ESC European Society of Cardiology

European Journal of Preventive Cardiology (2024) **31**, 1863–1875
https://doi.org/10.1093/eurjpc/zwae184

FULL RESEARCH PAPER
Lipids & atherosclerosis

Effects of omega-3 fatty acids on coronary revascularization and cardiovascular events: a meta-analysis

Monica Dinu[1], Francesco Sofi[1,2], Sofia Lotti [1], Barbara Colombini[1], Anna Vittoria Mattioli[3], Alberico L. Catapano[4,5], Manuela Casula [4,5], Andrea Baragetti [4,5], Nathan D. Wong[6], Philippe Gabriel Steg [7], and Giuseppe Ambrosio [8]*

[1]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [2]Unit of Clinical Nutrition, Careggi University Hospital, Florence, Italy; [3]Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy; [4]IRCCS MultiMedica, Milan, Italy; [5]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [6]Division of Cardiology, University of California, Irvine, USA; [7]Université Paris-Cité, INSERM U1148, FACT French Alliance for Cardiovascular Trials, AP-HP Hopital Bichat, Paris, France; and [8]Division of Cardiology, Center for Clinical and Translational Research—CERICLET, University of Perugia School of Medicine, Ospedale S. Maria della Misericordia, Via S. Andrea delle Fratte, 06156 Perugia, Italy

Received 14 January 2024; revised 16 April 2024; accepted 18 May 2024; online publish-ahead-of-print 13 June 2024

See the editorial comment for this article 'Navigating omega-3s', by O.R. Sapir *et al.*, https://doi.org/10.1093/eurjpc/zwae261.

Aims Benefits of pharmacologic omega-3 fatty acid administration in cardiovascular prevention are controversial. Particularly, effects on coronary revascularization are unclear; also debated are specific benefits of eicosapentaenoic acid (EPA). We investigated incident coronary revascularizations, myocardial infarction (MI), stroke, heart failure (HF), unstable angina, and cardiovascular death, in subjects randomized to receive EPA or EPA + docosahexaenoic acid (EPA + DHA) vs. control.

Methods and results Meta-analysis of randomized controlled trials (RCTs) was conducted after MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library search. Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines were followed for abstracting data and assessing data quality and validity. Data were pooled using a random effects model. Eighteen RCTs with 134 144 participants (primary and secondary cardiovascular prevention) receiving DHA + EPA ($n = 52\,498$), EPA alone ($n = 14\,640$), or control/placebo ($n = 67\,006$) were included. Follow-up ranged from 4.5 months to 7.4 years. Overall, compared with controls, omega-3 supplementation reduced the risk of revascularization [0.90, 95% confidence interval (CI) 0.84–0.98; $P = 0.001$; P-heterogeneity = 0.0002; $I^2 = 68\%$], MI (0.89, 95% CI 0.81–0.98; $P = 0.02$; P-heterogeneity = 0.06; $I^2 = 41\%$), and cardiovascular death (0.92, 95% CI 0.85–0.99; $P = 0.02$; P-heterogeneity = 0.13; $I^2 = 33\%$). Lower risk was still observed in trials where most participants (≥60%) were on statin therapy. Compared with DHA + EPA, EPA alone showed a further significant risk reduction of revascularizations (0.76, 95% CI 0.65–0.88; $P = 0.0002$; P-interaction = 0.005) and all outcomes except HF.

Conclusion Omega-3 fatty acid supplementation reduced the risk of cardiovascular events and coronary revascularization, regardless of background statin use. Eicosapentaenoic acid alone produced greater benefits. The role of specific omega-3 molecules in primary vs. secondary prevention and the potential benefits of reduced revascularizations on overall health status and cost savings warrant further research.

Lay summary It is debated whether pharmacologic administration of omega-3 fatty acids reduces cardiac events. In particular, it is unclear whether benefits are actually restricted to the use of eicosapentaenoic acid (EPA), or whether combined administration of EPA + docosahexaenoic acid (DHA) is needed; furthermore, little is known about possible benefits of omega-3 fatty acids in reducing incidence of coronary revascularization procedures. In this meta-analysis of all published evidence of clinical trials comparing EPA alone or EPA + DHA vs. control (134 144 participants), we demonstrate the following:

* Corresponding author. Tel: +390755271509, Email: giuseppe.ambrosio@unipg.it

- In the overall analysis of all trials, omega-3 supplementation reduced the risk of myocardial infarction and cardiovascular death, to a modest extent. However, when trials administering EPA alone were separately analysed, a further significant risk reduction for cardiovascular outcomes was demonstrated. Importantly, these benefits were also observed in subjects who were already taking statins as part of their chronic therapy.
- Administration of omega-3 fatty acids, particularly EPA alone, was also associated with a substantial decrease in the risk for subsequent coronary revascularizations. Reduction of revascularization procedures may induce additional benefits on overall health status and associated cost savings.

Keywords Omega-3 fatty acids • Coronary revascularization • Eicosapentaenoic acid • Docosahexaenoic acid • Cardiovascular prevention • Health costs

Introduction

Treatments aimed at reducing low-density lipoprotein cholesterol (LDL-C), namely statins, ezetimibe, PCSK9 inhibitors, and bempedoic acid, have consistently been shown to reduce the risk of cardiovascular events.[1–8] Besides LDL-C, hypertriglyceridaemia is thought to contribute to development and progression of atherosclerotic coronary plaques[9–15]; this concept would make a reduction of triglyceride levels an attractive target to further decrease cardiovascular risk. However, whilst fibrates, niacin, and omega-3 fatty acids (FAs) can significantly lower triglyceride levels, their effects on preventing cardiovascular events have been inconsistent.[16–29]

More recently, trials with new formulations and higher doses of omega-3 FAs have revamped the interest in treating hypertriglyceridaemia,[30,31] but their role in cardiovascular prevention is still debated.[9,32] It is also unclear whether the effect of administration of eicosapentaenoic acid (EPA) alone is similar—or superior—to that of EPA plus docosahexaenoic acid (DHA).[9,32–34]

Cardiovascular prevention trials typically focus on reduction in major events, less attention being paid to coronary revascularization; however, as pointed out by Ohman and Nanna,[35] 'The time has come… to come to harmony with the notion that lower is better for *both* prevention *and* revascularization'. However, meta-analyses of omega-3 trials, whilst assessing major cardiovascular events, have paid no or little attention to the effects on coronary revascularizations.[36–48] Yet, coronary revascularization, whether by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, is an impactful event for patients' health whilst entailing patient discomfort, periprocedural risks, and substantial costs.

Accordingly, the aim of this study was to systematically review and meta-analyse published randomized trial evidence on the effects of EPA alone and of combined EPA + DHA administration on coronary revascularization and on major cardiovascular events. We also evaluated the effects of omega-3 FAs when administered to subjects already on chronic statin therapy.

Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A standardized protocol identifying research question, search strategy, and inclusion and exclusion criteria was developed before starting the review. The protocol was registered in https://www.crd.york.ac.uk/PROSPERO/ (ID: CRD42022308171).

Study search, selection, and extraction of data were performed independently by two investigators (M.D. and S.L.). Conflicts were resolved by discussion with the third author (F.S.) and consensus.

Search strategy

A literature search was performed using Medline, Embase, Scopus, Web of Science, and Cochrane Library, through 20 June 2023, without language restrictions. References of the identified studies and previous reviews were also screened. Search terms, used in combination as MeSH terms and text words, were as follows: 'Omega-3', 'n-3 fatty acids', 'PUFA', 'eicosapentaenoic acid', 'docosahexaenoic acid', 'EPA', 'DHA', 'fish oil', 'marine oil', 'revascularization', 'percutaneous coronary intervention', 'percutaneous coronary angioplasty', 'coronary artery bypass graft', 'cardiovascular event', 'MACE', 'myocardial infarction', 'stroke', 'unstable angina', 'sudden death', and 'heart failure'. Full search strategy is provided in Supplementary material online, *Table S1*.

Data selection

Inclusion criteria were pre-determined following the PICOS (Population, Intervention, Comparator, Outcome, and Study) framework (see Supplementary material online, *Table S2*). Randomized controlled trials (RCTs) including ≥500 participants in primary or secondary cardiovascular prevention comparing the effects of pharmacologic omega-3 FA formulations (EPA, DHA), or their combination, vs. placebo or control were considered eligible. Outcomes of interest were as follows: coronary revascularization (PCI and CABG) and adverse cardiovascular events (myocardial infarction [MI], stroke, unstable angina [UA], heart failure [HF], and cardiovascular death). We excluded observational studies, trials conducted on patients with severe diseases, or when intervention consisted of dietary advice, owing to variability in the amount of omega-3 reported in food items. Trials where cardiovascular outcomes were assessed only as safety outcomes were excluded. Decision to include studies was based on title, abstract, and full-text screening.

Data extraction

Data from studies fulfilling the inclusion criteria were extracted by the two authors (M.D. and S.L.) using a standardized data extraction form. Disagreements were resolved by consensus or in conference with the third author (F.S.). The following data were extracted: first author, year of publication, country of study, characteristics of participants, sex distribution, intervention arm and its composition, control arm, length of follow-up, number of participants in each arm, use of statins, outcomes definition, and number of events in the intervention and control arms. The main outcome was coronary revascularization, reported as PCI and/or CABG; secondary outcomes were major cardiovascular events (MI, stroke, UA, HF, and cardiovascular death). Where reported, the specific outcome was analysed (e.g. MI). Otherwise, the composite outcome 'cardiovascular death/events' was used, as specified in *Table 1*. Data were stored at https://zenodo.org/records/10409649.

Quality assessment

The two authors (M.D. and S.L.) independently assessed the risk of bias for each trial using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0),[56] which consists of five domains: (i) bias arising from the randomization process, (ii) bias due to deviations from intended intervention, (iii) bias due to missing data, (iv) bias in outcome measurement, and (v) bias in selection of reported result. Any evaluation with 'no' indicates a high risk of bias, whilst 'yes' indicates a low risk of bias. 'Unclear' rating indicates an unclear or unknown risk of bias. Based on those domains, the overall risk of bias of studies was defined as 'low', 'some concerns', and 'high'.

Statistical analysis

Data were collected in a Microsoft Excel table and analysed using Review Manager 5.3 for Macintosh (Copenhagen, Denmark). A random effects

Table 1 Characteristics of randomized controlled trials evaluating the effect of omega-3 fatty acid supplementation on coronary revascularization and other cardiovascular events

Study	Country	Study population	Sex	Intervention dose/day	Control dose/day	Follow-up	*n* int, age	*n* ctr, age	Use of statins	Outcome	Outcome definition	*n*/*n* int	*n*/*n* ctr	Side effects int	Side effects ctr
Cairns *et al.*, 1996	Canada	Patients undergoing elective PCI (50% with previous MI)	82% M	18 capsules MaxEPA 5.4 g n-3 PUFA (3.2 g EPA + 2.2g DHA)	18 capsules placebo (18 g corn oil)	6 days before PCI and 4.5 months after PCI	325, 57 (31–78)	328, 56 (29–76)	Not reported	Revascularization	PCI or CABG	75/325	67/328	122 GI, 17 bleeding	101 GI, 38 bleeding
EMPAR[49]			18% F							MI UA	Non-fatal MI UA	3/325 34/325	5/328 27/328		
Marchioli *et al.*, 2001	Italy	Patients surviving a recent MI (≤3 months)	85% M	1 capsule ethyl esters of n-3 PUFA (0.85–0.88 g EPA + DHA)	No placebo	42 months	2835, NA	2828, NA	3934 (46%) participants were under cholesterol-lowering drugs at the end of the study	Revascularization	PTCA or CABG	588/2835	575/2828	NA	NA
GISSI-prevenzione[17]			15% F							MI	Non-fatal MI	104/2835	113/2828		
										Stroke	Fatal and non-fatal stroke	50/2835	40/2828		
										CVD death	CVD death	144/2835	204/2828		
Yokoyama *et al.*, 2007[a]	Japan	Hypercholesterolaemic patients with or without CVD	31% M	Three capsules Mochida Pharmaceuticals (1.8 g EPA) + 10 mg pravastatin or 5 mg simvastatin[b]	10 mg pravastatin or 5 mg simvastatin[b]	55 months	9326, 61 ± 8	9319, 61 ± 9	9098 (98%) in intervention group and 8905 (97%) in control group	Revascularization	CABG or PTCA	191/9326	222/9319	352 GI, 105 bleeding	155 GI, 60 bleeding
JELIS[18]			69% F							MI UA Coronary death	Non-fatal MI UA Sudden cardiac death and fatal MI	62/9326 147/9326 29/9326	83/9319 193/9319 31/9319		
Tavazzi *et al.*, 2008	Italy	Patients with heart failure	78% M	One capsule ethyl esters of n-3 PUFA (0.85–0.88 g EPA + DHA)	One capsule matching placebo	47 months	3494, 67 ± 11	3481, 67 ± 11	778 (22%) in intervention group and 801 (23%) in control group were taking 10 mg/day of rosuvastatin	MI	Non-fatal MI	87/3494	104/3481	96 GI	92 GI
GISSI-HF[19]			22% F							Stroke HF	Non-fatal stroke Hospitalization for HF	72/3494 978//3494	59/3481 995/3481		
Einvik *et al.*, 2010[c]	Norway	Hypercholesterolaemic patients with or without CVD	100% M	Four capsules Pikasol	Two capsules Pikasol placebo (corn oil)	36 months	282, 70 ± 3	281, 70 ± 3	Not reported	CVD death CVD death/ events	CVD death CVD death, non-fatal MI, revascularization, stroke, and surgery on abdominal aortic aneurysm	712/3494 32/282	765/3481 36/281	NA	NA
DOIT[50]				2.4 g n-3 PUFA (1.18 g EPA + 0.84 g DHA + 3.5 mg tocopherols/g)											

