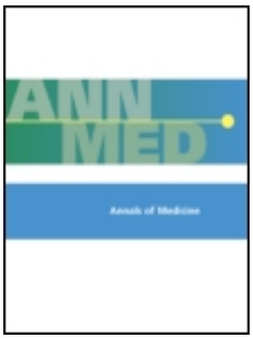

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ORIGINAL ARTICLE

Prevention of sudden cardiac death with omega-3 fatty acids in patients with coronary heart disease: A meta-analysis of randomized controlled trials

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Abstract

Aim. To systematically review trials concerning the effects of omega-3 fatty acids on sudden cardiac death (SCD), cardiac death, and all-cause mortality in coronary heart disease (CHD) patients.

Methods. PubMed, Embase, and the Cochrane database (1966–2007) were searched. We identified randomized controlled trials that compared dietary or supplementary intake of omega-3 fatty acids with control diet or placebo in CHD patients. Eligible studies had at least 6 months of follow-up data, and cited SCD as an end-point. Two reviewers independently assessed methodological quality. Meta-analysis of relative risk was carried out using the random effect model.

Results. Eight trials were identified, comprising 20,997 patients. In patients with prior myocardial infarction (MI), omega-3 fatty acids reduced relative risk (RR) of SCD (RR = 0.43; 95% CI: 0.20–0.91). In patients with angina, omega-3 fatty acids increased RR of SCD (RR = 1.39; 95% CI: 1.01–1.92). Overall, RR for cardiac death and all-cause mortality were 0.71 (95% CI: 0.50–1.00) and 0.77 (95% CI: 0.58–1.01), respectively.

Conclusions. Dietary supplementation with omega-3 fatty acids reduces the incidence of sudden cardiac death in patients with MI, but may have adverse effects in angina patients.

Key words: *Meta-analysis, omega-3 fatty acids, randomized controlled trials, sudden cardiac death*

Sudden cardiac death (SCD) is a major public health problem and accounts for 450,000 deaths annually in the United States (1). SCD is responsible for 50% of the mortality from cardiovascular disease in developed countries. Omega-3 fatty acids intake is associated with lower risk of cardiac arrhythmias, including SCD (2–4). Evidence from a population-based prospective cohort study (4) and animal studies (5) indicates that omega-3 fatty acids may protect against ventricular arrhythmia. These mechanisms may be important in reducing the incidence of SCD and cardiac death in people with coronary heart disease (CHD).Although a previous meta-analysis has reported that omega-3 fatty acids can reduce the incidence of fatal myocardial infarction (MI), SCD, and overall mortality (6), there are still some areas of uncertainty. First, although the earlier meta-analysis focused on randomized controlled trials (RCTs), it is not known whether these results are consistent for generalized clinical practice. Second, a number of RCTs have been published since the earlier report was published, and their impact on the pooled evidence was unknown (7–9). We therefore reviewed a larger number of RCTs in order to investigate further the effect of dietary or supplementary intake of omega-3 fatty acids on SCD, cardiac death, and all-cause mortality.

Methods

We conducted a literature search using PubMed, Embase, and the Cochrane databases (1966 through

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Key message

- Dietary supplementation with omega-3 fatty acids reduces the incidence of sudden cardiac death in patients with myocardial infarction, but may have adverse effects in angina patients.

June 2007) and limited our search to RCTs comparing dietary or non-dietary intake of omega-3 fatty acids with control diet or placebo. We carried out a detailed evaluation of references from original articles and related reviews found in the literature search.

The search terms used were 'omega-3 fatty acid', 'fish oil', 'dietary therapy', and 'cardiovascular disease', individually and in combination. The articles found were then examined to determine whether SCD data were reported. We excluded studies if they were not RCTs, if participants had undergone implantable cardioverter defibrillators, or if the follow-up duration was <6 months. Two investigators independently assessed study eligibility for inclusion in meta-analysis, as well as study quality. Disagreements were resolved by consensus.

Statistical analysis

For studies using a factorial design, data on all patients were used in this analysis. We did not assess publication bias (10), because each pooled estimate included fewer than ten trials. Statistical heterogeneity was assessed using the I^2 test (we considered I^2 values $<25\%$ to denote low heterogeneity, while values $>75\%$ denoted high heterogeneity) and the chi-square test ($P<0.10$ indicated heterogeneity). In the presence of statistical heterogeneity, we conducted a random effects meta-analysis.

