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Prevention of Cardiovascular Events and Mortality With Icosapent Ethyl in Patients With Prior Myocardial Infarction

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ABSTRACT

BACKGROUND REDUCE-IT was a double-blind trial that randomized 8,179 statin-treated patients with controlled low-density lipoprotein cholesterol and moderately elevated triglycerides to icosapent ethyl (IPE) or placebo. There was a significant reduction in the primary endpoint, including death from cardiovascular (CV) causes. The specific impact of IPE among patients with prior myocardial infarction (MI) was unknown.

OBJECTIVES Our goal was to examine the benefit of IPE on ischemic events among patients with prior MI in REDUCE-IT.

METHODS We performed post hoc analyses of patients with prior MI. The primary endpoint was CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina. The key secondary endpoint was CV death, MI, or stroke.

RESULTS A total of 3,693 patients had a history of prior MI. The primary endpoint was reduced from 26.1% to 20.2% with IPE vs placebo; HR: 0.74 (95% CI: 0.65-0.85; $P = 0.00001$). The key secondary endpoint was reduced from 18.0% to 13.3%; HR: 0.71 (95% CI: 0.61-0.84; $P = 0.00006$). There was also a significant 35% relative risk reduction in total ischemic events ($P = 0.0000001$), a 34% reduction in MI ($P = 0.00009$), a 30% reduction in CV death ($P = 0.01$), and a 20% lower rate of all-cause mortality ($P = 0.054$), although there was a slight increase in atrial fibrillation. Sudden cardiac death and cardiac arrest were also significantly reduced by 40% and 56%, respectively.

CONCLUSIONS Patients with a history of prior MI in REDUCE-IT treated with IPE demonstrated large and significant relative and absolute risk reductions in ischemic events, including CV death. (A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. [REDUCE-IT]; NCT01492361) (J Am Coll Cardiol 2022;79:1660–1671) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Prior myocardial infarction (MI) is strongly associated with recurrent ischemic events.[1] Patients with elevated low-density lipoprotein cholesterol (LDL-C) and/or triglyceride levels are at especially high risk for repeat major adverse cardiac events.[2-5] For these patients, the American Heart Association/American College of Cardiology Multisociety Guideline on the Management of Blood Cholesterol recommends intensification of cholesterol pharmacotherapy with a target LDL-C of 70 mg/dL, but there have been limited recommendations for goal triglyceride levels.[6-8] A myriad of therapeutic options have been developed to achieve lower LDL-C and triglyceride levels, including HMG-CoA reductase inhibitors, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors.[9,10] Although effective, residual cardiovascular (CV) risk persists.[6,11,12]

SEE PAGE 1672

Recently, icosapent ethyl (IPE) has emerged as an important additive agent. IPE is an ethyl ester of the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) with pharmacological properties that reduce plaque volume, mitigate inflammation, promote nitric oxide release, and encourage membrane stabilization.[13-21] The REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl [IPE]-Intervention Trial) was a multinational, double-blind, randomized, placebo-controlled trial that found significant reductions in important ischemic events with IPE.[2,22-26] Specifically, treatment with IPE led to a lower incidence of the primary endpoint (composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization), the key secondary endpoint (composite of CV death, nonfatal MI, or nonfatal stroke), and individual components of those endpoints.[27-29] The specific impact of IPE among statin-treated patients with elevated triglycerides and prior MI was unknown.

In this subgroup analysis of the REDUCE-IT trial, our goal was to examine the effect of IPE on the occurrence of ischemic events among patients with prior MI and whether a history of revascularization affects the degree of benefit.

METHODS

STUDY DESIGN AND CLINICAL ENDPOINTS. The REDUCE-IT trial was a phase 3b, double-blind, placebo-controlled trial that randomized 8,179 statin-treated patients with either established CV disease or diabetes plus other risk factors, each with controlled LDL-C and moderately elevated triglycerides to either 4 g IPE daily (2 g twice daily) or matching placebo.[2] The trial was approved by the central Institutional Review Board or local ethics committees at each participating site. The primary endpoint was the composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. The key secondary endpoint was the composite of CV death, nonfatal MI, or nonfatal stroke. Other endpoints included individual CV death, MI, stroke, coronary revascularization, and hospitalization for unstable angina. Sudden cardiac death and cardiac arrest were also prespecified, blindly adjudicated endpoints. Patients with prior MI were included among those enrolled with established CV disease. Additional specifics regarding the trial methods have previously been published.[2,30]

STATISTICAL ANALYSIS. Post hoc analyses were performed to evaluate the effect of IPE on clinical outcomes among 3,693 patients identified with prior MI. Prespecified analyses included nonfatal and silent MI. All efficacy analyses were performed according to the intention-to-treat principle. Time-to-event outcomes were estimated by Kaplan-Meier analysis and compared using the log-rank test. HRs and 95% CIs were generated using a Cox proportional hazards model computed to determine the risk of the primary and key secondary endpoints according to the use of IPE vs placebo. The model was stratified by the 3 randomization factors of CV risk category (established CV disease or diabetes plus risk factors), geographic region, and baseline ezetimibe use. The *P* values and 95% CIs presented in this post hoc subgroup analysis were not adjusted for multiplicity. All tests were based on 2-sided 5% significance level. Relative risk reduction (RRR) was calculated for further assessment of risk between the IPE and placebo treatment groups. Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. Among the 8,179 patients enrolled in the REDUCE-IT

