Title

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

Journal

Journal of the American Heart Association, 11(6)

ISSN

2047-9980

Authors

Peterson, Benjamin E
Bhatt, Deepak L
Steg, Ph Gabriel
et al.

Publication Date

2022-03-15

DOI

10.1161/jaha.121.022937

Peer reviewed

Journal of the American Heart Association

ORIGINAL RESEARCH

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

Benjamin E. Peterson, MD, MPH; Deepak L. Bhatt, MD, MPH; Ph. Gabriel Steg, MD; Michael Miller, MD; Eliot A. Brinton, MD; Terry A. Jacobson, MD; Steven B. Ketchum, PhD; Rebecca A. Juliano, PhD; Lixia Jiao, PhD; Ralph T. Doyle, Jr., BA; Craig Granowitz, MD, PhD; C. Michael Gibson, MD; Duane Pinto, MD; Robert P. Giugliano, MD, SM; Matthew J. Budoff, MD; Jean-Claude Tardif, MD; Subodh Verma, MD, PhD; Christie M. Ballantyne, MD; on behalf of the REDUCE-IT Investigators*

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

Correspondence to: Deepak L. Bhatt, MD, MPH, FAHA, Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, 75 Francis Street, Boston, MA 02115. E-mail: DLBhattMD@post.Harvard.edu

*A complete list of the REDUCE-IT investigators can be found in the Appendix S1.

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022937

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Icosapent ethyl greatly reduced first occurrences of cardiovascular events among patients who had elevated triglycerides despite statin therapy and a history of prior percutaneous coronary intervention; number needed to treat$^{4.8\ years}$=12.
- There were also significant reductions in total ischemic events (first and subsequent), cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization.

What Are the Clinical Implications?

- Patients with prior percutaneous coronary intervention and elevated triglycerides despite statin therapy are at extremely high risk for recurrent cardiovascular events.
- Icosapent ethyl could benefit a large proportion of patients with a history of prior percutaneous coronary intervention, and such patients should be screened for eligibility.

Nonstandard Abbreviations and Acronyms

EPA	eicosapentaenoic acid
MACE	major adverse cardiovascular events
NNT	number needed to treat
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
STRENGTH	Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia

Patients who undergo percutaneous coronary intervention (PCI) are at increased risk for subsequent cardiovascular events when compared with patients with other cardiovascular risk factors.[1] 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.[2–4] Yet, many patients still experience recurrent events, especially those with diabetes and elevated triglycerides.[5–8]

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.[9,10] 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.[11–14] 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.[15–18] Treatment with icosapent ethyl also substantially reduced instances of first and subsequent revascularization events.[19–21]

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.[9] 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 covariable 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%, $NNT^{4.8\ years}=19$ (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

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 (%)	138 (7.9)	150 (9.0)	288 (8.5)	0.28
Statin intensity, n (%)				0.22
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)	
Missing	3 (0.2)	9 (0.5)	12 (0.4)	
Body mass index (kg/m^2), 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.

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. Icosapent ethyl also resulted in a significant 34% reduction in first events (HR, 0.66; 95% CI, 0.58–0.76; *P*<0.001), a significant 40% reduction in second events (HR, 0.60; 95% CI,

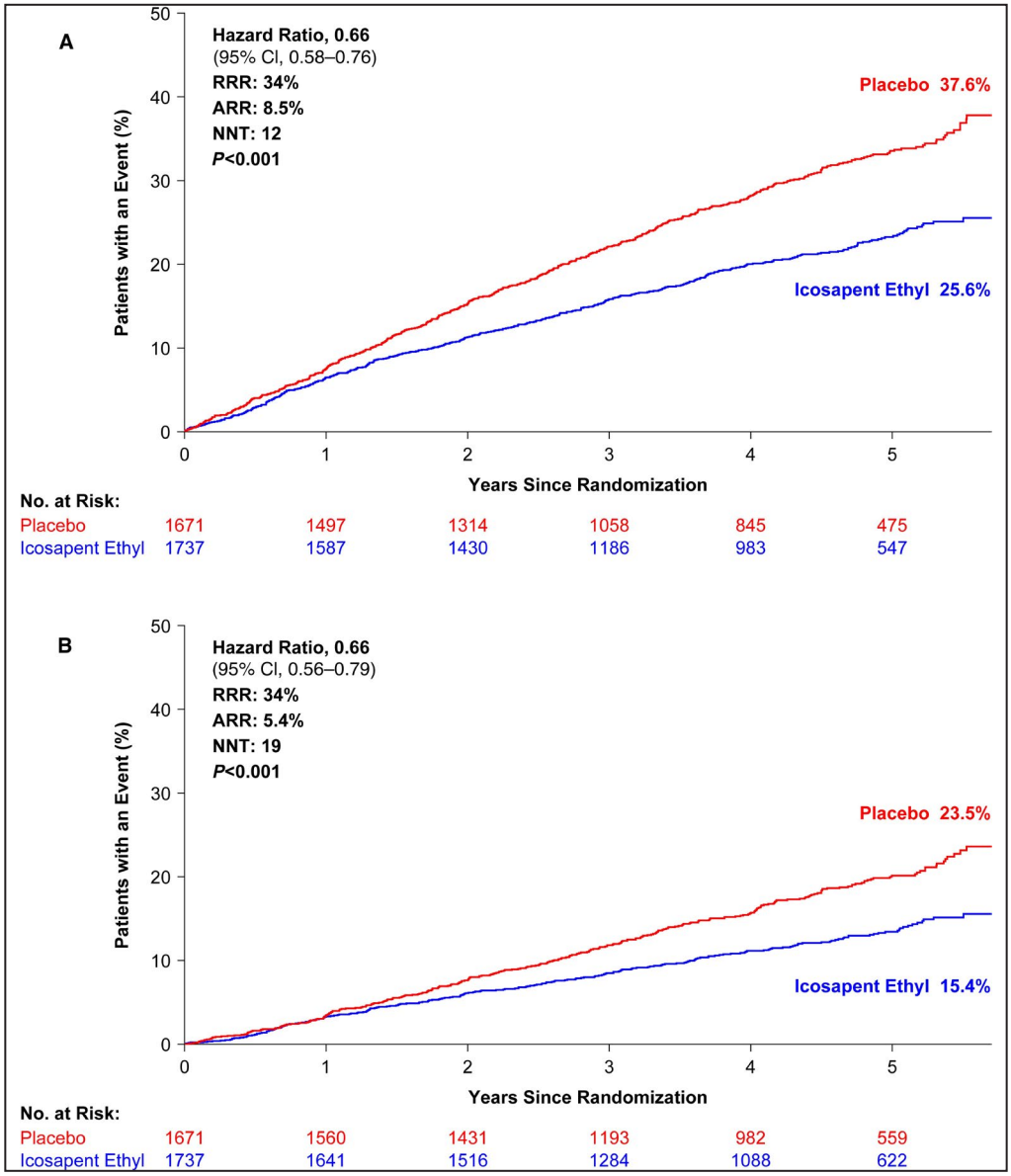


Figure 1. Kaplan-Meier curves showing (A) time to primary composite end point (first cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina requiring hospitalization) and (B) time to key secondary composite end point (first cardiovascular death, myocardial infarction, or stroke) among patients with prior percutaneous coronary intervention (PCI) treated with icosapent ethyl vs placebo.
ARR indicates absolute risk reduction; NNT, number needed to treat; and RRR, relative risk reduction.

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%

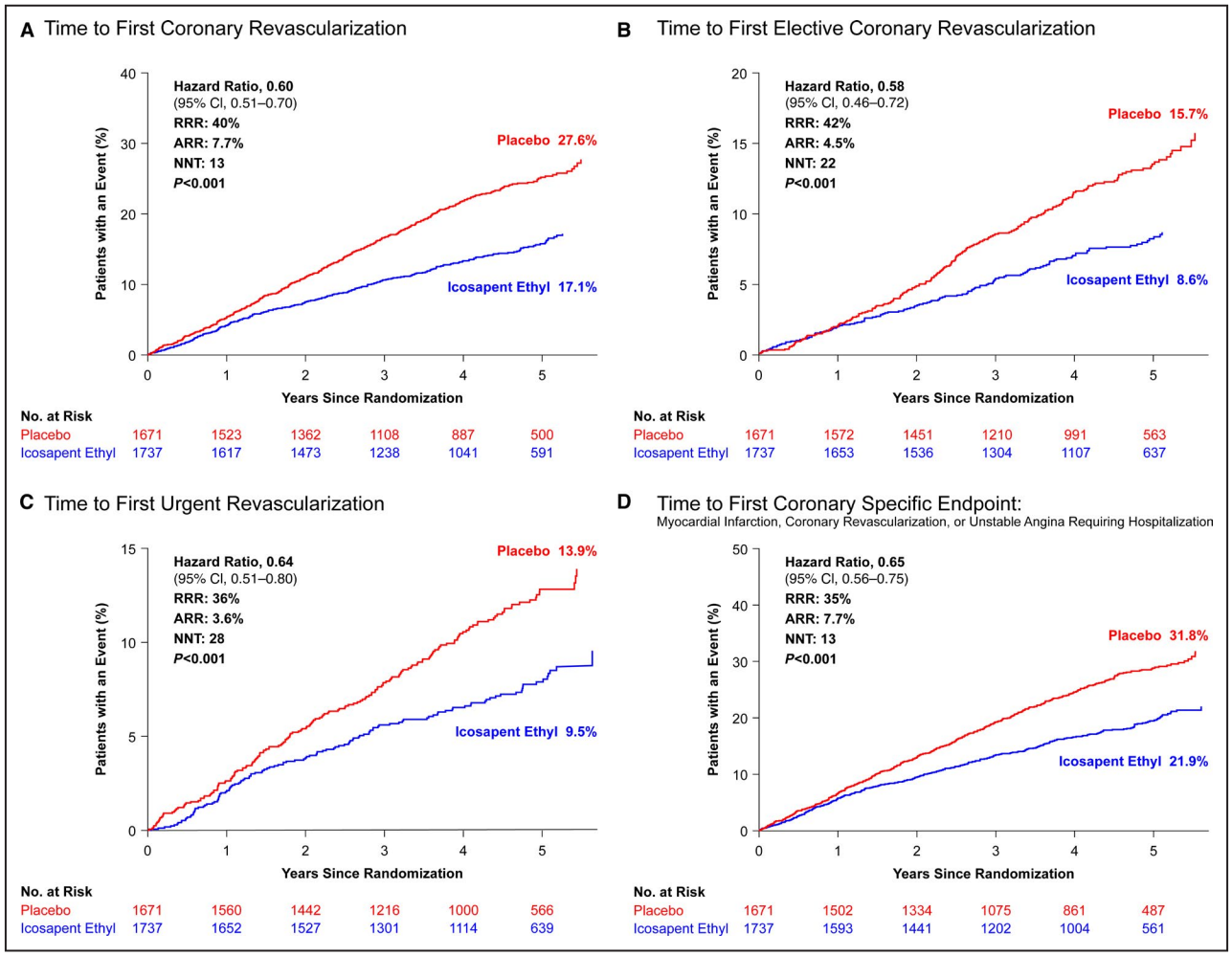


Figure 2. Kaplan-Meier curves showing (A) time to first coronary revascularization, (B) time to first elective coronary revascularization, (C) time to first urgent revascularization, (D) time to first coronary specific end point: myocardial infarction, coronary revascularization, or unstable angina requiring 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.

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$^{4.8\ \text{years}}$ 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]

End point	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	Log-Rank *P* value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Primary Composite End point	362/1737 (20.8)	491/1671 (29.4)	0.66 (0.58–0.76)	<0.001
Key Secondary Composite End point	208/1737 (12.0)	290/1671 (17.4)	0.66 (0.56–0.79)	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	181/1737 (10.4)	248/1671 (14.8)	0.68 (0.56–0.82)	<0.001
Fatal or Nonfatal Myocardial Infarction	141/1737 (8.1)	198/1671 (11.8)	0.66 (0.53–0.82)	<0.001
Urgent or Emergent Revascularization	144/1737 (8.3)	205/1671 (12.3)	0.65 (0.52–0.80)	<0.001
Cardiovascular Death	55/1737 (3.2)	81/1671 (4.8)	0.64 (0.46–0.90)	0.01
Hospitalization for Unstable Angina	75/1737 (4.3)	118/1671 (7.1)	0.59 (0.44–0.79)	<0.001
Fatal or Nonfatal Stroke	39/1737 (2.2)	59/1671 (3.5)	0.62 (0.41–0.92)	0.02
Total Mortality/Nonfatal Myocardial Infarction/Nonfatal Stroke	255/1737 (14.7)	325/1671 (19.4)	0.72 (0.61–0.85)	<0.001
Total Mortality	108/1737 (6.2)	124/1671 (7.4)	0.82 (0.63–1.06)	0.13

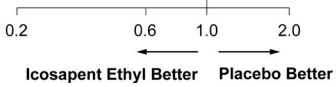


Figure 3. Hierarchical testing of end points: patients with prior percutaneous coronary intervention treated with icosapent ethyl vs placebo.
HR indicates hazard ratio.

