

ORIGINAL INVESTIGATIONS

# Effects of Icosapent Ethyl on Total Ischemic Events

## From REDUCE-IT

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### ABSTRACT

**BACKGROUND** In time-to-first-event analyses, icosapent ethyl significantly reduced the risk of ischemic events, including cardiovascular death, among patients with elevated triglycerides receiving statins. These patients are at risk for not only first but also subsequent ischemic events.

**OBJECTIVES** Pre-specified analyses determined the extent to which icosapent ethyl reduced total ischemic events.

**METHODS** REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) randomized 8,179 statin-treated patients with triglycerides  $\geq 135$  and  $< 500$  mg/dl (median baseline of 216 mg/dl) and low-density lipoprotein cholesterol  $> 40$  and  $\leq 100$  mg/dl (median baseline of 75 mg/dl), and a history of atherosclerosis (71% patients) or diabetes (29% patients) to icosapent ethyl 4 g/day or placebo. The main outcomes were total (first and subsequent) primary composite endpoint events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) and total key secondary composite endpoint events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). As a pre-specified statistical method, we determined differences in total events using negative binomial regression. We also determined differences in total events using other statistical models, including Andersen-Gill, Wei-Lin-Weissfeld (Li and Lagakos modification), both pre-specified, and a post hoc joint frailty analysis.

**RESULTS** In 8,179 patients, followed for a median of 4.9 years, 1,606 (55.2%) first primary endpoint events and 1,303 (44.8%) subsequent primary endpoint events occurred (which included 762 second events, and 541 third or more events). Overall, icosapent ethyl reduced total primary endpoint events (61 vs. 89 per 1,000 patient-years for icosapent ethyl versus placebo, respectively; rate ratio: 0.70; 95% confidence interval: 0.62 to 0.78;  $p < 0.0001$ ). Icosapent ethyl also reduced totals for each component of the primary composite endpoint, as well as the total key secondary endpoint events (32 vs. 44 per 1,000 patient-years for icosapent ethyl versus placebo, respectively; rate ratio: 0.72; 95% confidence interval: 0.63 to 0.82;  $p < 0.0001$ ).

**CONCLUSIONS** Among statin-treated patients with elevated triglycerides and cardiovascular disease or diabetes, multiple statistical models demonstrate that icosapent ethyl substantially reduces the burden of first, subsequent, and total ischemic events. (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial [REDUCE-IT]; [NCT01492361](https://clinicaltrials.gov/ct2/show/study/NCT01492361)) (J Am Coll Cardiol 2019;73:2791-802) © 2019 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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## ABBREVIATIONS AND ACRONYMS

**CI** = confidence interval  
**EPA** = eicosapentaenoic acid  
**HR** = hazard ratio  
**LDL-C** = low-density lipoprotein cholesterol  
**MI** = myocardial infarction  
**RR** = rate ratio

Despite the tremendous advance of statin therapy in secondary and primary prevention, ischemic events continue to occur in patients with cardiovascular risk factors such as elevated triglycerides, atherosclerosis, or diabetes (1-4). In addition to their initial events, such patients are at substantial risk for recurrent, potentially fatal events. Assessment of these recurrent events provides a perspective on the total atherosclerotic event burden that these patients face (5-11). From a patient's perspective (and also for physicians and payors), it is not only first events that are important, but subsequent events as well.

One marker of this residual cardiovascular risk that predisposes patients to initial and recurrent ischemic events is elevated triglyceride levels (12,13). Multiple epidemiological and genetic analyses have demonstrated an independent association with increased cardiovascular risk (14). Among several properties,

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icosapent ethyl reduces triglyceride levels and other lipids and lipoproteins without increasing low-density lipoprotein cholesterol (LDL-C) when compared with placebo, and has also been reported to have anti-inflammatory and plaque stabilizing properties, as well as stabilizing effects on cell membranes

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(15-19). Recently, icosapent ethyl has been demonstrated to reduce the first occurrence of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina in REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), with a 25% relative risk reduction and a 4.8% absolute risk reduction (number needed to treat [NNT] of 21) (20). The time to first occurrence of the key secondary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was also reduced with icosapent ethyl, with a 26% relative risk reduction and a 3.6% absolute risk reduction (NNT of 28). The results were also consistent across each of the primary and key secondary endpoint components and appear to be applicable to a substantial proportion of patients in clinical practice (21).

We sought to determine the effect of icosapent ethyl on total ischemic events (first and subsequent events) to better characterize the totality of the ischemic event burden across the overall study population.

