Supplemental Material

This appendix has been provided by the authors to give readers additional information about their work.
Supplement to: Peterson BE, Bhatt DL, Steg PG, et. al. Reduction of Revascularization Events in Patients with Hypertriglyceridemia with Icosapent Ethyl: Insights from REDUCE-IT REVASC.

Contents

Supplemental Methods for Total Events Analyses.

To improve the performance and validity of our statistical models for total (first and subsequent events), 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). This is referred to as the reduced dataset. Statistical analyses using the full adjudicated endpoint events dataset without exclusions for this bundling approach are referred to as the full dataset.

Supplemental Table I. Baseline Demographics (A) and Medications (B) by On-Study Revascularization Status – ITT Population.

A. Baseline Demographics

	On Study Revasc. (N=920)	No On Study Revasc. (N=7259)	Overall (N=8179)	P-value[4]
Age (years)[1]				0.32
n	920	7259	8179	
Mean (SD)	63.5 (8.39)	63.4 (8.40)	63.4 (8.40)	
Median	64.0	64.0	64.0	
Min, Max	45.0, 85.0	44.0, 92.0	44.0, 92.0	
Age Group, n (%)				0.19
<65 Years	478 (52.0%)	3938 (54.2%)	4416 (54.0%)	
≥65 Years	442 (48.0%)	3321 (45.8%)	3763 (46.0%)	
Sex, n (%)				<0.0001
Male	750 (81.5%)	5072 (69.9%)	5822 (71.2%)	
Female	170 (18.5%)	2187 (30.1%)	2357 (28.8%)	
Ethnicity, n (%)				0.006
Hispanic Or Latino	23 (2.5%)	322 (4.4%)	345 (4.2%)	
Not Hispanic Or Latino	897 (97.5%)	6937 (95.6%)	7834 (95.8%)	
Race, n (%)				0.004
White	847 (92.1%)	6532 (90.0%)	7379 (90.2%)	
Black or African American	18 (2.0%)	140 (1.9%)	158 (1.9%)	
Asian	32 (3.5%)	414 (5.7%)	446 (5.5%)	
American Indian or Alaska Native	4 (0.4%)	25 (0.3%)	29 (0.4%)	
Native Hawaiian or Other Pacific Islander	1 (0.1%)	9 (0.1%)	10 (0.1%)	
Other	1 (0.1%)	64 (0.9%)	65 (0.8%)	
Multiple	17 (1.8%)	74 (1.0%)	91 (1.1%)	
Missing	0	1 (0.0%)	1 (0.0%)	
Weight (Kg)				0.001
n	920	7238	8158	
Mean (SD)	94.8 (17.77)	92.7 (18.46)	93.0 (18.39)	

	On Study Revasc. (N=920)	No On Study Revasc. (N=7259)	Overall (N=8179)	P-value[4]
Median	93.0	91.0	91.1	
Min, Max	49.9, 197.3	40.8, 189.4	40.8, 197.3	
Height (cm)				<0.0001
n	920	7230	8150	
Mean (SD)	173.2 (8.89)	171.1 (9.76)	171.3 (9.69)	
Median	174.0	172.0	172.0	
Min, Max	145.4, 199.0	137.2, 208.0	137.2, 208.0	
BMI (Kg/m^2)				0.57
n	919	7230	8149	
Mean (SD)	31.5 (5.13)	31.6 (5.48)	31.6 (5.44)	
Median	30.8	30.8	30.8	
Min, Max	19.5, 57.4	16.4, 65.0	16.4, 65.0	
BMI Group				0.40
<25 Kg/m^2	60 (6.5%)	555 (7.6%)	615 (7.5%)	
≥25 to <30 Kg/m^2	331 (36.0%)	2510 (34.6%)	2841 (34.7%)	
≥30 Kg/m^2	528 (57.4%)	4165 (57.4%)	4693 (57.4%)	
Missing	1 (0.1%)	29 (0.4%)	30 (0.4%)	
Waist Circumference (cm)				0.07
n	905	7151	8056	
Mean (SD)	107.4 (12.72)	106.6 (13.48)	106.7 (13.40)	
Median	106.7	105.0	105.4	
Min, Max	71.0, 160.0	44.0, 182.9	44.0, 182.9	
Geographic Region, n (%)				<0.0001
Westernized	769 (83.6%)	5042 (69.5%)	5811 (71.0%)	
Non-Westernized[2]	151 (16.4%)	2217 (30.5%)	2368 (29.0%)	
Cardiovascular Risk Category, n (%)				<0.0001
Established Cardiovascular Disease	770 (83.7%)	5015 (69.1%)	5785 (70.7%)	
Diabetes plus Risk Factors	150 (16.3%)	2244 (30.9%)	2394 (29.3%)	
Ezetimibe Use, n (%)				0.0001
No	834 (90.7%)	6821 (94.0%)	7655 (93.6%)	
Yes	86 (9.3%)	438 (6.0%)	524 (6.4%)	

	On Study Revasc. (N=920)	No On Study Revasc. (N=7259)	Overall (N=8179)	P-value[4]
Renal Impairment (eGFR<60 ml/min/1.73m^2), n (%)				0.64
Yes	210 (22.8%)	1606 (22.1%)	1816 (22.2%)	
No	710 (77.2%)	5647 (77.8%)	6357 (77.7%)	
Missing	0	6 (0.1%)	6 (0.1%)	
Baseline eGFR, n (%)				0.10
<60 mL/min/1.73m^2	210 (22.8%)	1606 (22.1%)	1816 (22.2%)	
≥60 and <90 mL/min/1.73m^2	522 (56.7%)	3933 (54.2%)	4455 (54.5%)	
≥90 mL/min/1.73m^2	188 (20.4%)	1714 (23.6%)	1902 (23.3%)	
Missing	0	6 (0.1%)	6 (0.1%)	
Diabetes, n (%)				0.38
No Diabetes at Baseline	403 (43.8%)	2986 (41.1%)	3389 (41.4%)	
Both Type I and Type II Diabetes	0	1 (0.0%)	1 (0.0%)	
Type I Diabetes	8 (0.9%)	49 (0.7%)	57 (0.7%)	
Type II Diabetes	509 (55.3%)	4220 (58.1%)	4729 (57.8%)	
Missing	0	3 (0.0%)	3 (0.0%)	
Type I or II [3]	517 (56.2%)	4270 (58.8%)	4787 (58.5%)	0.84
BMI <25 Kg/m^2	27 (5.2%)	245 (5.7%)	272 (5.7%)	
BMI ≥ 25 to <30 Kg/m^2	151 (29.2%)	1206 (28.2%)	1357 (28.3%)	
BMI ≥ 30 Kg/m^2	339 (65.6%)	2799 (65.6%)	3138 (65.6%)	
BMI Missing	0	20 (0.5%)	20 (0.4%)	
Hypertension[5], n (%)				0.48
Yes	790 (85.9%)	6294 (86.7%)	7084 (86.6%)	
No	130 (14.1%)	965 (13.3%)	1095 (13.4%)	
Metabolic Syndrome[6], n (%)				0.86
Yes	850 (92.4%)	6695 (92.2%)	7545 (92.2%)	
No	70 (7.6%)	564 (7.8%)	634 (7.8%)	
Impaired Glucose Metabolism[7], n (%)				0.33
Yes	348 (37.8%)	2623 (36.1%)	2971 (36.3%)	
No	572 (62.2%)	4629 (63.8%)	5201 (63.6%)	
Missing	0	7 (0.1%)	7 (0.1%)	

