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CLINICAL FOCUS: CARDIOMETABOLIC CONDITIONS
REVIEW

Can pleiotropic effects of eicosapentaenoic acid (EPA) impact residual cardiovascular risk?

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ABSTRACT

Residual cardiovascular (CV) risk persists even in statin-treated patients with optimized low-density lipoprotein cholesterol (LDL-C) levels. Other pathways beyond cholesterol contribute to CV risk and the key to reducing residual risk may be addressing non-cholesterol risk factors through pleiotropic mechanisms. The purpose of this review is to examine the literature relating to the potential role of the omega-3 fatty acid eicosapentaenoic acid (EPA) in reducing residual CV risk. The literature shows that EPA can robustly lower plasma triglyceride (TG) levels without raising LDL-C levels and documents EPA to have a broad range of beneficial effects on the atherosclerotic pathway, including those on lipids, lipoproteins, inflammation, oxidation, phospholipid membranes, and the atherosclerotic plaque itself. Clinical imaging studies have consistently demonstrated that EPA decreases plaque vulnerability and prevents plaque progression. The evidence therefore points to a potential role for EPA to reduce residual CV risk. A large randomized study of statin-treated Japanese patients demonstrated that EPA ethyl ester reduced major coronary events by 19% ($P = 0.011$). However, while there has been significant benefit demonstrated in this and another Japanese CV outcomes study, the question as to whether EPA can play a role in reducing residual CV risk remains to be addressed in broader populations. The large, global, ongoing, randomized, placebo-controlled REDUCE-IT study of high-risk statin-treated patients with persistent hypertriglyceridemia is currently underway to investigate the potential of icosapent ethyl (high-purity prescription EPA ethyl ester) as an add-on therapy to reduce residual CV risk.

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1. Introduction

Residual risk of cardiovascular (CV) disease persists even in patients who achieve optimal low-density lipoprotein cholesterol (LDL-C) levels on statin treatment [1]. There is mounting evidence that statin add-on therapy can help further reduce CV risk [2,3]. The results from the recent FOURIER trial are instructive and serve as a call to action regarding residual CV risk [3]. This study evaluated a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor (evolocumab) as an add-on therapy in patients with CV disease who were receiving moderate- to high-intensity statin therapy (at least 20 mg atorvastatin) with or without ezetimibe. Thus, the PCSK9 inhibitor was an add-on to an assumed 20–30% reduction of events from statin therapy. In fact, the PCSK9 inhibitor/statin group achieved a mean 59% reduction in LDL-C from baseline compared with statin alone, and this was associated with a 15% reduction in the risk of the primary composite CV endpoint. However, it is important to note that, despite achieving a median LDL-C of 30 mg/dL, residual risk still remained as evidenced by the annual event rate at year 3 in the evolocumab arm of was 12.6% (Figure 1) [3]. These findings underscore that, although LDL-C has been a central tenet of CV risk management, targeting LDL-C alone is not sufficient.

Pleiotropic pathways beyond cholesterol contribute to CV risk. Thus, a key to reducing residual risk will be addressing non-cholesterol risk factors. The omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) has been documented to have beneficial effects on a range of atherogenic parameters, multiple steps along the atherogenic pathway, and plaque formation, all of which may have important implications for residual CV risk. Here we provide a brief review of the pleiotropic effects of EPA with a focus on atherosclerotic plaque studies and discuss the potential role of EPA as an add-on therapy to statins for reducing residual CV risk.

2. Pleiotropic effects of EPA

2.1. Effects of EPA on lipids and lipoproteins

EPA has favorable effects on various atherogenic parameters including reductions in the plasma levels of triglycerides (TGs), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apoB), remnant-like particle cholesterol (RLP-C), apolipoprotein C-III (apoC-III), and oxidized low-density lipoprotein (ox-LDL) particles [4,5]. Importantly, EPA does not increase LDL-C levels [5].

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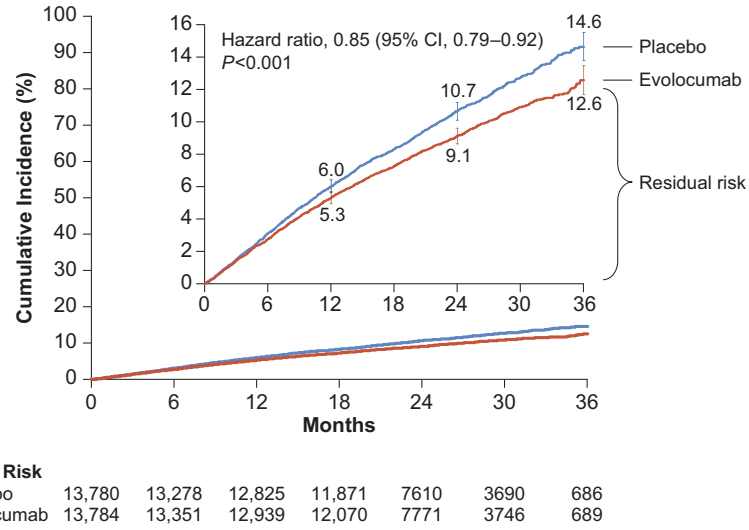

