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Assessing the impact of omega-3 fatty acids on ventricular tachyarrhythmia and survival in patients with ICDs: A systematic review and meta-analysis

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ABSTRACT

Background: Recent studies investigating the effects of fish oil on shocks administered by ICDs in patients with ventricular tachycardias produced inconclusive results. This systematic review aims to evaluate the effectiveness of omega-3 polyunsaturated fatty acids in lowering the risk of life-threatening VTs among individuals with implantable cardioverter-defibrillators.

Methods: We searched five databases, including Central, PubMed, EMBASE, Web of Science, and Scopus, for studies evaluating the efficacy of omega-3 polyunsaturated fatty acids (PUFAs) for the prevention of ICD events for VT or VF, published up to December 1, 2023.

Results: Four trials were finally included in the study. The pooled risk ratios for mortality and ICD events were 0.87 (95% CI:0.58–1.32) and 0.75 (95% CI:0.48–1.18), respectively.

Conclusion: No significant effect was discovered to support the antiarrhythmic properties or survival advantages of n-3 polyunsaturated fatty acids (PUFA) in individuals with implanted implantable cardioverter-defibrillators (ICD).

1. Introduction

Ventricular tachycardia (VT) is an abnormal cardiac rhythm originating from tissue located below the penetrating AV bundle, resulting in a fast ventricular rate exceeding 100 beats per minute (bpm) [1]. VT may cause complications, including syncope, cardiogenic shock, ventricular fibrillation, electrical storm, cardiac arrest, and sudden cardiac death (SCD). Commonly used primary therapies for reducing the occurrence of VT include the administration of antiarrhythmic drugs (AAD), performing catheter ablation, and then exploring the utilization of implantable cardioverter-defibrillators (ICDs) when considered suitable [2,3].

The ICD serves as an essential tool for preventing sudden cardiac death in high-risk individuals who experience VT following a myocardial infarction, as suggested by various significant trials [2,4,5]. However, multiple studies have demonstrated that receiving an ICD shock, regardless of whether it is appropriate or improper, may lead to a higher risk of mortality. Simultaneously, multiple ICD shocks can potentially induce clinical post-traumatic stress disorder and diminish the patients' quality of life [5–10].

Epidemiological studies show that consuming very long-chain n-3 polyunsaturated fatty acids (also known as omega-3 PUFAs) found in fish or fish oil can lower the risk of cardiovascular death [11–14]. Also, the research conducted by McLennan and his colleagues in the late 1980s confirmed the antiarrhythmic features of n-3 fatty acids in rats and marmosets [15–17]. This is corroborated by other fundamental research indicating that n-3PUFA decreases surrogate indicators of arrhythmia caused by excessive Ca^{2+} [18].

Abbreviations: AAD, antiarrhythmic drugs; BPM, beats per minute; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; n-3 PUFAs, omega-3 polyunsaturated fatty acids; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial; RR, risk ratio; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

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Recent studies investigating the effects of fish oil on shocks administered by ICDs in patients with VT produced inconclusive results [19–22]. Thus, the objective of this systematic review is to assess the efficacy of omega-3 PUFAs in lowering the risk of life-threatening VT and improving survival in patients with ICDs. Specifically, we aim to address the following research question: Does the supplementation of omega-3 PUFAs reduce the risk of life-threatening ventricular tachyarrhythmias and improve survival in patients with implantable cardioverter-defibrillators?

2. Methods

This systematic review adhered to the established methodological standards and reporting guidelines for conducting rigorous reviews. We followed the protocols outlined in the Cochrane Handbook [23] and the PRISMA statement for conducting systematic reviews [24]. Before initiating the review, we registered our protocol in the International Prospective Register of Systematic Reviews (PROSPERO, Registration ID: CRD42024498333), which detailed our planned search approach, eligibility criteria, and intended outcomes for analysis.

