

New Insights into Icosapent Ethyl for Patients with Residual Cardiovascular Risk

These oral and poster presentations took place from 29th August to 1st September 2020, as part of the European Society of Cardiology (ESC) Congress 2020

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Meeting Summary

In this article, the authors share and discuss data reported in four posters at the European Society of Cardiology (ESC) Congress 2020, held from 29th August to 1st September 2020. These data come from, or are related to, the REDUCE-IT trial, a double-blind, randomised controlled trial of icosapent ethyl, a purified ester of eicosapentaenoic acid, versus placebo. A total of 8,179 patients who had been prescribed statin therapy but continued to have elevated triglycerides (TG) were enrolled.

The first poster considers icosapent ethyl for cardiovascular (CV) risk reduction in a subgroup of the UK Biobank population that fit REDUCE-IT patient inclusion criteria. The second poster presents an accumulation of data, from prespecified interim analyses to final analyses. The third poster reports a reduction in total ischaemic events across the full range of baseline low-density lipoprotein cholesterol (LDL-C) and other key subgroups. The final poster presents the outcomes by baseline statin type and statin category (i.e., lipophilic versus lipophobic).

Introduction

REDUCE-IT was a Phase IIIb, double-blind, placebo-controlled trial that randomised 8,179 patients to receive icosapent ethyl (4 g/day) or placebo.^{1,2} Icosapent ethyl (Vascepa®, Amarin Pharma, Inc., Bridgewater, New Jersey, USA) is a novel formulation of highly purified eicosapentaenoic acid. Patients were on stable statin therapy and had either established CV disease (CVD) or diabetes, plus additional CV risk factors, elevated TG levels between 1.7 and 5.6 mmol/L, and LDL-C between 1.0 and 2.6 mmol/L. Patients were followed for a median of 4.9 years and a maximum of 6.2 years.

The primary endpoint was a composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularisation, or unstable angina requiring hospitalisation, and the key secondary endpoint was a composite of CV death, MI, or stroke.¹⁻³ Time to first event analysis showed a relative risk reduction of 24.8% (hazard ratio [HR]: 0.75; 95% confidence interval [CI]: 0.68–0.83; $p < 0.001$) for the primary endpoint and 26.5% (HR: 0.74; 95% CI: 0.65–0.83; $p < 0.001$) for the key secondary endpoint, with an absolute risk reduction of 4.8% and 3.6%, respectively.²⁻⁴ Icosapent ethyl was associated with marked reductions in primary composite and key secondary endpoints, with a number needed to treat of 21 (95% CI: 15–33) for the primary and 28 (95% CI: 20–47) for key secondary endpoints, over a median of 4.9 years.

The following posters present the results of modelling to assess the use of icosapent ethyl in a subgroup of the UK Biobank that fits REDUCE-

IT inclusion criteria, and further analyses using REDUCE-IT data to assess the benefit of icosapent ethyl in patients with residual CV risk.

The Effect of Elevated Triglycerides and Purified Eicosapentaenoic Acid for Cardiovascular Risk Reduction in the UK Biobank Population

Doctor Dina Radenkovic

Elevated plasma TG are associated with insulin resistance, metabolic syndrome, and major adverse CV events (MACE). In REDUCE-IT, an absolute risk reduction in MACE of 4.8% was observed with icosapent ethyl compared to placebo, reflecting a 25% relative risk reduction and a number needed to treat of 21.² Consequently, in 2019, the U.S. Food and Drug Administration (FDA) approved icosapent ethyl for CV risk reduction in select statin-treated patients with elevated TG.⁵

Dr Radenkovic and colleagues modelled the REDUCE-IT inclusion criteria, utilising data from the UK Biobank to evaluate the effects of icosapent ethyl administration on risk reduction of MACE in the UK population. The UK Biobank is a panomic resource that holds data on 500,000 participants who have been followed-up for at least 10 years.⁶ Age- and sex-adjusted rates of CVD in the UK Biobank participants are representative of the general UK population.

