Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA 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, **Amarin**, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda.

This presentation includes off-label and/or investigational uses of drugs.

REDUCE-IT was sponsored by Amarin Pharma, Inc.

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Global Principal Investigator and Steering Committee Chair

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

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Deepak L. Bhatt MD, MPH (Chair and Global 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

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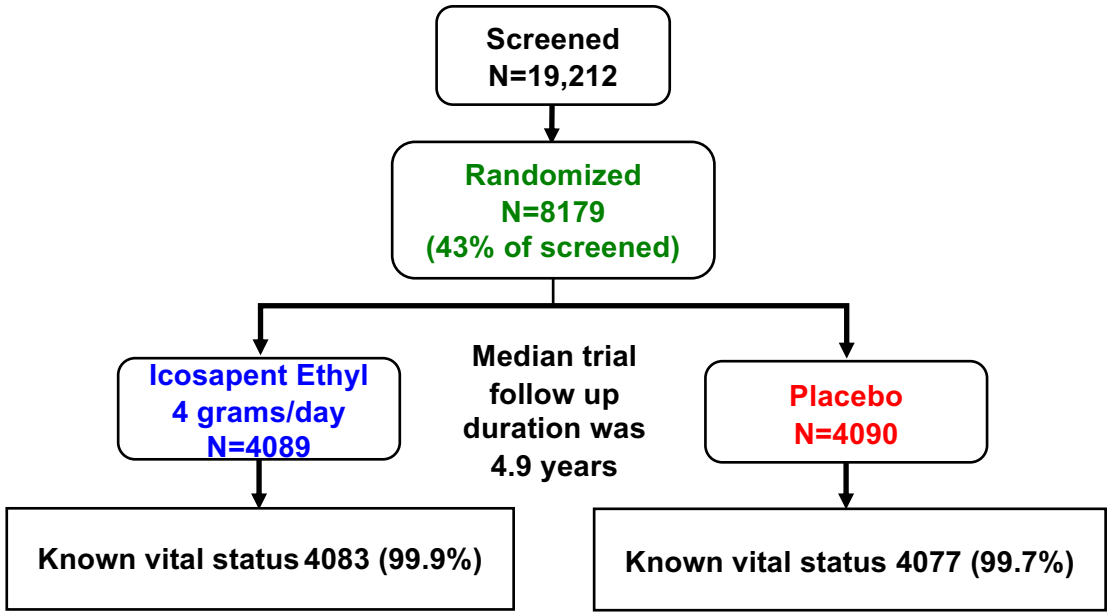
Independent Academic Statistical Analysis

Stuart J. Pocock PhD, John Gregson PhD

REDUCE-IT Design



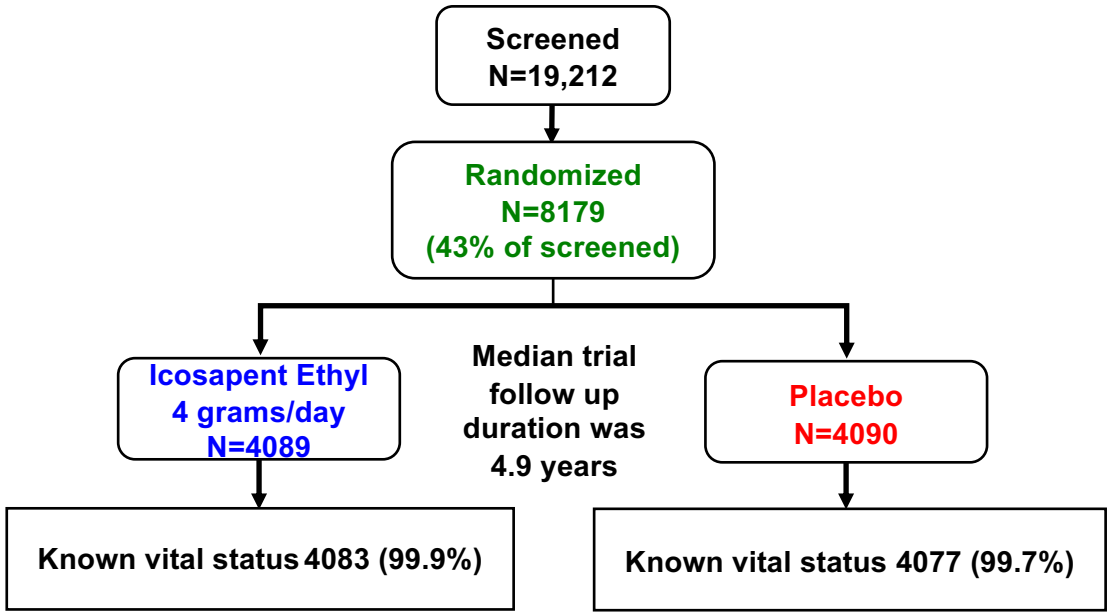
Primary Endpoint Events: CV death, nonfatal MI, nonfatal stroke, coronary revasc, hospitalization for unstable angina

Key Secondary Endpoint Events: CV death, nonfatal MI, nonfatal stroke

Double-blind study; Events adjudicated by CEC that was blinded to treatment during adjudication

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019; 380:11-22.

REDUCE-IT Design



1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)
2. Fasting TG levels ≥135 mg/dL and <500 mg/dL
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

Primary Endpoint Events: CV death, nonfatal MI, nonfatal stroke, coronary revasc, hospitalization for unstable angina

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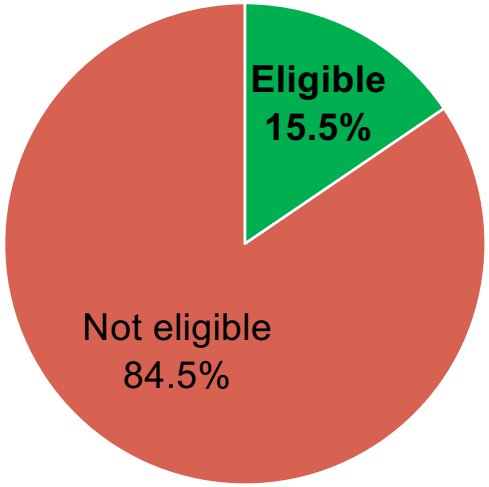
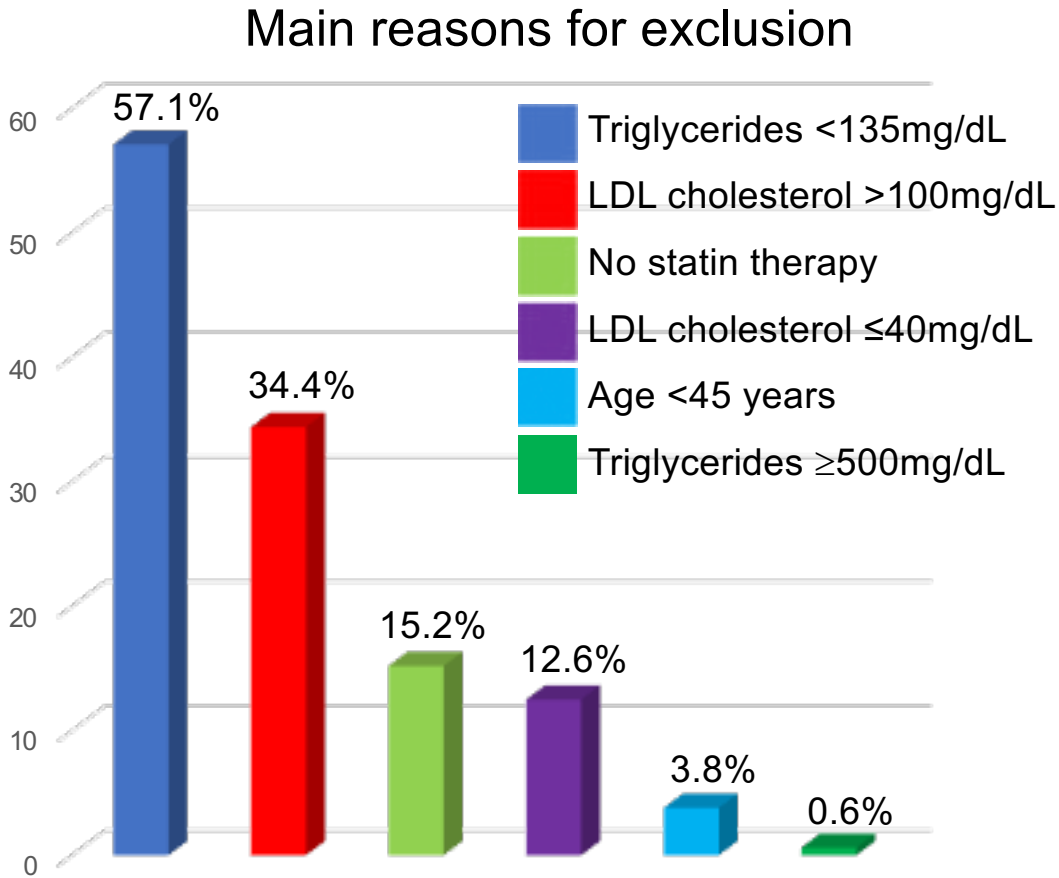
Generalizability of REDUCE-IT in Patients with Stable CAD

An analysis of 24,146 patients from the CLARIFY registry



Key Inclusion Criteria for CLARIFY Analysis

- Statin-treated men or women
- Age ≥45 years with either established CV disease OR age ≥50 years with diabetes mellitus and at least one additional CV risk factor
- AND triglycerides ≥135 and <500 mg/dL
- AND LDL-cholesterol >40 and ≤100 mg/dL



Picard F, Bhatt DL, Ducrocq G, et al. Steg PG. *JACC.* 2019.

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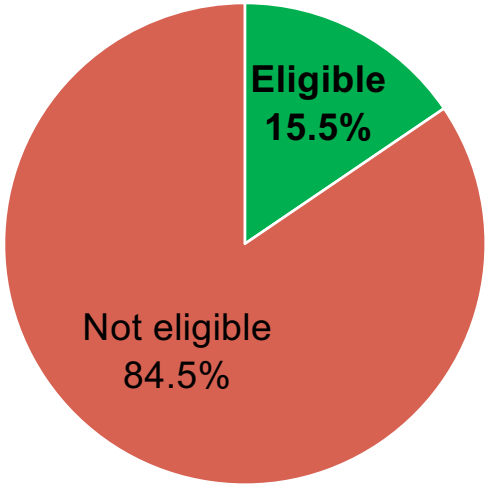

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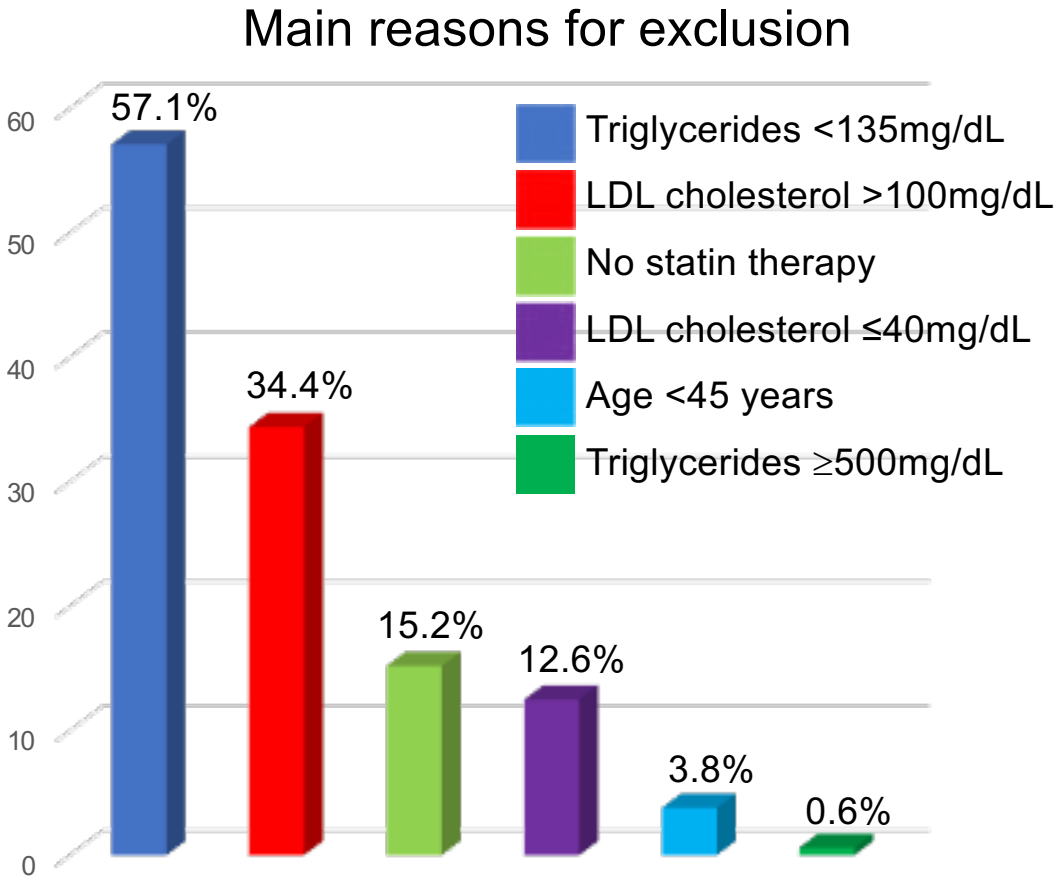
- Age ≥45 years with either established CV disease OR age ≥50 years with diabetes mellitus and at least one additional CV risk factor
- AND triglycerides ≥135 and <500 mg/dL
- AND LDL-cholesterol >40 and ≤100 mg/dL

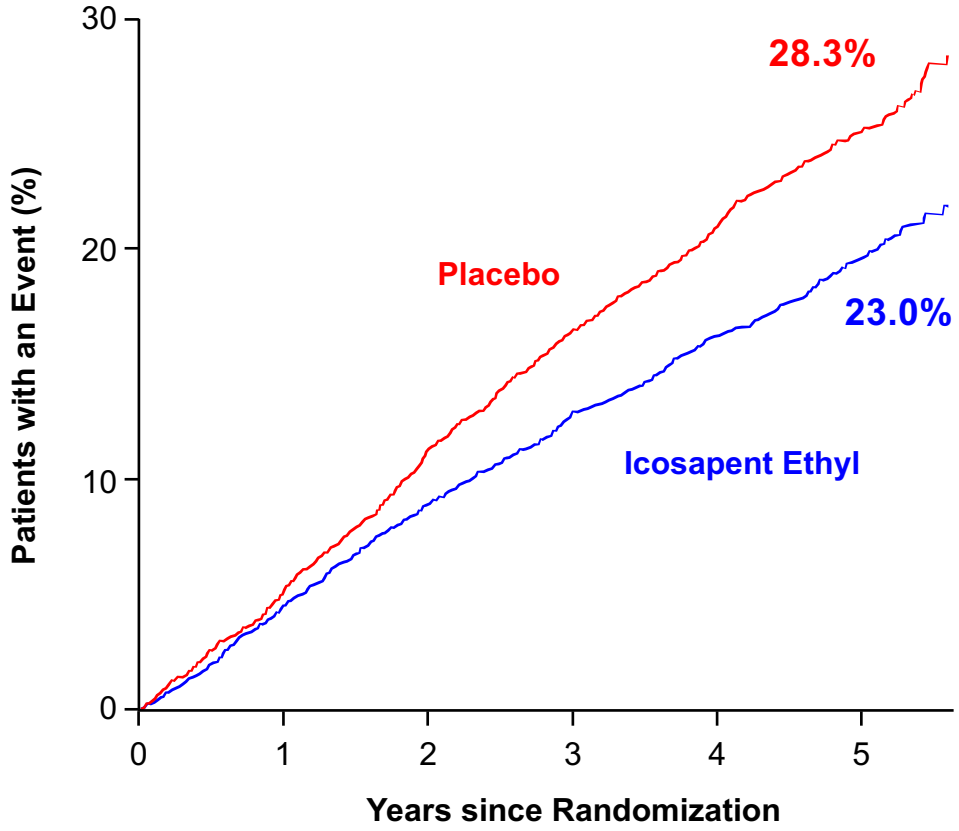
NOTE: REDUCE-IT also enrolled patients with PAD, CVD, and DM with at least one risk factor



Picard F, Bhatt DL, Ducrocq G, et al. Steg PG. *JACC.* 2019.

