SYSTEMATIC REVIEW AND META-ANALYSIS

Received: 13 MAY 2026 | Accepted: 27 JUN 2026 | **DOI:** https://doi.org/10.57849/ulisboa.fm.jscml.0000051.2026

JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

Omega-3 Polyunsaturated Fatty Acids and Ventricular Arrhythmias in Patients with Implanted Cardioverter-Defibrillator: Systematic Review with Meta-analysis

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ABSTRACT: **Background:** Omega-3 polyunsaturated fatty acids (PUFA) are one of the most common supplements taken around the world, due to many beliefs in its positive effect on cardiovascular disease and cardiovascular related death. Nevertheless, despite showing promising results on *in vitro* and *in vivo* animal studies, PUFA's cardiovascular and, more specifically, antiarrhythmic role is still not well established in humans. Patients with implanted cardioverter-defibrillator (ICD) are a subset of individuals at a greater risk of suffering deadly arrythmias, which have a device that can detect, register and intervene in those arrhythmias. We aimed to understand the antiarrhythmic influence of omega-3 PUFA in patients with ICD. **Methods:** In this systematic review we searched randomized controlled trials regarding the arrhythmic effects of omega-3 PUFA supplementation on ICD patients, comparing to either placebo or no intervention at all. Results were pooled using a random effects model and reported using Hazard ratio (HR) with a 95% confidence interval (CI). **Results:** Of the 5 retrieved studies for review, 4 (n=1714) were included in the meta-analysis. Compared to placebo, there was not a significant risk reduction of ventricular arrhythmia or death (HR =0.88, 95% CI 0.71-1.10). The presence or absence of coronary disease as well as the severity of left ventricular systolic dysfunction did not influence the results. However, when excluding the first published study (n=200), a significant risk reduction of ventricular arrhythmias or death was observed with n-3 PUFA on ICD patients (HR 0.80, 95% CI 0.67-0.96; p= 0.014). **Conclusion:** The best available evidence does not support the recommendation of using omega-3 PUFA on ICD patients to reduce death or significant arrhythmias.

KEYWORDS: Fish-oil; Omega-3; n-3; Polyunsaturated fatty acids; PUFA; Eicosapentaenoic acid; EPA; Docosahexaenoic acid; DHA; Sudden cardiac death; SCD; Ventricular arrhythmias; Ventricular tachycardia; Ventricular fibrillation; Implanted Cardioverter-defibrillator; ICD.

BACKGROUND

Omega-3 polyunsaturated fatty acids (PUFA), present in fish oils, have been the target of many studies trying to find specific effects on both cardiovascular (CV) and metabolic systems. A Cochrane systematic review on the role of omega-3 fatty acids, namely long-chain omega 3 (LCn3) and/or alpha-linolenic acid (ALA), on primary and secondary prevention of CV disease, included 86 randomized controlled trials (162,796 participants). It was found little or no effect of increasing LCn3 and ALA on reduction of all-cause mortality and CV mortality. long-chain omega 3 appears to slightly reduce coronary heart disease (CAD) mortality and events, even though ALA showed little to no effect. On the other hand, CV events and arrhythmia seem to have a slight reduction in risk with ALA and little to no effect with increase in LCn3[1].

Some studies regarding the CV effect of these molecules showed a reduction in mortality due to a decrease in fatal arrhythmias rather than other nonfatal CV diseases. Some examples are the DART trial and more recently the GISSI Prevenzione trial. They studied patients with recent myocardial infarction, showing a reduction in all-cause mortality and death from CV causes on the patients, either with a diet containing fish oils or supplemented with n-3 PUFA, respectively. However, they failed to show a reduction in nonfatal myocardial infarctions. This reduction in all-cause mortality seemed to be a result of a major decrease in sudden cardiac death (SCD), reigniting an interest in the potential antiarrhythmic properties of fish oil[2–5]. Nevertheless, the evidence is still inconclusive as for the role of n-3 PUFA, particularly their potential antiarrhythmic benefits[2].

The aim of this review was to evaluate the effects of n-3 PUFA supplementation on the incidence of arrhythmias in patients with Implantable Cardioverter Defibrillators (ICD).

METHODS

This systematic review with meta-analysis was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews[6].

Eligibility criteria

In this systematic review and meta-analysis, we included randomized controlled clinical trials in which dietary supplementation was used to increase n-3 PUFA intake, compared to either placebo or no intervention, in patients with ICD, to assess its effect on ventricular arrhythmias.

Trials were included irrespective of follow-up time, n-3 PUFA supplementation amount or respective serum levels of n-3 PUFA quantification. These eventual differences in study design and subsequent results will be further analysed and described in the results and discussion of this review. The studies had to include patients with ICD irrespective of its implantation indication, duration, comorbidities, age or sex. The intervention had to be dietary supplementation of n-3 PUFA in a form of fish oil or its refined components, such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or alpha-linolenic acid (ALA), irrespective of dose.

Trials were eligible if comparing n-3 PUFA supplementation, of any form, versus a control group comprised of patients with ICD taking either placebo or no intervention at all.

Information sources and search strategy

The bibliographic databases Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions were searched with results from January 2023 and updated in November 2025. The EBM Reviews - Cochrane Central Register of Controlled Trials was also searched for relevant material for inclusion in the review.

The supplementary data regarding the search strategy is further detailed in this review's appendix (*Appendix 1. Search strategy*).

