Omega-3 Fatty Acid: A Role in the Management of Cardiac Arrhythmias?

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Abstract

Objective: The objective of this study was to review and evaluate published evidence on the use of omega-3 fatty acid in the prevention and treatment of atrial and ventricular arrhythmias. Postulated mechanisms of the antiarrhythmic effects of omega-3 fatty acid are discussed.

Data sources: Peer-reviewed articles/abstracts published in English language were identified from MEDLINE and Current Content databases (both 1966 to May 15, 2008) using the search terms fish oil, omega-3 fatty acid, sudden death, ventricular arrhythmia, and atrial fibrillation. Citations from available articles were also reviewed for additional references. Abstracts presented at recent professional meetings are also reviewed.

Study selection and data extraction: Observational studies and interventional clinical studies published on omega-3 fatty acid or fish consumption and atrial or ventricular arrhythmias and sudden cardiac death are selected. The design and results of the studies are evaluated.

Data synthesis: Several mechanisms have been postulated to explain the antiarrhythmic effect of omega-3 fatty acid. It is believed that omega-3 fatty acid has an indirect effect on the autonomic nervous system, inhibits the fast, voltage-dependent sodium and L-type calcium channels, restores a favorable omega-6 fatty acid/omega-3 fatty acid balance, and exerts anti-inflammatory effects. While the majority of observational evidence demonstrated that increased consumption of omega-3 fatty acid was associated with reduction in risk of sudden cardiac death, in ventricular arrhythmia, there was evidence suggesting that omega-3 fatty acid in patients experiencing nonischemic ventricular arrhythmia may be proarrhythmic. Other studies demonstrated a neutral effect. In terms of management of atrial fibrillation, short-term small-scale studies demonstrated that the use of omega-3 fatty acid preoperatively may reduce the incidence of postoperative atrial fibrillation. However, such observations were not consistent with those reported from retrospective cohorts.

Conclusions: Additional studies are needed to evaluate the effect of omega-3 fatty acid before it can be routinely recommended for the management of arrhythmia.

Introduction

Despite the advances made in pharmacologic and nonpharmacologic (devices and surgical procedures) management of cardiac arrhythmias, supraventricular and ventricular arrhythmias continue to be a major public health problem that affects many Americans. In 2001, $2.7 billion ($6,634 per discharge) was paid to Medicare beneficiaries for cardiac arrhythmias. Among all, atrial fibrillation (AF) continues to be the most common type of supraventricular arrhythmia. At age 40, lifetime risks for AF were 26.0% for men and 23.0% for women. Other types of supraventricular arrhythmias affect roughly 570,000 individuals per year. In terms of ventricular arrhythmias, the prevalence of sudden cardiac death accounts for about 300,000–400,000 deaths annually in the United States, including 250,000 people a year who die of coronary heart disease (the most important cause of sudden cardiac death) without being hospitalized. Once a patient has suffered 1 episode of life-threatening arrhythmias, the recurrence rate is as high as 30%–50% in 2 years.
Even in patients who have received implantable cardioverter defibrillators (ICD), sudden cardiac death recurrence rates still average 1%–2% annually. \(^1\)

Antiarrhythmic agents help terminate and prevent arrhythmias. However, many of them require close therapeutic monitoring due to their side-effect and drug interaction profiles, such as prolongation of the QT interval causing tor- sade de pointes. \(^2\) Therefore, research has focused on finding alternative, safer, preventive, and therapeutic strategies. Beginning in 1970, when 2 Danish epidemiologists made an observation correlating eating fish and fish oil and lower mortality from heart disease in Greenland Eskimos, \(^3\) fish oil and its cardiovascular protective effects has been under close attention of cardiologists. In the 1980s, a group of Australian investigators reported that omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oil, prevented fatal cardiac arrhythmias in rats with atherosclerosis developed from consuming a high saturated fat diet. \(^4\) These findings were later confirmed by another group of investigators in a canine model. \(^5\) Omega-3 fatty acid was then thought to be a potentially safer therapeutic alternative for arrhythmia management in humans. This paper reviews the postulated mechanisms of the antiarrhythmic effect of omega-3 fatty acid, and the epidemiologic as well as clinical evidence available to date of the effectiveness of using omega-3 fatty acid for the management of different types of arrhythmias.

**Data Sources and Selection**

Peer-reviewed papers/abstracts were identified from MEDLINE\(^6\) and Current Content databases (both from 1966 to May 15, 2008) using the search terms fish oil, omega-3 fatty acid, sudden death, ventricular arrhythmia, and AF. Citations from available papers were also reviewed for additional references. Abstracts presented at recent professional meetings were also reviewed.