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

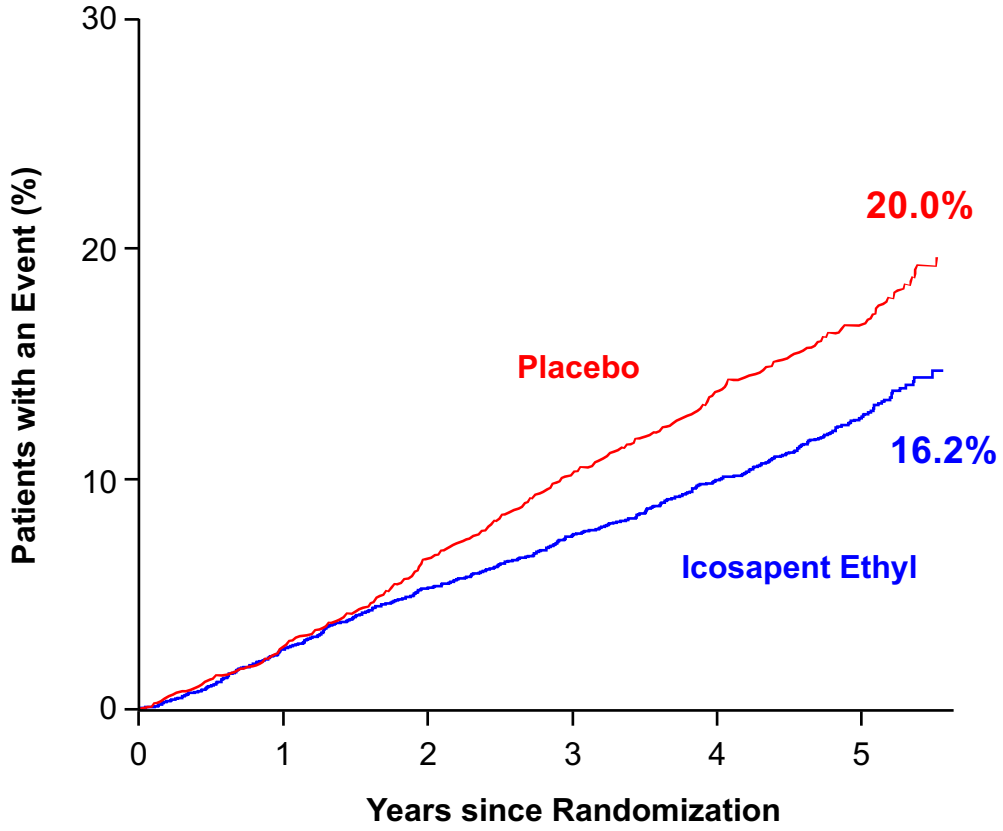
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

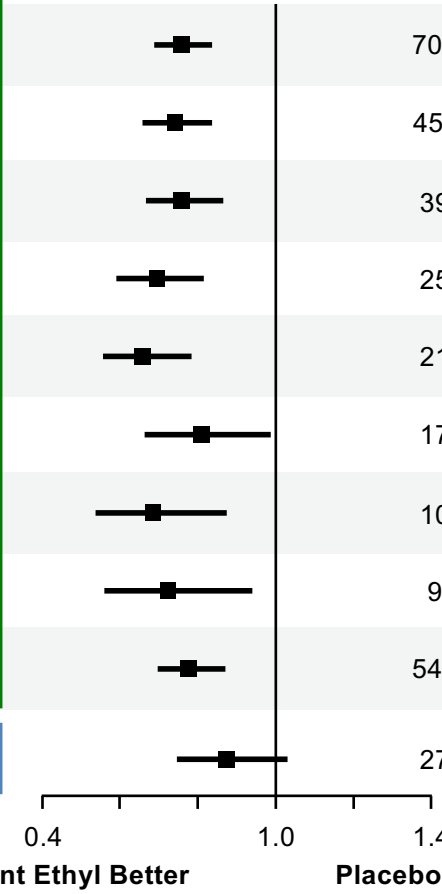
Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

Prespecified Hierarchical Testing



Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

Methods – Subsequent and Total Events

First events were significantly reduced, including CV death

- However, patients with non-fatal events are at increased risk for subsequent ischemic events

Multiple validated statistical models used to examine subsequent events

- Negative binomial regression (prespecified)
- Andersen-Gill (prespecified)
- Wei-Lin-Weissfeld with Li and Lagakos modification (prespecified)
- Joint-frailty (*post hoc*)

Key Baseline Characteristics

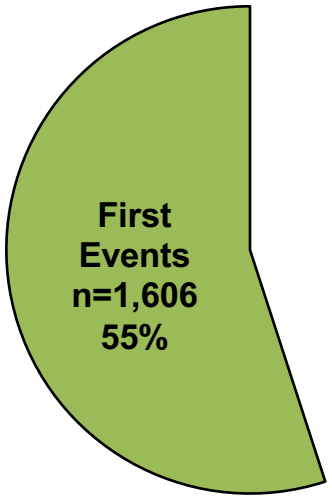
	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years)	64	64
Female, %	28.4%	29.2%
CV Risk Category, %		
Secondary Prevention Cohort	70.7%	70.7%
Primary Prevention Cohort	29.3%	29.3%
Prior Atherosclerotic Coronary Artery Disease, %	58.4%	58.5%
Prior Atherosclerotic Cerebrovascular Disease, %	15.7%	16.2%
Prior Atherosclerotic Peripheral Artery Disease, %	9.5%	9.5%
LDL-C (mg/dL), Median (Q1-Q3)	74 (62 - 88)	76 (63 - 89)
Triglycerides (mg/dL), Median (Q1-Q3)	217 (177 - 272)	216 (176 - 274)
Triglyceride Category (by Tertiles)*		
≥81 to ≤190 mg/dL	median 163 mg/dL	
>190 to ≤250 mg/dL	median 217 mg/dL	
>250 to ≤1401 mg/dL	median 304 mg/dL	

*Baseline TG calculated as average of final screening TG and subsequent TG value from date of randomization.

Key Medical Therapy

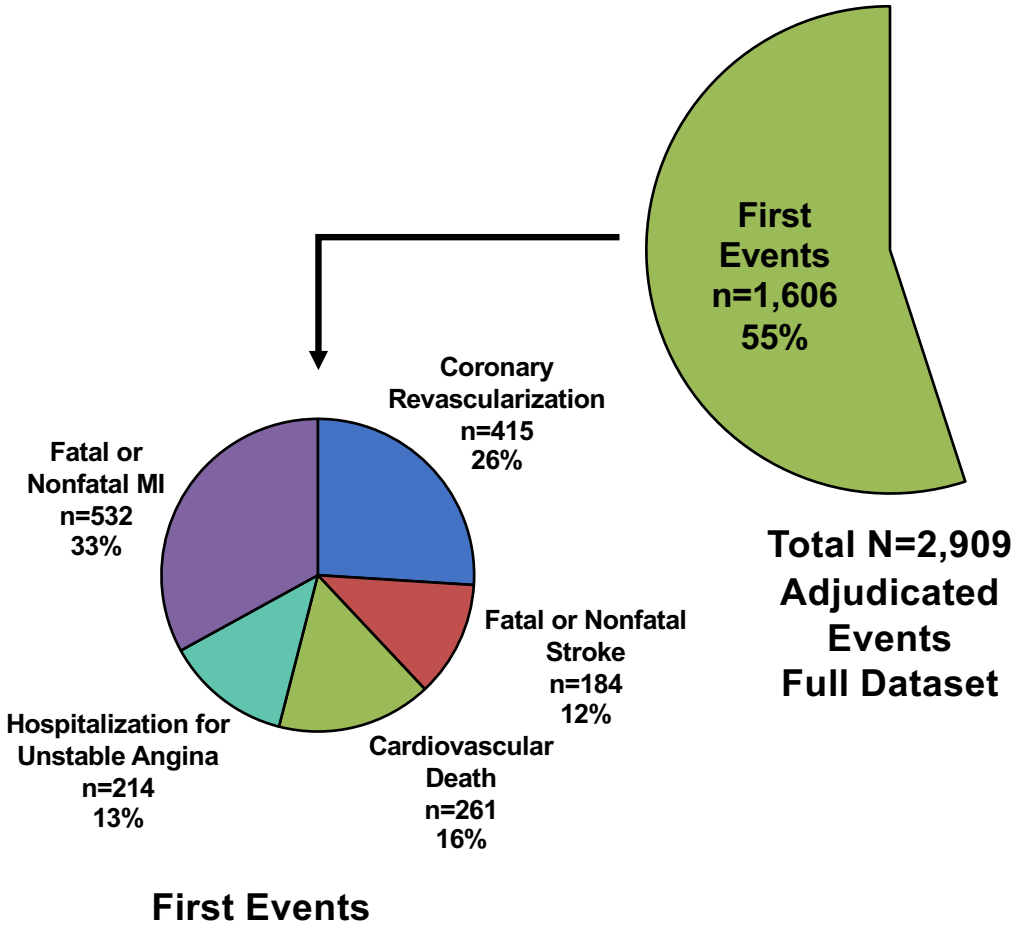
	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Antiplatelet	3257 (79.7%)	3236 (79.1%)
One Antiplatelet	2416 (59.1%)	2408 (58.9%)
Two or More Antiplatelets	841 (20.6%)	828 (20.2%)
Anticoagulant	385 (9.4%)	390 (9.5%)
ACEi or ARB	3164 (77.4%)	3176 (77.7%)
Beta Blocker	2902 (71.0%)	2880 (70.4%)
Statin	4077 (99.7%)	4068 (99.5%)

Proportions of First and Subsequent Events



Total N=2,909
Adjudicated
Events
Full Dataset

Proportions of First and Subsequent Events



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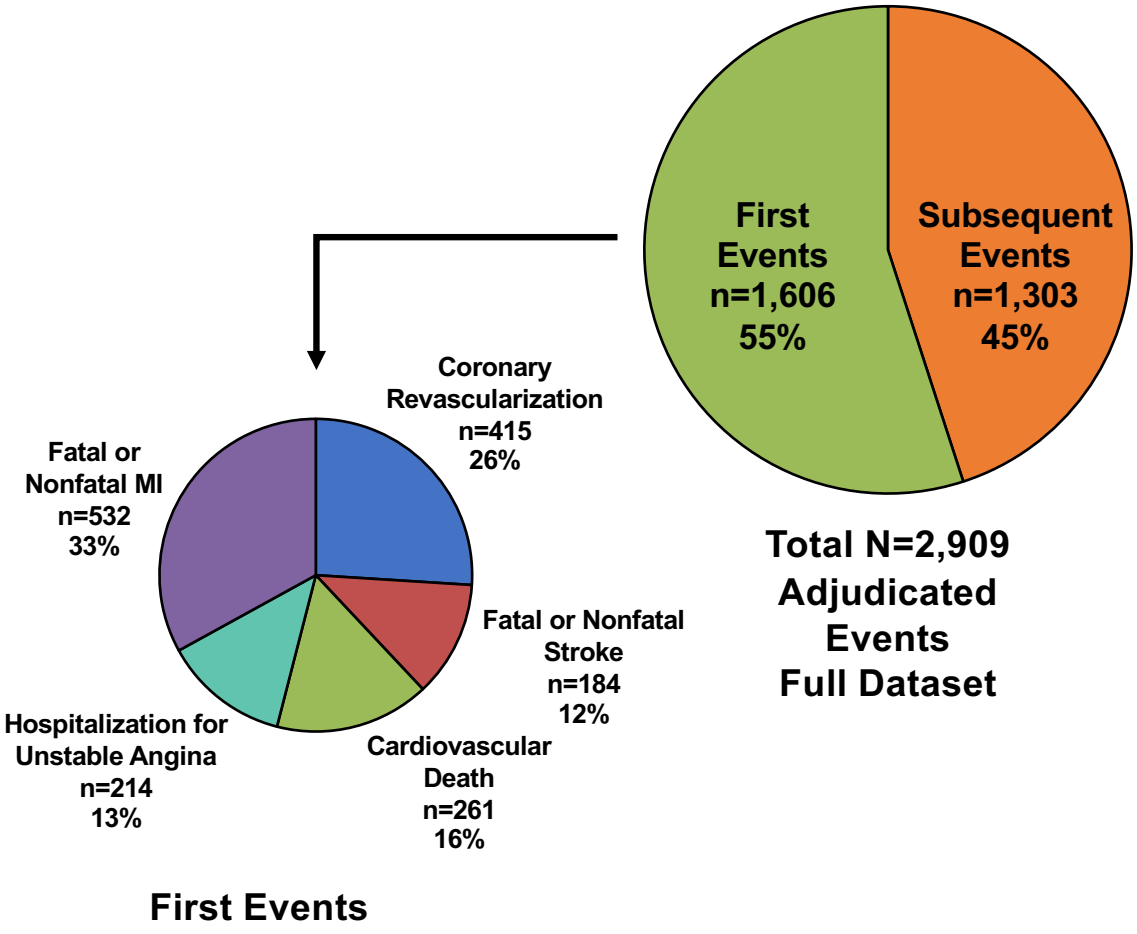