Continued

Table 1 *Continued*

Study	Country	Study population	Sex	Intervention dose/day	Control dose/day	Follow-up	*n* int, age	*n* ctr, age	Use of statins	Outcome	Outcome definition	*n*/*n* int	*n*/*n* ctr	Side effects int	Side effects ctr
Galan *et al.*, 2010	France	Patients with acute coronary or cerebral ischaemic event within the 12 months before	79% M	0.6 g n-3 PUFA (0.4 g EPA + 0.2 g DHA)	Placebo (mineral oil)	56 months	1253, 60 (56–69)	1248, 61 (55–68)	544 (86%) in intervention group and 544 (87%) in control group were under lipid-lowering agents	Revascularization	Coronary and peripheral arteries revascularization, angioplasties	152/1253	156/1248	NA	NA
SU.FOL.OM3[20]			21% F												
										MI	Non-fatal MI	32/1253	28/1248		
										Stroke	Fatal and non-fatal stroke	29/1253	28/1248		
										CVD death	CVD death	20/1253	20/1248		
Rauch *et al.*, 2010	German	Patients with MI within 3–14 days before	74% M	One capsule Pronova Biocare	One capsule placebo Pronova Biocare (1 g olive oil)	12 months	1925, 64 (54–72)	1893, 64 (54–72)	1562 (81%) in intervention group and 1551 (82%) in control group were taking statins	Revascularization	PCI and CABG	466/1919	482/1654	NA	NA
			26% F	0.84 g n-3 PUFA (0.46 g EPA + 0.38 g DHA)											
OMEGA[21]										MACCE	Major adverse cerebrovascular and cardiovascular events	182/1752	149/1701		
Bosch *et al.*, 2012	40 locations (Europe and America)	Patients with dysglycaemia at high risk for CV events (a subgroup with evidence of CVD)	65% M	One capsule Omacor	One capsule placebo (1 g olive oil)	6 years	6281, 63.5 ± 7.8	6255, 63.6 ± 7.9	3331 (53%) in intervention group and 3408 (55%) in control group were taking statins	Revascularization	Revascularization	866/6281	896/6225	NA	NA
ORIGIN[27]			35% F	0.84 g n-3 PUFA (0.46 g EPA + 0.38 g DHA)						MI	Fatal and non-fatal MI	344/6281	316/6225		
										Stroke	Fatal and non-fatal stroke	314/6281	336/6225		
										UA	UA	724/6281	725/6225		
										HF	Hospitalization for HF	331/6281	320/6225		
										CVD death	CVD death	574/6281	581/6255		
Roncaglioni *et al.*, 2013	Italy	Patients with multiple CV risk factors but not MI	62% M	1 g ethyl esters of n-3 PUFA (0.87 g EPA + DHA)	Placebo (olive oil)	60 months	6239, 64 ± 9	6266, 64 ± 10	2544 (41%) in intervention group and 2594 (41%) in control group were taking statins	Revascularization	Arterial revascularization	334/6239	347/6266	200 GI	186 GI
R&P[22]			38% F												
										MI	Non-fatal MI	80/6239	90/6266		
										Stroke	Non-fatal stroke	80/6239	60/6266		
										UA	Angina	143/6239	148/6266		
										HF	Hospitalization for HF	96/6239	142/6266		
										CVD death	CVD death	142/6239	137/6266		
Bonds *et al.*, 2014	USA	Patients with stable CVD	43% M	1 g n-3 PUFA (0.65 g EPA + 0.35 g DHA)	Placebo (olive oil)	60 months	2147, 75 ± 11	2056, 74 ± 11	44% of all study population was taking statins	CVD death/ events	CVD death (sudden death, MI, heart failure, or stroke death);	183/2147	187/2056	119 GI	145 GI

Continued

Table 1 *Continued*

Study	Country	Study population	Sex	Intervention dose/day	Control dose/day	Follow-up	*n* int, age	*n* ctr, age	Use of statins	Outcome	Outcome definition	*n*/*n* int	*n*/*n* ctr	Side effects int	Side effects ctr
											CVD events (MI, stroke, UA, revascularization, HF, and resuscitated cardiac arrest)				
AREDS-2[23]			57% F												
Bowman *et al.*, 2018	UK	Patients with diabetes mellitus, but without evidence of CVD	63% M	One capsule	One capsule placebo (olive oil)	7.4 years	7740, 63 ± 9	7740, 63 ± 9	5791 (75%) in intervention group and 5862 (76%) in control group were taking statins	Revascularization	Any revascularization	368/7740	356/7740	NA	NA
ASCEND[26]			37% F	0.84 g n-3 PUFA (0.46 g EPA + 0.38 g DHA)											
										MI	Non-fatal MI	186/7740	200/7740		
										Stroke	Non-fatal stroke	217/7740	214/7740		
										CVD death	CVD death	186/7740	228/7740		
Bhatt *et al.*, 2019	11 countries	Patients with established CVD or diabetes	71% M	4 g icosapent ethyl (EPA)	4 g placebo (pharmaceutical-grade mineral oil)	4.8 years	4089, 64 (57–69)	4090, 64 (57–69)	All	MI	Non-fatal MI	237/4089	332/4090	588 GI	602 GI
REDUCE-IT[30]			29% F												
										Stroke	Non-fatal stroke	85/4089	118/4090		
										UA	Hospitalization for UA	108/4089	157/4090		
										HF	Hospitalization for HF	141/4089	144/4090		
										CVD death	CVD death	174/4089	213/4090		
Manson *et al.*, 2019	USA	Patients without cancer, stroke, and revascularization	49% M	One fish oil capsule	Placebo	5.3 years	12 933, 67 ± 7	12 938, 67 ± 7	8890 (35%) participants were taking statins	Revascularization	PCI or CABG	247/12 933	294/12 938	10 783 GI; 370 bleeding	10 691 GI; 374 bleeding
VITAL[28]			51% F	0.84 g n-3 PUFA (0.46 g EPA + 0.38 g DHA)											
										MI	Non-fatal MI	132/12 933	174/12 938		
										Stroke	Non-fatal stroke	126/12 933	122/12 938		
										CVD death	CVD death	142/12 933	148/12 938		
Djoussé *et al.*, 2020	USA	Patients without cancer, stroke, and revascularization	49% M	One fish oil capsule	Placebo	5.3 years	12 908, NA	12 916, NA	Not reported	HF	First hospitalization for HF	244/12 908	255/12 916	NA	NA
VITAL-HF[51]			51% F	0.84 g n-3 PUFA (0.46 g EPA + 0.38 g DHA)											
Nicholls *et al.*, 2020	USA	Patients at high risk for CVD (a subgroup with evidence of CVD)	65% M	4 g/day omega-3 carboxylic acid Epanova (2.2 g EPA + 0.8 g DHA)	Placebo (corn oil)	42 months	6539, 63 ± 9	6539, 63 ± 9	All	Revascularization	Elective and non-elective revascularization	414/6539	441/6539	1616 GI; 322 bleeding	959 GI; 322 bleeding
STRENGTH[31]			35% F												
										MI	Non-fatal MI	218/6539	226/6539		
										Stroke	Non-fatal stroke	142/6539	125/6539		
										UA	Hospitalization for UA	87/6539	104/6539		
										HF	Hospitalization for HF	142/6539	128/6539		
										CVD death	CVD death	228/6539	211/6539		

