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Effect of supplemented intake of omega-3 fatty acids on arrhythmias in patients with ICD: fish oil therapy may reduce ventricular arrhythmia

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Abstract
Purpose The aim of this study was to evaluate the effects of fish oils, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on ventricular tachyarrhythmic episodes (VTEs) in implantable cardioverter defibrillator (ICD) recipients with ischemic cardiomyopathy.
Methods One hundred five ICD recipients with ischemic cardiomyopathy received 3.6 g of EPA and DHA and placebo for 6 months, each at a random order, with a 4-month washout period between treatments. Eighty-seven patients completed the 16-month study protocol. The primary end point was any VTE (including sustained and non-sustained ventricular tachycardias at a rate of >150 bpm) as recorded by the ICDs. Secondary end points included device therapy (anti-tachycardia pacing (ATP) or shocks).
Results During treatment with fish oils, there was a significant increase in EPA and DHA concentrations in red blood cells (RBCs) and subcutaneous fat tissue. Among 87 patients who completed the study protocol, the mean number of VTEs was significantly lower during treatment with fish oil (1.7) vs. placebo (5.6; p = 0.035). Appropriate device therapy for VTE occurred in 18 (21%) patients. Fish oil therapy was associated with a trend toward fewer VTEs terminated with ATP (2.8 ± 13.7 vs. 0.5 ± 2.1, respectively; p = 0.077). VTE terminated by ICD shocks, however, was rare, and rates were similar between both groups (0.11 ± 0.6 vs. 0.10 ± 0.4, p = not significant, respectively).
Conclusions Our data suggest that fish oil therapy may be associated with a reduction in the frequency of VTE in ICD recipients with ischemic cardiomyopathy.

Keywords Fish oils · Omega-3 polyunsaturated fatty acids (PUFAs) · Eicosapentaenoic acid (EPA) · Docosahexaenoic acid (DHA) · Ventricular tachycardia (VT)

1 Introduction

Numerous epidemiological studies, case-control studies, and clinical randomized trials have demonstrated the effects of fish oil or omega-3 polyunsaturated fatty acids (PUFAs) (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) on major cardiovascular events [1–5], particularly those related to sudden cardiac death as well as all-cause mortality in patients with prior myocardial infarction [6]. Possible mechanisms have been proposed including improvement in endothelial [7] and vascular functions [8] and their hypolipidemic properties [9–11]. Anti-inflammatory effects [12–14], decrease in blood pressure [15], anti-aggregant effects [16, 17], and possible plaque-stabilizing effects [18] were also suggested. However, the most established mechanism is related to their anti-arrhythmic effects [19–21].

However, despite numerous experimental and animal model studies published over the years, supporting the beneficial electrophysiological cardiac effects of PUFAs [22–25], results are still conflicting [26–28].

As implantable cardioverter defibrillators (ICDs) offer the opportunity to monitor arrhythmic events, we sought to further investigate whether omega-3 PUFAs exert an effect on

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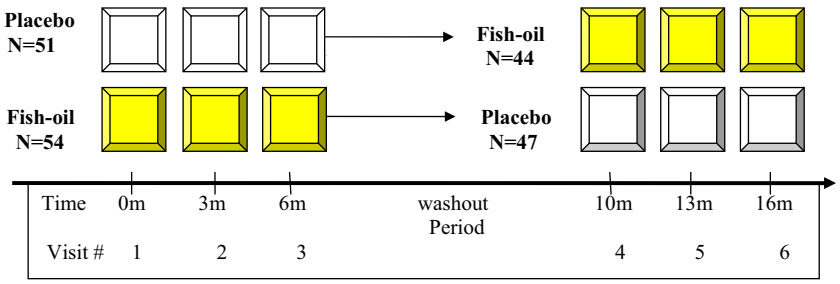


Fig. 1 Study design

ventricular tachyarrhythmic episodes (VTEs) in ICD recipients with ischemic cardiomyopathy.

