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ω-3 Fatty acids, atherosclerosis progression and cardiovascular outcomes in recent trials: new pieces in a complex puzzle

Jason H Y Wu[1] and **Dariush Mozaffarian**[1,2,3]

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[2]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA

[3]Division of Cardiovascular Medicine and Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

The cardiovascular effects of seafood-derived n-3 polyunsaturated fatty acids (n-3 PUFA) have been examined in a diverse and continually expanding array of studies ranging from in vitro molecular experiments to large randomised controlled trials. In contrast to earlier trials, recent clinical trials have not observed significant effects of n-3 PUFA supplementation on cardiovascular disease (CVD) events.[1,2] These mixed findings have stimulated renewed debate and interest about the role of n-3 PUFA for CVD prevention and treatment.

Sekikawa and colleagues investigated whether circulating n-3 PUFA levels were associated with differences in new-onset of coronary artery calcification (CAC) between middle-aged men in Japan and the USA.[3] Measurement of CAC by electron beam CT provides an estimate of overall coronary atherosclerotic burden. While CAC does not necessarily identify with plaque morphology or propensity for rupture, overall CAC burden does predict future risk of clinical CVD events. In this case, investigating the association of circulating n-3 PUFA with serial measures of CAC addresses the interesting hypothesis that these fats might slow atherosclerosis progression, providing mechanistic insight that would be complimentary to studies of clinical endpoints. In this investigation, Japanese men had substantially (~150%) higher circulating n-3 PUFA than did US men, consistent with much higher levels of seafood consumption in Japan. Japanese men also had a substantially lower incidence of new CAC (rate ratio=0.26, 95%CI=0.09 to 0.73), compared with US men, which was not explained by adjustment for conventional CVD risk factors including age, systolic blood pressure, cholesterol, triglycerides, BMI, diabetes, smoking and hypertension medication. In contrast, the association between country (Japan vs USA) and incident CAC was attenuated following adjustment for serum n-3 PUFA. The authors concluded that n-3 PUFA may have antiatherosclerotic effects at levels observed in Japan.

Correspondence to Dr Jason H Y Wu, 665 Huntington Ave, Kresge Building-913, Boston, MA, 02115, USA; jasonwu@hsph.harvard.edu.

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While this analysis has several strengths, including use of objective n-3 PUFA biomarkers and repeated CAC measures, its major weakness is the essentially ecological design, comparing incident CAC between two groups of men in very different countries (Japan vs USA). A multitude of differences exist between Japan and the USA, including in environmental risks, cultural practices, behavioural and other dietary habits. Some of these between-population differences are so large, and so difficult to fully account for, that the extent of residual confounding (bias) is likely to be large. In addition to the challenge of confounding by large differences between populations, this analysis can suffer from ecologic fallacy in that differences in n-3 PUFA (the exposure) and CAC (the outcome) between populations may not correspond to the relationship of n-3 PUFA with CAC within each population. In other words, while average n-3 PUFA levels are higher in Japanese than in Americans, and while average incident CAC rates are lower, it is not necessarily true that the Japanese individuals with higher n-3 PUFA levels have lower CAC rates than Japanese with lower n-3 PUFA levels, or that the American individuals with lower n-3 PUFA levels have higher CAC rates than Americans with higher n-3 PUFA levels. The authors present crude (unadjusted) levels of n-3 PUFA according to incident CAC within Japanese and within Americans, but state that these differences were not statistically significant, and do not report multivariable-adjusted findings. To properly address these twin limitations, within-population analyses are necessary, that is, evaluating the multivariate-adjusted association of serum n-3 PUFA with incident CAC within Japanese and within Americans in this study. Yet, such within-population analyses were not reported, likely owing to very small numbers of incident CAC cases within each population (n=10 in Japan; n=15 in the USA). Thus, whereas the hypothesis investigated by this study is of significant research interest, the limitations of the essentially ecologic design allow few meaningful conclusions about effects of ω-3s on atherosclerosis to be derived from these results.

n-3 PUFA have multiple established physiologic benefits that would be expected to reduce atherosclerosis and CVD risk.[4] In meta-analyses of controlled trials, n-3 PUFA consumption lowers resting heart rate, blood pressure and plasma triglycerides; improves endothelial function; and increases adiponectin levels.[4–6] In other trials, n-3 PUFA reduce inflammatory biomarkers, reduce myocardial oxygen demand, and enhance cardiac function and filling.[47–9] In cellular and animal experiments, n-3 PUFA reduce ischaemia-induced resting membrane depolarisation and reduce risk of ischaemic-induced ventricular fibrillation.[10] Additional cellular and molecular effects include changes in cellular membrane structure and fluidity, interaction with and modulation of ion channels and signalling proteins, regulation of gene expression via nuclear receptors and transcription factors, and transformation to potent downstream metabolites that modulate central inflammatory and vascular processes.[4] A large number of prospective observational studies in both primary and secondary prevention settings have consistently found that individuals who eat moderate amounts of fish or dietary n-3 PUFA have substantially lower risk of cardiac death than those who eat little or none.[4] In contrast, observational studies suggest much smaller to no benefits of dietary n-3 PUFA for non-fatal coronary disease.[11] Interestingly, the dose-response for cardiac death appears non-linear, with a relatively steep dose-response from 0 up to ~250 mg/day of n-3 PUFA, and then little additional benefit thereafter.[12]