Continued

Table 1 *Continued*

Study	Country	Study population	Sex	Intervention dose/day	Control dose/day	Follow-up	*n* int, age	*n* ctr, age	Use of statins	Outcome	Outcome definition	*n*/*n* int	*n*/*n* ctr	Side effects int	Side effects ctr
Kalstad *et al.*, 2021	Norway	Patients with MI within 2–3 weeks	71% M	Three capsules Pikasol 1.8 g n-3 PUFA (0.93 g EPA + 0.66 g DHA)	Three capsules placebo (corn oil)	24 months	505, 74 (72–78)	509, 74 (72–78)	488 (97%) in intervention group and 490 (96%) in control group were taking statins	Revascularization	Unscheduled revascularization	14/505	21/509	183 bleeding	178 bleeding
OMEMI[52]			29% F												
										MI	Non-fatal MI	39/505	35/509		
										Stroke	Stroke	17/505	12/509		
										HF	Hospitalization for HF	20/505	17/509		
Peterson *et al.*, 2021	11 countries	Patients with established CVD or diabetes	71% M	4 g icosapent ethyl (EPA)	4 g placebo (pharmaceutical-grade mineral oil)	4.8 years	4089, 64 (57–69)	4090, 64 (57–69)	All	Revascularization	Any revascularization	376/4089	544/4090	588 GI	602 GI
REDUCE-IT[53]			29% F												
RESPECT-EPA, 2023[54,55]	Japan	Patients with chronic CAD	83% M	1.8 g icosapent ethyl (EPA)	Standard statin	5 years	1225, 68 (20–79)	1235, 68 (20–79)	All	Revascularization	Elective and non-elective revascularization	75/1225	106/1235	42 GI; 27 bleeding	15 GI; 32 bleeding
			17% F												
										MI	Non-fatal MI	16/1225	22/1235		
										Stroke	Non-fatal stroke	21/1225	28/1235		
										UA	Hospitalization for UA	10/1225	9/1235		
										CVD death	CVD death	56/1225	63/1235		

ACS, acute coronary syndrome; AP, angina pectoris; AREDS-2, Age-Related Eye Disease Study 2; ASCEND, A Study of Cardiovascular Events in Diabetes; BTM, biomedical test material; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DOIT, Diet and Omega-3 Intervention Trial; EPA, eicosapentaenoic acid; F, females; GI, gastrointestinal side effects; GISSI, Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; HF, heart failure; OMEMI, Omega-3 Fatty acids in Elderly with Myocardial Infarction; IVUS, intravascular ultrasound; JELIS, Japan EPA Lipid Intervention Study; M, males; MACE, major adverse cardiovascular events; MACCE, major adverse cerebrovascular and cardiovascular events; NA, not available; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; R&P, The Risk and Prevention Study Collaborative Group; QCAA, quantitative coronary angiographic analysis; STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia; SU.FOL.OM3, Supplementation en Folates et Omega-3 trial; UA, unstable angina; VITAL, VITamin D and OmegA-3 TriaL.

[a]Data also for primary and secondary prevention.

[b]For serious hypercholesterolaemia, the daily dose of statin was increased to 20 mg pravastatin or 10 mg simvastatin.

[c]One hundred and forty-two subjects in the treatment group received dietary counselling.

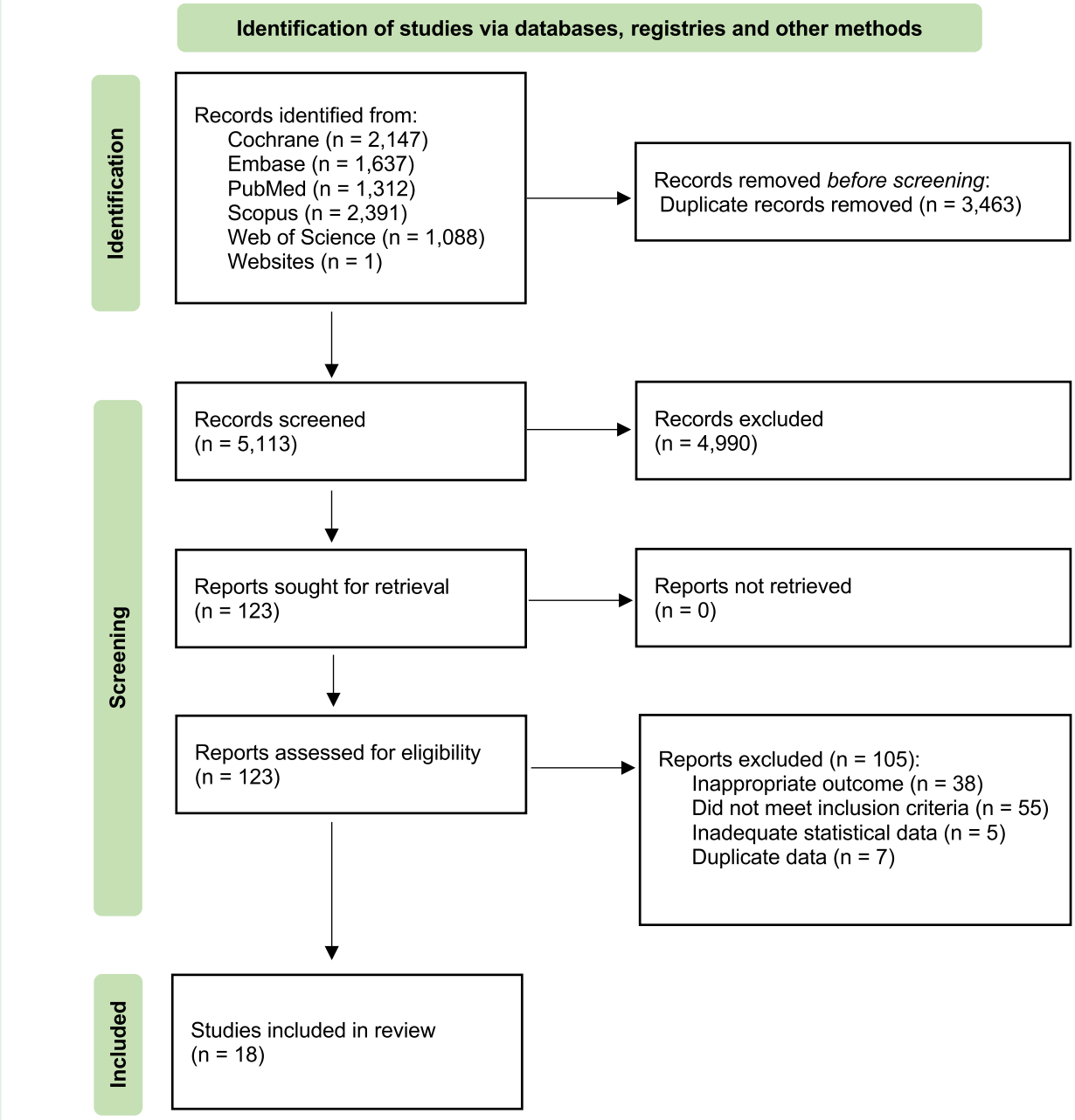


Figure 1 PRISMA flow diagram of study identification and inclusion.