**Postulated Mechanisms of Antiarrhythmic Effects**

Fatty acids are an integral component of all cellular membranes. They interact with membrane proteins to affect receptor function, enzyme activity, signal transduction, and membrane excitability. \(^5\) Polyunsaturated fatty acids in nature belong to 2 main classes: the omega-6 fatty acid and the omega-3 fatty acid. Omega-6 fatty acid is found mainly in vegetable oil and omega-3 fatty acid mainly in fish, fish-eating animals, or flaxseeds. \(^7\) Both omega-3 and omega-6 fatty acid are essential fatty acid, meaning humans cannot synthesize them from precursor molecules. Omega-3 fatty acid is metabolized to EPA and DHA in the human body and is believed to possess a cardiovascular protective effect. \(^8\) Omega-6 fatty acid is metabolized to form arachidonic acid, which maintains hemostatic balance in the system when produced in small quantity, but if produced in large quantity, may contribute to formation of thrombus and atheromas, and to inflammatory disorders. \(^9\)

It is still unclear exactly how omega-3 fatty acids exert their antiarrhythmic effects, and whether such effects come from the EPA component or the DHA component or both is unknown. However, several mechanisms have been postulated. Structurally, omega-3 fatty acids have structures similar to other that of antiarrhythmic agents used currently in that they have a long acyl hydrocarbon tail, greater than 2 unsaturated carbon–carbon double bonds, and a free carboxyl group at one end. \(^10\) It is also believed that omega-3 fatty acids may have an indirect effect through cardiac control of the autonomic nervous system, increasing heart rate variability and baroreflex sensitivity. \(^11,12\) A high variability in heart rate is an indication of good cardiac adaptability, implying a well-functioning autonomic control mechanism, thus lowering the risk of arrhythmia. \(^13\) Electrophysiologically, omega-3 fatty acids may also exert an antiarrhythmic effect by inhibiting the fast, voltage-dependent sodium and L-type calcium channels. \(^14,15\) Chryssohoou and colleagues evaluated the association of fish consumption and electrocardiographic changes in 3042 healthy subjects in Greece and demonstrated that compared to nonconsumers of fish, those who consumed >300 g fish per week had a mean 13.5% lower in QTc interval, \(^p< 0.01\) \) after adjustment of confounding factors and had a 29.2% lower likelihood of having QTc intervals of greater than 0.45 seconds \(^p = 0.03\) \). Long QTc intervals is a well-known risk of developing torsi de de pointes. \(^2\) Therefore, reducing the risk of prolonged QTc interval may be one of the mechanisms to explain the reduced risk of ventricular arrhythmias. Omega-3 fatty acids are thought to act on the final common pathway affecting excitability of the cardiac myocyte and prevent calcium overload during stress. In addition, by incorporating more omega-3 fatty acids into cardiac membrane phospholipids, they may reduce the omega-6 fatty acid/omega-3 fatty acid ratio, which may shift the myocardium from a proarrhythmic to an antiarrhythmic state. \(^16\) Finally, omega-3 fatty acids may have direct effects on the inositol lipid cycle and cell signaling on the cell membrane, via their anti-inflammatory effects mediated by eicosanoids. \(^17\)

**Evidence in Reduction of Sudden Death**

Table 1 summarizes the different studies on the use of omega-3 fatty acid in the management of arrhythmias.

**Retrospective cohort and case–control studies**

Early observational studies have demonstrated lower rates of cardiovascular disease in population with high fish consumption, such as the Greenland Eskimos, \(^3\) Japanese, \(^18\) and Alaskan natives. \(^19\) Subsequently, Daviglus and colleagues have established an association between increase fish consumption and reduction in nonsudden cardiac death, \(^20\) and the Physician’ Health Study as well as the Nurses’ Health study have found an association between fish consumption and reduction of sudden death. \(^21,22\)

Siscovick et al. performed a population-based case–control study assessing whether dietary intake of omega-3 fatty acid was associated with reduced risk in primary cardiac arrest. \(^23\) A total of 334 case patients with primary cardiac arrest between 1988 and 1994 and 493 population-based control cases were examined. All case and control subjects were free of prior clinical heart disease and other major comorbidity. Compared with no dietary intake of omega-3 fatty acid, consumption of 5.5 g of omega-3 fatty acid per month (equivalent of 1 fatty fish meal per week) was associated with a 50% reduction in the risk of primary cardiac arrest (odds ratio: 0.5, 95% confidence interval (CI) 0.4–0.8). Compared with an omega-3 fatty acid level of 3.3% of total fatty acids

