# The Benefits of Marine Omega-3s for the Prevention and Treatment of Cardiovascular Disease

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**Studies providing approximately 1-2 grams of marine omega-3s in the secondary prevention setting have noted significant reductions in major coronary events and mortality. Additionally, providing 1-gram of marine omega-3s in those with chronic heart failure has been shown to significantly reduce mortality.**

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## Abstract

**There has been a raging debate whether marine omega-3s are effective for the prevention of cardiovascular disease. Our review paper discusses the landmark clinical studies testing the benefits of marine omega-3s. Moreover, for the first time, the REDUCE-IT study tested a high dose of marine omega-3s (4 grams of icosapent ethyl per day) on top of statin therapy in patients with established cardiovascular disease or with diabetes and additional risk factors with concomitant high triglyceride levels and noted a highly significant 25% reduction in the primary endpoint. Thus, in patients who are not in the early post myocardial infarction setting, high dose marine omega-3s (4 grams per day) may be required to provide cardiovascular benefit when given on top of optimized medical therapy.**

## Introduction

Ever since the 1940s, marine omega-3s have been suggested to provide cardiovascular benefits. This idea began when Ehrstrom discovered that the Greenland Inuit had approximately one-third the atherosclerotic disease compared to the general population in Finland.[1] It was also documented in the 1970s that the Greenland Inuit had lower rates of myocardial infarction compared to Danish controls.[2] Considering that the Greenland Inuit's diet was rich in marine omega-3s (coming from whale and seal meat and blubber) it was only logical to assume that their diet may have something to do with their protection from heart disease. In 1978, Dyerberg et al. noted that Greenlanders had high blood levels of EPA and suggested that the high intake of marine omega-3s may protect them against thrombosis and atherosclerotic events.[2] Later on, several population studies also noted that those with higher intakes of marine omega-3s have a lower risk of cardiovascular disease. Our paper will review these population studies as well as clinical studies testing marine omega-3s for the prevention of cardiovascular disease.

## Observational data

The Japanese have a long history of consuming a diet high in seafood. In fact, Japan is one of the highest consumers of fish and shellfish in the world,[3] with an omega-3 index

(eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA] in red blood cells) of around 10%.[4] Japan is also known for having a long life expectancy and lower risk of cardiovascular disease compared to Western populations, which correlates, at least partly, with a high intake of fish.[3, 5]

In the Adventist Health Study 2, a prospective cohort study encompassing over 73,000 participants, only pesco-vegetarian Seventh Day Adventists had a significant reduction in all-cause mortality and ischemic heart disease compared to controls.[6] Furthermore, a meta-analysis of 12 prospective cohort studies in 672,389 individuals found that compared to those who never consumed fish, those consuming approximately 2 oz. (60 grams) of fish per day had a significant 12% reduction in all-cause mortality.[7] Another meta-analysis of nine prospective cohort studies found that a higher intake of fish was associated with a lower risk of stroke.[8] Both lower intakes of fish (two to four times a week) and higher intakes ($\geq$ 5 times a week) were associated with a reduced risk of stroke (-13% and -31%, respectively).[8]

## Older Clinical Trials

### *Patients with Hypercholesterolemia (with and without a history of heart disease)*

### JELIS

The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) trial tested 1.8 grams of EPA in 18,645 hypercholesterolemic patents who were also randomized to statin therapy. The addition of 1.8 grams of EPA on top of statin therapy lead to a significant 19% reduction in the primary endpoint, which was any major coronary event (including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting) compared to statin therapy alone. This benefit was mainly driven by those with a history of coronary artery disease, whereby 1.8 grams of EPA lead to a significant 19% reduction in major coronary events. However, in those without a history of coronary artery disease the 18% reduction in major coronary events was non-significant.[9] Additionally, there was a significant 20% reduction in the incidence of recurrent stroke in the secondary prevention cohort.[10]

### *Patients with Stable Coronary Artery Disease*

### SCIMO

The Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 fatty acids (SCIMO) was a randomized, double-blind placebo-controlled trial performed in 223 patients with angiographically proven coronary artery disease.[11] The study randomized patients to either fish oil or placebo. Patients in the fish oil group were given 3.3 grams of EPA/DHA for the first three months and 1.65 grams EPA/DHA for the next 21 months. All capsules contained 4 mg of alpha-tocopherol as an antioxidant (the peroxide values were 0.5 in the placebo capsules and 0.6 in the fish oil capsules). Angiograms taken at baseline and two years later were evaluated for 80 of 112 patients in the placebo group and 82 of 111 in the fish oil group. Compared to placebo more patients in the fish oil group had mild plaque regression (7 vs. 14) and moderate regression (0 vs. 2), respectively. The authors stated, "…coronary segments in the fish oil group showed less progression and more regression than did coronary segments in the placebo group.". Additionally, there was a trend for fewer cardiovascular events in those receiving fish oil. The authors concluded, "…in our study, patients with coronary artery disease who consumed approximately 1.5 grams of omega-3 fatty acids per day for two years had less progression and more regression of coronary artery disease on coronary angiography than did comparable patients who ingested a placebo… In conclusion, in our study, dietary intake of w-3 fatty acids, approximately 1.5 g/d for two years, modestly mitigated the course of human coronary atherosclerosis, as assessed by angiography. Fewer cardiovascular events were noted. The dose and the preparation used were safe and well tolerated."[11]