Subgroup analysis was conducted to establish the effect of clinical heterogeneity between studies on the conclusions of systematic reviews. Because the effect of omega-3 fatty acids on CHD may vary between angina patients and MI patients (including acute and post-MI), we specified subgroup analyses to examine the heterogeneity of the results on the basis of the percentage of the population that had experienced MI at baseline (including both acute MI and post-MI patients). Hierarchical cluster analysis was used to cluster eight RCTs into two subsets using SPSS 15.0 for Windows. The optimal cut-off point is $<50\%$ or $>80\%$. Four RCTs were included in the subgroup analysis (9,11–13). We believe that the angina subgroup is represented in the subgroup of patients with low incidence of MI, for the following reasons. All patients in the study by Burr had stable angina. The percentages of the patients with histories of angina in the study by Leaf and in JELIS were 88% and 79%, respectively. It is reasonable to assume that least 50% of the patients in the CART study (11) must have had angina symptoms (50% of the patients had previous myocardial infarction), which would drive patients to accept percutaneous transluminal coronary angioplasty. Results were reported as relative risk (RR) with 95% confidence intervals (CIs). Studies of small sample volume trials may exhibit exaggerated treatment effects (11,12,14,15). Excluding them may result in increased internal validity but could reduce external validity of the analysis. In addition, the selection of a random versus fixed effects model in meta-analyses is controversial. The use of a random effects model in the calculation of CIs results in wider intervals, and therefore a more conservative estimate of treatment effect compared with a fixed effects model. To reconcile these issues, sensitivity analysis was conducted whereby the systematic review was re-analyzed excluding small sample size studies and using a random effects model. All data analyses were performed using Cochrane Collaboration Review Manager 5.0.

Abbreviations

SCD	sudden cardiac death
CHD	coronary heart disease
MI	myocardial infarction
RCT	randomized controlled trials
PTCA	percutaneous transluminal coronary angioplasty
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
CART	the Coronary Angioplasty Restenosis Trial
JELIS	Japan eicosapentaenoic acid lipid intervention study
GISSI-P	the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
CI	confidence interval
RR	relative risk
ATPase	adenosine triphosphatase
CAST	Cardiac Arrhythmia Suppression Trial

Results

Search results

Figure 1 describes the stages of the systematic review process using the Quality of Reporting of Meta-analyses (QUOROM) statement (16). Of 306

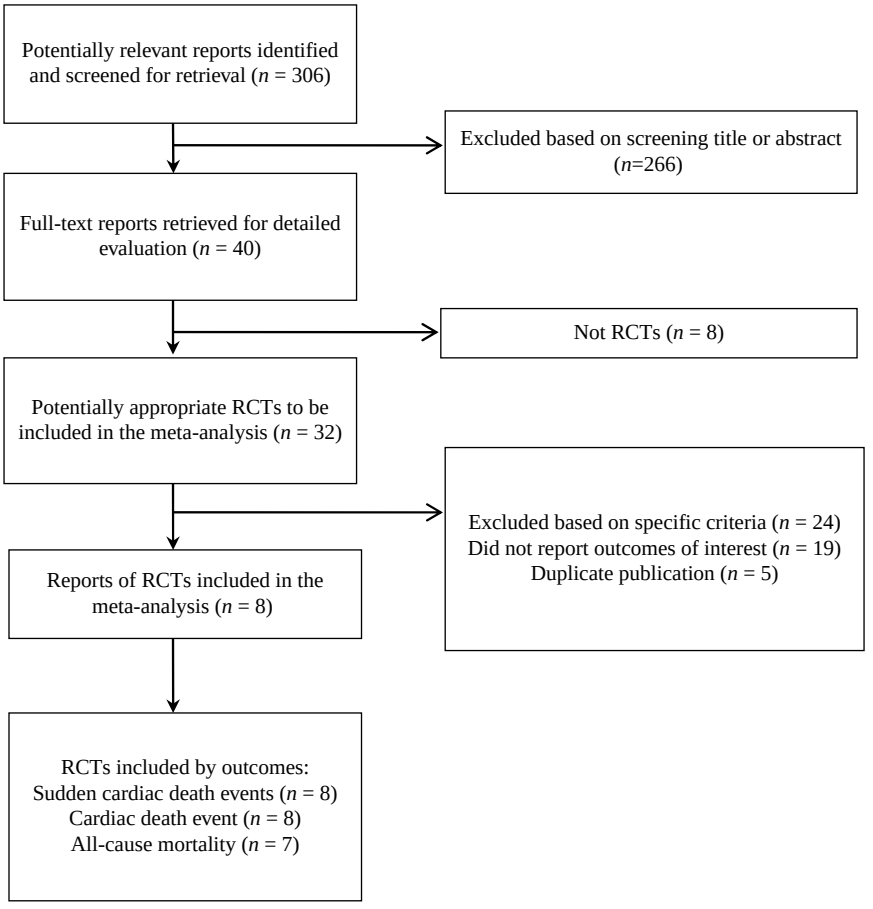

Figure 1. The selection process for RCTs of omega-3 fatty acids. The Quality of Reporting of Meta-analyses (QUOROM) flow diagram describes the screening process and exclusion criteria for RCTs of omega-3 fatty acids. Eight trials met the inclusion criteria. (RCT = randomized controlled trial.)

