OMEGA-3 FATTY ACIDS COMPARED TO PLACEBO IN SECONDARY PREVENTION OF MYOCARDIAL REINFARCTION

A Research Project by

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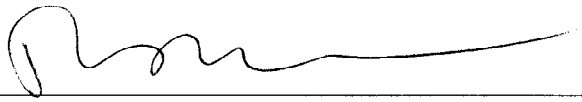

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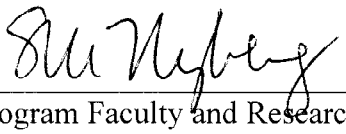

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ABSTRACT

Introduction: While much research has been done investigating omega-3 polyunsaturated fatty acids and the primary prevention of coronary heart disease, few studies focus on secondary prevention of myocardial reinfarction in populations with established coronary heart disease. Further, studies that examine omega-3 polyunsaturated fatty acid therapy in patients with established coronary heart disease have shown an inconsistent association between omega-3 polyunsaturated fatty acid intake and the risk of myocardial reinfarction. This study aims to investigate the cardioprotective properties of long chain omega-3 fatty acids.

Methodology: A systematic review of evidence-based literature was performed using Medline and Cochrane databases. Studies reviewed include randomized controlled trials, meta-analyses and systematic reviews of randomized controlled trials, and cohort studies. Studies reviewed included the following criteria: 1) randomized trials comparing dietary or supplemental intake of omega-3 fatty acids with a control diet or placebo, 2) trials reporting cardiac endpoints such as fatal or nonfatal myocardial infarction and overall mortality, 3) trials following patients with established coronary heart disease for at least 6 months.

Results: Ten studies make up the literature review of this evidence based medicine report. Five of these studies are Level 1 randomized controlled trials, two are Level 1 meta-analyses of randomized controlled trials, and three are Level 2 prospective cohorts. Evidence-based studies show that incorporating fatty fish or omega-3 fatty acids supplementation into the diet reduces all cause mortality between 15-30%. Results also show a decrease in myocardial reinfarction of 20-25% with supplementation of omega-3

fatty acids. Perhaps the strongest evidence to incorporate omega-3 fatty acids into the diet is the prevention of cardiac arrhythmias and sudden cardiac death. Studies report an 11-81% decrease in sudden cardiac death due to fatal cardiac arrhythmias. Although individual studies reviewed showed a decrease in morbidity and mortality due to coronary heart disease, when compared their findings were inconsistent.

Conclusion: The majority of the literature shows a decrease in myocardial reinfarction in patients already diagnosed with coronary heart disease with the incorporation of fatty fish intake or supplementation with long chain omega-3 fatty acids. However, the quality of studies conducted to this point is suboptimal and more studies are needed to confirm and further define the health benefits of omega-3 fatty acids for preventing subsequent cardiovascular events. At this time there is insufficient evidence to make a recommendation to include omega-3 fatty acids for prevention of myocardial reinfarction in patients with existing coronary heart disease.

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INTRODUCTION

Cardiovascular disease is the leading cause of death in the United States. For the last two decades national dietary recommendations have focused on reducing the intake of dietary fat in order to decrease the risk of cardiovascular disease. Today it has become apparent that a diet low in fat may not provide the health benefits once thought. It has become increasingly evident that different types of fat have different effects on the body[1]. For example, a higher intake of saturated fat is linked to development of atherosclerosis and hypertension while mounting evidence shows that a diet high in polyunsaturated fatty acids may reduce the risk of coronary heart disease (CHD) and improve the prognosis after a cardiovascular event[2].

Polyunsaturated fatty acids include omega-3 and omega-6 fatty acids. Essential for growth and development, omega-3 fatty acids are structural components of phospholipid membranes in tissues throughout the body[3]. Omega-3 fatty acids consist of long chain fatty acids and short chain fatty acids. Short chain omega-3 fatty acids include alpha-linolenic acids (ALA) and are found in soy and canola oils as well as flaxseed and walnuts. Long chain omega-3 fatty acids include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and are found primarily in fatty fish like mackerel, halibut, herring, salmon, and tuna[4]. EPA and DHA supplements are referred to as "fish oils". It is hypothesized that the long chain fatty acids - EPA and DHA - have many beneficial cardiovascular properties including anti-inflammatory, anti-arrhythmic, and anti-thrombogenic properties[5].