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\(^1\) Cheng and Santoni.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>Duration of follow-up</th>
<th>Effect of arrhythmias</th>
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<tbody>
<tr>
<td>Siscovick et al24</td>
<td>Case–control</td>
<td>Consumption of fish oil 5.5 g/day versus no consumption</td>
<td>Sudden cardiac death</td>
<td>6 years</td>
<td>Fish oil reduce primary cardiac arrest (OR:0.5, 95% CI 0.4–0.8)</td>
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<tr>
<td>DART25</td>
<td>Randomized, open label, dietary intervention study. 2033 acute MI</td>
<td>1. Reduction of fat intake; vs. 2. Increase in fiber intake; vs. 3. Increase in fish intake; 4. Placebo</td>
<td>Sudden cardiac death, Primary: Cardiac arrest</td>
<td>2 years</td>
<td>Consumption of fish reduces 2-year mortality by 29% (p &lt; 0.05)</td>
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<td>No significant changes in death from ischemic heart disease. Investigators implied that the significant changes in total mortality were attributed to reduce death from cardiac arrhythmia.</td>
</tr>
<tr>
<td>Lyon Diet Heart Study26</td>
<td>Prospective, randomized, single-blinded, secondary prevention study 605 acute MI</td>
<td>1. Mediterranean α-linolenic-rich; vs. 2. Control</td>
<td>Primary endpoint: all cause mortality, Secondary endpoint: cardiovascular mortality.</td>
<td>27 months</td>
<td>Mediterranean diet reduces all-cause and cardiovascular mortality, including SCD (8 in control group, 0 in Mediterranean diet group) p value not available.</td>
</tr>
<tr>
<td>Indian Experiment on Infarct Survival Study27</td>
<td>Randomized, open labeled placebo control trial. 406 acute MI</td>
<td>1. EPA 1.08 g/day; vs. 2. α-linolenic acid 2.9 g/day; vs. 3. Placebo</td>
<td>Primary: Total fatal and nonfatal cardiovascular events Secondary: recurrent MI, cardiac death, cardiac arrhythmias, left ventricular enlargement, angina pectoris</td>
<td>1 year</td>
<td>Sudden death: EPA: 1.6% Mustard oil: 1.6% Placebo: 6.6% (p &lt; 0.05 for both fish oil versus placebo and mustard oil versus placebo)</td>
</tr>
<tr>
<td>GISSI Prevenzione28</td>
<td>Prospective, open-labeled, randomized control study 11324 Acute MI</td>
<td>1. Omega-3 fatty acid 1 g/day; vs. 2. vitamin E 300 mg/day; vs. 3. Omega-3 fatty acid + vitamin E; vs. 4. Placebo</td>
<td>Primary: Combined incidence of death, nonfatal MI and stroke. Secondary: Separate component of primary endpoint Events: MI, arrhythmia, cardiac death</td>
<td>3.5 years</td>
<td>Sudden death: Omega-3 fatty acid 1.9% vitamin E 2.3% Omega-3 fatty acid + vitamin E 2.4% Placebo 3.5% (p &lt; 0.05 for all treatment compared to placebo)</td>
</tr>
<tr>
<td>Cardiovascular Heart Study29</td>
<td>Cohort study 3900 history of cardiac disease</td>
<td>Consume fish ≥ 3 times weekly vs. &lt; 1 time weekly</td>
<td>Sudden death: Arrhythmic death ≥3 times weekly 3% &lt;1 time weekly 7% p &lt; 0.05</td>
<td>9.3 years</td>
<td>(continued)</td>
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<tr>
<td>Study</td>
<td>Study design/N</td>
<td>Treatment</td>
<td>Endpoint</td>
<td>Duration of follow-up</td>
<td>Effect of arrhythmias</td>
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<td>JELIS&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Double-blind, randomized, placebo-controlled study. 18,645 Japanese patients with hyperlipidemia on statins</td>
<td>1. EPA 1.8 g daily; vs. 2. Placebo</td>
<td>Primary: Major coronary events. Secondary: coronary death, sudden death</td>
<td>4.6 years</td>
<td>Sudden death EPA 0.1%. Placebo 0.1% $p = \text{ns}$</td>
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<tr>
<td>Raitt et al.&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Double-blind, randomized, placebo-controlled. 200 patients with nonischemic induced VT/VF, ICD placed</td>
<td>1. Fish oil 1.8 g/day; vs. 2. Placebo</td>
<td>Primary: recurrent VT/VF</td>
<td>24 months</td>
<td>VT/VF at 24 months: Fish oil group: 79%. Placebo group: 65% $p = 0.007$</td>
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<tr>
