Treatment With Icosapent Ethyl to Reduce Ischemic Events in Patients With Prior Percutaneous Coronary Intervention: Insights From REDUCE-IT PCI

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BACKGROUND: Patients who undergo percutaneous coronary intervention (PCI) are at increased risk for recurrent cardiovascular events despite aggressive medical therapy.

METHODS AND RESULTS: This post hoc analysis focused on the subset of patients with prior PCI enrolled in REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial), a multicenter, randomized, double-blind, placebo-controlled trial of icosapent ethyl versus placebo. Icosapent ethyl was added to statins in patients with low-density lipoprotein cholesterol <100 mg/dL and fasting triglycerides 135–499 mg/dL. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. There were 8179 patients randomized in REDUCE-IT followed for a median of 4.9 years, and 3408 (41.7%) of them had a prior PCI with a median follow-up of 4.8 years. These patients were randomized a median of 2.9 years (11 days to 30.7 years) after PCI. Among patients treated with icosapent ethyl versus placebo, there was a 34% reduction in the primary composite end point (hazard ratio [HR], 0.66; 95% CI, 0.58–0.76; P<0.001; number needed to treat 4.8 years =12) and a 34% reduction in the key secondary composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.66; 95% CI, 0.56–0.79; P<0.001; NNT 4.8 years =19) versus placebo. Similarly, large reductions occurred in total coronary revascularizations and revascularization subtypes. There was also a 39% reduction in total events (rate ratio, 0.61; 95% CI, 0.52–0.72; P<0.001).

CONCLUSIONS: Among patients treated with statins with elevated triglycerides and a history of prior PCI, icosapent ethyl substantially reduced the risk of recurrent events during an average of ~5 years of follow-up with a number needed to treat of only 12.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01492361.

Key Words: eicosapentaenoic acid ■ icosapent ethyl ■ prevention ■ revascularization

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Patients who undergo percutaneous coronary intervention (PCI) are at increased risk for subsequent cardiovascular events when compared with patients with other cardiovascular risk factors. In recent years, efforts to improve stent design, lower low-density lipoprotein cholesterol, and modify inflammation and platelet activity have resulted in some reductions in repeat events among patients who undergo coronary stenting. Yet, many patients still experience recurrent events, especially those with diabetes and elevated triglycerides.

The REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) trial was designed to test the effectiveness of icosapent ethyl 4 g/day (a highly purified form of eicosapentaenoic acid [EPA]) versus placebo among patients with established cardiovascular disease or diabetes and additional risk factors. The significant reduction in first and total major adverse cardiovascular events (MACE) among patients who were treated with icosapent ethyl was out of proportion to the degree of reduction in triglycerides. These large reductions occurred in patients with diabetes, patients with only modestly elevated triglycerides, patients in the United States, and patients across numerous other prespecified subgroups. Treatment with icosapent ethyl also substantially reduced instances of first and subsequent revascularization events.

The aim of the present post hoc analysis of the REDUCE-IT trial was to study the effects of icosapent ethyl versus placebo among patients who have been treated previously with PCI.

**METHODS**

The data that support the findings of this study may be made available from the corresponding author on reasonable request.

**Patient Population and Treatment**

The design of the REDUCE-IT trial has been published previously. REDUCE-IT was a double-blind, multicenter, placebo-controlled, randomized trial comparing the effects of icosapent ethyl in high-risk patients treated with statins with persistently elevated triglycerides. After a screening period of up to 60 days, patients were randomized to receive icosapent ethyl 4 g daily (2 g twice daily) versus a matching placebo. Patients were enrolled in REDUCE-IT if they were at least 45 years of age and had established cardiovascular disease or at least 50 years of age and had diabetes and additional risk factors. In this present post hoc analysis, patients were analyzed only if they had a prior PCI, such as balloon angioplasty or stenting (drug-eluting or bare-metal stents). Patients were included regardless of the amount of time elapsed between PCI and enrollment, though planned coronary intervention (such as PCI or coronary bypass surgery) was an exclusion criterion. Patients could be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery. Of note, randomization to icosapent ethyl versus placebo was stratified according to cardiovascular risk (established cardiovascular disease versus diabetes plus risk), geographic region, and ezetimibe use. In addition to prior PCI, all patients had been treated with a stable dose of statin for at least 4 weeks and had low-density lipoprotein cholesterol under 100 mg/dL as well as...
serum triglycerides from 135–499 mg/dL. Other key inclusion and exclusion criteria for REDUCE-IT have been published previously. All sites received ethics approval from relevant institutional review boards, and informed consent was obtained.

Statistical Analysis
In this post hoc analysis, we analyzed patients enrolled in REDUCE-IT who had a prior PCI. The primary and key secondary end points for this analysis were the same as the main REDUCE-IT trial. The primary composite end point was the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. The key secondary composite end point (or hard MACE end point) was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

The intention-to-treat principle guided all analyses. Baseline characteristics were compared among groups using the Wilcoxon rank sum test for continuous variables and Chi-square test for categorical variables. Hazard ratios (HRs) and 95% CIs were generated using Cox proportional-hazard models that included risk stratum (established cardiovascular disease versus diabetes plus cardiovascular risk factors), geographic region, and ezetimibe use as covariates. It has been shown in other analyses that patients benefited from icosapent ethyl versus placebo regardless of baseline triglyceride levels, so this was not included as a covariate in this analysis. With Kaplan-Meier analysis, we compared the time to events among patients randomized to icosapent ethyl versus placebo, with log-rank P values also stratified by risk stratum, geographic region, and ezetimibe use.

As with other REDUCE-IT analyses, we employed various statistical methods in comparing the risk for total (first and subsequent) events among patients treated with icosapent ethyl versus placebo.17 We used the negative binomial regression model to calculate rates and rate ratios (RRs) for total cardiovascular events. In supportive analyses, the modified Wei-Lin-Weissfeld method (Li and Lagakos modification taking into account death as a terminating event) was applied to calculate HRs for the time to the first and second, and a negative binomial model for rate ratios of third and greater events.22 As a sensitivity analysis, the Gray’s test was applied to the primary composite end point considering noncardiovascular death as a competing event. In addition to the primary and key secondary end points, results for additionally prespecified secondary end points in the original testing hierarchy are presented. Further post hoc explorations included time to total coronary revascularization and various revascularization subtypes (eg, elective, emergent, and urgent) as well as a coronary-specific composite end point of myocardial infarction, coronary revascularization, or unstable angina. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS
Baseline Characteristics
Of the 8179 patients enrolled in REDUCE-IT, 3408 (41.7%) had a prior PCI. In the 2559 patients with reported dates of PCI, the median time from PCI was 2.9 years, ranging from 11 days to 30.7 years. There were 675 (26.4%) patients with a PCI ≤1 year before randomization and 1884 (73.6%) with a PCI more than 1 year before randomization. Among patients in this study, the median age was 63 years, 20.7% were female, 96.3% were on moderate- or high-intensity statin therapy, and the median triglyceride level was 218 mg/dL (Q1, Q3; 178.5 mg/dL, 274.5 mg/dL). There were no significant differences in baseline characteristics among patients randomized to icosapent ethyl versus placebo (Table 1).

Clinical End Points
During a median follow-up of 4.8 years, the rates of the primary composite end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization) were 20.8% among patients treated with icosapent ethyl and 29.4% among patients treated with placebo (HR, 0.66; 95% CI, 0.58–0.76; P < 0.001). This represents a 34% relative risk reduction, an 8.5% absolute risk reduction, and a number needed to treat (NNT) of 12 patients to prevent 1 MACE event over a median of 4.8 years. The reduction in the primary end point with icosapent ethyl was similar in patients whose most recent PCI occurred ≤1 year before randomization (20.0% versus 29.7%, HR, 0.65; 95% CI, 0.48–0.89; P=0.007) and >1 year before randomization (20.3% versus 27.9%; HR, 0.68; 95% CI, 0.57–0.83; P<0.001). There was also a 34% reduction in the rate of the key secondary end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in patients treated with icosapent ethyl versus placebo (12.0% versus 17.4%, HR, 0.66; 95% CI, 0.56–0.79; P<0.001). The absolute risk reduction was 5.4%, NNT4.8 years=19 (Figure 1).

