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$n-3$ PUFAs in cardiovascular disease

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ABSTRACT

Many large, randomised clinical trials and some meta-analyses have shown that treatment with $n-3$ polyunsaturated fatty acids ($n-3$ PUFAs) is associated with consistent benefits on cardiovascular (CV) events, primarily due to a reduction of coronary and CV deaths in patients with coronary heart disease. At variance with such evidence, some clinical trials and meta-analyses showing a neutral effect of $n-3$ PUFAs have been recently published, raising concern about the consistency of the evidence on the CV benefits of $n-3$ PUFAs. Several methodological and clinical aspects of these recent trials deserve to be considered. Indeed, the low rate of events or the overoptimistic expectations of the benefit of $n-3$ PUFAs used for sample size calculation led to an inadequate statistical power of several studies. The improvement of background medical therapy, serum baseline levels of $n-3$ PUFAs, and different doses and/or treatment duration might have downplayed the benefit of $n-3$ PUFAs. Similarly to old drugs shown to be effective some years ago, it is possible that the benefits of treatment with $n-3$ PUFAs are not as great in a modern CV prevention strategy so rich in many effective drugs compared with past trials testing CV drugs when less effective therapies were available.

1. Introduction

Since the first reports on a protective effect of fish intake on coronary heart disease (CHD) published 50 years ago [1,2], the wide range of potentially important properties of $n-3$ polyunsaturated fatty acids ($n-3$ PUFAs) that might play a relevant role in the maintenance of healthy cardiac function have been investigated in many observational studies and randomised clinical trials (RCTs). Many of these studies and several meta-analyses have reported that fish and $n-3$ PUFA intake was associated with a significantly reduced risk of cardiovascular (CV) events, primarily due to reduction of CHD and CV death [3–6]. On the other hand, some recent RCTs and meta-analyses showed mixed findings, raising concern about the consistency of the evidence on the CV benefits of $n-3$ PUFAs.

The aim of the present article was to critically review recent studies as well as meta-analyses reporting data on neutral CV effects of $n-3$ PUFAs in patients with CHD in order to summarise the results that are available to date and, possibly, to give a useful contribution to the debate on the CV effects of $n-3$ PUFAs.

2. Cardiovascular events

The most recent large trials testing the effect of $n-3$ PUFAs in patients with CV disease (CVD) are listed in Table 1. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione trial represents one of the studies that provided stronger evidence on the beneficial CV effects of $n-3$ PUFAs in CHD [8]. It was an open-label, randomised controlled trial that tested the efficacy of oral administration of 1 g daily of $n-3$ PUFAs and vitamin E on morbidity and mortality in 11 323 Italian patients with recent myocardial infarction (MI). After 3.5 years of follow-up, $n-3$ PUFA therapy significantly reduced the first combined primary endpoint (death, non-fatal MI and non-fatal stroke) by 15% [95% confidence interval (CI) 3–27%; $p = 0.02$] as well as the co-primary endpoint (CV death, non-fatal MI and non-fatal stroke) by 20% (95% CI 6–32%; $p = 0.006$) compared with the control group. Secondary analyses of the components of the primary endpoints showed that almost all of the benefit observed in the combined endpoints was attributable to the reduction in fatal events: total mortality, 20% (95% CI 6–23%); CV death, 30% (95% CI 13–44%); CHD death, 35% (95% CI 16–49%); and sudden cardiac death (SCD), 44% (95% CI 24–60%) [8].

At variance with GISSI-Prevenzione results, some recent RCTs did not confirm the beneficial effects of $n-3$ PUFAs on fatal CV events. The Japan EPA Lipid Intervention Study (JELIS) [9] was a large-scale trial conducted in more than 18 000 hypercholesterolaemic Japanese patients who were randomised to $n-3$ PUFA treatment (1.8 g/day) in combination with statin versus statin alone. After a mean follow-up of

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Table 1
Recent large clinical trials on the cardiovascular (CV) effects of *n*−3 polyunsaturated fatty acids (*n*−3 PUFAs) in patients with coronary heart disease (CHD).