Recent research into the efficacy of omega-3 fatty acids in primary and secondary prevention of coronary heart disease is rapidly growing. The cardio-protective benefits

of omega-3 fatty acids in primary prevention of coronary heart disease include anti-inflammatory, anti-thrombogenic, anti-hypertensive and triglyceride-lowering properties[5]. Although these benefits are important to those already diagnosed with coronary heart disease, it is thought that anti-arrhythmic properties as well as retardation and stabilization of atherosclerotic plaques, and improvement of endothelial and vascular function are more significant to those already diagnosed with CHD[5-7]. While the literature favorably promotes the use of omega-3 fatty acids in the primary prevention of coronary heart disease, there is less scientific data to support the benefits of omega-3 fatty acids in populations with established coronary heart disease.

While prevention of myocardial reinfarction is multi-factorial, the majority of the evidence points to omega-3 fatty acid's anti-arrhythmic benefit. It is hypothesized that omega-3 fatty acids prevent the development of fatal arrhythmias by helping to stabilize the myocytes and prevent fast-voltage-dependent sodium and calcium currents[5]. Another important property of omega-3 fatty acids is its anti-inflammatory effect. Metabolites of omega-3 fatty acids interfere with the arachidonic acid cascade and act as a competitive inhibitor of cyclo-oxygenase which results in reduction of the production of prostaglandins and leukotrienes. Omega-3 fatty acids also beneficially influence haemostasis by decreasing collagen-induced platelet aggregation leading to a decreased risk of thrombosis[8].

Although important to cell membranes, an excess of omega-6 fatty acids has been shown to metabolically oppose the anti-inflammatory benefits of omega-3 fatty acids. It is thought that humans evolved on diets lower in omega-6 fatty acids and higher in omega-3 fatty acids than are consumed today[1]. The majority of polyunsaturated fatty

acids consumed in American diets come from omega-6 fatty acids in the form of meats, grains, and seeds and may promote the inflammatory process contributing to the increasing incidence of cardiovascular disease in the United States[9].

Background

During the last 30 years, omega-3 fatty acids have emerged as a topic of scientific scrutiny and public interest. In the 1970's, epidemiological studies of Greenland Eskimos linked their diet, rich in omega-3 fatty acids, to a low incidence of cardiovascular mortality. Despite nearly forty-percent of total caloric intake coming from fat, cardiovascular events such as stroke and myocardial infarction were nearly non-existent. When compared to age- and gender-matched Danish controls, the Greenland Inuit population had a lower incidence of coronary heart disease, thrombosis, and myocardial infarction[10, 11]. In addition, research shows promising evidence indicating that moderate doses of omega-3 fatty acids not only reduce the risk of cardiovascular disease, but also decrease mortality due to myocardial reinfarction, sudden dearth, and overall mortality in patients already diagnosed with coronary heart disease.

Purpose of Study

While much research has been done to investigate omega-3 fatty acids and the prevention of coronary heart disease, few studies have focused on secondary prevention and myocardial reinfarction in populations with established coronary heart disease. Further, studies that investigate omega-3 polyunsaturated fatty acid therapy in patients with established coronary heart disease have shown an inconsistent association between omega-3 fatty acids intake and the risk of myocardial reinfarction. This study aims to

investigate the protective properties of long chain omega-3 fatty acids, particularly DHA and EPA. This study will focus on both dietary and supplemental interventions in populations with established coronary heart disease and the prevalence of myocardial reinfarction, sudden dearth, and overall mortality.

METHODOLOGY

A systematic review of evidence-based literature was performed using Medline and Cochrane databases. The following search terms were utilized in Cochrane and Medline with limits to English language and randomized controlled trials:

1. omega-3 fatty acids AND heart disease AND prevention
2. omega-3 fatty acids AND secondary prevention
3. omega-3 fatty acids AND myocardial reinfarction
4. omega-3 fatty acids AND sudden death
5. eicosapentaenoic acid
6. docosahexaenoic acid

Studies reviewed include randomized controlled trials, meta-analyses and systematic reviews of randomized controlled trials, and cohort studies from 1971 to 2006. 1971 was chosen as the beginning year because that was when the dietary habits of the Greenland Inuit population were first studied. Additional background information was retrieved from literature reviews and evidence reports.

Studies reviewed included the following criteria: 1) randomized trials comparing dietary or supplemental intake of omega-3 fatty acids with a control diet or placebo, 2) trials reporting cardiac endpoints such as fatal or nonfatal MI and overall mortality, 3) trials following patients with established coronary heart disease for at least 6 months.