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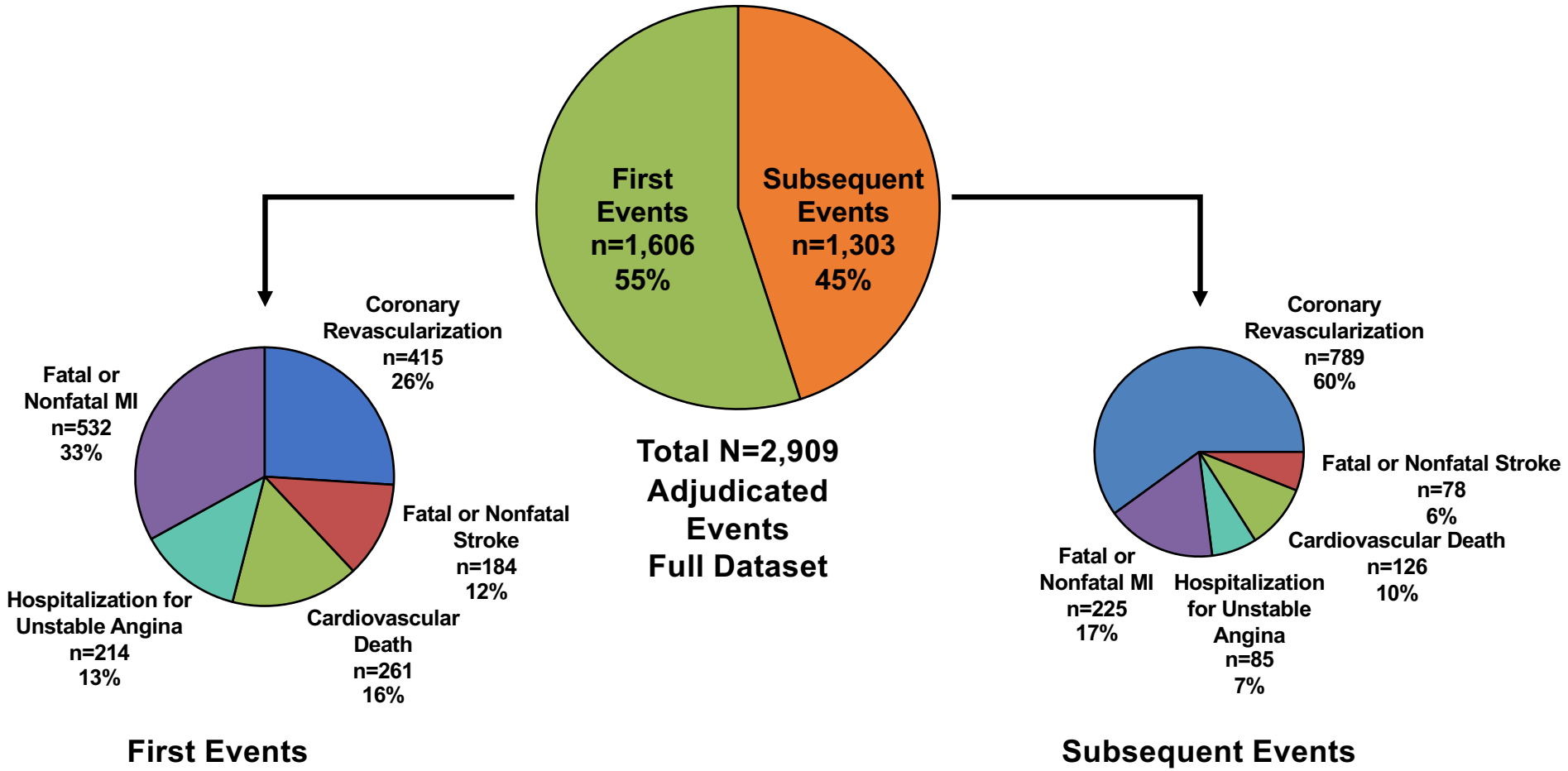
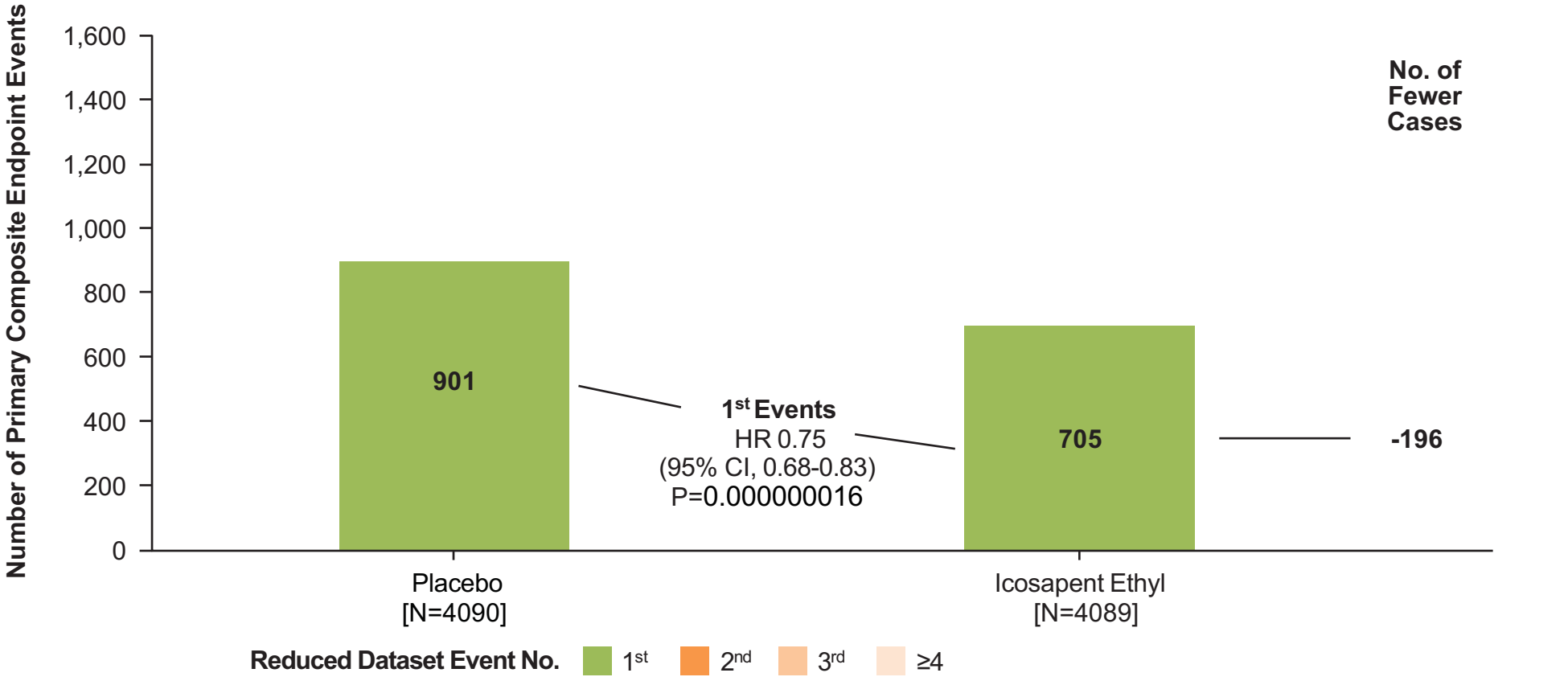


Event Counts

Events on the Same Day:

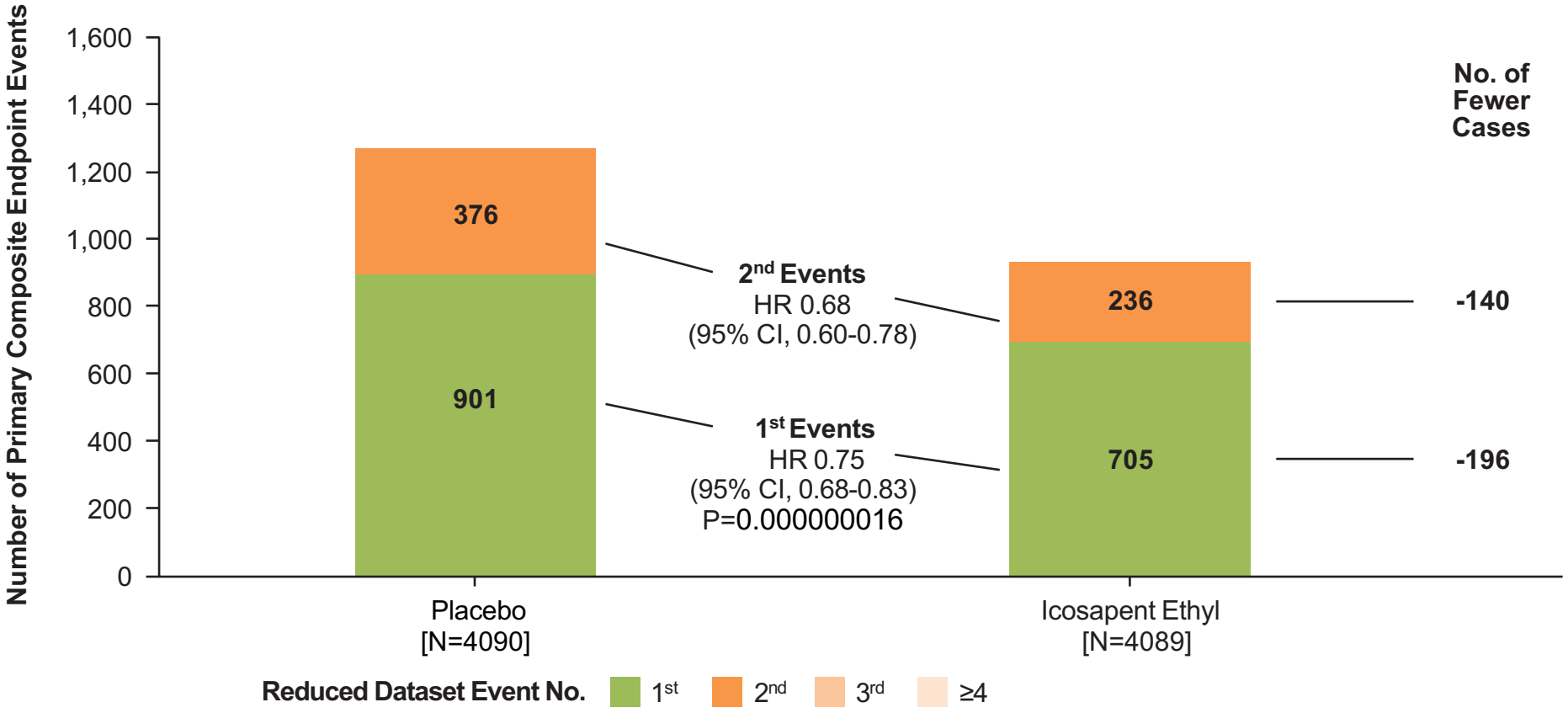
- To improve model performance an event-bundling approach was employed
  - Nonfatal events occurring on the same day as a CV death were excluded and, at most, one nonfatal event was counted on any given day
  - Analyses using this approach are identified as using the “Reduced Dataset” – a more conservative approach
  - Results are qualitatively very similar to our prespecified approach using the “Full Dataset”

First and Subsequent Events



Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

First and Subsequent Events



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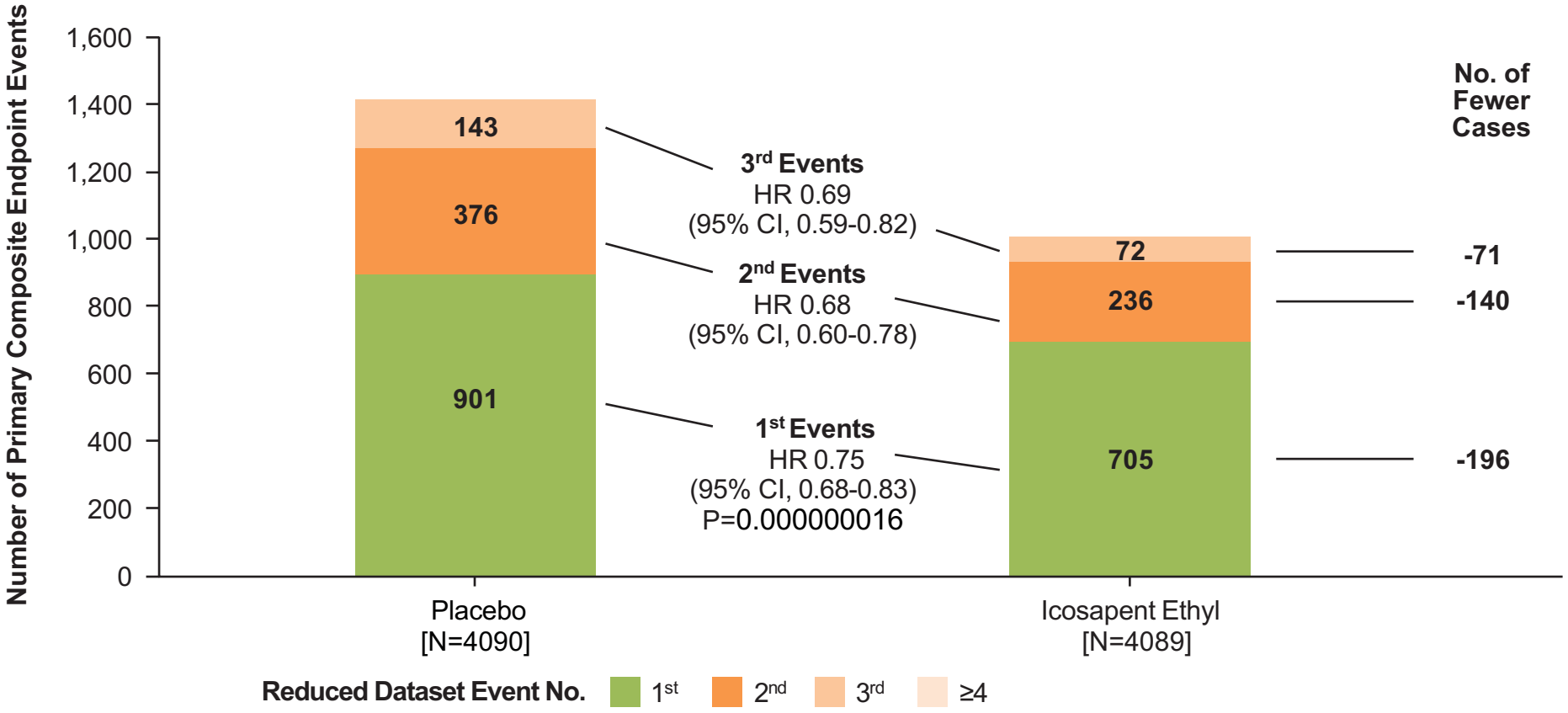

