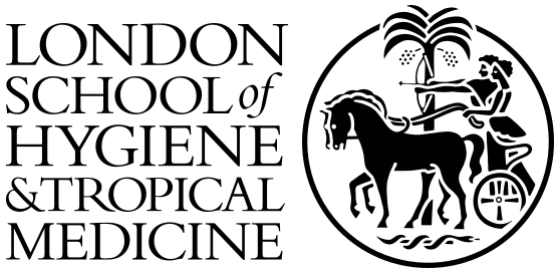

Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT

Deepak L. Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD, Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD, Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD, Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, John Gregson, PhD, Stuart J. Pocock, PhD, Christie M. Ballantyne, MD, on Behalf of the REDUCE-IT Investigators

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Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT

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Brief Title: Ischemic Event Reduction with Icosapent Ethyl

*A complete list of the REDUCE-IT trial investigators can be found at NEJM.org in the supplemental appendix of Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019;380:11-22.

Short tweet: REDUCE-IT found large, statistically significant reductions in first, recurrent, and total ischemic events with icosapent ethyl versus placebo.

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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 The Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) randomized 8,179 statin-treated patients with triglycerides ≥135 and <500 mg/dL (median baseline of 216 mg/dL) and LDL-cholesterol >40 and ≤100 mg/dL (median baseline of 75 mg/dL), and a history of atherosclerosis (71% patients) or diabetes (29% patients) to icosapent ethyl 4g/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 versus 89 per 1000 patient years for icosapent ethyl versus placebo, respectively; RR 0.70, 95% CI 0.62-0.78, P<0.0001). Icosapent ethyl also reduced each component of the primary composite endpoint, as well as the total key secondary endpoint events (32 versus 44 per 1000 patient years for icosapent ethyl versus placebo, respectively, RR 0.72, 95% CI 0.63-0.82, 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.

TRIAL REGISTRATION clinicaltrials.gov identifier: NCT01492361

Keywords: Icosapent ethyl, eicosapentaenoic acid

Condensed Abstract: The results of analyses by multiple statistical models presented here for REDUCE-IT (median follow-up of 4.9 years) demonstrate that icosapent ethyl 4 grams daily significantly reduced the rate of total primary endpoint events (RR 0.70, 95% CI 0.62-0.78, P<0.0001), each primary endpoint component, including cardiovascular death, and total key secondary endpoint events in statin-treated patients with elevated triglycerides and established cardiovascular disease or diabetes at risk for not only first but also subsequent ischemic events.

Abbreviations

CEC = Clinical Endpoint Committee
CI = confidence interval
CRP = C-reactive protein
EPA = eicosapentaenoic acid
HR = hazard ratio

LDL = low density lipoprotein
MI = myocardial infarction
REDUCE-IT = Reduction of Cardiovascular Events with EPA - Intervention Trial
TG = Triglyceride

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 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 epidemiologic and genetic analyses have demonstrated an independent association with increased cardiovascular risk (14). Among several properties, icosapent ethyl reduces triglyceride levels and other lipids and lipoproteins without increasing LDL-cholesterol 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 (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 the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), 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, and nonfatal stroke was also reduced with icosapent ethyl, with a 26% relative risk reduction and a 3.6% absolute risk reduction (NNTof 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 impact of icosapent ethyl on total ischemic events (first and subsequent events) to characterize better 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 grams twice daily with meals) or placebo (Online Figure 1, Online Figure 2). Approximately 1,612 events were projected necessary for 90% power to detect a 15% relative risk reduction after accounting for two protocol pre-specifed interim analyses (final two-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 one of two treatment arms on 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 patients from 2011 to 2016. 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 ≥45 years of age with established cardiovascular disease (secondary prevention stratum) or ≥50 years old with type 2 or type 1 diabetes mellitus requiring treatment with medication, and to have at least one additional cardiovascular risk factor (primary prevention stratum) (21,22).

Patients had fasting triglycerides of ≥135 mg/dL and <500 mg/dL and LDL-cholesterol >40 mg/dL and ≤100 mg/dL. The initial version of the protocol permitted a 10% variance in the lower qualifying triglyceride levels of ≥150 mg/dL, therefore patients with triglycerides ≥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 ≥ four weeks with well-controlled LDL-C to investigate the potential benefit of icosapent ethyl 4g/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 months, 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 two 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 holds

consistent with 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 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-squared 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 event, second event, 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 a 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 employed, whereby nonfatal events occurring on the same day as a cardiovascular death were excluded, and at most, one nonfatal event was counted on any given day (e.g., for coronary revascularization occurring after an MI which 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 supplementary materials.

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, 4, and 5). The proportions of first and subsequent primary endpoint events, overall and by component type, are depicted in Figure 1. There 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 1000 patient years for icosapent ethyl versus placebo, respectively, rate ratio (RR) 0.70, 95% CI 0.62-0.78, P<0.0001 (**Central Illustration**, Figure 2a). Using the Wei-Lin-Weissfeld model, the first occurrence of a primary composite endpoint was reduced with icosapent ethyl versus placebo (HR 0.75, 95% CI 0.68-0.83, P <0.0001) as was the second occurrence (hazard ratio [HR] 0.68, 95% CI 0.60-0.78, 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 1000 patient years for icosapent ethyl versus placebo, respectively (RR 0.72, 95% CI 0.63-0.82, 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 employed (Online Tables 3,

4, and 5). Total events for each component of the primary endpoint were also significantly reduced (Figure 4, Online Figure 3).

The risk differences for every 1000 patients treated for five years with icosapent ethyl for the five 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% (573/705) of icosapent ethyl and 81.8% (737/901) 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% (188/236) and 79.5% (299/376) of patients with a second event, 68.1% (49/72) and 74.1% (106/143) of patients with a third event, and 68.0% (17/25) and 71.6% (48/67) 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 one *post hoc* analyses with various 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 five years, approximately 159 total primary endpoint 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 (12,18,19,53-57).

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 fatal, with icosapent ethyl there was a trend towards increased serious bleeding albeit with no significant increases in adjudicated hemorrhagic stroke, serious central nervous system bleeding, or gastrointestinal bleeding. 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 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 EPA levels. EPA has unique lipid and lipoprotein, anti-inflammatory, anti-platelet, anti-thrombotic, 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 1000 patients treated with icospent 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.

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 employed in this manuscript 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 explore further 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 one year in the placebo group than in the icosapent ethyl group). Such changes are common in statin-treated patients within cardiovascular outcome studies (58). 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).

In conclusion, icosapent ethyl four grams daily (two grams 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.

Clinical Perspectives

Competency in Patient Care: Icosapent ethyl 4 grams daily reduces first and subsequent cardiovascular events by 30%. Its use should be strongly considered to reduce residual risk in patients with elevated triglycerides receiving statin therapy.

Translational Outlook: Ongoing analyses of multiple biomarkers collected in REDUCE-IT may provide additional insight into the biological mechanisms behind the large degree of relative and absolute risk reductions with icosapent ethyl seen in a variety of important ischemic events, including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization.

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Figure Legends

Central Illustration. Distribution of First and Subseqent Primary Composite Endpoint Events in the Reduced Dataset for Patients Randomized 1:1 to Icosapent Ethyl Versus Placebo. Abbreviations: CI = confidence interval; HR = hazard ratio; RR = rate ratio. Hazard ratios (HR) and 95% confidence intervals (CI) for between treatment group comparisons were generated using Li-Lagakos-modified Wei-Lin-Weissfeld (WLW) method for the 1st event, 2nd event, and 3rd event categories. Rate ratio (RR) and 95% CI for between group comparisons used a negative binomial model for additional events beyond 1st, 2nd, 3rd occurrences, i.e., 4th 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.

Figure 1. Proportion of First and Subsequent Primary Composite Endpoint Events, Overall and by Component. Abbreviations: MI = myocardial infarction. Analyses are based on total adjudicated event dataset without accounting for multiple endpoints occuring 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, nonfatal stroke, coronary revascularization, hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke.

Figure 2. Total (First and Subsequent) and Time to First Primary Composite (2A) Endpoint Events and Key Secondary Composite (2B) Endpoint Events. Abbreviations: CI = confidence interval; HR = hazard ratio; RR = rate ratio.*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 DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380:11-22. Primary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, 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.

Figure 3. Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences. Abbreviations: CI = confidence interval; R = rate ratio. P values from Negative Binomial model and Li-Lagakos-modified Wei-Lin-Weissfeld (WLW) models as indicated. Analyses are based on reduced dataset accounting for statisical 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, hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke. For the modified WLW analysis, 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).

Figure 4. Total Primary and Key Secondary Composite Endpoints and Each Individual Component or Other Composite Endpoints. Abbreviations: CI = confidence interval; HR, hazard ratio*; P* values from Negative Binomial model. Primary composite endpoint events: cardiovascular death. nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, hospitalization for unstable angina. Key secondary composite endpoint events: cardiovascular

death, nonfatal myocardial infarction, 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.

Figure 5. Risk Differences for 1000 Patients Treated For 5 Years with Icosapent Ethyl Versus Placebo for the Total Components of the Composite Primary Endpoint.

Abbreviations: MI = myocardial infarction. 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.

Table 1: Total Primary and Key Secondary Composite Endpoint Accounting for Statistical Handling of Multiple Endpoints Occuring in a Single Calendar Day as a Single Event

n (%)	Primary composite endpoint			Key secondary composite endpoint		
	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)
Total events before reduction	1185 (40.7)	1724 (59.3)	2909* (100)	590 (42.0)	816 (58.0)	1406 (100)
Total events after reductionł	1076 (41.0)	1546 (59.0)	2622 (100)	558 (42.1)	767 (57.9)	1325 (100)
Fatal events	174 (45.0)	213 (55.0)	387 (100)	174 (45.0)	213 (55.0)	387 (100)
Nonfatal events	902 (40.4)	1333 (59.6)	2235 (100)	384 (40.9)	554 (59.1)	938 (100)

Percentages are based on the total number of randomized patients within each category.