## METHODS

**STUDY DESIGN AND PARTICIPANTS.** The details of the REDUCE-IT design have been previously published (22). Briefly, patients were randomized in a double-blind manner to icosapent ethyl 4 g/day (2 g twice daily with meals) or placebo (Online Figures 1 and 2). Approximately 1,612 events were projected necessary for 90% power to detect a 15% relative risk reduction after accounting for 2 protocol pre-specified interim analyses (final 2-sided alpha level = 0.0437). This resulted in a target patient population of approximately 7,990 patients. Among all randomized patients, 70.7% were enrolled on the basis of secondary prevention and 29.3% for primary prevention. Patients were randomized to 1 of 2 treatment arms in a 1:1 ratio using a computer-generated randomization schema. Study medication and placebo capsules were similar in size and appearance to maintain blinding. Randomization was stratified according to cardiovascular risk cohort (secondary or primary prevention), use of ezetimibe (yes/no), and by geographical region (Westernized, Eastern European, and Asia Pacific countries). There were 473 sites in 11 countries randomizing and following patients from 2011 to 2018. The protocol was submitted to and approved by appropriate health authorities, ethics committees, and institutional review boards. Trial completion occurred after achieving the approximate number of pre-specified necessary events.

To be eligible, patients were required to be either  $\geq 45$  years of age with established cardiovascular disease (secondary prevention stratum) or  $\geq 50$  years of age with type 2 or 1 diabetes mellitus requiring treatment with medication, and to have at least 1 additional cardiovascular risk factor (primary prevention stratum) (20,22).

Patients had fasting triglycerides of  $\geq 135$  and  $< 500$  mg/dl and LDL-C  $> 40$  and  $\leq 100$  mg/dl. The initial version of the protocol permitted a 10% variance in the lower qualifying triglyceride level of  $\geq 150$  mg/dl; therefore, patients with triglycerides  $\geq 135$  mg/dl were randomized. After approximately 60% of the patients were enrolled, an amendment increased the lower limit of permissible triglyceride levels to 200 mg/dl with no variability allowance. The study included 841 (10.3%) patients with baseline triglyceride levels  $< 150$  mg/dl. Patients were required to be on stable statin therapy for  $\geq 4$  weeks with well-controlled LDL-C to investigate the potential benefit of icosapent ethyl 4 g/day beyond the current standard of care. Additional inclusion and exclusion criteria published previously (22) are provided in the Online Appendix.

After randomization, follow-up visits continued at 4 and 12 months and annually thereafter in this event-driven trial until approximately 1,612 primary efficacy endpoint events occurred, after which patients made a final end-of-study visit.

The original projected annual primary endpoint event rate for the REDUCE-IT placebo group was 5.9%; this was derived prior to study initiation (and therefore, prior to the 2 interim analyses conducted by the data monitoring committee) and was based on data available from cardiovascular outcome trials with similar high-risk statin-treated patients and reported endpoint components similar to the primary endpoint in REDUCE-IT (23-29). The observed annualized primary endpoint event rate for placebo patients in REDUCE-IT was 5.74%, which is consistent with historical cardiovascular outcome studies, including those published since the design of REDUCE-IT, with comparable patient populations and expanded or hard major adverse cardiovascular events (MACE) (4,8,9,30-44).

For the present pre-specified analysis, the primary outcome was the total of first plus subsequent ischemic events consisting of the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Protocol Amendment 2 (July 2016) designated the composite of hard MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) as the “key secondary

**TABLE 1** Total Primary and Key Secondary Composite Endpoints Accounting for Statistical Handling of Multiple Endpoint Events Occurring in a Single Calendar Day as a Single Event

	Primary Composite Endpoint			Key Secondary Composite Endpoint		
	Icosapent Ethyl (n = 4,089)	Placebo (n = 4,090)	Overall (n = 8,179)	Icosapent Ethyl (n = 4,089)	Placebo (n = 4,090)	Overall (n = 8,179)
Total events before reduction	1,185 (40.7)	1,724 (59.3)	2,909* (100.0)	590 (42.0)	816 (58.0)	1,406 (100.0)
Total events after reduction†	1,076 (41.0)	1,546 (59.0)	2,622 (100.0)	558 (42.1)	767 (57.9)	1,325 (100.0)
Fatal events	174 (45.0)	213 (55.0)	387 (100.0)	174 (45.0)	213 (55.0)	387 (100.0)
Nonfatal events	902 (40.4)	1,333 (59.6)	2,235 (100.0)	384 (40.9)	554 (59.1)	938 (100.0)

Values are n (%). Percentages are based on the total number of randomized patients within each category (see also [Online Figures 3 and 4](#)). Primary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. \*A single event was experienced by 844 patients (844 events) and 2 or more events were experienced by 762 patients (2,065 events), for a total of 1,606 patients experiencing a total of 2,909 events. †Reduction means: 1) any nonfatal events on the same day as death are removed; and 2) if 2 nonfatal events occur on the same day, only the first one is counted.

endpoint” per suggestions from the Food and Drug Administration and with REDUCE-IT Steering Committee concordance. Exploratory analyses of the total of first and subsequent events were also performed for the key secondary composite endpoint.