Five levels of evidence were utilized to classify the studies. Level 1 studies include high quality systematic reviews of randomized controlled trials and individual randomized controlled trials. Level 2 studies include systematic reviews of cohort studies, individual cohort studies, lower quality randomized controlled trials and non

randomized controlled trials. Level 3 studies include systematic reviews of case control studies and individual case control studies. Level 4 studies included case series studies and Level 5 studies include expert opinion and consensus viewpoint papers.

RESULTS

Primary Prevention of CHD

For decades it has been recognized that certain population such as those living in Greenland as well as some Mediterranean countries have lower rates of cardiovascular diseases when compared to their Western counterparts. It is also well known that these populations have a high intake of long-chain omega-3 fatty acids, DHA and EPA. Early cohort studies of American populations also revealed a decreased prevalence of cardiovascular diseases when fish or fish oil supplements were included in one's diet.

The Physicians Health Study, published in 1995, was a prospective cohort study that followed 20,551 male physicians for 11 years. In this landmark study, Morris et al investigated the effects of aspirin on cardiovascular disease and beta-carotene on cancer. Due to the early termination of the aspirin component, the opportunity to study dietary intake of fish and cardiovascular events arose. At baseline, participants completed questionnaires on health status, risk factors for cardiovascular disease, dietary habits, and exercise. Information on cardiovascular events and food frequency questionnaires were completed yearly for up to eleven years. It was found that weekly consumption of at least one serving of fish resulted in a 30% reduction in total mortality when compared to those physicians who consumed less than one serving of fish per week. However no relationship between non-fatal cardiac endpoints and fish consumption was found. Researchers concluded omega-3 fatty acids may be the ingredient responsible for the cardioprotective benefit of fish[12].

The Nurses' Health Study carried out by Hu et al found similar results. Published in 2002, this prospective cohort study followed 84,688 women, aged 34-59, for 16 years.

Again, food frequency questionnaires were used to assess fish intake. Questionnaires were completed at baseline and years 4, 6, 10, and 14. It was found that those women who consumed fish as little as one to three times a month saw a cardioprotective benefit while those who consumed fish 5 or more times a week saw the greatest decrease in coronary heart disease. Those in the highest quartile had a 31% lower risk of a non-fatal MI compared to those in the lowest quartlie[13].

In 1999, Daviglus et al published another early landmark cohort study, the Western Electric Study. This trial investigated the relationship between fish consumption and the 30-year risk of death due to myocardial infarction. Dietary information including patterns, frequency and quantity was obtained from 1,822 men, aged 40-55 years as well as baseline health assessments. Yearly health assessments were done by exam for the next 10 years and then by questionnaire for the next fifteen years. It was concluded that fish consumption of at least 35 grams per day led to a 42% decline in the rate of death due to coronary heart disease and an even greater decline in non-sudden death due to myocardial infarction was found (relative risk 0.62 and 0.56 respectively)[14].

Secondary Prevention of CHD

Recent epidemiological research and randomized controlled trials involving omega-3 fatty acids suggest a role for dietary fish intake and fish oil supplements, particularly EPA and DHA, in the secondary prevention of coronary heart disease. However, despite nearly 30 years of research the guidelines of most cardiology societies are just beginning to integrate omega-3 fatty acids into secondary prevention therapy.

The Diet and Reinfarction Trial (DART) published in 1989, was the fist trial to investigate the effects of dietary fish or fish oil on the survival of men with a recent MI.

In this study, Burr et al randomly assigned 2,033 Welsh men to one of four groups. Groups consisted of a control group, a group educated on the reduction of fat intake *and* an increase in fish intake, a group only educated on fish intake, and a group only educated on fiber cereal intake. At the end of 2 years, Burr et al found that there was a 29% (relative risk 0.71) decrease in total mortality and deaths due to CHD in the groups educated on the intake of fatty fish. Researchers found no differences in subjects who acquired their omega-3 fatty acids in the form of fatty fish or fish oil supplements[15]. To date, this clinical landmark trial still offers some of the most convincing evidence for the cardioprotective benefits of omega-3 fatty acids in those with established CHD.

