Review Article

Omega-3 Fatty Acids and Cardiovascular Outcomes: Focus on the REDUCE-IT and VITAL Studies

Dr. Peeyush Jain, MBBS, MD (Medicine), DM (Cardiology)

Director, Non-invasive Cardiology and Head, Department of Preventive Cardiology, Fortis-Escorts Heart Institute, New Delhi 110 025, India

Abstract

Previous randomised controlled trials of marine omega-3 (n-3) fatty acids have been inconclusive. The recent REDUCE-IT study in patients with or at high risk of cardiovascular disease found a highly significant positive clinical outcome with highly purified eicosapentaenoic acid ethyl ester. Another recent study, the VITAL study, used marine n-3 fatty acids but showed negative results. The VITAL study was much larger but it was a primary prevention study, whereas the participants in the REDUCE-IT study had a much higher risk. The formulation of n-3 fatty acids was different between the two studies—the active comparator n-3 fatty acid arm in the VITAL study included a mixture of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). In addition, there was a considerable difference in the dosing between the two trials. Therefore, whether these factors account for differences in results is conjectural. Beneficial effects of alpha linolenic acid (ALA) of plant origin on vascular inflammation, thrombosis, arrhythmogenesis and vascular events also remain inconclusive.

Keywords

- Alpha-linolenic acid (ALA)
- Eicosapentaenoic acid (EPA)
- Docosahexanoic acid (DHA)
- REDUCE-IT study
- VITAL study

Introduction

Omega-3 (n-3 or ω-3) fatty acids consist of alpha-linolenic acid (ALA), an essential fatty acid of plant origin, and long-chain eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), the primary source of which is fish, particularly fatty fish. Sources of ALA include vegetable oils such as mustard, rapeseed and rice-bran oils and nuts, particularly walnuts. N-3 fatty acids have long been perceived to be beneficial for the cardiovascular (CV) system, largely based on epidemiological observations of cardioprotective effects of fish consumption.

Fish and marine sources of n-3 fatty acid

In observational studies, fish intake was found to be associated with lower risk of fatal coronary artery disease (CAD) and, to a lesser extent, fatal stroke but not non-fatal CAD.[1,2] The reduction in the risk of fatal CAD could be due to the antiarrhythmic effects of EPA and DHA. Other possible benefits of marine n-3 fatty acids are decreasing blood pressure and heart rate variability, reducing serum triglyceride levels, improving endothelial function and having anti-inflammatory effect.[3]

Received: 16-05-2019; Revised: 23-05-2019; Accepted: 03-06-2019
Disclosures: This article has not received any funding and has no vested commercial interest.
Acknowledgments: None

Findings indicating fish as a heart-healthy food has ignited randomised controlled trials of long chain n-3 fatty acid supplementation for many years; however, the trials and meta-analyses based on them have generated conflicting or inconclusive results (Table 1). Four out of five older trials demonstrated benefits, but no newer trials did.[4] This may be due to more aggressive evidence-based lipid- and BP-lowering drug treatment that have emerged in recent years, which may render additional benefits of fish oil more difficult.[4] A systematic review of studies restricted to patients with established CAD or prior myocardial infarction (MI) reported a 20% risk reduction for CV death with EPA and DHA supplementation.[5]

Table 1: Systematic Reviews and Meta-analyses of Observational Studies and Randomised Controlled Trials for Cardiovascular Outcomes with n-3 Fatty Acids of Plant and Marine Origin *Modified from: Mozaffarian D: Nutrition in Cardiovascular and Metabolic Diseases in Braunwald's Heart Disease. 11th Ed. In Zipes DP, Libby P, Bonow RO et al. (eds): Elsevier Inc., 2019, pp 986*

	Endpoint	No. of Studies	No. of Subjects	No. of Events	Unit	RR	95% CI	Reference
n-3 from plant sources	CHD	5 PCs	89,700	5,788	High vs. Low	0.94	0.85–1.04	Pan A, et al. 2012[a]
	Stroke	3 PCs	98,410	1,300	High vs. Low	0.96	0.78–1.17	Pan A, et al. 2012[a]
n-3 from marine sources	CHD	16 PCs	422,786	9,089	Top vs. Bottom Tertile	0.87	0.78–0.97	Chowdhury R, et al. 2014[b]
	Fatal CHD	16 PCs, 5 RCTs	363,003	5,951	250 mg/d vs. None	0.64	0.50–0.80	Mozaffarian D, et al. 2006[c]
	Stroke	8 PCs	242,076	5,238	High vs. Low	0.90	0.81–1.01	Larsson S, et al. 2012[d]

