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Omega-3 polyunsaturated fatty acids supplementation and cardiovascular outcomes: do formulation, dosage, and baseline cardiovascular risk matter? An updated meta-analysis of randomized controlled trials

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ABSTRACT

The recent publication of the REDUCE-IT study has reopened the debate about the efficacy of omega-3 fatty acids in reducing the risk of cardiovascular (CV) events. This meta-analysis aims at investigating the effect of omega-3 long-chain polyunsaturated fatty acids (n-3 PUFA) administration on CV outcomes in published randomized clinical trials (RCTs), with a focus on the role of dose, type of n-3 PUFA, and different CV risk at baseline.

This meta-analysis was conducted according to the PRISMA reporting guidelines. PubMed, Cochrane and EMBASE were searched since inception to March 2020. Inclusion criteria were: (1) RCTs; (2) including subjects with previous CV events; (3) administration of n-3 PUFA ≥ 1 g/day dosage for ≥1 year; (4) effects on all-cause mortality, cardiac death, major adverse cardiovascular events (MACE), fatal/nonfatal myocardial infarction (MI), or fatal/nonfatal stroke reported. Odds ratios (ORs) with 95 % confident intervals (95 %CI) were estimated.

16 RCTs were included in the meta-analysis accounting for 81,073 participants. Supplementation of n-3 PUFA was associated with a significant risk reduction of cardiac mortality (OR 0.91 [95 % CI, 0.85 − 0.98]), MACE (OR 0.90 [95 % CI, 0.82 − 0.99]), and MI (OR 0.83 [95 % CI, 0.71 − 0.98]). In subgroup analyses, the risk reduction of cardiac mortality and MI was confirmed only in RCTs that enrolled patients in secondary prevention (-21 % and -31 %, respectively). Moreover, only the administration of more than 1 g per day of n-3 PUFA was effective in reducing the risk of cardiac death (-35 %), MACE (-24 %), and MI (-33 %). Finally, EPA + DHA supplementation was only associated with a significant risk reduction of cardiac death compared with EPA administered alone (-8 %). Conversely, the efficacy of EPA administered alone seemed to be greater in terms of risk reduction of MACE (-25 %) or MI (-30 %) than the combined EPA + DHA supplementation.

The pharmacological approach with n-3 PUFA significantly improves cardiovascular outcomes, with higher benefit achieved by patients in secondary CV prevention, using more than 1 g/day, and taking EPA administered alone.

1. Background

Population studies have shown an inverse association between consumption of omega-3 long-chain polyunsaturated fatty acids (n-3 PUFA) and cardiovascular disease (CVD) [1,2]. Health authorities around the world suggest consumption of the equivalent of at least 1–2 oily fish meals a week, which provides 250–500 milligram per day of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) [3–5]. Intakes of long-chain n-3 PUFA well above those recommended for general health have therapeutic applications [6], with evidence of its association with fewer cardiac deaths in both healthy individuals and those with pre-existing CVD.

Mechanistic studies have demonstrated that n-3 PUFA possess several properties that may confer a protective influence against a range of

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Table 1
Characteristics of Randomized Control Trials.

Source	Trial	Year	Country	Men %	Mean age years	Prevention[a]	Statin %	Duration years	n-3 type	n-3 g/day	Control	Jadad score
Singh et al. [58]	IEIS-4	1997	India	93	48.9	secondary	nr	1	EPA + DHA	1.8	Placebo (aluminium hydroxide)	11
Marchioli et al. [45]	GISSI-Prevenzione	1999	Italy	85	59.4	secondary	4.7	3.5	EPA + DHA	1	no treatment	9
Von Schacky et al. [59]	SCIMO	1999	Germany	80	58.4	secondary	25.6	2	EPA + DHA	3 – 6	placebo (non-marine FA)	12
Nilsen et al. [60]	–	2001	Norway	79	64.0	secondary	7.2	2	EPA + DHA	4	placebo (corn oil)	8
Brouwer et al. [61]	SOFA	2006	Europe	85	61.5	mixed	45.5	1	EPA + DHA	2	placebo (sunflower oil)	13
Svensson et al. [62]	OPACH	2006	Denmark	65	67.0	secondary	19.5	2	EPA + DHA	1.7	placebo (olive oil)	12
Yokoyama et al. [15]	JELIS	2007	Japan	32	61.0	mixed	100.0	5	EPA	1.8	standard care	10
Tavazzi et al. [29]	GISSI-HF	2008	Italy	78	67.0	mixed	22.3	4.5	EPA + DHA	1	placebo (nr)	12
Rauch et al. [31]	OMEGA	2010	Germany	74	64.0	secondary	94.2	1	EPA + DHA	1	placebo (olive oil)	13
Einvik et al. [63]	DOIT	2010	Norway	100	70.1	mixed	19.0	3	EPA + DHA	2.4	placebo (corn oil)	12
Bosch et al. [33]	ORIGIN	2012	Multicenter	65	63.5	mixed	53.0	7	EPA + DHA	1	placebo (olive oil)	13
Macchia et al. [64]	FORWARD	2013	Argentina	55	66.1	mixed	nr	1	EPA + DHA	1	placebo (olive oil)	11
Roncaglioni et al. [35]	R&P Study	2013	Italy	62	64.0	mixed	41.4	5	EPA + DHA	1	placebo (olive oil)	12
Bonds et al. [34]	AREDS2	2014	USA	43	74.0	mixed	44.0	5	EPA + DHA	1	placebo (nr)	10
Nosaka et al. [65]	–	2017	Japan	76	70.5	secondary	100.0	1	EPA	1.8	placebo (nr)	10
Bhatt et al. [17]	REDUCE-IT	2019	Multicenter	71	64.0	mixed	100.0	6	EPA	4	placebo (mineral oil)	12

