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A systematic review and meta-analysis of the impact of ω-3 fatty acids on selected arrhythmia outcomes in animal models

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Abstract

Epidemiological studies and clinical trials report the beneficial effects of fish or fish oil consumption on cardiovascular disease outcomes including sudden death. We performed a systematic review of the literature on controlled animal studies that assessed the effects of ω-3 fatty acids on selected arrhythmia outcomes. On the basis of predetermined criteria, 27 relevant animal studies were identified; 23 of these were feeding studies, and 4 were infusion studies. Across species, fish oil, eicosapentaenoic acid, and/or docosahexaenoic acid appear to have beneficial effects on ventricular tachycardia (VT) and fibrillation (VF) in ischemia- but not reperfusion-induced arrhythmia models; no effect on the incidence of death and infarct size; and inconsistent results with regard to arrhythmia score, VF threshold, ventricular premature beats or length of time in normal sinus rhythm, compared to ω-6, monounsaturated, or saturated fatty acids, and no treatment controls. In a meta-analysis of 13 studies using rat models, fish oil but not α-linolenic acid supplementation showed a significant protective effect for ischemia- and reperfusion-induced arrhythmias by reducing the incidence of VT and VF. It is not known whether ω-3 fatty-acid supplementation has antiarrhythmic effects in other disease settings not related to ischemia.

1. Introduction

Cardiac arrhythmias, or heart-rhythm disturbances, are an important cause of sudden death (abrupt, unexpected loss of heart function or cardiac arrest). According to the American Heart Association's Heart and Stroke Statistical Update for 2005, arrhythmias were a direct cause of 37 892 deaths in the United States and were an underlying or contributing cause of another 484 000 deaths [1]. In addition to causing sudden cardiac death, arrhythmias can compromise normal coronary blood flow and result in impaired oxygenation of the heart muscle (myocardial ischemia) or death of cardiac muscle tissue (myocardial infarction or heart attack). Arrhythmias can also lead to or are associated with other cardiovascular conditions, such as stroke, congestive heart failure, and peripheral embolism.

Epidemiological studies and clinical trials in humans have reported beneficial effects of fish and/or fish oil consumption on cardiovascular outcomes. In particular, fish oil intake appears to have a significant impact on the incidence of sudden death in humans, with a decrease reported in 4 of 6 randomized controlled trials [2-5], 2 prospective cohort studies [6,7], and 1 case control study [8]. It is hypothesized that long-chain ω-3 fatty acids prevent sudden death by suppressing life-threatening cardiac arrhythmias. Testing this hypothesis in humans has proven difficult given feasibility issues related to accurate measurement of arrhythmic events as well as monitoring the large number of subjects that would be needed to obtain a sufficient number of events. Consequently, several investigators have developed animal models of arrhythmia to directly assess the antiarrhythmic potential of ω-3 fatty acids. More recently, a few prospective randomized placebo-controlled double-blind clinical trials in

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high-risk individuals, such as those with an implantable cardiac defibrillator, severe left ventricular hypertrophy, and severe heart failure, have been initiated to address this issue [9-11]. Preliminary results from one study of 200 patients with implantable cardiac defibrillators [11] showed that among patients having previously experienced an episode of ventricular tachycardia (VT) there was a significant increase in VT or ventricular fibrillation (VF) in patients receiving fish oil supplements compared to those taking an olive oil placebo. In contrast, results from a pilot study [12] showed that infusion of ω-3 fatty acids reduced the ability to induce sustained VF in 5 of 7 patients. However, the small sample size, the absence of a placebo group, and the absence of randomization are considerable limitations of this later study. These findings have renewed interest in defining the mechanism(s) of action of ω-3 fatty acids on the genesis and conduction of electrical activity in the heart.

The aim of the present article is to systematically review the literature and to summarize the analysis of results obtained from controlled animal studies on the impact of ω-3 fatty acids on selected arrhythmia outcomes.

2. Methods

2.1. Literature search strategy and data extraction

A comprehensive search of the scientific literature (Medline, Pre-Medline, Embase, Biological Abstracts, Commonwealth Agricultural Bureau of Health) was conducted to identify controlled animal studies evaluating the impact of ω-3 fatty acids (α-linolenic acid [ALA], eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) on arrhythmia outcomes. The last update was conducted on April 18, 2004. Retrieved articles were reviewed, and citation analysis of key articles was performed using Science Citation Index. Abstracts identified through the literature search were screened using prespecified eligibility criteria [13]. Only English-language primary experimental studies were included. Reports published only as letters or abstracts were excluded.

