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Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

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ABSTRACT

BACKGROUND

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).

CONCLUSIONS

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361.)

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Among patients with cardiovascular risk factors who are receiving treatment for secondary or primary prevention, the rates of cardiovascular events remain high.[1-3] Even in patients receiving appropriate treatment with statins, a substantial residual cardiovascular risk remains.[4] In such patients, an elevated triglyceride level serves as an independent marker for an increased risk of ischemic events, as shown in epidemiologic and mendelian randomization studies.[5-9] In randomized trials, medications that reduce triglyceride levels, such as extended-release niacin and fibrates, have not reduced the rates of cardiovascular events when administered in addition to appropriate medical therapy, including statins.[10] Contemporary trials and recent meta-analyses of n–3 fatty acid products have not shown a benefit in patients receiving statin therapy.[11-13]

In the Japan EPA Lipid Intervention Study (JELIS), 18,645 Japanese patients with hypercholesterolemia were randomly assigned to receive either low-intensity statin therapy plus 1.8 g of eicosapentaenoic acid (EPA) daily or statin therapy alone (there was no placebo group). The risk of major coronary events was significantly lower, by 19%, in the group that received EPA plus statin therapy than in the group that received statin therapy alone.[14]

These considerations led to the design of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT).[15] Icosapent ethyl is a highly purified and stable EPA ethyl ester that has been shown to lower triglyceride levels and is used as an adjunct to diet in adult patients who have triglyceride levels of at least 500 mg per deciliter (5.64 mmol per liter).[16,17] In addition, icosapent ethyl may have antiinflammatory, antioxidative, plaque-stabilizing, and membrane-stabilizing properties.[18-21] We hypothesized that the risk of cardiovascular events would be lower with icosapent ethyl therapy than with placebo among patients in whom elevated triglyceride levels served as a marker of residual risk despite statin therapy.

Methods

Trial Design

The design of REDUCE-IT has been published previously.[15] In brief, REDUCE-IT was a phase 3b randomized, double-blind, placebo-controlled trial comparing icosapent ethyl (2 g twice daily with food [total daily dose, 4 g]) with a placebo that contains mineral oil to mimic the color and consistency of icosapent ethyl. Randomization was stratified according to cardiovascular risk stratum (secondary-prevention cohort or primary-prevention cohort, with primary prevention capped at 30% of enrolled patients), use or no use of ezetimibe, and geographic region. Further details of the study design are provided in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Patients were enrolled and followed at 473 participating sites in 11 countries. The first patient underwent randomization on November 28, 2011, and the last on August 4, 2016.

The trial was sponsored by Amarin Pharma. The steering committee, which consisted of academic physicians (see the Supplementary Appendix), and representatives of the sponsor developed the protocol, available at NEJM.org, and were responsible for the conduct and oversight of the study, as well as the interpretation of the data. The sponsor was responsible for the collection and management of the data. The protocol was approved by the relevant health authorities, institutional review boards, and ethics committees. All the data analyses were performed by the sponsor, and the primary, secondary, and tertiary adjudicated end-point analyses were validated by an independent statistician from the data and safety monitoring committee. The first author vouches for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Eligibility

Patients could be enrolled if they were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional risk factor. Eligible patients had a fasting triglyceride level of 150 to 499 mg per deciliter (1.69 to 5.63 mmol per liter) and a low-density lipoprotein (LDL) cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter) and had been receiving a stable dose of a statin for at least 4 weeks; because of the intraindividual variability of triglyceride levels, the initial protocol allowed for a 10% lower triglyceride level from the target lower limit, which permitted patients to be enrolled if they had a triglyceride level of at least 135 mg per deciliter (1.52 mmol per liter). The first protocol amendment in May 2013 changed the lower limit of the acceptable triglyceride level

from 150 mg per deciliter to 200 mg per deciliter (2.26 mmol per liter), with no allowance for variability. Patients were excluded if they had severe heart failure, active severe liver disease, a glycated hemoglobin level greater than 10.0%, a planned coronary intervention or surgery, a history of acute or chronic pancreatitis, or known hypersensitivity to fish, shellfish, or ingredients of icosapent ethyl or placebo. Further details regarding inclusion and exclusion criteria are provided in Tables S1 and S2 in the Supplementary Appendix. Written informed consent was obtained from all patients.

END POINTS

The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis. While the steering committee and the sponsor remained unaware of the trial-group assignments, a second protocol amendment in July 2016 designated the key secondary end point as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis. After the primary efficacy end-point analysis was performed, the prespecified secondary efficacy end points were examined in a hierarchical fashion in the following order: the key secondary efficacy end point; a composite of cardiovascular death or nonfatal myocardial infarction; fatal or nonfatal myocardial infarction; emergency or urgent revascularization; cardiovascular death; hospitalization for unstable angina; fatal or nonfatal stroke; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke; and death from any cause. Prespecified tertiary end points are listed in the Supplementary Appendix. Adjudication of all the above events was performed by an independent clinical end-point committee whose members were unaware of the trial-group assignments and lipid levels.