REDUCE-IT: Accumulation of Data Across Prespecified Interim Analyses to Final Results

Doctor Brian Olshansky

Patients with plasma TG between >2.94 and ≤ 11.28 (10^{th} decile), compared to those with plasma TG between >0.23 and ≤ 0.77 mmol/L (baseline), had a greater risk (HR: 5.44) of combined CV outcomes (stroke, coronary heart disease, and atherosclerosis). Risk was correlated with increasing plasma cholesterol and TG levels, and survival was inversely correlated with increasing TG. Data from $>200,000$ UK Biobank participants were used to train the relevant models (i.e., Cox proportional-hazards and DeepSurvival).

Of UK Biobank participants, 3,563 matched with the REDUCE-IT inclusion criteria. Assuming icosapent ethyl had the same effect on the UK Biobank population as in REDUCE-IT, 29% of participants given icosapent ethyl would have suffered an adverse outcome within the UK Biobank during follow-up, compared to the 37% not taking icosapent ethyl. Thus, MACE would have decreased from 1,318 to 1,037, a reduction of 281 individuals, and 13 patients would need to be treated to prevent one from experiencing an event over a median follow-up of 4.9 years.

Dr Radenkovic's analysis concluded that elevated TG increased risk of CV events in the UK Biobank population, and that icosapent ethyl may reduce CV morbidity in this database. As icosapent ethyl has been shown to be safe and well tolerated, it should become an important tool for CV risk reduction. Dr Radenkovic emphasised the applicability of the methodology, which could be used for modelling other treatments and diseases among the UK Biobank population. Additionally, the use of icosapent ethyl may be extended because of its vast pleiotropic effects, including suppression of proinflammatory pathways, stimulation of phagocytosis of macrophages and other immune cells, association with better lung gas exchange in intensive care units, and antithrombotic properties.^{7,8}

REDUCE-IT, an event-driven trial, randomised 8,179 statin-treated patients with elevated TG and increased CV risk to icosapent ethyl or placebo.¹ In REDUCE-IT, 1,612 primary endpoint events (CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, or hospitalisation for unstable angina) were targeted for a projected 90% power to detect a 15% relative-risk reduction. Two interim analyses were performed by an independent, unblinded data and safety monitoring committee (DMC). The sponsor, steering committee, and clinical endpoint committee were blinded to the final database lock. Dr Olshansky and colleagues considered the efficacy and safety of icosapent ethyl at two prespecified interim and final analyses.⁹

The first interim analysis, performed after approximately 60% of the targeted number of primary endpoint events ($n=953$), occurred with a median follow-up of 2.9 years, and the second interim analysis was conducted at approximately 80% of accrued events ($n=1,218$) with a median follow-up of 3.7 years. The final analysis, including 1,606 events, was conducted at a median follow-up of 4.9 years.

Before decisions were made about study continuation at each interim analysis, the DMC discussed the need for a mature dataset to support robustness and consistency of the final efficacy and safety findings. Decisions to continue the study were guided by an analysis plan and prespecified decision-making processes that included assessments of safety, efficacy, primary composite endpoint formal analyses, and informal robustness analyses, with no futility stopping requirements.

Dr Olshansky reported that, compared to placebo, icosapent ethyl reduced the primary composite endpoint by 23% in the first (HR: 0.77; 95% CI: 0.68–0.87; $p=0.00005$) and second (HR: 0.77; 95% CI: 0.69–0.87; $p=0.0000008$) interim analyses, and by 25% (HR: 0.75; 95% CI: 0.68–0.83; $p=0.00000001$) in the final analysis. Similarly, compared to placebo, icosapent ethyl

reduced key secondary endpoint events by 29% (HR: 0.71; 95% CI: 0.60–0.83; $p=0.00005$) in the first interim analysis, 28% (HR: 0.72; 95% CI: 0.62–0.83; $p=0.000009$) in the second interim analysis, and 26% (HR: 0.74; 95% CI: 0.65–0.83; $p=0.000006$) in the final analysis.

