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Eicosapentaenoic Acid Based Therapies: Fish Facts and Stories

Aravind Reddy Kuchkuntla[1], Sri Harsha Patllola[2] and Tamim Rajjo[3]

[1]Internal Medicine, Rosalind Franklin University of Medicine and Science, North Chicago, IL

[2]Research Fellow Cardiothoracic surgery, Mayo Clinic Rochester

[3]Assistant professor, Department of Family Medicine, Mayo clinic, Rochester

ABSTRACT

The significant hypo-lipidemic, anti-thrombotic and anti-inflammatory features of EPA created extensive interest in preventive cardiology from the early 90s, since then several clinical studies were conducted to study the mechanisms and benefits of fish oil use. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential FAs therefore, they must be provided in diet or in the form of supplements. The supplements are low dose combinations of EPA and DHA have no significant benefits in terms of CVD prevention in clinical trials. However, a high dose Ethyl ester formulation of EPA has shown a 25% reduction of major adverse coronary events in the secondary prevention. Cardio-protective potential of EPA is attributed to its triglyceride lowering effect, reduction in inflammatory markers, improving coronary plaque stability, anti-platelet effect and improvements of over-all metabolic profile. We intend to provide preventive and therapeutic potentials of EPA in CVD, mechanisms of cardio protection, available evidence and future trails.

***Corresponding author**

Aravind Reddy Kuchkuntla,PGY 2, Internal Medicine Rosalind Franklin University of Medicine North Chicago, IL. E-mail: aravindreddy1989@gmail.com

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Introduction

Omega 3 (ω – 3) FAs have been extensively researched over the last few decades and their preventive and therapeutic role in cancer, inflammation, coronary artery disease (CAD), obesity, diabetes mellitus and neurological diseases is well established [1, 2]. Evidence from observational studies have shown improved cardiovascular outcomes with fish oil use but these findings were not consistently reported in clinical trials [3]. Previously, AHA recommended consumption of fish twice a week for general population, fish oil 1g/day in patients with cardiovascular disease (CVD) for secondary prevention and 2g/day to 4g/day as adjunct to diet in patients with hypertriglyceridemia [4]. In the most recent guidelines no specific recommendations were made in patients with CVD as results from VITAL and REDUCE-IT trials were awaited [5]. These trials have now reported different results in terms of the CVD outcomes with REDUCE IT trail reporting 25% reduction in major cardiac adverse events in secondary prevention group. Several reviews have comprehensively published the outcomes of combined fish oils; therefore we intend to limit our review to Eicosapentaenoic acid (EPA) and its ethyl ester formulation that was investigated in REDUCE IT clinical trial. This review will provide preventive and therapeutic potentials of EPA in CVD, mechanisms of cardio protection, available formulations, recent evidence and future developments.

Polyunsaturated Fatty Acid Chemistry and Metabolism

Fatty acids (FA) are the simplest form of lipids constituting basic components of triglycerides (TG), phospholipids (PL) and cholesterol esters (CE). PUFAs are defined as long chain FA (13 to 21 carbon atoms) with more than 2 double bonds within the carbon chain. Alpha linolenic acid (ALA, 18:3n-3), linoleic acid (LA, 18:2n-6) are short chain PUFAs while Eicosapentaenoic acid (EPA, 20:5n-3), docosahexaenoic acid (DHA 22: 6n-3) and arachidonic acid (AA, 20:4n-6) are long chain PUFAs. The first double bond represented as n minus determines the physiological properties of the FA and based on this ω – 3 and ω – 6 FAs classification was made. ω – 3 and ω – 6 signifies that the first double bond position is at the third and sixth carbon–carbon bond respectively from the terminal CH3 end (ω) of carbon chain.

Both ω – 3 and ω – 6 FAs share a common metabolic pathway but their end products having opposing physiologic effects. Elongases and desaturases serve as enzymes in PUFA metabolism for elongation of the carbon chain by adding 2 carbons at a time and by adding double bonds within the carbon chain respectively. LA and ALA are essential fatty acids and are to be supplemented in diet as the human desaturase enzyme cannot insert double bonds beyond the 10th carbon atom of the carbon chain. ALA and LA are precursors for synthesis of long chain ω – 3 (EPA, DHA) and long chain ω – 6 FA (AA) respectively. LA is metabolized by the Δ5, Δ6 desaturase and Δ6 elongase in a series of reactions with intermediate steps to form AA, the precursor for Eicosanoids [6]. AA undergoes oxygenation catalyzed by cyxlooxygenase (COX) and lipoxygenase (LOX) to form prostaglandin G2 (PG), precursors of thromboxane (Prostaglandin H2) and 4-series leukotrienes [7]. Eicosanoids derived from the ω – 6 FAs pathway are largely pro-inflammatory and pro-thrombotic and have a significant role in the pathogenesis of arteriosclerosis, bronchial