A standardized data extraction form was designed to ensure consistency across reviewers. Data extracted regarding the intervention included animal species used, animal characteristics, control and experimental diets (including detailed description of any ω-3 fatty acids), dosage, duration of feeding or infusion, and outcomes.

2.2. Arrhythmia outcomes evaluated

Outcomes evaluated (summarized in Table 1) included incidence of death, VT (a run of 4 or more consecutive ventricular premature electrical depolarizations), VF (a signal for which individual QRS deflections can no longer be distinguished from one another and for which a rate can no longer be measured), ventricular fibrillation threshold (VFT—amount of current required to induce VF), ventricular premature beats (VPB—isolated ventricular premature electrical depolarizations with discrete and identifiable premature QRS complexes), length of time in normal sinus rhythm (TSR), arrhythmia score (AS—a hierarchical scale of 0 to 9 during coronary artery occlusion and a slightly modified version of the scale during reperfusion), and infarct size (IS—the underperfused ischemic regions determined by dye exclusion and expressed as a percentage of wet weight in both ventricles). Effects on intermediate outcomes such as heart rate, coronary flow, and electrocardiogram results such as QT interval prolongation were not included.

Table 1
Definition of arrhythmia outcomes evaluated

Arrhythmia outcome	Definition
Death	Incidence of death
VT	A run of 4 or more consecutive ventricular premature electrical depolarizations
VF	A signal for which individual QRS deflections can no longer be distinguished from one another and for which a rate can no longer be measured
VFT	Amount of current required to induce VF
VPB	Isolated ventricular premature electrical depolarizations with discrete and identifiable premature QRS complexes
TSR	Length of time in normal sinus rhythm
AS	A hierarchical scale of 0 to 9 during coronary artery occlusion and a slightly modified version of the scale during reperfusion
IS	The underperfused ischemic regions determined by dye exclusion and expressed as a percentage of wet weight in both ventricles

2.3. Arrhythmia models used

Ischemia-induced arrhythmia (IM—measured shortly after ischemia procedure), ischemia-reperfusion arrhythmia (IRM—measured shortly after ischemia followed by reperfusion procedure), spontaneous arrhythmia (S) models, and those induced by programmed electrical stimulation were included. The duration of ischemia and/or reperfusion was categorized using the following scheme: 5-minute ischemia (*a*), 15-minute ischemia (*b*), 20-minute ischemia (*c*), 3-hour ischemia (*d*), 5-minute ischemia + 5-minute reperfusion (*e*), 5-minute ischemia + 10-minute reperfusion (*f*), 15-minute ischemia + 5-minute reperfusion (*g*), 15-minute ischemia + 10-minute reperfusion (*h*), 20-minute ischemia + 20-minute reperfusion (*i*), 20-minute ischemia + 5-minute reperfusion (*j*), 36-minute ischemia + 1-hour reperfusion (*k*), 1-hour ischemia + 4-hour reperfusion (*l*), 90-minute infusion + 30-minute reperfusion (*m*), 10-minute ischemia + 1-hour reperfusion (*n*), exercise + ischemia (*o*).

2.4. Categories of dietary comparisons

Because diet composition and the structure of the comparisons are a key aspect of study design, a 4-level categorization scheme was devised based on the fatty acid and/or level of fat contained in the comparison diet. The first category includes ω-3 (fish, soybean, canola, linseed

[or flaxseed] oils) relative to ω-6 polyunsaturated fatty acids (PUFAs) (eg, corn, safflower, sunflower oils). The ω-6 comparison oils have the longest fatty acid chains normally consumed by humans and are most similar to EPA and DHA. They provide a similar level of dietary fat and have a similar number of double bonds. The second category includes ω-3 fatty acids relative to monounsaturated fatty acids (MUFAs) (eg, olive oil). As with ω-6 comparison oils, MUFA oils have the longest fatty acid chains normally consumed by humans. They contain one double bond and provide a similar level of dietary fat. The third category includes ω-3 fatty acids relative to saturated fatty acids (SFAs) (eg, butter, lard, coconut oil, sheep fat). These SFAs provide a level of dietary fat in the comparison diet that is similar to the level obtained with ω-3 fatty acids. The fourth category includes ω-3 fatty acids relative to a control group (eg, standard chow). Standard chow is most different from the ω-3–enriched diet because no "counterbalancing" fatty acids are contained in this comparison diet.

In some studies, certain dietary comparisons conducted by the investigators were not relevant to this article, or there were more than one comparison group. In such instances, only those components of the analysis that addressed the objectives of this article were extracted, using the scheme described above (order of comparison: first to fourth category).