2.1. Search strategy

We performed a comprehensive literature search across five databases -CENTRAL, PubMed, Embase, Web of Science, and Scopus - to identify studies published up to December 1st, 2023, that evaluated the efficacy of omega-3 polyunsaturated fatty acids (PUFAs) in preventing implantable cardioverter defibrillator (ICD) events for ventricular tachycardia (VT) or ventricular fibrillation (VF). Our search utilized a combination of Mesh terms as well as free text keywords relevant to the research question. Further details on the search syntax for each database are provided in Supplementary Table S1. We manually screened the reference lists of eligible articles to identify other relevant studies through backward citation tracking. We also checked for studies that have cited the included articles to find more recent publications through forward citation tracking.

2.2. Study selection

Two independent reviewers (A.S. and S.A.P.) screened eligibility, assessing retrieved studies' titles, abstracts, and full texts against predefined inclusion and exclusion criteria. Any disagreements were resolved through panel discussion, and when no consensus was reached, a third reviewer (M.H.) made the final judgment. We included only randomized controlled trials that evaluated the efficacy of omega-3 polyunsaturated fatty acids (PUFAs) in preventing implantable cardioverter defibrillator (ICD) events. Reviews, editorials, case reports/series, and observational studies were excluded.

The primary outcome of interest was to compare the occurrence of ICD events and mortality between two groups – those treated with PUFAs versus placebo control.

2.3. Data extraction

A standardized data extraction form was created to collect relevant details from each included study systematically. The two reviewers (A.S. and S.A.P.) independently extracted data including first author name, publication year, study population characteristics (country, gender distribution), blinding method, timing of PUFA treatment initiation, duration of treatment and follow-up period, how ICD events were assessed, number of study arms, PUFA dosing, disease profile of participants, incidence of ICD events and all-cause mortality for each study arm. Any discrepancies in extracted data were discussed to reach a consensus.

2.4. Risk of bias assessment

A.A. and M.M. evaluated the methodological quality of the research by employing the Cochrane risk of bias assessment tool for randomized trials [25]. This tool assesses the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain was judged as low risk, high risk, or unclear risk of bias. Each of the 7 domains was assigned a score of 1 point if the study was determined to have a low risk of bias for that domain. Studies receiving a total score of 5 points or higher across all domains were categorized as having an overall low risk of bias. Inconsistencies were addressed with the assistance of a third reviewer (M.H.).

2.5. Data synthesis and statistical analysis

Statistical analyses were performed with Stata Corp (2017) Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. Point estimates and 95 % confidence intervals (CIs) for the prevalence of mortality, bradycardia, electrical cardioversion, stroke, and MI in two groups were calculated. Random or fixed-effect models will assess pooled risk ratios (RRs) with a 95 % confidence interval (CI). The random-effects model was selected because of considerable methodological heterogeneity among studies. The between-study heterogeneity was assessed by Cochran's Q test and the I^2 statistic. Between-study heterogeneity was quantified using Cochran's Q statistic and I^2 test. We assessed publication bias statistically through Egger's regression test, with a p-value less than 0.05 indicating significant bias [26,27]. The funnel plot was not used for publication bias assessment because fewer than ten studies were in each analysis [28].

3. Results

A PRISMA flow diagram outlines the study selection process and results (Fig. 1). Our comprehensive database search identified 1846 records screened for duplicates, leaving 1389 studies for title/abstract review. We excluded 1363 papers at this stage as it was clear from the title and abstract that the topic or outcomes were irrelevant to this review. The full texts of the remaining 26 articles were assessed for eligibility based on the predefined criteria. Following a full-text review, four randomized controlled trials met the inclusion criteria and were included in the quantitative synthesis. Hence, four eligible RCTs were identified and *meta*-analyzed after systematic literature screening to evaluate the research question.

3.1. Study characteristics

All four eligible studies were multicenter; two were conducted in the U.S. [21,22] and two in Europe [19,20]. The total sample size across studies was 1,714 participants, with individual study sample sizes ranging from 200 to 566. Mean participant age ranged from 61.5 to 65.5 years, and the majority of participants were male (83.1 % to 88.3 %). The median follow-up duration of studies ranged from 12 months [19,21] to 30 months [20]. The details on each study charachteristics are presented in Table 1.

