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ORIGINAL RESEARCH

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

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

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

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

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For Sources of Funding and Disclosures, see page 9.

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## 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<sup>4,8</sup> 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

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

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

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

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.<sup>9</sup> 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.<sup>17</sup> 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.<sup>22</sup> 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  $\leq 1$  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  $\leq 1$  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%,  $\text{NNT}^{4.8 \text{ years}} = 19$  (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) <sup>†</sup>	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 <sup>2</sup> ), 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.

<sup>†</sup>Age (y) is at randomization.

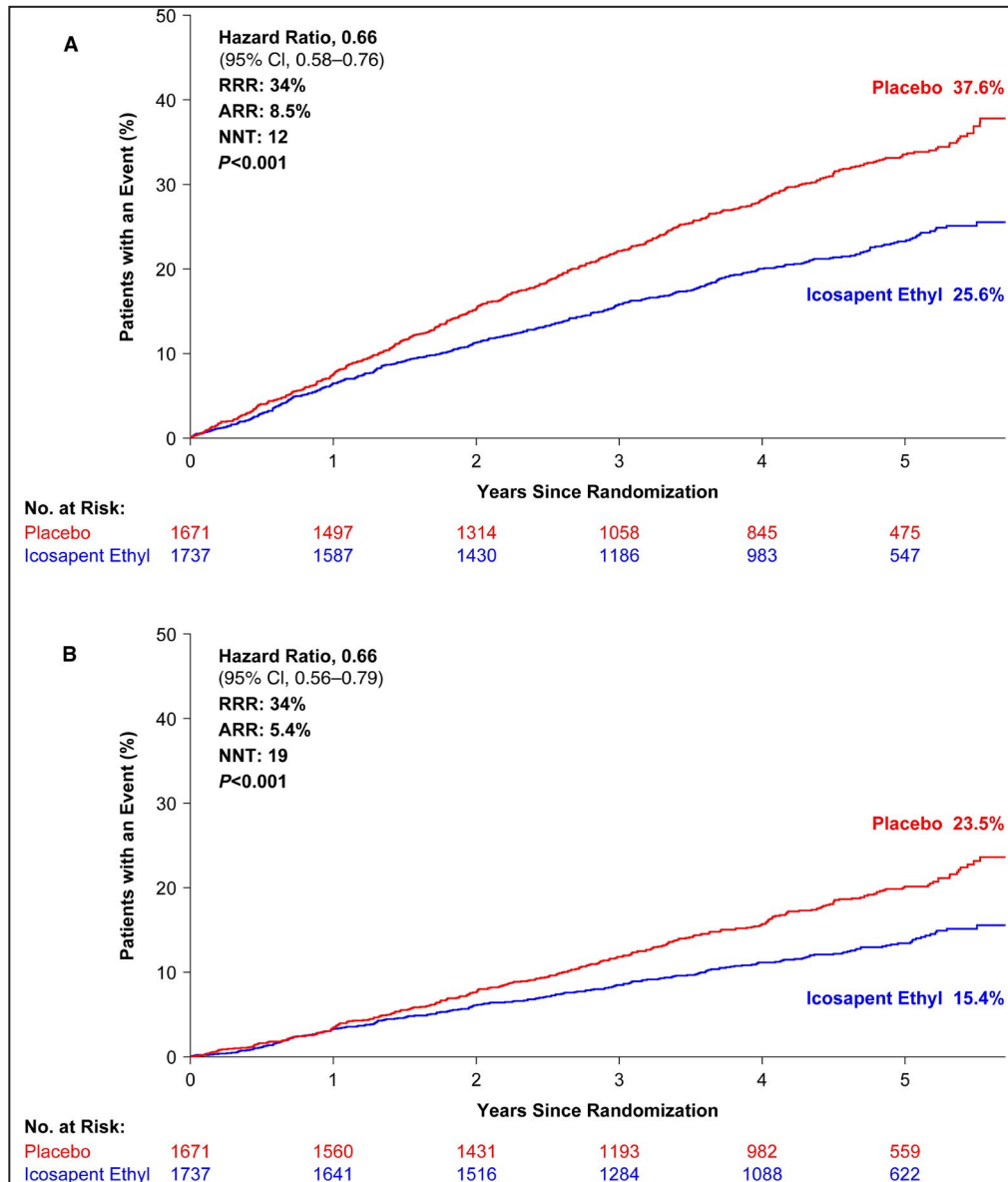
requiring hospitalization (HR, 0.65; 95% CI, 0.56–0.75; *P*<0.001) (Figure 2). There was no significant difference in the safety or efficacy of icosapent ethyl versus placebo among patients taking single- or dual-antiplatelet therapy or a combined antithrombotic regimen (Figure S1). In addition, there 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).