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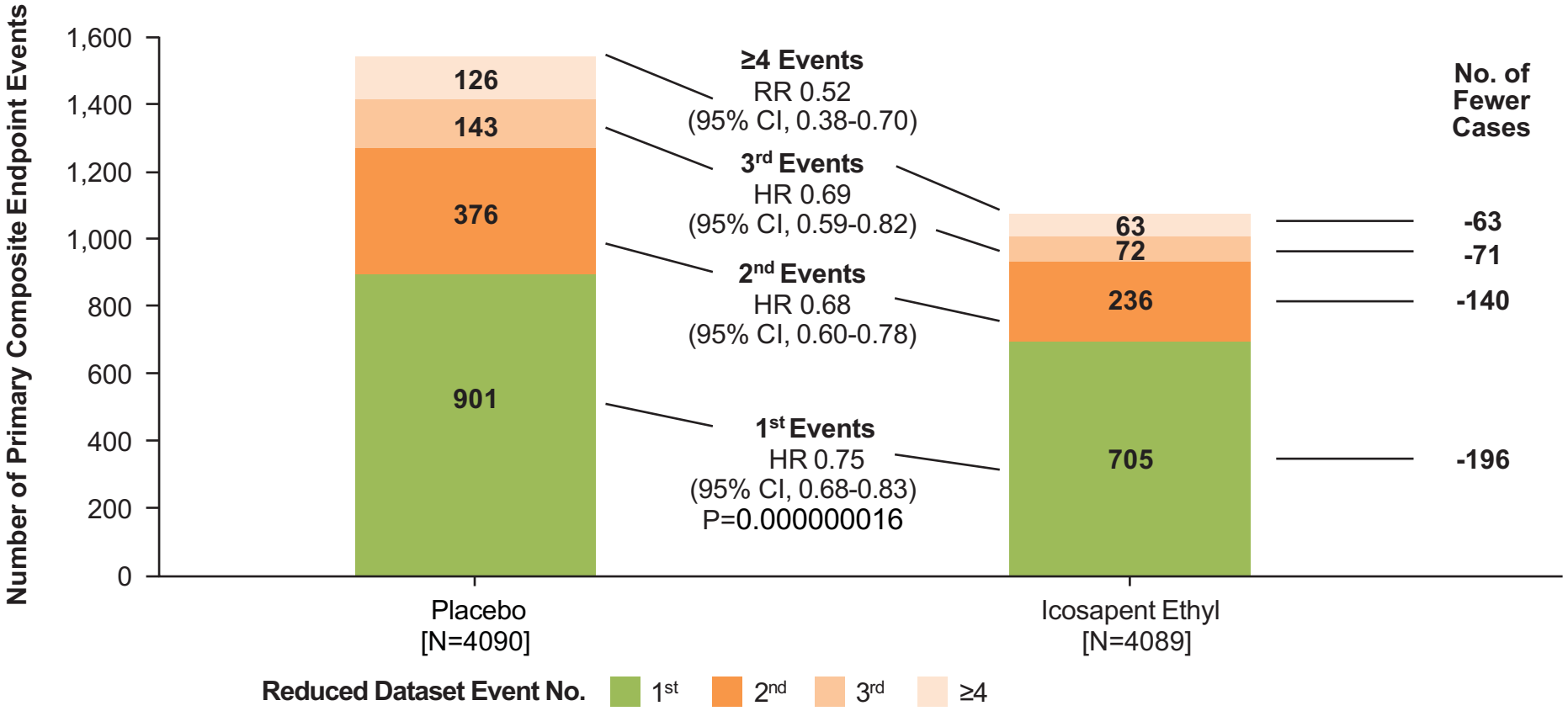

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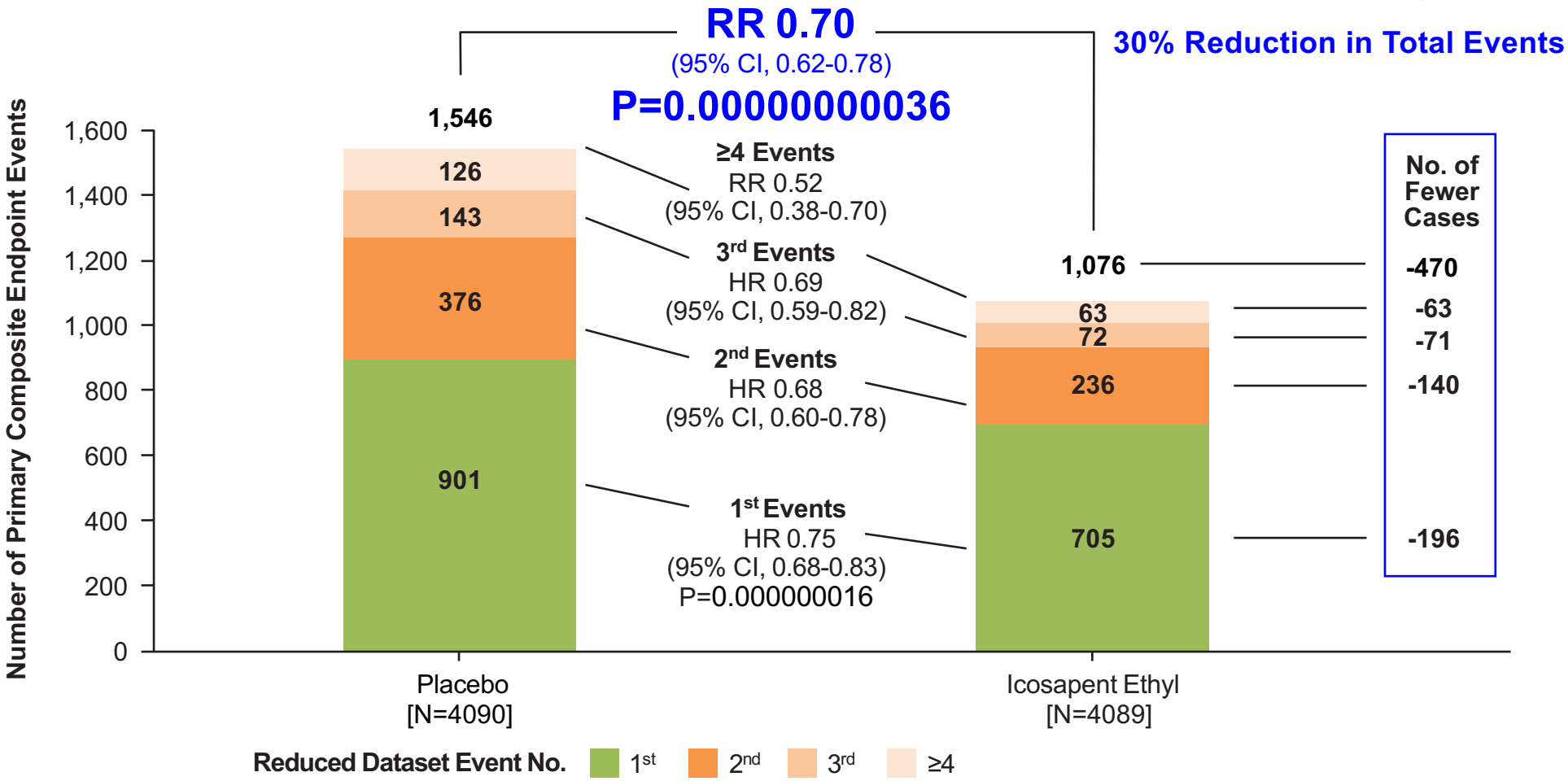

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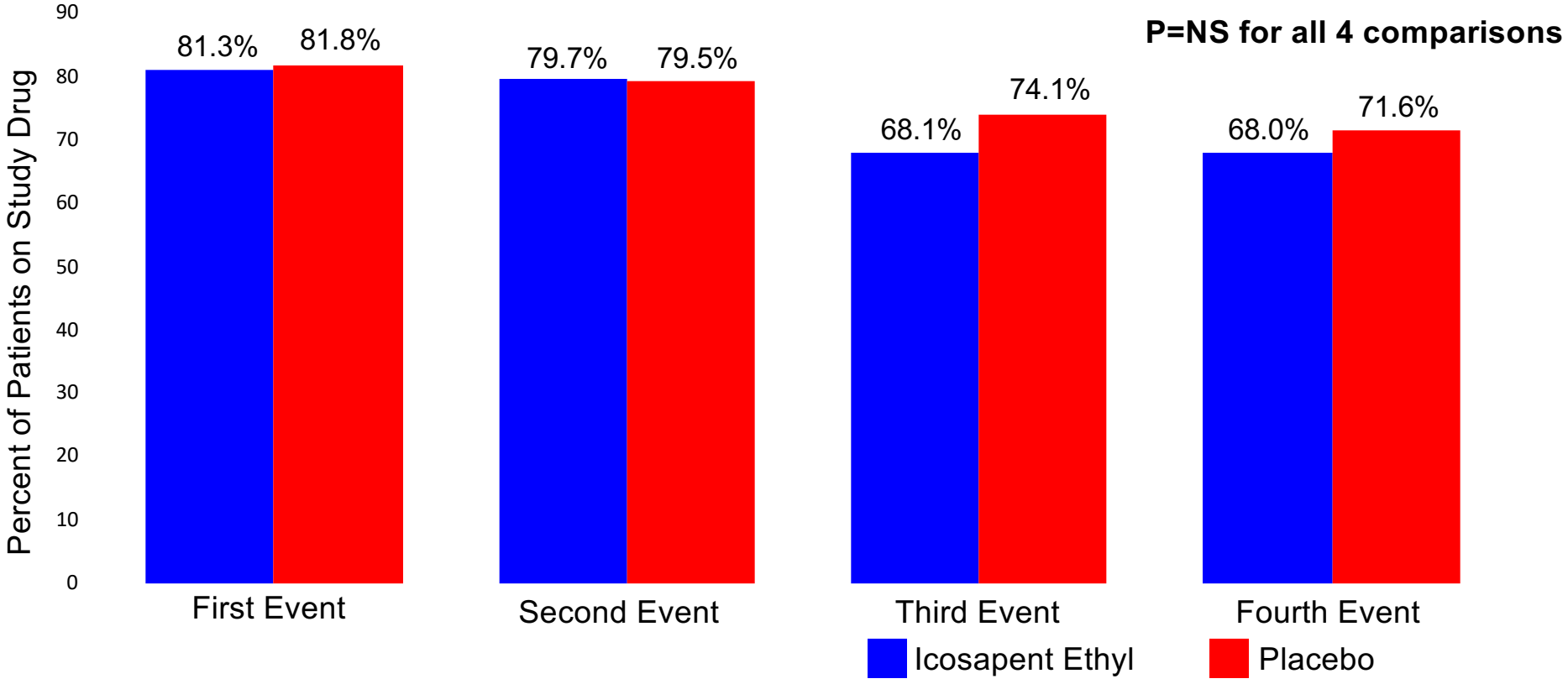
Adherence

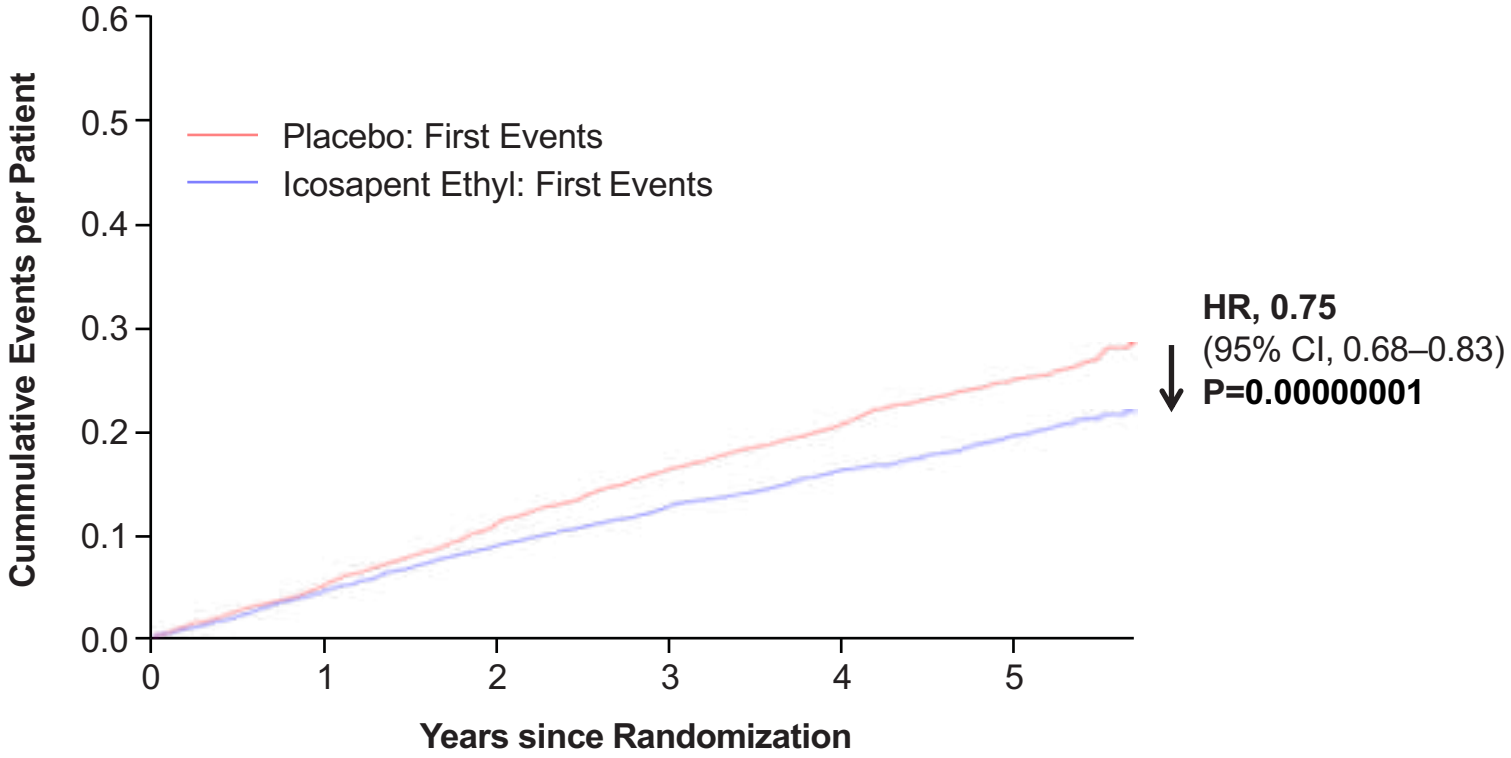
- As is common in long-term trials, study drug adherence waned over time
- Despite this, there was strong sustained treatment effect on total events