Thus, compared to placebo, icosapent ethyl improved primary and key secondary composite endpoints in both interim analyses; the significance persisted until the final analysis. The benefit of icosapent ethyl versus placebo remained consistent, with similar robustness across individual endpoint components. The clarity of findings in both the study as a whole and in patient subgroups improved steadily across endpoints with a greater number of events.

Data from a continuous landmark analysis of the primary composite endpoint showed consistent, statistically significant benefits of icosapent ethyl versus placebo, starting at 21 months postrandomisation. Similarly, a continuous landmark analysis of key secondary endpoints showed consistent, statistically significant benefits of icosapent ethyl versus placebo, starting at 25 months postrandomisation.

The DMC discussed stopping the trial because of the overwhelming efficacy at each interim analysis. They considered historical examples of failed CV outcome studies for TG-lowering and mixed omega-3 therapies. They reflected on overestimations of the final demonstrated benefit when incomplete datasets are used and weighed societal impacts of fuller datasets before recommending continuation of the trial beyond each interim analyses.

Dr Olshansky and colleagues concluded that consistent, potent efficacy of icosapent ethyl emerged early, within a few months of treatment, and persisted across two prespecified interim analyses until the final analyses. The mature dataset demonstrated highly statistically significant reductions in primary and key secondary endpoints, allowing robust analyses to support overall efficacy and safety conclusions. By allowing the REDUCE-IT dataset to mature fully, physicians and patients were provided with consistent and reliable efficacy and safety data. This provided a basis for clinical decisions

regarding icosapent ethyl in CV risk reduction for many of the important subsets of patients included in REDUCE-IT.

REDUCE-IT: Total Ischaemic Events Reduced Across the Full Range of Baseline LDL-C and Other Key Subgroups

Doctor Deepak Bhatt

As previously mentioned, icosapent ethyl reduced time to first primary endpoint ischaemic events by 25% compared to placebo in REDUCE-IT.^{2,3} In addition to reducing first events, icosapent ethyl also significantly reduced second (HR: 0.68; 95% CI: 0.60–0.77), third (HR: 0.70; 95% CI: 0.59–0.83), and fourth or more (rate ratio [RR]: 0.46; 95% CI: 0.36–0.60) events.^{10,11} Overall, icosapent ethyl was associated with a 31% (RR: 0.69; 95% CI: 0.61–0.77; $p<0.001$) reduction in total (i.e., first and subsequent) primary endpoint ischaemic events compared to placebo.^{10,11} Similar reductions in both first and total key secondary endpoint ischaemic events were observed. Dr Bhatt and colleagues further explored the extent to which icosapent ethyl reduced total primary and key secondary events across prespecified baseline biomarker subgroups (TG, LDL-C, and high-sensitivity C-reactive protein [CRP]).

Total events analyses of prespecified biomarker subgroups demonstrated robust and generally consistent findings for the primary and key secondary composite endpoints. Dr Bhatt reported significant reductions in total primary (range: 24% [RR: 0.76; 95% CI: 0.63–0.91] to 39% [RR: 0.61; 95% CI: 0.48–0.76]) and secondary (range: 24% [RR: 0.76; 95% CI: 0.61–0.96] to 37% [RR: 0.63; 95% CI: 0.48–0.83]) endpoint event rates across all different cut-points of included baseline biomarkers.