	On Study Revasc. (N=920)	No On Study Revasc. (N=7259)	Overall (N=8179)	P-value[4]
Statin Intensity, n (%)				0.03
Low	52 (5.7%)	469 (6.5%)	521 (6.4%)	
Moderate	548 (59.6%)	4560 (62.8%)	5108 (62.5%)	
High	319 (34.7%)	2197 (30.3%)	2516 (30.8%)	
Missing	1 (0.1%)	33 (0.5%)	34 (0.4%)	
hsCRP (mg/L), Median (Q1-Q3)	2.1 (1.1-4.4)	2.2 (1.1-4.5)	2.2 (1.1-4.5)	0.83
Triglycerides (mg/dL), Median (Q1-Q3)	221.3 (178.5 284.3)	215.5 (175.5-271.5)	216.0 (176.0-272.5)	0.02
HDL-C (mg/dL), Median (Q1-Q3)	39.0 (33.5-44.5)	40.0 (35.0-46.0)	40.0 (35.0-46.0)	<0.0001
LDL-C (mg/dL), Median (Q1-Q3)	75.0 (63.0-89.0)	75.0 (62.0-89.0)	75.0 (62.0-89.0)	0.95
Triglycerides Category				0.29
< 150 mg/dL	90 (9.8%)	751 (10.3%)	841 (10.3%)	
150 - <200 mg/dL	251 (27.3%)	2133 (29.4%)	2384 (29.1%)	
≥ 200 mg/dL	579 (62.9%)	4371 (60.2%)	4950 (60.5%)	
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL	222 (24.1%)	1395 (19.2%)	1617 (19.8%)	0.0004
EPA (µg/mL), Median (Q1-Q3)	26.6 (18.0-39.8)	26.0 (17.0-40.1)	26.1 (17.1-40.0)	0.35

Note: Percentages are based on the number of subjects randomized to each treatment group in the ITT population (N) except as noted below.
[1] Age (years) is at Randomization.
[2] Eastern Europe, Asia Pacific.
[3] Percentages are based on the number of subjects with Type 1 or Type 2 diabetes.
[4] To assess balance between treatment groups, p-values are reported from a chi-square test for categorical variables and Wilcoxon test for continuous variables. Missing categories are excluded from any comparisons.
[5] Hypertension as identified on the CRF “Cardiovascular History.”
[6] For the diagnosis of metabolic syndrome, refer to Appendix D of the study protocol “Criteria for the diagnosis of metabolic syndrome.”
[7] Impaired glucose metabolism is based on Visit 2 FBG of 100-125 mg/dL.

Note: 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 will be used, unless this value is missing. If the LDL-C Preparative Ultracentrifugation value is missing, then another LDL-C value will 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 Hopkins University investigators (Martin 2013).
For all other lipid and lipoprotein marker parameters, wherever possible, baseline will be 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 is available, the single available value will be used as baseline.

B. Baseline Medications

Medication taken at Baseline	On Study Revasc. (N=920)	No On Study Revasc. (N=7259)	p-value[1]
Anti-Diabetes	472 (51.3%)	3914 (53.9%)	0.13
Anti-Hypertensive	884 (96.1%)	6906 (95.1%)	0.20
Anti-Platelet	813 (88.4%)	5680 (78.2%)	<0.0001
One Anti-platelet	516 (56.1%)	4308 (59.3%)	0.06
Two or more Anti-platelets	297 (32.3%)	1372 (18.9%)	<0.0001
Anticoagulant	86 (9.3%)	689 (9.5%)	0.89
Anticoagulant plus Anti-platelet	40 (4.3%)	234 (3.2%)	0.07
No Antithrombotic	61 (6.6%)	1124 (15.5%)	<0.0001
ACE	452 (49.1%)	3791 (52.2%)	0.08
ARB	275 (29.9%)	1929 (26.6%)	0.03
ACE or ARB	716 (77.8%)	5624 (77.5%)	0.81
Beta Blockers	701 (76.2%)	5081 (70.0%)	<0.0001

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.
Note: Percentages are based on the number of subjects in each group (On Study Revasc./No On Study Revasc.) in the ITT population (N).
Note: Dual anti-platelets were classified as such if both components have a robust history of regulatory approval affirming anti-platelet effects, thus excluding combinations where one element lacks robust regulatory approval (e.g. Aspirin + Magnesium Oxide is classified as a single agent because the latter component lacks robust regulatory support as an anti-platelet agent).
[1] To assess balance between groups, p-values comparing 'On Study Revasc.', 'No On Study Revasc.' groups are reported from a chi-square test.

Supplemental Table II. Time to Coronary Revascularization from Date of Randomization by One Month Increments – ITT Population.

Endpoint	Icosapent Ethyl (N=4089)	Placebo (N=4090)	HR (95% CI)[1]	Log-Rank P-value
Coronary Revascularization	**376 (9.2%)**	**544 (13.3%)**	**0.66 (0.58, 0.76)**	**<0.0001**
1 Month	7 (0.2%)	11 (0.3%)	0.63 (0.25, 1.64)	0.34
2 Months	11 (0.3%)	27 (0.7%)	0.41 (0.20, 0.82)	0.009
3 Months	19 (0.5%)	37 (0.9%)	0.51 (0.29, 0.89)	0.02
4 Months	26 (0.6%)	40 (1.0%)	0.65 (0.39, 1.06)	0.08
5 Months	34 (0.8%)	51 (1.2%)	0.66 (0.43, 1.02)	0.06
6 Months	41 (1.0%)	63 (1.5%)	0.65 (0.44, 0.96)	0.03
7 Months	49 (1.2%)	73 (1.8%)	0.67 (0.46, 0.96)	0.03
8 Months	61 (1.5%)	80 (2.0%)	0.75 (0.54, 1.05)	0.10
9 Months	72 (1.8%)	89 (2.2%)	0.80 (0.59, 1.09)	0.16
10 Months	77 (1.9%)	97 (2.4%)	0.79 (0.58, 1.06)	0.11
11 Months	85 (2.1%)	114 (2.8%)	0.74 (0.56, 0.98)	0.03
12 Months	96 (2.3%)	125 (3.1%)	0.76 (0.58, 0.99)	0.04
13 Months	106 (2.6%)	138 (3.4%)	0.76 (0.59, 0.98)	0.03
14 Months	110 (2.7%)	150 (3.7%)	0.72 (0.57, 0.93)	0.01
15 Months	119 (2.9%)	161 (3.9%)	0.73 (0.58, 0.93)	0.01
16 Months	128 (3.1%)	171 (4.2%)	0.74 (0.59, 0.93)	0.01
17 Months	136 (3.3%)	185 (4.5%)	0.73 (0.58, 0.91)	0.004
18 Months	141 (3.4%)	197 (4.8%)	0.71 (0.57, 0.88)	0.002
19 Months	150 (3.7%)	203 (5.0%)	0.73 (0.59, 0.90)	0.003
20 Months	159 (3.9%)	208 (5.1%)	0.76 (0.61, 0.93)	0.008
21 Months	165 (4.0%)	222 (5.4%)	0.73 (0.60, 0.90)	0.003
22 Months	173 (4.2%)	235 (5.7%)	0.73 (0.60, 0.89)	0.001
23 Months	180 (4.4%)	247 (6.0%)	0.72 (0.59, 0.87)	0.0007
24 Months	182 (4.5%)	257 (6.3%)	0.70 (0.58, 0.84)	0.0002
25 Months	195 (4.8%)	272 (6.7%)	0.71 (0.59, 0.85)	0.0002
26 Months	199 (4.9%)	280 (6.8%)	0.70 (0.58, 0.84)	0.0001
27 Months	207 (5.1%)	292 (7.1%)	0.70 (0.58, 0.83)	<0.0001
28 Months	217 (5.3%)	302 (7.4%)	0.71 (0.59, 0.84)	<0.0001
29 Months	225 (5.5%)	311 (7.6%)	0.71 (0.60, 0.84)	<0.0001
30 Months	228 (5.6%)	318 (7.8%)	0.70 (0.59, 0.84)	<0.0001
31 Months	232 (5.7%)	331 (8.1%)	0.69 (0.58, 0.81)	<0.0001
32 Months	240 (5.9%)	344 (8.4%)	0.68 (0.58, 0.81)	<0.0001
33 Months	246 (6.0%)	348 (8.5%)	0.69 (0.59, 0.82)	<0.0001
34 Months	249 (6.1%)	359 (8.8%)	0.68 (0.58, 0.80)	<0.0001
35 Months	256 (6.3%)	367 (9.0%)	0.68 (0.58, 0.80)	<0.0001
36 Months	266 (6.5%)	376 (9.2%)	0.69 (0.59, 0.81)	<0.0001
37 Months	273 (6.7%)	385 (9.4%)	0.69 (0.59, 0.81)	<0.0001
38 Months	277 (6.8%)	390 (9.5%)	0.69 (0.59, 0.81)	<0.0001
39 Months	280 (6.8%)	397 (9.7%)	0.69 (0.59, 0.80)	<0.0001
40 Months	283 (6.9%)	407 (10.0%)	0.68 (0.58, 0.79)	<0.0001
41 Months	285 (7.0%)	413 (10.1%)	0.67 (0.58, 0.78)	<0.0001
42 Months	292 (7.1%)	419 (10.2%)	0.68 (0.58, 0.79)	<0.0001