asthma and other chronic inflammatory diseases [8, 9]. ALA the precursor of ω – 3 FAs and is metabolized by the same set of desaturases and elongases involved in ω – 6 pathway to form EPA in the initial enzymatic reactions [6]. EPA is further metabolized by Δ4 desaturase and Δ5 elongase to form DHA that undergoes both enzymatic and non-enzymatic oxidation to form more potent anti-inflammatory substances such as D and E series of resolvins, isoprostanes, protectins etc [10].

Though the body can synthesize EPA and DHA, the ability is limited; therefore they are considered as essential FAs too and must be supplemented in diet. One reason is low content of ALA compared to LA in the western diet, increasing the availability of LA for desaturases and elongases resulting in formation of AA and promoting a pro-inflammatory state [11-14]. In addition to poor dietary content of ALA, imbalance of EPA and AA becomes greater as conversion of dietary ALA to EPA and DHA is less than 5% and 0.5% respectively [15].

EPA: The Beginnings

Observational studies from the mid-90s have established high cholesterol level as a significant risk factor for MI [16]. However in 1970's, an observational study reported an age adjusted mortality of myocardial infarction to be 1/10th in Greenland Eskimos compared to people of Denmark despite noticing no differences in the amount of fat and cholesterol content in the diet [17, 18]. The significantly low CAD incidence was attributed to the eating habits of the Eskimos who consumed high amounts of fish rich in ω – 3 FAs [19, 20]. With high intake of fish, Eskimos had high blood levels of EPA that effected the lipoprotein pattern to have low triglycerides (TG), LDL, VLDL and high HDL [21].

EPA: Cardio-Protective Mechanisms

Anti-Inflammatory Effect

EPA use has shown to reduce local vascular inflammation and systemic inflammation by effecting expression of anti-inflammatory genes [22]. In an exploratory analysis of MARINE and ANCHOR trials, the effect of Icosapent Ethyl (IPE) on level of circulating inflammatory markers after 12 weeks of therapy was reported as median placebo-adjusted percent change from baseline. In an intent to treat (ITT) analysis of MARINE trial, significant reductions in the 4g IPE group compared to placebo in lipoprotein-associated lipase A2 (Lp-PLA2) (14%; $P < 0.001$) and high-sensitivity C-reactive protein (hs-CRP) (36%; $P < 0.01$) were reported. In ANCHOR trial 4g/day IPE resulted in significant reductions in hs-CRP (22%; $P < 0.0001$), oxidized LDL (ox-LDL) (13%; $P < 0.0001$) and Lp-PLA2 (19%; $P < 0.0001$). All these inflammatory markers determine the risk of CVD recurrence and use of IPE has shown to improve biomarkers involved in arteriosclerosis. Anti-oxidant mechanisms of EPA at therapeutic levels are proposed due to its incorporation into the phospholipid layer and resulting in the following: (i) inhibiting glucose induced changes in the phospholipid composition (ii) reducing the fluidity of the phospholipid membrane and (iii) inhibiting the formation of cholesterol crystalline domains that are typically present in the atherosclerotic plaques [23, 24].

EPA exerts anti-inflammatory effects by: (i) reducing the Pentraxin 3 (PTX3) formation from macrophages and vascular smooth muscles improving plaque stability [25, 26]. (ii) reducing systemic inflammation by lowering levels of hs-CRP [27]. (iii) reducing genetic expression of nuclear factor (NF)-κB that upregulates cytokine gene expression [28]. (iv) reduced expression of genes peroxisome proliferator activated receptor (PPAR)-γ pathway [29]. (v) reducing foam cells and T cells in atherosclerotic plaques (vi) effecting gene expression of interferon pathway and cyclic AMP mediated signaling pathways [30]. (vii) causing dose dependent inhibition of neutrophil respiratory burst reducing cytokine production especially in elderly population[31] (viii) reducing production of PGE2 from mononuclear cells (ix) increasing anti-oxidative ability of HDL by increasing activity of paraoxanase-1 and also improving the cholesterol efflux ability of HDL from macrophages [32]. (x) Modulating adipokine gene expression in adipose tissue along with increasing adiponectin [33].