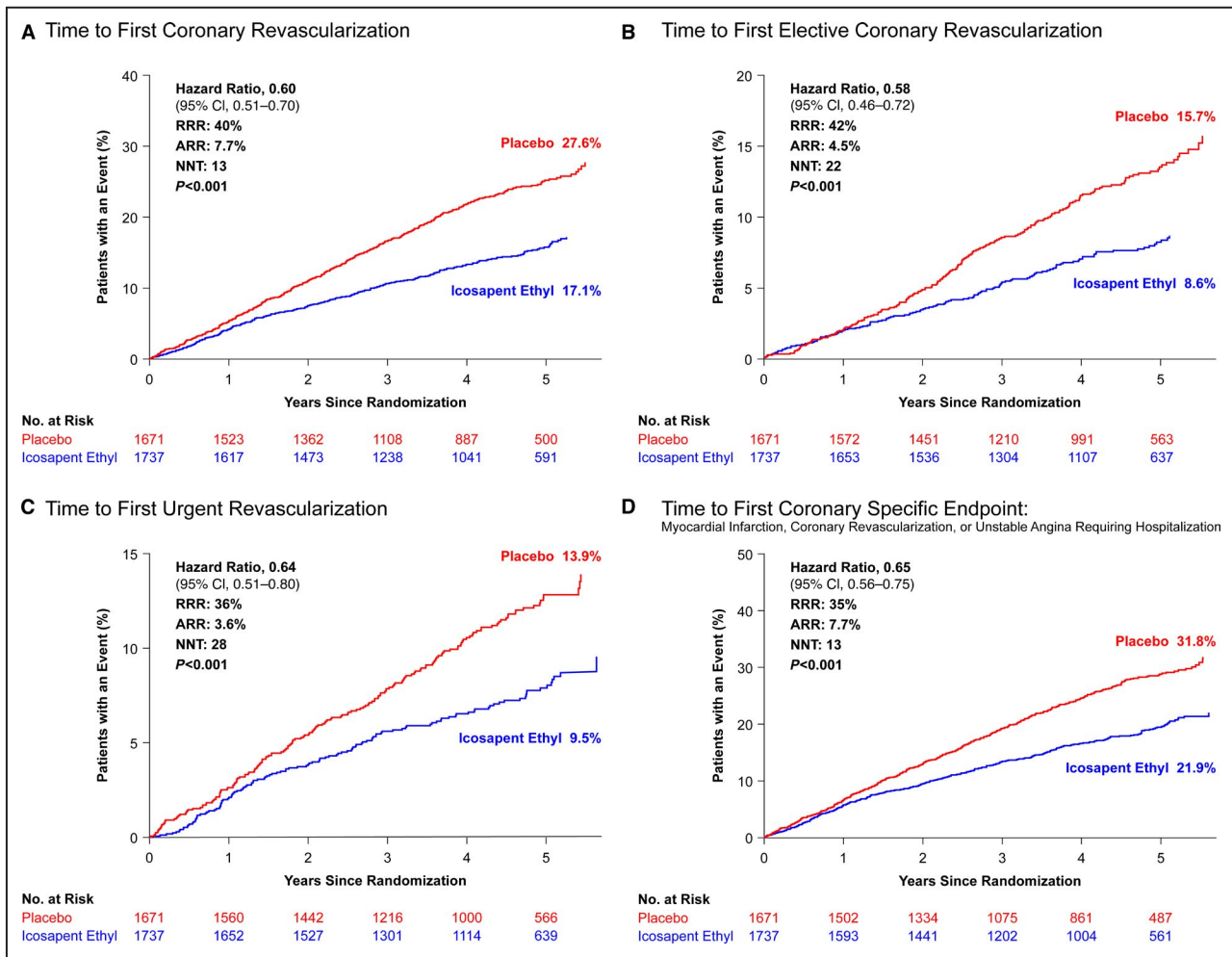
### Safety and Adverse Events

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<sup>4,8 years</sup> 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,<sup>23</sup> 50 at 7 years in IMPROVE-IT (The Improved Reduction of Outcomes: Vytarin Efficacy International Trial),<sup>24</sup> 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).<sup>25–27</sup>

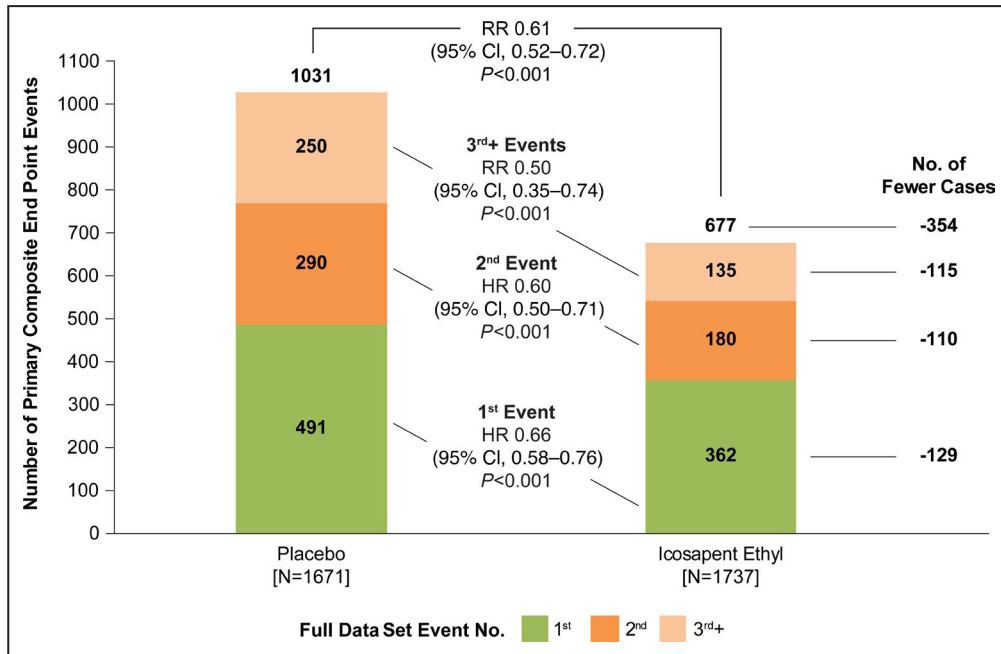
The patient population in this subgroup analysis of REDUCE-IT reflects a large proportion of patients who undergo PCI in US, Canadian, and European registries.<sup>28–31</sup> Representative qualities include moderately elevated baseline triglycerides, with 50% of patients being <218 mg/dL and 96.3% on a moderate- or high-intensity statin. The distribution of age, sex, and typical comorbidities also highly reflects contemporary populations undergoing PCI.<sup>1</sup> 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.<sup>2</sup> Contemporary guidelines and consensus statements consistently recommend the use of icosapent ethyl in this patient population.<sup>32,33</sup>

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.<sup>34–36</sup> As well, older clinical trials have shown mixed results with respect to prevention of MACE events.<sup>37–41</sup> 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.<sup>11,42</sup> 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.<sup>43,44</sup>

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.<sup>16,45</sup> In REDUCE-IT EPA, the on-treatment levels of EPA correlated directly with reduction in the primary, key secondary, and individual cardiovascular end points.<sup>46</sup> 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.<sup>34</sup> 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.<sup>47-51</sup>

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.<sup>52,53</sup> 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.<sup>43</sup>

## 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<sup>4,8 years</sup> of 12 and 19, respectively, and consistent benefit across the hierarchical end points. These data highlight the substantial positive impact of icosapent ethyl on patients in the REDUCE-IT population, including patients with a history of prior PCI.