<td>Leaf et al.&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Double-blind, randomized, placebo-controlled. Study 402 with ICD for secondary prevention of SCD</td>
<td>1. Fish oil 4 g/day; vs. 2. Placebo</td>
<td>Primary: Recurrent VT/VF confirmed by ICD event.</td>
<td>12 months</td>
<td>High noncompliance rate (35%). Sudden death Fish oil: 3 Olive oil: 1 Intention-to-treat analysis: Reduce VT/VF by 28% ($p = \text{ns}$) On-treatment analysis: Reduce VT/VF by 38% ($p &lt; 0.05$)</td>
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<td>SOFA&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Double-blind, randomized, placebo-controlled. 546 patients with ICD</td>
<td>1. Fish oil 2 g/day; vs. 2. Placebo</td>
<td>Primary: VT/VF events or death confirmed by ICD event.</td>
<td>12 months</td>
<td>VT/VF Fish oil 13% Placebo 34% $p &lt; 0.05$ HR for recurrent ventricular arrhythmia: 0.91, 95% CI 0.66–1.26</td>
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<tr>
<td>Metcalf et al.&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Prospective, open-labeled, not randomized, 12 patients with ischemic cardiomyopathy received fish oil, 14 controlled.</td>
<td>1. Fish oil 3 g per day 2. No treatment</td>
<td>VT inducibility in electrophysiology laboratory</td>
<td>6 weeks</td>
<td>Noninducible VT: Fish oil 42% No treatment: 7% $p = 0.003$</td>
</tr>
<tr>
<td>Study</td>
<td>Design/Study Details</td>
<td>Consumption of omega-3 fatty acid</td>
<td>Events: AF</td>
<td>Incidence of AF (rate per 10,000 person-year/adjusted HR)</td>
<td>Details</td>
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<tr>
<td>Frost et al. (^{38})</td>
<td>Retrospective cohort study. 47,949 patients from the Danish Diet, Caner and Health Study Cohort. No AF at baseline</td>
<td>Consumption of omega-3 fatty acid</td>
<td>Events: AF</td>
<td>5.7 years</td>
<td>Incidence of AF (rate per 10,000 person-year/adjusted HR)</td>
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<tr>
<td>Brouwer et al. (^{39})</td>
<td>Retrospective cohort Study 5184 healthy subjects from Rotterdam Cohort. No AF at baseline</td>
<td>Dietary intake of EPA and DHA</td>
<td>Events: AF</td>
<td>6.4 years</td>
<td>Incidence of AF (rate per 1000 person-year/adjusted RR)</td>
</tr>
<tr>
<td>Mozaffarian et al. (^{40})</td>
<td>Prospective cohort study. 4815 patients</td>
<td>Dietary intake of different kind of fish dishes.</td>
<td>Events: AF</td>
<td>12 years</td>
<td>Incidence of AF (rate per 1000 person-year/adjusted HR)</td>
</tr>
<tr>
<td>Calo et al. (^{41})</td>
<td>Open-labeled, randomized controlled study. 160 patients undergoing CABG surgery</td>
<td>1. Omega-3 fatty acid 2 g/day at least 5 days before surgery and until hospital discharge; vs. Placebo</td>
<td>Primary: AF</td>
<td>At hospital discharge</td>
<td>Omega-2 fatty acid reduce postoperative AF (15.2% vs. 33%, (p = 0.013))</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CABG, coronary artery bypass graft; CI, confidence interval; DART, Diet and Reinfarction Trial; DHA, docosahexaenoic acid; HR, hazard ratio; EPA, eicosapentaenoic acid; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico; ICD, implantable cardiac defibrillator; JELIS, Japan EPA Lipid Intervention Study; MI, myocardial infarction; ns, non-significant; OR, odds ratio; RR, relative risk; SCD, sudden cardiac death; SOFA, Study on Omega-3 Fatty Acids and Ventricular Arrhythmia; VT, ventricular tachycardia; VF, ventricular fibrillation.
in red blood cell membrane (the mean of the lowest quartile), an omega-3 fatty acid level of 5% of total fatty acids in red blood cell membrane (the mean of the third quartile) was associated with a 70% reduction in the risk of primary cardiac arrest (odds ratio: 0.3, 95% CI 0.2–0.6). More recently, the fatty acid concentrations of previously collected blood from the Physicians’ Health Study (94 had sudden death and 184 were age- and smoking habit-matched controls) were analyzed. Blood levels of omega-3 fatty acid were inversely related to the risk of sudden death, after adjustment of all confounder factors.

