Clinical trials of eicosapentaenoic acid (EPA) prescription products for the treatment of hypertriglyceridemia

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ABSTRACT

Introduction: Hypertriglyceridemia is common and increases cardiovascular risk. Fish oil decreases triglyceride levels, but also increases low-density lipoprotein (LDL) cholesterol, which may negate any cardiovascular benefits. EPA, a component of fish oil, reduces triglyceride levels without increasing LDL cholesterol.

Areas covered: Two forms of purified EPA ethyl ester are available on prescription. This review considers the clinical trials of these purified esters to treat hypertriglyceridemia and shows that the EPA ethyl esters reduce triglyceride levels and reduce cardiovascular events.

Expert opinion: To date, the effects of the purified EPA ethyl esters on cardiovascular events have only been tested in subjects taking statins. With statin treatment, if hypertriglyceridemia persists, it may be worthwhile considering adding an EPA ethyl ester. However, as the fibrates reduce the triglyceride levels by similar amounts to the EPA ethyl esters, while increasing the levels of HDL cholesterol, they are an alternative to EPA ethyl esters in combination with statins. As the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors reduce triglycerides to a similar extent to the EPA ethyl ester, while reducing LDL cholesterol levels to a greater extent than the statins, they should be considered as an alternative to the statin/EPA ethyl ester combination.

1. Introduction

The recent large reductions in cardiovascular morbidity and mortality are probably due to the use of medicines (predominantly statins) to reduce low-density lipoprotein (LDL) cholesterol [1]. Nevertheless, heart disease remained the leading cause of death in the USA in 2016, and stroke was the seventh leading cause [2]. It has been suggested that other lipid factors may be associated with cardiovascular and cerebrovascular morbidity and mortality. These include low levels of high-density lipoprotein (HDL) cholesterol and high levels of triglycerides [3,4].

Cardiovascular risk is higher in subjects with high triglycerides (580 mg/dl, 6.6 mmol/L) than in subjects with levels of 70 mg/dl (0.8 mmol/L) [5]. Also, hypertriglyceridemia is a higher predictor of cardiovascular disease in women than men [6]. Importantly, hypertriglyceridemia remains a cardiovascular risk factor in subjects who have their LDL cholesterol levels controlled with statins [7].

Hypertriglyceridemia is quite common, as when hypertriglyceridemia is defined as being ≥150 mg/dl (1.70 mmol/l), 24% of adults have it [1]. One approach to lowering triglycerides is fish oil, which contains a mixture of the long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish oil reduces triglycerides in subjects with hypertriglyceridemia, but it has also been shown to increase LDL cholesterol [8]. As high levels of LDL cholesterol are known to have detrimental cardiovascular effects, any beneficial effects of decreasing triglycerides with fish oil are likely to be negated.

The effects of EPA and DHA on lipids have been studied separately and consistently shown to reduce triglycerides [9,10]. An early 2000 study showed that in mildly hyperlipidemic men, EPA or DHA 4 g for 6 weeks reduced triglycerides by 0.37 and 0.45 mmol/L, respectively, and DHA increases LDL cholesterol by 8% [9]. When the studies with EPA and DHA were pooled in 2010, EPA and DHA reduced triglyceride levels by 45.8 mg/dL and 25.1 mg/dL, respectively. EPA had no significant effect on LDL or HDL cholesterol, whereas DHA increased LDL and HDL cholesterol by 7.23 and 4.49 mg/dL, respectively [10]. Given that DHA increases LDL cholesterol, EPA alone may be preferable to DHA in the treatment of hypertriglyceridemia.