Baseline characteristics were compared between treatment groups using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. The analysis of total cardiovascular events was pre-specified in the study protocol. There are several methods for analyzing first and subsequent (recurrent) event data. As a pre-specified statistical method, we used the negative binomial regression model to calculate rates and rate ratios for total cardiovascular events, which accounts for the variability in each patient’s risk of events (45-47). As pre-specified supportive analyses, we used the modified Wei-Lin-Weissfeld method (Li and Lagakos modification) to calculate hazard ratios for the time to the first, second, or third event (48,49). An additional pre-specified analysis, the Andersen-Gill model using a Cox proportional-hazard with the counting-process formulation, was performed to model the total events (50,51). In addition, to account for informative censoring due to cardiovascular death, we calculated the hazard ratio for total nonfatal events using a joint frailty model (52). The joint frailty model simultaneously estimates hazard functions for nonfatal and fatal cardiovascular events and takes into account the fact that patients who are prone to have nonfatal events have an elevated risk of cardiovascular death. Our application of the joint frailty model used a gamma distribution for the frailty term.

To improve the performance and validity of our statistical models, a bundling approach was used, whereby nonfatal events occurring on the same day as a cardiovascular death were excluded, and at most,

1 nonfatal event was counted on any given day (e.g., for coronary revascularization occurring after an MI that eventually resulted in the patient’s death, only the death would be included). Statistical analyses using the full adjudicated endpoint events dataset without exclusions for this bundling approach are also included in the [Online Appendix](#).

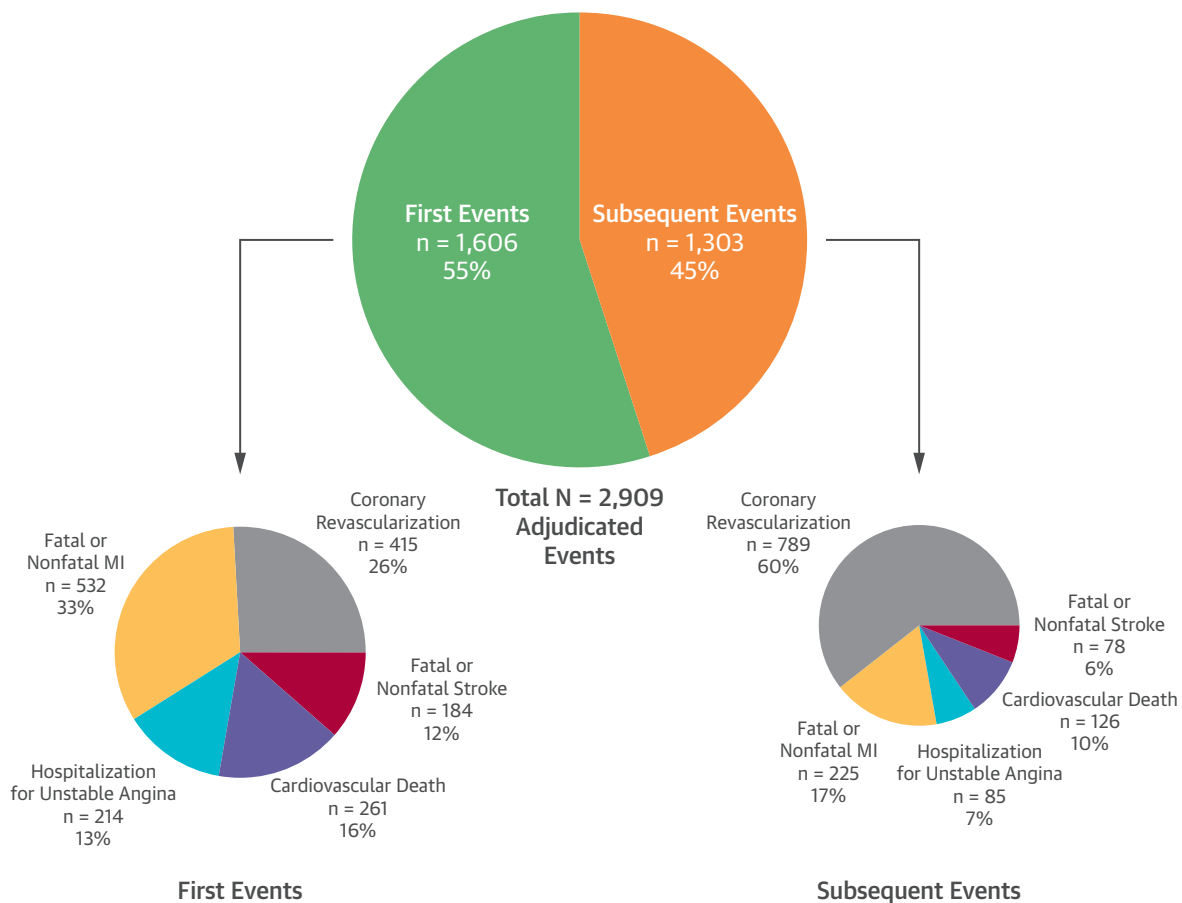
All efficacy analyses were conducted in accordance with the intention-to-treat principle. All tests were based on a 2-sided nominal significance level of 5% with no adjustments for multiple comparisons, consistent with pre-specified plans for such endpoints. All statistical analyses were conducted using SAS version 9.4 software (Cary, North Carolina). All analyses of first, subsequent, and total events were independently generated and validated by Drs. Gregson and Pocock.