Study selection and data collection

Two reviewers independently screened the titles and abstracts retrieved from the electronic search. Duplicated publications were manually screened and excluded. The articles that met criteria or were unclear were further assessed through full-text analysis. Reasons for study exclusion were recorded in both screening stages.

Subsequently, study characteristics and corresponding outcomes were independently collected into a standardized form. These include the following: author, year of publication, number of participants, population demographics, comorbidities and concurrent medication, follow-up time, patient compliance, daily n-3 supplementation dose, control used, primary endpoint and resulting statistical results.

Study risk of bias assessment

The risk of bias of the included studies was independently assessed by two reviewers using the second version of Cochrane Risk of Bias Tool for randomized controlled trials (RoB-2)[7]. We used the six predefined domains (randomization process; deviations from the intended interventions; missing outcome data; measurement of the outcome; selection of the reported result). An additional domain (risk of bias arising from period and carryover effects) was used to assess the bias of the crossover study using the specific RoB2 tool for crossover randomised controlled trials (RCTs).

Both the domains and overall risk of bias were qualitatively classified as low, some concerns or high risk of bias, in accordance with the respective tools' algorithm.

Statistical analysis

A random-effects meta-analysis was performed based on the data retrieved from four out of the five selected studies. The pooled forest plots and statistic results were obtained using Stata 17.0 software. Since the primary outcome is a time-to-event outcome, hazard ratio (HR) presents as the most suitable form of presenting the results of the intervention at study[8]. These results were presented using 95% confidence intervals (CI).

The heterogeneity was evaluated primarily by visual inspection of forest plots and statistically using the Chi^2 for heterogeneity (threshold P > 0.10) test and I^2. The I^2 statistic indicates the percentage of the considered variability which is due to heterogeneity and not by chance or sampling error. An I^2 value below 40% indicates that heterogeneity may not be important, between 30 and 60% may be moderate, between 50 and 90% may be substantia and above 75% it is considerable. Note that in low numbered studies the Chi^2 for heterogeneity and I^2 statistics may raise some uncertainty in their respective interpretations[9].

Continuing the investigation on heterogeneity between studies and their respective demographic and intervention characteristics differences, both a subgroup analysis and a meta-regression were performed. The subgroup analysis on the primary outcome was performed according to the differences in study population, namely in patients with and without CAD and the lower left ventricular ejection fraction (LVEF) subgroups of each study. The meta-regression was performed according to the differences in each studies' main demographics (age, sex, comorbidities such as CAD, mean LVEF and intervention differences in omega-3 supplementation dosage.

Assessment of confidence in Evidence

The assessment of the certainty in evidence was conducted by two reviewers resorting to the Grading of Recommendations, Assessment, and Evaluation (GRADE) norms[9]. The GRADEpro software was used to generate a summary table of evidence with the corresponding grading of the quality of evidence assessment.

RESULT

Study selection

The databases search resulted in a pool of 336 articles. After manually removing 97 duplicates, 239 studies were screened by their title and abstract. Subsequently 38 studies were selected for full-text assessment. The reasons for exclusion were recorded in both screening stages. At the end of full-text evaluation phase, five randomized controlled trials were included (figure 1).

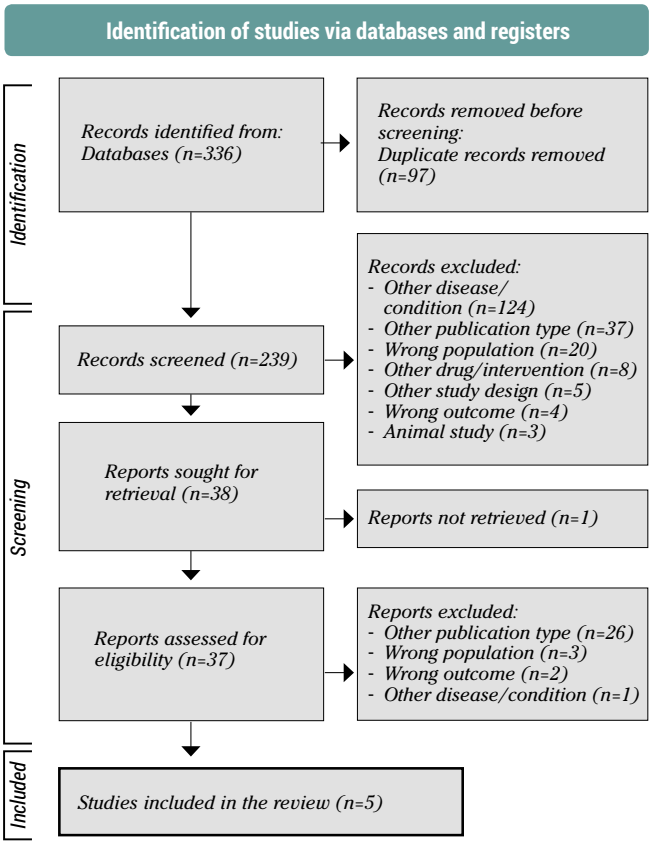


FIGURE 1. Flow diagram of database search, screening and study selection based on PRISMA 2020 flow diagram for new systematic reviews[6]

TABLE 1. Demographic characteristics of included patients.