A decade later in 1999, the GISSI-Prevenzione (Gruppo Italiano per lo Studio della Sopravivvivenza nell'Infarto Miocardio) trial found comparable results. In this randomized control trial, 11,324 Italian men and women with a recent MI were randomized to one of four groups. One group received Omacor©, a fish oil supplement with 850 mg of EPA and DHA, once a day. The second group received 300mg of vitamin E once a day. The third group received both the fish oil and vitamin E, while the fourth group received neither supplement. All subjects were also receiving standard care to reduce CHD risk factors including beta-blockers, statins, aspirin, and ACE-inhibitors. At the end of 3½ years, Marchiolo et al found that those subjects taking Omacor© experienced a 25% reduction in all-cause mortality, a 30% reduction in cardiovascular endpoints including fatal- and non-fatal MIs and strokes. Because subjects were already on a CHD risk reduction regimen, these results suggest that the effects of omega-3 fatty acids as secondary prevention after a myocardial infraction may prove to be more potent than once thought. Further, these promising results were achieved in an Italian

population already consuming a Mediterranean-style diet high in fatty fish. In western populations, where high amounts of saturated fats are consumed, even greater benefits of omega-3 fatty acids may be seen[8,17].

The Lyon Diet Heart Study, published by de Lorgeril et al in 1999, investigated the effects of a Mediterranean diet high in fish, bread, fruit, vegetables, and the non-marine omega-3 fatty acid, a-linolenic acid, in foods like walnuts and olive and canola oils. This Mediterranean diet was compared to a western diet higher in animal fat in 600 post-myocardial infarction patients. In this randomized secondary prevention trial, 3 outcomes were followed: cardiac death and non-fatal myocardial infarction, secondary endpoints such as unstable angina, stroke, heart failure, pulmonary embolism and peripheral embolism along with cardiac death or non-fatal MI, and secondary endpoints along with hospitalization. Subjects were assigned to a diet group and followed for 46 months. de Lorgeril et al found that a Mediterranean style diet lowered cardiac morbidity and mortality by 70% when compared to those assigned to a western diet. Researchers found that alpha-linolenic acid plasma concentrations were significantly and inversely associated with the risk of myocardial reinfarction in particularly fatal reoccurrences, as well as secondary endpoints. The rate of cardiac death and nonfatal MI in the control group was 4.07 per hundred patients per year compared to1.24 per hundred patients per year in the experimental group. However, it is impossible to tell if the increased intake of long chain omega-3 fatty acids DHA and EPA in fish or the increased intake of short chain omega-3 fatty acids alpha-linolenic acid in nuts and oils led to the cardioprotective effect of the Mediterranean style diet. Researchers concluded that a comprehensive strategy to decrease the risk of myocardial reinfarction should include a pharmacological

approach as well as lifestyle modifications including a cardioprotective diet high in both long and short chain omega-3 fatty acids[16,18].

In a 1997 randomized controlled trial in India, Singh et al investigated the effects of omega-3 fatty acids in 404 patients with suspected acute myocardial infarction. Patients were randomized to receive a daily supplement of fish oil containing of 1.8 grams EPA and DHA, mustard oil containing 2.0 grams of alpha linolenic acid, or a placebo. Singh et al found that supplementation with fish oil and mustard oil resulted in a significant reduction in total cardiac events including fatal and non-fatal myocardial reinfarction after 28 days (16.4% and 18.3% vs. 28.7% respectively $p<0.05$). After one year of follow up it was found that those patients randomized to the fish oil group were significantly less likely to experience a repeat infarction compared to the placebo group (18.0 % vs. 43.3% $p<0.05$). While those assigned to the mustard oil group experienced a reduced risk of reinfarction, these results were not found to be statistically significant. Again, researchers concluded that the findings of this study support the cardioprotective effect of omega-3 fatty acids but agree a larger study is warranted to confirm their conclusions[19].

In a similar study carried out by Nilsen et al in 2001, the effects of high dose omega-3 fatty acids supplementation compared to corn oil supplementation on serum triglycerides and HDL cholesterol were evaluated in 300 patients. Patients were followed for 1-2 years after they suffered a myocardial infarction. Patients were divided into 2 groups: the experimental group received 2 capsules of Omacor©, a fish oil supplement while the control group received corn oil. A significant increase in HDL-cholesterol concentration was noted in the Omacor© group compared to the corn oil group. A

significant decrease in triglycerides was also noted in the Omacor© group. This decrease was not noted in the corn oil group. However, despite a favorable effect on serum lipids, no clinical benefit was found in the group randomized to receive Omacor©. 28% of those in the fish oil group and 24% of those in the corn oil group experienced at least one cardiac event in the one year follow-up period. Researchers concluded that perhaps their chosen dose of fish oil was not the optimum dose needed to see a reduction in cardiac events following a prior myocardial infarction. They further deduced that the corn oil may have exerted a protective effect similar to the effect of Omacor©[20].