The study conducted by Leaft et al. employed the highest dose of PUFAs among the included studies (4.0 g/day containing 2.6 g of n-3 fatty acids) [21], while Finzi et al. administered the lowest dose of PUFAs (1.0 g/day containing 850 mg of PUFAs) [20]. The other two used a nearly similar dose (1.8 and 2.0 g/day) [19,22]. Although all studies' intervention capsules contained eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), their ratio differed. The survey by Leaf et al. did not denote the EPA/DHA ratio [21]. The highest EPA percentage was employed in the study by Finzi et al. (54.5 %) [20]; the supplements of the other two studies consisted of 42 % and 48.3 % EPA

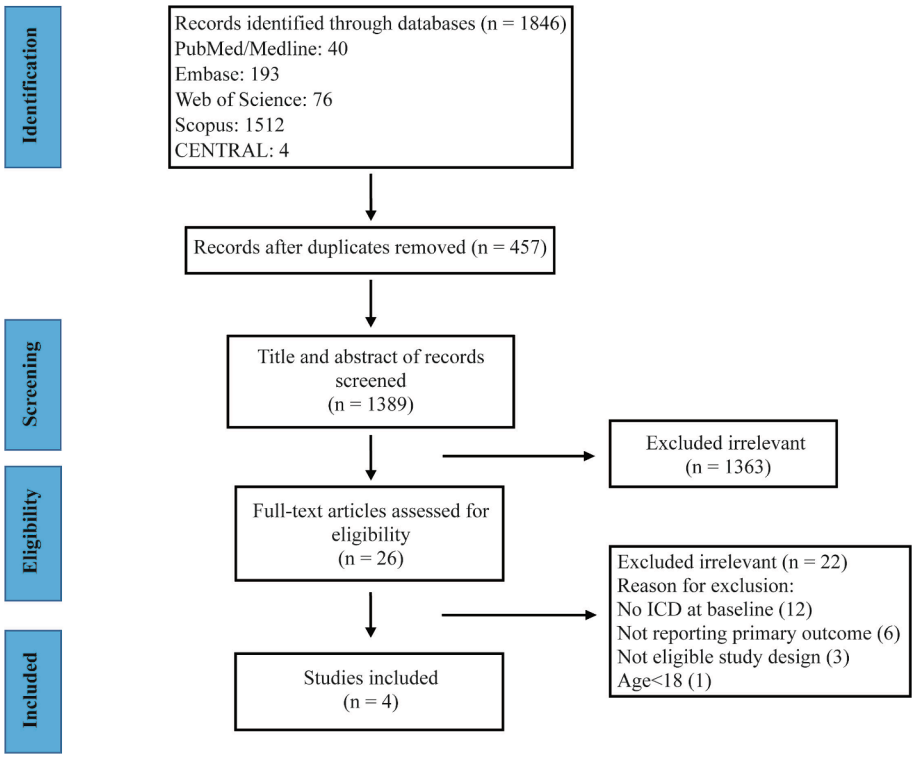

Fig. 1. Flow chart of study selection for inclusion in the systematic review and *meta*-analysis.

along with 30 % and 34.8 % DHA, respectively [19,22]. Considering the antioxidant composition of supplements, the supplement provided in one study consisted of a similar amount of antioxidants in both intervention and placebo groups [19]. In contrast, in another study, only supplements provided to the intervention group contained antioxidants [21]. The other two studies did not declare the antioxidant composition of their supplements [20,22]. The details of PUFAs and placebo regimens are summarized in Table 2.