2.5. Statistical analysis

When there were more than 6 comparisons for an outcome, meta-analyses using random-effects model [14] were performed. In these analyses, fish oils and ALA oils were analyzed separately. Only feeding studies that compared the effect of ω-3 PUFAs relative to ω-6 PUFAs on the risk of death, VT, and/or VF in rats had enough comparisons to be meta-analyzed. Data are presented as follows: within the table and figures, studies are clustered into ALA or fish oils, first sorted by comparison group and then by species. Frequently, studies had more than one comparison and used more than one experimental protocol. As a result, some studies will appear multiple times in the same table or figure.

3. Results

We identified 1807 abstracts that met the predetermined search criteria [13]. After screening, 274 articles were retrieved and reviewed. Of these, 27 whole animal studies were accepted. A summary of these studies is depicted in Table 2. In 23 of the studies, ω-3 fatty acid supplements were added to the animals' diet for varying durations (5 days-129 weeks) before the experimental protocols for inducing arrhythmias were implemented ("feeding studies" where the fatty acids are incorporated into the cell membrane before influencing cell function and/or rehabilitation). In the remaining 4 studies, ω-3 fatty acids were infused intravenously over a 40- to 90-minute period, and the effect on induced or spontaneous arrhythmias was assessed ("infusion studies" where the ω-3 fatty acids function in free or unbound form). With regard to species of animal studied, 14 used rat models, 8 used dog models, 3 used monkey models, 1 used a piglet model, and 1 used a rabbit model. The amount of ω-3 fatty acid supplemented to the animals' diet varied widely from 0.3 to 5.2 g/100 g of diet for ALA and 1.0 to 5.5 g/100 g of diet for fish oils, EPA, and/or DHA. Among the infusion studies, a similar variability in the dosage and form of ω-3 (esterified to glycerol to form triglyceride or bound to albumin) was observed. Three studies [15,29,31] used isolated working heart models.

3.1. Study quality

A series of guidelines for the study of arrhythmias in ischemia, infarction, and reperfusion provide some insights into the quality of whole animal studies included in this review [42]. The authors' conclusions regarding the conduct of research on arrhythmias in animal studies include the need for blinding and randomization, using multiple animal models, detailed information about the animals, contemporary controls, explicit exclusion criteria, and clear reporting of treatments and outcome criteria. Of the 27 whole animal studies, only 3 studies explicitly reported the randomization to treatment, and no study reported blinded analyses of the results. Animal characteristics and housing conditions were described in most studies. Contemporary controls were used in all but the monkey studies. Exclusion criteria were rarely used or reported.

3.2. Effect of ALA supplementation

Fig. 1 summarizes the effects of ALA supplementation relative to ω-6 PUFAs, MUFAs, or SFAs, and no treatment controls on selected arrhythmogenic outcomes. Three feeding studies [15-17] with 4 comparisons found no beneficial effect of ALA containing oils relative to ω-6 PUFAs on the incidence of death, VT, VF, VPB, TSR, AS, or IS. Among the 2 infusion studies, 1 [40] reported a beneficial effect of albumin-bound ALA on the incidence of VT and VF, whereas the other [41] reported no significant effect on the incidence of VT and VPB at low concentrations, and toxic effects at higher concentrations.

3.3. Effect of fish oils, EPA, and/or DHA supplementation

Fig. 2 summarizes the effects of fish oils, EPA, and/or DHA supplementation relative to ω-6 PUFAs, MUFAs, SFAs, and no treatment controls on selected arrhythmogenic outcomes.

3.3.1. Incidence of death

Ten studies evaluated the effect of fish oil or EPA relative to ω-6 PUFAs, SFAs, or no treatment controls on the incidence of death. Two studies [21,36] reported a significant decrease, whereas 8 studies showed no beneficial effect [16,18-20,23,32-34].

Table 2
Summary of animal studies evaluating the effect of ω-3 supplementation on selected arrhythmia outcomes