STATISTICAL ANALYSIS

In this event-driven trial, it was estimated that approximately 1612 adjudicated primary end-point events would be necessary to provide the trial with 90% power to detect a 15% lower risk of the primary composite end point in the icosapent ethyl group than in the placebo group. We estimated that a sample size of approximately 7990 patients would be required to reach that number of primary end-point events. The primary efficacy analysis was based on the time from randomization to the first occurrence of any component of the primary composite end point. If the risk of the primary composite end point was significantly lower with icosapent ethyl than with placebo at a final two-sided alpha level of 0.0437 (as determined with the use of O'Brien–Fleming boundaries generated with the Lan–DeMets alpha-spending function approach after accounting for two prespecified interim efficacy analyses), the key secondary end point and other prespecified secondary end points were to be tested in a hierarchical fashion at the same final alpha level of 0.0437. All analyses were performed according to the intention-to-treat principle. Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model that included trial-group assignment as a covariate, stratified according to cardiovascular risk category, geographic region, and use of ezetimibe. Log-rank P values from a Kaplan–Meier analysis that was stratified according to the three randomization factors are reported to evaluate the timing of events in the two trial groups. With respect to the tertiary and subgroup efficacy analyses, 95% confidence intervals (which were not adjusted for multiple comparisons) are reported. An independent data and safety monitoring committee oversaw the study and performed two prespecified interim efficacy reviews.

RESULTS

PATIENTS

A total of 19,212 patients were screened, of whom 8179 (43%) underwent randomization. At the time of database lock, vital status was available for 99.8% of the patients; 152 patients (1.9%) did not complete the final study visits, and 578 patients (7.1%) withdrew consent. Details regarding the disposition of the patients are provided in Figure S2 in the Supplementary Appendix.

The baseline characteristics of the patients are shown in Table 1. Among the patients who underwent randomization, 70.7% were enrolled on the basis of secondary prevention (i.e., patients had established cardiovascular disease) and 29.3% on the basis of primary prevention (i.e., patients had diabetes mellitus and at least one additional risk factor). The median age of the patients was 64 years; 28.8% were female, and 38.5% were from the United States. At baseline, the median

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Icosapent Ethyl (N = 4089)	Placebo (N = 4090)
Age		
Median (IQR) — yr	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yr — no. (%)	1857 (45.4)	1906 (46.6)
Male sex — no. (%)	2927 (71.6)	2895 (70.8)
White race — no. (%)†	3691 (90.3)	3688 (90.2)
Body-mass index‡		
Median (IQR)	30.8 (27.8–34.5)	30.8 (27.9–34.7)
≥30 — no. (%)	2331 (57.0)	2362 (57.8)
Geographic region — no. (%)§		
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	2906 (71.1)	2905 (71.0)
Eastern European	1053 (25.8)	1053 (25.7)
Asia–Pacific	130 (3.2)	132 (3.2)
Cardiovascular risk stratum — no. (%)		
Secondary-prevention cohort	2892 (70.7)	2893 (70.7)
Primary-prevention cohort	1197 (29.3)	1197 (29.3)
Ezetimibe use — no. (%)	262 (6.4)	262 (6.4)
Statin intensity — no. (%)		
Low	254 (6.2)	267 (6.5)
Moderate	2533 (61.9)	2575 (63.0)
High	1290 (31.5)	1226 (30.0)
Data missing	12 (0.3)	22 (0.5)
Diabetes — no. (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2367 (57.9)	2363 (57.8)
No diabetes at baseline	1695 (41.5)	1694 (41.4)
Data missing	0	3 (0.1)
Median high-sensitivity CRP level (IQR) — mg/liter	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median triglyceride level (IQR) — mg/dl	216.5 (176.5–272.0)	216.0 (175.5–274.0)
Median HDL cholesterol level (IQR) — mg/dl	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median LDL cholesterol level (IQR) — mg/dl	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Distribution of triglyceride levels — no./total no. (%)		
<150 mg/dl	412/4086 (10.1)	429/4089 (10.5)
≥150 to <200 mg/dl	1193/4086 (29.2)	1191/4089 (29.1)
≥200 mg/dl	2481/4086 (60.7)	2469/4089 (60.4)
Triglyceride level ≥200 mg/dl and HDL cholesterol level ≤35 mg/dl — no. (%)	823 (20.1)	794 (19.4)
Median eicosapentaenoic acid level (IQR) — μg/ml	26.1 (17.1–40.1)	26.1 (17.1–39.9)