Endpoint	Icosapent Ethyl (N=4089)	Placebo (N=4090)	HR (95% CI)[1]	Log-Rank P-value
Coronary Revascularization	**376 (9.2%)**	**544 (13.3%)**	**0.66 (0.58, 0.76)**	**<0.0001**
43 Months	293 (7.2%)	427 (10.4%)	0.67 (0.58, 0.78)	<0.0001
44 Months	300 (7.3%)	436 (10.7%)	0.67 (0.58, 0.78)	<0.0001
45 Months	307 (7.5%)	447 (10.9%)	0.67 (0.58, 0.77)	<0.0001
46 Months	313 (7.7%)	454 (11.1%)	0.67 (0.58, 0.77)	<0.0001
47 Months	314 (7.7%)	464 (11.3%)	0.66 (0.57, 0.76)	<0.0001
48 Months	318 (7.8%)	469 (11.5%)	0.66 (0.57, 0.76)	<0.0001
49 Months	324 (7.9%)	477 (11.7%)	0.66 (0.57, 0.76)	<0.0001
50 Months	327 (8.0%)	487 (11.9%)	0.65 (0.56, 0.75)	<0.0001
51 Months	333 (8.1%)	498 (12.2%)	0.65 (0.56, 0.74)	<0.0001
52 Months	333 (8.1%)	503 (12.3%)	0.64 (0.56, 0.73)	<0.0001
53 Months	339 (8.3%)	505 (12.3%)	0.65 (0.56, 0.74)	<0.0001
54 Months	344 (8.4%)	510 (12.5%)	0.65 (0.57, 0.75)	<0.0001
55 Months	346 (8.5%)	513 (12.5%)	0.65 (0.57, 0.75)	<0.0001
56 Months	349 (8.5%)	517 (12.6%)	0.65 (0.57, 0.75)	<0.0001
57 Months	351 (8.6%)	521 (12.7%)	0.65 (0.57, 0.74)	<0.0001
58 Months	357 (8.7%)	523 (12.8%)	0.66 (0.57, 0.75)	<0.0001
59 Months	360 (8.8%)	524 (12.8%)	0.66 (0.58, 0.76)	<0.0001
60 Months	362 (8.9%)	528 (12.9%)	0.66 (0.58, 0.75)	<0.0001
61 Months	365 (8.9%)	533 (13.0%)	0.66 (0.58, 0.75)	<0.0001
62 Months	368 (9.0%)	535 (13.1%)	0.66 (0.58, 0.76)	<0.0001
63 Months	370 (9.0%)	536 (13.1%)	0.66 (0.58, 0.76)	<0.0001
64 Months	372 (9.1%)	537 (13.1%)	0.67 (0.58, 0.76)	<0.0001
65 Months	373 (9.1%)	537 (13.1%)	0.67 (0.59, 0.76)	<0.0001
66 Months	374 (9.1%)	540 (13.2%)	0.67 (0.58, 0.76)	<0.0001
67 Months	374 (9.1%)	542 (13.3%)	0.66 (0.58, 0.76)	<0.0001
68 Months	375 (9.2%)	543 (13.3%)	0.66 (0.58, 0.76)	<0.0001
69 Months	375 (9.2%)	543 (13.3%)	0.66 (0.58, 0.76)	<0.0001
70 Months	375 (9.2%)	543 (13.3%)	0.66 (0.58, 0.76)	<0.0001
71 Months	375 (9.2%)	543 (13.3%)	0.66 (0.58, 0.76)	<0.0001
72 Months	375 (9.2%)	543 (13.3%)	0.66 (0.58, 0.76)	<0.0001
73 Months	375 (9.2%)	544 (13.3%)	0.66 (0.58, 0.76)	<0.0001
74 Months	375 (9.2%)	544 (13.3%)	0.66 (0.58, 0.76)	<0.0001
75 Months	376 (9.2%)	544 (13.3%)	0.66 (0.58, 0.76)	<0.0001

Note: Events that occurred after the timepoint are censored to the timepoint.
[1] Hazard ratio, 95% CI are from a Cox proportional hazard model with treatment as factor and stratified by geographic region, CV risk category, and use of ezetimibe.

Supplemental Table III. Summary of Recurrences of Coronary Revascularization Endpoint Events Using the Full (A) and Reduced Datasets (B).

A. Summary of Recurrences of Coronary Revascularization Using Andersen and Gill Model and Wei-Lin-Weissfeld Model – Full Dataset – ITT Population

	Icosapent Ethyl (N=4089)		Placebo (N=4090)	
Analysis	**Event (%)**	**Rate/1000 pt-yr**	**Event (%)**	**Rate/1000 pt-yr**
Coronary Revascularization				
1st occurrence event	376 (9.20)	22.50	544 (13.30)	33.67
2nd occurrence event	66 (1.61)	3.77	130 (3.18)	7.57
3rd occurrence event	14 (0.34)	0.80	38 (0.93)	2.19
4th occurrence event	8 (0.20)	0.45	11 (0.27)	0.63
5th occurrence event	3 (0.07)	0.17	4 (0.10)	0.23
6th occurrence event	2 (0.05)	0.11	2 (0.05)	0.11
7th occurrence event	2 (0.05)	0.11	2 (0.05)	0.11
8th occurrence event	1 (0.02)	0.06	NA	NA
9th occurrence event	1 (0.02)	0.06	NA	NA

Note: The number of subjects with events in the ITT Population within each treatment group (n). The number of subjects in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is 1000 × n/pt-yrs.