Authors (Year)	Experimental groups	Participants	Age, yr, mean (SD)	Male sex	White	CAD/IHD	Previous MI	HTN	DM2	Current smoker	NYHA class					Ejection fraction					Medication								
											I	II	III	IV	NA	QM % (*SD*)	<30%	<35%	<40%	≥40%	ACEi	Amd	β-Blocker	CCB	Digoxin	Diuretic	Sotalol	Statin
Raitt et al (2005)[13]	Fish oil	n=100	63 (13)	86	94	75	55	46	24	NR	25	13	48	14	0	36 (16)	46	NR	57	33	66	0	74	9	NR	54	0	54
	Placebo	n=100	62 (13)	86	97	71	56	55	23		28	14	50	8	0	34 (15)	37		56	34	66	0	73	13		52	0	41
Leaf et al (2005)[23]	Fish oil	n=200	65.7 (0.82)	169	191	151	NR	NR	NR	30	47	66	20	0	51	32.9 (1.00)	102	NR	142	45	121	31	132	16	NR	104	23	NR	
	Placebo	n=202	65.3 (0.82)	165	195	163				23	54	75	10	1	45	34.2 (1.05)	99		138	58	114	31	118	15		99	33		
Brouwer et al (2006)[21]	Fish oil	n=273	60.5 (12.8)	231	NR	187	167	143	45	44	23	65	4	0	0	36.9 (15)	87	NR	NR	NR	151	59	145	15	NR	109	21	NR	NR
	Placebo	n=273	62.4 (11.4)	228		197	175	134	42	23	39	47	5	2	0	37.0 (15)	95				160	50	155	13		116	15		
Finzi et al (2011)[22]	Fish oil	n=278	64.9 (9.5)	250	NR	NR	161	113	65	39	0	176	101	1	0	28.1 (6.5)	NR	NR	273	5	209	106	214	12	NR	254	NR	95	
	Placebo	n=288	64.8 (9.8)	250			162	143	77	50	0	186	100	2	0	28.7 (6.9)			283	5	223	98	223	17		270		83	
Weisman et al* (2017)[12]		n=105	0 (9.6)	99	NR	105	NR	39	27	NR	27	53	18	0	7	NR	NA	68	NA	NA	NR	35	89	11	NR	NR	14	NR	83	NR

*Cross-over study with a duration of 6 months per intervention with a 4 month wash out period between Fish oil supplementation and Sunflower oil with corn oil control. **ACEi:** angiotensin converting-enzyme inhibitor; **Amd:** amiodarone; **CAD:** coronary artery disease; **CCB:** calcium-channel blocker; **DM2:** type 2 diabetes mellitus; **HTN:** hypertension; **IHD:** ischemic heart disease; **MI:** myocardial infarction; **NA:** not applicable; **NR:** not reported; **NYHA:** New-York Heart Association; **QM:** quantitative mean; **SD:** standard deviation; **Yr:** year

Study characteristics

Each study's main demographic characteristics are listed below (Table 1). Out of the five selected randomized controlled trials, four are parallel in design and one is a cross-over study. Each study sample size ranged from 105 to 566 patients, with a total, across all studies, of 1819 participants constituted mostly by males. There was also a high prevalence of ischemic heart disease and, to a lesser degree, hypertension. As an indication for ICD, in specific circumstances, heart failure is also well represented and characterized in each study with a reduced mean LVEF across all the four earlier trials. Duration of follow-up ranged from one year to approximately two and a half years in the parallel designed studies and six months per intervention in each arm, with a 4-month washout period, in the cross-over study. Moreover, daily doses of n-3 fatty acids ranged from 0.8 grams to 3.6 grams, with different concentrations of DHA, EPA and other refined components. Olive oil was used as a control in *Raitt et al*[13] and *Leaf et al*[23], whereas sunflower oil was used in *Brouwer et al*[21] and combined with corn oil in *Weisman et al*[12]. Finally, *Finzi et al*[22] used a placebo as control.

The primary end point in the studies of *Raitt et al*[13], *Leaf et al*[23], *Brouwer et al*[21] and *Finzi et al*[22] was time to first ICD intervention, in response to an episode of either Ventricular tachycardia (VT) or Ventricular fibrillation (VF) and all-cause mortality. On the other hand, *Weisman et al*[12] presented its results in number of VT recorded by the ICD and device therapy/shocks as primary and secondary outcomes, respectively. All studies' primary outcomes were performed based on intention to treat analysis. *Leaf et al*[23] also presented an adjusted result for probable ICD interventions (events without an electrogram documentation of ventricular arrhythmia available but which had other data suggesting successful VF/VT termination), corresponding to a significant re-

duction in relative risk (RR) to 0.69 (95% CI 0.49-0.97; p=0.033). We chose to use the unadjusted RR, where only recorded and reviewed episodes were taken into account (RR= 0.72 CI 95%, 0.51-1.01; p=0.057).

The remaining study characteristics and summary of statistical results are further detailed in Table 2.

The risk of bias of the primary outcome (performed based on intention to treat) of every selected study was done using Cochrane's RoB2 tool, as presented in the table below (Table 3). The period and carryover effects domain is only applicable to the cross-over study of *Weisman et al*[12].

TABLE 2. Summary of study characteristics and results.