2 Methods

We performed a double-blind crossover placebo-controlled study to evaluate the effects of oral supplementation of omega-3 fatty acids (EPA and DHA) on the occurrence of VTEs in ICD recipients with ischemic cardiomyopathy (trial registration site: SHEBA-04-3494-DL-CTIL; registration number: NCT00290056).

3 Patients

Nine hundred fifty ICD patients' medical charts were screened in two participating medical centers in Israel, and 420 patients were found eligible to participate in the study. While 315 of them refused to participate, 105 patients were enrolled to the study from November 2005 to July 2008. Study participants had ICD of various brands (Medtronic, Biotronik, Boston Scientific, St. Jude).

4 Study design (Fig. 1)

Eligible patients received 3.6 g of EPA and DHA fish oils or placebo for a 6-month period each, with a 4-month washout period between treatments, at a random order of treatments. The active gel capsule consisted of 400-mg EPA, 200-mg DHA, 40-mg oleic acid, 2-mg tocopherol-vitamin E as an anti-oxidant, and 3–30 mg of other omega-3 fatty acids. Each capsule provided 1 g of fat and 10 cal. All patients were instructed to take six capsules per day for the entire intervention period. The placebo gel capsules contained half sunflower oil and half corn oil. Fish oil and placebo capsules were identical in size and taste. Capsules were provided, packed, and randomized by Altman Taam-Teva Company which had no role in any aspect of the study design.

All participants and electrophysiologists who took care of patients were blinded to treatment throughout the two treatment periods. Patients visited the ICD clinic at baseline and at scheduled visits (3, 6, 10, 13, and 16 months). At each visit, the ICD was interrogated and the data were analyzed and recorded together with additional clinical data, medication use, and adverse events in a customized form. At the time of regular follow-up visits or following patient-perceived ICD therapy, all stored electrograms were collected and adjudicated separately by two board-certified electrophysiologists. In case of disagreement, a third adjudicator provided a final decision.

Additional data and tests such as food frequency questionnaire, Beck inventory questionnaire, SF-36 quality-of-life questionnaire, blood withdrawal, and subcutaneous fat biopsy were also obtained during the visit times.

5 Blood and subcutaneous fat samples

Blood and subcutaneous fat biopsy samples were obtained only at Sheba Medical Center. The quantification of EPA and DHA concentrations in red blood cells and fat tissue was used as an objective measure of EPA and DHA consumption and absorption in each particular patient before and during participation in the study. Results of blood tests for EPA and DHA were also used to verify adherence to protocol (in addition to capsule count). A sample of superficial subcutaneous adipose tissue, from the mid-lateral abdomen area, was obtained without anesthesia by needle aspiration as described previously [29].

6 Device programming and follow-up

Investigators were discouraged from changing antiarrhythmic therapy and performing radio frequency ablation of ventricular arrhythmia during the study period. Detection criteria for VTE were prespecified for each device in order to maximize the diagnostic capability for the detection of ventricular and atrial arrhythmias. For all devices, VT detection was programmed to a rate of >150 beats per minute for a duration of 10 s. Ventricular fibrillation (VF) was programmed above

200 beats per minute for a duration of 10 s. Discrimination features were turned on in VT zone according to each device's specifications.

7 End points

The primary end point was defined as the detection of any VTE (comprising both sustained and non-sustained arrhythmias) as recorded by the ICD. Secondary end points included appropriate ICD therapies, including anti-tachycardia pacing (ATP) or shock.

8 Statistical analysis

The effect of omega-3 PUFA (EPA and DHA), on the occurrence of cardiac arrhythmic events, was evaluated both on intention-to-treat and on-treatment analysis basis of all patients as randomized. The null hypothesis assumed no differences in the incidence of spontaneously occurring ventricular arrhythmia. Comparison was performed between the 6-month period of supplemented omega-3 PUFA therapy and the 6-month treatment with placebo. We expected to identify at least a 50% difference in the electrophysiological outcomes between the two treatment periods, which we considered as clinically significant. We assumed 30% incidence without intervention and <15% incidence after intervention.