## RESULTS

A total of 8,179 patients were randomized and followed for a median of 4.9 years. The baseline characteristics were well matched across the icosapent ethyl and placebo groups ([Online Table 1](#)). At baseline, median triglyceride levels were 216 mg/dl, with median LDL-C levels of 75 mg/dl. Additional baseline characteristics across treatment groups and for patients with no events, a single event, and multiple subsequent events are shown in [Online Tables 1 and 2](#), respectively.

**TOTAL EVENTS FOR THE PRIMARY EFFICACY ENDPOINT.** Across 8,179 randomized patients, there were 1,606 (55.2%) first primary endpoint events and 1,303 (44.8%) additional primary endpoint events, for a total of 2,909 endpoint events ([Table 1](#), [Online Figures 3 to 5](#)). The proportions of first and subsequent primary endpoint events, overall and by component type, are depicted in [Figure 1](#). There

**FIGURE 1** Proportion of First and Subsequent Primary Composite Endpoint Events, Overall and by Component

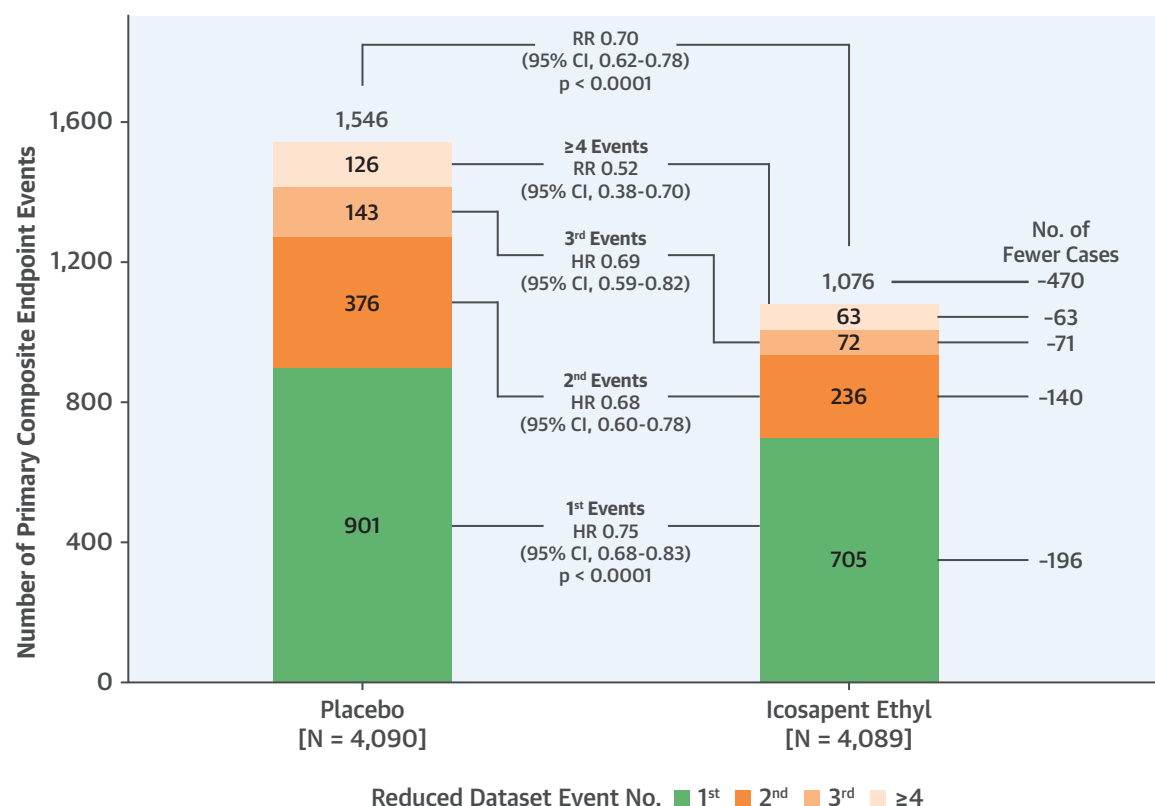


Analyses are based on the total adjudicated event dataset without accounting for multiple endpoints occurring in a single calendar day by counting as a single event. Of the 1,303 subsequent events, 762 were second events, 272 third events, and 269 fourth or more events. Primary composite endpoint events: cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular death, nonfatal MI, or nonfatal stroke.

