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ORIGINAL RESEARCH ARTICLE

Icosapent Ethyl Reduces Ischemic Events in Patients With a History of Previous Coronary Artery Bypass Grafting: REDUCE-IT CABG

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BACKGROUND: Despite advances in surgery and pharmacotherapy, there remains significant residual ischemic risk after coronary artery bypass grafting surgery.

METHODS: In REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial), a multicenter, placebo-controlled, double-blind trial, statin-treated patients with controlled low-density lipoprotein cholesterol and mild to moderate hypertriglyceridemia were randomized to 4 g daily of icosapent ethyl or placebo. They experienced a 25% reduction in risk of a primary efficacy end point (composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina) and a 26% reduction in risk of a key secondary efficacy end point (composite of cardiovascular death, myocardial infarction, or stroke) when compared with placebo. The current analysis reports on the subgroup of patients from the trial with a history of coronary artery bypass grafting.

RESULTS: Of the 8179 patients randomized in REDUCE-IT, a total of 1837 (22.5%) had a history of coronary artery bypass grafting, with 897 patients randomized to icosapent ethyl and 940 to placebo. Baseline characteristics were similar between treatment groups. Randomization to icosapent ethyl was associated with a significant reduction in the primary end point (hazard ratio [HR], 0.76 [95% CI, 0.63–0.92]; *P*=0.004), in the key secondary end point (HR, 0.69 [95% CI, 0.56–0.87]; *P*=0.001), and in total (first plus subsequent or recurrent) ischemic events (rate ratio, 0.64 [95% CI, 0.50–0.81]; *P*=0.0002) compared with placebo. This yielded an absolute risk reduction of 6.2% (95% CI, 2.3%–10.2%) in first events, with a number needed to treat of 16 (95% CI, 10–44) during a median follow-up time of 4.8 years. Safety findings were similar to the overall study: beyond an increased rate of atrial fibrillation/flutter requiring hospitalization for at least 24 hours (5.0% vs 3.1%; *P*=0.03) and a nonsignificant increase in bleeding, occurrences of adverse events were comparable between groups.

CONCLUSIONS: In REDUCE-IT patients with a history of coronary artery bypass grafting, treatment with icosapent ethyl was associated with significant reductions in first and recurrent ischemic events.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01492361.

Key Words: coronary artery bypass ■ eicosapentaenoic acid ■ fatty acids ■ fatty acids, omega-3 ■ lipids ■ prevention and control ■ triglycerides

Coronary artery bypass grafting (CABG) remains an important management option for patients with complex multivessel coronary artery disease (CAD) or left main stem disease.[1–4] However, progressive native CAD, along with graft failure, endows patients with significant post-CABG residual ischemic risk despite secondary

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ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- A subgroup of patients from REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) with a history of coronary artery bypass grafting was analyzed to evaluate the efficacy of icosapent ethyl treatment in the reduction of cardiovascular events in this high-risk patient population.
- Randomization to icosapent ethyl was associated with significant reductions in risk of first and total occurrences of primary and key secondary efficacy end points among statin-treated patients with elevated triglycerides and a history of coronary artery bypass grafting.

What Are the Clinical Implications?

- Considering the significant residual risk for cardiovascular outcomes after coronary artery bypass grafting, new options are needed in this population.
- Icosapent ethyl is an important pharmacotherapeutic option, and its use should be considered for eligible patients with a history of coronary artery bypass grafting.

Nonstandard Abbreviations and Acronyms

CABG	coronary artery bypass grafting
CAD	coronary artery disease
EPA	eicosapentaenoic acid
HR	hazard ratio
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
OMT	optimal medical therapy
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
RR	rate ratio

prevention interventions.[5–8] For example, subanalyses of the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) and EMPA-REG OUTCOME (Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trials demonstrate significant residual risk in patients with a history of CABG despite intensive lipid-lowering (with PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibition) or SGLT2 (sodium–glucose transport protein 2)–inhibition therapy, respectively. In ODYSSEY OUTCOMES, while low-density lipoprotein cholesterol (LDL-C) was targeted to a level of 25 to 50 mg/dL in the treatment group, patients randomized to alirocumab with a history CABG still had a 4-point major adverse cardiovascular event (MACE) rate of 24.5%.[9] In the EMPA-REG OUTCOME trial, a subgroup analysis of patients with diabetes and a history of CABG yielded a 3-point MACE rate of 10.6% in patients allocated to empagliflozin.[10] Thus, newer approaches to reduce ongoing ischemic risk in patients with CABG are required.

REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) investigated the efficacy of 4 g daily icosapent ethyl, a purified and stable eicosapentaenoic acid (EPA) ethyl ester, in reducing cardiovascular outcomes among at-risk patients on stable statin therapy with persistent hypertriglyceridemia.[11] After a median follow-up time of 4.9 years, a 25% relative risk reduction in the primary end point (composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina) and a 26% relative risk reduction in the key secondary end point (composite of cardiovascular death, myocardial infarction, stroke) were observed in patients randomized to icosapent ethyl compared with placebo ($P<0.0001$ for both comparisons), with no differences in the rates of adverse events between the 2 treatment groups other than bleeding and atrial fibrillation.[12] Herein, we present the analyses of patients with a history of CABG enrolled in REDUCE-IT.