Patients treated with icosapent ethyl experienced a significant 40% reduction in the risk of repeat coronary revascularization versus those treated with placebo (17.1% versus 27.6%; HR, 0.60; 95% CI, 0.51–0.70; P<0.001), with similar reductions in elective and urgent revascularization. There was also a significant reduction in the combined coronary end point of myocardial infarction, coronary revascularization, or unstable angina.
requiring hospitalization (HR, 0.65; 95% CI, 0.56–0.75; P < 0.001) (Figure 2). There was no significant difference in the safety or efficacy of icosapent ethyl versus placebo among patients taking single- or dual-antiplatelet therapy or a combined antithrombotic regimen (Figure S1). In addition, there were similar reductions in cardiovascular end points among women and men randomized to icosapent ethyl versus placebo (Figure S2).

Testing in patients with prior PCI across the original prespecified hierarchical end points showed significant reductions in the primary and key secondary end points as well as in the following end points: cardiovascular death or nonfatal myocardial infarction; fatal or nonfatal myocardial infarction; urgent or emergent coronary revascularization; cardiovascular death; hospitalization for unstable angina; fatal or nonfatal stroke; and all-cause mortality, myocardial infarction, or stroke (Figure 3). There were similar reductions in the primary and key secondary end points when accounting for noncardiovascular death as a competing risk factor (Figure S3). It should be noted that although the patients enrolled in REDUCE-IT with cardiovascular risk factors and no history of PCI were a somewhat heterogeneous group, they had fewer cardiovascular events and derived a smaller in magnitude but still significant benefit from treatment with icosapent ethyl versus placebo (Figure S4).

## Total Events

Of the 1708 events that occurred during follow-up, 853 (49.9%) were first events, 470 (27.5%) were second events, and 385 (22.5%) were third or greater events. During follow-up, 1031 events occurred among patients treated with placebo and 677 events occurred among patients treated with icosapent ethyl. Using the negative binomial regression model, there was a significant 39% reduction in total (first and subsequent) events (RR, 0.61; 95% CI, 0.52–0.72; P < 0.001) among patients treated with icosapent ethyl versus placebo (Figure S4).

### Table 1. Baseline Characteristics

|                      | Icosapent ethyl (N=1737) | Placebo (N=1671) | Overall (N=3408) | P value* |
|----------------------|--------------------------|------------------|------------------|----------|
| Age, y, median (Q1–Q3) | 63.0 (57.0–69.0)         | 63.0 (56.0–69.0) | 63.0 (57.0–69.0) | 0.73     |
| Female sex, n (%)    | 350 (20.1)               | 354 (21.2)       | 704 (20.7)       | 0.46     |
| White race, n (%)    | 1606 (92.5)              | 1539 (92.1)      | 3145 (92.3)      | 0.70     |
| Westernized region, n (%) | 1385 (79.7)              | 1313 (78.6)      | 2698 (79.2)      | 0.40     |
| Cardiovascular risk category, n (%) |                    |                  |                  | 0.91     |
| Established cardiovascular disease | 1644 (94.6)              | 1583 (94.7)      | 3227 (94.7)      |          |
| Diabetes+risk factors | 93 (5.4)                 | 88 (5.3)         | 181 (5.3)        |          |
| Ezetimibe use, n (%) | 136 (7.9)                | 150 (9.0)        | 286 (8.5)        | 0.28     |
| Statin intensity, n (%) | 3 (0.2)                  | 9 (0.5)          | 12 (0.4)         |          |
| Low                  | 59 (3.4)                 | 57 (3.4)         | 116 (3.4)        |          |
| Moderate             | 962 (55.4)               | 970 (58.0)       | 1932 (56.7)      |          |
| High                 | 713 (41.0)               | 635 (38.0)       | 1348 (39.6)      |          |
| Body mass index (kg/m²), median (Q1-Q3) | 30.5 (27.7–33.8)          | 30.3 (27.5–33.6) | 30.4 (27.7–33.7) | 0.32     |
| Triglycerides (mg/dL), median (Q1-Q3) | 218.0 (180.5–271.5)       | 217.5 (177.5–277.0) | 218.0 (178.5–274.5) | 0.82     |
| High-density lipoprotein cholesterol (mg/dL), median (Q1-Q3) | 39.0 (34.0–45.0)          | 39.0 (34.0–45.5) | 39.0 (34.0–45.5) | 0.90     |
| Low-density lipoprotein cholesterol (mg/dL), median (Q1-Q3) | 73.0 (61.0–87.0)          | 74.0 (62.0–87.0) | 74.0 (61.0–87.0) | 0.37     |
| Triglycerides category, n (%) |                  |                  |                  | 0.37     |
| <150 mg/dL           | 154 (8.9)                | 167 (10.0)       | 321 (9.4)        |          |
| 150 to <200 mg/dL    | 511 (29.4)               | 464 (27.8)       | 975 (28.6)       |          |
| ≥200 mg/dL           | 1071 (61.7)              | 1040 (62.2)      | 2111 (61.9)      |          |

*To assess balance between treatment groups, P values are reported from a Chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables. Missing categories are excluded from any comparisons.

*Age (y) is at randomization.
0.50–0.71; \( P<0.001 \)), and a significant 50% reduction in third or greater events (HR, 0.50; 95% CI, 0.35–0.74; \( P<0.001 \)) (Figure 4).

**Safety and Adverse Events**

As in the primary REDUCE-IT trial, among patients with a prior PCI treated with icosapent ethyl, there was a small increase in the number of patients who had adverse events of documented atrial fibrillation or flutter requiring emergency treatment (115 [6.6%] versus 75 [4.5%], \( P=0.007 \)) or who had positively adjudicated end points of atrial fibrillation or flutter requiring hospitalization (59 [3.4%] versus 36 [2.2%]; \( P=0.04 \)). There was no increase in total bleeding, any of the bleeding subtypes, or trial-related adverse events (Table 2).

**DISCUSSION**

Among the 3408 patients in REDUCE-IT with a prior PCI, icosapent ethyl taken 4 g daily (2 g twice daily) versus placebo resulted in a significant 34% reduction in the primary end point and a significant 34%
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reduction in the key secondary (hard MACE) end point. Even larger reductions occurred in second events, third or greater events, and total events. There were also significant reductions in total ischemic events, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization. The NNT 4.8 years to prevent 1 MACE event among patients treated with PCI over ~5 years was 12. In comparison, the NNT to prevent 1 MACE event was 22 over 5 years in the FRISC-II (Framingham and Fast Revascularization During Instability in Coronary Artery Disease) trial, 23 50 at 7 years in IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial), 24 67 at 2.2 years in FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), 63 at 2.8 years in ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 25-27

The patient population in this subgroup analysis of REDUCE-IT reflects a large proportion of patients who undergo PCI in US, Canadian, and European registries. 28-31 Representative qualities include moderately elevated baseline triglycerides, with 50% of patients being <218 mg/dL and 96.3% on a moderate- or high-intensity statin. The distribution of age, sex, and typical comorbidities also highly reflects contemporary populations undergoing PCI. 1 Furthermore, this trial enrolled patients from November 2011 to August 2016 as the latest generation of drug-eluting stents were employed, ameliorating the usual difficulty of interpreting clinical events in trials that had events during periods that used prior PCI technologies. 2 Contemporary guidelines and consensus statements consistently recommend the use of icosapent ethyl in this patient population. 32,33

Figure 2. Kaplan-Meier curves showing (A) time to first coronary revascularization, (B) time to first elective coronary revascularization, (C) time to first urgent revascularization, (D) time to first coronary specific end point: myocardial infarction, coronary revascularization, or unstable angina requiring hospitalization, among patients with prior percutaneous coronary intervention treated with icosapent ethyl vs placebo. ARR indicates absolute risk reduction; NNT, number needed to treat; and RRR, relative risk reduction.
These findings of the overall REDUCE-IT trial and this present analysis contrast sharply with neutral results from other contemporary clinical trials of moderate-to high-dose omega-3 fatty acid supplementation, such as the recent STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia) and OMEMI (The Omega-3 Fatty Acids in Elderly with Myocardial Infarction) trials.34–36 As well, older clinical trials have shown mixed results with respect to prevention of MACE events.37–41 In contrast, EPA in a highly purified form has shown a 19% benefit with respect to MACE in the open-label JELIS (Japan EPA Lipid Intervention Study) at 1.8 g per day and a 25%...