* Median low-density lipoprotein (LDL) cholesterol level at baseline differed significantly between the trial groups (P=0.03); there were no other significant between-group differences in baseline characteristics. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. In general, the baseline value was defined as the last nonmissing measurement obtained before randomization. The baseline LDL cholesterol value as measured by means of preparative ultracentrifugation was used in our analyses; however, if the preparative ultracentrifugation value was missing, the LDL cholesterol value measured by another method was used in the following order of priority: the value obtained by means of direct measurement of LDL cholesterol, the value derived with the use of the Friedewald equation (only for patients with a triglyceride level <400 mg per deciliter), and the value derived with the use of the calculation published by Johns Hopkins University investigators.[22] At the first and second screening visits, the LDL cholesterol value obtained by direct measurement was used if at the same visit the triglyceride level was higher than 400 mg per deciliter. At all remaining visits, the LDL cholesterol value was obtained by means of direct measurement or preparative ultracentrifugation if at the same visit the triglyceride level was higher than 400 mg per deciliter. For all other measures of lipid and lipoprotein markers, whenever possible, the baseline value was derived as the arithmetic mean of the value obtained at visit 2 (day 0) and the value obtained at the preceding screening visit. If only one of these values was available, that single value was used as the baseline value. CRP denotes C-reactive protein, HDL high-density lipoprotein, and IQR interquartile range. Percentages may not total 100 because of rounding.

† Race was reported by the investigators.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Eastern European region includes Poland, Romania, Russia, and Ukraine, and Asia–Pacific region includes India.

LDL cholesterol level was 75.0 mg per deciliter (1.94 mmol per liter), the median high-density lipoprotein cholesterol level was 40.0 mg per deciliter (1.03 mmol per liter), and the median triglyceride level was 216.0 mg per deciliter (2.44 mmol per liter).[22]

FOLLOW-UP AND EFFECTS ON LIPIDS

The median duration of follow-up was 4.9 years (maximum, 6.2 years). The median change in triglyceride level from baseline to 1 year was a decrease of 18.3% (–39.0 mg per deciliter [–0.44 mmol per liter]) in the icosapent ethyl group and an increase of 2.2% (4.5 mg per deciliter [0.05 mmol per liter]) in the placebo group; the median reduction from baseline (as estimated with the use of the Hodges–Lehmann approach) was 19.7% greater in the icosapent ethyl group than in the placebo group (a 44.5 mg per deciliter [0.50 mmol per liter] greater reduction; P<0.001). The median change in LDL cholesterol level from baseline was an increase of 3.1% (2.0 mg per deciliter [0.05 mmol per liter]) in the icosapent ethyl group and an increase of 10.2% (7.0 mg per deciliter [0.18 mmol per liter]) in the placebo group — a 6.6% (5.0 mg per deciliter [0.13 mmol per liter]) lower increase with icosapent ethyl than with placebo (P<0.001). The results with respect to levels of EPA and lipid, lipoprotein, and inflammatory biomarkers are provided in Table S4 in the Supplementary Appendix.

CLINICAL END POINTS

A total of 1606 adjudicated primary end-point events occurred. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001), an absolute between-group difference of 4.8 percentage points (95% CI, 3.1 to 6.5); the number needed to treat to avoid one primary end-point event was 21 (95% CI, 15 to 33) over a median follow-up of 4.9 years.[23,24] The event curves based on a Kaplan–Meier analysis of the primary efficacy end point are provided in Figure 1A. The results of time-to-event analyses of each component of the primary end point are provided in Figure S3 in the Supplementary Appendix. A key secondary efficacy end-point event (Fig. 1B) occurred in 11.2% of the patients in the icosapent ethyl group, as compared with 14.8% of the patients in the placebo group (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001), corresponding to an absolute between-group difference of 3.6 percentage points (95% CI, 2.1 to 5.0); the number needed to treat to avoid one key secondary end-