METHODS

Study Design and Patient Characteristics

The data that support the findings of this study may be made available from the corresponding author on reasonable request. The study protocol and main findings of REDUCE-IT have been previously published.[11,12] REDUCE-IT was an international, phase IIIB, double-blind trial in which statin-stabilized patients were randomized 1:1 to receive either 4 g daily icosapent ethyl or placebo. All sites received ethics approval from relevant institutional review boards, and informed consent was obtained.

All enrolled patients were required to be on a stable statin dose for at least 4 weeks at baseline with an LDL-C between 41 mg/dL and 100 mg/dL and a triglyceride level between 135 mg/dL and 500 mg/dL. Severe heart failure, active severe liver disease, planned coronary intervention or surgery, glycohemoglobin level greater than 10.0%, history of acute or chronic pancreatitis, and known hypersensitivity to fish, shellfish, or ingredients within icosapent ethyl or placebo constituted exclusion criteria for this trial. The trial included 2 central strata of patients: patients with diabetes plus additional risk factors or patients with established cardiovascular disease. Participants were included in the diabetes plus risk factors group if they were at least 50 years of age, had been diagnosed with type I or type II diabetes that necessitated medical management, and had at least one additional risk factor. The established cardiovascular disease group was comprised of patients of at least 45 years of age with a documented history of CAD, cerebrovascular or carotid disease, or peripheral artery disease.

Table. Baseline Characteristics of Patients With a History of Coronary Artery Bypass Grafting

	Icosapent Ethyl (N = 897)	Placebo (N = 940)	Overall (N = 1837)	*P* Value
Age, median (Q1–Q3), y	66.0 (60.0–72.0)	66.0 (60.0–71.0)	66.0 (60.0–71.0)	0.82
Female, n (%)	123 (13.7)	150 (16.0)	273 (14.9)	0.18
White race, n (%)	819 (91.3)	873 (92.9)	1692 (92.1)	0.21
Westernized region, n (%)	744 (82.9)	787 (83.7)	1531 (83.3)	0.65
Cardiovascular risk category, n (%)				0.79
Established cardiovascular disease	862 (96.1)	901 (95.9)	1763 (96.0)	
Diabetes + risk factors	35 (3.9)	39 (4.1)	74 (4.0)	
Ezetimibe use, n (%)	90 (10.0)	95 (10.1)	185 (10.1)	0.96
Statin intensity, n (%)				0.67
Low	43 (4.8)	37 (3.9)	80 (4.4)	
Moderate	515 (57.4)	543 (57.8)	1058 (57.6)	
High	338 (37.7)	357 (38.0)	695 (37.8)	
Missing	1 (0.1)	3 (0.3)	4 (0.2)	
Body mass index, median (Q1–Q3), kg/m^2	29.8 (27.4–33.4)	30.4 (27.6–34.0)	30.1 (27.5–33.7)	0.04
Triglycerides median (Q1–Q3), mg/dL	221.5 (175.5–282.5)	221.3 (177.5–279.3)	221.5 (176.5–281.0)	0.80
HDL-C, median (Q1–Q3), mg/dL	39.0 (34.0–45.0)	39.5 (34.5–45.0)	39.5 (34.0–45.0)	0.18
LDL-C, median (Q1–Q3), mg/dL	74.0 (61.0–87.0)	76.0 (63.0–89.0)	75.0 (62.0–88.0)	0.19
Triglycerides category, n (%)				0.66
<150 mg/dL	89 (9.9)	82 (8.7)	171 (9.3)	
150 to <200 mg/dL	252 (28.1)	270 (28.7)	522 (28.4)	
≥200 mg/dL	554 (61.8)	588 (62.6)	1142 (62.2)	

HDL-C indicates high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

Approximately 71% of patients in the study comprised the established cardiovascular disease stratum. The current analysis of REDUCE-IT was conducted on all patients in the trial with a history of CABG before randomization.

End Points and Follow-Up

REDUCE-IT used a 5-point MACE composite with cardiovascular death, coronary revascularization, nonfatal myocardial infarction, nonfatal stroke, or unstable angina as the primary efficacy end point in a time-to-event analysis. A 3-point MACE composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was prespecified as the key secondary end point in a time-to-event analysis. Using a hierarchical testing methodology, predetermined secondary efficacy end points were analyzed in the following order after the primary efficacy end point: (1) the key secondary efficacy end point; (2) cardiovascular death or nonfatal myocardial infarction composite; (3) myocardial infarction (fatal or nonfatal); (4) emergent or urgent revascularization; (5) cardiovascular death; (6) unstable angina leading to hospitalization; (7) stroke (fatal or nonfatal); (8) all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke composite; and (9) all-cause mortality. During REDUCE-IT, an independent committee blinded to randomized treatment and patient lipid levels was responsible for adjudicating all clinical end points.