Three studies did not find evidence to support the beneficial effect of PUFA on the rate of appropriate ICD intervention [19,20,22]. Only one study found a significantly lower rate of ICD interventions in patients receiving PUFA for at least 11 months compared to their control counterparts (per protocol analysis). Risk ratios for ICD events and mortality are described in Table 3, and the pooled risk ratios of mortality and ICD events between groups are presented in Fig. 2 and Fig. 3, respectively. Time to first ICD intervention or death was significantly prolonged, according to the study by Leaf et al. [21]. The other studies did not find evidence of a difference in time to ICD intervention between PUFA and placebo groups [19,20,22]. Leaf et al. reported a significant decrease in the Hazard Ratio (HR) of ICD events in patients receiving PUFA compared to placebo in the subset of patients with spontaneous VT and LVEF $\geq$ 30 % [21]. On the contrary, another study found that the incidence of ICD intervention episodes in the subset of patients who implanted ICD due to VT and were receiving PUFA was significantly higher compared to their control counterparts who were receiving a placebo, suggesting an arrhythmogenic effect for PUFA in this subset of patients (Fig. 3) [22].

3.2. Risk of bias assessment

According to the Cochrane Risk of Bias assessment, all studies were categorized as low-risk (Table 4).

3.3. Publication bias

The Egger test indicated that there is no considerable publication bias among the final included studies (Fig. 4)($p = 0.73$).

4. Discussion

In-virto experiments show that dietary omega-3 fatty acid supplementation reduces susceptibility to experimentally induced arrhythmias [29]. Short-term intravenous administration also has antiarrhythmic effects in animal models [15,30]. At a cellular level, omega-3 fatty acids inhibit sodium, potassium, and calcium currents, reduce calcium overload and release from the sarcoplasmic reticulum, and may affect gap junction function and inflammatory signaling - all of which could contribute to antiarrhythmic effects [31]. However, the translation of these mechanisms to dietary supplementation is uncertain.

Observational studies and some clinical trials suggest that dietary intake of long-chain omega-3 fatty acids (EPA and DHA) from fish reduces the risk of sudden cardiac death, likely through antiarrhythmic effects [18]. However, the results of trials specifically examining the effect of n-3 PUFAs on ventricular arrhythmias in patients with ICDs have been mixed [32]. Our comprehensive *meta*-analysis of RCTs did not reveal any evidence of the beneficial effects of n-3 PUFA on the occurrence of VT/VT in patients with implanted ICDs. Additionally, we found no significant impact of n-3 PUFA supplementation on mortality in this population.

Several factors may contribute to the contradictory results observed in included studies. First, the included studies used varying dosages and compositions of omega-3 PUFAs, which could have influenced the results. Leaf et al.'s research administered a daily dose of 2.6 g of n-3 fatty acids [21], significantly higher than the second-largest dosage of 1.26 g, administered by Raitt et al. [22], and nearly double the amount. The dosages in the remaining two studies were below 1 g of n-3 fatty acids per day [19,20]. Moreover, in two of the four studies reviewed [19,21], the fish oil capsules were noted to contain antioxidants. Among these, only the study conducted by Leaf et al. reported positive effects of n-3 PUFAs on ICD events and mortality, specifically through the use of fish oil capsules enriched with antioxidants, whereas the placebo group did not receive these benefits [21]. In contrast, the study by Brouwer et al.,

Table 1
Baseline characteristics of the final included studies.