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%

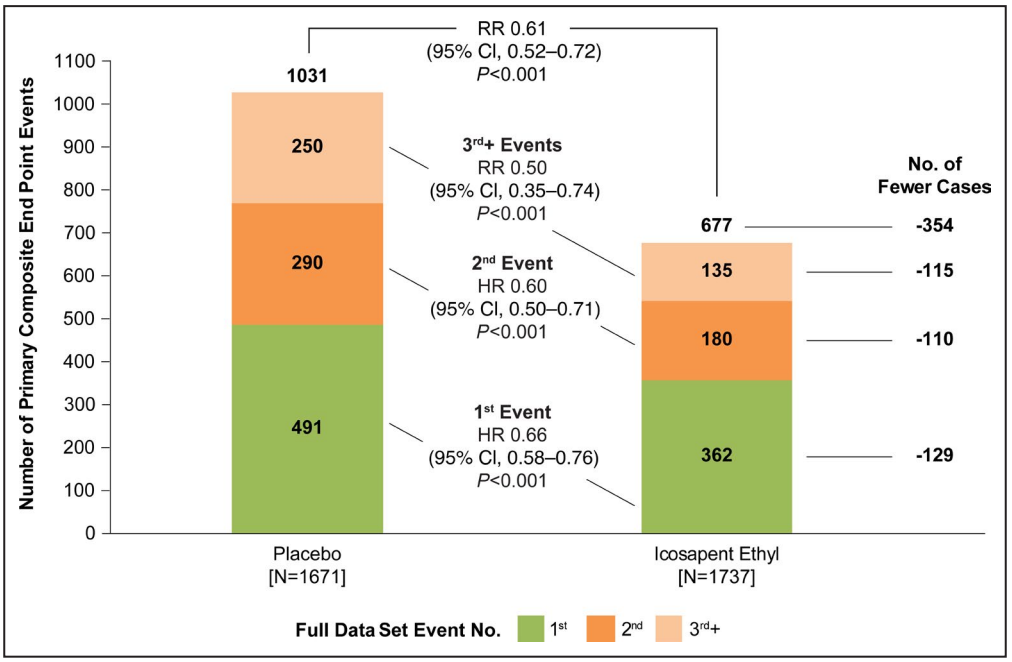


Figure 4. First, second, third or greater, and total events among patients with prior percutaneous coronary intervention treated with icosapent ethyl vs placebo.
HR indicates hazard ratio; and RR, rate ratio.

Table 2. Adverse Events

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.

reduction in MACE at 4 g per day in REDUCE-IT.[11,42] In each of these trials, and even recently among patients with COVID-19, high-dose EPA in the form of icosapent ethyl has been well tolerated.[43,44]

It may be that any benefit from omega-3 fatty acid treatment is most directly tied to EPA alone, whereas other omega-3 fatty acids, such as docosahexaenoic acid, may attenuate the benefit of EPA.[16,45] In REDUCE-IT EPA, the on-treatment levels of EPA correlated directly with reduction in the primary, key secondary, and individual cardiovascular end points.[46] This suggests a dose-dependent class effect specific to EPA rather than a broader impact associated with omega-3 fatty acid supplementation alone. In REDUCE-IT, the average patient taking icosapent ethyl experienced a 386% increase in serum EPA levels. Although some of the patients in STRENGTH receiving an EPA and docosahexaenoic acid mixture experienced a similar degree of elevation of EPA levels, they did not reap the same benefit.[34] Further investigation may inform why this same benefit was not seen in the presence of simultaneous high-dose docosahexaenoic acid supplementation. However, it is known that EPA and docosahexaenoic acid have very different tissue distribution and disparate effects on membrane stabilization and fluidity, formation of cholesterol rafts and crystals, rates of lipid oxidation in lipoproteins and cells, inflammatory modulation, transcriptional regulation, and endothelial function.[47–51]

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.[52,53] 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

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 NNTs$^{4.8\ years}$ 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

Received October 29, 2021; accepted January 27, 2022.

Affiliations

Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA (B.E.P., D.L.B., R.P.G.); Université de Paris, AP-HP (Assistance Publique-Hôpitaux de Paris), Hôpital Bichat, FACT (French Alliance for Cardiovascular Trials), INSERM U-1148, Paris, France (P.G.S.); Department of Medicine, University of Maryland School of Medicine, Baltimore, MD (M.M.); Utah Lipid Center, Salt Lake City, UT (E.A.B.); Department of Medicine, Office of Health Promotion and Disease Prevention, Emory University School of Medicine, Atlanta, GA (T.A.J.); Amarin Pharma, Inc. (Amarin), Bridgewater, NJ (S.B.K., R.A.J., L.J., R.T.D., C.G.); Baim Clinical Research Institute, Boston, MA (C.M.G., D.P.); David Geffen School of Medicine, Lundquist Institute, Torrance, CA (M.J.B.); Montreal Heart Institute, Université de Montréal, Quebec, Canada (J.T.); Division of Cardiac Surgery, St Michael's Hospital, University of Toronto, Ontario, Canada (S.V.); and Department of Medicine, Baylor College of Medicine, Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart and Vascular Center, Houston, TX (C.M.B.).

Acknowledgments

The authors thank K. Keating from Amarin and S. Mercuro from BWH for editorial assistance (limited to formatting and collation of coauthor comments); and the investigators, the study coordinators, and especially the patients who participated in REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial). The academic steering committee along with the sponsor designed REDUCE-IT.

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 Lixia Jiao, an employee of Amarin, and were validated independently by Qi Gao, MS, from Baim Clinical Research Institute with funding from Amarin.

Sources of Funding

The main REDUCE-IT trial and this analysis have been funded by Amarin.

Disclosures

Dr Bhatt serves as the Chair and International Principal Investigator for REDUCE-IT, with research funding from Amarin to Brigham and Women's Hospital. Dr Bhatt also discloses the following relationships—Advisory Board: Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: Boston VA Research Institute, DRS.LINQ (stock options), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the EXCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the National Institutes of Health-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and US national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda. Dr Miller reports receiving consulting fees from Amarin and Akcea. Dr Brinton reports receiving fees as a speaker from Amarin, Amgen, Kowa, Regeneron, and Sanofi-Aventis, and consulting fees from Akcea, Amarin, Amgen, Esperion, Kowa, Medicure, PTS Diagnostics, Regeneron, and Sanofi-Aventis. Dr Jacobson reports receiving consulting fees from Amgen, Esperion, Novartis, Regeneron, and Sanofi. Dr Steg reports receiving research grant funding from Amarin, Bayer, Merck, Sanofi, and Servier; and speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer-Ingelheim, Bristol-Myers Squibb, Idorsia, Lilly, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron, Sanofi, and Servier. Dr Ketchum, R.T. Doyle, Dr Juliano, Dr Jiao, and Dr Granowitz report being employed by and being stock shareholders of Amarin Pharma. Dr Tardif reports receiving grant support from AstraZeneca, Esperion, and Ionis, grant support and consulting fees from DalCor, grant support and fees for serving as co-chairman of an executive committee from Pfizer, grant support and fees for serving on an executive committee from Sanofi, and grant support and consulting fees from Servier and holding a minor equity interest in DalCor and a patent (US 9 909 178 B2) on Dalcetrapib for Therapeutic Use. Dr Gibson reports research grant support and consulting fees from Amarin. Dr Pinto reports consulting fees from Abbott Vascular, Abiomed, Boston Scientific, Medtronic, Teleflex and consulting fees and stock options from NuPulseCV. Dr Giugliano reports that his institution received research grant support from Amgen, Bristol-Myers Squibb, Merck, and The Medicines Company for clinical trials in lipid therapies, and honoraria for continuing medical education programs and/or consulting from Akcea, Amarin, Agmen, Bristol-Myers Squibb, CVS Caremark, Daiichi Sankyo, GlaxoSmithKline, Merck, and Pfizer. Dr Budoff has received grant support and is on the speaker's bureau for Amarin Pharmaceuticals. Dr Verma holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and

reports receiving research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group. He is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. Dr Ballantyne reports receiving consulting fees from Arrowhead, AstraZeneca, Eli Lilly, Matinas BioPharma, Merck, Boehringer Ingelheim, Novo Nordisk, Denka Seiken, and Gilead and grant support (paid to his institution) and consulting fees from Amarin, Amgen, Esperion, Novartis, Regeneron, Sanofi-Synthelabo, and Akcea. Dr Peterson has no disclosures to report.

Supplemental Material

Appendix S1. REDUCE-IT Investigators
Figures S1–S4

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757
2. Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer-generation ultrathin strut drug-eluting stents versus older second-generation thicker strut drug-eluting stents for coronary artery disease. *Circulation*. 2018;138:2216–2226. doi: 10.1161/CIRCULATIONAHA.118.034456
3. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165. doi: 10.1093/eurheartj/ehy394
4. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e563–e595. doi: 10.1161/CIR.0000000000000677
5. Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330–343. doi: 10.1016/j.jacc.2018.04.061
6. Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016. doi: 10.1016/s0140-6736(03)13636-7
7. Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Hypertriglyceridemia in statin-treated US adults: the National Health and Nutrition Examination Survey. *J Clin Lipidol*. 2019;13:100–108. doi: 10.1016/j.jacl.2018.11.008
8. Rosinger A, Carroll MD, Lacher D, Ogden C. Trends in total cholesterol, triglycerides, and low-density lipoprotein in US adults, 1999–2014. *JAMA Cardiol*. 2017;2:339–341. doi: 10.1001/jamacardio.2016.4396
9. Bhatt DL, Steg PG, Brinton EA, Jacobson TA, Miller M, Tardif J-C, Ketchum SB, Doyle RT, Murphy SA, Soni PN, et al. Rationale and design of REDUCE-IT: reduction of cardiovascular events with icosapent ethyl-intervention trial. *Clin Cardiol*. 2017;40:138–148. doi: 10.1002/clc.22692
10. Wang X, Verma S, Mason RP, Bhatt DL. The road to approval: a perspective on the role of icosapent ethyl in cardiovascular risk reduction. *Curr Diab Rep*. 2020;20:65. doi: 10.1007/s11892-020-01343-7
11. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22. doi: 10.1056/NEJMoa1812792
12. Boden WE, Bhatt DL, Toth PP, Ray KK, Chapman MJ, Lüscher TF. Profound reductions in first and total cardiovascular events with icosapent ethyl in the REDUCE-IT trial: why these results usher in a new era in dyslipidaemia therapeutics. *Eur Heart J*. 2020;41:2304–2312. doi: 10.1093/eurheartj/ehz778
13. Bhatt DL, Steg PG, Miller M, Juliano RA, Ballantyne CM. Reply: ischemic event reduction and triglycerides. *J Am Coll Cardiol*. 2019;74:1849–1850. doi: 10.1016/j.jacc.2019.08.007
14. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Jiao L, Tardif JC, Gregson J, Pocock SJ, Ballantyne CM, et al. Reduction in first and total ischemic events with icosapent ethyl across baseline triglyceride tertiles. *J Am Coll Cardiol*. 2019;74:1159–1161. doi: 10.1016/j.jacc.2019.06.043
15. Bhatt DL, Miller M, Brinton EA, Jacobson TA, Steg PG, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, et al. REDUCE-IT USA: results from the 3146 patients randomized in the United States. *Circulation*. 2020;141:367–375. doi: 10.1161/CIRCULATIONAHA.119.044440
16. Bhatt DL. REDUCE-IT: residual cardiovascular risk in statin-treated patients with elevated triglycerides: now we can REDUCE-IT! *Eur Heart J*. 2019;40:1174–1175. doi: 10.1093/eurheartj/ehz179
17. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, et al. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. *J Am Coll Cardiol*. 2019;73:2791–2802. doi: 10.1016/j.jacc.2019.02.032
18. Olshansky B, Bhatt DL, Miller M, Steg PG, Brinton EA, Jacobson TA, Ketchum SB, Doyle Jr RT, Juliano RA, Jiao L, et al. REDUCE-IT INTERIM: accumulation of data across prespecified interim analyses to final results. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:e61–e63. doi: 10.1093/ehjcvp/pvaa118
19. Peterson BE, Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Juliano RA, Jiao L, Doyle RT, et al. Reduction in revascularization with icosapent ethyl: insights from REDUCE-IT revascularization analyses. *Circulation*. 2021;143:33–44. doi: 10.1161/CIRCULATIONAHA.120.050276
20. Bhatt RD, Libby P, Verma S, Mason RP, Bhatt DL. The role of eicosapentaenoic acid in reducing important cardiovascular events, including coronary revascularization. *Prog Cardiovasc Dis*. 2021;S0033–0620(21):00095-5. doi: 10.1016/j.pcad.2021.08.003
21. Kosmopoulos A, Verma S, Meglis G, Bhatt DL, Verma R, Mazer CD, Voisine P. Generalizability of reduction of cardiovascular events with icosapent ethyl-intervention trial in patients with a history of coronary artery bypass graft surgery. *Curr Opin Cardiol*. 2021;36:172–178. doi: 10.1097/HCO.0000000000000800
22. Li QH, Lagakos SW. Use of the Wei-Lin-Weissfeld method for the analysis of a recurring and a terminating event. *Stat Med*. 1997;16:925–940. doi: 10.1002/(sici)1097-0258(19970430)16:8<925:aid-sim545>3.0.co;2-2
23. Lagerqvist B, Husted S, Kontny F, Ståhle E, Swahn E, Wallentin L. Fast Revascularisation during InStability in Coronary artery disease (FRISC-II) Investigators. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet*. 2006;368:998–1004. doi: 10.1016/S0140-6736(06)69416-6
24. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489
25. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. doi: 10.1056/NEJMoa1615664
26. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. doi: 10.1056/NEJMoa1801174
27. Steg PG, Szarek M, Bhatt DL, Bittner VA, Brégeault M-F, Dalby AJ, Diaz R, Edelberg JM, Goodman SG, Hanotin C, et al. Effect of alirocumab on mortality after acute coronary syndromes. *Circulation*. 2019;140:103–112. doi: 10.1161/CIRCULATIONAHA.118.038840
28. Picard F, Bhatt DL, Ducrocq G, Elbez Y, Ferrari R, Ford I, Tardif JC, Tendera M, Fox KM, Steg PG, et al. Generalizability of the REDUCE-IT trial in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2019;73:1362–1364. doi: 10.1016/j.jacc.2019.01.016
29. Lawler PR, Kotrri G, Koh M, Goodman SG, Farkouh ME, Lee DS, Austin PC, Udell JA, Ko DT. Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies. *Eur Heart J*. 2020;41:86–94. doi: 10.1093/eurheartj/ehz767
30. Ferrières J, Bataille V, Puymirat E, Schiele F, Simon T, Danchin N. FAST-MI investigators. Applicability of the REDUCE-IT trial to the FAST-MI registry. Are the results of randomized trials relevant in routine clinical practice? *Clin Cardiol*. 2020;43:1260–1265. doi: 10.1002/clc.23437