Statistical Analysis

The time from randomization to the first event of any component of the primary 5-point MACE was used for the primary analysis. Time to total (first plus subsequent or recurrent) ischemic events of the primary composite end point was provided as supportive analysis. In the current analyses, all tests were based on a 2-sided α level of 5% without multiplicity adjustment. Randomization was stratified according to cardiovascular risk, geographic region, and baseline use of ezetimibe; stratifying according to these 3 factors and using treatment as a covariate, hazard ratios (HR) and 95% CIs were generated from Cox regression models. To analyze and compare the timing of events between the 2 treatments, a stratified Kaplan–Meier analysis was performed, and the associated *P* values were generated using the log-rank test. Total events analysis was conducted using a negative binomial model to calculate rates and rate ratios (RR) and 95% CIs. Additionally, as a supportive analysis, the Li and Lagakos–modified Wei-Lin-Weissfeld method was used to calculate HR and 95% CIs for time to the first or second events and negative binomial model for third+ events. All statistical analyses were conducted using SAS version 9.4 software.

RESULTS

Baseline Characteristics

After screening 19212 patients for inclusion in REDUCE-IT, 8179 underwent randomization. Of these, 1837 (22.5%) patients had a history of CABG; 897 were randomized to icosapent ethyl and 940 to placebo. Baseline characteristics (overall and by treatment allocation) are shown in the Table and Tables S1 through S3.

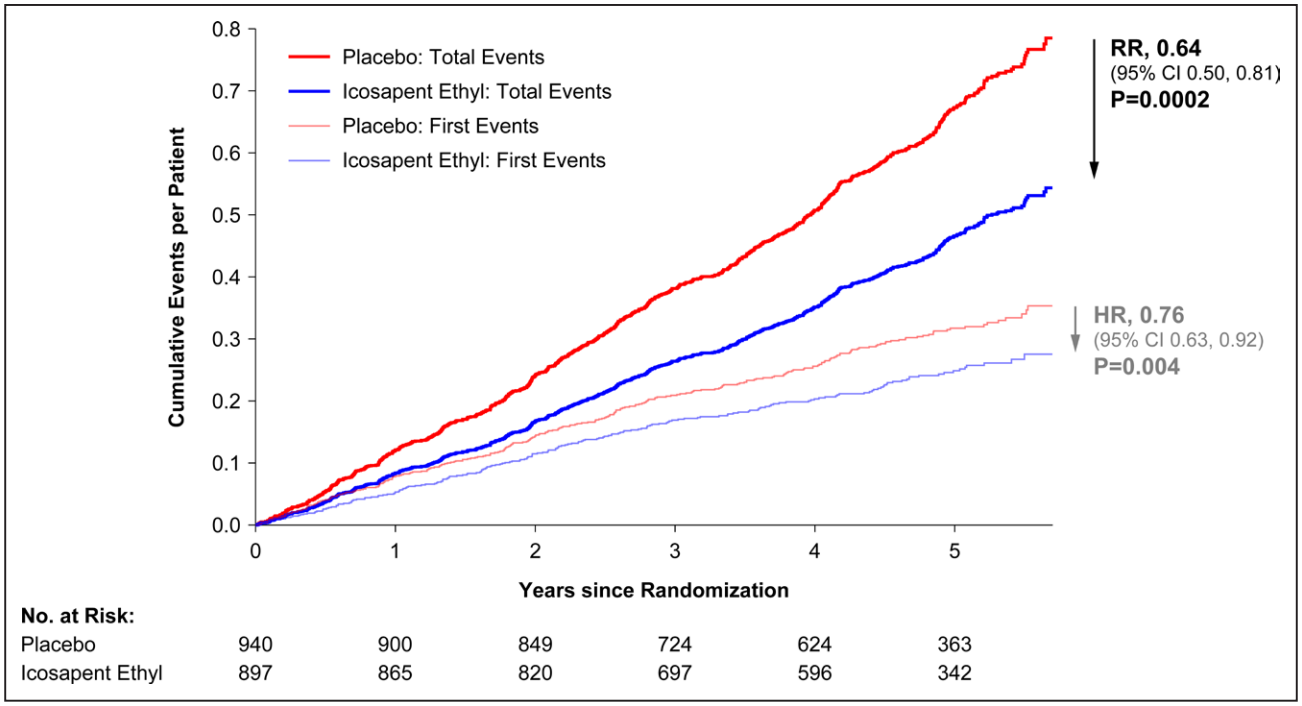

Figure 1. Cumulative incidence of first and total (first plus subsequent or recurrent) primary efficacy end point events.
Event curves for the primary efficacy end point (a composite of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, coronary revascularization, or unstable angina). Total event curves are based on the total adjudicated event dataset without accounting for multiple end point events occurring in a single calendar day as 1 single event. Although included in statistical analyses, events occurring after 5.7 years are not represented visually in the graph because of their limited number. HR indicates hazard ratio; and RR, rate ratio.

The median age was 66 years, and 14.9% of the population was female; these demographics were similar across treatment groups. Other baseline variables, including lipid levels and intensity of statin use, were also largely comparable.