were 762 second events, 272 third events, and 269 fourth or more events. Overall, total (first and subsequent) primary endpoint event rates were reduced to 61 from 89 per 1,000 patient-years for icosapent ethyl versus placebo, respectively, rate ratio (RR): 0.70; 95% confidence interval (CI): 0.62 to 0.78;  $p < 0.0001$  (Central Illustration, Figure 2A). Using the modified Wei-Lin-Weissfeld model, the first occurrence of a primary composite endpoint was reduced with icosapent ethyl versus placebo (hazard ratio [HR]: 0.75; 95% CI: 0.68 to 0.83;  $p < 0.0001$ ) as was the second occurrence (HR: 0.68; 95% CI: 0.60 to 0.78;  $p < 0.0001$ ). There was a 30% relative risk reduction in the total (first and subsequent) ischemic events for the primary composite endpoint with icosapent ethyl. First events were reduced by 25%,

second events by 32%, third events by 31%, and fourth or more events by 48%. The cumulative events over time are shown in Figure 2. Total key secondary endpoint event rates were significantly reduced to 32 from 44 per 1,000 patient-years for icosapent ethyl versus placebo, respectively (RR: 0.72; 95% CI: 0.63 to 0.82;  $p < 0.0001$ ) (Figure 2B). The times to first occurrence, second occurrence, third occurrence, or fourth occurrence of the primary composite endpoint were consistently reduced (Figure 3) with icosapent ethyl. There were similar results for the models irrespective of whether bundling and/or single event accounting was used (Online Tables 3 to 5). Total events for each component of the primary endpoint were also significantly reduced (Figure 4, Online Figure 3).

**CENTRAL ILLUSTRATION** Distribution of First and Subsequent Primary Composite Endpoint Events in the Reduced Dataset for Patients Randomized 1:1 to Icosapent Ethyl Versus Placebo



Bhatt, D.L. et al. J Am Coll Cardiol. 2019;73(22):2791-802.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for between treatment group comparisons were generated using Li-Lagakos-modified Wei-Lin-Weissfeld method for the first, second, and third event categories. Rate ratio (RR) and 95% CI for between group comparisons used a negative binomial model for additional events beyond first, second, and third occurrences, i.e., fourth event or more and overall treatment comparison. Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event.

The risk differences for every 1,000 patients treated for 5 years with icosapent ethyl for the 5 components of the composite primary endpoint are shown in [Figure 5](#). Approximately 159 total primary endpoint events could be prevented within that timeframe: 12 cardiovascular deaths, 42 myocardial infarctions, 14 strokes, 76 coronary revascularizations, and 16 episodes of hospitalization for unstable angina.

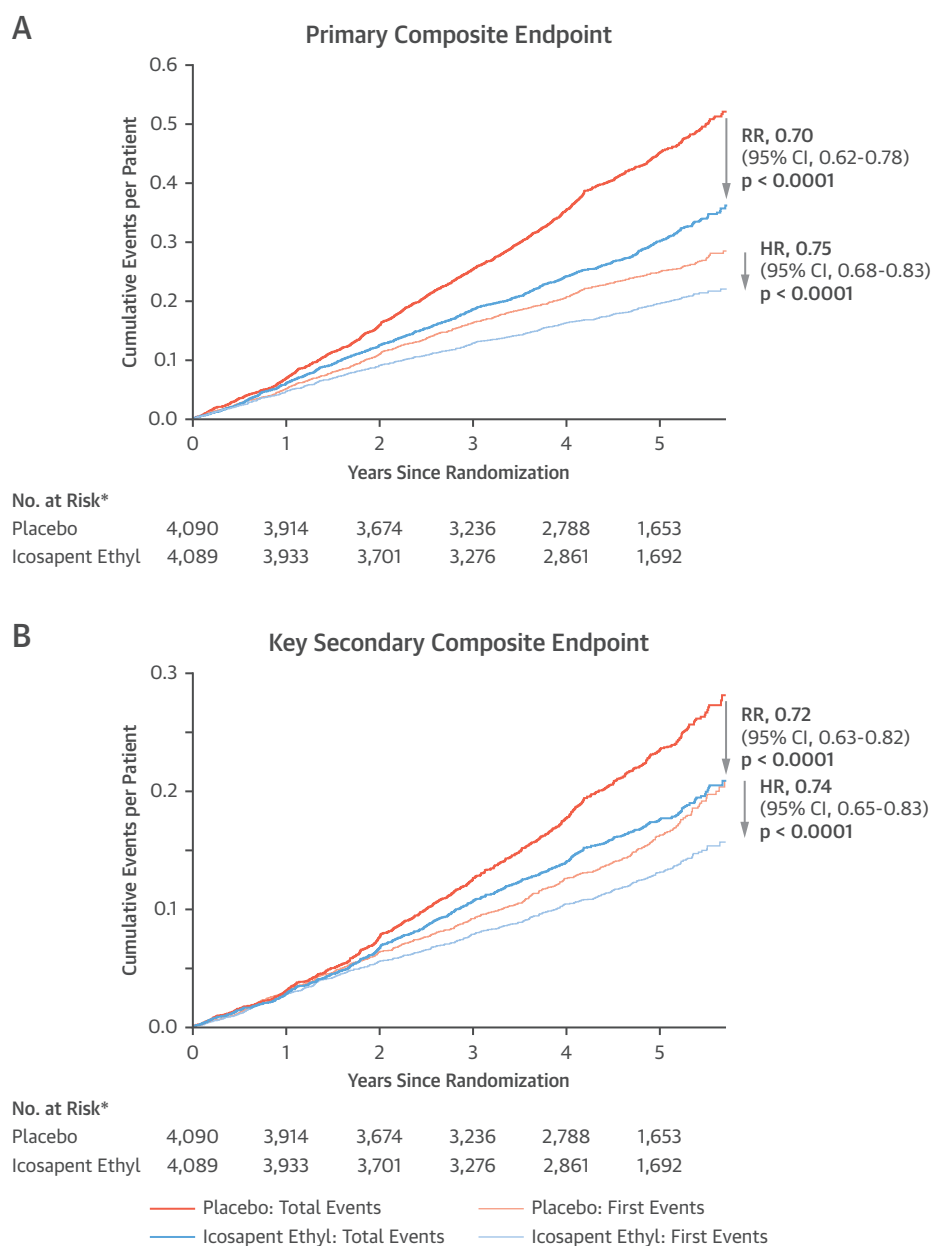
We explored study drug adherence in patients with recurrent events. At the time of a first primary endpoint event (fatal or nonfatal), 81.3% (573 of 705) of icosapent ethyl and 81.8% (737 of 901) of placebo patients with a first primary endpoint event were receiving randomized study drug. At the time of subsequent primary endpoint events (fatal or nonfatal), 79.7% (188 of 236) and 79.5% (299 of 376) of patients with a second event, 68.1% (49 of 72) and