	Treatment Comparison (Icosapent Ethyl /Placebo)		
Analysis	**HR[1]**	**95% CI[1]**	**P-value[1]**
Andersen and Gill (AG) Model and Proportional Means Model			
Intensity Model (AG Model)	0.64	(0.57, 0.71)	<0.0001
Proportional Means Model	0.64	(0.55, 0.73)	<0.0001
Modified Wei-Lin-Weissfeld Model			
Noncommon effects, 1st occurrence event	0.67	(0.58, 0.76)	<0.0001
Noncommon effects, 2nd occurrence event	0.49	(0.37, 0.66)	<0.0001
Noncommon effects, 3rd occurrence event	0.36	(0.19, 0.66)	0.001
Noncommon effects, 4th occurrence event	0.71	(0.29, 1.77)	0.47
Noncommon effects, 5th occurrence event	0.73	(0.16, 3.26)	0.68
Noncommon effects, 6th occurrence event	0.97	(0.14, 6.92)	0.98
Noncommon effects, 7th occurrence event	0.97	(0.14, 6.90)	0.98

Note:
[1]Hazard ratio and its 95% CI, and p-value are reported from Andersen & Gill (1982) model for common effect and Wei-Lin-Weissfeld Model for noncommon effects respectively, with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

B. Summary of Recurrences of Coronary Revascularization Using Andersen and Gill Model and Wei-Lin-Weissfeld Model – Reduced Dataset – ITT Population

	Icosapent Ethyl (N=4089)		Placebo (N=4090)	
Analysis	**Event (%)**	**Rate/1000 pt-yr**	**Event (%)**	**Rate/1000 pt-yr**
Coronary Revascularization				
1st occurrence event	376 (9.20)	22.50	544 (13.30)	33.67
2nd occurrence event	64 (1.57)	3.66	128 (3.13)	7.45
3rd occurrence event	13 (0.32)	0.74	38 (0.93)	2.19
4th occurrence event	8 (0.20)	0.45	10 (0.24)	0.58
5th occurrence event	3 (0.07)	0.17	4 (0.10)	0.23
6th occurrence event	2 (0.05)	0.11	2 (0.05)	0.11
7th occurrence event	2 (0.05)	0.11	2 (0.05)	0.11
8th occurrence event	1 (0.02)	0.06	NA	NA

Note: The number of subjects with events in the ITT Population within each treatment group (n). The number of subjects in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is 1000 × n/pt-yrs.

	Treatment Comparison (Icosapent Ethyl/Placebo)		
Analysis	**HR[1]**	**95% CI[1]**	**P-value[1]**
Andersen and Gill (AG) Model and Proportional Means Model			
Intensity Model (AG Model)	0.64	(0.57, 0.71)	<0.0001
Proportional Means Model	0.64	(0.55, 0.73)	<0.0001
Modified Wei-Lin-Weissfeld Model			
Noncommon effects, 1st occurrence event	0.67	(0.58, 0.76)	<0.0001
Noncommon effects, 2nd occurrence event	0.49	(0.36, 0.66)	<0.0001
Noncommon effects, 3rd occurrence event	0.33	(0.18, 0.63)	0.0006
Noncommon effects, 4th occurrence event	0.79	(0.31, 1.99)	0.61
Noncommon effects, 5th occurrence event	0.73	(0.16, 3.26)	0.68
Noncommon effects, 6th occurrence event	0.97	(0.14, 6.91)	0.98
Noncommon effects, 7th occurrence event	0.91	(0.13, 6.50)	0.93

Note:
[1]Hazard ratio and its 95% CI, and p-value are reported from Andersen & Gill (1982) model for common effect and Wei-Lin-Weissfeld Model for noncommon effects respectively, with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Supplemental Table IV. Summary of EPA Changes Over Time. On Study Positively Adjudicated Coronary Revascularization versus No Revascularization

Visit/Change/Statistic	Revascularization (N=920)	No Revascularization (N=7259)	Group difference (Revascularization-No Revascularization) Median[1]	95% CI[1]	P-value[2]
Visit 2 - Day 0: Randomization					
Observed Values					
n	824	6238			
Mean (SD)	32.0 (21.95)	32.4 (26.32)			
Median (Q1, Q3)	26.6 (18.0, 39.8)	26.0 (17.0, 40.1)	0.5	(-0.6, 1.7)	0.35
IQR	21.8	23.1			
CV%	68.6	81.2			
Visit 4 - Day 360					
Observed Values					
n	763	5542			
Mean (SD)	81.6 (89.95)	91.5 (89.95)			
Median (Q1, Q3)	37.4 (19.3, 129.0)	50.9 (20.8, 150.0)			
IQR	109.7	129.2			
CV%	110.2	98.3			
Change from Baseline					
n	714	5168			
Mean (SD)	50.1 (90.56)	59.0 (89.93)			
Median (Q1, Q3)	5.9 (-6.5, 98.8)	15.5 (-4.7, 119.0)	-5.0	(-8.1, -2.0)	0.001
IQR	105.3	123.7			
CV%	180.9	152.5			
P-value[3]	<0.0001	<0.0001			
Percent Change from Baseline					
n	714	5168			
Mean (SD)	260.2 (725.23)	293.9 (581.40)			
Median (Q1, Q3)	31.2 (-24.6, 308.8)	68.4 (-19.6, 425.3)	-16.5	(-26.9, -6.6)	0.001
IQR	333.4	444.9			
CV%	278.7	197.8			
P-value[3]	<0.0001	<0.0001			
Visit 5 - Day 720					
Observed Values					
n	728	5207			
Mean (SD)	91.8 (101.94)	106.5 (103.97)			
Median (Q1, Q3)	42.0 (23.2, 142.0)	55.0 (25.2, 176.0)			
IQR	118.8	150.8			
CV%	111.0	97.6			
Change from Baseline					
n	680	4808			
Mean (SD)	60.1 (101.30)	72.9 (102.24)			