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CV = cardiovascular

EPA = eicosapentaenoic acid

IPE = icosapent ethyl

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

PCI = percutaneous coronary intervention

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics in Patients With Prior MI

	Icosapent Ethyl (N = 1,870)	Placebo (N = 1,823)
Age, y[a]		
Mean ± SD	62.6 ± 8.67	62.5 ± 8.70
Median (Q1-Q3)	63.0 (56.0-69.0)	63.0 (56.0-69.0)
Min, max	45.0, 88.0	45.0, 91.0
Sex		
Male	1,517 (81.1)	1,465 (80.4)
Female	353 (18.9)	358 (19.6)
Race		
White	1,720 (92.0)	1,688 (92.6)
Non-White	150 (8.0)	135 (7.4)
BMI, kg/m^2		
n	1,868	1,816
Mean ± SD	30.7 ± 4.82	30.9 ± 4.94
Median (Q1-Q3)	30.3 (27.5-33.4)	30.3 (27.4-33.7)
Min, max	18.3, 59.9	19.1, 55.7
Geographic region		
Westernized	1,274 (68.1)	1,224 (67.1)
Non-Westernized	596 (31.9)	599 (32.9)
Ezetimibe use		
No	1,737 (92.9)	1,688 (92.6)
Yes	133 (7.1)	135 (7.4)
Statin intensity		
Low	67 (3.6)	67 (3.7)
Moderate	1,109 (59.3)	1,083 (59.4)
High	692 (37.0)	663 (36.4)
Missing	2 (0.1)	10 (0.5)
Diabetes		
No diabetes at baseline	1,125 (60.2)	1,084 (59.5)
Type 1	13 (0.7)	13 (0.7)
Type 2	731 (39.1)	725 (39.8)
Type 1 and type 2	1 (0.1)	0 (0.0)
Missing	0 (0.0)	1 (0.1)
hsCRP, mg/L	2.0 (1.0-4.2)	2.0 (1.0-4.0)
Triglycerides, mg/dL	219.5 (179.5-277.0)	220.0 (178.5-278.0)
HDL-C, mg/dL	39.0 (34.0-45.0)	39.0 (34.0-45.0)
LDL-C, mg/dL	75.0 (63.0-89.0)	75.0 (63.0-89.0)
Triglycerides category		
<150 mg/dL	173 (9.3)	183 (10.0)
150-<200 mg/dL	537 (28.7)	509 (27.9)
≥200 mg/dL	1,158 (61.9)	1,130 (62.0)
Missing	2 (0.1)	1 (0.1)
Triglycerides ≥200 mg/dL and HDL-C ≤35 mg/dL	429 (22.9)	417 (22.9)
EPA, μg/mL	28.1 (18.2-42.4)	27.3 (17.2-41.6)

Values are n (%) or median (Q1-Q3), unless otherwise indicated. There were no significant between-group differences in baseline characteristics in patients with prior myocardial infarction (MI). [a]Age (y) is at randomization.
BMI = body mass index; EPA = eicosapentaenoic acid; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

trial, 3,693 (45.2%) had a prior MI within a median of 4.8 years before randomization. Baseline characteristics of patients with prior MI consisted of a median age of 63.0 years, 711 (19.3%) women, and 1,483 (40.2%) with diabetes (Table 1). The median baseline LDL-C level was 75.0 mg/dL (IQR: 63.0-89.0 mg/dL), the median high-density lipoprotein cholesterol level was 39.0 mg/dL (IQR: 34.0-45.0 mg/dL), and the median triglyceride level was 220 mg/dL (IQR: 179.0-277.5 mg/dL). Baseline medication use was similar between groups, with high rates of use of dual antiplatelet therapy, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and beta-blockers (Table 2).

Rates of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) at baseline were also similar among patients with prior MI randomized to either treatment arm. Among patients with prior MI, 81.6% in the IPE treatment arm had previously undergone PCI compared with 78.7% in the placebo arm, and 34.6% in the IPE treatment arm had previously undergone CABG compared with 36.1% in the placebo arm.

CLINICAL OUTCOMES. Median time to follow-up was 4.8 years (IQR: 3.2-5.3 years). Maximum follow-up was 6.2 years. In patients with a prior MI, IPE significantly reduced the incidence of the primary composite endpoint from 26.1% to 20.2% compared with placebo (HR: 0.74; 95% CI: 0.65-0.85; $P = 0.00001$) (Central Illustration). The key secondary composite endpoint was reduced from 18.0% to 13.3% (HR: 0.71; 95% CI: 0.61-0.84; $P = 0.00006$) (Figures 1 and 2). These results equate to a 26% RRR in the primary composite endpoint and a 29% reduction in the key secondary composite endpoint, with absolute risk reductions of 5.9% and 4.7%, respectively.