31. Picard F, Bhatt DL, Ducrocq G, Ohman EM, Goto S, Eagle KA, Wilson PWF, Smith SC Jr, Elbez Y, Steg PG. Generalizability of the REDUCE-IT trial and cardiovascular outcomes associated with hypertriglyceridemia among patients potentially eligible for icosapent ethyl therapy: an analysis of the REduction of Atherothrombosis for Continued Health (REACH) registry. *Int J Cardiol*. 2021;340:96–104. doi: 10.1016/j.ijcard.2021.08.031
32. Arnold SV, Bhatt DL, Barsness GW, Beatty AL, Deedwania PC, Inzucchi SE, Kosiborod M, Leiter LA, Lipska KJ, Newman JD, et al. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e779–e806. doi: 10.1161/CIR.0000000000000766
33. Virani SS, Morris PB, Agarwala A, Ballantyne CM, Birtcher KK, Kris-Etherton PM, Ladden-Stirling AB, Miller M, Orringer CE, Stone NJ. 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;78:960–993. doi: 10.1016/j.jacc.2021.06.011
34. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH Randomized clinical trial. *JAMA*. 2020;324:2268–2280. doi: 10.1001/jama.2020.22258
35. Kalstad AA, Myhre PL, Laake K, Tveit SH, Schmidt EB, Smith P, Nilsen DWT, Tveit A, Fagerland MW, Solheim S, et al. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized controlled trial. *Circulation*. 2020;143:528–539. doi: 10.1161/CIRCULATIONAHA.120.052209
36. Olshansky B, Bhatt DL, Chung MK. Omega-3 fatty acids effect on major cardiovascular events in patients at high cardiovascular risk. *JAMA*. 2021;325:1332–1333. doi: 10.1001/jama.2021.0824
37. Manson JE, Cook NR, Lee I-M, Christen W, Bassuk SS, Mora S, Gibson H, Albert CM, Gordon D, Copeland T, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380:23–32. doi: 10.1056/NEJMoa1811403
38. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. *JAMA Cardiol*. 2018;3:225–234. doi: 10.1001/jamacardio.2017.5205
39. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379:1540–1550. doi: 10.1056/NEJMoa1804989
40. ORIGIN Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309–318. doi: 10.1056/NEJMoa1203859
41. Khan SU, Lone AN, Khan MS, Virani SS, Blumenthal RS, Nasir K, Miller M, Michos ED, Ballantyne CM, Boden WE, et al. Effect of omega-3 fatty acids on cardiovascular outcomes: a systematic review and meta-analysis. *EClinicalMedicine*. 2021;38: doi: 10.1016/j.eclinm.2021.100997
42. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090–1098. doi: 10.1016/S0140-6736(07)60527-3
43. Kosmopoulos A, Bhatt DL, Meglis G, Verma R, Pan Y, Quan A, Teoh H, Verma M, Jiao L, Wang R, et al. A randomized trial of icosapent ethyl in ambulatory patients with COVID-19. *iScience*. 2021;24:103040. doi:10.1016/j.isci.2021.103040
44. Pareek M, Mason RP, Bhatt DL. Icosapent ethyl: safely reducing cardiovascular risk in adults with elevated triglycerides. *Expert Opin Drug Saf*. 2022;21:31–42. doi: 10.1080/14740338.2021.1954158
45. Granger CB, Nelson AJ, Pagidipati NJ. Risk of total events with icosapent ethyl: can we reduce it? *J Am Coll Cardiol*. 2019;73:2803–2805. doi: 10.1016/j.jacc.2019.03.492
46. REDUCE-IT EPA Trial Shows Association Between Higher EPA Levels, Reduced CV Events - American College of Cardiology. Accessed November 23, 2020. https://www.acc.org/latest-in-cardiology/articles/2020/03/24/16/41/mon-1045-eicosapentaenoic-acid-levels-in-reduce-it-acc-2020.
47. Mason RP, Libby P, Bhatt DL. Emerging mechanisms of cardiovascular protection for the omega-3 fatty acid eicosapentaenoic acid. *Arterioscler Thromb Vasc Biol*. 2020;40:1135–1147. doi: 10.1161/ATVBAHA.119.313286
48. Sherratt SCR, Juliano RA, Copland C, Bhatt DL, Libby P, Mason RP. EPA and DHA containing phospholipids have contrasting effects on membrane structure. *J Lipid Res*. 2021;62: doi: 10.1016/j.jlr.2021.100106
49. Sherratt SCR, Dawoud H, Bhatt DL, Malinski T, Mason RP. Omega-3 and omega-6 fatty acids have distinct effects on endothelial fatty acid content and nitric oxide bioavailability. *Prostaglandins Leukot Essent Fatty Acids*. 2021;173: doi: 10.1016/j.plefa.2021.102337
50. Bhatt DL. Mechanisms of action, efficacy, and safety of icosapent ethyl: from bench to bedside. *Eur Heart J Suppl J Eur Soc Cardiol*. 2020;22:J1–J2. doi: 10.1093/eurheartj/suaa114
51. Bhatt DL, Budoff MJ, Mason RP. A revolution in omega-3 fatty acid research. *J Am Coll Cardiol*. 2020;76:2098–2101. doi: 10.1016/j.jacc.2020.09.005
52. Budoff MJ, Bhatt DL, Kinninger A, Lakshmanan S, Muhlestein JB, Le VT, May HT, Shaikh K, Shekar C, Roy SK, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41:3925–3932. doi: 10.1093/eurheartj/ehaa652
53. Budoff MJ, Muhlestein JB, Bhatt DL, Le Pa VT, May HT, Shaikh K, Shekar C, Kinninger A, Lakshmanan S, Roy SK, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: a prospective, placebo-controlled randomized trial (EVAPORATE): interim results. *Cardiovasc Res*. 2021;117:1070–1077. doi: 10.1093/cvr/cvaa184

Supplemental Material

Appendix S1. REDUCE-IT Trial Investigators

Steering Committee

Deepak L. Bhatt MD, MPH (Chair and Principal Investigator), Christie M. Ballantyne MD, Eliot A. Brinton MD, Terry A. Jacobson MD, Michael Miller MD, Ph. Gabriel Steg MD, Jean-Claude Tardif MD

Global Principal Investigator

Deepak L. Bhatt, MD, MPH, Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs in the Heart and Vascular Center at Brigham and Women's Hospital, and the Principal Investigator and Steering Committee Chair for REDUCE-IT

The Netherlands National Coordinating Investigator

Fabrice MAC Martens, MD PhD, Board, Werkgroep Cardiologische centra Nederland (WCN; Dutch Network for Cardiovascular Research)

The Netherlands National Leader Office

Astrid Schut, MSc, Managing Director, Werkgroep Cardiologische centra Nederland (WCN; Dutch Network for Cardiovascular Research)

Data Monitoring Committee

Brian Olshansky MD (Chair), Mina Chung MD, Al Hallstrom PhD, Lesly Pearce MS (non-voting independent statistician)

Independent Statistical Center Support for Data Monitoring Committee

Cyrus Mehta PhD, Rajat Mukherjee PhD

Clinical Endpoint Committee

C Michael Gibson MD MS (Chair), Anjan K. Chakrabarti MD MPH, Eli V. Gelfand MD, Robert P. Giugliano MD SM, Megan Carroll Leary MD, Duane S. Pinto MD MPH, Yuri B. Pride MD

Amarin Operational and Statistical Team

Substantial Support Across the Study

Steven Ketchum PhD (President of R&D, Chief Scientific Officer, SVP) and team: Ramakrishna Bhavanthula MS, Gertrude Chester, Christina Copland PhD MPH, Katelyn Diffin MBA, Ralph Doyle Jr, Kurt Erz, Alex Giaquinto PhD, Paula Glanton MS, Angela Granger BA, Craig Granowitz MD PhD, Richard H Iroudayassamy BS, Lixia Jiao PhD, Rebecca Juliano PhD, James Jin PhD, Dimitry Klevak MS, Hardik Panchal MS, Robert Wang PhD, Shin-Ru Wang MS

Study Design and Initiation

Gerard Abate MD, Peggy J Berry MBA, Rene Braeckman PhD, Declan Doogan MD, Anne Elson, Amy HauptmannBaker, Isabel Lamela, Catherine Lubeck, Mehar Manku PhD, Sabina Murphy MPH, Monica Sanford, William Stirtan PhD, Paresh Soni MD PhD

Additional Operational and Statistical Support

Arnaud Bastien MD, Demetria Foster, Evangelito Gascon, Judith Johnson, Lasbert Latona MS, Gang Liu, PhD, Sandra Palleja MD, Nelly Sanjuan, Jimmy Shi MS, William Stager PhD, Mukund Venkatakrishnan MS, Ahmed Youssef-Agha PhD, Julie Zhu MD

Independent Statistical Support Center: Cytel, Inc.

Leela Aertker MS, Suresh Ankolekar PhD, Lisa Goldberg MS, Natasa Rajicic ScD, Jianfen Shu PhD, Heng Zou MS

Trial Operations

Bioclinica (data management)

Covance (central research laboratory)

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

United States Investigators and Institutions:

United States Principal Investigators and Previous Principal Investigators

N=number of participants randomized; (site number)

N=3146 (100) Magdy Mikhail, (101) Gamil Dawood, (102) N. Mathew Koshy, (103) Sandip K. Mukherjee, (104) Rafik Abadier, (105) Andrea L. Lawless, (106) William P. McGuinn, (107) Howard Weintraub, (108) Kathryn Rohr, Edmund Claxton, Robert J. Weiss, (110) Terry D. Klein, (111) Mani Nallasivan, (114) Stephen Crowley, (115) Marilyn King, (116) Anthony D. Alfieri, (117) David Fitz-Patrick, (118) Irving Loh, (119) Nolan J. Mayer, (120) Rakesh Prashad, (121) Samuel Lederman, Debra Weinstein, (122) Harold E. Bays, (124) Keith Chu, Alireza Maghsoudi, (125) Paul D. Thompson, (129) Jeff Carstens, (130) Anna Chang, (131) Kenneth R. Cohen, (132) Julius Dean, (135) Howard S. Ellison, (136) Bernard Erickson, (137) Enrique A. Flores, (138) Daniel W. Gottlieb, (139) Paul Grena, (140) John R. Guyton, (141) Peter H. Jones, (142) John M. Joseph, (143) Norman E. Lepor, (144) Sam Lerman, (146) Robert D. Matheney, (147) Theodore R. Pacheco, (149) Michael B. Russo, (151) John Rubino, (152) Edward S. Pereira, Albert A. Seals, (154) Eduardo Viera, (155) Alan D. Steljes, (156) Jason Thompson, (158) Shaival Kapadia, (161) Michael McIvor, (162) Jorge E. Salazar, Jose O. Santiago, Ralph Vicari, (164) Martin R. Berk, (165) William A. Kaye, (166) Marcus McKenzie, (167) David Podlecki, (169) Brian D. Snyder, (171) Stephen Nash, (185) David M. Herrington, (186) Wallace Johnson, (189) Joseph R. Lee, Ronald Blonder, (190) Alpa M. Patel, Ramon Castello, Susan Greco, (191) Dean J. Kereiakes, (192) Venkatesh K. Nadar, (193) Mark Nathan, (194) Ranganatha P. Potu, (196) Robert Sangrigoli, (197) Richard Smalling, (199) Mitchell Davis, (203) Robert Braastad, James McCriskin, Kunal Bodiwala, (204) Joe L. Hargrove, (205) Mark W. Graves, (206) George Emlein, (207) Raegan W. Durant, (208) James W. Clower, (209) Rohit Arora, (211) Narendra Singh, (212) Lisa Warsinger Martin, (213) W Herbert Haught, (214) Marc P. Litt, (215) Michael D. Klein, (216) Peter Hoagland, (217) Michael Goldstein, (220) Marco S. Mazzella, Daniel H. Dunker, (221) Brian H. Kahn, Carlos S. Ince Jr., (222) Frank A. McGrew, (223) Jay Lee, David Pan, (224) Salman A. Khan, Uri Elkayam, (225) Wasim Deeb, (226) Anne C. Goldberg, (227) Christopher S. Brown, (228) Wayne N. Leimbach, (229) Thomas S. Backer, (230) David R. Sutton, (231) Matthew J. Budoff, (233) Joel Gellman, (234) Anu R. George, (235) Alan S. Hoffman, (237) Mark Kates, Kishlay Anand, Robert Bear, (239) Brendan J. Cavanaugh, (240) Ramon G. Reyes, (241) Rodolfo Sotolongo, (243) Kenneth Sabatino, (244) Kevin Gallagher, (246) Ehab Sorial, (248) Chris Geohas, (249) Kathleen E. Magness, (250) Bernard P. Grunstra, Frederik A. Martin, (251) William S. Knapp, Mel E. Lucas, (252) John J. Champlin, (253) Jason Demattia, (255) Patrick H. Peters Jr., (256) Judith Kirstein, (257) William J. Randall, (258) Cezar S. Staniloae, (259) Jennifer G. Robinson, (260) Alexander Adler, (261) Christopher Case, (263) Andrew J. Kaplan, (264) Gregory F. Lakin, Krishan K. Goyle, (265) Michael J. DiGiovanna, (267) Chester L. Fisher, (268) Michael Lillestol, (269) Michael Robinson, (270) Robert G. Perry, (272) Lawrence S. Levinson, (273) Brian G. Everhart, Robert D. Madder, (274) Earl F. Martin, Earl E. Martin, (275) Imtiaz Alam, (277) Jose Mari L. Elacion, (278) Robina Poonawala, (279) Taddese T. Desta, Jerome A. Robinson, (280) Gilbert J. Martinez, (281) Jakkidi S. Reddy, (283) Jeffrey D. Wayne, (284) Samuel Mujica Trenche, Westbrook I. Kaplan, Rubin H. Saavedra, Michael D. DiGregorio, (285) Barry D. Bertolet, (287)