**Figure 3.** Hierarchical testing of end points: patients with prior percutaneous coronary intervention treated with icosapent ethyl vs placebo.

HR indicates hazard ratio.

**Figure 4.** First, second, third or greater, and total events among patients with prior percutaneous coronary intervention treated with icosapent ethyl vs placebo.

HR indicates hazard ratio; and RR, rate ratio.
The exploratory nature as well as the lack of adjustment for multiple comparisons limited this post hoc analysis; REDUCE-IT was not powered for this or other subgroup analyses. With the post hoc nature of these analyses, all P values should be considered hypothesis-generating. As noted previously, patients with prior PCI had higher event rates and derived greater benefit from icosapent ethyl versus placebo. Although the time period from PCI to randomization was known in most patients, there was a subset of patients in which this was not known. Among the 24.9% of this subset and the remainder of patients, the distribution of randomization to icosapent ethyl versus placebo was equivalent. Double blinding also eliminated bias arising from this issue. The prerandomization extent of coronary artery disease and revascularization strategy (complete versus incomplete) among patients with a prior PCI was not known. Randomization was not stratified by history of PCI, and because there is potential for confounding, this subgroup finding needs corroboration in future studies. Future investigation will be required to gain a better understanding of whether icosapent ethyl reduced the rates of in-stent restenosis versus de novo plaque events as vessel- and lesion-specific data are not available in REDUCE-IT. Also, had patients been enrolled soon after PCI when risk

This table summarizes the adverse events observed in the REDUCE-IT trial:

| Adverse event, n (%) | Icosapent ethyl (N=1737) | Placebo (N=1671) | P value |
|----------------------|--------------------------|------------------|---------|
| Atrial fibrillation/flutter requiring emergency treatment* | 115 (6.6) | 75 (4.5) | 0.007 |
| Atrial fibrillation/flutter requiring hospitalization ≥24 hours† | 59 (3.4) | 36 (2.2) | 0.04 |
| Bleeding events+hemorrhagic stroke‡ | 226 (13.0) | 205 (12.3) | 0.54 |
| Total bleeding events | 221 (12.7) | 202 (12.1) | 0.60 |
| Gastrointestinal bleeding | 60 (3.5) | 56 (3.4) | 0.92 |
| Central nervous system bleeding | 13 (0.8) | 7 (0.4) | 0.26 |
| Other bleeding | 171 (9.8) | 155 (9.3) | 0.60 |
| Hemorrhagic stroke | 5 (0.3) | 5 (0.3) | 1.00 |
| Severe TEAE | 378 (21.8) | 365 (21.8) | 0.97 |
| Serious TEAE | 593 (34.1) | 584 (34.9) | 0.64 |

TEAE indicates treatment emergent adverse event.

*Includes atrial fibrillation/flutter TEAEs and excludes positively adjudicated events. P value is based on Fisher’s Exact test.

†Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours of hospitalization clinical events by the Clinical Endpoint Committee. P value is based on stratified log-rank test.

‡Multiple bleeding TEAEs of the same preferred term are counted only once within each preferred term. Events that were positively adjudicated as clinical end points are not included in bleeding TEAEs. P values are based on Fisher’s Exact test.

Although the precise molecular mechanism of benefit from icosapent ethyl/EPA still requires some elucidation, the EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in the People With High Triglycerides Taking Statin Therapy) trial has recently shed some important light on the gross vascular mechanism of benefit. A total of 80 patients who had atherosclerotic coronary plaques with at least 20% stenosis on multidetector coronary computed tomography and a median baseline fasting triglyceride level of 259 mg/dL were randomized to icosapent ethyl 4 g daily versus placebo. Final follow-up imaging at 18 months showed a significant 17% reduction in low-attenuation plaque volume in patients treated with icosapent ethyl (whereas patients taking placebo nearly doubled their low-attenuation plaque volume). Significant reductions also occurred in fibrofatty, fatty, total noncalcified, and total plaque volumes. Thus, high-dose EPA therapy seems to result in significantly increased plaque stability and even plaque reduction, which could at least partially contribute to this marked reduction in cardiovascular events among high-risk patients.

Limitations

The exploratory nature as well as the lack of adjustment for multiple comparisons limited this post hoc analysis; REDUCE-IT was not powered for this or other subgroup analyses. With the post hoc nature of these analyses, all P values should be considered hypothesis-generating. As noted previously, patients with prior PCI had higher event rates and derived greater benefit from icosapent ethyl versus placebo. Although the time period from PCI to randomization was known in most patients, there was a subset of patients in which this was not known. Among the 24.9% of this subset and the remainder of patients, the distribution of randomization to icosapent ethyl versus placebo was equivalent. Double blinding also eliminated bias arising from this issue. The prerandomization extent of coronary artery disease and revascularization strategy (complete versus incomplete) among patients with a prior PCI was not known. Randomization was not stratified by history of PCI, and because there is potential for confounding, this subgroup finding needs corroboration in future studies. Future investigation will be required to gain a better understanding of whether icosapent ethyl reduced the rates of in-stent restenosis versus de novo plaque events as vessel- and lesion-specific data are not available in REDUCE-IT. Also, had patients been enrolled soon after PCI when risk

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is highest, the degree of benefit seen here may have been even greater, especially if future studies validate the use of a loading dose.43

CONCLUSIONS

Icosapent ethyl versus placebo resulted in significant and clinically meaningful reductions in cardiovascular events in this post hoc analysis. In patients with a prior PCI, the reductions in first and total primary end point events were 34% and 39%, respectively. There were large reductions in the primary and key secondary (hard MACE) end points, with NNTs4.8 years of 12 and 19, respectively, and consistent benefit across the hierarchical end points. These data highlight the substantial positive impact of icosapent ethyl on patients in the REDUCE-IT population, including patients with a history of prior PCI.

ARTICLE INFORMATION

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Author contributions: This specific post hoc analysis was proposed and designed by the study chair (the second author of this paper). The first draft was written by the first author and extensively revised by the second author and then circulated to the remainder of the authors, all of whom provided critical revisions to the paper. The statistical analyses were performed by Lixa Jiao, an employee of Amarin, and were validated independently by Qi Gao, MS, from Baim Clinical Research Institute with funding from Amarin.

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Supplemental Material
Appendix S1. REDUCE-IT Investigators
Figures S1–S4

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Linda Goedhart, Hanneke van Meurs, Rachel Langenberg, Jacqueline Rijsewem, (711) Jacqueline Hoogendijk, Lindy Swinkels-Diepenmaat, Wouter van Kempen / Marloes de Louw-Jansen, Dominique Bierens-Peters, (712) Willem W. van Kempen, Marianne E. Wittekoek, Irmaina Agous / Geert Schenk, (713) Willem W. van Kempen, Janneke Wittekoek, Kevin Cox, Deborah F. Julia, Jan JC Jonker / Roel Janssen, (714) Willem W. van Kempen, Marianne E. Wittekoek, Melchor Nierman, Hilligje Katerberg, Jan JC Jonker / Irene van der Haar, (715) Willem W. Van Kempen, Taco van Mesdag, Janneke Wittekoek, Jan JC Jonker, Leyda M. Alvarez Costa / Manon Schensema, (716) Salomé Zweeckhorst, Lindy Swinkels-Diepenmaat, Stefanie Schipperen, Willem W. van Kempen, Deborah Font Julia, Jan JC Jonker, Lauri Hanewinckel / Joyce Olsthoorn, (718) Johan C. Berends, Arie C. van der Spek, Roy van der Berg, Rob J. Timmermann / Ingrid Boerema