A meta-analysis of randomized controlled trials investigated the use of omega-3 fatty acid supplementation in the care of coronary heart disease patients was undertaken by Yzebe et al in 2004. Ten randomized controlled trials with 14,727 patients were included. Studies included both dietary intervention and omega-3 fatty acid supplementation. Patients were followed for an average of 37 months. Researchers found that omega-3 fatty acid supplementation in CHD patients significantly reduced all cause mortality by 16% (relative risk 0.84) and fatal myocardial infarctions by 24% (relative risk 0.76). Researchers deemed only five of the ten studies as being of good quality. Limiting factors included the imprecise nature of dietary reporting, differences in standard of care received, and multiple complex dietary changes investigated. While Yzebe et al found a significant inverse relationship between omega-3 fatty acid supplementation and CHD, no recommendation was made for systematic treatment. Researchers agree that larger, better quality studies are warranted before omega-3 fatty acids supplementation can be incorporated into an already heavy pharmaceutical barrage for CHD patients[21].

Butcher et al performed a second meta-analysis of randomized controlled trials which produced similar results in 2002. Eleven trials with 15,806 patients were included. Nine trials were designed using omega-3 fatty acids supplementation and two trials utilized dietary intervention. Patients were followed for an average of 20 months. Researchers found a decrease in mortality due to myocardial reinfarction (risk ratio 0.7, $p<0.001$), sudden death (risk ratio 0.7, $p< 0.01$) and overall mortality (risk ratio 0.8, $p<0.001$) in patients diagnosed with coronary heart disease and treated with fish oil. Again limitations plagued this review as researchers noted that the amount and type of omega-3 supplementation varied considerably. Further, dietary reporting may not be a reliable method of estimating omega-3 fatty acid intake. Another limitation is the open intervention design and unblinded clinical endpoint evaluations which could have resulted in an overestimation of the treatment results. Once more, researchers call for better quality trials to study the benefits of omega-3 fatty acid supplementation in conjunction with the standard of care including statins, anti-platelets, and beta-blockers[22].

Arrhythmias and Sudden Cardiac Death

While there is growing evidence to support that omega-3 fatty acids possess anti-thrombotic, anti-atherogenic and vasoprotective properties, it may be the anti-arrhythmic property of omega-3 fatty acids that is most important. The anti-arrhythmic mechanism of action of omega-3 fatty acids has been investigated in experimental studies on canine models and clinical intervention trials in humans. It is thought that omega-3 fatty acids produce anti-arrhythmic benefits because they increase the ventricular fibrillation threshold, increase heart rate variability, limit reperfusion injury and ischemic damage, and influence membrane ion channels to create a stabilizing effect[7,23].

The DART trail was the first human trial to show possible anti-arrhythmic benefits. A reduced mortality after myocardial infarction in those instructed to eat fatty fish was found, however, there was no decrease in the number of non-fatal MIs. Scientists concluded this finding to mean that the most probable cardioprotective mechanism was unlikely to be anti-thrombogenic and more likely anti-arrhythmic. Thus, patients consuming omega-3 fatty acids had a lower mortality rate after a myocardial infarction, possible due to a decrease in sudden cardiac death due to fatal cardiac arrhythmias[15,24].

In the GISSI trial, a significant 45% relative reduction in sudden cardiac death was found[17]. After reanalyzing the results of GISSI trial in 2002, it was found that the 53% reduction in risk of sudden cardiac death was significant after only four months of treatment with omega-3 fatty acids. After 3.5 years, treatment was found to be highly significant and accounted for nearly 59% of the decrease in mortality. As in the DART study, there was no decrease in non-fatal myocardial reinfarctions in those treated with omega-3 fatty acids. Scientists concluded that the reduction in cardiovascular mortality resulted primarily from prevention of sudden cardiac death due to fatal arrhythmias[15].