Additional endpoints, including fatal or nonfatal MI, CV death, and fatal or nonfatal stroke showed similar reductions (Figures 2 and 3). There was a 34% RRR in fatal or nonfatal MI ($P = 0.00009$), a 30% RRR in CV death ($P = 0.01$), and a nonsignificant 21% RRR in fatal or nonfatal stroke, with absolute risk reductions of 3.7%, 1.9%, and 0.7% for fatal or nonfatal MI, CV death, and fatal or nonfatal stroke, respectively. Rates of sudden cardiac death (40% RRR; $P = 0.02$) and cardiac arrest (56% RRR; $P = 0.02$) were also significantly decreased (Figures 4 and 5). All-cause mortality was lower with IPE than placebo (7.3% vs 8.9%; HR: 0.80; 95% CI: 0.64-1.00; $P = 0.054$) (Figure 2).

In addition to significant reductions in time to first events, there were significant reductions in total ischemic events (first and subsequent) among patients with prior MI treated with IPE (Central Illustration, Figure 1). IPE resulted in a 35% RRR in total primary ischemic events ($P = 0.0000001$) and a 32% RRR in the total key secondary ischemic events ($P = 0.00005$) when compared with placebo. Laboratory markers of inflammation and hyperlipidemia were also lower when compared with baseline in both groups. Specifically, triglycerides, non-high-density

TABLE 2 Baseline Medications in Patients With Prior MI

Medication Taken at Baseline	Icosapent Ethyl (N = 1,870)	Placebo (N = 1,823)
Antidiabetes	638 (34.1)	628 (34.4)
Antihypertensive	1,813 (97.0)	1,771 (97.1)
Antiplatelet	1,690 (90.4)	1,645 (90.2)
1 antiplatelet	1,143 (61.1)	1,092 (59.9)
≥2 antiplatelets	547 (29.3)	553 (30.3)
Anticoagulant	197 (10.5)	178 (9.8)
Anticoagulant + antiplatelet	79 (4.2)	71 (3.9)
ACE inhibitor or ARB	1,449 (77.5)	1,448 (79.4)
ACEi	1,041 (55.7)	1,039 (57.0)
ARB	425 (22.7)	427 (23.4)
Beta-blocker	1,580 (84.5)	1,517 (83.2)

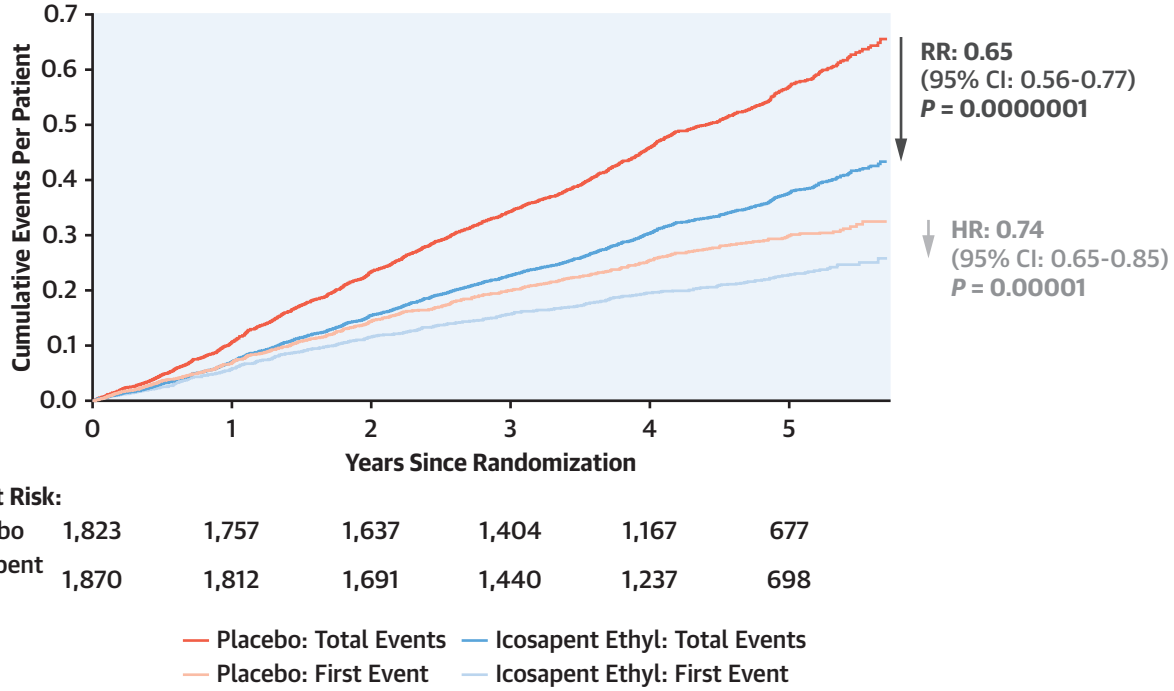
Values are n (%). There were no significant between-group differences in baseline characteristics in patients with prior myocardial infarction (MI).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

lipoprotein cholesterol, and hsCRP decreased by 13.1%, 7.8%, and 41.2%, respectively, at the end of the study among those treated with IPE vs placebo.

Interestingly, IPE led to reductions in the primary composite endpoint in patients regardless of whether they had experienced a prior MI (HR: 0.74; 95% CI: 0.65-0.85) or had atherosclerosis but not experienced a prior MI (HR: 0.69; 95% CI: 0.57-0.84) (P_{int} = 0.59) (Figure 6). When stratified by a history of coronary revascularization with PCI or CABG, patients with prior MI who did or did not have a history of prior coronary revascularization demonstrated consistent reductions in adverse CV outcomes (Figure 7).