Author, year	Animal model	Control arm[a]	ω-3 arm	Amount (g/100 g of diet)		Duration (wk)	Total N
				ALA	EPA + DHA		
Feeding studies							
ω-3 PUFAs vs ω-6 PUFAs							
Isensee, 1994 [15]	Rat	Corn	Linseed	5.2	–	10	19
Abeywardena, 1995 [16]	Rat	SSO	Soybean	0.3	–	39	36
McLennan, 1995 [17]	Rat	SSO	Soybean	1.1	–	12	27
McLennan, 1995 [17]	Rat	SSO	Canola	1.2	–	12	30
Hock, 1987 [18]	Rat	Corn	Menhaden	0.1	1.0	4	27
McLennan, 1988 [19]	Rat	SSO	Tuna	NR	3.7	52	20
McLennan, 1990 [20]	Rat	SSO	Tuna	NR	3.7	39	14
Hock, 1990 [21]	Rat	Corn	Menhaden	0.1	1.0	4	43
Charnock, 1991 [22]	Rat	SSO	Fish oil	NR	2.1	44	20
McLennan, 1993 [23]	Rat	SSO	Fish oil	NR	2.6	12	27
Isensee, 1994 [15]	Rat	Corn	Sardine oil	0.0	3.0	10	19
Abeywardena, 1995 [16]	Rat	SSO	MaxEPA	0.2	2.6	39	36
Anderson, 1996 [24]	Rat	SAF	MaxEPA	NR	41% TF	8	14
Charnock, 1992 [25]	Monkey	SSO	Fish oil	0.1	1.2	103	NR
McLennan, 1992 [26]	Monkey	SSO	Tuna	NR	2.8	129	29
McLennan, Bridle, 1993 [27]	Monkey	SSO	Fish oil	0.1	1.7	16	10
ω-3 PUFAs vs MUFAs							
McLennan, 1996 [28]	Rat	Olive	EPAe, DHAe, EPAe + DHAe	–	5% TF	5	20
ω-3 PUFAs vs SFAs							
Yang, 1993 [29]	Rat	Butter	Fish oil	NR	5.4	5[d]	17
al Makdessi, 1995 [30]	Rat	Coconut	Sardine	0.1	2.9	10	27
Pepe, 1996 [31]	Rat	Sheep fat	Fish oil	0.2	5.5	16	20
Chen, 1994 [32]	Rabbit	Coconut	Fish oil	NR	5.2	2	27
Hartog, 1987 [33]	Piglet	Lard	Mackerel	0.1	1.2	16	13
ω-3 PUFAs vs no treatment controls							
Culp, 1980 [34]	Dog	Friskies	Menhaden	NR	1.3	5-7	27
Oskarsson, 1993 [35]	Dog	Chow	MaxEPA	–	1.6 g/d[b]	6	21
Otsuji, 1993 [36]	Dog	OY Co	EPAe	–	1.1 g/d[b]	8	20
Kinoshita, 1994 [37]	Dog	OY Co	EPAe	–	1.0 g/d[b]	8	10
Infusion studies							
ω-3 PUFAs vs ω-6 PUFAs							
Billman, 1994 [38]	Dog	Soybean	Fish oil emulsion[c]	–	4.1 mL	50-60 min	8
Billman, 1997 [39]	Dog	Soybean or saline	Fish oil emulsion[c,d]	–	0.4-4.1 mL	40-60 min	13
Billman, 1999 [40]	Dog	Soybean or saline	ALAa	0.86 g[b]	–	90 min	8
			EPAa	–	0.85 g[b]	90 min	7
			DHAa	–	0.78 g[b]	90 min	8
ω-3 PUFAs vs no treatment controls							
Lo, 1991 [41]	Dog	Buffer	ALA	180 mg[b] 270 mg[b] 540 mg[b]	–	NR	8

SSO indicates sunflower seed oil; SAF, safflower oil; OY Co, Oriental Yeast Company; e, esterified form; a, albumin bound; NR, not reported.
[a] For the purposes of this review, only the optimal comparison group was chosen (refer to categories of diet comparisons under Methods section).
[b] Calculated as amount of ω-3 (mg) * average body weight of animal (kg).
[c] EPA + DHA in free form and/or EPA + DHA as triglyceride.
[d] EPA + DHA in free form.

3.3.2. Ventricular tachycardia

Five feeding studies [15,16,19,23,27] and 3 infusion studies [38-40] that evaluated the effect of fish oils or EPA relative to ω-6 PUFAs or no treatment controls on the incidence of VT using an IM model reported a significant decrease, whereas 3 studies [20,22,37] reported no significant effect.

An IRM model was used to induce VT in 11 feeding studies. A significant decrease in the incidence of VT was observed in 6 studies [15,19,21,29-31] comparing fish oils