citations initially identified, full-text versions of 32 potentially relevant studies were retrieved for detailed evaluation. Ultimately, eight RCTs met the inclusion criteria and were included in our systematic review (7–9,11–15).

Qualitative findings

Tables I and II summarize the characteristics and quality of the included studies. We reviewed the methodological quality of these trials using the Jadad scoring system (17). Trials included in the systematic review included a total of 20,997 participants (10,507 patients in the intervention group and 10,490 patients in the control group). The mean age of the study populations ranged between 48.5 and 63 years; the percentage of men was from 31% to 100%. The incidence of MI was >80% in four trials (7,8,14,15), and was <51% in four trials (9,11–13). The median follow-up duration was 33 months (range: 6–108 months). Of these RCTs, all eight reported SCD and cardiac death, while seven reported all-cause mortality.

Effect of omega-3 fatty acids on SCD

When pooling data from all eight RCTs (20,997 patients) using a random effect model, there was a non-significant trend toward reduced SCD events in the populations receiving omega-3 fatty acids (RR = 0.71; 95% CI: 0.43–1.18) compared to controls (Figure 2). Among the omega-3 fatty acids-treated group, 206 patients died (19.6%) compared with 248 controls (23.6%). We stratified the eight pooled studies by the incidence of MI (including acute or post-MI): one group had >80% and the other had <51% MI incidence. A significant 57% relative risk reduction in SCD was observed in the high-incidence MI subgroup (RR = 0.43; 95% CI: 0.20–0.91). A negative effect of omega-3 fatty acids on SCD was observed (RR = 1.39; 95% CI: 1.01–1.92) in the low-incidence MI subgroup.

Table I. Characteristics of randomized controlled trials of omega-3 fatty acid in the meta-analysis.

Study	Inclusion criteria	Regimen	History of MI (%)	Regimen	Age (years)	Men (%)	Mean follow-up (month)	Statin (%)	Beta-blocker (%)	Jadad [a]
de Lorgeril 1994	Post MI	Intervention	100	Alpha-linolenic acid, ~2 g/d	53.5	89.4	46	-	60.2	3
		Control	100	Dietary advice	53.5	92.1		-	63.4	
Leaf A 1994	CHD with PTCA	Intervention	33	4.1 g/d EPA; 2.8 g/d DHA	63	77	6	-	-	3
		Control	33	Corn oil	58	81		-	-	
Singh RB 1997	Suspected AMI	Intervention	90.1	1.08 g/d EPA; 0.72 g/d DHA	48.5	91.8	12	-	29.4	5
		Control	84.6	$Al(OH)_3$, 0.1 g/d	49.2	93.3		-	24.9	
CART 1999	CHD with PTCA	Intervention	51	Omega-3 fatty acid 5.1 g/d	60	74.5	6	9.2	76.5	5
		Control	50	Corn oil	59	80.7		16.7	72.9	
GISSI-P 2002	Post MI	Intervention	100	EPA, 0.3 g/d; DHA 0.6 g/d	59.2	85.7	42	4.6	43.9	2
		Control	100	No intervention	59.4	84.9		4.9	44.2	
Singh RB 2002	High risk CHD	Intervention	83	Rich in linolenic acid (3.487–4.963 g/d)[b]	49	91	24	7	-	3
		Control	83	Diet	48	88		6	-	
Burr 2003	Stable angina	Intervention	0	Oily fish 2 portions/week or fish oil (Maxepa) 3 g/day (0.54 g/d EPA; 0.36 g/d DHA)[c]	61	100	108	-	42.4	2
		Control	0	Fruit vegetables and oats	61	100		-	40.6	
JELIS 2007	CHD	Intervention	30.0	EPA, 1.8 g/d with statin	61	32	55	97	9	3
		Control	27.2	Statin alone	61	31		98	8	

[a]Used to assess the quality of randomized controlled trials (range 1–5).
[b]The food composition was available in the web site: http://www.nal.usda.gov/fnic/foodcomp/search/ and http://www.nutritiondata.com/facts/fats-and-oils/507/2.
[c]The Maxepa composition was available in the web site: http://www.epgonline.org/viewdrug.cfm/letter/M/language/LG0001/drugId/DR001189/drugName/MAXEPA
AMI = acute myocardial infarction; CART = the Coronary Angioplasty Restenosis Trial; CHD = coronary heart disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GISSI-P = the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; JELIS = Japan eicosapentaenoic acid lipid intervention study. MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty;- = not available.