The rate of positively adjudicated atrial fibrillation hospitalization was higher in the IPE treated patients with prior MI than in the placebo patients with prior MI (3.6% vs 2.2%; log-rank P = 0.01) (Supplemental Table 1). Among patients with atherosclerosis but without prior MI, the rate of positively adjudicated atrial fibrillation hospitalization was similar between the 2 groups (2.1% vs 2.2%) (Supplemental Table 2). The occurrence of heart failure was similar between

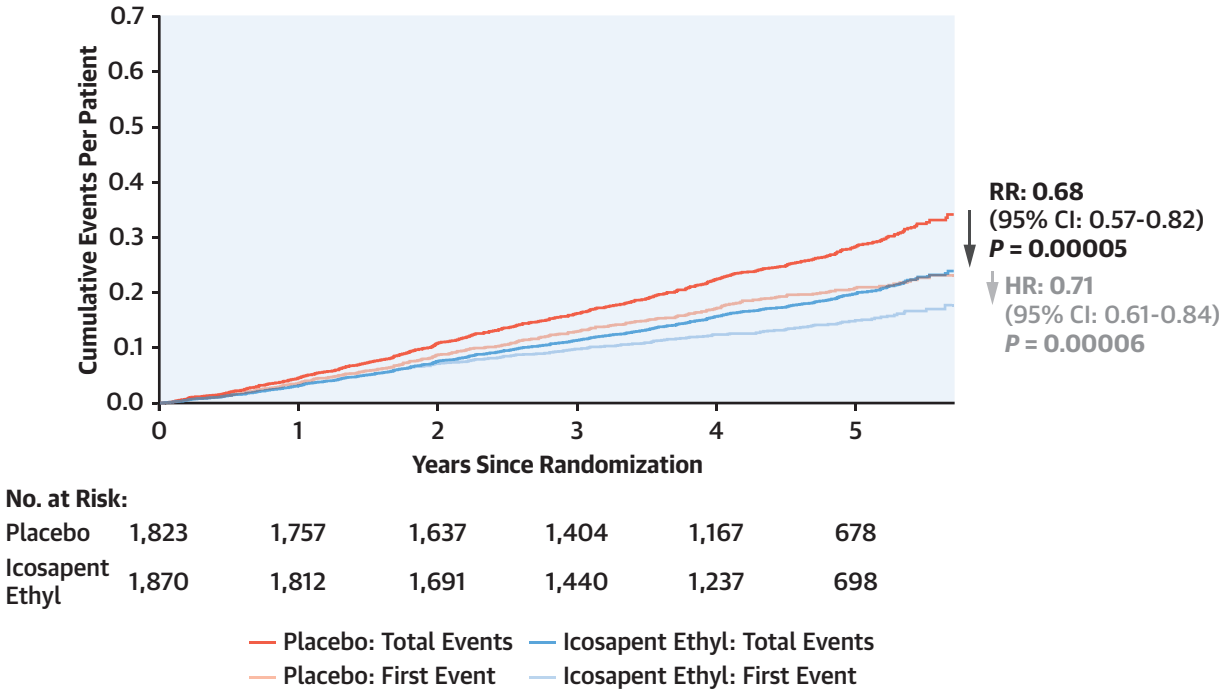
CENTRAL ILLUSTRATION Cumulative Incidence Curves of the Primary Composite Endpoint in Patients With Prior Myocardial Infarction



Gaba P, et al. J Am Coll Cardiol. 2022;79(17):1660-1671.

Compared with patients with prior myocardial infarction (MI) in the placebo arm, patients in the icosapent ethyl arm experienced significantly lower first and total composite of cardiovascular death, fatal and nonfatal MI (including silent MI), fatal and nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. Kaplan-Meier estimates were used to depict the cumulative incidence for first occurrence of the primary composite endpoint. The mean cumulative function was used to depict the cumulative incidence for total occurrence of the primary composite endpoint. No adjustments for multiple testing were applied. RR = rate ratio.

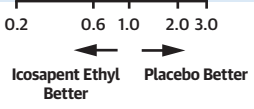
FIGURE 1 Cumulative Incidence Curves of the Key Secondary Composite Endpoint in Patients With Prior MI



Compared with patients with prior myocardial infarction (MI) in the placebo arm, patients in the icosapent ethyl arm experienced significantly lower first and total composite of cardiovascular death, fatal and nonfatal MI (including silent MI), or fatal and nonfatal stroke. Kaplan-Meier estimates were used to depict the cumulative incidence for first occurrence of the key secondary composite endpoint. The mean cumulative function was used to depict the cumulative incidence for total occurrence of the key secondary composite endpoint. No adjustments for multiple testing were applied. RR = rate ratio.