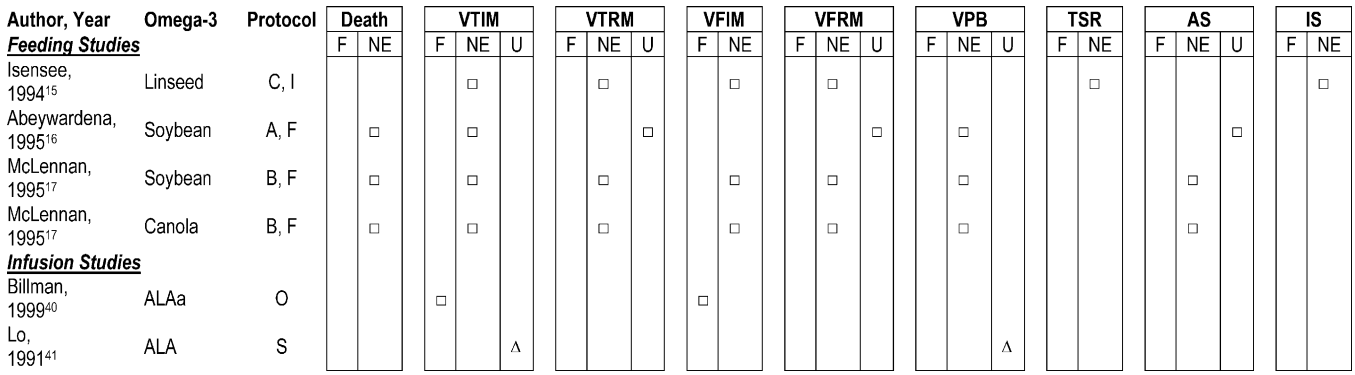

Fig. 1. Summary of the effects of ALA supplementation on selected arrhythmia outcomes in various animal models. Results are expressed as "favorable" (F; $P < .05$), "no effect" (NE; $P > .05$), or "unfavorable" (U; $P < .05$) relative to the comparison group. Dietary comparison groups include ALA vs ω-6 PUFAs (□) and ALA vs no treatment controls (△). Refer to Methods section (arrhythmia models) for a description of protocol codes.

or EPA to ω-6 PUFAs or SFAs. No significant differences were observed in 5 studies [16,20,23,24,33].

3.3.3. Ventricular fibrillation

Ten feeding studies [15,19,20,22,23,25-28,37] with 12 comparisons and 3 infusion studies [38-40] evaluated the effect of fish oil or EPA and/or DHA relative to ω-6 PUFAs, MUFAs, or no treatment controls on the incidence of VF using an IM-induced and/or electrical stimulation–induced arrhythmia model. Ten [15,22,23,25,27,28,38-40] reported a significant decrease, whereas 5 [19,20,26,28,37] reported no significant effect.

Among the 11 feeding studies that evaluated the effect of fish oil or EPA relative to ω-6 PUFAs or SFAs on the