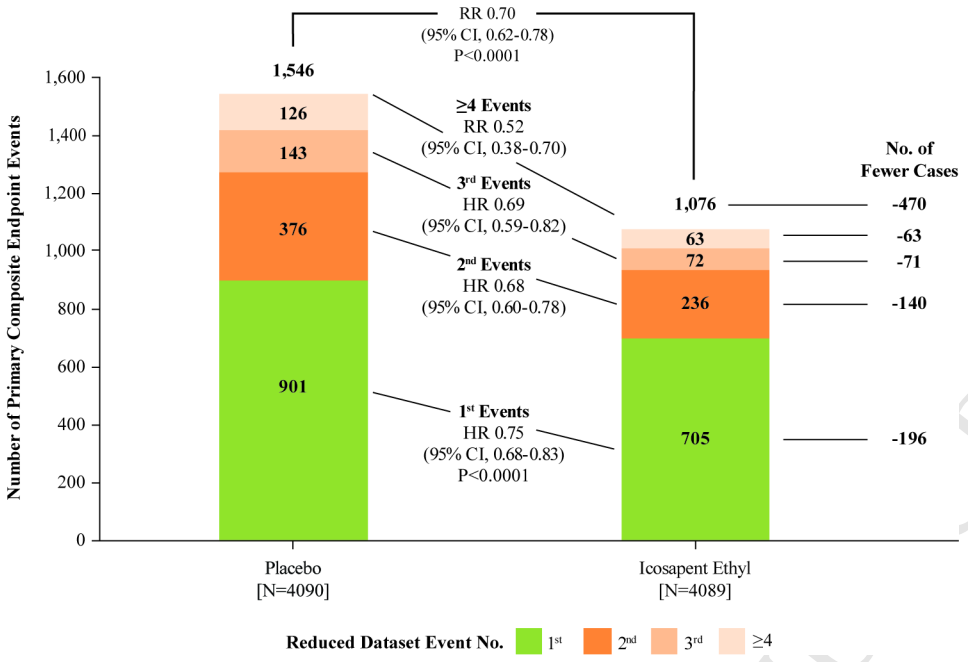
Note: See also Online Figures 3 and 4

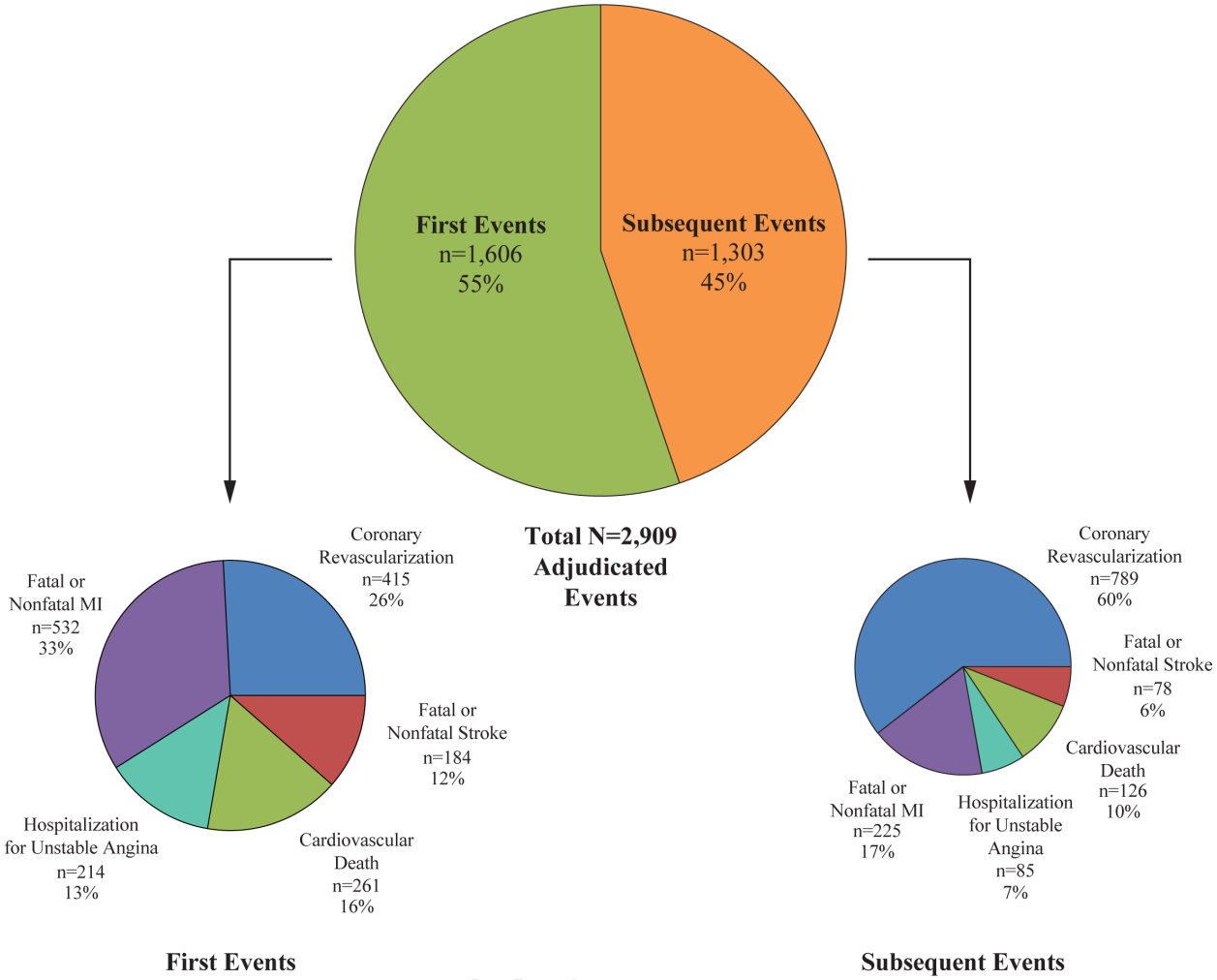
Primary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, hospitalization for unstable angina

Key secondary composite endpoint events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke.

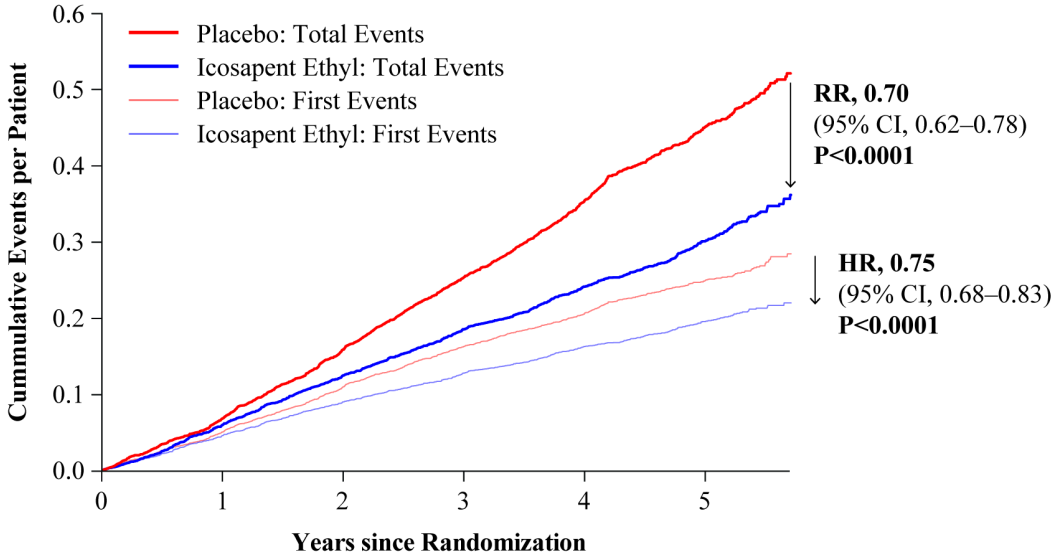
* A single event was experienced by 844 patients (844 events) and 2 or more events were experienced by 762 patients (2,065) events, for a total of 1,606 patients experiencing a total of 2,909 events.

ł 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.