[a]Prevention: mixed prevention trials include studies where some but not all participants have CHD at baseline.

CVD states [7]. These include modulating cell membrane function, with favourable effects on cardiac rhythm, endothelial function, and the inflammatory, oxidative, and thrombotic pathways implicated in atherosclerosis [8,9]. Furthermore, n-3 PUFA favourably modulate triglyceride-rich lipoprotein metabolism [10].

In the pre-statin era, the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione study demonstrated that administration of low-dose prescription n-3 PUFA in patients with recent myocardial infarction (MI) was associated with a reduction in cardiovascular (CV) events [11], likely due to a significant reduction in fatal cardiac arrhythmias post MI. Moreover, there has been a great deal of controversy about the role of supplementation with n-3 PUFA EPA and DHA in the prevention of CVD [12]: some trials testing n-3 PUFA have shown dramatic benefit for reducing all-cause mortality, CV mortality, sudden cardiac death (SCD), major coronary heart disease (CHD) events and even stroke [13–15], while other trials have failed to confirm similar benefits. A 2013 meta-analysis of 11 randomized controlled trials (RCTs) [16] showed protective effects of n-3 PUFA supplements (at least 1 g per day, and for at least 1 year) on cardiac death (relative risk (RR), 0.68; 95 % CI, 0.56 to 0.83), SCD (RR, 0.67; 95 % CI, 0.52 to 0.87), and MI (RR, 0.75; 95 % CI, 0.63 to 0.88), but failed to find statistically significant associations with all-cause mortality or stroke. More recently, results from the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention) trial, designed to investigate the effect of high dose icosapent ethyl (4 g per day) in addition to statin treatment in a high CV risk population specifically with elevated triglyceride (TG) levels, showed a dramatic 25 % reduction in CV events, as well as an important reduction (-20 %) of the risk of CV death [17].

These inconsistent results warrant a better understanding of the effects of omega-3 fatty acids on the subtypes of cardiovascular diseases, and their use in secondary prevention and patients at high CV risk where the impact of residual CV events on a background of optimal, evidence based, lipid-lowering therapy is a remarkable clinical challenge even in a context of extremely low LDL-cholesterol (LDL-C) levels as achieved with a combination high-intensity statin-ezetimibe-PCSK9 inhibitors. Therefore, the objective of our study was to perform a meta-analysis of all the available RCTs on CV secondary prevention and patients at high (and very high) CV risk to investigate the CV preventive effect of omega-3 fatty acid administration through supplements (no dietary counselling), with a focus on the role of dose and type of n-3 PUFA administered, as well as its effects in populations with different CV risk at baseline.

2. Methods

This meta-analysis was conducted according to the PRISMA reporting guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for systematic reviews and meta-analyses [18].

2.1. Literature searches and study selection

Comprehensive literature searches using the PubMed, Cochrane Library and EMBASE databases were conducted. Literature searches, which covered studies published up to March 2020, were designed to identify RCTs that examined the association between use of n-3 PUFA and CHD outcomes (see Supplementary material).

The search was restricted to English language and articles available as full text (studies published as abstract were excluded). Supplementary literature searches included examining previously published reviews to identify pertinent studies that may not have been captured in our electronic searches. All selected articles were screened by 2 researchers, with minor differences resolved by discussion and consultation with a third researcher.

