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The Role of Eicosapentaenoic Acid for Residual Cardiovascular Risk Despite Statin Therapy

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Introduction

Cardiovascular disease (CVD) was responsible for over 840,000 deaths in the United States in 2016 and costs an estimated $352 billion annually in both direct and indirect costs. Approximately every 40 seconds, an American will have an acute myocardial infarction (AMI), and at a similar rate an American will have a stroke. In patients who experienced AMI from 2010 to 2016, statin use at hospital discharge increased from 92% to 99%. Nonetheless, cardiovascular disease remains the leading cause of death in the United States and more than one million coronary events are expected to occur in individuals in 2019; approximately 335,000 of those cases will be recurrent coronary events. [1] Understanding the risk factors for CVD and then reducing those risks have the potential to decrease the impact of this disease.

Of the multiple risk factors for CVD, dyslipidemia ranks high. The essence of this "lipid hypothesis" generated decades ago was the assumption of a positive relationship between low-density lipoprotein cholesterol and the incidence of coronary disease. Although, significant evidence supporting elevated cholesterol as a primary risk factor for cardiovascular disease and major cardiovascular events was found, critics of the hypothesis believed that the postulation of causality was incompletely supported by those findings. [2] Accordingly, lowering low-density lipoprotein cholesterol with an HMG-CoA reductase inhibitor might provide incomplete protection from cardiovascular disease as is possibly evidenced by the residual risk a patient may have despite statin therapy.

The first HMG-CoA reductase inhibitor was discovered in 1978 and became commercially available in 1987 when the US FDA advisory panel voted unanimously for

approval of the medication after clinical trials demonstrated its ability to significantly reduce plasma cholesterol compared with dietary modifications and other available medications such as bile acid sequestrants, fibrates, and nicotinic acid. Subsequent studies and trials with HMG-CoA reductase inhibitors (aka, statins) further demonstrated substantial risk reduction for cardiovascular events such as myocardial infarction and stroke without any increase in non-cardiovascular mortality.[3] Statins have since revolutionized the treatment of hyper-cholesterolemia and are the agents of choice for treatment and prevention of atherosclerotic cardiovascular disease. Indications for prescribing statins have broadened over time with the implementation of the American College of Cardiology (ACC) risk stratification calculator that gauges the risk of atherosclerotic cardiovascular disease (ASCVD) based on lipid levels and other risk factors. The ACC partnered with the American Heart Association (AHA) and created guidelines that stratified risk levels, and then specified the intensity of statin therapy according to the degree of risk. However, despite using these guidelines and the significant reduction in cardiovascular events attributed to the lipid lowering effects of statins, many patients still had residual risk for CVD.

Hence, other means of reducing harmful lipids were researched. Nevertheless, statins were proven extremely efficacious. For this reason, instead of simply substituting statins with another agent, add-on therapy for lipid reduction was also explored along with investigating effects produced solely by other agents. Omega-3-fatty acid supplements, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were examined for lipid-lowering effects. Indeed, both EPA and DHA decreased both triglycerides (TG) and non-high-density lipoproteins (non-HDL) and thereby, could possibly reduce the CVD risks and events.

EVOLVE II was a randomized controlled trial (RCT) that investigated the efficacy and safety of Epanova®, a lipid-regulating agent containing omega-3 carboxylic acid, which is a mixture of both EPA and DHA. An intermediate dose of Epanova® compared with olive oil significantly lowered TG and non-HDL levels in patients with severe hypertriglyceridemia (SHTG). Based on these findings, a clinical benefit from this agent for prevention of CVD risk and events was proposed.[4]

The ROMANTIC trial was another randomized controlled trial that examined the safety and efficacy of adding omega-3 fatty acids (FAs) to statin therapy in patients with persistent elevations in TG despite statin therapy. This multicenter, double-blind, parallel group, placebo-controlled study was just an eight-week trial that showed reductions in TG and non-HDL.[5]

Both EVOLVE II and ROMANTIC were limited by small sample sizes (162 and 201 participants, respectively), restricted generalizability (only Caucasians and middle-aged Asians, respectively, were studied) and short durations (12 weeks and 8 weeks, respectively). Nonetheless, these trials revealed significant improvements in TG and non-HDL levels, resulting from EPA and DHA combination therapy. By virtue of the lipid hypothesis, the evidence from these studies could be extrapolated to mean that omega-3 FAs may reduce CVD events, but these studies were not designed to measure this outcome.

