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Understanding why REDUCE-IT was positive – Mechanistic overview of eicosapentaenoic acid☆

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ABSTRACT

The REDUCE-IT study found that patients at elevated risk for cardiovascular disease (CVD) who were already taking statins obtained a marked benefit by taking 4 g/d of eicosapentaenoic acid ethyl esters (icosapent ethyl, IPE; Vascepa) over about 5 years. Although approved for triglyceride (TG) lowering, IPE had only a modest TG-lowering effect in REDUCE-IT, largely because median TG levels were relatively low already. Hence the question of what mechanisms IPE might be working through is of great interest. At present, it appears that the best mechanistic candidates would be anti-platelet effects and/or anti-inflammatory effects. Whatever the cause, the powerful effects of IPE on CVD risk have renewed interest in the clinical utility of omega-3 fatty acids.

Contents

The purpose of this review is to consider some of the possible mechanisms to explain the beneficial effects of icosapent ethyl (IPE; Vascepa, Amarin Corporation) in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) study.[1] (Also see Nelson et al.[2] and Barow et al.[3] who have previously published comprehensive reviews of this topic.) In November of 2018 the results of REDUCE-IT were released. REDUCE-IT used IPE, which is eicosapentaenoic acid (EPA) in ethyl ester form, versus placebo in patients with persistent hypertriglyceridemia despite statin use. REDUCE-IT enrolled over 8000 high-risk patients with mixed dyslipidemia and followed for approximately five years. Inclusion criteria included triglycerides (TGs) of 135 to 499 mg/dL as well as known CVD or diabetes and at least one other CV risk factor. Average low-density lipoprotein cholesterol (LDL cholesterol (LDL-C) was ~75 mg/dL (on statins) and average TG levels were ~216 mg/dL. Participants were randomized to either 4 g/d IPE or a placebo. IPE significantly reduced major cardiovascular disease (CVD) events by 25% and other secondary CVD endpoints by between 20 and 35%. A follow-up paper reporting effects on all ischemic events (not just the first one as in Bhatt et al.[4]) found similar protection.[5]

Abbreviations: ApoB, apolipoprotein B-100; AMI, acute myocardial infarction; ANCHOR, (study name, not an abbreviation); CVD, cardiovascular disease; COX, cyclo-oxygenase; CRP, C-reactive protein; CYP450, cytochrome-P450; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EPEA, eicosapentaenoyl-ethanolamine; HDL, high density lipoprotein; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; JELIS, Japan EPA Lipid Intervention Study; IPE, icosapenta ethyl; LDL, low density lipoprotein; Lp-PLA2, lipoprotein-associated phospholipase A2; LOX, lipoxygenase; MCP-1, monocyte chemoattractant protein-1; Ox-LDL, oxidized LDL; PTX-3, Pentraxin-3; REDUCE-IT, reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; TG, triglycerides; TxA, thromboxane A.

☆ Disclosures: The author is the founder and President of OmegaQuant Analytics, LLC, a commercial laboratory specializing in the analysis of fatty acids. He also serves on the Scientific Advisory Board for the Seafood Nutrition Partnership, a non-profit organization promoting greater seafood consumption.

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Possible mechanisms

Measured CVD risk factors affected by IPE in REDUCE-IT

In REDUCE-IT, the effects of 4 g of IPE were reported on rather few classic CVD risk factors.[1] Only changes in basic lipids and lipoproteins and in one inflammatory marker, C-reactive protein (CRP) were presented. TGs were reduced by a net of 15%, non- high-density lipoprotein cholesterol (HDL-C) by 9%, apolipoprotein B-100 (ApoB) by 10% and CRP by 52%. For context, baseline levels of each of these four markers were not markedly abnormal: 216 mg/dL, 119 mg/dL, 83 mg/dL and 2.2 mg/L. How much would these changes be expected to change risk based on past trials? Kastelein and Stroes[6] reported that the reduction in non-HDL-C observed in REDUCE-IT would be expected to lower CVD risk by only about 6%–8%, and the relatively small decrease in CRP (0.65 mg/L) seen in the IPE group could, in theory, reduce risk by about 5%. Interestingly, there were no differences in the *clinical* impact of IPE in patients with higher vs lower baseline levels of any of these markers, or whether TG levels were normalized or not. These observations suggest that effects on these classic risk factors (or on blood pressure or on glycemic status, neither of which was altered) cannot explain why IPE reduced overall risk for CVD. Therefore, it is reasonable to look elsewhere.