Figure 1. CV events can be reduced by statin add-on therapy but residual risk remains. Cumulative event rates for the primary efficacy endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) in the FOURIER trial [3]. Bars indicate 95% confidence intervals (CI). The Kaplan–Meier rates for the primary endpoint in the evolocumab group vs the placebo group were as follows: at 1 year, 5.3% (95% CI, 4.9–5.7) vs 6.0% (95% CI, 5.6–6.4); at 2 years, 9.1% (95% CI, 8.6–9.6) vs 10.7% (95% CI, 10.1–11.2); and at 3 years, 12.6% (95% CI, 11.7–13.5) vs 14.6% (95% CI, 13.8–15.5). *P* values were calculated using log-rank tests. Inset shows the same data on an enlarged y axis. From *The New England Journal of Medicine*, 'Evolocumab and clinical outcomes in patients with cardiovascular disease,' Sabatine et al. [3]. Copyright ©2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

A high-purity prescription form of EPA ethyl ester, icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ), is approved by the United States Food and Drug Administration as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia [6]. Data from phase 3 randomized clinical studies in patients with hypertriglyceridemia (the MARINE and ANCHOR studies) demonstrate that icosapent ethyl has a range of beneficial effects on atherogenic parameters including reductions in the levels of TGs, non-HDL-C, apo B, apoC-III, RLP-C, and markers of atherosclerotic inflammation (i.e. ox-LDL, lipoprotein-associated phospholipase A_2, and high-sensitivity C-reactive protein) without raising levels of LDL-C compared with placebo [7–13].

2.2. Pleiotropic effects of EPA in the atherosclerotic pathway

The evidence supporting beneficial effects of EPA on multiple steps of the atherosclerotic pathway has been reviewed extensively [4,14]. Figure 2 provides an overview of the pleiotropic effects of EPA in the atherosclerotic pathway [15].

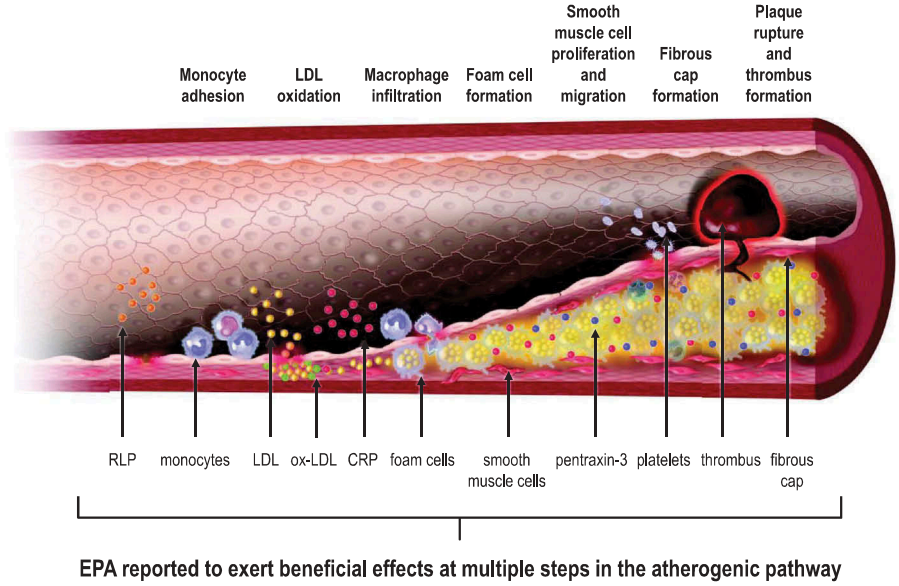

Figure 2. Atherosclerosis is a multistep process ranging from endothelial dysfunction to plaque development, progression, and rupture, leading to thrombus formation and cardiovascular events. EPA has been reported to have beneficial effects on many of these steps. CRP, C-reactive protein; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; ox-LDL, oxidized low-density lipoprotein; RLP, remnant-like particle. Adapted from *The American Journal of Pathology*, 173(5), Lamon BD and Hajjar DP, Inflammation at the molecular interface of atherogenesis: an anthropological journey, 1253–1264 [15], Copyright ©2008, with permission from Elsevier.