9 Power calculation and sample size considerations

The sample size was based on estimation of 30% incidence of ventricular tachyarrhythmia among ICD recipients, and was adequate to detect a 50% difference in the combined rate of VTEs between the 6-month treatment periods. This estimation was based on a recent trial with 400 ICD recipients (70% primary prevention ICD), where VTEs occurred in approximately 30% of the ICD recipients within 6 months of implant [30].

Accordingly, sample size was increased by 10% in order to minimize the chance of inadequate power due to patient dropout for any reason. Sample size of 100 patients was sufficient to yield a power of 89.6% to obtain a statistically significant result at $\alpha = 0.05$ (two-tailed test). Anthropometric data were summarized using mean and standard deviation. The non-parametric McNemar test was used to compare paired proportions, incorporating mixed modeling that takes into account the number of patients with treated episodes. All statistical analyses were performed using the SPSS software (version 17). A p value of <0.05 was considered significant.

Table 1 Baseline characteristics

Characteristic	Number (%)
Age, mean ± SD	70 ± 9.6
Male	99 (94)
BMI, mean ± SD	27 ± 3.4
Hypertension	39 (37)
Diabetes mellitus	27 (26)
Chronic atrial fibrillation	7 (7)
Paroxysmal atrial fibrillation	17 (17)
Previous cardiac surgery	
s/p CABG	39 (37)
s/p Mitral valve replacement	2 (2)
s/p Aortic valve replacement	1 (1)
Ejection fraction <35%	68 (65)
NYHA functional class	
I	27 (28)
II	53 (54)
III	18 (18)
Not assessed	7 (7)
Medications	
Beta-blocker	89 (85)
Amiodarone	35 (33)
Sotalol	14 (13)
Mexilen	5 (5)
Anti-aggregants	87 (83)
Calcium channel blockers	11 (10)
ICD indication	
History of SCD/VT	53 (51)
Syncope and inducible VT	13 (12)
Prophylactic MADIT I (NSVT in 24-h ECG Holter +EF ≤40% + EPS-inducible VT)	30 (29)
Prophylactic MADIT II (EF ≤35%)	7 (7)
Others	2 (2)
Device type	
Single chamber	14 (13)
Dual chambers	68 (65)
CRT	23 (22)
Time since ICD implantation at study entry in months, mean ± SD, range	37 ± 32, 1–195

BMI body mass index, *CABG* coronary artery bypass graft, *LVEF* left ventricular ejection fraction, *SCD* sudden cardiac death, *VT* ventricular tachycardia, *CRT* cardiac resynchronization therapy

10 Results

10.1 Dropouts, adverse effects, and adherence

One hundred five patients were enrolled into the study. Eighty-seven patients (83%) completed the full study protocol (Table 1). Eighteen patients (17%) dropped out at different times. Of them, two (1.9%) underwent device extraction, three