Two forms of the purified EPA ethyl ester are available on prescription for clinical use. These are ethyl icosapentate (icosapent; Epadelt), which is available in Japan only, and icosapent ethyl (Vascepa) previously known as eicosapentaenoic acid ethyl ester (AMR101), which has been approved in the USA. Both contain highly purified ethyl ester, and no DHA prescription for clinical use. These are ethyl icosapentate (icosapent; Epadelt), which is available in Japan only, and icosapent ethyl (Vascepa) previously known as eicosapentaenoic acid ethyl ester (AMR101), which has been approved in the USA. Both contain highly purified ethyl ester, and no DHA produced by slight differences in the purification process [11]. There are also differences in the capsule size and dosing regimens (ethyl icosapentate; 300, 600, and 900 mg capsules for dosing of 1.8–2.7 g/day: icosapent ethyl; 500 and 1000 mg capsules for dosing at 4 g/day) [11]. This review is of the effects of these purified EPA ethyl esters on lipid levels and cardiovascular end points. As measurements of triglycerides

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are of the triglyceride-rich lipoproteins, and the lipoproteins rather than the triglyceride may be responsible for the increased cardiovascular risk [5], the effects of icosapent ethyl on lipoproteins are also considered in this review.

2. Clinical trial with ethyl icosapentate: JELIS

The Japan EPA Lipid Intervention Study (JELIS) was an open-label trial testing the effects of ethyl icosapentate, in addition to statins, in 18,645 subjects with LDL cholesterol levels of ≥4.4 mol/L. The subjects had an average age of 61 years, 16% had diabetes, and the baseline triglyceride and LDL cholesterol levels were 1.74 and 4.70 mmol/l, respectively. Ethyl icosapentate was tested in two subgroups, as secondary prevention in 3664 subjects with coronary artery disease and as primary prevention in the other subjects who did not have coronary artery disease. Subjects were randomized to receive ethyl icosapentate, 600 mg three times/day, and statins, or statins alone (pravastatin or simvastatin), and were monitored for an average of 4.6 years. Treatment increased EPA levels by 70%. Ethyl icosapentate had no effect on LDL cholesterol levels but reduced triglycerides by about 5%. The primary endpoint was any major coronary event (cardiac death, fatal and nonfatal myocardial infarction and other non-fatal events), and this occurred significantly less in the ethyl icosapentate group (2.8%) than in the control group (3.5%). This reduction was in unstable angina and non-fatal coronary events (non-fatal myocardial infarction, unstable angina, and events of angio-plasty, stenting or coronary artery bypass). The risks of coronary death or sudden cardiac death or of fatal or non-fatal myocardial infarction were not altered by ethyl icosapentate. The primary and secondary prevention subgroups had similar cardiovascular findings to the group as a whole [12]. Subsequently, ethyl icosapentate was shown to reduce the incidence of stroke as secondary prevention, but not as primary prevention [13]. Although adverse effects were higher with ethyl icosapentate than in the control group, they were predominantly mild gastrointestinal disturbances [12].

3. Clinical trials with icosapent ethyl

3.1. MARINE

In the phase 3 MARINE study (the multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension), after a period of diet, lifestyle and medication stabilization, subjects with triglycerides ≥500 and ≤2000 mg/dl were enrolled. The enrolled subjects had a mean age of about 53 years, BMI of 31, and about 25% were using statins, and 27% had diabetes. Subjects (229) were randomized to icosapent ethyl 4 g/day (two 1-g capsules taken orally twice/day), icosapent ethyl 2 g/day or placebo [14]. After 12 weeks, icosapent ethyl 4 g and 2 g/day had increased the plasma EPA levels by 792% and 402%, respectively, without altering the levels of DHA [15]. Baseline mean triglyceride level was ~670 mg/dl, and after 12 weeks, triglycerides were reduced by 33% and 20% by icosapent ethyl 4 g and 2 g/day, respectively, with no significant change in LDL or HDL cholesterol. There was no apparent excess of adverse effects with icosapent ethyl [14].

In MARINE, the effect of icosapent ethyl on lipoproteins was also investigated, as these are also indicators of cardiovascular disease. Thus, apolipoprotein B-100 (ApoB, which is the major protein constituent of the particles of LDL), intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL), may be a better predictor of coronary artery risk than LDL cholesterol itself [16]. Apolipoprotein C-III (ApoC-III) is an important regulator of triglyceride-rich lipoprotein metabolism and triglyceride homeostasis, and elevated levels may lead to atherosclerosis [17]. Remnant lipoproteins are a sub-fraction of triglyceride-rich lipoproteins composed primarily of IDL and VLDL, and these remnants are predictive for cardiovascular events in subjects with coronary artery disease, after they have achieved their LDL cholesterol goals with statins [18].