First Author, Publication Year	Study Design	Centers and Country/countries	Sample Size (Intervention/ Control)	Male (%)	Age (mean ± SD)		Comorbidities		ICD Events Detection Method
					Intervention Arm	**Control Arm**	**Intervention Arm**	**Control Arm**	
Brouwer [19], 2005	randomized, parallel, placebo-controlled, double-blindtrial	26 cardiology clinics in 8 European countries: Poland, Germany, the Netherlands, the United Kingdom, the Czech Republic, Belgium, Austria, and Switzerland	546 (273/ 273))	459 (84.06)	60.5 ± 12.8	62.4 ± 11.4	IHD: 187 (73 %) Previous MI: 167 (61 %) HTN: 143 (53 %) DM: 45 (17 %) NYHA FC: I: 85 (31 %) II: 100 (37 %) III: 27 (10 %) IV: 2 (1 %)	IHD: 197 (79 %) Previous MI: 175 (64 %) HTN: 134 (49 %) DM: 42 (15 %) NYHA FC: I: 102 (37 %) II: 93 (34 %) III: 25 (9 %) IV: 0 (0 %)	Participants had follow-up appointments at their cardiology clinic at baseline and four months, eight months, and 12 months post-enrollment. During these visits, data on ICD function were collected remotely through telemetry and stored for analysis.
Finzi [20], 2011	randomized, placebo-controlled, double-blindtrial	89 centers in Italy and Switzerland	566 (278/288)	500 (88.33)	64.9 ± 9.5	64.8 ± 9.8	Previous MI: 161 (57.9 %) HTN: 113 (40.7 %) DM: 65 (23.4 %) NYHA FC: I: 0 (0 %) II: 176 (63.3 %) III: 101 (36.3 %) IV: 1 (0.4 %)	Previous MI: 162 (56.2 %) HTN: 143 (49.7 %) DM: 77 (26.7 %) NYHA FC: I: 0 (0 %) II: 186 (64.6 %) III: 100 (34.7 %) IV: 2 (0.7 %)	The ICD data was collected remotely through telemetry at each follow-up visit and stored for analysis. Additionally, any unscheduled clinical visits were documented to ensure complete follow-up of ICD data. (patients had at least one follow-up visit.)
Raitt [22], 2005	randomized, parallel, placebo-controlled, double-blind	Six medical centers in the United States	200 (100/100)	172 (86.00)	63 ± 13 in	63 ± 13	Previous MI: 55 (55 %) HTN: 46 (46 %) DM: 24 (24 %) NYHA FC: I: 25 (25 %) II: 13 (13 %) III: 48 (48 %) IV: 14 (14 %)	Previous MI: 56 (56 %) HTN: 55 (55 %) DM: 23 (23 %) NYHA FC: I: 28 (28 %) II: 14 (14 %) III: 50 (50 %) IV: 8 (8 %)	At all visits, the ICD memory was checked for the occurrence of the episodes. (from randomization till two years at three-month intervals)
Leaf [21], 2005	randomized, placebo-controlled, double-blindtrial	18 United States centers	402 (200/202)	334 (83.08)	65.7 ± 0.82	65.3 ± 0.82	CAD: 151 (76 %) NYHA FC: I: 47 (23.5 %) II: 66 (33 %) III: 20 (10 %) IV: 0 (0 %)	CAD: 163 (81 %) NYHA FC: I: 54 (26.7 %) II: 75 (37.1 %) III: 10 (5 %) IV: 1 (0.5 %)	Participants were asked to return to their designated medical centers every three months to have the data from their ICDs downloaded.

DM: Diabetes Mellitus; HTN: Hypertension; ICD: Implantable Cardioverter Defibrillator; IHD: Ischemic Heart Disease; MI: Myocardial Infarction; NYHA FC: New York Heart Association Functional Classification; SD: Standard Deviation

which included tocopherol (an antioxidant) in both the fish oil capsules and placebos, found no reduction in the incidence of a combined outcome of ICD intervention and mortality [19]. Given the substantial sample sizes of these investigations, it is unlikely that the lack of significant findings in Brouwer et al.'s study could be attributed to insufficient sample size. Consequently, the beneficial effects of n-3 PUFAs observed by Leaf et al. could potentially be due to the higher dose of n-3 fatty acids, the inclusion of antioxidants exclusive to the intervention group, or a combination of both factors. The current evidence does not allow for a conclusive evaluation of these hypotheses, underscoring the need for further research into the benefits of high-dose n-3 fatty acids and the potential synergistic effects when combined with antioxidants.

The experience of conflicting results from two randomized trials, DART-1989 by Burr et al. and DART-2002 by Ness et al., regarding the

Table 2
Details of PUFAs and placebo regimens.