We included studies which met the following criteria: (1) randomized, controlled trials; (2) including subjects at high CV risk and with

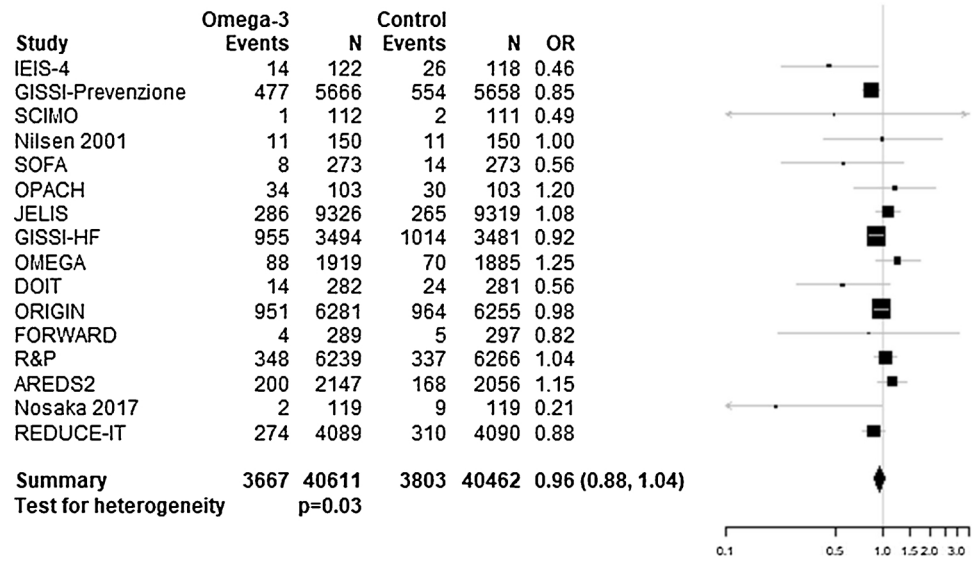

Fig. 1. Meta-analysis of omega-3 fatty acid supplements for all-cause mortality.

previous CV events (RCTs conducted only on subjects free from CVD at baseline were not eligible); (3) studying the administration of omega-3 fatty acid supplements at least 1 g per day dosage and for at least 1 year; (4) investigating all-cause mortality, cardiac death, major adverse cardiovascular events (MACE), MI (fatal or nonfatal) and/or stroke (fatal or nonfatal) as primary or secondary outcomes; (5) reporting quantitative estimates of the exposure-outcome association or sufficient data to calculate it.

2.2. Data extraction and quality assessment

The following data were collected from each included RCT (Table 1): first author, publication year, country, number of participants and their main characteristics (e.g. gender, mean [SD] age, type of prevention [primary/secondary or secondary]), study duration, omega-3 dosage, investigated outcomes, and number of events in the treatment and in the control group. Moreover, we retrieved TG values at baseline and at the end of follow-up for both study's arms (Supplementary Table 1). Where not available in published articles, authors were contacted to obtain missing information.

Quality assessment of the included RCTs was evaluated using the Jadad scale [19], and accordingly a score ranging from zero (very poor) to 13 points (rigorous) was calculated.

2.3. Data synthesis and statistical analysis

Data were analysed according to the intention-to-treat principle. Odds ratios (ORs) with 95 % CIs were used as summary statistics. For clinical outcomes, a continuity correction of 0.5 in case of rare events was applied, which is commonly used for trials with zero events in only one arm [20]. We pooled the estimates by using both the Mantel & Haenszel method (fixed-effects model) and the DerSimonian & Laird method (random-effects model). When a significant heterogeneity was found (tested by Cochrane's Q test and measured with the I^2 statistic [21]), the results from the random-effects model were presented.

An influence analysis was also conducted by omitting one study at a time, in order to identify to what extent the results were influenced by a single study [22]. Publication bias was evaluated visually by examining the funnel plot measuring the standard error as a function of effect size, as well as statistically by using Egger's regression method [23].

Several subgroup analyses were conducted to identify potential sources of inter-study variation. We performed stratified analyses based on dose of n-3 PUFA equal or above 1 g per day, baseline CV risk of patients enrolled (RCTs including subjects only in secondary prevention or both in primary and/or secondary prevention), and administration of EPA + DHA rather than EPA alone.

All tests were considered statistically significant for p-values less than 0.05. The analyses and the corresponding graphical visualization of forest and funnel plots were conducting using R Software Program Version 3.6.2.

