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Fourth Study to Show Consistent Benefit of Highly Purified Eicosapentaenoic Acid on Cardiovascular Outcomes: Results From RESPECT-EPA

In the open-label Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid (RESPECT-EPA), treatment with eicosapentaenoic acid (EPA)–only omega-3 fatty acid was associated with a clinically significant reduction of 21.5% in cardiovascular (CV) risk in the primary endpoint, achieving borderline statistical significance (*P*=0.054) and a significant 26.6% reduction in the secondary composite endpoint (*P*=0.03) vs statin monotherapy in patients with established CV disease (CVD; **Figure**).[1] Compared with patients receiving statins alone, patients receiving purified EPA plus statin therapy had a higher occurrence of gastrointestinal disorders (3.4% vs 1.2%; *P*<0.001) and new-onset atrial fibrillation (3.1% vs 1.6%; *P*=0.017). This is the fourth trial of purified EPA to demonstrate its benefit on CV outcomes in patients with existing CVD.[2-4] By contrast to mixed omega-3 fatty acids containing EPA and docosahexaenoic acid, which failed to show CV benefit (eg, Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia [STRENGTH], Risk and Prevention Study, Alpha Omega),[5-7] EPA-only formulations are the only omega-3 fatty acid treatment to show consistent benefit in CV outcomes.[2-4,8,9]

Persistent Risk in Individuals With Established CVD

People with established CVD are at high risk for recurrent CV events. The 5-year rate of recurrent myocardial infarction (MI), stroke, heart failure, or CV-related death in individuals with CVD is 5 times greater than that of people without known CVD.[10] Low-density lipoprotein cholesterol (LDL-C) remains the chief therapeutic target for reducing CVD risk because overwhelming evidence indicates that "lower is better."[11] For more than 30 years, statins have remained the mainstay treatment approach for reducing LDL-C levels and CVD events. Nevertheless, residual CVD risk persists even in statin-treated patients with very low levels of LDL-C,[12] suggesting that other factors beyond LDL-C may contribute to persistent CVD risk and are critically important to address.[13] As such, increased efforts have been dedicated to developing novel agents that can provide adjunctive benefit to statins so as to further reduce residual CVD risk.[14] Purified EPA is one such agent.

RESPECT-EPA

RESPECT-EPA included 2460 Japanese patients treated with statins who were aged 20 to 79 years with chronic coronary artery disease and a low EPA-to-arachidonic acid ratio (<0.4).[1] Patients were randomized in a 1:1 ratio to purified EPA 1.8 g/day plus statin therapy (n=1225) or statin monotherapy (n=1235). The primary endpoint was a composite of CV death, nonfatal MI, nonfatal cerebral infarction, unstable angina pectoris requiring emergency hospitalization and coronary revascularization procedure, and revascularization procedure based on clinical findings. The secondary endpoint was sudden cardiac death, MI, unstable angina, and coronary revascularization. At baseline, patients' median age was 68 years, approximately 54% had a history of MI, and their median LDL-C level was 80.6 mg/dL. Levels of EPA significantly increased from 48.5 at baseline to 140.5 µg/dL at the 3-year follow-up in the EPA group (*P*<0.05) vs 46.6 to 51.5 µg/dL, respectively, in the statin monotherapy group (nonsignificant).[1]

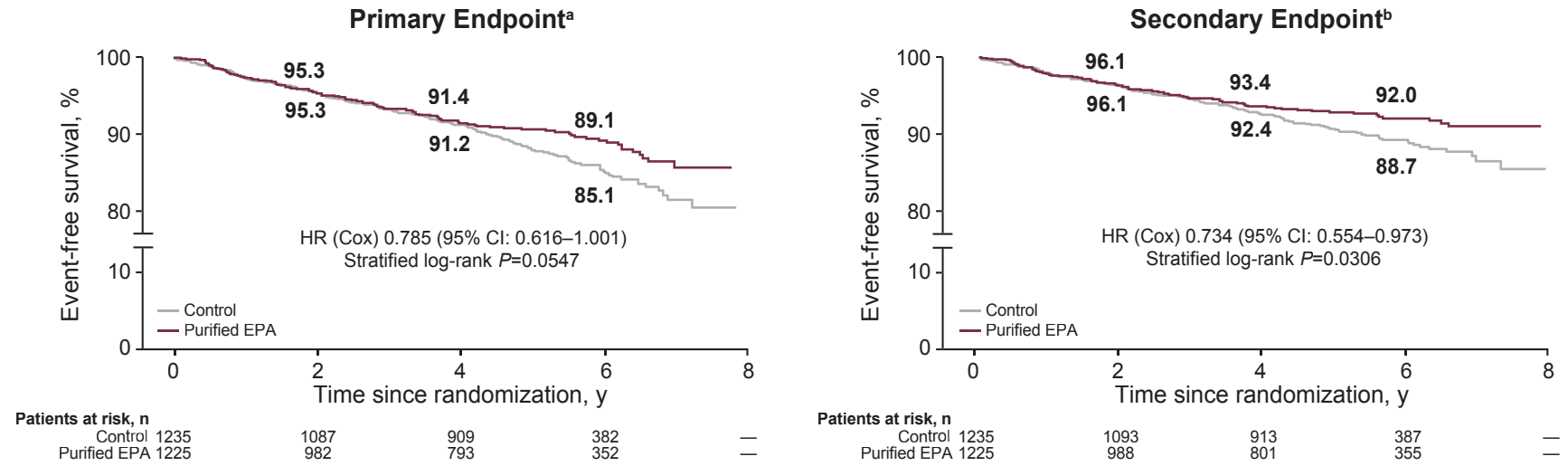
Results of RESPECT-EPA Consistent With 3 Other Trials