Ukraine N=836 (885) Iryna Mudruk, Anna Khrystoforova, / (886) Serhii Kyselov, / (887) Yaroslava V. Hilova, / (888) Pavlo Logoida / Pavlo Logoida, (889) Nataliia A. Sanina, / (890) Ilona P. Golikova, Olena O. Nemchyna / Ilona P. Golikova, Ilona P. Golikova, (891) Ivan I. Isaichikov, Olga B. Potapova / Iurii V. Gura, (892) Larysa Berestetska, / (893) Olena O. Kulianda, / (895) Oleksandr Tantsura, / (897) Oleksandr S. Kulbachuk, / (898) Volodymyr Petsentyi, Ihor Biskub / Ihor Biskub, (899) Tetyana Handych, (900) Oleg Lagkuti, Alyna Gagarina, / (937) Taras Chendey, / (938) Oksana F. Bilonko, / (939) Olena Matova, Larysa Bezrodna, Olena Yarynkina, Tetiana Ovdienko, Volodymyr Randchenko, Maryna Mospan / Tetiana Ovdienko, (940) Olena Butko, Olga Romanenko, / (941) Mykhailo Pavelko, Iryna Sichkaruk, / (942) Svitlana O. Lazareva, Olena A. Kudyryk / Inessa M. Koltsun, Inessa M. Koltsun, (943) Tetiana Magdalits, / (944) Sergei Zadorozhniy, Kira Kompaniiets, / (945) Andrii Ivanov, Sergiy Romanenko, Pavlo Kaplan, / (946) Vadym Y. Romanov, / (947) Oksana P. Mykytyuk / Nataliia S. Zaitseva, (948) Sergiy N. Pyvovar, / (949) Lyudmyla Burdeuna, / (951) Emerita Serdobinska, / (952) Tatiana I. Shevchenko, Igor I. Ivanytskyi / Igor I. Ivanytskyi, Igor I. Ivanytskyi, / (953) Olena V. Khyzhnyak, (954) Ganna Smirnova, Nataliia Kalinkina, Olena Keting, Olena Skyllana, Olga Kashanska, Anna Shevelok, Marina Khristichenko, / (955) Ievgenii Y. Titov, Danilenko O. Oleksander / Nataliia S. Polenova, (956) Nataliia Altunina, / (957) Viktoriia Kororaieva, / (958) Stanislav Zborovskiy, Leonid Kholopov, Iurii Suliman, Lanna Lukashenko, / (959) Stanislav Shvaykin, (960) Olexandr M. Glavatskiy, Roman O. Sychov, Roman L. Kulynych, / (961) Oleksandr A. Skarzhhevskiy, Nataliia V. Dovgan, / (962) Marta Horbach, / (964) Olya Cherkasova, Iryna Tyshchenko, (965) Liudmyla Todoriuk, Svitlana Kizimenko, Nataliia Brodi, Oleksandr Ivanko / Olga Garbarchuk, (985) Liudmyla Alieksieieva, / (992) Tetiana L. Shandra, / (994) Olena Beregova, / (996) Larisa An Bodretska, / (997) Svitlana S. Naskalova / Ivanna A. Antoniuk-Shcheglova, Olena V. Bondarenko, (998) / Natalia G. Andreieva, (999) Iryna I. Vakalyuk, Olha S. Chovganyuk, Nataliia R. Artemenko /

Russian Federation N=709 (850) Kiril A. Maltsev, / (851) Natalia Kalishevich, / (901) Natalia G. Kondratyeva, Svetlana A. Nikitina, Maria V. Martjanova, / (902) Anna V. Sokolova, Dmitrii O. Dragunov, / (903) Olga Kolesnik, / (904) Vera Larina, (905) Oxana V. Tsygankova, (906) Maria Ivanova, Illia A Karpov, Elena M Aronova, Ekaterina S. Vedernikova, / (908) Ekaterina I. Lubinskaya, (909) Taras Y. Burak, / (910) Sergey I. Skichko, Farhad Rasulev / Ekaterina B. Soldatova, (911) Alexander L. Fenin / Ilya I. Laptev, (912) Elena E. Luchkina, (913) Alexandr
Akatov, Natalia V, Polenova, Natalia N, Slavina, Irina N, Korovnika, Marina Yu, Prochorova, (914) Regina Shakirova, (915) Elena N, Andreicheva, (916) Olga A, Krasnova, (917) Tinatin V, Lobzhanidze, Tatiana B, Dmitrova, (918) Viktoria V, Stakhiv, Maria I, Pechatnikova, Alexandra V, Panova, Maria Y, Tipikina, (919) Oxana P, Rotar, (921) Nikolay A, Bokovin, Saule K, Karabalieva, Farid Y, Tumarov / Elena V, Vasileva, (922) Natalya Gennadevna Lozhkina, (923) Ekaterina V, Filippova, Alisa I, Shaskaeva / Ekanerina V, Filippova (Deilik), (924) Natalia Yu, Tolkacheva, Elena N, Domracheva, Andrey N, Ryabikov, (925) Inga T, Abesadze / Marianna Z, Alugishvili, (926) Elena P, Nikolaeva / Nadezda V, Smirnova, Valentina I, Rodionova, (927) Polina V, Dolovstaya, (928) Igor E, Yunonin, (929) Sergey V, Kadin, Tatyana S, Sveklina, / (930) Anna V, Bushmanova / Anna V, Bushmanova, (931) Elena L, Barkov, Irina S, Gomova, Yana V, Brytkova / Tatiana B, Ivanova, (932) Marina Y, Zubareva, / (933) Inga Skopets, / (934) Lybov A, Galashevskaya, / (935) Emilia D, Butinskaya / Olga G, Gusarova, (936) Natalia B, Kalishevich, Yana R, Pavlova, Marianna P, Serebrenitskaya, Vitalina F, Grygorieva, Gulnara R, Kuchaeva, / (966) Inna A, Vasileva, / (968) Gulnara I, Ospanova, (969) / Yulia V, Vahrusheva, Irina A, Semenova, (970) Irina E, E, Mikhailova, Olga O, Kvasova, Valeria D, Shurygina, Alexey E, Rivin, Alexey O, Saveliev / Alexey A, Saveliev, (972) Olesya O, Milyaeva, Nadezhda N, Lapshina, Ninel A, Lantsova, / (973) Pavel V, Alexandrov, / (974) / Evgeniy A, Orlikov, (975) Alla Falkovskaya, Tatiana Ripp, Sergei Triss, Stanislav Pekarskiy / Sitkova Ekaterina, (976) / Evgeniya N, Zhuravleva, (977) Olga Perova, / (978) Galina Kovaleva, Liubov Koroleva / Liubov Koroleva, (979) Lydia Mishchenko, (980) Boris P, Garshin, / (982) Svetlana A, Kutuzova, Lyudmila I, Provotorova / Igor P, Zadvorny, (983) Olga V, Okhapkina / Anatoly O, Khrustalev, (987) Tatiana Suworova, / (988) / Elena S, Shaf, (989) Varvara A, Vershinina, Andrey A, Kozulin, / (990) Oxana A, Oleynik / Irina Y, Martynova, (991) Natalia V, Kizhvatoa, / (993) Alla S, Salasyuk, Vera V, Tsoma, Alla A, Ledyaeva, Elena V, Chumachek / South Africa N=414 (416) SC Blignaut / Tersia Y, Alexander, Chano Du Plessis, (417) Thirumani Govender, Samatha M, Du Toit, Leya Motola / Areesh Gassiep, Christina Naude (Smit), Marli Terblanche, Marlien Snoer (Kruger), Berenice Pillay, (418) De Vries Basson, Clive H, Corbett / Marisa E, Theron, (419) / Bianca Fouche, Mareli E, Coetzee, (420) Pieter Odendall / Frederik H, Van Wijk, Anna-Mari Conradie, Trudie Van der Westhuizen, (421) / Carine Tredoux, (422) Mohamed S, Mookdham, Andie J, Van der Merwe / Karin Snyman, Gerda Smal, (423) / Yvonne De Jager, (424) Thomas A, Mabin / Annuus King, (425) / Lindy L, Henley, (426) / Brenda M, Zwane, Jane Robinson, (427) / Marinda Karsten, Andonia M, Page, Valerie Nsabiyumva, Charmaine Krahenbuhl, (430) Jaiprakash D, Patel, Yunus E, Motola / Ayesha Dawood, Nondumiso B, Koza, Lenore MS Peters, Shavashni Ramlachan, (431) Wilhelm J, Bodenstein, Pierre Roux / Lizelle Fouche, Cecilia M, Boshoff, (432) Haroon M, Mitha / Fathima Khan, (433) Henry P, Cyster / Helen Cyster, (435) E, C, Wessels / Florence J, Jacobs, (437) Melanie A, Sebastian / Deborah A, Sebastian, Nadia Mahomed, (439) Ignatius P, Immink / Celia Cotzee, (440) Tanja Cronje / Madele Roscher, Maria Le Roux, (441) Yvonne A, Trinder / Poland N=359 (602) Renata Wnętrzak-Michalska / Magdalena Piszczek, (603) Andrzej Piela, Ewa Czernecka, Dorota Knychas, Alina Walczak, Izabella Gładysz / Katarzyna Filas, Ewelina Kiluk, Krzysztof Świgło, Iwona Jędrzejczyk, Kamila Łuczyńska, (604) / Katarzyna Tymendorf,
India N=262  (501) Bivin Wilson / Krithika Velusamy, Swaidha S. Sadhiq, (502) / Bhavani Siddeshi, (503) M Bhanukumar / Abhishek Srivatsav, Madhan Ramesh, Sri Harsha Chalasani, Mini Johnson, Prashanth Gopu, Jeesa George, Sowmya Reddy, Swetha Tessy Thara Eleena (504) Damodara Rao Kodem / Haritha N. Nakkella, Padma Kumari Mandula, Anjan Kumar Vuriya, Syamala Rajana, (505) / Aruna Kale, (506) Tiwari Rajeev / Raina Jain, Vinip Jain, (507) Srilakshmi Mandayam Adhyapak / Lumin Sheeba, Uma C R, Ramya R, (509) Aditya V. Kulkarni / M S. Ganachari, Ruma Samberek, (510) / Mohammad Bilal, Nungshijungla Kalyan Chakravarthy / Ravi Badhavath, Sranan Kumar, Meenakshi Simhadri, Farooque Salamuddin, Venkat Prasad, (513) Vivek Dwivedi, Sudha Sarna / Tilak Arora, Deepak Chawla, (514) Archantha Sathe / Chaware Gayatree, (515) / Ajeet Nanda, Ram Avtar, Jyoti Sharma, (516) Vaibhavi P S Sasirekha D, Deepthi Kobbajji / Ramya Ningappa, Shwetha Shree, Chandrashekhar K Nandini M R Sowjanyaswani N Sonika G Rathna L Priyanka R (517) / Rupal J. Shriramaker, (518) Lakshmi Vinutha Reddy, K Sumathi, Babitha Devi / Bina N. Naik, Rohini Manjunath, Rajeshwari Ashok, (524) / Tony V. Kunjumon, Jesline Thomas, (525) / Shaik Samdhani, (526) Kasthuri Selvam / Poongothai Subramani, Nandakumar Parthasarathy, (527) Nirmal K. Bohra / Anvesh K. Gatla