EPA has been shown to increase the levels of nitric oxide and improve endothelial and vascular function [14,16–18] and have beneficial effects on monocytes and macrophages, including decreased adhesion of monocytes, decreased macrophage accumulation, and decreased foam cell accumulation [19–22]. Anti-inflammatory effects of EPA include beneficial modulation of pro- and anti-inflammatory cytokine levels [23,24] and reduction of high-sensitivity C-reactive protein levels [11]. EPA is a substrate for a class of pro-resolving mediators called resolvins, which promote resolution of vascular inflammation [4,14,25,26]. For example, the EPA-derived resolvin RvE1 has been shown to act on leukocytes to modulate adhesion molecules and to exhibit antiplatelet actions [27]. In addition, EPA has been associated with decreased expression of genes involved in the NF-κB pathway [28]. Other antiatherosclerotic mechanisms of EPA include antioxidant effects of EPA in both lipoproteins and cell membranes, including the inhibition of cholesterol crystalline domains [18,29–31]. Beneficial effects of EPA on atherosclerotic plaque have been demonstrated in preclinical studies as well as multiple clinical studies and are described in more detail in the next section.

2.3. Effects of EPA on plaque

The effects of EPA on atherosclerotic plaque have been investigated in animal and clinical studies [32]. Preclinical data from animal models support beneficial effects of EPA on atherosclerotic lesions including stable morphology, reduction of established plaques, and decreased inflammation [33–35]. Based on clinical data, EPA appears to be incorporated rapidly into advanced atherosclerotic plaques, and to a greater extent than the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA) [22]. In a randomized study of 121 patients undergoing carotid endarterectomy, the proportion of EPA, but not DHA, in carotid plaques was significantly higher in patients who consumed omega-3 fatty acids versus placebo prior to surgery [22].

Multiple clinical studies have evaluated the effects of EPA (often in combination with a statin) on atherosclerotic plaques using a range of plaque imaging modalities including coronary angiography, computed tomographic angiography, multidetector computed tomography, and carotid artery intima-media thickness as measured by ultrasound, intravascular ultrasound, and optical coherence tomography [21,36–47]. Key results of these studies are highlighted in Table 1. Collectively, these studies demonstrate that EPA consistently has beneficial effects on atherosclerotic plaques. Reported effects of EPA on plaques include decreases in the lumen diameter [36], percentage of stenosis [36], plaque volume [38,43,45], lipid volume [45], and intima-media thickness [39–41]; increases in fibrous-cap thickness [21,46,47] and fibrous volume [44]; and prevention of plaque progression [37].

3. Impact of EPA on CV outcomes

Two clinical studies conducted in Japan suggest that EPA may reduce risk of CV events [48,49]. The effect of EPA on CV outcomes was evaluated in the Japan EPA Lipid Intervention Study (JELIS) [48]. Patients with hypercholesterolemia with or without coronary artery disease were randomized to treatment with either EPA 1.8 g/day plus a statin (pravastatin 10 mg/day or simvastatin 5 mg/day; n = 9326) or a statin alone (n = 9319) [48]. The EPA used was a highly purified ethyl ester formulation available in Japan [48]. The 5-year cumulative rate of major coronary events was lower in the EPA/statin group compared with the statin-alone group (2.8% vs. 3.5%), representing a 19% relative reduction in risk for major coronary events in the EPA group (P = 0.011) [48]. This CV risk reduction was accompanied by a 9% reduction in TG levels in the EPA/statin group versus a 4% reduction in the

Table 1. Effects of EPA on atherosclerotic plaques in clinical studies.

Imaging method	Key findings
Angiography	• Significant decreases in lumen diameter (P = 0.020) and % stenosis (P = 0.026) in EPA-plus-statin group vs. statin-alone group [36] • EPA was significantly associated with prevention of plaque progression compared with EPA plus DHA (P = 0.0061) in statin-treated patients with ACS [37]
MDCT	• Significant reduction in soft-plaque volume in EPA group but not in ezetimibe group; significant improvements in EPA group in plaque area (P = 0.017), lumen area (P = 0.004), and plaque volume vs. ezetimibe group (P = 0.036) [38]
Carotid ultrasound	• Significant decrease in IMT with EPA treatment vs. baseline (P < 0.05); IMT correlated with blood EPA concentration and EPA/AA ratio (P < 0.01) [39] • Significant annual decrease in mean IMT (P = 0.029) and maximal IMT (P = 0.0008) in EPA group vs. control group [40] • Significant decrease from baseline in maximal IMT with EPA treatment (P < 0.0001 after 6 and 12 months) [41] • No difference in change in baPWV observed between EPA/statin vs. statin-alone groups (P = 0.29); carotid β index was decreased in EPA/statin group vs. statin-alone group (P = 0.02) [42]
IVUS and IB-IVUS	• Significant reduction in coronary plaque volume (total atheroma volume and % change in atheroma volume) in EPA-plus-statin group vs. statin-alone group (P < 0.01) [43] • Significant reduction in lipid volume (P = 0.005) and significant increase in fibrous volume (P = 0.01) in EPA-plus-statin group vs. statin-alone group [44] • Significant reductions in plaque and lipid volumes in EPA-plus-statin group vs. statin-alone group (P-value not given) [45]
OCT	• EPA-plus-statin group had significantly increased fibrous-cap thickness (P < 0.0001), numerically decreased lipid arc (P = 0.27) and length (P = 0.13), and significantly less macrophage accumulation (P = 0.02) vs. statin-alone group [21] • EPA-plus-statin group had significantly increased fibrous-cap thickness (P = 0.0003) and decreased lipid arc (P = 0.0074) vs. statin-alone group [46] • Fibrous-cap thickness increased in both groups but to a greater extent in EPA group (P = 0.001 EPA vs. control); no change in lipid arc observed in either group (P = 0.106 EPA; P = 0.603 control) [47]