74.1% (106 of 143) of patients with a third event, and 68.0% (17 of 25) and 71.6% (48 of 67) of patients with a fourth event were receiving randomized study drug in the icosapent ethyl and placebo groups, respectively. Therefore, the majority of the first, second, third, and fourth events occurred while patients were on randomized study treatment. Numerical differences in study drug adherence among patients with recurrent events were not statistically significant between treatment groups.

## DISCUSSION

We found large and significant reductions in total ischemic events with icosapent ethyl versus placebo in these total event analyses of REDUCE-IT. Three pre-specified and 1 post hoc analyses with various

**FIGURE 2** Total (First and Subsequent) and Time to First Primary Composite Endpoint Events and Key Secondary Composite Endpoint Events

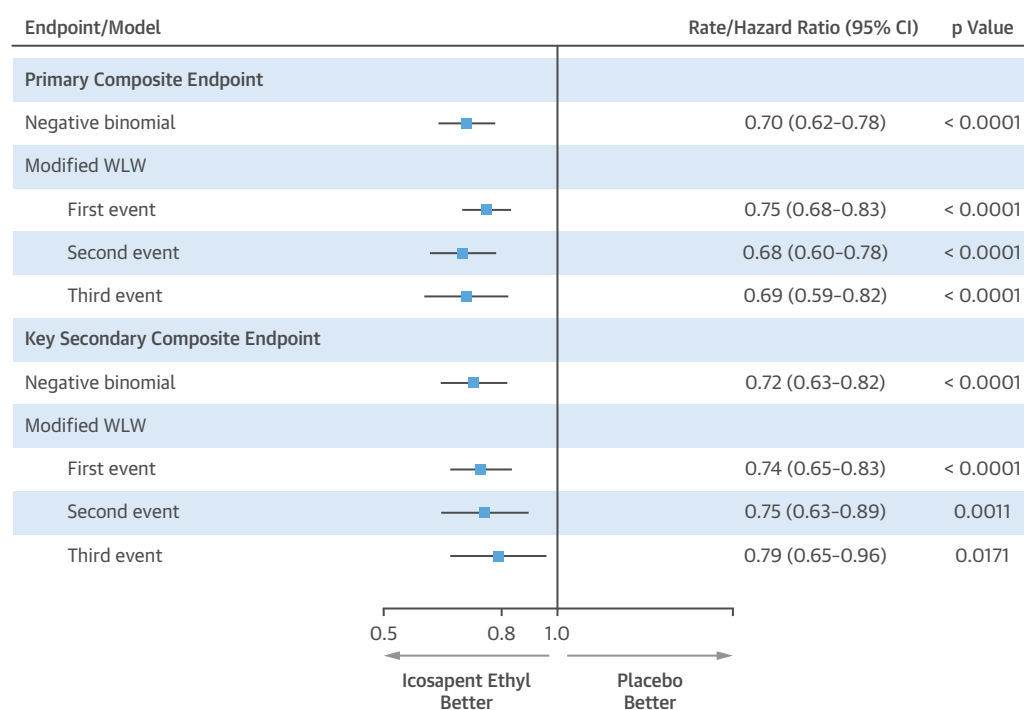


\*No. at risk = number of patients at risk for recurrent events. The number of patients at risk for the first occurrence of an endpoint event were presented previously in Bhatt et al. (20). (A) Primary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. (B) Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event. CI = confidence interval; HR = hazard ratio; RR = rate ratio.

statistical methodologies demonstrated consistent effects on total ischemic events, with substantial relative and absolute risk reductions. There was a 30% relative risk reduction in the total (first and

subsequent) ischemic events for the primary composite endpoint with icosapent ethyl. For every 1,000 patients treated with icosapent ethyl for 5 years, approximately 159 total primary endpoint



**FIGURE 3** Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences

The p values are from negative binomial model and Li-Lagakos-modified Wei-Lin-Weissfeld (WLW) models as indicated. Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event. Primary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. For the modified WLW analysis, the second event is defined as nonfatal second event or cardiovascular death, and third event is defined as nonfatal third event or cardiovascular death. Due to the low number of fourth or more events, only first, second, and third events are displayed (please see [Online Figure 3](#)). CI = confidence interval.

events could be prevented. Total events for the hard MACE key secondary endpoint also demonstrated large and clinically meaningful reductions, which further corroborated the significant reduction in important ischemic events seen with the primary endpoint.