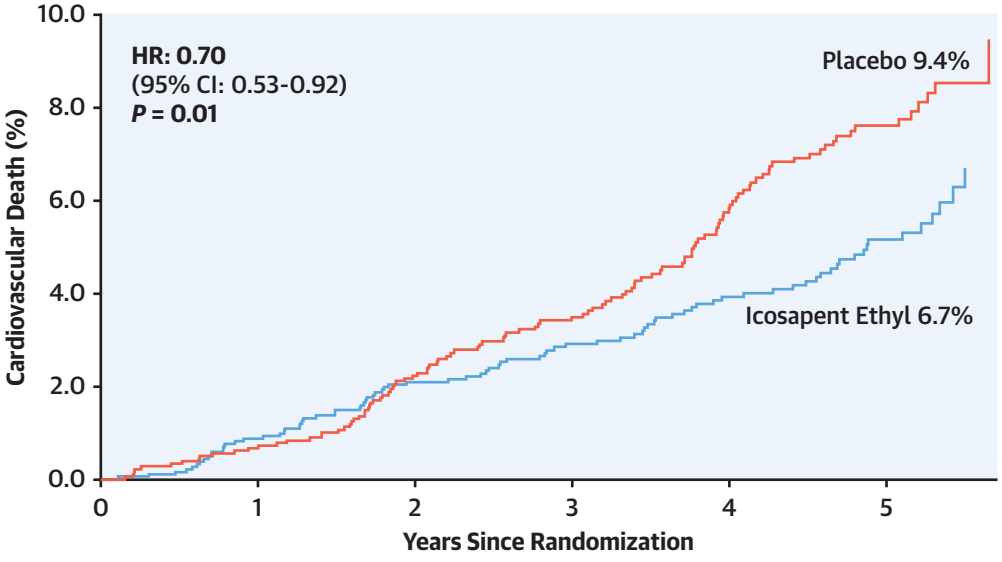
FIGURE 2 Primary and Secondary Endpoints in Patients With Prior MI

Endpoint	Icosapent Ethyl	Placebo	Icosapent Ethyl vs Placebo	*P* Value
	n/N (%)	*n/N (%)*	*Hazard Ratio (95% CI)*	
Primary Composite Endpoint	378/1,870 (20.2)	475/1,823 (26.1)	0.74 (0.65-0.85)	0.00001
Key Secondary Composite Endpoint	248/1,870 (13.3)	328/1,823 (18.0)	0.71 (0.61-0.84)	0.00006
Cardiovascular Death or Nonfatal Myocardial Infarction	215/1,870 (11.5)	285/1,823 (15.6)	0.71 (0.60-0.85)	0.0002
Fatal or Nonfatal Myocardial Infarction	147/1,870 (7.9)	211/1,823 (11.6)	0.66 (0.53-0.81)	0.00009
Urgent or Emergent Revascularization	124/1,870 (6.6)	188/1,823 (10.3)	0.62 (0.49-0.78)	0.00003
Cardiovascular Death	84/1,870 (4.5)	116/1,823 (6.4)	0.70 (0.53-0.92)	0.01
Hospitalization for Unstable Angina	65/1,870 (3.5)	99/1,823 (5.4)	0.63 (0.46-0.86)	0.003
Fatal or Nonfatal Stroke	51/1,870 (2.7)	62/1,823 (3.4)	0.79 (0.55-1.14)	0.21
Total Mortality / Nonfatal Myocardial Infarction / Nonfatal Stroke	292/1,870 (15.6)	367/1,823 (20.1)	0.75 (0.64-0.87)	0.0002
Total Mortality	136/1,870 (7.3)	163/1,823 (8.9)	0.80 (0.64-1.00)	0.054



Among patients with prior myocardial infarction (MI), the majority of clinical endpoints, including the individual endpoints of cardiovascular death, MI, stroke, coronary revascularization, or unstable angina requiring hospitalization, were consistently lower with icosapent ethyl treatment compared with placebo. No adjustments for multiple testing were applied.

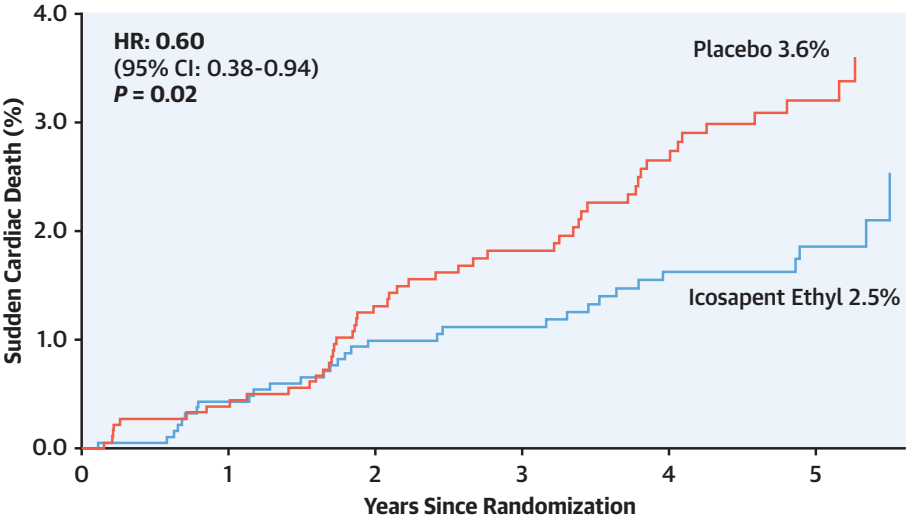
FIGURE 3 Cardiovascular Death in Patients With Prior MI



No. at Risk:						
Placebo	1,823	1,757	1,637	1,404	1,167	678
Icosapent Ethyl	1,870	1,812	1,691	1,440	1,237	698

Among patients with prior myocardial infarction (MI), cardiovascular death was significantly lower with icosapent ethyl treatment compared with placebo. No adjustments for multiple testing were applied.