Risk factors affected by IPE in other trials

There is only one other study that examined the effects on risk factors of 4 g of IPE in statin-treated patients with residual hypertriglyceridemia living in Western countries (i.e., patients similar to those in REDUCE-IT), and that study was ANCHOR.[7] ANCHOR was a multi-center, placebo-controlled trial testing the effects of both 2- and 4-g of IPE vs placebo on a variety of CVD risk factors in 702 patients (the only caveat in this comparison is that ANCHOR lasted only 12 weeks whereas effects on risk factors in REDUCE-IT were based on at least 1 year of IPE treatment. So, some risk markers might not have been affected by IPE in ANCHOR but could have been altered in REDUCE-IT).

What were the effects of 4 g of IPE in ANCHOR? Other than the reductions in apoB, non-HDL-cholesterol, TG, and CRP as also reported by Bhatt et al.[4] significant reductions were also seen in apoC-III and remnant lipoproteins.[8] Treatment also lowered levels of more directly atherogenic markers: lipoprotein-associated phospholipase A2 (Lp-PLA2) and oxidized LDL (Ox-LDL), but not interleukin 6 (IL-6) or intercellular adhesion molecule-1 (ICAM-1).[9] Ox-LDL particles are more readily taken up by endothelial macrophages and can thus directly contribute to the development of arterial plaque. Similarly, Lp-PLA2, an enzyme carried by LDL into the arterial intima, can accelerate hydrolysis of Ox-LDL phospholipids to lysophosphatidylcholine and oxidized free fatty acids, which subsequently activate ICAM-1, an adhesion molecule that facilitates attachment of circulating leukocytes to the endothelium, ultimately promoting vascular inflammation. As CRP production is at least partially controlled by IL-6 levels, the lack of effect of IPE on this protein (in concert with a reduction in CRP) is unexpected. Perhaps the fact that an elevated IL-6 was not an inclusion criterion for either ANCHOR or REDUCE-IT (explaining the only modestly increased levels at baseline) might explain the lack of observed effect of IPE on IL-6. Overall, effects of IPE on both Lp-PLA2 and Ox-LDL levels probably contributed to the vascular benefits observed in REDUCE-IT.

Risk factors affected by EPA ethyl esters in other settings

Many studies of the effects of lower doses of EPA ethyl esters (typically 1.8 g/d) were reported, and virtually all of them are from Japan.[1] These have been nicely summarized by both Nelson et al.[2] and Barow et al.,[3] and thus will only be briefly reviewed here. This is not only to avoid redundancy, but because the relevance of these studies to the REDUCE-IT study is unclear. The studies considered here used both a lower dose of IPE and were conducted in Japan, where there is a much higher background intake (and thus blood level) of EPA (and docosahexaenoic acid, DHA, the most abundant omega-3 fatty acid in vivo) than in Western populations[10]. What IPE does in *that* setting (half the dose given to patients with already very high EPA and DHA levels) may have little to do with what happened in REDUCE-IT. On the other hand, the use of 4 g in REDUCE-IT produced final plasma EPA levels of 144 μg/mL which is similar to the 160 μg/mL observed in studies with 1.8 g of EPA in statin-treated patients in Japan.[11] Thus, the mechanisms of action suggested by studies in Japanese patients taking 1.8 g of EPA may in fact apply to REDUCE-IT.