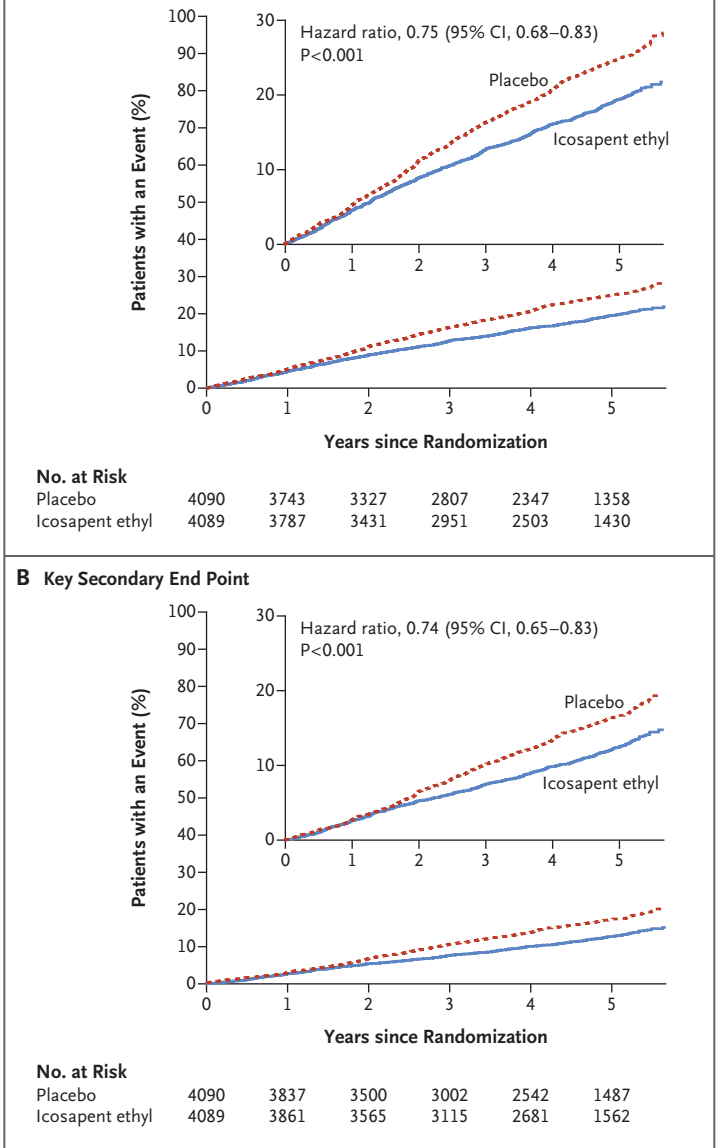

Figure 1. Cumulative Incidence of Cardiovascular Events.

Panel A shows the Kaplan–Meier event curves for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. Panel B shows the Kaplan–Meier event curves for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the two trial groups, in a time-to-event analysis. In each panel, the inset shows the same data on an expanded y axis. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	
Risk stratum				0.14
Secondary-prevention cohort	559/2892 (19.3)	738/2893 (25.5)	0.73 (0.65–0.81)	
Primary-prevention cohort	146/1197 (12.2)	163/1197 (13.6)	0.88 (0.70–1.10)	
Region				0.30
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	551/2906 (19.0)	713/2905 (24.5)	0.74 (0.66–0.83)	
Eastern Europe	143/1053 (13.6)	167/1053 (15.9)	0.84 (0.67–1.05)	
Asia–Pacific	11/130 (8.5)	21/132 (15.9)	0.49 (0.24–1.02)	
Ezetimibe use				0.64
No	649/3827 (17.0)	834/3828 (21.8)	0.75 (0.67–0.83)	
Yes	56/262 (21.4)	67/262 (25.6)	0.82 (0.57–1.16)	
Sex				0.33
Male	551/2927 (18.8)	715/2895 (24.7)	0.73 (0.65–0.82)	
Female	154/1162 (13.3)	186/1195 (15.6)	0.82 (0.66–1.01)	
Race				0.18
White	646/3691 (17.5)	812/3688 (22.0)	0.77 (0.69–0.85)	
Other	59/398 (14.8)	89/401 (22.2)	0.60 (0.43–0.83)	
Age				0.004
<65 yr	322/2232 (14.4)	460/2184 (21.1)	0.65 (0.56–0.75)	
≥65 yr	383/1857 (20.6)	441/1906 (23.1)	0.87 (0.76–1.00)	
From the United States				0.14
Yes	281/1548 (18.2)	394/1598 (24.7)	0.69 (0.59–0.80)	
No	424/2541 (16.7)	507/2492 (20.3)	0.80 (0.71–0.91)	
Diabetes at baseline				0.56
Yes	433/2394 (18.1)	536/2393 (22.4)	0.77 (0.68–0.87)	
No	272/1695 (16.0)	365/1694 (21.5)	0.73 (0.62–0.85)	
Baseline estimated GFR				0.41
<60 ml/min/1.73 m^2	197/905 (21.8)	263/911 (28.9)	0.71 (0.59–0.85)	
≥60 to <90 ml/min/1.73 m^2	380/2217 (17.1)	468/2238 (20.9)	0.80 (0.70–0.92)	
≥90 ml/min/1.73 m^2	128/963 (13.3)	170/939 (18.1)	0.70 (0.56–0.89)	
Baseline triglycerides				0.45
≥200 mg/dl	430/2481 (17.3)	559/2469 (22.6)	0.73 (0.64–0.83)	
<200 mg/dl	275/1605 (17.1)	342/1620 (21.1)	0.79 (0.67–0.93)	
Baseline triglycerides				0.83
≥150 mg/dl	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68–0.83)	
<150 mg/dl	65/412 (15.8)	90/429 (21.0)	0.79 (0.57–1.09)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.04
Yes	149/823 (18.1)	214/794 (27.0)	0.62 (0.51–0.77)	
No	554/3258 (17.0)	687/3293 (20.9)	0.79 (0.71–0.88)	
Baseline statin intensity				0.12
High	232/1290 (18.0)	310/1226 (25.3)	0.69 (0.58–0.82)	
Moderate	424/2533 (16.7)	543/2575 (21.1)	0.76 (0.67–0.86)	
Low	48/254 (18.9)	45/267 (16.9)	1.12 (0.74–1.69)	
Baseline LDL cholesterol (derived) in thirds				0.62
≤67 mg/dl	244/1481 (16.5)	302/1386 (21.8)	0.72 (0.61–0.85)	
>67 to ≤84 mg/dl	248/1347 (18.4)	307/1364 (22.5)	0.81 (0.68–0.96)	
>84 mg/dl	213/1258 (16.9)	292/1339 (21.8)	0.74 (0.62–0.89)	
Baseline high-sensitivity CRP				0.07
≤2 mg/liter	288/1919 (15.0)	407/1942 (21.0)	0.68 (0.58–0.79)	
>2 mg/liter	417/2167 (19.2)	494/2147 (23.0)	0.81 (0.71–0.93)	