In MARINE, icosapent ethyl (4 g/day) reduced the concentrations of small LDL cholesterol particles and large VLDL particles, and the particle concentrations correlated with the ApoB concentrations. Icosapent ethyl did not change the size of the LDL or HDL particles [19]. In MARINE, icosapent ethyl also reduced plasma levels of ApoC-III [20] and remnant-like particle cholesterol [21]. Subgroup analysis for the women in MARINE showed that the reductions in lipids and lipoproteins with icosapent ethyl were comparable to those observed in the overall study [22].

3.2. ANCHOR

ANCHOR was another phase 3 trial investigating the effect of icosapent ethyl on triglyceride levels and was limited to subjects who had their LDL cholesterol levels controlled with statins to ≤40 and <100 mg/dl. Subjects had to undergo a period of diet, lifestyle, and medication stabilization period, and had to have triglycerides of ≥185 mg/dl on two occasions with one level being ≥200 mg/dl. The enrolled subjects (702) had a mean age of about 61 years, BMI (Body Mass Index) of 33 kg/m², about 73% had diabetes, and baseline triglycerides were ~260 mg/dl. Subjects were randomized to icosapent ethyl 4 g/day or 2 g/day, or placebo, and triglycerides were reduced by 22% and 10% by icosapent ethyl 4 g and 2 g/day, respectively. The lower dose of icosapent ethyl has no effect on LDL or HDL cholesterol, whereas there were small decreases in LDL and HDL cholesterol of 6% and 4%, respectively, with icosapent ethyl 4 g/day. Like the results in MARINE, there were no clear-cut excess of adverse effects with icosapent ethyl [23].
In ANCHOR, icosapent ethyl reduced the concentrations of total and small LDL and HDL particles, and total, large, and medium VLDL particles, and reduced the size of LDL, VLDL, and HDL particles. Associated with these reductions in particles, were reductions in ApoB [24]. Icosapent ethyl also reduced the plasma levels of ApoC-III levels and of remnant-like particle cholesterol in ANCHOR [20,21]. Subgroup analysis for the women in ANCHOR showed that the reductions in lipids, lipoproteins and in some markers of atherosclerotic inflammation with icosapent ethyl were comparable to those observed in the overall study [22].

In MARINE and ANCHOR, icosapent ethyl decreased some markers of atherosclerotic inflammation; oxidized LDL, high-sensitivity C-reactive protein (hsCRP), and lipoprotein-associated phospholipase A2, but not others (intercellular adhesion molecule-1 and interleukin-6) [25]. Most of the subjects in MARINE and ANCHOR had the metabolic syndrome, and in these subjects, in addition to reducing triglycerides and LDL cholesterol, icosapent ethyl reduced ApoB and hsCRP levels [26].

### 3.3. REDUCE-IT

The REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial) was a phase 3b multicentre, randomized, double-blind trial sponsored by Amarin Pharma, the makers of icosapent ethyl. REDUCE-IT compared icosapent ethyl to placebo as both primary and secondary prevention of cardiovascular disease. To be enrolled, initially subjects had to have fasting triglyceride levels of 150–499 mg/dl (1.69–5.63 mmol/l), but the lower limit was subsequently changed to 200 mg/dl. Subjects also had to have LDL cholesterol levels of 41–100 mg/dl (1.06–2.59 mmol/l), despite statin treatment. For primary prevention, subjects had to be ≥50 years of age with diabetes, and one additional risk factor for cardiovascular disease, and for secondary prevention ≥45 years of age with established cardiovascular disease. Subjects were randomized to icosapent ethyl (2 g/twice daily) or matching placebo [27].

The 8179 subjects enrolled had a mean age of 64 years, were predominantly white (90%), and 58% had type 2 diabetes; 29% were enrolled for primary, and 71% for secondary prevention. After a median follow-up of 4.9 years, triglycerides had been reduced by 18% from a baseline of 217 to 178 mg/dl in the icosapent group, while increasing by 2% in the placebo group. LDL cholesterol increased from a baseline of 74 mg/dl by 2% in the icosapent group while increasing by 10% in the placebo group, while there were minimal changes in HDL cholesterol (40–41 mg/dl in the icosapent vs. 40–42 mg/dl in the placebo group) [27].

