ARTICLE

# Omega-3 fatty acids have little or no cardiovascular protection: An interventional study

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## ABSTRACT

**Background:** There is a great deal of public belief in the cardiovascular benefits of omega-3 fats. Recent trials on the effects of omega-3 fatty acids in cardiovascular issues are unclear or have failed to demonstrate significant benefits in reducing cardiovascular events. The current study aims to perform a human trial using omega-3 fatty acids as a supplementation to test its effectiveness on cardiovascular diseases. **Methods:** A randomized interventional study was carried out in 145 patients in the age group of 18 or older at any risk of cardiovascular disease. A treatment period of 6 months with supplementation of daily dose of 360 mg of EPA and 480 mg of DHA for one group and to the other group, atorvastatin 10 mg were given. Biochemical and clinical evaluations were performed for the baseline, 3rd and the 6th months to assess the effectiveness of omega-3 fatty acids on cardiovascular diseases. **Results:** The changes in the biochemical parameters total cholesterol, High density lipoprotein (HDL), Low density lipoprotein (LDL), and triglycerides among the omega-3 fatty acid group and statin group were as 218.17 vs 204.45, 55.24 vs 60.3, 142.9 vs 132.4 and 168.95 vs 152.5, respectively with a p value of 0.0001. Omega-3 supplements were shown to have little to no effect on the risk of cardiovascular diseases according to the research. **Conclusion:** The better evidence identified in this research does not demonstrate any cardiovascular protection with the supplementation of omega-3 fats.

**Keywords:** omega-3; fatty acids; cardiovascular disease; statin; eicosapentaenoic acid; docosahexaenoic acid

## 1. Introduction

Heart and blood vessel abnormalities are referred to as cardiovascular diseases (CVDs). Cerebral vascular diseases (such as ischemic stroke and transient ischemic attack), coronary artery disease, peripheral arterial disease (diseases of the blood vessels to the arms and legs), deep vein thrombosis (blood clots formed in the legs that can move to the heart and lungs), congenital heart disease, and rheumatic and congenital heart disease

are all examples of vascular diseases<sup>[1]</sup>. CVD is the leading cause of mortality in the world, accounting for more than a third of all worldwide fatalities. In 2015, 7.4 million individuals died from coronary heart disease and 6.7 million died from stroke, a total of 17.7 million people who died from cardiovascular disease. Approximately 82 percent of the 17 million premature deaths due by non-communicable illnesses in 2015 occurred in low- and middle-income countries, and 37 percent of these fatalities were attributed to cardiovascular

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disorders<sup>[1]</sup>.

For omega-3 fats with a longer chain like docosahexanoic acid (DHA), eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA), salmon is the best source because of the abundance of these fats in fish. Plant and grass fed omega-3 fatty acids include alpha-linolenic acid (ALA), which is partly converted to longer chain omega-3 fatty acids in human bodies<sup>[2,3]</sup>. Omega-3 and omega-6 fatty acids are two of the most common polyunsaturated fatty acids (PUFAs). PUFAs, like other fatty acids, have a carboxyl group at one end and a methyl group at the other end of the chain. Two or more double bonds in the fatty acid chain differentiate PUFAs from saturated and monounsaturated fatty acids.

Carbon-carbon double bonds are found three carbons from the methyl end of omega-3 fatty acids (omega-3s). It is possible to get omega-3 fatty acids through foods like flaxseed and fish, in addition to dietary supplements like fish oil. ALA, EPA, and DHA are the three omega-3 fatty acids on which the majority of scientific study has focused on. ALA has 18 carbon atoms, but EPA and DHA have 20 and 22 carbon atoms, respectively, making them “long-chain” omega-3s.

The amount of carbon atoms and the number of double bonds are widely used to identify PUFAs. C18:3n-3 ALA, for example, has 18 carbons, three double bonds, and is an omega-3 fatty acid known as C18:3n-3. EPA and DHA are both designated as C20:5n-3 and C22:6n-3, respectively. One of the characteristics of omega-6s is that they include carbon-carbon double bonds that are six carbons from the methyl end. There are two primary omega-6s: linoleic acid (C18:2n-6) and arachidonic acid (C20:4n-6).