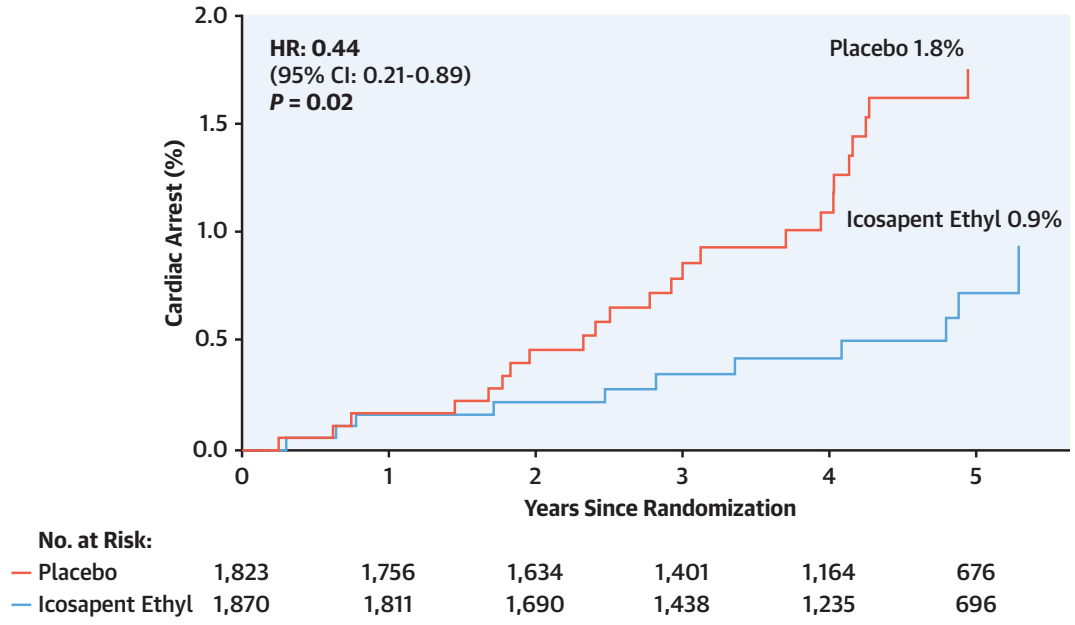
FIGURE 4 Sudden Cardiac Death in Patients With Prior MI



No. at Risk:						
Placebo	1,823	1,757	1,637	1,404	1,167	678
Icosapent Ethyl	1,870	1,812	1,691	1,440	1,236	698

Among patients with prior myocardial infarction (MI), sudden cardiac death was significantly lower with icosapent ethyl treatment compared with placebo. No adjustments for multiple testing were applied.

FIGURE 5 Cardiac Arrest in Patients With Prior MI



Among patients with prior myocardial infarction (MI), cardiac arrests were significantly lower with icosapent ethyl treatment compared with placebo. No adjustments for multiple testing were applied.

the 2 groups (4.9% vs 4.9%). The rate of bleeding was higher in the IPE treated patients with prior MI than in the placebo patients with prior MI (10.6% vs 8.7%; Fisher exact $P = 0.05$); no difference was observed in serious bleeding (2.7% vs 2.2%; Fisher exact $P = 0.46$) in patients with prior MI between the IPE treatment and placebo arms.

DISCUSSION

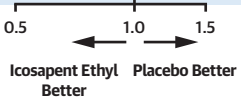
In this analysis of REDUCE-IT, among statin-treated patients with prior MI, controlled LDL-C, and moderately elevated triglycerides, we found significant reductions in adverse CV outcomes with IPE. The primary composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina was significantly lower in patients with prior MI who received IPE 4 g daily compared with those who received placebo, in keeping with the original trial results. IPE also led to significant reductions in the primary composite endpoint in patients with atherosclerosis without a prior MI. The key secondary endpoint of CV death, nonfatal MI, or nonfatal stroke was also significantly lower in patients with prior MI treated with IPE vs those treated with placebo, as were CV death, sudden cardiac death, and cardiac arrest.

Of note, the delayed divergence of the Kaplan-Meier curves for sudden cardiac death and cardiac arrest is likely explained by the slow but steady reduction in plaque volume, mitigation of inflammation, improvements in endothelial function, and membrane stabilization as has been demonstrated with EPA.[15-18]

When patients with prior MI were further stratified by a history of coronary revascularization, patients who did or did not have a history of prior coronary revascularization had similar reductions in the primary and key secondary endpoints. Rates of recurrent urgent or emergent revascularization were significantly lower in the IPE treatment arm, as previously demonstrated in the overall REDUCE-IT population.[31,32] The safety of IPE among patients with prior MI was consistent with the main study findings in the entire population, with increased rates of atrial fibrillation and of minor bleeding, although no significant increase in major bleeding despite a very high rate of use of antithrombotic therapy, including dual antiplatelet therapy and anticoagulation.[33,34] There were no differences in overall

FIGURE 6 Forest Plot of Primary and Secondary Endpoints by History of Prior MI in Patients With Established CV Risk