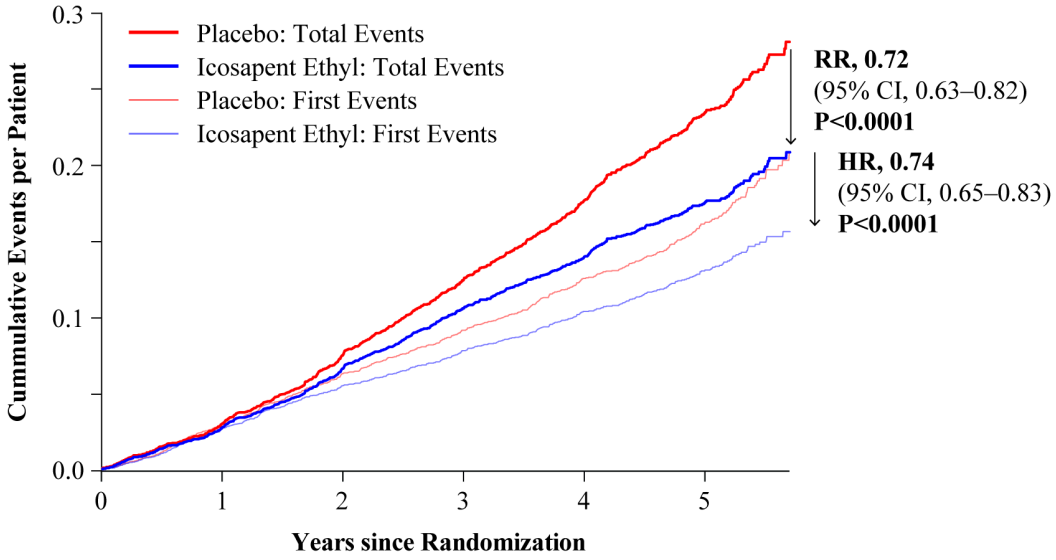
A Primary Composite Endpoint



No. at Risk*

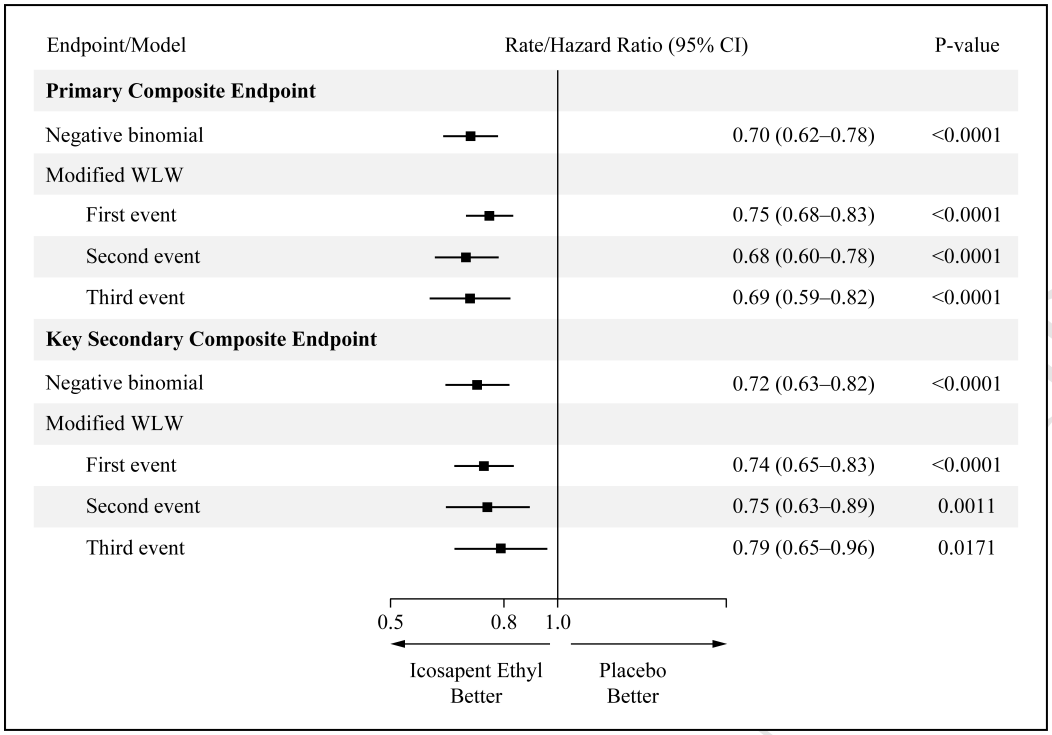
Placebo	4090	3914	3674	3236	2788	1653
Icosapent Ethyl	4089	3933	3701	3276	2861	1692

B Key Secondary Composite Endpoint

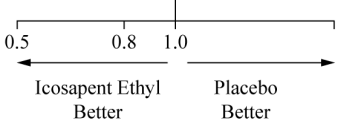


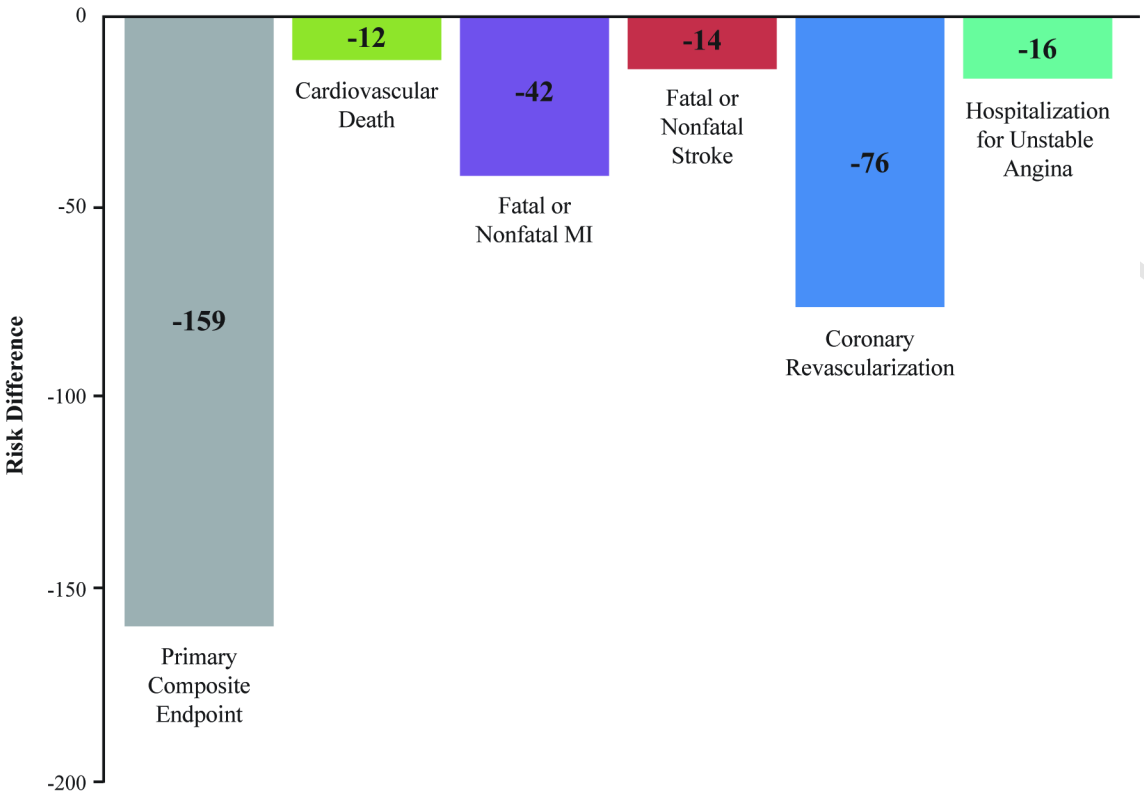
No. at Risk*

Placebo	4090	3914	3674	3236	2788	1653
Icosapent Ethyl	4089	3933	3701	3276	2861	1692



Endpoint	Icosapent Ethyl rate per 1000 patient years	Placebo rate per 1000 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





Online Appendix

Online Table 1. Baseline Characteristics of Patients in Icosapent Ethyl and Placebo Treatment Groups

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Demographics			
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)	0.7446
Age ≥65 years, n (%)	1857 (45.4%)	1906 (46.6%)	0.2815
Male, n (%)	2927 (71.6%)	2895 (70.8%)	0.4245
White, n (%)[2]	3691 (90.3%)	3688 (90.2%)	0.9110
BMI (kg/m^2), Median (Q1-Q3)	30.8 (27.8 - 34.5)	30.8 (27.9 - 34.7)	0.3247
BMI ≥30, n (%)[3]	2331 (57.0%)	2362 (57.8%)	0.5287
Stratification Factors			
Geographic Region, n (%)			0.9924
Westernized [4]	2906 (71.1%)	2905 (71.0%)	
Eastern Europe [5]	1053 (25.8%)	1053 (25.7%)	
Asia Pacific [6]	130 (3.2%)	132 (3.2%)	
CV Risk Category, n (%)			0.9943
Secondary Prevention	2892 (70.7%)	2893 (70.7%)	
Primary Prevention	1197 (29.3%)	1197 (29.3%)	

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)	0.9977
Statin Intensity and Diabetes Status			
Statin Intensity, n (%)			0.1551
Low	254 (6.2%)	267 (6.5%)	
Moderate	2533 (61.9%)	2575 (63.0%)	
High	1290 (31.5%)	1226 (30.0%)	
Missing	12 (0.3%)	22 (0.5%)	
Diabetes, n (%)			0.9926
Type 1 Diabetes	27 (0.7%)	30 (0.7%)	
Type 2 Diabetes	2367 (57.9%)	2363 (57.8%)	
No Diabetes at Baseline	1695 (41.5%)	1694 (41.4%)	
Missing	0	3 (0.1%)	
Laboratory Measurements			
hsCRP (mg/L), Median (Q1-Q3)	2.2 (1.1 - 4.5)	2.1 (1.1 - 4.5)	0.7197
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)	0.9120
Triglycerides Category, n (%)			0.8297
<150 mg/dL	412 (10.1%)	429 (10.5%)	
150 to < 200 mg/dL	1193 (29.2%)	1191 (29.1%)	
≥ 200 mg/dL	2481 (60.7%)	2469 (60.4%)	
Triglycerides Tertiles, n (%)			0.4887

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Lowest (≤190 mg/dL)	1378 (33.7%)	1381 (33.8%)	
Middle (>190 – ≤250 mg/dL)	1370 (33.5%)	1326 (32.4%)	
Upper (>250 mg/dL)	1338 (32.7%)	1382 (33.8%)	
Missing	3 (0.1%)	1	
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL, n (%)	823 (20.1%)	794 (19.4%)	0.4019
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)	0.1370
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)	0.0284
LDL-C Tertiles, n (%)			0.0556
Lowest (≤67 mg/dL)	1481 (36.2%)	1386 (33.9%)	
Middle (>67 – ≤84 mg/dL)	1347 (32.9%)	1364 (33.3%)	
Upper (>84 mg/dL)	1258 (30.8%)	1339 (32.7%)	
Missing	3 (0.1%)	1	
EPA (µg/mL), Median (Q1-Q3)	26.1 (17.1 - 40.1)	26.1 (17.1 - 39.9)	0.8867
Cardiovascular Disease History[7]			
Prior Atherosclerotic Cardiovascular Disease (ASCVD), n (%)	2816 (68.9%)	2835 (69.3%)	0.6667
Prior Atherosclerotic Coronary Artery Disease and Related Morbidities	2387 (58.4%)	2393 (58.5%)	0.9107
Ischemic Dilated Cardiomyopathy	137 (3.4%)	109 (2.7%)	0.0702
Myocardial Infarction	1938 (47.4%)	1881 (46.0%)	0.2065