model using DerSimonian and Laird method, which incorporated both within- and between-study variability, was implemented. The Mantel–Haenszel method was used, and the risk ratio (RR) with 95% confidence interval (CI) was reported as an effect measure for each study. Pooled results were reported as RR with 95% CI with two-sided *P*-values. A $P < 0.05$ was considered statistically significant.

Statistical heterogeneity amongst studies was estimated using the χ^2 Cochran's *Q*-test with I^2 statistics, which provides an estimate of the amount of variance due to heterogeneity rather than sampling error. I^2 exceeding 50% was considered substantial heterogeneity. Sources of heterogeneity were explored through subgroup analyses based on type of intervention (EPA + DHA vs. EPA alone), EPA + DHA dose (≤0.9 g/day vs. > 0.9 g/day, as median dose), EPA dose (≤0.7 g/day vs. > 0.7 g/day, as median dose), statin use (<60% vs. ≥ 60% of study population, as median value), and primary vs. secondary cardiovascular prevention.

To establish the robustness of the results, a sensitivity analysis was conducted by 'leave-one-out' approach, removing each study one-by-one from the meta-analyses and recalculating the summary estimate. When ≥10 studies were available, the possibility of publication bias was explored by visual inspection of funnel plot of effect size against standard error.

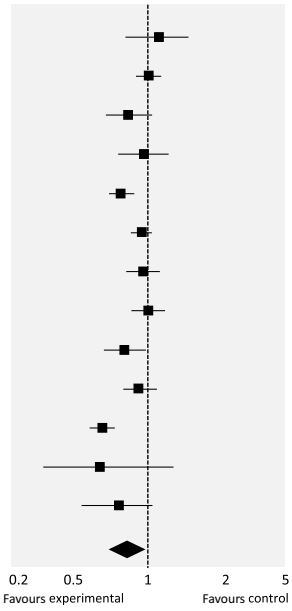
Results

Literature search

Figure 1 shows the selection process, according to PRISMA guidelines. The initial search yielded 8576 articles; after elimination of duplicates and records screening, 123 articles were identified as potentially relevant.

A

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio (95% CI)
Cairns et al., 1996	75	325	67	328	1.13 [0.84, 1.51]
Marchioli et al., 1999	588	2,835	575	2,828	1.02 [0.92, 1.13]
Yokoyama et al., 2007	191	9,326	222	9,319	0.86 [0.71, 1.04]
Galan et al., 2010	152	1,235	156	1,248	0.97 [0.79, 1.20]
Rauch et al., 2010	466	1,919	482	1,654	0.83 [0.75, 0.93]
Bosch et al., 2012	866	6,281	896	6,225	0.96 [0.88, 1.04]
Roncaglioni et al., 2013	334	6,239	347	6,266	0.97 [0.84, 1.12]
Bowman et al., 2018	368	7,740	356	7,740	1.03 [0.90, 1.19]
Manson et al., 2019	247	12,933	294	12,938	0.84 [0.71, 0.99]
Nicholls et al., 2020	414	6,539	441	6,539	0.94 [0.82, 1.07]
Peterson et al., 2021	376	4,089	544	4,090	0.69 [0.61, 0.78]
Kalstad et al., 2021	14	505	21	509	0.67 [0.35, 1.31]
RESPECT-EPA, 2023	75	1,225	106	1,235	0.77 [0.58, 1.04]
Total (95% CI)	**4,166**	**61,209**	**4,507**	**60,919**	**0.90 [0.84, 0.98]**

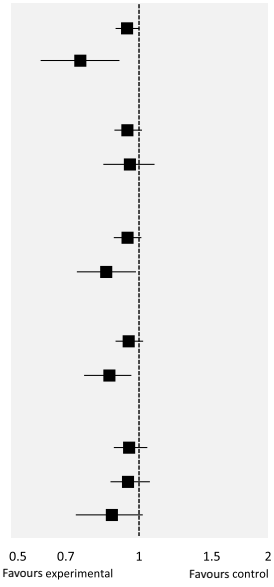


Heterogeneity: Tau² = 0.01; Chi² = 37.15, df = 12 (P = 0.0002); I² = 68%

Test for overall effect: Z = 2.59 (P = 0.010)

B

	No. of studies	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio (95% CI)	P	I², %	P-het	P-int
Type of intervention										
EPA + DHA	10	3,524	46,569	3,635	46,275	0.95 [0.90, 1.00]	0.06	33%	0.15	0.005
EPA	3	642	14,540	872	14,644	0.76 [0.65, 0.88]	0.0002	44%	0.17	
EPA + DHA dose*										
≤0.9 g/day	7	3,021	39,200	3,106	38,899	0.94 [0.88, 1.01]	0.09	45%	0.09	0.81
>0.9 g/day	3	503	7,369	529	7,376	0.96 [0.82, 1.13]	0.65	17%	0.30	
EPA dose										
≤0.7 g/day	7	3,021	39,200	3,106	38,899	0.94 [0.88, 1.01]	0.09	45%	0.09	0.20
>0.7 g/day	6	1,145	22,009	1,401	22,020	0.84 [0.72, 0.99]	0.04	70%	0.005	
Statin use										
<60% of study population	5	2,110	28,613	2,179	28,585	0.97 [0.91, 1.03]	0.32	18%	0.30	0.07
≥60% of study population	8	2,056	32,596	2,328	32,334	0.86 [0.77, 0.96]	0.007	69%	0.002	
Study population										
Primary CV prevention	3	949	26,912	997	26,944	0.95 [0.85, 1.07]	0.38	42%	0.18	
Secondary CV prevention	6	1,370	8,062	1,407	7,802	0.92 [0.82, 1.04]	0.21	56%	0.04	0.58
Combination **	4	1,847	26,235	2,103	26,173	0.86 [0.73, 1.01]	0.06	84%	0.0002	



*Only studies involving supplementation with combined EPA + DHA were considered in this sub-analysis.
** Combination of primary and secondary CV prevention

Figure 2 Comparison of omega-3 fatty acid supplementation vs. control on the risk of incident coronary revascularization in the overall analysis (*A*) and in subgroup analysis according to various characteristics (*B*). *P* denotes the *P*-value from the *Z* test that examines whether the pooled estimate of effect is statistically significant. I^2 refers to the magnitude of the heterogeneity. P_{het} is the probability of the null hypothesis that there is no heterogeneity amongst studies.