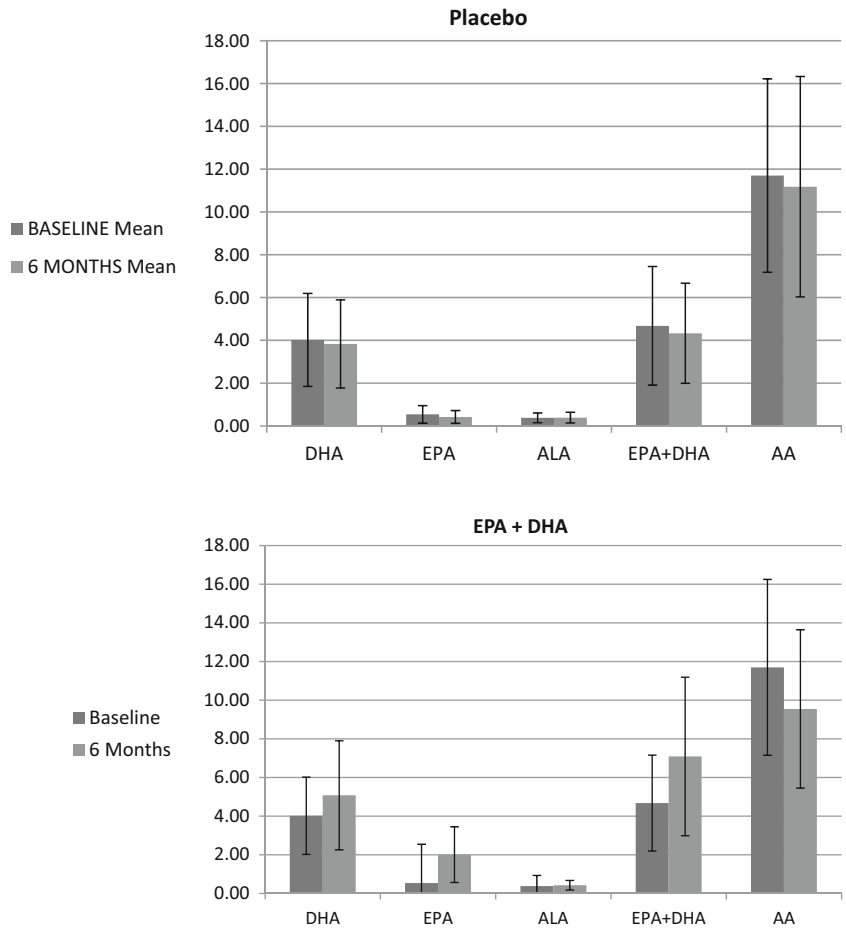


Fig. 2 RBC fatty acid levels at baseline and after 6-month fish oil treatment (% of total fatty acids)

(2.8%) died, and six patients (5.7%) reported minor side effects (gastrointestinal discomfort and skin rash) and decided to quit. Adherence, as assessed by capsule count and fatty acid quantification in RBC and fat depot, was good throughout the study; overall, 74 patients (92%) were estimated to take more than 80% of their capsules.

10.2 Omega-3 PUFA content of RBC and subcutaneous fat tissue

At baseline RBC, PUFA content reflected the typical level of the western population. As expected, EPA, DHA, and alpha-linoleic acid (ALA) concentrations in RBCs changed significantly during the 6-month PUFA treatment: after 6 months of PUFA supplementation, DHA and EPA increased and arachidonic acid (AA) decreased. Mean EPA and DHA concentrations (Omega-3 Index) were 4.18 and 7.09% of total fatty acids prior and after PUFA treatment, respectively ($p < 0.001$) (Fig. 2). During placebo treatment, most fatty acid concentrations did not show any differences. Similarly, we found no concentration change of ALA in response to 6-month PUFA supplementation. This observation is in line with other reports [31, 32].

At baseline, the mean proportion (% of total fatty acids) of fat depot DHA, EPA, ALA, and AA in study participants were 0.38, 0.18, 1.14, and 0.79, respectively (Fig. 3). EPA and DHA but not ALA increased significantly in fat depot after 6 months of EPA + DHA supplementation.

10.3 VTE detections

Among 87 patients who completed the study protocol, a total of 18 (21%) patients experienced appropriate ICD therapies. Mean number of VTE episodes, as detected by ICD interrogations, was significantly lower during treatment with fish oil (5.56 vs. 1.7, $p = 0.035$). Treatment with fish oil was associated with a marginally significant reduction in mean number of VTE episodes terminated with ATP (2.8 ± 13.7 vs. 0.5 ± 2.1, $p = 0.077$). Appropriate ICD shocks, however, were infrequent, and apparently, no difference was found between the groups (0.11 ± 0.6 vs. 0.10 ± 0.4, respectively) (Fig. 4).

Of note, there was no significant interaction between the order of study participation (PUFA vs. placebo) and the reported outcomes.