CHD, coronary heart disease; CI, confidence interval; PC, prospective cohort; RR, relative risk; RCT, randomised controlled trial,
a Pan A, Chen M, Chowdhury R, Wu JH, Sun Q, Campos H, et al. Alpha-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr. 2012;96:1262–1273.
b Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:398–406.
c Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006;296:1885–1899.
d Larsson SC, Orsini N, Wolk A. Long-chain omega-3 polyunsaturated fatty acids and risk of stroke: a meta-analysis. Eur J Epidemiol. 2012;27:895–901.

REDUCE-IT

The 'Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT),[6] is a recent large double-blind, placebo-controlled study that found a highly significant positive clinical outcome with n-3 fatty-acid supplementation. Participants were patients with cardiovascular disease (CVD) aged ³ 45 years or those with diabetes with >1 additional risk factor for CVD aged ³ 50 years who had fasting serum triglyceride (TG) levels between 135 mg/dL and 499 mg/dL, low density lipoprotein cholesterol (LDL-C) between 40 mg/dL and 99 mg/dL and were on stable statin therapy with or without ezetimibe. Out of 19,212 screened patients, 8179 were randomised to either a highly purified eicosapentaenoic acid ethyl ester (icosapent ethyl, 2 g, BID; n = 4089) or placebo (n = 4090). Median trial follow-up was 4.9 years. The combined primary endpoint events were CV death, non-fatal MI, non-fatal stroke, coronary revascularisation and hospitalisation for unstable angina. The key secondary endpoint events were CV death, non-fatal MI and non-fatal stroke. At the end of follow-up, the primary endpoint was reached in 23% and 28.3% of the individuals in the Icosapent group and the placebo group, respectively (absolute risk reduction, ARR: 4.8%; relative risk reduction, RRR: 24.8%; hazard ratio, HR: 0.75; 95% confidence interval, CI: 0.68–0.83; p = 0.00000001; number needed to treat, NNT: 21) (Figure 1). The key secondary endpoint was reached in 16.2% and 20% of the individuals in the Icosapent group and the placebo group, respectively (ARR: 3.6%; RRR: 26.5%; HR 0.74; 95% CI: 0.68–0.83; p = 0.0000006; NNT: 28) (Figure 2). The first

event as well as the total number of events were reduced in the active treatment group. Outcomes in terms of pre-specified CV death or non-fatal MI, fatal or non-fatal MI, urgent or emergent revascularisation, hospitalisation for unstable angina and fatal or non-fatal stroke were better in the Icosapent group than in the placebo group. There was 13% reduction in total mortality in the Icosapent group, which did not reach statistical significance. In conclusion, compared with placebo, 4 g/day of icosapent ethyl reduced total CV events by 30%, including 25% reduction in the first CV events, 32% reduction in the second CV events, 31% reduction in the third CV events and 48% reduction in the subsequent CV events in these statin-treated, high-risk patients with baseline serum triglyceride levels of >100 mg/dL.

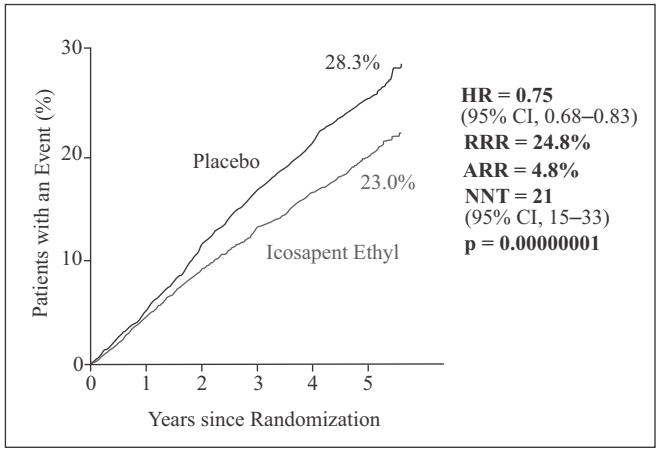

Figure 1: Primary endpoint events of the REDUCE-IT. *Adapted from: Bhatt DL, et al. N Eng J Med. 2019;380(1):11–22.*[6]
ARR, absolute risk reduction; CI, confidence interval; NNT, number needed to treat; RRR, relative risk reduction