3. Results

3.1. Descriptive study characteristics

The flow diagram of the literature searches and study selection is shown in Supplementary Fig. 1. Finally, 16 RCTs were included in the meta-analysis accounting for 81,073 participants. The main study characteristics of the RCTs are summarized in Table 1 and in Supplementary Table 1. Samples sizes in the included studies ranged from 206 to 18,645 patients, and mean participant age ranged from an average of 49–74 years. Baseline TG levels were 150 mg/dL or more in six trials, up to 216.5 mg/dL in one trial. In thirteen out of sixteen RCTs, patients were randomly assigned to receive DHA and EPA in combination or placebo. The three remaining studies where phase 3 RCTs evaluating the effect of EPA administered alone. Overall, the dosage of n-3 PUFA intake ranged between 1 g per day and 6 g per day, with follow-ups ranging from 1 up to 7 years.

All studies were of high methodological quality, with the Jadad score ranging from 8 to 13 points.

3.2. Meta-analyses results

All the 16 RCTs, with a total of 40,611 patients in the omega-3 fatty acid arm and 40,462 in the control arm, were included in the analysis of all-cause mortality (Fig. 1). We found that the treatment with a supplementation of omega-3 was not associated with a statistically significant change in all-cause mortality compared with placebo (OR 0.96 [95 % CI, 0.88–1.04]). Conversely, the analysis of 13 studies showed a significant reduction of 9 % of the risk of cardiac mortality between the two groups (OR 0.91 [95 % CI, 0.85 − 0.98], Fig. 2). Analysing non-cardiac deaths (evaluated as difference between "all-cause mortality" and "cardiac death" in 12 RCTs), we found that the treatment with a supplementation of omega-3 was not associated with a statistically significant change in non-cardiac mortality compared with placebo (OR 1.01 [95 % CI, 0.94–1.08], data not shown). Compared with placebo,

Study	Omega-3 Events	N	Control Events	N	OR
IEIS-4	14	122	26	118	0.46
GISSI-Prevenzione	209	5666	258	5658	0.80
SCIMO	0	112	1	111	0.33
Nilsen 2001	8	150	8	150	1.00
SOFA	6	273	13	273	0.45
JELIS	29	9326	31	9319	0.93
GISSI-HF	613	3494	661	3481	0.91
OMEGA	28	1919	29	1885	0.95
DOIT	3	282	7	281	0.42
ORIGIN	574	6281	581	6255	0.98
R&P	101	6239	95	6266	1.07
AREDS2	12	2147	9	2056	1.28
Nosaka 2017	1	119	5	119	0.19
Summary	**1598**	**36130**	**1724**	**35972**	**0.91 (0.85, 0.98)**
Test for heterogeneity		**p=0.28**			

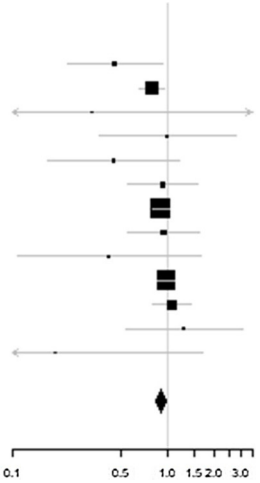

Fig. 2. Meta-analysis of omega-3 fatty acid supplements for cardiac mortality.

Study	Omega-3 Events	N	Control Events	N	OR
IEIS-4	30	122	56	118	0.36
GISSI-Prevenzione	547	5666	608	5658	0.89
SCIMO	2	112	7	111	0.27
Nilsen 2001	91	150	89	150	1.06
SOFA	65	273	62	273	1.06
OPACH	28	103	29	103	0.95
JELIS	262	9326	324	9319	0.80
GISSI-HF	1635	3494	1687	3481	0.94
OMEGA	182	1919	149	1885	1.22
DOIT	32	282	36	281	0.87
ORIGIN	2055	6281	2087	6255	0.97
FORWARD	4	289	4	297	1.03
R&P	484	6239	467	6266	1.04
AREDS2	183	2147	187	2056	0.93
Nosaka 2017	11	119	24	119	0.40
REDUCE-IT	459	4089	606	4090	0.73
Summary	**6070**	**40611**	**6422**	**40462**	**0.9 (0.82, 0.99)**
Test for heterogeneity		**p=<0.001**			

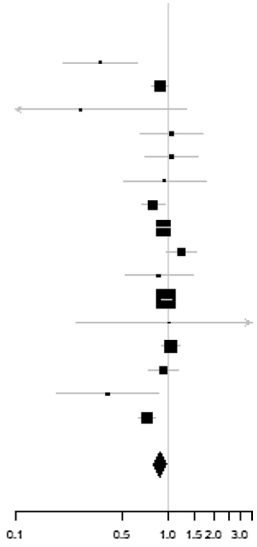

Fig. 3. Meta-analysis of omega-3 fatty acid supplements for major adverse cardiovascular events.