In contrast to the consistent findings of prospective cohort studies, clinical trials have generated mixed findings, with a striking temporal difference between earlier trials (four of five demonstrated benefits), and more recent trials (six of six failed to show significant effects) (table 1). What might explain these divergent results? First, it is possible that n-3 PUFA have no significant effects on CVD, and that benefits seen in the earlier clinical trials represent biased findings. Yet, based on the well-established and diverse experimental and physiologic benefits of n-3 PUFA, and the highly consistent lower risk of cardiac death observed in prospective observational studies from around the world, this explanation seems implausible. A second explanation is that n-3 PUFA have little effect in the presence of aggressive background medical treatment. In the recent trials, use of antihypertensive, lipid-lowering and antiplatelet medications was very high, which could have reduced the ability to demonstrate additional benefit with n-3 PUFA supplementation. This possible interaction by background medication use has been examined in two trials, the earlier GISSI-Prevenzione trial which showed benefit,[13] and the later Outcome Reduction with an initial Glargine Intervention (ORIGIN) trial which did not.[14] Although statistical power in these subgroup analyses was limited, neither trial found evidence supporting effect modification by statin or β-blocker use.[1314] Consequently, currently insufficient evidence exists to suggest that more extensive medication use in the recent trials explains their null findings.

Two other issues may account for the divergent results of earlier versus later n-3 PUFA clinical trials. First, in most of the earlier trials, benefits were seen for cardiac mortality, consistent with observational studies that this would be the major CVD benefit, at least at doses up to 1 g/day. All of the more recent trials evaluated composite CVD endpoints that included both fatal and non-fatal events,[113] and several altered and expanded their primary endpoint during follow-up due to lower-than-anticipated event rates. Post hoc power calculations indicate that most of these trials were substantially under-powered to detect a clinically meaningful effect on CHD death,[4] the endpoint most likely to be influenced by these doses of n-3 PUFA. On the other hand, ORIGIN was sufficiently powered to investigate CHD death (N=547 total events), and yet still demonstrated null findings.

Second, with increasing media and public health attention on cardiovascular benefits of fish and n-3 PUFA, the background dietary fish consumption or use of fish oils supplements at enrolment was generally higher in more recent trials than in earlier studies. While direct comparison between trials is difficult due to lack of standardised dietary assessment, secular trends suggest increased fish and fish oil consumption over time. In the USA, for example, nearly 20% of middle-aged to older adults reported fish oil supplement use in 2006, compared with <5% in 1990.[15] Similarly, high prevalence of fish oil supplement use and increases in fish intake have also been observed in other countries.[1617] Based on dose-response modelling, n-3 PUFA have non-linear benefits on cardiac death, with little additional effects at intakes above 250 mg/day.[18] Thus, more subjects in the recent trials may have already been consuming enough dietary n-3 PUFA so that additional modest supplementation (eg, 1 g/day) would produce little benefit.

These two factors—the use of composite CVD endpoints, on which n-3 PUFA may have smaller effects at modest doses compared with cardiac death, and a high background intake of fish—may together make it difficult to demonstrate benefits of modest fish oil

supplementation. Correspondingly, the expectation that n-3 PUFA supplementation would achieve a 20%–30% risk reduction (a usual assumption in the power calculations of these trials) may have been unrealistic. Consistent with this, a recent trial-level meta-analysis demonstrated ~10% risk reduction in cardiac death, but no significant benefits for composite CVD endpoints.[1] Moving forward, subject-level meta-analysis of existing trials would be extremely useful to determine if benefits are larger in patients receiving fewer medications or consuming less dietary n-3 PUFA. Furthermore, additional trials are needed that carefully consider these important issues in their design and conduct, including background use of medication, a focus on cardiac death versus composite endpoints, and the possible influence of background dietary n-3 PUFA. Trials testing higher doses (eg, up to 4 g/day) and longer durations of treatment would also be crucial to determine if high-dose, sustained treatment reduces total CVD. Ideally, trials should target specific clinical outcomes based on prior knowledge of biological properties and dose-response effects of n-3 PUFA, and focus on populations who may obtain largest benefits (eg, those with little or no fish intake). Emerging evidence suggests that n-3 PUFA could also protect against other cardiac diseases including atrial fibrillation and congestive heart failure,[19,20] which should also be examined in appropriately designed trials using higher doses of n-3 PUFA. Continued well-designed observational studies, including those investigating surrogate endpoints such as CAC, will also provide crucial complementary evidence, but will require stronger study designs than cross-sectional or ecological analysis. Overall, the cumulative evidence still favours likely cardiovascular benefits of n-3 PUFA, and moderate dietary intake of fatty fish should be one cornerstone of a heart-healthy diet.[21]