Atherosclerotic Plaque Changes

Studies have reported that EPA content in the plaque phospholipids is inversely related to plaque instability, inflammation and number of T cells [34]. In a study to evaluate the composition of the coronary plaque changes at 6 months using integrated back scatter intravascular ultrasound (IVUS), patients with stable angina pectoris and dyslipidemia on high intensity statin therapy were randomized to receive EPA (1800 mg/day) or placebo after PCI with bare metal stents [25]. Significant increases in the level of EPA and significant reduction in AA were noted along with significant improvement in the EPA/AA ratio. IVUS showed significant reduction in the lipid volume of the plaque at the end of 6 months in the EPA group (18.5 ± 1.3mm3 vs 15 ± 1.5mm3; p=0.007). On comparing between the two groups, significant reduction in the lipid volume (-3.5 ± 0.2mm3 vs 1.5 ± 1mm3; p=0.005) and significant increase in the fibrous volume (2.7 ± 0.2mm3 vs -2.2 ± 0.8mm3; p=0.01) were reported. The reduction in plaque lipid volume and increased plaque fibrous content stabilizes the plaque making them less vulnerable to rupture [35]. On evaluating the inflammatory cytokine levels from coronary sinus samples in the same study, significant reductions in the PTX 3 and monocyte chemo attractant protein-1 (MCP 1) were seen. The reduction in the lipid volume was significantly co-related to the reductions in PTX 3 and MCP 1 in the EPA group which are indicators of local inflammation. Again similar reductions in PTX3 were reported along with reduced macrophage accumulation in patients treated with statin and EPA compared to statin alone [35]. They also reported a significant increase in the fibrous cap thickness at 9 months on EPA + statin compared to lone statin use (102.2 ± 28.8μm vs 70 ± 10.6μm; $P < 0.0001$) along with significant reduction in macrophage accumulation in the combination group (3% vs 12 %; $P = 0.02$). Another RCT of stable CAD, sub-group analysis showed significant reductions in PTX 3, in patients receiving high intensity statin with EPA compared to moderate intensity statin [26].

In a study, 193 patients with CAD status post PCI were randomized to receive pitavastatin and pitavastatin plus EPA (1800mg/day) for 6 to 8 months. Significant reductions in total atheroma volume were seen by IVUS in the combination group. The study also concluded that EPA had favorable effects in patients with stable angina versus patients with acute coronary syndromes [36]. In a similar study design with a smaller study sample (n=50) followed for 48 weeks, oxidative stress was evaluated by comparing aortic stiffness using β-carotid index and brachial ankle pulse wave velocity. Significant reductions were reported in the β-carotid index in the combination group at the end of the study compared to statin use alone (-2.7 vs -0; $P = 0.02$). No significant changes were reported in the carotid intima (IMT) thickness and plaque score [37]. Another study of 81 Japanese diabetic patients showed annual decrease in mean IMT and maximum IMT compared to control group (mean IMT: −0.029 ± 0.112mm vs 0.016 ± 0.109 mm; P= 0.029) (max IMT: −0.084 ± 0.113mm vs −0.005 ± 0.108 mm; P= 0.0008) and concluded that EPA is an independent predictor of mean IMT improvement (r = 0.067).[38] Altering ratio of

methionine and cysteine/cystine in diabetic patients has also been investigated and in an 8-weeks study of 2g EPA therapy, significant reductions in methionine and cysteine along with a significant reduction in atherogenic index of plasma calculated as a function of [Log(Triglycerides/HDL-Cholesterol)] was reported [39].