Table II. Data on cardiac death and SCD in randomized controlled trials of omega-3 fatty acid.

Study	Regimen	No. of patients	SCD	Cardiac death	All-cause mortality
de Lorgeril 1994	Intervention	302	0	3	8
	Control	303	8	16	20
Leaf A 1994	Intervention	275	0	0	0
	Control	276	1	2	2
Singh RB 1997	Intervention	122	2	14	14
	Control	118	8	26	26
CART 1999	Intervention	250	1	1	1
	Control	250	1	3	3
GISSI-P 2002	Intervention	5665	111	247	477
	Control	5658	154	306	554
Singh RB 2002	Intervention	499	6	18	24
	Control	501	16	33	38
Burr 2003	Intervention	1571	73	180	283
	Control	1543	47	139	242
JELIS 2007	Intervention	1823	13	18	-
	Control	1841	13	21	-

CART = the Coronary Angioplasty Restenosis Trial; GISSI-P = the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; JELIS = Japan eicosapentaenoic acid lipid intervention study; SCD = sudden cardiac death; - = not available.

We detected significant heterogeneity within this subgroup comparison ($I^2 = 53\%$, $P = 0.09$). Retrospective exploration of heterogeneity identified one trial that seemed to differ from the others (15), in that enrolled patients did not receive cholesterol-lowering therapy. Exclusion of this trial removed the statistical heterogeneity ($I^2 = 0\%$, $P = 0.44$) and did not affect the findings of evidence of a difference in SCD (RR = 0.67; 95% CI: 0.53–0.84).

Effect of omega-3 fatty acids on cardiac death

Eight RCTs reported cardiac death for patients receiving omega-3 fatty acids compared with control patients. Systematic review revealed a pooled relative risk for cardiac death prevention of 0.71 (95% CI: 0.50–1.00) (Figure 3), indicating the evidence of a statistically non-significant difference in cardiac death prevention.