These retrospective cohort studies provided an insight into the potential association of omega-3 fatty acid consumption and arrhythmic events. However, retrospective large population base studies share a common limitation: there may be unknown confounding factors that are not adjusted. In addition, dietary consumption of omega-3 fatty acid was difficult to track in a retrospective manner. Thus, a potential effect in differences in dietary consumption could not be eliminated.

**Prospective studies**

Several prospective cohort studies have been performed to evaluate the association between omega-3 fatty acid consumption and arrhythmias. The Diet and Reinfarction Trial (DART) was a randomized, open-label, dietary intervention study of 2000 Welsh men with a recent myocardial infarction. They were randomized to 3 types of dietary interventions: (1) reduction in fat intake; (2) increase in the consumption of fiber; and (3) increase in fatty fish intake to at least 2 fish meals weekly. At 2 years, the men in the fish arm had significantly lower cardiovascular mortality (29% reduction) compared to the other groups. The mortality due to arrhythmias was not recorded. However, because there was no documented reduction in new infarcts, the investigators attributed the reduction in mortality to possible reduction in arrhythmic death, the other most common reason for death in patients with recent myocardial infarction. The major limitations of the DART study included the lack of complete assurance that the patients would always adhere to the dietary interventions that were prescribed to them, as well as the fact that the different type of fiber and fish consumed might have contributed to different individual results. In addition, because the actual incidence of arrhythmic death was not captured, it cannot be completely certain that the reduction of death is due to reduction in arrhythmic death.

The Lyon Heart Study was a prospective, randomized, single-blinded, secondary prevention study comparing the effect of a Mediterranean α-linolenic-rich diet to the usual diet. The 302 subjects receiving the Mediterranean diet had a significant 70% reduction in all cause mortality and morbidity, including the prevention of sudden death (8 in control group, 0 in the Mediterranean diet group). However, it is difficult to differentiate which component of the Mediterranean diet is producing the cardioprotective effect, because complex dietary differences exist, including increased intake of grains, fruits and vegetables, alcohol, and omega-3 fatty acid.

The Indian Experiment on Infarct Survival study is a randomized, placebo-controlled trial, evaluating the cardioprotective effects of treatment with fish oil (EPA 1.08 g/day, n = 122), mustard oil (α-linolenic acid, 2.9 g/day, n = 120), or placebo (aluminum hydroxide) (n = 118) in patients with acute myocardial infarction. Treatments began at a mean of 18 hours after the symptoms of acute myocardial infarction in all 3 groups. After 1 year, the total cardiac events were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% versus 34.7%, p < 0.01). When analyzed separately, total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly fewer cardiac deaths compared with the placebo group (11.4% versus 22.0%, p < 0.05). Besides reduction in recurrent infarction, the fish oil and mustard oil groups also showed a significant reduction in total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group. The major limitation in this study again is the reliability of patient adherence to the treatment prescribed. In addition, there may be cross-contamination between groups if the patients also consumed a lot of fish or mustard from other food sources.

The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico Prevenzione (GISSI-prevenzione) trial is an open-labeled, randomized, controlled trial looking at the effectiveness of omega-3 fatty acid and α-lotocopherol in reducing mortality in patients with prior myocardial infarction. Subjects were randomly assigned to receive 1 g of omega-3 fatty acid (n = 2836), 300 mg of vitamin E (n = 2830), or no treatment (n = 2830). After 3.5 years, the treatment with omega-3 fatty acid resulted in a significant reduction of risk of sudden death in 4 months by 45% (relative risk 0.55, 95% CI 0.40–0.76). Similar limitations apply to this study in terms of reliability of patient adherence to the treatment prescribed, as well as cross-contamination among groups of patients who consumed fish and vitamin E from other food sources.

The Cardiovascular Heart Study cohort examined the relation between risk of ischemic heart disease mortality due to arrhythmia and fish consumption, based on dietary recall and verified by plasma phospholipid omega-3 fatty acid content. Three thousand nine hundred and ten (3910) adults aged >65 years without history of cardiovascular disease were followed up for approximately 9.3 years. Among 247 deaths from ischemic heart disease, 148 arrhythmic deaths were identified. Arrhythmic death was decreased significantly by 68% among those with a baseline fish consumption of >3 times weekly compared to those who consumed fish <1 time weekly (p = 0.001). Although the investigators used plasma phospholipids omega-3 fatty acid content to verify fish consumption, the amount of fish consumption was obtained through dietary recall and was subject to recall bias, especially when patients were followed for an average of 9.3 years.

