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The benefits of icosapent ethyl in addressing residual risk: What is the evidence?

I will be talking about the benefits of icosapent ethyl in addressing residual risk. Here, you can see my disclosures.

Omega-3 fatty acids have complex biological actions. They have potential mechanisms of cardioprotection. In high doses, they can lower triglyceride-rich lipoproteins, have anti-inflammatory and anti-thrombotic effects. They can augment pro-resolving mediators and stabilize membranes, EPA more so than DHA. The three marine-derived omega-3 fatty acids are EPA, DPA, and DHA. Our topic today is icosapent ethyl, which is a stable, highly-purified ethyl ester of EPA.

Observational studies have shown that increased consumption of fish is associated with lower cardiovascular events. However, low-dose omega-3 fatty acid supplementation has failed to offer cardioprotection in several randomized clinical trials as well as a large meta-analysis of 10 trials showing no significant advantage in terms of cardioprotection.

However, EPA has several positive effects on the plaque. Similar to statins, it can improve endothelial function, decrease adhesion molecules, decrease the necrotic core, and increase the fibrous cap, overall reducing plaque atheroma volume. Unlike statins, it doesn't affect LDL levels as significantly, has no effect of calcification on the plaque, but resolvins can really affect platelet reactivity. Resolvin E1 has antiplatelet functions and a protective role in animal models of atherosclerosis.

Two imaging studies, CHERRY and EVAPORATE have looked at the effects of EPA on plaque on CTs. Here, you see the results of the EVAPORATE study where low attenuation plaque was significantly decreased in CT in patients with coronary atherosclerosis after an 18-month treatment of icosapent ethyl in high doses.

JELIS was the first study to show efficacy of high-dose EPA. In more than 18,000 Japanese patients with high cholesterol, 1.8 gram EPA supplementation was tested and the primary endpoint was reduced by 19%, which was driven mostly by the reduction in the secondary prevention group. However, this study was criticized because it was open-label and used only low-intensity statins.

Then came the REDUCE-IT trial in over 8,000 patients randomly assigned to receive two grams of icosapent ethyl twice a day or placebo. The primary endpoint was a composite of cardiovascular death, nonfatal MI, stroke, coronary revasc, or unstable angina with a follow-up of five years.

At the end of one year, triglycerides were reduced by around 20% and high sensitivity CRP around 40%.

Here, you see the main outcome of the study. The primary endpoint of five-point MACE was significantly reduced by 25% in the icosapent ethyl group regardless of baseline lipids.

A subgroup analysis from patients who suffered a recent acute coronary syndrome showed even more significant reductions in first and recurrent events.

When the subgroup analysis was performed, it was seen that on-treatment EPA tertiles predict cardiovascular outcomes and the patients with higher EPA levels seemed to derive greater benefits.

Another subgroup looked at first and total primary and secondary endpoints in patients with prior myocardial infarction. You can see that those who had a prior MI benefited significantly more than the overall group.

The burden of first subsequent and total ischemic events was also substantially reduced as well as first and total strokes with high-dose icosapent ethyl.

Then came the STRENGTH trial, this time using a mixed omega-3 preparation, EPA plus DHA. In over 13,000 statin-treated patients with high cardiovascular risk, this trial looked at the effects of this mixed omega-3 preparation but failed to show any cardiovascular benefit in terms of primary MACE and core MACE, and the trial was stopped for futility.

A much smaller trial, the OMEMI trial, also looked at a mixed omega-3 fatty acid supplementation in elderly patients with recent MI, also failing to show substantial benefit in primary outcomes.

When we look at the risk associated with omega-3 fatty acids, what did we learn from these trials? First of all, O-3 in REDUCE-IT and STRENGTH, atrial fibrillation was increased significantly, but in REDUCE-IT, this was accompanied by a significant reduction in stroke despite higher rate of atrial fibrillation. Also, bleeding rates were higher in the REDUCE-IT trial in the active comparator arm.

What explains the differences between these two trials? First of all, the active treatment was high-dose icosapent ethyl with EPA only in the REDUCE-IT trial, whereas it was a mix EPA, DHA preparation, omega-3 carboxylic acid in the STRENGTH trial. In the REDUCE-IT, patients with higher risk had less high-intensity statin use and had a much longer follow-up. The LDL changes were different as well.

In the STRENGTH, the LDL cholesterol increased more than placebo. Percent EPA level change was also different because in the REDUCE-IT trial, plasma EPA levels increased to much higher levels than the STRENGTH trial. One difference was the placebo which was mineral oil in the REDUCE-IT and corn oil in the STRENGTH trial. This may have explained some of the changes in LDL cholesterol in the placebo group. However, after careful examination, EMA concluded a putative negative effect of the mineral oil should not account for more than 3% of the MACE events.

One explanation can also be that EPA and DHA have contrasting effects on the cell membranes, where EPA preserves the membrane structure and distribution of cholesterol, inhibits lipid oxidation, and has anti inflammatory effects. Whereas DHA is more concentrated in brain and retinal membranes and can increase membrane fluidity.

A new index of inflammation is high pericoronary adipose tissue attenuation, which can be seen on CT. In a small study, high plasma levels of EPA, but not DHA, were associated with lower pericoronary adipose tissue attenuation, and significantly higher values of EPA were seen in patients with lower PCAT.

A recent trial announced at the American Heart Association Congress is the RESPECT-EPA trial. This is an open-label randomized controlled trial of over 2,000 Japanese patients with coronary artery disease on a statin. These patients all had low EPA to arachidonic acid ratio. Icosapent ethyl was given in 1.8 gram-doses versus control, and the primary endpoint was reduced in this trial, but the trial was criticized for having no placebo control and being underpowered.

Today, we have interventions to reduce triglyceride-rich lipoproteins to decrease cardiovascular risk. The main important thing we should take care of is lifestyle and managing other risk factors. High-intensity statins are the first-line therapy, but to reduce triglyceride-rich lipoproteins, we have the options of icosapent ethyl which may be considered according to the ACC consensus and European guidelines. Fibrates recommended may be considered in the European guidelines, and new therapies to inhibit ApoC3 or angiopoietin-like 3 which are extremely potent, but we need outcome trials with these.

The 2021 European guidelines on cardiovascular prevention are recommending in high-risk patients with triglycerides about 1.5 mmol/L or 135 mg/dL, despite statins and lifestyle, high-dose icosapent ethyl may be considered in combination with a statin. Thank you for your attention.