Chapter from the book *Cardiac Defibrillation - Prediction, Prevention and Management of Cardiovascular Arrhythmic Events*

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ICDs in Clinical Trials: Assessment of the Effects of Omega-3 Polyunsaturated Fatty Acids from Fish Oils on Ventricular Tachycardia and Ventricular Fibrillation

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1. Introduction

In its most recent assessment, the American Heart Association (AHA) estimated that in the United States alone there were 5.8 million people with heart failure (HF) in 2006 (Lloyd-Jones, Adams et al. 2010). HF is further estimated to be affecting 23 million people worldwide (McMurray, Petrie et al. 1998). Sudden cardiac death (SCD) is the cause of 28-68\% of all mortalities in heart failure patients, the majority of which is due to ventricular tachycardia (VT) or ventricular fibrillation (VF) (Engelstein ED 1998). Implanted cardioverter-defibrillators (ICDs) have been used for nearly 30 years to effectively stop VT or VF, thereby significantly improving sudden cardiac arrhythmic death outcomes in high risk patients (DiMarco 2003). Despite the major success of ICDs, implanted patients continue to experience VT and VF episodes and a range of possible side effects that make it desirable to use ICDs only in situations where necessary.

Anti-arrhythmic drugs are used to reduce the frequency of ventricular arrhythmias in patients with frequent ICD shock. They reduce the ventricular rate of VT so that there is better hemodynamic tolerance and more responsiveness to termination by anti-tachycardia pacing or low energy cardioversion. These drugs also suppress other arrhythmias that cause symptoms or interfere with ICD function and cause “inappropriate” shocks (which may
occur in up to 29 percent of ICD patients with substantial impact on their quality of life) (Knilans and Prystowsky 1992; Steinberg, Martins et al. 2001). These "inappropriate" shocks are caused by a variety of arrhythmias including sinus tachycardia, atrial fibrillation, and nonsustained ventricular tachycardia (Pacifico, Hohnloser et al. 1999; Nanthakumar, Paquette et al. 2000). However, anti-arrhythmic drugs are not always well tolerated.

Ultimately, ICD patients are expected to have further arrhythmic episodes and experience ICD shocks which, along with the risks of discharge and "inappropriate" shock, can significantly and adversely affect the patients’ quality of life. Therefore, it is essential to find ways to prevent recurrent episodes of arrhythmias that lead to VT and VF.

Since the first observation of low risk of cardiac death in the study of Greenland Eskimos (Kromann and Green 1980) with high intakes of Omega-3 polyunsaturated fats (PUFAs) from sea mammals and fish, Omega-3 PUFAs have been suggested to have potential beneficial anti-arrhythmic properties (Burr, Fehily et al. 1989; Armstrong, Wieland et al. 1994) and hence have been considered for the treatment of high risk patients with arrhythmias (especially those at immediate risk, i.e. VT/VF patients). ICD patients, are high risk individuals and have been of particular interest in clinical trials investigating the effects of PUFAs on ventricular arrhythmias. Because ICDs are capable of terminating arrhythmias and recording their occurrence and their specific types, the risk of mortality is greatly reduced and the end point which might have resulted in death is averted. Therefore, such studies also have the potential to allow for a crossover design (Leaf, Albert et al. 2005; Raitt, Connor et al. 2005; Brouwer, Zock et al. 2006).

But, are Omega-3 PUFAs an appropriate, effective, and sustainable treatment for averting VT and VF?

Randomized controlled trials in ICD patients have produced powerful and illuminating data regarding the role of this dietary supplement and could potentially have much to offer for other dietary and lifestyle intervention trials.

2. Ventricular fibrillation and fish

Sustained ventricular arrhythmias, which include VT and VF, are the most common cause of sudden cardiac death (SCD) and are hence considered the most relevant endpoint in regards to the harder SCD endpoint when assessing their occurrence using ICDs (Engelstein ED 1998).