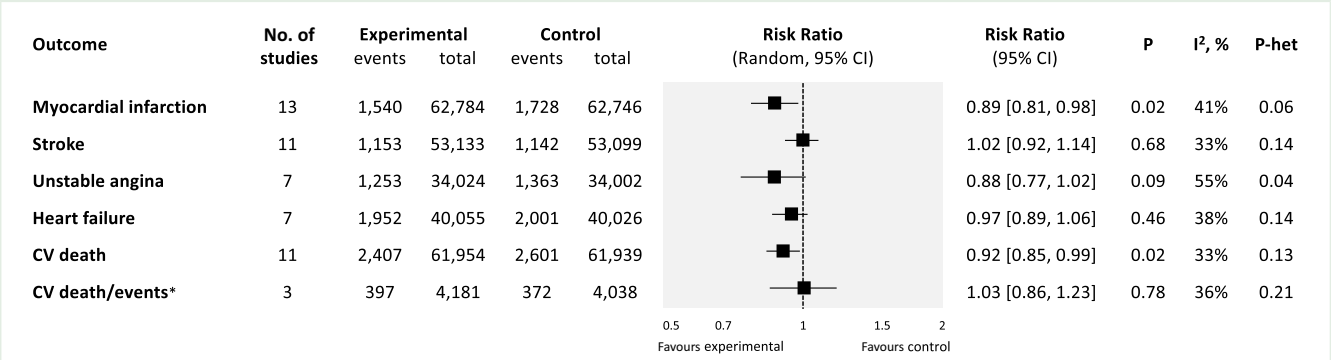


Figure 3 Comparison of omega-3 fatty acid supplementation vs. control on the risks of major cardiovascular events. * denotes original studies reporting only the composite outcome 'cardiovascular death/events'. *Table 1* specifies for each individual study what was included in the composite outcome.

After full-text evaluation, 18 articles met inclusion criteria[17–23,26–28,30,31,49–55] and were included in the analysis (*Table 1*; Supplementary material online, *References*). Those articles actually referred to 15 clinical trials, since for GISSI, REDUCE-IT, and VITAL, the original article did not report all the outcomes considered in our meta-analysis, which were retrieved from subsequent publications from those trials. Data for RESPECT-EPA were obtained integrating information presented during the 2022 American Heart Meeting[55] with that presented by Nishizaki *et al.*[54] and recently published by Gaba *et al.*[57]

Table 1 summarizes study characteristics. Fourteen articles reported data comparing EPA + DHA vs. control and three EPA alone vs. control. The overall analysis included a total of 134 144 participants, randomized to EPA + DHA ($n = 52\,498$), EPA alone ($n = 14\,640$), and control ($n = 67\,006$). The dose of omega-3 FA ranged from 0.6 to 5.4 g/day. Four studies included subjects in primary prevention, eight studies were of secondary prevention, and six studies included participants either in primary or secondary prevention (*Table 1*). The proportion of participants on background statins was <60% in six studies and ≥60–100% in nine trials; information on statin use could not be found for three trials, which were considered as enrolling participants with <60% statin use. Follow-up ranged from 4.5 months to 7.4 years. The patients' mean age was 65 years; the proportion of women enrolled varied from 0 to 69%.

Further information according to the use of EPA + DHA vs. EPA alone, demographics, risk factors [age, body mass index, smoking status, cardiovascular disease (CVD) at baseline, diabetes, dyslipidaemia, and hypertension], and statin use is shown in Supplementary material online, *Table S3*.

According to RoB 2.0 evaluation, 13 articles were considered at low risk of bias, 4 had some concerns, and 1 trial had a high risk of bias (see Supplementary material online, *Figure S1*).

Coronary revascularization

Two trials did not report data on coronary revascularization. The remaining 13 ($n = 122\,128$) reported 8673 coronary revascularization events, which we analysed collectively, as only two studies provided PCI and CABG data separately (*Figure 2A*). Overall, omega-3 FA supplementation was associated with a modest but significant reduction in the risk of coronary revascularization (RR 0.90, 95% CI 0.84–0.98; $P = 0.01$) compared with controls; between-study heterogeneity was significant ($I^2 = 68\%$; P-heterogeneity = 0.0002).

When overall data were analysed according to pre-specified characteristics, the reduction in the risk of coronary revascularization varied under different conditions. Specifically, the reduction was more pronounced with EPA alone (0.76, 95% CI 0.65–0.88; $P = 0.0002$; P-interaction = 0.005). There was a numerically greater benefit of doses of EPA >0.7 g/day (0.84, 95% CI 0.72–0.99) and in studies where ≥60% of participants were taking statins (0.86, 95% CI 0.77–0.96), but the interaction values did not reach statistical significance ($P = 0.81$ and 0 = 0.07, respectively). There was no clear impact of dose for studies with combined EPA + DHA administration, and there was no clear heterogeneity of benefit according to whether studies focused on primary prevention, secondary prevention, or combined prevention cohorts (*Figure 2B*).

Other cardiovascular events

A total of 13 trials ($n = 125\,530$) reported 3268 MIs (in most cases non-fatal MIs, in some cases fatal and non-fatal MIs together; *Table 1*), 11 trials ($n = 106\,232$) reported 2295 events of stroke, 7 trials ($n = 68\,026$) reported 2616 events of UA, 7 trials ($n = 80\,081$) reported 3953 HF events, and 11 trials ($n = 123\,893$) reported 5008 cardiovascular deaths. For three studies ($n = 8219$), 769 'cardiovascular deaths/events' were only presented as aggregate.

Omega-3 FA supplementation was associated with reduced risk of MI (0.89, 95% CI 0.81–0.98; $P = 0.02$) and cardiovascular death (0.92, 95% CI 0.85–0.99; $P = 0.02$) compared with controls, with no significant effect on stroke, UA, HF, and on the composite outcome 'cardiovascular deaths/events' (*Figure 3*). Between-study heterogeneity was significant only for UA ($I^2 = 55\%$; P-heterogeneity = 0.04). Details of the results of each study with respect to individual endpoints are provided as Supplementary material online, *Figure S2*.

Subgroup analyses and interaction P-values for cardiovascular events (other than revascularization) are shown in *Table 2*. Trials testing EPA vs. control alone achieved a greater reduction in the risk of MI (0.72, 95% CI 0.632–0.83; $P < 0.00001$), stroke (0.73, 95% CI 0.575–0.935; $P = 0.012$), UA (0.74, 95% CI 0.632–0.865; $P < 0.0001$), and cardiovascular death (0.84, 95% CI 0.72–0.99; $P = 0.04$) than trials comparing EPA + DHA. Further differences were observed according to EPA dose, with higher benefits at >0.7 g/day for MI (0.83, 95% CI 0.71–0.99; $P = 0.04$) and UA (0.81, 95% CI 0.68–0.96; $P = 0.02$). When events were analysed according to background statin use, benefit appeared numerically greater in studies, in which ≥60% of participants were on statins.