The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or unstable angina, and this occurred in significantly less subjects in the icosapent ethyl group (17.2%), compared to the placebo group (22.0%). The benefit with icosapent ethyl was greater as secondary prevention (19.3% vs. 22.5%) than for primary prevention (12.2% vs. 13.6%), but similar between subjects with and without diabetes [27].

The secondary composite end point was cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, and this also occurred significantly less in subjects in the icosapent ethyl group (11.2%) than the placebo group (14.8%). The benefit of icosapent ethyl was again greater as secondary prevention (12.5% vs. 16.9%) than primary prevention (8.2% vs. 9.8%), and also greater in subjects with diabetes (11.9% vs. 16.3%) than those without diabetes (10.2% vs. 12.7%) [27].

Analysis of individual endpoints showed that icosapent ethyl significantly reduced cardiovascular death (4.3% vs. 5.2%), fatal or nonfatal myocardial infarction (6.1% vs. 8.7%) coronary revascularization (9.2% vs. 13.3%), hospitalizations for unstable angina (2.6% vs. 3.8%), and fatal or nonfatal stroke (2.4% vs. 3.3%) [27].

The benefits of icosapent ethyl on the primary and secondary composite endpoints were similar regardless of the baseline levels of triglycerides; ≥200 mg/dl vs. <200 mg/dl or 150 mg/dl vs. <150 mg/dl. As these cardiovascular benefits were independent of the triglyceride levels attained after 1 year, the authors suggested that some of the benefits of icosapent ethyl may be independent of triglyceride lowering [27].

Although the overall rate of adverse events was not different between the icosapent ethyl and placebo group, the rates of atrial fibrillation were higher in the icosapent ethyl than the placebo group (5.3% vs. 3.9%), as were the rates of peripheral edema (6.5% vs. 5.0%). The rates of diarrhea, constipation, and gastrointestinal adverse effects were slightly, but significantly, lower with icosapent ethyl than placebo [27].

### 4. Expert opinion

#### 4.1. It is not possible to compare JELIS with ethyl icosapentate and REDUCE-IT with icosapent ethyl

It is not possible to directly compare JELIS and REDUCE-IT for several reasons. Firstly, the trials are in different populations. JELIS, the cardiovascular outcomes trial with ethyl icosapentate, was in Japanese subjects, who often have higher amounts of fish oils in their diet than other populations. REDUCE-IT was in a mainly White/Caucasian diet. In their discussion, the authors of REDUCE-IT compared it to JELIS and commented that the levels of plasma triglycerides reached in both studies were similar despite different doses being used (REDUCE-IT, 4 g day of icosapent ethyl; JELIS, 1.8 g day of ethyl icosapentate). Thus, it may be appropriate to continue to use the different dosing regimens in the two populations to reduce triglyceride levels.

Secondly, it is not possible to directly compare JELIS and REDUCE-IT, as there were other differences in the populations enrolled. For instance, LDL cholesterol control with statins was minor in JELIS with subjects having baseline levels of 4.70 mmol/l, but good in REDUCE-IT, where LDL cholesterol baseline was 1.94 mmol/l. Thus, ethyl icosapentate should probably be tested in subjects with statin use that gives good control of LDL cholesterol, and this is presently happening in RESPECT-EPA. RESPECT-EPA (UMIN000012069; Randomized trial for evaluation in secondary prevention efficacy of combination therapy – statin and eicosapentenoic acid) is comparing ethyl icosapentate against placebo, in subjects taking...
statins [28]. Presumably, statin use will be optimized in RESPECT-EPA to overcome this criticism of JELIS, and to make it more comparable to REDUCE-IT.

To compare ethylicosapentate and icosapent ethyl in a clinical trial would require a single comparison trial of the doses used in JELIS and REDUCE-IT and both Japanese and Caucasian populations with similar background statin treatments. Unfortunately, to my knowledge, no such trial is planned.