To generate carbon-carbon double bonds, the human body can only do so once it reaches carbon 9 from the methoxy end of a lipid acid. In this regard, the necessary fatty acids ALA and linoleic acid are referred to be “non-essential” Conversion to EPA and DHA is possible, however the rate of ALA to EPA and EPA to DHA conversion is believed to be

less than 15%. The only feasible strategy to boost EPA and DHA levels in the body is to consume these fatty acids directly through meals and/or dietary supplements.

Hydrolysis of dietary lipids occurs in the intestines after they have been ingested. To absorb the hydrolysis products, which are monoglycerides and free fatty acids the micelles include bile salts the enterocytes passively diffuse the hydrolysis products into them. The absorption rate is around 95%, which is comparable to that of other consumed fats, making the procedure efficient. Free fatty acids are predominantly absorbed into chylomicrons in the intestines and reach the circulatory system via the lymphatic system. Upon entering the circulation, lipoprotein particles transport lipids to various organs, where they can be oxidised, converted, or stored as adipose tissue.

The phospholipids that make up cell membranes are made up of omega-3 fatty acids, which have significant roles in the body. The retina, brain, and sperm all have a high concentration of DHA. Omega-3 and omega-6 fatty acids, in addition to their structural role in cell membranes, supply energy for the body and are utilised to generate eicosanoids. In the body’s circulatory, respiratory, immunological, and endocrine systems, eicosanoids are signalling molecules with similar chemical structures to fatty acids from which they are produced.

A majority of omega-6-derived inflammatory mediators, vasoconstriction agents, and platelet aggregators are more effective than omega-3-derived mediators. However, there are exceptions. Due to the fact that both ALA and linoleic acid compete for the same enzymes, ALA inhibits linoleic acid metabolism. Like arachidonic acid, EPA and DHA can compete with one other for the role of producing eicosanoid precursors in the body. Eicosanoid equilibrium is shifted toward reduced inflammation when EPA and DHA concentrations are higher than arachidonic acid concentration.

Omega-6/omega-3 ratio may influence the

aetiology of many chronic illnesses, such as cardiovascular disease and cancer, however the ideal ratio has not been established. According to some researchers, these ratios lack specificity and are unresponsive to the concentration of a certain fatty acid. EPA and DHA blood levels are significantly more crucial than reducing linoleic acid or arachidonic acid levels.

This may be done by measuring individual omega-3s in plasma or serum phospholipids and using the proportion of total fatty acids by weight to indicate omega-3 status. Mean values for EPA and DHA in serum or plasma phospholipids among U.S. individuals who are not taking omega-3 supplements vary from 3% to 4%, according to experts. Plasma and serum fatty acid levels, on the other hand, might change significantly dependent on an individual's most recent meal, therefore they do not accurately represent long-term dietary intake.

Omega-3 status may also be assessed by measuring erythrocyte fatty acids, which is an indicator of long-term intakes of roughly 120 days. "omega-3 index" where the amount of omega-3 in the membranes is indicated in percentage terms can be used as a substitute for measuring tissue EPA and DHA concentrations. In Western societies with poor fish consumption, EPA and DHA generally account for 3% to 5% of erythrocyte fatty acids. Erythrocyte EPA and DHA concentrations in Japan are almost double those in Western populations.

The omega-3 fatty acids have been shown to lower blood pressure, alter lipid profiles, modulate arterial lipoprotein lipase levels, reduce thrombotic tendency, produce anti-inflammatory effects and anti-arrhythmic effects, improve vascular endothelial function, and increase plaque stability and paraoxonase levels, all of which have been linked to cardiovascular disease prevention<sup>[4-8]</sup>.