The most well-known of the Japanese EPA studies is the 2007 Japan EPA Lipid Intervention Study (JELIS).[12] This trial found that 1.8 g/d of Epadel (the Japanese version of IPE) significantly reduced risk for certain CVD endpoints, not only in a Japanese population (which was remarkable in and of itself), but in a Japanese cohort on statin therapy. Multiple follow-up studies from JELIS have reported that the cardioprotective effects of EPA were more pronounced in 1) secondary rather than primary prevention settings,[13] 2) patients with peripheral artery disease,[14] 3) subjects with multiple CVD risk factors,[15] and 4) those with impaired glucose metabolism.[16] The incidence of recurrent (but not first) stroke was also reduced in JELIS.[17] Thus, JELIS provided strong evidence for CVD risk reduction with about ½ the dose of EPA ethyl esters as used in REDUCE-IT even on a background diet rich in EPA and DHA. JELIS was generally confirmed in REDUCE-IT, suggesting that achieving a certain blood/tissue level of EPA is what affords protection, and this level may be reached by supplementing with EPA and/or consuming a diet high in omega-3 rich seafoods.

Other more recent studies of EPA in Japan include ones in which vascular function was improved by EPA administration to diabetic patients[18] and in coronary artery disease patients.[11] Another paper reported that the anti-inflammatory and anti-oxidative properties of HDL particles were improved in dyslipidemic patients treated for four weeks with 1.8 g/d of EPA.[19] The authors proposed that EPA can convert “dysfunctional” into “functional” HDL. Several studies have focused on coronary atherosclerosis itself. In one,[20] coronary artery plaque characteristics in patients randomized post percutaneous coronary intervention to usual care or EPA (1.8 g/d) were compared after 9 months of treatment. The EPA group had a greater increase in fibrous-cap thickness and a greater decrease in macrophage accumulation and the incidence of intimal microvessels. Pentraxin-3 (PTX-3) levels were also lower in the EPA group. Niki et al.[21] reported that PTX-3 and monocyte chemoattractant protein-1 (MCP-1) were lower in their EPA group, Watanabe et al.[22] showed 193 CHD patients randomized to pitavastatin or statin + EPA therapy and followed-up 6–8 months that plaque volumes were reduced, and plaque composition was altered toward a more stable phenotype. Taken together, these Japanese trials strongly suggest that EPA treatment can stabilize coronary artery plaques via anti-inflammatory pathways leading to lower rates of acute coronary events.

[1] The Japanese have been the leaders in studying the effects of EPA (as opposed to EPA + DHA) largely because a Japanese company, Mochida Pharmaceutical, developed EPA ethyl esters (generic name, eicosapentate ethyl; trade name, Epadel) in 1990 and marketed it for the last nearly 30 years for the treatment of hypertriglyceridemia and atherosclerosis obliterans. Hence, there was considerable financial incentive for exploring the effects of EPA ethyl esters in Japan. Vascepa is essentially the same molecule as Epadel. Indeed, in 2018 Amarin and Mochida announced a partnership to jointly develop future EPA-based products (see https://investor.amarincorp.com/news-releases/news-release-details/amarin-and-mochida-announce-collaboration-future-development-epa).

Epidemiologic support for a benefit of EPA in atherosclerosis

Urabe et al.[23] showed that Japanese patients with plasma EPA levels above (versus below) the median (61 μg/mL) had a lower prevalence of high-risk coronary artery plaques. The relationship was similar but less clear for plasma DHA concentrations (above vs below 146 μg/mL). No relationships with plaque characteristics were observed above vs below median arachidonic acid levels (199 μg/mL). Accordingly, the plasma EPA:arachidonic acid ratio was no better risk predictor than was the simpler metric, plasma EPA concentration. Another example of the prognostic value of EPA came from a study from our laboratory in which we found that red blood cell EPA levels added significant predictive ability to the GRACE (Global Registry of Acute Coronary Events) score which is used to estimate risk for death in survivors of acute myocardial infarctions (AMI).[24] A 2019 publication from Block et al.[25] reported that plasma phospholipid EPA levels were a significant predictor of risk for heart failure in the Multi-Ethnic Study of Atherosclerosis. A similar observation was made by Mozaffarian et al. in the Cardiovascular Health Study cohort.[26] Hence, there is support for the view that circulating levels of EPA (and DHA as well) may have clinically-relevant, prognostic value.[27]