AA: arachidonic acid; ACS: acute coronary syndrome; baPWV: brachial ankle pulse wave velocity; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; IB-IVUS: integrated backscatter intravascular ultrasound; IMT: intima-media thickness; IVUS: intravascular ultrasound; MDCT: multi-detector row computed tomography; OCT: optical coherence tomography.

statin-alone group, and a 25% reduction in LDL-C levels in both groups [48]. The relative reduction in major coronary events was comparable across a range of LDL-C levels, suggesting that reduction in serum LDL-C levels was not a key factor in the observed CV risk reduction [48]. Additional support for the potential role of EPA in CV risk reduction comes from a prospective, single-center, randomized, open-label trial of 241 Japanese patients with acute coronary syndrome undergoing primary percutaneous coronary intervention (PCI) [49]. Patients were randomized to EPA 1.8 g/day (purified ethyl ester) plus a statin (pitavastatin 2 mg/day) or statin alone [49]. Early initiation of EPA/statin within 24 h after successful PCI resulted in a significantly lower risk of CV events compared with statin alone (relative risk of CV events at 1 year, 9.2% for EPA/statin, and 20.2% for statin alone; absolute risk reduction 11%; $P = 0.02$) [49]. Notably, there were no significant differences in LDL-C reduction between groups, and no significant changes in TG levels in either group [49]. The authors suggest possible pleiotropic mechanisms of EPA for the observed effects, including antiarrhythmic effects and attenuation of inflammation through multiple pathways, including lowering arachidonic acid content in membrane phospholipids and conversion to resolvins and protectins [49]. Other potential mechanisms discussed include inhibition of endothelial activation, decreased plasma ICAM-1 levels, and inhibition of monocyte adhesion to endothelial cells, as well as other mechanisms involving atherosclerotic plaque discussed earlier [49]. In both these studies, a significant CV risk reduction was observed with EPA add-on therapy despite minimal changes in lipids, supporting the concept that targeting factors other than, or in addition to, lowering lipids may be a key to addressing residual CV risk. An important limitation of these two studies is that they were conducted in Japanese-only populations, and thus extension of these findings to broader populations has yet to be tested.

The potential role of prescription omega-3-fatty acid products for reducing residual CV risk in statin-treated patients is being examined in large ongoing global outcomes studies [50,51]. The prescription EPA-only product, icosapent ethyl (4 g/day), is being evaluated in a global, phase 3, randomized, double-blind, controlled study (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial [REDUCE-IT]; NCT01492361) to determine whether it can reduce ischemic events in statin-treated patients with high TG levels and elevated CV risk [51]. The Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH; NCT02104817) study is investigating a prescription combination of EPA and DHA [50]. Based upon approximations of past large CV outcomes trials, the populations under investigation in STRENGTH and REDUCE-IT represent a relatively large population [52–56]. Results from REDUCE-IT are anticipated to further define the role of icosapent ethyl in patients with hypertriglyceridemia who are at risk for CV events.

4. Conclusion

It has been shown that even with potent LDL-C lowering, substantial residual risk of CV events remains. The need to address non-lipid risk factors for CV disease is evident. EPA has been shown to have beneficial pleiotropic effects on atherosclerosis, including those on lipids, lipoproteins, inflammation, oxidation, and phospholipid membranes, and clinical imaging studies have consistently demonstrated that EPA decreases plaque vulnerability and prevents plaque progression. Thus, the evidence points to a potential role for EPA to reduce residual CV risk, but while there has been significant benefit demonstrated in Japanese CV outcomes studies, this remains to be proven in broader populations. The results of the ongoing REDUCE-IT study will elucidate whether the EPA-only omega-3 fatty acid icosapent ethyl can reduce residual CV risk in a broad statin-treated patient population with persistent hypertriglyceridemia and CV risk factors such as diabetes.

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Declaration of interest

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