Clinical End Points

There was a total of 462 positively adjudicated primary end point events in patients with a history of CABG; in particular, 22.0% of patients randomized to icosapent ethyl and 28.2% of patients randomized to placebo had a primary end point event (HR, 0.76 [95% CI, 0.63–0.92]; *P*=0.004). This yielded an absolute risk reduction with icosapent ethyl of 6.2% (95% CI, 2.3%–10.2%), with a number needed to treat of 16 (95% CI, 10–44) during a median follow-up time of 4.8 years. The event curves produced from a Kaplan–Meier analysis of the first occurrences of the primary efficacy end point and from a nonparametric cumulative mean function using the Nelson–Aalen estimator of the total (first plus subsequent or recurrent) occurrences of the primary efficacy end point based on treatment allocation are presented in Figure 1. In addition to reducing the occurrence of first primary efficacy end point events, treatment with icosapent ethyl was associated with significant reductions in the occurrence of recurrent events. Further details are provided in Figure 2. Specifically, as shown in Figure 2 for primary end point events, significant reductions in first events (HR, 0.76 [95% CI, 0.64–0.92]; *P*=0.004), second events (HR, 0.67 [95% CI, 0.53–0.84]; *P*=0.0007) and third or further events (RR, 0.53 [95% CI, 0.30–0.94]; *P*=0.03) were noted in the treatment group. As such, treatment with icosapent ethyl was associated with RR of 0.64 ([95% CI, 0.50–0.81]; *P*=0.0002) compared with placebo for occurrence of total (first plus subsequent or recurrent) ischemic events.

A total of 327 key secondary efficacy end point events occurred among patients with a history of CABG, specifically 14.7% in the icosapent ethyl group and 20.7% in the placebo group (HR, 0.69 [95% CI, 0.56–0.87]; *P*=0.001). This yielded an absolute risk reduction of 6.0% (95% CI, 2.5%–9.5%) with a number needed to treat of 17 (95% CI, 11–39) during a median follow-up time of 4.8 years. The event curves from a Kaplan–Meier analysis of the first key secondary efficacy end point events are presented in Figure 3, as are total (first plus subsequent or recurrent) event curves. As observed for primary end point events, there were significant reductions in key secondary end point first events (HR, 0.70 [95% CI, 0.56–0.87]; *P*=0.002) and second events (HR, 0.66 [95% CI, 0.48–0.89]; *P*=0.007), resulting in significant reductions in total (first plus subsequent or recurrent) key secondary end point events (RR, 0.63 [95% CI, 0.48–0.82]; *P*=0.0008; Figure S1).

Hierarchical testing of primary and secondary end points was according to a prespecified sequence. A forest plot demonstrating this hierarchical sequence in