## ARTICLE INFORMATION

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

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### 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

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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. 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## Supplemental Material

Appendix S1. REDUCE-IT Investigators  
Figures S1–S4

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# 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**

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### **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

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### **Substantial Support Across the Study**

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**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 Weerd / 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 Groenberg, (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 Rijssenmus, (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 Hanewinkel / 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 Zadorozhnyi, Kira Kompaniits, / (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. Skarzhevskiy, 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. Bodenstern, 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 Świąło, 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 Tessa 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) Polyclinic 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 Kardiologichnyi Dyspanser, m. Uzhhorod, (900) Infarction Dprt of City Clinic Hosp. #6, Simferopol, AR Crimea, (937) Zakarpattya Regional Clinical Cardiology Dispensary, Dept. of General Cardiology, Uzhhorod National University, Chair of Hospital Therapy, Uzhhorod, (938) City Clinical Hospital #1, Vinnitsa, (939) State Institution, National Scientific Center, NAMS Institute of Cardiology M.D. Strazhesko, Department of Essential Hypertension, Kiev, (940) Kharkiv Medical Academy of Postgraduate Education, City Clinical Hospital #8, Kharkiv, (941) Lutsk City Clinical Hospital, Lutsk, (942) Kharkiv City Clinical Hospital #27, Kharkiv, (943) Kharkiv Medical Academy of Postgraduate Education, Kharkiv, (944) Lugansk Regional Cardiological Dispensary, Luhansk, (945) Dnipropetrovsk Medical Academy, Dnipropetrovsk Joint Emergency Hospital, Dnipro, (946) State Institution, National Scientific Center, The M.D. Strazhesko Institute of Cardiology, National Academy of Medical Sciences of Ukraine, Kiev, (947) City Clinical Hospital №3, Chernivtsi, (948) National Institute of Therapy N.A. L. Malaya NAMS, Kharkiv, (949) National Pirogov Memorial Medical University, Vinnytsya, (951) Clinic of State Institution, Institute of Therapy NAMS Ukraine L.T. Maloy, Kharkiv, (952) HSEE of Ukraine, Ukrainian Medical Stomatological Academy, Poltava, (953) Odessa National Medical University, Center of Reconstructive and Recovery Medicine (University Clinic), Odessa, (954) Institute of Urgent and Recovery Surgery, Donetsk, (955) State Institution National Scientific Centre, Acad. M.D. Strazhesko Institute of Cardiology of 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, Treatment 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, Zaporizhzhia, (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