Canada N=250  (172) / Cheryl Horbatuk, (173) / Julie Sills, (175) E B. Davey / Liz Paramonczyk, Olga Raczanelli, (176) David Crowley / Sandy Strybosch, (177) Andre Belanger, Jean Palardy, Alicia Schifferlin / Sylvie Gauthier, (178) Norman Kalyniuk, Shawn D. Whatley / Heather Lappala, Grishma Patel, Matthew Reeve, (181) Catherine Moran / Jody Everitt, (182) / Teresa Ferrari, (188) / Christine Bouffard, (200) Jirir Frohlich, Gordon Francis, John Mancini, Gregory Bondy, Debbie DeAngelis, Patricia Fulton / Debbie DeAngelis, Patricia Fulton, (201) David W. Blank / Angela Lombardo, Mylene Roy, (202) / Jackie Chow, (219) Hyman Fox, William J. Grootendorst, Angela Hutchinson, Hyman Fox / Sharon M. Chan, (271) / Christie Fitzgerald, (361) / Teresa Ferrari, (395) / Lynn Wilkins, Rebecca L. Raymond, Arlene Reyes (397) Lavoie Marc Andre / Denis Fortin, (659) Helene Ouimet, Thanh-Thao Ton-Nu, Martine Dussureault, Marie-Helene Blain / Madeleine Roy, Nathalie Kopajko, Chantal Fleury, (660) / Karine Maheux

Romania N=202  (801) Gabriela Valentina Ciobotaru, (803) Maria C. Constantinescu / Carmen-Lucia Gherghinescu, (804) Ana-Maria Avram, (805) Ioan Mantineanu / Radu I. Cojjan, (806) Octavian M. Pirvu, (808) Aura Simpetrean, Lucian Pop, Delia Lupu, (809) Radu Usvat, Ana Petrisor, (810) Nicoleta Dumitru, (811) Camelia Morju, (812) / Adelina Gheorgita, (813) Magda V. Mitu, (814) Cosmin Macarie, (815) Ana Maria Pop, (816) Maria-Catalina Diaconu, (817) Iulia Grancea, (818) Mihaela Cosma / Mihaela Cosma, (819) Mihaela Crisan /
Australia N=189  (301) / Elizabeth Herron, (302) Anthony M. Dart, Paul Nestel / Sally B. Kay, Kaye S. Carter, (303) Imran Badshah, Ashley Makepeace / Jocelyn Drinkwater, Michelle England, (304) / Azette Rafei, Kylie Patterson, (305) Alicia Jenkins, Sybil McAuley / Sue M. Kent, (306) / Joy E. Vibert, Leonie Perrett, (307) Thomas David / Samantha L. Kaye, Monika O'Connor, (308) Nimalie J. Perera / Nicole T. Lai, Kerry A. Kearins, (309) Christina Dicamillo, Heather Anderson / Louise Ferguson, (310) / Sharon D. Radtke, (311) Charles T. Thamarappillil / Janice M. Boys, (312) / Anita K. Long, Toni Shanahan, (313) Michael Nyguyen / Nicole Forrest, Gill Tulloch, Della Greenwell, (314) Sarah L. Price, Aye N. Tint, Priya K. Sumithran / Tamara L. Debreceni, Lisa Walker, Mary Caruana, Kira Edwards, Maria Statopoulos, Cilla Haywood, (315) Dimitar Sajkov / Sharen Pringle, Anne Tabner, Kathrina Bartolay, Chamindi Abeyratne, Kylie Bragg, (317) Patrick Mulhern, Peter Purnell, Randall Hendriks / Gill Tulloch, (319) Lyn Williams, Jane Hamlyn / Aurelia Connelly, Jan Hoffman

New Zealand N=134  (402) Samantha Bailey, Jane Kerr / Zarnia Morrison, Sarah Maeder, Roberta McEwan, Prasanna Kunasekera, Patrice McGregor, Jo Young, Sharon Berry, (405) Rick Cutfield, Michelle Choe, Catherine McNamara / Narrinder K. Shergill, (406) / Petra Crone, (408) Miles G. Williams, Keith Dyson / Diana H. Schmid, Audrey C. Doak, Melissa Spooner, (411) Colin Edwards / Anne Turner, Grainne M. McAnnally, (414) Raewyn A. Fisher, Fraser B. Hamilton, Denis H. Friedlander / Melissa R. Kirk, Jayne E. Scales, (415) / Marguerite A. McLelland, (442) Neelam A. Dalman / Cathy E. Vickers, Carolyn Jackson, (444) / Wendy Coleman, (445) Phillip I. Garden / Wendy F. Arnold