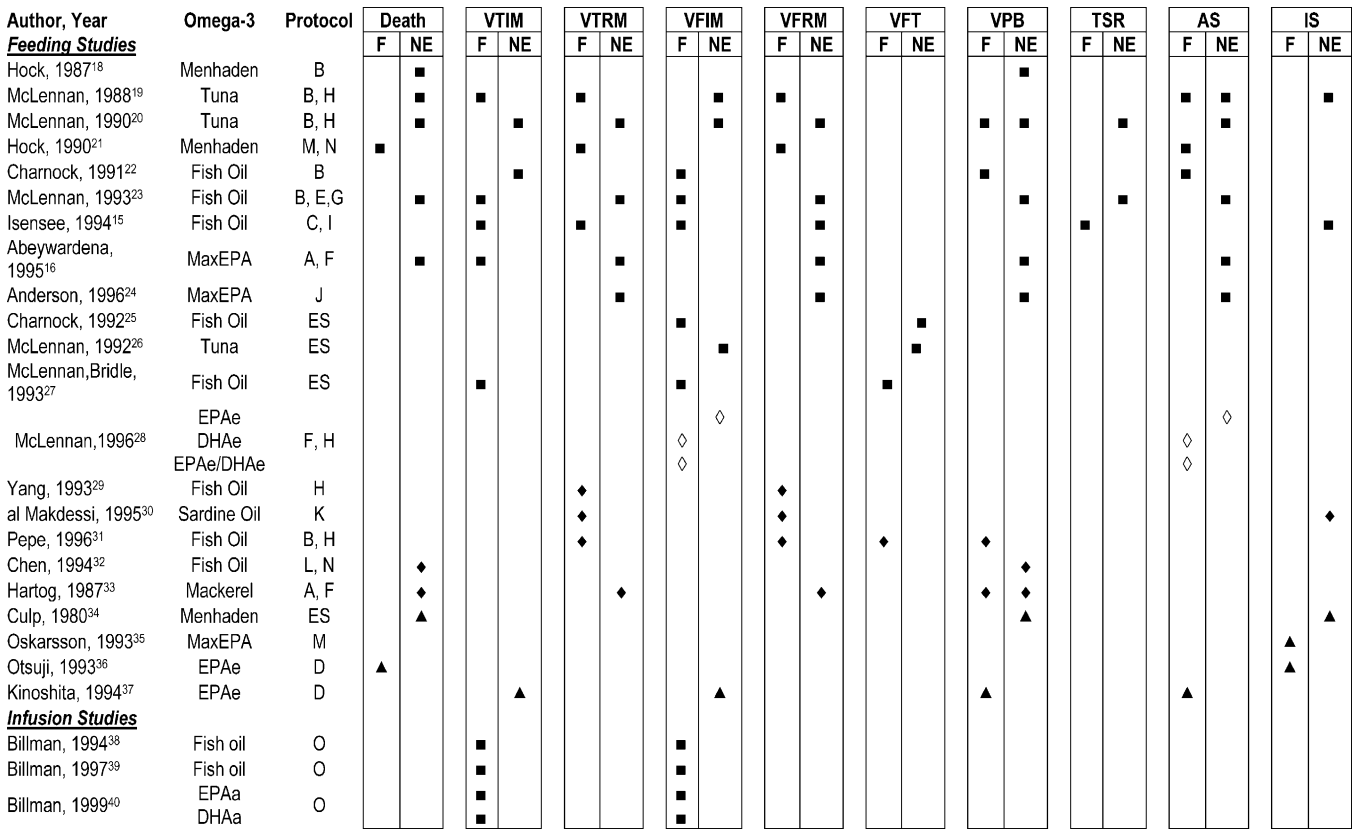

Fig. 2. Summary of the effects of fish oil, EPA, and/or DHA supplementation on selected arrhythmia outcomes in various animal models. Results are expressed as "favorable" (F; $P < .05$) or "no effect" (NE; $P > .05$) relative to the comparison group. Dietary comparison groups include fish oil vs ω-6 PUFAs (■), fish oil vs MUFAs (◇), fish oil vs SFAs (◆), and fish oil vs no treatment controls (▲). Refer to Methods section (arrhythmia models) for a description of protocol codes.