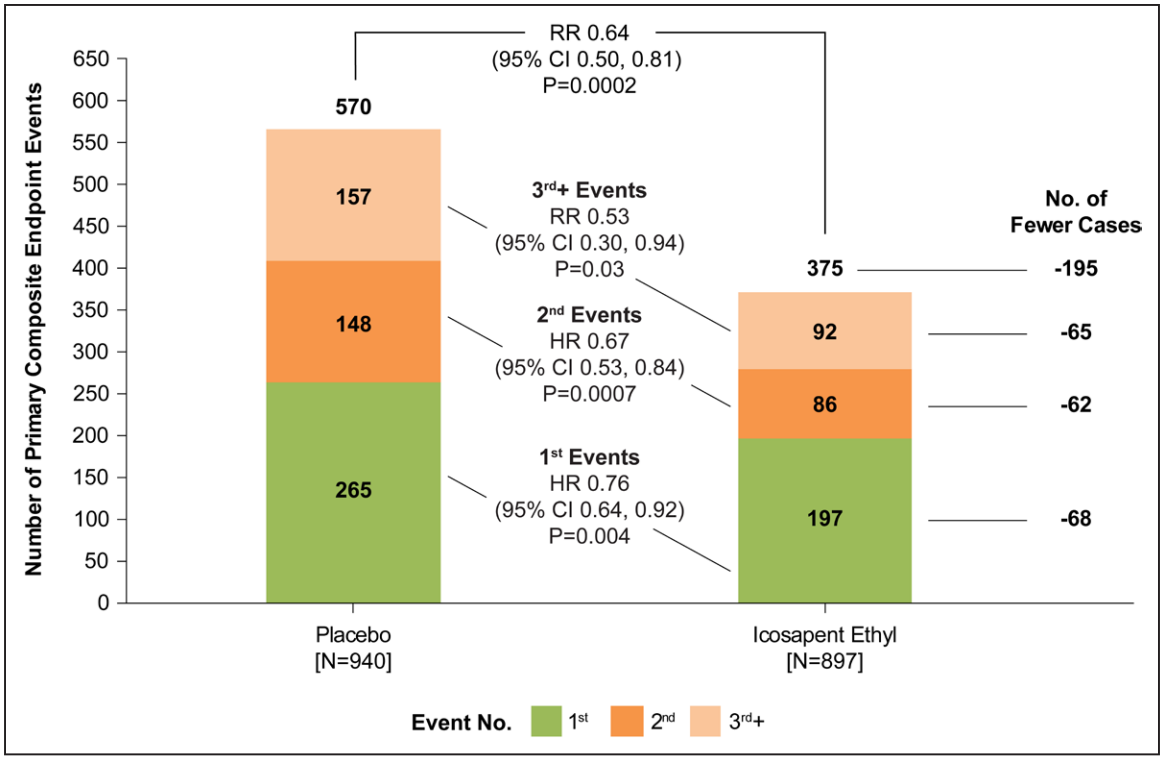

Figure 2. Rates of first and recurrent primary end point events based on treatment allocation.
Analyses are based on the total adjudicated event dataset without accounting for multiple end point events occurring in a single calendar day as 1 single event. HRs and 95% CIs for between treatment group comparisons were generated using Li-Lagakos–modified Wei-Lin-Weissfeld method for the first and second event categories. RRs and 95% CIs for between group comparisons used a negative binomial model for additional events beyond first and second occurrences (ie, third event or more and overall treatment comparison). Patients randomized to the study drug had significantly fewer occurrences of first, second, third or more, and total primary efficacy end point events. HR indicates hazard ratio; and RR, rate ratio.

the subgroup of patients with a history of CABG and of patients with a history of atherosclerotic cardiovascular disease without CABG is displayed in Figure 4. In patients with a history of CABG, icosapent ethyl was also associated with significant reductions in cardiovascular death or nonfatal myocardial infarction (12.7% vs 18.3%; HR, 0.68 [95% CI, 0.53–0.86]; *P*=0.001), fatal or nonfatal myocardial infarction (8.2% vs 13.3%; HR, 0.60 [95% CI, 0.45–0.81]; *P*=0.0005), urgent or emergent revascularization (6.4% vs 9.9%; HR, 0.62 [95% CI, 0.44–0.86]; *P*=0.004), and a composite of total mortality, nonfatal myocardial infarction, and nonfatal stroke (18.1% vs 23.3%; HR, 0.76 [95% CI, 0.62–0.93]; *P*=0.008). The icosapent ethyl group showed a trend toward reduction in cardiovascular death, but this difference did not reach statistical significance (5.7% vs 8.0%; HR, 0.71 [95% CI, 0.50–1.02]; *P*=0.06). The remaining end points were associated with HRs below unity but did not reach statistical significance and included rates of hospitalization for unstable angina (4.2% vs 4.7%; HR, 0.91 [95% CI, 0.59–1.41]; *P*=0.67), rates of fatal or nonfatal stroke (3.2% vs 3.8%; HR, 0.86 [95% CI, 0.53–1.40]; *P*=0.54), and all-cause mortality (9.3% vs 11.1%; HR, 0.84 [95% CI, 0.63–1.12]; *P*=0.24). Of note, compared with patients with a history of atherosclerotic cardiovascular disease without CABG, patients with a history of CABG generally had higher risk for events, but similar relative risk reductions, as supported by the nonsignificant interaction *P* values.

Safety and Adverse Events

Consistent with the full REDUCE-IT study population, comparable rates of total treatment-emergent adverse events and events leading to study drug withdrawal were documented between the treatment groups. Bleeding-related adverse events were greater with icosapent ethyl in the patients with a history of CABG. Also, in accordance with the full study population, patients with a history of CABG randomized to icosapent ethyl had higher rates of atrial fibrillation or flutter requiring hospitalization for at least 24 hours (5.0% vs 3.1%; *P*=0.03). Additional safety- and adverse event–related data are provided in Tables S4 through S7.

DISCUSSION

In this subgroup analysis of REDUCE-IT, daily treatment with 4 g of icosapent ethyl led to a statistically significant 24% reduction in the risk of first primary composite end