Endpoint	Icosapent Ethyl	Placebo	Icosapent Ethyl vs Placebo	Int. *P* Value
	n/N (%)	*n/N (%)*	*Hazard Ratio (95% CI)*	
Primary Composite Endpoint				0.59
Prior MI	378/1,870 (20.2)	475/1,823 (26.1)	0.74 (0.65-0.85)	
Without Prior MI	181/1,022 (17.7)	263/1,068 (24.6)	0.69 (0.57-0.84)	
Key Secondary Composite Endpoint				0.97
Prior MI	248/1,870 (13.3)	328/1,823 (18.0)	0.71 (0.61-0.84)	
Without Prior MI	113/1,022 (11.1)	161/1,068 (15.1)	0.72 (0.56-0.91)	
Cardiovascular Death or Nonfatal Myocardial Infarction				0.77
Prior MI	215/1,870 (11.5)	285/1,823 (15.6)	0.71 (0.60-0.85)	
Without Prior MI	95/1,022 (9.3)	131/1,068 (12.3)	0.75 (0.57-0.97)	
Fatal or Nonfatal Myocardial Infarction				0.83
Prior MI	147/1,870 (7.9)	211/1,823 (11.6)	0.66 (0.53-0.81)	
Without Prior MI	61/1,022 (6.0)	92/1,068 (8.6)	0.68 (0.50-0.95)	
Urgent or Emergent Revascularization				0.99
Prior MI	124/1,870 (6.6)	188/1,823 (10.3)	0.62 (0.49-0.78)	
Without Prior MI	54/1,022 (5.3)	89/1,068 (8.3)	0.61 (0.43-0.86)	
Cardiovascular Death				0.30
Prior MI	84/1,870 (4.5)	116/1,823 (6.4)	0.70 (0.53-0.92)	
Without Prior MI	46/1,022 (4.5)	53/1,068 (5.0)	0.91 (0.61-1.35)	
Hospitalization for Unstable Angina				0.84
Prior MI	65/1,870 (3.5)	99/1,823 (5.4)	0.63 (0.46-0.86)	
Without Prior MI	28/1,022 (2.7)	44/1,068 (4.1)	0.66 (0.41-1.06)	
Fatal or Nonfatal Stroke				0.90
Prior MI	51/1,870 (2.7)	62/1,823 (3.4)	0.79 (0.55-1.14)	
Without Prior MI	27/1,022 (2.6)	37/1,068 (3.5)	0.76 (0.46-1.24)	
Total Mortality / Nonfatal Myocardial Infarction / Nonfatal Stroke				0.71
Prior MI	292/1,870 (15.6)	367/1,823 (20.1)	0.75 (0.64-0.87)	
Without Prior MI	142/1,022 (13.9)	184/1,068 (17.2)	0.79 (0.63-0.98)	
Total Mortality				0.27
Prior MI	136/1,870 (7.3)	163/1,823 (8.9)	0.80 (0.64-1.00)	
Without Prior MI	76/1,022 (7.4)	79/1,068 (7.4)	1.01 (0.73-1.38)	



Among all patients, patients with prior myocardial infarction (MI) experienced more consistent lower incidence of adverse events with icosapent ethyl treatment compared with placebo. No adjustments for multiple testing were applied.

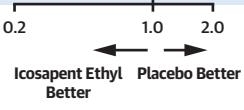
tolerability between prior MI patients treated with IPE vs placebo.

The rate of atrial fibrillation was slightly higher among patients treated with IPE vs placebo. Similar arrhythmogenic associations have been noted with other omega-3 fatty acid compounds in the VITAL (Vitamin D and Omega-3) trial and the STRENGTH (STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia) trial.[35,36] However, the mechanistic basis remains unclear. Experimental studies evaluating EPA (IPE is the ethyl ester of EPA) have illustrated its unique ability to stabilize cell membrane models and potentially reduce the occurrence of malignant ventricular arrhythmias.[37] Given these contradicting data, further prospective studies are needed to understand the relationship between IPE and increased atrial arrhythmias.

High-intensity statins, ezetimibe, and proprotein convertase subtilisin/kexin type-9 inhibitors have all been shown to reduce recurrent ischemic events in patients with prior MI.[10,38,39] Potent antithrombotic therapy also has an important role in patients with prior MI who are at low bleeding risk.[40-44] Now, the present analyses provide compelling data in support of an additional axis of risk reduction via IPE.[45,46] Prior studies have demonstrated the generalizability of the overall REDUCE-IT results.[42-44]

FIGURE 7 Primary and Secondary Endpoints by History of Prior Coronary Revascularization in Patients With Prior MI