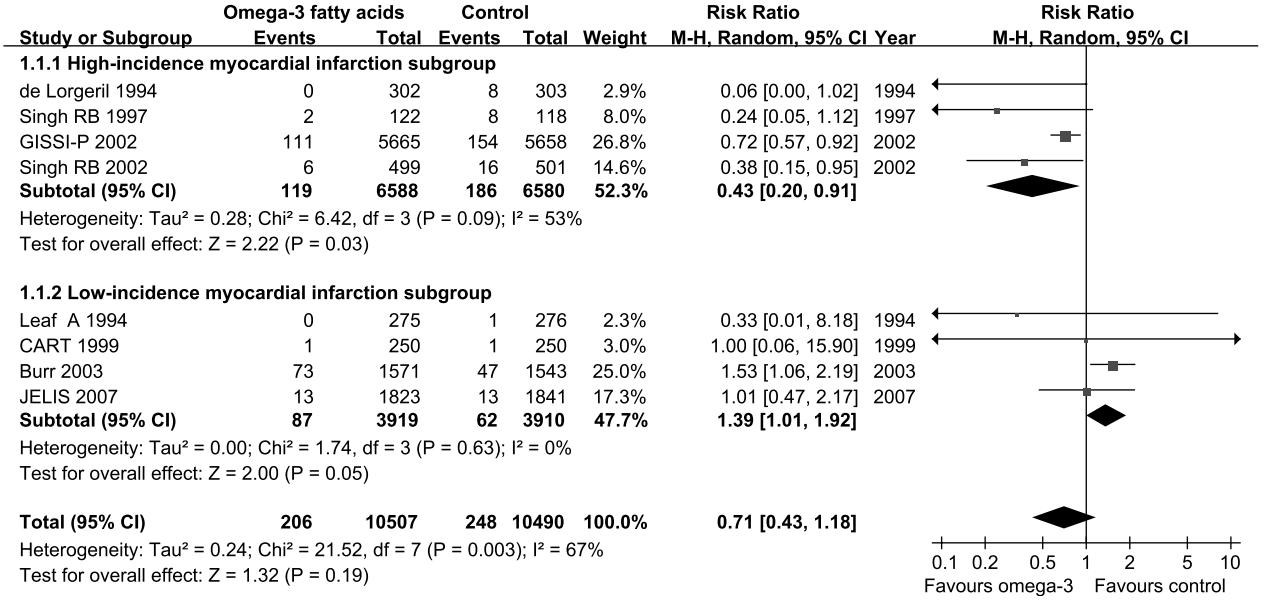

Figure 2. Prevention of sudden cardiac death with omega-3 fatty acids. Analysis of the randomized controlled trial (RCT) subgroup with a low proportion of myocardial infarction patients revealed a statistically non-significant trend of reduced sudden cardiac death. However, the subgroup with high proportion of myocardial infarction patients demonstrated a significant reduction in sudden cardiac death (SCD). Individual and pooled analysis demonstrated a non-significant 29% relative risk reduction (relative risk reduction = 1 − relative risk, so one minus the relative risk of SCD (0.71) = 0.29) in sudden cardiac death.

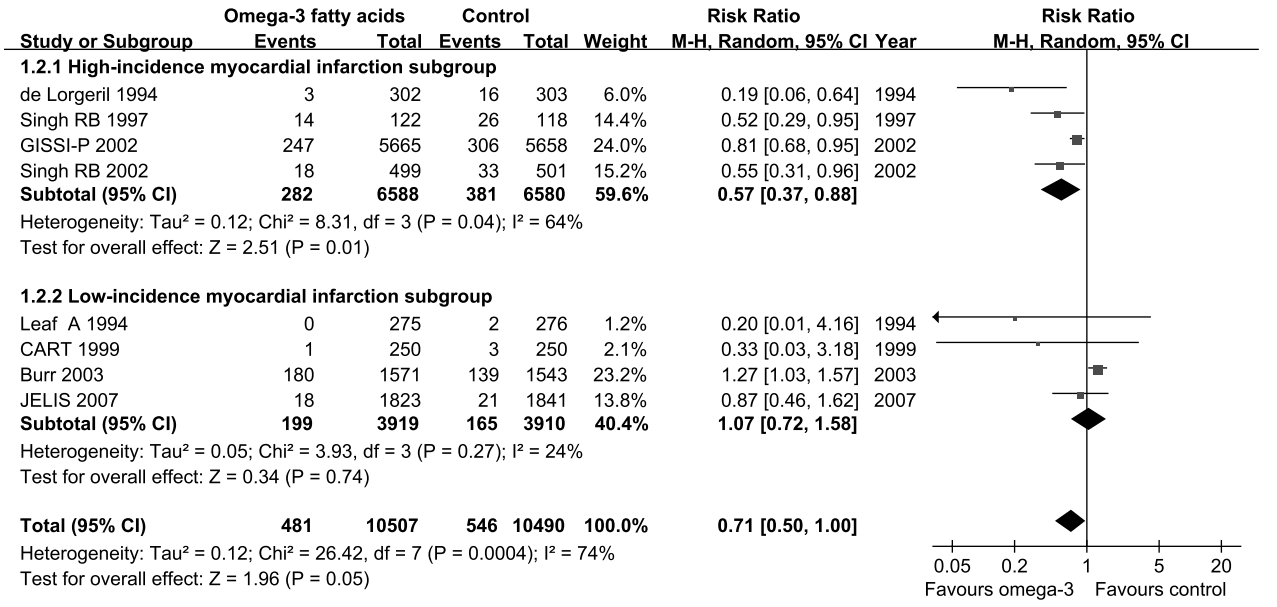

Figure 3. Prevention of cardiac death with omega-3 fatty acids. The high-incidence myocardial infarction subgroup showed a significant reduction in cardiac death. Individual and pooled analysis demonstrated a non-significant 29% relative risk reduction (relative risk reduction = 1 − relative risk, so one minus the relative risk of sudden cardiac death (SCD) (0.71) = 0.29) in cardiac death.

In the RCTs with high MI incidence, omega-3 fatty acids reduced cardiac death (RR = 0.57; 95% CI: 0.37–0.88); excluding the trial by de Lorgeril (15) did not affect the conclusion of the systematic review (RR = 0.76; 95% CI: 0.66–0.88) ($I^2 = 0\%$, $P = 0.49$). Administration of omega-3 fatty acids did not reduce the cardiac death in the RCTs with low MI incidence (RR = 1.07; 95% CI: 0.72–1.58).