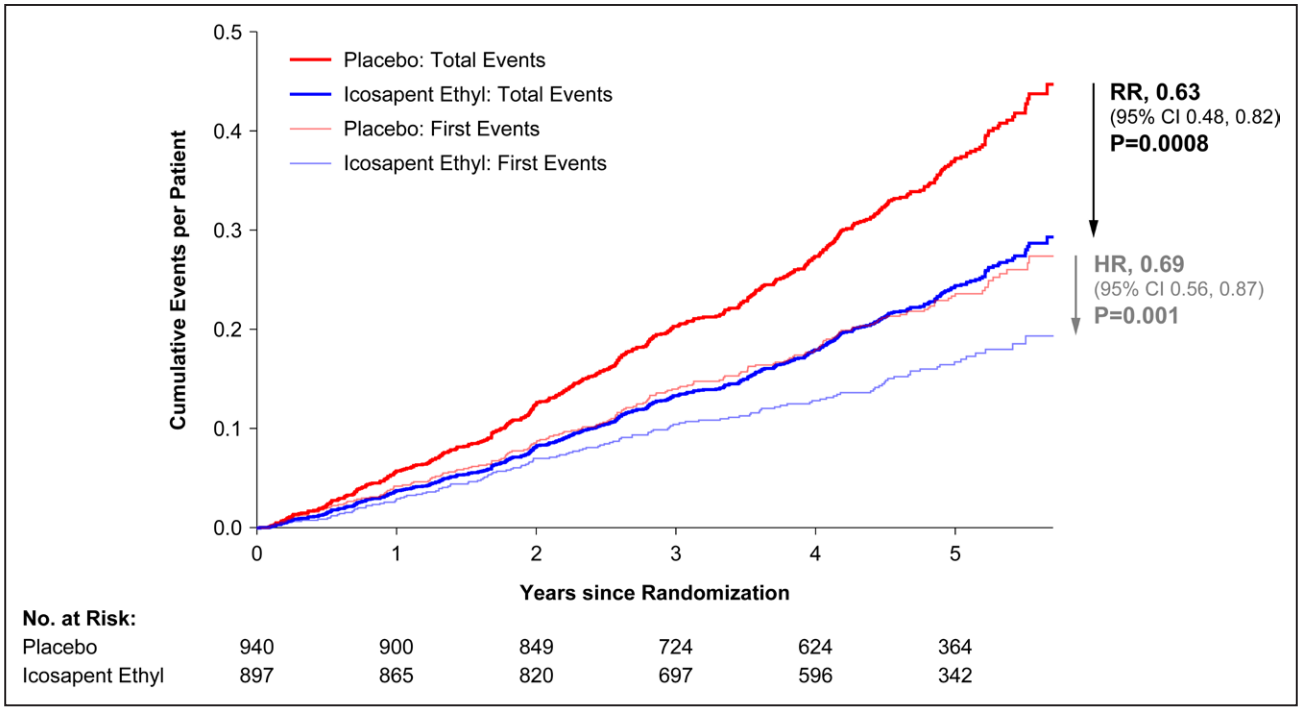

Figure 3. Cumulative incidence of first and total (first plus subsequent or recurrent) key secondary efficacy end point events. Event curves for the key secondary efficacy end point (a composite of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction). Total event curves are based on the total adjudicated event dataset without accounting for multiple end point events occurring in a single calendar day as 1 single event. Although included in statistical analyses, events occurring after 5.7 years are not represented visually in the graph because of their limited number. HR indicates hazard ratio; and RR, rate ratio.

points, including cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, coronary revascularization, or unstable angina, when compared with placebo in patients with a history of CABG. Similar reductions were observed in first occurrences of secondary end points, including a 31% relative risk reduction in the key secondary composite end point of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction. Finally, benefit extended to recurrent events, as demonstrated in substantial reductions in total (first plus subsequent or recurrent) event analysis. This analysis further contributes to the breadth of literature from REDUCE-IT demonstrating the efficacy of icosapent ethyl in reducing clinically important cardiovascular events in at-risk patients. These data are consistent with previous analyses that have demonstrated a significant 32% reduction in total cardiovascular events.[13] Similarly, an analysis of the reduction in revascularization in REDUCE-IT reported a 34% and 36% reduction in first and total revascularization events among patients randomized to icosapent ethyl. Notably, that investigation also described a 39% reduction in need for CABG, making icosapent ethyl the first non-LDL-C–lowering therapy to have reduced this end point in a randomized, double-blind trial.[14]

Previous literature has suggested that elevated triglycerides are associated with an increased risk of ischemic cardiovascular events and mortality.[15–19] But with some notable exceptions[20,21]; agents that reduce triglyceride levels, including certain omega-3 fatty acid mixtures, have not demonstrated reduction in cardiovascular events in modern trials or meta-analyses.[22–28]

Several investigations have attempted to illuminate the complex and multifaceted mechanisms of icosapent ethyl.[29] In the 12-week ANCHOR trial, treatment with EPA 4 g daily versus mineral oil placebo was associated with reductions in triglycerides, apolipoprotein B, very low-density lipoprotein cholesterol, LDL-C, non–high-density lipoprotein cholesterol, and total cholesterol. Additionally, reductions in some markers of inflammation and atherogenesis, including high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and oxidized LDL, were documented in patients treated with icosapent ethyl compared with placebo.[30,31] EPA uniquely reduces triglyceride levels without significantly increasing LDL-C in patients with elevated triglycerides.[30,32,33] Hypothetically, this is a result of how it reduces the synthesis of triglyceride-rich lipoproteins and very low-density lipoproteins as well as increases the elimination of triglycerides and of apolipoprotein B–containing lipoproteins, including triglyceride-rich lipoproteins and LDL.[20,32,34,35]

However, current literature suggests that the benefits of icosapent ethyl are likely derived from a constellation of effects beyond simply lowering triglycerides or other classic cardiovascular risk factors.[36–38] Indeed, the consistent and statistically significant reductions in a variety of clinically important end points reported across

