

Omega-3 Fatty Acids & Ventricular Arrhythmias

contradictory findings of two randomized, blinded, controlled trials may possibly be explained by different patient populations in the two studies. The Leaf study had a higher portion of subjects with coronary artery disease than the Raitt study and a high percentage of the patients had an ICD placed for cardiac arrest. In contrast, while the Raitt study reported that 73% of its subjects had coronary artery disease, it also stated that 38% had nonischemic cardiomyopathy. Sixty-seven percent of the subjects had an ICD placed for VT, precisely the subgroup in whom fish oil was associated with higher rates of recurrent ventricular arrhythmias. A reasonable explanation for the disparate findings in patients at high risk for sudden death is that fish oil is beneficial for patients whose arrhythmias are related to acute ischemia, but may have adverse effects in patients with idiopathic cardiomyopathy whose primary arrhythmia is VT. The present evidence suggests that fish oil is beneficial for patients following acute myocardial infarction, should not be routinely used in patients with chronic stable angina pectoris and should be avoided in people with primary ventricular tachycardia and idiopathic cardiomyopathy. As with all healthcare interventions, the potential benefits of fish oil must be weighed against possible adverse effects for each individual person.

References

- 1) Murnaghan MF. Effect of fatty acids on the ventricular arrhythmia threshold in the isolated heart of the rabbit. *Br J Pharmacol* 1981;73:909-15.
- 2) McLennan PL, Abeywardena MY, Charnock JS. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. *Am Heart J* 1988;116:709-17.
- 3) McLennan PL. Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats. *Am J Clin Nutr* 1993;57:207-12.
- 4) McLennan PL, Bridle TM, Abeywardena MY, Charnock JS. Dietary lipid modulation of ventricular fibrillation threshold in the marmoset monkey. *Am Heart J* 1992;123:1555-61.
- 5) Billman GE, Hallaq H, Leaf A. Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids. *Proc Natl Acad Sci USA* 1994;91:4427-30.
- 6) Billman GE, Kang JX, Leaf A. Prevention of ischemia-induced cardiac sudden death by n-3 polyunsaturated fatty acids in dogs. *Lipids* 1997;32:1161-8.
- 7) Leaf A, Xiao YF. The modulation of ionic currents in excitable tissues by n-3 polyunsaturated fatty acids. *J Membr Biol* 2001;184:263-71.
- 8) Leaf A, Xiao YF, Kang JX, Billman GE. Membrane effects of the n-3 fish oil fatty acids, which prevent fatal ventricular arrhythmias. *J Membr Biol* 2005;206:129-39.
- 9) Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995;274:1363-7.
- 10) Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and decreased risk of sudden cardiac death. *JAMA* 1998;279:23-8.
- 11) Albert CM, Campos H, Stampfer MJ, et al. Blood long-chain n-3 fatty acids and risk of sudden death. *N Engl J Med* 2002;346:1113-8.
- 12) Mozaffarian D, Lemaitre RN, Kuller LH, et al. Cardiac benefits of fish consumption may depend on the type of fish meal consumed. The Cardiovascular Health Study. *Circulation* 2003;107:1372-7.
- 13) Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757-61.
- 14) GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447-55.
- 15) Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subject subjects by fish oil n-3 fatty acid intake. *Circulation* 2005;112:2762-8.
- 16) Raitt MH, Conner WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators. A randomized controlled trial. *JAMA* 2005;293:2884-91.
- 17) Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation* 1999;99:2452-7.
- 18) Kang JX, Leaf A. Effects of long-chain polyunsaturated fatty acids on the contraction of neonatal rat cardiac myocytes. *Proc Natl Acad Sci USA* 1994;91:9886-90.
- 19) Kang JX, Xiao YF, Leaf A. Free long-chain polyunsaturated fatty acids reduce membrane electrical excitability in neonatal rat cardiac myocytes. *Proc Natl Acad Sci USA* 1995;92:3997-4001.
- 20) Marchioli R, Barzi F, Bomba E, et al. 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. *Circulation* 2002;105:1897-1903.
- 21) Macchia A, Levantesi G, Franzosi MG, et al. Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids. *Eur J Heart Fail* 2005;7:904-9.
- 22) Burr ML, Ashfield-Watt PAL, Dunstan FDJ, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003;57:193-200.
- 23) Christensen JH, Riahi S, Schmidt EB, et al. n-3 Fatty acids and ventricular arrhythmias in patients with ischaemic heart disease and implantable cardioverter defibrillators. *Europace* 2005;7:338-44.

Omega-3 Fatty Acids & Ventricular Arrhythmias

Who benefits? Who does not?

 **ProThera**
10439 Double R Blvd.
Reno, NV 89521
1-888-488-2488

Omega-3 Fatty Acids & Ventricular Arrhythmias

Who benefits? Who does not?