Lipid Changes

EPA supplementation reduces TG and VLDL and its efficacy was investigated in MARINE and ANCHOR trials.[40] MARINE trial included 229 patients with TG levels between 500mg/dl to 2000mg/dl and randomized patients to recieve 2g/day IPE, 4g/day IPE and placebo for 12 weeks [41]. At 12 weeks, percent change in TG from baseline was -7% and -26.6% in 2g/day and 4g/day respectively. In patients receiving statins, the placebo corrected median TG reduced to 65% in 4g/day and 40% in 2g/day. In patients with a baseline TG > 750mg/dl placebo-corrected median TG levels significantly reduced by 45.4% (P < 0.0001) in 4g/day group compared to 32.9% (P < 0.0016) in 2g/day group. Reductions in baseline non HDLC (-7.7%), lipoprotein lipase A2 (-17.1%), VLDL (-19.5%) were reported in patients receiving 4g/day dose of IPE, but the reductions were minimal in 2g/day group. ANCHOR trial (n=702) was a similarly designed study but included high risk cardiovascular disease patients with TG levels between 200mg/dl to 5000mg/dl with controlled LDL level (>40 and <100 mg/dl) on statin [42]. Similar reductions in TG from baseline (-17.5% in 4g/day and -5.6% in 2g/day) and other lipoproteins were reported along with greater reductions in TG in sub-groups treated with high intensity statin. These two studies proved the efficacy of IPE in lowering TG and that effect was greater when treated in combination with a statin. In an exploratory analysis of MARINE trial the increase in EPA corresponding to increased IPE dose was concluded as the mechanism for the hypo-triglyceridemic effect [43].

In a meta-analysis including randomized placebo controlled trials of EPA (n=10; EPA dose: 1.8g/day), DHA (n=17; DHA dose: 0.7-3g/day), or EPA versus DHA (n=6; EPA dose: 2.2 to 4.0 g/day, DHA dose: 2.3 to 4g/day) differential effects on lipids by EPA and DHA were reported [44]. One of 10 EPA vs placebo studies did not report LDL levels, therefore pooled analysis of 9 RCTs showed a non-significant reduction of LDL 1.76 mg/dl (95% CI: −1.85, 5.36) compared to placebo. 12 DHA trials reported LDL change and the pooled estimate showed a significant increase in the LDL C 7.23 mg/dl (95% CI: 3.98, 10.5) compared to placebo. Reductions in TG were significant in both EPA and DHA only studies comparing to placebo with a pooled estimate of 45.8 mg/dl (95% CI: 9.62 to 82.0) for EPA and 25.1 mg/dl (95% CI: 19.5 to 30.7) for DHA. On comparing EPA vs DHA, magnitude of TG reduction was higher with DHA with additional elevated HDL C.

Literature supporting improved cardiovascular outcomes with statin use is well established [45, 46]. apart from lowering LDL C, apolipoprotein B levels (apoB), lipoprotein concentration and particle size which are also important predictors for atherogenic risk [47]. Evidence suggests that small dense LDL particles are associated with a threefold risk of myocardial inflation and their levels are usually related to a lower HDL and high triglyceride levels—a combination of findings referred to as atherogenic lipoprotein phenotype [48]. In an exploratory analysis of the MARINE trial, effects of 2g/day (n=63) and 4g/day (n=61) on lipoprotein particle size and concentration were evaluated by nuclear magnetic resonance (NMR) spectroscopy in patients with very high TG levels [49]. In the patients included in the analysis, median TG and LDL changes from baseline were -26.4% in 4g/day; -7% in 2g/day and -6.5% in 4g/day. -2.9% in 2g/day respectively. At the end of 12 weeks, significant median placebo adjusted percent reductions in lipoprotein concentrations were reported in large VLDL (-27.9%; P = 0.02), total LDL (-16.3% P = 0.006), small LDL C (-25.6%; P < 0.001), total HDL (-7.4%; P = 0.006) and increased concentrations in medium VLDL (28%, P = 0.02) in 4g/day group. In the 2g/day group, significant reductions in small LDL C concentrations were reported compared to placebo (-12.8%; P = 0.02). LDL particle concentration was lower in patients on statins despite a smaller patient sample on statins on statins. In terms of particle size 4g/day significantly reduced VLDL particle size (28.6%, P 5 .0017). The atherogenic lipoprotein particle concentration (LDL and VLDL) correlated with ApoB at week 12 (r = 0.623; P < 0001). The study concluded that LDL lowering potential of EPA could be attributed to the effects on Apo B and increase in particle size of VLDL and LDL could confer cardio-protective benefit and be helpful to assess residual cardiovascular risk. Increase in LDL particle size was also reported in a trial that randomized patients to EPA (1.8g/day) and placebo for six months.[50] At 6 months significant reductions in serum TC, non-HDLC, apo B, TG-rich lipoproteins (TRLs)-related markers that include TG, VLDL fraction, RLP C apo C2, and apo C3 were seen. Increase in LDL-C/apoB ratio, a rough indicator of LDL particle size was reported and the increase in size is due to EPA's action on TG metabolism lowering VLDL thereby lowering apoB. Authors also concluded that the reduction in TRLs was correlated to the increasing particle size of LDL and the use of EPA and statin were independent predictors for the LDL particle size.