### *Early Post Myocardial Infarction*

### DART

Advice to consume fatty fish (~ 2.5 grams of EPA/week or 300 grams of fatty fish every week) in the diet and reinfarction trial (DART) produced a significant 29% reduction in total mortality in the first two years in patients who experienced a first myocardial infarction (average time after myocardial infarction was 41 days).[12] Total number of myocardial infarctions were not significantly reduced with fatty fish. There was a non-significant reduction in ischemic heart disease events in those advised to consume fish versus those not advised (12.5% vs. 14.6%).[12] In a post-hoc analysis of DART, those who were supplemented with 3 grams of fish oil per day (Maxepa) also had a significant reduction in all-cause

mortality and ischemic heart disease mortality versus control.[13]

### GISSI-P

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevention trial was a randomized trial in 11,324 patents given omega-3 polyunsaturated fatty acids early after a myocardial infarction (< 3 months). Supplementation with 1 gram of marine omega-3s caused a significant 20% decrease in all-cause mortality, 30% decrease in cardiovascular mortality and a 45% decrease in sudden cardiac death. Thus, when given early after a myocardial infarction, 1 gram of marine omega-3s was found to significantly reduce mortality and was well tolerated. In 2003, the European Society of Cardiology recommended that fish oil be part of standard patient treatment after a heart attack.[14]

### GISSI-HF

The Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure (GISSI-HF) trials was a randomized placebo-controlled trial in 6,935 patients with chronic heart failure of New York Heart Association functional class II-IV. Those given 1 gram of EPA plus DHA for 3.9 years had a significant 8% reduction in death or cardiovascular hospitalization.[15] Moreover, mortality was significantly reduced by 9% and cardiovascular death was significantly reduced by 10%. The number needed to treat to prevent one death was 56 and the number needed to treat to prevent one death or hospitalization due to cardiovascular reasons was 44.

## More Recent Clinical Trials

### *No History of Heart Disease*

### VITAL

VITAL was a randomized controlled trial in 25,871 patients over the age of 50 who had no prior history of cardiovascular disease. Participants were given 1 gram of fish oil (containing 460 mg of EPA and 380 mg of DHA).[16] During a median follow-up of 5.3 years there was a non-significant 8% reduction in the risk of major adverse cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes). However, 840 mg of EPA plus DHA produced a significant 28% reduction in myocardial infarction, 50% reduction in death from myocardial infarction, 22% reduction in percutaneous coronary revascularization and a 17% reduction in total coronary heart disease. In those consuming less than 1.5 fish meals per week there was a significant 19% reduction in the primary endpoint and 40% reduction in myocardial infarction. In the approximately 20% of the participants who were African there was a significant 36% reduction in all-cause mortality and a 77% reduction in myocardial infarction.[16]

### *Diabetics Without a History of Heart Disease*

### ASCEND

The ASCEND (A Study of Cardiovascular Events in Diabetes) study was a randomized trial in 15,480 diabetic patients without known atherosclerotic cardiovascular disease. Patients were given 1-gram of omega-3 fatty acids or matching placebo. During a mean follow-up of 7.4 years there was a non-significant 3% reduction in the primary endpoint of serious vascular events.[17] There was also no significant difference in the secondary endpoint of serious vascular events or revascularization. However, there was a significant 18% reduction in vascular death in those given 1-gram of omega-3 fatty acids. Thus, 1-gram of marine omega-3s in diabetic patients without a history of heart disease may lower the risk of vascular death.