Neil J. Fraser, (289) Terence T. Hart, (290) Ronald J. Graf, (291) David A. Jasper, Michael Dunn, (292) Dan A. Streja, (293) David J. Strobl, (295) Nan Jiang, (296) Vicki Kalen, (297) Richard Mascolo, (298) Mercedes B. Samson, (299) Michael Stephens, (350) Bret M. Bellard, (353) Mario Juarez, (356) Patrick J. McCarthy, (357) John B. Checton, (358) Michael Stillabower, Edward Goldenberg, (359) Amin H. Karim, (360) Naseem Jaffrani, (362) Robert C. Touchon, (363) Erich R. Fruehling, Clayton J. Friesen, Pradipta Chaudhuri, (364) Frank H. Morris, (365) Robert E. Broker, (367) Rajesh J. Patel, (368) Susan Hole, (370) Randall P. Miller, (371) Francisco G. Miranda, (373) Sadia Dar, (374) Shawn N. Gentry, (375) Paul Hermany, (376) Charles B. Treasure, (377) Miguel E. Trevino, (379) Raimundo Acosta, Anthony Japour, (380) Samuel J. Durr, (381) Thomas Wang, (383) Om P. Ganda, (384) Perry Krichmar, (386) James L. Arter, (387) Douglas Jacoby, (388) Michael A. Schwartz, (389) Amer Al-Karadsheh, (393) Nelson E. Gencheff, (394) John A. Pasquini, (396) Richard Dunbar, Sarah Kohnstamm, (398) Hector F. Lozano, (399) Francine K. Welty, (653) Thomas L. Pitts, (654) Brian Zehnder, (655) Salah El Hafi, (656) Mark A. King, (657) Arnold Ghitis, (661) Marwan M. Bahu, (662) Hooman Ranjbaran Jahromi, Ronald P. Caputo, (663) Robert S. Busch, (664) Michael D. Shapiro, (665) Suhail Zavaro, (668) Munib Daudjee, (669) Shahram Jacobs, (670) Vipul B. Shah, (671) Frank Rubalcava, (672) Mohsin T. Alhaddad, Henry Lui, (678) Raj T. Rajan, (679) Fadi E. Saba, (680) Mahendra Pai N Gunapooti, Tshiswaka B. Kayembe, (681) Timothy Jennings, (683) Robert A. Strzinek, (685) Michael H. Shanik, (686) Pradeep K. Singh, (687) Alastair C. Kennedy, (688) Howard Rubenstein, (690) Ramin Manshadi, (691) David M. Herrington

United States Sub Investigators / Study Coordinators and Site Staff
N=number of participants; (site number)

N=3146 (100) / Joanne Ladner, (101) / Lily Kakish, Ashley Kakish, (102) / Amy L. Little, (103) Jaime Gerber / Nancy J. Hinchion, Janet Guarino, (104) Denise Raychok / Susan Budzinski, (105) Kathleen Kelley-Garvin / April Beckord, Jessica Schlinder, (107) Arthur Schwartzbard / Stanley Cobos, (108) Deborah Freeman, David Abisalih, Dervilla McCann / Kylie Guy, Jennifer Chase, Stacey Samuelson, Madeline Cassidy, Marissa Tardif, Jaime Smith, (110) / Brenna Sprout, (111) Nanette Riedeman / Julie Goza, Lori Johnson, (114) Chad Kraske, Sheila Hastings / Chris Dutka, Stephanie Smith, Toni McCabe, (115) / Kathleen Maloney, (116) Paul Alfieri, Vinay Hosemane, Chanhsamone Syravanh, / (117) Cindy Pau, April Limcoiloc, Tabitha Carreira, Taryn S. Kurosawa / Taryn S. Kurosawa, (118) Razmig Krumian, Krista Preston, Ashraf Nashed, Daria Schneidman-Fernandez, Jack Patterson, John Tsakonas / Jennifer Esaki, Lynn Sprafka, Porous Patel, (119) / Brian Mitchell, Erin M. Ross, (120) / Donna Miller, Akash Prashad, (121) / Kristina M. Feyler, Natasha Juarbe, Sandra Herrera, (122) / Sarah M. Keiran, Becky Whitehead, Whitney Asher, Coury Hobbs, (124) / Abbey Elie, Jean Brooks, (125) / Amanda L. Zaleski, Brenda Foxen, (129) / Barb Lapke, (130) / Philippa Wright, (131) Bristol Pavol / Gwen Carangi, (132) / Marla Turner, (135) Howard S. Ellison, Katharine W. Sanders / Rikita S. Delamar, Virginia L. Wilson, Sarah M. Harvel, Alison M. Cartledge, Kaitlyn R. Bailey, (136) Kathleen Mahon, Timothy Schuchard / Jen Humbert, (137) Mark C. Hanson, Michael P. Cecil, James S. Abraham / Lorie Benedict, Claudia Slayton, (138) Curtis S. Burnett / Rachel W. Ono-Lim, (139) / Sharon Budzinski, (140) / Shubi A. Khan, (141) / Sharon Goss, Terry

Techmanski, (142) Farida Valliani / Rimla Joseph, (143) / Edith Flores, Laurn Contreras, Ana Aguillon, (144) / Carrie-Ann Silvia, Maria Martin, (146) Edmund K. Kerut, Leslie W. Levenson, Louis B. Glade, Brian J. Cospolich, Maureen W. Stein, Stephen P. LaGuardia, Thelma L. Sonza, Tracy M. Fife / Melissa Forschler, Jasmyne Watts, (147) / Judy Fritsch, (149) / Emese Futchko, (151) / Sarah Utech, (152) Scott B. Baker, Miguel F. Roura, David R. Sutton, Scott A. Segel, James S. Magee / Cathy Jackson, Rebecca F. Goldfaden, (154) / Liudmila Quas, (155) / Elizabeth C. Ortiz, (156) Michael Simpson, Robert Foster, Christopher Brian, James Trimm, Michael Bailey, Brian Snoddy, Van Reeder, Rachel Wilkinson, Harold Settle, Cynthia Massey, Angela Maiola, Michele Hall / Shelly Hall, Wanda Hall, (158) Mark Xenakis / Janet Barrett, (161) Giovanni Campanile, David Anthou / Susan F. Neill, (162) Steven Karas, Enrique Polanco, Norberto Schechtman / Grace Tischner, Kay Warren, Cynthia St Cyr, Menna Kuczinski, Latrina Alexander, (164) / Maricruz Ibarra, (165) Barry S. Horowitz, Jaime Steinsapir / Jeanette Mangual-Coughlin, Brittany Mooney, (166) / Precilia Vasquez, Kathleen Rodkey, Alexandria Biberstein, Christine Ignacio, (167) Irina Robinson / Marcia Hibberd, (169) Lisa B. Hoffman, Daniel J. Murak, Raghupathy Varavenkataraman / Theresa M. Ohlson Elliott, Linda A. Cunningham, Heather L. Palmerton, Sheri Poole, (171) / Jeannine Moore, Helene Wallace, (185) Ted Chandler, Robert Riley, Farah Dawood, Amir Azeem, Michael Cammarata, Ashleigh Owen, Shivani Aggarwal, Waqas Qureshi, Mohamed Almahmoud, Abdullahi Oseni, Adam Leigh, Erin Barnes, Adam Pflum, Amer Aladin / Karen Blinson, Vickie Wayne, Lynda Doomy, Michele Wall, Valerie Bitterman, (186) /Cindi Young, Rachel Grice, Lioubov Poliakova, (189) Jorge Davalos, David Rosenbaum, Mark Boulware, Heather Mazzola, J. Russell Strader, Russell Linsky, David Schwartz / Elizabeth Graf, Alicia Gneiting, Melissa Palmblad, Ashley Donlin, Emily Ensminger, Hillary Garcia, (190) Dawn Robinson, Carolyn Tran, Jeffrey Jacqmein, Darlene Bartilucci, Michael Koren / Barbara Maluchnik, Melissa Parks, Jennifer Miller, (191) / Cynthia DeFosse, (192) Albert B. Knouse, Jr / Amy Delancey, (193) Stephanie Chin, Thomas Stephens / Mag Sohal, Juana Ingram, (194) Swarooparani Kumar / Heather Foley, Nina Smith, (196) / Vera McKinney, Linda Schwarz, Judith Moore, (197) Hildreth Vernon Anderson, Stefano Sdringola-Maranga, Ali Denktas / Elizabeth Turrentine, Rhonda Patterson, (199) John Marshall / Terri Tolar, Donna Patrick, (203) / Pamela Schwartzkopf, (204) Anthony M. Fletcher, Frances R. Harris / Sherry Clements, Tiffany Brown, (205) William Smith / Stacey J. Baehl, Robin Fluty, (206) Daniel VanHamersveld, Dennis Breen, Nancy Bender / Beverly Stafford, Tamika Washington, (207) / Margaret N. Pike, (208) Mark A. Stich, / (209) Evyan Jawad, Amin Nadeem / Jill Nyland, (211) / Rhonda Hamer, Kendra Calhoun, Charlotte Mall, Samuel Cadogan, Kati Raynes, (212) Richard Katz / Lorraine Marshall, (213) Rashida Abbas, Jay L. Dinerman, John T. Hartley, III / Beth Lamb, Lisa Eskridge, Donna Raymond, (214) / Kristy Clemmer, (215) / Denise M. Fine, Paula Beardsley, (216) / Janet Werner, Bette Mahan, Courtney VanTol, (217) Robert Herman / Christine Raiser-Vignola, Felicia McShan, (220) Stefanie A. Neill, David R. Blick, Michael J. Liston / Denetta K. Nelson, Sandra K. Dorrell, Patricia Wyman, (221) Ambereen Quraishi, Fernando Ferro, Frank Morris / Vicki J. Coombs, Autumn M. Mains, Austin A. Campbell, Jeanne Phelps, Cheryl A. Geary, Ellen G. Sheridan, Jean M. Downing, (222) Arie Swatkowski, Tish Redden / Brian Dragutsky, Susan Thomas, Candace Mitchell, Diana Barker, Elanie Turcotte, Deborah Segerson, Jill Guy, (223) / Karena De La Mora, Jennifer Hong, Dennis Do, Rose Norris, (224) Faisal Khan / Hector Montero, (225) Stacy Kelly-White, Alan Cleland,

Rosalyn Alcalde-Crawford, Melissa Morgan, Brijmohan Sarabu, Megan Minor / Shweta Kamat, Stephanie M. Estes, Nancee Harless, Alicia Disney, (226) / Jodi L. Pagano, (227) Chad M. Alford, Noel W. Bedwell, Warren D. Hardy, Kevin DeAndrade / Jessica G. Elmore, (228) Eric G. Auerbach, Anthony W. Haney / Miriam H. Brooks, (229) Jose Torres, Lois Roper, Terry Backer, Katie Backer / Lois Roper, (230) John G. Evans, James S. Magee, Ricardo A. Silva, Lorraine H. Dajani, Scott A. Segel / Veronica Yousif, Tammy Ross, Rebecca F. Goldfaden, (231) Sion K. Roy, Ronald Oudiz / Sajad Hamal, Ferdinand Flores, (233) / Amor Leahy, Debra Ayer, (234) Swapna George / Chrisi Carine Stewart, Elvira Orellana, (235) Cristina Boccalandro / Mary Rangel, (237) Suzanne Hennings, Carl Vanselow, Teri Victor, Darlene Birdwell, Paul Haas, Anthony Sandoval / Gina Ciavarella, Caroline Saglam, (239) / Amy Bird, (240) Keith Beck, Brian Poliquin, David Dominguez, Brittany Tenorio / Harvonya Perkins, Esther San Roman, (241) Paris Bransford, Christy Lowrance, Marcy Broussard / Mary Ellis, Bobbi Skiles, Jessica Hamilton, Kathryn Hall, Diego Olvera, (243) / Kathleen Maloney, (244) / Julee A. Hartwell, (246) / Nevien Sorial, (248) Kishlay Anand, Mary Rickman, Kevin Berman, Nirav Mehta / Annie Laborin, Caroline Saglam, (249) Rodger Rothenberger / Sarah Beauvilliers, (250) / Kathy Morrell, (251) Michael P. Schachter, Cindy L. Perkins, Elizabeth A. Gordon / Jennifer Lauer, Kim Bichsel, Kelly Oliver, (252) / Leslie J. Mellor, (253) Candice Demattia / Jennifer Schomburg, Yenniffer Moreno, Eduardo Mansur-Garza, (255) Lena Rippstein / Lorie Chacon, Andrea Pena, (256) Michelle King / Susan Richardson, Annette Jessop, Nicole Tucker, Whitney Royer, (257) Gilbert Templeton, Ann Moell, Christine Weller / Melissa J. Botts, Gretel Hollon, (258) / Elsa Homberg-Pinassi, (259) Paula Forest, Aref Bin Abhulhak / Devona Chun-Furlong, Deborah Harrington, Emily Harlynn, Marjorie Schmitt, Constance Shelsky, Patricia Feldick, Mary Cherrico, (260) Courtney Jagle, Nicholas Warnecke, Debra Myer / Deanna J. Ruder, Albina Underwood, (261) Alan Rauba, George Carr / Barbara Oberhaus, Jessica Vanderfeltz, (263) Mary Jo Stucky-Heil, Dale R. Gibson / Vonnie Fuentes, (264) Kimberly L. Talbot, William C. Simon / Katlyn J. Grimes, Christina R. Wheeler, Cassaundra Shultz, Rhonda A. Metcalf, Jennifer L. Hill, Michelle R. Oliver, (265) / Basharat Ahmad, Fouzal Azeem, Abdul Rahim, (267) George H. Freeman, Dawn Bloch / Heather Freeman, (268) Jamie Brown / Sarah Rosbach, Pamela Melander, Nick Taralson, Alex Liu, Katlyn Harms, (269) Mahfouz Michale / Jose Lopez, (270) Maria Revoredo, / (272) / Shari Edevane, Sarah Shawley, (273) Timothy L. Jackson, Michael J. Oliver / Dina DeSalle, (274) Patricia J. Matlock, Ionna M. Beraun / Heather Hendrix, Garrett Bromley, Ashley Niemerski, Gabby Teran, Sonia Guerrero, Murtaza Marvi, Zehra Palanpurwala, Andrea Torres, Patty Gloyd, Michelle Conger, Andrea Pena, (275) Aziz Laurent / Olia Nayor, (277) Catalina S. Villanueva, (278) Munira Khambati / Tabetha J. Mumford, Melanie J. Castillo, (279) Taddese Desta, Jerome Robinson / La Shawn Woods, Anita H. Bahri, Nancy Herrera, (280) Cecilia Casaclang, Jeffrey R. Unger, Geraldine Martinez, Mia K. Moon, Stephen M. Mohaupt / Larry Sandoval, Louisito Valenzuela, Victora Ramirez, Nelly Mata, Veronica Avila, Marisol Patino, Cynthia Montano-Pereira, Omar Barnett, (281) William M. Webster / Lorraine M. Christensen, Leighna Bofman, Melanie Livingston, Stacey Adams, (283) Joseph Hobbs / Stacey Adams, Leesa Koskela, Mia Katz, (284) Samuel Mujica-Trenche / Franklin Cala, Noreen T. Rana, Jennifer Scarlett, Milagros Cala Anaya, (285) / Marsha R. Jones, Kelly D. Hollis, Debbie Roth, Kristin Eads, Tina Watts, (287) / Judy Perkins, (289) / Alice Arnold, (290) Daniel C. Ginsberg / Denise Quinn, (291) / Nicole Cureton, (292) David B.