More recently, the Japan EPA Lipid Intervention Study (JELIS) reported contradictory results. In this study, 18,645 Japanese patients with hyperlipidemia who were on statins were recruited and randomized in open-labeled fashion, to receive either 1.8 g of EPA daily (n = 9326) or no treatment (n = 9319). At mean 4.6 years of follow-up, patients receiving EPA had a significant reduction in major coronary event (2.6% versus 3.5%, p = 0.011). However, incidence of sudden cardiac death and coronary death did not differ between groups. Although EPA appears to be promising in this...
study in reducing major coronary event, EPA did not demonstrate an antiarrhythmic effect. It is important to note that patients in the JELIS study already consumed a significant amount of fish in their diet. Therefore, additional supplements may not have exerted any demonstrable benefits.

**Evidence in Ventricular Arrhythmia**

As most large-scale observational and interventional studies demonstrated that dietary changes or supplements increasing the intake of omega-3 fatty acids in patients with coronary artery diseases were associated with a significant reduction in the risk of sudden cardiac death, specific studies have been performed to evaluate the effect of omega-3 fatty acid for secondary prevention in patients susceptible to cardiac arrhythmias.

**Prospective studies**

Raitt and colleagues performed a randomized trial enrolling 200 patients who have received ICD because of a recent episode of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) not due to acute myocardial infarction. Patients were assigned to receive fish oil 1.8 g per day (73% omega-3 fatty acid) or placebo (olive oil). Although more patients in the fish oil group received ICD therapy for VT/VF at 6, 12, and 24 months’ follow-up, the differences were not statistically significant. In the subset of 133 patients whose qualifying arrhythmia was VT, 61%, 66%, and 79% of patients in the fish oil group had VT/VF at 6, 12, and 24 months compared with 37%, 43%, and 65% of patients in the control group (p = 0.007). Recurrent VT/VF events were more common in patients randomized to receive fish oil (p < 0.001). A subset of 49 patients was enrolled into the study during the time they had their ICD implantation. These patients underwent electrophysiologic testing during the time and 3 months later. There were no differences in terms of percentage inducible VT/VF at baseline and at 3 months in patients receiving fish oil or placebo (% inducible VT/VF: baseline 39% [fish oil] versus 46% [placebo]; 3-month 62% [fish oil] versus 56% [placebo]). Therefore, the study results appeared to suggest that fish oil may actually be proarrhythmic in patients who have received an ICD for secondary prevention of sudden cardiac death, particularly in patients whose qualifying arrhythmia for ICD is sustained VT. However, comparing these results to previous studies, it is important to note that the enrolled patient populations differ, especially with regard to time of onset of myocardial infarction. Unlike previous studies, these patients developed sustained VT/VF not due to myocardial infarction. Perhaps fish oil only benefits certain types of ventricular arrhythmia. In addition, olive oil was used as the control agent in this study. It was known that consumption of monounsaturated fat such as olive oil may also decrease risk of cardiovascular disease. Therefore, the results may simply have indicated that olive oil was better than fish oil in reducing recurrent VT/VF but not that fish oil was proarrhythmic. Further studies need to explore this question.

Leaf and colleagues evaluated the potential antiarrhythmic effects of fish oil in patients who had received an ICD for secondary prevention of sudden cardiac death. Four hundred and two (402) patients who received an ICD within the previous year because of cardiac arrest, sustained VT, or syncope with inducible VT or VF were randomized to receive either fish oil 4 g per day (65% omega-3 fatty acid) or placebo (olive oil). Although patients in the fish oil group experienced a 28% reduction in incidence of recurrent VT/VF or all-cause mortality at 12-month follow-up, this difference was not statistically significant. However, because the study has relatively high noncompliance rate (35%), on-treatment analysis revealed a significant risk reduction of 38% with regard to recurrent VT/VF and all cause mortality. Similarly, this study also utilized olive oil as control. Therefore, the beneficial effect of olive oil cardiovascularly could not be ruled out.