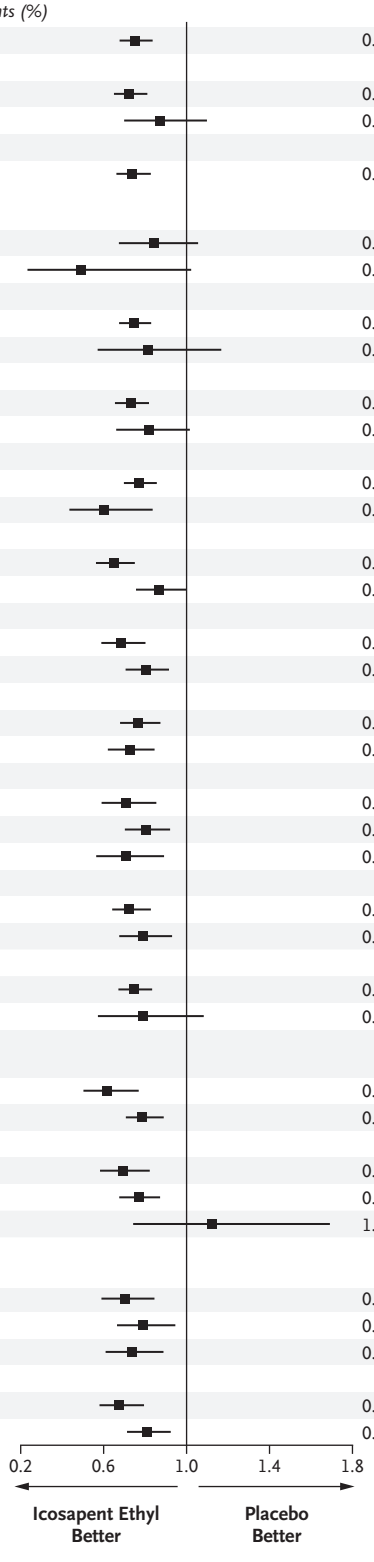

Figure 2 (facing page). Primary Efficacy Composite End Point in Selected Prespecified Subgroups.

Shown are the hazard ratios and 95% confidence intervals for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, as assessed in a time-to-event analysis, in selected prespecified subgroups of the intention-to-treat population (all patients who underwent randomization). The confidence intervals shown for the subgroup analyses have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible. Race was reported by the investigators. Eastern European region includes Poland, Romania, Russia, and Ukraine, and Asia–Pacific region includes India. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. CRP denotes C-reactive protein, GFR glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein. The LDL cholesterol value obtained by means of preparative ultracentrifugation was used. If the preparative ultracentrifugation value was missing, the LDL cholesterol value measured by another method was used in the following order of priority: the nonmissing value obtained by means of direct measurements of LDL cholesterol, the value derived with the use of the Friedewald equation, and the value derived with the use of the calculation published by Johns Hopkins University investigators.[22]

point event was 28 (95% CI, 20 to 47) over a median follow-up 4.9 years.[23,24]

The rates of the primary and key secondary efficacy end points in selected prespecified subgroups are provided in Figures 2 and 3; the findings show a consistent benefit with icosapent ethyl. Baseline triglyceride levels (≥150 vs. <150 mg per deciliter or ≥200 or <200 mg per deciliter) had no influence on the primary or key secondary efficacy end points (Figs. 2 and 3). The attainment of triglyceride levels of 150 mg per deciliter or higher or below 150 mg per deciliter at 1 year after randomization also had no influence on the efficacy of icosapent ethyl as compared with placebo with respect to the primary or key secondary efficacy end point (Fig. S4 in the Supplementary Appendix). In a post hoc analysis, we found no substantial difference in the benefit of icosapent ethyl as compared with placebo with respect to the primary end point according to whether the patients who received placebo had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels.

In the prespecified hierarchical testing of end points (Fig. 4), the rates of all individual and composite ischemic end points (except for death from any cause — the last secondary end point in the hierarchy) were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). The rate of death from any cause was 6.7% in the icosapent ethyl group and 7.6% in the placebo group (hazard ratio, 0.87; 95% CI, 0.74 to 1.02). The results for selected prespecified tertiary end points, which were not adjusted for multiple comparisons, are provided in Table S3 in the Supplementary Appendix. Among these results, the rates of adjudicated sudden cardiac death were 1.5% in the icosapent ethyl group and 2.1% in the placebo group (hazard ratio, 0.69; 95% CI, 0.50 to 0.96), and the rates of cardiac arrest were 0.5% and 1.0%, respectively (hazard ratio, 0.52; 95% CI, 0.31 to 0.86).