Omega-3 fatty acids are widely believed to have a positive impact on cardiovascular health. Adults in the United States consume an average of 0.72 grammes of EPA and DHA per day from dietary supplements, compared to 0.41 grammes per day

from meals<sup>[9]</sup>, according to data from the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2008. However, national public health recommendations differ. A piece of oily fish should be included in at least two parts of fish per week for persons with or at high risk of cardiovascular disease, according to the National Institute for Health and Clinical Excellence in the UK. According to this, "omega-3 fatty acid compounds" "should not be provided for primary or secondary prophylaxis of CVD"<sup>[10]</sup>. Eating fatty fish at least twice a week is also a recommendation from the American Heart Association (AHA). The AHA recommends that people with coronary artery disease take omega-3 supplements since they may not acquire enough omega-3 from their diets alone.

Omega-3 fatty acid consumption has been linked to decreased cardiovascular disease (CVD) mortality rates in epidemiological studies<sup>[11,12]</sup>. Randomized controlled trials (RCTs) have been the subject of several systematic reviews, with varying degrees of success. A meta-analysis of studies with more than 36,000 participants and a minimum follow-up of six months indicated that omega-3 fats had no influence on death from any cause or cardiovascular events. More recent systematic evaluations<sup>[13]</sup> show that omega-3 fats do not reduce the risk of death due to any cause or any of the several CVDs.

Others, on the other hand, have focused on specific outcomes or circumstances where CVD prevention was evident: after heart surgery<sup>[14]</sup>, for the prevention of sudden cardiac death<sup>[15]</sup>, for the reduction of CVD mortality and sudden cardiac death (although with no effect on all-cause mortality)<sup>[16]</sup>, for CVD mortality<sup>[17]</sup>, and for the reduction of stroke risk in women (although with no effect on stroke overall)<sup>[18]</sup>. Although Kwak found that a low-quality study had a negligible influence on cardiovascular mortality, a few papers have claimed solely good results (reductions in cardiovascular events, cardiac death and coronary events). These contradictory findings have sparked a lot of discussion and led to a lot of muddle. Agency for

Healthcare Research and Quality evaluation meta-analysed risk variables thoroughly, but found very little RCT data on the benefits of omega-3 fats on clinical cardiovascular disease outcomes<sup>[19]</sup>. A human trial was conducted in this study to explore the efficiency of omega-3 fatty acids in cardiovascular disorders in order to clear up any misunderstandings.

## 2. Patients and methods

### 2.1. Study design

A prospective, randomized, interventional study was carried out in the department of Cardiology, ESI hospitals, Chennai, India.

### 2.2. Sample size

PS-Power and the Sample size calculator were used to determine the sample size. Using a 1:1 ratio of independent sample t-tests with an alpha-error of 0.05 and an 80 percent power of the research (1-) with an adequate 8.5 percent differences and standard deviation of 0.05. 164 patients were enrolled. (82 in a group exposed to statins and 82 in a group exposed to omega-3 fatty acids).

Calculation:

$$\begin{aligned}\text{Sample size} &= \frac{2 (Z_{\alpha/2} + Z_{\beta})^2 P(1 - P)}{(P_1 - P_2)^2} \\ &= \frac{2 (1.96 + 0.842)^2 0.27(1 - 0.27)}{(0.17 - 0.37)^2} \\ &= 74.25 \\ &= 74 \text{ patients / group}\end{aligned}$$

### 2.3. Study criteria

145 patients of age 18 years or older at any risk of cardiovascular disease, having total cholesterol level ranging 200-250 mg/dl and triglyceride ranging 150-200 mg/dl (with or without existing cardiovascular disease), including those with current or previous cardiovascular disease, with diabetes

mellitus, asthma, and hypertension were included in the study. Participants who consumed any source of omega-3 fatty acids more than three times per week were excluded. Other exclusion criteria were Patients who are pregnant, with more cholesterol level, undergoing heart or renal transplantation, with HIV, on hemodialysis or any other renal problem.

### 2.4. Study procedure

Patients who met the study's eligibility requirements were enrolled. Forms were filled out by patients to acquire demographic information after they had given written consent. The patients were randomly divided into two arms. After randomization, eligible subjects in one arm received capsule of omega-3 fatty acids 1 g (460 mg of EPA and 380 mg of DHA) while the other arm received atorvastatin 10 mg with the diet control for six months. Compliance was checked by every seven days once. An analysis of each subject's dietary data was performed by nutrition staff using the Nutrition Data Systems programme. During the six-month trial period, participants were advised to stick to their normal routines and diets.