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	P-value	Int. P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*		
Primary Composite Endpoint					0.55
Prior CABG	197/897 (22.0)	265/940 (28.2)	0.76 (0.63, 0.92)	0.004	
ASCVD w/o prior CABG	371/2030 (18.3)	484/1992 (24.3)	0.71 (0.62, 0.82)	<0.0001	
Key Secondary Composite Endpoint					0.69
Prior CABG	132/897 (14.7)	195/940 (20.7)	0.69 (0.56, 0.87)	0.001	
ASCVD w/o prior CABG	236/2030 (11.6)	303/1992 (15.2)	0.74 (0.62, 0.88)	0.0005	
Cardiovascular Death or Nonfatal Myocardial Infarction					0.46
Prior CABG	114/897 (12.7)	172/940 (18.3)	0.68 (0.53, 0.86)	0.001	
ASCVD w/o prior CABG	203/2030 (10.0)	252/1992 (12.7)	0.77 (0.64, 0.92)	0.005	
Fatal or Nonfatal Myocardial Infarction					0.32
Prior CABG	74/897 (8.2)	125/940 (13.3)	0.60 (0.45, 0.81)	0.0005	
ASCVD w/o prior CABG	138/2030 (6.8)	180/1992 (9.0)	0.73 (0.59, 0.91)	0.006	
Urgent or Emergent Revascularization					0.95
Prior CABG	57/897 (6.4)	93/940 (9.9)	0.62 (0.44, 0.86)	0.004	
ASCVD w/o prior CABG	123/2030 (6.1)	186/1992 (9.3)	0.62 (0.50, 0.78)	<0.0001	
Cardiovascular Death					0.64
Prior CABG	51/897 (5.7)	75/940 (8.0)	0.71 (0.50, 1.02)	0.06	
ASCVD w/o prior CABG	83/2030 (4.1)	100/1992 (5.0)	0.80 (0.60, 1.07)	0.14	
Hospitalization for Unstable Angina					0.05
Prior CABG	38/897 (4.2)	44/940 (4.7)	0.91 (0.59, 1.41)	0.67	
ASCVD w/o prior CABG	56/2030 (2.8)	101/1992 (5.1)	0.53 (0.38, 0.73)	<0.0001	
Fatal or Nonfatal Stroke					0.60
Prior CABG	29/897 (3.2)	36/940 (3.8)	0.86 (0.53, 1.40)	0.54	
ASCVD w/o prior CABG	49/2030 (2.4)	66/1992 (3.3)	0.72 (0.50, 1.04)	0.08	
Total Mortality/Nonfatal Myocardial Infarction/ Nonfatal Stroke					0.88
Prior CABG	162/897 (18.1)	219/940 (23.3)	0.76 (0.62, 0.93)	0.008	
ASCVD w/o prior CABG	282/2030 (13.9)	342/1992 (17.2)	0.78 (0.67, 0.92)	0.002	
Total Mortality					0.76
Prior CABG	83/897 (9.3)	104/940 (11.1)	0.84 (0.63, 1.12)	0.24	
ASCVD w/o prior CABG	136/2030 (6.7)	146/1992 (7.3)	0.90 (0.71, 1.13)	0.36	

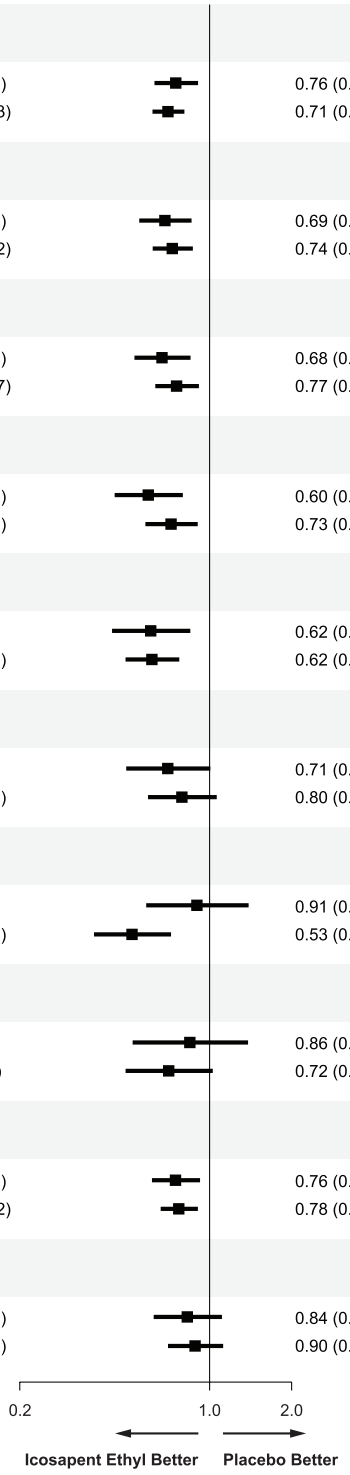

Figure 4. Prespecified efficacy end point testing hierarchy.
Efficacy testing across the prespecified testing hierarchy established for the full patient population supports substantial risk reduction in patients with previous CABG (as well as in patients with ASCVD without previous CABG). Previous CABG includes all patients with previous CABG; ASCVD without previous CABG includes patients with established cardiovascular disease without previous CABG. ASCVD indicates atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; and HR, hazard ratio.