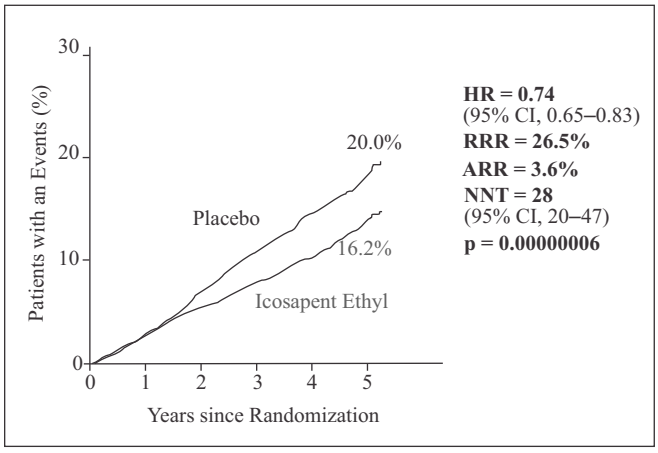

Figure 2: Key secondary endpoint events of the REDUCE-IT. *Adapted from: Bhatt DL, et al. N Eng J Med. 2019;380(1):11–22.*[6]
ARR, absolute risk reduction; CI, confidence interval; NNT, number needed to treat; RRR, relative risk reduction; HR, hazard ratio

These findings are significant because patients in both groups received optimal medical therapy as per the current recommendations (Table 2). More than 99% of patients in both groups were on statin therapy. Benefits of icosapent ethyl observed in this study cannot be attributed to serum triglyceride reduction because the beneficial effects were observed irrespective of baseline serum triglyceride levels (Table 3). Moreover, event reduction was delayed, observed after 1 year of initiation of therapy.

Table 2: Key medical therapy in the REDUCE-IT study.

	Icosapent Ethyl (N = 4089)	**Placebo (N = 4090)**
Antiplatelet	3257 (79.7%)	3236 (79.1%)
One Antiplatelet	2416 (59.1%)	2408 (58.9%)
Two or more Antiplatelets	841 (20.6%)	828 (20.2%)
Anticoagulant	385 (9.4%)	390 (9.5%)
ACEi or ARB	3164 (77.4%)	3176 (77.7%)
Beta Blocker	2902 (71.0%)	2880 (70.4%)
Statin	4077 (99.7%)	4068 (99.5%)

Adapted from: Bhatt DL, et al. N Eng J Med. 2019;380(1):11–22.[6]
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers

VITAL Study

Vitamin D and Omega-3 Trial (VITAL) is another study of marine n-3 fatty acids, which was published alongside REDUCE-IT, but with negative results.[7] It was a randomised, placebo-controlled trial of vitamin D_3 (2000 IU/day) and marine n-3 fatty acids (1 g/day) in a 2 x 2 factorial design in the primary prevention of CVD and cancer among men aged >50 years and women aged >55 years. Primary end points were major CV events (a composite of MI, stroke or death from CV causes) and invasive cancer of any type. Secondary end points were individual components of the composite CV end point, the composite end point plus coronary revascularisation, site-specific cancers and death from cancer. A total of 25,871 participants underwent randomisation. After a median follow-up of 5.3 years, a major CV event occurred in 386 participants in the n-3 group and in 419 in the placebo group (HR, 0.92; p = 0.24). Invasive cancer was diagnosed in 820 participants in the n-3 group and in 797 participants in the placebo group (HR, 1.03; p = 0.56). In the analyses of key secondary end points, the HR were as follows: expanded composite end point of CV events, 0.93; total MI, 0.72; total stroke, 1.04; death from CV causes, 0.96; death from cancer, 0.97 and death from any cause, 1.02. No excess risks of bleeding or other serious adverse events were observed. Supplementation with n-3 fatty acids did not result in a lower incidence of major CV events or cancer compared to the placebo in this study.