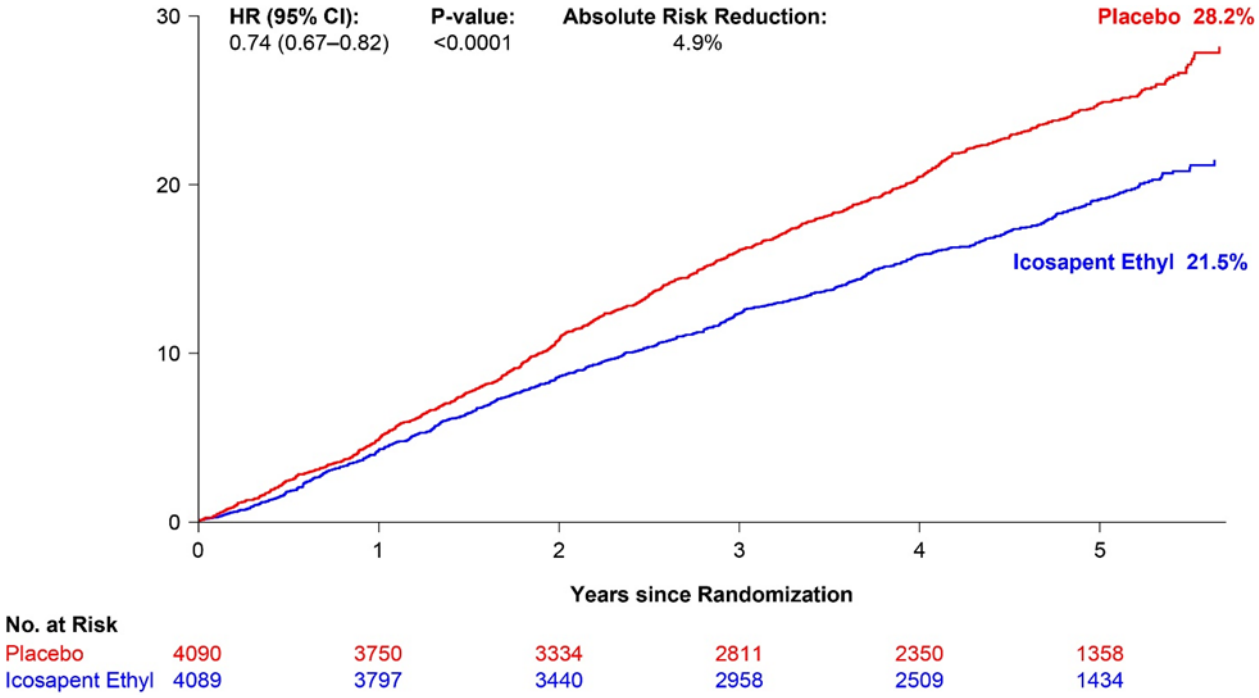
Visit/Change/Statistic	Revascularization (N=920)	No Revascularization (N=7259)	Group difference (Revascularization-No Revascularization) Median[1]	95% CI[1]	P-value[2]
Median (Q1, Q3)	9.9 (-2.1, 110.9)	19.2 (-1.2, 143.8)	-4.8	(-8.2, -1.7)	0.002
IQR	113.0	145.0			
CV%	168.7	140.3			
P-value[3]	<0.0001	<0.0001			
Percent Change from Baseline					
n	680	4808			
Mean (SD)	275.3 (571.65)	345.3 (647.49)			
Median (Q1, Q3)	45.3 (-7.9, 403.1)	87.8 (-5.0, 514.2)	-17.4	(-29.1, -6.4)	0.002
IQR	411.0	519.2			
CV%	207.7	187.5			
P-value[3]	<0.0001	<0.0001			
Visit 6 - Day 1080					
Observed Values					
n	618	4376			
Mean (SD)	91.3 (104.92)	103.6 (103.00)			
Median (Q1, Q3)	42.0 (22.4, 138.0)	53.1 (24.5, 173.0)			
IQR	115.6	148.5			
CV%	114.9	99.4			
Change from Baseline					
n	579	4031			
Mean (SD)	59.3 (105.77)	70.7 (101.87)			
Median (Q1, Q3)	9.3 (-3.9, 107.6)	16.9 (-2.1, 140.3)	-5.2	(-8.7, -1.9)	0.002
IQR	111.5	142.4			
CV%	178.4	144.1			
P-value[3]	<0.0001	<0.0001			
Percent Change from Baseline					
n	579	4031			
Mean (SD)	258.7 (513.74)	342.8 (714.01)			
Median (Q1, Q3)	39.0 (-14.6, 346.8)	77.3 (-8.4, 496.2)	-19.7	(-31.8, -8.3)	0.0006
IQR	361.4	504.6			
CV%	198.6	208.3			
P-value[3]	<0.0001	<0.0001			
Visit 7 - Day 1440					
Observed Values					
n	526	3707			
Mean (SD)	84.8 (90.11)	102.3 (102.53)			
Median (Q1, Q3)	42.7 (20.7, 129.0)	50.9 (23.6, 168.0)			
IQR	108.3	144.4			
CV%	106.2	100.2			
Change from Baseline					
n	490	3381			
Mean (SD)	52.3 (90.40)	69.4 (101.97)			
Median (Q1, Q3)	7.9 (-5.7, 100.7)	15.5 (-3.0, 138.7)	-6.6	(-10.3, -3.0)	0.0002

Visit/Change/Statistic	Revascularization (N=920)	No Revascularization (N=7259)	Group difference (Revascularization-No Revascularization) Median[1]	95% CI[1]	P-value[2]
IQR	106.4	141.7			
CV%	172.8	146.8			
P-value[3]	<0.0001	<0.0001			
Percent Change from Baseline					
n	490	3381			
Mean (SD)	230.1 (421.10)	335.9 (668.56)			
Median (Q1, Q3)	33.7 (-21.4, 315.8)	75.5 (-12.6, 498.4)	-23.3	(-36.2, -11.3)	0.0001
IQR	337.2	511.0			
CV%	183.0	199.0			
P-value[3]	<0.0001	<0.0001			
Visit 8 - Day 1800					
Observed Values					
n	286	2075			
Mean (SD)	84.9 (96.68)	99.3 (97.48)			
Median (Q1, Q3)	36.3 (20.1, 139.0)	49.8 (22.8, 168.0)			
IQR	118.9	145.2			
CV%	113.9	98.1			
Change from Baseline					
n	266	1856			
Mean (SD)	53.6 (95.46)	67.8 (96.97)			
Median (Q1, Q3)	6.0 (-6.6, 109.0)	15.4 (-2.4, 136.3)	-7.0	(-11.7, -2.6)	0.002
IQR	115.6	138.7			
CV%	178.1	143.0			
P-value[3]	<0.0001	<0.0001			
Percent Change from Baseline					
n	266	1856			
Mean (SD)	231.0 (417.76)	329.7 (593.47)			
Median (Q1, Q3)	29.9 (-25.7, 331.8)	69.7 (-10.5, 513.1)	-24.5	(-41.3, -9.1)	0.002
IQR	357.5	523.7			
CV%	180.9	180.0			

Visit/Change/Statistic	Revascularization (N=920)	No Revascularization (N=7259)	Group difference (Revascularization-No Revascularization) Median[1]	95% CI[1]	P-value[2]
P-value[3]	<0.0001	<0.0001			
Last Visit					
Observed Values					
n	650	4827			
Mean (SD)	82.4 (95.93)	96.9 (99.04)			
Median (Q1, Q3)	37.3 (20.7, 114.0)	46.6 (23.2, 161.0)			
IQR	93.3	137.8			
CV%	116.5	102.2			
Change from Baseline					
n	605	4430			
Mean (SD)	50.3 (96.13)	63.2 (99.56)			
Median (Q1, Q3)	6.1 (-5.4, 89.3)	12.4 (-3.7, 129.6)	-5.2	(-8.3, -2.3)	0.0005
IQR	94.7	133.3			
CV%	191.1	157.4			
P-value[3]	<0.0001	<0.0001			
Percent Change from Baseline					
n	605	4430			
Mean (SD)	219.9 (438.30)	309.3 (652.38)			
Median (Q1, Q3)	29.0 (-19.3, 311.2)	58.1 (-13.8, 438.0)	-16.4	(-26.9, -6.5)	0.001
IQR	330.5	451.7			
CV%	199.3	210.9			
P-value[3]	<0.0001	<0.0001			

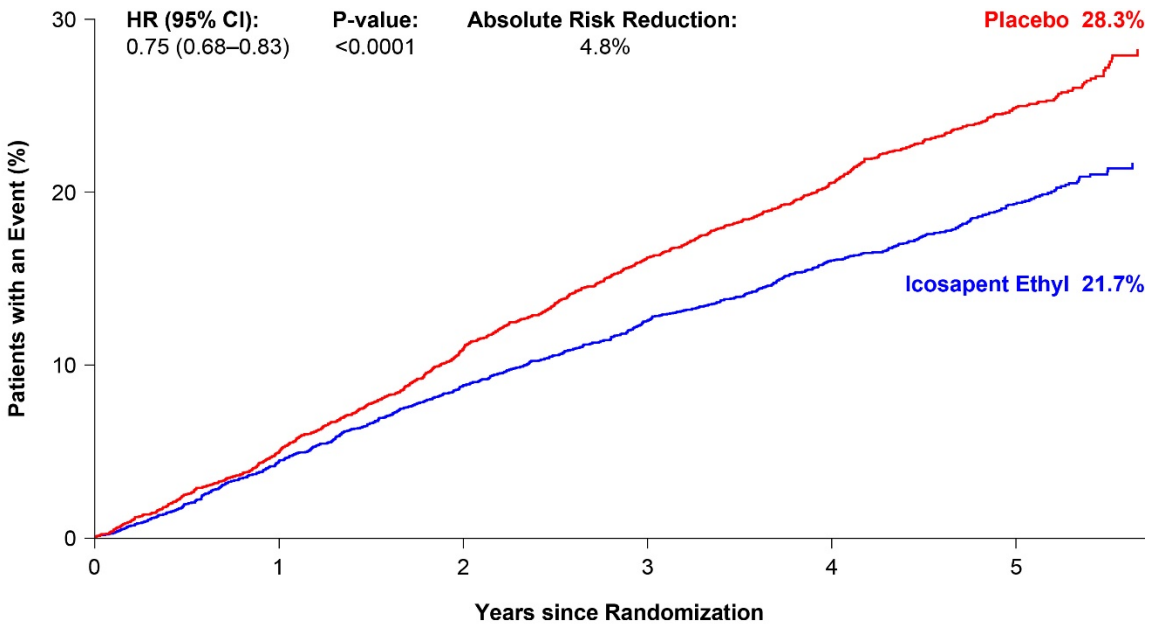
[1] Based on Hodges-Lehmann Estimation
[2] P-Value from Wilcoxon rank-sum test
[3] P-value from Wilcoxon Signed-Rank test