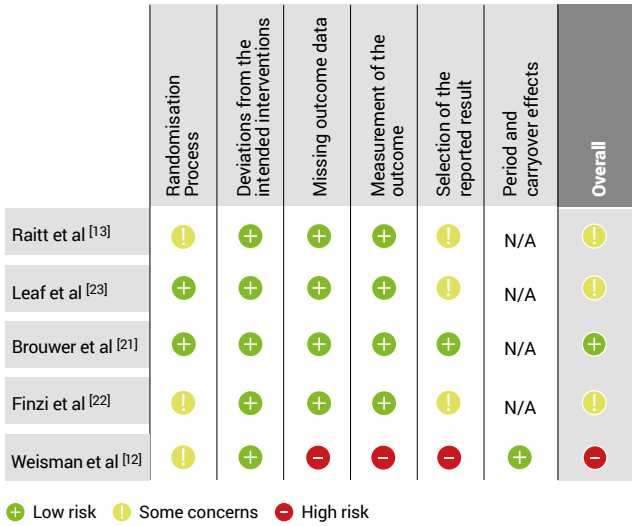
Authors	Experimental groups	Participants	Duration of follow-up, yr	Compliance, No (%)	Daily dose of omega-3 (EPA, DHA and other PUFAs), grams	Control	Primary endopoint	Event rate, %		
								6M	12M	24M
Raitt et al[13]	Fish oil	n=100	2	98 (98)	1.3	Olive oil	Time to 1st episode of VT/VF leading to ICD therapy	46	51	65
	Placebo	n=100		94 (94)				36	41	59
Leaf et al[23]	Fish oil	n=200	1	127 (64)	2.6	Olive oil	Time to first ICD discharge for VT/VF; All-cause mortality	NR	28	NA
	Placebo	n=202		133 (66)					39	
Brouwer et al[21]	Fish oil	n=273	1	244 (89)	0.9	High-oleic sunflower oil	ICD intervention for VT/VF; All-cause mortality	NR	30	NA
	Placebo	n=273		248 (91)					33	
Finzi et al[22]	Fish oil	n=278	2.5	278 (100)	0.8	Placebo	Time to ICD intervention due to VF/VT; No of VT and VF episodes	NA		
	Placebo	n=288		288 (100)						
Weisman et al*[12]	Cross-over study	n=105	0.5	87 (83)	3.6	Sunflower and corn oil	Number of ICD-recorded TV	NA		

*Cross-over study with a duration of 6 months per intervention with a 4 month wash out period between Fish oil supplementation and Sunflower oil with corn oil control.
CI: confidence interval; **DHA:** docosahexaenoic acid; **EPA:** eicosapentaenoic acid; **ICD:** Implantable cardioverter defibrillator; **M:** months; **No:** number; **NR:** Not reported; **PUFA:** Polyunsaturated fatty acids; **VF:** ventricular fibrillation; **VT:** ventricular tachycardia; **Yr:** year

Risk of bias

The overall risk of bias amongst the studies raised some concerns. The 3 studies of *Raitt et al*[13], *Finzi et al*[22] and *Weisman et al*[12] raised some concerns regarding the randomization process domain, due to absent information in the reports regarding the concealment of allocation. Unlike *Brouwer et al*[21], the four studies of *Raitt et al*[13], *Leaf et al*[23], *Finzi et al*[22] and *Weisman et al*[12] did not report a pre-specified analysis plan before the unblinded outcome data was available for analysis, raising some concerns in the selection of the reported results domain. The later presented its results mostly in mean values of each outcome, represented in bar graphs without appropriate listing of each analysis results, and did not present any detailed results regarding any differences between cross-over arms. Therefore, it was classified as a higher risk of bias in the missing data, measurement of outcome and selection of the reported results domains.

TABLE 3. Risk of Bias Analysis using Cochrane Risk of Bias Tool for randomized controlled trials (RoB-2).



N/A: not applicable.

Primary outcome – Time to ICD intervention or death

A meta-analysis was performed with the results pooled from four (*Raitt et al*[13], *Leaf et al*[23], *Brouwer et al*[21], *Finzi et al*[22]) out of the selected five studies for review, as a consequence of *Weisman et al*[12] not reporting the required outcome.

Overall, there was no statistically significant difference in time to first ICD intervention due to VF/TV or all-cause mortality between fish oil and placebo in our 1714 ICD patient meta-analysis (combined HR=0.88, 95% CI 0.71-1.10; overall effect p-value = 0.26). Although not statistically significant (Chi^2 for heterogeneity p=0.13), there was moderate heterogeneity between the four analyzed studies (I^2= 45.45%) (Figure 2).

When performing the meta-analysis omitting successively each of the studies, it was noted a statistically significant difference in time to first ICD intervention, benefiting n-3 supplementation, when excluding the *Raitt et al*[13] trial (HR=0.80, CI 95%; 0.67-0.96; p=0.014). There was no significant deviation from the overall meta-analysis when excluding each one of the other included studies (Figure 3).