First Author, Publication Year	Intervention Arm	Control Arm	Duration of Therapy
Brouwer [19], 2005	The treatment regimen consisted of 2 g per day of fish oil (4 capsules), providing an average total of 961 mg of omega-3 polyunsaturated fatty acids, including 464 mg of EPA, 335 mg of DHA, and 162 mg of other omega-3 PUFAs (48.3 % EPA, 34.8 % DHA). Fish oil contained 3000 ppm of tocopherol as antioxidant.	The placebo comprised 2 g per day of high-oleic sunflower oil capsules. Notably, placebo capsules also contained 3000 ppm of the antioxidant tocopherol. The oils were purchased from Loders Croklaan, Wormerveer, the Netherlands, and encapsulated by Banner BV, Tilburg, the Netherlands.	12 months
Finzi [20], 2011	One capsule per day of 1 g n-3 PUFA (850 mg EPA and DHA as ethyl esters in the average ratio of 1.2:1).	Matching placebo	September 2004 till December 2007
Raitt [22], 2005	1.8 g/d of fish oil, consisting of: 42 % EPA 30 % DHA	Olive oil: 73 % oleicacid, 12 % palmitic acid, 0 % EPA/DHA. Oils were provided by Hoffman LaRoche Inc (Nutley, NJ) as ethyl esters of the fatty acids.	24 months
Leaf [21], 2005	4 × 1.0-g gelatin capsules per day containing a total dose of 2.6 g of EPA and DHA omega-3 fatty acid ethyl esters The fish oil capsules contained the antioxidants. (tocopherol [2.5 mg/g] and butylated hydroxytoluene [0.02 %])	4 × 1.0-g capsules of olive oil of identical appearance The placebo contained no antioxidants.	12 months

DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; n-3 PUFA: Omega-3 Polyunsaturated Fatty Acids; PPM: parts per million

Table 3
The risk ratio of ICD events and mortality in groups.

First Author, Publication Year	Risk Ratio for ICD Events (Lower limit of 95 %CI-Upper limit of 95 % CI)	Weight (%)	Risk Ratio for Mortality (Lower limit of 95 %CI-Upper limit of 95 % CI)	Weight (%)
Brouwer [19], 2005	0.926 (0.710–1.208)	25.21	0.571 (0.244–1.340)	17.31
Finzi [20], 2011	0.772 (0.598–0.995)	25.40	1.095 (0.826–1.452)	51.12
Raitt [22], 2005	1.183 (0.886–1.579)	24.82	0.400 (0.130–1.233)	11.14
Leaf [21], 2005	0.373 (0.276–0.506)	24.57	1.094 (0.512–2.339)	20.42
Overall	0.752 (0.477–1.184)	100.00	0.874 (0.580–1.320)	100

effects of fish oil on heart disease outcomes, may also provide an explanation for the lack of a beneficial antiarrhythmic effect of n-3 PUFAs in our study [33,34]. In DART-1989, fish oil reduced mortality in men recovering from myocardial infarction (MI) [33], while in DART-2002, fish oil capsules were associated with an increased risk of cardiac and sudden death in men with stable angina [34]. The authors propose that this discrepancy may be explained by differences between the trials, such as the acute post-MI period in DART-1989 versus chronic stable angina in DART-2002, and the use of fish oil capsules rather than dietary fish in DART-2002 [35].

Other evidence, including the GISSI-Prevenzione trial, supports an antiarrhythmic effect of dietary supplementation with n-3 PUFAs, especially post-MI or during acute ischemia, which may explain the rapid reduction in mortality seen in DART-1989 [36]. Burr et al. proposed a molecular hypothesis whereby fish oil has antiarrhythmic effects after acute ischemia by broadly resynchronizing disrupted ion fluxes but may destabilize the re-equilibrated ion currents present in chronic heart disease, especially if given as a concentrated rapid bolus (capsules) rather than gradual absorbtion (dieatary supplementation with fish meal) [35]. This also accords with observations by Raitt et al. [22], which excluded patients with etiology of acute MI, showed a significantly increased rate of recurrent episodes of VT/VF in patients recieving fish oil supplementation.