### 2.5. Biochemical measurements

EDTA tubes were used to obtain blood samples from the peripheral circulation following an overnight fast. To avoid future freeze-thaw cycles, the plasma was immediately held at 280 °C for further examination. There were three traditional measures of lipids: total cholesterol (TC), high density lipoprotein (HDL), and triglyceride (TG). Low-density lipoprotein (LDL) was calculated by the Friedewald equation. All lipid measurements were conducted on a Cobas 6,000 automatic analyzer. The biochemical parameters were determined for the baseline, 3rd and the 6th month.

### 2.6. Assessment of vascular function

Blood pressure and pulse rate were recorded using the vascular screening equipment. Cuffs were placed on the upper arms of the individual while they were in a supine posture for 10 minutes before the

measurements were taken.

## 2.7. Statistical analyses

For parametric variables, all data are reported as the mean standard deviation (SD). The Mann-Whitney U test and the paired student's t-test were used to calculate p-values for parametric and nonparametric variables, respectively. Based on the Wilcoxon signed-rank test, the results were compared to the baseline.

## 3. Results

The baseline biochemical characteristics of 145 patients enrolled in both the groups are shown in **Table 1**. Out of 145 participants recruited for the study, 140 completed both arms of the study and also completed all clinical and laboratory tests. The entire study flow chart is given in **Figure 1**. The mean age of the patient for both the groups was 56.4 and 57.1 respectively in which 84 (60%) were male and 56 (40%) were female. Majority of the patients were hypertensive with the mean systolic pressure of 148.2 mmHg and 147 mmHg for both the groups. About 74 patients were found to have diabetes and using anti diabetic drugs and 45 patients were found to have coronary artery disease like angina pectoris and myocardial infarction and were on medication for their respective conditions. The mean BMI of the patients was 30.65 and were categorized under overweight and obese. The subjects were on lipid modifying treatment and the mean total cholesterol was 223.85 mg/dl.

The follow up period was 6 months in which patients of both the group received their medications meant to their conditions. Diet was controlled over fatty foods for all the patients. The changes in the biochemical parameters total cholesterol, HDL, LDL and triglycerides among the omega-3 fatty acid group and statin group were as 218.17 vs 204.45, 55.24 vs 60.3, 142.9 vs 132.41 and 168.95 vs 152.5, respectively with a p value of 0.0001 and the same is presented in **Table 2** and **3**. No significant changes were observed and the omega-3 supplements have little or no effect on the risk of cardiovascular diseases according to the research. Among 124 (88.57%) hypertensive patients, no significant changes were observed in the systolic blood pressure and diastolic blood pressure in both the groups. The changes in the biochemical and clinical parameters expected with that of the omega-3 fatty acids group was not statistically significant. The changes in the clinical and biochemical parameters were illustrated in **Figure 2**. After a six-month follow-up, patients with cardiovascular disease who took omega-3 fatty acid supplements had no reduced risk of cardiovascular events than those who used statins. There were no significant differences in the incidence of cardiovascular events between the two groups. Benefits may persist after antihypertensive and statin treatment. Patients with hypertension may benefit from antihypertensive treatment and a lipid-lowering statin months after taking the medication.

**Table 1.** Baseline clinical characteristic of the study participants

Characteristics	Omega-3 fatty acids (N = 70)	Statins (N = 70)	p value
Age (years)	56.4 ± 7.7	57.1 ± 8.4	0.6187
Male	42 (30%)	42 (30%)	
Female	28 (20%)	28 (20%)	
BMI (kg/m <sup>2</sup> )	30.7 ± 3.05	30.6 ± 3.08	0.7709
Hypertensive	62 (44.2%)	62 (44.2%)	
Systolic	148.2 ± 12.8	147 ± 12.4	0.5485
Diastolic	88.7 ± 4.7	88.8 ± 5.7	0.8738
Diabetes mellitus	29 (20.7%)	29 (20.7%)	
Total cholesterol	223.9 ± 10.5	223.8 ± 11.0	0.9813
HDL	51.6 ± 5.6	51.1 ± 3.6	0.5742
LDL	146.1 ± 7.1	145.72 ± 6.7	0.7353
Serum triglyceride	173.3 ± 13.4	174.7 ± 12.2	0.5301
Cardiovascular disease	22 (15.7%)	23 (16.4%)	

BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein. Data represented as mean ±SD for parametric and nonparametric variables respectively and as n (%) for categorical variables.