Efficacy of purified EPA in RESPECT-EPA is supported by data from 3 other trials, namely the Japan EPA Lipid Intervention Study (JELIS), the Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial (REDUCE-IT), and a Japanese study investigating early initiation of EPA combined with a statin following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome.[2-4] JELIS was the first large trial to demonstrate the benefit of EPA on CV outcomes. It was an open-label study involving 18,645 Japanese patients in the primary and secondary prevention settings. Study participants received EPA 1.8 g/day plus a statin or a statin alone. At a median of 4.6 years, EPA plus statin therapy was associated with a 19% reduction in CV events vs statin therapy alone (*P*=0.011).[2]

JELIS helped to inform the study design of the pivotal phase 3b study REDUCE-IT, which was a randomized, double-blind, placebo-controlled study involving 8179 patients treated with statins who were 45 years or older with established CVD or 50 years or older with diabetes mellitus and at least 1 additional risk factor.[3] Study participants were randomized to receive a highly purified ethyl ester of EPA (icosapent ethyl [IPE]) at a dose of 2 g twice daily or placebo. After a follow-up of 4.9 years, the researchers observed a 25% reduction in the composite outcome of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina with IPE vs placebo (*P*<0.001).[3]

A study by Nosaka et al,[4] which was a prospective, randomized, open-label trial involving 238 patients with acute coronary syndrome treated with PCI, reported a 58% reduction in CV events among patients receiving purified EPA 1.8 g daily with a statin compared with statin therapy alone after 1 year of follow-up.

Figure. Event-free survival for primary and secondary endpoints of RESPECT-EPA with purified EPA vs statin therapy[1]



EPA, eicosapentaenoic acid; MI, myocardial infarction. [a]Composite of cardiovascular death, nonfatal MI, nonfatal ischemic stroke, unstable angina, and coronary revascularization. [b]Sudden cardiac death, MI, unstable angina, and coronary revascularization.

Pleiotropic Mechanisms of Action: On-Treatment Serum EPA Levels Are Primary Driver of Reduced CV Events

JELIS was the first CV outcomes trial to demonstrate that a higher plasma EPA level was inversely associated with risk of a major coronary event (P=0.018).[15] This was confirmed in REDUCE-IT when serum EPA levels appeared to be associated with most of the relative risk reduction achieved by IPE,[16] with only minimal contribution by levels of triglycerides, LDL-C, high-density lipoprotein cholesterol (HDL-C), apolipoprotein B, high-sensitivity C-reactive protein, and non–HDL-C.[3]

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Results from RESPECT-EPA further support existing evidence that purified EPA as an add-on to a statin significantly reduces residual CV risk in patients with established CVD.

Following the results of REDUCE-IT, some experts have speculated that the substantial reduction in CV events was partially attributable to the negative effects of the mineral oil placebo; however, JELIS did not include a mineral oil placebo, and neither did the study by Nosaka et al or RESPECT-EPA, and yet reductions in CV events in these studies were comparable with, if not better than, those observed in REDUCE-IT (19%, 58%, 22%, and 25%, respectively),[1-4] helping to put that hypothesis to rest. The mechanisms by which EPA exerts its effectiveness are not yet fully elucidated.[3] However, lowering of lipid levels does not appear to be the primary driver.[17] Consistent with JELIS and REDUCE-IT results, post hoc analysis from RESPECT-EPA also suggests that EPA serum levels may be the chief factor in reducing CV risk: excluding patients with an EPA increase of no more than 30 µg/mL from baseline increased the reduction in the primary endpoint with EPA vs statin monotherapy to 27.5% (P=0.02).[1] Studies show that EPA has pleiotropic mechanisms of action that go beyond lipid lowering, including anti-inflammatory, antioxidant, and antithrombotic effects, and cell-membrane and plaque stabilization, all of which may improve vascular and coronary health.[17] A recent systematic review and meta-analysis assessed the effect of EPA added to statin treatment on coronary plaque volumes and compared it with the effect of mixed omega-3 fatty acids.[18] After pooling data from 7 EPA-only and 4 mixed omega-3 fatty acids studies, EPA-only treatment resulted in greater plaque volume reductions than mixed omega-3 fatty acids. Adding mixed omega-3 fatty acids did not result in significant plaque volume changes vs statin treatment alone, providing a potential mechanistic explanation for the null findings in CV outcome trials with mixed products.

Conclusion and Recommendations

Results from RESPECT-EPA further support existing evidence that purified EPA as an add-on to a statin significantly reduces residual CV risk in patients with established CVD and at high risk for recurrent CV events. RESPECT-EPA showed similar benefit as the REDUCE-IT and JELIS trials, confirming that EPA is the compound responsible for CV risk reduction in these trials. US and international medical societies have updated their guidelines, now recommending IPE for CV risk reduction.[19-22] The benefits of EPA are due to myriad of pleiotropic effects and depend on the achieved EPA level; thus, patient adherence should be promoted.

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Conflict of interest disclosure

JRN is on the speakers bureau for Amarin Pharma, Inc., Amgen, and Esperion. He is a stockholder of Amgen and on the advisory board for Amarin Pharma, Inc. **MJB** is on the speakers bureau for Amarin Pharma, Inc.