Introduction

Over the past 25-years a substantial body of evidence has been developed to show that omega-3 fatty acids alter mammalian cardiac excitability and decrease the risk of ventricular arrhythmias and sudden cardiac death.¹⁻⁸ Observational studies in humans have found that consumption of 1-2 fatty fish meals weekly and higher blood levels of long chain omega-3 fatty acids are associated with a reduction in the risk of sudden cardiac death, but not non-fatal myocardial infarction.⁹⁻¹² Two large, controlled clinical trials have shown that fish consumption and fish oil supplementation reduce total cardiovascular disease mortalities and decrease the risk of sudden cardiac death.^{13,14} Studies of fish oil in patients at high-risk for ventricular arrhythmias who have received implantable cardiac defibrillators have yielded conflicting data. One study suggested fish oil may reduce potentially lethal ventricular arrhythmias.¹⁵ A second study not only found no protective benefit, it suggested fish oil may have a proarrhythmic effect especially in patients with ventricular tachycardia.¹⁶ The accumulated evidence suggests that fish oil has heterogeneous anti-arrhythmic properties. Its effects may vary according to the type of arrhythmia, the underlying cardiac disorder if any, amount of dietary fish consumption, and other factors. This review examines the anti-arrhythmic properties of fish oil and critically evaluates the present clinical evidence as to which patients may benefit and who may not benefit from fish oil supplementation.

Omega-3 Fatty Acid Electrophysiology in Animal Models & Tissue Cultures

Early work by Murnaghan using the isolated Ringer-perfused rabbit heart found that long chain saturated and monounsaturated fatty acids potentiated while long chain polyunsaturated fatty acids antagonized hypoxemia-mediated reductions in ventricular arrhythmia threshold.¹ McLennan and co-workers demonstrated that dietary fish oil over a period of months modified myocardial vulnerability to arrhythmic stimuli during coronary occlusion and reperfusion reducing the incidence and severity of ventricular fibrillation in rats^{2,3} and marmosets.⁴ Billman and colleagues evaluated the anti-arrhythmic properties of fish oil using a highly reproducible dog model of lethal ischemic arrhythmias involving coronary artery occlusions. They found that intravenous infusions of fish oil emulsion with either 65% or 70% free omega-3 fatty acids prevented ischemic-induced ventricular fibrillation in 7 of 8 dogs.⁵ In a similar second experiment, the investigators found that 1 to 10 gram infusions of free omega-3 fatty acids prevented ventricular fibrillation in 10 of 13 dogs tested. The omega-3 fatty acids were not apparently incorporated

into membrane phospholipids. The omega-3 anti-arrhythmic effects were associated with reduced heart rate, shortened action potential duration (QT-interval), prolonged atrioventricular conduction time (P-R interval) and reduced left ventricular systolic pressure.⁶ Follow-up studies by the same investigators found that eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha-linolenic acid all had similar anti-arrhythmic properties.¹⁷

Using a cultured neonatal rat cardiomyocyte preparation, Leaf and coworkers found that EPA slowed the rate of spontaneous contraction without diminishing the force of contraction.¹⁸ They also found that EPA prevented arrhythmias expected when toxic concentrations of calcium or ouabain were added to the culture medium. EPA and DHA were both found to reduce sarcolemmal excitability by 50%.¹⁹ Subsequent work by these investigators⁷ has demonstrated that omega-3 fatty acids:

- Inhibit fast-voltage-dependant sodium current (I_{NA}) in a concentration dependant manner;
- Stabilize the inactive state of the I_{NA} channel;
- Accelerate I_{NA} channel transition from a resting to an inactive state;
- Prolong the effective refractory period;
- Inhibit the voltage-gated L-type calcium current & sarcoplasmic reticulum calcium release in a reversible concentration-dependant manner;
- Prevent cytosolic calcium overload;
- Inhibit repolarizing outward potassium current I_{to} , fast outward potassium current & delayed-rectifier current;
- Activate inward potassium current; and
- Stabilize myocyte resting membrane potential.

Omega-3 Fatty Acids & Prevention of Arrhythmias after Myocardial Infarction

Two large prospective, randomized, controlled clinical trials have suggested anti-arrhythmic properties of omega-3 fatty acids in dietary fish or fish oil supplements have significant beneficial effects on outcomes following acute myocardial infarction. The Diet and Reinfarction Trial (DART) randomized 2033 men to receive or not receive dietary advice on reduced fat intake, increased fish intake and increased fiber intake. Subjects intolerant of increased fish consumption were asked to take fish oil.¹³ DART found that after 2 years, modest fish intake (300 g/wk) or fish oil significantly reduced the risk of death by 29%