Supplemental Figure I. Kaplan-Meier Curve for Time to Primary Composite Endpoint Excluding Elective Revascularizations that Occurred within 90 Days of Randomization.



CI = confidence interval; HR = hazard ratio; No at risk = number of patients at risk.
Note: The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses. Absolute risk reduction is based on the observed event rates of 17.0% for icosapent ethyl and 21.9% for placebo.

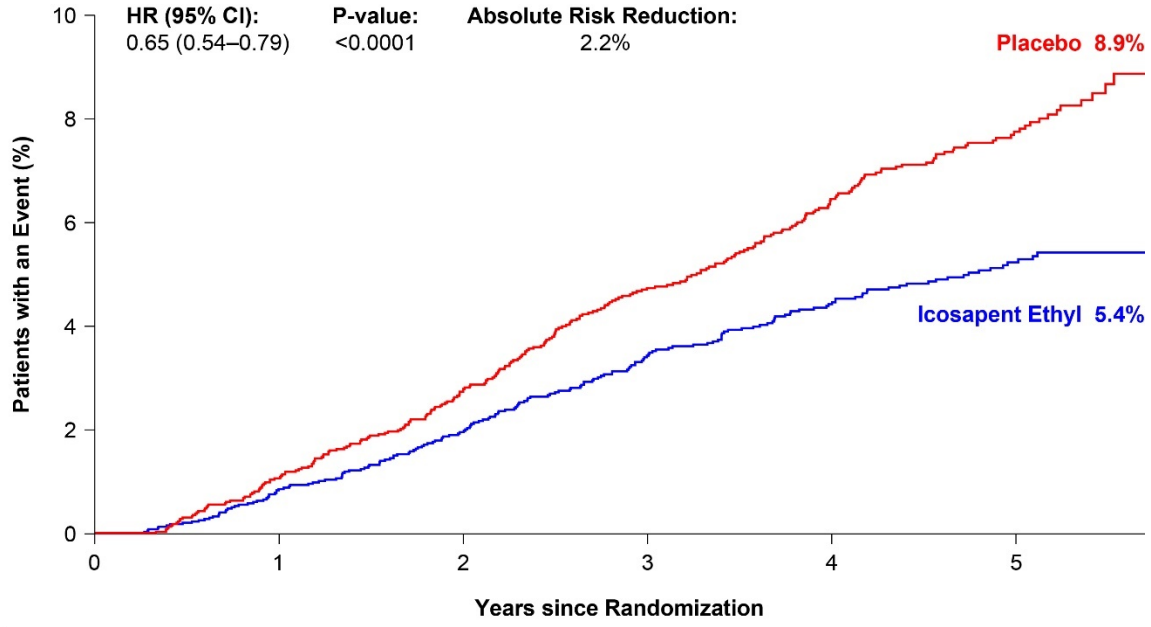
Supplemental Figure II. Kaplan-Meier Curve for Time to Primary Composite Endpoint Excluding Elective Revascularizations that Occurred within 30 Days of Randomization.



No. at Risk						
Placebo	4090	3747	3331	2809	2349	1358
Icosapent Ethyl	4089	3790	3433	2953	2505	1431

CI = confidence interval; HR = hazard ratio; No at risk = number of patients at risk.
Note: The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses. Absolute risk reduction is based on the observed event rates of 17.2% for icosapent ethyl and 22.0% for placebo.

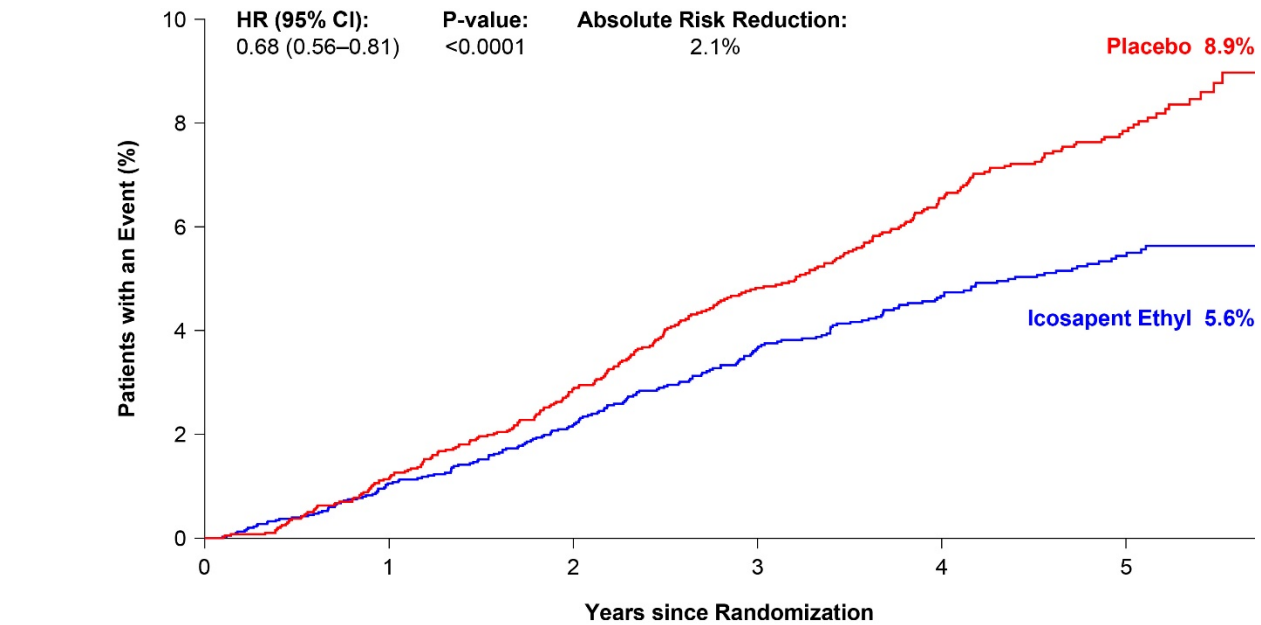
Supplemental Figure III. Kaplan-Meier Curve for Time to Elective Revascularizations Excluding Elective Events that Occurred within 90 Days of Randomization.



No. at Risk						
Placebo	4090	3871	3570	3093	2630	1540
Icosapent Ethyl	4089	3899	3629	3172	2733	1600

CI = confidence interval; HR = hazard ratio; No at risk = number of patients at risk.
Note: The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses. Absolute risk reduction is based on the observed event rates of 4.5% for icosapent ethyl and 6.6% for placebo.