Non-United States Institutions

Country listing by enrollment; N=number of participants randomized per country; (site number)

The Netherlands N=1678  WCN  (701) Bravis Hospital, Roosendaal, (702) Deventer Hospital, Cardiology Department, Deventer, (703) Spaarnegasthuis, Hoofddorp, (704) Gelre Ziekenhuis, Zutphen, (705) Tweesteden Ziekenhuis, Tilburg, (706) Admiraal D'Ruyter Ziekenhuis, Goes, (707) Tergooi, Blaricum, (708) Canisius Wilhelmina Ziekenhuis, Nijmegen, (709) Alrijne Hospital, Leiderdorp, (719) HMC Bronovo, Den Haag, (720) Stichting CRE Enschede, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, (721) Beatrix Hospital, Gorinchem, (722) Langeland Ziekenhuis, Cardiology Department, Zoetermeer, (723) Medisch Centrum Leeuwarden, Leeuwarden, (724) Spaarne Gasthuis, Haarlem, (725) St Elisabeth Hospital, Tilburg, (726) Bernhoven Hospital, Uden, (727) Franciscus Gasthuis & Vlietland, Schiedam, (728) Noordwest Ziekenhuis, Den Helder, (729) Jeroen Bosch Hospital, Hertogenbosch, (731) Groene Hart Ziekenhuis, Gouda, (732) Meander Medical Center, Amersfoort, (733) Ikazia Hospital Rotterdam, Rotterdam, (734) Máxima Medisch Centrum, Veldhoven, (735) Ziekenhuis Stjansdal, Harderwijk, (736) Tjongerschans Ziekenhuis, Cardiology Department, Heerenvoorde, (737) Franciscus Gasthuis, Rotterdam, (738) ZGT, Almelo and Hengelo, (739) D & A Research, Sneek, (740) Zuyderland Mc, Heerlen, (741) Martini Ziekenhuis, Groningen, (742) Gelderse Vallei Ziekenhuis, EDE, (743) IJsselland Ziekenhuis, Capelle aan den IJssel;  non-WCN  (710) Andromed Rotterdam, Rotterdam, (711) Andromed Eindhoven, Eindhoven, (712) Andromed Leiden, Leiderdorp, (713) Andromed Oost BV, Velp,
(714) Andromed Zoetermeer BV, Zoetermeer, (715) Andromed Noord, Groningen, (716) Andromed Breda, Breda, (718) Gemini Ziekenhuis, Den Helder

**Ukraine N=836** (885) State Instituicio, D.F.Chebotarev Institute of Gerontology of NAMS, Kiev, (886) Department of Internal Diseases-1 of Zaporizhzya State Medical University, Zaporizhzya City Clinical Hospital of Emergency Care, Zaporizhzya, (887) The State Institute of Therapy, L.T. Malaya of Ukrainian National Academy of Medical Science, Kharkov, (888) Policlinic of Administration of Medical Services and Rehabilitation of Artem State Holding, Kiev, (889) State Institution, Ukrainian State Scientific and Research Institute of Medical and Social Problems of Disability of Ministry of Health of Ukraine, Dnipro, (890) National Scientific Center M.D. Strazhesko Institute of Cardiology, Kiev, (891) Communal Institution, Central Clinical Hospital #4 of Zavodsky District, Zaporizhzya, (892) Kiev City Clinical Hospital #7, Therapeutic dpt #2, Kiev, (893) Medical Center, Desna, Ltd, Ternopil, (894) LTD Cardiology Clinic, Heart and Vessels, Kiev, (895) Clinic of State Institution, Ukrainian State Institute of Medical and Social Problems of Disability Ministry of Public Health, Dnipro, (897) State Institute, Zaporizhzya Medical Academy of Postgraduate Education of Ministry of Health of Ukraine, Department of Family Medicine With Course of Dermatovenereology and Psychiatry Based On Municipal Institution: Zaporyzhyzya 9th City Multidisciplinary Clinical Hospital, Cardiology Department, Zaporizhzya, (898) Volyn Regional Clinical Hospital, Department of Cardiosurgery, Lutsk, (899) Zakarpatskiy Oblasny Klinichny Kardiologichnyi Dyspanser, m. Uzhhorod, (900) Infarction Dprt of City Clinic Hosp. #6, Simferopol, AR Crimea, (937) Zakarpattya Regional Clinical Cardiology Dispensary, Dept. of General Cardiology, Uzhhorod National University, Chair of Hospital Therapy, Uzhhorod, (938) City Clinical Hospital #1, Vinnitsa, (939) State Institution, National Scientific Center, NAMS Institute of Cardiology M.D. Strazhesko, Department of Essential Hypertension, Kiev, (940) Kharkiv Medical Academy of Postgraduate Education, City Clinical Hospital #8, Kharkiv, (941) Lutsk City Clinical Hospital, Lutsk, (942) Kharkiv City Clinical Hospital #27, Kharkiv, (943) Kharkiv Medical Academy of Postgraduate Education, Kharkiv, (944) Lugansk Regional Cardiological Dispensary, Luhansk, (945) Dnipropetrovsk Medical Academy, Dnipropetrovsk Joint Emergency Hospital, Dnipro, (946) State Institution, National Scientific Center, The M.D. Strazhesko Institute of Cardiology, National Academy of Medical Sciences of Ukraine, Kiev, (947) City Clinical Hospital №3, Chernivtsi, (948) National Institute of Therapy N.A. L. Malaya NAMS, Kharkiv, (949) National Pirogov Memorial Medical University, Vinnytsya, (951) Clinic of State Institution, Institute of Therapy NAMS Ukraine L.T. Maloy, Kharkiv, (952) HSEE of Ukraine, Ukrainian Medical Stomatological Academy, Poltava, (953) Odessa National Medical University, Center of Reconstructive and Recovery Medicine (University Clinic), Odessa, (954) Institute of Urgent and Recovery Surgery, Donetsk, (955) State Institution National Scientific Centre, Acad. M.D. Strazhesko Institute of Cardiology of Naciona Ams of Ukraine, Kiev, (956) Kiev Municipal Clinical Hospital #12, Department of Cardiology; O. O. Bogomolets National Medical University, Kiev, (957) Saint Catherine Odessa, Treatmnt and Diagnostic Center LLC, Odesa, (958) Central City Clinical Hospital #1, Donetsk, (959) Communal Institution, Odesa Regional Cardiological Dispensary, Odesa, (960) Zaporizhzya Regional Clinical Hospital, Zaporizhzya, (961) National Scientific Center, NAMS Strazhesko Institute of Cardiology, Kiev, (962) Communal City Clinical Hospital #8, Lviv, (963) Ivano-Frankivsk Regional Clinical
Cardiological Center, Ivano-Frankivsk, (964) City Clinical Hospital #9, Department of Cardiology; State Institution, Dnipropetrovsk Medical Academy of Moh, Dnipro, (965) Kyiv City Clinical Hospital #1, Department of Emergency Cardiology, Kiev, (985) Kyiv City Oleksandriivska Clinical Hospital, Kiev, (992) Cherkasy Regional Cardiological Center, Cherkasy, (994) Kyiv Emergency Care Hospital, Infarction Department, Kiev, (996) The Institute of Gerontology NAMS D.F.Chebotarev, Kiev, (997) D.F. Chebotarev Institute of Gerontology, National Academy of Medical Sciences, Kiev, (998) Odesa Regional Clinical Hospital, Department of Cardiosurgery, Odesa, (999) Ivano-Frankivsk National Medical University, Ivano-Frankivsk