Study	Omega-3 Events	N	Control Events	N	OR
IEIS-4	25	122	48	118	0.38
GISSI-Prevenzione	223	5666	233	5658	0.95
SCIMO	1	112	4	111	0.24
SOFA	1	273	3	273	0.33
OPACH	4	103	13	103	0.28
JELIS	73	9326	97	9319	0.75
GISSI-HF	107	3494	129	3481	0.82
OMEGA	87	1919	78	1885	1.10
DOIT	11	282	9	281	1.23
ORIGIN	344	6281	316	6255	1.09
FORWARD	1	289	1	297	1.03
R&P	80	6239	90	6266	0.89
AREDS2	28	2147	30	2056	0.89
Nosaka 2017	1	119	0	119	3.03
REDUCE-IT	250	4089	355	4090	0.69
Summary	**1236**	**40461**	**1406**	**40312**	**0.83 (0.71, 0.98)**
Test for heterogeneity		**p=0.002**			

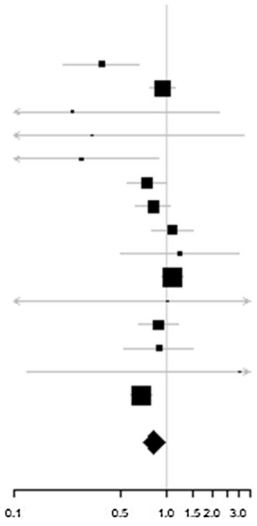

Fig. 4. Meta-analysis of omega-3 fatty acid supplements for myocardial infarction.

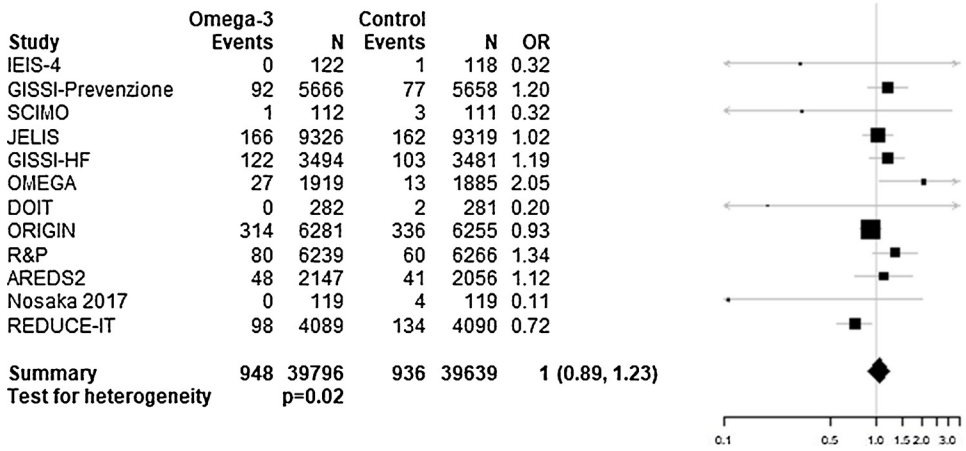

Fig. 5. Meta-analysis of omega-3 fatty acid supplements for stroke.

the supplementation of n-3 PUFA was also associated with a significant risk reduction of MACE (Fig. 3, OR 0.90 [95 % CI, 0.82 − 0.99], 16 RCTs) and of MI (Fig. 4, OR 0.83 [95 % CI, 0.71 − 0.98], 15 RCTs). Finally, there was not statistical evidence that omega-3 fatty acid intake reduced the risk of stroke (Fig. 5), with an OR of 1.00 (95 % CI, 0.89–1.23, 12 RCTs).

Visual examination of funnel plots and statistical testing of data from the RCTs for each outcome revealed no apparent publication bias (Supplementary Fig. 2). Influence analysis showed that the protective effects of omega-3 on the risk of cardiac death or MACE became not statistically significant by excluding the GISSI-Prevenzione, and that the benefit on the risk of MACE or MI became not statistically significant by excluding the IEIS-4, the JELIS or the REDUCE-IT trials (Supplementary Table 2).

3.3. Baseline patients' CV risk

In subgroup analyses (Fig. 6) by type of prevention (secondary or mixed), no apparent effect modification was found by prevention status among participants in RCTs regarding the risk of all-cause mortality, and stroke. However, the risk reduction of cardiac mortality associated with the supplementation of n-3 PUFA was confirmed only in the sub-analyses of RCTs that enrolled patients in secondary prevention (OR 0.79 [95 % CI, 0.67 − 0.93]) compared with OR 0.95 [95 % CI, 0.87–1.03] for patients in primary/secondary prevention), while the positive effects on MACE reached the statistical significance only in the sub-analyses of RCTs that enrolled patients in primary/secondary prevention, though the estimates were comparable.