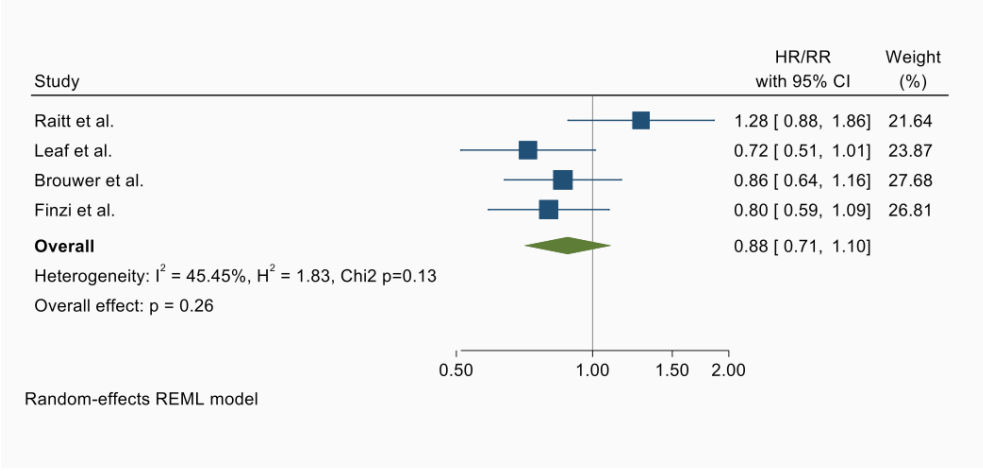


FIGURE 2. Forest plot for time to ICD intervention in ICD patients with omega-3 supplementation.

CI: confidence interval; HR: hazard ratio; RR: relative risk. Raitt et al[13]; Leaf et al[23] ; Brouwer et al[21]; Finzi et al[22] ; Weisman et al[12] .

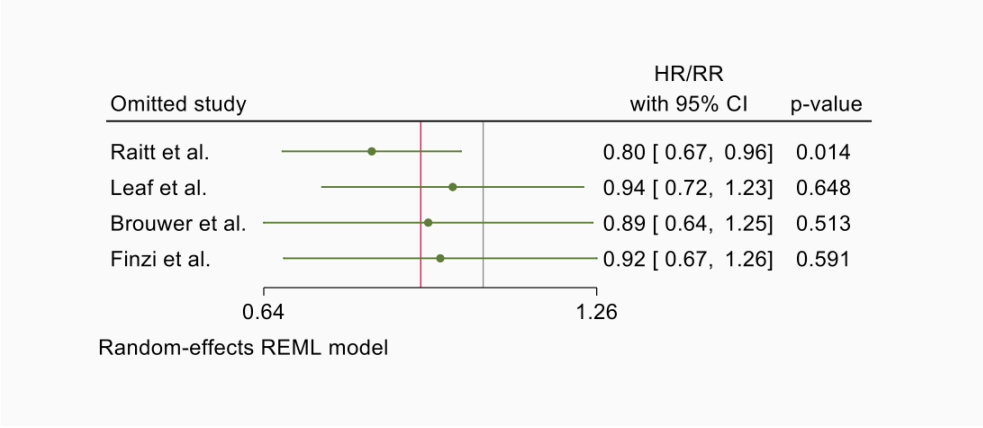


FIGURE 3. Omitted studies analysis.

CI: confidence interval; HR: hazard ratio; RR: relative risk. Raitt et al[13]; Leaf et al[23] ; Brouwer et al[21]; Finzi et al[22] ; Weisman et al[12] .

Subgroup analyses and meta-regression

In respects to the differences in demographics presented by each of the studies, we conducted a subgroup analysis between patients with CAD or its absence and between the subgroups with lower ejection fractions in every trial.

Three of the included studies in the meta-analyses (*Raitt et al*[13], *Leaf et al*[23], *Brouwer et al*[21]) reported the number of patients with CAD included. It was not found any statistically significant difference between fish oil supplementation and placebo in patients with ICD, regarding time to first ICD intervention either in each individual study or in the overall analysis (overall HR=0.92, CI 95%, 0.58-1.44; p value = 0.70) (Figure 4). Although not statistically significant and contrasting with the other studies, *Raitt et al*[13] showed a proarrhythmic effect in patients with CAD taking fish oil supplementation. However, we cannot ignore that in this specific subgroup analysis there is a substantial heterogeneity (I^2=77.45%) between the considered trials (Figure 4).

The absence of CAD and its respective results was only reported in *Raitt et al*[13] and *Leaf et al*[23], each without significant results regarding the beneficial antiarrhythmic effect of n-3 PUFA in patients without CAD. This subgroup analysis resulted in an unsignificant heterogeneity (I^2=0%), which can be the result of few included studies (Figure 4).

Regarding patients with low LVEF, in the Leaf et al[23] trial ICD patients with LVEF lower than 30%, we observed a significant antiarrhythmic benefit in supplementing with omega-3 PUFA over placebo. However, when considering the overall lower LVEF subgroups reported, we did not find a statistically significant difference between the intervention and control groups. Heterogeneity was moderate (I^2=50.34%) (Figure 5).

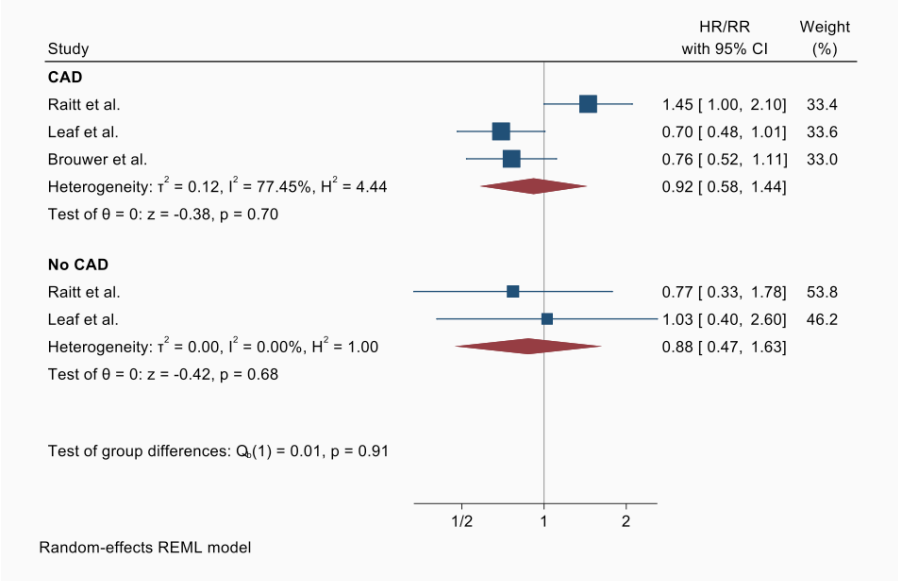


FIGURE 4. Subgroup analysis by presence or absence of coronary artery disease (CAD).