4.1.1. Are there mechanism/s, other than reducing triglycerides, that underlie the cardiovascular benefits of EPA?

In their discussion, the authors of REDUCE-IT consider that some of the benefits of icosapent ethyl may be independent of triglyceride lowering [27]. As icosapent ethyl was shown to reduce the markers on atherosclerotic inflammation in MARINE and ANCHOR, one possibility is that anti-inflammatory properties contribute to the cardiovascular benefit. Indeed, it has been suggested that it is the anti-inflammatory properties that are responsible for the short-term (one month [29]) and long-term benefits (one year [30]): cardiovascular benefits of ethyl icosapentate in subjects undergoing percutaneous coronary interventions for acute myocardial infarction/acute coronary syndromes. In this study, ethylicosapentate 1800 mg/day reduced C-reactive protein [29], but had no effect on triglycerides levels, which were not elevated at baseline [30]. In another study, where EPA had no effect on triglycerides or LDL cholesterol, it was shown to increase coronary fibrous-cap thickness in subjects with thin-cap fibroatheroma. In this study, in addition to decreasing arterial inflammatory markers (hs-CRP and PTX3, acute phase response protein), EPA increased the EPA/arachidonic acid ratio and decreased macrophage accumulation [31].

However, in a clinical trial showing ethyl icosapentate reduced coronary plaque volume in subjects with coronary heart disease on intensive statin treatment, ethyl icosapentate 1800 mg/day did not reduce high-sensitivity C-reactive proteins (hs-CRP) or triglyceride levels, which were not elevated at baseline [32]. Thus, mechanisms additional to reducing triglycerides or anti-inflammatory effects may be involved in the cardiovascular benefits of EPA. These mechanisms include modifying platelet membranes to reduce platelet procoagulant activity and thrombus formation [33] and improving cell membrane fluidity to confer an antioxidant effect [34].

4.2. Why not ezetimibe instead of ethyl icosapentate or icosapent ethyl?

Ezetimibe inhibits the absorption of cholesterol. In subjects after coronary syndromes, being treated with simvastatin, in IMPROVE-IT (Improved reduction of outcomes: Vytorin efficacy international trial), ezetimibe further reduced the levels of LDL cholesterol, and reduced triglyceride levels by ~10% [35]. This addition of ezetimibe to simvastatin resulted in a reduction of the primary endpoint of death from cardiovascular causes, major coronary event or nonfatal stroke [35]. To compare the effects of ethylicosapentate or icosapent ethyl to ezetimibe on cardiovascular endpoints, a comparison clinical trial will be necessary with the same background statin treatment.

4.3. Why not fibrates instead of ethyl icosapentate or icosapent ethyl?

The medicines most commonly used to lower triglyceride levels are the fibrates, which are PPARa agonists. According to Cochrane reviews, the commonly used fibrates have a modest effect in lowering the risk of cardiovascular disease in primary [36] and secondary prevention [37]. Pemafibrate, which is more potent at lowering triglycerides, and has less adverse effects, than the commonly used fenofibrate, is being developed for clinical use [38]. A major advantage the fibrates have over ethyl icosapentate/icosapent ethyl is that they also increase HDL cholesterol levels, which is known to be beneficial in preventing cardiovascular disease. Thus, the cardiovascular benefits of ethyl icosapentate or icosapent ethyl will need to be shown to be greater than those of the fibrates for EPA use to supersede the fibrates. To determine, a clinical trial comparing the cardiovascular benefits of ethyl icosapentate/icosapent ethyl with fibrates like pemafibrate would be useful.

4.4. Does ethyl icosapentate or icosapent ethyl have benefits in the presence of PCSK9 inhibitors?

The monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9), such as evolocumab and alirocumab, reduce LDL cholesterol levels to a greater extent than the statins, increase HDL cholesterol levels and lower triglyceride levels [39,40]. The effects of evolocumab or alirocumab on triglycerides are similar to those of icosapent in REDUCE-IT. In subjects being treated with statins, evolocumab and alirocumab reduced the risk of cardiovascular events [39,40]. It will be of interest to determine whether ethyl icosapentate/icosapent ethyl have any cardiovascular benefits in subjects being treated with PCSK9 inhibitors.

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