3.4. Dose of n-3 PUFA

Stratified analyses based on levels of n-3 PUFA above and below 1 g per day (Fig. 6), highlight a relevant clinical benefit of the supplementation of omega-3 on CHD outcomes only when administered at high doses. Only the administration of more than 1 g per day of n-3 PUFA seems to be effective in reducing the risk of cardiac death (OR 0.65 [95 % CI, 0.47 − 0.91] vs OR 0.93 [95 % CI, 0.86–1.00]), MACE (OR 0.76 [95 % CI, 0.63 − 0.92] vs OR 0.97 [95 % CI, 0.92–1.01]), and MI (OR 0.67 [95 % CI, 0.58 − 0.77] vs OR 0.99 [95 % CI, 0.90–1.09]).

3.5. Administration of EPA + DHA or EPA

In subgroup analyses (Fig. 6) by type of administration (EPA + DHA rather than EPA alone), the efficacy of EPA alone seems to be greater compared with the supplementation with EPA + DHA in terms of risk reduction of MACE (OR 0.75 [95 % CI, 0.63 − 0.83] vs OR 0.96 [95 % CI, 0.88–1.04]) and MI (OR 0.70 [95 % CI, 0.60 − 0.81] vs OR 0.88 [95 % CI, 0.74–1.04]).

4. Discussion

4.1. Principal findings

Based on available RCTs on the effect of n-3 PUFA administration, our study showed a non-significant reduction in all-cause mortality. Conversely, compared to placebo, omega-3 fatty acids led to a significant risk reduction of cardiac death (-9 %), MACE (-10 %), and myocardial infarction (-17 %). Our results are in agreement with other pooled analyses of RCTs [24–26] or prospective cohort studies [27].

Looking at the individual studies, the results are not always consistent. In general, early trials [15,28,29] reported beneficial effects on CV outcomes, whereas more recent trials [30–35] reported neutral effects. This discrepancy might be attributed to methodological limitations of later trials, including short intervention duration, lengthy event-to-enrollment interval in secondary prevention, wide range of omega-3 dose adopted (as supplemental foods or capsules), high background omega n-3 [36] and advancements in background therapy. As an example, in GISSI-Prevenzione [13], only 5 % of participants at baseline and 45 % of participants at follow-up used cholesterol-lowering medications, whereas approximately 80 % of participants in OMEGA used lipid-lowering agents.

Our meta-analysis confirms the results of previous aggregate analyses on the effects of omega-3 supplementation on stroke risk by showing a non-significant increase of the risk [37]. In a sub-analysis of JELIS according to the presence of a history of stroke [14], in the secondary prevention groups, 1.8 g of EPA significantly suppressed stroke incidence in the low-dose statins group, while there was no beneficial effect of EPA combined with statin therapy in the primary prevention group. In the REDUCE-IT trial [17], stroke was significantly decreased by 4 g of EPA therapy. With this evidence, the effectiveness of n-3 PUFAs for prevention of stroke is yet to be elucidated.

4.2. Findings by baseline patients' CV risk

The results of subgroup meta-analyses showed a tendency towards a greater beneficial effect in trials restricted to secondary CV prevention subjects. This suggests that the population that could benefit most from omega-3 treatment is composed by subjects at higher CV risk. This hypothesis is also supported by the meta-analysis of Alexander et al. [27], in which the reduction of CHD risk was more evident in participants with elevated TG levels or elevated LDL-C levels. Moreover, it could explain the results of REDUCE-IT [17], showing a relevant risk reduction of ischemic (fatal or nonfatal) events among patients receiving statin therapy and who had a fasting TG levels of 135–499 mg/