Over the last 6 years, 3 double-blind, placebo controlled, randomized studies have been published that used fish oils in patients with ICDs to observe time to first ventricular arrhythmia event post ICD implantation (Leaf, Albert et al. 2005; Raitt, Connor et al. 2005; Brouwer, Zock et al. 2006). None of these trials successfully demonstrated whether or not Omega-3 PUFA supplementation has any preventive effects in ICD patients. These studies were first summarized in a meta-analysis by Jenkins et al. (Figure 1) in which they showed a small non-significant overall effect with a relative risk of 0.93 [95% CI, 0.70-1.24] when comparing the incidence of first ICD discharge in Omega-3 PUFA supplementation versus the placebo (Jenkins, Josse et al. 2008).

Another meta-analysis in the following year confirmed the original findings of Jenkins et al. Bouwer et al. showed a non-significant beneficial effect from fish oil in terms of ventricular tachyarrhythmias or death when compared to a placebo (Hazard ratio (HR) of 0.90 [95% CI; 0.67-1.22]) (Brouwer, Raitt et al. 2009). In their sub group analyses, Brouwer and colleagues showed that the potential beneficial role of fish oils in ventricular arrhythmias was non-significant across all subject types: the HR for fish oils vs. placebo in patients with an
ejection fraction (EF) ≤30 was 0.80 [95% CI 0.58-1.12]. In patients with established coronary artery disease at baseline, the HR was 0.79 [95% CI 0.6-1.06]. Lastly, in patients with an EF>30 the risk was actually increased, though not significantly, with an HR of 1.18 [95% CI 0.64-2.18].

Moreover, with further data available to them as the original authors of two of the published studies (Brouwer and Raitt); they were also able to pool their data to perform more subgroup analyses that showed a range of deleterious outcomes in various subject types (Figure 2). Most notably, Brouwer et al. showed significantly higher risk of ventricular tachyarrhythmia in patients who used fish oils and were also on lipid-lowering medications with an adjusted HR of 1.48 [95% CI 1.01-2.18].

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**Fig. 1.** Meta-analysis of implantable cardioverter defibrillator discharge in studies of fish-oil supplementation. Adapted from Jenkins et al., CMAJ 2008 (Jenkins, Josse et al. 2008).

<table>
<thead>
<tr>
<th>Study Name</th>
<th>No. of Events</th>
<th>Relative Risk (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf et al., 2005</td>
<td>57/200</td>
<td>0.74 (0.56-0.98)</td>
<td>33.12</td>
</tr>
<tr>
<td>Raith et al., 2006</td>
<td>51/100</td>
<td>1.24 (0.92-1.69)</td>
<td>31.33</td>
</tr>
<tr>
<td>Brouwer et al., 2005</td>
<td>81/273</td>
<td>0.90 (0.70-1.15)</td>
<td>35.55</td>
</tr>
<tr>
<td>Overall</td>
<td>P=67.9%</td>
<td>0.93 (0.70-1.24)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

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**Fig. 2.** Hazard ratios of fish oil treatment for time to first ventricular tachyarrhythmia in the pooled analyses (Raitt, Connor et al. 2005; Brouwer, Zock et al. 2006) in the entire study population (primary analysis) and subgroups (subgroup analyses). Adjustments were made for age, gender, ejection fraction, smoking status, New York Heart Association class for angina pectoris, New York Heart Association class for dyspnoea, valvular heart disease, prior myocardial infarction, cardiomyopathy, ventricular tachycardia as index arrhythmia, ventricular fibrillation as index arrhythmia, and use of anti-arrhythmic medication at baseline. Adapted from: Brouwer et al., European Heart Journal 2009 (Brouwer, Raitt et al. 2009).
3. Atrial fibrillation and fish

Although VT and VF are the major concerns with regards to ICD patients, they are not the only arrhythmias; for long considered a benign and inconsequential type of arrhythmia, Atrial Fibrillation (AF) is now becoming a large concern globally. It is the most common arrhythmia in clinical practice, resulting in approximately 1/3 of admissions due to cardiac rhythm disturbances. In 1996/1997 alone, the ATRIA investigators estimated 2.3 million North Americans to have AF (Go, Hylek et al. 2001). Friberg et al. also illustrated that hospital admissions due to AF increased 66% between the late 1970s and late 1990s and continue to rise (Friberg, Buch et al. 2003).