**Table 2.** Biochemical parameters before CVD before (baseline) and after six-month ingestion of omega-3 fatty acids and statins

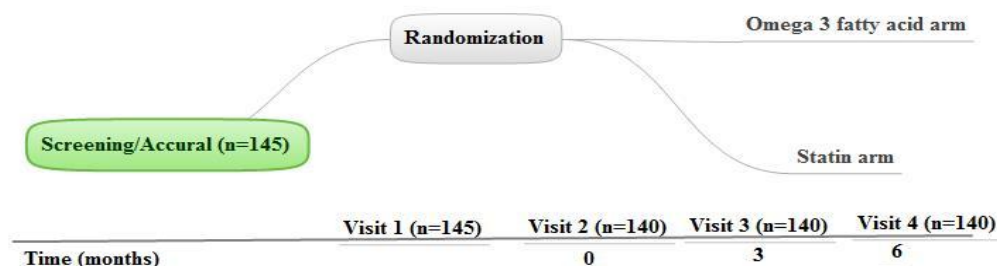
Clinical findings			
Characteristics	Omega-3 fatty acids (N=70)	Statins (N=70)	P value
Heart rate (bpm)			
Baseline parameters	67.7	66.4	0.5248
3 months	66.1	66.6	0.9812
6 months	69.5	67.7	0.0864
P	>0.05	<0.001	
Systolic blood pressure (mmHg)			
Baseline parameters	148.2 ± 12.8	147 ± 12.4	0.5485
3 months	146.7 ± 12.1	140 ± 10.07	0.0005
6 months	145.57 ± 11.75	135.28 ± 7.74	0.0001
P	>0.05	<0.001	
Diastolic blood pressure (mmHg)			
Baseline parameters	88.7 ± 4.7	88.8 ± 5.7	0.8738
3 months	87.42 ± 5.29	85.85 ± 5.51	0.0878
6 months	86.14 ± 5.18	82.57 ± 5.01	0.0001
P	>0.05	<0.001	

Data are shown as mean ± standard deviation. Unpaired T test was used to determine significance.

**Table 3.** Biochemical parameters before CVD before (baseline) and after 6-month ingestion of omega-3 fatty acids and statins

Laboratory findings			
Total cholesterol (mg/dl)			
Baseline parameters	223.9 ± 10.5	223.8 ± 11.0	0.9813
3 months	221.55 ± 10.69	215.5 ± 10.45	0.0009
6 months	218.17 ± 10.79	204.45 ± 9.29	0.0001
P	>0.05	<0.001	
HDL (mg/dl)			
Baseline parameters	51.6 ± 5.6	51.1 ± 3.6	0.5742
3 months	53.91 ± 4.05	54.88 ± 3.38	0.1261
6 months	55.24 ± 3.88	60.3 ± 2.70	0.0001
P	>0.05	<0.001	
LDL (mg/dl)			
Baseline parameters	146.1 ± 7.1	145.72 ± 6.7	0.7353
3 months	144.71 ± 6.98	138 ± 5.94	0.0001
6 months	142.9 ± 6.80	132.41 ± 5.43	0.0001
P	>0.05	<0.001	
Serum triglycerides (mg/dl)			
Baseline parameters	173.3 ± 13.4	174.7 ± 12.2	0.5301
3 months	171.57 ± 13.45	161.8 ± 9.96	0.0001
6 months	168.95 ± 13.26	152.5 ± 8.76	0.0001
P	>0.05	<0.001	

Data are shown as mean ± standard deviation. HDL: high density lipoprotein; LDL: low density lipoprotein. Unpaired T test were used to determine significance.