Triglyceride rich apo B lipoproteins undergo lipolysis in liver to form remnant like cholesterol particle cholesterol(RLP) that include chylomicron remnants in the non-fasting state and dense sub-fractions of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein.[51] These are strong markers for cardiovascular disease and residual cardiovascular disease. Uptake of these lipoproteins by macrophages and monocytes in the endothelial layer causes formation of lipid filled foam cells and disrupts fibrinolysis resulting in endothelial dysfunction and plaque progression [52, 53]. Exploratory analysis of MARINE trial, compared to placebo showed significant reductions in RPL C -29.8% (P < 0.004) in 4g/day IPE and it reached -56.8% (P = 0.02) in patients on statins.[54] Again the reductions were much higher in patients with higher baseline TG to begin with (-37.5% in TG >750mg/dl vs -26.1% in TG < 750mg/dl; P=0.06). In ANCHOR trial, reduction with 4g/day IPE was -22.2% in patients with baseline TG below 259mg/dl and -33.3% in patients above 259mg/dl. The reductions were higher in patients on moderate to high intensity statin. The mechanisms of EPA resulting in lower RLP C are unclear, but it could be possible by limiting hepatic release of VLDL or increasing its clearance.

As already mentioned, TRLs add significant residual risk of CVD, apolipoprotein CIII can interfere with TRL metabolism adding to the risk. Apolipoprotein CII activates endothelial lipoprotein lipase and breaks down TG rich particles whereas Apo C III inhibits lipolysis of TG rich lipoproteins leading to their accumulation in the plasma causing hypertriglyceridemia [55]. Evidence suggests that Apo CIII is an independent predictor of angiographic coronary artery disease progression. In post-hoc analysis of MARINE and ANCHOR trials total plasma Apo CIII was measured at baseline and after 12 weeks of IPE. IPE 4 g/day significantly reduced median ApoC-III levels by 25.1% (P < .0001) in the MARINE study and by 19.2% (P < 0001) in the ANCHOR study compared to placebo. In ANCHOR trial all the patients received statin therapy and the levels in Apo CIII reduction were significant in patients

on high intensity statin and moderate intensity statin (24.6% and 17.2%). Significant correlations between baseline levels ApoC-III and baseline levels of TG (r = 0.69–0.84) baseline levels of non-HDL-C (r = 0.42– 0.65) were also related.

Higher level of non HDL C is also associated with increased risk of cardiovascular disease and findings from JELIS study confirmed this association [56]. In a sub-analysis of the JELIS study population, patients were sub-grouped based on whether goal LDL C and non HDL C (<30mg/dl) was reached in EPA and non EPA group. Based on this a total of 8 sub-groups were made, the risk of cardiovascular disease was assessed in different groups within EPA group and non-EPA group and then compared between EPA and non EPA group. In the non EPA group patients who did not reach non HDL goal had higher incidence of CAD (HR, 2.18; 95%CI: 1.46-3.30; P < 0.001) compared to patients who reached the goal. In the non EPA group a strong positive association was seen between levels of non HDL C and CAD than compared to LDL C (HR, 1.35; 95%CI: 1.11-1.66; P = 0.003 and HR: 1.19; 95%CI: 1.00-1.42; P = 0.05). Even in sub-group analysis of patients in EPA group no significant increases in incidence of CAD were noted despite not reaching non HDL C and LDL goal. The authors concluded that EPA suppressed the risk of CAD by 38% (HR: 0.62; 95%CI, 0.43-0.88; P = 0.007).

Effects on Platelets

High dose EPAs inhibit platelet aggregation and patients usually have an increased bleeding time [57]. Effects of low dose (900mg/day) and high dose EPA (1800mg/day) vs placebo for 8 weeks on platelet function were evaluated in non-insulin dependent diabetic patients.[58] Both low and high doses caused significant increase in EPA/AA ratio and the elevated levels were sustained for a period of 4 weeks after intervention and reached values closer to the baseline. At 8-weeks PAF induced platelet aggregation was significantly decreased at both the doses (72 ± 11 to 40 ± 30% in the 1800-mg group; P = 0.039); and (75 ± 7 to 35 ± 21% in the 900-mg group; P = 0.016). The ADP aggregation was significantly reduced in the 1800-mg group (79 ± 9 to 56 ± 23%; P = 0.031). EPA also has a role in reducing platelet activation and also reduced mean platelet volume [59].