multiple subgroups within the REDUCE-IT population suggest a modulation of multiple cardioprotective pathways. From an inflammatory perspective, the metabolism of omega-3 fatty acids like EPA into thromboxane A3/prostacyclin[34,39] may allow for a reduction in inflammation with two central mechanisms. First, in competing with omega-6 fatty acids for cyclooxygenase enzymes, EPA reduces the production of thromboxane A2 (a platelet activator and atherothrombotic agent).[34,40] Second, prostacyclin itself affords protective benefits through antiplatelet and antithromboxane effects as well as the ability to induce vasodilatation and smooth muscle relaxation.[34] The anti-inflammatory effects of EPA can also be traced to its transformation into resolvins and protectins, which are instrumental in resolving the inflammatory state after acute insults (eg, infection or tissue injury) by initiating neutrophil apoptosis.[41] EPA and its metabolites may also dampen chronic inflammatory processes through, for example, suppressing the development of inflammatory T-cells in favor of resolutory ones.[42] Binding of the macrophage receptor G-protein–coupled receptor 120 is also a proven vehicle for the omega-3 fatty acids to exert anti-inflammatory effects.[43,44]

Cell membrane stabilization, for which EPA effects differ from DHA, and the consequent antioxidation and antiarrhythmic effects, have been identified as potentially important elements of the omega-3 fatty acid mechanism.[34,45,46] In particular, EPA can prevent the cultivation of glucose-induced cholesterol crystalline domains,[47] likely because of its specific intramembrane physiochemical conformation.[34] With respect to lipid oxidation, as aforementioned, previous investigations have discovered that EPA provision to patients with high triglycerides leads to significantly reduced levels of oxidized LDL.[31] These findings are likely a consequence of the molecular structure of EPA, specifically the unique combination of chain length and number of conjugated double bonds, which allows for these antioxidant abilities.[48] Given that oxidized LDL contributes to foam cell synthesis[34] and may have associations with atherosclerosis,[49–51] metabolic syndrome,[52] and clinical cardiac risk,[53–55] this capability may offer significant cardioprotection. Finally, the reduction of arterial stiffness[56–59] and antiplatelet effects[60–63] that EPA causes may also explain some of the significant findings reported in this investigation and others.

In the EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy) trial, 80 patients treated with a statin who had persistently elevated triglyceride levels were randomized to either placebo or icosapent ethyl and followed up with coronary computed tomographic angiography 9 and 18 months after randomization. At 18 months follow-up, patients treated with icosapent ethyl had significant reductions from baseline (17%) in low-attenuation plaque volume, while patients randomized to placebo had more than double their low-attenuation plaque volume compared with baseline. Similarly, significant differences in the rates of fibrous and fibrofatty plaque volume progression were documented in the trial.[64] These results mirrored observations from the CHERRY (Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography) trial, which documented significant reductions in coronary plaque volume when EPA was used in combination with high dose pitavastatin compared with pitavastatin treatment alone.[65]

Finally, it is also important to place the findings reported herein within the broader context of available optimal medical therapy (OMT) for patients with previous revascularization. Current guidelines recommend the use of an antiplatelet agent, statin, β-blocker, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in eligible patients after surgical revascularization.[66] With respect to the choice of antiplatelet agent, evidence from the randomized CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial suggests that clopidogrel affords greater cardiovascular protection, as well as a lower risk of bleeding, compared with aspirin in postcardiac surgery patients.[67] The clinical benefit of OMT after revascularization procedures has also been demonstrated in subanalyses of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial, with patients on OMT at 5 years having a 36% relative lower mortality at 5 years postoperatively compared with patients not on OMT,[68] and an absolute risk reduction of mortality of nearly 7% at 10 years postoperatively compared with patients on ≤2 classes of medications.[69] Of particular interest, at 5 years postoperatively, OMT was not only an independent predictor of survival, but also appeared to have a more significant treatment effect than the mode of revascularization.[68]

Despite these clear benefits, there remains an inadequate level of OMT usage in postrevascularization patients. Among the SYNTAX population, only 41.3% and 46.1% of patients were taking OMT at discharge and at 5 years, respectively; these numbers were consistently lower among CABG-treated patients compared with their percutaneous coronary intervention–treated counterparts.[68,69] While the current findings certainly suggest that icosapent ethyl should be considered as an addition to the physician's armamentarium in medically managing the revascularized patient, this broader context highlights the need for knowledge dissemination and system-level changes to improve uptake of evidence-based medical therapy.[70–72]

The generalizability of REDUCE-IT findings in patients with a history of CABG has been evaluated using the Quebec Heart Database. In a large (N=12 641), contemporary, Canadian cohort of patients on statin therapy with a history of CABG, 21.9%, 33.6%, and 26.4% would be eligible for icosapent ethyl, according to REDUCE-IT,

Health Canada, and US Food and Drug Administration criteria, respectively.[73] Nevertheless, there are important limitations that should be considered when interpreting the results of this investigation. First and foremost, these post hoc subgroup analyses should be considered exploratory and hypothesis-generating. Furthermore, data surrounding the index CABG procedure were not collected. Consequently, time from CABG to randomization, conduits used, use of cardiopulmonary bypass, or other operative variables were not available for analysis.

In summary, we herein report that in patients with a history of CABG, compared with placebo, icosapent ethyl treatment is associated with marked relative and absolute risk reductions with respect to first and recurrent ischemic events. These data support the consideration of icosapent ethyl as an important adjunct therapy for secondary prevention of adverse cardiac outcomes in patients post-CABG.

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Supplemental Material

Tables S1–S7

Figure S1

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