The exploding world of EPA metabolites

When considering the mechanisms by which IPE reduced CVD events in REDUCE-IT, one should perhaps begin at the very beginning of the "omega-3 story" with the studies by Dyerberg and Bang and colleagues in Greenland Inuits.[28] In their seminal 1978 in the paper in Lancet, presciently (and tentatively) entitled, "Eicosapentaenoic acid and prevention of atherosclerosis and thrombosis?" Dyerberg et al.[29] synthesized the following observations into their hypothesis - that the high EPA levels in the Inuit diet reduced risk for thrombosis and AMI- 1) residents of coastal Greenland living off traditional foods had very low rates of AMI, 2) these Inuits had high levels of EPA (and DHA) in their blood, 3) their bleeding times were prolonged, 4) EPA could substitute for arachidonic acid as a substrate for platelet cyclooxygenase (COX) lowering production of thromboxane A2 (TxA2), 5) EPA could be made into a relatively inactive form of thromboxane (TxB3), and 6) EPA-treated platelets showed marked reductions in aggregation. In the 40 years that have passed since that seminal paper was published, this hypothesis remains a live possibility. What has changed remarkably is the discovery of a bewildering array of EPA (and DHA) metabolites with biological activity.

Gabbs et al. summarized many of the known (as of 2015) biomolecules produced from EPA via COX, lipoxygenase (LOX), and cytochrome-P450 (CYP450) pathways (Fig. 1). In addition to these molecules, EPA can also be converted into endocannabinoids: eicosapentaenoyl-ethanolamine (EPEA) and eicosapentenoyl-glycerol[30] agonists competing with arachidonic acid-derived species for cannabinoid receptors. Remarkably, the endocannabinoids themselves can serve as substrates for COX, LOX and CYP450, producing even more oxygenated metabolites[31] (Fig. 2). EPA can even covalently bond with both dopamine and serotonin in the central nervous system, and these molecules have biological activity in certain model systems.[30]