The Study on Omega-3 Fatty acids and ventricular Arrhythmia was a randomized, parallel, placebo-controlled, double-blind trial that enrolled 546 patients with ICD and prior documented malignant VT/VF, evaluating the effect of fish oil in preventing recurrent arrhythmic events. Patients were assigned to either 2 g per day of fish oil (n = 273) or placebo (sunflower seed oil) (n = 273). Fish oil did not significantly reduce recurrent VT/VF events and all-cause mortality (hazard ratio: 0.86; 95% CI, 0.64–1.16) in a follow-up of a median of 356 days. In a prespecified subgroup analyses, the hazard ratio (HR) was 0.91 (95% CI, 0.66–1.26) for fish oil versus placebo in the 411 patients who had experienced VT in the year before the study, and 0.76 (95% CI, 0.52–1.11) for 332 patients with prior myocardial infarctions. Therefore, this study did not demonstrate that omega-3 fatty acid has protective effect against ventricular arrhythmia in patients with ICD. Sunflower seed oil, however, also contains a high level of polyunsaturated fatty acid and has been demonstrated to favorably alter cholesterol profile and factor VII coagulant activity. Therefore, the lack of cardioprotective effect of omega-3 fatty acid demonstrated in this study may have been due to the fact that both groups of patients were receiving cardioprotective effect from the different oils used.

Metcalfe and colleagues evaluated the change in inducibility of VT in 12 patients with ischemic heart disease who had documented inducible VT, before and after 6 weeks of supplementation of fish oil of 3 g per day. Fourteen (14) other patients (who received no treatment) were also enrolled to control for fluctuations of inducibility. At the end of the 6-week treatment period, 42% of patients in the fish oil group had no inducible VT, 42% required more aggressive stimulation in order to induce VT, 8% required identical stimulation for VT induction, and 8% required less stimulation to induce VT (compared to 7%, 36%, 36%, and 21%, respectively, in the control group) (p = 0.003). The investigators concluded that fish oil may have an antiarrhythmic effect. It is important to note, however, that this study enrolled a very small number of patients, and additional dietary consumption of fish oil or other polyunsaturated fatty acid was not controlled. Larger studies are needed to confirm the results.

Flaxseed, another rich source of alpha-linolenic acid, an omega-3-fatty acid, has not been studied in humans to determine whether it possesses a similar antiarrhythmic effect as omega-3 fatty acid from fish. However, supplementing flaxseed in the diet of 16 rabbits has been demonstrated to protect them against VF induced by ischemic reperfusion. Studies need to be performed to confirm whether a similar effect exists in humans.

Given the conflicting results of these trials, recommendation of routinely using fish oil therapy in all patients at risk...
for life-threatening VT cannot be made. Possible reasons for the discordant outcomes may include differences in underlying cause of VT/VF, and differences in patients’ background diet omega-3 and omega-6 fatty acid content. As mentioned before, the use of olive oil and sunflower seed oil as control may have masked some of the beneficial effect of omega-3 fatty acid if it existed. More studies with enough power to evaluate the effects of this supplement in a variety of subgroups are necessary.

Evidence in Atrial Fibrillation

In recent years, in addition to VT/VF, omega-3 fatty acid has also been investigated for preventing and treating AF.

Retrospective cohort

Frost and colleagues examined the association between consumption of omega-3 fatty acid from fish and risk of AF or flutter. Thirty-eight thousand nine hundred and forty-nine (47,949) patients from the Danish Diet, Cancer, and Health Study cohort were evaluated for consumption of omega-3 fatty acids from fish and risk of AF or flutter. During a follow-up of approximately 5.7 years, AF or flutter had developed in 556 subjects. There was no significant difference in incident of AF and atrial flutter among patients in different quintile of omega-3 fatty acids consumption. However, when the lowest quintile of omega-3 fatty acids consumption was used as a reference, the adjusted hazard rate ratio in quintiles 2, 3, 4, and 5 were 0.86, 1.08, 1.01, and 1.34 ($p$ for trend = 0.006). The investigators concluded that consumption of n-3 fatty acids from fish was not associated with a reduction in risk of AF or flutter, although they cannot exclude the possibility of residual confounding caused by a lack of information on intake of fish-oil supplements.

Brouwer and colleagues utilized data from 5184 subjects from the Rotterdam Study Cohort to evaluate the association of dietary intake of EPA and DHA and incidence of AF. After a mean follow-up of 6.4 years, 312 subjects developed AF. Intake of EPA and DHA in the third tertile ($\geq$144 mg/d) compared with the first tertile ($\leq$43 mg/d) did not demonstrate any change in risk of AF (relative risk 1.18, 95% CI 0.88–1.57). In addition, no association was observed with daily fish intake of $>20$ g compared with no fish intake (relative risk 1.17, 95% CI 0.87–1.57). Therefore, this study concluded that intakes of EPA and DHA and the consumption of fish were not associated with the onset of AF and did not support a general antiarrhythmic effect of omega-3 fatty acid. Since this is a retrospective cohort study, the presence of other potential confounders cannot be ruled out.