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Unstable Angina	1017 (24.9%)	1015 (24.8%)	0.9592
Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities, n (%)	641 (15.7%)	662 (16.2%)	0.5457
Carotid Disease	343 (8.4%)	372 (9.1%)	0.2730
Ischemic Stroke	267 (6.5%)	242 (5.9%)	0.2529
Transient Ischemic Attack	194 (4.7%)	181 (4.4%)	0.4925
Prior Atherosclerotic Peripheral Arterial Disease, n (%)	387 (9.5%)	388 (9.5%)	1.0000
ABI <0.9 Without Symptoms of Intermittent Claudication	97 (2.4%)	76 (1.9%)	0.1073
Peripheral Artery Disease	377 (9.2%)	377 (9.2%)	1.0000
Prior Non-Atherosclerotic Cardiovascular Disease, n (%)	3649 (89.2%)	3645 (89.1%)	0.8868
Prior Structural Cardiac Disorders	827 (20.2%)	866 (21.2%)	0.2997
Heart Failure	703 (17.2%)	743 (18.2%)	0.2583
Hypertrophic Cardiomyopathy	23 (0.6%)	20 (0.5%)	0.6507
Non-Ischemic Dilated Cardiomyopathy	35 (0.9%)	29 (0.7%)	0.4552
Non-Rheumatic Valvular Heart Disease	150 (3.7%)	163 (4.0%)	0.4892
Rheumatic Valvular Heart Disease	17 (0.4%)	9 (0.2%)	0.1215
Prior Cardiac Arrhythmias	229 (5.6%)	243 (5.9%)	0.5377

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Atrio-Ventricular Block Above First Degree	51 (1.2%)	54 (1.3%)	0.8444
Sick Sinus Syndrome	30 (0.7%)	32 (0.8%)	0.8987
Supra-Ventricular Tachycardia Other Than Atrial Fibrillation /Atrial flutter	74 (1.8%)	77 (1.9%)	0.8696
Sustained Ventricular Tachycardia	34 (0.8%)	34 (0.8%)	1.0000
Torsades De Pointes	1 (0.0%)	3 (0.1%)	0.6249
Ventricular Fibrillation	61 (1.5%)	65 (1.6%)	0.7877
Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders, n (%)	3568 (87.3%)	3566 (87.2%)	0.9472
Arterial Embolism	12 (0.3%)	9 (0.2%)	0.5229
Deep Vein Thrombosis	70 (1.7%)	60 (1.5%)	0.3785
Hypertension	3541 (86.6%)	3543 (86.6%)	0.9741
Hypotension	45 (1.1%)	33 (0.8%)	0.1745
Pulmonary Embolism	31 (0.8%)	42 (1.0%)	0.2396
Non-Ischemic Stroke	79 (1.9%)	84 (2.1%)	0.7518
Hemorrhagic Stroke	18 (0.4%)	22 (0.5%)	0.6350
Stroke of Unknown Origin	63 (1.5%)	62 (1.5%)	0.9285
Other Prior Conditions or Investigations Influencing Cardiovascular Risk			

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
BaselineLaboratory Abnormalities, n (%)	1783 (43.6%)	1707 (41.7%)	0.0893
Renal Disorders	470 (11.5%)	429 (10.5%)	0.1474
Creatinine Clearance (CRCL) >30 and <60 ML/Min	309 (7.6%)	286 (7.0%)	0.3279
Macroalbuminuria	34 (0.8%)	24 (0.6%)	0.1909
Microalbuminuria	146 (3.6%)	134 (3.3%)	0.4664
Proteinuria	75 (1.8%)	63 (1.5%)	0.3046
Other Morbidities	173 (4.2%)	173 (4.2%)	1.0000
Pancreatitis	14 (0.3%)	9 (0.2%)	0.3067
Retinopathy	161 (3.9%)	167 (4.1%)	0.7782
Carotid Stenosis [8]			
n	316	346	
Mean (%) (SD)	59.0 (21.04)	56.9 (22.99)	0.4101
Medication Taken at Baseline			
Anti-Diabetic, n (%)	2190 (53.6%)	2196 (53.7%)	0.9036
Anti-Hypertensive	3895 (95.3%)	3895 (95.2%)	0.9605
Anti-Platelet[9]	3257 (79.7%)	3236 (79.1%)	0.5514

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
One Anti-platelet	2416 (59.09%)	2408 (58.88%)	0.8469
Two or more Anti-platelets	841 (20.57%)	828 (20.24%)	0.7171
Anticoagulant	385 (9.4%)	390 (9.5%)	0.8531
Anticoagulant plus Anti-platelet	137 (3.4%)	137 (3.4%)	0.9984
No Antithrombotic	584 (14.3%)	601 (14.7%)	0.5965
ACE	2112 (51.7%)	2131 (52.1%)	0.6825
ARB	1108 (27.1%)	1096 (26.8%)	0.7598
ACE or ARB	3164 (77.4%)	3176 (77.7%)	0.7662
Beta Blockers	2902 (71.0%)	2880 (70.4%)	0.5812

Abbreviations: ABI = ankle brachial index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

In general, the baseline value is defined as the last non-missing measurement obtained prior to the randomization.
The baseline LDL-C value obtained via Preparative Ultracentrifugation was used, unless this value was missing. If the LDL-C Preparative Ultracentrifugation value was missing, then another LDL-C value was be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators (1).
For all other lipid and lipoprotein marker parameters, wherever possible, baseline was derived as the arithmetic mean of the Visit 2 (Day 0) value and the preceding Visit 1 (or Visit 1.1) value. If only one of these values was available, the single available value was used as baseline.

[1] P-value comparing two treatment groups is from a Wilcoxon test for continuous variables and a Chi-Square test for categorical variables.
[2] Race as reported by the investigators.
[3] Body-mass index is the weight in kilograms divided by the square of the height in meters.
[4] Westernized region includes Australia, Canada, Netherlands, New Zealand, United States, and South Africa.
[5] Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.

[6] Asia Pacific region includes India.
[7] The summary is based on the data collected from CV history Case Report Form (CRF).
[8] Two outliers of Carotid Stenosis (%) with a value over 100% are excluded from the analysis. Carotid Stenosis (%) data reported in categorical format of >x% and <y% is analysed as x% and y%, respectively; and data reported as x% to y% is analysed as an average of x% and y%.
[9] Anti-platelet medications were classified as dual if both components have a regulatory approval affirming anti-platelet effects. Combinations where one element lacks such regulatory approval were excluded (e.g. aspirin + magnesium oxide is classified as a single agent because the latter component is not approved as an anti-platelet agent).

Online Table 2. Baseline Characteristics of Patients with No Primary Endpoint Events, a Single Event, or Multiple Events

	No Events (N=6573)	**1 Event (N=844)**	**Multiple Events (N=762)**	***P* Value [1]**
Demographics				
Age (years), Median (Q1-Q3)	63.0 (57.0 - 69.0)	65.0 (59.0 - 71.0)	64.0 (58.0 - 70.0)	0.0400
Age ≥ 65 years, n (%)	2939 (44.7%)	456 (54.0%)	368 (48.3%)	0.0217
Male, n (%)	4556 (69.3%)	661 (78.3%)	605 (79.4%)	0.5972
White, n (%)[2]	5921 (90.1%)	765 (90.6%)	693 (90.9%)	0.8328
BMI (kg/m^2), Median (Q1-Q3)	30.8 (27.8 - 34.6)	31.1 (27.8 - 34.7)	30.8 (28.0 - 34.2)	0.2609
BMI ≥ 30, n (%)[3]	3762 (57.2%)	499 (59.1%)	432 (56.7%)	0.4656
Stratification Factors				
Geographic Region				0.0082
Westernized [4]	4547 (69.2%)	639 (75.7%)	625 (82.0%)	
Eastern Europe [5]	1796 (27.3%)	185 (21.9%)	125 (16.4%)	
Asia Pacific [6]	230 (3.5%)	20 (2.4%)	12 (1.6%)	
CV Risk Category as Randomized, n (%)				<.0001
Secondary Prevention	4488 (68.3%)	640 (75.8%)	657 (86.2%)	
Primary Prevention	2085 (31.7%)	204 (24.2%)	105 (13.8%)	

	No Events (N=6573)	**1 Event (N=844)**	**Multiple Events (N=762)**	***P* Value [1]**
Ezetimibe Use, n (%)	401 (6.1%)	59 (7.0%)	64 (8.4%)	0.2892
Statin Intensity and Diabetes Status				
Statin Intensity, n (%)				0.7138
Low	428 (6.5%)	49 (5.8%)	44 (5.8%)	
Moderate	4141 (63.0%)	519 (61.5%)	448 (58.8%)	
High	1974 (30.0%)	274 (32.5%)	268 (35.2%)	
Missing	30 (0.5%)	2 (0.2%)	2 (0.3%)	
Diabetes, n (%)				0.4420
Type 1 Diabetes	44 (0.7%)	5 (0.6%)	8 (1.0%)	
Type 2 Diabetes	3774 (57.4%)	511 (60.5%)	445 (58.4%)	
No Diabetes at Baseline	2752 (41.9%)	328 (38.9%)	309 (40.6%)	
Missing	3 (0.0%)	0	0	
Laboratory Measurements				
hsCRP (mg/L), Median (Q1-Q3)	2.1 (1.1 - 4.4)	2.4 (1.2 - 5.3)	2.4 (1.2 - 4.6)	0.3325
Triglycerides (mg/dL), Median (Q1-Q3)	215.5 (176.0 - 272.0)	215.5 (175.0 - 270.3)	223.0 (178.5 - 285.5)	0.0701
Triglycerides Category				0.2017
< 150 mg/dL	686 (10.4%)	79 (9.4%)	76 (10.0%)	
150 to <200 mg/dL	1922 (29.2%)	259 (30.7%)	203 (26.6%)	

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
≥ 200 mg/dL	3961 (60.3%)	506 (60.0%)	483 (63.4%)	
Triglycerides Tertiles, n (%)				0.1993
Lowest (≤190 mg/dL)	2235 (34.0%)	287 (34.0%)	237 (31.1%)	
Middle (>190 – ≤250 mg/dL)	2167 (33.0%)	283 (33.5%)	246 (32.3%)	
Upper (>250 mg/dL)	2167 (33.0%)	274 (32.5%)	279 (36.6%)	
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL	1254 (19.1%)	173 (20.5%)	190 (24.9%)	0.0336
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (35.0 - 46.0)	39.5 (34.4 - 45.5)	38.8 (33.5 - 44.5)	0.0631
LDL-C (mg/dL), Median (Q1-Q3)	75.0 (62.0 - 89.0)	75.0 (63.0 - 88.0)	75.0 (63.0 - 89.0)	0.7384
LDL-C Tertiles, n (%)				0.5416
Lowest (≤67 mg/dL)	2321 (35.3%)	283 (33.5%)	263 (34.5%)	
Middle (>67 – ≤84 mg/dL)	2156 (32.8%)	302 (35.8%)	253 (33.2%)	
Upper (>84 mg/dL)	2092 (31.8%)	259 (30.7%)	246 (32.3%)	
EPA (µg/mL), Median (Q1-Q3)	26.2 (17.2 - 40.4)	24.6 (15.9 - 36.7)	26.9 (17.7 - 40.2)	0.0120
Cardiovascular Disease History [7]				