Fittingoff, Mohammed I. Iqbal, Stephen R. White / Edith Sisneros, Michelle Ducca, David Streja, Danny Campos, (293) / Jennifer L. Boak, (295) / Farzeen Amir, (296) / Felice Anderson, (297) James J. Kmetzo / Mary O. Bongarzone, Dawn Scott, (298) / Mary Grace De Leon, (299) / Cynthia Buda, (350) William Graettinger, Michelle Alex, William Graettinger, / (353) Erika Hess, James Govoni / Melissa Bartel, (356) Travis L. Monchamp / Julie S. Roach, Sara Gibson, (357) / Amy M. Allfrey, Kristen Timpy, Kathy Bott, Karin A. Soucy, (358) / Jean Willis, (359) / Cecilia A. Valerio, Anusha Chunduri, (360) / Rebecca Coker, Nicole Vidrine, (362) Ellen A. Thompson, Mark A. Studeny / Melissa K. Marcum, Tammy S. Monway, (363) Douglas L. Kosmicki / Melissa J. Kelley, Corey M. Godfrey, Susan L. Krenk, Randy R. Holcomb, Deb K. Baehr, Mary K. Trauernicht, (364) David Rowland Lowry, Betty Bondy Herts, Jeanne E Phelps, Jean-Marie Downing, Carol Gamer Dignon, (365) / Elisabeth S. Cockrill, (367) Pravinchandra G. Chapla / Diane Fera, (368) Margaret Chang, Patricia Fredette / Tamie Ashby, Renee Bergin, (370) Zebediah A. Stearns, David B. Ware / Rachael M. Boudreaux, (371) Francisco G. Miranda / Joanna Rodriguez, (373) Robert McKenzie, Amanda Huber, Rebecca Sommers, Heather Rowe, Stacy McLallen, Michale Haynes / Ashley Adamson, Janice Henderson, Lori McClure, (374) / Beverly A. Harris, (375) / Laura Ference, Sue Meissner-Dengler, (376) / Lisa Treasure, Doreen Nicely, (377) Timothy L. Light / Tracey A. Osborn, Kimberly J. Mai, (379) Pablo Vivas, Jose Rios / Dunia Rodriguez, (380) Roger DeRaad, James Walder, Oscar Bailon / Denice Hockett, Debbie Anderson, Kelli McIntosh, Amber Odegard, Andrew Shepherd, Mary Seifert, (381) Laurence Kelley, Rajendra Shetty, Michael Castine, David Brill, Gregory Fisher / Nicole Richmond, Kathleen Gray, Patricia Miller, (383) / Charlene Coneys, (384) / Yarixa Chanza, Monica Sumoza, (386) Victoria M. Caudill, Kelly D. Harris, Courtney A. Manion / Melody J. Lineberger-Moore, Julie J. Wolfe, Barbara J. Rosen, (387) / Patricia DiVito, (388) / Janet L. Moffat, (389) Christina Michaelis, Prashant Koshy / Diana Perea, Ghaith Al Yacoub, Stephanie Sadeghi, (393) Thomas D. LeGalley, Rudolph F. Evonich, William J. Jean, Gary M. Friesen, John M. Pap, David A. Pesola, Mark D. Cowan, Kristofer M. Dosh / Dianna Larson, Adele M. Price, Jodi A. Nease, Jane E. Anderson, Lori A. Piggott, (394) Robert Iwaoka, Kevin Sharkey, Edward McMillan / Laurie Lowder, Latisha Morgan, Kyle Davis, Tara Caldwell, Erica Breglio, Jasmine Summers, Rachel Poulimas, (396) / Muhammad Zahid, Hamid Syed, Maria Escobar, Jacob Levy, Rahma Warsi, (398) Carol Ma, Puxiao Cen / Kimberly A. Cawthon, Delores B. Barnes, Deanna G. Allen, Margaret L. Warrington, Carol R. Stastny, Robin J. Michaels, (399) / Mohamad Saleh, (653) John Sorin / Sunny Rathod, Urakay Juett, (654) Steven Spencer, Aziza Keval, Jill McBride, Shane Young, Catherine Baxter, Carol Rasmussen, Shari L. Coxe / (655) Luis Campos, Shahin Tavackoli / Diana Beckham, Darlynee Sanchez, (656) Karanjit Basrai / Dorian Helms, Erica Clinton, Kasie Smith, (657) Arnold Ghitis, Henry Cusnir / Mary Klaus Clark, (661) Madhavagopal V. Cherukuri / Ameta Scarfaru, (662) Stephen D. Nash / Jeannine Moore, Helene Wallace, (663) Loretta C. Grimm, / (664) / Anna Grace, Kylie McElheran, (665) / Dino Subasic, (668) / Zedrick Buhay, (669) / Janet Litvinoff, Tamika Washington, (670) Deepak Shah / Shannon Cervantes, Freda Usher, (671) Farra Yasser, Theodore Trusevich, Ronnie L. Garcia, Jamison Wyatt, Rahul Bose / Holllilyn Miska, Traci Spivey, (672) Amy B. Wren, Katie E. Vance / Lani L. Holman, Pam Gibbons, (678) / Elaine Eby, Sandra Shepard, (679) Soratree Charoenthongtrakul, (680) / Brett Snodgrass, Mohammed Nazem, Shelly Keteenburg, Prathima Murthy, (681) Frederic Prater / Ashley Rumfelt, (683) / Christina

Eizensmits, (685) / Lisa Iannuzzi, (686) / Pourus R. Patel, (687) / Clellia Bergamino, Elizabeth McFeaters, (688) Botros Rizk, Emiljia Pflaum / Danny Kalish, (690) / Rex Ambatali, Mona Ameli, Delaina Sanguinetti / Mona Ameli, (691) Rakesh Vaidya / Karen Blinson, Lynda Doomy, Vickie Wayne

United States Institutions

N=number of participants randomized; (site number)

N=3146 (100) The Center for Clinical Trials, Inc., Biloxi, MS, (101) The Center for Clinical Trials, Mobile, AL, (102) Velella Research, Sarasota, FL, (103) Yale New Haven Health, North Haven, CT, (104) Nature Coast Clinical Research, Inverness, FL, (105) Biofortis, Inc, Addison, IL, (106) North Ohio Heart Center, Sandusky, OH, (107) New York University School of Medicine, New York, NY, (108) Maine Research Associates, Lewiston, ME, (110) Heartland Research Associates, LLC, Wichita, KS, (111) Merced Heart Associates, Merced, CA, (114) Aurora Denver Cardiology, Aurora, CO, (115) Clearwater Cardiovascular Consultants, Clearwater, FL, (116) Alfieri Cardiology, Wilmington, DE, (117) East-West Medical Research Institute, Honolulu, HI, (118) Westlake Medical Research, Westlake Village, CA, (119) Ventura Cardiology Consultants Medical Group, Inc., Ventura, CA, (120) Ocala Research Institute, Inc, Ocala, FL, (121) Altus Research, Inc, Lake Worth, FL, (122) L-Marc Research Center, Louisville, KY, (124) Carient Heart & Vascular, Manassas, VA, (125) Hartford Hospital, Hartford, CT, (129) Chi Health Research Center, Omaha, NE, (130) John Muir Physician Network Clinical Research Center, Concord, CA, (131) New West Physicians, Golden, CO, (132) St. Vincent's Research - Southside, Jacksonville, FL, (135) Rockdale Medical Research Associates, Conyers, GA, (136) Centracare Heart & Vascular Center, St. Cloud, MN, (137) Georgia Heart Specialists, LLC, Covington, GA, (138) Daniel W. Gottlieb, M.D., P.S., Burien, WA, (139) Cardiology Consultants of Philadelphia, Yardley, PA, (140) Duke University Medical Center, Durham, NC, (141) Baylor College of Medicine, Houston, TX, (142) Trinity Clinical Research Associates, Inc., Carrollton, TX, (143) Westside Medical Associates of Los Angeles, Beverly Hills, CA, (144) Jellinger and Lerman, MD PA Dba The Center for Diabetes and Endocrine Care, Fort Lauderdale, FL, (146) West Jefferson Heart Clinic of Louisiana, Marrero, LA, (147) North Ohio Heart Center, Lorain, OH, (149) Penn State Health Medical Group - Berks Cardiology, Wyomissing, PA, (151) PMG Research of Raleigh, Raleigh, NC, (152) East Coast Institute for Research, LLC, Jacksonville, FL, (154) Gables Research, Miami, FL, (155) Steljes Cardiology, Henderson, NV, (156) Birmingham Heart Clinic, Birmingham, AL, (158) Cardiovascular Associates of Virginia, Bon Secours St. Mary's Hospital, Midlothian, VA, (161) Foundation Research, Key West, FL, (162) Melbourne Internal Medicine Associates, Melbourne, FL, (164) Cardiovascular Research Institute of Dallas, Dallas, TX, (165) Metabolic Research Institute, Inc., West Palm Beach, FL, (166) Legacy Heart Center, Plano, TX, (167) Longmont Medical Research Network, Longmont, CO, (169) Southgate Medical Group, LLP, West Seneca, NY, (171) Syracuse Preventive Cardiology, Syracuse, NY, (185) Wake Forest University Health Sciences, Winston-Salem, NC, (186) University of Maryland School of Medicine, Baltimore, MD, (189) Memorial Hospital, University of Colorado Health, Colorado Springs, CO, (190) Jacksonville Center for Clinical Research Ltd, Jacksonville, FL, (191) The Lindner Research