CI: confidence interval; HR: hazard ratio; RR: relative risk. Raitt et al[13]; Leaf et al[23]; Brouwer et al[21].

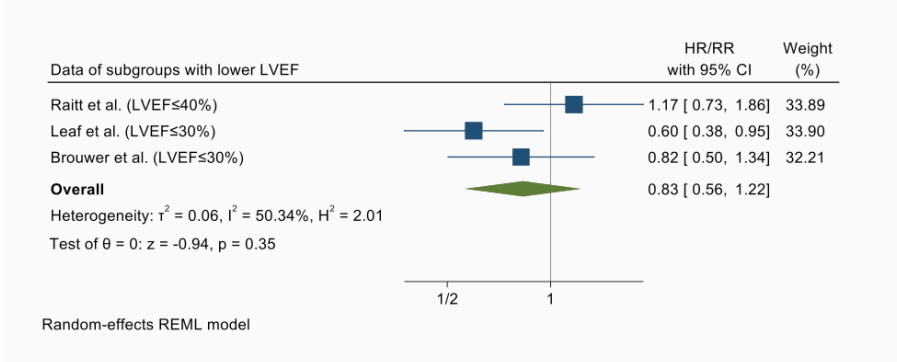


FIGURE 5. Subgroup analysis by lower left ventricle ejection fraction (LVEF).

CI: confidence interval; HR: hazard ratio; RR: relative risk. Raitt et al[13]; Leaf et al[23]; Brouwer et al[21].

In respect of the meta-regressions, we considered patients mean age, percentage of male patients, percentage of participants with CAD, mean LVEF in each study and finally the omega-3 supplementation dosage in in each study. Reviewing each of the generated meta-regression scatter plots (Suppl data 2), we can see a decrease of the predicted HR with the increase of each studies population mean age, with the lowering of LVEF and with the augmentation of omega-3 supplemented dosage. On the other hand, we note a progressive but discreet increase in predicted HR with the increase in the percentage of male population and CAD patients in each study. None of the observed meta-regression results prove to be significant as their corresponding 95% CI crosses the no effect line.

Reporting bias and certainty of evidence

The supplementary summary of findings table was generated according to the GRADE approach to evaluate the time to first ICD intervention or mortality outcome analyzed in the meta-analysis.

We accessed a very low certainty of evidence as a result of the concerns raised by the risk of bias of three of the four studies selected for meta-analysis. Inconsistency was also downgraded due to the moderate heterogeneity between studies' results. Finally, we also downgraded imprecision owing to the small effect of the intervention which has the possibility of no effect as the confidence interval crosses the no-effect line (Table 4).

DISCUSSION

This meta-analysis of four randomized controlled trials did not demonstrate a statistically significant protective role of n-3 PUFA supplementation on the incidence of life-threatening ventricular arrhythmias.

Even though our study is, to our knowledge, the first meta-analysis to include four studies regarding the potential antiarrhythmic effect of n-3 PUFA in patients with ICD, our results are still in line with previous reports[10–12]. The previously described unsignificant tendency to an antiarrhythmic effect of PUFA on ICD patients was corroborated by our study. In addition, our study found a narrower confidence interval and an even lower heterogeneity between studies than had ever been reported before[10–12].

One interesting finding was the omitted study analysis where, when excluding the *Raitt et al* trial[13], we obtained a statistically significant result concerning the protective effect of omega-3 PUFA. This trial, in contrast with any other studies reviewed, reported that there was no risk reduction of VT/VF in patients with ICD taking omega-3 supplementation and even found a significant proarrhythmic effect in patients with recent sustained VT[13]. Being the only one of four analyzed

TABLE 4. Summary of findings table according to the GRADE approach.

Certainty assessment							Summary of findings		
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With Placebo	Study event rates (%) With Omega-3	Relative effect (95% CI)
Time to ICD intervention or mortality (follow-up: median 12 months)									
1714 (4 RCTs)[10, 12-14]	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	863 participants	851 participants	**HR 0.88** (0.71 to 1.10) [Time to ICD intervention or mortality]

CI: confidence interval; **OR:** odds ratio.

[a] Of the 4 randomized controlled trials assessed for risk of bias using ROB2 tool, only one represents a low risk of bias, while the other 3 represent an unclear risk of bias due to unclear information mainly regarding the randomization process and the selection of reported results. Thus, we considered the overall risk of bias as serious.

[b] In order to judge inconsistency we used I^2 and Chi^2 for heterogeneity statistical tests. Due to a non-statistically significant Chi^2 for heterogeneity (p=0.13) and a moderate heterogeneity represented by a I^2 of 45.45% we chose to consider inconsistency as serious.