Platelet derived micro-particles (PDMP) released from platelets have pro-thrombinase activity especially in diabetics and are associated with hypercoagulability. A total of 191 hyperlipidemic diabetic patients received either EPA (1800mg/day), pitavastatin or both for 6 months.[60] Patients who received EPA (0.6 ± 2.0 vs. 8.0 ± 1.7 U/ml; P <0.01) or combination therapy (11.2 ± 2.0 vs. 4.5 ± 2.7 U/ml; P < 001) had significant reductions in PDMP at 6 months compared to baseline. In another study that included diabetic patients with atherosclerotic obliterans, pitavastatin + EPA therapy has significantly reduced the biomarkers involved in the platelet activation pathway along with a significant increase in adiponectin at 12 months [61].

RBC changes

EPA is incorporated into the RBC cell membrane and it does so by displacing ω – 6 FA in a direct dose response relation, reducing the ω – 6/ω – 3 ratio [62]. The concentration of EPA in RBC increases with the increase in duration of treatment especially in elder patients and the dose response linear relation is seen with both 2g/day and 4g/day doses of IPE [63, 64]. The proportion of EPA and DHA in the RBC has been used a risk predictor for cardiovascular mortality and is defined as the Omega 3 index. It has proven to have an inverse relationship with cardiovascular mortality and the maximum cardio-protective benefit is assumed to be at an index greater than 8% and the least with an index of 4% [65]. EPA supplementation can cause increased red cell deformability (p<0.001) and reduced whole blood viscosity (p<0.02) [57].

Effects on Other Cardiovascular Risk Factors

Apart from the direct effects on the plaque progression, platelet inhibition and reducing endothelial injury, EPA supplementation can improve several other factors associated with heart disease. In patients with diabetes or impaired glucose tolerance, EPA has also shown to: (i) reduce incremental glucose peak (ii) reduce endothelial dysfunction demonstrated as improved flow mediated dilation [66]. (iii) reduce oxidative stress by increasing activity of superoxide dismutase activity and glutathione peroxidase [67]. (iv) Reduce fasting blood sugar and improve HbA1c [68]. (v) Improving insulin resistance (HOMA-IR) [69](vi) Reduce albuminuria in patients with nephropathy [70]. Hemodynamic changes with EPA supplementation alone are lowering of systolic and diastolic blood pressure, however DHA in combination with EPA has shown to improve vasoreactivity and arterial compliance along with reductions in heart rate [71, 72] EPA has also shown to reduce lipid peroxidation and levels of remnant lipoproteins in patients with chronic kidney disease on dialysis [73].

Peripheral arterial disease (PAD) is a risk factor for CVD and is usually co-present with other risk factors such as male gender, smoking and old age. In a sub-analysis of the JELIS trial of patients with PAD, EPA supplementation group had a lower risk of major cardiovascular events comparedto the control group (HR: 0.44; 95% CI: 0.19–0.97, P=0.041). In another retrospective cohort study of PAD patients who have undergone infra-inguinal vein by-pass, patency rates were significantly higher in the EPA group compared to control group at 1, 3 and 5 years [74].

EPA Prescription Formulations

Prescription ω – 3 products containing both DHA and EPA include Lovaza (omega-3-acid ethyl esters, GlaxoSmithKline), Omtryg (omega-3-acid ethyl esters A, Trygg Pharma, Inc.) and Epanova (omega-3-carboxylic acids/polyunsaturated free FAs, AstraZeneca Pharmaceuticals LP). Vascepa (icosapent ethyl, Amarin Pharma Inc. Bedminster, NJ) approved by FDA in 2012 and Epadel (Ethyl icosapentate; icosapent, Mochida Pharmaceutical Co, Ltd, Tokyo, Japan) approved in Japan in 1998 contain purified ethyl ester of EPA [75]. Vascepa is available in 500 mg and 1000 mg capsules and daily dose recommended is 2g twice daily with food. Epadel is available as 300, 600 and 900mg tablets and the daily recommended dose is 1.8g twice BID with food [76].