Endpoint	Icosapent Ethyl	Placebo	Icosapent Ethyl vs Placebo	Int. *P* Value
	n/N (%)	*n/N (%)*	*Hazard Ratio (95% CI)*	
Primary Composite Endpoint	378/1,870 (20.2)	475/1,823 (26.1)	0.74 (0.65-0.85)	0.75
Prior Coronary Revascularization	305/1,469 (20.8)	384/1,423 (27.0)	0.73 (0.63-0.85)	
No Prior Revascularization	73/401 (18.2)	91/400 (22.8)	0.78 (0.57-1.06)	
Key Secondary Composite Endpoint	248/1,870 (13.3)	328/1,823 (18.0)	0.71 (0.61-0.84)	0.86
Prior Coronary Revascularization	196/1,469 (13.3)	255/1,423 (17.9)	0.72 (0.60-0.87)	
No Prior Revascularization	52/401 (13.0)	73/400 (18.3)	0.70 (0.49-1.00)	
Cardiovascular Death or Nonfatal Myocardial Infarction	215/1,870 (11.5)	285/1,823 (15.6)	0.71 (0.60-0.85)	0.89
Prior Coronary Revascularization	169/1,469 (11.5)	223/1,423 (15.7)	0.71 (0.58-0.86)	
No Prior Revascularization	46/401 (11.5)	62/400 (15.5)	0.73 (0.50-1.07)	
Fatal or Nonfatal Myocardial Infarction	147/1,870 (7.9)	211/1,823 (11.6)	0.66 (0.53-0.81)	0.83
Prior Coronary Revascularization	125/1,469 (8.5)	176/1,423 (12.4)	0.66 (0.53-0.83)	
No Prior Revascularization	22/401 (5.5)	35/400 (8.8)	0.62 (0.36-1.05)	
Urgent or Emergent Revascularization	124/1,870 (6.6)	188/1,823 (10.3)	0.62 (0.49-0.78)	0.70
Prior Coronary Revascularization	110/1,469 (7.5)	163/1,423 (11.5)	0.63 (0.49-0.80)	
No Prior Revascularization	14/401 (3.5)	25/400 (6.3)	0.53 (0.27-1.02)	
Cardiovascular Death	84/1,870 (4.5)	116/1,823 (6.4)	0.70 (0.53-0.92)	0.60
Prior Coronary Revascularization	55/1,469 (3.7)	79/1,423 (5.6)	0.66 (0.47-0.93)	
No Prior Revascularization	29/401 (7.2)	37/400 (9.3)	0.79 (0.48-1.28)	
Hospitalization for Unstable Angina	65/1,870 (3.5)	99/1,823 (5.4)	0.63 (0.46-0.86)	0.79
Prior Coronary Revascularization	57/1,469 (3.9)	88/1,423 (6.2)	0.61 (0.44-0.86)	
No Prior Revascularization	8/401 (2.0)	11/400 (2.8)	0.65 (0.26-1.63)	
Fatal or Nonfatal Stroke	51/1,870 (2.7)	62/1,823 (3.4)	0.79 (0.55-1.14)	0.87
Prior Coronary Revascularization	39/1,469 (2.7)	46/1,423 (3.2)	0.81 (0.53-1.24)	
No Prior Revascularization	12/401 (3.0)	16/400 (4.0)	0.76 (0.36-1.61)	
Total Mortality / Nonfatal Myocardial Infarction / Nonfatal Stroke	292/1,870 (15.6)	367/1,823 (20.1)	0.75 (0.64-0.87)	0.96
Prior Coronary Revascularization	233/1,469 (15.9)	290/1,423 (20.4)	0.75 (0.63-0.89)	
No Prior Revascularization	59/401 (14.7)	77/400 (19.3)	0.74 (0.53-1.04)	
Total Mortality	136/1,870 (7.3)	163/1,823 (8.9)	0.80 (0.64-1.00)	0.64
Prior Coronary Revascularization	98/1,469 (6.7)	120/1,423 (8.4)	0.77 (0.59-1.01)	
No Prior Revascularization	38/401 (9.5)	43/400 (10.8)	0.87 (0.56-1.35)	



Among patients with prior myocardial infarction (MI), clinical endpoints, including the primary composite endpoint; the key secondary composite endpoint; and the individual endpoints of cardiovascular death, MI, stroke, coronary revascularization, or unstable angina requiring hospitalization, were consistently lower with icosapent ethyl treatment compared with placebo regardless of history of prior coronary revascularization. No adjustments for multiple testing were applied.

STUDY LIMITATIONS. First, these data include both prespecified and post hoc analyses. REDUCE-IT was designed and powered for the primary composite endpoint. It was not powered for subgroup analyses, making the results of this analysis hypothesis-generating. Second, enrollment was not stratified by prior MI or time since MI. Third, patients were not enrolled at the time of their MI. Finally, no adjustments were made for multiple comparisons. Future randomized trials should examine early initiation of IPE at the time of presentation with MI. A loading dose of IPE has been studied and may be useful in the context of acute MI.[21]

CONCLUSIONS

In this subgroup analysis of the REDUCE-IT trial, among patients with prior MI treated with statins who have controlled LDL-C and moderately elevated triglycerides, IPE led to significant reductions in both first and total ischemic events. The benefits of IPE in patients with prior MI were consistent across subgroups with or without a history of prior revascularization. There were significant reductions in CV death, sudden cardiac death, and cardiac arrest, but a slightly higher rate of atrial fibrillation. The effects of IPE were similar among patients with and without prior MI.

Altogether, these data highlight the unequivocal benefits of IPE and its substantial CV risk reduction in patients with established CV disease who have experienced a prior MI. Furthermore, these analyses strongly encourage routine treatment with IPE in eligible patients with prior MI for further reduction of CV risk.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

IPE reduces ischemic events, including cardiac arrest and CV death in statin-treated patients with hypertriglyceridemia and prior MI.

TRANSLATIONAL OUTLOOK:

Future trials should examine whether starting IPE at the time of a MI can prevent early ischemic events.

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KEY WORDS clinical trials, icosapent ethyl, ischemic events, myocardial infarction

APPENDIX For supplemental tables, please see the online version of this paper.