Prospective studies

A population-based prospective cohort study performed by Mozaffarian and colleagues enrolled 4815 patients of $>65$ of age who did not have AF at baseline. Each patient’s usual dietary intake was assessed. After a follow-up period of 12 years, consumption of tuna or other broiled or baked fish was significantly associated with a reduction in the incidence of AF (HR: 0.72, 95% CI 0.58–0.91). Reduction in risk was also observed with intake $\geq$5 times per week as compared with $<1$ time per month (HR 0.69, 95% CI 0.52–0.91). The beneficial effect was not observed with the consumption of fried fish or fish sandwiches. Because the data for the number of times of fish consumption per week were based on patient recall, recall biases could not be ruled out.

Calo and colleagues performed an open-labeled, randomized, controlled study in 160 patients undergoing coronary artery bypass surgery evaluating the effect of omega-3 fatty acid in preventing postoperative AF. Patients were randomized to receive omega-3 fatty acid 2 g per day or usual care for at least 5 days before surgery and until the day of discharge. Patients undergoing valvular surgery and those with a previous history of AF were excluded from the study. The incidence of postoperative AF was significantly reduced in the omega-3 fatty acid group compared with placebo (15.2% versus 33%, $p = 0.013$). Although the study results are limited by the relatively short follow-up period and can only be applied to the low-risk cardiac surgery population, they provide insights into the potential antiarrhythmic effects of omega-3 fatty acid in this patient population.

Future Perspective and Conclusions

Results from observational and smaller-scale clinical studies suggest that omega-3 fatty acids may prevent sudden cardiac death by suppressing life-threatening VT/VF, as well as possibly reducing AF in certain patient populations. Although this makes fish oil an attractive alternative to other antiarrhythmic agents for arrhythmia management, its efficacy has not been definitively proven and contradicting evidence exists. This may be due to the different population studied, different formulation of omega-3 fatty acid used, the differences in the consumption of fish versus fish oil supplements, and the different comparative oil used for control. There may be other beneficial ingredients in addition to omega-3 fatty acid when consuming fish instead of just consuming supplements. In addition, the exact mechanisms of omega-3 fatty acid need to be explored further. Whether the benefits come from EPA or DHA or both needs to be explored. There is preliminary evidence indicating that there may be differences in their effect on cholesterol profile and that only DHA has been demonstrated to improve endothelial function and prevent platelet aggregation. Furthermore, whether it is the amount of omega-3 fatty acid consumed or the percentage of omega-6 versus omega-3 fatty acid presented in the system that are actually contributing to the observed effect is to be determined. None of the studies evaluated the concurrent consumption of omega-6 fatty acid or the amount of omega-6 fatty acid present in the system. Therefore, more studies are needed before one can routinely recommend the use of omega-3 fatty acid for arrhythmia management. In addition, since omega-3 fatty acid was first studied for prevention of sudden cardiac death, the management of acute myocardial infarction has been improved over the last few years, including early revascularization by percutaneous coronary intervention (PCI), the routine use of $\beta$-blockers, statins and angiotensin converting enzyme inhibitors, as well as utilization of cardiac rehabilitation to improve quality of life. Therefore, the beneficial effect of omega-3 fatty acid needs to be studied in the condition of modern treatment of myocardial infarction. In addition, a highly purified form of omega-3 fatty acid (Lovaza\textsuperscript{R}, GlaxoSmithKline, Philadelphia, PA) has recently been officially approved by the United States Food and Drug Administration for management of hypertriglyceridemia. The highly purified form of omega-3 fatty acid
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is free of any mercury contamination and is considered a prescription medication. The OMEGA study (Highly purified omega-3 fatty acids for secondary prevention of sudden cardiac death after myocardial infarction) utilizes this formulation to evaluate the effect of omega-3 fatty acid on the rate of sudden cardiac death within 1 year after acute myocardial infarction in about 3466 patients. Secondary endpoints include total mortality, nonfatal cardiovascular events, rhythm abnormalities in Holter monitoring, and depression score. Results of this study are anticipated to be available in 2008. Regarding the use of omega-3 fatty acid in AF, data are sparse compared to sudden cardiac death and ventricular arrhythmia. Furthermore, dose-response needs to be established and with long-term use, most evidence in the side-effect profile need to be explored. In conclusion, additional studies are needed to evaluate the effect of omega-3 fatty acid in AF of different etiology before this therapy can be recommended.

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References


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