There were significant reductions in the first, subsequent, and total ischemic events for each individual component of the composite primary endpoint. This benefit of icosapent ethyl across a variety of different ischemic endpoints (e.g., coronary, cerebral, fatal and nonfatal events, and revascularizations) indicates that the drug benefit is not likely to be explained by triglyceride lowering alone and suggests strongly that there are multiple mechanisms of action of the drug beyond triglyceride lowering that may work together to achieve the observed benefits. Preclinical mechanistic investigations and smaller clinical studies support this contention (12,18,19,53–56).

Icosapent ethyl was well tolerated with no significant differences in rates of serious adverse events versus placebo (20). Although overall rates were low in both treatment groups, and none of the events were study-drug related and fatal, with icosapent ethyl there was a trend toward increased serious bleeding albeit with no significant increases in serious central nervous system bleeding, gastrointestinal bleeding, or adjudicated hemorrhagic stroke. There was a small but statistically significant increase in hospitalization for atrial fibrillation or flutter endpoints noted in REDUCE-IT (20). Nevertheless, the large number of important ischemic events averted with the drug, including a significant reduction in fatal and nonfatal stroke (28%), cardiac arrest (48%), sudden death (31%), and cardiovascular death (20%), is indicative of a very favorable risk-benefit profile (20).

Study drug adherence in patients with recurrent events was strong in both treatment groups at the time of their first primary endpoint event, decreasing



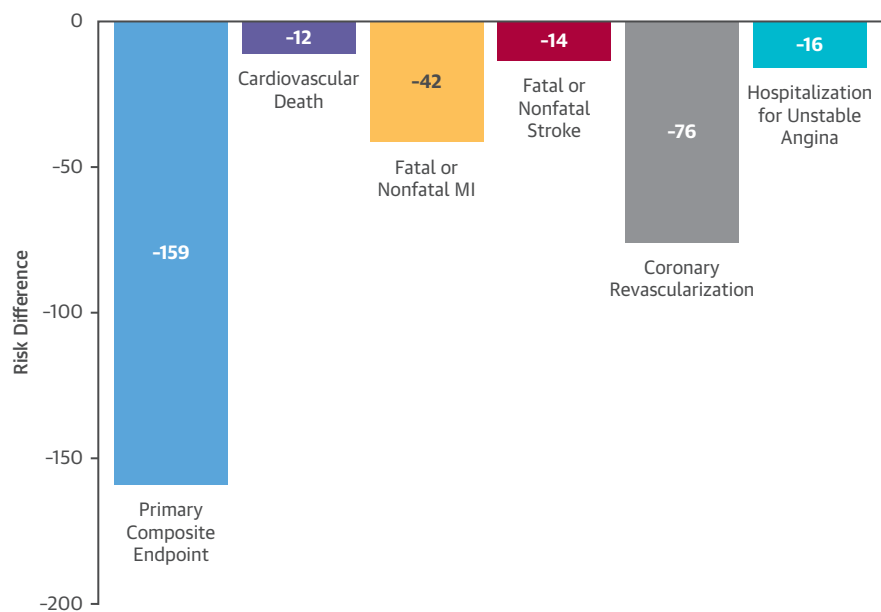
**FIGURE 4** Total Primary and Key Secondary Composite Endpoints and Individual Components or Other Composite Endpoints

Endpoint	Icosapent Ethyl Rate per 1,000 Patient Years	Placebo Rate per 1,000 Patient Years		Rate Ratio (95% CI)	p Value
Primary composite endpoint	61	89		0.70 (0.62-0.78)	< 0.0001
Key secondary composite endpoint	32	44		0.72 (0.63-0.82)	< 0.0001
Cardiovascular death	10	12		0.81 (0.66-0.99)	0.0362
Fatal or nonfatal myocardial infarction	17	26		0.67 (0.56-0.80)	< 0.0001
Fatal or nonfatal stroke	6	9		0.68 (0.52-0.91)	0.0078
Coronary revascularization	27	42		0.64 (0.56-0.74)	< 0.0001
Hospitalization for unstable angina	7	10		0.69 (0.54-0.89)	0.0041

0.5      0.8      1.0  
← Icosapent Ethyl Better      Placebo Better →

The p values are from the negative binomial model. Primary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event. CI = confidence interval.