Study	Pt group	No. of pts	Treatment/ daily dose	Control	Follow-up	Endpoints	No. (%) of events in control group	RR (95% CI)	Study power for		
									30% RRR	20% RRR	15% RRR
GISSI-Prevenzione [7]	Pts with recent (≥3 months) MI	11 323	EPA and DHA (average ratio 1:2) 850–882 mg (alone, *n* = 2835; plus Vit.E, *n* = 2830)	Vit. E alone (*n* = 2830) or no supplement (*n* = 2828)	3.5 years (38 417.9 p/y)	**Death, non-fatal MI and non-fatal stroke**	795 (14.1)	0.85 (0.74–0.98) †	>99%	>99%	90%
						CV death, non-fatal MI and non-fatal stroke	621 (11.0)	0.80 (0.68–0.94) ‡	>99%	97%	81%
						All fatal events	554 (9.8)	0.79 (0.66–0.93) ‡	>99%	95%	77%
						CV deaths	370 (6.5)	0.70 (0.56–0.86) §	>99%	83%	57%
						Cardiac deaths	306 (5.4)	0.65 (0.51–0.82) §	98%	75%	49%
						Coronary deaths	258 (4.6)	0.68 (0.53–0.88) ‡	96%	67%	42%
						Sudden deaths	154 (2.7)	0.55 (0.39–0.77) §	80%	44%	26%
						Non-fatal MI	233 (4.1)	0.91 (0.70–1.18)	94%	62%	38%
						Non-fatal stroke	57 (1.0)	1.22 (0.75–1.97)	37%	17%	11%
						Coronary deaths + non-fatal MI	475 (8.4)	0.78 (0.65–0.94) ‡	>99%	91%	69%
						Fatal + non-fatal stroke	77 (1.4)	1.22 (0.81–1.85)	50%	24%	14%
JELIS [9]	Pts with total cholesterol ≥6.5 mmol/l	18 645	EPA 1800 mg/day (*n* = 9326) plus statin	Statin alone (*n* = 9319)	4.6 years (mean)	**Major coronary events**	324 (3.5)	0.81 (0.69–0.95) †	>99%	77%	51%
						SCD	17 (0.2)	1.06 (0.55–2.07)	13%	7%	5%
						Fatal MI	14 (0.2)	0.79 (0.36–1.74)	13%	7%	5%
						Non-fatal MI	83 (0.9)	0.75 (0.54–1.04) *	55%	27%	15%
						Unstable angina	193 (2.1)	0.76 (0.62–0.95) †	86%	54%	33%
						Revascularisation	222 (2.4)	0.86 (0.71–1.05)	93%	60%	37%
						CHD death + MI	113 (1.2)	0.78 (0.59–1.03) *	66%	33%	19%
						Fatal + non-fatal MI	93 (1.0)	0.77 (0.56–1.05) *	57%	28%	17%
						CHD death	31 (0.3)	0.94 (0.57–1.56)	19%	9%	6%
						Non-fatal CHD	297 (3.2)	0.81 (0.68–0.96) †	98%	3%	47%
OMEGA [14]	Pts with recent (3–14 days) MI	3851 (3804 included in the endpoint analysis)	*n*−3 PUFAs 1 g/day (EPA 460 mg + DHA 380 mg) (*n* = 1919)	Olive oil 1 g/day (*n* = 1885)	1 year	**SCD**	29 (1.5)	0.95 (0.56–1.60)	19%	10%	7%
						Total mortality	70 (3.7)	1.25 (0.90–1.72)	47%	22%	14%
						MACCE	149/1701 (8.8)	1.21 (0.96–1.52)	87%	50%	30%
						Revascularisation	482/1654 (29.1)	0.93 (0.80–1.08)	>99%	98%	86%
						ICD-terminated VT/VF	2 (0.1)	4.47 (0.97–20.74) *	<1%	<1%	<1%
		4837					335 (13.8)	1.01 (0.87–1.17)	>99%	82%	56%