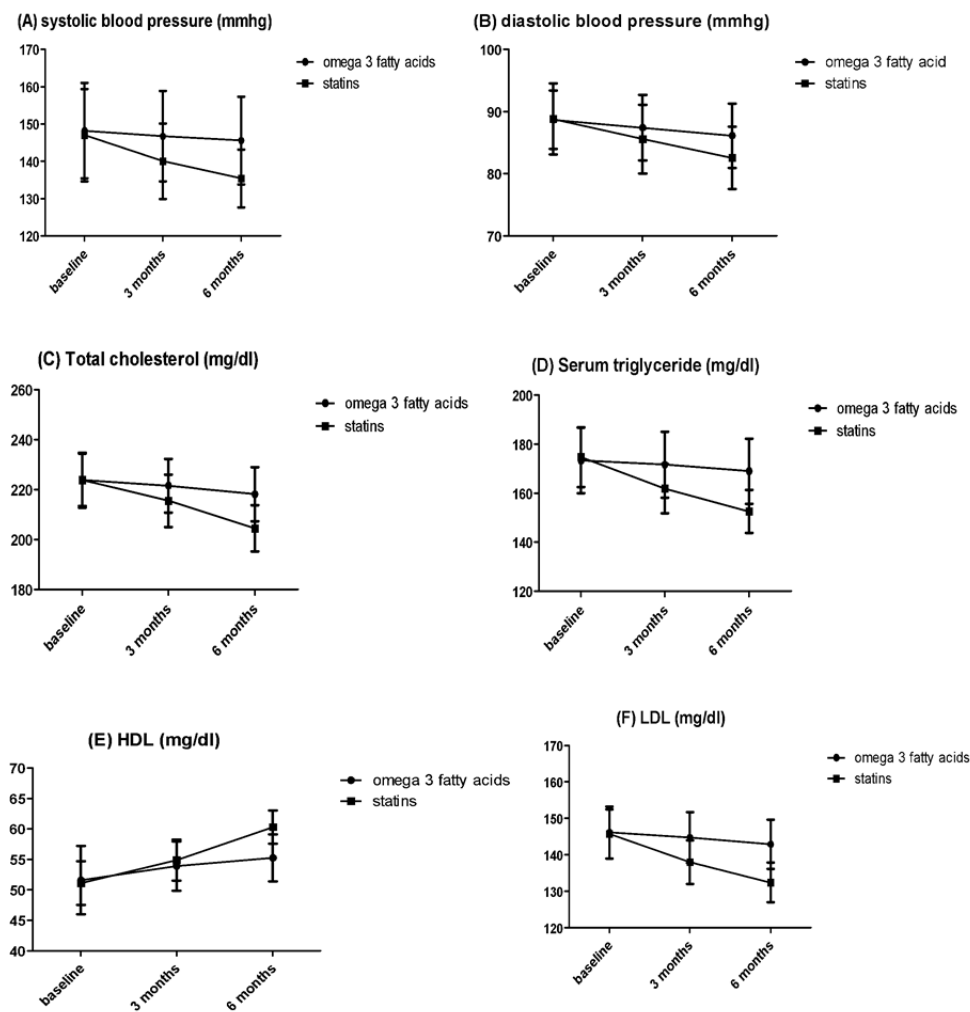


**Figure 1.** Study design. Participants were screened through an exclusion/inclusion criteria, baseline laboratory tests and a pregnancy test for females. Once eligibility was confirmed, subjects were randomized and received atorvastatin for a period of 6 month for one arm and omega-3 fatty acid for a period of 6 month for the other arm.

## 4. Discussions

Cardiovascular disease risk is not reduced by omega-3 fatty acid supplementation. Despite the prevalent idea that omega-3 supplements are beneficial,

this study shows that this is not the case. Omega-3 supplements have previously been supported by studies that have a significant risk of bias. In this study, the best evidence found did not support a health advantage. Omega-3 supplements should not be utilized to prevent cardiovascular disease, ac-



**Figure 2.** Mean percentage change of systolic blood pressure (A), diastolic blood pressure (B), serum levels of total cholesterol (C), serum triglyceride (D), HDL (E), LDL (F). Data represented as mean  $\pm$  SD. \*\*p, 01, \*\*\*p, 001 compared with baseline.

cording to the findings of this study. If omega-3 is vital to human health, then it's likely that foods high in omega-3 might be included in a healthy diet.