The highest reductions in both primary and key secondary total events were in patients with high TG (≥ 2.3 mmol/L) and low high-density lipoprotein-cholesterol (HDL-C; < 0.9 mmol/L), a subgroup of patients who have been of interest in prior and ongoing trials. Icosapent ethyl reduced the total primary and secondary

endpoint event rate in this group by 39% (RR: 0.61; 95% CI: 0.48–0.76) and 37% (RR: 0.63; 95% CI: 0.48–0.83), respectively. Median baseline LDL-C levels in ascending tertiles (≤ 1.7 , >1.7 – 2.2 , >2.2 mmol/L) were 1.5, 2.0, and 2.5 mmol/L, respectively. There were large, significant relative reductions in total primary endpoint events with icosapent ethyl across LDL-C tertiles (35% [RR: 0.65; 95% CI: 0.53–0.79], 28% [RR: 0.72; 95% CI: 0.59–0.87], and 27% [RR: 0.73; 95% CI: 0.60–0.89], respectively; interaction $p=0.62$), with parallel substantial absolute risk reductions. Similarly, significant relative reductions in total key secondary endpoint events of 33% (RR: 0.67; 95% CI: 0.53–0.87), 28% (RR: 0.72; 95% CI: 0.57–0.90), and 24% (RR: 0.76; 95% CI: 0.61–0.96) across ascending LDL-C tertiles were observed (interaction $p=0.77$), along with substantial absolute risk reductions. Large, significant total event reductions in both primary and key secondary endpoints were also reported for patients with baseline high sensitivity CRP, both above (primary [RR: 0.76; 95% CI: 0.65–0.88]; secondary [RR: 0.75; 95% CI: 0.63–0.89]) and below (primary [RR: 0.62; 95% CI: 0.52–0.73]; secondary [RR: 0.67; 95% CI: 0.55–0.82]) 2 mg/L.

Dr Bhatt concluded that icosapent ethyl (dosed at 2 g twice daily) significantly reduced total ischaemic events in statin-treated patients with elevated TG and well-controlled LDL-C (<2.6 mmol/L). In the first-event analysis, reductions in total events were observed across a variety of biomarker subgroups, including all baseline levels of TG, LDL-C, and high sensitivity CRP. In addition, a substantial reduction across already low LDL-C tertiles, and in the subgroups with or without low HDL-C but with elevated TG, was evident. Icosapent ethyl is an important option to reduce the high burden of total atherosclerotic events beyond statins and other modern therapies.

REDUCE-IT: Outcomes by Baseline Statin Type

Doctor Deepak Bhatt

Patients with elevated TG have high residual atherosclerotic CVD (ASCVD) risk despite LDL-C control with statin therapy.^{12–14} In REDUCE-IT,

icosapent ethyl significantly reduced time to first occurrence of the primary composite endpoint and the key secondary endpoint events versus placebo. There were also substantial reductions in lipid parameters associated with TG (-19.7% ; $p<0.001$) and non-HDL-C (-13.1% ; $p<0.001$) with icosapent ethyl versus placebo, as well as modest reductions in LDL-C (-6.6% ; $p<0.001$) and apolipoprotein B (ApoB; -9.7% ; $p<0.001$).² However, the mechanisms for the ASCVD benefit of icosapent ethyl are not fully understood.^{2,15}

Dr Bhatt and colleagues analysed data from REDUCE-IT to explore the impact of baseline and concomitant statin types and lipophilic versus lipophobic statin categories on ASCVD outcomes and on LDL-C and ApoB levels, and to further consider the relevance of LDL-C pathways in the observed benefit of icosapent ethyl on ASCVD. Of the 8,179 participants enrolled in REDUCE-IT, the largest proportion took atorvastatin ($n=3,265$; 39.9%) at baseline, followed by simvastatin ($n=2,461$; 30.1%), rosuvastatin ($n=1,755$; 21.5%), pravastatin ($n=617$; 7.5%), lovastatin ($n=129$; 1.6%), fluvastatin ($n=23$; 0.3%), and pitavastatin ($n=21$; 0.3%). Approximately 70% ($n=5,683$; 69.5%) and 30% ($n=2,368$; 29.0%) took a lipophilic (hydrophobic: atorvastatin, simvastatin) or lipophobic (hydrophilic: rosuvastatin, pravastatin) statin, respectively, at baseline. For concomitant use (while on study), the largest proportion of patients enrolled in REDUCE-IT used atorvastatin ($n=4,048$; 49.5%), followed by simvastatin ($n=2,576$; 31.5%), rosuvastatin ($n=2,170$; 26.5%), pravastatin ($n=739$; 9.0%), lovastatin ($n=160$; 2.0%), fluvastatin ($n=31$; 0.4%), and pitavastatin ($n=33$; 0.4%). Almost three-quarters ($n=6,068$; 74.2%) took a lipophilic statin and one-third ($n=2,836$; 34.7%) took a lipophobic statin concomitantly. The distribution of baseline and concomitant statin use in each arm was similar to the overall cohort.