Effect of omega-3 fatty acids on all-cause mortality

Seven RCTs (17,333 participants) explored the incidence of all-cause mortality in patients receiving omega-3 fatty acids compared to control patients. Overall, there was no significant reduction in all-cause mortality in patients who received omega-3 fatty acids (RR = 0.77; 95% CI: 0.58–1.01) (Figure 4). However, results from the subgroup of trials

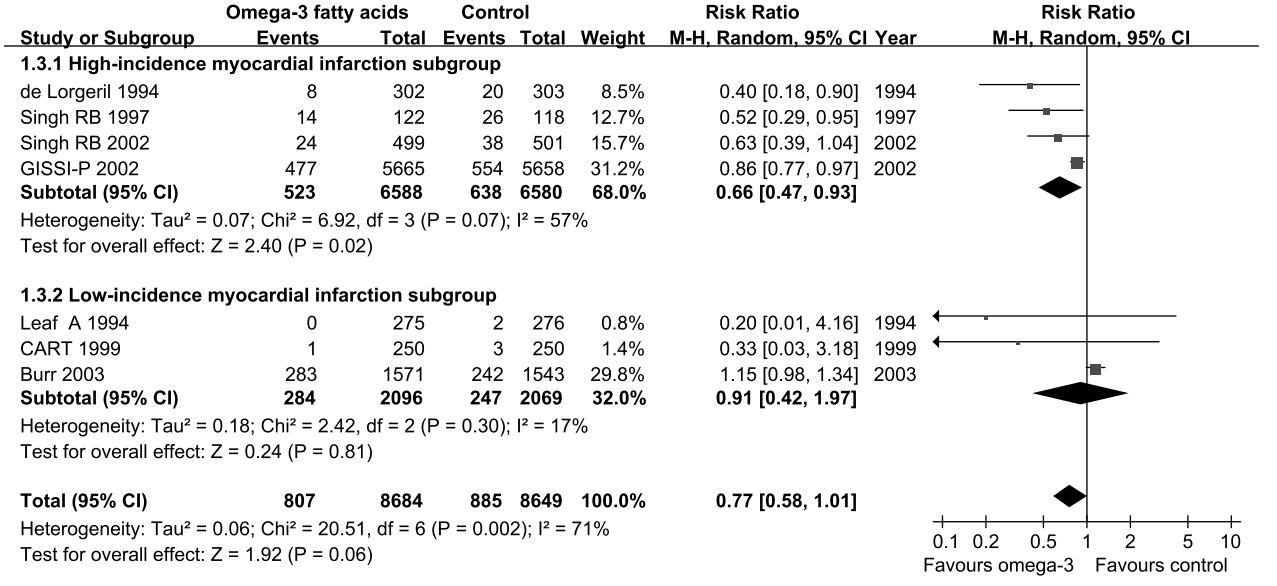

Figure 4. Effect of omega-3 fatty acids on all-cause mortality. The high-incidence myocardial infarction subgroup experienced a significant reduction in all-cause mortality. Individual and pooled analysis demonstrated a non-significant 23% relative risk reduction (relative risk reduction = 1 − relative risk, so one minus the relative risk of sudden cardiac death (SCD) (0.77) = 0.23) in all-cause mortality.