After 17 years, data from the Physician Health Study was also re-evaluated to investigate further the effects of fish consumption and sudden cardiac death. Baseline blood levels of long chain omega-3 fatty acids from 94 men who died of sudden cardiac death were analyzed. It was found that there was a significant, inverse relationship between baseline whole-blood long-chain omega-3 fatty acid levels and the risk of sudden cardiac death. When men in the lowest quartile were compared with those in the highest, an 81% reduction in the risk of sudden death was found[12]. It is, however,

important to note that only a baseline level of serum long chain omega-3 fatty acids was obtained and may not reflect accurate serum levels over time.

The Lyon Trial also supports the hypothesis that omega-3 fatty acids have a beneficial effect on sudden cardiac death. In the intervention group, there were no reports of sudden cardiac death while 8 cases were recorded in the control[16]. Again, the intervention group had a complex diet, making it difficult for investigators to target the increase in fish intake as the reason for cardioprotective benefits. Singh et al showed similar results. After one year, there were fewer deaths due to sudden death in the fish oil group compared to the control group (11.2 % compared to 22.0%). Once more, researchers concluded that the findings of this study support the cardioprotective effect of omega-3 fatty acids but agree a larger study is warranted to confirm their conclusions[19].

DISCUSSION

In the years since the early epidemiological studies of the Greenland Inuit populations evidence supporting the use of omega-3 fatty acids in primary and secondary prevention of coronary heart disease has grown considerably. In fact, the American Heart Association recommends 1 gram of EPA+DHA per day either from fatty fish or supplementation in patients with documented coronary heart disease. However, the favorable effects of omega-3 fatty acids are not consistently reproduced in the clinical setting and the majority of health care providers do not include omega-3 fatty acids as part of post-myocardial infarction therapy.

Ten studies make up the literature review of this evidence based medicine report. Five of these studies are Level 1 randomized controlled trials, two are Level 1 meta-analyses of randomized controlled trials, and three are Level 2 prospective cohorts. The above evidence suggests that supplementation with omega-3 fatty acids in patients with existing coronary heart disease decreases the incidence of all cause mortality, fatal myocardial reinfarction, and sudden death due to fatal cardiac arrhythmias. Evidence-based studies suggest that incorporating fatty fish or omega-3 fatty acids supplementation into the diet reduces all cause mortality between 15-30%. Results also show a decrease in myocardial reinfarction of 20-25% with supplementation of omega-3 fatty acids. Perhaps the strongest evidence to incorporate omega-3 fatty acids into the diet is the prevention of cardiac arrhythmias and sudden cardiac death. The above research shows a significant inverse relationship between omega-3 fatty acid supplementation and sudden cardiac death. Studies report an 11-81% decrease in sudden cardiac death due to fatal cardiac arrhythmias.

Table 1

Studies showing a decrease in 4 outcomes due to omega-3 fatty acid supplementation in patients diagnosed with CHD

	Non-fatal MI	Fatal MI	SCD	All-Cause M/M
Nilsen et al				
Singh et al	♥	♥	♥	
Burr et al		♥	♥	♥
Marchioli et al	♥	♥	♥	♥
De Lorgeril et al	♥	♥	♥	
Bucher et al	♥	♥	♥	
Yzebe et al	♥	♥		
Morris et al				♥
Hu et al	♥			
Daviglus et al	♥		♥	

*SCD – Sudden cardiac death M/M – morbidity and mortality MI –myocardial infarction

Research into the cardioprotective benefits of omega-3 polyunsaturated fatty acids suggests that supplementation is warranted. However, much of the body of evidence collected to date is plagued by limitations. Many of the landmark trials were designed using dietary interventions. Trials like the Physician's Health Study, Nurse's Health Study, and Western Electric Study relied on dietary recall in order to track fish consumption. This method is less than optimal for estimating intake of omega-3 polyunsaturated fatty acids. Further, those who reported a high intake of fish were more likely to have a healthier lifestyle that those who did not consume fish on a regular basis. Additionally, the type of fish and the method of preparation are not reported. Such

information is important because the type of fish and method of cooking creates variation in the amount of EPA and DHA.

Studies like the LYON and DART were designed with dietary education on the benefits of a Mediterranean style diet and fatty fish intake. Both of these interventions warranted multiple complex dietary changes that made it difficult to differentiate which component of the diet was most beneficial. This was also the case in the Indian trial, Corn trial, and the GISSI trial where multiple interventions such as mustard oil, corn oil and vitamin E, respectively, were employed. This again created complexity when distinguishing which component was responsible for the findings.