Center, Cincinnati, OH, (192) Capital Area Research, Newport, PA, (193) University Healthcare Alliances/Cardiology Consultants Medical Group, Walnut Creek, CA, (194) Nature Coast Clinical Research, Crystal River, FL, (196) Doylestown Health Cardiology, Doylestown, PA, (197) University of Texas Health Science Center of Houston, Houston, TX, (199) Northeast Georgia Heart Center, Gainesville, GA, (203) Advocate Medical Group Cardiology/Pulmonology, Normal, IL, (204) Cardiology and Medicine Clinic, P.A., Little Rock, AR, (205) Research Institute of Deaconess Clinic, Evansville, IN, (206) Sacramento Heart and Vascular Research, Sacramento, CA, (207) University of Alabama at Birmingham, Birmingham, AL, (208) Westside Center for Clinical Research, Jacksonville, FL, (209) Captain James A. Lovell Federal Health Care Center, North Chicago, IL, (211) Atlanta Heart Specialists, LLC, Cumming, GA, (212) George Washington University School of Medicine and Health Sciences - Medical Faculty Associates, Washington, DC, (213) Heart Center Research, LLC, Huntsville, AL, (214) Baptist Heart Specialists, Jacksonville, FL, (215) Boston Medical Center, Boston, MA, (216) San Diego Cardiac Center, San Diego, CA, (217) Long Island Gastrointestinal Research Group LLP, Great Neck, NY, (220) Kansas City Cardiology, Lee's Summit, MA, (221) Spectrum Clinical Research at Overlea Personal Physicians, Baltimore, MD, (222) Stern Cardiovascular Foundation, Germantown, TN, (223) Orange County Heart Institute & Research Center, Orange, CA, (224) Metabolic Clinic and Research Center, Los Angeles, CA, (225) Baptist Endocrinology, Jacksonville, FL, (226) Washington University School of Medicine, St. Louis, MO, (227) Mobile Heart Specialists, Mobile, AL, (228) Oklahoma Heart Institute, Tulsa, OK, (229) Atlanta Cardiology Consultants, Roswell, GA, (230) East Coast Institute for Research, LLC, Jacksonville, FL, (231) Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA, (233) Broward Health, Fort Lauderdale, FL, (234) Seven Corners Medical Research Center, Falls Church, VA, (235) Office of Dr. Alan S. Hoffman, Houston, TX, (237) Clinical Research Advantage Inc., Glendale, AZ, (239) New Mexico Heart Institute, PA, Albuquerque, NM, (240) BFHC Research, San Antonio, TX, (241) Southeast Texas Clinical Research Center, Beaumont, TX, (243) Clearwater Cardiovascular Consultants, Safety Harbor, FL, (244) United Medical Associates, Vestal, NY, (246) N & N Research and Management Corp., Fall River, MA, (248) Clinical Research Advantage, Phoenix, AZ, (249) PMA Medical Specialists, LLC, Phoenixville, PA, (250) PMG Research of Bristol, Bristol, TN, (251) Prime Care Research, LLC, Florissant, MS, (252) Med Center Medical Clinic, Carmichael, CA, (253) DM Clinical Research, Houston, TX, (255) Texas Medical Research Associates, LLC, San Antonio, TX, (256) Advanced Clinical Research, West Jordan, UT, (257) Primed Clinical Research, Dayton, OH, (258) NYU Langone Medical Associates Chelsea, New York, NY, (259) University of Iowa, College of Public Health, Preventive Intervention Center, Iowa City, IA, (260) Methodist Medical Center of Illinois, Peoria, IL, (261) Jefferson City Medical Group, P.C., Jefferson City, MS, (263) Cardiovascular Associates of Mesa, Mesa, AZ, (264) Professional Research Network of Kansas, LLC, Wichita, KS, (265) DiGiovanna Institute for Medical Education & Research, North Massapequa, NY, (267) Health Research of Hamilton Roads, Newport News, VA, (268) Lillestol Research LLC, Fargo, ND, (269) Clinica Medica San Miguel, Los Angeles, CA, (270) Pembroke Clinical Trials, Miami Lakes, FL, (272) Clinical Research Associates of Central PA, LLC, Altoona, PA, (273) Heritage Valley Medical Group, Inc., Beaver, PA, (274) Martin Diagnostic Clinic/DM Clinical Research, Tomball, TX, (275)

Austin Center for Clinical Research, Austin, TX, (277) Center for Clinical Trials, LLC, Paramount, CA, (278) Family Practice Center South, Austin, TX, (279) Precision Research Institute, San Diego, CA, (280) Catalina Research Institute, LLC, Montclair, CA, (281) Sierra Clinical Research, Roseville, CA, (283) Clinical Trials Research, Lincoln, CA, (284) Viable Research Management; Alas Science Clinical Research, Las Vegas, NV, (285) Cardiology Associates Research, LLC, Tupelo, MS, (287) Arcturus Healthcare, Plc, Troy Internal Medicine Research Division, Troy, MI, (289) Terence Hart MD, Tuscumbia, AL, (290) Multicare Research Institute, Tacoma, WA, (291) Quality Clinical Research, Omaha, NE, (292) Infosphere Clinical Research, INC., Omaha, NE, (293) Sparrow Clinical Research Institute, Lansing, MI, (295) Dairy Ashford Family Practice, Houston, TX, (296) Eclipse Clinical Research, Tucson, AZ, (297) Doylestown Health Cardiology, Doylestown, PA, (298) American Clinical Trials, Hawaiian Gardens, CA, (299) Fleming Island Center for Clinical Research, Fleming Island, FL, (350) Reno Clinical Trials, Sparks, NV, (353) Panacea Clinical Research, San Antonio, TX, (356) Endocrinology Services Northwest, Bend, OR, (357) Monmouth Cardiology Associates, Eatontown, NJ, (358) Christiana Care Health System, Newark, DE, (359) Angiocardiac Care of Texas, Houston, TX, (360) Alexandria Cardiology Clinic/Cambridge Medical Trials, Alexadria, LA, (362) Marshall Cardiology, Huntington, WV, (363) Nebraska Heart Institute, Hastings, NE, (364) Lutherville Personal Physicians, Lutherville, MD, (365) Hillcrest Clinical Research, LLC, Simpsonville, SC, (367) Lycoming Internal Medicine, Inc., Jersey Shore, PA, (368) Riverside Clinical Research, Edgewater, FL, (370) Horizon Research Group of Opelousas, LLC, Eunice, LA, (371) New Horizon Research Center, Miami, FL, (373) HCCA Clinical Research Solutions, Smryna, TN, (374) HCCA Clinical Research Solutions, Columbia, TN, (375) Grandview Lehigh Valley Health Services, Buxmont Cardiology Division, Sellersville, PA, (376) Cardiovascular Research of Knoxville, Knoxville, TN, (377) Innovative Research of West Florida, Clearwater, FL, (379) Research Physicians Network Alliance, Miami Beach, FL, (380) Black Hills Cardiovascular Research, Rapid City, SD, (381) Adventist Health Care Inc., Takoma Park, MD, (383) Joslin Diabetes Center, Boston, MA, (384) Research Physicians Network Alliance, Pembroke, FL, (386) CaroMont Heart & Vascular, Gastonia, NC, (387) Penn Presbyterian Medical Center, Philadelphia, PA, (388) Dupage Medical Group Cardiology, Winfield, IL, (389) Endocrine IPS, PLLC, Houston, TX, (393) UP Health System Marquette, Marquette, MI, (394) Novant Health Clinical Research, Charlotte, NC, (396) VA Medical Center, Philadelphia, Philadelphia, PA, (398) Florida Hospital, Orlando, FL, (399) Beth Israel Deaconess Medical Center, Boston, MA, (653) Diverse Clinical Research Center of Chicago, LLC, Chicago, IL, (654) Exodus Healthcare Network, Magna, UT, (655) Med-Tech LP, Houston, TX, (656) Trinity Medical Research, Inc, Roseville, CA, (657) Heart & Health Institute Westside, Plantation, FL, (661) Biltmore Cardiology, Phoenix, AZ, (662) SJH Cardiology, Liverpool, NY, (663) Albany Medical Center, Division of Community Endocrine, Albany, NY, (664) Oregon Health and Science University, Portland, OR, (665) Triwest Research Associates, El Cajon, CA, (668) Mercury Clinical Research, Inc, Houston, TX, (669) Shahram Jacobs, MD Inc, Sherman Oaks, CA, (670) Carolina Heart Specialists, LLC, Lancaster, SC, (671) Mission Research Institute, New Braunfels, TX, (672) Apex Cardiology, P.C., Jackson, TN, (678) Nova Clinical Research, Bradenton, FL, (679) Professional Health Care of Pinellas, St. Petersburg, FL, (680) Center for Advanced Medicine and Research, St. Peters, MO, (681) Clinical Research Professionals,

Chesterfield, MO, (683) Protenium Clinical Research, Hurst, TX, (685) Endocrine Associates of Long Island, PC, Smithtown, NY, (686) Synergist Research, LLC, Lancaster, CA, (687) Geodyssey Research, LLC, Vero Beach, FL, (688) The Center for Clinical Trials, Saraland, AL, (690) Manshadi Heart Institute, Inc, Stockton, CA, (691) W.G. (Bill) Hefner Salisbury VA Medical Center/ Kernersville Health Care Center, Kernersville, NC

Non-United States Investigators and Institutions:

Non-United States Principal Investigators and Previous Principal Investigators
Country listing by enrollment; N=number of participants randomized per country; (site number)

The Netherlands N=1678 ***Werkgroep Cardiologische centra Nederland (WCN)*** (701) Martinus AW Broeders, Dorman Henrikus, (702) Fabrice MAC Martens, (703) Adrianus FM Kuijper, (704) Nadea Al-Windy, (705) Michael Magro, Karim Hamraoui, (706) Ismail Aksoy, Guy L.J. Vermeiren, HWO Roeters van Lennep, (707) Gerard Hoedemaker, (708) Johannes Jacobus Remmen, (709) Kjell Bogaard, Dirk van der Heijden, (719) Nicole MJ Knufman, Joost Frederiks, (720) Johannes Willem Louwerenburg, (721) Piet van Rossum, Johannes Milhous, (722) Peter van der Meer, (723) Arno van der Weerdt, Rob Breedveld, (724) Mitran Keijzers, (725) Walter Hermans, (726) Ruud van de Wal, Peter AG Zwart, (727) Marc MJM van der Linden, Gerardus Zwiers, (728) Dirk J. Boswijk, Jan Geert Tans, (729) Jacob van Eck, (731) Maarten V. Hessen, (732) Barnabas JB Hamer, (733) Stieneke Zoet-Nugteren, (734) Lucien Theunissen, (735) EA van Beek, (736) Remco Nijmeijer, (737) Pieter R. Nierop, (738) Gerard Linssen, (739) H.P. Swart, (740) Timo Lenderink, (741) Gerard L. Bartels, (742) Frank den Hartog, (743) Brian J. Berg van den; ***non-WCN*** (710) Wouter van Kempen, (711) Susanne Kentgens, Gloria M. Rojas Lingan, Martinus M. Peeters, (712) Gloria M. Rojas Lingan, Hilligje Keterberg, Melchior Nierman, Annemieke K. den Hollander, (713) Jacqueline Hoogendijk, (714) Gloria M. Rojas Lingan, (715) Christine Voors-Pette, (716) Vicdan Kose, (718) Peter Viergever

Ukraine N=836 (885) Larysa Yena, (886) Viktor Syvolap, (887) Mykola P. Kopytsya, (888) Olga Barna, (889) Svitlana S. Panina, (890) Mykhailo I. Lutai, (891) Oxana V. Shershnyova, (892) Iryna Luzkiv, (893) Larysa S. Bula, (894) Sergii Zotov, Ivan Vyjhovaniuk, (895) Olena Lysunets, (897) Volodymyr I. Koshlia, (898) Nataliya Sydor, (899) Myroslava F. Vayda, (900) Olexiy Ushakov, (937) Mykola Rishko, (938) Viktor P. Shcherbak, (939) Yevgeniya Svyshchenko, (940) Vira Tseluyko, (941) Andriy Yagensky, (942) Viktoriia I. Zolotaikina, (943) Olga Godlevska, (944) Larysa Ivanova, (945) Olena Koval, (946) Olena I. Mitchenko, (947) Galyna Y. Kardash, (948) Yurii S. Rudyk, (949) Mykola Stanislavchuk, (951) Volodymyr Ivanovych Volkov, (952) Olena G. Karlinskaya, (953) Susanna A. Tykhonova, (954) Nikolay Vatutin, Ganna Smirnova, (955) Volodymyr M. Kovalenko, (956) Viktor Lizogub, (957) Denys Sebov, (958) Oleksandr Dyadyk, (959) Svetlana Andrievskaya, (960) Mykola P. Krasko, (961) Alexander N. Parkhomenko, (962) Lidiya Horbach, (963) Iryna G. Kupnovytska, (964) Tetyana Pertseva, (965) Oleksandr Karpenko, (985) Dmytro Reshotko, (992) Svitlana V. Zhurba, (994) Leonid Rudenko, (996) Viktoriia Yu Zharinova, (997) Valerii B. Shatylo, (998) Yuriy I. Karpenko, (999) Mariya A. Orynchak

Russian Federation N=709 (850) Tatiana R. Kameneva, (851) Elena Zherlitsina, (901) Diana N. Alpenidze, (902) Grigoriy P. Arutyunov, (903) Elena Baranova, (904) Boris Bart, (905)

Dmitriy I. Belenkiy, (906) Svetlana A. Boldueva, (908) Elena A. Demchenko, (909) Vera V. Eltishcheva, (910) Alexander M. Gofman, (911) Boris M. Goloshchekin, (912) Ivan Gennadyevich Gordeev, (913) Nikolay Gratsianskiy, (914) Gadel Kamalov, (915) Niyaz R. Khasanov, (916) Irina M. Kholina, (917) Zhanna D. Kobalava, (918) Elena V. Kobeleva, (919) Alexandra O. Konradi, (921) Victor A. Kostenko, (922) Andrey Dmitrievich Kuimov, (923) Polina Y. Ermakova, (924) Sofia K. Malyutina, (925) Alexey V. Panov, (926) Natalia V. Polezhaeva, (927) Olga Reshetko, (928) Nataliya P. Shilkina, (929) Sergey B. Shustov, (930) Elena A. Smolyarchuk, (931) Raisa I. Stryuk, (932) Elena Yurievnar Solovieva, Andrey V. Susekov, (933) Natalia Vezikova, (934) Svetlana N. Ivanova, (935) Alexander A. Petrov, (936) Vladimir O. Konstantinov, (966) Alina S. Agafina, (967) Victor Gurevich, (968) Konstantin N. Zrazhevskiy, (969) Tatiana V. Supryadkina, (970) Nikita B. Perepech, (971) Vadim L. Arkhipovskiy, (972) Dmitry Yu Butko, (973) Irina A. Zobenko, (974) Olga V. Orlikova, (975) Viktor Mordovin, (976) Olga L. Barbarash, (977) Anastasiya Lebedeva, (978) Vladimir Nosov, (979) Oleg V. Averkov, Elena P. Pavlikova, (980) Yuri B. Karpov, (982) Marina Lvovna Giorgadze, (983) Oleg A. Khrustalev, (987) Mikhail Arkhipov, (988) Tatiana A. Raskina, (989) Julia V. Shilko, (990) Yulia Samoilova, (991) Elena D. Kosmacheva, (993) Sergey V. Nedogoda