SAFETY AND ADVERSE EVENTS

The overall rates of adverse events that occurred while the patients were in the trial and the rates of serious adverse events leading to discontinuation of the trial drug or placebo did not differ significantly between the trial groups (Table S5 in the Supplementary Appendix). The only serious adverse event that occurred at a frequency of at least 2% was pneumonia (2.6% in the icosapent ethyl group and 2.9% in the placebo group, P=0.42). Adverse events that occurred in at least 5% of patients are reported in Table S6 in the Supplementary Appendix. The rate of atrial fibrillation was significantly higher in the icosapent ethyl group than in the placebo group (5.3% vs. 3.9%), as was the rate of peripheral edema (6.5% vs. 5.0%), but the rate of anemia was significantly lower in the icosapent ethyl group than in the placebo group (4.7% vs. 5.8%), as were the rates of diarrhea (9.0% vs. 11.1%) and gastrointestinal adverse events (33.0% vs. 35.1%) (Table S7 in the Supplementary Appendix). The rate of the prespecified adjudicated tertiary end point of heart failure did not differ significantly between the icosapent ethyl group and the placebo group (4.1% and 4.3%, respectively). The rate of the prespecified adjudicated tertiary end point of hospitalization for atrial fibrillation or flutter was significantly higher in the icosapent ethyl group than in the placebo group (3.1% vs. 2.1%, P=0.004). The overall rates of serious adverse bleeding

Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65–0.83)	
Risk stratum				0.41
Secondary-prevention cohort	361/2892 (12.5)	489/2893 (16.9)	0.72 (0.63–0.82)	
Primary-prevention cohort	98/1197 (8.2)	117/1197 (9.8)	0.81 (0.62–1.06)	
Region				0.54
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	358/2906 (12.3)	473/2905 (16.3)	0.73 (0.64–0.84)	
Eastern European	93/1053 (8.8)	117/1053 (11.1)	0.78 (0.59–1.02)	
Asia–Pacific	8/130 (6.2)	16/132 (12.1)	0.47 (0.20–1.10)	
Ezetimibe use				0.46
No	426/3827 (11.1)	569/3828 (14.9)	0.73 (0.64–0.82)	
Yes	33/262 (12.6)	37/262 (14.1)	0.87 (0.54–1.39)	
Sex				0.44
Male	353/2927 (12.1)	474/2895 (16.4)	0.72 (0.62–0.82)	
Female	106/1162 (9.1)	132/1195 (11.0)	0.80 (0.62–1.03)	
Race				0.13
White	418/3691 (11.3)	538/3688 (14.6)	0.76 (0.67–0.86)	
Other	41/398 (10.3)	68/401 (17.0)	0.55 (0.38–0.82)	
Age				0.06
<65 yr	200/2232 (9.0)	290/2184 (13.3)	0.65 (0.54–0.78)	
≥65 yr	259/1857 (13.9)	316/1906 (16.6)	0.82 (0.70–0.97)	
From the United States				0.38
Yes	187/1548 (12.1)	266/1598 (16.6)	0.69 (0.57–0.83)	
No	272/2541 (10.7)	340/2492 (13.6)	0.77 (0.66–0.91)	
Baseline diabetes				0.29
Yes	286/2394 (11.9)	391/2393 (16.3)	0.70 (0.60–0.81)	
No	173/1695 (10.2)	215/1694 (12.7)	0.80 (0.65–0.98)	
Baseline estimated GFR				0.77
<60 ml/min/1.73 m^2	152/905 (16.8)	205/911 (22.5)	0.71 (0.57–0.88)	
≥60 to <90 ml/min/1.73 m^2	229/2217 (10.3)	296/2238 (13.2)	0.77 (0.64–0.91)	
≥90 ml/min/1.73 m^2	78/963 (8.1)	105/939 (11.2)	0.70 (0.52–0.94)	
Baseline triglycerides				0.62
≥200 mg/dl	290/2481 (11.7)	371/2469 (15.0)	0.75 (0.65–0.88)	
<200 mg/dl	169/1605 (10.5)	235/1620 (14.5)	0.71 (0.58–0.86)	
Baseline triglycerides				0.68
≥150 mg/dl	421/3674 (11.5)	546/3660 (14.9)	0.74 (0.65–0.84)	
<150 mg/dl	38/412 (9.2)	60/429 (14.0)	0.66 (0.44–0.99)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.50
Yes	101/823 (12.3)	136/794 (17.1)	0.68 (0.53–0.88)	
No	356/3258 (10.9)	470/3293 (14.3)	0.75 (0.65–0.86)	
Baseline statin intensity				0.10
High	151/1290 (11.7)	210/1226 (17.1)	0.66 (0.54–0.82)	
Moderate	270/2533 (10.7)	361/2575 (14.0)	0.74 (0.63–0.87)	
Low	37/254 (14.6)	32/267 (12.0)	1.20 (0.74–1.93)	
Baseline LDL cholesterol (derived) in thirds				0.97
≤67 mg/dl	157/1481 (10.6)	196/1386 (14.1)	0.73 (0.59–0.90)	
>67 to ≤84 mg/dl	157/1347 (11.7)	208/1364 (15.2)	0.75 (0.61–0.93)	
>84 mg/dl	145/1258 (11.5)	202/1339 (15.1)	0.74 (0.60–0.91)	
Baseline hsCRP				0.97
≤2 mg/liter	183/1919 (9.5)	245/1942 (12.6)	0.73 (0.61–0.89)	
>2 mg/liter	276/2167 (12.7)	361/2147 (16.8)	0.73 (0.63–0.86)	