### *Cardiovascular Disease or Diabetics with Hypertriglyceridemia and Other Risk Factors*

### REDUCE-IT

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) study was a multicenter, randomized, double-blind, placebo-controlled trial involving 8,179 patients with established cardiovascular disease or diabetes with hypertriglyceridemia and at least one additional risk factor who had been receiving statin therapy. Patients were randomized to either 4 grams of icosapent ethyl (2 grams twice daily with food) or placebo and were followed for 4.9 years.[18] Those given 4 grams of icosapent ethyl had a significant 25% reduction in the primary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) with a number needed to treat of 21. Those given 4 grams of icosapent ethyl also had a significant 26% reduction in the key secondary

**Table 1. Disease states that may benefit from marine omega-3 supplementation**

| Study | Patient population | Dose of omega-3 | Benefit |
|---|---|---|---|
| JELIS | 18,645 hypercholesterolemic patients on statin therapy | 1.8 g EPA | Significant 19% reduction in the primary endpoint |
| DART | 2,033 men who experienced a first myocardial infarction (average time post-MI was 41 days) | ~ 2.5 grams of EPA/week or 300 grams of fatty fish every week | Significant 29% reduction in total mortality in the first 2 years |
| GISSI-P | 11,324 patents early after a myocardial infarction (< 3 months). | 1-gram of marine omega-3s | Significant 20% decrease in all-cause mortality, 30% decrease in cardiovascular mortality and a 45% decrease in sudden cardiac death. |
| GISSI-HF | 6,935 patients with chronic heart failure | 1-gram of marine omega-3s | Significant 8% reduction in death or cardiovascular hospitalization, 9% reduction in all-cause mortality and 10% reduction in cardiovascular death |
| VITAL | 25,871 patients over the age of 50 who had no prior history of cardiovascular disease. | 1-gram of marine omega-3s | Significant 28% reduction in myocardial infarction, 50% reduction in death from myocardial infarction, 22% reduction in percutaneous coronary revascularization and a 17% reduction in total coronary heart disease. |
| ASCEND | 15,480 diabetic patients without known atherosclerotic cardiovascular disease | 1-gram of marine omega-3s | Significant 18% reduction in vascular death |
| REDUCE-IT | 8,179 patients with established cardiovascular disease or diabetes with hypertriglyceridemia and at least one additional risk factor who had been receiving statin therapy. | 4-grams of icosapent ethyl | Significant 25% reduction in the primary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) and a significant 26% reduction in the key secondary efficacy endpoint of major adverse cardiovascular events (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). |

efficacy endpoint of major adverse cardiovascular events (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) with a number needed to treat of 28. These benefits were noted on top of statin therapy (> 99% of participants were on statin therapy).[18]

## Meta-Analyses of Randomized Controlled Trials and Cohort Studies

A Danish prospective cohort study (the Danish Diet, Cancer and Health cohort study) followed nearly 25,000 healthy subjects for almost eight years and found that an intake of omega-3 polyunsaturated fatty acids > 1.08 grams/day was associated with a 19% lower risk for acute coronary syndrome versus those eating 0.39 grams/day or less.[19] This suggests that the commonly recommended intake of only 250 mg/day of EPA and DHA (1-2 servings/week of fatty fish) in primary prevention may be insufficient.

A meta-analysis of 14 randomized controlled trials (RCTs) involving 32,656 patients found that omega-3 fatty acid supplements significantly decreased death from cardiac causes (-12%), sudden cardiac death (-14%), death from all causes (-8%) and myocardial infarction (-15%).[20] When RCTs with a long-term administration (at least one year) and higher dose (at least 1 gram/day) were included the benefits were even stronger on cardiac death (-32%), sudden death (-33%) and myocardial infarction (-25%).[21]

Two other meta-analyses of randomized controlled trials noted that dietary or supplemental omega-3 fatty acids decrease all-cause mortality (-16-20%), fatal myocardial infarction (-24%) and sudden death (-30%).[22,23] Furthermore, a systematic review of 11 randomized, placebo-controlled clinical trials noted that long-chain marine omega-3 supplements decrease all-cause mortality (-8%), non-fatal cardiovascular events

(-8%), sudden cardiac death (-13%), cardiovascular death (-13%) in those consuming an average dose of 1.8 grams/day for 2.2 years.[24]

## Marine Omega-3s: Importance of Dose and Formulation

It is important when supplementing with marine omega-3s to use a quality supplement. Fish oil supplements should be molecularly distilled to remove mercury and filter out other environmental toxins such as persistent organic pollutants. Enteric-coated fish oil may also help reduce side effects such as belching and fishy aftertaste.

## Summary

Studies providing approximately 1-2 grams of marine omega-3s in the secondary prevention setting have noted significant reductions in major coronary events and mortality. Additionally, providing 1-gram of marine omega-3s in those with chronic heart failure has been shown to significantly reduce mortality. Table 1 summarizes the disease states that may benefit from marine omega-3 supplementation. While there are some studies suggesting benefit of marine omega-3s in the primary prevention setting, larger longer-term trials are required to confirm these benefits.

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## Disclosure

JJD is author of The Salt Fix, Superfuel and The Longevity Solution. JHO is an owner of a nutraceutical company which sells omega-3 supplements. **MM**