Another limitation when trying to combine and compare data is that nearly every trial investigates varying amounts and ratios of EPA and DHA, creating an almost impossible task when trying to translate the results to a clinical setting.

The body of literature to support the use of omega-3 polyunsaturated fatty acids in those diagnosed with coronary heart disease looks promising however more studies are called for before a systematic recommendation can be made. Many of the studies in this review were done outside of the United States, but further research is necessary to insure the validity of applying the results to US populations. In addition, randomized controlled trials should involve more women and minority groups.

Also needed is the continued exploration of the most beneficial dose of omega-3 PUFAs as well as the most optimal ratio of EPA to DHA. Studies should also explore the efficacy dietary fish versus fish oil supplements. Finally, it is important to know the optimal length of intervention and how long the benefits are retained after stopping omega-3 polyunsaturated fatty acid therapy.

CONCLUSION

The majority of the literature shows a decrease in myocardial reinfarction in patients already diagnosed with coronary heart disease with the incorporation of fatty fish intake or supplementation with long chain omega-3 fatty acids. The evidence appears especially strong for a beneficial effect of omega-3 fatty acids in preventing sudden cardiac death due to fatal cardiac arrhythmias. However, the quality of studies conducted to this point is suboptimal and more studies are needed to confirm and further define the health benefits of omega-3 fatty acids for preventing subsequent cardiovascular events. At this time there is insufficient evidence to make a recommendation to include omega-3 fatty acids for prevention of myocardial reinfarction in patients with existing coronary heart disease.

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Appendix 1

Author	N	Title of Study	Level of Study	Findings
Nilsen	300	Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol (2001)	Randomized Controlled Trial Level 1	Nilsen et al found no significant benefit of omega-3 fatty acid supplementation despite favorable effects on serum lipids in patient diagnosed with coronary heart disease.
Singh	404	Randomized, Double-Blind, Placebo-Controlled Trial of Fish Oil and Mustard Oil in Patients with Suspected Acute Myocardial Infarction: The Indian Experiment of Infarct Survival-4 (1997)	Randomized Controlled Trial Level 1	Singh et al found that the omega-3 fatty acids supplement group had significantly less cardiac events and cardiac deaths.
Burr		Effects of changes in fat, fish, and fiber intakes on death and myocardial reinfarction (1997)	Randomized Controlled Trial Level 1	Burr et al found that increased intake in fish among men with coronary heart disease may reduce the risk of myocardial reinfarction.
Marchioli	11,324	Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione.	Randomized Controlled Trial Level 1	Marchioli et al found that omega-3 fatty acid supplementation led to significantly lowered risk of cardiac events especially sudden cardiac death.
de Lorgeril	600	Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study	Randomized Controlled Trial Level 1	De Lorgeril et al found that a Mediterranean diet is cardioprotective reducing both morbidity and mortality due to cardiac endpoints.
Bucher	15,806	N-3 Polyunsaturated Fatty Acids in Coronary Heart Disease: A Meta-analysis of Randomized Controlled Trials (2002)	Meta-analysis of RCT Level 1	Bucher at al found that dietary and non dietary intake of omega-3 fatty acids reduced overall mortality, mortality due to MI, and sudden death in patients with coronary heart disease.
Yzebe	14,727	Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials (2004)	Meta-analysis RCT Level 1	Yzebe et al found that all cause mortality and death due to myocardial reinfarction was decreased in those taking fish oil however due to the suboptimal quality of the studies no recommendation to include fish oil was made.
Morris		Fish consumption and cardiovascular disease in the physicians' health study: a prospective study (1995)	Prospective Cohort Level 2B	Morris et al found that moderate fish oil consumption does not lower the risk for cardiac disease however when data was reanalyzed it was found that fish consumption at least one time a week reduces risk of cardiac death especially sudden cardiac death.
Hu	84,688	Fish and omega-3 fatty acid intake and risk of coronary heart disease in women (2002)	Prospective Cohort Level 2B	Hu et al found that women who consumed higher amounts of fish were at lower risk for coronary heart disease and deaths due to coronary heart disease.
Daviglus	1,822	Fish consumption and the 30-year risk of fatal myocardial infarction (1997)	Prospective Cohort Level 2B	Daviglus et al found that there was an inverse relationship between fish consumption and death from coronary heart disease, especially non sudden death from myocardial infraction.

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