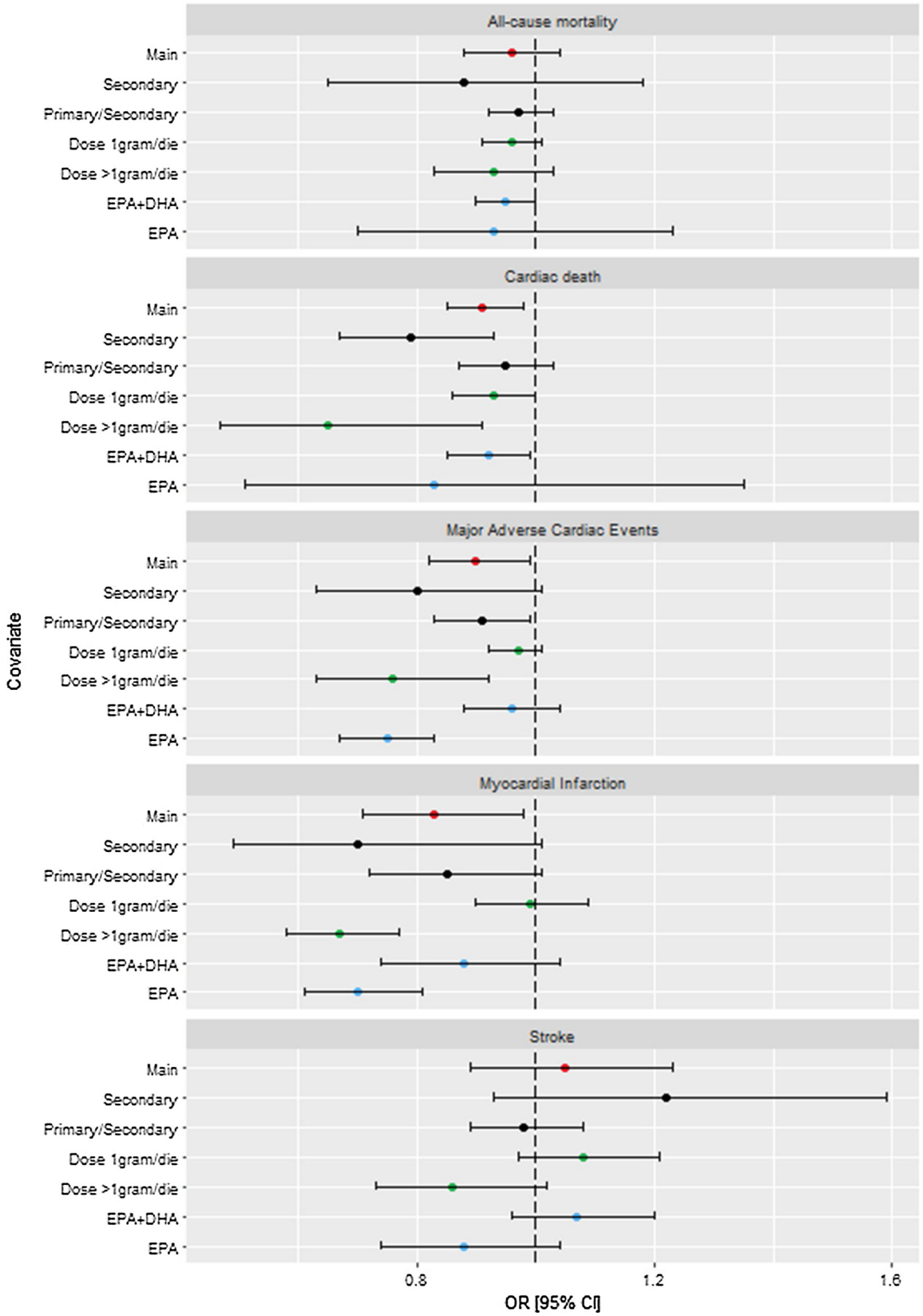

Fig. 6. Subgroup meta-analyses based on dose of omega-3 fatty acid supplements, type of prevention, and type of omega-3 fatty acid administrated.

dL. These results might be of clinical relevance for the current pharmacological approaches in secondary prevention (and high and very high risk patients) where a remarkable residual risk of CV events is observed even at extremely low LDL-C levels, i.e. FOURIER [38] where MACE were observed in 14.4 % diabetic patients after 36 months of statin-PCSK9 inhibitors therapy median LDL-C of 0.8 mmol/L (30 mg/dL). Moreover, it is possible that the beneficial effects of n-3 PUFAs are merely more likely to be detectable because of greater numbers of

events. This is suggested by the stratified analysis of the JELIS trial [15]: after a mean follow-up of 4.6 years, the composite frequency of the primary endpoint in all patients for the EPA group (1.8 g) was 19 % lower than in controls, with beneficial effects of EPA being comparable in both the secondary prevention and the primary prevention subgroups, although significant only in the former.