Total (First and Subsequent) Events

Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Primary Composite Endpoint



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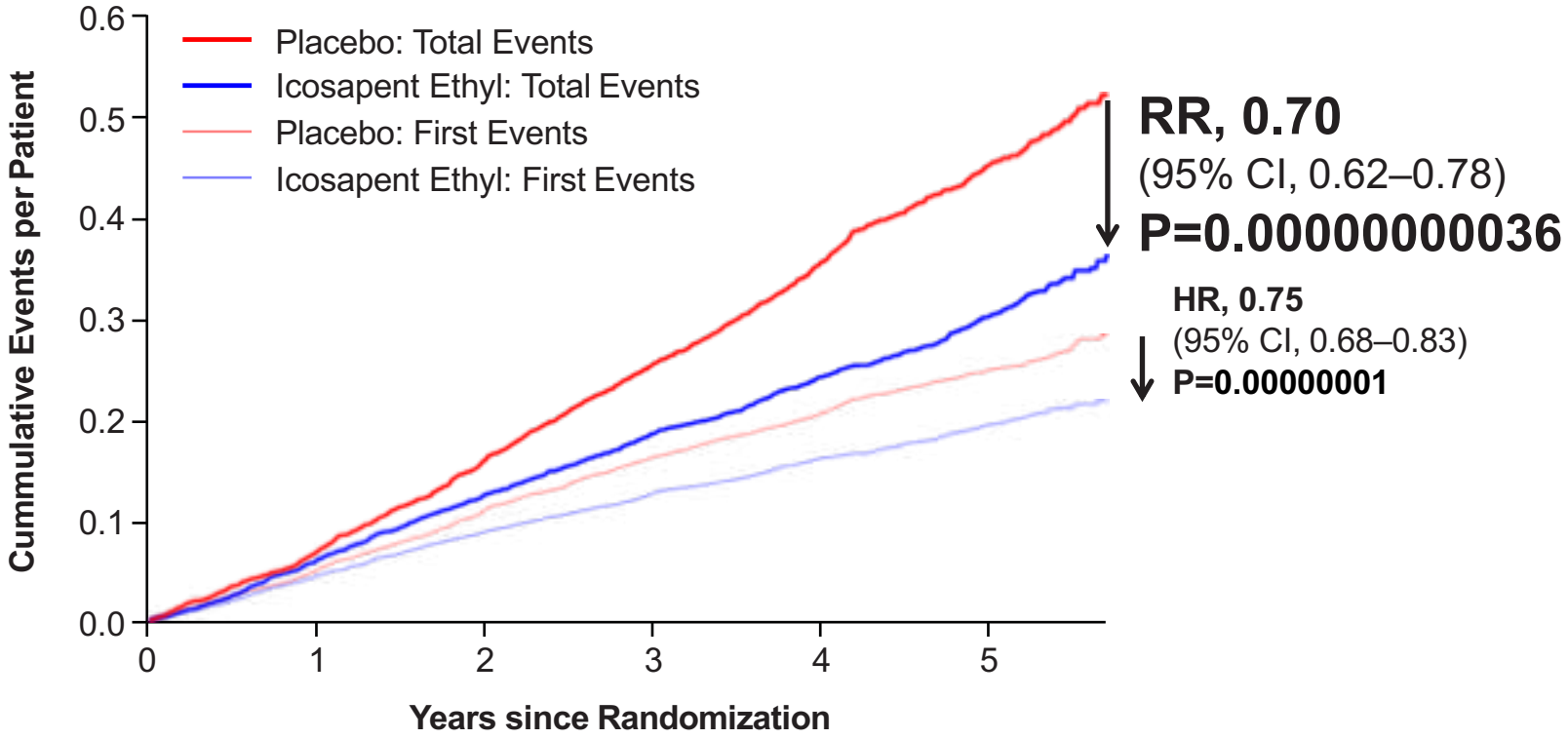
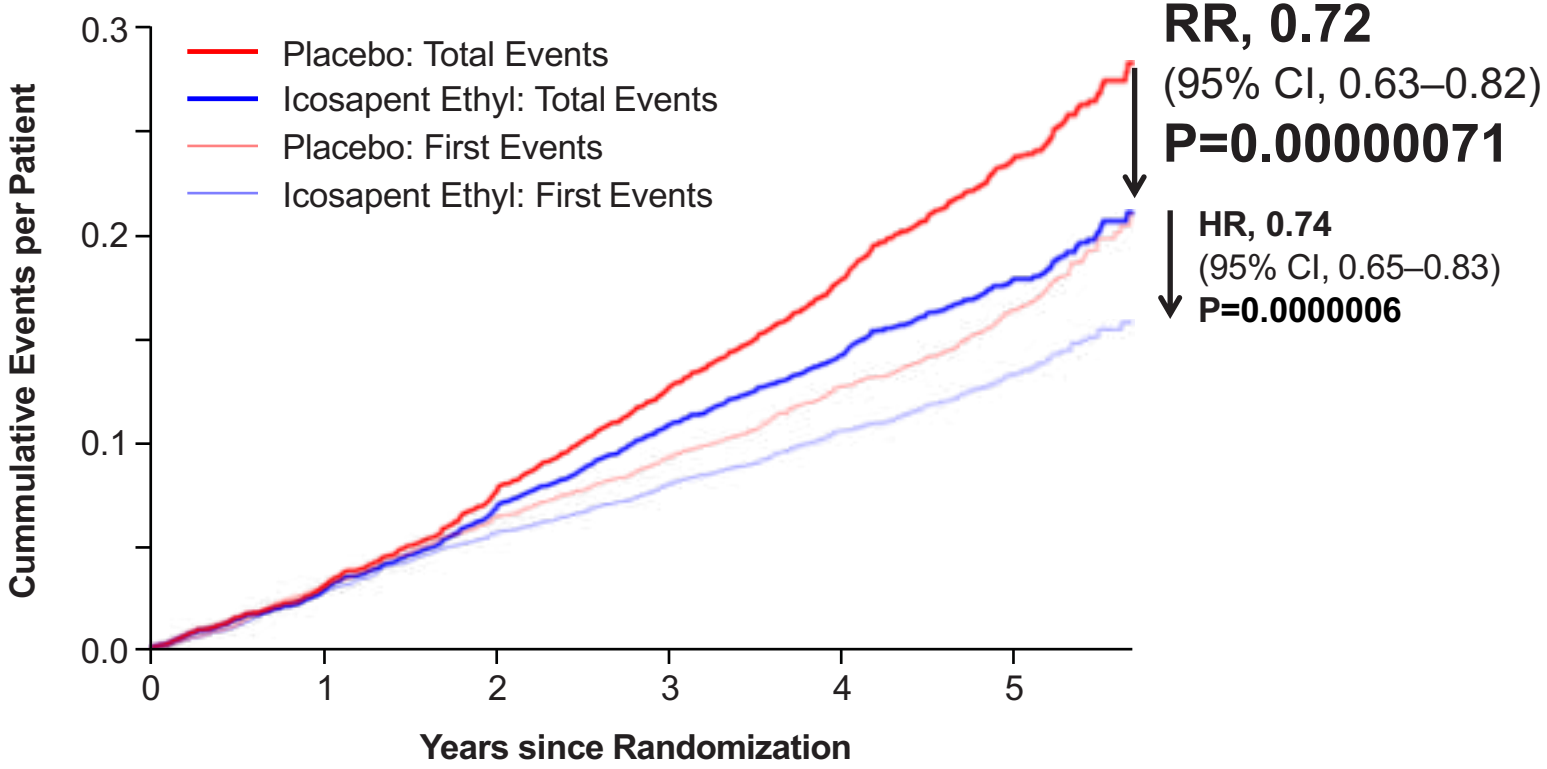


Total (First and Subsequent) Events

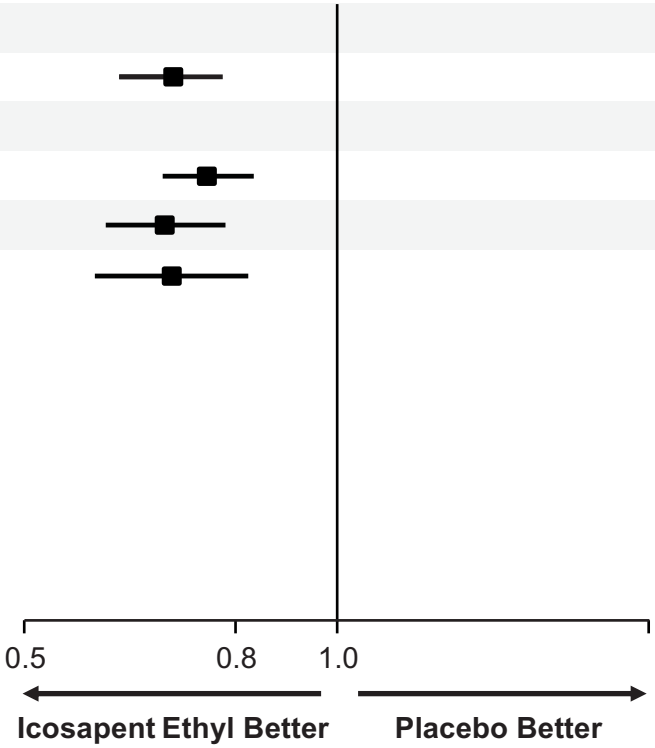
Key Secondary: CV Death, MI, Stroke

Key Secondary Composite Endpoint



Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences

Endpoint/Model	Rate/Hazard Ratio (95% CI)	P-value
Primary Composite Endpoint		
Negative binomial	0.70 (0.62–0.78)	3.6×10^{-10}
Modified WLW		
First event	0.75 (0.68–0.83)	1.6×10^{-8}
Second event	0.68 (0.60–0.78)	1.8×10^{-8}
Third event	0.69 (0.59–0.82)	2.0×10^{-5}



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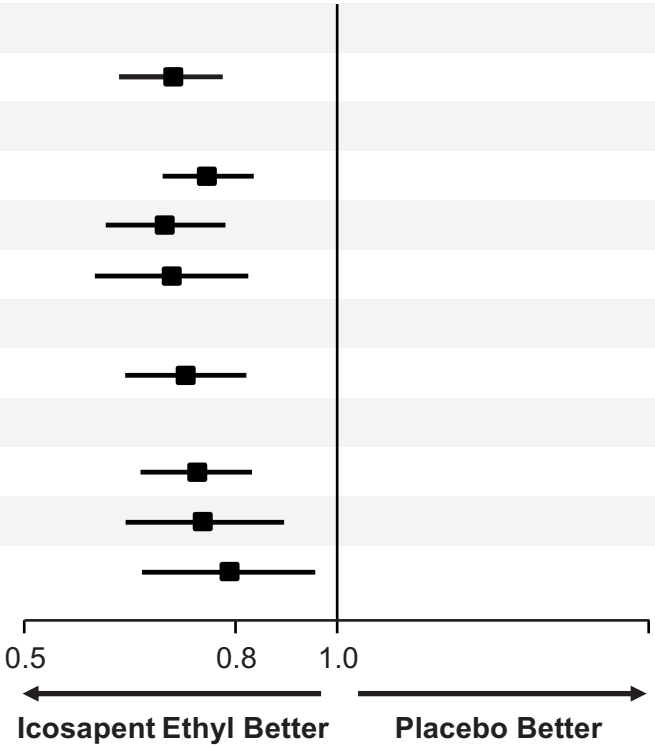
Second event	0.68 (0.60–0.78)	1.8×10^{-8}
Third event	0.69 (0.59–0.82)	2.0×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.72 (0.63–0.82)	7.1×10^{-7}
Modified WLW		
First event	0.74 (0.65–0.83)	7.0×10^{-7}
Second event	0.75 (0.63–0.89)	1.1×10^{-3}
Third event	0.79 (0.65–0.96)	0.017



Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001

***P (interaction) = 0.17**

Limitations

The "Reduced Dataset" was *post hoc*

- Though the prespecified "Full Dataset" produces effect sizes at least as large, and more extreme p values

The joint frailty model was *post hoc*

- Though all other models used were prespecified, with consistent results

Cannot formally comment on cost-effectiveness

- Likely cost-effective given large reduction in total events
- These data will provide critical information for cost-effectiveness analyses now underway

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events

Conclusions

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- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events
- **48%** reduction in fourth or more cardiovascular events

Conclusions

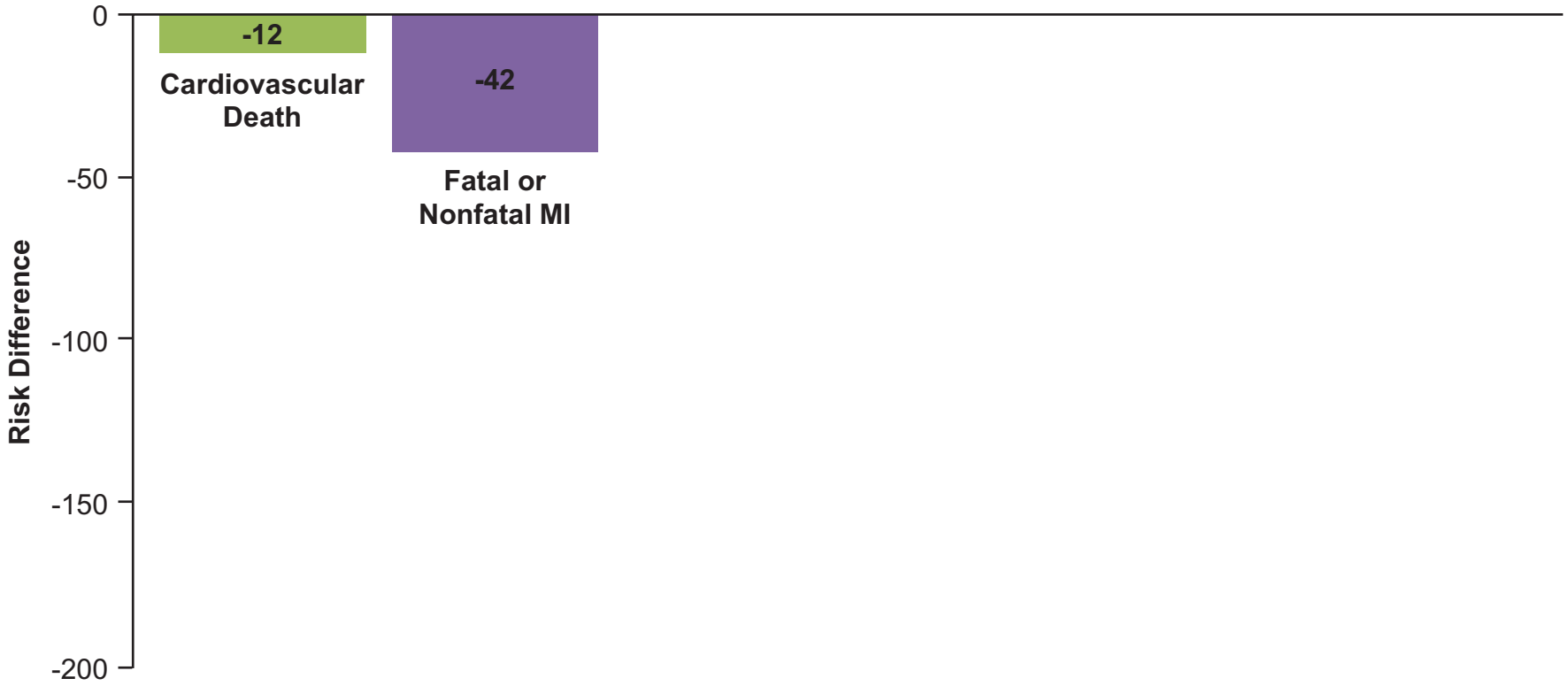
Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events
- **48%** reduction in fourth or more cardiovascular events