[c] In our meta-analysis the results include the possibility a small effect of the intervention (HR=0.88, CI 95% 0.71 - 1.10) with the possibility of no effect. Therefore, we chose to classify imprecision as serious.

studies reporting a tendency of proarrhythmic effect of n-3 PUFA and the consequent significant effect of its exclusion from the analysis, we must ask what differences this study may bare which considerably impacted its results. A previous meta-analysis found an unsignificant increase in risk of VT/VF in patients taking fish oil, who simultaneously had VT at entry and did not take any antiarrhythmics[11]. Since the Rait trial included patients with VT at entry and excluded patients taking any class I or III antiarrhythmics, this could have influenced its results. Further studies with better discrimination of subgroup results in patients with and without VT at entry and class I and class III antiarrhythmics, may help us understand omega-3 PUFAs' true effect on these populations and clarify not only the differences in results in previous studies, but also comprehend the true effect of this intervention on fatal ventricular arrhythmias.

Due to the higher incidence of SCD resulting from ventricular arrhythmias (VT/VF) in patients with CAD, it may prove to be fundamental to understand the true effect of n-3 PUFAs on this specific population[14–16]. The protective antiarrhythmic effect of PUFA had been demonstrated before in animal models namely with ischemic insults in dogs' hearts resulting in VF which were promptly prevented when injecting omega-3 PUFA[17]. However, this evidence in humans is still ambiguous and many hypothesize if the early described protective effect of n-3 on CV mortality is due to an overall reduction in CV events rather than an antiarrhythmic effect operating amongst the mechanisms of SCD[3,4,18–21].

In our systematic review, *Weisman et al*[12] was the only study to just include patients with ICD with concomitant ischemic cardiomyopathy. Even though it analyzed the mean number of interventions and not the time to first intervention, which impeded us from comparing to our other studies in our meta-analysis, the outcome results were rather interesting. In this 105-patient cross-over study, there was a significantly lower incidence of ICD interventions in patients taking 3.6 grams of omega-3 PUFA than patients in the control arm with sunflower and corn oil (mean number of VT registered 1.7 Vs. 5.6; p= 0.035).

Some have hypothesized that particularly in individuals who suffered MI, there is a greater risk for reentry arrhythmias in the surrounding ischemic tissue which now has different rates of conduction and n-3 PUFA can then hyperpolarize these partially depolarized cells preventing the initiation of arrhythmic events in the ischemic scars[5]. *Leaf et al*[23] also argued that, even though the partially depolarized cells around the ischemic tissue may become unexcitable in the presence of n-3 PUFA, this effect is not seen, at least to a same degree, in the heathy myocardium, which can continue to function normally[5]. In our meta-analysis we could not find a significant protective antiarrhythmic benefic of using omega-3 on the subgroup of patients with CAD (HR=0.92, CI 95%, 0.58-1.44; p value = 0.70). However, we did not find a proarrhythmic effect on ICD patients without CAD either (HR=0.88, CI 95%, 0.47-1.83; p value= 0.68). The data collected did not permit a subgroup analysis of patients with previous MI, which should be interesting to compare with the positive results reported by *Weisman et al*[12] in this specific ICD population.

Regarding lower LVEF, despite overall results not being statistically significant (HT=0.83, CI 95%, 0.56-1.22; p= 0.35), when we observe the groups with LVEF lower than 30% we see a tendency to a benefit in the use of n-3 PUFA for preventing ventricular arrhythmia in this subgroup of ICD patients, and a clearly significant protective effect on the *Leaf et al*[23] trial population. However, we must not ignore the fact that in this subgroup analysis we used each studies' reported results for each considered LVEF, that resulted in some studies as *Raitt et al*[13] also including patients between 30 and 40% LVEF. This heterogeneity could have impacted results but is also an indication to further study not only the potential antiarrhythmic effect of PUFA on patients with reduced LVEF, but also potential differences within this population which can impact the indication or contraindication of the intervention being studied.

Some of the limitations we found regard differences between inclusion criteria in each study. For example, patients enrolled in *Finzi et al*[22] had a considerably lower mean LVEF (28.4%), and all its included patients had heart failure with LVEF below 35%[22]. Also in this study, more than half of the patients had ICD for primary prevention, while the other three considered trials only included patients with ICD for secondary prevention, i.e. had a previous episode of ventricular arrhythmia. This may mean that these patients had a lower risk of arrhythmia than patients which endured a VF/VT event.

Another limitation of this meta-analysis was the wide amplitude of fish oil daily supplementation between studies (0.8-2.6 grams), and their respective differences in PUFA refined components concentration (EPA and DHA). All the included trials measured red blood cell and plasma n-3 PUFA levels in both intervention and control groups, with a statistically significant increase

across all participants taking fish oil supplementation versus control. Although the *Finzi et al* study[22] had the lowest daily intake of fish oil supplement (0.8g), in its main trial – the GISSI trial – patients with a recent myocardial infarction taking the same daily amount of fish oil still had a significant reduction in total deaths, CV deaths and SCD[3].

Additionally, compliance in studies was another limitation found, majorly in Leaf et al, where it never surpassed 64 and 66% in the fish oil and placebo arms, respectively[23].

All these factors might have contributed to the lack of statistically significant results obtained. Furthermore, the differences in reported results between studies, particularly the results in each subgroup, hampered their comparative analysis. If available in the future, this additional data could help us better understand the true role of omega-3 PUFAs on ventricular arrhythmias.