South Africa N=414 (416) Kathleen Coetzee, (417) Lesley J. Burgess, (418) FC R. Theron, (419) Iftikhar O. Ebrahim, (420) Gerbrand A. Haasbroek, (421) Maria Pretorius, (422) Julien S. Trokis, (423) Dorothea V. Urbach, (424) Mark J. Abelson, (425) Adrian R. Horak, (426) Aysha E. Badat, (427) Ellen M. Makotoko, Hendrik Du Toit Theron, (430) Padaruth Ramlachan, (431) Clive H. Corbett, (432) Ismail H. Mitha, (433) Hendrik FM Nortje, (435) Dirkie J. Jansen van Rensburg, (437) Peter J. Sebastian, (439) FC J. Bester, (440) Louis J. van Zyl, (441) Brian L. Rayner

Poland N=359 (602) Elżbieta Błach, (603) Magda Dąbrowska, (604) Grzegorz Kania, (605) Agata E. Kelm-Warchol, (606) Leszek P. Kinasz, (607) Janusz Korecki, (608) Mariusz Kruk, (609) Ewa Laskowska-Derlaga, (610) Andrzej Madej, (612) Krzysztof Saminski, (613) Katarzyna Wasilewska, (614) Katarzyna Szymkowiak, (616) Małgorzata Wojciechowska, (617) Natalia Piorowska, Andrzej Dyczek

India N=262 (501) Rajpal K. Abhaichand, (502) Ramesh B. Byrapaneni, (503) Basavanagowdappa Hattur, (504) Malipeddi Bhaskara Rao, (505) Nitin Ghaisas, Sujit Shankar Kadam, (506) Jugal B. Gupta, (507) Santhosh M. Jayadev, (509) V A. Kothiwale, (510) Atul Mathur, (511) Vijay Bhaskar, Ravi K. Aluri, Udaya P. Ponangi, (513) Mukesh K. Sarna, (514) Sunil Sathe, (515) Manish K. Sharma, Jilendra Pal Singh Sawhney, (516) Chakrabhavi B. Keshavamurthy, Arun Srinivas, (517) Hemant P. Thacker, (518) A Sharda, (524) Johny Joseph, (525) Sunil Dwivedi, (526) Viswanathan Mohan, (527) Rajendra K. Premchand

Canada N=250 (172) Jacques Bedard, (173) Jean Bergeron, (175) Ronald Collette, (176) David Crowley, (177) Richard Dumas, (178) Sam Henein, (181) Geoff Moran, (182) William F. O'Mahony, (188) Michael O'Mahony, (200) Sammy Chan, (201) Mark H. Sherman, (202) Graham C. Wong, (219) Brian D. Carlson, (271) Milan K. Gupta, David Borts, (361) Sean R. Peterson, Martyn Chilvers, (395) Allan J. Kelly, (397) Jean C. Gregoire, (659) Simon Kouz, (660) Josep Rodés Cabau

Romania N=202 (801) Minodora Andor, (803) Mircea Cinteza, (804) Radu Ciudin, (805) Radu I. Cojan, (806) Roxana O. Darabont, (808) Dan-Lucian Dumitrascu, (809) Carmen Fierbinteanu-Braticievici, (810) Ana Gabriela Fruntelata, (811) Constantin Militaru, (812) Bogdon E. Minescu, Doina Luminita Serban, (813) Florin Mitu, (814) Dorel Nastase Melicovici, (815) Ovidiu Petrascu, (816) Octavian M. Pirvu, (817) Cristian Podoleanu, (818) Calin Pop, (819) Rodica-Valentina V. Stanescu-Cioranu, (820) Adrian Tase, (821) Cristina Voiculet

Australia N=189 (301) Constantine N. Aroney, (302) Anthony M. Dart, (303) Timothy Davis, (304) Karam Kostner, (305) David N. O'Neal, (306) Peter W. Purnell, (307) Bhuwanendu B. Singh, (308) David R. Sullivan, (309) Peter Thompson, (310) Gerald F. Watts, (311) Adam F. Blenkhorn, (312) John V. Amerena, (313) Rafeeq Samie, Randall Hendriks, (314) Joseph Proietto, (316) Nikolai Petrovsky, (317) Alan Whelan, (319) David Colquhoun

New Zealand N=134 (402) Russell S. Scott, (405) Simon C. Young, (406) Tammy Pegg, Samuel JS Wilson, Andrew W. Hamer, (408) Richard A. Luke, (411) Hamish H. Hart, (414) Gerard P. Devlin, (415) Gerard T. Wilkins, (442) Ian F. Ternouth, (444) Samraj Nandra, Bruno S. Loeprich, Nicole McGrath, (445) Stuart L. Tie

Non-United States Sub Investigators / Study Coordinators and Site Staff
Country listing by enrollment; N=number of participants randomized per country; (site number)

The Netherlands N=1678 ***WCN*** (701) Rob J. Bos, Alexandra Wils / Tamara Jacobs, (702) Erik A. Badings / Lillian A. Ebels-Tuinbeek, Mayke L. Scholten, (703) / Esther Bayraktar-Verver, Debby Zweers, Manoek Schiks, Carolien Kalkman, (704) / Tineke Tiemes, Jeanette Mulderij, (705) Walter Hermans / Katarzyna Dabrowska, Wilma Wijnakker, Riny Van de Loo, Jeanne de Graauw, (706) / Giny Reijnierse, (707) / Mirjam van der Zeijst, (708) / Mariska Scholten, (709) / Henk R. Hofmeijer, Antoinette van Dijk-van der Zanden, (719) / Dineke J. van Belle, (720) Jan Van Es / Gera Van Buchem, Wendy Zijda, Harald Verheij, Linnea Oldenhof-Janssen, Martina Bader, Marije Löwik, (721) / Sandra Stuij, (722) Pascal Vantrimpont / Krista van Aken, Karen Hamilton, (723) Arno van der Weerdt / Han Blömer, Gabriela van Laerhoven, (724) Raymond Tukkie, Maarten Janssen, Gerard Verdel, Jon Funke Küpper, Bob van Vlies / Caroline Kalkman, Joke Vooges, Marinella Vermaas, (725) / Jeanne de Graauw, Riny Van de Loo, Rachel Langenberg, (726) Niek Haenen, Frans Smeets, Arko Scheepmaker, Marcel Grosfeld / Ilvy Van Lieshout, Marleen van den Berg, (727) / Marian Wittekoek, (728) / Petra Mol, Antionette Stapel, (729) Margaretha Sierevogel / Nancy van der Ven, Annemiek Berkelmans, (731) Eric Viergever / Hanneke Kramer, Wilma Engelen, Karen V. Houwelingen, (732) Thierry X. Wildbergh, Arend Mosterd / Coriet Hobé-Rap, Marjan van Doorn, Petra Bunschoten, (733) Michel Freericks, Mireille Emans / Petra Den Boer-Penning, Els Verlek, Christine Freericks, (734) Cornelis de Nooijer / Christina Welten, Ingrid Groenenberg, (735) / Claudia van der Horst, Esther Vonk, (736) Geert Tjeerdsma, Gerard M. Jochemsen / Corinne van Daalen, (737) / Ingrid Y. Danse, (738) / Lucy Kuipers, Anke Pieterse, (739) Antonius Oomen, Daan de Waard, Willem Jan Flu, Zusan Kromhout / Petra Van der Bij, (740) Rob Feld / Brigitta Hessels-Linnemeijer, Rob Lardinois, (741) Jan L. Posma / Zwanette R. Aukema-Wouda, Marjolijn Hendriks-van Woerden, (742) / Desiree van Wijk, (743) Driek P. Beelen / Ingrid H. Hendriks; ***non-WCN*** (710) Jan J. Jonker, Stefanie Schipperen, Vicdan Köse, Gloria Rojas /

Linda Goedhart, Hanneke van Meurs, Rachel Langenberg, Jacqueline Rijssemus, (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 Zweekhorst, 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 Petsentiy, 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 Ovdiienko, Volodymyr Randchenko, Maryna Mospan / Tetiana Ovdiienko, (940) Olena Butko, Olga Romanenko, / (941) Mykhailo Pavelko, Iryna Sichkaruk, / (942) Svitlana O. Lazareva, Olena A. Kudryk / 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, Nataliya Kalinkina, Olena Keting, Olena Sklyanna, 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. Skarzhevskyi, Nataliia V. Dovgan, / (962) Marta Horbach, / (964) Olga Cherkasova, Iryna Tyshchenko, / (965) Liudmyla Todoriuk, Svitlana Kizim, 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. Andreeva, (999) Iryna I. Vakalyuk, Olha S. Chovganyuk, Nataliya 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. Luchinkina, (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) Viktoriya 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. Sharkaeva / 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. Barkova, 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. Savelyev / Alexey A. Savelyev, (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 Suvorova, / (988) / Elena S. Shaf, (989) Varvara A. Vershinina, Andrey A. Kozulin, / (990) Oxana A. Oleynik / Irina Y. Martynova, (991) Natalia V. Kizhvatova, / (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 Motala / 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. Mookdam, Andie J. Van der Merwe / Karin Snyman, Gerda Smal, (423) / Yvonne De Jager, (424) Thomas A. Mabin / Annusca 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. Motala / 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,

(605) Wojciech Piesiewicz, (606) Wojciech L. Kinasz / Stefan Samborski, Ilona Bartuś, (607) / Gramzyna Latocha Korecka, Ewa Gulaj, (608) / Jolanta Sopa, (609) Bogusław Derlaga, / (610) Marcin Baisiak, / (612) Allicia Kowalisko, Edyta Stainszewska-Marasazlek, Bartosz Szafran / Malgorzata Swiatkiewicz, (613) Artur Racewicz, Sławomir Grycel, Jerzy Supronik / Sylwia Walendziuk, Magdalena Tarantowicz, Agata Stasiak, (614) Anna Sidorowicz-Białynicka, Marek Dwojak, Ewa Jaźwińska-Tarnawska / Katarzyna Kupczyk, Kamila Martowska, Kamila Kulon, (617) / Katarzyna Gajda

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, Vipin Jain, (507) Srilakshmi Mandayam Adhyapak / Lumin Sheeba, Uma C R, Ramya R, (509) Aditya V. Kulkarni / M S. Ganachari, Ruma Sambrekar, (510) / Mohammad Bilal, Nungshijungla (511) Kalyan Chakravarthy / Ravi Badhavath, Sravan Kumar, Meenakshi Simhadri, Farooque Salamuddin, Venkat Prasad, (513) Vivek Dwivedi, Sudha Sarna / Tilak Arora, Deepak Chawla, (514) Archana Sathe / Chaware Gayatree, (515) / Ajeet Nanda, Ram Avtar, Jyoti Sharma, (516) Vaibhavi P S Sasirekha D, Deepthi Kobbajji / Ramya Ningappa, Shwetha Shree, Chandrashekar K Nandini M R Sowjanya S Devika I G Yashaswini N Sonika G Rathna L Priyanka R (517) / Rupal J. Shrimanker, (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 Racanelli, (176) David Crowley / Sandy Strybosch, (177) Andre Belanger, Jean Palardy, Alicia Schiffrin / 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, Mylène 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 André / Denis Fortin, (659) Hélène Ouimet, Thanh-Thao Tôn-Nu, Martine Dussureault, Marie-Hélène 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 Manitiu / Radu I. Cojan, (806) Octavian M. Pirvu, (808) Aura Sinpetrean, Lucian Pop, Delia Lupu, / (809) Radu Usvat, Ana Petrisor, / (810) Nicoleta Dumitru, / (811) Camelia Moruju, / (812) / Adelina Gheorghita, (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) Christinia 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 Stathopoulos, Cilla Haywood, (316) 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. McAnnalley, (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 De 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, Heerenveen, (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 Institutio, D.F.Chebotarev Institute of Gerontology of NAMS, Kiev, (886) Department of Internal Diseases-1 of Zaporizhzhya State Medical University, Zaporizhzhya City Clinical Hospital of Emergency Care, Zaporizhzhya, (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, Zaporizhzhia, (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, Zaporizhzhia 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: Zaporyzhzhya 9th City Multidisciplinary Clinical Hospital, Cardiology Department, Zaporizhzhia, (898) Volyn Regional Clinical Hospital, Department of Cardiosurgery, Lutsk, (899) Zakarpatskyi Oblasnyi Klinichnyi Kardiolohichnyi 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 Nacional Ams of Ukraine, Kiev, (956) Kiev Municipal Clinical Hospital #12, Department of Cardiology; O. O. Bogomolets National Medical University, Kiev, (957) Saint Catherine Odessa, Treatmnent and Diagnostic Center LLC, Odesa, (958) Central City Clinical Hospital #1, Donetsk, (959) Communal Institution, Odesa Regional Cardiological Dispensary, Odesa, (960) Zaporizhzhia Regional Clinical Hospital, Zaporizhzhea, (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 Oleksandrivska 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

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 Cliical Hospital, Saint Petersburg, (936) Science and Research Institute of Experimental Medicine, Saint Petersburg, (966) Saint Petersburg State Budget Healthcare Institution, City Hospital #40 of Kurortniy 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 (416) Paarl Research Centre, Paarl, (417) TREAD Research cc, Cape Town, (418) Durbanville Medi-Clinic, Durbanville, (419) Unitas Hospital, Pretoria, (420) Somerset West Clinical Trial Unit, Somerset West, (421) Tiervlei Trial Centre, Bellville, (422) Langeberg Clinical Trials, Cape Town, (423) Synexus Helderberg, Somerset West, (424) Helderberg Research Institute, Somerset West, (425) Vincent Pallotti Hospital, Cape Town, (426) Wits Clinical Research Bara, Soweto, (427) Cardiology Research, Bloemfontein, (430) Newkwa Medical Centre, Durban, (431) Corbod Research Pty Ltd, Panorma, (432) Worthwhile Clinical Trials, Johannesburg, (433) Dr HFM Nortje Clinical Trials, Cape Town, (435) Drs' Joynt Venter and Associates, Witbank, (437) Dr P J Sebastian, Durban, (439) Boanerges Clinical Research, Bloemenstein, Free State, (440) Clinical Projects Research Centre, Worcester, (441) University of Cape Town, Cape Town