A murine study, however, did test the effect of omega-3 FAs on CVD, but without examining lipid levels. In 2015 Madingou et al. used 115 male Sprague-Dawley mice, to investigate the impact of EPA and DHA alone and in combination on induced myocardial infarct size. The mice experienced diminished infarct size with both EPA and DHA individually, but did

not obtain the same cardio-protection with the combination of EPA and DHA.[6] Researchers speculated that this disparity might be due competition for like receptors. Alternatively, instead of receptor competition, the achievement of cardio-protection could have been mediated by increased protein kinase B (Akt) activity (with EPA and DHA alone) and decreased caspace-3 activity (with DHA only). Although the results from this study cannot be applied directly to humans, the findings did suggest a mechanism whereby omega-3-FAs could be cardio-protective.

Other researchers have explored the specific relationships between EPA or DHA and cardiovascular disease. A study in Japan by Nishizaki et al. examined patients' levels of EPA, DHA, and arachidonic acid (AA) in relation to a diagnosis of acute coronary syndrome (ACS). Patients with the lowest EPA/AA ratio had a greater probability of experiencing ACS compared with patients with the lowest DHA/AA ratio.[7] A similar analysis by Iwamatsu et al. found that the found that the EPA/AA ratio, which was low, was more closely associated with ACS than the DHA/AA ratio.[8]

Trials such as ROMANTIC or EVOLVE II have suggested that supplementation with polyunsaturated fatty acids (PUFAs), specifically omega-3-fatty acids, may confer cardiovascular benefits via reducing harmful lipids. However direct evidence establishing that EPA therapy lowers CVD events is lacking. Nonetheless, studies linking low EPA levels with an increased risk of ACS suggest a role for EPA supplementation in patients with residual CVD despite optimized statin therapy. Thus, whether adding EPA to statin therapy reduces CVD events in addition to reducing the CVD risk factors of dyslipidemia will be examined.

Discussion

In a retrospective cohort-based analysis including more than 11,000 patients, after adjustments for patient characteristics and concurrent medical therapy including statin use, Greene et al. found that omega-3 fatty acid treatment was independently associated with decreased risk of cardiovascular events in individuals after experiencing acute myocardial infarction.[9] In a subsequent prospective, open-label, blind end point randomized trial, Nosaka et al. determined that early initiation of EPA combined with a statin in patients treated with successful primary PCI (percutaneous coronary intervention) after ACS reduced subsequent cardiovascular events.[10] This study was the first to specifically assess the additive effect of EPA with a statin on cardiovascular events including death, nonfatal myocardial infarction, nonfatal stroke, and occurrence of new lesions requiring PCI or CABG. The trial also investigated the incidence of hospitalization for heart failure in those who received EPA and statin combination therapy compared to statin monotherapy. Absolute risk reduction was calculated at 11.0% and EPA/AA ratios were notably increased within a few days of initiating EPA at a dose of 1800 mg/day. Though outcomes were assessed at 3-month intervals for only one year, the possible anti-inflammatory and anti-arrhythmic effects of EPA in the early phase after acute coronary syndrome may have contributed to both short- and long-term benefits and outcomes for patients.