Comparisons of omega-3 supplementation on all outcomes according to type of intervention, EPA + DHA dose, EPA dose, statin use, and primary vs. secondary cardiovascular prevention are presented as Supplementary material online, *Figures S3–S8*.

Table 2 Subgroup analysis for events other than revascularization

	Myocardial infarction				Stroke				Unstable angina				Heart failure				CV death			
	n	RR (95% CI)	I^2 (P_{het})	P_{int}	*n*	RR (95% CI)	I^2 (P_{het})	P_{int}	*n*	RR (95% CI)	I^2 (P_{het})	P_{int}	*n*	RR (95% CI)	I^2 (P_{het})	P_{int}	*n*	RR (95% CI)	I^2 (P_{het})	P_{int}
Type of intervention																				
EPA + DHA	10	0.95 (0.88, 1.02)	2% (0.42)	0.001	9	1.05 (0.96, 1.14)	0% (0.50)	0.006	4	0.98 (0.90, 1.07)	0% (0.50)	0.002	6	0.96 (0.87, 1.07)	48% (0.09)	0.005	8	0.93 (0.85, 1.01)	47% (0.06)	0.32
EPA	3	0.72 (0.63, 0.83)	0% (0.92)		2	0.73 (0.57, 0.93)	33% (0.14)		3	0.74 (0.63, 0.86)	0% (0.54)		1	0.98 (0.78, 1.23)	—		3	0.84 (0.72, 0.99)	0% (0.83)	
EPA + DHA dose[a]																				
≤0.9 g/day	7	0.93 (0.83, 1.03)	27% (0.22)	0.59	7	1.03 (0.94, 1.13)	1% (0.41)	0.33	2	0.99 (0.90, 1.08)	0% (0.88)	0.99	4	0.93 (0.83, 1.06)	63% (0.05)	0.16	7	0.91 (0.83, 0.99)	44% (0.10)	0.1
>0.9 g/day	3	0.98 (0.83, 1.16)	0% (0.66)		2	1.16 (0.93, 1.46)	0% (0.56)		2	0.98 (0.66, 1.47)	54% (0.14)		2	1.12 (0.90, 1.40)	0% (0.85)		1	1.08 (0.90, 1.30)	—	
EPA dose																				
≤0.7 g/day	7	0.93 (0.83, 1.03)	27% (0.22)	0.3	7	1.03 (0.94, 1.13)	1% (0.41)	0.56	2	0.99 (0.90, 1.08)	0% (0.88)	0.05	3	0.92 (0.77, 1.09)	75% (0.02)	0.37	7	0.91 (0.83, 0.99)	44% (0.10)	0.75
>0.7 g/day	6	0.83 (0.71, 0.99)	40% (0.14)		4	0.93 (0.68, 1.28)	63% (0.05)		5	0.81 (0.68, 0.96)	32% (0.21)		4	1.01 (0.89, 1.13)	0% (0.73)		4	0.94 (0.80, 1.09)	29% (0.24)	
Statin use																				
<60% of study population	6	0.91 (0.79, 1.04)	37% (0.16)	0.72	5	1.08 (0.93, 1.25)	34% (0.20)	0.35	3	1.00 (0.91, 1.09)	0% (0.59)	0.001	4	0.93 (0.83, 1.06)	63% (0.05)	0.26	5	0.92 (0.83, 1.02)	55% (0.06)	0.82
≥60% of study population	8	0.87 (0.76, 1.01)	43% (0.10)		6	0.96 (0.81, 1.15)	40% (0.14)		4	0.76 (0.66, 0.87)	0% (0.61)		3	1.05 (0.89, 1.23)	0% (0.70)		6	0.90 (0.81, 1.01)	15% (0.09)	
Study population																				
Primary CVD prevention	3	0.86 (0.75, 0.98)	0% (0.40)	0.83	3	1.07 (0.93, 1.23)	19% (0.29)	0.37	1	0.97 (0.77, 1.22)	—	0.19	2	0.82 (0.58, 1.14)	79% (0.03)	0.4	3	0.92 (0.80, 1.07)	27% (0.25)	0.51
Secondary CVD prevention	6	0.92 (0.78, 1.07)	0% (0.73)		5	1.13 (0.92, 1.39)	0% (0.58)		2	1.24 (0.81, 1.89)	0% (0.81)		2	0.98 (0.91, 1.06)	0% (0.56)		4	0.85 (0.72, 1.01)	49% (0.12)	
Primary and secondary CVD prevention combined	4	0.87 (0.70, 1.08)	81% (0.001)		3	0.92 (0.74, 1.14)	67% (0.05)		4	0.83 (0.68, 1.00)	73% (0.01)		3	1.03 (0.92, 1.15)	0% (0.75)		4	0.96 (0.86, 1.08)	31% (0.23)	

I^2 refers to the magnitude of the heterogeneity. P_{het} is the probability of the null hypothesis that there is no heterogeneity between studies.
n, number of studies; CI, confidence interval; CV, cardiovascular; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; RR, risk ratio.
[a]Only studies involving supplementation with combined EPA + DHA were considered in this subanalysis.

Sensitivity analysis and publication bias

To verify that results were not driven by any single trial, a 'leave-one-out' sensitivity analysis was performed. Quantitative summary measures of RR with 95% CI remained unchanged for coronary revascularization and most other outcomes, except for MI and cardiovascular death. Removal of the studies by Manson *et al.*[28] and Bhatt *et al.*[30] changed the effect on MI from significant in the main analysis to non-significant in the sensitivity analysis; similarly, removal of the studies by Bowman *et al.*,[26] Bhatt *et al.*,[30] and Tavazzi *et al.*[19] changed the effect on cardiovascular death from significant to non-significant. Finally, exclusion of RESPECT-EPA did not change the results of the various outcomes (see Supplementary material online, *Table S4*).

Publication bias was assessed for coronary revascularization, MI, stroke, and cardiovascular death (i.e. the outcomes reported in ≥10 studies) using funnel plots (see Supplementary material online, *Figure S9*). The shape of the funnel plot showed small asymmetry, suggesting evidence of some publication bias.

Discussion

In this large meta-analysis, based on 134 144 subjects, administration of omega-3 FAs reduced the risk of incident coronary revascularization, with an associated reduction of MI and cardiac death. To our knowledge, this is the first meta-analysis to specifically focus on coronary revascularization. Also novel, and possibly of major relevance, is the finding that taking into account the specific molecules of omega-3 FAs administered, benefit on the various outcomes was marginal in studies, which employed a combination of DHA + EPA, but instead, it was substantially greater when EPA alone was administered. Finally, we also report that the relative benefits of EPA supplementation appeared consistent, if not greater, in trials, in which most patients were taking statins as background therapy.