With the aim to investigate the effectiveness of the supplementation of EPA and DHA with respect to atorvastatin, no significant changes was observed in the levels of cholesterol and triglycerides levels in the group exposed to omega-3 fatty acids. The intake of 1 g capsules of omega-3 fatty acids that comprised 360 mg of EPA and 480 mg of DHA, had no beneficial effect in cardiovascular protection as it does not reduce the serum cholesterol, HDL, LDL and serum triglycerides effectively in the patients after 6 months follow up with high cholesterol levels and triglycerides levels. The patients with conditions like coronary artery disease, myocardial infarction, and ischemic heart disease also does not respond

with omega-3 fatty acids supplementation.

There were 2 dropouts in the study because of the poor medication adherence and follow up. The mean body mass index of 145 patients was 30.65 ( $p = 0.7709$ ) which denote obesity. Lipid modifying treatment was given to the patients with omega-3 fatty acids 1 g (360 mg EPA and 480 mg DHA) and atorvastatin 10 mg. Omega-3 fatty acid have no beneficiary effect on the risk and prevalence of cardiovascular deaths and events in patients who had coronary artery disease, myocardial infarction and ischemic heart disease. And also no effect in developing myocardial infarction in patients who had high cholesterol and triglyceride levels and with increased BMI. The risk can be reduced by reducing the levels of cholesterol and triglycerides with diet modification and drugs like statins which is effective.

In the study, patients with high cholesterol (>250 mg/dl) and triglyceride (>200 mg/dl) levels were excluded to minimize the risk of fatal conditions and morbidity rate. Studies have been performed previously to find out the effect of omega-3 fatty acids in cardiovascular diseases. One of the randomized controlled trials (RCT) evaluated omega-3 fatty acids in myocardial infarction patients<sup>[20-23]</sup>. It was concluded that there is no effect on rate of major cardiovascular events in patients with myocardial infarction<sup>[24,25]</sup>. A new systematic review published, combines the results of seventy-nine randomized trials involving 112,059 people<sup>[26-28]</sup>. Some of these research looked at the impact of omega-3 lipids on heart and circulatory problems, as opposed to a normal or low intake of omega-3. When it came to most of the outcomes they looked at, researchers found that boosting long-chain omega-3 had no effect. It was concluded with a high degree of certainty that long-chain omega-3 fats had no influence on mortality risk at all. Omega-3 fatty acid supplementation reduced the risk of mortality from any cause by 8.8%, compared to 9% in the control groups. Long-chain omega-3 fats (containing EPA and DHA) were shown to have no effect on the risk of cardiovascular disease, coronary mortality or stroke or cardiac abnormalities when taken in supplement form<sup>[29-32]</sup>.

The findings of this study are so compelling that omega-3 fatty acids have little or no influence on most cardiovascular disease outcomes as mentioned in the previous comprehensive analysis. The findings of this study, which contradict the widely held idea that long-chain omega-3 supplements protect the heart by reducing blood pressure or reducing cholesterol, can be trusted. Taking long-chain omega-3 (fish oil, EPA, or DHA) supplements did not improve heart health or lower the risk of stroke, according to the research. Long-chain omega-3 fats appear to have little or no influence on cardiovascular health. The tiny number of studies on the health benefits of eating more oily fish is inconclusive, however, as to whether it protects our hearts.

## 5. Conclusions

This study suggests that the omega-3 fatty acids have no effect on cardiovascular health. It does not alter the risk of cardiovascular events like myocardial infarction, coronary artery disease and ischemic heart disease in patients and the patients with increased risk of developing cardiovascular disease. Omega-3 fatty acids (EPA and DHA) may slightly reduce the triglyceride level and increase the HDL level but there is no evidence that it reduces the risk of developing heart disease.

## Conflict of interest

The authors declare no conflict of interest.

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