The posited anti-inflammatory effects of EPA from the above trial were consistent with results from a previous open-label study using surrogate endpoints in a small sample of at-risk patients. In that study, Nishio et al. assessed the impact of EPA and statin therapy compared to statin monotherapy on the stabilization of vulnerable plaques in patients with untreated

dyslipidemia and vulnerable plaques identified by thin cap fibroatheroma detected by multivessel optical coherence tomography (OCT). No significant difference in levels of low-density lipoprotein or cardiovascular events were found between the two groups of 15 patients each. Nonetheless, after nine months, the EPA group had a greater increase in fibrous-cap thickness and a greater decrease in lipid length and arc, findings indicative of increased plaque stability. Researchers also noted decreased pentraxin-3 levels as well as decreased macrophage accumulation in the EPA and statin group both findings indicative of reduced inflammation.[11] These results suggested a benefit secondary to suppression of arterial inflammation, and researchers believed this mechanism would contribute to greater stabilization of unstable plaques and ultimately lead to decreased cardiovascular events. When linked to subsequent research, this mechanism provides a potential means to reduce cardiovascular risk that statins alone do not achieve.

Niki et al. further explored the effect of EPA on coronary plaque components and local inflammatory cytokines after adding purified EPA ester to the existing treatment regimens of patients with dyslipidemia. Their blocked-randomization, open-label, single-center study provided evidence that the addition of EPA to strong statins was associated with a reduction in the lipid content of plaques in coronary arteries as observed by integrated backscatter intravascular ultrasound. Although some inherent limitations to IB-IVUS and the sample size of 59 patients are limitations, a significant reduction in lipid volume and a significant increase in fibrous volume were only noted in the group receiving EPA in addition to a statin. Similarly, inflammatory cytokines, pentraxin-3 and monocyte chemoattractant protein-1 were not different in the group receiving statin monotherapy, but decreased in those receiving EPA.[12]

A more recent study by Watanabe et al. examined the effects of combination therapy with EPA and pitavastatin (PTV) compared with PTV alone on coronary plaque regression and stabilization as measured by integrated backscatter intravascular ultrasonography (CHERRY). This prospective, randomized, non-blinded, parallel, multicenter study which studied 193 patients with coronary heart disease following PCI, and which had greater power than previous related studies, produced evidence that EPA and statin combination therapy achieved significant lipid volume reduction as well as significant reduction in total atheroma volume compared to statin monotherapy.[13] Moreover, researchers noted no significant difference in the incidence of adverse events between the two groups including undesired elevation of low-density lipoprotein cholesterol. These results were congruent with previous reports detailing the anti-inflammatory and anti-oxidative effects conferred by EPA therapy and suggested that EPA was safe and efficacious for reducing residual cardiovascular risks that existed despite optimized statin therapy.

Conclusion

Statins remain the pharmacologic agents of choice for reducing the risk of atherosclerotic cardiovascular disease. Despite treatment with high intensity statins, many patients have residual risk of CVD. Omega-3 fatty acids have been identified as a potential means to address this residual risk and do so via mechanisms different from those of HMG-CoA reductase agents. Although research specifically supporting the efficacy of EPA over other polyunsaturated fatty acids is limited, retrospective and observational studies suggest a strong correlation between low EPA levels (but not DHA levels) and increased cardiovascular disease events. Furthermore, unlike DHA, EPA has not been associated with unintended increases of

low-density lipoprotein cholesterol (a CVD risk factor). Evidence from several recent trials revealed that EPA therapy, in addition to statins, reduced major cardiovascular events such as death, myocardial infarction, or stroke, and decreased various biomarkers and risk factors for cardiovascular events without increasing non-cardiovascular mortality. The proposed and identified mechanisms by which EPA reduced cardiovascular risk support the prediction of both short and long-term cardio-protective benefits and suggest potential benefits and indications for other conditions such as dementia and depression (EPA's use for these latter conditions are also being investigated). Additionally, researchers have not defined any significant increase in adverse effects when comparing EPA and statin combination therapy with statin monotherapy. Accordingly, clinicians may consider prescription EPA for patients, especially for those who have significant residual cardiovascular risk despite treatment with a high intensity statin. Nonetheless, further research will be necessary to confirm EPA's long-term safety, its efficacy for clinical (rather than surrogate) outcomes, patient acceptance, and potential applications for its use in both primary and secondary prevention of cardiovascular disease. Finally, improving risk stratification tools may direct (or limit) certain treatments to specific subsets of the population and thus optimize utilization of resources.

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