Poland N=359 (602) Synexus Polska Sp. Z O.o., Katowice, (603) Synexus Sp. Z O.o., Warsaw, (604) Centrum Medyczne Ogrodowa, Skierniewice, (605) Centrum Medyczne Nzoz As-Medica

Sp.Z O.o., Zgierz, (606) ZSGL LeK, Mikołów, (607) Podlaski Osrodek Kardiologiczny, Bialystok, (608) Institute of Cardiology, Warsaw, (609) Specjalistyczny Gabinet Lekarski Internistyczno-Kardiologiczny Ewa Laskowska-Derlaga, Tarnów, (610) NZOZ SALVIA, Katowice, (612) Centrum Kardiologiczne Pro Corde Sp. Z O.o., Wroclaw, (613) Osteo-Medic Sc, Bialystok, (614) Synexus Sp. Z O.o., Wrocław, (616) Przychodnia Specjalistyczna PROSEN; Department of Experimental and Clinical Physiology, Laboratory of Center for Preclinical Research, Medical University of Warsaw, Warsaw, (617) Centrum Nowoczesnych Terapii, Dobry Lekarz, Krakow

India N=262 (501) G.Kuppuswamy Naidu Memorial Hospital, Coimbatore, Tamilnadu, (502) Medwin Hospitals, Hyderabad, Telangana, (503) JSS Medical College Hospital, Mysuru, Karnataka, (504) Mycure Hospital, Visakhapatnam, Andhra Pradesh, (505) Shatabdi Super Specialty Hospital, Suyojit City Center, Opp. Mahamarg Bus Stand, Nashik, Maharashtra, (506) SR Kalla Memorial Gastro and General Hospital, Jaipur, (507) St. John's Medical College Hospital, Koramangla, Karnataka, (509) KLE Dr. Prabhakar Kore Hospital, Nehru Nagar, (510) Fortis Escorts Heart Institute, New Delhi, (511) Gleneagle Global Hospitals, Hyderabad, Telangana, (513) Monilek Hospital and Research Center, Jaipur, (514) Cardiac Care & Counselling Center, Pune, Maharashtra, (515) Dharma Vira Heart Cente, Sir Ganga Ram Hospital, New Delhi, (516) Vikram Hospital Pvt. Ltd, Mysore, Karnataka, (517) Bhatia Hospital, Mumbai, Maharastra, (518) Endocrinology Diabetes Centre, Bangalore, Karnataka, (524) Caritas Hospital, Kottayam, Kerala, (525) Vikram Hospital, Bangalore, Karnataka, (526) Madras Diabetes Research Foundation, Chennai, Tamilnadu, (527) Krishna Institute of Medical Sciences, Secunderabad, Telanagana

Canada N=250 (172) Recherche Clinique London, Sherbrooke, Québec, (173) Clinique Des Maladies Lipidiques De Québec, Québec, (175) Ronald Collette, MD, Burnaby, (176) DCTM Clinical Trials Group, Strathroy, Ontario, (177) Centre de recherche clinique de Laval, Laval, Québec, (178) SKDS Research Inc., Newmarket, Ontario, (181) Moran Medical Centre, Collingwood, Ontario, (182) Corunna Clinical Research Centre, Corunna, Ontario, (188) London Road Diagnostic Clinic, Sarnia, Ontario, (200) Heathy Heart Program, Vancouver, (201) McGill University Health Centre, Royal Victoria Hospital, Montreal, Québec, (202) Vancouver General Hospital, Vancouver, British Columbia, (219) North Road Clinical Research, Coquitlam, British Columbia, (271) Brampton Research Associates, Brampton, Ontario, (361) Sarnia Institute of Clinical Research, Sarnia, Ontario, (395) Alta Clinical Research Inc, Edmonton, Alberta, (397) Montreal Heart Institute, Montreal, Québec, (659) Centre de Sante et de Services Sociaux de Lanaudière, St-Charles-Borromée, Québec, (660) Institut Universitaire De Cardiologie Et De Pneumologie Du Québec, Université Laval, Québec

Romania N=202 (801) Medical Center Medcalis SRL, Timisoara, (803) Universitary Emergency Hospital, Cardiology Ward I, Bucuresti, (804) Centrul Medical International Bucuresti Dacia, Bucuresti, (805) Emergency County Hospital, Sibiu, (806) Mediclass Sananova SRL, Bucharest, (808) Clinic County Emergency Hospital Cluj-Napoca, Cluj-Napoca, (809) Universitary Emergency Hospital Bucharest, Bucharest, (810) Ilro Medical Clinic, Bucharest, (811) CardioMed SRL, Craiova, (812) Spitalul Judetean De Urgenta Braila, Braila, (813)

University of Medicine and Pharmacy Grigore T. Popa, Rehabilitation Hospital, Department of Cardiovascular Rehabilitation, Lasi, (814) Spitalul Clinic Judetean De Urgenta, Tirgu Mures, (815) Spitalul Clinic Judetean De Urgenta, Sibiu, (816) Centrul Med Plus SRL Bucuresti, Bucuresti, (817) Centrul Medical Galenus, Tirgu Mures, (818) CMI Cardiologie, Baia Mare, (819) SC Clinica Angiomed, Bucharest, (820) Spitalul De Urgenta Arges, Pitesti, (821) CMI Cardiologie, Constanta

Australia N=189 (301) Holy Spirit Northside Hospital, Brisbane, QLD, (302) The Alfred Hospital Heart Centre, Melbourne, VIC, (303) Fremantle Hospital, Fremantle, WA, (304) Dr Heart Pty Ltd, Woolloongabba, QLD, (305) St. Vincents Hospital (Melb) Dept. of Medicine, Fitzroy, VIC, (306) Joondalup Cardiovascular Trials Foundation, Joondalup, WA, (307) Launceston General Hospital, Launceston, TAS, (308) Royal Prince Alfred Hospital, Sydney, NSW, (309) Sir Charles Gairdner Hospital, Nedlands, (310) Royal Perth Hospital, School of Medicine and Pharmacology, Medical Research Foundation, Perth, WA, (311) Lismore Base Hospital Cardiac Catheter Lab, Northern Rivers Cardiovascular Clinic, Lismore, NSW, (312) Barwon Health University Hospital Geelong, Geelong, VIC, (313) Fiona Stanley Hospital, Murdoch, WA, (314) Austin Health, Heidelberg Heights, VIC, (316) Flinders Medical Centre and Flinders University, Bedford Park, SA, (317) Cardiovascular Trials WA (South), Bateman, WA, (319) Core Research Group Pty Ltd, Brisbane, QLD

New Zealand N=134 (402) Lipid and Diabetes Research, Christchurch, (405) Waitemata District Health Board, Diabetes Service, Auckland, (406) Cardiology Department, Nelson Hospital, Nelson, (408) Hawke's Bay District Health Board, Hastings, (411) Waitemata District Health Board, Auckland, (414) Cardiology Clinical Trials Unit, Waikato District Health Board, Hamilton, (415) Southern District Health Board, Dunedin Hospital, Dunedin, (442) Taranaki Base Hospital, New Plymouth, (444) Northland District Health Board, Whangarei, (445) Bay of Plenty Clinical Trials Unit, Tauranga

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)	146/618 (23.6)	185/612 (30.2)	0.74 (0.60, 0.92)	0.007	
Warfarin OR Rivaroxaban OR Apixaban	13/31 (41.9)	9/28 (32.1)	1.02 (0.43, 2.42)	0.97	
Both Anticoagulants + Any Anti-Platelet Above	16/49 (32.7)	23/52 (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)	0.89	
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	15/49 (30.6)	7/52 (13.5)	2.35 (0.95, 5.78)	0.06	
Serious Bleeding	56/1737 (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)	20/618 (3.2)	15/612 (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, 9.76)	0.17	

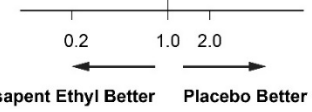


Figure S2. Forest Plot of Efficacy End Points in Hierarchical Testing Order by Sex Among Patients with Prior PCI.

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					0.88
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					0.81
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					0.69
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					0.81
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 Revascularization	144/1737 (8.3)	205/1671 (12.3)	0.65 (0.52, 0.80)	<0.0001	
Gender					1.00
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					0.91
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					0.66
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					0.46
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	255/1737 (14.7)	325/1671 (19.4)	0.72 (0.61, 0.85)	0.0001	
Gender					0.78
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					0.70
Male	78/1387 (5.6)	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	

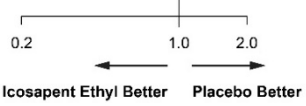
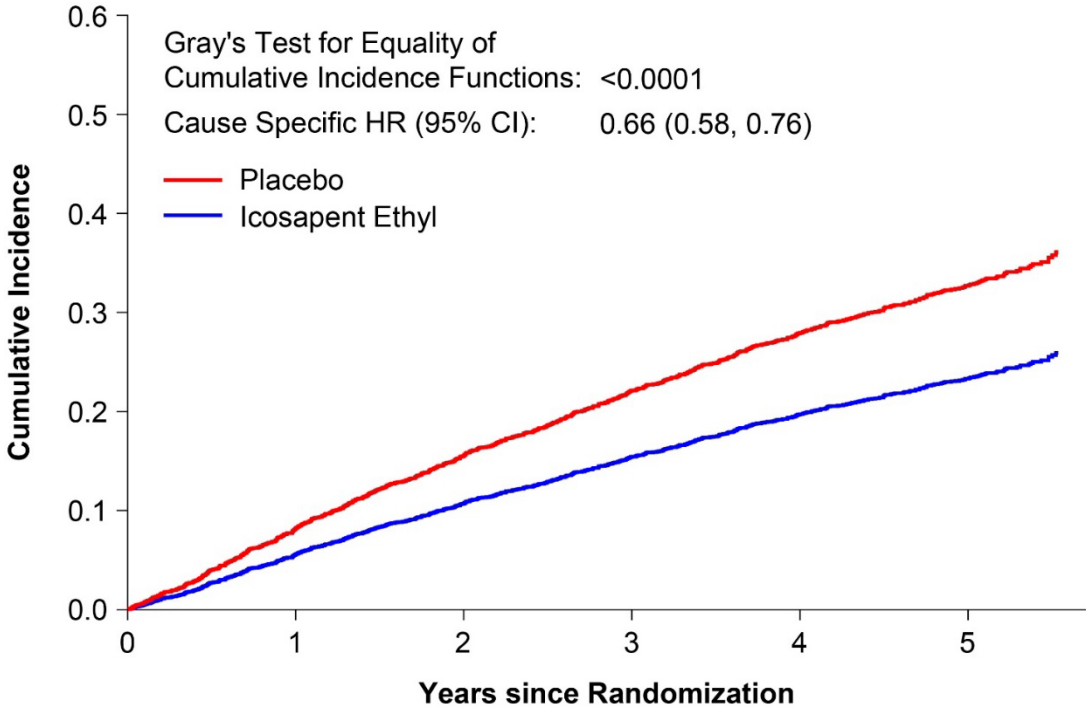


Figure S3. Cumulative Incidence Plots of A. Primary Composite End Point and B. Key Secondary Composite End Point with Non-CV Death as Competing Risk Among Patients with Prior PCI.

A.



B.

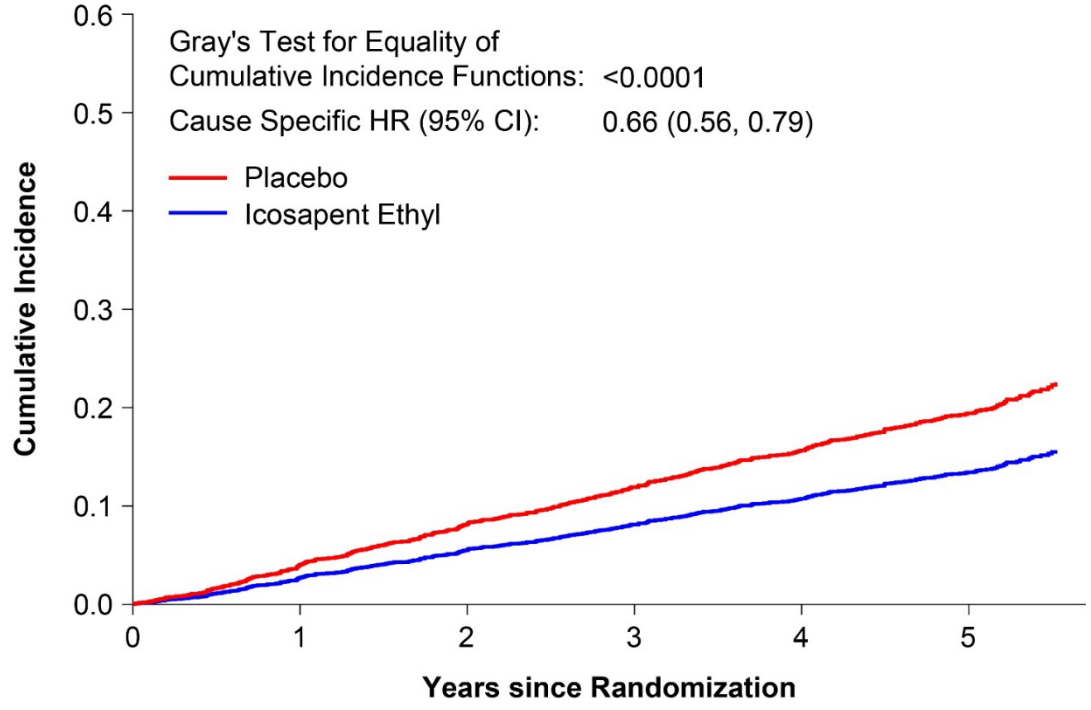


Figure S4. Forest Plot of Primary and Key Secondary Composite End Points for Patients With or Without Prior PCI

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