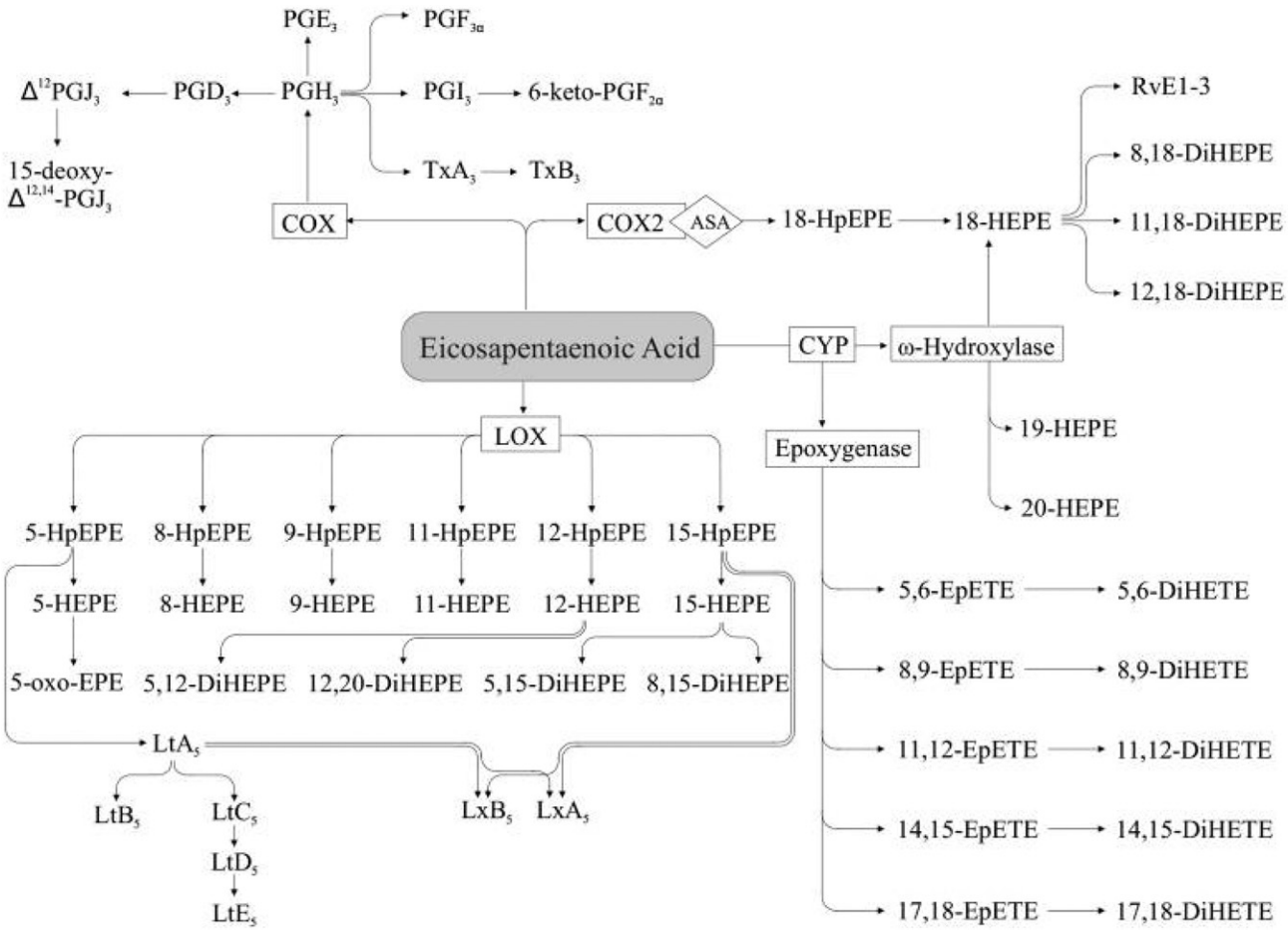

Fig. 1. EPA-derived oxylipins. ASA, acetylsalicylic acid; COX, cyclooxygenase; CYP, cytochrome P450; DiHEPE, dihydroxyeicosapentaenoic acid; DiHETE, dihydroxyeicosatetraenoic acid; EpETE, epoxyeicosatetraenoic acid; HEPE, hydroxyeicosapentaenoic acid; HpEPE, hydroperoxyeicosapentaenoic acid; LOX, lipoxygenase; Lt, Leukotriene; Lx, lipoxin; oxo-EPE, oxoeicosapentaenoic acid; Rv, resolvin; Tx, thromboxane. (From Gabbs et al.[36] Reprinted with permission).