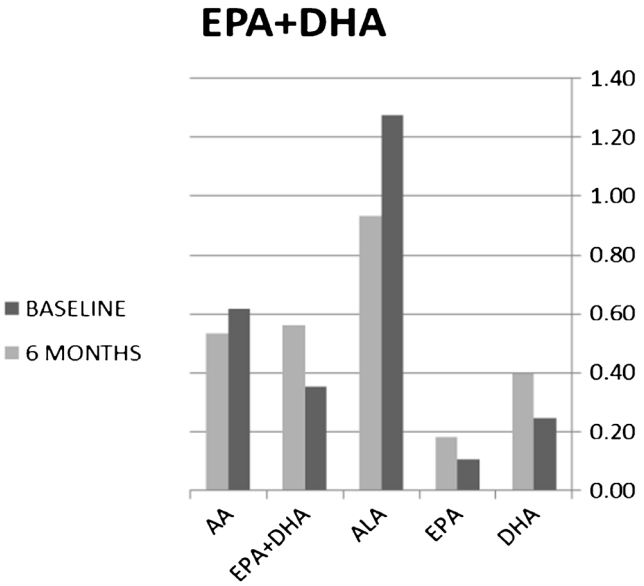


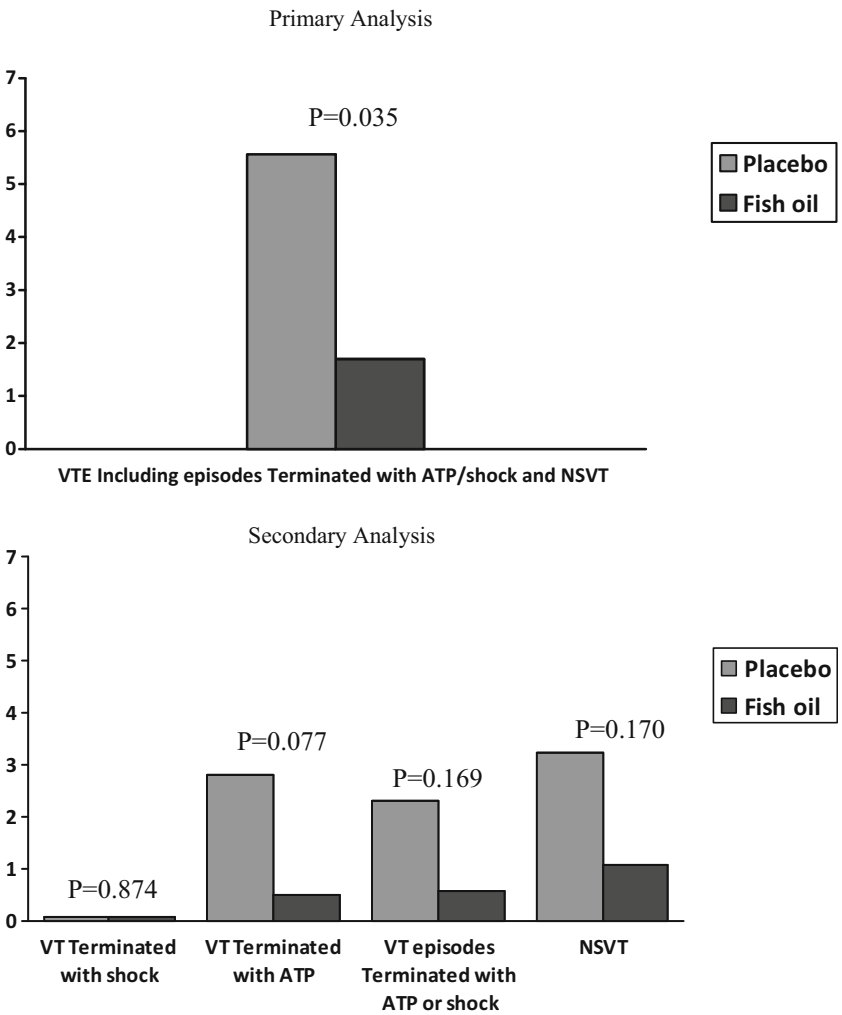
Fig. 3 Subcutaneous adipose fatty acid levels at baseline and after 6-month fish oil treatment (% of total fatty acids)