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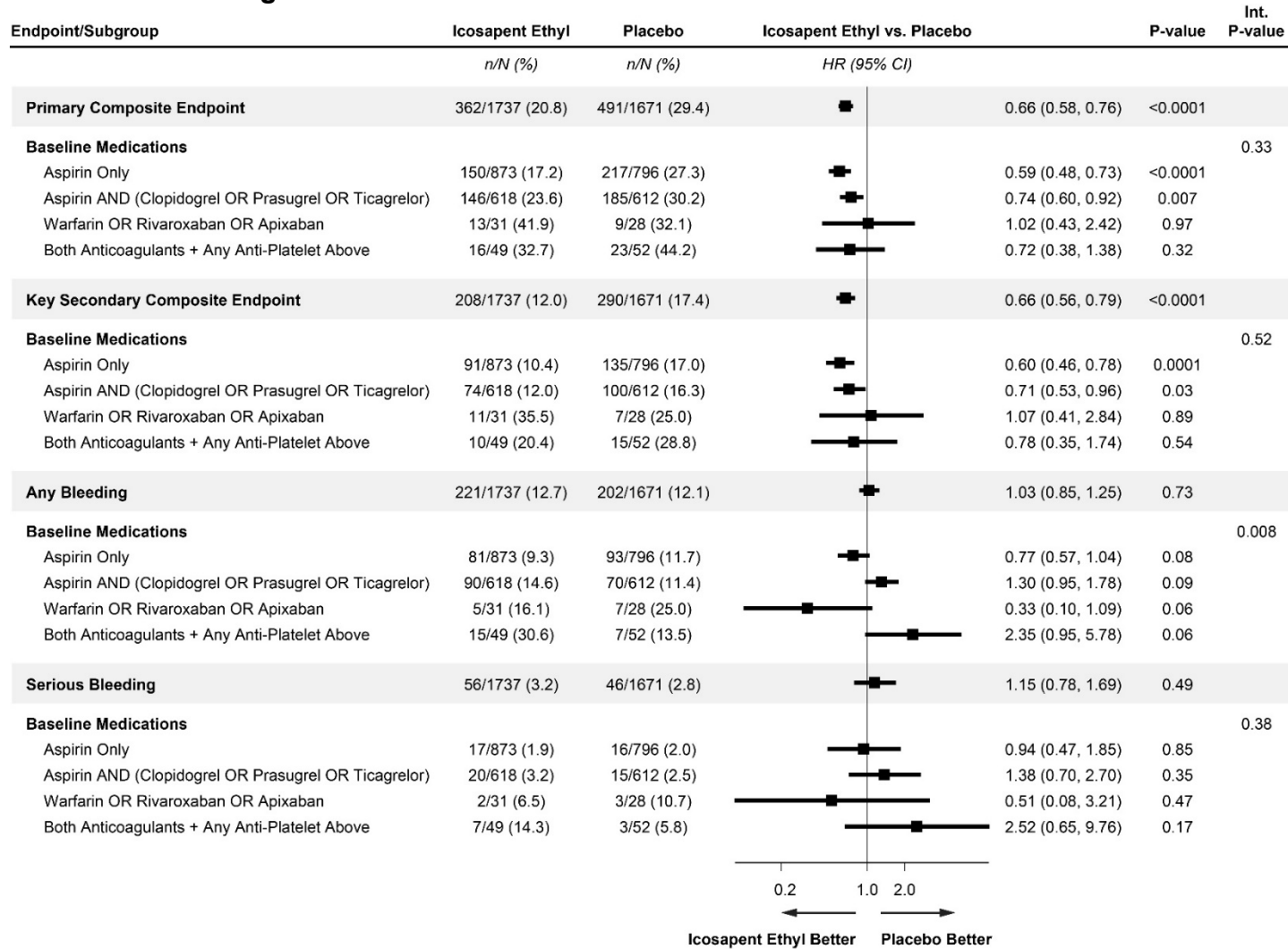
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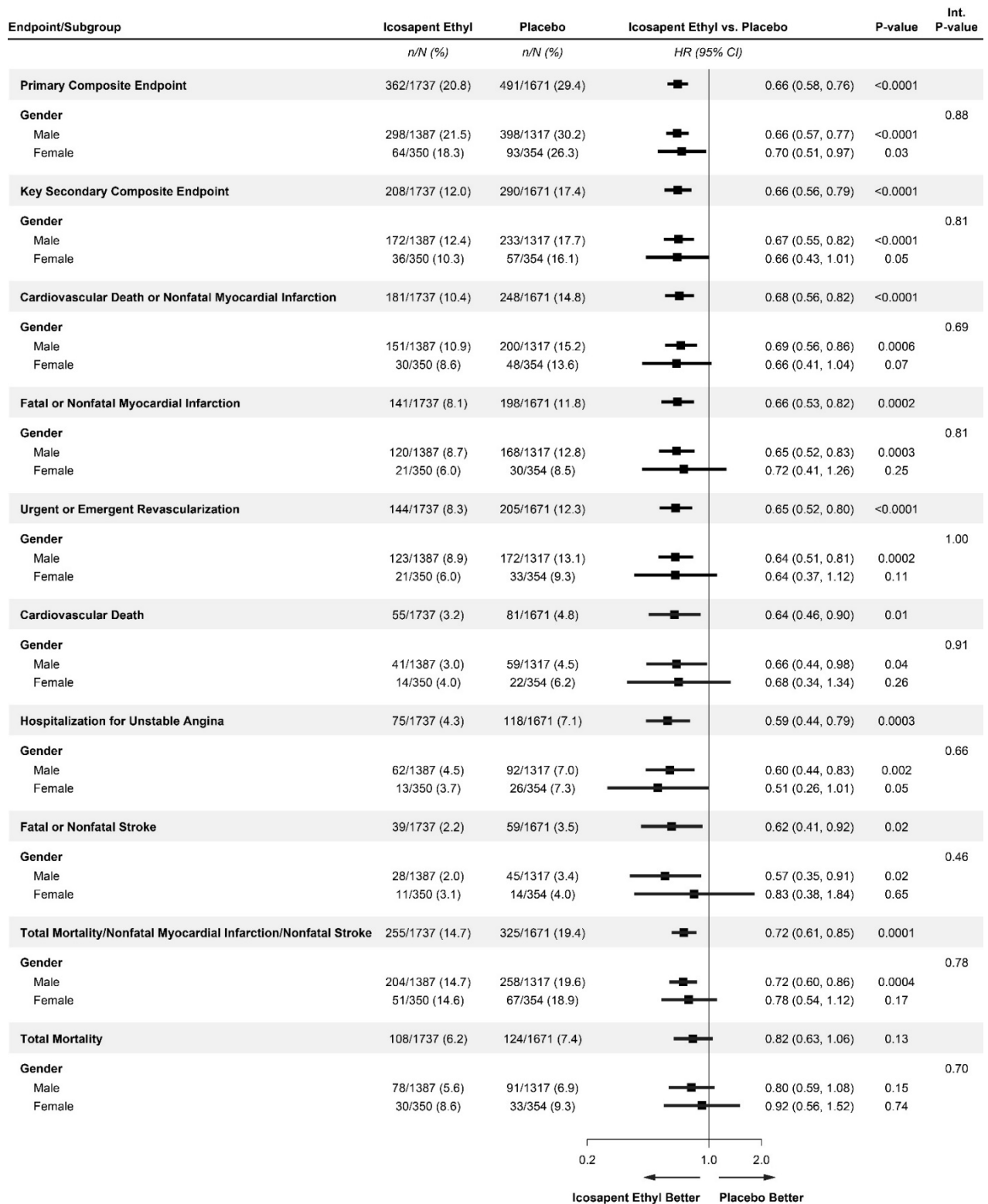
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**Figure S1. Efficacy and Safety of Icosapent Ethyl Among Patients with Prior PCI, Stratified by Baseline Antithrombotic Regimen.**