**Russian Federation N=709**  
(850) State Budget Healthcare Institution of City Moscow, City Clinical Hospital N.A. M.P. Konchalovskogo of Healthcare Department, Zelenograd, (851) Saint Petersburg State Budget Healthcare Institution, City Consultative and Diagnostic Center #1, Saint Petersburg, (901) State Health Care Institution City Hospital #117, Saint Petersburg, (902) State Budget Healthcare Institution of Moscow, City Clinical Hospital #4 of The Healthcare Department, Moscow, (903) First Saint Petersburg State Medical University N.A.Acad.I.P.Pavlov of The Ministry of Healthcare of Russian Federation, Saint Petersburg, (904) Pirogov Russian National Research Medical University, Moscow, (905) City Clinical Emergency Hospital#2, Novosibirsk, (906) State Inst City Multidiscipline Hospital# 2, Saint Petersburg, (908) Almazov National Medical Research Centre, Saint Petersburg, (909) Autonomous Non-Profit Organization: Medical Center Alliance, Kirovsk, (910) Central Clinical Hospital of The Russian Academy of Sciences, Moscow, (911) Saint Petersburg State Budget Institution of Healthcare, City Hospital #15, Saint Petersburg, (912) City Clinical Hospital #15 O.M.Filatov, Moscow, (913) FSBHI Clinical Hospital #123 of FMBA, Moscow, (914) Kazan State Medical University, Kazan, (915) Scientific Research Medical Complex, State Budget Institution of Healthcare Clinical Hospital #2, LLC, Kazan, (916) Saint Petersburg State Budget Institution of Healthcare, City Hospital #9, Saint Petersburg, (917) State Budget Healthcare Institution of City Moscow, City Clinical Hospital N.A. V.V.Vinogradova of Healthcare Department, Moscow, (918) International Clinic MEDEM, LLC, Saint Petersburg, (919) Almazov National Medical Research Centre, Saint Petersburg, (921) Saint Petersburg State Budget Institution of Healthcare, City Outpatient Clinic #109, Saint Petersburg, (922) Novosibirsk State Medical University, Novosibirsk, (923) Medinet, LLC, Saint Petersburg, (924) Research Institute of Internal and Preventive Medicine, Branch of The Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, (925) Almazov National Medical Research Centre, Saint Petersburg, (926) Saint Petersburg State Budgetary Healthcare Institution, City Pokrovskaya Hospital, Saint Petersburg, (927) Saratov Regional Veterans Hospital, Saratov, (928) State Healthcare Institution of Yaroslavl Region, Clinical Hospital #8, Yaroslavl, (929) Federal State Budget Military Educational Institution of Higher Professional Education, Military Medical Academy, S.M. Kirov of Ministry of Defence of Russian Federation, Saint Petersburg, (930) The Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of Ministry of Healthcare of The Russian Federation (Sechenovskiy University), Moscow, (931) Moscow State Medical and Dental University N.A A.I. Evdokimov of The Ministry of Health, Moscow, (932) FGBU, National Medical Research Center of Cardiology, Ministry of Health
Of Care of Russia, Moscow, (933) State Budget Institution of Healthcare, Republican Hospital V.A. Baranov, of The Ministry of Healthcare of Karelia Republic, Petrozavodsk, (934) State Budget Healthcare Institution of Arkhangelsk Region, Arkhangelsk Regional Clinical Hospital, Arkhangelsk, (935) Leningrad Regional Clinical Hospital, Saint Petersburg, (936) Science and Research Institute of Experimental Medicine, Saint Petersburg, (966) Saint Petersburg State Budget Healthcare Institution, City Hospital #40 of Kurortnyi District, Saint Petersburg, (967) Federal State Budget Institution of Healthcare, Clinical Hospital #122 N.A. L.G. Sokolov Under Federal Medical and Biological Agency of Russia, Saint Petersburg, (968) City Hospital # 38 N A Semashko, Saint Petersburg, (969) State Budget Institution of Healthcare of Arkhangelsk Region, The First City Clinical Hospital E.E. Volosevich, Arkhangelsk, (970) Cardio-Centre, Chernaja Rechka, Saint Petersburg, (971) Central Outpatient Department at Federal State Budget Institution of Healthcare, Northern Medical Clinical Center N.A. Semashko of Federal Medical-Biological Agency, Arkhangelsk, (972) Saint Petersburg State Official Institution of Healthcare, Mariinskaya Ambulatory, Saint Petersburg, (973) Sanatorium Chernaya Rechka, Saint Petersburg, (974) State Healthcare Institution, Regional Clinical Cardiology Dispensary, Saratov, (975) Cardiology Research Institute, Tomsk National Research Medical Center of Russian Academy of Sciences, Tomsk, (976) Research Institute of Complex Issues of Cardiovascular Diseases (NII KPSSZ), Kemerovo, (977) Panaceya Clinic, LLC, Moscow, (978) Nizhny Novgorod Regional Clinical Hospital N.A.Semashko, Nizhny Novgorod, (979) Moscow Hospital #15 O.M.Filatov, Moscow, (980) Budgetary Healthcare Institution of Voronezh Region, Voronezh City Clinical Hospital of Emergency Medical Care #1, Voronezh, (982) Autonomous Healthcare Institution, Voronezh Regional Clinical Consultative and Diagnostic Center, Voronezh, (983) Yaroslavl Regional Clinical Hospital, Yaroslavl, (987) Medical Union New Hospital, LLC, Ekaterinburg, (988) Hospital of Veterans Wars, Kemerovo, (989) State Budget Healthcare Institution of Sverdlovsk Region, Sverdlovsk Regional Clinical Hospital #1, Ekaterinburg, (990) Siberian State Medical University, Tomsk, (991) State Budget Healthcare Institution, Scientific and Research Institute, Regional Clinical Hospital #1 N.A., Krasnodar, (993) Volgograd State Medical University, Department of Therapy and Endocrinology, Volgograd

**South Africa N=414**  
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Figure S1. Efficacy and Safety of Icosapent Ethyl Among Patients with Prior PCI, Stratified by Baseline Antithrombotic Regimen.

| Endpoint/Subgroup                              | Icosapent Ethyl | Placebo | Icosapent Ethyl vs. Placebo | P-value | Int. P-value |
|-----------------------------------------------|-----------------|---------|-----------------------------|---------|--------------|
|                                               | n/N (%)         | n/N (%) | HR (95% CI)                 |         |              |
| Primary Composite Endpoint                    | 362/1737 (20.8) | 491/1671 (29.4) | 0.66 (0.58, 0.76) | <0.0001 |
| Baseline Medications                          |                 |         |                             | 0.33    |              |
| Aspirin Only                                  | 150/873 (17.2)  | 217/796 (27.3) | 0.59 (0.48, 0.73) | <0.0001 |
| Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 146/818 (23.6)  | 185/812 (30.2) | 0.74 (0.60, 0.92) | 0.007   |
| Warfarin OR Rivaroxaban OR Apixaban           | 13/31 (41.9)    | 9/26 (32.1)   | 1.02 (0.43, 2.42) | 0.97    |
| Both Anticoagulants + Any Anti-Platelet Above | 16/49 (32.7)    | 23/62 (44.2)  | 0.72 (0.38, 1.38) | 0.32    |
| Key Secondary Composite Endpoint              | 208/1737 (12.0) | 290/1671 (17.4) | 0.66 (0.56, 0.79) | <0.0001 |
| Baseline Medications                          |                 |         |                             | 0.52    |              |
| Aspirin Only                                  | 91/873 (10.4)   | 135/796 (17.0) | 0.60 (0.46, 0.78) | 0.0001  |
| Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 74/618 (12.0)   | 100/612 (16.3) | 0.71 (0.53, 0.96) | 0.03    |
| Warfarin OR Rivaroxaban OR Apixaban           | 11/31 (35.5)    | 7/28 (25.0)   | 1.07 (0.41, 2.84) | 0.69    |
| Both Anticoagulants + Any Anti-Platelet Above | 10/49 (20.4)    | 15/52 (28.8)  | 0.78 (0.35, 1.74) | 0.54    |
| Any Bleeding                                  | 221/1737 (12.7) | 202/1671 (12.1) | 1.03 (0.85, 1.25) | 0.73    |
| Baseline Medications                          |                 |         |                             | 0.008   |              |
| Aspirin Only                                  | 81/873 (9.3)    | 93/796 (11.7) | 0.77 (0.57, 1.04) | 0.08    |
| Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 90/618 (14.6)   | 70/612 (11.4) | 1.30 (0.95, 1.78) | 0.09    |
| Warfarin OR Rivaroxaban OR Apixaban           | 5/31 (16.1)     | 7/28 (25.0)   | 0.33 (0.10, 1.09) | 0.06    |
| Both Anticoagulants + Any Anti-Platelet Above | 10/49 (30.6)    | 7/62 (13.5)   | 2.35 (0.95, 5.78) | 0.06    |
| Serious Bleeding                              | 55/1737 (3.2)   | 46/1671 (2.8) | 1.15 (0.78, 1.69) | 0.49    |
| Baseline Medications                          |                 |         |                             | 0.38    |              |
| Aspirin Only                                  | 17/873 (1.9)    | 16/796 (2.0)  | 0.94 (0.47, 1.85) | 0.85    |
| Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 20/818 (3.2)    | 15/812 (2.5)  | 1.38 (0.70, 2.70) | 0.35    |
| Warfarin OR Rivaroxaban OR Apixaban           | 2/31 (6.5)      | 3/28 (10.7)   | 0.51 (0.08, 3.21) | 0.47    |
| Both Anticoagulants + Any Anti-Platelet Above | 7/49 (14.3)     | 3/52 (5.8)    | 2.52 (0.65, 8.76) | 0.17    |
Figure S2. Forest Plot of Efficacy End Points in Hierarchical Testing Order by Sex Among Patients with Prior PCI.