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Prior Atherosclerotic Cardiovascular Disease (ASCVD)	4370 (66.5%)	633 (75.0%)	648 (85.0%)	<0.0001
Prior Atherosclerotic Coronary Artery Disease and Related Morbidities	3662 (55.7%)	542 (64.2%)	576 (75.6%)	<0.0001
Myocardial Infarction	2931 (44.6%)	430 (50.9%)	458 (60.1%)	0.0002
Unstable Angina	1497 (22.8%)	236 (28.0%)	299 (39.2%)	<0.0001
Ischemic Dilated Cardiomyopathy	164 (2.5%)	46 (5.5%)	36 (4.7%)	0.5707
Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities	965 (14.7%)	173 (20.5%)	165 (21.7%)	0.5816
Carotid Disease	543 (8.3%)	90 (10.7%)	82 (10.8%)	1.0000
Ischemic Stroke	380 (5.8%)	64 (7.6%)	65 (8.5%)	0.5203
Transient Ischemic Attack	254 (3.9%)	61 (7.2%)	60 (7.9%)	0.6371
Prior Atherosclerotic Peripheral Arterial Disease	548 (8.3%)	109 (12.9%)	118 (15.5%)	0.115
Peripheral Artery Disease	534 (8.1%)	106 (12.6%)	114 (15.0%)	0.1679
ABI <0.9 Without Symptoms of Intermittent Claudication	132 (2.0%)	24 (2.8%)	17 (2.2%)	0.5269
Prior Non-Atherosclerotic Cardiovascular Disease	5836 (88.8%)	775 (91.8%)	683 (89.6%)	0.1420
Prior Structural Cardiac Disorders	1289 (19.6%)	234 (27.7%)	170 (22.3%)	0.0133
Heart Failure	1099 (16.7%)	200 (23.7%)	147 (19.3%)	0.0337
Hypertrophic Cardiomyopathy	32 (0.5%)	6 (0.7%)	5 (0.7%)	1.0000
Non-Ischemic Dilated Cardiomyopathy	49 (0.7%)	11 (1.3%)	4 (0.5%)	0.1239
Non-Rheumatic Valvular Heart Disease	225 (3.4%)	54 (6.4%)	34 (4.5%)	0.0996

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Rheumatic Valvular Heart Disease	22 (0.3%)	3 (0.4%)	1 (0.1%)	0.6265
Prior Cardiac Arrhythmias	354 (5.4%)	65 (7.7%)	53 (7.0%)	0.6322
Atrio-Ventricular Block Above First Degree	77 (1.2%)	15 (1.8%)	13 (1.7%)	1.0000
Sick Sinus Syndrome	49 (0.7%)	5 (0.6%)	8 (1.0%)	0.4056
Supra-Ventricular Tachycardia Other Than Atrial fibrillation/Atrial flutter	115 (1.7%)	24 (2.8%)	12 (1.6%)	0.0934
Sustained Ventricular Tachycardia	50 (0.8%)	10 (1.2%)	8 (1.0%)	0.8179
Torsades De Pointes	3 (0.0%)	0 (0.0%)	1 (0.1%)	0.4745
Ventricular Fibrillation	95 (1.4%)	16 (1.9%)	15 (2.0%)	1.0000
Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders	5716 (87.0%)	752 (89.1%)	666 (87.4%)	0.3125
Hypotension	52 (0.8%)	9 (1.1%)	17 (2.2%)	0.0754
Hypertension	5669 (86.2%)	750 (88.9%)	665 (87.3%)	0.3544
Non-Ischemic Stroke	123 (1.9%)	24 (2.8%)	16 (2.1%)	0.4231
Hemorrhagic Stroke	32 (0.5%)	4 (0.5%)	4 (0.5%)	1.0000
Stroke of Unknown Origin	92 (1.4%)	20 (2.4%)	13 (1.7%)	0.3826
Arterial Embolism	9 (0.1%)	11 (1.3%)	1 (0.1%)	0.0069
Deep Vein Thrombosis	90 (1.4%)	20 (2.4%)	20 (2.6%)	0.7514
Pulmonary Embolism	49 (0.7%)	12 (1.4%)	12 (1.6%)	0.8391
Other Prior Conditions or Investigations Influencing Cardiovascular Risk	4870 (74.1%)	642 (76.1%)	587 (77.0%)	0.6799

	No Events (N=6573)	**1 Event (N=844)**	**Multiple Events (N=762)**	***P* Value [1]**
Prior Metabolic Disorders	3988 (60.7%)	530 (62.8%)	477 (62.6%)	0.9588
Type 1 Diabetes	45 (0.7%)	5 (0.6%)	8 (1.0%)	0.4056
Type 2 Diabetes	3774 (57.4%)	511 (60.5%)	445 (58.4%)	0.3872
Baseline Laboratory Abnormalities	2725 (41.5%)	395 (46.8%)	370 (48.6%)	0.4842
Renal Disorders	660 (10.0%)	129 (15.3%)	110 (14.4%)	0.6737
Creatinine Clearance >30 And <60 mL/Min	430 (6.5%)	83 (9.8%)	82 (10.8%)	0.5651
Proteinuria	100 (1.5%)	20 (2.4%)	18 (2.4%)	1.0000
Macroalbuminuria	43 (0.7%)	7 (0.8%)	8 (1.0%)	0.7964
Microalbuminuria	217 (3.3%)	38 (4.5%)	25 (3.3%)	0.2468
Other Morbidities	275 (4.2%)	42 (5.0%)	29 (3.8%)	0.2754
Pancreatitis	19 (0.3%)	2 (0.2%)	2 (0.3%)	1.0000
Retinopathy	259 (3.9%)	42 (5.0%)	27 (3.5%)	0.1758
Carotid Stenosis[8]				
n	503	86	73	
Mean (%) (SD)	57.0(21.94)	58.2(22.85)	63.5(21.67)	0.1582
Medication Taken at Baseline				

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Anti-Diabetic	3498 (53.2%)	478 (56.6%)	410 (53.8%)	0.2548
Anti-Hypertensive	6239 (94.9%)	817 (96.8%)	734 (96.3%)	0.6008
Anti-Platelet	5138 (78.2%)	691 (81.9%)	664 (87.1%)	0.0037
One Anti-platelet	3912 (59.52%)	486 (57.58%)	426 (55.91%)	0.4980
Two or more Anti-platelets	1226 (18.65%)	205 (24.29%)	238 (31.23%)	0.0019
Anticoagulant	560 (8.5%)	125 (14.8%)	90 (11.8%)	0.0780
Anticoagulant plus Anti-platelet	185 (2.8%)	46 (5.5%)	43 (5.6%)	0.8661
No Antithrombotic	1060 (16.1%)	74 (8.8%)	51 (6.7%)	0.1212
ACE	3424 (52.1%)	429 (50.8%)	390 (51.2%)	0.8880
ARB	1743 (26.5%)	235 (27.8%)	226 (29.7%)	0.4220
ACE or ARB	5090 (77.4%)	645 (76.4%)	605 (79.4%)	0.1518
Beta Blockers	4541 (69.1%)	655 (77.6%)	586 (76.9%)	0.7368

Abbreviations: ABI = ankle brachial index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

In general, the baseline value is defined as the last non-missing measurement obtained prior to the randomization.
The baseline LDL-C value obtained via Preparative Ultracentrifugation was used, unless this value was missing. If the LDL-C Preparative Ultracentrifugation value was missing, then another LDL-C value was be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators (1).
For all other lipid and lipoprotein marker parameters, wherever possible, baseline was derived as the arithmetic mean of the Visit 2 (Day 0) value and the preceding Visit 1 (or Visit 1.1) value. If only one of these values was available, the single available value was used as baseline.

[1] P-value comparing Single Event group with Multiple Events group is from a Wilcoxon test for continuous variables and a Chi-Square test for categorical variables.
[2] Race as reported by the investigators.
[3] Body-mass index is the weight in kilograms divided by the square of the height in meters.
[4] Westernized region includes Australia, Canada, Netherlands, New Zealand, United States, and South Africa.
[5] Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.
[6] Asia Pacific region includes India.
[7] The summary is based on the data collected from CV history Case Report Form (CRF).
[8] Two outliers of Carotid Stenosis (%) with a value over 100% are excluded from the analysis. Carotid Stenosis (%) data reported in categorical format of >x% and <y% is analysed as x% and y%, respectively; and data reported as x% to y% is analysed as an average of x% and y%.
[9] Anti-platelet medications were classified as dual if both components have a regulatory approval affirming anti-platelet effects. Combinations where one element lacks such regulatory approval were excluded (e.g. aspirin + magnesium oxide is classified as a single agent because the latter component is not approved as an anti-platelet agent).