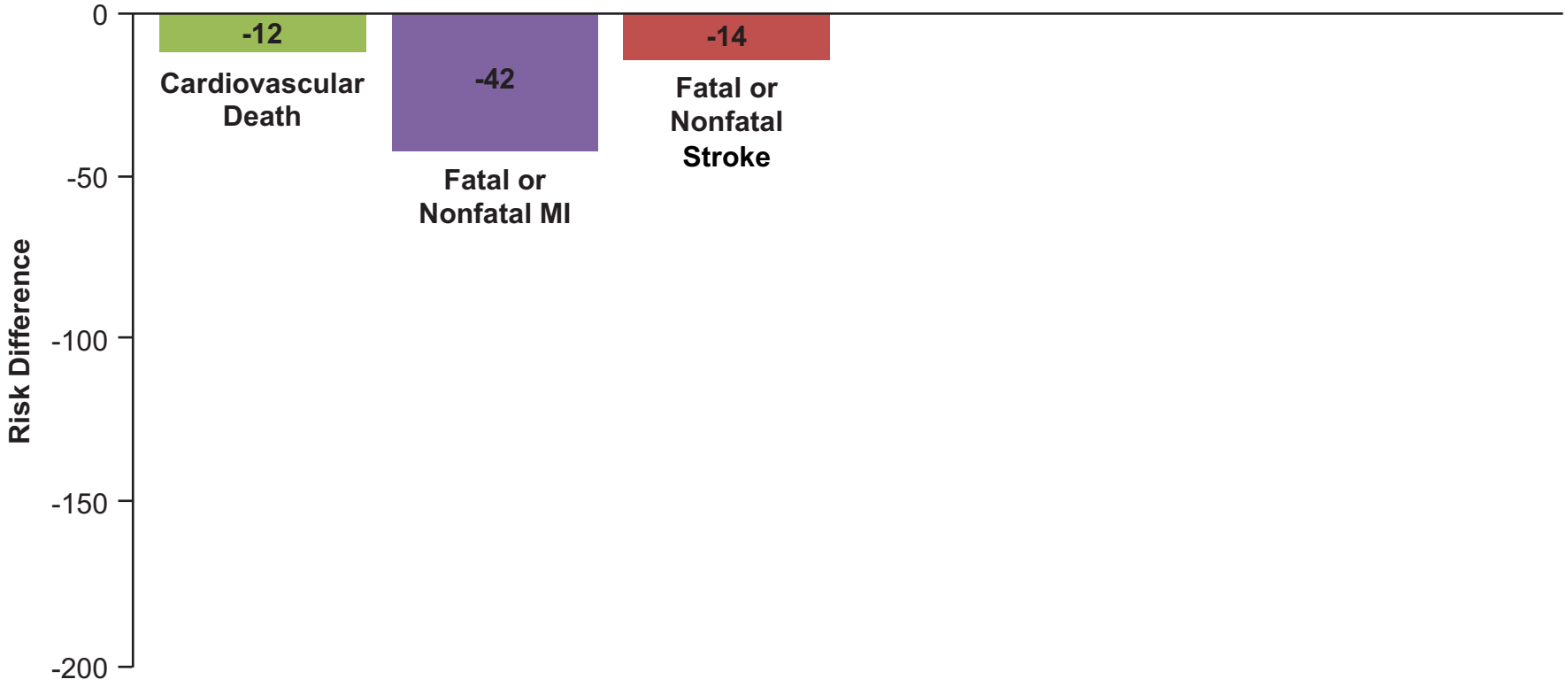
Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides > ~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:

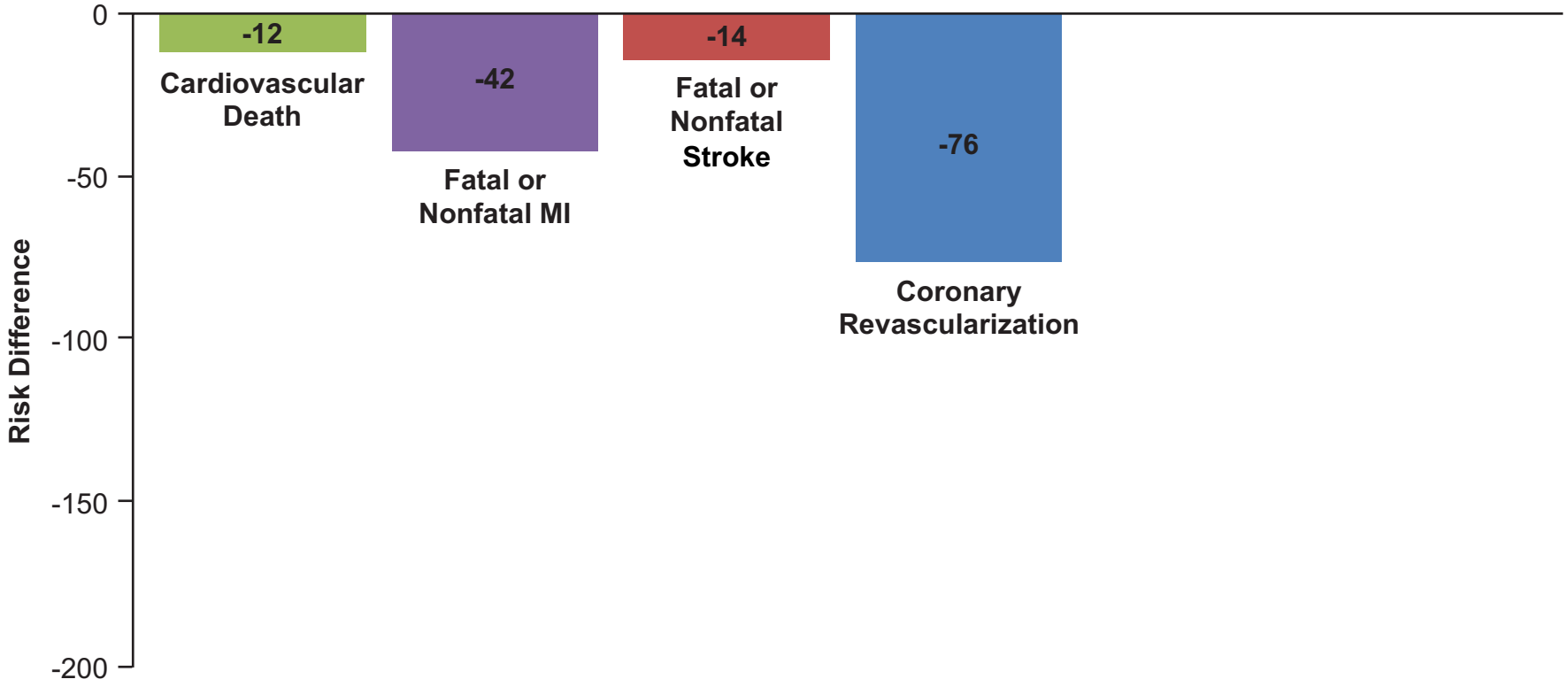
For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



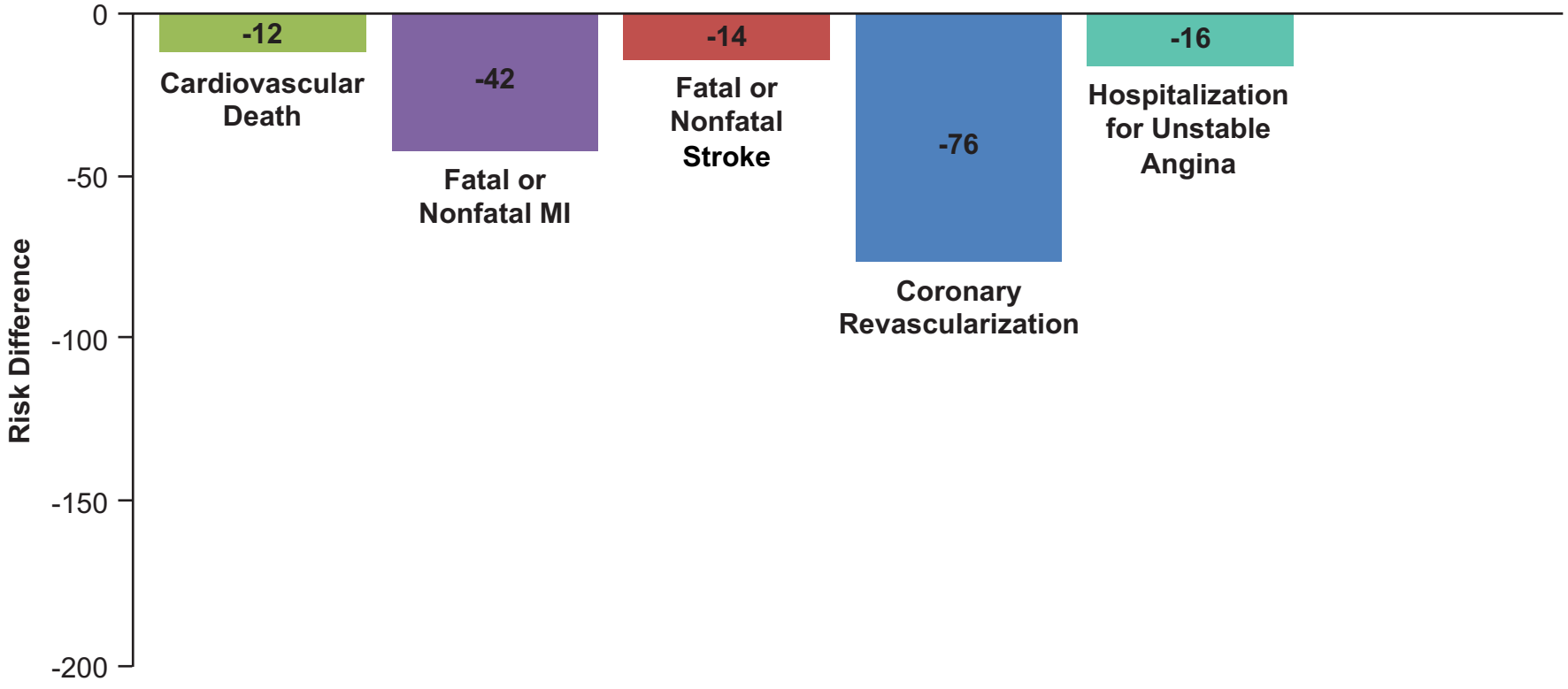
For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



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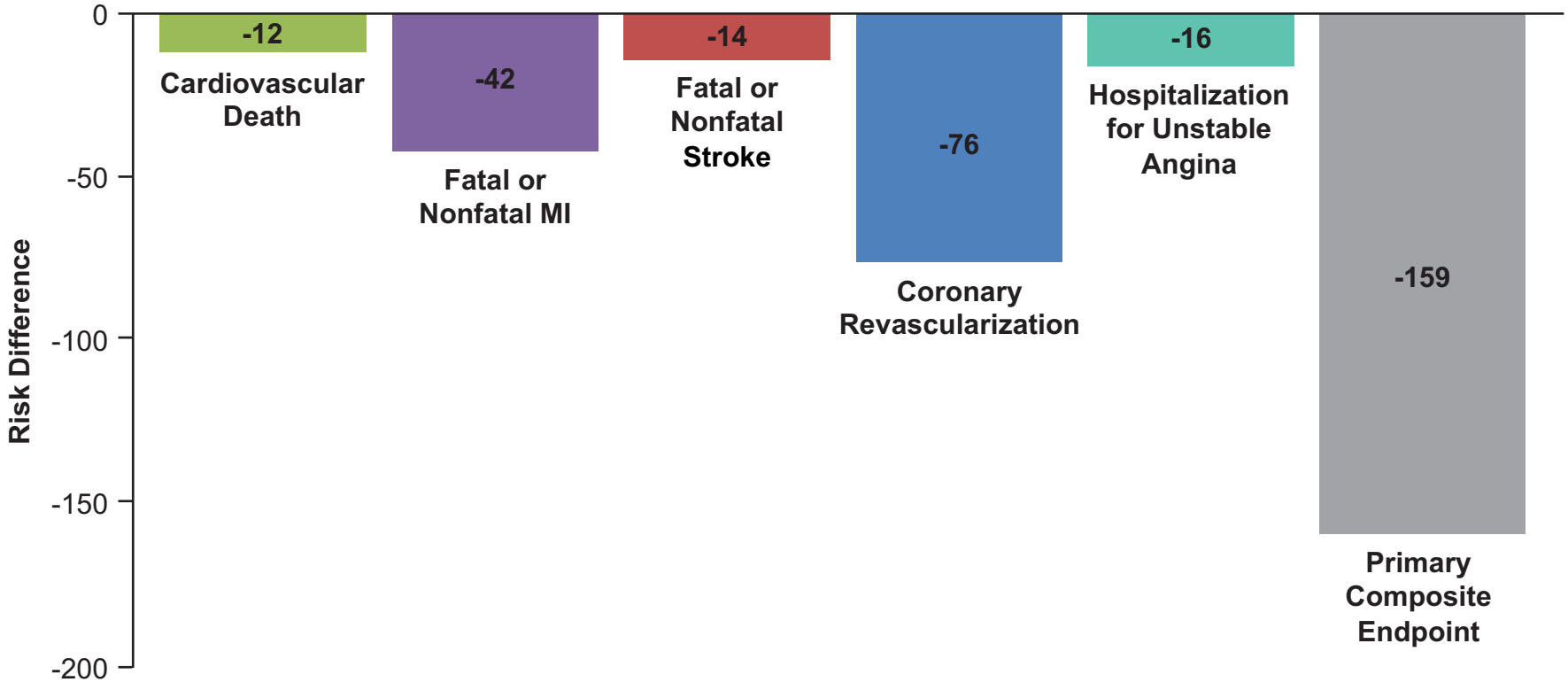

We thank the investigators, the study coordinators, and especially the 8,179 patients in REDUCE-IT!