Supplemental Figure IV. Kaplan-Meier Curve for Time to Elective Revascularization Excluding Elective Events that Occurred within 30 Days of Randomization.

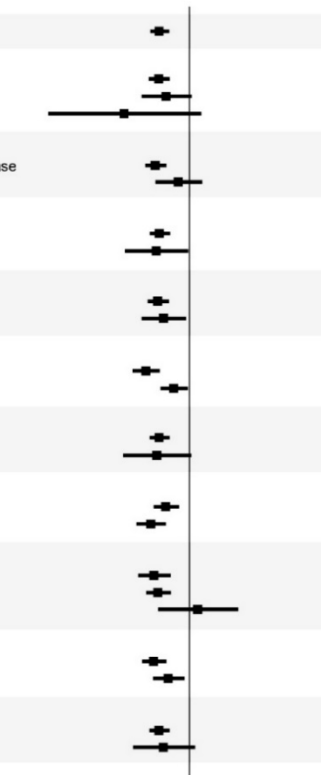


No. at Risk						
Placebo	4090	3868	3567	3090	2627	1539
Icosapent Ethyl	4089	3891	3621	3166	2728	1596

CI = confidence interval; HR = hazard ratio; No at risk = number of patients at risk.
Note: The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses. Absolute risk reduction is based on the observed event rates of 4.6% for icosapent ethyl and 6.7% for placebo.

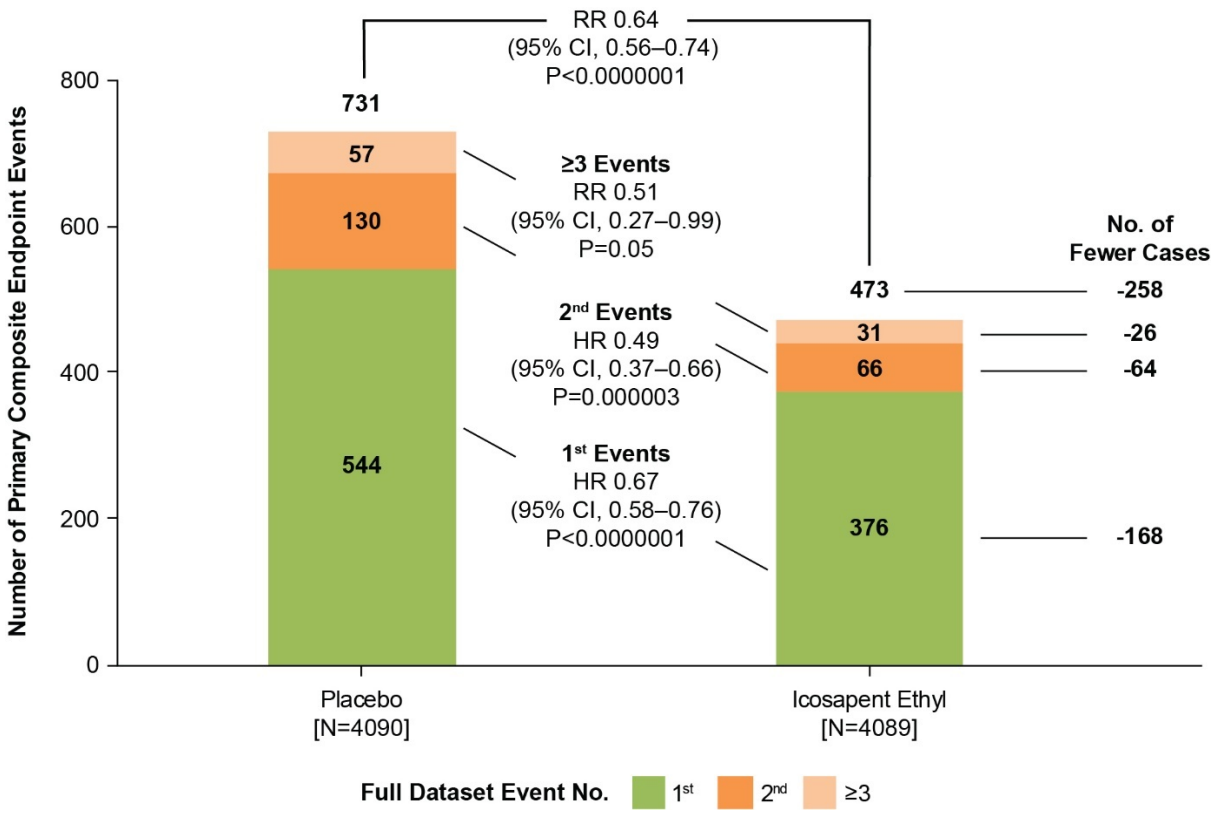
Supplemental Figure V. Time to Revascularization for the ITT Population and by Baseline Characteristics Subgroups.