The contrasting results highlight the importance of considering the patient population, the presence of acute versus chronic cardiac conditions, and delivery form of fish oil when evaluating its effects on arrhythmic risk and cardiac mortality. This evidence suggest that the antiarrhythmic properties of omega-3 PUFAs may be more pronounced in specific subgroups of ICD patients depending on their pre-existing cardiac status [32,35]. The included studies did not consistently report subgroup analyses based on these factors, which limits our ability to identify patient characteristics that may modify the response to omega-3 PUFAs supplementation.

We hypothesize that supplementation with omega-3 PUFAs may not provide significant antiarrhythmic or survival benefits in all patients with implanted ICDs and further research is needed to identify subgroups of patients who may benefit from omega-3 PUFA supplementation. Moreover, the decision to initiate omega-3 PUFAs supplementation in ICD patients should be individualized, considering the patient's overall cardiovascular risk profile, dietary habits, and potential drug interactions. Clinicians should engage in shared decision-making with patients, discussing the potential benefits and limitations of omega-3 PUFAs supplementation in the context of their specific clinical situation.

4.1. Limitations

One of the strengths of our systematic review is the inclusion of studies with large sample sizes and multi-nationality, which reduces the risk of failing to detect evidence of the benefits of omega-3 PUFAs due to insufficient statistical power. However, it is crucial to acknowledge that while the sample size and multi-nationality are strengths, they do not eliminate the possibility of inadequate power to detect significant effects. The limited number of studies included in our *meta*-analysis precluded dose-dependent analyses, adjusting for the EPA-DHA ratio, and the accompanying antioxidant composition of fish oil capsules. Future research should focus on dose-dependent analyses to determine the optimal dosage and composition of omega-3 PUFAs for potential antiarrhythmic effects in patients with implanted ICDs.

5. Conclusion

We did not find evidence supporting the antiarrhythmic characteristic or survival benefit of n-3 PUFAs in patients with implanted ICD. Considering the large sample size, these negative findings do not seem to be attributable to the number of participants, while our findings might be influenced by the various EPA to DHA ratios, total dosage of n-3 PUFA, and anti-oxidant composition of provided capsules.

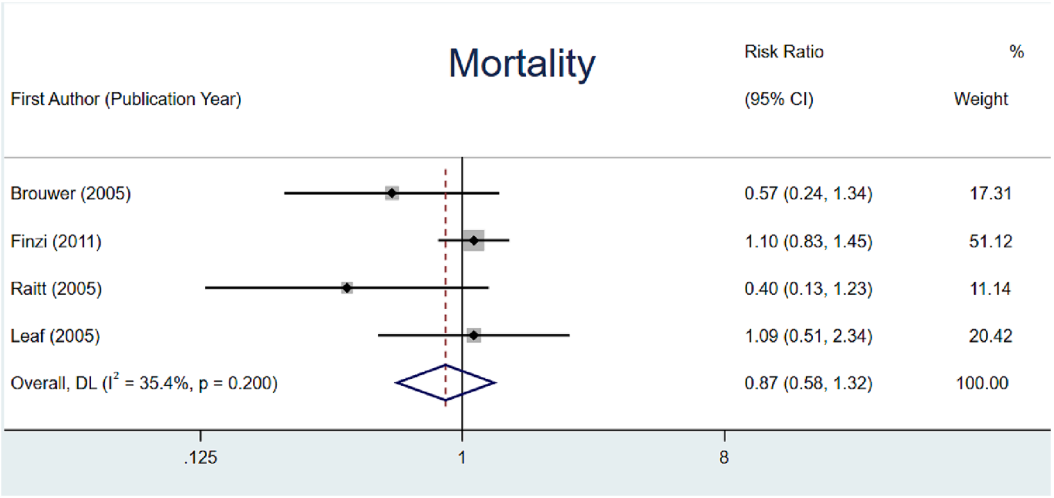

Fig. 2. The pooled risk ratio of mortality between groups. ($tau^2 = 0.0655$, Cochran's Q value = 4.64, p-value = 0.200).