11 Discussion

This prospective, double-blind crossover study further examined the possible anti-arrhythmic potential of high-dose omega-3 PUFA supplementation, in ICD recipients with ischemic cardiomyopathy. We demonstrated that the 6-month therapy with PUFA was associated with a significant reduction of VTE in this study population. Notably, these results were driven by a reduction in non-sustained ventricular tachycardias (NSVTs) and sustained VTs terminated by ATPs, whereas the reduction in VTs terminated by shock therapy with fish oil therapy was not statistically significant possibly due to the very low rates of ICD shocks during the trial.

These findings are in keeping with a few previous studies that reported reduction in sudden death in post-infarct patients supplemented with fish oil [33, 34] and a tendency toward decreased arrhythmia in patients with established coronary artery disease [35]. Other reports, however, including a recently published meta-analysis, did not support this hypothesis.

Fig. 4 Primary arrhythmia episodes (mean number of episodes)



These differences might be attributed to dissimilarities in studies' populations: while we included only patients with ischemic cardiomyopathy, others included mixed populations of patients. In addition, we used higher dosage of PUFA. The only study that included similar patients, with a majority of patients (79%) suffering of ischemic heart disease and relatively high doses of EPA and DHA supplementation, did report a significant reduction of VTE in post-MI patients [28].

Of note, our study design is different from prior studies (crossover design), comparing fish oil and placebo in the same individual after a washout period. Thus, it offers a better assessment of PUFA's effect on VTE. Additional advantage is attributed to the method that we used to ensure that a patient received an adequate intake of PUFA. We actually demonstrated increased concentrations of EPA and DHA not only in RBC, but also in subcutaneous fat, which directly reflects fatty acid metabolism in adipose tissues [29].

Finally, all randomized trials related to this topic included ICD recipients for secondary prevention, hence patients with previous arrhythmia episodes. In our cohort, more than a third of the patients underwent ICD implantation for primary prevention, based on MADIT/MADIT II indications. This may explain the lower rate of events throughout the study period. We speculate that this cohort may have less established substrate for VTEs and, therefore, may have better response to prophylactic therapy with PUFA.

11.1 Study limitations

Our study has several limitations. The most important is its relatively small sample size and the relatively low event rates. This may obscure the magnitude of potential benefits of fish oil supplementation. Although there were adequate events of VTE (combined sustained and non-sustained), demonstrating significant decrease of arrhythmia attributed to PUFA, it was mainly driven by a decrease in NSVTs and ATP. The significance of NSVT episodes in patients with cardiovascular disease is still questionable, and prior studies showed that suppression of VTE was not correlated with a reduction in sudden death. While several studies reported an association with increased mortality [36–38] and ICD therapies [39], others showed no effects [40–42]. Furthermore, the event rates of ICD therapies due to sustained VT or VF during this study were lower than expected, suggesting that the study was underpowered to make any statements regarding the effects of PUFA on neither ICD therapies nor sudden death. Our data collection is based on device interrogation, and there could be VTEs not recorded by the device and not included in our analysis; however, since all patients had similar device programming, we do not believe that it can affect our conclusion. Finally, loss of data due to early termination and exclusion of subjects who did not complete the full study protocol is a recognized disadvantage of a crossover study setting in ICD trials compared with parallel trials [43]. In this study, 17% of the patients failed to complete the protocol for various reasons. We partially compensated for this weakness by increasing in advance the number of patients in the trial by 10% above calculated number.

12 Conclusions

This prospective randomized crossover study demonstrates a protective effect of omega-3 EPA and DHA therapy on VTEs in ICD recipients with ischemic cardiomyopathy. Significant increase of PUFA tissue concentration during intervention period was confirmed by adipose biopsy and RBC analysis. Possible anti-arrhythmic effects of PUFA supplementation need to be further validated in larger clinical trials.

Compliance with ethical standards

Ethical statement The study was approved by the ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All persons gave their informed consent prior to their inclusion in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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