Online Table 3. Hazard Ratios for Pre-Specified Analyses of Total for Primary and Key Secondary Composite Endpoint Events Using the Reduced Dataset

		Primary composite endpoint				Key secondary composite endpoint			
		Unadjusted RR/HR (95% CI)	Unadjusted p-value	Adjusted RR/HR (95% CI)	Adjusted p-value	Unadjusted RR/HR (95% CI)	Unadjusted p-value	Adjusted RR/HR (95% CI)	Adjusted p-value
Negative binomial		0.68 (0.61, 0.77)	1.5×10^{-10}	0.70 (0.62, 0.78)	3.6×10^{-10}	0.71 (0.62, 0.82)	8.9×10^{-7}	0.72 (0.63, 0.82)	7.1×10^{-7}
Andersen-Gill (I)		0.69 (0.64, 0.74)	3.5×10^{-21}	0.69 (0.64, 0.74)	3.3×10^{-21}	0.72 (0.64, 0.80)	2.4×10^{-9}	0.72 (0.64, 0.80)	2.4×10^{-9}
Andersen-Gill (II)		0.69 (0.61, 0.77)	9.1×10^{-11}	0.69 (0.61, 0.77)	5.2×10^{-11}	0.72 (0.63, 0.82)	1.2×10^{-6}	0.72 (0.63, 0.82)	1.0×10^{-6}
Modified WLW	First event	0.76 (0.69, 0.83)	2.7×10^{-8}	0.75 (0.68, 0.83)	1.6×10^{-8}	0.74 (0.65, 0.83)	7.4×10^{-7}	0.74 (0.65, 0.83)	7.0×10^{-7}
	Second event	0.69 (0.60, 0.79)	2.7×10^{-8}	0.68 (0.60, 0.78)	1.8×10^{-8}	0.75 (0.63, 0.89)	1.1×10^{-3}	0.75 (0.63, 0.89)	1.1×10^{-3}
	Third event	0.69 (0.59, 0.82)	2.1×10^{-5}	0.69 (0.59, 0.82)	2.0×10^{-5}	0.79 (0.65, 0.96)	.0170	0.79 (0.65, 0.96)	.0171

Abbreviations: CI = confidence interval; HR = hazard ratio; RR = rate ratio; WLW = Wei-Lin-Weisfeld.

Rate ratios (RR) are presented for results from negative binomial model; Hazard ratios (HR) are presented for results from Andersen Gill (I) model, Andersen Gill (II) model, and modified Wei-Lin-Weisfeld model.
Unadjusted analyses only included treatment group in the model; Adjusted analyses also included stratification factors (cardiovascular risk category, geographic region, and use of ezetimibe) as covariate, in addition to treatment group in the model.

Negative binomial model (2-4).

Andersen Gill (I) model is based on an intensity model with model-based variance estimate and was a pre-specified methodology (5).
Andersen Gill (II) model is based on a proportional means model with cluster-robust standard errors, with the cluster set to the patient ID. This is an updated methodology (6).
Wei-Lin-Weisfeld model is based on Li-Lagakos modification (7,8). In this modified WLW analysis, second event is defined as nonfatal second event or cardiovascular death, and third event is defined as nonfatal third event or cardiovascular death.
Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day as a single event.

Online Table 4. Results from Joint Frailty Model for Primary and Key Secondary Composite Endpoints Using the Reduced Dataset

		Nonfatal Cardiovascular Event		Cardiovascular Death	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Primary composite endpoint	Unadjusted	0.66 (0.60, 0.73)	7.40×10^{-17}	0.80 (0.65, 0.98)	0.0282
	Adjusted	0.67 (0.61, 0.74)	7.20×10^{-16}	0.80 (0.65, 0.98)	0.0306
Key secondary composite endpoint	Unadjusted	0.68 (0.59, 0.78)	3.30×10^{-8}	0.79 (0.63, 0.99)	0.0366
	Adjusted	0.68 (0.59, 0.78)	4.30×10^{-8}	0.79 (0.63, 0.99)	0.0380

Abbreviations: CI, confidence interval; HR, hazard ratio.

Joint frailty model is based on Rondeau (2007) implemented in the frailtypack R package (9). Default settings were used, except that 3 knots were used to model the baseline hazard function (to improve speed given that we know from the mean cumulative plots that the shape of the baseline hazard function is unlikely to be complex) and recurrentAG==TRUE (i.e., thereby assuming independence between events conditional on the frailty term).

Unadjusted analyses only included treatment group in the model; Adjusted analyses also included stratification factors (cardiovascular risk category, geographic region, and use of ezetimibe) as covariate, in addition to treatment group in the model.

Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day as a single event.

Online Table 5. Hazard and Rate Ratios for Pre-Specified Analyses for Primary and Key Secondary Composite Endpoints Using the Full Dataset

	Primary Composite Endpoint				Key Secondary Composite Endpoint			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	RR/HR (95% CI)	p-value	RR/HR (95% CI)	p-value	RR/HR (95% CI)	p-value	HR (95% CI)	p-value
Negative binomial	0.67 (0.60, 0.76)	1.6×10^{-10}	0.69 (0.61, 0.77)	4.4×10^{-10}	0.71 (0.62, 0.81)	1.4×10^{-6}	0.71 (0.62, 0.82)	1.2×10^{-6}
Andersen-Gill (I)	0.68 (0.63, 0.74)	3.4×10^{-22}	0.68 (0.63, 0.74)	3.0×10^{-22}	0.71 (0.64, 0.79)	1.8×10^{-10}	0.71 (0.63, 0.79)	1.7×10^{-10}
Andersen-Gill (II)	0.68 (0.61, 0.77)	4.5×10^{-11}	0.68 (0.61, 0.76)	3.4×10^{-11}	0.71 (0.62, 0.81)	4.1×10^{-7}	0.71 (0.62, 0.81)	3.4×10^{-7}
Modified WLW								
First event	0.76 (0.69, 0.83)	2.7×10^{-8}	0.75 (0.68, 0.83)	1.7×10^{-8}	0.74 (0.65, 0.83)	7.4×10^{-7}	0.74 (0.65, 0.83)	7.1×10^{-7}
Second event	0.69 (0.61, 0.78)	4.6×10^{-9}	0.68 (0.60, 0.77)	3.1×10^{-9}	0.75 (0.63, 0.89)	0.0011	0.75 (0.63, 0.89)	0.0011
Third event	0.70 (0.60, 0.83)	2.2×10^{-5}	0.70 (0.60, 0.83)	2.1×10^{-5}	0.79 (0.65, 0.96)	0.0170	0.79 (0.65, 0.96)	0.0171

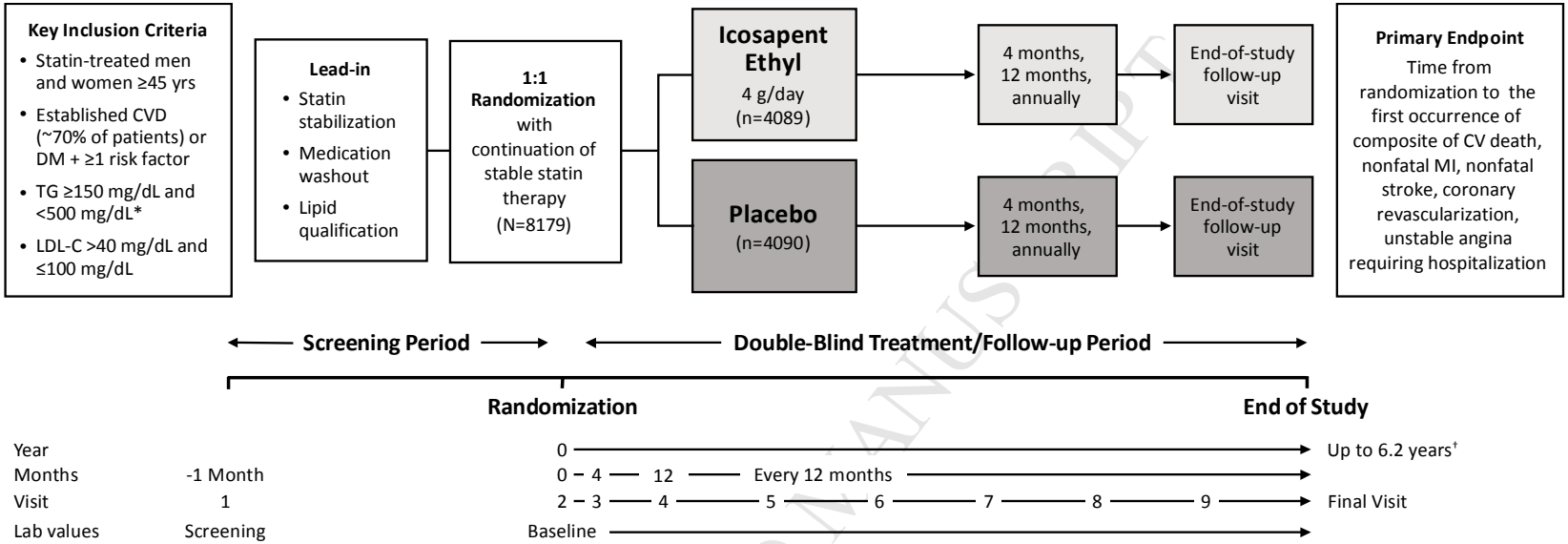
Abbreviations: CI, confidence interval; HR, hazard ratio; RR, rate ratio; WLW, Wei-Lin-Weisfeld.

Rate ratios (RR) are presented for results from negative binomial model; Hazard ratios (HR) are presented for results from Andersen Gill (I) model, Andersen Gill (II) model, and modified Wei-Lin-Weisfeld model.
Unadjusted analyses only included treatment group in the model; Adjusted analyses also included stratification factors (cardiovascular risk category, geographic region, and use of ezetimibe) as covariate, in addition to treatment group in the model.

Negative Binomial model (2-4).
Andersen Gill (I) model is based on an intensity model with model-based variance estimate and was a pre-specified methodology (5).
Andersen Gill (II) model is based on a proportional means model with cluster-robust standard errors, with the cluster set to the patient ID. This is an updated methodology (6).

Wei-Lin-Weisfeld is based on Li-Lagakos modification (7,8). In this modified WLW analysis, second event is defined as nonfatal second event or cardiovascular death, and third event is defined as nonfatal third event or cardiovascular death.
Analyses are based on total adjudicated event dataset without accounting for multiple endpoints occurring in a single calendar day as a single event.

Online Figure 1. Study Design



Abbreviations: CVD = cardiovascular disease, DM = diabetes mellitus, LDL-C = low density lipoprotein cholesterol, MI = myocardial infarction, TG =triglyceride.

*Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

†Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years)

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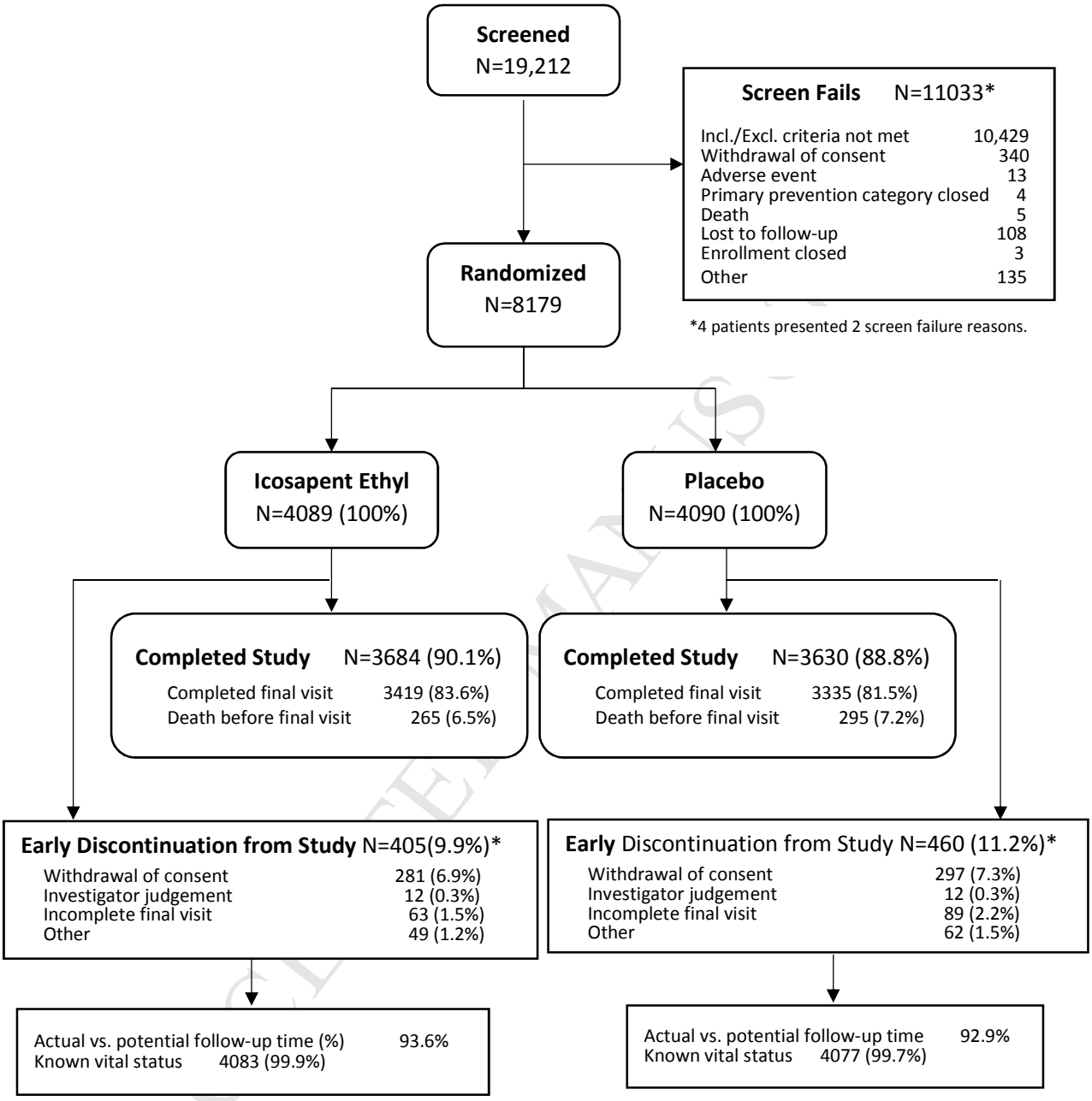
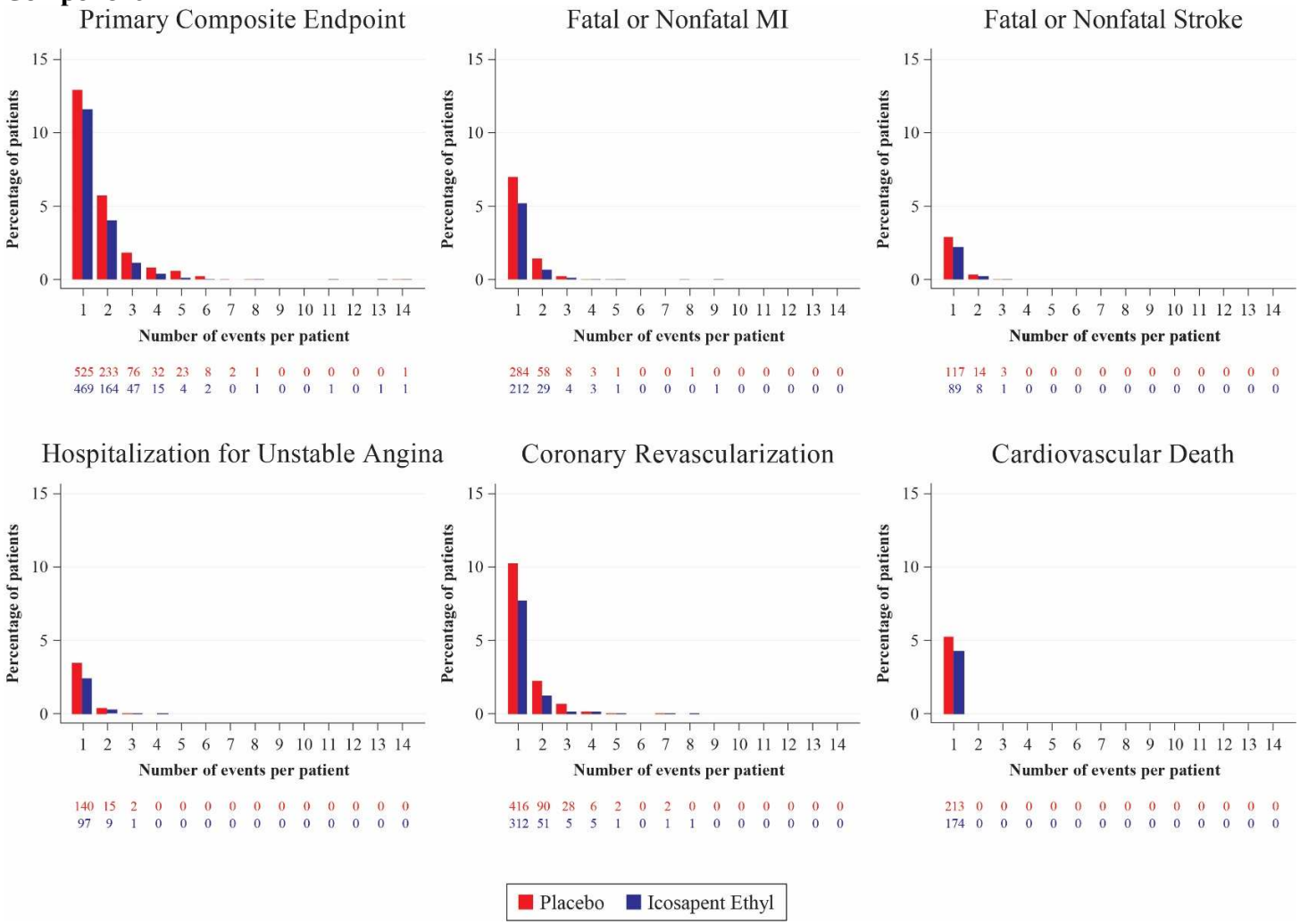
Online Figure 2. CONSORT Diagram



* Early discontinuation from study (9.9% icosapent ethyl; 11.2% placebo) includes patients that discontinued after having a primary event (25 [0.6%] icosapent ethyl;52 [1.3% placebo) and prior to having an event (380 [9.3%icosapent ethyl; 408 [10.0%] placebo).
Incl denotes inclusion, excl exclusion.

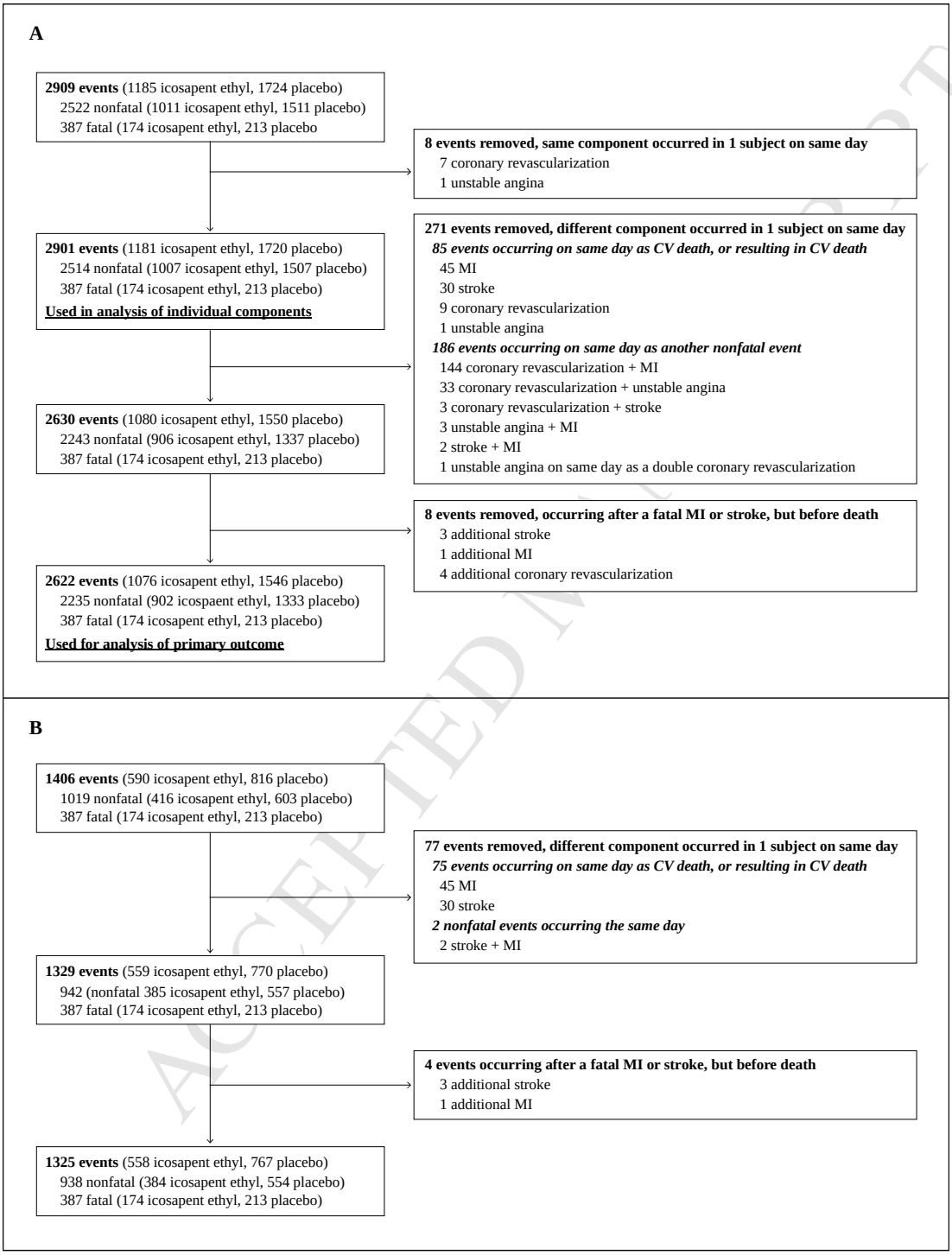
Reproduced from Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11-22; permission pending.