EPA: Cardiovascular Outcomes

JELIS

Japan EPA lipid Intervention Study (JELIS) was the first RCT that evaluated the effectiveness of purified EPA ethyl ester in combination with lipid lowering HMG –CoA reductase inhibitor on the incidence of major coronary events [77]. The study was designed as prospective, open label blinded end-point clinical trial that included patients with hypercholesterolemia on treatment with statin. The study population was into primary prevention and secondary prevention strata with primary end point being major coronary events and secondary end points of all-cause mortality, mortality and morbidity of CAD, stroke, peripheral artery disease and cancer. Of the 18,645 patients enrolled, 15,000 were in primary prevention strata and 3,645 were in the secondary prevention group and were randomized to EPA (Epadel 600mg; Mochida Pharmaceutical Co, Ltd, Tokyo, Japan) or control. In primary prevention group 7,513 patients received EPA and 7,487 served as controls and in the secondary prevention group 1,813 received

EPA and 1,832 served as control. Incidence of cardiovascular events was evaluated after a 4.6 year follow up.

The mean age of all the participants was 61 ± 8 years in the EPA group (n=9326) and 32% were male. At the end of 4.6 years, primary end point was seen in total of 586 patients of which 262 were in the EPA group. The incidence of major coronary events was lower in the EPA group compared to control at 5 years (HR: 0.81; 95% CI: 0.69-0.95; P = 0.011), the incidence based on the strata was: primary prevention strata (HR: 0.82; 95% CI: 0.63 – 1.06; P = 0.13) and secondary prevention strata (HR: 0.81; 95% CI: 0.6-0.99; P = 0.04). The cumulative incidence of 5 year major coronary events was 2.8% in EPA group and 3.5% in controls with a significant relative risk reduction of 19% in the EPA group and a 19% reduction of major coronary events in the secondary prevention group. Other significant findings included lower frequency of unstable angina 24% (HR: 0.76; 95% CI: 0.62-0.95; P = 0.01) and lower non-fatal coronary events-19% (HR: 0.81; 95% CI: 0.68-0.96; P = 0.15). The reductions in major coronary events in the EPA group were not related to the levels of baseline LDL C, suggesting that it did not completely attribute to the lower event rates. In the secondary prevention group, reductions were significant in unstable angina (0.73; 95% CI: 0.55-0.95; P = 0.01) and non-significant reductions of 25% coronary death, 25 fatal or non-fatal myocardial infarction and 18% in non-fatal coronary events was reported. The higher reduction and strong inverse relation in non-fatal coronary artery events was attributed to high fish consumption and in addition to an overall low incidence of CAD in Japanese population [78].

In terms of safety, 11.7% patients discontinued therapy due to adverse related to the drug. Though adverse events were significantly higher in the EPA group they were minor and included: arthralgia (1.6%), gastrointestinal discomfort (3.8%), cutaneous reactions (1.7%) and hemorrhage (1.1%). The findings of this trial did not show any mortality benefit or reduced risk of sudden cardiac death, a finding reported in observational studies with high fish intake and also secondary prevention DART trial and GISSI trail that have used EPA+DHA combinations [79-81]. Limitations of this study were an open label design, no placebo group, use of low dose statin and patient population from a single country.

Reduce It

REDUCE IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial) is a phase 3b randomized double blind placebo controlled trial designed to assess the safety and benefit of IPE compared with placebo in reducing cardiovascular events in patients with high CV risk on treatment with statins and elevated TG levels [82]. The primary endpoints were a composite of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The secondary endpoints are a composite of CV death, nonfatal MI, or nonfatal stroke. The patient follow-up period was planned to continue until 1612 primary end-points events took place to detect a 15% lower risk of events in the IPE group compared to placebo with a power of 90%.

After enrollment, patients were randomized in a 1:1 ratio to receive either IPE 2mg twice a day (n=4089) or a placebo (n=4090) [83]. Randomization was stratified into primary prevention (DM+1 risk factor; 29.3%) and secondary prevention (established CAD; 70.7%) strata. The median age of the all the patients was 64 years and 28% of them were female. After a median duration of follow up for 4.9 years, a total of 1606 primary end point results were reported during the study period. The primary end-point occurred in 17.2% patients in IPE group compared to 22% in placebo group (HR: 0.75; 95% CI: 0.68-0.83; P < 0.0001). Overall, the risk of primary end point was reduced by 25% in IPE group compared to placebo. Secondary end point (composite of CV death, nonfatal MI, or nonfatal stroke) was also 26% lower in the IPE group compared to placebo (HR: 0.74; 95% CI: 0.65-0.83; P < 0.001). Secondary endpoint was reached in 11.2 % patients in the IPE group and 14.8% in the placebo group. The primary and secondary end point rates were lower in secondary prevention strata compared to primary prevention, but as this sub-group analysis was not adjusted.