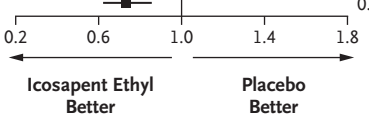

Figure 3 (facing page). Key Secondary Efficacy Composite End Point in Selected Prespecified Subgroups.

Shown are the hazard ratios and 95% confidence intervals for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, as assessed in a time-to-event analysis, in selected prespecified subgroups of the intention-to-treat population. The confidence intervals shown for the subgroup analyses have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.

events that occurred while the patients were in the trial were 2.7% in the icosapent ethyl group and 2.1% in the placebo group (P=0.06), although there were no fatal bleeding events in either group; there were no significant differences between the icosapent ethyl group and the placebo group in the rates of adjudicated hemorrhagic stroke (0.3% vs. 0.2%, P=0.55), serious central nervous system bleeding (0.3% vs. 0.2%, P=0.42), or gastrointestinal bleeding (1.5% vs. 1.1%, P=0.15) (Table S8 in the Supplementary Appendix).

DISCUSSION

In REDUCE-IT, the risk of the primary composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, assessed in a time-to-event analysis, was significantly lower, by 25%, among the patients who received 2 g of icosapent ethyl twice daily than among those who received placebo, corresponding to an absolute between-group difference of 4.8 percentage points in the rate of the end point and a number needed to treat of 21. The risk of the key secondary composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis was also significantly lower, by 26%, in the icosapent ethyl group than in the placebo group, corresponding to an absolute between-group difference of 3.6 percentage points in the rate of the end point and a number needed to treat of 28. Prespecified hierarchical testing of other secondary end points revealed that the risks of a variety of fatal and nonfatal ischemic events were lower in the icosapent ethyl group than in the placebo group, including a 20% lower risk of cardiovascular death. The benefits were observed against a background of appropriate statin use among patients who had a median LDL cholesterol level of 75.0 mg per deciliter at baseline.

The overall rates of adverse events were similar in the trial groups. Serious adverse events related to bleeding occurred in more patients in the icosapent ethyl group than in the placebo group, although the overall rates were low; there were no fatal bleeding events in either group, and the rates of adjudicated hemorrhagic stroke, serious central nervous system bleeding, and serious gastrointestinal bleeding were not significantly higher in the icosapent ethyl group than in the placebo group. The rate of hospitalization for atrial fibrillation or flutter was significantly higher in the icosapent ethyl group than in the placebo group, although the rates were low. The rates of adverse events and serious adverse events leading to discontinuation of trial drug were similar in the two groups.

The results of REDUCE-IT stand apart from the negative findings of several contemporary trials of other agents that also lower triglyceride levels, including other n–3 fatty acids, extended-release niacin, fenofibrate, and cholesteryl ester transfer protein inhibitors.[10-13] It is not known whether the lack of benefit from n–3 fatty acids in previous trials may be attributable to the low dose or to the low ratio of EPA to docosahexaenoic acid (DHA).[12,13] Both the formulation (a highly purified and stable EPA ethyl ester) and dose (total daily dose of 4 g) used in REDUCE-IT were different from those in previous outcome trials of n–3 fatty acids. JELIS, which compared a combination of statin therapy and pure EPA with statin therapy alone, showed that the risk of ischemic events was significantly lower in the group that received the combination treatment than in the group that received statin therapy alone.[14] Although the dose of EPA administered in JELIS (1.8 g daily) was lower than the EPA-equivalent dose used in REDUCE-IT (4 g daily), it resulted in a plasma EPA level (170 μg per milliliter in a Japanese population) similar to that attained in a previous 12-week lipid study in which a total daily dose of 4 g of icosapent ethyl was used in a Western population (183 μg per milliliter)[25,26] and similar to that attained in the current trial. However, unlike the current trial, JELIS included an open-label design without a placebo group, used a low-intensity statin, and was conducted in a single country; patients also had higher levels of LDL cholesterol at baseline (182 mg per

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—

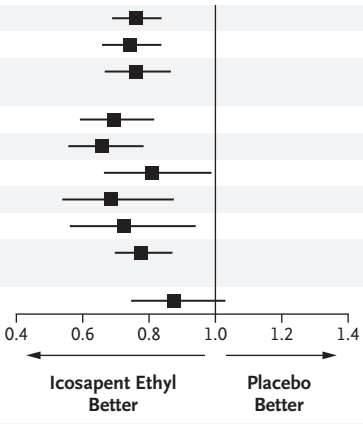

Figure 4. Hierarchical Testing of End Points.