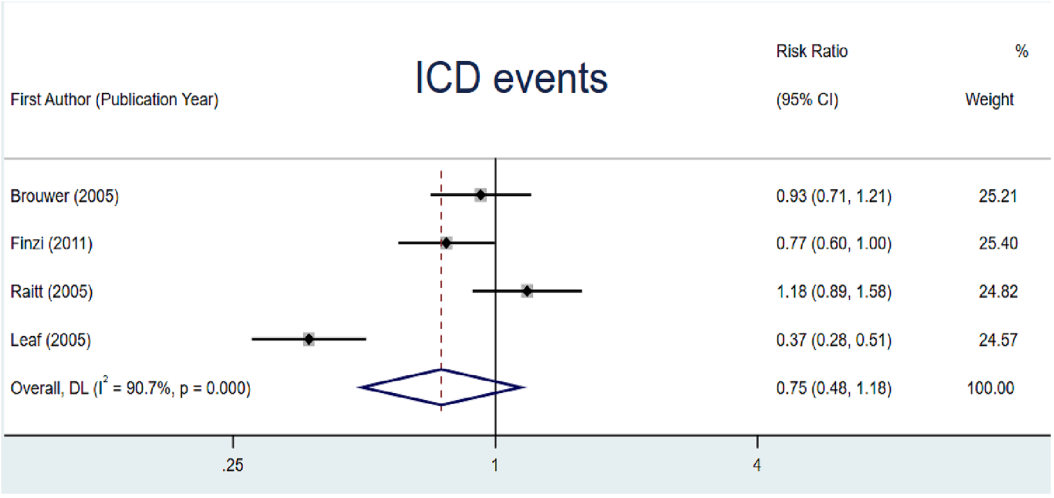

Fig. 3. The pooled risk ratio of ICD implantation between groups. ($tau^2 = 0.1945$, Cochran's Q value = 32.24, p-value < 0.0001).

Table 4
Risk of bias assessment of included studies.

First Author, Publication Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Researchers (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Brouwer [19], 2005	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Finzi [20], 2011	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Raitt [22], 2005	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Leaf [21], 2005	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk

Declarations

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Claude 2.1 in order to ensure English language fluency and native quality writing. Claude was consulted regarding grammar, word choice, sentence structure, and overall clarity of expression. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethics Approval and Consent to Participate

N/A.

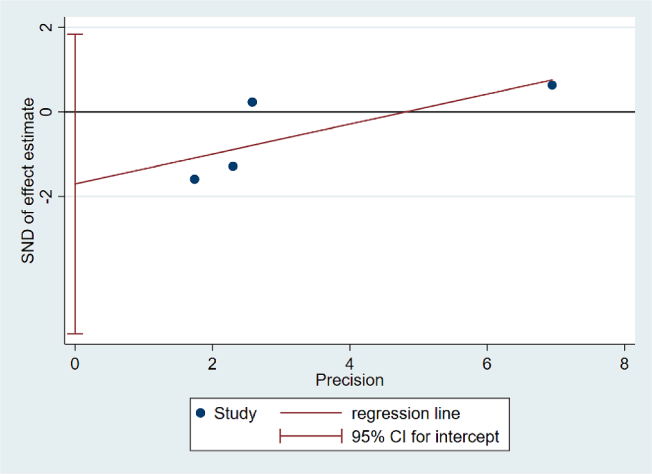

Fig. 4. Egger graph for small-study effect assessment.

Availability of Data and Materials

The datasets used (extracted data from included studies) and analyzed during the current study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Erfan Kohansal: Writing – original draft, Methodology. **Amir Askarinejad:** Writing – original draft, Formal analysis, Conceptualization. **MohammadHossein MozafaryBazargany:** Methodology, Writing – original draft. **Amirreza Sabahizadeh:** Investigation, Data curation. **SeyedAbbas Pakmehr:** Data curation, Investigation. **Majid Haghjoo:** Conceptualization, Methodology, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101397.

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