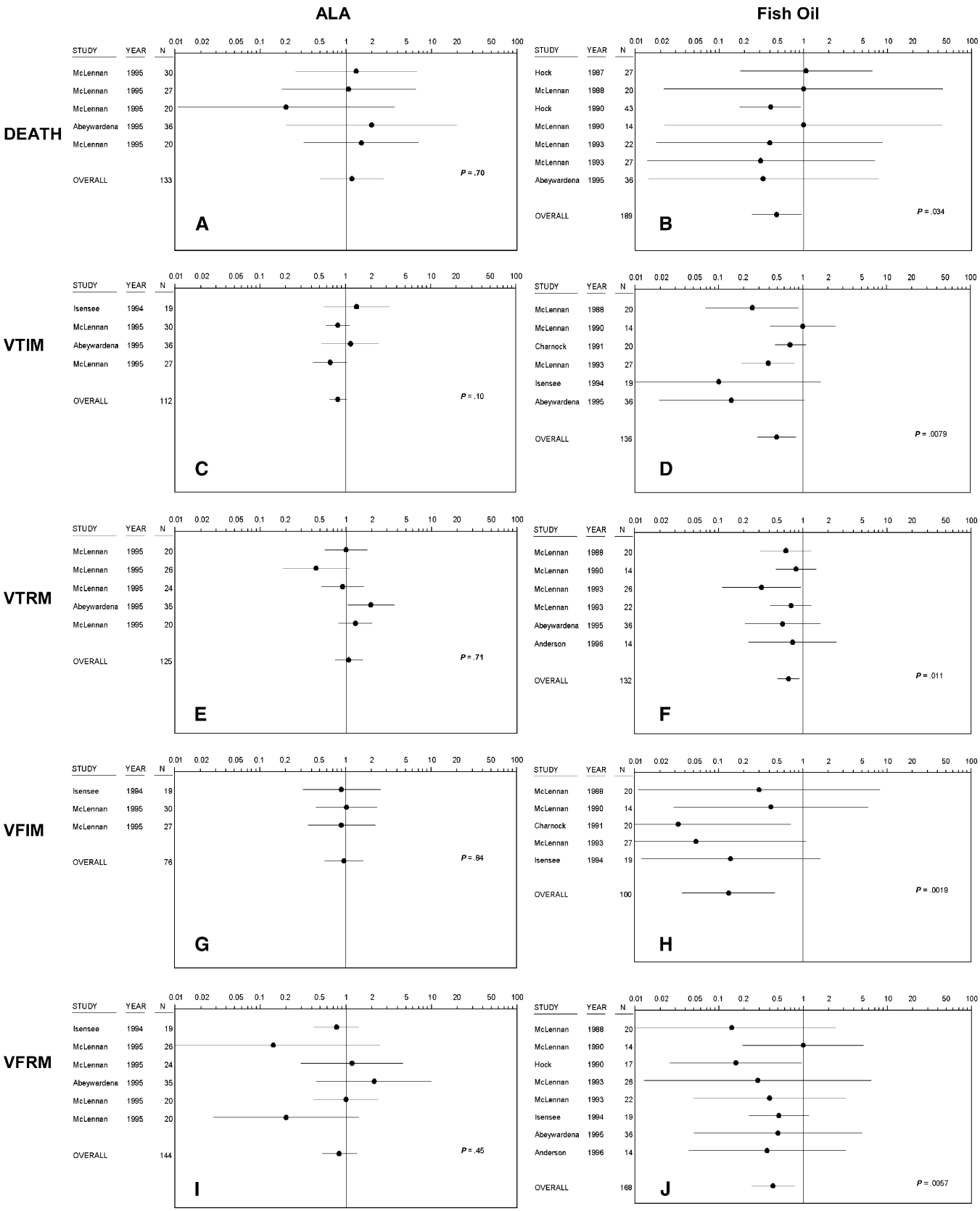

Fig. 3. Meta-analysis of the effect of ALA or fish oil supplementation relative to ω-6 supplementation on incidence of death (A, B), VTIM (C, D), VTRM (E, F), VFIM (G, H), and VFRM (I, J), respectively.

incidence of VF using an IRM model, 5 studies [19,21,29-31] reported a significant decrease, whereas 6 studies [15,16,20,23,24,33] reported no significant effect.

3.3.4. Ventricular fibrillation threshold

Four feeding studies evaluated the effect of fish oil or EPA relative to ω-6 PUFAs or SFAs on VFT. Two studies [27,31] reported a significant increase in the threshold current needed to induce VF, whereas 2 studies [25,26] reported no significant effect.

3.3.5. Ventricular premature beats

Twelve feeding studies with 13 comparisons evaluated the effect of fish oil or EPA relative to ω-6 PUFAs, SFAs, or no treatment controls on the number of VPBs. Five [20,22,31,33,37] reported a significant decrease, whereas 8 [16,18,20,23,24,33,34] reported no significant effect.

3.3.6. Length of TSR

Among the 3 feeding studies that evaluated the effect of fish oil or EPA relative to ω-6 PUFAs on TSR, 1 study [15] reported a significant increase, whereas 2 studies [20,23] reported no significant effect.

3.3.7. Arrhythmia score

Nine feeding studies with 12 comparisons compared AS between animals fed fish oils, EPA, and/or DHA relative to those fed ω-6 PUFAs, MUFAs, or no treatment controls. Six [19,21,22,28,37] reported a significantly lower score, whereas 6 [16,19,20,23,24,28] reported no significant change.

3.3.8. Infarct size

Two feeding studies [35,36] found significantly smaller ischemia-induced IS in animals fed EPA compared to those fed SFAs. Four studies [15,19,30,34] using fish oils or EPA found no reductions in IS when compared to animals fed ω-6 PUFAs, SFAs, or no treatment controls.

3.4. Meta-analysis on the effect of ω-3 PUFAs on arrhythmia outcomes

Results of the meta-analysis showed that relative to ω-6 fatty acid supplementation, ALA supplementation had no significant effect on the incidence of death (Fig. 3A; risk ratio [RR] = 1.2, 95% CI: 0.51-2.6), VTIM (Fig. 3C; RR = 0.82, 95% CI: 0.65-1.0), VTRM (Fig. 3E; RR = 1.1, 95% CI: 0.73-1.6), VFIM (Fig. 3G; RR = 0.95, 95% CI: 0.56-1.6), or VFRM (Fig. 3I; RR = 0.84, 95% CI: 0.52-1.3) in studies using rat models.

The significantly reduced RR of death with fish oil supplementation (Fig. 3B; RR 0.47, 95% CI 0.23-0.93) was due to a single study [21] as determined by sensitivity analysis. After removing this study, the combined RR became nonsignificant (RR 0.64, 95% CI 0.19-2.1). The RR for fish oil supplementation on the incidence of VTIM (Fig. 3D; RR = 0.49, 95% CI: 0.29-0.83), VTRM (Fig. 3F; RR = 0.68, 95% CI: 0.50-0.91), VFIM (Fig. 3H; RR = 0.21, 95% CI: 0.07-0.63), and VFRM (Fig. 3J; RR = 0.44, 95% CI: 0.25-0.79) was significantly lower relative to ω-6 supplementation.