Use of atorvastatin, rosuvastatin, simvastatin, or pravastatin as single agents accounted for 96.1% of REDUCE-IT patients. Patients on one of these four statins at baseline were included in a Cox proportional-hazards regression model, which showed a similar benefit of icosapent ethyl on primary and key secondary endpoints across baseline statin types (interaction primary $p=0.61$; key secondary $p=0.49$). A similar benefit was also seen across lipophilic/lipophobic statin categories (interaction primary $p=0.46$; key

secondary p=0.66). Individual baseline statin type (interaction p=0.98) and lipophilic/lipophobic category (interaction p=1.00) had no meaningful impact on the modest median LDL-C changes from baseline to 1 year (range: -5.8 to -8.4%), observed with icosapent ethyl versus placebo. Similarly, baseline statin type (interaction p=0.96) and lipophilic/lipophobic category (interaction p=0.98) did not impact ApoB changes from baseline to 2 years (range: -8.7 to -11.7) observed with icosapent ethyl versus placebo. Results were similar for primary and key secondary composite endpoint outcomes and for changes in LDL-C and ApoB by concomitant statin use.

Dr Bhatt concluded that there were no meaningful treatment differences in primary or key secondary endpoints across individual statin types or lipophilic/lipophobic groups. A similar lack of treatment difference was observed in LDL-C changes from baseline to 1 year. Therefore, LDL-C and ApoB changes and ASCVD risk reduction observed in REDUCE-IT appear to be independent of the type or lipophilicity of concomitant statin therapy, and of LDL-C levels.² These data provide clinicians with additional insight regarding concomitant statin therapy considerations when prescribing icosapent ethyl, and suggest there are important mechanisms of action for the substantial ASCVD risk reduction observed with icosapent ethyl that are distinct from the LDL receptor pathway.

Summary

These posters provide further support for icosapent ethyl as an important tool in CV risk reduction. Modelling data presented by Dr Radenkovic suggest that icosapent ethyl may reduce CV morbidity in the UK in patients who meet REDUCE-IT inclusion criteria with implications for wider potential use. Further analyses of REDUCE-IT data provide additional evidence for a beneficial effect of icosapent ethyl in statin-treated patients with elevated TG and well-controlled LDL-C. Dr Olshansky confirmed that allowing the REDUCE-IT dataset to mature fully, despite icosapent ethyl efficacy emerging early, provided physicians and patients with robust, consistent, and reliable efficacy and safety data upon which to base clinical decisions for icosapent ethyl in CV risk reduction. Dr Bhatt showed that, in addition to reducing time to first events, icosapent ethyl significantly reduced total ischaemic events across a variety of biomarker subgroups, highlighting its potential role as a further treatment option to reduce the high burden of total atherosclerotic events. Dr Bhatt also reported no meaningful treatment differences in primary or key secondary endpoints across individual statin types or lipophilic/lipophobic groups. He concluded that these data provide clinicians with additional insight regarding concomitant statin therapy considerations when prescribing icosapent ethyl, and suggest other mechanisms of action apart from the LDL receptor pathway, which might explain the substantial reduction in ASCVD risk observed with icosapent ethyl.

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