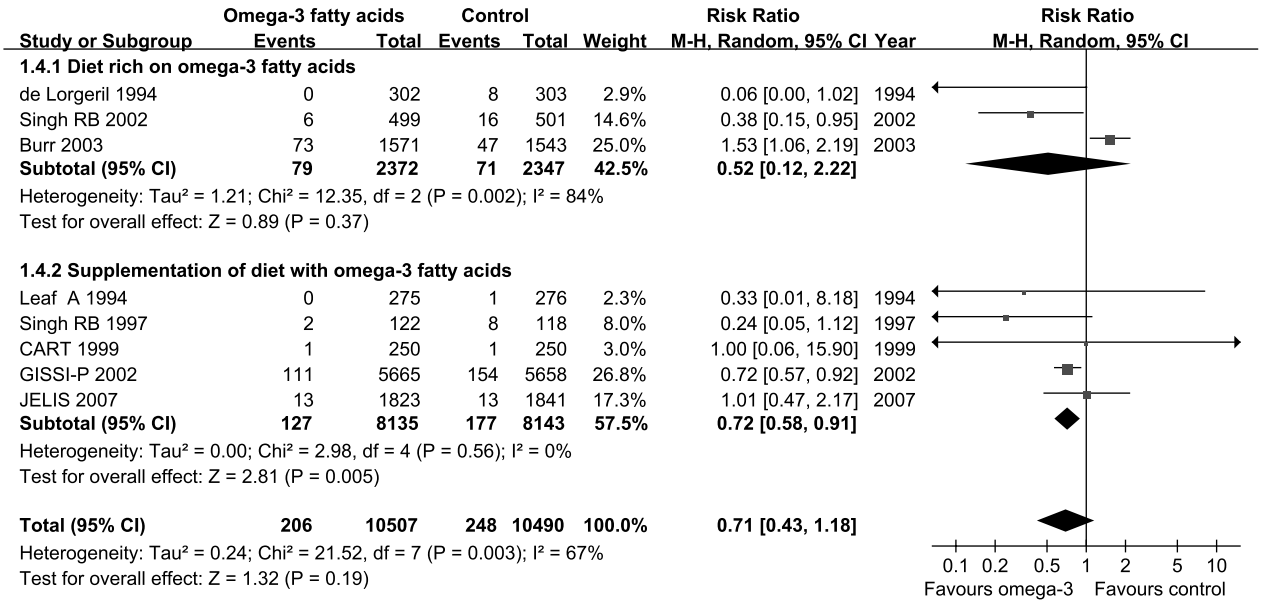

Figure 5. Effect of dietary or supplement sources of omega-3 fatty acids on sudden cardiac death. Sudden cardiac death was reduced in the randomized controlled trials (RCTs) in which omega-3 fatty acids were administered as a supplement (RR = 0.72; 95% CI: 0.58–0.91), but not in RCTs with diet or dietary advice (RR = 0.52; 95% CI: 0.12 to 2.22).

with high MI incidence demonstrated a benefit (RR = 0.66; 95% CI: 0.47–0.93).

The systematic review revealed moderate heterogeneity ($I^2 = 57\%$, $P = 0.07$). Exclusion of the trial by de Lorgeril (15) reduced this heterogeneity ($I^2 = 24.4\%$, $P = 0.26$), and did not affect the conclusion of the systematic review (RR = 0.70; 95% CI: 0.52–0.95).

Effect of dietary or supplementary sources of omega-3 fatty acids on SCD

In our meta-analysis, three trials with diet or dietary advice (8,13,15) and five trials with omega-3 fatty acid supplements (7,9,11,12,14) were reviewed. We specified subsets using the random effect model in order to estimate the claimed benefits of receiving omega-3 fatty acids through supplements or in the diet. Sudden cardiac death was reduced in the RCTs in which omega-3 fatty acids were administered as a supplement (RR = 0.72; 95% CI: 0.58–0.91), but not in RCTs with diet or dietary advice (RR = 0.52; 95% CI: 0.12–2.22) (Figure 5).

Sensitivity analysis

The four trials (11,12,14,15) demonstrating the largest treatment effect were also the four smallest and together accounted for 10% of patients in the pooled analysis. Although publication bias could result in an overestimation of treatment effect, this would be unlikely to produce a qualitative change in the result of this analysis, given the relatively large number of patients in the analysis. Indeed, a sensitivity analysis, which excluded all reports of $<1{,}000$ patients (11,12,14,15), still found similar relative risk results for SCD (RR = 1.02; 95% CI: 0.97–1.07), cardiac death (RR = 1.02; 95% CI: 0.97–1.07) and all-cause mortality (RR = 1.02; 95% CI: 0.97–1.07). After the study by Burr et al. was excluded due to methodological limitations, the RR for sudden cardiac death was 0.94 (95% CI: 0.46–1.94), and heterogeneity was slightly reduced ($I^2 = 0\%$, $P = 0.80$).

Discussion

Our systematic review of eight RCTs indicates that omega-3 fatty acids may have an effect on prevention of SCD in patients with MI (including acute and post-MI patients). The benefit of reduction in cardiac death and all-cause mortality were driven largely by reduction in SCD.

These results differed from those of recent systematic reviews (6,18–21) by suggesting that omega-3 fatty acids could protect against SCD in patients with MI, but not for patients who have angina. Although Bucher et al. (6) assessed the effect of long omega-3 fatty acids on SCD over at least 6 months in patients with CHD and found significant protection from SCD (RR = 0.8; 95% CI: 0.6–0.9), the patients were not stratified further, and two recent studies investigated by Burr et al. (13)

and Yokoyama et al. (9) were not included in their systematic review. Hooper et al. (21) demonstrated that omega-3 fatty acids did not have a clear effect on total mortality and combined cardiovascular events, but this meta-analysis and other meta-analyses (19–21) did not pool the results of SCD. Considering that UK guidelines encourage the general public to eat more oily fish, and higher amounts are advised after myocardial infarction (supported by trials after myocardial infarction), the authors posited that it was probably not appropriate to recommend a high intake of omega-3 fatty acids for people who have angina but have not had a myocardial infarction. The results of our systematic review add new evidence to support this position.