4. Discussion

Summarizing the results from feeding studies that compared fish oils, EPA, and/or DHA to ω-6 PUFAs, MUFAs, SFAs, or no treatment controls across various animal species, we conclude that fish oil supplementation appears to be antiarrhythmic, as depicted by its ability to reduce VT and VF in IM models. No significant or consistent benefit was observed with ALA supplementation. The meta-analysis results from rat studies support these findings.

With regard to the other arrhythmia outcomes evaluated, fish oils, EPA, and/or DHA did not show any significant effect on the incidence of death and IS. Results were inconsistent for VTRM, VFRM, VFT, VPB, TSR, and AS. It must be noted that in most of the studies that showed a nonsignificant reduction in the incidence of death, VT, and VF, the lack of significance was likely due to limited statistical power. Only 1 study [31] reached the minimum group size needed to detect a 50% reduction in arrhythmic effects [43]. In addition, the majority of the animal models used to assess the antiarrhythmic effects of ω-3 PUFAs involved acute IM or RM. These types of induced arrhythmias are not dependent upon structural defects that might be expected to develop during chronic ischemia or when fibrosis and myofibril disarray may be expected to affect arrhythmogenesis [44]. Thus, differences in the arrhythmia model employed may also have influenced the outcomes examined.

Among the 4 infusion studies, 3 studies [38-40] using a canine model of sudden cardiac death reported acute antiarrhythmic effects for albumin-bound ALA, EPA plus DHA, or fish oil emulsion. The other study [41], which also used a canine model, found no effect of ALA supplementation on VT and VPB at low doses and toxic effects at high doses.

5. Mechanism of action

The potential mechanism(s) responsible for the observed antiarrhythmic effect of EPA and DHA has yet to be fully elucidated. Data from in vitro studies using isolated hearts/cardiomyocytes from animals fed ω-3 PUFAs suggest that the incorporation of ω-3 PUFAs into cardiac membrane phospholipids [45] increases membrane fluidity [46] and subsequently affects the function of transporters, such as β-adrenergic receptors involved in cell signaling receptors [47] and enzymes such as Na^+,K^+-ATPase, Ca^{2+}-ATPase, cyclooxygenase, and phospholipase [37,48-50] embedded in the membrane bilayers. This, in turn, could influence the production of a variety of eicosanoids that lower the susceptibility to arrhythmias, thus preventing VF during myocardial ischemia and reperfusion [51]. In contrast,

extensive work by Leaf et al [52] using cultured neonatal rat cardiomyocytes where the ω-3 PUFAs are directly added to the culture medium suggests that ω-3 PUFAs, functioning in the free or unbound form, directly affect electrophysiological processes in the cardiac muscle [13,52-54]. ω-3 PUFAs were shown to electrically stabilize cardiomyocytes by modulating conductance and prolonging the duration of the inactivated state of ion channels in the sarcolemma, particularly the fast, voltage-dependent sodium current [55-57] and the L-type calcium current [58,59], which underlie the initial upstroke and plateau phases of the cardiac action potential. However, these effects were also observed with ω-6 PUFAs. Further work demonstrating the specificity of these effects on the basis of individual PUFAs, as well as confirmation of these findings from other laboratories, is needed.

6. Limitations and future research

The meta-analysis is based on published studies; consequently, it is limited by its observational design. To increase statistical power, our meta-analysis combined different strains of the same species of animal (eg, Wistar rats and Sprague-Dawley rats) across different age groups of animals. This could introduce "noise" for the observed effects. Although the random-effects model takes the variability between studies into account, the relative risks of the arrhythmic outcomes are based on summary statistics without access to primary data of individual studies. The observed effects from meta-analysis were therefore not adjusted for other factors that could affect the outcomes, such as the amount of ω-6 PUFAs, MUFAs, or SFAs in the animals' diet. We tried to minimize the confounding factors by choosing the optimal comparison from each study (Methods section), so that all comparisons in the meta-analysis were iso-caloric and had minimum differences in the fatty-acid compositions in the diets. However, the fatty-acid compositions in the diets were not totally controlled due to different sources of added fats between groups.

In conclusion, data from animal studies evaluating the effect on ω-3 supplementation relative to other dietary fatty acids or no treatment controls suggest a potential antiarrhythmic effect with fish oil, EPA, and/or DHA, but not with ALA. This conclusion is consistent with the observational data in humans. It is unknown whether these effects will be observed in other disease settings, not related to ischemia. In addition, the relevance of these fish oil studies to the prevention of sudden cardiac death as a consequence of cardiac arrhythmias in humans remains unclear, and further studies are needed.

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