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Letter

Is there a role for omega-3 fatty acids in cardiovascular disease risk reduction?

A recent meta-analysis published in *EClinicalMedicine* examined the effectiveness of omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on cardiovascular (CV) outcomes [1]. Mixed EPA/DHA formulations were indicated to have moderate certainty in reducing CV mortality and outcomes. Greater relative reductions in incident CV events were observed with EPA alone trials. The authors conclude that EPA and DHA have inherently different physico-chemical properties that influence CV risk reduction.

Our concern is that the authors assert mixed EPA/DHA formulations remain a viable treatment to reduce CV risk in patients using contemporary care. This conclusion is derived from a meta-analysis disproportionately influenced by older trials conducted without broad statin use [1]. In particular, the large GISSI-P and GISSI-HF trials enrolled subjects with 5% and 23% on statins, respectively (Table 1) [2,3]. By contrast, STRENGTH tested an EPA/DHA formulation (4 g/d) in patients on maximum statin treatment and terminated early for futility [1]. Similarly, the OMEMI trial failed to meet its primary endpoint when EPA/DHA (1.8 g/d) was combined with high statin use (Table) [1]. Like other TG-lowering agents (*e.g.*, fibrates, niacin), mixed EPA/DHA treatments do not add incremental benefit in risk reduction on top of statins [4]. The benefits of icosapent ethyl (IPE) are attributed to dose, formulation and direct effects of EPA on inflammation, platelet activity and endothelial function beyond changes in lipoprotein levels [5].

We recommend that the authors repeat the meta-analysis after removing older trials performed without broad statin use to ascertain a potential role for omega-3 fatty acids as part of contemporary medical therapy in CV patients.

Table 1
Cardiovascular outcome trials with omega-3 fatty acids since 1999.

	GISSI-P (11324)	JELIS (18645)	GISSI-HF (6975)	REDUCE-IT (8179)	OMEMI (1027)	STRENGTH (13078)
Publication Date	1999	2007	2008	2019	2020	2020
Population	Recent MI (<3 months)	Hypercholesterolemic	Chronic HF (NYHA functional class II-IV)	High cardiovascular risk, elevated TG	Elderly patients w/ recent acute MI	High cardiovascular risk, elevated TG, low HDL
Formulation[†]	EPA/DHA ethyl esters (850 mg/d)	IPE (1.8 g/d EPA)	EPA/DHA ethyl esters (850 mg/d)	IPE (4 g/d EPA)	EPA/DHA (1.8 g/d)	EPA/DHA carboxylic acids (4 g/d)
Statin Use	BL: 5%, EOS: 46%	100%	22.3–23.0%	100%	96.3–96.6%	100%
Primary End Point	Death, non-fatal MI, non-fatal stroke	Major coronary events	Death, and death or CV hospitalization (co-primary endpoints)	Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	Composite of nonfatal AMI, unscheduled revascularization, stroke, all-cause death, HF hospitalization after 2 years	Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina
HR, 95% CI of Primary Endpoint	0.85, 0.74-0.98 (p=0.023)	0.81, 0.69-0.95 (p=0.011)	Death – 0.91, 0.833-0.998 (p=0.041) Death or CV hospitalization – 0.92, 0.849-0.999 (p=0.009)	0.75, 0.68-0.83 (p=0.00000001)	1.08, 0.82-1.41 (p=0.60)	0.99, 0.90-1.09 (p=0.84)

[†] IPE, icosapent ethyl. Abbreviations are: BL, baseline; EOS, end of study; HF, heart failure; MI, myocardial infarction; NHYA, New York Heart Association; TG, triglyceride(s).

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Declaration of Competing Interest

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