The clinical benefits of omega-3 fatty acids in CHD have been demonstrated in these trials and may be related to the ability of omega-3 fatty acids to prevent calcium overload by maintaining the activity of L-type calcium channels during periods of stress (22) and to increase the activity of cardiac microsomal Ca^{2+}/Mg^{2+} ATPase (adenosine triphosphatase) (23). A reduction in Na^{+}–Ca^{2+} exchanger currents by omega-3 fatty acids might attenuate delayed depolarization (24).

As has been demonstrated with other substances that influence cardiac electrophysiology, the effects of omega-3 fatty acids may be antiarrhythmic or proarrhythmic depending on the underlying substrate and/or arrhythmogenic trigger (25). In line with the observation in CAST (Cardiac Arrhythmia Suppression Trial), omega-3 fatty acids may also cause arrhythmia through sodium channel blockade and action potential shortening. It is possible that omega-3 fatty acids, which have been demonstrated to shorten refractory periods (24) and slow ventricular conduction through effects on the sodium channel (26) and cell-to-cell coupling (27), may promote re-entry.

Heterogeneity of patient populations may explain the conflicting outcomes of clinical trials with increased intake of omega-3 fatty acids, regarding propensity to cardiac arrhythmias (28). The various patient subpopulations represent different arrhythmogenic mechanisms. Increased consumption of omega-3 fatty acids was antiarrhythmic in patients with a prior myocardial infarction. The antiarrhythmic effects of omega-3 fatty acids in this patient population may have been based on suppression of triggered activity due to spontaneous Ca^{2+} release and prolonged action potentials (29). Harmful effects of omega-3 fatty acids were observed in patients with acute ischemia. The arrhythmia mechanism in these patients may have been based on re-entry (30).

However, some fish species can also contain harmful environmental contaminants. For example, methyl mercury is present at low levels in water systems (lakes, rivers, reservoirs, oceans, etc.) but bioconcentrated in the aquatic food chain, reaching peak levels in large and old predatory fish and marine mammals. Therefore, dietary omega-3 fatty acids have a different effect from omega-3 fatty acid supplements. The study by Guallar et al. suggests that high mercury contents may diminish the antiarrhythmic effects of fish consumption on cardiovascular health (31).

A causal mechanism for the association between methyl mercury and heart disease is suggested by the apparent antagonistic interaction of methyl mercury and the omega-3 fatty acids contained in fish. This relationship may reflect the opposing effects of the antioxidant properties of the omega-3 fatty acids and the oxidative/lipid peroxidation stress exerted by methyl mercury (32). However, methyl mercury also potentially exerts toxicity through a variety of other mechanisms, including microtubule alternation and the impairment of calcium homeostasis (33). Other mechanisms may also be in play, such as the mercury-selenium interaction. A protective effect of selenium may partly account for conflicting results of mercury exposure and coronary heart disease (34). The omega-3 fatty acids are more abundant in fatty fish, and methyl mercury concentration also varies by species of fish (although not necessarily by fat content). This may explain inconsistent results among studies of the cardiovascular benefits of fish consumption.

In summary, patients with MI are susceptible to malignant arrhythmia. Omega-3 fatty acids may contribute most significantly to relative risk reduction in the high-incidence MI subgroup. Another subgroup analysis of low-incidence MI patients did not demonstrate a consistent reduction in SCD, cardiac death, or all-cause mortality. Therefore, it is probably appropriate to recommend a high intake of omega-3 fatty acids for people who have an MI. Moreover, more high-quality RCTs of long duration are needed.

Study limitation

The duration of treatment and follow-up varied between trials (from 6 months for CHD, to 108 months for the study by Burr). However, because these trials were small and contributed only few events (11,12,14,15), it is less likely that the summary estimates for SCD, cardiac death, and all-cause mortality were affected. Additional prospective research is required to determine the impact

of use of omega-3 fatty acids in patients with CHD, and to clarify the mechanisms responsible for any reduction in SCD. The OMEGA trial (35) will randomize 3,800 patients with a history of MI to use omega-3 fatty acid supplementation in the experiment group and placebo group. The mean follow-up is 12 months and the primary end-point is SCD incidence. This trial, combined with our systematic review, should provide further information on the end-points of SCD.

Conclusions

Evidence supports the use omega-3 fatty acids in the preventive treatment of SCD in patients with prior MI, but not in patients with angina.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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