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT

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Article available at http://www.onlinejacc.org/content/early/2019/03/01/j.jacc.2019.02.032
Slides available for download at https://www.ACC.org


reduce-it

Baseline Triglyceride Levels

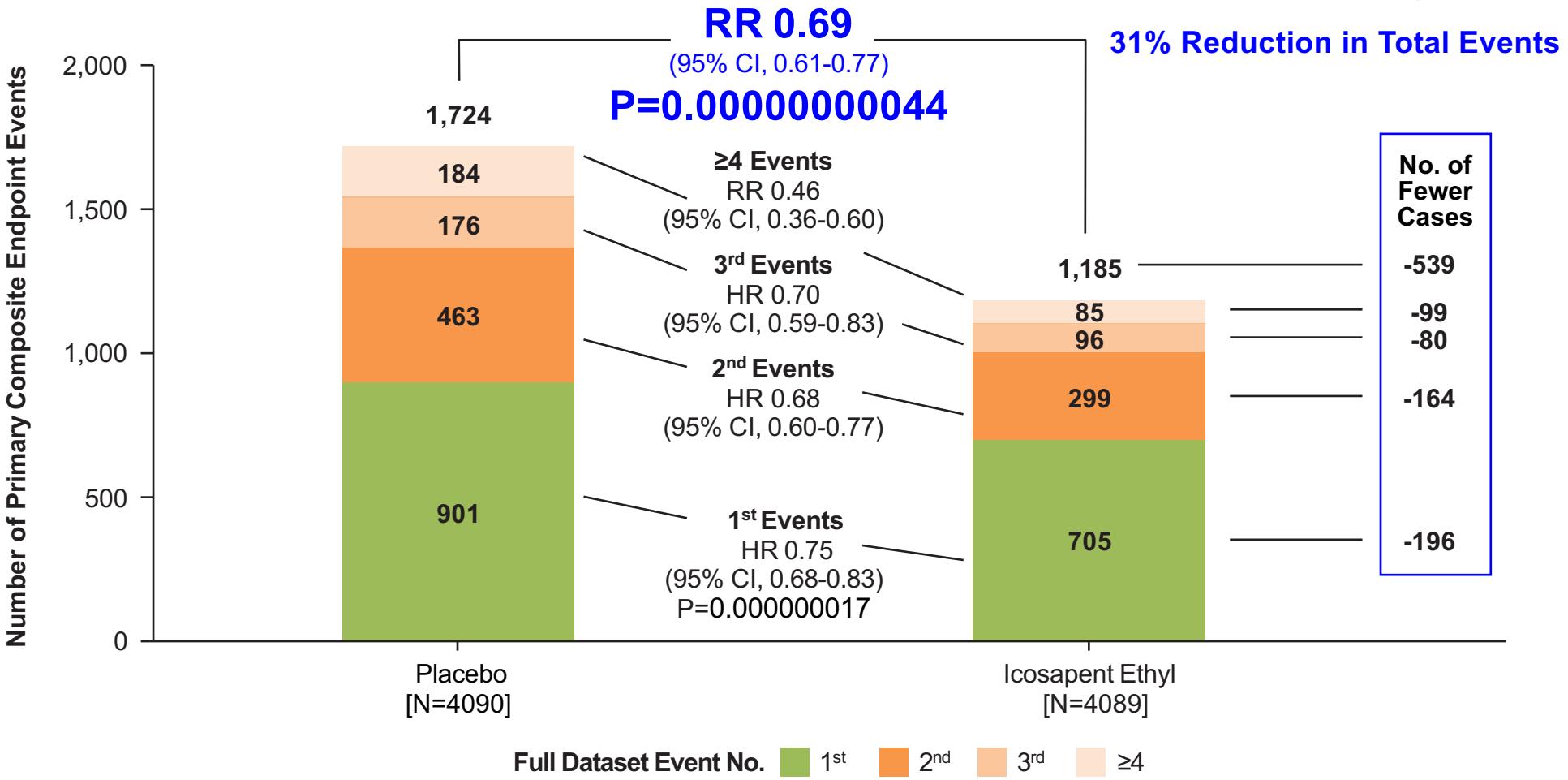
REDUCE-IT patients underwent a screening visit to determine eligibility, including testing of statin-stabilized triglyceride (TG) levels. Patients meeting inclusion and exclusion criteria, including TG levels could then be entered in the study at a subsequent randomization visit. Patients not meeting all entry criteria could undergo one additional screening visit and if qualified – could be enrolled at a subsequent randomization visit.

TGs were also measured from blood drawn at the randomization visit, but randomization values were not utilized for study qualification. Randomization values did not always fall within the inclusion criteria that were previously met at a qualifying visit.

Each patient's baseline TG value was calculated as the average of the final screening TG and the subsequent TG value from date of randomization. Therefore, the baseline TG levels ranged from 81 mg/dL to 1401 mg/dL.

The lowest baseline TG tertile range was ≥81 to ≤190 mg/dL (median 163 mg/dL), the middle tertile range was >190 to ≤250 mg/dL (median 217 mg/dL), and the uppermost tertile range was >250 to ≤1401 mg/dL (median 304 mg/dL).

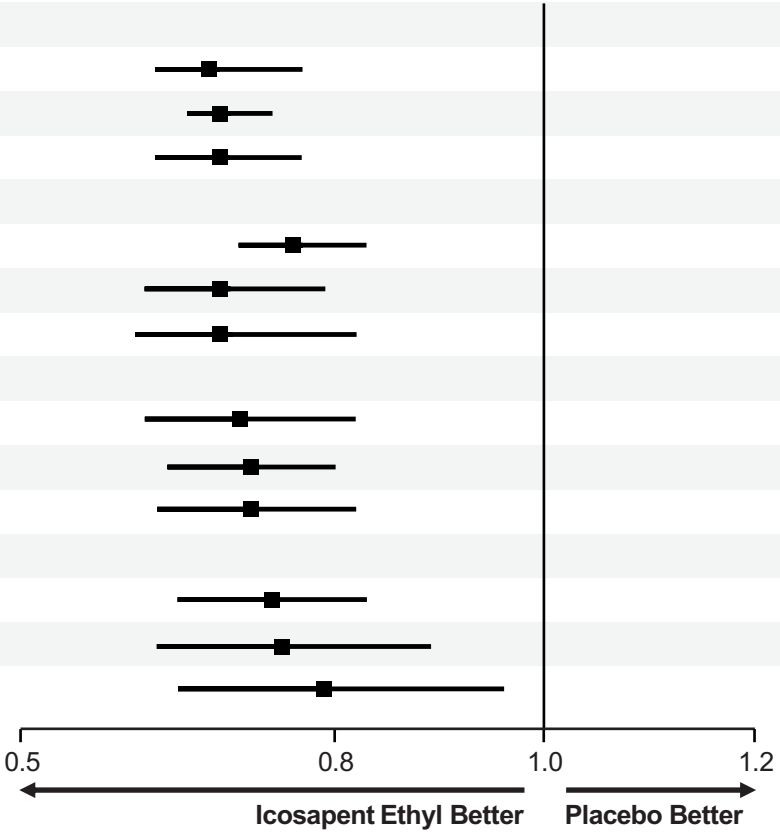
Distribution of First and Subsequent Events



Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

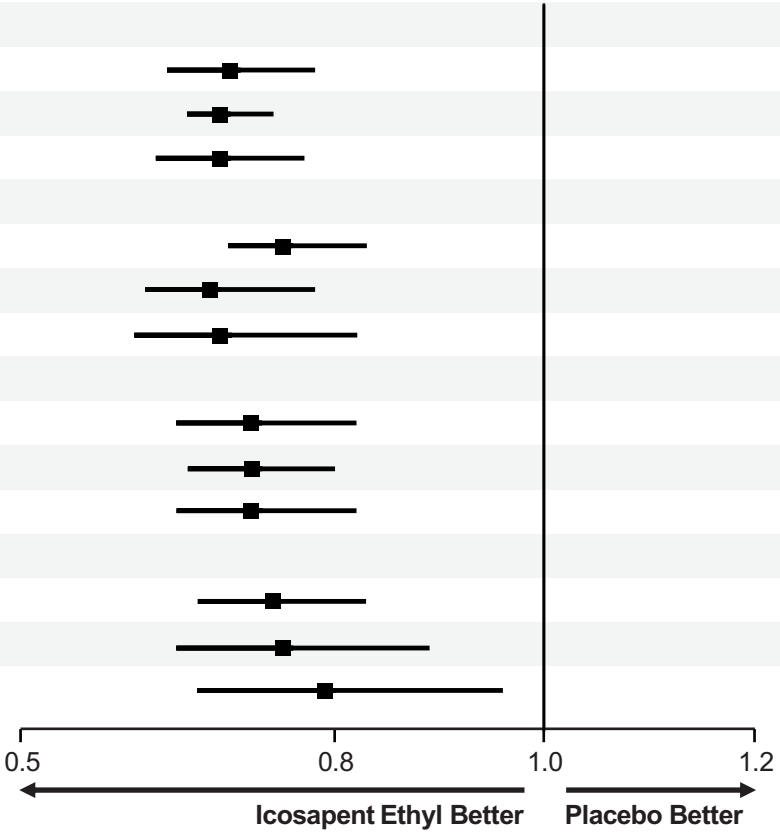
Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Unadjusted)

Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Primary Composite Endpoint		
Negative binomial	0.68 (0.61, 0.77)	1.5×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.5×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	9.1×10^{-11}
Modified WLW		
First event	0.76 (0.69, 0.83)	2.7×10^{-8}
Second event	0.69 (0.60, 0.79)	2.7×10^{-8}
Third event	0.69 (0.59, 0.82)	2.1×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.71 (0.62, 0.82)	8.9×10^{-7}
Andersen-Gill (I)	0.72 (0.64, 0.80)	2.4×10^{-9}
Andersen-Gill (II)	0.72 (0.63, 0.82)	1.2×10^{-6}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.4×10^{-7}
Second event	0.75 (0.63, 0.89)	1.1×10^{-3}
Third event	0.79 (0.65, 0.96)	0.0170



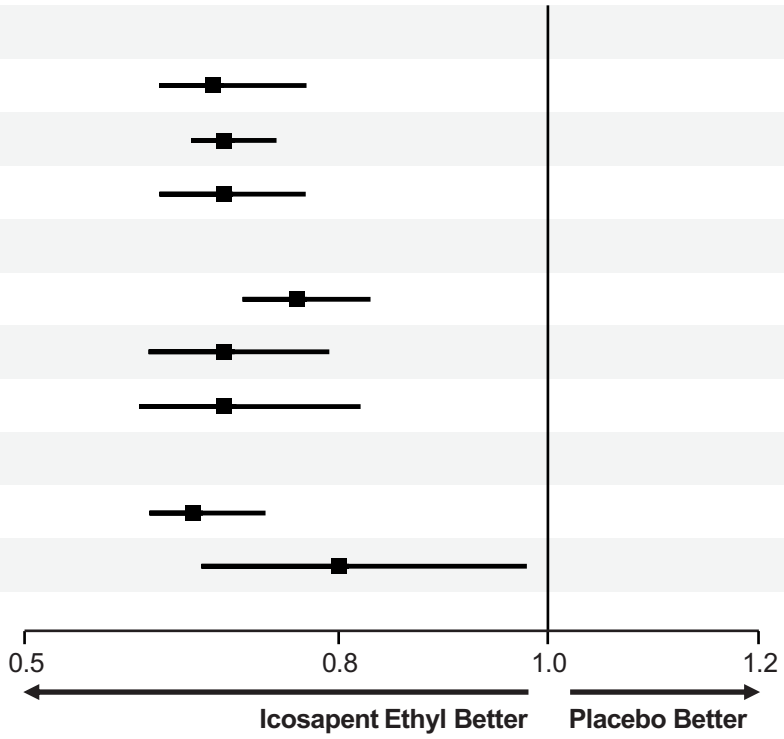
Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Adjusted)

Endpoint/Model	Adjusted Rate/Hazard Ratio (95% CI)	Adjusted P-value
Primary Composite Endpoint		
Negative binomial	0.70 (0.62, 0.78)	3.6×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.3×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	5.2×10^{-11}
Modified WLW		
First event	0.75 (0.68, 0.83)	1.6×10^{-8}
Second event	0.68 (0.60, 0.78)	1.8×10^{-8}
Third event	0.69 (0.59, 0.82)	2.0×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.72 (0.63, 0.82)	7.1×10^{-7}
Andersen-Gill (I)	0.72 (0.64, 0.80)	2.4×10^{-9}
Andersen-Gill (II)	0.72 (0.63, 0.82)	1.0×10^{-6}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.0×10^{-7}
Second event	0.75 (0.63, 0.89)	1.1×10^{-3}
Third event	0.79 (0.65, 0.96)	0.0171



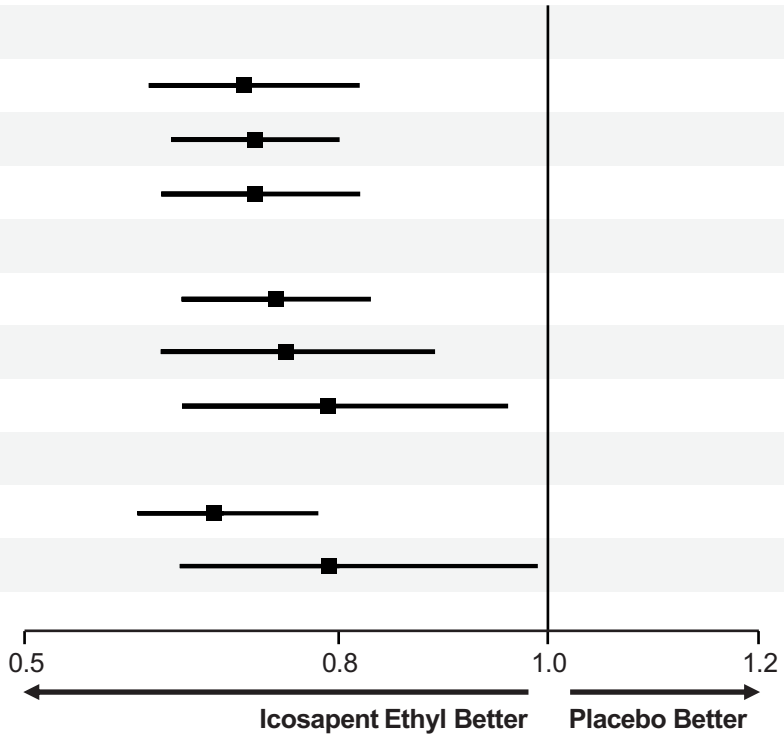
Total Primary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Unadjusted)

Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Primary Composite Endpoint		
Negative binomial	0.68 (0.61, 0.77)	1.5×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.5×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	9.1×10^{-11}
Modified WLW		
First event	0.76 (0.69, 0.83)	2.7×10^{-8}
Second event	0.69 (0.60, 0.79)	2.7×10^{-8}
Third event	0.69 (0.59, 0.82)	2.1×10^{-5}
Joint Frailty		
Non-fatal cardiovascular event	0.66 (0.60, 0.73)	7.40×10^{-17}
Cardiovascular death	0.80 (0.65, 0.98)	0.0282



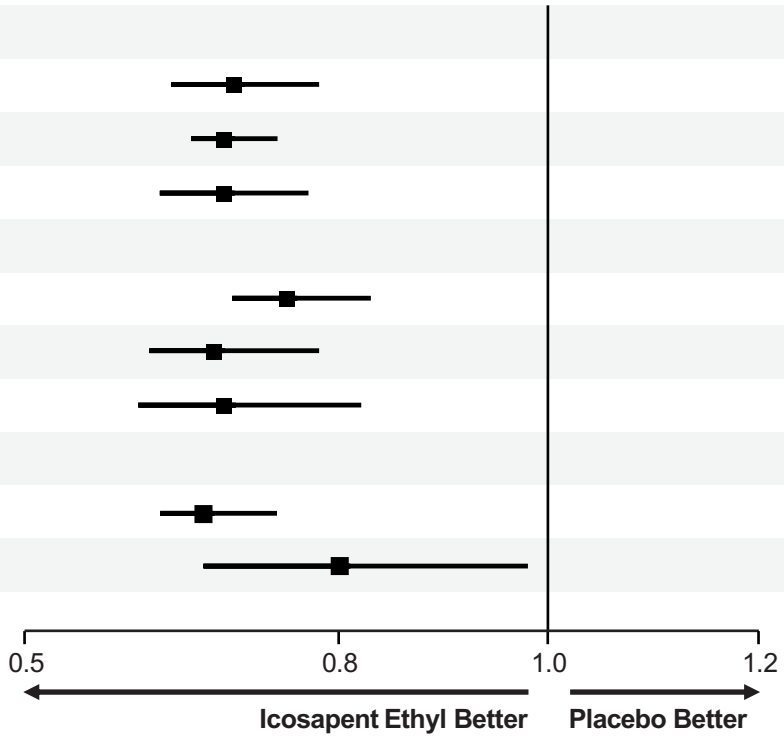
Total Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Unadjusted)

Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Key Secondary Composite Endpoint		
Negative binomial	0.71 (0.62, 0.82)	8.9×10^{-7}
Andersen-Gill (I)	0.72 (0.64, 0.80)	2.4×10^{-9}
Andersen-Gill (II)	0.72 (0.63, 0.82)	1.2×10^{-6}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.4×10^{-7}
Second event	0.75 (0.63, 0.89)	1.1×10^{-3}
Third event	0.79 (0.65, 0.96)	.0170
Joint Frailty		
Non-fatal cardiovascular event	0.68 (0.59, 0.78)	3.30×10^{-8}
Cardiovascular death	0.79 (0.63, 0.99)	0.0366



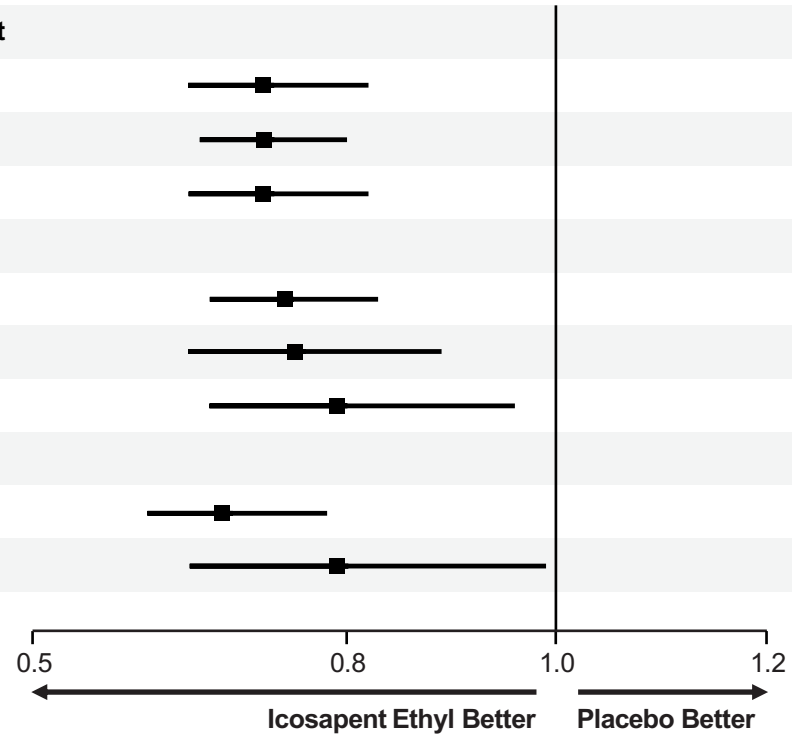
Total Primary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Adjusted)

Endpoint/Model	Adjusted Rate/Hazard Ratio (95% CI)	Adjusted P-value
Primary Composite Endpoint		
Negative binomial	0.70 (0.62, 0.78)	3.6×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.3×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	5.2×10^{-11}
Modified WLW		
First event	0.75 (0.68, 0.83)	1.6×10^{-8}
Second event	0.68 (0.60, 0.78)	1.8×10^{-8}
Third event	0.69 (0.59, 0.82)	2.0×10^{-5}
Joint Frailty		
Non-fatal cardiovascular event	0.67 (0.61, 0.74)	7.20×10^{-16}
Cardiovascular death	0.80 (0.65, 0.98)	0.0306



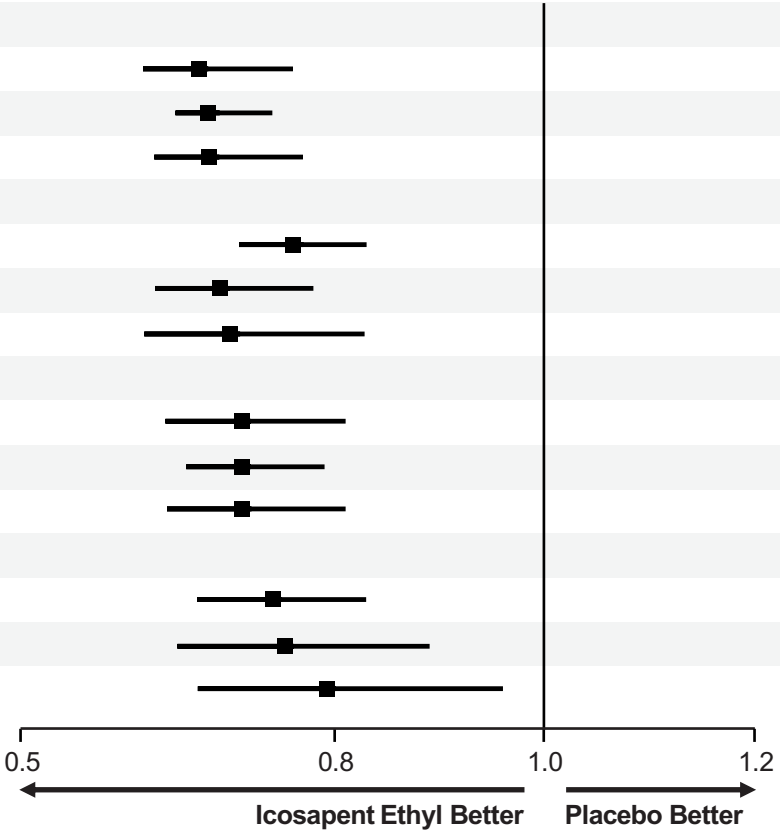
Total Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Adjusted)

Endpoint/Model	Adjusted Rate/Hazard Ratio (95% CI)	Adjusted P-value
Key Secondary Composite Endpoint		
Negative binomial	0.72 (0.63, 0.82)	7.1×10^{-7}
Andersen-Gill (I)	0.72 (0.64, 0.80)	2.4×10^{-9}
Andersen-Gill (II)	0.72 (0.63, 0.82)	1.0×10^{-6}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.0×10^{-7}
Second event	0.75 (0.63, 0.89)	1.1×10^{-3}
Third event	0.79 (0.65, 0.96)	.0171
Joint Frailty		
Non-fatal cardiovascular event	0.68 (0.59, 0.78)	4.30×10^{-8}
Cardiovascular death	0.79 (0.63, 0.99)	0.0380



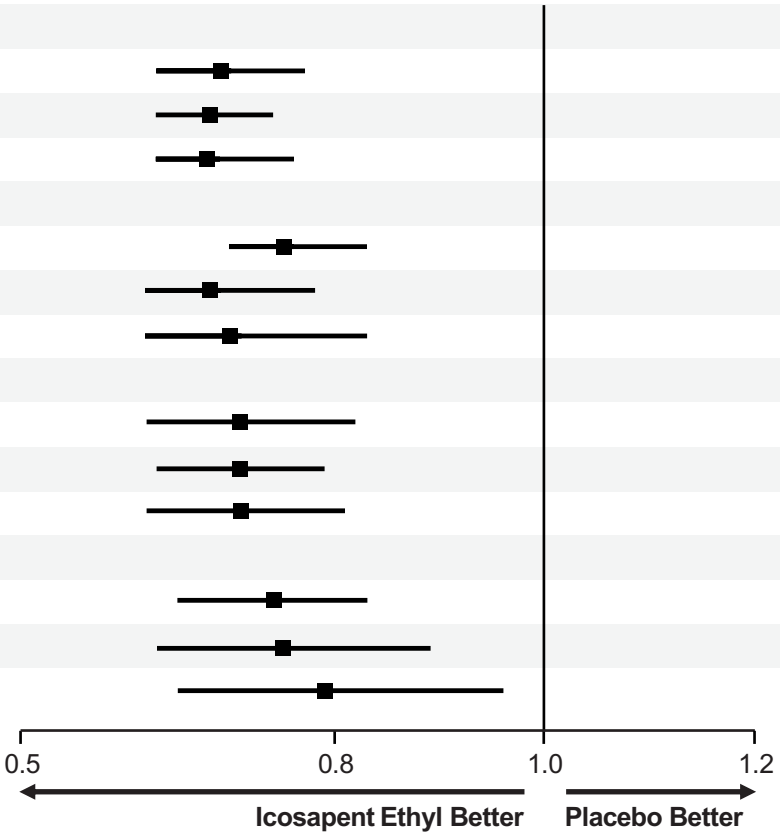
Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Full Dataset, Unadjusted)

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



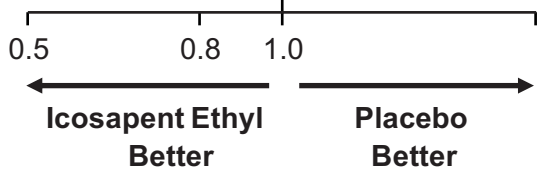
Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Full Dataset, Adjusted)

Endpoint/Model	Adjusted Rate/Hazard Ratio (95% CI)	Adjusted P-value
Primary Composite Endpoint		
Negative binomial	0.69 (0.61, 0.77)	4.4×10^{-10}
Andersen-Gill (I)	0.68 (0.63, 0.74)	3.0×10^{-22}
Andersen-Gill (II)	0.68 (0.61, 0.76)	3.4×10^{-11}
Modified WLW		
First event	0.75 (0.68, 0.83)	1.7×10^{-8}
Second event	0.68 (0.60, 0.78)	3.1×10^{-9}
Third event	0.70 (0.60, 0.83)	2.1×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.71 (0.62, 0.82)	1.2×10^{-6}
Andersen-Gill (I)	0.71 (0.63, 0.79)	1.7×10^{-10}
Andersen-Gill (II)	0.71 (0.62, 0.81)	3.4×10^{-7}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.1×10^{-7}
Second event	0.75 (0.63, 0.89)	0.0011
Third event	0.79 (0.65, 0.96)	0.0171



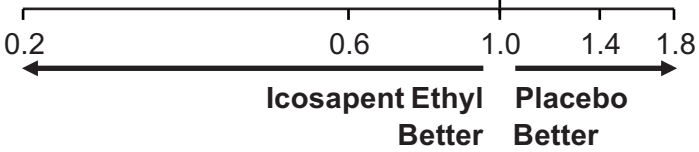
Total Primary and Key Secondary Composite Endpoints and Each Individual Component or Other Composite Endpoints

Endpoint	Icosapent Ethyl rate per 1000 patient years	Placebo rate per 1000 patient years	Rate Ratio (95% CI)	P-value
Primary composite endpoint	61	89	0.70 (0.62–0.78)	3.6×10^{-10}
Key secondary composite endpoint	32	44	0.72 (0.63–0.82)	7.1×10^{-7}
Cardiovascular death	10	12	0.81 (0.66–0.99)	0.0362
Fatal or nonfatal myocardial infarction	17	26	0.67 (0.56–0.80)	6.7×10^{-6}
Fatal or nonfatal stroke	06	09	0.68 (0.52–0.91)	0.0078
Coronary revascularization	27	42	0.64 (0.56–0.74)	3.1×10^{-10}
Hospitalization for unstable angina	07	09	0.69 (0.54–0.89)	0.0041



Primary Composite Endpoint: Time to First Event by Baseline TG Tertiles

TIME TO FIRST EVENT – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	HR (95% CI)	P-value
	n/N (%)	n/N (%)		
Primary Composite Endpoint (ITT)	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	233/1378 (16.9)	291/1381 (21.1)	0.79 (0.66–0.94)	0.0069
>190 to ≤250 mg/dL	246/1370 (18.0)	283/1326 (21.3)	0.80 (0.68–0.95)	0.0121
>250 to ≤1401 mg/dL	226/1338 (16.9)	327/1382 (23.7)	0.68 (0.57–0.80)	<0.0001



***P (interaction) = 0.33**