There are several explanations for the divergence between the results of the REDUCE-IT study and those of the VITAL study, all of which need further evaluation. First, although the sample size in the VITAL study was much larger, it was a primary prevention study, whereas REDUCE-IT recruited subjects with a much higher risk for secondary prevention. Second, the formulation of n-3 fatty acids was different between the two studies: the active comparator n-3 fatty acid arm of the VITAL study included a mixture of EPA and DHA and it was a highly purified ester of EPA in REDUCE-IT. DHA, but not EPA, is known to increase LDL-C, and this may have somewhat attenuated the effect of n-3 fatty-acid supplementation in the VITAL study. Finally, there was a considerable difference in the dosing between the two trials: the dose of EPA ester in the REDUCE-IT study was 4 g/day, which is closer to recommended therapeutic dose of n-3 fatty acid supplementation, whereas it was 1 g EPA/DHA in the VITAL study.

Table 3: Total endpoint events by baseline TG tertiles in the REDUCE-IT study.

Total Events- Primary Composite Endpoint/Subgroup	**Icosapent Ethyl** Rate per 1000 Patient Years	**Placebo** Rate per 1000 Patient Years	**RR (95% CI)**	**p-value**
Primary Composite Endpoint	61.1	88.8	0.70 (0.62-0.78)	<0.0001
Baseline TG Tertiles*				
⩾81 to ⩽190 mg/dL	56.4	74.5	0.74 (0.61-0.90)	0.0025
>190 to ⩽250 mg/dL	63.2	86.8	0.77 (0.63-0.95)	0.0120
>250 to ⩽1401 mg/dL	64.4	107.4	0.60 (0.50-0.73)	<0.0001
0.2 0.6 1.0 1.4 1.8 **Icosapent Ethyl Better** **Placebo Better**				***p (Interaction) = 0.17**

RR, relative risk *Adapted from: Bhatt DL, et al. N Eng J Med. 2019;380(1):11–22.6*

Plant Sources of n-3 Fatty Acids

Beneficial effects of ALA of plant origin on vascular inflammation, thrombosis and arrhythmogenesis remain inconclusive.[8] It is not known whether the beneficial effects of marine long-chain n-3 fatty acids may be extrapolated to ALA, which is a shorter chain n-3 fatty acid. Observational evidence for the role of ALA in CAD and stroke reduction is conflicting, although a meta-analysis of several prospective cohort studies reported a 21% decrease in the risk of fatal CAD of borderline statistical significance.[9] PREDIMED (Prevention with Mediterranean Diet) Study, a randomised trial with primary subjects at high CV risk who were assigned to Mediterranean diet supplemented with extra-virgin olive oil or mixed nuts (some of which are rich in ALA) and compared with low fat diet.[10] The primary endpoint was major CV events consisting of MI, stroke or death from CV causes. The trial was stopped after a median follow-up of 4.8 years. Primary end-point HR for the groups assigned to a Mediterranean diet with extra-virgin olive oil was 0.70 and that for Mediterranean diet with nuts was 0.72 when compared with the control group. Therefore, among subjects at high CV risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major CV events. These outcomes should be attributed to an overall effect of Mediterranean diet rather than olive oil and nuts. Therefore, the issue whether dietary ALA or supplements are cardioprotective remains open and worthy of further evaluation.

References

1. He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation. 2004;109;2705–11.

2. He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, et al. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke. 2004;35:1538–42.

3. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011;58:2047–2067

4. Wu JH, Mozaffarian D. Omega-3 fatty acids, atherosclerosis progression and cardiovascular outcomes in recent trials: new pieces in a complex puzzle. Heart. 2014;100:530–3.

5. León H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systemic review. Br Med J. 2008;337:a2931.

6. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Reduction in total ischemic events in the reduction of cardiovascular events with icosapent ethyl-intervention trial. N Eng J Med. 2019;380:11–22.

7. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N Eng J Med. 2019;380:23–44.

8. Wendland E, Farmer A, Glasziou P, Neil A. Effect of alpha linolenic acid on cardiovascular risk markers: a systemic review. Heart. 2006;92:166–9.

9. Brouwer IA, Katan MB, Zock PL. Dietary alpha-linolenic acidis associated with reduced risk of fatal coronary heart disease, but increased prostate cancer risk; a meta-analysis. J Nutr. 2004;134:919–22.

10. Estruch R, Ros E, Salas-Salvadó J, et al. for the PREDIMED Study Investigators. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. N Engl J Med. 2018;378:2441–2.

Address for correspondence:
Dr. Peeyush Jain
Email ID: peeyush.jain@fortishealthcare.com