Previous meta-analyses have explored the effects of omega-3 on cardiovascular outcomes.[36–48] This meta-analysis, besides being more updated, adds to existing literature in several aspects. First, it is the only one, which, in addition to other outcomes of interest, specifically investigates revascularization, a relevant clinical outcome, which also entails substantial cost implications to the healthcare system given how commonly done these procedures are; secondly, we were able to separately assess the effects of EPA alone vs. combined treatment with EPA + DHA; thirdly, we performed a subanalysis of the effects according to background statin therapy of participants; finally, on a methodological side, to limit heterogeneity found in previous reports, we purposely excluded (i) trials, in which outcomes were indirectly inferred from adverse events, and (ii) studies, in which intervention consisted of dietary advice.

One-fourth of US adults, including nearly one-third of those on statin therapy, have elevated triglyceride levels.[13] In the overall analysis of trials administering EPA alone or combined treatment with EPA + DHA, a significant reduction was observed with respect to cardiovascular death and incidence of MI and coronary revascularizations, whereas incidence of stroke, UA, and HF was unaffected. Instead, the beneficial effect on revascularizations, and also MI, stroke, and UA, was much more prominent in studies, which administered EPA alone.

The 24% relative risk reduction in coronary revascularization observed with administration of EPA alone compares with the reduction seen in trials of statins vs. placebo, which also averaged 24% reduction (per 1.0 mmol/L reduction in LDL-C).[1–4] Interestingly, the benefits of EPA administration were not seen when EPA was administered along with DHA, as reduction in incident revascularizations was a mere 5%. Of note, this figure closely matches the non-significant 6% reduction in revascularizations recently observed in the STRENGTH trial, which administered 4 g/day of a formulation of EPA + DHA.[31]

The observation that reduction in events was largely confined to studies administering EPA alone, and not observed in studies employing the combination of EPA + DHA, may provide an explanation for the discrepant results previously reported with respect to the effects of omega-3 supplementation, which used a variety of different formulations of these molecules. Reasons for the seemingly peculiar effects of EPA when administered alone are unclear, but appear not directly related to the decrease of triglyceride levels. EPA and DHA have different chemical structures, which may lead to divergent effects on susceptibility to oxidation of lipoproteins, and on stabilization of cell membranes, both favourably influenced by EPA but not DHA[33,34,58–65]; beneficial effects of EPA, but not DHA, have also been reported on markers of inflammation and on endothelial and platelet function.[33,34,58–65] Thus, the fact that DHA may exert disparate or even contrasting pharmacological effects compared with EPA suggests that addition of DHA might diminish or counteract the benefits of EPA, thus explaining the failure of combined formulations of EPA + DHA to show significant benefits.

It has been suggested that threshold concentrations of EPA should be achieved to elicit cardiovascular benefits.[32,64] Our meta-analysis cannot directly test this hypothesis, as plasma concentration data were not available; however, when we analysed the studies with respect to the dose of EPA administered, we observed greater benefits with EPA treatment at higher doses, consistent with the hypothesis that higher concentrations of EPA are beneficial. Mechanistically, the benefits of EPA on coronary revascularizations are supported by data from the EVAPORATE trial, which showed that administration of EPA at 4 g/day resulted in positive changes on multiple parameters of coronary plaque volume and composition.[66]

The significant reduction observed in incident coronary revascularizations, in addition to its obvious benefits on patients' health and overall quality of life, may also translate into significant reduction of expenses associated with revascularization procedures, which are a substantial component of health costs of management of patients with chronic ischaemic syndromes.[35,67]

In the present meta-analysis, we were also able to investigate the results of omega-3 supplementation with respect to background cholesterol-lowering therapy taken by participants. In studies (pooling EPA alone and EPA + DHA), in which the majority (or all) of the participants were on statins as part of their chronic therapy regimen, a significant 14% reduction in coronary revascularization, and in incident UA, could still be observed. This finding expands on what previously reported by Irfan *et al.*,[43] indicating that there might be additional advantage to be gained in cardiovascular prevention by going the extra mile with lipid-lowering therapies and at the same time that additional benefits might be achieved through a pharmacological intervention non-directly acting on cholesterol levels.

Limitations

As in all meta-analyses, our results are influenced by the intrinsic quality of the studies analysed and by differences in enrolment criteria and patient populations. Some studies provided only aggregate data for patients in either primary or secondary prevention, and therefore, we cannot specifically elaborate on this issue nor is it possible to discriminate between first revascularization and repeat revascularizations of the same or newer lesions. Also, with respect to coronary revascularization, data available do not allow to look at PCI and CABG separately. Heterogeneity across studies also emerged, which however does not seemingly affect the robustness of overall findings; another limitation worth mentioning is represented by the different length of follow-up amongst studies, which may have influenced both time of exposure to the drugs tested and the time for events to accrue. Finally, as the trials analysed spanned over a considerable length of time, it is possible that changes in contemporary

management of such patients may have introduced some unknown and unmeasurable benefits.

Conclusions

This large meta-analysis, involving a total of 134 144 subjects, shows that omega-3 FA supplementation significantly reduced risk of coronary revascularization and major cardiac events. These beneficial effects were not substantially affected by concomitant statin use. Interestingly, the benefit was largely restricted to administration of EPA alone and was not seen when EPA was administered along with DHA. Further studies may clarify the role of specific omega-3 FA molecules, and of their most appropriate dose, in preventing cardiovascular events in primary and in secondary prevention. At the same time, the cost savings achievable through the substantial reduction in revascularizations could be significant and deserve further investigation.[67]

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

Presented in part at the Annual Meeting of the American Heart Association, Philadelphia, PA, 10–13 November 2023.

Author contribution

M.D.: data extraction, data quality assessment, statistical calculations, and final review. F.S.: conceptualization, statistical oversight, data analysis, manuscript drafting, and final review. S.L.: data extraction, data quality assessment, and statistical calculations. B.C.: data extraction, data quality assessment, and statistical calculations. A.V.M.: critical review of results and final review. A.L.C.: critical review of results and final review. M.C.: data analysis, statistical oversight, and final review. A.B.: data analysis, statistical oversight, and final review. P.G.S.: critical review of results and final review. N.D.W.: critical review of results and final review. G.A.: conceptualization, data analysis, manuscript drafting, and final review.

Funding

This work has been partly supported by the Italian Ministry of Health—Ricerca Corrente to IRCCS MultiMedica.

Conflict of interest: The Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, and the Center for Clinical and Translational Research—CERICLET, University of Perugia School of Medicine, Perugia, Italy, received an unconditioned research grant from Amarin, not shared with the authors.

Data availability

Data were from published information, retrieved through Medline, Embase, Scopus, Web of Science, and Cochrane Library. Data are publicly accessible through https://zenodo.org/records/10409649 and in its online Supplementary material.

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