Shown is the prespecified plan for hierarchical testing of end points. The rates of all end points up to death from any cause were significantly lower in the icosapent ethyl group than in the placebo group.

deciliter [4.71 mmol per liter] before initiation of statin therapy) and lower baseline triglyceride values (151 mg per deciliter [1.70 mmol per liter]) than the patients in REDUCE-IT.

Metabolic data provide evidence that icosapent ethyl–based formulations do not raise LDL cholesterol levels, whereas DHA-based formulations do.[27] The results of the current trial should not be generalized to other n–3 fatty acid preparations — in particular, dietary-supplement preparations of n–3 fatty acid mixtures, which are variable and unregulated and which have not been shown to have clinical benefit.

A triglyceride level of 150 mg per deciliter or higher was an initial inclusion criterion in REDUCE-IT (although the required level was subsequently changed to ≥200 mg per deciliter); however, owing to allowance for variability in these levels, 10.3% of enrolled patients had triglyceride levels lower than 150 mg per deciliter at baseline. The observed cardiovascular benefits were similar across baseline levels of triglycerides (<150, ≥150 to <200, and ≥200 mg per deciliter). In addition, the significantly lower risk of major adverse cardiovascular events with icosapent ethyl than with placebo appeared to occur irrespective of the attained triglyceride level at 1 year (≥150 or <150 mg per deciliter), which suggests that the cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level. These observations suggest that at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events than that with placebo may be explained by metabolic effects other than a reduction of triglyceride levels.[28]

Mechanisms responsible for the benefit of icosapent ethyl observed in REDUCE-IT are currently not known. The timing of the divergence of the Kaplan–Meier event curves suggests a delayed onset of benefit, which may reflect the time that is needed for a benefit from a reduction in triglyceride levels to be realized or may indicate that other mechanisms are involved. The modestly higher rate of bleeding events with icosapent ethyl suggests that there may be an antithrombotic mechanism of action. However, it is unlikely that an antithrombotic effect would reduce the rate of elective revascularization. Also, if the full explanation involved an antiplatelet or anticoagulant effect, one might expect a large increase in the rate of major bleeding events, which was not observed.[29] It is possible that membrane-stabilizing effects could explain part of the benefit.[20,21,30] Stabilization or regression of coronary plaque (or both) may also play a part.[19,31] Our observation of lower rates of cardiac arrest and sudden cardiac death with icosapent ethyl than with placebo in the current trial might support that mechanism, although these findings should be viewed as exploratory. It is also possible that the difference in high-sensitivity C-reactive protein level observed in REDUCE-IT may contribute to the benefit; the Canakinumab Antiinflam-

matory Thrombosis Outcome Study (CANTOS) showed a significant reduction in the risk of ischemic events with treatment targeted at inflammation.[32-35] Blood samples obtained during REDUCE-IT have been banked for biomarker and genetic analyses that may provide more information regarding mechanisms of action.

Ongoing trials of moderate-to-high doses of pure EPA ethyl ester will provide further information on the effects of these agents.[10,36] These trials include the Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and EPA (RESPECT-EPA; UMIN Clinical Trials Registry number, UMIN000012069), a secondary prevention outcomes trial involving statin-treated patients in Japan, and the Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE; ClinicalTrials.gov number, NCT02926027), which is examining changes in coronary plaque over 9 to 18 months.

Our trial has certain limitations. First, at the time the trial was designed, there was relatively little use of ezetimibe or data supporting its use.[37] However, subgroup analyses do not suggest a differential benefit for patients taking ezetimibe. Similarly, proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors were not available for the majority of the patients in the trial.[38] Second, if mineral oil in the placebo affected statin absorption in some patients, this might have contributed to differences in outcomes between the groups. However, the relatively small differences in LDL cholesterol levels between the groups would not be likely to explain the 25% lower risk observed with icosapent ethyl, and a post hoc analysis suggested a similar lower risk regardless of whether there was an increase in LDL cholesterol level among the patients in the placebo group. Although JELIS was designed as an open-label study that did not use a mineral oil placebo, it showed a 19% lower risk of ischemic events with statin therapy plus EPA than with statin therapy alone.

In conclusion, among patients with elevated triglyceride levels who were receiving statin therapy, the risk of major ischemic events, including cardiovascular death, was significantly lower with 2 g of icosapent ethyl twice daily (total daily dose, 4 g) than with placebo.

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