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs Placebo	Interaction P-value
	n/N(%)	n/N(%)	HR (95% CI)	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58 – 0.76)	
Region				0.57
Western	314/2906 (10.8%)	455/2905 (15.7%)	0.66 (0.57 – 0.76)	
Eastern	57/1053 (5.4%)	77/1053 (7.3%)	0.73 (0.52 – 1.03)	
Asia Pacific	5/130 (3.8%)	12/132 (9.1%)	0.41 (0.14 – 1.17)	
Risk Category				0.08
Established Cardiovascular Disease	306/2892 (10.6%)	464/2893 (16.0%)	0.63 (0.55 – 0.73)	
Diabetes + Risk Factors	70/1197 (5.8%)	80/1197 (6.7%)	0.86 (0.63 – 1.19)	
Ezetimibe Use				0.84
No	342/3827 (8.9%)	492/3828 (12.9%)	0.67 (0.58 – 0.77)	
Yes	34/262 (13.0%)	52/262 (19.8%)	0.64 (0.41 – 0.98)	
Sex				0.63
Male	306/2927 (10.5%)	444/2895 (15.3%)	0.65 (0.56 – 0.75)	
Female	70/1162 (6.0%)	100/1195 (8.4%)	0.71 (0.52 – 0.96)	
Age Group				0.005
<65 Years	178/2232 (8.0%)	300/2184 (13.7%)	0.55 (0.46 – 0.67)	
≥65 Years	198/1857 (10.7%)	244/1906 (12.8%)	0.81 (0.67 – 0.98)	
White vs Non-White				0.98
White	346/3691 (9.4%)	501/3688 (13.6%)	0.66 (0.58 – 0.76)	
Non-White	30/398 (7.5%)	43/401 (10.7%)	0.64 (0.40 – 1.03)	
Baseline Diabetes				0.13
Diabetes	223/2394 (9.3%)	294/2393 (12.3%)	0.73 (0.61 – 0.87)	
No Diabetes	153/1695 (9.0%)	250/1694 (14.8%)	0.59 (0.48 – 0.72)	
Baseline Statin Intensity				0.12
High	129/1290 (10.0%)	190/1226 (15.5%)	0.62 (0.49 – 0.77)	
Moderate	220/2533 (8.7%)	328/2575 (12.7%)	0.65 (0.55 – 0.78)	
Low	27/254 (10.6%)	25/267 (9.4%)	1.13 (0.65 – 1.95)	
TG≥200 mg/dL vs <200 mg/dL				0.15
TG≥200 mg/dL	228/2481 (9.2%)	351/2469 (14.2%)	0.62 (0.52 – 0.73)	
TG<200 mg/dL	148/1605 (9.2%)	193/1620 (11.9%)	0.75 (0.61 – 0.93)	
TG≥150 mg/dL vs <150 mg/dL				0.89
TG≥150 mg/dL	341/3674 (9.3%)	489/3660 (13.4%)	0.66 (0.58 – 0.76)	
TG<150 mg/dL	35/412 (8.5%)	55/429 (12.8%)	0.70 (0.46 – 1.08)	
TG≥200 and HDL-C≤35				0.19
Yes	79/823 (9.6%)	143/794 (18.0%)	0.50 (0.38 – 0.65)	
No	296/3258 (9.1%)	401/3293 (12.2%)	0.72 (0.62 – 0.84)	
US vs Non-US				0.30
US	153/1548 (9.9%)	242/1598 (15.1%)	0.61 (0.50 – 0.75)	
Non-US	223/2541 (8.8%)	302/2492 (12.1%)	0.71 (0.59 – 0.84)	
Baseline hsCRP ≤2 vs >2 mg/L				0.03
≤2 mg/L	165/1919 (8.6%)	275/1942 (14.2%)	0.57 (0.47 – 0.70)	
>2 mg/L	211/2167 (9.7%)	269/2147 (12.5%)	0.76 (0.64 – 0.91)	
Baseline eGFR				0.93
<60 mL/min/1.73m²	85/905 (9.4%)	125/ 911 (13.7%)	0.63 (0.48 – 0.84)	
60-<90 mL/min/1.73m²	212/2217 (9.6%)	310/2238 (13.9%)	0.67 (0.56 – 0.80)	
≥90 mL/min/1.73m²	79/963 (8.2%)	109/939 (11.6%)	0.69 (0.51 – 0.92)	
Baseline LDL-C (Derived) by Tertiles				0.72
≤67 mg/dL	130/1481 (8.8%)	183/1386 (13.2%)	0.63 (0.50 – 0.79)	
>67-≤84 mg/dL	131/1347 (9.7%)	185/1364 (13.6%)	0.72 (0.57 – 0.89)	
>84 mg/dL	115/1258 (9.1%)	176/1339 (13.1%)	0.65 (0.51 – 0.82)	
Baseline HDL-C by Tertiles				0.13
≥17-≤36.5 mg/dL	139/1416 (9.8%)	218/1368 (15.9%)	0.58 (0.47 – 0.71)	
>36.5-≤43.5 mg/dL	132/1324 (10.0%)	167/1353 (12.3%)	0.80 (0.63 – 1.00)	
>43.5 mg/dL	103/1337 (7.7%)	157/1359 (11.6%)	0.65 (0.50 – 0.83)	
Baseline ApoB by Tertiles				0.64
≥17.5-≤76 mg/dL	131/1488 (8.8%)	172/1393 (12.3%)	0.69 (0.55 – 0.87)	
>76-≤89 mg/dL	121/1297 (9.3%)	192/1302 (14.7%)	0.61 (0.48 – 0.76)	
>89-≤207 mg/dL	122/1275 (9.6%)	179/1352 (13.2%)	0.69 (0.55 – 0.87)	
Baseline Non-HDL by Tertiles				0.97
≥60.5-≤109 mg/dL	119/1409 (8.4%)	158/1326 (11.9%)	0.68 (0.53 – 0.86)	
>109-≤127.5 mg/dL	125/1363 (9.2%)	190/1387 (13.7%)	0.65 (0.52 – 0.81)	
>127.5-≤244 mg/dL	132/1314 (10.0%)	196/1376 (14.2%)	0.67 (0.53 – 0.83)	
Baseline Triglycerides by Tertiles				0.07
≥81.25-≤190 mg/dL	128/1378 (9.3%)	165/1381 (11.9%)	0.76 (0.61 – 0.96)	
>190-≤250 mg/dL	129/1370 (9.4%)	162/1326 (12.2%)	0.72 (0.57 – 0.91)	
>250-≤1401 mg/dL	119/1338 (8.9%)	217/1382 (15.7%)	0.54 (0.43 – 0.68)	



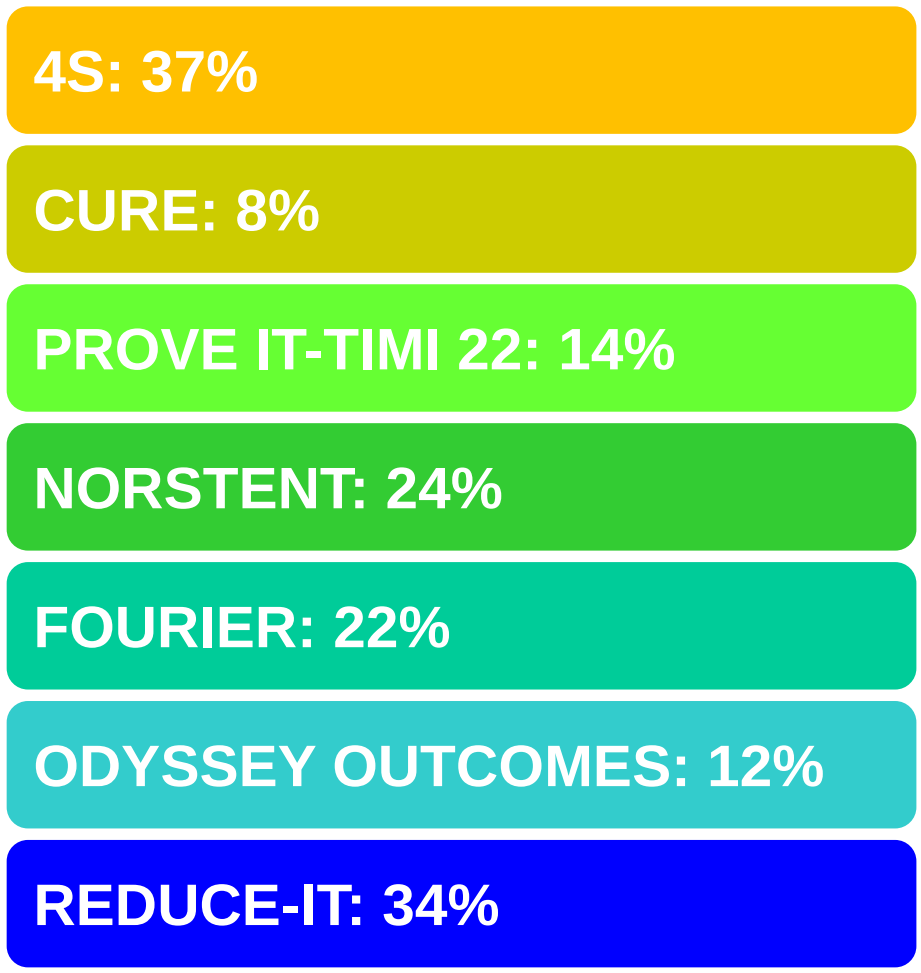
ApoB = apolipoprotein B; CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL-C = high density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; TG = triglycerides; US = United States.

Supplemental Figure VI. Distribution of First and Subsequent Coronary Revascularization Events in the Full Dataset for Patients Randomized 1:1 to Icosapent Ethyl Versus Placebo.



Hazard ratios (HRs) and 95% confidence intervals (CIs) for between group comparisons were generated using Li-Lagakos-modified Wei-Lin-Weissfeld method for first and second event categories. Rate ratio (RR) and 95% CI for group comparisons used a negative binomial model for additional events beyond first and second occurrences, i.e., third event or more and overall treatment comparison.

Supplemental Figure VII. Comparison of relative risk reductions in revascularization in major clinical trials.



Revascularization was defined as “coronary intervention” or “coronary revascularization” in 4S, NORSTENT, FOURIER, and REDUCE-IT, “revascularization” in PROVE IT-TIMI 22, “revascularization procedure” in CURE, and “ischemia-driven revascularization” in ODYSSEY OUTCOMES.