| Endpoint/Subgroup                              | Icosapent Ethyl | Placebo | Icosapent Ethyl vs. Placebo | P-value | Int. P-value |
|-----------------------------------------------|----------------|---------|-----------------------------|---------|--------------|
|                                               | n/N (%)        | n/N (%) | HR (95% CI)                 |         |              |
| Primary Composite Endpoint                     | 362/1737 (20.8) | 491/1671 (29.4) | 0.66 (0.58, 0.76)          | <0.0001 |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 298/1387 (21.5) | 398/1317 (30.2) | 0.66 (0.57, 0.77)          | <0.0001 |              |
| Female                                        | 64/350 (18.3)  | 93/354 (26.3)  | 0.70 (0.51, 0.97)          | 0.03    |              |
| Key Secondary Composite Endpoint               | 208/1737 (12.0)| 290/1671 (17.4)| 0.66 (0.56, 0.79)          | <0.0001 |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 172/1387 (12.4) | 233/1317 (17.7) | 0.67 (0.55, 0.82)          | <0.0001 |              |
| Female                                        | 36/350 (10.3)  | 57/354 (16.1)  | 0.66 (0.43, 1.01)          | 0.05    |              |
| Cardiovascular Death or Nonfatal Myocardial Infarction | 181/1737 (10.4) | 248/1671 (14.8) | 0.68 (0.56, 0.82)          | <0.0001 |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 151/1387 (10.9) | 200/1317 (15.2) | 0.69 (0.56, 0.86)          | 0.0006  |              |
| Female                                        | 30/350 (8.6)   | 48/354 (13.6)  | 0.66 (0.41, 1.04)          | 0.07    |              |
| Fatal or Nonfatal Myocardial Infarction       | 141/1737 (8.1) | 198/1671 (11.8)| 0.66 (0.53, 0.82)          | 0.0002  |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 120/1387 (8.7) | 168/1317 (12.8)| 0.65 (0.52, 0.83)          | 0.0003  |              |
| Female                                        | 21/350 (6.0)   | 30/354 (8.5)  | 0.72 (0.41, 1.26)          | 0.25    |              |
| Urgent or Emergent Rervascularization         | 144/1737 (8.3) | 205/1671 (12.3)| 0.65 (0.52, 0.80)          | <0.0001 |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 123/1387 (8.9) | 172/1317 (13.1)| 0.64 (0.51, 0.81)          | 0.0002  |              |
| Female                                        | 21/350 (6.0)   | 33/354 (9.3)  | 0.64 (0.37, 1.12)          | 0.11    |              |
| Cardiovascular Death                          | 55/1737 (3.2)  | 81/1671 (4.8)  | 0.64 (0.46, 0.90)          | 0.01    |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 41/1387 (3.0)  | 59/1317 (4.5)  | 0.66 (0.44, 0.98)          | 0.04    |              |
| Female                                        | 14/350 (4.0)   | 22/354 (6.2)  | 0.68 (0.34, 1.34)          | 0.26    |              |
| Hospitalization for Unstable Angina           | 75/1737 (4.3)  | 118/1671 (7.1)| 0.59 (0.44, 0.79)          | 0.0003  |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 62/1387 (4.5)  | 92/1317 (7.0)  | 0.60 (0.44, 0.83)          | 0.002   |              |
| Female                                        | 13/350 (3.7)   | 26/354 (7.3)  | 0.51 (0.26, 1.01)          | 0.05    |              |
| Fatal or Nonfatal Stroke                      | 39/1737 (2.2)  | 59/1671 (3.5)| 0.62 (0.41, 0.92)          | 0.02    |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 28/1387 (2.0)  | 45/1317 (3.4)  | 0.57 (0.35, 0.91)          | 0.02    |              |
| Female                                        | 11/350 (3.1)   | 14/354 (4.0)  | 0.83 (0.38, 1.84)          | 0.65    |              |
| Total Mortality/Nonfatal Myocardial Infarction/Nonfatal Stroke | 259/1737 (14.7) | 325/1671 (19.4)| 0.72 (0.61, 0.85)          | 0.0001  |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 204/1387 (14.7) | 258/1317 (19.6)| 0.72 (0.60, 0.86)          | 0.0004  |              |
| Female                                        | 51/350 (14.6)  | 67/354 (18.9) | 0.78 (0.54, 1.12)          | 0.17    |              |
| Total Mortality                               | 108/1737 (6.2)| 124/1671 (7.4)| 0.82 (0.63, 1.06)          | 0.13    |              |
| Gender                                        |                |         |                             |         |              |
| Male                                          | 78/1387 (6.6)  | 91/1317 (6.9)  | 0.80 (0.59, 1.08)          | 0.15    |              |
| Female                                        | 30/350 (8.6)   | 33/354 (9.3)  | 0.92 (0.56, 1.52)          | 0.74    |              |
Figure S3. Cumulative Incidence Plots of A. Primary Composite End Point and B. Key Secondary Composite End Point with Non-CV Death as Competing Risk Among Patients with Prior PCI.

A.

Gray's Test for Equality of Cumulative Incidence Functions: <0.0001
Cause Specific HR (95% CI): 0.66 (0.58, 0.76)

B.

Gray's Test for Equality of Cumulative Incidence Functions: <0.0001
Cause Specific HR (95% CI): 0.66 (0.56, 0.79)
Figure S4. Forest Plot of Primary and Key Secondary Composite End Points for Patients With or Without Prior PCI

| Endpoint/Subgroup            | Icosapent Ethyl       | Placebo            | Icosapent Ethyl vs. Placebo | P-value | Interaction P-value |
|------------------------------|-----------------------|--------------------|------------------------------|---------|---------------------|
|                              | n/N (%)               | n/N (%)            | HR (95% CI)                  |         |                     |
| Primary Composite Endpoint   |                       |                    |                              | 0.11    |                     |
| Prior PCI                    | 362/1737 (20.8)       | 491/1671 (29.4)    | 0.66 (0.58, 0.76)            | <0.0001 |                     |
| ASCVD w/o PCI                | 215/1248 (17.2)       | 281/1310 (21.5)    | 0.79 (0.66, 0.95)            | 0.01    |                     |
| Key Secondary Composite Endpoint |                      |                    |                              | 0.39    |                     |
| Prior PCI                    | 208/1737 (12.0)       | 290/1671 (17.4)    | 0.66 (0.56, 0.79)            | <0.0001 |                     |
| ASCVD w/o PCI                | 159/1248 (12.7)       | 220/1310 (16.8)    | 0.75 (0.61, 0.91)            | 0.005   |                     |

0.2 1.0 2.0
Icosapent Ethyl Better Placebo Better