In conclusion, this meta-analysis did not find a significant antiarrhythmic effect of n-3 PUFA on ICD patients. A significant result was only evident after excluding the first 200 patient published study which had different exclusion criteria than the others included. Despite previously reported positive results in patients with ischemic cardiomyopathy and in those with low LVEF, our subgroup analysis did not find significant results in these subsets of participants. These results do not support the systematic prescription of n-3 PUFA for patients with ICD. However, this systematic review raised new potential hypothesis regarding potential interactions with antiarrhythmic drugs that merit further studies.

DECLARATION OF INTERESTS:

DC has participated in educational meetings and/or attended a conferences or symposia (including travel, accommodation and/or hospitality) with Bial, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, Ferrer, Pfizer, Novartis and Roche. The remaining authors have nothing to declare.

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SUPPLEMENTARY DATA

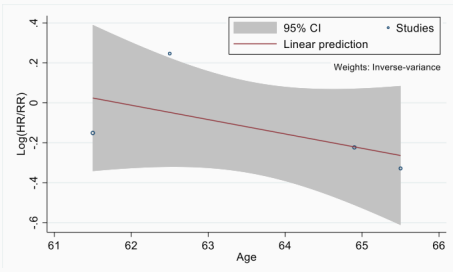
1. SEARCH STRATEGY

#	Searches
1	exp Fatty Acids/
2	exp fatty acids, unsaturated/
3	exp Fatty Acids, Omega-3/
4	exp Fatty Acids, Omega-6/
5	alpha-Linolenic Acid/
6	Docosahexaenoic Acids/
7	Eicosapentaenoic Acid/
8	(omega 3 or omega 6).tw.
9	polyunsaturat$ fatty acid$.tw.
10	PUFA.tw.
11	exp Fish Oils/
12	exp linseed oil/
13	(EFA or EPA or MaxEPA or DHA or ALA).tw.
14	(oil$ adj3 (fish$ or flax or linseed)).tw.
15	omega 3 fatty acid/
16	(fish adj3 (diet* or nutrit* or oil* or supplement*)).ti,ab.
17	(fish adj3 capsul*).ti,ab.
18	exp salmoniformes/ or tuna/
19	(eicosapentaen* or icosapentaen*).ti,ab.
20	(eicosapentaen* or icosapentaen*).ti,ab.
21	Linolen*.ti,ab.
22	alpha*linolen*.ti,ab.
23	alphalinolen*.ti,ab.
24	exp Defibrillators/
25	(icd or icds).af.
26	(defibrillat* or defibrilat*).af.
27	(crt or crts).af.
28	electrover*.af.
29	((resynch* or re*synch*) adj3 (therap* or treatment* or device*)).af.
30	(cardiover* or (cardio adj ver*) or cardioconver* or (cardio adj conver*)).af.
31	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
32	24 or 25 or 26 or 27 or 28 or 29 or 30
33	31 and 32
34	randomized controlled trial.pt.
35	controlled clinical trial.pt.
36	randomized.ab.
37	placebo.ab.
38	clinical trials as topic.sh.
39	randomly.ab.
40	trial.ti.
41	34 or 35 or 36 or 37 or 38 or 39 or 40
42	33 and 41
43	exp animals/ not humans.sh.
44	42 not 43

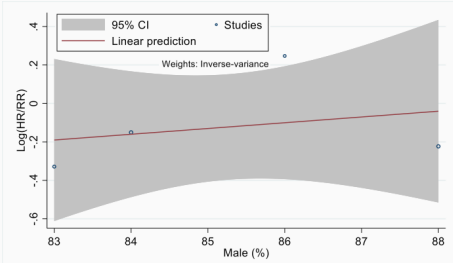
#	Database: Web of Science Core Collection
#1	(defibrillat* or defibrilat*) (All Fields) OR (icd or icds) (All Fields) OR (cardiover* or cardioconver*) (All Fields)
#2	(ALL=((omega3 OR omega-3 OR omega6 OR omega-6 OR fish oil)))
#3	ALL=(EFA or EPA or MaxEPA or DHA or ALA or PUFA)
#4	#3 OR #2
#5	#4 AND #1
#6	TS=(random* OR allocat*)
#7	#6 AND #5

2. META-REGRESSION SCATTER PLOTS

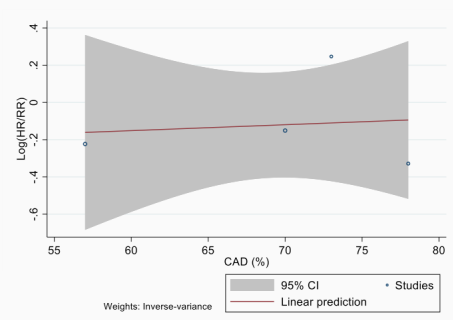
2.1. Age



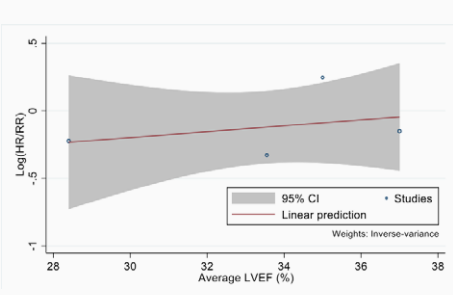
2.2. Male (%)



2.3. CAD (%)



2.4. LVEF (%)



2.5. Omega-3 dose (g)