**FIGURE 5** Risk Differences for 1,000 Patients Treated For 5 Years With Icosapent Ethyl Versus Placebo for the Primary Composite Endpoint and Individual Components or Other Composite Endpoints



Analyses are based on total adjudicated event dataset without accounting for multiple endpoints occurring in a single calendar day by counting as a single event. MI = myocardial infarction.

somewhat across both treatment groups from the occurrence of the first to the fourth event. For example, at the time of a first occurrence of a fatal or nonfatal primary endpoint event, 81.3% of icosapent ethyl and 81.8% of placebo patients with a first primary endpoint event were on study drug; these rates decreased to 68.0% and 71.6% for patients with a fourth primary endpoint event.

The REDUCE-IT primary study results (20) and the recurrent and total endpoint event findings discussed herein stand in stark contrast to cardiovascular outcome studies with other agents that lower triglyceride levels and with low-dose omega-3 fatty acid mixtures, where cardiovascular outcome benefit has not been consistently observed in statin-treated patients (13). However, the REDUCE-IT results are aligned with the JELIS study results (17). The distinction of the cardiovascular benefits observed in REDUCE-IT and JELIS from the lack of cardiovascular benefits observed in statin-treated populations with add-on omega-3 fatty acid mixtures is likely due specifically to the high eicosapentaenoic acid (EPA) levels. EPA has unique lipid and lipoprotein, anti-inflammatory, antiplatelet, antithrombotic, and cellular modifying effects, all of which may contribute to benefits in atherosclerotic processes such as reduced development, slowed progression, and increased stabilization of atherosclerotic plaque (19,54-56). The aggregate contribution of these EPA-related effects may contribute to the large observed reductions in total ischemic events with icosapent ethyl.

The REDUCE-IT patients represent a population at high risk for ischemic events, as suggested by the annualized placebo primary endpoint event rate (5.74%), which was expected per study design and is consistent with historical data for similar high-risk statin-treated patient populations. It is therefore not surprising that the total atherosclerotic event burden was also high for REDUCE-IT patients. Substantial and consistent risk reduction with icosapent ethyl was observed in the total event analyses for the primary endpoint, for each contributing component, and for the key secondary endpoint. Time-to-first-event results provide NNT values (21 for the primary endpoint; 28 for the key secondary endpoint); the total event analyses results provide incremental evidence of substantial reduction of the total atherosclerotic event burden with icosapent ethyl in these patients, with 159 total primary endpoint events prevented for every 1,000 patients treated with icosapent ethyl for 5 years. Given the broad inclusion criteria and relatively few exclusion criteria, these results are likely generalizable to a large proportion of at-risk statin-treated patients with atherosclerosis or

diabetes (21). Based on the favorable reductions in total ischemic endpoint events, a cost-effectiveness analysis is planned.

**STUDY LIMITATIONS.** A limitation of this pre-specified analysis is that it is exploratory, and one of the methods utilized was post hoc (joint frailty model). Also, total event statistical models can have limitations; yet each total event analysis model used in this paper provides sophisticated statistical handling of subsequent events, with some distinct and some overlapping strengths. Despite differences in statistical methodologies, the consistency of findings across the models speaks to the robustness of the study conclusions and the underlying cardiovascular outcomes data. Current analyses of study drug adherence in relation to recurrent events are descriptive. In future analyses, we plan to further explore the possible correlations between clinical outcomes and study drug adherence, including consideration of possible legacy effects of icosapent ethyl. As published previously (20), some biomarkers in the placebo treatment group increased from baseline (e.g., median low-density lipoprotein cholesterol was 5 mg/dl higher at 1 year in the placebo group than in the icosapent ethyl group). Such changes are common in statin-treated patients within cardiovascular outcome studies (57). Importantly, those biomarker differences had no discernible effect on cardiovascular outcomes in the REDUCE-IT placebo group; additionally, the placebo group event rate was as projected during the design phase of REDUCE-IT and was also consistent with event rates from other cardiovascular outcome studies with similar high-risk statin-treated patients (7,23,25,27).

## CONCLUSIONS

Icosapent ethyl 4 g daily (2 g twice daily) significantly reduces total ischemic events in statin-treated patients with well-controlled LDL-C and cardiovascular risk factors including elevated triglycerides; benefits were consistently observed across a variety of individual ischemic endpoints. In such patients, icosapent ethyl presents an important treatment option to further reduce the total burden of atherosclerotic events beyond statin therapy alone.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL

**OUTCOMES:** In the REDUCE-IT trial, administration of icosapent ethyl, 4 g daily, reduces total cardiovascular events by 30% in patients with elevated triglycerides receiving statin therapy.

**TRANSLATIONAL OUTLOOK:** Ongoing analyses of biomarkers collected in the trial may provide additional insight into the mechanisms responsible for the risk reductions associated with icosapent ethyl seen across a variety of ischemic cardiovascular events.

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**KEY WORDS** eicosapentaenoic acid, icosapent ethyl

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**APPENDIX** For a list of trial investigators and supplemental Methods, figures, and tables, please see the online version of this paper.