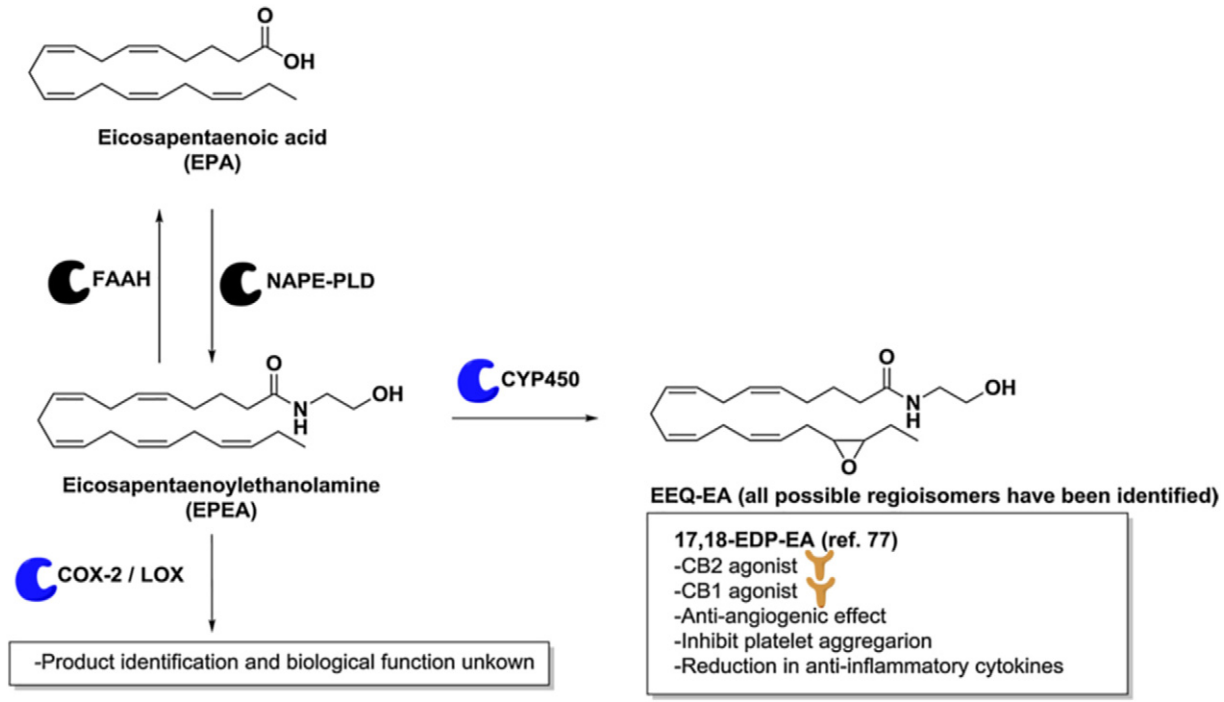

Fig. 2. The metabolism of EPA into eicosapentaenoylethanolamine (EPEA) and subsequent further conversion into epoxyeicosatetraenoic acid ethanolamide (EEQ-EA) and other epoxides via cytochrome P450 (CYPP450). Fatty acid amide hydrolase (FAAH); N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), cyclooxygenase (COX); lipoxygenase (LOX), cannabinoid receptor (CB). (From de Bus et al.[31] Reprinted with permission).

What other EPA metabolites remain to be discovered is obviously unknown, but adducts with proteins, nucleic acids, carbohydrates or other complex biomolecules would no longer be surprising.

It is beyond the scope of this review to recount in depth the impact that EPA appears to have on all biological systems. Suffice it to say that essentially all of EPA's metabolites are either non- or anti-inflammatory. For example, at a gene regulatory level, EPA has been shown to reduce the expression of genes in the NF-κB pathway and genes for pro-inflammatory peptides (i.e., interleukin-1B, MCP-1, and tumor necrosis factor A). At the same time, EPA up-regulates the expression of microsomal glutathione S-transferase 1, an enzyme involved in the prevention of inflammation through detoxification of reactive oxygen species.[32] Laguna and colleagues recently reported that a precursor of resolvin E1, 18-monohydroxy EPA, signals through a G-protein coupled receptor (Erv1/Chemr23) to reduce the uptake of oxidized LDL and to reduce phagocytosis, which together favorably influenced atherosclerosis in a mouse model.[33] The reader is referred to Calder's excellent review on the effects of omega-3 fatty acids on inflammation[34] and to Allaire et al. who compared EPA to DHA in humans and reported somewhat stronger effects on inflammatory markers for the latter than the former.[35]

Conclusion

This short overview of the known effects of EPA in biological systems does not lead us to one definitive reason for "why REDUCE-IT was successful." The term pleiotrophic comes to mind when considering the multitude of ways in which the body utilizes this one omega-3 fatty acid. Opportunities for future researchers to uncover and capitalize on the cardioprotective effects of EPA appear to be endless.

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