More recently, AF has also been implicated as an independent predictor of VT/VF incidence in ICD patients. Stein et al. showed that ICD patients with AF had a multi-variate adjusted HR of 1.89 [95% CI 1.33-2.69] for VT/VF occurrence in the first year after implantation (Stein, Mittal et al. 2009). Similar findings were also produced by other previous trials, including the PROFIT and the 'JEWEL-AF-study' (Stein, Euler et al. 2002; Klein, Lissel et al. 2006). Fish oils have therefore been proposed as effective in the treatment and prevention of AF. It is hypothesized that Omega-3 PUFAs preserve normal electrophysiological function (Richardson, Iaizzo et al. 2011). Despite postulated mechanisms, a recent meta-analysis suggests that there is much heterogeneity in the current literature and complexity of AF pathology. Therefore, these PUFAs require further studies prior to solidly claiming their place as a potential therapy. Liu et al. demonstrated that Omega-3 PUFA intake was not significantly associated with a reduction in AF episodes (an odds ratio (OR) of 0.81 [95%CI, 0.57-1.15] for AF incidence) in patients with established heart disease, such as those who have had a coronary artery bypass graft (CABG), persistent AF, or open heart surgery (Liu, Korantzopoulos et al. 2011). In an editorial in the same publication (Liu, Korantzopoulos et al. 2011), Drs. Ramadeen and Dorian elaborated on the reasons why this meta-analysis did not show the anticipated outcomes that were observed in the animal studies (Ramadeen and Dorian 2011; Richardson, Iaizzo et al. 2011). Dorian et al. discussed the mechanisms by which Omega-3 PUFAs can be potentially beneficial may not in fact be due to their antiarrhythmic properties (Ramadeen and Dorian 2011) which in other trials have also been questioned since in some, Omega-3 PUFAs showed pro-arrhythmic activity (Raitt, Connor et al. 2005), but rather due to preventing structural remodelling and fibrosis through their anti-inflammatory properties (Ramadeen, Laurent et al. 2010; Saravanan, Davidson et al. 2010). However, for Omega-3 PUFAs to have any potential efficacy in patients with arrhythmias, their use must be established long before the disease progresses into longer episodes of AF (persistent and permanent). Thus, those with existing heart disease may experience no benefit.

4. Fish oils as the solution

It can be said with absolute certainty that the collapse of our fish stocks due to overfishing is inevitable at the current rate of consumption. Global catches have been declining since the late 1980s (Figure 3A) (Watson and Pauly 2001), and the number of collapsed stocks has been increasing exponentially since 1950 (Figure 3B) (Worm, Barbier et al. 2006; Costello, Gaines et al. 2008). The number and rate of extinctions of marine populations have increased catastrophically and will continue. When projected forward these data indicate a complete collapse of commercially exploited stocks by 2050 (Pauly, Alder et al. 2003; Worm, Barbier et al. 2006).
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Fig. 3. Global Fishery Trends. (A) Global catch trends from 1950 to 2000, corrected for overreporting by China (Watson and Pauly 2001). (B) Stock collapse: Decline to 10% of their respective historic maximum yield in fish whose stocks have been exploited (n < 10 000; in 64 large marine ecosystems) (RFAD-2007; Worm, Barbier et al. 2006; Costello, Gaines et al. 2008). Adapted from Jenkins et al., CMAJ 2009 (Jenkins, Sievenpiper et al. 2009).