In hierarchical testing for pre-specified secondary end points and sub group analysis, significant differences (all p < 0.04) between IPE and placebo group were reported in (i) rate of cardiovascular death or non-fatal MI 9.6% vs 12.4% (HR: 0.75; 95% CI: 0.66 – 0.86) (ii) fatal or non-fatal MI 6.1% vs 8.7% (HR: 0.69; 95% CI: 0.58 – 0.81) (iii) urgent emergency revascularization 5.3% vs 7.8% (HR: 0.65; 95% CI: 0.55 – 0.78) (iv) cardiovascular death 4.3% vs 5.2% (HR: 0.80; 95% CI: 0.66 – 0.98) (v) hospitalization for unstable angina 2.6% vs 3.8% (HR: 0.68; 95% CI: 0.53 - 0.87) (vi) death from any cause, non-fatal MI or non-fatal stroke 13.4% vs 16.9% (HR: 0.77; 95% CI: 0.69 – 0.86).

In terms of safety, adverse effects such as diarrhea, peripheral edema, anemia and constipation were more frequently reported in the IPE group and were statistically significant on comparison to placebo. Patients on IPE also had higher rates of atrial fibrillation (5.3% vs 3.9%; P = 0.003), higher frequency of bleeding events (2.7% vs 2.1%; P = 0.06) compared to placebo, but the rates of serious bleeding events such as central nervous system bleeding or gastrointestinal bleeding were not significantly higher compared to placebo with no fatal bleeding events in both the groups. The strengths of the study include a diverse population from 11 countries, use of high dose purified IPE and majority of the patients were on moderate to high intensity statin. However, the study has few limitations: (i) use of mineral oil as placebo could have affected statin absorption in the control group contributing to the elevated levels of LDLC (10.9%), non HDL C (10.4%) and triglycerides (2.2%) at the end of study compared to the baseline levels. This could have exaggerated the differences in atherogenic lipoproteins on comparing IPE vs placebo group. (ii) Use of mineral oil might have affected the comparison of adverse events between groups -- especially serious bleeding events (iii) a greater than predicted benefit in cardiovascular outcomes in relation to reduction of TG and non HDL C level was reported. The observed median change of 14mg/dl in non HDL C should have translated into a 6-8% benefit but the reduction observed was a 25%.

Future Clinical Trials

EVAPORATE study (Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy) is planning to evaluate the effects of IPE 4 g/d on atherosclerotic plaque characteristics in a North American population of statin-treated patients with coronary atherosclerosis with TG levels of 200 to 499 mg/dl, and LDL C levels of 40 to 115 mg/dl.[84]. RESPECT-EPA trial (Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy - Statin and Eicosapentaenoic Acid) is a randomized controlled trial in focusing on secondary prevention in patients with established cardiovascular disease and are on statin. STRENGTH (Study to Assess STatin Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia) is a randomized, double-blind, placebo-controlled parallel group design including subjects with hypertriglyceridemia plus low

HDL and high risk for CVD [85]. Patients will be randomized 1:1 to corn oil + statin or high dose Epanova + statin and will be compared for rates of major adverse cardiac events.

Conclusions

Secondary prevention of CVD is primarily focused on lowering LDLC with statins with newer recommendations encouraging use of ezetimibe or PCSK9 inhibitors in patients not reaching the target LDL [86]. However, it is important to understand that high residual risk of CVD exists despite controlled LDL C levels. Conditions such as metabolic syndrome, chronic inflammatory diseases, elevated triglycerides, high hs-CRP, elevated lipoprotein A2, elevated apoB and low ankle brachial index are considered as enhancers of atherosclerotic CVD. EPA in combination with statins has now shown to improve biomarkers that increase the risk of residual CVD. Evidence suggests use of moderate to high intensity statin in combination with high doses of EPA might be beneficial in secondary prevention of CVD risk, but evidence is not supportive for their use for primary prevention [87, 88]. The results from exploratory analysis of REDUCE IT, RESPECT-EPA and STRENGTH trial might provide a better insight into the mechanisms and outcomes of EPA therapies respectively with possibly their results determining the extent of ω – 3 FA use in future.

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