compared to the mortality rate in subjects not given dietary fish advice. The absolute risk reduction was 3.5%. The decreased total mortality rate was almost entirely due to a 32.5% decrease in the risk of death from ischemic heart disease. Fish or fish oil consumption had no effect on the incidence of non-fatal myocardial infarction. The reduction in total and ischemic heart disease mortalities without an effect on rates of recurrent myocardial infarction has been interpreted to indicate that fish oil reduces mortality by decreasing the incidence of arrhythmia-mediated sudden cardiac death.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione (GISSI-Prevenzione) is the largest trial to date assessing the effect of long chain omega-3 fatty acids on outcomes following acute myocardial infarction.¹⁴ GISSI-Prevenzione randomized 11,324 patients to 1 gram fish oil containing 570-588 mg of DHA and 280-294 mg of EPA as ethyl esters, 300 milligrams vitamin E, both or neither. After 3.5 years of follow-up, fish oil reduced all cause mortality by 20.2% (2.1% absolute risk reduction). Cardiovascular death was reduced by 30% (2% absolute risk reduction). Sudden cardiac death was decreased by 45% (1.6% absolute risk reduction). Time-course reanalysis of the original GISSI-Prevenzione data found that fish oil imparted an early benefit with a 41% reduction in total mortality by 3 months and a 53% reduction in the risk of sudden death by 4 months.²⁰ Subgroup analysis found that fish oil particularly benefited patients with reduced left ventricular ejection fractions.²¹ As with DART, the findings from GISSI-Prevenzione suggest that the greatest cardiac benefits to fish oil lie with its anti-arrhythmic properties.

Omega-3 Fatty Acids & Chronic Stable Angina Pectoris

A single study conducted by the DART principal investigator and colleagues assessed the long-term effect of increased dietary fish or fish oil intake on outcomes in patients with chronic stable angina pectoris.²² After 3 to 9 years of follow-up, mortality was 26% greater in people assigned to increased fish intake. The risk of sudden death was increased by 54%. The excess risk was largely among subjects given fish oil. The increase in mortality was confined to the second phase of the trial. An analysis of the data to evaluate the possibility of an interaction between fish oil and medications found that fish oil interacted favorably with beta-blockers to reduce the risk of sudden death. No adverse fish oil-medication interactions were apparent. The authors speculate that fish oil intake may have been associated with an increase in risk-taking behavior although the reasons for the observed increase in mortality with fish oil in this population are entirely unclear.

Omega-3 Fatty Acids & High Risk Patients with Implantable Cardiac Defibrillators

Christensen and co-workers evaluated the relation between serum omega-3 fatty acids and the incidence of ventricular arrhythmias over a 12-month period in patients with an implantable cardiac defibrillator (ICD).²³ They found that patients with low serum omega-3 fatty acid levels had a higher incidence of ventricular arrhythmias compared to patients with higher serum omega-3 fatty acid levels.

Leaf and co-investigators randomized 402 patients (78% with coronary artery disease) with ICDs to either 4 grams daily of fish oil (2.6 grams EPA plus DHA) or olive oil.¹⁵ The primary end point was time to first ICD event for ventricular tachycardia or fibrillation (VT or VF). Fish oil prolonged the time to first ICD event by 28%, but this failed to reach significance ($p=0.057$). When probable episodes of VT and VF were included in the analysis the beneficial affect of fish oil became statistically significant. A high proportion (35%) of subject's did not comply with consuming either the fish oil or olive oil. When on-treatment analysis was confined to subjects compliant for at least 11 months, fish oil significantly prolonged the time to first ICD event by 38%. When multivariant analysis was performed adjusting for multiple variables, fish oil reduced the risk of an ICD event for VT or VF by a highly significant 48%. The study suggested that regular consumption of fish oil may reduce the risk of potentially fatal ventricular arrhythmias.

In contrast, a trial by Raitt and co-workers found that omega-3 fatty acids in fish oil may be proarrhythmic in patients with ICDs.¹⁶ These investigators randomized 200 patients (73% with coronary artery disease) with ICDs to either 1.8 grams daily of fish oil or olive oil. The primary end point was time to first ICD treatment for VT or VF. At 6, 12 and 24 months, more patients receiving fish oil had ICD therapy for VT or VF than did patients randomized to placebo. The difference was not statistically significant, but the trend was clear. In subjects whose ICD qualifying arrhythmia was VT, fish oil was associated with a significant increase in recurrent VT or VF events suggesting that omega-3 fatty acids may have proarrhythmic properties in this patient subset.

Summary

Omega-3 fatty acids have clear, unequivocal anti-arrhythmic properties. Animal models suggest that omega-3 anti-arrhythmic activities are most pronounced in the setting of acute ischemia and reperfusion. Human interventional trials have found that fish oil reduces mortality and sudden death in patients following acute myocardial infarction. However, in patients with chronic ischemic heart disease manifested by angina pectoris, fish oil has been found in one unblinded study to increase the risk of sudden death. The situation is murkier in patients with ICDs at high risk for sudden death due to ventricular arrhythmia. The