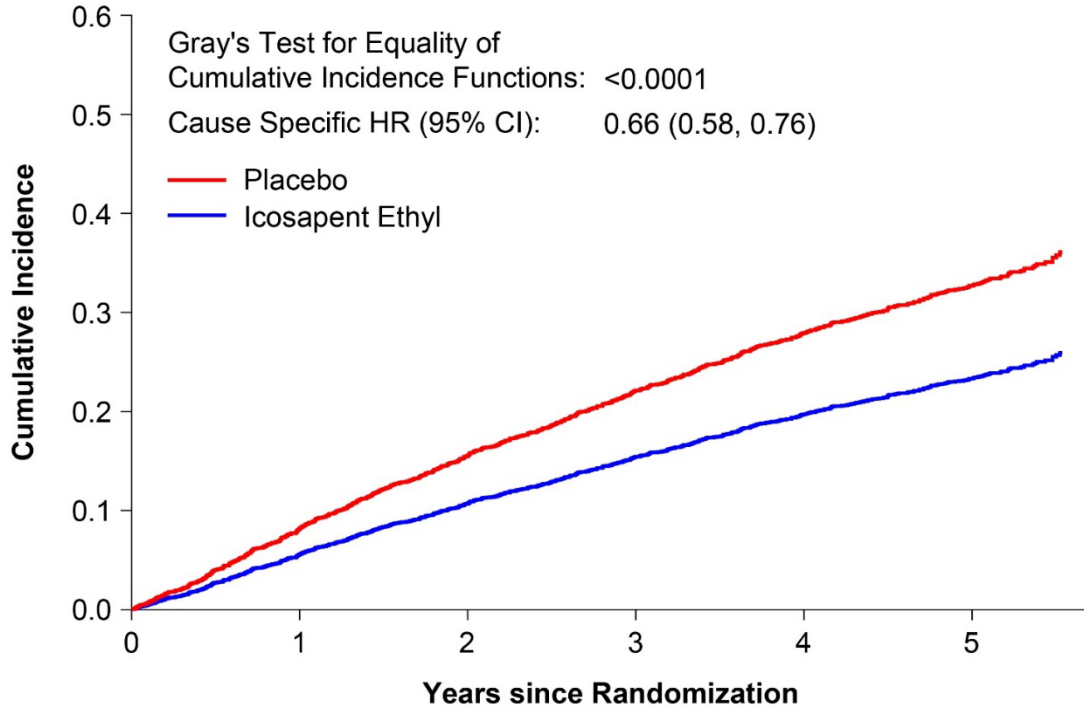


**Figure S2. Forest Plot of Efficacy End Points in Hierarchical Testing Order by Sex Among Patients with Prior PCI.**

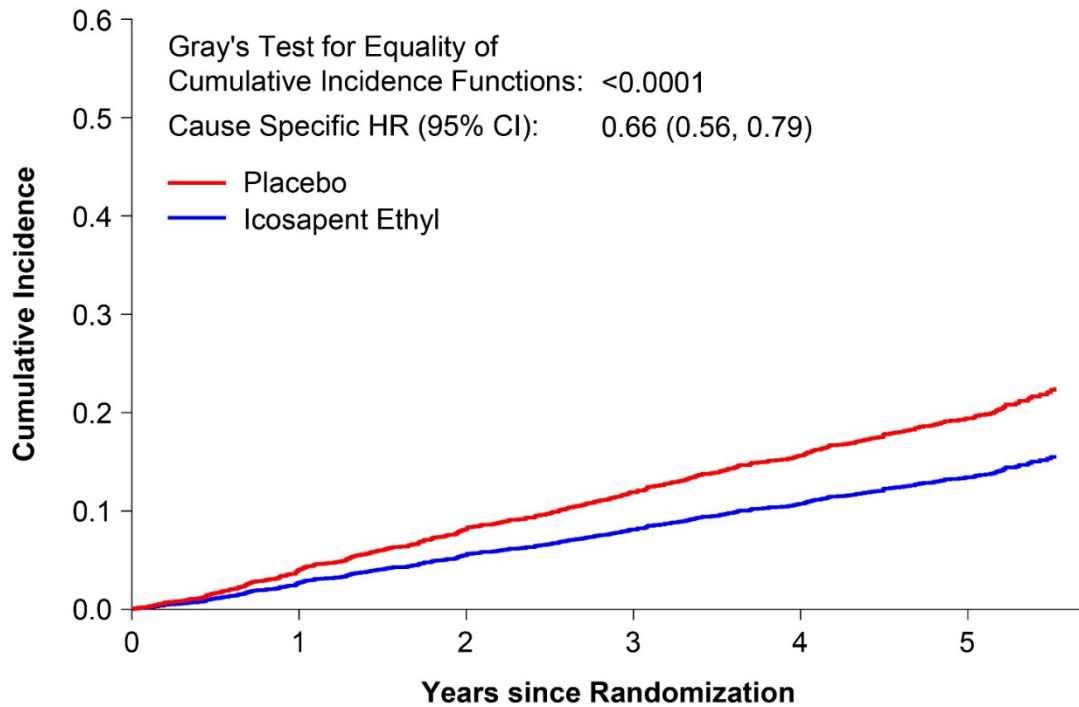


**Figure S3. Cumulative Incidence Plots of A. Primary Composite End Point and B. Key Secondary Composite End Point with Non-CV Death as Competing Risk Among Patients with Prior PCI.**

A.



B.



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