4.3. Findings by dose of n-3 PUFA

Dose seems to be a stronger determinant of n-3 PUFA efficacy. Indeed, our stratified analyses based on dose of n-3 PUFA clearly highlight a significant clinical impact only for daily dose > 1 g. This could explain the results of two recent large trials on patients in primary prevention. In the ASCEND trial in patients with diabetes but without manifestation of atherosclerotic CV disease, the administration of 1 g per day of n-3 PUFA over a mean follow-up of 7.4 years did not reduce the risk of a serious vascular event (nonfatal MI or stroke, transient ischemic attack, or vascular death) [39]. Furthermore, the VITAL trial on more than 25,000 participants in primary CV prevention showed that the administration of 1 g/day of marine omega-3 was not significantly associated with a reduction of major CV events [40,41]. Administered at higher doses, omega n-3 PUFA are associated with effects on TG-rich lipoproteins, inflammation, and platelet aggregation [42,43], whereas at lower dose there is no effect on lipids and platelet aggregation and a marginal impact on inflammation [44]. The GISSI-Prevenzione trial first highlighted the lack of a TG-lowering effect of the 1 g/day dose of omega n-3 [45] (Supplementary Table 1).

Clinical research has further established that low doses of omega n-3 PUFA are not effective in reducing TGs compared with higher doses, even in people with elevated TG levels [46]. TG-rich lipoproteins and particularly their remnants are highly atherogenic, as highlighted by a robust and unequivocal evidence coming from epidemiological [47], interventional [48], and genetic Mendelian-randomization based studies [49], strongly suggesting that the clinical benefit of lowering TG levels is similar to the clinical benefit of lowering LDL-C levels.

The results from the REDUCE-IT trial suggest that elevated TGs could be a useful biomarker for identifying patients who may experience the greatest benefit from prescription omega n-3 PUFA. Moreover, the reduction in CV events risk may be independent of achieving a specific target for fasting TGs [50]. Several lines of evidence suggest that the clinical outcomes results seen in REDUCE-IT may be accounted for more than just the effect on TG-rich lipoproteins. EPA supplementation was associated with a significant further reduction in C-reactive protein (CRP), additional to what measured at baseline with background statin therapy. Moreover, in REDUCE-IT, serious bleeding events occurred in 2.7 % of the patients in the EPA group and in 2.1 % in the placebo group ($p = 0.06$), suggesting a clinically relevant effect of EPA supplementation on platelet aggregation as previously reported [42,43]. Recent large clinical trial unequivocally highlighted the clinical impact of pharmacological approaches targeting inflammation [51] and coagulation pathways [52] to significantly reduce CVD events.

4.4. Findings by administration of EPA + DHA or EPA

Another peculiarity of the REDUCE-IT trial is that both the dose (total daily dose of 4 g) and the formulation (a highly purified and stable EPA ethyl ester) were different from those in previous outcome trials of n-3 fatty acids. In our sub-analysis by type of omega-3, EPA alone (3 trials) was associated with a significant and greater reduction in risk of MACE and MI. Biologic effects of omega n-3 PUFA could alter several inflammatory and oxidative stress pathways and both EPA and DHA appear to have at least some beneficial effects on inflammation and oxidative stress, being associated with lower CRP, IL-6 and fibrinogen levels [53,54], but studies providing a head-to-head comparison of EPA alone and EPA + DHA agents on TGs, as well as on relevant biomarkers of inflammation, platelets aggregation, are not available. In a previous review of several uncontrolled studies, both DHA and EPA supplementation reduced ex-vivo platelet aggregation in response to collagen [55]. The clinical relevance of such modest and not always consistent differential effects of EPA compared to DHA on LDL and/or HDL is unclear [56]. The potential cardiovascular disease benefit from 4 g/day of a DHA-containing prescription omega n-3 PUFA, was tested in the STRENGTH trial [57] in ≈13,000 patients across 21 countries. This trial was recently stopped early for futility; detailed analyses of the trial will be possible upon publication.

5. Conclusions

Omega-3 fatty acids supplementation in patients on secondary CV prevention or at high CV risk leads to a significant risk reduction of cardiac death by 9 %, MACE by 10 %, and myocardial infarction by -17 %, while it has no significant effect on all-cause mortality nor on risk of stroke. Subgroup meta-analyses suggest that these effects are seen only when omega-3 are supplemented at a dose > 1 g/day and in patients at higher CV risk on secondary prevention. The effect of omega-3 on MACE and MI were driven by the EPA supplementation. These results fully support the current recommendations by the 2019 ESC/EAS and ACC/AHA guidelines (as well as FDA recommendations) to use high dose EPA in combination with statin in high/very high CV risk patients with persistent mild to moderate elevation of plasma triglycerides to achieve a further and relevant reduction of CV events.

Author contributions

MC, EO, ALC and AZ were responsible for the study concept and design. MG and FG were responsible for literature search, study selection, and data collection. EO did the analysis. ALC contributed to the interpretation of the results. MC and AZ wrote the manuscript and all authors critically revised for important intellectual content and approved the final manuscript.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.105060.

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