Online Figure 3. Total Events by Number of Events per Patient for the Primary Composite Endpoint and for Each Component



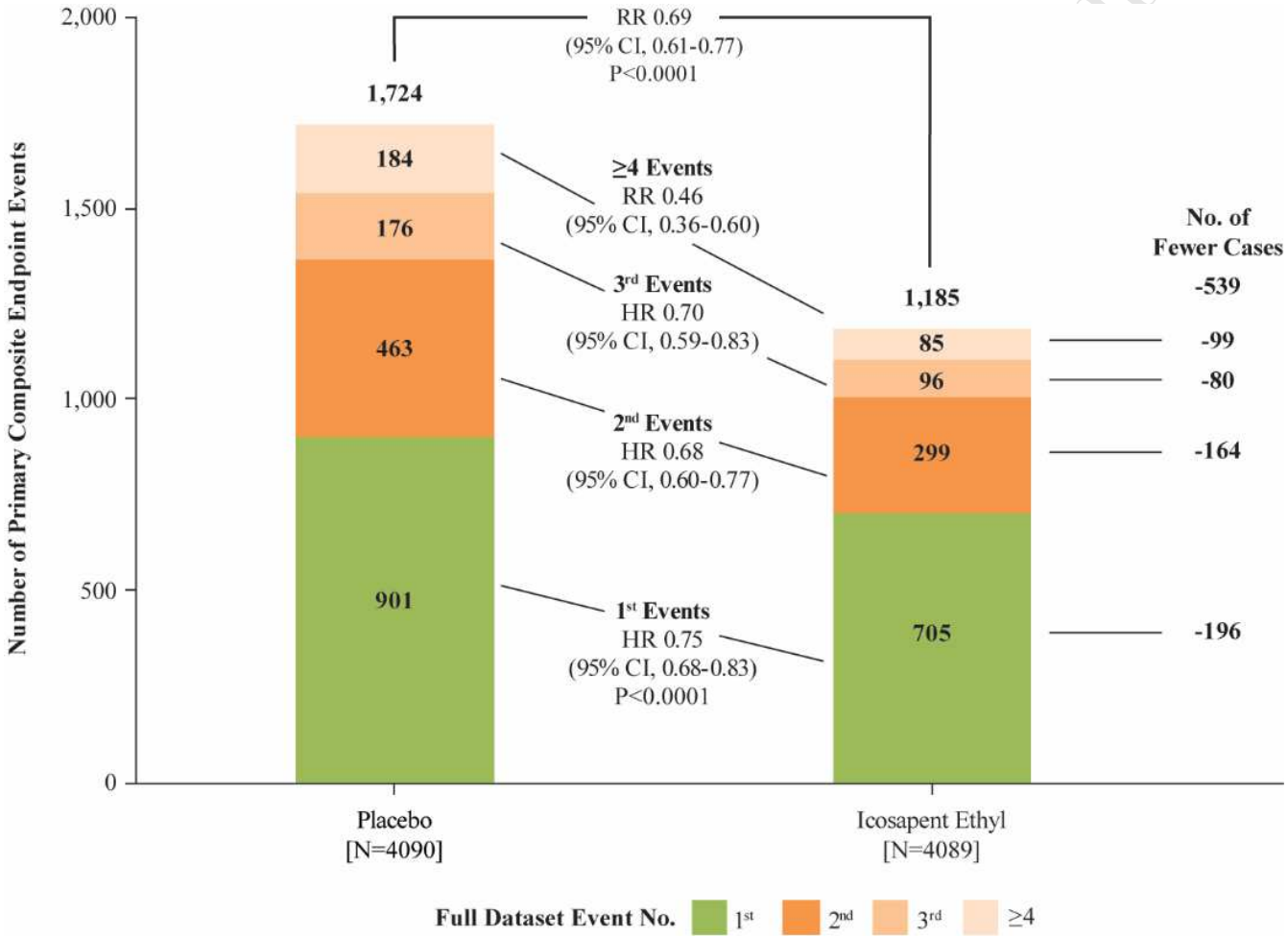
Analyses are based on total adjudicated event dataset without accounting for multiple endpoints occurring in a single calendar day as a single event.

Online Figure 4. Flow Chart of Total Primary (A) and Key Secondary (B) Composite Endpoint Events Accounting



MI = myocardial infarction. Unstable angina indicates hospitalization for unstable angina.

Online Figure 5. Distribution of First and Subsequent Primary Composite Endpoint Events in the Full Dataset for Patients Randomized 1:1 to Icosapent Ethyl Versus Placebo



Abbreviations: CI = confidence interval; HR = hazard ratio; RR = rate ratio.

Hazard ratios (HR) and 95% confidence intervals (CI) for between treatment group comparisons were generated using Li-Lagakos-modified Wei-Lin-Weissfeld (WLW) method for the 1st event, 2nd event, and 3rd event categories. Rate ratio (RR) and 95% CI for between group comparisons used a negative binomial model for additional events beyond 1st, 2nd, 3rd occurrences, i.e., 4th 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.

Methods: Study Design and Participants

A complete description of methods for REDUCE-IT was previously published (Bhatt 2017). Within this Appendix we summarize: select inclusion/exclusion criteria; the prespecified definitions for primary and key secondary endpoints, the total event analysis outcome measure and methodological details describing handling conventions for specific event combinations:

Select Inclusion/Exclusion Criteria:

The secondary prevention stratum consisted of patients with documented coronary artery disease (≥50% stenosis in at least two major epicardial coronary arteries with or without prior revascularization; prior MI; hospitalization for non-ST-segment elevation acute coronary syndrome with ST-segment deviation or positive biomarkers); documented cerebrovascular disease (prior ischemic stroke; symptomatic ≥50% carotid stenosis; asymptomatic carotid disease with ≥70% stenosis; history of carotid revascularization); or documented peripheral artery disease (ankle-brachial index <0.9 with symptoms of intermittent claudication; history of aorto-iliac or peripheral surgery or intervention).

Primary prevention patients were to have no documented cardiovascular disease as defined above, to have diabetes, be ≥50 years old and have at least one of the following additional cardiovascular risk factors: increased age of ≥55 years if male or ≥65 years if female; cigarette smoker or stopped smoking within 3 months before first visit; blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic or on antihypertensive medication; HDL-cholesterol ≤40 mg/dL for men or ≤50 mg/dL for women; hs-CRP >3 mg/L; creatinine clearance >30 and <60 mL/min; non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation; micro- or macro-albuminuria; or asymptomatic ankle-brachial index <0.9.

Exclusion criteria included (but were not limited to) severe heart failure, severe liver disease, poorly controlled hypertension, hemoglobin A1c levels >10.0%, planned coronary intervention, familial lipoprotein lipase deficiency, intolerance or hypersensitivity to statins, history of acute or chronic pancreatitis, and hypersensitivity to fish, shellfish, or ingredients of icosapent ethyl or placebo. All patients provided written informed consent.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the time from randomization to the first occurrence of the composite of the following clinical events:

- CV death
- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs)
- Nonfatal stroke
- Coronary revascularization
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

Key Secondary Efficacy Endpoint:

The key secondary efficacy endpoint is the time from randomization to the first occurrence of the composite of:

- CV death
- Nonfatal MI (including silent MI)
- Nonfatal stroke.

Total event analysis outcome:

The prespecified total event analysis was defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

Exploratory analyses of the total of first and subsequent events were also performed for the key secondary composite endpoint.

All clinical endpoint events used in these efficacy analyses were adjudicated by an independent Clinical Endpoint Committee (CEC) whose members (specialists in cardiology or neurology) were blinded to treatment assignment. The CEC charter pre-specified handling conventions for specific event combinations. During adjudication, the CEC charter stipulated that cases of unstable angina leading to myocardial infarction within 48 hours were to be considered a single pathophysiologic process and counted as a single myocardial infarction. Episodes of ischemic chest discomfort separated from the myocardial infarction by a quiescent period of more than 48 hours were to be considered as two separate events. In cases of non-ST elevation myocardial infarctions and percutaneous coronary intervention, elevated baseline cardiac troponin values that were stable or falling and were followed by a rise in biomarkers of 20% or more were to constitute evidence of a second infarction due to the intervention itself. Additionally, patients with a transient ischemic attack (symptoms resolving within 24 hours) followed by a stroke (either ischemic or hemorrhagic) were to be considered as having two separate events. An imaging study taken during the transient ischemic attack and which demonstrated necrosis or hemorrhage was to indicate a stroke instead of a transient ischemic attack even if symptoms resolved within 24 hours. Lastly, conversion of an ischemic stroke to hemorrhagic stroke was to be considered a single event and a single pathophysiologic process.

REDUCE-IT Trial Investigators

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Trial Operations

Bioclinica (data management)

Covance (central research laboratory)

Syneos Health™ (formerly inVentiv Health; principal contract research organization)

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