The current data on ICD patients in the three trials summarized first by the Jenkins et al. meta-analysis in 2008 and further investigated by the Brouwer et al. meta-analysis in 2009, certainly ascertains the uncertainty of the benefits of fish oils in this population of patients with heart disease (Jenkins, Josse et al. 2008; Brouwer, Raitt et al. 2009). Brower et al., further elaborates on the potential harms of Omega-3 PUFAs from fish in this population of ICD users, from the population of the combined studies of Raitt et al. and Brouwer et al. (Raitt, Connor et al. 2005; Brouwer, Zock et al. 2006; Brouwer, Raitt et al. 2009).

In regards to fish oil benefits for AF prevention, studies show variable results and are overall inconclusive (Liu, Korantzopoulos et al. 2011). Despite the proposed 2.5-fold increase by 2050 in AF prevalence (Go, Hylek et al. 2001), the lack of certainty on the therapeutic role of fish oils contrasts with the certainty that increased fish consumption will simply shorten the survival of fish stocks with little or no human health benefit. Therefore, continuing to advocate fish consumption to confer health benefits may at present be inappropriate.

5. Conclusion

In conclusion, Omega-3 PUFAs may have some potential beneficial effects in heart disease, likely not because of having potential anti-arrhythmic effects, as was long postulated, but possibly through their anti-inflammatory properties that may in the long term prevent structural remodelling, and damage to the electrical conduction pathways of the myocardium provided it is initiated before structural remodelling begins (Ramadeen and Dorian 2011). However, Omega-3 PUFAs have not been shown to be effective in ICD studies and may possibly be harmful in preventing VT/VF episodes after remodelling and fibrosis has occurred (Liu, Korantzopoulos et al. 2011; Jenkins, Josse et al. 2008; Brouwer, Raitt et al. 2009).

To gamble the existence of our planet’s fish stocks (Jenkins, Sievenpiper et al. 2009) on inconclusive data instead of using lifestyle modifications and appropriate pharmaceutical
treatments, that can be as beneficial, is not responsible, both for patients and planetary health. It is therefore important to consider the use of other sustainable sources of Omega-3 PUFAs, such as the recently developed algal sources by Martek and DuPont pharmaceutical companies (Arterburn, Oken et al. 2008; Surette 2008), for future exploration of their potential benefits in heart disease as well as other diseases.

Lastly, ICDs in randomized controlled clinical trials have certainly shown their merit in assessing the different potential benefits or harms of various treatments, since the discharge of implantable cardioverter defibrillators can be used as a surrogate marker for sudden death while avoiding death. For example, in the case of fish oils the larger compiled data from the Brouwer et al. meta-analysis quite clearly demonstrated some of the unexpected harmful effects of high fish oil intake in ICD patients on statin therapy (Brouwer, Raitt et al. 2009). Ergo, future larger trials with other detailed measurements, including diet and lifestyle data, can be used to assess further outcomes and help address controversial questions that will form the basis of future guidelines.

6. Disclosure

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Laura Chiavaroli holds a casual Clinical Research Coordinator position at Glycemic Index Laboratories, Toronto, CANADA.
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7. References


Ramadeen, A. and P. Dorian "Omega-3 polyunsaturated fatty acids: food or medicine?" *Heart* 97(13): 1032-3.


Millions of people throughout the world currently depend on appropriate, timely shocks from implantable cardioverter defibrillators (ICDs) to avoid sudden death due to cardiovascular malfunctions. Therefore, information regarding the use, applications, and clinical relevance of ICDs is imperative for expanding the body of knowledge used to prevent and manage fatal cardiovascular behavior. As such, the apt and timely research contained in this book will prove both relevant to current ICD usage and valuable in helping advance ICD technology. This book is divided into three comprehensive sections in order to cover several areas of ICD research. The first section introduces defibrillator technology, discusses determinants for successful defibrillation, and explores assessments of patients who receive defibrillation. The next section talks about predicting, preventing, and managing near catastrophic cardiovascular events, and research presented in the final section examine special cases in ICD patients and explore information that can be learned through clinical trial examinations of patients with defibrillators. Each chapter of this book will help answer critical questions about ICDs.

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