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Table 1

Large randomised controlled trials of n-3 polyunsaturated fatty acids (PUFA) and CVD*

Trials	Population/background fish or n-3 PUFA intake	Intervention	Duration of follow-up	Events	RR (95% CI)	Achieved power†
DART[22]	2033 men with recent (average ~1 month prior) MI	Advice to consume fatty fish 2 servings/ week versus usual care	2 years	IHD events, n=276 IHD deaths, n=194	0.84 (0.66–1.07) 0.68 (0.49–0.94)	0.69 0.57
GISSI-Prevenzione Trial[23]	11 324men with recent (≤3 months prior) MI	882 mg/day EPA+DHA versus usual care	3.5 years	Cardiac deaths, n=520 Sudden deaths, n=286	0.78 (0.65–0.92) 0.74 (0.58–0.93)	0.91 0.69
DART 2[24]	3114 men with angina	Advice to consume fatty fish 2 servings/ week versus usual care	3–9 years	Cardiac deaths, n=319 Sudden deaths, n=120	1.26 (1.00–1.58) 1.54 (1.06–2.23)	0.65 0.26
JELIS[25]	18 645men and women with total cholesterol ≥6.5 mmol/L	1.8 g/day EPA versus usual care	5 years	Major coronary events, n=586 Coronary deaths, n=60 Sudden deaths, n=35	0.81 (0.69–0.95) 0.94 (0.57–1.56) 1.06 (0.55–2.07)	0.93 0.17 0.13
GISSI-Heart Failure[26]	6975 patients with chronic congestive heart failure	882 mg/day EPA+DHA versus placebo	3.9 years	Total mortality, n=1969 Cardiovascular death, n=1477 Sudden deaths, n=632	0.91 (0.83–0.99) 0.90 (0.81–0.99) 0.93 (0.79–1.08)	>0.99 >0.99 0.94
Alpha Omega Trial[27]	4837 patients with a history of past (average ~4.3 years prior) MI	376 mg/day EPA+DHA versus a combined control group receiving either placebo or ALA 1.9 g/day	3.3 years	Major cardiovascular events, n=671 CHD deaths, n=138	1.01 (0.87–1.17) 0.98 (0.68–1.32)	0.96 0.36
OMEGA Trial[28]	3851 patients with recent (≤2 weeks prior) MI	840 mg/day EPA+DHA versus placebo	1 year	Major cardiovascular events, n=331 Sudden deaths, n=57	1.21 (0.96–1.52) 0.95 (0.56–1.60)	0.72 0.17
SU.FOL.OM3[29] 2010	2501 patients with a history of past (average ~100 days prior) acute coronary or cerebral ischaemic event	600 mg/day EPA+DHA versus a combined control group receiving either placebo or B vitamins (5-methyltetrahydrofolate, 560 μg; B_6, 3 mg and B_{12}, 20 μg)	4.2 years	Major cardiovascular events, n=157 CHD deaths, n=40	1.08 (0.79–1.47) Not reported	0.4 0.14
ORIGIN[14]	12 536 patients at high risk for CVD and had IFG, IGT or diabetes	900 mg/day EPA+DHA versus placebo	6.2 years	CVD deaths, n=1155 Arrhythmia death‡, n=547	0.98 (0.87–1.10) 1.10 (0.93–1.30)	>0.99 0.87
Risk and prevention study[2]	12 513patients with multiple cardiovascular risk factors, or atherosclerotic vascular disease, but not MI	850 mg/day EPA+DHA versus placebo	5 years	CVD deaths, n=279 CHD deaths, n=158	1.03 (0.82, 1.30) 1.07 (0.78–1.46)	0.61 0.38

*Adapted from Mozaffarian and Wu.[4]

†Based on the actual number of events, two-sided α=0.05, and a relative risk reduction of 25% for n-3 fatty acid treatment.

‡Sudden deaths, non-sudden deaths, unwitnessed deaths, resuscitation after cardiac arrest.

ALA, alpha-linolenic acid; CHD, coronary heart disease; CVD, cardiovascular disease; DART, Diet and Reinfarction Trial; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IHD, ischemic heart disease; JELIS, Japan EPA Lipid Intervention Study, MI, myocardial infarction; ORIGIN, Outcome Reduction with an initial Glargine Intervention; SUFOLOM3, Supplementation en Folates et Omega-3.